Supplemental Online Content

Sonbol MB, Riaz IB, Naqvi SAA, et al. Systemic therapy and sequencing options in advanced hepatocellular carcinoma: and network meta-analysis. *JAMA Oncol*. Published online October 22, 2020. doi:10.1001/jamaoncol.2020.4930

This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods: Search Strategy

3.9.20 PubMed (884) ((((((((((((((((((("Carcinoma, Hepatocellular/drug therapy"[Mesh]) OR "Liver Neoplasms/drug therapy"[Mesh]) OR "metastatic liver cancer") OR "advanced liver cancer") OR "advanced hepatocellular carcinoma") OR "metastatic hepatocellular carcinoma") OR ("metastatic HCC" OR "advanced HCC"))) OR "Carcinoma, Hepatocellular"[Mesh]) OR "Liver Neoplasms"[Mesh])) AND (((((((((("Antineoplastic Agents" [Pharmacological Action]) OR "Protein Kinase Inhibitors" [Pharmacological Action]) OR "Protein Kinase Inhibitors"[Mesh]) OR "Immunotherapy"[Mesh]) OR "Placebos"[Mesh]) OR "Drug Therapy"[Mesh]) OR "drug therapy" [Subheading])) OR (antineoplastic* OR "kinase inhibitor" OR TKI OR placebo*)))) AND (advanced [tiab] OR unresectable [tiab] OR metastas* [tiab] OR metastat* [tiab])))) AND ((("Mortality"[Mesh] OR "Survival"[Mesh] OR "mortality" [Subheading] OR "Survival Analysis"[Mesh] OR "Survival Rate"[Mesh] OR "Progression-Free Survival"[Mesh])) OR "Treatment Outcome"[Mesh]))) AND Clinical Trial, Phase III[ptyp])) OR ((((((((((((((((("Carcinoma, Hepatocellular/drug therapy"[Mesh]) OR "Liver Neoplasms/drug therapy"[Mesh]) OR "metastatic liver cancer") OR "advanced liver cancer") OR "advanced hepatocellular carcinoma") OR "metastatic hepatocellular carcinoma") OR ("metastatic HCC" OR "advanced HCC"))) OR "Carcinoma, Hepatocellular"[Mesh]) OR "Liver Neoplasms"[Mesh])) AND (((((((((("Antineoplastic Agents" [Pharmacological Action]) OR "Protein Kinase Inhibitors" [Pharmacological Action]) OR "Protein Kinase Inhibitors"[Mesh]) OR "Immunotherapy"[Mesh]) OR "Placebos"[Mesh]) OR "Drug Therapy"[Mesh]) OR "drug therapy" [Subheading])) OR (antineoplastic* OR "kinase inhibitor" OR TKI OR placebo*)))) AND (advanced [tiab] OR unresectable [tiab] OR metastas* [tiab] OR metastat* [tiab])))) AND ((("Mortality"[Mesh] OR "Survival"[Mesh] OR "mortality" [Subheading] OR "Survival Analysis"[Mesh] OR "Survival Rate"[Mesh] OR "Progression-Free Survival"[Mesh])) OR "Treatment Outcome"[Mesh]))) AND (first-line [tiab] OR second-line OR phase 3 OR phase III)) Filters: English

3.9.20 Embase <1974 to 2020 March 05> Search Strategy

1 exp liver cell carcinoma/dt [Drug Therapy] (19997)
2 exp liver cell carcinoma/ (150324)
3 liver tumor/ (47639)
4 exp liver tumor/dt [Drug Therapy] (36718)
5 exp liver tumor/ (271624)
6 "metastatic liver cancer".mp. (774)
7 "advanced hepatocellular carcinoma".mp. (4263)
8 "advanced liver cancer".mp. (207)
9 "metastatic hepatocellular carcinoma".mp. (655)
10 ("metastatic HCC" or "advanced HCC").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (5097)
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 (272148)
12 exp antineoplastic agent/ (2176079)
13 exp protein kinase inhibitor/ (528060)
14 exp immunotherapy/ (210424)
15 exp placebo/ (347388)
16 exp drug therapy/ (2744031)
17 (antineoplastic* or "kinase inhibitor" or TKI or placebo*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (1022721)
18 12 or 13 or 14 or 15 or 16 or 17 (4632164)
19 advanced.ti. or advanced.ab. or unresectable.ti. or unresectable.ab. or metastas*.ti. or metastas*.ab. (1066581)
20 (first-line or second-line).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (158079)

21 exp survival/ or exp progression free survival/ or exp survival analysis/ or exp survival rate/ (1097914)
22 exp mortality/ (1045813)
23 exp treatment outcome/ (1617063)
24 21 or 22 or 23 (3196327)
25 11 and 19 (84926)
26 18 and 25 (42174)
27 24 and 26 (23155)
28 20 and 27 (2482)
29 ("phase III" or "phase 3").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (132222)
30 28 and 29 (457)
31 limit 27 to phase 3 clinical trial (537)
32 30 or 31 (796)
33 limit 32 to english language (784)

3.9.20 Scopus (543) ((((TITLE-ABS-KEY ("hepatocellular carcinoma" OR "advanced hepatocellular carcinoma" OR "metastatic hepatocellular carcinoma" OR "metastatic HCC" OR "advanced HCC") OR TITLE-ABS-KEY ("advanced liver cancer" OR "metastatic liver cancer"))) AND (TITLE-ABS-KEY (antineoplastic OR "protein Kinase inhibitors" OR pki OR immunotherapy OR placebo*))) AND (TITLE-ABS-KEY ("survival rate" OR mortality OR "progression-free survival" OR "treatment outcome"))) AND ((TITLE-ABS-KEY ("phase III" OR "phase 3")) OR (TITLE-ABS-KEY (first-line OR second-line))) AND (LIMIT-TO (LANGUAGE , "English"))

3.9.20 Web of Science (102) TOPIC: ("hepatocellular carcinoma" OR "advanced hepatocellular carcinoma" OR "metastatic hepatocellular carcinoma" OR "metastatic HCC" OR "advanced HCC") OR TOPIC: ("advanced liver cancer" OR "metastatic liver cancer") AND TOPIC: (antineoplastic OR "protein Kinase inhibitors" OR pki OR immunotherapy OR placebo*) AND TOPIC: ("survival rate" OR mortality OR "progression-free survival" OR "treatment outcome") AND TOPIC: ("phase III" OR "phase 3") OR TOPIC: (first-line OR second-line) Refined by: LANGUAGES: (ENGLISH) Indexes=SCI-EXPANDED, ESCI Timespan=All years

3.9.20 EBM Reviews - Cochrane Database of Systematic Reviews <2005 to March 4, 2020> Search Strategy (14)
1 hepatocellular carcinoma.mp. [mp=title, short title, abstract, full text, keywords, caption text] (171)
2 (unresectable or metastas* or metastat* or advanced).mp. [mp=title, short title, abstract, full text, keywords, caption text] (2164)
3 1 and 2 (87)
4 (antineoplastic* or PKI or protein kinase inhibitors or placebo).mp. [mp=title, short title, abstract, full text, keywords, caption text] (6789)
5 (first-line or second-line or "phase 3" or "phase III").mp. [mp=title, short title, abstract, full text, keywords, caption text] (2137)
6 3 and 4 (61)
7 5 and 6 (14)

Clinical Trials (16) Hepatocellular Carcinoma Metastatic OR hepatocellular carcinoma unresectable AND antineoplastic* OR immunotherapy OR protein kinase inhibitor* AND phase 3

Author supplied (3)

DATABASE	RESULTS	DUPLICATES	REMAINING
PubMed	884	91	793
Embase	784	65	719
Scopus	543	244	299
Web of Science	102	46	56
Cochrane Database of Systematic Reviews	14	0	14
ClinicalTrials.gov	16	0	16
Author supplied	3	0	3
TOTAL	2346	446	1900

Study Name	Arm	# pts	ECOG PS (0,1,2)%	Median Age (Range)	Race/Region %	Sex (male %)	Child Pugh Score
Cheng 2019 (IMBRAVE); Finn 2020	Atezo+Bev	336	0 (62%), 1 (38%)	64 (26-88)	White (37%), Asian (56%%)	82	A (99%), B (1%)
	Sorafenib	165	0 (62%), 1 (38%)	66 (33-87)	White (32%), Asian (58%%)	83	A (100%)
Yau 2019 (CheckMate459)	Nivolumab	371					NR
	Sorafenib	372					NR
Kudo 2018	Lenvatinib	478	0 (64%), 1(36%)	63 (20-88)	White (28%), Asian (70%), Other (2%)	85	A (99%), B (1%)
	Sorafenib	476	0 (63%), 1 (37%)	62 (22-88)	White (30%), Asian (68%), Other (2%)	84	A (99%), B (1%)
Cheng 2013 (Sunitinib)	Sunitinib	530	0 (52.5%), 1 (46.8%)	59 (18-85)	White (20.9%), Black (1.1%), Asian (77.5%), Other 0.4%	82.3	A (99.8%)
	Sorafenib	544	0 (52.9%), 1 (46.7%)	59 (18-84)	White (20.6%), Black (1.8%), Asian (76.8%), Other (0.7%)	84.4	A (99.4%)
Cainap 2013	Linifanib	514	0, 62.8%, 1, 37.2%	59 (21-84)	Outside Asia 34 %, Asian 66.6%	86.4	A (93.2%), B (5.8%)
	Sorafenib	521	0, 66.2%, 1, 33.8%	60 (23-87)	Outside Asia 32.8 %, Asian 67.2	83.7	A (95%), B (5%)
Johnson 2013	Brivanib	577	0, 64%, 1, 36%	61 (19-87)	Asia (60%), Europe (23%), America (15%), other (2%)	84	A (92%), B (8%)
	Sorafenib	578	0, 61%, 1, 39%	60 (25-89)	Asia (64%), Europe (23%), America (11%), other (1%)	84	A (92%), B (8%)
Cheng 2009 Asian Sharp	Sorafenib	150	0, 25.3 %, 1, 69.3%, 2, 5.3%	51 (23-86)	Asian	84.7	A (97.3%), B (2.7%)
	Placebo	76	0, 27.6%, 1, 67.1 %, 2, 5.3%	52 (25-79)	Asian	86.8	A (97.4%), B (2.6%)
Liovett 2007 Sharp	Sorafenib	299	0, 54%, 1, 38%, 2, 8%	mean: 64.9 $\pm$ 11.2	Europe/Australasia 88%, North America 9%, Central and South America 3%	87	A (95%), B (5%)
	Placebo	303	0, 54%, 1, 39%, 2, 7%	mean: 66.3 $\pm$ 10.2	Europe/Australasia 87%, North	87	A (98%), B (2%)

					America 10%, Central and South America 4%		

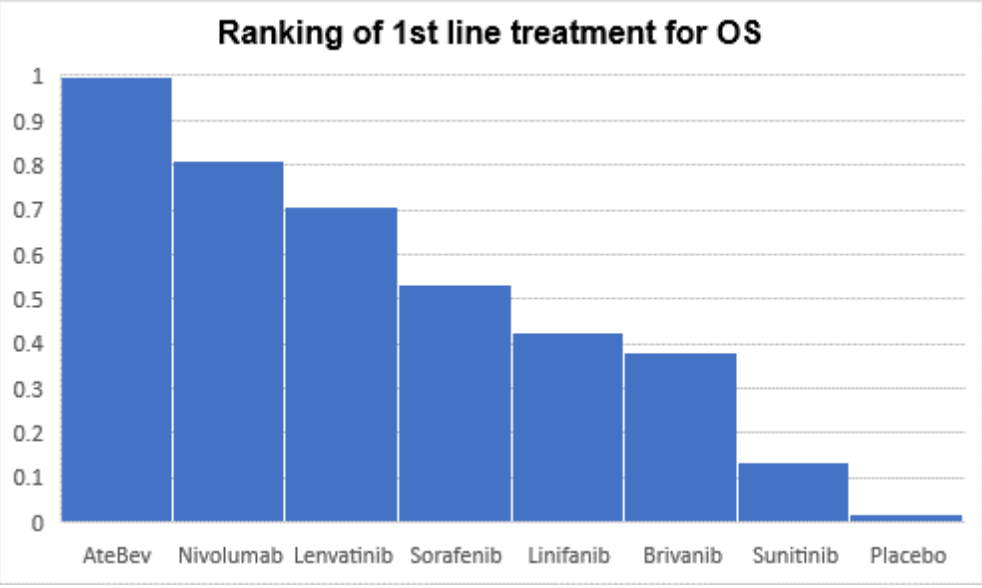
eTable1: Baseline characteristics for patients included in the first-line trials

eTable2: Baseline characteristics for patients included in the second-line trials

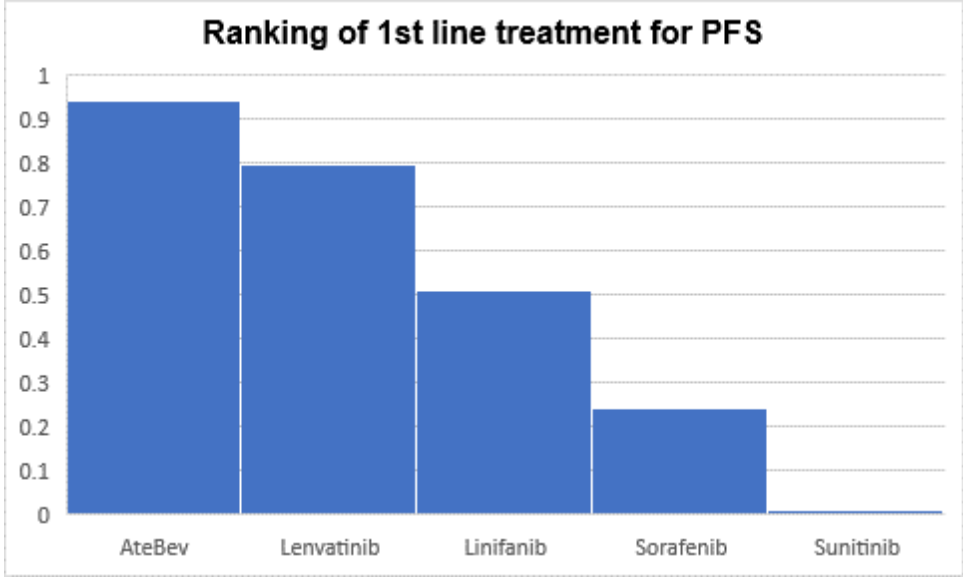
	Arm	# pts	ECOG PS (0,1,2)%	Median Age (Range)	Race %	Sex (male %)	Child Pugh Score
Finn 2020	***Pembrolizumab***	278	0 (58.3%), 1 (41.7%)	67 (18-91)	Asian w/o Japan (24.1%), European Union (34.5%), Japan (14.4%), USA (7.6%), Other (19.4%)	226 (81.3)	A5(63.3%), A6(36.3%), B7(0.4%)
	Placebo	135	0 (52.6%), 1(47.4%)	65 (23-89)	Asian w/o Japan (23%), European Union (31.9%), Japan (14.1%), USA (11.9%), Other (19.3%)	112 (83)	A5(63.7%), A6(34.8%), B7(1.5%)
BRUIX 2018	***Regorafenib***	379	0: 247 (65), 1: 132 (35)	64 (54-71)	White: 138 (36), Asian: 156 (41), Black: 6 (2), Other/NR: 79 (21)	88%	A (98%), B (1%)
	Placebo	194	0: 130 (67), 1: 64 (33)	62 (55-68)	White: 68 (35), Asian: 78 (40), Black: 2 (1), Other/NR: 46 (24)	88%	A (97%), B (3%)
AbuAlfa2018	***cabozantinib***	470	(0) 52%, (1) 48%, (2) <1%	64 (22-86)	Asian: 159 (34%), Non-Asian: 280 (60%), Other 31 (6%)	81%	A (98%), B (1%)
	Placebo	237	(0) 55%, (1) 45%, (2) 0	64 (24-86)	Asian: 82 (35%), Non-Asian: 143 (60%), Other 12(5%)	85%	A (99%), B (1%)
REACH Zhu 2015	***Ramucirumab***	283	0: 159 (56), 1: 124 (44)	64 (28-87)	White: 139 (49), Asian: 131 (46), Other: 13 (5)	236 (83)	Child Pugh A (98%)
	Placebo	282	0: 153 (54), 1: 129 (46)	62 (25-85)	White: 137 (49), Asian: 135 (48), Other: 10 (4)	242 (86)	Child Pugh A (98%)
Liovet 2013	***Brivanib***	263	0: 151 (57), 1: 102 (39), 2: 10 (4)	64 (19-89)	White: 122 (46), Asian: 125 (48), Black/African American 10 (4), other: 6 (2)	216 (82)	A (92%), B (7%), (1%)
	Placebo	132	0: 81 (61), 1: 46 (35), 2: 5 (4)	62 (19-87)	White: 66 (50), Asian: 59 (45), Black/African American 6 (5), other: 1 (1)	113 (86)	A (91%), B (9%)

eFigure 1: Network plot for overall-survival (left) and progression-free survival (right) for first-line trials: The thickness of the connecting line corresponds to the number of trials between comparators. AteBev: atezolizumab and bevacizumab.

eFigure 2: Ranking of 1st line treatments for overall survival.



eFigure 3: Ranking of 1st line treatments for progression-free survival.

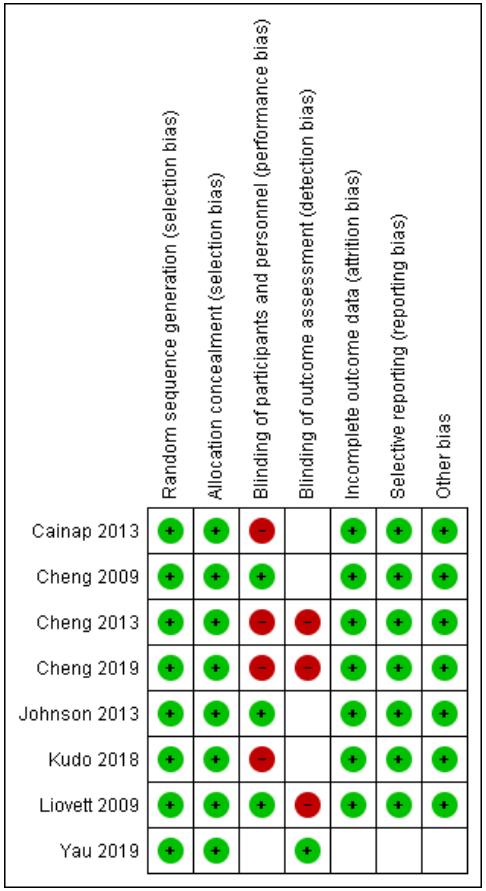


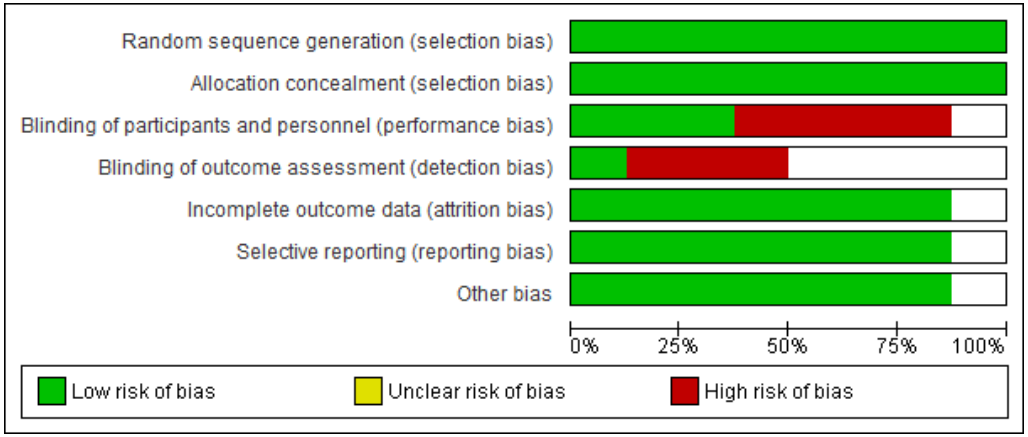
eTable 3: A. Ranking of first-line treatments for overall survival (left) and progression-free survival (right) based on P-score.

Ranking - OS			Ranking - PFS	
1st line treatment	**P-score**		**1st line treatment**	**P-score**
AteBev	0.9965		AteBev	0.9416
Nivolumab	0.8115		Lenvatinib	0.7971
Lenvatinib	0.705		Linifanib	0.5102
Sorafenib	0.5343		Sorafenib	0.241
Linifanib	0.423		Sunitinib	0.01
Brivanib	0.379			
Sunitinib	0.1318			
Placebo	0.0181			

eFigure 4

Risk of bias graph for first-line studies: review authors' judgements about each risk of bias item presented as percentages across all included studies.





eTable 4 GRADE

eTable 4a. Certainty of Evidence Table (GRADE). First line treatment - Overall survival

:

Certainty assessment							№ of patients		Effect		
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**1st line OS**	**Risk of Death in Control**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**
AteBev vs Nivolumab - Overall survival											
2	randomized trials	not serious	not serious	not serious	not serious	none			**HR 0.68** (0.48 to 0.98)		⨁⨁⨁⨁ HIGH
AteBev vs Lenvatinib - Overall survival											
2	randomized trials	not serious	not serious	not serious	not serious	none			**HR 0.63** (0.44 to 0.89)		⨁⨁⨁⨁ HIGH
AteBev vs Sorafenib - Overall survival											
7	randomized trials	not serious	not serious	not serious	not serious	none			**HR 0.58** (0.42 to 0.80)		⨁⨁⨁⨁ HIGH

Certainty assessment							№ of patients		Effect		
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**1st line OS**	**Risk of Death in Control**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**
AteBev vs Linifanib - Overall survival											
2	randomized trials	not serious	not serious	not serious	not serious	none			**HR 0.55** (0.39 to 0.78)		⊕⊕⊕⊕ HIGH
AteBev vs Sunitinib - Overall survival											
2	randomized trials	not serious	not serious	not serious	not serious	none			**HR 0.45** (0.32 to 0.63)		⊕⊕⊕⊕ HIGH
AteBev vs Placebo - Overall survival											
3	randomized trials	not serious	not serious	not serious	not serious	none		58.7%[&]	**HR 0.40** (0.28 to 0.56)	**289 fewer per 1,000** (from 368 fewer to 197 fewer)	⊕⊕⊕⊕ HIGH
Nivolumab vs Lenvatinib - Overall survival											
2	Randomized trials	not serious	not serious	not serious	serious	none			**HR 0.92** (0.74 to 1.16)		⊕⊕⊕◯ MODERATE

Certainty assessment							№ of patients		Effect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	1st line OS	Risk of Death in Control	Relative (95% CI)	Absolute (95% CI)	Certainty
Nivolumab vs Sorafenib - Overall survival											
7	Randomized trials	not serious	not serious	not serious	serious	none			**HR 0.85** (0.71 to 1.01)		⊕⊕⊕◯ MODERATE
Nivolumab vs Linifanib - Overall survival											
2	randomized trials	not serious	not serious	not serious	serious	none			**HR 0.81** (0.64 to 1.02)		⊕⊕⊕◯ MODERATE
Nivolumab vs Sunitinib - Overall survival											
2	randomized trials	not serious	not serious	not serious	not serious	none			**HR 0.65** (0.52 to 0.82)		⊕⊕⊕⊕ HIGH
Nivolumab vs Placebo - Overall survival											
3	randomized trials	not serious	not serious	not serious	not serious	none		58.7%[&]	**HR 0.59** (0.47 to 0.73)	**181 fewer per 1,000** (from 247 fewer to 111 fewer)	⊕⊕⊕⊕ HIGH

Certainty assessment							№ of patients		Effect		
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**1st line OS**	**Risk of Death in Control**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**
Lenvatinib vs Sorafenib - Overall survival											
7	randomized trials	not serious	not serious	not serious	serious	none			**HR 0.92** (0.79 to 1.07)		⊕⊕⊕◯ MODERATE
Lenvatinib vs Linifanib - Overall survival											
2	randomized trials	not serious	not serious	not serious	serious	none			**HR 0.88** (0.71 to 1.08)		⊕⊕⊕◯ MODERATE
Lenvatinib vs Sunitinib - Overall survival											
2	randomized trials	not serious	not serious	not serious	not serious	none			**HR 0.71** (0.58 to 0.87)		⊕⊕⊕⊕ HIGH
Lenvatinib vs Placebo - Overall survival											
3	randomized trials	not serious	not serious	not serious	not serious	none		58.7%[&]	**HR 0.63** (0.52 to 0.77)	**160 fewer per 1,000** (from 218 fewer to 93 fewer)	⊕⊕⊕⊕ HIGH

Certainty assessment							№ of patients		Effect		
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**1st line OS**	**Risk of Death in Control**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**
Sorafenib vs Linifanib - Overall survival											
7	randomized trials	not serious	not serious	not serious	serious	none			**HR 0.95** (0.82 to 1.11)		⊕⊕⊕◯ MODERATE
Sorafenib vs Sunitinib - Overall survival											
7	randomized trials	not serious	not serious	not serious	not serious	none			**HR 0.77** (0.67 to 0.89)		⊕⊕⊕⊕ HIGH
Sorafenib vs Placebo - Overall survival											
7	randomized trials	not serious	not serious	not serious	not serious	none	143/299 (47.8%)	178/303 (58.7%)	**HR 0.69** (0.61 to 0.78)	**130 fewer per 1,000** (from 170 fewer to 89 fewer)	⊕⊕⊕⊕ HIGH
Linifanib vs Sunitinib - Overall survival											
2	randomized trials	not serious	not serious	not serious	not serious	none			**HR 0.81** (0.66 to 0.99)		⊕⊕⊕⊕ HIGH

Certainty assessment							№ of patients		Effect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	1st line OS	Risk of Death in Control	Relative (95% CI)	Absolute (95% CI)	Certainty
Linifanib vs Placebo - Overall survival											
3	randomized trials	not serious	not serious	not serious	not serious	none		58.7%[&]	**HR 0.72** (0.59 to 0.88)	**116 fewer per 1,000** (from 181 fewer to 46 fewer)	⊕⊕⊕⊕ HIGH
Sunitinib vs Placebo - Overall survival											
3	randomized trials	not serious	not serious	not serious	serious	none		58.7%[&]	**HR 0.89** (0.74 to 1.08)	**42 fewer per 1,000** (from 107 fewer to 28 more)	s⊕⊕⊕◯ MODERATE

CI: Confidence interval; **HR:** Hazard Ratio

*Although risk of bias is moderate for the included studies due to lack of blinding of outcome assessments, but the outcome of overall survival is independent of blinded assessment.

**Confidence intervals include appreciable benefits and harms

[&] Baseline risk of death based on SHARP trial. Risk of death in other placebos is assumed to be similar to SHARP trial due to lack of head to head comparison between other agents and placebo.

eTable 4b. Certainty of Evidence Table (GRADE). First line treatment – Progression Free survival

Certainty assessment							Effect	
№ of studies	Study design	Risk of bias*	Inconsistency	Indirectness	Imprecision	Other considerations	HR† (95% CI)	Certainty
AteBev vs Lenvatinib - Progression free survival								
Network meta-analysis (2 trials)	randomized trials	not serious	not serious	not serious	serious**	none	**HR 0.89** (0.67 to 1.19)	⊕⊕⊕◯ MODERATE
AteBev vs Linifanib - Progression free survival								
Network meta-analysis (2 trials)	randomized trials	not serious	not serious	not serious	not serious	none	**HR 0.73** (0.55 to 0.97)	⊕⊕⊕⊕ HIGH
AteBev vs Sorafenib - Progression free survival								
Network meta-analysis (4 trials)	randomized trials	not serious	not serious	not serious	not serious	none	**HR 0.59** (0.46 to 0.75)	⊕⊕⊕⊕ HIGH
AteBev vs Sunitinib - Progression free survival								
Network meta-analysis (2 trials)	randomized trials	not serious	not serious	not serious	not serious	none	**HR 0.52** (0.40 to 0.69)	⊕⊕⊕⊕ HIGH
Lenvatinib vs Linifanib - Progression free survival								
Network meta-analysis (2 trials)	randomized trials	not serious	not serious	not serious	serious**	none	**HR 0.81** (0.66 to 1.01)	⊕⊕⊕◯ MODERATE
Lenvatinib vs Sorafenib - Progression free survival								
Network meta-analysis (4 trials)	randomized trials	not serious	not serious	not serious	not serious	none	**HR 0.66** (0.57 to 0.77)	⊕⊕⊕⊕ HIGH
Lenvatinib vs Sunitinib - Progression free survival								
Network meta-analysis (2 trials)	randomized trials	not serious	not serious	not serious	not serious	none	**HR 0.58** (0.48 to 0.72)	⊕⊕⊕⊕ HIGH

Certainty assessment							Effect	
№ of studies	Study design	Risk of bias*	Inconsistency	Indirectness	Imprecision	Other considerations	HR† (95% CI)	Certainty
Linifanib vs Sorafenib - Progression free survival								
Network meta-analysis (4 trials)	randomized trials	not serious	not serious	not serious	not serious	none	**HR 0.81** (0.70 to 0.94)	⊕⊕⊕⊕ HIGH
Linifanib vs Sunitinib - Progression free survival								
Network meta-analysis (2 trials)	randomized trials	not serious	not serious	not serious	not serious	none	**HR 0.72** (0.58 to 0.88)	⊕⊕⊕⊕ HIGH
Sorafenib vs Sunitinib - Progression free survival								
Network meta-analysis (4 trials)	randomized trials	not serious	not serious	not serious	serious**	none	**HR 0.88** (0.77 to 1.01)	⊕⊕⊕◯ MODERATE

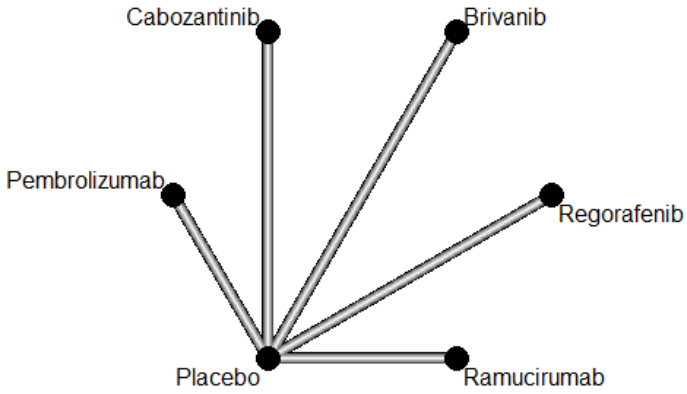
CI: Confidence interval; **HR:** Hazard Ratio

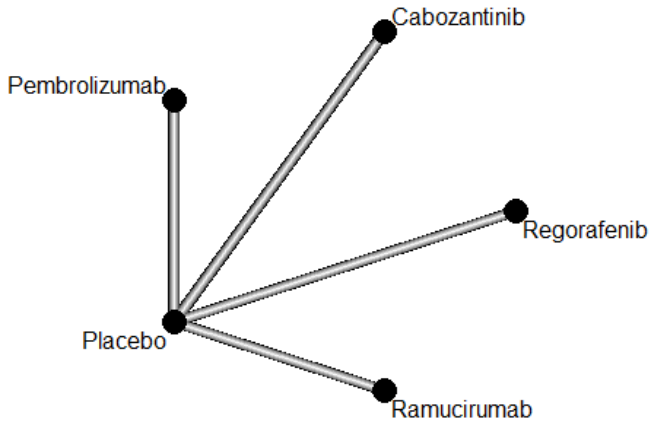
*Although risk of bias is moderate for the included studies due to lack of blinding of outcome assessments, but the outcome of overall survival is independent of blinded assessment.

**Confidence intervals include appreciable benefits and harms

†Insufficient data to estimate absolute effects

eFigure 5: Network plot for overall-survival (left) and progression-free survival (right) for second-line trials: The thickness of the connecting line corresponds to the number of trials between comparators.

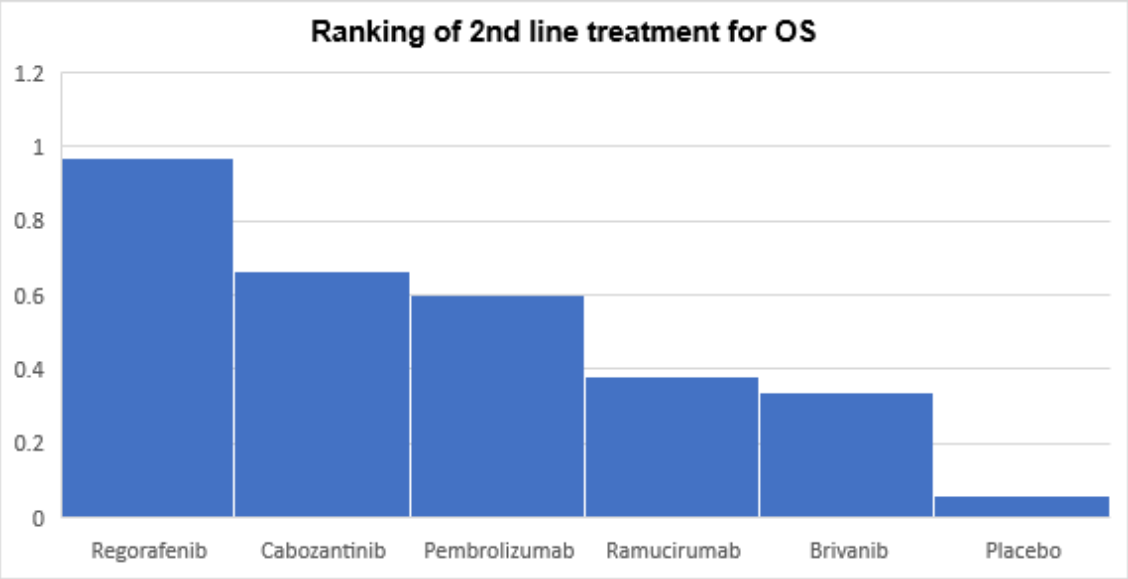




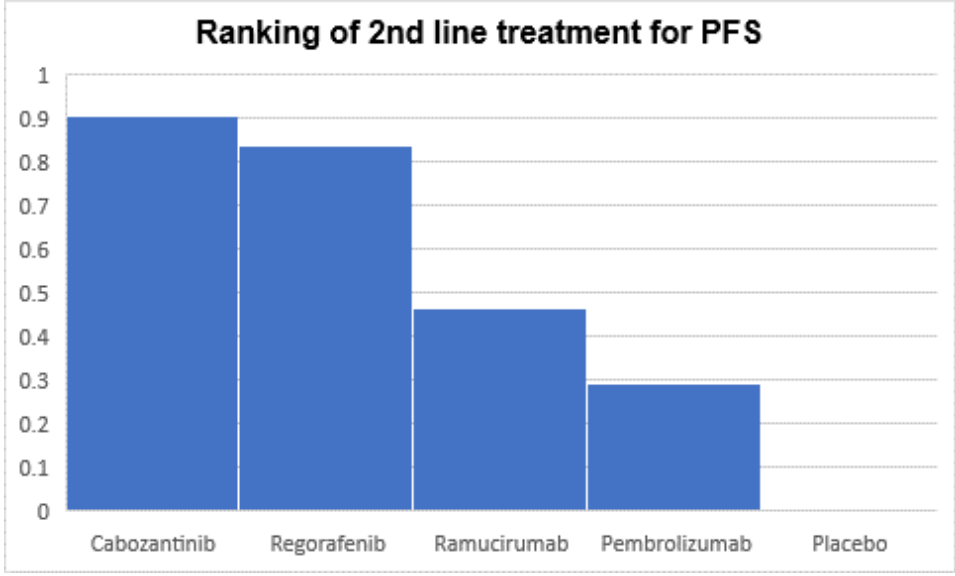
eTable5: Ranking of second-line treatments for overall survival (left) and progression-free survival (right) based on P-score

Ranking - OS				Ranking - PFS	
2nd line treatment	**P-score**			**2nd line treatment**	**P-score**
Regorafenib	0.9673			Cabozantinib	0.9045
Cabozantinib	0.662			Regorafenib	0.8393
Pembrolizumab	0.5998			Ramucirumab	0.4659
Ramucirumab	0.3793			Pembrolizumab	0.2897
Brivanib	0.3344			Placebo	0.0006
Placebo	0.0572				

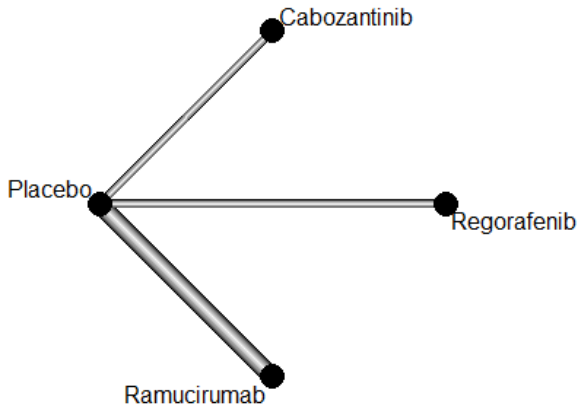
eFigure6: Ranking of 2nd line treatments for overall survival



eFigure7: Ranking of 2nd line treatments for progression-free survival



eFigure8: Network plot for AFP≥ 400 subgroup analysis: The thickness of the connecting line corresponds to the number of trials between comparators.



eTable 6: League table showing indirect comparisons among AFP≥ 400 subgroup analysis

A. Overall survival

League table showing indirect comparisons - overall survival (> 400 AFP)				
Comparator	Treatment			
	Regorafenib			
	0.99 (0.68; 1.42)	**Ramucirumab**		
	0.96 (0.63; 1.45)	0.97 (0.69; 1.37)	**Cabozantinib**	
	0.68 (0.50; 0.92)	0.69 (0.56; 0.84)	0.71 (0.54; 0.94)	**Placebo**

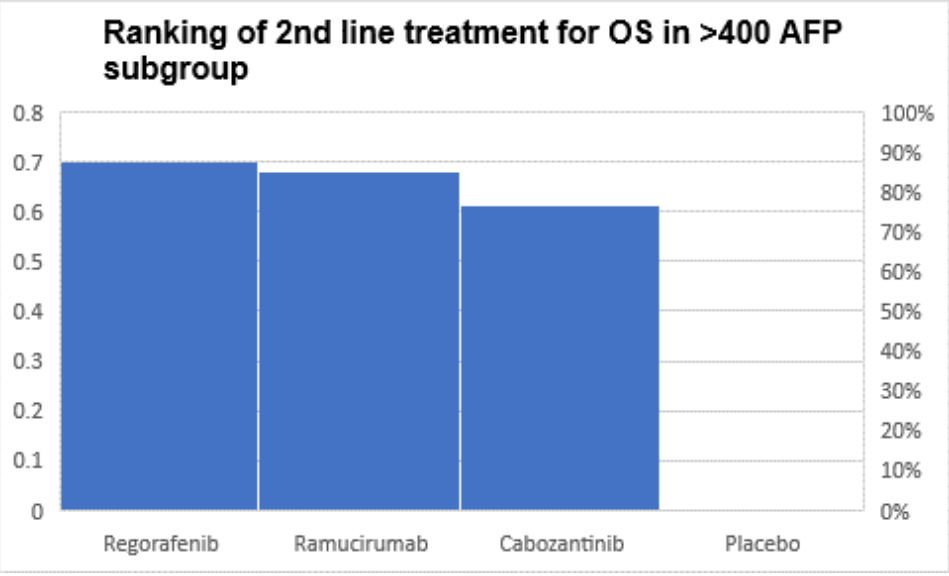
B. Progression-free survival

League table showing indirect comparisons - progression free survival (> 400 AFP)				
Comparator	Treatment			
	Cabozantinib			
	0.79 (0.34; 1.87)	**Regorafenib**		
	0.75 (0.35; 1.57)	0.94 (0.45; 1.99)	**Ramucirumab**	
	0.42 (0.23; 0.77)	0.53 (0.29; 0.97)	0.56 (0.37; 0.87)	**Placebo**

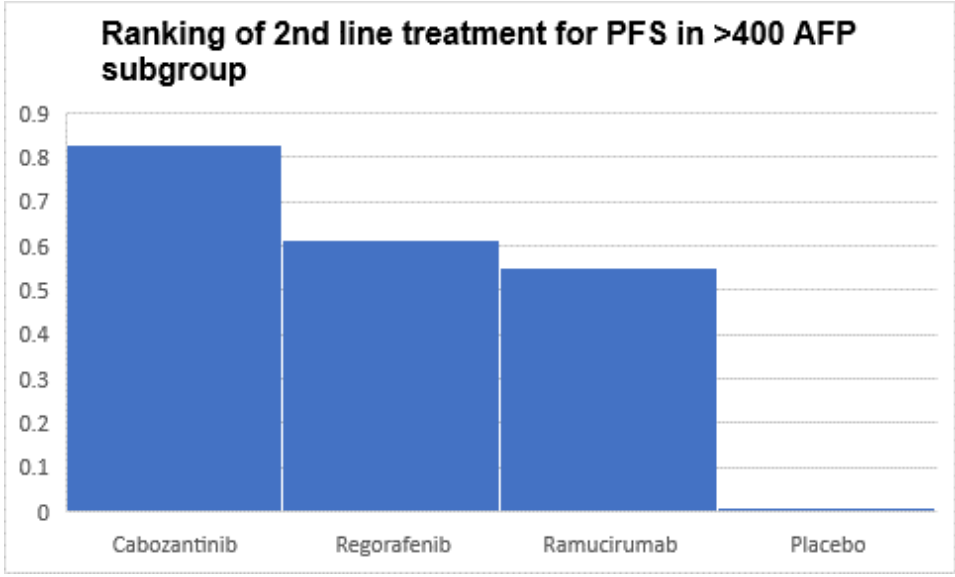
eTable 7: Ranking of AFP≥ 400 subgroup analysis for overall survival (left) and progression-free survival (right) based on P-score

Ranking - OS in >400 AFP subgroup			Ranking - PFS in >400 AFP subgroup	
2nd line treatment	**P-score**		**2nd line treatment**	**P-score**
Regorafenib	0.7015		Cabozantinib	0.8269
Ramucirumab	0.6788		Regorafenib	0.6136
Cabozantinib	0.6148		Ramucirumab	0.5503
Placebo	0.0048		Placebo	0.0092

eFigure9: Ranking of AFP≥ 400 subgroup analysis for overall survival

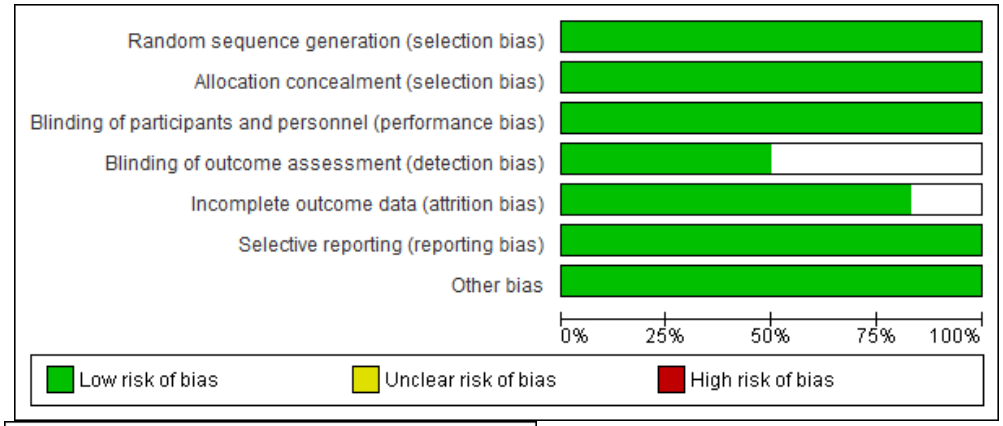


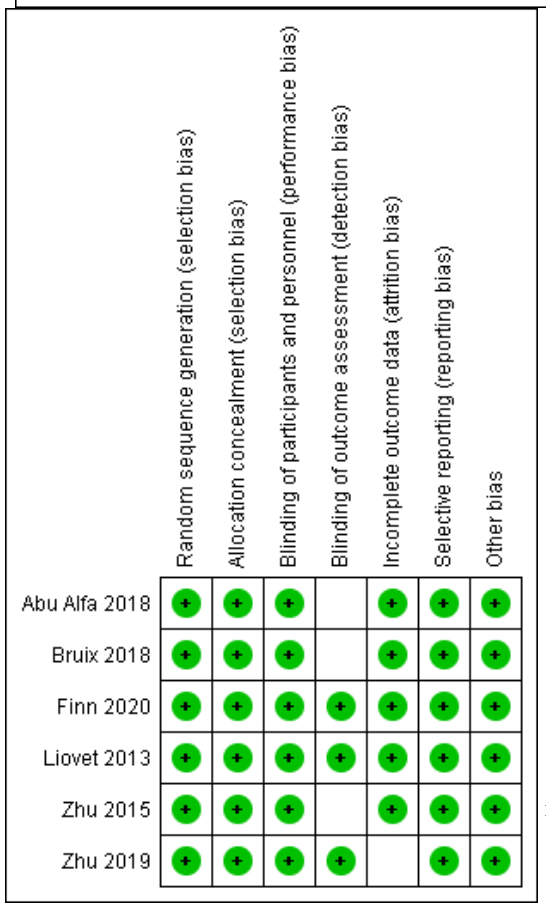
eFigure10: Ranking of AFP≥ 400 subgroup analysis for progression-free survival



eFigure11:

Risk of bias graph for second-line trials: review authors' judgements about each risk of bias item presented as percentages across all included studies.





eTable 8A: Certainty of Evidence Table (GRADE). Second line treatment – Overall survival

:

Certainty assessment							№ of patients		Effect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	2nd line OS		Relative (95% CI)	Absolute (95% CI)	Certainty
Regorafenib vs Cabozantinib - Overall survival											
2	randomized trials	not serious	not serious	not serious	serious	none			**HR 0.82** (0.62 to 1.07)		⨁⨁⨁◯ MODERATE
Regorafenib vs Pembrolizumab - Overall survival											
2	randomized trials	not serious	not serious	not serious	serious	none			**HR 0.79** (0.58 to 1.08)		⨁⨁⨁◯ MODERATE
Regorafenib vs Ramucirumab - Overall survival											
2	randomized trials	not serious	not serious	not serious	not serious	none			**HR 0.71** (0.54 to 0.93)		⨁⨁⨁⨁ HIGH
Regorafenib vs Brivanib - Overall survival											

Certainty assessment							№ of patients		Effect		
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**2nd line OS**		**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**
2	randomized trials	not serious	not serious	not serious	not serious	none			**HR 0.70** (0.51 to 0.96)		⊕⊕⊕⊕ HIGH
Regorafenib vs Placebo - Overall survival											
5	randomized trials	not serious	not serious	not serious	not serious	none	317/379 (83.6%)	174/194 (89.7%)	**HR 0.62** (0.51 to 0.75)	**141 fewer per 1,000** (from 211 fewer to 79 fewer)	⊕⊕⊕⊕ HIGH
Cabozantinib vs Pembrolizumab - Overall survival											
2	randomized trials	not serious	not serious	not serious	serious	none			**HR 0.97** (0.71 to 1.33)		⊕⊕⊕◯ MODERATE
Cabozantinib vs Ramucirumab - Overall survival											
2	randomized trials	not serious	not serious	not serious	serious	none			**HR 0.87** (0.67 to 1.14)		⊕⊕⊕◯ MODERATE
Cabozantinib vs Brivanib - Overall survival											

Certainty assessment							№ of patients		Effect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	2nd line OS		Relative (95% CI)	Absolute (95% CI)	Certainty
2	randomized trials	not serious	not serious	not serious	serious	none			**HR 0.85** (0.62 to 1.17)		⊕⊕⊕◯ MODERATE
Cabozantinib vs Placebo - Overall survival											
5	randomized trials	not serious	not serious	not serious	not serious	none	317/470 (67.4%)	167/237 (70.5%)	**HR 0.76** (0.63 to 0.92)	**100 fewer per 1,000** (from 168 fewer to 30 fewer)	⊕⊕⊕⊕ HIGH
Pembrolizumab vs Ramucirumab - Overall survival											
2	randomized trials	not serious	not serious	not serious	serious	none			**HR 0.90** (0.66 to 1.22)		⊕⊕⊕◯ MODERATE
Pembrolizumab vs Brivanib - Overall survival											
2	randomized trials	not serious	not serious	not serious	serious	none			**HR 0.88** (0.62 to 1.25)		⊕⊕⊕◯ MODERATE
Pembrolizumab vs Placebo - Overall survival											

Certainty assessment							№ of patients		Effect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	2nd line OS		Relative (95% CI)	Absolute (95% CI)	Certainty
5	randomized trials	not serious	not serious	not serious	serious	none	180/278 (64.7%)	101/135 (74.8%)	**HR 0.78** (0.61 to 1.00)	**89 fewer per 1,000** (from 179 fewer to 0 fewer)	⊕⊕⊕◯ MODERATE
Ramucirumab vs Brivanib - Overall survival											
2	randomized trials	not serious	not serious	not serious	serious	none			**HR 0.98** (0.71 to 1.34)		⊕⊕⊕◯ MODERATE
Ramucirumab vs Placebo - Overall survival											
5	randomized trials	not serious	not serious	not serious	serious	none	240/283 (84.8%)	263/282 (93.3%)	**HR 0.87** (0.72 to 1.05)	**28 fewer per 1,000** (from 76 fewer to 9 more)	⊕⊕⊕◯ MODERATE
Brivanib vs Placebo - Overall survival											
5	randomized trials	not serious	not serious	not serious	serious	none	183/263 (69.6%)	101/132 (76.5%)	**HR 0.89** (0.69 to 1.15)	**41 fewer per 1,000** (from 133 fewer to 46 more)	⊕⊕⊕◯ MODERATE

CI: Confidence interval; **HR:** Hazard Ratio

*Confidence intervals include appreciable benefits and harms

eTable 8b. Certainty of Evidence Table (GRADE). Second line treatment – Progression free survival

Certainty assessment							Effect	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HR** (95% CI)	Certainty
Cabozantinib vs Regorafenib - Progression free survival								
Network meta-analysis (2 trials)	randomized trials	not serious	not serious	not serious	serious*	none	**HR 0.96** (0.73 to 1.26)	⊕⊕⊕◯ MODERATE
Cabozantinib vs Ramucirumab - Progression free survival								
Network meta-analysis (2 trials)	randomized trials	not serious	not serious	not serious	not serious	none	**HR 0.71** (0.55 to 0.92)	⊕⊕⊕⊕ HIGH
Cabozantinib vs Pembrolizumab - Progression free survival								
Network meta-analysis (2 trials)	randomized trials	not serious	not serious	not serious	not serious	none	**HR 0.61** (0.46 to 0.82)	⊕⊕⊕⊕ HIGH
Cabozantinib vs Placebo - Progression free survival								
Network meta-analysis (4 trials)	randomized trials	not serious	not serious	not serious	not serious	none	**HR 0.44** (0.37 to 0.53)	⊕⊕⊕⊕ HIGH
Regorafenib vs Ramucirumab - Progression free survival								
Network meta-analysis (2 trials)	randomized trials	not serious	not serious	not serious	not serious	none	**HR 0.74** (0.56 to 0.98)	⊕⊕⊕⊕ HIGH
Regorafenib vs Pembrolizumab - Progression free survival								
Network meta-analysis (2 trials)	randomized trials	not serious	not serious	not serious	not serious	none	**HR 0.64** (0.47 to 0.87)	⊕⊕⊕⊕ HIGH
Regorafenib vs Placebo - Progression free survival								
Network meta-analysis (4 trials)	randomized trials	not serious	not serious	not serious	not serious	none	**HR 0.46** (0.37 to 0.57)	⊕⊕⊕⊕ HIGH
Ramucirumab vs Pembrolizumab - Progression free survival								
Network meta-analysis (2 trials)	randomized trials	not serious	not serious	not serious	serious*	none	**HR 0.86** (0.64 to 1.15)	⊕⊕⊕◯ MODERATE
Ramucirumab vs Placebo - Progression free survival								

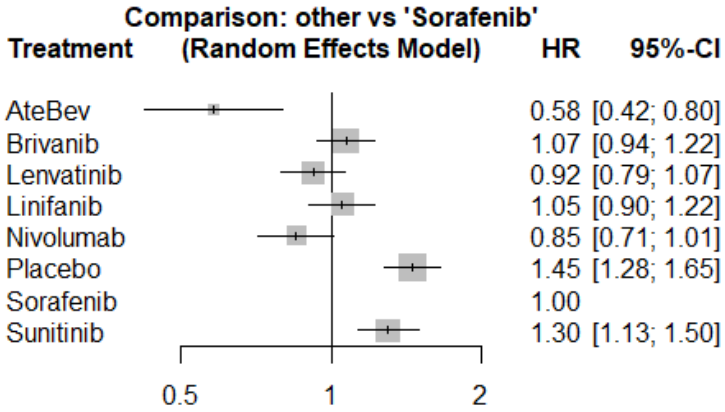
Certainty assessment							Effect	
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**HR** (95% CI)**	**Certainty**
Network meta-analysis (4 trials)	randomized trials	not serious	not serious	not serious	not serious	none	**HR 0.62** (0.52 to 0.74)	⊕⊕⊕⊕ HIGH
Pembrolizumab vs Placebo - Progression free survival								
Network meta-analysis (4 trials)	randomized trials	not serious	not serious	not serious	not serious	none	**HR 0.72** (0.57 to 0.90)	⊕⊕⊕⊕ HIGH

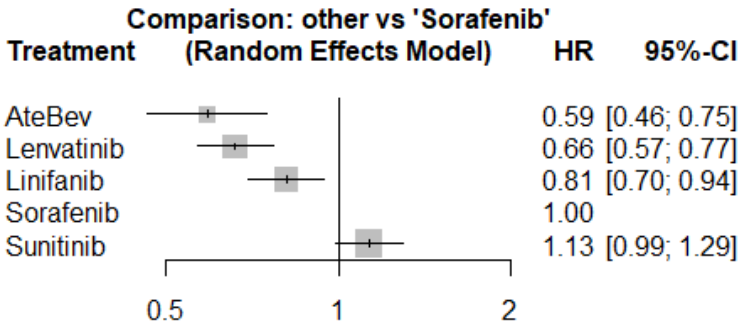
CI: Confidence interval; **HR:** Hazard Ratio

*Confidence intervals include appreciable benefits and harms

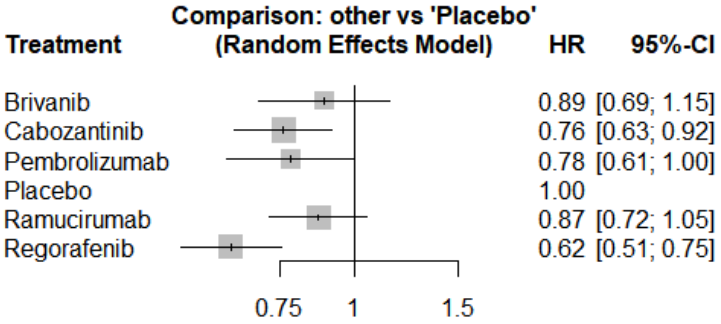
**Insufficient data to estimate absolute effects

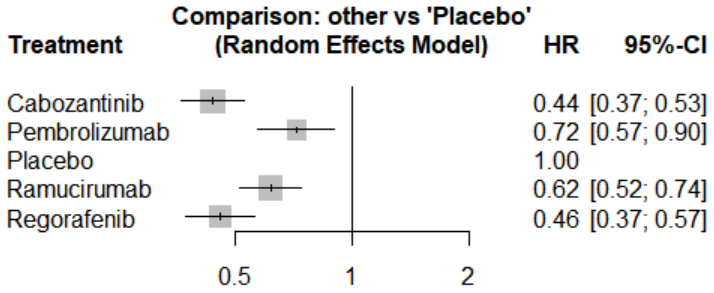
eFigure 12: forest plot of Frequentist network meta-analysis using random-effects model for overall survival (OS) (left) and progression-free survival (PFS) (right) in 1st line of treatment





eFigure 13: Figure showing forest plot of Frequentist network meta-analysis using random-effects model for overall survival (OS) (left) and progression-free survival (PFS) (right) in 2nd line of treatment





eFigure 14: Figure showing forest plot of Frequentist network meta-analysis using random-effects model for overall survival (OS) (left) and progression free survival (PFS) (right) in 2nd line of treatment for subgroup ≥400 AFP