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CADTH DRUG REIMBURSEMENT REVIEW

Pharmacoeconomic Report

ATEZOLIZUMAB (TECENTRIQ)

(Hoffman-La Roche Limited)

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

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

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

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Abbreviations

BCLC Barcelona Clinic liver cancer

CDR CADTH Common Drug Review

EQ-5D-5L EuroQoL-Five Dimension-5-Level

HCC hepatocellular carcinoma

ICER incremental cost-effectiveness ratio

LY life-year

NMA network meta-analysis

NOC notice of compliance

PSM partitioned-survival model

QALY quality-adjusted life year

SoC standard of care

Executive Summary

The executive summary is comprised of two tables (Table 1: Background and Table 2: Economic Evaluation) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Atezolizumab (Tecentriq), 60 mg / mL vial in combination with bevacizumab 100 mg or 400 mg vials for intravenous infusion.
Submitted price	Atezolizumab, 1200 mg / 20 mL, intravenous infusion: $6,776.00 per vial
Indication	Atezolizumab in combination with bevacizumab for the first-line treatment of adult patients with unresectable or metastatic hepatocellular carcinoma (HCC) who require systemic therapy.
Health Canada approval status	NOC
Health Canada review pathway	Standard review
NOC date	August 7, 2020
Reimbursement request	Atezolizumab in combination with bevacizumab, for the treatment of patients with unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy. Maintenance on either atezolizumab or bevacizumab should continue until loss of clinical benefit or unacceptable toxicity.
Sponsor	Hoffmann-La Roche Limited.
Submission history	Previously reviewed: Yes Non-Small Cell Lung Cancer: Indication: For the treatment of patients with locally advanced or metastatic non-small cell lung cancer who have progressed on or after systemic chemotherapy until loss of clinical benefit Recommendation date: June 20, 2018 Recommendation: Reimburse under the following conditions: (i) cost-effectiveness being improved to an acceptable level; and (ii) the drug plan cost of treatment with atezolizumab should not exceed the public drug plan cost of treatment with the least costly alternative immunotherapy. Small Cell Lung Cancer: Indication: For the first-line treatment of patients with extensive stage small cell lung cancer (ES-SCLC) in combination with a platinum-based chemotherapy and etoposide. Maintenance with atezolizumab should be continued until loss of clinical benefit or unacceptable toxicity. Recommendation date: January 30, 2020 Recommendation: Do not reimburse. Advanced or Metastatic Triple-Negative Breast Cancer: Recommendation: withdrawn by the sponsor on February 12, 2020 Non-Squamous Non-Small Cell Lung Cancer: Indication: For the treatment of metastatic EGFR and/or ALK positive non-squamous non-small cell lung cancer in patients who have progressed on treatment with targeted therapies. Maintenance atezolizumab should be continued until loss of clinical benefit or unacceptable toxicity. Maintenance bevacizumab should be continued until disease progression or unacceptable toxicity. Recommendation: Do not reimburse.

HCC = hepatocellular carcinoma; mg = milligram; mL = milliliter NOC = Notice of Compliance

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model (PSM)
Target population	Adult patients with unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy
Treatment	Atezolizumab in combination with bevacizumab
Comparators	Standard of care (SoC) consists of sorafenib or lenvatinib
Perspective	Canadian publicly funded health care payer
Outcomes	Quality-adjusted life-years (QALYs); Life-Years (LYs)
Time horizon	Lifetime (10 years)
Key data source	IMbrave150 phase III, open-label trial reporting overall survival (OS) and progression-free survival (PFS) for atezolizumab in combination with bevacizumab, compared with sorafenib. Comparative efficacy of atezolizumab plus bevacizumab compared with lenvatinib was obtained from a network meta-analysis (NMA) that reported hazard ratios for the relative treatment effects for OS and PFS.
Submitted results for base case (and key scenario analyses as required)	The sequential ICER for atezolizumab plus bevacizumab was: • Atezolizumab plus bevacizumab vs lenvatinib: $328,622 per QALY (2.07 incremental QALYs, $332,281 incremental costs).
Key limitations	• Several issues were identified with the extrapolation of the clinical efficacy data within the submitted economic evaluation. As OS data was not mature there was uncertainty regarding extrapolations beyond final data cut-offs in the trial. Clinical experts noted that the sponsor's chosen extrapolated curves were highly optimistic leading to significant long-term survival gains with no evidence to substantiate these claims. • The comparative efficacy of atezolizumab plus bevacizumab and lenvatinib is associated with uncertainty. The NMA used data from populations that may not be comparable and excluded key comparators and trials. The NMA-derived estimates were informed by a sparsity of data and wide credible intervals around the estimates may have contributed to greater imprecision. Therefore, the magnitude of the clinical benefit of atezolizumab plus bevacizumab versus lenvatinib is uncertain. • Uncertainty exists as to the elicitation of utility values. The sponsor used a regression analysis to determine treatment-specific utility weights that accounted for progression status and the occurrence of adverse events without sufficient description of the methods. This deviates from best practice guidelines that recommend utility weights be based on health states. Furthermore, ongoing treatment may be a stronger predictor of quality of life than progression indicated by patients' willingness to remain on treatment despite progression, and the full impact of acute or severe adverse events would not be captured in routine utility questionnaires. • The proportion of patients receiving subsequent therapy was not representative of Canadian clinical practice, with fewer patients on atezolizumab plus bevacizumab receiving subsequent therapy than patients on sorafenib or lenvatinib. According to clinical experts and published real world evidence, patients treated with sorafenib received subsequent treatment at a similar proportion to patients treated with atezolizumab plus bevacizumab. • Total drug acquisition costs of sorafenib may have been overestimated due to the sponsor's choice of the time-to-off-treatment parametric curve applied in the base case.
CADTH reanalysis results	• CADTH conducted a reanalysis which included: selecting alternative parametric survival distributions for OS and PFS for atezolizumab plus bevacizumab, and OS for sorafenib; applying health state utilities based on patients being on or off treatment and removing treatment specific utilities; assuming an equal proportion of patients receive subsequent therapy regardless of first-line treatment; and, selecting an alternative parametric survival distribution for time-to-off treatment with sorafenib. • Based on CADTH reanalyses, the sequential ICER for atezolizumab plus bevacizumab versus sorafenib is $771,970 per QALY;

Component	Description
	• At a price reduction of 99% for atezolizumab, the ICER for atezolizumab plus bevacizumab is $309,306 per QALY gained. It is highly unlikely that atezolizumab plus bevacizumab would be considered cost-effective at a conventionally accepted ICER threshold ($50,000), unless there were significant price reductions for both atezolizumab and bevacizumab.

HCC = hepatocellular carcinoma; ICER = incremental cost-effectiveness ratio; LY = life-year; NMA = network meta-analysis; OS = overall survival; PSM = partitioned survival model; SoC = standard of care; QALY= quality-adjusted life-year.

Conclusions

CADTH undertook reanalyses of the sponsor's economic submission to address some of the identified limitations. The changes which had the largest impact on the model results included selecting alternative parametric survival distributions for OS and PFS for atezolizumab plus bevacizumab. Based on CADTH reanalyses, the sequential ICER for atezolizumab plus bevacizumab compared to lenvatinib was $771,970 per QALY gained. The results are primarily driven by the combined cost of treatment for atezolizumab plus bevacizumab. With a 99% price reduction for atezolizumab, the ICER decreases to $309,306 per QALY, exceeding $50,000 per QALY, as the cost of bevacizumab remains high.

Overall, it is highly unlikely that atezolizumab plus bevacizumab would be considered a cost-effective use of Canadian healthcare resources, at a $50,000 per QALY threshold, even if substantial price reductions were obtained for both atezolizumab and bevacizumab.

Based on the sponsor's submitted budget impact analysis, the total incremental budget impact is estimated to be $[redacted] over the first three years. CADTH reanalyses suggest that the estimated budget impact of introducing atezolizumab plus bevacizumab would be similar at $199,200,041 over three years. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this economic information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Stakeholder Input Relevant to the Economic Review

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

Economic Review

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

Appendix 1: Cost Comparison Table

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

Appendix 2: Submission Quality

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

Appendix 3: Additional Information on the Submitted Economic Evaluation

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

Appendix 5: Submitted BIA and CADTH Appraisal

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

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