pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Cabozantinib (Cabometyx) for Hepatocellular Carcinoma

April 22, 2020

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INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: info@pcodr.ca
Website: www.cadth.ca/pcodr

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List of Abbreviations

AE Adverse events
AFP alpha-fetoprotein
AUC Area under the curve
BCLC Barcelona Clinic Liver Cancer
BSC Best supportive care
CGP Clinical Guidance Panel
CI Confidence intervals
CMH Cochran-Mantel-Haenszel
CR Complete response
CT Computed tomography
DCR disease control rate
DMC Data monitoring committee
DOR Duration of response
ECOG Eastern Cooperative Oncology Group
EOT End of treatment EQ-5D VAS EuroQol five dimension scale visual analog scale
EQ-5D-3L EuroQol five dimension scale
FACT-G Functional Assessment of Cancer Therapy-General
FACT-Hep Functional Assessment of Cancer Therapy Hepatobiliary
GFR Glomerular filtration rate
HCC Hepatocellular carcinoma
HR Hazard ratio
HRQoL health-related quality of life
ILD Interstitial lung disease
IQR Interquartile range
ITT Intention-to-treat
LSM least-squares mean
MID Minimally important difference
mRECIST modified Response Evaluation Criteria in Solid Tumors
MRI Magnetic resonance imaging
NCI-CTCAE National Cancer Institute Common Terminology Criteria for Adverse Events
ORR objective response rate
OS overall survival
pERC pCODR Expert Review Committee
PFS Progression-free survival
PR Partial response
RECIST Response Evaluation Criteria in Solid Tumors
SAE Serious adverse event
SD Stable disease
SD Standard deviation
TACE Transarterial Chemoembolization
TEAE treatment-emergent adverse events
TTP time to progression

1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding cabozantinib for hepatocellular carcinoma (HCC). The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding cabozantinib for HCC conducted by the Gastrointestinal Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on cabozantinib for HCC, a summary of submitted Provincial Advisory Group Input on cabozantinib for HCC, and a summary of submitted Registered Clinician Input on cabozantinib for HCC, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the effectiveness and safety of cabozantinib (Cabometyx) for the treatment of adult patients with unresectable HCC after prior therapy. The Health Canada approved indication is more narrow, for the treatment of patients with HCC who have been previously treated with sorafenib which is different than the sponsor's reimbursement request.[1] The sponsor has noted that lenvatinib was not an approved and used agent when the clinical trials were conducted for cabozantinib, phase 3 clinical evidence is not available for the use of cabozantinib after prior lenvatinib is not available. According to the sponsor, there are also no data at this time to suggest that the efficacy of cabozantinib would differ based on prior sorafenib or lenvatinib.

Cabozantinib is available in 20mg, 40mg and 60mg film coated tablets. The recommended dose of cabozantinib is 60mg once daily. As per the Health Canada Product Monograph, treatment with cabozantinib should be continued until the patient no longer experiences clinical benefit or experiences unacceptable toxicity.[1]

1.2 Key Results and Interpretation

Systematic Review Evidence

The systematic review included one phase III randomized, double-blind, placebo-controlled study of cabozantinib in previously treated patients with advanced hepatocellular carcinoma (HCC): CELESTIAL. The trial was conducted at more than 100 sites globally in 19 countries (including Canada). A total of 707 patients were randomized to receive cabozantinib (n=470) plus best supportive care or placebo plus best supportive care (n=237). The primary endpoint was overall survival. Progression free survival and objective response rate were secondary endpoint, while health-related quality of life and safety were exploratory endpoints considered.[2,3]

Eligible patients included adults (age 18 and older) who had a histological or cytological diagnosis of HCC that is not amenable to a curative treatment approach, received prior sorafenib, progression following at least 1 prior systemic treatment for HCC. Additional eligibility criteria included: ECOG performance status 0 or 1, Child-Pugh Score "A", adequate hematologic and renal function.[2,3]

Overall, CELESTIAL was a well-designed double-blind, placebo-controlled RCT. Study objectives were clearly stated, had strong randomisation and allocation concealment methods, is adequately powered, and uses well validated outcome measures that are relevant to the objectives. Adjustments for multiplicity were planned for the analyses of the efficacy endpoint (OS, PFS and ORR). Patients were stratified appropriately for major clinical factors with the exception of the combination of vascular invasion and extra-hepatic spread. Internal validity is therefore likely strong.

However, in addition to the short follow-up period in the trial, there are a few limitations that should be considered when interpreting the results of the trial, affecting either external or internal validity:

- Recruited patients were a selected group with Child Pugh A and ECOG PS 0 or 1, Thus, cabozantinib was not investigated in patients with more advanced liver disease or poor performance status. Patients were required to have progressed on sorafenib prior to study entry. Sorafenib intolerance status was not collected for patients upon study entry and therefore the efficacy in patients who discontinue sorafenib due to intolerability is uncertain.
- Due to the dose modifications for toxicity, the median daily dose was 36 mg of cabozantinib, lower than in the pooled population (41mg) and notably lower than the starting dose of 60mg.
- Although sorafenib intolerance was not a specified patient population requested for reimbursement, sorafenib intolerant patients were a subgroup of interest to the CGP. An ad-hoc analysis for a sorafenib intolerant population was provided by the sponsor based on time on prior sorafenib (<3 months) in the CELESTIAL trial. Of note, sorafenib intolerance was not pre-defined in the trial and as a result of the exploratory nature of this ad-hoc analysis and lack of pre-defined sorafenib intolerant population, it is difficult to assess with certainty the effect of cabozantinib for this subgroup of interest.
- There was a favorable imbalance in the proportion of patients with macrovascular invasion (MVI): 27% in the cabozantinib group versus 34% in the placebo group. As noted by CGP, MVI is a prognostic factor. This imbalance may have had an influence on trial outcomes, compromising internal validity.
- As well, the trial did not compare cabozantinib to active therapies of interest (i.e. no direct comparison to relevant active agents such as regorafenib), therefore, direct comparative efficacy and safety data (cabozantinib compared to active therapies) are not available.
- Response rates were investigator assessed and not independently assessed; as a result, there may be a risk of investigator bias.
- Although HRQoL was pre-specified in the protocol, results should be considered exploratory in nature since HRQoL analysis was not considered in the adjustment for multiplicity.
- There may be potential for confounding due to subsequent therapies, however the magnitude and direct of this effect are unknown.

Of note, the second interim analysis results (data cut-off date: June 1, 2017) presented are considered the final analysis as per recommendation by the independent data monitoring committee to terminate the trial early for efficacy following review of the second planned interim analysis because the trial met its primary endpoint of OS.[4]

Overall, a statistically significant overall survival advantage in favour of cabozantinib compared to placebo was observed.[2,3] The benefit of cabozantinib is further supported by the progression-free survival benefit observed.[2,3] With respect to health-related quality of life, apart from week 5, where clinically meaningful changes from baseline favoured placebo, there appeared to be no clinically meaningful detriment in quality of life.[5] Finally, there were more treatment related adverse events, grade 3 or 4 adverse events, and withdrawal due to adverse events reported in the cabozantinib group compared to the placebo group.[2,3] Refer to Table 1.1.

Table 1.1: Highlights of Key Outcomes[2,3,5]

	CELESTIAL	
	Cabozantinib (N=470)	**Placebo (N=237)**
Primary Outcome: OS, median	**10.2 months**	**8.0 months**
HR (95%CI)	**0.76(0.63 to 0.92)**	
p-value	**0.005**	
Key Secondary Outcome: PFS, median	**5.2 months**	**1.9 months**
HR (95%CI)	**0.44(0.36 to 0.52)**	
p-value	**<0.0001**	
Key Secondary Outcome: ORR, %(95%CI)	**4 (2-6)**	**<1 (0-2)**
p-value	**0.009**	
Exploratory Outcome: HrQoL – EQ-5D-5L		
The EQ-5D-5L questionnaire completion rate was >85% in each treatment group until week 33, after which there were n<20 of patients in the placebo group completed the questionnaire. The largest treatment difference post-baseline occurred at week 5 for mobility and usual activities; the effect size differences was in favour of placebo of 0.51 and 0.55 respectively, indicating a potentially clinically meaningful change from baseline. The proportion of patients in the cabozantinib and placebo group with any problem at week 5 was 61% compared to 32% for mobility and 68% compared to 43% for usual activities.[5] At baseline, the mean EQ-Index scores were 0.792 in the cabozantinib group compared to 0.855 in the placebo group. At week 5, EQ-Index change from baseline was -0.117 in the cabozantinib group compared with -0.019 in the placebo group, favouring placebo. After which difference in mean change from baseline with respect to EQ-Index values were not considered clinically meaningful (<0.06) through Week 25 (beyond Week 25, there were less than 20 patients in the placebo group).[5] At baseline, the mean EQ-VAS scores were similar among the two groups 73.5 in the cabozantinib group compared to 76.1 in the placebo group. Difference in mean change from baseline with respect to EQ-VAS values were not considered clinically meaningful (<7) through Week 33 (beyond Week 33, there were less than 20 patients in the placebo group).[5]		
Exploratory Outcome: Safety, n (%)	**Cabozantinib (N=467)**	**Placebo (N=237)**
Grade 3 or 4	**316(68)**	**86(36)**
AE (any grade)	**460(99)**	**219(92)**
TRAE	**439(94)**	**148(62)**
WDAE	**96(21)**	**10(4.2)**
AE = adverse event, CI = confidence interval, HR = hazard ratio, HRQoL = health-related quality of life, OS = overall survival, ORR = objective response rate, PFS = progression free survival, SD = standard deviation, TRAE = treatment-related adverse event, WDAE = withdrawal due to adverse event *HR < 1 favours cabozantinib Data cut-off date: June 1, 2017		

Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

From a patient's perspective, patients value increased survival and control of symptoms and side-effects, as HCC has a significant impact on the quality of life of patients. Patients expressed a desire for a sufficient level of independence to allow them to continue with their daily activities. HCC prognosis is generally poor as the disease is often diagnosed at a later stage when it has significantly progressed, which limits treatment options. The current standard of first-line treatment for HCC patients is sorafenib, which has been associated with a poor quality of life due to significant side-effects. The CLF also noted that lenvatinib is a new systematic treatment has been approved in Canada but it is not yet available for reimbursement on provincial formularies; therefore, patients who are able to access lenvatinib pay for it out of pocket. Regorafenib is a second-line treatment option for patients who have been treated with sorafenib; however, it is only reimbursed in a few Canadian provinces. A consistent theme emphasized throughout the patient input was the lack of access to treatments in Canada. The CLF concluded that due to poor prognosis of the disease and the limited treatment options, there is a need for new treatment options.

The CLF emphasized the difficulty of treating HCC, as it is usually an outcome of a pre-existing and progressive underlying liver disease. The patient may already be experiencing the effects of liver function impairment such as cirrhosis, hepatic encephalopathy and abdominal pain and swelling. Treatment depends on the stage and speed of the tumor growth, as well as the general health of the liver. The probability of cure usually decreases as the size of the tumour increases. In the global survey, approximately 80% of the patient respondents (205 out of 256) who were treated with sorafenib were more likely to rate their quality of life as poor. For patients who have been on sorafenib, the only second-line treatment option is regorafenib which also has significant side-effects such as hand-foot skin reactions (HSFR), fatigue, diarrhea, and hypertension; however, the CLF noted that most of these side effects can be controlled by modifying the dose of the drug. The CLF commented that although regorafenib is not a cure, it fulfills a current unmet need of an additional second-line treatment for HCC in the palliative phase.

Provincial Advisory Group (PAG) Input

Input was obtained from **all nine** provinces (Ministries of Health and/or cancer agencies) and federal drug plan participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Priority of cabozantinib relative to regorafenib and sequencing with lenvatinib

Economic factors:

- Potential for drug wastage

Registered Clinician Input

One joint input on behalf of two registered clinicians from Cancer Care Ontario (CCO) and one joint input on behalf of six registered clinicians was submitted for the review of cabozantinib for patients with HCC, who have been previously treated with sorafenib. Based on the results of the CELESTIAL trial, all clinicians agreed that cabozantinib is an effective treatment for patients with advanced HCC who have been previously treated with sorafenib. Cabozantinib has been demonstrated to have a larger survival benefit compared to regorafenib, along with significantly longer progression-free PFS, and a similar adverse effect profile compared to other TKIs used in the HCC setting such as regorafenib and sorafenib. Sequencing options were presented by each clinician input based on currently available data and clinical opinion. Overall, the clinicians concluded that cabozantinib is a highly effective, emerging treatment that can fulfill a significant current unmet need for HCC patients. It is important to note that at the time of the initial input for cabozantinib was received regorafenib was pending pricing negotiation; however, as of November 2019, funding fo regorafenib is available in some provinces.

Summary of Supplemental Questions

The objective of this supplemental section was to summarize and critically appraise the sponsor-submitted match-adjusted indirect comparison of cabozantinib versus regorafenib for second-line treatment of advanced HCC in patients who have received sorafenib in the first line. This MAIC was of particular relevance given:

- PAG identified regorafenib as a relevant comparison and indicated interest in receiving data comparing cabozantinib with regorafenib. As well, PAG indicated an interest in the role of regorafenib versus cabozantinib as preferred treatment for HCC after prior therapy.

- The sponsor submitted a MAIC to estimate the efficacy and safety of cabozantinib versus regorafenib in order to inform their cost-effectiveness model.

Overall, the results of this MAIC should be interpreted with caution. An RCT comparing cabozantinib and regorafenib (in the same population) is required in order to determine the comparative efficacy of cabozantinib and regorafenib.

The Methods Team identified the following limitations and considerations to the MAIC:

- The methodology used for the statistical comparison between the median OS and PFS estimates for the cabozantinib and regorafenib treatment arms is unclear and as a result, any conclusive statements about the comparative effectiveness of the two drugs is not recommended. [6]

- The MAIC is unanchored for the median OS and PFS. Unanchored estimates of log odds ratios were performed for diarrhea and PPE since there were no occurrence of diarrhea or PPE in the placebo group. The unanchored approach assumes that all treatment effect modifiers and prognostic variable are accounted for;[7] therefore, results should be interpreted with this in mind. The recommended approach for identifying prognostic factors and effect modifiers is to begin with the literature and clinical experts' opinion, followed by what is available from the eligible trials, and noting what prognostic factors and effect modifiers were not included (because they were not available) but should be considered. It appears that a different approach for the MAIC was used. First, baseline characteristics available for matching were identified, followed by the clinical expert opinion. It is worth noting however that the CGP confirmed that the prognostics factors included for matching were appropriate and there were no other missing prognostic factors.

- The population in the MAIC is not representative of the entire requested reimbursement population: adults with hepatocellular carcinoma after prior therapy. Therefore, conclusions should be limited to the population in the MAIC (i.e., second line population, after treatment with sorafenib as prior systemic therapy) and not generalizable to the entire requested reimbursement population.

- Moreover, the population in the MAIC does not include the entire CELESTIAL population: it does not include patients with more than 2 prior therapies except for prior sorafenib, or third line patients. Additionally, because sorafenib intolerance was not prespecified in the CELESTIAL trial, information pertaining to this population is uncertain. Therefore, conclusions should be limited to the population in the MAIC (i.e., second line population, after treatment with sorafenib) and not generalizable to the entire CELESTIAL population.

- The large difference (>45%) in effective sample size compared to the original sample size, suggests that the trial populations are too different to compare.[7]

- The sponsor noted that the systematic literature review was conducted prior to the publication of the CELESTIAL trial. The Methods team consider this (i.e. CELESTIAL was noted included in the systematic literature review report) a limitation of the submitted systematic literature review report and the recommended approach would have been to update the report to include a new cut-off date thereby including the CELESTIAL trial in the report, so that the trials (including CELESTIAL) could be compared. The Methods team noted that it is unclear if the author did a comprehensive comparison of the two trials (RESORCE and CELESTRIAL) as well as if a quality assessment on CELESTRAL trial was done.

- As well, there is insufficient detail to understand what study design differences are unaccounted for and remain potential sources of bias in the MAIC.

- Other important outcomes identified in the systematic review protocol (Section 6), such as health-related quality of life, ORR, SAEs, WDAEs were not assessed in the MAIC.

- It is worth noting that the proportional hazards assumption was not satisfied; therefore, it cannot be assumed that the hazard ratios are constant, rather it must be assumed that hazard ratios are time dependent.

See section 7.1 for more information.

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

[Table 2]: Assessment of generalizability of evidence for cabozantinib for advanced HCC

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td>Population</td><td>ECOG Performance Status</td><td>The CELESTIAL trial included participants with ECOG PS of 0-1.[2]<table><tr><th>ECOG PS</th><th>Cabozantinib (N=470)</th><th>Placebo (N=237)</th></tr><tr><td>0</td><td>245 (52)</td><td>131 (55)</td></tr><tr><td>1</td><td>224 (48)</td><td>106 (45)</td></tr></table></td><td>Do the trial results apply to patients with ECOG PS 2?</td><td>The CGP agree that only patients with an ECOG performance status of 0-1 should be eligible as there is no clinical evidence to support the use of cabozantinib in patients with ECOG 2 or higher. The CGP note that this primarily due to concerns around toxicity of treatment, for example fatigue, for patients with lower PS.</td></tr>
<tr><td></td><td>Child-Pugh score</td><td>Although patients were required to have Child-Pugh class A in the trial, 7 patients (1%) of patients had Child-Pugh class B.</td><td>Do the trial results apply to patients with Child-Pugh class B?</td><td>The CGP agree that only patients with Child Pugh A should be eligible as patients with Child Pugh B status were excluded from the trial.</td></tr>
<tr><td></td><td>Patients co-infected with hepatitis</td><td>The CELESTIAL trial included patients that were exposed to hepatitis C (HCV) and hepatitis B viruses (HBV).<table><tr><th>Etiology of Disease</th><th>Cabozantinib (N=470)</th><th>Placebo (N=237)</th></tr><tr><td>HBV</td><td>178 (38)</td><td>89 (38)</td></tr><tr><td>HCV</td><td>113 (24)</td><td>55 (23)</td></tr></table>A subgroup analysis of OS and PFS for these patients demonstrated a HR for OS of 1.11 (0.72-1.71) for patients with HCV (without HBV) and a HR for OS of 0.69 (0.51 – 0.94) for HBV (with or without HCV). The HR for PFS for HCV (without HBV) was 0.61 (0.42-0.88) and 0.31 (0.23-0.42) for HBV (with or without HCV).[2]</td><td>Would patients who are coinfected with hepatitis C or hepatitis B be eligible for treatment with cabozantinib?</td><td>Patients were stratified for etiological factor (HBV, with or without HCV, HCV without HBV). The CGP agree that the PFS subgroup analysis supports the use of cabozantinib for patients with HBV and/or HCV.</td></tr>
<tr><td></td><td>Intolerant to Sorafenib</td><td>Patients were required to have progressed on sorafenib prior to study. Intolerance to sorafenib was not an inclusion/exclusion criterion and no</td><td>Are the findings of the CELESTIAL trial generalizable to patients</td><td>The findings of the CELESTIAL trial are generalizable to patients who may be intolerant to sorafenib or</td></tr>
</table>

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
		definition of sorafenib intolerance was provided in the CELESTIAL trial and therefore the efficacy in patients who discontinue sorafenib due to intolerability is uncertain.	who may be sorafenib intolerant or progress early on sorafenib (and thus, received some prior systemic therapy)?	who may have progressed early on sorafenib since these patients were not specifically excluded. In an exploratory analysis provided by the sponsor, patients who were on sorafenib for < 3 months derived a benefit from cabozantinib versus placebo median OS 8.9 versus 6.9 months; HR 0.71 (0.47-1.10).[8]
Intervention	**Line of therapy and sequencing**	The CELESTIAL trial included patients who had received greater than one prior systemic therapy but were excluded if they received greater than 2 prior lines of systemic therapy. Of the 470 patients in the cabozantinib group, 454 (97%) received sorafenib in first line as per while 25 (5%) received sorafenib in second line. There were 14 (3%) patients in the cabozantinib group who received prior PD-1/PD-L1 therapies, and 19 (4.0%) who received TKI therapies other than sorafenib.[5]	Are the findings of the CELESTIAL trial generalizable to patients who receive greater than 2 lines of prior systemic therapy received some prior systemic therapy)?	The CGP agree that the results of the CELESTIAL trial are not generalizable to patients who receive greater than 2 lines of prior systemic therapy.
	Subsequent therapies	Six patients went on to receive regorafenib after treatment with cabozantinib however efficacy and safety data for these patients were not available.	What treatment options would be available to patients upon progression of cabozantinib? Is there evidence to sequence regorafenib after cabozantinib?	After progression on cabozantinib, fit patients should be encouraged to enrol in clinical trials as there are no evidence based therapies. There is no evidence yet to support the use of regorafenib in the third-line setting after cabozantinib. The optimal sequencing of TKIs for HCC is unknown as the landscape is evolving.
Comparator	**Placebo Regorafenib (MAIC)**	The comparator in the CELESTIAL trial was placebo.		Placebo was the appropriate control at the time of trial inception. The Sponsor performed a Match Adjusted Indirect Comparison (MAIC) comparing cabozantinib versus regorafenib for 2nd line treatment of HCC patients who had received prior sorafenib. The overall survival outcomes were

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
				comparable between cabozantinib and regorafenib. Since sorafenib intolerance status was not collected for patients upon study entry, clinicians may prescribe cabozantinib for sorafenib intolerant patients and regorafenib for sorafenib tolerant patients.

Burden of illness

An estimated 3000 new cases of hepatocellular cancer (HCC) will be diagnosed in Canada in 2019, with a 5 year overall survival (OS) of 19%. The intent of treatment for patients with hepatocellular carcinoma who have received prior therapy is palliative care. Median survival in the absence of treatment in this setting is less than 8 months and progression free survival on second line multitargeted TKIs is around 3 months. Therefore, quality of life and toxicity are of utmost importance. Second line treatment options have yet to be compared directly in adequate powered phase III trials.

Table 1.1. Current Canadian treatment paradigm for HCC patients with Child Pugh A liver function[a]

Indication	Therapeutic options
First line	Sorafenib * Lenvatinib ~
Second line (after sorafenib)	Regorafenib ~ Cabozantinib

* Funded in Canada
~ pERC recommended pending price
[a] Category 1 recommendation from NCCN HCC guideline[9]

Effectiveness

In the phase III CELESTIAL trial, 707 patients previously treated with sorafenib were randomized to cabozantinib or placebo.[2] In contrast to the RESORCE trial that evaluated regorafenib in this setting, patients in the CELESTIAL trial could have received up to two prior systemic therapies for advanced HCC (27% of patients on the trial), and there were no stipulations regarding tolerance of sorafenib in the first line setting. Median OS was significantly longer with cabozantinib compared to placebo (10.2 months versus 8.0 months, HR 0.76; 95% CI, 0.63 to 0.92; P=0.005). The ESMO magnitude of clinical benefit scale (MCBS) is a standardized, validated tool to stratify the magnitude of clinical benefit for a novel therapy at the time of approval. The ESMO-MCBS Working Group evaluated the CELESTIAL trial and determined the MCBS score was 3, corresponding to a moderate benefit in a non-curative setting.[10] Median PFS was 5.2 months with cabozantinib and 1.9 months with placebo (HR 0.44; 95% CI, 0.36 to 0.52; P<0.001), and the investigator assessed objective response rates were 4% and less than 1%, respectively (P=0.009).[10]

Safety

In the CELESTIAL trial dose interruptions 84% of cabozantinib-treated patients. The median average daily dose was 35.8 mg for cabozantinib and 58.9 mg for placebo, with a median time to first dose reduction of 38 days in the cabozantinib group.[2] Dose reductions due to any adverse events occurred in 62% of patients treated with cabozantinib compared to 13% of patients with placebo. Discontinuation of treatment for treatment related adverse events was higher in the cabozantinib arm (16%) compared to the placebo group (3%). Adverse events leading to treatment discontinuation included palmar-plantar erythrodysesthesia, fatigue, decreased appetite, diarrhea, and nausea. The most common grade 3 or 4 adverse events in the cabozantinib group were higher compared to placebo, specifically palmar– plantar erythrodysesthesia (17%, vs. 0% with placebo), hypertension (16% vs. 2%), increased AST (12% vs. 7%), fatigue (10% vs. 4%), and diarrhea (10% versus 2%).[2]

<u>Methodological considerations</u>

Patients were stratified appropriately for major clinical factors with the exception of the combination of vascular invasion and extra-hepatic spread. Since the factors were combined, the rate of vascular invasion was 27% in the cabozantinib arm and 34% in the placebo arm, favouring the cabozantinib arm. The forest plot for patients with macrovascular invasion still showed a trend for OS and PFS favouring cabozantinib over placebo. Response rate was investigator assessed; however, overall survival was the

primary endpoint. The rates of subsequent treatment with systemic anticancer therapy was 25% in the cabozantinib arm and 30% in the placebo arm respectively, however, there are no standard third or later lines of therapy for HCC. The CGP noted that though post-progression therapy would not be considered a significant co-intervention, data with respect to the reasons that patients received subsequent therapy were not available. In addition, patients could continue blinded study treatment after radiological disease progression if they continued to receive benefit as per assessment by the investigator. A relatively high proportion of patients in both arms continued blinded treatment after radiological disease progression (32% in the cabozantinib and 49% in the placebo group).[5] This blinded treatment after radiological disease progression continued possibly until symptomatic progression as they were achieving clinical benefit or covering the time until new therapy was administered. As mentioned previously, there are no standard third or later lines of therapy for HCC, and treatment beyond radiological progression as long as the patient is receiving clinical benefit would be appropriate.

Need

After progression on sorafenib, both cabozantinib and regorafenib have demonstrated an improvement in survival in advanced HCC patients previously treated with sorafenib. Both agents are endorsed by the CCO HCC guideline.[11] Regorafenib significantly improved OS compared to placebo in advanced HCC patients in the RESORCE trial (median OS 10.6 months regorafenib versus 7.8 months placebo, HR 0·63 (95% CI 0·50–0·79; one-sided p<0·0001).[12] Patients in the RESORCE trial had tolerated prior sorafenib (≥400 mg daily for at least 20 of the 28 days before discontinuation).[12]

Lenvatinib is available in Canada for the first-line treatment of HCC and it is currently under provincial reimbursement negotiations. The CGP noted that though the CELESTIAL trial did not include patients that had prior treatment with lenvatinib, however, the results of the CELTESTIAL trial can be generalized to patients who receive prior sorafenib or lenvatinib as there is currently no data to suggest that second-line therapies would be less effective following lenvatinib.

The CGP noted a real world study evaluating the eligibility for new HCC treatments using eligibility criteria from the trials as well as modified eligibility criteria. From this study, approximately 28% of patients would be ineligible to receive regorafenib due to intolerance to sorafenib. The CGP noted that for those patients who are intolerant to sorafenib and therefore unable to receive regorafenib, cabozantinib would be a valuable treatment option as the CELESTIAL trial did not identify sorafenib tolerance as an inclusion or exclusion criteria and therefore patients that may have been intolerant to sorafenib were included in the study. In an exploratory analysis provided by the sponsor, patients who were on sorafenib for < 3 months derived a benefit from cabozantinib versus placebo median OS 8.9 versus 6.9 months; HR 0.71 (0.47-1.10).[13]

Matched indirect comparison of cabozantinib and regorafenib

The sponsor performed a matched indirect comparison of individual patient data from the CELESTIAL trial and data from the RESORCE trial. Patients in the CELESTIAL trial had received prior sorafenib however the trial did not define sorafenib intolerance as an inclusion/exclusion criterion. The RESORCE trial included only sorafenib tolerant patients (i.e. excluded sorafenib-intolerant patients), whereas the CELESTIAL trial included both sorafenib tolerant and sorafenib-intolerant patients as sorafenib intolerance was not defined as an inclusion/exclusion criterion in the CELESTIAL trial. Patients in both trials had Child-Pugh A liver function, ECOG 0-1. The CELESTIAL trial included second and third line patients, while the RESORCE trial included only second line patients who progressed on sorafenib in the first line. For the purposes of the MAIC, only second line patients of CELESTIAL (defined as the patients that have experienced only one prior systemic nonradiation anticancer agent) were included, and all third line patients (of which there are none in RESORCE) were excluded. Matching and weighting was done for all relevant baseline characteristics.

Cabozantinib significantly improved progression-free survival (PFS), with an additional 2.4 months provided vs. regorafenib. The median PFS for weighted cabozantinib was5.6 months (95% CI: 4.9 - 7.3) while the PFS for regorafenib was 3.1 (95% CI 2.8-4.2) months.)[6] Median OS was also favorable with

cabozantinib (11.4 months versus 10.8 months with regorafenib), though statistical significance was not met.[6] It is to be noted that the sponsor used the mRECIST criteria for regorafenib as defined in the RESORCE trial while the RECIST criteria was used for cabozantinib as per the CELESTIAL trial.

Using non-placebo-adjusted analyses, rates of diarrhea were significantly lower with regorafenib than with cabozantinib. No other AEs were found to be disproportionately more likely in one treatment regimen than the other.

Additionally, Kudo et al., reported the percent of dose reductions and discontinuations due to adverse events in Table 1.4 below. Dose reduction or discontinuation because of treatment related AEs was more common with cabozantinib indicating that cabozantinib may have a slightly higher toxicity than regorafenib.

Table 1.2. Safety analysis: CELESTIAL versus RESORCE[14]

	Cabozantinib	Regorafenib
Treatment duration	3.8 months	3.6 months
Dose reduction due to adverse event (%)	62	48
Discontinuation due to treatment related adverse event (%)	16	10

Even after matching, bias may still occur in MAIC due to an imbalance in unobserved factors. The MAIC cannot replace a true RCT. In this MAIC, both trials had very similar designs, however, patients in the RESORCE trial had longer median duration of sorafenib therapy and must have tolerated sorafenib to enter the trial. The large difference (>45%) in effective sample size compared to the original sample size, suggests that the trial populations are too different to compare Residual confounding may have been introduced by other systematic differences. Comparisons of survival estimates were non-placebo adjusted and therefore do not respect within-study randomisation. There is limited information on the methodology used for the statistical comparison between the median OS and PFS estimates and as a result, any conclusive statements about the comparative effectiveness of the two drugs is unknown. In addition, the population in the MAIC is not representative of the entire requested reimbursement population: adults with hepatocellular carcinoma after prior therapy. Therefore, conclusions from the MAIC should be limited to the population in the MAIC (i.e., second line population, after treatment with sorafenib as prior systemic therapy) and not generalizable to the entire requested reimbursement population. The CGP noted that given the limitations and considerations noted above, the results of this MAIC should be interpreted with caution. An RCT comparing cabozantinib and regorafenib (in the same population) is required in order to determine the comparative efficacy of cabozantinib and regorafenib.

Quality of life

In the CELESTIAL trial, quality of life was assessed as an exploratory endpoint using the EQ-5D-5L. The minimally important difference (MID) in EQ-5D (UK scores) has been established as 0.06 to 0.08 for the EQ-Index and 7 for the VAS. The largest treatment difference post-baseline occurred at week 5 for mobility and usual activities. At week 5, the EQ-Index change from baseline was -0.117 in the cabozantinib group compared with -0.019 in the placebo group, favouring placebo Despite the side effects observed with treatment with cabozantinib, there was overall no clinically meaningful differences noted in quality of life compared to placebo.[15]

1.3 Conclusions

The Clinical Guidance Panel unanimously concluded that there is net clinical benefit for cabozantinib for advanced HCC patients, ECOG 0-1, with Child Pugh A liver function previously treated with an oral TKI (sorafenib or lenvatinib). This is based on one well conducted randomized trial that demonstrated a clinically relevant improvement in overall survival (10.2 months versus 8.0 months, HR 0.76; 95% CI, 0.63 to 0.92; P=0.005, a difference in median OS of 2.2 months) with cabozantinib compared to placebo after prior sorafenib, irrespective of tolerance to sorafenib as the CELESTIAL trial did not include patients based on sorafenib intolerance. Toxicities were manageable and overall there were no clinically meaningful detriments to quality of life. The secondary endpoint of PFS was also significantly improved with a median PFS of 5.2 months with cabozantinib compared to 1.9 months with placebo (HR 0.44; 95% CI, 0.36 to 0.52; P<0.001). The oral route of cabozantinib administration was noted to be an enabler to implementation by PAG and is preferred by patients. Patient input noted increased survival, and control of symptoms and side effects as the most important outcomes.

The Clinical Guidance Panel also considered that:

- There is no data to suggest that the efficacy of second line HCC treatments would be influenced by first line therapy. This approach has also been used for paradigm shifts in other tumor sites such as the advent of first line immunotherapy for advanced renal cell carcinoma and advances in HER2 positive metastatic breast cancer. Lenvatinib has become a first line treatment option for patients with advanced HCC based on data from the pivotal REFLECT trial. Emerging data suggests that atezolizumab and bevacizumab may become a new first line treatment option for advanced HCC (ESMO Asia 2019).[16,17] Further data on the efficacy of cabozantinib after first line therapies other than sorafenib may become available through clinical trials or real-world evidence.
- The submitted MAIC of cabozantinib and regorafenib demonstrated no OS difference between the two agents. The MAIC cannot replace an RCT nor real-world efficacy data. There is insufficient evidence to determine comparative effectiveness of cabozantinib and regorafenib.
- The side effect profile of cabozantinib and regorafenib are slightly different. Grade 3 or 4 palmar-plantar erthrodysesthesia, diarrhea, and asthenia are more common with cabozantinib than regorafenib whereas regorafenib causes more hyperbilirubinemia than cabozantinib. If a patient was intolerant of one agent but did not progress, it would be reasonable to switch to the alternative agent.
- Cabozantinib demonstrated a benefit in PFS and OS in the subset of patients who had two prior systemic therapies. Patients with preserved performance status and liver function would derive clinical benefit from cabozantinib in this setting. Although this was a prespecified subgroup analysis, no adjustments were made for multiplicity, and confidence intervals were descriptive and wide.

2 BACKGROUND CLINICAL INFORMATION

2.1 Description of the Condition

In 2019, an estimated 3000 new cases of hepatocellular cancer (HCC) will be diagnosed in Canada, with a 5 year overall survival (OS) of 19%. From 1984 to 2015, the annual percent change in Canadian age-standardized incidence rates of HCC was an increase by 0.2% in men and 2.7% in women.[18] HCC is a challenging disease to treat as it often appears in the setting of underlying hepatic cirrhosis which can lead to underlying hepatic impairment. Systemic therapy is often not well tolerated in patients with underlying hepatic dysfunction. Thus, the treatment approach and consequent prognosis of patients with HCC depends upon the extent of disease, hepatic functional reserve and performance status. Child-Pugh class is the most commonly employed metric to assess hepatic reserve, and includes the parameters of serum levels of INR, albumin and bilirubin as well as clinical evidence of ascites or encephalopathy.(Table 1)

Table 1: Child-Pugh Classification

Factor	1 point	2 points	3 points
Total bilirubin (μmon/L)	<34	34-50	>50
Serum albumin (g/L)	>35	28-35	<28
INR	<1.7	1.7 – 2.3	>2.3
Ascites	None	Mild	Moderate-Severe
Encephalopathy	None	Grade I-II	Grade III-IV

Important risk factors for the development of HCC include hepatitis B virus (HBV) infection, chronic hepatitis C virus (HCV) infection, hereditary hemochromatosis, nonalcoholic fatty liver disease and cirrhosis of almost any cause. Chronic medical conditions such as obesity, alcoholism, and diabetes mellitus are predisposing factors for HCC.

2.2 Accepted Clinical Practice

Although there are many staging systems used for HCC, the BCLC staging system is the most widely used prognostic and treatment algorithm for HCC by Canadian clinicians (Figure 1). The staging system includes prognostic factors related to tumour status, liver function and performance status. Per the BCLC algorithm, the prognosis for patients with advanced, unresectable HCC with preserved hepatic reserve is poor with a median overall survival of less than one year.[10]

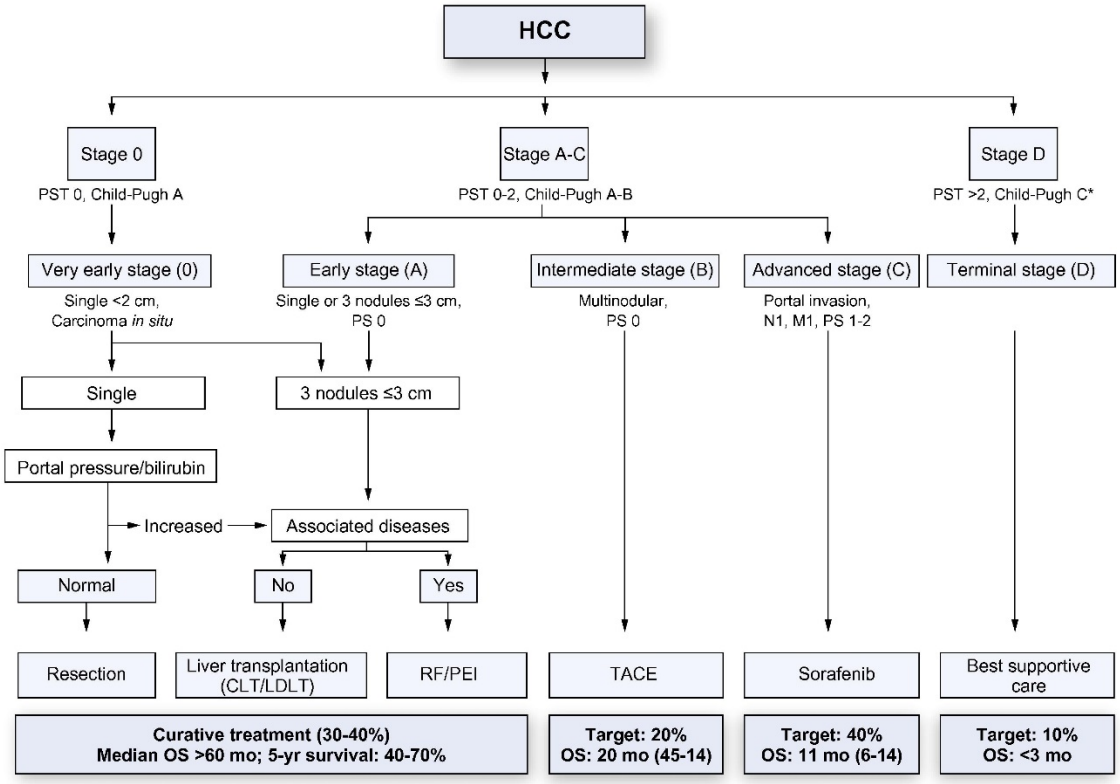


Figure 1: Barcelona Clinic Liver Cancer Staging System for HCC in Canada

Source: EASL-EORTC. 2012. Copyright 2012 Elsevier. Reprinted in accordance with CC BY-NC-ND 4.0.[19]

HCC is considered to be a chemotherapy -refractory tumour. Lenvatinib was shown to be non-inferior to sorafenib in patients who had not received prior systemic therapy and as such should be considered alongside sorafenib in the Figure 1 above.[19,20]

First line therapy

Sorafenib is an oral multi-tyrosine kinase inhibitor (TKI) that inhibits the RAF-kinase and VEGFR intracellular kinase pathways. The SHARP trial was a multicentre, European, randomized, double-blinded placebo controlled study in patients with advanced, inoperable HCC and Child-Pugh class A hepatic reserve, ECOG 0-2, comparing sorafenib therapy to placebo.[21] The median OS in the sorafenib arm was 10.7 months versus 7.9 months in the placebo arm (HR = 0.69; 95% CI, 0.55–0.87; p < 0.001). The magnitude of survival benefit with sorafenib in SHARP was similar to that demonstrated in a parallel phase III trial conducted in the Asian-Pacific population, in which hepatitis B was the main cause of HCC.[12] In this subsequent trial, the median overall survival was 6.5 months in the sorafenib arm versus 4.2 months in the placebo (HR = 0.68; 95% CI, 0.50–0.93; p = 0.014). The inferior survival outcome observed in both arms of this study compared with the SHARP trial, is believed to be due to the fact that the patients had a higher proportion of Hepatitis B and more advanced disease (ECOG 1–2 or metastatic disease). Based on these data, sorafenib is currently approved and funded across Canada for the first-line systemic treatment of Child-Pugh A class patients with advanced HCC.

Lenvatinib is an inhibitor of VEGFR-1, VEGFR-2, and VEGFR-3, as well as fibroblast growth factor receptors (FGFR) 1 to 4, platelet-derived growth factor receptor (PDGFR) alpha, RET, and KIT. The REFLECT trial demonstrated the non-inferiority of lenvatinib to sorafenib for OS as first line therapy for unresectable HCC, ECOG PS 0-1, and Child Pugh A liver function (median OS 13.6 versus. 12.3 months for lenvatinib versus. sorafenib, HR 0·92, 95% CI 0·79–1·06).[20]

The role of immunotherapy in first-line Child-Pugh class A HCC is yet to be clearly established. The CheckMate 459 study randomized 759 patients with advanced HCC to nivolumab versus sorafenib. Overall survival was not significantly improved with nivolumab (median OS 16.4 months with nivolumab versus 14.7 months with sorafenib, p = 0.0752) despite a significant improvement in the objective response rate (15% with nivolumab versus 7% with sorafenib).[22]

Preliminary data on the phase III IMbrave150 study was presented at ESMO Asia. This trial randomized 501 patients with advanced HCC, Child Pugh A, ECOG 0-1 to atezolizumab plus bevacizumab versus sorafenib.[23] There was a significant improvement in the coprimary endpoints of OS (median OS not reached for atezolizumab plus bevacizumab versus 13.2 months with sorafenib, HR 0.58, 95% CI 0.42-0.79, p = 0.0006), as well as PFS (HR 0.59, 95% CI 0.47-0.76, p< 0.0001). The combination of atezolizumab plus bevacizumab also delayed the time to deterioration of quality of life compared to sorafenib (EORTC QLC-C30, 11.2 months versus 3.6 months, HR 0.63, 95% CI 0.46-0.85).[23] This combination is not available in Canada.

Second line therapy for patients with Child Pugh A liver function

Many therapies have been evaluated in phase III trials for HCC patients who have progressed on first line sorafenib, with an ECOG 0-1 and Child Pugh A liver function such as regorafenib, ramucirumab, pembrolizumab, and cabozantinib.

Regorafenib targets a number of angiogenic kinases (including VEGFR), stromal and oncogenic receptor TKIs. In the phase 3 RESORCE trial, a survival benefit for regorafenib was demonstrated in patients who tolerated prior sorafenib as first-line treatment, but had progressed, and had an ECOG performance status of 0-1.[12] When compared to placebo, regorafenib was associated with a statistically significant improvement in OS (10.6 months versus 7.8 months, HR = 0.63) in addition to increased disease control rates (65% versus 36%). Grade 3-4 adverse events included hypertension (15% versus 5%), hand-foot skin reaction (13% versus 1%) fatigue (9% versus 5%) and diarrhea (3% versus 0%).[12] Despite these adverse events, quality of life as assessed by EQ-5D and FACT-Hep, was not significantly worse with regorafenib compared to placebo.

<u>Second line therapies not available in Canada</u>
Ramucirumab is an anti-VEGFR2 recombinant monoclonal immunoglobulin G subclass 1 (IgG1) antibody. The REACH-2 trial randomized 292 patients with a serum AFP $\geq$ 400 ng/mL who had progressed on prior sorafenib to ramucirumab or placebo. Treatment with ramucirumab was associated with significantly improved overall survival (8.5 months versus 7.3 months, hazard ratio 0.71, 95% CI 0.53-0.95).[24]

Pembrolizumab was evaluated in a randomized, double blind phase III trial versus placebo in patients with advanced HCC with intolerance to or progression on or after sorafenib (KEYNOTE-240).[25] The improvements in OS did not meet the prespecified level of statistical significance [median OS 13.9 months pembrolizumab versus 10.6 months placebo, HR 0.781 (95% CI: 0.661-0.998; p=0.0238)]. Response rates were significantly higher with pembrolizumab versus placebo (18.3% versus 4.4 %, p=0.00007), and the median duration of response was 13.8 months with pembrolizumab.

Nivolumab was reviewed by the pCODR Expert Review Committee in November 2018 for the treatment of advanced HCC in patients who are intolerant or previously progressed on sorafenib, however, pERC did not recommend reimbursement of nivolumab.

<u>Cabozantinib for second line HCC</u>
Cabozantinib is an oral potent multitargeted TKI that inhibits inhibitor MET, AXL, VEGFR-1, VEGFR-2, and VEGFR-3.[26] High levels of MET expression are associated with resistance to sorafenib in

preclinical models.[27,28] In the phase III CELESTIAL trial, 707 patients previously treated with sorafenib were randomized to cabozantinib or placebo.[2] In contrast to the RESORCE trial that evaluated regorafenib, patients could have received up to two prior systemic therapies for advanced HCC, and there were no stipulations regarding tolerance of sorafenib in the first line setting. Median overall survival was significantly longer with cabozantinib compared to placebo (10.2 months versus 8.0 months, HR 0.76; 95% CI, 0.63 to 0.92; P=0.005). This was approved by the FDA in January 2019 for treatment of patients with HCC who have been previously treated with sorafenib.

Regorafenib, cabozantinib, and ramucirumab have all demonstrated statistically significant improvements in OS compared to placebo in phase III trials of HCC patients previously treated with sorafenib with Child Pugh A liver function. Median survival in the absence of treatment in this setting is less than 8 months and progression free survival on second line multitargeted TKIs is around 3 months. Therefore, quality of life and toxicity are of utmost importance. Second line treatment options have yet to be compared directly in adequate powered phase III trials.

2.3 Evidence-Based Considerations for a Funding Population

The expected population for cabozantinib would be patients with advanced, inoperable HCC previously treated with sorafenib who have Child-Pugh A hepatic reserve, based on the eligibility of the CELESTIAL trial. Given the toxicities of cabozantinib, it would not be considered for patients with ECOG PS of 2 or worse, or a Child-Pugh score of greater than 6. Two Japanese studies have estimated that 35 to 37% of sorafenib-treated patients may be eligible for second-line regorafenib. Presumably, a higher proportion of patients would be eligible for cabozantinib as the CELESTIAL trial did not mandate prior tolerance of sorafenib. A Canadian study estimated that 13.1% of patients would be eligible for second line therapy.[13]

2.4 Other Patient Populations in Whom the Drug May Be Used

Lenvatinib has become a first line treatment option for patients with advanced HCC based on data from the pivotal REFLECT trial. Emerging data suggests that atezolizumab and bevacizumab may become a new first-line treatment option for advanced HCC. There is no data to suggest that the efficacy second line HCC treatments would be influenced by first line therapy. The CELESTIAL trial only included patients who were treated with sorafenib. However, as treatment paradigms evolve, cabozantinib may be considered in patients who have progressed on first line therapy for HCC. Further data on the efficacy of cabozantinib after first line therapies other than sorafenib may become available through clinical trials or real-world evidence.

3 SUMMARY OF PATIENT GROUP INPUT

The Canadian Liver Foundation (CLF) provided input on cabozantinib (Cabometyx) for the treatment of hepatocellular carcinoma (HCC) in adults after prior therapy. The CLF conducted an online survey from October 21 to October 28th, 2019 which was promoted on the CLF website, via CLF social media channels and to CLF patient, caregiver and healthcare professional connections across Canada. The online survey was available in English, French and Chinese. The two respondents of the CLF survey were both health professionals. Although CLF provided the input from health professionals, only patient input highlighting the patient experience is noted below. The CLF commented that patients were particularly challenging to recruit specifically for this input due to the limited number of patients who specifically meet the eligibility criteria of the drug (i.e. patients with unresectable hepatocellular carcinoma with prior therapy) and the limited number of patients who have experience with cabozantinib. The CLF therefore included insights from approximately 45 liver cancer patients across Canada that were not directly solicited for the purpose of this submission but were obtained from other routinely collected information from patients through CLF's national toll-free help line, as well as via email and other online and in-person means of communication with patients. Additionally, the CLF also included input from a 2016 global survey of patients living with HCC. The CLF was one of the participating international health charities representing Canada among the 13 countries included in the survey. Out of the 256 respondents to this global survey, 8 were from Canada.

From a patient's perspective, patients value increased survival and control of symptoms and side-effects, as HCC has a significant impact on the quality of life of patients. Patients expressed a sufficient level of independence to allow them to continue with their daily activities. HCC prognosis is generally poor as the disease is often diagnosed at a later stage when it has significantly progressed, which limits treatment options. The current standard of first-line treatment for HCC patients is sorafenib, which has been associated with a poor quality of life due to significant side-effects. The CLF also noted that lenvatinib is a new systematic treatment has been approved in Canada but it is not yet available for reimbursement on provincial formularies; therefore, patients who are able to access lenvatinib pay for it out of pocket. The CLF noted that regorafenib is a second-line treatment option for patients who have been treated with sorafenib; however, it is only reimbursed in a few Canadian provinces. A consistent theme emphasized throughout the patient input was the lack of access to treatments in Canada. The CLF concluded that due to poor prognosis of the disease and the limited treatment options, it is imperative that more options such as cabozantinib are accessible to HCC patients in Canada.

Of note, quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification. Please see below for a summary of specific input received from the patient groups.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with HCC

Liver cancer is the sixth most common cancer worldwide and the second most common cause of death from cancer. It is relatively more common in men than in women and is one of the fastest growing cancers in Canada. HCC is the most common type of liver cancer, accounting for 71.9% of liver cancers in males and females. The CLF commented that HCC is challenging to treat once it progresses to the later stages as surgery is barely an option and treatment options are limited.

A total of 8 Canadian patients from the global survey commented on the significant mental and emotional distress of living with the disease, using words such as fear, worry, shock, scared and sad to describe their experience. Below are some key comments from patients:

"My worst symptom is pain and being uncomfortable all the time. Mornings are the worst. I feel dazed and confused. I can hardly eat anything. When I eat, I throw up right away. But worst of all is knowing that there is nothing that can be done for me. I am devastated. The knowledge that I will die and leave my wife and my kids without a father is unbearable."

"I cannot help and participate in daily activities. I am a burden on my family. They have to do everything for me. I am in pain all the time. I cannot sleep at night and am groggy and confused during the day."

3.1.2 Patients' Experiences with Current Therapy for HCC

The CLF emphasized the difficulty of treating HCC, as it is usually an outcome of a pre-existing and progressive underlying liver disease. The patient may already be experiencing the effects of liver function impairment such as cirrhosis, hepatic encephalopathy and abdominal pain and swelling. Treatment depends on the stage and speed of the tumor growth, as well as the general health of the liver. The probability of cure usually decreases as the size of the tumour increases.

In the global survey, approximately 80% of the patient respondents (205 out of 256) who were treated with sorafenib were more likely to rate their quality of life as poor. For patients who have been on sorafenib, the only second-line treatment option is regorafenib which also has significant side-effects such as hand-foot skin reactions (HSFR), fatigue, diarrhea, and hypertension; however, the CLF noted that most of these side effects can be controlled by modifying the dose of the drug. The CLF commented that although regorafenib is not a cure, it fulfills a current unmet need of an additional second-line treatment for HCC in the palliative phase.

The following are comments expressed by CLF patient contacts regarding their experiences with current therapy:

"I am currently being treated for my HCC and the pain is the worst. I am in pain all the time." - CLF patient contact.

"I feel better after treatment and was hopeful for a while that it will work out. My energy level has increased, even the itching (pruritus) got better. But then my doctor told me that the treatment has stopped working and I just wanted to die right there." – CLF patient contact

3.1.3 Impact of HCC and Current Therapy on Caregivers

The CLF was not able to recruit any caregivers for this patient input. Therefore, there was no input on the impact of HCC and current therapy on caregivers.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for Cabozantinib or New Therapies

The CLF reiterated that the quality of life of patients who are on sorafenib, the current standard of first-line treatment for HCC, is low as it is associated with significant side effects.

One CLF patient contact expressed hopes for maintaining a sufficient level of independence to be able to care for themselves and regain the ability to spend time with family and friends. Specifically, one caregiver, who responded as per the 2016 global survey of patients living with HCC, hoped that a new treatment would decrease the symptom of ascites, which can improve their range of movement and other associated complications.

The following are comments expressed by CLF patient and caregiver contact regarding their expectation for new therapies:

“I want a treatment which will allow me to spend time with my family and friends. I want to be able to function during the day, care for myself such as take a shower on my own, dress myself, and cook for myself.” – CLF patient contact

"I would like to see a new treatment that decreases the symptom of ascites, which would improve the range of movement and other complications that follow." - CLF caregiver contact

3.2.2 Patient Experiences To Date with Cabozantinib

The CLF was not able to recruit any patients who had experience with cabozantinib.

3.3 Companion Diagnostic Testing

N/A

3.4 Additional Information

The CLF further commented on the severity of the disease and the current state of treatments and prognosis. If diagnosed earlier, patients have more options for treatments such as surgical resection, liver transplant, ablation, chemoembolization and radioembolization. However, many patients are not diagnosed early enough as they do not show signs of having liver cancer until the damage to the liver has significantly progressed. Once a patient is diagnosed with HCC, the current standard for first-line treatment in Canada is systemic therapy with sorafenib and then second-line treatment with regorafenib. The CLF emphasizes that the possibility of adding a new treatment option at the later advanced stages offers hope to patients who have very limited options. This will ensure the best possible outcomes to prolong survival and improve quality of life for patients and their families.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from **all nine** provinces (Ministries of Health and/or cancer agencies) and federal drug plan participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Priority of cabozantinib relative to regorafenib and sequencing with lenvatinib

Economic factors:

- Potential for drug wastage

Please see below for more details.

4.1 Currently Funded Treatments

Sorafenib is the standard of care in first-line treatment of metastatic HCC and is funded in all provinces. Lenvatinib is also currently under review at pCODR for the first-line treatment of adult patients with unresectable HCC. After failure on sorafenib, best supportive care is available. PAG identified that there are no current treatments for patients with HCC after prior therapy (e.g., sorafenib). The comparator in the CELESTIAL trial was best supportive care, this is a relevant comparator. Regorafenib received a conditional positive reimbursement recommendation for treatment of HCC after sorafenib. At this time, regorafenib is under provincial consideration and PAG is seeking data comparing cabozantinib with regorafenib.

4.2 Eligible Patient Population

PAG is seeking clarity on the eligible patient population. PAG noted that sorafenib is funded for provinces with advanced HCC not amenable to local therapy in patients with performance status of ECOG 0-2 and Child-Pugh A liver function. The funding request from the submitter does not specify Child-Pugh status and the CELESTIAL study enrolled patients with ECOG 0 or 1 and Child-Pugh A liver function. In addition, PAG noted that the trial included patients who are co-infected with hepatitis and is seeking confirmation that these patients would be eligible for treatment with cabozantinib.

Patients in the CELESTIAL study had received prior sorafenib and PAG is seeking guidance on eligibility for cabozantinib for patients who had received other first-line treatments (e.g., lenvatinib) or were intolerant to sorafenib.

If recommended for reimbursement, patients who are currently receiving other second-line treatments (e.g., regorafenib), would need to be addressed on a time-limited basis.

There is a potential for indication creep to patients who had not received prior therapy (i.e., first-line treatment), particularly for patients who are intolerant to first-line sorafenib, as well as patients that were not included in the trial (e.g., patients with Child-Pugh B liver function and poor performance status).

4.3 Implementation Factors

The recommended daily dose of cabozantinib is 60mg. The availability of 20, 40, and 60mg tablets may be easier for dose reductions. Dose adjustment can be accomplished by changing the tablet strength dispensed, PAG identified that this may result in drug wastage of previously dispensed tablets of a higher strength. PAG is seeking information on the dose intensity and the frequency of dose adjustments.

Although the availability of three different strengths is an enabler for ease of dose adjustments, PAG expressed concerns if all tablet strengths are the same price. The flat pricing would be a barrier as there would be added costs for dose modifications. For example, a patient on a 60mg daily dose may be dispensed the smaller tablet strengths, to allow for the possible need of dose reductions. However, this dispensing strategy would cost more than dispensing the 60mg tablets. There are also concerns with the potential for drug wastage for patients who may be dispensed the 60mg tablets but do not tolerate and then have dose reduced prior to finishing the amount of 60mg tablets dispensed.

PAG is seeking clarity on treatment duration and criteria for treatment discontinuation as treatment with cabozantinib is recommended "until patient no longer experiences clinical benefit or experiences unacceptable toxicity".

Cabozantinib is a once daily oral drug. PAG noted that cancer centers would be familiar with administration of cabozantinib, particularly dispensing and side effects. These would be enablers to implementation. However, additional pharmacy and nursing resources would be required for dispensing and monitoring as well as treating adverse events (e.g., Palmar-Plantar Erythrodysesthesia).

PAG noted that cabozantinib is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home, and no chemotherapy chair time would be required. PAG identified the oral route of administration is an enabler to implementation.

However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients and their families. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

4.4 Sequencing and Priority of Treatments

PAG noted that some patients, who have failed sorafenib, are being treated with regorafenib obtained through private insurance or a manufacturer's access program. PAG is seeking information on the use of cabozantinib in third-line after regorafenib in second-line. In addition, PAG is seeking whether there is information to guide sequencing of cabozantinib and regorafenib in patients who have failed first-line sorafenib. As lenvatinib for first-line HCC is currently under review at pCODR, PAG is also seeking guidance on the use of cabozantinib in the second-line setting following lenvatinib in the first-line setting.

4.5 Companion Diagnostic Testing

None.

4.6 Additional Information

None.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

One joint input on behalf of two clinicians from Cancer Care Ontario (CCO) and one joint input on behalf of six registered clinicians was submitted for the review of cabozantinib for patients with hepatocellular carcinoma (HCC), who have been previously treated with sorafenib. Based on the results of the CELESTIAL trial, all clinicians agreed that cabozantinib is an effective treatment for patients with advanced HCC who have been previously treated with sorafenib. Cabozantinib has been demonstrated to have a larger survival benefit (OS) compared to regorafenib, along with significantly longer progression-free survival (PFS), and a similar adverse effect profile compared to other TKIs used in the HCC setting such as regorafenib and sorafenib. Sequencing options were presented by each clinician input based on currently available data and clinical opinion. Overall, the clinicians concluded that cabozantinib is a highly effective, emerging treatment that can fulfill a significant current unmet need for HCC patients.

Please see below for details from the clinician input(s).

5.1 Current Treatment(s) for Hepatocellular Carcinoma

Clinician input from the joint input of six registered clinicians listed the following therapies for HCC:

1. First-line: lenvatinib or sorafenib

2. Second-line (can be considered post-Lenvatinib as well): cabozantinib, regorafenib (in patients who have tolerated sorafenib) and ramucirumab (in patients with Alpha-fetoprotein greater than 400)

3. Nivolumab should be considered in patients who are intolerant to TKI.

The joint input from clinicians also mentioned the current availability of the above treatments in Canada. Funding is pending for lenvatinib as it recently received a positive conditional pCODR recommendation in August 2019. Regorafenib is pending implementation in Canadian provinces, ramucirumab is currently not funded in Canada and nivolumab has not been recommended for reimbursement. Furthermore, the clinicians explained that the most appropriate comparator for cabozantinib is regorafenib as it has received a conditional positive reimbursement recommendation for treatment of HCC after sorafenib.

The clinicians from CCO also indicated regorafenib as a second-line option and mentioned that there are currently no trials comparing regorafenib to cabozantinib.

5.2 Eligible Patient Population

The clinicians from CCO noted that the following groups of patients would be considered for treatment with cabozantinib: patients who have received other first-line treatments or were intolerant to sorafenib, patients with Child-Pugh B liver function and patients with an ECOG PS status of 2.

The joint input from six registered clinicians recommended cabozantinib for patients who have received other first line treatments with or were intolerant to sorafenib; however, they cautioned that more studies are needed to advise the use of cabozantinib for patients with Child-Pugh B liver function and patients with an ECOG PS status of 2.

IMPLEMENTATION QUESTIONS: The eligibility criteria for the CELESTIAL trial included a specific patient population compared to the broader funding request. In clinical practice, is there evidence to extend the use of cabozantinib to (provide all other eligibility criteria are met):

a) Patients who had received other first-line treatments (e.g., lenvatinib) or were intolerant to sorafenib?

- The joint clinician input referred to their previously submitted clinician input for lenvatinib (pCODR 10175) in February 2019, which reported that numerous options are available for second-line treatment following intolerance to sorafenib or patients with progressive disease. Although lenvatinib and sorafenib are different in terms of their targets, currently there is no evidence to support that second-line therapies would be as effective following first-line treatment with lenvatinib. The clinicians concluded in the submission that it is reasonable to use regorafenib or cabozantinib after lenvatinib. Furthermore, in the Final Clinician Guidance Report for Lenvatinib released on July 2019, the following was stated by the Clinical Guidance Panel: "*There is no known rationale to suggest that the efficacy of second line HCC treatments would be influenced by the first line therapy. Medical oncologists extrapolate the efficacy of second line therapies after a new standard first line therapy is established across multiple tumor sites…*"

- The clinicians advised to review the updated Cancer Care Ontario Guideline: Non-Surgical Management of Advanced Hepatocellular Carcinoma (Report Date: May 23, 2019). The objective of this guideline is to make recommendations regarding the non-surgical treatment of advanced hepatocellular carcinoma (HCC). A few excerpts from the report were presented by the clinicians as follows:

1. Recommendation 4: Currently, regorafenib and cabozantinib are the two tyrosine kinase-inhibitors used in the second-line setting after sorafenib that provide a survival benefits and are options for HCC patients with stable liver function and who are otherwise in good condition.
    - For second-line therapy, the cabozantinib trial include patients who could not tolerate sorafenib. In the regorafenib trial, patients were required to have previously tolerated a minimum dose of 400 mg for ≥ 21/28 days. Although none of the trials specifically assessed lenvatinib, both second cabozantinib and regorafenib are reasonable options for patients who progress on lenvatinib.
    - Since the side-effects of both regorafenib and cabozantinib are different, it is reasonable for a patient to switch between the drugs before progression, if one drug is intolerable in the second-line setting.

The clinicians further presented evidence for Recommendation 4 in the report:

- Regorafenib combined with best supportive care (BSC) had significantly better survival than placebo/BSC in the RESORCE trial (HR, 0.63; 95% CI, 0.50 to 0.79, p<0.0001)

- Cabozantinib had significantly better survival than placebo in the CELESTIAL trial (HR, 0.76; 95% CI, 0.63 to 0.92; p=0.005)

b) Patients with Child-Pugh B liver function?

- The joint clinician input explained that drug trials for HCC usually enroll patients with Child-Pugh A liver function that are not representative of all HCC patients. However, it was asserted that the inclusion/exclusion criteria of the CELESTIAL clinical trial are generally reasonable.

The clinicians cautioned however that further studies are needed to determine the safety and efficacy of available treatments for HCC patients who have compromised liver function. A current study is underway which includes a cohort of patients with Child-Pugh B liver function for whom additional data will be collected. The clinicians also mentioned that there are current opportunities in Canada to collect data from patients with advanced HCC. A database has been created by one of the clinicians on patients with HCC which could be utilized to gather real-world evidence of patients that have compromised liver functions.

c) Patients with ECOG PS of 2

- The clinicians from the joint clinician input stated that ongoing studies are needed for patients that have a poor ECOG performance status. It was noted that fatigue can be a side effect of first-line therapy which can affect ECOG performance status. Additionally, the above-mentioned database can also be utilized to gather real-world evidence for patients with a poor ECOG performance status. The clinicians concluded that with more options for second-line therapies, it is likely that patients can be identified earlier for therapy which can preserve ECOG status.

5.3 Relevance to Clinical Practice

The clinicians from CCO reported that they do not have experience with using the cabozantinib. Input for this section from the joint clinician input was provided by a single clinician who was an investigator in the CELESTIAL trials and has experience with treating patients with cabozantinib.

The clinician noted a significant unmet medical need for HCC patients who have progressed on previous systemic therapy for whom cabozantinib has demonstrated a significant clinical benefit.
The clinician further commented that clinical research has started to focus on optimizing a treatment algorithm in the HCC setting. In the absence of a direct comparison between available second-line options, some aspects of the randomized controlled trials can help determine how new treatments should be used. For example:

- Regorafenib should not be offered to patients who are intolerant to sorafenib.
- Cabozantinib can be offered to patients who are intolerant to sorafenib.
- The results of the CELESTIAL trial support cabozantinib as the preferred second or subsequent line therapy for the treatment of HCC (BCLC stage C) patients.

To further support this statement, the clinician also referred to the previous submission of Lenvatinib/Lenvima for HCC, for which a final recommendation was published in July 2019 as stated in Section 5.2, subsection a). In the pCODR final Clinical Guidance Report, the following was stated: "*There is no known rationale to suggest that the efficacy of second line HCC treatments would be influenced by the first line therapy. Thus, in clinical practice, cabozantinib would be an option for patients who received front line treatment with sorafenib **or** lenvatinib*."

Furthermore, the clinician noted that a naïve direct comparison conducted by the manufacturer (of cabozantinib) between cabozantinib and regorafenib in a second-line HCC population (post-sorafenib) demonstrated a larger survival benefit (OS) with cabozantinib: 4.1 months (cabozantinib) versus 2.8 months (regorafenib). While the clinician recognizes that these results are to be interpreted with caution, the clinician concluded that there is a sign of larger survival benefit with cabozantinib as a second line treatment. Additionally, it was highlighted that the CELESTIAL inclusion criteria were broader than in the RESORCE trial (evaluating regorafenib), which better represented a real-world population.

The clinician reiterated that in terms of efficacy, cabozantinib appears to have larger survival benefit (OS) compared to regorafenib, along with significantly extended progression-free survival (PFS) as demonstrated in the CELESTIAL trial. The adverse effect profile of cabozantinib is similar to other TKIs in the HCC setting and consistent with the safety profile of cabozantinib in previous studies and indications.

The clinician listed the following contraindications:

- Unstable angina which is symptomatic congestive heart failure
- Gastrointestinal disorders that are at a high risk of perforation or fistula
- Pregnancy

5.4 Sequencing and Priority of Treatments with New Drug Under Review

IMPLEMENATION QUESTION: If cabozantinib was available:

a) Regorafenib received a conditional positive reimbursement recommendation for treatment of HCC after sorafenib. In what clinical scenarios would cabozantinib or regorafenib be the preferred treatment for HCC after prior therapy? Please comment on the preference considering patient preference, efficacy, safety, and administration.

Clinicians input from CCO did not recommend one treatment in favour of the other. The clinicians stated that both cabozantinib and regorafenib have significant toxicities, but neither of the registered trials included quality of life measures that would enable clinicians and patients to choose between the two therapies.

Clinician input from the joint clinician input recommended cabozantinib for patients who discontinue sorafenib due to toxicity. Regorafenib is not recommended for this group of patients. For patients who have progressed on either sorafenib or lenvatinib, both regorafenib and cabozantinib are options in the second line, with preference for cabozantinib due to the emerging evidence on its efficacy.

b) Is there evidence to inform sequencing of cabozantinib with regorafenib?

Clinicians from CCO stated that there is currently no data that would inform sequencing, especially if the checkpoint inhibitor first-line trials are positive versus sorafenib.

However, Clinician input from the joint clinician input noted that cabozantinib may be used third line TKI treatment, considering that the CELESTIAL trial included patients who had up to two lines of previous treatment, as long as one line was sorafenib.

5.5 Companion Diagnostic Testing

N/A

5.6 Implementation Questions

N/A

5.7 Additional Information

The clinicians from the joint clinician input acknowledged that treatments for metastatic HCC have been evolving over the past few years and the results of further trials are going to be available soon. They concluded that based on the current evidence available, cabozantinib can be sequenced after first-line treatment with sorafenib or lenvatinib. Nonetheless, the clinicians noted that the sequencing may change in the future according to the results of new trials.

The clinicians from CCO acknowledged that the survival benefit of cabozantinib is statistically significant but as with regorafenib, it is clinically modest. The clinicians anticipate it is unlikely that the cost-effectiveness threshold will be met. Additionally, the clinicians commented that currently, there are several randomized phase 3 trials that involve immune checkpoint inhibits in the first-line. If the results of the trials are positive, there might be uncertainty regarding the efficacy of the current trials of second-line treatment with cabozantinib or regorafenib.

6 SYSTEMATIC REVIEW

6.1 Objectives

To perform a systematic review to evaluate the efficacy and safety of cabozantinib indicated for the treatment of advanced hepatocellular carcinoma in adult patients (aged 18 years and above) after prior therapy.

Supplemental Questions relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7.

- Critical appraisal of the sponsor's submitted match-adjusted indirect comparison (MAIC) comparing cabozantinib with regorafenib

6.2 Methods

Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

Table 6.1: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
• Published or unpublished phase III and IV RCTs • In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of cabozantinib should be included	• Adults aged 18 and above with advanced hepatocellular carcinoma who have received prior systemic therapy Subgroups: • Patients with hepatic impairment • Patients with renal impairment	• Cabozantinib	• BSC • Regorafenib • Nivolumab[a]	• **OS** • **PFS** • **HRQOL** • ORR **Safety:** • AEs • SAEs • WDAEs • AEs of interest o Hair loss o Hair colour change o Nausea o Diarrhea o Constipation o Stomach pain o fistula
Abbreviations: BSC = best supportive care; ORR = objective response rate, OS = overall survival, PFS = progression free survival, AE=adverse events; IV = intravenous; HRQoL=health-related quality of life; RCT=randomized controlled trial; SAE=serious adverse events; WDAE=withdrawal due to adverse events				
Notes: * Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions). [a]Nivolumab (Opidivo) has received Health Canada approval for the treatment of HCC; however, is currently not funded in Canadian jurisdictions				

6.3 Results

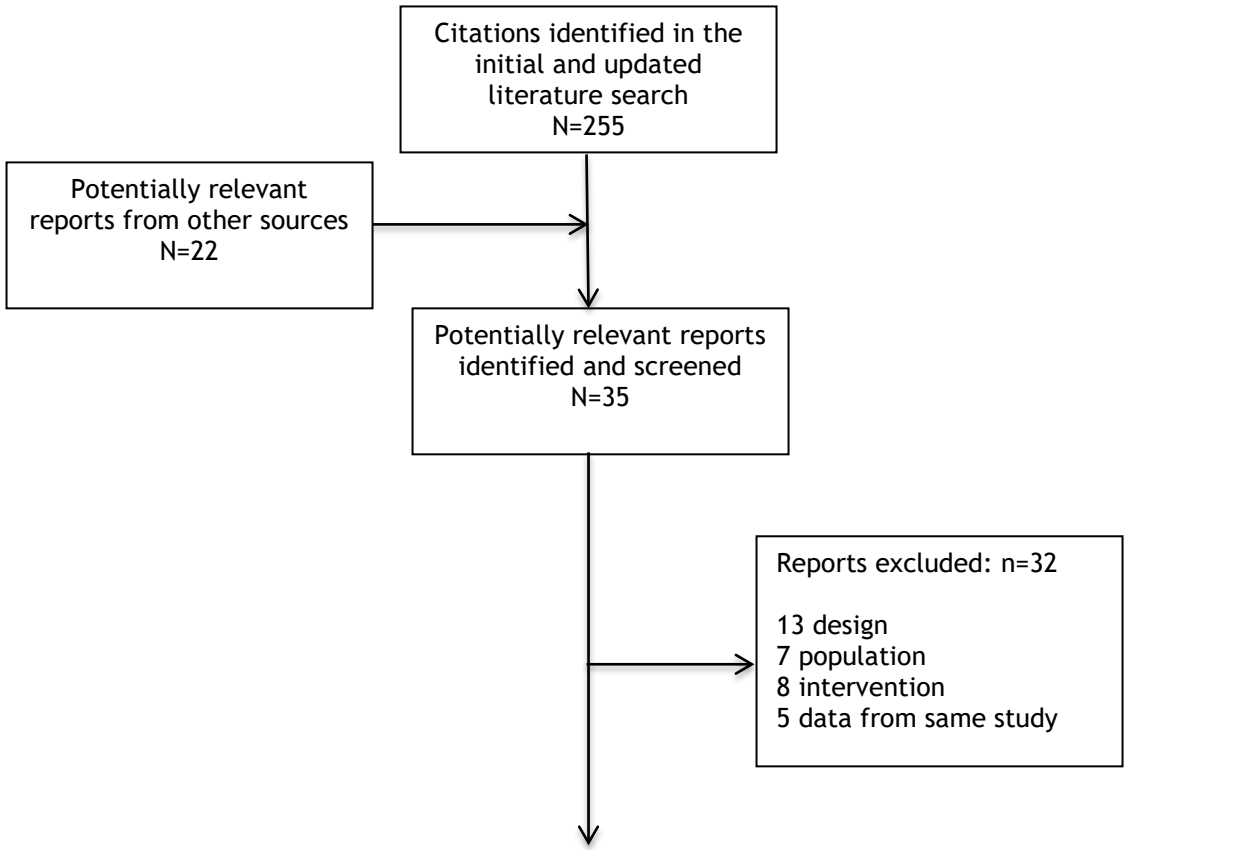
6.3.1 Literature Search Results

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Of the 255 potentially relevant reports identified, two reports were included in the pCODR systematic review. Both reports described the same study called the CELESTIAL trial. One is the public record of the completed phase III trial published on the US government website.[29] The other is the peer-reviewed paper resulting from the CELESTIAL trial, published in the New England Journal of Medicine by Abou-Alfa et al in 2018.[2,3]

Other reports were excluded because they were of the wrong study design, described a patient population not relevant to this review or included duplicate data.

Figure 6.1 QUOROM Flow Diagram for Inclusion and Exclusion of Studies



Note: Additional data related to CELESTIAL were also obtained through the sponsor: Press Release,[4] Clinical Study Report,[30] Checkpoint Response,[8,31] Quality of life Poster,[15] Statistical Analysis Plan[32]

6.3.2 Summary of Included Studies

One clinical trial, CELESTIAL, was identified that met the selection criteria of the pCODR systematic review. Key characteristics of the trial, including design, eligibility criteria and outcomes of interest, are summarized in Table 6.2. Specific aspects of trial quality, including sample size, statistical considerations, and efficacy analyses are summarized in Table 6.3.

Detailed Trial Characteristics

Table 6.2: Summary of Trial Characteristics of the Included Studies

Trial Design	Eligibility Criteria	Intervention	Trial Outcomes
CELESTIAL NCT01908426 XL184-309 Phase III randomized double-blind, placebo-controlled trial N=707 Multi-centre international trial with 107 sites in USA, Australia, Canada, Belgium, France, Germany, Italy, Ireland, Hong Kong, Korea, Netherlands, New Zealand, Poland, Romania, Singapore, Spain, Taiwan, UK, Patient enrollment dates: Sep 2013 Included two patient groups: Cabozantinib, 60 mg Placebo Second interim analysis (i.e., final analysis) Data cut-off date: June 1, 2017 Planned analyses: PFS if OS is statistically significant; sensitivity analysis of PFS censored at various events	<u>Key inclusion criteria:</u> • Age ≥ 18 years • Histological or cytological diagnosis of HCC • disease not amenable to cure • Received prior sorafenib • Progression following at least 1 prior systemic treatment for HCC • Recovery to from toxicities related to any prior treatments • ECOG performance status of 0 or 1 • Adequate hematologic and renal function • Child-Pugh Score of A • Antiviral therapy per local standard of care if active hepatitis B (HBV) infection • Female patients of childbearing potential must not be pregnant at screening <u>Key exclusion criteria:</u> • Fibrolamellar carcinoma or mixed hepatocellular cholangiocarcinoma	Oral Cabozantinib, 60 mg pill, taken once per day versus Placebo pill, taken once per day	<u>Primary outcome:</u> OS <u>Secondary outcomes:</u> PFS ORR using RESIST version 1.1 <u>Exploratory:</u> HRQOL (EQ-5D-5L) Safety

Trial Design	Eligibility Criteria	Intervention	Trial Outcomes
Funding: Exelixis	• Receipt of more than 2 prior systemic therapies for advanced HCC • Any type of anticancer agent (including investigational) within 2 weeks before randomization • Radiation therapy within 4 weeks (2 weeks for radiation for bone metastases) or radionuclide treatment within 6 weeks of randomization • Prior cabozantinib treatment • Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery and stable for at least 3 months before randomization • Concomitant anticoagulation, at therapeutic doses, with anticoagulants. • Serious illness other than cancer that would preclude safe participation • untreated or incompletely treated varices with bleeding or high risk for bleeding • Moderate or severe ascites • Pregnant or lactating females		

Trial Design	Eligibility Criteria	Intervention	Trial Outcomes
	• Diagnosis of another malignancy within 2 years before randomization, except for superficial skin cancers, or localized, low-grade tumors		
Abbreviations: HCC = hepatocellular carcinoma, ECOG = Eastern Cooperative Oncology Group Performance Status, HRQoL = health related quality of life; OS = overall survival, ORR = objective response rate, PFS = progression-free survival, RESIST = response evaluation criteria for solid tumors			

Source: Extracted from Clinicaltrials.gov NCT01908426[29]

Table 6.3: Select quality characteristics of the included CELESTIAL trial

Trial Quality Characteristics	CELESTIAL
Treatment versus comparator	• Cabozantinib 60 mg tablet once daily • Placebo once daily
Primary outcome	OS
Required sample size	Estimated sample size: 760 patients with 621 deaths required.
Randomization method	Randomization was stratified by etiology of disease and geographic region, extrahepatic spread, and macrovascular invasion. Patients randomized in 2:1 ratio by IVRS/IWRS
Allocation concealment (y/n)	Yes
Blinding	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
ITT Analysis (y/n)	Yes
Efficacy Analysis	N = 707 Cabozantinib n=470, Placebo n=237
Final Analysis (y/n)	Yes*
Early termination (y/n)	Yes* as per recommendation by the independent data monitoring committee
Ethics approval (y/n)	Y
Abbreviations: OS = overall survival, ITT = intent to treat, IVRS/IWRS = interactive voice response system/interactive web response system * The second interim analysis is considered the final analysis, as by then the trial had met its primary endpoint of OS (prespecified critical p value ≤ 0.021)	

Source: Extracted from Clinicaltrials.gov NCT01908426[29] and Ipsen Press Release[4]

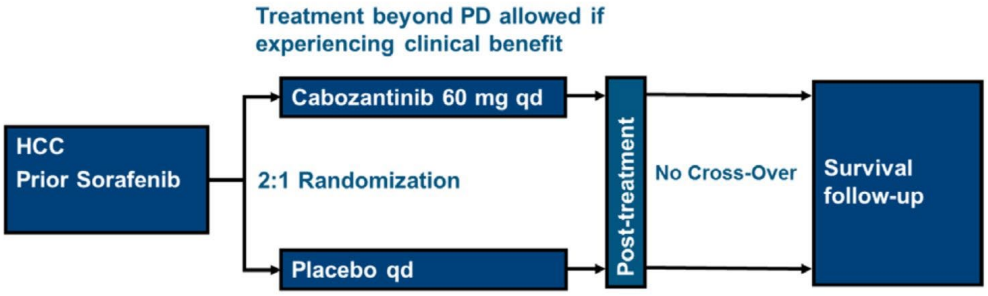
a) Trial

CELESTIAL is a phase III randomized, double-blind, placebo-controlled study of cabozantinib in patients with advanced HCC conducted at more than 100 sites globally in 19 countries (including Canada). The trial was designed to enroll 760 patients (though 707 patients were randomized) with advanced HCC who received prior sorafenib and may have received up to two prior

systemic cancer therapies for HCC and had adequate liver function. The study commenced on September 26, 2013, and enrollment of the trial was completed in September 2017. Actual primary completion date was October 16, 2017, while the estimate study completion date was October of 2019.[29]

Visual summaries of the design of CELESTIAL are presented in Figure 6.2.

Figure 6.2: design of CELESTIAL trial.[5]



Source: EPAR EMA[5]

Funding

The trial was funded by the Exelixis corporation, a partner of the sponsor: Ipsen Biopharmaceuticals Canada Inc.[33]

Key Eligibility Criteria

The CELESTIAL trial included adult patients (age 18 and older) who had a histological or cytological diagnosis of HCC that is not amenable to a curative treatment approach, had received prior sorafenib, progression following at least 1 prior systemic treatment for HCC. Additional eligibility criteria included: ECOG performance status 0 or 1, Child-Pugh Score A, and adequate hematologic and renal function, based upon meeting protocol defined laboratory criteria within 7 days before randomization.

Blinding

This was a double-blind study. Placebo was indistinguishable from cabozantinib. Allocation was concealed from patients, investigators, study centres, sponsor and any affiliated contract research organization. No patients were unblinded prior to the data cut-off date. An independent data monitoring committee monitored unblinded safety data to protect subject welfare and to provide recommendations regarding study conduct.[5]

Protocol Amendments

The original CELESTIAL protocol (dated March 12, 2013) was amended twice. First, on April 23, 2014, three inclusion criteria were clarified: (i) patients without prior histological or cytological diagnosis of HCC required a biopsy; (ii) lower limit of serum albumin was 2.8 g/dL; (iii) HbA1c testing window was extended to 28 days prior to randomization. And four exclusion criteria were clarified: (i) patients with Crohn's disease excluded; (ii) patients with disease invading the inferior vena cava excluded; (iii) patients with active hepatitis infection controlled with

antiviral therapy eligible; (iv) patients with history of variceal bleeding treated with adequate endoscopic therapy eligible.[5]

The first amendment also included additional post-screening Child-Pugh testing time points, the addition of QT prolongation to the list of potential cabozantinib AEs requiring management, and the introduction of a Maintenance Phase, which patients were to enter when sufficient data had been collected to evaluate all study endpoints.[5]

The second amendment took place on July 12, 2016, and introduced an Open Label Phase so that, "following demonstration of statistically significant and clinically meaningful improvement in OS by cabozantinib, patients in the placebo group who met specific eligibility criteria could crossover to receive cabozantinib."[5]

Key Efficacy Endpoints & Statistical Analysis Plan

The primary outcome of CELESTIAL was OS, defined as the time from randomization to death from any cause, for a duration of 45 months. The analysis was based on a second planned interim analysis prespecified to be performed at approximately the 75% information fraction (i.e., at approximately 466 deaths). For patients who are alive at the time of data cut-off but are permanently lost to follow-up, duration of OS was right censored at the date the patient was last known to be alive. Patients who withdrew consent from survival follow-up and were alive were also right censored at the date the patient withdrew consent from survival follow-up. Patients alive on or after the data cut-off or patients who died after the data cut-off date were right censored at the data cut-off date.[5]

Secondary efficacy endpoints were objective response rate (ORR) per RECIST 1.1 and progression-free survival (PFS), also per RECIST 1.1.[5] For safety endpoints, the last observation before first day of study treatment was considered baseline.

The hypothesis testing between the two treatment groups was performed using the stratified log-rank test with a 2-sided α=0.05 level of significance. The median duration of OS and the associated 95% confidence interval (CI) for each treatment arm was estimated using the Kaplan-Meier method. The stratified hazard ratio (HR) and its 95% CI was estimated using a Cox proportional-hazard model with treatment group as the independent variable and stratified by the same randomization stratification factors (disease etiology, geographic location, and the presence of extrahepatic spread of disease and/or macrovascular invasion) as were used for the log-rank test.[2,5]

Up to three analyses of OS were planned: two interim analyses and a final analysis that would occur when 50%, 75% and 100% deaths had been observed. Inflation of Type I error associated with interim analyses was controlled using a Lan-DeMets O'Brien-Fleming alpha-spending function.[5,32] Interim analysis results were evaluated by the independent data monitoring committee; this allowed the trial to be terminated early if the null hypothesis for OS was rejected in favour of cabozantinib. No formal futility analyses were planned.[5]

The second interim analysis (data cut-off date June 1, 2017) is considered the final analysis, as by then the trial had met its primary endpoint of OS (prespecified critical p value $\leq$ 0.021; the independent data monitoring committee recommended to terminate the trial early for efficacy following review of the second planned interim analysis).[4]

Duration of PFS, the secondary efficacy endpoint, was defined as the time of randomization to the earlier of the following events: progressive disease as determined by Investigator (per RECIST 1.1, which is defined by a $\geq$ 20% increase in the sum of the longest diameter of target lesions from baseline) or death due to any cause. Only if OS results were statistically significant (either interim or final), did the hypothesis testing of PFS between the two treatment groups occur using the stratified log-rank test at the two-sided α =0.04 level of

significance. The same stratification factors used for OS were used for PFS: disease etiology, geographic location, and the presence of extrahepatic spread of disease and/or macrovascular invasion. The Kaplan-Meier method was used to estimate the median duration of PFS and the associated 95% CI for each treatment group. The HR was estimated using a Cox regression model and included the same stratification factors noted for the log-rank test mentioned above.[5]

Objective response rate (ORR) was a secondary endpoint considered in the trial. ORR was determined by radiologic measurements of tumors every 8 weeks after randomization until either disease progression or discontinuation of study treatment, up to 45 months. Objective response rate was assessed per the Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.0) for target lesions and assessed by MRI: Complete Response (CR), Disappearance of all target lesions; Partial Response (PR), >=30% decrease in the sum of the longest diameter of target lesions; Overall Response (OR) = CR + PR. The ORR was defined as the proportion of patients experiencing a CR or PR, confirmed ≥28 days after the response was first observed, as determined by the Investigator using RECIST 1.1. The hypothesis testing of ORR between the two treatment groups occurred only if the result of either an interim or final OS analysis achieved statistical significance. Since statistical significance for OS was achieved the second interim analysis, ORR was tested.

As per the CELESTIAL trial, subjects could continue blinded study treatment after radiological disease progression if they continued to receive benefit as per the opinion of the investigator. It was noted that 32% in the cabozantinib and 49% in the placebo group continued blinded treatment after radiological disease progression possibly until symptomatic progression. The median number of day that treatment continued as reported in the EPAR assessment report was short, but the full range was not presented: the median (Q1 to 3) was 13.50 (5.00 to 64.50) days in the cabozantinib arm and 7.00 (4.00 to 29.00) days in the placebo group.[5]

Health-related quality of life (HRQoL) was an exploratory endpoint considered in the trial. HRQoL was assessed by the EuroQoL Health questionnaire instrument (EQ-5D-5L). An effect size for change from baseline equal to or greater than 0.3 was considered potentially clinically meaningful and the minimal important difference established in the literature was between 0.06 and 0.08 for EQ-Index and 7 for the EQ-VAS.[5]

b) Populations

For the overall survival (OS) outcome, a total of 621 deaths planned with two interim analyses (at 50% and 75% information) and a final analysis would provide the study with 90% power for a 2-sided log-rank test with a 5% level of significance to detect a 31.6% increase in OS (HR = 0.76). Actual enrolment was 707 patients.

A total of 1023 patients were assessed for eligibility, 707 underwent randomization. Of those, 237 received placebo, and while 470 were slated to receive cabozantinib, 467 actually received cabozantinib. And the end of the study, 73 patients (99.4%) remained on cabozantinib and 26 (11.0%) remained on placebo.

All patients in the CELESTIAL trial had received prior sorafenib and were included in the study regardless of whether they had been intolerant of or had progressed on prior sorafenib. The sponsor had noted that since tolerance was not an inclusion/exclusion criterion, no definition for sorafenib intolerance was created or used in the trial. The sponsor also noted that the RESORCE trial[12] which evaluated the safety and efficacy of regorafenib in sorafenib tolerant patients had a median time on sorafenib of 7.8 months, while the CELESTIAL trial had a median time on sorafenib of 5.3 months. The sponsor noted that approximately 2% - 3% of patients in the CELESTIAL trials were treated with sorafenib for <1 month while 23-25% of patients were treated with sorafenib for <3 months, suggesting that sorafenib intolerant patients had shorter duration of time on sorafenib.[8] In addition, 6 patients in the cabozantinib treatment arm received prior regorafenib; however, efficacy results for these patients were not available.

There were no patients in the cabozantinib treatment group who received prior lenvatinib. Refer to Table 6.4 for a complete list of prior non-radiation anticancer therapy for HCC in the ITT population. These data on duration of treatment of prior sorafenib were used to complete a post-hoc analysis for OS and PFS in the CELESTIAL trial population and is reported in Efficacy Outcomes below in Table 6.14.

Table 6.4: Prior Non-radiation Anticancer Therapy for HCC (ITT Population).

Subject Characteristic	Cabozantinib (N = 470)	Placebo (N = 237)
Therapy type for HCC, n (%)[a]		
Systemic therapy	470 (100)	237 (100)
Local liver-directed therapy	209 (44)	113 (48)
Local other locations	2 (0.4)	0
Number of prior systemic anticancer regimens for advanced HCC per subject, n (%)		
0	3 (0.6)[b]	0
1	335 (71)	174 (73)
2	130 (28)	62 (26)
≥3[c]	2 (0.4)	1 (0.4)
Progression on most recent prior systemic agent for HCC, n (%)	459 (98)	231 (97)
Median (range) time from progression on most recent prior systemic agent for HCC to randomization, months	1.61 (0.0, 100.8)	1.68 (0.2, 69.4)
Progression while receiving sorafenib for HCC, n (%)	452 (96)	232 (98)
Progression while receiving sorafenib as most recent prior systemic agent for HCC, n (%)	322 (69)	166 (70)
Sorafenib for HCC at any time, n (%)[a]	470 (100)	237 (100)
Sorafenib for advanced HCC, n (%)	467 (99)	236 (100)
First-line per CRF	454 (97)	228 (96)
Second-line per CRF	25 (5)	18 (8)
Adjuvant sorafenib for HCC	5 (1)	2 (0.8)
Other route of sorafenib administration for HCC	3 (0.6)	1 (0.4)
Median (range) duration of prior sorafenib for HCC, months Total duration of prior sorafenib (months) for HCC, n (%)	5.32 (0.3, 70.0)	4.80 (0.2, 76.8)
< 1 month	11 (2)	8 (3)
≥ 1 to < 3 months	117 (25)	54 (23)
≥ 3 to < 6 months	130 (28)	67 (28)
≥ 6 months	211 (45)	108 (46)
Other prior non-radiation systemic anticancer agents, n (%)[a]		
PD-1/PD-L1 therapies	14 (3.0)	3 (1.3)
Anti-CTLA-4 therapies	3 (0.6)	0
Ramucirumab	8 (1.7)	1 (0.4)
TKI therapies (other than sorafenib)	19 (4.0)	12 (5.1)
Regorafenib	6 (1.3)	2 (0.8)
Axitinib	4 (0.9)	1 (0.4)
Investigational drug	5 (1.1)	3 (1.3)
Lenvatinib	0	1 (0.4)

Cytotoxic chemotherapy[d]	41 (8.7)	30 (13)
Received prior TACE for HCC, n (%)	203 (43)	111 (47)
Median number of prior chemoembolizations per subject [e]	0 (0, 18)	0 (0, 17)
0, n (%)	267 (57)	126 (53)
1, n (%)	70 (15)	32 (14)
2, n (%)	48 (10)	20 (8)
≥ 3, n (%)	85 (18)	59 (25)
Other liver-directed therapy (from surgery CRF), n (%)	54 (11)	30 (13)

[a] Prior systemic agents could be taken together but are summarized separately. Subjects may be counted in more than one category.
[b] Three subjects on the cabozantinib arm received prior systemic anticancer therapy that was administered for adjuvant HCC treatment but not for advanced HCC treatment per the CRFs.
[c] In the cabozantinib arm, Subject 3366-3517 received sorafenib (multiple instances) and doxorubicin, and Subject 9102-3262 received sorafenib and concomitant bevacizumab plus rapamycin (recorded as separate regimens). In the placebo arm, Subject 1513-3278 received sunitinib and multiple instances of sorafenib. These three subjects were not included in the table of eligibility deviations regarding line of therapy.
[d] Specific systemic cytotoxic chemotherapeutic agents received by ≥ 1% of subjects in either arm were: doxorubicin, oxaliplatin, cisplatin, gemcitabine, capecitabine, fluorouracil
[e] Multiple episodes of TACE on the same day were counted as a single administration.
Prior therapies were defined as having a start date prior to first dose of study treatment.

Source: EPAR EMA[5]

Patients in the CELESTIAL trial received the following prior therapies other than sorafenib, as summarized in the Table 6.5 below. Among these patients, other therapeutic products, followed by anthracyclines and related substances, and then protein kinase inhibitors were the most common previous therapies used in the first line other than sorafenib.

Table 6.5: Number and duration of previous therapies used in first line other than sorafenib.[8]

		Cabozantinib (N=35) n (%)	**Placebo (N=19) n (%)**
Medication Class	Anthracyclines and related substances	9 (23.08)	5 (23.81)
	Detoxifying agents for antineoplastic treatment	1 (2.56)	0
	Monoclonal antibodies	6 (15.38)	1 (4.76)
	Other antineoplastic agents	0	1 (4.76)
	Other immunosuppressants	0	1 (4.76)
	Other therapeutic products	12 (30.77)	5 (23.81)
	Platinum compounds	4 (10.26)	2 (9.52)
	Protein kinase inhibitors	5 (12.82)	3 (14.29)
	Pyrimidine analogues	2 (5.13)	3 (14.29)
Duration of Medication (Weeks)	N	35	19
	Mean (SD)	19.96 (42.23)	19.81 (15.65)
	Median (Q1 - Q3)	11.86 (6.29 - 18.00)	19.14 (5.14 - 31.43)
	Min - Max	0.14 - 256.86	2.14 - 51.43

Overall, baseline characteristics were balanced between the two groups with the exception of macrovascular invasion. The CELESTIAL patient population comprised of a majority of male (81%) patients with a median age of 64 years. Over half patient population had an ECOG performance status of zero and one patient with an ECOG performance status of two was inadvertently enrolled. A summary of all demographic criteria is provided in Table 6.6 below.

Table 6.6: Baseline demographics and clinical characteristics of the cohort of CELESTIAL.

	Cabozantinib (N = 470)	Placebo (N = 237)
Age, median (range), years	64 (22-86)	64 (24-86)
Sex, n (%)		
Male	379 (81)	202 (85)
Female	91 (19)	35 (15)
Geographic region, n (%)		
Asia*	116 (25)	59 (25)
Europe	231 (49)	108 (46)
North America (Canada/United States)	108 (23)	59 (25)
Australia/New Zealand	15 (3)	11 (5)
Race, n (%)†		
White	264 (56)	130 (55)
Asian	159 (34)	82 (35)
Black	8 (2)	11 (5)
Other	8 (2)	2 (1)
Not reported	31 (7)	12 (5)
ECOG performance status, n (%)		
0	245 (52)	131 (55)
1	224 (48)	106 (45)
2‡	1 (<1)	0
Etiology of disease, n (%)§		
HBV	178 (38)	89 (38)
HCV	113 (24)	55 (23)
Dual HBV and HCV infection	8 (2)	4 (2)
Alcohol_	112 (24)	39 (16)
Nonalcoholic steatohepatitis	43 (9)	23 (10)
Other	24 (5)	16 (7)
Unknown	75 (16)	47 (20)
Child-Pugh class, n (%)		
A	462 (98)	235 (99)
B‡	7 (1)	2 (1)
Missing	1 (<1)	0
BCLC stage, n (%)‖		

	Cabozantinib (N = 470)	Placebo (N = 237)
B (intermediate)	42 (9)	23 (10)
C (advanced)	427 (91)	214 (90)
Extrahepatic spread of disease, n (%)	369 (79)	182 (77)
Macrovascular invasion, n (%)	129 (27)	81 (34)
Extrahepatic spread of disease and/or macrovascular invasion, n (%)	398 (85)	200 (84)
Sites of disease, n (%)		
Liver**	395 (84)	216 (91)
Bone	60 (13)	34 (14)
Visceral (excluding liver)	215 (46)	105 (44)
Lung	184 (39)	91 (38)
Adrenal gland	51 (11)	24 (10)
Lymph Node	155 (33)	71 (30)
Number of sites (including liver)		
1	144 (31)	72 (30)
2	172 (37)	91 (38)
≥3	154 (33)	74 (31)
Alpha-fetoprotein (ng/mL), n (%)		
< 400	278 (59)	136 (57)
≥ 400	192 (41)	101 (43)
Number of prior systemic anticancer regimens for advanced HCC, n (%)		
0¶	3 (1)	0
1	335 (71)	174 (73)
2	130 (28)	62 (26)
≥3	2 (<1)	1 (<1)
Prior systemic anticancer therapy, n (%)		
Sorafenib	470 (100)	237 (100)
Regorafenib	6 (1)	2 (1)
Lenvatinib	0	1 (<1)
Tivantinib	1 (<1)	2 (1)
Ramucirumab	8 (2)	1 (<1)
Anti-PD-1/PD-L1	14 (3)	3 (1)

Exelixis, 2013 #385BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; PD-1, programmed death-1; PD-L1, programmed death-ligand 1. Significant differences between treatment groups are indicated by _ for P < 0.05 and ** for P < 0.01. *Asia included Hong Kong, South Korea, Singapore, and Taiwan. †Race was self reported by the patients. ‡Although patients were required to have ECOG performance status of 0 or 1 and Child-Pugh class A, a few patients had ECOG performance status of 2 or Child-Pugh class B. § Etiology per case report form. Some patients had more than one disease etiology category. ‖ BCLC status1 was assigned retrospectively, using macrovascular invasion as a surrogate for portal vein invasion. One patient in the cabozantinib group had unknown BCLC status. ¶Three subjects in the cabozantinib group received prior

systemic anticancer therapy that was administered for adjuvant treatment but not for advanced hepatocellular carcinoma treatment. # Time from initial pathologic diagnosis of HCC to randomization missing for 1 patient in the cabozantinib group and 2 patients in the placebo group. Total duration of treatment on prior sorafenib missing for 1 patient in the cabozantinib group.

Source: NEJM, Abou-Alfa et al., 379(1):54-63. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[2]

Child Pugh Status

The sponsor noted that Child Pugh scores were collected at screening and every 8 weeks after randomization. At baseline, the majority of patients in both the cabozantinib and placebo groups were Child Pugh A. The table below captures data on the number of patients who maintained their Child Pugh A status in the ITT population. Data timepoints of 9 weeks, 25 weeks and 49 weeks were chosen to illustrate the differences in Child Pugh status while on study treatment. For instance, at week 9, day 1 80% of patients in the cabozantinib group were classified as Child-Pugh A compared to 48% of patients in the placebo group. At week 25, day 1, 86% of in the cabozantinib group were classified as Child-Pugh A compared to 92% of patients in the placebo group. At week 41, day 1, 92% of in the cabozantinib group were classified as Child-Pugh A compared to 90% of patients in the placebo group.

Table 6.7: Shift Since Baseline in Child-Pugh Score (ITT Population).

		Child-Pugh A	Child-Pugh B	Child-Pugh C	Child-Pugh A	Child-Pugh B	Child-Pugh C
Baseline		Cabozantinib (N=470), n (%)			Placebo (N=237)		
		462 (98%)	7 (1%)	1 (0.2%)*	235 (99%)	2 (0.8%)	0
At week 9, Day 1		Cabozantinib (N=249)			Placebo (N=136)		
	Child Pugh A	198(80%)	39 (16%)	2 (0.8%)	113(48%)	20 (15%)	0
	Child Pugh B	3 (1.2%)	6 (2.4%)	0	1 (0.7%)	2 (1.5%)	0
	Child Pugh A to B conversion rate	39/249 (16%)			20/136 (15%)		
At week 25, Day 1		Cabozantinib (N=144)			Placebo (N=37)		
	Child Pugh A	124(86%)	16 (11%)	1 (0.7%)	34 (92%)	1 (2.7%)	0
	Child Pugh B	1(0.7%)	2 (1.4%)	0	1 (2.7%)	1 (2.7%)	0
At week 41, Day 1		Cabozantinib (n=65)			Placebo (n=10)		
	Child Pugh A	60 (92%)	5 (7.7%)	0	9 (90%)	1 (10%)	0
	Child Pugh B	0	0	0	0	0	0

Source: Ipsen[8,31]

c) ***Interventions***

Patients received either oral cabozantinib 60mg or matched placebo, both in combination with best supportive care, after a 2 hour fast.[5] Patients were supplied with cabozantinib as 60-mg and 20-mg yellow film-coated tablets, and visually identical placebo tablets. Patients continued treatment while they experienced clinical benefit (even after disease progression per RECIST 1.1) until unacceptable toxicity, the need for subsequent systemic anticancer therapy or liver-directed local anticancer therapy, or other reasons for treatment discontinuation. Crossover between treatment groups was not allowed. Two dose reductions (in decrements of 20 mg cabozantinib or matched placebo) were allowed for the management or prevention of worsening of an AE or toxicity.[5]

Patients continued the assigned treatments as long as they derived clinical benefit, as judged by the investigator, or until they had unacceptable AEs. Dose reductions and dose interruptions occurred in 62% and 84%, respectively, of cabozantinib-treated patients. The median time to first dose reduction was 38 days, and to first dose interruption was 28 days. In the cabozantinib group, 57% of patients had first dose reduction to 40 mg due to an AE, and 13% of patients on the placebo arm had a first dose reduction to 40 mg due to an AE; 33% and 3.0% of patients, respectively, had a second dose reduction to 20 mg due to an AE; 38% of patients received 60 mg as their lowest dose, 29% received 40 mg, and 33% received 20 mg. As allowed per the protocol, 9 patients re-escalated study treatment from 40 mg to 60 mg. The median time on treatment (excluding dose interruptions) for the three respective dose levels was 28, 33, and 73 days.[5,8] The median average daily dose for the cabozantinib group was 35.8 mg, while the median average daily dose for the placebo group was 58.9 mg.[2,3]

The majority of patients (99% in each study arm) used at least one concomitant medication during the trial. Table 6.8 lists the most commonly used drugs. Of note, ACE inhibitors, natural opium alkaloids, and proton pump inhibitors were the most common concomitant medications for both the cabozantinib and placebo groups.

Table 6.8: Summary of frequent medications (≥20% of patients in either treatment arm) (Safety population).

Medication (WHO Preferred Name)	Cabozantinib (N=467) n (%)	Placebo (N=237) n (%)
With at least one medication	462 (99)	234 (99)
ACE inhibitors, plain	96 (21)	33 (14)
Anilides	160 (34)	71 (30)
Paracetamol	152 (33)	69 (29)
Antipropulsives	162 (35)	29 (12)
Loperamide	157 (34)	29 (12)
Dihydropyridine derivatives	155 (33)	62 (26)
Amlodipine	124 (27)	53 (22)
Glucocorticoids	120 (26)	60 (25)
Natural opium alkaloids	190 (41)	106 (45)
Morphine	90 (19)	50 (21)
Nucleoside and nucleotide reverse transcriptase inhibitors	140 (3)	76 (32)
Other opioids	95 (20)	52 (22)
Propulsives	111 (24)	41 (17)
Proton pump inhibitors	234 (50)	106 (45)
Pantoprazole	92 (20)	40 (17)
Sulfonamides, plain	116 (25)	56 (24)
Furosemide	107 (23)	54 (23)
Unspecified herbal and traditional medicine	103 (22)	36 (15)

Source: Clinical Study Report[30]

Patients receiving non-protocol anticancer therapy (NPACT) had to discontinue study treatment upon first day of NPACT. NPACT in this case refers to radiation therapy (other than to bone) or surgery to reset tumor lesions. The incidence of systemic non-radiation and local liver-directed systemic NPACT was 26% in the cabozantinib group and 33% in the placebo group. The incidence of systemic non-radiation NPACT was 25% (n=117) in the cabozantinib group and 30% (n=70) in the placebo group. The incidence of local liver-

directed non-radiation NPACT was 3.2% (n=15) in the cabozantinib group and 5.5% (n=13) in the placebo group.[5]

Subsequent Anti-cancer Therapies

Any non-radiation systemic or local liver directed anticancer therapy was given as a subsequent therapy to 123 (26%) of patients in the cabozantinib group and 78 (33%) of patients in the placebo group. Of these patients 19 (4%) and 4 (2%) of patients received sorafenib after cabozantinib and placebo, respectively. Regorafenib was given as a subsequent anticancer therapy to 11 (2%) and 3 (1%) of patients receiving cabozantinib and placebo, respectively. Anti-PD-1/PD-L1 treatments were given to 23 (5%) of patients in the cabozantinib group and 15 (6%) of patients in the placebo group. Of note, one patient in the cabozantinib arm received lenvatinib as a subsequent treatment. Details regarding the reasons related to patients discontinuation and which patients receiving subsequent therapy were not available. Additional details with respect to subsequent anticancer therapies are summarized in Table 6.9.

Table 6.9: Subsequent Anticancer Therapies:[2]

Table S3. Subsequent Anticancer Therapy

	Cabozantinib (N=470)	Placebo (N=237)
Any non-radiation systemic or local liver-directed anticancer therapy, n (%)	123 (26)	78 (33)
Any systemic anticancer therapy, %	117 (25)	70 (30)
Sorafenib	19 (4)	4 (2)
Regorafenib	11 (2)	3 (1)
Anti-PD-1/PD-L1	23 (5)	15 (6)
Lenvatinib	1 (<1)	0
Cytotoxic chemotherapy	57 (12)	40 (17)
Investigational agent	28 (6)	17 (7)
Any non-radiation local liver-directed anticancer therapy, n (%)	15 (3)	13 (5)

PD-1, programmed death-1; PD-L1, programmed death-ligand 1.

Source: NEJM, Abou-Alfa et al., 379(1):54-63. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[2]

d) Patient Disposition

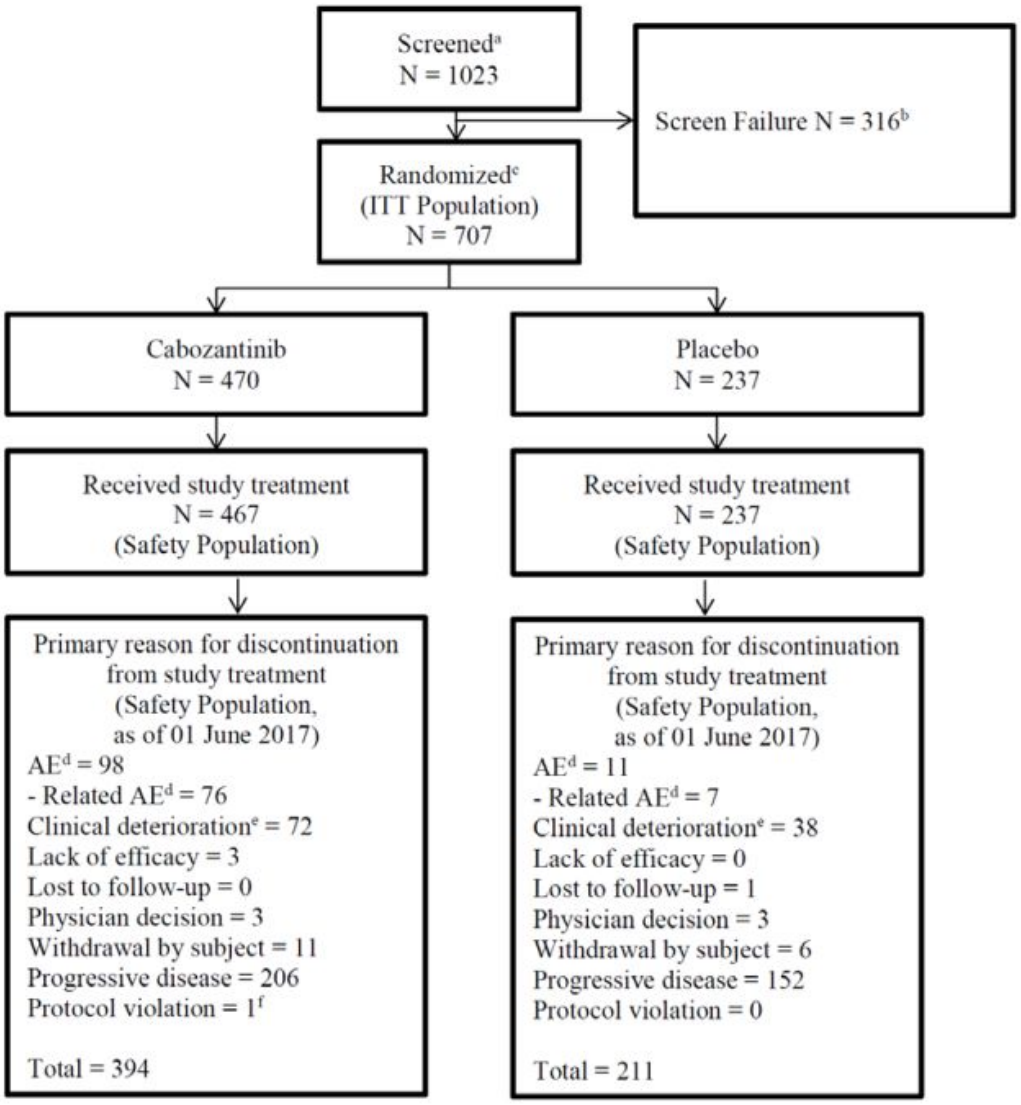
The ITT population was defined as all patients randomized regardless if they received treatment or received the correct treatment while the safety population was defined as all randomized patients that received any amount of treatment (either cabozantinib or placebo). ITT population was used for efficacy analyses (n=707; 470 patients in the cabozantinib arm and 237 patients in the placebo arm) and safety population was used for safety/harms analyses (n=704; 467 patients in the cabozantinib arm and 237 patients in the placebo arm). Three patients in the ITT population were randomised to cabozantinib but no study treatment was given; no justification for why the three patients did not receive treatment was given.[5] This is distinct from the Safety population, which consisted of all randomized patients who received any amount of study treatment. Analyses based on the safety population were performed according to the actual treatment received. Patients

randomized to placebo who received any amount of cabozantinib in error were summarized in the cabozantinib group.

As of June 1, 2017 (cut-off date), 605 patients in the Safety Population discontinued study treatment: 394 patients (84%) in the cabozantinib arm and 211 patients (89%) in the placebo arm. There was a higher rate of treatment discontinuation due to AEs in the cabozantinib arm (21% versus 5% in the placebo arm), including AEs related to study treatment (16% versus 3%). However, there was a higher rate of disease progression in the placebo arm (cabozantinib 44% versus placebo 64).[5,29] Additionally, 73 patients in the cabozantinib group and 26 patients in the placebo group completed study treatment while 397 patients in the cabozantinib group and 211 patients in the placebo group did not complete the study treatment.

The flow of patients through the study and a summary of reasons for study discontinuation is presented in Figure 6.3 below.

Figure 6.3: Flow of participants through the CELESTIAL trial.[5]



AE=adverse event, ITT=intention to treat

Source: EPAR EMA[5]

e) Data Analysis

Eligible patients were randomised in a 2:1 fashion to receive cabozantinib or matched placebo. Randomisation was stratified by the following: Disease aetiology (HBV [with or without HCV], HCV [without HBV], other), geographic region (Asia, Other), extrahepatic disease spread and/or presence of microvascular invasion.

Hypothesis testing was performed using the stratified log-rank test using the same stratification factors as those used to stratify the randomisation, and a 2-sided α=0.05 level of significance.[32] The median duration of OS and the associated 95% CI for each treatment arm was estimated using the Kaplan-Meier method. The stratified HR and its 95% CI were estimated using a Cox proportional hazard model with treatment group as the independent variable.[5]

The study was powered (90% power for a 2-sided log-rank test at 5% level of significance) to detect a 31.6% increase in OS (HR-0.76) and required a sample size od 760 patients for a total of 621 events and two interim analyses.[5]

The multiplicity issue resulting from analysis of OS,PFS and ORR, and planning two interim analyses for testing OS was addressed by using a fixed-sequence testing procedure, modified Bonferroni procedure, and alpha-spending function. All other statistical evaluations of efficacy were considered to be exploratory.[32]

f) Limitations/Sources of Bias

Overall, CELESTIAL was a well-designed double-blind, placebo-controlled RCT. The study objectives were clear, the study has strong randomisation and allocation concealment methods, is adequately powered, and used well validated outcome measures that are relevant to the objectives. Adjustments for multiplicity were planned for the analyses of the efficacy endpoint (OS, PFS and ORR). Patients were stratified appropriately for major clinical factors with the exception of the combination of vascular invasion and extra-hepatic spread. Internal validity is therefore likely strong.

However, in addition to the short follow-up period in the trial, there are some limitations that should be considered when interpreting the results of the trial, affecting either external or internal validity:

- Recruited patients were a selected group with Child Pugh A and ECOG PS 0 or 1, Thus, cabozantinib was not investigated in patients with more advanced liver disease or poor performance status. Patients were required to have progressed on sorafenib prior to study entry. Sorafenib intolerance status was not collected for patients upon study entry and therefore the efficacy in patients who discontinue sorafenib due to intolerability is uncertain.
- Due to the dose modifications for toxicity, the median daily dose was 36 mg of cabozantinib, lower than in the pooled population (41mg) and notably lower than the starting dose of 60mg.
- Although sorafenib intolerance was not a specified patient population requested for reimbursement, sorafenib intolerant patients were a subgroup of interest to the CGP. An ad-hoc analysis for the sorafenib intolerant population was provided by the sponsor based on patients who had tolerated sorafenib <3 months, however, sorafenib intolerance was not pre-defined in the trial and as a result of the exploratory nature of this analysis and lack of pre-defined sorafenib intolerant population, it is difficult to assess with certainty the effect of cabozantinib for this subgroup of interest.
- There was a favorable imbalance in the proportion of patients with macrovascular invasion (MVI): 27% in the cabozantinib group versus 34% in the placebo group. As noted

by CGP, MVI is a prognostic factor. This imbalance may have had an influence on trial outcomes, compromising internal validity.

- As well, the trial did not compare cabozantinib to active therapies of interest (i.e. no direct comparison to relevant active agents such as regorafenib), therefore, direct comparative efficacy and safety data (cabozantinib compared to active therapies) are not available.
- Response rates were investigator assessed and not independently assessed; as a result, there may be a risk of investigator bias.
- Although HRQoL was pre-specified in the protocol, results should be considered exploratory in nature since HRQoL analysis was not considered in the adjustment for multiplicity.
- There may be potential for confounding due to subsequent therapies, however the magnitude and direct of this effect are unknown.

Efficacy Outcomes

A summary of efficacy outcomes of the CELESTIAL study is presented in Table 6.11, with details of each outcome measure provided in subsections below.

Efficacy outcomes

The results presented are based on the data cut-off date of June 1, 2017, at which point 484 deaths had been observed, representing 78% of the 621 deaths planned for the prespecified final analysis. The median follow-up for overall survival was 22.9 months. Results were analysed in the ITT population. Table 6.10 below highlight the key efficacy outcomes from the trial.[5]

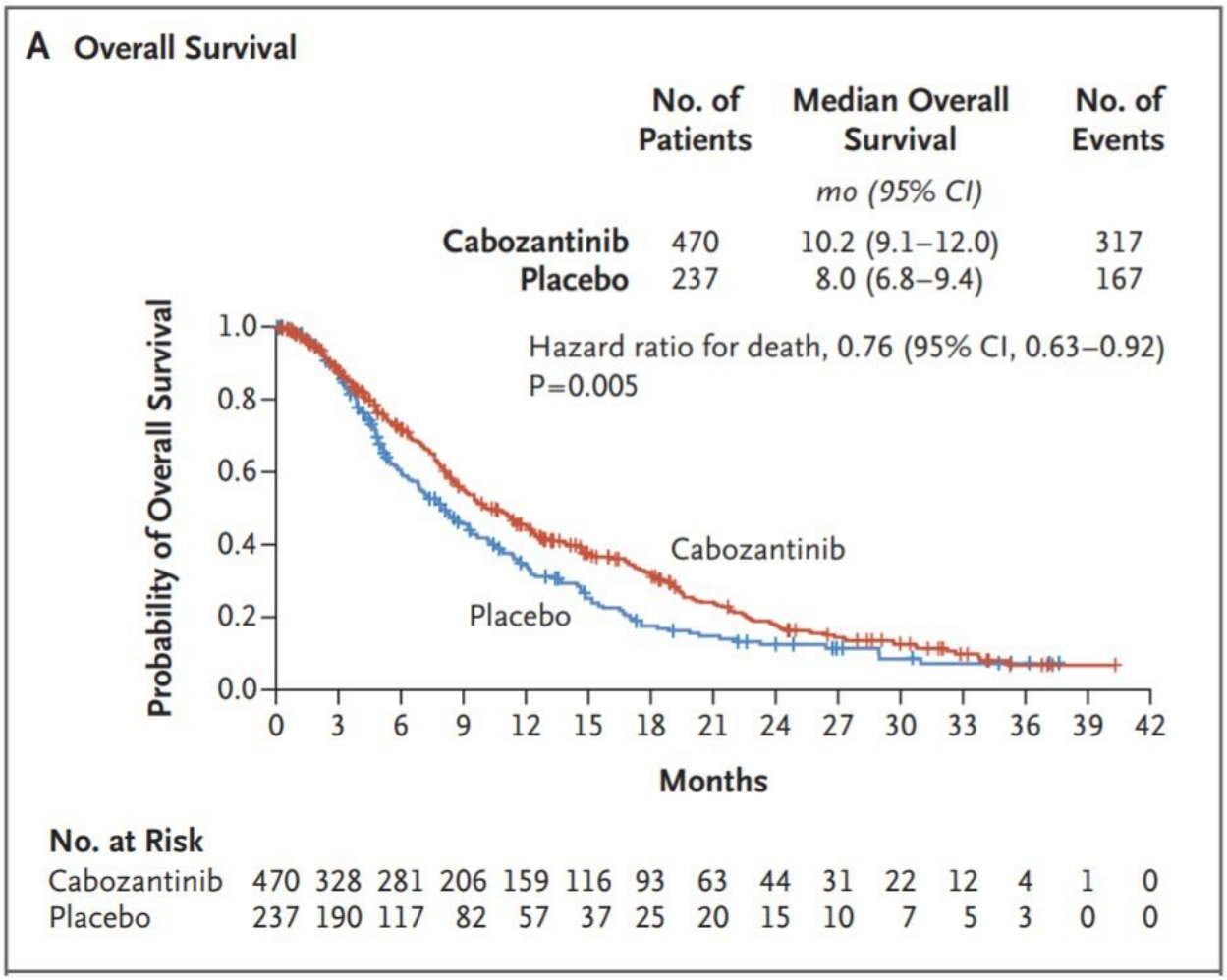
Table 6.10: Summary of efficacy outcomes reported for CELESTIAL trial.

	CELESTIAL	
	Cabozantinib (N=470)	**Placebo (N=237)**
Primary Outcome: OS, median	**10.2 months**	**8.0 months**
HR (95%CI)	**0.76(0.63 to 0.92)**	
p-value	**0.005**	
Key Secondary Outcome: PFS, median	**5.2 months**	**1.9 months**
HR (95%CI)	**0.44(0.36 to 0.52)**	
p-value	**<0.0001**	
Key Secondary Outcome: ORR, %(95%CI)	**4 (2-6)**	**<1 (0-2)**
p-value	**0.009**	

Overall Survival (OS)

Median duration of OS was 10.2 versus 8.0 months in the cabozantinib and placebo groups respectively, an estimated 2.2-month difference in the medians. See Figure 6.5. The landmark estimate of the proportions of patients that were event-free at 12 months was 46% compared with 34%.The statistically significant (p=0.005) adjusted HR was 0.76 (95% CI of 0.63 to 0.92), suggesting that the risk of dying was smaller in the cabozantinib group, compared to the placebo group. The unadjusted HR was 0.77 (95%CI 0.64-0.93), p=0.0072.[5]. At the 6 month landmark analysis, 72% of patients (95% CI 67-76) were alive in the cabozantinib group while 61 % (95% CI 54-67) were alive in the placebo group. Approximately 46% (95% CI 41-50) of patients in the cabozantinib arm were alive at 1 year, while 34% (95% CI 38-41) of patients were alive in the placebo arm. At 18 months, 32% of patients (95% CI 27-37) of patients were alive in the cabozantinib group while 18% (95% CI 12-24) were alive in the placebo group. At 24 months (2 years), 18% (95% CI, 14-22) of patients were alive in the cabozantinib arm and 13% (95% CI 8 – 18) of patients were alive in the placebo arm.[2]

Fig 6.5: Kaplan–Meier Analysis of Overall Survival Survival.[2,3]



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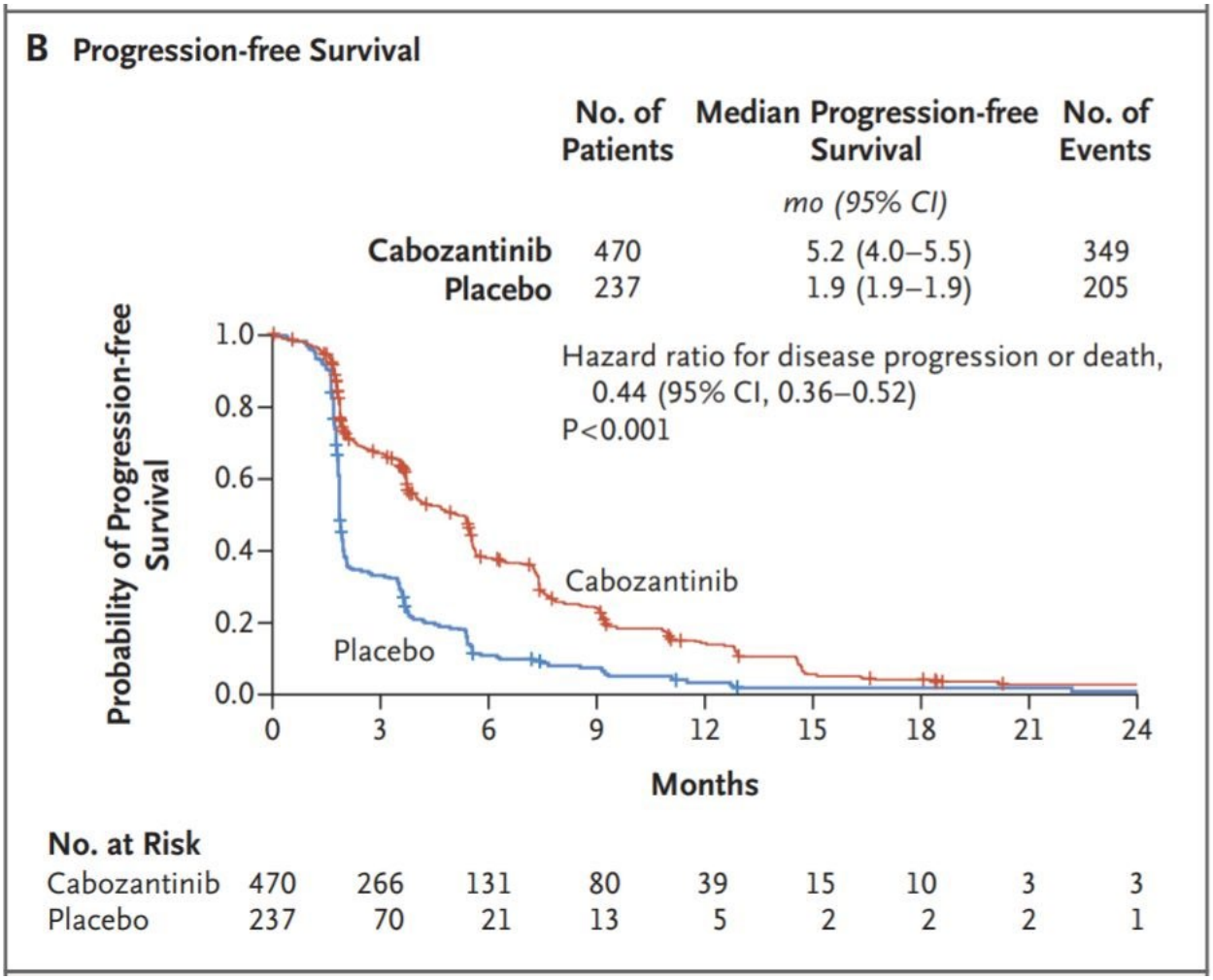
Progression-Free Survival (PFS)

The median duration of PFS was 5.2 months for those patients receiving cabozantinib versus 1.9 months for those receiving placebo. See Figure 6.7 HR (adjusted for stratification factors diseases etiology, geographic region and spread of extrahepatic disease) for PFS was 0.44 (95% CI of 0.36 to 0.52). Because the OS results were statistically significant at the interim analysis PFS, was tested between treatment groups. The stratified log-rank test at the two sided α =0.04 level of significance was used.

Figure 6.7: Kaplan–Meier Analysis of Progression-free Survival.[2]



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The KM PFS curves, especially that for placebo shows a drop at 2 months, the time of the first follow-up assessment. This accounts for >50% of patients in the placebo group.[5]

Table 6.11 Sensitivity Analyses of PFS (ITT Populations)[5]

PFS Analysis	Cabozantinib No. of Events/ Subjects (%) Median Duration (mo)	Placebo No. of Events/ Subjects (%) Median Duration (mo)	Stratified Hazard Ratio	95% CI	Stratified Logrank p-value
Primary analysis, PFS1[a]	349/470 (74) 5.2	205/237 (86) 1.9	0.44	0.36, 0.52	<0.0001
PFS2[b]	374/470 (80) 4.4	211/237 (89) 1.9	0.46	0.38, 0.55	<0.0001
PFS3[c]	356/470 (76) 4.7	207/237 (87) 1.9	0.44	0.37, 0.53	<0.0001

[a] PFS1 analysis: earlier of radiographic progression per RECIST 1.1 or death due to any reason.
[b] PFS2 analysis: the following were PFS events – radiographic progression per RECIST 1.1, death due to any reason, systemic or local liver-directed NPACT, radiation (other than to bone), tumour resection, treatment discontinuation due to clinical deterioration.
[c] PFS3 analysis: the following were PFS events – radiographic progression per RECIST 1.1, death due to any reason, treatment discontinuation due to clinical deterioration

Source: EPAR EMA[5]

Efficacy Outcomes for the Sorafenib Intolerant Patients from CELESTIAL

At the request of CADTH, the sponsor provided efficacy data for patients receiving cabozantinib based on prior treatment and duration of treatment with sorafenib. It should be noted that this was a post-hoc analysis. Table 6.12 below summarizes the overall survival of patients based on duration of treatment of sorafenib further broken down by <3 months, 3-6 months, and ≥ 6 months. Overall, median OS and PFS was higher in patients whose duration of sorafenib treatment was longer.

Table 6.12: Overall Survival and Progression Free Survival with Prior Sorafenib[8]

	Prior Sorafenib Only		**Duration of Treatment of Prior Sorafenib**					
			<3 months		**3 to <6 months**		**≥6 months**	
	Cabo N=331	**Pbo N=164**	**Cabo N=89**	**Pbo N=47**	**Cabo N=98**	**Pbo N=43**	**Cabo N=143**	**Pbo N=74**
Median OS s(Months)	11.3	7.2	8.9	6.9	11.5	6.5	12.3	9.2
OS HR (95% CI)	0.70 (0.55-0.88)		0.72 (0.47 – 1.10)		0.65 (0.43-1.00)		0.82 (0.58-1.16)	
Median PFS (Months)	5.5	1.9	3.8	1.8	5.4	1.9	5.7	1.9
PFS HR (95% CI)	0.40 (0.32-0.50)		0.35 (0.23-0.52)		0.37 (0.25-0.56)		0.48 (0.35-0.67)	

cabo = cabozantinib; CI = confidence interval; HR = hazard ratio; OS = overall survival; PFS = progression-free survival; pbo = placebo.
Source: Ipsen[8]

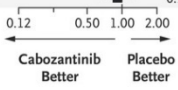
OS and PFS in Subgroups

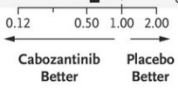
The incidence of systemic non-radiation and local liver-directed systemic non-protocol anticancer therapy (NPACT) was 26% in the cabozantinib and 33% in the placebo groups. These patients had to discontinue treatment but were included in the per protocol analysis.

There was a generally consistent effect with the overall population on OS with HRs <1 across most subgroups with ≥20 patients in each group. No OS benefit was observed in patients from the Asian region (HR=1.01, 95% CI: 0.68, 1.48), with HCV but without HBV (HR=1.11, 95% CI: 0.72, 1.71), and patients without extrahepatic spread and/or macrovascular invasion (HR=0.99, 95% CI: 0.59, 1.65). See Figure 6.6 for a forest plot of overall survival and progression-free survival.

Figure 6.6: Overall Survival and Progression-free Survival in Selected Subgroups.[2]

Subgroup	No. of Patients		Overall Survival			Progression-free Survival		
	Cabozantinib	Placebo	Cabozantinib (no. of events)	Placebo (no. of events)	Hazard Ratio for Death (95% CI)	Cabozantinib (no. of events)	Placebo (no. of events)	Hazard Ratio for Disease Progression or Death (95% CI)
Overall	470	237	317	167	0.76 (0.63–0.92)	349	205	0.44 (0.36–0.52)
Age								
<65 yr	240	124	159	86	0.81 (0.62–1.05)	179	107	0.45 (0.35–0.57)
≥65 yr	230	113	158	81	0.74 (0.56–0.97)	170	98	0.46 (0.35–0.59)
Sex								
Male	379	202	254	143	0.79 (0.64–0.97)	285	175	0.49 (0.40–0.59)
Female	91	35	63	24	0.68 (0.42–1.09)	64	30	0.31 (0.20–0.49)
ECOG performance-status score								
0	245	131	154	93	0.69 (0.53–0.89)	184	118	0.39 (0.31–0.50)
1	224	106	162	74	0.87 (0.66–1.14)	164	87	0.54 (0.41–0.70)
Alpha-fetoprotein								
<400 ng/ml	278	136	175	89	0.81 (0.62–1.04)	199	115	0.47 (0.37–0.60)
≥400 ng/ml	192	101	142	78	0.71 (0.54–0.94)	150	90	0.42 (0.32–0.55)
Geographic region								
Asia	116	59	79	38	1.01 (0.68–1.48)	86	50	0.46 (0.32–0.67)
Other region	354	178	238	129	0.71 (0.57–0.88)	263	155	0.45 (0.37–0.56)
Race								
Asian	159	82	112	56	0.86 (0.63–1.19)	117	71	0.43 (0.32–0.58)
Non-Asian	280	143	185	102	0.75 (0.59–0.96)	209	124	0.47 (0.38–0.59)
EHS or MVI, or both								
Yes	398	200	272	145	0.73 (0.60–0.90)	298	174	0.45 (0.37–0.54)
No	72	37	45	22	0.99 (0.59–1.65)	51	31	0.46 (0.29–0.74)
EHS								
Yes	369	182	251	135	0.72 (0.58–0.89)	276	159	0.46 (0.37–0.56)
No	101	55	66	32	0.96 (0.63–1.46)	73	46	0.45 (0.31–0.66)
MVI								
Yes	129	81	103	61	0.75 (0.54–1.03)	101	72	0.42 (0.31–0.58)
No	339	156	213	106	0.80 (0.64–1.01)	246	133	0.48 (0.38–0.59)
Etiologic factor								
HBV (with or without HCV)	178	89	123	63	0.69 (0.51–0.94)	132	77	0.31 (0.23–0.42)
HCV (without HBV)	105	51	67	30	1.11 (0.72–1.71)	76	44	0.61 (0.42–0.88)
Other (without HBV or HCV)	187	97	127	74	0.72 (0.54–0.96)	141	84	0.48 (0.36–0.63)
No. of previous systemic regimens								
1	335	174	223	121	0.74 (0.59–0.92)	252	152	0.43 (0.35–0.52)
2	130	62	90	45	0.90 (0.63–1.29)	94	52	0.58 (0.41–0.83)





Source: NEJM, Abou-Alfa et al., 379(1):54-63. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[2]

Objective Response Rate (ORR)

In the cabozantinib group, n=18 (4%) patients had a BOR (Best Overall Response) of PR (Partial Response) compared with n=1 (0.6%) patients in the placebo group (p=0.0059). The rate of stable disease in the cabozantinib group was higher than placebo (60% versus 33%) and in line with regorafenib (65% versus 36%). Conversely, more patients in the placebo group had progressive disease as BOR (21% cabozantinib versus 55% placebo). See Table 6.13 for a summary of objective response rates per investigator.

Table 6.13: Objective Response Rate per Investigator (ITT Population).[5]

	Cabozantinib (N = 470)	Placebo (N = 237)
Best overall response, n (%)[a]		
Confirmed complete response (CR)	0	0
Confirmed partial response (PR)	18 (4)	1 (0.4)
Stable disease (SD)	282 (60)	78 (33)
Unconfirmed PR (uPR)	13 (3)	2 (0.8)
Progressive disease (PD)	98 (21)	131 (55)
Missing	72 (15)	27 (11)
No post-baseline assessments	65 (14)	22 (9)
No qualifying post-baseline assessment on/ before the primary PFS analysis censoring or event date	7 (1)	5 (2)
Objective response rate (CR+PR), n (%)	18 (4)	1 (0.4)
95% CI	(2.3, 6.0)	(0.0, 2.3)
Treatment difference (cabozantinib - placebo) (95% CI)[b]	3.4 (1.49, 5.33)	
Critical p-value to reject null hypothesis of equal ORR	0.01	
Observed stratified CMH test p-value per IxRS[c]	0.0086	
Observed unstratified Fisher exact test p-value	0.0059	
Unstratified odds ratio per IxRS (95% CI)	9.4 (1.2, 70.8)	
Stratified odds ratio per IxRS (95% CI)[c]	9.4 (1.2, 71.0)	

a Best overall response was assessed based on RECIST 1.1 criteria and was calculated based on subjects in the ITT population. A CR or PR was not considered as an objective response if a subject progressed or received subsequent anti-cancer therapy prior to the first CR or PR. To be classified as a CR or PR, confirmation of response must have occurred > 28 days after the response was first observed.
b Using asymptotic confidence limits based on large number theorem
c Stratification factors (per IxRS) as described previously

Source: EPAR EMA[5]

Quality of Life

Health Related and Quality of Life

EuroQol Health questionnaire (EQ-5D-5L)

HRQoL was assessed as an exploratory endpoint in the CELESTIAL trial, using the EuroQoL 5D 5-level instrument (EQ-5D-5L), which provides a generic measure of HRQoL. EQ-5D-5L comprises of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The patient is asked to indicate his/her health state by ticking identifying the most appropriate statement in each of the five dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. Those digits are then combined into a 5-digit number that describes the patient's health state. Patients completed the questionnaire at baseline, every four weeks until week 25, followed by every 8 weeks until radiographic assessments discontinued.[5]

As well, a visual analogue scale (VAS), on which patients were to quantitate their health between 100 ("the best health you can imagine") and 0 ("the worst health you can imagine") was applied.

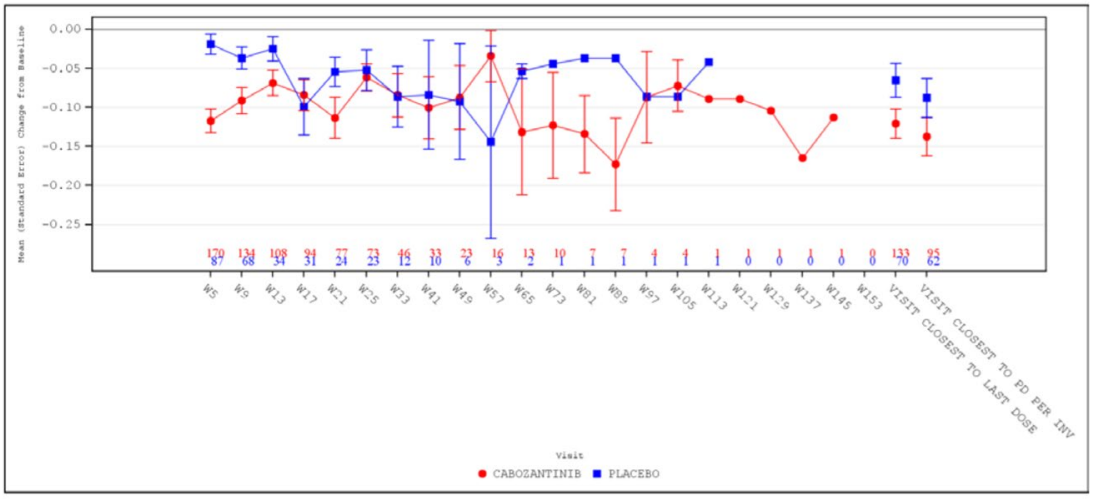
An effect size for change from baseline equal to or greater than 0.3 was considered potentially clinically meaningful and the minimal important difference established in the literature was between 0.06 and 0.8 for EQ-Index and 7 for the EQ-VAS.

The EQ-5D-5L questionnaire completion rate (number of patients who completed all questions/patients still on study) was >85% in each treatment group until week 33, after which there were n<20 of patients in the placebo group completed the questionnaire. The largest

treatment difference post-baseline occurred at week 5 for mobility and usual activities; the effect size differences was in favour of placebo of 0.51 and 0.55 respectively, indicating a potentially clinically meaningful change from baseline. The proportion of patients in the cabozantinib and placebo group with any problem at week 5 was 61% compared to 32% for mobility and 68% compared to 43% for usual activities.[5]

At baseline, the mean EQ-Index scores were 0.792 in the cabozantinib group compared to 0.855 in the placebo group. At week 5, EQ-Index change from baseline was -0.117 in the cabozantinib group compared with -0.019 in the placebo group, favouring placebo. After which, the difference in mean change from baseline with respect to EQ-Index values were not considered clinically meaningful (<0.06) through Week 25 (beyond Week 25, there were less than 20 patients in the placebo group).[5] Refer to Figure 6.7.

At baseline, the mean EQ-VAS scores were similar among the two groups 73.5 in the cabozantinib group compared to 76.1 in the placebo group. Difference in mean change from baseline with respect to EQ-VAS values were not considered clinically meaningful (<7) through Week 33 (beyond Week 33, there were less than 20 patients in the placebo group).[5] Refer to Figure 6.8.[15]

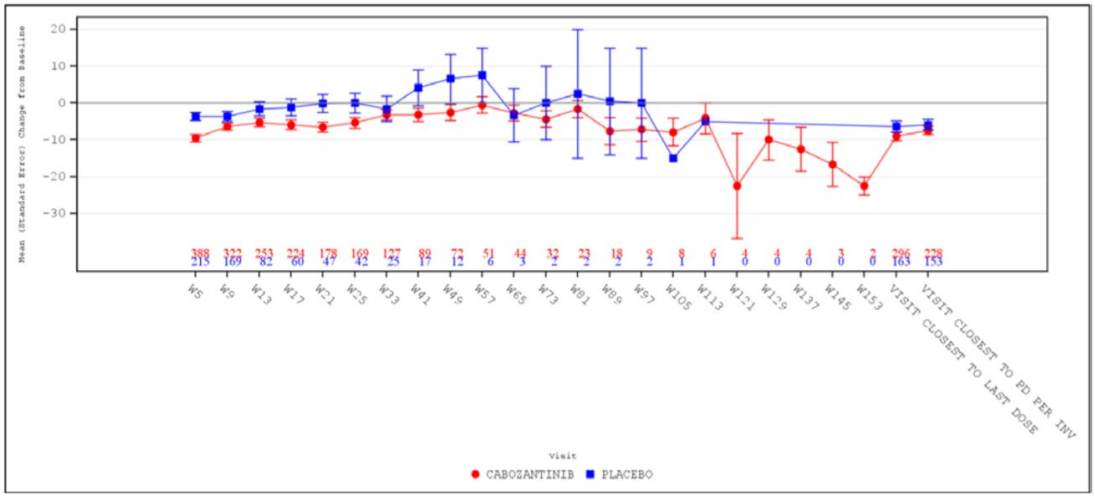


EQ-Index is scored from 0 to 1. A higher score indicates better health-related quality of life status. Number of subjects at baseline with EQ-Index scores - 206 in the cabozantinib and 96 in the placebo arm

Figure 6.7: Mean (± Standard Error) Change from Baseline of EQ-Index Score (ITT Population; Countries which EQ-Index is Validated).[5]

Source: EPAR EMA[5]

Figure 6.8: Mean (± Standard Error) Change from Baseline of EQ-VAS Score (ITT Population).[5]



EQ-VAS is scored from 0 (worst health you can imagine) to 100 (best health you can imagine).
Original number of subjects at baseline was 452 (cabozantinib) and 234 (placebo)

Source: EPAR EMA[5]

Harms Outcomes

As per the safety analysis population, there were 704 patients who received study treatment, 467 in the cabozantinib and 237 in the placebo group. The rate of discontinuation of treatment due to adverse events (AEs) that were considered to be related to treatment was 16% (n=76) in the cabozantinib group and 3% (n=7) in the placebo group. Adverse events that occurred at ≥ 10% were higher in the cabozantinib group compared to the placebo group. The most common AEs in ≥ 10% of patients leading to treatment discontinuation in patients in the cabozantinib group were palmar-plantar erythrodysesthesia (n=11, 2.4%), fatigue (n=7,1.5%), decreased appetite (n=5, 1.1%), diarrhea (n=5, 1.1%), and nausea (n=5, 1.1%).[30] Approximately 82 (18%) of patients in the cabozantinib group and 14 (5.9%) of patients in the placebo group had treatment-related serious adverse events. Grade 3 or 4 adverse events were reported in 316 (68%) of patients in the cabozantinib group versus 86 (36%) of patients in the placebo group. See Table 6.14 for frequent adverse events.

Death was slightly less frequent in the cabozantinib group (317, 67%) versus placebo (167, 70%) using the ITT population. While 99% (n=460) of cabozantinib and 92% (n=219) of placebo patients experienced any AE, serious AEs were more frequent in the cabozantinib group (50% versus 37%). Similarly, treatment-related serious AEs were more frequent in the cabozantinib group (18% versus 5.9%).[30] Harms outcomes are summarized in Table 6.14.

Table 6.14: Adverse Events Reported in at Lease 10% of Patients in the Cabozantinib and Placebo Group.[2]

Event	Cabozantinib (N=467)			Placebo (N=237)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Any adverse event	460 (99)	270 (58)	46 (10)	219 (92)	80 (34)	6 (3)
Diarrhea	251 (54)	45 (10)	1 (<1)	44 (19)	4 (2)	0
Decreased appetite	225 (48)	27 (6)	0	43 (18)	1 (<1)	0
Palmar–plantar erythrodysesthesia	217 (46)	79 (17)	0	12 (5)	0	0
Fatigue	212 (45)	49 (10)	0	70 (30)	10 (4)	0
Nausea	147 (31)	10 (2)	0	42 (18)	4 (2)	0
Hypertension	137 (29)	73 (16)	1 (<1)	14 (6)	4 (2)	0
Vomiting	121 (26)	2 (<1)	0	28 (12)	6 (3)	0
Increase in aspartate aminotransferase level	105 (22)	51 (11)	4 (1)	27 (11)	15 (6)	1 (<1)
Asthenia	102 (22)	31 (7)	1 (<1)	18 (8)	4 (2)	0
Dysphonia	90 (19)	3 (1)	0	5 (2)	0	0
Constipation	87 (19)	2 (<1)	0	45 (19)	0	0
Abdominal pain	83 (18)	7 (1)	1 (<1)	60 (25)	10 (4)	0
Weight loss	81 (17)	5 (1)	0	14 (6)	0	0
Increase in alanine aminotransferase level	80 (17)	23 (5)	0	13 (5)	5 (2)	0
Mucosal inflammation	65 (14)	8 (2)	0	5 (2)	1 (<1)	0
Pyrexia	64 (14)	0	0	24 (10)	1 (<1)	0
Upper abdominal pain	63 (13)	3 (1)	0	31 (13)	0	0
Cough	63 (13)	1 (<1)	0	26 (11)	0	0
Peripheral edema	63 (13)	4 (1)	0	32 (14)	2 (1)	0
Stomatitis	63 (13)	8 (2)	0	5 (2)	0	0
Dyspnea	58 (12)	15 (3)	0	24 (10)	1 (<1)	0
Rash	58 (12)	2 (<1)	0	14 (6)	1 (<1)	0
Ascites	57 (12)	17 (4)	1 (<1)	30 (13)	11 (5)	0
Dysgeusia	56 (12)	0	0	5 (2)	0	0
Hypoalbuminemia	55 (12)	2 (<1)	0	12 (5)	0	0
Headache	52 (11)	1 (<1)	0	16 (7)	1 (<1)	0
Thrombocytopenia	52 (11)	16 (3)	0	1 (<1)	0	0
Insomnia	49 (10)	1 (<1)	0	17 (7)	0	0
Dizziness	48 (10)	2 (<1)	0	15 (6)	0	0
Dyspepsia	47 (10)	0	0	7 (3)	0	0
Anemia	46 (10)	18 (4)	1 (<1)	19 (8)	12 (5)	0
Back pain	46 (10)	5 (1)	0	24 (10)	1 (<1)	0
Increase in serum bilirubin level	45 (10)	10 (2)	4 (1)	17 (7)	2 (1)	2 (1)
Decrease in platelet count	45 (10)	13 (3)	4 (1)	7 (3)	2 (1)	0

* Listed are adverse events, regardless of causality, that were reported in at least 10% of patients in either group. Severity was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

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6.4 Ongoing Trials

No ongoing trials meeting our search criteria were found.

7 SUPPLEMENTAL QUESTIONS

7.1 Critical Appraisal of the Sponsor submitted MAIC comparing cabozantinib versus regorafenib

7.1.1 Objective

To summarize and critically appraise the methods and findings of the sponsor-submitted match-adjusted indirect comparison (MAIC) of cabozantinib versus regorafenib for second-line treatment of advanced hepatocellular carcinoma (HCC) in patients who have received sorafenib in the first line.[34] As seen in Section 6 Systematic Review, no RCT comparing cabozantinib with regorafenib were identified in the search.

7.1.2 Findings

Objectives and Scope of ITC

PAG identified regorafenib as a relevant comparator and indicated interest in data comparing cabozantinib with regorafenib. As well, PAG was seeking guidance on what clinical scenarios would cabozantinib or regorafenib be the preferred treatment for HCC after prior therapy.

Due to a lack of head to head trials evaluating cabozantinib and regorafenib, the sponsor submitted a MAIC to estimate the efficacy and safety of cabozantinib versus regorafenib in order to inform their cost-effectiveness model.

Overall survival, progression-free survival, and grade 3-4 treatment emergent drug related adverse events affecting at least 5% of patients in any arm of either trial were considered.

Systematic Literature Review

According to the sponsor, a systematic literature review was conducted to identify the relevant studies for the comparison. Upon request, the sponsor provided the systematic literature review report. The sponsor noted that the systematic literature review was conducted prior to the publication of the CELESTIAL trial. The Methods team consider this (i.e. CELESTIAL was noted included in the systematic literature review report) a limitation of the submitted systematic literature review report and the recommended approach would have been to update the report to include a new cut-off date thereby including the CELESTIAL trial in the report, so that the trials (including CELESTIAL) could be compared. The Methods team noted that it is unclear if the author did a comprehensive comparison of the two trials (RESORCE and CELESTIAL) as well as if a quality assessment on CELESTIAL trial was done. The main analysis for the indirect comparison submitted by the sponsor was based on the results of two trials: the CELESTIAL trial[2] that compared cabozantinib (n=470) to placebo (n=237) and the RESORCE trial[12,35] that compared regorafenib (n=379) to placebo (n=194).

ITC Feasibility Assessment

The sponsor assessed whether a valid indirect treatment comparison (ITC) approach (e.g. Bucher) to indirectly compare cabozantinib and regorafenib was feasible. First, the sponsor explained that the two identified trials were very similar in study designs (i.e., both trials were double blinded, placebo controlled RCTs). Then, the sponsor acknowledged that there were considerable differences in the patient characteristics between the two identified studies:

1) differences in baseline characteristics between the trials: ethnic mix, region, ECOG performance status, number of prior treatments and duration of prior sorafenib treatment;

2) the RESORCE trial included sorafenib tolerant patients (i.e. excluded sorafenib-intolerant patients), whereas the CELESTIAL trial included both sorafenib tolerant and sorafenib-intolerant patients;
3) the RESORCE trial included only patients that had progressed on sorafenib in the first line (i.e. patients with prior therapies except sorafenib were excluded), whereas the CELESTIAL trial excluded patients with more than two prior therapies (i.e. prior therapy was not limited to sorafenib in the first line). In other words, the CELESTIAL trial included second and third line patients, while the RESORCE trial included only second line patients who progressed on sorafenib in the first line.

As a result, due to considerable differences in the patient characteristics between the two identified studies, the sponsor concluded that an indirect treatment comparison using the entire CELESTIAL trial population could not be performed. The sponsor also assessed potential effect modifiers in the second line only patient population of CELESTIAL and compared them to patients in RESORCE; the sponsor found that there remained differences in ethnic mix, region, ECOG performance status, and duration of prior sorafenib treatment and because of this, the sponsor concluded that an indirect treatment comparison using the second line only patient population of CELESTIAL could not be performed as a result of the variation in the patient characteristics. Therefore, the sponsor chose to conduct a MAIC, as it provides a method of comparing absolute treatment effects while reducing the risk of bias associated with naïve unadjusted comparisons and adjusts for heterogeneity (i.e. potential biases related to treatment effect modifiers).

Since third line patients were not included in the RESORCE trial, only second line patients from the CELESTIAL trial were included in the MAIC. Of the 707 patients in CELESTIAL that were randomized (470 patients assigned to cabozantinib and 237 assigned to placebo), 495 patients represented the pure second line population of CELESTIAL (i.e., who received second-line therapy after sorafenib as the only prior therapy; 331 in the cabozantinib group and 164 in the placebo group). It is important to note, however, that there were other differences in inclusion/exclusion criteria of the trials that were not addressed in the MAIC (i.e., third line population or patients who are sorafenib-intolerant).

Methods

The sponsor identified a total of 13 baseline characteristics available for matching: gender, age, geographical region, ECOG performance, Child-Pugh class, duration of prior sorafenib treatment, extrahepatic disease, macrovascular invasion, aetiology of HCC (Hepatitis B, alcohol use and Hepatitis C), AFP level, and race. The sponsor considered two scenarios to assess the impact of choosing different baseline characteristics for matching: 1) based on clinical expert consultation for prognostic variables of PFS, OS and AEs (which was considered as the base case) and 2) baseline characteristics selected for matching using an automatic variable selection method (which was considered the sensitivity analysis).[34] In the base case, weighting was based upon the following baseline characteristics: age, geographical region, ECOG performance, Child-Pugh class, duration of prior sorafenib treatment, extrahepatic disease, macrovascular invasion, aetiology of HCC (Hepatitis B, alcohol use and Hepatitis C), AFP level, and race;[6] Of note, it is unclear if a literature search was performed to identify prognostic and effector modifiers prior to the selection of available baseline characteristics for matching or clinical expert consultation. However, the CGP agreed that these were appropriate prognostic variables and effect modifiers for matching and that no other prognostic factors were missing. Only results of the base case are presented since the base case was considered in the economic model and a stepwise approach for identifying effect modifiers is data driven and not a recommended approach to effect modifier selection.[36] The reported results are taken from a poster by Kelly et al.[6]

Survival Outcomes

In a poster by Kelly et al.,[6] overall PFS and OS based on Kaplan-Meier plots were compared between cabozantinib (weighted population of patients in CELESTIAL who had received sorafenib as

the only first line therapy) and regorafenib. Using only patients who had received sorafenib as the only prior therapy, median PFS and OS for cabozantinib and placebo from weighted CELESTIAL Kaplan-Meier plots and median PFS and OS for regorafenib and placebo in RESORCE from published literature were reported. As well, median PFS and OS with cabozantinib (weighted population of patients who had received sorafenib as the only prior therapy in CELESTIAL) and regorafenib were compared based on fitted and extrapolated Kaplan-Meier plots [parametric models were fitted to the individual-level data (for PFS: generalised gamma; for OS: log-logistic based on Akaike information criterion, Bayesian information criterion, and validation through visual assessment) since the proportional hazards assumption between regorafenib and cabozantinib was violated].[34]

Safety Outcomes

The safety outcomes included hypertension, increased aspartate aminotransferase (AST), fatigue, diarrhoea, palmer-plantar erythrodysesthesia (PPE) and elevated bilirubin; these were based on frequencies of grade 3 or 4 drug-related treatment-emergent adverse events (TEAEs) affecting > 5% of patients in any group of CELESTIAL or RESORCE. Using log scale odds ratios (ORs), an anchored approach for AST, fatigue, and elevated bilirubin; and an unanchored approach for diarrhoea and PPE were performed to compare cabozantinib and regorafenib.[6] It is worth noting that since there were no occurrence of diarrhea or PPE in the placebo group, an unanchored approach was necessary; and that prognostic factors were not identified and included for the unanchored analyses.

Results

Baseline characteristics of patients

Table 7.1 includes a summary of sample sizes and baseline characteristics of patients assessed in this MAIC. After matching, baseline characteristics appear to be balanced across trials for the selected prognostic factors and effect modifiers, except for the proportion of females.

Table 7.1 - Sample sizes and baseline characteristics of patients.[6]

	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

[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 group.

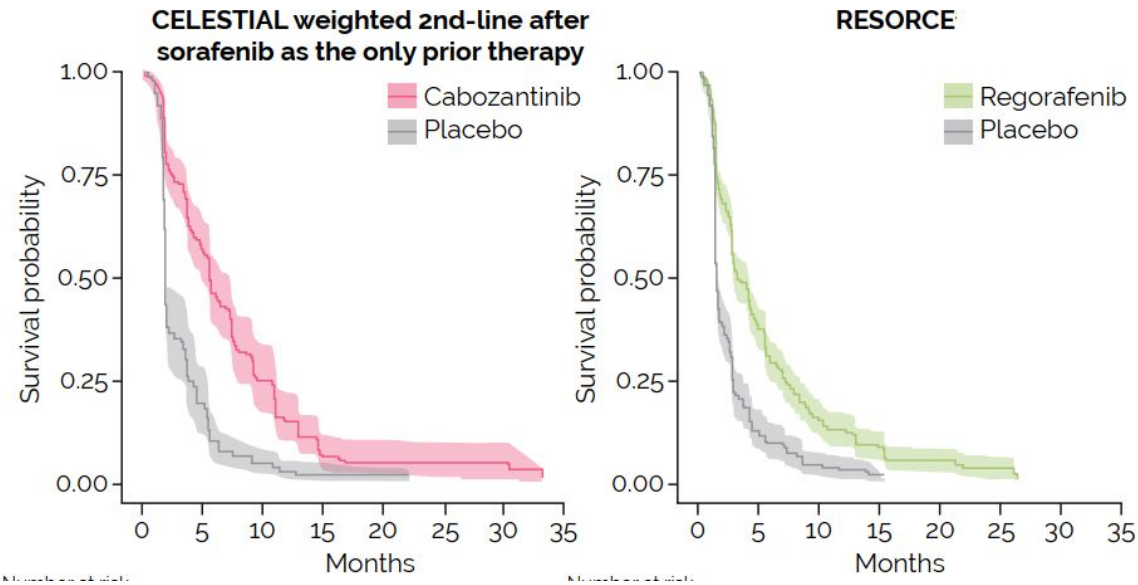
Source: ILCA poster[6]

Note: The table has a reporting error, the column stated" 2nd-line after sorafenib only[a,c] (weighted") is not related to RESORCE and instead is related to CELESTIAL. Therefore, when interpreting the baseline characteristics, "2nd-line after sorafenib only[a,c] (weighted)" should be compared to "As reported."

Progression Free Survival (PFS)

The median PFS was 5.6 months (95% CI=4.9–7.3) for weighted cabozantinib versus 1.9 months (95% CI=1.9–2.1) for weighted placebo; similarly, in RESORCE the median PFS was 3.1 months (95% CI=2.8–4.2) for regorafenib and 1.5 months (95% CI=1.4–1.6) for placebo.

Figure 7.1: Kaplan-Meier plots for progression-free survival.[6]

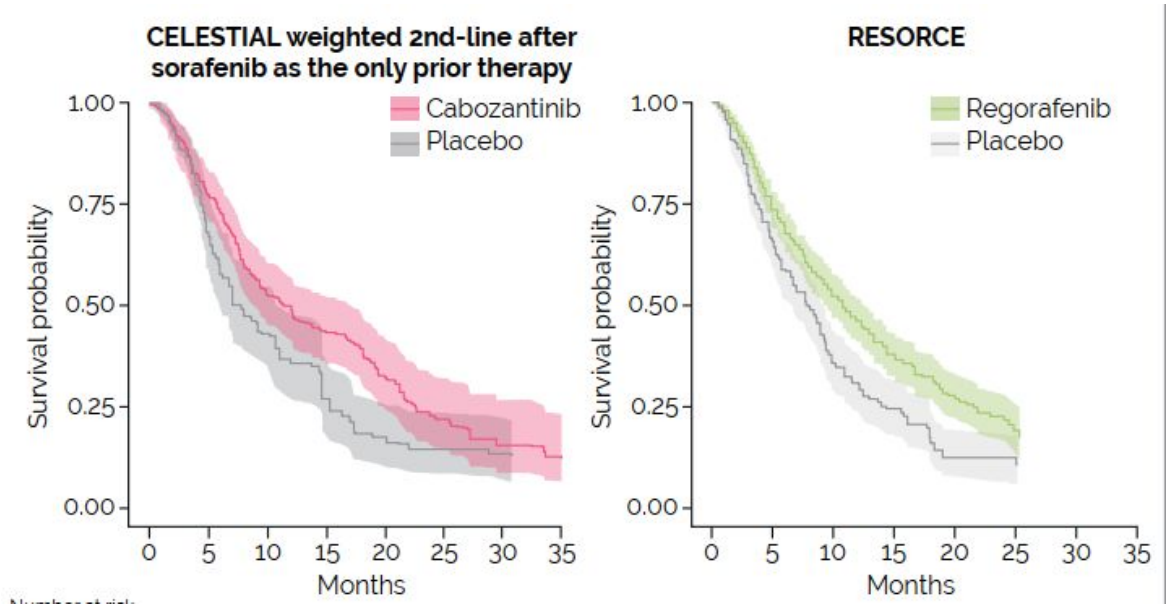


Source:ILCA poster[6]

Overall Survival (OS)

The difference in OS for weighted cabozantinib versus regorafenib was not statistically significant (p = 0.3474; non-placebo-adjusted comparison). Median OS was 11.4 months (95% CI=8.9–17.0) for weighted cabozantinib months versus weighted placebo, 7.2 months (95% CI=6.1–10.8); while median OS was 10.6 months (95% CI=9.1–12.1) for regorafenib versus placebo, 7.8 months (95% CI=6.3–8.8). Figure 7.2 presents the survival curves of the two trials for OS.

Figure 7.2: Kaplan-Meier plots for overall survival.[6]

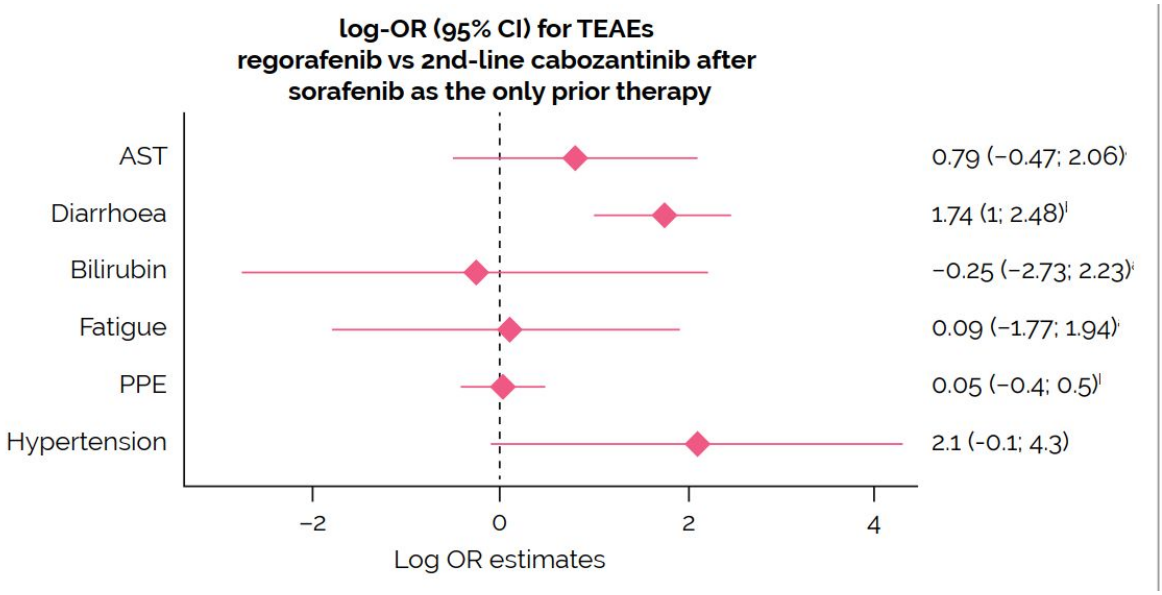


Source: ILCA poster[6]

Safety

No differences were found between cabozantinib and regorafenib with respect to the following TRAEs: hypertension, AST, fatigue, PPE and bilirubin. The sponsor noted that in anchored (placebo-adjusted) analysis, ORs were large and 95% Cis were wide which may be due to low numbers of events, particularly in the CELESTIAL placebo arm. By using the unanchored (non-placebo-adjusted) analyses, rates of diarrhoea were significantly lower with regorafenib than with cabozantinib..[6] This is depicted in Figure 7.3 which shows the log-odds of treatment-emergent adverse events.

Figure 7.3: frequency of grade ≥3 related TEAEs in >5% of patients.[6]



Source: ILCA poster[6]

Conclusions and Critical Appraisal

Kelly et al. acknowledged that bias due to an imbalance in unobserved factors may still occur in MAIC even after matching and that a MAIC cannot control for confounding and bias to the same extent as randomization would.[6]

Kelly et al. also acknowledged the following limitations:

- Residual confounding may have been introduced by other systematic differences, such as the differences in patients' adherence to treatment.

- Within-study randomisation was not respected since comparisons of survival estimates were unanchored.

- CELESTIAL and RESORCE were only powered to compare OS; the trials were not powered to compare PFS and TEAE rates. As well, statistical power is further reduced by the removal of cases through the MAIC method.[6]

Apart from the limitations noted above, the Methods Team identified the following additional limitations and considerations to the MAIC:

- The methodology used for the statistical comparison between the median OS and PFS estimates in the cabozantinib and regorafenib treatment arms is unclear and as a result, any conclusive statements about the comparative effectiveness of the two drugs is not recommended.[6]

- The MAIC is unanchored for the median OS and PFS. Unanchored estimates of log odds ratios were performed for diarrhea and PPE since there were no occurrence of diarrhea or PPE in the placebo group. The unanchored approach assumes that all treatment effect modifiers and prognostic variable are accounted for[7]; therefore, results should be interpreted with this in mind. The recommended approach for identifying prognostic factors and effect modifiers is to begin with the literature and clinical experts' opinion, followed by what is available from the trial, and noting what prognostic factors and effect modifiers were not included (because they were not available) but should be considered. It appears that a different approach for the MAIC was used. First, baseline characteristics available for matching were identified, followed by the clinical expert opinion. It is worth noting however that the CGP confirmed that the prognostics factors included for matching were appropriate and there were no other missing prognostic factors.

- The population in the MAIC is not representative of the entire requested reimbursement population: adults with hepatocellular carcinoma after prior therapy. Therefore, conclusions should be limited to the population in the MAIC (i.e., second line population, after treatment with sorafenib as prior systemic therapy) and not generalizable to the entire requested reimbursement population.

- Moreover, the population in the MAIC does not use the entire CELESTIAL population: it does not include patients with more than 2 prior therapies except for prior sorafenib, or third line patients. Additionally, because sorafenib intolerance was not prespecified in the CELESTIAL trial, information pertaining to this population is uncertain. Therefore, conclusions should be limited to the population in the MAIC (i.e., second line population, after treatment with sorafenib as a prior systemic therapy) and not generalizable to the entire CELESTIAL population.

- The large difference (>45%) in effective sample size compared to the original sample size, suggests that the trial populations are too different to compare.[7]

- The sponsor noted that the systematic literature review was conducted prior to the publication of the CELESTIAL trial. The Methods team consider this (i.e. CELESTIAL was noted included in the systematic literature review report) a limitation of the submitted systematic literature review report and the recommended approach would have been to update the report to include a new cut-off date thereby including the CELESTIAL trial in the report, so that the trials (including CELESTIAL) could be compared. The Methods team noted that it is unclear if the author did a comprehensive comparison of the two trials (RESORCE and CELESTRIAL) as well as if a quality assessment on CELESTRAL trial was done.

- As well, there is insufficient detail to understand what design differences are unaccounted for and remain potential sources of bias in the MAIC.

- Other important outcomes identified in the systematic review protocol (Section 6), such as health-related quality of life, ORR, SAEs, WDAEs were not assessed.

- It is worth noting that the proportional hazards assumption was not satisfied; therefore, it cannot be assumed that the hazard ratios are constant, rather it must be assumed that hazard ratios are time dependent.

Given the limitations and considerations noted above, the results of this MAIC should be interpreted with caution. An RCT comparing cabozantinib and regorafenib (in the same population) is required in order to determine the comparative efficacy of cabozantinib and regorafenib.

8 COMPARISON WITH OTHER LITERATURE

None identified.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Gastrointestinal Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on cabozantinib for HCC. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Gastrointestinal Clinical Guidance Panel is comprised of 3 oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via Ovid platform

Database(s): Cochrane Central Register of Controlled Trials (CENTRAL); Embase (1974 to present); MEDLINE All (1946 to present)

#	Searches	Results
1	(Cabometyx* or cabozantinib* or Cometriq* or Cabozanix* or Kabometics* or BMS-907351 or BMS907351 or XL-184 or XL184 or 1C39JW444G or DR7ST46X58).ti,ab,ot,kf,kw,hw,nm,rn.	4472
2	exp liver neoplasms/ or (((hepatocellular or hepato-cellular or liver* or hepatic or hepatobiliary or hepato-biliary) adj5 (cancer* or carcinoma* or tumor* or tumour* or neoplas* or malignan* or adenocarcinoma* or adenoma* or hemangioma* or haemangioma* or angioma* or granuloma* or carcinogen* or sarcoma* or metastasis)) or hepatoma* or hepatocarcinoma* or hepato-carcinoma* or hepatocarcinogenesis or hepato-carcinogenesis* or HCC or hepatoblastoma* or hepato-blastoma*).ti,ab,kf,kw.	601425
3	1 and 2	711
4	3 use cctr	48
5	3 use medall	92
6	limit 5 to english language	90
7	4 or 6	138
8	*cabozantinib/ or (Cabometyx* or cabozantinib* or Cometriq* or Cabozanix* or Kabometics* or BMS-907351 or BMS907351 or XL-184 or XL184).ti,ab,kw,dq.	2595
9	exp liver tumor/ or (((hepatocellular or hepato-cellular or liver* or hepatic or hepatobiliary or hepato-biliary) adj5 (cancer* or carcinoma* or tumor* or tumour* or neoplas* or malignan* or adenocarcinoma* or adenoma* or hemangioma* or haemangioma* or angioma* or granuloma* or carcinogen* or sarcoma* or metastasis)) or hepatoma* or hepatocarcinoma* or hepato-carcinoma* or hepatocarcinogenesis or hepato-carcinogenesis* or HCC or hepatoblastoma* or hepato-blastoma*).ti,ab,kw,dq.	559549
10	8 and 9	366
11	10 use oemezd	230
12	limit 11 to english language	224
13	12 and conference abstract.pt.	91
14	12 not conference abstract.pt.	133

15	7 or 14	271
16	remove duplicates from 15	189
17	limit 13 to yr="2014 -Current"	75
18	or/16-17	264

2. Literature search via PubMed

A limited PubMed search was performed to retrieve citations not found in the MEDLINE search.

Search	Query	Items found
#6	Search **(#5 AND publisher[sb])**	6
#5	Search **(#1 AND (#2 OR #3 OR #4))**	100
#4	Search **hepatoma*[tiab] OR hepatocarcinoma*[tiab] OR hepato-carcinoma*[tiab] OR hepatocarcinogenesis[tiab] OR hepato-carcinogenesis*[tiab] OR HCC[tiab] OR hepatoblastoma*[tiab] OR hepato-blastoma*[tiab]**	87418
#3	Search **(hepatocellular[tiab] OR hepato-cellular[tiab] OR liver*[tiab] OR hepatic[tiab] OR hepatobiliary[tiab] OR hepato-biliary[tiab]) AND (cancer*[tiab] OR carcinoma*[tiab] OR tumor[tiab] OR tumors[tiab] OR tumour[tiab] OR tumours[tiab] OR neoplas*[tiab] OR malignan*[tiab] OR adenocarcinoma*[tiab] OR adenoma*[tiab] OR hemangioma*[tiab] OR haemangioma*[tiab] OR angioma*[tiab] OR granuloma*[tiab] OR carcinogen*[tiab] OR sarcoma*[tiab] OR metastasis[tiab] OR metastases[tiab] OR metastatic[tiab])**	260641
#2	Search **liver neoplasms [mh]**	159918
#1	Search **(cabozantinib[Supplementary Concept] OR Cabometyx*[tiab] OR cabozantinib*[tiab] OR Cometriq*[tiab] OR Cabozanix*[tiab] OR Kabometics*[tiab] OR BMS-907351[tiab] OR BMS907351[tiab] OR XL-184[tiab] OR XL184[tiab] OR 1C39JW444G[rn] OR DR7ST46X58[rn])**	762

3. Cochrane Central Register of Controlled Trials (CENTRAL)

(searched via Ovid)

4. Grey literature search via:

Clinical trial registries:

US National Library of Medicine. ClinicalTrials.gov

https://clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: Cabometyx OR cabozantinib OR Cometriq OR Cabozanix OR Kabometics OR BMS-907351 OR BMS907351 OR XL-184 OR XL184 | liver OR hepatic OR hepatocellular OR hepatobiliary OR hepatoma OR hepatocarcinoma OR hepato-carcinoma OR HCC OR hepatoblastoma OR hepatocarcinogenesis

Select international agencies including:

US Food and Drug Administration (FDA)
https://www.fda.gov/

World Health Organization (WHO)
http://apps.who.int/trialsearch/

European Medicines Agency (EMA)
https://www.ema.europa.eu/

Search: Cabometyx OR cabozantinib, hepatocellular carcinoma

Conference abstracts:

American Society of Clinical Oncology (ASCO)
https://www.asco.org/

European Society for Medical Oncology (ESMO)
https://www.esmo.org/

San Antonio Breast Cancer Symposium (SABCS)
https://www.sabcs.org/2019-SABCS

Search: Cabometyx OR cabozantinib, hepatocellular carcinoma— last five years

Detailed Methodology

The literature search for clinical studies was performed by an information specialist from the pCODR Methods Team using the abovementioned search strategy, which was peer-reviewed according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[37]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were cabozantinib (Cabometyx) and hepatocellular carcinoma.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents but not limited by publication year.

The search is considered up to date as of February 20, 2020.

Grey literature (literature that is not commercially published) was identified by searching websites from relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters).[38] Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trial registries (US National Institutes of Health's clinicaltrials.gov and Canadian Partnership Against Cancer Corporation's Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO) and San Antonio Breast Cancer Symposium (SABCS) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the CADTH Clinical Guidance Panel. As well, the manufacturer of the drug was contacted for additional information, as required by the pCODR Review Team.

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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