SUPPLEMENTARY MATERIALS

Comparative Efficacy of Cabozantinib and Ramucirumab After Sorafenib for Patients with Hepatocellular Carcinoma and Alpha-fetoprotein ≥ 400 ng/mL: A Matching-Adjusted Indirect Comparison

Jörg Trojan,[1]* Patrick Mollon,[2] Bruno Daniele,[3] Florence Marteau,[2] Lidia Martín,[4] Yuxin Li,[5] Qing Xu,[6] Fabio Piscaglia,[7] Renata Zaucha,[8] Debashis Sarker,[9] Ho Yeong Lim,[10] Marino Venerito[11]

[1] Universitätsklinikum Frankfurt, Frankfurt am Main, Germany

[2] Ipsen Pharma, Boulogne-Billancourt, France

[3] Ospedale del Mare, Naples, Italy

[4] Ipsen Pharma, Barcelona, Spain

[5] IQVIA Ltd, London, UK

[6] IQVIA Inc, Beijing, China

[7] University of Bologna, Bologna, Italy

[8] Medical University of Gdańsk, Gdańsk, Poland

[9] King's College London, London, UK

[10] Samsung Medical Center, Seoul, South Korea

[11] Otto von Guericke University Hospital, Magdeburg, Germany

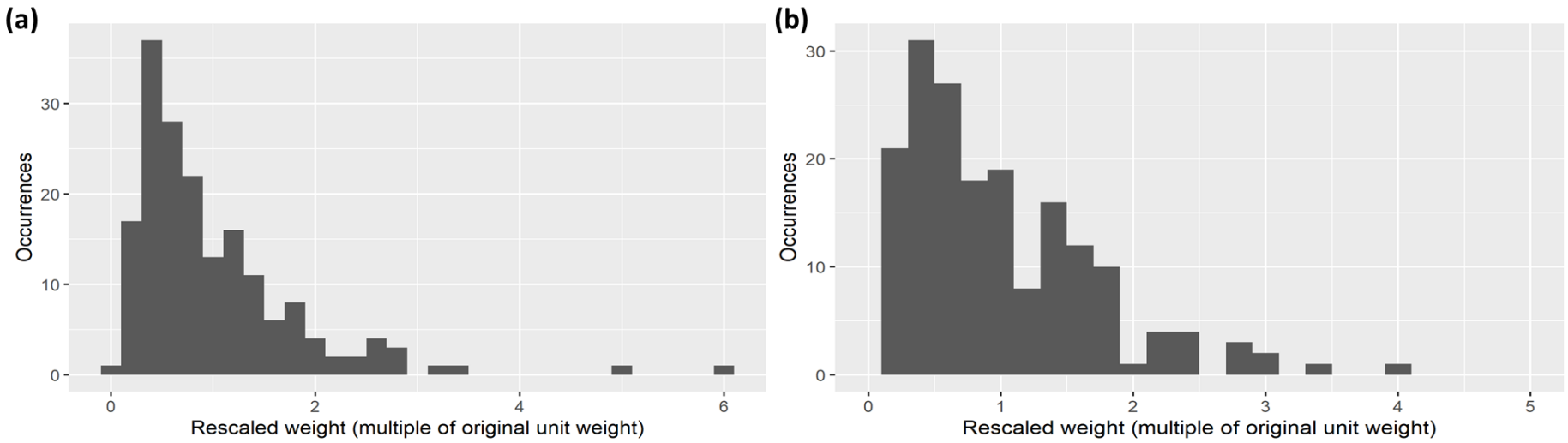

Fig. S1 Histograms of (rescaled) weights applied to the individual patient data from CELESTIAL for (**a**) the primary analysis and (**b**) the sensitivity analysis.

The histogram for the primary analysis (**a**) shows some very large, rescaled weights, with a maximum at 6. For the sensitivity analysis (**b**), the presence of extreme weights is reduced (the maximum rescaled weight is 4), and the rescaled weights are closer to 1, resulting in an approximate effective sample size for the sensitivity analysis that is very close to the original sample size. Although the sensitivity analysis, therefore, provides greater statistical power and precision than the primary analysis, it does not match patients on some characteristics that are considered to be clinically important effect modifiers (e.g., etiology nonviral, etiology hepatitis B, etiology hepatitis C and Barcelona Clinic Liver Cancer stage B)

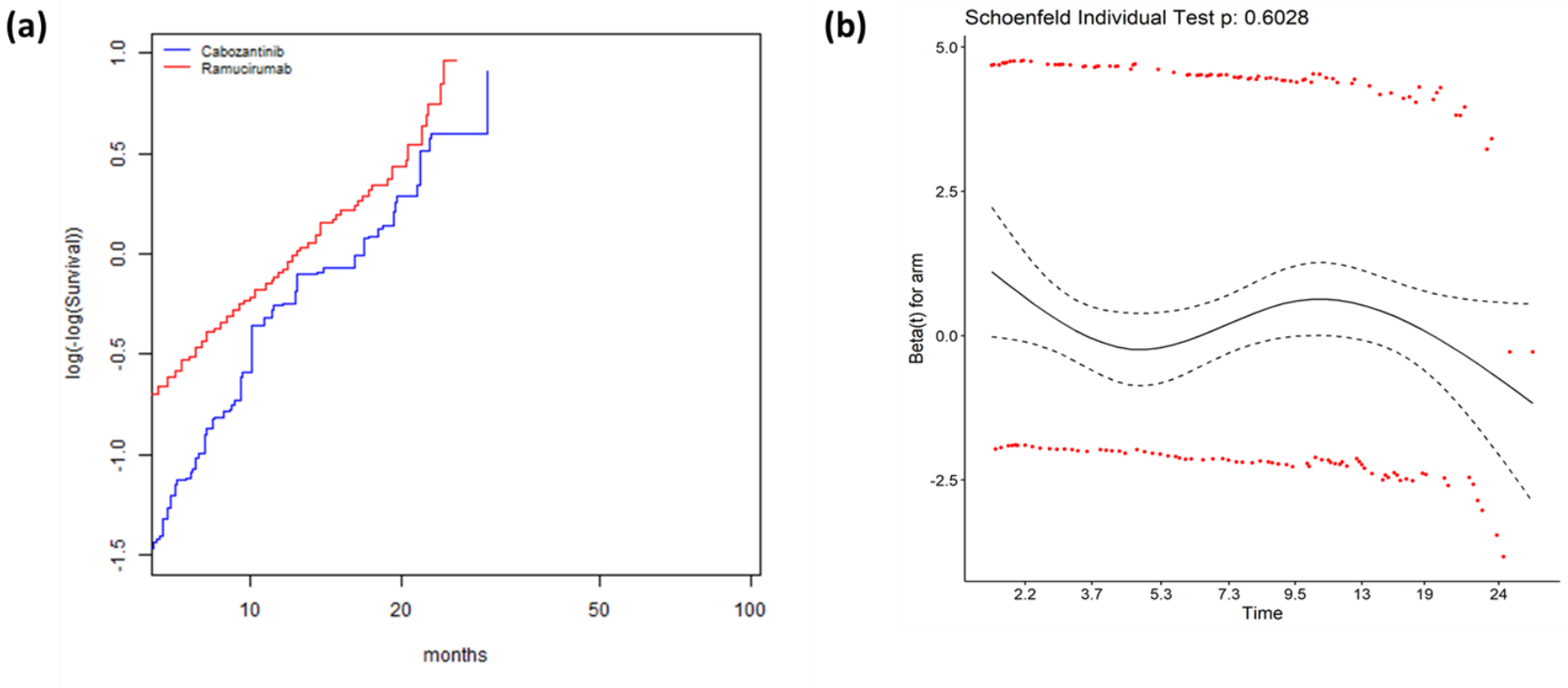

Fig. S2 Proportional hazards assumption tests (**a**) Log cumulative hazard plot and (**b**) scaled Schoenfeld residuals and Grambsch–Therneau test for OS (primary analysis).

OS overall survival

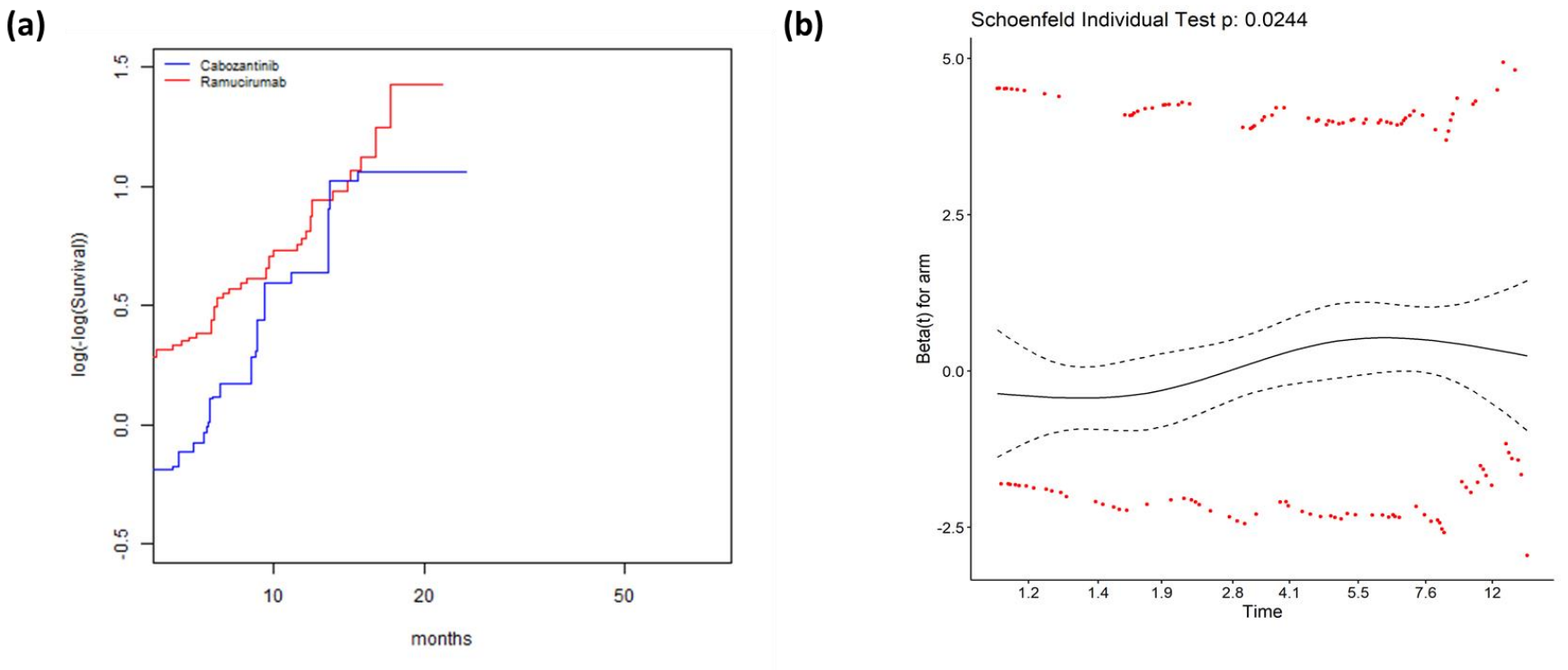

Fig. S3 Proportional hazards assumption tests (**a**) Log cumulative hazard plot and (**b**) scaled Schoenfeld residuals and Grambsch–Therneau test for PFS (primary analysis).

PFS progression-free survival

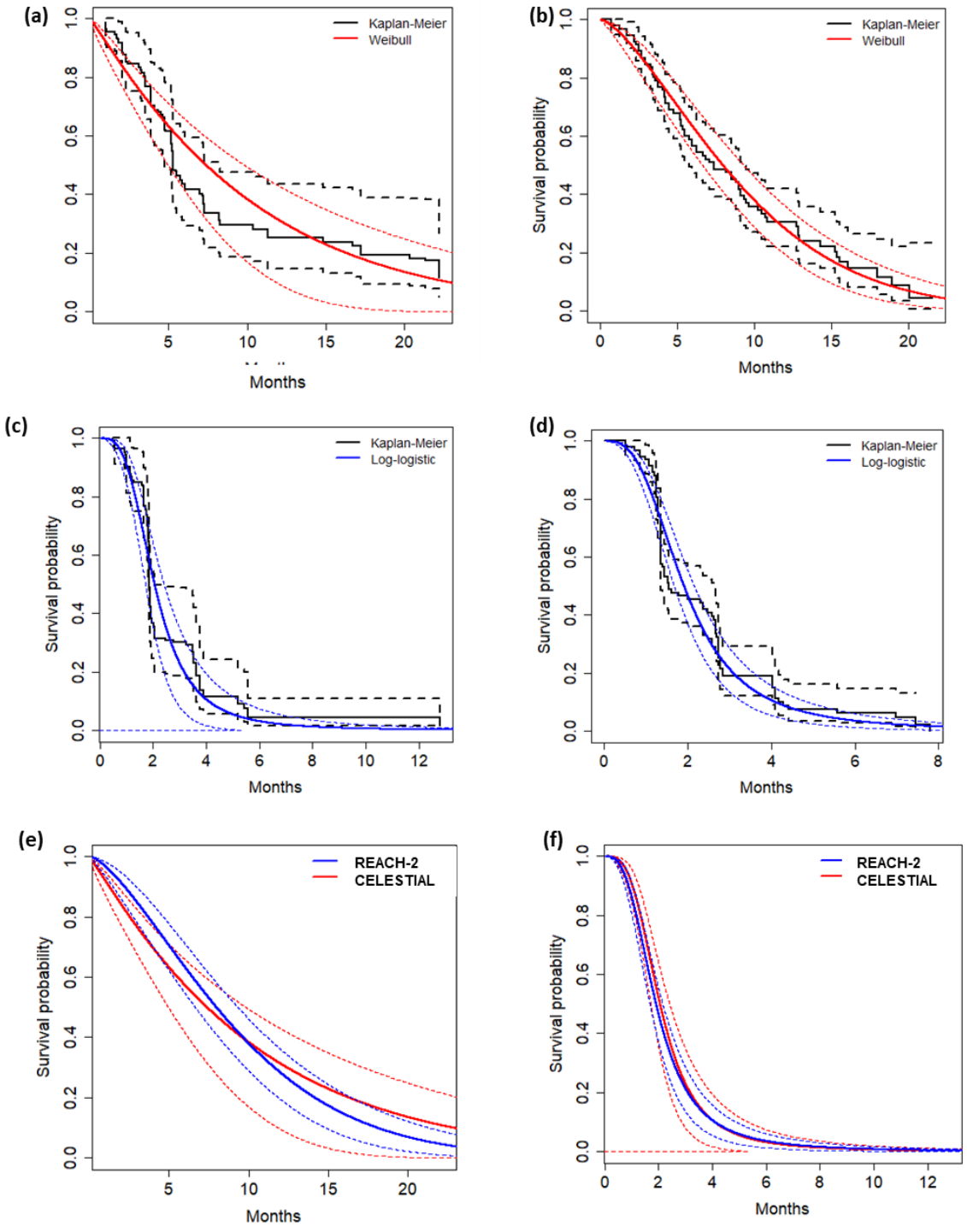

Fig. S4 Kaplan–Meier curves for the matching-adjusted and parametric modelling analyses **(a)** CELESTIAL OS **(b)** REACH-2 OS **(c)** CELESTIAL PFS **(d)** REACH-2 PFS and superposition of the CELESTIAL and REACH-2 parametric modelling analysis for **(e)** OS and **(f)** PFS (primary analysis; placebo arms)

Using best-fit models: Log-logistic (OS) and Weibull (PFS). Apparent separation of the CELESTIAL and REACH-2 placebo curves for OS **(e)** was not significant and reflects uncertainty in the analysis caused by the small patient numbers (CELESTIAL, n = 44; REACH-2, n = 95). The median (95% CI) estimates were not significantly different for the two arms; overall, the REACH-2 placebo curve largely falls within the broad confidence bands around the CELESTIAL placebo curve

OS overall survival, *PFS* progression-free survival

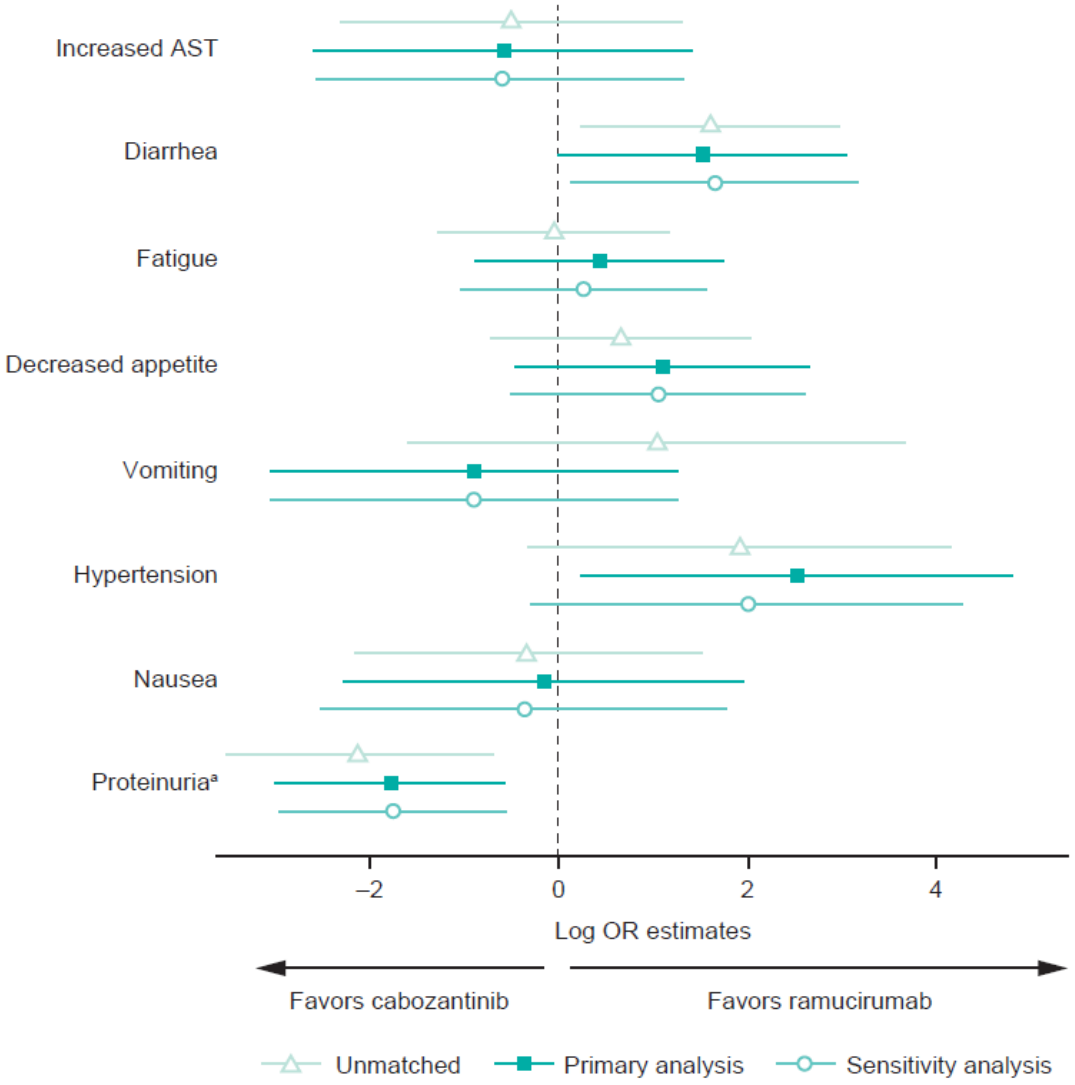

Fig. S5 Forest plot of any grade TRAE log OR (95% CI) estimates for the unmatched and matching-adjusted second-line CELESTIAL populations compared with the REACH-2 population.

[a]Unanchored analysis

AST aspartate aminotransferase, *CI* confidence interval, *OR* odds ratio, *TRAE* treatment-related adverse event

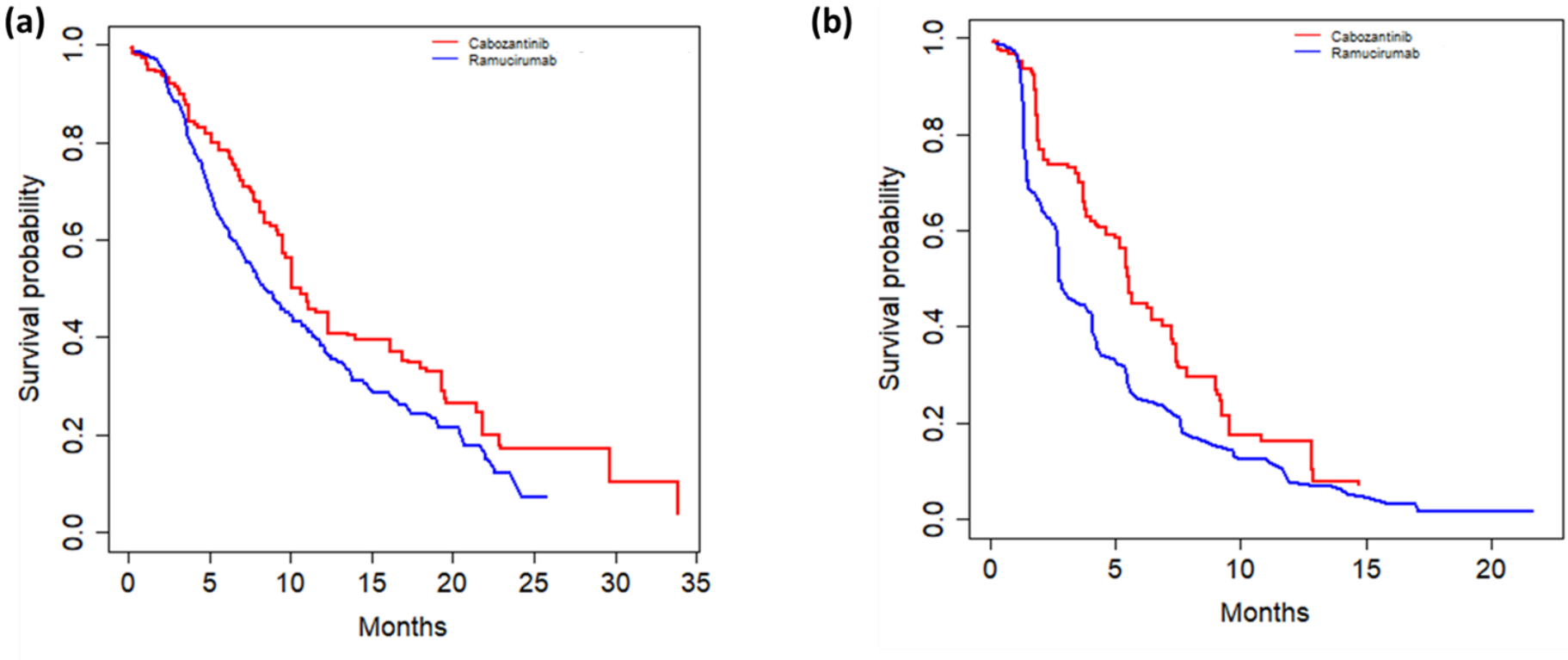

Fig. S6 Weighted Kaplan–Meier curves for (**a**) OS and (**b**) PFS of the matching-adjusted CELESTIAL population and the REACH-2 population (sensitivity analysis).

OS overall survival, *PFS* progression-free survival

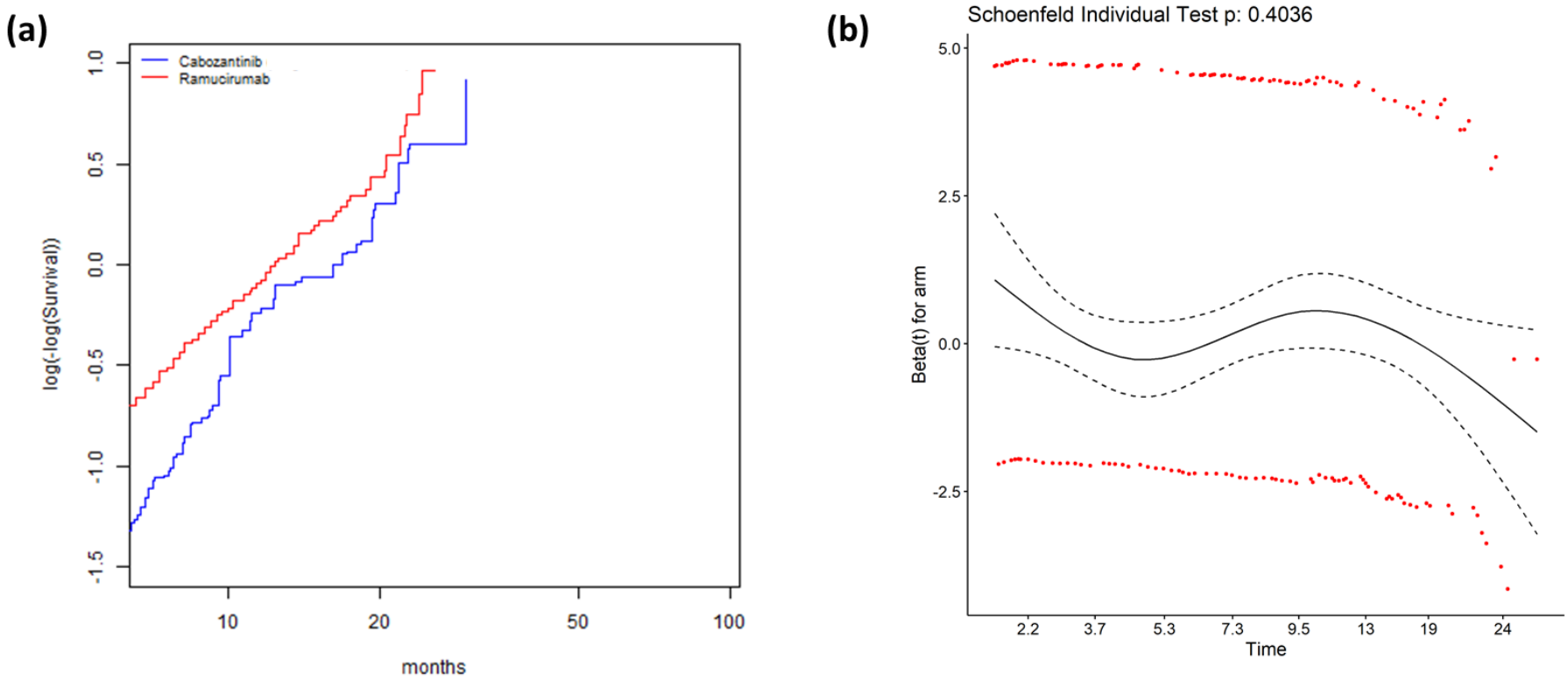

Fig. S7 Proportional hazards assumption tests (**a**) Log cumulative hazard plot and (**b**) scaled Schoenfeld residuals and Grambsch–Therneau test for OS (sensitivity analysis).

OS overall survival

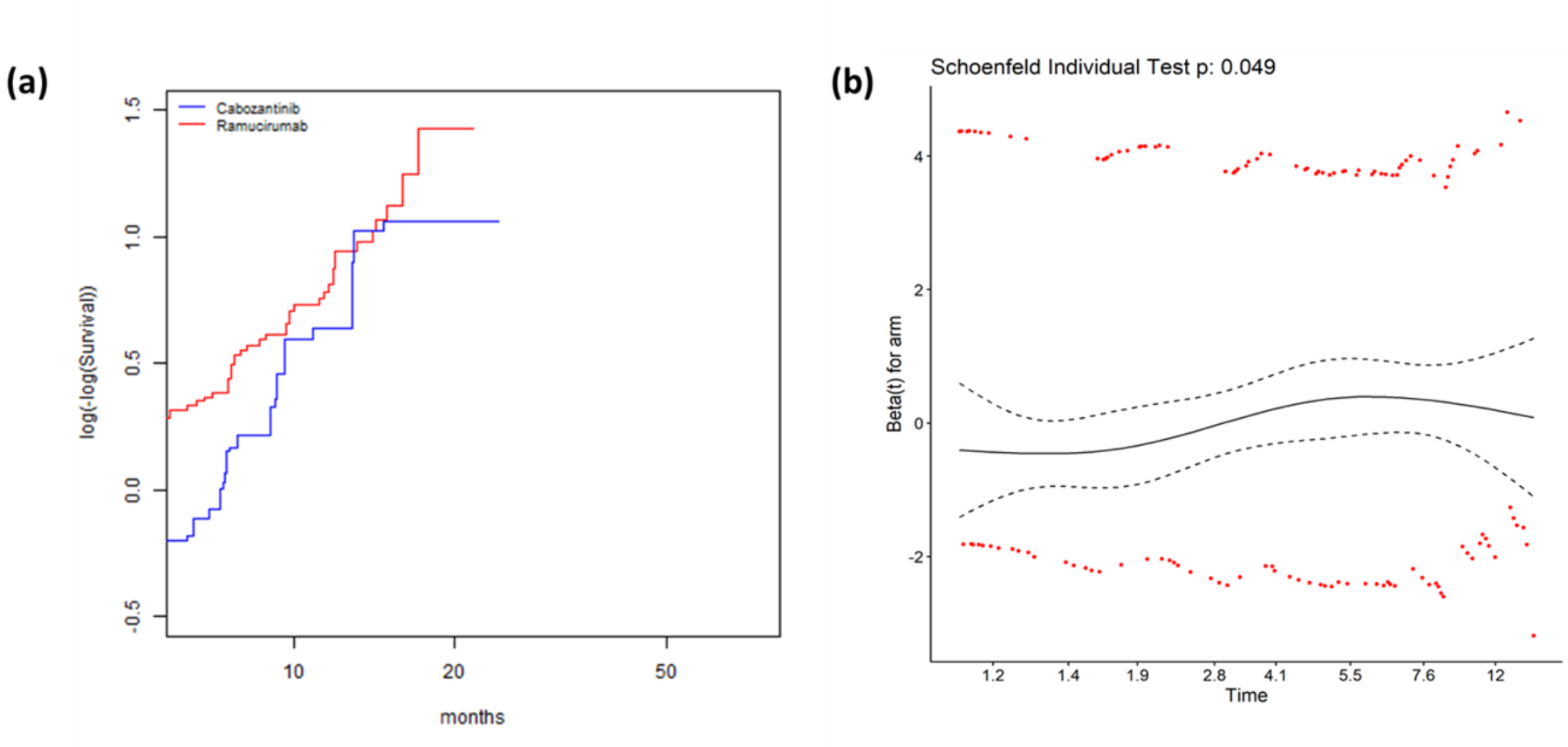

Fig. S8 Proportional hazards assumption tests (**a**) Log cumulative hazard plot and (**b**) scaled Schoenfeld residuals and Grambsch–Therneau test for PFS (sensitivity analysis).

PFS progression-free survival

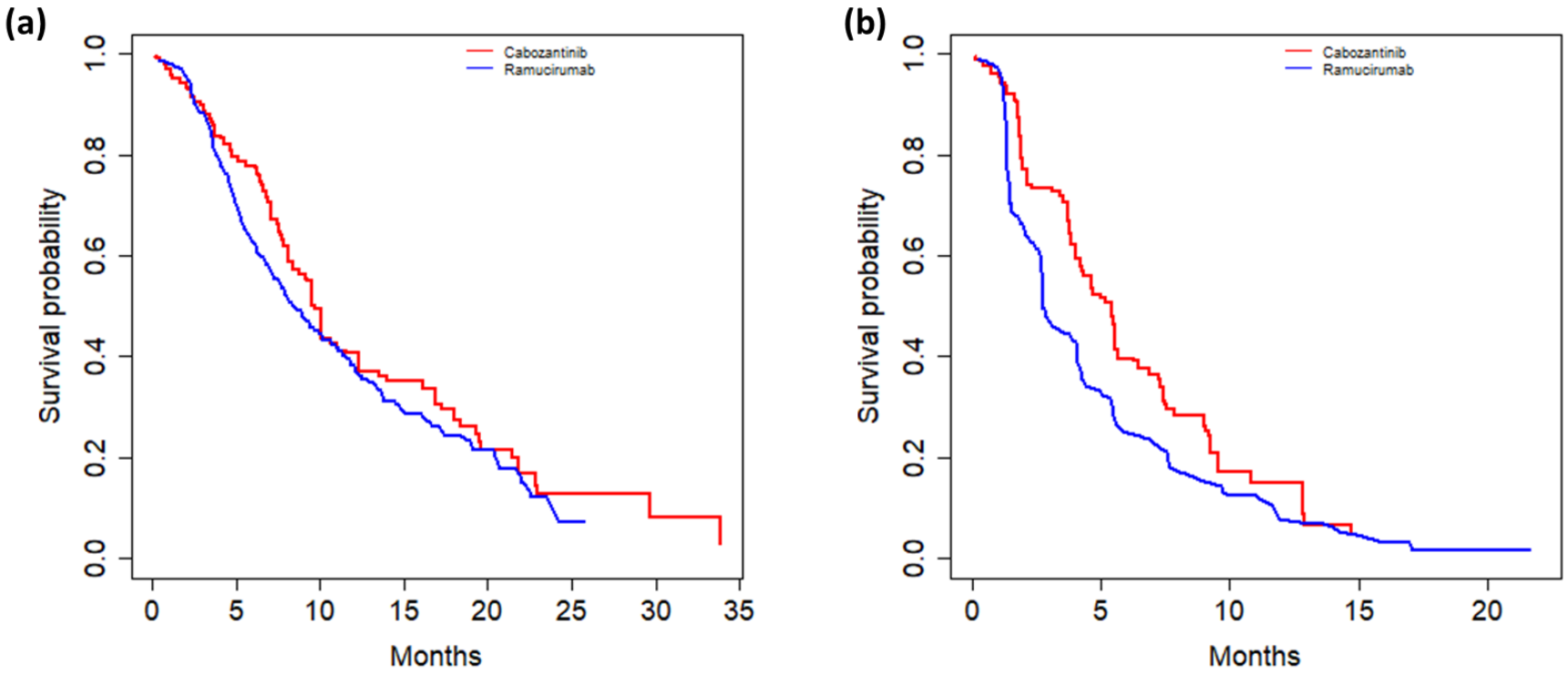

Fig. S9 Weighted Kaplan–Meier curves for (**a**) OS and (**b**) PFS of the matching-adjusted CELESTIAL population and the REACH-2 population (validation analysis).

OS overall survival, *PFS* progression-free survival

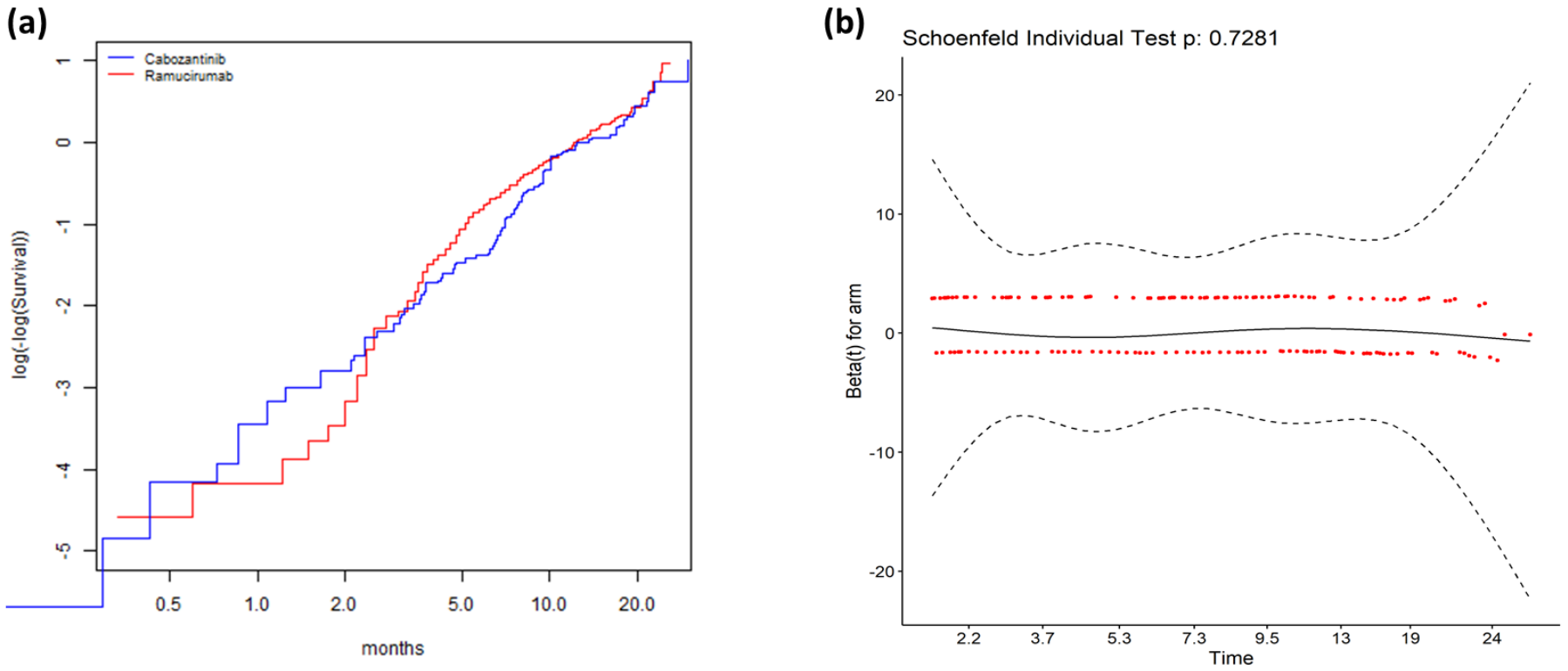

Fig. S10 Proportional hazards assumption tests (**a**) Log cumulative hazard plot and (**b**) scaled Schoenfeld residuals and Grambsch–Therneau test for OS (validation analysis).

OS overall survival

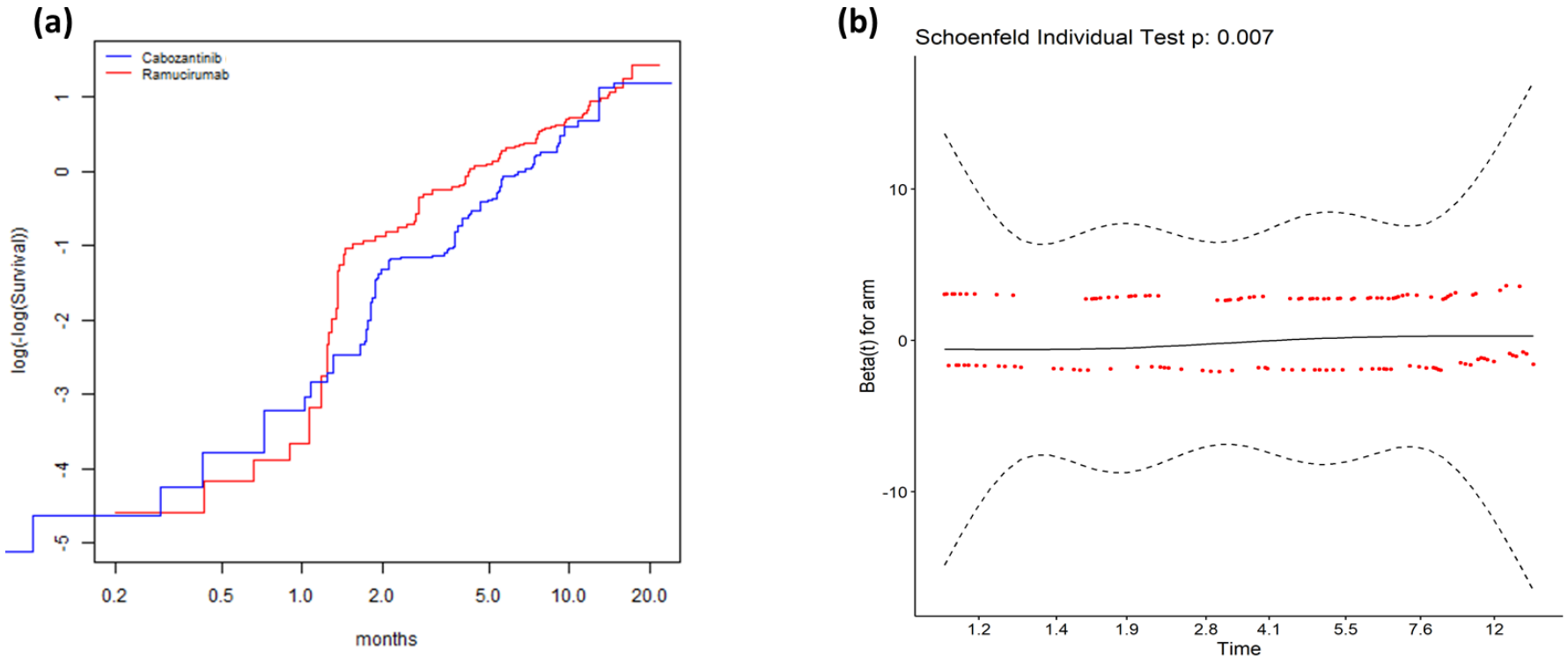

Fig. S11 Proportional hazards assumption tests (**a**) Log cumulative hazard plot and (**b**) scaled Schoenfeld residuals and Grambsch–Therneau test for PFS (validation analysis).

PFS progression-free survival

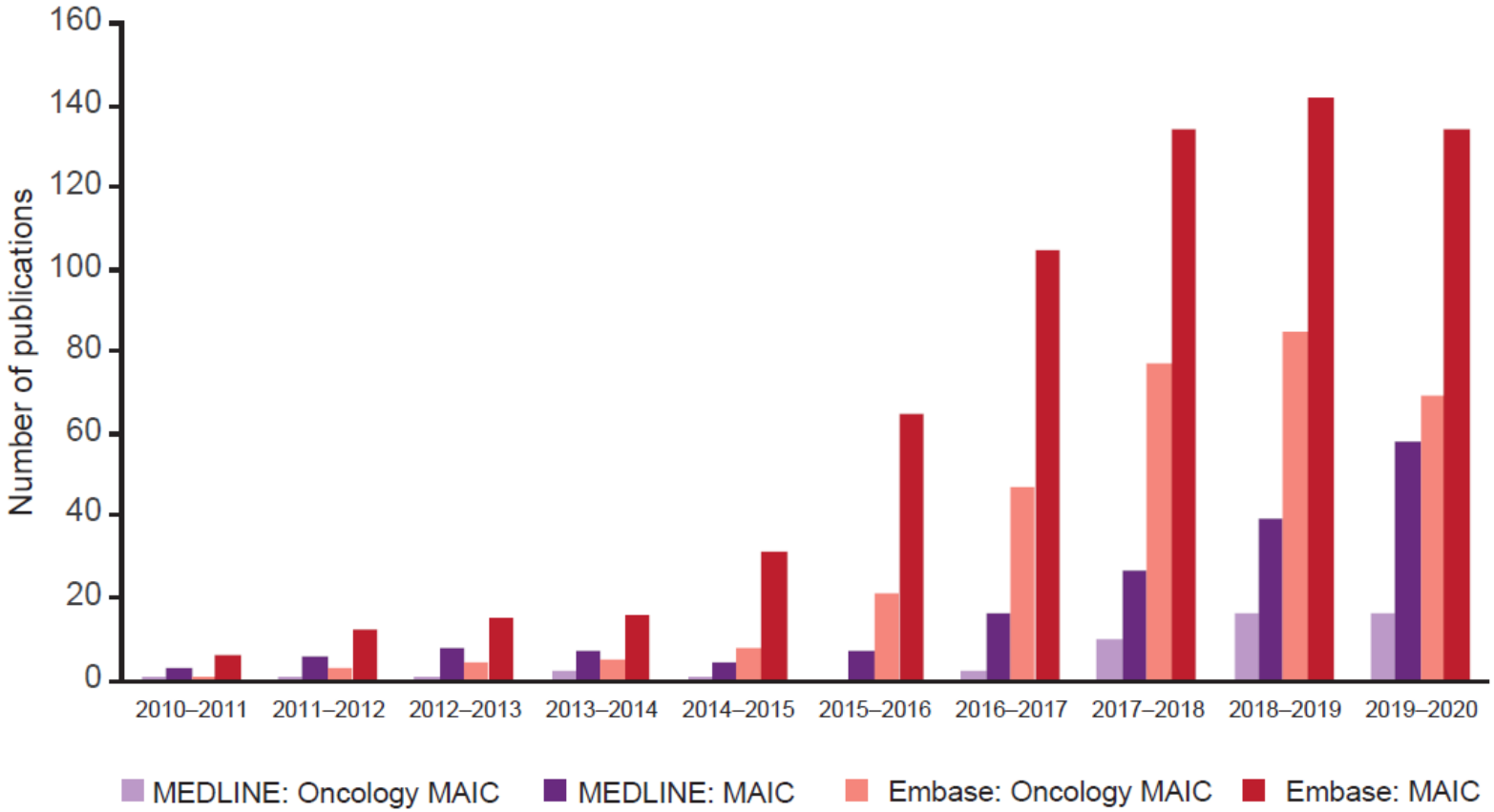

Fig. S12 MAIC and oncology-related MAIC publications listed in MEDLINE and Embase annually between 2010 and 2020 (to December 7, 2020).[a]

[a]Data are based on systematic review of the MEDLINE/Embase bibliometric databases conducted on December 7, 2020. MAIC publications are defined as those containing the following in the title or abstract (MEDLINE) of as keywords (Embase): ("matching adjusted indirect comparison" OR "matching-adjusted indirect comparison") OR (MAIC and matching$). Oncology MAIC publications are defined as those containing any of the MAIC publication search terms AND title/abstract terms (MEDLINE) or keyword (Embase) indicative of a cancer-related publication: "cancer" OR "oncology" OR "neoplasm" OR "tumor" OR "tumour".

MAIC matching-adjusted indirect comparison

Table S1 Assessment of the design characteristics considered to be relevant for comparability[1, 2]

	CELESTIAL	REACH-2
Study design	Phase 3 placebo-controlled	Phase 3 placebo-controlled
Randomization	2:1 randomized to cabozantinib and placebo	2:1 randomized to ramucirumab and placebo
Blinding	Double-blind	Double-blind
Intervention	Cabozantinib (+ BSC)	Ramucirumab (+ BSC)
Posology	Oral once daily	IV injection on day 1 of each 14-day cycle
Main inclusion criteria		
≥ 18 years of age	✓	✓
HCC (defined by histology or cytology)	✓	✓[a]
Prior sorafenib therapy[b]	✓	✓
Trial therapy administered as 2L treatment	X[c]	✓
Child–Pugh score < 7 (Child–Pugh Class A)	✓	✓
BCLC stage B or C disease	X[d]	✓
Disease not amenable to locoregional therapy or refractory to locoregional therapy	✓	✓
ECOG Performance Status of 0 or 1	✓	✓
Baseline AFP ≥ 400 mg/mL	X	✓
Key exclusion criteria		
Concurrent malignancy	✓[e]	✓
Previous brain metastases	✓	✓
Hepatic locoregional therapy following prior systemic therapy[f]	NS	✓
Prior immunotherapy	✓[g]	✓
Pregnancy	✓	✓

[a]Or a diagnosis of cirrhosis and a tumor with classical HCC imaging characteristics

[b]Available as a continuous variable for CELESTIAL and as a dichotomous variable (< 5 months or ≥ 5 months) for REACH-2

[c]Eligible patients had received no more than two prior therapies (i.e., a mixed 2L and 3L population)

[d]Calculable, but not an inclusion criterion

[e]Diagnosis of another malignancy in the 2 years before randomization, except for superficial skin cancers or localized low-grade tumors

[f]In the 28 days before randomization

[g]In the 2 weeks before randomization

2L second-line, *3L* third-line, *AFP* alpha-fetoprotein, *BCLC* Barcelona Clinic Liver Cancer, *BSC* best supportive care, *ECOG* Eastern Cooperative Oncology Group, *HCC* hepatocellular carcinoma, *IV* intravenous, *NS* not specified

Table S2 Baseline characteristics of the unadjusted 2L CELESTIAL population with AFP ≥ 400 ng/mL and the REACH-2 population

Baseline characteristic[a]	CELESTIAL 2L population with AFP ≥ 400 ng/mL (*N* = 178)		REACH-2 (*N* = 292)	
	Cabozantinib (*n* = 114)	Placebo (*n* = 64)	Ramucirumab (*n* = 197)	Placebo (*n* = 95)
Age, years, median (IQR)	63 (53–69)	62 (54–69)	64 (58–73)	64 (56–71)
Age ≥ 65 years, %	44	39	48	48
Female, %	27	13	22	17
Race, %				
Asian	35	42	52	47
White	57	52	30	33
Other	2	5	1	2
Not reported	6	2	17	18
Region, %				
Asia	29	30	49	47
Rest of world	71	70	51	53
ECOG Performance Status, %				
0	54	50	57	58
1	46	50	43	42
BCLC stage, %[a]				
B (intermediate)	NR	NR	17	21
C (advanced)	NR	NR	83	79
Child–Pugh score, %[b]				
A (5 points)	58	55	62	57
A (6 points)	42	45	38	43
Duration of prior sorafenib treatment				
< 5 months, %	50	64	56	60
Median (IQR), months	4.8 (2.6–9.0)	3.8 (2.1–7.1)	4.1 (2.3–8.4)	4.1 (2.8–7.2)
Baseline HCC disease, %[c]				
Extrahepatic disease	75	78	72	74
Macrovascular invasion	26	50	36	35
HCC etiology, %				
Hepatitis B	44	45	36	38
Alcohol use	23	17	24	22
Hepatitis C	21	25	24	29
Nonalcoholic steatohepatitis	11	9	10	4

Potential effect-modifying baseline differences are highlighted in red

[a]All percentages are subject to rounding.

[b]Measured at study entry.

[b]Per CRF

2L second-line, *AFP* alpha-fetoprotein, *BCLC* Barcelona Clinic Liver Cancer, *CRF* case report form, *ECOG* Eastern Cooperative Oncology Group, *HCC* hepatocellular carcinoma, *IQR* interquartile range, *NR* not reported

Table S3 AIC/BIC for parametric models fitted to the OS data

Model (OS)	Cabozantinib			Ramucirumab			Sum Rank
	AIC (weighted)	BIC (weighted)	Rank	AIC	BIC	Rank	
Primary analysis							
Exponential	593.72	596.45	5	1037.13	1040.41	6	11
Weibull[a]	582.72	588.19	1	1023.65	1030.22	4	5
Gompertz	585.00	590.47	3/2	1033.08	1039.65	5	8/7
Log-logistic	588.34	593.81	4	1017.24	1023.81	1	5
Log-normal	596.98	602.46	6	1018.72	1025.29	3	9
Gen gamma	584.70	592.91	2/3	1018.59	1028.44	2	4/5
Sensitivity analysis							
Exponential	612.36	615.09	4	1037.13	1040.41	6	10
Weibull[a]	604.72	610.19	1	1023.65	1030.22	4	5
Gompertz	605.02	610.49	2	1033.08	1039.65	5	7
Log-logistic	612.70	618.17	5	1017.24	1023.81	1	6
Log-normal	622.30	627.77	6	1018.72	1025.29	3	9
Gen gamma	606.35	614.56	3	1018.59	1028.44	2	5
Validation analysis							
Exponential	573.47	576.21	5	1037.13	1040.41	6	11
Weibull[a]	564.89	570.36	1	1023.65	1030.22	4	5
Gompertz	567.51	572.98	3/2	1033.08	1039.65	5	8/7
log-logistic	570.01	575.49	4	1017.24	1023.81	1	5
log-normal	577.36	582.84	6	1018.72	1025.29	3	9
Gen gamma	566.89	575.1	2/3	1018.59	1028.44	2	4/5

[a]Selected as best-fit model

AIC Akaike Information Criterion, *BIC* Bayesian Information Criterion, *OS* overall survival

Table S4 AIC/BIC for parametric models fitted to the PFS data

Model (PFS)	Cabozantinib			Ramucirumab			Sum Rank
	AIC (weighted)	BIC (weighted)	Rank	AIC	BIC	Rank	
Primary analysis							
Exponential	497.05	499.79	5	903.03	906.31	5	10
Weibull	489.85	495.32	3	897.73	904.30	4	7
Gompertz	497.46	502.94	6	904.95	911.52	6	12
Log-logistic[a]	485.79	491.26	1	873.45	880.01	3	4
Log-normal	491.99	497.46	4	868.57	875.13	1	5
Gen gamma	488.60	496.80	2	869.76	879.61	2	4
Sensitivity analysis							
Exponential	514.68	517.42	5	903.03	906.31	5	10
Weibull	509.57	515.05	3	897.73	904.30	4	7
Gompertz	515.75	521.23	6	904.95	911.52	6	12
Log-logistic[a]	506.61	512.08	1	873.45	880.01	3	4
Log-normal	513.94	519.41	4	868.57	875.13	1	5
Gen gamma	509.02	517.22	2	869.76	879.61	2	4
Validation analysis							
Exponential	483.49	486.23	6	903.03	906.31	5	11
Weibull	476.69	482.16	2	897.73	904.3	4	6
Gompertz	483.18	488.66	5	904.95	911.52	6	11
log-logistic[a]	475.97	481.45	1	873.45	880.01	3	4
log-normal	482.69	488.17	4	868.57	875.13	1	5
Gen gamma	477	485.21	3	869.76	879.61	2	5

[a]Selected as best-fit model

AIC Akaike Information Criterion, *BIC* Bayesian Information Criterion, *PFS* progression-free survival

Table S5 Median and mean with 95% CI survival times for the modeled matching-adjusted CELESTIAL and REACH-2 placebo curves

	Weighted KM analysis				Parametric modeling analysis	
	Overall survival		Progression-free survival		Overall survival[a]	Progression-free survival[b]
Placebo population	**Mean (95% CI)**	**Median (95% CI)**	**Mean (95% CI)**	**Median (95% CI)**	**Mean (95% CI)**	**Median (95% CI)**
Ramucirumab (*N* = 95)	8.6 (7.3–9.8)	7.4 (5.8–9.4)	2.6 (2.1–3.2)	1.6 (1.4–2.6)	8.0 (6.6–9.3)	1.9 (1.7–2.2)
Matching-adjusted cabozantinib (primary analysis) (*ESS* = 44)	6.2 (4.7–7.6)	5.3 (4.8–8.2)	2.3 (1.8–2.7)	1.9 (1.8–2.1)	7.5 (5.3–9.7)	2.1 (1.7–2.3)
Matching-adjusted cabozantinib (sensitivity analysis) (*ESS* = 46)	6.2 (4.7–7.6)	5.3 (4.8–7.3)	2.3 (1.8–2.7)	1.9 (1.9–2.0)	7.4 (4.9–9.8)	2.1 (1.7–2.4)
Unmatched cabozantinib (2L population with AFP ≥ 400 ng/mL) (*n* = 64)	7.6 (5.5–9.6)	5.2 (4.3–7.0)	2.7 (1.9–3.6)	1.9 (1.8–1.9)	NE	NE
Full (2L and 3L) cabozantinib CELESTIAL (*N* = 237)	9.4 (8.3–10.6)	8.0 (6.9–9.7)	4.7 (3.7–5.6)	1.9 (1.9–2.0)	NE	NE

[a]Log-logistic model selected as best-fit model for the matching-adjusted CELESTIAL placebo OS curve

[b]Weibull model selected as best-fit model for the matching-adjusted CELESTIAL placebo PFS curve

2L second-line, *AFP* alpha-fetoprotein, *CI* confidence interval; *ESS* effective sample size; *KM* Kaplan–Meier, *NE* not evaluated

Table S6 Baseline matching characteristics used in the MAIC, before and after matching (sensitivity analysis)[a]

Baseline characteristic	CELESTIAL 2L population with AFP ≥ 400 ng/mL		REACH-2 population
	Unmatched (*N* = 105)	Matching-adjusted (*N* = 119)	Published (*N* = 292)
Age < 65 years, %	57.87	51.71	51.71
Female, %	21.91	20.21	20.21
Mean duration of prior sorafenib treatment < 5 months, months	44.94	57.19	57.19
Extrahepatic disease, %	76.40	72.26	72.26
Macrovascular invasion, %	34.83	35.27	35.27
AFP, median $\log_{10}$(AFP)[b]	3.94	3.00	3.53
ALBI grade 1, %	34.83	48.97	48.97

[a]Matching variables selected as potential effect modifiers by statistical modeling

[b]Reported as median of $\log_{10}$(AFP), given the magnitude of difference in median (IQR) AFP for the pre-matched CELESTIAL and REACH-2 populations

2L second-line, *AFP* alpha-fetoprotein, *ALBI* albumin–bilirubin, *IQR* interquartile range, *MAIC* matching-adjusted indirect comparison

Table S7 Median and mean survival times with 95% CI for parametrically modeled matching-adjusted cabozantinib and ramucirumab curves

	Overall survival		Progression-free survival	
Treatment	**Mean (95% CI)**	**Median (95% CI)**	**Mean (95% CI)**	**Median (95% CI)**
Ramucirumab	11.6 (10.2, 13.0)	9.70 (8.5, 10.9)	4.9 (4.3, 5.58)	4.0 (3.4, 4.5)
Matching-adjusted cabozantinib (primary analysis)	14.5 (12.1, 17.5)	11.57 (9.1, 14.1)	6.9 (5.9, 8.0)	5.8 (4.4, 7.2)
Matching-adjusted cabozantinib (sensitivity analysis)	14.3 (12.0, 17.1)	11.35 (8.9, 13.9)	6.9 (5.9, 7.9)	5.7 (4.3, 7.1)
Unmatched cabozantinib (2L population with AFP ≥ 400 ng/mL)	11.5 (9.7, 13.5)	9.30 (7.6, 11.0)	5.7 (4.8, 6.8)	4.6 (3.8, 5.4)
Unmatched cabozantinib (2L population)	22.4 (18.1, 28.7)	11.27 (10.0, 12.7)	7.0 (6.2, 7.9)	5.2 (4.6, 5.8)
Full (2L and 3L) cabozantinib CELESTIAL	20.4 (17.1, 25.1)	10.46 (9.4, 11.5)	7.4 (6.5, 8.5)	4.6 (4.2, 5.0)

Median 95% CIs are computed by estimated median of fitted values ± 1.96 × estimated median SE

2L second-line, *3L* third-line, *AFP* alpha-fetoprotein, *CI* confidence interval, *SE* standard error

Table S8 Log OR (95% CI) and *p* values for TRAEs reported in at least 5% of patients in any arm of the CELESTIAL or REACH-2 trials (sensitivity analysis)

TRAE	Unmatched analysis		Matched-adjusted analysis	
	Log OR (95% CI)	***p* value**	**Log OR (95% CI)**	***p* value**
Any grade				
Increased AST	–0.50 (–2.32, 1.32)	0.6019	–0.61 (–2.56, 1.33)	0.5476
Diarrhea	1.61 (0.23, 2.99)	0.0220	1.65 (–0.13, 3.18)	0.0329
Fatigue	–0.05 (–1.29, 1.18)	0.9377	0.25 (–1.06, 1.56)	0.7167
Decreased appetite	0.66 (–0.72, 2.05)	0.3519	1.06 (–0.51, 2.63)	0.1878
Vomiting	1.05 (–1.58, 3.69)	0.4430	–0.9 (–3.06, 1.27)	0.4247
Hypertension	1.92 (–0.33, 4.16)	0.0942	1.99 (–0.29, 4.27)	0.0874
Nausea	–0.33 (–2.17, 1.52)	0.7413	–0.36 (–2.50, 1.78)	0.7535
Proteinuria[a]	–2.11 (–3.52, –0.70)	0.0034	–1.76 (–2.96, –0.55)	0.0045
Grade 3/4				
Increased AST[a]	2.28 (1.02, 3.55)	0.0004	1.64 (0.3, 2.98)	0.0161
Fatigue[a]	2.24 (0.70, 3.77)	0.0044	2.64 (1.15, 4.14)	0.0006
Hypertension	16.34 (14.73, 17.94)	< 0.0010	16.68 (15.03, 18.33)	< 0.0010
Leading to discontinuation				
Any TRAE	0.40 (–1.57, 2.36)	0.7509	1.05 (–0.96, 3.06)	0.3110

[a]Unanchored analysis because no AEs occurred in at least one of the placebo arms of the trials

AST aspartate aminotransferase, *CI* confidence interval, *OR* odds ratio, *TRAE* treatment-related adverse event

Table S9 Baseline matching characteristics used in the MAIC, before and after matching (validation analysis)[a]

Baseline characteristics	CELESTIAL 2L population with AFP ≥ 400 ng/mL		REACH-2 population
	Unmatched (*N* = 202)	Matching-adjusted (*N* = 128)	Unmatched (*N* = 292)
Age under 65 years, %	57.87	51.71	51.71
Female, %	21.91	20.21	20.21
Duration of prior sorafenib treatment < 5 months, %[b]	44.94	57.19	57.19
Extrahepatic disease, %	76.40	72.26	72.26
Macrovascular invasion, %	34.83	35.27	35.27
Etiology, %			
Hepatitis B	44.38	36.64	36.64
Hepatitis C	22.47	26.03	26.03
Nonviral[c]	30.34	31.51	31.51
ALBI grade 1, %	34.83	48.97	48.97
BCLC stage B, %	8.99	18.49	18.49

[a]Matching variables selected as potential effect modifiers by expert clinical panel

[b]Categorization of prior sorafenib treatment use in (and published for) the REACH-2 trial

[c]HCC of nonviral etiology was not recorded directly in the REACH-2 trial. Estimate is derived from the sum of patients with etiology of alcohol use plus nonalcoholic steatohepatitis fatty liver, using the total REACH-2 population size as the denominator. There might be overlap in patients between these two etiology categories

2L second-line, *AFP* alpha-fetoprotein, *ALBI*, albumin–bilirubin, *BCLC* Barcelona Clinic Liver Cancer, *HCC* hepatocellular carcinoma, *IQR* interquartile range, *MAIC* matching-adjusted indirect comparison

Table S10 Log OR (95% CI) and *p* values for TRAEs reported in at least 5% of patients in any arm of CELESTIAL or REACH-2 (cabozantinib vs ramucirumab) for the primary and validation matching-adjusted analyses

TRAE	Primary matched-adjusted analysis		Validation matched-adjusted analysis	
	Log OR (95% CI)	***p* value**	**Log OR (95% CI)**	***p* value**
Any grade				
Increased AST	–0.58 (–2.59, 1.42)	0.5799	–0.37 (–2.23, 1.49)	0.7089
Diarrhea	1.53 (0.00, 3.05)	0.0499	1.41 (–0.09, 2.91)	0.0658
Fatigue	0.44 (–0.89, 1.76)	0.5288	0.03 (–1.27, 1.33)	0.9690
Decreased appetite	1.10 (–0.46, 2.66)	0.1691	0.94 (–0.5, 2.38)	0.2023
Vomiting	–0.90 (–3.06, 1.27)	0.4247	–0.9 (–3.06, 1.27)	0.4247
Hypertension	2.52 (0.23, 4.81)	0.0305	2.76 (0.5, 5.02)	0.0168
Nausea	–0.15 (–2.27, 1.97)	0.8968	0.13 (–1.76, 2.02)	0.9046
Proteinuria[a]	–1.78 (–2.99, –0.56)	0.0043	–2.21 (–3.68, –0.74)	0.0033
Grade 3/4				
Increased AST[a]	1.79 (0.47, 3.11)	0.0078	2.08 (0.79, 3.36)	0.0016
Fatigue[a]	2.72 (1.23, 4.22)	0.0004	2.55 (1.04, 4.05)	0.0010
Hypertension	16.92 (15.20, 18.65)	< 0.0010	16.81 (15.16, 18.46)	< 0.0010
Leading to discontinuation				
Any TRAE	1.16 (–0.89, 3.20)	0.2709	1.29 (–0.72, 3.30)	0.2086

[a]Unanchored analysis because no AEs occurred in at least one of the placebo arms of the trials

AST aspartate aminotransferase, *CI* confidence interval, *OR* odds ratio, *TRAE* treatment-related adverse event

REFERENCES

1. Abou-Alfa GK, Meyer T, Cheng AL, El-Khoueiry AB, Rimassa L, Ryoo BY, et al. Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. N Engl J Med. 2018;379(1):54-63. doi:10.1056/NEJMoa1717002.

2. Zhu AX, Kang YK, Yen CJ, Finn RS, Galle PR, Llovet JM, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2019;20(2):282-96. doi:10.1016/s1470-2045(18)30937-9.