

Appendix

Search strategy

Pubmed:

((((((((((((sorafenib[Title/Abstract]) OR sunitinib[Title/Abstract]) OR bevacizumab[Title/Abstract]) OR pazopanib[Title/Abstract]) OR temsirolimus[Title/Abstract]) OR everolimus[Title/Abstract]) OR axitinib[Title/Abstract]) OR Cabozantinib[Title/Abstract]) OR IFN-alpha[Title/Abstract]) OR IL-2[Title/Abstract]) OR Nivolumab[Title/Abstract]) OR Immune checkpoint blockade[Title/Abstract])) AND (("Carcinoma, Renal Cell"[Mesh]) OR (((renal cancer[Title]) OR renal carcinoma[Title]) OR kidney cancer[Title]) OR kidney carcinoma[Title]))
Filter: Controlled Clinical Trial

Cochrane Library:

#1 sorafenib:ti,ab,kw or sunitinib:ti,ab,kw or bevacizumab:ti,ab,kw or temsirolimus:ti,ab,kw or pazopanib:ti,ab,kw (Word variations have been searched)

#2 everolimus:ti,ab,kw or afatinib:ti,ab,kw or cabozanitinb:ti,ab,kw or IFN:ti,ab,kw or IL-2:ti,ab,kw (Word variations have been searched)

#3 nivolumab:ti,ab,kw or Immune checkpoint blockade:ti,ab,kw (Word variations have been searched)

#4 MeSH descriptor: [Carcinoma, Renal Cell] explode all trees

#5 #1 or #2 or #3

#6 #4 and #5, Filter: Trials

Web of science

1 (((((((((((Topic: (sorafenib) OR Topic: (sunitinib)) OR Topic: (bevacizumab)) OR Topic: (pazopanib)) OR Topic: (temsirolimus)) OR Topic: (everolimus)) OR Topic: (afatinib)) OR Topic: (cabozanitinb)) OR Topic: (IFN)) OR Topic: (IL-2)) OR Topic: (nivolumab)) OR Topic: (Immune checkpoint blockade))

2 Title: (renal cell carcinoma) OR Title: (renal cancer) OR Title: (renal carcinoma) OR Title: (kidney cancer) OR Title: (kidney carcinoma)

3 #2 AND #1

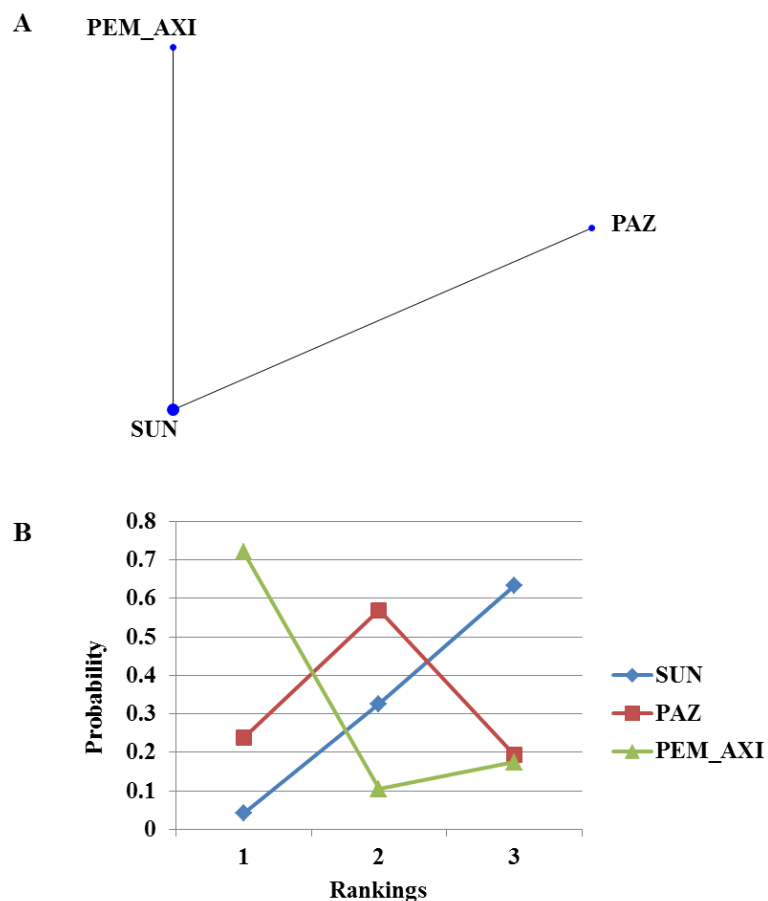
4 #2 AND #1 Document Types: CLINICAL TRIAL

ClinicalTrials.gov:

Category: “renal cell carcinoma OR renal cancer OR renal carcinoma OR kidney cancer OR kidney carcinoma, Studies With Results”

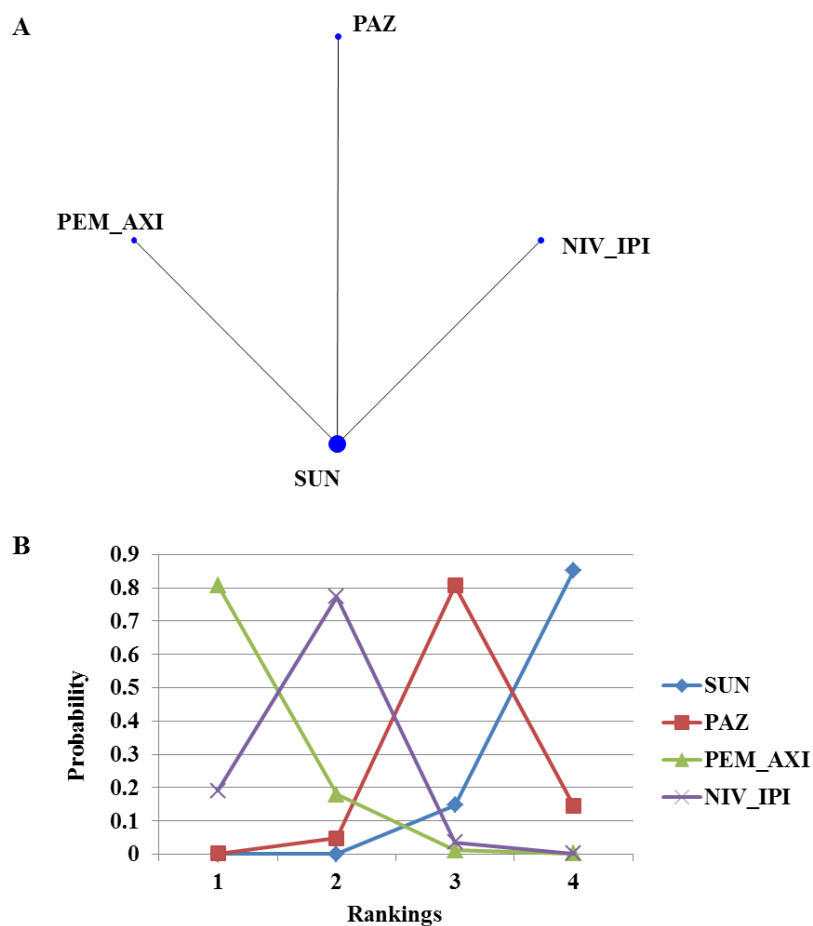
(<http://clinicaltrials.gov/>)

Appendix figure 1 Analysis of overall survival for patients with favorable-risk disease.

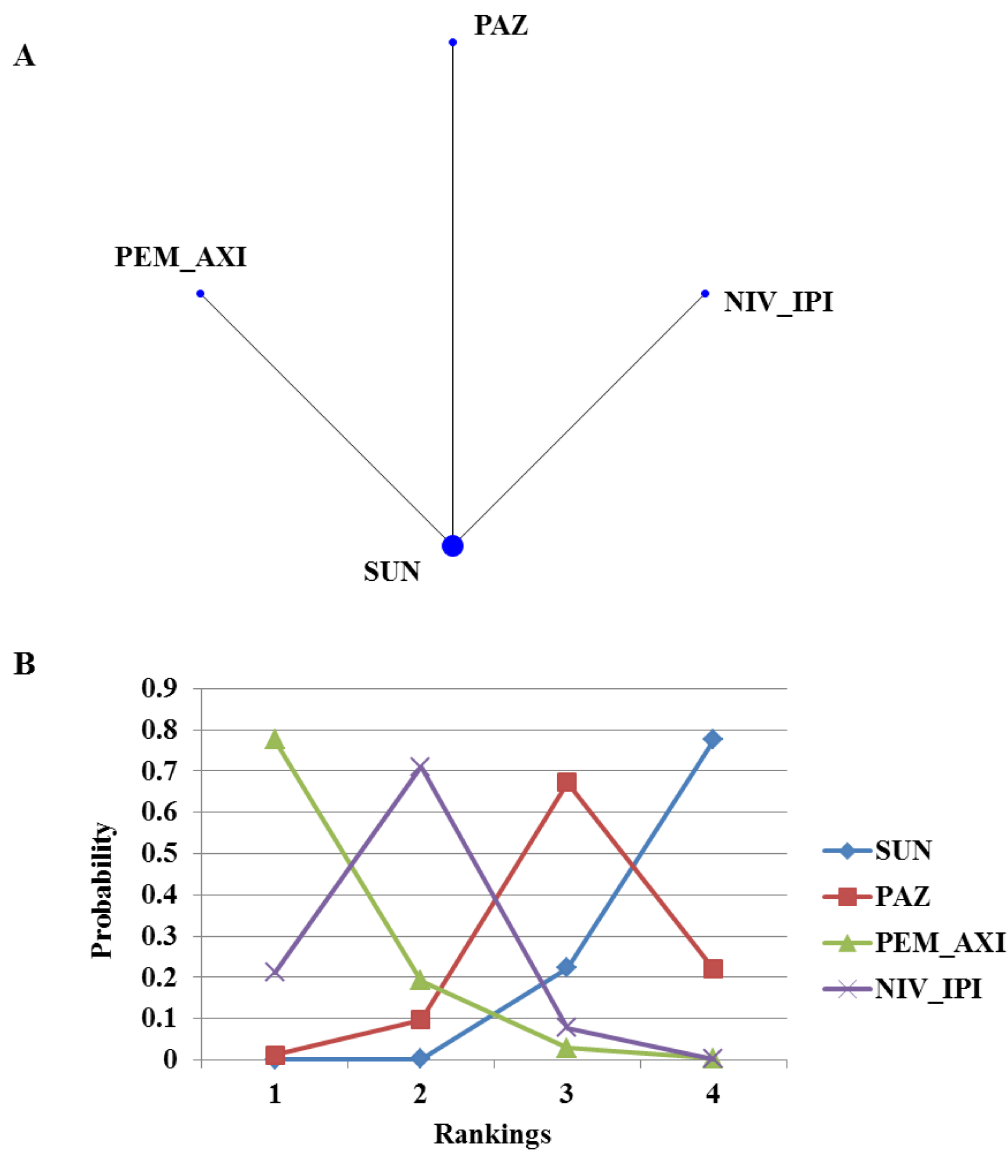


(A) network diagram: the size of every treatment node corresponds to the number of randomly assigned patients. The width of the lines is proportional to the number of trials. (B) Ranking of treatments in terms of overall survival. Rankograms were drawn according to distribution of the ranking probabilities. Ranking indicates the probability to be the best treatment, the second best, the third best, and so on in terms of overall survival, among the three treatments. SUN = sunitinib. PAZ = pazopanib. PEM_AXI = pembrolizumab plus axitinib.

Appendix figure 2 Analysis of overall survival for patients with intermediate-risk disease.



(A) network diagram: the size of every treatment node corresponds to the number of randomly assigned patients. The width of the lines is proportional to the number of trials. (B) Ranking of treatments in terms of overall survival. Rankograms were drawn according to distribution of the ranking probabilities. Ranking indicates the probability to be the best treatment, the second best, the third best, and so on in terms of overall survival, among the four treatments. SUN = sunitinib. PAZ = pazopanib. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI = pembrolizumab plus axitinib.

Appendix figure 3 Analysis of overall survival for patients with poor-risk disease.

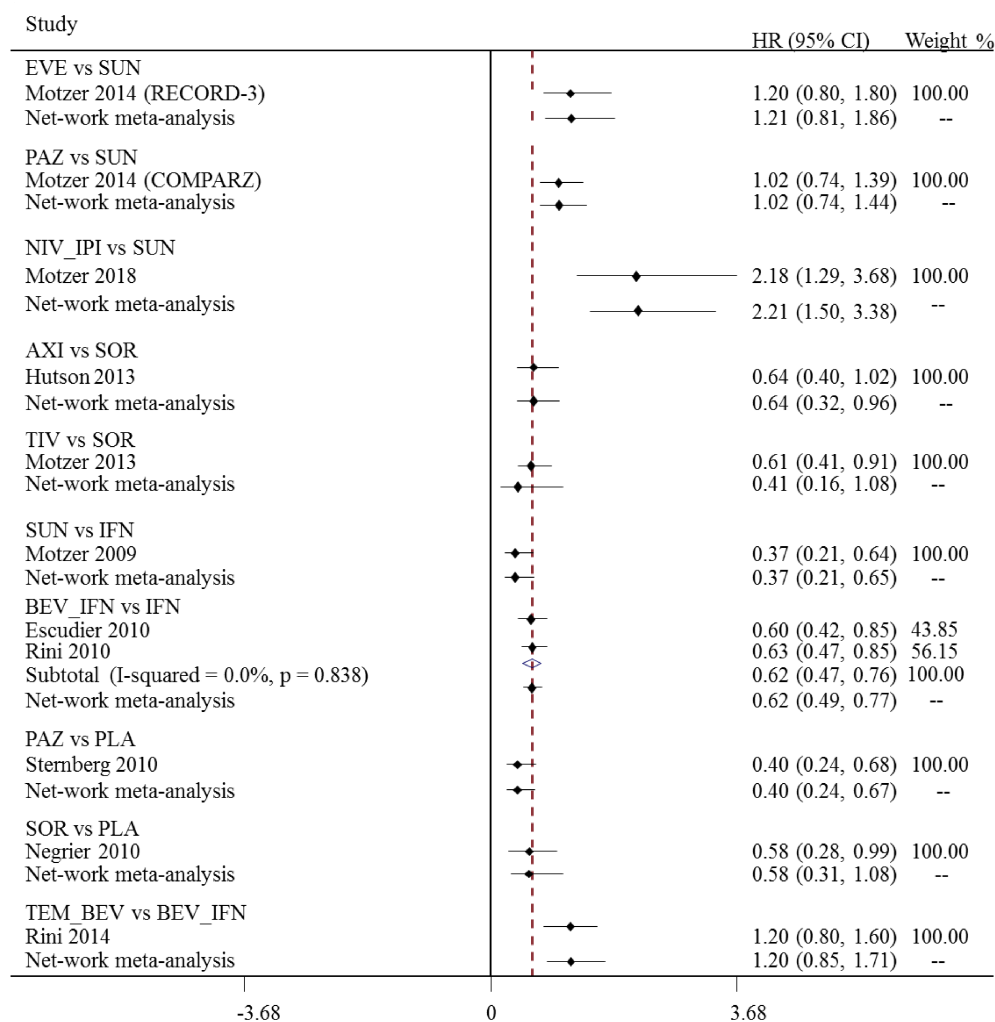
(A) network diagram: the size of every treatment node corresponds to the number of randomly assigned patients. The width of the lines is proportional to the number of trials. (B) Ranking of treatments in terms of overall survival. Rankograms were drawn according to distribution of the ranking probabilities. Ranking indicates the probability to be the best treatment, the second best, the third best, and so on in terms of overall survival, among the four treatments. SUN = sunitinib. PAZ = pazopanib. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI = pembrolizumab plus axitinib.

Appendix figure 4: Pooled odds ratios for overall adverse events by Bayesian network meta-analysis

SUN	2.28 (0.27, 23.95)	1.05 (0.03, 45.23)	0.34 (0.08, 1.40)	0.38 (0.05, 2.41)	1.61 (0.17, 19.17)
	PAZ	0.46 (0.01, 34.72)	0.15 (0.01, 1.94)	0.16 (0.01, 2.69)	0.68 (0.03, 18.38)
		CAB	0.33 (0.01, 14.72)	0.36 (0.00, 18.55)	1.57 (0.02, 115.31)
			NIV_IPI	1.12 (0.10, 11.68)	4.77 (0.32, 84.86)
				PEM_AXI	4.31 (0.22, 98.04)
					AVE_AXI

The column treatment is compared with the row treatment. ORs lower than 1 favor the column-defining treatment. Numbers in parentheses indicate 95% credible intervals. Stepwise comparison of treatments did not find significant differences in rates of overall adverse events. SUN = sunitinib. PAZ = pazopanib. CAB = cabozantinib. NIV_IPI = nivolumab plus ipilimumab, PEM_AXI = pembrolizumab and axitinib, AVE_AXI= avelumab plus axitinib.

Appendix figure 5 Pooled hazard ratios for progression-free survival by Bayesian network-analysis and traditional meta-analysis



HR = hazard ratio. CI=confidence interval for traditional meta-analysis and credible interval for Bayesian network meta-analysis. SUN = sunitinib. PLA = placebo. IFN = interferon- α . SOR = sorafenib. PAZ = pazopanib. AXI = axitinib. EVE = everolimus. TIV = tivozanib. BEV_IFN = bevacizumab plus interferon- α . TEM_BEV = temsirolimus plus bevacizumab. NIV_IPI = nivolumab plus ipilimumab.

Appendix figure 6 Cochrane risk of bias tool assessment

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Choueiri 2017	+	+	-	+	+	+	?
Escudier 2010 (AVOREN)	+	+	+	+	+	+	?
Hutson 2013	+	+	-	+	+	+	+
Motzer 2009	+	+	-	?	+	+	+
Motzer 2013	+	+	-	?	+	+	?
Motzer 2014 (COMPARZ)	+	+	-	?	+	+	+
Motzer 2014 (RECORD-3)	+	?	-	?	+	+	?
Motzer 2018 (CheckMate 214)	+	+	?	+	+	+	?
Motzer 2019 (JAVELIN Renal 101)	+	+	-	+	+	+	+
Negrier 2010 (TARGET)	+	+	+	+	+	+	+
Procopio 2013 (ROSORC)	+	+	-	-	+	+	?
Rini 2010 (CALGB 90206)	+	+	+	+	+	+	+
Rini 2014 (INTORACT)	+	+	-	+	+	+	+
Rini 2019 (KEYNOTE-426)	+	+	-	+	+	+	+
Sternberg 2010 (VEG105192)	+	+	+	+	+	+	?

Appendix Table 1: For advanced/metastatic RCC of favorable-risk, comparison of hazard ratios (95% CI) for **progression-free survival** from fixed and random models.

Treatment compared with SUN	Fixed Model	Random Model
PLA	2.54 (1.37- 4.70)	2.79 (0.005-4812)
IFN	2.69 (1.54-4.67)	2.57 (0.05-18.24)
SOR	1.47 (0.61-3.49)	1.56 (0.001-2735)
PAZ	1.02 (0.74-1.39)	1.03 (0.05-142.4)
AXI	0.93 (0.33-2.54)	0.95 (0.001-22200)
EVE	1.20 (0.80-1.80)	1.28 (0.03-66.05)
BEV_IFN	1.65 (0.90 -2.99)	1.54 (0.01-24.08)
TEM_BEV	1.98 (0.98 -3.96)	1.92 (0.02-155.90)
TIV	0.89 (0.34-2.35)	0.96 (0.001-11940)
NIV_IPI	2.18 (1.47-3.25)	2.16 (0.05-52.46)
PEM_AXI	0.64 (0.24-1.69)	0.64 (0.01-64.60)
AVE_AXI	0.57 (0.34-0.96)	0.57 (0.01-33.4)
DIC	9.68	11.19

Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PLA = placebo. IFN = interferon- α . SOR = sorafenib. PAZ = pazopanib. AXI = axitinib. EVE = everolimus. BEV_IFN = bevacizumab plus interferon- α . TEM_BEV = temsirolimus plus bevacizumab. TIV = tivozanib. NIV_IPI = nivolumab plus ipilimumab, PEM_AXI = pembrolizumab and axitinib, AVE_AXI= avelumab plus axitinib. Bold type font indicates significant values.

Appendix Table 2: For advanced/metastatic RCC of intermediate-risk, comparison of hazard ratios (95% CI) for **progression-free survival** from fixed and random models.

Treatment compared with SUN	Fixed Model	Random Model
PLA	1.99 (1.29-3.14)	2.00 (0.01-1366)
IFN	2.57 (1.88-3.54)	2.56 (0.02-283)
SOR	0.95 (0.47-1.91)	0.95 (0.002- 5382)
PAZ	0.98 (0.80-1.18)	0.98 (0.02- 94.94)
AXI	0.80 (0.36-1.81)	0.80 (0.001- 7618)
EVE	1.50 (1.11-2.01)	1.50 (0.02-121.20)
CAB	0.63 (0.44-0.97)	0.65 (0.01- 64.02)
BEV_IFN	1.69 (1.18-2.41)	1.60 (0.01- 895.10)
TEM_BEV	1.88 (1.22-2.81)	1.81 (0.002- 4299)
TIV	0.76 (0.36-1.65)	0.79 (0.001- 15210)
NIV_IPI	0.66 (0.53-0.81)	0.67 (0.01- 64.51)
PEM_AXI	0.52 (0.35-0.81)	0.52 (0.02-10.67)
AVE_AXI	0.62 (0.47-0.83)	0.60 (0.02-10.67)
DIC	1.97	2.92

Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PLA = placebo. IFN = interferon- α . SOR = sorafenib. PAZ = pazopanib. AXI = axitinib. EVE = everolimus. CAB = cabozantinib. BEV_IFN = bevacizumab plus interferon- α . TEM_BEV = temsirolimus plus bevacizumab. TIV = tivozanib. NIV_IPI = nivolumab plus ipilimumab, PEM_AXI = pembrolizumab and axitinib, AVE_AXI= avelumab plus axitinib. Bold type font indicates significant values.

Appendix Table 3: For advanced/metastatic RCC of poor-risk, comparison of hazard ratios (95% CI) for **progression-free survival** from fixed and random models.

Treatment compared with SUN	Fixed Model	Random Model
IFN	1.87 (0.81- 4.32)	1.88 (0.03- 137.70)
EVE	1.73 (0.96- 2.99)	1.68 (0.02- 89.46)
CAB	0.74 (0.35-1.58)	0.75 (0.01- 54.64)
BEV_IFN	1.50 (0.60-3.62)	1.50 (0.01- 344.20)
TEM_BEV	1.20 (0.42-3.30)	1.22 (0.001- 1196)
NIV_IPI	0.57 (0.43-0.76)	0.57 (0.01- 36.17)
PEM_AXI	0.43 (0.23-0.80)	0.44 (0.01-53.85)
AVE_AXI	0.55 (0.28-1.10)	0.55 (0.01-43.91)
DIC	9.91	11.42

Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. IFN = interferon- α .

EVE = everolimus. CAB = cabozantinib. BEV_IFN = bevacizumab plus interferon- α . TEM_BEV = temsirolimus plus bevacizumab. NIV_IPI = nivolumab plus ipilimumab, PEM_AXI = pembrolizumab and axitinib, AVE_AXI= avelumab plus axitinib. Bold type font indicates significant values.

Appendix Table 4: Comparison of odds ratios (95% CI) for **high-grade adverse event** from consistency and inconsistency models.

Treatment compared with SUN	Consistency Model	Inconsistency Model
PLA	0.40 (0.02, 8.55)	0.39 (0.02, 8.91)
SOR	2.83 (0.06, 150.75)	2.65 (0.05, 160.98)
PAZ	1.07 (0.12, 9.19)	1.05 (0.12, 9.74)
TIV	1.98 (0.02, 201.54)	1.85 (0.02, 209.34)
CAB	0.92 (0.09, 8.13)	0.95 (0.09, 9.10)
SOR_IL-2	5.29 (0.06, 499.51)	4.89 (0.05, 495.91)
NIV_IPI	0.49 (0.05, 4.26)	0.50 (0.06, 4.41)
	1.30 (0.15, 12.14)	1.30 (0.15, 13.03)
	1.00 (0.11, 8.77)	0.98 (0.11, 8.56)
Random Effects Standard Deviation	0.85 (0.07, 1.69)	0.85 (0.07, 1.70)
Inconsistency Standard Deviation	NA	0.87 (0.04, 1.70)

Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PLA = placebo. SOR = sorafenib. PAZ = pazopanib. TIV = tivozanib. CAB = cabozantinib. SOR_IL-2= sorafenib plus interleukin-2. NIV_IPI = nivolumab plus ipilimumab, PEM_AXI = pembrolizumab and axitinib, AVE_AXI= avelumab plus axitinib. Stepwise comparison of treatments did not find significant differences in rates of high-grade adverse events.

Appendix Table 5: Comparison of odds ratios (95% CI) for **overall-grade adverse event** from consistency and inconsistency models.

Treatment compared with SUN	Consistency Model	Inconsistency Model
PAZ	2.28 (0.27, 23.95)	2.25 (0.30, 24.19)
CAB	1.05 (0.03, 45.23)	1.14 (0.03, 61.85)
NIV_IPI	0.34 (0.08, 1.40)	0.33 (0.08, 1.37)
PEM_AXI	0.38 (0.05, 2.41)	0.41 (0.06, 2.56)
AVE_AXI	1.61 (0.17, 19.17)	1.60 (0.15, 18.66)
Random Effects Standard Deviation	0.52 (0.04, 1.03)	0.53 (0.04, 1.02)
Inconsistency Standard Deviation	NA	0.53 (0.02, 1.02)

Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PAZ = pazopanib. CAB = cabozantinib. NIV_IPI = nivolumab plus ipilimumab, PEM_AXI = pembrolizumab and axitinib, AVE_AXI= avelumab plus axitinib. Stepwise comparison of treatments did not find significant differences in rates of overall-grade adverse events.

Appendix Table 6: Comparison of results from primary analysis and sensitivity analysis for trials assessing approved targeted drugs.

Treatment	Primary Analysis	Sensitivity Analysis
	PFS HR (95% CI) vs SUN	PFS HR (95% CI) vs SUN
PLA	2.63 (1.47-4.71)	2.55 (1.38 -4.66)
IFN	2.70 (1.59-4.51)	2.71 (1.55 -4.71)
SOR	1.47 (0.61-3.59)	1.48 (0.62 -3.55)
PAZ	1.03 (0.74-1.44)	1.02 (0.75 -1.41)
AXI	0.98 (0.36-2.76)	0.95 (0.35 -2.54)
EVE	1.21 (0.81-1.86)	1.20 (0.80-1.80)
BEV_IFN	1.66 (0.94 -2.88)	1.67 (0.92 -3.07)
TEM_BEV	1.96 (1.04 -3.63)	2.00 (1.01 -4.03)
TIV	0.92 (0.37-2.33)	NA
NIV_IPI	2.21 (1.50-3.38)	2.18 (1.46-3.20)

HR = hazard ratio. CI = confidence interval. Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PLA = placebo. IFN = interferon- α . SOR = sorafenib. PAZ = pazopanib. AXI = axitinib. EVE = everolimus. BEV_IFN = bevacizumab plus interferon- α . TEM_BEV = temsirolimus plus bevacizumab. TIV = tivozanib. NIV_IPI = nivolumab plus ipilimumab. Bold type font indicates significant values.