Matching-adjusted indirect comparison of cabozantinib versus regorafenib in advanced hepatocellular carcinoma

Poster #: 17

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BACKGROUND

- Cabozantinib and regorafenib are tyrosine kinase inhibitors (TKIs) approved for the treatment of advanced hepatocellular carcinoma (aHCC) in patients who have progressed on or after prior sorafenib, based on findings from the randomised, placebo-controlled, phase 3 trials CELESTIAL[1] and RESORCE,[2] respectively.
- There are no head-to-head studies comparing these two agents.

OBJECTIVE

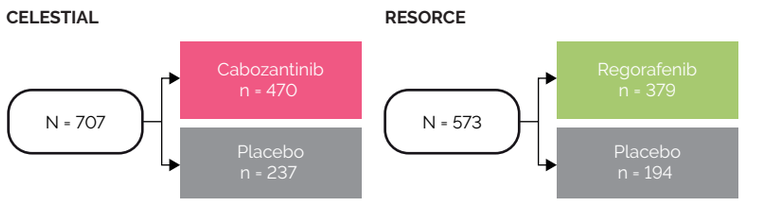
- This matching-adjusted indirect comparison (MAIC) compared cabozantinib vs regorafenib for 2nd-line treatment of aHCC in patients who received sorafenib as the only prior systemic therapy, using data from CELESTIAL and RESORCE.

METHODS

Study population

- CELESTIAL and RESORCE study designs are shown in **Figure 1**.
- This MAIC assessed patients enrolled in CELESTIAL who received 2nd-line therapy after sorafenib as the only prior therapy (n = 495; cabozantinib, n = 331; placebo, n = 164).

Figure 1. CELESTIAL and RESORCE study designs



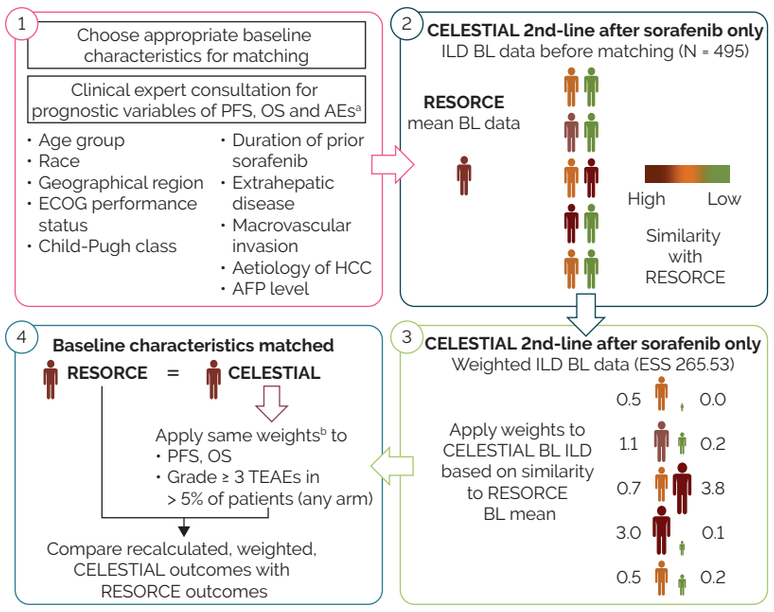
- Patients who had progressed on or after prior sorafenib
- Up to 2 previous systemic treatments allowed (27% of patients received 3rd-line treatment)

- Patients who had progressed on prior sorafenib
- No other previous systemic treatments allowed
- Sorafenib-intolerant patients were excluded

Patient matching and indirect comparison

- Patients in CELESTIAL who had received sorafenib as the only prior therapy were matched to patients in RESORCE using selected baseline characteristics considered by clinical experts to have the greatest impact on efficacy and safety outcomes (**Figure 2**).
- For each baseline characteristic, individual-level data (ILD) from CELESTIAL were weighted based on similarity to aggregate data (means) from RESORCE (for which no ILD were available).

Figure 2. Patient matching and indirect comparison



[a]Based on the opinion of clinical experts, the most important baseline characteristics were observed in both trials and adjusted for in the matching. [b]Weights applied to outcomes in treatment and placebo arms.
Figure modified with kind permission from Nash *et al. Rheumatol Ther* 2018;5:99–122.
AFP, alpha-fetoprotein; BL, baseline; ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; HCC, hepatocellular carcinoma; ILD, individual-level data; PFS, progression-free survival; OS, overall survival; TEAE, treatment-emergent adverse event.

Indirect comparisons and statistical analyses

- Survival outcomes
  - Overall progression-free survival (PFS) and overall survival (OS) based on Kaplan-Meier plots were compared between cabozantinib (weighted population of patients who had received sorafenib as the only prior therapy in CELESTIAL) and regorafenib using log-rank test (non-placebo-adjusted comparison).
    - For regorafenib Kaplan-Meier plots, approximated ILD were generated using digitisation of published RESORCE data.[2]
  - Median PFS and OS (with 95% confidence intervals [CI]) for cabozantinib and placebo (population of patients who had received sorafenib as the only prior therapy) were derived from weighted CELESTIAL Kaplan-Meier plots; median PFS and OS with regorafenib and placebo in RESORCE were derived from published data.[2]
  - Median PFS and OS with cabozantinib (weighted population of patients who had received sorafenib as the only prior therapy in CELESTIAL) and regorafenib were also compared based on fitted and extrapolated Kaplan-Meier plots (5 years follow-up).
    - Candidate parametric models were fitted to the ILD to model PFS (generalised gamma model) and OS (log-logistic model).
- Safety outcomes
  - Based on frequencies of grade 3 or 4 drug-related treatment-emergent adverse events (TEAEs) affecting > 5% of patients in any arm of CELESTIAL or RESORCE; this included:
    - hypertension, increased aspartate aminotransferase (AST), fatigue, diarrhoea, palmer-plantar erythrodysesthesia (PPE) and elevated bilirubin.
  - TEAE outcomes were compared between cabozantinib vs regorafenib using placebo-adjusted and non-placebo-adjusted analyses and using log-scale odds ratios (ORs).

RESULTS

Sample sizes and baseline characteristics

- After matching, baseline characteristics were balanced across trials (**Table 1**)

Table 1. Sample sizes and baseline characteristics

	CELESTIAL		RESORCE	
	Full study population[a,1]	2nd-line after sorafenib only[a,b] (unweighted)	2nd-line after sorafenib only[a,c] (weighted)	As reported[a,2]
Sample sizes				
Treatment	470	331	187.3[d]	379
Placebo	237	164	81.2[d]	194
Overall	707	495	265.5[d]	573
Characteristic (% of patients unless stated otherwise)				
Age under 65 years	51.49	53.33	54.97	54.97
White	55.73	58.18	35.95	35.95
Asia geographical region	24.75	22.83	37.7	37.7
ECOG status 0	53.18	56.97	65.79	65.79
Child-Pugh class A	98.73	98.79	97.91	97.91
Mean duration of sorafenib treatment (months)	8.24	7.65	11.63	11.63
Extrahepatic disease	77.93	76.16	71.9	71.9
Macrovascular invasion	29.79	29.41	28.62	28.62
Hepatitis B aetiology	37.82	37.37	37.7	37.7
Alcohol use aetiology	21.76	21.52	25.31	25.31
Hepatitis C aetiology	23.86	25.10	20.77	20.77
AFP > 400 ng/mL	41.44	40.81	43.46	43.46
Female	17.82	17.58	18.63	12.04

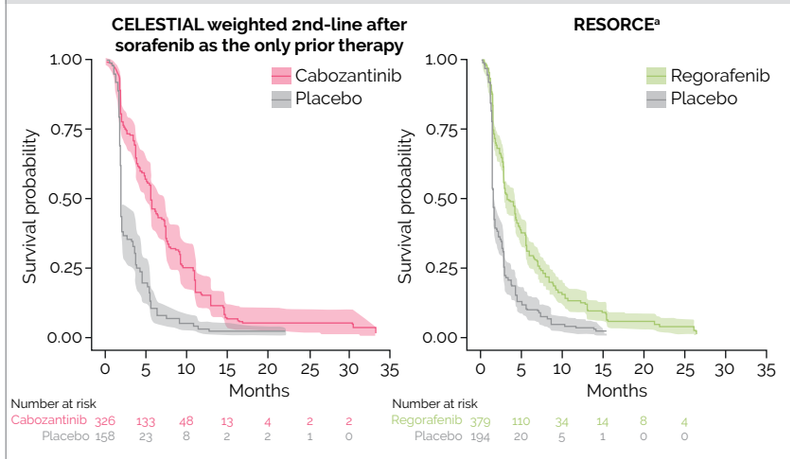
Matched characteristics

[a]Enrolled and randomised patients (efficacy analysis population). [b]Patients with unavailable baseline characteristics were included in the analyses of the unweighted data sets (2nd-line, n = 11). [c]Patients with unavailable baseline characteristics were excluded from the weighted analyses. [d]Effective sample size (ESS); overall ESS non-additive with respect to each treatment arm.

Progression-free survival

- Overall PFS was significantly longer at the 5% level for weighted cabozantinib after sorafenib as the only prior therapy vs regorafenib (p = 0.0005; non-placebo-adjusted comparison; log-rank test) (**Figure 3**).
- Median (95% CI) PFS was longer with weighted cabozantinib after sorafenib as the only prior therapy than with regorafenib:
  - Weighted cabozantinib, 5.6 (4.9–7.3) months; weighted placebo, 1.9 (1.9–2.1) months.
  - Regorafenib, 3.1 (2.8–4.2) months; placebo, 1.5 (1.4–1.6) months.[2]
- Median PFS with weighted cabozantinib after sorafenib as the only prior therapy was similar to data previously reported in patients receiving 2nd-line therapy in CELESTIAL:
  - Unweighted cabozantinib, 5.5 (4.6–5.7) months; unweighted placebo, 1.9 (1.9–1.9) months.[3]

Figure 3. Kaplan-Meier plots for progression-free survival



[a]Based on approximated individual-level data using digitisation of published RESORCE Kaplan-Meier plot[2].

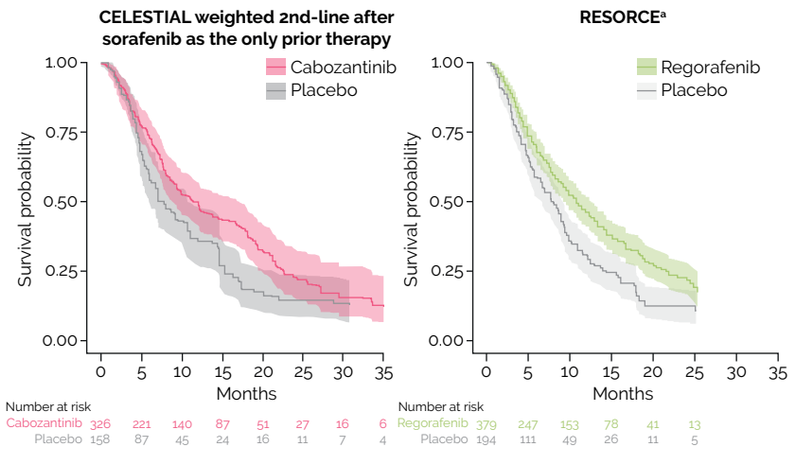
Overall survival

- OS was longer for weighted cabozantinib after sorafenib as the only prior therapy vs regorafenib, but the difference was not statistically significant (p = 0.3474; non-placebo-adjusted comparison; log-rank test) (**Figure 4**).
- Median (95% CI) OS was similar between weighted cabozantinib after sorafenib as the only prior therapy and regorafenib:
  - Weighted cabozantinib, 11.4 (8.9–17.0) months; weighted placebo, 7.2 (6.1–10.8) months.
  - Regorafenib, 10.6 (9.1–12.1) months; placebo, 7.8 (6.3–8.8) months.[2]
- Median OS with weighted cabozantinib after sorafenib as the only prior therapy was similar to data previously reported in patients receiving 2nd-line therapy in CELESTIAL:
  - Unweighted cabozantinib, 11.3 (9.5–13.9) months; unweighted placebo, 7.2 (5.8–9.3) months.[3]

Survival comparisons during extrapolated, 5-year follow-up

- Upon fitting and extrapolating selected models, weighted cabozantinib after sorafenib as the only prior therapy was associated with longer median PFS than regorafenib; median OS was similar between the two treatments:
  - Median (95% CI) PFS: cabozantinib, 5.49 (4.92–6.13) months; regorafenib, 3.39 (3.05–3.78) months.
  - Median (95% CI) OS: cabozantinib, 11.40 (10.01–12.96) months; regorafenib, 10.29 (9.15–11.56) months.

Figure 4. Kaplan-Meier plots for overall survival

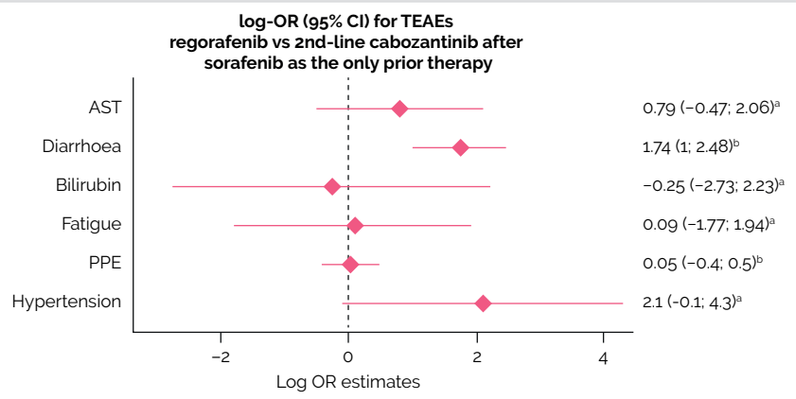


[a]Based on approximated individual-level data using digitisation of published RESORCE Kaplan-Meier plot[2].

Safety

- In placebo-adjusted analyses, log-OR estimates were large and 95% CIs were wide (**Figure 5**).
- This may be due to low numbers of events, particularly in the CELESTIAL placebo arm.
- Using non-placebo-adjusted analyses, rates of diarrhoea were significantly lower with regorafenib than with cabozantinib (**Figure 5**).

Figure 5. Frequency of grade ≥ 3 related TEAEs in > 5% of patients



The vertical dashed line indicates a log OR of 0, which corresponds to an OR of 1 (no difference between treatment groups).
[a]Placebo-adjusted analysis. [b]Non-placebo-adjusted analysis performed owing to few/no events in placebo arms.
AST, aspartate aminotransferase; CI, confidence interval; OR, odds ratio; PPE. palmer-plantar erythrodysesthesia; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- In patients with aHCC who received 2nd-line treatment after sorafenib as the only prior therapy and were matched for baseline characteristics to patients receiving regorafenib:
  - median PFS was significantly longer with cabozantinib than with regorafenib
  - median OS was longer with cabozantinib than with regorafenib, but the difference in OS was not significant
  - rates of diarrhoea were lower with regorafenib than with cabozantinib (but sample sizes small in safety comparisons).
- Even after matching, bias may still occur in MAIC due to imbalance in unobserved factors, and it cannot replace a head-to-head randomised control trial.
  - Limitations
    - Both trials had similar designs, but residual confounding may have been induced by other systematic differences (e.g. adherence to treatment).
    - Comparisons of survival estimates were non-placebo adjusted and as such do not respect within-study randomisation; adjustment for all prognostic variables would be hard to meet.
    - Individual trials were only powered to compare OS, not PFS and TEAE rates; statistical power is further reduced owing to reduction of sample sizes via MAIC.
- PFS and OS differences between cabozantinib and regorafenib in this MAIC are similar to those previously reported in unmatched patients receiving 2nd-line therapy after sorafenib as the only prior therapy.

References

1. Abou-Alfa GK *et al. N Eng J Med* 2018;379:54–63;
2. Bruix J *et al. Lancet* 2017;389:56–66
3. Kelley RK *et al.* ASCO 2018, poster 4088.

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