REVIEW

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Melanoma Management

The role of chemotherapy in the modern management of melanoma

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Practice points

- Dacarbazine remains a standards of care for patients requiring chemotherapy.
- Initial analysis of a Phase III trial examining the efficacy of nab-paclitaxel in melanoma showed an improvement in progression-free survival, but the updated results showed no improvement in overall survival.
- Combination chemotherapy improves response rates in melanoma; however, it has not been shown to provide an overall survival benefit and is associated with increased toxicity.
- Although huge advances have been made by using targeted and immune treatments in melanoma, there remains a role for chemotherapy in patients who do not have a targetable mutation or who have disease progression on targeted therapy, and for those who do not respond or who cannot receive immunotherapy.
- The development of novel agents will be important for future advances in the chemotherapeutic treatment of melanoma.

SUMMARY The last 4 years have seen dramatic changes in the treatment of advanced melanoma, largely based on advances in targeted therapy and immunotherapy. This article examines the role of chemotherapy in the modern management of melanoma. We examine the evidence for promising new agents and discuss their position in the sequencing of treatment options for patients with advanced disease. In addition, we discuss the combination of chemotherapy with targeted treatments and immune therapies. Finally, we discuss future areas of research for ensuring that we maximize the potential of all agents available to us and identify new, effective treatments.

KEYWORDS
- advances
- biochemotherapy
- chemotherapy
- melanoma

Melanoma has been increasing in incidence over the last two decades. In 2013, it is estimated that 76,690 people were diagnosed with melanoma in the USA and 9480 died from the disease [1]. Prior to 2011, treatment options for metastatic/unresectable melanoma were very limited and outcomes were poor, with median survival durations of between 9 and 12 months [2]. Recent advances in our understanding of the molecular basis of cell signaling and of immune checkpoint blockade have rapidly been translated into effective new treatment options for many patients with melanoma. The discovery of the role of oncogenic *BRAF* in the activation of the MAPK pathway in approximately 50% of patients has led to three drugs being licensed by the US FDA in advanced disease (vemurafenib, dabrafenib and trametinib) and both *BRAF* inhibitors available in Europe. [3–6]. Eligible patients being treated with vemurafenib can expect a response rate of 57%, a progression-free survival (PFS) of approximately 6 months and overall survival (OS) of >13 months [3]. Combination *BRAF* and *MEK* inhibition have been shown in Phase III studies to be superior

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to *BRAF* inhibitors alone. The Combi-D study compared the combination of dabrafenib (150 mg orally twice daily) and trametinib (2 mg orally once daily) with dabrafenib plus placebo. At a median follow-up of 9 months, the primary end point of PFS was 9.3 months in the combination arm compared with 8.8 months with monothearpy (hazard ratio [HR] for progression or death: 0.75; 95% CI: 0.57–0.99; p = 0.03). Overall response rates were higher with dabrafenib and trametinib in combination compared to dabrafenib (67 vs 51%, respectively; p = 0.002). Rates of adverse events were similar in the two groups, except for fever being more common with the combination (51% vs 28%). The incidence of cutaneous squamous cell carcinomas was lower with addition of a *MEK* inhibitor as postulated and seen in earlier phase studies (2 vs 9%) [7]. The combination of vemurafenib and cobimetinib compared with vemurafenib monotherapy has similiarly shown an improvement in progression free survival (9.9 vs 6.2 months; HR for death or disease progression: 0.51; 95% CI: 0.39–0.68; p < 0.001) and response rates (68 vs 45%; p < 0.001) in favor of the combination [7,8]. The Combi-V study randomized 705 patients to vemurafenib or the combination of dabrafenib and trametinib. 704 patients were randomly assigned 1:1 to receive the combination of dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) or vemurafenib (960 mg twice daily) orally as first-line therapy. The primary end point was overall survival. Patients receiving combination therapy had better outcomes with significantly better response rate (64 vs 51%; p < 0.001), median progression-free survival (11.4 vs 7.3 months; HR: 0.56; p < 0.001) and 12 months overall survival (72 vs 65%; HR: 0.69; p = 0.005) [9].

Understanding the molecular basis of checkpoint control in the interaction of T cells and antigen-presenting cells led to the development of the anti-CTLA-4 antibody ipilimumab, the first treatment to show a survival benefit in melanoma in more than 20 years. Hodi *et al.* demonstrated an OS advantage of a median of 10.1 months with ipilumumab alone compared with 6.4 months for the gp100 peptide vaccine alone in a second-line study (HR: 0.66; p = 0.003) [10]. Importantly, of those patients who had a complete or partial response (ORR of 10.9%) in the ipilimumab-alone arm, 60% maintained a response for 2 years. Results from a range of studies with ipilimumab have confirmed that a proportion of patients become long-term survivors [11]. The identification of the role of PD-1 and the PD-L1 in exhausting activated T-cell interactions with antigens led to the development of a number of blocking antibodies. A Phase I study of the anti-PD-1 antibody nivolumab in 107 patients with melanoma has shown very promising results, with an objective response rate of 31% at the 3 mg/kg dose level and a median duration of response of 2 years for those patients who had responded [12]. A randomized Phase III study comparing nivolumab 3 mg/kg versus investigators choice chemotherapy (ICC; dimethyl triazeno imidazole carboxamide [DTIC (dacarbazine)] 1000 mg/m2 or carboplatin AUC6 + paclitaxel 175 mg/m2) in patients failing ipilimumab randomized 405 patients 2:1 to nivolumab versus ICC. Despite a higher incidence of adverse prognostic factors in the nivolumab arm (history of brain metastases: 20% vs 14%; raised LDG: 51% vs 33%), there was a higher response rate in favor of the nivolumab arm (51% vs 35%; p < 0.001). Overall survival data are awaited [13]. A phase III study of nivolumab 3 mg/kg two-times weekly vs DTIC 100 mg/m2 three-times weekly randomized 418 treatment-naive patients without a *BRAF* mutation. Nivolumab was superior to DTIC for overall response rate (40.0% vs 13.9%; odds ratio: 4.06; P < 0.001), median progression-free survival 5.1 months versus 2.2 months (HR for death or progression of disease: 0.43; P < 0.001) and 1 year overall rate of survival (72.9% vs 42.1%; HR for death: 0.42; p < 0.001) [14].

In an early phase study of the combination of nivolumab and ipilimumab given concurrently, the cohort testing 1 mg/kg nivolumab with 3 mg/kg ipilumumab had an objective reponse rate of 53%, with a tumor reduction of 80% or more [15]. These results came at the expense of toxicity, with 53% of patients treated with combination ipilumumab/nivolumab experiencing grade 3 or 4 toxicities (mainly immune-related, which in general responded to glucocorticoid treatment). These early studies highlight the potential power of the immune system for rapid and extensive response coupled with long-term control of advanced melanoma.

Before the advent of targeted therapy and immunotherapy, dacarbazine was a standard of care for patients with advanced melanoma, despite the majority of patients not experiencing

any clinical benefit. Notwithstanding these advances in systemic therapy, there remains a real need for effective chemotherapy. Acquired resistance is inevitable in the majority of patients being treated with targeted therapy [16], and approximately 50% of patients with melanoma have wild-type *BRAF* and therefore will gain no benefit from current targeted agents. Furthermore, the majority of patients do not achieve long-term survival from currently licensed immunotherapy agents.

The Phase III results from the PD-1/PD-L1 antibodies are awaited; however, even if they show similar response rates to the initial studies, a proportion of patients will still require alternative treatment options upon progression.

Chemotherapy

The first Phase I trial of DTIC was conducted in 1976 [17]. It is currently the only chemotherapy that is licensed in Europe for the treatment of metastatic melanoma, with a standard starting dose of 800–1000 mg/m^2 every 21 days. In Phase III trials, as a standard arm against other treatments and regimens, DTIC has been found to have a response rate of 5–12%, with a median OS of 5.6–9.1 months [18–21]. DTIC is generally well tolerated, with the most common toxicities observed being leukopenia, thrombocytopenia, fatigue, nausea and vomiting.

Temozolomide is an alkylating agent with a broad spectrum of antitumor activity and manageable toxicity. Both temozolomide and DTIC are prodrugs of the active alkylating agent 5-(3-methyltriazen-1-yl)imidazole-4-carboximide. Temozolomide is an oral treatment and has advantages compared with DTIC in its ability to cross the blood–brain barrier. The disadvantage of it being an oral medication is that it relies on patient compliance and effective absorption. In a Phase II study comparing patients with brain metastases who had received prior chemotherapy (n = 34) with those patients who had not (n = 117), a clinical benefit (partial response + complete response + stable disease) of 36% was seen in patients who had received no prior chemotherapy and of 18% for those who had received previous treatment [22]. The median OS was 3.2 months for the whole population (range: 0–41.8 months) [22]. Middleton *et al.* conducted a Phase III study randomizing 305 patients to receive either DTIC 250 mg/m^2 for days 1–5 every 21 days (n = 149) or temozolomide 200 mg orally for days 1–5 every 28 days for up to 12 cycles (n = 156) [20]. In the intention-to-treat (ITT) population, an objective response rate was observed in 13.5% of patients in the temzolomide arm and 12.1% in the DTIC arm. There was a trend towards improved outcomes for temozolomide, with a median OS of 7.9 months in the temozolomide arm compared with 5.7 months in the DTIC arm (p = 0.054) [20]. The European Organisation for Research and Treatment of Cancer (EORTC) 18072 Phase III study examined the role of dose-intensified temozolomide [23]. A total of 859 patients were randomized to receive oral temozolomide at 150 mg/m^2 daily for 7 consecutive days every 2 weeks or DTIC administered as an intravenous infusion of 1000 mg/m^2 on day 1 every 3 weeks. The median OS was 9.1 months in the temozolomide arm versus 9.4 months in the DTIC arm (HR: 1.00; 95% CI: 0.86–1.17; p = 0.99) [23]. Both of these studies excluded patients with pre-existing brain metastases. Temozolomide is not licensed in melanoma, but is used off-label in many countries.

Fotemustine is an alkylating agent with high liposolubility and good penetration through the blood–brain barrier. Avril *et al.* randomized 229 patients to receive either fotemustine or DTIC [21]. Fotemustine was found to have a significantly better ORR in the ITT population (15.2 vs 6.8%; p = 0.043). A longer but not significant OS difference (7.3 months with fotemustine vs 5.6 months with DTIC; p = 0.067) was observed [21]. However, there was no difference in time to progression (1.8 vs 1.9 months). In addition, fotemustine was found to cause considerably more hematological toxicities, particularly thrombocytopenia.

Weekly paclitaxel has been examined in a number of Phase II and III trials, which are summarized in **Table 1**. As a single agent, response rates range from 3 to 17% [24] and the median PFS was found to be approximately 1.8 months [25,26]. Common side effects include alopecia, nausea, lethargy and diarrhea. In the SYMMETRY Phase III trial, paclitaxel was used as the comparator treatment arm and showed an ORR of 4% and a median OS of 11.4 months [25]. Paclitaxel has not been compared directly to DTIC in the Phase III setting, but is used off-label, particularly in the second-line setting.

Single-agent platinum compounds have been previously investigated in the Phase II setting, with partial response rates of approximately

Table 1. Phase II and III paclitaxel trials in melanoma.

Study (author)	Treatment arms	Number per arm	ORR (CR/PR)	CRR (CR/PR/SD)	Median PFS/TTP	Median OS	Ref.
Phase II P single agent (Walker *et al.*)	P 80 mg/m^2, 3 weeks on, 1 week off	27	0%	30%	PFS: 1.8 months	7.6 months	[27]
Phase II P single agent (Einzig *et al.*)	P 250 mg/m^2 every 21 days	34	14%	–	–	–	[28]
Randomized Phase II P vs P plus carboplatin (Zimpfer-Rechner *et al.*)[†]	P 80 mg/m^2 every week for 6 weeks, repeated every 8 weeks	18	0%	28%	TTP: 54 days	218 days	[29]
	P 80 mg/m^2 and carboplatin 200 mg/m^2 every week for 6 weeks, repeated every 8 weeks	16	0%	19%	TTP: 57 days	209 days	
Phase II, randomized, double-blind trial of P ± elesclomol (O'Day *et al.*)	P 80 mg/m^2, 3 weeks on, 1 week off	28	3.6%	39.3%	PFS: 1.8 months (95% CI: 1.6–3.4)	7.8 months[‡]	[30]
	P 80 mg/m^2 plus eclesclomol 213 mg/m^2, 3 weeks on, 1 week off	53	15.1%	62.3%	PFS: 3.7 months (95% CI: 2.5–5.5)	11.9 months	
Phase III SYMMETRY study; randomized, double-blind trial of P ± elesclomol (O'Day *et al.*)[§]	P 80 mg/m^2, 3 weeks on, 1 week off	326	4%	18%	PFS: 1.9 months	11.4 months	[26]
	P 80 mg/m^2 plus eclesclomol 213 mg/m^2, 3 weeks on, 1 week off	325	7%	22%	PFS: 3.4 months	10.6 months	

[†]Trial stopped early due to ORR of <10%.
[‡]Crossover allowed.
[§]Trial closed early due to the finding of an imbalance in total deaths favoring paclitaxel, predominantly in patients with high lactate dehydrogenase levels.
CR: Complete response; CRR: Clinical response rate; ORR: Overall response rate; OS: Overall survival; P: Weekly paclitaxel; PFS: Progression-free survival; PR: Partial response; SD: Stable disease; TTP: Time to progression.

10% [30]. A Phase II study examining WR-2721 (an organic thiophosphate compound that was thought to be protective of normal tissues against cisplatin) with high-dose cisplatin was conducted in 36 patients and reported a partial response rate of 53%, with a median duration of response of 4.5 months (range: 1–8 months) [30].

Combination chemotherapy

Combination chemotherapy has also been investigated in the hope that the additive/synergistic effect of more than one agent would improve outcomes.

The Dartmouth regimen (DTIC 220 mg/m^2 and cisplatin 25 mg/m^2 on days 1–3, carmustine 150 mg/m^2 on day 1 every other cycle and tamoxifen 10 mg orally twice daily) showed early promise in Phase II trials, with response rates of 55% in 20 patients with metastatic melanoma [31]. However, this was not borne out in the Phase III setting when compared with DTIC alone. A multicenter Phase III trial randomized 240 patients to receive the Dartmouth regimen or DTIC [18]. While there was a trend towards a higher response rate with the combination therapy (18.5 vs 10.2%), there was no significant difference in median OS: 7.7 months for the Dartmouth arm (95% CI: 6.3–8.9) compared with 6.3 months for DTIC (95% CI: 5.4–8.7; p = 0.52) [18]. Patients receiving combination therapy were significantly more likely to experience grade 3 or 4 adverse events [18].

Legha *et al.* investigated the combination of cisplatin 20 mg/m^2 on days 2–4, vinblastine 1.6 mg/m^2 on days 1–5 and DTIC 800 mg/m^2 on day 1 every 21 days in 52 patients. They found an ORR of 40% (95% CI: 27–55%) [32]. The median OS was 9 months, although this was improved to a median of 12 months for responders. The treatment was associated with toxicities consisting of neutropenia, nausea, vomiting, diarrhea and partial hair loss [32]. This regimen has been thereafter extensively used as comparator treatment arm in Phase II–III trials versus the same regimen in combination with IL-2 and FN-α.

Combination carboplatin/paclitaxel (CP) has been investigated in two Phase III studies that

have examined the benefit of adding sorafenib, a multikinase inhibitor, to the doublet. Hauschild *et al.* investigated CP plus sorafenib or placebo in 270 patients who had progressed on prior temozolomide or DTIC [33]. They found that there was no significant improvement in OS, PFS or ORR with the addition of sorafenib. They demonstrated an ORR of 11% for the CP plus placebo arm, with a median PFS of 17.9 weeks and a median OS of 42 weeks. Flaherty *et al.* examined the doublet in combination with sorafenib in the first-line setting in a Phase III study randomizing 823 chemotherapy-naive patients to receive CP plus sorafenib or placebo [34]. There was no additional benefit for sorafenib. The CP plus placebo arm had an ORR of 18.2% (95% CI: 14.6–22.2%), with a median PFS of 2.8 months (95% CI: 1.7–3.4) and median OS of 11.3 months (95% CI: 9.8–12.2). As a result of these studies, the CP combination has become a widely used regimen in advanced melanoma in many countries, particularly North America.

A systemic review of 41 trials in 2003 showed that combination chemotherapy was associated with a higher response rate, but patients experienced more toxicity, and there was no survival benefit [35].

Biochemotherapy

Immunomodulating agents such as IFN-α and IL-2 have been shown to have clinical activity in melanoma and indicated that strategies to potentiate the immune system against melanoma could be successful. In Phase II studies, low-dose IFN-α has been found to have an ORR of approximately 20% [36]. Low-dose IL-2 is associated with very low response rates of between 2 and 3%; however, high-dose IL-2 has a response rate of 16% in selected patients, with 6% of patients achieving a complete response and half of responders having durable responses lasting over 2 years [36]. However, high-dose IL-2 has considerable toxicity and therefore it should only be used for selected patients with good performance status and few comorbidities in specialist centers that are experienced in using it. Studies of combination immunotherapy suggest that the combination of IFN-α and IL-2 is superior to IL-2 alone [36]. A number of studies have compared chemotherapy to chemotherapy plus immunotherapy (biochemotherapy) with variable efficacy. A published meta-analysis of 18 trials of biochemotherapy versus chemotherapy in >2600 patients with metastatic melanoma reported a clear benefit of biochemotherapy in terms overall response (odds ratio: 0.59; 95% CI: 0.49–0.72; $p < 0.00001$) [36]. However, there was no overall benefit in OS (odds ratio: 0.99; 95% CI: 0.91–1.08; $p = 0.9$). Increased hematological toxicity was observed for patients receiving biochemotherapy; however, there was considerable heterogeneity across trials, rendering these data difficult to interpret [36]. There are a number of Phase I/II studies currently recruiting using chemotherapy in order to lymphodeplete patients prior to IL-2 and an infusion of tumor-infiltrating lymphocytes (TILS) in order to assess T-cell adoptive transfer strategies in patients with metastatic melanoma. Cell transfer therapy with TILs has been shown to mediate durable complete responses in patients who have been heavily pretreated [37].

Combination with immunotherapy & targeted therapy

The recognition of the role of immunotherapy and targeted therapy as key treatment strategies in advanced melanoma gave rise to a number of studies looking at combinations of chemotherapy with these new agents (summarized in **Table 2**). While many of these studies were based on supportive preclinical data, others were more empirical, based on the hope that combining two agents with activity in melanoma would result in at least additive effects. Overall, the outcomes of studies to date have been disappointing, and no combination has yet found its way into established clinical practice.

A large, Phase III, double-blind, randomized controlled study compared the combination of DTIC and ipilumumab 10 mg/m^2 versus DTIC and placebo [38]. This study showed a survival benefit for the ipilumumab plus DTIC combination, with a median OS of 11.2 vs 9.1 months (HR: 0.72; $p = 0.0009$) and significantly better 1-, 2- and 3-year survival rates [38]. However, the toxicity profile differed from that seen with ipilimumab 3 mg/kg, with a similar rate of colitis despite the higher dose of ipilimumab and grade 3 hepatotoxicity in 23% of patients receiving the combination. The survival benefit of adding DTIC to ipilimumab was modest compared with that seen with ipilimumab alone in the second-line setting, and the hepatotoxicity is a major concern. To date, this combination has not been submitted for license.

The combination of ipilimumab and fotemustine was assessed in a Phase II single-arm study

Table 2. Combination chemotherapy with immune and targeted treatments in melanoma.

Study (author)	Treatment arms	Number per arm	ORR (CR/PR)	CRR (CR/PR/SD)	Median PFS/TTP	Median OS	Ref.
Phase III, DTIC ± ipilumumab (Robert *et al.*)	DTIC plus placebo	252	10.3%	30.1%	–	9.1 months	[39]
	DTIC plus ipilumumab	250	15.2%	33.2%	–	11.2 months	
Phase II, fotemustine and ipilumumab (Di Giacomo *et al.*)	Ipilumumab and fotemustine	86	29.1%	46.5%	5.3 months	13.3 months	[40]
Phase II, sorafenib plus DTIC (McDermott *et al.*)	DTIC plus placebo	50	12%	–	11.7 weeks	–	[41]
	DTIC plus sorafenib	51	24%	–	21.1 weeks	–	
Phase III, sorafenib plus CP (Hauschild *et al.*)	CP plus placebo	135	11%	62%	17.9 weeks	42 weeks	[34]
	CP plus sorafenib	135	12%	66%	17.4 weeks	42 weeks	
Phase III, sorafenib plus DTIC (Flaherty *et al.*)	CP plus placebo	413	18.2%	56.9%	4.9 months	11.3 months	[35]
	CP plus sorafenib	410	20.5%	61%	4.2 months	11.1 months	
Phase II, DTIC plus selumetinib or placebo (Robert *et al.*)	DTIC plus placebo	46	40%†	69%	3.0 months	10.5 months	[42]
	DTIC plus selumetinib	45	26%†	48%	5.6 months	13.9 months	
DOC-MEK study, docetaxel plus placebo or selumetinib (Gupta *et al.*)	Docetaxel plus placebo	–	14%	–	–	–	[43]
	Docetaxel plus selumetinib	–	32%	–	–	–	
BEAM study, CP plus placebo or bevacizumab (Kim *et al.*)	CP plus placebo	71	16.4%	–	4.2 months	9.2 months‡	[44]
	CP plus bevacizumab	143	25.5%	–	5.6 months	12.3 months	

†Unconfirmed.
‡At 17 months of follow-up.
CP: Carboplatin/paclitaxel; CRR: Clinical response rate; DTIC: Dimethyl triazeno imidazole carboxamide; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival; PR: Partial response; SD: Stable disease; TTP: Time to progression.

by the Italian Network for Cancer Biotherapy (NIBIT) group [39]. The combination was investigated in 86 patients with or without brain metastases. Patients received induction treatment of 10 mg/kg intravenous ipilimumab every 3 weeks to a total of four doses and 100 mg/m^2 intravenous fotemustine weekly for 3 weeks and then every 3 weeks from week 9 to week 24. Based on immune-related criteria, 25 patients achieved an objective response (29.1%; 95% CI: 19.8–39.8), with ten out of 20 patients (50%) with brain metastases achieving disease stability or response within the brain (five patients had undetectable disease on scan) [39]. With a median follow-up of 10.8 months, the median immune-related PFS for all patients was 5.3 months (95% CI: 3.4–7.1). Grade 3 or 4 toxicity occurred in 55% patients, with the most common being myelotoxicity.

Targeted agents have also begun to be investigated in combination with chemotherapy agents. Sorafenib is a multikinase inhibitor that inhibits the activity of both *CRAF* and *BRAF* in addition to *MEK* and *ERK* phosphorylation [44]. As previously discussed, no benefit for sorafenib in combination with CP was found in two Phase III studies [33,34]. A Phase II study of sorafenib in combination with DTIC has shown more promise. McDermott *et al.* randomized 101 chemotherapy-naive patients to receive DTIC plus placebo or sorafenib [40]. A trend to increased response with sorafenib was seen, with an ORR of 24% for sorafenib versus 12% in the placebo arm (p = 0.193). The median PFS in the sorafenib plus DTIC arm was 21.1 versus 11.7 weeks in the placebo plus dacarbazine arm (HR: 0.665; p = 0.068) [40]. Notably, none of the sorafenib studies selected patients based on *BRAF* mutation status.

A double-blind, randomized Phase II study comparing DTIC plus placebo or selumetinib, a *MEK*1/2 inhibitor as first-line treatment in patients with *BRAF*-mutated melanoma showed no significantly different median OS between the two groups (13.9 vs 10.5 months, respectively; HR: 0.93; 80% CI: 0.67–1.28;

p = 0.39), but improved PFS in the combination arm (5.6 vs 3.0 months. respectively; HR: 0.63; 80% CI: 0.47–0.84; p = 0.021) [41]. The DOC-*MEK* trial looked at docetaxel with placebo versus docetaxel with selumetinib [42]. 83 patients with wild-type *BRAF* were randomized to receive docetaxel or selumetinib and docetaxel for six cycles, followed by selumetininb maintenance. The response rate was 32% for the combination versus 14% for docetaxel (p = 0.059), with a nonsignifiant improvement in PFS (HR: 0.753; p = 0.13) [42].

The role of bevacizumab in the treatment of advanced melanoma was evaluated in the BEAM study. This double-blind Phase II study randomized 214 patients to either CP plus bevacizumab or placebo. A nonsignificant improvement in PFS of 5.6 versus 4.2 months for the CP plus bevacizumab arm (HR: 0.78; p = 0.14) and a median OS of 12.3 months for the bevacizumab arm versus 9.2 months in the CP arm (HR: 0.79; p = 0.19) was observed [43].

So far, the results of studies combining targeted therapy or immunotherapy with chemotherapy have been disappointing, with no clear clinical benefit, although a better appreciation of the importance of the sequencing of treatment has been obtained. The emergence of more effective chemotherapy agents may change this in due course.

Modern chemotherapy agents

The last decade has seen the evaluation of a number of new chemotherapy agents in advanced melanoma, with Phase III studies following on from promising Phase II trials (summarized in **Table 3**). However, with one exception, the results have been disappointing. **Table 4** summarizes trials that are currently in progress with results awaited.

Tasisulam is a small-molecule drug with dual antiangiogenesis and proapoptotic effects. Although there remains uncertainty regarding its mechanism of action, it is thought that tasisulam inhibits progress through the cell cycle at the G2 checkpoint. In addition, it blocks VEGF [45,50]. A Phase II study demonstrated evidence of its clinical activity and acceptable toxicity [45]. Sixty-eight previously treated patients with metastatic melanoma were found to have an ORR of 18% (90% C: 5.3–18.2%), and clinical response rate (CRR; partial response + complete response + stable disease) of 47.1% (90% CI: 37.1–57.0%). The median PFS and OS were 2.6 months (90% CI: 1.5–2.9) and 9.6 months (90% CI: 7.1–11.9), respectively [45]. This led to a Phase III study comparing tasisulam with paclitaxel. The study was suspended in 2010 after 336 patients had been randomized due to safety concerns because of an imbalance of possible treatment-related deaths (13 vs 0), which were thought to be due to low tasisulam clearance [51]. The response rate was 3.0 versus 4.8%, with a median PFS of 1.94 versus 2.14 months (p = 0.048). The median OS was 6.77 months for tasisulam versus 9.36 months in the paclitaxel arm (p = 0.121) [51].

Elesclomol is a novel agent that induces reactive oxygen species in cancer cells beyond their antioxidant capacity for removal, thereby promoting cell cycle arrest and apoptosis [52]. A Phase II double-blind study randomized 81 patients on a 2:1 ratio to receive paclitaxel or paclitaxel and elesclomol [29]. ORRs for the elesclomol plus paclitaxel and paclitaxel groups were 15 and 3%, respectively. The addition of elesclomol to paclitaxel yielded a doubling of the median PFS (112 vs 56 days), with a 41.7% risk reduction for disease progression/death (HR: 0.583; p = 0.035) [29]. Based on these results, the SYMMETRY Phase III trial randomized 651 chemotherapy-naive patients with metastatic melanoma to receive paclitaxel or paclitaxel plus elesclomol [25]. The ORR was 7% in the combination group and 4% in the paclitaxel group (p = 0.12). There was no significant difference in OS in the ITT population; the median OS was 10.6 months in the combination group and 11.4 months in the paclitaxel group (p = 0.18). However, upon interim subgroup analysis, patients with a raised lactate dehydrogenase level performed significantly worse on the combination (median OS of 6.0 months for the combination group vs 7.8 months for the control group; HR: 1.37; p = 0.04) and the study was terminated early because of this [25].

Allovectin-7 is a DNA plasmid containing the genes coding for foreign human HLA-B7 (an allogeneic MHC class I protein) heavy chain and β2-microglobulin, inserted into a simplified eukaryotic expression vector (pBR322) [53]. It was developed with the aim of reversing the downmodulation of the HLA class I/II MHC molecules utilized by melanoma cells in order to evade immunosurveillance. Phase II studies showed that intratumoural injection of allovectin-7 resulted in local responses of approximately 10% [53]. A Phase III trial randomized 202 patients to receive either DTIC alone

Table 3. Modern chemotherapy agents in melanoma.

Study (author)	Treatment arms	Number per arm	ORR (CR/PR)	CRR (CR/PR/SD)	Median PFS/TTP	Median OS	Ref.
Phase II, tasisulam (Kirkwood *et al.*)	Tasisulam	68	18%	47.1%	2.6 months	9.6 months	[46]
Phase II, paclitaxel plus elesclomol or placebo (O'Day *et al.*)	Paclitaxel plus placebo	28	3%	–	–	7.8 months	[30]
	Paclitaxel plus elesclomol	53	15%	–	–	11.9 months	
Phase III (SYMMETRY), paclitaxel plus placebo or elesclomol (O'Day *et al.*)	Paclitaxel plus placebo	326	4%	22%	1.9 months	11.4 months	[26]
	Paclitaxel plus elesclomol	325	7%	18%	3.4 months	10.6 months	
Phase II, nab-paclitaxel (Hersh *et al.*)	Nab-paclitaxel (chemotherapy naive)	37	21.6%	48.6%	4.5 months	9.6 months	[47]
	Nab-paclitaxel (pretreated)	37	2.7%	37.8%	3.5 months	12.1 months	
Phase II, carboplatin plus nab-paclitaxel (Kottschade *et al.*)	Carboplatin plus nab-paclitaxel (chemotherapy naive)	41	25.6%	–	4.5 months	11.1 months	[48]
	Carboplatin plus nab-paclitaxel (pretreated)	35	8.8%	–	4.1 months	10.9 months	
Phase III, DTIC versus nab-paclitaxel (Hersh *et al.*; Del Vecchio *et al.*)	DTIC	265	11%	27%	2.5 months	10.5 months	[49,50]
	Nab-paclitaxel	264	15%	39%	4.8 months	12.6 months	

CRR: Clinical response rate; DTIC: Dimethyl triazeno imidazole carboxamide; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival; PR: Partial response; SD: Stable disease; TTP: Time to progression.

(800 mg/m^2) given intravenously every 28 days or DTIC at the same dose plus allovectin-7 (10 μg) given by intratumoral injection into a single tumor nodule on days 3 and 10 of each 28-day cycle. The response rates were 11.6% for DTIC and 13.2% for the combination. There was no improvement seen with allovectin-7; the median times to progression were 1.6 months for DTIC and 1.9 months for the combination, and the median OS was 9.2 and 10.8 months, respectively [53].

Nab-paclitaxel was originally developed with the aim of avoiding the requirement for the Cremophor® (BASF, Aktiengesellschaft, Germany) solvent used in standard paclitaxel formulations and is associated with hypersensitivity. Furthermore, nab-paclitaxel can bind SPARC, a protein that is highly expressed on melanoma cells, which researchers believed would result in more efficient drug delivery. Compared with solvent-based paclitaxel, nab-paclitaxel exhibits linear pharmacokinetics, with an approximately tenfold increase in maximum concentration and an approximately threefold higher area under the curve of unbound paclitaxel and enhanced transport across endothelial cell monolayers [54,55]. In addition, a 33% higher paclitaxel concentration in tumor xenografts was found in preclinical studies [56].

Two Phase II studies showed initial clinical activity with ORRs of between 21 and 27% and a median OS of between 11 and 12 months [46,47]. A Phase III open-label trial randomized 529 patients with chemotherapy-naive metastatic melanoma to receive DTIC or nab-paclitaxel at a dose of 150mg/m^2 [57]. In the ITT population, the median PFS values were 4.8 and 2.5 months in the nab-paclitaxel and DTIC arm, respectively (HR: 0.792; 95.1% CI: 0.631–0.992; p = 0.044) [58]. Unfortunately, the promising PFS results have not been translated into a significant OS benefit. The final OS results showed a nonsignificant trend in the median OS benefit of 12.6 months for nab-paclitaxel versus 10.5 months for DTIC (HR: 0.897; 95% CI: 0.738–1.089; p = 0.271) [48]. A subgroup analysis showed the outcome to be independent of *BRAF* mutation status or metastatic stage. Subsequent therapies including ipilumumab and *BRAF* inhibitors were well balanced between the arms [48]. Grade 3 or 4 neuropathy was seen in 25% of patients receiving nab-paclitaxel versus 0% for DTIC (p < 0.001). The improvement to grade ≤1 was 67 days [49].

Conclusion & future perspective

The majority of studies examining chemotherapy-based agents as treatments for melanoma have been disappointing. There has been no significantly increased benefit over DTIC in head-to-head comparisons and therefore this remains a standard of care.

So where does chemotherapy fit into the modern management of melanoma? There remains a role for chemotherapy in patients who do not have a mutation for which a targeted treatment is available, who have disease progression on targeted therapy and who do not respond or who cannot receive an immune treatment. Furthermore, studies have consistently shown that some patients do benefit from chemotherapy, although this is the exception. The two major disadvantages of ipilimumab are the slow onset of clinical activity in the majority of patients and the relatively low response rate [10]. However, early results regarding the PD-1 inhibitor nivolumab in combination with ipilumumab showed that the ORR (as per WHO criteria) for patients in the concurrent regimen group was 40% with frequent but manageable toxicities [15]. At maximum doses, objective responses occurred in nine out of 17 patients (53%; 95% CI: 28–77%), including three with a complete response [15]. Those who responded experienced an 80% or more reduction in tumor at the first tumor assessment [15]. Better understanding of how best to sequence treatments in order to maximize benefits will be a focus of studies in the next few years, and chemotherapy will remain an important treatment option, although more often used as a salvage therapy after failure of more effective treatments.

To date, the data on combining chemotherapy and targeted therapy have been disappointing. However, our experience with these drug combinations is limited, and further research is required in order to determine whether there is synergism between chemotherapy and newer agents. The combination of chemotherapy with ipilumumab seems more promising, with early Phase II data suggesting a benefit with the addition of fotemustine to ipilumumab [39]. Some chemotherapy agents, such as cyclophosphamide, are known to have immune-modulating effects; therefore, further research is needed in order to understand whether this can be utilized with immunotherapies [59]. Timing and dosage is likely to be important in augmenting these effects while minimizing toxicity.

Finally, the development of novel agents will be key to future successes with chemotherapy-based treatments. The development of nab-paclitaxel has shown how progress can be made in drug delivery to melanoma cells that, although not yet resulting in an improvement in OS, has increased our understanding of cellular transport mechanisms. Further understanding of cell replication and repair will be important in future therapies, as well as understanding of why melanoma cells are particularly resistant to historical chemotherapy agents. Dysregulation of apoptosis represents one of the key mechanisms by which melanoma acquires drug resistance. This could be due to the expression of apoptotic inhibitors, p53 mutations and surviving

Table 4. Trials currently in progress in melanoma.

Trial	Main inclusion	Arms	Phase
PACMEL	Advanced *BRAF*-wild-type melanoma	Paclitaxel with or without GSK1120212	II
Tesetaxel	Advanced melanoma (not ocular/mucosal)	Tesetaxel monotherapy, open label, single arm	II
Pazopanib and paclitaxel	Advanced melanoma, first line	Pazopanib and paclitaxel, open label, single arm	II
ADI-PEG 20 plus cisplatin	Advanced melanoma	ADI-PEG 20 plus cisplatin, open label, single arm	I
Carboplatin, paclitaxel and bevacizumab ± everolimus	Metastatic melanoma	Carboplatin, paclitaxel and bevacizumab ± everolimus, open label	II
Nab-paclitaxel plus ipilimumab	Advanced melanoma	Nab-paclitaxel plus ipilumumab, single arm	II
Decitabine, temozolomide and panobinostat	Metastatic melanoma	Decitabine, temozolomide and panobinostat, single arm	I/II

expression, all of which are potential future targets for treatments in combination with chemotherapy [60]. The identification of new, effective chemotherapy agents remains a clinical priority, based on ongoing clinical need.

A new era in melanoma has finally been realized with the discovery of new methods of targeting cells and augmenting immune responses; however, chemotherapy still remains an important weapon that should not be forgotten in future research.

Financial & competing interests disclosure

Paul Lorigan has recieved honoraria from, and serves in an advisory role to, Roche, GSK, BMS, Merck, Amgen, Celgene and Novartis. Rebecca Lee has recieved honorarium from Roche. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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