CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Nivolumab (Opdivo) for Hepatocellular Carcinoma

November 29, 2018

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FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories with the exception of Quebec, which does not participate in pCODR at this time.

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List of Abbreviations

AE(s)	Adverse event(s)
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BICR	Blinded independent central review
BSC	Best supportive care
CLF	Canadian Liver Foundation
CGP	Clinical Guidance panel
CI	Confidence interval
CR	Complete response
CT	Computed tomography
DBL	Database lock
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EQ-5D	EuroQOL-5 Dimensions
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HCC	Hepatocellular carcinoma
HR	Hazard ratio
INV	Investigator assessment
ILD	Individual level data
ITC(s)	Indirect treatment comparison(s)
KM	Kaplan Meier
MAIC	Matching adjusted indirect treatment comparison
MCID	Minimal clinically important difference
NCI	National Cancer Institute
ORR	Objective response rate
OS	Overall survival
pCODR	pan-Canadian Oncology Drug Review
pERC	pCODR Expert Review Committee
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
HRQOL	Health-related quality of life
(m) RECIST	(modified) Response Evaluation Criteria for Solid Tumours
RCT(s)	Randomized controlled trial(s)
SAE(s)	Serious adverse event(s)
SAP	Statistical analysis plan
TKI(s)	Tyrosine kinase inhibitor(s)
TTR	Time-to-response
TTP	Time-to-progression
VAS	Visual analogue scale
VEGR	Vascular endothelial growth factor
2L	Second-line

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 nivolumab (Opdivo) for HCC. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

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

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

1.1 Introduction

The objective of this review is to evaluate the safety and efficacy of nivolumab (Opdivo) for the treatment of adult patients with advanced (not amendable to curative therapy or local therapeutic measures) or metastatic HCC who are intolerant to or have progressed on sorafenib therapy.

The reimbursement request is in line with the approved Health Canada indication. Nivolumab received the Notice of Compliance with conditions from Health Canada in March 2018, pending the results of trials to verify its clinical benefit. The marketing authorization with conditions is primarily based on tumour objective response rate and duration of response. An improvement in survival or disease-related symptoms has not yet been established. Nivolumab is a fully human monoclonal immunoglobulin G4 antibody developed by recombinant deoxyribonucleic acid technology.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

One clinical trial was identified that met the selection criteria of the pCODR systematic review. CheckMate 040 is an ongoing, international, non-comparative, open-label, multi-centred phase 1/2 trial evaluating the efficacy and safety of nivolumab in patients with advanced HCC who were either treatment naïve or previously treated with sorafenib.[1] The pCODR submission is focused on patients treated in the 2L in the dose expansion phase of CheckMate 040. The dose expansion phase was conducted at 39 sites in 11 countries including Canada, and included a small number of Canadian patients.[2] The trial was funded by the drug Manufacturer Bristol-Myers Squibb.

The CheckMate 040 trial included patients who met the following criteria:[1]

- Male or female, aged at least 18 years with histologically confirmed advanced HCC that was not amenable to curative surgery or local treatment
- With or without HCV or HBV infection; HBV infection required patients be receiving effective anti-viral therapy and have a viral load less than 100 IU/ml at trial screening
- Previously untreated; or with disease progression while receiving at least one previous line of therapy that included sorafenib; or deemed intolerant[i] of or refused sorafenib treatment
- Child-Pugh score of ≤6 (Child-Pugh A)
- ECOG performance status of ≤1

CheckMate 040 was originally designed as a phase 1 dose escalation trial. During an interim analysis of the phase 1 data, encouraging treatment responses (CR, durable responses, favourable OS) were observed across all four etiologic subtypes of patients included in the trial (sorafenib untreated/intolerant, sorafenib progressor, HCV infected, and HBV infected), which prompted the addition of an expansion phase (phase 2; protocol amendment 4, October 29, 2014) that included four parallel patient cohorts by etiologic subtype.[2]

The primary outcome of CheckMate 040 was ORR by BICR with tumour assessment based on RECIST version 1.1, and investigator assessment serving as a sensitivity analysis.[2] Key secondary outcomes included CR rate, DCR, DOR, TTR, TTP, and PFS, all evaluated by either BICR or investigator assessment, and OS.[3] Patient reported HRQOL was considered an exploratory endpoint of the trial.[1]

An initial evaluation of efficacy was carried out on March 15, 2016, which showed consistent investigator-assessed response rates across the four expansion cohorts.[2] Based on this evaluation, the SAP of the trial was amended to conduct pooled efficacy analyses that combined patients from the four cohorts in order to strengthen the estimate of ORR.[2] The pooled analyses were focused to 2L patients (n=145) who had progressed on or were intolerant to sorafenib regardless of etiology.[2] The 2L patients comprise 68% of the original trial population.

Pooled efficacy and safety results in 2L patients have been published in conference form (poster) based on an updated analysis (March 17, 2017 DBL).[4] Additional data on efficacy were provided to pCODR as part of the pCODR submission.[2] Data on HRQOL in 2L patients have not been published, and were provided to pCODR as part of the submission based on an additional updated analysis (November 29, 2016 DBL).[2] Data contained in a recent EMA Assessment report were also used to supplement reporting of the CheckMate 040 trial.[3]

Patients in the expansion cohort were enrolled between January 2015 and November 2015.[3] The 2L cohort comprised a majority of patients who had progressed on or after treatment with sorafenib (91%, n=132); a much smaller proportion of patients were considered sorafenib intolerant (8.3%, n=12).[3] One patient (1%) in the trial had refused sorafenib treatment.[3] The median duration of prior sorafenib treatment among the cohort was 3.8 months (range, 0.1-48.1) and the median time from discontinuation of sorafenib

[i] Intolerance to sorafenib was defined as follows:

- Grade 2 drug-related AE that persisted in spite of comprehensive supportive therapy according to institutional standards AND persisted or recurred after sorafenib treatment interruption of at least 7 days and dose reduction by one dose level (to 400 mg once daily).
- Grade 3 drug-related AE that persisted in spite of comprehensive supportive therapy according to institutional standards OR persisted or recurred after sorafenib treatment interruption of at least 7 days and dose reduction by one dose level (to 400 mg once daily).

until the start of nivolumab was 2.2 months (range, 0.1-44.7). There were 27 patients (18.6%) in the cohort who had prior systemic therapies (≥2) in addition to sorafenib.[3] The time from initial diagnosis to first dose of nivolumab was ≥5 years in 20% of patients.[3] The majority of patients were from trial sites in Asia (49%) and Europe (40%), with the remaining (11%) from the US and Canada.[3] Most patients were male (77%), Asian or White (98%), and under age 65 (56%);[3] median age of patients in the cohort was 63 years. In terms of etiology, most patients were uninfected (50%); HBV and HCV infection was present in 30% and 21% of patients, respectively. Patients were predominantly BCLC stage C (89%), Child-Pugh score 5 (67%), and ECOG performance status of 0 (64%). Extrahepatic metastases and vascular invasion were present in 71% and 40% of patients, respectively.

Nivolumab was administered intravenously to patients every two weeks at a dose of 3 mg/kg until disease progression, unacceptable toxicity, or treatment discontinuation.[1] The trial permitted treatment beyond disease progression in patients still tolerant and benefiting clinically from nivolumab. Dose modifications were not permitted but dose delays of up to six weeks (42 days) from the last dose of nivolumab were allowed.[2] The median duration of treatment among the 2L cohort was 5.26 months;[3] and 78 patients (54%) were treated beyond disease progression.[4]

At the time of the pooled efficacy analysis, 24 (17%) 2L patients remained on treatment with nivolumab and 121 (83%) had discontinued. The primary reason for treatment discontinuation was PD (n=107, 74%).[4]

Efficacy

The key outcomes of the CheckMate 040 trial are summarized in Table 1. The pooled efficacy results are based on a median follow-up time of approximately 15 months.

ORR by BICR – primary outcome[2]

Among the 2L patient cohort the ORR by BICR was 14.5% (95% CI, 9.2-21.3). Of note, this ORR estimate did not reach the clinical significance threshold pre-specified in the SAP as the lower confidence limit was less than 10%. The ORR by BICR was comprised mainly of PRs (17%; n=24), and the CR rate was 1% (n=2). Comparatively, the estimates of ORR by investigator assessment (sensitivity analysis) and by mRECIST criteria (exploratory analysis) were higher at 19.3% (95% CI, 13.2-26.7) and 18.6% (95% CI, 12.6-25.9),[3] respectively. Responses were observed across the four etiologic cohorts; ORR estimates ranged between 12.5% and 14.0% by BICR, and from 14.0% to 26.7% by investigator assessment (Table 1). It was reported that the majority of investigator-assessed responses (64%; 18/28) occurred in ≤3 months; and responses were ongoing (at DBL) in 39% (11/28) of patients.[4]

Secondary Outcomes[2]

The median DOR among 2L expansion patients was 16.6 months (95% CI, 9.7-not available) by BICR. The median TTR was 2.8 months (range, 1.2-7.0). The investigator-assessed estimate of DOR was not estimable and was 2.7 months (95% CI, 1.2-9.6) for TTR.

Median PFS by BICR among the 2L expansion patients was 2.8 months (95% CI, 2.6-4.0), which was based on 119 progression events; PFS by investigator assessment was 4.1 months (95% CI, 2.8-5.5).

By the March 17, 2017 DBL, a total of 81 deaths had occurred among the 2L expansion cohort;[3] median OS was 15.6 months (95 % CI, 13.24-18.89). At 12 and 18 months the estimated OS rates were 60% (95% CI, 54.1-67.5) and 44% (95% CI, 35.3-51.9), respectively. Median OS estimates were similar by etiology at 16.3 (95% CI, 11.3-19.94) months in uninfected patients, 14.9 months (95% CI, 9.3-not estimable) in HBV-infected patients and not reached in HCV-infected patients.

Health-related Quality of Life[2]

Health-related QOL was assessed using the EQ-5D. A score difference of 0.08 was considered the MCID for the EQ-5D utility index; and a score difference of 7 was considered the MCID for the EQ-5D VAS.[1] Patients in the trial completed QOL assessments at baseline and every six weeks until week 25.[1] The HRQOL analyses are based on the 120 patients in the 2L cohort who had a baseline assessment and at least one post-baseline assessment.

Among 2L patients the EQ-5D questionnaire completion rate decreased after baseline (100%), ranging from 95.8% at week seven to 51.7% at week 25. It was reported that EQ-5D index scores were stable while on treatment with no significant changes from baseline (mean 0.85; 95% CI, 0.82-0.89) to week 25 (mean 0.83; 95% CI, 0·77-0·87); mean change from baseline was –0.014 (95% CI, –0·06-0·03). This change from baseline did not meet the MCID of 0.08. Considering the individual dimensions of the EQ-5D index, there were no patients who reported extreme problems with mobility and self-care at any assessment time point; and the proportions of patients reporting extreme problems with usual activities, pain and anxiety/depression were below ≤5% at all assessment time points. EQ-5D-VAS scores were also stable, with no significant changes from baseline (mean 74.5; 95% CI, 69.9-79.2) to week 25 (mean 75.8; 95% CI, 69.3-82.4); mean change from baseline was 3.1 (95% CI, –1.0-7.6). This change from baseline did not meet the MCID for VAS of 7.

Analysis of EQ-5D index and VAS scores by etiology showed similar results to the whole 2L patient cohort, with the exception of patients with HBV infection who experienced a clinically meaningful improvement in VAS scores (mean 7.4; 95% CI, 0.1-14.7).

Safety[2]

All grade AEs, regardless of causality, were reported in 99.3% of patients in the 2L cohort. The most frequently reported all-cause AEs were fatigue (35.9%), pruritus (28.3%), diarrhea (26.9%), abdominal pain (24.1%), cough (22.1%), and decreased appetite (21.4%). All-cause grade 3-4 AEs occurred in 49% of patientsand were mostly attributable to abdominal pain (3.4%) and fatigue (2.8%). Treatment discontinuations due to any AE occurred in 11% of patients.

All grade AEs related to study drug occurred in 74.5% of patients, with the most common being fatigue (24.1%), pruritus (18.6%), and rash (15.9%). Increases in AST and ALT abnormalities, all-grade and grade 3-4, were attributable to nivolumab in 5.5% and 6.9%, and 2.8% and 2.1%, of patients, respectively. These increases were reported as mostly asymptomatic, not associated with changes in other hepatic measures, reversible, and

manageable with established algorithms. Similarly, increases in amylase (any grade: 2.8%; grade 3/4: 1.4%) and lipase (any grade: 3.4% grade 3/4: 3.4%) were asymptomatic and not associated with clinical pancreatitis. Drug-related SAEs occurred in 9% of patients; and drug-related treatment discontinuations occurred in 2% of patients and included stomatitis, polyarthritis and pneumonitis.

As of the November 29, 2016 DBL, a total of 65 (45%) deaths had occurred in the 2L patient cohort; 91% of deaths were due to disease progression. It was reported that eight (5.5%) and 29 (20%) patients died within 30 and 100 days of last nivolumab dose, respectively. One patient death was deemed related to nivolumab; after eight months of treatment and achieving a PR, this patient discontinued nivolumab and started treatment with sorafenib and after three weeks on treatment developed grade 3 pneumonitis and, despite treatment with steroids, died 159 days post-nivolumab treatment.

Table 1: Highlights of key outcomes in the 2L expansion cohort of the CheckMate 040 trial.[2]

Outcome	CheckMate 040 2L Expansion Cohort (n=145)	
DBL	March 17, 2017	
Median Follow-up	14.9 months	
Efficacy		
	BICR Assessment	Investigator Assessment
ORR, n	21	28
% (95% CI)	14.5 (9.2-21.3)	19.3 (13.2-26.7)
CR, n (%)	2 (1.4)	4 (2.8)
PR, n (%)	19 (13.1)	24 (16.6)
SD, n (%)	60 (41.4)	65 (44.8)
PD, n (%)	56 (38.6)	47 (32.4)
NE, n (%)	8 (5.5)	5 (3.4)
ORR by Etiology		
Uninfected	n=72	n=72
ORR, n	9	14
% (95% CI)	12.5 (5.9-22.4)	19.4 (11.1-30.5)
CR, n (%)	0 (0)	2 (2.8)
PR, n (%)	9 (12.5)	12 (16.7)
HCV-infected	n=30	n=30
ORR, n	6	8
% (95% CI)	20.0 (7.7-38.6)	26.7 (12.3-45.9)
CR, n (%)	1 (3.3)	1 (3.3)
PR, n (%)	5 (5.6)	7 (23.3)
HBV-infected	n=43	n=43
ORR, n	6	6
% (95% CI)	14.0 (5.3-27.9)	14.0 (5.3-27.9)
CR, n (%)	1 (2.3)	1 (2.3)
PR, n (%)	5 (11.6)	5 (11.6)
DOR, median (95% CI)	16.6 (9.7-NA)	NA (9.5-NA)
TTR, median (range)	2.8 (1.2-7.0)	2.7 (1.2-9.6)
PFS, median (95% CI)	2.8 (2.6-4.0)	4.1 (2.8-5.5)
OS, median (95% CI)	15.6 (13.2-18.9)	
Safety		
All cause any grade AEs/grade 3/4	99.3%/49%	
Drug-related any grade AEs/grade 3/4	74.5%/16.6%	
Drug-related SAEs/grade 3/4	9%/4.1%	

Treatment discontinuations due to AEs	11%
Abbreviations: AEs - adverse events; **BICR** - blinded independent central review; **DBL** - database lock; **DOR** - duration of response; **CI** - confidence interval; **CR** - complete response; **HBV** - hepatitis B virus; **HCV** - hepatitis C virus; **NA** - not available; **ORR** - objective response rate; **OS** - overall survival; **PFS** - progression-free survival; **SAEs** - serious AEs; **TTR** - time-to-response; **2L** - second-line.	

Limitations

- The pCODR submission was based on data from the CheckMate 040 trial;[1] this trial is an ongoing, single-group, open-label, phase 1/2 trial with no active treatment or placebo control group. As such, it is difficult to draw conclusions on the efficacy of nivolumab in the absence of a comparison to other available treatment options (regorafenib, BSC). Considering the incidence of HCC, it could be argued that the choice of a phase 2 design is a limitation of the trial. Other agents have been evaluated in phase 3 trials,[5-8] and not all have confirmed positive phase 2 findings.[6-8]
- The submission is based on data from a small subgroup of patients (n=145) from the expansion phase of the trial; those who progressed on or were intolerant to sorafenib (2L). A proportion (n=27; approximately 19%) of these patients actually received nivolumab beyond the 2L, as they had previously been treated with other anti-cancer therapies in addition to sorafenib. Considering these patients were heavily pretreated, it is possible that the efficacy estimates obtained in the CheckMate 040 trial may be conservative compared to a patient population solely comprised of 2L patients.
- The submission is based on pooled data analyses for the 2L patient subgroup from an updated DBL that was performed after 15 months of follow-up. The SAP of the trial[2] was amended to include pooled efficacy analyses prior to the primary efficacy analysis; however, looks at the trial data informed the SAP amendment. Over the course of the trial multiple efficacy analyses have been performed but the SAP did not specify any adjustments for multiple comparison testing, which serves to control for type 1 error (false positives). As well, the trial was only powered for the primary outcome and may not be sufficiently powered to reliably estimate other important endpoints (OS, PFS). Consequently, the pCODR Methods Team has concerns about the reliability of the efficacy estimates obtained. Caution is also warranted in interpreting the results of pre-specified subgroup analyses, as the sample sizes in most of these groups were small, and in making comparisons by etiology. CheckMate 040 was not a randomized trial, and therefore efficacy estimates by etiology subgroup are confounded by differences in important baseline prognostic factors.
- The open-label design of the trial makes it susceptible to selection, reporting and performance biases, as trial patients and investigators were aware of the treatment being administered. Specifically:
    - In approximately 20% of patients in the 2L cohort the time from initial diagnosis to first dose of nivolumab was ≥ 5 years;[3] and the median time from initial diagnosis to first dose of nivolumab was 26.5 months [comparatively, in the RESORCE trial (regorafenib)[5] this time span was 21 months]. Considering the median five-year survival rate of patients with HCC is in the range of 5-6%,[9] there appears to have been selection bias in the trial for more indolent (better prognosis) HCC tumours, which further complicates interpretations of efficacy outcomes as the estimates obtained may be influenced by factors other than treatment.
    - Reporting/performance bias is also a concern for subjective outcomes like safety and QOL. In open-label trials the behaviour of patients, investigators

and/or assessors may be influenced by knowledge of the drug under study and its side effects.

- The primary outcome of the trial was ORR by BICR. While this endpoint can be considered appropriate for a phase 2 trial, the pCODR Methods Team questions its appropriateness for the purpose of regulatory and funding decisions. Median OS is an achievable outcome in 2L treatment of HCC,[3] and therefore, should be the primary endpoint for measuring clinical benefit. As indicated above, phase 3 trials of other agents in HCC have failed to demonstrate an OS benefit despite initial response rates, demonstrating ORR is not a surrogate for OS in HCC.

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

One patient group, the Canadian Liver Foundation provided input for the review. The patient group conducted online questions and patients, caregivers and health care professionals responded to the survey. Patient input indicated that the number of patients who meet the criteria for the target population of this review is very limited and that they were not able to survey patients who had direct experience with nivolumab for HCC. From a patient perspective, commonly reported symptoms associated with HCC that greatly affect quality of life include fatigue, abdominal pain and nausea. Patient input emphasized poor quality of life as a result of HCC, and the desperation patients feel thinking they are a burden to their families, being plagued with side effects, and having limited treatment options for their disease. The patient group stated that sorafenib is the only available treatment for patients with advanced stage HCC.

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:

- Sequencing of available therapies, including chemotherapy

Economic factors:

- Intravenous administration requiring additional chemotherapy chair time.

Registered Clinician Input

One joint clinician input was provided from three oncologists. The clinician input suggested an unmet need among patients with HCC, and that nivolumab would be useful to patients, if made available. The clinicians expressed that it is not clear that the funding request for nivolumab should be based on a phase 1/2 trial, as a phase two trial may not be sufficient to influence a drug reimbursement recommendation.

Summary of Supplemental Questions

The following supplemental question was identified during development of the review protocol as relevant to the pCODR review of nivolumab for advanced HCC:

- Critical appraisal of the Manufacturer-submitted MAIC of nivolumab to relevant comparators as 2L treatment for advanced HCC

The Manufacturer conducted ITCs[10] in order to provide comparative efficacy estimates between nivolumab and relevant comparators as 2L treatment for advanced HCC in patients who progressed or were intolerant to sorafenib. The ITCs performed included covariate-adjusted and MAIC analyses to derive comparative estimates for the outcomes of OS and PFS. These analyses were funded by the Manufacturer and have not been fully published or peer-reviewed. The methods and results of the ITCs were critically appraised by the pCODR Methods Team according to the recommendations of the ISPOR Task Force on Indirect Treatment Comparisons[11] and best practice principles for MAIC.[12] The critical appraisal focused on the ITCs performed that were considered by pCODR to be appropriate comparators in the Canadian context, which included nivolumab compared to BSC and regorafenib. Further, the comparisons to BSC that were reviewed were those from the RESORCE and BRISK-PS trials, as these trials were considered the most relevant for comparison in terms of patient population, size, and recency. For OS, the results of the covariate-adjusted analysis and MAICs were consistent, and showed a statistically significant treatment benefit for nivolumab when compared to BSC/placebo and regorafenib. For PFS, a treatment benefit was shown for nivolumab that was marginally better than BSC/placebo; however, no difference in PFS was observed when nivolumab was compared to regorafenib. The pCODR Methods Team concluded the ITC results should be interpreted with caution considering a number of limitations associated with the analyses that raise uncertainty in the treatment estimates obtained. Refer to Section 7.1 for more information and the complete critical appraisal of the ITCs.

Comparison with Other Literature

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

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence from the CheckMate 040 trial;[2] an assessment of the limitations and sources of bias associated with the trial can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of generalizability of evidence for nivolumab (Opdivo) in advanced HCC.

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence from CheckMate 040 - 2L expansion population (n=145)[2]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td rowspan="3">Population</td><td>BCLC Stage</td><td>The trial did not limit eligibility by BCLC stage. The majority of patients were BCLC stage C (89%).

<table><tr><td>BCLC Stage</td><td>n (%)</td></tr><tr><td>A</td><td>2 (1)</td></tr><tr><td>B</td><td>14 (10)</td></tr><tr><td>C</td><td>129 (89)</td></tr></table>
Subgroup analyses were performed; ORR by BICR by stage were as follows:

<table><tr><td>BCLC Stage</td><td>ORR % (95% CI)</td></tr><tr><td>A</td><td>50 (1.3-98.7)</td></tr><tr><td>B</td><td>0 (0-23.2)</td></tr><tr><td>C</td><td>15.1 (9.3-22.5)</td></tr></table></td><td>Does stage limit the interpretation of the trial results with respect to the target population?</td><td>Nivolumab should only be used for the treatment of patients with BCLC stage B or C.</td></tr>
<tr><td>Performance Status</td><td>The trial limited eligibility to patients with an ECOG performance status of 0-1.

<table><tr><td>ECOG PS</td><td>n (%)</td></tr><tr><td>0</td><td>93 (64)</td></tr><tr><td>1</td><td>52 (36)</td></tr></table>
No subgroup analyses were performed by ECOG performance status.</td><td>Does performance status limit the interpretation of the trial results (efficacy or toxicity) with respect to the target population?</td><td>Nivolumab should only be used for the treatment of patients with an ECOG performance status of 0-1.</td></tr>
<tr><td>Child Pugh Score</td><td>The trial required patients have a Child Pugh score of 6 or less (Child Pugh A).</td><td>Does Child Pugh score limit the interpretation of the trial results (efficacy</td><td>Nivolumab should only be used for the treatment of patients with Child Pugh score of 6 or less (i.e., Child Pugh A).</td></tr>
</table>

Domain	Factor	Evidence from CheckMate 040 - 2L expansion population (n=145)[2]	Generalizability Question	CGP Assessment of Generalizability
		<table><tr><td>Child Pugh</td><td>n (%)</td></tr><tr><td>5</td><td>97 (67)</td></tr><tr><td>6</td><td>46 (32)</td></tr><tr><td>7 or above</td><td>2 (1)</td></tr></table> No subgroup analyses were performed by Child Pugh score.	or toxicity) with respect to the target population?	
	Metastatic Sites	The trial excluded patients with brain metastases.	Did the exclusion of patients with certain sites of metastatic disease limit the interpretation of the trial results with respect to the target population?	Brain metastases is not common in patients with relapsed or refractory HCC. Therefore, the CGP agree that nivolumab does not need to be expanded to include those with asymptomatic brain metastases.
Intervention	Line of therapy	The majority of included patients had progressed on or after treatment with sorafenib (n=132; 91%). A small proportion of patients were deemed sorafenib intolerant (n=12; 8.3%). There was a proportion of patients (n=27; 18.6%) who had ≥2 prior systemic therapies in addition to sorafenib.	Are the results of the trial generalizable to other lines of therapy?	In a setting where regorafenib is available following sorafenib, there is no reliable information from the data submitted on the efficacy of nivolumab in the third line setting. The use of nivolumab in the first line setting is out of scope for this review.
Outcome	Appropriateness of primary outcome	The primary outcome of the trial was ORR by BICR. Secondary outcomes included CR rate, DCR, DOR, TTR, TTP, and PFS, all evaluated by either BICR or investigator assessment, and OS.	Is the primary outcome appropriate for the trial design?	The primary outcome of the trial was ORR by BICR. In prior studies of systemic therapies in advanced HCC, ORR have only been rarely observed. Tumour ORR have not been validated as a surrogate endpoint for OS in HCC.

Abbreviations: AE(s) - adverse events; **BCLC** - Barcelona Clinic Liver Cancer; **BICR** - blinded independent review; **CGP** - Clinical Guidance Panel; **CR** - complete response; **DCR** - disease control rate; **DOR** - duration of response; **ECOG** - Eastern Cooperative Oncology Group; **ORR** - objective response rate; **OS** - overall survival; **PFS** - progression-free survival; **PS** - performance status; **TTP** - time-to-progression, **TTR** - time-to-response.

1.2.4 Interpretation

Effectiveness

Nivolumab is a fully human immunoglobulin G4 monoclonal antibody that targets the PD-1 immune checkpoint signalling pathway, affecting the antitumor activity of tumor suppressed effector T cell responses. Conditions such as cirrhosis and viral hepatitis result in immunosuppression in the hepatocellular cancer tumor microenvironment, making immune checkpoint inhibitors potential therapeutic targets. The clinical efficacy of nivolumab, the first PD-1 inhibitor in advanced hepatocellular carcinoma was demonstrated in a multicentre, single arm, phase 1/2, open label, non-comparative, dose escalation and expansion study across multiple hepatocellular carcinoma etiologies who were previously treated or untreated with sorafenib (CheckMate 040).[1] The expansion phase of the trial (phase 2), specifically the pooled data analyses for the 2L patient subgroup was considered in this review. Eligible patients had a Child-Pugh score of 6 or less in the expansion phase, and an ECOG performance status of 1 or less. Effective antiviral therapy was required for patients with HBV infection, but this was not required for those with HCV infections. Nivolumab was given at 3 mg/kg every 2 weeks in the dose-expansion phase in four cohorts: sorafenib untreated or intolerant without viral hepatitis, sorafenib progressors without viral hepatitis, HCV infected and HBV infected. The primary endpoint of the phase 2 expansion phase was tumor objective response rate (by BICR using RECIST 1.1). The objective response rate was 14.5% (95% CI, 9.2-21.3) in the 2nd line dose expansion cohort. The duration of response was 16.6 months (95% CI, 9.7-NA) with a median progression free survival of 2.8 months (95% CI, 1.2-7.0). The median OS in this cohort was 15.6 months (95% CI, 13.2-18.9 months).

Quality of life was an exploratory endpoint and was measured with the EQ-5D questionnaire. Treatment with nivolumab did not significantly alter patient reported EQ-5D-3L index scores.

The ORR were similar in those patients who had not previously been treated with sorafenib or were intolerant and in patients with disease progression on sorafenib. No conclusions can be made regarding different clinical efficacy in those infected with HBV or HCV. Importantly, in prior studies of systemic therapies in advanced HCC, objective response rates have only been rarely observed. Objective responses occurred irrespective of PD-L1 expression on tumor cells.

Safety

The median duration of nivolumab therapy was 5.26 months in the 2L cohort. The median number of treatment cycles was 12 and most patients received >90% of planned dose intensity. Fifty-four percent of patients in this cohort were treated beyond disease progression.

The most common treatment related adverse events for patients on nivolumab was fatigue (35.9%), pruritis (28.3%), diarrhea (26.9%), abdominal pain (24.1%), cough (22.1%), and decreased appetite (21.4%). Treatment discontinuation due to any AE occurred in 11% of patients. Drug related SAEs occurred in 9% of patients and drug-related treatment discontinuations occurred in 2% of patients (stomatitis, polyarthritis and pneumonitis). One patient death was considered to be related to nivolumab (pneumonitis). The toxicities observed with nivolumab were expected and manageable.

Burden of Illness and Need

An estimated 2,500 new cases of HCC were diagnosed in Canada in 2017.[13] Sorafenib (also an oral-multi-tyrosine kinase agent that inhibits RAF-kinase and VEGFR intracellular kinases), is currently approved and funded across Canada for the first-line systemic treatment of with advanced HCC no longer amenable to locoregional therapy and/or with metastatic disease, who have Child-Pugh Class A liver function.

Until recently, no standard treatment options for patients beyond sorafenib therapy outside of a clinical trial. Patient Advocacy Group input from CLF affirms that patients with HCC face a poor prognosis, and that while there are treatment options that are approved by Health Canada, there are currently no funded treatment options for patients following sorafenib progression. In April 2018, regorafenib, another TKI, was recommended for funding in patients previously treated with sorafenib. However, it is currently not funded in any province.

PAG identified the additional burden of intravenous administration of nivolumab in this patient population. Other concerns raised by PAG included the dosing schedule of nivolumab in comparison to use of nivolumab in other tumour types. Given the availability of regorafenib in the 2nd line setting, PAG also raised the role of nivolumab in the 3rd line setting. Additional guidance regarding the definition of sorafenib intolerance was recommended.

In summary, nivolumab is a novel parenteral therapy that has demonstrated encouraging clinical activity as measured by tumor response in a patient population with limited treatment options. In HCC, tumor objective response rates have not been validated as a surrogate endpoint for OS. The OS observed in this single arm trial is encouraging. However, given the sample size of the study and the lack of a comparative arm, interpretation and generalizability of the findings are limited. Furthermore, no further data regarding the efficacy of nivolumab in the 2nd line treatment of HCC will be available given the lack of ongoing confirmatory studies in this setting. The safety profile of nivolumab in this tumor setting appears acceptable and appears to be similar to larger studies conducted in other tumour types.

Following the posting of the Initial Recommendation, the Submitter provided feedback requesting that pERC reconsider reimbursement of nivolumab for patients with HCC who are intolerant to or have discontinued sorafenib due to intolerance and/or toxicity. The Submitter noted that there is an unmet need for these patients as there are no treatment options currently available. While regorafenib is an option for patients with HCC following progression on sorafenib, regorafenib is not available for patients with HCC who are intolerant to sorafenib.

In response to the Submitter's feedback, the CGP notes that in the CheckMate-040 expansion 2L cohort, only 12 (8.3%) patients were deemed intolerant to sorafenib (see Section 6.3.2.1 (Detailed trial characteristics) for the definition of intolerance to sorafenib used in the CheckMate-040 trial). These patients were included in the pooled 2L expansion phase population of the trial (n=145) which also included patients that experienced disease progression on sorafenib.

The CGP agree that there is an unmet need for patients who are intolerant to sorafenib. The CGP also note that toxicity from sorafenib is very common and very few patients are able to tolerate the recommended dose. Furthermore, it is common for patients to stop treatment with sorafenib due to toxicity. In addition, the CGP note that in clinical practice, it is common that patients will not start treatment with sorafenib due to a

possible decrease in quality of life. However, these patients were not captured in the CheckMate-040 trial.

1.3 Conclusions

The Clinical Guidance Panel concludes that there ***may be*** a net overall clinical benefit with the use of nivolumab in adult patients with advanced (not amenable to curative therapy or local therapeutic measures) or metastatic HCC who are intolerant to or have progressed on sorafenib therapy, with Child-Pugh Class A hepatic reserve and an ECOG performance status of 0-1 based on the current limited evidence from the CheckMate-040 trial.

In reaching this conclusion, the CGP considered:

- Effectiveness: The response rate observed in the multi-centre, single arm study associated with an encouraging OS benefit. The lack of a comparative arm and sample size of the CheckMate 040 study is acknowledged by the panel. Furthermore, the lack of a comparative arm is a major barrier to estimating the effectiveness of nivolumab in this patient population. Subsequent ongoing randomized trials involve upfront randomization between sorafenib versus nivolumab in the treatment-naïve setting and will not provide additional data in the intolerant or 2L setting.[14]
- In a setting where regorafenib is available following sorafenib, no reliable information can be obtained from the data submitted on the efficacy of nivolumab in the 3rd line setting.
- Safety: The toxicities observed with nivolumab in this patient population were expected, manageable, and similar to those observed in larger studies of other tumour types.
- Need: Nivolumab offers a potentially clinically effective therapy in a disease setting where other available options are limited and may be associated with potentially significant toxicity.
- There are no data from RCTs to clearly establish the superiority of nivolumab to BSC in advanced HCC patients who are intolerant to or have progressed on sorafenib therapy. However, conducting a phase 3 RCT may be feasible in this setting. There are ongoing randomized controlled trials in similar patient populations comparing other therapies to BSC. Specifically the phase 3 RESORCE trial evaluating regorafenib versus BSC[5] and the ongoing phase 3 trial evaluating pembrolizumab monotherapy versus best supportive care in advanced HCC patients previously treated with systemic therapy.[15] The estimated study completion date of this trial is February 1, 2019. The ongoing first-line studies of immune check point inhibitors versus sorafenib may limit the interest in a phase 3 2L trial.
- In the absence of comparative studies of nivolumab and relevant comparators, the Manufacturer conducted ITCs to provide comparative efficacy estimates between nivolumab and relevant comparators as 2L treatment for advanced HCC in patients who have progressed or are intolerant to sorafenib. For OS, the results of the covariate-adjusted analysis and MAICs were consistent, and indicated a statistically significant treatment benefit for nivolumab compared to BSC/placebo and regorafenib. For PFS, a treatment benefit was shown for nivolumab that was marginally better than BSC/placebo; however, no difference in PFS was observed when nivolumab was compared to regorafenib. Data on other important outcomes, including ORR, safety and HRQOL were not analyzed. The overall conclusions of the ITC are limited because of the differences in patient characteristics among the included studies and methodological limitations identified. Overall, the results of the ITC should be interpreted with caution. The comparative efficacy of nivolumab to BSC and regorafenib is uncertain.

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

Over the last two decades, the incidence of HCC in Canada has increased by 3.1% per year in men, and 2.1% per year in women attributed in part to rising immigration from countries where risk factors for HCC such as hepatitis B and C, are endemic. Approximately 2,500 new cases of HCC will be diagnosed in Canada in 2017.[13] HCC is a challenging disease to treat as it typically appears in the setting of underlying hepatic cirrhosis which is often associated with hepatic impairment. Thus the treatment approach and consequent prognosis of patients with HCC depends upon not only the extent of the cancer, but also underlying hepatic function and performance status of the patient. Table 1 outlines Child-Pugh class, the most commonly employed tool to determine hepatic reserve, and includes the parameters of serum levels of INR, albumin and bilirubin as well as clinical evidence of ascites or encephalopathy.

Table 1: Child-Pugh Classification

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

A variety of important risk factors for the development of HCC have been identified. Among the most important are alcohol use, hepatitis B carrier state, chronic hepatitis C virus infection, hereditary hemochromatosis and aflatoxin exposure.

2.2 Accepted Clinical Practice

Although there are several staging systems in use for HCC, the BCLC staging system is the most widely used prognostic and treatment algorithm for HCC in the Canadian system (Figure 1). The staging system incorporates prognostic factors related to tumour status, liver function and patient performance status. As per the BCLC algorithm, the prognosis for patients with advanced, unresectable HCC with preserved hepatic reserve (stage C) is poor with a median OS of less than one year.[16]

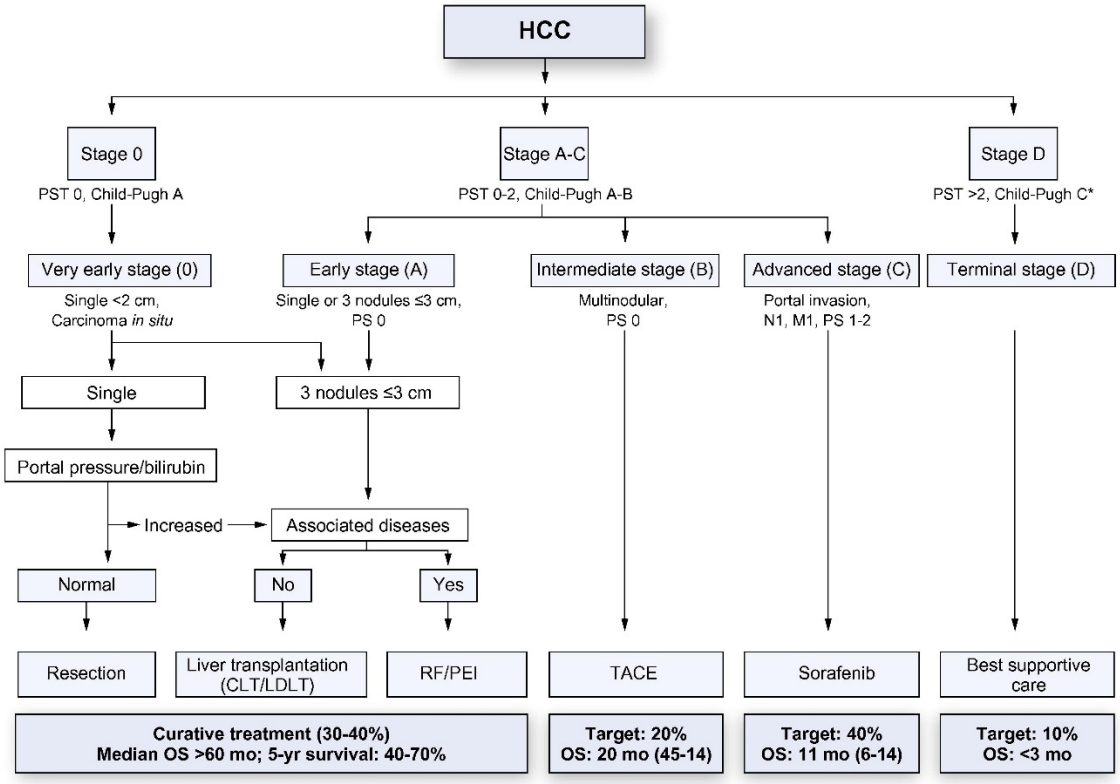


Figure 1: Barcelona Clinic Liver Cancer Staging System for HCC in Canada.

HCC is considered to be a chemotherapy-refractory tumour. Sorafenib is an oral multi-tyrosine kinase inhibitor that inhibits the RAF-kinase and VEGFR intracellular kinase pathways. The SHARP trial was a multicentre, European, randomized, double-blinded placebo controlled study in patients with advanced, inoperable HCC and Child-Pugh class A hepatic reserve comparing sorafenib therapy to placebo.[17] The median OS in the sorafenib arm was 10.7 months versus 7.9 months in the placebo arm (HR=0.69; 95% CI, 0.55–0.87; p<0.0001). In addition, sorafenib showed a significant benefit in terms of TTP assessed by independent radiological review with a median TTP of 5.5 months for sorafenib and 2.8 months for placebo (p<0.0001). It is of note that this represents a selected patient population – in the SHARP trial, only 602/902 (67%) of screened patients were eligible for randomization.[17]

The magnitude of survival benefit with sorafenib in SHARP was similar to that demonstrated in a parallel phase III trial conducted in the Asian-Pacific population, in which hepatitis B was the main cause of HCC.[18] 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, 0.50–0.93; p=0.014). The inferior survival outcome observed in both arms of this study compared with the SHARP investigation, is believed to be due to the fact that the patients had a higher proportion of Hepatitis B and more advanced disease (ECOG 1–2 or metastatic disease). The most common grade 3 drug-related adverse events with sorafenib included hand-foot syndrome and diarrhea which occurred in 8-10.7% and 8-6%, respectively.[17,18] Based on these data, sorafenib is currently approved and funded across Canada for the first-line systemic treatment of Child-Pugh A class patients with advanced HCC.

There are currently no standard treatment options for patients beyond sorafenib therapy. Evidence is emerging that stereotactic body radiotherapy (SBRT) in carefully selected patients may provide additional local control with or without concurrent sorafenib and clinical trials are currently underway. Regorafenib is also an oral multikinase inhibitor, structurally similar to sorafenib, and targets a number of angiogenic kinases (including VEGFR), stromal and oncogenic receptor TKIs. In the phase 3 RESORCE trial[5], a survival benefit for regorafenib (160mg p.o. daily for three weeks on and one week off) was demonstrated in patients progressing after first-line treatment with sorafenib who maintained an ECOG performance status of 0-1 and Child-Pugh A liver function. When compared to placebo, regorafenib was associated with a statistically significant improvement in OS (10.6 months versus 7.8 months, HR=0.63) in addition to increased disease control rates (65% versus 36%). Grade 3-4 AEs included hypertension (15% versus 5%), hand-foot skin reaction (13% versus 1%) fatigue (9% versus 5%) and diarrhea (3% versus 0%).[5] Despite these AEs, HRQOL as assessed by EQ-5D and FACT-Hep, was not significantly worse with regorafenib compared to placebo.[5] In April of 2018, pERC conditionally recommended the funding of regorafenib for patients with unresectable HCC who have been previously treated with sorafenib conditional on the cost-effectiveness being improved.

More recently, the post-sorafenib HCC landscape continues to change with the results of studies examining the efficacy of immune check point inhibitors. In the US, the FDA granted accelerated approval to nivolumab for patients with HCC following prior sorafenib. This was based on a phase 1/2 CheckMate-040 trial with 262 patients in which the overall response rate was 15% with 3 patients experiencing a complete response.[1] Furthermore, the median DOR was 17 months. The FDA also approved pembrolizumab (an anti-PD1 antibody) based on a phase 2 study in HCC patients after prior sorafenib, which demonstrated an ORR of 16.3% with a median DOR of 8.2 months.[19] There is an ongoing phase III study of pembrolizumab monotherapy versus BSC in advanced HCC patients previously treated with systemic therapy.[15] In addition, studies examining the potential for therapeutic effects of SBRT and immune check point inhibitors are only now currently underway, with results on safety and tolerability not expected for at least a couple of years.

2.3 Evidence-Based Considerations for a Funding Population

The expected population for nivolumab use would be patients with advanced, inoperable HCC who experienced progression or intolerance to sorafenib, with Child-Pugh class A hepatic reserve, based upon the eligibility criteria in the CheckMate-040 trial.[1] Given the associated toxicities of nivolumab, its use would not be considered in patients with an ECOG PS of 2 or worse, or a Child-Pugh score of 6 or greater (Child-Pugh B and C).

2.4 Other Patient Populations in Whom the Drug May Be Used

Currently there are no other HCC patient populations that would be considered for nivolumab therapy.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient group, CLF, provided input for this review on nivolumab for HCC. CLF conducted an online questionnaire modelled on the CADTH, CDR, pCODR Programs submissions template. Patients, caregivers and health care professionals were invited to complete the survey, which was available for completion between May 1, 2018 and May 15, 2018. CLF promoted its survey on their website, through social media, an e-newsletter and to CLF patients, caregivers and health care professionals across Canada. CLF included the opinion from six health professionals to provide background context in managing the use of the drug under review.

CLF indicated that the number of patients who meet the criteria for the target population of this review (i.e. patients with advanced stage HCC previously treated with sorafenib) is *"very limited",* and that the number of patients with direct experience with nivolumab further limits the pool of patients. CLF highlighted the difficulty it experienced in securing direct Canadian patient input for this submission. Consequently, CLF supplemented its submission with non-nominal comments from approximately 40 Canadian CLF patient contacts, unrelated to its survey for this submission, but whom CLF thought could still provide valuable input for this pCODR review. In addition, CLF included response data from the first Global Survey of People Living with HCC, conducted in 2016; CLF was one of the international health charities who participated in the survey. Of the 256 respondents who were included in the Global Survey of People Living with HCC (Global Survey), eight were Canadian.

From a patient perspective, commonly reported symptoms associated with HCC that greatly affect quality of life include fatigue, abdominal pain and nausea. Patient contacts from CLF emphasized their poor quality of life as a result of HCC, and the desperation they feel thinking they are a burden to their families, being plagued with side effects, and having limited treatment options for their disease. CLF stated that sorafenib is the only available treatment for patients with advanced stage HCC. Reports of many side effects and reduced quality of life were reported by patients as part of the Global Survey, as well as CLF patient contacts with experience taking sorafenib.

Please see below for a summary of specific input from CLF. Quotes are reproduced as they appeared in the surveys, with no modifications made for spelling, punctuation or grammar.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with HCC

CLF stated that liver cancer is the sixth most common cancer worldwide, and prevalence of the disease is expected to increase over the next decade. CLF indicated that HCC is the most common type of liver cancer in Canada, accounting for 71.9% of liver cancers among both men and women. CLF posits that the increasing prevalence of HCC, which is an indication of increasing prevalence of late-stage and end-stage liver disease, is driven primarily by an aging population of individuals with hepatitis B and hepatitis C, and the increasing prevalence of non-alcoholic fatty liver disease (NAFLD).

As mentioned previously, CLF included information about patients' experiences with HCC using the Global Survey of People Living with HCC; a total of 256 respondents provided information regarding symptoms of HCC impacting their quality of life. Respondents of the Global Survey indicated fatigue due to their condition as impacting their quality of life the most, followed by abdominal pain and nausea; other symptoms mentioned by respondents included appetite loss, weight loss, diarrhea, skin disorders and alopecia. The following quote was provided by a CLF patient contact in regards to patient experiences with HCC:

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

Patients responding to the Global Survey also indicated feelings of emotional and mental distress, in addition to the physical ailments related to HCC; they expressed feelings of fear, worry, shock, and sadness. The following quotes were provided by CLF from patient contacts; they also expressed feelings of worry and fear related to their condition, in addition to feeling worry from thinking they are burdensome to their families.

- *"I cannot help and participate in daily activities. I am a burden on my family. They have to do everything for me. I am in pain all the time. I cannot sleep at night and am groggy and confused during the day."*
- *"My worst symptom is pain and being uncomfortable all the time. Mornings are the 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 kids without a father is unbearable."*

3.1.2 Patients' Experiences with Current Therapy for HCC

CLF posits that patients with HCC often have pre-existing progressive liver diseases affecting liver function, such as cirrhosis, jaundice, and abdominal pain and swelling (ascites), which make treatment of HCC difficult. Stage of the tumour, speed of tumour growth and health of the liver affect treatment of HCC, with cure rates generally decreasing with increasing tumour size. CLF stated that sorafenib is the current standard of care for patients with HCC with well-preserved liver function (Child-Pugh A). However, patients responding to the Global Survey were more likely to indicate their quality of life as being poor if their most recent treatment was sorafenib. Quotes from CLF patient contacts indicated experiencing both severe side effects, and relief from disease symptoms due to sorafenib. However, there were also feelings of dread after experiencing intolerance to sorafenib.

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

3.1.3 Impact of HCC and Current Therapy on Caregivers

As indicated previously by CLF, sorafenib, which is the current standard of care for patients with advanced stage HCC, comes with many side effects and reduces patient's quality of life. CLF emphasized that there is a great need for new and better treatment options for this vulnerable population of HCC patients.

- *"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."*

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Nivolumab

As mentioned previously, no patients responded to CLF's survey, therefore there were no direct responses from patients who had experience with nivolumab for HCC. CLF indicated that use of nivolumab in clinical settings in Canada has been limited, restricting CLF's ability to receive patient feedback.

3.3 Additional Information

CLF mentioned that, unlike patients who are diagnosed with liver cancer in later stages, patients who are diagnosed early are presented with many treatment options; surgical resection, liver transplant, ablation and chemoebolization exist as treatment options for liver cancer patients who are diagnosed early. Many patients with liver cancer in Canada are not diagnosed early, as symptoms do not express themselves until the liver is damaged and there is progression to later stages of cancer. Sorafenib stands as the standard of care for patients with advanced stage HCC in Canada. CLF emphasized the poor survival prognosis especially of patients who are diagnosed at advanced stages of their liver cancer, and that new treatment options provide patients and their families with hope.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

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

Overall Summary

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

Clinical factors:

- Sequencing of available therapies, including chemotherapy

Economic factors:

- Intravenous administration requiring additional chemotherapy chair time.

Please see below for more details.

4.1 Currently Funded Treatments

Sorafenib is the standard of care in first line treatment of metastatic HCC and is funded in all provinces. After failure on sorafenib, best supportive care is available. PAG noted that the Checkmate 040 study is a phase 1/2, open-label, non-comparative, dose escalation and expansion trial and is seeking information on comparison of nivolumab with best supportive care.

At the time of the PAG input, PAG also noted that regorafenib is undergoing review for treatment of HCC after sorafenib. Regorafenib recently received a conditional reimbursement recommendation conditional on the cost-effectiveness being improved to an acceptable level. At this time, no provinces are currently funding regorafenib. PAG is seeking data comparing nivolumab with regorafenib in patients who have failed sorafenib.

4.2 Eligible Patient Population

PAG is seeking clarity on the eligible patient population. PAG noted that sorafenib is funded for patients with advanced HCC not amenable to local therapy in patients with performance status of ECOG 0-2 and Child-Pugh A liver function. The funding request from the manufacturer does not specify Child-Pugh status and the Checkmate 040 study had two phases where the eligibility based on liver function differed slightly and enrolled patients only with ECOG 0 or 1. In addition, PAG noted that the trial included patients who are co-infected with hepatitis and is seeking confirmation that these patients would be eligible for treatment with nivolumab.

The funding request is for patients who were treated with sorafenib and failed sorafenib or were intolerant to sorafenib. PAG is seeking guidance on when patients would be deemed intolerant to sorafenib and be eligible for treatment with nivolumab. Although there was a cohort of patients in the Checkmate 040 trial who were not previously treated with sorafenib (patients who refused sorafenib were also eligible), PAG identified that there should be clarity that first line treatment with nivolumab as an option to sorafenib or for patients not eligible for sorafenib (e.g. Child-Pugh B) is out of scope of this review and is not considered in this funding request.

4.3 Implementation Factors

As nivolumab is administered intravenously, chemotherapy chair time and nursing resources would be required to administer nivolumab.

PAG noted that the Checkmate 040 trial is a dose escalation trial and is seeking clarity on the dose and treatment duration. The dose of 3mg/kg up to maximum of 240mg, administered every two weeks, has been implemented for other cancers. PAG is seeking clarification that this dosing strategy and other dosing strategies (e.g. 480mg every 4 weeks) would be appropriate for HCC, as with other cancers.

PAG identified that there will be some patients who have been previously treated with sorafenib and who are currently being treated or have been treated with other therapies at the time of nivolumab funding and use of nivolumab in these patients would need to be considered in next steps for stakeholders.

PAG is also seeking clarity on treatment duration and guidance on whether retreatment with nivolumab would be appropriate in those patients who have been on a treatment break, but develop disease progression during this treatment break.

4.4 Sequencing and Priority of Treatments

PAG noted that some patients, who have failed sorafenib, are being treated with regorafenib obtained through private insurance or a manufacturer's access program. PAG is seeking information on the use of nivolumab in third line after regorafenib in second line. In addition, PAG is seeking whether there is information to guide sequencing of nivolumab and regorafenib in patients who have failed first line sorafenib.

4.5 Companion Diagnostic Testing

None.

4.6 Additional Information

PAG also noted that there is an ongoing phase 3 trial comparing nivolumab with sorafenib in first line and indicated that a submission would be required for funding consideration of nivolumab as first line treatment.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

One joint clinician input was provided from three oncologists.

The clinician input stated that nivolumab could be generalized to patients with hepatocellular carcinoma (HCC) who are Child-Pugh A to B7. While nivolumab could provide a treatment option to Child-Pugh B7 patients, who otherwise would not be eligible for standard care sorafenib. However, it was noted that some clinicians in the group were unsure whether Child-Pugh B7 patients should be treated with nivolumab. The clinician input suggested an unmet need among patients with HCC, and that nivolumab would be useful to patients, if made available. The clinicians expressed that it is not clear that the funding request for nivolumab should be based on a phase 1/2 trial, as a phase two trial may not be sufficient to influence a drug reimbursement recommendation.

Please see below for a summary of specific input received from the registered clinician(s).

5.1 Current Treatment(s) for HCC

Based on the clinician input, lenvatinib is an alternative therapy to first-line sorafenib. However, the clinician input stated that lenvatinib would not be useful to patients who were sorafenib intolerant, as both lenvatinib and sorafenib belong to the same class of drugs. Clinicians noted that regorafenib showed clinical benefit after progression, potentially resulting in less toxicity than what is seen among advanced metastatic colorectal cancer patients; it should be noted that regorafenib is not a currently funded treatment option for these patients.

5.2 Eligible Patient Population

Some clinicians indicated that nivolumab could be generalizable to Child-Pugh A to B7 patients. The clinicians noted that since Child-Pugh B7 patients cannot receive sorafenib, the introduction of nivolumab could provide these patients with a treatment option. The clinicians noted that the funding request captured the needs of patients in the clinical setting. However, there was uncertainty among some clinicians as to whether Child-Pugh B7 patients were intended to be included. Some clinicians stated that the use of nivolumab should be based on phase 3 RCT data and therefore restricted only to Child Pugh A patients, and the decision to use nivolumab for other subgroup of patients should not be left to the discretion of the clinician.

5.3 Relevance to Clinical Practice

The clinicians indicated that currently there is an unmet need and limited treatment options for patients with HCC. One clinician noted that one of their patients was responding well to nivolumab.

5.4 Sequencing and Priority of Treatments with New Drug Under Review

The clinician input indicated that currently there are phase 3 trials underway using nivolumab as first-line therapy. However, as the current funding request for nivolumab does not pertain specifically to the first-line indication, the clinicians mentioned support for use of nivolumab in the second-line; in the meantime, if the drug is available, the clinicians providing input suggested that nivolumab is worth using. While the currently ongoing phase three trials might affect future treatment sequencing, the clinicians noted that there is currently no routine second-line treatment; therefore, the use of nivolumab in second-line would not replace any other therapy.

5.5 Companion Diagnostic Testing

None.

5.6 Additional Information

The clinicians expressed uncertainty regarding whether the funding request for nivolumab should be based on a phase 1/2 trial as a phase two trial may not be sufficient to influence a reimbursement recommendation. The opinion of the clinicians emphasized that the decision to approve nivolumab for use among patients should be based on phase three RCT data.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of nivolumab in adult patients with unresectable advanced (not amenable to local treatment) or metastatic HCC who are intolerant to or have progressed on sorafenib.

Note: Supplemental Questions most relevant to the pCODR review and to the PAG were identified while developing the review protocol and are outlined in section 7.

- Critical appraisal of the Manufacturer-submitted MAIC of nivolumab to relevant comparators as 2L treatment in advanced HCC

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

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

Table 3: Trial Selection Criteria.

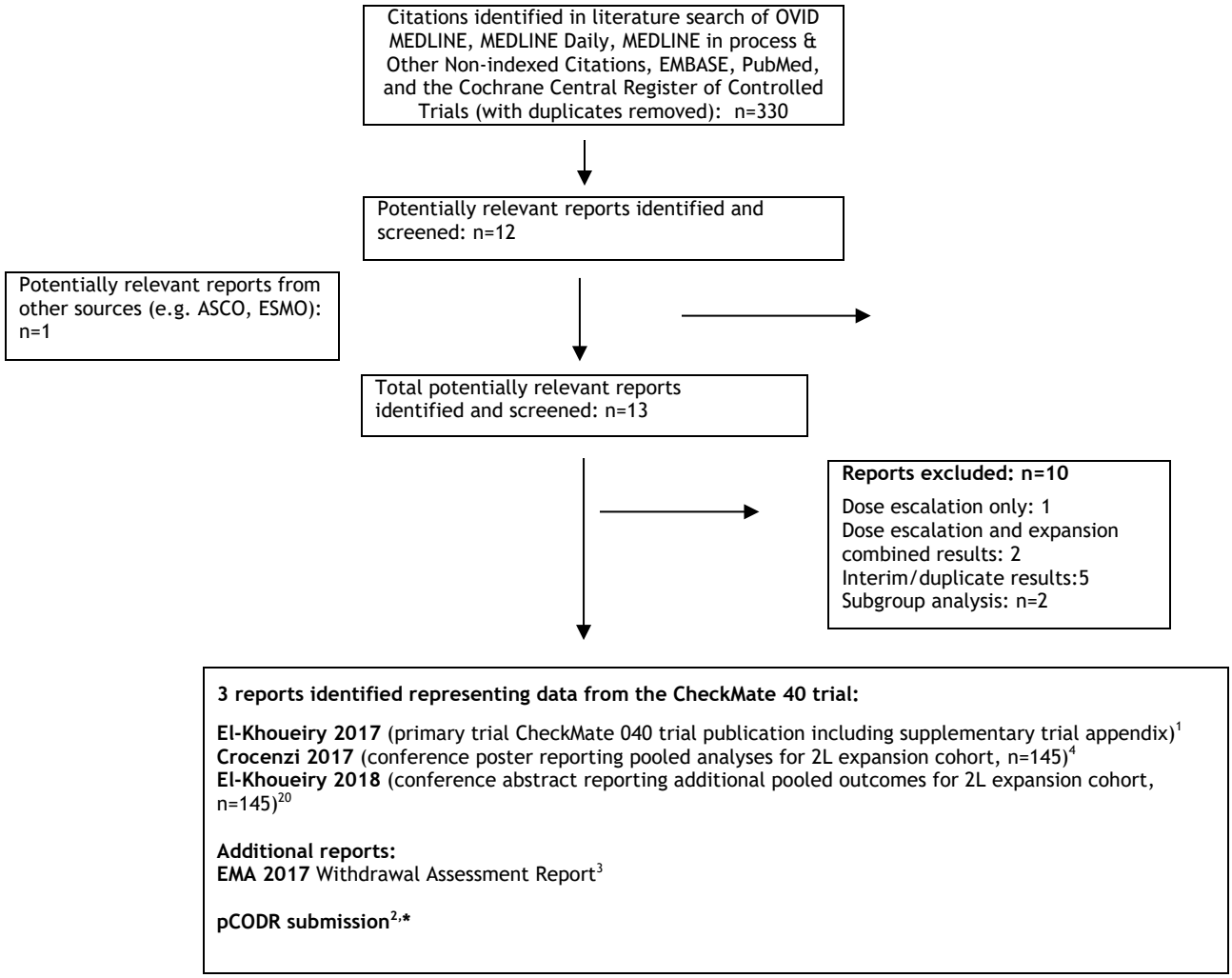
Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
• Published or unpublished RCTs • In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of nivolumab should be included	• Patients with unresectable locally advanced (not amenable to local treatment) or metastatic HCC who are intolerant to, or have progressed on sorafenib Subgroups of interest: • Hepatitis infection (B or C) • Child Pugh (A, B)	• Nivolumab	• BSC • Regorafenib**	Primary: • OS • PFS • **HRQOL** Secondary • ORR • DOR • DCR Safety • AEs • SAEs • WDAEs • AEs of interest o Fatigue o Immune-related AEs
Abbreviations: AE(s) - adverse event(s); **BSC** - best supportive care; **DCR** - disease control rate; **DOR** - duration of response; **HCC** - hepatocellular carcinoma; **HRQOL** - health-related quality of life; **ORR** - objective response rate; **OS** - overall survival; **PFS** - progression-free survival; **SAE(s)** - serious adverse events; **WDAEs** - withdrawals due to adverse events.				
Notes: * Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions). ** Regorafenib is an appropriate comparator in patients who are tolerant to sorafenib but have progressed. Regorafenib is not currently funded for this indication in Canada.				

6.3 Results

6.3.1 Literature Search Results

Of the 330 potentially relevant reports identified, three reports were included in the pCODR systematic review[1,4,20] and ten reports were excluded.[21-30] Reports were excluded because they reported results on dose escalation only,[21] did not report results separate for the 2L dose expansion patient cohort,[23,28] reported earlier/interim or duplicate study results,[22,24-27] or reported patient subgroup analyses not of interest to this review.[29,30]

Figure 2. QUOROM Flow Diagram for Inclusion and Exclusion of studies



**Note: Additional data related to the CheckMate 040 trial were also obtained through requests to the Submitter by pCODR.*

6.3.2 Summary of Included Studies

One clinical trial, CheckMate 040, was identified that met the selection criteria of the pCODR systematic review.[1] Key characteristics of the trial, including design, eligibility criteria and outcomes of interest, are summarized in Table 4. Specific aspects of trial quality, including sample size, statistical considerations, and efficacy analyses are summarized in Table 5.

6.3.2.1 Detailed Trial Characteristics

Table 4: Trial Characteristics of the Included CheckMate 040 trial (dose expansion phase).[1]

Trial Design	Eligibility Criteria[B]	Intervention	Trial Outcomes
CheckMate 040 NCT01658878 CA209040 Open-label, non-comparative, multi-centre, phase 1 (dose escalation) and phase 2 (dose expansion) trial[A] N=214 (dose expansion phase) 39 sites in 11 countries including Canada, USA, UK, Germany, Spain, Italy, China, Japan, South Korea, Taiwan, and Singapore. Patient Enrolment Dates: November 26, 2012 to August 8, 2016 Included four patient cohorts by etiologic subtype: • Sorafenib untreated or intolerant[G] • Sorafenib progressor[G] • HCV infected • HBV infected Data cut-off dates: August 8, 2016 Final Analysis Date: July 9, 2019[31] Funding: Bristol-Myers Squibb	<u>Key Inclusion Criteria:</u> • Age ≥18 years • Histologically confirmed HCC not amenable to curative surgery or local treatment[C] • For uninfected[D] sorafenib naïve or intolerant patients, patients must either have never received sorafenib or were deemed intolerant according to definition of intolerance used in the trial[E] • For uninfected[D] sorafenib progressors, patients must have documented radiographic or symptomatic progression during or after sorafenib therapy • For HCV or HBV infected cohorts,[F] patients must have received sorafenib and either be intolerant[E] or have documented radiographic symptomatic progression during or after sorafenib therapy • Child Pugh scores of 6 or less (Child Pugh A) • ECOG PS of ≤1 • Adequate organ and bone marrow function <u>Key Exclusion Criteria:</u> • Previous treatment with agents targeting T-cell costimulation or checkpoint pathways (PD-L1, PD-L2, CD137, CTLA-4) • Coinfection with HBV and HCV, active infection with HBV and hepatitis D virus, HIV infection • Brain metastases • History of hepatic	Nivolumab 3 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity	<u>Primary:</u> • ORR by BICR using RECIST version 1.1[2] <u>Secondary:</u> • CR rate • DOR • Time-to-response • DCR • TTP • TTP rate • PFS • OS • ORR by PD-L1 expression <u>Exploratory:</u> • HRQOL (EQ-5D and EQ-VAS) • ORR by mRECIST

Trial Design	Eligibility Criteria[B]	Intervention	Trial Outcomes
	encephalopathy • Any prior or clinically significant ascites by physical examination requiring active paracentesis for control • Malignancies occurring within previous 3 years • Active or history of autoimmune disease • Active drug or alcohol abuse		

Abbreviations: **CR** - complete response; **DCR** - disease control rate; **DOR** - duration of response; **ECOG** - Eastern Cooperative Oncology Group; **EQ-5D** - European Quality of Life-5 Dimensions Utility Index; **VAS** - Visual Analog Scale; **HBV** - hepatitis B virus; **HCC** - hepatocellular carcinoma; **HCV** - hepatitis C virus; **HRQOL** - patient reported health-related quality of life; **ORR** - objective response rate; **OS** - overall survival; **PFS** - progression-free survival; **PS** - performance status; **(m)RECIST** - (modified) response evaluation criteria for solid tumours; **TTP** - time-to-progression.

Notes:
[A] - The pCODR review focused on the dose expansion phase (phase 2) of the trial.
[B] - Eligibility criteria apply to the dose expansion phase of the trial.
[C] - Use of archival tissue samples was permitted. Fresh tumour biopsy was required at baseline if no other record of histological diagnosis was available.
[D] - Uninfected cohorts allowed the enrolment of patients who had prior infection with HCV or HBV but no active viral replication (negative for HCV RNA and HBV DNA and/or surface antigen).
[E] - Definition of sorafenib intolerance:[2]
- CTCAE Grade 2 drug-related adverse event which 1) persisted in spite of comprehensive supportive therapy according to institutional standards AND 2) persisted or recurred after sorafenib treatment interruption of at least 7 days and dose reduction by one dose level (to 400 mg once daily)
- CTCAE Grade 3 drug-related adverse event which 1) persisted in spite of comprehensive supportive therapy according to institutional standards OR 2) persisted or recurred after sorafenib treatment interruption of at least 7 days and dose reduction by one dose level (to 400 mg once daily).

[F] - Patients with HBV infection were required to be receiving effective antiviral therapy and have a viral load less than 100 IU/ml at trial screening; anti-viral therapy was not required for patients with HCV infection.
[G] - Patients were without hepatitis viral infection.

a) Trial

CheckMate 040 is an ongoing, international, non-comparative, open-label, multi-centred phase 1/2 trial evaluating the efficacy and safety of nivolumab in patients with advanced HCC who were either treatment naïve or previously treated with sorafenib (2L).[1] The pCODR submission is focused on patients treated in the 2L in the dose expansion phase (phase 2) of CheckMate 040. The dose expansion phase was conducted at 39 sites in 11 countries including Canada (Table 4), and included a small number of Canadian patients.[2]

Funding

The trial was funded by the drug Manufacturer, Bristol-Myers Squibb. The trial authors, along with the Manufacturer, were responsible for trial design and aspects of trial conduct including recruitment of patients, data collection, data interpretation, and the final manuscript.[1] The Manufacturer was responsible for data analysis.[1] Almost all trial authors reported potential conflicts of interest

related to compensation from the drug Manufacturer for either employment and stock ownership, consultancy or speaking fees, research support, and honoraria.[1]

Eligibility Criteria

The CheckMate 040 trial included patients who met the following criteria:[1]

- Male or female, aged at least 18 years with histologically confirmed advanced HCC that was not amenable to curative surgery or local treatment
- With or without HCV or HBV infection; HBV infection required patients be receiving effective anti-viral therapy and have a viral load less than 100 IU/ml at trial screening
- Previously untreated; or with disease progression while receiving at least one previous line of therapy that included sorafenib; or deemed intolerant[ii] of or refused sorafenib treatment.
- Child-Pugh score of ≤6 (Child-Pugh A)
- ECOG performance status of ≤1

For a more detailed list of the key eligibility criteria used in the trial refer to Table 4.

Protocol Amendments[2]

CheckMate 040 was originally designed as a phase 1 dose escalation trial (Figure 3). During an interim analysis of the phase 1 data, encouraging treatment responses (CR, durable responses, favourable OS) were observed across all four etiologic subtypes of patients included in the trial (sorafenib untreated/intolerant, sorafenib progressor, HCV infected, and HBV infected). The responses observed were considered superior to those in the first-line setting with sorafenib; consequently, this prompted the addition of an expansion phase to the trial (amendment 4, October 29, 2014) that included four parallel patient cohorts by etiologic subtype (Figure 2). In the absence of a standard second-line therapy to serve as a comparator for efficacy and safety, the Submitter indicated a single-arm trial design was deemed appropriate to establish clinical benefit. An amendment was also made to the SAP, which is discussed below under Sample Size.

Outcomes and Disease Assessment

The primary outcome of CheckMate 040 was ORR by BICR with tumour assessment based on RECIST version 1.1, and investigator assessment (RECIST version 1.1) serving as a sensitivity analysis.[2]

Key secondary outcomes of the trial included CR rate, DCR, DOR, TTR, TTP, and PFS, all evaluated by either BICR or investigator assessment, OS, and response stratified by PD-L1 expression.[3] Patient reported HRQOL and responses by mRECIST criteria were considered exploratory endpoints.[1]

Tumour assessments were conducted with CT of the chest, abdomen and pelvis at baseline, every six weeks for one year, and then every 12 weeks until disease progression or treatment discontinuation.[2] If a patient was determined to have

[ii] Intolerance to sorafenib was defined as follows:

- Grade 2 drug-related AE that persisted in spite of comprehensive supportive therapy according to institutional standards AND persisted or recurred after sorafenib treatment interruption of at least 7 days and dose reduction by one dose level (to 400 mg once daily)
- Grade 3 drug-related AE that persisted in spite of comprehensive supportive therapy according to institutional standards OR persisted or recurred after sorafenib treatment interruption of at least 7 days and dose reduction by one dose level (to 400 mg once daily).

progression by investigator assessment but was judged to still be benefiting from treatment, treatment was continued until PD was confirmed.[2]

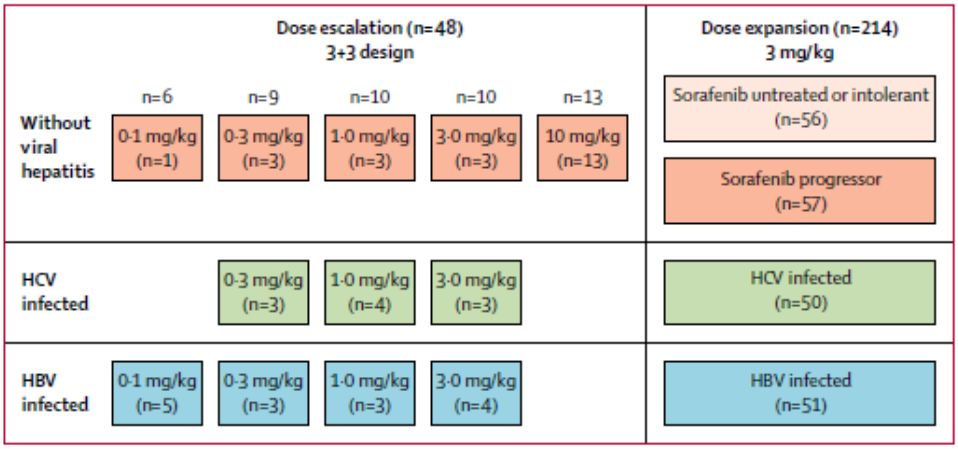


Figure 3: Study design (as per trial protocol) of the dose escalation and dose expansion phases of the CheckMate 040 trial.

From The Lancet. El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. 2017; 389: 2494, © 2018 Elsevier. Reprinted with permission from Elsevier.

Sample Size

For the dose expansion phase (phase 2), a sample size of approximately 200 patients (50 per patient cohort) was selected to better estimate the efficacy of nivolumab (Table 5). This sample size was based on a hypothetical response rate of 20% (10 responses out of 50 patients), where the lower bound of the 95% CI would be 10%.[1]

An initial evaluation of efficacy in the dose expansion cohort was carried out in March 15, 2016, which showed consistent investigator-assessed response rates across the four expansion cohorts.[2] Based on this evaluation, the SAP of the trial was amended to conduct pooled efficacy analyses that combined patients from the four cohorts in order to strengthen the estimate of ORR.[2] The pooled analyses were focused to 2L patients (n=145) who had progressed on or were intolerant to sorafenib regardless of etiology. The 2L patients comprise 68% of the original trial population. The Submitter confirmed to pCODR that the SAP was amended (finalized) prior to the primary analysis of efficacy (August 8, 2016 DBL). This analysis was planned to occur at least six months after the last patient's first dose of study medication.[2]

Data Analyses[2]

Figure 4 provides a schematic illustrating the composition of the 2L patient cohort, which is the basis of the pooled efficacy analyses and the pCODR submission. Of note, the primary trial publication of CheckMate 040 does not report pooled efficacy results and therefore results presented in that report[1] are not the focus of the pCODR review. Pooled efficacy and safety results have been published in conference form (poster) based on an updated analysis (March 17, 2017 DBL).[4] Additional data on efficacy were provided to pCODR as part of the submission.[2] Data on HRQOL in 2L patients have not been published, and were provided to

pCODR as part of the submission based on an additional updated analysis (November 29, 2016 DBL).[2] Data contained in a recent EMA Assessment report were also used to supplement reporting of the CheckMate 040 trial.[3]

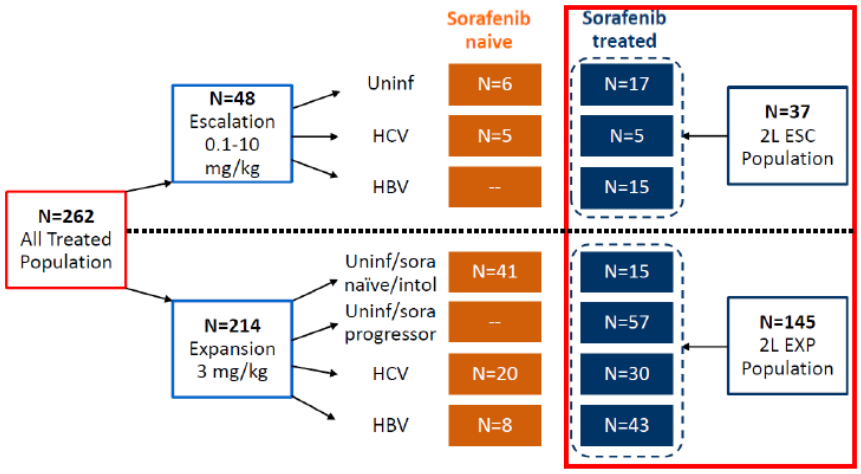


Figure 4: Schematic breakdown of the all treated patient population in the CheckMate 040 trial and illustration of the post-sorafenib (2L) patient cohort that is the basis of the pooled analyses and pCODR submission.[3]

The pooled analysis of the primary outcome, ORR by BICR, was presented with a corresponding two-sided 95% CI using the Clopper-Pearson method. The same analysis method was used for other categorical endpoints (CR rate, DCR). Time-to-event outcomes (DOR, TTR, PFS, TTP, and OS) were estimated using KM methods; median survival time and two-sided 95% CI were derived based on the Brookmeyer and Crowley method using log-log transformation. Survival rates at fixed time points were also calculated. Patients were followed up for survival every three months. The SAP pre-specified subgroup analyses (based on age, gender, region, hepatic spread/vascular invasion, and BCLC and AFP categories at baseline); further, it also indicated results of these analyses would be shown based on disease type and select efficacy populations. No adjustments for multiplicity to control the risk of type 1 error (false positives) were indicated in the SAP.

Health-related QOL was assessed using the EQ-5D-3L,[1] which is comprised of a descriptive system along five dimensions (mobility, self-care, usual activities, plain/discomfort, and anxiety/depression) that generates an index utility score, and a VAS. Each dimension has three levels (no problems, some problems, extreme problems). The index score is calculated by combining responses from each dimension, and ranges from 0 (death) to 1 (full health). The VAS requires patients rate their health on a 100-point scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). A score difference of 0.08 is considered the MCID for the EQ-5D utility index; and a score difference of 7 is considered the MCID for the EQ-5D VAS. Patients in the trial completed QOL assessments at baseline and every six weeks until week 25. Analysis of EQ-5D scores

was presented using descriptive statistics and no adjustments were made for missing data.

For the assessment of safety, AEs were graded using NCI CTCAE version 4.03 with assessments performed continuously during treatment up to 100 days after the last dose of nivolumab, or until all treatment-related AEs were resolved to baseline or deemed irreversible by investigator.[1] These analyses included all treated 2L patients.

Table 5: Select quality characteristics of the included CheckMate 040 trial.

Trial Quality Characteristics	CheckMate 040
Treatment versus Comparator	• Nivolumab monotherapy • Non-comparative (no control group; four patient cohorts)
Primary outcome	• ORR by BICR
Required sample size	• A sample size of approximately 50 patients per patient cohort (n=200) was chosen to provide estimates of efficacy; for a hypothetical response rate of 20%, the lower bound of the 95% CI would be 10%
Randomization method	• Not applicable
Allocation concealment (yes/no)	• No
Blinding	• Open label • BICR outcome assessment
ITT analysis (yes/no)	• No
Efficacy analyses	• August 8, 2016 DBL (efficacy analyses based on all expansion phase patients, n=214; trial publication) • November 29, 2016 DBL (pooled analysis of 2L sorafenib intolerant/progressors patient cohort, n=145; unpublished) • March 17, 2017 DBL (updated pooled analysis of 2L sorafenib intolerant/progressors patient cohort; published in conference poster form)
Final analysis (yes/no)	• No • Final analysis expected in 2019[31]
Early termination (yes/no)	• No
Ethics approval (yes/no)	• Yes
Abbreviations: BICR - blinded independent central review; CI - confidence interval; DBL - data base lock; ITT - intent-to-treat; ORR - objective response rate; 2L - second-line.	

b) Populations[2]

Patients in the expansion cohort were enrolled between January 2015 and November 2015.[3] The baseline characteristics of the 2L patient cohort are summarized in Table 6. The 2L cohort comprised a majority of patients who had progressed on or after treatment with sorafenib (91%, n=132); a much smaller proportion of patients were considered sorafenib intolerant (8.3%, n=12).[3] One patient (1%) in the trial had refused sorafenib treatment.[3] The median duration of prior sorafenib treatment among the cohort was 3.8 months (range, 0.1-48.1) and the median time from discontinuation of sorafenib until the start of nivolumab was 2.2 months (range, 0.1-44.7). There were 27 patients (18.6%) in the cohort who had prior systemic therapies (≥2) in addition to sorafenib.[3] The time from initial diagnosis to first dose of nivolumab was ≥5 years in 20% of patients.[3] The majority of patients were from trial sites in Asia (49%) and Europe (40%), with the remaining (11%) from the US and Canada.[3] Most patients were male (77%), Asian or White (98%), and under age 65 (56%);[3] median age of patients in the cohort was 63 years. In terms of etiology, most patients were uninfected (50%); HBV and HCV infection was present in 30% and 21% of patients, respectively. Patients were predominantly BCLC stage C (89%), Child-Pugh score 5 (67%), and ECOG performance status of 0

(64%). Extrahepatic metastases and vascular invasion were present in 71% and 40% of patients, respectively.

Table 6: Baseline demographics and clinical characteristics of the 2L expansion cohort in the CheckMate 040 trial.[2]

Characteristic	2L EXP (n = 145)
Median age (range), years	63.0 (19–81)

Characteristic	2L EXP (n = 145)
Male sex, n (%)	112 (77)
Race, n (%)	
White	67 (46)
Black or African American	3 (2)
Asian	75 (52)
ECOG PS, n (%)	
0	93 (64)
1	52 (36)
BCLC stage, n (%)	
A	2 (1)
B	14 (10)
C	129 (89)
Child-Pugh Score, n (%)	
5	97 (67)
6	46 (32)
7 or above	2 (1)
VI present, n (%)	41 (28)
EHS present, n (%)	103 (71)
AFP ≥400 µg/L[a]	55 (38)
HCC etiology, n (%)	
HBV	43 (30)
HCV	30 (21)
Uninfected	72 (50)
PD-L1 expressing tumour cells, n (%)	
≥1%	25 (17)
<1%	102 (70)
Unable to determine	18 (12)
Prior treatment for HCC, n (%)	
Surgery	95 (66)
Radiotherapy	36 (25)
Local treatment	85 (59)
Median time from initial HCC diagnosis to OPDIVO start, years (range)	2.2 (0.0–24.6)
Prior sorafenib treated, n (%)	
Progressor	132 (91)
Intolerant	12 (8)
Neither progressor nor intolerant	1 (1)
Median duration of sorafenib therapy, months (range)	3.8 (0.1–69.8)
Median time from sorafenib start to OPDIVO start, months (range)	8.7 (1.2-70.5)
Median time from sorafenib discontinuation to OPDIVO start, months (range)	2.2 (0.1–44.7)

Key: 2L EXP, second-line expansion; AFP, alpha fetoprotein; BCLC, Barcelona clinic liver cancer; ECOG PS, Eastern Cooperative Oncology Group (ECOG) performance status; EHS, extrahepatic spread; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; VI, vascular invasion.

[a]Nine patients did not have baseline AFP values available.

Source: BMS, Data on file (DBL: March 17, 2017)

c) Interventions

Based on results of the dose escalation phase of the trial and previous studies of nivolumab in other tumour types, nivolumab was administered intravenously to patients every two weeks at a dose of 3 mg/kg until disease progression, unacceptable toxicity, or treatment discontinuation.[1] As previously mentioned, the trial permitted treatment beyond disease progression in patients still tolerant and benefiting clinically from nivolumab.

Dose Modifications and Delays

Dose modifications (reductions or escalations) were not permitted in the trial. Dose delays of up to six weeks (42 days) from the last dose of nivolumab were permitted according to protocol-defined criteria for specific AEs.[2]

Duration of Treatment

The median duration of treatment among the 2L cohort was 5.26 months.[3] The median number of treatment cycles was 12 (range, 1-41) and most patients received >90% of the planned dose intensity (77.2%).[2] There were 78 patients (54%) in the 2L cohort who were treated beyond disease progression.[4]

Concomitant Therapy and Procedures

Corticosteroids were permitted in topical, ocular, intranasal, intra-articular, and inhalational forms, and for the purposes of prophylaxis or treatment of AEs or non-autoimmune conditions.[2] Bisphosphonates were allowed for the treatment of bone metastases, and palliative local therapy procedures (limited field radiation, surgical resection) were permitted according to protocol-specified criteria.[2] Prohibited treatment included locoregional therapy for HCC, concurrent anti-cancer therapy or investigational agents, systemic steroids >10 mg within 14 days of dosing, and immunosuppressive agents (except for the treatment of AEs).[2]

The most frequently used concomitant medications among the 2L cohort included analgesics (73.8%), antacids for the treatment of peptic ulcers and flatulence (71.7%), antibacterial (46.2%) and antiviral medications (35.9%), and psycholeptics (40%).[2]

Subsequent Therapy

No data on the subsequent treatments received by patients after nivolumab were provided in the pCODR submission; however, some data were reported in the EMA report based on the August 8 DBL.[3] At that time, 31% of 2L patients had received anti-cancer therapy after nivolumab; subsequent systemic therapy was received by 15.2% of patients and included sorafenib (3.4%), herbs (2.8%), doxorubicin (2.1%), and fluorourcil (2.1%). Subsequent non-systemic therapy received by patients included radiotherapy (13.1%), locoregional treatment for HCC (12.4%) and surgery (4.1%).

d) Patient Disposition

At the time of the updated pooled efficacy analysis (March 17, 2017 DBL; median follow-up approximately 15 months), 24 (17%) 2L patients remained on treatment with nivolumab and 121 (83%) had discontinued.[4] The primary reason for treatment discontinuation was PD (n=107, 74%), followed by study drug toxicity (n=5, 3%), other reasons that included patient request and withdrawal of consent (n=5, 3%), unrelated AEs (n=3, 2%), and death (n=1, 1%).[4]

Data on the protocol deviations that occurred during the trial were not provided in the submission to pCODR; a request for this information was made and the data were obtained.[2] Deviations that could potentially affect the interpretability of the trial results occurred in 10 patients (7%).These deviations were attributed to the receipt of concurrent (prohibited) anti-cancer therapy (radiotherapy and excision of spinal lesions) in 9 (6.2%) patients. The remaining patient (<1%) was found without evaluable disease at baseline.

e) Limitations/Sources of Bias

- The pCODR submission was based on data from the CheckMate 040 trial;[1] this trial is an ongoing, single-group, open-label, phase 1/2 trial with no active treatment or placebo control group. As such, it is difficult to draw conclusions on the efficacy of nivolumab in the absence of a comparison to other available treatment options (regorafenib, BSC). Considering the incidence of HCC, it could be argued that the choice of a phase 2 design is a limitation of the trial. Other agents have been evaluated in phase 3 trials,[5-8] and not all have confirmed positive phase 2 findings.[6-8]
- The submission is based on data from a small subgroup of patients (n=145) from the expansion phase of the trial; those who progressed on or were intolerant to sorafenib (2L). A proportion (n=27; approximately 19%) of these patients actually received nivolumab beyond the 2L, as they had previously been treated with other anti-cancer therapies in addition to sorafenib. Considering these patients were heavily pretreated, it is possible that the efficacy estimates obtained may be conservative compared to a patient population solely comprised of 2L patients.
- The submission is based on pooled data analyses for the 2L patient subgroup from an updated DBL that was performed after 15 months of follow-up. The SAP of the trial[2] was amended to include pooled efficacy analyses prior to the primary efficacy analysis; however, looks at the trial data informed the SAP amendment. Over the course of the trial multiple efficacy analyses have been performed but the SAP did not specify any adjustments for multiple comparison testing, which serves to control for type 1 error (false positives). As well, the trial was only powered for the primary outcome and may not be sufficiently powered to reliably estimate other important endpoints (OS, PFS). Consequently, the pCODR Methods Team has concerns about the reliability of the efficacy estimates obtained. Caution is also warranted in interpreting the results of pre-specified subgroup analyses, as the sample sizes in most of these groups were small, and in making comparisons by etiology. CheckMate 040 was not a randomized trial, and therefore efficacy estimates by etiology subgroup are confounded by differences in important baseline prognostic factors.

- The open-label design of the trial makes it susceptible to selection, reporting and performance biases, as trial patients and investigators were aware of the treatment being administered. Specifically:
    - In approximately 20% of patients in the 2L cohort the time from initial diagnosis to first dose of nivolumab was ≥ 5 years;[3] and the median time from initial diagnosis to first dose of nivolumab was 26.5 months [comparatively, in the RESORCE trial (regorafenib)[5] this time span was 21 months]. Considering the median five-year survival rate of patients with HCC is in the range of 5-6%,[9] there appears to have been selection bias in the trial for more indolent (better prognosis) HCC tumours, which further complicates interpretations of efficacy outcomes as the estimates obtained may be influenced by factors other than treatment.
    - Reporting/performance bias is also a concern for subjective outcomes like safety and QOL. In open-label trials the behaviour of patients, investigators and/or assessors may be influenced by knowledge of the drug under study and its side effects.
- The primary outcome of the trial was ORR by BICR. While this endpoint can be considered appropriate for a phase 2 trial, the pCODR Methods Team questions its appropriateness for the purpose of regulatory and funding decisions. Median OS is an achievable outcome in the 2L treatment of HCC,[3] and therefore, should be the primary endpoint for measuring clinical benefit. As indicated above, phase 3 trials of other agents in HCC have failed to demonstrate an OS benefit despite initial response rates, demonstrating ORR is not a surrogate for OS in HCC.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

The pooled efficacy results in the 2L patient cohort are based on an updated analysis of the trial data (March 17, 2017 DBL). The median follow-up time of patients was approximately 15 months.

Efficacy Outcomes[2]

ORR by BICR – primary outcome

ORR, based on assessments by BICR (RECIST v1.1), was defined as the proportion of treated patients whose best overall response was a CR or PR, where best overall response was determined between the date of first dose of study drug and the date of first objectively documented progression or date of subsequent anti-cancer therapy, whichever occurred first.

The results for ORR by BICR are summarized in Table 10. Among the 2L patient cohort the ORR by BICR was 14.5% (95 CI, 9.2-21.3). Of note, this ORR estimate did not reach the clinical significance threshold pre-specified in the SAP as the lower confidence limit was less than 10%. The ORR by BICR was comprised mainly of PRs (17%; n=24); the CR rate was 1% (n=2). Comparatively, the estimates of ORR by investigator assessment (sensitivity analysis) and by mRECIST criteria (exploratory analysis) were higher at 19.3% (95% CI, 13.2-26.7) and 18.6% (95% CI, 12.6-25.9)[3], respectively. Responses were observed across the four etiologic cohorts; ORR estimates ranged between 12.5% and 14.0% by BICR, and from 14.0% to 26.7% by investigator assessment. It was reported that the majority of investigator-assessed responses (64%; 18/28) occurred in ≤3 months; and responses were ongoing (at DBL) in 39% (11/28) of patients.[4] The response estimates by pre-specified patient subgroups are available in Table 11.

DOR and TTR (BICR)
The median DOR among 2L expansion patients was 16.6 months (95% CI, 9.7-not available) by BICR. The median TTR was 2.8 months (range, 1.2-7.0). The investigator-assessed estimate of DOR was not estimable and was 2.7 months (95% CI, 1.2-9.6) for TTR.

PFS
The median PFS by BICR among the 2L expansion patients was 2.8 months (95% CI, 2.6-4.0), which was based on 119 progression events; PFS by investigator assessment was 4.1 months (95% CI, 2.8-5.5).

OS
By the March 17, 2017 DBL, a total of 81 deaths had occurred among the 2L expansion cohort;[3] median OS was 15.6 months (95 % CI, 13.24-18.89; Figure 5). At 12 and 18 months the estimated OS rates were 60% (95% CI, 54.1-67.5) and 44% (95% CI, 35.3-51.9), respectively. Median OS estimates were similar by etiology at 16.3 (95% CI, 11.3-19.94) months in uninfected patients, 14.9 months (95% CI, 9.3-not estimable) in HBV-infected patients and not reached in HCV-infected patients.

Table 10: Efficacy outcomes in the 2L expansion cohort of the CheckMate 040 trial.[2]

Efficacy Outcome	CheckMate 040 2L Expansion Cohort (n=145)	
DBL	March 17, 2017	
Median Follow-up	14.9 months	
	BICR Assessment	Investigator Assessment
ORR, n	21	28
% (95% CI)	14.5 (9.2-21.3)	19.3 (13.2-26.7)
CR, n (%)	2 (1.4)	4 (2.8)
PR, n (%)	19 (13.1)	24 (16.6)
SD, n (%)	60 (41.4)	65 (44.8)
PD, n (%)	56 (38.6)	47 (32.4)
NE, n (%)	8 (5.5)	5 (3.4)
ORR by Etiology		
Uninfected	n=72	n=72
ORR, n	9	14
% (95% CI)	12.5 (5.9-22.4)	19.4 (11.1-30.5)
CR, n (%)	0 (0)	2 (2.8)
PR, n (%)	9 (12.5)	12 (16.7)
HCV-infected	n=30	n=30
ORR, n	6	8
% (95% CI)	20.0 (7.7-38.6)	26.7 (12.3-45.9)
CR, n (%)	1 (3.3)	1 (3.3)
PR, n (%)	5 (5.6)	7 (23.3)
HBV-infected	n=43	n=43
ORR, n	6	6
% (95% CI)	14.0 (5.3-27.9)	14.0 (5.3-27.9)
CR, n (%)	1 (2.3)	1 (2.3)
PR, n (%)	5 (11.6)	5 (11.6)
DOR, median (95% CI)	16.6 (9.7-NA)	NA (9.5-NA)
TTR, median (range)	2.8 (1.2-7.0)	2.7 (1.2-9.6)
PFS, median (95% CI)	2.8 (2.6-4.0)	4.1 (2.8-5.5)
OS, median (95% CI)	15.6 (13.2-18.9)	

Abbreviations: DBL - database lock; DOR - duration of response; CI - confidence interval; CR - complete response; HBV - hepatitis B virus; HCV - hepatitis C virus; NA - not available; ORR - objective response rate; OS - overall survival; PFS - progression-free survival; TTR - time-to-response; 2L - second-line.

Table 11: Efficacy (ORR by BICR) by pre-specified subgroups in the 2L expansion cohort of the CheckMate 040 trial.[2]

Characteristic	ORR, % (95% CI)
Age, years	
<65	13.6 (7.0, 23.0)
≥65–<75	12.5 (4.7, 25.2)
≥75–<85	25.0 (7.3, 52.4)
Region	
US/Canada	18.8 (4.0, 45.6)
Europe	10.3 (3.9, 21.2)
Asia	16.9 (9.0, 27.7)
Gender	
Male	15.2 (9.1, 23.2)
Female	12.1 (3.4, 28.2)
VI or EHS presence	
Yes	15.3 (9.3, 23.0)
No	7.7 (0.9, 25.1)
AFP category at baseline	
<400 µg/L	11.8 (5.8, 20.6)
≥400 µg/L	18.2 (9.1, 30.9)
BCLC stage	
A	50.0 (1.3, 98.7)
B	0 (0.0, 23.2)
C	15.1 (9.3, 22.5)

Key: 2L EXP, second-line expansion; AFP, alpha fetoprotein; BICR, blinded independent central review; CI, confidence interval; CR, complete response; EHS, extrahepatic spread; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; VI, vascular invasion.
Source: BMS, Data on file (DBL: November 29, 2016)

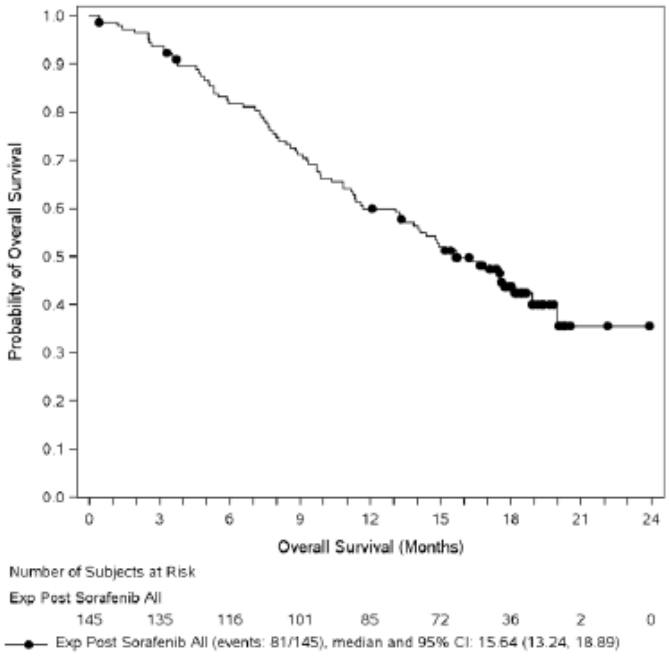


Figure 5: OS in the 2L expansion cohort in CheckMate 040. [2]

Health-related Quality of Life[2]

Data on QOL, which was an exploratory endpoint of CheckMate 040, are based on an updated analysis with a DBL of November 29, 2016 and includes 120 patients in the 2L cohort who had a baseline assessment and at least one post-baseline assessment. Among patients in the 2L expansion cohort the EQ-5D questionnaire completion rate decreased after baseline (100%), ranging from 95.8% at week seven to 51.7% at week 25. It was reported that EQ-5D index scores were stable while on treatment with no significant changes from baseline (mean 0.85; 95% CI, 0.82-0.89) to week 25 (mean 0.83; 95% CI, 0·77-0·87); mean change from baseline was –0.014 (95% CI, –0·06-0·03). This change from baseline did not meet the MCID of 0.08. Considering the individual dimensions of the EQ-5D index, there were no patients who reported extreme problems with mobility and self-care at any assessment time point; and the proportions of patients reporting extreme problems with usual activities, pain and anxiety/depression were below ≤5% at all assessment time points.

EQ-5D-VAS scores were also stable, with no significant changes from baseline (mean 74.5; 95% CI, 69.9-79.2) to week 25 (mean 75.8; 95% CI, 69.3-82.4); mean change from baseline was 3.1 (95% CI, –1.0-7.6). This change from baseline did not meet the MCID for VAS of 7.

Analysis of EQ-5D index and VAS scores by etiology showed similar results to the whole 2L patient cohort, with the exception of patients with HBV infection who experienced a clinically meaningful improvement in VAS scores (mean 7.4; 95% CI, 0.1-14.7).

Safety[2]

The analysis of safety was also based on the November 29, 2016 updated analysis; a summary of safety outcomes is provided in Table 12. It was reported that this assessment of safety was similar to that observed at the March 2017 DBL analysis, and to the safety profile observed in the entire CheckMate 040 study population.

All grade AEs, regardless of causality, were reported in 99.3% of patients in the 2L cohort. The most frequently reported all-cause AEs were fatigue (35.9%), pruritus (28.3%), diarrhea (26.9%), abdominal pain (24.1%), cough (22.1%), and decreased appetite (21.4%). All-cause grade 3-4 AEs occurred in 49% of patients; and were mostly attributable to abdominal pain (3.4%) and fatigue (2.8%). Treatment discontinuations due to any AE occurred in 11% of patients.

All grade AEs related to study drug occurred in 74.5% of patients, with the most common being fatigue (24.1%), pruritus (18.6%), and rash (15.9%). Increases in AST and ALT abnormalities, all-grade and grade 3-4, were attributable to nivolumab in 5.5% and 6.9%, and 2.8% and 2.1%, of patients, respectively. These increases were reported as mostly asymptomatic, not associated with changes in other hepatic measures, reversible, and manageable with established algorithms. Similarly, increases in amylase (any grade: 2.8%; grade 3/4: 1.4%) and lipase (any grade: 3.4% grade 3/4: 3.4%) were asymptomatic and not associated with clinical pancreatitis. Drug-related SAEs occurred in 9% of patients; and drug-related treatment discontinuations occurred in 2% of patients and included stomatitis, polyarthritis and pneumonitis.

As of the November 29, 2016 DBL, a total of 65 (45%) deaths had occurred in the 2L patient cohort; 91% of deaths were due to disease progression. It was reported that

eight (5.5%) and 29 (20%) patients died within 30 and 100 days of last nivolumab dose, respectively. One patient death was deemed related to nivolumab; after eight months of treatment and achieving a PR, this patient discontinued nivolumab and started treatment with sorafenib and after three weeks on treatment developed grade 3 pneumonitis and, despite treatment with steroids, died 159 days post-nivolumab treatment.

Table 12: Safety outcomes in the 2L expansion cohort of the CheckMate 040 trial. [2]

	Any Grade, n (%)	Grade 3-4, n (%)
All-cause AEs	**144 (99.3)**	**71 (49.0)**
Most frequent all-cause AEs (≥20% of any grade)		
Diarrhea	39 (26.9)	2 (1.4)
Abdominal pain	35 (24.1)	5 (3.4)
Fatigue	52 (35.9)	4 (2.8)
Pruritus	41 (28.3)	1 (0.7)
Decreased appetite	31 (21.4)	2 (1.4)
Cough	32 (22.1)	0
All-cause AEs by organ system		
Endocrine	14 (9.7)	0
Gastrointestinal	39 (26.9)	2 (1.4)
Hepatic	31 (21.4)	21 (14.5)
Pulmonary	2 (1.4)	1 (0.7)
Renal	4 (2.8)	1 (0.7)
Skin	60 (41.4)	2 (1.4)
Hypersensitivity/infusion reactions	5 (3.4)	0
Drug-related AEs	**108 (74.5)**	**24 (16.6)**
Most frequent drug-related AEs (≥15% of patients)		
Fatigue	35 (24.1)	3 (2.1)
Pruritus	27 (18.6)	1 (0.7)
Rash	23 (15.9)	1 (0.7)
Drug-related select AEs by organ system		
Endocrine	12 (8.3)	0
Gastrointestinal	22 (15.2)	2 (1.4)
Hepatic	12 (8.3)	5 (3.4)
Pulmonary	2 (0.4)	1 (0.7)
Renal	1 (0.7)	0
Skin	44 (30.3)	2 (1.4)
Hypersensitivity/Infusion reactions	5 (3.4)	0
Investigations		
Aspartate transaminase increased	8 (5.5)	4 (2.8)
Alanine transaminase increased	10 (6.9)	3 (2.1)
Amylase increased	4 (2.8)	2 (1.4)
Lipase increased	5 (3.4)	5 (3.4)
Drug-related SAEs	**13 (9.0)**	**6 (4.1)**
Investigations	1 (0.7)	1 (0.7)
Respiratory, thoracic and mediastinal disorders	3 (2.1)	1 (0.7)
Pneumonitis	2 (1.4)	1 (0.7)
Injury, poisoning and procedural complications	2 (1.4)	0
Infusion related reaction	2 (1.4)	0

Denominator for all outcomes based on the total 2L EXP population of CheckMate 040 (n = 145).

Key: 2L EXP, second-line expansion; AE, adverse event; SAE, serious adverse event.

Source: BMS, Data on file (DBL: November 29, 2016)

6.4 Ongoing Trials

No ongoing trials assessing nivolumab as 2L treatment in adult patients with advanced HCC, who are intolerant to or have progressed on sorafenib, were identified.

7 SUPPLEMENTAL QUESTIONS

The following supplemental question was identified during development of the review protocol as relevant to the pCODR review of nivolumab for advanced HCC:

- Critical appraisal of the Manufacturer-submitted MAIC of nivolumab to relevant comparators as 2L treatment in advanced HCC

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

7.1 Critical appraisal of the Manufacturer-submitted MAIC of nivolumab to relevant comparators as 2L treatment in advanced HCC

7.1.1 Objective

The literature search undertaken by pCODR for this submission did not identify any RCTs that directly compared nivolumab to other 2L treatment options for advanced HCC. In the absence of comparative evidence, an ITC of nivolumab with relevant comparators was required. The objective of this section is to summarize and critically appraise the methods and results of the Manufacturer-submitted ITCs,[10] which provide evidence for the efficacy of nivolumab versus available treatment options. The critical appraisal focused on the ITCs performed that were considered by pCODR to be appropriate comparators in the Canadian context; namely, nivolumab compared to BSC and regorafenib (refer to Table 3 in Section 6.2.1). Further, the comparisons to BSC that were reviewed by pCODR were those from the RESORCE and BRISK-PS trials,[5,6] as these trials were considered the most relevant trials for comparison in terms of patient population, size, and recency.

7.1.2 Findings

Objectives and Scope of ITC

The Manufacturer, Bristol-Myers Squibb, conducted ITCs in order to derive comparative efficacy estimates needed to inform the pCODR clinical and economic evaluations (cost-effectiveness and budget impact models) of nivolumab against relevant comparators. The scope of the analyses performed included, (1) covariate-adjusted and MAIC analyses to derive comparative estimates for the outcomes of OS and PFS; and (2), development of parametric survival curves for the purpose of extrapolating OS and PFS data. The parametric survival modeling analyses are not reviewed here. Safety and HRQOL endpoints were not considered for analyses. It should be noted that the ITCs included the 2L expansion patients from CheckMate 040 who either previously progressed or were considered intolerant to sorafenib (n=145).

Systematic Review

The Manufacturer reported that a systematic literature review was conducted to identify eligible trials to be included in analyses; however, no details on the methods used (e.g., selection criteria, databases searched, study quality assessment) were reported. After seeking additional information from the Manufacturer, it was confirmed that standard evidence databases (Medline, Embase, Cochrane Library with no date limit applied) and grey literature sources (conference proceedings of ASCO, ESMO, and AASLD for years 2014-2016; and organization websites (e.g., EMA, FDA, CADTH) were searched in November 2016. Eligible studies were selected based on the criteria in Table 14.

Specific outcomes were not pre-specified as eligibility criteria for the ITC, however, studies were required to have reported on OS. Included trials were assessed for bias using the NICE methodology checklist for RCTs; the quality assessments performed for the BRISK-PS and RESORCE trials did not identify any bias concerns.

Table 14: Inclusion and exclusion criteria of systematic literature review.

Characteristics	Inclusion Criteria	Exclusion Criteria
Population	• Adult patients • Advanced HCC Advanced stage refers to the following or a combination of the following stages: o BCLC Stage B, C, or D o Locally advanced, advanced, or metastatic o Unresectable o End-stage disease o Terminal disease • Unsuitable for local or locoregional therapy	• Pediatric patients • Resectable disease • BCLC Stage A • Studies evaluating adjuvant and/or neo adjuvant therapies
Line of Therapy	• Patients receiving 2L or later lines of therapy	• Treatment naïve or patients receiving 1L therapy
Study Design	• RCTs of any design (parallel, cross-over) • Non-RCTs including comparative observational studies • Single arm studies • Systematic reviews and meta-analyses of RCTs*	• Preclinical studies • Comments, letters, editorials • Case reports, case series • Pharmacokinetic and economic studies
Interventions	• Nivolumab • Sorafenib • Atezolizumab • Bevacizumab • Cabozantinib • Ramucirumab • Erlotinib • MSC2156119J/ tepotinib • Regorafenib • Pembrolizumab • Tivantinib • Doxorubicin • Lenvatinib • Tremelimumab • Durvalumab • Ipilimumab • BSC/palliative care (as reported in articles/studies)	• Studies evaluating adjuvant and/or neoadjuvant therapies were excluded • Studies evaluating chemoembolisation/localised therapy were excluded • Any non-pharmacological treatment such as surgery and/or radiotherapy • Studies evaluating chemo-radiotherapy were also excluded (chemotherapy + radiotherapy)
Comparators	• Placebo • Any treatment from the list above • Non-comparative evidence: Studies were included if at least one treatment arm comprised an intervention from the list of interventions • Comparative evidence: Studies were included if at least one treatment arm comprised an intervention from	• Studies were not excluded based on comparators

Characteristics	Inclusion Criteria	Exclusion Criteria
	the list of interventions and comparators	
Language	• Studies published in English	• Non-English publications
Abbreviations: 1L - first line; 2L - second line; BCLC - Barcelona Clinic Liver Cancer; BSC - best supportive care; HCC - hepatocellular carcinoma; RCTs - randomised controlled trials.		
Notes: * Systematic reviews and meta-analyses of RCTs were included and flagged. Bibliographies of these reports were screened to check of the literature searches missed any potentially relevant studies.		

A total of 31 trials were identified by the literature review. Of these, ten met the eligibility criteria and were included, and 21 were excluded (Table 15). The primary reasons for excluding trials were due to a treatment arm not of interest or unavailability of OS or PFS data. The ten trials evaluated the following relevant treatments (a total of nine treatment arms) for comparison to nivolumab: BSC/placebo (nine trials), regorafenib (one trial), sorafenib (one trial), and tivantinib (one trial). At the time the ITC analyses were being planned, results of the phase 3 trial comparing trivantinib to BSC/placebo (ARQ197-215) were not yet available. The trial was subsequently published and deemed a negative trial for failing to meet its primary endpoint. As such, trivanitinib is not considered an appropriate comparator and was solely maintained in analyses for the purpose of transparency. Of the ten included trials, two trials only provided OS outcome data.

Table 15. Included and excluded trials from the Manufacturer-performed systematic review.

Trial	Treatment
Included Trials	
ARQ 197-215 (Santoro 2013)	Tivantinib Placebo/BSC
BRISK-PS- (Llovet 2013) (CA182-034)	Placebo/BSC Brivanib (treatment not of interest)
CheckMate 040 (CA209-040)	Nivolumab
EVOLVE-1 (Zhu 2014)	Placebo/BSC Everolimus (treatment not of interest)
Kang 2015	Placebo/BSC Axitinib (treatment not of interest)
REACH (Zhu 2015)	Placebo/BSC Ramucirumab (treatment not of interest)
RESORCE (Bruix 2016)	Regorafenib Placebo/BSC
Rimassa 2013	Sorafenib Placebo/BSC
OS data only	
Abou-Alfa 2016	Placebo/BSC ADIpeg 20 (A) plus best supportive (treatment not of interest)
Lavarone 2015	Placebo/BSC
Excluded Trials	
Small sample size and use of TTP rather than PFS	
Bruix 2013	Regorafenib (n=36)
Sangro 2013	Tremelimumab (n=21)
Yau 2012	Bevacizumab+erlotinib (n=10)
Lack of OS/PFS data	
AbdelWahab 2015	Bevacizumab±erlotnib
Abou-Alfa 2015	Sorafenib+doxorubicin
Baek 2011	Sorafenib

Trial	Treatment
Balsom 2010	Sorafenib
Ghassan 2012	Sorafenib+doxorubicin
Pazo Cid 2010	Bevacizumab
Santoro 2013	Tivantinib
Zolfino 2011	Sorafenib
No prior sorafenib treatment	
Kim 2011	Sorafenib
Treatment arm not of interest	
Chelis 2012	Bevacizumab+temsirolimus
Duffy	Tremelimumab plus TACE or RFA
Gabriela Chiorean 2012	Erlotinib+docetaxel
Heo 2013	JX594+sorafenib
Kaseb 2016	Bevacizumab+erlotinib
Liu 2015	Doxorubicin+dacarbazine
Martell 2012	Tivantinib+sorafenib
SHELTER (Bitzer 2012)	Resminostat+sorafenib Resminostat
SHELTER (Bitzer 2016)	Resminostat+sorafenib Resminostat
Abbreviations: BSC - best supportive care; OS - overall survival; PFS - progression-free survival; TTP - time to progression.	

Data Sources

As previously indicated, the pCODR critical appraisal of the ITC focused on the BSC/placebo and regorafenib treatment groups from the RESORCE and BRISK-PS trials. For the CheckMate 040 and BRISK-PS trials, ILD (individual level data) were available for analyses. The ILD from CheckMate 040 are based on the March 2017 DBL. For the RESORCE trial, outcome data were obtained from digitized KM curves (referred to as pseudo ILD); KM curves were digitized using GetData Graph Digitizer 2.26 and pseudo ILD were created using the Guyot algorithm. The available efficacy data and analyses performed for the comparisons of interest to the pCODR review are summarized in Table 16. Outcome data from the CheckMate 040 trial were available based on RECIST and mRECIST response criteria, which permitted like-for-life comparisons of PFS to the treatment groups in the BRISK-PS and RESORCE trials.

Table 16: Available efficacy data and analyses performed for comparisons of interest.

Nivolumab versus Comparator	Trial for Comparator	ITC Analysis Method	Outcome Analyses
BSC	BRISK-PS (CA182-034)	ILD covariate analysis	OS PFS (mRECIST)
	RESORCE	MAIC	OS OS (n=132 for CheckMate 040) OS (n=108 for CheckMate 040) PFS (RECIST 1.1) PFS (mRECIST) PFS (RECIST 1.1 and n=132)* PFS (RECIST 1.1 and n=108)*
Regorafenib	RESORCE	MAIC	OS OS (n=132 for CheckMate 040)

Nivolumab versus Comparator	Trial for Comparator	ITC Analysis Method	Outcome Analyses
			OS (n=108 for CheckMate 040) PFS (RECIST 1.1) PFS (mRECIST) PFS (RECIST 1.1 and n=132)* PFS (RECIST 1.1 and n=108)*

Abbreviations: BSC - best supportive care; ILD - individual-level data; MAIC - matched-adjusted indirect comparisons, mRECIST - modified Response Evaluation Criteria in Solid Tumors; OS - overall survival; PFS - progression-free survival; RECIST - Response Evaluation Criteria in Solid Tumors.

*Sensitivity analysis.

Methods

Assessment of Heterogeneity

In order to determine the feasibility of performing ITCs, the inclusion criteria, baseline characteristics of included patients, and the outcomes reported in each trial were reviewed and compared to identify sources of heterogeneity (Table 17). Any clinically meaningful differences identified between trials were considered in analyses using covariate adjustment or matching. Clinicians were consulted in determining whether any observed differences between trials were clinically meaningful, and whether they could be prognostic and lead to differences in efficacy outcomes.

Considering the inclusion criteria of the CheckMate 040, RESORCE and BRISK-PS trials, clinicians identified time since sorafenib discontinuation and time on sorafenib to be potential prognostic factors that could influence OS and PFS outcomes in a comparison between CheckMate 040 and BRISK-PS. Cox proportional hazard models were fitted for both trials (for OS and PFS) with a covariate for time on sorafenib and, separately, for time since sorafenib discontinuation. The OS outcome for CheckMate-040 with the covariate for time since sorafenib discontinuation was the only model that had a significant covariate parameter (p=0.005; HR=0.94, 95% CI, 0.90-0.98); all other models examined did not yield statistically significant results. It was concluded that these two prognostic factors are difficult to capture and adjust for across trials, and have a questionable effect on outcomes; so neither were considered further for covariate adjustment or matching. The authors identified this as a limitation of the analyses.

In terms of baseline patient characteristics, the authors judged the included trials to be reasonably well balanced for key patient characteristics. Considering the CheckMate 040, RESORCE and BRISK-PS trials, the pCODR Methods Team agreed that treatment groups appeared well-balanced overall, but did note differences in the proportions of patients included in the three trials by race (White and Asian), who were sorafenib intolerant, had macrovascular invasion and/or extrahepatic disease, and alpha-fetoprotein level ≥400ng/mL. The following variables were identified as clinically important and were considered for inclusion into covariate adjusted and matched analyses:

- Gender (male versus female)
- Age (continuous; and based on two subgroups based on median)
- Region (Asia versus non-Asia)
- Hepatitis B (yes/no)
- Hepatitis C (yes/no)
- ECOG performance status (0 versus 1)
- Child-Pugh (A versus B)
- Macrovascular invasion (yes/no)
- Extrahepatic spread (yes/no)
- Alpha-fetoprotein (≥400ng/mL)

Selection of Variables for Covariate Adjustment and Matching

In order to identify the specific variables to be used for adjustment and matching a number of analyses were performed prior to performing the ITCs. These analyses were performed using ILD from the CheckMate 040 and BRISK-PS trials; therefore, variable selection was not informed by the trials with pseudo ILD. The analyses performed are described below.

Firstly, the correlations between covariates were assessed. If covariates were highly correlated, then one variable was chosen over another to avoid problems with model fitting. Secondly, individual relationships between each variable on OS and, separately, on PFS were assessed using Cox proportional hazard regression models; the univariate analyses were descriptive in nature, but variables with highly non-significant results and minimal effects on OS/PFS were excluded from adjustments/matching since they were not considered to be prognostic factors for the outcomes of OS and PFS. Finally, backwards selection of variables was performed to determine the list of covariates to be included in final analyses. The variables of gender, age, region, hepatitis B and hepatitis C were included in the model regardless of their significance level as these variables were deemed important from an epidemiological and clinical perspective. The remaining variables (ECOG, macrovascular invasion, extrahepatic spread, and alpha-fetoprotein level) were removed from the models one-by-one based on the least significant variable until all remaining variables in the model were statistically significant ($p<0.20$). The variables included in the final covariate-adjusted and MAIC analyses included:

- Gender (male, female)
- Age (continuous)
- Region (Asia versus non-Asia)
- Hepatitis B (yes versus no)
- Hepatitis C (yes versus no)
- ECOG PS (0 versus 1)
- Alpha-feto protein (AFP) (<400 or >=400ng/mL) (for the ILD comparison with placebo/BSC from the BRISK-PS trial)

Table 17: Comparison of key inclusion criteria, baseline patient characteristics and efficacy outcomes in the CheckMate 040, RESORCE and BRISK-PS trials.

Trial	CheckMate 040	RESORCE		BRISK-PS
Drug	Nivolumab	Regorafenib	Placebo/BSC	Placebo/BSC
n	145	379	194	132
Key Inclusion Criteria				
BCLC Stage B or C	B or C	B or C		B or C
Documented radiologic PD during sorafenib, %	91%	100%		88%
Sorafenib intolerant, %	8%	0%		15%
Time since first-line sorafenib discontinued	No minimum requirement; 69% <3 months; 10% 3-6 months; 21% > 6 months	Within 10 weeks		At least 8 days (estimated)
Minimum duration of sorafenib treatment	No minimum requirement	Received for 20 of the last 28 days		Unknown
ECOG PS	0-1	0-1		0-2
Child-Pugh A liver function	A	A		A or B
Baseline Patient Characteristics, n (%) unless otherwise specified				
Male	112 (77)	333 (88)	171 (88)	113 (86)
Age: mean, median (range) years	61.4, 63 (19-81)	NR, 64 (19-85)	NR, 62 (23-83)	61.1, 62.5 (19-87)
Race:				
White	67 (46)	138 (36)	68 (35)	66 (50)
Asian	75 (52)	156 (41)	78 (40)	59 (45)
Black	3 (2)	6 (2)	2 (1)	6 (5)
Other/not reported	0 (0)	79 (21)	46 (24)	1 (1)
Etiology of HCC:				
Alcohol use	28 (19)	90 (24)	55 (28)	36 (27)
Hepatitis B	49 (34)	143 (38)	73 (38)	45 (34)
Hepatitis C	43 (30)	78 (21)	41 (21)	35 (27)
NASH	10 (7)	25 (7)	13 (7)	NR
Other	4 (3)	28 (7)	10 (5)	12 (9)
Unknown	NR	66 (17)	32 (16)	NR
ECOG PS:				
0	93 (64)	247 (65)	130 (67)	81 (62)
1	52 (36)	132 (35)	64 (33)	46 (38)
2	0(0)	0 (0)	0 (0)	5 (0)
BCLC stage:				
A	2 (1)	1 (0.3)	0 (0)	1 (1)
B	14 (10)	53 (14)	22 (11)	19 (14)
C	129 (89)	325 (86)	172 (89)	112 (85)
Child-Pugh class:				
A	143 (99)	373 (98)	188 (97)	120 (91)
B	2 (1)	5 (1)	6 (3)	12 (9)
C	0 (0)	0 (0)	0 (0)	0 (0)
Macrovascular invasion	41 (28)	110 (29)	54 (28)	24 (18)
Extrahepatic disease	103 (71)	265 (70)	147 (76)	NR (74)
Macrovascular invasion and/or extrahepatic disease	119 (82)	304 (80)	162 (84)	94 (71)
Alpha-fetoprotein ≥400ng/mL	55 (38)	162 (43)	87 (45)	128 (41)
Cirrhosis present	NR	285 (75)	144 (74)	NR
Efficacy Outcomes				
Median OS (95% CI), months	15.64 (13.24-18.89)	10.6 (9.1-12.1)	7.8 (6.3-8.8)	8.21 (6.14, 10.32)
Median PFS RECIST 1.1 (95% CI), months	2.79 (2.63-4.04)	3.4 (2.9-4.2)	1.5 (1.4-1.5)	NA
Median PFS mRECIST (95% CI), months	2.83 (2.63-4.04)	3.1 (2.8-4.2)	1.5 (1.4-1.6)	2.69 (1.58-2.83)

Abbreviations: BCLC - Barcelona Clinic Liver Cancer; CI - confidence interval; ECOG PS - Eastern Cooperative Oncology Group performance status; HCC - hepatocellular carcinoma; mRECIST - modified Response Evaluation Criteria in Solid Tumors; NASH - nonalcoholic steatohepatitis; NA - not available; NR - not reported; OS - overall survival; PFS - progression-free survival; RECIST - Response Evaluation Criteria in Solid Tumors.

Statistical Analyses

Since the CheckMate 040 trial was a non-comparative single-group trial, a formal ITC using a common or anchored comparator was not possible. Consequently, based on the available evidence, the authors used two alternative approaches to perform an ITC of nivolumab with relevant comparators.

Covariate-adjusted Analyses

For the two trials (CheckMate 040 and BRISK-PS) with ILD, a comparison between nivolumab and BSC/placebo was performed using a covariate-adjusted Cox proportional hazards regression model in order derive an HR and corresponding 95% CI for both treatment groups. Median (95% CI) survival estimates were calculated, and KM curves were generated for both treatment groups. Results based on an analysis unadjusted for differences in covariates between the treatment groups were also presented.

MAIC Analyses

For the remaining trial (RESORCE), ILD were not available and therefore pseudo ILD were used for the comparisons between nivolumab and placebo/BSC, and nivolumab and regorafenib. Unanchored MAICs were performed to adjust the CheckMate 040 data to the patient characteristics observed in the comparator trial. The MAIC calculates analysis weights for each patient in the CheckMate 040 trial, such that the re-weighted population matches the comparator trial in terms of the distributions of the matched variables. A HR is derived between the re-weighted nivolumab data and the pseudo ILD for each comparator treatment group, separately, from a weighted Cox proportional hazards regression model. Median (95% CI) survival estimates were calculated, and KM curves were generated for each treatment group. Results based on analyses that used unweighted data for the nivolumab treatment group were also presented. Comparisons of the baseline characteristics of the trials pre- and post-matching were not provided. Follow-up with the Manufacturer confirmed that the matching process resulted in the nivolumab ILD having exactly the same distributions of patients as the comparator trials for the matched variables but the actual data demonstrating the matching process were not provided.

A number of sensitivity analyses were performed to assess the robustness of the ITC results (for OS and PFS), which included the following:

- Pseudo ILD were produced from KM curves for the BSC/placebo treatment group of the BRISK-PS trial in order to perform a MAIC and compare the MAIC treatment estimate against the covariate-adjusted estimate.
- All patients in the RESORCE trial had documented radiologic progression while on sorafenib; comparatively, in CheckMate 040, 91% of patients (n=132) had documented radiologic progression. Sensitivity analyses were performed using two different definitions of progression while on sorafenib: patients identified using data for prior sorafenib use (n=132), and patients identified using data for reason for discontinuation of prior cancer therapy (n=108).

Results

The results of the ITCs are presented in Table 18.

Covariate-adjusted Analyses

- The KM curves for the comparison of nivolumab versus BSC/placebo for OS and PFS (using data from the BRISK-PS trial) are presented in Figures 6 and 7, respectively.

- For OS, the covariate-adjusted Cox proportional hazards model produced a HR of 0.48 (95% CI, 0.35-0.65; p<0.0001), suggesting a statistically significant reduction in the risk of death with nivolumab compared to BSC/placebo. Median OS was significantly longer in the nivolumab treatment group at 15.6 months (95% CI, 13.2-18.9) compared to 8.2 months (95% CI, 6.14-10.4) with BSC/placebo. A similar result was obtained for the unadjusted analysis (Table 18).
- For PFS (by mRECIST criteria), the covariate-adjusted Cox proportional hazards model produced a HR of 0.76 (95% CI, 0.58-0.99; p=0.040), suggesting a marginally statistically significant reduction in the risk of progression or death with nivolumab compared to BSC/placebo. Median PFS was 2.8 months (95% CI, 2.6-4.0) in the nivolumab treatment group and 2.6 months (95% CI, 1.5-2.8) in the BSC/placebo treatment group. A similar result was obtained for the unadjusted analysis (Table 18).

MAIC Analyses

- The KM curves for the comparison of nivolumab versus BSC/placebo for OS and PFS (using data from the RESORCE trial) are presented in Figures 8 and 9, respectively. For this comparison the matching process reduced the effective sample size of the nivolumab treatment group from 145 to 118.13.
  - For OS, the MAIC produced a HR of 0.42 (95% CI, 0.31-0.55; p<0.0001), suggesting a statistically significant reduction in the risk of death with nivolumab compared to BSC/placebo. Median OS was estimated at 16.7 months (95% CI, 13.2-19.9) in the nivolumab treatment group compared to approximately 8.0 months (95% CI, 6.4-8.9) in the BSC/placebo group. A similar result was obtained for the unweighted analysis (Table 18).
  - For PFS (by RECIST), the MAIC produced a HR of 0.56 (95% CI, 0.44-0.71; p<0.0001), suggesting a statistically significant reduction in the risk of progression or death with nivolumab compared to BSC/placebo. Median PFS was estimated at 2.8 months (95% CI, 2.63-4.11) in the nivolumab treatment group compared to approximately 1.6 months (95% CI, 1.55-1.59) in the BSC/placebo group. Similar results were obtained for the unweighted analysis and by mRECIST criteria (Table 18).
- The KM curves for the comparison of nivolumab versus regorafenib for OS and PFS (using data from the RESORCE trial) are presented in figures 10 and 11, respectively. For this comparison the matching process reduced the effective sample size of the nivolumab treatment group from 145 to 112.98.
  - For OS, the MAIC produced a HR of 0.64 (95% CI, 0.50-0.83; p=0.0008) suggesting a statistically significant reduction in the risk of death with nivolumab compared to regorafenib. Median OS estimates were 16.7 months (95% CI, 13.2-19.9) in the nivolumab treatment group compared to 10.8 months (95% CI, 9.2-12.3) in the regorafenib group. A similar result was obtained for the unweighted analysis (Table 18).
  - For PFS, the MAIC produced a HR of 1.07 (95% CI, 0.89-1.33; p=0.52), suggesting no statistically significant difference in the risk of progression or death between nivolumab and regorafenib; median PFS estimates were 2.8 months (95% CI, 2.63-4.11) in the nivolumab group and 3.5 months (95% CI, 2.89-4.24) in the regorafenib group. A similar result was obtained for the unweighted analysis and by mRECIST criteria (Table 18).

- Sensitivity analyses
    - When pseudo ILD, produced from the KM curve of the placebo/BSC treatment group in the BRISK-PS trial, were used in a sensitivity analysis (matching reduced the effective sample size of the nivolumab treatment group from 145 to 128.87), the MAIC produced HRs that were similar to the covariate-adjusted analysis for both OS and PFS (data not shown).
    - When different definitions (populations) of sorafenib progressors were used in sensitivity analyses, the HRs changed (increased, indicating lower magnitude) for both OS and PFS, for BSC and regorafenib; however, the direction and significance of the results remained the same.

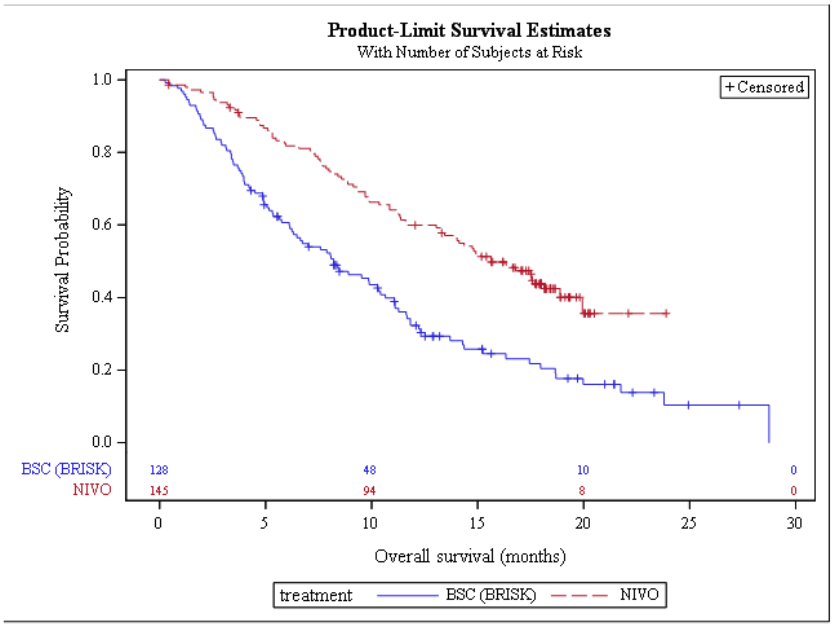
Table 18: Results of the Manufacturer submitted ITCs comparing nivolumab to BSC and regorafenib.

Treatment Comparison	Comparator data source (Analysis)	Nivolumab versus Comparator HR (95% CI); p-value OS	Nivolumab versus Comparator HR (95% CI); p-value PFS (mRECIST)	Nivolumab versus Comparator HR (95% CI); p-value PFS (RECIST 1.1)
Nivolumab versus BSC	BRISK-PS-PS (unadjusted)	0.48 (0.36-0.65) <0.0001	0.77 (0.59-0.99) 0.0424	NA
	BRISK-PS-PS (covariate adjusted)	0.48 (0.35-0.65) <0.0001	0.76 (0.58-0.99) 0.0402	NA
Nivolumab versus BSC	RESORCE (unweighted)	0.43 (0.32-0.57) <.0001	0.55 (0.43-0.70) <0.0001	0.55 (0.43-0.70) <.0001
	RESORCE (MAIC)	0.42 (0.31-0.55) <.0001	0.55 (0.44-0.70) <0.0001	0.56 (0.44, 0.71) <0.0001
Nivolumab versus regorafenib	RESORCE (unweighted)	0.67 (0.52-0.86) 0.0019	1.03 (0.83-1.28) 0.7865	1.05 (0.85-1.31) 0.6507
	RESORCE (MAIC)	0.64 (0.50-0.83) 0.0008	1.03 (0.83-1.27) 0.7846	1.07 (0.87-1.33) 0.5163

Abbreviations: BSC - best supportive care; **CI** - confidence interval; **HR** - hazard ratio; **ILD** - individual level data) **ITC** - indirect treatment comparison; **MAIC** - matching adjusted indirect treatment comparison; **mRECIST** - modified Response Evaluation Criteria in Solid Tumors; **NA** - not available; **OS** - overall survival; **PFS** - progression-free survival; **RECIST** - Response Evaluation Criteria in Solid Tumors version 1.1.

Conclusions of the ITCs

The ITC report submitted by the Manufacturer concluded that, based on the covariate-adjusted and MAIC analyses, 2L nivolumab for HCC performs consistently favourably against BSC/placebo and other treatment comparators, including regorafenib, especially for the outcome of OS. The authors acknowledged the major limitation of using single arm studies in ITCs; that the treatment effects observed are confounded by trial differences and unmeasured confounders. In contrast, formal ITCs with a common comparator allow for some element of controlling for unmeasured confounders through the use of within-trial relative effects. However, the authors noted that after matching populations where possible, they believe there is no clear reason to believe the CheckMate 040 trial results are unduly biased in favourable of nivolumab.



Key: BSC, best supportive care; NIVO, nivolumab; OS, overall survival.

Figure 6: Kaplan-Meier curve of OS for the comparison of nivolumab versus BSC/placebo (using data from the BRISK-PS trial).

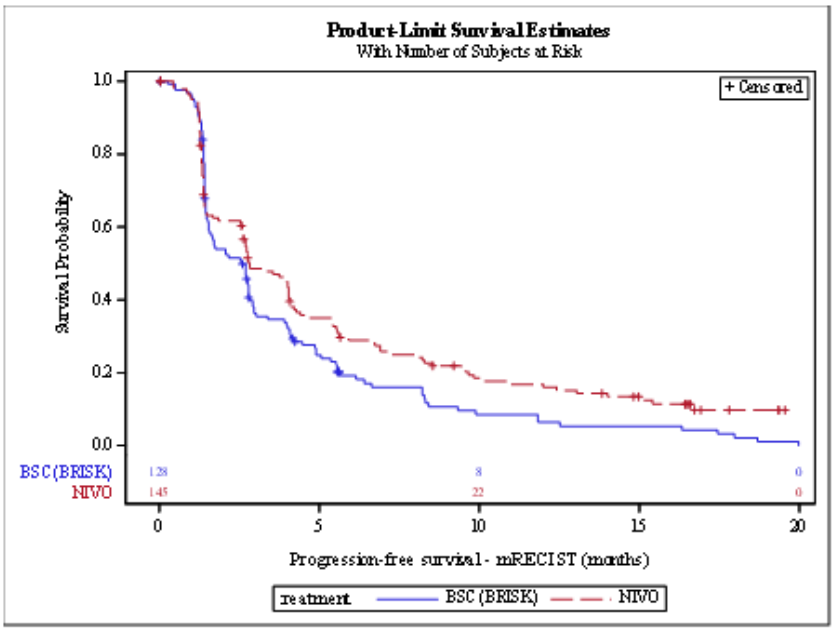
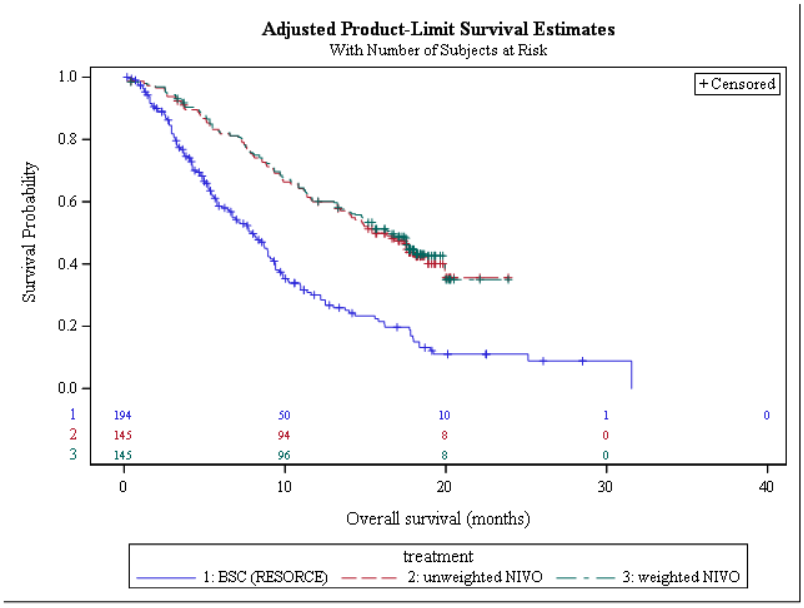
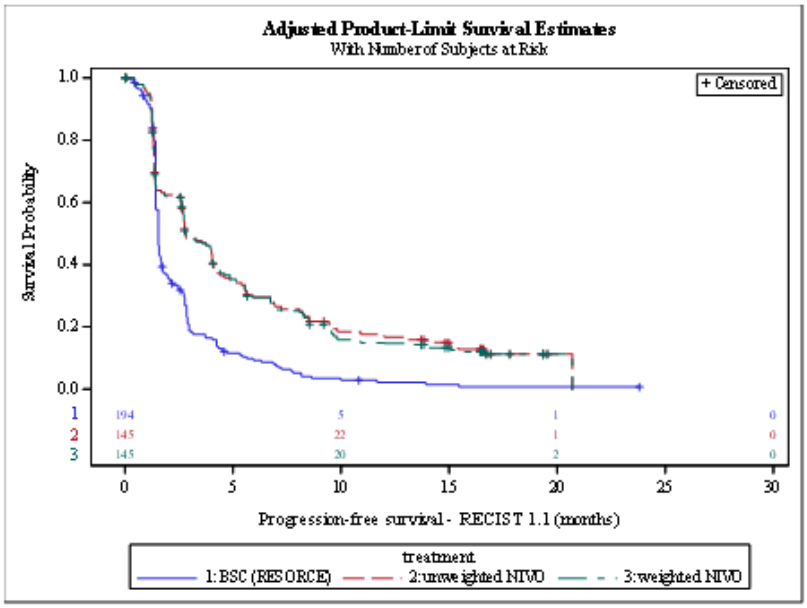


Figure 7: Kaplan-Meier curve of PFS (modified RECIST) for the comparison of nivolumab versus BSC/placebo (using data from the BRISK-PS trial).



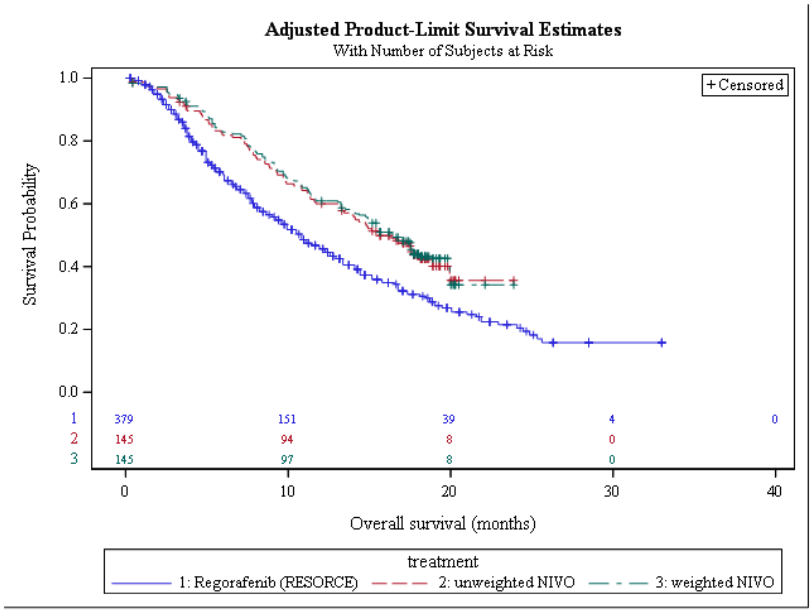
Key: BSC, best supportive care; NIVO, nivolumab; OS, overall survival.

Figure 8: Kaplan Meier curve of OS for the comparison of nivolumab versus BSC/placebo (using data from the RESORCE trial).



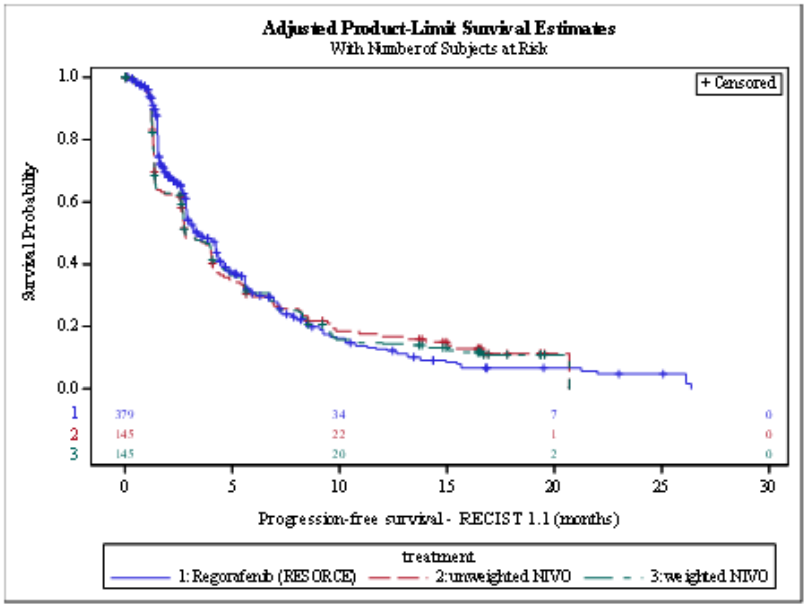
Key: BSC, best supportive care; NIVO, nivolumab; PFS, progression-free survival; RECIST, Response Evaluation

Figure 9: Kaplan Meier curve of PFS (RECIST 1.1) for the comparison of nivolumab versus BSC/placebo (using data from the RESORCE trial).



Key: NIVO, nivolumab; OS, overall survival.

Figure 10: Kaplan Meier curve of OS for the comparison of nivolumab versus regorafenib (using data from the RESORCE trial).



Key: NIVO, nivolumab; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

Figure 11: Kaplan Meier curve of PFS (RECIST 1.1) for the comparison of nivolumab versus regorafenib (using data from the RESORCE trial).

Critical Appraisal

The quality of the Manufacturer-submitted ITCs were assessed according to the recommendations set out by the IPSOR Task Force on Indirect Treatment Comparisons,[11] as well best practice principles for performing MAIC, outlined by Signorovitch et al (2012).[12] The limitations of the ITCs identified by the pCODR Methods Team are summarized below, and should be considered when interpreting the results:

- The patient populations of the trials included in the ITCs (CheckMate 040, BRISK-PS, RESORCE) align with the target population of this review, and were similar in terms of important baseline patient characteristics. However, there were also notable differences, including the percentages of patients who were sorafenib intolerant, had documented PD while on sorafenib, and macrovascular invasion or extrahepatic spread, as well as unknown differences in the duration of previous sorafenib treatment and time since sorafenib treatment. These variables were not included in adjusted/weighted analyses. As acknowledged by the authors, these imbalances, known and unknown, are likely treatment effect modifiers that confound the treatment estimates obtained.
- The authors provided a clear explanation for the selection of specific variables used for covariate-adjustment and matching. Clarification from the Manufacturer indicated that the selection of variables was based on ILD from two trials (CheckMate 040 and BRISK-PS); and thus matching was not performed based on observed imbalances between CheckMate 040 and the other comparator trials. While the selected variables may be the most appropriate for an ITC between CheckMate 040 and BRISK-PS, they may not be the most appropriate for matching to the other comparator trials. Consequently, this introduces uncertainty in the treatment estimates obtain for the other comparisons (RESORCE).
- The authors identified the use of mixed-quality, digitised KM data for treatment comparators, as a limitation of the analyses as the survival data obtained from these curves may not be completely representative of actual trial data. However, they did highlight the consistency of results across the different trials using ILD and MAIC methods.
- The Manufacturer confirmed to pCODR that the outcome data being compared did in fact differ in terms of assessment method. BICR versus investigator-assessed outcomes (PFS) are not always highly concordant and therefore can introduce variation across trials that is not accounted for by covariate adjustment or weighting.
- The limitations identified by the pCODR Methods Team relating to the CheckMate 040 trial, including selection bias trial towards more indolent (better prognosis) HCC tumours (refer to section 6.3.2.1, limitations) should be considered when interpreting the results of the ITCs.
- Data on other important outcomes, including ORR, HRQOL, and safety were not analyzed.
- The ITC report was funded and performed by authors hired by the Manufacturer and therefore the results should be interpreted considering this conflict of interest.

7.1.3 Summary

The Manufacturer conducted ITCs[10] in order to provide comparative efficacy estimates between nivolumab and relevant comparators as 2L treatment for advanced HCC in patients who progressed or were intolerant to sorafenib. The ITCs performed included covariate-adjusted and MAIC analyses to derive comparative estimates for the outcomes of OS and PFS. These analyses were funded by the Manufacturer and have not been fully published or peer-reviewed. The methods and results of the ITCs were critically appraised by the pCODR Methods Team according to the recommendations of the IPSOR Task Force on Indirect Treatment Comparisons[11] and best practice principles for MAIC.[12] The critical appraisal focused on the ITCs performed that were considered by pCODR to be appropriate

comparators in the Canadian context, which included nivolumab compared to BSC and regorafenib. Further, the comparisons to BSC that were reviewed were those from the RESORCE and BRISK-PS trials, as these trials were considered the most relevant for comparison in terms of patient population, size, and recency. For OS, the results of the covariate-adjusted analysis and MAICs were consistent, and showed a statistically significant treatment benefit for nivolumab when compared to BSC/placebo and regorafenib. For PFS, a treatment benefit was shown for nivolumab that was marginally better than BSC/placebo; however, no difference in PFS was observed when nivolumab was compared to regorafenib. The pCODR Methods Team concluded the ITC results should be interpreted with caution considering a number of limitations associated with the analyses that raise uncertainty in the treatment estimates obtained.

8 COMPARISON WITH OTHER LITERATURE

No comparison with other literature was included in this review.

9 ABOUT THIS DOCUMENT

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

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

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report.

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

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** April 2018, **Embase** 1974 to 2018 May 14, **Ovid MEDLINE(R) ALL** 1946 to May 14, 2018

#	Searches	Results
1	(Opdivo* or nivolumab* or MDX 1106 or MDX1106 or BMS936558 or BMS 936558 or ONO4538 or ONO 4538 or 31YO63LBSN or HSDB 8256 or HSDB8256).ti,ab,ot,kf,kw,hw,rn,nm.	10406
2	exp liver neoplasms/	398231
3	(hepatoma* or HCC or hepatocarcinoma or ((hepatocellular or liver or hepatic) adj3 (cancer* or carcinoma* or tumor* or tumour* or neoplasm* or malignan* or sarcoma*))).ti,ab,kf,kw.	364342
4	2 or 3	510827
5	1 and 4	544
6	5 use cctr	15
7	5 use medall	52
8	*nivolumab/ or (Opdivo* or nivolumab* or MDX 1106 or MDX1106 or BMS936558 or BMS 936558 or ONO4538 or ONO 4538 or HSDB 8256 or HSDB8256).ti,ab,kw,dq.	7220
9	exp liver cancer/	363391
10	(hepatoma* or HCC or hepatocarcinoma or ((hepatocellular or liver or hepatic) adj3 (cancer* or carcinoma* or tumor* or tumour* or neoplasm* or malignan* or sarcoma*))).ti,ab,kw,dq.	362994
11	9 or 10	490869
12	8 and 11	302
13	12 use oemezd	239
14	13 and conference abstract.pt.	80
15	limit 14 to yr="2013 -Current"	80
16	limit 15 to english language	80
17	13 not 14	159
18	6 or 7 or 17	226
19	remove duplicates from 18	182
20	limit 19 to english language	177
21	16 or 20	257

2. Literature search via PubMed

A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#10	Search #8 AND #9	11
#9	Search publisher[sb]	516420
#8	Search #1 AND #7	120
#7	Search #2 OR #3 OR #6	276565

#6	Search #4 AND #5	216122
#5	Search cancer*[tiab] OR carcinoma*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR neoplasm*[tiab] OR malignan*[tiab] OR sarcoma*[tiab]	2937261
#4	Search hepatocellular[tiab] OR liver[tiab] OR hepatic[tiab]	891152
#3	Search hepatoma*[tiab] OR hepatocarcinoma[tiab] OR HCC[tiab]	72461
#2	Search Liver neoplasms[MeSH]	149841
#1	Search opdivo*[tiab] OR nivolumab*[tiab] OR MDX 1106[tiab] OR MDX1106[tiab] OR BMS936558[tiab] OR BMS 936558[tiab] OR ONO4538[tiab] OR ONO 4538[tiab] OR HSDB 8256[tiab] OR HSDB8256[tiab]	1993

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

4. Grey Literature search via:

Clinical Trial Registries:

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

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

Search: Opdivo (nivolumab), metastatic hepatocellular carcinoma (HCC)

Select international agencies including:

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

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

Search: Opdivo (nivolumab), metastatic hepatocellular carcinoma (HCC)

Conference abstracts:

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

European Society for Medical Oncology (ESMO)
http://oncologypro.esmo.org/Meeting-Resources
Search: Opdivo (nivolumab), metastatic hepatocellular carcinoma (HCC) – last 5 years

Literature Search Methods

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

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-May 14, 2018) with in-process records & daily updates via Ovid; Embase (1974-May 14, 2018) via Ovid; The Cochrane Central Register of Controlled Trials (April 2018) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Nivolumab - Opdivo. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, but not limited by publication year.

The search is considered up to date as of September 5, 2018.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. One member of the pCODR Methods Team independently 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 pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

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

Writing of the Review Report

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

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

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