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CADTH DRUG REIMBURSEMENT REVIEW

Pharmacoeconomic Report

BRIGATINIB (ALUNBRIG)

(Takeda Canada Inc.)

Indication: For the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) previously untreated with an ALK inhibitor.

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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

AIC	Akaike Information Criterion
ALK	anaplastic lymphoma kinase
BIC	Bayesian Information Criterion
BIRC	blinded independent review committee
DoT	Duration on treatment
ICER	incremental cost-effectiveness ratio
ITC	indirect treatment comparison
LY	life-year
MAIC	matched-adjusted indirect comparison
NSCLC	non-small cell lung cancer
OS	overall survival
pCODR	pan-Canadian Oncology Drug Review
PERC	pCODR Expert Review Committee
PFS	progression-free survival
QALY	quality-adjusted life-year
RECIST	Response Evaluation Criteria in Solid Tumors

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	brigatinib (Alunbrig), oral tablets
Submitted price	brigatinib, 30 mg: $112.32 per tablet brigatinib, 90 mg and 180 mg: $336.96 per tablet
Indication	For the first line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC)
Health Canada approval status	Approved
Health Canada review pathway	Standard
NOC date	March 3, 2021
Reimbursement request	Adult patients with ALK-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC previously untreated with an ALK inhibitor
Sponsor	Takeda Canada Inc.
Submission history	Previously reviewed: Yes Indication: adult patients with ALK-positive metastatic NSCLC who have progressed on or who were intolerant to an ALK inhibitor (crizotinib) Recommendation date: August 1, 2019 Recommendation: Do not reimburse

ALK = anaplastic lymphoma kinase; NOC = Notice of Compliance; NSCLC = non-small cell lung cancer

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Adult patients with anaplastic lymphoma kinase (ALK)-positive locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) previously untreated with an ALK inhibitor (per the reimbursement request)
Treatment	Brigatinib
Comparators	• Crizotinib • Alectinib
Perspective	Canadian publicly funded health care payer
Outcome	QALYs, LYs
Time horizon	Lifetime (30 years)
Key data sources	• ALTA-1L trial – brigatinib vs crizotinib • Unanchored matched-adjusted indirect comparison (MAIC; ALTA-1L trial, ALEX trial, ASCEND-4 trial) – brigatinib vs alectinib (crizotinib was not included in the analysis)
Submitted results for base case	• Brigatinib was more costly and produced more QALYs than alectinib and crizotinib • Incremental cost-effectiveness ratio (ICER) for brigatinib vs. crizotinib was $113,007 per QALY (inc. cost: 126,266; incr. QALYs: 1.12) • Alectinib was extendedly dominated through crizotinib and brigatinib[a]
Key limitations	• The sponsor's base case assumed Duration on Treatment (DoT) was equal to progression-free survival (PFS) for each treatment. Trial-observed DoT for each comparator and feedback from clinical experts consulted by CADTH indicated that PFS underestimates DoT. • The sponsor incorporated treatment-specific utilities, which does not reflect CADTH guidelines. • The CADTH Clinical Review identified several limitations with the sponsor's unanchored MAIC between brigatinib and alectinib. The clinical review concluded that internal validity of the results of the sponsor's unanchored MAIC was low quality. CADTH attempted to address the uncertainty in the comparative efficacy data by applying the comparative estimates from a sponsor's results must be interpreted with caution and recommended the use of a published network meta-analysis (NMA) that included comparisons between brigatinib versus alectinib and brigatinib versus crizotinib instead. While the estimates from this source were considered more appropriate due to the use of established methods and rigorous reporting, the CADTH Clinical Review noted that limitations remain, and results should be interpreted with caution.

CADTH reanalysis results	• CADTH reanalyses included: the revision of data used to inform how DoT was modeled for brigatinib and crizotinib; the application of alternate literature estimates for each health state's utility weights; and, the use of a published NMA's hazard ratios to characterize overall survival and PFS between brigatinib and alectinib. CADTH was unable to address potential uncertainty in the extrapolation of OS for crizotinib.
	• CADTH found:
	  ○ Brigatinib was dominated by alectinib (brigatinib is more costly, less effective)
	  ○ Alectinib vs. crizotinib: ICER = $56,986 per QALY
	  ○ At a WTP threshold of $50,000 per QALY, brigatinib had a 0% chance of being cost-effective compared to alectinib. A price reduction of at least 46% would be required for total costs associated with brigatinib to be those of alectinib.

ALK = anaplastic lymphoma kinase; DoT = duration on treatment; incr. = incremental; ICER = incremental cost-effectiveness ratio; LY = life-year; NMA = network meta-analysis; NSCLC = non-small cell lung cancer; PSM = partitioned survival model; QALY= quality-adjusted life-year; vs. = versus; inc. = incremental; WTP = willingness to pay

[a] Treatment has a higher ICER when compared to the next more effective treatment

Conclusions

The ALTA-1L study reported that, in adult patients with anaplastic lymphoma kinase (ALK)-positive locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) previously untreated with an ALK inhibitor, the difference in progression-free survival was statistically significant between brigatinib and crizotinib. However, overall survival was immature in both comparators and the net survival benefit observed for brigatinib compared with crizotinib was not statistically significant during the course of the trial (two years). The assumed and extrapolated difference in mortality between these comparators is a key driver in the economic analysis.

CADTH undertook reanalyses to address limitations relating to data on treatment duration used to inform model parameters; the type of the utility weights applied to each health state; and, the hazard ratios characterizing overall survival and progression-free survival between brigatinib and alectinib. Based on the CADTH sequential analysis, brigatinib was dominated (more costly, less effective) by alectinib. The probability that brigatinib was cost-effective compared to alectinib at a willingness-to-pay threshold of $50,000 per QALY gained was 0%. No price reduction analysis was conducted, as the base case suggested that brigatinib produced fewer QALYs than alectinib.

CADTH's Clinical Review found that results from a published NMA were more methodologically rigorous than the sponsor's submitted unanchored MAIC for estimating relative treatment effect. However, in addition to notable parameter uncertainty in OS and PFS curves within the NMA, the CADTH Clinical Review also noted methodological limitations within the NMA that contribute additional uncertainty to the estimates of the hazard ratios. Additionally, the lack of data for time on treatment for alectinib resulted in the CADTH estimate of incremental cost of brigatinib (compared to alectinib) being disproportionately high. These limitations suggest that CADTH's assessment of the cost-effectiveness of brigatinib is associated with uncertainty.

Based on the sponsor's submitted budget impact analysis, introducing brigatinib was associated with an estimated budget-impact of [redacted] over the first three years. CADTH re-analyses estimated a budget impact of $8,878,577 ($1,491,797 in year 1, $3,155,075 in year 2, $4,231,705 in year 3).

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

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Appendix 1: Cost Comparison Table

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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.

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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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