CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Lenvatinib (Lenvima) for Hepatocellular Carcinoma

July 24, 2019

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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 lenvatinib (Lenvima) for hepatocellular carcinoma. 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 lenvatinib (Lenvima) for hepatocellular carcinoma 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 lenvatinib (Lenvima) for hepatocellular carcinoma, a summary of submitted Provincial Advisory Group Input on lenvatinib (Lenvima) for hepatocellular carcinoma, and a summary of submitted Registered Clinician Input on lenvatinib (Lenvima) for hepatocellular carcinoma, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The purpose of this review is to evaluate the safety and efficacy of lenvatinib on patient outcomes in the first line treatment of adult patients with unresectable hepatocellular carcinoma (HCC).

Lenvatinib is an oral, multiple receptor tyrosine kinase inhibitor (TKI). The Health Canada regulatory approval has been granted for the first-line treatment of adult patients with unresectable hepatocellular carcinoma (HCC). The reimbursement request is for the same population as the Health Canada approval. The recommended daily dose of lenvatinib is 8mg (two 4 mg capsules) once daily for patients with a body weight of <60kg and 12 mg (three 4 mg capsules) once daily for patients with a body weight of ≥60 kg.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one randomized controlled trial (RCT), the REFLECT trial (n=954), and the results are summarized below.

REFLECT

REFLECT was an international, multi-centre, open-label, phase 3, non-inferiority (NI), randomized controlled trial (RCT) of lenvatinib versus sorafenib in first-line treatment of patients with advanced, unresectable hepatocellular carcinoma (HCC) with no prior systemic therapy. Eligible patients were randomized in a 1:1 to ratio to receive either 8 mg/day (<60 kg bodyweight) or 12 mg/day (≥60 kg bodyweight) of lenvatinib (n=478) once daily, or 400 mg of sorafenib (n=476) twice daily, administered in 28-day cycles for both treatment arms. A total of 476 patients in the lenvatinib arm, and 475 patients in the sorafenib arm were treated, and participants continued treatment until objectively documented PD, development of unacceptable toxicity, participant request to stop treatment, or withdrawal of consent.[5]

The primary endpoint of REFLECT was overall survival (OS), and non-inferiority (NI) was demonstrated if the upper limit of two-sided 95% confidence interval of the lenvatinib vs. sorafenib treatment effect was lower than the margin, set at 1.08. The NI margin was set using the lower-limit method on log hazard ratio (HR) and preserved 60% of the upper limit of the two-sided 95% CI of the pooled HR of the sorafenib vs. placebo effect from historical trials. Following the test for NI, superiority was also tested. Secondary outcomes included investigator-assessed progression-free survival (PFS), time to progression (TTP), and objective response rate (ORR), health related quality of life (HRQoL), and safety outcomes. Patient-reported outcomes (HRQoL) were measured using two European Organisation for Research and Treatment of Cancer (EORTC) questionnaires, the EORTC Quality of Life Questionnaire C30 (EORTC QLQ-C30) and the HCC-specific questionnaire, the EORTC QLQ-HCC18.[5] Exploratory endpoints included disease control rate (DCR), clinical benefit rate (CBR), duration of response (DOR), and post-hoc independent imaging review (IIR) assessment of PFS, TTP, ORR, and DCR.[8]

The majority of study participants were <65 years of age (58%), male (84%), Asian (69%), and had a body weight ≥60 kg (69%). Participants almost exclusively had a liver function of Child-Pugh class A (99%), and the majority had Barcelona Clinic Liver Cancer (BCLC) stage C disease (79%). Baseline characteristics were generally well balanced between the study arms, with the exception of a higher proportion of patients in the lenvatinib arm with baseline α-fetoprotein (AFP) concentration ≥200 ng/mL (46%) compared to the sorafenib arm (39%). Additionally, aetiology of chronic liver disease differed between the two treatment arms, with more hepatitis B virus (HBV) aetiology participants in the lenvatinib arm (53% vs. 48% in sorafenib), and more participants with hepatitis C virus (HCV) aetiology in the sorafenib arm (26% vs. 19% in lenvatinib).[5]

Efficacy

The key efficacy outcomes of the REFLECT trial are presented in Table 1 (data cut-off as of November 16th, 2016 at 701 deaths). The median duration of follow-up in the lenvatinib arm was 27.7 months (IQR: 23.3-32.8) and 27.2 months (IQR: 22.6-31.3) in the sorafenib arm.[5]

Overall survival: The median OS was 13.6 months (95% CI: 12.1, 14.9) in the lenvatinib group (351 deaths) and 12.3 months (95% CI: 10.4, 13.9) in the sorafenib group (350 deaths), with a HR of 0.92 (95% CI: 0.79, 1.06). The REFLECT trial statistically demonstrated NI for OS of lenvatinib against sorafenib, with an upper limit of the CI that was below the NI margin of the trial. Statistical superiority of lenvatinib was not demonstrated. The OS exploratory analyses consistently demonstrated NI across all subgroups, with the exception of superiority being demonstrated of lenvatinib vs. sorafenib in participants with baseline AFP concentration ≥200 ng/mL.[5]

Progression-free survival: Lenvatinib showed statistically significant improvement in investigator-assessed PFS based on mRECIST. The median PFS in the lenvatinib arm (349 PD events) was almost double that of the sorafenib arm (367 PD events) at 7.4 months (95% CI: 6.9, 8.8) compared to 3.7 months (95% CI: 3.6, 4.6), respectively. Exploratory post-hoc analyses using masked IIR supported these results (Table 1). Statistical superiority of lenvatinib vs. sorafenib was demonstrated across all subgroups, with the exception of the following subgroups: females, Western region, and HCV aetiology of liver disease, where neither superiority nor NI was demonstrated.[5]

Time to progression: Investigator-assessed TTP demonstrated statistically significant superiority based on mRECIST criteria. TTP was twice as long in the lenvatinib arm at 8.9 months (95% CI: 7.4, 9.2) compared to 3.7 months (95% CI: 3.6, 5.4) in the sorafenib arm (HR: 0.63; 95% CI: 0.53, 0.73). Exploratory post-hoc analyses using

masked IIR supported these results (Table 1). Statistical superiority was demonstrated across all subgroups, with the exception of the following subgroups: females, Western region, and HCV aetiology of liver disease. Neither superiority nor NI was demonstrated in the female and HCV aetiology of liver disease subgroups, and only NI was demonstrated in the Western region for TTP.[5]

Objective response rate: Investigator assessed ORR, measured using mRECIST criteria, was statistically significantly higher in the lenvatinib arm (ORR: 24.1%; 95% CI: 20.2, 27.9) than the sorafenib arm (ORR: 9.2%; 95% CI: 6.6, 11.8). The odds of experiencing a complete or partial response were three times higher in the lenvatinib arm compared to the odds of experiencing a response in the sorafenib arm (OR: 3.13; 95% CI: 2.15, 4.56; p <0.0001). Exploratory post-hoc analyses using masked IIR indicated a substantially higher ORR in the lenvatinib arm (40.6%) compared to the sorafenib arm (12.4%), as shown in Table 1. Duration of objective response (DOR) was reported to be longer for the sorafenib arm (DOR: 11.2 months; 95% CI: 5.6, 16.6) compared to lenvatinib (DOR: 7.3 months, 95% CI: 5.6, 7.7) by investigator assessment based on mRECIST criteria.[5,8]

Disease control rate and clinical benefit rate: The DCR was higher in the lenvatinib group (DCR: 75.5%; 95% CI: 71.7, 79.4) than in the sorafenib group (DCR: 60.5%; 95% CI: 56.1, 64.9) based on investigator review according to mRECIST. CBR was not reported.[5]

Quality of Life

Study compliance was high (>90%) for the patient outcome measures throughout the study, however patient numbers declined at later cycles (<50% at cycle 6) limiting interpretation at these later time points.[8] Baseline scores were for all domains in the EORTC QLQ-HCC18 and EORTC QLQ-C30 were similar and declined in both treatment arms. There was no statistically significant difference in the summary scores of the EORTC QLQ-HCC18 between the two arms (HR: 0.87; 95% CI: 0.75, 1.01).[5] The overall median time to clinically significant worsening of HRQoL was similar between lenvatinib (1.7 months; 95% CI: 1.05, 1.84) and sorafenib (1.8 months; 95% CI: 1.05, 1.84).[12] A clinically meaningful delay in deterioration was observed for nutrition and body image from EORTC QLQ-HCC18 domains, and in role functioning, pain, and diarrhoea based on EORTC QLQ-C30 domains.[4]

Harms

In both treatment arms, 99% of participants (470 and 472 events in lenvatinib and sorafenib, respectively) experienced any grade treatment emergent adverse events (TEAEs). Treatment-related TEAEs occurred in 94% (n=447) of participants in the lenvatinib arm and 95% (n=452) of participants in the sorafenib arm. A higher proportion of grade ≥3 TEAEs (75% vs. 67%), treatment-related grade ≥ 3 TEAEs (57% vs. 49%), serious TEAEs (43% vs. 30%), and serious treatment-related TEAEs (18% vs.10%) occurred in the lenvatinib arm compared to the sorafenib arm, respectively. Adjusted by patient-years, the AE rate was 18.9 episodes per patient-year in the lenvatinib group and 19.7 episodes per patient-year in the sorafenib arm.[5]

Any grade TEAEs: The top 3 frequently occurring any-grade TEAEs in the lenvatinib arm were hypertension (42%), diarrhea (39%), decreased appetite (34%), whereas it was palmar-plantar erthrodysaesthesia (52%), diarrhea (46%), and hypertension (30%) in the sorafenib arm. Overall, there were 15 commonly (≥15% of participants) occurring TEAEs in the lenvatinib arm compared to 10 TEAEs in the sorafenib arm.[5]

Grade 3 or higher TEAEs: The most commonly occurring grade ≥3 TEAE in both arms was hypertension, occurring more frequently in the lenvatinib arm (23%) than the sorafenib arm (14%). In the lenvatinib arm, hypertension was followed by decreased weight (8%) and increased blood bilirubin (7%), whereas in the sorafenib arm hypertension was followed by palmar-plantar erthrodysaesthesia (11%) and elevated aspartate aminotransferase (8%) as the most commonly occurring grade ≥3 TEAEs. Overall, there were 6 commonly (≥5% of participants) occurring grade ≥3 TEAEs in the lenvatinib arm compared to 4 in the sorafenib arm.[5]

Withdrawals due to AEs (WDAEs): Approximately 20% (n=94) of participants withdrew study drug due to TEAEs in the lenvatinib arm compared to 15% (n=69) in the sorafenib arm.[8]

Deaths: Treatment-related fatal AEs occurred in twice as many participants in the lenvatinib arm (n=11; 2%) compared to the sorafenib arm (n=4, 1%).[5]

[Table 1.1]: Highlights of Key Outcomes

	REFLECT	
Primary Outcome	**Lenvatinib (n=478)**	**Sorafenib (n=476)**
Overall survival		
Median, months (95% CI)	13.6 (12.1, 14.9)	12.3 (10.4, 13.9)
HR (95%CI)	0.92 (0.79, 1.06)	
p-value†	NR	
Secondary Outcomes‡ (Investigator Assessed)		
Progression-free survival		
Median, months (95% CI)	7.4 (6.9, 8.8)	3.7 (3.6, 4.6)
HR (95% CI)	0.66 (0.57, 0.77)	
p-value††	<0.0001	
Time to progression		
Median, months (95% CI)	8.9 (7.4, 9.2)	3.7 (3.6, 5.4)
HR (95%CI)	0.63 (0.53, 0.73)	
p-value††	<0.0001	
Objective response rate		
Best response (CR + PR), % (95% CI)	24.1 (20.2, 27.9)	9.2 (6.6, 11.8)
OR (95%CI)	3.13 (2.15, 4.56)	
p-value††	<0.0001	
DOR, median, months (95% CI)	7.3 (5.6, 7.7)	11.2 (5.6, 16.6)
HrQoL		
TCW (based on EORTC QLQ-C30)		
Median, months (95% CI)	1.7 (1.05, 1.84)	1.8 (1.05, 1.84)
HR (95% CI)	0.87 (0.75, 1.01)	
p-value‡‡	0.0742	
Harms Outcome, n (%)	**Lenvatinib (n=476)**	**Sorafenib (n=475)**
TEAEs (any grade)	470 (99%)	472 (99%)
Grade ≥3 TEAEs	357 (75%)	316 (67%)
Serious TEAEs	205 (43%)	144 (30%)
Treatment-related TEAEs (any grade)	447 (94%)	452 (95%)
Treatment-related TEAEs (grade ≥3)	270 (57%)	231 (49%)
Treatment-related serious TEAEs	84 (18%)	48 (10%)
WDAEs	94 (20%)	69 (15%)
Fatal TEAEs	11 (2%)	4 (1%)
Exploratory Endpoints	**Lenvatinib (n=478)**	**Sorafenib (n=476)**
Disease control rate		
Best response (CR + PR + SD), % (95% CI)	75.5 (71.7, 79.4)	60.5 (56.1, 64.9)
Clinical benefit rate		
Best response (CR + PR + durable SD), % (95% CI)	NR	NR

	REFLECT	
IIR-assessed progression-free survival‡		
Median, months (95% CI)	7.3 (5.6, 7.5)	3.6 (3.6, 3.7)
HR (95%CI)	0.64 (0.55, 0.75)	
p-value††	<0.0001	
IIR-assessed time to progression‡		
Median, months (95% CI)	7.4 (7.2, 9.1)	3.7 (3.6, 3.9)
HR (95%CI)	0.60 (0.51, 0.71)	
p-value††	<0.0001	
IIR-assessed objective response rate‡		
Best response (CR + PR), % (95% CI)	40.6 (36.2, 45.0)	12.4 (9.4, 15.4)
OR (95%CI)	5.01 (3.59, 7.01)	
p-value††	<0.0001	
DOR, median, months (95% CI)	7.4 (5.6, 9.2)	15.8 (5.8, NE)

Data cut-off date: November 16th, 2016
†Non-inferiority margin for the HR or lenvatinib vs sorafenib is 1.08.
‡Assessed using mRECIST criteria.
††p-value is for the stratified log-rank test for the superiority of lenvatinib vs. sorafenib.
‡‡Nominal p-value.
Abbreviations:
CI = confidence interval; **CR** = complete response; **DOR** = duration of response; **HR =** hazard ratio; **HRQoL =** health-related quality of life; **IIR =** independent imaging review; **NE** = not estimable; **NR** = not reported; **OR** = odds ratio; **ORR** = objective response rate; **PR** = partial response; **SAE** = serious adverse event; **SD** = standard deviation; **TCW**= time to clinically meaningful worsening; **TEAE** = treatment-emergent adverse event; **WDAE** = withdrawal due to adverse event
Sources:
EMA Assessment report[8]
Kudo 2018[5]
Clinicaltrials.gov[12]

Limitations

The key limitations of the REFLECT trial include:

- The REFLECT trial had an open-label design, which is susceptible to investigator and participant biases.
- Clinical justifications and considerations for the selection of the margin may have been inadequately justified.
- The dose duration of sorafenib was shorter than in historical trials of sorafenib vs. placebo, which may be influenced by investigator biases associated with an open-label study design.
- There was 51% agreement on the timing of disease progression between investigator and IIR assessment, which may be due to investigator biases associated with an open-label study design.
- Imbalances in baseline AFP concentrations and aetiology of liver disease between treatment arms could have influenced the magnitude and direction of the treatment effect.
- Types of post-treatment anticancer therapies differed between the treatment arms, which could have influenced the magnitude and direction of the treatment effect.
- Patients were censored if there was no disease progression at time of treatment discontinuation. Treatment discontinuation for reasons other than disease progression occurred more frequently in the lenvatinib arm. This censoring rule may have biased the magnitude and direction of treatment effect towards lenvatinib for PFS and TTP. A sensitivity analysis where patients were not censored if they did not experience progressive disease or death was provided, and while the direction of the treatment effect was similar to the primary analysis, there was a reduction in the magnitude of the treatment

effect. TTP results of the sensitivity analysis were consistent with the primary analysis.

- The proportional hazards (PH) assumption was not met for PFS in the REFLECT trial, however this was deemed an acceptable violation due to the nature of the study design (non-inferiority). Nonetheless, hazard ratios must be interpreted with some degree of caution.

1.2.2 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 perspective, patients rated their most important symptoms or problems to control for HCC as fatigue (60%), pain (60%), weight loss and/or lack of appetite (40%), not sleeping/restless (20%) and living with uncertainty (20%). Other factors influencing quality of life included appetite loss, weight loss, diarrhea, skin disorder and alopecia. HCC patients also expressed deep mental and emotional impact such as fear, worry, shock, and sadness. Five respondents to the global survey answered what treatments they were currently using as lenvatinib (60%), chemotherapy (40%), trans-arterial chemoembolization (TACE)(40%), radiation therapy (20%), surgery (20%), and liver transplant (20%). In addition, patients who responded to the qualitative interviews had begun treatment with sorafenib and two patients had additionally received regorafenib. All the patients from the qualitative interviews were currently on lenvatinib. The most common side-effects of the current treatments for patients were numbness, pain, or tingling in hands of feet, dry or peeling skin, skin redness, pruritus (skin itchiness), loss of appetite, diarrhea, weight loss, fatigue, stomach cramps, bleeding, constipation, weakness, and dry mouth. Patient respondents noted that lenvatinib generally maintained or improved their quality of life. The most common side effects with lenvatinib are diarrhea, nausea, hypertension, Patients value an additional treatment option in the first-line setting for improving and managing their HCC symptoms and increasing survival.

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 lenvatinib relative to sorafenib and sequencing with regorafenib

Economic factors:

- Weight-based dosing may lead to dosing errors

Registered Clinician Input

One joint input from six registered clinicians at the BC Cancer Agency was provided for the pCODR review of lenvatinib for the first line treatment of adult patients with unresectable hepatocellular carcinoma (HCC). A summary of the input is provided below.

According to the clinician input, sorafenib is currently the standard first line therapy for HCC. The clinicians believe that lenvatinib would be an appropriate and preferable first-line therapy owing to its milder side effect profile. Sorafenib toxicity manifests more frequently as hand-foot syndrome, a relatively impactful disorder, whereas lenvatinib more readily elevates the risk of hypertension, which is easer to manage. Clinicians highlighted that an advantage of lenvatinib is tumour size reduction which may allow local therapies to be considered. Clinicians believed that the inclusion and exclusion criteria of the phase 3 trial can be applied in Canadian clinical practice. Clinicians deemed that regorafenib, cabozantinib, and possibly sorafenib, would be suitable next-line therapies after lenvatinib. They believed that both lenvatinib and sorafenib should be available as first-line options for HCC to allow drug switching due to tolerance issues.

Summary of Supplemental Questions

There were no supplemental questions identified for this review.

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.

1.2.3 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 lenvatinib (Lenvima) for advanced unresectable hepatocellular carcinoma (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 REFLECT[13] trial included participants with ECOG PS of 0-1.</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 lenvatinib in patients with ECOG 2 or higher. The CGP note that this primarily due to concerns around toxicity of treatment for patients with lower PS.</td></tr>
<tr><td></td><td>Child-Pugh score</td><td>The REFLECT[13] trial included participants with Child-Pugh Class B. However, only 8 participants (1%) with liver function of Child-Pugh class B were included.</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>Liver occupation, clear invasion of bile duct, or portal vein invasion at the main portal branch</td><td>The REFLECT[13] trial excluded participants with 50% of higher liver occupation, obvious invasions of the bile duct, or portal vein invasion at the main portal branch (Vp4).</td><td>Do the trial results apply to patients with significant liver occupation, clear invasion of bile duct, or portal vein invasion at the main portal branch? Is this reflective of patients seen in this setting in clinical practice?</td><td>The CGP agree that the trial should not be generalized to patients with ≥ 50% of liver occupation, clear invasion of the bile duct or portal vein invasion at the main portal branch.</td></tr>
<tr><td></td><td>Brain metastases</td><td>The REFLECT trial[13] excluded participants with a history of or current brain or subdural metastases.</td><td>Do the trial results apply to participants with brain metastases?</td><td>The CGP agree that the REFLECT trial results should not be generalized to patients with brain metastases.</td></tr>
<tr><td></td><td>Regional and aetiological differences</td><td>There are known aetiological differences of liver disease in HCC patients from different regions, with patients from the Asia-Pacific generally having HBV or HCV aetiology of liver cirrhosis. The REFLECT trial[13] included a higher proportion of patients from the Asia-Pacific with a higher proportion of patients with HBV or HCV aetiology of liver disease. There is also evidence to suggest that patients with HCV aetiology may have a better response to sorafenib, whereas patients with HBV aetiology may have a better response to lenvatinib.
<table>
<tr><th>Population Characteristic</th><th>Lenvatinib n=478</th><th>Sorafenib n=476</th><th>Total n=954</th></tr>
<tr><td>Region</td><td></td><td></td><td></td></tr>
<tr><td>Western</td><td>157 (33%)</td><td>314 (33%)</td><td>157 (33%)</td></tr>
</table></td><td>Are the results of the full population generalizable or reflective of the Canadian population? Can lenvatinib be reasonably expected to perform similarly across all regions and aetiologies of liver disease?</td><td>Despite the differences in aetiology among patients in different regions, the CGP agreed that as Western patients were included in the REFLECT trial, the results of the trial are generalizable to this patient population. See section 2.2</td></tr>
</table>

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
		Asia-Pacific: 321 (67%) / 640 (67%) / 321 (67%) Etiology Hepatitis B: 251 (53%) / 228 (48%) / 479 (50%) Hepatitis C: 91 (19%) / 126 (26%) / 217 (23%) Alcohol: 36 (8%) / 21 (4%) / 57 (6%) Other: 38 (8%) / 32 (7%) / 70 (7%) Unknown: 62 (13%) / 69 (14%) / 131 (14%)		
Intervention	**Line of therapy and sequencing**	The REFLECT trial[13] demonstrated that lenvatinib was not clinically worse in terms of efficacy compared to sorafenib, the only relevant comparator in first-line treatment for patients with no prior systemic therapy.	Are there particular patient populations that would benefit most or would be more suitable for lenvatinib compared to sorafenib in first-line?	There are no particular patient populations that would be more suitable for lenvatinib compared to sorafenib.
	Maintenance therapy	REFLECT trial[13] did not use lenvatinib in patients to maintain responses or as a bridge to transplant.	Can clinicians use lenvatinib to maintain any responses from local regional therapy or use as a bridge to transplant?	The efficacy of lenvatinib in this setting is unknown and therefore the CGP do not support the use of lenvatinib as maintenance therapy at this point.
	Subsequent therapies	Currently, regorafenib is approved (not funded in any provinces) in the second-line setting following sorafenib treatment. There are no approved second-line treatments after lenvatinib. Some participants in the REFLECT trial[13] received second-line sorafenib. Post-hoc exploratory analyses revealed lenvatinib responders who received sorafenib had an OS 26.2 months (95% CI: 18.2, 34.6).	What treatment options would be available to patients upon progression of lenvatinib? Is there evidence to sequence regorafenib or sorafenib after lenvatinib?	The efficacy of second line HCC treatments after lenvatinib are unknown, and further data may be available through observational trials. Despite the lack of evidence, the CGP acknowledge that there is no 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.
Comparator	**Sorafenib**	The comparator in the REFLECT trial[13] was sorafenib. Patients included in the trial received no prior systemic therapy.	Are the findings of the REFLECT trial generalizable to patients who may be sorafenib intolerant or progress early on sorafenib (and thus, received some prior systemic therapy)?	The CGP agree that the results of the REFLECT trial are not generalizable to patients who progress on sorafenib.
Outcomes	**Appropriate selection of**	An in-depth assessment of the selection of the margin is highlighted in section 6.3.2.1. Generally,	Was the selection of the margin adequately justified?	Appropriate.

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
	the margin and demonstration of non-inferiority	concerns were raised regarding the historical evidence of sensitivity to drug effects (relative vs. absolute effects, which may differ by population), the constancy assumption, and the quality of the trial. Specifically it was highlighted that historical studies of patients with sorafenib vs. placebo involved patients with a poorer prognosis compared to the REFLECT trial[13]; the REFLECT trial excluded patients with ≥50% liver occupation, clear invasion into the bile duct or **portal vein invasion at the main portal branch** whereas this same exclusion was not applied in historical trials of sorafenib vs. placebo; and the REFLECT trial was open-label (whereas historical studies of sorafenib vs. placebo were double-blind). Further, median OS demonstrated in these trials was less than 1 year, and 60% of the upper limit of the pooled treatment effect of sorafenib vs. placebo was preserved to set the margin. In addition, the proportional hazards assumption was not met for overall survival.	Is there confidence the trial demonstrated non-inferiority?	There were a number of concerns identified in the selection of the margin including: differences in the populations and study designs of the historical sorafenib vs. placebo trials and the REFLECT trial, and the clinical justification for the preservation of 60% of the upper limit of the treatment effect of sorafenib vs. placebo. Nonetheless, the methods team and CGP came to a consensus that the selection of the non-inferiority margin (1.08) was acceptable. However, in light of the limitations of the selection of the margin, lenvatinib in clinical practice should be used only in similar conditions to that of the REFLECT trial in terms of patient population, line of therapy, and administration to obtain similar efficacy and safety.
	Secondary outcomes (PFS, TTP)	Although there was generally good agreement between investigator and masked IIR assessment of secondary outcomes, there was poor agreement on the timing of PD (51%) in the REFLECT trial[13] with investigator assessment declaring PD later than BICR assessment (overall late discordance rate of 62.3%).[8] The censoring rules of patients who discontinued treatment for reasons other than PD may have biased the results in favour of lenvatinib, as patients who discontinued for reasons other than PD was higher in this group. Additionally, the proportional hazards assumption was not met for PFS and TTP.	Is there confidence in the secondary outcomes as reported in the trial? Is the degree of potential bias introduced by investigator assessment acceptable?	The independent radiology review showed similar results that support the investigator assessed endpoints
	Safety	The safety profiles between the two treatments differed. The adverse event rate adjusted by person-years was similar in both groups. Overall, there were more commonly occurring TEAEs in the lenvatinib group vs. the sorafenib group.	Are there certain patients who would benefit from the safety profile associated with lenvatinib vs. sorafenib? Does the combination of efficacy results (OS, PFS) and safety	No subgroup was identified that would benefit from the safety profile of lenvatinib vs sorafenib.

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
			profile support the use of lenvatinib over sorafenib - if so, in which situations?	
Setting	**Countries participating in the trial**	The trial was conducted in 154 sites in 20 countries including Canada, China, Hong Kong, Japan, South Korea, Malaysia, Philippines, Singapore, Taiwan, Thailand, Belgium, France, Germany, Israel, Italy, Poland, Russia, Spain, UK, and USA. However, only 1 site with 1 patient enrolled was from Canada.	Are there known differences in the practice patterns between countries? Could these affect the applicability or implementation of lenvatinib in Canada?	The CGP agree that the trial results are generalizable to the Canadian population.

1.2.4 Interpretation

Burden of Illness and Need

An estimated 2,500 new cases of HCC were diagnosed in Canada in 2017.[14] As per the BCLC algorithm, the prognosis for patients with advanced, unresectable HCC with preserved hepatic reserve (stage C) is poor with a median overall survival of less than one year.[15] HCC is a challenging disease to treat as it typically appears in the setting of underlying hepatic cirrhosis which is often associated with hepatic impairment. Thus, the treatment approach and consequent prognosis of patients with HCC depends upon not only the extent of the cancer, but also underlying hepatic function and performance status of the patient. Sorafenib is currently the only approved and reimbursed treatment across Canada for the first-line systemic treatment of Child-Pugh A class patients with advanced HCC.

The REFLECT trial[13] was a well conducted, multi-centre, randomized, open-label, non-inferiority Phase III study to compare the efficacy and safety of lenvatinib versus sorafenib as a first-line systemic treatment in subjects with unresectable HCC, ECOG PS 0-1, and Child Pugh A liver function. Baseline imbalances in AFP concentrations, number of disease sites, as well as etiology of chronic liver disease between the two arms are unlikely to influence clinical activity of lenvatinib, although an increased number of disease sites would mean poor prognosis for those patients. Very few patients were lost to follow up (three in the lenvatinib arm, one in the sorafenib arm).

The open-label nature of the trial does not affect the primary endpoint of OS, which is the most relevant and unbiased measure of efficacy. Although the justifications and considerations for the selection of the margin may have been inadequate, the selected upper limit for non-inferiority (1.08) is both clinically relevant and conservative. There may have been investigator bias in terms of adjudication of progression and response. The independent radiology review (IRR) assessment provides an unbiased evaluation of TTP and RR. There was 51% agreement on the timing of disease progression between investigator and IIR assessment, which may be due to investigator biases associated with an open-label study design and technical difficulty in assessing mRECIST in HCC. A target lesion was defined as the whole lesion for RECIST assessment and opposed to the contrast-enhanced portion of the lesion at the arterial phase for mRECIST assessment.

Effectiveness

The REFLECT trial demonstrated the non-inferiority of lenvatinib to sorafenib for OS, the primary endpoint of the study, median OS 13.6 vs. 12.3 months for lenvatinib vs. sorafenib, HR 0·92, 95% CI 0·79–1·06). Superiority could not be shown. Imbalances in second line therapies, AFP, and etiolology of liver disease may have influenced the magnitude and direction of the treatment effect, especially for overall survival.

At the end of study treatment, patients randomized to sorafenib were eligible for potential second-line trials specifically requiring enrollment of sorafenib failures and/or sorafenib-intolerant patients, while lenvatinib patients would probably be ineligible for such trials. A higher proportion of subjects received post-study treatment in the sorafenib arm 38.7% versus lenvatinib 32.6%. These factors might favour the sorafenib arm, but no definitive conclusions can be made. An exploratory analysis to illustrate the magnitude of effect that these imbalances in post-treatment anti-cancer therapy use as a covariate within the economic analysis was performed for the NICE review of lenvatinib. The expected life extension associated with lenvatinib was increased to over 4 months compared to sorafenib.

Subgroup analyses for OS revealed that the effect of lenvatinib and sorafenib on OS was generally consistent across subgroups. Amongst the subgroup analyses, the only exception was the Western Region where the median OS for lenvatinib was 13.6 months compared to 14.2 months for sorafenib, resulting in an HR of 1.08 (95% CI: 0.82, 1.42). This HR does not deviate far from 1.00 and the median OS difference is only 0.6 months. The clinical challenge in treating many patients with HCC is that there are two major competing causes for mortality: the cancer which primarily affects the liver, and underlying liver disease that put the patient at risk for HCC. Thus, systemic therapy for HCC may control the cancer, but in some patients, progression of the underlying liver disease may contribute to the underlying cause of death.

Secondary investigator assessed endpoints also favoured the lenvatinib arm. Lenvatinib treatment resulted in improvement over sorafenib for PFS (median PFS, 7.4 vs 3.7 months, respectively; HR=0.66; 95% CI of 0.57, 0.77, P<0.00001). Median TTP with lenvatinib was longer than that of sorafenib: 8.9 months for lenvatinib versus 3.7 months for sorafenib (HR = 0.63; P<0.00001). Acknowledging the caveats of cross trial comparisons, the SHARP trial provides a metric for a clinically relevant improvement in time to progression for HCC. The REFLECT trial had stricter inclusion criteria than the SHARP trial, and different patient population. In the SHARP trial, treatment with sorafenib improved IRR assessed TTP by an absolute difference of 2.7 months (5.5 months with sorafenib versus 2.8 months for placebo, 0.58; 95% CI, 0.45 to 0.74; P<0.001), p<0.0001) according to RECIST version 1.0. In the REFLECT trial, the median IIR TTP according to RECIST 1.1 was 3.7 months with sorafenib versus 7.4 months with lenvatinib (HR 0.61, 95% CI 0.51-0.72, p < 0.0001), an absolute difference of 3.7 months. Patients were censored if there was no disease progression at time of treatment discontinuation. Treatment discontinuation for reasons other than disease progression occurred more frequently in the lenvatinib arm. This censoring rule may have biased the magnitude and direction of treatment effect towards lenvatinib for PFS and TTP. A sensitivity analysis where patients were not censored if they did not experience progressive disease or death was provided, and while the direction of the treatment effect was similar to the primary analysis of PFS, there was a reduction in the magnitude of the effect. TTP results of the sensitivity analysis were consistent with the primary analysis.

The PH assumption was not met for PFS in the REFLECT trial, however, this was deemed as an acceptable violation of the assumption of the model. Nonetheless, the HRs should be interpreted with some caution.

Based on the p-value (p=0.2902) of the PH global test for OS, the null hypothesis that there are PH between the two treatment arms was retained. However, visual inspection of the log-cumulative hazard plot revealed there may be some convergence of the treatment arms, and thus indicative of non-proportional hazards.11 Given the study design is a NI trial, the methods and economic team did not deem this as a violation of the PH assumption.

The investigator assessed ORR was significantly higher for lenvatinib compared with sorafenib (24.1% vs. 9.2%) mainly due to an increase in the proportion of lenvatinib patients with PR (22.8 vs. 8.8%). The duration of response was numerically longer for sorafenib (11.2 vs. 7.3 months), with overlapping 95% confidence intervals. The proportion with durable stable disease (≥23 weeks) was higher in the lenvatinib arm (34.9% vs. 29.2%). The results of IIR using mRECIST or RECIST 1.1 supported the results of the investigator-based assessments or ORR, TTP, and PFS.

The overall median time to clinically significant worsening of HRQoL was similar between lenvatinib (1.7 months; 95% CI: 1.05, 1.84) and sorafenib (1.8 months; 95% CI: 1.05, 0.84). Analysis of time to clinically meaningful deterioration showed that role functioning

(nominal p=0·0193), pain (nominal p=0·0105), and diarrhea (nominal p<0·0001) from EORTC QLQ-C30, and nutrition (nominal p=0·0113) and body image (nominal p=0·0051) from EORTC QLQ-HCC18 were observed earlier in patients treated with sorafenib than in those treated with lenvatinib. It is very challenging to improve quality of life in HCC patients with systemic therapy. In the original SHARP trial, the median time to symptomatic progression (which was defined as either a decrease of 4 or more points from the baseline score on the FHSI8 questionnaire or an ECOG status of 4 or death, whichever occurred first) did not differ significantly between the sorafenib group and the placebo group.

SAFETY

Treatment-emergent adverse events of grade 3 or higher occurred at similar rates in the lenvatinib and sorafenib arms (episodes per patient-year 3·2 vs 3·3). The most common treatment-emergent adverse events among patients who received lenvatinib were hypertension, diarrhoea, decreased appetite, and decreased weight. In the sorafenib arm, the most common treatment-emergent adverse events were palmar-plantar erythrodysaesthesia (hand-foot syndrome), diarrhoea, hypertension, and decreased appetite. Fatal adverse events due to treatment occurred in 11 (2%) lenvatinib treated patients and four (1%) in the sorafenib group. A higher proportion of patients randomized to lenvatinib discontinued treatment due to adverse events compared to sorafenib (13.2% versus 9.0%). However, there was no detrimental effect on global quality of life and more participants in the sorafenib arm discontinued treatment due to radiological progression (n=347; 72.9%) than the lenvatinib arm (n=311; 65.1%). The toxicity of lenvatinib was overall manageable, by dose interruptions and dose reductions. Hypertension can be managed with antihypertensive medications and usually does not cause symptoms, in contrast, hand- foot syndrome can affect daily activities such as standing and walking. This was I alignment with input from registered clinicians.

1.3 Conclusions

The Clinical Guidance Panel concluded that there may be a net overall clinical benefit to lenvatinib in the treatment of advanced HCC, with Child Pugh A liver function, ECOG 0-1, based on one well-conducted randomized controlled trial that demonstrated non-inferiority in overall survival for lenvatinib compared with sorafenib and similar adverse event profiles between the two drugs. Lenvatinib significantly improved clinically relevant secondary endpoints such as progression free survival, time to progression, and response rate compared to sorafenib. Progression free survival and time to progression are important endpoints due to imbalances in second line therapy which may have favoured the sorafenib treated patients. According to the ESMO magnitude of clinical benefit scale, for the overall population, lenvatinib demonstrated a clinically relevant improvement in progression free survival over sorafenib (score 4/5).[73] However, there were uncertainties with regard to the magnitude of the progression free survival benefit in Western patients. Additionally, the proportional hazards assumption was not met for progression free survival. The side effect profile of lenvatinib may be preferable for some patients, as hypertension is asymptomatic, whereas hand-foot syndrome can affect daily activities; this did not translate into any significant differences in quality of life summary scores.

The Clinical Guidance Panel also considered from a clinical perspective:

- There is an expanding number of second line options for HCC, which could have potentially affected overall survival in this trial. Second line trials have inclusion criteria that mandate prior treatment with sorafenib. The efficacy of second line HCC treatments such as regorafenib, cabozantinib, pembrolizumab, and nivolumab after lenvatinib are unknown, and

further data may be available through observational trials or real-world evidence. This is in alignment with input from registered clinicians.

- The CGP further agreed that patients who meet the REFLECT trial criteria should be selected to receive lenvatinib while patients with Child Pugh A liver function and either: ECOG PS 2, greater than or equal to 50% of liver involvement, clear invasion of the bile duct or portal vein invasion at the main portal branch may qualify for treatment with sorafenib.
- 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. For example, pertuzumab and trastuzumab-emtansine revolutionized the treatment of metastatic HER2 positive breast cancer. The combination of pertuzumab, trastuzumab, docetaxel became the new standard first line therapy after the results of the CLEOPATRA trial were published in 2015.[16] However, the standard second line therapy remained trastuzumab-emtansine[17], based on the results of the pivotal EMILIA trial (published in 2012), even though none of the patients treated with trastuzumab-emtansine in the trial received prior pertuzumab.[18]
- The CGP would support the use of regorafenib after lenvatinib if clinically warranted. For jurisdictions that permitted this sequence, the CGP do not anticipate that there will be a preference to use sorafenib upfront for the sole reason of ensuring that patients can qualify for regorafenib or other second line therapies.
- Since 2008, sorafenib has been the only systemic therapy option for patients with advanced HCC. Additional options are needed for patients with a median survival of approximately one year. While the incidence of adverse events was similar, sorafenib-related hand-foot syndrome is a significant and functionally limiting toxicity, thus the safety profile of lenvatinib may be preferred by clinicians and patients.
- The following patients were excluded from the trial, and thus the results cannot be generalized to these populations: ECOG PS 2, Child-Pugh B, greater than or equal to 50% of liver involvement, clear invasion of the bile duct or portal vein invasion at the main portal branch, brain metastases, liver transplantation.
- This trial did not evaluate the efficacy of lenvatinib to maintain any responses from local regional therapy or its use as a bridge to transplant. The REFLECT trial cannot be generalized to patients who progress early on sorafenib.
- For patients who have not progressed on sorafenib but are intolerant, it would be reasonable to switch to lenvatinib although this strategy was not directly addressed in the REFLECT trial. For patients who have not progressed radiographically on lenvatinib but are lenvatinib intolerant, it would be reasonable to consider switching to sorafenib. This is in alignment with input from registered clinicians.
- For patients with intermediate-stage HCC or who are unable to receive TACE, it would be reasonable to include them in the reimbursement population as long as patients have Child Pugh A status (unresectable HCC). This is in alignment with input from registered clinicians.

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Gastrointestinal Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

Over the last two decades, the incidence of HCC (liver cancer) in Canada has increased by 3.1% per year in men, and 2.1% per year in women attributed in part to rising immigration from countries where risk factors for HCC such as hepatitis B and C, are endemic. Approximately 2,500 new cases of HCC will be diagnosed in Canada in 2017[14]. Among the most important risk factors for the development of HCC are alcohol use, hepatitis B carrier state, chronic hepatitis C virus infection, hereditary hemochromatosis and aflatoxin exposure. HCC is a challenging disease to treat as it typically appears in the setting of underlying hepatic cirrhosis which is often associated with hepatic impairment. Thus, the treatment approach and consequent prognosis of patients with HCC depends upon not only the extent of the cancer, but also underlying hepatic function and performance status of the patient. Child-Pugh class is the most commonly employed tool to determine 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)

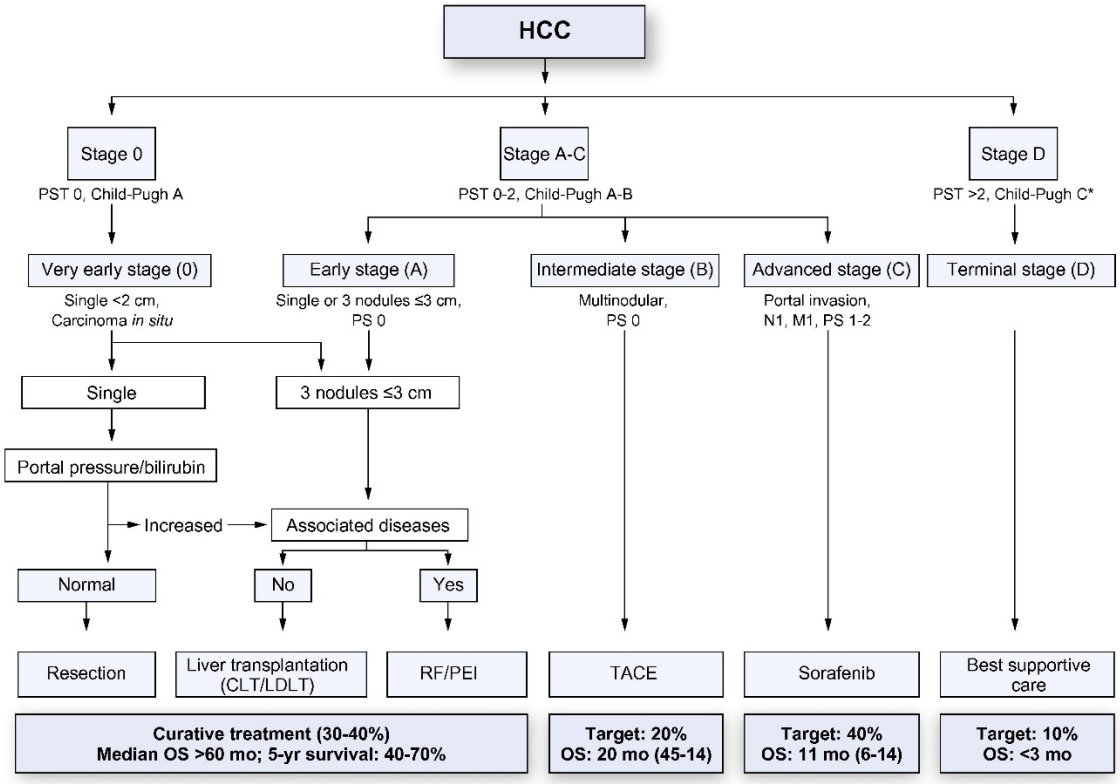
Table 1: Child-Pugh Classification

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

2.2 Accepted Clinical Practice

Although there are several staging systems in use for HCC, the Barcelona Clinic Liver Cancer (BCLC) staging system is the most widely used prognostic and treatment algorithm for HCC in the Canadian system (Figure 1). The staging system incorporates prognostic factors related to tumour status, liver function and patient performance status. As per the BCLC algorithm, the prognosis for patients with advanced, unresectable HCC with preserved hepatic reserve (stage C) is poor with a median overall survival of less than one year.[15]

Figure 1:



EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2012;56(4):908-943. Copyright © 2012 European Association for the Study of the Liver. Reproduced according to the 2012 Creative Commons Licence LC BY-NC-ND version 4.0[19]

HCC is considered to be a chemotherapy - refractory tumour. Sorafenib is an oral multi-tyrosine kinase inhibitor 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 comparing sorafenib therapy to placebo.[20] The median OS in the sorafenib arm was 10.7 months vs 7.9 months in the placebo arm (HR = 0.69; 95% CI, 0.55–0.87; p < 0.0001). In addition, sorafenib showed a significant benefit in terms of TTP assessed by independent radiological review with a median TTP of 5.5 months for sorafenib and 2.8 months for placebo (p<0.0001). It is of note that this represents a selected patient population – in the SHARP trial, only 602/902 (67%) of screened patients were eligible for randomization.[20]

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.[21] 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 investigation, 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). The most common grade 3 drug-related adverse events with sorafenib included hand-foot syndrome and diarrhea which occurred in 8-10.7% and 8-6% respectively.[20,21] 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.

There are currently no standard treatment options for patients beyond sorafenib therapy. Regorafenib is also an oral multikinase inhibitory, structurally similar to sorafenib, and targets a number of angiogenic kinases (including VEGFR), stromal and oncogenic receptor TKIs. In the phase 3 RESORCE trial[13], a survival benefit for regorafenib (160mg p.o. daily for 3 weeks on and 1 week off) was demonstrated in patients progressing after first-line treatment with sorafenib who maintained an ECOG performance status of 0-1 and Child-Pugh A liver function. 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% vs 36%). Grade 3-4 adverse events included hypertension (15% vs 5%), hand-foot skin reaction (13% vs 1%) fatigue (9% vs 5%) and diarrhea (3% vs 0%).[13] Despite these adverse events, quality of life as assessed by EQ-5D and FACT-Hep, was not significantly worse with regorafenib compared to placebo.[13]In April, 2018, pERC conditionally recommended the funding of regorafenib for patients with unresectable HCC who have been previously treated with sorafenib depending on cost-effectiveness.

Cabozantinib is a potent inhibitor of hepatocyte growth factor/c-MET, VEGFR-1, VEGFR-2, and VEGFR-3.[22] High levels of MET expression are associated with resistance to sorafenib in preclinical models.[23,24] In the phase III CELESTIAL trial, 707 patients previously treated with sorafenib were randomized to cabozantinib or placebo.[25] 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.[26]

More recently, the post-sorafenib HCC landscape continues to change with the results of studies examining the efficacy of immune check point inhibitors. In the US, the FDA granted accelerated approval to nivolumab for patients with HCC following prior sorafenib. This was based on a phase I/II CheckMate-040 trial with 262 patients in which the overall response rate was 15% with 3 patients experiencing a complete response. Furthermore, the median duration of response was 17 months. The FDA also approved pembrolizumab[27] (an anti-PD1 antibody) based on a phase II study in HCC patients after prior sorafenib, which demonstrated an overall response rate of 16.3% with a median duration of response of 8.2 months. There is an ongoing phase III study of pembrolizumab monotherapy versus best supportive care in advanced HCC patients previously treated with systemic therapy.

Patients with unresectable hepatocellular cancer, not amenable to local therapies	
First line	Sorafenib
Second line (after sorafenib)	Regorafenib Cabozantinib

2.3 Evidence-Based Considerations for a Funding Population

The expected population for lenvatinib use would be patients with unresectable hepatocellular carcinoma with Child-Pugh class A hepatic reserve, BCLC stage B or C, ECOG performance status of 0-1, and no prior systemic therapy for advanced disease. In addition, patients had a histological or cytological diagnosis of HCC, and did not have involvement of >50 percent of the liver nor invasion of the main portal vein at the main portal branch or biliary tree.[5]

2.4 Other Patient Populations in Whom the Drug May Be Used

Patients with imaging pathognomonic for HCC do not always require a biopsy, in contrast to the clinical trial evaluating lenvatinib which mandated a histological or cytological confirmation of the diagnosis. HCC patients who have not progressed on sorafenib, but experience treatment related adverse events that require discontinuing sorafenib. There is no safety or efficacy data for the use of lenvatinib in patients with HCC in an orthotopic transplanted liver. Forthcoming evidence regarding the efficacy and safety of lenvatinib in the aforementioned populations will likely be observational in nature.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

The following patient advocacy groups provided input on Lenvatinib (Lenvima) for hepatocellular carcinoma (HCC), and their input is summarized below: Canadian Cancer Survivor Network (CCSN) and Canadian Liver Foundation (CLF).

To gather information for this review, CLF invited patients, caregivers from access Canada to complete an online survey modelled on the CADTH pCODR program submission guideline. The survey was available from January 28 to February 6, 2019. CLF promoted the survey on their website, social media channels, e-newsletter and CLF patient, caregiver and health care professional contacts across the country. The survey was available in English, French and Chinese. CLF reported that demographic information was voluntarily provided and is as follows: 2 patients, 1 caregiver and 5 health care professionals, for a total of 8 respondents. One patient was between 55-64 years and another was 65 years and older, of these two patients, one was noted to be male and the other female. The one caregiver was between 18-24 years of age and reported as female. Both of the two patients and one caregiver who responded indicated that they had experience with unresectable HCC but not with the treatment under review. In addition to this, CLF has also included non-nominal input from approximately 40 patient contacts from across Canada which was collected from liver cancer patients who have contacted the CLF through the national toll-free helpline or for support via email and other online/in-person communication channels. To further supplement the patient input, CLF has included a reference to a global survey of people living with HCC, conducted in 2016. There was a total of 256 respondents to the global patient survey from 13 countries, of which 8 respondents were from Canada.

The Canadian Cancer Survivor Network (CCSN) conducted a survey from January 28th to February 14th through SurveyMonkey. This survey was publicized on CCSN's website, social media, and in CCSN's newsletter to over 10,000 subscribers. In addition, an email about the survey was also circulated to over 35 individuals and professionals in the liver cancer, hepatology and interventional radiology fields, with requests to distribute amongst their networks. CCSN noted that the survey was completed by five Canadian patients with HCC, three of which were currently taking lenvatinib. CCSN also provided eight qualitative interviews with Canadian HCC patients who are currently taking lenvatinib, which included seven men and one woman.

From a patient perspective, patients rated their most important symptoms or problems to control for HCC as fatigue (60%), pain (60%), weight loss and/or lack of appetite (40%), not sleeping/restless (20%) and living with uncertainty (20%). Other factors influencing quality of life included appetite loss, weight loss, diarrhea, skin disorder and alopecia. HCC patients also expressed deep mental and emotional impact such as fear, worry, shock, and sadness. Five respondents to the global survey answered what treatments they were currently using as lenvatinib (60%), chemotherapy (40%), trans-arterial chemoembolization (TACE) (40%), radiation therapy (20%), surgery (20%), and liver transplant (20%). In addition, patients who responded to the qualitative interviews had begun treatment with sorafenib and two patients had additionally received regorafenib. All the patients from the qualitative interviews were currently on lenvatinib. The most common side-effects of the current treatments for patients were numbness, pain, or tingling in hands of feet, dry or peeling skin, skin redness, pruritus (skin itchiness), loss of appetite, diarrhea, weight loss, fatigue, stomach cramps, bleeding, constipation, weakness, and dry mouth. Patient respondents noted that lenvatinib generally maintained or improved their quality of life. The most common side effects with lenvatinib are diarrhea, nausea, hypertension, Patients value an additional treatment option in the first-line setting for improving and managing their HCC symptoms and increasing survival.

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 advocacy groups.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Hepatocellular Carcinoma

The Canadian Liver Foundation (CLF) noted that hepatocellular carcinoma (HCC) is the most common type of liver cancer and accounts of 71.9 % of liver cancers in males and females in Canada. CLF noted that the increasing prevalence of HCC in Canada is an indicator of the increasing prevalence of late-stage and end-stage liver disease, primarily driven by hepatitis B and hepatitis C. However, there is an increasing prevalence of non-alcoholic fatty liver disease (NAFLD), which is often not diagnosed in early stages, and is contributing to an increase in numbers of HCC cases. If left undiagnosed and unmanaged, NAFLD can lead to HCC, and the diagnosis of HCC at later stages ultimately leads to poorer outcomes as surgery is no longer an option.

In addition to the above, CCSN reported survey results related to the symptoms which affected patients' day to day living and quality of life, in particular which symptoms are the most important to patients to control as well as well as experiences with Lenvatinib, discussed in section 3.1.2.

CLF reported that according to the global survey from 2016, of 256 patients living with HCC, fatigue had the biggest impact on quality of life, followed by abdominal pain and nausea. Other factors influencing quality of life included appetite loss, weight loss, diarrhea, skin disorder and alopecia. HCC patients also expressed deep mental and emotional impact such as fear, worry, shock, and sad.

The respondents of the CLF survey of patients, caregivers noted that living with HCC impacted or seriously impacted their ability to work, travel, exercise, conduct household chores, spend time with family and friends, andfulfill family obligations. The quotes below illustrate responses from CLF patient contacts:

"*I have no social life any more. I cannot go anywhere for fear of falling asleep. I need to wear a diaper due to incontinence and feel very uncomfortable about that. I am tired all the time"*

"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."

"My worst symptom is pain and being uncomfortable all the time. Mornings are the worse. 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."

CCSN noted that patients reported symptoms or problems they experienced with HCC which affected their day to day living and quality of life as living with uncertainty (80%), fatigue (60%), weight loss and/or lack of appetite (60%), pain (60%), not sleeping/restless (40%), stigma & judgement from others (20%), isolation or loneliness (20%) and anxiety, panic attacks and/or depression (20%).In addition to the symptoms, patients also added the following quotes:

"My primary liver tumor was found and resected four years ago, but I have a metastatic hepatocellular carcinoma on the C1, C2, etc. cervical vertebrae, which cannot be removed and has caused frequent very intense headache pains by pressing on cranial nerves coming out of intervertebral foramina."

"diarrhea from current medication is severe and results in pain in lower gi tract."

3.1.2 Patients' Experiences with Current Therapy for HCC

CLF noted that HCC is often difficult to treat as it is usually a result of a pre-existing and progressive underlying liver disease. The patient may be experiencing the effects of liver function impairment such as cirrhosis, hepatic encephalopathy, abdominal pain, and swelling (ascites). The treatment of HCC depends on the state and speed of tumour growth as well as the health of the liver. CLF reported that as tumour size increases, cure rates generally decrease.

The current standard for first-line HCC for patients with well-preserved liver function is sorafenib. However, CLF noted that the results of the global survey indicated that patients treated with sorafenib were more likely to rate their current quality of life as poor. CLF has provided some additional quotes copied below for context.

"*I am currently being treated for my HCC and the pain is the worse. I am in pain all the time.*"

"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."

In addition, CCSN asked questions pertaining to the management of hepatocellular carcinoma, including which therapies and treatments they are currently using to treat their disease, how effective these therapies and treatments have been, which side-effects they experiences, and whether they have had issues accessing current therapies and treatment. Five respondents answered what treatments they were currently using as lenvatinib (60%), chemotherapy (40%), trans-arterial chemoembolization (TACE)(40%), radiation therapy (20%), surgery (20%), and liver transplant (20%). Eighty percent of survey respondents reported that their needs in their current therapies are being acceptably met. One respondent indicated that their needs were not being met, the quote below elaborates on this point. CCSN also included questions on the survey asking patient respondents of their expectations of a new drug; however, no responses were received. Eighty percent of respondents reported no issues accessing treatment, while 20% (one respondent) reported an issue with financial hardship due to cost of treatment.

"I have not had any real help in dealing with the severe diarrhea and subsequent pain. I have a sore and inflamed tongue that is also making eating very unpleasant. I am using Imodium PRN and warm saline oral rinses. I did have high blood pressure when first on the drug but my GP was able to control that with an addition to my current blood pressure meds."

Health care professionals who responded to the CLF online survey noted the treatment options they have used as well as the percentage of Health care professional respondents who had experience (%). The types of treatment were noted as follows: radiation therapy (100%), regorafenib for second-line systemic treatment (100%), sorafenib for first-line systemic treatment (100%), transarterial chemoembolization (TACE) (100%), tumor ablation (100%), surgery (80%), nivolumab for second line immunotherapy (20%), and transarterial radioembolization (TARE) (20%). The most common side-effects reported for patients from the health care professionals were numbness, pain, or tingling in hands of feet, dry or peeling skin, skin redness, pruritus (skin itchiness), loss of appetite, diarrhea, weight loss, fatigue, weakness, and dry mouth.

The caregiver who responded to the CLF online survey noted that the patient for whom she was providing care had undergone different treatments for HCC, including tumor ablation, transarterial chemoembolization (TACE) and systemic treatment with sorafenib. The caregiver noted that the patient's most intolerable side effects were pruritus (skin itchiness), loss of appetite and numbness/pain/tingling in hands or feet.

CLF also noted that patients & caregivers who responded to the online survey felt that it was "very important" that patients have access to new treatments for unresectable HCC. Quotes from patient and caregiver contacts from the CLF survey are noted below:

"*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*

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

3.1.3 Impact of HCC and Current Therapy on Caregivers

CCSN did not report on the impact of HCC and current therapy on caregivers.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Lenvatinib (Lenvima)

The CLF online survey responses from health care professionals indicated that all five of the health care professionals had experience with treating patients with lenvatinib. The health care professionals noted that patients were on lenvatinib for 1-6 months. The health care professionals noted that the most common side-effects were high blood pressure, diarrhea, joint and muscle aches, decreased appetite and weight loss, stomatitis (mouth sores), headaches and protein in the urine. The health care professionals also noted that the side-effects were somewhat or very well tolerated by patients.

CCSN included three patient respondents who had experience with lenvatinib. These patients accessed lenvatinib through a compassionate access program. In answering a question on which therapies were most effective, one patient respondent stated that lenvatinib had been the most effective while the other patients rated lenvatinib as somewhat effective. Patients noted lenvatinib as an additional treatment option with positive outcomes along with transplantation and radiation. Two patients expressed the positive effects of lenvatinib as follows:
"The tumour growth appears to have stopped for now"
"It has given me hope of improvement in my prognosis"

In addition, CCSN provided information on three patient respondents who expressed negative effects with lenvatinib. These negative effects are described below:
"Minor diarrhea and possible cause for pain on foot soles"
"The GI side effects: painful diarrhea and tongue inflammation, hypertension and fatigue"
"diarrhea, nausea, high blood pressure".

Two of the respondents noted that diarrhea and high blood pressure were unacceptable side effects of the treatment and three respondents state that fatigue was also not an acceptable side effect. In addition, when asked to define what issues they felt better able to manage with lenvatinib compared to other treatments, all respondents praised the ease of use of lenvatinib, while two respondents praised the reduction in side effects from other medications or treatments, as well as better managing the disease progression.

CCSN also asked patients what expectations they had for their long-term health and well being as a result of taking lenvatinib. The patients' responses are noted below:

"being alive a bit longer"
"I hope that it will shrink or arrest growth of my tumours and prolong my life without too adversely affecting the quality of my life."
"that it is going to do the job it is supposed to do"

*Lastly, CCSN asked p*atient respondents if they had anything else to add. Two respondents left these comments:

"Lenvima doesn't seem to be able to shrink my tumor, but it looks like it stopped its growth, which is probably why I didn't have any more headache pains from pressed cranial nerves"
"Because I do not have any substantial indication of whether or not I am benefitting from this drug ie no CT results, some of my answers are best guesses. I am unsure at this time whether the current side effects and the toll they are taking on me are worth continuing with this therapy. I hope next month's CT will give me some guidance."

CCSN provided qualitative interviews from 8 patients with experience with lenvatinib, 7 men and 1 woman from Ontario, BC, and NWT territories. The following table outlines questions & responses of these patients.

Question	Summary of responses
What has your treatment timeline looked like? E.g. what treatments have you taken before and/or after lenvatinib?	All 8 of the respondents had previous experience with sorafenib and or/regorafenib. All subjects interviewed began treatment with sorafenib, two respondents also used regorafenib. Significant side-effects with sorafenib and/or regorafenib was the main reason for switching to lenvatinib. All patients are currently taking levatinib for their HCC. Patient responses copied below for reference: *"I was on sorafinib for a couple of months before the switch (June 20 – August 10); my doctor switched me because I was essentially housebound on sorafinib – stomach cramps, fatigue, bleeding, constipation"* *"The side effects from regorafenib and sorafenib were so significant that I was unable to tolerate them, even at the lowest doses. Not tolerating these medications made me very anxious and afraid of my disease progressing. When I had the option to try Lenvima it was a night and day difference. And now that I can tolerate the Lenvima well I have regained much hope for my cancer to not metastasize quickly and my scans have demonstrated this to be true for the time being."*
Can you describe in more detail how lenvatinib has or has not improved your quality of life?	All eight patients reported that their quality of life has either stayed the same or has greatly improved with lenvatinib. Patient responses copied below for reference: *"For the last 5 months I have been taking Lenvima as a result of the excruciating side effects related to sorafenib, and as a result was taking such a small dose that my tumour growth resumed. And the position of my tumour is beside my vertebra in my neck so attached to nerves in my head and throat. When my tumour grows I have excruciating headaches, and problems swallowing as a result of muscular contractions in my throat. With Lenvima my tumour has stopped growing (seen in 2 MRI scans to date), I have not had a headache in months and my swallowing has improved tremendously. "*

Question	Summary of responses
	"My quality of life seems about the same; I still have chronic fatigue but I'm able to do the things I did before like go to the movies, see friends, shopping; that part hasn't changed, which is good." *"It's been about a month and I really haven't seen any change or significant improvement."* *"I'm very happy, I haven't had any other challenges or side effects; I'm satisfied because the other drug gave me lots of problems. I know I am a happy father."* *"I have definitely been able to get out more – I can exercise more, just do more things in general; I am actually feeling pretty good."* *"With the Lenvima I am back to doing normal activities, however sometimes a bit tired. But on a normal day I have the energy to do activities and manage my day-to-day routine."* *"I am now able to resume most of my normal routines, including going swimming, and my last CT scan showed a decrease in tumour size so I am very pleased with the results to date."*
What challenges, if any, have you faced in dealing with the side effects of lenvatinib?	In each case, CCSN has noted that patients are still dealing with some side-effects of lenvatinib. Seven of the eight respondents indicated that the side effects from lenvatinb are significantly reduced compared with their prior treatments with sorafenib and/or regorafenib. The eighth patient reported that the side effects (problem with his feet) continue to be significant. Patient responses copied below for reference: *"On Lenvima, I had a short-lived increase in blood pressure; however is now stable. On the 10gm dose I had no side effects so my doctor increased to 14 mg. As a result I have some mouth sores that only appeared with the higher dose. While it makes it a bit harder to eat and some discomfort, overall the positives of the medication have outweighed the negatives."* *"I have had some thickening of the skin on the bottom of my feet as a result of the Lenvima, but no blisters. I was able to tolerate a 4mg dose extremely well so my doctor tried to increase to 8mg; however, some of my side effects returned so we decided to reduce back to a 4mg dose with limited side effects."* *"Mostly, it's just tiredness, though Lenvima seems to be lowering my platelets; right now, my doctor and I are trying to strike a balance between keeping my platelets up and being able to stay on Lenvima."* *"I have had very few side effects with Lenvima, especially compared with sorafenib. I do have some issues with my feet, kind of like callouses, and my podiatrist has provided me with some solutions to help alleviate the pain. I also have some muscle weakness, especially when I sit for a long time; I need to wake my muscles up to stand up."*
Do you believe that the benefits of lenvatinib outweigh the side-effects? Why or why not?	CCSN reported that seven of the eight respondents agreed that lenvatinib benefits outweigh the side effects. It is to be noted that the eighth patient has seen no discernable change. Patient responses copied below for reference: *"Oh yes, right now I am satisfied; I hope it will help me live a little longer or clear the cancer right up; I just need to be sure to use the cream three times a day and drink lots of water; I don't know why, but that really helps me."*

Question	Summary of responses
	"Definitely. My tumours are shrinking, my alpha beta proteins are way down; I even told my doctor that the side effects are minimal; I am tolerating Lenvima much better that the sorafinib." *"I'm sure that if I didn't have the option to take Lenvima then I would be much worse. I was not a candidate for surgery or other treatments, so I do feel that Lenvima is at least giving me a few more months of life."* *"Another benefit of Lenvima is that I can take it with food and fits much easier into my daily life, while sorafenib had to be on an empty stomach and it was very hard to organize my day to allow for 3 hours fasting. "* *"The benefits of Lenvima absolutely outweigh the side effects. Since I was unable to tolerate either of the other medications, this has been an easy transition for me. It also allows me to stay positive."* *"The benefits of Lenvima far outweigh the side effects; especially compared with the side effects of sorafenib including nausea, vomiting and significant blood pressure issues."* *"The side effects I experienced are much improved compared with the regorafenib and sorafenib I had been on prior to Lenvima. I feel that Lenvima is working well and my cancer is being better managed."*
Would you recommend that lenvatinib be available to all patients with HCC who qualify for it? Why or why Not?	For all the patients surveyed, CCSN reported that there is a degree of optimism related to their treatment with lenvatinib. All patients surveyed believed that lenvatinib should be made available as a potential treatment option. Patient responses copied below for reference: *"I think everyone should be able to try it and see if it works for them; I've learned along the way that we are all different and that not everything works for everyone but I do think that the choice should be available. My experience has been very positive so far."* *"Absolutely, my family and I would recommend that Lenvima be made available to all patients who qualify for it"* *"I see tremendous benefit with Lenvima and recommended it highly to those who would need it."* *"Lenvima is making a difference for me so I would absolutely recommend it to anyone who qualifies for it. It is providing our family with hope and we are thankful for the pharmaceutical company that allowed us to try it and are hopeful that it will help extend my life by months or even years."* *"I firmly believe that Lenvima is working for me, and feel that it should be made available to anyone who might be well-served to try it."*

3.3 Additional Information

The CLF noted that if diagnosed early, a patient with liver cancer has more options for treatment, including surgical resection, liver transplant, ablation, chemoembolization and radioembolization. However, many patients are not diagnosed early as they do not show symptoms of having liver cancer until it has already progressed. The possibility of adding a new treatment option at the advanced stage of HCC offers hope to patients and their families who would otherwise have limited options. CLF noted that they believe patients and their physicians should have access to a broad range of treatment options regardless of

geographic location, financial status, treatment status, or disease severity, in order to ensure the best possible outcomes for patients. CLF also notes that it should be up to the physicians to make individual treatment recommendations based on the needs of their patients.

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. 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 lenvatinib relative to sorafenib and sequencing with regorafenib

Economic factors:

- Weight-based dosing may lead to dosing errors

Please see below for more details.

4.1 Factors Related to Comparators

Sorafenib is the standard of care in first line treatment of metastatic HCC and is funded in all provinces. The comparator in the phase 3 non-inferiority REFLECT trial, was sorafenib, this is a relevant comparator.

4.2 Factors Related to 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 manufacturer does not specify Child-Pugh status and the REFLECT study enrolled patients only with ECOG 0 or 1. 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 lenvatinib. In addition, whether patients with intermediate-stage HCC who are unable to receive TACE would be eligible for lenvatinib.

If recommended for reimbursement, the following subgroup of patients would need to be addressed on a time-limited basis:

- Patients who are currently being treated with sorafenib
- Patients who do not tolerate sorafenib and who have recently discontinued sorafenib due to intolerance

There is a potential for indication creep to Child-Pugh score B (pivotal trial only included Child-Pugh score A) as well as to patients who have recently completed local regional therapy for HCC. Clinicians may want to use lenvatinib to maintain any responses from local regional therapy or as a bridge to a liver transplant.

4.3 Factors Related to Implementation Costs

The recommended daily dose of lenvatinib is 8 mg (two 4 mg capsules) once daily for patients with a body weight of <60 kg and 12 mg (three 4 mg capsules) once daily for patients with a body weight of ≥60 kg. The weight-based dosing may lead to potential

dosing errors to be prescribed or administered with lenvatinib.

Although packaging according to dose may improve patient adherence, PAG identified that potential dose adjustments for lenvatinib may result in drug wastage as well as patient confusion, if dose adjustments are made prior to finishing the capsules dispensed.

Lenvatinib is a once daily oral drug. PAG noted that cancer centers would be familiar with administration of lenvatinib, particularly dispensing and side effects. These would be enablers to implementation. However, additional nursing and pharmacy resources would be required for monitoring of adverse events (e.g., hypertension).

PAG noted that lenvatinib 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 is seeking guidance on the place in therapy for lenvatinib and which patient population would benefit most from the treatment and which patient population would be best suited for treatment with other available therapies (i.e. sorafenib). There may be a preference in the first-line setting to use sorafenib as this would allow for a subsequent line of therapy with regorafenib.

Regorafenib for treatment of HCC after sorafenib recently received a conditional reimbursement recommendation conditional on the cost-effectiveness being improved to an acceptable level. At this time, no provinces are currently funding regorafenib. PAG is seeking guidance on second-line treatments following lenvatinib, particularly given regorafenib is indicated after sorafenib and that the REFLECT trial is a non-inferiority trial between lenvatinib and sorafenib

4.5 Companion Diagnostic Testing

None.

4.6 Additional Information

None.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

One joint input from six registered clinicians was provided for the pCODR review of lenvatinib for the first line treatment of adult patients with unresectable hepatocellular carcinoma (HCC). Clinicians were oncologist from different organizations: one was from BC Cancer, three were from various Ontario cancer centres and one was from a cancer centre in Alberta. A summary of the input is provided below.

According to the clinician input, sorafenib is currently the standard first line therapy for HCC. The clinicians believe that lenvatinib would be an appropriate and preferable first-line therapy owing to its milder side effect profile. Sorafenib toxicity manifests more frequently as hand-foot syndrome, a relatively impactful disorder, whereas lenvatinib more readily elevates the risk of hypertension, which is easer to manage. Clinicians highlighted that an advantage of lenvatinib is tumour size reduction which may allow local therapies to be considered. Clinicians believed that the inclusion and exclusion criteria of the phase 3 trial can be applied in Canadian clinical practice. Clinicians deemed that regorafenib, cabozantinib, and possibly sorafenib, would be suitable next-line therapies after lenvatinib. They believed that both lenvatinib and sorafenib should be available as first-line options for HCC to allow drug switching due to tolerance issues.

Please see below for a summary of specific input received from the registered clinicians.

5.1 Current Treatment(s) for this Hepatocellular Carcinoma

The clinician input indicated that both sorafenib (SOR) and lenvatinib (LEN) have data supporting their use in the first line setting. SOR is the only approved first line therapy and has been the standard of care for almost ten years. However, clinicians indicated that 40-50% of patients incur significant toxicities, with the major symptom being hand-foot syndrome (HFS). According to clinicians, these toxicities can be debilitating and negatively affect quality of life.

5.2 Eligible Patient Population

The clinicians who provided input indicated that LEN offers a new option for patients. While the drug shows similarities to SOR, a number of side effects occur at a much lower rate. The clinicians cited rates of HFS occurrence (52% with SOR vs 27% with LEN) and high grade HFS (11% for SOR vs 3% for LEN). In contrast, LEN is reportedly associated with higher rates of hypertension (SOR: ~30%, LEN: 42%). Clinicians see hypertension as more easily managed than HFS, which is more deleterious to a patient's day-to-day abilities.

Clinicians noted that in addition to the increased response rate afforded by LEN (25% versus 9% for SOR), the drug may provide symptomatic benefit with a greater likelihood of tumour size reduction which may allow for further opportunities for localized treatments.

According to the clinicians providing input, the inclusion/exclusion criteria are reasonable and in line with all current first and second line trials. They consider LEN a reasonable choice for first-line patients and it may be suitable for patients who appear to have an intolerance to SOR. Patients would need to have maintained a Child Pugh score of A and have no evidence of radiological progression.

5.3 Relevance to Clinical Practice

Clinicians providing input would tend to use the new treatment as first line therapy in advanced or metastatic HCC. They added that although tyrosine kinase inhibitors (TKIs) have many side effects that can impact quality of life, most patients are likely to tolerate LEN better than SOR. They cited the comparative phase 3 trial REFLECT that demonstrated overall similar side effect rates, but they

highlighted that patients were on LEN nearly twice as long, inflating the risk of treatment-related adverse events.

Clinicians reiterated that LEN-associated hypertension (as observed with other TKIs) is generally easily managed. Nevertheless, patients with poorly controlled hypertension may be better suited for SOR or re-evaluated for LEN if hypertension management can be improved. Clinicians argued that LEN-associated hypertension is better tolerated than SOR-associated HFS, while the latter drug also leads to more GI toxicity and asthenia.

5.4 Sequencing and Priority of Treatments with Lenvatinib

Clinicians providing input noted that numerous phase 3 trials for HCC will be reported in the next 1-2 years, further shaping our understanding of the sequence of drugs and drug combinations for HCC. Cabozantinib, regorafenib and ramucirumab are among the available options for second line therapy following either intolerance to sorafenib or progressive disease. Clinicians remarked that although LEN and SOR differ somewhat in their targets, there is no available data to suggest that current second-line therapies would be less effective following LEN. As a result, they believe it would be reasonable to use regorafenib or cabozantinib after LEN. Clinicians explained that all available second line therapies, and likely future immunotherapies, have novel targets that differ from both SOR and LEN. Clinicians believe both drugs should be available in the first-line setting to allow patients the opportunity to switch in case of severe adverse effects.

5.5 Companion Diagnostic Testing

This aspect does not apply to the current review according to the clinician input.

5.6 Additional Information

None.

5.7 Implementation Questions

5.7.1 The eligibility criteria for the REFLECT trial included a specific patient population compared to the broader funding request. In clinical practice, is there evidence to extend the use of lenvatinib to the following populations (provide all other eligibility criteria are met):

Clinicians commented that patients who would be excluded from the reimbursement population, due to the inclusion/exclusion criteria of the REFLECT trial, generally represent <10% pf patients in clinical practice. These patients also have a worse prognosis. Although these patients were excluded, there is no data to suggest that lenvatinib would be less effective in these sub-groups of patients.

5.7.1.1 Patients with intermediate-stage HCC who are unable to receive TACE?

According to the clinicians, patients who are intolerant to, have a contraindication to, or have progressed on local regional therapy should be eligible for LEN. They indicated that data exist to extend the use of LEN to patients with intermediate-stage HCC who are unable to receive TACE. Technically, if patients have a contraindication for TACE or previous TACE with progression, systemic treatment would be the next available therapy. Clinicians further

noted that the REFLECT trial included 21% of patients with intermediate stage disease. Clinicians would use LEN in intermediate-stage HCC unable to receive TACE.

5.7.2 Patients with Child-Pugh B liver function?

Clinicians noted that there is no available data supporting use of LEN or other tyrosine kinase inhibitors in Child Pugh B liver function. Further data would be required.

5.7.3 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. In what clinical scenarios would lenvatinib or sorafenib be the preferred treatment for first-line unresectable HCC? Please comment on the preference considering patient preference, efficacy, safety, and administration?

Clinicians answered that first-line therapy should include the option of SOR or LEN. Consideration should be made for patients switching therapies due to side effect issues in the absence of radiological progression. Aside from specific situations (such as main portal vein invasion or severe/uncontrolled hypertension), the higher response rate and generally more acceptable side effects of LEN would make it the best choice for most patients.

Clinicians further added that LEN would be preferred as it has similar demonstrated clinical efficacy and better safety. Regorafenib would be a reasonable second line therapy if a clinician trial is not available. One physician contributing to the input noted that Asian patients seem to have a higher risk of developing HFS. He would consider LEN over SOR in these patients.

The clinician input suggests that LEN would be preferred in HCC patients where a response is required to improve clinical symptoms or to allow access to localized treatments. Additionally, it was suggested that LEN should be considered for patients that you are trying to bridge to liver transplant where prolonged PFS is important. Clinicians reiterated that patients who are intolerant of but have not progressed on SOR could also be considered for LEN particularly if the main reason for SOR intolerance is hand-foot syndrome. By the same logic, SOR would be preferred in patients who have hypertension that is poorly controlled despite a number of available anti-hypertensive medications.

5.7.4 What treatment options would be available to patients upon progression of lenvatinib? Regorafenib for treatment of HCC after sorafenib recently received a conditional reimbursement recommendation conditional on the cost-effectiveness being improved to an acceptable level. At this time, no provinces are currently funding regorafenib. In clinical practice, is there evidence to sequence regorafenib or sorafenib after lenvatinib?

The clinicians who answered this question believed it would be reasonable to treat patients with SOR after LEN. While most second line trials were after SOR, recent data presented at ASCO showed that patients still received second line therapy post LEN and had a median survival of 20 months. If they demonstrated a response to LEN, survival was around 25 months. Therefore, clinicians think it would be reasonable to consider regorafenib or

possibly SOR after LEN. They referred to emerging trial data regarding sequencing and immunotherapy that will be released in 2019 which may inform the sequencing question.

Clinicians further discussed the potential role of cabozantinib. Should it be funded in the future, it could be potentially used as a third-line TKI treatment since the CELESTIAL trial included patients who had up to two lines of previous treatment as long as one line was SOR. They added that second-line therapies should be funded following progression on any first-line therapy (SOR or LEN). However, they noted that there are no data to guide therapy choice following LEN. Such data would only become available from database analyses or phase 4 trials.

5.7.5 For patients intolerant to sorafenib, is there evidence to use regorafenib or lenvatinib?

Clinicians cited evidence supporting the use of regorafenib for those who are intolerant to SOR and further commented that LEN would be a reasonable clinical alternative.

6 SYSTEMATIC REVIEW

6.1 Objectives

The objective of this systematic review is to evaluate the safety and efficacy of lenvatinib (Lenvima) in the first-line treatment of adult patients with unresectable, advanced, hepatocellular carcinoma (HCC).

6.2 Methods

6.2.1 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 RCTs In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of lenvatinib should be included.	Adult patients (≥18 years of age) with advanced, unresectable, HCC with no prior systemic therapy for disease <u>Subgroups:</u> - BCLC Stage B (ineligible for TACE) vs. C - Child-Pugh class A - ECOG PS 0 vs. 1 - Age (<65; ≥ 65 years) - Weight (<60kg; ≥60kg) - Aetiology (hepatitis B; hepatitis C; alcohol; other) - AFP (<200ng; ≥200ng) - Macrovascular invasion - Extra hepatic spread - Numbers and sites of metastases - Liver cirrhosis - Baseline hypertension	Lenvatinib (Lenvima)	Sorafenib (Nexavar)	<u>Primary:</u> - OS - PFS - HRQoL <u>Secondary:</u> - TTP - ORR - CBR <u>Safety:</u> - AEs - TEAEs - SAEs - WDAEs

Abbreviations: **AFP** = alpha-fetoprotein; **AE** = adverse event; **BCLC** = Barcelona Clinic Liver Cancer; **BID** = twice daily; **CBR** = clinical benefit rate; **ECOG PS** = Eastern Cooperative Oncology Group Performance Status; **HCC** = hepatocellular carcinoma; **HRQoL** = health-related quality of life; **kg** = kilograms; **mg** = milligrams; **ng** = nanograms; **ORR** = objective response rate; **OS** = overall survival; **PFS** = progression-free survival; **QD** = once daily; **RCT** = randomized controlled trial; **SAE** = serious adverse event; **TACE** = transcatheter arterial chemoembolization; **TEAEs** = treatment-emergent adverse events; **TTP** = time to progression; **vs.** = versus; **WDAEs** = withdrawals due to adverse events

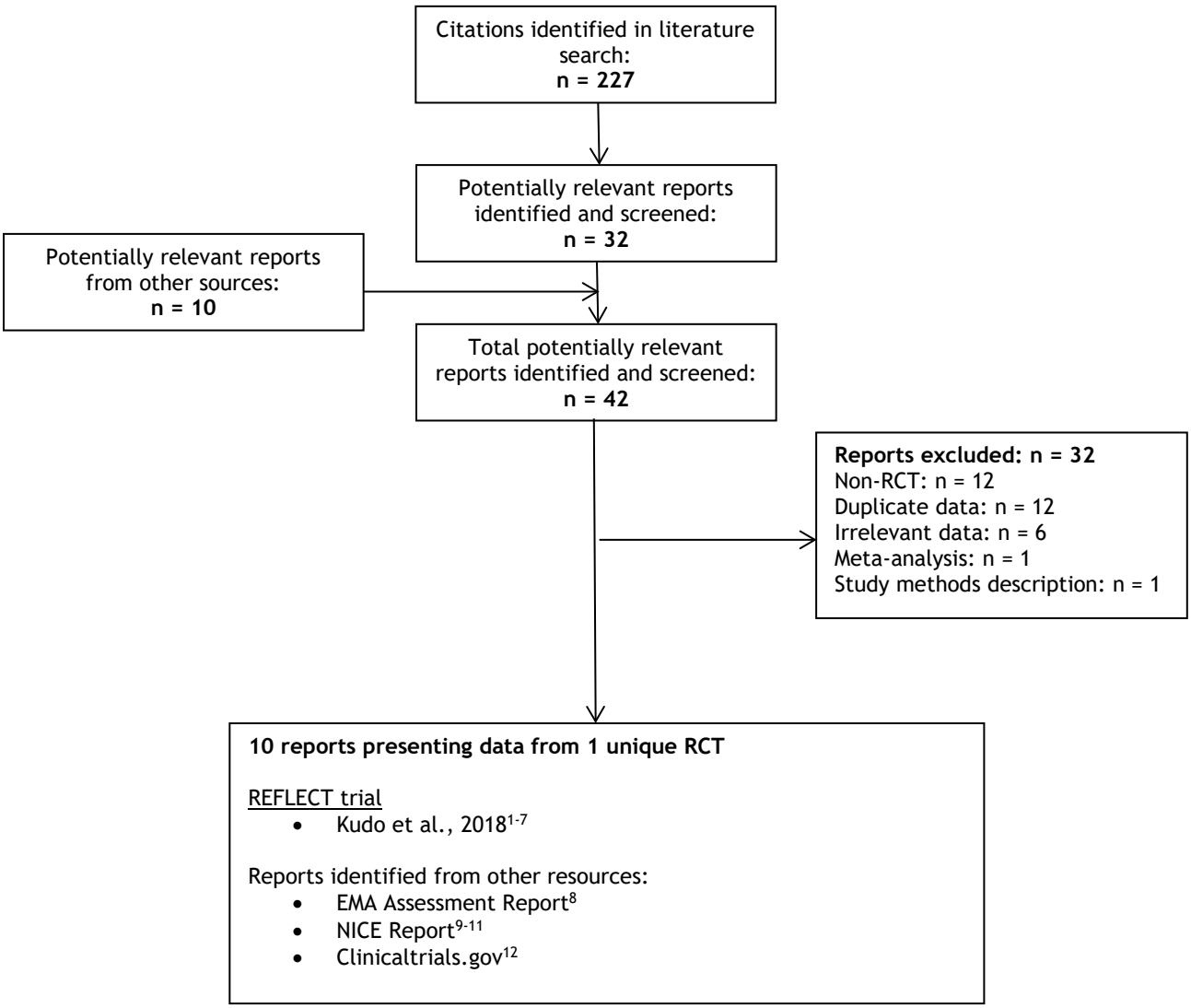
** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.3 Results

6.3.1 Literature Search Results

Of the 50 potentially relevant citations identified, 9 citations reporting data from one clinical trial were included in the pCODR systematic review, and 41 citations were excluded. Citations were excluded because they included irrelevant study types (non-RCTs and meta-analysis)[28-40], contained duplicate data[41-52], irrelevant data[52-57], and the citation included study methods description only.[58] Figure 6.1 illustrates the PRISMA flow diagram for the study selection process.

Figure 6.1. Sample QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to the REFLECT trial was also obtained through requests to the Submitter by pCODR.[59,60]

6.3.2 Summary of Included Studies

One randomized clinical trial, REFLECT, met the selection criteria for this systematic review. Key trial characteristics, including study design, eligibility criteria, intervention details, and trial outcomes, are summarized in Table 6.2.[5]

6.3.2.1 Detailed Trial Characteristics

Table 6.2: Summary of Trial Characteristics of the REFLECT trial[5]

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study: REFLECT NCT01761266 E7080-G000-304 **Characteristics:** Open-label randomised (1:1), head-to-head, non-inferiority, phase III trial N= 954 randomized (lenvatinib = 478 and sorafenib = 476) N= 951 treated (2 not treated in lenvatinib, 1 not treated in sorafenib) **Setting:** 154 sites in 20 countries including Canada, China, Hong Kong, Japan, South Korea, Malaysia, Philippines, Singapore, Taiwan, Thailand, Belgium, France, Germany, Israel, Italy, Poland, Russia, Spain, UK, and USA. **Patient Enrolment Dates:** March 1st, 2013 to July 30th, 2015 **Data cut-off dates:** Final analysis: November 13th, 2016 **Funding:** Eisai Limited	<u>Key Inclusion Criteria:</u> • Histological or cytological confirmed diagnosis of unresectable HCC; clinically confirmed diagnosis of HCC according to AASLD • Cirrhosis of any etiology or with chronic hepatitis B or C infection • Stage B (not applicable for TACE) or C based on BCLC staging • Liver function status Child-Pugh score A • ECOG PS 0 or 1 • Adequate bone marrow, liver, renal, pancreatic, and blood coagulation function • Adequately controlled blood pressure (<150/90 mmHG) with ≤ 1 antihypertensive medication • At least 1 measurable hepatic or non-hepatic target lesion by CT scan or MRI according to mRECIST • Survival expectation of ≥ 12 weeks <u>Key Exclusion Criteria:</u> • Any prior systemic anticancer therapy (including chemotherapy, sorafenib, investigational agents) • Any anticancer therapy (such as surgery, TACE, etc.) or blood enhancing treatment within 28 days prior to randomization • HCC with ≥ 50% liver occupation, clear invasion into the bile duct; or portal vein invasion at the main portal branch (Vp4) • Ongoing toxicities (≥ Grade 2 severity) per CTCAE version 4.0 from prior anticancer therapy • Significant cardiac impairment • GI malabsorption; GI bleeding event or active hemoptysis within 28 days prior to randomisation • Bleeding or thrombotic disorders, or use of anticoagulants (except LMWH) • Active malignancy other than HCC7, melanoma in-situ, basal or squamous cell carcinoma or the skin, or carcinoma in-situ of the cervix, within past 36 months • Meningeal carcinomatosis	<u>Intervention:</u> Lenvatinib - 8mg (two 4mg oral capsules) for patients <60kg or 12mg (three 4mg oral capsules) for patients ≥60kg QD <u>Comparator:</u> Sorafenib - 400mg oral tablets BID	<u>Primary:</u> - OS <u>Secondary:</u> - PFS - TTP - ORR - HRQoL - Plasma PK <u>Safety</u> - AEs - TEAEs - SAEs <u>Exploratory</u> - DCR - CBR

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	• Prior or current brain or subdural metastases • Proteinuria (≥1g/24h) • HIV positive or active infection requiring treatment (except hepatitis) • History of drug or alcohol dependency • Allergy or contraindication to CT or MRI contrast agents • Major surgery planned during study or within 3 weeks of study start • Prior liver transplant		

Abbreviations: AASLD = American Association for the Study of Liver Diseases; AE = adverse event; BCLC = Barcelona Clinic Liver Cancer; BID = twice daily; CBR = clinical benefit rate; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; DCR = disease control rate; ECOG PS = Eastern Cooperative Oncology Group Performance Status; GI = gastrointestinal; HCC = hepatocellular carcinoma; HIV = human immunodeficiency virus; HRQoL = health-related quality of life; LMWH = low molecular weight heparin; mg = milligrams; mRECIST = modified response evaluation criteria in solid tumors; MRI = magnetic resonance imaging; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; QD = once daily; SAE = serious adverse event; TACE = transarterial chemoembolization; TEAEs = treatment-emergent adverse events; TTP = time to progression

Table 6.3: Select quality characteristics of included studies of lenvatinib in patients with

Study	Treatment vs. Comparator	Primary outcome	Required s=Sample Size	Sample Size	Randomization Method	Allocation Concealment	Blinding	ITT Analysis	Final Analysis	Early Termination	Ethics Approval
REFLECT	Lenvatinib vs sorafenib	OS	940	954	1:1 based on a computer-generated randomization scheme with a block size of 2; reviewed and approved by independent statistician	Yes, via interactive voice-web response system	No	Yes	Yes	No	Yes

a) Trials

REFLECT was an open-label, phase 3, non-inferiority (NI), randomized controlled trial (RCT) of lenvatinib versus sorafenib in first-line treatment of patients with advanced, unresectable hepatocellular carcinoma (HCC) with no prior systemic therapy. This study was conducted at 154 sites in 20 countries, which are listed in Table 6.2, and included 1 patient from the single, participating site in Canada.[5]

Trial Design

The REFLECT study included a pre-randomization, randomization, and extension phase, illustrated in Figure 6.2[8].

Pre-randomization Phase

The pre-randomization phase included a screening period to determine eligibility, and a baseline period to evaluate disease characteristics prior to randomization.[8] Key inclusion criteria included a histological, cytological, or clinically (according to AASLD criteria) confirmed diagnosis of HCC, classified as Stage B (not applicable to TACE) or Stage C based on BCLC. Participants with liver function status of Child-Pugh score A, ECOG PS 0 or 1, cirrhosis of any etiology, or concurrent hepatitis B or C infections were included. Participants with prior anticancer systemic therapy, HCC with ≥50% liver occupation, clear invasion into the bile duct or main portal branch invasion (Vp4), and significant cardiovascular impairment were excluded.[5] Additional eligibility criteria can be found in Table 4.

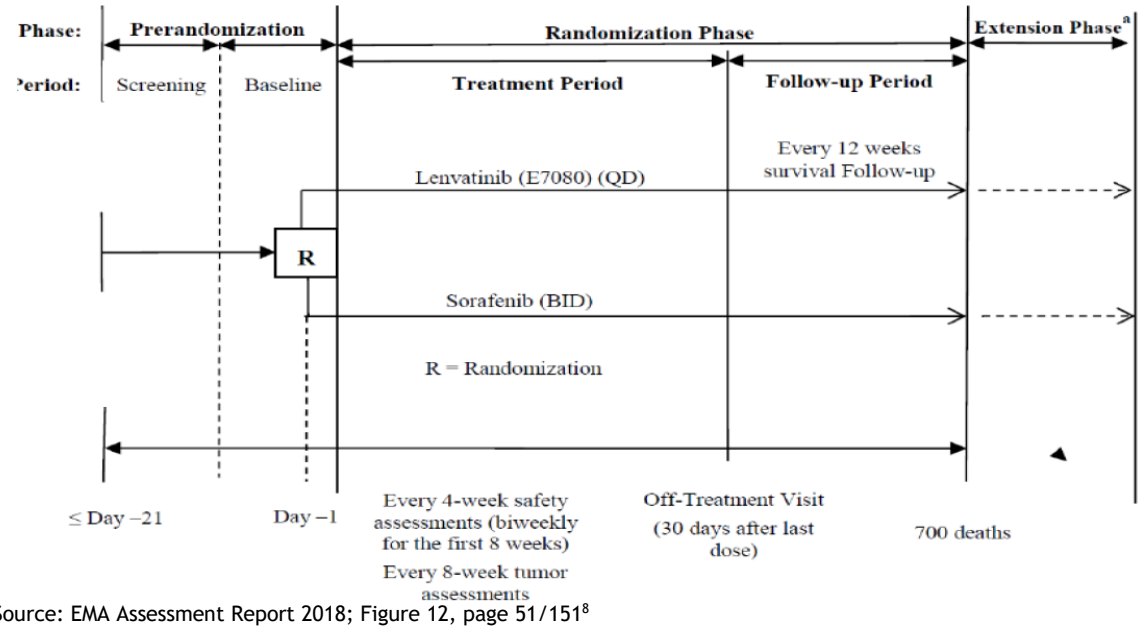
Randomization Phase

The randomization phase included a treatment and follow-up period, and ended when the target number of events (700 deaths) among the two treatment groups occurred, which was the time of data cut-off for the primary study analysis (November 13th, 2016).[8] Participants were randomly assigned in a 1:1 ratio to receive either lenvatinib or sorafenib, and allocation was concealed via an interactive voice-web response system. Allocation of treatment was stratified by region (Asia-Pacific, which included China, Hong Kong, Japan, South Korea, Malaysia, Philippines, Singapore, Taiwan, and Thailand; or Western, which included Belgium, United Kingdom, Spain, Germany, Italy, Poland, France, USA, Canada, Israel, and Russia); macroscopic portal vein invasion, extrahepatic spread, or both (yes or no); ECOG PS (0 or 1); and bodyweight (<60kg or ≥60kg). A randomization block size of 2 was used. The treatments were not masked to the patients or investigators, as the study was open-label. The treatment period began at the time of randomization and consisted of 28-day cycles of study drug until participants discontinued treatment (and completed an off-treatment visit within 30 days of their last dose). The follow-up period began immediately after the off-treatment visit, and participants were followed every 12 weeks for survival. Follow-up continued for as long as the participant remained alive or until the sponsor terminated the study or withdrew consent.[5]

Extension Phase

The extension phase also included a treatment and follow-up period. All participants still on treatment at the end of the randomization phase continued the same study treatment in the extension phase.[8] As of the data cut-off date, 27 participants receiving lenvatinib and 25 participants receiving sorafenib were in the extension phase.[5]

Figure 6.2. REFLECT Study Design



Source: EMA Assessment Report 2018; Figure 12, page 51/151[8]

Study Endpoints, Disease Assessments, and Statistical Analyses

Primary Endpoint

The primary endpoint was overall survival (OS), measured from the date of randomization until the date of death from any cause. Assuming a 5% dropout, 700 deaths were required for the primary analysis.[5] OS was tested for NI using the full analysis set (FAS), which included all participants who were randomized as per the randomization treatment group. The primary efficacy analysis for NI was also analyzed with the protocol set (PPS), which included all participants who were randomized and had at least 1 dose of the assigned study drug, as a secondary analysis group.[8] Participants who were alive at the data-cut-off date were censored at this time point, and those who were lost to follow-up were censored at the last date they were known to be alive.[5] The 95% confidence interval (CI) lower-limit method on log HR was used to determine the NI margin, set at 1.08, which preserved 60% of the effect of the pooled HR, 0.6865 (95% CI: 0.5709, 0.8255), of the sorafenib vs. placebo effect estimated from the SHARP trial and Asia-Pacific trial of sorafenib vs placebo.[5,20,21,59] The pooled HR was calculated using the meta-analysis method proposed by Parmar et al., 1998.[59] The power of the study to declare NI was 97% based on a margin of 1.08 and true HR of 0.80.[5] NI was declared if the upper limit of the two-sided HR of lenvatinib vs. sorafenib, estimated using a Cox proportional hazard model with treatment groups as a factor and stratified by the randomization stratification factors (region, presence of main portal vein invasion and/or extrahepatic spread, ECOG PS, and body weight), was less than 1.08. If NI, was declared then OS was tested for superiority using a stratified log-rank test with the randomization stratification factors, and the type 1 error rate set at 0.05 (2-sided). The power of the study to declare superiority was 82% with assumed true HR of 0.80. Multiplicity adjustments were not required for the testing of NI and superiority due to the closed testing principle. The median OS and cumulative probability of OS at selected time points for each treatment

group was calculated using Kaplan-Meier estimates and presented with 2-sided 95% CIs, and Kaplan-Meier estimates were plotted over time.[8]

Secondary Endpoints
Secondary endpoints included progression-free survival (PFS), time to progression (TTP), objective response rate (ORR), and health-related quality of life (HRQoL). After NI was declared, secondary efficacy outcomes were tested and the fixed sequence procedure was used to control the overall type I error rate at $\alpha = 0.05$ (2-sided).[5] The secondary efficacy outcomes were tested for superiority at the 5% level in a pre-specified order (PFS, TTP, ORR, HRQoL) until the first non-significant outcome occurred. Results of subsequent endpoints after a non-significant outcome would be for descriptive purposes only.[8] PFS, TTP, and ORR, were evaluated by tumor assessments that occurred every 8 weeks. CT or MRI imaging techniques were used to examine the liver, and tumor assessments were conducted by local investigators in accordance with mRECIST. Participants who discontinued treatment without radiological progressive disease (PD) continued tumor assessments every 8 weeks until PD or the start of another anticancer treatment.

HRQoL was measured at baseline, day 1 of every treatment cycle, and at the off-treatment visit. HRQoL was assessed using two European Organisation for Research and Treatment of Cancer (EORTC) questionnaires, the EORTC Quality of Life Questionnaire C30 (EORTC QLQ-C30) and the HCC-specific questionnaire, the EORTC QLQ-HCC18.[5] The EORTC QLQ-C30, consists of 30 questions associated with 5 functional scales (physical, role, emotional, cognitive, and social functioning), 9 symptom scales (fatigue, nausea and vomiting, pain, dyspneoa, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties), and a single global health status score. The QLQ-HCC18 consists of 18 questions specifically related to HCC and included 8 symptom scales (fatigue, jaundice, body image, nutrition, pain, and fever, sex life, and abdominal swelling). Raw scores were calculated as the average of the items that contributed to the scale, and raw scores were standardized to range from 0 – 100. Increases in scores for functional domains were improvements, while increases in scores for symptoms were deterioration. A clinically relevant change in score on any scale of the EORTC QLQ-C30 has been estimated to 10 points.[61] Additionally, the European Quality of Life (EuroQoL) EQ-5D-3L was also used to complement other QoL instruments, which measures current health status on a visual analogue scale (VAS), and assesses health outcomes that cover 5 domains (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), which are used to generate a health utility index (HUI).[12]

Statistical analyses for secondary efficacy endpoints were conducted as follows:

- **PFS:** PFS was defined as the time from the date of randomization to the date of first documentation of PD, or date of death, whichever occurred first. The test for a difference in PFS between treatment groups was performed using a long-rank test stratified by randomization stratification factors, and the associated HR and 95% CI was calculated using Cox proportional hazards model with treatment group as a factor and stratified by the randomization stratification factors. For each treatment group, median PFS and cumulative probability of PFS with 95% CIs for selected time points were calculated, and Kaplan-Meier estimates of PFS were plotted over time.[8] Participants were censored for PFS in the following situations:
    - No baseline tumor assessments (censored at date of randomization)

    - No progression at the time of data cut-off or discontinuation from study treatment (censored at date of last adequate radiologic assessment prior to or on the date of data cut-off or discontinuation)
    - New anticancer treatment started (censored at date of last adequate radiologic assessment prior to or on the date of new anticancer therapy)
    - Death or progression after more than one missed visit (defined as death or PD >125 days after last tumor assessment) or after 28 days from the last dose of study treatment (censored at date of last adequate radiologic assessment before missed tumor assessments)[59]
- **TTP:** TTP was defined as the time from the date of randomization to the date of first documentation of PD. The same evaluation technique as PFS was used for TTP, with the exception that death was censored.[8]
- **ORR:** ORR was defined as the proportion of participants who had the best overall response of complete response (CR) or partial response (PR). If ORR could not be determined, then participants were considered as having no ORR. The statistical difference in ORR between treatment groups was evaluated using the Cochran-Mantel-Haenszel chi-square test with the stratification factors as strata, tested at $\alpha = 0.05$ (2-sided). The odds ratio (ORs) and 95% CI for the difference in ORR were calculated as well as the rate (with 95% CI) within each treatment group.[8]
- **HRQoL:** The primary analysis involved cross-sectional analyses for each patient reported outcome variable using the cross-sectional population (CSP; includes participants alive at a single, specified QoL data collection time point with available cycle-specific QoL data). Descriptive analyses included scores at each cycle and change from baseline. Simple comparative analyses using one-sample paired t-tests and two-sample t-tests were used to test for score changes between time points for each treatment group, and the differences between treatment arms for overall score and change from baseline, respectively. Secondary analyses included hierarchal testing of the EORTC QLQ-HCC18 and QLQ-30 domains, if a domain was found to be non-significant, further testing was stopped. The longitudinal period population (LPP; included participants who have survived from baseline to a specified cycle or treatment discontinuation and has QoL data for that time point) was used in mixed models to estimate the effect of treatment assignment on change in domain scores from baseline. Sensitivity analyses were conducted using the PPS population. Longitudinal modelling of the EQ-5D-3L HUI, EQ-5D-3L VAS, and EORTC QLQ-C30 summary scores will be conducted to estimate the effect of treatment assignment on change from baseline if the LPP sample size permitted.

Exploratory Endpoints

Select subgroup analyses were conducted within each subgroup for primary and secondary outcomes. Exploratory endpoints included the disease control rate (DCR) and clinical benefit rate (CBR). The DCR was defined as the proportion of subjects with a best overall response (BOR) of complete response (CR), partial response (PR), or stable disease (SD). BOR of SD was at least 7 weeks after randomization, and participants where ORR could not be determined were considered to have uncontrolled disease. The CBR was defined as the proportion of subjects who had a BOR of CR or PR or durable SD, which is SD duration of ≥ 23 weeks after randomization.[8] The difference in DCR and CBR were evaluated in a similar procedure to ORR. Post-hoc exploratory tumor assessments, using mRECIST and

RECIST version 1.1., were conducted by a masked central independent imaging review (IIR).[59]

Safety Assessments
The safety analysis set included participants who received at least 1 dose of study treatment. Safety assessments included recording vital signs, haematological and biochemical laboratory testing, urinalysis, and electrocardiography, and were regularly monitored and assessed throughout the study.[5,8]

Sample Size

Sample size was estimated based on the required number of events (deaths) to detect NI and superiority of lenvatinib to sorafenib in OS. The following assumptions were used to estimate the target events:

- Exponential distribution of OS.
- An improvement in OS of 2.5 months with the objective of achieving a HR of 0.8 was considered to be of marked clinical benefit, based on a median OS of sorafenib of 10 months.
- The power of the study to declare NI was 97%, based on an assumed true HR of 0.80 and NI margin of 1.08.
- The power of the study to declare superiority was 82% based on an assumed true HR of 0.80, and a type 1 error rate of 5% (2-sided).

Based on these assumptions, the required number of events was estimated to be approximately 666 deaths for the PPS. Assuming 5% dropout in the PPS due to major protocol deviations, approximately 700 deaths would be required at the time of the primary analysis. Two interim analyses for futility, conducted at approximately 30% and 70% of the target number of events, were taken into account. It was estimated 940 subjects were to be randomized to observe the required number of events, which equated to a minimum of 470 per treatment group based on a 1:1 randomization ratio.[8]

Funding

The trial was funded by Eisai Inc. No competing interests were declared by 5 of the authors, and 2 authors declared non-Eisai related potential conflicts of interest. All other authors (15 in total) reported potential conflicts of interest related to compensation from Eisai Inc. in the form of employment, grants, personal fees, non-financial support, consultancy fees, research funding, and honoraria. Of the 15 authors, 6 were employed directly by Eisai Inc., and these authors played a significant part in the study design, data collection, data analysis, data interpretation, and writing of the report.[5]

b) Populations

A total of 954 participants were enrolled and randomized to lenvatinib (n=478) and sorafenib (n=476). Demographic characteristics are summarized in Table 6.4. The median age of the lenvatinib group was 63.0 (20-88), and 62.0 (22-88) in the sorafenib group, with a slightly older population in the lenvatinib group (43% ≥ 65 years of age in the lenvatinib group vs. 40% in the sorafenib group). Overall, baseline and disease characteristics were balanced between groups. Participants were predominately male (84%), and from the Asia-Pacific region (67%). The majority of participants had an ECOG PS of 0 (63%); Child-Pugh A liver function (99%); BCLC stage C disease (79%); bodyweight ≥ 60 kg (69%); and extrahepatic

spread (61%). In both treatment arms, 43% had one involved disease site, whereas 57% had two or more involved disease sites. Approximately one-third of participants were receiving concurrent systemic antiviral therapy for hepatitis B or C, and 70% had previous anticancer procedures. Between treatment groups, differences in baseline characteristics are highlighted below:

- Aetiology of chronic liver disease:
    - More participants in the lenvatinib arm had an underlying aetiology of liver disease from hepatitis B (53%) and alcohol (8%) compared to sorafenib (48% and 4%, respectively).
    - More participants in the sorafenib arm had an underlying aetiology of liver disease from hepatitis C (26%) compared to lenvatinib (19%).
- Baseline α-fetoprotein (AFP) concentration :
    - A higher proportion of participants in the lenvatinib arm had an AFP concentration ≥ 200ng (46%) compared to sorafenib (39%).
- Involved disease sites:
    - The lenvatinib arm had a slightly higher proportion of participants with ≥ 3 involved disease sites (22%) compared to the sorafenib arm (18%).[5]

Table 6.4: Baseline demographics and clinical characteristics

	Lenvatinib (n=478)	Sorafenib (n=476)	Total (n=954)
Age (years), median (range)	63·0 (20–88)	62·0 (22–88)	62·0 (20–88)
Age group (years)			
<65	270 (56%)	283 (59%)	553 (58%)
≥65 to <75	150 (31%)	126 (26%)	276 (30%)
≥75	58 (12%)	67 (14%)	125 (13%)
Sex			
Male	405 (85%)	401 (84%)	806 (84%)
Female	73 (15%)	75 (16%)	148 (16%)
Region			
Western	157 (33%)	157 (33%)	314 (33%)
Asia-Pacific	321 (67%)	319 (67%)	640 (67%)
Race			
White	135 (28%)	141 (30%)	276 (29%)
Asian	334 (70%)	326 (68%)	660 (69%)
Other	9 (2%)	9 (2%)	18 (2%)
Bodyweight (kg)			
<60	153 (32%)	146 (31%)	299 (31%)
≥60	325 (68%)	330 (69%)	655 (69%)
Eastern Cooperative Oncology Group performance status			
0	304 (64%)	301 (63%)	605 (63%)
1	174 (36%)	175 (37%)	349 (37%)
Child-Pugh class			
A	475 (99%)	471 (99%)	946 (99%)
B	3 (1%)	5 (1%)	8 (1%)
Macroscopic portal vein invasion			
Yes	109 (23%)	90 (19%)	199 (21%)
No	369 (77%)	386 (81%)	755 (79%)
Extrahepatic spread			
Yes	291 (61%)	295 (62%)	586 (61%)
No	187 (39%)	181 (38%)	368 (39%)
Macroscopic portal vein invasion, extrahepatic spread, or both			
Yes	329 (69%)	336 (71%)	665 (70%)
No	149 (31%)	140 (29%)	289 (30%)
Underlying cirrhosis based on masked independent imaging review			
Yes	356 (74%)	364 (76%)	720 (75%)
No	122 (26%)	112 (24%)	234 (25%)
Barcelona Clinic Liver Cancer stage			
B (intermediate stage)	104 (22%)	92 (19%)	196 (21%)
C (advanced stage)	374 (78%)	384 (81%)	758 (79%)
Involved disease sites			
Liver	441 (92%)	430 (90%)	871 (91%)
Lung	163 (34%)	144 (30%)	307 (32%)
Involved disease sites per patient*			
1	207 (43%)	207 (43%)	414 (43%)
2	167 (35%)	183 (38%)	350 (37%)
≥3	103 (22%)	86 (18%)	189 (20%)

Aetiology of chronic liver disease			
Hepatitis B	251 (53%)	228 (48%)	479 (50%)
Hepatitis C	91 (19%)	126 (26%)	217 (23%)
Alcohol	36 (8%)	21 (4%)	57 (6%)
Other	38 (8%)	32 (7%)	70 (7%)
Unknown	62 (13%)	69 (14%)	131 (14%)
Baseline α-fetoprotein concentration (ng/mL)			
Number of patients	471 (99%)	463 (97%)	934 (98%)
Mean (SD)	17 507·5 (105 137·4)	16 678·5 (94 789·5)	17 096·5 (100 088·8)
Median (IQR)	133·1 (8·0–3730·6)	71·2 (5·2–1081·8)	89·0 (6·3–2120·2)
Baseline α-fetoprotein concentration group (ng/mL)			
<200	255 (53%)	286 (60%)	541 (57%)
≥200	222 (46%)	187 (39%)	409 (43%)
Missing	1 (<1%)	3 (1%)	4 (<1%)
Concomitant systemic antiviral therapy for hepatitis B or C	163 (34%)	149 (31%)	312 (33%)
Previous therapy			
Previous anticancer procedures	327 (68%)	344 (72%)	671 (70%)
Radiotherapy	49 (10%)	60 (13%)	109 (11%)

Data are mean (SD) or n (%) unless otherwise specified. *One patient had no baseline target lesion.

Reprinted from Lancet vol. 391/10126. Kudo M, Finn RS, Quin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. P.1163-1173., Copyright 2018, with permission from Elsevier.

c) Interventions

Treatment Dosing Schedule

Study treatments were administered orally in 28-day cycles as follows:

- Lenvatinib was administered in two doses based on bodyweight, 12 mg/day (≥60 kg) or 8 mg/day (<60 kg), once daily.
- Sorafenib was administered at 400 mg, twice daily.[5]

Patients remained on study treatment until objectively documented PD, development of unacceptable toxicity, participant request, and withdrawal of consent.[8]

Treatment Duration, Exposure, and Intensity

The median duration of treatment was longer in the lenvatinib group (5.7 months; IQR: 2.9-11.2), compared to the sorafenib group (3.7 months; IQR: 1.8-7.4).[5] In the lenvatinib arm, 41% (51% receiving 8 mg and 36% receiving 12 mg) of participants received 100% of their planned starting dose, and 27.7% (24% receiving 8 mg and 30% receiving 12 mg) received 80% of their planned starting dose. Thus, 75% (8 mg) and 66% (12 mg) of patients received at least 80% of their planned dose. Three participants accidentally received higher than planned doses once each; 2 patients received 24 mg and 1 patient received 120 mg. Overall, 65% of participants in the sorafenib arm received at least 80% of their planned dose (33.9% received 100% of the planned dose and 31.2% received 80% of the planned dose).[8]

Dosing intensity for participants in the lenvatinib arm, on average, was 88% of the planned dose and 83% for participants in the sorafenib arm. The mean dose intensity was 7.0 mg and 10.5 mg in the 8 mg/day and 12 mg/day groups in the lenvatinib arm, respectively, and 663.8 mg in the sorafenib arm.[8]

Previous Anticancer Procedures

Overall, 70.3% of participants reported having any previous anticancer procedure, and approximately 55.6% reported 1-2 previous procedures. The most commonly reported previous procedure in both treatment groups was transarterial chemoembolization (51.5%). Other procedures included radiofrequency ablation, hepatectomy, hepatic intra-arterial chemotherapy, cryoablation, percutaneous ethanol injection, and other (included primarily microwave therapy, pulmonary resections, biopsies, and hepatectomy). Approximately 11.4% of participants had previous radiotherapy, and just under half of these participants had radiotherapy within 3 months of randomization. The median time from the end of the most recent procedure to randomization was similar in both lenvatinib and sorafenib, at 3.8 months (IQR 2.0, 6.7) and 3.7 months (IQR 2.1, 5.9), respectively.[8]

Concomitant Medications

Over 95% of participants received at least 1 concomitant medication, which were only used to improve symptoms and treat complications. The only exception was palliative radiotherapy that was used to treat non-target lesions, primarily bone lesions, in 2.7% of participants in the lenvatinib arm and 1.9% of participants in the sorafenib arm. Most concomitant medications were balanced between arms with the exception of anti-hypertensives and thyroid preparations, which were more commonly administered in the lenvatinib group (72.8% and 13.6%, respectively) compared to the sorafenib group (67.6% and 4.6%, respectively). Loperamide use was higher in the sorafenib group (24.4%) than the lenvatinib group (15.9%), as well as dermatological emollients.[8]

Subsequent Interventions

During survival follow-up, more participants in the sorafenib group received any anticancer medication (38.7%) and any anticancer procedure (27.3%), compared to the lenvatinib group (32.6% and 25.5%, respectively). Sorafenib was the most commonly used anticancer medication, given to a higher proportion of lenvatinib-treated participants (n=121; 25.3%) compared to sorafenib-treated participants (n=56; 11.8%) who were retreated or continued on sorafenib during survival follow-up. Investigational agents were given to a higher proportion of sorafenib-treated participants than lenvatinib-treated participants (9.5% and 3.1%, respectively), as many second-line trials targeted sorafenib failures or sorafenib-intolerant participants.[8] Of note, regorafenib was given to a total of 10 patients, 2 (0.4%) in the lenvatinib arm, and 8 (1.7) in the sorafenib arm.[59] Anticancer procedures during follow-up were comparable between groups, with TACE, regional chemotherapy, and radiotherapy to the bone being the most common given to 14.4%, 4.8%, and 5.0%, of lenvatinib-treated participants and 17.0%, 5.3%, and 4.8% of sorafenib-treated participants, respectively.[8]

d) Patient Disposition

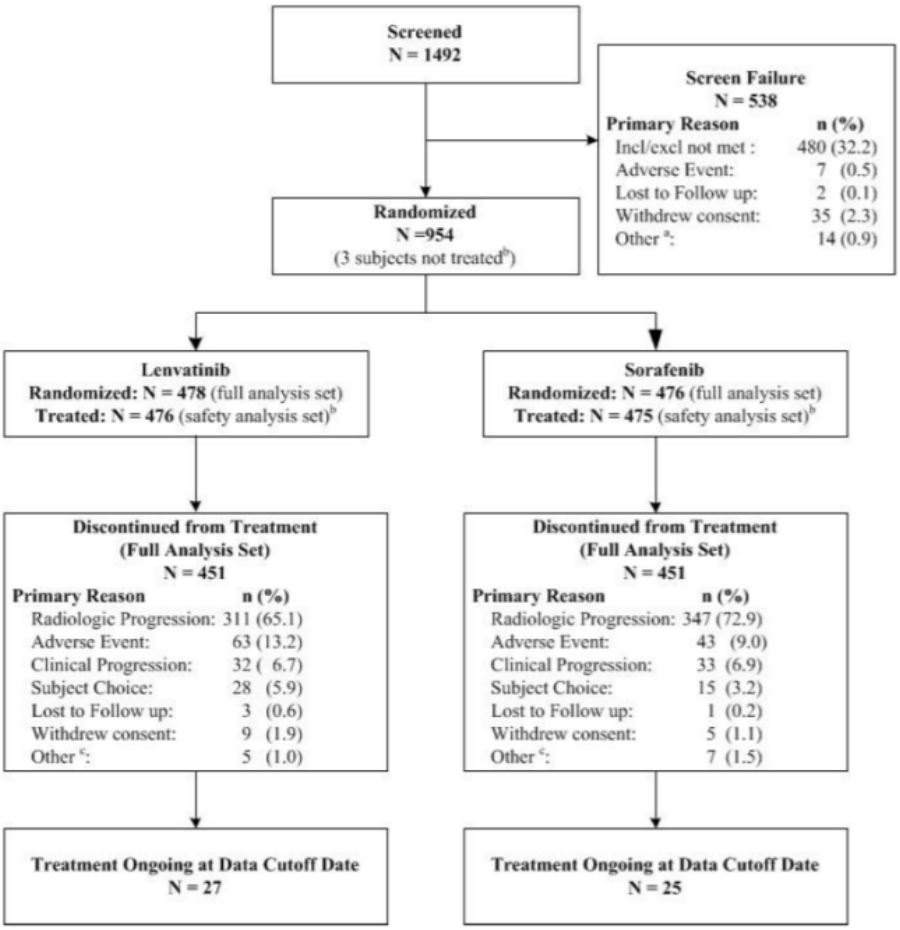
The participant disposition flow diagram for REFLECT is illustrated in Figure 6.3. Of 1492 patients assessed for eligibility, 538 were screening failures due to ineligibility (n=480), adverse events (n=7), lost to follow-up (n=2), withdrew consent (n=35), or other reasons (n=14). Other reasons for screen failure included expiration of the 21-day window and worsening of the participants' condition. A total of 954

participants were randomly assigned to treatment (full analysis set), of which 478 were assigned to lenvatinib and 476 were assigned to sorafenib. Two participants in lenvatinib did not meet eligibility criteria and were not treated as they were randomized in error. One participant in sorafenib chose not to receive treatment following randomization. All other participants (n = 951; safety analysis set) received the assigned treatment.[8]

As of the November 13th, 2016, cut-off date, 27 participants in the lenvatinib arm and 25 participants in the sorafenib arm were actively receiving treatment. All participants receiving treatment or in survival follow-up at this date were entered into the extension phase of the study. In both treatment arms, 451 participants discontinued treatment. The most common reason for discontinuation was PD. More participants in the sorafenib arm discontinued treatment due to radiological progression (n=347; 72.9%) than the lenvatinib arm (n=311; 65.1%). A higher proportion of participants in the lenvatinib arm discontinued treatment due to AEs compared to the sorafenib arm (13.2% vs. 9.0%, respectively). Overall, more participants in the lenvatinib arm (n=103; 21.5%) discontinued for reasons other the disease progression which include AEs, subject choice, withdrawal of consent, and lost to follow-up, compared to the sorafenib arm (n=64; 13.4%). Additional reasons for discontinuation included clinical progression, participant choice, lost to follow-up, withdrew consent, and other reasons (such as randomization in error; participant or investigator choice; participant required surgery, liver transplantation, or needed prohibited medication).[8]

The overall number of protocol deviations was low and similar in both treatment groups, with major protocol deviations occurring with 11 participants (2.3%) in the lenvatinib arm and 13 participants in the sorafenib arm (2.7%). The most common reason for a protocol deviation involved eligibility criteria not being met, with 8 participants (1.7%) affected in the lenvatinib arm compared to 7 (1.5%) of participants in the sorafenib arm. Other protocol deviations included prohibited procedures or concomitant medications were administered, screening or baseline assessments were not conducted, and study drug dosing errors and noncompliance. These are outlined in Table 6.5.[8]

Figure 6.3: Participant disposition flow diagram for the REFLECT trial



Data cutoff date: 13 Nov 2016.
a: Other reasons for screening failure varied, with the most common reasons being expiration of the 21-day screening window (n=4) and worsening of the subject's condition (n=3).
b: Two subjects randomized to lenvatinib were not treated as they were randomized in error, and 1 subject randomized to sorafenib chose not to receive treatment; therefore the Safety Analysis Set includes 476 subjects in the lenvatinib arm and 475 subjects in the sorafenib arm.
c: "Other" reasons for discontinuation in the lenvatinib arm included randomization in error (n=2; not treated); subject required surgery (n=2) and investigator choice (n=1). In the sorafenib arm, "other" reasons included investigator choice (n=5); need for a prohibited medication (warfarin; 1 subject); and discontinuation to undergo liver transplantation (n=1).
Source: EMA Assessment Report, 2018; Figure 13, page 58/151[8]

Table 6.5: Major protocol deviations in the REFLECT trial

	Lenvatinib (N=478) n (%)	Sorafenib (N=476) n (%)	Total (N=954) n (%)
No. of subjects with at least 1 major protocol deviation	11 (2.3)	13 (2.7)	24 (2.5)
Discontinuation criteria[a]	0 (0.0)	1 (0.2)	1 (0.1)
Eligibility criteria not met	8 (1.7)	7 (1.5)	15 (1.6)
Prohibited concomitant medication (warfarin)	0 (0.0)	1 (0.2)	1 (0.1)
Improper procedure[b]	0 (0.0)	1 (0.2)	1 (0.1)
Prohibited procedure	2 (0.4)	2 (0.4)	4 (0.4)
Screening/baseline assessment not done	0 (0.0)	1 (0.2)	1 (0.1)
Study drug dosing error/noncompliance	1 (0.2)	0 (0.0)	1 (0.1)

Data cutoff date: 13 Nov 2016.
Percentages are based on the total number of subjects within the relevant treatment group in the Full Analysis Set.
One sorafenib subject (Subject 17021001) had 2 major protocol deviations.
a: Subject developed a Grade 4 hemorrhage on study, but was not discontinued from study treatment by the investigator.
b: Subject's protocol deviation was mistakenly classified as "improper procedure" in the database. The subject did not meet Inclusion criterion #10 as the baseline Child-Pugh was 8 (Class B).

Source: EMA Assessment Report, 2018; Table 32, page 61/151

e) Limitations/Sources of Bias

Discussion of the selection of the NI margin, assay sensitivity, and overall interpretations

The NI margin and assay sensitivity are two key properties critical to the design and conduct of a NI clinical trial. Regulatory guidance and the robust literature on NI study designs consistently state both clinical and statistical significance should be considered when setting the NI margin.[62-65] Assay sensitivity refers to the ability of the trial to have detected a difference between treatments, if such a difference exists, which depends on sorafenib retaining its demonstrated effectiveness from previous phase 3 trials. To conclude assay sensitivity is demonstrated, the following 3 considerations must be taken into account: (1) historical evidence of sensitivity to drug effects (HESDE); (2) the constancy assumption; and (3) the quality of the new trial.[64] These considerations in relation to assay sensitivity and the choice of NI margin, as well as associated limitations, are discussed below.

HESDE

HESDE is demonstrated when there are consistent findings in prior, appropriately designed and conducted, studies with the active comparator used in the NI study against placebo (in this case, sorafenib vs. placebo).[64] The SHARP trial and Asia-Pacific trial had almost identical relative treatment effects, with HRs of 0.69 (95% CI: 0.55, 0.87) and 0.68 (95% CI: 0.50, 0.93), respectively.[20,21] There have also been a number of phase 3 studies conducted over the last decade that have failed to show superiority or non-inferiority against sorafenib, which reinforces the consistency of the effectiveness of this treatment. It can be reasonable concluded that HESDE is demonstrated on the basis of relative effects, however it must be noted that absolute treatment effects differed in these two populations, with an overall, lower median OS in both the sorafenib and placebo arms in the Asia-Pacific

trial. Specifically, in the Asia-Pacific trial the median OS for the sorafenib arm was 6.5 months (95% CI: 5.56, 7.56) and in the placebo arm it was 4.2 months (95% CI: 3.75, 5.46), whereas the median OS in the sorafenib arm of the SHARP trial was 10.7 months (95% CI: 9.4, 13.3) compared to 7.9 months (95% CI: 6.8, 9.1) in the placebo arm.[19,20,21] These differences have been largely attributed to baseline differences in the Asia-Pacific trial when compared to the SHARP trial. In the Asia-Pacific trial, more patients had extrahepatic spread, poorer ECOG PS, higher concentrations of AFP, and a greater number of hepatic tumor lesions, which may be indicative of more advanced disease and poorer prognosis.[19,20,21] However, regional differences that relate to aetiology as a prognostic factor cannot be entirely ruled out. HBV was a predominate aetiology of liver cirrhosis in the Asia-Pacific trial, and HCV and alcohol were predominate aetiologies in the SHARP trial (Western population).[19,20,21] Recent meta-analyses have suggested HCV-positivity may predict sorafenib benefit, and similar benefit has not been demonstrated in analyses with HBV-positive subgroups.[66] This would question whether sorafenib performs consistently, in terms of absolute effects, across all populations and aetiologies of liver cirrhosis. In the REFLECT trial, 67% of the population was from the Asia-Pacific compared to 27% of the pooled population of the two sorafenib vs. placebo trials, resulting in different profiles for etiology (Table 6.6) when comparing current study with historical studies of sorafenib vs. placebo.[5,20,21] An exploratory post-hoc analysis of OS in only patients with a history of HBV from the REFLECT trial also revealed that numerically, OS was worse in patients treated with sorafenib (median OS: 10.2 months; 95% CI: 8.6, 12.4) compared to lenvatinib (median OS: 13.4 months; 95% CI: 11.6, 14.6).[3] This in combination with information reported in a recent network meta-analysis (NMA), which explored the efficacy of sorafenib and lenvatinib by hepatitis etiology and reported greater efficacy of lenvatinib in HBV-positive patients, support potential differential treatment effects for these two treatments by etiology.[6] Stratification or adjustment by etiology was not accounted for in the study design.

Table 6.6 REFLECT trial baseline characteristics by geographical region (Asia-Pacific vs. Western)

	Lenvatinib (n=478)		Sorafenib (n=476)	
Aetiology of hepatocellular carcinoma	Asia-Pacific n=321 (100.0)	Western n =157 (100.0)	Asia-Pacific n=319 (100.0)	Western n=157 (100.0)
Hepatitis B	212 (66.0)	39 (24.8)	197 (61.8)	31 (19.7)
Hepatitis C	50 (15.6)	41 (26.1)	70 (21.9)	56 (35.7)
Alcohol	17 (5.3)	19 (12.1)	8 (2.5)	13 (8.3)
Other	17 (5.3)	21 (13.4)	11 (3.4)	21 (13.4)
Unknown	25 (7.8)	37 (23.6)	33 (10.3)	36 (22.9)

Characteristic	Lenvatinib (n=478)		Sorafenib (n=476)	
	Asia-Pacific	Western	Asia-Pacific	Western
Age, mean (SD)	60.0 (11.76)	63.8 (11.15)	60.2 (11.87)	63.3 (12.06)
ECOG PS 0	206 (64.2)	98 (62.4)	204 (63.9)	97 (61.8)
AFP levels ≥200 ng/mL	157 (48.9)	65 (41.4)	137 (42.9)	50 (31.8)
Aetiology of HCC-Hepatitis B	212 (66.0)	39 (24.8)	197 (61.8)	31 (19.7)
Aetiology of HCC-Hepatitis C	50 (15.6)	41 (26.1)	70 (21.9)	56 (35.7)
Aetiology of HCC-Alcohol	17 (5.3)	19 (12.1)	8 (2.5)	13 (8.3)

All data reported are n (%) unless otherwise stated, *including radiotherapy
Abbreviations: AFP, alpha-fetoprotein. Red box = company highlighted imbalances (these were not pre-specified randomisation stratification factors)

Source: Adapted from the Committee for Medicinal Products for Human Use. Assessment report: Lenvima. (European public assessment report). London (GB): European Medicines Agency; 2018 Jun 28.[67]

Constancy Assumption

The constancy assumption involves assessing whether the current NI trial is similar to historical studies by considering study design and conduct features.[64] Comparison of key population characteristics between the SHARP trial, Asia-Pacific trial, and REFLECT trial, are presented in Table 6.7. Differences in overall population characteristics are noted below:

- As mentioned under HESDE, regional differences in the patient population and respective aetiologies differ between the REFLECT trial and the sorafenib vs. placebo trials. Overall, 50% of the patients in the REFLECT trial have a HBV etiology and 6% have an alcohol-related etiology of disease compared to 33% and 19% respectively, in the pooled sorafenib vs. placebo trials. Please note, there may have been a higher proportion of participants in the sorafenib vs. placebo trials (SHARP trial and Asia-Pacific trial) with an alcohol-related etiology, as this information was not published, while the 19% mentioned above only includes patients from the SHARP trial. The proportion of patients with HCV etiology was similar between the REFLECT trial and the pooled sorafenib vs. placebo trials (23% in both).
- There were a higher proportion of participants with MVPI (38% vs. 21%), BCLC Stage C disease (86% vs. 79%), ECOG PS of 1-2 (54% vs. 37%), and ≥ 3 disease sites (53% vs. 20%) in the pooled sorafenib vs. placebo trials compared to the REFLECT trial, respectively. Note: Only 7% of participants had an ECOG PS of 2 in the sorafenib vs. placebo trials, and patients with ECOG PS of 2 were excluded in the REFLECT trial.
- A higher proportion of participants in the REFLECT trial had EHS (61%) compared to participants in the pooled sorafenib vs. placebo trials (56%).[5,20,21,68]

Table 6.7: Comparison of population characteristics from the SHARP trial, Asia-Pacific trial, and REFLECT trial[5,20,21,68]

	Sorafenib vs. Placebo							Lenvatinib vs. Sorafenib		
	SHARP trial		Asia-Pacific trial		Total (Pooled)			REFLECT trial		
Population Characteristics	Sorafenib	Placebo	Sorafenib	Placebo	Sorafenib	Placebo	TOTAL	Lenvatinib	Sorafenib	TOTAL

	Sorafenib vs. Placebo							Lenvatinib vs. Sorafenib		
	SHARP trial		**Asia-Pacific trial**		**Total (Pooled)**			**REFLECT trial**		
	n=299	n=303	n=150	n=76	n=449	n=379	n=828	n=478	n=476	n=954
Region										
Western	299 (100%)	303 (100%)	-	-	299 (67%)	303 (80%)	602 (73%)	157 (33%)	157 (33%)	314 (33%)
Asia-Pacific	-	-	150 (100%)	76 (100%)	150 (33%)	76 (20%)	226 (27%)	321 (67%)	321 (67%)	640 (67%)
Etiology										
Hepatitis B	56 (19%)	55 (18%)	106 (71%)	59 (78%)	162 (36%)	114 (30%)	276 (33%)	251 (53%)	228 (48%)	479 (50%)
Hepatitis C	87 (29%)	82 (27%)	16 (11%)	3 (4%)	103 (23%)	85 (22%)	188 (23%)	91 (19%)	126 (26%)	217 (23%)
Alcohol*	79 (26%)	80 (26%)	-	-	79 (18%)	80 (21%)	159 (19%)	36 (8%)	21 (4%)	57 (6%)
Other*	28 (9%)	29 (10%)	-	-	28 (6%)	29 (8%)	55 (7%)	38 (8%)	32 (7%)	70 (7%)
Unknown*	49 (16%)	56 (19%)	-	-	77 (17%)	70 (18%)	147 (17%)	62 (13%)	69 (14%)	131 (14%)
MPVI (present)	108 (26%)	123 (41%)	54 (36%)	26 (34%)	162 (36%)	149 (39%)	311 (38%)	109 (23%)	90 (19%)	199 (21%)
EHS (present)	159 (53)	150 (50)	103 (69%)	52 (68%)	262 (58%)	202 (53%)	464 (56%)	291 (61%)	295 (62%)	586 (61%)
BCLC Stage										
Stage B	54 (18%)	51 (17%)	7 (5%)	3 (4%)	61 (14%)	54 (14%)	115 (14%)	104 (22%)	92 (19%)	196 (21%)
Stage C	244 (82%)	252 (83%)	143 (95%)	73 (96%)	387 (86%)	325 (86%)	712 (86%)	374 (78%)	384 (81%)	758 (79%)
ECOG PS										
0	161 (54%)	164 (54%)	38 (25%)	21 (28%)	199 (44%)	185 (49%)	385 (46%)	304 (64%)	301 (63%)	605 (63%)
1	114 (38%)	117 (39%)	104 (69%)	51 (67%)	218 (49%)	168 (44%)	386 (47%)	174 (36%)	175 (37%)	349 (37%)
2	24 (8%)	22 (7%)	8 (5%)	4 (5%)	32 (7%)	26 (7%)	58 (7%)	-	-	-
Number of disease sites**										
1	-	-	20 (13%)	5 (7%)	109 (24%)	99 (26%)	208 (25%)	207 (43%)	207 (43%)	414 (43%)
2	-	-	52 (35%)	27 (35%)	86 (19%)	79 (21%)	165 (20%)	167 (35%)	183 (38%)	350 (37%)
≥ 3	-	-	78 (53%)	44 (58%)	242 (54%)	200 (53%)	442 (53%)	103 (22%)	86 (18%)	189 (20%)
Unknown	-	-	-	-	12 (3%)	1 (<1%)	13 (2%)			

Abbreviations: BLCL = Barcelona clinic liver cancer; **ECOG PS** = Eastern Cooperative Oncology Performance Status; **EHS** = extrahepatic spread; **MVPI** = macrovascular portal vein invasion

*Asia-Pacific trial did not specify participants with alcohol, other, and unknown etiology. Totals include only the SHARP trial participants where this information is available, as a proportion of the total population, and thus serve as an estimate.

**The SHARP trial did not specify number of disease sites. A meta-analysis of the 2 trials provided an estimate for the total for the 2 trials. However, 1 participant was excluded from the SHARP trial in the sorafenib arm in the meta-analysis report due to BCLC stage D disease at study entry.

Differences in eligibility included the exclusion of patients with 50% or higher liver occupation, obvious invasion of the bile duct, or invasion of the main portal vein in the REFLECT trial, which were not excluded in the sorafenib vs. placebo trials.[5,20,21] Duration of treatment in the sorafenib arm of the REFLECT trial (median duration of treatment: 3.7 months; IQR: 1.8-7.4) was shorter than in the SHARP trial (median duration of treatment: 5.3 months; IQR: 0.2, 16.1; information not available for the Asia-Pacific trial), however similar duration of treatment and TTP was reported in the REFLECT and SHARP trials.[5,20] TTP is subject to a degree of bias, and agreement between investigator assessed and masked IIR on the time of PD was 51%.[8]

Quality of Trial

The trial was overall, well conducted. However, since REFLECT was open-label (and the sorafenib vs. placebo trials were not), the possibility of investigator and participant biases remain a concern.[5,20,21]

Assessment of choice of margin and assay sensitivity

As outlined earlier in section 6, the choice of the NI margin was based on a meta-analysis of two pivotal trials that investigated sorafenib vs. placebo, the SHARP trial and the Asia-Pacific trial.[8,20,21] Given the above considerations with regards to potential response differences based on etiology, this may be a possible limitation in setting the NI margin. Additionally, it is not clear if the constancy assumption was fulfilled, given the population in the sorafenib vs placebo trials had a population with an overall poorer prognosis than that of the REFLECT trial. The median OS for sorafenib was longer than reported in historical trials, which may be partially explained by a better prognosis of the population included in the REFLECT trial. The REFLECT trial was also open-label, and although justified due to the complexity of the study treatment, remains a limitation in terms of demonstrating assay sensitivity. Additionally, the clinical significance of preserving 60% of the upper limit of the treatment effect of the sorafenib vs. placebo trials was not articulated, which is an important consideration since sorafenib remains the only treatment option in this setting and median OS is less than a year. The combination of these clinical considerations raises the concern that the NI margin for this study should have been more conservative. The efficacy of lenvatinib should be carefully interpreted and used in line with the study criteria, given that non-inferiority was demonstrated using a NI margin that preserves 60% of the upper limit of the treatment effect of sorafenib vs. placebo from populations with a poorer prognosis, than the population of the REFLECT trial. These considerations may inform why superiority in terms of OS was not demonstrated, despite a number of secondary outcomes showing superiority of lenvatinib over sorafenib, which may be subject to a number of biases. The above points should also inform the interpretation of future indirect treatment comparisons of lenvatinib vs. placebo, and the potential to produce optimistic efficacy results, which could lead to biocreep without careful consideration.

Key limitations and sources of bias include:

- REFLECT had an open-label study design, which is susceptible to reporting and performance biases, especially with respect to secondary outcomes as trials patients and investigators were not blinded to study treatment. Although masked IIR was used to support investigator assessed outcomes and minimize bias, biases related to timing of evaluation based on treatment arm remains a concern (51% agreement between investigator and IIR assessment of timing of disease progression).
- Clinical justifications and considerations for the selection of the margin may have been inadequate to demonstrate assay sensitivity.
- There were a higher proportion of patients with AFP ≥200 ng/mL, a marker of poorer prognosis with HCC, and a smaller proportion of participants with HCV-positive etiology, a predictor of sorafenib benefit, in the lenvatinib arm compared to the sorafenib arm.[5,66,68,69] It is speculated this may have favoured sorafenib. Although higher AFP concentrations are a prognostic factor for HCC, there was no clinical justification for the specific AFP concentration cut-off used in this trial. Additionally, the exploratory

subgroup analyses demonstrated a marked benefit in OS for participants with HBV etiology (compared to HCV and alcohol) and superiority in OS in participants with AFP ≥200 ng/mL.[5] A recent NMA also reported greater lenvatinib efficacy over sorafenib in HBV-positive patients.[6] An exploratory post-hoc analysis of OS in patients with a history of HBV from the REFLECT trial also revealed that numerically, OS was worse in patients treated with sorafenib (median OS: 10.2 months; 95% CI: 8.6, 12.4) compared to lenvatinib (median OS: 13.4 months; 95% CI: 11.6, 14.6).[3] Both subgroups, AFP ≥200 ng and HBV-positive, constituted a higher proportion in the lenvatinib arm compared to the sorafenib arm, and thus, this may favour lenvatinib.[5] Subgroup analyses are exploratory, and these observations are speculative. However, stratification by AFP and etiology should have considered given the growing evidence reporting on potential difference in response based on these factors.

- Median OS observed in the study may be influenced by post-treatment anticancer therapies. Overall, OS was 2.5 months longer in the lenvatinib arm when compared to the sorafenib arm in both those who received post-treatment anticancer therapy and those who did not. The sorafenib arm received more subsequent anticancer therapies overall compared to the lenvatinib arm, which may have favoured sorafenib as more participants with post-treatment anticancer therapies may have longer survival. A higher proportion of participants in the lenvatinib arm received sorafenib compared to the sorafenib arm, whereas in the sorafenib arm, a higher proportion received investigational agents as post-treatment anticancer therapies.[8] These post-treatment therapies are of unknown clinical benefit and it is unknown how these may have influenced outcomes. For example, post-hoc exploratory analyses in lenvatinib responders who subsequently received sorafenib had a median OS of 26months (95% CI: 18.2, 34.6), which is double the median OS of the lenvatinib arm overall.[1] Due to insufficient information on survival by type of subsequent therapies and by treatment arm, the direction and magnitude of the effect due to the type of subsequent therapy is unknown and cannot be estimated.
- The dose duration of sorafenib was shorter than in historical trials, which may be influenced by investigator biases associated with the open-label study design and may favour lenvatinib.[5,20,21]
- Treatment discontinuation for reasons other than disease progression, such as AEs or participant choice, was more common in the lenvatinib group. Censoring patients with no disease progression at the time of treatment discontinuation for key secondary outcomes (PFS and TTP) may have biased the direction and magnitude of the effect in favour of lenvatinib. A sensitivity analysis where patients were not censored if they did not experience progressive disease or death was provided, and while the direction of the treatment effect was similar to the primary analysis of PFS, there was a reduction in the magnitude of the effect. TTP results of the sensitivity analysis were consistent with the primary analysIs.[9]
- The PH assumption was not met for PFS in the REFLECT trial, however, this was deemed as an acceptable violation of the assumption of the model. Nonetheless, the HRs should be interpreted with some caution.[10]

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Efficacy analyses were performed on the full analysis set (FAS), which included 954 participants; 478 in the lenvatinib arm and 476 in the sorafenib arm. As of the cut-off date of November 13th, 2016, the median duration of survival follow-up was 27.7 months (95% CI: 26.4, 29.4) in the lenvatinib arm and 27.2 months (95% CI: 25.9, 28.4) in the sorafenib arm.[5]

Primary Endpoint

Overall Survival (OS)

Illustrated in Figure 6.4, median overall survival was 13.6 months (95% CI: 12.1, 14.9) in the lenvatinib group and 12.3 months (95% CI: 10.4, 13.9) in the sorafenib group, with a HR of 0.92 (95% CI: 0.79, 1.06). Overall, 351 deaths occurred in the lenvatinib arm, and 350 deaths occurred in the sorafenib arm. The REFLECT trial statistically demonstrated NI for OS of lenvatinib against sorafenib, with an upper limit of the CI that was below the NI margin of the trial, which was set at 1.08.[5] Statistical superiority of lenvatinib was not demonstrated.[5] Overall survival rate at 6, 12, and 24 months in the lenvatinib arm was 80.8%, 55.0%, and 29.9 %, and in the sorafenib arm it was 75.2%, 50.0%, and 26.2%, respectively Table 6.8.[8] Based on the p-value (p=0.2902) of the PH global test for OS, the null hypothesis that there are PH between the two treatment arms was retained. However, visual inspection of the log-cumulative hazard plot revealed there may be some convergence of the treatment arms, and thus indicative of non-proportional hazards.[11] Given the study design is a NI trial, the methods and economic team did not deem this as a violation of the PH assumption.

Supportive analyses were conducted with the per protocol set (PPS), which produced similar results and are illustrated in Table 6.9.[8] Exploratory subgroup analyses of OS are illustrated in Figure 6.5A, and NI is demonstrated consistently across all subgroups (upper limit of HR CI < 1.0). Lenvatinib showed superiority in participants with AFP ≥ 200ng/mL compared to sorafenib (HR: 0.78; 95% CI: 0.63, 0.98) for OS.[5] OS was also adjusted by baseline AFP (<200 ng/ml; ≥200 ng/ml) with the randomization stratification factors, and marginal superiority of lenvatinib (HR: 0.856; 95% CI: 0.736, 0.995) was demonstrated in this sensitivity analysis. Given a higher proportion of participants in the lenvatinib arm had baseline AFP ≥200 ng/ml, which in subgroup analyses revealed superior OS outcomes, results of the adjustment for AFP may have been driven by this difference.[8]

OS by subsequent therapy was also explored, and median OS was approximately 9 months longer in those who received subsequent anticancer therapies (procedures or medications) than those who did not in both treatment arms. The median OS was 19.5 months (95% CI: 15.7, 23.0) in those with post-treatment anticancer therapy compared to 10.5 months (95% CI: 8.6, 12.2) in those who did not in the lenvatinib arm. In the sorafenib arm, median OS was 17.0 months (95% CI: 14.2, 18.8) in participants who received subsequent anticancer therapies compared to 7.9 months (95% CI: 6.6, 9.7) in those who did not. Median OS was 2.5 months longer in the lenvatinib arm compared to sorafenib in both those who received post-treatment anticancer therapy and those who did not. Adjustment for the use of any post-treatment anticancer therapies (yes/no), in addition to the stratification factors, resulted in a HR of 0.87 (95% CI: 0.75, 1.01) maintaining NI. The results were consistent for the Asia-Pacific region, but less certain in the Western region due to the large CI that extended beyond the NI margin (results were exploratory),

presented in Table 6.10.[8] Subsequent therapies differed between the treatment groups, and analyses adjusting by type of therapy were not conducted with the exception of one limited post-hoc exploratory analysis. This was conducted on a subset of lenvatinib responders in the REFLECT trial who subsequently received sorafenib (n = 35), and the median OS was reported as 26 months (95 CI%: 18.5, 34.6).[1] Median OS was similar in both treatment arms in participants who received sorafenib as a post-treatment therapy.[60] The type of subsequent therapy may have influenced OS, as these differed between treatment groups.

OS by region adjusted for stratification factors was explored in the same table, Table 6.10, without adjustment for post-treatment therapy. In the Asia-Pacific region, NI for OS was maintained. Similar to the models adjusted by any post-treatment therapy, NI was not maintained in the Western region (HR: 1.08, 95% CI: 0.82, 1.42).[8]

Figure 6.4: Kaplan-Meier estimates of overall survival by treatment group

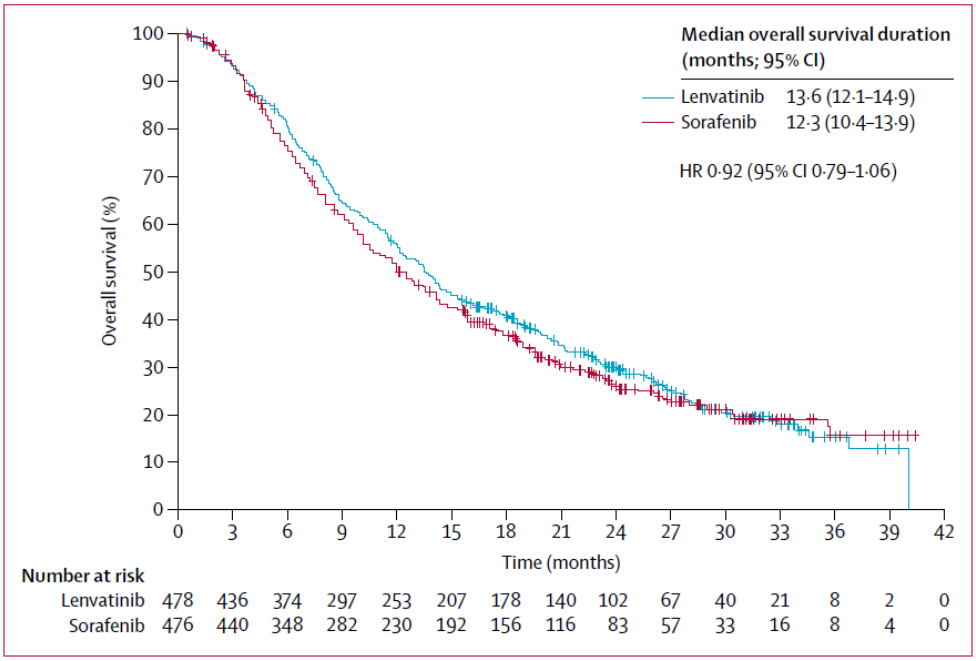


Figure 2: **Overall survival outcomes**

Kaplan-Meier estimates of overall survival by treatment group. HR=hazard ratio.

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Table 6.8: Overall survival based on randomization stratification factors in the full analysis set

	Lenvatinib (N=478) n (%)	**Sorafenib (N=476) n (%)**
Deaths, n (%)	351 (73.4)	350 (73.5)
Censored Subjects, n (%)	127 (26.6)	126 (26.5)
Lost to follow-up	5 (1.0)	11 (2.3)
Withdrawal of consent	13 (2.7)	8 (1.7)
Alive	109 (22.8)	107 (22.5)
Median Overall Survival (months)[a] (95% CI)	13.6 (12.1, 14.9)	12.3 (10.4, 13.9)
Overall Survival Rate (%) (95% CI) [b] at		
6 Months	80.8 (76.9, 84.1)	75.2 (71.0, 78.8)
12 Months	55.0 (50.4, 59.4)	50.0 (45.4, 54.5)
24 Months	29.9 (25.6, 34.2)	26.2 (22.1, 30.5)
Stratified Cox Model Hazard Ratio (95% CI) [c,d]	0.92 (0.79, 1.06)	

Data cutoff date: 13 Nov 2016.
Noninferiority margin for the HR of lenvatinib versus sorafenib is 1.08.
a: 95% CIs are estimated with a generalized Brookmeyer and Crowley method.
b: OS rate & 95% CI calculated using Kaplan-Meier product-limit method and Greenwood Formula.
c: Hazard ratio is for lenvatinib vs. sorafenib, based on a Cox model including treatment group as a factor. Efron method was used for ties.
d: Stratified by region (Region 1: Asia-Pacific; Region 2: Western), macroscopic portal vein invasion or extrahepatic spread or both (yes, no), ECOG PS (0, 1) and body weight (<60 kg, ≥60 kg).

Source: EMA, 2018, Table 40, 67/151[8]

Table 6.9: Overall survival based on the per protocol set population

	Lenvatinib (N = 467) n (%)		Sorafenib (N = 462) n (%)
Deaths, n (%)	342 (73.2)		339 (73.4)
Censored Patients, n (%)	125 (26.8)		123 (26.6)
Lost to follow-up	5 (1.1)		11 (2.4)
Withdrawal of consent	12 (2.6)		7 (1.5)
Alive	108 (23.1)		105 (22.7)
Overall Survival (months)			
Median (95% CI)	13.7 (12.2–15.1)		12.3 (10.6–14.2)
Hazard Ratio (95% CI)		0.91 (0.78–1.06)	
Duration of Survival Follow-up (months)			
Median (95% CI)	27.7 (26.4–29.3)		27.1 (25.9–27.7)

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Figure 6.5: Subgroup analyses of overall survival (A) and progression free survival (B) in the REFLECT trial

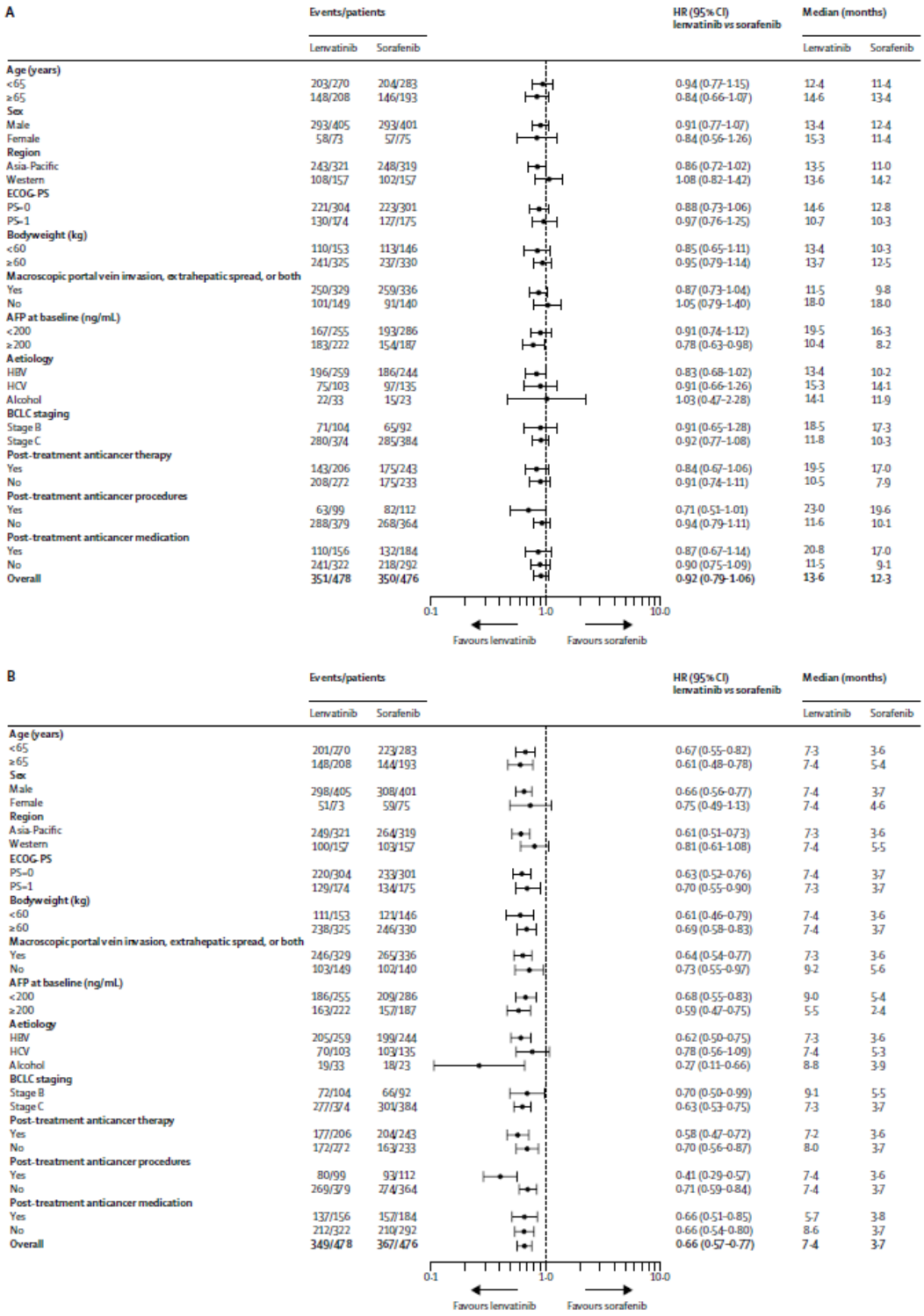

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Table 6.10: Overall survival adjusted by use of post-treatment anticancer treatment, overall and by region in the REFLECT trial

	Stratified Cox Model Hazard Ratio (95% CI)[a]	
	Without Adjustment	With Adjustment[b]
Overall	0.92 (0.79, 1.06)	0.87 (0.75, 1.01)
Region		
Asia-Pacific	0.86 (0.72, 1.02)	0.83 (0.70, 1.00)
Western	1.08 (0.82, 1.42)	0.93 (0.70, 1.23)

For the Asia-Pacific and Western regions, the stratification factor of "region" was not included.
a: Hazard ratio is for lenvatinib: sorafenib, based on a Cox model including treatment group as a factor. The Efron method used for correction of tied events. Stratified by region (Region 1: Asia-Pacific; Region 2: Western), macroscopic portal vein invasion or extrahepatic spread or both (yes, no), ECOG PS (0, 1), and body weight (<60 kg, ≥60 kg).
b: Status of posttreatment anticancer therapy (yes/no) was used as an additional covariate factor.

Source: EMA report, 2018; Table 47 77/151[8]

Secondary Endpoints

PFS, TTP, and ORR were evaluated by investigator assessment using mRECIST for the primary analyses, and all demonstrated statistical superiority of lenvatinib over sorafenib ($p<0.0001$).[5] Masked IIR for tumor assessment using mRECIST and RECIST were conducted for exploratory and supportive purposes, and conducted on 99.5% of the tumor assessment scans. The masked IIR identified 4 participants in the lenvatinib arm and 1 participant in the sorafenib arm that did not have disease at screening. Additionally, based on mRECIST criteria, the IIR identified 18 participants in the lenvatinib arm and 15 participants in the sorafenib arm that did not have lesions meeting the requirements for a target lesion at baseline. Overall agreement for best overall response (BOR) was 62.6% between IIR and investigator assessments, with higher agreement for sorafenib (70%), than lenvatinib (55.2%). There was high agreement between IIR and investigator assessments for SD and PD in the sorafenib arm, and poor agreement for PR in the lenvatinib arm. Overall, there was 51% agreement between IIR and investigator review on the timing of PD using mRECIST, for patients assessed by both IIR and investigator review as having PD. Early discordance rates (EDR) and late discordance rates (LDR) were similar between treatment arms, however, overall the late discordance rate was 62.3% indicating investigators declared the timing of PD to be later than that of the IIR at a higher frequency.[8]

Results for all investigator (using mRECIST) and masked IIR (using mRECIST and RECIST) assessed secondary efficacy outcomes (PFS, TTP, ORR) and some exploratory outcomes (DCR only) are summarized in Table 6.11.[5]

Table 6.11: Investigator and masked IIR assessed secondary and exploratory efficacy outcomes using mRECIST and RECIST criteria

	Lenvatinib (n=478)	Sorafenib (n=476)	Effect size (95% CI)	p value
Investigator review according to mRECIST				
Overall survival (months)	13·6 (12·1–14·9)	12·3 (10·4–13·9)	HR 0·92 (0·79–1·06)	..
Progression-free survival (months)	7·4 (6·9–8·8)	3·7 (3·6–4·6)	HR 0·66 (0·57–0·77)	<0·0001
Time to progression (months)	8·9 (7·4–9·2)	3·7 (3·6–5·4)	HR 0·63 (0·53–0·73)	<0·0001
Objective response (%, 95% CI)	115 (24·1%, 20·2–27·9)	44 (9·2%, 6·6–11·8)	OR 3·13 (2·15–4·56)	<0·0001
Complete response	6 (1%)	2 (<1%)	..	..
Partial response	109 (23%)	42 (9%)	..	..
Stable disease	246 (51%)	244 (51%)	..	..
Durable stable disease lasting ≥23 weeks	167 (35%)	139 (29%)	..	..
Progressive disease	71 (15%)	147 (31%)	..	..
Unknown or not evaluable	46 (10%)	41 (9%)	..	..
Disease control rate (%, 95% CI)	361 (75·5%, 71·7–79·4)	288 (60·5%, 56·1–64·9)	..	..
Masked independent imaging review according to mRECIST				
Progression-free survival (months)	7·3 (5·6–7·5)	3·6 (3·6–3·7)	HR 0·64 (0·55–0·75)	<0·0001
Time to progression (months)	7·4 (7·2–9·1)	3·7 (3·6–3·9)	HR 0·60 (0·51–0·71)	<0·0001
Objective response (%, 95% CI)	194 (40·6%, 36·2–45·0)	59 (12·4%, 9·4–15·4)	OR 5·01 (3·59–7·01)	<0·0001
Complete response	10 (2%)	4 (1%)	..	..
Partial response	184 (38%)	55 (12%)	..	..
Stable disease	159 (33%)	219 (46%)	..	..
Durable stable disease lasting ≥23 weeks	84 (18%)	90 (19%)	..	..
Progressive disease	79 (17%)	152 (32%)	..	..
Unknown or not evaluable	46 (10%)	46 (10%)	..	..
Disease control rate (%, 95% CI)	353 (73·8%, 69·9–77·8)	278 (58·4%, 54·0–62·8)	..	..
Masked independent imaging review according to RECIST 1.1				
Progression-free survival (months)	7·3 (5·6–7·5)	3·6 (3·6–3·9)	HR 0·65 (0·56–0·77)	<0·0001
Time to progression (months)	7·4 (7·3–9·1)	3·7 (3·6–5·4)	HR 0·61 (0·51–0·72)	<0·0001
Objective response (%, 95% CI)	90 (18·8%, 15·3–22·3)	31 (6·5%, 4·3–8·7)	OR 3·34 (2·17–5·14)	<0·0001
Complete response	2 (<1%)	1 (<1%)	..	..
Partial response	88 (18%)	30 (6%)	..	..
Stable disease	258 (54%)	250 (53%)	..	..
Durable stable disease lasting ≥23 weeks	163 (34%)	118 (25%)	..	..
Progressive disease	84 (18%)	152 (32%)	..	..
Unknown or not evaluable	46 (10%)	43 (9%)	..	..
Disease control rate (%, 95% CI)	348 (72·8%, 68·8–76·8)	281 (59·0%, 54·6–63·5)	..	..

Data are presented as median (95% CI) or n (%) unless otherwise indicated. mRECIST=modified Response Evaluation Criteria in Solid Tumours. HR=hazard ratio. OR=odds ratio.

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Progression-Free Survival (PFS)

Lenvatinib showed statistically significant improvement in investigator-assessed PFS based on mRECIST. Overall, 349 PD events occurred in the lenvatinib arm, whereas 367 PD events occurred in the sorafenib arm. The median PFS in the lenvatinib arm was double that of the sorafenib arm at 7.4 months (95% CI: 6.9, 8.8) compared to 3.7 months (95% CI: 3.6, 4.6), respectively, and Kaplan-Meier estimates are illustrated in Figure 6.6. The risk of progressive disease or death was reduced by 34% with lenvatinib compared to sorafenib (HR: 0.66; 95%: 0.57, 0.77; p<0.0001).[5] Masked IIR using mRECIST for PFS evaluation Table 6.11 supported these results. It is important to note the PH assumption was not met, which was confirmed by both visual inspection of the log-cumulative hazard plot and the PH global test, which yielded a value of <0.0001.[11] Given the study design is NI, the methods and economic team deemed this to be an acceptable violation of the assumption. The

log-cumulative hazard plot is illustrated in Figure 6.7, which shows a clear crossover in survival probability for PFS over time between the lenvatinib and sorafenib arms until the two arms close together at the end of the analysis time.[11] The duration of response was longer in the sorafenib arm (11.2 months vs. 7.3 months in the lenvatinib arm), which may partially explain this effect.[8] The graph seems to indicate that less patients may delay progression or death with sorafenib compared to lenvatinib initially, but those patients that respond may have a durable response over time. On the other hand, it appears more patients may have delayed progression or death with lenvatinib initially, however the response is not sustained over time. [10]

In almost all exploratory subgroup analyses, illustrated in Figure 6.5B, statistical superiority (upper limit of 95% HR CI<1.0) in PFS is demonstrated with the exception of females, Western region, and HCV aetiology subgroups.[5] However, as the study was not powered to detect differences between subgroups, these results are exploratory.

A sensitivity analysis where patients were not censored if they did not experience PD or death at the time of treatment discontinuation (or data cut-off), was conducted, and a 28% reduction in the risk of PD or death was reported (HR: 0.72; 95% CI: 0.63, 0.83; p<0.00001).[59] While the direction of the treatment effect was similar to the primary analysis of PFS, there was a reduction in the magnitude of the effect by 6%.[5,59]

Figure 6.6: Kaplan-Meier estimates of progression-free survival by treatment group

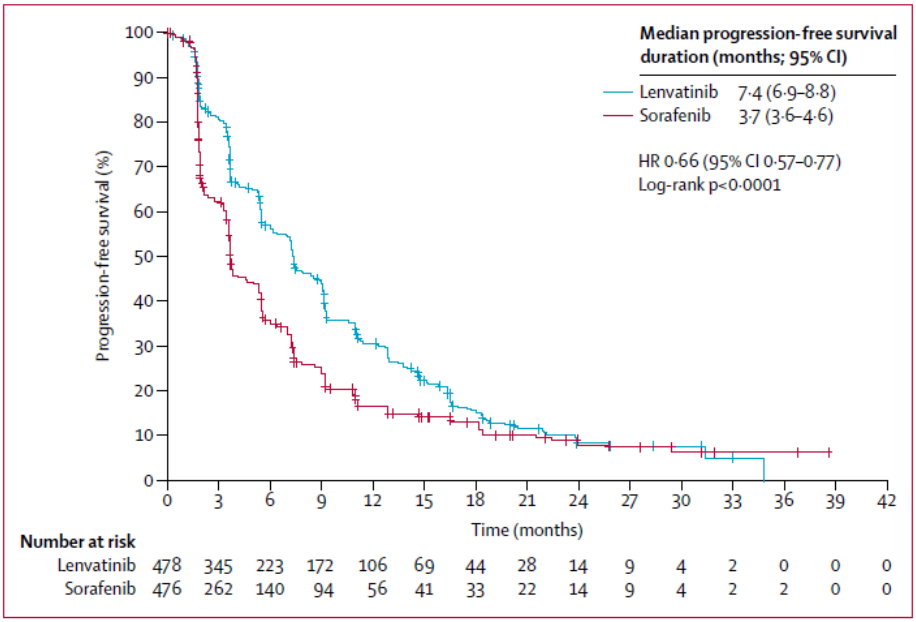

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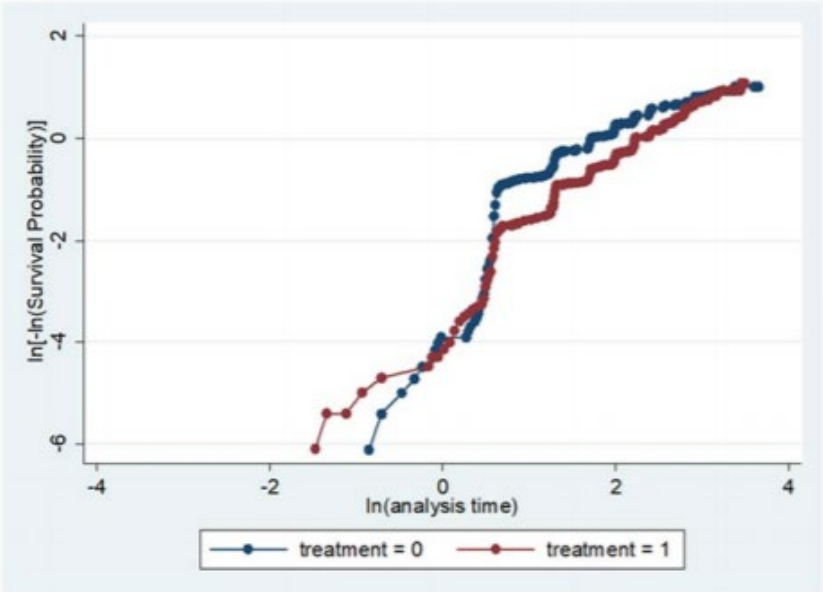
Figure 6.7: Log-cumulative hazard plot for PFS in the REFLECT trial



Source: Checkpoint Responses[60]

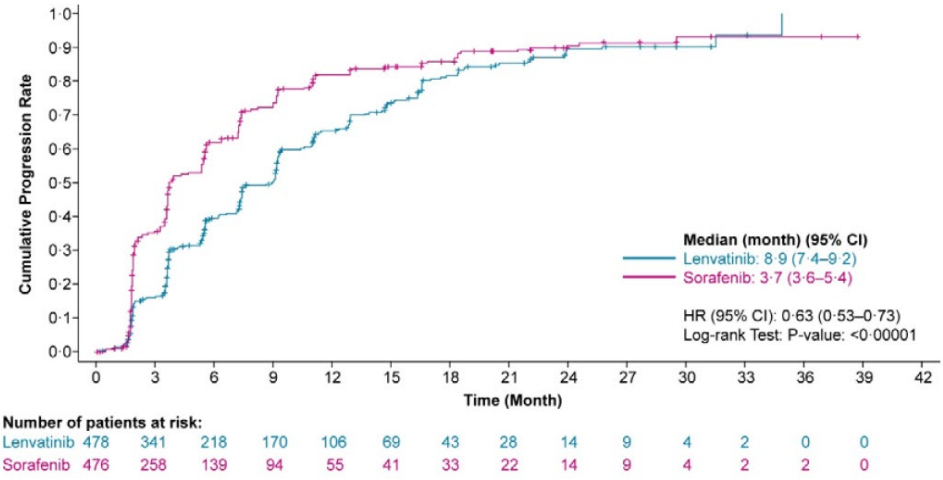
Time to Progression (TTP)

Similar to PFS, TTP was statistically significant and twice as long in the lenvatinib arm at 8.9 months (95% CI: 7.4, 9.2) compared to 3.7 months (95% CI: 3.6, 5.4) in the sorafenib arm (HR: 0.63; 95% CI: 053, 0.73). Masked IIR Kaplan-Meier estimates are illustrated in Figure 6.8. Masked IIR using mRECIST for TTP evaluation Table 6.11 supported these results, although median OS was shorter estimated at 7.4 months (95% CI: 7.2, 9.1) for the lenvatinib arm.[5]

TTP demonstrated statistically significant superiority (upper limit of 95% HR CI <1.0) in almost all subgroups, with the exception of females, Western region, and HCV etiology subgroups. Subgroup analyses are exploratory and are illustrated in Figure 6.9.[5]

A sensitivity analysis where patients were not censored if they did not experience PD or death at the time of treatment discontinuation (or data cut-off) was conducted, and the results were consistent with the primary analysis.[59]

Figure 6.8: Kaplan-Meier estimates of time to progression by treatment group



CI, confidence interval; HR, hazard ratio.

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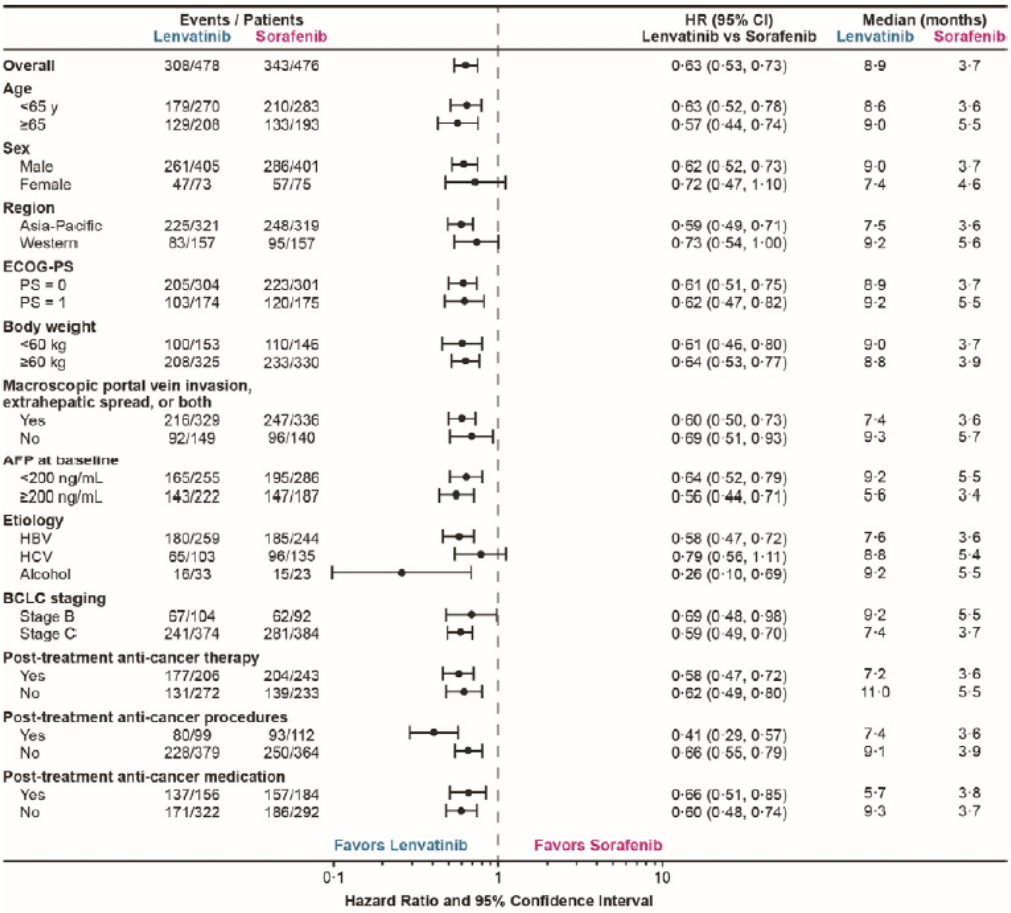
Figure 6.9: Subgroup analyses of time to progression in the REFLECT trial



AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; HR, hazard ratio.

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Objective Response Rate (ORR)

ORR (CR + PR) was also statistically significantly higher in the lenvatinib arm (ORR: 24.1%; 95% CI: 20.2, 27.9) than the sorafenib arm (ORR: 9.2%; 95% CI: 6.6, 11.8). The odds of experiencing a CR or PR was 3 times greater in the lenvatinib arm compared to the odds in the sorafenib arm based on investigator assessment using mRECIST(OR: 3.13;95% CI: 2.15, 4.56; p-value < 0.00001).CRs occurred in 6 (1%) patients and PRs occurred in 109 (23%) patients in the lenvatinib arm compared to 2 (>1%) CRs and 42 (9%) PRs in the sorafenib arm. More participants in the sorafenib arm were evaluated to have PD (31%) compared to the lenvatinib arm (15%). Masked IIR results differed, presented in Table 6.11, and the ORR was remarkably higher in the lenvatinib arm (40.6%) compared to the sorafenib arm (12.4%).[5] These differences were attributed to more rigorous training of the IIR on mRECIST compared to investigators.

Duration of objective response (DOR) was reported to be longer for the sorafenib arm (DOR: 11.2 months; 95% CI: 5.6, 16.6) compared to lenvatinib (DOR: 7.3

months, 95% CI: 5.6, 7.7) by investigator assessment based on mRECIST criteria. By masked IIR, the findings were reversed and the duration of response was slightly longer in the lenvatinib arm with a median of DOR 7.3 month compared to 6.2 months in the sorafenib arm, however the number of responders was much lower in the sorafenib arm (n=59) as reported in Table 6.11.[8]

Exploratory Endpoints

The DCR was higher in the lenvatinib group (DCR: 75.5%; 95% CI: 71.7, 79.4) than in the sorafenib group (DCR: 60.5%; 95% CI: 56.1, 64.9) based on investigator review according to mRECIST Table 6.11.[5] CBR was not reported.

Quality of Life

Study compliance was high (>90%) for the patient outcome measures throughout the study, however, due to decline in patient numbers over the course of the study, interpretation was limited at later cycles. Less than 50% of the population was observed at cycle 6 and less than 25% at cycle 12. No imputations for missing outcomes were conducted.[8]

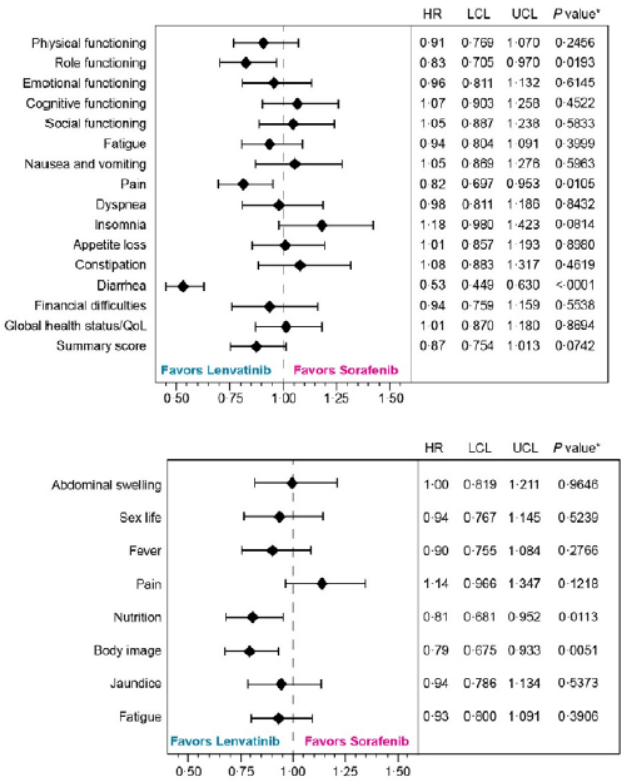
Baseline scores for all domains in the EORTC QLQ-HCC18, EORTC QLQ-C30, and EQ-5D-3L were similar between treatment arms and declined in both groups. The summary score was no statistically significant between the treatment arms (HR: 0.87; 95% CI: 0.75, 1.01).[5] The overall median time to clinically significant worsening (TCW) of HRQoL (measured from baseline to the off-treatment visit) was similar between lenvatinib (1.7 months; 95% CI: 1.05, 1.84) and sorafenib (1.8 months; 95% CI: 1.05, 1.84).[12] There were no significant differences in TCW in most domains between the 2 arms (Figure 6.10). A clinically meaningful delay in deterioration for lenvatinib vs. sorafenib was observed for nutrition (4.1 vs. 2.8 months, respectively; p = 0.0060) and body image (2.8 vs. 1.9 months, respectively; p = 0.004) from the EORTC QLQ-HCC18 domains. Based on EORTC QLQ-C30 domains, a clinically meaningful delay in deterioration for lenvatinib vs. sorafenib was observed for role functioning (2.0 versus 1.9 months, respectively; p = 0.0098), pain (2.0 versus 1.8 months, respectively; p = 0.0060), and diarrhoea (4.6 versus 2.7 months, respectively; p < 0.0001).[4]

Based on the EQ-5D-3L, TCW was similar between lenvatinib (2.8 months; 95% CI: 2.17, 3.65) and sorafenib (1.9 months; 95% CI: 1.84, 2.33) measured using the VAS. Almost identical results for TCW for the lenvatinib arm (2.8 months, 95% CI: 1.97, 3.52) and sorafenib arm (1.9 months; 95% CI: 1.84, 2.66) were obtained using the HUI measure of the EQ-5D-3L.[12] All results in this section are exploratory based on the fixed sequence procedure to control for the type I error rate.

Additional exploratory analyses revealed that the likelihood of patients experiencing a 2-grade categorical deterioration (deterioration of 2 categories on the verbal response scale) over the course of the post-baseline treatment period was statistically equivalent for most EORTC QLQ-C30 and EORTC QLQ-HCC18 items (OR ~ 1.0). Patients treated with sorafenib were 38% less likely to observe a 2-grade deterioration in pain in the shoulder (OR=0.71; 95% CI: 0.56, 0.90; p=0.0046), whereas patients treated with lenvatinib were 25% less likely to observe a 2-grade deterioration in weight being too low (OR=1.25; 95% CI: 1.00, 1.56; p=0.0485) and 27% less likely to observe a 2-grade deterioration in activity reduction (OR: 1.27; 95% CI: 1.02; 1.58; p=0.0358).[7]

Figure 6.10: Forest plot of time to clinically meaningful worsening hazard ratios comparing lenvatinib and sorafenib using EORTC QLQ-C30 and QLQ-HCC18 domains

Top: Analysis of QLQ-C30 questionnaire scores. Bottom: Analysis of HCC18 questionnaire scores.



* Nominal p-value
HCC, hepatocellular carcinoma; HR, hazard ratio; LCL, lower control limit; QLQ-C30, quality-of-life questionnaire C30; UCL, upper control limit.

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Harms Outcomes

The analyses for safety (harms) outcomes were conducted on the safety analysis set (i.e., patients who received at least 1 dose of study treatment), which included 951 patients (476 in the lenvatinib arm and 475 in the sorafenib arm). Treatment-emergent adverse events (TEAEs) occurred in 99% of participants in both treatment arms, with 94% in the lenvatinib arm and 95% in the sorafenib arm being treatment-related. A higher proportion of grade ≥ 3 TEAEs (75% vs. 67%), treatment-related grade ≥ 3 TEAEs (57% vs. 49%), serious TEAEs (43% vs. 30%), serious treatment-related TEAEs (18% vs.10%) occurred in the lenvatinib arm compared to the sorafenib arm, respectively. Adjusted by patient-years, the AE rate was 18.9 episodes per patient-year in the lenvatinib group and 19.7 episodes per patient-year in the sorafenib arm.[5]

Illustrated in Table 6.12, there were 9 commonly occurring (≥20%) any grade TEAEs in the lenvatinib arm, which included hypertension (42%), diarrhea (39%), decreased appetite (34%), decreased weight (31%), fatigue (30%), palmar-plantar erthrodysaesthesia (27%), proteinuria (25%), dysphonia (24%), and nausea (20%). In the sorafenib arm, there were 7 commonly occurring (≥20%) any grade TEAEs, which included palmar-plantar erthrodysaesthesia (52%), diarrhea (46%), hypertension (30%), decreased appetite (27%), fatigue (25%), alopecia (25%), and decreased weight (22%). There were 6 commonly occurring (≥5%) grade ≥3 TEAEs in the lenvatinib group, which included hypertension (23%), decreased weight (8%), increased blood bilirubin (7%), proteinuria (6%), decreased platelet count (5%), and elevated aspartate aminotransferase (5%). In the sorafenib arm, there were 4 common (≥5%) grade ≥3 TEAEs, which included hypertension (14%), palmar-plantar erthrodysaesthesia (11%), elevated aspartate aminotransferase (8%), and increased blood bilirubin (5%).[5]

TEAEs led to dose reductions in 184 (39%) participants in the lenvatinib arm and 185 (39%) participants in the sorafenib arm. A higher proportion of dose interruptions due to TEAEs occurred in the lenvatinib arm (n=248; 52%) compared to the sorafenib arm (n=193; 41%). Approximately 20% (n=94) of participants withdrew study drug due to TEAEs in the lenvatinib arm compared to 15% (n=69) in the sorafenib arm.[8]

Treatment-related fatal AEs occurred in twice as many participants in the lenvatinib arm (n=11; 2%) compared to the sorafenib arm (n=4, 1%). In the lenvatinib arm, fatal AEs included hepatic failure (n=3), cerebral hemorrhage (n=3), and respiratory failure (n=2), whereas in the sorafenib arm tumor hemorrhage, ischemic stroke, respiratory failure, and sudden death (n=1 for each) resulted in fatality.[5]

In post-hoc exploratory analyses on a subgroup of patients treated with lenvatinib, those who experienced AEs of interest had a reduced risk of death compared to those who did not, as shown in Table 6.13. AEs of interest included commonly occurring AEs in the lenvatinib arm such as hypertension, diarrhea, proteinuria, dysphonia, and hypothyroidism.[2] This is similar to research on commonly occurring AEs with sorafenib, specifically dermatological AEs, which are associated with a greater probability of longer survival.[70]

Table 6.12: Adverse events in the REFLECT trial

	Lenvatinib (n=476)	Sorafenib (n=475)
Total treatment-emergent adverse events	470 (99%)	472 (99%)
Total treatment-related treatment-emergent adverse events	447 (94%)	452 (95%)
Treatment-emergent adverse events of grade ≥3	357 (75%)	316 (67%)
Treatment-related treatment-emergent adverse events of grade ≥3	270 (57%)	231 (49%)
Serious treatment-emergent adverse events	205 (43%)	144 (30%)
Serious treatment-related treatment-emergent adverse events	84 (18%)	48 (10%)
Treatment-emergent adverse events occurring in ≥15% of patients in either treatment group		
Palmar-plantar erythrodysaesthesia		
Any grade	128 (27%)	249 (52%)
Grade ≥3	14 (3%)	54 (11%)
Diarrhoea		
Any grade	184 (39%)	220 (46%)
Grade ≥3	20 (4%)	20 (4%)
Hypertension		
Any grade	201 (42%)	144 (30%)
Grade ≥3	111 (23%)	68 (14%)
Decreased appetite		
Any grade	162 (34%)	127 (27%)
Grade ≥3	22 (5%)	6 (1%)
Decreased weight		
Any grade	147 (31%)	106 (22%)
Grade ≥3	36 (8%)	14 (3%)
Fatigue		
Any grade	141 (30%)	119 (25%)
Grade ≥3	18 (4%)	17 (4%)
(Table 3 continues in next column)		

	Lenvatinib (n=476)	Sorafenib (n=475)
(Continued from previous column)		
Alopecia		
Any grade	14 (3%)	119 (25%)
Grade ≥3	0	0
Proteinuria		
Any grade	117 (25%)	54 (11%)
Grade ≥3	27 (6%)	8 (2%)
Dysphonia		
Any grade	113 (24%)	57 (12%)
Grade ≥3	1 (<1%)	0
Nausea		
Any grade	93 (20%)	68 (14%)
Grade ≥3	4 (1%)	4 (1%)
Abdominal pain		
Any grade	81 (17%)	87 (18%)
Grade ≥3	8 (2%)	13 (3%)
Decreased platelet count		
Any grade	87 (18%)	58 (12%)
Grade ≥3	26 (5%)	16 (3%)
Elevated aspartate aminotransferase		
Any grade	65 (14%)	80 (17%)
Grade ≥3	24 (5%)	38 (8%)
Hypothyroidism		
Any grade	78 (16%)	8 (2%)
Grade ≥3	0	0
Vomiting		
Any grade	77 (16%)	36 (8%)
Grade ≥3	6 (1%)	5 (1%)
Constipation		
Any grade	76 (16%)	52 (11%)
Grade ≥3	3 (1%)	0
Rash		
Any grade	46 (10%)	76 (16%)
Grade ≥3	0	2 (<1%)
Increased blood bilirubin		
Any grade	71 (15%)	63 (13%)
Grade ≥3	31 (7%)	23 (5%)

Data are presented as n (%).

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Table 6.13: Overall survival by adverse events of interest (AEIs) in lenvatinib patients (n = 478) in the REFLECT trial

AE	AEI, n (%)	No AEI, n (%)	Hazard Ratio for OS	95% CI	*P*-value
Hypertension	201 (42%)	277 (58%)	0.64	0.52-0.80	0.00005
Diarrhea	184 (38%)	294 (62%)	0.72	0.58-0.90	0.00314
Proteinuria	117 (24%)	361 (76%)	0.76	0.60-0.98	0.03042
Dysphonia	113 (24%)	365 (76%)	0.86	0.68-1.11	0.24708
Hypothyroidism	78 (16%)	400 (84%)	0.72	0.54-0.96	0.02377

Source: Sung et al., 2019.

6.4 Ongoing Trials

Table 6.14: Ongoing trials of lenvatinib in hepatocellular carcinoma

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study:[71] NCT03775395 **Characteristics:** Quadruple-blinded, randomised, active-controlled, phase III trial **Estimated enrolment:** n = 250 **Number of centres and number of countries:** 1 site in China **Patient Enrolment Dates:** December 12th, 2018 (ongoing) **Estimated study completion:** December 1st, 2021 **Funding:** Sun Yat-sen University	Key Inclusion Criteria: • 18 - 75 years of age • Diagnosis of HCC based on EASL • Stage C disease based on BCLC staging • Liver function status Child-Pugh score A • ECOG PS 0-2 • No prior treatment • One measurable HCC lesion based on EASL criteria • Adequate organ function Key Exclusion Criteria: • Evidence of hepatic decompensation including ascites, GI bleeding, or hepatic encephalopathy • History of HIV • History of organ allograft • CNS metastases • Cardiac ventricular arrhythmias requiring anti-arrhythmic therapy • Evidence of bleeding diathesis	Intervention: Hepatic arterial infusion chemotherapy (HAIC) consisting of oxaliplatin, fluorouracil, and leucovorin with lenvatinib Comparator: HAIC consisting of oxaliplatin, fluorouracil, and leucovorin with sorafenib	Primary: - OS Secondary: - TTP - Safety - PFS

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study:[72] LEAP-002 NCT03713593 **Characteristics:** Double-blinded, randomised (1:1), active-controlled, superiority, phase III trial **Estimated enrolment:** n = 750 **Number of centres and number of countries:** 114 sites in USA, Australia, Chile, China, Colombia, France, Germany, Ireland, Italy, Japan, Korea, Mexico, New Zealand, Poland, Russia, Spain, Taiwan, Thailand, Turkey, and United Kingdom, **Patient Enrolment Dates:** December 31st, 2018 (ongoing) **Estimated study completion:** July 23rd, 2022 **Funding:** Merck Sharp & Dohme Corp.	Key Inclusion Criteria: • ≥ 18 years of age • Histological, radiological, or cytological confirmed diagnosis of HCC • Stage B (not amenable or refractory to locoregional therapy and not amenable to curative treatment) or C disease based on BCLC staging • Liver function status Child-Pugh score A • ECOG PS 0 or 1 • One measurable HCC lesion based on RECIST 1.1 as confirmed by BICR • Survival expectation of >3 months • HBV-positive patients allowed if virus well controlled Key Exclusion Criteria: • Had esophageal or gastric variceal bleeding in the last 6 months • Pre-existing grade ≥3 GI or non-GI fistula • Received prior systematic chemotherapy for HCC or for any other malignancy in the past 3 years • History of HIV • Active TB • Active infection requiring systemic therapy with the exception of HBV and HCV • CNS metastases • Significant cardiovascular impairment	Intervention: Lenvatinib + pembrolizumab Comparator: Lenvatinib + saline placebo	Primary: - PFS - OS Secondary: - ORR - DOR - DCR - Safety - TTP
Study:[73] NCT03905967 **Characteristics:** Open-label, randomised, active-controlled, phase III trial **Estimated enrolment:** n = 336 **Number of centres and number of countries:** 1 site in China **Patient Enrolment Dates:** April 15th, 2019 (ongoing) **Estimated study completion:** June 15th, 2023 **Funding:** Sun Yat-sen University	Key Inclusion Criteria: • 18 - 75 years of age • Diagnosis of HCC based on AASLD 2018 guidelines • Liver function status Child-Pugh score A • ECOG PS 0-1 • No prior treatment • One measurable HCC lesion based on mRECIST criteria • Adequate organ function Key Exclusion Criteria: • Preoperative imaging that revealed diffuse intrahepatic lesions or invasion to main portal vein, inferior vena cava, or primary branch bile duct • History of hepatic encephalopathy, refractory ascites, gastric varices • History of HIV, syphilis infection • History of organ allograft • CNS metastases • Contraindication to TACE • Severe organ dysfunction • Other malignant tumors within 5 years	Intervention: Transarterial chemoembolization (TACE) with lenvatinib Comparator: Lenvatinib monotherapy	Primary: - OS Secondary: - TTP

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	• Active severe infection > grade 2 (CTCAE v.4)		

Abbreviations:
AASLD = American Association for the Study of Liver Diseases; **BCLC** = Barcelona Clinic Liver Cancer; **BICR** = blinded independent central review; **CTCAE** = Common Terminology Criteria for Adverse Events; **CNS** = central nervous system; **DCR** = disease control rate; **DOR** = duration of response; **EASL** = European Association for the Study of the Liver; **ECOG PS** = Eastern Cooperative Oncology Group Performance Status; **GI** = gastrointestinal; **HAIC** = Hepatic arterial infusion chemotherapy; **HBV** = hepatitis B virus; **HCC** = hepatocellular carcinoma; **HCV** = hepatitis C virus; **HIV** = human immunodeficiency virus; **mRECIST** = modified response evaluation criteria in solid tumors; **ORR** = objective response rate; **OS** = overall survival; **PFS** = progression-free survival; **RECIST** = response evaluation criteria in solid tumors; **TACE** = transarterial chemoembolization; **TB** = tuberculosis; **TTP** = time to progression

7 SUPPLEMENTAL QUESTIONS

No supplemental question considered to be relevant to the review was identified.

8 COMPARISON WITH OTHER LITERATURE

No relevant evidence or results were identified from within published literature.

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 lenvatinib (Lenvima) 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. The manufacturer, as the primary data owner, did not agree to the disclosure of some clinical information which was provided to pERC for their deliberations, and this information has been redacted in this publicly posted Guidance Report.

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 CGP is comprised of three clinicians. 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): **EBM Reviews - Cochrane Central Register of Controlled Trials** January 2019, **Embase** 1974 to 2019 February 21, **Ovid MEDLINE(R) ALL** 1946 to February 21, 2019

Search Strategy:

#	Searches	Results
1	(lenvima* or lenvatinib* or kisplyx* or E 7080 or E7080 or ER-203492-00 or ER203492-00 or EE083865G2 or 3J78384F61).ti,ab,ot,kf,kw,hw,rn,nm.	2006
2	Carcinoma, Hepatocellular/ or exp liver neoplasms/	410056
3	(hepatoma* or (liver adj3 carcinoma*) or hepatocellular carcinoma* or hepatocarcinoma* or liver cancer* or HCC).ti,ab,kf,kw.	301565
4	((hepatocellular or liver or hepatic) adj3 (cancer* or carcinoma* or tumor* or tumour* or neoplas* or malignan* or adenocarcinoma* or adenoma*)).ti,ab,kf,kw.	324342
5	2 or 3 or 4	529853
6	1 and 5	420
7	6 use cctr	20
8	6 use medall	71
9	*lenvatinib/	472
10	(lenvima* or lenvatinib* or kisplyx* or E 7080 or E7080 or ER-203492-00 or ER203492-00).ti,ab,kw,dq.	1321
11	9 or 10	1334
12	exp liver tumor/	251347
13	(hepatoma* or (liver adj3 carcinoma*) or hepatocellular carcinoma* or hepatocarcinoma* or liver cancer* or HCC).ti,ab,kw,dq.	301641
14	((hepatocellular or liver or hepatic) adj3 (cancer* or carcinoma* or tumor* or tumour* or neoplas* or malignan* or adenocarcinoma* or adenoma*)).ti,ab,kw,dq.	322613
15	12 or 13 or 14	475155
16	11 and 15	253
17	16 use oemezd	164
18	16 and conference abstract.pt.	73

19 16 not conference abstract.pt.	180
20 limit 18 to yr="2014 -Current"	66
21 7 or 8 or 19	184
22 remove duplicates from 21	124
23 20 or 22	188
24 limit 23 to english language	173

2. **Literature search via PubMed**
   A limited PubMed search was performed to capture records not found in MEDLINE.

History

Search	Query	Items found
#8	Search **#6 AND #7** Filters: **English**	6
#7	Search **publisher[sb]** Filters: **English**	528574
#6	Search **#1 AND #5** Filters: **English**	72
#5	Search **#2 OR #3 OR #4** Filters: **English**	231380
#4	Search **(hepatocellular*[tiab] OR liver*[tiab] OR hepatic*[tiab]) AND (cancer[tiab] OR cancers[tiab] OR carcinoma*[tiab] OR tumour[tiab] OR tumor[tiab] OR tumours[tiab] OR tumors[tiab] OR tumourous[tiab] OR tumorous[tiab] OR neoplas*[tiab] OR malignan*[tiab] OR adenocarcinoma*[tiab] OR adenoma*[tiab])** Filters: **English**	201806
#3	Search **hepatoma*[tiab] OR hepatocellular carcinoma*[tiab] OR hepatocarcinoma[tiab] OR HCC [tiab]** Filters: **English**	99983
#2	Search **"Carcinoma, Hepatocellular"[Mesh]** Filters: **English**	67218
#1	Search **lenvima[tiab] OR lenvatinib[tiab] OR E 7080[tiab] OR E7080[tiab] OR ER-203492-00[tiab] OR ER203492-00[tiab]** Filters: **English**	359

3. Cochrane Central Register of Controlled Trials (Central)
   Searched via Ovid

4. Grey Literature search via:

Clinical Trial Registries:

U.S. NIH ClinicalTrials. gov
http://www.clinicaltrials.gov/

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

Search: Lenvima (lenvatinib) AND unresectable hepatocellular carcinoma (HCC)

Select international agencies including:

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

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

Search: Lenvima (lenvatinib) AND unresectable hepatocellular carcinoma (HCC)

Conference abstracts:

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

European Society for Medical Oncology (ESMO)

http://oncologypro.esmo.org/Meeting-Resources

Search: Lenvima (lenvatinib) AND unresectable hepatocellular carcinoma (HCC) – last 5 years

Detailed Methodology

The literature search was performed by the pCODR Methods Team using the search strategy above.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (May 2018) 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 Lenvima (lenvatinib) 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 June 5, 2019.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - 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) and the European Society for Medical Oncology (ESMO) 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 Clinical Guidance Panel. In addition, 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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