Comparative Efficacy of Cabozantinib and Regorafenib for Advanced Hepatocellular Carcinoma

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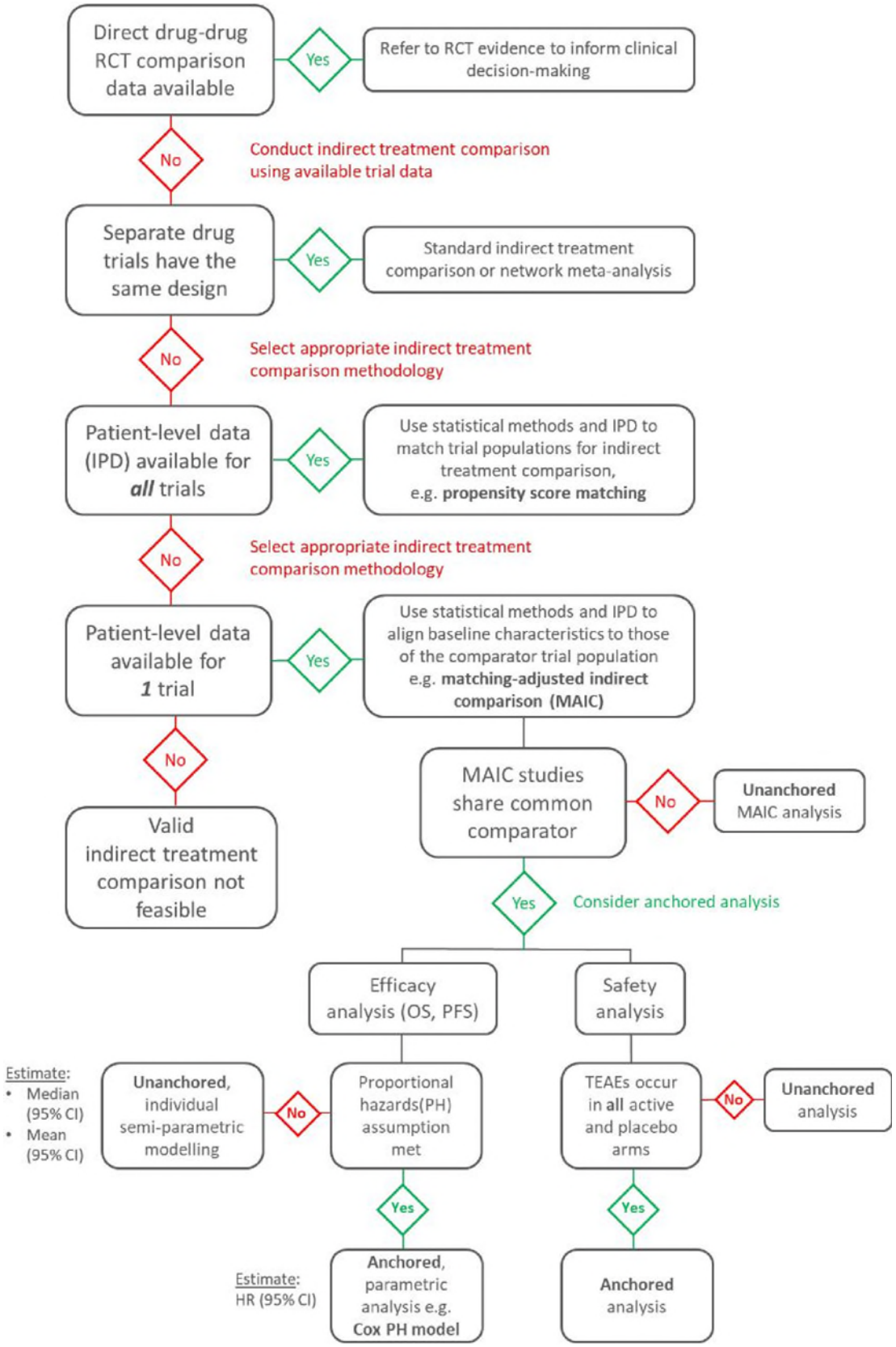
Figure S1 Simplified decision tree summarizing the rationale for selecting the analysis approach used



CI confidence interval, *IPD* individual patient data, *HR* hazard ratio, *MAIC* matching-adjusted indirect comparison, *PH* proportional hazards, *RCT* randomized controlled trial, *TEAE* treatment-emergent adverse events

Proportional hazards (PH) modeling is compatible with an anchored analysis and is preferable to an unanchored analysis, where valid. For an anchored analysis to be valid, the PH assumption must be justified. It is important to validate the PH assumption because parametric models (e.g. Cox Proportional Hazards) make stronger assumptions than semi-parametric alternatives. PH modeling applies a single hazard ratio to the entire modeling period, which requires the treatment effect to be proportional over time and for the survival curves fitted to each treatment group to be a similar shape. If this assumption cannot be justified, an unanchored approach is advised [1]. The PH assumption can be tested by visual inspection of the log-cumulative hazard plots for OS and PFS (to ensure that there is no pattern of non-parallelism) and by visual inspection of the scaled Schoenfeld residuals and the Grambsch–Therneau test based on the scaled Schoenfeld residuals (to ensure no systematic departure from the horizontal) [1, 2].

In the current analysis, differences between the CELESTIAL and RESORCE trials prevented use of a standard indirect treatment comparison. As individual patient data were only available to the investigators for the CELESTIAL trial population, a matching-adjusted indirect comparison approach was selected as a valid method of comparison. As the PH assumption was not satisfied for either survival outcome (OS or PFS), an unanchored analysis was conducted in accordance with NICE DSU TSD 14 guidelines, which state that if the PH assumption does not seem appropriate, it is most sensible to fit separate parametric models of the same type [1].For the safety analysis, where TEAEs of interest occurred in all treatment arms, an anchored analysis was conducted; where this was not the case (i.e. for Palmar-plantar erythrodysesthesia and diarrhea), an unanchored analysis was carried out.

Figure S2 Log-cumulative hazard plots for overall survival (a) and progression-free survival (b) for cabozantinib versus regorafenib in the matching-adjusted second-line CELESTIAL population and the RESORCE population

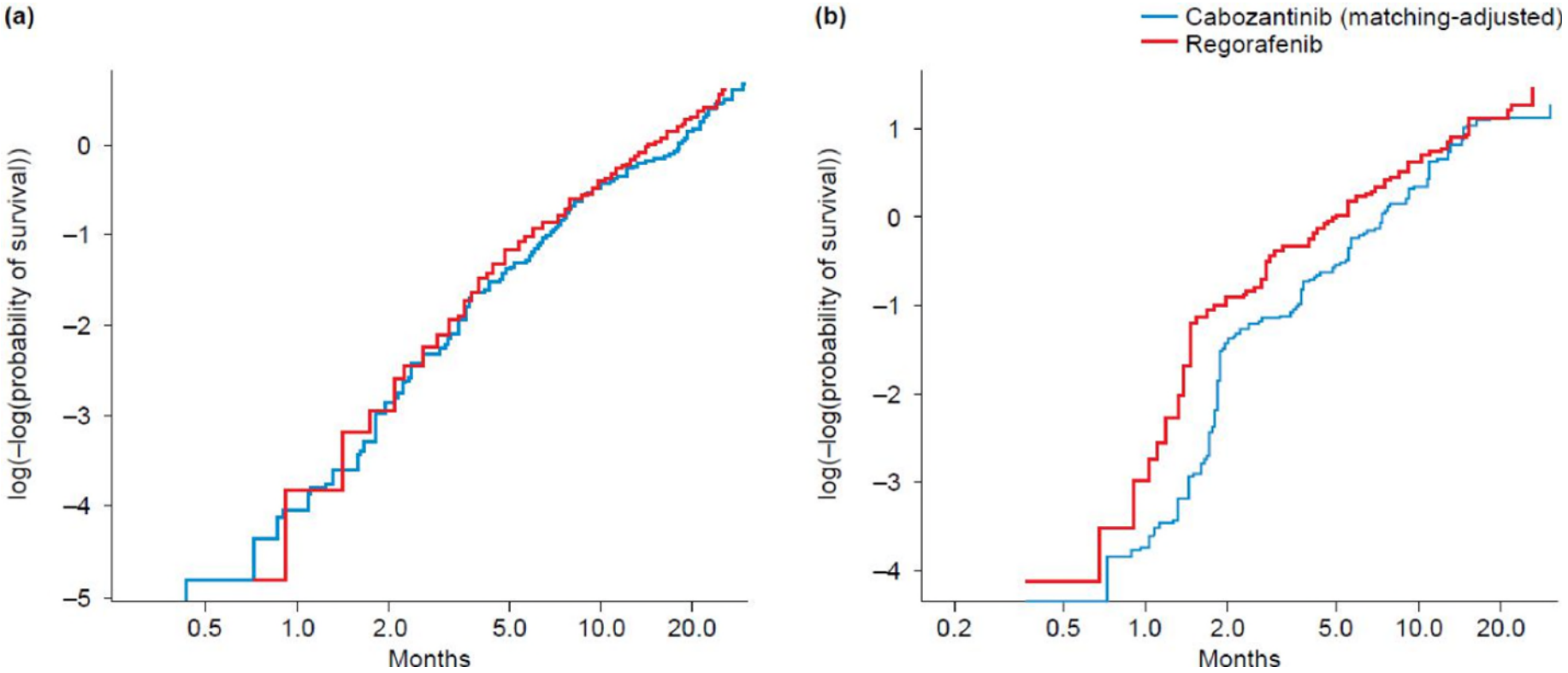
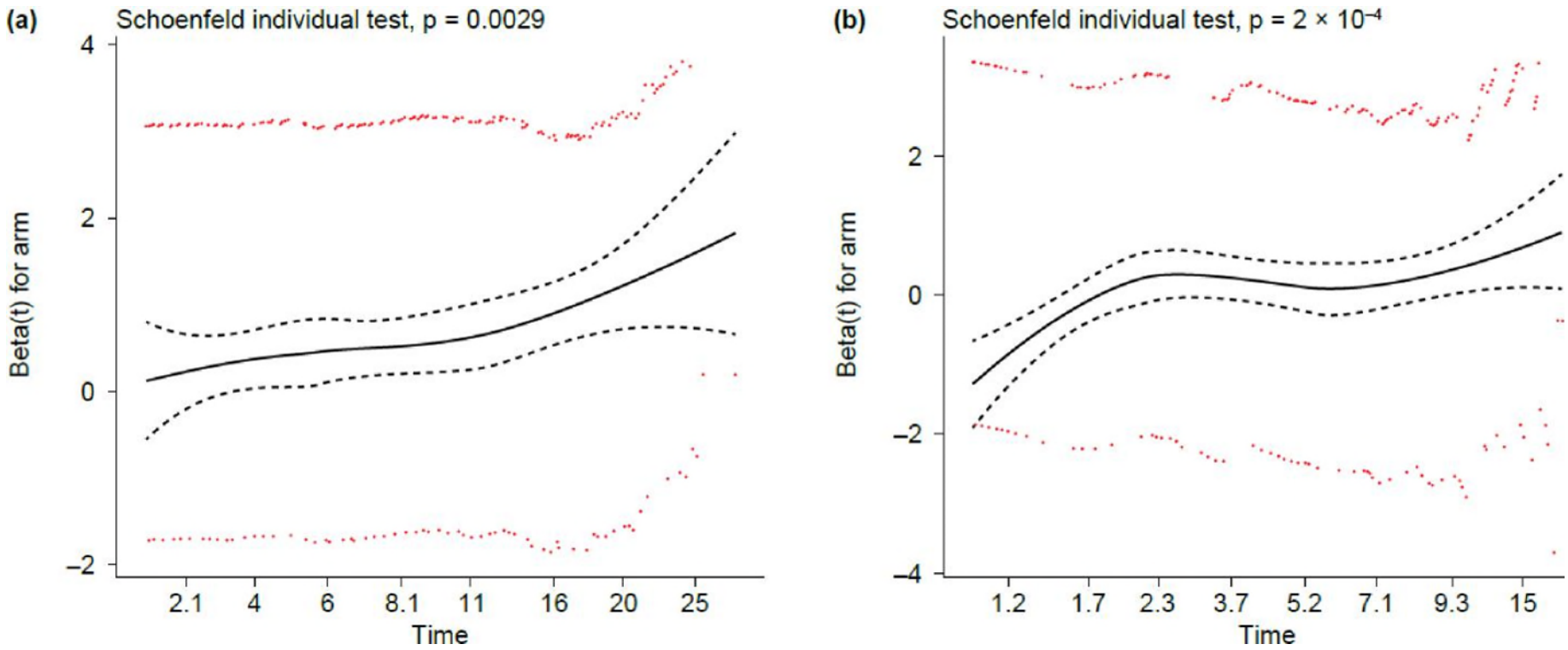


Figure S3 Scaled Schoenfeld residuals for overall survival (a) and progression-free survival (b) for cabozantinib versus regorafenib in the matching-adjusted second-line CELESTIAL population and the RESORCE population



Smooth spline fit with dashed lines representing standard error and red dots representing outliers

Table S1 Assessment of the design characteristics considered relevant for comparability[3, 4]

	CELESTIAL	RESORCE
Intervention	Cabozantinib + BSC	Regorafenib + BSC
Study design	Phase 3 placebo-controled	Phase 3 placebo-controled
Randomization	2:1 randomized to cabozantinib and placebo	2:1 randomized to regorafenib and placebo
Blinding	Double-blind	Double-blind
Posology	Oral once daily	Oral once daily
Crossover	Not allowed	NR
Best supportive care	NR	NR
Main inclusion criteria		
Histological or cytological diagnosis of HCC	I	I
Subject has disease not amenable to curative treatment approach	I	NR
Received prior sorafenib	I	I
Progression following: ≥ 1 prior systemic HCC therapies	I	I
≤ 2 prior systemic therapies	I	X
ECOG Performance Status score of 0 or 1	I	I
Adequate hematologic and renal function	I	I
Child–Pugh score of A	I	I
Antiviral therapy per local standard of care if active hepatitis B infection	I	NR
BCLC stage B or C	NR	I
Tolerability of prior treatment with sorafenib[a]	NR	I
Life expectancy of at least 3 months	NR	I

[a]RESORCE excluded sorafenib-intolerant patients; CELESTIAL did not exclude sorafenib-intolerant patients

BCLC Barcelona Clinic Liver Cancer, *BSC* best supportive care, *HCC* hepatocellular carcinoma, *NR* not recorded

Table S2 Comparison of selected patient characteristics between CELESTIAL (overall population) and RESORCE (overall population) [3, 4]

		CELESTIAL (N = 707)		RESORCE (N = 573)	
		Cabozantinib (N = 470)	**Placebo (N = 237)**	**Regorafenib (N = 379)**	**Placebo (N = 194)**
Median age, years		64	64	64	62
Female, %		19	15	12	12
Race, %	Asian	34	35	41	40
	Black or African American	2	5	2	1
	White	56	55	36	35
	Other/NR	7	5	21	24
Region, %	Asia	25	25	38	38
	Rest of world	75	75	62	62
ECOG Performance Status, %	0	52	55	65	67
	1	48	45	35	33
BCLC state on entry, %	A (early)	NR	NR	0.3	0
	B (intermediate)	NR	NR	14	11
	C (advanced)	NR	NR	86	89
Child–Pugh score at entry, %	A	98	99	98	97
	B	1	0.8	1	3
Prior treatment, %	1 systemic therapy	71	73	100	100
	2 systemic therapies	28	26	0	0
Duration of prior sorafenib, median (IQR) (months)		5.32 (0.3, 70.0)	4.80 (0.2, 76.8)	7.8 (4.2, 14.5)	7.8 (4.4, 14.7)
Baseline HCC disease per CRF, % extrahepatic spread		79	77	70	76
Etiology of disease, %	HBV (without known HCV)	36	36	NR	NR
	HCV (without known HBV)	22	22	NR	NR
	HBV and HCV	2	2	NR	NR
	HBV ± known HCV	38	38	38	38
	HCV ± known HBV	24	23	21	21
Alpha fetoprotein, %	< 400 ng/mL	59	57	57	55
	≥ 400 ng/mL	41	43	43	45

Clear differences in the baseline characteristics of the overall population of CELESTIAL and the overall population of RESORCE can be seen for race, region, ECOG Performance Status, number of prior treatments, and duration of prior sorafenib treatment between the trials

BCLC Barcelona Clinic Liver Cancer, *CRF* case report form, *ECOG* Eastern Cooperative Oncology Group, *HBV* hepatitis B virus, *HCC* hepatocellular carcinoma, *HCV* hepatitis C virus, *IQR* interquartile range, *NR* not reported

Table S3 AIC and BIC values for the candidate models fitted to the overall survival data

	Unmatched second-line cabozantinib		Matching-adjusted second-line cabozantinib		Regorafenib	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	1647.81	1651.60	1678.56	1682.34	1740.62	1744.56
Weibull	1635.25	1642.82	1672.09	1679.67	1727.96	1735.84
Gompertz	1643.49	1651.06	1678.39	1685.96	1739.24	1747.11
Log-logistic	1636.40	1643.98	1668.20	1675.78	1716.81	1724.68
Log-normal	1646.09	1653.66	1675.18	1682.75	1712.17	1720.05
Generalized gamma	1634.37	1645.73	1668.37	1679.74	1714.10	1725.92

The model with the lowest AIC and BIC for regorafenib is the log-normal. However, the log-normal performs relatively poorly against the cabozantinib data (e.g. it gives the highest BIC for weighted cabozantinib in Scenario 2). The Weibull model fits the cabozantinib data well (e.g. it gives the lowest AIC; however, its fit to the regorafenib data is mediocre (fourth lowest AIC and BIC values). Both the log-logistic and generalized gamma models give good fits (always within the three lowest AIC/BIC values) for both treatments. The log-logistic distribution is selected to model the OS outcome as it appears to fit the weighted cabozantinib data better upon visual assessment.

AIC Akaike's Information Criterion, *BIC* Schwarz's Bayesian Information Criterion

	Unmatched second-line cabozantinib		Matching-adjusted second-line cabozantinib		Regorafenib	
	AIC	BIC	AIC	BIC	AIC	BIC

Table S4 AIC and BIC values for the candidate models fitted to the progression-free survival data

Exponential	1439.30	1443.09	1480.30	1484.09	1641.66	1645.60
Weibull	1419.50	1427.08	1457.16	1464.73	1634.92	1642.79
Gompertz	1436.25	1443.82	1476.18	1483.75	1643.38	1651.26
Log-logistic	1412.23	1419.80	1453.83	1461.41	1590.28	1598.15
Log-normal	1417.85	1425.43	1467.01	1474.58	1577.40	1585.27
Generalized gamma	1410.04	1421.40	1450.61	1461.97	1575.13	1586.94

The model with the lowest AIC for regorafenib is the generalized gamma and that with the lowest BIC is the log-normal. For cabozantinib, the model with the lowest AIC is the generalized gamma and that with the lowest BIC is the log-logistic. The generalized gamma also gives low BIC values (the second lowest BIC). Hence, the generalized gamma is selected as the winning model for the PFS outcome.

AIC Akaike's Information Criterion, *BIC* Schwarz's Bayesian Information Criterion

Table S5 Median survival estimates for the CELESTIAL and RESORCE populations: extrapolated 5-year parametric models for active treatment (a) and placebo (b) arms

(a) Survival estimate[a]	CELESTIAL population			RESORCE
	Overall (N = 470)	Unmatched second-line cabozantinib (N = 331)	Matching-adjusted second-line cabozantinib (ESS = 187)	Regorafenib (N = 379)
OS, mean (95% CI) months	20.41 (17.22–24.90)	22.35 (18.12–28.72)	24.65 (19.57–32.79)	21.17 (17.12–27.42)
OS, median (95% CI) months	10.46 (9.46–11.58)	11.27 (9.96–12.73)	11.40 (10.01–12.96)	10.29 (9.15–11.56)
PFS, mean (95% CI) months	6.45 (5.87–7.18)	6.98 (6.24–7.92)	7.17 (6.46–8.03)	6.04 (5.09–8.33)
PFS, median (95% CI) months	4.73 (4.32–5.19)	5.17 (4.62–5.79)	5.49 (4.92–6.13)	3.39 (3.05–3.78)

[a]log-logistic and generalized gamma models selected to fit the full cabozantinib OS and PFS data, respectively
CI confidence interval, *ESS* effective sample size, *OS* overall survival, *PFS* progression-free survival

() Survival estimate[a]	second-line CELESTIAL placebo arm (ESS = 81)	Matching-adjusted RESORCE placebo arm (N = 194)
OS, median (95% CI) months	8.27 (7.00–9.76)	7.30 (6.30–8.47)
PFS, median (95% CI) months	2.35 (2.11–2.61)	1.87 (1.68–2.09)

[a]log-logistic and generalized gamma models selected to fit the CELESTIAL placebo OS and PFS data, respectively
CI confidence interval, *ESS* effective sample size, *OS* overall survival, *PFS* progression-free survival

Table S6 Log-ORs for selected grade 3 or 4 treatment-emergent adverse events in the CELESTIAL trial (matching-adjusted and unmatched, second-line population) compared with the RESORCE trial population

TEAE	Second-line CELESTIAL population	Log-OR	95% CI	Standard error	*p* value
Anchored analysis					
Increased AST	Unmatched	0.89	–0.31, 2.09	0.61	0.1478
	Matching-adjusted	0.79	–0.47, 2.06	0.65	0.2201
Diarrhea	Unmatched	NA	NA	NA	NA
	Matching-adjusted	NA	NA	NA	NA
Elevated bilirubin	Unmatched	–0.55	–3.01, 1.91	1.25	0.6732
	Matching-adjusted	–0.25	–2.73, 2.23	1.26	0.8558
Fatigue	Unmatched	0.07	–1.65, 1.79	0.88	0.9404
	Matching-adjusted	0.09	–1.77, 1.94	0.95	0.9313
Hypertension	Unmatched	1.73	–0.45, 3.91	1.11	0.1207
	Matching-adjusted	2.1	–0.1, 4.3	1.12	0.0611
Unanchored analysis					
Diarrhea	Unmatched	1.55	0.8, 2.3	0.38	1×10^{-4}
	Matching-adjusted	1.74	1, 2.48	0.38	0.001
Palmar-plantar erythrodysesthesia	Unmatched	0.3	–0.17, 0.77	0.24	0.2103
	Matching-adjusted	0.05	–0.4, 0.5	0.23	0.848

AST aspartate aminotransferase, *CI* confidence interval, *NA* not applicable, *OR* odds ratio, *TEAE* treatment-emergent adverse event

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