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CADTH PCODR FINAL CLINICAL GUIDANCE REPORT

Clinical Report

ATEZOLIZUMAB (TECENTRIQ)

(Hoffman La-Roche Limited)

Indication: In combination with bevacizumab, for the first-line treatment of adult patients with unresectable or metastatic hepatocellular carcinoma who require systemic therapy.

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

AE	adverse event
AFP	alpha fetoprotein
ALT	alanine transaminase
AST	aspartate aminotransferase
BCLC	Barcelona Clinic Liver Cancer
CCO	Cancer Care Ontario
CCSN	Canadian Cancer Survivor Network
CGOEN	Canadian Gastrointestinal Oncology Evidence Network
CGP	Clinical Guidance Panel
CI	confidence interval
CLF	Canadian Liver Foundation
CNS	central nervous system
CR	complete response
CrIs	credible intervals
DAC	Drug Advisory Committee
DIC	deviance information criterion
DOR	duration of response
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGD	esophagogastroduodenoscopy
EHS	extrahepatic spread
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D	EuroQol 5-Dimensions
EQ-5D-5L	EuroQol 5-Dimensions 5-Levels
FE	fixed effects
FGFR	fibroblast growth factor receptors
GI	gastrointestinal
GHS	global health score
HBV	hepatitis B virus
HCV	hepatitis C virus
HCC	hepatocellular carcinoma
HCC mRECIST	hepatocellular carcinoma-specific modified RECIST
HR	hazard ratio
imRECIST	immune-modified RECIST
IO	immuno-oncology
IRF	independent review facility

ITC	indirect treatment comparison
ITT	intention-to-treat
MDD	minimum detectable difference
MVI	macrovascular invasion
NMA	network meta-analysis
OR	objective response
ORR	objective response rate
OS	overall survival
PAG	Provincial Advisory Group
pCODR	CADTH pan-Canadian Oncology Drug Review
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
pERC	pCODR Expert Review Committee
PFS	progression-free survival
PR	partial response
PRO	patient-reported outcome
QoL	quality of life
QLQ-C30	Quality of Life Questionnaire Core 30
RCT	randomized controlled trial
RE	random effects
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
RT	radiation therapy
SAE	serious adverse event
SIRT	selective internal radiotherapy
TACE	transarterial chemoembolization
TKI	tyrosine kinase inhibitor
TTD	time to deterioration
TTP	time to progression
VEGFR	vascular endothelial growth factor receptor
WDAE	withdrawal due to adverse event

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 atezolizumab (Tecentriq) in combination with bevacizumab 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 conducted by the Clinical Guidance Panel (CGP) and the CADTH Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group (PAG); 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, a summary of submitted Provincial Advisory Group Input, and a summary of submitted Registered Clinician Input, 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 atezolizumab in combination with bevacizumab for the treatment of patients with unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy.

On August 7, 2020, Health Canada issued marketing authorization without conditions for atezolizumab in combination with bevacizumab for the first-line treatment of adult patients with unresectable or metastatic hepatocellular carcinoma (HCC) who require systemic therapy. The funding request is in line with this indication, with the additional clarification that maintenance atezolizumab and bevacizumab should continue until loss of clinical benefit or unacceptable toxicity.

According to the product monograph, atezolizumab is an Fc-engineered humanized immunoglobulin G1 (IgG1) monoclonal antibody. By directly binding to programmed death-ligand 1 (PD-L1), atezolizumab blocks the interactions between PD-L1 with the PD-1 and B7.1 receptors found on T cells, subsequently releasing programmed cell death protein 1 (PD-1)/PD-L1 pathway-mediated inhibition of the immune response and reactivating the anti-tumour immune response. The recommended dose of atezolizumab when used for the treatment of unresectable or metastatic HCC is 1200 mg administered as an intravenous (IV) infusion over 60 minutes, followed by 15 mg/kg of bevacizumab; the combination administered every three weeks. Atezolizumab is available as single-use vials containing 60mg/mL solution for dilution (for IV infusion). It is available in two sizes, either 840 mg per 14 mL or 1200 mg per 20 mL.[1]

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

One randomized controlled trial was identified that met the selection criteria of this review. IMbrave150 is an international, multi-centre, open-label, phase III, randomized, superiority trial that compares atezolizumab in combination with bevacizumab to sorafenib monotherapy, in patients with locally advanced or metastatic, and/or unresectable HCC who have not received prior systemic treatment. Patients ≥ 18 years of age with HCC deemed not amenable to curative surgical and/or locoregional therapies, or had progressed thereafter, were randomized in a 2:1 ratio to receive intravenous (IV) atezolizumab plus bevacizumab on Day 1 of each 21-day cycle, or oral sorafenib twice a day until loss of clinical benefit or unacceptable toxicity occurred. Patients were also required to have a Child-Pugh liver function score of A and Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. The study enrolled 501 patients, with 336 randomized to atezolizumab plus bevacizumab and 165 patients randomized to the sorafenib treatment groups. Randomization was stratified by region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), baseline α-fetoprotein (AFP) levels (< 400 ng/mL vs. ≥ 400 ng/mL), and ECOG PS (0 vs. 1).[2]

Tumour response was assessed by investigators and a central independent review facility (IRF) using Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) and HCC-specific modified RECIST (HCC mRECIST). Treatment was continued until

loss of clinical benefit; patients who met the criteria for radiographic disease progression per RECIST v1.1 were permitted to continue the assigned study treatment if certain criteria were met, including continued clinical benefit and no evidence of unequivocal disease progression. After treatment discontinuation, patients were followed until study withdrawal, loss to follow-up, or until study termination.[2]

The primary efficacy outcome was the co-primary endpoint of overall survival (OS) and progression-free survival by IRF assessment (PFS-IRF) and according to RECIST v1.1. Key secondary endpoints included objective response rate by IRF assessment (ORR-IRF) according to RECIST v1.1 and HCC mRECIST. Several other exploratory secondary endpoints, such as time to progression (TTP) and time to deterioration in patient-reported outcomes (PROs) were also investigated. Unstratified analysis of the co-primary endpoints were performed for several pre-specified subgroups, including age, Barcelona Clinic Liver Cancer (BCLC) stage, ECOG PS, geographic region, HCC etiology, and macrovascular invasion (MVI) and/or extrahepatic spread (EHS).[2]

Patient enrolment occurred over approximately 10 months (March 15, 2018 to January 30, 2019). The median duration of follow-up was 8.6 months with a data cut-off date of August 29, 2019 for the final PFS and interim OS analysis. At the time of data cut-off, 108 patients (32.1%) in the atezolizumab plus bevacizumab group and 84 patients (50.9%) in the sorafenib group had discontinued from the trial, mostly due to death.[2]

Baseline demographics and characteristics were generally well balanced between the two treatment groups. A slightly higher proportion of patients randomized to the sorafenib group were 65 years of age or older (47.9% atezolizumab plus bevacizumab vs. 55.2% sorafenib). The atezolizumab plus bevacizumab group had a higher proportion of patients with EHS (63.1% vs. 56.4%), although a slightly higher proportion of patients in the sorafenib group had MVI (38.4% vs. 43.0%). Overall, enrolled patients were predominantly male (82.6%, n=414), Asian (56.7%, n=284), with ECOG PS of 0 (62.3%, n=312), Child-Pugh score of A5 (72.1%, n=360), and BCLC Stage C disease (Advanced; 81.6%, n=409). Notably, most patients had presence of MVI and/or EHS (75.4%, n=378), and hepatitis B was the predominant etiology of HCC (47.9%, n=240). Approximately half of enrolled patients (49.1%, n=246) had received at least one prior local therapy for HCC.[2]

At the time of data cut-off, 43.5% of patients (n=146) in the atezolizumab plus bevacizumab group were still receiving treatment, and 24.4% of patients (n=82) were in follow-up.[2] Nine patients were receiving atezolizumab monotherapy, while the remaining 127 patients were receiving atezolizumab plus bevacizumab combination therapy.[3] In the sorafenib group, 14.5% of patients (n=24) were still receiving treatment, whereas 34.5% (n=57) were in follow-up. Notably, the median duration of treatment was different between sorafenib (2.8 months) and atezolizumab (7.4 months) or bevacizumab (6.9 months). After assigned study treatment, a greater proportion of patients in the sorafenib group received at least one subsequent systemic anti-cancer therapy than patients treated with atezolizumab plus bevacizumab (44.2%; n=73 sorafenib vs. 20.5%; n=69 atezolizumab plus bevacizumab); treatment in the second, third, and fourth line settings were all received by a higher proportion of patients treated with sorafenib.[2] In the atezolizumab plus bevacizumab group, sorafenib was the most frequently prescribed subsequent regimen overall (n=33), administered mostly in the second-line setting (n=31).[2,4] For patients randomized to the sorafenib group, lenvatinib was the most frequently prescribed subsequent therapy (n=23), followed by regorafenib (n=20) and nivolumab (n=16), administered mostly in the second- and third-line settings.[4]

Analysis of events for PFS and OS were conducted in the intention-to-treat (ITT) population, and the safety analysis included patients who received at least one partial or full dose of study medication. PROs were measured mainly using European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30); the HCC disease-specific treatment questionnaire (EORTC QLQ-HCC18) was used as part of exploratory analyses.[2]

Efficacy

A brief summary highlighting the key outcomes of the trial is provided in Table 1. Final analysis for OS data was planned for after 312 deaths had occurred. At the data cut-off date, 161 patients had died, including 96 patients (28.6%) in the atezolizumab plus bevacizumab group and 65 patients (39.4%) in the sorafenib group. Median OS was not reached for patients randomized to atezolizumab plus bevacizumab and was 13.2 months for patients randomized to sorafenib. The interim OS analysis data demonstrated a statistically significant difference between treatment groups, favouring atezolizumab plus bevacizumab (hazard ratio [HR] 0.58; 95% CI 0.42 to 0.79; p<0.001). A statistically significant benefit in the co-primary endpoint of PFS was also demonstrated

for atezolizumab plus bevacizumab. In total, 197 patients (58.6%) in the atezolizumab plus bevacizumab group and 109 patients (66.1%) in the sorafenib group had experienced disease progression or died, with median PFS of 6.8 months in patients randomized to atezolizumab plus bevacizumab treatment group compared to 4.3 months in patients randomized to sorafenib. The corresponding HR for disease progression or death was 0.59 (95% CI, 0.47 to 0.76; p<0.001).[2]

Sensitivity analyses also showed consistent results with the primary analysis. Subgroup analyses for the co-primary endpoints of OS and PFS were also generally consistent with the ITT population, with point estimates for HRs favouring treatment with atezolizumab plus bevacizumab. An exception was OS in patients with BCLC Stage B, where results favoured sorafenib treatment (HR 1.09; 95% CI 0.33 to 3.53); however, this should be interpreted with caution due to wide confidence intervals that were not adjusted for multiple comparisons, and the study was also not powered to detect differences in subgroups. Other key secondary endpoints such as objective response rate (which included complete response or partial response by IRF assessment) also supported the co-primary endpoints showing favourable results for atezolizumab plus bevacizumab. Specifically, ORR-IRF per RECIST v1.1 was 27.3% (95% CI, 22.5 to 32.5) and 11.9% (95% CI, 7.4 to 18.0) in the atezolizumab plus bevacizumab and sorafenib groups, respectively. The ORR-IRF per HCC mRECIST, another key secondary endpoint, was 33.2% (95% CI, 28.1 to 38.6) in the atezolizumab plus bevacizumab group and 13.3% (95% CI, 8.4 to 19.6) in the sorafenib group.[2]

Measures of quality of life, namely time to deterioration in three specific EORTC QLQ-C30 subscale scores (i.e., global health score/quality of life, physical functioning, and role functioning) was a secondary endpoint. A clinically meaningful delay in deterioration for all three subscales was observed in the atezolizumab plus bevacizumab group compared to patients treated with sorafenib.[2] Exploratory analysis of other patient-reported symptoms, such as anorexia, diarrhea, fatigue, and pain also showed a clinically meaningful delay in deterioration for patients who received atezolizumab plus bevacizumab.[5]

Safety

Adverse events (AEs) were evaluated in a safety population consisting of 329 patients in the atezolizuab plus bevacizumab group and 156 patients in the sorafenib group (Table 1). Broadly, a similar number of patients in each treatment group experienced an AE due to any cause (all grades; 98.2%, n=323 atezolizumab plus bevacizumab vs. 98.7%, n=154 sorafenib). Grade 3 or 4 AEs due to any cause were also comparable (56.5%, n=186 atezolizumab plus bevacizumab versus 55.1%, n=86 sorafenib). A higher proportion of patients treated with atezolizumab plus bevacizumab (38.0%, n=125) experienced a serious adverse event (SAE) compared to patients treated with sorafenib (30.8%, n=48), though no specific cause was identified; the difference in incidence of identified SAEs were less than 2% between treatment groups.[2] Reported AEs were consistent with the known safety profile of atezolizumab and bevacizumab except for peripheral edema which occurred [redacted], though were of grade 1 or 2 in severity and considered non-serious.[5] Immune-mediated AEs of atezolizumab were comparable to the known safety profile except for the following which occurred at a higher incidence than anticipated: immune-related hepatitis (43.2%, including diagnosis and abnormal liver function tests), immune-related hyperthyroidism (4.6%), and immune-mediated diabetes mellitus (2.4%).[5]
(Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until April 30, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

A higher proportion of patients treated with sorafenib experienced an adverse event (AE) deemed related to treatment compared to patients who received atezolizumab plus bevacizumab (any grade, 94.2%, n=147 for sorafenib vs. 83.9%, n=276). Grade 3 or 4 treatment-related AEs were also experienced by a greater proportion of patients treated with sorafenib (45.5%, n=71 for sorafenib vs. 35.6%, n=117). [redacted][2]
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The most commonly reported (≥ 10%) treatment-related AEs of any grade in the atezolizumab plus bevacizumab group were hypertension (23.7%), proteinuria (18.8%), fatigue (15.2%), elevated aspartate aminotransferase (AST, 14.0%), pruritis (13.1%), infusion-related reaction (10.9%), diarrhea (10.3%), elevated alanine aminotransferase (ALT, 10.3%), and reduced appetite (10.3%). In patients who received sorafenib, the most common (≥ 10%) treatment-related AEs were palmer-planter erythrodysesthesia syndrome (48.1%), diarrhea (42.9%), hypertension (19.9%), reduced appetite (19.9%), rash (16.7%), fatigue (15.4%), alopecia (13.5%), nausea (12.8%) and asthenia (10.3%). The most common (≥ 5%) grade 3 or 4 treatment-related AEs was hypertension (10.3%) in the atezolizumab plus bevacizumab group; and in patients treated with sorafenib, the most commonly reported grade 3 or 4 treatment-related AEs were hypertension (9%) and palmer-plantar erythrodysesthesia syndrome (8.3%). Overall, the most common grade 3 or 4 treatment-related AE in both treatment groups was hypertension. For the atezolizumab plus bevacizumab combination, infusion-related reactions as well as elevated AST and ALT were reported more frequently with the atezolizumab component, whereas hypertension and proteinuria were attributed more often to the bevacizumab component. Of the most frequently reported (≥ 1%) treatment-related SAEs, [redacted][5]

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In patients who received sorafenib treatment, 10.3% had discontinued the study drug due to an adverse event. In the atezolizumab plus bevacizumab group, adverse events led to discontinuation of one component of the combination in 15.5% of patients, and both components were stopped in 7.0%. Patients experienced an adverse event that led to discontinuation of bevacizumab (14.6%, n=48) more often than atezolizumab (8.5%, n=28). Main reasons for discontinuation of atezolizumab were autoimmune hepatitis, GI hemorrhage, increased transaminases, or infusion-related reactions, whereas bevacizumab was most frequently discontinued due to GI hemorrhage, esophageal hemorrhage, esophageal varices hemorrhage, or proteinuria. Discontinuation of sorafenib was largely due to dermatological reactions (e.g., rash, toxic skin eruption) or related to hepatic adverse effects (e.g., hepatic cirrhosis, elevated liver function tests).[2] Overall, adverse events leading to discontinuation was deemed related to treatment in [redacted].[5]

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Deaths due to an AE occurred in 4.6% and 5.8% of patients in the atezolizumab plus bevacizumab (n=15) and sorafenib (n=9) groups, respectively.[2] [redacted][5]

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Limitations

Overall, the IMbrave150 trial was a well-designed randomized controlled trial (RCT) and there were no major concerns with the conduct of the trial. Measured outcomes were clinically important and relevant to patients with HCC. The randomization method and sample size were adequate, and a stratified randomization procedure was used based on known prognostic factors to minimize

potential imbalances between the study groups that might lead to biased results. Eligibility criteria were well defined and appropriate. The study population characteristics overall reflect patients who would be eligible for systemic treatment for HCC in Canada, although there were a slightly higher number of Asian patients (56.7%), patients with prior liver resection (28.7%), and HBV etiology (47.9%) than generally seen in the Canadian patient population.[2,4] The populations used for analyses were appropriate, with the key efficacy analysis conducted according to the ITT principle. However, there are a few key limitations and potential sources of bias that were noted by the CADTH Methods Team, as outlined below:

- Due to the open-label study design, the investigators and patients were aware of the treatment allocation. It is possible that due to this knowledge of the assigned treatment, the trial results may be at risk for biases related to the lack of blinding which can affect the measurement and reporting of outcomes. Accordingly, the results may be biased in favour of the atezolizumab plus bevacizumab group compared to the sorafenib group. This could be particularly important in the reporting of subjective outcomes (e.g., adverse effects, patient-reported symptoms and outcomes) by the patients and care providers. Treatment response and disease progression were measured by a central, blinded independent review facility to reduce investigator bias.
- Final analysis of OS was scheduled for after 312 deaths, which had yet to occur (161 deaths occurred by data cut-off date).[2] Current OS data is immature and reflects the first interim analysis. As the co-primary OS endpoint was met at the first interim analysis, this analysis was considered as definitive by the study sponsors.[5] Although the study is still ongoing, the event-driven second interim analysis of OS will no longer be performed; instead, a time-driven descriptive OS analysis is planned with data cut-off date in August 2020, approximately 12 months after the first interim analysis.[4] According to the sponsors, final descriptive analysis is also under discussion.[6] As median OS had not been reached in the atezolizumab plus bevacizumab group with the current duration of follow-up (median 8.6 months), the absolute difference between the two treatment groups in this endpoint is unknown. The magnitude of benefit over time will need to be confirmed with longer follow-up data, and this change in the pre-specified analysis plan contributes to uncertainty in the degree of sustained effect of atezolizumab plus bevacizumab.
- During the survival follow-up period, patients were permitted to receive subsequent treatment for HCC, which included tyrosine kinase inhibitors (TKIs) and immunotherapies (18.8% of patients in atezolizumab plus bevacizumab group received a subsequent TKI; 18.8% of patients in the sorafenib group received subsequent immunotherapy; 26.1% of patients in the sorafenib group received a different TKI). Overall, a higher proportion of patients randomized to sorafenib received subsequent therapy (20.5% atezolizumab plus bevacizumab vs. 44.2% sorafenib, second-line and beyond).[2] This may confound the assessment of OS by prolonging survival beyond what would have occurred with frontline treatment alone and overestimating survival benefit, possibly in favour of sorafenib, though the effects of each treatment arm and the benefit of atezolizumab plus bevacizumab over sorafenib were maintained over time.
- To account for interim analyses as well as co-primary and key secondary endpoints, overall Type I error rate was appropriately controlled using a graphical approach. There were many predefined subgroup analyses and multiple secondary efficacy outcomes assessed in the trial that were not adjusted to account for multiple comparison testing to control the risk of Type I error. The trial was not powered to test specific hypotheses in these additional subgroups and outcomes; therefore, results of the subgroup analyses should be interpreted as exploratory in nature. Analyses of secondary endpoints (other than ORR-IRF per RECIST v1.1 and HCC mRECIST), and exploratory endpoints were not adjusted for multiplicity; these results may be considered as supplemental to the primary and key secondary endpoints, but should also be interpreted with caution. Although pre-specified, PROs were not adjusted for multiplicity and thus should only be considered descriptive.
- Although the dose of sorafenib in the trial reflects what is recommended in the product monograph[7], prescribers often opt to use a lower starting dose of 200 mg twice a day to improve tolerability; daily dose is gradually increased as tolerated, until target dose is achieved. Thus, starting patients in the clinical trial at 400 mg twice a day may have contributed to more AEs (e.g., diarrhea, fatigue, palmer-planter erythrodysesthesia syndrome) and reduced tolerability compared to what would normally be anticipated in Canadian clinical practice. In the trial, 37.2% of patients treated with sorafenib required a dose adjustment due to an AE.[2]

Table 1: Highlights of Key Outcomes

	IMbrave150	
	Atezolizumab plus bevacizumab	Sorafenib
Efficacy Outcomes – Overall ITT Population	**N=336**	**N=165**
Co-Primary Outcome – OS*		
Median, months (95% CI)	NE	13.2 (10.4 to NE)
Events, n (%)	96 (28.6)	65 (39.4)
Stratified HR (95% CI) †	0.58 (0.42 to 0.79)	
p-value*	<0.001	
Co-Primary Outcome – PFS by IRF (RECIST v1.1)		
Median, months (95% CI)	6.8 (5.7 to 8.3)	4.3 (4.0 to 5.6)
Events, n (%)	197 (58.6)	109 (66.1)
Stratified HR (95% CI) †	0.59 (0.47 to 0.76)	
p-value	<0.001	
Secondary Outcome (Key) – ORR by IRF (RECIST v1.1)		
ITT population with baseline measurable disease, N	326	159
Confirmed ORR, % (95% CI)	27.3 (22.5 to 32.5)	11.9 (7.4 to 18.0)
Difference, n	15.4	
p-value	<0.001	
Secondary Outcome (Key) – ORR by IRF (HCC mRECIST)		
ITT population with baseline measurable disease, N	325	158
Confirmed ORR, % (95% CI)	33.2 (28.1 to 38.6)	13.3 (8.4 to 19.6)
Difference, n	19.9	
p-value	<0.001	
Secondary Outcome – TTP by IRF (RECIST v1.1)		
Median, months (95% CI)	[redacted]	[redacted]
Events, n (%)	[redacted]	[redacted]
Stratified HR (95% CI) †	[redacted]	
HRQoL – TTD (EORTC QLQ-C30)	**N=336**	**N=165**
Physical Functioning		
Median, months (95% CI)	13.1 (9.7 to NE)	4.9 (3.5 to 6.2)
Stratified HR (95% CI) †	0.53 (0.39 to 0.73)	
Role Functioning		
Median, months (95% CI)	9.1 (6.5 to NE)	3.6 (2.2 to 6.0)
Stratified HR (95% CI) †	0.62 (0.46 to 0.84)	
Global Health Status / Quality of Life		
Median, months (95% CI)	11.2 (6.0 to NE)	3.6 (3.0 to 7.0)
Stratified HR (95% CI) †	0.63 (0.46 to 0.85)	
Harms Outcomes, n (%)	**N=329**	**N=156**
AE (any grade)	323 (98.2)	154 (98.7)
Treatment-related AE (any grade)	276 (83.9)	147 (94.2)
Treatment-related Grade 3-4 AE	117 (35.6)	71 (45.5)

	IMbrave150	
Treatment-related Grade 5	[redacted]	[redacted]
Treatment-related SAE	[redacted]	[redacted]
WDAE (any component)	51 (15.5)	16 (10.3)
WDAE (both components)	23 (7.0)	NA

AE = adverse event; CI = confidence interval; EORTC QLQ-C-30 = European Organisation for Research and Treatment of Cancer HCC-Specific Quality of Life Questionnaire; HR = hazard ratio, HRQoL= health-related quality of life; IRF = independent review facility; ITT = intention-to-treat; NE = not evaluable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; SAE = serious adverse event; TTD = time to deterioration; TTP = time to progression; WDAE = withdrawal due to adverse event

* OS results represent data from first interim analysis. Based on 52% information (161 deaths of 312 anticipated), the multiplicity-adjusted two-sided significance level was 0.0033.

† HR < 1 favours atezolizumab plus bevacizumab; stratification factors include geographic region (Asia [excluding Japan] vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP level (< 400 vs. ≥ 400 ng/mL)

Source: Finn et al., 2020[2] and Clinical Study Report[5]

(Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this efficacy and safety information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until April 30, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

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

The following patient groups provided input on atezolizumab (Tecentriq) plus bevacizumab (Avastin) for the first-line treatment of adult patients with unresectable or metastatic HCC who require systemic therapy. Their input is summarized below: Canadian Cancer Survivor Network (CCSN) and Canadian Liver Foundation (CLF).

From the patient perspective, pain and confusion were common symptoms of HCC; additionally, a lump or feeling of heaviness in the upper belly, weakness or deep fatigue, and bloating or swelling of the belly were specified to impact day-to-day life and quality of life (QoL). It was highlighted that patients experience a deep mental and emotional impact in addition to physical symptoms; patients commonly described their disease experience using the words fear, worry, shock, scared, and sad. Both patient groups reported that patients are currently treated with chemotherapy (e.g. anti-metabolite), immunotherapy, targeted therapy (e.g., sorafenib and lenvatinib), combination of immunotherapy and targeted therapy (e.g. atezolizumab plus bevacizumab), surgical removal of part of the liver, tumour ablation, and radiation. Treatment-related side effects from the aforementioned therapies included diarrhea, decreased appetite, numbness, pain, tingling in hands and feet, dry or peeling skin, and headache. Further, sorafenib and lenvatinib were specifically reported to induce significant side effects, which greatly reduces patient QoL. CCSN caregiver respondents most commonly reported fatigue and emotional drain as issues associated with caring for someone with HCC; however, anxiety/worrying, management of medications, hours spent in medical appointments, inability to plan ahead, anger, and feelings of helplessness were also mentioned. Overall, patients and caregivers value having access to new treatments for unresectable HCC that are associated with less side effects, improve QoL, and allow for patients to be active enough to attend social functions and complete daily tasks independently.

Provincial Advisory Group (PAG) Input

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

Clinical factors:

- Place in therapy and sequencing with currently available treatments

Economic factors:

- Clarity on disease progression and treatment duration
- Discontinuation rules

Registered Clinician Input

A total of two registered clinician inputs were provided on behalf of two clinicians from Cancer Care Ontario (CCO) Gastrointestinal Drug Advisory Committee (DAC) and eight clinicians from the Canadian Gastrointestinal Oncology Evidence Network (CGOEN) for the review of atezolizumab (Tecentriq) in combination with bevacizumab (Avastin, biosimilars) for the first-line treatment of adult patients with unresectable or metastatic HCC who require systemic therapy. Sorafenib and lenvatinib, which are oral TKIs, were reported to be currently available drugs for first-line systemic treatment of HCC in Canada. Sorafenib is currently funded and lenvatinib recently received a recommendation for funding. In current clinical practice, lenvatinib may be preferred in patients who are symptomatic or have rapidly progressive disease; however, the different side effect profile of lenvatinib and sorafenib may also inform treatment selection. The clinicians from CCO specified that sorafenib and lenvatinib are approved for patients with an ECOG PS of 0 or 1 and Child-Pugh class A liver function.

Both inputs indicated that there is an unmet need for more effective first-line systemic therapies as sorafenib and lenvatinib provide modest improvements in survival. Both the CCO and CGOEN clinicians indicated that the inclusion and exclusion criteria of the pivotal trial (IMbrave150) can be generally applied in clinical practice. However, the CCO clinicians noted that patients in the pivotal trial were required to undergo assessment of varices by upper endoscopy, which is a common practice but not mandated in clinical practice. The CCO and CGOEN clinicians noted that atezolizumab plus bevacizumab has greater efficacy, and acceptable safety and tolerability compared to currently available treatments as demonstrated by the pivotal trial. Additionally, they noted that patients treated with atezolizumab plus bevacizumab had longer time to deterioration in QoL than those treated with sorafenib. Regarding safety and tolerability, the CCO clinicians highlighted that treatment with atezolizumab plus bevacizumab is associated with increased risk of upper GI bleeding and immune adverse events that are not associated with sorafenib or lenvatinib. The AEs observed in both arms were consistent with the known safety profile for each of the individual treatments. Moreover, it was highlighted that the duration of exposure to sorafenib was considerably shorter, which demonstrates the tolerability of atezolizumab plus bevacizumab.

The CGOEN clinicians stated that majority of patients with advanced HCC, Child-Pugh class A cirrhosis, should receive atezolizumab plus bevacizumab as front-line treatment in the absence of contraindications to bevacizumab or to anti–PD-L1 antibodies such as active autoimmune diseases, recent stroke or myocardial infarction, recent bleeding, and arterial thrombotic events. Both inputs noted that patients unable to undergo endoscopic surveillance for esophageal or gastric varices, patients with untreated or incompletely treated esophageal or gastric varices, or patients that do not meet standard criteria for atezolizumab plus bevacizumab should be treated with sorafenib or lenvatinib. The CGOEN clinicians stated that atezolizumab plus bevacizumab addresses the need for more effective and tolerable first-line therapies for HCC, and both inputs reported that atezolizumab plus bevacizumab would replace existing treatments (sorafenib and lenvatinib) except in patients with contraindications to the treatment combination.

Summary of Supplemental Questions

Summary and critical appraisal of a sponsor-submitted indirect treatment comparison (ITC) / network meta-analysis (NMA)

The available clinical trial did not capture all relevant comparators for the economic model and analysis supporting this submission. Consequently, the sponsor supplied an ITC to relevant comparators based on a systematic review of treatments for locally advanced metastatic hepatocellular cancer.[8] The objective of the ITC was to compare atezolizumab in combination with bevacizumab compared to other interventions used in clinical practice for first-line treatment for locally advanced metastatic HCC.

NMA results were provided for only two outcomes: OS and PFS.[9] [redacted] The level 1 analysis included systemic therapies considered standard of care in HCC (sorafenib, nivolumab, lenvatinib). [redacted]

[redacted][8]

(Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until April 30, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

Three trials were included in the level 1 network including four interventions (atezolizumab plus bevacizumab, lenvatinib, nivolumab, and sorafenib). In the level 3 network, five trials were included examining five interventions (atezolizumab plus bevacizumab, lenvatinib, nivolumab, sorafenib, and selective internal radiotherapy [SIRT]). The OS results from the level 1 analysis found that atezolizumab plus bevacizumab was favoured compared to sorafenib. For the OS level 3 analysis, [redacted]. For both level 1 and level 3 analyses, there was insufficient evidence of difference from lenvatinib and nivolumab.

(Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until April 30, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

The PFS results did not provide evidence that atezolizumab plus bevacizumab differed from other treatments. No results for any other effectiveness outcome were provided. There were no results reported on any of the harms outcomes.

The systematic review methods were moderately conducted with limitations including that the literature search results were focused on studies written in English and the search may not have captured all relevant trials. Although heterogeneity was observed in baseline characteristics across the studies included in the network, the CGP deemed that this was not clinically meaningful. Appropriate random effects models were selected to attempt to account for between-study heterogeneity but due to the sparseness of the network, informative priors were used for between-study heterogeneity, which was not assessed in sensitivity analysis for their influence on the results of the NMA. In addition, a number of other limitations were identified such as the analyses were overly restricted, resulting in few trials being eligible for inclusion in the NMA; the dataset was relatively sparse, leading to broad credible intervals (Crls) and potential failure to detect real differences; inability to analyze all outcome results and no data were reported on harms; and not all sensitivity analyses were possible due to a dearth of data. Thus, these limitations must be considered when drawing conclusions based on the results of the NMA.

Comparison with Other Literature

The CADTH Clinical Guidance Panel and the CADTH 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 6.3.2.1e.

Table 2: Assessment of generalizability of evidence for atezolizumab plus bevacizumab for unresectable hepatocellular carcinoma

Domain	Factor	Evidence (IMbrave150 Trial[2])	Generalizability Question	CGP Assessment of Generalizability
Population	BCLC stage of disease	The approved Health Canada indication is for the first-line treatment of adult patients with unresectable or metastatic HCC who require systemic therapy. In the IMbrave150 trial, patients with locally advanced or metastatic, and/or unresectable disease were included. Most enrolled patients had BCLC Stage C disease. Baseline BCLC stage of disease are as follows: BCLC Stage: A: Atezolizumab plus bevacizumab N=336: 8 (2%); Sorafenib N=165: 6 (4%) B: 52 (15%); 26 (16%) C: 276 (82%); 133 (81%)	Can the results be applied to patients with very early or early stage HCC (BCLC Stage 0 or A) who have unresectable disease?	The CGP agree that patients with very early or early stage HCC (BCLC Stage 0 or A) would not be eligible for atezolizumab plus bevacizumab. Localized treatment would be offered to these patients. Patients who are not eligible for local therapies would be eligible for atezolizumab plus bevacizumab.
	Organ dysfunction	Inclusion criteria of the IMbrave150 trial required patients to have adequate liver and renal function, as well as adequate hematological lab values (i.e., ANC ≥ 1.5 x 10^9/L, PLT ≥ 75 x 10^9/L, Hg ≥ 90g/L, lymphocytes ≥ 0.5 x 10^9/L) within 7 days prior to randomization.	Does the exclusion of patients with organ dysfunction or suboptimal hematological lab values limit the interpretation of the trial results with respect to the target population?	Patients should have adequate liver and renal function and adequate hematological lab values to be eligible for atezolizumab plus bevacizumab.
	Prior solid organ transplant	The IMbrave150 trial excluded patients with prior solid organ transplant.	Does the exclusion of patients with prior (liver) transplant limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice)?	No, the safety of atezolizumab plus bevacizumab in patients with a solid organ transplant is unknown.
	Esophageal or gastric varices	Prior to study enrolment, patients with untreated or incompletely treated esophageal or gastric varices were required to undergo an EGD and treated per local standard of care prior to enrolment. Patients with untreated or incompletely treated	Is this representative of standard Canadian clinical practice and the patient population eligible for systemic treatment? Would this procedure be a requirement before	Undergoing an EGD is a change in practice. This would be required prior to treatment but would represent standard of care if varices are

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence
(IMbrave150 Trial[2])</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td></td><td>esophageal and/or gastric varices with bleeding or high risk for bleeding were excluded from the trial.</td><td>initiating treatment with atezolizumab plus bevacizumab?

If patients do not undergo an EGD (or not treated), would they be eligible for atezolizumab plus bevacizumab?

Would patients with untreated or incompletely treated esophageal and/or gastric varices with bleeding or high risk for bleeding be eligible for atezolizumab plus bevacizumab?</td><td>seen on a CT scan regardless of systemic therapy.

An EGD would be strongly recommended prior to treatment with atezolizumab plus bevacizumab.

Patients with untreated or incompletely treated esophageal and/or gastric varices or those at high risk for bleeding should not be treated with atezolizumab plus bevacizumab.</td></tr>
<tr><td></td><td>Regional and etiological differences</td><td>One of the stratification factors for randomization was geographical region (Asia excluding Japan vs. rest of the world), based on regional differences in etiology of liver disease contributing to HCC. In Western countries and Japan, the main risk factors are HCV infection and alcoholic cirrhosis, whereas in Asian and African countries, the main risk factor is HBV infection. Japan was also not included as part of Asia due to the median OS of advanced HCC patients resembling more closely to Western countries. The IMbrave150 trial included 40% of patients from Asia (excluding Japan) and 60% of patients from the rest of the world. Overall, most patients had HCC etiology attributed to HBV. Baseline regional characteristics and etiology of HCC are as follows:
<table>
<tr><th>Population characteristic</th><th>Atezolizumab plus bevacizumab N=336</th><th>Sorafenib N=165</th></tr>
<tr><td>Region</td><td></td><td></td></tr>
<tr><td>Asia (excluding Japan)</td><td>133 (40%)</td><td>68 (41%)</td></tr>
<tr><td>Rest of world</td><td>203 (60%)</td><td>97 (59%)</td></tr>
</table></td><td>Are the results of the full population generalizable to the Canadian population?

Can atezolizumab plus bevacizumab be reasonably expected to perform similarly across all regions and etiologies of liver disease?</td><td>The results are generalizable to the Canadian population. Atezolizumab plus bevacizumab appeared to benefit patients across etiologies and regions.</td></tr>
</table>

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence
(IMbrave150 Trial[2])</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>Etiology</td><td></td><td></td></tr>
<tr><td>HBV</td><td>164 (49%)</td><td>76 (46%)</td></tr>
<tr><td>HCV</td><td>72 (21%)</td><td>36 (22%)</td></tr>
<tr><td>Alcohol</td><td>35 (10%)</td><td>23 (14%)</td></tr>
<tr><td>Other</td><td>38 (11%)</td><td>16 (10%)</td></tr>
</table>

Results of the subgroup analyses for the co-primary endpoints, specific to the above characteristics are as follows:
<table>
<tr><th colspan="4">Overall Survival</th></tr>
<tr><td>Subgroup</td><td>N</td><td>Events (n)
Atezolizumab plus bevacizumab</td><td>Events (n)
Sorafenib</td></tr>
<tr><td>Region</td><td></td><td></td><td></td></tr>
<tr><td rowspan="2">Asia (excl. Japan)</td><td>201</td><td>34</td><td>27</td></tr>
<tr><td colspan="3">HR 0.53 (95% CI, 0.32 to 0.87)</td></tr>
<tr><td rowspan="2">Rest of world</td><td>300</td><td>62</td><td>38</td></tr>
<tr><td colspan="3">HR 0.65 (95% CI, 0.44 to 0.98)</td></tr>
<tr><td>Etiology</td><td></td><td></td><td></td></tr>
<tr><td rowspan="2">HBV</td><td>240</td><td>44</td><td>31</td></tr>
<tr><td colspan="3">HR 0.51 (95% CI 0.32 to 0.81)</td></tr>
<tr><td rowspan="2">HCV</td><td>108</td><td>18</td><td>15</td></tr>
<tr><td colspan="3">HR 0.43 (95% CI 0.22 to 0.87)</td></tr>
<tr><td rowspan="2">Nonviral</td><td>153</td><td>34</td><td>19</td></tr>
<tr><td colspan="3">HR 0.91 (95% CI 0.52 to 1.60)</td></tr>
<tr><th colspan="4">Progression-Free Survival</th></tr>
<tr><td>Subgroup</td><td>N</td><td>Events (n)
Atezolizumab plus bevacizumab</td><td>Events (n)
Sorafenib</td></tr>
<tr><td>Region</td><td></td><td></td><td></td></tr>
<tr><td rowspan="2">Asia (excl. Japan)</td><td>201</td><td>75</td><td>46</td></tr>
<tr><td colspan="3">HR 0.46 (95%CI 0.31 to 0.67)</td></tr>
<tr><td rowspan="2">Rest of world</td><td>300</td><td>122</td><td>63</td></tr>
<tr><td colspan="3">HR 0.70 (95% CI 0.52 to 0.96)</td></tr>
<tr><td>Etiology</td><td></td><td></td><td></td></tr>
</table>
</td><td></td><td></td></tr>
</table>

Domain	Factor	Evidence (IMbrave150 Trial[2])				Generalizability Question	CGP Assessment of Generalizability
		HBV	240	98	53		
			HR 0.47 (95% CI 0.33 to 0.67)				
		HCV	108	39	19		
			HR 0.69 (95% CI 0.39 to 1.20)				
		Nonviral	153	60	37		
			HR 0.71 (95% CI 0.47 to 1.08)				

ANC = absolute neutrophil count; BCLC = Barcelona Clinic liver cancer; EGD = esophagogastroduodenoscopy; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; Hg = hemoglobin; HR = hazard ratio; OS = overall survival; PLT = platelet

1.2.4 Interpretation

Burden of Illness and Need

In 2020, it is estimated that there will be 3100 new cases of HCC and that 1450 Canadians will die of this disease.[10] Lenvatinib became the standard HCC therapy based on the REFLECT trial, in which lenvatinib was non-inferior to sorafenib for patients with advanced HCC and Child Pugh A liver function (median OS of 13.6 for lenvatinib vs. 12.3 months for sorafenib, HR 0.92, 95% CI 0.79–1.06).[11] Prior to the IMbrave150 trial, no therapy demonstrated improved overall survival compared to sorafenib.

Effectiveness

IMbrave150 was a phase III trial that randomized patients with unresectable HCC and Child Pugh A liver function to atezolizumab plus bevacizumab or sorafenib in a 2:1 ratio. The coprimary end points were overall survival and progression-free survival in the intention-to-treat population, as assessed at an independent review facility according to Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1). In the intent to treat analysis, atezolizumab plus bevacizumab significantly improved overall survival when compared to sorafenib (HR 0.58, 95% CI 0.42-0.79, p < 0.001). For patients treated with atezolizumab plus bevacizumab, median OS was not reached at time of analysis but OS at 12 months was 67.2% (95% CI 61.3 to 73.1%). In the sorafenib arm, median OS was 13.2 months with an OS at 12 months of 54.6% (95% CI 45.2 to 64.0%).[2] Survival data in the IMbrave150 trial is immature (161 deaths, out of a planned 312) and represents the first interim OS analysis which was conducted after the preplanned number of progression or death events were observed.[2] Nevertheless, the data represents a large, clinically relevant improvement in survival which is supported by the secondary outcomes of PFS, response rate, and time to deterioration in QoL. Median PFS was 6.8 months with atezolizumab plus bevacizumab versus 4.3 months with sorafenib (HR 0.59, 95% CI, 0.47 to 0.76; P<0.001). The independently assessed RECIST v1.1 response rate was 27.3% (95% CI, 22.5 to 32.5) with atezolizumab plus bevacizumab versus 11.9% (95% CI, 7.4 to 18.0) with sorafenib (P<0.001). The HCC–specific mRECIST response rate was 33.2% (95% CI, 28.1 to 38.6) with atezolizumab plus bevacizumab versus 13.3% (95% CI, 8.4 to 19.6) with sorafenib, (P<0.001). Complete responses, measured by RECIST v1.1 occurred in eighteen patients (5.5%) in the atezolizumab plus bevacizumab group, compared to no patients in the sorafenib group. Treatment with atezolizumab plus bevacizumab also showed a clinically meaningful delay in deterioration in QoL as assessed by the EORTC QLQ-C30 questionnaire (median time to deterioration, 11.2 months with atezolizumab plus bevacizumab versus 3.6 months with sorafenib; HR, 0.63; 95% CI, 0.46 to 0.85).[2]

Safety

The most commonly reported adverse events related to treatment in the atezolizumab plus bevacizumab group were hypertension (23.7%), proteinuria (18.8%), fatigue (15.2%), elevated AST (14.0%), and pruritis (13.1%). The most commonly reported grade 3 or 4 treatment-related AEs were hypertension (10.3%) and elevated AST (4.3%). For patients who received sorafenib, the most common treatment-related AEs were palmar-plantar erythrodysesthesia syndrome (48.1%), diarrhea (42.9%), hypertension (19.9%), reduced appetite (19.9%), rash (16.7%), and fatigue (15.4%). The most commonly reported grade 3 or 4 treatment-related AE were hypertension (9%) and palmer-plantar erythrodysesthesia syndrome (8.3%). Adverse events leading to death occurred in 15 patients (4.6%) in the atezolizumab plus bevacizumab treated patients compared to 9 patients (5.8%) in the sorafenib group. The percentage of patients who discontinued any treatment component due to adverse events was 15.5% in the atezolizumab plus bevacizumab group compared to 10.3% in the sorafenib group. All patients were evaluated for the presence of varices prior to study treatment due to the possible increased risk of bleeding associated with bevacizumab. Those with untreated or incompletely treated esophageal and/or gastric varices with bleeding or high-risk for bleeding were not eligible for the study. Bleeding of any grade attributed to bevacizumab occurred in 25.2% of the patients, whereas bleeding occurred in 17.3% of sorafenib treated patients. The incidence of upper GI bleeding was 7.0% in the atezolizumab plus bevacizumab arm compared to 4.5% in the sorafenib arm. Grade 3 or 4 hepatitis (laboratory abnormality) occurred in 16.7% of patients on atezolizumab plus bevacizumab compared to 14.1% of patients treated with sorafenib. Grade 3 or 4 potentially immune related toxicities such as colitis and nephritis were both less than 1% in patients treated with atezolizumab plus bevacizumab, no patients experienced grade 3 or 4 pneumonitis or adrenal insufficiency. Grade 3 or 4 infusion reactions occurred in 2.4% of patients on atezolizumab plus bevacizumab.[2] The rate of hospitalizations due to an adverse event occurred in 35.3% of patients treated with atezolizumab plus bevacizumab compared to 28.6% of patients who received sorafenib.[4] The incidence and severity of treatment-related AEs observed in patients treated with atezolizumab plus bevacizumab were consistent with the known side effects of these drugs and the underlying disease.

1.3 Conclusions

The Clinical Guidance Panel (CGP) concluded that there is a net clinical benefit to the combination of atezolizumab plus bevacizumab for unresectable or metastatic HCC patients with Child Pugh A liver function. This conclusion is based on one high-quality RCT that demonstrated a clinically and statistically significant benefit in overall survival for atezolizumab plus bevacizumab compared to sorafenib. In the trial, frontline treatment with the combination of atezolizumab plus bevacizumab reduced the risk of death by 42% compared with sorafenib for patients with HCC. This was supported by the co-primary endpoint of PFS as well as secondary endpoints including tumor response rate for treatment with the combination compared to sorafenib. Importantly, atezolizumab plus bevacizumab showed a clinically meaningful delay in time to deterioration in quality of life with an acceptable side effect profile compared to sorafenib.

In making this conclusion the CGP also considered that:

- Atezolizumab plus bevacizumab is likely to be the standard first line treatment for HCC patients. This is supported by input from registered clinicians.
- The IMbrave150 trial compared atezolizumab plus bevacizumab to sorafenib. Lenvatinib is another treatment option in Canada that is funded in some provinces and currently under consideration in others. In the sponsor submitted ITC, the numerical values for the hazard ratios for OS and PFS favored atezolizumab plus bevacizumab relative to all treatments including lenvatinib.[8,9] However, the credible intervals (CrIs) for the hazards ratios did not provide evidence that atezolizumab plus bevacizumab differed from the other treatments (it was only superior compared to sorafenib for OS). Refer to Section 7 for a summary and critical appraisal of the NMA included in this submission.
- The CGP agree that atezolizumab plus bevacizumab would be the preferred treatment option over lenvatinib for patients at low risk of bleeding and with no contraindications to immunotherapy. Patients who are deemed suitable for treatment with atezolizumab plus bevacizumab should undergo an esophagogastroduodenoscopy (EGD) prior to starting atezolizumab plus bevacizumab as per the IMbrave150 trial protocol.
- PD-L1 testing was not required for trial enrolment. There are currently no biomarkers that identify patients who are most likely to benefit from atezolizumab plus bevacizumab.
- For patients who stop either atezolizumab or bevacizumab due to intolerance, it would be reasonable to continue treatment with the remaining agent in the absence of progression if the clinician determines there would be clinical benefit. This strategy was permitted in the clinical trial.
- There is uncertainty on the optimal sequencing of available agents following first line treatment with atezolizumab plus bevacizumab. The most common second line therapy for patients on the IMbrave150 trial was an antiangiogenic TKI that would normally be used in the first line setting (sorafenib or lenvatinib). Real world data and clinical trials may inform the issue of sequencing in the future. The CGP support the use of lenvatinib after discontinuation of atezolizumab plus bevacizumab for progression or intolerance. Additionally, in the REFLECT trial, lenvatinib was non-inferior to sorafenib for OS and superior for PFS and response rate in the first line setting for HCC. This is similar to the treatment paradigm for metastatic RCC when immunotherapy became the standard first line treatment.

Table 3: CADTH Clinical Guidance Panel Response to Provincial Advisory Group Implementation Questions

PAG Implementation Questions	CGP Response
Currently Funded Treatments	
The first-line standard of care for patients with unresectable HCC is treatment with sorafenib, which is funded in all jurisdictions. Lenvatinib is another option that is under consideration for funding by the provinces. The IMbrave150 trial compared atezolizumab plus bevacizumab to sorafenib. PAG is also seeking comparative information with lenvatinib.	The IMbrave150 trial compared atezolizumab plus bevacizumab to sorafenib. Only indirect comparisons can be made between atezolizumab plus bevacizumab and lenvatinib. The CGP agree that atezolizumab plus bevacizumab would be the preferred treatment option over lenvatinib for patients at low risk of bleeding and with no contraindications to immunotherapy.
Eligible Patient Population	
PAG is seeking clarity on whether the following patients would be eligible for treatment with atezolizumab plus bevacizumab: • Patients with ECOG performance score ≥ 2 • Patients with CNS metastases • Patient with fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC • Patients with Child-Pugh score B liver function • Patients with intermediate stage HCC unable to receive TACE	• The CGP agree that only patients with ECOG 0-1 should be eligible for treatment with atezolizumab plus bevacizumab as there is no clinical trial evidence to support the use of atezolizumab plus bevacizumab in patients with an ECOG ≥2. The CGP note that this is due to concerns around toxicity for treatment. • CNS metastases is uncommon in patients with HCC. However, The CGP agree that patients with treated CNS metastases who are stable and not on steroids would be eligible for treatment with atezolizumab plus bevacizumab. • Patients with fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC would not be eligible for atezolizumab plus bevacizumab. • The CGP agree that patients with Child-Pugh B liver function would not be eligible for atezolizumab plus bevacizumab. • The CGP agree that patients with intermediate stage HCC who are unable to receive TACE would be eligible for atezolizumab plus bevacizumab, as long as other eligibility criteria are met for the combination treatment (e.g., Child-Pugh class A, no risk of bleeding).
PAG noted that the trial excluded patients who had local therapy in the 28 days prior to initiation and seeks confirmation these patients (including those who had TACE) would not be candidates for atezolizumab plus bevacizumab.	The CGP confirm that patients who had local therapy in the 28 days prior to initiation (including those who had TACE) would not be candidates for atezolizumab plus bevacizumab.

PAG Implementation Questions	CGP Response
Implementation Factors	
PAG is seeking clarity on treatment duration and treatment until "loss of clinical benefit" with a definition of disease progression and treatment duration to assist in the development of stopping rules for atezolizumab plus bevacizumab.	Patients should continue treatment with atezolizumab plus bevacizumab according to the IMbrave150 study protocol. Treatment should be continued until unacceptable toxicity or loss of clinical benefit. In the trial, loss of clinical benefit was determined by the investigator after an assessment of biochemical and radiographic data, as well as clinical status (e.g., symptomatic deterioration such as pain due to disease). Patients who met the criteria for radiographic disease progression per RECIST v1.1 were permitted to continue the assigned study treatment if the following requirements were met: a) investigator determines that available data indicates there is evidence of clinical benefit; b) no signs or symptoms indicating unequivocal disease progression; c) no decline in ECOG PS attributed to disease progression; d) no tumour progression at critical sites that cannot be managed by medical interventions allowed in the protocol (e.g., leptomeningeal disease).
PAG seeks guidance on the management of instances wherein one of the biologic drugs need to be discontinued (e.g., if atezolizumab has to be stopped, should bevacizumab be discontinued and vice versa).	For patients who stop either atezolizumab or bevacizumab due to intolerance, it would be reasonable to continue treatment with the remaining agent in the absence of progression if the clinician determines there would be clinical benefit. Monotherapy with the remaining agent should stop if the patient develops intolerance or has progression. This strategy was permitted in the IMbrave150 trial.
Sequencing and Priority of Treatment	
PAG is seeking guidance on the appropriate place in therapy and sequencing with other drug regimens for HCC. In particular: circumstances justifying the preferential use of atezolizumab plus bevacizumab, sorafenib or lenvatinib. • Switching from atezolizumab plus bevacizumab to other first line drugs due to intolerance • PAG seeks clarity on the place in therapy of current first line kinase inhibitors (sorafenib and lenvatinib) relative to atezolizumab plus bevacizumab, including evidence on their use after failure of atezolizumab plus bevacizumab. • Appropriateness of retreatment with atezolizumab plus bevacizumab if the disease progresses after the regimen is discontinued. • Given the distinct toxicity profiles for atezolizumab and bevacizumab, appropriateness of discontinuing one of the two drugs in cases of intolerance, while maintaining the other until loss of response. If this situation, PAG seeks confirmation that progression on one of the agents entails the termination of the entire regimen.	There is limited evidence and uncertainty on the optimal sequencing of available agents following first line treatment with atezolizumab plus bevacizumab. The most common second line therapy for patients on the IMbrave150 trial was an antiangiogenic TKI that would normally be used in the first line setting. The most common second-line treatments received by patients in the IMbrave150 trial include[4]: • After atezolizumab plus bevacizumab: sorafenib (n=31), lenvatinib (n=22), regorafenib (n=3), cabozantinib (n=2), ramucirumab (n=2) • After sorafenib: lenvatinib (n=15), regorafenib (n=15), nivolumab (n=12), cabozantinib (n=5), pembrolizumab (n=5) The CGP support the following treatment sequence for HCC patients who maintain ECOG status of 0-1 and Child-Pugh A liver function: • First line: atezolizumab plus bevacizumab • Second line: lenvatinib (or sorafenib if intolerant to lenvatinib) • Third line: regorafenib or cabozantinib

PAG Implementation Questions	CGP Response
	This proposal aligns with the input from registered clinician regarding sequencing. It also follows the paradigm established in other disease sites such as metastatic renal cell carcinoma with the introduction of first line nivolumab plus ipilimumab for intermediate/poor risk disease and metastatic HER 2 positive breast cancer with the advent of pertuzumab, trastuzumab, and taxane based therapy. If patients had intolerance to, but did not progress on first-line treatment with atezolizumab plus bevacizumab, it would be reasonable to switch to lenvatinib. The IMbrave150 trial did not have specific guidelines regarding re-treatment with atezolizumab plus bevacizumab upon disease progression. The CGP agree that re-treatment would be reasonable if the treatment was discontinued for reasons other than progression (ex. treatment break, intolerance). Re-treatment would be reasonable if progression occurs more than 6 months after stopping treatment with atezolizumab plus bevacizumab.
Companion Diagnostic Testing	
PAG would like confirmation that PD-L1 testing is not required.	PD-L1 testing was not required for trial enrolment. There are currently no biomarkers that identify patients who are most likely to benefit from atezolizumab plus bevacizumab.

CGP = Clinical Guidance Panel; CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HCC = hepatocellular carcinoma; PAG = Provincial Advisory Group; TACE = transarterial chemoembolization

2 Background Clinical Information

This section was prepared by the pCODR gastrointestinal CGP. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

In 2020, it is estimated that 3,100 new cases of HCC will be diagnosed in Canada. In addition, 1,450 Canadians are predicted to die from this disease, which has a five-year OS of 19%.[10] From 1984 to 2015, the annual percent change in Canadian age-standardized incidence rates of HCC increased by 2.7% in women. In men, the annual percentage change from 1984 to 2011 was 3.8% per year, and thereafter stabilized from 2011 to 2015 at 0.2%.[12] HCC is a challenging disease to treat as it commonly occurs in the setting of underlying hepatic cirrhosis, which can lead to underlying hepatic impairment. Systemic therapy is often not well tolerated in patients with underlying hepatic dysfunction. Thus, the treatment approach and consequent prognosis of patients with HCC depends upon the extent of disease, hepatic functional reserve, and performance status. Child-Pugh class is the most commonly employed metric to assess hepatic reserve, which includes parameters of serum levels of International Normalized Ratio (INR), albumin, and bilirubin as well as clinical evidence of ascites and encephalopathy (Table 4).

Important risk factors for the development of HCC vary geographically and includes HBV infection, chronic HCV infection, hereditary hemochromatosis, non-alcoholic fatty liver disease, and cirrhosis of almost any cause. Chronic medical conditions such as obesity, alcoholism, and diabetes mellitus are predisposing factors for HCC.

Table 4: Child-Pugh Classification

Criteria	Score 1 Point	Score 2 Points	Score 3 Points
Encephalopathy	Grade 0	Grade 1 or 2 (or suppressed with medications)	Grade 3 or 4 (or refractory)
Ascites	None	Suppressed with medications	Refractory
Bilirubin	Under 34 µM	Between 34 at 50 µM	Over 50 µM
Albumin	Over 35 g/L	Between 28 and 35 g/L	Under 28 g/L
PT-INR	Under 1.7	Between 1.7 and 2.2	Over 2.2
Encephalopathy: Grade 0: Normal cognition Grade 1: Euphoria, fluctuation in level of consciousness, and slurred or disoriented speech Grade 2: Drowsiness, inappropriate behavior, and loss of sphincteric control Grade 3: Marked confusion, stupor, and incoherent speech Grade 4: Coma			
Grade A	Total score of 5 to 6	Considered “well-compensated liver function”	
Grade B	Total score of 7 to 9	Considered “significant functional impairment”	
Grade C	Total score of 10 to 15	Considered “decompensated liver function”	

Source: Hepatocellular carcinoma. Clinical practice guideline GI-007 – Version 8. Copyright © 2020 Alberta Health Services. Reprinted in accordance with Creative Commons license CC BY-NC 4.0.[13]

2.2 Accepted Clinical Practice

Although there are many staging systems used for HCC, the BCLC staging system is the most widely used prognostic and treatment algorithm for HCC by Canadian clinicians (Figure 1). The staging system includes prognostic factors related to tumour status, liver function, and patient performance status. Per the BCLC algorithm, the prognosis for patients with advanced, unresectable HCC with preserved hepatic reserve is poor with a median OS of less than one year.[14] HCC is considered to be a chemotherapy-refractory tumour.

Sorafenib is an oral multi-TKI that inhibits the rapidly accelerated fibrosarcoma (RAF) intracellular kinase and vascular endothelial growth factor receptor (VEGFR) cell surface kinase pathways. The SHARP trial was a European, multi-centre, double-blinded placebo RCT that compared sorafenib therapy to placebo in patients with advanced, inoperable HCC; Child-Pugh Class A hepatic reserve; and ECOG PS of 0-2.[15] The median OS in the sorafenib arm was 10.7 months versus 7.9 months in the placebo arm (HR=0.69; 95% CI, 0.55 to 0.87; p<0.001).[15] The magnitude of survival benefit with sorafenib in the SHARP trial 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.[16] In this subsequent trial, the median OS was 6.5 months in the sorafenib arm versus 4.2 months in the placebo (HR=0.68; 95% CI, 0.50 to 0.93; p=0.014).[16] The inferior survival outcome observed in both arms of the study conducted in the Asian-Pacific population, compared with the SHARP trial, is believed to be due to the higher proportion of hepatitis B and advanced disease (ECOG PS of 1–2 or metastatic disease). Based on these data, sorafenib is currently approved and funded across Canada for the first-line systemic treatment of Child-Pugh A Class patients with advanced HCC.

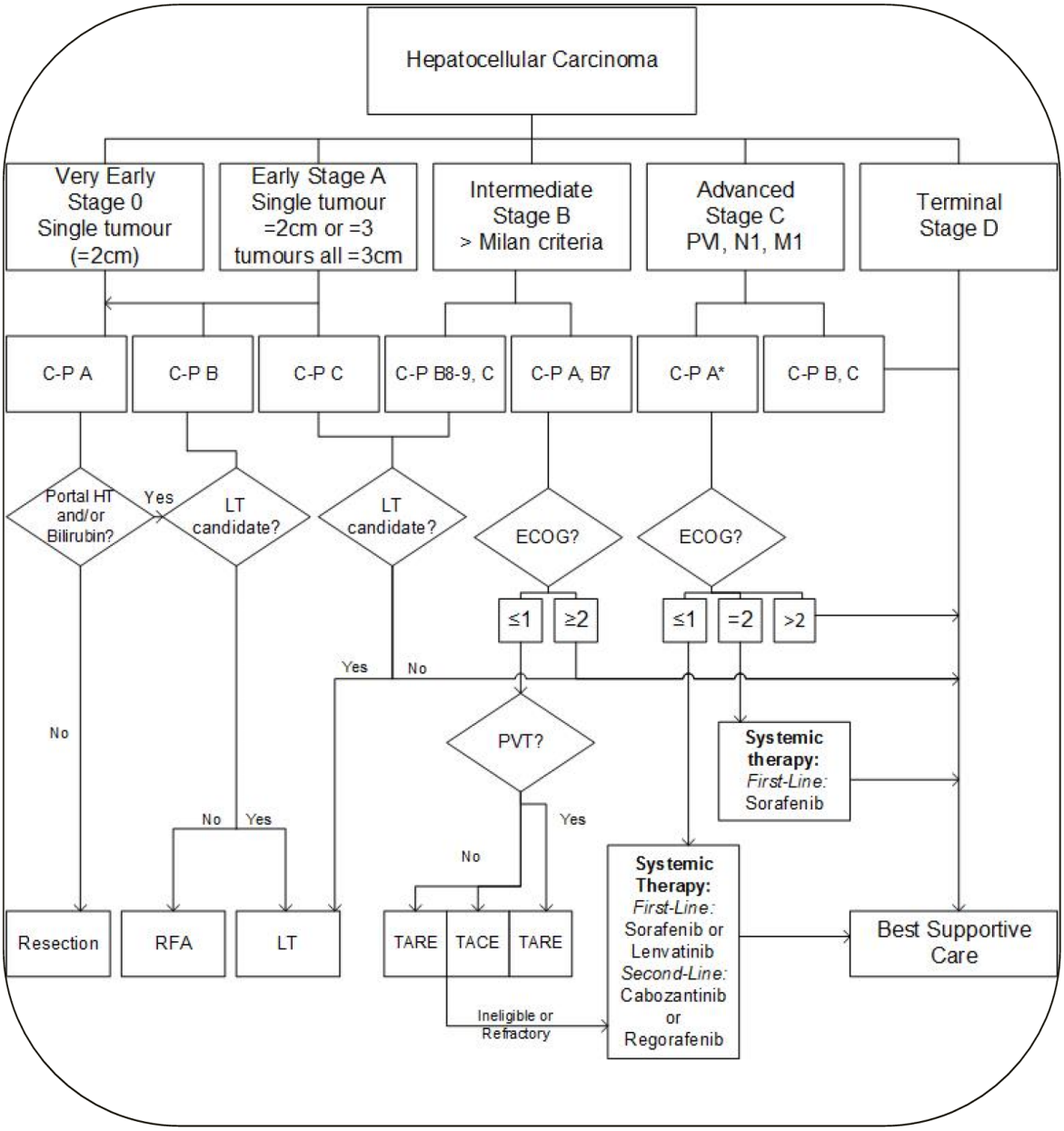
Over the past 15 years, numerous phase III trials have been conducted in the first line setting in HCC that did not demonstrate superiority to sorafenib. For instance, sunitinib (NCT00699374)[17]; nivolumab (CheckMate 459 trial/ NCT02576509)[18]; brivanib (BRISK FL trial/ NCT00858871)[19]; linifanib (NCT01009593)[20]; and erlotinib (SEARCH trial/ NCT00901901)[21].

Lenvatinib is an oral inhibitor of VEGFR-1, VEGFR-2, and VEGFR-3, as well as fibroblast growth factor receptors (FGFR) 1 to 4, platelet-derived growth factor receptor (PDGFR)-alpha, rearranged during transfection (RET), and KIT. The REFLECT trial demonstrated the non-inferiority of lenvatinib to sorafenib for OS as first-line therapy for unresectable HCC, ECOG PS 0-1, and Child-Pugh Class A liver function (median OS: 13.6 vs. 12.3 months for lenvatinib vs. sorafenib, HR=0.92; 95% CI, 0.79 to 1.06).[11] Lenvatinib has become a first-line treatment option for patients with advanced HCC based on data from the REFLECT trial. In August of 2019, lenvatinib was recommended for reimbursement by pERC and is available for reimbursement in some provinces.

More recently, the phase III IMbrave150 trial randomly assigned advanced HCC patients in a 2:1 ratio to the atezolizumab plus bevacizumab combination arm or sorafenib arm (total N = 501).[2] Eligible patients had an ECOG PS of 0-1 and Child-Pugh Class A liver function. There was significant improvement in the co-primary endpoints of OS (OS at 12 months: 67.2% for atezolizumab plus bevacizumab vs. 54.6% for sorafenib; HR=0.58; 95% CI, 0.42 to 0.79; p<0.001), as well as PFS (HR=0.59; 95% CI, 0.47 to 0.76; p<0.0001). The combination of atezolizumab plus bevacizumab also delayed the time to QoL deterioration compared to sorafenib (EORTC QLC-C30; 11.2 months vs. 3.6 months, HR=0.63; 95% CI, 0.46 to 0.85). The IMbrave150 trial is the only study in the first line setting that demonstrated superiority over sorafenib.[2]

There are currently no standard treatment options for patients beyond sorafenib or lenvatinib therapy. Regorafenib is also an oral multi-kinase inhibitor, structurally similar to sorafenib, and targets a number of angiogenic kinases (including VEGFR), stromal and oncogenic receptor TKIs. In the phase III RESORCE trial, a survival benefit for regorafenib (160mg orally administered daily for three weeks on and one week off) was demonstrated in patients progressing after first-line treatment with sorafenib who maintained an ECOG PS of 0-1 and Child-Pugh A liver function.[22] When compared to placebo, regorafenib was associated with a statistically significant improvement in OS (10.6 months vs. 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%). Despite these AEs, quality of life, as assessed by EuroQol 5-Dimensions (EQ-5D) and Functional Assessment of Cancer Therapy – Hepatobiliary (FACT-Hep), was not significantly worse with regorafenib compared to placebo.[22] In April of 2018, pERC conditionally recommended the funding of regorafenib for patients with unresectable HCC who have been previously treated with sorafenib—dependent on the condition of cost-effectiveness being improved to an acceptable level. Moreover, cabozantinib is a potent inhibitor of hepatocyte growth factor receptor/c-MET, VEGFR-1, VEGFR-2, and VEGFR-3.[23] High levels of MET expression are associated with resistance to sorafenib in pre-clinical models.[24,25] In the phase III CELESTIAL trial, 707 patients previously treated with sorafenib were randomized to cabozantinib or placebo.[26] Median OS was significantly longer with cabozantinib compared to placebo (10.2 months vs. 8.0 months, HR=0.76; 95% CI, 0.63 to 0.92; P=0.005).[26] In April of 2020, pERC conditionally recommended the funding of cabozantinib in adult patients with unresectable HCC in the second-line setting following progression on sorafenib or lenvatinib—dependent on the condition of cost-effectiveness being improved to an acceptable level.

Figure 1: Algorithm for the Management of HCC According to the Updated Alberta Health Services Clinical Practice Guidelines



Milan criteria = single HCC ≤5 cm or 3 HCC largest ≤3 cm, PVI = portal vein invasion; N1 = lymph node metastasis; M1 = metastasis; portal HT = portal hypertension (splenomegaly, esophageal varices, ascites, platelets <100 or hepatic venous pressure gradient >10 mmHg); LT candidate = liver transplant candidate = total tumour volume <115 mm3 and alphafetoprotein <400 ng/mL, age <70 (if age 65-69, no major comorbidities), good social support and appropriate abstinence and rehabilitation if addiction issues; ECOG PS = Eastern Cooperative Oncology Group performance status; PVT = portal vein thrombosis (bland); RFA = radiofrequency ablation; TACE = transarterial chemoembolization; TARE = transarterial radioembolization with yttrium90 microspheres; SBRT = stereotactic body radiotherapy.
Source: Hepatocellular carcinoma. Clinical practice guideline GI-007 – Version 8. Copyright © 2020 Alberta Health Services. Reprinted in accordance with Creative Commons license CC BY-NC 4.0.[13]

3 Summary of Patient Advocacy Group Input

The following patient groups provided input on atezolizumab (Tecentriq)-bevacizumab (Avastin) for the first-line treatment of adult patients with unresectable or metastatic HCC who require systemic therapy and their input is summarized below: Canadian Cancer Survivor Network (CCSN) and Canadian Liver Foundation (CLF). The CCSN utilized SurveyMonkey to collect most of the data provided in the input. In total, there were 15 respondents; the majority of respondents were from the US (13 of 15), one respondent was from Canada, five identified as male, and 10 identified as female. The CLF provided input from a survey created in 2020 (referred to as the "CLF Online Survey-2020" henceforth), a global survey created in 2016 (referred to as the "Global Survey-2016" henceforth), and the CLF communication channels (respondents referred to as CLF patient/caregiver contacts). The CLF Online Survey-2020 was available online from May 20 to June 1, 2020 (in English and French) and was promoted on the CLF website and social media to patients, caregivers, and health care professionals across Canada. The survey received a total of three responses from one patient, one caregiver, and one liver specialist; however, only the patient and caregiver responses are included in this patient input summary. The CLF's input also refers to a global survey that was conducted in 2016 to gather information from people living with HCC. The CLF was one of the participating international health charities; namely, Canada represented one of 13 countries and eight out of the 256 respondents were from Canada. Results of the global survey were presented at the World Congress of GI Cancer 2017. Additionally, the CLF included non-nominal input collected from approximately 45 liver cancer patients across Canada who have contacted the CLF through the following communication channels (intent to provide information and support): national toll-free help line (telephone), email, other online mediums, and in-person communication. Of note, these additional comments from CLF patient contacts are not in direct response to this review but may still provide valuable patient insight to be considered during the review process. Refer to Table 5 for a summary of the information gathering used by patient groups.

Table 5: Summary of the Information Gathering Used by the Patient Groups

Patient Group	Information Gathering Method and Number of Respondents
CCSN	1. Survey (5 patients, 8 caregivers, total: 15 respondents)* • One of the five patient respondents had treatment experience with atezolizumab plus bevacizumab¥
CLF	1. CLF Online Survey-2020 (1 patient , 1 caregiver, 1 health care professional) • One patient respondent who had no experience with any HCC treatments (including atezolizumab plus bevacizumab) ○ Female, age: 65 and over • One caregiver respondent who had experience caring for a patient with treatment experience with atezolizumab plus bevacizumab± ○ Female, age: 45-54 2. Global Survey-2016 (8 patient respondents from Canada, total: 256 respondents) 3. CLF Communication Channels (approximately 45 patient contacts across Canada)

*There was a total of 15 survey respondents; however, 5 reported being patient respondents and 8 reported being caregiver respondents—not all respondents answered this question. Thus, it is unknown whether 2 respondents were patients or caregivers.

¥Patient received other therapies, including chemotherapy and radiotherapy, before receiving atezolizumab plus bevacizumab.

±Patient received anti-metabolite chemotherapy and underwent tumour ablation and surgery to treat their HCC.

From the patient perspective, pain and confusion were common symptoms of HCC; additionally, a lump or feeling of heaviness in the upper belly, weakness or deep fatigue, and bloating or swelling of the belly were specified to impact day-to-day life and QoL. It was highlighted that patients experience a deep mental and emotional impact in addition to physical symptoms; patients commonly described their disease experience using the words fear, worry, shock, scared, and sad. Further, approximately 80% of the Global Survey-2016 respondents reported their current QoL as poor. Both patient groups reported that patients are currently treated with chemotherapy (e.g. anti-metabolite), immunotherapy, targeted therapy (e.g., sorafenib and lenvatinib), combination of immunotherapy and targeted therapy (e.g. atezolizumab plus bevacizumab), surgical removal of part of the liver, tumour ablation, and radiation. Namely, chemotherapy was the most commonly reported treatment. Treatment-related side effects from the aforementioned therapies included diarrhea, decreased appetite, numbness, pain, tingling in hands and feet, dry or peeling skin, and headache. Further, sorafenib and lenvatinib were reported to induce significant side effects, which greatly reduces patient QoL.

According to the Global Survey-2016, patients whose most recent treatment was sorafenib were more likely to rate their current QoL as poor. CCSN caregiver respondents most commonly reported fatigue and emotional drain as issues associated with caring for someone with HCC; however, anxiety/worrying, management of medications, hours spent in medical appointments, inability to plan ahead, anger, and feelings of helplessness were also mentioned. Namely, balancing life responsibilities was the most challenging adverse effect related to the caregiver role. Overall, patients and caregivers value having access to new treatments for unresectable HCC that are associated with less side effects, improve QoL, and allow for patients to be active enough to attend social functions and complete daily tasks independently.

Two patients had experience with atezolizumab plus bevacizumab. One patient stated that compared to chemotherapy and radiotherapy, atezolizumab plus bevacizumab was better at controlling symptoms and disease progression, associated with less side effects, and easier to use, and would recommend atezolizumab plus bevacizumab be made available to all patients who qualify. The other patient indicated that atezolizumab plus bevacizumab was "*extremely effective*" and their QoL was "*more so improved*;" specifically, it was highlighted that atezolizumab plus bevacizumab is the first treatment to improve their mental and physical health as they continued to work as a specialist physician and started mountain biking. Both patients experienced side effects related to atezolizumab plus bevacizumab, including diarrhea. Overall, the patients noted that side effects were tolerable. Overall, the patient groups highlighted the rarity of HCC and the poor survival prognosis of the disease particularly in the advanced stages. Thus, emphasizing that the possibility of a new first-line treatment option offers hope to patients and their families who would otherwise have very limited options. The CLF believes that 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.

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

3.1 Condition and Current Therapy Information

3.1.1 Patients' Experiences

The CCSN reported on how patients were diagnosed with HCC; the following were specified in decreasing order: biopsy (8 responses), contrast-enhanced CT (7 responses), MRI (4 responses), blood tests (4 responses), and ultrasound (2 responses). Further, the responses included in the CCSN's input are reflective of two patients who were "just treated or in treatment", one patient in the "middle stage (2 or 3)" of the disease, and one patient in the "late stage (4) of the disease." Namely, a lump or feeling of heaviness in the upper belly, weakness or deep fatigue, and bloating or swelling of the belly were reported to impact day-to-day life and QoL.

The CLF highlighted that HCC is the most common type of liver cancer and accounts for 71.9% of liver cancers in males and females in Canada. They noted that the increasing prevalence of HCC in Canada is an indicator of the increasing prevalence of late-stage and end-stage liver disease, driven primarily by the aging population of patients with chronic hepatitis B and hepatitis C; in addition to, the increasing prevalence of non-alcoholic fatty liver disease, currently estimated at 20% of eight million Canadians. Non-alcoholic fatty liver disease may lead to HCC if left undiagnosed and unmanaged. Surgery is typically not a treatment option for patients who are diagnosed with HCC in the later stages. In addition to the physical symptoms of HCC, patients experience a deep mental and emotional impact; all Canadian patients (n=8) from the Global Survey-2016 described their experience using the words fear, worry, shock, scared, and sad. According to the Global Survey-2016, approximately 80% of respondents reported their current QoL as poor. Notably, the symptoms of ascites were highlighted to be particularly debilitating by the caregiver respondent of the CLF Online Survey-2020 who stated that they would like to see a new treatment that reduces the symptom of ascites as this would improve a patient's range of movement and associated complications. Moreover, pain and confusion were commonly reported among patient accounts of their experience with HCC:

- "*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*." – CLF patient contact

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

3.1.2 Patients' Experiences with Current Therapy

The CCSN reported that patients were currently treated with chemotherapy (2 responses), immunotherapy (2 responses), surgical removal of part of the liver (2 responses), and radiation (1 response). Namely, diarrhea and decreased appetite were specified as treatment-related adverse effects.

The CLF highlighted that HCC is often difficult to treat as it is usually a result of a pre-existing and progressive underlying liver disease, which means the patient may already be experiencing cirrhosis, hepatic encephalopathy, and abdominal pain and swelling (ascites). Accordingly, treatment of HCC depends on the stage and the speed of tumour growth and the health of the liver; cure rates generally decrease as the tumour size increases. The current standard for first-line treatment for HCC patients with well-preserved liver function (Child-Pugh A) is systemic treatment with sorafenib. Lenvatinib is a newer systemic treatment that has been recently approved in Canada but it is not yet available for reimbursement in all provincial formularies; thus, most patients are unable to access this drug if they are unable to pay out-of-pocket. Moreover, the only publicly-funded option in Canada for second-line therapy is regorafenib; however, it is not yet available for reimbursement in all provinces across Canada. Namely, regorafenib is indicated as a second-line treatment for liver cancer for patients who have unresectable HCC and who have been previously treated with sorafenib. For HCC that has progressed to the palliative treatment phase, there are currently no other treatment options for patients who have been treated with sorafenib or lenvatinib, with patients progressing to the final disease stages before passing away. Notably, sorafenib and lenvatinib result in significant side effects, which greatly reduce patient QoL. According to the Global Survey-2016, patients whose most recent treatment was sorafenib were more likely to rate their current QoL as poor.

The one patient respondent to the CLF Online Survey-2020 stated they had not received any treatment for their HCC. However, the one caregiver reported that the HCC patient they were caring for had received the following treatments for HCC: anti-metabolite chemotherapy, tumour ablation, surgery, and atezolizumab plus bevacizumab for one to six months, and during which, the patient experienced numbness, pain, tingling in hands or feet, dry or peeling skin, and headache that were described to be "*somewhat intolerable*" treatment-related side effects. One patient reported that treatment increased their energy level and improved itching (pruritus); however, another patient reported that despite receiving treatment their pain persisted (treatments not specified)—accounted in the following statements:

- *"I feel better after treatment, and was hopeful for a while that it will work out. My energy level has increased, even the itching (pruritus) got better. But then my doctor told me that the treatment has stopped working and I just wanted to die right there."* – CLF patient contact
- *"I am currently being treated for my HCC and the pain is the worst. I am in pain all the time."* – CLF patient contact

3.1.3 Impact on Caregivers

The CCSN survey received a total of eight caregiver responses but only three caregivers responded to the questions included in the input summarized below. When asked to identify issues that a caregiver for someone with HCC experiences, the only issues that were mentioned by more than one caregiver was fatigue and emotional drain (2 responses each). The other issues specified included anxiety/worrying, management of medications, hours spent in medical appointments, inability to plan ahead, anger, and feelings of helplessness (1 response each). One caregiver stated that balancing life responsibilities was the most challenging adverse effect related to their caregiver role. Similarly, the following response from one caregiver reflects how caring for someone with HCC affects a caregiver's daily routine or lifestyle by being time consuming; "*it does require some of my time, but we do it for the love of our family members. Hospital staff and government help was exceptional throughout the entire process*." The CLF Online Survey-2020 reported that the caregiver role for a patient with HCC impacts or seriously impacts the caregiver's ability to work, travel, exercise, conduct household chores, spend time with family and friends, and fulfil family obligations.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for New Therapies

CCSN summarized that patients seek treatments that are associated with less treatment-related side effects and improve QoL. Further, the caregiver and patient respondent to the CLF Online Survey-2020 indicated that it was "*very important*" that patients and physicians have access to new treatments for unresectable HCC. One patient highlighted that they want a treatment that would allow for them to be active enough to attend social functions and complete daily tasks independently. In their own words, "*I want a treatment which will allow me to spend time with my family and friends. I want to be able to function during the day, care for myself such as take a shower on my own, dress myself, and cook for myself*." – CLF patient contact. Furthermore, as mentioned above, the caregiver respondent of the CLF Online Survey-2020 noted that they would like to see a new treatment that reduces the symptom of ascites—in their own words—"*I would like to see a new treatment that decreases the symptom of ascites, which would improve the range of movement and other complications that follow*." –CLF caregiver contact.

3.2.2 Patient Experiences to Date

The CCSN reported on the treatment experience with atezolizumab plus bevacizumab of a female patient living in Quebec who accessed the treatment through a clinical trial. This patient received other therapies, including chemotherapy and radiotherapy, before receiving atezolizumab plus bevacizumab. Compared to chemotherapy and radiotherapy, she reported that atezolizumab plus bevacizumab was better at controlling symptoms and disease progression, associated with less side effects, and easier to use. She noted that she experienced adverse effects from atezolizumab plus bevacizumab, which included diarrhea and loose stools, decreased appetite, and asthenia (physical weakness) but noted that they were well tolerated overall. Notably, she recommended that atezolizumab plus bevacizumab be made available to all patients who qualify for it.

The CLF provided input from the caregiver respondent of the CLF Online Survey-2020 who provided input on behalf of a patient with unresectable HCC who had experience with atezolizumab plus bevacizumab for one to six months. The patient accessed atezolizumab plus bevacizumab through the patient access program provided by Hoffman-La Roche Ltd. The patient's experience with the treatment combination was described to be "*extremely effective*," and their QoL was reported to be "*more so improved*." The patient experienced side effects including diarrhea, high blood pressure, joint and muscle aches, nausea, and headaches that were reported to be "*somewhat or very well tolerated*." The caregiver highlighted the improvement of the patient's mental and physical health with atezolizumab plus bevacizumab. In her words, "*this is the first treatment my husband has had that has shown clear benefit. As a result, his mental health has improved and all along he has continued to work (he is a specialist physician) and has even started mountain biking."*

3.3 Companion Diagnostic Testing

None to report.

3.4 Additional Information

The CCSN wanted to highlight to the CADTH review team and pERC that they regret not being able to reach more HCC patients on clinical trials despite HCC being a rare cancer. Given the small number of respondents included in the submitted input who were mostly from the US, the CCSN is aware of the limitations of the input; nevertheless, they appreciate the additional time to provide input. The CLF wanted to highlight to the CADTH review team and pERC that HCC survival prognosis is poor, especially if diagnosed at or progressed to an advanced stage of the disease; thus, the possibility of adding a new first-line treatment option for HCC offers hope to patients and their families who would otherwise have very limited options. In summary, the CLF believes that 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.

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 CADTH 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) participating in pCODR. PAG identified the following as factors that could impact the implementation of atezolizumab plus bevacizumab:

Clinical factors:
- Place in therapy and sequencing with currently available treatments

Economic factors:
- Clarity on disease progression and treatment duration
- Discontinuation rules

Please see below for more details.

4.1 Currently Funded Treatments

The first-line standard of care for patients with unresectable HCC is treatment with sorafenib, which is funded in all jurisdictions. Lenvatinib is another option that is under consideration for funding by the provinces. The IMbrave150 trial compared atezolizumab plus bevacizumab to sorafenib. PAG is also seeking comparative information with lenvatinib.

4.2 Eligible Patient Population

The reimbursement request of atezolizumab plus bevacizumab is for the treatment of patients with unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy. Maintenance atezolizumab plus bevacizumab should be continued until loss of clinical benefit or unacceptable toxicity. In view of the characteristics of the patient population in the IMbrave150 trial, PAG is seeking clarity on whether the following patients would be eligible for treatment with atezolizumab plus bevacizumab:

- Patients with ECOG performance score ≥ 2
- Patients with central nervous system (CNS) metastases
- Patient with fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC
- Patients with Child-Pugh score B liver function
- Patients with intermediate stage HCC unable to receive transarterial chemoembolization (TACE)

PAG identified a potential time-limited need to switch patients who initiated first-line sorafenib or lenvatinib, and have not progressed, to atezolizumab plus bevacizumab. PAG also noted potential indication creep to patients who failed sorafenib, lenvatinib and/or any other prior systemic therapy. PAG noted that the trial excluded patients who had local therapy in the 28 days prior to initiation and seeks confirmation these patients (including those who had TACE) would not be candidates for atezolizumab plus bevacizumab.

4.3 Implementation Factors

The recommended dose of atezolizumab is 1200 mg administered by intravenous infusion over 60 minutes, followed by 15 mg/kg bevacizumab administered by intravenous infusion over 90 minutes, with a minimum of 5 minutes between dosing. Atezolizumab and bevacizumab are administered on day 1 of each 21-day cycle, until loss of clinical benefit or unacceptable toxicity. PAG commented that bevacizumab 15 mg/kg may be given over 30 minutes in some centres.

PAG noted that there would be no drug wastage as atezolizumab is supplied as 1200mg vials and the flat dosing is an enabler to implementation. There is some concern with drug wastage for bevacizumab, although PAG noted that bevacizumab is already

funded for many tumour sites and vial sharing with this larger patient population can minimize drug wastage in larger cancer centres. Vial sharing is not always possible in smaller outreach centres.

PAG is seeking clarity on treatment duration and treatment until “loss of clinical benefit” with a definition of disease progression and treatment duration to assist in the development of stopping rules for atezolizumab plus bevacizumab. PAG seeks guidance on the management of instances wherein one of the biologic drugs need to be discontinued (e.g., if atezolizumab has to be stopped, should bevacizumab be discontinued and vice versa).

PAG noted that the high prevalence of HCC combined with the high cost drug combination may have a substantial impact on drug program budgets. PAG noted the use of a bevacizumab biosimilar may be considered by jurisdictions.

Atezolizumab plus bevacizumab is aiming to replace oral drugs in the same setting; it would therefore require additional healthcare resources (particularly for maintenance treatment) such as: nursing, pharmacy, clinic visits given treatment is every three weeks, chair time, and supportive care. Additional resources would be required for pre-medication, drug preparation, drug administration, and monitoring and management of adverse effects (infusion related reactions, immune related adverse events, and bevacizumab-related). PAG also noted that both drugs are known to clinicians and are used together for other indications, but since the drugs are new to the HCC space, treating liver clinicians may not be familiar with the adverse effects. Greater monitoring would also be required as both atezolizumab and bevacizumab have unique toxicities specific to each agent, significant toxicities are likely when these drugs are used in combination.

Atezolizumab and bevacizumab, being intravenous drugs, would be administered in an outpatient chemotherapy center for appropriate administration and monitoring of toxicities. Intravenous oncology drugs would be fully funded in all jurisdictions for eligible patients, which is an enabler for patients. However, in some areas, patients would need to travel far to an outpatient chemotherapy center, which would be a barrier to for these patients.

4.4 Sequencing and Priority of Treatments

PAG is seeking guidance on the appropriate place in therapy and sequencing with other drug regimens for HCC. In particular:

- Circumstances justifying the preferential use of atezolizumab plus bevacizumab, sorafenib or lenvatinib.
- Switching from atezolizumab plus bevacizumab to other first line drugs due to intolerance
- PAG seeks clarity on the place in therapy of current first line kinase inhibitors (sorafenib and lenvatinib) relative to atezolizumab plus bevacizumab, including evidence on their use after failure of atezolizumab plus bevacizumab.
- Appropriateness of retreatment with atezolizumab plus bevacizumab if the disease progresses after the regimen is discontinued.
- Given the distinct toxicity profiles for atezolizumab and bevacizumab, appropriateness of discontinuing one of the two drugs in cases of intolerance, while maintaining the other until loss of response. If this situation, PAG seeks confirmation that progression on one of the agents entails the termination of the entire regimen.

4.5 Companion Diagnostic Testing

PAG would like confirmation that PD-L1 testing is not required.

4.6 Additional Information

None.

5 Summary of Registered Clinician Input

A total of two registered clinician inputs were provided on behalf of two clinicians from Cancer Care Ontario (CCO) Gastrointestinal Drug Advisory Committee (DAC) and eight clinicians from the Canadian Gastrointestinal Oncology Evidence Network (CGOEN) for the review of atezolizumab (Tecentriq) in combination with bevacizumab (Avastin, biosimilars) for the first-line treatment of adult patients with unresectable or metastatic HCC who require systemic therapy. Sorafenib and lenvatinib, which are oral TKIs, were reported to be currently available drugs for first-line systemic treatment of HCC in Canada. Sorafenib is currently funded and lenvatinib recently received a recommendation for funding. In current clinical practice, lenvatinib may be preferred in patients who are symptomatic or have rapidly progressive disease; however, the different side effect profile of lenvatinib and sorafenib may also inform treatment selection. The clinicians from CCO specified that sorafenib and lenvatinib are approved for patients with an ECOG PS of 0 or 1 and Child-Pugh class A liver function. In the second-line setting, only regorafenib is currently available in some provinces while cabozantinib recently received a positive conditional pERC recommendation in March 2020.

Both inputs indicated that there is an unmet need for more effective first-line systemic therapies as sorafenib and lenvatinib provide modest improvements in survival. Both the CCO and CGOEN clinicians indicated that the inclusion and exclusion criteria of the pivotal trial can be generally applied in clinical practice. However, the CCO clinicians noted that patients in the pivotal trial were required to undergo assessment of varices by upper endoscopy, which is a common practice but not mandated in clinical practice. Furthermore, they specified that the majority of enrolled patients in the IMbrave150 (pivotal trial) had hepatitis B etiology, which does not match the typical patient population in Ontario. The CCO and CGOEN clinicians noted that atezolizumab plus bevacizumab has greater efficacy and acceptable safety and tolerability compared to currently available treatments as demonstrated by the pivotal trial. Additionally, they noted that patients treated with atezolizumab plus bevacizumab had longer time to deterioration in QoL than those treated with sorafenib. Regarding safety and tolerability, the CCO clinicians highlighted that treatment with atezolizumab plus bevacizumab is associated with increased risk of upper GI bleeding and immune adverse events that are not associated with sorafenib or lenvatinib. However, there was no indication of bevacizumab increasing the risk of immuno-oncology (IO) toxicity of atezolizumab. The AEs observed in both arms were consistent with the known safety profile for each of the individual treatments. Moreover, it was highlighted that the duration of exposure to sorafenib was considerably shorter, which demonstrates the tolerability of atezolizumab plus bevacizumab.

The CGOEN clinicians stated that majority of patients with advanced HCC, Child-Pugh class A cirrhosis, should receive atezolizumab plus bevacizumab as front-line treatment in the absence of contraindications to bevacizumab or to PD-L1 antibodies such as active autoimmune diseases, recent stroke or myocardial infarction, recent bleeding, and arterial thrombotic events. Both inputs noted that patients unable to undergo endoscopic surveillance for esophageal or gastric varices, patients with untreated or incompletely treated esophageal or gastric varices, or patients that do not meet standard criteria for atezolizumab plus bevacizumab should be treated with sorafenib or lenvatinib. The CGOEN clinicians stated that atezolizumab plus bevacizumab addresses the need for more effective and tolerable first-line therapies for HCC, and both inputs reported that atezolizumab plus bevacizumab would replace existing treatments (sorafenib and lenvatinib) except in patients with contraindications to the treatment combination. The CGOEN clinicians specified that in the absence of contraindications to atezolizumab or bevacizumab (e.g., recent bleeding/thrombosis, autoimmune disease, liver transplant, etc.), the treatment combination would be preferred over sorafenib in most patients with advanced HCC not amenable to local treatment because of the observed greater efficacy and similar tolerability between atezolizumab plus bevacizumab and sorafenib. The CCO clinicians noted that the role of sorafenib and lenvatinib in the second-line setting is unknown, and the CGOEN clinicians specified that no direct evidence exists; however, in the absence of direct evidence, the CGOEN clinicians recommend that lenvatinib and sorafenib should be administered in the second-line setting and cabozantinib, regorafenib, and ramucirumab should be administered in the third-line setting—if a patient progresses on first-line treatment of atezolizumab plus bevacizumab. The CCO clinicians supported the switch to sorafenib or lenvatinib if a patient is intolerant to atezolizumab plus bevacizumab and stated that both agents would need to be stopped if a patient becomes intolerant to atezolizumab plus bevacizumab. Alternatively, the CGOEN clinicians specified that it would be likely for the drug causing side effects to be stopped if it could be identified reliably. Additionally, the CCO and CGOEN clinicians noted that there is no direct evidence to support re-treatment with atezolizumab plus bevacizumab if the disease progresses after the regimen is discontinued.

Please see below for details from the clinician inputs.

5.1 Current Treatments

Sorafenib and lenvatinib were reported to be the currently administered drugs for first-line systemic treatment of HCC in Canada, which is consistent with the provincial funding of current treatments by CADTH. Both oral agents are TKIs with lenvatinib being a multiple TKI. Namely, sorafenib was approved approximately 10 years ago and is currently funded. However, lenvatinib is currently recommended for funding, as it received a positive pERC recommendation in July 2019; accordingly, the CGOEN clinicians anticipate lenvatinib to be implemented across Canada very soon. The CCO clinicians specified that sorafenib and lenvatinib are approved for patients with an ECOG PS of 0 or 1 and Child-Pugh class A liver function. In present clinical practice, lenvatinib may be preferred in patients who are symptomatic or have rapidly progressive disease; however, the different side effect profile of lenvatinib and sorafenib may also inform treatment selection. Notably, the CGOEN clinicians highlighted that lenvatinib appears to have better clinical activity as lenvatinib demonstrated a better PFS and response rate and similar OS to sorafenib in the phase 3 REFLECT trial that compared sorafenib and lenvatinib in the first-line setting (NCT01761266).

Additionally, the CGOEN clinicians elaborated upon treatment in the second-line setting and stated that only regorafenib is currently available in some provinces as a second-line option; however, treatment with cabozantinib following disease progression with either sorafenib or lenvatinib (TKIs) recently received a positive conditional pERC recommendation (March 2020).

5.2 Eligible Patient Population

The CCO and CGOEN clinicians highlighted that the patient population in the reimbursement request represents an unmet need. The CGOEN clinicians noted that HCC is an aggressive tumour that is usually diagnosed late in its course; thus, the majority of HCC patients are not eligible for surgical resection because of tumour extent or underlying liver dysfunction. Namely, in Canada, the 5-year OS for liver cancer is 19%. Further, both inputs indicated that sorafenib and lenvatinib provide only modest benefit or improvements in survival; thus, there is an unmet need for more effective systemic therapies for patients with unresectable HCC. The CGOEN clinicians added that lenvatinib and sorafenib may result in treatment-related side effects and may potentially elicit a negative impact on patients' QoL.

The CCO and CGOEN clinicians noted that the inclusion and exclusion criteria of the pivotal trial can be applied in clinical practice. The CCO clinicians specified that the eligibility criteria for sorafenib and lenvatinib of an ECOG PS of 0 or 1 and Child-Pugh class A liver function matches the eligibility criteria for atezolizumab plus bevacizumab. However, they highlighted that patients in the pivotal trial were required to undergo assessment of varices by upper endoscopy, which is a common practice but not mandated in clinical practice. Namely, the CGOEN clinicians stated that the criteria of the pivotal trial are generally reasonable and applicable to a significant proportion of their patients.

Furthermore, the CCO clinicians noted that there is no subgroup of patients beyond the study population they would prefer to use atezolizumab plus bevacizumab in or that atezolizumab plus bevacizumab should be limited to. They stated that the majority of enrolled patients had hepatitis B etiology, which does not match the typical patient population in Ontario. However, they noted that there may be future data demonstrating efficacy by PD-L1 status, which could change eligibility for treatment with atezolizumab plus bevacizumab.

5.3 Relevance to Clinical Practice

Of note, none of the clinicians providing input on behalf of CCO reported experience with administering atezolizumab plus bevacizumab for the indication under review and three out of the eight clinicians providing input on behalf of the CGOEN reported experience with administering atezolizumab plus bevacizumab for the indication under review.

The CCO and CGOEN clinicians noted that atezolizumab plus bevacizumab has greater efficacy and acceptable safety and tolerability compared to currently available treatments as demonstrated by the pivotal trial. The CGOEN clinicians stated that atezolizumab plus bevacizumab resulted in statistically significant and clinically meaningful improvements in OS and PFS when compared to sorafenib; namely, this is the first clinical study in over a decade to demonstrate superior OS over the standard of care in unresectable HCC. Additionally, they noted that patients treated with atezolizumab plus bevacizumab had longer time to deterioration in QoL than those treated with sorafenib, which reinforces the clinical benefit of atezolizumab plus bevacizumab.

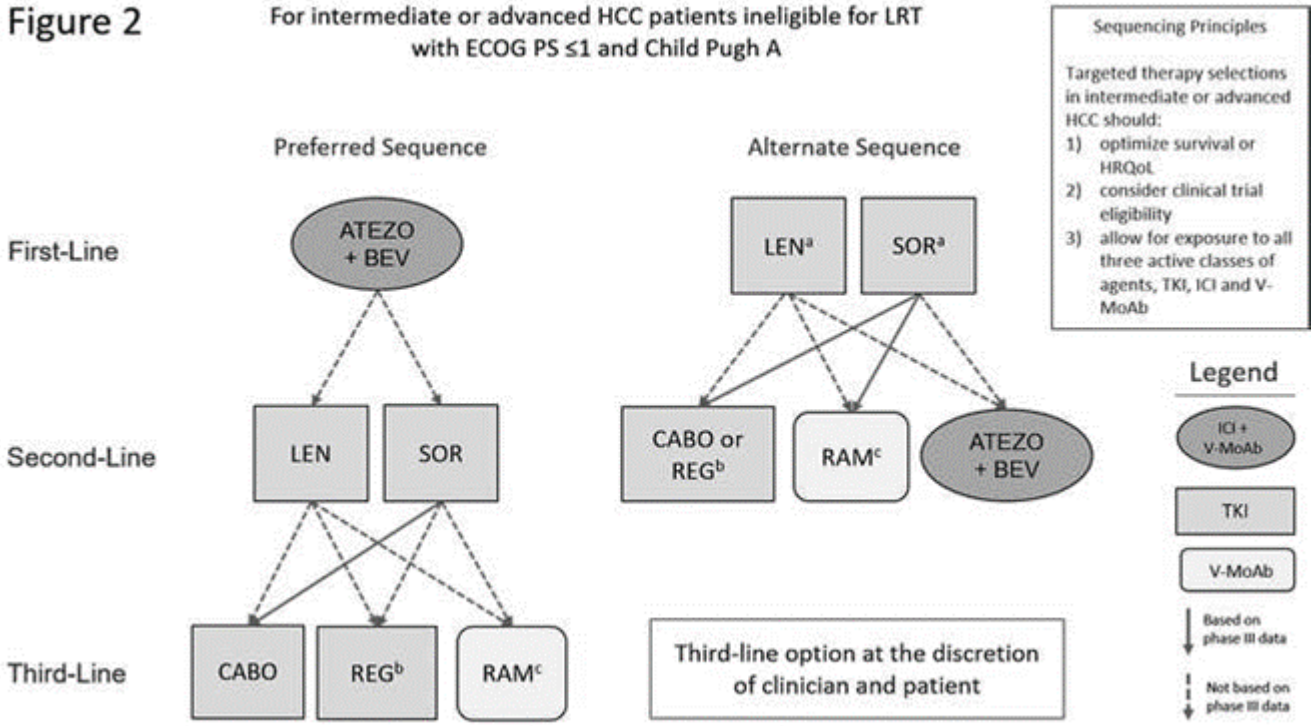
Regarding safety and tolerability, the CCO clinicians highlighted the higher risk of upper GI bleeding and immune adverse events associated with atezolizumab plus bevacizumab that are not associated with sorafenib or lenvatinib. However, they noted that they were not aware of the specific rate of IO events for the experimental arm due to atezolizumab in the pivotal trial but would expect it to be consistent with known rates of IO toxicity for atezolizumab). Further, they stated that there was no indication of bevacizumab increasing the risk of IO toxicity of atezolizumab. The CGOEN clinicians felt that atezolizumab plus bevacizumab was generally well-tolerated and toxicities were managed. In the pivotal trial, it was summarized that the incidence of AEs leading to treatment discontinuation was similar between the atezolizumab plus bevacizumab and sorafenib arms; however, fewer patients treated with atezolizumab plus bevacizumab suffered GI AEs or hand-foot skin reaction. Of note, the range of AEs differed between the treatment arms but the observed AEs were consistent with the known safety profile for each of the individual treatments. Moreover, it was highlighted that the duration of exposure to sorafenib was considerably shorter than the duration of exposure to atezolizumab plus bevacizumab, which demonstrates the tolerability of atezolizumab plus bevacizumab. Additionally, the CGOEN clinicians reported on the results of the longitudinal assessment of PROs in the pivotal trial; treatment with atezolizumab plus bevacizumab resulted in a clinically meaningful delay in deterioration of patient-reported physical functioning, role-functioning, and QoL compared with sorafenib. Thus, from a QoL and patient perspective, the combination was superior to sorafenib. Namely, the clinicians noted that time to deterioration is an important measure as it reflects patient functioning and well-being.

The CGOEN clinicians stated that the majority of patients with advanced HCC, Child-Pugh class A cirrhosis, should receive atezolizumab plus bevacizumab as front-line treatment in the absence of contraindications to bevacizumab or to anti–PD-L1 antibodies such as active autoimmune diseases, recent stroke or myocardial infarction, recent bleeding, and arterial thrombotic events. Both inputs noted that patients unable to undergo endoscopic surveillance for esophageal or gastric varices (assessed with esophagogastroduodenoscopy), patients with untreated or incompletely treated esophageal or gastric varices (treated according to local clinical practice), or who do not meet the standard criteria for atezolizumab plus bevacizumab should be treated with sorafenib or lenvatinib. Additionally, the CCO clinicians reported coinfection with hepatitis B and hepatitis C virus as a contraindication to atezolizumab plus bevacizumab. Overall, the CCO clinicians stated that there are no contraindications to current treatments that would make atezolizumab plus bevacizumab favourable; alternatively, the CGOEN clinicians stated that atezolizumab plus bevacizumab addresses the need for more effective and tolerable first-line therapies for HCC. Lenvatinib and sorafenib have a range of toxicities such as fatigue, diarrhea, hand-foot skin reaction, and anorexia that often require dose interruptions and reductions; nevertheless, the main motivation to use atezolizumab plus bevacizumab is attributed to the greater efficacy as demonstrated in the pivotal trial.

5.4 Sequencing and Priority of Treatments with New Drug Under Review

The CCO clinicians stated that atezolizumab plus bevacizumab would replace existing first line treatments except in patients with contraindications to the treatment combination. The CGOEN clinicians stated that there are data lacking on how to sequence agents after progression on atezolizumab plus bevacizumab; however, based on current information it is reasonable to sequence TKIs such as sorafenib, lenvatinib, cabozantinib, and regorafenib as second- and third-line therapy after atezolizumab plus bevacizumab. Preferably, upon disease progression following front-line treatment of atezolizumab plus bevacizumab, the CGOEN clinicians recommend that lenvatinib or sorafenib should be options in the second-line setting followed by cabozantinib, regorafenib, or ramucirumab in the third-line setting. The clinicians noted that sequencing after first-line atezolizumab plus bevacizumab is not based on phase III data. The CGOEN further commented that the treatment paradigm for metastatic HCC has been rapidly changing over the past few years and attempts to generate algorithmic approaches to the treatment of HCC are difficult since new treatments are evolving rapidly; nevertheless, the following graphic illustrates the optimal sequencing of systemic therapies proposed by the CGOEN clinicians (Figure 2).

Figure 2: Potential Sequencing Algorithm of Systemic Therapies for Advanced HCC, CGOEN



Abbreviations: ATEZO = atezolizumab; BEV = bevacizumab; CABO = cabozantinib; ECOG = Eastern Cooperative Oncology Group; HCC = hepatocellular carcinoma; HRQoL = health-related quality of life; ICI = immune checkpoint inhibitor; LEN = lenvatinib; LRT = locoregional therapy; PS = performance status; RAM = ramucirumab; REG = regorafenib; SOR = sorafenib; TKI = tyrosine kinase inhibitor; V-MoAb = anti-VEGF(R) monoclonal antibody.

[a] Patients who are unsuitable for first-line ATEZO+BEV or those who started a TKI prior to ATEZO+BEV availability.

[b] Patients with demonstrated ability to tolerate sorafenib.

[c] Patients with baseline α-fetoprotein ≥400 ng/mL only.

Source: Lim et al. J Natl Cancer Inst. 2020 Sep 8, by permission of Oxford University Press.[27]

5.4.1 Under what circumstances is use of atezolizumab plus bevacizumab preferred over sorafenib or lenvatinib and vice versa in the first line setting?

The CCO and CGOEN clinicians stated a preference to use atezolizumab plus bevacizumab, sorafenib, or lenvatinib in the first-line setting would be based on contraindications a patient may have. The CGOEN clinicians specified that in the absence of contraindications to atezolizumab or bevacizumab (e.g., recent bleeding/thrombosis, autoimmune disease, liver transplant, etc.), the treatment combination would be preferred over sorafenib in most patients with advanced HCC not amenable to local treatment. This preference is attributed to the greater efficacy and at least similar tolerability between atezolizumab plus bevacizumab and sorafenib.

5.4.2 Is there evidence to support sequencing of sorafenib/lenvatinib or regorafenib/cabozantinib as second and subsequent line agents, respectively?

The CCO and CGOEN clinicians indicated that there is no direct evidence to support the sequencing of sorafenib/lenvatinib or regorafenib/cabozantinib as second and subsequent line agents, respectively. The CCO clinicians noted that the role of sorafenib and lenvatinib in the second-line setting is unknown. The CGOEN clinicians specified that no direct evidence exists; however, 20% of patients treated with atezolizumab plus bevacizumab in the pivotal trial had subsequent treatment with a TKI.

5.4.3 Is there evidence to support re-treatment with atezolizumab plus bevacizumab if the disease progresses after the regimen is discontinued?

The CCO and CGOEN clinicians indicated that there is no direct evidence to support re-treatment with atezolizumab plus bevacizumab if the disease progresses after the regimen is discontinued. The CCO clinicians additionally stated that this practice should not be supported and the CGOEN clinicians specified that this practice was not addressed in the pivotal trial.

5.5 Companion Diagnostic Testing

The CCO and CGOEN clinicians reported that no companion diagnostic test is required. Namely, the CCO clinicians stated that there is no requirement for PD-L1 testing.

5.6 Implementation Questions

5.6.1 If a patient is intolerant to atezolizumab or bevacizumab, would one drug causing side effects be stopped and therapy continue with a single agent, or would the entire therapy stop?

Upon patient intolerance, there were differing opinions regarding the need for a patient to stop the single agent causing side effects or both agents. The CCO clinicians stated that both agents would need to be stopped if a patient is intolerant to atezolizumab or bevacizumab. Alternatively, the CGOEN clinicians specified that it is likely that the drug causing side effects would be stopped if it could be identified reliably; thus, patients would receive a single agent.

5.6.2 Would clinicians switch from atezolizumab plus bevacizumab to other first line drugs due to intolerance?

Upon patient intolerance to atezolizumab plus bevacizumab, the CCO and CGOEN clinicians supported the practice to switch to sorafenib or lenvatinib (other first-line drugs). Namely, the CGOEN clinicians also support switching to atezolizumab plus bevacizumab if a patient is intolerant to sorafenib or lenvatinib in the first-line setting if there is no evidence of progression and no contraindications.

5.7 Additional Information

None to report.

6 Systematic Review

6.1 Objectives

The primary objective of this systematic review is to evaluate the safety and efficacy of atezolizumab (Tecentriq), in combination with bevacizumab (Avastin; biosimilars), compared to standard of care in Canada for the treatment of patients with unresectable HCC who have not received prior systemic therapy.

Supplemental questions and comparison with other literature most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in Section 7.

- Summary and critical appraisal of a sponsor-submitted ITC/NMA comparing atezolizumab plus bevacizumab to relevant comparators used in clinical practice for the first-line treatment of patients with locally advanced or metastatic 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 CADTH 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 CADTH Methods Team are provided in Appendix A.

Table 6: 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 efficacy and safety of atezolizumab plus bevacizumab should be included.
	Adults (≥ 18 years of age) with unresectable HCC with no prior systemic therapy for disease.
	
	Subgroups:
	• BCLC stage:
	  ○ B (intermediate), C (advanced)
	• ECOG PS
	  ○ 0, 1
	• Child-Pugh class
	  ○ A, B
	• Aetiology of HCC
	  ○ HBV, HCV, alcohol use, other
	• Geographical region
	  ○ Asia, rest of world
	• Macrovascular invasion
	• Extrahepatic spread
	• Prior non-systemic treatment
		Atezolizumab
		+
		Bevacizumab
			• Sorafenib
			• Lenvatinib
				Efficacy†
				• OS
				• PFS
				• ORR
				• TTP
				• **HRQoL**
				
				Safety
				• **AEs**
				• **TRAEs**
				• **SAEs**
				• **WDAEs**

Abbreviations: AE = adverse events; BCLC = Barcelona Clinic Liver Cancer; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCC mRECIST = modified RECIST for HCC; HCV = hepatitis C virus; HRQoL = health-related quality of life; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial; RECIST = Response Evaluation Criteria in Solid Tumors; RT = radiation therapy; SAE = serious adverse effect; TRAEs = treatment-related adverse events; TTP = time to progression; WDAEs = withdrawals due to adverse events
* Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)

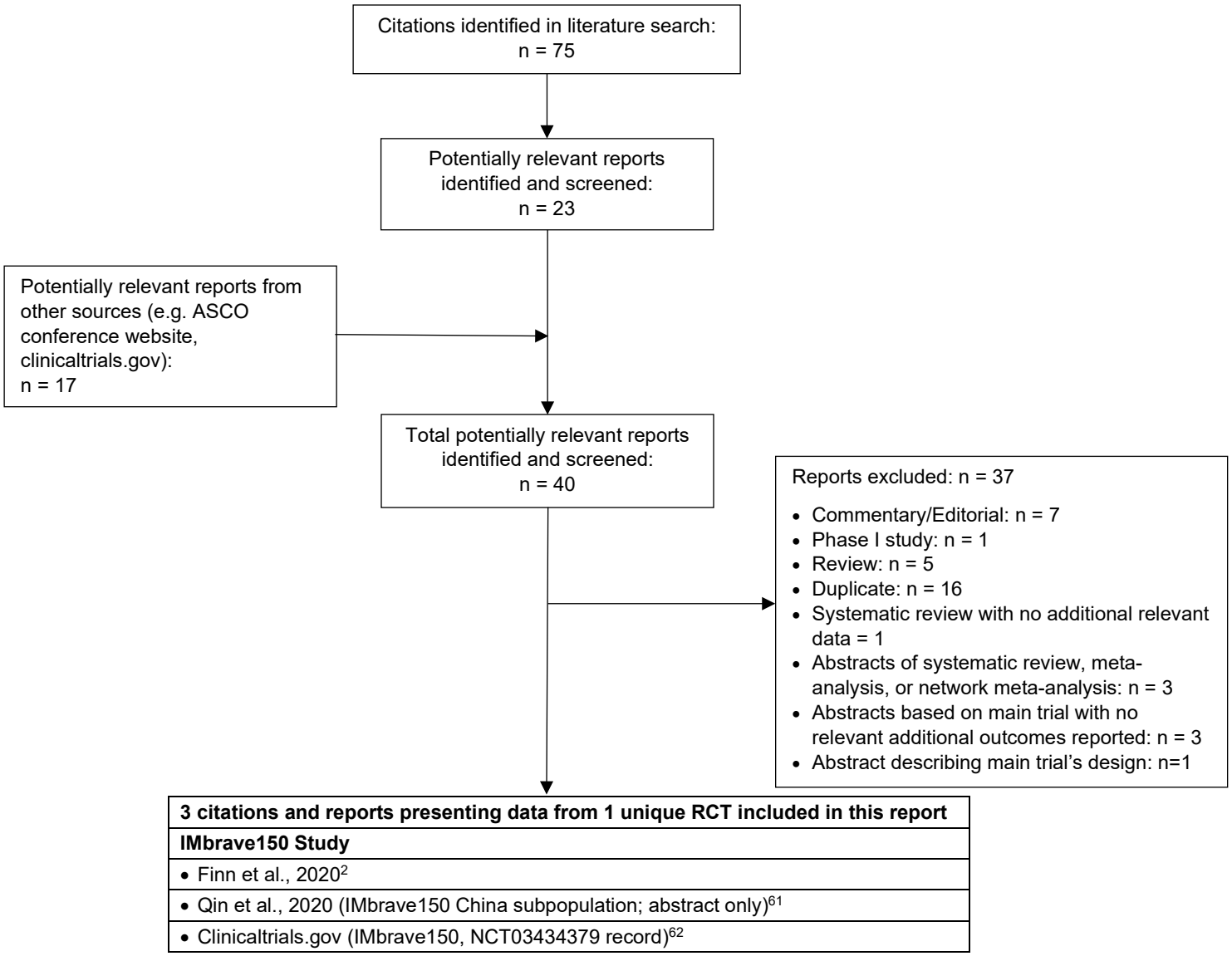
† PFS, TTP, ORR measured according to RECIST and HCC mRECIST

6.3 Results

6.3.1 Literature Search Results

The literature search initially identified 75 potentially relevant reports. Another 17 potentially relevant reports from other sources, including literature search updates and conference websites were found. After preliminary screening, a total of 40 citations were deemed potentially relevant, of which citations were ultimately excluded because the trial design was not relevant to this review[28] (i.e., phase Ib) or they were reviews[29-33] or commentary/editorial in nature[34-40]. Furthermore, although abstracts with content related to the IMbrave150 trial were identified, they were excluded as the outcomes were not relevant[41-43] or were descriptions of the trial design only[44]. Several duplicate citations of the IMbrave150 study[45,46] (including presentations of study design[47-49], analysis of subgroups[50]) and the phase I trial[51-57] (GO30140 study) were also found, all of which were conference abstracts. Two meta-analyses[9,58] and one systematic review[59] were identified, but were excluded as they were available only as a conference abstract. A fully published systematic review on immune checkpoint inhibitors in patients with advanced hepatocellular carcinoma was also found, but was excluded as no additional comparative data relevant to this review was identified.[27] After completion of screening, one unique study[2] was identified to be included in this review. Data from the China subpopulation of the pivotal trial is also available as an abstract and will be summarized briefly at the end of Section 6.[60]

Figure 3: Flow Diagram for Study Selection



ASCO = American Society of Clinical Oncology
Note: Additional data related to studies IMbrave150 were also obtained through requests to the Sponsor by CADTH[3,5,8,63,64]

6.3.2 Summary of Included Studies

One randomized controlled trial[2] that met the selection criteria of this review was identified. IMbrave150 was an open-label, randomized, phase III trial that compared atezolizumab in combination with bevacizumab to sorafenib monotherapy in patients with unresectable hepatocellular carcinoma. Key characteristics of the IMbrave150 trial are summarized in Table 7. Of note, since a phase III trial was identified, studies of other clinical trial phases (e.g., phase I or II) are not summarized in this review.

6.3.2.1 Detailed Trial Characteristics

Table 7: Summary of trial characteristics of the included studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study[2,62] IMbrave150 NCT03434379 **Characteristics** Phase III, open-label, randomized (2:1), active-controlled trial N= 501 randomized (336 = atezolizumab plus bevacizumab; 165 = sorafenib) N=485 treated (329 = atezolizumab plus bevacizumab; 156 = sorafenib) **Setting** 111 sites in 17 countries (Australia, Canada, China, Czech Republic, France, Germany, Hong Kong, Italy, Japan, Republic of Korea, Poland, Russia, Singapore, Spain, Taiwan, United Kingdom, United States). **Patient Enrolment** March 15, 2018 to January 30, 2019 **Data cut-off** August 29, 2019 **Final Analysis Date** Was originally scheduled to be conducted after	**Key Inclusion Criteria:** • ≥18 years with locally advanced or metastatic, and/or unresectable HCC* • No prior systemic treatment for HCC† • Disease not amenable to curative surgical and/or locoregional therapies, or had progressed thereafter‡ • ≥1 measurable untreated lesion (RECIST v1.1) • ECOG PS 0 or 1 • Child-Pugh class A • Adequate hematologic and end-organ function§ • Documented virology status of hepatitis (HBV and HCV serology test)¶ <u>Key Exclusion Criteria:</u> • History of malignancy other than HCC < 5 years prior to screening# • Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC • Prior allogeneic stem cell or solid organ transplantation • Local therapy to liver < 28 days prior to starting study treatment** • RT < 28 days and abdominal/ pelvic RT < 60 days prior to study treatment†† • Major surgical procedure, open biopsy, or significant traumatic injury < 28 days prior to study treatment or abdominal surgery, abdominal interventions or significant abdominal traumatic injury < 60 days prior to starting study treatment • Metastatic disease involving major airways or blood vessels, or centrally located mediastinal tumor masses of large volume. Patients with vascular invasion of the portal or hepatic veins were permitted to enroll. • Symptomatic, untreated, or actively progressing CNS metastases • Co-infection of HBV and HCV	**Intervention** Atezolizumab 1200 mg IV plus Bevacizumab 15 mg/kg IV Administered as infusions on Day 1 of each 21-day Cycle. <u>Comparator</u> Sorafenib 400 mg PO BID Treatment continued until loss of clinical benefit or unacceptable toxicity occurred.	**Primary:** • Co-primary endpoints ○ OS ○ PFS per IRF (RECIST v1.1) **Secondary:** • PFS per INV (RECIST v1.1) • Per INV and IRF (RECIST v1.1) ○ ORR ○ TTP ○ DOR • Per IRF (HCC mRECIST) ○ PFS ○ ORR ○ TTP ○ DOR • PFS and OS by baseline AFP • TTD: EORTC QLQ-C30 (QoL, physical and role function) **Exploratory Efficacy:** • Per INV (imRECIST) ○ PFS ○ TTP ○ ORR ○ DOR • PROs§§ ○ EORTC QLQ-C30 ○ EORTC QLQ-HCC18

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes

approximately 312 deaths have occurred (33 months after first enrolment). However, as the co-primary OS endpoint was met at the first interim analysis, the Sponsor confirmed that any further updated analysis will be considered descriptive.
 	
Funding
F. Hoffmann-La Roche / Genentech
	• Active or history of autoimmune disease or immune deficiency
	• Moderate or severe ascites
	• History of hepatic encephalopathy
	• History of IPF, organizing pneumonia, drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT; radiation pneumonitis in the radiation field was permitted.
	• Significant CV disease (NYHA ≥ Class II, MI, or CVA < 3 months prior to study treatment), unstable arrhythmia, or unstable angina
	• History of congenital LQTS or corrected QT interval >500 ms
	• History of hypertensive crisis or hypertensive encephalopathy
	• History of leptomeningeal disease
	• Untreated or incompletely treated esophageal and/or gastric varices with bleeding or high risk for bleeding‡‡
	• Prior bleed from esophageal and/or gastric varices <6 months prior to start of study treatment
	• Hemoptysis (≥ 2.5 mL/episode) within 1 month prior to study treatment
	• Evidence of bleeding diathesis or significant coagulopathy
	• Abdominal or tracheoesophageal fistula, GI perforation, or intra-abdominal abscess < 6 months prior to starting study treatment
	• Intra-abdominal inflammatory process < 6 months prior to starting study treatment, (e.g., active peptic ulcer disease, diverticulitis, colitis)
	• Inadequately controlled arterial hypertension
	• Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) < 6 months prior to initiation of study treatment
	• Uncorrectable electrolyte disorder affecting serum potassium, magnesium, or calcium levels
	• Uncontrolled tumor-related pain; patients requiring pain medication must be on a stable regimen at study entry
	• Treatment with:
	  ○ strong CYP3A4 inducers < 14 days prior to study treatment initiation
	  ○ systemic immunostimulatory agents		

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	○ systemic immunosuppressants (e.g., cyclophosphamide, azathioprine, methotrexate) ○ aspirin (> 325 mg/day), dipyridamole, ticlopidine, clopidogrel, or cilostazol < 10 days of first study drug dose ○ full-dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic purpose < 10 days prior to study treatment start ○ chronic daily use of NSAID		

AFP = α-fetoprotein; BID = twice a day; CNS = central nervous system; CVA = cerebrovascular accident; CV = cardiovascular; CYP3A4 = cytochrome P450 3A4; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC = European Organisation for Research and Treatment of Cancer; GI = gastrointestinal; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCC mRECIST = modified RECIST for HCC; HCV = hepatitis C virus ; INV = investigator; imRECIST = immune-modified RECIST; IPF = idiopathic pulmonary fibrosis; IRF = independent review facility; IV = intravenous; LQTS = long QT syndrome; MI = myocardial infarction; NSAID = nonsteroidal anti-inflammatory drug; NYHA = New York Heart Association; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PO = orally; PRO = patient reported outcome; QoL = quality of life; QLQ-C30 = Quality of Life Questionnaire (for cancer) Core 30; QLQ-HCC18 = HCC-Specific Quality of Life Questionnaire; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; RT = radiation therapy; TTP = time to progression

* Diagnosis of HCC confirmed by histologic or cytologic analysis, or clinically by American Association for the Study of Liver Diseases (AASLD) criteria in cirrhotic patients. Patients without cirrhosis require histological confirmation of diagnosis.

† Previous use of herbal therapies/traditional Chinese medicines with anti-cancer activity included in the label was permitted, provided that they were discontinued prior to randomization.

‡ Prior locoregional therapy (e.g., radiofrequency ablation, percutaneous ethanol or acetic acid injection, cryoablation, high-intensity focused ultrasound, transarterial chemoembolization, transarterial embolization, etc.) was permitted, provided the target lesion(s) had not been previously treated with local therapy or the target lesion(s) within the field of local therapy had subsequently progressed in accordance with RECIST v1.1.

§ Specified laboratory test results, obtained < 7 days prior to randomization, include:

- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (1500/µL) without granulocyte colony-stimulating factor support
- Lymphocyte count ≥ 0.5 x 10^9/L (500/µL)
- Platelet count ≥ 75 x 10^9/L (75,000/µL) without transfusion
- Hemoglobin ≥ 90 g/L (9 g/dL); patients may receive transfusion to meet this criterion
- Aspartate aminotransferase (AST), Alanine transaminase (ALT), and alkaline phosphatase (ALP) ≤ 5x upper limit of normal (ULN)
- Serum bilirubin ≤ 3x ULN
- Serum creatinine ≤ 1.5x ULN or creatinine clearance ≥ 50 mL/min (Cockcroft-Gault formula)
- Serum albumin ≥ 28 g/L (2.8 g/dL) without transfusion
- For patients not receiving therapeutic anticoagulation: International Normalized Ratio (INR) or activated partial thromboplastin time (aPTT) ≤ 2x ULN
- Urine dipstick for proteinuria < 2+

¶ Required for patients with active HBV: HBV DNA < 500 IU/mL obtained < 28 days prior to starting study treatment, plus anti-HBV treatment (per local standard of care; e.g., entecavir) for at least 14 days prior to study entry and for the length of the study

Exception: malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate > 90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer

** Local therapy includes radiofrequency ablation, percutaneous ethanol or acetic acid injection, cryoablation, high-intensity focused ultrasound, transarterial chemoembolization, transarterial embolization, etc. Patients were also excluded if they were not recovered from side effects of any such procedure.

†† Exception: palliative radiotherapy to bone lesions within 7 days prior to study treatment initiation were permitted

‡‡ Patients with untreated or incompletely treated esophageal or gastric varices must undergo an esophagogastroduodenoscopy (EGD) and treated per local standard of care prior to enrolment.

§§ Various assessments were performed to evaluate PROs of disease and treatment-related symptoms, such as mean scores, mean change in scores from baseline, proportion of patients with clinically meaningful change in select scales, maintenance of TTD across timepoints, and proportion of responses to subscales measuring abdominal pain and itching.

Source: Finn et al., 2020.[2]

a) Trials

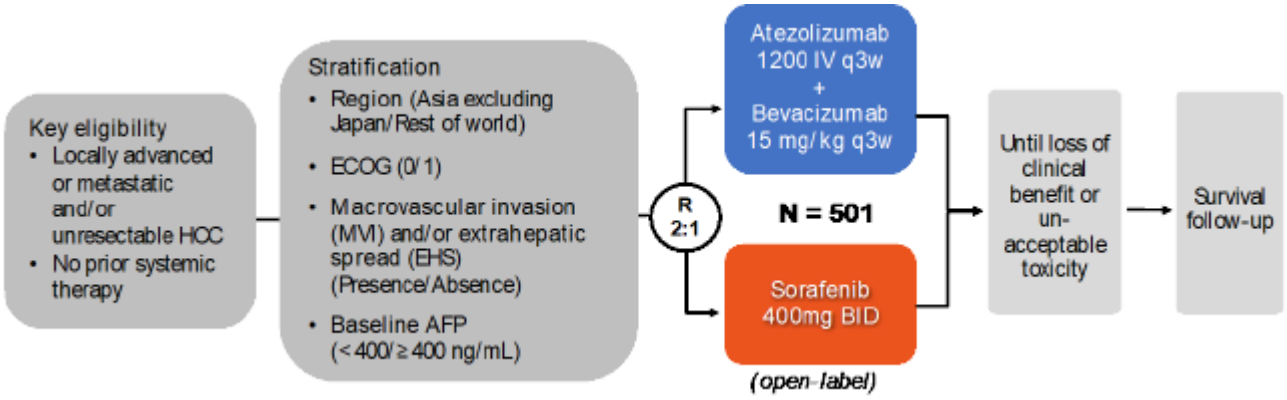
IMbrave150 is an ongoing, international, open-label, phase III, randomized, active-controlled trial of atezolizumab in combination with bevacizumab, compared to sorafenib monotherapy, in patients with locally advanced or metastatic, and/or unresectable HCC who had not received prior systemic treatment.[2] This study is being conducted at 111 sites in 17 countries, which are listed in Table 7, and included five Canadian patients representing the provinces of Ontario (n=1) and Quebec (n=4).[65]

Trial Design

Screening and Randomization: Patients were screened up to 28 days prior to study entry. Key inclusion and exclusion criteria are outlined in Table 7 above. Briefly, patients were adults who had locally advanced or metastatic, and/or unresectable HCC whose disease was not amenable to curable surgical and/or locoregional therapies or had progressed thereafter. Enrolled patients had not received prior systemic treatment for HCC, had an ECOG PS of 0 to 1, and Child-Pugh class A. Patients with known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC were excluded, as were patients with coinfection of hepatitis B and C. Patients with prior solid organ transplantation were also excluded. Prior radiation therapy (RT), locoregional therapy to the liver, and surgical procedures were permitted, if they had not occurred within 28 days of initiating study treatment (60 days for abdominal/pelvic RT or abdominal surgery). Furthermore, for those who had received curative surgical and/or locoregional therapies, the lesion(s) must have subsequently progressed. Prior to study enrolment, patients with untreated or incompletely treated esophageal or gastric varices were required to undergo an EGD and treated per local standard of care. Patients with untreated or incompletely treated esophageal and/or gastric varices with bleeding or high risk for bleeding were excluded from the trial.[2]

Eligible patients were assigned in a 2:1 ratio, using a permuted-block randomization method, to receive open-label treatment with atezolizumab plus bevacizumab or sorafenib. Atezolizumab plus bevacizumab was administered as IV infusions every 21 days (3-week cycles) and sorafenib was administered orally twice daily. Randomization, performed through an interactive voice or web-based response system within 3 business days of the first dose, was stratified by region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), baseline α-fetoprotein (AFP) levels (< 400 ng/mL vs. ≥ 400 ng/mL), ECOG PS (0 vs. 1).[2] The study design is briefly summarized in Figure 4 below.

Figure 4: Overview of IMbrave150 Study Design



BID, twice-daily; AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; q3w, every 3 weeks.
Source: pCODR Submission; Clinical Summary Document[8]

Disease Assessment: Tumours were evaluated using CT scans (with contrast) or MRI scans of the chest, abdomen, and pelvis; the same radiographic procedure and technique was used throughout the study for each patient. Scans were submitted to an independent review facility (IRF) for evaluation of response efficacy endpoints as well as secondary progression. Responses were assessed using RECIST v1.1 and immune-modified RECIST (imRECIST). Endpoints were also measured using HCC-specific modified RECIST (HCC mRECIST). Although measure of disease progression was based mostly on RECIST v1.1, in rare cases, it may also have been determined based on symptomatic deterioration.[2]

Assessment of tumour(s) occurred at baseline, every 6 weeks (± 1 week) for 54 weeks after starting treatment, and then every 9 weeks (± 1 week) thereafter. Such assessments were continued until radiographic disease progression (per RECIST v1.1) or for patients who continue treatment beyond radiographic disease progression, until loss of clinical benefit according to the investigator. Tumour assessments also continued until disease progression for patients who discontinued the study drug for reasons such as toxicity. For patients who experienced radiographic disease progression (per RECIST v1.1), tumour assessments occurred until the latter of disease progression according to imRECIST or clinical benefit was lost. Patients who did not experience disease progression continued to have tumour assessments, regardless of initiating new anticancer treatment, until withdrawal of consent, death, or termination of study by the sponsor. Physical examinations, including presence and degree of enlarged lymph nodes, splenomegaly, and hepatomegaly were also recorded as part of tumour assessments.[2]

At screening, archival tissue sample, if available, was obtained for exploratory biomarker analysis. CT scan with contrast or MRI scan of the head was also performed to screen for and evaluate CNS metastases.[2]

Monitoring and Follow-up: Various laboratory tests were performed, at baseline, on Day 1 of each treatment cycle, and at treatment discontinuation (≤ 30 days after last dose). These included coagulation, hematology, and chemistry panels, along with AFP in blood. Serum samples for pharmacokinetic and anti-drug antibody assays as well as serum and plasma samples for exploratory biomarker research were also collected during treatment. Levels of thyroid-stimulating hormone (TSH), free T3 and free T4 were also collected at screening, every 4 cycles, and at treatment discontinuation. At screening, HBV and HCV serology tests were performed. Patients with a positive test for HBsAg had further testing for HBcAb, quantitative HBsAg, and HBV DNA, whereas patients with a positive test for HCV antibody received further testing for HCV RNA on Day 1 of Cycles 5 and 9, and at treatment discontinuation. Results of a limited physical exam, ECOG PS, and PROs were collected within 96 hours of Day 1 of each treatment cycle and at discontinuation of treatment.[2]

The treatment discontinuation visit occurred 30 days (or earlier) after the last dose of study drug was given. If treatment was discontinued due to reasons other than progressive disease or loss of clinical benefit, patients were continued to be followed for tumour response and PRO assessments. During post-treatment follow-up, information on survival and initiation of new anti-cancer treatment was collected approximately every 3 months until death, loss to follow-up, study withdrawal, or until study termination.[2]

Study Endpoints

Primary Endpoint

Primary efficacy outcome for IMbrave150 was the co-primary endpoint of:

- Overall survival (OS)
  - Defined as time from date of randomization to the date of death from any cause
- Progression-free survival by IRF assessment (PFS-IRF)
  - Defined as time from randomization to the date that the first of the following occurs: a) disease progression according to RECIST v1.1 or b) death from any cause[2]

Analysis of events for OS and PFS were conducted in the ITT population. A two-sided log-rank test was performed as primary analysis for comparison of outcomes between the treatment groups, with stratification based on the following factors:

- Geographic region (Asia excluding Japan vs. rest of the world)
- Macrovascular invasion and/or extrahepatic spread (presence vs. absence)
- Baseline AFP level (< 400 vs. ≥ 400 ng/mL)[2]

Although ECOG PS was a stratification factor at randomization, it was removed from the primary analysis to avoid risk of over-stratification. To estimate median OS and PFS for each treatment group, the Kaplan-Meier (K-M) approach was used, with the Brookmeyer-Crowley method applied to estimate the 95% confidence interval (CI). A stratified Cox proportional-hazards model was used to estimate hazard ratios (HR) and corresponding 95% CIs for each treatment effect, employing the same stratification factors as those used for the primary log-rank test.[2]

For the OS assessment, patients who were alive at the time of data cut-off were censored at the last date known to be alive; those with no post-baseline data were censored at the date of randomization. For the PFS assessment, patients who had not experienced

disease progression or death by the data cut-off date were censored at the time of last tumour assessment; patients with no post-baseline tumour assessment were censored at the date of randomization.[2]

A pre-specified sensitivity analysis was performed on the unstratified log-rank test to check the robustness of the stratified log-rank test results. Sensitivity analysis was also performed to determine the impact of missing scheduled tumour assessments on the co-primary endpoint of PFS-IRF per RECIST v1.1. This was set to be done if >5% of patients in either treatment arm missed two or more consecutive tumour assessments that were scheduled immediately prior to date of disease progression or death.[2]

Subgroup analyses of the co-primary efficacy endpoints were pre-specified for the following variables: age, BCLC stage, ECOG PS, geographic region, HCC etiology, MVI and/or EHS, PD-L1 expression in tumour tissue (if sample available), race, and sex. Due to the potentially limited number of patients in each subgroup, performed analyses were unstratified.[2]

Secondary Endpoint

Several secondary efficacy endpoints were specified in IMbrave150, as outlined in the table below.

Table 8: Summary of secondary endpoints

Secondary Endpoint	Definition	Measured population
ORR-IRF as per: • RECIST v1.1* and • HCC mRECIST*	Proportion of patients who had an OR (includes CR or PR) according to an IRF and measured by RECIST v1.1 and HCC mRECIST separately. A confirmed OR was defined as CR or PR seen at two consecutive tumour assessments that were apart by ≥28 days. Patients who do not have a post-baseline tumour assessment, or who do not meet these criteria were considered non-responders.	ITT with measurable disease at baseline
ORR-INV as per RECIST v1.1	Proportion of patients who had an OR (includes CR or PR) according to the investigator, as measured by RECIST v1.1. A confirmed OR was defined as CR or PR seen at two consecutive tumour assessments that were apart by ≥28 days. Patients who do not have a post-baseline tumour assessment, or who do not meet these criteria were considered non-responders.	ITT with measurable disease at baseline
DOR-IRF as per: • RECIST v1.1 and • HCC mRECIST	Time from date of first occurrence of documented OR (CR or PR) until date of first disease progression or death. Measured by IRF and determined separately according to RECIST v1.1 and HCC mRECIST. A confirmed OR was defined as CR or PR seen at two consecutive tumour assessments that were apart by ≥28 days. Patients were censored at time of last tumour assessment if there was no documented disease progression or death. If there were no tumour assessments performed after date of first occurrence of an OR (CR or PR), patients were censored at date of the first occurrence.	Patients who had an OR†
DOR-INV as per RECIST v1.1	Time from date of first occurrence of documented OR (CR or PR) until date of first disease progression or death. Measured by investigators and determined as per RECIST v1.1. Censoring rules were the same as DOR-IRF above.	Patients who had an OR†
PFS-INV as per RECIST v1.1	As defined under primary outcome above, with disease progression determined by investigator and according to RECIST v1.1.	ITT with measurable disease at baseline
PFS-IRF as per HCC mRECIST	As defined under primary outcome above, with disease progression determined by IRF and according to HCC mRECIST.	ITT with measurable disease at baseline
TTP-IRF as per: • RECIST v1.1 and • HCC mRECIST	Date of randomization to date of first documentation of tumour progression, according to IRF and measured by RECIST v1.1 and HCC mRECIST. Patients were censored at the date of last tumour assessment if no progression was identified. Censoring occurred at the date of randomization for patients who had no post-baseline tumour assessment.	ITT population
TTP-INV as per RECIST v1.1	Date of randomization to date of first documentation of tumour progression, according to investigator and measured by RECIST v1.1. Patients were censored at the date of last tumour assessment if no progression was identified.	ITT population

Secondary Endpoint	Definition	Measured population
	Censoring occurred at the date of randomization for patients who had no post-baseline tumour assessment.	
Subgroup analysis; serum AFP level for: • PFS-IRF, PFS-INV per RECIST v1.1 • OS	Measured using baseline AFP levels of < 400 ng/mL vs. ≥ 400 ng/mL. Analysis methods used were similar to those used for co-primary endpoints; stratified analyses conducted using two factors: geographic region (Asia excluding Japan vs. rest of world) and macrovascular invasion and/or extrahepatic spread (presence vs. absence).	ITT population
TTD	Time from randomization to first deterioration in one of the following EORTC QLQ-C30 subscales: Physical function, Role function, or Global health status /QoL. A clinically significant deterioration was deemed as ≥ 10-point decrease in score from baseline, and had to be maintained for two consecutive assessments, or for one assessment if followed by death from any cause within three weeks. Censoring occurred at date of randomization for patients without a post-baseline assessment. Patients who had not experienced deterioration prior to data cut-off, discontinuation of study treatment, or initiation of new anti-cancer therapy were censored at the last available assessment date prior to or at the time that the earliest of such events occur.	ITT population

AFP = α-fetoprotein; CR = complete response; DOR-INV = Duration of Response by investigator assessment; DOR-IRF = Duration of Response by IRF assessment; HCC = hepatocellular carcinoma; HCC mRECIST = modified RECIST for HCC; IRF = independent review facility; ITT = intention-to-treat; OR = objective response; ORR-INV = Objective Response Rate by investigator assessment; ORR-IRF = Objective Response Rate by IRF assessment; OS = overall survival; PFS-INV = Progression-Free Survival by investigator assessment; PFS-IRF = Progression-Free Survival by IRF assessment; PR = partial response; QoL = quality of life; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; TTD = Time to Deterioration; TTP-INV = Time to Progression by investigator assessment; TTP-IRF = Time to Progression by IRF assessment

* Only confirmed ORR-IRF according to RECIST v1.1 and HCC mRECIST were considered key secondary endpoints and controlled for multiplicity

† Non-randomized population; comparisons between treatment arms are only for descriptive purpose

Source: Finn et al., 2020[2]

Exploratory Outcomes

Efficacy endpoints that were exploratory in nature included investigator assessed PFS, TTP, ORR, DOR as measured according to imRECIST criteria. This modified criterion incorporates components that account for initial apparent radiographic progression and subsequent delayed response that may occur with immunotherapy. Thus, imRECIST is thought to better characterize the anti-tumour activity of these pharmacotherapeutic agents.[2]

Numerous other exploratory outcomes were also investigated in IMbrave150, including analyses of pharmacokinetic parameters, immunogenicity (e.g., presence of anti-drug antibodies), and tissue or blood-based biomarkers. Though optional, archival tumour tissue samples taken at baseline were used for exploratory biomarker research including analysis of PD-L1, genes or gene signatures related to tumour immunobiology, somatic mutations, or cytokine associated T-cell activation. The co-primary endpoints were also analyzed based on various biomarkers in tumour tissue, such as PD-L1 protein expression, T effector gene signature expression, CD8 protein expression or CD8+ T cell localization.[2]

Patient-Reported Outcomes: Quality of life (QoL) was measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the accompanying HCC disease-specific treatment questionnaire (EORTC QLQ-HCC18). Health status utility scores used in health economic analyses were obtained through the EuroQol 5-Dimension Questionnaire, 5-level version (EQ-5D-5L). Patient-reported outcomes (PROs) relating to disease and treatment-related symptoms experienced by study participants were measured as part of secondary and exploratory outcomes. Specifically, PRO-related secondary outcomes measured TTD in three EORTC QLQ-C30 subscales (i.e., Global health score (GHS)/ QoL, Physical functioning, and Role functioning). For all subscales of EORTC QLQ-C30 and QLQ-HCC 18, mean summary scores and change from baseline were analyzed as part of exploratory analyses. A minimally important difference (MID) for clinically meaningful change was deemed as 10-points based on previously published literature. Heath status measured by EQ-5D-5L was also considered exploratory. The questionnaires were completed by patients on Day 1 of each treatment cycle prior to any other

assessments, discussions of patient's health, or administration of study treatment. Questionnaires were also administered at treatment discontinuation. During post-treatment follow-up, questionnaires were completed every 3 months for 1 year, unless withdrawal of consent or study termination occurs first. The ITT population was used for analysis of PRO completion and time-to-deterioration, whereas the PRO-evaluable population, defined as all randomized patients who have a baseline and at least one post-baseline assessment, were used for descriptive visit summaries as well as analyses involving change from baseline or proportions. Analyses were performed based on the group patients were randomized to, regardless of whether they received the assigned treatment.[2]

EORTC QLQ-C30 is a validated instrument consisting of 30 questions. The questionnaire assesses five aspects of patient functioning (i.e., cognitive, emotional, physical, role, social), three symptoms scales (i.e., fatigue, pain, nausea and vomiting), global health status/QoL, and six single items (i.e., appetite loss, constipation, diarrhea, dyspnea, insomnia, financial difficulties) over the past week. Each score is converted onto a scale of 0 to 100 points; higher scores in the functional and global health scales implies better functioning or global health status, whereas higher scores in the symptom and single item scales indicate worse symptoms or problems. EORTC QLQ-HCC18 is an HCC disease-specific assessment to be used along with EORTC QLQ-C30 and consists of 18 questions. The questionnaire includes measures for six multi-item symptom scales (i.e., body image, fatigue, fevers, jaundice, nutrition, pain), as well as two single-items (i.e., abdominal swelling, sexual interest) over the past week.[2]

Safety: All patients who received at least one full or partial dose of the study drug were included in the safety analysis population and were analyzed according to the actual treatment received. Adverse events (AEs) were categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) terms and severity was measured using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.[2]

Patients were monitored throughout the study for safety and tolerability. Prior to each dose, patients were assessed for toxicity. For patients randomized to receive atezolizumab plus bevacizumab, vital signs including blood pressure, respiratory rate, pulse, and temperature were measured before, during, and after infusions. All AEs were reported until the earlier of 30 days after the last dose of treatment or initiation of new anti-cancer treatment. AEs of special interest and serious AEs (SAEs) were reported until at least 90 days after last dose of treatment or when new anti-cancer therapy was initiated. AEs that occurred were followed until deemed resolved, stable, or new anti-cancer therapy was started.[2]

Numerous AEs of special interest were specified in the study, including drug-induced liver injury, pneumonitis, colitis, endocrinopathies, systemic lupus erythematosus, neurological disorders, and myopathies. Any grade of CNS bleed, as well as GI abscess, perforation or fistula were also closely monitored for, as well as any arterial thromboembolic events.[2]

Statistical Analysis

Sample Size: Two patient populations were specified for this study: a global population and a China subpopulation. Separate analyses were performed for each population group; the primary publication and this report focuses on the global population.[2]

For the global population, approximately 480 patients were planned for enrolment. Sample size was determined based on overall survival and the number of deaths required to demonstrate efficacy. To detect a HR of 0.71, corresponding with median OS improvement of 4.9 months, approximately 312 deaths were required to achieve 80% overall power, with difference detected using a log-rank test at two-sided significance level of 0.048. A HR of 0.783 was deemed as the minimum detectable difference (MDD) of OS, representing improvement of median OS by 3.3 months. The anticipated duration of recruitment was 10 months, with final analysis of OS expected to occur approximately 33 months after randomization of the first patient.[2]

To detect an improvement in the IRF-assessed PFS, approximately 308 events were required for primary PFS analysis. This was deemed to provide 97% power to achieve a target HR of 0.55, corresponding with a median improvement in PFS of 3.3 months (from 4 to 7.3 months), with difference detected using a log-rank test at a two-sided significance level of 0.002. This target also ensured a minimal follow-up of approximately 6 months for all patients. A HR of 0.688, corresponding to median PFS improvement of 1.8 months (from 4 to 5.8 months), was deemed as the MDD in PFS. The anticipated cutoff date for primary PFS analysis was expected to occur approximately 16 months after randomization of first patient.[2]

As part of sample size calculations, it was assumed that the median duration of PFS in the control arm (i.e., patients receiving sorafenib) was 4 months and OS was 12 months. Furthermore, assumed drop-out rates over 12 months were 5% for atezolizumab plus bevacizumab and 10% for sorafenib.[2]

Interim Analyses and Multiplicity: No interim analyses were planned for PFS. For OS, two interim analyses were pre-specified. The first interim OS analysis was performed at the time of the primary PFS analysis; approximately 172 deaths were anticipated at this time with a respective OS MDD in HR of 0.633, corresponding with median OS improvement of 6.9 months. The second OS interim analysis was planned for when 243 deaths had occurred, estimated as approximately 24 months after first person had entered the study. This corresponds with median OS improvement of 4.6 months and OS MDD in HR of 0.728.[2]

A group sequential design was used for testing the OS endpoint to account for conducing two interim analyses. An alpha spending using the Lan-DeMets method to approximate the O'Brien-Fleming boundaries were applied to control for the overall Type I error rate at the two-sided significance level of 0.048 for the OS co-primary endpoint.[2] The projected stopping boundaries and analysis timing for OS are show in Table 6.

Table 9: Stopping Boundaries and Analysis Timing, Overall Survival

Analysis Timing	Planned Information Fraction	Number of Events/ Analysis timing (estimated)	Stopping Boundary (Two-Sided p-Value)	
			Alpha can be recycled to OS (i.e. OS alpha = 0.05)	Alpha cannot be recycled to OS (i.e. OS alpha = 0.048)
1st OS interim analysis	55%	172/16 months*	MDD HR ≤ 0.636 (p-value ≤ 0.005)	MDD HR ≤ 0.633 (p-value ≤ 0.005)
2nd OS interim analysis	78%	243/24 months	MDD HR ≤ 0.73 (p-value ≤ 0.021)	MDD HR ≤ 0.728 (p-value ≤ 0.02)
OS final analysis	100%	312/33 months	MDD HR ≤ 0.784 (p-value ≤ 0.043)	MDD HR ≤ 0.783 (p-value ≤ 0.041)

HR = hazard ratio; MDD = minimum detectable difference; OS = overall survival; PFS = progression-free survival.

Analysis timing shown in the table is projected based on protocol assumptions. Actual timing depends on the exact time that the required events have accrued.

*The 1st OS interim analysis will be conducted when approximately 308 PFS events have occurred. It is anticipated that approximately 172 OS events have been observed at time of primary PFS analysis.

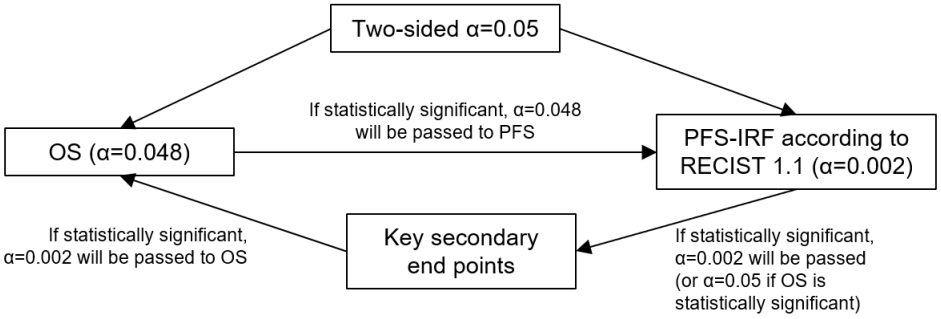
MDD HR is estimated based on proportional hazard assumption.

Source: From N Engl J Med, Finn et al., 382:1894-905. Copyright © 2020 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[2]

Hypothesis testing was formally performed on co-primary and key secondary endpoints. Overall Type I error was strongly controlled at 5% (two-sided significance level of 0.05) by graphical approach involving splitting and recycling. As a first step of this ordered statistical testing procedure, the overall two-sided significance level of 0.05 was split into a two-sided significance level of 0.048 for OS and 0.002 for PFS; with this, OS and PFS (as assessed by IRF, according to RECIST v1.1) were initially tested in parallel. If OS was deemed statistically significant, the initially allocated two-sided significance of 0.048 could be recycled to PFS, so that PFS could

be tested at a two-sided significance level of 0.05 (rather than 0.002). If PFS was deemed statistically significant, then the initially allocated two-sided significance level of 0.002 (or 0.05 if OS was statistically significant) was recycled for formal testing, in hierarchical fashion, of key secondary endpoints. Testing of key secondary endpoints started with confirmed ORR (as assessed by IRF) according to RECIST v1.1; if statistically significant, confirmed ORR (as assessed by IRF) according to HCC mRECIST was then tested next. If confirmed ORR per RECIST v1.1 was not statistically significant, the latter (confirmed ORR per HCC mRECIST) was not tested. If PFS and all key secondary endpoints were statistically significant at a two-sided significance level of 0.002, OS could be tested at a two-sided significance level of 0.05 (rather than 0.048). Specifics of the control strategy for Type I error can be seen in Figure 5. Subgroups analyzed for the co-primary endpoints were not adjusted for multiple comparisons.[2]

Figure 5: Strategy for Type I Error-Rate Control



OS, overall survival; PFS, progression-free survival; PFS-IRF, progression-free survival as assessed by independent review facility; RECIST, Response Evaluation Criteria In Solid Tumors.

Source: From N Engl J Med, Finn et al., 382:1894-905. Copyright © 2020 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[2]

At the time of data cut-off, 308 occurrence of disease progression or death were recorded, including 161 deaths. Based on this observation, the multiplicity-adjusted two-sided α-level was 0.0033 for the first interim analysis of OS.[2] As all tested efficacy endpoints had reached statistical significance at their pre-specified efficacy boundaries, no alpha recycling was required. Specifically, statistical significance was seen with OS at two-sided alpha of 0.0033; PFS-IRF (per RECIST v1.1) at alpha of 0.002; secondary endpoints of ORR-IRF (per RECIST v1.1) and ORR-IRF (per HCC mRECIST) each at alpha of 0.002. Furthermore, as the co-primary OS endpoint was met at the first interim analysis, this analysis was considered as definitive for OS, and future analysis of OS are to be considered descriptive only.[5] Although the study is still ongoing, the event-driven second interim analysis of OS will not be performed according to the sponsors; instead, a time-driven descriptive OS analysis is planned with data cut-off date in August 2020, approximately 12 months after the first interim analysis.[4] Also according to the sponsors, a final descriptive analysis is under discussion.[6]

Protocol Amendments: The original protocol was issued on October 18, 2017, and three amendments were subsequently made in March 2018, September 2018, and February 2019. Amendments from version 3 (September 2018) included a few notable changes, which were finalized 3 months prior to enrolment of the last patient.[4] A key update included a change to one of the co-primary endpoints from investigator-assessed ORR to IRF-assessed PFS (previously a secondary endpoint), as ORR was being investigated extensively in a separate phase Ib study (GO30140). Eligibility criteria were also modified to improve safety of patients enrolled into the study. Notably, an exclusion criterion of prior bleeding due to esophageal and/or gastric varices within 6 months of starting study treatment was added, as these patients were thought to be at increased risk of (re-)bleed.

The latest amendment reflects a modification to the statistical analysis plan to include a second interim analysis for OS (when 243 events had occurred). As a result, the first and final OS analyses were also adjusted so that the first interim analysis was to occur after approximately 172 events (previously 169), and the final analysis was to occur after approximately 312 events (previously 307); such changes were made to ensure an overall power of 80% was achieved for OS. This update to the statistical analysis plan was in anticipation of changes to the treatment of HCC, including improved access to second-line therapies and beyond, including

immunotherapy targeting the PD-1/PD-L1 axis. Changes were also made to update the method of controlling overall Type I error from a group sequential weighted Holm procedure to a graphical approach.[2]

b) Populations

A total of 501 patients at 111 sites spanning 17 countries were randomly assigned to receive atezolizumab plus bevacizumab (336 patients) or sorafenib (165 patients) between March 15, 2018 and January 30, 2019. Overall, of the total number of patients enrolled, the median age was 65 years (interquartile range 56-71 years), 82.6% (n=414) were male, 56.7% (n=284) were Asian and 34.9% (n=175) were White. Notably, most enrolled patients had ECOG PS of 0 (62.3%, n=312), Child-Pugh score of A5 (72.1%, n=360), BCLC Stage C disease (Advanced; 81.6%, n=409), as well as presence of MVI and/or EHS (75.4%, n=378). The predominant etiology of HCC in the enrolled patients was hepatitis B (47.9%, n=240), and approximately half of patients (49.1%, n=246) had received at least one prior local therapy for HCC.[2] Almost 30% of patients (n=99, 29.5% in atezolizumab plus bevacizumab; n=45, 27.3% in sorafenib arms) had prior surgical resection of the liver.[4]

Baseline demographics and characteristics were generally well balanced between the two treatment groups. A slightly lower proportion patients randomized to the atezolizumab plus bevacizumab group were 65 years of age or older (47.9% atezolizumab plus bevacizumab vs. 55.2% sorafenib). The atezolizumab plus bevacizumab group had a higher proportion of patients with EHS (63.1% vs. 56.4% for sorafenib), although a slightly lower proportion compared to the sorafenib group had MVI (38.4% vs. 43.0% for sorafenib). When grouped together, a slightly higher proportion of patients in the atezolizumab plus bevacizumab group compared to the sorafenib group had the presence of MVI, EHS spread, or both (76.8% vs. 72.7%). Proportion of patients who received at least one prior local therapy was generally well balanced between the two groups, with the most common therapy being TACE followed by radiofrequency ablation (RFA).[2] Detailed baseline demographic and clinical characteristics are presented in Table 10.[2]

Table 10: Baseline Characteristics

Characteristic	Atezolizumab plus Bevacizumab (n = 336)	Sorafenib (n = 165)
Median age (IQR), years	64 (56, 71)	66 (59, 71)
Age ≥ 65 years, n (%)	161 (48)	91 (55)
Male, n (%)	277 (82)	137 (83)
Race, n (%)		
White	123 (37)	52 (32)
Asian	188 (56)	96 (58)
Black or African American	6 (1.8)	4 (2.4)
Unknown	19 (6)	12 (7)
Geographic region, n (%)		
Asia excluding Japan	133 (40)	68 (41)
Rest of the world*	203 (60)	97 (59)
Diagnosis confirmation method		
Clinical	116 (35)	65 (39)
Histology	150 (45)	62 (38)
Both	70 (21)	38 (23)
ECOG performance status, n (%)		
0	209 (62)	103 (62)
1	127 (38)	62 (38)
Child-Pugh score		
A5	239 (72)	121 (73)
A6	94 (28)	44 (27)
B7	1 (< 1)	0
Barcelona Clinic liver cancer stage		
A (Early)	8 (2)	6 (4)
B (Intermediate)	52 (15)	26 (16)
C (Advanced)	276 (82)	133 (81)
AFP at baseline ≥ 400 ng/mL	126 (38)	61 (37)
Macrovascular invasion present, n (%)	129 (38)	71 (43)
Extrahepatic spread present, n (%)	212 (63)	93 (56)
Macrovascular invasion and/or extrahepatic spread present, n (%)	258 (77)	120 (73)
Varices at baseline	88 (26)	43 (26)
Varices treated at baseline	36 (11)	23 (14)
Etiology of hepatocellular carcinoma, n (%)		
Hepatitis B	164 (49)	76 (46)
Hepatitis C	72 (21)	36 (22)
Nonviral	100 (30)	53 (32)
Alcohol	35 (10)	23 (14)
Other	38 (11)	16 (10)
Unknown†	27 (8)	14 (8)
Alcohol use, n (%)		
Current	48 (14)	25 (15)
Never	121 (36)	61 (37)
Previous	166 (50)	79 (48)
PD-L1 status, n‡	124	58
TC and IC <1%	45 (36)	25 (43)
TC or IC ≥1%	79 (64)	33 (57)
TC ≥5% or IC ≥5%	46 (37)	17 (29)
TC ≥10% or IC ≥10%	12 (10)	5 (9)
Prior local therapy for hepatocellular carcinoma, n (%)		
At least one treatment	161 (48)	85 (52)
Transarterial chemoembolization	130 (39)	70 (42)
Radiofrequency ablation	47 (14)	24 (15)
Prior radiotherapy	34 (10)	17 (10)

AFP, α fetoprotein; ECOG, Eastern Cooperative Oncology Group; IC, tumor-infiltrating immune cell; IQR, interquartile range; PD-L1, programmed death-ligand 1; TC, tumor cell.
Summary statistics are based on the full population indicated in the header, except for PD-L1 status.

* Includes USA, Australia, New Zealand, and Japan.

† Includes unknown non-hepatitis B and C causes.

‡ Provision of archival or pretreatment fresh tissue was not mandatory for this trial and, consequently, tissue was collected from 182 of 501 (36%) enrolled patients. PD-L1 expression on IC and TC was assessed retrospectively by the SP263 immunohistochemistry assay (Ventana Medical Systems; Tucson, AZ). The TC score is the percentage of total TCs expressing PD-L1. The IC score is the number of ICs expressing PD-L1 as a percentage of tumor area.

Source: From N Engl J Med, Finn et al., 382:1894-905. Copyright © 2020 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[2]

c) Interventions

Patients were randomized in a 2:1 ratio to one of two treatment arms, administered in 21-day cycles:

- Atezolizumab plus bevacizumab administered sequentially on Day 1, with ≥ 5 minutes between agents:
  - Atezolizumab 1200 mg IV
    - Infused over 60 (±15) minutes for first dose, and if tolerated, over 30 (±10) minutes for subsequent infusions
  - Bevacizumab 15 mg/kg IV
    - Infused over 90 (±15) minutes for first dose, and if tolerated, over 60 (±10) minutes then 30 (±10) minutes for subsequent infusions
- Sorafenib 400 mg orally twice a day, continuously
  - Administered as 2 x 200 mg tablets 12 hours apart, on an empty stomach (i.e., 1 hour before or 2 hours after a meal)[2]

Treatment was continued until unacceptable toxicity or loss of clinical benefit. The latter was determined by investigator, after an integrated assessment of biochemical and radiographic data, as well as clinical status (e.g., symptomatic deterioration such as pain due to disease). Patients who met the criteria for radiographic disease progression per RECIST v1.1 were permitted to continue the assigned study treatment if the following requirements were met: a) investigator determines that available data indicates there is evidence of clinical benefit; b) no signs or symptoms indicating unequivocal disease progression; c) no decline in ECOG PS attributed to disease progression; d) no tumour progression at critical sites that cannot be managed by medical interventions allowed in the protocol (e.g., leptomeningeal disease). Patients were considered to have continued treatment after progression if study treatment was continued for longer than three weeks after investigator assessed radiographic disease progression (RECIST v1.1). During the study, 21.1% of patients (n=71) treated with atezolizumab plus bevacizumab and 12.1% of patients (n=20) treated with sorafenib continued treatment beyond radiographic progression.[4] Treatment could also have been discontinued for other reasons such as a use of another anti-cancer treatment, medical condition jeopardizing patient's safety if treatment was continued, pregnancy, or as deemed appropriate by trial sponsor.[2]

Premedication was not permitted prior to the first dose of atezolizumab or bevacizumab; however, if an infusion-related reaction was experienced, antihistamines, antipyretics, and/or analgesics were permitted prior to subsequent doses at the investigator's discretion.[2]

Temporary or permanent interruption of atezolizumab or bevacizumab due to toxicity was permitted based on detailed management guidelines for specific adverse events. Dose modifications were not permitted. For bevacizumab, dose was adjusted only if there was a > 10% change in weight from baseline. If either atezolizumab or bevacizumab were withheld or discontinued, continuation of the other drug was permitted as long as the patient was deemed to be experiencing clinical benefit according to investigator's judgement and discussion with the Medical Monitor. Dose alteration or interruption of sorafenib was permitted for management of toxicities. If reduction in sorafenib dose was required, 400 mg once daily was given; if further reduction was necessary, 400 mg every other day was administered. Dose re-escalated was permitted if the patient had received a stable dose for three weeks.[2] Details on number of patients who had a dose alteration or suspension are discussed in detail under Section 6.3.2.2 (Detailed Outcome Data and Summary of Outcomes; Harms Outcomes - Treatment Modification or Discontinuation Due to Adverse Event).

Treatment Exposure: At the time of data cut-off (August 29, 2019), the median duration of treatment was 7.4 months for atezolizumab, 6.9 months for bevacizumab, and 2.8 months for sorafenib. The median dose intensities were high and similar for all three agents, though the mean dose intensity for sorafenib was lower than atezolizumab and bevacizumab. Specifically, the median (range) dose intensities were 98% (54 to 104%) for atezolizumab, 97% (44 to 104%), and 96% (27 to 100%) for sorafenib, whereas the mean (± standard deviation) dose intensities were: 95±7% for atezolizumab, 93±10% for bevacizumab, and 84±20% for sorafenib.[2]

Concomitant and Subsequent Medications: Several therapies were prohibited during the study. For example, concomitant treatment with systemic immunostimulatory agents (e.g., interferons, interleukin-2), systemic immunosuppressants (e.g., azathioprine, methotrexate), chronic use of non-steroidal anti-inflammatory drugs (NSAIDs), and full-dose anticoagulants, antithrombotic or antiplatelet agents were prohibited. Routine use of corticosteroids and TNF-α inhibitors were permitted with caution at the discretion of the investigator; however, as these agents may attenuate immunologic effects of atezolizumab, alternatives were preferred. Corticosteroids or other immunosuppressive agents were recommended at the investigator's discretion for acute

management of immune-related toxicities associated with atezolizumab. Low-dose aspirin (< 325 mg/day) was permitted, with co-administration of a proton pump inhibitor strongly encouraged.[2]

Palliative RT that does not interfere with target tumour lesions was permitted, though bevacizumab and sorafenib were held during treatment. Other local treatment, including surgery, radiotherapy, radiofrequency ablation, and stereotactic radiosurgery, was permitted in patients who experienced mixed response and required local therapy for control of three or fewer non-target lesions.[2]

During the study, palliative radiotherapy was given to five patients (1.5%) in the atezolizumab plus bevacizumab group and 1 patient (0.6%) in the sorafenib group. The main site of radiation treatment was bone, although one patient in the atezolizumab plus bevacizumab group received palliative radiotherapy to the liver. A small number of patients (three in each arm; 0.9% vs. 1.8% for atezolizumab plus bevacizumab and sorafenib, respectively) also received cancer-related surgery. One person in the atezolizumab plus bevacizumab treatment group received curative surgery for removal of new bone lesions which was not considered to impact target and non-target lesions; most other surgeries were palliative in nature on bone, esophagus, liver, or another undefined location and were performed more often in the sorafenib group (1.8%) vs the atezolizumab plus bevacizumab group (0.3%).[5]

The proportion of patients taking concomitant non-cancer treatment, including those that may have been started prior to study treatment, were generally similar between groups. Classes of medications most commonly reported (used by ≥30% of patients in both arms), listed for atezolizumab plus bevacizumab and sorafenib groups respectively, include: proton pump inhibitors (46.5% vs. 48.1%), opioid analgesics (33.1% vs. 36.5%), calcium channel blockers (41.3% vs. 34.6%), nucleoside/nucleotide analogues (40.1% vs. 34.0%), and corticosteroids (40.1% vs. 31.4%, including topical). Additionally, several medications were used more frequently in one treatment group; for example, greater use in the sorafenib arm was reported for anti-diarrheals (7.9% vs. 30.8%) and dermatologic agents (14.6% vs. 42.3%), whereas patients in the atezolizumab plus bevacizumab group reported greater use of analgesics (35.6% vs. 25.6%) and loop diuretics (25.8% vs.15.4%). During the study, anticoagulants were administered to 12.5% of patients in the atezolizumab plus bevacizumab group and 14.1% of patients in the sorafenib group.[5]

After the assigned study treatment, a greater proportion of patients in the sorafenib group (44.2%, n=73) than those in the atezolizumab plus bevacizumab group (20.5%, n=69) received at least one subsequent systemic anti-cancer therapy; treatment in the second, third, and fourth line settings were all received by a higher proportion of patients treated with sorafenib. Subsequent treatment in the atezolizumab plus bevacizumab group was administered mostly in the second-line setting.[2] Tyrosine kinase inhibitors were most frequently prescribed to patients in the atezolizumab plus bevacizumab group, with sorafenib being prescribed to 33 patients across all subsequent lines of therapy.[2,4] In the second-line setting, sorafenib was most commonly prescribed (n=31), followed by lenvatinib (n=22); in the third-line setting, regorafenib (n=4) was prescribed slightly more often than other agents, followed by sorafenib (n=2), nivolumab (n=2), or chemotherapy (oxaliplatin, n=2).[4] For patients randomized to the sorafenib group, subsequent treatment was frequently administered in the second and third-line setting, with TKIs and immunotherapies commonly prescribed.[2] Overall, lenvatinib was the most commonly prescribed subsequent treatment (n=23), regardless of line in therapy; this was followed by regorafenib (n=20) and nivolumab (n=16). In the second-line setting, lenvatinib (n=15), regorafenib (n=15), and nivolumab (n=12) were prescribed most commonly, and lenvatinib (n=4), nivolumab (n=4), regorafenib (n=3), and ramucirumab (n=3) were agents prescribed most frequently as third-line therapy. Of note, atezolizumab and bevacizumab were prescribed in two patients each, all in the second-line setting, although it is unclear if these were given in combination to the same two patients, or as monotherapy in four separate patients.[4] An overview of subsequent treatment can be found in Table 11; prescribed second and third-line therapy for each treatment group can be found in Tables 12 and 13.

Table 11: Subsequent Local, Systemic, Surgical, and Radiologic Therapy, ITT population

	Atezolizumab plus Bevacizumab (n=336)	Sorafenib (n=165)
Total number of patients with at least one systemic treatment	69 (20.5)	73 (44.2)
Total number of treatments	95	124
Line of therapy		
Second line	62 (18.5)	68 (41.2)
Third line	11 (3.3)	19 (11.5)
Fourth line	1 (0.3)	4 (2.4)
Not applicable	7 (2.1)	7 (4.2)
Regimen		
Tyrosine kinase inhibitor	63 (18.8)	43 (26.1)
Angiogenesis inhibitor (monoclonal antibodies)	2 (0.6)	5 (3.0)
Chemotherapy	4 (1.2)	10 (6.1)
Immunotherapy†	4 (1.2)	31 (18.8)
Others	2 (0.6)	5 (3.0)
Total number of patients with at least one local treatment		
Radiofrequency ablation	1 (0.3)	0
Transarterial embolization	2 (0.6)	2 (1.2)
Transarterial chemoembolization	4 (1.2)	4 (2.4)
Transcatheter arterial infusion	1 (0.3)	2 (1.2)
Transarterial radioembolization	1 (0.3)	0
Total number of patients with at least one surgical treatment	5 (1.5)	1 (0.6)
Total number of patients with at least one radiotherapy treatment	9 (2.7)	7 (4.2)

*Multiple cases within a specific line of therapy and regimen for a patient were counted once.

†Anti–programmed death-1, anti–programmed death-ligand 1, and anti–cytotoxic T-lymphocyte–associated protein 4.

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Table 12: Second and Third-Line Therapy, Atezolizumab Plus Bevacizumab Treatment Group

Second-Line Therapy			Third-Line Therapy		
Category	Treatment	N	Category	Treatment	N
TKIs	Cabozantinib	2	TKIs	Lenvatinib	1
TKIs	Lenvatinib	22	TKIs	Regorafenib	4
TKIs	Regorafenib	3	TKIs	Sorafenib	2
TKIs	Sorafenib	31	Immunotherapy	Nivolumab	2
Immunotherapy	Investigational Drug	1			
Immunotherapy	Pembrolizumab	1			
Angiogenesis Inhibitors (mAbs)	Ramucirumab	2			
Others	BLU-554 (FGFR4 Inhibitor)	1			

Abbreviations: FGFR4 = Fibroblast Growth Factor Receptor 4; mAbs = monoclonal antibody; TKI = tyrosine kinase inhibitor.

List excludes treatment classified as unknown or unspecified.

Chemotherapy was also given as subsequent therapy but has not been included in this table. The chemotherapy category includes the following agents (n):

- Second-line: carboplatin (1), fluorouracil (1), folinic acid (1), gemcitabine hydrochloride (1), oxaliplatin (1)
- Third-line: calcium folinate (1), capecitabine (1), fluorouracil (1), oxaliplatin (2), pegylated arginine deiminase (1)

Source: Adapted from Checkpoint Meeting Response, August 6, 2020 (Hoffman La-Roche)[4]

Table 13: Second and Third-Line Therapy, Sorafenib Treatment Group

Second-Line Therapy			Third-Line Therapy		
Category	Treatment	N	Category	Treatment	N
TKIs	Apatinib Mesylate	1	TKIs	Cabozantinib	1
TKIs	Cabozantinib	5	TKIs	Lenvatinib	4
TKIs	Lenvatinib	15	TKIs	Regorafenib	3
TKIs	Regorafenib	15	TKIs	Sorafenib	1
Immunotherapy	Atezolizumab	2	Immunotherapy	Nivolumab	4
Immunotherapy	Durvalumab	3	Immunotherapy	Tislelizumab	1
Immunotherapy	IRX-2 (Cytokines)	2	Angiogenesis Inhibitors (mAbs)	Ramucirumab	3
Immunotherapy	Nivolumab	12			
Immunotherapy	Pembrolizumab	5			
Immunotherapy	Sintilimab	1			
Immunotherapy	Tislelizumab	1			
Immunotherapy	Tremelimumab	3			
Angiogenesis Inhibitors (mAbs)	Bevacizumab	2			
Others	Thalidomide	2			

Abbreviations: mAbs = monoclonal antibody; TKI = tyrosine kinase inhibitor.

List excludes treatment classified as unknown or unspecified.

Chemotherapy was also given as subsequent therapy, but has not been included in this table. The chemotherapy category includes the following agents (n):

- Second-line: bufalin/cinobufagin/resibufogenin (1), calcium folinate (1), capecitabine (1), cyclophosphamide (3), etoposide (1), fluorouracil (1), oxaliplatin (1), tegafur/uracil (1)
- Third-line: calcium folinate (1), capecitabine (1), fluorouracil (1), oxaliplatin (1), pegylated arginine deiminase (1)

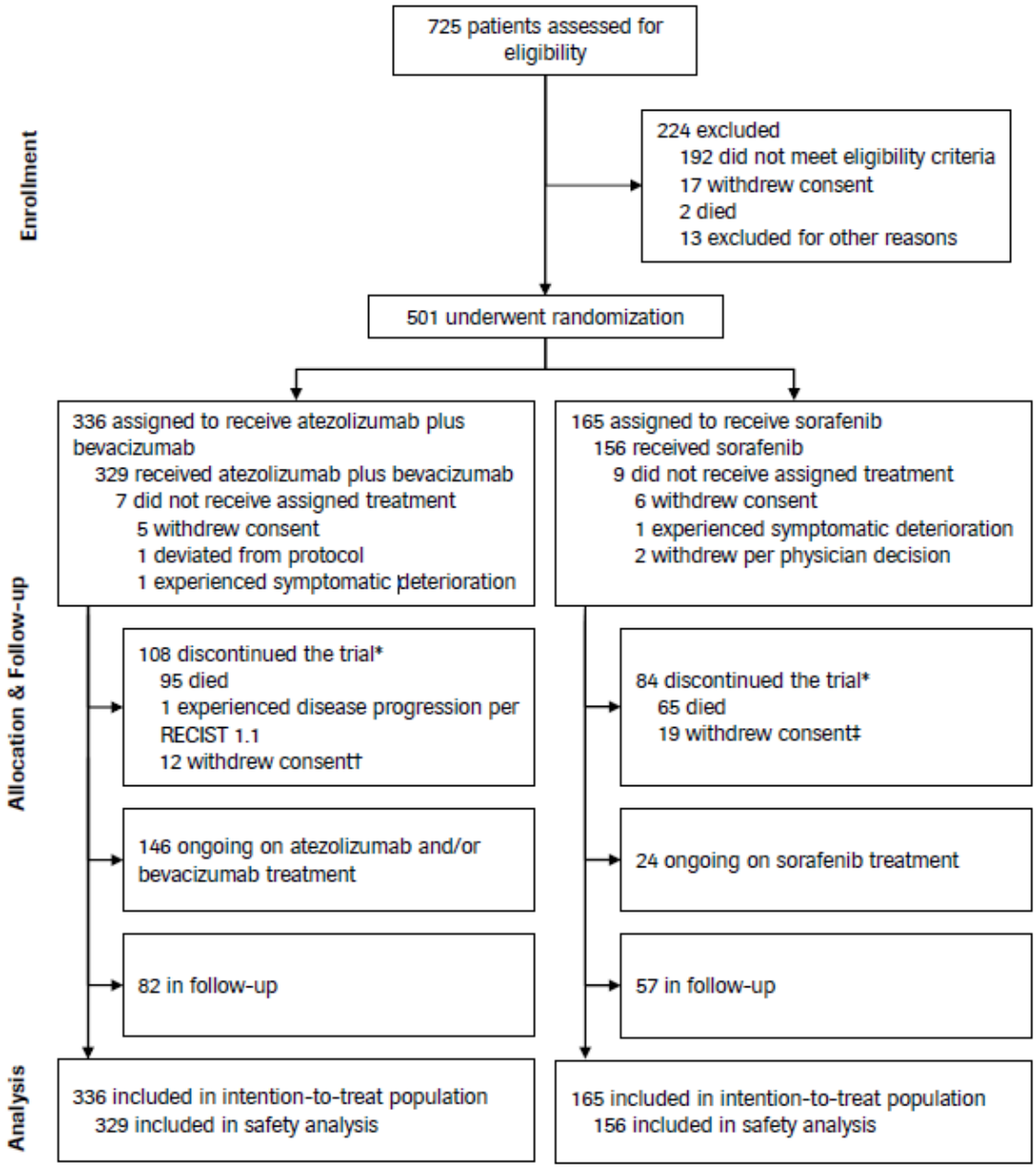
Source: Adapted from Checkpoint Meeting Response, August 6, 2020 (Hoffman La-Roche)[4]

d) Patient Disposition

The patient disposition diagram is outlined in Figure 6. A total of 725 patients were screened and 224 were excluded, mostly due to not meeting eligibility criteria (n=192); 17 patients were excluded due to consent withdrawal, 13 were excluded for other reasons (details unknown), and two patients had died.[3,4] A total of 501 patients were randomized to either atezolizumab plus bevacizumab (n=336) or sorafenib (n=165). Seven patients in the atezolizumab plus bevacizumab group, and nine patients in the sorafenib group did not receive treatment, resulting in a safety population of 485 patients: 329 patients received atezolizumab plus bevacizumab and 156 patients received sorafenib. Of those who received treatment, 183 patients (55.6%) in the atezolizumab plus bevacizumab group and 132 patients (84.6%) in the sorafenib group had discontinued randomized study treatment by the data cut-off date.[2] [redacted][5] Further details on reasons for treatment discontinuation can be found in Table 14. At the time of data cut-off, 146 patients (43.5%) the atezolizumab plus bevacizumab group and 24 patients (14.5%) in the sorafenib group were still continuing at least one component of randomized treatment.[2]
(Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until April 30, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

At the time of data cut-off (median follow-up of 8.6 months), in the ITT population, a total of 108 patients (32.1%) in the atezolizumab plus bevacizumab group and 84 patients (50.9%) in the sorafenib group had withdrawn from the trial completely, mainly due to death. Of those remaining, in the atezolizumab plus bevacizumab treatment group, 146 patients (43.5%) were still receiving treatment (nine were receiving atezolizumab monotherapy and the rest were receiving combination therapy) and 82 patients (24.4%) were in the follow-up phase.[2,3] In the sorafenib treatment group, 24 patients (14.5%) were still receiving treatment, and 57 patients (34.5%) were in follow-up. At the data cut-off date, there were a total of 161 deaths, accounting for 96 patients (28.6%) randomized to atezolizumab plus bevacizumab and 65 patients (39.4%) randomized to sorafenib.[2] In summary, at the data cut-off date, most patients randomized to atezolizumab plus bevacizumab were still enrolled in the study and close to 45% were still receiving treatment, whereas most patients randomized to sorafenib had discontinued the trial, and of those remaining, most were in the follow-up phase (only approximately 15% were still receiving treatment).[2]

Figure 6: Summary of Patient Disposition



RECIST 1.1, Response Evaluation Criteria In Solid Tumors version 1.1.

*Discontinued the study completely. †Including the 5 patients who withdrew consent and were not treated. ‡Including the 6 patients who withdrew consent and were not treated

Source: Supplemental Checkpoint Questions, August 31, 2020 (Hoffman La-Roche).[63]

Table 14: Reasons for Study Treatment Discontinuation, Safety Population

Source: Clinical Study Report; Table 8, Pg.82[5]

(Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until April 30, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

Protocol Deviations: [redacted].[5] Regarding the latter category, specific deviations in the atezolizumab plus bevacizumab group included missing components of lab panels, missing urinalysis (for patients on bevacizumab), missing HCV or HBV tests, slightly out of window lab tests, as well as missing source documents. The difference in proportion of patients (i.e., slightly higher in the atezolizumab plus bevacizumab group) was deemed by the study sponsors to ultimately not have an impact on the study's integrity, or the safety and efficacy results as well as main conclusions.[3] [redacted].[5]

(Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until April 30, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

e) Limitations/Sources of Bias

Overall, the IMbrave150 trial was a well-designed RCT and there were no major concerns with the conduct of the trial. Measured outcomes were clinically important and relevant to patients with HCC. The randomization method and sample size were adequate, and a stratified randomization procedure was used based on known prognostic factors to minimize potential imbalances between the study groups that might lead to biased results. Eligibility criteria were well defined and appropriate. The study population characteristics overall reflect patients who would be eligible for systemic treatment for HCC in Canada, although there were a slightly higher number of Asian patients (56.7%), patients with prior liver resection (28.7%), and HBV etiology (47.9%) than generally seen in

the Canadian patient population. The populations used for analyses were appropriate, with the key efficacy analysis conducted according to the ITT principle. The study protocol was approved by institutional review boards or ethics committees at each study center and the trial was conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. Unmasked safety and trial conduct data were reviewed by an independent data monitoring committee approximately every six months. However, there are a few key limitations and potential sources of bias that were noted by the CADTH Methods Team, as outlined below.

- Due to the open-label study design, the investigators and patients were aware of the treatment allocation. It is possible that due to this knowledge of the assigned treatment, the trial results may be at risk for biases related to the lack of blinding which can affect the measurement and reporting of outcomes. Accordingly, the results may be biased in favour of the atezolizumab plus bevacizumab group compared to the sorafenib group. This could be particularly important in the reporting of subjective outcomes (e.g., adverse effects, patient-reported symptoms and outcomes) by the patients and care providers. However, treatment response and disease progression were measured by a central, blinded independent review facility to reduce investigator bias. Rationale for the open-label study design was to spare patients in the sorafenib group from receiving placebo infusions and surmised that that the unique toxicity profile of each treatment may lead to identification of treatment assignment even in a blinded study, which are reasonable considerations.
- To account for interim analyses as well as co-primary and key secondary endpoints, overall Type I error rate was appropriately controlled using a graphical approach. There were many predefined subgroup analyses and multiple secondary efficacy outcomes assessed in the trial that were not adjusted to account for multiple comparison testing to control the risk of Type I error. The trial was not powered to test specific hypotheses in these additional subgroups and outcomes; therefore, results of the subgroup analyses should be interpreted as exploratory in nature. Analyses of secondary endpoints (other than ORR-IRF per RECIST v1.1 and HCC mRECIST) and exploratory endpoints were also not adjusted for multiplicity; these results may be considered as supplemental to the primary and key secondary endpoints but should also be interpreted with caution.
- Final analysis of OS was scheduled for after 312 deaths, which had yet to occur (161 deaths occurred by data cut-off date).[2] Current OS data is immature and reflects the first interim analysis. As the co-primary OS endpoint was met at the first interim analysis, this analysis was considered as definitive by the study sponsors.[5] Although the study is still ongoing, the event-driven second interim analysis of OS will no longer be performed; instead, a time-driven descriptive OS analysis is planned with a data cut-off date in August 2020, approximately 12 months after the first interim analysis.[4] According to the sponsors, a final descriptive analysis is also under discussion.[6] As median OS had not been reached in the atezolizumab plus bevacizumab group with the current duration of follow-up (median 8.6 months), the absolute difference between the two treatment groups in this endpoint is unknown. The magnitude of benefit over time will need to be confirmed with longer follow-up data, and this change in the pre-specified analysis plan contributes to uncertainty in the degree of sustained effect of atezolizumab plus bevacizumab.
- Although the dose of sorafenib reflects what is recommended in the product monograph[7], prescribers often opt to use a starting dose of 200 mg twice a day to improve tolerability; daily dose is gradually increased as tolerated, until target dose is achieved. Thus, starting patients in the clinical trial at 400mg twice a day may have contributed to more AEs (e.g., diarrhea, fatigue, palmer-planter erythrodysesthesia syndrome) and reduced tolerability compared to what would normally be anticipated in Canadian clinical practice. In the trial, 37.2% of patients treated with sorafenib required a dose adjustment due to an AE.[2]
- Median duration of treatment was 2.8 months for sorafenib, 7.4 months for atezolizumab, and 6.9 months for bevacizumab.[2] The differences in treatment duration between the two groups should be considered when interpreting AEs that may be related to length of exposure, though this may be reflective of the real world.
- Use of concurrent medications were similar between arms; however, dermatologic and anti-diarrheal agents were more common in the sorafenib arm, and analgesics and loop diuretics were more commonly administered to patients randomized to atezolizumab plus bevacizumab, which are reflective of the AEs reported in this study. During the study, anticoagulants were administered to 12.5% of patients in the atezolizumab plus bevacizumab group and 14.1% of patients in the sorafenib group, which may have impacted the risk of bleeding in these patients overall.[5]
- Patients were permitted to continue treatment beyond radiographic disease progression (as measured by RECIST v1.1), given that there was evidence of clinical benefit. During the study, 21.1% of patients (n=71) treated with atezolizumab plus bevacizumab and 12.1% of patients (n=20) treated with sorafenib continued treatment beyond radiographic progression.[4] In an open-label trial setting, this may have contributed to the decision to continue or discontinue treatment, and to the imbalance in the number of patients who received subsequent therapy in each arm.

- During the survival follow-up period, patients were permitted to receive subsequent treatment for HCC, which included TKIs and immunotherapies (18.8% of patients in atezolizumab plus bevacizumab group received a subsequent TKI; 18.8% of patients in the sorafenib group received subsequent immunotherapy). Overall, a higher proportion of patients randomized to sorafenib received subsequent therapy (20.5% atezolizumab plus bevacizumab vs. 44.2% sorafenib, second-line and beyond).[2] This may confound the assessment of OS by prolonging survival beyond what would have occurred with frontline treatment alone and overestimating survival benefit, possibly in favour of sorafenib, though the effects of each treatment arm and the benefit of atezolizumab plus bevacizumab compared to sorafenib were maintained over time.
- PROs were assessed regardless of disease progression and receipt of subsequent anti-cancer therapy in both treatment groups. Thus, QoL data may be confounded by impact of progressed disease and/or subsequent treatment. Although pre-specified, PROs were also not adjusted for multiplicity and thus should only be considered descriptive. Using confirmed readings (e.g., ≥ 10-point deterioration maintained over two consecutive assessments) to identify time to deterioration reduced risk of bias. Compliance rates for the EORTC QLQ-C30 questionnaire in both groups (ITT population) was 93% or greater from baseline until treatment Cycle 17; thereafter, compliance was 80% or greater until discontinuation of remaining treatment.[2] However, fewer than 50% of patients randomized to atezolizumab plus bevacizumab were remaining in the ITT population by Cycle 12, and by Cycle 5 for sorafenib, limiting the data available for analysis beyond this point.[5]

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Efficacy analyses were performed using the ITT population, which included all patients randomized to treatment. At the data cut-off date of August 29, 2019, the overall median duration of follow-up was 8.6 months (8.9 months and 8.1 months in the atezolizumab plus bevacizumab and sorafenib groups, respectively).[2]

Co-Primary Endpoints

a) Overall Survival (OS)

At the data cut-off date, there was a total of 161 deaths: 96 patients (28.6%) in the atezolizumab plus bevacizumab group and 65 patients (39.4%) in the sorafenib group had died. Median OS had not been reached in the atezolizumab plus bevacizumab group; in patients randomized to sorafenib treatment, the estimated median OS was 13.2 months (95% CI, 10.4 to not reached). The corresponding stratified HR for death was 0.58 (95% CI, 0.42 to 0.79, p<0.001). Overall survival was longer in patients randomized to atezolizumab plus bevacizumab, with a six-month survival rate of 84.8% (95% CI, 80.9 to 88.7%) compared to 72.2% (95% CI, 65.1 to 79.4%) in patients randomized to sorafenib treatment. At 12 months, the survival rate for patients in the atezolizumab plus bevacizumab group was 67.2% (95% CI, 61.3 to 73.1%) compared to 54.6% (95% CI, 45.2 to 64.0%) in the sorafenib group.[2]

b) Progression-Free Survival measured by IRF (PFS-IRF), according to RECIST v1.1

At the data cut-off date, there was a total of 306 patients who had experienced disease progression or death: 197 patients (58.6%) in the atezolizumab plus bevacizumab group and 109 patients (66.1%) in the sorafenib group had experienced a PFS event. Disease progression was the main contributor to PFS events, occurring in 48.5% of patients in both treatment groups (n=163 in atezolizumab plus bevacizumab, n=80 in sorafenib); death was the earliest contributing event in 10.1% (34 patients) and 17.6% (29 patients) in the atezolizumab plus bevacizumab and sorafenib groups, respectively. Estimated median PFS was 6.8 months (95% CI, 5.7 to 8.3 months) in the atezolizumab plus bevacizumab group and 4.3 months (95% CI, 4.0 to 5.6 months) in the sorafenib group. The corresponding stratified HR for disease progression or death was 0.59 (95% CI, 0.47 to 0.76, p<0.001).[2] Progression-free survival was also longer in patients randomized to atezolizumab plus bevacizumab, with a six-month PFS rate of 54.5% (95% CI, 49.1 to 60.0%) compared to 37.2% (95% CI, 29.0 to 45.3%) in patients randomized to sorafenib treatment.[2,5] The K-M curves for the co-primary endpoints are shown below.

Figure 7: Kaplan-Meier Analysis for Overall and Progression-free Survival, ITT population

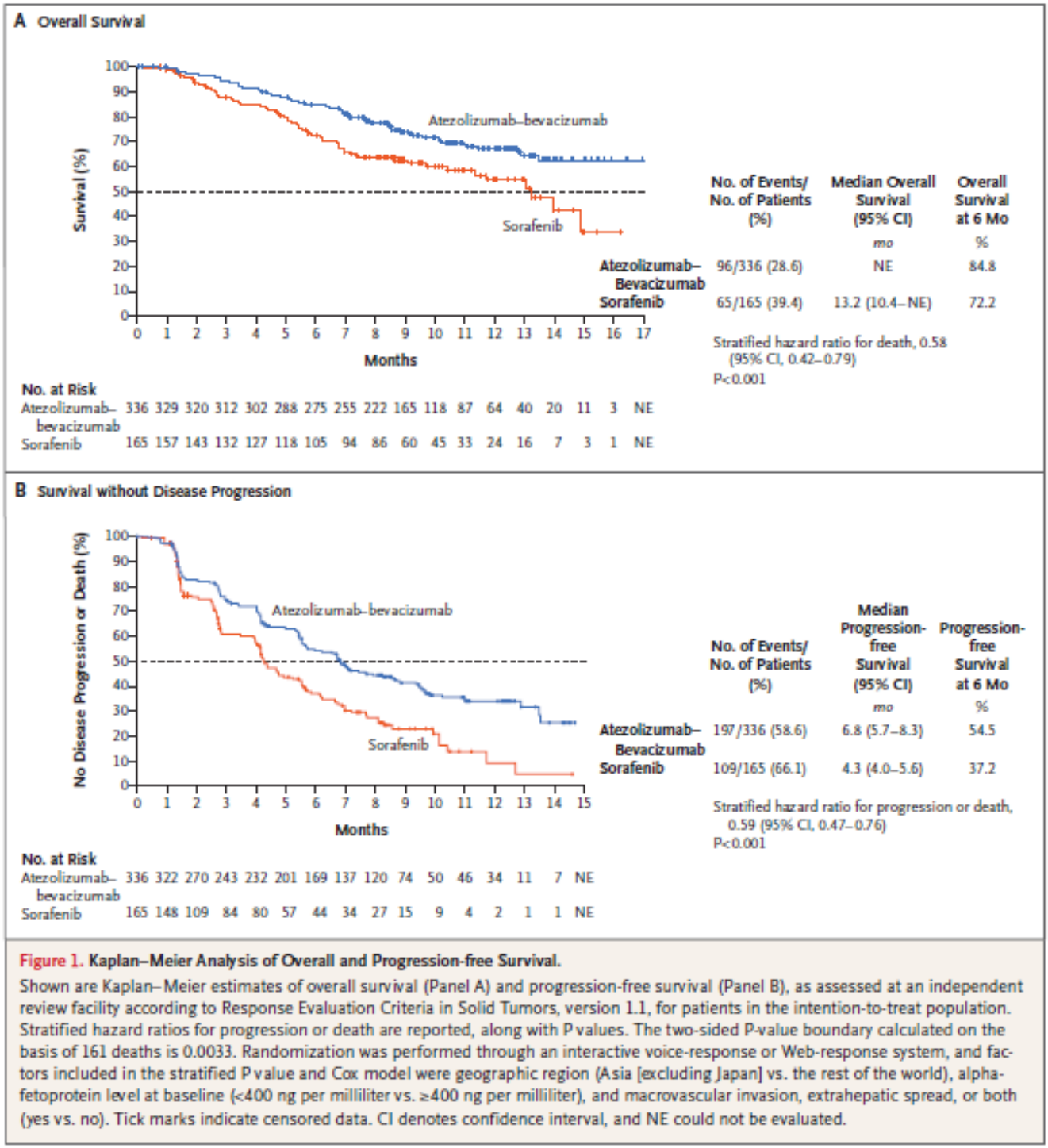


Figure 1. Kaplan–Meier Analysis of Overall and Progression-free Survival.

Shown are Kaplan–Meier estimates of overall survival (Panel A) and progression-free survival (Panel B), as assessed at an independent review facility according to Response Evaluation Criteria in Solid Tumors, version 1.1, for patients in the intention-to-treat population. Stratified hazard ratios for progression or death are reported, along with P values. The two-sided P-value boundary calculated on the basis of 161 deaths is 0.0033. Randomization was performed through an interactive voice-response or Web-response system, and factors included in the stratified P value and Cox model were geographic region (Asia [excluding Japan] vs. the rest of the world), alpha-fetoprotein level at baseline (<400 ng per milliliter vs. ≥400 ng per milliliter), and macrovascular invasion, extrahepatic spread, or both (yes vs. no). Tick marks indicate censored data. CI denotes confidence interval, and NE could not be evaluated.

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Sensitivity and Subgroup Analyses

Unstratified analysis of the co-primary endpoints of OS and PFS-IRF (per RECIST v1.1) were consistent with the stratified analysis results: unstratified HR for OS was 0.60 (95% CI 0.44 to 0.82; p=0.0012) and the unstratified HR for PFS was 0.59 (95% CI, 0.47 to 0.75; p<0.0001). Sensitivity analysis performed to account for missed scheduled tumour assessments also showed results which were consistent with the primary analysis, supporting PFS-IRF benefit for patients randomized to the atezolizumab plus bevacizumab arm ([redacted]).[5] Specifically, 2% of patients in the atezolizumab plus bevacizumab group (n=7) and 5% of patients in the sorafenib group (n=9) had missed two or more consecutive assessment visits prior to date of disease progression or death, thus were censored at the last tumour assessment prior to the most recent visit.[3] The number of patients who experienced a PFS event in this sensitivity analysis was [redacted].[5]

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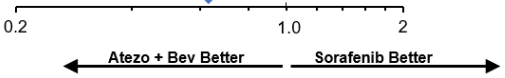
Prespecified subgroup analyses of the co-primary endpoints generally showed a trend of treatment effect favouring atezolizumab plus bevacizumab. For OS, the majority of hazard ratios suggested benefit with atezolizumab plus bevacizumab; however, results for patients with BCLC Stage B (n=78) suggested favourable benefit with sorafenib treatment, with a HR of 1.09 (95% CI 0.33 to 3.53). Also, the confidence intervals crossed 1.0 for several subgroups, with the most significant crossovers seen in patients with no EHS at study entry, no MVI and/or EHS at study entry, and with nonviral etiology of HCC (see Figure 8A). For PFS, all hazard ratio point estimates suggested benefit with atezolizumab plus bevacizumab, though confidence intervals also crossed 1.0 for several subgroups. The most significant crossovers were seen for patients with BCLC Stage B, AFP ≥ 400 ng/mL, no MVI and/or EHS at study entry, and hepatitis C associated HCC (see Figure 8B). Subgroups where the confidence interval included unity (1.0) for both OS and PFS were: BCLC Stage B, AFP ≥ 400 ng/mL, no MVI and/or EHS at baseline, and nonviral etiology of HCC. However, the small sample sizes and corresponding wide confidence intervals contribute to the uncertainty and difficulty in drawing definitive conclusions. Also, the study was not powered to detect differences in subgroups; thus, results should be interpreted with caution.[2]

Figure 8: Subgroup Analysis for Overall and Progression-Free Survival, ITT population

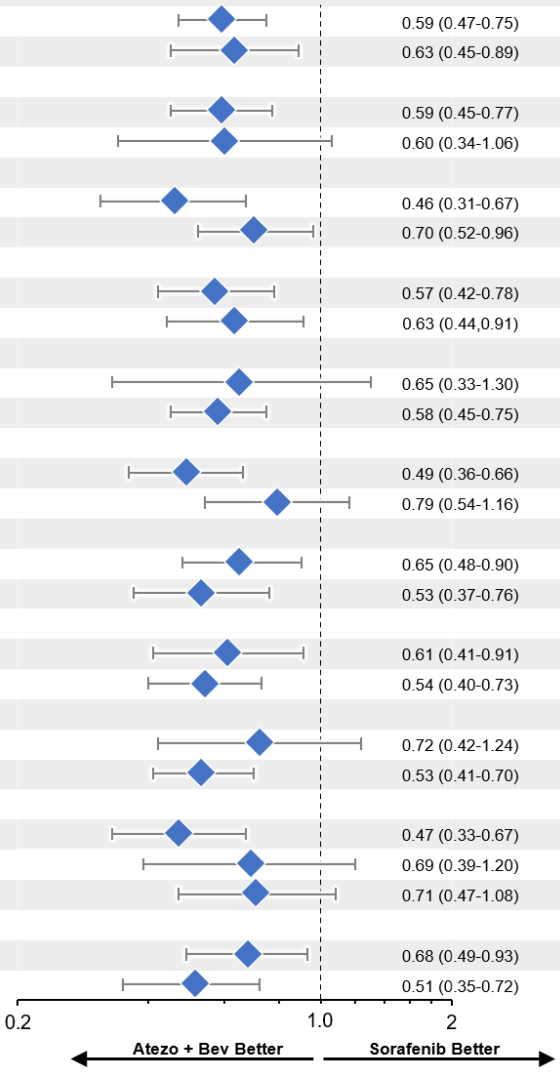
A. Overall Survival

Subgroup	No. of Patients	No. of Events Atezo + Bev	No. of Events Sorafenib	Hazard Ratio for Death (95% CI)
All patients	501	96	65	0.60 (0.44-0.82)
Age ≥65 years	252	39	32	0.58 (0.36-0.92)
Sex				
Male	414	86	53	0.66 (0.47-0.92)
Female	87	10	12	0.35 (0.15-0.81)
Geographic region				
Asia (excluding Japan)	201	34	27	0.53 (0.32-0.87)
Rest of world	300	62	38	0.65 (0.44-0.98)
ECOG performance status score				
0	312	50	31	0.67 (0.43-1.06)
1	189	46	34	0.51 (0.33-0.80)
Barcelona Clinic liver cancer stage				
B	78	9	4	1.09 (0.33-3.53)
C	409	86	61	0.54 (0.39-0.75)
AFP category				
<400 ng/ml	314	45	36	0.52 (0.34-0.81)
≥400 ng/ml	187	51	29	0.68 (0.43-1.08)
MVI at study entry				
No	301	47	29	0.64 (0.40-1.02)
Yes	200	49	36	0.58 (0.38-0.89)
Extrahepatic spread at study entry				
No	196	29	20	0.77 (0.43-1.36)
Yes	305	67	45	0.50 (0.34-0.73)
MVI and/or EHS at study entry				
No	123	12	9	0.69 (0.29-1.65)
Yes	378	84	56	0.55 (0.39-0.77)
Etiology				
Hepatitis B	240	44	31	0.51 (0.32-0.81)
Hepatitis C	108	18	15	0.43 (0.22-0.87)
Nonviral	153	34	19	0.91 (0.52-1.60)
Prior local therapy				
No	255	55	37	0.57 (0.38-0.87)
Yes	246	41	28	0.63 (0.39-1.01)



B. Progression-Free Survival

Subgroup	No. of Patients	No. of Events Atezo + Bev	No. of Events Sorafenib	Hazard Ratio for Progression or Death (95% CI)
All patients	501	197	109	0.59 (0.47-0.75)
Age ≥65 years	252	88	58	0.63 (0.45-0.89)
Sex				
Male	414	161	90	0.59 (0.45-0.77)
Female	87	36	19	0.60 (0.34-1.06)
Geographic region				
Asia (excluding Japan)	201	75	46	0.46 (0.31-0.67)
Rest of world	300	122	63	0.70 (0.52-0.96)
ECOG performance status score				
0	312	113	61	0.57 (0.42-0.78)
1	189	84	48	0.63 (0.44,0.91)
Barcelona Clinic liver cancer stage				
B	78	22	13	0.65 (0.33-1.30)
C	409	172	95	0.58 (0.45-0.75)
AFP category				
<400 ng/ml	314	109	70	0.49 (0.36-0.66)
≥400 ng/ml	187	88	39	0.79 (0.54-1.16)
MVI at study entry				
No	301	116	58	0.65 (0.48-0.90)
Yes	200	81	51	0.53 (0.37-0.76)
Extrahepatic spread at study entry				
No	196	63	41	0.61 (0.41-0.91)
Yes	305	134	68	0.54 (0.40-0.73)
MVI and/or EHS at study entry				
No	123	36	21	0.72 (0.42-1.24)
Yes	378	161	88	0.53 (0.41-0.70)
Etiology				
Hepatitis B	240	98	53	0.47 (0.33-0.67)
Hepatitis C	108	39	19	0.69 (0.39-1.20)
Nonviral	153	60	37	0.71 (0.47-1.08)
Prior local therapy				
No	255	108	59	0.68 (0.49-0.93)
Yes	246	89	50	0.51 (0.35-0.72)



AFP = α-fetoprotein; atezo = atezolizumab; bev = bevacizumab; ECOG = Eastern Cooperative Oncology Group; EHS = extrahepatic spread; MVI = macrovascular invasion.

Forest plot of subgroup analysis of overall survival (panel A) and progression-free survival (panel B) in the intention-to-treat population by baseline demographic and disease characteristics. Hazard ratios are from unstratified analyses. Confidence intervals for subgroup analyses are not adjusted for multiple comparisons. Barcelona Clinic liver cancer stage A is not shown because there were only 14 patients and the estimation was not meaningful.

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Key Secondary Outcomes: As results for PFS were statistically significant, objective response rates, as measured by IRF (ORR-IRF), were tested sequentially. The number of patients in the ITT population with measurable disease at baseline, according to RECIST v1.1, was 326 and 159 for the atezolizumab plus bevacizumab and sorafenib groups, respectively; when objective response (OR) was measured with HCC mRECIST, there was one less patient in each treatment group (i.e. 325 and 158 patients). The confirmed ORR-IRF according to RECIST v1.1 was 27.3% (95% CI, 22.5 to 32.5) in the atezolizumab plus bevacizumab group and

11.9% (95% CI, 7.4 to 18.0) in the sorafenib group, reflecting a 15.4% difference favouring atezolizumab plus bevacizumab (p<0.001). Similarly, the confirmed ORR-IRF according to HCC mRECIST was 33.2% (95% CI, 28.1 to 38.6) and 13.3% (95% CI, 8.4 to 19.6) in patients randomized to atezolizumab plus bevacizumab and sorafenib, respectively, reflecting a 19.9% difference in favour of atezolizumab plus bevacizumab treatment (p<0.001).[2]

Of patients who experienced a confirmed OR, a greater proportion of patients in both treatment groups achieved partial response than complete response. For ORR according to RECIST v1.1, 21.8% of patients (n=71) in the atezolizumab plus bevacizumab arm achieved partial response and 5.5% (n=18) achieved complete response. In patients randomized to sorafenib, 11.9% (n=19) achieved partial response while none experienced complete response. At the data cut-off date, a higher proportion of patients in the atezolizumab plus bevacizumab group were experiencing ongoing OR compared to patients randomized to sorafenib (86.5%%, n=77 of 89 in atezolizumab plus bevacizumab vs. 68.4%, n=13 of 19 in sorafenib group). Of the disease response categories, stable disease was achieved by the highest proportion of patients in both treatment groups (46.3% atezolizumab plus bevacizumab, 43.4% sorafenib); followed by partial response in patients treated with atezolizumab plus bevacizumab (21.8%) and progressive disease in patients treated with sorafenib (24.5%). A similar pattern was seen for ORR according to HCC mRECIST, though a higher proportion of patients in both treatment groups experienced complete response, and a lower proportion of patients in both arms had ongoing OR at the time of data cut-off compared to ORR measured according to RECIST v1.1.[2] Details of disease response can be found in Table 15 below.

Table 15: Secondary Efficacy Outcomes – Disease Response, ITT population with measurable disease at baseline

Table 2. Secondary Efficacy Outcomes.*

Variable	RECIST 1.1			HCC-Specific mRECIST		
	Atezolizumab–Bevacizumab (N=326)	Sorafenib (N=159)	Difference (P Value)†	Atezolizumab–Bevacizumab (N=325)	Sorafenib (N=158)	Difference (P Value)†
Confirmed objective response — no. (% [95% CI])‡	89 (27.3 [22.5–32.5])	19 (11.9 [7.4–18.0])	15.4 (<0.001)	108 (33.2 [28.1–38.6])	21 (13.3 [8.4–19.6])	19.9 (<0.001)
Complete response — no. (%)	18 (5.5)	0		33 (10.2)	3 (1.9)	
Partial response — no. (%)	71 (21.8)	19 (11.9)		75 (23.1)	18 (11.4)	
Stable disease — no. (%)	151 (46.3)	69 (43.4)		127 (39.1)	66 (41.8)	
Disease control rate — no. (%)§	240 (73.6)	88 (55.3)		235 (72.3)	87 (55.1)	
Progressive disease — no. (%)	64 (19.6)	39 (24.5)		66 (20.3)	40 (25.3)	
Could not be evaluated — no. (%)	8 (2.5)	14 (8.8)		10 (3.1)	14 (8.9)	
Data missing — no. (%)	14 (4.3)	18 (11.3)		14 (4.3)	17 (10.8)	
Ongoing objective response at data cutoff — no./total no. (%)	77/89 (86.5)	13/19 (68.4)		84/108 (77.8)	13/21 (61.9)	

* Included are patients who presented with measurable disease according to the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1), and according to hepatocellular carcinoma (HCC)–specific modified RECIST (mRECIST), as assessed at an independent review facility. CI denotes confidence interval.
† The difference is the between-group difference (atezolizumab–bevacizumab minus sorafenib) in the percentage of patients with confirmed response, expressed in percentage points. The P value was derived from a Cochran–Mantel–Haenszel test. Randomization, which was performed through an interactive voice-response or Web-response system, included as stratification factors geographic region (Asia excluding Japan vs. the rest of the world), alpha-fetoprotein level (<400 ng per milliliter vs. ≥400 ng per milliliter) at baseline, and macrovascular invasion, extrahepatic spread, or both (yes vs. no).
‡ Confirmed objective response was defined as a response (complete or partial) seen at two consecutive tumor assessments at least 28 days apart.
§ The control rate is the sum of complete response, partial response, and stable disease.

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Secondary Endpoints Relevant to Current Review

PFS measured by IRF (PFS-IRF), according to HCC mRECIST: [redacted]

[redacted][5]

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TTP measured by IRF (TTP-IRF), according to RECIST v1.1: [redacted][5]

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Results of TPP-IRF measured using HCC mRECIST were similar to TPP-IRF according to RECIST v1.1.

Quality of Life

Patient-reported outcomes measuring TTD in three specific EORTC QLQ-C30 subscales (i.e., GHS/QoL, Physical functioning, and Role functioning) were considered as secondary endpoints; other analyses such as mean change in score from baseline or proportion of patients with clinically meaningful change in select scores were considered exploratory.

Compliance rates (i.e., completion of at least one question) for the EORTC QLQ-C30 questionnaire in the ITT population was 93% or greater from baseline until treatment Cycle 17; thereafter, compliance was 80% or greater until discontinuation of remaining treatment.[2] [redacted][3] However, fewer than 50% of patients randomized to atezolizumab plus bevacizumab were remaining in the ITT population by Cycle 12, and by Cycle 5 for sorafenib. Baseline scores for GHS/QoL, physical functioning, and role functioning were comparable between the two treatment arms, with mean (with standard deviation) scores as follows:[5]

- GHS/QoL: 71.04 (21.07) atezolizumab plus bevacizumab vs. 68.79 (21.20) sorafenib
- Physical functioning: 85.73 (16.32) atezolizumab plus bevacizumab vs. 84.82 (17.75) sorafenib
- Role functioning: 85.01 (23.03) atezolizumab plus bevacizumab vs. 85.75 (21.60) sorafenib

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Compared to treatment with sorafenib, atezolizumab plus bevacizumab showed a clinically meaningful delay in deterioration of GHS/QoL, physical functioning, and role functioning subscales. Specifically, for the GHS/QoL subscale, median TTD was 11.2 months with atezolizumab plus bevacizumab compared to 3.6 months with sorafenib (HR 0.63; 95% CI, 0.46 to 0.85). For the physical functioning subscale, median time to deterioration was 13.1 months and 4.9 months for atezolizumab plus bevacizumab and sorafenib groups, respectively (HR 0.53; 95% CI, 0.39 to 0.73), and median time to deterioration for the role functioning subscale was 9.1 months compared to 3.6 months for the atezolizumab plus bevacizumab and sorafenib groups, respectively (HR 0.62; 95% CI, 0.46 to 0.84).[2]

Exploratory analysis of TTD for patient-reported symptoms of anorexia, diarrhea, fatigue, and pain, also showed clinically meaningful delay in patients treated with atezolizumab plus bevacizumab compared to those who received sorafenib. Mean change in scores, measured from baseline through Cycle 5, when fewer than 50% of patients randomized to sorafenib remained, also showed a favourable trend (i.e., less significant deterioration in symptoms, functioning, and QoL) for patients randomized to the atezolizumab plus bevacizumab group.[5]

Harms Outcomes

Adverse Events (AEs): AEs were evaluated in the safety population, comprised of 329 patients in the atezolizumab plus bevacizumab group and 156 patients in the sorafenib group.[2]

AEs of any grade, due to any cause, were reported in 98.2% (n=323) and 98.7% (n=154) of patients in the atezolizumab plus bevacizumab and sorafenib groups, respectively.[2] Reported events were consistent with the known AE profile of atezolizumab and bevacizumab except for peripheral edema which occurred in [redacted], though were of Grade 1 or 2 severity and considered non-serious.[5] Severe AEs of Grade 3 or 4 occurred in 56.5% (n=186) of patients in the atezolizumab plus bevacizumab group and 55.1% (N=86) in the sorafenib group. Serious adverse events (SAEs) were seen in 38.0% of patients (n=125) treated with atezolizumab plus bevacizumab, and 30.8% of patients (n=48) treated with sorafenib. Though SAEs occurred more frequently in the atezolizumab plus bevacizumab group, no specific cause was identified; the difference in incidence of identified SAEs were less than 2% between treatment groups.[2] Hospitalizations due to an adverse event occurred in a greater proportion of patients treated with atezolizumab plus bevacizumab (35.3%; n=114) compared to sorafenib (28.6%; n=44).[4]
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Treatment-Related Adverse Events: AEs of any grade deemed related to treatment occurred in 83.9% of patients (n=276) treated with atezolizumab plus bevacizumab and 94.2% of patients (n=147) who received sorafenib. The frequency of adverse effects attributed to each component of the atezolizumab plus bevacizumab combination was similar; 252 patients (76.6%) had at least one AE related to atezolizumab, and similarly, 241 patients (73.3%) experienced at least one AE related to the bevacizumab component. Grade 3-4 treatment-related AEs were reported in 35.6% of patients (n=117) in the atezolizumab plus bevacizumab group and 45.5% of patients (n=71) in the sorafenib group.[5] The most common treatment-related AE of any grade and of Grade 3 or 4 in severity are seen in Table 16. Briefly, the most common (≥ 10%) treated-related AEs of any grade in the atezolizumab plus bevacizumab group were hypertension (23.7%), proteinuria (18.8%), fatigue (15.2%), elevated AST (14.0%), pruritis (13.1%), infusion-related reaction (10.9%), diarrhea (10.3%), elevated ALT (10.3%), and reduced appetite (10.3%). In patients who received sorafenib, the most common (≥ 10%) treatment-related AEs of any grade were palmer-planter erythrodysesthesia syndrome (48.1%), diarrhea (42.9%), hypertension (19.9%), reduced appetite (19.9%), rash (16.7%), fatigue (15.4%), alopecia (13.5%), nausea (12.8%) and asthenia (10.3%). The most commonly reported (≥ 5%) grade 3 or 4 treatment-related AE in the atezolizumab plus bevacizumab group was hypertension (10.3%); the most common (≥ 5%) grade 3 or 4 treatment-related AEs in the sorafenib group were hypertension (9.0%) and palmer-plantar erythrodysesthesia syndrome (8.3%). Furthermore, of the Grade 3 or 4 treatment-related AEs, a higher incidence (≥2% difference) of the following were reported in the atezolizumab plus bevacizumab group: increased AST, increased ALT, proteinuria, and infusion-related reactions. A higher incidence (by ≥ 2%) of palmer-plantar erythrodysesthesia syndrome, diarrhea, reduced appetite, hypophosphatemia, rash, reduced bilirubin was reported in patients treated with sorafenib. Of the atezolizumab plus bevacizumab combination, infusion-related reactions as well as elevated AST and ALT were reported more frequently with the atezolizumab component, whereas hypertension and proteinuria were attributed more often to the bevacizumab component.[2]

[redacted][5]

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Table 16: Treatment-Related Adverse Events, Safety Population

Treatment-Related Adverse Events with an Incidence of ≥10% of Any Grade, or Events of Grade 3 or 4 with an Incidence of ≥2% in Either Group, n (%)	Atezolizumab plus Bevacizumab (n = 329)		Sorafenib (n = 156)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Hypertension	78 (23.7)	34 (10.3)	31 (19.9)	14 (9.0)
Proteinuria	62 (18.8)	9 (2.7)	7 (4.5)	1 (0.6)
Fatigue	50 (15.2)	5 (1.5)	24 (15.4)	5 (3.2)
Aspartate aminotransferase increase	46 (14.0)	14 (4.3)	11 (7.1)	4 (2.6)
Pruritus	43 (13.1)	0	13 (8.3)	0
Infusion-related reaction	36 (10.9)	7 (2.1)	0	0
Diarrhea	34 (10.3)	1 (0.3)	67 (42.9)	6 (3.8)
Alanine aminotransferase increase	34 (10.3)	7 (2.1)	4 (2.6)	0
Decreased appetite	33 (10.0)	2 (0.6)	31 (19.9)	6 (3.8)
Rash	29 (8.8)	0	26 (16.7)	4 (2.6)
Platelet count decrease	27 (8.2)	8 (2.4)	15 (9.6)	1 (0.6)
Blood bilirubin increase	27 (8.2)	2 (0.6)	9 (5.8)	4 (2.6)
Nausea	21 (6.4)	0	20 (12.8)	0
Asthenia	11 (3.3)	0	16 (10.3)	3 (1.9)
Alopecia	3 (0.9)	0	21 (13.5)	0
Palmar-plantar erythrodysesthesia syndrome	2 (0.6)	0	75 (48.1)	13 (8.3)
Hypophosphatemia	3 (0.9)	1 (0.3)	7 (4.5)	5 (3.2)

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AEs of Special Interest: A higher proportion of patients treated with sorafenib (82.1%, n=128) experienced an AE deemed to be of special interest by trial investigators, compared to those treated with atezolizumab plus bevacizumab (68.7%, n=226). The most significant differences were seen in the incidence of rash related to sorafenib; hypothyroidism and infusion-related reactions associated with atezolizumab; and hypertension, hemorrhage, and proteinuria, more frequently related to bevacizumab use.[2] Details of these AEs of special interest, regardless of cause, can be seen in Table 17. Of patients who experienced an AE of special interest, a greater proportion of patients treated with atezolizumab plus bevacizumab than sorafenib (12.2% vs. 3.2%) received systemic corticosteroid treatment within 30 days of the AE onset.[5]

Immune-mediated AEs were also captured as part of the AEs of special interest and occurred in both treatment arms. Of the most frequently reported AEs of special interest, a higher incidence of immune-mediated rash occurred in the sorafenib arm (19.5% atezolizumab plus bevacizumab vs. 61.5% sorafenib) and immune-mediated hypothyroidism was more frequent in the atezolizumab plus bevacizumab arm (10.9% vs. 2.6%). Incidence of immune-mediated hepatitis was comparable between the two treatment groups. Approximately 40% of patients in each group (43.2% atezolizumab plus bevacizumab vs. 39.7% sorafenib) experienced an event categorized under immune-mediated hepatitis which included diagnosis of hepatitis and liver function test abnormalities. Of patients who experienced immune-mediated hepatitis, a clinical diagnosis of was made in approximately 13% of patients in both groups. Overall, compared to the known safety profile of atezolizumab, a higher incidence than anticipated was reported for immune-related hepatitis, immune-related hyperthyroidism (4.6%), and immune-mediated diabetes mellitus (2.4%).[5]

Bleeding/hemorrhage was noted as an AE of special interest for bevacizumab. A higher proportion of patients in the atezolizumab plus bevacizumab group (25.2%) had experienced bleeding/ hemorrhage compared to patients treated with sorafenib (17.3%). Most were of Grade 1 or 2 in severity; 6.4% and 5.7% in the atezolizumab plus bevacizumab and sorafenib groups, respectively, had experienced Grade 3-4 hemorrhage. Five patients (1.5%) in the atezolizumab plus bevacizumab group and one patient (0.6%) in the sorafenib group and had experienced Grade 5 bleeding/hemorrhage. Of the fatal events in patients who received atezolizumab plus

bevacizumab, GI hemorrhage was responsible in three patients, and esophageal varices bleed and subarachnoid hemorrhage were responsible in one patient, each. Serious bleeding/hemorrhage was reported in 9.1% of patients treated with atezolizumab plus bevacizumab and 7.7% of patients who received sorafenib. Study treatment was discontinued due to hemorrhage in 16 patients (4.9%) in the atezolizumab plus bevacizumab group and one patient (0.6%) in the sorafenib groups.[5] Specific to upper GI bleed (which included the events of GI hemorrhage, upper GI hemorrhage, esophageal hemorrhage, esophageal varices hemorrhage, gastric varices hemorrhage, and gastric ulcer hemorrhage), the incidence was 7% in the atezolizumab plus bevacizumab group and 4.5% in the sorafenib group.[2,64]

Table 17: Adverse Events of Special Interest, Safety Population

All-Causality Adverse Events of Special Interest by Medical Concept*	Atezolizumab plus Bevacizumab (n = 329)		Sorafenib (n = 156)	
Atezolizumab related, n (%)	**All grade**	**Grade 3 or 4**	**All grade**	**Grade 3 or 4**
Patients with at least one event	226 (68.7)	85 (25.8)	128 (82.1)	47 (30.1)
Hepatitis (diagnosis, laboratory abnormality)†	142 (43.2)	70 (21.3)	62 (39.7)	26 (16.7)
Hepatitis (laboratory abnormality)†	126 (38.3)	55 (16.7)	54 (34.6)	22 (14.1)
Hepatitis (diagnosis)†	43 (13.1)	23 (7.0)	20 (12.8)	8 (5.1)
Rash	64 (19.5)	2 (0.6)	96 (61.5)	21 (13.5)
Hypothyroidism	36 (10.9)	0	4 (2.6)	0
Infusion-related reaction	36 (10.9)	8 (2.4)	0	0
Hyperthyroidism	15 (4.6)	1 (0.3)	0	0
Pancreatitis	9 (2.7)	3 (0.9)	6 (3.8)	5 (3.2)
Diabetes mellitus	8 (2.4)	1 (0.3)	0	0
Colitis	6 (1.8)	2 (0.6)	1 (0.6)	1 (0.6)
Pneumonitis	4 (1.2)	0	0	0
Nephritis	3 (0.9)	2 (0.6)	0	0
Systemic immune activation	1 (0.3)	1 (0.3)	0	0
Autoimmune hemolytic anemia	1 (0.3)	0	0	0
Adrenal insufficiency	1 (0.3)	0	0	0
Ocular inflammatory toxicity	1 (0.3)	0	0	0
Severe cutaneous reactions	0	0	1 (0.6)	1 (0.6)
Vasculitis	1 (0.3)	0	0	0
Bevacizumab related, n (%)				
Patients with at least one event	190 (57.8)	76 (23.1)	76 (48.7)	29 (18.6)
Hypertension	102 (31.0)	50 (15.2)	40 (25.6)	19 (12.2)
Bleeding/hemorrhage	83 (25.2)	21 (6.4)	27 (17.3)	9 (5.8)
Proteinuria	70 (21.3)	10 (3.0)	13 (8.3)	1 (0.6)
Thromboembolic event–venous	10 (3.0)	5 (1.5)	5 (3.2)	2 (1.3)
Thromboembolic event–arterial	9 (2.7)	4 (1.2)	2 (1.3)	1 (0.6)
Congestive heart failure	1 (0.3)	0	2 (1.3)	0
Wound healing complications	2 (0.6)	1 (0.3)	0	0
Fistula/abscess (nongastrointestinal)	0	0	1 (0.6)	0
Gastrointestinal perforation	1 (0.3)	0	0	0

* Grouped Medical Dictionary for Regulatory Activities (MedDRA) preferred terms.

† Hepatitis (diagnosis) (e.g., hepatic failure, liver injury, etc.) and hepatitis (laboratory abnormality) (e.g., alanine aminotransferase increase, blood bilirubin increase, etc.) were grouped per MedDRA preferred terms based on adverse event terms reported by the investigators.

Source: From N Engl J Med, Finn et al., 382:1894-905. Copyright © 2020 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[2]

Treatment Modification or Discontinuation Due to Adverse Event: A higher proportion of patients treated with sorafenib (60.9%, n=95) required a dose modification or interruption due to an adverse event compared to patients treated with atezolizumab plus bevacizumab (49.5%, n=163). Since dose modification to address AEs was not permitted in the atezolizumab plus bevacizumab group, all 163 patients had experienced interruption of treatment. In the sorafenib arm, 41.0% of patients (n=64) experienced a

treatment interruption, and 37.2% of patients (n=58) had a dose adjustment due to an AE.[2] [redacted][5]

(Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this safety information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until April 30, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

Study treatment was discontinued due to an adverse event in 15.5% of patients (n=51) treated with atezolizumab plus bevacizumab and 10.3% of patients (n=16) treated with sorafenib. Of patients who discontinued atezolizumab plus bevacizumab, 7.0% (n=23) had both components withdrawn, and 8.5% of patients (n=28) discontinued only one of the two agents in the combination. Patients experienced an adverse event that led to discontinuation of bevacizumab (14.6%, n=48) more often than atezolizumab (8.5%, n=28). Main reasons for discontinuation of atezolizumab were autoimmune hepatitis, GI hemorrhage, increased transaminases, or infusion-related reactions, whereas bevacizumab was most frequently discontinued due to GI hemorrhage, esophageal hemorrhage, esophageal varices hemorrhage, or proteinuria. Discontinuation of sorafenib was largely due to dermatological reactions (e.g., rash, toxic skin eruption) or related to hepatic adverse effects (e.g., hepatic cirrhosis, elevated liver function tests).[2] [redacted][5]

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Deaths Due to Adverse Event: At data cutoff, 4.6% and 5.8% of patients in the atezolizumab plus bevacizumab (n=15) and sorafenib (n=9) groups, respectively, had experienced a fatal AE (i.e., Grade 5).[2] [redacted][5]

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China Subpopulation Analysis

The IMbrave150 study included a subpopulation that enrolled patients with Chinese ancestry and residence in Mainland China, Hong Kong, or Taiwan with enrollment sites recognized by the China FDA. The trial aimed to include approximately 135 patients in this subpopulation and had an extended recruitment period beyond the global enrollment phase to achieve this number. Patients were also randomized in a 2:1 ratio, received the same treatment, and followed the same schedule of activities as the global study population. A subgroup analysis based on the China subpopulation was performed, including patients from both enrollment phases. As with the global population, the primary efficacy objective of this subpopulation was to compare efficacy of atezolizumab plus bevacizumab to sorafenib, using the co-primary endpoints of PFS-IRF per RECIST v1.1 and OS. However, no formal hypothesis testing was performed as the China subpopulation was not powered to demonstrate statistical significance. Analyses were to be conducted when enough PFS and/or OS events had occurred to demonstrate ≥ 80% probability of maintaining 50% risk reduction compared to what was estimated from the global population. The PFS analysis was predicted to occur at the time of primary PFS analysis for the global population. Methods of analyses were the same for the China subpopulation as the global population; however, as all patients were recruited from the same geographical region, only macrovascular invasion (presence vs. absence) and

baseline AFP level (< 400 vs. ≥ 400 ng/mL) were used as factors in the stratified analyses. Results, briefly discussed below, were summarized separately from the global population and is currently only available in abstract form.[2]

In total, 194 patients were enrolled in the China subpopulation (137 from global enrollment phase and 57 from the extension phase), with 133 patients randomized to atezolizumab plus bevacizumab treatment and 61 randomized to sorafenib. Compared to the global population, patients in the Chinese subpopulation had higher rates of HBV, macrovascular invasion and/or hepatic spread, as well as α-fetoprotein levels ≥ 400 ng/mL. In addition, the Chinese subpopulation had a higher proportion of patients with BCLC Stage C disease. Overall, baseline demographics were balanced between the two treatment arms.[61]

Results of the co-primary endpoint analysis in the China subpopulation were overall consistent with the global population. The median duration of treatment was 6.0 months for atezolizumab, 5.5 months for bevacizumab, and 2.8 months for sorafenib. At a median follow-up of 7.2 months for atezolizumab plus bevacizumab and 5.6 months for sorafenib, the stratified HR for OS was 0.44 (95% CI, 0.25 to 0.76). The median PFS-IRF according to RECIST v1.1 was 5.7 months for atezolizumab plus bevacizumab and 3.2 months for sorafenib, with a stratified HR of 0.60 (95% CI, 0.40 to 0.90). The ORR-IRF according to RECIST v1.1 was 25% for atezolizumab plus bevacizumab and 7% for sorafenib, whereas ORR-IRF according to HCC mRECIST was 30% for atezolizumab plus bevacizumab and 9% for sorafenib. Time to deterioration in quality of life was also delayed by atezolizumab plus bevacizumab compared to sorafenib.[61]

The safety population consisted of 132 patients in the atezolizumab plus bevacizumab group, and 58 patients in the sorafenib group. AEs of Grade 3 or 4 severity were reported in 59% of patients treated with atezolizumab plus bevacizumab and 47% of patients treated with sorafenib. Fatal (Grade 5) AEs occurred in 2% of patients in the atezolizumab plus bevacizumab group and 3% of patients in the sorafenib group. In each group, treatment withdrawal due to AE occurred in 2% of patients.[61]

6.4 Ongoing Trials

One trial was identified as potentially relevant to this review. The study (NCT04180072)[66] is a phase II, open-label, single-arm trial investigating atezolizumab in combination with bevacizumab in adults with advanced unresectable HCC and documented chronic hepatitis B infection, who have not received prior systemic treatment. Enrolled patients are required to have an adequate liver function reserve (i.e., Child-Pugh class A) and ECOG PS of 0 or 1. Anti-HBV treatment is administered according to local standard of care starting 1-2 weeks prior to entry and continued throughout the study. The trial investigators hypothesize that the safety profile of atezolizumab plus bevacizumab would be similar between previously studied patient populations and those enrolled in this ongoing trial.[66] However, as this study is not a randomized-controlled trial, it was deemed to not add any further relevant comparative efficacy data to our current knowledge and thus was ultimately excluded from this section.

7 Supplemental Questions

The following supplemental question were identified during development of the review protocol as relevant to the pCODR review of atezolizumab plus bevacizumab:

- Summary and critical appraisal of a sponsor-submitted indirect treatment comparison (ITC) / network meta-analysis (NMA) comparing atezolizumab plus bevacizumab to relevant comparators used in clinical practice for the first-line treatment of patients with locally advanced or metastatic HCC.

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Critical Appraisal of Sponsor-Submitted Indirect Treatment Comparison

7.1.1 Objective

The available clinical trial did not capture all relevant comparators for the economic model and analysis supporting this submission. Consequently, the sponsor supplied an ITC to relevant comparators based on a systematic review of treatments for locally advanced metastatic hepatocellular cancer.[8] The objective of the ITC was to compare atezolizumab in combination with bevacizumab compared to other interventions used in clinical practice for first-line treatment for locally advanced metastatic hepatocellular cancer.

7.1.2 Findings

A single sponsor-provided ITC was provided as part of the submission and has been described and critically appraised in the sections below.

Methods

Systematic review

[redacted][8].

(Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until April 30, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

[redacted][8]

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Table 18: PICOS Eligibility Criteria

PICOS Item	Eligibility Criteria
Population	[redacted]
Intervention	
Comparators	

PICOS Item	Eligibility Criteria
Outcomes	[redacted]

Source: pCODR Submission[8]
(Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until April 30, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

[redacted][8,67]

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Methods for indirect treatment comparison

[redacted][8]

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[redacted][8] The analyses for the NMA were conducted under a Bayesian framework where both fixed effect (FE) and random effects (RE) models were examined.[9] [redacted][8] For the RE models, informative priors were used for the between-study standard deviations based on empirical research by Turner et al. (2015) since the network was too sparse to estimate a RE model using uninformative priors.[8,9] [redacted][8]

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[redacted][8]

(Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until April 30, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

The subgroups that were examined included regions (Asian-Pacific vs non-Asian-Pacific), viral etiology (HBV, HCV, or non-viral), MVI, EHS, and [redacted].[8,9] [redacted][8]

(Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed

pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until April 30, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

Results

Systematic review results and NMA feasibility assessment

[redacted][8]

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Construction of the networks

NMA results were provided for only two outcomes: OS and PFS.[9] [redacted] The level 1 analysis included systemic therapies considered standard of care in hepatocellular cancer (sorafenib, nivolumab, lenvatinib). [redacted][8]

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There were three trials included in the Level 1 analysis (IMbrave150, CheckMate 459, REFLECT).[9] The network diagram is presented in Figure 9. [redacted]

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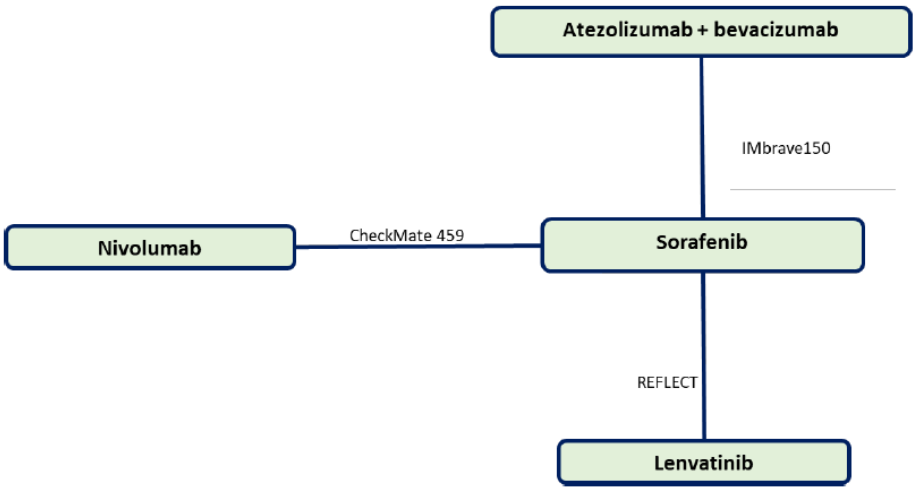
Figure 9: Level 1 evidence network diagram (n=3 trials)



Source: pCODR Submission[8]

Figure 10: Level 3 evidence network diagram (n=5 trials)

[redacted]

Source: pCODR Submission[8]
(Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until April 30, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

Trial characteristics

[redacted]

[redacted][8]

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Table 19: Treatment Characteristics for the Five Trials Included in the Network Meta-analysis

Trial	Treatment Details	Schedule	Mean # sessions/other	Additional details
[redacted]				

b.i.d = twice daily; Gy = grays; HCC = hepatocellular carcinoma; IQR = interquartile range; MBq = megabecquerel; NR = not reported; SD = standard deviation; SIRT = selective internal radiotherapy.

Source: pCODR Submission[8]
(Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until April 30, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

Assessment of Homogeneity

The trial characteristics presented in Table 20 were assessed for their homogeneity. The median age and gender were generally consistent across the trials. For Asia-Pacific regions, the trials varied with [redacted] 40% in CheckMate459, 40% in IMbrave150, and 67% in REFLECT.[8,9] [redacted][8] The CheckMate 459 trial included a larger proportion of patients with non-viral aetiology (45%) compared with IMbrave150 (30-32%) and REFLECT (26-28%).[9] [redacted] The proportion of patients with MVI was [redacted] compared with the IMbrave150 trial (about 40%) and the REFLECT trial (about 20%); this was not reported in the CheckMate 459 trial.[8,9]
(Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until April 30, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

Table 20: Trial Characteristics for the Five Trials Included in the Network Meta-analysis

Trial	Tx	Median Age Years	Gender Male (%)	Asia-Pacific Regions (%)	ECOG PS (%)	Child-Pugh Class (%)	BCLC Stage (%)	AFP (%)	Prior Tx (%)	Aetiology (%)	PD-L1 Status ≥1%	EHS/MVI
[redacted]												

AFP = alpha fetoprotein; Atezo+Bev = atezolizumab plus bevacizumab; BCLC = Barcelona Clinic Liver Cancer; ECOG PS = Eastern Cooperative Oncology Group performance status; EHS = extrahepatic spread; HBV = hepatitis B virus; HCV = hepatitis C virus; L = liters; MVI = macrovascular vein invasion;; NR = not reported; PD-L1 = programmed death-ligand 1; SIRT = selective internal radiotherapy; tx = treatment; µg = micrograms.

Source: pCODR Submission[8]

(Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until April 30, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

[redacted][8]

(Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until April 30, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

Table 21: Risk of Bias Results for the SARAH, SIRVENIB, and REFLECT Trials

Trial	Random Sequence Generation	Allocation Concealment	Blinding (Participants & Personnel)	Blinding Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other
[redacted]							

Source: pCODR Submission[8]

(Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until April 30, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

For OS, definitions were not provided for the IMbrave150 or CheckMate 459 trials. [redacted][8] Sub-groups examined in the NMA included Asia-Pacific patients (APAC), EHS, HBV, HCV, non-viral aetiology, MVI, and [redacted].[8,9] [redacted][8]

(Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until April 30, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

For PFS, the definition varied across the trials, with most using RECIST versions 1.1. [redacted][8] Subgroups examined in the NMA included APAC, EHS, HBV, HCV, non-viral aetiology, MVI, and [redacted][8,9] [redacted][8]

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[redacted]

[redacted][8]

(Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until April 30, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

Results of NMA

ITT population: Overall survival

Table 22 summarizes the HRs and 95% credible intervals (CrIs) for OS in the ITT population for the level 1 network. The estimates in both the fixed effect and random effects analyses were similar with similar goodness-of-fit (DICs [redacted] for the FE model and RE models, respectively). The RE model was chosen as the primary results, since the FE model did not improve the model fit due to the known sources of heterogeneity in the network, which can be accounted for in the RE model.[8] The estimated HRs from the RE model showed a numerical reduction in hazards for atezolizumab plus bevacizumab relative to lenvatinib, nivolumab, and sorafenib with HRs of 0.63, 0.68, and 0.58, respectively. Based on the CrI, atezolizumab plus bevacizumab was favored relative to sorafenib (95% CrI: 0.35, 0.99) but not favored relative to lenvatinib and nivolumab (95% CrI: 0.32, 1.25 and 0.35, 1.38, respectively).[9] For the fixed effect analysis, atezolizumab plus bevacizumab were favored relative to all comparators, but as mentioned, these results do not account for study heterogeneity.[8]

(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed.)

Table 22: OS in the ITT population, random effects, level 1 network*

Treatment Comparison	Hazard Ratio (95% Credible Interval)
Atezolizumab plus Bevacizumab vs. Lenvatinib	0.63 (0.32, 1.25)
Atezolizumab plus Bevacizumab vs. Nivolumab	0.68 (0.35, 1.38)
Atezolizumab plus Bevacizumab vs. Sorafenib	0.58 (0.35, 0.99)

*NMA using a Cox Proportional Hazards model with random effects under a Bayesian framework

Source: pCODR Submission[8], Vogel et al., 2020[9]

Table 23 summarizes the subgroup analysis results with the random effects HRs and 95% CrIs for OS in the ITT population for the level 1 network. The results were generally consistent with the primary model results across all subgroup analyses, with numerical reductions in HRs for atezolizumab plus bevacizumab across all subgroups. The only population for which the HR approached the null was for those with non-viral aetiology and EHS (compared to sorafenib only). Based on the CrI, atezolizumab plus bevacizumab was favored relative to sorafenib for the following subgroups: HBV (95% CrI: [redacted]), HCV (95% CrI: [redacted]), and those with MVI/EHS (95% CrI: [redacted]). None of the CrIs favored atezolizumab plus bevacizumab relative to lenvatinib or nivolumab.

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Table 23: OS in the ITT population by sub-group, random effects, level 1 network*

Sub-group	Atezolizumab plus Bevacizumab vs. Lenvatinib HR (95% CrI)	Atezolizumab plus Bevacizumab vs. Nivolumab HR (95% CrI)	Atezolizumab plus Bevacizumab vs. Sorafenib HR (95% CrI)
[redacted]			

APAC = Asia-Pacific; CrI = credible interval; EHS = extrahepatic spread; HBV = hepatitis B virus; HCV = hepatitis C virus; HR = hazard ratio; MVI = macrovascular vein invasion.

*NMA using a Cox Proportional Hazards model with random effects under a Bayesian framework

Source: pCODR Submission[8]

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Table 24 summarizes the HRs and 95% CrIs for OS in the ITT population for the level 3 network. The estimates in both fixed effect and random effects analyses were similar with similar goodness-of-fit (DICs [redacted] for the FE model and RE models, respectively). *(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed.)*

The RE model was chosen as the primary results since the FE model did not improve the model fit and due to the known sources of heterogeneity in the network, which can be accounted for in the RE model. The estimated HRs from the RE model showed [redacted]

(Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until April 30, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

Table 24: OS in the ITT population, random effects, level 3 network*

Treatment Comparison	HR (95% CrI)
[redacted]	

HR = hazard ratio; CrI = credible interval; SIRT = selective internal radiotherapy

*NMA using a Cox Proportional Hazards model with random effects under a Bayesian framework

Source: pCODR Submission[8]

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Table 25 summarizes the subgroup analysis results with the random effects HRs and 95% CrIs for OS in the ITT population for the level 3 network. [redacted]

(Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until April 30, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

Table 25: OS in the ITT population by sub-group, random effects, level 3 network*

Sub-group	Atezolizumab plus Bevacizumab vs. Lenvatinib HR (95% CrI)	Atezolizumab plus Bevacizumab vs. Nivolumab HR (95% CrI)	Atezolizumab plus Bevacizumab vs. Sorafenib HR (95% CrI)	Atezolizumab plus Bevacizumab vs. SIRT HR (95% CrI)
[redacted]				

APAC = Asia-Pacific; CrI = credible interval; EHS = extrahepatic spread; HBV = hepatitis B virus; HCV = hepatitis C virus; HR = hazard ratio; MVI = macrovascular vein invasion; NA = not available; SIRT = selective internal radiotherapy.

*NMA using a Cox Proportional Hazards model with random effects under a Bayesian framework; †For this analysis, the efficacy of comparator in EHS and MVI negative population was used.

Source: pCODR Submission[8]

(Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until April 30, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

ITT population: Progression free survival

Table 26 summarizes the HRs and 95% CrIs for PFS in the ITT population for the level 1 network. The estimates in both fixed effect and random effects analyses were similar with similar goodness-of-fit (DICs 5.92 and 5.95 for the FE model and RE models, respectively). The RE model was chosen as the primary results since the FE model did not improve the model fit and due to the known sources of heterogeneity in the network, which can be accounted for by the RE model. The estimated HRs from the RE model showed a numerical reduction in hazards for atezolizumab plus bevacizumab relative to lenvatinib, nivolumab, and sorafenib with HRs of 0.91, 0.63, and 0.59, respectively. Based on the CrI, atezolizumab plus bevacizumab was not favored relative to lenvatinib, nivolumab, or sorafenib (95% CrI: 0.23, 3.65; 0.17, 2.59; and 0.23, 1.58, respectively). For the fixed effect analysis, atezolizumab plus bevacizumab were favored relative to nivolumab and sorafenib but not lenvatinib; as mentioned, these results do not account for study heterogeneity.

Table 26: PFS in the ITT population, random effects, level 1 network*

Treatment Comparison	HR (95% CrI)
Atezolizumab plus Bevacizumab vs. Lenvatinib	0.91 (0.23, 3.65)
Atezolizumab plus Bevacizumab vs. Nivolumab	0.63 (0.17, 2.59)
Atezolizumab plus Bevacizumab vs. Sorafenib	0.59 (0.23, 1.58)

CrI = credible interval; HR = hazard ratio.

*NMA using a Cox Proportional Hazards model with random effects under a Bayesian framework

Source: pCODR Submission[8], Vogel et al., 2020[9]

Subgroup analyses were not conducted for PFS for the level 1 network, as not all trials used the RECIST v1.1 criteria consistently.

Table 27 summarizes the HRs and 95% CrIs for PFS in the ITT population for the level 3 network. The estimates in both fixed effect and random effects analyses were similar and provided similar goodness-of-fit (DICs [redacted] for the FE model and RE models, respectively).
(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed.)
The RE model was chosen as the primary results since the FE model did not improve the model fit and due to the known sources of heterogeneity in the network, which can be accounted for by the RE model. The estimated HRs from the RE model showed a numerical reduction in hazards for atezolizumab plus bevacizumab relative to lenvatinib, nivolumab, sorafenib, and SIRT with HRs of [redacted], respectively. Based on the CrI, atezolizumab plus bevacizumab was not favored relative to all comparators. For the fixed effect analysis, atezolizumab plus bevacizumab were favored relative to nivolumab, sorafenib, and SIRT but not lenvatinib; as mentioned, these results do not account for study heterogeneity.
(Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until April 30, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

Table 27: PFS in the ITT population, random effects, level 3 network*

Treatment Comparison	HR (95% CrI)
[redacted]	

HR = hazard ratio; CrI = credible interval; SIRT = selective internal radiotherapy.

*NMA using a Cox Proportional Hazards model with random effects under a Bayesian framework

Source: pCODR Submission[8]
(Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until April 30, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

Table 28 summarizes the subgroup analysis results with the random effects HRs and 95% CrIs for PFS in the ITT population for the level 3 network. Results were not available for the lenvatinib and nivolumab comparators. For sorafenib and SIRT, the results were generally consistent with the primary model results across all sub-group analyses when available, with numerical reductions in HRs for atezolizumab plus bevacizumab across all subgroups. Based on the CrI, atezolizumab plus bevacizumab was not favored relative to any comparators across all sub-groups.

Table 28: PFS in the ITT population by sub-group, random effects, level 3 network*

Sub-group	Atezolizumab plus Bevacizumab vs. Lenvatinib HR (95% CrI)	Atezolizumab plus Bevacizumab vs. Nivolumab HR (95% CrI)	Atezolizumab plus Bevacizumab vs. Sorafenib HR (95% CrI)	Atezolizumab plus Bevacizumab vs. SIRT HR (95% CrI)
[redacted]				

APAC = Asian-Pacific; CrI = credible interval; EHS = extrahepatic spread; HBV = hepatitis B virus; HCV = hepatitis C virus; HR= hazard ratio; MVI = macrovascular vein invasion; NA = not available; SIRT = selective internal radiotherapy.

*NMA using a Cox Proportional Hazards model with random effects under a Bayesian framework; †For this analysis, the efficacy of comparator in EHS and MVI negative population was used.

Source: pCODR Submission[8]

(Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until April 30, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

Critical appraisal of NMA

Table 29 summarizes the critical appraisal of the NMA using the International Society for Pharmacoeconomics and Outcomes (ISPOR) criteria. The principal limitations of the NMA concern sparseness of the data and structure of the network, the variable duration of follow-up across included studies, and potential violation of the transitivity assumption. These limitations result in imprecision of estimates and uncertainty around the long-term extrapolation of fitted models.

[redacted]

(Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until April 30, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

[redacted] Extrapolation of long-term survival from short term follow-up carries high uncertainty and risk of bias.

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Table 29: ISPOR questionnaire to assess the credibility of an indirect treatment comparison or network meta-analysis‡

ISPOR Questions	Details and Comments
1. Is the population relevant?	Unclear. The population of interest is adult patients ≥18 years with locally advanced or metastatic HCC who received no prior systemic therapy. Results across all trials are only reported for the ITT population. **The inclusion and exclusion criteria were not reported for any of the included trials (only a summary section was provided in the systematic review report that said that there was variability in the inclusion criteria across the trials) so it is difficult to determine whether any of the trials excluded relevant patient populations**.
2. Are any critical interventions missing?	No. The level 1 analysis was most relevant to the Canadian population.
3. Are any relevant outcomes missing?	Yes. **There was insufficient data to create networks for the planned outcomes of**: • TTP • DOR • ORR • Response rates – complete response (CR), partial response (PR), stable disease (SD) • Duration of treatment • All-grade treatment related adverse events (AEs) • Treatment related Grade 3 or 4 AEs • Treatment related SAEs • Tolerability: Dose reductions and interruptions, discontinuation (any reason), discontinuation (due to AEs) • HRQoL **Furthermore, pairwise meta-analyses may have been possible for these outcomes, yet these results were not reported**.
4. In the context (e.g., settings and circumstances) applicable to your population?	Yes. Level 1 analysis was most applicable to Canada.
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	Unclear. A comprehensive search was described, with prespecified search and selection criteria. Multiple databases were used to identify studies. Grey literature and abstracts were included, although fully published data was preferentially used. However, not all of the interventions predefined in the PICO eligibility criteria were specifically searched for (as noted under question 2). Furthermore, **the included trials in the network were restricted to those conducted after the 2007 approval of sorafenib in the US that reported outcome data for OS and/or PFS, which may have led to relevant data being excluded in the ITC**.
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	Unclear. 55 unique trials were identified for inclusion into the review and 23 formed a connected network. **It is unclear what interventions were examined in the 33 trials that were not connected to the network**. Only three trials were included in the level 1 (main) analysis and five trials were included in the level 3 (secondary) analysis overall. **Furthermore, the number of interventions included in the analysis was greater than the number of trials, which is not advisable in NMA, due to sparsity of data, which may lead to erroneous results.**
7. Is it apparent that poor quality studies were included thereby leading to bias?	Unclear. **The results were only available for three of the five included trials and were missing for the most important trial (IMbrave150)**.
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	**Unclear, as the risk of bias results were only provided for three of five trials** (yet this was not a major source of bias for these three trials).
9. Are there systematic differences in treatment effect modifiers (i.e., baseline patient or study characteristics that impact the treatment effects) across the	As noted above in the *Assessment of similarity across the trials* section, differences were noted across the trials regarding the following variables: Asia-Pacific regions, Child-Pugh class, BCLC stage, viral aetiology, PD-L1 status, and MVI. However, the CGP panel deemed that these differences were not clinically significant.

ISPOR Questions	Details and Comments
different treatment comparisons in the network?	
10. If yes (i.e., there are such systematic differences in treatment effect), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	Potential treatment effect modifiers were explored in the systematic review and NMA feasibility report, which was performed prior to the NMA.
11. Were statistical methods used that preserve within-study randomization?	The network was analyzed with a fixed-effect model and random-effects model, which preserves within-study randomization.
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e., closed loops) was agreement in treatment effects (i.e., consistency) evaluated or discussed?	Not applicable. The network was star-shaped and contained no closed loops for evaluation.
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	Not applicable.
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	Yes, several sub-group analyses were performed for the OS outcome. For PFS, subgroup analyses were conducted for the level 3 (secondary) analysis but not the most applicable analysis (level 1 or main analysis).
15. Was a valid rationale provided for the use of random effects or fixed effects models?	Yes.
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	A random effects model was used. Uninformative prior distributions were used for all variables except for the between-study variance, which would be difficult to estimate given the small number of included studies. An informative prior was used for between-study variance, based on an independently published systematic review of NMAs. No sensitivity analyses were reported that explored the influence of the prior distributions.
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analyses with pre-specified covariates performed?	Yes, several subgroup analyses were performed.
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Yes.
19. Are the individual study results reported?	Yes.
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analyses?	No.
21. Are all pairwise contrasts between interventions as obtained with the	Yes.

ISPOR Questions	Details and Comments
network meta-analysis reported along with measures of uncertainty?	
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	Yes.
23. Is the impact of important patient characteristics on treatment effects reported?	Yes, several subgroup analyses were performed.
24. Are the conclusions fair and balanced?	Unclear. No specific conclusions were presented.
25. Were there any potential conflicts of interest?	Yes. Manufacturer-sponsored ITC.
26. If yes, were steps taken to address these?	No.

† Adapted from Jansen et al. Indirect Treatment Comparison/Network Meta-Analysis Study Questionnaire to Assess Relevance and Credibility to Inform Health Care Decision Making: An ISPOR-AMCP-NPC Good Practice Task Force Report.[68]

‡ Bolded comments are considered a weakness of the ITC.

7.1.3 Summary

Three trials were included in the level 1 network including four interventions (atezolizumab plus bevacizumab, lenvatinib, nivolumab, and sorafenib). In the level 3 network, five trials were included examining five interventions (atezolizumab plus bevacizumab, lenvatinib, nivolumab, sorafenib, and SIRT). The OS results from the level 1 analysis found that atezolizumab plus bevacizumab was favoured compared to sorafenib. For the OS level 3 analysis, [redacted]. For both level 1 and level 3 analyses, there was insufficient evidence of difference from lenvatinib and nivolumab.
(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed.)

The PFS results did not provide evidence that atezolizumab plus bevacizumab differed from other treatments. No results for any other effectiveness outcome were provided. There were no results reported on any of the harms outcomes.

The systematic review methods were moderately conducted with limitations including that the literature search results were focused on studies written in English and the search may not have captured all relevant trials. Although heterogeneity was observed in baseline characteristics across the studies included in the network, the CGP deemed that this was not clinically meaningful. Appropriate random effects models were selected to attempt to account for between-study heterogeneity but due to the sparseness of the network, informative priors were used for between-study heterogeneity, which was not assessed in the sensitivity analysis for their influence on the results of the NMA. In addition, a number of other limitations were identified including the analyses were overly restricted, resulting in few trials being eligible for inclusion in the NMA; the dataset was relatively sparse, leading to broad CrIs and potential failure to detect real differences; inability to analyze all outcome results and no data were reported on harms; and not all sensitivity analyses were possible due to a dearth of data. Thus, these limitations must be considered when drawing conclusions based on the results of the NMA.

8 Comparison with Other Literature

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

9 About this Document

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

CADTH 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 Procedures for the CADTH pan-Canadian Oncology Drug Review. The sponsor, as the primary data owner, did not agree to the disclosure of some clinical information which was provided to pERC for their deliberations. 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.

Appendix 1: Literature Search Strategy and Detailed Methodology

1. Literature search via Ovid platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials May 2020, Embase 1974 to 2020 June 17, Ovid MEDLINE(R) ALL 1946 to June 16, 2020

Search Strategy

#	Searches	Results
1	(atezolizumab* or Tecentriq* or Tecntriq* or RG-7446 or RG7446 or MPDL-3280A or MPDL3280A or 52CMI0WC3Y).ti,ab,ot,kf,kw,hw,nm,rn.	7249
2	Bevacizumab/ or (bevacizumab* or avastin* or altuzan* or NSC 704865 or NSC704865 or rhuMAb-VEGF or rhumabvegf or 2S9ZZM9Q9V or avastyn* or bivastin* or bevastim* or bevax* or lumiere* or zirabev* or mvasi* or ainex or kyomarc or ABP215 or ABP 215 or R345 or R 345 or R435 or R 435 or HSDB8080 or HSDB 8080).ti,ab,ot,kf,kw,hw,rn,nm.	86102
3	exp liver neoplasms/	444362
4	((hepatocellular or hepato-cellular or liver* or hepatic or hepatobiliary or hepato-biliary) adj5 (cancer* or carcinoma* or tumor* or tumour* or neoplas* or malignan* or adenocarcinoma* or adenoma* or hemangioma* or haemangioma* or angioma* or granuloma* or carcinogen* or sarcoma* or metastasis or metastases or metastatic)).ti,ab,kf,kw.	474359
5	(hepatoma* or hepatocarcinoma* or hepato-carcinoma* or hepatocarcinogenesis or hepato-carcinogenesis* or HCC or hepatoblastoma* or hepato-blastoma*).ti,ab,kf,kw.	227770
6	or/3-5	640050
7	1 and 2 and 6	227
8	7 use medall	17
9	limit 8 to english language	17
10	7 use cctr	41
11	*atezolizumab/ or (atezolizumab* or Tecentriq* or Tecntriq* or RG-7446 or RG7446 or MPDL-3280A or MPDL3280A).ti,ab,kw,dq.	4328
12	*Bevacizumab/ or (bevacizumab* or avastin* or altuzan* or NSC 704865 or NSC704865 or rhuMAb-VEGF or rhumabvegf or avastyn* or bivastin* or bevastim* or bevax* or lumiere* or zirabev* or mvasi* or ainex or kyomarc or ABP215 or ABP 215 or R345 or R 345 or R435 or R 435 or HSDB8080 or HSDB 8080).ti,ab,kw,dq.	55237
13	exp Liver tumor/	277087
14	((hepatocellular or hepato-cellular or liver* or hepatic or hepatobiliary or hepato-biliary) adj5 (cancer* or carcinoma* or tumor* or tumour* or neoplas* or malignan* or adenocarcinoma* or adenoma* or hemangioma* or haemangioma* or angioma* or granuloma* or carcinogen* or sarcoma* or metastasis or metastases or metastatic)).ti,ab,kw,dq.	473066
15	(hepatoma* or hepatocarcinoma* or hepato-carcinoma* or hepatocarcinogenesis or hepato-carcinogenesis* or HCC or hepatoblastoma* or hepato-blastoma*).ti,ab,kw,dq.	227599
16	or/13-15	603439
17	11 and 12 and 16	129
18	17 use oemezd	72
19	limit 18 to english language	71
20	19 not conference abstract.pt.	31
21	9 or 10 or 20	89
22	remove duplicates from 21	68
23	19 and conference abstract.pt.	40

#	Searches	Results
24	limit 23 to yr="2015 -Current"	40
25	22 or 24	108

2. Literature search via PubMed

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

Search	Query	Results
#9	Search: **#8 AND publisher[sb]** Filters: **English**	2
#8	Search: **#1 AND #2 AND #6** Filters: **English**	19
#7	Search: **#1 AND #2 AND #6**	19
#6	Search: **#3 OR #4 OR #5**	330,103
#5	Search: **hepatoma*[tiab] OR hepatocarcinoma*[tiab] OR hepato-carcinoma*[tiab] OR hepatocarcinogenesis[tiab] OR hepato-carcinogenesis*[tiab] OR HCC[tiab] OR hepatoblastoma*[tiab] OR hepato-blastoma*[tiab]**	91,699
#4	Search: **(hepatocellular[tiab] OR hepato-cellular[tiab] OR liver*[tiab] OR hepatic[tiab] OR hepatobiliary[tiab] OR hepato-biliary[tiab]) AND (cancer*[tiab] OR carcinoma*[tiab] OR tumor[tiab] OR tumors[tiab] OR tumour[tiab] OR tumours[tiab] OR neoplas*[tiab] OR malignan*[tiab] OR adenocarcinoma*[tiab] OR adenoma*[tiab] OR hemangioma*[tiab] OR haemangioma*[tiab] OR angioma*[tiab] OR granuloma*[tiab] OR carcinogen*[tiab] OR sarcoma*[tiab] OR metastasis[tiab] OR metastases[tiab] OR metastatic[tiab])**	271,613
#3	Search: **liver neoplasms [mh]**	164,425
#2	Search: **Bevacizumab[MeSH] OR bevacizumab*[tiab] OR avastin*[tiab] OR altuzan*[tiab] OR NSC 704865[tiab] OR NSC704865[tiab] OR rhuMAb-VEGF[tiab] OR rhumabvegf [tiab] OR 2S9ZZM9Q9V[rn] OR avastyn*[tiab] OR bivastin*[tiab] OR bevastim*[tiab] OR bevax*[tiab] OR lumiere*[tiab] OR zirabev*[tiab] OR mvasi*[tiab] OR ainex[tiab] OR kyomarc[tiab] OR ABP215[tiab] OR ABP 215[tiab] OR R345[tiab] OR R-345[tiab] OR R435[tiab] OR R-435[tiab] OR HSDB8080[tiab] OR HSDB 8080[tiab]**	18,286
#1	Search: **atezolizumab[Supplementary Concept] OR atezolizumab*[tiab] OR Tecentriq*[tiab] OR Tecntriq*[tiab] OR RG-7446[tiab] OR RG7446[tiab] OR MPDL-3280A[tiab] OR MPDL3280A[tiab] OR 52CMI0WC3Y[rn]**	1,082

3. Cochrane Central Register of Controlled Trials (CENTRAL)

(searched via Ovid)

4. Grey literature search via:

Clinical trial registries:
US National Library of Medicine. ClinicalTrials.gov
https://clinicaltrials.gov/

World Health Organzation
http://apps.who.int/trialsearch/

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

Health Canada's Clinical Trials Database
https://health-products.canada.ca/ctdb-bdec/index-eng.jsp

The European Clinical Trial Register
https://www.clinicaltrialsregister.eu/ctr-search/search
Search: Tecentriq/atezolizumab, Avastin/bevacizumab, HCC

Select international agencies including:
US Food and Drug Administration (FDA)
https://www.fda.gov/

European Medicines Agency (EMA)
https://www.ema.europa.eu/
Search: Tecentriq/atezolizumab, Avastin/bevacizumab, HCC

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

European Society for Medical Oncology (ESMO)
https://www.esmo.org/
Search: Tecentriq/atezolizumab, Avastin/bevacizumab, HCC — last five years

Detailed Methodology

The literature search for clinical studies was performed by an information specialist from the pCODR Methods Team using the abovementioned search strategy, which was peer-reviewed according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[69]

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

No filters were applied to limit 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 September 17, 2020.

Grey literature (literature that is not commercially published) was identified by searching websites from relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters).[70] Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trial registries (US National Institutes of Health's clinicaltrials.gov and Canadian Partnership Against Cancer Corporation's Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) 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 CADTH Clinical Guidance Panel. As well, the manufacturer of the drug was contacted for additional information, as required by the pCODR Review Team.

Study Selection

One member of the CADTH Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. One member of the pCODR Methods Team made the final selection of studies to be included in the review.

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 CADTH 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 CADTH:

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

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