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Systemic treatments for metastatic cutaneous melanoma (Review)

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[Intervention Review]

Systemic treatments for metastatic cutaneous melanoma

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ABSTRACT

Background

The prognosis of people with metastatic cutaneous melanoma, a skin cancer, is generally poor. Recently, new classes of drugs (e.g. immune checkpoint inhibitors and small-molecule targeted drugs) have significantly improved patient prognosis, which has drastically changed the landscape of melanoma therapeutic management. This is an update of a Cochrane Review published in 2000.

Objectives

To assess the beneficial and harmful effects of systemic treatments for metastatic cutaneous melanoma.

Search methods

We searched the following databases up to October 2017: the Cochrane Skin Group Specialised Register, CENTRAL, MEDLINE, Embase and LILACS. We also searched five trials registers and the ASCO database in February 2017, and checked the reference lists of included studies for further references to relevant randomised controlled trials (RCTs).

Selection criteria

We considered RCTs of systemic therapies for people with unresectable lymph node metastasis and distant metastatic cutaneous melanoma compared to any other treatment. We checked the reference lists of selected articles to identify further references to relevant trials.

Data collection and analysis

Two review authors extracted data, and a third review author independently verified extracted data. We implemented a network meta-analysis approach to make indirect comparisons and rank treatments according to their effectiveness (as measured by the impact on survival) and harm (as measured by occurrence of high-grade toxicity). The same two review authors independently assessed the risk of bias of eligible studies according to Cochrane standards and assessed evidence quality based on the GRADE criteria.

Main results

We included 122 RCTs (28,561 participants). Of these, 83 RCTs, encompassing 21 different comparisons, were included in meta-analyses. Included participants were men and women with a mean age of 57.5 years who were recruited from hospital settings. Twenty-nine studies included people whose cancer had spread to their brains. Interventions were categorised into five groups: conventional chemotherapy (including single agent and polychemotherapy), biochemotherapy (combining chemotherapy with cytokines such as interleukin-2 and interferon-alpha), immune checkpoint inhibitors (such as anti-CTLA4 and anti-PD1 monoclonal antibodies), small-molecule targeted drugs

used for melanomas with specific gene changes (such as BRAF inhibitors and MEK inhibitors), and other agents (such as anti-angiogenic drugs). Most interventions were compared with chemotherapy. In many cases, trials were sponsored by pharmaceutical companies producing the tested drug: this was especially true for new classes of drugs, such as immune checkpoint inhibitors and small-molecule targeted drugs.

When compared to single agent chemotherapy, the combination of multiple chemotherapeutic agents (polychemotherapy) did not translate into significantly better survival (overall survival: HR 0.99, 95% CI 0.85 to 1.16, 6 studies, 594 participants; high-quality evidence; progression-free survival: HR 1.07, 95% CI 0.91 to 1.25, 5 studies, 398 participants; high-quality evidence. Those who received combined treatment are probably burdened by higher toxicity rates (RR 1.97, 95% CI 1.44 to 2.71, 3 studies, 390 participants; moderate-quality evidence). (We defined toxicity as the occurrence of grade 3 (G3) or higher adverse events according to the World Health Organization scale.)

Compared to chemotherapy, biochemotherapy (chemotherapy combined with both interferon-alpha and interleukin-2) improved progression-free survival (HR 0.90, 95% CI 0.83 to 0.99, 6 studies, 964 participants; high-quality evidence), but did not significantly improve overall survival (HR 0.94, 95% CI 0.84 to 1.06, 7 studies, 1317 participants; high-quality evidence). Biochemotherapy had higher toxicity rates (RR 1.35, 95% CI 1.14 to 1.61, 2 studies, 631 participants; high-quality evidence).

With regard to immune checkpoint inhibitors, anti-CTLA4 monoclonal antibodies plus chemotherapy probably increased the chance of progression-free survival compared to chemotherapy alone (HR 0.76, 95% CI 0.63 to 0.92, 1 study, 502 participants; moderate-quality evidence), but may not significantly improve overall survival (HR 0.81, 95% CI 0.65 to 1.01, 2 studies, 1157 participants; low-quality evidence). Compared to chemotherapy alone, anti-CTLA4 monoclonal antibodies is likely to be associated with higher toxicity rates (RR 1.69, 95% CI 1.19 to 2.42, 2 studies, 1142 participants; moderate-quality evidence).

Compared to chemotherapy, anti-PD1 monoclonal antibodies (immune checkpoint inhibitors) improved overall survival (HR 0.42, 95% CI 0.37 to 0.48, 1 study, 418 participants; high-quality evidence) and probably improved progression-free survival (HR 0.49, 95% CI 0.39 to 0.61, 2 studies, 957 participants; moderate-quality evidence). Anti-PD1 monoclonal antibodies may also result in less toxicity than chemotherapy (RR 0.55, 95% CI 0.31 to 0.97, 3 studies, 1360 participants; low-quality evidence).

Anti-PD1 monoclonal antibodies performed better than anti-CTLA4 monoclonal antibodies in terms of overall survival (HR 0.63, 95% CI 0.60 to 0.66, 1 study, 764 participants; high-quality evidence) and progression-free survival (HR 0.54, 95% CI 0.50 to 0.60, 2 studies, 1465 participants; high-quality evidence). Anti-PD1 monoclonal antibodies may result in better toxicity outcomes than anti-CTLA4 monoclonal antibodies (RR 0.70, 95% CI 0.54 to 0.91, 2 studies, 1465 participants; low-quality evidence).

Compared to anti-CTLA4 monoclonal antibodies alone, the combination of anti-CTLA4 plus anti-PD1 monoclonal antibodies was associated with better progression-free survival (HR 0.40, 95% CI 0.35 to 0.46, 2 studies, 738 participants; high-quality evidence). There may be no significant difference in toxicity outcomes (RR 1.57, 95% CI 0.85 to 2.92, 2 studies, 764 participants; low-quality evidence) (no data for overall survival were available).

The class of small-molecule targeted drugs, BRAF inhibitors (which are active exclusively against BRAF-mutated melanoma), performed better than chemotherapy in terms of overall survival (HR 0.40, 95% CI 0.28 to 0.57, 2 studies, 925 participants; high-quality evidence) and progression-free survival (HR 0.27, 95% CI 0.21 to 0.34, 2 studies, 925 participants; high-quality evidence), and there may be no significant difference in toxicity (RR 1.27, 95% CI 0.48 to 3.33, 2 studies, 408 participants; low-quality evidence).

Compared to chemotherapy, MEK inhibitors (which are active exclusively against BRAF-mutated melanoma) may not significantly improve overall survival (HR 0.85, 95% CI 0.58 to 1.25, 3 studies, 496 participants; low-quality evidence), but they probably lead to better progression-free survival (HR 0.58, 95% CI 0.42 to 0.80, 3 studies, 496 participants; moderate-quality evidence). However, MEK inhibitors probably have higher toxicity rates (RR 1.61, 95% CI 1.08 to 2.41, 1 study, 91 participants; moderate-quality evidence).

Compared to BRAF inhibitors, the combination of BRAF plus MEK inhibitors was associated with better overall survival (HR 0.70, 95% CI 0.59 to 0.82, 4 studies, 1784 participants; high-quality evidence). BRAF plus MEK inhibitors was also probably better in terms of progression-free survival (HR 0.56, 95% CI 0.44 to 0.71, 4 studies, 1784 participants; moderate-quality evidence), and there appears likely to be no significant difference in toxicity (RR 1.01, 95% CI 0.85 to 1.20, 4 studies, 1774 participants; moderate-quality evidence).

Compared to chemotherapy, the combination of chemotherapy plus anti-angiogenic drugs was probably associated with better overall survival (HR 0.60, 95% CI 0.45 to 0.81; moderate-quality evidence) and progression-free survival (HR 0.69, 95% CI 0.52 to 0.92; moderate-quality evidence). There may be no difference in terms of toxicity (RR 0.68, 95% CI 0.09 to 5.32; low-quality evidence). All results for this comparison were based on 324 participants from 2 studies.

Network meta-analysis focused on chemotherapy as the common comparator and currently approved treatments for which high- to moderate-quality evidence of efficacy (as represented by treatment effect on progression-free survival) was available (based on the above results) for: biochemotherapy (with both interferon-alpha and interleukin-2); anti-CTLA4 monoclonal antibodies; anti-PD1 monoclonal antibodies; anti-CTLA4 plus anti-PD1 monoclonal antibodies; BRAF inhibitors; MEK inhibitors, and BRAF plus MEK inhibitors. Analysis (which included 19 RCTs and 7632 participants) generated 21 indirect comparisons.

The best evidence (moderate-quality evidence) for progression-free survival was found for the following indirect comparisons:

• both combinations of immune checkpoint inhibitors (HR 0.30, 95% CI 0.17 to 0.51) and small-molecule targeted drugs (HR 0.17, 95% CI 0.11 to 0.26) probably improved progression-free survival compared to chemotherapy;
• both BRAF inhibitors (HR 0.40, 95% CI 0.23 to 0.68) and combinations of small-molecule targeted drugs (HR 0.22, 95% CI 0.12 to 0.39) were probably associated with better progression-free survival compared to anti-CTLA4 monoclonal antibodies;
• biochemotherapy (HR 2.81, 95% CI 1.76 to 4.51) probably lead to worse progression-free survival compared to BRAF inhibitors;
• the combination of small-molecule targeted drugs probably improved progression-free survival (HR 0.38, 95% CI 0.21 to 0.68) compared to anti-PD1 monoclonal antibodies;
• both biochemotherapy (HR 5.05, 95% CI 3.01 to 8.45) and MEK inhibitors (HR 3.16, 95% CI 1.77 to 5.65) were probably associated with worse progression-free survival compared to the combination of small-molecule targeted drugs; and
• biochemotherapy was probably associated with worse progression-free survival (HR 2.81, 95% CI 1.54 to 5.11) compared to the combination of immune checkpoint inhibitors.

The best evidence (moderate-quality evidence) for toxicity was found for the following indirect comparisons:
• combination of immune checkpoint inhibitors (RR 3.49, 95% CI 2.12 to 5.77) probably increased toxicity compared to chemotherapy;
• combination of immune checkpoint inhibitors probably increased toxicity (RR 2.50, 95% CI 1.20 to 5.20) compared to BRAF inhibitors;
• the combination of immune checkpoint inhibitors probably increased toxicity (RR 3.83, 95% CI 2.59 to 5.68) compared to anti-PD1 monoclonal antibodies; and
• biochemotherapy was probably associated with lower toxicity (RR 0.41, 95% CI 0.24 to 0.71) compared to the combination of immune checkpoint inhibitors.

Network meta-analysis-based ranking suggested that the combination of BRAF plus MEK inhibitors is the most effective strategy in terms of progression-free survival, whereas anti-PD1 monoclonal antibodies are associated with the lowest toxicity.

Overall, the risk of bias of the included trials can be considered as limited. When considering the 122 trials included in this review and the seven types of bias we assessed, we performed 854 evaluations only seven of which (< 1%) assigned high risk to six trials.

Authors' conclusions

We found high-quality evidence that many treatments offer better efficacy than chemotherapy, especially recently implemented treatments, such as small-molecule targeted drugs, which are used to treat melanoma with specific gene mutations. Compared with chemotherapy, biochemotherapy (in this case, chemotherapy combined with both interferon-alpha and interleukin-2) and BRAF inhibitors improved progression-free survival; BRAF inhibitors (for BRAF-mutated melanoma) and anti-PD1 monoclonal antibodies improved overall survival. However, there was no difference between polychemotherapy and monochemotherapy in terms of achieving progression-free survival and overall survival. Biochemotherapy did not significantly improve overall survival and has higher toxicity rates compared with chemotherapy.

There was some evidence that combined treatments worked better than single treatments: anti-PD1 monoclonal antibodies, alone or with anti-CTLA4, improved progression-free survival compared with anti-CTLA4 monoclonal antibodies alone. Anti-PD1 monoclonal antibodies performed better than anti-CTLA4 monoclonal antibodies in terms of overall survival, and a combination of BRAF plus MEK inhibitors was associated with better overall survival for BRAF-mutated melanoma, compared to BRAF inhibitors alone.

The combination of BRAF plus MEK inhibitors (which can only be administered to people with BRAF-mutated melanoma) appeared to be the most effective treatment (based on results for progression-free survival), whereas anti-PD1 monoclonal antibodies appeared to be the least toxic, and most acceptable, treatment.

Evidence quality was reduced due to imprecision, between-study heterogeneity, and substandard reporting of trials. Future research should ensure that those diminishing influences are addressed. Clinical areas of future investigation should include the longer-term effect of new therapeutic agents (i.e. immune checkpoint inhibitors and targeted therapies) on overall survival, as well as the combination of drugs used in melanoma treatment; research should also investigate the potential influence of biomarkers.

PLAIN LANGUAGE SUMMARY

Systemic treatments (tablets or injections) taken for metastatic melanoma (expanded from its starting point to other parts of the body)

Background

Melanoma is the most dangerous common skin cancer. Early diagnosis offers the best chance of cure. People affected by early stage melanoma represent about 70% to 80% of all those with melanoma and can be treated by surgical removal of the original tumour (known as the primary tumour). However, when a primary melanoma is detected at a later stage, there is a risk of disease spreading to the nearest lymph nodes (glands that are part of the body's immune system) and distant sites, such as the lungs, liver, bone and brain. In this case, systemic chemotherapy (giving drugs that kill cells throughout the body) and biochemotherapy (chemotherapy combined with substances that can improve the immune response, known as immunostimulating cytokines, such as interleukin-2 and interferon-alpha) have been

the main treatments for over three decades. However, only few people experience spontaneous (i.e. not resulting from therapy) regression of the primary tumour.

Over the past few years, new classes of drugs have been used with promising results. We aimed to look at how new systemic treatments compare with older therapies, as well as with each other, in terms of survival, acceptability, tumour response, and quality of life. We assessed these outcomes in people with metastatic melanoma (AJCC TNM stage IV).

Review question

We aimed to assess the effects of systemic treatments for people with metastatic cutaneous melanoma (melanoma of skin tissue). We searched for relevant trials up to October 2017 and included 122 studies.

We summarised the results of melanoma treatments (delivered systemically), such as conventional chemotherapy, biochemotherapy, as well as newer drug classes, such as immune checkpoint inhibitors (anti-CTLA4 and anti-PD1 monoclonal antibodies, which increase the anti-tumour activity of the immune system), small-molecule targeted drugs (BRAF inhibitors, which are used only for melanomas containing specific BRAF gene mutations that promote tumour progression, and MEK inhibitors, which work on the same molecular pathway), and anti-angiogenic drugs (which reduce blood supply to cancer cells). We compared these treatments with conventional chemotherapy.

Study characteristics

All 122 studies were randomised controlled trials that enrolled participants with metastatic cutaneous melanoma and compared different systemic treatments (28,561 participants). Study participants were adults of either sex, with a mean age of 57.5 years. There were 29 studies that included people whose cancer had spread to the brain, which is important because the detection and treatment of brain metastases often present unique challenges. Most treatments were compared with chemotherapy, and all studies were set in hospitals. Frequently, the pharmaceutical company who produced a tested drug also sponsored the study in which it was assessed, especially in the case of new classes of drugs, such as immune checkpoint inhibitors and small-molecule targeted drugs.

Key results

Compared to conventional chemotherapy, several treatments can improve the progression-free survival of people with metastatic melanoma. These include biochemotherapy (high-quality evidence), anti-CTLA4 monoclonal antibodies plus chemotherapy (moderate-quality evidence), anti-PD1 monoclonal antibodies (moderate-quality evidence), BRAF inhibitors (high-quality evidence), MEK inhibitors (moderate-quality evidence), and anti-angiogenic drugs (moderate-quality evidence). However, no difference was found for use of a combination of several chemotherapy agents (polychemotherapy) (high-quality evidence). Moreover, the combination of immune checkpoint inhibitors (anti-PD1 plus anti-CTLA4 monoclonal antibodies) performed better than anti-CTLA4 monoclonal antibodies alone (high-quality evidence), but anti-PD1 monoclonal antibodies performed better than anti-CTLA4 monoclonal antibodies (high-quality evidence). The combination of small-molecule inhibitors (BRAF plus MEK inhibitors) lead to better results than BRAF inhibitors alone (moderate-quality evidence), for people with melanoma that has a BRAF gene change .

Anti-PD1 monoclonal antibodies improved patients' overall survival compared with either standard chemotherapy (high-quality evidence) or anti-CTLA4 monoclonal antibodies (high-quality evidence). Compared to chemotherapy alone, both BRAF inhibitors (high-quality evidence), and anti-angiogenic agents combined with chemotherapy (moderate-quality evidence) also prolong overall survival, but anti-CTLA4 monoclonal antibodies plus chemotherapy (low-quality evidence), MEK inhibitors (low-quality evidence), combined multiple chemotherapeutic agents (polychemotherapy) (high-quality evidence), or biochemotherapy (high-quality evidence) did not lead to significantly improved overall survival. WE also found that the combination of small-molecule inhibitors performed better than BRAF inhibitors alone (high-quality evidence). No data on overall survival were available for anti-CTLA4 monoclonal antibodies alone compared with the combination of anti-CTLA4 plus anti-PD1 monoclonal antibodies.

In terms of toxicity (defined as occurrence of high-grade side effects), biochemotherapy (high-quality evidence), anti-CTLA4 monoclonal antibodies (moderate-quality evidence), polychemotherapy (moderate-quality evidence), and MEK inhibitors (moderate-quality evidence) were associated with worse toxicity compared to chemotherapy. In contrast, anti-PD1 monoclonal antibodies appear to be better tolerated than chemotherapy alone. Anti-PD1 monoclonal antibodies also appeared to be better tolerated than anti-CTLA4 monoclonal antibodies. However, evidence quality supporting these findings was assessed as low. Furthermore, the frequency of side effects did not differ significantly between anti-PD1 plus anti-CTLA4 monoclonal antibodies versus anti-CTLA4 monoclonal antibodies alone (low-quality evidence), anti-angiogenic drugs combined with chemotherapy versus chemotherapy (low-quality evidence), BRAF inhibitors versus chemotherapy (low-quality evidence), and BRAF plus MEK inhibitors versus BRAF inhibitors alone (moderate-quality evidence).

We also conducted an analysis that compared treatments that had not been directly compared in a study. This is known as a network meta-analysis. For the outcome of progression-free survival, looking at only the best evidence available, we found the following results (please note that because the highest quality level was moderate, the following results can only be deemed probable):
• both combination of immune checkpoint inhibitors and combination of small-molecule targeted drugs were favoured compared to chemotherapy;
• both BRAF inhibitors and combination of small-molecule targeted drugs were favoured compared to anti-CTLA4 monoclonal antibodies;

• biochemotherapy led to less favourable results than BRAF inhibitors;
• the combination of small-molecule targeted drugs was favoured compared to anti-PD1 monoclonal antibodies;
• both biochemotherapy and MEK inhibitors led to less favourable results than the combination of small-molecule targeted drugs; and
• biochemotherapy led to less favourable results than the combination of immune checkpoint inhibitors

For the outcome of toxicity, looking at only the best evidence available, we found the following results (again, evidence quality was no higher than moderate):
• combination of immune checkpoint inhibitors led to less favourable results than chemotherapy;
• combination of immune checkpoint inhibitors led to less favourable results than BRAF inhibitors;
• the combination of immune checkpoint inhibitors led to less favourable results than anti-PD1 monoclonal antibodies; and
• biochemotherapy was favoured compared to the combination of immune checkpoint inhibitors.

Our results suggest that the combination of small-molecule targeted drugs (BRAF plus MEK inhibitors) is the most effective treatment strategy, for people with melanoma that has a BRAF gene change, at least in terms of progression-free survival; however, this combination therapy is burdened by a higher rate of severe toxicity compared to effects observed among people treated with anti-PD1 monoclonal antibodies, which can be used in all melanoma types, and rank highest in terms of tolerability.

These results need long-term analysis from randomised trials to be confirmed, with special attention to effects on patients' overall survival.

Quality of the evidence

GRADE findings showed that most evidence was high- to moderate-quality for three (overall survival, progression-free survival and tumour response) out of four outcomes (toxicity). Evidence quality was reduced due to small numbers of participants in some comparisons, differences between the studies, and poor reporting of trials.

Summary of findings 1. Anti-PD1 monoclonal antibodies versus chemotherapy

Anti-PD1 monoclonal antibodies compared with chemotherapy for the treatment of metastatic melanoma

Patient or population: people with cutaneous melanoma

Settings: hospital (metastatic disease)

Intervention: anti-PD1 monoclonal antibodies

Comparison: chemotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Chemotherapy	Anti-PD1				
Overall survival†	**600 per 1000†**	**320 per 1000†** (290 to 360)	**HR 0.42** (0.37 to 0.48)	N = 418 (n = 1)	⊕⊕⊕⊕ **high**[a]	-
Progression-free survival†	**850 per 1000†**	**610 per 1000†** (520 to 690)	**HR 0.49** (0.39 to 0.61)	N = 957 (n = 2)	⊕⊕⊕⊖ **moderate**[b]	-
Tumour response	**81 per 1000**	**277 per 1000** (193 to 398)	**RR 3.42** (2.38 to 4.92)	N = 1367 (n = 3)	⊕⊕⊕⊕ **high**[a]	-
Toxicity (≥ G3)	**300 per 1000**	**165 per 1000** (93 to 291)	RR**0.55** (0.31 to 0.97)	N = 1360 (n = 3)	⊕⊕⊖⊖ **low**[c]	-

* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

† Numbers presented refer to event rates (i.e. death rates and progression rates).

CI: confidence interval; **HR:** hazard ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

Assumed risk in the control population: 1-year overall survival rate = 40%.
Assumed risk in the control population: 1-year progression-free survival rate = 15%.
Assumed risk in the control population: tumour response rate across control arms of included trials.
Assumed risk in the control population: toxicity rate across control arms of included trials.
[a] Not downgraded: high-quality evidence.
[b] Downgraded by one level: inconsistency (between-study heterogeneity).
[c] Downgraded by two levels: inconsistency (between-study heterogeneity) and imprecision (CI includes both a meaningful benefit (relative risk reduction > 25%) and a small/null benefit (relative risk reduction < 10%)).

Summary of findings 2. Anti-PD1 monoclonal antibodies versus anti-CTLA4 monoclonal antibodies

Anti-PD1 monoclonal antibodies compared with anti-CTLA4 monoclonal antibodies for the treatment of metastatic melanoma

Patient or population: people with cutaneous melanoma

Settings: hospital (metastatic disease)

Intervention: anti-PD1 monoclonal antibodies

Comparison: anti-CTLA4 monoclonal antibodies

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Anti-CTLA4	Anti-PD1				
Overall survival†	**600 per 1000†**	**438 per 1000†** (423 to 454)	**HR 0.63** (0.60 to 0.66)	N = 764 (n = 1)	⊕⊕⊕⊕ **high[a]**	-
Progression-free survival†	**850 per 1000†**	**641 per 1000†** (612 to 679)	**HR 0.54** (0.50 to 0.60)	n = 1465 (n = 2)	⊕⊕⊕⊕ **high[a]**	-
Tumour response	**157 per 1000**	**388 per 1000** (315 to 477)	**RR 2.47** (2.01 to 3.04)	N = 1465 (n = 2)	⊕⊕⊕⊕ **high[a]**	-
Toxicity (≥ G3)	**398 per 1000**	**278 per 1000** (215 to 362)	**RR 0.70** (0.54 to 0.91)	N = 1465 (n = 2)	⊕⊕⊖⊖ **low[b]**	-

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

† Numbers presented refer to event rates (i.e. death rates and progression rates).

CI: confidence interval; **RR:** risk ratio; **HR:** hazard ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Assumed risk in the control population: 1-year overall survival rate = 40%.
Assumed risk in the control population: 1-year progression-free survival rate = 15%.
Assumed risk in the control population: tumour response rate across control arms of included trials.
Assumed risk in the control population: toxicity rate across control arms of included trials.
[a] Not downgraded: high-quality evidence.
[b] Downgraded by two levels: inconsistency (between-study heterogeneity) and imprecision (CI includes both a meaningful benefit (relative risk reduction > 25%) and a small/null benefit (relative risk reduction < 10%).

Summary of findings 3. Anti-CTLA4 monoclonal antibodies plus chemotherapy versus chemotherapy

Anti-CTLA4 monoclonal antibodies plus chemotherapy compared with chemotherapy for the treatment of metastatic melanoma

Patient or population: people with cutaneous melanoma

Settings: hospital (metastatic disease)

Intervention: anti-CTLA4 monoclonal antibodies plus chemotherapy (combo)

Comparison: chemotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative Effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Chemotherapy	Combo				
Overall survival†	**600 per 1000†**	**524 per 1000†** (449 to 604)	**HR 0.81** (0.65 to 1.01)	N = 1157 (n = 2)	⊕⊕⊖⊖ **low[a]**	-
Progression-free survival†	**850 per 1000†**	**763 per 1000†** (697 to 825)	**HR 0.76** (0.63 to 0.92)	N = 502 (n = 1)	⊕⊕⊕⊖	-

					moderate[b]	
Tumour response	**100 per 1000**	**128 per 1000** (92 to 177)	**RR 1.28** (0.92 to 1.77)	N = 1157 (n = 2)	⊕⊕⊕⊖ **moderate**[c]	-
Toxicity (≥ G3)	**352 per 1000**	**595 per 1000** (419 to 852)	**RR 1.69** (1.19 to 2.42)	N = 1142 (n = 2)	⊕⊕⊕⊖ **moderate**[d]	-

* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

† Numbers presented refer to event rates (i.e. death rates and progression rates).

CI: confidence interval; **HR:** hazard ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Assumed risk in the control population: 1-year overall survival rate = 40%.
Assumed risk in the control population: 1-year progression-free survival rate = 15%.
Assumed risk in the control population: tumour response rate across control arms of included trials.
Assumed risk in the control population: toxicity rate across control arms of included trials.
[a] Downgraded by two levels: inconsistency (between-study heterogeneity) and imprecision (CI includes both a meaningful benefit (relative risk reduction > 25%) and a harmful effect).
[b] Downgraded by one level: imprecision (CI includes both a meaningful benefit (relative risk reduction > 25%) and a small/null benefit (relative risk reduction < 10%)).
[c] Downgraded by one level: imprecision (CI includes both a meaningful benefit (relative risk increase > 25%) and a harmful effect).
[d] Downgraded by one level: inconsistency (between-study heterogeneity).

Summary of findings 4. Anti-CTLA4 monoclonal antibodies with versus without anti-PD1 monoclonal antibodies

Anti-CTLA4 plus anti-PD1 monoclonal antibodies compared with anti-CTLA4 monoclonal antibodies for the treatment of metastatic melanoma

Patient or population: people with cutaneous melanoma

Settings: hospital (metastatic disease)

Intervention: Anti-CTLA4 plus Anti-PD1 monoclonal antibodies (combo)

Comparison: Anti-CTLA4 monoclonal antibodies

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Anti-CTLA4	Combo				
Overall survival	See comment	See comment	See comment	See comment	See comment	Outcome not measured
Progression-free survival†	**750 per 1000**†	**425 per 1000**† (375 to 478)	**HR 0.40** (0.35 to 0.46)	N = 738 (n = 2)	⊕⊕⊕⊕ **high**[a]	-
Tumour response	**182 per 1000**	**636 per 1000** (376 to 1073)	**RR 3.50** (2.07 to 5.92)	N = 738 (n = 2)	⊕⊕⊕⊕ **high**[a]	-
Toxicity (≥ G3)	**521 per 1000**	**818 per 1000** (442 to 1521)	**RR 1.57** (0.85 to 2.92)	N = 764 (n = 2)	⊕⊕⊖⊖ **low**[b]	-

* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

† Numbers presented refer to event rates (i.e. progression rates).

CI: confidence interval

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Assumed risk in the control population: 1-year progression-free survival rate = 25%.
Assumed risk in the control population: tumour response rate across control arms of included trials.
Assumed risk in the control population: toxicity rate across control arms of included trials.
[a] Not downgraded: high-quality evidence.
[b] Downgraded by two levels: inconsistency (between-study heterogeneity) and imprecision (CI includes both a meaningful harm (relative risk increase > 25%) and a beneficial effect)

Summary of findings 5. BRAF inhibitors versus chemotherapy

BRAF inhibitors compared with chemotherapy for the treatment of metastatic melanoma

Patient or population: people with cutaneous melanoma

Settings: hospital (metastatic disease)

Intervention: BRAF inhibitors

Comparison: chemotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Chemotherapy	BRAF inhibitors				
Overall survival†	**600 per 1000†**	**307 per 1000†** (226 to 407)	**HR 0.40** (0.28 to 0.57)	N = 925 (n = 2)	⊕⊕⊕⊕ **high**[a]	-
Progression-free survival†	**850 per 1000†**	**401 per 1000†** (328 to 475)	**HR 0.27** (0.21 to 0.34)	N = 925 (n = 2)	⊕⊕⊕⊕ **high**[a]	-
Tumour response	**82 per 1000**	**556 per 1000** (397 to 778)	**RR 6.78** (4.84 to 9.49)	N = 925 (n = 2)	⊕⊕⊕⊕ **high**[a]	-
Toxicity (≥ G3)	**341 per 1000**	**433 per 1000** (163 to 1135)	**RR 1.27** (0.48 to 3.33)	N = 408 (n = 2)	⊕⊕⊖⊖ **low**[b]	-

* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

† Numbers presented refer to event rates (i.e. death rates and progression rates).
CI: confidence interval; **HR:** hazard ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Assumed risk in the control population: 1-year overall survival rate = 40%.
Assumed risk in the control population: 1-year progression-free survival rate = 15%.
Assumed risk in the control population: tumour response rate across control arms of included trials.
Assumed risk in the control population: toxicity rate across control arms of included trials.

[a] Not downgraded: high-quality evidence.
[b] Downgraded by two levels: inconsistency (between-study heterogeneity) and imprecision (CI includes both a meaningful harm (relative risk increase > 25%) and a meaningful benefit (relative risk reduction > 25%)).

Summary of findings 6. MEK inhibitors versus chemotherapy

MEK inhibitors compared with chemotherapy for the treatment of metastatic melanoma

Patient or population: people with cutaneous melanoma

Settings: hospital (metastatic disease)

Intervention: MEK inhibitors

Comparison: chemotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Chemotherapy	MEK inhibitors				
Overall survival†	**600 per 1000†**	**541 per 1000†** (412 to 682)	**HR 0.85** (0.58 to 1.25)	N = 496 (n = 3)	⊕⊕⊙⊙ **low[a]**	-
Progression-free survival†	**850 per 1000†**	**667 per 1000†** (549 to 781)	**HR 0.58** (0.42 to 0.80)	N = 496 (n = 3)	⊕⊕⊕⊙ **moderate[b]**	-
Tumour response	**138 per 1000**	**277 per 1000** (186 to 413)	**RR 2.01** (1.35 to 2.99)	N = 496 (n = 3)	⊕⊕⊕⊕ **high[c]**	-
Toxicity (≥ G3)	**413 per 1000**	**665 per 1000** (446 to 995)	**RR 1.61** (1.08 to 2.41)	N = 91 (n = 1)	⊕⊕⊕⊙ **moderate[d]**	-

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

† Numbers presented refer to event rates (i.e. death rates and progression rates).
CI: confidence interval; **RR:** risk ratio; **HR:** hazard ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Assumed risk in the control population: 1-year overall survival rate = 40%.
Assumed risk in the control population: 1-year progression-free survival rate = 15%.
Assumed risk in the control population: tumour response rate across control arms of included trials.
Assumed risk in the control population: toxicity rate across control arms of included trials.
[a] Downgraded by two levels: inconsistency (between-study heterogeneity) and imprecision (CI includes both a meaningful benefit (relative risk reduction > 25%) and a harmful effect).
[b] Downgraded by one level: inconsistency (between-study heterogeneity).
[c] Not downgraded: high-quality evidence.
[d] Downgraded by one level: imprecision (sample size lower than optimal information size, calculated to be equal to 400 participants).

Summary of findings 7. BRAF plus MEK inhibitors versus BRAF inhibitors

BRAF plus MEK inhibitors compared with BRAF inhibitors for the treatment of metastatic melanoma

Patient or population: people cutaneous melanoma

Settings: hospital (metastatic disease)

Intervention: BRAF inhibitor plus MEK inhibitor (combo)

Comparison: BRAF inhibitor

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	BRAF inhibitor	Combo				
Overall survival†	**350 per 1000†**	**260 per 1000†** (204 to 321)	**HR 0.70** (0.59 to 0.82)	N = 1784 (n = 4)	⊕⊕⊕⊕ **high[a]**	-
Progression-free survival†	**700 per 1000†**	**490 per 1000†** (411 to 574)	**HR 0.56** (0.44 to 0.71)	N = 1784 (n = 4)	⊕⊕⊕⊖ **moderate[b]**	-
Tumour response	**494 per 1000**	**652 per 1000** (593 to 721)	**RR 1.32** (1.20 to 1.46)	N = 1784 (n = 4)	⊕⊕⊕⊕ **high[a]**	-
Toxicity (≥ G3)	**495 per 1000**	**500 per 1000**	**RR 1.01** (0.85 to 1.20)	N = 1774	⊕⊕⊕⊖	-

	(421 to 594)		(n = 4)	**moderate**[b]	

* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

† Numbers presented refer to event rates (i.e. death rates and progression rates).

CI confidence interval; **HR:** hazard ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Assumed risk in the control population: 1-year overall survival rate = 65%.
Assumed risk in the control population: 1-year progression-free survival rate = 30%.
Assumed risk in the control population: tumour response rate across control arms of included trials.
Assumed risk in the control population: toxicity rate across control arms of included trials.
[a] Not downgraded: high-quality evidence.
[b] Downgraded by one level: inconsistency (between-study heterogeneity).

Summary of findings 8. Anti-angiogenic drugs plus chemotherapy versus chemotherapy

Anti-angiogenic drugs plus chemotherapy compared with chemotherapy for the treatment of metastatic melanoma

Patient or population: people with cutaneous melanoma

Settings: hospital (metastatic disease)

Intervention: Anti-angiogenic drug plus chemotherapy (combo)

Comparison: chemotherapy

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Chemotherapy	**Combo**				
Overall survival†	**600 per 1000**†	**423 per 1000**† (338 to 524)	**HR 0.60** (0.45 to 0.81)	N = 324 (n = 2)	⊕⊕⊕⊖ **moderate**[a]	-

Progression-free survival†	**850 per 1000†**	**730 per 1000†** (627 to 825)	**HR 0.69** (0.52 to 0.92)	N = 324 (n = 2)	⊕⊕⊕⊖ **moderate**[a]	-
Tumour response	**104 per 1000**	**178 per 1000** (100 to 315)	**RR 1.71** (0.96 to 3.03)	N = 324 (n = 2)	⊕⊕⊕⊖ **moderate**[a]	-
Toxicity (≥ G3)	**272 per 1000**	**185 per 1000** (25 to 1447)	**RR 0.68** (0.09 to 5.32)	N = 324 (n = 2)	⊕⊕⊖⊖ **low**[b]	-

* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

† Numbers presented refer to event rates (i.e. death rates and progression rates).
CI: confidence interval; **HR:** hazard ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Assumed risk in the control population: 1-year overall survival rate = 40%.
Assumed risk in the control population: 1-year progression-free survival rate = 15%.
Assumed risk in the control population: tumour response rate across control arms of included trials.
Assumed risk in the control population: toxicity rate across control arms of included trials.
[a] Downgraded by one level: imprecision (sample size lower than optimal information size, calculated to be equal to 400 participants).
[b] Downgraded by two levels: inconsistency (between-study heterogeneity) and imprecision (sample size lower than optimal information size, calculated to be equal to 400 participants).

Summary of findings 9. Biochemotherapy versus chemotherapy

Biochemotherapy compared with chemotherapy for the treatment of metastatic melanoma

Patient or population: people with cutaneous melanoma

Settings: hospital (metastatic disease)

Intervention: biochemotherapy (chemotherapy combined with both interferon-alpha and interleukin-2)

Comparison: chemotherapy

Outcomes	Illustrative comparative risks* (95% CI)	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence	Comments

	Assumed risk	Corresponding risk			(GRADE)	
	Chemotherapy	Biochemotherapy				
Overall survival†	**600 per 1000†**	**577 per 1000†** (537 to 621)	**HR 0.94** (0.84 to 1.06)	N = 1317 (n = 7)	⊕⊕⊕⊕ **high**[a]	-
Progression-free survival†	**850 per 1000 °**	**818 per 1000†** (793 to 847)	**HR 0.90** (0.83 to 0.99)	N = 964 (n = 6)	⊕⊕⊕⊕ **high**[a]	-
Tumour response	**192 per 1000**	**262 per 1000** (214 to 321)	**RR 1.36** (1.12 to 1.66)	N = 770 (n = 7)	⊕⊕⊕⊕ **high**[a]	-
Toxicity (≥ G3)	**631 per 1000**	**852 per 1000** (719 to 1000)	**RR 1.35** (1.14 to 1.61)	N = 631 (n = 2)	⊕⊕⊕⊕ **high**[a]	-

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

† Numbers presented refer to event rates (i.e. death rates and progression rates).
CI: confidence interval; **RR:** risk ratio; **HR:** hazard ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Assumed risk in the control population: 1-year overall survival rate = 40%.
Assumed risk in the control population: 1-year progression-free survival rate = 15%.
Assumed risk in the control population: tumour response rate across control arms of included trials.
Assumed risk in the control population: toxicity rate across control arms of included trials.
[a] Not downgraded: high-quality evidence.

Summary of findings 10. Polychemotherapy versus chemotherapy

Polychemotherapy compared with chemotherapy for the treatment of metastatic melanoma

Patient or population: people with cutaneous melanoma

Settings: hospital (metastatic disease)

Intervention: polychemotherapy

Comparison: chemotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Chemotherapy	Polychemotherapy				
Overall survival†	**600 per 1000†**	**596 per 1000†** (541 to 655)	**HR 0.99** (0.85 to 1.16)	N = 594 (n = 6)	⊕⊕⊕⊕ **high**[a]	-
Progression-free survival†	**850 per 1000†**	**869 per 1000†** (822 to 907)	**HR 1.07** (0.91 to 1.25)	N = 398 (n = 5)	⊕⊕⊕⊕ **high**[a]	-
Tumour response	**143 per 1000**	**182 per 1000** (146 to 226)	**RR 1.27** (1.02 to 1.58)	N = 1885 (n = 5)	⊕⊕⊕⊖ **moderate**[b]	-
Toxicity (≥ G3)	**189 per 1000**	**372 per 1000** (272 to 512)	**RR 1.97** (1.44 to 2.71)	N = 390 (n = 3)	⊕⊕⊕⊖ **moderate**[c]	-

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

† Numbers presented refer to event rates (i.e. death rates and progression rates).
CI: confidence interval; **RR:** risk ratio; **HR:** hazard ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Assumed risk in the control population: 1-year overall survival rate = 40%.
Assumed risk in the control population: 1-year progression-free survival rate = 15%.
Assumed risk in the control population: tumour response rate across control arms of included trials.
Assumed risk in the control population: toxicity rate across control arms of included trials.
[a] Not downgraded: high-quality evidence.
[b] Downgraded by one level: imprecision (CI includes both a meaningful benefit (relative risk increase > 25%) and a small/null benefit (relative risk increase < 10%)).

[c] Downgraded by one level: imprecision (sample size lower than optimal information size, calculated to be equal to 400 participants).

BACKGROUND

A glossary of terms used is provided in Table 1.

Description of the condition

Cutaneous melanoma is one of the deadliest forms of skin cancer. According to epidemiological data provided by the International Agency for Research on Cancer (IARC), its worldwide incidence in 2008 was estimated to be 199,627 new cases, with 46,372 deaths (Ferlay 2010). In the USA, cutaneous melanoma ranked fifth in men (44,250 new cases per year, representing 5% of all cancers) and sixth in women (32,000 new cases per year, representing 4% of all cancers) among all tumour histotypes (Siegel 2012). The highest incidence is observed in Australia and New Zealand where melanoma is the fourth most commonly diagnosed cancer (Australian and New Zealand 2008).

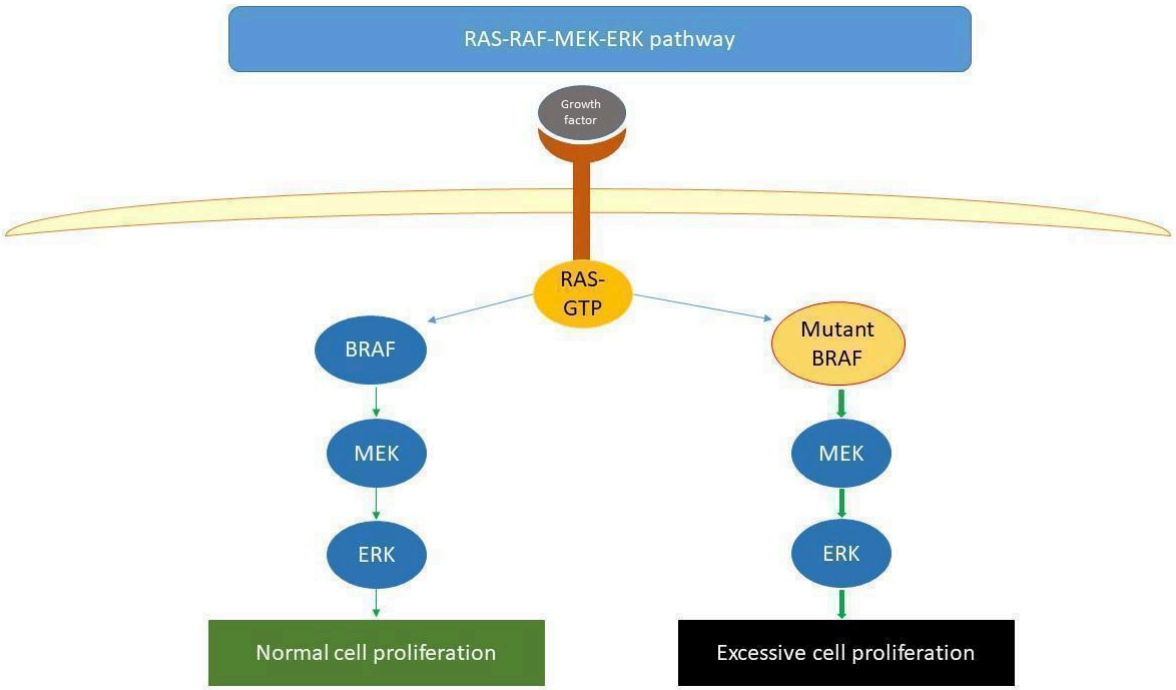
Melanoma incidence differs widely across Europe, ranging from 19.2/100,000 persons per year in Switzerland to 2.2/100,000 persons per year in Greece (Forsea 2012). As well as geographical differences, melanoma incidence has been increasing worldwide over the past 30 years at a greater pace than any other malignancy (Little 2012; Siegel 2012), which makes its management a key issue for national healthcare systems. Melanoma is potentially curable in the early stages with the surgical removal of the primary tumour (McKinnon 2005; Mocellin 2011; Pasquali 2013; Sladden 2009).

Once melanoma metastasises (i.e. spreads to lymph nodes, distant organs or both) due to its intrinsic biological aggressiveness and its typical resistance to medical therapy (both chemotherapy and radiotherapy) (Serrone 1999), survival is poor or very poor, with a median overall survival of 24 months for those with American Joint Committee on Cancer (AJCC) TNM stage IIIC disease (unresectable lymph node metastasis), and nine months for people with AJCC TNM stage IV disease (distant metastasis) (Balch 2001; Balch 2009). Overall, fewer than 35% (AJCC TNM stage IIIC) and 12% (AJCC TNM stage IV) of these people are still alive five years after their diagnosis (Balch 2001; Balch 2009).

Metastatic cutaneous melanoma (unresectable AJCC TNM stage IIIC and stage IV) is usually treated with systemic medical therapy (Garbe 2011), and is characterised by a dismal prognosis (median overall survival usually ranges between 10 and 16 months, Balch 2009). Surgery is feasible only in very few select cases showing a very limited tumour burden (Gyorki 2013; Wevers 2013), and radiotherapy is considered only for symptom palliation (Stevens 2006; Testori 2009).

New insights into the prognosis of people with metastatic melanoma come from molecular profiling of primary tumour and distant metastases. Recently, molecular studies have identified aberrant activation of the mitogen-activated protein kinase (MAPK) pathway and mutations in proteins along the RAS-RAF-MEK-ERK pathway (Figure 1) in cutaneous (50% BRAF-mutated, 15% NRAS-mutated, and up to 17% c-Kit-mutated in chronically sun damaged people) and mucosal melanoma (11% BRAF-mutated, 5% NRAS-mutated, 21% c-Kit-mutated) (Scolyer 2011). Determination of the mutational status of a melanoma enables identification of those who may be suitable for new treatments, such as BRAF and c-Kit inhibitors.

Figure 1. RAS-RAF-MEK-ERK pathway. Copyright © 2018 Claire Gorry: reproduced with permission.



Description of the intervention

Until 2011, conventional treatment for those who have metastatic melanoma included the chemotherapeutic alkylating agent dacarbazine (and its orally available derivative, temozolomide) and the immunostimulatory cytokine, interleukin-2 (approved for metastatic melanoma treatment only in the USA). However, neither drug has been shown to provide any significant survival benefit in a randomised controlled trial (RCT) (Garbe 2011). When dacarbazine was associated with other chemotherapeutic agents (polychemotherapy) or immunostimulatory cytokines such as interferon-alpha or interleukin-2 (biochemotherapy), only some improvement in tumour response without any survival advantage was reported (Ives 2007).

Different immunotherapy regimens (including biotherapy and vaccination regimens) can lead to tumour shrinkage and confer a durable and complete response in some people who have this condition. This prompted investigators to test newer immunomodulating agents including the immune checkpoint inhibitor ipilimumab, a monoclonal antibody blocking the T-cell lymphocyte-associated antigen-4 (i.e. CTLA4, a co-inhibitory molecule involved in the control of immune responses mediated by T-lymphocytes) (Kirkwood 2008; Kirkwood 2012; Mocellin 2013b). In 2010, the anti-CTLA4 strategy was the first treatment demonstrated to be associated with a survival advantage for people with metastatic melanoma (Hodi 2010).

The breakthrough results obtained with anti-CTLA4 monoclonal antibodies have changed the perspective of melanoma therapy along with another pivotal discovery, which is the impressive tumour response rates (up to 90%) observed with vemurafenib (a small-molecule inhibitor of mutated BRAF, an oncogene involved in cell survival or proliferation) (Arkenau 2011) in participants with metastatic melanoma harbouring BRAF activating mutations (Flaherty 2012; Long 2012; Sosman 2012).

Agents that have been tested in RCTs for the systemic treatment of metastatic melanoma can be categorised into five main groups based on their predominant mechanism of action (Garbe 2011; Ives 2007; Kirkwood 2012; Arkenau 2011):

1. conventional chemotherapy (which act mainly through DNA damage);
2. biochemotherapy (combination of chemotherapy plus immunostimulating cytokines);
3. immune checkpoint inhibitors (which override the signalling/activation of immune checkpoints, which have been hijacked by cancer cells to evade T-cell-mediated death, thus stimulating the immune system against malignant cells);
4. small-molecule targeted drugs (which inhibit the protein products of oncogenes specifically activated in malignant cells); and
5. a miscellany of other treatments (such as anti-angiogenic drugs, which inhibit cancer vascularisation).

Conventional chemotherapy

Dacarbazine has been the mainstay of metastatic melanoma therapy (and thus the reference drug for this disease) for over three decades. Dacarbazine was approved for the treatment of metastatic melanoma by the USA Food and Drug Administration (FDA) in 1975, although its efficacy in terms of survival has never been proven in a RCT (Crosby 2000; Huncharek 2001). Dacarbazine is an alkylating agent that produces DNA damage by adding a methyl group to the guanine base in the O6 position. Ultimately, the DNA damage caused by dacarbazine is believed to prompt programmed cell death (apoptosis) (National Toxicology Program 2011). Several trials have tested the hypothesis that dacarbazine-based polychemotherapy regimens might be more effective than dacarbazine alone; however, these trials showed only some improvement in tumour response rates without showing any convincing survival benefit (Bajetta 2006; Ridolfi 2002). These disappointing results led people to consider cutaneous melanoma as one of the most chemoresistant tumours in humans (La Porta 2007; La Porta 2009).

Biochemotherapy

In the oncology field, the term 'biotherapy' generally refers to the use of cytokines to treat cancer. We focused on two cytokines that have been extensively tested for the treatment of people with melanoma: interferon-alpha and interleukin-2.

Interferon-alpha was the first cytokine that demonstrated activity in metastatic melanoma, with 10% to 20% tumour response being observed (Belardelli 2002; Schadendorf 2009). The main mechanism of action of interferon-alpha is immunostimulation, although other mechanisms have been hypothesised (antiproliferative, differentiation-inducing, pro-apoptotic, and anti-angiogenic) (Pasquali 2010). Interferon-alpha is the only drug currently approved for the adjuvant (i.e. postoperative) treatment of melanoma after radical removal of regional lymph-node metastasis by surgery (AJCC TNM stage III) (Eggermont 2009; Garbe 2011; Mocellin 2010; Mocellin 2013).

Interleukin-2 is an immunostimulant cytokine mainly involved in T-cell proliferation (Kirkwood 2012). When tested in people with metastatic melanoma, interleukin-2 showed a 15% to 20% response rate (4% of long-term responses) (Schwartzentruber 2011; Tarhini 2005). Interleukin-2 treatment is burdened by a remarkable (although reversible) toxicity usually requiring hospitalisation (and sometimes admission to an intensive care unit) for management.

Biotherapy agents have been coupled with chemotherapy agents (a combination called biochemotherapy) and compared to chemotherapy alone (Ives 2007). Generally, biochemotherapy has shown higher tumour response rates compared to chemotherapy, but significant improvement in survival of people with metastatic melanoma does not appear to be achievable with this approach (Hamm 2008; Keilholz 2002).

Immune checkpoint inhibitors

Melanoma is considered to be a form of immunogenic tumour (able to produce an immune response) on the basis of some spontaneously occurring melanoma regressions and some durable tumour responses observed after treatment with a variety of immunostimulating agents (Kirkwood 2008; Kirkwood 2012). The higher mutation rate observed in primary and metastatic melanoma compared with other tumour types has been suggested as the mechanism behind melanoma immunogenicity (Mocellin 2003). In particular, mutated proteins might represent tumour-specific antigens (a substance that invokes the body's immune response) that can be selectively recognised by the immune system on melanoma cells. Moreover, melanoma cells often

express epitopes derived from proteins involved in melanin synthesis, which makes them suitable for tumour-selective immune treatment (Mocellin 2009).

Several attempts have been made to activate the immune system against cancer cells. However, it appears evident that tumours can easily elude both naturally occurring and vaccine-elicited immune surveillance (Mocellin 2008) and metastasise to distant sites. Therefore, investigators have turned their attention to these mechanisms of tumour-immune escape. It has been found that malignant cells can evade the body's natural immune response through immunosuppressive circuits whose activity is mediated by specific molecules (such as CTLA4 and PD1) collectively named immune checkpoints (Hamid 2013; Mocellin 2013a; Ribas 2013).

Therefore, a new paradigm in cancer treatment emerged when investigators found that anti-CTLA4 monoclonal antibodies (e.g. ipilimumab) can improve the survival of people with metastatic melanoma by inhibiting the CTLA4 checkpoint and ultimately unleashing the immune response against malignant cells (Hodi 2010). Since then, several RCTs have been conducted or are under way out to test the efficacy of this new strategy in melanoma (Robert 2011) as well as in non-melanoma cancers (Kirkwood 2012).

Small-molecule targeted drugs

Although the expression 'targeted therapy' usually refers to a variety of therapeutic strategies selectively targeting cancer-specific molecular derangements, for the sake of clarity regarding treatment classification, we exclusively referred to the use of small-molecule inhibitors of oncogenes specifically activated in malignant melanoma cells (Mocellin 2010a; Thompson 2009).

Molecular biological studies have demonstrated that melanoma cells harbour a range of gene or protein alterations that can be targeted to develop tumour-specific therapies (Thompson 2009). For instance, about 65% of melanomas harbour mutations affecting the RAS-RAF-MEK-ERK pathway (Davies 2002; Long 2011). The drugs (small-molecule inhibitors) targeting this pathway, such as sorafenib (a RAF inhibitor) and selumetinib (a MEK inhibitor), showed limited antitumour activity in participants with metastatic melanoma (Flaherty 2013; Hauschild 2009; Kirkwood 2012a). In contrast, high tumour response rates (up to 90%) were observed when BRAF inhibitors (with or without MEK inhibitors) were tested in people with metastatic melanoma harbouring activating mutations of the BRAF gene (the most common is known as V600E because the amino acid valine (V) is substituted by glutamic acid (E) at position 600 of the protein BRAF) (Hauschild 2012; McArthur 2014). These mutations constitutionally activate the BRAF kinase, which ultimately stimulates cell proliferation and opposes apoptosis (therefore, mutated BRAF acts as an oncogene). Although complete responses are uncommon (< 5%), these drugs prolong the survival of those who have BRAF-mutated metastatic melanoma (compared to traditional dacarbazine treatment) (Sosman 2012). After this breakthrough discovery, several RCTs have been completed and others are under way to test the efficacy of this new strategy in melanoma as well as in non-melanoma cancers harbouring the mutated version of BRAF as well as other molecular derangements (Klein 2013; Menzies 2013). Similarly, c-Kit inhibitors have been tested in people with metastatic melanoma harbouring activating mutations of the c-Kit protein kinase (Guo 2011; Scolyer 2011).

Other treatments (including anti-angiogenic drugs)

Other strategies have been investigated to treat metastatic melanoma, which cannot be classified to the nominated five drug classes. For instance, as in the field of infectious diseases, vaccines (such as those targeting gp100, a melanoma associated antigen) can be used to manipulate the host immune system to elicit a tumour-specific immune response against malignant tumours (Mocellin 2005). This strategy, known as active-specific immunotherapy because it chiefly involves the adaptive immune response, has long been tested in oncology, mainly in people with cutaneous melanoma (Mocellin 2004). Despite the promising preclinical evidence and the variety of vaccination regimens tested so far, no vaccine formulation has been proven to significantly change the natural history of metastatic melanoma (Chi 2011). However, in 2011, a RCT showed that the combination of a gp100-based vaccine with interleukin-2 provided a survival advantage for people who have metastatic melanoma (Schwartzentruber 2011). Other immunostimulating agents, such as naturally occurring growth factors (e.g. granulocyte and macrophage colony stimulating factor (GM-CSF)) and bioproducts from bacteria (e.g. Bacillus Calmette-Guérin (BCG) and *Corynebacterium parvum*), have been tested in clinical trials, usually in combination with other agents, but results have generally been unsatisfactory (Mocellin 2008).

Promising results have been recently reported with anti-angiogenic agents, a class of drugs aimed to reduce blood supply to malignant cells (Ashour 2017). This approach has been proven to be effective against a variety of tumour types, such as colorectal cancer (Jayson 2016), but investigation in those with melanoma is still in its infancy (Cui 2013; Kim 2012).

A miscellany of anticancer agents have also been tested in association with chemotherapy to increase the efficacy of conventional cytotoxic drugs. Among these agents there are anti-oestrogenic drugs (e.g. tamoxifen, a medication widely used against breast cancer) (Jager 2015), multi-kinase inhibitors (e.g. sorafenib, a small-molecule inhibitor approved for the treatment of different solid tumours such as kidney carcinoma) (Gentile 2017), and drugs with pro-apoptotic properties (e.g. elesclomol, a compound supposed to increase the activity of chemotherapy by generating reactive oxygen species) (Caino 2016).

Why it is important to do this review

Many systemic treatments have been and continue to be tested for the management of metastatic cutaneous melanoma, although only recent results appear to provide affected people with new hope to improve life expectancy. No systematic reviews or meta-analyses have been performed on all systemic therapies tested so far for the treatment of metastatic skin melanoma. Two previous Cochrane Reviews (Crosby 2000; Sasse 2007) partially covered the chemotherapy (chemotherapy versus best supportive care) and the biochemotherapy (biochemotherapy versus chemotherapy) fields, respectively. This review updates both previous Cochrane Reviews and broadened the scope. Since the reviews were published, many trials have been conducted to test new chemotherapeutic regimens based on conventional cytotoxic chemotherapeutics; traditional immunotherapy (e.g. interleukin-2, interferon-alpha); and most of all, new agents, including co-inhibitory molecular inhibitors (such as the anti-CTLA4 or anti-PD1 monoclonal antibodies) and small molecular inhibitors (such as BRAF and MEK inhibitors).

Therefore, it is of utmost importance to provide physicians (especially oncologists and dermatologists) and investigators involved in melanoma treatment and research with a systematic assessment, and where feasible, meta-analysis of the available evidence regarding the therapeutic regimens tested in RCTs to date. We planned to descriptively and quantitatively summarise the evidence in this field and provide readers with coverage of the therapeutic efficacy as well as toxicity, quality of life, and economic burden issues.

A protocol for this review has been published (Pasquali 2014). Gorry 2018 (currently at protocol stage) will assess neoadjuvant treatment for malignant and metastatic cutaneous melanoma.

OBJECTIVES

To assess the beneficial and harmful effects of systemic treatments for metastatic cutaneous melanoma.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) testing systemic therapies for the treatment of metastatic cutaneous melanoma.

Types of participants

People with unresectable lymph node metastasis (AJCC TNM stage IIIC) and distant metastatic (AJCC TNM stage IV) cutaneous melanoma. No restrictions in terms of age, sex, drug dosage, radiologic examination, or treatment duration were applied.

Types of interventions

We considered all comparisons of systemic therapies for the treatment of metastatic cutaneous melanoma, including:

- polychemotherapy (experimental arm) versus single-agent chemotherapy (comparator arm);
- biochemotherapy (experimental arm) versus chemotherapy (comparator arm);
- immune checkpoint inhibitors (experimental arm) versus any other agent (comparator arm);
- small-molecule targeted drugs (experimental arm) versus any other agent (comparator arm);
- chemotherapy plus other agents (e.g. anti-angiogenic drugs) (experimental arm) versus chemotherapy alone (comparator arm); and
- other comparisons (e.g. single agent chemotherapy verus other single agent chemotherapy).

Types of outcome measures

Primary outcomes

1. Overall survival: defined as time from randomisation until death from any cause (effect measure: hazard ratio (HR)).
2. Progression-free survival: defined as time from randomisation until diagnosis of disease recurrence (local or distant/metastatic) (effect measure: HR).
3. Toxicity: defined as the occurrence of grade 3 (G3) or higher adverse events according to the World Health Organization (WHO) scale (Brundage 1993) (effect measure: relative risk (RR)).

Secondary outcomes

1. Tumour response: defined as incidence of complete plus partial tumour response according to WHO or Response Evaluation Criteria In Solid Tumors (RECIST) criteria (Therasse 2002) (effect measure: RR).
2. Quality of life (since there are no standardised disease-specific scales and questionnaires to assess the quality of life of people with cutaneous melanoma, we described findings from studies).
3. Economic evaluation (expressed as cost-utility analysis with the quality-adjusted life years (QALYs)).

Search methods for identification of studies

We aimed to identify all relevant RCTs regardless of language or publication status (published, unpublished, in press, or in progress).

Electronic searches

We searched the following databases up to 4 October 2017:

- the Cochrane Skin Group Specialised Register using the search strategy 'melanoma and (metastatic or metastas* or "stage iv" or "stage 4")';
- the Cochrane Central Register of Controlled Trials (CENTRAL) 2017, Issue 9, in the Cochrane Library using the strategy in Appendix 1;
- MEDLINE via Ovid (from 1946) using the strategy in Appendix 2;
- Embase via Ovid (from 1974) using the strategy in Appendix 3; and
- LILACS (Latin American and Caribbean Health Science Information database, from 1982) using the strategy 'melanoma and metasta$'.

We also searched the American Society of Clinical Oncology (ASCO) database up to February 2017 using the terms "melanoma", "randomised" and "metastatic".

Trials registers

We searched the following trials registers up to February 2017 using the key words "melanoma" and "randomised":

- ISRCTN registry (www.isrctn.com);
- ClinicalTrials.gov (www.clinicaltrials.gov);
- Australian New Zealand Clinical Trials Registry (www.anzctr.org.au);
- World Health Organization International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/); and
- EU Clinical Trials Register (www.clinicaltrialsregister.eu).

Searching other resources

References from included studies

We checked the references of included studies for further references to relevant trials.

Adverse effects

We did not perform a separate search for adverse effects of the target interventions. However, we examined data on adverse effects from the included studies we identified.

Data collection and analysis

Selection of studies

Two review authors (SM and SP) selected trials independently by checking the titles and abstracts identified using the search methods described. The same two review authors retrieved the full text of all possibly relevant studies and assessed the eligibility of each study. We resolved discordant evaluations by discussion to reach consensus. We included trials with mixed disease stages if they reported outcomes separately for metastatic disease.

Data extraction and management

Two review authors (SM and SP) independently compared similarity among studies eligible for inclusion in terms of interventions and outcomes. The same two review authors also extracted relevant data for colation in a database. Review authors extracted the following details were extracted using a data extraction form that had been piloted previously:

1. Trial methods, sequence generation, method of concealment of allocation, masking of participants, trialists, and outcome assessors, exclusion of participants after randomisation, proportion and reasons for losses at follow up.
2. Participants' country of origin and study setting, sample size, tumour stage, inclusion and exclusion criteria.
3. Intervention group, type of treatment, dose and frequency, duration of intervention and follow up.
4. Control group, type of treatment, dose and frequency, duration of intervention and follow up.
5. Outcomes: primary and secondary outcomes as specified in Types of outcome measures.

A third review author (AH) independently verified the extracted data. We resolved discordant evaluations on all data necessary for the final analysis by discussion and final consensus. The review authors were not blinded to the names of trial authors, journals where the trial results were published, or institutions where the trials were conducted. In case of multiple publications reporting on the same RCT, we chose the most recent and complete publication.

Assessment of risk of bias in included studies

Two review authors (SM and SP) independently assessed the included studies in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The review authors compared their evaluations and resolve possible inconsistencies.

We assessed the risk of bias in included trials by considering the following aspects:

1. the method of generation of the randomisation sequence;
2. the method of allocation concealment;
3. the blinding of participants, clinicians, and outcome assessors;
4. the presence of incomplete outcome data; and
5. selective outcome reporting.

This information is recorded in a 'Risk of bias' table, which is part of the Characteristics of included studies table for each study.

We reported the risk of bias for each study in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions*:

- low risk of bias (plausible bias unlikely to seriously alter the results) if all criteria were met;
- unclear risk of bias (plausible bias that raises some doubt about the results) if one or more criteria were assessed as unclear; or
- high risk of bias (plausible bias that seriously weakens confidence in the results) if one or more criteria were not met.

Measures of treatment effect

Overall survival and progression-free survival

We measured the treatment effect on participant survival as hazard ratios (HR), which is defined as the ratio between the risk of event in the experimental arm and the same risk in the comparator arm participants. We reported each HR along with its 95% confidence interval (CI). HR values lower or greater than one indicate a favourable or unfavourable effect of the experimental versus the comparator treatment, respectively.

We extracted all available summary statistics from all reports of the included trials for the outcome measures considered. We extracted HRs directly from original studies when reported; if unreported, we calculated HRs from Kaplan-Meier survival curves using dedicated methods (Parmar 1998; Tierney 2007). Whenever feasible, unadjusted HRs were used.

As well as HRs (which is a relative measure of treatment effect), we also provided readers with an absolute measure of treatment effect. To achieve this aim, we used the calculated summary HRs (obtained from meta-analysis of eligible trials) and the one-year overall (or progression-free) survival rate in the control population of participants with metastatic cutaneous melanoma; we then calculated the mortality (or progression) rates in the experimental and control groups (reported in 'Summary of findings' tables) using methods described by Altman (Altman 1999; Altman 2002). Briefly, if at some specified time (t) the survival probability in the control group is $S_c(t)$, then the survival probability in the active group is $[S_c(t)]^h$, where h is the meta-analysis HR comparing the treatment groups: mortality rates are then simply calculated as 1-S. These absolute risks (events rates) can be used to simply calculate the absolute risk reduction (ARR = event rate for experimental treatment minus event rate for comparison treatment), which can be in turn used to calculate the number needed to treat for an additional beneficial outcome (NNTB = 1/ARR) (Higgins 2011).

In the event that some studies presented their findings as odds ratios (OR) for death at different time points (rather than reporting the preferred measure HR) (Case 2002), we considered the reported OR as surrogate measure of treatment effect on the survival outcome of interest; we then used sensitivity analysis to investigate the potential influence of this suboptimal measure of treatment effect on the results of meta-analysis of time-to-event (survival) data.

Tumour response

We measured the treatment effect on tumour response as risk ratio (RR), that is, the ratio between the overall response rate in

the experimental arm and that in the comparator arm. According to this definition, the RR corresponds to the rate of complete or partial responses in the experimental treatment compared to the comparator. We reported each RR along with its 95% CI. RR values higher or lower than one indicate a favourable or unfavourable effect of the experimental versus the comparator treatment, respectively.

Toxicity

We measured the treatment effect on treatment-related side-effects (toxicity) as RR, that is, the ratio between the toxicity rate in the experimental arm and that in the comparator arm. We reported each RR along with its 95% CI. RR values lower or higher than one indicate a favourable or unfavourable effect of the experimental versus the comparator treatment, respectively.

Quality of life and economic analysis

We expected that no homogeneous data would be available from the literature for quality of life because of the lack of a melanoma-specific questionnaire. Lack of homogeneity may prevent pooling of data; in this case, we descriptively reported data.

When dealing with economic analysis, we considered cost-utility analysis with quality-adjusted life years.

Unit of analysis issues

Cross-over and cluster-design trials

Because cross-over trials (where each participant is allocated not to a single intervention - as happens in parallel group trials - but to a sequence of treatments) are typically used to assess treatments with a temporary effect in the management of stable (i.e. chronic) disease, we did not expect to find cross-over trials dedicated to the treatment of metastatic melanoma, usually (and unfortunately) a rapidly evolving condition. However, we did not want to exclude these types of studies a priori, should any have been found. Such trials would require special methods to be included in a meta-analysis (e.g. considering the findings specific for the first treatment, if available) to avoid the 'carry over' effect (i.e. the impact of the second treatment may be affected by a the effect of the first treatment), as recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Moreover, sensitivity analysis to asses the impact of such design trials on summary effects would be performed.

Similarly, although we were unaware of cluster design trials, we did not want to exclude these types of studies a priori, should any have been found. In this case, sensitivity analysis to asses the impact of such design trials on summary effects would have been performed.

Studies with multiple treatment groups

For multiple-arm trials that compared two (or more) experimental arms with the same control arm, we took within-study correlation into consideration as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We computed a composite effect size for the comparison of each experimental arm versus the control arm; we then calculated the correlation factor (r) based on the number of cases in each arm, which enabled us to compute the variance (V) of the composite effect size, as suggested by Borenstein and Higgins (Borenstein 2009). Using this variance, we computed the standard error and then the 95% CI of the composite effect.

Network meta-analysis

Given that direct comparisons between key therapies had not been published (e.g. immune checkpoint inhibitors versus small-molecule targeted drugs), we used the network meta-analysis methodology to compute estimates of indirect comparisons and generate treatment ranking (Cipriani 2013; Mills 2013). To perform this network meta-analysis, studies need to satisfy the principle of transitivity. For instance, indirect comparisons can be performed when different trials share the same participant population in terms of first- or second-line treatment and presence or absence of severe clinical conditions, such as brain metastasis. We then evaluated consistency (i.e. heterogeneity) within loops (e.g. for a comparison between therapies A and B, the included study must have directly compared A and B and both treatments with a third common comparator, C) using the methods for assessing heterogeneity as described. We used a random-effects model to estimate HR (progression-free survival and overall survival) and RR (tumour response and toxicity). We also used multivariate random-effects meta-regression to estimate consistency and inconsistency. We performed analyses using the 'mvmeta' package (Chaimani 2013; White 2011) for Stata (Stata 2017).

Dealing with missing data

We contacted trial authors for clarification where data were missing or unclear.

We extracted results for intention-to-treat analysis whenever provided. In studies reporting per-protocol analysis results only, we performed an available-case analysis.

Assessment of heterogeneity

We assessed the consistency of results (effect sizes) among studies using the two standard heterogeneity tests: the Chi^2 based Cochran Q-test and the I^2 statistic (Higgins 2011). To be more conservative, we considered that heterogeneity was statistically substantial when the Cochran Q-test P value was less than 0.1 (i.e. the alpha level of significance for this test was set at 10%). In addition, we considered inconsistency across studies as low, moderate, and high for I^2 statistic values lower than 25%, between 25% and 50%, and greater than 50%, respectively. We considered heterogeneity as significant when the I^2 statistic was greater than 50%, the Q-test P value was less than 0.1, or both. We applied the random-effects model to calculate the overall effect (which assumes that studies do not share the same common effect and assigns a weight to each study taking into account both within-study and between-study variance), using the inverse-variance method.

Assessment of reporting biases

We planned to construct funnel plots to detect publication and small study effect biases if we included at least 10 studies in meta-analysis (Borenstein 2009; Higgins 2011). We planned to investigate funnel plot asymmetry with the Egger linear regression approach and the Begg rank correlation test (these tests will be considered statistically significant for P values less than 0.1). To avoid duplicate study bias, we only considered the study with the longest follow-up length when multiple reports for the same trial were available.

Data synthesis

Two review authors (SM and SP) performed all meta-analyses according to the guidelines reported in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

For time-to-event (i.e. survival) outcomes, we used RevMan 5.3 (RevMan 2014) to estimate pooled HRs and 95% CIs using the random effects model (Borenstein 2009; Higgins 2011).

For binary outcomes, we used RevMan 5.3 to estimate pooled RRs and 95% CIs using the random effects model.

For the network meta-analysis we used the 'mvmeta' package (Chaimani 2013; White 2011) for Stata (Stata 2017).

We planned to include at least one 'Summary of findings' table for the primary outcomes for the most important comparison. We also planned inclusion of further 'Summary of findings' tables where there were several major comparisons or need to summarise findings for different populations. We used the GRADE approach to assess the quality of evidence for all primary and key secondary outcomes for all main comparisons. We considered downgrading evidence based on five domains: risk of bias, inconsistency, imprecision, indirectness; and publication bias. Overall quality of evidence could be assessed as high, moderate, low or very low (Guyatt 2008; Higgins 2011).

Subgroup analysis and investigation of heterogeneity

We performed subgroup analysis and meta-regression to investigate potential sources of between-study heterogeneity. Planned subgroups or covariates included: year of publication, untreated or previously treated distant metastasis, inclusion or exclusion of brain metastasis, and duration of follow-up. Further details of investigation of heterogeneity are presented in Assessment of heterogeneity.

Sensitivity analysis

We investigated potential sources of between-study heterogeneity by excluding trials at high risk of bias and each single trial to ascertain their role in affecting summary statistics.

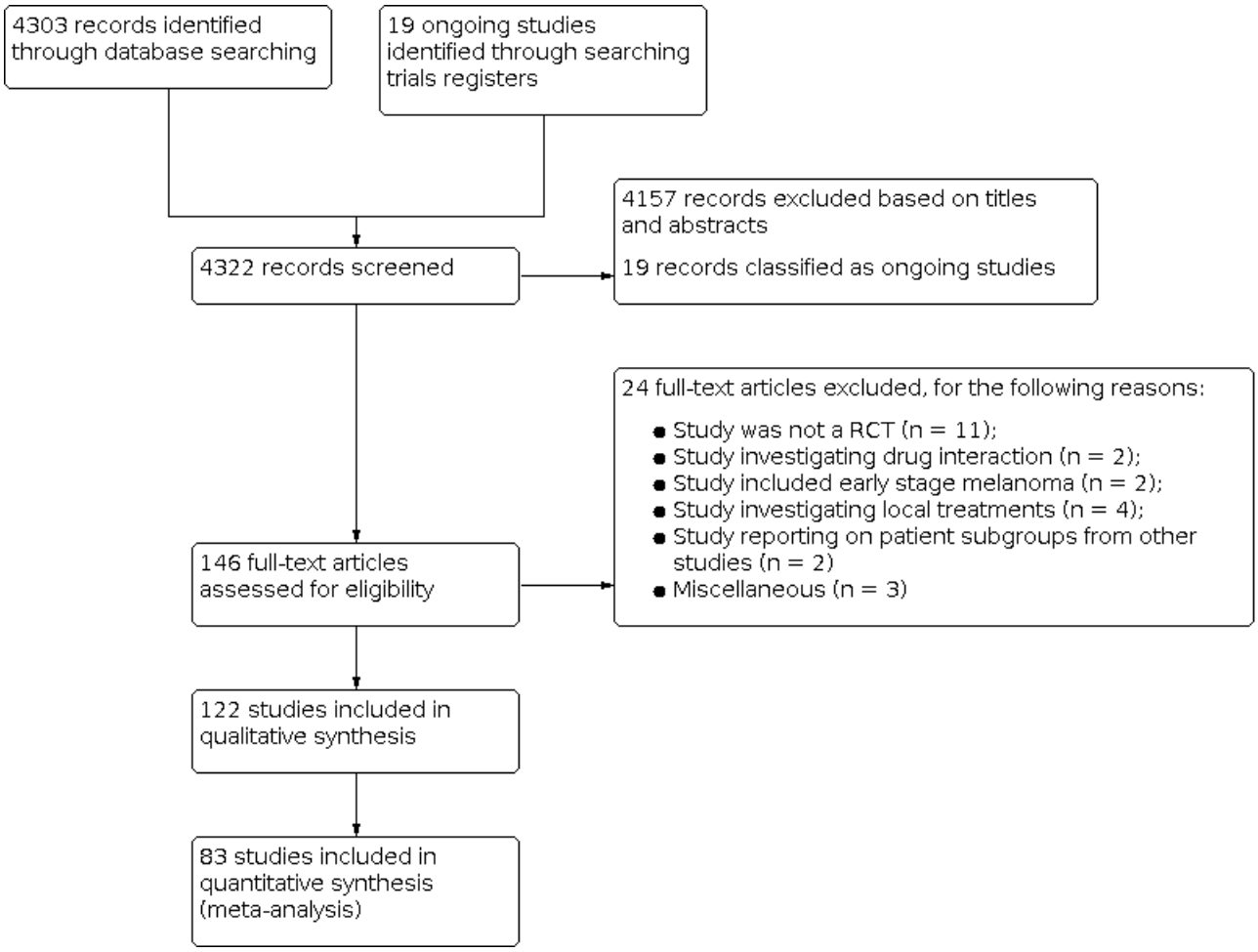
RESULTS

Description of studies

Results of the search

The database searches (see Electronic searches) retrieved 4303 records. We also identified 19 ongoing studies (see Characteristics of ongoing studies). We excluded 4157 references based on titles and abstracts. We obtained the full text of the remaining 146 studies. We excluded 24 studies (see Characteristics of excluded studies), and included 122 studies (Characteristics of included studies). See the study flow diagram for a full description of our screening process (Figure 2).

Figure 2. Study flow diagram.



Included studies

Review findings were based on data reported in the full-text reports of the 122 included randomised controlled trials (RCTs). Descriptions of studies are presented in Characteristics of included studies.

Design

Most included studies were phase III RCTs (n = 76, 62%) or phase II RCTs (n = 41, 34%). We also included one phase I RCT and RCTs with mixed designs (n = 4, 3%). All trials were designed as parallel-group studies (neither cross-over trials nor cluster design trials were found for inclusion).

Double-blinding design was employed in 23 trials (19%) (Cui 2013; Eisen 2010; Flaherty 2013a; Glaspy 2009; Gupta 2014; Hauschild 2009a; Hodi 2010a; Kefford 2010; Kim 2012; Larkin 2015; Lawson 2015; Long 2015; McDermott 2008; Middleton 2015; O'Day 2009; O'Day 2011; O'Day 2013; Postow 2015; Robert 2011; Robert 2013; Robert 2015a; Rusthoven 1996; Wolchok 2010). The remaining 99 studies (81%) were open label design.

In many cases, trials were sponsored by pharmaceutical companies producing the tested drug: this was especially true for new classes of drugs, such as immune checkpoint inhibitors and small-molecule targeted drugs.

Sample sizes

There was significant variation in sample size among the included RCTs, ranging from 30 (Gorbonova 2000) to 945 (Larkin 2015) participants.

Participants

Overall, the 122 RCTs randomised 28,561 participants. Eighty-nine trials (73%) were conducted in untreated participants (N = 20,737). Previously treated participants (N = 3450) were enrolled in 30 trials (25%): in 20 of these RCTs both untreated and previously treated participants were enrolled. In three trials systemic treatments were administered after surgery for distant metastasis (2%). Included studies were conducted in adults with no restriction for enrolling both men and women (mean men:women ratio = 1.38). Mean age was 57.5 years (range: 18 to 87 years). Participants with brain metastasis (N = 741) were included in 29 studies (24%), although definitions for allowing inclusion of this condition differed across trials (Characteristics of included studies). All trials enrolled participants from a hospital, with unresectable locoregional disease (AJCC TNM stage IIIC) or metastatic cutaneous melanoma (AJCC TNM stage IV). Many reports stated “metastatic or locoregionally advanced disease”, but then did not report data separately.

Interventions

All studies investigated systemic treatments as per eligibility criteria. Several drugs and schedules were tested. Description of drugs and scheduled for each study are reported in Characteristics of included studies tables. Overall, dacarbazine was the most used drug across the trials (n = 50, 46%). The following treatment comparisons were investigated:

- polychemotherapy (experimental arm) versus single-agent chemotherapy (comparator arm): 21 RCTs;
- biochemotherapy (experimental arm) versus chemotherapy (comparator arm): 34 RCTs;
- immune checkpoint inhibitors (experimental arm) versus any other agent (comparator arm): 11 RCTs;
- small-molecule targeted drugs (experimental arm) versus any other agent (comparator arm): 9 RCTs;
- chemotherapy plus other agents (e.g. anti-angiogenic drugs, tamoxifen, elesclomol) (experimental arm) versus chemotherapy alone (comparator arm): 34 RCTs; and
- other comparisons (e.g. single agent chemotherapy versus other single agent chemotherapy): 13 RCTs.

Outcomes

We evaluated the following outcomes for each study:

- progression-free survival: 89 RCTs (73%);
- overall survival: 105 RCTs (94%);
- tumour response: 117 RCTs (96%);
- toxicity: 118 RCTs (97%);
- participants' quality of life: 12 RCTs (11%); and
- cost analysis: 1 RCT (< 1%).

Excluded studies

We reported the reasons for exclusion of 24 studies in the Characteristics of excluded studies. The reasons for exclusion were that the study: was not a randomised trial (n = 11); investigated mechanisms of action of a drug (or drug interaction with other drugs) (n = 2); investigated early stage melanoma (not advanced/metastatic melanoma) (n = 2); investigated either local or loco-regional therapies (n = 4); investigated subgroups of participants of particular interest from RCTs already included in this review (n = 2); investigated both melanoma and other tumour types, but melanoma-specific data could not be extracted (n = 1); gathered data from three RCTs already included in this review (n = 1); and reported the preliminary results of a RCT already included in this review (n = 1).

Ongoing studies

We searched for phase III RCTs, either open to recruitment or following up participants, investigating participants with metastatic melanoma. We identified open studies in 'recruiting and 'not yet recruiting' phases and active studies not yet recruiting.

We identified 19 phase III RCTs (see Characteristics of ongoing studies). These studies will investigate two new classes of anticancer drugs for melanoma (i.e. immune checkpoint inhibitors ipilimumab, nivolumab, and pembrolizumab; and the targeted drugs dabrafenib, vemurafenib, and trametinib) in tumours harbouring mutations in proteins other than BRAF, such as NRAS, which is also believed to play a role in melanoma progression. Studies also investigate combinations of these drugs and in association with other agents, such as interferon-alpha and interleukin-2.

Studies awaiting classification

There are no studies awaiting classification.

Risk of bias in included studies

Figure 3 and Figure 4 summarise the risk of bias for included studies.

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

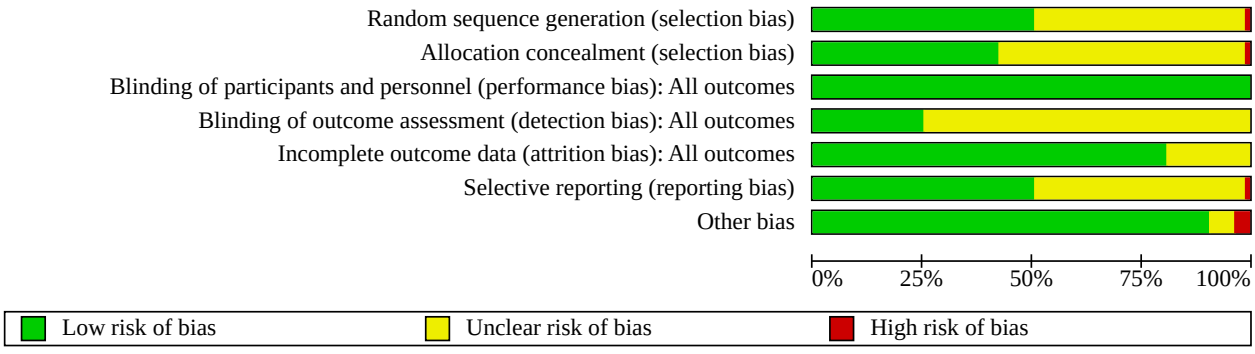


Figure 4. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

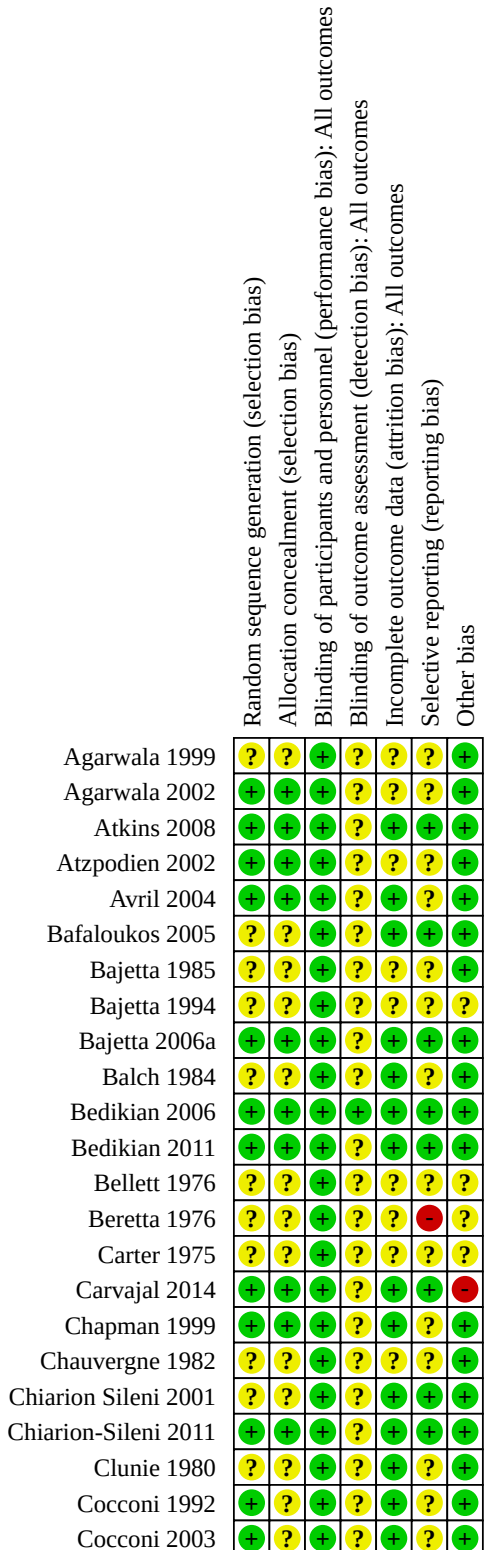
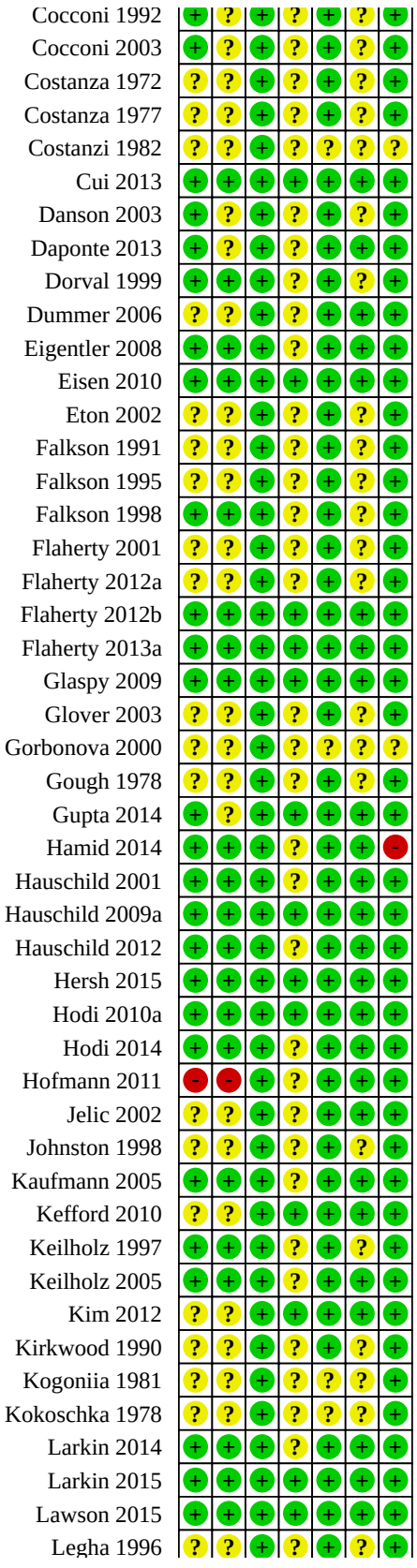


Figure 4. (Continued)



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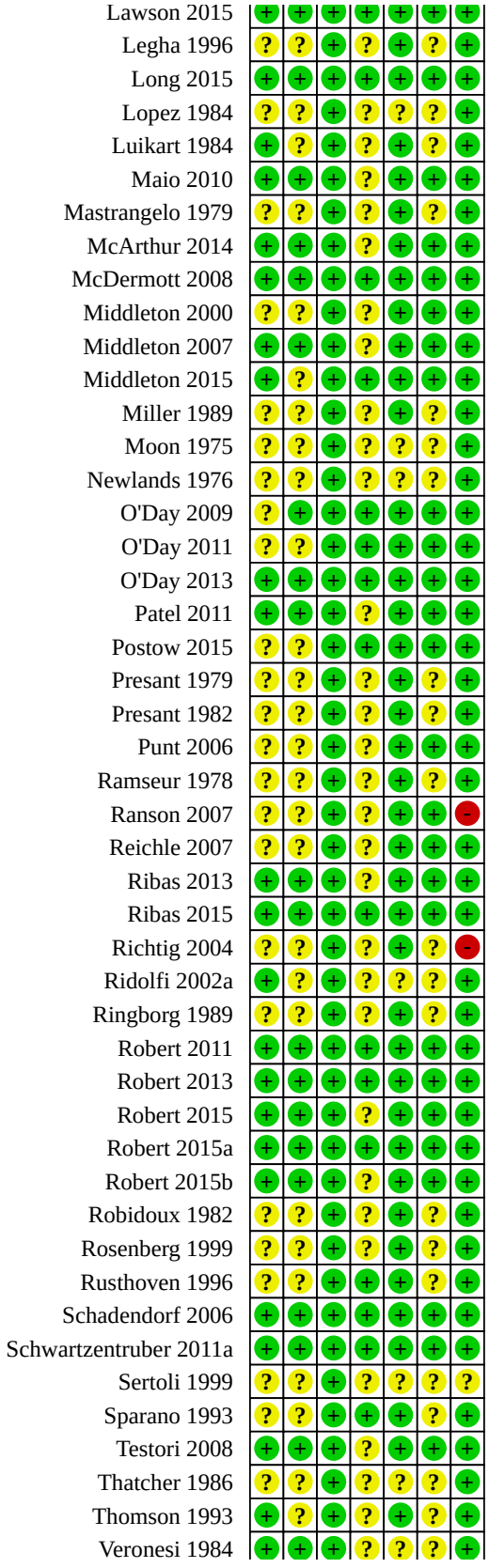
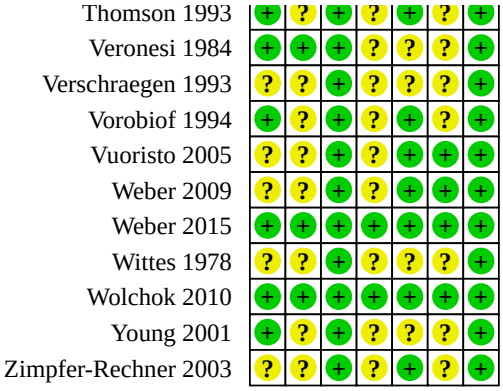


Figure 4. (Continued)



Overall, the risk of bias of included studies can be considered as limited. Considering the 122 included studies and the seven bias domains assessed, we performed 854 evaluations (Figure 4): only seven evaluations (< 1%) assigned high risk of bias for six trials (Beretta 1976; Carvajal 2014; Hamid 2014; Hofmann 2011; Ranson 2007; Richtig 2004). We assessed that only 21 studies (17%) were at low risk of bias for all domains (Bedikian 2006; Cui 2013; Eisen 2010; Flaherty 2012b; Flaherty 2013a; Glaspy 2009; Hauschild 2009a; Hersh 2015; Hodi 2010a; Larkin 2015; Lawson 2015; Long 2015; McDermott 2008; O'Day 2013; Ribas 2015; Robert 2013; Robert 2015a; Schadendorf 2006; Schwartzentruber 2011a; Weber 2015; Wolchok 2010). We assessed a further 22 trials (18%) at low risk of bias for four domains and one domain at unclear risk of bias (Atkins 2008; Bajetta 2006a; Bedikian 2011; Chiarion-Sileni 2011; Eigentler 2008; Gupta 2014; Hauschild 2001; Hauschild 2012; Hodi 2014; Kaufmann 2005; Keilholz 2005; Larkin 2014; Maio 2010; McArthur 2014; Middleton 2007; Middleton 2015; O'Day 2009; Patel 2011; Ribas 2013; Robert 2015; Robert 2015b; Testori 2008). Most included studies (n = 73, 60%) were assessed at unclear risk of bias for two or more domains.

Allocation

Random sequence generation

In most included RCTs (n = 62, 51%), the risk of selection bias due to issues linked to random sequence generation was judged to be low. Information regarding random sequence generation was lacking so the risk was assessed as unclear in 59 studies (48%). One study (Hofmann 2011) that compared dacarbazine to best supportive care in pre-treated participants with metastatic melanoma was assessed at high risk of bias: initially enrolled participants were randomly assigned to either chemotherapy or best supportive care, but enrolment was slow and allocation appeared to be based on physician's choice.

Allocation concealment

In most included RCTs (n = 69, 56%) the risk of selection bias due to issues linked to allocation concealment was judged to be unclear, which was mainly due to the lack of information reported in published study reports. In 52 studies (43%), we judged this domain at low risk of bias. One study (Hofmann 2011) was assessed at high risk of selection bias due to lack of allocation concealment (see 'Random sequence generation' risk of bias assessment).

Blinding

Performance bias

All included RCTs were deemed at low risk of performance bias. In particular, 23 studies (19%) (Cui 2013; Eisen 2010; Flaherty 2013a; Glaspy 2009; Gupta 2014; Hauschild 2009a; Hodi 2010a; Kefford 2010; Kim 2012; Larkin 2015; Lawson 2015; Long 2015; McDermott 2008; Middleton 2015; O'Day 2009; O'Day 2011; O'Day 2013; Postow 2015; Robert 2011; Robert 2013; Robert 2015a; Rusthoven 1996; Wolchok 2010) were designed as double-blinded trials, and were assessed at low risk of bias for this domain. The remaining 99 trials (81%) were designed as open label studies, with no blinding of participants or personnel. However, we judged that in this setting (metastatic melanoma), with the treatments tested and the outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judge the risk of performance bias as low for these RCTs.

No studies were assessed at high risk of performance bias.

Detection bias

The risk of detection bias was found to be low in 31 RCTs (25%). There was insufficient information reported in the remaining 91 studies (75%) to permit judgement and were assessed at unclear risk of bias for this domain.

No studies were assessed at high risk of detection bias.

Incomplete outcome data

Most included RCTs (n = 99, 81%) were judged to be at low risk of attrition bias. There was insufficient information reported in the remaining 23 (19%) studies to permit judgement and were assessed at unclear risk of bias for this domain.

No studies were assessed at high risk of bias of attrition detected.

Selective reporting

Most included RCTs (n = 62, 51%) were found to be at low risk of reporting bias. There was insufficient information reported in 59 studies (48%) to permit judgement and were assessed at unclear risk of selective reporting bias. One study (Beretta 1976) was assessed at high risk of reporting bias because data from one of the four trial arms were not analysed for unclear reasons.

Other potential sources of bias

We did not find any other sources of bias in most included RCTs (n = 111, 91%). There was insufficient available information to permit judgement for seven studies (6%). We detected a high risk of bias in four trials (3%); Carvajal 2014 and Hamid 2014 showed a potential conflict of interest between some authors and the funding body; drug dosage was amended in Ranson 2007; and Richtig 2004 was stopped when approximately 50% of planned participants were enrolled.

Effects of interventions

See: **Summary of findings 1** Anti-PD1 monoclonal antibodies versus chemotherapy; **Summary of findings 2** Anti-PD1 monoclonal antibodies versus anti-CTLA4 monoclonal antibodies; **Summary of findings 3** Anti-CTLA4 monoclonal antibodies plus chemotherapy versus chemotherapy; **Summary of findings 4** Anti-CTLA4 monoclonal antibodies with versus without anti-PD1 monoclonal antibodies; **Summary of findings 5** BRAF inhibitors versus chemotherapy; **Summary of findings 6** MEK inhibitors versus chemotherapy; **Summary of findings 7** BRAF plus MEK inhibitors versus BRAF inhibitors; **Summary of findings 8** Anti-angiogenic drugs plus chemotherapy versus chemotherapy; **Summary of findings 9** Biochemotherapy versus chemotherapy; **Summary of findings 10** Polychemotherapy versus chemotherapy

We analysed outcomes according to descriptions in Types of outcome measures. Each outcome was investigated for the pre-established interventions described in Types of interventions. Findings from included studies were meta-analysed when a drug (or a drug regimen) was tested in at least two studies. Accordingly, 39 studies were not included in the meta-analyses. (Table 2 presents reasons for exclusion from meta-analysis). Quantitative analysis was performed with findings from 83 studies for five different types of interventions: conventional chemotherapy, biochemotherapy, immune checkpoint inhibitors, small-molecule targeted drugs, and other agents (including anti-angiogenic drugs) (Table 3).

We presented 10 comparisons in relation to overall survival, progression-free survival, tumour response, and toxicity (≥ G3) in 'Summary of findings' tables:

1. anti-PD1 monoclonal antibodies compared with chemotherapy (Summary of findings 1);
2. anti-PD1 monoclonal antibodies compared with anti-CTLA4 monoclonal antibodies (Summary of findings 2);
3. anti-CTLA4 monoclonal antibodies plus chemotherapy compared with chemotherapy alone (Summary of findings 3);
4. anti-PD1 plus Anti-CTLA4 monoclonal antibodies compared with anti-CTLA4 monoclonal antibodies (Summary of findings 4);
5. BRAF inhibitors compared with chemotherapy (Summary of findings 5);
6. MEK inhibitors compared with chemotherapy (Summary of findings 6);
7. BRAF plus MEK inhibitors compared with BRAF inhibitors alone (Summary of findings 7);
8. anti-angiogenic drugs plus chemotherapy compared with chemotherapy alone (Summary of findings 8);
9. biochemotherapy compared with chemotherapy alone (Summary of findings 9); and
10. polychemotherapy compared with chemotherapy alone (Summary of findings 10).

Overall survival

Polychemotherapy versus single agent chemotherapy

We included 14 studies that compared cytotoxic polychemotherapy and single agent chemotherapy (Bafaloukos 2005; Bellett 1976; Carter 1975; Chapman 1999; Chauvergne 1982; Chiarion Sileni 2001; Costanza 1972; Costanza 1977; Glover 2003; Kogoniia 1981; Lopez 1984; Luikart 1984; Zimpfer-Rechner 2003). Hazard ratios (HRs) were directly available or could be extrapolated for six studies (Bafaloukos 2005; Chapman 1999; Chauvergne 1982; Chiarion Sileni 2001; Luikart 1984; Zimpfer-Rechner 2003). Polychemotherapy and single agent chemotherapy was administered to 312 and 282 participants, respectively. Meta-analysis suggested a similar risk of death between polychemotherapy and single agent chemotherapy (Analysis 1.1, HR 0.99, 95% CI 0.85 to 1.16; heterogeneity: Tau^2 = 0.00; Chi^2 = 3.86, df = 5, P = 0.57; I^2 = 0%; high-quality evidence).

Biochemotherapy versus chemotherapy

Chemotherapy with interferon-alpha versus without interferon-alpha

This comparison included 15 studies (Bajetta 1994; Bajetta 2006a; Danson 2003; Daponte 2013; Dorval 1999; Falkson 1991; Falkson 1995; Falkson 1998; Gorbonova 2000; Kaufmann 2005; Kirkwood 1990; Maio 2010; Thomson 1993; Vorobiof 1994; Young 2001). Hazard ratios (HRs) were directly available from or could be extrapolated for 11 studies (Bajetta 1994; Bajetta 2006a; Danson 2003; Daponte 2013; Dorval 1999; Falkson 1991; Falkson 1998; Kaufmann 2005; Thomson 1993; Vorobiof 1994; Young 2001). Overall, 942 participants were allocated to chemotherapy with interferon-alpha and 843 to chemotherapy alone. Meta-analysis suggested a lower risk of death for the combination of chemotherapy and interferon-alpha, although this difference was not statistically significant (Analysis 4.1, HR 0.87, 95% CI 0.73 to 1.04) and between-study heterogeneity was remarkable (heterogeneity: Tau^2 = 0.06; Chi^2 = 37.19, df = 10, P < 0.0001; I^2 = 73%; low-quality evidence). We did not identify any particular study driving heterogeneity results in a sensitivity analysis. All participants were previously untreated and without brain metastases. Heterogeneity dropped remarkably (I^2 = 9%) when only studies published after 2000 were considered (HR 0.95, 95% CI 0.84 to 1.08), but increased (I^2 = 85%) when only studies published before 2000 were included (HR 0.75, 95% CI 0.52 to 1.07). Heterogeneity also dropped when Vorobiof 1994 was excluded from analysis (heterogeneity: Tau^2 = 0.02; Chi^2 = 16.45, df = 9, P = 0.06; I^2 = 45%), without changing the effect estimate (HR 0.94, 95% CI 0.83 to 1.07).

Chemotherapy with interleukin-2 versus without interleukin-2

Two studies provided data for this comparison (Hauschild 2001; Keilholz 2005); it was not possible to extract HR data from Sertoli 1999. Overall, 320 participants were allocated to chemotherapy plus interleukin-2 and 324 participants to chemotherapy alone. Analysis suggested a small and statistically non-significant benefit for combination therapy of chemotherapy and interleukin-2 (Analysis 5.1, HR 0.95, 95% CI 0.82 to 1.11; heterogeneity: Tau^2 = 0.00; Chi^2 = 0.45, df = 1, P = 0.50; I^2 = 0%; high-quality evidence).

Chemotherapy with interferon-alpha and interleukin-2 versus without interferon-alpha and interleukin-2

Data for this comparison were available from seven studies (Atkins 2008; Atzpodien 2002; Eton 2002; Johnston 1998; Middleton 2007; Ridolfi 2002a; Rosenberg 1999). Overall, 659 participants were allocated to chemotherapy with both interferon-alpha and interleukin-2 and 658 participants to chemotherapy alone. Analysis suggested a slightly lower risk of death associated with combination therapy of chemotherapy plus interleukin-2 and interferon-alpha, although this difference was not statistically significant (Analysis 6.1, HR 0.94, 95% CI 0.84 to 1.06; heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 7.61$, df = 6, P = 0.27; $I^2 = 21\%$; high-quality evidence). We also analysed those trials enrolling only previously untreated patients with metastatic melanoma (biochemotherapy used as first-line treatment) (Atkins 2008; Eton 2002; Middleton 2007; Ridolfi 2002a; Rosenberg 1999) and found a similar effect size with higher heterogeneity (Analysis 7.1, HR 0.96, 95% CI 0.83 to 1.10; heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 6.64$, df = 4, P = 0.16; $I^2 = 40\%$). The leave-one-out procedure suggested Rosenberg 1999 to be the study driving heterogeneity (HR 0.92, 95% CI 0.83 to 1.04; heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.42$, df = 3, P = 0.70; $I^2 = 0\%$); however, we could not explain why this trial caused heterogeneity.

Immune checkpoint inhibitors

Anti-CTLA4 monoclonal antibodies plus chemotherapy versus chemotherapy alone (first line)

Two studies provided data for this comparison (Ribas 2013; Robert 2011): in Ribas 2013 the anti-CTLA4 monoclonal antibody tremelimumab did not add any significant advantage to chemotherapy; and in Robert 2011 the anti-CTLA4 monoclonal antibody ipilimumab significantly increased the efficacy of chemotherapy (HR 0.72, 95% CI 0.59 to 0.88). Overall, 578 participants were allocated to anti-CTLA4 monoclonal antibodies and chemotherapy and 579 to chemotherapy alone. Meta-analysis suggested a lower risk of death for combination therapy of anti-CTLA and chemotherapy, although this difference was not statistically significant (Analysis 10.1, HR 0.81, 95% CI 0.65 to 1.01; heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 2.99$, df = 1, P = 0.08; $I^2 = 67\%$; low-quality evidence). High level heterogeneity detected in this analysis was likely to be linked to the effects caused by participants in Ribas 2013 who failed chemotherapy subsequently being treated with tremelimumab, which potentially nullified the difference between the study arms due to this anti-CTLA4 monoclonal antibody.

Anti-CTLA4 monoclonal antibodies with immune stimulating agents versus without immune stimulating agents (second line)

This comparison included two studies (Hodi 2010a; Hodi 2014). Overall, 526 participants were allocated to anti-CTLA4 monoclonal antibodies with immune stimulating agents: melanoma antigen gp100 (Hodi 2010a) and granulocyte-macrophage colony-stimulating factor (GM-CSF) (Hodi 2014), and 259 participants were allocated to anti-CTLA4 monoclonal antibodies alone. Data from the meta-analysis suggested a lower risk of death for combination therapy of anti-CTLA and immune stimulating agents, although this difference was not statistically significant (Analysis 11.1 HR 0.83, 95% CI 0.52 to 1.33; heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 5.42$, df = 1, P = 0.02; $I^2 = 82\%$; low-quality evidence). High level heterogeneity was likely due to a different effect of association between ipilimumab with either gp100 (Hodi 2010a, HR 1.04, 95% CI 0.83 to 1.30) or GM-CSF (HR 0.64, 95% CI 0.46 to 0.90).

Anti-PD1 monoclonal antibodies versus chemotherapy

This comparison included three studies (Ribas 2015; Robert 2015a; Weber 2015). Overall survival was a study endpoint only for Robert 2015a so meta-analysis could be performed. In Robert 2015a, 210 participants were allocated to anti-PD1 monoclonal antibodies and 208 participants to chemotherapy alone. Results from Robert 2015a showed that anti-PD1 monoclonal antibodies significantly reduced the risk of death from any cause (Analysis 12.1, HR 0.42, 95% CI 0.37 to 0.48; high-quality evidence).

Anti-PD1 monoclonal antibodies versus anti-CTLA4 monoclonal antibodies

This comparison included two studies (Larkin 2015; Robert 2015b). Overall survival was a study endpoint only for Robert 2015b so meta-analysis could not be performed. In Robert 2015b, 556 participants were allocated to anti-PD1 monoclonal antibodies and 208 to chemotherapy alone. Results from Robert 2015b suggested a statistically significant lower risk of death for anti-PD1 monoclonal antibodies (Analysis 13.1; HR 0.63, 95% CI 0.60 to 0.66; high-quality evidence).

Anti-CTLA4 monoclonal antibodies with anti-PD1 monoclonal antibodies versus without anti-PD1 monoclonal antibodies

This comparison included two studies (Larkin 2015; Postow 2015) which did not investigate overall survival.

Small-molecule targeted drugs

BRAF inhibitors versus chemotherapy

This comparison included two studies (Hauschild 2012; McArthur 2014). Overall, 524 participants were allocated to single agent BRAF inhibitor and 401 participants to chemotherapy alone. Data from the meta-analysis suggested a statistically significant lower risk of death for single agent BRAF inhibitor (Analysis 18.1, HR 0.40, 95% CI 0.28 to 0.57; heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 1.04$, df = 1, P = 0.31; $I^2 = 4\%$; high-quality evidence).

MEK inhibitors versus chemotherapy

This comparison included three studies (Flaherty 2012b; Gupta 2014; Robert 2013). Overall, 300 participants were allocated to single agent MEK inhibitor treatment and 196 participants to chemotherapy alone. Data from the meta-analysis suggested a lower risk of death for single agent MEK inhibitor, although the difference was not statistically significant (Analysis 19.1, HR 0.85, 95% CI 0.58 to 1.25; heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 4.63$, df = 2, P = 0.10; $I^2 = 57\%$; low-quality evidence; downgraded due to inconsistency and imprecision).

BRAF inhibitors with MEK inhibitors versus without MEK inhibitors

This comparison included four studies (Flaherty 2012a; Larkin 2014; Long 2015; Robert 2015). Overall, 918 participants were allocated to combination therapy of BRAF plus MEK inhibitors and 866 participants to single agent BRAF inhibitor. Data from the meta-analysis suggested a statistically significant lower risk of death for combination therapy (Analysis 20.1, HR 0.70, 95% CI 0.59 to 0.82, heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.15$, df = 3, P = 0.98; $I^2 = 0\%$; high-quality evidence).

Chemotherapy with versus without other agents

Chemotherapy with Bacillus Calmette-Guérin (BCG) versus without BCG

This comparison included six studies (Costanzi 1982; Mastrangelo 1979; Newlands 1976; Ramseur 1978; Veronesi 1984; Verschraegen 1993). HRs were available or extractable for two studies (Newlands 1976; Verschraegen 1993). Overall, 74 participants were allocated to chemotherapy with BCG and 80 to chemotherapy alone. Analysis suggested a lower risk of death for combination of chemotherapy and BCG, although the difference was not statistically significant (Analysis 8.1, HR 0.87, 95% CI 0.61 to 1.25; heterogeneity: Tau^2 = 0.00; Chi^2 = 0.50, df = 1, P = 0.48; I^2 = 0%; moderate-quality evidence; downgraded due to imprecision).

Chemotherapy with *Corynebacterium parvum* versus without *C parvum*

This comparison included seven studies (Clunie 1980; Gough 1978; Kokoschka 1978; Presant 1979; Robidoux 1982; Thatcher 1986; Veronesi 1984). HRs were directly available or could be extrapolated for four RCTs (Clunie 1980; Kokoschka 1978; Presant 1979; Robidoux 1982). Overall, 114 participants were allocated to chemotherapy with *C parvum* and 128 participants to chemotherapy alone. Analysis suggested a slightly lower risk of death for combination of chemotherapy and *C parvum,* although this difference was not statistically significant (Analysis 9.1, HR 0.95, 95% CI 0.74 to 1.22; heterogeneity: Tau^2 = 0.00; Chi^2 = 0.79, df = 3, P = 0.85; I^2 = 0%; moderate-quality evidence; downgraded due to imprecision).

Chemotherapy with tamoxifen versus without tamoxifen

We included four trials for this comparison (Agarwala 1999; Cocconi 1992; Falkson 1998; Rusthoven 1996). HRs were either directly reported or could be extrapolated. Tamoxifen-based polychemotherapy was administered to 326 participants and 317 participants received cytotoxic chemotherapy alone. Tamoxifen was associated with a non-statistically significant slightly higher risk of death (Analysis 2.1, HR 1.03, 95% CI 0.80 to 1.33; heterogeneity: Tau^2 = 0.04; Chi^2 = 7.58, df = 3, P = 0.06; I^2 = 60%; low-quality evidence; downgraded due to inconsistency and imprecision). Leave-one-out analysis suggested that heterogeneity was mainly related to Cocconi 1992 (HR 1.13, 95% CI 0.96 to 1.33, heterogeneity: Tau^2 = 0.00; Chi^2 = 1.52, df = 2, P = 0.47; I^2 = 0%): however, we could not explain why this trial caused heterogeneity.

Chemotherapy with anti-angiogenic drugs versus without anti-angiogenic drugs

This comparison included two studies (Cui 2013; Kim 2012). Overall, 199 participants were allocated to standard chemotherapy plus anti-angiogenic therapies and 125 participants to chemotherapy alone. Data from the meta-analysis suggested a statistically significant lower risk of death for combination of chemotherapy and anti-angiogenic agents (Analysis 17.1, HR 0.60, 95% CI 0.45 to 0.81; heterogeneity: Tau^2 = 0.00; Chi^2 = 0.71, df = 1, P = 0.40; I^2 = 0%; moderate-quality evidence; downgraded due to imprecision - there were fewer than 400 participants, so the sample size was smaller than optimal information size).

Chemotherapy with sorafenib versus without sorafenib

This comparison included three studies (Flaherty 2013a; Hauschild 2009a; McDermott 2008). Overall, 596 participants were allocated to standard chemotherapy plus sorafenib and 598 participants to chemotherapy alone. Analysis suggested a similar risk of death for combination of chemotherapy and sorafenib (Analysis 15.1, HR 1.00, 95% CI 0.88 to 1.14; heterogeneity: Tau^2 = 0.00; Chi^2 = 0.03, df = 2, P = 0.99; I^2 = 0%; high-quality evidence).

Chemotherapy with elesclomol versus without elesclomol

This comparison included two studies (O'Day 2011; O'Day 2013). Overall survival was a study endpoint only for O'Day 2013 so meta-analysis could not be performed. In O'Day 2013, 325 participants were allocated to chemotherapy plus elesclomol and 326 participants to chemotherapy alone. Results from O'Day 2013 suggested a statistically significant lower risk of death for chemotherapy alone, although the difference was not statistically significant (Analysis 16.1, HR 1.10, 95% CI 0.92 to 1.32; moderate-quality evidence; downgraded due to imprecision).

Other comparisons

Single agent chemotherapy versus another single agent chemotherapy

Meta-analysis was feasible for two different single agent drug regimens: dacarbazine and temozolomide. Three trials were included (Chiarion-Sileni 2011; Middleton 2000; Patel 2011). Overall, 659 and 654 participants were allocated to temozolomide and dacarbazine, respectively. Temozolomide was associated with a small and non statistically significant survival improvement compared to single agent dacarbazine (Analysis 3.1, HR 0.98, 95% CI 0.85 to 1.12; heterogeneity: Tau^2 = 0.00; Chi^2 = 2.33, df = 2, P = 0.31; I^2 = 14%; high-quality evidence).

Progression-free survival

Polychemotherapy versus single agent chemotherapy

We included 14 studies that compared cytotoxic polychemotherapy to single agent chemotherapy (Bafaloukos 2005; Bellett 1976; Carter 1975; Chapman 1999; Chauvergne 1982; Chiarion Sileni 2001; Costanza 1972; Costanza 1977; Glover 2003; Kogoniia 1981; Lopez 1984; Luikart 1984; Zimpfer-Rechner 2003). HRs were either available or extractable for five studies (Bafaloukos 2005; Glover 2003; Chiarion Sileni 2001; Luikart 1984; Zimpfer-Rechner 2003). Cytotoxic polychemotherapy and single agent chemotherapy were administered for 219 and 179 participants, respectively. Data from the meta-analysis suggested a slightly higher risk of melanoma progression for polychemotherapy, although this difference did not reach statistical significance (Analysis 1.2, HR 1.07, 95% CI 0.91 to 1.25; heterogeneity: Tau^2 = 0.00; Chi^2 = 0.87, df = 4, P = 0.93; I^2 = 0%; high-quality evidence).

Biochemotherapy versus chemotherapy

Chemotherapy with interferon-alpha versus without interferon-alpha

This comparison included 15 studies (Bajetta 1994; Bajetta 2006a; Danson 2003; Daponte 2013; Dorval 1999; Falkson 1991; Falkson 1995; Falkson 1998; Gorbonova 2000; Kaufmann 2005; Kirkwood 1990; Maio 2010; Thomson 1993; Vorobiof 1994; Young 2001). HRs were directly available or could be extrapolated from six studies (Bajetta 1994; Bajetta 2006a; Daponte 2013; Falkson 1991; Falkson 1998; Kaufmann 2005). Overall, 671 participants were allocated to chemotherapy with interferon-alpha and 610 participants to chemotherapy alone. Data from the meta-analysis suggested a lower risk of death for combination of chemotherapy and interferon-alpha, although this difference was not statistically significant (Analysis 4.2, HR 0.87, 95% CI 0.74 to 1.01; heterogeneity:

Tau² = 0.02; Chi² = 13.32, df = 5, P = 0.02; I² = 62%; low-quality evidence; downgraded due to inconsistency and imprecision). High heterogeneity appeared to result from inclusion of Falkson 1991: when this trial was omitted from analysis, heterogeneity dropped to 0% (in this sensitivity analysis the effect size was also reduced: HR 0.92, 95% CI 0.84 to 1.00). However, we could not explain why Falkson 1991 caused heterogeneity.

Chemotherapy with interleukin-2 versus without interleukin-2

This comparison included two studies (Hauschild 2001; Keilholz 2005). Progression-free survival was a study endpoint only for Keilholz 2005 so meta-analysis could not be performed. Keilholz 2005 randomised 183 participants to receive chemotherapy plus interleukin-2 and 180 participants to receive chemotherapy alone. Findings reported by Keilholz 2005 suggested a statistically significant lower risk of melanoma progression for chemotherapy alone, although the difference was not statistically significant (Analysis 5.2, HR 0.87, 95% CI 0.70 to 1.08; moderate-quality evidence; downgraded due to imprecision).

Chemotherapy with interferon-alpha and interleukin-2 versus without interferon-alpha and interleukin-2

This comparison included seven studies (Atkins 2008; Atzpodien 2002; Eton 2002; Johnston 1998; Middleton 2007; Ridolfi 2002a; Rosenberg 1999). HRs either were directly available or could be extrapolated for six studies (Atkins 2008; Atzpodien 2002; Eton 2002; Johnston 1998; Middleton 2007; Ridolfi 2002a). Overall, 488 participants were allocated to chemotherapy with both interferon-alpha and interleukin-2 and 476 to chemotherapy alone. Meta-analysis suggested a statistically significant better progression-free survival for biochemotherapy (Analysis 6.2, HR 0.90, 95% CI 0.83 to 0.99; heterogeneity: Tau² = 0.00; Chi² = 5.22, df = 5, P = 0.39; I² = 4%; high-quality evidence). This result was also confirmed when studies investigating first-line treatment were considered (Analysis 7.2, HR 0.86, 95% CI 0.76 to 0.99).

Immune checkpoint inhibitors

Anti-CTLA4 monoclonal antibodies plus chemotherapy versus chemotherapy alone (first line)

Two studies reported this comparison (Ribas 2013; Robert 2011) but HR data were not extractable from Ribas 2013. Robert 2011 randomised 250 participants to receive anti-CTLA4 monoclonal antibodies plus chemotherapy and 252 participants to receive chemotherapy alone. Findings suggested a statistically significant better progression-free survival for combination of anti-CTLA plus chemotherapy (Analysis 10.2, HR 0.76, 95% CI 0.63 to 0.92; moderate-quality evidence; downgraded due to imprecision).

Anti-CTLA4 monoclonal antibodies with immunostimulating agents versus without immunostimulating agents (second line)

This comparison included two studies (Hodi 2010a; Hodi 2014). Overall, 526 participants were allocated to anti-CTLA4 monoclonal antibodies combined with immunostimulating agents (gp100 in Hodi 2010a and GM-CSF in Hodi 2014), and 259 to anti-CTLA4 monoclonal antibodies alone. Meta-analysis suggested a better progression-free survival for anti-CTLA monoclonal antibodies alone, although the difference was not statistically significant (Analysis 11.2, HR 1.06, 95% CI 0.75 to 1.51; heterogeneity: Tau² = 0.05; Chi² = 3.61, df = 1, P = 0.06; I² = 72%; low-quality evidence; downgraded due to inconsistency and imprecision). The inclusion of trials testing two different immunostimulating agents may explain high between-study heterogeneity.

Anti-PD1 monoclonal antibodies versus chemotherapy

This comparison included three studies (Ribas 2015; Robert 2015a; Weber 2015). HRs were either available or extractable for Ribas 2015 and Robert 2015a. Overall, 570 participants were allocated to anti-PD1 monoclonal antibodies and 387 to chemotherapy alone. Meta-analysis suggested a statistically significant better progression-free survival for participants allocated to anti-PD1 monoclonal antibodies (Analysis 12.2, HR 0.49, 95% CI 0.39 to 0.61; heterogeneity: Tau² = 0.01; Chi² = 2.26, df = 1, P = 0.13; I² = 56%; moderate-quality evidence; downgraded due to inconsistency).

Anti-PD1 monoclonal antibodies versus anti-CTLA4 monoclonal antibodies

This comparison included two studies (Larkin 2015; Robert 2015b). Overall, 872 participants were allocated to anti-PD1 monoclonal antibodies and 593 to anti-CTLA4 monoclonal antibodies. Meta-analysis suggested a statistically significant better progression-free survival for participants treated with anti-PD1 monoclonal antibodies (Analysis 13.2, HR 0.54, 95% CI 0.50 to 0.60; heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1, P = 0.72; I² = 0%; high-quality evidence).

Anti-CTLA4 monoclonal antibodies with anti-PD1 monoclonal antibodies versus without anti-PD1 monoclonal antibodies

This comparison included two studies (Larkin 2015; Postow 2015). Overall, 386 participants were allocated to combination therapy with anti-PD1 plus anti-CTLA4 monoclonal antibodies and 352 to anti-CTLA4 monoclonal antibodies alone. Meta-analysis suggested a statistically significant better progression-free survival for participants treated with combination treatment (Analysis 14.1, HR 0.40, 95% CI 0.35 to 0.46; heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1, P = 0.78; I² = 0%; high-quality evidence).

Small-molecule targeted drugs

BRAF inhibitors versus chemotherapy

This comparison included two studies (Hauschild 2012; McArthur 2014). Overall, 524 participants were allocated to single agent BRAF inhibitor and 401 to chemotherapy alone. Meta-analysis showed that single agent BRAF inhibitor was associated with a statistically significant better progression-free survival (Analysis 18.2, HR 0.27, 95% CI 0.21 to 0.34, heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 1, P = 0.63; I² = 0%; high-quality evidence).

MEK inhibitors versus chemotherapy

This comparison included three studies (Flaherty 2012b; Gupta 2014; Robert 2013). Overall, 300 participants were allocated to single agent MEK inhibitor and 196 to chemotherapy alone. Meta-analysis suggested a statistically significantly better progression-free survival for single agent MEK inhibitor (Analysis 19.2, HR 0.58, 95% CI 0.42 to 0.80; heterogeneity: Tau² = 0.05; Chi² = 4.75, df = 2, P = 0.09; I² = 58%; moderate-quality evidence; downgraded due to inconsistency). The three studies included different participants populations and this may explain high between-study heterogeneity. Gupta 2014 enrolled participants with wild-type BRAF melanomas and Flaherty 2012b tested a MEK inhibitor in both pre-treated and untreated participants. When Flaherty 2012b was excluded from the meta-analysis,

heterogeneity was reduced to 0%, and effect size decreased (HR 0.67, 95% CI 0.53 to 0.85).

BRAF inhibitors with versus without MEK inhibitors

This comparison was reported in four studies (Flaherty 2012a; Larkin 2014; Long 2015; Robert 2015). Overall, 918 participants were allocated to combination of BRAF and MEK inhibitors and 866 to single agent BRAF inhibitor. Meta-analysis suggested a statistically significant better progression-free survival for combination therapy (Analysis 20.2, HR 0.56, 95% CI 0.44 to 0.71); however, despite studies sharing similar designs, between-study heterogeneity was high (Tau^2 = 0.04; Chi^2 = 9.82, df = 3, P = 0.02; I^2 = 69%; moderate-quality evidence; downgraded due to inconsistency). Sensitivity analysis showed that Long 2015 determined heterogeneity; the I^2 value dropped to 9% when this study was excluded from analysis, with only minimal change in effect size (HR 0.52, 95% CI 0.44, 0.61).

Chemotherapy with versus without other agents

Chemotherapy with Bacillus Calmette-Guérin (BCG) versus without BCG

Six studies investigated this comparison (Costanzi 1982; Mastrangelo 1979; Newlands 1976; Ramseur 1978; Veronesi 1984; Verschraegen 1993). However, the studies did not investigate progression-free survival, nor were HRs available or extractable.

Chemotherapy with *Corynebacterium parvum* versus without *C parvum*

Seven studies investigated this comparison (Clunie 1980; Gough 1978; Kokoschka 1978; Presant 1979; Robidoux 1982; Thatcher 1986; Veronesi 1984). However, the studies did not investigate progression-free survival, nor were HRs available or extractable.

Chemotherapy with versus without tamoxifen

Four studies investigated this comparison (Agarwala 1999; Cocconi 1992; Falkson 1998; Rusthoven 1996). HRs were either available or extractable for Falkson 1998 and Rusthoven 1996. Tamoxifen-based polychemotherapy was administered to 238 participants and 237 participants received chemotherapy alone. Tamoxifen was associated with a non statistically significant slightly higher risk of melanoma progression (Analysis 2.2, HR 1.06, 95% CI 0.93 to 1.22; heterogeneity: Tau^2 = 0.00; Chi^2 = 0.29, df = 1, P = 0.59; I^2 = 0%; high-quality evidence).

Chemotherapy with sorafenib versus without sorafenib

This comparison included three studies (Flaherty 2013a; Hauschild 2009a; McDermott 2008). Overall, 596 participants were allocated to standard chemotherapy plus sorafenib and 598 to chemotherapy alone. Meta-analysis suggested better progression-free survival for participants undergoing chemotherapy plus sorafenib, although the difference was not statistically significant (Analysis 15.2, HR 0.89, 95% CI 0.73 to 1.09; heterogeneity: Tau^2 = 0.01; Chi^2 = 2.94, df = 2, P = 0.23; I^2 = 32%; moderate-quality evidence; downgraded due to imprecision).

Chemotherapy with elesclomol versus without elesclomol

This comparison was reported by two studies (O'Day 2011; O'Day 2013). Overall, 378 participants were allocated to standard chemotherapy plus elesclomol and 354 to chemotherapy alone. Meta-analysis suggested better progression-free survival for participants undergoing chemotherapy plus elesclomol, although the difference was not statistically significant (Analysis 16.2, HR 0.75, 95% CI 0.50 to 1.13; heterogeneity: Tau^2 = 0.06; Chi^2 = 3.23, df = 1, P = 0.07; I^2 = 69%; low-quality evidence; downgraded due to inconsistency and imprecision).

Chemotherapy with anti-angiogenic drugs versus without anti-angiogenic drugs

This comparison was reported by two studies (Cui 2013; Kim 2012). Overall, 199 participants were allocated to standard chemotherapy plus anti-angiogenic therapies and 125 to chemotherapy alone. Meta-analysis suggested a statistically significant progression-free survival benefit for combination of chemotherapy and anti-angiogenic agents (Analysis 17.2, HR 0.69, 95% CI 0.52 to 0.92; heterogeneity: Tau^2 = 0.01; Chi^2 = 1.17, df = 1, P = 0.28; I^2 = 14%; moderate-quality evidence; downgraded due imprecision - sample size was smaller than optimal information size).

Other comparisons

Single agent chemotherapy versus other single agent chemotherapy

Meta-analysis was feasible for two different single agent drug regimens: dacarbazine and temozolomide. Three trials were included (Chiarion-Sileni 2011; Middleton 2000; Patel 2011). Overall, 659 and 654 participants were allocated to temozolomide and dacarbazine, respectively. Temozolomide was associated with a statistically non-significant progression-free survival improvement compared to single agent dacarbazine (Analysis 3.2, HR 0.87, 95% CI 0.74 to 1.03; heterogeneity: Tau^2 = 0.01; Chi^2 = 3.08, df = 2, P = 0.21; I^2 = 35%; moderate-quality evidence; downgraded due to imprecision).

Toxicity

Polychemotherapy versus single agent chemotherapy

This comparison included 15 studies (Bajetta 1994; Bajetta 2006a; Danson 2003; Daponte 2013; Dorval 1999; Falkson 1991; Falkson 1995; Falkson 1998; Gorbonova 2000; Kaufmann 2005; Kirkwood 1990; Maio 2010; Thomson 1993; Vorobiof 1994; Young 2001). Description of ≥ G3 toxicity, expressed as the number of participants experiencing toxicity, was available from three studies (Costanza 1977; Chauvergne 1982; Glover 2003). Cytotoxic polychemotherapy and single agent chemotherapy were administered in 241 and 149 participants, respectively, with a statistically significant higher rate of high-grade toxicity among those undergoing polychemotherapy (Analysis 1.4, RR 1.97, 95% CI 1.44 to 2.71; I^2 = 42%; moderate-quality evidence).

Biochemotherapy versus chemotherapy

Chemotherapy with interferon-alpha versus without interferon-alpha

This comparison included 13 studies (Bajetta 1994; Bajetta 2006a; Danson 2003; Daponte 2013; Dorval 1999; Falkson 1991; Falkson 1995; Falkson 1998; Gorbonova 2000; Kaufmann 2005; Thomson 1993; Vorobiof 1994; Young 2001). Description of ≥ G3 toxicity, expressed as number of participants experiencing toxicity, was available from three studies (Bajetta 1994; Falkson 1991; Maio 2010). Overall, 579 participants were allocated to chemotherapy plus interferon-alpha and 212 to chemotherapy alone. Meta-analysis suggested a non statistically significant higher rate of ≥ G3 toxicity for the combined regimen (Analysis 4.4, RR 1.72, 95% CI 0.37 to 7.95; heterogeneity: Tau^2 = 1.16; Chi^2 = 5.51, df = 2, P = 0.06; I^2 =

64%; low-quality evidence; downgraded due to inconsistency and imprecision).

Chemotherapy with interleukin-2 versus without interleukin-2

This comparison included two studies (Hauschild 2001; Keilholz 2005). Overall, 320 participants were allocated to chemotherapy plus interleukin-2 and 324 to chemotherapy alone. Description of ≥ G3 toxicity, expressed as number of participants experiencing toxicity, was unavailable from the studies.

Chemotherapy with interferon-alpha plus interleukin-2 versus without interferon-alpha plus interleukin-2

This comparison included seven studies (Atkins 2008; Atzpodien 2002; Eton 2002; Johnston 1998; Middleton 2007; Ridolfi 2002a; Rosenberg 1999). Description of ≥ G3 toxicity, expressed as number of participants experiencing toxicity, was available from Johnston 1998 and Middleton 2007. Analysis suggested a statistically significant higher ≥ G3 toxicity for combined chemotherapy, interferon-alpha and interleukin-2 (Analysis 6.4, RR 1.35, 95% CI 1.14 to 1.61; heterogeneity: Tau^2: 0.00, Chi^2 = 0.50, df = 1, P = 0.48; I^2 = 0%; high-quality evidence). When the analysis was restricted to the first-line setting, results (based on a single study - Middleton 2007) were similar (Analysis 7.4, RR 1.45, 95% CI 1.12 to 1.87).

Immune checkpoint inhibitors

Anti-CTLA4 monoclonal antibodies plus chemotherapy versus chemotherapy alone (first line)

This comparison included two studies (Ribas 2013; Robert 2011). Overall, 578 participants were allocated to anti-CTLA4 monoclonal antibodies plus chemotherapy and 579 to chemotherapy alone. Meta-analysis suggested a statistically significant higher rate of ≥ G3 toxicity for combined anti-CTLA and chemotherapy (Analysis 10.4, RR 1.69, 95% CI 1.19 to 2.42; heterogeneity: Tau^2 = 0.06; Chi^2 = 6.51, df = 1, P = 0.01; I^2 = 85%; moderate-quality evidence; downgraded due to inconsistency).

Anti-CTLA4 monoclonal antibodies with immune stimulating agents versus without immune stimulating agents (second line)

This comparison included two studies (Hodi 2010a; Hodi 2014) Overall, 526 participants were allocated to anti-CTLA4 monoclonal antibodies plus immune stimulating agents (gp100 in Hodi 2010a and GM-CSF in Hodi 2014), and 259 to anti-CTLA4 monoclonal antibodies alone. Meta-analysis suggested higher rates of ≥ G3 toxicity for the combined regimen, although the difference was not statistically significant (Analysis 11.4, RR 0.87, 95% CI 0.69 to 1.11; heterogeneity: Tau^2 = 0.02; Chi^2 = 2.08, df = 1, P = 0.15; I^2 = 52%; low-quality evidence; downgraded due to inconsistency and imprecision).

Anti-PD1 monoclonal antibodies versus chemotherapy

This comparison included three studies (Ribas 2015; Robert 2015a; Weber 2015). Overall, 847 participants were allocated to anti-PD1 monoclonal antibodies and 520 to chemotherapy alone. Meta-analysis showed a statistically significant lower ≥ G3 toxicity rate for anti-PD1 monoclonal antibodies (Analysis 12.4, RR 0.55, 95% CI 0.31 to 0.97; heterogeneity: Tau^2 = 0.21; Chi^2 = 14.24, df = 2, P = 0.0008; I^2 = 86%; low-quality evidence; downgraded due to inconsistency and imprecision).

Anti-PD1 monoclonal antibodies versus anti-CTLA4 monoclonal antibodies

This comparison included two studies (Larkin 2015; Robert 2015b). Overall, 872 participants were allocated to anti-PD1 monoclonal antibodies and 593 to anti-CTLA4 monoclonal antibodies. Meta-analysis showed a statistically significant lower ≥ G3 toxicity rate for anti-PD1 monoclonal antibodies (Analysis 13.4, RR 0.70, 95% CI 0.54 to 0.91; heterogeneity: Tau^2 = 0.02; Chi^2 = 2.14, df = 1, P = 0.14; I^2 = 53%; low-quality evidence; downgraded due to inconsistency and imprecision).

Anti-CTLA4 monoclonal antibodies with anti-PD1 monoclonal antibodies versus without anti-PD1 monoclonal antibodies

This comparison included two studies (Larkin 2015; Postow 2015). Overall, 386 participants were allocated to combination therapy with anti-PD1 and anti-CTLA4 monoclonal antibodies and 352 to anti-CTLA4 monoclonal antibodies alone. Meta-analysis suggested a higher ≥ G3 toxicity rate for anti-CTLA4 monoclonal antibodies, although the difference was not statistically significant (Analysis 14.3, RR 1.57, 95% CI 0.85 to 2.92; heterogeneity: Tau^2 = 0.16; Chi^2 = 5.00, df = 1, P = 0.03; I^2 = 80%; low-quality evidence; downgraded due to inconsistency and imprecision).

Small-molecule targeted drugs

BRAF inhibitors versus chemotherapy

This comparison included two studies (Hauschild 2012; McArthur 2014). Overall, 524 participants were allocated to single agent BRAF inhibitor and 401 to chemotherapy alone. Meta-analysis suggested a higher ≥ G3 toxicity rate for single agent BRAF inhibitor, although the difference was not statistically significant (Analysis 18.4, RR 1.27, 95% CI 0.48 to 3.33; heterogeneity: Tau^2 = 0.43; Chi^2 = 8.35, df = 1, P = 0.004; I^2 = 88%; low-quality evidence; downgraded due to inconsistency and imprecision).

MEK inhibitors versus chemotherapy

This comparison included three studies (Flaherty 2012b; Gupta 2014; Robert 2013). Description of ≥ G3 toxicity, expressed as number of participants experiencing toxicity, was available only from Robert 2013. There was a statistically significant higher ≥ G3 toxicity rate reported for MEK inhibitor (Analysis 19.4, RR 1.61, 95% CI 1.08 to 2.41; moderate-quality evidence; downgraded due to imprecision).

BRAF inhibitors with versus without MEK inhibitors

This comparison included four studies (Flaherty 2012a; Larkin 2014; Long 2015; Robert 2015). Overall, 918 participants were allocated to combination of BRAF and MEK inhibitors and 866 to single agent BRAF inhibitor. Meta-analysis suggested a lower ≥ G3 toxicity rate for combination therapy, although the difference was not statistically significant (Analysis 20.4, RR 1.01, 95% CI 0.85 to 1.20; heterogeneity: Tau^2 = 0.02; Chi^2 = 8.24, df = 3, P = 0.04; I^2 = 64%; moderate-quality evidence; downgraded due to inconsistency).

Chemotherapy with versus without other agents

Chemotherapy with Bacillus Calmette-Guérin (BCG) versus without BCG

Six studies investigated this comparison (Costanzi 1982; Mastrangelo 1979; Newlands 1976; Ramseur 1978; Veronesi 1984; Verschraegen 1993). Description of ≥ G3 toxicity, expressed as

number of participants experiencing toxicity, was unavailable from these studies.

Chemotherapy with *Corynebacterium parvum* versus without *C parvum*

Seven studies investigated this comparison (Clunie 1980; Gough 1978; Kokoschka 1978; Presant 1979; Robidoux 1982; Thatcher 1986; Veronesi 1984). Description of ≥ G3 toxicity, expressed as number of participants experiencing toxicity, was unavailable from these studies.

Chemotherapy with tamoxifen versus without tamoxifen

Four studies investigated this comparison; all had either available or extractable HRs (Agarwala 1999; Cocconi 1992; Falkson 1998; Rusthoven 1996). Description of ≥ G3 toxicity, expressed as number of participants experiencing toxicity, was available in only from Falkson 1998. Falkson 1998 administered tamoxifen-based polychemotherapy and single agent chemotherapy to 134 and 137 participants, respectively. There was a non statistically significant lower rate of ≥ G3 toxicity among participants undergoing tamoxifen-based polychemotherapy (Analysis 2.4, RR 0.70, 95% CI 0.38 to 1.28; moderate-quality evidence; downgraded due to imprecision).

Chemotherapy with sorafenib versus without sorafenib

This comparison included three studies (Flaherty 2013a; Hauschild 2009a; McDermott 2008). Overall, 596 participants were allocated to standard chemotherapy plus sorafenib and 598 to chemotherapy alone. Meta-analysis suggested a higher ≥ G3 toxicity rate for chemotherapy plus sorafenib, although the difference was not statistically significant (Analysis 15.4, RR 1.08, 95% CI 0.93 to 1.26; heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 3.40$, df = 2, P = 0.18; $I^2 = 41\%$; moderate-quality evidence; downgraded due to imprecision).

Chemotherapy with elesclomol versus without elesclomol

This comparison included two studies (O'Day 2011; O'Day 2013). Overall, 378 participants were allocated to standard chemotherapy plus elesclomol and 354 to chemotherapy alone. Description of ≥ G3 toxicity, expressed as number of participants experiencing toxicity, was available in only from O'Day 2013. O'Day 2013 reported a marginally statistically significant higher toxicity for chemotherapy plus elesclomol (Analysis 16.4, RR 1.22, 95% CI 1.00 to 1.50; moderate-quality evidence; downgraded due to imprecision).

Chemotherapy with anti-angiogenic drugs versus without anti-angiogenic drugs

This comparison included two studies (Cui 2013; Kim 2012). Overall, 199 participants were allocated to standard chemotherapy plus anti-angiogenic drugs bevacizumab (Kim 2012) and endostar (Cui 2013) and 125 to chemotherapy alone. Meta-analysis suggested a higher ≥ G3 toxicity rate for chemotherapy alone, although the difference was not statistically significant (Analysis 17.4, RR 0.68, 95% CI 0.09 to 5.32; heterogeneity: $Tau^2 = 1.53$; $Chi^2 = 2.34$, df = 1, P = 0.13; $I^2 = 57\%$; low-quality evidence; downgraded due to inconsistency and imprecision).

Other comparisons

Single agent chemotherapy versus other single agent chemotherapy

Meta-analysis was feasible for the comparison between dacarbazine and temozolomide. Three trials were included (Chiarion-Sileni 2011; Middleton 2000; Patel 2011). Description of ≥ G3 toxicity, expressed as number of participants experiencing toxicity, was available from two studies (Middleton 2000; Patel 2011). Overall, 585 and 579 participants were allocated to temozolomide and dacarbazine, respectively. Temozolomide was found to be less toxic than dacarbazine, which had higher incidence of ≥ G3 toxicity, although the difference was not statistically significant (Analysis 3.4, RR 1.15, 95% CI 0.98 to 1.35; heterogeneity: Tau^2: 0.00, $Chi^2 = 0.62$, df = 1, P = 0.43; $I^2 = 0\%$; moderate-quality evidence; downgraded due to imprecision).

Objective tumour response

Polychemotherapy versus single agent chemotherapy

This comparison included 15 studies (Bajetta 1994; Bajetta 2006a; Danson 2003; Daponte 2013; Dorval 1999; Falkson 1991; Falkson 1995; Falkson 1998; Gorbonova 2000; Kaufmann 2005; Kirkwood 1990; Maio 2010; Thomson 1993; Vorobiof 1994; Young 2001). Cytotoxic polychemotherapy and single agent chemotherapy was administered in 1124 and 761 participants, respectively. Meta-analysis showed a statistically significant higher response rate for polychemotherapy (Analysis 1.3, RR 1.27, 95% CI 1.02 to 1.58; heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.43$, df = 7, P = 0.61; $I^2 = 0\%$; moderate-quality evidence; downgraded due to imprecision).

Biochemotherapy versus chemotherapy

Chemotherapy with interferon-alpha versus without interferon-alpha

This comparison included 15 studies (Bajetta 1994; Bajetta 2006a; Danson 2003; Daponte 2013; Dorval 1999; Falkson 1991; Falkson 1995; Falkson 1998; Gorbonova 2000; Kirkwood 1990; Kaufmann 2005; Maio 2010; Thomson 1993; Vorobiof 1994; Young 2001). Overall, 1403 participants were allocated to chemotherapy with interferon-alpha and 1061 to chemotherapy alone. Meta-analysis suggested a statistically significant higher objective response for combination of chemotherapy and interferon (Analysis 4.3, RR 1.36, 95% CI 1.12 to 1.66; heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 16.93$, df = 14, P = 0.26; $I^2 = 17\%$; high-quality evidence).

Chemotherapy with interleukin-2 versus without interleukin-2

This comparison included three studies (Hauschild 2001; Keilholz 2005; Sertoli 1999). Overall, 381 participants were allocated to chemotherapy with interleukin-2 and 354 to chemotherapy alone. Meta-analysis suggested a higher response rate for chemotherapy alone, although the difference was not statistically significant (Analysis 5.3, RR 0.85, 95% CI 0.64 to 1.13; heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.68$, df = 2, P = 0.71; $I^2 = 0\%$; moderate-quality evidence; downgraded due to imprecision).

Chemotherapy with interferon-alpha and interleukin-2 versus without interferon-alpha and interleukin-2

This comparison included seven studies (Atkins 2008; Atzpodien 2002; Eton 2002; Johnston 1998; Middleton 2007; Ridolfi 2002a; Rosenberg 1999). Overall, 474 participants were allocated to chemotherapy with both interferon-alpha and interleukin-2 and 296 to chemotherapy alone. Meta-analysis showed a statistically significant higher response rate for biochemotherapy (Analysis 6.3, RR 1.36, 95% CI 1.11 to 1.67; heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.16$, df = 6, P = 0.41; $I^2 = 3\%$; high-quality evidence). When the analysis was restricted to the first-line setting, results were similar (Analysis 7.3, RR 1.45, 95% CI 1.15 to 1.83; heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.25$, df = 4, P = 0.37; $I^2 = 6\%$).

Immune checkpoint inhibitors

Anti-CTLA4 monoclonal antibodies plus chemotherapy versus chemotherapy alone (first line)

This comparison included two studies (Ribas 2013; Robert 2011). Overall, 578 participants were allocated to anti-CTLA4 monoclonal antibodies and chemotherapy and 579 to chemotherapy alone. Meta-analysis suggested a higher response rate for the combined regimen, although the difference was not statistically significant (Analysis 10.3, RR 1.28, 95% CI 0.92 to 1.77; heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.68$, df = 1, P = 0.41; $I^2 = 0\%$; moderate-quality evidence; downgraded due to imprecision).

Anti-CTLA4 monoclonal antibodies with immunostimulating agents versus without immunostimulating agents (second line)

This comparison included two studies (Hodi 2010a; Hodi 2014) Overall, 526 participants were allocated to anti-CTLA4 monoclonal antibodies and with immunostimulating agents (gp100 in Hodi 2010a and GM-CSF in Hodi 2014), and 259 to anti-CTLA4 monoclonal antibodies alone. Meta-analysis suggested a higher response rate for the combined regimen, although the difference was not statistically significant (Analysis 11.3, RR 0.74, 95% CI 0.38 to 1.47; heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 2.53$, df = 1, P = 0.11; $I^2 = 60\%$; low-quality evidence; downgraded due to inconsistency and imprecision).

Anti-PD1 monoclonal antibodies versus chemotherapy

This comparison included three studies (Ribas 2015; Robert 2015a; Weber 2015). Overall, 847 participants were allocated to anti-PD1 monoclonal antibodies and 520 to chemotherapy alone. Meta-analysis showed a statistically significant higher response rate for anti-PD1 monoclonal antibodies (Analysis 12.3, RR 3.42, 95% CI 2.38 to 4.92; heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 2.35$, df = 2, P = 0.31; $I^2 = 15\%$; high-quality evidence).

Anti-PD1 monoclonal antibodies versus anti-CTLA4 monoclonal antibodies

This comparison included two studies (Larkin 2015; Robert 2015b). Overall, 872 participants were allocated to anti-PD1 monoclonal antibodies and 593 to anti-CTLA4 monoclonal antibodies. Meta-analysis showed a statistically significant higher response rate for anti-PD1 monoclonal antibodies (Analysis 13.3, RR 2.47, 95% CI 2.01 to 3.04; heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.87$, df = 1, P = 0.35; $I^2 = 0\%$; high-quality evidence).

Anti-CTLA4 monoclonal antibodies with anti-PD1 monoclonal antibodies versus without anti-PD1 monoclonal antibodies

This comparison included two studies (Larkin 2015; Postow 2015). Overall, 386 participants were allocated to combination therapy with anti-PD1 anti-CTLA4 monoclonal antibodies and 352 to anti-CTLA4 monoclonal antibodies alone. Meta-analysis showed a statistically significant higher response rate for the combined regimen (Analysis 14.2, RR 3.50, 95% CI 2.07 to 5.92; heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 1.63$, df = 1, P = 0.20; $I^2 = 39\%$; high-quality evidence).

Small-molecule targeted drugs

BRAF inhibitors versus chemotherapy

This comparison included two studies (Hauschild 2012; McArthur 2014). Overall, 524 participants were allocated to single agent BRAF inhibitor and 401 to chemotherapy alone. Meta-analysis showed a statistically significant higher response rate for single agent BRAF inhibitor (Analysis 18.3, RR 6.78, 95% CI 4.84 to 9.49; heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.10$, df = 1, P = 0.75; $I^2 = 0\%$; high-quality evidence).

MEK inhibitors versus chemotherapy

This comparison included three studies (Flaherty 2012b; Gupta 2014; Robert 2013). Overall, 300 participants were allocated to single agent MEK inhibitor and 196 to chemotherapy alone. Meta-analysis showed a statistically significant higher response rate for single agent MEK inhibitor (Analysis 19.3, RR 2.01, 95% CI 1.35 to 2.99; heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.51$, df = 2, P = 0.47; $I^2 = 0\%$; high-quality evidence).

BRAF inhibitors with MEK inhibitors versus without MEK inhibitors

This comparison included four studies (Flaherty 2012a; Larkin 2014; Long 2015; Robert 2015). Overall, 918 participants were allocated to combination of BRAF and MEK inhibitors and 866 to single agent BRAF inhibitor. Meta-analysis showed a statistically significant higher response rate for combination therapy (Analysis 20.3, RR 1.32, 95% CI 1.20 to 1.46; heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.90$, df = 3, P = 0.27; $I^2 = 23\%$; high-quality evidence).

Chemotherapy with other agents versus without other agents

Chemotherapy with Bacillus Calmette-Guérin (BCG) versus without BCG

Six studies investigated this comparison (Costanzi 1982; Mastrangelo 1979; Newlands 1976; Ramseur 1978; Veronesi 1984; Verschraegen 1993). Overall, 658 participants were allocated to chemotherapy with BCG and 649 to chemotherapy alone. Meta-analysis suggested a higher response rate for chemotherapy alone, although the difference was not statistically significant (Analysis 8.2, RR 0.85, 95% CI 0.65 to 1.12; heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.76$, df = 5, P = 0.45; $I^2 = 0\%$; moderate-quality evidence; downgraded due to imprecision).

Chemotherapy with *Corynebacterium parvum* versus without *C parvum*

Seven studies investigated this comparison (Clunie 1980; Gough 1978; Kokoschka 1978; Presant 1979; Robidoux 1982; Thatcher 1986; Veronesi 1984). Overall, 247 participants were allocated to chemotherapy with *C parvum* and 290 to chemotherapy alone. Meta-analysis suggested a higher response rate for chemotherapy plus *C parvum*, although the difference was not statistically significant (Analysis 9.2, RR 1.03, 95% CI 0.77 to 1.38; heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.63$, df = 6, P = 0.47; $I^2 = 0\%$; moderate-quality evidence; downgraded due to imprecision).

Chemotherapy with tamoxifen versus without tamoxifen

Four studies investigated this comparison (Agarwala 1999; Cocconi 1992; Falkson 1998; Rusthoven 1996). Tamoxifen-based polychemotherapy was administered to 326 participants and 317 received cytotoxic chemotherapy alone. Tamoxifen was associated with a non statistically significant higher response rate (Analysis 2.3, RR 1.33, 95% CI 0.94 to 1.89; heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 3.44$, df = 3, P = 0.33; $I^2 = 13\%$; moderate-quality evidence; downgraded due to imprecision).

Chemotherapy with sorafenib versus without sorafenib

This comparison included three studies (Flaherty 2013a; Hauschild 2009a; McDermott 2008). Overall, 596 participants were allocated to standard chemotherapy plus sorafenib and 598 to chemotherapy alone. Meta-analysis suggested a higher response rate for chemotherapy plus sorafenib, although the difference was not statistically significant (Analysis 15.3, RR 1.17, 95% CI 0.91 to 1.50; heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.41$, df = 2, P = 0.49; $I^2 = 0\%$; moderate-quality evidence; downgraded due to imprecision).

Chemotherapy with elesclomol versus without elesclomol

This comparison included two studies (O'Day 2011; O'Day 2013). Overall, 378 participants were allocated to standard chemotherapy plus elesclomol and 354 to chemotherapy alone. Meta-analysis suggested a higher response rate for chemotherapy plus elesclomol, although the difference was not statistically significant (Analysis 16.3, RR 1.86, 95% CI 0.98 to 3.50; heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.12$, df = 1, P = 0.73; $I^2 = 0\%$; moderate-quality evidence; downgraded due to imprecision).

Chemotherapy with anti-angiogenic drugs versus without anti-angiogenic drugs

This comparison included two studies (Cui 2013; Kim 2012). Overall, 199 participants were allocated to standard chemotherapy plus anti-angiogenic drugs bevacizumab (Kim 2012) and endostar (Cui 2013) and 125 to chemotherapy alone. Meta-analysis suggested a statistically significant higher response rate for the combination of chemotherapy plus anti-angiogenic agents, although the difference was not statistically significant (Analysis 17.3, RR 1.71, 95% CI 0.96 to 3.03; heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.20$, df = 1, P = 0.65; $I^2 = 0\%$; moderate-quality evidence; downgraded due to imprecision).

Other comparisons

Single agent chemotherapy versus other single agent chemotherapy

Meta-analysis was feasible for the comparison between temozolomide and dacarbazine. Three trials were eligible (Chiarion-Sileni 2011; Middleton 2000; Patel 2011). Overall, 659 and 654 participants were allocated to temozolomide and dacarbazine, respectively. Temozolomide was associated with a non statistically significant higher response rate compared to single agent dacarbazine (Analysis 3.3, RR 1.21, 95% CI 0.85 to 1.73; heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 2.75$, df = 2 (P = 0.25); $I^2 = 27\%$; moderate-quality evidence; downgraded due to imprecision).

Quality of life

Polychemotherapy versus single agent chemotherapy

No data were available for this comparison.

Biochemotherapy versus chemotherapy

Chemotherapy with interferon-alpha versus without interferon-alpha

The effect on quality of life after dacarbazine plus recombinant interferon-alpha was compared to dacarbazine alone for participants with metastatic malignant melanoma. In Young 2001, no differences in quality of life were observed between treatment groups. The same finding was reported in Thomson 1993 but fatigue and activity, as measured using linear analogue scale of assessment (LASA) scale and functional living index respectively, both improved in the combination treatment group.

Chemotherapy with interferon-alpha and interleukin-2 versus without interferon-alpha and interleukin-2

Chiarion-Sileni 2003 used the Rotterdam Symptom Checklist (RSCL) questionnaire to compare quality of life in advanced melanoma participants receiving biochemotherapy or chemotherapy. Deterioration in overall quality of life reported with biochemotherapy was significantly worse than with chemotherapy. Mean scores decreased in all domains in the biochemotherapy group, but in the chemotherapy group, only activity level and physical symptom distress scores showed deterioration.

Interleukin-2 with histamine versus without histamine

This comparison was assessed in Agarwala 2002 but quality of life was evaluated and reported in an extension study (Beusterien 2003). Three distinct assessments were completed by participants at different time points. Overall State of Health (OSH) and General Health Perception (GHP) scores did not differ significantly between groups. However, Quality of Well Being Scale - Self-Administered (QWB-SA) scores deteriorated more quickly over time in the interleukin-2 only group compared to the interleukin-2 plus histamine group. This led to a significant difference in median quality-adjusted survival duration in favour of the interleukin-2 plus histamine group.

Immune checkpoint inhibitors

Anti-CTLA4 monoclonal antibodies (first line)

Sherrill 2013 conducted a quality-adjusted time without symptoms of disease or toxicity of treatment (Q-TWIST) analysis for participants with untreated stage III/IV melanoma to compare quality of life after ipilimumab plus dacarbazine versus placebo plus dacarbazine. Quality-adjusted survival was not significantly different between the groups during the first year of study (0.50 months favouring the ipilimumab/dacarbazine group) but after extended follow-up, this difference gradually increased to 1.5 months, 2.36 months and 3.28 months at 2, 3 and 4 years, respectively.

Anti-CTLA4 monoclonal antibodies with immunostimulating agents versus without other immunostimulating agents (second line)

This comparison was evaluated in Revicki 2012 where health-related quality of life (HRQoL) outcomes were assessed during the study's 12 week treatment induction period for participants with stage III or IV melanoma. Ipilimumab with or without gp1000 vaccine was compared to gp100 vaccine alone and was shown to have no significant negative impact on HRQoL compared to gp100 alone. Constipation was reported to be significantly improved in the ipilimumab arms compared to the gp100 alone arm.

Anti-PD1 monoclonal antibodies versus chemotherapy

In KEYNOTE-002, a randomised, controlled phase II trial, participants with ipilimumab-refractory melanoma were treated with either pembrolizumab (anti-PD1 monoclonal antibody) or chemotherapy (Ribas 2015). In terms of health-related quality of life, participants treated with pembrolizumab consistently reported less deterioration in individual function and symptoms scales when compared to those treated with chemotherapy. Furthermore, fewer participants in the pembrolizumab group reported decrements of more than 10 points in the global health status quality of life score compared to the chemotherapy group.

Small-molecule targeted drugs

BRAF inhibitors versus chemotherapy

In Grob 2014, single agent dabrafenib (a BRAF inhibitor) was found to be superior to dacarbazine chemotherapy in improving quality of life for participants with metastatic melanoma in the BREAK-3 study. More specifically, on the basis of EORTC QLQ-C30 questionnaires, there was an enhancement of emotional and social functioning as well as an improvement in unwanted symptoms such as nausea and vomiting, appetite loss, diarrhoea, fatigue, dyspnoea and insomnia.

MEK inhibitors versus chemotherapy

In Schadendorf 2014, participants with BRAF mutated metastatic melanoma from the METRIC study were assessed in terms of quality of life after receiving the MEK inhibitor trametinib as a single agent versus chemotherapy. Based on EORTC QLQ-C30 questionnaires the trametinib group showed improvement from baseline in various parameters including better global health, physical, role, and social functioning as well as reduction in fatigue, pain, insomnia, nausea and vomiting, constipation and dyspnoea.

BRAF inhibitors with versus without MEK inhibitors

Impact on quality of life with the combination of dabrafenib and trametinib versus dabrafenib monotherapy in participants with BRAF mutated metastatic melanoma was evaluated in Schadendorf 2015. Global health dimension scores from baseline were better in the combination therapy group. A trend favouring combination therapy was also observed for pain, insomnia as well as physical, social, role, emotional and cognitive functioning. However, the opposite trend was reported for nausea and vomiting, diarrhoea, dyspnoea and constipation with significant improvements from baseline in the dabrafenib monotherapy group.

Other comparisons

Kiebert 2003 investigated temozolomide versus dacarbazine and assessed quality of life in participants being treated for metastatic melanoma. Kiebert 2003 found that treatment with temozolomide led to functional improvements, improved emotional well-being and decreased symptoms compared to treatment with dacarbazine. At 12 weeks post-treatment, participants in the temozolomide group reported better EORTC QLQ-C30 subscale scores in all but two function and symptom categories with better physical functioning, less fatigue and reduced sleep disturbances. Improvements in all symptoms except diarrhoea were in favour of temozolomide at week 24 and there was near significant enhancement in cognitive functioning.

Fotemustine versus dacarbazine

Avril 2004 assessed fotemustine versus dacarbazine. No significant difference was observed between treatment arms.

Vindesine versus observation

Quality of life after adjuvant treatment with single agent vindesine was compared to observation alone in participants with metastasised melanoma after complete metastasectomy in Eigentler 2008. However, feedback from EORTC-QLQ questionnaires was insufficient to draw any conclusions.

Polychemotherapy versus best supportive care

Best supportive care plus a polychemotherapy regimen consisting of cisplatin, vindesine and dacarbazine was compared to best supportive care alone for quality of life impact in participants with advanced melanoma in Hofmann 2011. Despite the deterioration in global health status reported in both arms, no statistically significant difference was observed between the treatments in any aspect of quality of life based on EORTC QLQ-C30 questionnaires.

Economic evaluation

The economic aspects of various treatments were assessed in a single study; therefore no reliable conclusions could be drawn (Middleton 2000). The treatment costs of single agent dacarbazine and single agent temozolomide for advanced malignant melanoma were evaluated by Hillner 2000 and compared as part of a post hoc economic analysis independent from the actual clinical trial (Middleton 2000). Hillner 2000 combined costs and survival duration to analyse the incremental cost-effectiveness of temozolomide over dacarbazine. Despite dacarbazine displaying a trend toward superior cost-effectiveness, statistically, temozolomide was deemed to be equally effective, if not better at improving survival, with a higher but acceptable incremental cost per life-year below the threshold of USD 50,000.

We identified one ongoing phase III RCT (NCT02821013) which plans to evaluate the economic aspects of continuous versus intermittent anti-PD-1 therapy in participants with metastatic melanoma.

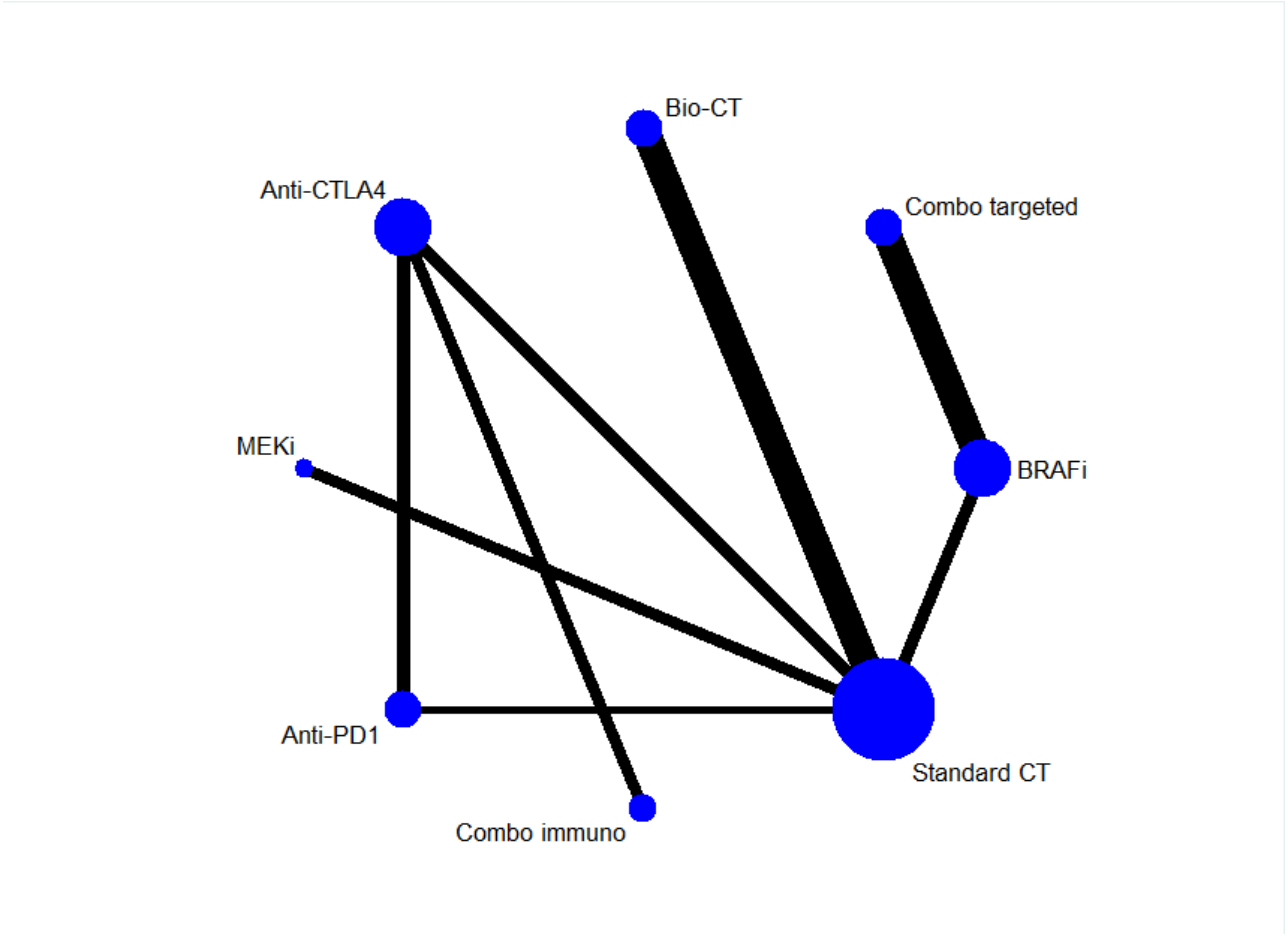
Network meta-analysis findings

We focused attention on four drug classes (chemotherapy, biochemotherapy, immune checkpoint inhibitors and small-molecule targeted drugs) and two primary outcomes (progression-free survival and toxicity) for the network meta-analysis. Reasons for this decision are provided in the following sections.

Drug classes

Chemotherapy was chosen as the most common treatment among the included trials, which made chemotherapy the ideal common comparator (a key feature in network meta-analysis, especially when performed according to the augmented data technique as suggested by White 2015, as we did; see Figure 5). We applied the following principles for other drug classes:

Figure 5. Network plot



1. We chose drug classes for which high-quality evidence was available for effects on patient survival based on direct comparison data. This choice was dictated by the need to include high-quality data in the analysis: network meta-analysis enables indirect comparisons to be made and generate treatment ranking (information not provided by conventional pair-wise meta-analysis). However, reliability of findings unavoidably hinges on the quality of imputed data.
2. We aimed to reduce the complexity of the network (by decreasing the number of nodes connecting each drug regimen to the common comparator, especially when few trials or only one trial represented a single drug regimen) and increase the robustness of the network (by decreasing the number of drug regimens analysed, especially when few trials or only one trial represented a single drug regimen), and therefore, decrease the likelihood of model instability or lack of model convergence.
3. We focused our attention on drugs currently approved for melanoma treatment to provide information that is most useful in routine clinical practice.

Outcomes

We chose one survival outcome (progression-free survival) to represent treatment benefit, and toxicity to represent treatment harm. We chose to investigate progression-free survival instead of overall survival because:

1. Progression-free survival is widely accepted as a surrogate of overall survival, especially in the advanced/metastatic setting (as was the case for this review); progression-free survival is generally used as the outcome for drug approval in this setting.
2. Data for overall survival are not yet mature for recent treatments (such as immune checkpoint inhibitors and small-molecule targeted drugs), which are currently acknowledged as the most effective therapies for people with melanoma.
3. Progression-free survival data are available for more studies compared to overall survival data (which is, at least in part, a corollary of the previous consideration).
4. Progression-free survival is virtually free from the issue (typical of overall survival) of the cross-over effect, that is, participants failing one treatment (e.g. less effective reference therapy) are given another treatment (e.g. more effective experimental therapy), which can confound the results of data analysis.

Adopting these criteria, a total of 19 studies were eligible for inclusion in the network meta-analysis (Atkins 2008; Eton 2002; Flaherty 2012a; Flaherty 2012b; Gupta 2014; Hauschild 2012; Larkin 2014; Larkin 2015; Long 2015; McArthur 2014; Middleton 2007; Postow 2015; Ribas 2013; Ridolfi 2002a; Robert 2011; Robert 2013; Robert 2015; Robert 2015a; Robert 2015b). Studies compared eight treatments: chemotherapy; biochemotherapy (with both interferon-alpha and interleukin-2); anti-CTLA4 monoclonal antibodies; anti-PD1 monoclonal antibodies; anti-CTLA4 plus anti-

PD1 monoclonal antibodies; BRAF inhibitors; MEK inhibitors; and BRAF plus MEK inhibitors (see network plot, Figure 5).

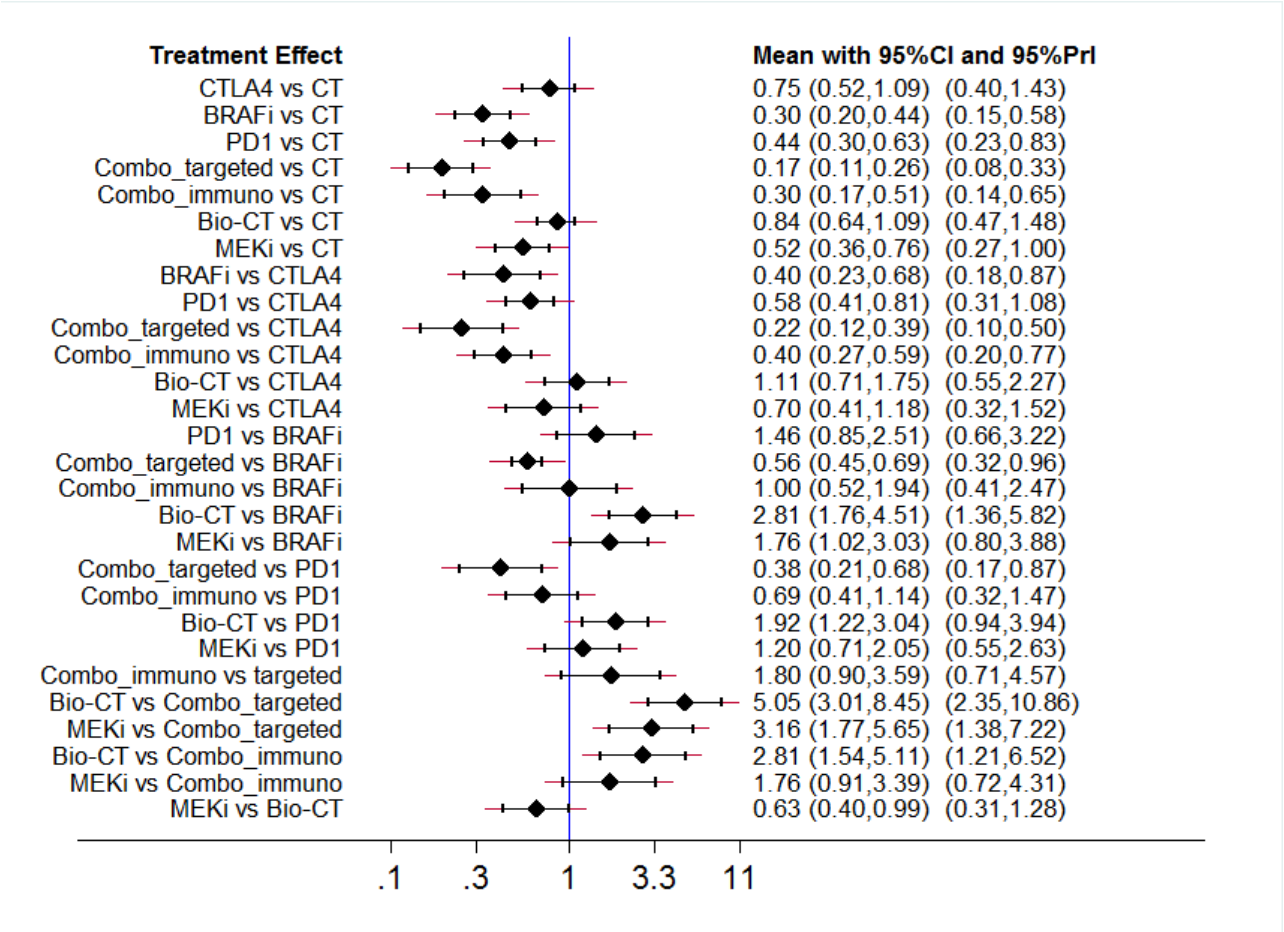
A total of 7632 participants were randomised to receive either conventional chemotherapy (N = 1777), biochemotherapy (N = 507), anti-CTLA4 monoclonal antibodies (N = 886), anti-PD1 monoclonal antibodies (N = 1407), anti-CTLA4 plus PD-1 monoclonal antibodies (N = 408), BRAF inhibitors (N = 1285), MEK inhibitors (N = 259), or BRAF plus MEK inhibitors (N = 918).

Progression-free survival

Progression-free survival data were available for all trials (Atkins 2008; Eton 2002; Flaherty 2012a; Flaherty 2012b; Gupta 2014; Hauschild 2012; Larkin 2014; Larkin 2015; Long 2015; McArthur 2014; Middleton 2007; Postow 2015; Ridolfi 2002a; Robert 2011; Robert 2013; Robert 2015; Robert 2015a; Robert 2015b) except Ribas 2013.

Network meta-analysis, which was conducted to investigate treatment modalities, generated 28 comparisons. Network meta-analysis results were consistent with standard pair-wise meta-analysis for seven comparisons: biochemotherapy versus chemotherapy; anti-PD1 monoclonal antibodies versus chemotherapy; anti-PD1 monoclonal antibodies versus anti-CTLA4 monoclonal antibodies; anti-CTLA4 plus anti-PD1 monoclonal antibodies versus anti-CTLA4 monoclonal antibodies; BRAF inhibitors versus chemotherapy; MEK inhibitors versus chemotherapy; and BRAF plus MEK inhibitors versus BRAF inhibitors (Figure 6).

Figure 6. Interval plot: network meta-analysis results for progression-free survival. The network included eight treatment modalities. The effect measure is reported as hazard ratio (HR). *CI: confidence interval; PrI: predictive interval.*



Overall, we did not observe statistically significant network inconsistency: the P value of the design-by-treatment interaction model (which addresses both loop and design inconsistency at the global network level) was equal to 0.764. A comparison between findings of conventional pair-wise meta-analysis and indirect comparisons generated by network meta-analysis was feasible only for the anti-PD1 versus anti-CTLA4 monoclonal antibodies comparison. The results showed a high correlation between both types of meta-analysis technique: the HR was 0.54 (95% CI 0.50 to 0.60) for conventional meta-analysis and 0.58 (95% CI 0.41 to 0.81) for network meta-analysis (ratio of ratio = 0.93, low risk of loop inconsistency).

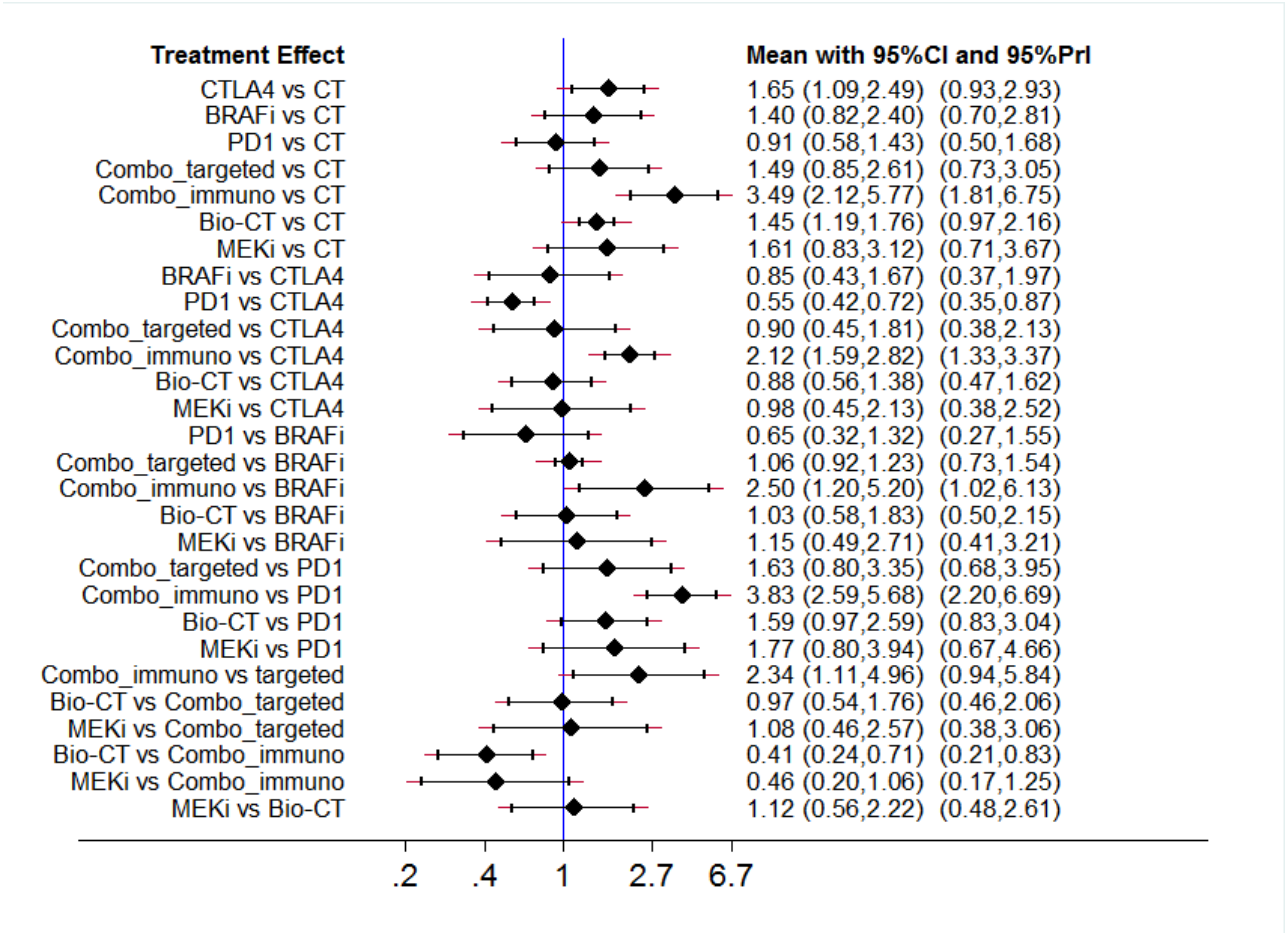
Indirect comparisons indicated that (Figure 6):

1. Compared to chemotherapy, both combination of immune checkpoint inhibitors (HR 0.30, 95% CI 0.17 to 0.51; moderate-quality evidence, downgraded due to indirectness) and combination of small-molecule targeted drugs (HR 0.17, 95% CI 0.11 to 0.26; moderate-quality evidence, downgraded due to indirectness) improved progression-free survival. Anti-CTLA4 monoclonal antibodies did not significantly improve progression-free survival (very low-quality evidence; downgraded due to inconsistency, imprecision and indirectness).
2. Compared to anti-CTLA4 monoclonal antibodies, both BRAF inhibitors (HR 0.40, 95% CI 0.23 to 0.68; moderate-quality evidence; downgraded due to indirectness), and combination of small-molecule targeted drugs (HR 0.22, 95% CI 0.12 to 0.39; moderate-quality evidence; downgraded due to indirectness) were associated with better progression-free survival. In contrast, neither biochemotherapy (very low-quality evidence; downgraded due to inconsistency, imprecision and indirectness) nor MEK inhibitors (very low-quality evidence; downgraded due to inconsistency, imprecision and indirectness) significantly differed from anti-CTLA4 monoclonal antibodies.
3. Compared to BRAF inhibitors, both biochemotherapy (HR 2.81, 95% CI 1.76 to 4.51; moderate-quality evidence, downgraded due to indirectness) and MEK inhibitors (HR 1.76, 95% CI 1.02 to 3.03; very low-quality evidence, downgraded due to inconsistency, imprecision and indirectness) were associated with worse progression-free survival. Neither anti-PD1 monoclonal antibodies (very low-quality evidence, downgraded due to inconsistency, imprecision and indirectness) nor combination of immune checkpoint inhibitors (very low-quality evidence, downgraded due to inconsistency, imprecision and indirectness) significantly differed from BRAF inhibitors.
4. Compared to anti-PD1 monoclonal antibodies, the combination of small-molecule targeted drugs improved progression-free survival (HR 0.38, 95% CI 0.21 to 0.68; moderate-quality evidence, downgraded due to indirectness), whereas biochemotherapy was associated with worse progression-free survival (HR 1.92, 95% CI 1.22 to 3.04; low-quality evidence, downgraded due to inconsistency and indirectness). Neither combination of immune checkpoint inhibitors (very low-quality evidence, downgraded due to inconsistency, imprecision and indirectness) nor MEK inhibitors (very low-quality evidence, downgraded due to inconsistency, imprecision and indirectness) significantly differed from anti-PD1 monoclonal antibodies.
5. Compared to the combination of small-molecule targeted drugs, both biochemotherapy (HR 5.05, 95% CI 3.01 to 8.45; moderate-quality evidence, downgraded due to indirectness) and MEK inhibitors (HR 3.16, 95% CI 1.77 to 5.65; moderate-quality evidence, downgraded due to indirectness) were associated with worse progression-free survival. Combination of immune checkpoint inhibitors did not significantly differ from combination of small-molecule targeted drugs (very low-quality evidence, downgraded due to inconsistency, imprecision and indirectness).
6. Compared to combination of immune checkpoint inhibitors, biochemotherapy was associated with worse progression-free survival (HR 2.81, 95% CI 1.54 to 5.11; moderate-quality evidence, downgraded due to indirectness). MEK inhibitors did not significantly differ from combination of immune checkpoint inhibitors (very low-quality evidence, downgraded due to inconsistency, imprecision and indirectness).
7. Compared to biochemotherapy, MEK inhibitors improved progression-free survival (HR 0.63, 95% CI 0.40 to 0.99; very low-quality evidence, downgraded due to inconsistency, imprecision and indirectness).

Toxicity

Toxicity data were available for all studies included in the network meta-analysis (Atkins 2008; Eton 2002; Flaherty 2012a; Flaherty 2012b; Gupta 2014; Hauschild 2012; Larkin 2014; Larkin 2015; Long 2015; McArthur 2014; Middleton 2007; Postow 2015; Ribas 2013; Ridolfi 2002a; Robert 2011; Robert 2013; Robert 2015; Robert 2015a; Robert 2015b) (Figure 7).

Figure 7. Interval plot: network meta-analysis results for high grade toxicity. The network included eight treatment modalities. The effect measure is reported as relative risk (RR). *CI: confidence interval; PrI: predictive interval.*



Network meta-analysis to investigate treatment modalities generated 28 comparisons. Network meta-analysis results were consistent with standard pair-wise meta-analysis for seven comparisons: biochemotherapy versus chemotherapy; anti-PD1 monoclonal antibodies versus chemotherapy; anti-PD1 monoclonal antibodies versus anti-CTLA4 monoclonal antibodies; anti-CTLA4 plus anti-PD1 monoclonal antibodies versus anti-CTLA4 monoclonal antibodies; BRAF inhibitors versus chemotherapy; MEK inhibitors versus chemotherapy; and BRAF plus MEK inhibitors versus BRAF inhibitors) (Figure 6).

A comparison between direct and indirect evidence (findings of conventional pair-wise meta-analysis versus findings of indirect comparisons generated by network meta-analysis) was feasible only for the anti-PD1 versus anti-CTLA4 monoclonal antibodies comparison. The results showed a good correlation between types of meta-analysis technique: the RR was 0.70 (95% CI 0.54 to 0.91) for conventional meta-analysis and 0.55 (95% CI 0.42 to 0.72) for network meta-analysis (ratio of ratio = 1.27, low risk of loop inconsistency). However, when we looked at the overall network inconsistency, we found a highly statistically significant inconsistency (treatment by design interaction model P = 0.001), which undermines the reliability of the following findings regarding indirect comparisons (Figure 7):

1. Compared to chemotherapy, both anti-CTLA4 monoclonal antibodies (RR 1.65, 95% CI 1.09 to 2.49; very low-quality evidence; downgraded due to inconsistency, imprecision and indirectness) and combination of immune checkpoint inhibitors (RR 3.49, 95% CI 2.12 to 5.77; moderate-quality evidence, downgraded due to indirectness) increased toxicity. Combination of small-molecule targeted drugs did not significantly differ from chemotherapy (very low-quality evidence; downgraded due to inconsistency, imprecision and indirectness).
2. None of BRAF inhibitors (very low-quality evidence; downgraded due to inconsistency, imprecision and indirectness), combination of small-molecule targeted drugs (very low-quality evidence; downgraded due to inconsistency, imprecision and indirectness), biochemotherapy (very low-quality evidence; downgraded due to inconsistency, imprecision and indirectness), or MEK inhibitors (very low-quality evidence; downgraded due to inconsistency, imprecision and indirectness) significantly differed from anti-CTLA4 monoclonal antibodies.
3. Compared to BRAF inhibitors, combination of immune checkpoint inhibitors increased toxicity (RR 2.50, 95% CI 1.20 to 5.20; moderate-quality evidence, downgraded due to indirectness). None of anti-PD1 monoclonal antibodies (very low-quality evidence; downgraded due to inconsistency,

imprecision and indirectness), biochemotherapy (very low-quality evidence; downgraded due to inconsistency, imprecision and indirectness) or MEK inhibitors (very low-quality evidence; downgraded due to inconsistency, imprecision and indirectness) significantly differed from BRAF inhibitors.

4. Compared to anti-PD1 monoclonal antibodies, the combination of immune checkpoint inhibitors increased toxicity (RR 3.83, 95% CI 2.59 to 5.68; moderate-quality evidence, downgraded due to indirectness). None of combination of small-molecule targeted drugs (very low-quality evidence, downgraded due to inconsistency, imprecision and indirectness), biochemotherapy (very low-quality evidence, downgraded due to inconsistency, imprecision and indirectness), or MEK inhibitors (very low-quality evidence, downgraded due to inconsistency, imprecision and indirectness) significantly differed from anti-PD1 monoclonal antibodies.
5. Compared to the combination of small-molecule targeted drugs, the combination of immune checkpoint inhibitors increased toxicity (RR 2.34, 95% CI 1.11 to 4.96; low-quality evidence, downgraded due to inconsistency and indirectness). Neither biochemotherapy (very low-quality evidence, downgraded due to inconsistency, imprecision and indirectness) nor MEK inhibitors (very low-quality evidence, downgraded due to inconsistency, imprecision and indirectness) significantly differed from the combination of small-molecule targeted drugs.
6. Compared to the combination of immune checkpoint inhibitors, biochemotherapy was associated with lower toxicity (RR 0.41, 95% CI 0.24 to 0.71; moderate-quality evidence, downgraded due to indirectness). MEK inhibitors did not significantly differ from the combination of immune checkpoint inhibitors (very low-quality evidence, downgraded due to inconsistency, imprecision and indirectness).
7. MEK inhibitors did not significantly differ from biochemotherapy (very low-quality evidence, downgraded due to inconsistency, imprecision and indirectness).

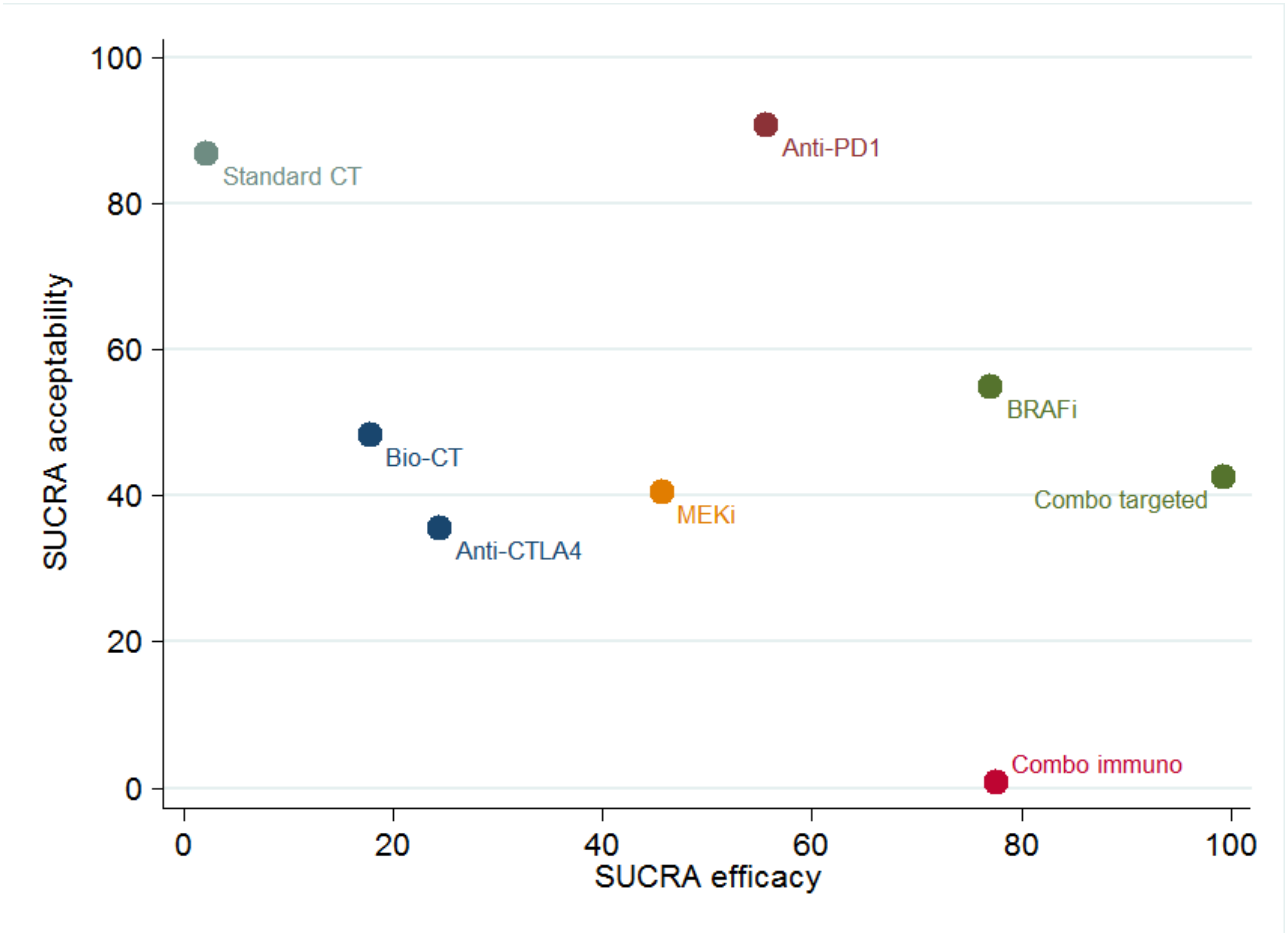
Ranking findings

Results of ranking analysis for progression-free survival (expressed as surface under the cumulative ranking (SUCRA) values, ranging from 0 (worst case) to 1 (best case)) suggested that the combination of BRAF plus MEK inhibitors is the best treatment option (SUCRA: 0.99), followed by BRAF inhibitors (SUCRA: 0.77) and combination of anti-CLA4 plus anti-PD1 monoclonal antibodies (SUCRA: 0.77), anti-PD1 monoclonal antibodies (SUCRA: 0.56), MEK inhibitors (SUCRA: 0.46), anti-CTAL4 monoclonal antibodies (SUCRA: 0.25), biochemotherapy (SUCRA: 0.18), and conventional chemotherapy (SUCRA: 0.02).

Ranking analysis results for (high grade) toxicity suggested that anti-PD1 monoclonal antibodies were associated with the best safety profile (SUCRA: 0.91), followed by chemotherapy (SUCRA: 0.87), BRAF inhibitors (SUCRA: 0.55), biochemotherapy (SUCRA: 48), the combination of BRAF plus MEK inhibitors (SUCRA: 0.42), MEK inhibitors (SUCRA: 0.41), anti-CTLA4 monoclonal antibodies (SUCRA: 0.36), and the combination of anti-CTLA4 plus anti-PD1 monoclonal antibodies (SUCRA: 0.01). However, these results cannot be considered fully reliable due to the finding of network inconsistency as described in the preceding paragraph.

The findings for both efficacy (progression-free survival) and acceptability (inverse of toxicity) were combined together in a bivariate ranking plot. Noticeably, in this plot toxicity is transformed into acceptability by using the inverse values of the corresponding relative risks: therefore, higher values indicate higher acceptability (due to lower toxicity) (Figure 8): accordingly, the ideal treatment (highest performance = best efficacy + best acceptability) should appear in the upper right corner of the plot. The combination of BRAF plus MEK inhibitors was associated with the highest treatment efficacy, but it was also associated with lower acceptability. In contrast, anti-PD1 monoclonal antibodies showed the best acceptability performance, but resulted less effective than the combination of small-molecule targeted drugs. Accordingly, no 'ideal' treatment is available.

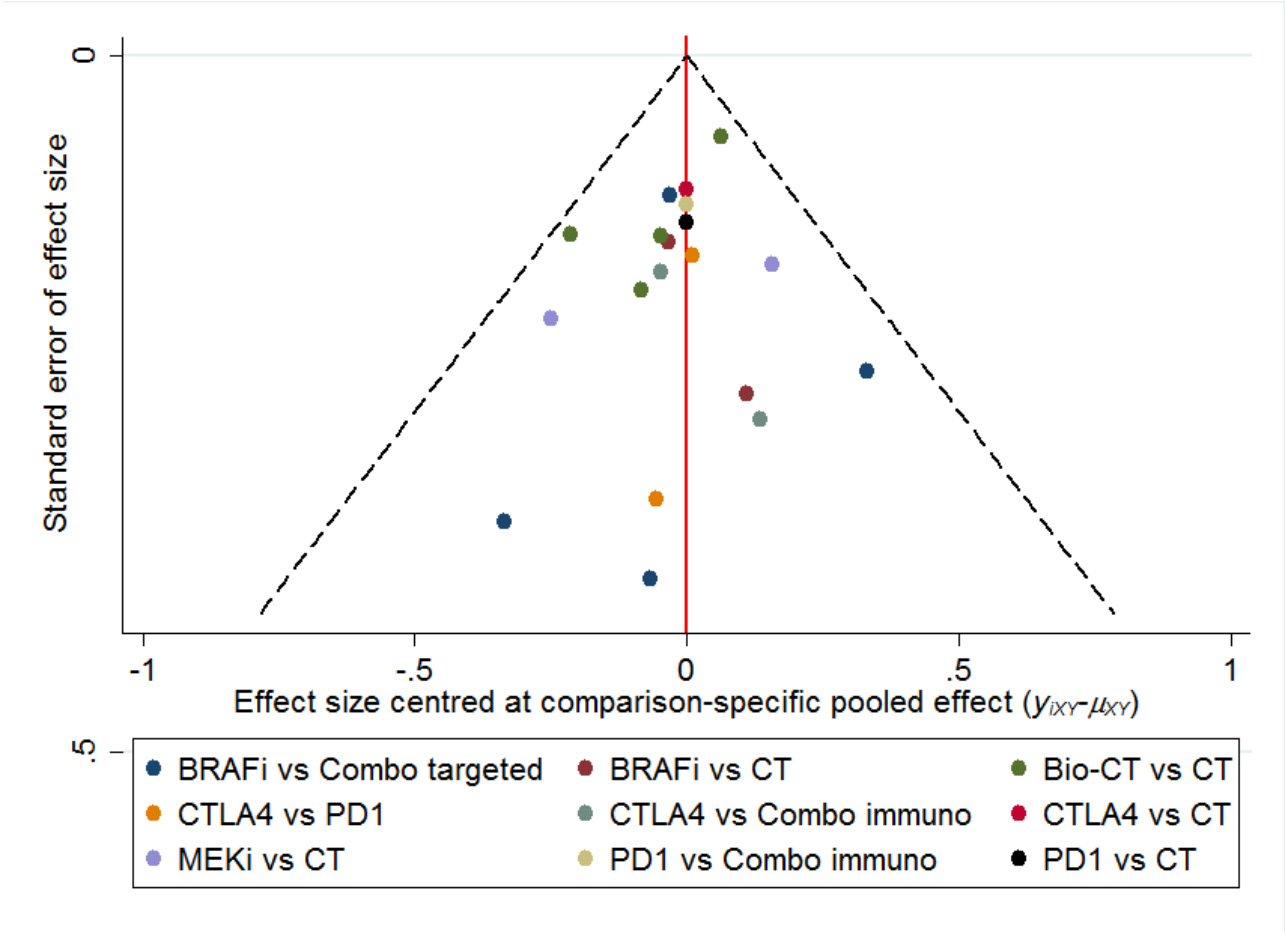
Figure 8. Ranking plot. Ranking plot representing simultaneously the efficacy (progression-free survival) on the *X* axis and the acceptability (the inverse of toxicity) on the *Y* axis. The network included eight treatments for patients with metastatic melanoma. Optimal treatment should be characterised by both high efficacy and acceptability and should be in the right upper corner of this graph.



Quality assessment of trials and evidence grading

None of the studies included in the network meta-analysis presented a severe risk of bias (as described in Risk of bias in included studies). Furthermore, the analysis of the comparison-adjusted funnel plot (a funnel plot specifically adapted for network meta-analysis) did not indicate any evident risk of publication bias (Figure 9). These findings, coupled with the absence of network inconsistency and the lack of violation of the transitivity assumption, enabled us to grade the evidence generated from indirect comparisons for progression-free survival with confidence.

Figure 9. Comparison adjusted funnel plot for network meta-analysis of progression-free survival



In contrast, significant network inconsistency detected during toxicity data analysis add some uncertainty on the findings observed for this outcome.

Other findings

Immunostimulating agents

Immunostimulating agents other than those described above (cytokines (e.g. interferon-alpha and interleukin-2), immune checkpoint inhibitors, bioproducts of bacteria such as BCG and *Cparvum*) have been tested in clinical trials for the treatment of people with metastatic melanoma. In particular, gp100 (a melanoma associated antigen) and granulocyte-macrophage colony stimulating factor (GM-CSF) were administered in association with anti-CTLA4 monoclonal antibody ipilimumab and evaluated in single RCTs (ipilimumab with gp100, Hodi 2010a; ipilimumab plus GM-CSF, Hodi 2014). The gp100 melanoma antigen was also tested in combination with interleukin-2 (Schwartzentruber 2011a). Another agent, thymosin-alpha, was tested in association with interferon and dacarbazine (Maio 2010). In single studies, these combinations, except gp100 plus ipilimumab, resulted in prolonged survival with minimal toxicity. GM-CSF significantly reduced ipilimumab toxicity.

When these findings were combined in a meta-analysis, the addition of immunostimulating agents had an impact on participants' overall survival (Analysis 21.1, HR 0.82, 95% CI 0.67 to 0.99). However, this result was characterised by high between-study heterogeneity (I^2 = 53%). Sensitivity analysis conducted using the leave-one-out procedure suggested that when Hodi 2010a was excluded, heterogeneity dropped to 0% and treatment effect was greater (HR 0.75, 95% CI 0.64 to 0.88): this effect was likely due to adding gp100 to ipilimumab did not add any therapeutic benefit. We also found a non-significant positive effect of immunostimulating agents on progression-free survival (HR 0.92, 95% CI 0.74 to 1.14, Analysis 21.2), although this result did not reach statistical significance and heterogeneity was high (I^2 = 74%). Again, analysis without Hodi 2010a yielded no heterogeneity (I^2 = 0%) and showed a statistically significant progression-free survival advantage (HR 0.82, 95% CI 0.73 to 0.92). Analysis for objective tumour response showed better response rates for combined treatment although with high heterogeneity (RR 1.23, 95% CI 0.60 to 2.50; I^2 = 72%, Analysis 21.3). Unfortunately, we could not identify the source of heterogeneity. Similarly, there was a non-significant reduction in high-grade toxicity (RR 0.92, 95% CI 0.77 to 1.08; I^2 = 45%, Analysis 21.4). We could not identify possible reasons for heterogeneity.

Lenalidomide did not improve tumour response (5.3% versus 5.8%; P = 0.82), time to progression (median 3.0 months versus 2.1 months; P = 0.19), or overall survival (median 5.9 months versus 7.4 months, respectively; P = 0.32) compared to placebo in participants with metastatic melanoma (Eisen 2010).

Taxanes

The taxanes docetaxel and paclitaxel were administered to participants enrolled in the control arm of several studies (Flaherty 2013a; Gupta 2014; Hamid 2014; Hauschild 2009a; Kim 2012; O'Day 2009; O'Day 2013; Weber 2015; Zimpfer-Rechner 2003). Paclitaxel was the experimental treatment in two studies (Bedikian 2011; Hersh 2015) and tested as docosahexaenoic acid-paclitaxel by Bedikian 2011 and nab-paclitaxel by Hersh 2015. Although docosahexaenoic acid-paclitaxel did not impact participant outcomes, nab-paclitaxel improved progression-free survival (the primary study endpoint) compared to dacarbazine (HR 0.79, 95% CI 0.63 to 0.99).

Adjuvant therapies after surgery

Three trials investigated different systemic therapeutic strategies after surgery: chemotherapy with vindesine (Eigentler 2008); chemo-immunotherapy with dacarbazine and *C parvum* (Balch 1984); and a polypeptide vaccine or GM-CSF (Lawson 2015) without showing any difference in either tumour response or prognosis.

DISCUSSION

Summary of main results

This Cochrane Review summarised the available evidence on systemic treatments for people with metastatic melanoma. While effectiveness of conventional chemotherapy alone has never been convincingly proven, our results suggest that more than one treatment is more effective than chemotherapy. For instance, the addition of immunostimulating cytokines (such as interleukin-2 and interferon-alpha) to chemotherapy (biochemotherapy) prolongs progression-free survival (high-quality evidence) (at the cost of higher rates of toxicity (high-quality evidence)), although this result does not translate into a significant overall survival benefit (high-quality evidence) (Summary of findings 9).

In recent years, two new classes of therapeutic agents have been implemented in the clinical setting: immune checkpoint inhibitors (anti-CTLA4 and anti-PD1 monoclonal antibodies) and small-molecule targeted drugs (BRAF and MEK inhibitors), which are active exclusively against BRAF-mutated melanoma. These new treatments have revolutionised the landscape of metastatic melanoma treatment. The results of our meta-analysis showed that when chemotherapy was combined with anti-CTLA4 monoclonal antibodies (ipilimumab and tremelimumab), progression-free survival was likely to be significantly improved compared to chemotherapy alone. However, this benefit is probably associated with higher toxicity rates (moderate-quality evidence) and comparative effectiveness may not translate into a significant overall survival advantage (Summary of findings 3). Compared to conventional chemotherapy, anti-PD1 monoclonal antibodies (nivolumab and pembrolizumab) improved overall survival (high-quality evidence), probably leads to longer progression-free survival (moderate-quality evidence), and may lead to a lower incidence of high-grade toxicity (low-quality evidence) (Summary of findings 1). When comparing both immune checkpoint inhibitors (i.e. anti-PD1 monoclonal antibodies and anti-CTLA4 monoclonal antibodies) against each other, anti-PD1 monoclonal antibodies improved overall survival and progression-free survival more than anti-CTLA4 monoclonal antibodies (both high-quality evidence), and the former may result in better toxicity (low-quality evidence) (Summary of findings 2). Moreover, the combination of anti-PD1 and anti-CTLA4 monoclonal antibodies yielded better results in terms of progression-free survival (high-quality evidence) compared to anti-CTLA4 monoclonal antibodies alone; there may be no significant difference in toxicity (low-quality evidence) (Summary of findings 4). No data for overall survival were available for this comparison.

Among small-molecule targeted drugs, BRAF inhibitors for BRAF-mutated melanoma significantly improved both progression-free survival and overall survival (both high-quality evidence) compared to conventional chemotherapy; there may be no significant difference in toxicity (low-quality evidence) (Summary of findings 5). Compared to chemotherapy, MEK inhibitors for BRAF-mutated melanoma probably increased progression-free survival (moderate-quality evidence), but are likely to have higher toxicity rates (moderate-quality evidence). MEK inhibitors may not significantly improve overall survival (Summary of findings 6). Interestingly, when a BRAF inhibitor was combined with a MEK inhibitor the combination therapy for BRAF-mutated melanoma performed better in terms of overall survival (high-quality evidence) and probably in terms of progression-free survival (moderate-quality evidence) compared to single agent BRAF inhibitor; however, there was likely to be no significant difference in toxicity (moderate-quality evidence) (Summary of findings 7). The results of BRAF inhibitors are exclusively limited to people with a BRAF-mutated melanoma, because this drug class is only active against this type of melanoma.

Chemotherapy combined with anti-angiogenic drugs (bevacizumab and endostar, both of which are recently implemented compounds) may also improve both overall survival (moderate-quality evidence) and progression-free survival (moderate-quality evidence) compared to chemotherapy alone (Summary of findings 8); the combination may have no difference on toxicity (low-quality evidence). Polychemotherapy did not result in significantly better survival (either overall or progression-free survival) than chemotherapy (both high-quality evidence) and probably burdens people being treated with higher toxicity rates (moderate-quality evidence) (Summary of findings 10).

We also conducted a network meta-analysis. The results of the network meta-analysis whose agreed with standard pair-wise meta-analysis results in terms of direct comparisons, and enabled us to make indirect comparisons between treatments not formally compared in clinical trials. Network meta-analysis findings suggested that a combination of BRAF and MEK inhibitors was the most effective treatment strategy for BRAF-mutated melanoma, at least in terms of progression-free survival (Figure 8). However, this combination therapy is burdened by a higher rate of severe toxicity compared to as observed among people treated with the anti-PD1 monoclonal antibodies, which were associated with the best acceptability (Figure 8).

Data on quality of life and costs were quite scarce, so conclusions could be drawn on these concepts (with special regard to the sustainability of newer agents, the cost of which is much higher than conventional chemotherapy agents).

Moreover, future research should focus on direct comparisons of drugs that have not been directly compared in randomised controlled trials (RCTs). The efficacy of combinations of new drug classes such as immune checkpoint inhibitors and small-molecule

targeted drugs (on which no data are yet available) should also be considered.

Overall completeness and applicability of evidence

This Cochrane Review provides an unprecedented overview of systemic treatments for people with metastatic melanoma. Overall, the available evidence was directly relevant and sufficiently comprehensive to appropriately address the review's aims.

Newly introduced classes of drugs (immune check point inhibitors and targeted drugs inhibiting BRAF or MEK) demonstrated significant therapeutic effects. An important aspect to note is that BRAF inhibitors are active only against BRAF-mutated melanoma, which represents roughly half of all metastatic melanoma. Results from our network meta-analysis suggest a combination of BRAF and MEK inhibitors to be the most effective treatment strategy for people with BRAF-mutated melanoma (Figure 8). However, this finding was based on data assessing progression-free survival only and should be confirmed by mature overall survival data.

Longer follow-up periods are needed before similar conclusions could be speculated for overall survival. In particular, data for anti-PD1 monoclonal antibodies combined with anti-CTLA4 agents are not yet sufficiently mature to inform a definitive overall survival analysis. The relatively short follow-up periods of trials reporting on immune checkpoint inhibitors and small-molecule targeted drugs are presented in Characteristics of included studies: long-term outcomes from these trials should improve the applicability of study results. In the meantime, because progression-free survival correlates well with overall survival (at least in the metastatic setting), and is therefore considered to be a reliable surrogate for overall survival (which is why many anticancer drugs are approved for clinical use worldwide on the basis of progression-free survival data only), our results provide useful information to make a reasonably reliable judgement on the usefulness of these therapies for the treatment of people with metastatic melanoma.

Data on quality of life and costs were very limited so conclusions could not be drawn. In particular, cost-effectiveness of new therapies is yet to be determined for metastatic melanoma (Cashin 2008). As a result, it is unclear how treatment for people living with melanoma can be sustained, particularly from a global point of view (Wise 2016).

Quality of the evidence

The available evidence (based on findings from 122 RCTs that involved 28,561 participants) on systemic treatments for people with metastatic melanoma informed identification of effective classes of drugs for improving objective tumour response, progression-free survival and overall survival.

Overall, the risk of bias of included studies can be considered as limited. Considering the 122 included studies and the seven bias domains assessed, we performed 854 evaluations (Figure 4): only seven evaluations (< 1%) assigned high risk of bias for six trials (Beretta 1976; Carvajal 2014; Hamid 2014; Hofmann 2011; Ranson 2007; Richtig 2004). Of note, none of the six high risk of bias trials were included in meta-analyses or contributed to any conclusions on treatment efficacy. We assessed that only 21 studies (17%) were at low risk of bias for all domains (Bedikian 2006; Cui 2013; Eisen 2010; Flaherty 2012b; Flaherty 2013a; Glaspy 2009; Hauschild 2009a; Hersh 2015; Hodi 2010a; Larkin 2015; Lawson 2015; Long 2015; McDermott 2008; O'Day 2013; Ribas 2015; Robert 2013; Robert 2015a; Schadendorf 2006; Schwartzentruber 2011a; Weber 2015; Wolchok 2010). We assessed a further 22 trials (18%) at low risk of bias for four domains and one domain at unclear risk of bias (Atkins 2008; Bajetta 2006a; Bedikian 2011; Chiarion-Sileni 2011; Eigentler 2008; Gupta 2014; Hauschild 2001; Hauschild 2012; Hodi 2014; Kaufmann 2005; Keilholz 2005; Larkin 2014; Maio 2010; McArthur 2014; Middleton 2007; Middleton 2015; O'Day 2009; Patel 2011; Ribas 2013; Robert 2015; Robert 2015b; Testori 2008). Most included studies (n = 73, 60%) were assessed at unclear risk of bias for two or more domains. Because uncertainty was mainly sustained by lack of information provided in study reports, our findings underscore the importance of mandating key information as a requirement for publishing trial results (and exploiting online repositories for supplemental material). This recommendation has been made many times by international guidelines, such as the CONSORT group (Schulz 2010).

GRADE assessment showed that most evidence was high- to moderate-quality for three of four outcomes (overall survival, progression-free survival and tumour response). GRADE evaluations of overall survival indicated high-quality evidence in 50% (9/18) assessments; moderate-quality evidence in four (22%) and low-quality evidence in five (28%) assessments. GRADE evaluations for progression-free survival indicated high-quality evidence in 35% (6/17) assessments; moderate-quality evidence in eight (47%) and low-quality evidence in five (18%) assessments. Assessment for tumour response found high-quality evidence in 42% (8/19) assessments; moderate-quality evidence for 53% (10/19) and low-quality evidence in one (5%) assessment. In contrast, evidence for toxicity was mainly moderate- to low-quality: only one of 16 evaluations was high quality (6%); moderate quality in 59% (8/16) and low-quality in 44% (7/16) assessments. The main reasons for downgrading evidence were inconsistency of findings (remarkable between-study heterogeneity) and imprecision of the effect estimate (mostly linked to confidence intervals including both a meaningful effect and a small/null effect or even a meaningful opposite effect). Of note, we could not find reasonable sources of between-study heterogeneity, and the definition of heterogeneity itself was limited by the often low number of studies available for each comparison and outcome. Formal assessment of publication bias was rarely feasible due to the few studies available for each comparison and outcome (mostly fewer than 10).

Limitations exist when investigating toxicity across trials because this is often reported as incidence of a given event (i.e. rates of study participants who developed an adverse event). consequently, the overall rate of participants who experienced toxicity (and its grade) was missing from several studies. Meta-analyses of toxicity are characterised by relevant heterogeneity, suggesting challenges in toxicity reporting.

Although eligible trials have similar inclusion criteria, some differences do exist, as shown in the Characteristics of included studies tables. In studies investigating small-molecule targeted drugs, all participants had BRAF mutated melanoma, but some studies testing immune checkpoint inhibitors enrolled both BRAF mutated and BRAF wild type melanomas, although participants with BRAF mutated disease were in the minority (Larkin 2014; Postow 2015). Theoretically, this may introduce bias when results of targeted therapy and immunotherapy were compared in the network meta-analysis: people with or without this mutation may

have an intrinsically different natural history. However, it should be noted that the association between BRAF mutational status and patient prognosis is quite controversial (Edlundh-Rose 2006; Long 2011; Meckbach 2014), which may minimises this risk of bias.

Criteria for inclusion of participants with brain metastases differed across trials. People with brain metastases were generally excluded or included only if no active disease was evident at imaging evaluation three months after brain treatment. However, both targeted drugs (Long 2012a) and immune checkpoint inhibitors (Di Giacomo 2012; Margolin 2012) have demonstrated therapeutic activity in this particular subgroup of people with advanced disease, although immune checkpoint inhibitor treatment showed little or no activity in those who were symptomatic.

As expected, the quality of evidence for network meta-analysis findings was generally lower than observed in direct comparison meta-analysis due to intrinsic indirectness (which was a reason for downgrading shared for all evaluations). GRADE assessment for progression-free survival found that 43% (9/21) provided moderate-quality evidence, 5% (1/21) provided low-quality evidence and 52% (11/21) provide very low-quality evidence. In line with evidence quality assessment in direct comparisons, quality of evidence for toxicity was lower than observed for efficacy outcomes. Most GRADE evaluations yielded low- (1/21, 5%) and very low-quality evidence (16/20, 76%); only 19% (4/21) of evaluations found moderate-quality evidence.

In many cases, trials were sponsored by pharmaceutical companies producing the tested drug: this was especially true for new classes of drugs, such as immune checkpoint inhibitors and small-molecule targeted drugs.

Potential biases in the review process

Our literature search was likely to detect all relevant randomised controlled trials. Nevertheless, it is always possible that we overlooked some potentially relevant trials; moreover, it is possible that some trials have not been indexed by the databases searched. However, the main conclusions of this review were based on trials that will be widely and well known by melanoma experts worldwide. Therefore, the included studies should represent the current knowledge in this field of cancer medicine reasonable well.

We did not contact the contact relevant individuals and organisations for information about unpublished or ongoing studies. There is a chance that some ongoing studies may have been completed and results may be available.

Agreements and disagreements with other studies or reviews

The present review had wider selection criteria compared to previous Cochrane Reviews on treatments for metastatic melanoma that investigated the effectiveness of chemotherapy (Crosby 2000) and biochemotherapy (Sasse 2007). Crosby 2000 aimed to assess whether conventional chemotherapy was superior to placebo (or best supportive care), but findings were inconclusive because no RCTs addressing this issue were found by the authors. In the present review, there was no formal evidence of superiority for chemotherapy compared to best supportive care or placebo, although this information was based on the findings of one study (Eisen 2010). Chemotherapy (with special regard to dacarbazine) has been the reference treatment in several contemporary trials testing new agents: our analysis showed that biochemotherapy, immune checkpoint inhibitors and small-molecule targeted drugs are more effective or likely to be more effective than conventional chemotherapy in terms of progression-free survival (Figure 8), and that the anti-PD1 antibodies (immune checkpoint inhibitor) and BRAF inhibitors (small-molecule targeted drugs) performed better than chemotherapy in terms of overall survival. Therefore, although it remains unclear whether or not chemotherapy is beneficial for people with metastatic melanoma, we can state that treatments which are more effective than chemotherapy are available currently.

Two previous reviews could not demonstrate that biochemotherapy was more effective than chemotherapy alone (Ives 2007; Sasse 2007). In this review, we found that biochemotherapy impacted favourably on participant progression-free survival. Both Ives 2007 and Sasse 2007 included fewer studies than this review; furthermore, they used number of events at fixed time points (using relative risks or odds ratios as effect measures), which we consider a non optimal way of analysing time to event (survival) data (we expressed survival data as hazard ratios).

Some network meta-analyses have been published recently on the treatment of metastatic melanoma. These have focused on the most recent therapeutic developments in this field, that is, the implementation of immune checkpoint inhibitors (anti-CTLA4 and anti-PD1 monoclonal antibodies) and small-molecule targeted drugs (BRAF and MEK inhibitors). Devji 2017 limited analysis to results obtained for participants with BRAF-mutated melanoma, and Ciren 2016 analysed only tumour response data (no survival data considered). Pasquali 2017 reported on both efficacy (survival) and toxicity findings. The results of all three network meta-analyses agree with our findings and results.

AUTHORS' CONCLUSIONS

Implications for practice

Based on network meta-analysis rankings, the review findings support the use of BRAF inhibitors (either alone or combined with MEK inhibitors), and anti-PD1 monoclonal antibodies (either alone or combined with anti-CTLA4 monoclonal antibodies) as effective treatments for people with metastatic melanoma in terms of progression-free survival, with consideration of the following.

1. BRAF inhibitors are effective only in people with BRAF-mutated melanoma;
2. BRAF inhibitors combined with MEK inhibitors are the most effective regimen in people with BRAF-mutated melanoma (at least in terms of progression-free survival); and
3. anti-PD1 monoclonal antibodies are the least toxic regimen, but the combination of immune checkpoint inhibitors has highest toxicity.

Implications for research

Randomised controlled trials with longer follow-up periods (12 to 24 months) for participants treated with new therapeutic agents immune checkpoint inhibitors and targeted therapies are needed to assess impact on overall survival. Other outcomes that need to be assessed include quality of life and issues relating to health economics, such as cost-effectiveness. More research is also required to test whether combinations of these therapies

or their sequential use can increase their effectiveness. This is particularly important for people with BRAF-mutated melanoma who can benefit from both BRAF inhibitors with or without MEK inhibitors and immune checkpoint inhibitors.

A common reason for downgrading evidence quality was imprecision: recruiting inadequate numbers of participants was an issue in some of the older included studies. This limitation has been recognised, and trials no longer tend to exhibit this problem. Future published trials should guarantee adequate reporting by adhering to guidelines such as CONSORT.

Identification of biomarkers for guide selection of people most responsive to immune checkpoint inhibitors is of paramount importance and should be intensively investigated.

It is also important to understand whether there is a role for combining traditional biochemotherapy (based on interleukin-2 and interferon-alpha) with immune checkpoint inhibitors or small-molecule targeted drugs. This issue is being addressed (at least in part) in ongoing trials.

Results of this Cochrane Review found that some drugs which are not currently used in clinical practice, such as anti-angiogenic agents (bevacizumab and endostar), oblimersen, and nab-paclitaxel, deserve further investigation to determine whether or not they can be added to the armamentarium of therapeutic interventions suitable to fight metastatic melanoma. Immune-stimulating agents, such as gp100 and GM-CSF, which can enhance the effectiveness of immune checkpoint inhibitors in the second-line setting, should be tested as first-line treatments to assess their clinical value as upfront therapy.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Agarwala 1999

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study. Single centre trial.
Participants	Untreated metastatic melanoma. Participants randomised: 56.
Interventions	**Two-arm trial:** • *Chemotherapy and tamoxifen:* Carboplatin 300 mg/m^2 IV and dacarbazine 1000 mg/m^2 IV on Day 1 every 4 weeks for at least 2 cycles to disease progression, tamoxifen 20 mg/day orally throughout the treatment period (N = 28); • *Chemotherapy:* Carboplatin 300 mg/m^2 IV and dacarbazine 1000 mg/m^2 IV on day 1 every 4 weeks for at least 2 cycles to disease progression (N = 28).
Outcomes	Progression-free survival. Overall survival. Tumour response.

Agarwala 1999 *(Continued)*

	Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: included. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomized". Comment: There was insufficient information about the sequence generation process to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and the outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Selective reporting (reporting bias)	Unclear risk	There was insufficient information to permit judgment.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Agarwala 2002

Study characteristics

Methods	Phase III parallel-group RCT. Open label study. Multicentre trial.
Participants	Untreated and previously treated metastatic melanoma. Participants randomised: 305.
Interventions	Two-arm trial:

Agarwala 2002 *(Continued)*

- IL-2 9 MIU/m² twice daily SC on days 1 to 2 of weeks 1 and 3, and 2 MIU/m² twice daily SC on days 1 to 5 of weeks 2 and 4 administered for 4 weeks of a 6-week cycle, plus histamine 1.0 mg twice daily SC on days 1 to 5 of weeks 1 to 4 for up to 8 cycles (12 months) (N = 153);
- IL-2 9 MIU/m² twice daily SC on days 1 to 2 of weeks 1 and 3, and 2 MIU/m² twice daily SC on days 1 to 5 of weeks 2 and 4 administered for 4 weeks of a 6-week cycle (N = 152).

Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: reported in a separate analysis (Beusterien 2003). The addition of subcutaneous histamine dihydrochloride to IL-2. treatment improved median quality-adjusted survival duration and did not adversely affect QoL. Participants with brain metastasis: included. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation
Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Selective reporting (reporting bias)	Unclear risk	Published reports include all expected outcomes. However, no protocol is available and thus it is unclear if all planned outcomes are reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Atkins 2008

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study. Multicentre trial.
Participants	Untreated metastatic melanoma. Participants randomised: 395.
Interventions	Two-arm trial: • Chemotherapy: Cisplatin IV daily on days 1 to 4, vinblastine IV daily on days 1 to 4, dacarbazine on day 1 only (N = 195); • Biochemotherapy: Cisplatin IV on days 1 to 4, vinblastine IV on days 1 to 4, dacarbazine on day 1 only, IL-2 IV daily on days 1 to 4, and IFN SC days 1 to 5 and on days 8, 10, and 12 (N = 200).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not reported. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Based on permuted blocks within strata, with dynamic balancing within main institutions and their affiliate networks". Comment: This method ensured low risk of selection bias
Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgement.
Incomplete outcome data (attrition bias)	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.

Atkins 2008 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Atzpodien 2002

Study characteristics

Methods	Phase III parallel-group RCT. Open label study. Multicentre trial.
Participants	Untreated and previously treated metastatic melanoma. Participants randomised: 124.
Interventions	Two-arm trial: • cisplatin 35 mg/m², IV, days 1 to 3, carmustine 150 mg/m², IV, day 1, cycles 1 and 3 only, dacarbazine 220 mg/m², IV, days 1 to 3, oral tamoxifen 20 mg/m², daily, IL-2 10x10^6 IU m/2, days 3 to 5, week 4; 5x10^6 IU m², days 1, 3, 5, week 5, and IFN-α 5x10^ IU (N = 64); • cisplatin 35 mg/m², IV, days 1 to 3, carmustine 150 mg/m², IV, day 1, cycles 1 and 3 only, dacarbazine 220 mg/m², IV, days 1 to 3, oral tamoxifen 20 mg/ m², daily)m/2, day 1, week 4; days 1, 3, 5, week 5 (N = 60).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: 12.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.
Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.
Blinding of participants and personnel (performance bias)	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention

Atzpodien 2002 *(Continued)*

All outcomes		was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Two patients were randomized, but did not receive therapy and were evaluated as progressive disease". Comment: There was insufficient information about completeness of outcome data to permit judgement.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Avril 2004

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study. Multicentre trial.
Participants	Untreated metastatic melanoma. Participants randomised: 229.
Interventions	Two-arm trial: • Fotemustine 100 mg/m^2 weekly for 3 consecutive weeks (days 1, 8, and 15) followed by a 5-week rest period (N = 112); • Dacarbazine 250 mg/m^2 daily for 5 days every 4 weeks (N = 117).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: no significant difference was observed between treatment arms. Participants with brain metastasis: included. Median follow-up: not available.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Avril 2004 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned". Comment: Risk was likely low because this was a multicentre trial with centralised randomisation.
Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "An independent centralized radiologic committee (two radiologists not involved in the study) performed a blinded review of all radiologic files of patients who had CR, PR, or stable disease on the investigator's evaluation. Imaging of patients declared progressive disease (PD) as a best response were not reviewed." Comment: It was unclear if this method was sufficient to ensure low risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced in across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Bafaloukos 2005

Study characteristics	
Methods	Phase II parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Participants randomised: 132.
Interventions	Two-arm trial: • Temozolomide 200 mg/m^2/day orally on days 1 to 5 every 4 weeks (N = 66); • Temozolomide 200 mg/m^2/day orally on days 1 to 5 and cisplatin 75 mg/m^2 IV on day 1 every 4 weeks (N = 66).
Outcomes	Progression-free survival. Overall survival. Tumour response.

Bafaloukos 2005 *(Continued)*

	Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised". Comment: There was insufficient information about the sequence generation process to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Bajetta 1985

Study characteristics

Methods	Phase II parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Participants randomised: 37.
Interventions	Two-arm trial: • Vindesine 3 mg/m^2 IV day 1, cisplatin 80 mg/m^2 IV day 2, etoposide 80 mg/m^2 IV days 1 to 3 (N = 18);

Bajetta 1985 *(Continued)*

	• Vindesine 3 mg/m² IV day 1, cisplatin 80 mg/m² IV day 2, lomustine 80 mg/m² IV day 1 (N = 19).
Outcomes	Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not reported. Quality of life: not reported. Participants with brain metastasis: not reported. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomization". Comment: There was insufficient information to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Selective reporting (reporting bias)	Unclear risk	There was insufficient information to permit judgment.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Bajetta 1994

Study characteristics

Methods	Phase III parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Participants randomised: 266.

Bajetta 1994 *(Continued)*

Interventions	Three-arm trial: • Dacarbazine 800 mg/m² IV days 1 and 21 (N = 82); • Dacarbazine 800 mg/m² IV days 1 and 21 plus IFN-α2a 3 mlU IM days 1 to 3 and 6 mlU days 4 to 6, and 9 mIU daily thereafter (N = 76); • Dacarbazine 800 mg/m² IV days 1 and 21 plus IFN-α2a 3 mlU IM 3 times weekly (N = 84).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: 36.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...randomization". Comment: There was insufficient information to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Selective reporting (reporting bias)	Unclear risk	There was insufficient information to permit judgment.
Other bias	Unclear risk	There was insufficient information to permit judgment.

Bajetta 2006a

Study characteristics

Bajetta 2006a *(Continued)*

Methods	Phase III parallel-group RCT. Open label study. Multicentre trial.
Participants	Untreated metastatic melanoma. Participants randomised: 151.
Interventions	Two-arm trial: • Chemotherapy: cisplatin 30 mg/m^2 IV on days 1 to 3, vindesine 2.5 mg/m^2 IV on day 1 only, dacarbazine 250 mg/m^2 IV on days 1 to 3 every 3 weeks for 6 cycles (N = 75); • Biochemotherapy: cisplatin 30 mg/m^2 IV on days 1 to 3, vindesine 2.5 mg/m^2 IV on day 1 only, dacarbazine 250 mg/m^2 IV on days 1–3, IL-2 mIU/day SC on days 1 to 5 and 8 to 15, IFN-α 5 mU/m^2 SC on days 1 to 5 every 3 weeks for 6 cycles (N = 76).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: allowed at disease progression. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized". Comment: Risk was likely low because this was a multicentre trial with centralised randomisation.
Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.

Bajetta 2006a *(Continued)*

Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Balch 1984

Study characteristics

Methods	Phase III parallel-group RCT. Open label study.
Participants	Resected advanced regional and distant metastasis from cutaneous melanoma. Number of participants: 136.
Interventions	Two-arm trial: • Chemo-immunotherapy: Dacarbazine and cyclophosphamide 600 mg/m^2 IV every 3 weeks for 9 cycles plus *C parvum* 4 mg/m^2 in 1 to 2 week cycle (N = 78); • Immunotherapy: *C parvum* 4 mg/m^2 weekly for 13 weeks (N = 78).
Outcomes	Progression-free survival. Overall survival. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: included. Median follow-up: 10 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.

Balch 1984 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	There was insufficient information to permit judgment.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Bedikian 2006

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study. Multicentre trial.
Participants	Untreated metastatic melanoma. Participants randomised: 771.
Interventions	Two-arm trial: • Oblimersen 7 mg/kg daily by continuous IV infusion for 5 days, and dacarbazine 1000 mg/m^2 IV every 3 weeks for up to 8 cycles (N = 386); • Dacarbazine 1000 mg/m^2 IV every 3 weeks for up to 8 cycles (N = 385).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not available (24 months minimum follow-up).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were centrally randomly assigned in a 1:1 ratio in blocks of four". Comment: This method ensured low risk of selection bias.
Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.

Bedikian 2006 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "An independent panel blinded to treatment assignment reviewed all radiologic responses." Comment: outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Bedikian 2011

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study. Multicentre trial.
Participants	Untreated metastatic melanoma. Participants randomised: 393.
Interventions	Two-arm trial: • Docosahexaenoic acid-paclitaxel 900 mg/m^2 IV on day 1 every 3 weeks (N = 194); • Dacarbazine 1000 mg/m^2 IV every 3 weeks for up to 8 cycles (N = 199).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not available.
Risk of bias	

Bedikian 2011 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients meeting the enrollment criteria were randomly assigned in blocks within each country." Comment: This method ensured low risk of selection bias
Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Bellett 1976

Study characteristics	
Methods	Phase II parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Randomised participants: 50.
Interventions	Two-arm trial: • Dacarbazine 2 mg/kg IV daily days 1 to 10 (N = 25); • Carmustine 1.5mg/m^2 IV day 1, vincristine 2 mg/m^2 IV day 1 (N = 25).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: allowed at disease progression. Quality of life: not reported.

Bellett 1976 *(Continued)*

	Participants with brain metastasis: included. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomized". Comment: There was insufficient information to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Selective reporting (reporting bias)	Unclear risk	There was insufficient information to permit judgment.
Other bias	Unclear risk	There was insufficient information to permit judgment.

Beretta 1976

Study characteristics

Methods	Phase III parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Randomised participants: 450.
Interventions	Four-arm study: • Dacarbazine 100 mg/m^2 IV daily days 1 to 5, vincristine 1.4 mg/m^2 IV days 1 and 15, Carmustine 100 mg/m^2 IV day 1 (N = 207); • Dacarbazine 100 mg/m^2 IV daily days 1 to 5, vincristine 1.4 mg/m^2 IV days 1 and 15, hydroxyurea 10 mg/kg IV days 7, 10, 13, 17, 21, 24 (N = 122); • Dacarbazine 100 mg/m^2 IV daily days 1 to 5, actinomycin D 0.05 mg/m^2 IV days 1 and 15, Carmustine 100 mg/m^2 IV day 1 (N = 98); • Dacarbazine 100 mg/m^2 IV daily days 1-5, actinomycin D 0.05 mg/m^2 IV days 1 and 15, Hydroxyurea 10 mg/kg IV days 7, 10, 13, 17, 21, 24 (N = 23).

Beretta 1976 *(Continued)*

Outcomes	Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not reported. Quality of life: not reported. Participants with brain metastasis: included. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomly allocated". Comment: There was insufficient information to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Selective reporting (reporting bias)	High risk	One arm (D) was closed early and participants' data were not analysed.
Other bias	Unclear risk	There was insufficient information to permit judgment.

Carter 1975

Study characteristics

Methods	Phase III parallel-group RCT. Open label study.
Participants	Untreated and previously treated metastatic melanoma. Number of participants:270.
Interventions	Four-arm trial:

Carter 1975 *(Continued)*

- Dacarbazine 4.5 mg/kg IV days 1 to 10 (N = 48);
- Dacarbazine 2.7 mg/kg IV days 1 to 5, lomustine 1.5 mg/kg orally day 2, and vincristine 0.027 mg/kg IV days 1, 5 every 6 weeks (N = 67);
- Dacarbazine 2.7 mg/kg IV days 1 to 5, carmustine 2.0 mg/kg IV day 2, and vincristine 0.027 mg/kg IV days 1, 5 every 6 weeks (N = 64);
- Dacarbazine 2.7 mg/kg IV days 1 to 5, carmustine 2.0 mg/kg IV day 2, and hydroxyurea 30 mg/kg IV days 2, 5, 9, 12, 16, 19 (N = 63).

Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: included. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised". Comment: There was insufficient information to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Selective reporting (reporting bias)	Unclear risk	There was insufficient information to permit judgment.
Other bias	Unclear risk	There was insufficient information to permit judgment.

Carvajal 2014

Study characteristics	
Methods	Phase II parallel-group RCT. Open label study. Multicentre trial.
Participants	Untreated and previously treated metastatic melanoma. Randomised participants: 106.
Interventions	Two-arm trial: • Ramucirumab 10 mg/kg and dacarbazine 1000 mg/m^2 every 3 weeks (N = 52); • Ramucirumab only 10 mg/kg every 3 weeks (N = 50).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Particpants with brain metastasis: excluded. Median follow-up: not available. Note: Both progression-free survival and overall survival appeared longer in the subset of participants who developed an adverse event of hypertension while receiving ramucirumab.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "One hundred and six patients were enrolled and randomised". Comment: Risk was likely low because this was a multicentre trial with centralised randomisation.
Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias)	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.

Carvajal 2014 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	High risk	There was a potential conflict of interest for some authors and the funding body which likely resulted in bias to the study methodology.

Chapman 1999

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study. Multicentre trial.
Participants	Untreated metastatic melanoma. Number of randomised participants: 240.
Interventions	Two-arm study: • *Polychemotherapy (Dartmouth regimen):* Dacarbazine 220 mg/m^2 IV and cisplatin 25 mg/m^2 IV days 1 to 3, carmustine 150 mg/m^2 IV day 1 every other cycle, and tamoxifen 10 mg orally twice daily every 3 weeks (N = 119); • *Single agent chemotherapy:* Dacarbazine 1000 mg/m^2 IV every 3 weeks (N = 121).
Outcomes	Overall survival. Tumour response. Toxicity.
Notes	Cross-over: cross-over to polychemotherapy was allowed at disease progression. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized". Comment: Risk was likely low because this was a multicentre trial with centralised randomisation.
Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not af-

Chapman 1999 *(Continued)*

		fect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Chauvergne 1982

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Randomised participants: 51.
Interventions	Two-arm study: • *Polychemotherapy:* Dacarbazine 250 mg/m^2 IV over 4 days every 3 weeks and detorubicin 120 mg/m^2, IV every 3 weeks (N = 23); • *Single-agent dacarbazine:* Dacarbazine 250 mg/m^2, IV, over 4 days every three weeks (N = 27).
Outcomes	Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Particpants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised". Comment: There was insufficient information about the sequence generation process to permit judgment.

Chauvergne 1982 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Chiarion Sileni 2001

Study characteristics	
Methods	Phase II parallel-group RCT. Open label study.
Participants	Untreated and previously treated metastatic melanoma. Participants randomised: 60.
Interventions	Two-arm trial: • Carmustine 150 mg/m^2 IV on day 1, dacarbazine 220 mg/m^2 IV daily on days 1 to 3, cisplatin 25 mg/m^2 IV daily on days 1 to 3, and tamoxifen 160 mg orally daily for 7 days before chemotherapy; the cycle was repeated every 4 weeks, with BCNU given every two cycles (N = 41); • Dacarbazine 1200 mg/m^2 IV on day 1 repeated every 3 weeks (N = 19).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: 31 months.

Chiarion Sileni 2001 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomized". Comment: There was insufficient information about the sequence generation process to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol (provided by the trial principal investigator) and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Chiarion-Sileni 2011

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study. Multicentre trial.
Participants	Untreated and previously treated metastatic melanoma. Participants randomised: 149.
Interventions	Two-arm trial: • Cisplatin 75 mg/m^2 IV on day 1 IL-2 3,000,000 IU SC twice daily from days 9 to 17, G-CSF 300 mg SC daily from days 6 to 12, temozolomide 200 mg/m^2 daily for 5 days every 4 weeks (N = 74); • Cisplatin 75 mg/m^2 IV on day 1, IL-2 3,000,000 IU SC twice daily from days 9 to 17, G-CSF 300 mg SC daily from days 6 to 12, dacarbazine 800 mg/m^2 IV on day 1 every 4 weeks (N = 75).
Outcomes	Incidence of CNS metastasis. Progression-free survival.

Chiarion-Sileni 2011 *(Continued)*

	Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: 46 weeks.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was performed centrally... using a minimisation method". Comment: randomisation method was adequate
Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol (provided by the trial principal investigator) and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Clunie 1980

Study characteristics

Methods	Phase II parallel-group RCT. Open label study.
Participants	Metastatic melanoma not previously treated with either Dacarbazine or C. parvum. Randomised participants: 49.

Clunie 1980 *(Continued)*

Interventions	Two-arm trial: • Chemotherapy: Dacarbazine 2.5 mg/kg IV daily for 5 days every 3 weeks (N = 27); • Chemo-immunotherapy: Dacarbazine 2.5 mg/kg IV daily for 5 days, *C parvum* 7 mg IM 1 week before starting dacarbazine and every 4 weeks thereafter (N = 22).
Outcomes	Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not reported. Quality of life: not reported. Participants with brain metastasis: included. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization data". Comment: There was insufficient information to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Cocconi 1992

Study characteristics

Methods	Phase III parallel-group RCT.

Cocconi 1992 *(Continued)*

	Open label study.
Participants	Metastatic melanoma not previously treated with either tamoxifen or dacarbazine. Randomised participants: 117.
Interventions	Two-arm trial: • Dacarbazine 250 mg/m^2 IV daily for 5 days every 3 weeks (N = 52); • Dacarbazine 250 mg/m^2 IV daily for 5 days every 3 weeks, tamoxifen 20 mg/m^2 orally (N = 60).
Outcomes	Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not reported. Quality of life: not reported. Participants with brain metastasis: included. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The allocation was made on the basis of randomly permuted blocks of two within strata". Comment: Randomisation method was adequate.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Cocconi 2003

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Randomised participants: 125.
Interventions	Two-arm trial: • Dacarbazine 250 mg/m² IV daily for 5 days every 3 weeks, tamoxifen 20 mg/m² orally (N = 57); • Vindesine 3 mg/m² IV weekly for 6 weeks, then every 2 weeks, tamoxifen 20 mg/m² orally (N = 59).
Outcomes	Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not reported. Quality of life: not reported. Participants with brain metastasis: included. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The allocation was made on the basis of randomly permuted blocks of two within strata". Comment: Randomisation method was adequate.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.

Cocconi 2003 *(Continued)*

Other bias	Low risk	The study appeared to be free of other sources of bias.

Costanza 1972

Study characteristics	
Methods	Phase II parallel-group RCT. Open label study.
Participants	Previously treated (no treatment in the previous 4 weeks) and untreated metastatic melanoma. Participants randomised: 140.
Interventions	Two-arm trial: • *Polychemotherapy:* Dacarbazine 100 mg/m² IV daily on days 1 to 5 and carmustine 75 mg/m² IV daily on days 1 to 2 every 30 days for 2 cycles (N = 65); • *Single agent chemotherapy:* Dacarbazine 100 mg/m² IV daily on days 1 to 5 every 30 days for 2 cycles (N = 77).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly allocated". Comment: There was insufficient information about the sequence generation process to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias)	Unclear risk	There was insufficient information to permit judgment.

Costanza 1972 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Costanza 1977

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Randomised participants: 415.
Interventions	Three-arm trial: • Dacarbazine 200 mg/m^2 IV for 5 days repeated every 3 weeks (N = NA); • Methyl-CCNU 200 mg/m^2 orally once every 6 weeks (N = NA); • Dacarbazine 150 mg/m^2 IV for 5 days every 3 weeks and methyl-CCNU 130 mg/m^2 orally once every 6 weeks (N = NA).
Outcomes	Overall survival. Tumour response. Toxicity.
Notes	Cross-over: allowed at disease progression. Quality of life: not reported. Participants with brain metastasis: included. Median follow-up: not available.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not af-

Costanza 1977 *(Continued)*

		fect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Costanzi 1982

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Particpants randomised: 286.
Interventions	Three-arm trial: • Polychemotherapy: Carmustine 150 mg/mm^2 orally day 1 every other course, hydroxyurea 1500 mg/m^2 IV days 1 to 5 orally, and dacarbazine 150 mg/mm^2 IV on days 1 to 5 (N = 95); • Polychemotherapy + immunotherapy: Carmustine 150 mg/mm^2 orally day 1 every other course, hydroxyurea 1500 mg/m^2 IV days 1 to 5 orally, and dacarbazine 150 mg/mm^2 IV days 1 to 5 BCG in 1 mL of fluid, by scarification on days 7, 14, 21 (N = 161); • Monochemotherapy + immunotherapy: Dacarbazine 250 mg/mm^2 IV days 1 to 5, BCG in 1 mL of fluid, by scarification on days 7, 14, 21 (N = 130).
Outcomes	Overall survival. Tumour response. Toxicity.
Notes	Cross-over: was not allowed at disease progression. Quality of life: not reported. Participants with brain metastasis: included. Median follow-up: not available.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomized".

Costanzi 1982 *(Continued)*

		Comment: There was insufficient information to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Selective reporting (reporting bias)	Unclear risk	There was insufficient information to permit judgment.
Other bias	Unclear risk	There was insufficient information to permit judgment.

Cui 2013

Study characteristics	
Methods	Phase II parallel-group RCT. Double-blind study.
Participants	Untreated metastatic melanoma harbouring no mutations in KRAS, NRAS, BRAF, or c-kit genes. Participants randomised: 114.
Interventions	Two-arm trial: • Dacarbazine 250 mg/m² IV daily on days 1 to 5 and endostar 7.5 mg/m² IV daily on days 1 to 14 every 3 weeks up to 12 cycles (N = 57); • Dacarbazine 250 mg/m² IV daily on days 1 to 5 (N = 57).
Outcomes	Overall survival. Progression-free survival. Tumour response. Toxicity.
Notes	Cross-over: not reported. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not available.

Cui 2013 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Simple stratified randomization with permuted blocks of size 2 was used to create a prospective randomization schedule". Comment: Randomisation method was adequate.
Allocation concealment (selection bias)	Low risk	Quote: "Random assignment of patients was performed by designated personnel at each participating site in a double-blind fashion such that the investigator and patient did not know the treatment assignment" Comment: Allocation was likely concealed.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind". Comment: This method ensured low risk of performance bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double-blind". Comment: This method ensured low risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Danson 2003

Study characteristics	
Methods	Phase II parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Number of participants: 181.
Interventions	Three-arm trial: • Temozolomide 200 mg/m^2 orally at 8-hour intervals, 5 doses every 4 weeks (N = 59); • Temozolomide 200 mg/m^2 orally once daily for 5 days, IFN-α-2b 5 mIU SC every Monday, Wednesday, and Friday for 5 doses every 4 weeks (N = 62); • Temozolomide 150 mg/m^2 orally once daily for 5 days, thalidomide 100 mg given orally once daily for 28 doses every 4 weeks (N = 60).
Outcomes	Progression-free survival. Overall survival.

Danson 2003 *(Continued)*

	Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: no significant difference was noted between arms. Participants with brain metastasis: included. Median follow-up: 6 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned, using permuted blocks". Comment: Randomisation method was adequate.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Daponte 2013

Study characteristics

Methods	Phase III parallel-group RCT. Open label study. Multicentre trial.
Participants	Untreated metastatic melanoma. Participants randomised: 260.
Interventions	Four arm trial:

Daponte 2013 *(Continued)*

- Fotemustine 100 mg/m² IV on day 1 and dacarbazine 900 mg/m² IV on day 2 every 3 weeks (N = 67);
- Fotemustine 100 mg/m² IV on day 1 and dacarbazine 900 mg/m² IV on day 2 every 3 weeks and IFN-α 5 mUI 3 times per week; (N = 69);
- Dacarbazine 900 mg/m² IV every 3 weeks (N = 71);
- Dacarbazine 900 mg/m² IV every 3 week and IFN-α 5 mUI 3 times per week; (N = 62).

Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: included. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized through a computerized procedure of permuted blocks centralized at the coordinating center" Comment: Randomisation method wad adequate.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Dorval 1999

Study characteristics

Dorval 1999 *(Continued)*

Methods	Phase III parallel-group RCT. Open label study. Multicentre trial.
Participants	Untreated and previously treated metastatic melanoma. Number of participants: 117.
Interventions	Two-arm trial: • Cisplatin 100 mg/m^2 day 1, IL-2 18x10^6 IU/m^2/day IV from day 3 to 6 and 17 to 21 repeated for 3 cycles (N = 49); • Cisplatin 100 mg/m^2 day 1, IL-2 18x10^6 IU/m^2/day IV from day 3 to 6 and 17 to 21, IFN-α 9x10^6 IU/m^2 3 days per week repeated for 3 cycles (N = 52).
Outcomes	Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not reported. Quality of life: not reported. Participants with brain metastasis: included. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized". Comment: Risk was likely low because this was a multicentre trial with centralised randomisation.
Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.

Dorval 1999 *(Continued)*

Other bias	Low risk	The study appeared to be free of other sources of bias.

Dummer 2006

Study characteristics	
Methods	Phase I-II parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Participants randomised: 150.
Interventions	Three-arm trial: • PEG-IFN 180 µg once weekly for 24 weeks (N = 48); • PEG-IFN 360 µg once weekly for 24 weeks (N = 59); • PEG-IFN 450 µg once weekly for 24 weeks (N = 49).
Outcomes	Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not reported. Quality of life: not reported. Participants with brain metastasis: included.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...randomly assigned patients". Comment: There was insufficient information to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.

Dummer 2006 *(Continued)*

Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Eigentler 2008

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study. Multicentre trial.
Participants	Particpants with metastasised melanoma after complete metastasectomy. Randomised participants: 139.
Interventions	Two-arm trial: • Vindesine 3 mg/kg IV twice a week the first 26 weeks following 3 mg/m^2 every 3 weeks for an additional 26 weeks and finally every 4 weeks for the remaining 52 weeks of the treatment period (N = 69); • Observation (N = 73).
Outcomes	Progression-free survival. Overall survival.
Notes	Cross-over: not reported. Quality of life: evaluation of the quality of life was insufficient because of the low feedback rate of the questionnaires. Participants with brain metastasis: not reported. Median follow-up: 46 months.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "...permuted block (size 12) randomization list" Comment: Randomisation method was adequate.
Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias)	Unclear risk	There was insufficient information to permit judgement.

Eigentler 2008 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Eisen 2010

Study characteristics	
Methods	Phase II/III parallel-group RCT. Double-blind study. Multicentre trial.
Participants	Previously treated metastatic melanoma. Participants randomised: 306.
Interventions	Two-arm trial: • Lenalidomide 25 mg orally days 1 to 21 of a 28-day cycle (N = 152); • Placebo (N = 154).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not reported. Quality of life: not investigated. Participants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized using an interactive voice response system". Comment: Risk was likely low because this was a multicentre trial with centralised randomisation.
Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.

Eisen 2010 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind". Comment: This method makes low the risk of performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double-blind". Comment: This method makes low the risk of detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Eton 2002

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Number of participants: 183.
Interventions	Two-arm trial: • Chemotherapy: cisplatin 20 mg/m^2 on days 1 to 4 and 22 to 25, vinblastine 2 mg/m^2 on days 1 to 4 and 22-25, and dacarbazine 800 mg/m^2 on days 1 and 22, 2 x 21-day cycles over a 6-week period (N = 92); • Biochemotherapy: cisplatin 20 mg/m^2 on days 1 to 4 and 22 to 25, vinblastine 1.5 mg/m^2 on days 1 to 4 and 22-25, and dacarbazine 800 mg/m^2 on days 1 and 22, IL-2 9 mIU/m^2 24 h continuous infusion on days 5 to 8, 17 to 20, and 26 to 29, and IFN-α 5 mU/m^2 SC on days 5 to 9, 17 to 21, and 26 to 30, 2 x 21-day cycles over a 6-week period (N = 91).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: allowed at disease progression. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: 52 months
Risk of bias	

Eton 2002 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...randomly assigned". Comment: There was insufficient information about the sequence generation process to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was insufficient information to permit judgment.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Falkson 1991

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Participants randomised: 64.
Interventions	Two-arm trial: • Dacarbazine 200 mg/m^2 IV for 5 days every 4 weeks (N = 32); • Dacarbazine 200 mg/m^2 IV for 5 days every 4 weeks started on week 4, IFN-α 15 mU/m^2 IV daily for 5 days per week for 3 weeks and thereafter 10 mU/m^2 3 days per week (N = 32).
Outcomes	Overall survival. Progression-free survival. Tumour response. Toxicity.
Notes	Cross-over: not reported.

Falkson 1991 *(Continued)*

	Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...randomized". Comment: There was insufficient information about the sequence generation process to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Falkson 1995

Study characteristics

Methods	Phase III parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Randomised participants: 73.
Interventions	Two-arm trial: • Dacarbazine 200 mg/m² IV daily days 1 to 5 repeated every 28 days (N = 36); • Dacarbazine 200 mg/m² IV daily days 1 to 5 repeated every 28 days, IFN-α 15x10^6 U/m² 1 day per week for 3 weeks followed by 10x10^6 U/m² SC 3 times per week (N = 36).
Outcomes	Overall survival.

Falkson 1995 *(Continued)*

	Progression-free survival. Tumour response. Toxicity.
Notes	Cross-over: not reported. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...randomized". Comment: There was insufficient information about the sequence generation process to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Falkson 1998

Study characteristics

Methods	Phase III parallel-group RCT. Open label study. Multicentre trial.
Participants	Untreated metastatic melanoma.

Falkson 1998 *(Continued)*

	Participants randomised: 258.
Interventions	Four-arm trial: • Dacarbazine 200 mg/m² IV for 5 days every 4 weeks (N = 69); • Dacarbazine 200 mg/m² IV for 5 days every 4 weeks started on week 4, IFN-α-2b 15 mU/m² IV daily for 5 days per week for 3 weeks and thereafter 10 mU/m² 3 days per week (N = 68); • Dacarbazine 200 mg/m² IV for 5 days every 4 weeks started on week 4, tamoxifen 20 mg orally daily continuously starting day 1 (N = 66); • Dacarbazine 200 mg/m² IV for 5 days every 4 weeks started on week 4, IFN-α-2b 15 mU/m² IV daily for 5 days per week for 3 weeks and thereafter 10 mU/m² 3 days per week, tamoxifen 20 mg orally daily continuously starting day 1 (N = 68).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not reported. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...randomized". Comment: Risk was likely low because this was a multicentre trial with centralised randomisation.
Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Flaherty 2001

Study characteristics	
Methods	Phase II parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Number of randomised participants: 81.
Interventions	Two-arm trial: • Inpatient biochemotherapy: dacarbazine 250 mg/m² IV and cisplatin 25 mg/m² IV daily on days 1 to 3, IFN-α-2b 5 mU/m² SC on days 6, 8, 10, 13, and 15, and IL-2 18.0 mU/m² IV daily on days 6 to 10 and 13 to 15 given every 4 weeks (N = 44); • Outpatient biochemotherapy: dacarbazine 250 mg/m² IV and cisplatin 25 mg/m² IV daily on days 1 to 3, IFN-α-2b 5 mU/m² SC on days 6, 8, 10, 13, and 15, and IL-2 5.0 mU/m² SC daily on days 6 to 10 and 13 to 15 given every 4 weeks (N = 37).
Outcomes	Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not reported. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomized". Comment: There was insufficient information about the sequence generation process to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "All measurements for response were confirmed by one of the coauthors (C.A.), who also was responsible for collection of data from individual centers." Comment: It was unclear if this method was sufficient to ensure low risk of detection bias.

Flaherty 2001 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	Published report include all expected outcomes. However, no protocol is available and thus it is unclear if all planned outcomes are reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Flaherty 2012a

Study characteristics	
Methods	Phase I-II parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma harboring activating mutations of BRAF. Participants randomised: 162.
Interventions	Three-arm trial: • Dabrafenib monotherapy 150 mg orally twice daily (N = 54); • Dabrafenib 150 mg orally twice daily + trametinib 1mg (N = 54); • Dabrafenib 150 mg orally twice daily + trametinib 2mg (N = 54).
Outcomes	Progression-free survival. Tumour response. Toxicity.
Notes	Cross-over: Dabrafenib 150 mg twice daily + trametinib 2 mg was allowed at disease progression. Quality of life: not reported. Participants with brain metastasis: enrolled if at least a 3-month history of stable disease. Median follow-up: 14 months.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned". Comment: There was insufficient information about the sequence generation process to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not af-

Flaherty 2012a *(Continued)*

		fect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no missing data across groups.
Selective reporting (reporting bias)	Unclear risk	Published report include all expected outcomes. However, no protocol is available and thus it is unclear if all planned outcomes are reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Flaherty 2012b

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study. Multicentre trial.
Participants	Previoulsy treated and untreated metastatic melanoma with a V600E or V600K BRAF mutation. Participants randomised: 322.
Interventions	Two-arm trial: • Trametinib 2 mg orally once daily (N = 214); • Dacarbazine 1000 mg/m^2 IV every 3 weeks or paclitaxel 175 mg/m^2 IV every 3 weeks (N = 108).
Outcomes	Overall survival. Progression-free survival. Tumour response. Toxicity.
Notes	Cross-over: Cross-over to trametinib was allowed at disease progression. Quality of life: QoL analysis was reported in a separated study (Schadendorf 2014). Trametinib was associated with less functional impairment, smaller declines in health status, and less exacerbation of symptoms than dacarbazine. Participants with brain metastasis: included when brain disease was stable. Median follow-up: not available.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned".

Flaherty 2012b *(Continued)*

		Comment: Risk was likely low because this was a multicentre trial with centralised randomisation.
Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "A blinded, independent central review of tumor assessments was performed." Comment: This method makes low the risk of detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Flaherty 2013a

Study characteristics	
Methods	Phase III parallel-group RCT. Double-blind study. Multicentre trial.
Participants	Metastatic melanoma not previously treated with either chemotherapy or MAP kinase pathway-targeted drugs. Participants randomised: 823.
Interventions	Two-arm trial: • Carboplatin at area under the concentration-time curve 6 and paclitaxel 225 mg/m^2 IV once every 21 days, placebo on days 2 to 19 every 21 days (N = 413); • Carboplatin at area under the concentration-time curve 6 and paclitaxel 225 mg/m^2 IV once every 21 days, sorafenib 400 mg orally twice per day on days 2 to 19 every 21 days (N = 410).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed.

Flaherty 2013a *(Continued)*

	Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned". Comment: Risk was likely low because this was a multicentre trial with centralised randomisation.
Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind". Comment: This method makes low the risk of performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double-blind". Comment: This method makes low the risk of detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Glaspy 2009

Study characteristics

Methods	Phase II/III parallel-group RCT. Double-blind study. Multicentre trial.
Participants	Untreated or previously treated (dacarbazine, temozolomide, IL-2, and/or IFN-α) metastatic melanoma. Randomised participants: 294.
Interventions	Two-arm trial: • Lenalidomide 5 mg orally plus placebo, looking identical to the 25 mg dose, daily for 28 days (N = 148); • Lenalidomide 25 mg orally for 21 days of every 28 days and placebo for the remaining 7 days (N = 146).
Outcomes	Progression-free survival.

Glaspy 2009 *(Continued)*

	Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised". Comment: Risk was likely low because this was a multicentre trial with centralised randomisation.
Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind". Comment: This method makes low the risk of performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double-blind". Comment: This method makes low the risk of detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Glover 2003

Study characteristics	
Methods	Phase II parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Participants randomised: 94.
Interventions	Two-arm trial:

Glover 2003 *(Continued)*

- Cisplatin 150 mg/m^2 IV and WR-2721 910 mg/m^2 IV every 3 weeks (N = 49);
- Cisplatin 150 mg/m^2 IV every 3 weeks (N = 45).

Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised". Comment: There was insufficient information about the sequence generation process to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Gorbonova 2000

Study characteristics

Methods	Phase II parallel-group RCT. Open label study.

Gorbonova 2000 *(Continued)*

Participants	Untreated metastatic melanoma. Randomised participants: 30.
Interventions	Two-arm study: • Cisplatin 100 mg/m^2 IV on day 3, aranoza 600 mg/m^2 IV on days 1 to 2 every 4 weeks (N = 14); • Cisplatin 100 mg/m^2 IV on day 3, aranoza 600 mg/m^2 IV on days 1 to 2, and IFN-α 3 mIU on days 5, 7, 9, 11, 13, 15, 17, 19 every 4 weeks (N = 14).
Outcomes	Tumour response
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	There was insufficient information to permit judgement.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was insufficient information to permit judgement.
Selective reporting (reporting bias)	Unclear risk	There was insufficient information to permit judgement.
Other bias	Unclear risk	There was insufficient information to permit judgement.

Gough 1978

Study characteristics

Methods	Phase II parallel-group RCT. Open label study.
Participants	Previuos treatment not reported.

Gough 1978 *(Continued)*

	Randomised participants: 36.
Interventions	Two-arm trial: • Dacarbazine 2.5 mg/kg IV daily on days 1 to 5 (N = 20); • Dacarbazine 2.5 mg/kg IV daily on days 1 to 5, and *C parvum* 7 mg SC daily on day -7 and 4 (N = 16).
Outcomes	Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients randomized". Comment: There was insufficient information about the sequence generation process to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Gupta 2014

Study characteristics

Methods	Phase II parallel-group RCT.

Gupta 2014 *(Continued)*

	Double-blind study.
Participants	Untreated metastatic wild-type BRAF melanoma. Randomised participants: 83
Interventions	Two-arm trial: • Docetaxel 75 mg/m² IV every 3 weeks up to 6 cycles, selumetinib 75 mg orally twice daily (N = 41); • Docetaxel 75 mg/m² IV every 3 weeks up to 6 cycles (N = 42).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: included. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...using a variable block size". Comment: This method ensured low risk of selection bias.
Allocation concealment (selection bias)	Unclear risk	Quote: "...masking". Comment: There was insufficient information about allocation concealment to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind". Comment: This method ensured low risk of performance bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double blind". Comment: This method ensured low risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Hamid 2014

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study. Multicentre trial.
Participants	Previosuly treated metastatic melanoma. Randomised participants: 336.
Interventions	Two-arm trial: • Tasisulam targeting an albumin-corrected exposure of 1200 to 6400 hour µg/mL on day 1 of a 28-day cycle; (N = 168); • Paclitxel 80 mg/m^2 on days 1, 8, and 15 of a 28-day cycle (N = 168).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: included. Median follow-up: 5 months.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned 1:1 to treatment with tasisulam or paclitaxel''. Comment: Risk was likely low because this was a multicentre trial with centralised randomisation.
Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias)	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.

Hamid 2014 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	High risk	There is a potential conflict of interest for some authors and the funding body which likely caused bias in the study methodology .

Hauschild 2001

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study. Multicentre trial.
Participants	Untreated metastatic melanoma. Randomised participants: 290.
Interventions	Two-arm trial: • Dacarbazine 850 mg/m² IV every 28 days, IFN-α 3 MIU/m² SC twice on day 1, once daily days 2 to 5; 5 MIU/m² SC 3 times a week from week 2 to 4 (N = 144); • Dacarbazine 850 mg/m² IV every 28 days, IFN-α 3 MIU/m² SC twice on day 1, once daily days 2 to 5; 5 MIU/m² SC 3 times a week from week 2 to 4, IL-2 4.5 MIU/m² for 3 hours IV on day 3; 9.0 MIU/m² IV day 3/4; 4.5 MIU/m² SC days 4 to 7 (N = 137).
Outcomes	Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized". Comment: Risk was likely low because this was a multicentre trial with centralised randomisation.
Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.
Blinding of participants and personnel (performance bias)	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention

Hauschild 2001 *(Continued)*

All outcomes		was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Hauschild 2009a

Study characteristics	
Methods	Phase III parallel-group RCT. Double-blind study.
Participants	Previously treated metastatic melanoma progressing under either temozolomide or dacarbazine. Participants randomised: 270.
Interventions	Two-arm trial: • Paclitaxel 225 mg/m^2 IV, carboplatin at area under curve 6 IV on day 1 of a 21-day cycle (N = 135); • Paclitaxel 225 mg/m^2 IV, carboplatin at area under curve 6 IV on day 1 of a 21-day cycle, sorafenib 400 mg orally twice daily on days 2 to 19 (N = 135).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Simple, stratified randomization with permuted blocks of size 4 was used to create a prospective randomization schedule that was implemented in a telephone based interactive voice recognition system".

Hauschild 2009a *(Continued)*

		Comment: Randomisation method was adequate.
Allocation concealment (selection bias)	Low risk	Quote: "Random assignment of eligible patients was performed by designated personnel at each participating site using the IVRS in a double-blind fashion such that the investigator, sponsor, and patient did not know the treatment assignment". Comment: Likely that allocation was concealed.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind". Comment: This method ensured low risk of performance bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double blind". Comment: This method ensured low risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Hauschild 2012

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study. Multicentre trial.
Participants	Untreated metastatic melanoma with BRAF V600E mutation. Participants randomised: 250.
Interventions	Two-arm trial: • Dabrafenib 150 mg twice daily (N = 187); • Dacarbazine 1000 mg/m^2 of body surface area by intravenous infusion every 3 weeks (N = 63).
Outcomes	Overall survival. Progression-free survival. Tumour response. Toxicity.
Notes	Cross-over: Cross-over to dabrafenib 150 mg twice daily was allowed at disease progression. Quality of life: Dabrafenib had functional and symptomatic benefit compared to dacarbazine (Grob 2014).

Hauschild 2012 *(Continued)*

Participants with brain metastasis: excluded unless they were without evidence of active central nervous system metastases for more than 3 months after surgery or stereotactic radiosurgery.

Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A centrally located, computerised, interactive, voice activated response system controlled assignment of patient treatment". Comment: Randomisation method was adequate.
Allocation concealment (selection bias)	Low risk	Quote: "Although investigators were aware of treatment group when assessing progression-free survival, a masked independent review committee (IRC) reviewed all scans and, per protocol, had to confirm progression before patients crossed over from dacarbazine to dabrafenib". Comment: Likely that allocation was concealed.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Hersh 2015

Study characteristics

Methods	Phase III parallel-group RCT. Open label study. Multicentre trial.
Participants	Untreated metastatic melanoma. Randomised participants: 529.
Interventions	Two-arm study: • Nab-paclitaxel 150 mg/m^2 IV on days 1, 8, and 15 every 4 weeks (N = 264);

Hersh 2015 *(Continued)*

	• Dacarbazine 1000 mg/m^2 IV every 3 weeks (N = 265).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized... via a centralized system". Comment: Risk was likely low because this was a multicentre trial with centralised randomisation.
Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...independent radiologic review". Comment: This method ensured low risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Hodi 2010a

Study characteristics	
Methods	Phase III parallel-group RCT. Double-blind study

Hodi 2010a *(Continued)*

Participants	HLA-A*0201–positive metastatic melanoma which had progressed during systemic treatment . Participants randomised: 676.
Interventions	Three-arm trial: • Ipilimumab 3 mg/kg + gp100 peptide vaccine every 3 weeks for 4 treatments (N = 403); • Ipilimumab 3 mg/kg every 3 weeks for 4 treatments (N = 137); • gp100 peptide vaccine for four treatments (N = 136).
Outcomes	Overall survival. Progression-free survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: Ipilimumab did not have a detrimental effect on QoL during the treatment induction phase (Revicki 2012). Participants with brain metastasis: participants with active, untreated metastases in the central nervous were excluded. Median follow-up: 21 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned". Comment: Risk was likely low because this was a multicentre trial with centralised randomisation.
Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “Double-blind”. Comment: This method ensured low risk of performance bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “Double-blind”. Comment: This method ensured low risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Hodi 2014

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study. Multicentre trial.
Participants	Untreated and previously treated (1 chemotherapy was allowed) metastatic melanoma. Patients randomised: 245.
Interventions	Two-arm study: • ipilimumab, 10 mg/kg, every 3 weeks IV for 4 doses then every 12 weeks + sargramostim (yeast-derived, rhu GM-CSF), 250 µg total dose SC on days 1 to14 of 21-day cycle (N = 123); • ipilimumab, 10 mg/kg, every 3 weeks IV for 4 doses then every 12 weeks (N = 122).
Outcomes	Overall survival. Progression-free survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: 13 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Stratified randomization based on permuted blocks within strata with dynamic institution balancing was used." Comment: Randomisation method was adequate.
Allocation concealment (selection bias)	Low risk	Quote: "Treatment assignments were obtained from the central randomization desk at the ECOG coordinating center." Comment: Risk was likely low because this was a multicentre trial with centralised randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Tumor responses were determined by the investigators using RECIST (Response Evaluation Criteria in Solid Tumors) criteria and were audited as a part of ECOG-ACRIN (American College of Radiology Imaging Network) standard procedures."

Hodi 2014 *(Continued)*

		Comment: It was unclear if this method was sufficient to ensure low risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Hofmann 2011

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study.
Participants	Previously treated metastatic melanoma. Participants randomised: 117.
Interventions	Two-arm study: • Best supportive care (N = 34); • Chemotherapy: Dacarbazine 450 mg/m^2 IV, cisplatin 50 mg/m^2 IV, and vindesine 3 mg/m^2 IV on day 1 and 8, every 4 weeks (N = 83).
Outcomes	Overall survival Tumour response Toxicity
Notes	Cross-over: was not allowed. Quality of life: No significant difference in the quality of life could be found. Participants with brain metastasis: included. Median follow-up: not available.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Quote: "After the first five patients, it was decided... that the centres have the option to enrol patients on a treatment preference basis (patients' choice) ". Comment: This domain was assessed at high risk of selection bias because initially enrolled participants were randomly assigned to either chemotherapy or best supportive care, but enrolment was slow and allocation appeared to be based on physician's choice.
Allocation concealment (selection bias)	High risk	Quote: "...patients' choice".

Hofmann 2011 *(Continued)*

		Comment: Unlikely that allocation was concealed.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "There was no centralized review of the radiology files provided." Comment: Overall, there was insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Jelic 2002

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study. Single centre trial.
Participants	Untreated metastatic melanoma. Participants randomised: 219.
Interventions	Four-arm study: • Standard dose dacarbazine arm: vincristine 1.4 mg/m^2 on day 1, carmustine 60 mg/m^2 on day 1, and dacarbazine 300 mg/m^2 per 24 h on days 2 to 5 (N = 49); • High-dose dacarbazine arm: vincristine 1.4 mg/m^2 on day 1, carmustine 60 mg/m^2 on day 1, and dacarbazine 600 mg/m^2 per 24 h on days 2 to 5 (N = 47); • 'Aggressive' regimen without dacarbazine: vindesine 3 mg/m^2 on day 1, bleomycin 7 mg/m^2 per 24 h on days 1 to 4, and cisplatin 30 mg/m^2 per 24 h on days 5 to 8 (N = 63); • 'Non-aggressive' regimen without dacarbazine: carmustine 100 mg/m^2 on day 1 and procarbazine 90 mg/m^2 per 24 h on days 1 to 10 (N = 60).
Outcomes	Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded.

Jelic 2002 *(Continued)*

	Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised". Comment: There was insufficient information to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Johnston 1998

Study characteristics

Methods	Phase II parallel-group RCT. Open label study.
Participants	Metastatic melanoma untreated or previously treated with no more than one previous systemic chemotherapy. Randomised participants: 65.
Interventions	Two-arm trial: • *Chemotherapy:* Carmustine 100 mg m/2 IV on day 1 on alternate courses, cisplatin 25 mg m^2 IV on days 1 to 3, dacarbazine 220 mg/m^2 IV on days 1 to 3, and tamoxifen 40 mg orally on days 1 to 3, every 4 weeks (N = 30); • *Biochemotherapy:* Carmustine 100 mg m/2 IV on day 1 on alternate courses, cisplatin 25 mg m^2 IV on days 1 to 3, dacarbazine 220 mg/m^2 IV on days 1 to 3, and tamoxifen 40 mg orally on days 1 to 3, every 4 weeks; IL-2 18 x 10^6 3 times daily SC, IL-2 9 x 10^6 twice daily SC on days -2 to -0; IFN-α 9 mU daily SC on days 1 to 3 (N = 35).
Outcomes	Progression-free survival.

Johnston 1998 *(Continued)*

	Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients who were randomized". Comment: There was insufficient information to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Kaufmann 2005

Study characteristics

Methods	Phase III parallel-group RCT. Open label study. Multicentre trial.
Participants	Untreated metastatic melanoma. Randomised participants: 294.

Kaufmann 2005 *(Continued)*

Interventions	Two-arm trial: • *Chemotherapy:* Temozolomide alone 200 mg/m^2 orally daily on days 1 to 5 every 4 weeks (N = 139); • *Biochemotherapy:* Temozolomide alone 200 mg/m^2 orally daily on days 1 to 5 every 4 weeks, and IFN-α 5 mU/m^2 SC daily on days 1, 3, and 5 every week (N = 143).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned without stratification". Comment: Risk was likely low because this was a multicentre trial with centralised randomisation.
Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "There was no centralized review of the radiologic files provided." Comment: It was unclear if this method ensured low risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Kefford 2010

Study characteristics

Kefford 2010 *(Continued)*

Methods	Phase II parallel-group RCT. Double-blind study.
Participants	Untreated metastatic melanoma. Participants randomised: 80.
Interventions	Two-arm trial: • Dacarbazine 1000 mg/m^2 every 3 weeks + bosentan 500 mg twice daily (N = 40); • Dacarbazine 1000 mg/m^2 every 3 weeks + placebo (N = 40).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomized". Comment: There was insufficient information about the sequence generation process to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “Double-blind”. Comment: This method ensured low risk of performance bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “Double-blind”. Comment: This method ensured low risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Keilholz 1997

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study. Multicentre trial.
Participants	Untreated and previously treated metastatic melanoma. Randomised participants: 138.
Interventions	Two-arm trial: • *Biochemotherapy:* IFN-α 10x10^6 U/m² SC on days 1 to 5, IL-2 18 mlU/m²/6 hours, 18 mlU/m 2/12 hours, 18 mlU/m 2/24 hours, and 4.5 mlU/m 2/24 hours x 3 IV days 3 to 8, cisplatin 100 mg/m² IV on day 1 every 4 weeks to a maximum of 4 cycles (N = 71); • *Biotherapy:* IFN-α 10x10^6 U/m² SC on days 1 to 5, IL-2 18 mlU/m²/6 hours, 18 mlU/m 2/12 hours, 18 mlU/m 2/24 hours, and 4.5 mlU/m 2/24 hours x 3 IV days 3 to 8 (N = 66).
Outcomes	Overall survival. Progression-free survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: > 2 years.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients randomized". Comment: Risk was likely low because this was a multicentre trial with centralised randomisation.
Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgement.

Keilholz 1997 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Keilholz 2005

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study. Multicentre trial.
Participants	Untreated metastatic melanoma. Randomised participants: 363.
Interventions	Two-arm trial: • *Chemo-immunotherapy:* Dacarbazine 250 mg/m^2 IV on days 1 to 3, cisplatin 30 mg/m^2 IV on days 1 to 3, IFN-α 10x10^6 U/m^2 SC on days 1 to 5 every 4 weeks to a maximum of 4 cycles (N = 71); • *Biochemotherapy:* Dacarbazine 250 mg/m^2 IV on days 1 to 3, cisplatin 30 mg/m^2 IV on days 1 to 3, IFN-α 10x10^6 U/m^2 SC on days 1 to 5, IL-2 18 mlU/m^2/6 hours, 18 mlU/m 2/12 hours, 18 mlU/m 2/24 hours, and 4.5 mlU/m 2/24 hours x 3 IV days 5 to 8 every 4 weeks to a maximum of 4 cycles (N = 66).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: 3.4 years.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned". Comment: Risk was likely low because this was a multicentre trial with centralised randomisation.
Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.

Keilholz 2005 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Kim 2012

Study characteristics	
Methods	Phase II parallel-group RCT. Double-blinded study.
Participants	Untreated metastatic melanoma. Randomised participants: 214.
Interventions	Two-arm trial: • Bevacizumab 15 mg/kg IV, carboplatin area under the curve, 5, and paclitaxel 175 mg/m^2 IV (N = 143); • Carboplatin area under the curve, 5, and paclitaxel 175 mg/m^2 IV (N = 71).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: 13 months.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Kim 2012 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "Random assignment was performed using an interactive voice response system". Comment: There was insufficient information about the sequence generation process to permit judgment.
Allocation concealment (selection bias)	Unclear risk	No sufficient information to judge
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind". Comment: This method ensured low risk of performance bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double-blind". Comment: This method ensured low risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Kirkwood 1990

Study characteristics	
Methods	Phase II parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Participants randomised: 74.
Interventions	Three-arm trial: • *Chemotherapy*: Dacarbazine 250 mg/m^2 IV daily on days 1 to 5 every 3 weeks (N = 24); • *Immunotherapy*: IFN-α 3 mIU SC daily on days 1 to 5, every week for 3 weeks, then 3 mIU/m^2 3 times a week (N = 23); • *Chemo-immunotherapy*: Dacarbazine 250 mg/m^2 IV daily on days 1 to 5 every 3 weeks, and IFN-α 3 mIU SC daily on days 1 to 5, every week for 3 weeks, then 3 mIU/m^2 3 times a week (N = 21).
Outcomes	Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded.

Kirkwood 1990 *(Continued)*

	Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised". Comment: There was insufficient information about the sequence generation process to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Kogoniia 1981

Study characteristics

Methods	Phase II parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Participants randomised: 132.
Interventions	Two-arm trial: • Dacarbazine 150 mg/m^2 IV daily on days 1 to 5 (N = 56); • Dacarbazine 150 mg/m^2 IV daily on days 1 to 5, vincristine 1.4 mg/m^2 IV on days 1, 8, 15, nitrosomethylurea 200 mg/m^2 IV days 3, 5, 10, 12, and dactinomycin 0.3 mg/m^2 IV days 1, 3, 5, 8, 10, 12 (N = 58).
Outcomes	Tumour response
Notes	Cross-over: cross-over was allowed at disease progression. Quality of life: not reported.

Kogoniia 1981 *(Continued)*

	Participants with brain metastasis: not reported. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Selective reporting (reporting bias)	Unclear risk	There was insufficient information to permit judgment.
Other bias	Low risk	No other sources of bias found.

Kokoschka 1978

Study characteristics

Methods	Phase II parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Randomised participants: 34.
Interventions	Two-arm trial: • *Chemotherapy* : Carmustine 200 mg/m^2 orally every 8 weeks (N = 19); • *Immuno-chemotherapy*: *C parvum* 1 mg IV, on days 1 to 4 and carmustine 200 mg/m^2 orally on day 8, repeated every 7 weeks (N = 15).
Outcomes	Overall survival. Tumour response. Toxicity.

Kokoschka 1978 *(Continued)*

Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised". Comment: There was insufficient information about the sequence generation process to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Larkin 2014

Study characteristics

Methods	Phase III parallel-group RCT. Open label study. Multicentre trial.
Participants	Untreated metastatic melanoma with BRAF V600 mutations. Participants randomised: 495.
Interventions	Two-arm trial: • Vemurafenib 960 mg twice daily orally + placebo (N = 248);

Larkin 2014 *(Continued)*

	• Vemurafenib 960 mg twice daily orally + cobimetinib 60 mg once daily for 21 days, followed by 7 days off (N = 247).
Outcomes	Overall survival. Progression-free survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: participants with previously treated brain metastases were eligible if they had at least a 3-week history of stable disease. Median follow-up: 7 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned". Comment: Risk was likely low because this was a multicentre trial with centralised randomisation.
Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "We performed a blinded, independent central review of tumor assessments." Comment: It is unclear if this method ensured low risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Larkin 2015

Study characteristics

Methods	Phase III parallel-group RCT.

Larkin 2015 *(Continued)*

	Double-blind study. Multicentre trial.
Participants	Untreated metastatic melanoma. Participants randomised: 945.
Interventions	Three-arm trial: • Nivolumab 3 mg/kg IV every 2 weeks (+ ipilimumab-matched placebo) (N = 316); • Nivolumab 1 mg/kg IV every 3 weeks + ipilimumab 3 mg/kg IV every 3 weeks for 4 doses, followed by nivolumab 3 mg/kg IV every 2 weeks for cycle 3 and beyond (N = 314); • Ipilimumab 3 mg/kg IV every 3 weeks for 4 doses (plus nivolumab-matched placebo) (N = 315).
Outcomes	Progression-free survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: participants with inactive brain metastasis were excluded. Median follow-up: > 9 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Enrolled patients were randomly assigned". Comment: Risk was likely low because this was a multicentre trial with centralised randomisation.
Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “Double-blind”. Comment: This method ensured low risk of performance bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “Double-blind”. Comment: This method ensured low risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	Quote: "Data on overall survival are insufficiently mature to present". Comment: Low risk of selective reporting.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Lawson 2015

Study characteristics	
Methods	Phase III parallel-group RCT. Double-blind study. Multicentre trial.
Participants	Participants underwent surgery for locally advanced or metastatic melanoma. Randomised participants: 815.
Interventions	HLA-A2–positive (serologically defined) • Granulocyte-macrophage colony-stimulating factor (GM-CSF, sargramostim) 250 g/d SC on day 1 through 14 of each 28-day cycle and multi-epitope peptide vaccination (PV) composed of tyrosinase 368-376(370D), gp100 209-217(210M), and MART-1(27-35) peptides 2 SC injections into 3 different sites on days 1 and 15 of cycle 1 and day 1 of subsequent cycles (N = 109); • GM-CSF placebo plus PV (N = 111); • GM-CSF and peptide placebo (N = 109); • GM-CSF and peptide placebo (N = 107). HLA-A2–negative group • GM-CSF (N = 190); • Placebo (N = 189).
Outcomes	Progression-free survival. Overall survival. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: participants who underwent surgery for brain metastasis were included. Median follow-up: 82 months.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Random assignment was conducted centrally by using permuted blocks within strata". Comment: Randomisation method was adequate.
Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “Placebo-controlled”. Comment: This method ensured low risk of performance bias.

Lawson 2015 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Placebo-controlled". Comment: The method ensured low risk of detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Legha 1996

Study characteristics	
Methods	Phase II parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Randomised participants:102.
Interventions	Two-arm study: • Chemotherapy and biotherapy regimens were alternating integrated initially (6-week intervals), (N = 40); • Subsequently, regiments were sequentially administered (participants were randomised to receive either chemotherapy immediately followed by biotherapy or the reverse sequence), (N = 62). Treatment schedules: • Chemotherapy: cisplatin 20 mg/m^2 IV daily for 4 days, vinblastine 1.6 mg/m^2 IV daily x 5 days, and dacarbazine 800 mg/m^2 IV daily, repeated every 3 weeks; • Biotherapy: IL-2,9 x 106 IU/mVd for 4 days and IFN-a 5 x 10^6 U/m^2 daily SC for 5 days.
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: participants with symptomatic brain metastasis were excluded. Median follow-up: 45 months. Note: Both biochemotherapy schedules were compared with a non-randomised group of participants who received chemotherapy alone.
Risk of bias	

Legha 1996 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned". Comment: There was insufficient information about the sequence generation process to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Long 2015

Study characteristics	
Methods	Phase III parallel-group RCT. Double-blind study. Multicentre trial.
Participants	Untreated metastatic melanoma with BRAF Val600Glu or Val600Lys mutations. Participants randomised: 423.
Interventions	Two-arm trial: • Dabrafenib 150 mg twice daily orally, and trametinib 2 mg once daily orally (N = 211); • Dabrafenib 150 mg twice daily + placebo (N = 212).
Outcomes	Overall survival. Progression-free survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed.

Long 2015 *(Continued)*

Quality of life: Dabrafenib and trametinib resulted in better preservation of health-related quality of life and pain improvement compared to dabrafenib monotherapy (Schadendorf 2015).

Participants with brain metastasis: participants with previously treated brain metastases were eligible if they had at least a 12-week history of stable disease.

Median follow-up: 9 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A centrally located, computerised, interactive, voice activated response system controlled the random assignment". Comment: Randomisation method was adequate.
Allocation concealment (selection bias)	Low risk	Quote: "Investigators, site staff, and patients were unaware of assignment throughout the study, and masking was maintained by using tablets and bottles of active drug and placebo that were identical in appearance. At the time of the primary analysis, only the sponsor and those assessing the data were made aware of treatment group assignments." Comment: Allocation likely concealed.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “Double blind”. Comment: The method ensured low risk of performance bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “Double blind”. Comment: This method ensured low risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Lopez 1984

Study characteristics

Methods	Phase II parallel RCT. Open label study.
Participants	Untreated metastatic melanoma. Participants randomised: 42.
Interventions	Two-arm trial: • SIngle agent chemotherapy: Dacarbazine 150 mg/m^2 IV daily on days 1 to 5 every 3 weeks (N = 19);

Lopez 1984 *(Continued)*

	• Polychemotherapy: Dacarbazine 150 mg/m² IV daily on days 1 to 5 and epirubicin 90 mg/m² on day 1 every 3 weeks (N = 22).
Outcomes	Tumour response. Toxicity.
Notes	Cross-over: not available. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...before randomisation". Comment: There was insufficient information to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Selective reporting (reporting bias)	Unclear risk	There was insufficient information to permit judgment.
Other bias	Low risk	No other sources of bias found.

Luikart 1984

Study characteristics

Methods	Phase III parallel RCT. Open label study.
Participants	Untreated metastatic melanoma. Participants randomised: 57.

Luikart 1984 *(Continued)*

Interventions	Two-arm study: • Monochemotherapy: Dacarbazine 250 mg/m² IV on days 1 to 10 (N = 24); • Polychemotherapy: Vinblastine 6 mg/m² daily IV on days 1 to 2, bleomycin 15 U/m² IV days 1 to 5, cisplatin 50 mg/m² IV on day 5 (N = 21).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: cross-over to polychemotherapy was allowed at disease progression. Quality of life: not reported. Participants with brain metastasis: included. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...random table of numbers". Comment: Randomisation method was adequate.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Maio 2010

Study characteristics

Methods	Phase III parallel-group RCT.

Maio 2010 *(Continued)*

	Open label study. Multicentre trial.
Participants	Untreated metastatic melanoma. Randomised participants: 488.
Interventions	Five-arm study: • *DIT1.6:* Dacarbazine 800 mg/m² IV on day 1, IFN 3 mU SC daily on days 11 to 18, thymosin-α 1.6 mg SC daily on days 8 to 11 and 15 to 18 (N = 97); • *DIT3.2:* Dacarbazine 800 mg/m² IV on day 1, IFN 3 mU SC daily on days 11 to 18, thymosin-α 3.2 mg SC daily on days 8 to 11 and 15 to 1 (N = 97); • *DIT6.4:* Dacarbazine 800 mg/m² IV on day 1, IFN 3 mU SC daily on days 11 to 18, thymosin-α 6.4 mg SC daily on days 8 to 11 and 15 to 1 (N = 98); • *DT:* Dacarbazine 800 mg/m² IV on day 1, thymosin-α 3.2 mg SC daily on days 8 to 11 and 15 to 1 (N = 99); • *DI:* Dacarbazine 800 mg/m² IV on day 1, IFN 3 mU SC daily on days 11 to 18 (N = 97).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned". "The randomization list was produced by the Internal Quality Control Unit of Biostatistics and Data Management". Comment: Randomisation method was adequate.
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was blinded and centralized". Comment: This method ensured low risk of selection bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Independent, blinded evaluation of tumor images was performed by Fondazione Biomedica Europea." Comment: It was unclear if this method ensured low the risk of detection bias.

Maio 2010 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Mastrangelo 1979

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study.
Participants	Untreated or previously treated (only treatments other than a nitrosurea was allowed) metastatic melanoma. Randomised participants: 62.
Interventions	Two-arm study: • *Chemotherapy:* methyl-lomustine 200 mg/m² orally every 8 weeks, and vincristine 2 mg IV every 4 weeks (N = 36); • *Biochemotherapy:* methyl-lomustine 200 mg/m² orally every 8 weeks, and vincristine 2 mg IV every 4 weeks, irradiated (15,000 rads) allogeneic (fresh-frozen) melanoma cells 1-2x10^8 SC, and BCG 2-4.5x10^6 organisms SC every 2 weeks (N = 36).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "...randomly allocated". Comment: There was insufficient information to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.

Mastrangelo 1979 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

McArthur 2014

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study. Multicentre trial.
Participants	Untreated metastatic melanoma with BRAF V600E e V600K mutations. Participants randomised: 675.
Interventions	Two-arm trial: • Vemurafenib 960 mg twice daily orally (N = 337); • Dacarbazine 1000 mg/m^2 IV every 3 weeks (N = 338).
Outcomes	Overall survival. Progression-free survival. Tumour response. Toxicity.
Notes	Cross-over: Cross-over to vemurafenib was allowed at disease progression. Quality of life: not reported. Participants with brain metastasis: excluded when metastases to the central nervous system had progressed or required treatment in the previous 3 months. Median follow-up: 12 months.
Risk of bias	

McArthur 2014 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned using an interactive voice recognition system supported by an independent vendor". Comment: Randomisation method adequate.
Allocation concealment (selection bias)	Low risk	Quote: "Patients and investigators were aware of treatment allocation" Comment: An independent review committee (IRC) had to confirm progression before participants crossed over from dacarbazine to dabrafenib.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	Secondary endpoints not reported will be subject of future publications.
Other bias	Low risk	The study appeared to be free of other sources of bias.

McDermott 2008

Study characteristics	
Methods	Phase II parallel-group RCT. Double-blind study.
Participants	Untreated metastatic melanoma. Randomised participants: 101.
Interventions	Two.arm study: • Dacarbazine 1000 mg/m^2 IV on day 1 every 3 weeks (N = 50); • Dacarbazine 1000 mg/m^2 IV on day 1 every 3 weeks and sorafenib 400 mg twice daily continuously (N = 50).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.

McDermott 2008 *(Continued)*

Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Simple stratified randomization with permuted blocks of size 4 was used by the sponsor to create a prospective randomization schedule that was provided to the vendor for the telephone-based interactive voice recognition system". Comment: Randomisation method was adequate.
Allocation concealment (selection bias)	Low risk	Quote: "Random assignment of eligible patients was performed by designated personnel at each participating site using the interactive voice recognition system in a double-blind fashion" Comment: Likely that allocation was concealed.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind". Comment: This method ensured low risk of performance bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double-blind". Comment: This method ensured low risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Middleton 2000

Study characteristics

Methods	Phase III parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Participants randomised: 305.
Interventions	Two-arm trial: • Temozolomide 200 mg/m^2 orally, daily for 5 days every 28 days (N = 156);

Middleton 2000 *(Continued)*

- Dacarbazine 250 mg/m^2 IV daily for 5 days every 21 days (N = 149).

Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: Temozolomide therapy significantly improved health-related QoL (Kiebert 2003). Participants with brain metastasis: excluded. Median follow-up: not available. Cost analysis: Temozolomide was associate with incremented cost-effectiveness (Hillner 2000).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised". Comment: There was insufficient information about the sequence generation process to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was no sufficient information to judge.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Middleton 2007

Study characteristics

Methods	Phase III parallel-group RCT.

Middleton 2007 *(Continued)*

	Open label study.
Participants	Untreated metastatic melanoma. Randomised participants: 241.
Interventions	Two-arm study: • IFN 3 MIU, SC once daily for 7 days, IL-2 2.4 MIU/m^2, SC, twice daily for 5 days, and histamine dihydrochloride 1 mg, SC twice a day for 5 days every 4 weeks (N = 119); • Dacarbazine 850 mg/m^2 IV every 3 weeks (N = 122).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Site-specific randomization codes were produced electronically for each stratified group". Comment: Randomisation method was adequate.
Allocation concealment (selection bias)	Low risk	Quote: "...site personnel called a central randomization desk". Comment: This method ensured low risk of selection bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was no sufficient information to judge.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Middleton 2015

Study characteristics	
Methods	Phase II parallel-group RCT. Double-blind study.
Participants	Untreated and previously treated metastatic melanoma. Randomised participants: 346.
Interventions	Three-arm study: • Veliparib 20 mg orally, twice daily on days 1 to 7 of each 28-day cycle, and temozolomide 150 mg/m^2 orally once daily on days 1 to 5 of every 28-day cycle, escalating to 200 mg/m^2 in cycle 2 as tolerated (N = 116); • Veliparib 40 mg orally, twice daily on days 1 to 7 of each 28-day cycle, and temozolomide 150 mg/m^2 orally once daily on days 1 to 5 of every 28-day cycle, escalating to 200 mg/m^2 in cycle 2 as tolerated (N = 115); • Temozolomide 150 mg/m^2 orally once daily on days 1 to 5 of every 28-day cycle, escalating to 200 mg/m^2 in cycle 2 as tolerated (N = 116).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Mediano follow-up: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized sequentially 1:1:1 using a computer-based model". Comment: Randomisation method was adequate.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind". Comment: The method ensured low risk of performance bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double-blind". Comment: The method ensured low risk of detection bias.

Middleton 2015 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Miller 1989

Study characteristics	
Methods	Phase II parallel-group RCT. Open label study.
Participants	Untreated and previously treated metastatic melanoma. Randomised participants: 53.
Interventions	Two-arm trial: • IFN-α 10 mU/m² SC 3 times weekly (N = 26); • IFN-α 10 mU/m² SC 3 times weekly, indomethacin 25 mg orally 3 times daily starting 1 day (N = 27);
Outcomes	Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Participants with liver metastasis were also excluded. Median follow-up: not available.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Treatment assignments were provided to the investigators by a Research Nurse using sealed envelopes." Comment: There was insufficient information to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.

Miller 1989 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Moon 1975

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Randomised participants: 120.
Interventions	Three-arm study: • Carmustine 150 mg/m^2 IV and vincristine 2 mg/m^2 IV every 30 days (N = 61); • Dacarbazine 300 mg/m^2 daily for 6 days every 30 days (N = 32); • Dacarbazine 100 mg/m^2 every 8 hours for 18 days every 30 days (N = 27).
Outcomes	Tumour response.
Notes	Cross-over: allowed. Quality of life: not reported. Participants with brain metastasis: included.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...randomly allocated". Comments: There was insufficient information to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.

Moon 1975 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Selective reporting (reporting bias)	Unclear risk	There was insufficient information to permit judgment.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Newlands 1976

Study characteristics	
Methods	Phase II parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Randomised participants: 56.
Interventions	Two-arm study: • Dacarbazine 100 mg/m^2 IV for 5 days, and ICRF 159 125 mg orally twice daily, every 5 weeks (N = 29); • Dacarbazine 100 mg/m^2 IV for 5 days, and ICRF 159 125 mg orally twice daily, every 5 weeks, irradiated allogeneic melanoma cells 2 x 10^7 SC, and BCG 50 µg SC 11 days after the end of the chemotherapy course (N = 27).
Outcomes	Overall survival. Tumour response.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "...randomly allocated". Comment: There was insufficient information to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias)	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention

Newlands 1976 *(Continued)*

All outcomes		was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Selective reporting (reporting bias)	Unclear risk	There was insufficient information to permit judgment.
Other bias	Low risk	The study appeared to be free of other sources of bias.

O'Day 2009

Study characteristics	
Methods	Phase II parallel-group RCT. Double-blind study.
Participants	Untreated and previously treated (1 chemotherapy was allowed) metastatic melanoma. Participants randomised: 81.
Interventions	Two-arm trial: • elesclomol 213 mg/m^2, and paclitaxel 80 mg/m^2 once weekly, during 3 weeks of every 4-week cycle (N = 53); • paclitaxel 80 mg/m^2 once weekly, during 3 weeks of every 4-week cycle (N = 28).
Outcomes	Overall survival. Progression-free survival. Tumour response. Toxicity.
Notes	Cross-over: cross-over to open-label elesclomol plus paclitaxel was allowed at disease progression. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: 3 months (for censored participants).

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "...using an interactive voice-response system".

O'Day 2009 *(Continued)*

		Comment: There was insufficient information about the sequence generation process to permit judgment.
Allocation concealment (selection bias)	Low risk	Quote: "Investigators and patients were blinded with respect to treatment assignment; unblinded site pharmacists were responsible for reconstituting study drugs at the pharmacy at each site". This method ensured low risk of selection bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind". This method ensured low risk of performance bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double blind". This method ensured low risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

O'Day 2011

Study characteristics	
Methods	Phase II parallel-group RCT. Double-blind study.
Participants	Untreated metastatic melanoma. Randomised participants: 129.
Interventions	Four-arm study: • Dacarbazine 1000 mg/m^2 every 3 week (N = 32): • Dacarbazine 1000 mg/m^2 and intetumumab 10 mg/kg every 3 weeks (N = 32); • Intetumumab 10 mg/kg every 3 weeks (N = 33); • Intetumumab 5 mg/kg every 3 weeks (N = 32).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: quote "Patients in the blinded dacarbazine-containing arms who could not tolerate dacarbazine were allowed to cross-over to open-label 10 mg/kg intetumumab monotherapy, and those on dacarbazine monotherapy who experienced progressive disease (PD) were allowed to cross over to open-label dacarbazine plus10 mg/kg intetumumab".

O'Day 2011 *(Continued)*

	Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: 24 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomisation was stratified". Comment: There was insufficient information to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "...blinded". Comment: The method ensured low risk of performance bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...blinded". Comment: The method ensured low risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

O'Day 2013

Study characteristics

Methods	Phase III parallel-group RCT. Double-blind study. Multicentre trial.
Participants	Untreated and previously treated (1 chemotherapy was allowed) metastatic melanoma. Participants randomised: 651.
Interventions	Two-arm trial: • elesclomol 213 mg/m^2 and paclitaxel 80 mg/m^2 once weekly, during 3 weeks of every 4-week cycle (N = 325); • paclitaxel 80 mg/m^2 once weekly, during 3 weeks of every 4-week cycle (N = 325).
Outcomes	Progression-free survival. Overall survival.

O'Day 2013 *(Continued)*

	Tumour response. Toxicity.
Notes	Cross-over: not reported. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...randomly assigned patients". Comment: Risk was likely low because this was a multicentre trial with centralised randomisation.
Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind". Comment: The method ensured low risk of performance bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind". Comment: The method ensured low risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Patel 2011

Study characteristics

Methods	Phase III parallel-group RCT. Open label study. Multicentre trial.
Participants	Untreated metastatic melanoma. Randomised participants: 859.
Interventions	Two-arm trial:

Patel 2011 *(Continued)*

	• Temozolomide 150 mg/m^2 (escalated dose) daily on days 1 to 7 every 2 weeks (N = 429); • Dacarbazine 1000 mg/m^2 daily on day 1 every 3 weeks (N = 430).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: 19 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation, performed centrally at the EORTC Headquarters, was stratified by performance status (0 versus 1) and institution, using a minimisation technique". Comment: Randomisation method was adequate.
Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Postow 2015

Study characteristics

Methods	Phase I dose-escalation parallel-group RCT.

Postow 2015 *(Continued)*

	Double-blinded study.
Participants	Untreated metastatic melanoma. Participants randomised: 142.
Interventions	Two-arm trial: • Nivolumab 1 mg/kg every 3 weeks, and ipilimumab 3 mg/kg every 3 weeks for 4 doses, followed by nivolumab 3 mg/kg every 2 weeks for cycle 3 and beyond (N = 95); • Ipilimumab 3 mg/kg every 3 weeks for 4 doses, followed by placebo every 2 weeks for cycle 3 and beyond (N = 47).
Outcomes	Progression-free survival. Tumour response. Toxicity.
Notes	Cross-over: cross-over was allowed at disease progression. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: > 11 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned". Comment: There was insufficient information about the sequence generation process to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind trial". Comment: The method ensured low risk of performance bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double-blind trial". Comment: The method ensured low risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Presant 1979

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Randomised participants: 120.
Interventions	Two-arm study: • Cyclophosphamide, 600 mg/m^2 IV on day 1, and dacarbazine 200 mg/m^2 IV daily on days 1 to 5 every 3 weeks (N = 65); • Cyclophosphamide, 600 mg/m^2 IV on day 1, dacarbazine 200 mg/m^2 IV daily on days 1 to 5 every 3 weeks, and *C parvum* 5 mg/m^2 IV on day 8 and 15 (N = 55).
Outcomes	Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomized". Comment: There was insufficient information to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.

Presant 1979 *(Continued)*

Other bias	Low risk	The study appeared to be free of other sources of bias.

Presant 1982

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Randomised participants: 195.
Interventions	Two-arm study: • Cyclophosphamide, 600 mg/m^2 IV on day 1, and dacarbazine 600 mg/m^2 IV daily on day 1 every 3 weeks (N = 65); • Cyclophosphamide, 400 mg/m^2 IV on day 1, dacarbazine 400 mg/m^2 IV daily on day 1 every 3 weeks, and piperazinedione 4 mg/m^2 IV on day 1 every 3 weeks (N = 55).
Outcomes	Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomized". Comment: There was insufficient information to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.

Presant 1982 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Punt 2006

Study characteristics	
Methods	Phase II parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Participants randomised: 93.
Interventions	Two-arm trial: • *Biochemotherapy:* cisplatin 30 mg/m² IV days 1 to 3, dacarbazine 250 mg/m² IV days 1 to 3, IFN-α 10 mU/m² days 1 to 5 SC, and IL-2 IV 1 mg/m² /6 h day 4, 1 mg/m² /12 h/day 5, 1 mg/m² /24 h day 6, 0.25 mg/m² / 24 h days 7 to 9 every 4 weeks for a maximum of 4 cycles (N = 45); • *Chemotherapy followed by biochemotherapy:* dacarbazine 850 mg/m² IV days 1 and 22 followed by cisplatin 30 mg/m² IV days 1 to 3, dacarbazine 250 mg/m² IV days 1 to 3, IFN-α 10 mU/m² days 1 to 5 SC, and IL-2 IV 1 mg/m² /6 h day 4, 1 mg/m² /12 h/day 5, 1 mg/m² /24 h day 6, 0.25 mg/m² / 24 h days 7 to 9 every 4 weeks for a maximum of 4 cycles (N = 44).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomisation was performed centrally". Comment: There was insufficient information about the sequence generation process to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.

Punt 2006 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Ramseur 1978

Study characteristics	
Methods	Phase II parallel-group RCT. Open label study.
Participants	Untreated and previously treated metastatic melanoma. Number of randomised participants: 28.
Interventions	Two-arm study: • Dacarbazine 250 mg/m^2 IV daily on days 1 to 5, and actinomycin D 0.5 mg daily on days 1 to 5 (N = 15); • Dacarbazine 250 mg/m^2 IV daily on days 1 to 5, actinomycin D 0.5 mg daily on days 1 to 5, BCG 0.5 mg SC every 5 weeks (N = 13);
Outcomes	Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: included. Median follow-up: not available.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly allocated". Comment: There was insufficient information to permit judgment.

Ramseur 1978 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Ranson 2007

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Randomised participants: 104.
Interventions	Two-arm trial: • Temozolomide 125 mg/m^2 orally on days 1 to 5 every 4 weeks and lomeguatrib 40 to 80 mg orally (N = 52); • Temozolomide 125 mg/m^2 orally on days 1 to 5 every 4 weeks (N = 52).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: quote "Patients experiencing disease progression in the TMZ alone arm were permitted to continue study treatment by changing to the LM/TMZ combination". Quality of life: not reported. Participants with brain metastasis: included. Median follow-up: not available.

Ranson 2007 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were to be randomly assigned". Comment: There was insufficient information to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	High risk	Quote: "In the course of the trial, it became apparent that MGMT persisted in tumor biopsy samples taken 24 to 72 hours after the end of cycle 1 LM/TMZ. Therefore, the trial was extended by 20 patients, with the LM dose in those assigned combination treatment being increased to 60 mg/d, then to 80 mg/d".

Reichle 2007

Study characteristics	
Methods	Phase II parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Participants randomised: 76.
Interventions	Two-arm trial: • Trofosfamide 50 mg orally 3 times daily for a maximum of 6 weeks (N = 32); • Trofosfamide 50 mg orally 3 times daily, rofecoxib 25 mg orally, and pioglitazone 60 mg orally for a maximum of 6 weeks (N = 35).
Outcomes	Progression-free survival. Overall survival. Tumour response.

Reichle 2007 *(Continued)*

	Toxicity.
Notes	Cross-over: cross-over to combination therapy was allowed at disease progression. Quality of life: not reported. Participants with brain metastasis: included (quote: "controlled brain metastasis"). Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised". Comment: There was insufficient information about the sequence generation process to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Ribas 2013

Study characteristics

Methods	Phase III parallel-group RCT. Open label study. Multicentre trial.
Participants	Untreated metastatic melanoma. Participants randomised: 655.
Interventions	Two-arm trial:

Ribas 2013 *(Continued)*

	• Tremelimumab 15 mg/kg once every 90 days for up to 4 cycles (N = 328); • Standard chemotherapy: single-agent DTIC 1000 mg/m^2 on day 1 of a 21-day cycle or single-agent temozolomide 200 mg/m^2 on days 1 to 5 of a 28-day cycle for up to 12 cycles (N = 327).
Outcomes	Overall survival. Progression-free survival. Tumour response. Toxicity.
Notes	Cross-over: cross-over to tremelimumab was not allowed for participants who progressed during standard chemotherapy. Cross-over to ipilimumab was allowed at disease progression. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned". Comment: Risk was likely low because this was a multicentre trial with centralised randomisation.
Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Tumor data assessed by investigators were reviewed by the sponsor to ensure compliance with RECIST criteria." Comment: It was unclear if this method ensured low risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Ribas 2015

Study characteristics

Ribas 2015 *(Continued)*

Methods	Phase III parallel-group RCT. Open label study. Multicentre trial.
Participants	Metastatic melanoma progressing after treatment with ipilimumab or BRAF and/or MEK inhibitors. Participants randomised: 540.
Interventions	Three-arm trial: • Pembrolizumab 2 mg/kg every 3 weeks (N = 180); • Pembrolizumab 10 mg/kg every 3 weeks (N = 181); • Investigator-choice chemotherapy (paclitaxel plus carboplatin, paclitaxel, carboplatin, dacarbazine, or oral temozolomide) (N = 179).
Outcomes	Overall survival. Progression-free survival. Tumour response. Toxicity.
Notes	Quality of life: pembrolizumab had smaller decrements in the individual function and symptoms scales. Cross-over: cross-over to pembrolizumab after progression under investigation-choice systemic chemotherapy was allowed. Participants who crossed-over were randomly assigned to receive either 2 mg/kg or 10 mg/kg pembrolizumab. Participants with brain metastasis: excluded. Median follow-up: 10 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Block randomisation with a block size of six in each stratum was used". Comment: Randomisation method was adequate.
Allocation concealment (selection bias)	Low risk	Quote: "Individual treatment assignment between pembrolizumab and chemotherapy was open label; investigators and patients were masked to assignment to pembrolizumab dose". Comment: Allocation likely concealed.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Investigators and patients were masked to assignment to pembrolizumab dose". Comment: The method ensured low risk of performance bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "investigators were masked to assignment to pembrolizumab dose". Comment: The method ensured low risk of detection bias.

Ribas 2015 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Richtig 2004

Study characteristics	
Methods	Phase II parallel-group RCT. Open label study.
Participants	Untreated and previously treated metastatic melanoma. Randomised participants: 47.
Interventions	Two-arm trial: • Temozolomide (Temodal®, AESCA, Traiskirchen, Austria) 150 mg m^{-2} daily orally on days 1–5 of each 28 days treatment cycle, in combination with IFN-α2b (Intron A®, AESCA) 10 MIU m^{-2} subcutaneously every other day (N = 20); • The same regimen of temozolomide but a fixed dose of 10 MIU every other day of IFN-α2b (N = 27)
Outcomes	Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: included. Median follow-up: not available.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "...randomised". Comment: There was insufficient information to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not af-

Richtig 2004 *(Continued)*

		fect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no missing data.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	High risk	Quote: "The study was stopped after the inclusion of approximately 50%". Comment: High risk of bias due to the trial stopping after approximately 50% of the planned participants were enrolled.

Ridolfi 2002a

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Participants randomised: 165.
Interventions	Two-arm trial: • *Chemotherapy:* cisplatin 75 mg/m^2 IV on day 1, dacarbazine 800 mg/m^2 IV on day 1, optional carmustine 100 mg/m^2 IV on day 1 every 3 weeks for 6 cycles (N = 89); • *Biochemiotherapy:* cisplatin 75 mg/m^2 IV on day 1, dacarbazine 800 mg/m^2 IV on day 1, optional carmustine 100 mg/m^2 IV on day 1, IFN-α-2b 3,000,000 UI IM 3 times weekly, IL-2 4,500,000 UI SC from days 3 to 5 and days 8 to 12 every 3 weeks for 6 cycles (N = 87).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Cross-over: allowed at disease progression. Quality of life: investigated in a separate analysis (Chiarion-Sileni 2003). Biochemotherapy worsened significantly quality of life compared to chemotherapy. Participants with brain metastasis: excluded. Median follow-up: 17 months.
Risk of bias	

Ridolfi 2002a *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...system of random permuted blocks within the strata (oncologic center variable) was used with a block size of four." Comment: Adequate randomisation method used.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	No protocol is available and thus it is unclear if all planned outcomes are reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Ringborg 1989

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Randomised participants: 119.
Interventions	Two-arm trial: • Dacarbazine 250 mg/m^2 IV daily days 1 to 5 every 4 weeks (N = 51); • Dacarbazine 250 mg/m^2 IV daily days 1 to 5 every 4 weeks, and vindesine 3 mg/m^2 IV on day 1 (N = 59).
Outcomes	Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: included.

Ringborg 1989 *(Continued)*

Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients... were randomized". Comment: There was insufficient information to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Robert 2011

Study characteristics

Methods	Phase III parallel-group RCT. Double-blinded study. Multicentre trial.
Participants	Untreated metastatic melanoma. Participants randomised: 502.
Interventions	Two-arm trial: • Ipilimumab 10 mg/kg + dacarbazine 850 mg /m^2 at weeks 1, 4, 7, and 10, followed by dacarbazine alone every 3 weeks through week 22 (N = 250); • Dacarbazine 850 mg/m^2 + placebo at weeks 1, 4, 7, and 10, followed by dacarbazine alone every 3 weeks through week 22 (N = 252).
Outcomes	Overall survival. Progression-free survival.

Robert 2011 *(Continued)*

	Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: A paper reported on quality-adjusted time without symptoms of disease or toxicity of treatment (Q-TWiST) (Sherrill 2013). Particpants treated with ipilimumab had little benefit in quality-adjusted survival during the first year. The benefits of ipilimumab has increased with extended survival after 2, 3, and 4 years. Participants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned". Comment: Risk was likely low because this was a multicentre trial with centralised randomisation.
Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “Double-blind”. Comment: The method ensured low risk of performance bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “Double-blind”. Comment: The method ensured low risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Robert 2013

Study characteristics

Methods	Phase II parallel-group RCT. Double-blind study.
Participants	Untreated metastatic melanoma with BRAF mutations. Randomised participants: 91.
Interventions	Two-arm trial:

Robert 2013 *(Continued)*

- Dacarbazine 1000 mg/m^2 IV on day 1 of every 3 weeks (N = 46);
- Dacarbazine 1000 mg/m^2 IV on day 1 and selumetinib 75 mg orally twice daily every 3 weeks (N = 45).

Outcomes	Overall survival. Progression-free survival. Tumour response. Toxicity.
Notes	Quality of life: not reported. Cross-over: not allowed. Participants with brain metastasis: Participants with either brain or spinal cord metastasis were eligible when asymptomatic, treated, and stable off treatment for > 3 months. Median follow-up: 12 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned by central interactive voice response system (1:1 ratio, block size four)." Comment: Randomisation method was adequate.
Allocation concealment (selection bias)	Low risk	Quote: "Patients, investigators, and the study team were masked to the treatment assigned." Comment: Allocation was likely concealed.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind". Comment: The method ensured low risk of performance bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double-blind". Comment: The method ensured low risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Robert 2015

Study characteristics

Methods	Phase III parallel-group RCT.

Robert 2015 *(Continued)*

	Open label study. Multicentre trial.
Participants	Untreated metastatic melanoma with BRAF V600E e V600K mutations. Participants randomised: 704.
Interventions	Two arm trial: • Dabrafenib 150 mg orally twice daily + trametinib 2 mg orally once daily (N = 352); • Vemurafenib 960 mg orally twice daily (N = 352).
Outcomes	Overall survival. Progression-free survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: This was reported in a separated analysis (Grob 2015). Combination of dabrafenib and trametinib adds a clear benefit over monotherapy with vemurafenib. Participants with brain metastasis: participants with previously treated brain metastases were eligible if they had at least a 12-week history of stable disease. Median follow-up: 10 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible patients were assigned". Comment: Risk was likely low because this was a multicentre trial with centralised randomisation.
Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.

Robert 2015 *(Continued)*

Other bias	Low risk	The study appeared to be free of other sources of bias.

Robert 2015a

Study characteristics	
Methods	Phase III parallel-group RCT. Double-blinded study. Multicentre trial.
Participants	Untreated metastatic melanoma without BRAF mutations. Participants randomised: 418.
Interventions	Two-arm trial: • Nivolumab 3 mg/kg IV every 2 weeks and dacarbazine-matched placebo every 3 weeks (N = 210); • Dacarbazine 1000 mg/m^2 IV every 3 weeks and nivolumab-matched placebo every 2 weeks (N = 208).
Outcomes	Overall survival. Progression-free survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not investigated. Participants with brain metastasis: participants with active brain metastasis were excluded. Median follow-up: 9 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned". Comment: Risk was likely low because this was a multicentre trial with centralised randomisation.
Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “Double-blind”. Comment: The method ensured low risk of performance bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “double-blind”. Comment: The method ensured low risk of detection bias.

Robert 2015a *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report. Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Robert 2015b

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study. Multicentre trial.
Participants	Metastatic melanoma that had no more than one previous systemic therapy for advanced disease (CTLA-4, PD-1, or PD-L1 inhibitors were not allowed). Participants randomised: 834.
Interventions	Three-arm trial: • Pembrolizumab 10 mg/kg every 2 weeks (N = 279); • Pembrolizumab 10 mg/kg every 3 weeks (N = 277); • Ipilimumab 3 mg/kg every 3 weeks (N = 278).
Outcomes	Overall survival. Progression-free survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported Participants with brain metastasis: participants with brain metastasis were excluded when they had active metastasis. Median follow-up: > 9 months.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned". Comment: Risk was likely low because this was a multicentre trial with centralised randomisation.

Robert 2015b *(Continued)*

Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Robidoux 1982

Study characteristics	
Methods	Phase II parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Randomised participants: 88.
Interventions	Two-arm trial: • Dacarbazine 250 mg/m² IV daily on days 1 to 5, and actinomycin-D 2 mg/m² IV on day 1, repeated every 3 to 4 weeks (N = 32); • Dacarbazine 250 mg/m² IV daily on days 1 to 5, actinomycin-D 2 mg/m² IV on day 1, repeated every 3 to 4 weeks, and *C parvum* 2 mg/m² IV daily on for 14 days before every third cycle of chemotherapy, plus 2 mg/m² IV daily on days 7 and 14 of each 3 to 4 weeks chemotherapy cycle (N = 33).
Outcomes	Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not available.

Robidoux 1982 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomized". Comment: There was insufficient information to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Rosenberg 1999

Study characteristics

Methods	Phase III parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Participants randomised: 102.
Interventions	Two-arm trial: • *Chemotherapy:* Tamoxifen 40 mg orally on day 1 followed by 10 mg orally twice daily on days 2 to 29, cisplatin 25 mg/m^2 IV on days 2 to 4 and days 23 to 25, and dacarbazine 220 mg/m^2 IV on days 2 to 4 and days 23 to 25 (N = 52); • *Biochemotherapy:* Tamoxifen 40 mg orally on day 1 followed by 10 mg orally twice daily on days 2 to 29, cisplatin 5 mg/m^2 IV on days 2 to 4 and days 23 to 25, and dacarbazine 220 mg/m^2 IV on days 2 to 4 and days 23 to 25, IL-2 720,000 IU/kg IV every 8 hours until grade 3 toxicity was reached, IFN-α-2b 6,000,000 U/m^2 SC beginning on days 5 and 26, by 4 days (N = 50).
Outcomes	Progression-free survival. Overall survival.

Rosenberg 1999 *(Continued)*

	Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: 42 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization between the two study arms was performed by the central data management office". Comment: There was insufficient information about the sequence generation process to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Rusthoven 1996

Study characteristics

Methods	Phase III parallel-group RCT. Double-blinded study.
Participants	Untreated metastatic melanoma. Randomised participants: 204.
Interventions	Two-arm trial:

Rusthoven 1996 *(Continued)*

- Carmustine 150 mg/m² IV on day 1, dacarbazine 220 mg/m² IV daily on days 1 to 3 and 22 to 24, and cisplatin 25 mg/m² IV daily on days 1 to 3 and on days 22 to 24 (N = 100);
- Carmustine 150 mg/m² IV on day 1, dacarbazine 220 mg/m² IV daily on days 1 to 3 and 22 to 24, cisplatin 25 mg/m² IV daily on days 1 to 3 and on days 22 to 24, and tamoxifen 160 mg orally daily for 7 days before chemotherapy and 40 mg orally daily throughout the remainder of the treatment cycle (N = 104).

Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Quality of life: not reported. Cross-over: participants were allowed to cross-over to tamoxifen-based regimen at disease progression. Participants with brain metastasis: participants with brain metastasis were eligible if they had completed planned surgery/radiotherapy, did not require glucocorticosteroids at study entry, and had stable disease in the brain at a repeat computed tomography (CT) scan 2 weeks before randomisation. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Before randomization, patients were stratified". Comment: There was insufficient information about the sequence generation process to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind". Comment: The method ensured low risk of performance bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double-blind". Comment: The method ensured low risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Schadendorf 2006

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study. Multicentre trial.
Participants	Untreated metastatic melanoma. Randomised participants: 108.
Interventions	Two-arm trial: • Dacarbazine 850 mg/m^2 IV on day 1 every 4 weeks (N = 55); • Autologous peptide-pulsed monocyte-derived dendritic cells SC every 2 weeks for the first five vaccinations, followed by vaccinations in 4-week intervals (N = 53).
Outcomes	Overall survival. Progression-free survival. Tumour response. Toxicity.
Notes	Quality of life: not reported. Cross-over: not allowed. Participants with brain metastasis: excluded. Median follow-up: 22 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised". Comment: Risk was likely low because this was a multicentre trial with centralised randomisation.
Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The study was externally monitored". Comment: The method ensured low risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.

Schadendorf 2006 *(Continued)*

Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Schwartzentruber 2011a

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study. Multicentre trial.
Participants	Untreated metastatic melanoma. Randomised participants: 185.
Interventions	Two-arm trial: • IL-2 720,000 IU/kg every 8 hours up to a maximum of 12 doses per cycle every 3 weeks (N = 94); • gp100:209-217(210M) plus incomplete Freund's adjuvant once per cycle, followed by IL-2 720,000 IU/kg every 8 hours up to a maximum of 12 doses per cycle every 3 weeks (N = 91).
Outcomes	Overall survival. Progression-free survival. Tumour response. Toxicity.
Notes	Quality of life: not reported. Cross-over: not allowed. Participants with brain metastasis: excluded. Median follow-up: 41 months.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Stratified randomization was performed with the use of random block sizes to ensure balance with respect to a potentially important prognostic feature." Comment: Randomisation method was adequate.
Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not af-

Schwartzentruber 2011a *(Continued)*

		fect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...blinded central radiologic review". Comment: The method ensured low risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Sertoli 1999

Study characteristics	
Methods	Phase II parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Participants randomised: 92.
Interventions	Two-arm trial: • Dacarbazine 800 mg/m^2 IV every 21 days, and IL-2 9 MIU SC daily on days 1 to 5 and 8 to 12, IFN 3 mU SC 3 times a week and tamoxifen 20 mg orally (N = 31); • Cisplatin 30 mg/m^2 IV daily on days 1 to 3, dacarbazine 250 mg/m^2 IV daily on days 1 to 3, and vindesine 2.5 mg/m^2 IV daily on day 1 every 28 days, IFN 3 mU SC 3 times weekly and tamoxifen 20 mg orally (N = 31); • Cisplatin 30 mg/m^2 IV daily on days 1 to 3, dacarbazine 250 mg/m^2 IV daily on days 1 to 3, vindesine 2.5 mg/m^2 IV daily on day 1 every 28 days, IL-2 6 MIU SC daily days 1 to 5 and 8 to 12 every 28 days, IFN 3 mU SC 3 times weekly and tamoxifen 20 mg orally (N = 30).
Outcomes	Overall survival. Progression-free survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Sertoli 1999 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "Patients... were randomized". Comment: There was insufficient information to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Selective reporting (reporting bias)	Unclear risk	There was insufficient information to permit judgment.
Other bias	Unclear risk	There was insufficient information to permit judgment.

Sparano 1993

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study.
Participants	Untreated and previously treated (only one chemotherapy line was allowed) metastatic melanoma. Participants randomised: 85.
Interventions	Two-arm trial: • IL-2 6 X 10^6 U/m^2 IV every 8 hours as tolerated for a maximum of 14 doses on days 1 to 5 and 15 to 19 (N = 44); • IL-2 6 X 10^6 U/m^2 IV every 8 hours as tolerated for a maximum of 14 doses on days 1 to 5 and 15 to 19 and IFN-α 3 X 10^6 U/m^2 IV every 8 hours as tolerated for a maximum of 14 doses on days 1 to 5 and 15 to19 (N = 41).
Outcomes	Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded.

Sparano 1993 *(Continued)*

Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised". Comment: There was insufficient information about the sequence generation process to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All responses were independently reviewed by the study's principal investigators and by a single radiologist". Comment: The method ensured low risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Testori 2008

Study characteristics

Methods	Phase III parallel-group RCT. Open label study. Multicentre trial.
Participants	Untreated metastatic melanoma. Participants randomised: 322.
Interventions	Two-arm trial: • Vitespen: first 4 injections were administered weekly, and subsequent injections were administered every other week (N = 215); • Physician's choice of treatment including at least one of the following: IL-2 (60 million U/m^2), DTIC (1000 mg/m^2), temozolomide (600 mg/m^2), tumour resection with or without additional therapy, any therapy licensed for the treatment of cancer (N = 107).
Outcomes	Progression-free survival.

Testori 2008 *(Continued)*

	Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: 9 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned". Comment: Risk was likely low because this was a multicentre trial with centralised randomisation
Allocation concealment (selection bias)	Low risk	Risk was likely low because this was a multicentre trial with centralised randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Thatcher 1986

Study characteristics

Methods	Phase III parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Randomised participants: 79.

Thatcher 1986 *(Continued)*

Interventions	Two-arm trial: • *C parvum* 2 mg/m² SC every 3 weeks for a maximum of 8 courses (N = 40); • Observation (N = 39). All participants who had disease progression were treated with dacarbazine 250 mg/m² IV daily on days 1 to 5 and actinomycin D 1.5 mg/m² IV on day 1 every 3 weeks.
Outcomes	Overall survival. Tumour response. Toxicity.
Notes	Quality of life: not reported. Cross-over: not allowed. Participants with brain metastasis: excluded. Median follow-up: > 36 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomized". Comment: However, there was insufficient information to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Thomson 1993

Study characteristics

Methods	Phase III parallel-group RCT.

Thomson 1993 *(Continued)*

	Open label study.
Participants	Untreated metastatic melanoma. Randomised participants: 170.
Interventions	Two-arm trial: • Dacarbazine 800 mg/m² IV on day 1 every 3 weeks (N = 83); • Darbazine IV on day 1 every 3 weeks dose was escalated from 200 mg/m² to 400 mg/m² to 800 mg/m² every 3 weeks if blood counts allowed and stayed at this dose thereafter, + IFN SC daily 3 times a week at a staring dose of 3 mU for 3 days, then 9 mU for 67 days, and thereafter 9 mU 3 times a week (N = 87).
Outcomes	Overall survival. Tumour response. Toxicity.
Notes	Quality of life: analysis of quality of life was reported in a different article (Coates 1993). There was no statistically significant difference in quality of life between treatment arms. Cross-over: not allowed. Participants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised centrally using a dynamic randomisation technique." Comment: This method ensured low risk of selection bias.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Veronesi 1984

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Randomised participants: 377.
Interventions	Three-arm study: • Dacarbazine 300 mg/m² IV daily on days 1 to 5 (N = 76 evaluable participants); • Dacarbazine 300 mg/m² IV daily on days 1 to 5, and BCG 6x10^8 IU SC daily on days 8, 15, 22 (N = 65 evaluable participants); • Dacarbazine 300 mg/m² IV daily on days 1 to 5, and *C parvum* 5 mg/m² SC daily on days 8 to 22 (N = 55 evaluable participants).
Outcomes	Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The composition of the series... was prepared by the coordinating center". Comment: This method ensured low risk of selection bias.
Allocation concealment (selection bias)	Low risk	Quote: "The envelopes... were opened at the moment of choice of treatment." Comment: This method ensured low risk of selection bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias)	Unclear risk	Reasons for exclusions not reported.

Veronesi 1984 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Verschraegen 1993

Study characteristics	
Methods	Phase II parallel-group RCT. Open label study.
Participants	Randomised participants: 103. Untreated and previously treated metastatic melanoma.
Interventions	Two-arm study: • Dacarbazine 800 mg/m^2 IV day 1, vindesine 1 mg/m^2 IV days 1 to 5 every 3 weeks (N = 51); • Dacarbazine 800 mg/m^2 IV day 1, vindesine 1 mg/m^2, IV days 1 to 5, and BCG1 0.5 mg/m^2 SC on days 7 and 14 every 3 weeks (N = 47).
Outcomes	Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: included. Median follow-up: not available.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised". Comment: There was insufficient information to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.

Verschraegen 1993 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Vorobiof 1994

Study characteristics	
Methods	Phase II parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Randomised participants: 60.
Interventions	Three-arm trials: • *Chemotherapy:* Vindesine 3 mg/m^2 IV weekly for 3 weeks, followed by vindesine 4 mg/m^2 IV each 21 days (N = 20); • *Immunotherapy:* IFN-α 6 mIU/m^2 SC 3 times weekly (N = 20); • *Chemo-immunotherapy:* Vindesine 3 mg/m^2 IV weekly for 3 weeks, followed by vindesine 4 mg/m^2 IV each 21 days; IFN-α 6 mIU/m^2 SC 3 times weekly (N = 20).
Outcomes	Overall survival. Tumour response. Toxicity.
Notes	Quality of life: not reported. Cross-over: not allowed. Participants with brain metastasis: excluded. Median follow-up: 13 months.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "...closed envelope random number technique". Comment: This method ensured low risk of selection bias.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.

Vorobiof 1994 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no missing data.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Vuoristo 2005

Study characteristics	
Methods	Phase II parallel-group RCT. Open label study.
Participants	Untreated and previously treated (only drugs other than dacarbazine were allowed) metastatic melanoma. Randomised participants: 106.
Interventions	Four-arm trial: • *Arm A:* DTIC 250 mg/m^2 IV daily on days 1 to 5 + IFN-α 3x10^6 mU SC daily starting on day 8 for 6 weeks and, thereafter, 6 mU 3 times weekly SC (N = 25); • *Arm B:* Dacarbazine 200 mg/m^2 IV daily on days 1 to 5, vincristine 1 mg/m^2 (maximum, 2 mg) IV daily on days 1 and 4, bleomycin 15 mg IV on days 2 and 5, and lomustine 80 mg orally on day 1 plus IFN-α 3x10^6 mU SC daily starting on day 8 for 6 weeks and, thereafter, 6 mU 3 times weekly SC (N = 31); • *Arm C:* DTIC + IFN-α 3x10^6 mU SC daily starting on day 8 for 6 weeks and, thereafter, 6 mU 3 times weekly SC (N = 25); • *Arm D:* Dacarbazine 200 mg/m^2 IV daily on days 1 to 5, vincristine 1 mg/m^2 (maximum, 2 mg) IV daily on days 1 and 4, bleomycin 15 mg IV on days 2 and 5, and lomustine 80 mg orally on day 1 + IFN-α 3x10^6 mU SC daily starting on day 8 for 6 weeks and, thereafter, 6 mU 3 times weekly SC (N = 25).
Outcomes	Overall survival. Progression-free survival. Tumour response. Toxicity.
Notes	Quality of life: not reported. Cross-over: not allowed.

Vuoristo 2005 *(Continued)*

	Participants with brain metastasis: excluded. Median follow-up: > 17 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The randomization was performed at the Finnish Cancer Registry and stratified for treatment arm by institution." Comment: There was insufficient information about the sequence generation process to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Weber 2009

Study characteristics

Methods	Phase II parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Randomised participants: 184.
Interventions	Four-arm trial: • PF-3512676 10 mg SC every 3 weeks (N = 46); • PF-3512676 40 mg SC every 3 weeks (N = 46); • PF-3512676 40 mg SC + dacarbazine 850 mg/m^2 IV on the first week of the cycle every 3 weeks (N = 45); • Dacarbazine 850 mg/m^2 IV on the first week of the cycle alone every 3 weeks (N = 39).
Outcomes	Progression-free survival.

Weber 2009 *(Continued)*

	Overall survival. Tumour response. Toxicity.
Notes	Quality of life: not reported. Cross-over: not allowed. Participants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised." Comment: There was insufficient information about the sequence generation process to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was no information sufficient to judge.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Weber 2015

Study characteristics

Methods	Phase III parallel-group RCT. Open label study.
Participants	Previously treated metastatic melanoma. Both BRAF mutant and non-mutant tumours were included. Randomised participants: 405.

Weber 2015 *(Continued)*

Interventions	Two-arm study: • Nivolumab 3 mg/kg every 2 weeks until progression or unacceptable toxic effects (N = 272); • Investigator choice chemotherapy: Dacarbazine 1000 mg/m^2 every 3 weeks or paclitaxel 175 mg/m^2 combined with carboplatin area under the curve 6 every 3 weeks until progression or unacceptable toxic effects (N = 133).
Outcomes	Tumour response. Toxicity.
Notes	Quality of life: not reported. Cross-over: not allowed. Participants with brain metastasis: excluded when brain metastases were active. Median follow-up: 8 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "We used permuted blocks (block size of six) within each stratum for randomisation." Comment: This method ensured low risk of selection bias.
Allocation concealment (selection bias)	Low risk	Quote: "using an interactive voice response system." Comment: This method ensured low risk of selection bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "those doing tumour assessments were masked to treatment assignment". Comment: The method ensured low risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Wittes 1978

Study characteristics

Methods	Phase II parallel-group RCT.

Wittes 1978 *(Continued)*

	Open label study.
Participants	Untreated metastatic melanoma. Randomised participants: 95.
Interventions	Three-arm trial: • Dacarbazine 800 mg/m² IV on day 1, vinblastine 6 mg/m² IV days 1 and 15 every 4 weeks (N = 29); • Dacarbazine 800 mg/m² IV on day 1, procarbazine 150 mg/m² orally daily days 1 to 14 inclusive (N = 34); • Dacarbazine 800 mg/m² IV on day 1, cyclophosphamide 100 mg/m² orally daily days 1 to 14 inclusive (N = 32).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Quality of life: not reported. Cross-over: not allowed. Participants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomized". Comment: There was insufficient information to permit judgment.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Wolchok 2010

Study characteristics	
Methods	Phase II parallel-group RCT. Double-blind study.
Participants	Previously treated metastatic melanoma. Participants randomised: 217.
Interventions	Two-arm trial: • Ipilimumab 10 mg/kg IV every 3 weeks for 4 cycles (induction) followed by maintenance therapy every 3 months (N = 73); • Ipilimumab 3 mg/kg IV every 3 weeks for 4 cycles (induction) followed by maintenance therapy every 3 months (N = 72); • Ipilimumab 0.3 mg/kg IV every 3 weeks for 4 cycles (induction) followed by maintenance therapy every 3 months (N = 72).
Outcomes	Overall survival. Tumour response. Toxicity.
Notes	Cross-over: not allowed. Quality of life: not reported. Participants with brain metastasis: included. Median follow-up: 9 months.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was done with a permuted block procedure" Comment: This method ensured low risk of selection bias.
Allocation concealment (selection bias)	Low risk	Quote: "Patients, treating doctors, and doctors' staff were unaware of the dose to which patients were assigned, whereas pharmacists were unmasked". Comment: This statement makes low the risk of selection bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blinded". Comment: The method ensured low risk of performance bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double blinded". Comment: The method ensured low risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.

Wolchok 2010 *(Continued)*

Selective reporting (reporting bias)	Low risk	No differences between protocol and published report.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Young 2001

Study characteristics	
Methods	Phase III parallel-group RCT. Open label study.
Participants	Untreated metastatic melanoma. Randomised participants: 61.
Interventions	Two-arm study: • Dacarbazine 950 mg/m^2 IV every 4 weeks for a maximum of 6 months or until disease progression (N = 31); • Dacarbazine 950 mg/m^2 IV every 4 weeks, IFN-α 4.5 mU SC 3 times weekly for a maximum of 6 months or until disease progression (N = 30).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Quality of life: There were no differences in quality of life between treatment groups. Cross-over: not allowed. Participants with brain metastasis: excluded. Median follow-up: not available.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "...random permuted blocks method" Comment: This method ensured low risk of selection bias.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.

Young 2001 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Zimpfer-Rechner 2003

Study characteristics	
Methods	Phase II parallel-group RCT. Open label study.
Participants	Previoulsy treated metastatic melanoma. Randomised participants: 40.
Interventions	Two-arm trial: • *Monochemotherapy:* paclitaxel 100 mg/m^2 IV on day 1 of each week for 6 weeks, followed by 2 weeks of rest. The cycle was repeated at day 57 (N = 21); • *Polychemotherapy:* paclitaxel 80 mg/m^2 IV on day 1 of each week for 6 weeks, and carboplatin 200 mg/m^2 IV on day 1 of each week for 6 weeks, followed by 2 weeks of rest. The cycle was repeated at day 57 (N = 19).
Outcomes	Progression-free survival. Overall survival. Tumour response. Toxicity.
Notes	Quality of life: not reported. Cross-over: not allowed. Participants with brain metastasis: included. Median follow-up: not available.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomized". Comment: There was insufficient information to permit judgment.

Zimpfer-Rechner 2003 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	There was insufficient information to permit judgment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As an open label study, no blinding of participants or personnel was possible. However, we believe that in this setting (metastatic melanoma), with the treatments tested and outcomes assessed, the knowledge of which intervention was received or administered (rather than the intervention itself), could not affect the outcomes under investigation. Therefore, we judged the risk of performance bias as low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	Published reports included all expected outcomes. However, no protocol was available so it was unclear if all planned outcomes were reported.
Other bias	Low risk	The study appeared to be free of other sources of bias.

Abbreviations: BCG - Bacillus Calmette-Guérin; BCNU - 1,3-bis(2-chloroethyl)-1-nitrosourea; CCNU - lomustine; ECOG - Eastern Cooperative Oncology Group; CR - complete response; G-CSF - granulocyte-colony stimulating factor; IFN - interferon-alpha; IFN-α - interferon-alpha; IL-2 - interleukin-2; IM - intramuscular; IV - intravenous; MAP - mitogen-activated protein; MGMT - methylguanine-DNA methyltransferase; NA - not applicable; PEG-IFN - pegylated interferon; PR - partial response; QoL - quality of life; RCT - randomised controlled trial; SC - subcutaneous.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Asemissen 2005	This study investigated mechanisms of interaction between interleukin-2 and histamine in a subgroup of 19 participants enrolled in a trial. This study was excluded because study endpoints did not match inclusion criteria; the study was about drug interaction and not patient survival or tumour response or toxicity.
Atzpodien 1995	This study is not an RCT.
Bleehen 1995	This study is not an RCT.
Buchbinder 2015	This study is not an RCT.
Bukowski 1983	This study investigated adjuvant therapy following radical resection of lymph node metastasis (participants were not affected with early stage and not advanced/metastatic melanoma).
Cashin 2008	This study is not an RCT.
Cormier 1997	This study investigated the effect of dopamine for reducing renal toxicity caused by interleukin-2.
Curl 2014	This study is not an RCT.
Downey 2007	This study is not an RCT.

Study	Reason for exclusion
Hill 1984	This study reported a retrospective analysis of participants who had experienced a complete tumour response in RCTs from the Central Oncology Group.
Hughes 2016	This RCT did not investigate systemic treatments for metastatic disease. Participants were randomised to receive a local treatment, liver infusion, for hepatic metastasis.
Hwu 2009	This article is a commentary on preliminary findings of a RCT already included in this review (Schwartzentruber 2011a).
Kaufman 2010	This study did not investigate systemic treatment. It tested direct injection of an oncolytic herpes simplex virus type 1 encoding granulocyte macrophage colony-stimulating factor into accessible melanoma lesions.
Kleeberg 1982	This study is not an RCT.
Lattanzi 1995	This study is not an RCT.
McDermott 2013	This study analysed selected participants experiencing long-term survival in Hodi 2010a.
Mornex 2003	This study investigated whole brain radiotherapy associated with fotemustine compared to fotemustine alone, and thus did not test effectiveness of systemic treatment.
Quirt 1983	This study investigated both participants with early stage and metastatic melanoma. This study was excluded because tumour stage of enrolled participants did not match our inclusion criteria (no separate findings for different stages were reported and thus we could not include even part of the results).
Richards 1999	This study is not an RCT.
Spieth 2008	This study is not an RCT.
Van Dyk 1975	This study was not an RCT.
Varker 2007	This study randomised participants with metastatic melanoma treated with bevacizumab to receive local interleukin-2 injections.
Weber 2013	This study gathered data from three different RCTs and focused on adverse events. This study was excluded because it is a secondary analysis pooling data from one RCT, Hodi 2010a, already included in this systematic review.
Yang 1995	This study enrolled both participants with metastatic melanoma and metastatic renal cell carcinoma. Information specifically regarding melanoma was not reported for any study endpoint.

RCT - randomised controlled trial.

Characteristics of ongoing studies *[ordered by study ID]*

NCT01280565

Study name	A phase 3 study to compare efficacy and safety of masitinib to dacarbazine in the treatment of patients with non-resectable or metastatic stage 3 or stage 4 melanoma carrying a mutation in the juxta membrane domain of C-Kit.
Methods	Phase III RCT.
Participants	Metastatic melanoma.

NCT01280565 *(Continued)*

	Estimated enrolment: 200.
Interventions	Two-arm trial: • masitinib 7.5 mg/kg/day; and • dacarbazine IV bolus at 1000 mg/m^2 once every three weeks.
Outcomes	**Primary outcome:** • Progression-free survival. **Secondary outcome:** • Overall survival.
Starting date	January 2011.
Contact information	Jean Jaques Grob, jean-jacques.grob@mail.ap-hm.fr
Notes	-

NCT01515189

Study name	Phase 3 trial in subjects with metastatic melanoma comparing 3 mg/kg ipilimumab versus 10 mg/kg ipilimumab.
Methods	Phase III RCT.
Participants	Metastatic melanoma. Estimated enrolment: 700.
Interventions	Two-arm trial: • ipilimumab 3 mg/kg IV once every 3 weeks for 4 doses; option for re-induction, until disease progression or unacceptable toxicity; and • ipilimumab 10 mg/kg IV once every 3 weeks for 4 doses; option for re-induction, until disease progression or unacceptable toxicity.
Outcomes	**Primary outcome:** • Overall survival. **Secondary outcomes:** • progression-free survival; • best overall response rate; • disease control rate; • duration of response; and • duration of stable disease.
Starting date	January 2012.
Contact information	88 recruiting sites (available at clinicaltrials.gov).
Notes	-

NCT01763164

Study name	Study comparing the efficacy of MEK162 versus dacarbazine in unresectable or metastatic NRAS mutation-positive melanoma.
Methods	Phase III RCT.
Participants	Metastatic melanoma. Estimated enrolment: 397.
Interventions	Two-arm study: • MEK162 45 mg orally twice daily; and • Dacarbazine 1000 mg/m^2 IV on day 1 and then every three weeks.
Outcomes	**Primary outcome:** • Progression-free survival. **Secondary outcomes:** • overall survival; • overall response rate; • time to objective response; • disease control rate; • duration of objective response; • number of participants with adverse events; • number of participants with serious adverse events; • global health status (EORTC QLQC30); and • global health status (EQ-5D).
Starting date	July 2013.
Contact information	167 recruiting sites (available at clinicaltrials.gov).
Notes	-

NCT01909453

Study name	Study comparing combination of LGX818 plus MEK162 versus vemurafenib and LGX818 monotherapy in BRAF mutant melanoma (COLUMBUS).
Methods	Phase III RCT.
Participants	Metastatic melanoma. Estimated enrolment: 900.
Interventions	Four-arm trial: • LGX818 450 mg daily + MEK162 45 mg twice a day; • Vemurafenib 960 mg twice a day; • LGX818 300 mg daily + MEK162 45 mg twice a day; • LGX818 300 mg daily.

NCT01909453 *(Continued)*

Outcomes	**Primary outcome:** • Progression-free survival. **Secondary outcomes:** • overall survival; • objective response rate; • time to response; • disease control rate; • duration of objective response; • safety and tolerability of combination and LGX818; • ECOG performance status; • time to definitive 1 point deterioration in ECOG performance status; • pharmacokinetics of LGX818 and MEK162; • time to definitive 10% deterioration in global health status (EORTC QLQC30); • global health status (EORTC QLQC30); • time to definitive 10% deterioration in the FACT-M melanoma subscale; and • global health status (EQ-5D).
Starting date	September 2013.
Contact information	230 recruiting sites (available at clinicaltrials.gov).
Notes	-

NCT01940809

Study name	Ipilimumab with or without dabrafenib, trametinib, and/or nivolumab in treating patients with melanoma that is metastatic or cannot be removed by surgery
Methods	Phase I RCT.
Participants	Metastatic melanoma. Estimated enrolment: 40.
Interventions	Five-arm trial: • participants receive dabrafenib orally twice daily and trametinib orally once daily for 25 days. Participants then receive ipilimumab IV over 90 minutes. Treatment with ipilimumab repeats every 3 weeks for 4 courses in the absence of disease progression or unacceptable toxicity; • participants receive dabrafenib orally twice daily and trametinib orally once daily for 25 days followed by nivolumab IV over 60 minutes and ipilimumab IV over 90 minutes every 3 weeks for 4 doses, followed by nivolumab monotherapy IV every 2 weeks continuously for up to 42 courses; • participants receive trametinib orally once daily for 25 days. Participants then receive ipilimumab IV over 90 minutes. Treatment with ipilimumab repeats every 3 weeks for 4 courses in the absence of disease progression or unacceptable toxicity; • participants receive trametinib orally once daily for 25 days followed by nivolumab IV over 60 minutes and ipilimumab IV over 90 minutes every 3 weeks for 4 doses, followed by nivolumab monotherapy IV every 2 weeks continuously for up to 42 courses; • participants receive dabrafenib orally twice daily for 25 days. Participants then receive ipilimumab IV over 90 minutes. Treatment with ipilimumab repeats every 3 weeks for 4 courses in the absence of disease progression or unacceptable toxicity;

NCT01940809 *(Continued)*

	• participants receive dabrafenib orally twice daily for 25 days followed by nivolumab IV over 60 minutes and ipilimumab IV over 90 minutes every 3 weeks for 4 doses, followed by nivolumab monotherapy IV every 2 weeks continuously for up to 42 courses; • participants receive ipilimumab IV over 90 minutes. Treatment repeats every 3 weeks for 4 courses in the absence of disease progression or unacceptable toxicity. Participants receive nivolumab IV over 60 minutes and ipilimumab IV over 90 minutes every 3 weeks for 4 doses, followed by nivolumab monotherapy IV every 2 weeks continuously for up to 42 courses.
Outcomes	**Primary outcome:** • Incidence of grade 3 or higher immune-related adverse events. **Secondary outcomes:** • disease-control rate; • proportion of participants receiving dabrafenib and trametinib with grade 3 or higher irAEs after disease progression on ipilimumab; and • response rate for the total treatment period.
Starting date	August 2013.
Contact information	• Brigham and Women's Hospital, Boston, MA, USA. Contact: Scott J Rodig, srodig@partners.org; • Dana-Farber Cancer Institute, Boston, MA, USA. Contact: Patrick A Ott, Patrick_ott@dfci.harvard.edu.
Notes	-

NCT01943422

Study name	Safety and efficacy study of vemurafenib and high-dose interferon alfa-2b in melanoma (12-107)
Methods	Phase I/II RCT
Participants	Metastatic melanoma. Estimated enrolment: 63.
Interventions	Three-arm study: • vemurafenib + high-dose interferon alfa-2b (10 mU/m^2/d); • vemurafenib + high-dose interferon alfa-2b (15 mU/m^2/d); • vemurafenib + high-dose interferon alfa-2b (20 mU/m^2/d).
Outcomes	**Primary outcomes:** • Number of participants with adverse events. **Secondary outcome:** • Progression-free survival.
Starting date	September 2013.
Contact information	John Kirkwood, MD, kirkwoodjm@upmc.edu
Notes	-

NCT02130466

Study name	A phase I/II study to assess the safety and efficacy of MK-3475 in combination with trametinib and dabrafenib in subjects with advanced melanoma.
Methods	Phase I/II RCT.
Participants	Metastatic melanoma. Estimated enrolment: 177.
Interventions	Four-arm trial: • Participants receive pembrolizumab intravenously (IV) on Days 1 and 22 of each 6-week cycle; dabrafenib capsules, 150 mg/day total, orally, in a divided dose twice daily starting on Day 1, through study treatment discontinuation; and trametinib tablets, 2 mg, orally, once daily starting on Day 1, through study treatment discontinuation; • Participants receive placebo IV on Days 1 and 22 of each 6-week cycle; dabrafenib capsules, 150 mg/day total, orally, in a divided dose twice daily starting on Day 1, through study treatment discontinuation; and trametinib tablets, 2 mg, orally, once daily starting on Day 1, through study treatment discontinuation; • Participants receive pembrolizumab IV on Days 1 and 22 of each 6-week cycle and trametinib tablets, 2 mg, orally, once daily starting on Day 1, through study treatment discontinuation; • Participants receive pembrolizumab IV on Days 1 and 22 of each 6-week cycle and dabrafenib capsules, 150 mg/day total, orally, in a divided dose twice daily starting on Day 1, through study treatment discontinuation.
Outcomes	**Primary outcomes:** • number of participants with dose-limiting toxicities; and • progression-free survival. **Secondary outcome:** • Objective response rate.
Starting date	May 2014.
Contact information	Toll Free Number 1-888-577-8839
Notes	-

NCT02224781

Study name	A randomized phase III trial of dabrafenib + trametinib followed by ipilimumab + nivolumab at progression vs. ipilimumab + nivolumab followed by dabrafenib + trametinib at progression in patients with advanced BRAFV600 mutant melanoma.
Methods	Phase III RCT.
Participants	Metastatic melanoma. Estimated enrolment: 300.
Interventions	Four-arm study:

NCT02224781 *(Continued)*

	• Arm A (immunotherapy) - immunotherapy induction (courses 1 - 2): participants receive nivolumab IV over 60 minutes and ipilimumab IV over 90 minutes on Days 1 and 22. Treatment repeats every 6 weeks for 2 courses in the absence of disease progression or unacceptable toxicity. Immunotherapy maintenance (courses 3 - 4): participants receive nivolumab IV over 60 minutes on Days 1, 15, and 29. Treatment repeats every 6 weeks for up to 12 courses in the absence of disease progression or unacceptable toxicity. Upon disease progression, participants re-register and pass to Arm C; • Arm B (BRAF inhibitor therapy) - participants receive oral dabrafenib twice daily and oral trametinib daily on Days 1 to 42. Courses repeat every 6 weeks in the absence of disease progression or unacceptable toxicity. Upon disease progression, participants re-register and passed to Arm D; • Arm C (BRAF inhibitor therapy) - participants receive oral dabrafenib twice daily and oral trametinib daily on Days 1 to 42. Courses repeat every 6 weeks in the absence of disease progression or unacceptable toxicity; • Arm D (immunotherapy): Immunotherapy induction (courses 1 - 2): participants receive nivolumab IV over 60 minutes and ipilimumab IV over 90 minutes on Days 1 and 22. Treatment repeats every 6 weeks for 2 courses in the absence of disease progression or unacceptable toxicity. Immunotherapy maintenance (courses 3 - 14): participants receive nivolumab IV over 60 minutes on Days 1, 15, and 29. Treatment repeats every 6 weeks for up to 12 courses in the absence of disease progression or unacceptable toxicity.
Outcomes	**Primary outcome:** • Overall survival. **Secondary outcomes:** • progression-free survival; • response rates; and • toxicity.
Starting date	July 2015
Contact information	Michael Atkins, ECOG-ACRIN Cancer Research Group
Notes	-

NCT02278887

Study name	Randomized phase III study comparing a non-myeloablative lymphocyte depleting regimen of chemotherapy followed by infusion of tumor infiltrating lymphocytes and interleukin-2 to standard ipilimumab treatment in metastatic melanoma.
Methods	Phase III RCT.
Participants	Metastatic melanoma. Estimated enrolment: 162.
Interventions	Two arm trial: • Non-myeloablative lymphocyte depleting regimen of chemotherapy followed by infusion of tumour infiltrating lymphocytes and interleukin-2; • Ipilimumab.
Outcomes	**Primary outcome:** • Progression-free survival.

NCT02278887 *(Continued)*

	Secondary outcome: • Immune-related progression-free survival. **Other outcome measure:** • Safety.
Starting date	September 2014.
Contact information	John BAG Haanen, j.haanen@nki.nl
Notes	-

NCT02339571

Study name	Randomized phase II/III study of nivolumab plus ipilimumab plus sargramostim versus nivolumab plus ipilimumab in patients with unresectable stage III or stage IV melanoma.
Methods	Phase III RCT.
Participants	Metastatic melanoma with brain metastasis. Estimated enrolment: 400.
Interventions	Two-arm trial: • *Induction therapy:* participants receive nivolumab IV over 60 minutes on Day 1, ipilimumab IV over 90 minutes on Day 1, and sargramostim SC on Days 1 to 14. Treatment repeats every 21 days for 4 courses in the absence of disease progression or unacceptable toxicity. *Maintenance therapy:* participants receive nivolumab and sargramostim as for induction therapy. Participants with PR, SD, or CR at 24 weeks may continue maintenance therapy in the absence of disease progression or unacceptable toxicity. • *Induction therapy:* participants receive nivolumab and ipilimumab as in Arm I. Treatment repeats every 21 days for 4 courses in the absence of disease progression or unacceptable toxicity. *Maintenance therapy:* participants receive nivolumab as for induction therapy. participants with PR, SD, or CR at 24 weeks may continue maintenance therapy in the absence of disease progression or unacceptable toxicity.
Outcomes	**Primary outcome:** • Overall survival. **Secondary outcomes:** • clinical response; • immune response; • incidence of toxicities; and • progression-free survival.
Starting date	September 2015.
Contact information	Frank Hodi, ECOG-ACRIN Cancer (Eastern Co-operative Oncology Group-American College of Radiology Imaging Network) Research Group
Notes	-

NCT02388906

Study name	A phase III, randomized, double-blind study of adjuvant immunotherapy with nivolumab versus ipilimumab after complete resection of stage IIIb/c or stage IV melanoma in subjects who are at high risk for recurrence (CheckMate 238: CHECKpoint Pathway and nivoluMAb Clinical Trial Evaluation 238).
Methods	Phase III RCT.
Participants	Metastatic melanoma with brain metastasis. Estimated enrolment: 800.
Interventions	Two-arm study: • ipilimumab IV infusion and placebo; • nivolumab IV infusion and placebo.
Outcomes	**Primary outcome:** • Overall survival. **Secondary outcome:** • Progression-free survival.
Starting date	March 2015.
Contact information	136 recruiting sites (available at clinicaltrials.gov).
Notes	-

NCT02416232

Study name	An open label non randomized access study of trametinib for patients with advanced unresectable (stage IIIc) or distant metastatic (stage IV) BRAF V600E/K mutation positive cutaneous melanoma.
Methods	Phase III non-RCT.
Participants	Metastatic melanoma with brain metastasis. Estimated enrolment: 250.
Interventions	Single arm study: participants will receive trametinib 2 mg orally once daily and, where appropriate, in combination with dabrafenib 150 mg orally twice daily.
Outcomes	**Primary outcomes:** • Frequency of adverse events (AE); • Proportion of the AEs; • Number of participants with serious adverse events (SAEs); and • Response rates to treatment
Starting date	March 2015.
Contact information	USA GSK Clinical Trials Call Center, GSKClinicalSupportHD@gsk.com

NCT02416232 *(Continued)*

Notes	-

NCT02460068

Study name	A randomized, phase III study of fotemustine versus the combination of fotemustine and ipilimumab or the combination of ipilimumab and nivolumab in patients with metastatic melanoma with brain metastasis (NIBIT-m^2).
Methods	Phase III RCT.
Participants	Metastatic melanoma with brain metastasis. Estimated enrolment: 168.
Interventions	Three-arm trial: • Fotemustine 100 mg/m^2 IV over 60 minutes once every week for 3 doses, and once every 3 weeks from week 9 for 6 doses; • Fotemustine 100 mg/m^2 IV over 60 minutes once a week for 3 weeks (Weeks 1, 2, 3) plus ipilimumab at 10 mg/kg IV over 90 minutes every 3 weeks for 4 cycles (Weeks 1, 4, 7, 10); fotemustine 100 mg/m^2 IV over 60 minutes once every 3 weeks from week 9 for 6 doses plus ipilimumab at 10 mg/kg IV over 90 minutes every 12 weeks from week 24; and • Ipilimumab 3 mg/kg IV over 90 minutes combined with nivolumab 1 mg/kg IV over 60 minutes every three weeks for 4 doses, then nivolumab 3 mg/kg IV over 60 minutes every two weeks.
Outcomes	**Primary outcome:** • Overall survival. **Secondary outcomes:** • safety (adverse events); • m-WHO and immune-related disease control rate in and outside the brain; • immune-related progression-free survival; • m-WHO progression-free survival; • objective response rate; • immune-related objective response rate; • time to response; • immune-related time to response; • duration of response; • immune-related duration of response; and • brain progression-free survival.
Starting date	December 2012
Contact information	Anna Maria Di Giacomo, PhD, MD, a.m.digiacomo@ao-siena.toscana.it
Notes	-

NCT02506153

Study name	A phase III randomized trial comparing physician/patient choice of either high dose interferon or ipilimumab to MK-3475 (pembrolizumab) in patients with high risk resected melanoma.
Methods	Phase III RCT.
Participants	Participants who underwent surgery for distant metastasis. Estimated enrolment: 1378.
Interventions	Two-arm trial: • *Induction therapy*: Participants receive high-dose recombinant interferon alfa-2B IV over 20 minutes on Days 1 to 5. Treatment repeats weekly for 4 weeks in the absence of disease progression or unacceptable toxicity. Or participants receive ipilimumab IV over 90 minutes on Day 1. Treatment repeats every 3 weeks for a total of 4 courses in the absence of disease progression or unacceptable toxicity. *Maintenance therapy:* Participants receive high-dose recombinant interferon alfa-2B SC on Days 1, 3, and 5. Treatment repeats every 6 weeks for up to 48 weeks in the absence of disease progression or unacceptable toxicity. Or participants receive ipilimumab IV over 90 minutes on Day 1. Treatment repeats every 12 weeks for 3 years in the absence of disease progression or unacceptable toxicity; • Participants receive pembrolizumab IV over 30 minutes on Day 1. Treatment repeats every 3 weeks for up to 52 weeks in the absence of disease progression or unacceptable toxicity.
Outcomes	**Primary outcomes:** • overall survival; • PD-L1 status; and • progression-free survival. **Secondary outcomes:** • B-Raf proto-oncogene, serine/threonine kinase (BRAF) mutation status; • quality of life; • incidence of toxicity; • long-term survival; and • post-relapse therapy.
Starting date	October 2015.
Contact information	314 recruiting sites (available at clinicaltrials.gov).
Notes	-

NCT02599402

Study name	Clinical trial of nivolumab (BMS-936558) combined with ipilimumab followed by nivolumab monotherapy as first-line therapy of subjects with histologically confirmed stage III (unresectable) or stage IV melanoma. CheckMate 401: CHECKpoint Pathway and nivoluMAb Clinical Trial Evaluation 401
Methods	Phase III RCT.
Participants	Metastatic melanoma with brain metastasis. Estimated enrolment: 615.

NCT02599402 *(Continued)*

Interventions	Two-arm study: • combination therapy nivolumab and ipilimumab; and • nivolumab.
Outcomes	**Primary outcome:** • Rate and frequency for high-grade (CTCAE v4.0 Grade 3 to 5) treatment-related, select adverse events. **Secondary outcomes:** • incidence of all high-grade (Grades 3 to 5), select adverse events; • median time to onset (Grades 3 to 4) of select adverse events; • median time to resolution (Grades 3 to 4) of select adverse events; • resolution of an adverse event; • overall survival; • safety; • tolerability; • objective response rate; and • progression-free survival.
Starting date	December 2015.
Contact information	41 recruiting sites (available at clinicaltrials.gov).
Notes	-

NCT02625337

Study name	Phase 2 study comparing pembrolizumab with intermittent/short-term dual MAPK pathway inhibition plus pembrolizumab in patients harboring the BRAFV600 mutation.
Methods	Phase II RCT.
Participants	Metastatic melanoma. Estimated enrolment: 32.
Interventions	Four-arm trial: • pembrolizumab monotherapy; • pembrolizumab combined with a short scheme of dabrafenib plus trametinib; • pembrolizumab combined with an intermediate scheme of dabrafenib plus trametinib; and • pembrolizumab combined with a long scheme of dabrafenib plus trametinib.
Outcomes	**Primary outcomes:** • Safety of different schemes of continuous/intermittent dabrafenib + trametinib during treatment with pembrolizumab as compared to pembrolizumab monotherapy. • Feasibility of different schemes of continuous/intermittent dabrafenib + trametinib during treatment with pembrolizumab as compared to pembrolizumab monotherapy as measured by adherence to the timelines in the study protocol. • The immune-activating capacity of different schemes of continuous/intermittent dabrafenib + trametinib during treatment with pembrolizumab as compared to pembrolizumab monotherapy.

NCT02625337 *(Continued)*

	Secondary outcomes: • response rates; • progression-free survival; and • long-term toxicities of intermittent dabrafenib + trametinib during treatment with pembrolizumab as compared to pembrolizumab monotherapy.
Starting date	January 2016.
Contact information	• Prof Christian U Blank, c.blank@nki.nl; • Loes M Pronk, l.pronk@nki.nl.
Notes	-

NCT02714218

Study name	Phase IIIb/IV, randomized, double blinded, study of nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg vs nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in subjects with previously untreated, unresectable or metastatic melanoma.
Methods	Phase III RCT.
Participants	Metastatic melanoma. Estimated enrolment: 304.
Interventions	Two-arm trial: • Nivolumab 3 mg/kg IV and Ipilimumab 1 mg/kg IV. • Nivolumab 1 mg/kg IV and Ipilimumab 3 mg/kg IV.
Outcomes	**Primary outcome:** • Incidence of drug-related grade 3 to 5 adverse events. **Secondary outcomes:** • objective response rate; • overall survival; • quality of life; and • progression-free survival.
Starting date	March 2016.
Contact information	52 recruiting sites (available at clinicaltrials.gov).
Notes	-

NCT02752074

Study name	A phase III randomized, double-blind, placebo-controlled study of pembrolizumab (MK-3475) in combination with epacadostat or placebo in subjects with unresectable or metastatic melanoma (Keynote-252 / ECHO-301).

NCT02752074 *(Continued)*

Methods	Phase III RCT.
Participants	Metastatic melanoma. Estimated enrolment: 600.
Interventions	Two-arm trial: • Pembrolizumab IV every 3 weeks starting at Day 1 (Week 1), and epacadostat orally daily starting at Day 1 (Week 1). • Pembrolizumab IV every 3 weeks starting at Day 1 (Week 1).
Outcomes	**Primary outcomes:** • progression-free survival; and • overall survival. **Secondary outcomes:** • objective response rate; and • safety and tolerability.
Starting date	June 2016.
Contact information	Merck Sharp & Dohme Corp 1-888-577-8839
Notes	-

NCT02821013

Study name	A randomized phase III trial of the duration of anti-PD-1 therapy in metastatic melanoma (STOP-GAP).
Methods	Phase III RCT.
Participants	Metastatic melanoma. Estimated enrolment: 550.
Interventions	Two-arm trial: • intermittent PD-1 Inhibitor therapy; • continuous PD-1 Inhibitor therapy.
Outcomes	**Primary outcome:** • Overall survival. **Secondary outcome:** • progression-free survival; • response rate; • duration of response; • number and severity of adverse events; • quality of life; and • economic evaluation.

NCT02821013 *(Continued)*

Starting date	June 2016.
Contact information	Janet Dancey, jdancey@ctg.queensu.ca
Notes	-

B-Raf – a protein; C-Kit – a protein; CR - complete response; CTCAE - Common Terminology Criteria for Adverse Events; EORTC QLQC30 - European Organization for Research and Treatment quality of life questionnaire (version 3.0); EQ-5D - EuroQol-5D; irAEs – immune-related adverse events; IV - intravenously; MAPK - mitogen-activated protein kinase; mWHO - modified WHO criteria; NRAS - neuroblastoma RAS viral oncogene; PR - partial response; PD-1 - an inhibitory receptor located on the surface of the T-cells; PD-L1 – programmed death-ligand 1; RCT – randomised controlled trial; SC - subcutaneously; SD - stable disease; Vs – versus.

DATA AND ANALYSES

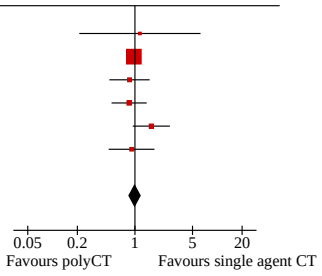
Comparison 1. Polychemotherapy versus single agent chemotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Overall survival	6	594	Hazard Ratio (IV, Random, 95% CI)	0.99 [0.85, 1.16]
1.2 Progression-free survival	5	398	Hazard Ratio (IV, Random, 95% CI)	1.07 [0.91, 1.25]
1.3 Tumour response	14	1885	Risk Ratio (M-H, Random, 95% CI)	1.27 [1.02, 1.58]
1.4 Toxicity (≥ G3)	3	514	Risk Ratio (M-H, Fixed, 95% CI)	1.97 [1.44, 2.71]

Analysis 1.1. Comparison 1: Polychemotherapy versus single agent chemotherapy, Outcome 1: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Polychemotherapy Total	Single agent CT Total	Weight	Hazard Ratio IV, Random, 95% CI
Bafaloukos 2005	0.1393	0.8643	65	62	0.9%	1.15 [0.21 , 6.25]
Chapman 1999	-0.0305	0.0983	119	121	66.1%	0.97 [0.80 , 1.18]
Chauvergne 1982	-0.1508	0.287	23	27	7.8%	0.86 [0.49 , 1.51]
Chiarion Sileni 2001	-0.1625	0.2507	41	19	10.2%	0.85 [0.52 , 1.39]
Luikart 1984	0.4574	0.265	45	32	9.1%	1.58 [0.94 , 2.66]
Zimpfer-Rechner 2003	-0.0943	0.3264	19	21	6.0%	0.91 [0.48 , 1.73]
Total (95% CI)			**312**	**282**	**100.0%**	**0.99 [0.85 , 1.16]**

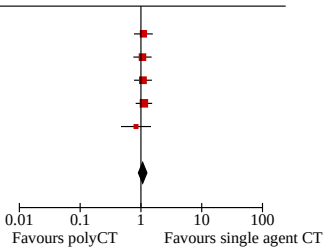
Heterogeneity: Tau² = 0.00; Chi² = 3.86, df = 5 (P = 0.57); I² = 0%
Test for overall effect: Z = 0.14 (P = 0.89)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Polychemotherapy versus single agent chemotherapy, Outcome 2: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Polychemotherapy Total	Single agent CT Total	Weight	Hazard Ratio IV, Random, 95% CI
Bafaloukos 2005	0.0943	0.1818	65	62	20.5%	1.10 [0.77 , 1.57]
Chiarion Sileni 2001	0.0583	0.1765	41	19	21.8%	1.06 [0.75 , 1.50]
Glover 2003	0.077	0.1726	49	45	22.8%	1.08 [0.77 , 1.51]
Luikart 1984	0.1133	0.1591	45	32	26.8%	1.12 [0.82 , 1.53]
Zimpfer-Rechner 2003	-0.1863	0.2902	19	21	8.1%	0.83 [0.47 , 1.47]
Total (95% CI)			**219**	**179**	**100.0%**	**1.07 [0.91 , 1.25]**

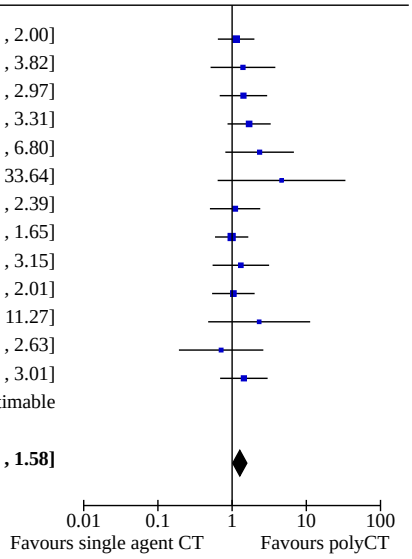
Heterogeneity: Tau² = 0.00; Chi² = 0.87, df = 4 (P = 0.93); I² = 0%
Test for overall effect: Z = 0.79 (P = 0.43)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Polychemotherapy versus single agent chemotherapy, Outcome 3: Tumour response

Study or Subgroup	Polychemotherapy Events	Total	Single agent CT Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bafaloukos 2005	19	65	16	62	14.7%	1.13 [0.64 , 2.00]
Bellett 1976	7	25	5	25	4.7%	1.40 [0.51 , 3.82]
Carter 1975	34	299	8	100	8.7%	1.42 [0.68 , 2.97]
Chapman 1999	20	119	12	121	10.6%	1.69 [0.87 , 3.31]
Chauvergne 1982	8	23	4	27	4.2%	2.35 [0.81 , 6.80]
Chiarion Sileni 2001	10	41	1	19	1.2%	4.63 [0.64 , 33.64]
Costanza 1972	12	62	9	51	7.8%	1.10 [0.50 , 2.39]
Costanza 1977	35	241	19	129	17.8%	0.99 [0.59 , 1.65]
Glover 2003	10	49	7	45	6.2%	1.31 [0.55 , 3.15]
Kogoniia 1981	14	58	13	56	10.9%	1.04 [0.54 , 2.01]
Lopez 1984	4	19	2	22	1.9%	2.32 [0.48 , 11.27]
Luikart 1984	4	45	4	32	2.8%	0.71 [0.19 , 2.63]
Ringborg 1989	15	59	9	51	8.7%	1.44 [0.69 , 3.01]
Zimpfer-Rechner 2003	0	19	0	21		Not estimable
Total (95% CI)		**1124**		**761**	**100.0%**	**1.27 [1.02 , 1.58]**
Total events:	192		109			

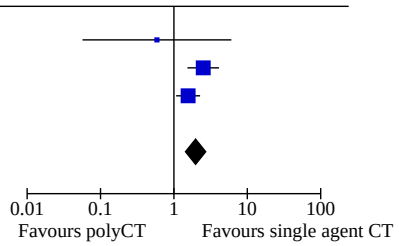
Heterogeneity: Tau² = 0.00; Chi² = 6.79, df = 12 (P = 0.87); I² = 0%
Test for overall effect: Z = 2.15 (P = 0.03)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Polychemotherapy versus single agent chemotherapy, Outcome 4: Toxicity (≥ G3)

Study or Subgroup	Polychemotherapy Events	Total	Single agent CT Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chauvergne 1982	1	23	2	27	4.2%	0.59 [0.06 , 6.06]
Costanza 1977	75	241	16	129	47.9%	2.51 [1.53 , 4.12]
Glover 2003	34	49	20	45	47.9%	1.56 [1.07 , 2.27]
Total (95% CI)		**313**		**201**	**100.0%**	**1.97 [1.44 , 2.71]**
Total events:	110		38			

Heterogeneity: Chi² = 3.43, df = 2 (P = 0.18); I² = 42%
Test for overall effect: Z = 4.21 (P < 0.0001)
Test for subgroup differences: Not applicable



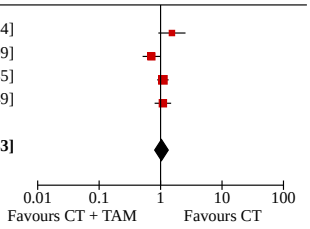
Comparison 2. Chemotherapy ± tamoxifen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Overall survival	4	643	Hazard Ratio (IV, Random, 95% CI)	1.03 [0.80, 1.33]
2.2 Progression-free survival	2	475	Hazard Ratio (IV, Random, 95% CI)	1.06 [0.93, 1.22]
2.3 Tumour response	4	643	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.94, 1.89]
2.4 Toxicity (≥ G3)	1	271	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.38, 1.28]

Analysis 2.1. Comparison 2: Chemotherapy ± tamoxifen, Outcome 1: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Chemotherapy + tamoxifen Total	Chemotherapy Total	Weight	Hazard Ratio IV, Random, 95% CI
Agarwala 1999	0.4253	0.2595	28	28	15.9%	1.53 [0.92 , 2.54]
Cocconi 1992	-0.3425	0.1688	60	52	24.9%	0.71 [0.51 , 0.99]
Falkson 1998	0.0862	0.1092	134	137	32.9%	1.09 [0.88 , 1.35]
Rusthoven 1996	0.0862	0.1578	104	100	26.3%	1.09 [0.80 , 1.49]
Total (95% CI)			**326**	**317**	**100.0%**	**1.03 [0.80 , 1.33]**

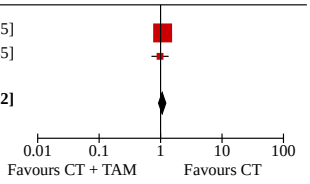
Heterogeneity: Tau² = 0.04; Chi² = 7.58, df = 3 (P = 0.06); I² = 60%
Test for overall effect: Z = 0.25 (P = 0.80)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Chemotherapy ± tamoxifen, Outcome 2: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Chemotherapy + tamoxifen Total	Chemotherapy Total	Weight	Hazard Ratio IV, Random, 95% CI
Falkson 1998	0.077	0.0763	134	137	82.3%	1.08 [0.93 , 1.25]
Rusthoven 1996	-0.0202	0.1644	104	100	17.7%	0.98 [0.71 , 1.35]
Total (95% CI)			**238**	**237**	**100.0%**	**1.06 [0.93 , 1.22]**

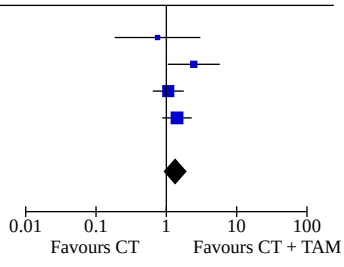
Heterogeneity: Tau² = 0.00; Chi² = 0.29, df = 1 (P = 0.59); I² = 0%
Test for overall effect: Z = 0.86 (P = 0.39)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Chemotherapy ± tamoxifen, Outcome 3: Tumour response

Study or Subgroup	Chemotherapy + tamoxifen Events	Total	Chemotherapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Agarwala 1999	3	28	4	28	6.0%	0.75 [0.18 , 3.05]
Cocconi 2003	17	60	6	52	15.4%	2.46 [1.05 , 5.76]
Falkson 1998	25	134	24	137	37.7%	1.06 [0.64 , 1.77]
Rusthoven 1996	31	104	21	100	40.9%	1.42 [0.88 , 2.30]
Total (95% CI)		**326**		**317**	**100.0%**	**1.33 [0.94 , 1.89]**
Total events:	76		55			

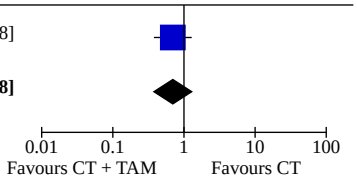
Heterogeneity: Tau² = 0.02; Chi² = 3.44, df = 3 (P = 0.33); I² = 13%
Test for overall effect: Z = 1.61 (P = 0.11)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: Chemotherapy ± tamoxifen, Outcome 4: Toxicity (≥ G3)

Study or Subgroup	Chemotherapy + tamoxifen Events	Total	Chemotherapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Falkson 1998	15	134	22	137	100.0%	0.70 [0.38 , 1.28]
Total (95% CI)		**134**		**137**	**100.0%**	**0.70 [0.38 , 1.28]**
Total events:	15		22			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.16 (P = 0.25)
Test for subgroup differences: Not applicable



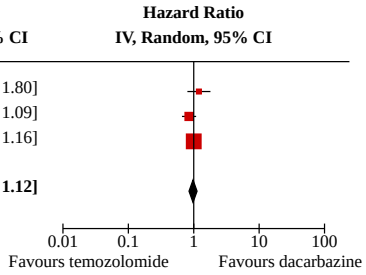
Comparison 3. Temozolomide versus dacarbazine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Overall survival	3	1313	Hazard Ratio (IV, Random, 95% CI)	0.98 [0.85, 1.12]
3.2 Progression-free survival	3	1313	Hazard Ratio (IV, Random, 95% CI)	0.87 [0.74, 1.03]
3.3 Tumour response	3	1313	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.85, 1.73]
3.4 Toxicity (≥ G3)	2	1164	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.98, 1.35]

Analysis 3.1. Comparison 3: Temozolomide versus dacarbazine, Outcome 1: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Temozolomide Total	Dacarbazine Total	Weight	Hazard Ratio IV, Random, 95% CI
Chiarion-Sileni 2011	0.1823	0.2069	74	75	11.5%	1.20 [0.80 , 1.80]
Middleton 2000	-0.1655	0.127	156	149	27.8%	0.85 [0.66 , 1.09]
Patel 2011	0	0.077	429	430	60.7%	1.00 [0.86 , 1.16]
Total (95% CI)			**659**	**654**	**100.0%**	**0.98 [0.85 , 1.12]**

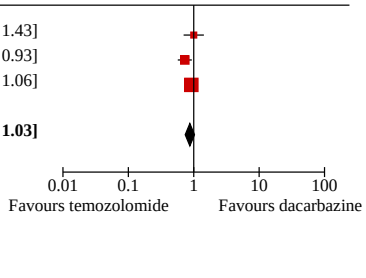
Heterogeneity: Tau² = 0.00; Chi² = 2.33, df = 2 (P = 0.31); I² = 14%
Test for overall effect: Z = 0.35 (P = 0.73)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: Temozolomide versus dacarbazine, Outcome 2: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Temozolomide Total	Dacarbazine Total	Weight	Hazard Ratio IV, Random, 95% CI
Chiarion-Sileni 2011	0	0.182	74	75	16.9%	1.00 [0.70 , 1.43]
Middleton 2000	-0.3148	0.1261	156	149	29.2%	0.73 [0.57 , 0.93]
Patel 2011	-0.0834	0.0713	429	430	53.9%	0.92 [0.80 , 1.06]
Total (95% CI)			**659**	**654**	**100.0%**	**0.87 [0.74 , 1.03]**

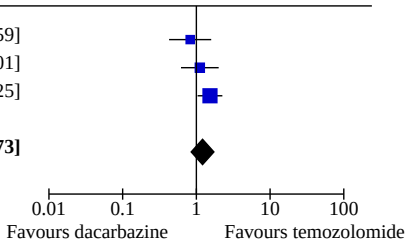
Heterogeneity: Tau² = 0.01; Chi² = 3.08, df = 2 (P = 0.21); I² = 35%
Test for overall effect: Z = 1.65 (P = 0.10)
Test for subgroup differences: Not applicable



Analysis 3.3. Comparison 3: Temozolomide versus dacarbazine, Outcome 3: Tumour response

Study or Subgroup	Temozolomide Events	Total	Dacarbazine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Chiarion-Sileni 2011	13	74	16	75	23.3%	0.82 [0.43 , 1.59]
Middleton 2000	21	156	18	149	27.7%	1.11 [0.62 , 2.01]
Patel 2011	58	429	38	430	49.0%	1.53 [1.04 , 2.25]
Total (95% CI)		**659**		**654**	**100.0%**	**1.21 [0.85 , 1.73]**
Total events:	92		72			

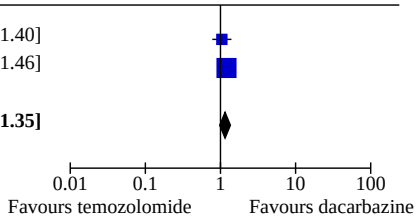
Heterogeneity: Tau² = 0.03; Chi² = 2.75, df = 2 (P = 0.25); I² = 27%
Test for overall effect: Z = 1.07 (P = 0.29)
Test for subgroup differences: Not applicable



Analysis 3.4. Comparison 3: Temozolomide versus dacarbazine, Outcome 4: Toxicity (≥ G3)

Study or Subgroup	Temozolomide Events	Total	Dacarbazine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Middleton 2000	59	156	54	149	30.9%	1.04 [0.78 , 1.40]
Patel 2011	150	429	125	430	69.1%	1.20 [0.99 , 1.46]
Total (95% CI)		**585**		**579**	**100.0%**	**1.15 [0.98 , 1.35]**
Total events:	209		179			

Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 1 (P = 0.43); I² = 0%
Test for overall effect: Z = 1.69 (P = 0.09)
Test for subgroup differences: Not applicable



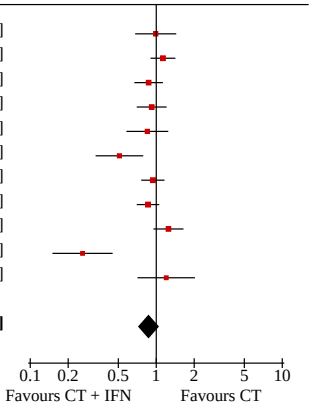
Comparison 4. Chemotherapy ± interferon-alpha

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Overall survival	11	1785	Hazard Ratio (IV, Random, 95% CI)	0.87 [0.73, 1.04]
4.2 Progression-free survival	6	1272	Hazard Ratio (IV, Random, 95% CI)	0.87 [0.74, 1.01]
4.3 Tumour response	15	2419	Risk Ratio (M-H, Random, 95% CI)	1.36 [1.12, 1.66]
4.4 Toxicity (≥ G3)	3	791	Risk Ratio (M-H, Random, 95% CI)	1.72 [0.37, 7.95]

Analysis 4.1. Comparison 4: Chemotherapy ± interferon-alpha, Outcome 1: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Chemotherapy + IFN Total	Chemotherapy Total	Weight	Hazard Ratio IV, Random, 95% CI
Bajetta 1994	-0.0101	0.1916	160	82	8.3%	0.99 [0.68 , 1.44]
Bajetta 2006a	0.1222	0.1161	72	72	10.9%	1.13 [0.90 , 1.42]
Danson 2003	-0.1393	0.1333	62	59	10.4%	0.87 [0.67 , 1.13]
Daponte 2013	-0.0834	0.1394	126	134	10.1%	0.92 [0.70 , 1.21]
Dorval 1999	-0.1625	0.195	52	49	8.2%	0.85 [0.58 , 1.25]
Falkson 1991	-0.6733	0.2221	30	31	7.4%	0.51 [0.33 , 0.79]
Falkson 1998	-0.0619	0.1085	135	136	11.2%	0.94 [0.76 , 1.16]
Kaufmann 2005	-0.1508	0.105	148	146	11.3%	0.86 [0.70 , 1.06]
Thomson 1993	0.2231	0.14	87	83	10.1%	1.25 [0.95 , 1.64]
Vorobiof 1994	-1.3471	0.2806	40	20	5.8%	0.26 [0.15 , 0.45]
Young 2001	0.1823	0.2678	30	31	6.1%	1.20 [0.71 , 2.03]
Total (95% CI)			**942**	**843**	**100.0%**	**0.87 [0.73 , 1.04]**

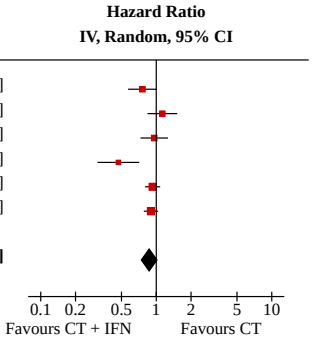
Heterogeneity: Tau² = 0.06; Chi² = 37.19, df = 10 (P < 0.0001); I² = 73%
Test for overall effect: Z = 1.58 (P = 0.11)
Test for subgroup differences: Not applicable



Analysis 4.2. Comparison 4: Chemotherapy ± interferon-alpha, Outcome 2: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Chemotherapy + IFN Total	Chemotherapy Total	Weight	Hazard Ratio IV, Random, 95% CI
Bajetta 1994	-0.2744	0.1468	160	82	14.6%	0.76 [0.57 , 1.01]
Bajetta 2006a	0.1222	0.1513	72	72	14.2%	1.13 [0.84 , 1.52]
Daponte 2013	-0.0408	0.1397	126	134	15.4%	0.96 [0.73 , 1.26]
Falkson 1991	-0.755	0.2123	30	31	9.5%	0.47 [0.31 , 0.71]
Falkson 1998	-0.0726	0.0768	135	136	22.9%	0.93 [0.80 , 1.08]
Kaufmann 2005	-0.1054	0.073	148	146	23.4%	0.90 [0.78 , 1.04]
Total (95% CI)			**671**	**601**	**100.0%**	**0.87 [0.74 , 1.01]**

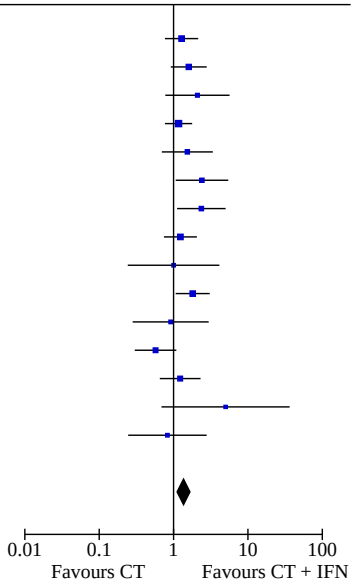
Heterogeneity: Tau² = 0.02; Chi² = 13.32, df = 5 (P = 0.02); I² = 62%
Test for overall effect: Z = 1.78 (P = 0.07)
Test for subgroup differences: Not applicable



Analysis 4.3. Comparison 4: Chemotherapy ± interferon-alpha, Outcome 3: Tumour response

Study or Subgroup	Chemotherapy + IFN Events	Total	Chemotherapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bajetta 1994	40	160	16	82	10.8%	1.28 [0.77 , 2.14]
Bajetta 2006a	24	72	15	72	9.7%	1.60 [0.92 , 2.79]
Danson 2003	11	62	5	59	3.6%	2.09 [0.77 , 5.66]
Daponte 2013	34	126	31	134	14.3%	1.17 [0.77 , 1.78]
Dorval 1999	13	52	8	49	5.5%	1.53 [0.70 , 3.37]
Falkson 1991	14	30	6	31	5.2%	2.41 [1.07 , 5.44]
Falkson 1995	17	37	7	36	5.9%	2.36 [1.11 , 5.01]
Falkson 1998	27	135	22	136	11.0%	1.24 [0.74 , 2.06]
Gorbonova 2000	3	14	3	14	1.9%	1.00 [0.24 , 4.13]
Kaufmann 2005	33	148	18	146	10.5%	1.81 [1.07 , 3.06]
Kirkwood 1990	4	21	5	24	2.7%	0.91 [0.28 , 2.97]
Maio 2010	27	389	12	99	7.7%	0.57 [0.30 , 1.09]
Thomson 1993	18	87	14	83	7.9%	1.23 [0.65 , 2.30]
Vorobiof 1994	10	40	1	20	1.0%	5.00 [0.69 , 36.37]
Young 2001	4	30	5	31	2.5%	0.83 [0.25 , 2.79]
Total (95% CI)		**1403**		**1016**	**100.0%**	**1.36 [1.12 , 1.66]**
Total events:	279		168			

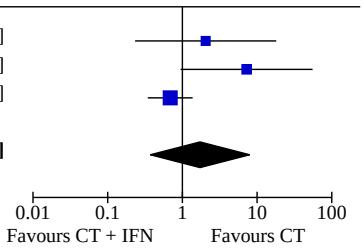
Heterogeneity: Tau² = 0.03; Chi² = 16.93, df = 14 (P = 0.26); I² = 17%
Test for overall effect: Z = 3.04 (P = 0.002)
Test for subgroup differences: Not applicable



Analysis 4.4. Comparison 4: Chemotherapy ± interferon-alpha, Outcome 4: Toxicity (≥ G3)

Study or Subgroup	Chemotherapy + IFN Events	Total	Chemotherapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bajetta 1994	4	160	1	82	25.4%	2.05 [0.23 , 18.05]
Falkson 1991	7	30	1	31	27.2%	7.23 [0.95 , 55.31]
Maio 2010	27	389	10	99	47.3%	0.69 [0.34 , 1.37]
Total (95% CI)		**579**		**212**	**100.0%**	**1.72 [0.37 , 7.95]**
Total events:	38		12			

Heterogeneity: Tau² = 1.16; Chi² = 5.51, df = 2 (P = 0.06); I² = 64%
Test for overall effect: Z = 0.70 (P = 0.49)
Test for subgroup differences: Not applicable



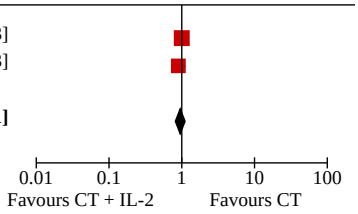
Comparison 5. Chemotherapy ± interleukin-2

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Overall survival	2	644	Hazard Ratio (IV, Random, 95% CI)	0.95 [0.82, 1.11]
5.2 Progression-free survival	1	363	Hazard Ratio (IV, Random, 95% CI)	0.87 [0.70, 1.08]
5.3 Tumour response	3	735	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.64, 1.13]

Analysis 5.1. Comparison 5: Chemotherapy ± interleukin-2, Outcome 1: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	CT + IL-2 Total	CT Total	Weight	Hazard Ratio IV, Random, 95% CI
Hauschild 2001	0	0.1075	137	144	52.9%	1.00 [0.81 , 1.23]
Keilholz 2005	-0.1054	0.1139	183	180	47.1%	0.90 [0.72 , 1.13]
Total (95% CI)			**320**	**324**	**100.0%**	**0.95 [0.82 , 1.11]**

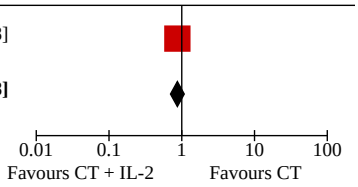
Heterogeneity: Tau² = 0.00; Chi² = 0.45, df = 1 (P = 0.50); I² = 0%
Test for overall effect: Z = 0.64 (P = 0.53)
Test for subgroup differences: Not applicable



Analysis 5.2. Comparison 5: Chemotherapy ± interleukin-2, Outcome 2: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	CT + IL-2 Total	CT Total	Weight	Hazard Ratio IV, Random, 95% CI
Keilholz 2005	-0.1393	0.1109	183	180	100.0%	0.87 [0.70 , 1.08]
Total (95% CI)			**183**	**180**	**100.0%**	**0.87 [0.70 , 1.08]**

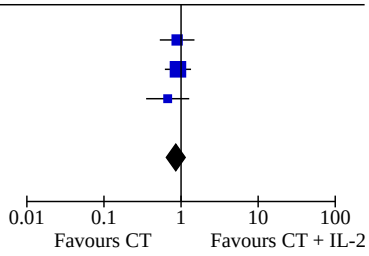
Heterogeneity: Not applicable
Test for overall effect: Z = 1.26 (P = 0.21)
Test for subgroup differences: Not applicable



Analysis 5.3. Comparison 5: Chemotherapy ± interleukin-2, Outcome 3: Tumour response

Study or Subgroup	CT + IL-2 Events	CT + IL-2 Total	CT Events	CT Total	Weight	Risk Ratio M-H, Random, 95% CI
Hauschild 2001	22	137	26	144	29.4%	0.89 [0.53 , 1.49]
Keilholz 2005	38	183	41	180	51.6%	0.91 [0.62 , 1.35]
Sertoli 1999	15	61	11	30	19.0%	0.67 [0.35 , 1.28]
Total (95% CI)		**381**		**354**	**100.0%**	**0.85 [0.64 , 1.13]**
Total events:	75		78			

Heterogeneity: Tau² = 0.00; Chi² = 0.68, df = 2 (P = 0.71); I² = 0%
Test for overall effect: Z = 1.10 (P = 0.27)
Test for subgroup differences: Not applicable



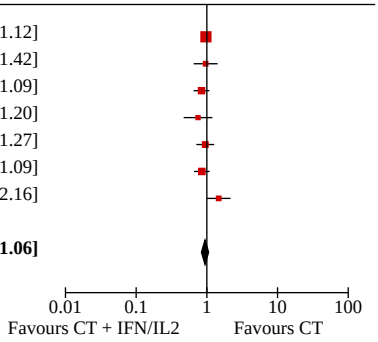
Comparison 6. Chemotherapy ± interferon-alpha and interleukin-2

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Overall survival	7	1307	Hazard Ratio (IV, Random, 95% CI)	0.94 [0.84, 1.06]
6.2 Progression-free survival	6	964	Hazard Ratio (IV, Random, 95% CI)	0.90 [0.83, 0.99]
6.3 Tumour response	7	1307	Risk Ratio (M-H, Random, 95% CI)	1.36 [1.11, 1.67]
6.4 Toxicity (≥ G3)	2	657	Risk Ratio (M-H, Random, 95% CI)	1.35 [1.14, 1.61]

Analysis 6.1. Comparison 6: Chemotherapy ± interferon-alpha and interleukin-2, Outcome 1: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	CT + IFN/IL-2 Total	CT Total	Weight	Hazard Ratio IV, Random, 95% CI
Atkins 2008	-0.0305	0.0734	210	206	33.4%	0.97 [0.84 , 1.12]
Atzpodien 2002	-0.0408	0.199	64	60	7.9%	0.96 [0.65 , 1.42]
Eton 2002	-0.1744	0.1308	92	91	15.8%	0.84 [0.65 , 1.09]
Johnston 1998	-0.2877	0.2384	35	30	5.7%	0.75 [0.47 , 1.20]
Middleton 2007	-0.0513	0.1486	119	122	13.0%	0.95 [0.71 , 1.27]
Ridolfi 2002a	-0.1625	0.1291	87	89	16.2%	0.85 [0.66 , 1.09]
Rosenberg 1999	0.3853	0.1966	52	50	8.1%	1.47 [1.00 , 2.16]
Total (95% CI)			**659**	**648**	**100.0%**	**0.94 [0.84 , 1.06]**

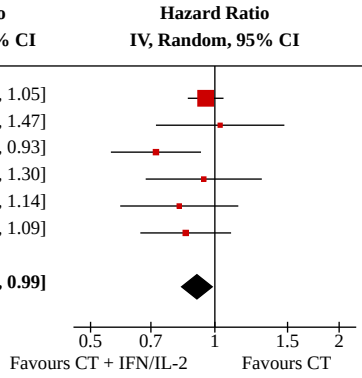
Heterogeneity: Tau² = 0.01; Chi² = 7.61, df = 6 (P = 0.27); I² = 21%
Test for overall effect: Z = 1.00 (P = 0.32)
Test for subgroup differences: Not applicable



Analysis 6.2. Comparison 6: Chemotherapy ± interferon-alpha and interleukin-2, Outcome 2: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	CT + IFN/IL-2 Total	CT Total	Weight	Hazard Ratio IV, Random, 95% CI
Atkins 2008	-0.0513	0.0508	210	206	59.1%	0.95 [0.86 , 1.05]
Atzpodien 2002	0.0296	0.1827	64	60	5.6%	1.03 [0.72 , 1.47]
Eton 2002	-0.3285	0.1282	92	91	11.1%	0.72 [0.56 , 0.93]
Johnston 1998	-0.0619	0.1652	35	30	6.8%	0.94 [0.68 , 1.30]
Middleton 2007	-0.1985	0.168	0	0	6.6%	0.82 [0.59 , 1.14]
Ridolfi 2002a	-0.1625	0.1291	87	89	10.9%	0.85 [0.66 , 1.09]
Total (95% CI)			**488**	**476**	**100.0%**	**0.90 [0.83 , 0.99]**

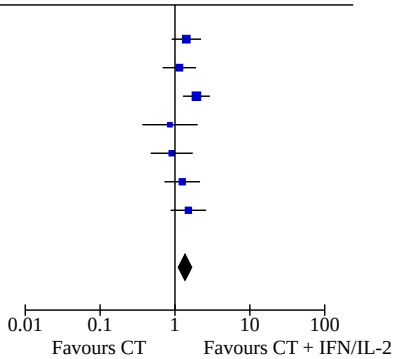
Heterogeneity: Tau² = 0.00; Chi² = 5.22, df = 5 (P = 0.39); I² = 4%
Test for overall effect: Z = 2.30 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 6.3. Comparison 6: Chemotherapy ± interferon-alpha and interleukin-2, Outcome 3: Tumour response

Study or Subgroup	CT + IFN/IL-2 Events	CT + IFN/IL-2 Total	CT Events	CT Total	Weight	Risk Ratio M-H, Random, 95% CI
Atkins 2008	39	210	27	206	19.5%	1.42 [0.90 , 2.23]
Atzpodien 2002	22	64	18	60	15.2%	1.15 [0.69 , 1.92]
Eton 2002	44	91	23	92	23.2%	1.93 [1.28 , 2.92]
Johnston 1998	8	35	8	30	5.6%	0.86 [0.37 , 2.01]
Middleton 2007	15	119	17	122	9.7%	0.90 [0.47 , 1.73]
Ridolfi 2002a	22	87	18	89	13.4%	1.25 [0.72 , 2.16]
Rosenberg 1999	22	52	14	50	13.5%	1.51 [0.88 , 2.61]
Total (95% CI)		**658**		**649**	**100.0%**	**1.36 [1.11 , 1.67]**
Total events:	172		125			

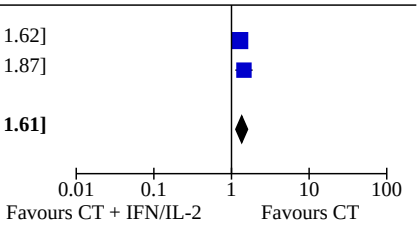
Heterogeneity: Tau² = 0.00; Chi² = 6.16, df = 6 (P = 0.41); I² = 3%
Test for overall effect: Z = 2.98 (P = 0.003)
Test for subgroup differences: Not applicable



Analysis 6.4. Comparison 6: Chemotherapy ± interferon-alpha and interleukin-2, Outcome 4: Toxicity (≥ G3)

Study or Subgroup	CT + IFN/IL-2 Events	CT + IFN/IL-2 Total	CT Events	CT Total	Weight	Risk Ratio M-H, Random, 95% CI
Johnston 1998	95	210	73	206	53.6%	1.28 [1.01 , 1.62]
Middleton 2007	72	119	51	122	46.4%	1.45 [1.12 , 1.87]
Total (95% CI)		**329**		**328**	**100.0%**	**1.35 [1.14 , 1.61]**
Total events:	167		124			

Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 1 (P = 0.48); I² = 0%
Test for overall effect: Z = 3.42 (P = 0.0006)
Test for subgroup differences: Not applicable



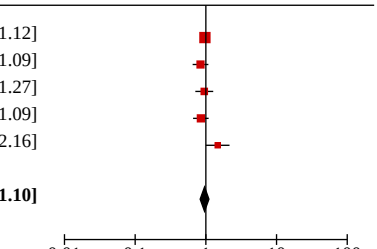
Comparison 7. Chemotherapy ± interferon-alpha and interleukin-2 (first line)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Overall survival	5	1118	Hazard Ratio (IV, Random, 95% CI)	0.96 [0.83, 1.10]
7.2 Progression-free survival	4	775	Hazard Ratio (IV, Random, 95% CI)	0.86 [0.76, 0.99]
7.3 Tumour response	5	1118	Risk Ratio (M-H, Random, 95% CI)	1.45 [1.15, 1.83]
7.4 Toxicity (≥ G3)	1	241	Risk Ratio (M-H, Random, 95% CI)	1.45 [1.12, 1.87]

Analysis 7.1. Comparison 7: Chemotherapy ± interferon-alpha and interleukin-2 (first line), Outcome 1: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	CT + IFN/IL-2 Total	CT Total	Weight	Hazard Ratio IV, Random, 95% CI
Atkins 2008	-0.0305	0.0734	210	206	33.8%	0.97 [0.84 , 1.12]
Eton 2002	-0.1744	0.1308	92	91	19.3%	0.84 [0.65 , 1.09]
Middleton 2007	-0.0513	0.1486	119	122	16.4%	0.95 [0.71 , 1.27]
Ridolfi 2002a	-0.1625	0.1291	87	89	19.7%	0.85 [0.66 , 1.09]
Rosenberg 1999	0.3853	0.1966	52	50	10.8%	1.47 [1.00 , 2.16]
Total (95% CI)			**560**	**558**	**100.0%**	**0.96 [0.83 , 1.10]**

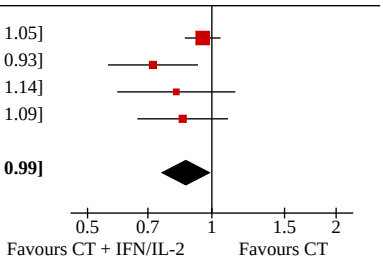
Heterogeneity: Tau² = 0.01; Chi² = 6.64, df = 4 (P = 0.16); I² = 40%
Test for overall effect: Z = 0.59 (P = 0.56)
Test for subgroup differences: Not applicable



Analysis 7.2. Comparison 7: Chemotherapy ± interferon-alpha and interleukin-2 (first line), Outcome 2: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	CT + IFN/IL-2 Total	CT Total	Weight	Hazard Ratio IV, Random, 95% CI
Atkins 2008	-0.0513	0.0508	210	206	48.6%	0.95 [0.86 , 1.05]
Eton 2002	-0.3285	0.1282	92	91	19.4%	0.72 [0.56 , 0.93]
Middleton 2007	-0.1985	0.168	0	0	12.8%	0.82 [0.59 , 1.14]
Ridolfi 2002a	-0.1625	0.1291	87	89	19.2%	0.85 [0.66 , 1.09]
Total (95% CI)			**389**	**386**	**100.0%**	**0.86 [0.76 , 0.99]**

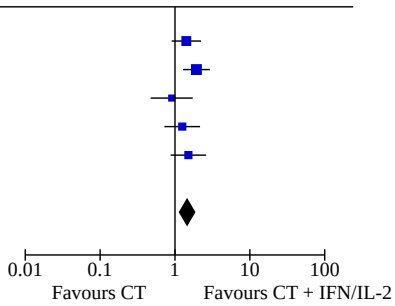
Heterogeneity: Tau² = 0.01; Chi² = 4.66, df = 3 (P = 0.20); I² = 36%
Test for overall effect: Z = 2.17 (P = 0.03)
Test for subgroup differences: Not applicable



Analysis 7.3. Comparison 7: Chemotherapy ± interferon-alpha and interleukin-2 (first line), Outcome 3: Tumour response

Study or Subgroup	CT + IFN/IL-2 Events	CT + IFN/IL-2 Total	CT Events	CT Total	Weight	Risk Ratio M-H, Random, 95% CI
Atkins 2008	39	210	27	206	24.5%	1.42 [0.90 , 2.23]
Eton 2002	44	91	23	92	28.9%	1.93 [1.28 , 2.92]
Middleton 2007	15	119	17	122	12.4%	0.90 [0.47 , 1.73]
Ridolfi 2002a	22	87	18	89	17.0%	1.25 [0.72 , 2.16]
Rosenberg 1999	22	52	14	50	17.1%	1.51 [0.88 , 2.61]
Total (95% CI)		**559**		**559**	**100.0%**	**1.45 [1.15 , 1.83]**
Total events:	142		99			

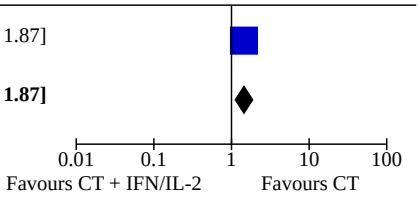
Heterogeneity: Tau² = 0.00; Chi² = 4.25, df = 4 (P = 0.37); I² = 6%
Test for overall effect: Z = 3.15 (P = 0.002)
Test for subgroup differences: Not applicable



Analysis 7.4. Comparison 7: Chemotherapy ± interferon-alpha and interleukin-2 (first line), Outcome 4: Toxicity (≥ G3)

Study or Subgroup	CT + IFN/IL-2 Events	CT + IFN/IL-2 Total	CT Events	CT Total	Weight	Risk Ratio M-H, Random, 95% CI
Middleton 2007	72	119	51	122	100.0%	1.45 [1.12 , 1.87]
Total (95% CI)		**119**		**122**	**100.0%**	**1.45 [1.12 , 1.87]**
Total events:	72		51			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.84 (P = 0.004)
Test for subgroup differences: Not applicable



Comparison 8. Chemotherapy ± Bacille Calmette-Guérin (BCG)

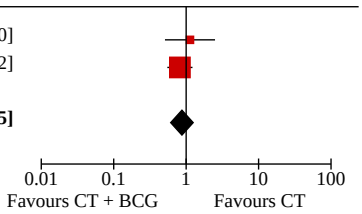
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Overall survival	2	154	Hazard Ratio (IV, Random, 95% CI)	0.87 [0.61, 1.25]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.2 Tumour response	6	770	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.65, 1.12]

Analysis 8.1. Comparison 8: Chemotherapy ± Bacille Calmette-Guérin (BCG), Outcome 1: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	CT + BCG Total	CT Total	Weight	Hazard Ratio IV, Random, 95% CI
Newlands 1976	0.1222	0.4059	27	29	20.1%	1.13 [0.51 , 2.50]
Verschraegen 1993	-0.1985	0.2038	47	51	79.9%	0.82 [0.55 , 1.22]
Total (95% CI)			**74**	**80**	**100.0%**	**0.87 [0.61 , 1.25]**

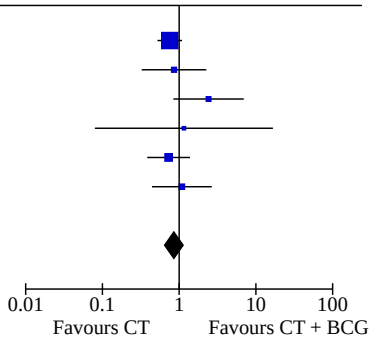
Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 1 (P = 0.48); I² = 0%
Test for overall effect: Z = 0.74 (P = 0.46)
Test for subgroup differences: Not applicable



Analysis 8.2. Comparison 8: Chemotherapy ± Bacille Calmette-Guérin (BCG), Outcome 2: Tumour response

Study or Subgroup	CT + BCG Events	CT + BCG Total	CT Events	CT Total	Weight	Risk Ratio M-H, Random, 95% CI
Costanzi 1982	67	291	29	95	56.0%	0.75 [0.52 , 1.09]
Mastrangelo 1979	6	31	7	31	8.1%	0.86 [0.32 , 2.26]
Newlands 1976	9	27	4	29	6.9%	2.42 [0.84 , 6.94]
Ramseur 1978	1	13	1	15	1.1%	1.15 [0.08 , 16.67]
Veronesi 1984	12	65	19	75	18.5%	0.73 [0.38 , 1.38]
Verschraegen 1993	8	47	8	51	9.5%	1.09 [0.44 , 2.66]
Total (95% CI)		**474**		**296**	**100.0%**	**0.85 [0.65 , 1.12]**
Total events:	103		68			

Heterogeneity: Tau² = 0.00; Chi² = 4.76, df = 5 (P = 0.45); I² = 0%
Test for overall effect: Z = 1.13 (P = 0.26)
Test for subgroup differences: Not applicable



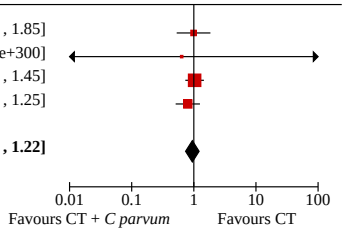
Comparison 9. Chemotherapy ± *Corynebacterium parvum*

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Overall survival	4	242	Hazard Ratio (IV, Random, 95% CI)	0.95 [0.74, 1.22]
9.2 Tumour response	7	537	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.77, 1.38]

Analysis 9.1. Comparison 9: Chemotherapy ± *Corynebacterium parvum*, Outcome 1: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	CT + *C parvum* Total	CT Total	Weight	Hazard Ratio IV, Random, 95% CI
Clunie 1980	-0.0101	0.3188	0	0	16.1%	0.99 [0.53 , 1.85]
Kokoschka 1978	-0.45	353.55	15	19	0.0%	0.64 [0.00 , 5.583070176485752e+300]
Presant 1979	0.0296	0.1757	55	65	52.9%	1.03 [0.73 , 1.45]
Robidoux 1982	-0.2231	0.2297	44	44	31.0%	0.80 [0.51 , 1.25]
Total (95% CI)			**114**	**128**	**100.0%**	**0.95 [0.74 , 1.22]**

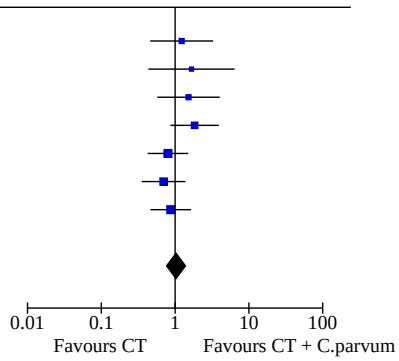
Heterogeneity: Tau² = 0.00; Chi² = 0.79, df = 3 (P = 0.85); I² = 0%
Test for overall effect: Z = 0.43 (P = 0.67)
Test for subgroup differences: Not applicable



Analysis 9.2. Comparison 9: Chemotherapy ± *Corynebacterium parvum*, Outcome 2: Tumour response

Study or Subgroup	CT + C.parvum Events	CT + C.parvum Total	CT Events	CT Total	Weight	Risk Ratio M-H, Random, 95% CI
Clunie 1980	6	22	6	27	9.0%	1.23 [0.46 , 3.28]
Gough 1978	4	16	3	20	4.8%	1.67 [0.43 , 6.40]
Kokoschka 1978	6	15	5	19	9.1%	1.52 [0.57 , 4.03]
Presant 1979	14	55	9	65	15.2%	1.84 [0.86 , 3.92]
Robidoux 1982	12	44	15	44	21.6%	0.80 [0.42 , 1.51]
Thatcher 1986	10	40	14	39	18.7%	0.70 [0.35 , 1.38]
Veronesi 1984	12	55	19	76	21.6%	0.87 [0.46 , 1.65]
Total (95% CI)		**247**		**290**	**100.0%**	**1.03 [0.77 , 1.38]**
Total events:	64		71			

Heterogeneity: Tau² = 0.00; Chi² = 5.63, df = 6 (P = 0.47); I² = 0%
Test for overall effect: Z = 0.19 (P = 0.85)
Test for subgroup differences: Not applicable



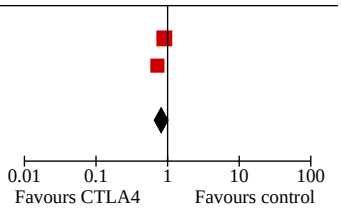
Comparison 10. Anti-CTLA4 monoclonal antibodies (first line)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Overall survival	2	1157	Hazard Ratio (IV, Random, 95% CI)	0.81 [0.65, 1.01]
10.2 Progression-free survival	1	502	Hazard Ratio (IV, Random, 95% CI)	0.76 [0.63, 0.92]
10.3 Tumour response	2	1157	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.92, 1.77]
10.4 Toxicity (≥ G3)	2	1142	Risk Ratio (M-H, Random, 95% CI)	1.69 [1.19, 2.42]

Analysis 10.1. Comparison 10: Anti-CTLA4 monoclonal antibodies (first line), Outcome 1: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Anti-CTLA4 Total	Control Total	Weight	Hazard Ratio IV, Random, 95% CI
Ribas 2013	-0.1054	0.0796	328	327	54.0%	0.90 [0.77 , 1.05]
Robert 2011	-0.3285	0.1016	250	252	46.0%	0.72 [0.59 , 0.88]
Total (95% CI)			**578**	**579**	**100.0%**	**0.81 [0.65 , 1.01]**

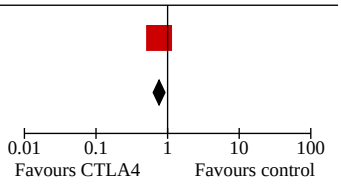
Heterogeneity: Tau² = 0.02; Chi² = 2.99, df = 1 (P = 0.08); I² = 67%
Test for overall effect: Z = 1.87 (P = 0.06)
Test for subgroup differences: Not applicable



Analysis 10.2. Comparison 10: Anti-CTLA4 monoclonal antibodies (first line), Outcome 2: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Anti-CTLA4 Total	Control Total	Weight	Hazard Ratio IV, Random, 95% CI
Robert 2011	-0.2744	0.0957	250	252	100.0%	0.76 [0.63 , 0.92]
Total (95% CI)			**250**	**252**	**100.0%**	**0.76 [0.63 , 0.92]**

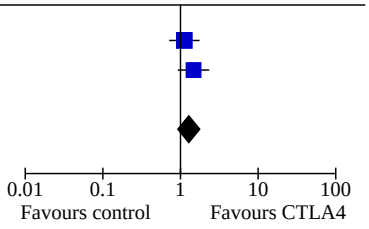
Heterogeneity: Not applicable
Test for overall effect: Z = 2.87 (P = 0.004)
Test for subgroup differences: Not applicable



Analysis 10.3. Comparison 10: Anti-CTLA4 monoclonal antibodies (first line), Outcome 3: Tumour response

Study or Subgroup	Anti-CTLA4 Events	Anti-CTLA4 Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Ribas 2013	36	328	32	327	51.8%	1.12 [0.71 , 1.76]
Robert 2011	38	250	26	252	48.2%	1.47 [0.92 , 2.35]
Total (95% CI)		**578**		**579**	**100.0%**	**1.28 [0.92 , 1.77]**
Total events:	74		58			

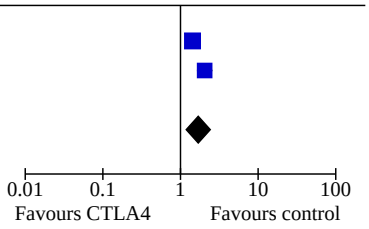
Heterogeneity: Tau² = 0.00; Chi² = 0.68, df = 1 (P = 0.41); I² = 0%
Test for overall effect: Z = 1.49 (P = 0.14)
Test for subgroup differences: Not applicable



Analysis 10.4. Comparison 10: Anti-CTLA4 monoclonal antibodies (first line), Outcome 4: Toxicity (≥ G3)

Study or Subgroup	Anti-CTLA4 Events	Anti-CTLA4 Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Ribas 2013	192	325	132	319	52.7%	1.43 [1.22 , 1.67]
Robert 2011	139	247	69	251	47.3%	2.05 [1.63 , 2.57]
Total (95% CI)		**572**		**570**	**100.0%**	**1.69 [1.19 , 2.42]**
Total events:	331		201			

Heterogeneity: Tau² = 0.06; Chi² = 6.51, df = 1 (P = 0.01); I² = 85%
Test for overall effect: Z = 2.91 (P = 0.004)
Test for subgroup differences: Not applicable



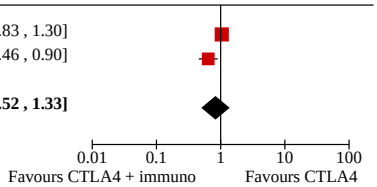
Comparison 11. Anti-CTLA4 monoclonal antibodies ± other immunostimulating agents (second line)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Overall survival	2	784	Hazard Ratio (IV, Random, 95% CI)	0.83 [0.52, 1.33]
11.2 Progression-free survival	2	785	Hazard Ratio (IV, Random, 95% CI)	1.06 [0.75, 1.51]
11.3 Tumour response	2	785	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.38, 1.47]
11.4 Toxicity (≥ G3)	2	785	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.69, 1.11]

Analysis 11.1. Comparison 11: Anti-CTLA4 monoclonal antibodies ± other immunostimulating agents (second line), Outcome 1: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	CTLA4 + immunostimulator Total	CTLA4 Total	Weight	Hazard Ratio IV, Random, 95% CI
Hodi 2010a	0.0392	0.1151	403	136	53.6%	1.04 [0.83 , 1.30]
Hodi 2014	-0.4463	0.1739	123	122	46.4%	0.64 [0.46 , 0.90]
Total (95% CI)			**526**	**258**	**100.0%**	**0.83 [0.52 , 1.33]**

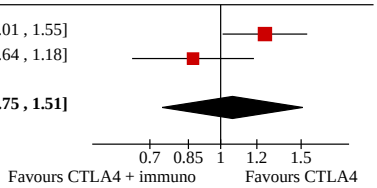
Heterogeneity: Tau² = 0.10; Chi² = 5.42, df = 1 (P = 0.02); I² = 82%
Test for overall effect: Z = 0.77 (P = 0.44)
Test for subgroup differences: Not applicable



Analysis 11.2. Comparison 11: Anti-CTLA4 monoclonal antibodies ± other immunostimulating agents (second line), Outcome 2: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	CTLA4 + immunostimulator Total	CTLA4 Total	Weight	Hazard Ratio IV, Random, 95% CI
Hodi 2010a	0.2231	0.1087	403	137	54.8%	1.25 [1.01 , 1.55]
Hodi 2014	-0.1393	0.1566	123	122	45.2%	0.87 [0.64 , 1.18]
Total (95% CI)			**526**	**259**	**100.0%**	**1.06 [0.75 , 1.51]**

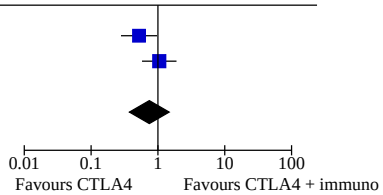
Heterogeneity: Tau² = 0.05; Chi² = 3.61, df = 1 (P = 0.06); I² = 72%
Test for overall effect: Z = 0.33 (P = 0.74)
Test for subgroup differences: Not applicable



Analysis 11.3. Comparison 11: Anti-CTLA4 monoclonal antibodies ± other immunostimulating agents (second line), Outcome 3: Tumour response

Study or Subgroup	CTLA4 + immunostimulator Events	Total	CTLA4 Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Hodi 2010a	23	403	15	137	49.1%	0.52 [0.28 , 0.97]
Hodi 2014	19	123	18	122	50.9%	1.05 [0.58 , 1.90]
Total (95% CI)		**526**		**259**	**100.0%**	**0.74 [0.38 , 1.47]**
Total events:	42		33			

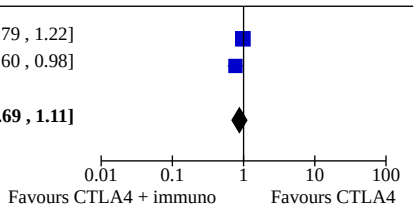
Heterogeneity: Tau² = 0.15; Chi² = 2.53, df = 1 (P = 0.11); I² = 60%
Test for overall effect: Z = 0.85 (P = 0.39)
Test for subgroup differences: Not applicable



Analysis 11.4. Comparison 11: Anti-CTLA4 monoclonal antibodies ± other immunostimulating agents (second line), Outcome 4: Toxicity (≥ G3)

Study or Subgroup	CTLA4 + immunostimulator Events	Total	CTLA4 Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Hodi 2010a	173	403	60	137	52.8%	0.98 [0.79 , 1.22]
Hodi 2014	55	123	71	122	47.2%	0.77 [0.60 , 0.98]
Total (95% CI)		**526**		**259**	**100.0%**	**0.87 [0.69 , 1.11]**
Total events:	228		131			

Heterogeneity: Tau² = 0.02; Chi² = 2.08, df = 1 (P = 0.15); I² = 52%
Test for overall effect: Z = 1.11 (P = 0.27)
Test for subgroup differences: Not applicable



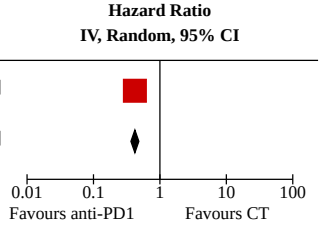
Comparison 12. Anti-PD1 monoclonal antibodies versus chemotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Overall survival	1	418	Hazard Ratio (IV, Random, 95% CI)	0.42 [0.37, 0.48]
12.2 Progression-free survival	2	957	Hazard Ratio (IV, Random, 95% CI)	0.49 [0.39, 0.61]
12.3 Tumour response	3	1367	Risk Ratio (M-H, Random, 95% CI)	3.42 [2.38, 4.92]
12.4 Toxicity (≥ G3)	3	1360	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.31, 0.97]

Analysis 12.1. Comparison 12: Anti-PD1 monoclonal antibodies versus chemotherapy, Outcome 1: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Anti-PD1/PDL1 Total	Chemotherapy Total	Weight	Hazard Ratio IV, Random, 95% CI
Robert 2015a	-0.8675	0.0701	210	208	100.0%	0.42 [0.37 , 0.48]
Total (95% CI)			**210**	**208**	**100.0%**	**0.42 [0.37 , 0.48]**

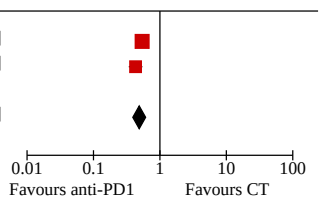
Heterogeneity: Not applicable
Test for overall effect: Z = 12.38 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 12.2. Comparison 12: Anti-PD1 monoclonal antibodies versus chemotherapy, Outcome 2: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Anti-PD1/PDL1 Total	Chemotherapy Total	Weight	Hazard Ratio IV, Random, 95% CI
Ribas 2015	-0.6162	0.093	360	179	55.5%	0.54 [0.45 , 0.65]
Robert 2015a	-0.844	0.1198	210	208	44.5%	0.43 [0.34 , 0.54]
Total (95% CI)			**570**	**387**	**100.0%**	**0.49 [0.39 , 0.61]**

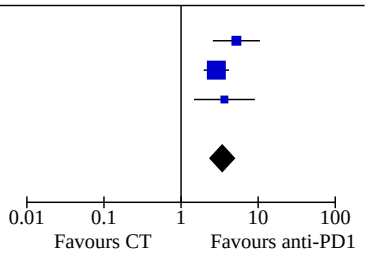
Heterogeneity: Tau² = 0.01; Chi² = 2.26, df = 1 (P = 0.13); I² = 56%
Test for overall effect: Z = 6.34 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 12.3. Comparison 12: Anti-PD1 monoclonal antibodies versus chemotherapy, Outcome 3: Tumour response

Study or Subgroup	Anti-PD1/PDL1 Events	Total	Chemotherapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ribas 2015	84	360	8	179	23.4%	5.22 [2.59 , 10.54]
Robert 2015a	84	210	29	208	61.9%	2.87 [1.97 , 4.18]
Weber 2015	38	277	5	133	14.7%	3.65 [1.47 , 9.06]
Total (95% CI)		**847**		**520**	**100.0%**	**3.42 [2.38 , 4.92]**
Total events:	206		42			

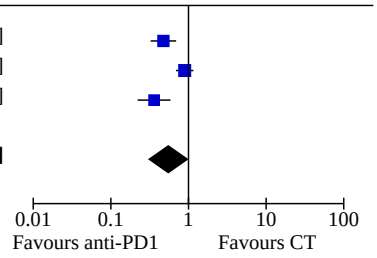
Heterogeneity: Tau² = 0.02; Chi² = 2.35, df = 2 (P = 0.31); I² = 15%
Test for overall effect: Z = 6.63 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 12.4. Comparison 12: Anti-PD1 monoclonal antibodies versus chemotherapy, Outcome 4: Toxicity (≥ G3)

Study or Subgroup	Anti-PD1/PDL1 Events	Total	Chemotherapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ribas 2015	43	360	45	179	33.4%	0.48 [0.33 , 0.69]
Robert 2015a	70	206	78	205	36.3%	0.89 [0.69 , 1.16]
Weber 2015	24	277	32	133	30.4%	0.36 [0.22 , 0.59]
Total (95% CI)		**843**		**517**	**100.0%**	**0.55 [0.31 , 0.97]**
Total events:	137		155			

Heterogeneity: Tau² = 0.21; Chi² = 14.24, df = 2 (P = 0.0008); I² = 86%
Test for overall effect: Z = 2.08 (P = 0.04)
Test for subgroup differences: Not applicable



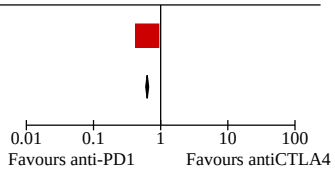
Comparison 13. Anti-PD1 monoclonal antibodies versus anti-CTLA4 monoclonal antibodies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 Overall survival	1	834	Hazard Ratio (IV, Random, 95% CI)	0.63 [0.60, 0.66]
13.2 Progression-free survival	2	1465	Hazard Ratio (IV, Random, 95% CI)	0.54 [0.50, 0.60]
13.3 Tumour response	2	1465	Risk Ratio (M-H, Random, 95% CI)	2.47 [2.01, 3.04]
13.4 Toxicity (≥ G3)	2	1435	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.54, 0.91]

Analysis 13.1. Comparison 13: Anti-PD1 monoclonal antibodies versus anti-CTLA4 monoclonal antibodies, Outcome 1: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Anti-PD1/PDL1 Total	Anti-CTAL4 Total	Weight	Hazard Ratio IV, Random, 95% CI
Robert 2015b	-0.462	0.0249	556	278	100.0%	0.63 [0.60 , 0.66]
Total (95% CI)			**556**	**278**	**100.0%**	**0.63 [0.60 , 0.66]**

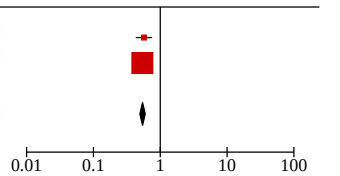
Heterogeneity: Not applicable
Test for overall effect: Z = 18.55 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 13.2. Comparison 13: Anti-PD1 monoclonal antibodies versus anti-CTLA4 monoclonal antibodies, Outcome 2: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Anti-PD1/PDL1 Total	Anti-CTAL4 Total	Weight	Hazard Ratio IV, Random, 95% CI
Larkin 2015	-0.5621	0.1438	316	315	10.6%	0.57 [0.43 , 0.76]
Robert 2015b	-0.6162	0.0496	556	278	89.4%	0.54 [0.49 , 0.60]
Total (95% CI)			**872**	**593**	**100.0%**	**0.54 [0.50 , 0.60]**

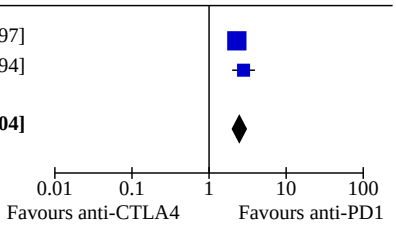
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%
Test for overall effect: Z = 13.02 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 13.3. Comparison 13: Anti-PD1 monoclonal antibodies versus anti-CTLA4 monoclonal antibodies, Outcome 3: Tumour response

Study or Subgroup	Anti-PD1 Events	Anti-PD1 Total	Anti-CTLA4 Events	Anti-CTLA4 Total	Weight	Risk Ratio M-H, Random, 95% CI
Larkin 2015	138	316	60	315	63.3%	2.29 [1.77 , 2.97]
Robert 2015b	185	556	33	278	36.7%	2.80 [1.99 , 3.94]
Total (95% CI)		**872**		**593**	**100.0%**	**2.47 [2.01 , 3.04]**
Total events:	323		93			

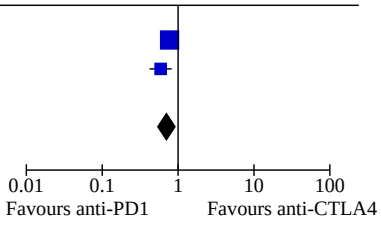
Heterogeneity: Tau² = 0.00; Chi² = 0.87, df = 1 (P = 0.35); I² = 0%
Test for overall effect: Z = 8.57 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 13.4. Comparison 13: Anti-PD1 monoclonal antibodies versus anti-CTLA4 monoclonal antibodies, Outcome 4: Toxicity (≥ G3)

Study or Subgroup	Anti-PD1/PDL1 Events	Anti-PD1/PDL1 Total	Anti-CTAL4 Events	Anti-CTAL4 Total	Weight	Risk Ratio M-H, Random, 95% CI
Larkin 2015	136	313	175	311	64.7%	0.77 [0.66 , 0.91]
Robert 2015b	65	555	51	256	35.3%	0.59 [0.42 , 0.82]
Total (95% CI)		**868**		**567**	**100.0%**	**0.70 [0.54 , 0.91]**
Total events:	201		226			

Heterogeneity: Tau² = 0.02; Chi² = 2.14, df = 1 (P = 0.14); I² = 53%
Test for overall effect: Z = 2.68 (P = 0.007)
Test for subgroup differences: Not applicable



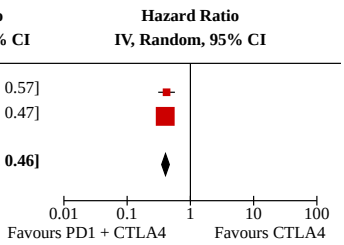
Comparison 14. Anti-PD1 monoclonal antibodies and anti-CTLA4 monoclonal antibodies versus anti-CTLA4 monoclonal antibodies alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.1 Progression-free survival	2	738	Hazard Ratio (IV, Random, 95% CI)	0.40 [0.35, 0.46]
14.2 Tumour response	2	738	Risk Ratio (M-H, Random, 95% CI)	3.50 [2.07, 5.92]
14.3 Toxicity (≥ G3)	2	764	Risk Ratio (M-H, Random, 95% CI)	1.57 [0.85, 2.92]

Analysis 14.1. Comparison 14: Anti-PD1 monoclonal antibodies and anti-CTLA4 monoclonal antibodies versus anti-CTLA4 monoclonal antibodies alone, Outcome 1: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Anti-PD1/PDL1 + anti-CTLA Total	Anti-CTLA4 Total	Weight	Hazard Ratio IV, Random, 95% CI
Larkin 2015	-0.8675	0.1549	314	315	20.9%	0.42 [0.31 , 0.57]
Postow 2015	-0.9163	0.0797	72	37	79.1%	0.40 [0.34 , 0.47]
Total (95% CI)			**386**	**352**	**100.0%**	**0.40 [0.35 , 0.46]**

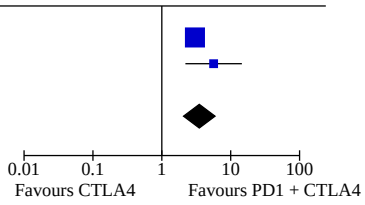
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.78); I² = 0%
Test for overall effect: Z = 12.79 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 14.2. Comparison 14: Anti-PD1 monoclonal antibodies and anti-CTLA4 monoclonal antibodies versus anti-CTLA4 monoclonal antibodies alone, Outcome 2: Tumour response

Study or Subgroup	Anti-CTLA Events	Anti-CTLA Total	Anti-PD1/PDL1+ anti-CTLA4 Events	Anti-PD1/PDL1+ anti-CTLA4 Total	Weight	Risk Ratio M-H, Random, 95% CI
Larkin 2015	181	314	60	315	76.8%	3.03 [2.36 , 3.87]
Postow 2015	44	72	4	37	23.2%	5.65 [2.20 , 14.52]
Total (95% CI)		**386**		**352**	**100.0%**	**3.50 [2.07 , 5.92]**
Total events:	225		64			

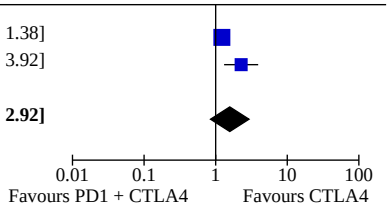
Heterogeneity: Tau² = 0.08; Chi² = 1.63, df = 1 (P = 0.20); I² = 39%
Test for overall effect: Z = 4.67 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 14.3. Comparison 14: Anti-PD1 monoclonal antibodies and anti-CTLA4 monoclonal antibodies versus anti-CTLA4 monoclonal antibodies alone, Outcome 3: Toxicity (≥ G3)

Study or Subgroup	Anti-PD1/PDL1 + anti-CTLA Events	Total	Anti-CTLA4 Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Larkin 2015	215	313	175	311	59.0%	1.22 [1.08 , 1.38]
Postow 2015	51	94	11	46	41.0%	2.27 [1.31 , 3.92]
Total (95% CI)		**407**		**357**	**100.0%**	**1.57 [0.85 , 2.92]**
Total events:	266		186			

Heterogeneity: Tau² = 0.16; Chi² = 5.00, df = 1 (P = 0.03); I² = 80%
Test for overall effect: Z = 1.44 (P = 0.15)
Test for subgroup differences: Not applicable



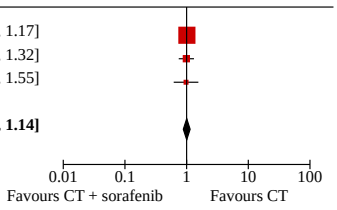
Comparison 15. Chemotherapy ± sorafenib

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.1 Overall survival	3	1194	Hazard Ratio (IV, Random, 95% CI)	1.00 [0.88, 1.14]
15.2 Progression-free survival	3	1194	Hazard Ratio (IV, Random, 95% CI)	0.89 [0.73, 1.09]
15.3 Tumour response	3	1194	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.91, 1.50]
15.4 Toxicity (≥ G3)	3	1194	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.93, 1.26]

Analysis 15.1. Comparison 15: Chemotherapy ± sorafenib, Outcome 1: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Chemotherapy + sorafenib Total	Chemotherapy Total	Weight	Hazard Ratio IV, Random, 95% CI
Flaherty 2013a	0.01	0.0761	410	413	72.5%	1.01 [0.87 , 1.17]
Hauschild 2009a	-0.01	0.1451	135	135	19.9%	0.99 [0.74 , 1.32]
McDermott 2008	-0.0218	0.2348	51	50	7.6%	0.98 [0.62 , 1.55]
Total (95% CI)			**596**	**598**	**100.0%**	**1.00 [0.88 , 1.14]**

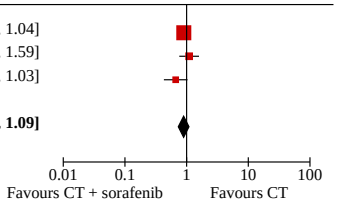
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 2 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.06 (P = 0.96)
Test for subgroup differences: Not applicable



Analysis 15.2. Comparison 15: Chemotherapy ± sorafenib, Outcome 2: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Chemotherapy + sorafenib Total	Chemotherapy Total	Weight	Hazard Ratio IV, Random, 95% CI
Flaherty 2013a	-0.1054	0.073	410	413	61.2%	0.90 [0.78 , 1.04]
Hauschild 2009a	0.0943	0.1876	135	135	22.1%	1.10 [0.76 , 1.59]
McDermott 2008	-0.408	0.2248	51	50	16.7%	0.66 [0.43 , 1.03]
Total (95% CI)			**596**	**598**	**100.0%**	**0.89 [0.73 , 1.09]**

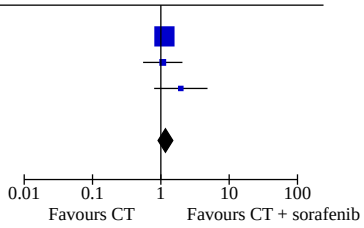
Heterogeneity: Tau² = 0.01; Chi² = 2.94, df = 2 (P = 0.23); I² = 32%
Test for overall effect: Z = 1.10 (P = 0.27)
Test for subgroup differences: Not applicable



Analysis 15.3. Comparison 15: Chemotherapy ± sorafenib, Outcome 3: Tumour response

Study or Subgroup	Chemotherapy + sorafenib Events	Total	Chemotherapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Flaherty 2013a	84	410	75	413	78.4%	1.13 [0.85 , 1.49]
Hauschild 2009a	16	135	15	135	14.0%	1.07 [0.55 , 2.07]
McDermott 2008	12	51	6	50	7.6%	1.96 [0.80 , 4.82]
Total (95% CI)		**596**		**598**	**100.0%**	**1.17 [0.91 , 1.50]**
Total events:	112		96			

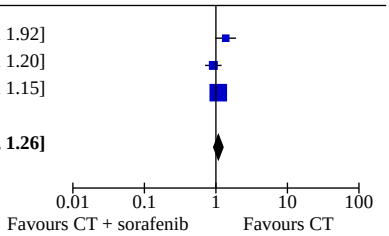
Heterogeneity: Tau² = 0.00; Chi² = 1.41, df = 2 (P = 0.49); I² = 0%
Test for overall effect: Z = 1.22 (P = 0.22)
Test for subgroup differences: Not applicable



Analysis 15.4. Comparison 15: Chemotherapy ± sorafenib, Outcome 4: Toxicity (≥ G3)

Study or Subgroup	Chemotherapy + sorafenib Events	Total	Chemotherapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Flaherty 2013a	35	51	25	50	15.9%	1.37 [0.98 , 1.92]
Hauschild 2009a	58	135	63	135	22.2%	0.92 [0.71 , 1.20]
McDermott 2008	346	410	323	413	61.9%	1.08 [1.01 , 1.15]
Total (95% CI)		**596**		**598**	**100.0%**	**1.08 [0.93 , 1.26]**
Total events:	439		411			

Heterogeneity: Tau² = 0.01; Chi² = 3.40, df = 2 (P = 0.18); I² = 41%
Test for overall effect: Z = 1.03 (P = 0.31)
Test for subgroup differences: Not applicable



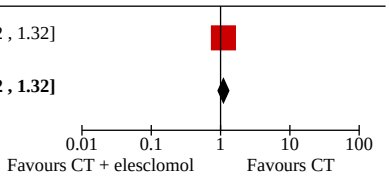
Comparison 16. Chemotherapy ± elesclomol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.1 Overall survival	1	651	Hazard Ratio (IV, Random, 95% CI)	1.10 [0.92, 1.32]
16.2 Progression-free survival	2	732	Hazard Ratio (IV, Random, 95% CI)	0.75 [0.50, 1.13]
16.3 Tumour response	2	732	Risk Ratio (M-H, Random, 95% CI)	1.86 [0.98, 3.50]
16.4 Toxicity (≥ G3)	1	651	Risk Ratio (M-H, Random, 95% CI)	1.22 [1.00, 1.50]

Analysis 16.1. Comparison 16: Chemotherapy ± elesclomol, Outcome 1: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	CT + elesclomol Total	CT Total	Weight	Hazard Ratio IV, Random, 95% CI
O'Day 2013	0.0953	0.0912	325	326	100.0%	1.10 [0.92 , 1.32]
Total (95% CI)			**325**	**326**	**100.0%**	**1.10 [0.92 , 1.32]**

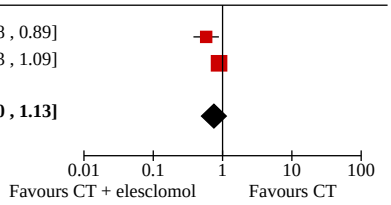
Heterogeneity: Not applicable
Test for overall effect: Z = 1.04 (P = 0.30)
Test for subgroup differences: Not applicable



Analysis 16.2. Comparison 16: Chemotherapy ± elesclomol, Outcome 2: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	CT + elesclomol Total	CT Total	Weight	Hazard Ratio IV, Random, 95% CI
O'Day 2009	-0.5447	0.2157	53	28	40.1%	0.58 [0.38 , 0.89]
O'Day 2013	-0.1165	0.1011	325	326	59.9%	0.89 [0.73 , 1.09]
Total (95% CI)			**378**	**354**	**100.0%**	**0.75 [0.50 , 1.13]**

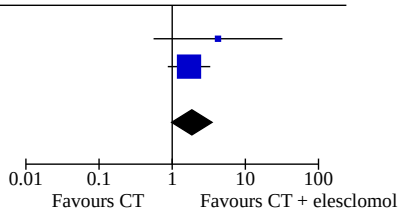
Heterogeneity: Tau² = 0.06; Chi² = 3.23, df = 1 (P = 0.07); I² = 69%
Test for overall effect: Z = 1.37 (P = 0.17)
Test for subgroup differences: Not applicable



Analysis 16.3. Comparison 16: Chemotherapy ± elesclomol, Outcome 3: Tumour response

Study or Subgroup	CT + elesclomol Events	CT + elesclomol Total	CT Events	CT Total	Weight	Risk Ratio M-H, Random, 95% CI
O'Day 2009	8	53	1	28	9.8%	4.23 [0.56 , 32.11]
O'Day 2013	22	325	13	326	90.2%	1.70 [0.87 , 3.31]
Total (95% CI)		**378**		**354**	**100.0%**	**1.86 [0.98 , 3.50]**
Total events:	30		14			

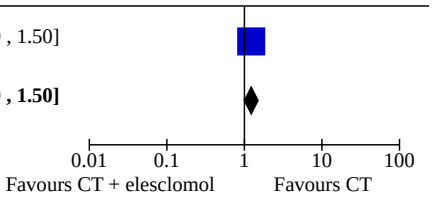
Heterogeneity: Tau² = 0.00; Chi² = 0.72, df = 1 (P = 0.40); I² = 0%
Test for overall effect: Z = 1.91 (P = 0.06)
Test for subgroup differences: Not applicable



Analysis 16.4. Comparison 16: Chemotherapy ± elesclomol, Outcome 4: Toxicity (≥ G3)

Study or Subgroup	CT + elesclomol Events	CT + elesclomol Total	CT Events	CT Total	Weight	Risk Ratio M-H, Random, 95% CI
O'Day 2013	133	325	109	326	100.0%	1.22 [1.00 , 1.50]
Total (95% CI)		**325**		**326**	**100.0%**	**1.22 [1.00 , 1.50]**
Total events:	133		109			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.97 (P = 0.05)
Test for subgroup differences: Not applicable



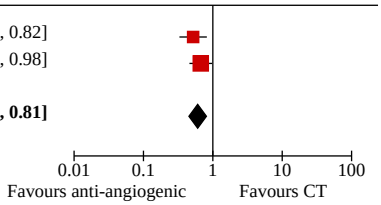
Comparison 17. Chemotherapy ± anti-angiogenic drugs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.1 Overall survival	2	324	Hazard Ratio (IV, Random, 95% CI)	0.60 [0.45, 0.81]
17.2 Progression-free survival	2	324	Hazard Ratio (IV, Random, 95% CI)	0.69 [0.52, 0.92]
17.3 Tumour response	2	324	Risk Ratio (M-H, Random, 95% CI)	1.71 [0.96, 3.03]
17.4 Toxicity (≥ G3)	2	324	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.09, 5.32]

Analysis 17.1. Comparison 17: Chemotherapy ± anti-angiogenic drugs, Outcome 1: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Anti-angiogenic Total	CT Total	Weight	Hazard Ratio IV, Random, 95% CI
Cui 2013	-0.6539	0.232	56	54	40.6%	0.52 [0.33 , 0.82]
Kim 2012	-0.4005	0.1919	143	71	59.4%	0.67 [0.46 , 0.98]
Total (95% CI)			**199**	**125**	**100.0%**	**0.60 [0.45 , 0.81]**

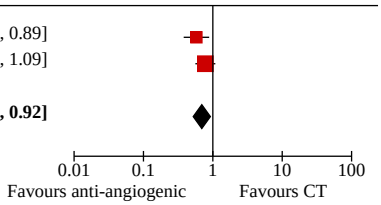
Heterogeneity: Tau² = 0.00; Chi² = 0.71, df = 1 (P = 0.40); I² = 0%
Test for overall effect: Z = 3.40 (P = 0.0007)
Test for subgroup differences: Not applicable



Analysis 17.2. Comparison 17: Chemotherapy ± anti-angiogenic drugs, Outcome 2: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Anti-angiogenic Total	CT Total	Weight	Hazard Ratio IV, Random, 95% CI
Cui 2013	-0.5447	0.2157	56	54	39.8%	0.58 [0.38 , 0.89]
Kim 2012	-0.2485	0.1691	143	71	60.2%	0.78 [0.56 , 1.09]
Total (95% CI)			**199**	**125**	**100.0%**	**0.69 [0.52 , 0.92]**

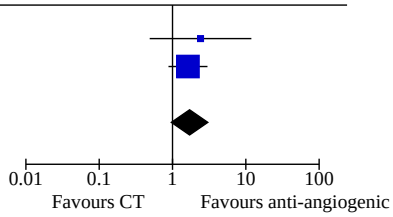
Heterogeneity: Tau² = 0.01; Chi² = 1.17, df = 1 (P = 0.28); I² = 14%
Test for overall effect: Z = 2.53 (P = 0.01)
Test for subgroup differences: Not applicable



Analysis 17.3. Comparison 17: Chemotherapy ± anti-angiogenic drugs, Outcome 3: Tumour response

Study or Subgroup	Anti-angiogenic Events	Anti-angiogenic Total	CT Events	CT Total	Weight	Risk Ratio M-H, Random, 95% CI
Cui 2013	5	56	2	54	12.8%	2.41 [0.49 , 11.90]
Kim 2012	36	143	11	71	87.2%	1.62 [0.88 , 3.00]
Total (95% CI)		**199**		**125**	**100.0%**	**1.71 [0.96 , 3.03]**
Total events:	41		13			

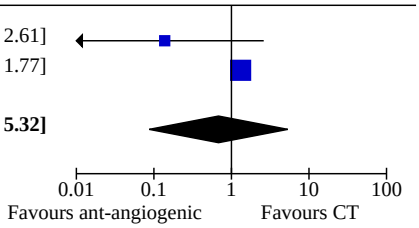
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 1 (P = 0.65); I² = 0%
Test for overall effect: Z = 1.84 (P = 0.07)
Test for subgroup differences: Not applicable



Analysis 17.4. Comparison 17: Chemotherapy ± anti-angiogenic drugs, Outcome 4: Toxicity (≥ G3)

Study or Subgroup	Anti-angiogenic Events	Anti-angiogenic Total	CT Events	CT Total	Weight	Risk Ratio M-H, Random, 95% CI
Cui 2013	0	56	3	54	29.1%	0.14 [0.01 , 2.61]
Kim 2012	82	143	31	71	70.9%	1.31 [0.97 , 1.77]
Total (95% CI)		**199**		**125**	**100.0%**	**0.68 [0.09 , 5.32]**
Total events:	82		34			

Heterogeneity: Tau² = 1.53; Chi² = 2.34, df = 1 (P = 0.13); I² = 57%
Test for overall effect: Z = 0.37 (P = 0.71)
Test for subgroup differences: Not applicable



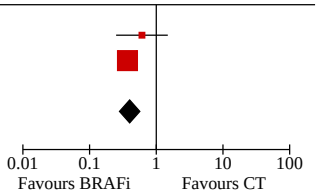
Comparison 18. Single agent BRAF inhibitor

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.1 Overall survival	2	925	Hazard Ratio (IV, Random, 95% CI)	0.40 [0.28, 0.57]
18.2 Progression-free survival	2	925	Hazard Ratio (IV, Random, 95% CI)	0.27 [0.21, 0.34]
18.3 Tumour response	2	925	Risk Ratio (M-H, Random, 95% CI)	6.78 [4.84, 9.49]
18.4 Toxicity (≥ G3)	2	925	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.48, 3.33]

Analysis 18.1. Comparison 18: Single agent BRAF inhibitor, Outcome 1: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	BRAF inhibitor Total	Chemotherapy Total	Weight	Hazard Ratio IV, Random, 95% CI
Hauschild 2012	-0.4943	0.4551	187	63	15.1%	0.61 [0.25 , 1.49]
McArthur 2014	-0.9943	0.18	337	338	84.9%	0.37 [0.26 , 0.53]
Total (95% CI)			**524**	**401**	**100.0%**	**0.40 [0.28 , 0.57]**

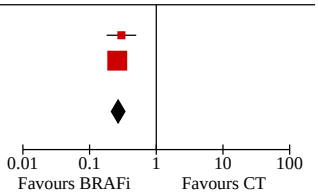
Heterogeneity: Tau² = 0.01; Chi² = 1.04, df = 1 (P = 0.31); I² = 4%
Test for overall effect: Z = 5.14 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 18.2. Comparison 18: Single agent BRAF inhibitor, Outcome 2: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	BRAF inhibitor Total	Chemotherapy Total	Weight	Hazard Ratio IV, Random, 95% CI
Hauschild 2012	-1.204	0.2606	187	63	20.9%	0.30 [0.18 , 0.50]
McArthur 2014	-1.3471	0.1339	337	338	79.1%	0.26 [0.20 , 0.34]
Total (95% CI)			**524**	**401**	**100.0%**	**0.27 [0.21 , 0.34]**

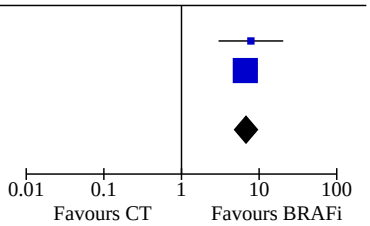
Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 1 (P = 0.63); I² = 0%
Test for overall effect: Z = 11.06 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 18.3. Comparison 18: Single agent BRAF inhibitor, Outcome 3: Tumour response

Study or Subgroup	BRAF inhibitor Events	BRAF inhibitor Total	Chemotherapy Events	Chemotherapy Total	Weight	Risk Ratio M-H, Random, 95% CI
Hauschild 2012	93	187	4	63	12.4%	7.83 [3.00 , 20.44]
McArthur 2014	192	337	29	338	87.6%	6.64 [4.63 , 9.52]
Total (95% CI)		**524**		**401**	**100.0%**	**6.78 [4.84 , 9.49]**
Total events:	285		33			

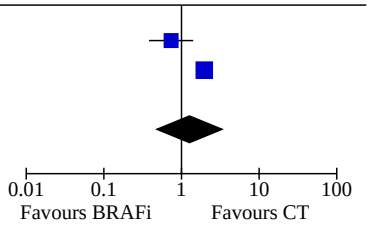
Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.75); I² = 0%
Test for overall effect: Z = 11.12 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 18.4. Comparison 18: Single agent BRAF inhibitor, Outcome 4: Toxicity (≥ G3)

Study or Subgroup	BRAF inhibitor Events	BRAF inhibitor Total	Chemotherapy Events	Chemotherapy Total	Weight	Risk Ratio M-H, Random, 95% CI
Hauschild 2012	24	187	11	63	44.6%	0.74 [0.38 , 1.41]
McArthur 2014	247	337	126	338	55.4%	1.97 [1.69 , 2.29]
Total (95% CI)		**524**		**401**	**100.0%**	**1.27 [0.48 , 3.33]**
Total events:	271		137			

Heterogeneity: Tau² = 0.43; Chi² = 8.35, df = 1 (P = 0.004); I² = 88%
Test for overall effect: Z = 0.48 (P = 0.63)
Test for subgroup differences: Not applicable



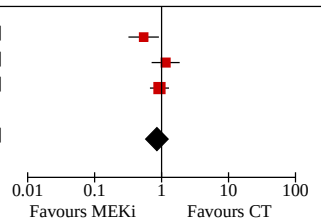
Comparison 19. Single agent MEK inhibitor

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19.1 Overall survival	3	496	Hazard Ratio (IV, Random, 95% CI)	0.85 [0.58, 1.25]
19.2 Progression-free survival	3	496	Hazard Ratio (IV, Random, 95% CI)	0.58 [0.42, 0.80]
19.3 Tumour response	3	496	Risk Ratio (M-H, Random, 95% CI)	2.01 [1.35, 2.99]
19.4 Toxicity (≥ G3)	1	91	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [1.08, 2.41]

Analysis 19.1. Comparison 19: Single agent MEK inhibitor, Outcome 1: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	MEK inhibitor Total	Chemotherapy Total	Weight	Hazard Ratio IV, Random, 95% CI
Flaherty 2012b	-0.6162	0.267	214	108	28.2%	0.54 [0.32 , 0.91]
Gupta 2014	0.1398	0.2461	41	42	30.6%	1.15 [0.71 , 1.86]
Robert 2013	-0.0726	0.1673	45	46	41.2%	0.93 [0.67 , 1.29]
Total (95% CI)			**300**	**196**	**100.0%**	**0.85 [0.58 , 1.25]**

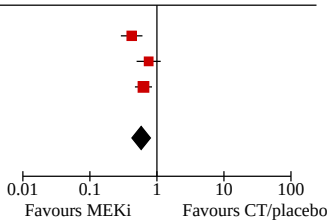
Heterogeneity: Tau² = 0.07; Chi² = 4.63, df = 2 (P = 0.10); I² = 57%
Test for overall effect: Z = 0.82 (P = 0.41)
Test for subgroup differences: Not applicable



Analysis 19.2. Comparison 19: Single agent MEK inhibitor, Outcome 2: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	MEK inhibitor Total	CT/placebo Total	Weight	Hazard Ratio IV, Random, 95% CI
Flaherty 2012b	-0.8675	0.189	214	108	32.3%	0.42 [0.29 , 0.61]
Gupta 2014	-0.2837	0.211	41	42	29.1%	0.75 [0.50 , 1.14]
Robert 2013	-0.462	0.1495	45	46	38.6%	0.63 [0.47 , 0.84]
Total (95% CI)			**300**	**196**	**100.0%**	**0.58 [0.42 , 0.80]**

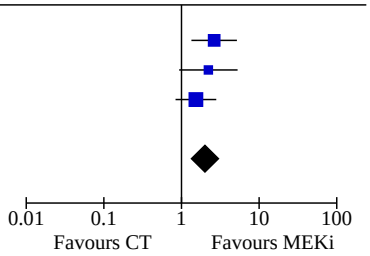
Heterogeneity: Tau² = 0.05; Chi² = 4.75, df = 2 (P = 0.09); I² = 58%
Test for overall effect: Z = 3.34 (P = 0.0008)
Test for subgroup differences: Not applicable



Analysis 19.3. Comparison 19: Single agent MEK inhibitor, Outcome 3: Tumour response

Study or Subgroup	MEK inhibitor Events	MEK inhibitor Total	Chemotherapy Events	Chemotherapy Total	Weight	Risk Ratio M-H, Random, 95% CI
Flaherty 2012b	47	214	9	108	35.0%	2.64 [1.34 , 5.17]
Gupta 2014	13	41	6	42	21.2%	2.22 [0.93 , 5.28]
Robert 2013	18	45	12	46	43.7%	1.53 [0.84 , 2.80]
Total (95% CI)		**300**		**196**	**100.0%**	**2.01 [1.35 , 2.99]**
Total events:	78		27			

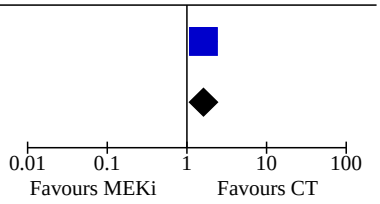
Heterogeneity: Tau² = 0.00; Chi² = 1.51, df = 2 (P = 0.47); I² = 0%
Test for overall effect: Z = 3.42 (P = 0.0006)
Test for subgroup differences: Not applicable



Analysis 19.4. Comparison 19: Single agent MEK inhibitor, Outcome 4: Toxicity (≥ G3)

Study or Subgroup	MEK inhibitor Events	MEK inhibitor Total	Chemotherapy Events	Chemotherapy Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Robert 2013	30	45	19	46	100.0%	1.61 [1.08 , 2.41]
Total (95% CI)		**45**		**46**	**100.0%**	**1.61 [1.08 , 2.41]**
Total events:	30		19			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.34 (P = 0.02)
Test for subgroup differences: Not applicable



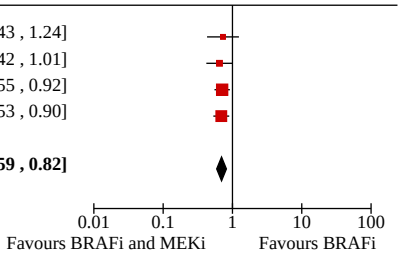
Comparison 20. Combination of BRAF and MEK inhibitors versus single agent BRAF inhibitor

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20.1 Overall survival	4	1784	Hazard Ratio (IV, Random, 95% CI)	0.70 [0.59, 0.82]
20.2 Progression-free survival	4	1784	Hazard Ratio (IV, Random, 95% CI)	0.56 [0.44, 0.71]
20.3 Tumour response	4	1784	Risk Ratio (M-H, Random, 95% CI)	1.32 [1.20, 1.46]
20.4 Toxicity (≥ G3)	4	1774	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.85, 1.20]

Analysis 20.1. Comparison 20: Combination of BRAF and MEK inhibitors versus single agent BRAF inhibitor, Outcome 1: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	BRAFi and MEKi Total	BRAFi Total	Weight	Hazard Ratio IV, Random, 95% CI
Flaherty 2012a	-0.3147	0.27	108	54	9.3%	0.73 [0.43 , 1.24]
Larkin 2014	-0.4308	0.2228	247	248	13.6%	0.65 [0.42 , 1.01]
Long 2015	-0.3425	0.1303	211	212	39.8%	0.71 [0.55 , 0.92]
Robert 2015	-0.3711	0.1346	352	352	37.3%	0.69 [0.53 , 0.90]
Total (95% CI)			**918**	**866**	**100.0%**	**0.70 [0.59 , 0.82]**

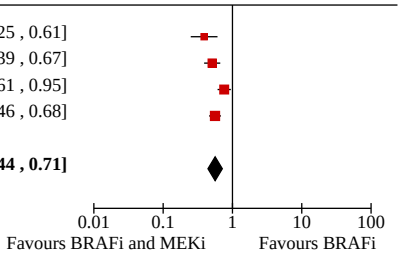
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 3 (P = 0.98); I² = 0%
Test for overall effect: Z = 4.41 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 20.2. Comparison 20: Combination of BRAF and MEK inhibitors versus single agent BRAF inhibitor, Outcome 2: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	BRAFi and MEKi Total	BRAFi Total	Weight	Hazard Ratio IV, Random, 95% CI
Flaherty 2012a	-0.9416	0.2269	108	54	16.2%	0.39 [0.25 , 0.61]
Larkin 2014	-0.6733	0.1369	247	248	25.4%	0.51 [0.39 , 0.67]
Long 2015	-0.2744	0.1122	211	212	28.4%	0.76 [0.61 , 0.95]
Robert 2015	-0.5798	0.1004	352	352	29.9%	0.56 [0.46 , 0.68]
Total (95% CI)			**918**	**866**	**100.0%**	**0.56 [0.44 , 0.71]**

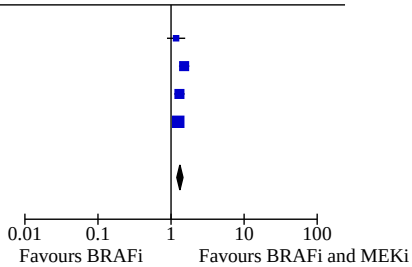
Heterogeneity: Tau² = 0.04; Chi² = 9.82, df = 3 (P = 0.02); I² = 69%
Test for overall effect: Z = 4.74 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 20.3. Comparison 20: Combination of BRAF and MEK inhibitors versus single agent BRAF inhibitor, Outcome 3: Tumour response

Study or Subgroup	BRAFi and MEKi Events	BRAFi and MEKi Total	BRAFi Events	BRAFi Total	Weight	Risk Ratio M-H, Random, 95% CI
Flaherty 2012a	68	108	29	54	10.3%	1.17 [0.88 , 1.56]
Larkin 2014	167	247	111	248	26.4%	1.51 [1.28 , 1.78]
Long 2015	140	211	108	212	26.3%	1.30 [1.11 , 1.53]
Robert 2015	226	352	180	352	37.0%	1.26 [1.10 , 1.43]
Total (95% CI)		**918**		**866**	**100.0%**	**1.32 [1.20 , 1.46]**
Total events:	601		428			

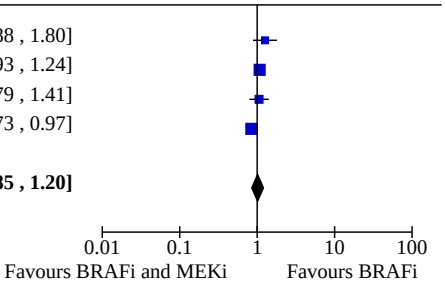
Heterogeneity: Tau² = 0.00; Chi² = 3.90, df = 3 (P = 0.27); I² = 23%
Test for overall effect: Z = 5.66 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 20.4. Comparison 20: Combination of BRAF and MEK inhibitors versus single agent BRAF inhibitor, Outcome 4: Toxicity (≥ G3)

Study or Subgroup	BRAFi and MEKi Events	BRAFi and MEKi Total	BRAFi Events	BRAFi Total	Weight	Risk Ratio M-H, Random, 95% CI
Flaherty 2012a	58	108	23	54	15.1%	1.26 [0.88 , 1.80]
Larkin 2014	159	254	139	239	32.7%	1.08 [0.93 , 1.24]
Long 2015	66	209	63	211	19.4%	1.06 [0.79 , 1.41]
Robert 2015	167	350	198	349	32.8%	0.84 [0.73 , 0.97]
Total (95% CI)		**921**		**853**	**100.0%**	**1.01 [0.85 , 1.20]**
Total events:	450		423			

Heterogeneity: Tau² = 0.02; Chi² = 8.24, df = 3 (P = 0.04); I² = 64%
Test for overall effect: Z = 0.15 (P = 0.88)
Test for subgroup differences: Not applicable



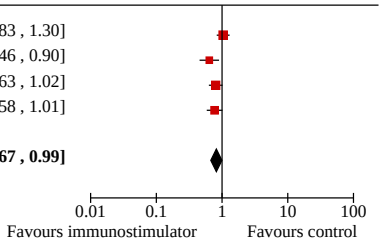
Comparison 21. Immunostimulating agents

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21.1 Overall survival	4	1458	Hazard Ratio (IV, Random, 95% CI)	0.82 [0.67, 0.99]
21.2 Progression-free survival	4	1458	Hazard Ratio (IV, Random, 95% CI)	0.92 [0.74, 1.14]
21.3 Tumour response	4	1451	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.60, 2.50]
21.4 Toxicity (≥ G3)	4	1458	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.77, 1.08]

Analysis 21.1. Comparison 21: Immunostimulating agents, Outcome 1: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Immunostimulator Total	Control Total	Weight	Hazard Ratio IV, Random, 95% CI
Hodi 2010a	0.0392	0.1151	403	137	28.9%	1.04 [0.83 , 1.30]
Hodi 2014	-0.4463	0.1739	123	122	19.3%	0.64 [0.46 , 0.90]
Maio 2010	-0.2231	0.1219	391	97	27.6%	0.80 [0.63 , 1.02]
Schwartzentruber 2011a	-0.2614	0.1402	91	94	24.3%	0.77 [0.58 , 1.01]
Total (95% CI)			**1008**	**450**	**100.0%**	**0.82 [0.67 , 0.99]**

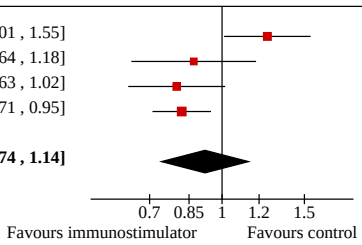
Heterogeneity: Tau² = 0.02; Chi² = 6.43, df = 3 (P = 0.09); I² = 53%
Test for overall effect: Z = 2.01 (P = 0.04)
Test for subgroup differences: Not applicable



Analysis 21.2. Comparison 21: Immunostimulating agents, Outcome 2: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Immunostimulator Total	Control Total	Weight	Hazard Ratio IV, Random, 95% CI
Hodi 2010a	0.2231	0.1087	403	137	25.7%	1.25 [1.01 , 1.55]
Hodi 2014	-0.1393	0.1566	123	122	20.2%	0.87 [0.64 , 1.18]
Maio 2010	-0.2231	0.1219	391	97	24.2%	0.80 [0.63 , 1.02]
Schwartzentruber 2011a	-0.1985	0.0735	91	94	29.9%	0.82 [0.71 , 0.95]
Total (95% CI)			**1008**	**450**	**100.0%**	**0.92 [0.74 , 1.14]**

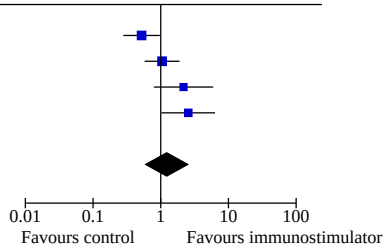
Heterogeneity: Tau² = 0.03; Chi² = 11.71, df = 3 (P = 0.008); I² = 74%
Test for overall effect: Z = 0.77 (P = 0.44)
Test for subgroup differences: Not applicable



Analysis 21.3. Comparison 21: Immunostimulating agents, Outcome 3: Tumour response

Study or Subgroup	Immunostimulator Events	Immunostimulator Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Hodi 2010a	23	403	15	137	28.1%	0.52 [0.28 , 0.97]
Hodi 2014	19	123	18	122	28.6%	1.05 [0.58 , 1.90]
Maio 2010	35	391	4	97	20.8%	2.17 [0.79 , 5.96]
Schwartzentruber 2011a	14	85	6	93	22.6%	2.55 [1.03 , 6.34]
Total (95% CI)		**1002**		**449**	**100.0%**	**1.23 [0.60 , 2.50]**
Total events:	91		43			

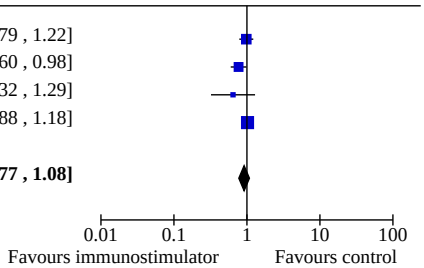
Heterogeneity: Tau² = 0.37; Chi² = 10.69, df = 3 (P = 0.01); I² = 72%
Test for overall effect: Z = 0.56 (P = 0.58)
Test for subgroup differences: Not applicable



Analysis 21.4. Comparison 21: Immunostimulating agents, Outcome 4: Toxicity (≥ G3)

Study or Subgroup	Immunostimulator Events	Immunostimulator Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Hodi 2010a	173	403	60	137	28.9%	0.98 [0.79 , 1.22]
Hodi 2014	55	123	71	122	25.6%	0.77 [0.60 , 0.98]
Maio 2010	26	391	10	97	5.3%	0.65 [0.32 , 1.29]
Schwartzentruber 2011a	73	91	74	94	40.3%	1.02 [0.88 , 1.18]
Total (95% CI)		**1008**		**450**	**100.0%**	**0.92 [0.77 , 1.08]**
Total events:	327		215			

Heterogeneity: Tau² = 0.01; Chi² = 5.48, df = 3 (P = 0.14); I² = 45%
Test for overall effect: Z = 1.04 (P = 0.30)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Glossary of terms used

Term	Explanation
Actinomycin-D	A polypeptide used as an antibiotic and antineoplastic agent as a result of its ability to inhibit transcription
AJCC TNM staging	This is the most widely used tumour staging classification system, which has been developed and constantly updated by the American Joint Committee on Cancer (AJCC) for describing the extent

Table 1. Glossary of terms used *(Continued)*

	of disease progression in people with cancer. It uses in part the TNM scoring system: **t**umour size, lymph **n**odes affected, **m**etastases. Individuals affected by specific tumour type are assigned to categories describing risk of death
AJCC TNM stage III	People at this disease stage have melanoma metastasis in their regional lymph node (i.e. the first lymph nodes draining the skin area affected by the melanoma)
AJCC TNM stage IIIC	Stage IIIC is a higher risk subgroup among people with lymph node metastasis. The category includes people with all primary tumour stages (T stages) and those with clinically positive lymph nodes, or 4 or more positive lymph nodes
AJCC TNM stage IV	People with this disease stage have melanoma metastasis to distant sites (e.g. lung, liver, brain, bone)
Anti-angiogenic agents	Drugs aimed to disrupt tumour vascularisation and reduce blood supply to malignant cells; examples include bevacizumab and endostar
Antigen	A substance that invokes the body's immune response
Aranoza	An alkylating agent that is used as a chemotherapy drug for various cancers including melanoma as part of combination chemotherapy regimens
Bacille Calmette-Guérin (BCG)	BCG is a vaccine used in the prevention of tuberculosis. However, it is also a form of cancer immunotherapy with established effects in superficial (non-muscle invading) bladder cancer
Bevacizumab	Bevacizumab (Avastin) is an angiogenesis inhibitor approved for use for people with various metastatic cancers. Bevacizumab acts through blockade of vascular endothelial growth factor A (VEGF-A) that prevents development of new vessels necessary for tumours to grow
Bleomycin	An antineoplastic agent used in chemotherapy regimens for various tumours. Belomycin acts through cleavage of DNA within cells
Biochemotherapy	A combination of chemotherapy plus immunostimulating cytokines, such as interleukin-2 and interferon-alpha
Bosentan	An endothelin receptor inhibitor that causes reduced DNA synthesis and promotes apoptosis through competitive antagonism with the anti-apoptotic factor endothelin-1, often secreted by cancer cells in an autocrine or paracrine manner
BRAF	A gene that makes a protein called B-Raf. BRAF is involved in sending signals within cells that direct their growth. In some cancers, this gene has mutated (Melanoma Institute Australia 2017)
Carmustine	An alkylating agent that prevents DNA replication and cell proliferation used in chemotherapy for various cancers
Cobimetinib	An inhibitor of MAPK kinase (MEK) approved for use in metastatic melanoma with BRAF V600E/K mutation usually in combination with a BRAF inhibitor
Corynebacterium parvum	*C parvum* is an aerobic, gram positive bacterium that has been reported to have antineoplastic potential
Cyclophosphamide	An alkylating agent used in auto-immune diseases and various tumours as a chemotherapy drug
Cytokine	Small proteins produced by a broad range of cells that are important in cell signalling; they are immunostimulating agents
Cytotoxic	Cell killing

Table 1. Glossary of terms used *(Continued)*

CTLA4 (cytotoxic T-cell lymphocyte-associated antigen-4)	CTLA4 is a receptor located on the surface of T-cells that down regulates the immune system (an immune checkpoint). The inhibition of this receptor with monoclonal antibodies, such as ipilimumab and tremelimumab, 'unleashes' the immune response to fight against malignant cells
Dabrafenib	An inhibitor of the BRAF kinase that has been approved for people with advanced melanoma carrying the BRAF V600E mutation
Dacarbazine	A chemotherapy drug that belongs to the family of alkylating agents that is used in the treatment of various cancers, including melanoma
Dendritic cell	These are antigen-presenting cells that link the innate to the adaptive immune systems via processing antigens and presenting them to T-lymphocytes. Their role is crucial for proper functioning of vaccines, including cancer vaccines
Elesclomol	A drug that causes the accumulation of reactive oxygen species to trigger apoptosis in cancer cells via oxidative stress. It is approved for use for people with metastatic melanoma
Endostar	A modified recombinant human endostatin that acts as an anti-angiogenic agent to prevent the formation of new blood vessels that are necessary for tumour growth and survival
Fotemustine	A chemotherapy drug that belongs to the family of alkylating agents and has been approved for the treatment of metastatic melanoma
G3 and G4	G3 (grade 3) and G4 (grade 4) toxicity refers to the highest degree of adverse events due to a systemic treatment. This system grades the toxicity related to a given system or organ (e.g. hepatic, cardiac, haematologic)
gp100	A known melanoma antigen that can be applied to develop a cancer vaccine through processing and presentation by dendritic cells to lymphocytes
Granulocyte macrophage - colony-stimulating factor (GM-CSF)	A cytokine that stimulates stem cells to give rise to granulocytes and monocytes and boosts the immune system
Hydroxyurea	A chemotherapy agent that acts through reducing the generation of deoxyribonucleotides, the building blocks of DNA, to inhibit adequate synthesis of DNA. It is used as a chemotherapy drug for people with myeloproliferative disorders
Immune checkpoints	Signalling proteins that protect against auto-immunity and regulate the immune response; these checkpoints can be hijacked by cancer cells to evade T-cell-mediated death, i.e. stopping an immune response to the tumour. CTLA4 and PD1 are both immune checkpoints
Immune checkpoint inhibitors	Drugs that override the signalling/activation of immune checkpoints to encourage cytotoxic T-cell recognition of cancer (i.e. an immune response). These are monoclonal antibodies blocking either CTLA4 or PD1 (two immune checkpoints), known as anti-CTLA4 and anti-PD1 monoclonal antibodies
Immunomodulating	Stimulates or suppresses the immune system
Immunostimulating	Stimulates an immune response
Interferon-alpha	Interferon-alpha is used for the postoperative treatment of people with AJCC TNM stages II (primary tumour at high risk of disease progression with negative lymph nodes) and III (positive lymph nodes) and to enhance the efficacy of chemotherapy in those who have metastatic melanoma
Interleukin-2	Interleukin-2 is a protein that regulates the activities of leucocytes (particularly lymphocytes) that are responsible for immunity. The receptor for interleukin-2 is expressed by lymphocytes. A recom-

Table 1. Glossary of terms used *(Continued)*

	binant form of human interleukin-2 has been approved by the FDA for the treatment of melanoma and renal cell cancer
Lomustine	An oral alkylating chemotherapeutic agent used mainly to treat brain tumours because it crosses the blood-brain barrier
MEK	Mitogen-activated protein kinase (MEK) is part of the MAPK signalling pathway (see 'RAS-RAF-MEK-ERK pathway' below), which is activated in melanoma
Monoclonal antibodies	Monoclonal antibodies are a type of targeted drug therapy; they work by recognising and finding specific proteins on cancer cells (they work in different ways depending on the protein they are targeting) (Cancer Research UK 2017)
Oblimersen	A bcl-2 antisense oligodeoxynucleotide that reduces cancer cell survival and proliferation by blocking the generation of the anti-apoptotic protein bcl-2 thus promoting programmed cell death in cancer cells
Oncogene	A gene thats activation or over expression favours cancer growth
Paclitaxel	A chemotherapy agent targeting the protein tubulin. The drug interferes with the dynamics of microtubule formation and breakdown leading to problems during cell division and triggering of apoptosis. DHA- and nab-paclitaxel are modified forms of the drug
PD1 (programmed cell death protein-1)	PD1 is a receptor located on the surface of the T-cells that down regulates the immune system (an immune checkpoint). The inhibition of this receptor with monoclonal antibodies, such as nivolumab and pembrolizumab, 'unleashes' immune response to fight against malignant cells
PF-3512676	An synthetic oligonucleotide that acts as a Toll-like receptor-9 (TLR-9) agonist. It is used as an immunomodulatory agent alone, or in combination with chemotherapy, to boost anti-tumour effects by enhancing B-cell proliferation and antigen-specific antibody production and cytokine secretion
Polychemotherapy	A combination of multiple chemotherapeutic agents
Procarbazine	An alkylating agent used as an antineoplastic chemotherapy drug in various tumours such as glioblastoma multiforme and Hodgkin's lymphoma
Programmed death-1 (PD-1)	PD-1 is an inhibitory receptor located on the surface of the T-cells that down regulates the immune system when bound by its ligands (PD-L1 and PD-L2, often found on cancer cells). The inhibition of this receptor with monoclonal antibodies, such as pembrolizumab and nivolumab, releases the brake on immune cells thus allowing them to freely fight malignant cells
Ramucirumab	A human monoclonal antibody that targets the vascular endothelial growth factor receptor 2 (VEGFR2) to block VEGF binding and thus inhibit angiogenesis. It is approved for use in advanced gastric adenocarcinoma and metastatic non-small cell lung carcinoma
RAS-RAF-MEK-ERK pathway	This is also known as 'MAPK/ERK pathway', which is a chain of proteins in the cell that communicates a signal from a receptor on the surface of the cell to the nucleus of the cell (where DNA is located). When one of the proteins in the pathway is mutated, it can be stuck in the 'on' or 'off' position, which is a necessary step in the development of many cancers, including melanoma. Drugs, such as BRAF and MEK inhibitors, can reverse this switch
Small-molecule inhibitors	Low molecular weight drugs targeting molecules mutated or overexpressed in tumours; examples include BRAF inhibitors (which block the BRAF protein) or MEK inhibitors (which block the MEK protein)
Sorafenib	An inhibitor of various tyrosine protein kinases including RAF
Selumetinib	An inhibitor of the MAPK kinase (MEK) downstream of BRAF

Table 1. Glossary of terms used *(Continued)*

T-cell	A white blood cell type, which plays a key role in immunity
Tasisulam	A small-molecule agent that induces apoptosis through the intrinsic mitochondrial pathway
Tamoxifen	A cytostatic hormonal therapeutic agent used mainly as a treatment for oestrogen receptor positive breast cancer. Tamoxifen acts through competing with oestrogen for its receptor thus reducing oestrogen-related effects in breast tissue such as DNA synthesis and cell proliferation
Temozolomide	An oral alkylating agent that can be used in chemotherapy regimens for various cancers such as glioblastoma multiforme
Trametinib	An inhibitor of MAPK kinase (MEK) 1 and 2 approved for use in people with V600E-mutated metastatic melanoma
Vemurafenib	A small-molecule inhibitor of mutated BRAF, an oncogene involved in cell survival or proliferation
Vincristine	An anti-mitotic agent that binds tubulin thus preventing cell proliferation and triggering apoptosis
Vindesine	An anti-mitotic agent that acts by targeting microtubules and preventing cell division thus useful as a chemotherapy drug in various cancers
Vitespen	A tumour-derived heat shock protein that is used as an adjuvant in cancer immunotherapy

Table 2. Reasons for excluding 39 studies from meta-analysis

Study ID	Reason for exclusion from meta-analysis
Hamid 2014	Single study investigating tasisulam
Kefford 2010	Single study investigating bosentan
Hofmann 2011	Single study comparing dacarbazine and best supportive care
Schadendorf 2006	Single study investigating dendritic cells therapy
Agarwala 2002	Single study investigating histamine with interleukin-2
Bajetta 1985	Different polychemotherapy regimens not compared in other studies
Beretta 1976	Different polychemotherapy regimens not compared in other studies
Cocconi 1992	Different polychemotherapy regimens not compared in other studies
Dummer 2006	Different PEG-interferon schedules tested
Flaherty 2001	Inpatient and outpatient interleukin-2-based regimens not compared in other studies
Glaspy 2009	Different lenalidomide schedules not compared in other studies
Jelic 2002	Different polychemotherapy regimens not compared in other studies
Keilholz 1997	Study comparing biochemotherapy versus biotherapy
Legha 1996	Study comparing alternating and sequential biochemotherapy and chemotherapy

Table 2. Reasons for excluding 39 studies from meta-analysis *(Continued)*

Miller 1989	Single study investigating Indomethacine with interferon
Moon 1975	Different single-agent chemotherapy regimens not compared in other studies
Presant 1982	Different polychemotherapy regimens not compared in other studies
Richtig 2004	Different temozolomide and interferon schedules tested
Wittes 1978	Different polychemotherapy regimens not compared in other studies
Vuoristo 2005	Different interferon-based regimens not compared in other studies
Punt 2006	Different biochemotherapy regimens not compared in other studies
Reichle 2007	Single study investigating chemotherapy and COX-2 inhibitor
Sparano 1993	Single study comparing interleukin-2 with versus without interferon-alpha
Wolchok 2010	Different ipilimumab schedules tested
Avril 2004	Single study comparing fotemustine and dacarbazine
O'Day 2011	Single study testing Intetumumab
Ranson 2007	Single study testing lomeguatrib
Hersh 2015	Single study testing nab-paclitaxel
Bedikian 2006	Single study testing oblimersen
Bedikian 2011	Single study testing DHA-paclitaxel
Weber 2009	Single study testing PF-3512676
Carvajal 2014	Single study testing ramucirumab
Balch 1984	Single study testing dacarbazine and *C parvum* after surgery
Eigentler 2008	Single study testing vindesine after surgery
Lawson 2015	Single study testing GM-CSF and a polypeptide vaccination after surgery
Eisen 2010	Single study testing lenalidomide
Middleton 2015	Single study testing veliparib
Testori 2008	Single study testing vetaspen

Table 3. Studies included in meta-analysis

Comparison	Experimental (class of) drug	Study ID

Table 3. Studies included in meta-analysis *(Continued)*

Polychemotherapy versus single agent chemotherapy	Polychemotherapy	Bellett 1976
		Carter 1975
		Chapman 1999
		Chauvergne 1982
		Chiarion Sileni 2001
		Costanza 1977
		Luikart 1984
		Ringborg 1989
		Zimpfer-Rechner 2003
		Bafaloukos 2005
		Glover 2003
		Costanza 1972
		Kogoniia 1981
		Lopez 1984
Biochemotherapy versus chemotherapy	Interferon-alpha	Bajetta 1994
		Bajetta 2006
		Dorval 1999
		Falkson 1991
		Falkson 1995
		Gorbonova 2000
		Kaufmann 2005
		Thomson 1993
		Vorobiof 1994
		Young 2001
		Kirkwood 1990
		Daponte 2013
		Falkson 1998
		Danson 2003

Table 3. Studies included in meta-analysis *(Continued)*

		Maio 2010
	Interleukin-2	Keilholz 2005
		Sertoli 1999
		Hauschild 2001
	Interleukin-2 plus interferon-alpha	Atkins 2008
		Atzpodien 2002
		Eton 2002
		Johnston 1998
		Middleton 2007
		Ridolfi 2002
		Rosenberg 1999
Immune checkpoint inhibitors versus chemotherapy (or other immune checkpoint inhibitors)	Anti-CTLA4 monoclonal antibodies	Hodi 2010
		Hodi 2014
		Ribas 2013
		Robert 2011
	Anti-PD1 monoclonal antibodies	Ribas 2015
		Robert 2015a
		Weber 2015
		Robert 2015b
	Anti-CTLA4 plus anti-PD1 monoclonal antibodies	Larkin 2015
		Postow 2015
Small-molecule targeted drugs versus chemotherapy (or other small-molecule targeted drugs)	BRAF inhibitors	Hauschild 2012
		McArthur 2014
	MEK inhibitors	Flaherty 2012b
		Gupta 2014
		Robert 2013
	BRAF plus MEK inhibitors	Flaherty 2012a
		Larkin 2014

Table 3. Studies included in meta-analysis *(Continued)*

		Long 2015
		Robert 2015
Chemotherapy with versus without other agents	Bacille Calmette-Guérin (BCG)	Costanzi 1982
		Mastrangelo 1979
		Newlands 1976
		Ramseur 1978
		Verschraegen 1993
		Veronesi 1984
	Corynebacterium parvum	Clunie 1980
		Gough 1978
		Presant 1979
		Robidoux 1982
		Thatcher 1986
		Kokoschka 1978
	Tamoxifen	Agarwala 1999
		Cocconi 1992
		Rusthoven 1996
	Anti-angiogenic drugs	Cui 2013
		Kim 2012
	Sorafenib	Flaherty 2013
		Hauschild 2009
		McDermott 2008
	Elesclomol	O'Day 2009
		O'Day 2013
Single agent chemotherapy versus other single agent chemotherapy	Temozolomide	Chiarion-Sileni 2011
		Middleton 2000
		Patel 2011

Hodi 2010a; Hodi 2014; Maio 2010; Schwartzentruber 2011a were included in a meta-analysis of immunostimulating agents.

APPENDICES

Appendix 1. CENTRAL (Cochrane Library) search strategy

#1 MeSH descriptor: [Melanoma] explode all trees
#2 MeSH descriptor: [Skin Neoplasms] explode all trees
#3 melanoma:ti,ab
#4 #1 or #2 or #3
#5 (metastatic or metastas*):ti,ab
#6 ("stage iv" or "stage 4"):ti,ab
#7 MeSH descriptor: [Neoplasm Metastasis] explode all trees
#8 #5 or #6 or #7
#9 #4 and #8

Appendix 2. MEDLINE (Ovid) search strategy

1. exp Melanoma/
2. exp Skin Neoplasms/
3. melanoma.ti,ab.
4. or/1-3
5. (metastatic or metastas$).ti,ab.
6. exp Neoplasm Metastasis/
7. ("stage iv" or "stage 4").ti,ab.
8. or/5-7
9. 4 and 8
10. randomized controlled trial.pt.
11. controlled clinical trial.pt.
12. randomized.ab.
13. placebo.ab.
14. clinical trials as topic.sh.
15. randomly.ab.
16. trial.ti.
17. 10 or 11 or 12 or 13 or 14 or 15 or 16
18. exp animals/ not humans.sh.
19. 17 not 18
20. 9 and 19

[Lines 10-19: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision)]

Appendix 3. Embase (Ovid) search strategy

1. exp melanoma/
2. melanoma.ti,ab.
3. 1 or 2
4. (metastatic or metastas$).ti,ab.
5. metastasis/ or exp skin metastasis/
6. ("stage iv" or "stage 4").ti,ab.
7. 4 or 5 or 6
8. crossover procedure.sh.
9. double-blind procedure.sh.
10. single-blind procedure.sh.
11. (crossover$ or cross over$).tw.
12. placebo$.tw.
13. (doubl$ adj blind$).tw.
14. allocat$.tw.
15. trial.ti.
16. randomized controlled trial.sh.
17. random$.tw.
18. or/8-17
19. exp animal/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
20. human/ or normal human/
21. 19 and 20

22. 19 not 21
23. 18 not 22
24. 3 and 7 and 23

WHAT'S NEW

Date	Event	Description
22 February 2019	Amended	Small amendment to wording of background in PLS after a query via Cochrane Library feedback

HISTORY

Protocol first published: Issue 5, 2014
Review first published: Issue 2, 2018

CONTRIBUTIONS OF AUTHORS

Simone Mocellin was the review contact person.
Sandro Pasquali and SImone Mocellin co-ordinated contributions from co-authors and wrote the final draft of the review.
Sandro Pasquali, Andreas V Hadjinicolaou and SImone Mocellin screened studies against eligibility criteria.
Sandro Pasquali obtained data on ongoing and unpublished studies.
Sandro Pasquali, Andreas V Hadjinicolaou and SImone Mocellin and appraised study quality.
Sandro Pasquali, Andreas V Hadjinicolaou and SImone Mocellin extracted data and sought additional information from trial authors.
Sandro Pasquali and Simone Mocellin entered data into RevMan.
Sandro Pasquali and Simone Mocellin analysed and interpreted data.
Sandro Pasquali and Simone Mocellin worked on the methods section.
Vanna Chiarion Sileni and Carlo Riccardo Rossi contributed to the writing of the review and critical revision.
Sandro Pasquali and Simone Mocellin drafted the clinical sections of the Background and responded to the clinical comments of the referees.
Sandro Pasquali and Simone Mocellin responded to methodology and statistics comments from external peer referees.
Simone Mocellin is the guarantor of the update.

DECLARATIONS OF INTEREST

Sandro Pasquali: nothing to declare.
Andreas V Hadjinicolaou: nothing to declare.
Vanna Chiarion Sileni: nothing to declare.
Carlo Riccardo Rossi: nothing to declare.
Simone Mocellin: nothing to declare.

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Internal sources

- University of Padova, Italy

External sources

- The National Institute for Health Research (NIHR), UK

  The NIHR, UK, is the largest single funder of the Cochrane Skin Group.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Network meta-analysis

Given that direct comparisons between key therapies were unavailable (e.g. immune checkpoint inhibitors versus small-molecule targeted drugs), we conducted a network meta-analysis to compute estimates of indirect comparisons and to generate treatment rankings (Cipriani 2013; Mills 2013).

Study selection

We used the following criteria to assess randomised controlled trials (RCTs) for inclusion:

1. studies reporting on the outcomes of interest, that is, progression-free survival (as an efficacy outcome) and severe toxicity (as a harm outcome); and
2. studies reporting on treatments for which high quality evidence of efficacy was available from direct comparisons and for which interventions are approved for routine use in clinical practice.

Further details on outcomes and treatments included in the network meta-analysis are reported in the Effects of interventions section (see *Network meta-analysis findings*).

We chose to include phase III and earlier phase studies because early phase trials were more likely to report on tumour response (which was a review secondary outcomes). Furthermore, early phase trials sometimes also describe survival findings (which was a review primary outcome). However, phase II trials are not designed to detect survival differences but rather tumour response differences.

We included trials with mixed disease stages if outcomes for metastatic disease were reported separately.

Evidence grading

We used the GRADE system adapted for network meta-analysis to assess evidence quality according to four levels: high-, moderate-, low-, and very low-quality (Salanti 2014).

Quality was downgraded by one level (serious concern) or two levels (very serious concern) for study limitations (risk of bias), evidence for publication bias (assessed by inspecting a funnel plot dedicated to network meta-analysis (Chaimani 2013)), indirectness (indirect population, intervention, control, outcomes; lack of transitivity assumption), inconsistency (between-study statistical heterogeneity, as suggested by network meta-analysis estimate of prediction interval crossing the null value), and imprecision (as suggested by wide confidence intervals estimated by network meta-analysis).

Statistical analysis

Review primary outcomes were progression-free survival and high-grade toxicity. The outcome measure for survival data was hazard ratio (HR) and 95% confidence interval (CI). The outcome measure for toxicity was relative risk (RR) and 95% CI.

Random-effects network meta-analysis was carried out within a frequentist setting (Hong 2013). A common heterogeneity parameter (Tau^2) was assumed across all comparisons, allowing the inclusion of comparisons based on a single RCT. Summary effects are presented with 95% CIs and predictive interval. Predictive intervals were calculated using between-study variance (Tau^2) and represents the interval where the results of future studies are expected to be, thus providing information on the magnitude of heterogeneity. They are calculated as $\mu \pm (t^{\alpha}_{df}) \times \sqrt{(\tau^2 + SE(\mu)^2}$, where t^{α}_{df} is the 100 x (1 - α/2)% percentile of the t-distribution with df degrees of freedom and μ is the meta-analysis effect estimate (Chaimani 2013).

The key assumption of network meta-analysis is transitivity (Donegan 2013). If information about comparisons A versus B and A versus C is available, then network meta-analysis can derive information regarding the BC comparison based on the transitivity equation (A versus B – A versus C = B versus C). Transitivity holds assuming that:

1. the common treatment, in this case conventional chemotherapy (used to compare different drug schedules indirectly), was similar when it appeared in different trials;
2. pair-wise comparisons did not differ substantially with respect to the distribution of effect modifiers; and
3. in principle, participants could be randomised to any of the treatments compared in the network.

Lack of transitivity can manifest as inconsistency between direct and indirect estimates ('loop inconsistency') or between estimates deriving from different study designs ('design inconsistency', which can occur when the relative effectiveness of treatment A versus B is different when estimated in studies with different designs, such as A versus B and A versus B versus C). We investigated inconsistency using a design-by-treatment interaction model, which addresses both loop and design inconsistency (Higgins 2012; White 2012).

Inconsistencies of single loops can be assessed with an inconsistency plot, where a ratio of ratio can be calculated as the ratio between the relative risk estimated by the conventional pair-wise meta-analysis and that estimated by the network meta-analysis. A ratio of ratio value close to the unit indicates that the results of the two techniques are in agreement; in general, values greater than 2 suggest high inconsistency (Chaimani 2013).

Network meta-analysis also provides a ranking probability curve of each treatment (rankogram) by calculating the probability of each treatment to achieve the best rank amongst all treatments. The surface under the cumulative ranking (SUCRA) line for each treatment, which equals one when a treatment is certain to be the best and zero when a treatment is certain to be the worst, was used for treatment ranking (Chaimani 2013; Salanti 2011). We also generated a bivariate ranking plot including both efficacy (progression-free survival) and

acceptability (the inverse of toxicity: low toxicity rates are associated with high SUCRA values): an ideal treatment should be characterised by both high efficacy and high acceptability so should appear in the right upper corner of the ranking plot.

A dedicated funnel plot (comparison-adjusted funnel plot) can be used to assess small-study effects (which includes publication bias) (Chaimani 2013). This plot takes into consideration that included studies estimate effects for different comparisons: therefore, there cannot be a single reference line against which symmetry can be assessed. In the absence of small-study effect the comparison-adjusted funnel plot should be symmetrical around the zero line.

All statistical tests were two-sided. Statistical analysis and graph generation was performed with Stata 11.2 (Stata 2017).

NOTES

Small amendment to wording of background in PLS after a query via Cochrane Library feedback in consulation with lead author.

INDEX TERMS

Medical Subject Headings (MeSH)

Angiogenesis Inhibitors [adverse effects] [therapeutic use]; Antibodies, Monoclonal [adverse effects] [therapeutic use]; Antineoplastic Agents [adverse effects] [therapeutic use]; Brain Neoplasms [secondary]; CTLA-4 Antigen [antagonists & inhibitors]; Disease-Free Survival; Drug Therapy, Combination [adverse effects]; Immunotherapy [methods]; Interferon-alpha [therapeutic use]; Interleukin-2 [therapeutic use]; Melanoma [mortality] [secondary] [*therapy]; Programmed Cell Death 1 Receptor [antagonists & inhibitors]; Proto-Oncogene Proteins B-raf [antagonists & inhibitors]; Randomized Controlled Trials as Topic; Skin Neoplasms [mortality] [*therapy]

MeSH check words

Female; Humans; Male; Middle Aged