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Targeted therapy for metastatic renal cell carcinoma (Review)

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TABLE OF CONTENTS

[Intervention Review]

Targeted therapy for metastatic renal cell carcinoma

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ABSTRACT

Background

Several comparative randomised controlled trials (RCTs) have been performed including combinations of tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors since the publication of a Cochrane Review on targeted therapy for metastatic renal cell carcinoma (mRCC) in 2008. This review represents an update of that original review.

Objectives

To assess the effects of targeted therapies for clear cell mRCC in patients naïve to systemic therapy.

Search methods

We performed a comprehensive search with no restrictions on language or publication status. The date of the latest search was 18 June 2020.

Selection criteria

We included randomised controlled trials, recruiting patients with clear cell mRCC naïve to previous systemic treatment. The index intervention was any TKI-based targeted therapy.

Data collection and analysis

Two review authors independently assessed the included studies and extracted data for the primary outcomes: progression-free survival (PFS), overall survival (OS) and serious adverse events (SAEs); and the secondary outcomes: health-related quality of life (QoL), response rate and minor adverse events (AEs). We performed statistical analyses using a random-effects model and rated the certainty of evidence according to the GRADE approach.

Main results

We included 18 RCTs reporting on 11,590 participants randomised across 18 comparisons. This abstract focuses on the primary outcomes of select comparisons.

1. Pazopanib versus sunitinib

Pazopanib may result in little to no difference in PFS as compared to sunitinib (hazard ratio (HR) 1.05, 95% confidence interval (CI) 0.90 to 1.23; 1 study, 1110 participants; low-certainty evidence). Based on the control event risk of 420 per 1000 in this trial at 12 months, this corresponds to 18 fewer participants experiencing PFS (95% CI 76 fewer to 38 more) per 1000 participants. Pazopanib may result in little to no difference in OS compared to sunitinib (HR 0.92, 95% CI 0.80 to 1.06; 1 study, 1110 participants; low-certainty evidence). Based on the control event risk of 550 per 1000 in this trial at 12 months, this corresponds to 27 more OSs (95% CI 19 fewer to 70 more) per 1000 participants. Pazopanib may result in little to no difference in SAEs as compared to sunitinib (risk ratio (RR) 1.01, 95% CI 0.94 to 1.09; 1 study, 1102 participants; low-certainty evidence). Based on the control event risk of 734 per 1000 in this trial, this corresponds to 7 more participants experiencing SAEs (95% CI 44 fewer to 66 more) per 1000 participants.

2. Sunitinib versus avelumab and axitinib

Sunitinib probably reduces PFS as compared to avelumab plus axitinib (HR 1.45, 95% CI 1.17 to 1.80; 1 study, 886 participants; moderate-certainty evidence). Based on the control event risk of 550 per 1000 in this trial at 12 months, this corresponds to 130 fewer participants experiencing PFS (95% CI 209 fewer to 53 fewer) per 1000 participants. Sunitinib may result in little to no difference in OS (HR 1.28, 95% CI 0.92 to 1.79; 1 study, 886 participants; low-certainty evidence). Based on the control event risk of 890 per 1000 in this trial at 12 months, this would result in 29 fewer OSs (95% CI 78 fewer to 8 more) per 1000 participants. Sunitinib may result in little to no difference in SAEs (RR 1.01, 95% CI 0.93 to 1.10; 1 study, 873 participants; low-certainty evidence). Based on the control event risk of 705 per 1000 in this trial, this corresponds to 7 more SAEs (95% CI 49 fewer to 71 more) per 1000 participants.

3. Sunitinib versus pembrolizumab and axitinib

Sunitinib probably reduces PFS as compared to pembrolizumab plus axitinib (HR 1.45, 95% CI 1.19 to 1.76; 1 study, 861 participants; moderate-certainty evidence). Based on the control event risk of 590 per 1000 in this trial at 12 months, this corresponds to 125 fewer participants experiencing PFS (95% CI 195 fewer to 56 fewer) per 1000 participants. Sunitinib probably reduces OS (HR 1.90, 95% CI 1.36 to 2.65; 1 study, 861 participants; moderate-certainty evidence). Based on the control event risk of 880 per 1000 in this trial at 12 months, this would result in 96 fewer OSs (95% CI 167 fewer to 40 fewer) per 1000 participants. Sunitinib may reduce SAEs as compared to pembrolizumab plus axitinib (RR 0.90, 95% CI 0.81 to 1.02; 1 study, 854 participants; low-certainty evidence) although the CI includes the possibility of no effect. Based on the control event risk of 604 per 1000 in this trial, this corresponds to 60 fewer SAEs (95% CI 115 fewer to 12 more) per 1000 participants.

4. Sunitinib versus nivolumab and ipilimumab

Sunitinib may reduce PFS as compared to nivolumab plus ipilimumab (HR 1.30, 95% CI 1.11 to 1.52; 1 study, 847 participants; low-certainty evidence). Based on the control event risk of 280 per 1000 in this trial at 30 months' follow-up, this corresponds to 89 fewer PFSs (95% CI 136 fewer to 37 fewer) per 1000 participants. Sunitinib reduces OS (HR 1.52, 95% CI 1.23 to 1.89; 1 study, 847 participants; high-certainty evidence). Based on the control event risk 600 per 1000 in this trial at 30 months, this would result in 140 fewer OSs (95% CI 219 fewer to 67 fewer) per 1000 participants. Sunitinib probably increases SAEs (RR 1.37, 95% CI 1.22 to 1.53; 1 study, 1082 participants; moderate-certainty evidence). Based on the control event risk of 457 per 1000 in this trial, this corresponds to 169 more SAEs (95% CI 101 more to 242 more) per 1000 participants.

Authors' conclusions

Based on the low to high certainty of evidence, several combinations of immune checkpoint inhibitors appear to be superior to single-agent targeted therapy in terms of PFS and OS, and with a favourable AE profile. Some single-agent targeted therapies demonstrated a similar or improved oncological outcome compared to others; minor differences were observed for AE within this group. The certainty of evidence was variable ranging from high to very low and all comparisons were based on single trials.

PLAIN LANGUAGE SUMMARY

Targeted drug treatment for kidney cancer which has spread

Review question

How effective is targeted drug treatment for patients with kidney cancer which has spread compared with other targeted drug treatments?

Background

Kidney cancer which has spread was treated over the last decade with a group of drugs called targeted therapy which act specifically on molecular pathways. However, the last few years have seen the emergence of a promising, newer group of drugs called immune checkpoint inhibitors which exploit the immune system (hence called immunotherapy). Some of these drugs are currently used in combinations. This review assesses how effective targeted therapies are in comparison with different targeted therapies, immune checkpoint inhibitors or different combinations of these drugs.

Study characteristics

We included only studies in which chance determined whether people got a targeted drug or other targeted drug, and which were reported in medical literature up to 18 June 2020. Most of the studies examined the effects on kidney cancer growth (called progression), survival (life expectancy) and serious unwanted effects.

Key results

We found 18 studies that answered our review question. Participants included in these trials had metastatic (cancer that has spread to other parts of the body) or advanced cancer that could not be removed by surgery. We reported up-to-date comparisons that are most important to doctors and participants.

1. Pazopanib versus sunitinib (targeted therapy versus targeted therapy)

Pazopanib may make little to no difference in progression, survival, and serious unwanted effects compared to sunitinib.

2. Sunitinib versus avelumab and axitinib (targeted agent versus immunotherapy + targeted agent)

Sunitinib probably results in more progression but may make little to no difference on death and serious unwanted effects compared to avelumab and axitinib.

3. Sunitinib versus pembrolizumab and axitinib (targeted agent versus immunotherapy + targeted agent)

Sunitinib probably results in more progression and death but may slightly reduce serious unwanted effects compared to pembrolizumab and axitinib.

4. Sunitinib versus nivolumab and ipilimumab (targeted therapy versus combinations of immunotherapy)

Sunitinib may result in more progression and serious unwanted effects compared to nivolumab and ipilimumab. Sunitinib results in more deaths compared to combinations.

Certainty of the evidence

The certainty of the evidence for most outcomes was low to high, meaning that there is some uncertainty regarding the findings. Nevertheless, there is sufficient data for us to make definitive conclusions regarding how these drugs should be used in the management of patients with kidney cancer which has spread.

SUMMARY OF FINDINGS

Summary of findings 1. Sorafenib compared to sunitinib (targeted agent versus targeted agent)

Patient or population: Treatment-naïve metastatic renal cell carcinoma (any cell type)
Setting: Germany and the Netherlands/muticentre/likely outpatient
Intervention: Sorafenib
Comparison: Sunitinib

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Sunitinib	Risk difference with Sorafenib
Progression-free survival (absolute effect size estimates based on survival rate at 10 months) follow-up: mean 10.3 months	365 (1 RCT)	⊕⊕⊖⊖ LOW [1 2]	HR 1.19 (0.92 to 1.53)	Study population	
				340 per 1000	63 fewer per 1000 (148 fewer to 31 more)
Overall survival (absolute effect size estimates based on survival rate at 24 months) follow-up: mean 10.3 months	365 (1 RCT)	⊕⊖⊖⊖ VERY LOW [3 4]	HR 0.99 (0.74 to 1.33)	Study population	
				550 per 1000	3 more per 1000 (98 fewer to 92 more)
Serious adverse events (Grade 3 or 4) assessed with: CTCAE v3.0	353 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1 4]	RR 0.99 (0.85 to 1.14)	Study population	
				670 per 1000	7 fewer per 1000 (101 fewer to 94 more)
Health-related quality of life [5]	not reported	-	-	-	-

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **CTCAE:** Common Terminology Criteria for Adverse Events;**HR:** Hazard ratio; **RCT**: Randomized controlled trial; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded by 1 level for study limitations; high risk of performance and detection bias and unclear risk of other bias
[2] Downgraded by 1 level for imprecision; confidence interval crossed the line of no difference and the assumed threshold of a clinically important difference (included harm and no harm)
[3] Downgraded by 1 level for study limitations; unclear risk of other bias
[4] Downgraded by 2 levels for imprecision; confidence interval crossed the line of no difference and the assumed threshold of a clinically important difference: wide confidence interval (included both benefit and harm)
[5] Health-related quality of life: no available data

Summary of findings 2. Pazopanib compared to sunitinib (targeted agent versus targeted agent)

Patient or population: Treatment-naïve metastatic renal cell carcinoma (clear cell type)
Setting: Multinational muticentre/likely outpatient
Intervention: Pazopanib
Comparison: Sunitinib

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Sunitinib	Risk difference with Pazopanib
Progression-free survival (absolute effect size estimates based on survival rate at 12 months) follow-up: not reported	1110 (1 RCT)	⊕⊕⊖⊖ LOW [1] [2]	HR 1.05 (0.90 to 1.23)	Study population	
				420 per 1000	18 fewer per 1000 (76 fewer to 38 more)
Overall survival (absolute effect size estimates based on survival rate at 24 months) follow-up: not reported	1110 (1 RCT)	⊕⊕⊖⊖ LOW [3] [4]	HR 0.92 (0.80 to 1.06)	Study population	
				550 per 1000	27 more per 1000 (19 fewer to 70 more)
Serious adverse events (Grade 3 or 4) assessed with: CTCAE v3.0	1102 (1 RCT)	⊕⊕⊖⊖ LOW [1] [2]	RR 1.01 (0.94 to 1.09)	Study population	
				734 per 1000	7 more per 1000 (44 fewer to 66 more)
Health-related quality of life (mean change value) assessed with: FACIT-F (higher scores indicating less fatigue) Scale from: 0 to 52	467 (1 RCT)	⊕⊕⊖⊖ LOW [5] [6]	-	The mean health-related quality of life (mean change value) was -6.5	MD 3.6 higher (1.76 higher to 5.44 higher)

follow-up: after 4 cycle

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **CTCAE:** Common Terminology Criteria for Adverse Events;**FACIT-F:** Functional Assessment of Chronic Illness Therapy–Fatigue scale; **HR:** Hazard ratio; **RCT**: Randomized controlled trial; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded by 1 level for study limitations; high risk of performance and detection bias and unclear risk of other bias
[2] Downgraded by 1 level for imprecision; confidence interval crossed the line of no difference and the assumed threshold of a clinically important difference (included harm and no harm)
[3] Downgraded by 1 level for study limitations; unclear risk of other bias
[4] Downgraded by 1 level for imprecision; confidence interval crossed the line of no difference and the assumed threshold of a clinically important difference (included no benefit and benefit)
[5] Downgraded by 1 level for study limitations; high risk of performance, detection and attrition bias and unclear risk of other bias
[6] Downgraded by 1 level for imprecision; confidence interval crossed the assumed threshold of a clinically important difference (3 points, included benefit and little benefit)

Summary of findings 3. Tivozanib compared to sorafenib (targeted agent versus targeted agent)

Patient or population: Treatment-naïve metastatic renal cell carcinoma (clear cell type)
Setting: Multinational muticentre/likely outpatient
Intervention: Tivozanib
Comparison: Sorafenib

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Sorafenib	Risk difference with Tivozanib
Progression-free survival (absolute effect size estimates based on survival rate at 12 months) follow-up: not reported	517 (1 RCT)	⊕⊕⊖⊖ LOW [1 2]	HR 0.79 (0.64 to 0.99)	Study population	
				360 per 1000	86 more per 1000 (4 more to 160 more)
Overall survival	517 (1 RCT)	⊕⊕⊖⊖ LOW [3 4]	HR 1.25 (0.95 to 1.64)	Study population	

(absolute effect size estimates based on survival rate at 24 months) follow-up: not reported				620 per 1000	70 fewer per 1000 (163 fewer to 15 more)
Serious adverse events (Grade 3 or 4) assessed with: CTCAE v3.0	516 (1 RCT)	⊕⊕⊖⊖ LOW [1 2]	RR 0.85 (0.74 to 0.97)	Study population	
				689 per 1000	103 fewer per 1000 (179 fewer to 21 fewer)
Health-related quality of life assessed with: EQ-5D Health State Index Scale from: -0.59 (worst health state) to 1 (best health state) follow-up: 12 months	506 (1 RCT)	⊕⊕⊖⊖ LOW [2 5]	-	The mean health-related quality of life was -0.06	MD 0.01 higher (0.05 lower to 0.07 higher)

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **CTCAE:** Common Terminology Criteria for Adverse Events;**EQ-5D:** EuroQol-5D; **HR:** Hazard ratio; **RCT**: Randomized controlled trial; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded by 1 level for imprecision; confidence interval crossed the assumed threshold of a clinically important difference (included benefit and little benefit)
[2] Downgraded by 1 level for study limitations; high risk of performance, detection and other bias
[3] Downgraded by 1 level for imprecision; confidence interval crossed the line of no difference and the assumed threshold of a clinically important difference (included harm and no harm)
[4] Downgraded by 1 level for study limitations; high risk of other bias
[5] Downgraded by 1 level for imprecision; confidence interval crossed the line of no difference and the assumed threshold of a clinically important difference (0.06 points, included benefit and no benefit)

Summary of findings 4. Sorafenib compared to pazopanib (targeted agent versus targeted agent)

Patient or population: Treatment-naïve metastatic renal cell carcinoma (any cell type)
Setting: Multinational muticentre/likely outpatient
Intervention: Sorafenib
Comparison: Pazopanib

Outcomes	№ of participants (studies)	Certainty of the evidence	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)

		(GRADE)		Risk with Pazopanib	Risk difference with Sorafenib
Progression-free survival (absolute effect size estimates based on survival rate at 12 months) follow-up: not reported	377 (1 RCT)	⊕⊕⊕⊖ MODERATE [1]	HR 1.92 (1.74 to 2.11)	Study population 380 per 1000	 224 fewer per 1000 (250 fewer to 194 fewer)
Overall survival (absolute effect size estimates based on survival rate at 24 months) follow-up: not reported	377 (1 RCT)	⊕⊕⊖⊖ LOW [2 3]	HR 1.22 (0.91 to 1.64)	Study population 520 per 1000	 70 fewer per 1000 (178 fewer to 32 more)
Serious adverse events (Grade 3 or 4) assessed with: CTCAE v4.03	366 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1 4]	RR 0.92 (0.78 to 1.09)	Study population 639 per 1000	 51 fewer per 1000 (141 fewer to 58 more)
Health-related quality of life (mean change value) assessed with: FACIT-F (higher scores indicating less fatigue) Scale from: 0 to 52 follow-up: not reported	267 (1 RCT)	⊕⊕⊖⊖ LOW [5 6]	-	The mean health-related quality of life was -9.9	MD 3.1 higher (1.82 lower to 8.02 higher)

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **CTCAE:** Common Terminology Criteria for Adverse Events;**FACIT-F:** Functional Assessment of Chronic Illness Therapy–Fatigue scale; **HR:** Hazard ratio; **RCT**: Randomized controlled trial; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded by 1 level for study limitations; unclear risk of selection, detection, and reporting bias and high risk of performance bias
[2] Downgraded by 1 level for study limitations; unclear risk of selection, and reporting bias

[3] Downgraded by 1 level for imprecision; confidence interval crossed the line of no difference and the assumed threshold of a clinically important difference (included harm and no harm)
[4] Downgraded by 2 levels for imprecision; confidence interval crossed the line of no difference and the assumed threshold of a clinically important difference: wide confidence interval (included both benefit and harm)
[5] Downgraded by 1 level for study limitations; unclear risk of selection, detection, and reporting bias and high risk of performance and attrition bias
[6] Downgraded by 1 level for imprecision; confidence interval crossed the line of no difference and the assumed threshold of a clinically important difference (3 points, included benefit and no benefit)

Summary of findings 5. Sunitinib compared to everolimus (targeted agent versus targeted agent)

Patient or population: Treatment-naïve metastatic renal cell carcinoma (any cell type)
Setting: Multinational muticentre/likely outpatient
Intervention: Sunitinib
Comparison: Everolimus

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Everolimus	Risk difference with Sunitinib
Progression-free survival (absolute effect size estimates based on survival rate at 12 months) follow-up: not reported	471 (1 RCT)	⊕⊕⊕⊖ MODERATE [1]	HR 0.71 (0.59 to 0.87)	Study population	
				300 per 1000	125 more per 1000 (51 more to 191 more)
Overall survival (absolute effect size estimates based on survival rate at 24 months) follow-up: not reported	471 (1 RCT)	⊕⊕⊖⊖ LOW [2 3]	HR 0.90 (0.72 to 1.11)	Study population	
				470 per 1000	37 more per 1000 (37 fewer to 111 more)
Serious adverse events (Grade 3 or 4) assessed with: CTCAE v3.0	469 (1 RCT)	⊕⊕⊕⊖ MODERATE [1]	RR 1.34 (1.14 to 1.59)	Study population	
				471 per 1000	160 more per 1000 (66 more to 278 more)
Health-related quality of life assessed with: EORTC QLQ-C30 (Global health status scale: high score represent better functioning) Scale from: 0 to 100 follow-up: 16 weeks	288 (1 RCT)	⊕⊕⊖⊖ LOW [1 4]	-	The mean health-related quality of life was 65.5	MD 5 lower (10.4 lower to 0.4 higher)

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **CTCAE:** Common Terminology Criteria for Adverse Events;**EORTC QLQ-C30:** European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; **HR:** Hazard ratio; **RCT**: Randomized controlled trial; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded by 1 level for study limitations; high risk of performance, detection and other bias
[2] Downgraded by 1 level for imprecision; confidence interval crossed the line of no difference and the assumed threshold of a clinically important difference (included benefit and no benefit)
[3] Downgraded by 1 level for study limitations; high risk of other bias
[4] Downgraded by 1 level for imprecision; confidence interval crossed the line of no difference and the assumed threshold of a clinically important difference (10 points, included harm and no harm)

Summary of findings 6. Sunitinib compared to avelumab + axitinib (targeted agent versus immunotherapy + targeted agent)

Patient or population: Treatment-naïve metastatic renal cell carcinoma (clear cell type)
Setting: Multinational muticentre/likely outpatient
Intervention: Sunitinib
Comparison: Avelumab + Axitinib

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Avelumab + Axitinib	Risk difference with Sunitinib
Progression-free survival (absolute effect size estimates based on survival rate at 12 months) follow-up: median 10.8 months	886 (1 RCT)	⊕⊕⊕⊖ MODERATE [1]	HR 1.45 (1.17 to 1.80)	Study population	
				550 per 1000	130 fewer per 1000 (209 fewer to 53 fewer)
Overall survival (absolute effect size estimates based on survival rate at 12 months) follow-up: median 12.0 months	886 (1 RCT)	⊕⊕⊖⊖ LOW [2 3]	HR 1.28 (0.92 to 1.79)	Study population	
				890 per 1000	29 fewer per 1000 (78 fewer to 8 more)

Serious adverse events (Grade 3 or 4) assessed with: CTCAE v4.03	873 (1 RCT)	⊕⊕⊖⊖ LOW [1] [2]	RR 1.01 (0.93 to 1.10)	Study population	
				705 per 1000	7 more per 1000 (49 fewer to 71 more)
Health-related quality of life [4]	Not reported	-	-	-	-

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **CTCAE:** Common Terminology Criteria for Adverse Events;**HR:** Hazard ratio; **RCT**: Randomized controlled trial; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded by 1 level for study limitations: high risk of performance bias and unclear risk of reporting bias
[2] Downgraded by 1 level for imprecision: confidence interval crossed the assumed threshold of a clinically important difference (included no benefit and harm)
[3] Downgraded by 1 level for study limitations: unclear risk of reporting bias
[4] Health-related quality of life: no available data

Summary of findings 7. Sunitinib compared to pembrolizumab + axitinib (targeted agent versus immunotherapy + targeted agent)

Patient or population: Treatment-naïve metastatic renal cell carcinoma (clear cell type)
Setting: Multinational muticentre/likely outpatient
Intervention: Sunitinib
Comparison: Pembrolizumab + Axitinib

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Pembrolizumab + Axitinib	Risk difference with Sunitinib
Progression-free survival (absolute effect size estimates based on survival rate at 12 months) follow-up: median 12.8 months	861 (1 RCT)	⊕⊕⊕⊖ MODERATE [1]	HR 1.45 (1.19 to 1.76)	Study population	
				590 per 1000	125 fewer per 1000 (195 fewer to 56 fewer)

Overall survival (absolute effect size estimates based on survival rate at 12 months) follow-up: median 12.8 months	861 (1 RCT)	⊕⊕⊕⊖ MODERATE [2]	HR 1.90 (1.36 to 2.65)	Study population	
				880 per 1000	96 fewer per 1000 (167 fewer to 40 fewer)
Serious adverse events (Grade 3 or 4) assessed with: CTCAE v4.0	854 (1 RCT)	⊕⊕⊖⊖ LOW [1 3]	RR 0.90 (0.81 to 1.02)	Study population	
				604 per 1000	60 fewer per 1000 (115 fewer to 12 more)
Health-related quality of life [4]	Not reported	-	-	-	-

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **CTCAE:** Common Terminology Criteria for Adverse Events;**HR:** Hazard ratio; **RCT**: Randomized controlled trial; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded by 1 level for study limitations; high risk of performance bias
[2] Downgraded by 1 level for imprecision; confidence interval crossed the assumed threshold of a clinically important difference (included harm and little harm)
[3] Downgraded by 1 level for imprecision; confidence interval crossed the line of no difference and the assumed threshold of a clinically important difference (included benefit and no benefit)
[4] Health-related quality of life: no available data

Summary of findings 8. Sunitinib compared to atezolizumab + bevacizumab (targeted agent versus immunotherapy + targeted agent)

Patient or population: Treatment-naïve metastatic renal cell carcinoma (clear cell type)
Setting: Multinational muticentre/likely outpatient
Intervention: Sunitinib
Comparison: Atezolizumab + Bevacizumab

Outcomes	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects* (95% CI)**	
				Risk with Atezolizumab + Bevacizumab	**Risk difference with Sunitinib**

Progression-free survival (absolute effect size estimates based on survival rate at 12 months) follow-up: range 15 months to 20.7 months	1117 (2 RCTs)	⊕⊕⊖⊖ LOW [1 2]	HR 1.18 (1.02 to 1.36)	Study population 480 per 1000	 59 fewer per 1000 (111 fewer to 7 fewer)
Overall survival (absolute effect size estimates based on survival rate at 24 months) follow-up: range 20.7 months to 24 months	1117 (2 RCTs)	⊕⊖⊖⊖ VERY LOW [2 3]	HR 0.99 (0.73 to 1.33)	Study population 630 per 1000	 3 more per 1000 (89 fewer to 84 more)
Serious adverse events (Grade 3 or 4) assessed with: CTCAE v4.0	1098 (2 RCTs)	⊕⊖⊖⊖ VERY LOW [2 4 5]	RR 1.22 (1.00 to 1.49)	Study population 446 per 1000	 98 more per 1000 (0 fewer to 218 more)
Health-related quality of life assessed with: MDASI (high score indicates worse QoL) Scale from: 0 to 10 follow-up: 12 weeks	691 (2 RCTs)	⊕⊕⊖⊖ LOW [1 2]	-	The mean health-related quality of life ranged from 0.56 to 1.57	MD 1 higher (0.68 higher to 1.32 higher)

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **CTCAE:** Common Terminology Criteria for Adverse Events;**HR:** Hazard ratio; **MDASI:** MD Anderson Symptom Inventory; **RCT**: Randomized controlled trial; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded by 1 level for imprecision; confidence interval crossed the assumed threshold of a clinically important difference (included harm and little harm)
[2] Downgraded by 1 level for study limitations; high and unclear risk of 1 or more domains.
[3] Downgraded by 2 levels for imprecision; confidence interval crossed the line of no difference and the assumed threshold of a clinically important difference: wide confidence interval (included both benefit and harm)
[4] Downgraded by 1 level for inconsistency; moderate to substantial heterogeneity: unexplained differences between study results
[5] Downgraded by 1 level for imprecision; confidence interval reached the line of no difference and crossed the assumed threshold of a clinically important difference (included harm and no harm)

Summary of findings 9. Sunitinib compared to IMA901 + sunitinib (targeted agent versus tumour vaccine + targeted agent)

Patient or population: Treatment-naïve metastatic renal cell carcinoma (clear cell type)
Setting: Multinational muticentre/likely outpatient
Intervention: Sunitinib
Comparison: IMA901 + Sunitinib

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with IMA901 + Sunitinib	Risk difference with Sunitinib
Progression-free survival (absolute effect size estimates based on survival rate at 12 months) follow-up: median 33.27 months	339 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1 2]	HR 0.95 (0.70 to 1.30)	Study population	
				590 per 1000	16 more per 1000 (86 fewer to 101 more)
Overall survival (absolute effect size estimates based on survival rate at 12 months) follow-up: median 33.27 months	339 (1 RCT)	⊕⊕⊖⊖ LOW [3 4]	HR 0.75 (0.54 to 1.04)	Study population	
				800 per 1000	46 more per 1000 (7 fewer to 86 more)
Serious adverse events (Grade 3 or 4) assessed with: CTCAE v4.0	334 (1 RCT)	⊕⊕⊖⊖ LOW [2 5]	RR 0.74 (0.59 to 0.95)	Study population	
				550 per 1000	143 fewer per 1000 (225 fewer to 27 fewer)
Health-related quality of life [6]	Not reported	-	-	-	-

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **CTCAE:** Common Terminology Criteria for Adverse Events;**HR:** Hazard ratio; **RCT**: Randomized controlled trial; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded by 2 levels for imprecision; confidence interval crossed the line of no difference and the assumed threshold of a clinically important difference: wide confidence interval (included both benefit and harm)
[2] Downgraded by 1 level for study limitations; high risk of performance and other bias

[3] Downgraded by 1 level for imprecision; confidence interval crossed the line of no difference and the assumed threshold of a clinically important difference (included benefit and no benefit)
[4] Downgraded by 1 level for study limitations: high risk of other bias
[5] Downgraded by 1 level for imprecision; confidence interval crossed the assumed threshold of a clinically important difference (included benefit and little benefit)
[6] Health-related quality of life: no available data

Summary of findings 10. Sunitinib compared to interferon-α (IFN-α) (targeted agent versus classic immunotherapy)

Patient or population: Treatment-naïve metastatic renal cell carcinoma (clear cell type)
Setting: Multinational muticentre/likely outpatient
Intervention: Sunitinib
Comparison: Interferon-α (IFN-α)

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Interferon-α (IFN-α)	Risk difference with Sunitinib
Progression-free survival (absolute effect size estimates based on survival rate at 6 months) follow-up: median 31 months	750 (1 RCT)	⊕⊕⊕⊖ MODERATE [1]	HR 0.54 (0.45 to 0.64)	Study population	
				400 per 1000	210 more per 1000 (156 more to 262 more)
Overall survival (absolute effect size estimates based on survival rate at 24 months) follow-up: median 31 months	750 (1 RCT)	⊕⊕⊖⊖ LOW [2 3]	HR 0.82 (0.67 to 1.00)	Study population	
				480 per 1000	68 more per 1000 (0 fewer to 132 more)
Serious adverse events (Grade 3 or 4) assessed as: CTCAE v3.0	735 (1 RCT)	⊕⊕⊕⊖ MODERATE [1]	RR 1.75 (1.43 to 2.16)	Study population	
				258 per 1000	194 more per 1000 (111 more to 300 more)
Health-related quality of life assessed with: EQ-5D Health State Index Scale from: -0.59 (worst health state) to 1 (best health state) follow-up: after 2 cycle	544 (1 RCT)	⊕⊕⊕⊖ MODERATE [4]	-	The mean health-related quality of life was 0.74	MD 0.01 lower (0.05 lower to 0.03 higher)

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval;**EQ-5D:** EuroQol-5D; **HR:** Hazard ratio; **RCT**: Randomized controlled trial; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded by 1 level for study limitations; unclear risk of selection bias and high risk of performance and other bias
[2] Downgraded by 1 level for study limitations; unclear risk of selection bias and high risk of other bias
[3] Downgraded by 1 level for imprecision; confidence interval reached the line of no difference and crossed the assumed threshold of a clinically important difference (included benefit and no benefit)
[4] Downgraded by 1 level for study limitations; unclear risk of selection and attrition bias and high risk of performance and other bias

Summary of findings 11. Temsirolimus compared to IFN-α (targeted agent versus classic immunotherapy)

Patient or population: Treatment-naïve metastatic renal cell carcinoma (any cell type [80% clear cell])
Setting: Multinational muticentre/likely outpatient
Intervention: Temsirolimus
Comparison: IFN-α

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with IFN-α	Risk difference with Temsirolimus
Progression-free survival (absolute effect size estimates based on survival rate at 12 months) follow-up: up to 80 months	416 (1 RCT)	⊕⊕⊖⊖ LOW [1,2]	HR 0.74 (0.60 to 0.91)	Study population	
				100 per 1000	82 more per 1000 (23 more to 151 more)
Overall survival survival (absolute effect size estimates based on survival rate at 12 months) follow-up: up to 80 months	416 (1 RCT)	⊕⊕⊕⊖ MODERATE [1]	HR 0.78 (0.63 to 0.97)	Study population	
				300 per 1000	91 more per 1000 (11 more to 168 more)
Serious adverse events (Grade 3 or 4) assessed with: CTCAE version: not reported	408 (1 RCT)	⊕⊕⊖⊖ LOW [1,2]	RR 0.86 (0.76 to 0.97)	Study population	
				780 per 1000	109 fewer per 1000 (187 fewer to 23 fewer)

Health-related quality of life assessed with: EQ-5D Health State Index Scale from: -0.59 (worst health state) to 1 (best health state) follow-up: not reported	401 (1 RCT)	⊕⊕⊖⊖ LOW [3 4]	-	The mean health-related quality of life was 0.66	MD 0.03 higher (0.01 lower to 0.07 higher)

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **CTCAE:** Common Terminology Criteria for Adverse Events;**EQ-5D:** EuroQol-5D; **HR:** Hazard ratio; **RCT**: Randomized controlled trial; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded by 1 level for imprecision; confidence interval crossed the assumed threshold of a clinically important difference (included benefit and no benefit)
[2] Downgraded by 1 level for study limitations; high risk of performance and detection bias
[3] Downgraded by 1 level for imprecision; confidence interval crossed the line of no difference and the assumed threshold of a clinically important difference (included benefit and no benefit)
[4] Downgraded by 1 level for study limitations; high risk of performance, detection and attrition bias

Summary of findings 12. Sunitinib compared to atezolizumab (targeted therapy versus immunotherapy)

Patient or population: Treatment-naïve metastatic renal cell carcinoma (clear cell type)
Setting: Multinational muticentre/likely outpatient
Intervention: Sunitinib
Comparison: Atezolizumab

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Atezolizumab	Risk difference with Sunitinib
Progression-free survival (absolute effect size estimates based on survival rate at 12 months) follow-up: median 20.7 months	204 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1 2]	HR 0.84 (0.58 to 1.22)	Study population	
				420 per 1000	63 more per 1000 (73 fewer to 185 more)
Overall survival	204	⊕⊖⊖⊖	HR 0.94	Moderate	

(absolute effect size estimates based on survival rate at 24 months) follow-up: median 20.7 months	(1 RCT)	VERY LOW [1] [3]	(0.58 to 1.54)	630 per 1000 [6]	18 more per 1000 (139 fewer to 135 more)
Serious adverse events (Grade 3 or 4) assessed with: CTCAE v4.0	203 (1 RCT)	⊕⊕⊕⊖ MODERATE [2]	RR 1.73 (1.32 to 2.27)	Study population	
				398 per 1000	291 more per 1000 (127 more to 506 more)
Health-related quality of life assessed with: MDASI (high score indicates worse QoL) Scale from: 0 to 10 follow-up: 12 weeks	157 (1 RCT)	⊕⊕⊖⊖ LOW [4] [5]	-	The mean health-related quality of life was 1.04	MD 1.46 higher (0.8 higher to 2.12 higher)

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **CTCAE:** Common Terminology Criteria for Adverse Events;**HR:** Hazard ratio; **MDASI:** MD Anderson Symptom Inventory; **RCT**: Randomized controlled trial; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded by 2 levels for imprecision; confidence interval crossed the line of no difference and the assumed threshold of a clinically important difference: wide confidence interval (included both benefit and harm)
[2] Downgraded by 1 level for study limitations; high risk of selection, performance and detection bias and unclear risk of other bias
[3] Downgraded by 1 level for study limitations; high risk of selection and unclear risk of other bias
[4] Downgraded by 1 level for imprecision; confidence interval crossed the assumed threshold of a clinically important difference (1 point, included harm and little harm)
[5] Downgraded by 1 level for study limitations; high risk of selection, performance and detection bias and unclear risk of other bias
[6] Baseline risk for overall survival in the atezolizumab group was assumed to be 63% (moderate risk) at 24 months as reported in Rini 2019b

Summary of findings 13. Bevacizumab + IFN compared to IFN (+ placebo) (targeted agent + classic immunotherapy versus classic immunotherapy)

Patient or population: Treatment-naïve metastatic renal cell carcinoma (clear cell type)
Setting: Multinational muticentre/likely outpatient
Intervention: Bevacizumab + IFN
Comparison: IFN (+ placebo)

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with IFN (+ placebo)	Risk difference with Bevacizumab + IFN
Progression-free survival (absolute effect size estimates based on survival rate at 12 months) follow-up: intervention: 13.3 months comparator: 12.8 months	1381 (2 RCTs)	⊕⊕⊕⊖ MODERATE [1]	HR 0.68 (0.60 to 0.77)	Study population 200 per 1000	 135 more per 1000 (90 more to 181 more)
Overall survival (absolute effect size estimates based on survival rate at 24 months) follow-up: intervention: 23 months comparator: 21 months	1381 (2 RCTs)	⊕⊕⊖⊖ LOW [1 2]	HR 0.88 (0.79 to 0.99)	Study population 500 per 1000	 43 more per 1000 (3 more to 78 more)
Serious adverse events (Grade 3 or 4) assessed with: CTCAE v3.0	1356 (2 RCTs)	⊕⊕⊕⊖ MODERATE [1]	RR 1.31 (1.20 to 1.42)	Study population 536 per 1000	 166 more per 1000 (107 more to 225 more)
Health-related quality of life [3]	Not reported	-	-	-	-

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **CTCAE:** Common Terminology Criteria for Adverse Events;**HR:** Hazard ratio; **RCT**: Randomized controlled trial; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded by 1 level for study limitations; high and unclear risk of 1 or more domains
[2] Downgraded by 1 level for imprecision; confidence interval crossed the assumed threshold of a clinically important difference (included benefit and little benefit)
[3] Health-related quality of life: no available data

Summary of findings 14. Temsirolimus + IFN-α compared to IFN-α (targeted agent + classic immunotherapy versus classic immunotherapy)

Patient or population: Treatment-naïve metastatic renal cell carcinoma (any cell type [80% clear cell])
Setting: Multinational muticentre/likely outpatient
Intervention: Temsirolimus + IFN-α
Comparison: IFN-α

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with IFN-α	Risk difference with Temsirolimus + IFN-α
Progression-free survival (absolute effect size estimates based on survival rate at 12 months) follow-up: up to 80 months	417 (1 RCT)	⊕⊕⊖⊖ LOW [1 2]	HR 0.76 (0.62 to 0.93)	Study population	
				100 per 1000	74 more per 1000 (17 more to 140 more)
Overall survival (absolute effect size estimates based on survival rate at 12 months) follow-up: up to 80 months	417 (1 RCT)	⊕⊕⊖⊖ LOW [3]	HR 0.93 (0.75 to 1.15)	Study population	
				300 per 1000	26 more per 1000 (50 fewer to 105 more)
Serious adverse events (Grade 3 or 4) assessed with: CTCAE version: not reported	408 (1 RCT)	⊕⊕⊖⊖ LOW [2 4]	RR 1.12 (1.02 to 1.22)	Study population	
				780 per 1000	94 more per 1000 (16 more to 172 more)
Health-related quality of life assessed with: EQ-5D Health State Index Scale from: -0.59 (worst health state) to 1 (best health state) follow-up: not reported	394 (1 RCT)	⊕⊕⊖⊖ LOW [5 6]	-	The mean health-related quality of life was 0.66	MD 0.03 higher (0.01 lower to 0.07 higher)

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **CTCAE:** Common Terminology Criteria for Adverse Events;**EQ-5D:** EuroQol-5D; **HR:** Hazard ratio; **RCT**: Randomized controlled trial; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded by 1 level for imprecision; confidence interval crossed the assumed threshold of a clinically important difference (included benefit and no benefit)
[2] Downgraded by 1 level for study limitations; high risk of performance and detection bias
[3] Downgraded by 2 levels for imprecision; confidence interval crossed the line of no difference and the assumed threshold of a clinically important difference: wide confidence interval (included both benefit and harm)
[4] Downgraded by 1 level for imprecision; confidence interval crossed the assumed threshold of a clinically important difference (included harm and no harm)
[5] Downgraded by 1 level for study limitations; high risk of performance, detection and attrition bias
[6] Downgraded by 1 level for imprecision; confidence interval crossed the line of no difference and the assumed threshold of a clinically important difference (included benefit and no benefit)

Summary of findings 15. Temsirolimus + bevacizumab compared to bevacizumab + IFN-α (targeted agent + targeted agent versus targeted agent + classic immunotherapy)

Patient or population: Treatment-naïve metastatic renal cell carcinoma (any cell type [80% clear cell])
Setting: Multinational muticentre/likely outpatient
Intervention: Temsirolimus + Bevacizumab
Comparison: Bevacizumab + IFN-α

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Bevacizumab + IFN-α	Risk difference with Temsirolimus + Bevacizumab
Progression-free survival (absolute effect size estimates based on survival rate at 12 months) follow-up: not reported	791 (1 RCT)	⊕⊕⊖⊖ LOW [1 2]	HR 1.10 (0.90 to 1.34)	Study population	
				420 per 1000	35 fewer per 1000 (107 fewer to 38 more)
Overall survival (absolute effect size estimates based on survival rate at 24 months) follow-up: not reported	791 (1 RCT)	⊕⊕⊕⊖ MODERATE [1]	HR 1.08 (0.90 to 1.30)	Study population	
				550 per 1000	26 fewer per 1000 (90 fewer to 34 more)
Serious adverse events (Grade 3 or 4) assessed with: CTCAE v3.0	784 (1 RCT)	⊕⊕⊖⊖ LOW [1 2]	RR 1.05 (0.98 to 1.13)	Study population	
				760 per 1000	38 more per 1000 (15 fewer to 99 more)
Health-related quality of life [3] assessed with: FKSI–15	no available data	-	-	-	-

Scale from: 0 to 60

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **CTCAE:** Common Terminology Criteria for Adverse Events;**FKSI:** Functional Assessment of Cancer Therapy–Kidney Symptom Index; **HR:** Hazard ratio; **RCT**: Randomized controlled trial; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded by 1 level for imprecision; confidence interval crossed the line of no difference and the assumed threshold of a clinically important difference (included harm and no harm)
[2] Downgraded by 1 level for study limitations; high risk of performance bias (we are not concerned with unclear risk of other bias)
[3] Health-related quality of life: no available data

Summary of findings 16. Everolimus + bevacizumab compared to IFN α-2a + bevacizumab (targeted agent + targeted agent versus targeted agent + classic immunotherapy)

Patient or population: Treatment-naïve metastatic renal cell carcinoma (any cell type)
Setting: Multinational muticentre/likely outpatient
Intervention: Everolimus + Bevacizumab
Comparison: IFN α-2a + Bevacizumab

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with IFN α-2a + Bevacizumab	Risk difference with Everolimus + Bevacizumab
Progression-free survival (absolute effect size estimates based on survival rate at 18 months) follow-up: not reported	365 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1] [2]	HR 0.91 (0.69 to 1.20)	Study population	
				250 per 1000	33 more per 1000 (61 fewer to 134 more)
Overall survival (absolute effect size estimates based on survival rate at 24 months)	365 (1 RCT)	⊕⊖⊖⊖ VERY LOW [2] [3]	HR 1.01 (0.75 to 1.36)	Study population	
				533 per 1000	3 fewer per 1000 (108 fewer to 91 more)

follow-up: not reported					
Serious adverse events (Grade 3 or 4) assessed with: CTCAE v3.0	361 (1 RCT)	⊕⊕⊖⊖ LOW [1 4]	RR 1.06 (0.95 to 1.18)	Study population	
				762 per 1000	46 more per 1000 (38 fewer to 137 more)
Health-related quality of life [5] assessed with: EORTC QLQ-C30 (Global health status scale: high score represent better functioning) Scale from: 0 to 100	no available data	-	-	-	-

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **CTCAE:** Common Terminology Criteria for Adverse Events;**EORTC QLQ-C30:** European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; **HR:** Hazard ratio; **RCT**: Randomized controlled trial; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded by 1 level for study limitations; unclear risk of selection, performance and other bias and high risk of detection bias
[2] Downgraded by 2 levels for imprecision; confidence interval crossed the line of no difference and the assumed threshold of a clinically important difference: wide confidence interval (included both benefit and harm)
[3] Downgraded by 1 level for study limitations; unclear risk of selection and other bias
[4] Downgraded by 1 level for imprecision; confidence interval crossed the line of no difference and the assumed threshold of a clinically important difference (included harm and no harm)
[5] Health-related quality of life: no available data

Summary of findings 17. Sunitinib compared to nivolumab + ipilimumab (targeted agent versus combinations of immunotherapy)

Patient or population: Treatment-naïve metastatic renal cell carcinoma (clear cell type); IMDC intermediate, poor risk patients only.
Setting: Multinational muticentre/likely outpatient
Intervention: Sunitinib
Comparison: Nivolumab + Ipilimumab

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)

				Risk with Nivolumab + Ipilimumab	Risk difference with Sunitinib
Progression-free survival (absolute effect size estimates based on survival rate at 30 months) follow-up: median 32.4 months	847 (1 RCT)	⊕⊕⊖⊖ LOW [1 2]	HR 1.30 (1.11 to 1.52)	Study population	
				280 per 1000	89 fewer per 1000 (136 fewer to 37 fewer)
Overall survival (absolute effect size estimates based on survival rate at 30 months) follow-up: median 32.4 months	847 (1 RCT)	⊕⊕⊕⊕ HIGH	HR 1.52 (1.23 to 1.89)	Study population	
				600 per 1000	140 fewer per 1000 (219 fewer to 67 fewer)
Serious adverse events (Grade 3 or 4) assessed with: CTCAE v4.0	1082 (1 RCT)	⊕⊕⊕⊖ MODERATE [2]	RR 1.37 (1.22 to 1.53)	Study population	
				457 per 1000	169 more per 1000 (101 more to 242 more)
Health-related quality of life assessed with: FKSI-19 (higher scores indicating fewer symptoms) Scale from: 0 to 76 follow-up: 24 weeks	460 (1 RCT)	⊕⊕⊕⊖ MODERATE [3]	-	The mean health-related quality of life was 2.6	MD 4.1 lower (5.75 lower to 2.45 lower)

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **CTCAE:** Common Terminology Criteria for Adverse Events;**FKSI:** Functional Assessment of Cancer Therapy–Kidney Symptom Index**HR:** Hazard ratio; **IMDC:** International Metastatic Renal Cell Carcinoma Database Consortium; **RCT**: Randomized controlled trial; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded by 1 level for imprecision; confidence interval crossed the assumed threshold of a clinically important difference (included harm and no harm)
[2] Downgraded by 1 level for study limitations; high risk of performance and detection bias
[3] Downgraded by 1 level for study limitations; high risk of performance and detection bias and unclear risk of attrition bias

Summary of findings 18. Pazopanib compared to placebo (targeted agent versus placebo)

Patient or population: Previous treated and treatment-naïve (54%) metastatic renal cell carcinoma (clear cell type)
Setting: Multinational muticentre/likely outpatient
Intervention: Pazopanib
Comparison: Placebo

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Placebo	Risk difference with Pazopanib
Progression-free survival (absolute effect size estimates based on survival rate at 12 months) follow-up: not reported	435 (1 RCT)	⊕⊕⊕⊕ HIGH	HR 0.46 (0.34 to 0.62)	Study population	
				180 per 1000	274 more per 1000 (165 more to 378 more)
Overall survival (absolute effect size estimates based on survival rate at 24 months) follow-up: not reported	435 (1 RCT)	⊕⊕⊖⊖ LOW [1]	HR 0.91 (0.72 to 1.16)	Study population	
				480 per 1000	33 more per 1000 (53 fewer to 110 more)
Serious adverse events (Grade 3 or 4) assessed with: CTCAE v3.0	435 (1 RCT)	⊕⊕⊕⊕ HIGH	RR 2.00 (1.40 to 2.85)	Study population	
				200 per 1000	200 more per 1000 (80 more to 370 more)
Health-related quality of life assessed with: EORTC QLQ-C30 (Global health status scale: high score represent better functioning but negative change from baseline represents a worsening condition) Scale from: 0 to 100 follow-up: 12 weeks	300 (1 RCT)	⊕⊕⊕⊕ HIGH	-	The mean health-related quality of life was -0.5	MD 3.1 lower (7.76 lower to 1.56 higher)

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **CTCAE:** Common Terminology Criteria for Adverse Events;**EORTC QLQ-C30:** European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; **HR:** Hazard ratio; **RCT**: Randomized controlled trial; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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[1] Downgraded by 2 levels for imprecision; confidence interval crossed the line of no difference and the assumed threshold of a clinically important difference (included both benefit and harm)

BACKGROUND

Description of the condition

Renal cell carcinoma (RCC) incidence represents about 2.2% of all invasive cancers and has a projected 2018 population age-standardised mortality rate of 1.8 per 100,000 worldwide (GLOBOCAN 2018; Howlader 2017). Two-thirds of cases occur in men. These figures include both renal cell carcinoma and the less common urothelial carcinoma of the renal pelvis: the latter is biologically related to bladder cancer and we do not consider it here. Renal cell carcinoma is divided into different pathologic subtypes, of which the clear cell subtype represents about 75% (Srigley 2013). The more uncommon subtypes are collectively referred to by clinicians as non-clear renal cell carcinomas: they respond differently to treatment as compared to clear cell renal cell carcinoma (Fernández-Pello 2017). Death from renal cell carcinoma is usually from metastases, either detected during staging of newly-diagnosed patients (Stage IV) or detected during follow-up after nephrectomy. A minority of patients are diagnosed with locally advanced disease which is too advanced for surgical resection but without metastatic findings. The term 'advanced renal cell carcinoma' has been used by authors to include both metastatic and locally advanced disease that have aspects that require separate consideration.

There has been great interest in finding more effective treatments for metastatic renal cell carcinoma. The search for specific targets for therapy goes back at least to Paul Ehrlich's 'magic bullet' over a century ago (Strebhardt 2008). This concept has gained renewed interest owing to the identification of multiple molecular targets and the potential for associated therapies that are target-specific and therefore might have greater efficacy with less toxicity (Sawyers 2004). Clinical proof of concept came with the remarkable success of single-agent imatinib for chronic myeloid leukaemia (Deininger 2005). Here we review the subsequent development of targeted therapy for metastatic renal cell carcinoma.

Description of the intervention

Prior to the development of targeted agents, renal cell carcinoma was one of the most drug-resistant malignancies. Hormonal and cytotoxic chemotherapy agents have not been demonstrated to improve overall survival (OS) for this condition, and remissions with those agents occur at a frequency similar to that seen with no therapy or with placebo (Gleave 1998; Oliver 1989). Until the past decades, immunotherapy was the main focus of the search for an effective drug therapy for renal cell carcinoma and was the main initial comparator for targeted therapy; it was the subject of a companion Cochrane Review (Coppin 2004). In summary, classic immunotherapy, for example interferon-alpha or interleukin-2, has been associated with very modest survival benefit at best. When targeted agents were first being evaluated, the immunotherapy agent interferon-alpha was considered the standard comparator for first-line therapy of metastatic renal cell carcinoma (Mickisch 2003; Motzer 2002); placebo-controlled trials have been appropriate in the second-line setting. One should be aware that the distribution of prognostic risk strata in clinical trials is changing to a more favourable profile, such that direct comparisons of interventions through head-to-head clinical trials remain essential (Patil 2010).

Molecular pathways with multiple targets that are of particular interest in renal cell carcinoma currently fall into two major groups: angiogenesis (Rini 2005), and intracellular signal transduction pathways (Adjei 2005). The presence of a target may or may not translate into benefit from a targeted agent (Bergsland 2006). Some agents have activity against multiple targets. Classic immunotherapies such as interferon-alpha may have anti-angiogenic activity but are considered a separate class of agent (Coppin 2004). Suitably large randomised controlled trials have a high financial and resource cost, so that selection of agents for phase III testing requires strategic decision-making (Roberts 2003).

A new class of drugs has been introduced into the treatment paradigm of clear cell RCC (Motzer 2015a). Immune checkpoint inhibitors are a new type of targeted immunotherapy and have been very successfully tested in other immunogenic tumours such as melanoma.

Since neither multi-kinase inhibitors nor immune checkpoint inhibitors are necessarily cytotoxic, it is possible that tumour shrinkage may not be a reliable indicator of drug activity (Stadler 2006); for example, objective stabilisation of previously progressive disease might result in extension of OS. This is especially the case for immune checkpoint inhibition which in second-line RCC treatment leads to prolonged OS without benefit in progression-free survival (PFS).

Drug therapy for metastatic renal cell carcinoma has yet to demonstrate curative potential. Improvement in OS is the preferred and definitive outcome of interest to patients, and is a realistic outcome if there is only one effective intervention for an incurable cancer, as was the situation for metastatic renal cell carcinoma at the beginning of the targeted era (i.e. from 2000 onwards). However, when participants with progressive cancer in one arm of a randomised trial are permitted cross-over to the other arm, as is commonly done for ethical reasons or to enhance recruitment, then any survival benefit (or detriment) of the investigational agent might be obscured; the same problem might happen if sequential active therapies are applied. For these reasons and as in other cancer sites, the duration of freedom from cancer progression may be accepted by regulatory bodies as adequate evidence of benefit for drug approval purposes (Johnson 2011). Surrogate endpoints such as PFS should preferably be accompanied by patient-reported outcomes.

How the intervention might work

Molecular analysis of renal cell carcinoma has shown that this cancer is not a homogeneous condition (Hacker 2010; Linehan 2005). A high proportion of sporadic clear cell renal cell carcinomas have biallelic abnormalities of the Von Hippel–Lindau (VHL) tumour-suppressor gene (Young 2009), whereas other subtypes do not. Absence of the active VHL gene produces results in unregulated activation of the hypoxia-inducible system and accumulation of growth factors such as vascular endothelial growth factor (VEGF). In subtypes such as papillary and chromophobe RCC, other pathways such as MET proto-oncogene (MET) and tuberous sclerosis (TSC) alterations have been identified through investigation of hereditary and sporadic forms. Therefore the mainstays of first-line therapy until now are multi-kinase inhibitors targeting predominantly the VEGF-receptor kinases but other targets are included to various degrees, such as MET, AXL receptor tyrosine kinase (AXL), platelet-derived growth factor receptor (PDGFR) and epidermal growth

factor receptor (EGFR). Immune checkpoint inhibitors targeting the programmed death-ligand (PD-L1) or its receptor (PD-1) have been tested successfully in second- and third-line treatments after failure of one or two lines of VEGFR-targeting therapies (Motzer 2015a). These drugs counteract the tumour-driven inhibition of T-cell receptor-mediated activation of IL-2 production and T-cell proliferation which leads to a successful anti-tumour T-cell-mediated immune activity. Currently, these drugs are tested in first-line trials in combination with either multi-kinase inhibitors or other monoclonal antibodies targeting circulating VEGF or anti-CTLA4 against the current first-line monotherapy with VEGFR-targeted therapies. With more treatment options being approved and investigated, it will be necessary to distinguish the impact of therapy on different molecularly-defined tumour types as well as on tumours which have been treated with previous lines of therapy to better select patients for a given drug based on their predicted outcome. Although available, the necessary technology is not yet used in clinical routine. The molecular complexities of both the disease (renal cell carcinoma) and the treatment (targeted therapy) are resulting in a rapidly-evolving and exciting phase in the history of the treatment of metastatic disease. According to Uzzo 2003, "an understanding of the basic biology of renal cell carcinoma is more advanced than that of any other solid malignancy." Further molecular subclassification within clear cell renal cell carcinoma may well become feasible (Kaelin 2008).

Why it is important to do this review

The topic of this review is systemic therapy of treatment-naïve metastatic renal cell carcinoma, an important type of malignancy for which the therapy has changed greatly over the past decade and continues to be a strong focus of development of new agents and comparative studies. This review is needed to provide an objective and up-to-date resource for researchers, clinicians and consumers.

This is an update of a Cochrane Review first published in 2008 and previously updated in 2011 (Coppin 2008; Coppin 2011). Since the last date of full literature search, a number of additional studies have been published and there is an evolving shift to using previously validated targeted agents as the comparator rather than placebo, quasi-placebo such as hormone therapy, or immunotherapy such as interferon-alpha. There is also increasing emphasis on second-line therapy now that targeted agents are established for first-line therapy of metastatic renal cell carcinoma. In addition, new agents such as immune checkpoint inhibitors are increasingly being compared against first-line standard therapies (Kuusk 2017).

This updated review reflects a restriction of scope in order to focus on metastatic renal cell carcinoma within the broader category of 'advanced disease' that additionally included locally-advanced cancers without metastases. The main reason for this change of scope is because the management of locally-advanced disease may include both systemic and surgical interventions, and therefore the complex interaction between the two modalities as well as additional outcomes such as resectability and local control rates. Other reasons include lack of criteria for inoperability that include both cancer and patient factors, and the possibility that drug response to the primary tumour might be different from the response of its metastases.

This review originates from a collaboration between the previous Cochrane Review authorship and the Renal Cell Carcinoma Guideline Panel of the European Association of Urology (EAU panel). Preliminary discussions with the EAU panel demonstrated a high level of overlap between the protocols of the two groups. This review is designed to minimise residual differences.

OBJECTIVES

To assess the effects of targeted therapies for clear cell mRCC in patients naïve to systemic therapy.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials, including randomised discontinuation trials in which treatment was stopped early because of obvious benefits or harms (Stadler 2006). Quasi-randomised trials such as alternate allocation were eligible for consideration. We excluded randomised phase I trials as well as cluster-randomised trials or trials of factorial design. Additionally, we imposed a stricter inclusion criterion of more than 100 patients per arm for study inclusion. This was a decision driven by pragmatic and methodological considerations, to avoid including small, methodologically-flawed and underpowered studies with low internal and external validity and high clinical and methodological heterogeneity, whose findings are highly unlikely to inform, guide or influence clinical practice.

Types of participants

Participants were eligible if: older than 18 years of age; they had mRCC histologically or pathologically verified at presentation or relapse; they had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2 or equivalent. No prior systemic treatment was allowed.

Exclusion criteria were: the presence of symptomatic brain metastases; a life expectancy of less than 12 weeks; a serious acute or chronic illness or recent history of cardiac event.

Studies which allow solid tumours other than renal cell carcinoma were eligible only if participants with renal cell carcinoma were stratified and reported separately from other tumour types.

Diagnosis must be reported using the standard criteria (e.g. TNM Classification of Malignant Tumors) valid at the time that the trial began.

A predominant clear cell renal cell carcinoma histology was required.

We excluded studies for analysis of oncological outcomes that are designed for or include more than 20% of participants without metastases (i.e. locally-advanced disease or unfit for nephrectomy). We included evaluation of adverse events if reported, however.

Types of interventions

Agents with known or presumed molecular targets were part of the therapeutic regimen of at least one study arm. Non-specific agents considered previously were no longer eligible, as they are of historic interest only; these include ABT-510, AE-941, and carboxyaminoimidazole. We excluded classic immunotherapy agents, including recombinant cytokines and their predecessors,

from the definition of targeted therapy, but they were allowed as part of combined regimens in any study arm (i.e. either as index interventions or as comparators).

Our approach to targeting immunotherapies (including PD1 or PD-L1 checkpoint inhibitors) deserves special mention. As the main focus of the review was on VEGF-targeted therapies on the basis of the earlier version of our review, and the fact that VEGF-targeted therapies have been established as the mainstay of treatment for mRCC at the inception of this review, we considered targeting immunotherapies as a comparator intervention. In addition, targeted immunotherapies for mRCC are being considered as an index intervention in a separate Cochrane Review (Unverzagt 2017).

See Table 1 for a list of targeted agents to be sought, although additional targeted agents were identified during the search process. Studies in which maintenance therapy by a targeted agent was the randomised variable were eligible. Studies of dose or schedule of a targeted agent were eligible. There were no restrictions on drug route, dose, or schedule.

We investigated the following comparisons of target agents listed in Table 1 versus control/comparator.

Intervention

1. Targeted agent

Comparator

1. Targeted agent other than the ones used in intervention
2. Targeted agent in combination with immunotherapy
3. Immunotherapy
4. Combinations of immunotherapy
5. Placebo

We considered whether the control arm has been validated by a prior randomised study.

Minimum duration of intervention

Minimum duration of intervention was four weeks.

Minimum duration of follow-up

Minimum duration of follow-up was 12 weeks. We evaluated extended follow-up periods after the trial termination only for adverse events.

Specific exclusion criteria

Studies observing neoadjuvant or adjuvant treatment or both with targeted agents were not eligible for analysis.

Types of outcome measures

Studies had to assess at least one efficacy outcome by allocation arm. We examined 'quality of life' outcomes where available, with reference to minimally important clinical differences where known for the assessment tools used. We evaluated adverse events in all studies. Our selection of outcomes for GRADE assessment was based on discussions amongst an expert panel (EAU panel) and authors of the previous review, and reflects outcomes of importance to stakeholders including patients, clinicians and healthcare providers.

Primary outcomes

1. Progression-free survival (PFS)
2. Overall survival (OS)
3. Serious adverse events (SAEs; Grade 3 or 4)

Secondary outcomes

1. Health-related quality of life (QoL)
2. Response rate
3. Minor adverse events (minor AEs; Grade 1 or 2)

Method and timing of outcome measurement

1. PFS: time from date of randomisation to date of clinical or radiological progression
2. OS: length of time from date of randomisation that participants are still alive
3. SAEs: all adverse events measured at any time that needed surgical, endoscopic, radiological or anesthesiological intervention, as well as any life-threatening complications after participants received at least one treatment in intervention or comparator groups, classified by Common Terminology Criteria for Adverse Events (CTCAE)
4. QoL: evaluated by a validated instrument such as Supplementary Quality of Life Questionnaire (SQLQ), Functional Assessment of Cancer Therapy (FACT), Functional Assessment of Cancer Therapy–Kidney Symptom Index (FKSI) or European Quality of Life-5 Dimensions (EQ-5D). If available, we focused on data of pre- to post-treatment evaluation
5. Response rate: measured by Response Evaluation Criteria in Solid Tumors (RECIST) or modified RECIST criteria (Eisenhauer 2009)
6. Minor AEs: all adverse events measured at any time that could be managed by observation or pharmacological treatment after participants received at least one treatment in intervention or comparator groups, classified by Common Terminology Criteria for Adverse Events (CTCAE)

We considered a 5% absolute risk difference as clinically important for primary outcomes (PFS, OS and SAEs); we considered a 10% absolute risk difference as clinically important for the secondary outcomes of response rate and minor AEs. We used published threshold for QoL instruments.

If time-to-event data were not available, we tried to assess the number of events per total for dichotomised outcomes at certain time points (e.g. at one, two, three, four, five years, or at the longest reported follow-up).

Main outcomes for 'Summary of findings' table

1. Progression-free survival
2. Overall survival
3. Serious adverse events
4. Quality of life

Search methods for identification of studies

Overall time frame: we conducted a search from 1 January 2000 (we found no earlier studies in the previous version of this review) to an agreed cut-off date that was at least one month before the date of search, to allow for indexing. We initially compared duplicate

searches from separate time segments for consistency. For example the current authors have completed a search to 18 June 2020 using the algorithm in Appendix 1, and the Canadian authors have searched to 30 June 2010 as described previously (Coppin 2008, electronically updated to 30 June 2011 for Coppin 2011).

There were no restrictions by language or publication status.

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, and LILACS databases, as well as trial registers ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (apps.who.int/trialsearch).

Searching other resources

1. We handsearched abstracts in the proceedings of the annual meetings of the American Urological Association, the European Cancer Conference (ECCO), the European Society of Medical Oncology (ESMO), and the American Society of Clinical Oncology (ASCO), all from 2000 to current year; and the annual ASCO genitourinary meeting (2008 to current year)
2. We handsearched the bibliographies of included primary studies and of recent systematic reviews of targeted therapies for metastatic or advanced renal cell carcinoma
3. We consulted clinical experts (EAU panel) to identify additional potentially important or seminal studies which may have been missed by the electronic searches
4. We tried to identify other potentially eligible trials or ancillary publications by searching the reference lists of included trials, systematic reviews, meta-analyses and health technology assessment reports. We also contacted authors of included trials to identify any additional information on the retrieved trials, and to determine if further trials exist that we may have missed. We also searched databases from regulatory agencies (European Medicines Agency (EMA) and US Food and Drugs Administration (FDA)) (Hart 2012; Schroll 2015).

Data collection and analysis

Selection of studies

Inclusion and exclusion of studies

Two review authors (FH; and LM or TL or AB or BL) independently conducted searches, assessed full-text records, and independently mapped records to potentially eligible studies for inclusion/exclusion. We resolved disagreements by discussion.

We referred to trials by their eight-digit NCT number where known. We classified studies as included studies, excluded studies, studies awaiting classification, or ongoing studies, in accordance with the criteria for each provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017a). We documented the search process in a study flow diagram.

We document reasons for exclusion of identified studies not suitable for this review in the Excluded studies table. We included studies that did not report on our primary or secondary outcomes, and considered them for qualitative analysis.

Data extraction and management

Two review authors (FH; and LM or TL or AB) independently extracted data using an agreed template which we had piloted, and resolved any disagreements by consensus, with recourse to a third review author (TL or AB) if needed. We constructed a master database of consensus-agreed data, which was available to all review authors.

Data extraction fields for each study included:

1. basic study design features (e.g. parallel-group randomised trial);
2. dates when the study was conducted;
3. study setting;
4. participant eligibility criteria and actual accrual by arm for age, race, gender, performance status, prior nephrectomy, prior systemic therapy, histologic subtype, and prognostic risk method and distribution;
5. stratification parameters, if any;
6. detailed interventions, including criteria for discontinuing therapy and cross-over to the investigational arm;
7. the sample size for each included study and for each intervention/comparator group;
8. details (such as dose, route, frequency, duration, as applicable) of each intervention/comparator relevant to this review;
9. treatment delivery evaluation such as time point of administration and masking of treatment in interventional/comparator groups;
10. frequency and protocol status (e.g. planned versus later protocol modification) of cross-over to the investigational arm;
11. details of the outcome definition for outcomes relevant to this review that were assessed in each study, method of outcome measurement for each outcome, timing of outcome measurement for each outcome, subgroups relevant to this review that were assessed for each outcome;
12. reported statistics for each time-dependent outcome, i.e. hazard ratio and two-sided log rank P value;
13. all adverse events reported by allocation;
14. study funding sources;
15. details of declarations of interest among the trialists.

We attempted to contact study investigators to obtain missing data for primary outcomes for eligible studies.

We report identified studies in the Characteristics of included studies table. If an eligible trial was ongoing and did not report any results, we collected information in the Characteristics of ongoing studies table.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents or multiple reports of a primary trial, we maximised the information yield by collating all available data and used the most complete data set aggregated across all known publications. We listed duplicate publications, companion documents, multiple reports of a primary trial and trial documents of included trials (such as trial registry information) as secondary references under the study ID of the included trial. We also listed duplicate publications, companion documents, multiple reports of a trial and trial documents of

excluded trials (such as trial registry information) as secondary references under the study ID of the excluded trial.

Data from clinical trial registers

In cases where data of included trials were available as study results in clinical trial registers such as ClinicalTrials.gov or similar resources, we made full use of this information and extracted data. If there was also a full publication of the trial, we collated and critically appraised all available data. If an included trial was marked as a completed study in a clinical trial register but no additional information (study results, publication or both) was available, we added this trial to the table Characteristics of studies awaiting classification.

Assessment of risk of bias in included studies

Two review authors (FH; and TL or ECH) independently used the latest version of the Cochrane tool for assessing risk of bias to construct a 'Risk of bias' table for each study, resolving disagreements by discussion (Higgins 2017b). If needed, a third review author (either AB or BL) was involved to enable us to reach consensus. We rated the following domains at low, high, or unclear risk of bias.

1. Random sequence generation
2. Allocation concealment
3. Blinding of participants and personnel
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective reporting
7. Other potential sources of bias

We assessed the 'Risk of bias' domains 'Blinding of participants and personnel', 'Blinding of outcome assessment', and 'Incomplete outcome data' on an outcome-specific basis, grouping subjective outcomes and objective outcomes for the blinding domains, and grouping outcomes according to similar completeness of data for the outcome-specific assessment of 'Incomplete outcome data'. We regarded all outcomes except for 'Overall survival of the total population' as susceptible to performance bias and detection bias. We summarised the risk of bias across domains for each outcome in each included study. We assessed the risk of attrition bias in three combined outcome groups that we defined by oncological, adverse event and quality-of-life outcomes. We present our judgements in a 'Risk of bias' summary and 'Risk of bias' graph.

Measures of treatment effect

When at least two included trials were available for a comparison and a given outcome, we tried to express dichotomous data as a risk ratio (RR) or odds ratio (OR) with 95% confidence intervals (CIs). For continuous outcomes measured on the same scale we estimated the intervention effect using the mean difference (MD) with 95% CIs. For continuous outcomes measuring the same underlying concept but using different measurement scales, we calculated the standardised mean difference (SMD). We expressed time-to-event data as a hazard ratio (HR) with 95% CIs.

Unit of analysis issues

If more than one comparison from the same trial was eligible for inclusion in the same meta-analysis, we either combined groups to create a single pairwise comparison or appropriately reduced the sample size so that the same participants do not contribute to multiple comparisons (splitting the 'shared' group into two or more groups). While the latter approach offered some solution to adjusting the precision of the comparison, it did not account for correlation arising from the same set of participants being in multiple comparisons (Higgins 2017a).

Dealing with missing data

We planned to perform intention-to-treat analyses where data were available; however, we did not impute missing data. We included studies that combine outcomes from metastatic and locally-advanced disease in tabulations if the locally-advanced subgroup is documented as less than 20% of the total participants randomised; we considered other studies separately.

Whenever possible, we obtained missing data from the authors of the included trials. We carefully evaluated important numerical data such as screened, randomly-assigned participants as well as intention-to-treat, and 'as treated' and 'per protocol' populations. We investigated attrition rates (e.g. dropouts, losses to follow-up, withdrawals), and we critically appraised issues concerning missing data and use of imputation methods (e.g. last observation carried forward).

Assessment of heterogeneity

In the event of substantial clinical or methodological heterogeneity, we did not report trial results as the pooled effect estimate in a meta-analysis. We identified heterogeneity (inconsistency) by visually inspecting the forest plots and by using a standard Chi^2 test with a significance level of $\alpha = 0.1$. In view of the low power of this test, we also considered the I^2 statistic, which quantifies inconsistency across trials, to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003). We interpret the I^2 statistic as follows.

1. 0% to 40%: may not be important
2. 30% to 60%: represents moderate heterogeneity
3. 50% to 90%: represents substantial heterogeneity
4. 75% to 100%: represents considerable heterogeneity

We attempted to determine possible reasons for heterogeneity by examining individual study and subgroup characteristics.

Assessment of reporting biases

We did not find 10 or more trials that investigate a particular outcome, and did not use funnel plots to assess small-trial effects. Several explanations may account for funnel plot asymmetry, including true heterogeneity of effect with respect to trial size, poor methodological design (and hence bias of small trials) and publication bias, so we were cautious in our interpretation of results (Sterne 2011).

Data synthesis

We conducted (or displayed) a meta-analysis only if we judged participants, interventions, comparisons and outcomes to be sufficiently similar to ensure an answer that is clinically meaningful. Unless good evidence showed homogeneous effects across trials, we primarily summarised low risk of bias data using a random-effects model (Wood 2008). We interpreted random-effects meta-analyses with due consideration for the whole distribution of effects, ideally by presenting a prediction interval (Higgins 2009).

This specifies a predicted range for the true treatment effect in an individual trial (Riley 2011). For rare events such as event rates below 1% we planned to use the Peto odds ratio, provided that there was no substantial imbalance between intervention and comparator group sizes, and that intervention effects were not exceptionally large. We also performed statistical analyses using Review Manager 5 software provided by Cochrane (Review Manager 2020), according to the statistical guidelines presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017a).

Statistical analysis

We anticipated analysis of four types of outcomes: categorical outcomes, such as tumour remission; single time-dependent outcomes, such as OS; quality-of-life surveys; and toxicity tables. Of these, methods for analysis of dichotomous outcomes were fully covered by standard Cochrane procedures (Deeks 2017). We considered multidimensional quality-of-life and toxicity outcomes individually. Time-dependent outcomes were potentially problematic. Where only a single study was available for a comparison, we accepted any standard statistical analysis, such as the log-rank test used by the author, but we preferred the hazard ratio and log-rank testing. For meta-analysis of multiple studies of the same type, we used extraction of a dichotomous endpoint such as survival at one year from randomisation (see also Measures of treatment effect above).

Subgroup analysis and investigation of heterogeneity

We planned to perform a subgroup analysis for the following.

1. Nephrectomy done or not done prior to treatment
2. ECOG performance status (0, 1 or 2)

Sensitivity analysis

We planned a sensitivity analysis for studies that were at a high risk of bias for sequence generation, allocation concealment and blinding versus studies at low risk of bias. We planned to conduct a separate meta-analysis for validation of results of studies at low risk of bias only.

Summary of findings and assessment of the certainty of the evidence

We present results for the outcomes as described in the Types of outcome measures section. We present the overall certainty of the evidence for each outcome according to the GRADE approach, which takes into account five criteria not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias), but also to external validity, such as directness of results (Guyatt 2008). For each comparison, two review authors (ECH, FH) independently rated the quality of evidence for each outcome as 'high', 'moderate', 'low', or 'very low', using GRADEpro Guideline Development Tool (GDT) software (GRADEpro GDT 2015). We resolved any disagreements by discussion or, if needed, by recourse to a third review author (TL, AB). For each comparison, we present a summary of the evidence for the main outcomes in a 'Summary of findings' table, which provides key information about the best estimate of the magnitude of the effect in relative terms and absolute differences for each relevant comparison of alternative management strategies; numbers of participants and studies addressing each important outcome; and the rating of the overall confidence in effect estimates for each outcome (Guyatt 2011; Schünemann 2017). We justified all decisions to downgrade the quality of trials using footnotes, and we made comments to aid the reader's understanding of the Cochrane Review where necessary.

RESULTS

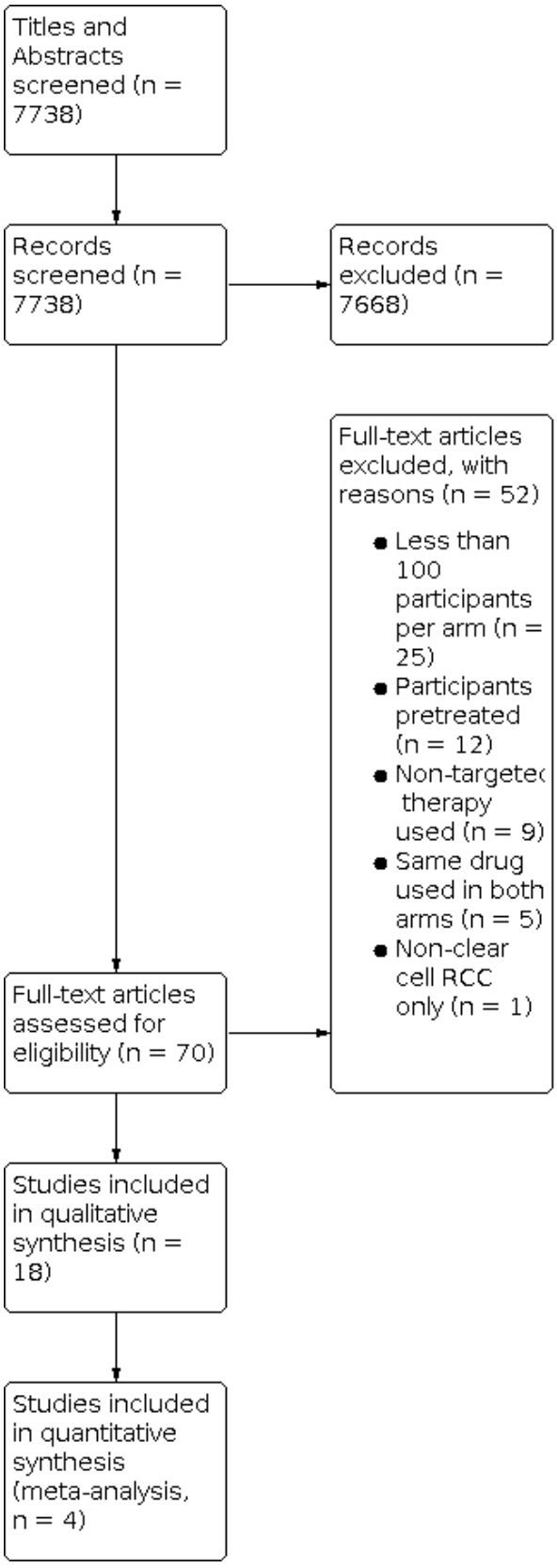
Description of studies

Our literature search identified 7738 records eligible for screening. We excluded 7668 records that did not meet our predefined inclusion criteria from further evaluation. Of these, we marked four as ongoing and included them in the Characteristics of ongoing studies section.

Results of the search

We found 70 titles and abstracts to be eligible for full-text evaluation. Of these, we selected 18 trials for qualitative synthesis and included four of them in a quantitative analysis. We excluded 52 articles; our reasons are presented in Figure 1 and under Characteristics of excluded studies.

Figure 1. Study flow diagram.



Included studies

Additional information on included studies is available in the following tables: Characteristics of included studies; Participants disposition (Table 2); and Baseline characteristics (Table 3).

Source of data

In total we included 18 trials in this review, all of which we identified by electronic database search. All trials were available as peer-reviewed publications and published in English. We contacted corresponding authors of nine trials to obtain additional information on results (Escudier 2017; Hudes 2007; Motzer 2010; Motzer 2014; Ravaud 2015; Retz 2019; Rini 2008; Rini 2014; Sternberg 2010). We received three replies (Retz 2019; Rini 2014; Sternberg 2010); and could include additional data for one trial (Retz 2019).

Study design and settings

Two of the 18 included randomised controlled trials were conducted with a double blind design in which participants and personnel were unaware of allocated intervention (Escudier 2010; Sternberg 2010). All other studies were open label without masking treatments. Three trials used a phase 2 trial design (McDermott 2018; Motzer 2014; Ravaud 2015); all others were performed in a phase 3 setting. Eight trials allowed a cross-over between treatment arms or to active treatment if disease progression occurred (Eichelberg 2015; Escudier 2010; McDermott 2018; Motzer 2010; Motzer 2013b; Motzer 2014; Retz 2019; Sternberg 2010). All trials were multicentre studies with an accrual period between 2003 and 2019.

Participants

Combining the numbers of all studies, there were 11,590 participants included of which 11,419 received the allocated treatment. All randomised participants were included in the efficacy analysis, 98% were assessed for safety. Most trials allowed only participants with a clear cell histology or a clear cell component. Six trials allowed any histology but 85% of the participants were diagnosed with clear cell renal cell carcinoma (Eichelberg 2015; Hudes 2007; Motzer 2014; Ravaud 2015; Retz 2019; Rini 2014). Median age amongst the total population was 61 years; 72% were males; and 9048 were treated with a nephrectomy prior to systemic therapy.

Interventions

Most trials had two arms comparing either two active treatments or an active treatment against placebo. Two trials had a design with multiple comparisons (Hudes 2007; McDermott 2018).

Five trials compared two different targeted therapies against each other; sorafenib versus sunitinib (Eichelberg 2015), pazopanib versus sunitinib (Motzer 2013a), tivozanib versus sorafenib (Motzer 2013b), sorafenib versus pazopanib (Retz 2019), sunitinib versus everolimus (Motzer 2014).

One trial compared pazopanib against a placebo (Sternberg 2010).

Four trials assessed the effectiveness of sunitinib against targeted immunotherapy in combination with targeted therapy. Avelumab and axitinib (Motzer 2019), pembrolizumab and axitinib (Rini 2019a), and atezolizumab and bevacizumab (Rini 2019b; McDermott 2018) were used as comparators. McDermott 2018 had a three-arm design which even included a direct comparison of sunitinib against atezolizumab. Another trial compared sunitinib against the combination of nivolumab and ipilimumab (Escudier 2017).

One trial compared sunitinib against a combination of tumour vaccine, chemotherapy and sunitinib (Rini 2016).

Interferon alpha was compared to targeted therapy or combinations of targeted therapy in four studies: sunitinib (Motzer 2010); temsirolimus (Hudes 2007); temsirolimus and interferon alpha (Hudes 2007); and bevacizumab and interferon alpha (Escudier 2010; Rini 2008).

Combinations of targeted therapies were used in two trials. Rini 2014 compared temsirolimus and bevacizumab against bevacizumab and interferon alpha; Ravaud 2015 compared everolimus and bevacizumab against interferon alpha and bevacizumab.

Outcomes

All included studies reported our primary outcomes PFS, OS and SAEs as well as response rates and minor AEs which were predefined secondary outcomes. An assessment of QoL was performed in 11 trials (Escudier 2017; Hudes 2007; McDermott 2018; Motzer 2010; Motzer 2013a; Motzer 2013b; Motzer 2014; Retz 2019; Rini 2014; Rini 2019b; Sternberg 2010).

Excluded studies

We excluded 52 trials at the stage of full-text screening. The main reasons for exclusion were: less than 100 participants in one treatment arm in 25 trials (Broom 2015; Bukowski 2007; Choueiri 2017; Cirkel 2016; Eisen 2015; Escudier 2009; Flaherty 2015; Hainsworth 2015; Jonasch 2010; Mulders 2012; Négrier 2011; Nosov 2012; Pal 2015; Pili 2015; Powles 2014; Powles 2016a; Powles 2016b; Procopio 2011; Ratain 2006; Rini 2013; Tannir 2016; Tannir 2018; Tomita 2014; Twardowski 2015; Yang 2003); participants were not treatment naïve in 12 studies (Choueiri 2015; Dorff 2015; Escudier 2010a; Hutson 2013; Hutson 2014; Jonasch 2017; Motzer 2008; Motzer 2014b; Motzer 2015a; Motzer 2015b; Motzer 2015c; Rini 2011); the intervention or comparison did not include a targeted therapy in nine trials (Escudier 2007; Gordon 2004; Hawkins 2016; Lee 2006; Madhusudan 2004; Ravaud 2008, Rini 2012; Srinivas 2005; Stadler 2005); both intervention and comparison arms used the same drug with different dosages in five trials (Atkins 2004; Bracarda 2010; Ebbinghaus 2007; Lee 2015; Motzer 2012); and one trial included only non-clear cell renal cell carcinoma participants (Armstrong 2016).

Risk of bias in included studies

For details, please refer to 'Characteristics of included studies' section, the 'Risk of bias' table, and each 'Summary of findings table', as well as Figure 2 and Figure 3.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study. Categories: green point (+) = low risk of bias; yellow point (?) = unclear risk of bias; red point (-) = high risk of bias.

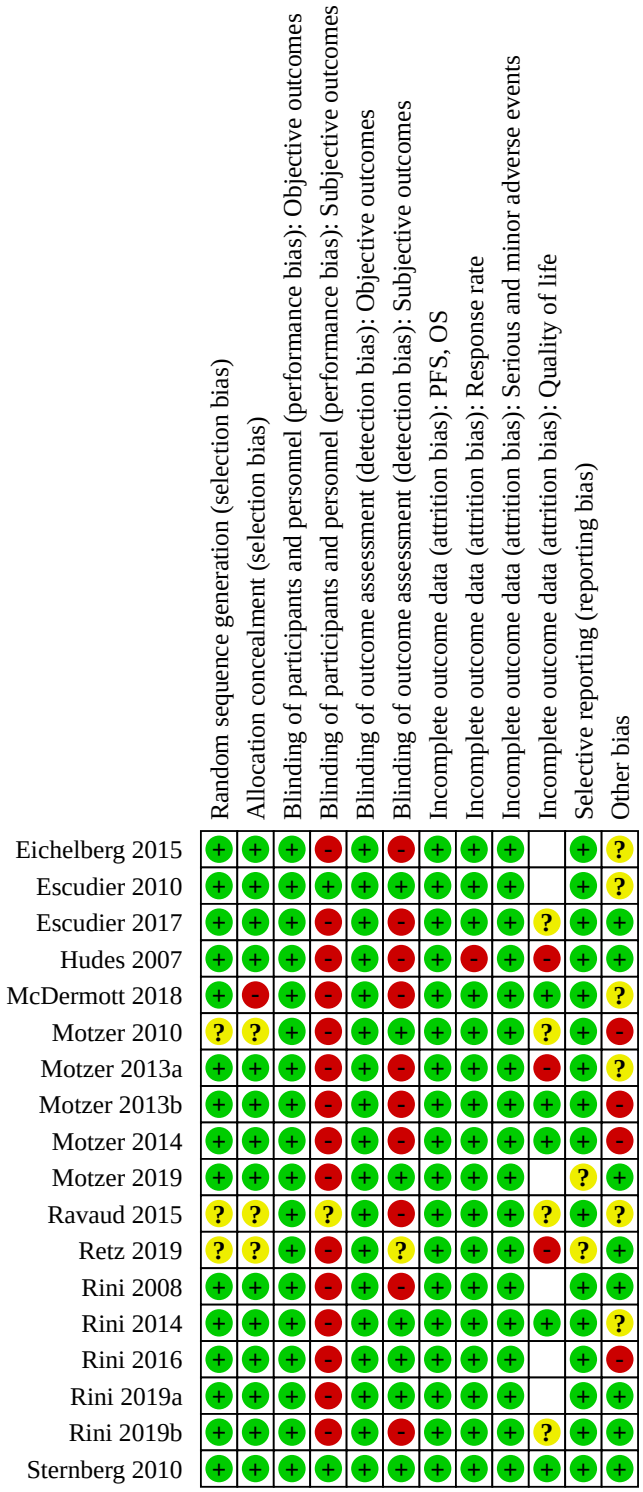
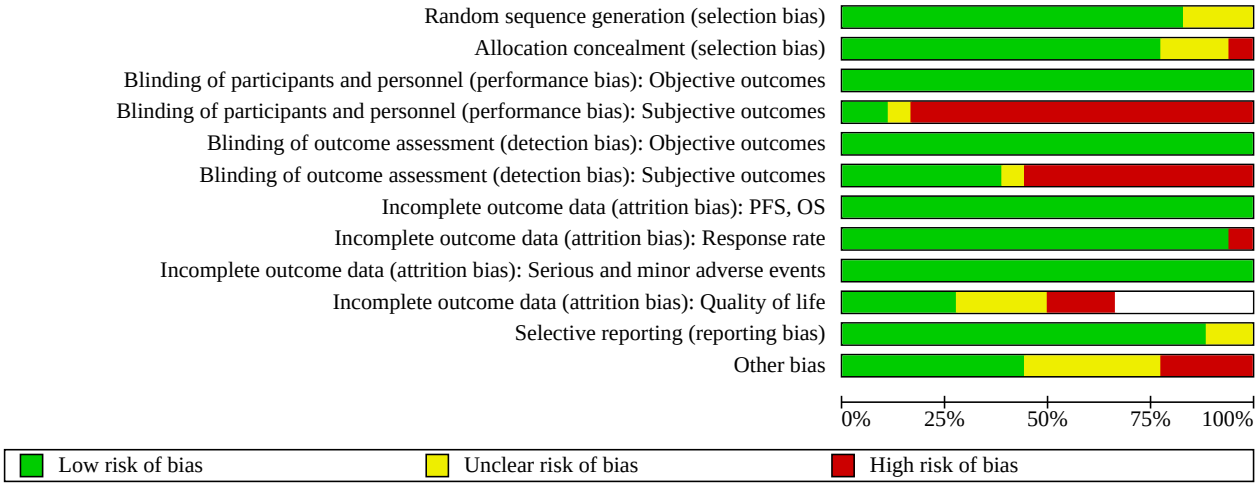


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Random sequence generation

We judged 15 trials to have a low risk of bias (Eichelberg 2015; Escudier 2010; Escudier 2017; Hudes 2007; McDermott 2018; Motzer 2013a; Motzer 2013b; Motzer 2014; Motzer 2019; Rini 2008; Rini 2014; Rini 2016; Rini 2019a; Rini 2019b; Sternberg 2010). The remaining three trials had an unclear risk of bias.

Allocation concealment

We judged 14 trials to have a low risk of bias (Eichelberg 2015; Escudier 2010; Escudier 2017; Hudes 2007; Motzer 2013a; Motzer 2013b; Motzer 2014; Motzer 2019; Rini 2008; Rini 2014; Rini 2016; Rini 2019a; Rini 2019b; Sternberg 2010). Three trials had an unclear risk of bias (Motzer 2010; Ravaud 2015; Retz 2019); and we judged one trial to have a high risk of bias (McDermott 2018).

Blinding

Blinding of participants and personnel

For objective outcomes we judged all studies to have a low risk of bias. For subjective outcomes we rated only two trials as low risk of bias (Escudier 2010; Sternberg 2010); and one we rated unclear risk of bias (Ravaud 2015). The remaining trials had a high risk of bias.

Blinding of outcome assessment

We rated all trials at low risk of bias for assessment of objective outcomes. Ten trials had a high risk of bias (Eichelberg 2015; Escudier 2017; Hudes 2007; McDermott 2018; Motzer 2013a; Motzer 2013b; Motzer 2014; Ravaud 2015; Rini 2008; Rini 2019b); one we rated unclear risk of bias (Retz 2019); and seven had a low risk of bias for subjective outcomes.

Incomplete outcome data

All studies had a low risk of bias for OS and PFS. One trial we judged to have a high risk of bias for tumour response data (Hudes 2007); the remaining trials we judged as low risk of bias. For QoL, we rated four trials as unclear risk of bias (Escudier 2017; Motzer 2010; Ravaud 2015; Rini 2019b); three trials at high risk of bias (Hudes 2007; Motzer 2013a; Retz 2019); five trials we judged at low risk of bias (.McDermott 2018; Motzer 2013b; Motzer 2014; Rini 2014; Sternberg 2010); and the remaining trials did not assess the QoL.

Selective reporting

Two studies had an unclear risk of bias (Motzer 2019; Retz 2019); the remaining 16 we judged at low risk because both the outcomes reported and the analytic approach in the published report matched those of the predefined protocol.

Other potential sources of bias

We found eight trials to have a low risk of bias (Escudier 2017; Hudes 2007; Motzer 2019; Retz 2019; Rini 2008; Rini 2019a; Rini 2019b; Sternberg 2010); six trials we rated unclear risk of bias (Eichelberg 2015; Escudier 2010; McDermott 2018; Motzer 2013a; Ravaud 2015; Rini 2014); and four studies had a high risk of bias (Motzer 2010; Motzer 2013b; Motzer 2014; Rini 2016)

Effects of interventions

See: **Summary of findings 1** Sorafenib compared to sunitinib (targeted agent versus targeted agent); **Summary of findings 2** Pazopanib compared to sunitinib (targeted agent versus targeted agent); **Summary of findings 3** Tivozanib compared to sorafenib (targeted agent versus targeted agent); **Summary of findings 4** Sorafenib compared to pazopanib (targeted agent versus targeted agent); **Summary of findings 5** Sunitinib compared to everolimus (targeted agent versus targeted agent); **Summary of findings 6** Sunitinib compared to avelumab + axitinib (targeted agent versus immunotherapy + targeted agent); **Summary of findings 7** Sunitinib compared to pembrolizumab + axitinib (targeted agent versus immunotherapy + targeted agent); **Summary of findings 8** Sunitinib compared to atezolizumab + bevacizumab (targeted agent versus immunotherapy + targeted agent); **Summary of findings 9** Sunitinib compared to IMA901 + sunitinib (targeted agent versus tumour vaccine + targeted agent); **Summary of findings 10** Sunitinib compared to interferon-α (IFN-α) (targeted

agent versus classic immunotherapy); **Summary of findings 11** Temsirolimus compared to IFN-α (targeted agent versus classic immunotherapy); **Summary of findings 12** Sunitinib compared to atezolizumab (targeted therapy versus immunotherapy); **Summary of findings 13** Bevacizumab + IFN compared to IFN (+ placebo) (targeted agent + classic immunotherapy versus classic immunotherapy); **Summary of findings 14** Temsirolimus + IFN-α compared to IFN-α (targeted agent + classic immunotherapy versus classic immunotherapy); **Summary of findings 15** Temsirolimus + bevacizumab compared to bevacizumab + IFN-α (targeted agent + targeted agent versus targeted agent + classic immunotherapy); **Summary of findings 16** Everolimus + bevacizumab compared to IFN α-2a + bevacizumab (targeted agent + targeted agent versus targeted agent + classic immunotherapy); **Summary of findings 17** Sunitinib compared to nivolumab + ipilimumab (targeted agent versus combinations of immunotherapy); **Summary of findings 18** Pazopanib compared to placebo (targeted agent versus placebo)

We performed two meta-analyses using studies which had the same population and the same comparison (Escudier 2010; McDermott 2018; Rini 2008; Rini 2019b). The remaining trials had considerable clinical heterogeneity and we judged them inappropriate for pooling of data and meta-analysis.

1. Sorafenib versus sunitinib

Please refer to Summary of findings 1.

Primary outcomes

Progression-free survival (PFS)

Sorafenib may reduce PFS when compared to sunitinib (HR 1.19, 95% CI 0.92 to 1.53; 1 study, 365 participants; low-certainty evidence; Analysis 1.1) although the CI also includes the possibility of no effect. Based on a control event risk of 340 per 1000 in this trial at 10 months, this corresponds to 63 fewer participants experiencing PFS (95% CI 148 fewer to 31 more) per 1000 participants. We rated the certainty of evidence as low due to study limitations (performance, detection and other bias) and imprecision, given that the CI was also compatible with little to no increase in PFS.

Overall survival (OS)

We are very uncertain how sorafenib compares to sunitinib for OS (HR 0.99, 95% CI 0.74 to 1.33; 1 study, 365 participants; very low-certainty evidence; Analysis 1.2). We rated the certainty of evidence as very low due to study limitations (other bias, downgraded one level) and imprecision (downgraded two levels), given that the CI was compatible with both an appreciable reduction in OS as well as an appreciable increase in OS.

Serious adverse events (SAEs, assessed with: CTCAE v3.0)

We are very uncertain how sorafenib compares to sunitinib with regard to SAEs (RR 0.99, 95% CI 0.85 to 1.14; 1 study, 353 participants; very low certainty evidence; Analysis 1.3). We rated the certainty of evidence as very low due to study limitations (performance, detection and other bias, downgraded one level) and imprecision (downgraded two levels), given that the CI was compatible with both an appreciable reduction in SAEs as well as an appreciable increase in SAEs.

Secondary outcomes

Quality of life (QoL)

We found no studies that reported this outcome.

Response rate (assessed with: RECIST version not reported)

Sorafenib may result in little to no difference in response rate as compared to sunitinib (RR 1.07, 95% CI 0.78 to 1.47; 1 study, 353 participants; low-certainty evidence; Analysis 1.4). Based on the control event risk of 290 per 1000 in this trial, this corresponds to 20 more response (95% CI 64 fewer to 136 more) per 1000 participants. We rated the certainty of evidence as low due to study limitations (performance, detection and other bias) and imprecision, given that the CI was also compatible with an appreciable increase in the response rate.

Minor adverse events (AEs, assessed with: CTCAE v3.0)

Sorafenib may result in little to no difference in minor AEs as compared to sunitinib (RR 1.13, 95% CI 0.77 to 1.65; 1 study, 353 participants; low-certainty evidence; Analysis 1.5). Based on the control event risk of 216 per 1000 in this trial, this corresponds to 28 more minor AEs (95% CI 50 fewer to 140 more) per 1000 participants. We rated the certainty of evidence as low due to study limitations (performance, detection and other bias) and imprecision, given that the CI was also compatible with an appreciable increase in minor AEs.

Subgroup analysis

We were unable to perform any of the predefined subgroup analyses.

Sensitivity analysis

We were unable to perform a sensitivity analysis because there was only one study.

2. Pazopanib versus sunitinib

Please refer to Summary of findings 2.

Primary outcomes

PFS

Pazopanib may result in little to no difference in PFS as compared to sunitinib (HR 1.05, 95% CI 0.90 to 1.23; 1 study, 1110 participants; low-certainty evidence; Analysis 2.1). Based on the control event risk of 420 per 1000 in this trial at 12 months, this corresponds to 18 fewer participants experiencing PFS (95% CI 76 fewer to 38 more) per 1000 participants. We rated the certainty of evidence as low due to study limitations (performance, detection and other bias) and imprecision, given that the CI was also compatible with an appreciable reduction in PFS.

OS

Pazopanib may result in little to no difference in OS compared to sunitinib (HR 0.92, 95% CI 0.80 to 1.06; 1 study, 1110 participants; low-certainty evidence; Analysis 2.2). Based on the control event risk of 550 per 1000 in this trial at 12 months, this corresponds to 27 more participants experiencing OS (95% CI 19 fewer to 70 more) per 1000 participants. We rated the certainty of evidence as low due to study limitations (other bias) and imprecision, given that the CI was also compatible with an appreciable increase in OS.

SAEs (assessed with: CTCAE v3.0)

Pazopanib may result in little to no difference in SAEs as compared to sunitinib (RR 1.01, 95% CI 0.94 to 1.09; 1 study, 1102 participants; low-certainty evidence; Analysis 2.3). Based on the control event risk of 734 per 1000 in this trial, this corresponds to seven more participants experiencing SAEs (95% CI 44 fewer to 66 more) per 1000 participants. We rated the certainty of evidence as low due to study limitations (performance, detection and other bias) and imprecision, given that the CI was also compatible with an appreciable increase in SAEs.

Secondary outcomes

QoL

Pazopanib may increase QoL as compared to sunitinib (MD 3.60, 95% CI 1.76 to 5.44; 1 study, 467 participants; low-certainty evidence; Analysis 2.4) assessed with FACIT-F (scale 0 to 52; higher scores indicating less fatigue; MCID: 3 points). We rated the certainty of evidence as low due to study limitations (performance, detection, attrition and other bias), and imprecision, given that the CI was also compatible with no increase in QoL.

Response rate (assessed by RECIST v1.0)

Pazopanib may result in little to no difference in response rate as compared to sunitinib (RR 1.24, 95% CI 1.02 to 1.50; 1 study, 1110 participants; low-certainty evidence; Analysis 2.5). Based on the control event risk of 248 per 1000 in this trial, this corresponds to 59 more response (95% CI 5 more to 124 more) per 1000 participants. We rated the certainty of evidence as low due to study limitations (performance, detection and other bias) and imprecision, given that the CI was also compatible with an appreciable increase in the response rate.

Minor AEs (assessed with: CTCAE v3.0)

Pazopanib probably results in little to no difference in minor AEs as compared to sunitinib (RR 1.00, 95% CI 0.81 to 1.23; 1 study, 1102 participants; moderate-certainty evidence; Analysis 2.6). Based on the control event risk of 237 per 1000 in this trial, this corresponds to no fewer minor AEs (95% CI 45 fewer to 55 more) per 1000 participants. We rated the certainty of evidence as moderate due to study limitations (performance, detection and other bias).

Subgroup analyses

We were unable to perform any of the predefined subgroup analyses.

Sensitivity analyses

We were unable to perform a sensitivity analysis because there was only one study.

3. Tivozanib versus sorafenib

Please refer to Summary of findings 3.

Primary outcomes

PFS

Tivozanib may extend PFS as compared to sorafenib (HR 0.79, 95% CI 0.64 to 0.99; 1 study, 517 participants; low-certainty evidence; Analysis 3.1). Based on the control event risk of 360 per 1000 in this trial at 12 months, this corresponds to 86 more participants experiencing PFS (95% CI 4 more to 160 more) per 1000 participants. We rated the certainty of evidence as low due to study limitations (performance, detection and other bias) and imprecision, given that the CI was also compatible with a little to no increase in PFS.

OS

Tivozanib may reduce OS as compared to sorafenib (HR 1.25, 95% CI 0.95 to 1.64; 1 study, 517 participants; low-certainty evidence; Analysis 3.2) although the CI also includes the possibility of no effect. Based on the control event risk of 620 per 1000 in this trial at 24 months, this would result in 70 fewer OSs (95% CI 163 fewer to 15 more) per 1000 participants. We rated the certainty of evidence as low due to study limitations (other bias) and imprecision, given that the CI was also compatible with little to no increase in OS.

SAEs (assessed with: CTCAE v3.0)

Tivozanib may reduce SAEs as compared to sorafenib (RR 0.85, 95% CI 0.74 to 0.97; 1 study, 516 participants; low-certainty evidence; Analysis 3.3). Based on the control event risk of 689 per 1000 in this trial, this corresponds to 103 fewer SAEs (95% CI 179 fewer to 21 fewer) per 1000 participants. We rated the certainty of evidence as low due to study limitations (performance, detection and other bias) and imprecision, given that the CI was also compatible with little to no reduction in SAEs.

Secondary outcomes

QoL

Tivozanib may result in little to no difference in QoL (assessed with EQ-5D; scale: −0.59 to 1; higher values reflect better QoL; MCID 0.06) as compared to sorafenib (MD 0.01, 95% CI −0.05 to 0.07; 1 study, 506 participants; low-certainty evidence; Analysis 3.4). We rated the certainty of evidence as low due to study limitations (performance, detection and other bias), and imprecision, given that the CI was also compatible with an increase in QoL.

Response rate (assessed by RECIST v1.0)

Tivozanib may increase the response rate as compared to sorafenib (RR 1.42, 95% CI 1.07 to 1.88; 1 study, 517 participants; low-certainty evidence; Analysis 3.5). Based on the control event risk of 233 per 1000 in this trial, this corresponds to 98 more responses (16 more to 205 more) per 1000 participants. We rated the certainty of evidence as low due to study limitations (performance, detection and other bias) and imprecision, given that the CI was also compatible with little to no increase in the response rate.

Minor AEs (assessed with: CTCAE v3.0)

Tivozanib may result in little to no difference in minor AEs as compared to sorafenib (RR 1.16, 95% CI 0.89 to 1.51; 1 study, 516 participants; low-certainty evidence; Analysis 3.6). Based on the control event risk of 280 per 1000 in this trial, this corresponds to 45 more minor AEs (95% CI 31 fewer to 143 more) per 1000 participants. We rated the certainty of evidence as low due to study limitations (performance, detection and other bias) and imprecision, given that the CI was also compatible with an appreciable increase in minor AEs.

Subgroup analyses

We were unable to perform any of the predefined subgroup analyses.

Sensitivity analyses

We were unable to perform a sensitivity analyses because there was only one study.

4. Sorafenib versus pazopanib

Please refer to Summary of findings 4.

Primary outcomes

PFS

Sorafenib probably reduces PFS as compared to pazopanib (HR 1.92, 95% CI 1.74 to 2.11; 1 study, 377 participants; moderate-certainty evidence; Analysis 4.1). Based on the control event risk of 380 per 1000 in this trial at 12 months, this corresponds to 224 fewer participants experiencing PFS (95% CI 250 fewer to 194 fewer) per 1000 participants. We rated the certainty of evidence as moderate due to study limitations (selection, performance, detection, and reporting bias).

OS

Sorafenib may reduce OS as compared to pazopanib (HR 1.22, 95% CI 0.91 to 1.64; 1 study, 377 participants; low-certainty evidence; Analysis 4.2) although the CI also includes the possibility of no effect. Based on the control event risk of 520 per 1000 in this trial at 24 months, this would result in 70 fewer OSs (95% CI 178 fewer to 32 more) per 1000 participants. We rated the certainty of evidence as low due to study limitations (selection and reporting bias) and imprecision, given that the CI was also compatible with little to no reduction in OS.

SAEs (assessed with: CTCAE v4.03)

We are very uncertain how sorafenib compares to pazopanib (RR 0.92, 95% CI 0.78 to 1.09; 1 study, 366 participants; very low certainty evidence; Analysis 4.3) with regard to SAEs. We rated the certainty of evidence as very low due to study limitations (selection, performance, detection, and reporting bias, downgrade one level) and imprecision (downgrade two levels), given that the CI was compatible with both an appreciable reduction in SAEs as well as an appreciable increase in SAEs.

Secondary outcomes

QoL

Sorafenib may increase QoL slightly (assessed with FACIT-F; scale 0 to 52; higher scores indicating less fatigue; MCID: 3 points) as compared to pazopanib (MD 3.10, 95% CI −1.82 to 8.02; 1 study, 267 participants; low-certainty evidence; Analysis 4.4). We rated the certainty of evidence as low due to study limitations (selection, performance, detection, attrition and reporting bias) and imprecision, given that the CI was also compatible with no increase in QoL.

Response rate (assessed with RECIST v1.1)

Sorafenib may reduce the response rate as compared to pazopanib (RR 0.62, 95% CI 0.47 to 0.81; 1 study, 377 participants; low-certainty evidence; Analysis 4.5). Based on the control event risk of 463 per 1000 in this trial, this corresponds to 176 fewer response (95% CI 245 fewer to 88 fewer) per 1000 participants. We rated the certainty of evidence as low due to study limitations (selection, performance, detection, and reporting bias) and imprecision, given that the CI was also compatible with no reduction in the response rate.

Minor AEs (assessed with: CTCAE v4.03)

Sorafenib may result in little to no difference in minor AEs (assessed with: CTCAE v4.03) as compared to pazopanib (RR 1.15, 95% CI 0.87 to 1.52; 1 study, 366 participants; low-certainty evidence; Analysis 4.6). Based on the control event risk of 328 per 1000 in this trial, this corresponds to 49 more minor AEs (95% CI 43 fewer to 170 more) per 1000 participants. We rated the certainty of evidence as low due to study limitations (selection, performance, detection, and reporting bias) and imprecision, given that the CI was also compatible with an appreciable increase in minor AEs.

Subgroup analyses

We were unable to perform any of the predefined subgroup analyses.

Sensitivity analyses

We were unable to perform a sensitivity analysis because there was only one study.

5. Sunitinib versus everolimus

Please refer to Summary of findings 5.

Primary outcomes

PFS

Sunitinib probably increases PFS as compared to everolimus (HR 0.71, 95% CI 0.59 to 0.87; 1 study, 471 participants; moderate-certainty evidence; Analysis 5.1). Based on the control event risk of 300 per 1000 in this trial at 12 months, this corresponds to 125 participants experiencing PFS (95% CI 51 more to 191 more) per 1000 participants. We rated the certainty of evidence as moderate due to study limitations (performance, detection and other bias).

OS

Sunitinib may result in little to no difference in OS as compared to everolimus (HR 0.90, 95% CI 0.72 to 1.11; 1 study, 471 participants; low-certainty evidence; Analysis 5.2). Based on the control event risk of 470 per 1000 in this trial at 24 months, this would result in 37 more OSs (95% CI 37 fewer to 111 more) per 1000 participants. We rated the certainty of evidence as low due to study limitations (other bias) and imprecision, given that the CI was also compatible with an appreciable increase in OS.

SAEs (assessed with: CTCAE v3.0)

Sunitinib probably increases SAEs as compared to everolimus (RR 1.34, 95% CI 1.14 to 1.59; 1 study, 469 participants; moderate-certainty evidence; Analysis 5.3). Based on the control event risk of 471 per 1000 in this trial, this corresponds to 160 more SAEs (95% CI 66 more to 278 more) per 1000 participants. We rated the certainty of evidence as moderate due to study limitations (performance, detection and other bias).

Secondary outcomes

QoL

Sunitinib may result in little to no difference in QoL (assessed with EORTC QLQ-C30; scale: 0 to 100; high score represent better functioning, MCID: 10 points) as compared to everolimus (MD −5.00, 95% CI −10.40 to 0.40; 1 study, 288 participants; low-certainty evidence; Analysis 5.4). We rated the certainty of evidence as low due to study limitations (performance, detection and other bias)

and imprecision, given that the CI was also compatible with a decrease in QoL.

Response rate (assessed with RECIST v1.0)

Sunitinib may increase response rate as compared to everolimus (RR 3.33, 95% CI 2.06 to 5.39; 1 study, 471 participants; low-certainty evidence; Analysis 5.5). Based on the control event risk of 80 per 1000 in this trial, this corresponds to 186 more responses (95% CI 85 more to 350 more) per 1000 participants. We rated the certainty of evidence as low due to study limitations (performance, detection and other bias) and imprecision, given that the CI was also compatible with little to no increase in response rate.

Minor AEs (assessed with: CTCAE v3.0)

Sunitinib probably results in little to no difference in minor AEs as compared to everolimus (RR 1.02, 95% CI 0.99 to 1.04; 1 study, 469 participants; moderate-certainty evidence; Analysis 5.6). Based on the control event risk of 971 per 1000 in this trial, this corresponds to 19 more minor AEs (95% CI 10 fewer to 39 more) per 1000 participants. We rated the certainty of evidence as moderate due to study limitations (performance, detection and other bias).

Subgroup analyses

We were unable to perform any of the predefined subgroup analyses.

Sensitivity analyses

We were unable to perform a sensitivity analysis because there was only one study.

6. Sunitinib versus avelumab + axitinib

Please refer to Summary of findings 6.

Primary outcomes

PFS

Sunitinib probably reduces PFS as compared to avelumab plus axitinib (HR 1.45, 95% CI 1.17 to 1.80; 1 study, 886 participants; moderate-certainty evidence; Analysis 6.1). Based on the control event risk of 550 per 1000 in this trial at 12 months, this corresponds to 130 fewer participants experiencing PFS (95% CI 209 fewer to 53 fewer) per 1000 participants. We rated the certainty of evidence as moderate due to study limitations (performance bias and reporting bias).

OS

Sunitinib may result in little to no difference in OS as compared to avelumab plus axitinib (HR 1.28, 95% CI 0.92 to 1.79; 1 study, 886 participants; low-certainty evidence; Analysis 6.2). Based on the control event risk of 890 per 1000 in this trial at 12 months, this would result in 29 fewer OSs (95% CI 78 fewer to 8 more) per 1000 participants. We rated the certainty of evidence as low due to study limitations (reporting bias) and imprecision given that the CI was also compatible with an appreciable reduction in OS.

SAEs (assessed with: CTCAE v4.03)

Sunitinib may result in little to no difference in SAEs as compared to avelumab plus axitinib (RR 1.01, 95% CI 0.93 to 1.10; 1 study, 873 participants; low-certainty evidence; Analysis 6.3). Based on the control event risk of 705 per 1000 in this trial, this corresponds to 7 more SAEs (95% CI 49 fewer to 71 more) per 1000 participants. We rated the certainty of evidence as low due to study limitations (performance bias and reporting bias) and imprecision given that the CI was also compatible with an increase in SAEs.

Secondary outcomes

QoL

We found no studies that reported this outcome.

Response rate (assessed with: RECIST v1.1)

Sunitinib probably reduces the response rate as compared to avelumab plus axitinib (RR 0.50, 95% CI 0.42 to 0.60; 1 study, 886 participants; moderate-certainty evidence; Analysis 6.4). Based on the control event risk of 514 per 1000 in this trial, this corresponds to 257 fewer responses (95% CI 298 fewer to 205 fewer) per 1000 participants. We rated the certainty of evidence as moderate due to study limitations (performance bias and reporting bias).

Minor AEs (assessed with CTCAE v4.03)

Sunitinib probably results in little to no difference in minor AEs as compared to avelumab plus axitinib (RR 0.97, 95% CI 0.78 to 1.19; 1 study, 873 participants; moderate-certainty evidence; Analysis 6.5). Based on the control event risk of 290 per 1000 in this trial, this corresponds to nine fewer minor AEs (95% CI 64 fewer to 55 more) per 1000 participants. We rated the certainty of evidence as moderate due to study limitations (performance bias and reporting bias)

Subgroup analyses

We were unable to perform any of the predefined subgroup analyses.

Sensitivity analyses

We were unable to perform a sensitivity analysis because there was only one study.

7. Sunitinib versus pembrolizumab + axitinib

Please refer to Summary of findings 7.

Primary outcomes

PFS

Sunitinib probably reduces PFS as compared to pembrolizumab plus axitinib (HR 1.45, 95% CI 1.19 to 1.76; 1 study, 861 participants; moderate-certainty evidence; Analysis 7.1). Based on the control event risk of 590 per 1000 in this trial at 12 months, this corresponds to 125 fewer participants experiencing PFS (95% CI 195 fewer to 56 fewer) per 1000 participants. We rated the certainty of evidence as moderate due to study limitations (performance bias).

OS

Sunitinib probably reduces OS as compared to pembrolizumab plus axitinib (HR 1.90, 95% CI 1.36 to 2.65; 1 study, 861 participants; moderate-certainty evidence; Analysis 7.2). Based on the control event risk of 880 per 1000 in this trial at 12 months, this would result in 96 fewer OSs (95% CI 167 fewer to 40 fewer) per 1000 participants. We rated the certainty of evidence as moderate due to imprecision, given that the CI was also compatible with little to no reduction in OS.

SAEs (assessed with CTCAE v4.0)

Sunitinib may reduce SAEs as compared to pembrolizumab plus axitinib (RR 0.90, 95% CI 0.81 to 1.02; 1 study, 854 participants; low-certainty evidence; Analysis 7.3) although the CI also includes the possibility of no effect. Based on the control event risk of 604 per 1000 in this trial, this corresponds to 60 fewer SAEs (95% CI 115 fewer to 12 more) per 1000 participants. We rated the certainty of evidence as low due to study limitations (performance bias) and imprecision, given that the CI was also compatible with little to no increase in SAEs.

Secondary outcomes

QoL

We found no studies that reported this outcome.

Response rate (assessed with: RECIST v1.1)

Sunitinib probably reduces the response rate as compared to pembrolizumab plus axitinib (RR 0.60, 95% CI 0.52 to 0.70; 1 study, 861 participants; moderate-certainty evidence; Analysis 7.4). Based on the control event risk of 593 per 1000 in this trial, this corresponds to 237 fewer response (95% CI 284 fewer to 178 fewer) per 1000 participants. We rated the certainty of evidence as moderate due to study limitations (performance bias)

Minor AEs (assessed with CTCAE v4.0)

Sunitinib may result in little to no difference in minor AEs as compared to pembrolizumab plus axitinib (RR 1.19, 95% CI 0.99 to 1.42; 1 study, 854 participants; low-certainty evidence; Analysis 7.5). Based on the control event risk of 333 per 1000 in this trial, this corresponds to 63 more minor AEs (95% CI 3 fewer to 140 more) per 1000 participants. We rated the certainty of evidence as low due to study limitations (performance bias) and imprecision, given that the CI was also compatible with an increase in minor AEs.

Subgroup analyses

We were unable to perform any of the predefined subgroup analyses.

Sensitivity analyses

We were unable to perform a sensitivity analysis because there was only one study.

8. Sunitinib versus atezolizumab + bevacizumab

Please refer to Summary of findings 8.

Primary outcomes

PFS

Sunitinib may reduce PFS as compared to atezolizumab plus bevacizumab (HR 1.18, 95% CI 1.02 to 1.36; 2 studies, 1117 participants; I^2 = 0%; low-certainty evidence; Analysis 8.1). Based on the control event risk of 480 per 1000 in this trial at 12 months, this corresponds to 59 fewer PFSs (95% CI 111 fewer to 7 fewer) per 1000 participants. We rated the certainty of evidence as low due to study limitations (high and unclear risk of one or more domains) and imprecision, given that the CI was also compatible with no reduction in PFS.

OS

We are very uncertain how sunitinib compares to atezolizumab plus bevacizumab for OS (HR 0.99, 95% CI 0.73 to 1.33; 2 studies, 1117 participants; I^2 = 37%; very low certainty evidence; Analysis 8.2). We rated the certainty of evidence as very low due to study limitations (high and unclear risk of one or more domains, downgrade one level) and imprecision (downgrade two levels), given that the CI was compatible with an appreciable reduction in the OS as well as an appreciable increase in OS.

SAEs (assessed with: CTCAE v4.0)

We are very uncertain how sunitinib compares to atezolizumab plus bevacizumab for SAEs as compared to atezolizumab + bevacizumab (RR 1.22, 95% CI 1.00 to 1.49; 2 studies, 1098 participants; I^2 = 64%; very low certainty evidence; Analysis 8.3). We rated the certainty of evidence as very low due to study limitations (high and unclear risk of one or more domains), inconsistency (unexplained differences between study results) and imprecision, given that the CI was compatible with no increase in SAEs as well as an appreciable increase in SAEs.

Secondary outcomes

QoL

Sunitinib may decrease QoL (assessed with MD Anderson Symptom Inventory Interference Score (MDASI); scale 0 to 10; higher scores indicate worse QoL; MCID 1.0) as compared to atezolizumab plus bevacizumab (MD 1.00, 95% CI 0.68 to 1.32; 2 studies, 691 participants; I^2 = 0%; low-certainty evidence; Analysis 8.4). We rated the certainty of evidence as low due to study limitations (high and unclear risk of one or more domains) and imprecision, given that the CI was compatible with possibly no decrease in QoL.

Response rate (assessed with: RECIST v1.1)

Sunitinib probably results in little to no difference in response rate as compared to atezolizumab plus bevacizumab (RR 0.91, 95% CI 0.77 to 1.07; 2 studies, 1117 participants; I^2 = 0%; moderate-certainty evidence; Analysis 8.5). Based on the control event risk of 357 per 1000 in this trial, this corresponds to 32 fewer responses (95% CI 82 fewer to 25 more) per 1000 participants. We rated the certainty of evidence as moderate due to study limitations (high and unclear risk of one or more domains).

Minor AEs (assessed with CTCAE v4.0)

Sunitinib may result in little to no difference in minor AEs as compared to atezolizumab plus bevacizumab (RR 0.85, 95% CI 0.74 to 0.97; 2 studies, 1098 participants; I^2 = 0%; low-certainty evidence; Analysis 8.6). Based on the control event risk of 467 per 1000 in this trial, this corresponds to 70 fewer minor AEs (95% CI 112 fewer to 14 fewer) per 1000 participants. We rated the certainty of evidence as low due to study limitations (high and unclear risk of one or more domains) and imprecision, given that the CI was also compatible with an appreciable reduction in minor AEs.

Subgroup analysis

We were unable to perform any of the predefined subgroup analyses.

Sensitivity analysis

We rated all of the included studies as high or unclear risk of bias and were unable to perform a sensitivity analysis.

9. Sunitinib versus IMA901 + sunitinib

Please refer to Summary of findings 9.

Primary outcomes

PFS

We are very uncertain about the effect of sunitinib on PFS as compared to IMA901 plus sunitinib (HR 0.95, 95% CI 0.70 to 1.30; 1 study, 339 participants; very low certainty evidence; Analysis 9.1). We rated the certainty of evidence as very low due to study limitations (performance and other bias, downgrade one level) and imprecision (downgrade two levels), given that the CI was compatible with an appreciable reduction in PFS as well as an appreciable increase in PFS.

OS

Sunitinib may result in little to no difference in OS as compared to IMA901 plus sunitinib (HR 0.75, 95% CI 0.54 to 1.04; 1 study, 339 participants; low-certainty evidence; Analysis 9.2). Based on the control event risk of 800 per 1000 in this trial at 12 months, this would result in 46 more OSs (95% CI 7 fewer to 86 more) per 1000 participants. We rated the certainty of evidence as low due to study limitations (other bias) and imprecision, given that the CI was also compatible with an increase in OS.

SAEs (assessed with CTCAE v4.0)

Sunitinib may reduce SAEs as compared to IMA901 plus sunitinib (RR 0.74, 95% CI 0.59 to 0.95; 1 study, 334 participants; low-certainty evidence; Analysis 9.3). Based on the control event risk of 550 per 1000 in this trial, this corresponds to 143 fewer SAEs (95% CI 225 fewer to 27 fewer) per 1000 participants. We rated the certainty of evidence as low due to study limitations (performance and other bias) and imprecision, given that the CI was also compatible with a small to no reduction in SAEs.

Secondary outcomes

QoL

We found no studies that reported this outcome.

Response rate (assessed with: RECIST v1.1)

Sunitinib may result in little to no difference in response rate as compared to IMA901 plus sunitinib (RR 0.87, 95% CI 0.64 to 1.19; 1 study, 339 participants; low-certainty evidence; Analysis 9.4). Based on the control event risk of 358 per 1000 in this trial, this corresponds to 47 fewer response (95% CI 129 fewer to 68 more) per 1000 participants. We rated the certainty of evidence as low due to study limitations (performance and other bias) and imprecision, given that the CI was also compatible with an appreciable reduction in response rate.

Minor AEs (assessed with CTCAE v4.0)

Sunitinib may result in little to no difference in minor AEs as compared to IMA901 plus sunitinib (RR 1.29, 95% CI 0.96 to 1.72; 1 study, 334 participants; low-certainty evidence; Analysis 9.5). Based on the control event risk of 312 per 1000 in this trial, this corresponds to 90 more minor AEs (95% CI 12 fewer to 225 more) per 1000 participants. We rated the certainty of evidence as low due to study limitations (performance and other bias) and imprecision, given that the CI was also compatible with an appreciable increase in minor AEs.

Subgroup analysis

We were unable to perform any of the predefined subgroup analyses.

Sensitivity analysis

We were unable to perform a sensitivity analysis because there was only one study.

10. Sunitinib versus interferon-α (IFN-α) (targeted agent versus classic immunotherapy)

Please refer to Summary of findings 10.

Primary outcomes

PFS

Sunitinib probably increases PFS as compared to IFN-α (HR 0.54, 95% CI 0.45 to 0.64; 1 study, 750 participants; moderate-certainty evidence; Analysis 10.1). Based on the control event risk of 400 per 1000 in this trial at six months, this corresponds to 210 more PFSs (95% CI 156 more to 262 more) per 1000 participants. We rated the certainty of evidence as moderate due to study limitations (selection, performance and other bias).

OS

Sunitinib may increase OS as compared to IFN-α (HR 0.82, 95% CI 0.67 to 1.00; 1 study, 750 participants; low-certainty evidence; Analysis 10.2) although the CI also includes the possibility of no effect. Based on the control event risk of 480 per 1000 in this trial at 24 months, this would result in 68 more OSs (95% CI 0 fewer to 132 more) per 1000 participants. We rated the certainty of evidence as low due to study limitations (selection and other bias) and imprecision, given that the CI was also compatible with no increase in OS.

SAEs (assessed with CTCAE v3.0)

Sunitinib probably increases SAEs as compared to IFN-α (RR 1.75, 95% CI 1.43 to 2.16; 1 study, 735 participants; moderate-certainty evidence; Analysis 10.3). Based on the control event risk of 258 per 1000 in this trial, this corresponds to 194 more SAEs (95% CI 111 more to 300 more) per 1000 participants. We rated the certainty of evidence as moderate due to study limitations (selection, performance and other bias).

Secondary outcomes

QoL

Sunitinib probably results in little to no difference in QoL (assessed with EQ-5D; scale: −0.59 to 1.00 with higher scores indicating better QoL; MCID 0.06) as compared to IFN-α (MD −0.01, 95% CI −0.05 to 0.03; 1 study, 544 participants; moderate-certainty evidence; Analysis 10.4). We rated the certainty of evidence as moderate due to study limitations (selection, performance and other bias).

Response rate (assessed with RECIST v1.0)

Sunitinib probably increases response rate as compared to IFN-α (RR 3.83, 95% CI 2.86 to 5.12; 1 study, 750 participants; moderate-

certainty evidence; Analysis 10.5). Based on the control event risk of 123 per 1000 in this trial, this corresponds to 347 more response (95% CI 228 more to 505 more) per 1000 participants. We rated the certainty of evidence as moderate due to study limitations (selection, performance and other bias).

Minor AEs (assessed with CTCAE v3.0)

Sunitinib probably results in little to no difference in minor AEs as compared to IFN-α (RR 1.03, 95% CI 1.00 to 1.05; 1 study, 735 participants; moderate-certainty evidence; Analysis 10.6). Based on the control event risk of 956 per 1000 in this trial, this corresponds to 29 more minor AEs (95% CI 0 fewer to 48 more) per 1000 participants. We rated the certainty of evidence as moderate due to study limitations (selection, performance and other bias).

Subgroup analysis

We were unable to perform any of the predefined subgroup analyses.

Sensitivity analysis

We were unable to perform a sensitivity analysis because there was only one study.

11. Temsirolimus versus IFN-α (targeted agent versus classic immunotherapy)

Please refer to Summary of findings 11.

Primary outcomes

PFS

Temsirolimus may increase PFS as compared to IFN-α (HR 0.74, 95% CI 0.60 to 0.91; 1 study, 416 participants; low-certainty evidence; Analysis 11.1). Based on the control event risk of 100 per 1000 in this trial at 12 months, this corresponds to 82 more PFSs (95% CI 23 more to 151 more) per 1000 participants. We rated the certainty of evidence as low due to study limitations (performance and detection bias) and imprecision, given that the CI was also compatible with a small or no increase in PFS.

OS

Temsirolimus probably increases OS as compared to IFN-α (HR 0.78, 95% CI 0.63 to 0.97; 1 study, 416 participants; moderate-certainty evidence; Analysis 11.2). Based on the control event risk of 300 per 1000 in this trial at 12 months, this would result in 91 more OSs (95% CI 11 more to 168 more) per 1000 participants. We rated the certainty of evidence as moderate due to imprecision, given that the CI was also compatible with a small or no increase in OS.

SAEs (assessed with CTCAE version not reported)

Temsirolimus may reduce SAEs as compared to IFN-α (RR 0.86, 95% CI 0.76 to 0.97; 1 study, 408 participants; low-certainty evidence; Analysis 11.3). Based on the control event risk of 780 per 1000 in this trial, this corresponds to 109 fewer SAEs (95% CI 187 fewer to 23 fewer) per 1000 participants. We rated the certainty of evidence as low due to study limitations (performance and detection bias) and imprecision, given that the CI was also compatible with a small or no reduction in SAEs.

Secondary outcomes

QoL

Temsirolimus may result in little to no difference in QoL (assessed with EQ-5D; scale −0.59 to 1.0 with higher values indicating better QoL; MCID: 0.06) as compared to IFN-α (MD 0.03, 95% CI −0.01 to 0.07; 1 study, 401 participants; low-certainty evidence; Analysis 11.4). We rated the certainty of evidence as low due to study limitations (performance, detection and attrition bias), and imprecision, given that the CI was also compatible with an increase in QoL.

Response rate (assessed with RECIST version not reported)

Temsirolimus may result in little to no difference in response rate as compared to IFN-α (RR 1.78, 95% CI 0.84 to 3.77; 1 study, 416 participants; low-certainty evidence; Analysis 11.5). Based on the control event risk of 48 per 1000 in this trial, this corresponds to 38 more response (95% CI 8 fewer to 134 more) per 1000 participants. We rated the certainty of evidence as low due to study limitations (performance, detection and attrition bias), and imprecision, given that the CI is also compatible with an appreciable increase in response rate.

Minor AEs (assessed with CTCAE version not reported)

Temsirolimus probably results in little to no difference in minor AEs as compared to IFN-α (RR 1.02, 95% CI 1.00 to 1.04; 1 study, 408 participants; moderate-certainty evidence; Analysis 11.6). Based on the control event risk of 985 per 1000 in this trial, this corresponds to 20 more minor AEs (95% CI 0 fewer to 39 more) per 1000 participants. We rated the certainty of evidence as moderate due to study limitations (performance and detection bias).

Subgroup analysis

We were unable to perform any of the predefined subgroup analyses.

Sensitivity analysis

We were unable to perform a sensitivity analysis because there was only one study.

12. Sunitinib versus atezolizumab (targeted therapy versus immunotherapy)

Please refer to Summary of findings 12.

Primary outcomes

PFS

We are very uncertain how sunitinib affects PFS as compared to atezolizumab (HR 0.84, 95% CI 0.58 to 1.22; 1 study, 204 participants; very low certainty evidence; Analysis 12.1). We rated the certainty of evidence as very low due to study limitations (selection, performance, detection and other bias, downgrade one level) and imprecision (downgrade two levels), given that the CI was compatible with both an appreciable reduction and increase in PFS.

OS

We are very uncertain how sunitinib affects OS as compared to atezolizumab (HR 0.94, 95% CI 0.58 to 1.54; 1 study, 204 participants; very low certainty evidence; Analysis 12.2). We rated the certainty of evidence as very low due to study limitations (selection and other bias, downgrade one level) and imprecision

(downgrade two levels), given that the CI was compatible with both an appreciable reduction and increase in OS.

SAEs (assessed with: CTCAE v4.0)

Sunitinib probably increases SAEs as compared to atezolizumab (RR 1.73, 95% CI 1.32 to 2.27; 1 study, 203 participants; moderate-certainty evidence; Analysis 12.3). Based on the control event risk of 398 per 1000 in this trial, this corresponds to 291 more SAEs (95% CI 127 more to 506 more) per 1000 participants. We rated the certainty of evidence as moderate due to study limitations (selection, performance, detection and other bias).

Secondary outcomes

QoL

Sunitinib may decrease QoL slightly (assessed with MD Anderson Symptom Inventory Interference Score (MDASI); scale 0 to 10; higher scores indicate worse QoL; MCID 1.0) as compared to atezolizumab (MD 1.46, 95% CI 0.80 to 2.12; 1 study, 157 participants; low-certainty evidence; Analysis 12.4). We rated the certainty of evidence as low due to study limitations (selection, performance, detection, attrition and other bias) and imprecision, given that the CI was also compatible with no decrease in QoL.

Response rate (assessed with: RECIST v1.1)

Sunitinib may result in little to no difference in response rate as compared to atezolizumab (RR 1.14, 95% CI 0.72 to 1.79; 1 study, 204 participants; low-certainty evidence; Analysis 12.5). Based on the control event risk of 252 per 1000 in this trial, this corresponds to 35 more response (95% CI 71 fewer to 199 more) per 1000 participants. We rated the certainty of evidence as low due to study limitations (selection, performance, detection and other bias) and imprecision, given that the CI was also compatible with an appreciable increase in response rate.

Minor AEs (assessed with: CTCAE v4.0)

Sunitinib probably reduces minor AEs as compared to atezolizumab (RR 0.50, 95% CI 0.35 to 0.71; 1 study, 203 participants; moderate-certainty evidence; Analysis 12.6). Based on the control event risk of 563 per 1000 in this trial, this corresponds to 282 fewer minor AEs (95% CI 366 fewer to 163 fewer) per 1000 participants. We rated the certainty of evidence as moderate due to study limitations (selection, performance, detection and other bias).

Subgroup analysis

We were unable to perform any of the predefined subgroup analyses.

Sensitivity analysis

We were unable to perform a sensitivity analysis because there was only one study.

13. Bevacizumab + IFN versus IFN (+ placebo)

Please refer to Summary of findings 13.

Primary outcomes

PFS

Bevacizumab plus IFN probably increases PFS as compared to IFN (+ placebo) (HR 0.68, 95% CI 0.60 to 0.77; 2 studies, 1381 participants; I^2 = 14%; moderate-certainty evidence; Analysis 13.1). Based on the control event risk of 200 per 1000 in this trial at 12 months, this corresponds to 135 more PFSs (95% CI 90 more to 181 more) per 1000 participants. We rated the certainty of evidence as moderate due to study limitations (high and unclear risk of one or more domains).

OS

Bevacizumab + IFN may result in little to no difference in OS as compared to IFN (+ placebo) (HR 0.88, 95% CI 0.79 to 0.99; 2 studies, 1381 participants; I^2 = 0%; low-certainty evidence; Analysis 13.2). Based on the control event risk of 500 per 1000 in this trial at 24 months, this would result in 43 more OSs (95% CI 3 more to 78 more) per 1000 participants. We rated the certainty of evidence as low due to study limitations (high and unclear risk of one or more domains) and imprecision, given that the CI was also compatible with an increase in OS.

SAEs (assessed with: CTCAE v3.0)

Bevacizumab plus IFN probably increases SAEs as compared to IFN (+ placebo) (RR 1.31, 95% CI 1.20 to 1.42; 2 studies, 1356 participants; I^2 = 0%; moderate-certainty evidence; Analysis 13.3). Based on the control event risk of 536 per 1000 in this trial, this corresponds to 166 more SAEs (95% CI 107 more to 225 more) per 1000 participants. We rated the certainty of evidence as moderate due to study limitations (high and unclear risk of one or more domains).

Secondary outcomes

QoL

We found no studies that reported this outcome.

Response rate (assessed with: RECIST v1.0)

Bevacizumab plus IFN may increase response rate as compared to IFN (+ placebo) (RR 2.45, 95% CI 1.74 to 3.45; 1 study, 595 participants; low-certainty evidence; Analysis 13.4). Based on the control event risk of 128 per 1000 in this trial, this corresponds to 186 more response (95% CI 95 more to 314 more) per 1000 participants. We rated the certainty of evidence as low due to study limitations (unclear risk of other bias) and imprecision, given that the CI was also compatible with a small or no increase response rate.

Minor AEs (assessed with: CTCAE v3.0)

Bevacizumab plus IFN may reduce minor AEs (grade 1 or 2) as compared to IFN (+ placebo) (RR 0.75, 95% CI 0.63 to 0.90; 1 study, 641 participants; low-certainty evidence; Analysis 13.5). Based on the control event risk of 493 per 1000 in this trial, this corresponds to 123 fewer minor AEs (95% CI 183 fewer to 49 fewer) per 1000 participants. We rated the certainty of evidence as low due to study limitations (unclear risk of other bias) and imprecision, given that the CI was also compatible with a small or no reduction in minor AEs.

Subgroup analysis

We were unable to perform any of the predefined subgroup analyses.

Sensitivity analysis

We rated all of the included studies as high or unclear risk of bias and were unable to perform a sensitivity analysis.

14. Temsirolimus + IFN-α versus IFN-α

Please refer to Summary of findings 14.

Primary outcomes

PFS

Temsirolimus plus IFN-α may increase PFS as compared to IFN-α (HR 0.76, 95% CI 0.62 to 0.93; 1 study, 417 participants; low-certainty evidence; Analysis 14.1). Based on the control event risk of 100 per 1000 in this trial at 12 months, this corresponds to 74 more PFSs (95% CI 17 more to 140 more) per 1000 participants. We rated the certainty of evidence as low due to study limitations (performance and detection bias) and imprecision, given that the CI was also compatible with little to no increase in PFS.

OS

Temsirolimus plus IFN-α may result in little to no difference in OS as compared to IFN-α (HR 0.93, 95% CI 0.75 to 1.15; 1 study, 417 participants; low-certainty evidence; Analysis 14.2). Based on the control event risk of 300 per 1000 in this trial at 12 months, this would result in 26 more OSs (95% CI 50 fewer to 105 more) per 1000 participants. We rated the certainty of evidence as low due to imprecision (downgrade two levels), given that the CI was also compatible with both an appreciable reduction or increase in OS.

SAEs (assessed with: CTCAE version not reported)

Temsirolimus plus IFN-α may increase SAEs as compared to IFN-α (RR 1.12, 95% CI 1.02 to 1.22; 1 study, 408 participants; low-certainty evidence; Analysis 14.3). Based on the control event risk of 780 per 1000 in this trial, this corresponds to 94 more SAEs (95% CI 16 more to 172 more) per 1000 participants. We rated the certainty of evidence as low due to study limitations (performance and detection bias) and imprecision, given that the CI was also compatible with little to no increase in SAEs.

Secondary outcomes

QoL

Temsirolimus plus IFN-α may result in little to no difference in QoL (assessed with EQ-5D; scale −0.59 to 1.0 with higher scores indicating better QoL; MCID 0.06) as compared to IFN-α (MD 0.03, 95% CI −0.01 to 0.07; 1 study, 394 participants; low-certainty evidence; Analysis 14.4). We rated the certainty of evidence as low due to study limitations (performance, detection and attrition bias), and imprecision, given that the CI was also compatible with an increase in QoL.

Response rate (assessed with: RECIST version not reported)

Temsirolimus plus IFN-α may result in little to no difference in response rate as compared to IFN-α (RR 1.68, 95% CI 0.79 to 3.57; 1 study, 417 participants; low-certainty evidence; Analysis 14.5). Based on the control event risk of 48 per 1000 in this trial, this corresponds to 33 more response (95% CI 10 fewer to 124 more) per 1000 participants. We rated the certainty of evidence as low due to study limitations (performance, detection and attrition bias), and imprecision, given that the CI was also compatible with an appreciable increase in response rate.

Minor AEs (assessed with: CTCAE version not reported)

Temsirolimus plus IFN-α probably results in little to no difference in minor AEs (grade 1 or 2) as compared to IFN-α (RR 1.00, 95% CI 0.98 to 1.02; 1 study, 408 participants; moderate-certainty evidence; Analysis 14.6). Based on the control event risk of 985 per 1000 in this trial, this corresponds to zero fewer minor AEs (95% CI 20 fewer to 20 more) per 1000 participants. We rated the certainty of evidence as moderate due to study limitations (performance and detection bias).

Subgroup analysis

We were unable to perform any of the predefined subgroup analyses.

Sensitivity analysis

We were unable to perform a sensitivity analysis because there was only one study.

15. Temsirolimus + bevacizumab versus bevacizumab + IFN-α

Please refer to Summary of findings 15.

Primary outcomes

PFS

Temsirolimus plus bevacizumab may result in little to no difference in PFS as compared to bevacizumab plus IFN-α (HR 1.10, 95% CI 0.90 to 1.34; 1 study, 791 participants; low-certainty evidence; Analysis 15.1). Based on the control event risk of 420 per 1000 in this trial at 12 months, this corresponds to 35 fewer PFSs (95% CI 107 fewer to 38 more) per 1000 participants. We rated the certainty of evidence as low due to study limitations (performance bias) and imprecision, given that the CI was also compatible with an appreciable reduction in PFS.

OS

Temsirolimus plus bevacizumab probably results in little to no difference in OS as compared to bevacizumab plus IFN-α (HR 1.08, 95% CI 0.90 to 1.30; 1 study, 791 participants; moderate-certainty evidence; Analysis 15.2). Based on the control event risk of 550 per 1000 in this trial at 24 months, this would result in 26 fewer OSs (95% CI 90 fewer to 34 more) per 1000 participants. We rated the certainty of evidence as moderate due to imprecision, given that the CI was also compatible with a reduction in OS.

SAEs (assessed with: CTCAE v3.0)

Temsirolimus plus bevacizumab may result in little to no difference in SAEs (grade 3 or 4) as compared to bevacizumab plus IFN-α (RR 1.05, 95% CI 0.98 to 1.13; 1 study, 784 participants; low-certainty evidence; Analysis 15.3). Based on the control event risk of 760 per 1000 in this trial, this corresponds to 38 more SAEs (95% CI 15 fewer to 99 more) per 1000 participants. We rated the certainty of evidence as low due to study limitations (performance bias) and imprecision, given that the CI was also compatible with an appreciable increase in SAEs.

Secondary outcomes

QoL

Rini 2014 reported QoL measured by Functional Assessment of Cancer Therapy–Kidney Symptom Index (FKSI)–15, which contains 15 questions representing concerns specific to patients with advanced kidney cancer and FKSI-Disease Related Symptoms (FKSI-DRS) subscale. We could not obtain a mean and standard

deviation in each arm, however, and therefore we were unable to estimate this outcome.

Response rate (assessed with: RECIST version not reported)

Temsirolimus plus bevacizumab probably results in little to no difference in response rate as compared to bevacizumab plus IFN-α (RR 0.99, 95% CI 0.79 to 1.24; 1 study, 791 participants; moderate-certainty evidence; Analysis 15.4). Based on the control event risk of 274 per 1000 in this trial, this corresponds to 3 fewer response (95% CI 57 fewer to 66 more) per 1000 participants. We rated the certainty of evidence as moderate due to study limitations (performance bias).

Minor AEs (assessed with: CTCAE v3.0)

Temsirolimus plus bevacizumab probably results in little to no difference in minor AEs as compared to bevacizumab plus IFN-α (RR 1.01, 95% CI 0.98 to 1.03; 1 study, 784 participants; moderate-certainty evidence; Analysis 15.5). Based on the control event risk of 967 per 1000 in this trial, this corresponds to 10 more minor AEs (95% CI 19 fewer to 29 more) per 1000 participants. We rated the certainty of evidence as moderate due to study limitations (performance bias).

Subgroup analysis

We were unable to perform any of the predefined subgroup analyses.

Sensitivity analysis

We were unable to perform a sensitivity analysis because there was only one study.

16. Everolimus + bevacizumab versus IFN α-2a + bevacizumab

Please refer to Summary of findings 16.

Primary outcomes

PFS

We are very uncertain how everolimus plus bevacizumab affects PFS as compared to IFN α-2a plus bevacizumab (HR 0.91, 95% CI 0.69 to 1.20; 1 study, 365 participants; very low certainty evidence; Analysis 16.1). We rated the certainty of evidence as very low due to study limitations (selection, performance, detection and other bias, downgrade one level) and imprecision (downgrade two levels), given that the CI was compatible with both an appreciable reduction and increase in PFS.

OS

We are very uncertain how everolimus plus bevacizumab affects OS as compared to IFN α-2a plus bevacizumab (HR 1.01, 95% CI 0.75 to 1.36; 1 study, 365 participants; very low certainty evidence; Analysis 16.2). We rated the certainty of evidence as very low due to study limitations (selection and other bias, downgrade one level) and imprecision (downgrade two levels), given that the CI was compatible with both an appreciable reduction and increase in OS.

SAEs (assessed with: CTCAE v3.0)

Everolimus plus bevacizumab may result in little to no difference in SAEs as compared to IFN α-2a plus bevacizumab (RR 1.06, 95% CI 0.95 to 1.18; 1 study, 361 participants; low-certainty evidence; Analysis 16.3). Based on the control event risk of 762 per 1000 in this trial, this corresponds to 46 more SAEs (95% CI 38 fewer to 137 more) per 1000 participants. We rated the certainty of evidence as low due to study limitations (selection, performance, detection and other bias) and imprecision, given that the CI was also compatible with an appreciable increase in SAEs.

Secondary outcomes

QoL

Ravaud 2015 reported time to deterioration of global health status measured by the European Organisation for the Research and Treatment of Cancer (EORTC)-Core Quality of Life Questionnaire (QLQ-C30) (NCT00719264). We could not obtain a mean and standard deviation in each arm, however, and therefore we were unable to estimate this outcome.

Response rate (assessed with: RECIST v1.0)

Everolimus plus bevacizumab probably results in little to no difference in response rate as compared to IFN α-2a plus bevacizumab (RR 0.97, 95% CI 0.69 to 1.35; 1 study, 365 participants; moderate-certainty evidence; Analysis 16.4). Based on the control event risk of 279 per 1000 in this trial, this corresponds to 8 fewer response (95% CI 86 fewer to 98 more) per 1000 participants. We rated the certainty of evidence as moderate due to study limitations (selection, performance, detection and other bias).

Minor AEs (assessed with CTCAE v3.0)

Everolimus plus bevacizumab probably results in little to no difference in minor AEs as compared to IFN α-2a plus bevacizumab (RR 0.63, 95% CI 0.34 to 1.16; 1 study, 361 participants; moderate-certainty evidence; Analysis 16.5). Based on the control event risk of 133 per 1000 in this trial, this corresponds to 49 fewer minor AEs (95% CI 88 fewer to 21 more) per 1000 participants. We rated the certainty of evidence as moderate due to study limitations (selection, performance, detection and other bias).

Subgroup analysis

We were unable to perform any of the predefined subgroup analyses.

Sensitivity analysis

We were unable to perform a sensitivity analysis because there was only one study.

17. Sunitinib versus nivolumab + ipilimumab (Targeted agent versus combinations of immunotherapy)

Please refer to Summary of findings 17.

Primary outcomes

PFS

Sunitinib may reduce PFS as compared to nivolumab plus ipilimumab (HR 1.30, 95% CI 1.11 to 1.52; 1 study, 847 participants; low-certainty evidence; Analysis 17.1). Based on the control event risk of 280 per 1000 in this trial at 30 months, this corresponds to 89 fewer PFSs (95% CI 136 fewer to 37 fewer) per 1000 participants. We rated the certainty of evidence as low due to study limitations (performance and detection bias) and imprecision, given that the CI was also compatible with no reduction in PFS.

OS

Sunitinib reduces OS as compared to nivolumab plus ipilimumab (HR 1.52, 95% CI 1.23 to 1.89; 1 study, 847 participants; high-certainty evidence; Analysis 17.2). Based on the control event risk 600 per 1000 in this trial at 30 months, this would result in 140 fewer OSs (95% CI 219 fewer to 67 fewer) per 1000 participants. We rated the certainty of evidence as high.

SAEs (assessed with: CTCAE v4.0)

Sunitinib probably increases SAEs (grade 3 or 4) as compared to nivolumab plus ipilimumab (RR 1.37, 95% CI 1.22 to 1.53; 1 study, 1082 participants; moderate-certainty evidence; Analysis 17.3). Based on the control event risk of 457 per 1000 in this trial, this corresponds to 169 more SAEs (95% CI 101 more to 242 more) per 1000 participants. We rated the certainty of evidence as moderate due to study limitations (performance and detection bias).

Secondary outcomes

QoL

Sunitinib probably reduces QoL (assessed with FKSI-19; scale 0 to 76 with higher scores indicating better QoL; MCID: 2) as compared to nivolumab plus ipilimumab (MD −4.10, 95% CI −5.75 to −2.45; 1 study, 460 participants; moderate-certainty evidence; Analysis 17.4). We rated the certainty of evidence as moderate due to study limitations (performance, detection and attrition bias).

Response rate (assessed with: RECIST v1.1)

Sunitinib may reduce response rate as compared to nivolumab plus ipilimumab (RR 0.70, 95% CI 0.58 to 0.84; 1 study, 847 participants; low-certainty evidence; Analysis 17.5). Based on the control event risk of 419 per 1000 in this trial, this corresponds to 126 fewer response (95% CI 176 fewer to 67 fewer) per 1000 participants. We rated the certainty of evidence as low due to study limitations (performance and detection bias) and imprecision, given that the CI was also compatible with little to no reduction in response rate.

Minor AEs (assessed with CTCAE v4.0)

Sunitinib may reduce minor AEs as compared to nivolumab plus ipilimumab (RR 0.74, 95% CI 0.64 to 0.86; 1 study, 1082 participants; low-certainty evidence; Analysis 17.6). Based on the control event risk of 459 per 1000 in this trial, this corresponds to 119 fewer minor AEs (95% CI 165 fewer to 64 fewer) per 1000 participants. We rated the certainty of evidence as low due to study limitations (performance and detection bias) and imprecision, given that the CI was compatible with little to no reduction in minor AEs.

Subgroup analysis

We were unable to perform any of the predefined subgroup analyses.

Sensitivity analysis

We were unable to perform a sensitivity analysis because there was only one study.

18. Pazopanib versus placebo (targeted agent versus placebo)

Please refer to Summary of findings 18.

Primary outcomes

PFS

Pazopanib increases PFS as compared to placebo (HR 0.46, 95% CI 0.34 to 0.62; 1 study, 435 participants; high-certainty evidence; Analysis 18.1). Based on the control event risk of 180 per 1000 in this trial at 12 months, this corresponds to 274 more PFSs (95% CI 165 more to 378 more) per 1000 participants.

OS

Pazopanib may result in little to no difference in OS as compared to placebo (HR 0.91, 95% CI 0.72 to 1.16; 1 study, 435 participants; low-certainty evidence; Analysis 18.2). Based on the control event risk of 480 per 1000 in this trial at 24 months, this would result in 33 more OSs (95% CI 53 fewer to 110 more) per 1000 participants. We rated the certainty of evidence as low due to imprecision (downgrade two levels), given that the CI was both compatible with an appreciable reduction and increase in OS.

SAEs (assessed with CTCAE v3.0)

Pazopanib increases SAEs as compared to placebo (RR 2.00, 95% CI 1.40 to 2.85; 1 study, 435 participants; high-certainty evidence; Analysis 18.3). Based on the control event risk in this trial of 200 per 1000, this corresponds to 200 more SAEs (95% CI 80 more to 370 more) per 1000 participants.

Secondary outcomes

QoL

Pazopanib results in little to no difference in QoL (assessed with EORTC QLQ-C30; scale 0 to 100 with higher values reflecting better QoL; MCID 10) as compared to placebo (MD −3.10, 95% CI −7.76 to 1.56; 1 study, 300 participants; high-certainty evidence; Analysis 18.4).

Response rate (assessed with: RECIST v1.0)

Pazopanib probably increases response rate as compared to placebo (RR 8.80, 95% CI 3.65 to 21.19; 1 study, 435 participants; moderate-certainty evidence; Analysis 18.5). Based on the control event risk of 34 per 1000 in this trial, this corresponds to 269 more response (95% CI 91 more to 696 more) per 1000 participants. We rated the certainty of evidence as moderate due to imprecision, given that the CI was also compatible with little to no increase in response rate.

Minor AEs (assessed with CTCAE v3.0)

Pazopanib probably increases minor AEs as compared to placebo (RR 1.31, 95% CI 1.13 to 1.52; 1 study, 435 participants; moderate-certainty evidence; Analysis 18.6). Based on the control event risk of 600 per 1000 in this trial, this corresponds to 186 more minor AEs (95% CI 78 more to 312 more) per 1000 participants. We rated the certainty of evidence as moderate due to imprecision, given that the CI was also compatible with little to no increase in minor AEs.

Subgroup analysis

We were unable to perform any of the predefined subgroup analyses.

Sensitivity analysis

We were unable to perform a sensitivity analysis because there was only one study.

DISCUSSION

For this review, we considered targeted therapies as the index intervention. This group of drugs included VEGFR-TKIs (e.g. sunitinib, sorafenib, pazopanib, tivozanib and axitinib), VEGF-inhibitors (e.g. bevacizumab) and mTOR inhibitors (e.g. everolimus or temsirolimus). Comparators included placebo, alternative targeted therapy (i.e. targeted therapy vs targeted therapy), cytokines (i.e. classic non-targeted immunotherapy, e.g. interferon-alpha), immune checkpoint inhibitors, or combinations of different classes of drugs. Immune checkpoint inhibitors included programmed death 1 inhibitors (PD-1), programmed death ligand 1 inhibitors (PD-L1) and cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) inhibitors (e.g. avelumab, pembrolizumab, atezolizumab, nivolumab and ipilimumab).

Summary of main results

One trial compared targeted agent (pazopanib) against placebo (Summary of findings 18). There was high quality evidence showing pazopanib was significantly superior to placebo in terms of PFS, but inferior in terms of incidence of SAEs. There was low certainty evidence showing no difference between the groups in terms of OS.

For the intra-group comparison of single-agent targeted therapy against each other, we found some differences between them (Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5). Pazopanib and tivozanib were both superior to sorafenib in terms of PFS but there were some differences in terms of OS; the certainty of evidence was moderate for pazopanib for PFS and low for OS but low for tivozanib for both PFS and OS. Sunitinib was superior to everolimus for PFS although there was no difference for OS, with moderate to low certainty of evidence for both outcomes. Sorafenib was inferior to sunitinib for PFS but there was no difference for OS (low and very low certainty evidence, respectively), nor between pazopanib versus sunitinib for PFS and OS (low certainty evidence for both). For AE, there was very low to low-certainty evidence that there were no statistically significant differences between the drugs, except for sunitinib versus everolimus; sunitinib appeared to have a higher incidence of SAEs compared with everolimus (moderate-certainty evidence).

Next, for the comparison of targeted therapy versus cytokines (i.e. classic non-targeted immunotherapy, Summary of findings 10; Summary of findings 11; Summary of findings 13; Summary of findings 14; Summary of findings 15; Summary of findings 16), there was low- to moderate-certainty evidence showing that single-agent targeted therapy was superior to single-agent interferon-alpha for PFS and OS (for sunitinib and temsirolimus). Regarding the incidence of SAEs, temsirolimus was better than interferon-alpha (low-certainty evidence), but sunitinib was worse than interferon-alpha (moderate-certainty evidence). The results for the comparison between combination of targeted therapies with each other or with interferon-alpha versus single-agent interferon-alpha suggest combinations of targeted therapy involving either bevacizumab or temsirolimus with interferon-alpha are superior to single-agent interferon-alpha for PFS (low- to moderate-certainty evidence) but there was no difference in OS (low-certainty evidence); however the targeted therapy combinations had a significantly higher incidence of SAEs (low- to moderate-certainty evidence). The comparison of combinations of targeted therapy (temsirolimus and bevacizumab, and everolimus and bevacizumab) versus combination of bevacizumab and interferon-alpha did not show any differences in PFS, OS nor SAEs (very low to moderate-certainty evidence).

For the comparison of targeted therapy versus combination of tumour vaccine (IMA901) with sunitinib, (Summary of findings 9), there was low-certainty evidence that single-agent sunitinib had significantly better OS and better SAEs profile compared with combination of IMA901 plus sunitinib.

For the comparison of single-agent targeted therapy (all based on sunitinib) versus immune checkpoint inhibitor, the results can be summarised into three sub-sections: (1) sunitinib versus single-agent immune checkpoint inhibitor (atezolizumab, Summary of findings 12); (2) sunitinib versus combination of targeted drug with immune checkpoint inhibitor (axitinib + avelumab; axitinib + pembrolizumab; and bevacizumab + atezolizumab; Summary of findings 6; Summary of findings 7; Summary of findings 8); and (3) sunitinib versus combination of immune checkpoint inhibitors (nivolumab + ipilimumab, Summary of findings 17). For the comparison of sunitinib versus atezolizumab, there were no significant differences between them for PFS and OS (very low certainty evidence); however, sunitinib had worse incidence of SAEs (moderate certainty evidence). For the comparison of sunitinib versus combination of targeted therapy with immune checkpoint inhibitor, sunitinib appeared to have worse PFS than two of the combinations (moderate-certainty evidence) and worse OS (moderate-certainty evidence) than one combination of targeted drug and immune checkpoint inhibitor; Sunitinib may have no difference or less SAEs compared to combinations (low-certainty evidence). Finally, for the comparison of sunitinib versus combination of immune checkpoint inhibitors (nivolumab + ipilimumab), sunitinib had worse PFS (low-certainty evidence), worse OS (high-certainty evidence) and worse incidence of SAEs (moderate-certainty evidence) compared with the combination of nivolumab and ipilimumab. Sunitinib was also associated with worse QoL (moderate-certainty evidence) and worse response rate (low-certainty evidence).

In summary, when comparing targeted therapy (i.e. sunitinib) against immune checkpoint inhibitor either singly or in combination, there was high- to moderate-quality evidence (from two trials) demonstrating sunitinib was inferior to a combination of targeted therapy with immune checkpoint inhibitor (i.e. axitinib + pembrolizumab), and a combination of immune checkpoint inhibitors (i.e. nivolumab + ipilimumab), in terms of OS. The result for PFS was also worse for sunitinib compared with the other combinations involving immune checkpoint inhibitors, with low- to moderate-certainty evidence across all studies. There was also moderate-quality evidence from two studies that sunitinib had worse incidence of SAEs compared with immune checkpoint inhibitors (involving atezolizumab as single agent, and nivolumab + ipilimumab combination). Although sunitinib was the comparator in all of those trials, a meta-analysis was only possible for the two studies which used the combination of atezolizumab and bevacizumab. This was due to considerable clinical heterogeneity across the trials namely in the use of eligibility criteria, primary endpoints (e.g. results reported only for the intention-to-treat the population or those with PD-L1 expression on tumour cells or tumour-infiltrating lymphocytes), inconsistent use validated risk scores such as the Memorial Sloan Kettering Cancer Center (MSKCC)

or International Metastatic RCC Database Consortium (IMDC) risks models, and experimental drugs used.

Overall completeness and applicability of evidence

We identified studies to include in this review by independent searches. Results were comparable and we resolved disagreements by discussion within the author group. We also identified trials through hand searching of conference proceedings and tried to acquire additional data whenever they were needed by contacting authors.

Participants were comparable amongst the identified studies, which all had a multicentre design. All except two trials (Motzer 2013b and Sternberg 2010) had a homogeneous population which had not received previous treatment. A phase 3 study was the favoured trial design which was used in 15 trials. Another three used a phase 2 design. All included studies investigated our primary and secondary outcomes except for QoL data, which was not available in seven trials.

We imposed strict criteria for study inclusion for methodological reasons which excluded studies with less than 100 participants per arm. This meant excluding the CABOSUN trial comparing cabozantinib versus sunitinib, an initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk (n = 157 in total) (Choueiri 2017). Guidelines panels of ESMO and EAU consider cabozantinib an alternative for IMDC intermediate- and poor-risk patients only who cannot receive immune checkpoint inhibitor combination therapies but on the same par as sunitinib and pazopanib, which have been tested in randomised controlled phase 3 trials in this setting (EAU Guidelines 2020; ESMO Clinical Practice Guidelines 2019). This decision was taken because CABOSUN was a randomised phase 2 trial in which cabozantinib had a PFS but no OS benefit compared to sunitinib. This was considered not enough evidence to argue that cabozantinib is qualitatively superior to sunitinib.

Quality of the evidence

We used GRADE to rate the quality of evidence and created 18 'Summary of findings' tables for the different comparisons. We rated most of the comparisons at a low to moderate level of evidence. The main reasons for downgrading were study limitations, especially those due to lack of blinding with the risk of performance and detection bias. Imprecision was another important factor for lowering the certainty of evidence in efficacy outcomes.

Potential biases in the review process

Two reviewers screened all search results independently. There were no language restrictions but all identified studies were published in the English language. We did not receive additional data after contacting authors except for one study, which could be a source of bias.

After publication of our protocol we amended our inclusion criteria. We chose to limit the number of participants to a minimum of 100 per study arm to ensure our evidence synthesis was based on more robust data by reducing the risk of small-study bias. We also chose to only include participants who were naïve to systemic therapy. This decision was mainly driven by the large number of studies assessing patients with metastatic renal cell carcinoma in the second-line treatment setting or beyond. Including these trials would have distracted us from the main focus of our review which was on the first-line treatment setting, and the burden of work would have become unfeasibly high.

For the interpretation of clinically important effect sizes, we used absolute effect estimates that were informed by the input of expert clinicians on our team; unless there were published thresholds (as was the case for quality of life instruments) we used 5% for the most patient-important primary outcomes of PFS and OS and 10% for the secondary outcomes of response rates and minor AEs. We recognise that different thresholds might lead to different interpretations and have therefore made all our judgments as transparent as possible.

Agreements and disagreements with other studies or reviews

A systematic review with a broader approach on systemic treatment for metastatic renal cell carcinoma was published in 2018 (Lalani 2018). In total 26 trials were identified for first and later line treatments. All studies of that review that met our inclusion criteria were also identified and included in our review. The authors expected combinations therapies to become the new promising standard of care in treatment-naïve renal cell carcinoma.

Another systematic review, also published in 2018, was focusing on first line systemic therapy for metastatic renal cell carcinoma (Wallis 2018). Of the 37 identified trials for a qualitative synthesis 13 were eligible for a quantitative synthesis. All trials that meet our inclusion criteria were part of our review. Cabozantinib was judged as being highly likely to provide the greatest PFS benefit, while the combination of nivolumab plus ipilimumab was most likely to provide the greatest OS benefit. The later combination was rated likely to have the most beneficial tolerance profile.

AUTHORS' CONCLUSIONS

Implications for practice

Single-agent vascular endothelial growth factor receptor-tyrosine kinase inhibitors (VEGFR TKI), having being the first-line treatment option in the management of metastatic RCC for years, appear to have been superseded by combinations of immune checkpoint inhibitors. However targeted therapy drugs have proved to be an effective treatment for those who cannot receive or tolerate immune checkpoint inhibition.

At present two immune checkpoint inhibitor-based combinations with proven OS benefit are available as new standard of care for first-line treatment of clear-cell mRCC (EAU Guidelines 2020; ESMO Clinical Practice Guidelines 2019). In terms of comparative effectiveness within this new group of drugs, interpretation of data is limited by the short follow-up of studies. ORR and PFS appear higher for the pembrolizumab plus axitinib combination than for ipilimumab plus nivolumab. With regard to complete response rates, it is possible they may improve for pembrolizumab plus axitinib, but decisive conclusions cannot be drawn at this stage.

Implications for research

Results of this review underpin the trend towards a wider field of application for targeted immunotherapy agents alone or in combination with classic targeted therapy in the first-line setting. However, some of these drugs are already successfully used in

further lines for treating metastatic renal cell carcinoma patients. Further research is needed to answer the question of how to sequence therapies. This is of special importance now that combinations of immune checkpoint inhibitors (pembrolizumab) and VEGFR-TKI (axitinib) are being used in treatment-naive patients. While it would be intuitive to use a VEGFR-TKI upon progression with dual immune checkpoint inhibitor combination such as ipilimumab and nivolumab this is less clear for combinations with VEGFR-TKI in the first-line treatment setting. In addition, some trials are investigating triple combinations such as ipilimumab plus nivolumab plus cabozantinib (Choueiri 2019), based on the emerging evidence that immune checkpoint inhibitor combination therapies are more effective than the same drugs in sequence.

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CHARACTERISTICS OF STUDIES

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

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* Indicates the major publication for the study

Eichelberg 2015

Study characteristics	
Methods	**Study type:** multicentre RCT
	Phase: 3
	Accrual period: February 2009 to December 2011
	Blinding: open label study
	Strata: MSKCC risk category
	IMC: data not found
	Crossover: from first to second line after disease progression
Participants	**Histology:** all histologies
	Prior systemic therapy: treatment-naïve
	Measurable disease: required
	Non-metastatic %: combined data not found
	M/F: 274/91
	Eligible PS: ECOG PS 1 or better

Eichelberg 2015 *(Continued)*

	Age median (range): 65 (39 to 84) **Prior nephrectomy:** 335 **Prognostic strata: system, good/intermediate/poor risk:** MSKCC; 153/202/2
Interventions	sorafenib 400 mg po twice daily followed, on progression or toxicity, by sunitinib 50 mg po daily 4 wks on, 2 wks off or vice versa
Outcomes	**PFS:** primary outcome (time from randomisation to confirmed progression or death during second-line therapy); secondary outcome (time from randomisation to confirmed progression or death during first-line therapy) **OS:** secondary endpoint **AE:** reported in toxicity table **QoL:** not analysed **RR:** secondary outcome **Other:** disease control rate, total time to progression, time to first-line treatment failure, cardiotoxicity
Funding Sources	German Cancer Society (DKG), Austrian Social Security Institutions, grants from industry study sponsor
Declarations of interest	Reported
Notes	Planned as a non-inferiority study, amended to a superiority design; power reduced from 90% to 85% due to slower rate of events than expected

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Central randomisation via fax"
Allocation concealment (selection bias)	Low risk	"the person who generated the randomisation list was not involved in the study project management, monitoring, or data management."
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Open label study design, participants and personnel not blinded to treatment; no effect on OS expected
Blinding of participants and personnel (performance bias) Subjective outcomes	High risk	Open label study design, participants and personnel not blinded to treatment; both arms treated with same drugs in different sequence
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Assessed by investigator; no effect on OS expected
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	PFS assessed by investigator
Incomplete outcome data (attrition bias)	Low risk	All patients reported, 5/7 did not receive treatment in first line

Eichelberg 2015 *(Continued)*
PFS, OS

Incomplete outcome data (attrition bias) Response rate	Low risk	All patients reported, 5/7 did not receive treatment in first line
Incomplete outcome data (attrition bias) Serious and minor adverse events	Low risk	All treated patients in first and second line reported
Selective reporting (reporting bias)	Low risk	All planned outcomes reported
Other bias	Unclear risk	Study design changed from non-inferiority design to superiority design after randomisation of 138 participants

Escudier 2010

Study characteristics	
Methods	**Study type:** multicentre RCT **Phase:** 3 **Accrual period:** June 2006 to October 2005 **Blinding:** double-blind study **Strata:** country, risk group **IMC:** data safety monitoring board used **Crossover:** not planned but at preplanned interim OS analysis, difference in PFS clinically and statistically significant and DSMB recommended that patients in the control group who had not experienced progression should cross over to receive bevacizumab
Participants	**Histology:** clear cell **Prior systemic therapy:** treatment-naïve **Measurable disease:** required **Non metastatic %:** data not found **M/F:** 457/192 **Eligible PS:** Karnofsky > 60 **Age median (range):** 61 (18 to 82) **Prior nephrectomy:** required **Prognostic strata: system, good/intermediate/poor risk %:** MSKCC 30/61/9
Interventions	Interferon-a2a 9 MU sc tiw (subcutaneous thrice weekly) plus either (1) BEVACIZUMAB 10 mg/kg IV q2w, or (2) placebo [crossed over at final PFS analysis if not progressed]
Outcomes	**PFS:** reported [protocol modified to permit final PFS analysis before mature OS data]

Escudier 2010 *(Continued)*

	OS: primary endpoint **AE:** reported in toxicity table **QoL:** not assessed **RR:** secondary outcome **Other:** -
Funding Sources	Industry sponsored
Declarations of interest	Reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“randomization was done centrally”
Allocation concealment (selection bias)	Low risk	Clearly described; interactive voice recognition system
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	"Double blind placebo controlled trial". Participants and personnel were blinded to treatment
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	"Double blind placebo controlled trial". Participants and personnel were blinded to treatment
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Investigator assessed, no effect on OS expected
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	PFS assessed by investigator who were blinded to treatment
Incomplete outcome data (attrition bias) PFS, OS	Low risk	4% in each arm lost or withdrew consent; intention to treat population analysed
Incomplete outcome data (attrition bias) Response rate	Low risk	4% in each arm lost or withdrew consent; intention to treat population analysed
Incomplete outcome data (attrition bias) Serious and minor adverse events	Low risk	All treated participants analysed
Selective reporting (reporting bias)	Low risk	All protocol endpoints reported

Escudier 2010 *(Continued)*

Other bias	Unclear risk	Early unblinding and addition of bevacizumab; recommended for unprogressed placebo-assigned patients by independent monitoring committee based on unplanned final PFS and preplanned interim survival analysis

Escudier 2017

Study characteristics	
Methods	**Study design:** multicentre RCT **Phase:** 3 **Accrual period:** October 2014 to February 2016 **Blinding:** open label study design **Strata:** IMDC score, region **IMC (independent monitoring committee):** a data and safety monitoring committee reviewed efficacy and safety **Crossover:** not planned
Participants	**Histology:** clear cell **Prior systemic therapy:** treatment-naïve **Measurable disease:** required **Non metastatic %:** data not found; at least 78% of participants had 2 or more target or non-target lesions **M/F:** 808/288 **Eligible PS:** Karnofsky PS 70% or better **Age median:** 62 (21 to 85) **Prior nephrectomy:** 890 **Prognostic strata: system, % good/intermediate/poor/NA risk:** IMDC risk score (0 vs. 1 or 2 vs. 3 to 6) and geographic region
Interventions	nivolumab 3 mg/kg + ipilimumab 1 mg/kg every 3 wk for 4 doses followed by nivolumab 3 mg/kg every 2 wk vs sunitinib 50 mg daily orally for 4 wk (6-wk cycles)
Outcomes	**PFS:** primary endpoint **OS:** primary endpoint **AE:** toxicity table reported **QoL:** reported **RR:** primary endpoint **Other:** -
Funding Sources	Industry sponsored

Escudier 2017 *(Continued)*

Declarations of interest	Published online
Notes	Stopped early

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Begins with the randomization call to the Interactive Voice Response System (IVRS)" (from protocol)
Allocation concealment (selection bias)	Low risk	"Begins with the randomization call to the Interactive Voice Response System (IVRS)" (from protocol)
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	"Open-label, phase 3 trial" participants and personnel were not blinded to treatment; no effect on OS expected
Blinding of participants and personnel (performance bias) Subjective outcomes	High risk	"Open-label, phase 3 trial" participants and personnel were not blinded to treatment
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	No effect on OS expected
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	(from protocol) Progression free survival; Tumor assessments for ongoing study treatment decisions will be completed by the investigator using RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 criteria Health related quality of life, Minor adverse events; Open label trial
Incomplete outcome data (attrition bias) PFS, OS	Low risk	All IMDC intermediate and poor risk patients analysed for efficacy as predefined outcome
Incomplete outcome data (attrition bias) Response rate	Low risk	All IMDC intermediate and poor risk patients analysed for efficacy as predefined outcome
Incomplete outcome data (attrition bias) Serious and minor adverse events	Low risk	All treated participants analysed
Incomplete outcome data (attrition bias) Quality of life	Unclear risk	More than 80% completion rate in both groups but final analysed participants were 44/425 (10.3%) in Nivolumab + Ipilimumab arm and 26/422 (6.1%) in sunitinib arm.
Selective reporting (reporting bias)	Low risk	All planned outcomes reported
Other bias	Low risk	Completed planned accrual

Hudes 2007

Study characteristics	
Methods	**Study type:** multicentre RCT **Phase:** 3 **Accrual period:** June 2003 to April 2005 **Blinding:** imaging **Strata:** according to the geographic location of the centre and nephrectomy status **IMC:** an independent data and safety monitoring committee reviewed the study at 6-month intervals **Crossover:** not allowed
Participants	**Histology:** all histologies **Prior therapy:** naïve **Measurable disease:** required (RECIST)Non metastatic %: <20M/F: 432/194 **Eligible PS:** Karnofsky > 50; actual KPS(> 70) = 17% **Age median (range):** 59 (23 to 86) **Prior nephrectomy:** 419 **Prognostic strata: system, % good/intermediate/poor risk:** MSKCC, -/26/74%
Interventions	TEMSIROLIMUS 25mg IV weekly, Interferon-a2a 3-18MU sc tiw, or both
Outcomes	**PFS:** secondary endpoint **OS:** primary endpoint **AE:** reported in toxicity table **QoL:** reported **RR:** (RECIST) **Other:** -
Funding Sources	Industry sponsored
Declarations of interest	Reported in main publication
Notes	Only poor risk (76%) and intermediate risk (26%) patients included in trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomly assigned in equal proportions, with the use of permuted blocks of three, to one of three treatment groups." Central randomisation presumed
Allocation concealment (selection bias)	Low risk	"Patients were randomly assigned in equal proportions, with the use of permuted blocks of three, to one of three treatment groups." Central randomisation presumed

Hudes 2007 *(Continued)*

Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Participants and personnel were not blinded to treatment, no effects on OS expected
Blinding of participants and personnel (performance bias) Subjective outcomes	High risk	Participants and personnel were not blinded to treatment, active treatment in all 3 groups
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Unblinded clinical investigator assessment, no effects on OS expected
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	Shorter investigator assessed PFS in comparison to independent radiologic assessment; which is explained by different inclusion criteria
Incomplete outcome data (attrition bias) PFS, OS	Low risk	Intention-to-treat population reported
Incomplete outcome data (attrition bias) Response rate	High risk	82% of ITT population reported; only selected participants included in analysis which underwent tumour assessment after the baseline
Incomplete outcome data (attrition bias) Serious and minor adverse events	Low risk	All treated participants reported
Incomplete outcome data (attrition bias) Quality of life	High risk	65% of participants were evaluable for QoL analysis
Selective reporting (reporting bias)	Low risk	All planned outcomes reported
Other bias	Low risk	Completed planned accrual; stopped early at the second interim analysis

McDermott 2018

Study characteristics	
Methods	**Study type:** multicentre RCT **Phase:** 2 **Accrual period:** January 2014 to March 2015 **Blinding:** open label design **Strata:** MSKCC risk category, prior nephrectomy status, and PD-L1 status **IMC:** "Independent review facility-assessed efficacy endpoints" **Crossover:** allowed

McDermott 2018 *(Continued)*

Participants	**Histology:** clear cell **Prior systemic therapy:** treatment-naïve **Eligible PS:** Karnowsky PS 70% or better **Measurable disease:** required **Non metastatic %:** not specified **M/F:** 230/75 **Age median (range):** 61 **Prior nephrectomy:** 184 **Prognostic strata: system, good/intermediate/poor risk:** MSKCC, 77/201/27
Interventions	atezolizumab 1200 mg IV q3w + bevacizumab 15 mg/kg IV q3w, atezolizumab alone or sunitinib 50 mg PO QD 4 wk on/2 wk off
Outcomes	**PFS:** co-primary endpoint **OS:** secondary endpoint **AE:** reported **QoL:** exploratory outcome **RR:** secondary endpoint **Other:** primary endpoint: percentage of participants with disease progression per response evaluation
Funding Sources	Industry sponsored
Declarations of interest	Published online
Notes	Crossover to atezolizumab + bevacizumab arm allowed on progression

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"interactive voice/web response system (IxRS)" used; "Stratified permuted block randomization was used to assign patients in a 1:1:1 ratio to one of three treatment arms"
Allocation concealment (selection bias)	High risk	"allocation was unmasked"
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	"The study was open-label"; participants and personnel were not blinded to treatment; no effect on OS expected
Blinding of participants and personnel (performance bias) Subjective outcomes	High risk	"The study was open-label"; participants and personnel were not blinded to treatment, all participants received an active treatment with different administration forms

McDermott 2018 *(Continued)*

Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Independent review facility (IRF)-assessed efficacy
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	Independent review facility (IRF)-assessed efficacy, no blinding used
Incomplete outcome data (attrition bias) PFS, OS	Low risk	ITT population reported, 1 patient did not receive treatment
Incomplete outcome data (attrition bias) Response rate	Low risk	ITT population reported, 1 patient did not receive treatment
Incomplete outcome data (attrition bias) Serious and minor adverse events	Low risk	All treated participants included in safety analysis
Incomplete outcome data (attrition bias) Quality of life	Low risk	"96 (95%) of 101 patients in the atezolizumab plus bevacizumab group and 93 (92%) of 101 patients in the sunitinib group completed the MDASI at baseline"
Selective reporting (reporting bias)	Low risk	All planned outcomes except for quality of life reported
Other bias	Unclear risk	Industry sponsored

Motzer 2010

Study characteristics	
Methods	**Study type:** multicentre RCT **Phase:** 3 **Accrual period:** August 2004 to October 2005 **Blinding:** imaging **Strata:** LDH, PS, nephrectomy status **IMC:** used for data and safety **Crossover:** study amended when sunitinib approved in January 2006 to allow cross-over of patients on IFN on documented disease progression as primary endpoint of PFS had been met – agreed with IMC
Participants	**Histology:** clear cell **Prior systemic therapy:** treatment-naïve **Measurable disease:** required **Non metastatic %:** metastatic disease required **M/F %:** 536/214

Motzer 2010 *(Continued)*

	Eligible PS: ECOG 0 to 1 **Age median (range):** 61 (27 to 87) **Prior nephrectomy:** 675 **Prognostic strata: system, good/intermediate/poor risk %:** MSKCC, 37/56/7%
Interventions	(1) SUNITINIB 50 mg oral daily for 4 weeks of 6-week cycle; (2) Interferon-alfa2a 9 MU sc tiw (with cross-over to SUNITINIB at disease progression, after second interim analysis)
Outcomes	**PFS:** primary endpoint **OS:** secondary endpoint **AE:** toxicity table, secondary endpoint **QoL:** secondary endpoint (FACT-G, FKSI) **RR:** secondary endpoint **Other:** cross-over post study
Funding Sources	Industry sponsored
Declarations of interest	Reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“patients were randomly assigned”, presumed central randomisation
Allocation concealment (selection bias)	Unclear risk	Data not found
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Open label study design, participants and personnel were not blinded to treatment, no effect on OS expected
Blinding of participants and personnel (performance bias) Subjective outcomes	High risk	Open label study design, participants and personnel were not blinded to treatment, 2 active treatments used with different administration forms
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Assessed by investigator, no effect on OS expected
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	"A blinded central review of radiologic images was used to assess the primary end point and the objective response rate"
Incomplete outcome data (attrition bias)	Low risk	8% of patients withdrew consent on the control arm (vs 1%, P < 0.001) but primary end- point was analysed by allocation

Motzer 2010 *(Continued)*
PFS, OS

Incomplete outcome data (attrition bias) Response rate	Low risk	All randomised participants analysed
Incomplete outcome data (attrition bias) Serious and minor adverse events	Low risk	All treated participants analysed
Incomplete outcome data (attrition bias) Quality of life	Unclear risk	No information on how many participants completed questionnaire found
Selective reporting (reporting bias)	Low risk	All planned outcomes reported
Other bias	High risk	Cross-over permitted after second interim analysis but planned accrual had been completed, OS analysis secondary endpoint

Motzer 2013a

Study characteristics	
Methods	**Study type:** multicentre RCT **Phase:** 3 **Accrual period:** Aug 2008 to Sep 2011 **Blinding:** open label design **Strata:** Karnofsky PS, LDH, nephrectomy status **IMC:** safety reviewed **Crossover:** not allowed
Participants	**Histology:** clear cell component **Prior systemic therapy:** treatment-naïve **Eligible PS:** Karnofsky 70% or more **Measurable disease:** required **Non metastatic %:** < 20 **M/F:** 813/297 **Age median (range):** 61 (18 to 88) **Prior nephrectomy:** 924 **Prognostic strata: system, good/intermediate/poor risk:** MSKCC, 303/650/119
Interventions	pazopanib 800 mg po vs sunitinib 50 mg po 4 wks on, 2 wks off
Outcomes	**PFS:** primary outcome as non-inferiority measure

Motzer 2013a *(Continued)*

	OS: secondary outcome **AE:** reported in toxicity table, secondary outcome **QoL:** secondary outcome **RR:** secondary outcome **Other:** medical resource utilization
Funding Sources	Industry sponsored
Declarations of interest	Published online
Notes	Non-inferiority design

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“GSK interactive voice response system called RAMOS (Registration And Medication Ordering System), by the investigator or authorized site staff for stratification and central randomization.” from protocol
Allocation concealment (selection bias)	Low risk	“GSK interactive voice response system called RAMOS (Registration And Medication Ordering System), by the investigator or authorized site staff for stratification and central randomization.” from protocol
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Open label study design, participants and personnel were not blinded to treatment, OS reported as secondary outcome
Blinding of participants and personnel (performance bias) Subjective outcomes	High risk	Open label study design, participants and personnel were not blinded to treatment, oral administered, active drugs used in both arms
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Not specifically reported but no effect on OS expected
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	"The primary end point was progression-free survival as assessed by independent review"; tumour response and PFS assessed independently, lack of blinding
Incomplete outcome data (attrition bias) PFS, OS	Low risk	ITT population assessed, 8 patients not treated
Incomplete outcome data (attrition bias) Response rate	Low risk	ITT population assessed, 8 patients not treated
Incomplete outcome data (attrition bias) Serious and minor adverse events	Low risk	All treated participants assessed

Motzer 2013a *(Continued)*

Incomplete outcome data (attrition bias) Quality of life	High risk	High losses in questionnaire completion rates
Selective reporting (reporting bias)	Low risk	All planned outcomes reported
Other bias	Unclear risk	Protocol amended to increase sample size for planned events, non-inferiority design

Motzer 2013b

Study characteristics	
Methods	**Study design:** multicentre RCT **Phase:** 3 **Accrual period:** February 2010 to August 2010 **Blinding:** open label design **Strata:** region, number of prior treatments, number of metastatic sites and organs involved **IMC:** data monitored not specified **Crossover:** at progression
Participants	**Histology:** clear cell component **Prior systemic therapy:** treatment-naïve; except for immunotherapy, chemotherapy, or hormonal therapy **Eligible PS:** ECOG PS 1 or better **Measurable disease:** required **Non metastatic %:** ≤ 21 **M/F:** 374/143 **Age median (range):** 59 (23 to 85) **Prior nephrectomy:** required **Prognostic strata: system, good/intermediate/poor risk:** MSKCC 157/333/27
Interventions	tivozanib 1.5 mg, 3 wks on/1 wks off vs sorafenib 400 mg bid
Outcomes	**PFS:** primary outcome **OS:** secondary outcome **AE:** secondary outcome **QoL:** secondary outcome **RR:** secondary outcome **Other:** tolerability, kidney specific symptoms

Motzer 2013b *(Continued)*

Funding Sources	Industry sponsored
Declarations of interest	Reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“An Interactive Voice Response / Interactive Web Response (IVR/IWR) system will be used for enrolment, randomization and drug management” from protocol
Allocation concealment (selection bias)	Low risk	“An Interactive Voice Response / Interactive Web Response (IVR/IWR) system will be used for enrolment, randomization and drug management” from protocol; central randomization
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	"This was an open-label, randomized phase III trial"; participants and personnel were not blinded to treatment, no effect on OS expected
Blinding of participants and personnel (performance bias) Subjective outcomes	High risk	"This was an open-label, randomized phase III trial"; participants and personnel were not blinded to treatment; oral administered, active drugs used in both arms
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Assessment not specified; no effect on OS expected
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	"The primary end point was progression-free survival (PFS) by independent review", open label trial design
Incomplete outcome data (attrition bias) PFS, OS	Low risk	ITT population analysed, 1 patient not treated in experimental arm
Incomplete outcome data (attrition bias) Response rate	Low risk	ITT population analysed, 1 patient not treated in experimental arm
Incomplete outcome data (attrition bias) Serious and minor adverse events	Low risk	All treated participants assessed for safety
Incomplete outcome data (attrition bias) Quality of life	Low risk	"HRQoL questionnaires were completed by more than 99% of patients in both arms at baseline. Completion rates decreased over time, in line with study dropout, falling below 50% after cycle 13"
Selective reporting (reporting bias)	Low risk	All planned outcomes reported
Other bias	High risk	Possible confounding of OS data by cross-over design

Motzer 2014

Study characteristics	
Methods	**Study design:** multicentre RCT **Phase:** 2 **Accrual period:** October 2009 to June 2011 **Blinding:** open label design **Strata:** MSKCC risk category **IMC:** data not found **Crossover:** within treatment arms from first to second line
Participants	**Histology:** any **Prior systemic therapy:** treatment-naïve **Eligible PS:** Karnofsky PS 70% or better **Measurable disease:** required **Non metastatic %:** not specified **M/F:** 342/129 **Age median (range):** 62 (20 to 89) **Prior nephrectomy:** 315 **Prognostic strata: system, good/intermediate/poor risk:** MSKCC, 139/263/67
Interventions	first line: everolimus 10 mg po; second line: sunitinib 50 mg po 4 wks on, 2 wks off vs first line: sunitinib 50 mg po 4 wks on, 2 wks off; second line everolimus 10 mg po
Outcomes	**PFS:** primary outcome for first line treatment **OS:** secondary outcome **AE:** reported in toxicity table **QoL:** reported **RR:** assessed as secondary outcome **Other:** tolerability, PFS after second line treatment
Funding Sources	Industry sponsored
Declarations of interest	Reported
Notes	Non-inferiority design

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

Motzer 2014 *(Continued)*

Random sequence generation (selection bias)	Low risk	"Patients were randomly assigned in a 1:1 manner; Interactive Voice Response System (IVRS) to randomize the patient"
Allocation concealment (selection bias)	Low risk	Patient randomisation list used; described in detail
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	"RECORD-3 [...] was an open-label, randomized, multicenter, phase II study...", no effects on OS expected
Blinding of participants and personnel (performance bias) Subjective outcomes	High risk	"RECORD-3 [...] was an open-label, randomized, multicenter, phase II study..."; same drugs with different sequence used in both arms but participants and personnel were not blinded to treatment
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Assessment not specified, no effect on OS expected
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	"The primary end point was to assess progression-free survival (PFS) non-inferiority of first-line everolimus compared with sunitinib by investigator assessment"
Incomplete outcome data (attrition bias) PFS, OS	Low risk	ITT population reported, 2 patients in control arm did not receive treatment
Incomplete outcome data (attrition bias) Response rate	Low risk	ITT population reported, 2 patients in control arm did not receive treatment
Incomplete outcome data (attrition bias) Serious and minor adverse events	Low risk	All treated participants reported
Incomplete outcome data (attrition bias) Quality of life	Low risk	High initial questionnaire completion rate, decreased in both arms over time
Selective reporting (reporting bias)	Low risk	All planned outcomes reported
Other bias	High risk	Difference in baseline performance status, non-inferiority design

Motzer 2019

Study characteristics	
Methods	**Study design:** multicentre RCT **Phase:** 3 **Accrual period:** March 2016 to December 2017 **Blinding:** open label design

Motzer 2019 *(Continued)*

	Strata: ECOG PS (0 or 1), geographic region **IMC:** external data monitoring committee used for efficacy and safety **Crossover:** not planned
Participants	**Histology:** clear cell renal cell carcinoma **Prior systemic therapy:** treatment-naïve **Eligible PS:** Karnofsky PS 70% or better **Measurable disease:** required **Non metastatic %:** not specified **M/F:** 660/226 **Age median (range):** 61 (27 to 88) **Prior nephrectomy:** 707 **Prognostic strata: system, good/intermediate/poor risk:** MSKCC, 196/576/96
Interventions	Avelumab administered at 10 mg/kg IV every 2 weeks in combination with Axitinib, 5 mg PO BID versus Sunitinib given at 50 mg PO QD on schedule 4/2
Outcomes	**PFS:** primary outcome among patients with PD-L1–positive tumours, secondary endpoint for overall population **OS:** primary outcome among patients with PD-L1–positive tumours, secondary endpoint for overall population **AE:** reported in toxicity table **QoL:** not assessed **RR:** assessed as secondary outcome **Other:** pharmacokinetic measures, tumour-tissue biomarker
Funding Sources	Industry sponsored
Declarations of interest	Reported online
Notes	Primary endpoints changed after protocol amendment in June 2017 to evaluate PFS or OS for PD-L1 positive participants

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"the study treatment assignment using the Interactive Response Technology (IRT) system (interactive web-based response [IWR]/interactive voice response [IVR] system)" from protocol
Allocation concealment (selection bias)	Low risk	"the study treatment assignment using the Interactive Response Technology (IRT) system (interactive web-based response [IWR]/interactive voice response [IVR] system)" from protocol

Motzer 2019 *(Continued)*

Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	"This was a multicenter, randomized, open-label, phase-3 trial..."; open label trial design, no effects on OS expected
Blinding of participants and personnel (performance bias) Subjective outcomes	High risk	"This was a multicenter, randomized, open-label, phase-3 trial..."; different drugs and administration form, participants and personnel were not blinded to treatment
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	OS assessment of PD-L1 positive population. The evaluation of PD-L1 status a priori to assessment of OS is not considered as objective. Trial design is open-label. However, we extracted OS result from overall population.
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	Primary and main secondary endpoints determined by blinded independent central review
Incomplete outcome data (attrition bias) PFS, OS	Low risk	ITT and PD-L1 population reported separately for PFS, 8 and 5 participants did not receive treatment
Incomplete outcome data (attrition bias) Response rate	Low risk	ITT and PD-L1 population reported separately, 8 and 5 participants did not receive treatment
Incomplete outcome data (attrition bias) Serious and minor adverse events	Low risk	All treated participants reported in toxicity table
Selective reporting (reporting bias)	Unclear risk	OS data not mature at time of publication, protocol amended after study start but initially planned outcomes reported
Other bias	Low risk	Planned accrual completed, protocol changes after study start.

Ravaud 2015

Study characteristics	
Methods	**Study type:** multicentre RCT **Phase:** 2 **Accrual period:** data not found **Blinding:** open label design **Strata:** MSKCC risk category **IMC:** used to analyse tumour responses **Crossover:** not allowed
Participants	**Histology:** predominantly clear-cell mRCC **Prior systemic therapy:** treatment-naïve

Ravaud 2015 *(Continued)*

	Eligible PS: Karnofsky PS 70% or better **Measurable disease:** required **Non metastatic %:** 0, metastatic disease mandatory **M/F:** 269/96 **Age median (range):** 60 (20 to 84) **Prior nephrectomy:** partial or radical nephrectomy mandatory **Prognostic strata: system, good/intermediate/poor risk:** MSKCC, 131/208/26
Interventions	Everolimus 10 mg po and bevacizumab 10mg/kg iv every 2 wks vs IFN 9 MIU 3 times per wk plus bevacizumab 10 mg/kg every 2 weeks
Outcomes	**PFS:** primary endpoint **OS:** secondary outcome **AE:** secondary outcome, reported in toxicity table **QoL:** not assessed **RR:** secondary outcome **Other:** duration of response
Funding Sources	Industry sponsored
Declarations of interest	Reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomized 1:1"
Allocation concealment (selection bias)	Unclear risk	Data not found
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	"open-label, phase II RECORD-2 trial"; personnel and participants were not blinded to treatment, different drug administration forms used, no effect on OS expected
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	"open-label, phase II RECORD-2 trial"; personnel and participants were not blinded to treatment, different drug administration forms used
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Tumor response and progression were evaluated by the local radiologist and independent central review
Blinding of outcome assessment (detection bias)	High risk	Tumor response and progression were evaluated by the local radiologist and independent central review; trial design is open-label

Ravaud 2015 *(Continued)*

Subjective outcomes		
Incomplete outcome data (attrition bias) PFS, OS	Low risk	ITT population reported, 3 patients did not receive treatment
Incomplete outcome data (attrition bias) Response rate	Low risk	ITT population reported, 3 patients did not receive treatment
Incomplete outcome data (attrition bias) Serious and minor adverse events	Low risk	All but 1 participant who received treatment were included in safety analysis
Incomplete outcome data (attrition bias) Quality of life	Unclear risk	No available data
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Unclear risk	Study not powered to show significant treatment effect

Retz 2019

Study characteristics	
Methods	**Study type:** multicentre RCT **Phase:** 3 **Accrual period:** June 2012 to November 2016 **Blinding:** open label design **Strata:** low versus intermediate MSKCC risk score, clear cell versus non-clear cell histology **IMC:** data not found **Crossover:** from first to second-line after disease progression
Participants	**Histology:** any **Prior systemic therapy:** treatment-naïve **Eligible PS:** Karnofsky PS 70% or better **Measurable disease:** required **Non metastatic %:** data not found **M/F:** 189/188 **Age median (range):** 68 (26 to 86) **Prior nephrectomy:** 328 **Prognostic strata: system, good/intermediate/poor risk:** MSKCC, 186/179/9

Retz 2019 *(Continued)*

Interventions	Sorafenib 400 mg bid orally until progression or intolerable toxicity, followed by pazopanib 800 mg once daily orally until progression or intolerable toxicity or vice versa
Outcomes	**PFS:** primary outcome **OS:** reported **AE:** reported **QoL:** planned **RR:** planned **Other:** time to first-line treatment failure, biomarker
Funding Sources	Technische Universität München
Declarations of interest	Reported online
Notes	MSKCC PS low or intermediate patients only, non-inferiority study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"377 patients were randomised"
Allocation concealment (selection bias)	Unclear risk	Data not found
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	"Phase III randomized, sequential, open-label study"; participants and personnel were not masked to treatment; no effect on OS expected
Blinding of participants and personnel (performance bias) Subjective outcomes	High risk	"Phase III randomized, sequential, open-label study"; participants and personnel were not masked to treatment; same drugs used in both arms
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Open label study design but no effect on OS expected
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	Data not found
Incomplete outcome data (attrition bias) PFS, OS	Low risk	Intention to treat population analysed
Incomplete outcome data (attrition bias) Response rate	Low risk	Intention to treat population analysed
Incomplete outcome data (attrition bias)	Low risk	83/189 (96.8%) and 183/188 (97.3%) population analysed in each arm

Retz 2019 *(Continued)*

Serious and minor adverse events		
Incomplete outcome data (attrition bias) Quality of life	High risk	136/189 (71.9%) and 131/188 (69.6%) population analysed in each arm
Selective reporting (reporting bias)	Unclear risk	Quality of life outcome not published in conference abstract
Other bias	Low risk	Not detected

Rini 2008

Study characteristics	
Methods	**Study type:** multicentre RCT **Phase:** 3 **Accrual period:** October 2003 to July 2005 **Blinding:** open label design **Strata:** nephrectomy status; prognostic risk **IMC:** Data Safety Monitoring Board **Crossover:** data not found
Participants	**Histology:** clear cell **Prior systemic therapy:** naïve **Measurable disease:** measurable or non-measurable disease **Non metastatic %:** not specified **M/F %:** 508/224 **Eligible PS:** Karnofsky; 100 to 70% **Age median:** 62 **Prior nephrectomy:** 620 **Prognostic strata: system, good/intermediate/poor risk %:** MSKCC, 26/64/10
Interventions	INTERFERON alfa-2b (Intron, Schering-Plough) 9 MU SC TIW (1) with, or (2) without, BEVACIZUMAB 10 mg/kg IV Q2weeks
Outcomes	**PFS:** secondary endpoint **OS:** primary endpoint **AE:** secondary endpoint, reported in toxicity table **QoL:** not assessed **RR:** secondary endpoint

Rini 2008 *(Continued)*

	Other: -
Funding Sources	Independent sponsoring
Declarations of interest	Reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A stratified random block design was used"; Central randomisation by cooperative groups (CALGB and NCI-Canada)
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	"There was no placebo infusion in this non blinded trial", participants and personnel were not blinded to treatment, no effect on OS expected
Blinding of participants and personnel (performance bias) Subjective outcomes	High risk	"There was no placebo infusion in this non blinded trial", participants and personnel were not blinded to treatment
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	"no independent review of radiographs"; Investigator assessment of total population, overall survival primary outcome assumed reliable
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	"no independent review of radiographs", assessed by investigator
Incomplete outcome data (attrition bias) PFS, OS	Low risk	All patients accounted for with small symmetric losses
Incomplete outcome data (attrition bias) Response rate	Low risk	All patients accounted for with small symmetric losses
Incomplete outcome data (attrition bias) Serious and minor adverse events	Low risk	On treated participant not reported
Selective reporting (reporting bias)	Low risk	All protocol outcomes reported
Other bias	Low risk	Planned accrual completed; independently sponsored and conducted

Rini 2014

Study characteristics	
Methods	**Study design:** multicentre RCT **Phase:** 3 **Accrual period:** April 2008 to October 2010 **Blinding:** open label design **Strata:** nephrectomy status, MSKCC risk category **IMC:** external data monitoring committee used **Crossover:** not allowed
Participants	**Histology:** clear cell component **Prior systemic therapy:** treatment-naïve **Eligible PS:** Karnofsky PS 70% or better **Measurable disease:** yes **Non metastatic %:** data not found **M/F:** 556/235 **Age median (range):** 58 (22 to 87) **Prior nephrectomy:** 673 **Prognostic strata: system, good/intermediate/poor risk:** MSKCC, 237/467/87
Interventions	Temsirolimus 25 mg iv weekly plus Bevacizumab 10 mg/kg iv every 2 weeks or IFN 9 million U[MIU] subcutaneously thrice weekly plus Bevacizumab 10 mg/kg IV every 2 weeks
Outcomes	**PFS:** independent assessment as primary endpoint **OS:** secondary endpoint **AE:** secondary endpoint **QoL:** assessed as exploratory objective **RR:** secondary endpoint **Other:** "Disease-related symptoms and quality of life were assessed as exploratory objectives."
Funding Sources	Industry sponsored
Declarations of interest	Reported in main publication
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"A computerized centrally located randomization system was used"
Allocation concealment (selection bias)	Low risk	"A computerized centrally located randomization system was used"
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	"randomized, open-label, multicenter, phase III study"; participants and personnel were not blinded to treatment, no effect on OS expected
Blinding of participants and personnel (performance bias) Subjective outcomes	High risk	"randomized, open-label, multicenter, phase III study"; participants and personnel were not blinded to treatment
Blinding of outcome assessment (detection bias)	Low risk	"Secondary end points were investigator-assessed PFS, independently assessed ORR, OS, and safety" no effect on OS expected

Rini 2014 *(Continued)*

Objective outcomes		
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	"Radiographic evaluations were conducted at screening and every 8 weeks, and tumor progression was assessed both by investigators and by an independent blinded assessment"
Incomplete outcome data (attrition bias) PFS, OS	Low risk	ITT population reported, 7 patients in 1 arm did not receive treatment
Incomplete outcome data (attrition bias) Response rate	Low risk	ITT population reported, 7 patients in 1 arm did not receive treatment
Incomplete outcome data (attrition bias) Serious and minor adverse events	Low risk	All treated participants reported in toxicity table
Incomplete outcome data (attrition bias) Quality of life	Low risk	"Completion rate for each questionnaire was uniformly high in both treatment arms, with rates above 90% among patients on treatment up to the end of treatment visit" assessed as exploratory outcome only
Selective reporting (reporting bias)	Low risk	All planned outcomes reported
Other bias	Unclear risk	Planned accrual almost completed (791 versus 800)

Rini 2016

Study characteristics	
Methods	**Study design:** multicentre RCT **Phase:** 3 **Accrual period:** December 2010 to December 2012 **Blinding:** open label design **Strata:** IMDC risk group, region, nephrectomy status **IMC:** data and safety monitored **Crossover:** not allowed
Participants	**Histology:** clear cell component **Prior systemic therapy:** treatment-naïve **Eligible PS:** Karnowsky PS 80% or better **Measurable disease:** required **Non metastatic %:** ≤ 28 **M/F:** 230/109 **Age median (range):** 61 (54 to 69)

Rini 2016 *(Continued)*

	Prior nephrectomy: 306 **Prognostic strata: system, good/intermediate/poor risk %:** IMDC, 91/241/7
Interventions	Sunitinib 50 mg po 4 wks on, 2 wks off vs sunitinib 50 mg po 4 wks on, 2 wks off and Cyclophosphamide (1 dose of 300 mg/m^2 iv) at visit D (3 days before the first vaccination at visit 1) and the vaccination schedule (GM-CSF 75 µg and IMA901 4.13 mg intradermally at each vaccination) included 6 vaccinations within the first 3 weeks (visits 1 to 6 on days 1, 2, 3, 8, 15, and 22, respectively) and a further 4 vaccinations at 3-week intervals (visits 7 to 10 on days 43, 64, 85, and 106, respectively)
Outcomes	**PFS:** secondary outcome **OS:** primary endpoint **AE:** reported in toxicity table, secondary outcome **QoL:** not assessed **RR:** secondary outcome **Other:** biomarker related OS
Funding Sources	Industry sponsored
Declarations of interest	Reported
Notes	Only favourable or intermediate risk according to the International Metastatic Database Consortium (IMDC) risk criteria patients included, all patients treated with sunitinib and evaluated for efficacy before randomisation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"...randomised centrally with an interactive web response system..."
Allocation concealment (selection bias)	Low risk	"...randomised centrally with an interactive web response system..."
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	"patients and investigators were not masked to treatment allocation", open label study design, no effect on OS expected
Blinding of participants and personnel (performance bias) Subjective outcomes	High risk	"patients and investigators were not masked to treatment allocation", open label study design
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	"The primary outcome was overall survival from randomisation until death of any cause as determined by local investigators"; no effect on OS expected
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	"progression-free survival from randomisation according to blinded, independent central review", "Best tumour response was assessed according to RECIST 1.1 and was based on centrally reviewed tumour images"
Incomplete outcome data (attrition bias)	Low risk	ITT population reported, 8 patients did not receive treatment

Rini 2016 *(Continued)*
PFS, OS

Incomplete outcome data (attrition bias) Response rate	Low risk	All randomised participants analysed
Incomplete outcome data (attrition bias) Serious and minor adverse events	Low risk	All treated participants analysed
Selective reporting (reporting bias)	Low risk	All planned outcomes reported
Other bias	High risk	All participants treated with 1 of the study drugs in run in phase, only responders randomised

Rini 2019a

Study characteristics	
Methods	**Study design:** multicentre RCT **Phase:** 3 **Accrual period:** October 2016 to January 2018 **Blinding:** open label design **Strata:** IMDC risk group (favourable, intermediate, or poor risk) and geographic region **IMC:** an independent data and safety monitoring committee oversaw the trial **Crossover:** not planned
Participants	**Histology:** clear-cell renal-cell carcinoma **Prior systemic therapy:** treatment-naïve **Eligible PS:** Karnowsky PS 70% or better **Measurable disease:** required **Non metastatic %:** < 99 **M/F:** 628/233 **Age median (range):** 62 (26 to 90) **Prior nephrectomy:** 715 **Prognostic strata: system, good/intermediate/poor risk %:** IMDC, 269/484/108
Interventions	Pembrolizumab 200 mg intravenously every 3 weeks plus Axitinib 5 mg orally twice daily versus Sunitinib 50 mg orally once daily for 4 weeks and then are off treatment for 2 weeks
Outcomes	**PFS:** co-primary outcome assessed by blinded, independent central review **OS:** co-primary outcome assessed by blinded, independent central review **AE:** reported in toxicity table, secondary outcome

Rini 2019a *(Continued)*

	QoL: not assessed **RR:** secondary outcome assessed by blinded, independent central review **Other:** duration of response
Funding Sources	Industry sponsored
Declarations of interest	Reported online
Notes	Planned accrual completed, primary endpoint for OS not met because of short follow up

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Treatment randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS)" from protocol
Allocation concealment (selection bias)	Low risk	"Treatment randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS)" from protocol; central randomisation
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	"In this open-label, phase 3 trial..." participants and personnel were not blinded to treatment, no effect on OS expected
Blinding of participants and personnel (performance bias) Subjective outcomes	High risk	"In this open-label, phase 3 trial..." different drugs and administration form, participants and personnel were not blinded to treatment
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	OS assessed by blinded, independent central review
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	Subjective primary and secondary efficacy endpoints assessed by blinded, independent central review
Incomplete outcome data (attrition bias) PFS, OS	Low risk	Intention to treat population analysed; < 1% in both groups did not receive treatment
Incomplete outcome data (attrition bias) Response rate	Low risk	Intention to treat population analysed; < 1% in both groups did not receive treatment
Incomplete outcome data (attrition bias) Serious and minor adverse events	Low risk	All treated participants reported in toxicity table
Selective reporting (reporting bias)	Low risk	All planned outcomes reported, no mature OS data available
Other bias	Low risk	Not detected

Rini 2019b

Study characteristics	
Methods	**Study design:** multicentre RCT **Phase:** 3 **Accrual period:** May 2015 to October 2016 **Blinding:** open label design **Strata:** PD-L1 expression, presence of liver metastasis, MSKCC risk category **IMC:** "An independent data monitoring committee reviewed safety data during the study on a periodic basis" **Crossover:** "No prespecified crossover was planned per protocol"
Participants	**Histology:** "clear-cell histology and/or a component of sarcomatoid carcinoma" **Prior systemic therapy:** treatment-naïve **Eligible PS:** Karnowsky PS 70% or better **Measurable disease:** required **Non metastatic %:** not specified **M/F:** 669/246 **Age median (range):** 61 (54 to 69) **Prior nephrectomy:** 664 **Prognostic strata: system, good/intermediate/poor risk %:** MSKCC, 179/629/107
Interventions	Atezolizumab administered at a fixed dose of 1200 milligrams (mg) via intravenous (IV) infusion on Days 1 and 22 of each 42-day cycle in combination with Bevacizumab administered at a dose of 15 milligrams per kilogram (mg/kg) via IV infusion on Days 1 and 22 of each 42-day cycle versus Sunitinib administered at a dose of 50 mg once daily, orally via capsule, on Day 1 through Day 28 of each 42-day cycle.
Outcomes	**PFS:** co-primary outcome by investigator assessment in patients with PD-L1 positive disease, secondary outcome in the ITT population **OS:** co-primary outcome in the intention-to-treat population, secondary outcome in the PD-L1 positive population **AE:** secondary outcome **QoL:** reported **RR:** secondary outcome **Other:**
Funding Sources	Industry sponsored
Declarations of interest	Reported in main publication
Notes	

Rini 2019b *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomly assigned (1:1) via an interactive voice and web response system to receive Atezolizumab plus Bevacizumab or Sunitinib." central randomisation presumed
Allocation concealment (selection bias)	Low risk	Central randomisation presumed
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	"The study was open label, and investigators and participants were not masked to treatment allocation" No effect on OS expected
Blinding of participants and personnel (performance bias) Subjective outcomes	High risk	"The study was open label, and investigators and participants were not masked to treatment allocation", different drugs and forms of administration used in experimental and control arm
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Assessment not specified but not effect on OS expected
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	"Co-primary endpoints were progression-free survival (RECIST 1.1) by investigator assessment in patients with PD-L1 positive disease" PFS results in PD-L1 population differ from independent assessment
Incomplete outcome data (attrition bias) PFS, OS	Low risk	Intention to treat population reported, 3 participants in experimental and 15 participants in control arm did not receive treatment
Incomplete outcome data (attrition bias) Response rate	Low risk	Intention to treat population reported, 3 participants in experimental and 15 participants in control arm did not receive treatment
Incomplete outcome data (attrition bias) Serious and minor adverse events	Low risk	All treated participants reported
Incomplete outcome data (attrition bias) Quality of life	Unclear risk	"386 (86%) of 451 patients in the atezolizumab plus bevacizumab group and 369 (83%) of 446 patients in the sunitinib group completed the MDASI at baseline"
Selective reporting (reporting bias)	Low risk	All planned outcomes reported
Other bias	Low risk	Planned accrual completed

Sternberg 2010

Study characteristics

Methods	**Study type:** multicentre RCT

Sternberg 2010 *(Continued)*

	Phase: 3 **Accrual period:** April 2006 to April 2007 **Blinding:** double-blind, placebo-controlled **Strata:** ECOG PS 0vs1; nephrectomy status; prior cytokine **IMC:** responsible for safety monitoring and to review interim overall survival data **Crossover:** allowed from placebo to active treatment
Participants	**Histology:** clear cell **Prior systemic therapy:** 1 line of cytokines permitted. **Measurable disease:** required **Non metastatic %:** < 18 **M/F:** 307/128 **Eligible PS:** ECOG 0 to 1 **Age median(range):** 59 (25 to 85) **Prior nephrectomy:** 385 **Prognostic strata: system, good/intermediate/poor risk %:** MSKCC; 39/54/3
Interventions	(1) PAZOPANIB 800 mg PO daily, vs (2) matched PLACEBO (2:1 randomization) Cross-over 48%
Outcomes	**PFS:** primary endpoint **OS:** principal secondary end point **AE:** toxicity table available, additional secondary end point **QoL:** reported **RR:** additional secondary end point **Other:** -
Funding Sources	Industry sponsored
Declarations of interest	Reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were centrally randomly assigned in a 2:1 ratio..."; central randomisation
Allocation concealment (selection bias)	Low risk	"Patients were centrally randomly assigned in a 2:1 ratio..."; central randomisation
Blinding of participants and personnel (performance bias)	Low risk	"was a placebo-controlled, randomized, double-blind, global, multicenter, phase III study"; participants and personnel were masked to treatment

Sternberg 2010 *(Continued)*

Objective outcomes		
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	"was a placebo-controlled, randomized, double-blind, global, multicenter, phase III study"; participants and personnel were masked to treatment
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	"All imaging scans were evaluated by an independent imaging-review committee (IRC) blinded to study treatment"
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	"All imaging scans were evaluated by an independent imaging-review committee (IRC) blinded to study treatment"
Incomplete outcome data (attrition bias) PFS, OS	Low risk	All patients accounted for, losses 6% (investigational) and 3% (control) unlikely significant, “completion rates > 90% across most of the assessment time points”
Incomplete outcome data (attrition bias) Response rate	Low risk	All patients accounted for, losses 6% (investigational) and 3% (control) unlikely significant, “completion rates > 90% across most of the assessment time points”
Incomplete outcome data (attrition bias) Serious and minor adverse events	Low risk	All treated participants analysed
Incomplete outcome data (attrition bias) Quality of life	Low risk	"Completion rates for QoL questionnaires were high across most of the assessment time points for each instrument"
Selective reporting (reporting bias)	Low risk	All protocol specified endpoints reported
Other bias	Low risk	Planned accrual completed

AE: adverse event; ECOG: Eastern Cooperative Oncology Group; F: female; IMC: independent monitoring committee; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; ITT: intention to treat; M: male; MSKCC: Memorial Sloan Kettering Cancer Center; OS: overall survival; PFS: progression-free survival; PS: performance status; QoL: quality of life; RCT: randomised controlled trial; RR: response rate; wks: weeks

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

Study	Reason for exclusion
Armstrong 2016	Non-clear cell renal cell carcinoma participants only, less than 100 participants per treatment arm included
Atkins 2004	Same targeted drug used in all treatment arms, less than 100 participants per treatment arm included, cytokine pretreatment required
Bracarda 2010	Same targeted treatment used in both arms, less than 100 participants per treatment arm included
Broom 2015	Less than 100 participants per treatment arm included

Study	Reason for exclusion
Bukowski 2007	Less than 100 participants per treatment arm included
Choueiri 2015	Participants were not treatment-naïve
Choueiri 2017	Less than 100 participants per treatment arm included
Cirkel 2016	Less than 100 participants per treatment arm included
Dorff 2015	Participants not treatment-naïve, less than 100 participants per treatment arm included
Ebbinghaus 2007	Same drug used in both treatment arms, less than 100 participants per treatment arm included
Eisen 2015	Less than 100 participants per treatment arm included
Escudier 2007	Treatment is not considered as targeted therapy
Escudier 2009	Less than 100 participants per treatment arm included
Escudier 2010a	Participants were not treatment naïve
Flaherty 2015	Less than 100 participants per treatment arm included
Gordon 2004	No treatment that is considered as targeted therapy was used in trial
Hainsworth 2015	Less than 100 participants per treatment arm included
Hawkins 2016	Treatment not considered as targeted therapy, any renal cell carcinoma histologies included
Hutson 2013	Participants were not treatment naïve
Hutson 2014	Participants were not treatment naïve
Jonasch 2010	Less than 100 participants per treatment arm included
Jonasch 2017	Participants were not treatment naïve
Lee 2006	Treatment not considered as targeted therapy
Lee 2015	Same study drugs used in both arms, less than 100 participants per treatment arm included
Madhusudan 2004	Treatment not considered as targeted therapy
Motzer 2008	Participants were not treatment-naïve
Motzer 2012	Same study drug used in both arms
Motzer 2014b	Participants were not treatment-naïve
Motzer 2015a	Participants were not treatment-naïve
Motzer 2015b	Participants were not treatment-naïve
Motzer 2015c	Participants were not treatment-naïve
Mulders 2012	Less than 100 participants per treatment arm included

Study	Reason for exclusion
Nosov 2012	Less than 100 participants per treatment arm included
Négrier 2011	Less than 100 participants per treatment arm included
Pal 2015	Less than 100 participants per treatment arm included, participants were not treatment-naïve
Pili 2015	Less than 100 participants per treatment arm included, participants were not treatment-naïve
Powles 2014	Less than 100 participants per treatment arm included, participants were not treatment-naïve
Powles 2016a	Less than 100 participants per treatment arm included, participants were not treatment-naïve
Powles 2016b	Less than 100 participants per treatment arm included, participants were not treatment-naïve
Procopio 2011	Less than 100 participants per treatment arm included
Ratain 2006	Less than 100 participants per treatment arm included, 84% of participants pretreated
Ravaud 2008	Treatment in control arm not eligible for comparisons
Rini 2011	Participants were not treatment-naïve
Rini 2012	Treatment in observational and control arm not eligible for comparison
Rini 2013	Less than 100 participants per treatment arm included
Srinivas 2005	Treatment not considered as targeted therapy
Stadler 2005	Treatment is not considered as targeted therapy
Tannir 2016	Less than 100 participants per treatment arm included, non-clear cell renal cell carcinoma only
Tannir 2018	Less than 100 participants per treatment arm included
Tomita 2014	Less than 100 participants per treatment arm included
Twardowski 2015	Less than 100 participants per treatment arm included, participants were not treatment-naïve
Yang 2003	Less than 100 participants per treatment arm included, participants were not treatment-naïve

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

Choueiri 2018

Study name	NCT03141177, CheckMate 9ER
Methods	**Study type:** multicentre RCT **Phase:** 3 **Accrual period:** data not found **Blinding:** open label study design **Strata:** IMDC risk score, PD-1 ligand 1 (PD-L1) tumour expression and geographic region

Choueiri 2018 *(Continued)*

	IMC: data not found
	Crossover: data not found
Participants	**Histology:** clear cell component
	Prior systemic therapy: no prior systemic therapy for RCC
	Measurable disease: required
	Eligible PS: data not found
	Non metastatic %: data not found
	M/F %: data not found
	Age median(range): data not found
	Prior nephrectomy: data not found
	Prognostic strata: system, good/intermediate/poor risk %: data not found
Interventions	Nivolumab and cabozantinib versus sunitinib
Outcomes	**PFS:** primary endpoint
	OS: secondary end point
	AE: secondary end point
	QoL: not planned
	RR: secondary end point
	Other: -
Starting date	July 2017
Contact information	
Notes	

Choueiri 2019

Study name	NCT03937219, Cosmic-313
Methods	**Study type:** multicentre RCT
	Phase: 3
	Accrual period: 25 June 2019 -
	Blinding: double-blind study design
	Strata: IMDC risk score and geographic region
	IMC: data not found
	Crossover: data not found
Participants	**Histology:** clear cell component

Choueiri 2019 *(Continued)*

	Prior systemic therapy: no prior systemic therapy for RCC **Measurable disease:** required **Eligible PS:** Karnofsky PS 70% or better **Non metastatic %:** data not found **M/F %:** data not found **Age median (range):** data not found **Prior nephrectomy:** data not found **Prognostic strata: system, good/intermediate/poor risk %:** data not found
Interventions	Cabozantinib + nivolumab + ipilimumab (4 doses) followed by cabozantinib + nivolumab vs Cabozantinib-matched placebo + nivolumab + ipilimumab (4 doses) followed by cabozantinib-matched placebo + nivolumab
Outcomes	**PFS:** primary endpoint **OS:** secondary end point **AE:** - **QoL:**- **RR:**- **Other:** -
Starting date	June 2019
Contact information	
Notes	

Grünwald 2018

Study name	NCT02959554, NIVOSWITCH
Methods	**Study design:** multicentre RCT **Phase:** 2 **Accrual period:** data not found **Blinding:** open label study design **Strata:** data not found **IMC:** data not found **Crossover:** data not found
Participants	**Histology:** clear cell component **Prior systemic therapy:** First-line treatment with a TKI for 10-12 weeks (limited to sunitinib or pazopanib) **Eligible PS:** ECOG-PS 0-2

Grünwald 2018 *(Continued)*

	Measurable disease: required **Non metastatic %:** data not found **M/F %:** data not found **Age median, years:** data not found **Prior nephrectomy:** data not found **Prognostic strata: system, good/intermediate/poor risk %:** data not found
Interventions	Nivolumab: 240 mg iv on D1 of every cycle (Q2W) for 16 weeks. After 16 weeks 480 mg iv on D1 of every cycle (Q4W) until disease progress, intolerable toxicity, withdrawal of consent or end of study versus Sunitinib: According to Standard of Care (SOC). Recommended dose is 50 mg PO once daily for 4 consecutive weeks followed by a 2-week rest period (schedule 4/2) to comprise a complete cycle of 6 weeks (until disease progress, intolerable toxicity, withdrawal of consent or end of study) or Pazopanib: According to Standard of Care (SOC). Recommended dose is 800 mg PO daily continuously (until disease progress, intolerable toxicity, withdrawal of consent or end of study)
Outcomes	**PFS:** secondary endpoint **OS:** primary end point **AE:** secondary end point **QoL:** secondary endpoint **RR:** secondary end point **Other:** -
Starting date	December 2016
Contact information	Principal Investigator: Prof. Dr. Viktor Grünwald
Notes	

Motzer 2018

Study name	NCT02811861
Methods	**Study design:** multicentre RCT **Phase:** 3 **Accrual period:** data not found **Blinding:** open label design **Strata:** data not found **IMC:** data not found **Crossover:** data not found
Participants	**Histology:** clear cell carcinoma **Prior systemic therapy:** treatment-naïve **Eligible PS:** Karnofsky PS 70% or better

Motzer 2018 *(Continued)*

	Measurable disease: required **Non metastatic %:** data not found **M/F %:** data not found **Age median, years:** data not found **Prior nephrectomy:** data not found **Prognostic strata: system, good/intermediate/poor risk %:** data not found
Interventions	lenvatinib 18 milligrams (mg) administered orally, once daily, plus everolimus 5 mg administered orally, once daily; Lenvatinib 20 mg administered orally, once daily, plus pembrolizumab 200 mg administered intravenously (IV), every 3 weeks; Sunitinib 50 mg administered orally, once daily, on a schedule of 4 weeks on treatment followed by 2 weeks off treatment
Outcomes	**PFS:** primary endpoint **OS:** planned **AE:** planned **QoL:** planned **RR:** primary endpoint **Other:** -
Starting date	**Trial start date**: 13 October 2016 **Trial completion date**: Estimated 15 January 2020
Contact information	**Responsible party/ principal investigator**: Eisai Inc.
Notes	Study based on results of phase 2 study data

AE: adverse event; ECOG: Eastern Cooperative Oncology Group; F: female; IMC: independent monitoring committee; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; IV; intravenous; M: male; OS: overall survival; PFS: progression-free survival; PO; per oral; PS: performance status; QoL: quality of life; RCC: renal cell carcinoma; RR: response rate; TKI: tyrosine kinase inhibitor

DATA AND ANALYSES

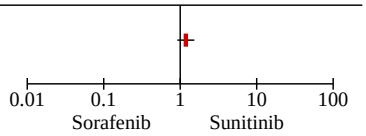
Comparison 1. Sorafenib versus Sunitinib

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Progression-free survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
1.2 Overall survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
1.3 Serious adverse events (Grade 3 or 4)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4 Response rate	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.5 Minor adverse events (Grade 1 or 2)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

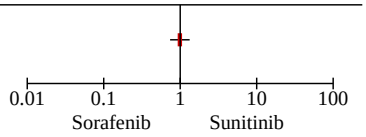
Analysis 1.1. Comparison 1: Sorafenib versus Sunitinib, Outcome 1: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Sorafenib Total	Sunitinib Total	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% CI
Eichelberg 2015	0.17	0.13	182	183	1.19 [0.92 , 1.53]	



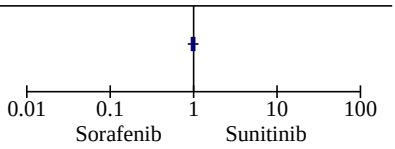
Analysis 1.2. Comparison 1: Sorafenib versus Sunitinib, Outcome 2: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Sorafenib Total	Sunitinib Total	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% CI
Eichelberg 2015	-0.01	0.15	182	183	0.99 [0.74 , 1.33]	



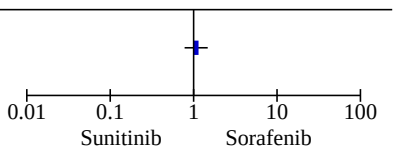
Analysis 1.3. Comparison 1: Sorafenib versus Sunitinib, Outcome 3: Serious adverse events (Grade 3 or 4)

Study or Subgroup	Sorafenib Events	Sorafenib Total	Sunitinib Events	Sunitinib Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Eichelberg 2015	117	177	118	176	0.99 [0.85 , 1.14]	



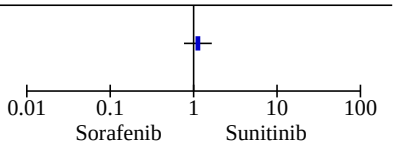
Analysis 1.4. Comparison 1: Sorafenib versus Sunitinib, Outcome 4: Response rate

Study or Subgroup	Sorafenib Events	Sorafenib Total	Sunitinib Events	Sunitinib Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Eichelberg 2015	55	177	51	176	1.07 [0.78 , 1.47]	



Analysis 1.5. Comparison 1: Sorafenib versus Sunitinib, Outcome 5: Minor adverse events (Grade 1 or 2)

Study or Subgroup	Sorafenib Events	Sorafenib Total	Sunitinib Events	Sunitinib Total	Risk Ratio M-H, Random, 95% CI
Eichelberg 2015	43	177	38	176	1.13 [0.77 , 1.65]

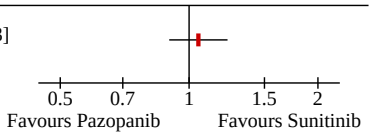


Comparison 2. Pazopanib versus Sunitinib

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Progression-free survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
2.2 Overall survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
2.3 Serious adverse events (Grade 3 or 4)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.4 Health-related quality of life	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.5 Response rate	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.6 Minor adverse events (Grade 1 or 2)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

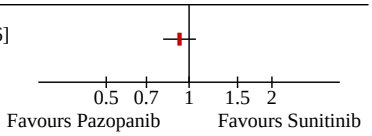
Analysis 2.1. Comparison 2: Pazopanib versus Sunitinib, Outcome 1: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Pazopanib Total	Sunitinib Total	Hazard Ratio IV, Random, 95% CI
Motzer 2013a	0.05	0.08	557	553	1.05 [0.90 , 1.23]



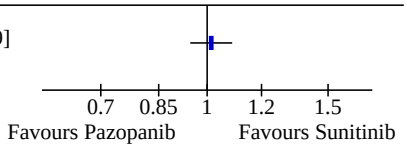
Analysis 2.2. Comparison 2: Pazopanib versus Sunitinib, Outcome 2: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Pazopanib Total	Sunitinib Total	Hazard Ratio IV, Random, 95% CI
Motzer 2013a	-0.08	0.07	557	553	0.92 [0.80 , 1.06]



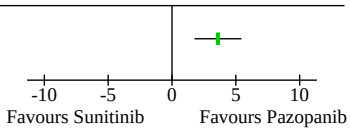
Analysis 2.3. Comparison 2: Pazopanib versus Sunitinib, Outcome 3: Serious adverse events (Grade 3 or 4)

Study or Subgroup	Pazopanib Events	Pazopanib Total	Sunitinib Events	Sunitinib Total	Risk Ratio M-H, Random, 95% CI
Motzer 2013a	412	554	402	548	1.01 [0.94 , 1.09]



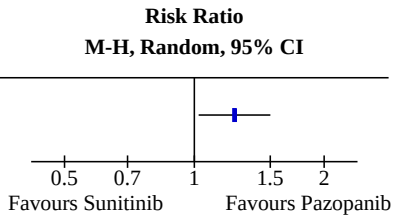
Analysis 2.4. Comparison 2: Pazopanib versus Sunitinib, Outcome 4: Health-related quality of life

Study or Subgroup	Pazopanib Mean	Pazopanib SD	Pazopanib Total	Sunitinib Mean	Sunitinib SD	Sunitinib Total	Mean Difference IV, Random, 95% CI
Motzer 2013a	-2.9	9.77	227	-6.5	10.51	240	3.60 [1.76 , 5.44]



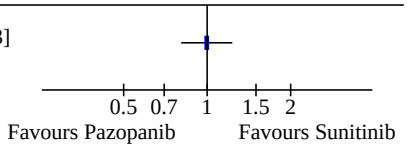
Analysis 2.5. Comparison 2: Pazopanib versus Sunitinib, Outcome 5: Response rate

Study or Subgroup	Pazopanib Events	Pazopanib Total	Sunitinib Events	Sunitinib Total	Risk Ratio M-H, Random, 95% CI
Motzer 2013a	171	557	137	553	1.24 [1.02 , 1.50]



Analysis 2.6. Comparison 2: Pazopanib versus Sunitinib, Outcome 6: Minor adverse events (Grade 1 or 2)

Study or Subgroup	Pazopanib Events	Pazopanib Total	Sunitinib Events	Sunitinib Total	Risk Ratio M-H, Random, 95% CI
Motzer 2013a	131	554	130	548	1.00 [0.81 , 1.23]



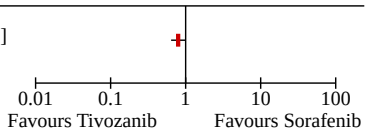
Comparison 3. Tivozanib versus Sorafenib

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Progression-free survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
3.2 Overall survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3 Serious adverse events (Grade 3 or 4)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.4 Health-related quality of life	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.5 Response rate	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.6 Minor adverse events (Grade 1 or 2)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

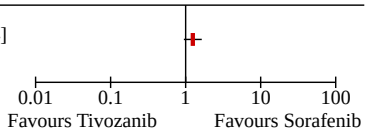
Analysis 3.1. Comparison 3: Tivozanib versus Sorafenib, Outcome 1: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Tivozanib Total	Sorafenib Total	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% CI
Motzer 2013b	-0.23	0.11	260	257	0.79 [0.64 , 0.99]	



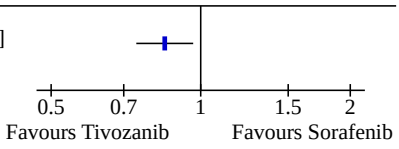
Analysis 3.2. Comparison 3: Tivozanib versus Sorafenib, Outcome 2: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Tivozanib Total	Sorafenib Total	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% CI
Motzer 2013b	0.22	0.14	260	257	1.25 [0.95 , 1.64]	



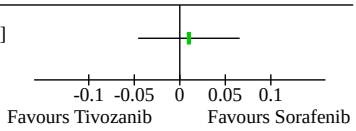
Analysis 3.3. Comparison 3: Tivozanib versus Sorafenib, Outcome 3: Serious adverse events (Grade 3 or 4)

Study or Subgroup	Tivozanib Events	Tivozanib Total	Sorafenib Events	Sorafenib Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Motzer 2013b	151	259	177	257	0.85 [0.74 , 0.97]	



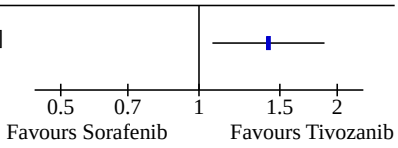
Analysis 3.4. Comparison 3: Tivozanib versus Sorafenib, Outcome 4: Health-related quality of life

Study or Subgroup	Tivozanib Mean	Tivozanib SD	Tivozanib Total	Sorafenib Mean	Sorafenib SD	Sorafenib Total	Mean Difference IV, Random, 95% CI
Motzer 2013b	-0.05	0.32	256	-0.06	0.32	250	0.01 [-0.05 , 0.07]



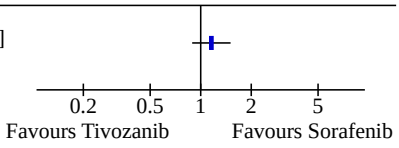
Analysis 3.5. Comparison 3: Tivozanib versus Sorafenib, Outcome 5: Response rate

Study or Subgroup	Tivozanib Events	Tivozanib Total	Sorafenib Events	Sorafenib Total	Risk Ratio M-H, Random, 95% CI
Motzer 2013b	86	260	60	257	1.42 [1.07 , 1.88]



Analysis 3.6. Comparison 3: Tivozanib versus Sorafenib, Outcome 6: Minor adverse events (Grade 1 or 2)

Study or Subgroup	Tivozanib Events	Tivozanib Total	Sorafenib Events	Sorafenib Total	Risk Ratio M-H, Random, 95% CI
Motzer 2013b	84	259	72	257	1.16 [0.89 , 1.51]

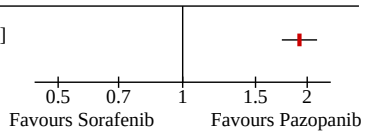


Comparison 4. Sorafenib versus Pazopanib

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Progression-free survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
4.2 Overall survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
4.3 Serious adverse events (Grade 3 or 4)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.4 Health-related quality of life	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.5 Response rate	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.6 Minor adverse events (Grade 1 or 2)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

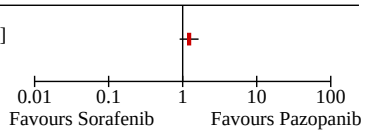
Analysis 4.1. Comparison 4: Sorafenib versus Pazopanib, Outcome 1: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Sorafenib Total	Pazopanib Total	Hazard Ratio IV, Random, 95% CI
Retz 2019	0.65	0.05	189	188	1.92 [1.74 , 2.11]



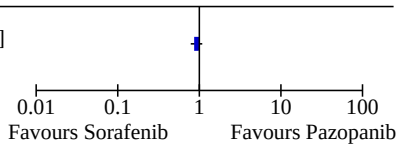
Analysis 4.2. Comparison 4: Sorafenib versus Pazopanib, Outcome 2: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Sorafenib Total	Pazopanib Total	Hazard Ratio IV, Random, 95% CI
Retz 2019	0.2	0.15	189	188	1.22 [0.91 , 1.64]



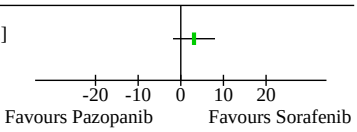
Analysis 4.3. Comparison 4: Sorafenib versus Pazopanib, Outcome 3: Serious adverse events (Grade 3 or 4)

Study or Subgroup	Sorafenib Events	Sorafenib Total	Pazopanib Events	Pazopanib Total	Risk Ratio M-H, Random, 95% CI
Retz 2019	108	183	117	183	0.92 [0.78 , 1.09]



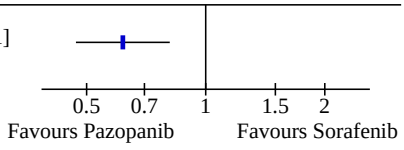
Analysis 4.4. Comparison 4: Sorafenib versus Pazopanib, Outcome 4: Health-related quality of life

Study or Subgroup	Sorafenib Mean	Sorafenib SD	Sorafenib Total	Pazopanib Mean	Pazopanib SD	Pazopanib Total	Mean Difference IV, Random, 95% CI
Retz 2019	-6.8	20	136	-9.9	21	131	3.10 [-1.82 , 8.02]



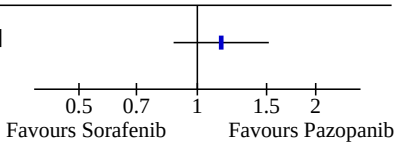
Analysis 4.5. Comparison 4: Sorafenib versus Pazopanib, Outcome 5: Response rate

Study or Subgroup	Sorafenib Events	Sorafenib Total	Pazopanib Events	Pazopanib Total	Risk Ratio M-H, Random, 95% CI
Retz 2019	54	189	87	188	0.62 [0.47 , 0.81]



Analysis 4.6. Comparison 4: Sorafenib versus Pazopanib, Outcome 6: Minor adverse events (Grade 1 or 2)

Study or Subgroup	Sorafenib Events	Sorafenib Total	Pazopanib Events	Pazopanib Total	Risk Ratio M-H, Random, 95% CI
Retz 2019	69	183	60	183	1.15 [0.87 , 1.52]

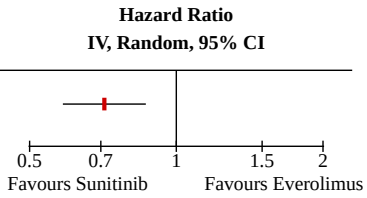


Comparison 5. Sunitinib versus Everolimus

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Progression-free survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
5.2 Overall survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
5.3 Serious adverse events (Grade 3 or 4)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.4 Health-related quality of life	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5.5 Response rate	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.6 Minor adverse events (Grade 1 or 2)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

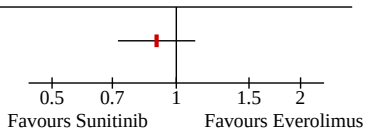
Analysis 5.1. Comparison 5: Sunitinib versus Everolimus, Outcome 1: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Sunitinib Total	Everolimus Total	Hazard Ratio IV, Random, 95% CI
Motzer 2014	-0.34	0.1	233	238	0.71 [0.59 , 0.87]



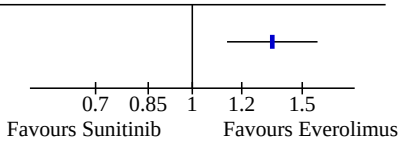
Analysis 5.2. Comparison 5: Sunitinib versus Everolimus, Outcome 2: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Sunitinib Total	Everolimus Total	Hazard Ratio IV, Random, 95% CI
Motzer 2014	-0.11	0.11	233	238	0.90 [0.72 , 1.11]



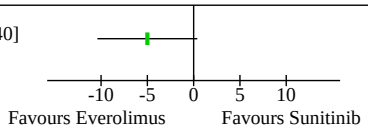
Analysis 5.3. Comparison 5: Sunitinib versus Everolimus, Outcome 3: Serious adverse events (Grade 3 or 4)

Study or Subgroup	Sunitinib Events	Sunitinib Total	Everolimus Events	Everolimus Total	Risk Ratio M-H, Random, 95% CI
Motzer 2014	146	231	112	238	1.34 [1.14 , 1.59]



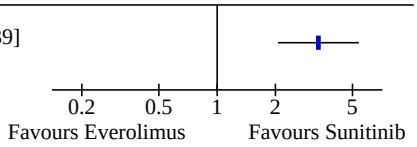
Analysis 5.4. Comparison 5: Sunitinib versus Everolimus, Outcome 4: Health-related quality of life

Study or Subgroup	Sunitinib Mean	Sunitinib SD	Sunitinib Total	Everolimus Mean	Everolimus SD	Everolimus Total	Mean Difference IV, Random, 95% CI
Motzer 2014	60.5	24.9	150	65.5	21.8	138	-5.00 [-10.40 , 0.40]



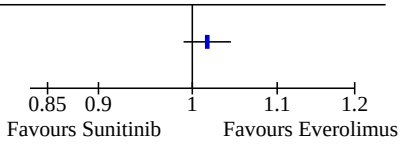
Analysis 5.5. Comparison 5: Sunitinib versus Everolimus, Outcome 5: Response rate

Study or Subgroup	Sunitinib Events	Sunitinib Total	Everolimus Events	Everolimus Total	Risk Ratio M-H, Random, 95% CI
Motzer 2014	62	233	19	238	3.33 [2.06 , 5.39]



Analysis 5.6. Comparison 5: Sunitinib versus Everolimus, Outcome 6: Minor adverse events (Grade 1 or 2)

Study or Subgroup	Sunitinib Events	Sunitinib Total	Everolimus Events	Everolimus Total	Risk Ratio M-H, Random, 95% CI
Motzer 2014	228	231	231	238	1.02 [0.99 , 1.04]

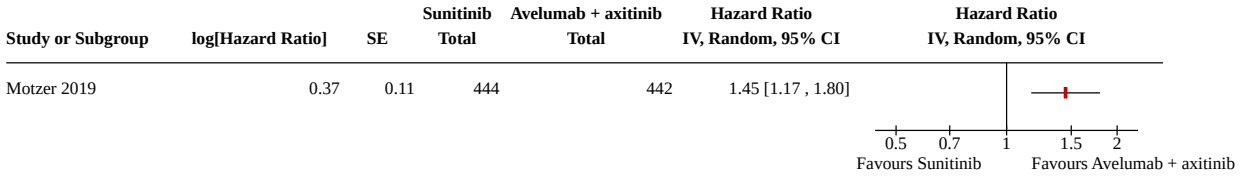


Comparison 6. Sunitinib versus Avelumab + Axitinib

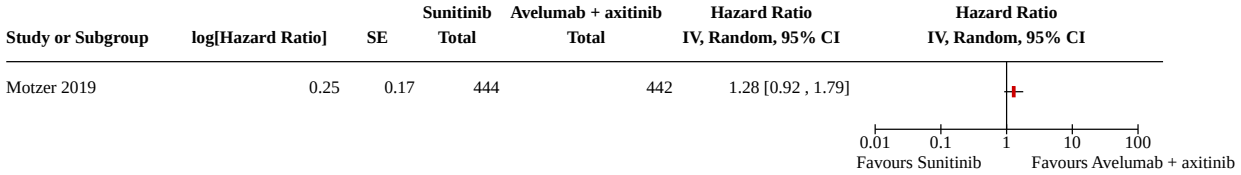
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Progression-free survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
6.2 Overall survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.3 Serious adverse events (Grade 3 or 4)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.4 Response rate	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.5 Minor adverse events (Grade 1 or 2)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

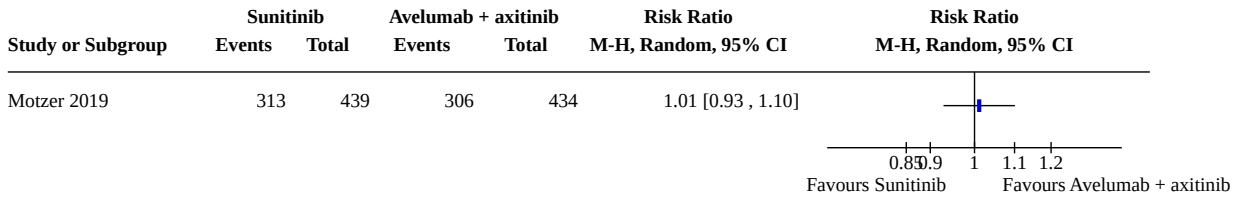
Analysis 6.1. Comparison 6: Sunitinib versus Avelumab + Axitinib, Outcome 1: Progression-free survival



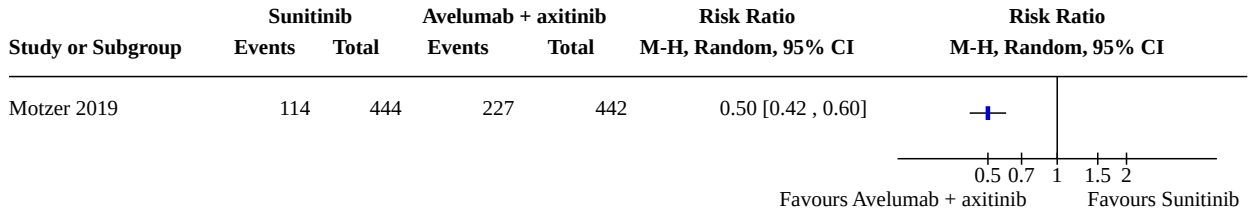
Analysis 6.2. Comparison 6: Sunitinib versus Avelumab + Axitinib, Outcome 2: Overall survival



Analysis 6.3. Comparison 6: Sunitinib versus Avelumab + Axitinib, Outcome 3: Serious adverse events (Grade 3 or 4)

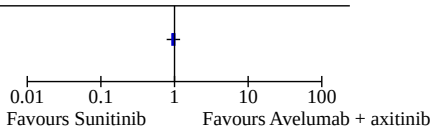


Analysis 6.4. Comparison 6: Sunitinib versus Avelumab + Axitinib, Outcome 4: Response rate



Analysis 6.5. Comparison 6: Sunitinib versus Avelumab + Axitinib, Outcome 5: Minor adverse events (Grade 1 or 2)

Study or Subgroup	Sunitinib Events	Sunitinib Total	Avelumab + axitinib Events	Avelumab + axitinib Total	Risk Ratio M-H, Random, 95% CI
Motzer 2019	123	439	126	434	0.97 [0.78 , 1.19]

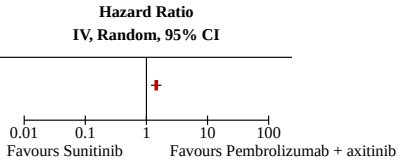


Comparison 7. Sunitinib versus Pembrolizumab + Axitinib

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Progression-free survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
7.2 Overall survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
7.3 Serious adverse events (Grade 3 or 4)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.4 Response rate	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.5 Minor adverse events (Grade 1 or 2)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

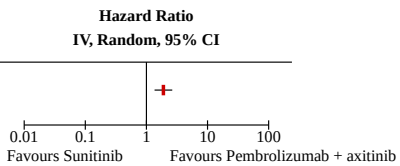
Analysis 7.1. Comparison 7: Sunitinib versus Pembrolizumab + Axitinib, Outcome 1: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Sunitinib Total	Pembrolizumab + axitinib Total	Hazard Ratio IV, Random, 95% CI
Rini 2019a	0.37	0.1	429	432	1.45 [1.19 , 1.76]

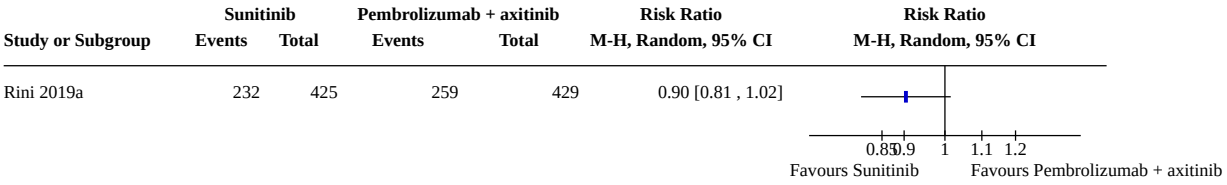


Analysis 7.2. Comparison 7: Sunitinib versus Pembrolizumab + Axitinib, Outcome 2: Overall survival

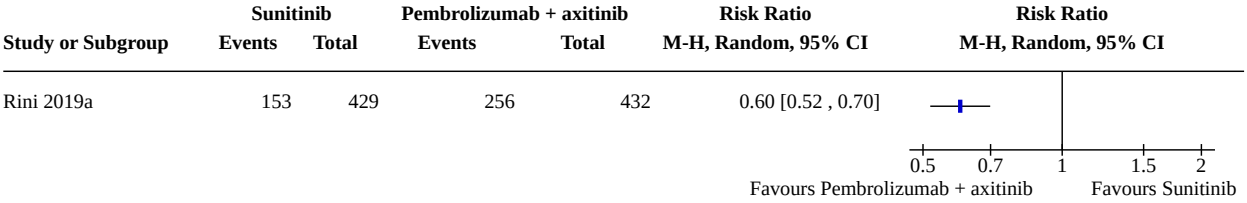
Study or Subgroup	log[Hazard Ratio]	SE	Sunitinib Total	Pembrolizumab + axitinib Total	Hazard Ratio IV, Random, 95% CI
Rini 2019a	0.64	0.17	429	432	1.90 [1.36 , 2.65]



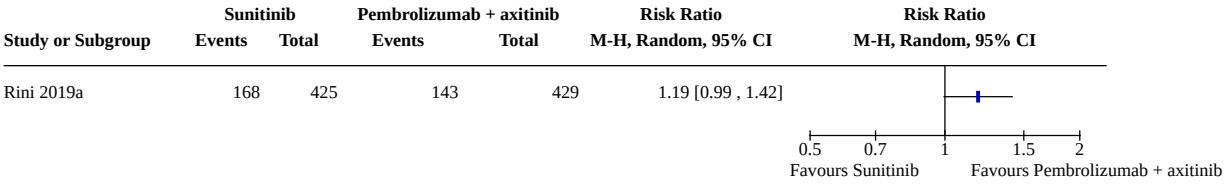
Analysis 7.3. Comparison 7: Sunitinib versus Pembrolizumab + Axitinib, Outcome 3: Serious adverse events (Grade 3 or 4)



Analysis 7.4. Comparison 7: Sunitinib versus Pembrolizumab + Axitinib, Outcome 4: Response rate



Analysis 7.5. Comparison 7: Sunitinib versus Pembrolizumab + Axitinib, Outcome 5: Minor adverse events (Grade 1 or 2)



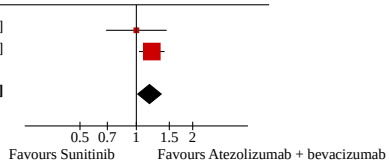
Comparison 8. Sunitinib versus Atezolizumab + Bevacizumab

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Progression-free survival	2	1117	Hazard Ratio (IV, Random, 95% CI)	1.18 [1.02, 1.36]
8.2 Overall survival	2	1117	Hazard Ratio (IV, Random, 95% CI)	0.99 [0.73, 1.33]
8.3 Serious adverse events (Grade 3 or 4)	2	1098	Risk Ratio (M-H, Random, 95% CI)	1.22 [1.00, 1.49]
8.4 Health-related quality of life	2	691	Mean Difference (IV, Random, 95% CI)	1.00 [0.68, 1.32]
8.5 Response rate	2	1117	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.77, 1.07]
8.6 Minor adverse events (Grade 1 or 2)	2	1098	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.74, 0.97]

Analysis 8.1. Comparison 8: Sunitinib versus Atezolizumab + Bevacizumab, Outcome 1: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Sunitinib Total	Atezolizumab + bevacizumab Total	Weight	Hazard Ratio IV, Random, 95% CI
McDermott 2018	0	0.19	101	101	15.1%	1.00 [0.69 , 1.45]
Rini 2019b	0.19	0.08	461	454	84.9%	1.21 [1.03 , 1.41]
Total (95% CI)			**562**	**555**	**100.0%**	**1.18 [1.02 , 1.36]**

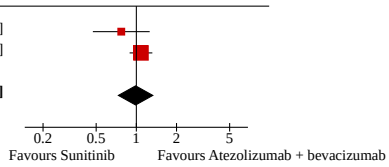
Heterogeneity: Tau² = 0.00; Chi² = 0.85, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 2.19 (P = 0.03)
Test for subgroup differences: Not applicable



Analysis 8.2. Comparison 8: Sunitinib versus Atezolizumab + Bevacizumab, Outcome 2: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Sunitinib Total	Atezolizumab + bevacizumab Total	Weight	Hazard Ratio IV, Random, 95% CI
McDermott 2018	-0.26	0.25	101	101	27.3%	0.77 [0.47 , 1.26]
Rini 2019b	0.08	0.1	461	454	72.7%	1.08 [0.89 , 1.32]
Total (95% CI)			**562**	**555**	**100.0%**	**0.99 [0.73 , 1.33]**

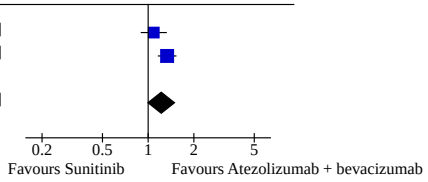
Heterogeneity: Tau² = 0.02; Chi² = 1.59, df = 1 (P = 0.21); I² = 37%
Test for overall effect: Z = 0.08 (P = 0.93)
Test for subgroup differences: Not applicable



Analysis 8.3. Comparison 8: Sunitinib versus Atezolizumab + Bevacizumab, Outcome 3: Serious adverse events (Grade 3 or 4)

Study or Subgroup	Sunitinib Events	Sunitinib Total	Atezolizumab + bevacizumab Events	Atezolizumab + bevacizumab Total	Weight	Risk Ratio M-H, Random, 95% CI
McDermott 2018	69	100	64	101	44.1%	1.09 [0.89 , 1.33]
Rini 2019b	240	446	182	451	55.9%	1.33 [1.16 , 1.54]
Total (95% CI)		**546**		**552**	**100.0%**	**1.22 [1.00 , 1.49]**
Total events:	309		246			

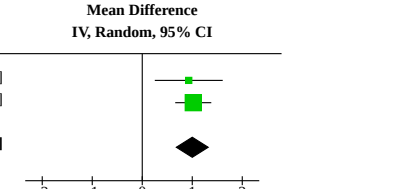
Heterogeneity: Tau² = 0.01; Chi² = 2.77, df = 1 (P = 0.10); I² = 64%
Test for overall effect: Z = 1.93 (P = 0.05)
Test for subgroup differences: Not applicable



Analysis 8.4. Comparison 8: Sunitinib versus Atezolizumab + Bevacizumab, Outcome 4: Health-related quality of life

Study or Subgroup	Sunitinib Mean	Sunitinib SD	Sunitinib Total	Atezolizumab + bevacizumab Mean	Atezolizumab + bevacizumab SD	Atezolizumab + bevacizumab Total	Weight	Mean Difference IV, Random, 95% CI
McDermott 2018	2.5	2.47	77	1.57	1.83	82	22.0%	0.93 [0.25 , 1.61]
Rini 2019b	1.58	2.05	248	0.56	2.19	284	78.0%	1.02 [0.66 , 1.38]
Total (95% CI)			**325**			**366**	**100.0%**	**1.00 [0.68 , 1.32]**

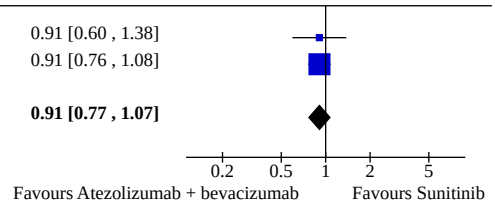
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%
Test for overall effect: Z = 6.16 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 8.5. Comparison 8: Sunitinib versus Atezolizumab + Bevacizumab, Outcome 5: Response rate

Study or Subgroup	Sunitinib Events	Sunitinib Total	Atezolizumab + bevacizumab Events	Atezolizumab + bevacizumab Total	Weight	Risk Ratio M-H, Random, 95% CI
McDermott 2018	29	101	32	101	15.1%	0.91 [0.60 , 1.38]
Rini 2019b	153	461	166	454	84.9%	0.91 [0.76 , 1.08]
Total (95% CI)		**562**		**555**	**100.0%**	**0.91 [0.77 , 1.07]**
Total events:	182		198			

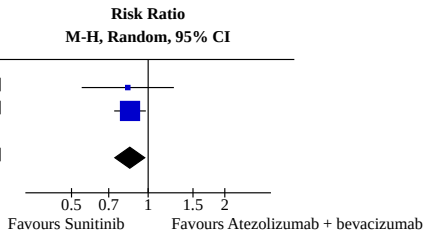
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%
Test for overall effect: Z = 1.16 (P = 0.24)
Test for subgroup differences: Not applicable



Analysis 8.6. Comparison 8: Sunitinib versus Atezolizumab + Bevacizumab, Outcome 6: Minor adverse events (Grade 1 or 2)

Study or Subgroup	Sunitinib Events	Sunitinib Total	Atezolizumab + bevacizumab Events	Atezolizumab + bevacizumab Total	Weight	Risk Ratio M-H, Random, 95% CI
McDermott 2018	28	100	34	101	10.5%	0.83 [0.55 , 1.26]
Rini 2019b	188	446	224	451	89.5%	0.85 [0.74 , 0.98]
Total (95% CI)		**546**		**552**	**100.0%**	**0.85 [0.74 , 0.97]**
Total events:	216		258			

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%
Test for overall effect: Z = 2.41 (P = 0.02)
Test for subgroup differences: Not applicable

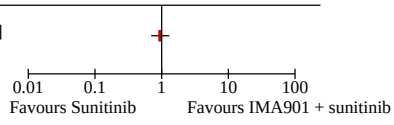


Comparison 9. Sunitinib versus IMA901 + Sunitinib

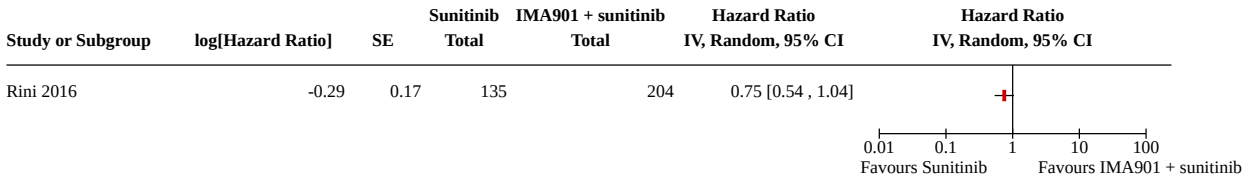
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Progression-free survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
9.2 Overall survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
9.3 Serious adverse events (Grade 3 or 4)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.4 Response rate	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.5 Minor adverse events (Grade 1 or 2)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 9.1. Comparison 9: Sunitinib versus IMA901 + Sunitinib, Outcome 1: Progression-free survival

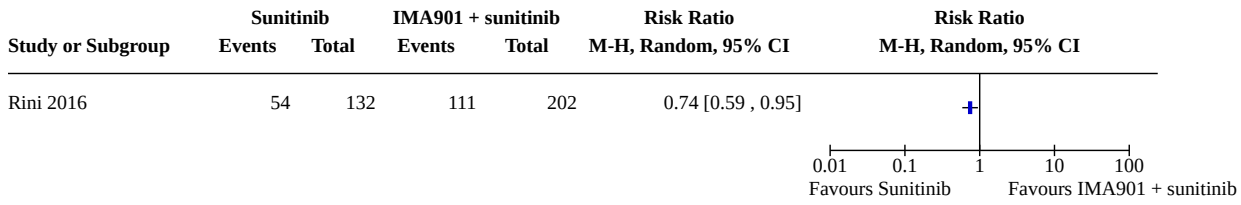
Study or Subgroup	log[Hazard Ratio]	SE	Sunitinib Total	IMA901 + sunitinib Total	Hazard Ratio IV, Random, 95% CI
Rini 2016	-0.05	0.16	135	204	0.95 [0.70 , 1.30]



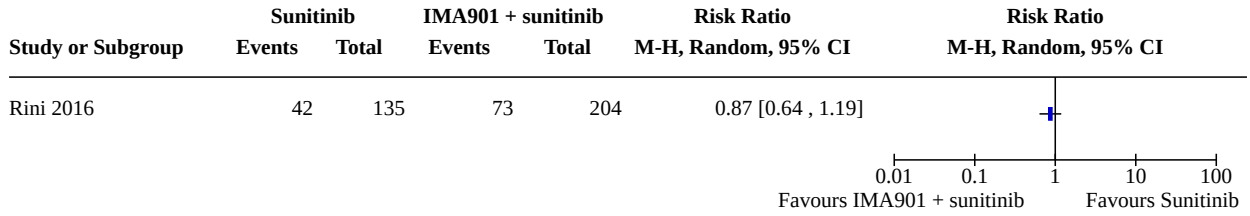
Analysis 9.2. Comparison 9: Sunitinib versus IMA901 + Sunitinib, Outcome 2: Overall survival



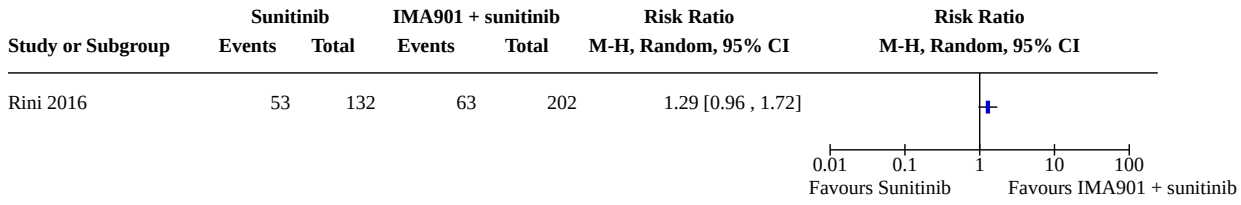
Analysis 9.3. Comparison 9: Sunitinib versus IMA901 + Sunitinib, Outcome 3: Serious adverse events (Grade 3 or 4)



Analysis 9.4. Comparison 9: Sunitinib versus IMA901 + Sunitinib, Outcome 4: Response rate



Analysis 9.5. Comparison 9: Sunitinib versus IMA901 + Sunitinib, Outcome 5: Minor adverse events (Grade 1 or 2)



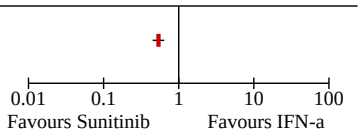
Comparison 10. Sunitinib versus Interferon-α (IFN-α)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Progression-free survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
10.2 Overall survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.3 Serious adverse events (Grade 3 or 4)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10.4 Health-related quality of life	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
10.5 Response rate	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10.6 Minor adverse events (Grade 1 or 2)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

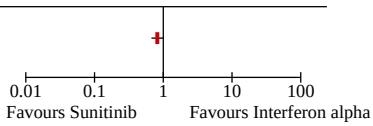
Analysis 10.1. Comparison 10: Sunitinib versus Interferon-α (IFN-α), Outcome 1: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Experimental Total	Control Total	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% CI
Motzer 2010	-0.62	0.09	375	375	0.54 [0.45 , 0.64]	



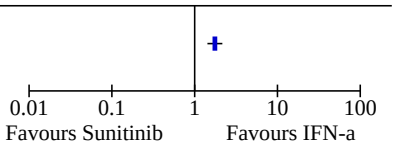
Analysis 10.2. Comparison 10: Sunitinib versus Interferon-α (IFN-α), Outcome 2: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Sunitinib Total	Interferon alpha Total	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% CI
Motzer 2010	-0.2	0.1	375	375	0.82 [0.67 , 1.00]	



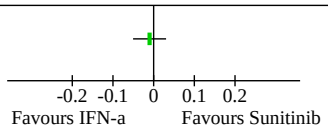
Analysis 10.3. Comparison 10: Sunitinib versus Interferon-α (IFN-α), Outcome 3: Serious adverse events (Grade 3 or 4)

Study or Subgroup	Sunitinib Events	Sunitinib Total	Interferon alpha Events	Interferon alpha Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Motzer 2010	170	375	93	360	1.75 [1.43 , 2.16]	



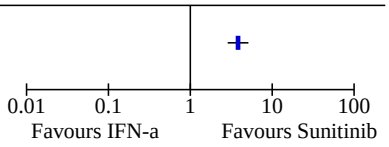
Analysis 10.4. Comparison 10: Sunitinib versus Interferon-α (IFN-α), Outcome 4: Health-related quality of life

Study or Subgroup	Sunitinib Mean	SD	Total	Interferon alpha Mean	SD	Total	Mean Difference IV, Random, 95% CI
Motzer 2010	0.73	0.25	311	0.74	0.23	233	-0.01 [-0.05 , 0.03]



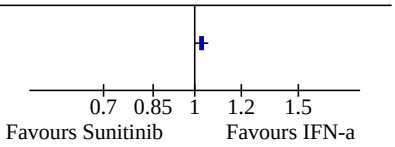
Analysis 10.5. Comparison 10: Sunitinib versus Interferon-α (IFN-α), Outcome 5: Response rate

Study or Subgroup	Sunitinib Events	Total	Interferon-alpha Events	Total	Risk Ratio M-H, Random, 95% CI
Motzer 2010	176	375	46	375	3.83 [2.86 , 5.12]



Analysis 10.6. Comparison 10: Sunitinib versus Interferon-α (IFN-α), Outcome 6: Minor adverse events (Grade 1 or 2)

Study or Subgroup	Sunitinib Events	Total	Interferon-alpha Events	Total	Risk Ratio M-H, Random, 95% CI
Motzer 2010	368	375	344	360	1.03 [1.00 , 1.05]

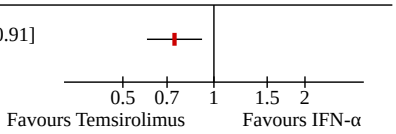


Comparison 11. Temsirolimus versus IFN-α

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Progression-free survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
11.2 Overall survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
11.3 Serious adverse events (Grade 3 or 4)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11.4 Health-related quality of life	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
11.5 Response rate	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11.6 Minor adverse events (Grade 1 or 2)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

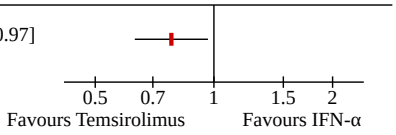
Analysis 11.1. Comparison 11: Temsirolimus versus IFN-α, Outcome 1: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Temsirolimus Total	IFN-α Total	Hazard Ratio IV, Random, 95% CI
Hudes 2007	-0.3	0.107	209	207	0.74 [0.60 , 0.91]



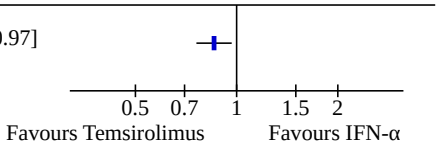
Analysis 11.2. Comparison 11: Temsirolimus versus IFN-α, Outcome 2: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Temsirolimus Total	IFN-α Total	Hazard Ratio IV, Random, 95% CI
Hudes 2007	-0.2485	0.109	209	207	0.78 [0.63 , 0.97]



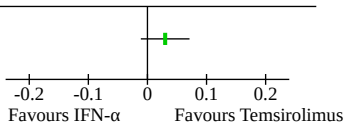
Analysis 11.3. Comparison 11: Temsirolimus versus IFN-α, Outcome 3: Serious adverse events (Grade 3 or 4)

Study or Subgroup	Temsirolimus Events	Temsirolimus Total	IFN-α Events	IFN-α Total	Risk Ratio M-H, Random, 95% CI
Hudes 2007	139	208	156	200	0.86 [0.76 , 0.97]



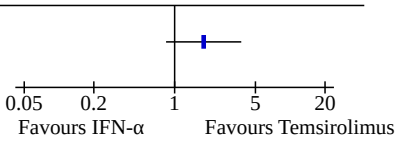
Analysis 11.4. Comparison 11: Temsirolimus versus IFN-α, Outcome 4: Health-related quality of life

Study or Subgroup	Temsirolimus Mean	Temsirolimus SD	Temsirolimus Total	IFN-α Mean	IFN-α SD	IFN-α Total	Mean Difference IV, Random, 95% CI
Hudes 2007	0.69	0.2	204	0.66	0.22	197	0.03 [-0.01 , 0.07]



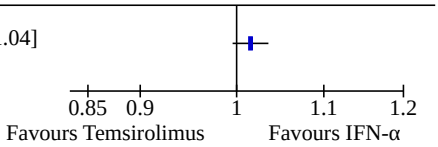
Analysis 11.5. Comparison 11: Temsirolimus versus IFN-α, Outcome 5: Response rate

Study or Subgroup	Temsirolimus Events	Temsirolimus Total	IFN-α Events	IFN-α Total	Risk Ratio M-H, Random, 95% CI
Hudes 2007	18	209	10	207	1.78 [0.84 , 3.77]



Analysis 11.6. Comparison 11: Temsirolimus versus IFN-α, Outcome 6: Minor adverse events (Grade 1 or 2)

Study or Subgroup	Temsirolimus Events	Temsirolimus Total	IFN-α Events	IFN-α Total	Risk Ratio M-H, Random, 95% CI
Hudes 2007	208	208	197	200	1.02 [1.00 , 1.04]

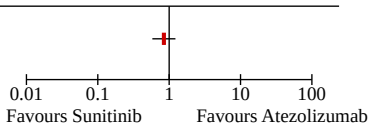


Comparison 12. Sunitinib versus Atezolizumab

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Progression-free survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
12.2 Overall survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
12.3 Serious adverse events (Grade 3 or 4)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
12.4 Health-related quality of life	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
12.5 Response rate	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
12.6 Minor adverse events (Grade 1 or 2)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

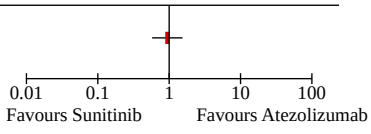
Analysis 12.1. Comparison 12: Sunitinib versus Atezolizumab, Outcome 1: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Sunitinib Total	Atezolizumab Total	Hazard Ratio IV, Random, 95% CI
McDermott 2018	-0.17	0.19	101	103	0.84 [0.58 , 1.22]



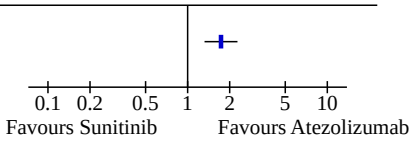
Analysis 12.2. Comparison 12: Sunitinib versus Atezolizumab, Outcome 2: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Sunitinib Total	Atezolizumab Total	Hazard Ratio IV, Random, 95% CI
McDermott 2018	-0.06	0.25	101	103	0.94 [0.58 , 1.54]



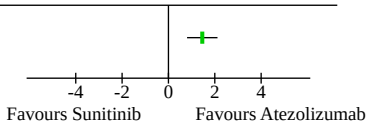
Analysis 12.3. Comparison 12: Sunitinib versus Atezolizumab, Outcome 3: Serious adverse events (Grade 3 or 4)

Study or Subgroup	Sunitinib Events	Sunitinib Total	Atezolizumab Events	Atezolizumab Total	Risk Ratio M-H, Random, 95% CI
McDermott 2018	69	100	41	103	1.73 [1.32 , 2.27]



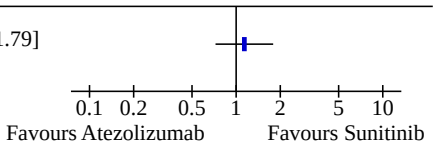
Analysis 12.4. Comparison 12: Sunitinib versus Atezolizumab, Outcome 4: Health-related quality of life

Study or Subgroup	Sunitinib Mean	Sunitinib SD	Sunitinib Total	Atezolizumab Mean	Atezolizumab SD	Atezolizumab Total	Mean Difference IV, Random, 95% CI
McDermott 2018	2.5	2.47	77	1.04	1.62	80	1.46 [0.80 , 2.12]



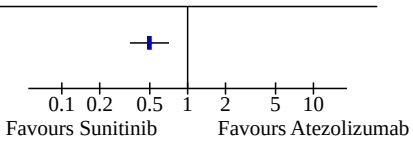
Analysis 12.5. Comparison 12: Sunitinib versus Atezolizumab, Outcome 5: Response rate

Study or Subgroup	Sunitinib Events	Sunitinib Total	Atezolizumab Events	Atezolizumab Total	Risk Ratio M-H, Random, 95% CI
McDermott 2018	29	101	26	103	1.14 [0.72 , 1.79]



Analysis 12.6. Comparison 12: Sunitinib versus Atezolizumab, Outcome 6: Minor adverse events (Grade 1 or 2)

Study or Subgroup	Sunitinib Events	Sunitinib Total	Atezolizumab Events	Atezolizumab Total	Risk Ratio M-H, Random, 95% CI
McDermott 2018	28	100	58	103	0.50 [0.35 , 0.71]



Comparison 13. Bevacizumab + IFN versus IFN (+ placebo)

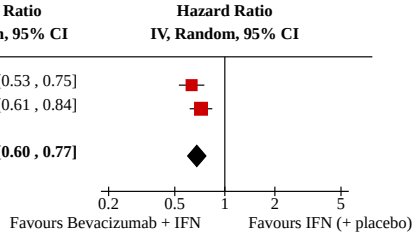
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 Progression-free survival	2	1381	Hazard Ratio (IV, Random, 95% CI)	0.68 [0.60, 0.77]
13.2 Overall survival	2	1381	Hazard Ratio (IV, Random, 95% CI)	0.88 [0.79, 0.99]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.3 Serious adverse events (Grade 3 or 4)	2	1356	Risk Ratio (M-H, Random, 95% CI)	1.31 [1.20, 1.42]
13.4 Response rate	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13.5 Minor adverse events (Grade 1 or 2)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 13.1. Comparison 13: Bevacizumab + IFN versus IFN (+ placebo), Outcome 1: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Bevacizumab + IFN Total	IFN (+ placebo) Total	Weight	Hazard Ratio IV, Random, 95% CI
Escudier 2010	-0.46	0.09	327	322	45.0%	0.63 [0.53 , 0.75]
Rini 2008	-0.33	0.08	369	363	55.0%	0.72 [0.61 , 0.84]
Total (95% CI)			**696**	**685**	**100.0%**	**0.68 [0.60 , 0.77]**

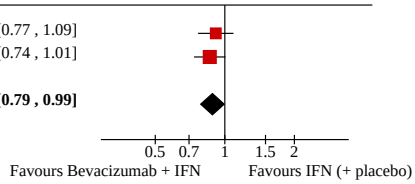
Heterogeneity: Tau² = 0.00; Chi² = 1.17, df = 1 (P = 0.28); I² = 14%
Test for overall effect: Z = 6.01 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 13.2. Comparison 13: Bevacizumab + IFN versus IFN (+ placebo), Outcome 2: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Bevacizumab + IFN Total	IFN (+ placebo) Total	Weight	Hazard Ratio IV, Random, 95% CI
Escudier 2010	-0.09	0.09	327	322	44.1%	0.91 [0.77 , 1.09]
Rini 2008	-0.15	0.08	369	363	55.9%	0.86 [0.74 , 1.01]
Total (95% CI)			**696**	**685**	**100.0%**	**0.88 [0.79 , 0.99]**

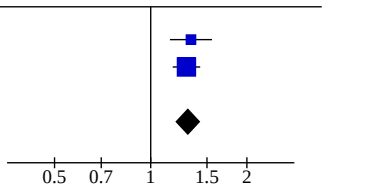
Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 1 (P = 0.62); I² = 0%
Test for overall effect: Z = 2.07 (P = 0.04)
Test for subgroup differences: Not applicable



Analysis 13.3. Comparison 13: Bevacizumab + IFN versus IFN (+ placebo), Outcome 3: Serious adverse events (Grade 3 or 4)

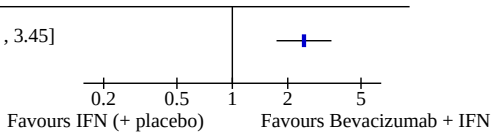
Study or Subgroup	Bevacizumab + IFN Events	Bevacizumab + IFN Total	IFN (+ placebo) Events	IFN (+ placebo) Total	Weight	Risk Ratio M-H, Random, 95% CI
Escudier 2010	203	337	137	304	30.0%	1.34 [1.15 , 1.56]
Rini 2008	289	366	213	349	70.0%	1.29 [1.17 , 1.43]
Total (95% CI)		**703**		**653**	**100.0%**	**1.31 [1.20 , 1.42]**
Total events:	492		350			

Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%
Test for overall effect: Z = 6.32 (P < 0.00001)
Test for subgroup differences: Not applicable



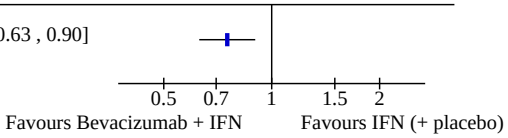
Analysis 13.4. Comparison 13: Bevacizumab + IFN versus IFN (+ placebo), Outcome 4: Response rate

Study or Subgroup	Bevacizumab + IFN Events	Total	IFN (+ placebo) Events	Total	Risk Ratio M-H, Random, 95% CI
Escudier 2010	96	306	37	289	2.45 [1.74 , 3.45]



Analysis 13.5. Comparison 13: Bevacizumab + IFN versus IFN (+ placebo), Outcome 5: Minor adverse events (Grade 1 or 2)

Study or Subgroup	Bevacizumab + IFN Events	Total	IFN (+ placebo) Events	Total	Risk Ratio M-H, Random, 95% CI
Escudier 2010	125	337	150	304	0.75 [0.63 , 0.90]

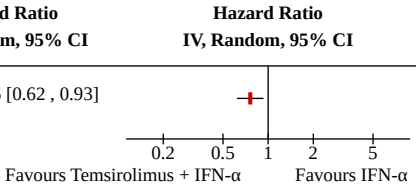


Comparison 14. Temsirolimus + IFN-α versus IFN-α

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.1 Progression-free survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
14.2 Overall survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
14.3 Serious adverse events (Grade 3 or 4)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
14.4 Health-related quality of life	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
14.5 Response rate	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
14.6 Minor adverse events (Grade 1 or 2)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

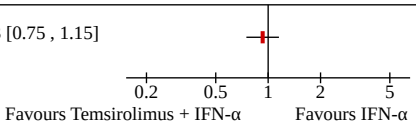
Analysis 14.1. Comparison 14: Temsirolimus + IFN-α versus IFN-α, Outcome 1: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Temsirolimus + IFN-α Total	IFN-α Total	Hazard Ratio IV, Random, 95% CI
Hudes 2007	-0.2744	0.1039	210	207	0.76 [0.62 , 0.93]



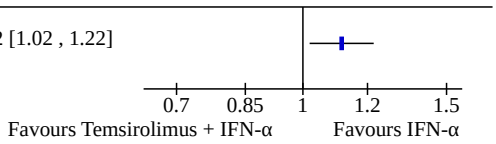
Analysis 14.2. Comparison 14: Temsirolimus + IFN-α versus IFN-α, Outcome 2: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Temsirolimus + IFN-α Total	IFN-α Total	Hazard Ratio IV, Random, 95% CI
Hudes 2007	-0.0726	0.1098	210	207	0.93 [0.75 , 1.15]



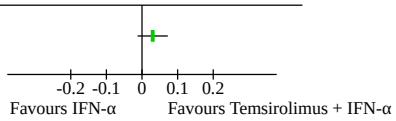
Analysis 14.3. Comparison 14: Temsirolimus + IFN-α versus IFN-α, Outcome 3: Serious adverse events (Grade 3 or 4)

Study or Subgroup	Temsirolimus + IFN-α Events	Total	IFN-α Events	Total	Risk Ratio M-H, Random, 95% CI
Hudes 2007	181	208	156	200	1.12 [1.02 , 1.22]



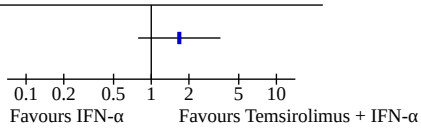
Analysis 14.4. Comparison 14: Temsirolimus + IFN-α versus IFN-α, Outcome 4: Health-related quality of life

Study or Subgroup	Temsirolimus + IFN-α Mean	SD	Total	IFN-α Mean	SD	Total	Mean Difference IV, Random, 95% CI
Hudes 2007	0.69	0.21	197	0.66	0.22	197	0.03 [-0.01 , 0.07]



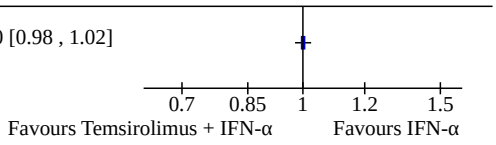
Analysis 14.5. Comparison 14: Temsirolimus + IFN-α versus IFN-α, Outcome 5: Response rate

Study or Subgroup	Temsirolimus + IFN-α Events	Total	IFN-α Events	Total	Risk Ratio M-H, Random, 95% CI
Hudes 2007	17	210	10	207	1.68 [0.79 , 3.57]



Analysis 14.6. Comparison 14: Temsirolimus + IFN-α versus IFN-α, Outcome 6: Minor adverse events (Grade 1 or 2)

Study or Subgroup	Temsirolimus + IFN-α Events	Total	IFN-α Events	Total	Risk Ratio M-H, Random, 95% CI
Hudes 2007	205	208	197	200	1.00 [0.98 , 1.02]

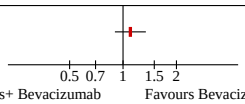


Comparison 15. Temsirolimus + Bevacizumab versus Bevacizumab + IFN-α

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.1 Progression-free survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
15.2 Overall survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
15.3 Serious adverse events (Grade 3 or 4)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
15.4 Response rate	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
15.5 Minor adverse events (Grade 1 or 2)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

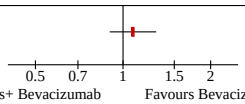
Analysis 15.1. Comparison 15: Temsirolimus + Bevacizumab versus Bevacizumab + IFN-α, Outcome 1: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Temsirolimus+ Bevacizumab Total	Bevacizumab + IFN-α Total	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% CI
Rini 2014	0.0953	0.1024	400	391	1.10 [0.90 , 1.34]	



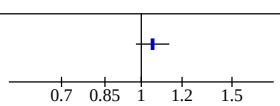
Analysis 15.2. Comparison 15: Temsirolimus + Bevacizumab versus Bevacizumab + IFN-α, Outcome 2: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Temsirolimus+ Bevacizumab Total	Bevacizumab + IFN-α Total	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% CI
Rini 2014	0.0785	0.0938	400	391	1.08 [0.90 , 1.30]	

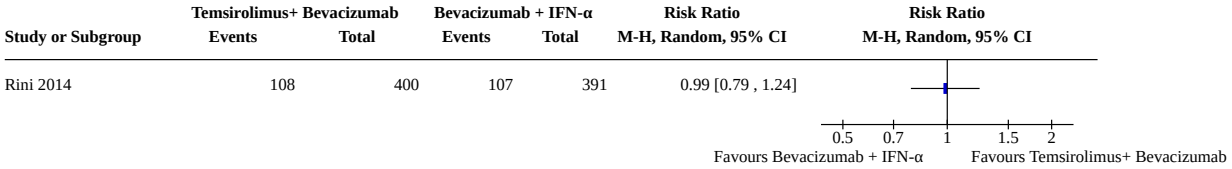


Analysis 15.3. Comparison 15: Temsirolimus + Bevacizumab versus Bevacizumab + IFN-α, Outcome 3: Serious adverse events (Grade 3 or 4)

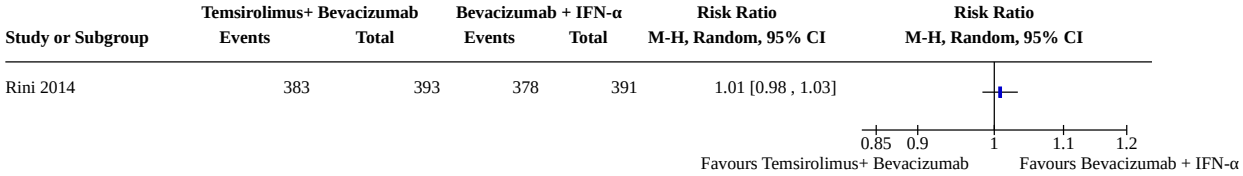
Study or Subgroup	Temsirolimus+ Bevacizumab Events	Total	Bevacizumab + IFN-α Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Rini 2014	314	393	297	391	1.05 [0.98 , 1.13]	



Analysis 15.4. Comparison 15: Temsirolimus + Bevacizumab versus Bevacizumab + IFN-α, Outcome 4: Response rate



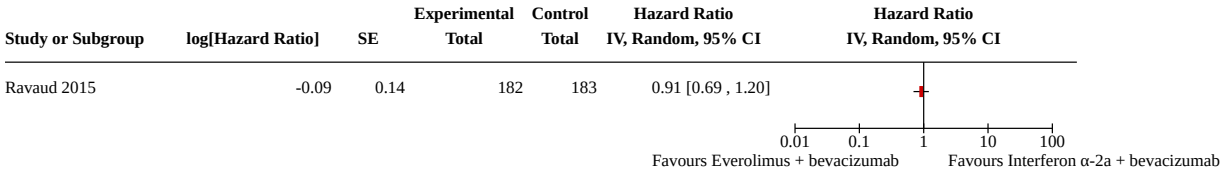
Analysis 15.5. Comparison 15: Temsirolimus + Bevacizumab versus Bevacizumab + IFN-α, Outcome 5: Minor adverse events (Grade 1 or 2)



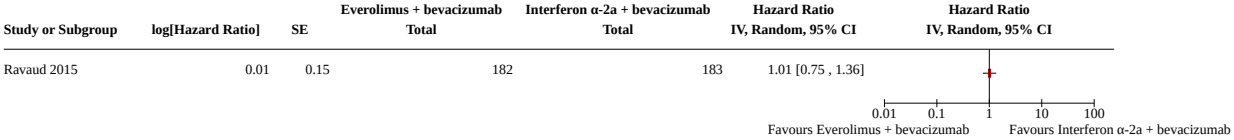
Comparison 16. Everolimus + Bevacizumab versus IFN α-2a + Bevacizumab

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.1 Progression-free survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
16.2 Overall survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
16.3 Serious adverse events (Grade 3 or 4)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
16.4 Response rate	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
16.5 Minor adverse events (Grade 1 or 2)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

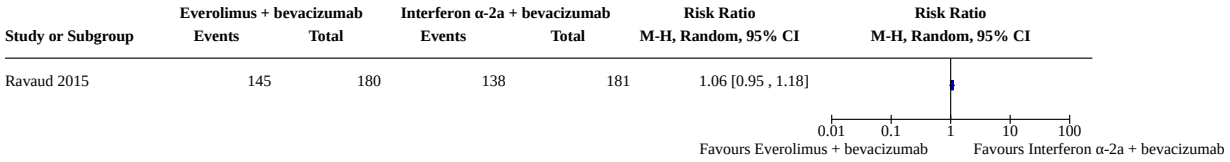
Analysis 16.1. Comparison 16: Everolimus + Bevacizumab versus IFN α-2a + Bevacizumab, Outcome 1: Progression-free survival



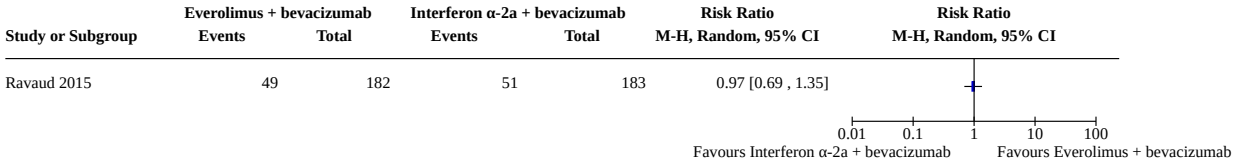
Analysis 16.2. Comparison 16: Everolimus + Bevacizumab versus IFN α-2a + Bevacizumab, Outcome 2: Overall survival



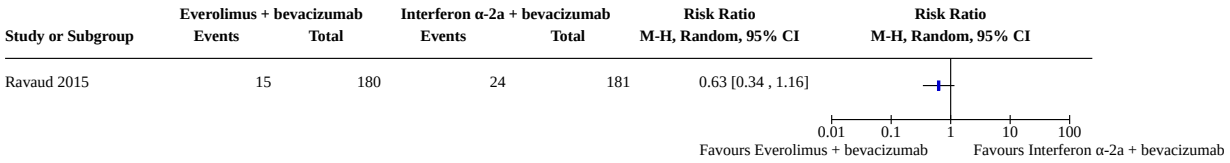
Analysis 16.3. Comparison 16: Everolimus + Bevacizumab versus IFN α-2a + Bevacizumab, Outcome 3: Serious adverse events (Grade 3 or 4)



Analysis 16.4. Comparison 16: Everolimus + Bevacizumab versus IFN α-2a + Bevacizumab, Outcome 4: Response rate



Analysis 16.5. Comparison 16: Everolimus + Bevacizumab versus IFN α-2a + Bevacizumab, Outcome 5: Minor adverse events (Grade 1 or 2)

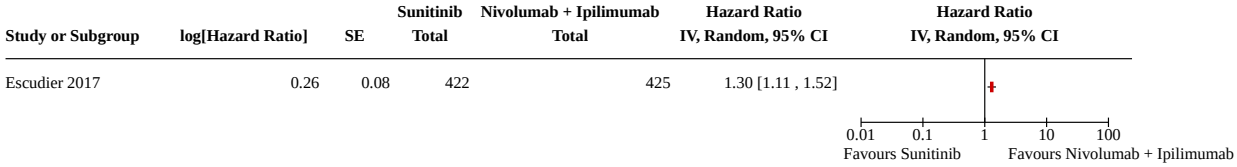


Comparison 17. Sunitinib versus Nivolumab + Ipilimumab

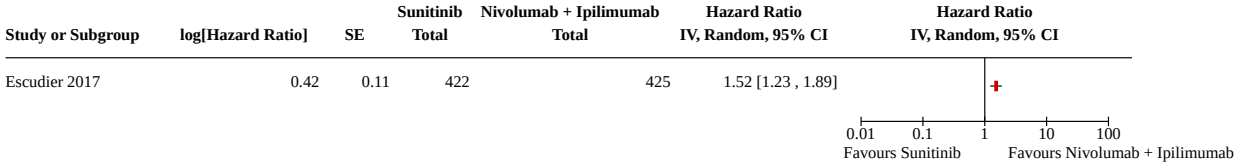
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.1 Progression-free survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
17.2 Overall survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
17.3 Serious adverse events (Grade 3 or 4)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.4 Health-related quality of life	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
17.5 Response rate	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
17.6 Minor adverse events (Grade 1 or 2)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

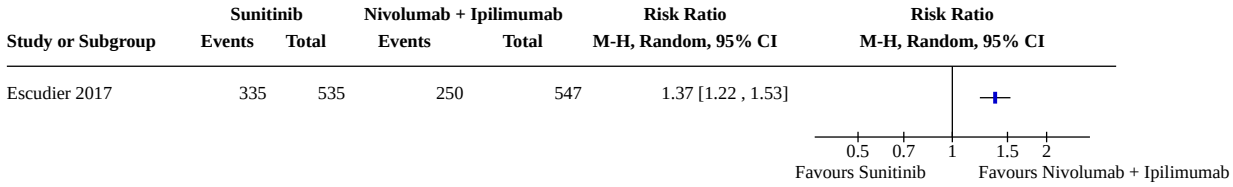
Analysis 17.1. Comparison 17: Sunitinib versus Nivolumab + Ipilimumab, Outcome 1: Progression-free survival



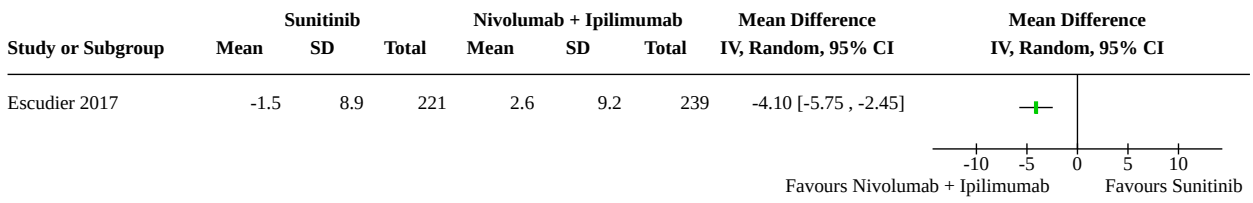
Analysis 17.2. Comparison 17: Sunitinib versus Nivolumab + Ipilimumab, Outcome 2: Overall survival



Analysis 17.3. Comparison 17: Sunitinib versus Nivolumab + Ipilimumab, Outcome 3: Serious adverse events (Grade 3 or 4)

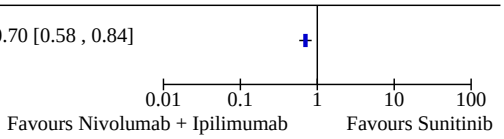


Analysis 17.4. Comparison 17: Sunitinib versus Nivolumab + Ipilimumab, Outcome 4: Health-related quality of life



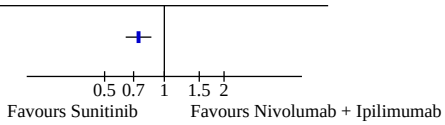
Analysis 17.5. Comparison 17: Sunitinib versus Nivolumab + Ipilimumab, Outcome 5: Response rate

Study or Subgroup	Sunitinib Events	Sunitinib Total	Nivolumab + Ipilimumab Events	Nivolumab + Ipilimumab Total	Risk Ratio M-H, Random, 95% CI
Escudier 2017	124	422	178	425	0.70 [0.58 , 0.84]



Analysis 17.6. Comparison 17: Sunitinib versus Nivolumab + Ipilimumab, Outcome 6: Minor adverse events (Grade 1 or 2)

Study or Subgroup	Sunitinib Events	Sunitinib Total	Nivolumab + Ipilimumab Events	Nivolumab + Ipilimumab Total	Risk Ratio M-H, Random, 95% CI
Escudier 2017	182	535	251	547	0.74 [0.64 , 0.86]

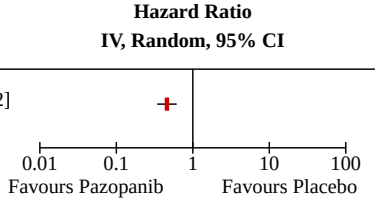


Comparison 18. Pazopanib versus Placebo

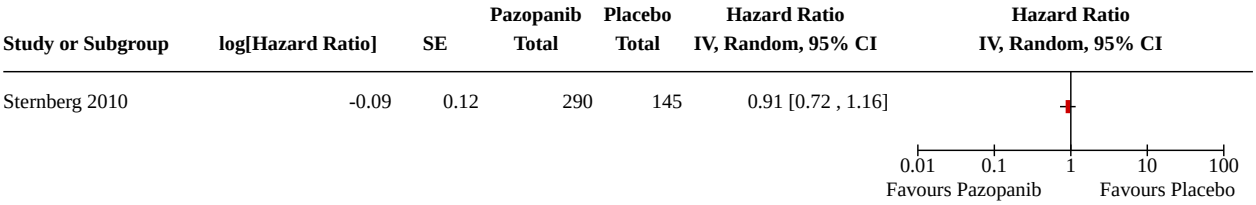
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.1 Progression-free survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
18.2 Overall survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
18.3 Serious adverse events (Grade 3 or 4)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
18.4 Health-related quality of life	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
18.5 Response rate	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
18.6 Minor adverse events (Grade 1 or 2)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 18.1. Comparison 18: Pazopanib versus Placebo, Outcome 1: Progression-free survival

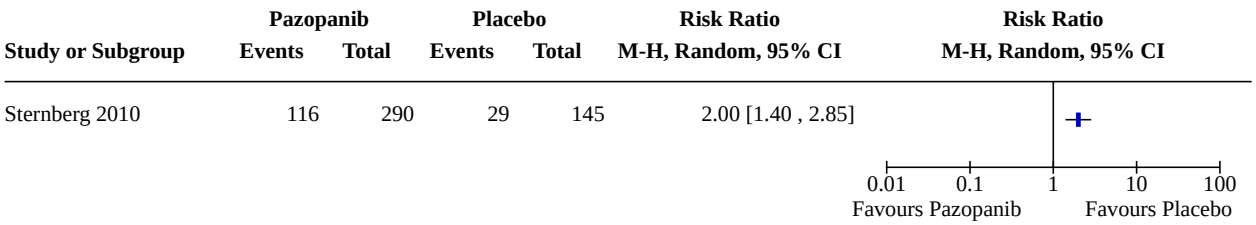
Study or Subgroup	log[Hazard Ratio]	SE	Pazopanib Total	Placebo Total	Hazard Ratio IV, Random, 95% CI
Sternberg 2010	-0.78	0.15	290	145	0.46 [0.34 , 0.62]



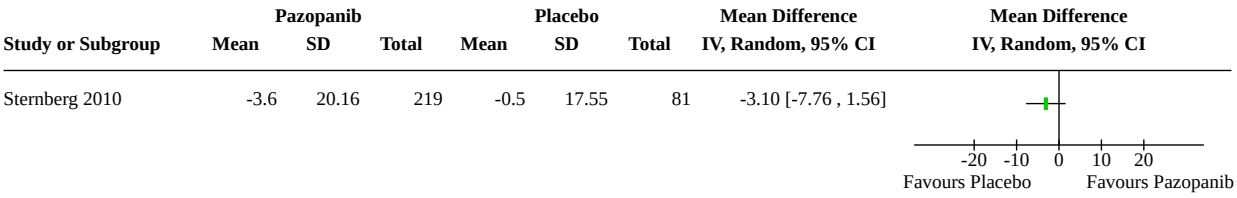
Analysis 18.2. Comparison 18: Pazopanib versus Placebo, Outcome 2: Overall survival



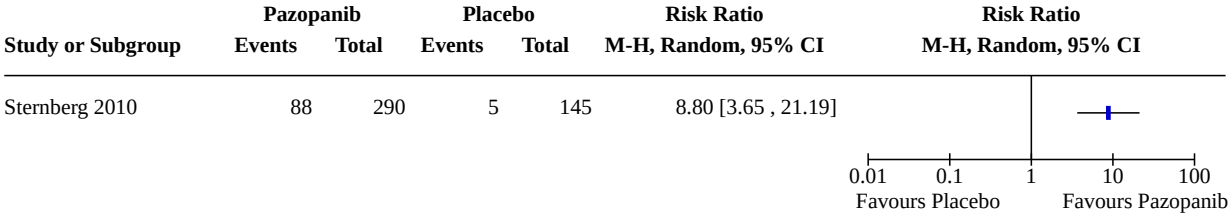
Analysis 18.3. Comparison 18: Pazopanib versus Placebo, Outcome 3: Serious adverse events (Grade 3 or 4)



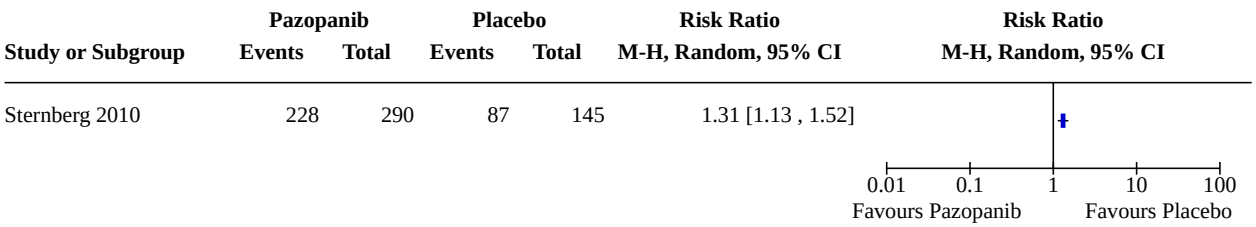
Analysis 18.4. Comparison 18: Pazopanib versus Placebo, Outcome 4: Health-related quality of life



Analysis 18.5. Comparison 18: Pazopanib versus Placebo, Outcome 5: Response rate



Analysis 18.6. Comparison 18: Pazopanib versus Placebo, Outcome 6: Minor adverse events (Grade 1 or 2)



ADDITIONAL TABLES

Table 1. Individual targeted agents to be searched

Axitinib
Bevacizumab
Dovitinib
Erlotinib
Everolimus
Lapatinib
Pazopanib
Sorafenib
Sunitinib
Temsirolimus
Tivozanib
Other agents identified during search

Table 2. Participants disposition

Studies	Intervention(s)/ Comparator(s)	Randomised (N)	Received treatment (N)	Discontinued treatment (N)	Efficacy analysis (N)	Safety analysis (N)
Eichelberg 2015	Soreafenib/ Sunitinib	182	177	161	182	177
	Sunitinib/ Sorafenib	183	176	156	183	176
Escudier 2010	Bevacizumab + IFN-a2a	327	325	206	327	337
	IFN-a2a + Placebo	322	316	274	322	304
Escudier 2017 1	Sunitinib	546	535	438	546	535
	Nivolumab + Ipilimumab	550	547	419	550	547
Hudes 2007	Temsirolimus	209	208	199	209	208
	Temsirolimus + Interferon	210	208	193	210	208
	Interferon	207	200	194	207	200
McDermott 2017	Sunitinib	101	100	83	101	100
	Atezolizumab + Bevacizumab	101	101	69	101	101

Table 2. Participants disposition *(Continued)*

	Atezolizumab	103	103	80	103	103
Motzer 2010	Sunitinib	375	375	127	375	375
	IFN-a2a	375	360	234	375	360
Motzer 2013a	Pazopanib	557	554	486	557	554
	Sunitinib	553	548	483	553	548
Motzer 2013b	Tivozanib	260	259	154	260	259
	Sorafenib	257	257	192	257	257
Motzer 2014	Sunitinib/ Everolimus	233	231	192	233	231
	Everolimus/ Sunitinib	238	238	201	238	238
Motzer 2019	Sunitinib	444	439	227	444	439
	Avelumab + Axitinib	442	434	187	442	434
Ravaud 2015	Everolimus + Bevacizumab	182	180	175	182	180
	Interferon + Bevacizumab	183	181	175	183	181
Retz 2019	Sorafenib/ Pazopanib	189	183	115	189	183
	Pazopanib/ Sorafenib	188	183	110	188	183
Rini 2008	Bevacizumab + IFN-a2b	369	366	355	369	366
	IFN-a2b	363	350	355	363	349
Rini 2014	Temsirolimus + Bevacizumab	400	393	372	400	393
	Temsirolimus + Interferon	391	391	354	391	391
Rini 2016	Sunitinib	135	130	23	135	132
	IMA901 + Sunitinib	204	185	28	204	202
Rini 2019a	Sunitinib	429	425	242	429	425
	Pembrolizumab + Axitinib	432	429	176	432	429
Rini 2019b	Sunitinib	461	446	308	461	446
	Atezolizumab + Bevacizumab	454	451	265	454	451
Sternberg 2010	Pazopanib	290	290	227	290	290
	Placebo	145	145	131	145	145
Total		11590	11419	8366	11590	11437

[1] Included overall population; but in the data and analyses section and summary of findings table, we used IMDC intermediate and poor risk patients for efficacy analysis.

Table 3. Baseline characteristics

Studies	Phase of study	Accrual	Blinding	RCC subtype	Prior therapy	Intervention / Comparator
Eichelberg 2015	3	Feb 2009 to Dec 2011	open label study	any, 87% clear cell	naïve	Soreafenib/Sunitinib
						Sunitinib/Sorafenib
Escudier 2010	3	Jun 2004 to Oct 2005	double-blind study	clear cell	naïve	Bevacizumab + IFN-a2a
						IFN-a2a + Placebo
Escudier 2017	3	Oct 2014 to Feb 2016	open label study	clear cell	naïve	Sunitinib
						Nivolumab + Ipilimumab
Hudes 2007	3	Jul 2003 to Apr 2005	open label study	any, 80% clear cell	naïve	Temsirolimus
						Temsirolimus + Interferon
						Inferferon
McDermott 2017	2	Jan 2014 to Mar 2015	open label study	clear cell	naïve	Sunitinib
						Atezolizumab + Bevacizumab
						Atezolizumab
Motzer 2010	3	Aug 2004 to Oct 2005	radiologic assessment	clear cell	naïve	Sunitinib
						IFN-a2a
Motzer 2013a	3	Aug 2008 to Sep 2011	open label study	clear cell	naïve	Pazopanib
						Sunitinib
Motzer 2013b	2	Feb 2010 to Aug 2010	open label study	clear cell	naïve	Tivozanib
						Sorafenib
Motzer 2014	2	Sep 2009 to Jun 2012	open label study	any, 85% clear cell	naïve	Sunitinib/ Everolimus
						Everolimus/ Sunitinib
Motzer 2019	3	Mar 2016 to Dec 2017	open label study	clear cell	naïve	Sunitinib
						Avelumab + Axitinib
Ravaud 2015	2	-	open label study	any 96% clear cell	naïve	Everolimus + Bevacizumab
						Interferon + Bevacizumab

Table 3. Baseline characteristics *(Continued)*

Retz 2019	3	Jun 2012 to Nov 2016	open label study	any, 87% clear cell	naïve	Sorafenib/ Pazopanib
						Pazopanib/ Sorafenib
Rini 2008	3	Oct 2003 to Jul 2005	open label study	clear cell	naïve	Bevacizumab + IFN-a2b
						IFN-a2b
Rini 2014	3	Apr 2008 to Oct 2010	open label study	any, 80% clear cell	naïve	Temsirolimus + Bevacizumab
						Bevacizumab + Inferferon
Rini 2016	3	Dec 2010 to Dec 2012	open label study	clear cell	naïve	Sunitinib
						IMA901 + Sunitinib
Rini 2019a	3	Oct 2016 to Jan 2018	open label study	clear cell	naïve	Sunitinib
						Pembrolizumab + Axitinib
Rini 2019b	3	May 2015 to Oct 2016	open label study	clear cell	naïve	Sunitinib
						Atezolizumab + Bevacizumab
Sternberg 2010	3	Apr 2006 to Apr 2007	double-blind study	clear cell	54% naive	Pazopanib
						Placebo

- denotes not reported

IFN: interferon; RCC: renal cell carcinoma

APPENDICES

Appendix 1. EAU panel search strategy

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MEDLINE 1946 to 2020 18 June
MEDLINE-In-Process and other Non-Indexed Citations 18 June 2020
1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomi?ed.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8
10. Carcinoma, Renal Cell/
11. (metastas* adj5 ((kidney or renal) adj2 (cancer* or carcinoma* or neoplasm* or tum?or* or mass*))).tw.
12. or/10-11
13. Chemotherapy, Cancer, Regional Perfusion/
14. thalidomide/
15. exp Antineoplastic Protocols/
16. exp Antineoplastic agents/

17. (axitinib or bevacizumab or dovitinib or erlotinib or everolimus or lapatinib or pazopanib or sorafenib or sunitinib or temsirolimus or thalidomide or tivozanib).tw.
18. antineoplastic$.tw.
19. or/13-18
20. 9 and 12 and 19
21. (conference or letter or editorial or comment*).pt.
22. exp animals/ not humans/
23. 20 not (21 or 22)
24. Limit 23 to yr="2001 -Current"
Embase 1974 to 2020 June 18
1. kidney carcinoma/
2. (metastas* adj5 ((kidney or renal) adj2 (cancer* or carcinoma* or neoplasm* or tum?or* or mass*))).tw.
3. 1 or 2
4. exp cancer chemotherapy/
5. exp Antineoplastic agent/
6. sorafenib/
7. sunitinib/
8. bevacizumab/
9. axitinib/
10. pazopanib/
11. everolimus/
12. temsirolimus/
13. interferon/
14. interleukin 2/
15. dovitinib/
16. tivozanib/
17. erlotinib/
18. (axitinib or bevacizumab or dovitinib or erlotinib or everolimus or lapatinib or pazopanib or sorafenib or sunitinib or temsirolimus or thalidomide or tivozanib).tw.
19. antineoplastic$.tw.
20. or/4-19
21. random.tw.
22. placebo.mp.
23. double-blind.tw.
24. or/21-23
25. 3 and 20 and 24
26. exp animals/ not humans/
27. (conference or letter or editorial or comment*).pt.
28. 25 not (26 or 27)
29. Limit 28 to yr="2001 -Current"
Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials
(The Cochrane Library, 18 June 2020) www.thecochranelibrary.com
1. MeSH descriptor Carcinoma, Renal Cell, this term only
2. (metastas* near/5 ((kidney or renal) near/2 (cancer* or carcinoma* or neoplasm* or tum?or* or mass*)))
3. (#1 OR #2)
4. (#3), from 2001 to current
LILACS
18 June 2020
http://lilacs.bvsalud.org/en/
(tw:(renal cell carcinoma or renal cancer or renal tumour$ or renal tumor$ or renal carcinoma$ or renal neoplasm$ or renal mass$ or kidney cancer or kidney tumour$ or kidney tumor$ or kidney neoplasm$ or kidney mass$)) OR (mh:(kidney neoplasms))
Type of study: Controlled Clinical Trial

Clinicaltrials.gov: http://clinicaltrials.gov
Basic search: metastatic renal cell carcinoma
WHO International Clinical Trials Registry Platform http://apps.who.int/
Basic search: metastatic renal cell carcinoma

Appendix 2. Survey of study investigators providing information on included studies

Study	Date trial author contacted (first)	Date trial author provided data (latest)	Data trial author provided (short summary)
Retz 2019	19 May 2019	27 May 2019	Health-related quality of life standard deviation

WHAT'S NEW

Date	Event	Description
27 August 2020	New citation required and conclusions have changed	In this update, we added new studies such as targeted therapy versus combinations of immunotherapy. We applied current MECIR standards as well as GRADE to assess the certainty of evidence. The conclusions of this review have changed.

HISTORY

Protocol first published: Issue 9, 2017
Review first published: Issue 10, 2020

Date	Event	Description
1 July 2010	New search has been performed	Complete update with additional studies, revised analysis, risk of bias assessment, and revised conclusions. Specifically, the search has been updated from the end of 2007 to June 2010, with 5 new eligible studies identified; analyses are now based on the nature of the control arm. Targeted agents have now been validated as first and second-line therapy choices for patients with advanced renal cancers of the clear cell subtype.
8 April 2010	New search has been performed	Converted to new review format.
14 January 2008	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Contributions to the protocol

This protocol version concept and design: Fabian Hofmann, Thomas BL Lam, Axel Bex

Submitted and revised protocol: final approval by all authors.

Contributions to the review

Fabian Hofmann (FH): conception and study design, drafting the protocol, searching for trials, study selection, extracting data, assessing risk of bias, performing data analysis, interpretation of data, and drafting the review.

Eu Chang Hwang (ECH): extracting data, assessing risk of bias, performing data analysis, interpretation of data.

Thomas BL Lam (TB): conception and study design, drafting the protocol, searching for trials, study selection, extracting data, assessing risk of bias, drafting the review and providing methodological advices on the review.

Axel Bex (AB): conception and study design, drafting the protocol, searching for trials, study selection, drafting the review and providing clinical advices on the review.

Yuhong Yuan (YY): creating search strategies, searching for trials and drafting the review.

Lorenzo SO Marconi (LM): searching for trials, study selection, extracting data, assessing risk of bias

Börje Ljungberg (BL): searching for trials, study selection, drafting the review and providing clinical advices on the review.

DECLARATIONS OF INTEREST

F Hofmann: declares the following relevant activities outside the submitted work: employed as a urologist, serves as guideline associate of European Association of Urology Renal Cell Carcinoma Guideline Panel and reports receiving no compensation for panel membership. Received payment from Ipsen for presenting at Ipsen-sponsored symposia and conferences.

EC Hwang: none known

LSO Marconi: none known

Yuhong Y: none known.

TBL Lam: declares the following relevant activity outside the submitted work: serves as member of European Association of Urology Renal Cell Carcinoma Guideline Panel and reports receiving no compensation for panel membership.

A Bex: declares the following relevant activities outside the submitted work: received consultancy support paid to his institution by Pfizer and Novartis for taking part in advisory boards; received payment from Pfizer and GlaxoSmithKline for presenting at Pfizer and GlaxoSmithKline sponsored symposia and conferences. These companies produce interventions (mTOR inhibitors and VEGF-targeting therapy) that are researched in the review. Dr. Bex also reports that he is principal investigator of the European Organisation for Research and Treatment of Cancer (EORTC) SURTIME trial, a randomised phase III trial comparing immediate versus deferred nephrectomy in patients with synchronous metastatic renal cell carcinoma, which is in part supported by a grant from Pfizer to the sponsor (EORTC).

B Ljungberg: declares the following relevant activities outside the submitted work: received support from Pfizer, GlaxoSmithKline and Novartis for advisory board attendance, most recently in early 2013, on the topic of renal cell carcinoma. Most interventions assessed in the review are produced by these companies.

SOURCES OF SUPPORT

Internal sources

- Fabian Hofmann, Sweden

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review is based on a published protocol (Hofmann 2017) and underwent some changes during the process of completion.

1. We expanded the scope to include newer immunotherapy agents. Several of these drugs have been compared to targeted agents mainly in first line treatment and the comparisons are included in this review.
2. We initially planned to include second and further line treatments into this review. Since the first publication of the protocol there has been a dramatic increase in available treatment options mainly in first, but also in second and further lines. We therefore chose to focus on treatment-naïve patients to retain a manageable review scope.
3. We restricted the number of participants per study arm to at least 100 which we considered as sufficient to make clinically substantial conclusions and at the same time limit small study bias.

NOTES

This is review is developed from the existing Cochrane Review entitled, "Targeted therapy for advanced renal cell carcinoma" (Coppin 2008).

We have based parts of the Methods section of this Cochrane protocol on a standard template established by the CMED Group.

INDEX TERMS

Medical Subject Headings (MeSH)

Antibodies, Monoclonal, Humanized [adverse effects] [therapeutic use]; Antineoplastic Agents [adverse effects] [*therapeutic use]; Antineoplastic Agents, Immunological [therapeutic use]; Axitinib [adverse effects] [therapeutic use]; Bevacizumab [adverse effects] [therapeutic use]; Bias; Carcinoma, Renal Cell [*drug therapy] [mortality]; Everolimus [adverse effects] [therapeutic use]; Indazoles; Ipilimumab [adverse effects] [therapeutic use]; Kidney Neoplasms [*drug therapy] [mortality] [pathology]; Phenylurea Compounds [adverse effects] [therapeutic use]; Progression-Free Survival; Protein Kinase Inhibitors [adverse effects] [*therapeutic use]; Pyrimidines [adverse effects] [therapeutic use]; Quality of Life; Quinolines [adverse effects] [therapeutic use]; Randomized Controlled Trials as Topic; Receptors, Vascular Endothelial Growth Factor [antagonists & inhibitors]; Sirolimus [adverse effects] [analogs & derivatives] [therapeutic use]; Sorafenib [adverse effects] [therapeutic use]; Sulfonamides [adverse effects] [therapeutic use]; Sunitinib [adverse effects] [therapeutic use]

MeSH check words

Adult; Humans