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CADTH Reimbursement Recommendation

Cemiplimab (Libtayo)

Indication: For the treatment of patients with locally advanced basal cell carcinoma (BCC) previously treated with a hedgehog pathway inhibitor

Sponsor: Sanofi Genzyme, a division of Sanofi-Aventis Canada Inc.

Final recommendation: Reimburse with conditions

CADTH

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Redactions: Confidential information in this document may be redacted at the request of the sponsor in accordance with the *CADTH Drug Reimbursement Review Confidentiality Guidelines.*

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.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Libtayo?

CADTH recommends that Libtayo should be reimbursed by public drug plans for the treatment of adult patients with locally advanced basal cell carcinoma (laBCC) previously treated with a hedgehog pathway inhibitor (HHI) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Libtayo should only be covered to treat adult patients who have laBCC that cannot be cured by surgery or radiation and are unlikely to benefit from further HHI therapy. Patients should have good performance status.

What Are the Conditions for Reimbursement?

Libtayo should only be reimbursed if it is prescribed by a clinician with expertise in treating cancer and managing side effects. The price of Libtayo must be lowered to be cost-effective and affordable.

Why Did CADTH Make This Recommendation?

Evidence from a clinical trial demonstrated that patients with laBCC treated with Libtayo experienced tumour shrinkage or the tumour completely disappeared. The committee considered the significant psychosocial burden of visible skin lesions and lack of alternative treatment options for patients with laBCC.

Based on CADTH's assessment of the health economic evidence, Libtayo does not represent good value to the health care system at the publicly listed price and requires at least a 97% price reduction. Based on public list prices, Libtayo is expected to cost the public drug plans an additional $40,205,838 over 3 years.

Additional Information

What Is LaBCC?

Basal cell carcinoma (BCC) is a type of skin cancer that starts in basal cells — cells found at the bottom of the top layer of skin, also known as the epidermis. Patients with BCC present with skin lesions that appear as open sores, red patches, scars, or growths that sometimes crust or bleed. BCC is considered locally advanced when the tumours grow deep into the skin or surrounding tissues, muscles, or nerves.

Unmet Needs in LaBCC

Patients with laBCC are treated with HHI therapy; however, there are no treatment options available for patients with tumours that cannot be cured by surgery or radiation and HHI therapy no longer works for them.

How Much Does Libtayo Cost?

Treatment with Libtayo is expected to cost approximately $10,933 per 28 days.

Recommendation

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) recommends that cemiplimab be reimbursed for the treatment of patients with locally advanced basal cell carcinoma (laBCC) previously treated with a hedgehog pathway inhibitor (HHI) only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One single-arm, open-label, phase II trial (Study 1620) evaluated the efficacy and safety of cemiplimab in a cohort of patients with laBCC (N = 84) who had previously been treated with an HHI and were not candidates for curative surgery or curative radiation therapy. The trial demonstrated an objective response rate (ORR) of 28.6% (95% confidence interval [CI], 19.2% to 39.5%) at the primary analysis (median follow-up was 13.53 months) and an ORR of 32.1% (95% CI, 22.4% to 43.2%) at an updated analysis based on approximately [redacted] of additional follow-up (median follow-up [redacted]). The duration of response (DOR) among patients achieving complete response or partial response was not reached at either analysis data cut-off date, with DOR ranging from 2.1 months to greater than 21.4 months at the primary analysis. pERC considered these response outcomes clinically meaningful in a rare patient population with no active treatment options after progression on, or intolerance to, HHI therapy and who experience substantial morbidity from their disease. The duration of follow-up in Study 1620 was short. At the updated analysis, the median progression-free survival (PFS) time in the laBCC cohort was [redacted] months and median overall survival (OS) time was [redacted] It is unlikely that mature survival data will be able to definitively confirm long-term benefit due to the single-arm trial design. Health-related quality of life (HRQoL) was identified as an outcome important to patients given the impact the disease has on physical appearance and psychosocial aspects of well-being. Although limitations were identified with the assessment of HRQoL in Study 1620, the available data suggested HRQoL was at least maintained in patients treated with cemiplimab; multiple measures of HRQoL either remained stable (i.e., function and symptom scales) or appeared improved (i.e., emotional scales). The safety data from Study 1620 did not identify any new safety signals associated with cemiplimab, and although more than half of patients experienced immune-related adverse events (AEs), pERC agreed these toxicities can be effectively managed in clinical practice through appropriate symptom management and supportive care. pERC considered patients with laBCC experience a high burden of disease symptoms and disfigurement, and that there is a significant unmet need for an active treatment option in patients who have progressed on, or are intolerant to, HHI therapy. Given the totality of the evidence, pERC concluded that cemiplimab met some of the needs identified by patients because it provides a second-line treatment option with manageable side effects and reasonable quality of life.

Owing to limitations with the sponsor's modelling approach and the lack of comparative data, CADTH was unable to determine a base case estimate of cost-effectiveness for the Health Canada–approved indication. CADTH conducted an exploratory reanalysis based on more plausible assumptions; however, CADTH could not address modelling assumptions that overestimated the incremental benefit of cemiplimab because of the structure of the submitted model. In this analysis, the incremental cost-effectiveness ratio (ICER) for

cemiplimab was $2,259,421 per quality-adjusted life-year (QALY) relative to best supportive care. In this analysis, a reduction in price of at least 97% is required for cemiplimab to be considered cost-effective at a $50,000 per QALY threshold. CADTH notes this exploratory analysis likely underestimates the true ICER.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason
Initiation	
1. Treatment with cemiplimab should only be reimbursed in adult patients (≥ 18 years) with laBCC who meet all of the following criteria: 1.1. histologically confirmed, unresectable, invasive BCC that is not amenable to curative surgery or curative radiation therapy 1.2. unlikely to benefit from HHI therapy for any of the following reasons: not better than stable disease after 9 months on HHI therapy, prior disease progression on HHI therapy, or intolerance to HHI therapy.	Evidence from Study 1620 showed that treatment with cemiplimab produced clinically meaningful and durable response outcomes in patients with laBCC that is not amenable to curative surgery or radiation therapy and who had been previously treated with or were intolerant to HHI therapy.
2. Patients should have good Performance Status.	Study 1620 enrolled patients with an ECOG Performance Status of 0 or 1. It is recognized that the Performance Status may be related to underlying cancer; therefore, for some patients, an improvement in Performance Status is expected after initiation of treatment, whereas for others, increased comorbidities may contribute to a poorer Performance Status. As such, treatment of patients with an ECOG Performance Status of ≥ 2 should be considered on a case-by-case basis by the treating clinician.
3. Patients must not have any of the following: 3.1. prior treatment with PD-1 or PD-L1 pathway inhibitors 3.2. untreated brain metastasis that are considered active 3.3. active autoimmune disease requiring treatment 3.4. active infection requiring treatment 3.5. prior treatment with idelalisib.	The CADTH review identified no evidence to demonstrate a treatment benefit of cemiplimab in patients with laBCC who have the characteristics listed in this condition. As noted in the Health Canada product monograph for cemiplimab, prior treatment with idelalisib may lead to severe stomatitis or skin reactions, such as Stevens-Johnson syndrome or toxic epidermal necrolysis.

Reimbursement condition	Reason
Renewal	
4. Renewal of cemiplimab should be based on all of the following criteria: 4.1. Response to treatment should be assessed by clinical assessment every 6 weeks to 8 weeks, and imaging should be performed at the discretion of the treating clinician. 4.2. More subjective measures should also be assessed, including maintenance or improvement in HRQoL, cancer symptoms, and functional status, as well as disfigurement changes. 4.3. A maximum treatment duration of 93 weeks.	In Study 1620, patients with radiologically measurable lesions were assessed every 9 weeks (cycle 1 to cycle 5) and every 12 weeks (cycle 6 to cycle 9) based on RECIST 1.1 criteria. Patients with only externally visible lesions were assessed according to digital medical photography and clinical response was scored according to modified bi-dimensional WHO criteria. For patients with lesions that were both visibly measurable with digital medical photography and radiologically measurable according to RECIST 1.1, composite scoring criteria were used. It is recognized that clinical assessment and imaging for laBCC are performed less frequently in Canadian clinical practice than in clinical trials. As such, clinical assessment of patients receiving cemiplimab should be performed every 6 weeks to 8 weeks or follow local practice standards, and imaging should be performed at the discretion of the treating clinician. In Study 1620, treatment with cemiplimab continued until evidence of symptomatic disease progression (increase in size or extension of lesions), unacceptable toxicity, or when the 93-week treatment period was completed regardless of dose delays.
Prescribing	
5. Cemiplimab should only be prescribed by a medical oncologist or associated team physician with expertise in cancer therapies and toxicity management.	To ensure that cemiplimab is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.
Pricing	
6. A reduction in price.	Based on an exploratory CADTH reanalysis, the ICER for cemiplimab is $2,259,421 when compared with BSC. CADTH notes this exploratory analysis likely underestimates the true ICER. A price reduction of at least 97% would be required for cemiplimab to be below a threshold of $50,000 per QALY compared to BSC.

BSC = best supportive care; ECOG = Eastern Cooperative Oncology Group; HHI = hedgehog inhibitor; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; laBCC = locally advanced basal cell carcinoma; PD-1 = programmed cell death 1; PD-L1 = programmed death ligand 1; QALY = quality-adjusted life-year; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1.

Implementation Guidance

Issues that may impact the drug plan's ability to implement a recommendation as identified by pERC and the drug plans are summarized in Table 2.

Table 2: Implementation Guidance From pERC

Condition # in Table 1	Implementation considerations and guidance
1.1	Eligibility for cemiplimab is based on whether laBCC is deemed unresectable or unsuitable for radiotherapy. The clinical experts indicated that community physicians may not be aware of the specific indications or contraindications to surgery and radiation therapy for patients with laBCC, therefore tumour eligibility for surgery and radiation therapy should be determined by a multidisciplinary tumour board. In Study 1620, focal palliative radiation was allowed for local control of a tumour if the patient had been on treatment for 24 weeks.
4.3	In Study 1620, patients with a confirmed complete response after a minimum of 48 weeks of treatment could discontinue treatment with cemiplimab. There may be other clinical factors to consider in these patients before discontinuing treatment; therefore, discontinuation of cemiplimab for this clinical situation should be at the discretion of the treating clinician. In Study 1620, patients were permitted to receive re-treatment with cemiplimab after they experienced disease progression off treatment following the completion of the initial 93 weeks of treatment if recurrence occurred within the first 7 follow-up visits, which were every 28 days, without any intervening systemic anticancer therapy. Oncologic principle and experience with other immunotherapies have shown that patients with recurrence that occurs beyond 6 months of completing treatment also may benefit from re-treatment. Therefore, for patients who experience disease recurrence after the completion of the initial 93 weeks of cemiplimab without any intervening systemic anticancer therapy, it would be reasonable to offer re-treatment with cemiplimab for an additional 48 weeks.

laBCC = locally advanced basal cell carcinoma.

Discussion Points

- Less than 1% of patients with BCC experience a more advanced form of the disease that has slowly progressed into deep surrounding tissues so that curative surgery or radiotherapy are not appropriate. These patients suffer significant physical morbidity that is associated with chronic pain and disfigurement and negative effects on psychosocial well-being. pERC acknowledged that there is a significant unmet need for an active second-line treatment option in this rare patient population. The standard first-line treatment for patients with unresectable laBCC is treatment with an HHI. Once patients with laBCC become intolerant to HHI therapy, or experience disease recurrence, best supportive care is currently the only available treatment option.
- Although pERC acknowledged that Study 1620 did not meet its primary outcome (ORR), pERC agreed with the clinical experts that the responses observed were clinically meaningful and durable in patients treated in a second-line treatment setting. pERC noted the limitations of the non-comparative evidence but also considered the rarity of the condition and physical and psychosocial morbidity associated with the disease.
- HRQoL was identified as an important outcome to patients. pERC noted that HRQoL in Study 1620 was measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the Skindex-16, a dermatology specific instrument. For the EORTC QLQ-C30, changes in scores over time for the global health status and HRQoL scale and the functional and symptom scales (with the exception of fatigue) did not exceed the prespecified minimally important difference (MID) at any assessment time point; for the Skindex-16, symptom and functioning scale

scores remained stable or improved (emotional scale) more than the MID to the end of the study. pERC discussed the limitations of the HRQoL data, including that the analyses were descriptive, that fewer patients contributed to assessments at later time points, and the potential for bias in favour of cemiplimab due to the open-label trial design. However, despite these limitations, pERC agreed the available data suggest that multiple measures of quality of life were at least maintained in patients treated with cemiplimab.

- pERC discussed the safety profile of cemiplimab from Study 1620 and considered it aligned with its known safety profile in other conditions. pERC discussed that clinicians are experienced in managing the AEs associated with immunotherapy and agreed that most toxicities can be effectively managed in clinical practice through appropriate symptom management and supportive care. Patients who had experience with cemiplimab indicated that their side effects were manageable, and clinicians with experience administering the drug indicated that it was well tolerated by patients.

Background

Cemiplimab has a Health Canada indication for the treatment of patients with laBCC previously treated with an HHI. The sponsor's reimbursement request for cemiplimab is aligned with the Health Canada–approved indication. Cemiplimab is administered at a dose of 350 mg as an IV infusion over 30 minutes every 3 weeks and is continued until symptomatic disease progression or unacceptable toxicity.

Cemiplimab is a recombinant human IgG4 monoclonal antibody that binds to the programmed cell death 1 (PD-1) receptor, inhibiting interaction with the ligands PD-L1 and PD-L2. The inhibitory action of cemiplimab acting on PD-1 counteracts this inhibition of the immune response, including the antitumour immune response of T cells.

Sources of Information Used by the Committee

To make their recommendation, pERC considered the following information:

- a review of 1 phase II, single-arm, non-randomized, open-label multicentre study (Study 1620, laBCC cohort)
- patients' perspectives gathered by 2 patient groups: Save Your Skin Foundation (SYSF) and the Melanoma Network of Canada (MNC)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with laBCC
- input from 1 clinician group: Ontario Health (Cancer Care Ontario)
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient and clinician groups who responded to CADTH's call for input and from clinical experts consulted by CADTH for the purpose of this review.

Patient Input

Input was provided for this review by 2 patient groups: SYSF and the MNC. SYSF gathered information from online surveys, virtual patient roundtables, and one-on-one conversations over the previous 6 months. All 23 patients consulted (women: n = 20; men: n = 3) had been diagnosed with BCC and 5 had experience with cemiplimab. It was not reported whether patients had experience with HHI therapy before receiving cemiplimab. A total of 19 out 23 patient respondents were from Canada; most of the Canadian responders were from Ontario. The MNC input was sourced from an online survey of 62 patients (women: n = 44; men: n = 18) and 45 caregivers. All but 1 of the patients were from Canada, with 50% located within the province of Ontario. Only 1 patient indicated they had experience with cemiplimab in metastatic disease; no patients had experience with HHI therapy.

In both surveys, patients highlighted the negative aspects of BCC and its treatment, including disfigurement, scarring, and associated self-esteem difficulties. Other key concerns mentioned by patients in both surveys were pain from the lesions and anxiety over finding recurrent disease. In the MNC survey, caregivers expressed that the disease caused much emotional stress with seeing their loved one in pain. Patients expressed a desire for less radiation and disfiguring surgery and greater access to treatments closer to home and their support network. Respondents from the SYSF submission who had experience with cemiplimab indicated that the side effects were manageable, and the benefits would outweigh the side effects. Of the 5 patients with experience with cemiplimab, 2 had no side effects, 2 patients had fatigue, and 1 patient had skin rash. The 1 patient from the MNC submission who had experience with cemiplimab indicated that having the option for therapy was worth experiencing treatment side effects, which included liver issues and flu-like symptoms.

Patients indicated that there are no other options for treatment at this stage of disease and the ability to access new treatments to eliminate disease and prevent recurrence is needed. Earlier diagnosis, access to specialists, and less invasive procedures were highlighted as important to patients and caregivers in the MNC survey.

Clinician Input

Input From Clinical Experts Consulted by CADTH

Two clinical experts with expertise in the diagnosis and management of laBCC highlighted the lack of options available for patients with laBCC who have failed HHI therapy, especially if response to HHI therapy is low and some patients cannot tolerate treatment side effects. Eligibility is based on whether the tumour is deemed unresectable or unsuitable for radiotherapy, which can be uncertain; therefore, the clinical experts suggested that tumour eligibility should be determined by a multidisciplinary tumour board. The main goals of therapy are to shrink the tumour and increase the HRQoL of patients with laBCC. The clinical experts highlighted the extreme importance of HRQoL in this patient population given the disfiguring nature of the disease. Treatment would usually be discontinued upon disease

progression (increase in size or extension of lesions), severe or intolerable side effects, or a lack of response after adequate duration of treatment (identified as 4 months to 6 months of treatment). According to the clinical experts, treatment with cemiplimab would be initiated by a medical oncologist or associated team physician with expertise in cancer therapies and toxicity management.

Clinician Group Input

One clinician group, Ontario Health (Cancer Care Ontario), provided input for this review. No major views contrary to those provided by the clinical experts consulted by CADTH were presented. Ontario Health echoed the lack of options for patients with laBCC who have failed HHI therapy and the importance of HRQoL outcomes, specifically relating to disfiguring lesions and surgical scarring.

Drug Program Input

The drug programs identified jurisdictional implementation issues related to relevant comparators, initiation and prescribing of therapy, generalizability, and care provision issues. pERC weighed evidence from the Study 1620 and other clinical considerations, including input from the clinical experts consulted by CADTH, to provide responses to the drug programs' implementation questions, which are presented in Table 3.

Table 3: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
There was no comparator in the pivotal trial submitted for consideration. The usual treatment in this setting is best supportive care. Chemotherapy with carboplatin and paclitaxel may occasionally be administered after disease progression with an HHI used for advanced (not amenable to local therapies) BCC.	pERC acknowledged the lack of a comparator as a limitation of Study 1620; however, currently there is no standard second-line treatment for patients with laBCC who have previously been treated with an HHI and have failed therapy or are intolerant to HHI.
Considerations for initiation of therapy	
The treatment protocol includes re-treatment for an additional 4 cycles for patients who complete 9 cycles without disease progression. Should patients who completed 9 cycles but subsequently experience disease progression while off treatment be eligible for re-treatment?	In Study 1620, patients were permitted to receive re-treatment with cemiplimab after they experienced progression off treatment following the completion of the initial 93 weeks of treatment if recurrence occurred within the first 7 follow-up visits, which occurred every 28 days. Oncologic principles and experience with other immunotherapies have shown that patients with recurrence that occurs beyond 6 months of completing treatment also may benefit from re-treatment. Therefore, for patients who experience disease recurrence after the completion of the initial 93 weeks of treatment with cemiplimab, it would be reasonable to offer re-treatment with cemiplimab for an additional 48 weeks.
Patients are required to have previously been treated with a HHI such as vismodegib or sonidegib. Vismodegib is funded in most Canadian jurisdictions. Sonidegib is not funded in any Canadian jurisdiction because it was not recommended for reimbursement by CADTH pCODR.	pERC acknowledged that only vismodegib is funded in most jurisdictions in Canada, but patients may have had access to sonidegib through clinical trials or paid for it themselves. pERC agreed that patients previously treated with either HHI should be eligible for cemiplimab.

Implementation issues	Response
Considerations for prescribing of therapy	
The usual starting dose of cemiplimab is 350 mg IV every 3 weeks. What is the maximum treatment duration? Should the maximum treatment duration be 93 weeks or until disease progression or unacceptable toxicity?	There are no data from Study 1620 for treating patients beyond the 93-week treatment schedule. In the absence of such data, pERC agreed that patients should be treated up to a maximum treatment duration of 93 weeks or until symptomatic disease progression or unacceptable toxicity, whichever occurs first.
Cemiplimab is administered as an IV infusion over 30 minutes through an IV line containing a sterile in-line or add-on filter (0.2 micron to 5 micron pore size). Sites will need to ensure they have appropriate supplies available to administer cemiplimab.	pERC acknowledged the administration requirements for cemiplimab.
Generalizability	
Study 1620 included patients who had mBCC, those with no better than stable disease for 9 months following HHI therapy, and an ECOG Performance Status of 0 and 1. Should treatment with cemiplimab be extended to the following patients: • mBCC patients • patients with no better than stable disease after 9 months on HHI therapy • patients who cannot tolerate or are ineligible for treatment with HHI therapy • patients with ECOG Performance Status ≥ 2?	The sponsor's reimbursement request aligns with the Health Canada indication, which only includes patients with laBCC. Patients with metastatic BCC were excluded from the Health Canada indication because of low patient numbers and immature interim results from Study 1620. Therefore, pERC's recommendation is focused to the laBCC population. The results from this cohort in Study 1620 should not be generalized to patients with metastatic BCC. pERC agreed with the clinical experts that most clinicians would wait 3 months to 5 months for a response before exploring other treatment options for patients with laBCC; therefore, it would be reasonable to offer cemiplimab to patients without a response (stable disease) after 9 months on HHI. Many patients discontinue HHI therapy due to toxicity (e.g., taste disturbances, muscle spasms, alopecia, weight loss, and fatigue). pERC agreed with the clinical experts that the criteria used in Study 1620 (any grade 3 or grade 4 AE deemed related to HHI or grade 2 myalgia, dysgeusia, anorexia, nausea, or diarrhea in patients with at least 3 months exposure to HHI) would be reasonable criteria to use for establishing intolerance to an HHI. Study 1620 enrolled patients with an ECOG Performance Status of 0 or 1. It is recognized that performance status may be related to the underlying cancer; therefore, for some patients, an improvement in status would be expected after initiation of treatment with cemiplimab, whereas for others, increased comorbidities may contribute to a poorer Performance Status. As such, treatment of patients with an ECOG Performance Status ≥ 2 should be considered on a case-by-case basis by the treating clinician.

Implementation issues	Response
Care provision issues	
Serious immune-mediated reactions can be severe to fatal and usually occur during the treatment course. Early diagnosis and appropriate management are essential to minimize life-threatening complications. Should cemiplimab be reimbursed, is a statement needed ensuring access to a treatment centre with expertise to manage these side effects, should they occur?	pERC agreed with the clinical experts that the oncology community is accustomed to the use of immunotherapies and their associated side effects and risks. Cemiplimab does not have any additional safety concerns beyond those that treatment centres (inpatient or outpatient) and prescribing clinicians are familiar with and are able to manage if they arise. Cemiplimab should be administered in cancer centres or centres supervised by physicians with expertise and with staffing (chemotherapy nurses, oncology pharmacists) to administer systemic therapies and manage treatment-related toxicities, particularly immune-mediated reactions, which can be severe or fatal and usually occur during the treatment course.
Preservative-free Intact vials are stored in the refrigerator and protected from light. Refrigerator space may be a concern for some pharmacies.	pERC acknowledged the refrigerator space requirement may be a challenge for some pharmacies.

AE = adverse event; BCC = basal cell carcinoma; ECOG = Eastern Cooperative Oncology Group; HHI = hedgehog inhibitor; pCODR = CADTH pan-Canadian Oncology Drug Review; pERC = pCODR Expert Review Committee.

Clinical Evidence

Description of Study

One phase II, single-arm, non-randomized, open-label multicentre study (Study 1620, laBCC: N = 84) was included in the systematic review. The primary objective of the study was to determine the efficacy of cemiplimab in achieving an objective tumour response in 2 cohorts of patients: those with laBCC and those with mBCC.

The study enrolled patients with either laBCC or mBCC who had previously received HHI therapy; however, the laBCC population was the focus of the CADTH review because the Health Canada indication and requested reimbursement request were restricted to this patient population.

In Study 1620, patients were treated with cemiplimab for up to 93 weeks or until progressive disease or unacceptable toxicity. Tumour response was assessed using a composite of Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST 1.1) for lesions with radiologically measurable components and modified WHO clinical criteria for lesions with externally visible components; responses were designated by blinded independent central review.

Most patients in the study with laBCC were men (66.7%) and White (67.9%). Infiltrative tumour histology accounted for 8.3% of laBCC lesions while the broad "other" category accounted for 66.7% of lesions with most (89.3%) located in the head or neck. The mean age of patients with laBCC was 69.1 (standard deviation [SD] = 12.8) years. The primary outcome was ORR by blinded independent central review; secondary outcomes included ORR by investigator assessment, DOR, PFS, OS, time to tumour response, disease control rate, and HRQoL.

Study 1620 was a single-arm, non-comparative trial; therefore, the primary outcome was based on rejecting the null hypothesis of an ORR equal to a chosen non-clinically meaningful response rate. In the laBCC group, the null hypothesis was an ORR equal to 20% that would be rejected if the lower bound of the 2-sided 95% CI excluded the value of 20%. This threshold was chosen to be consistent with what was determined to be clinically meaningful in previous trials for HHI therapy in advanced BCC, although these trials were conducted in the first-line setting. The assessment of secondary outcomes was descriptive.

The primary analysis of Study 1620 was conducted based on a data cut-off date of February 17, 2020, at which time the mean duration of patient follow-up was 13.53 months and the mean duration of treatment with cemiplimab was 52.80 weeks. An updated analysis was performed [redacted], at which time the mean duration of follow-up [redacted]

Outcome Results

The ORR at the time of the primary analysis was 28.6% (95% CI, 19.2% to 39.5%), which failed to meet the 20% pre-specified threshold based on the lower bound of the 95% CI. At the updated analysis, the pre-specified threshold was reached with an ORR of 32.1% (95% CI, 22.4% to 43.2%). At the primary analysis, the median Kaplan-Meier estimation of DOR in the 24 patients who achieved either a complete response or partial response had not been reached. The observed DORs ranged from 2.1 months to greater than 21.4 months with 79.2% of responders achieving a DOR greater than 6 months, and 45.8% of responders achieving a DOR greater than 12 months.

HRQoL was measured in Study 1620 using the EORTC QLQ-C30 and the Skindex-16. Changes over time in the global health status and HRQoL score of the EORTC QLQ-C30 were smaller than the MID estimate of 5 points to 10 points at both the primary and updated analysis. Analysis of EORTC QLQ-C30 functional and symptom scales showed scores consistent with the results for the global health status scale. Symptom scales remained stable over time with the exception of fatigue, which showed worsening in excess of the MID for the fatigue scale at cycle 7 and cycle 9, although patient numbers were reduced at these time points. An improvement in excess of the MID of 10 points or more was achieved in the emotion scale of the Skindex-16 at cycle 4 and maintained through the end of the study, while the symptom and functioning scales remained stable over time.

At the time of primary analysis, 45.2% of patients in the laBCC group had experienced a PFS event, with 39.3% of patients experiencing disease progression and 6.0% experiencing death. The median PFS time was 19.3 (95% CI, 8.6 to not estimable) months. At the updated analysis, [redacted]

At the time of primary analysis, death had occurred in 11.9% of patients and the median OS had not been reached. At the updated analysis, [redacted]

Harms Results

Treatment emergent adverse events (TEAEs) occurred in almost all patients (97.6% and 98.8% at the primary and updated analyses, respectively). Serious AEs occurred in 34.5% and 36.9% of patients at the primary and updated analyses, respectively, while TEAEs leading to treatment discontinuation occurred in 16.7% and 17.9% of patients, respectively. The most

common TEAE that led to a dose delay was diarrhea in 4.8% of patients, followed by blood creatinine increase, fatigue, and urinary tract infection, each occurring in 3.6% of patients. Deaths due to TEAEs occurred in 3.6% and 4.8% of patients at the primary and updated analyses, respectively, which included 1 occurrence of cachexia, malignant brain neoplasm, and acute kidney injury, respectively.

Immune-related AEs occurred in 56% and 58.3% of patients at the primary and updated analyses, respectively. This included 11.9% of patients who experienced grade 3 or higher TEAEs, 9.5% who experienced serious immune-related AEs, and 9.5% who experienced an immune-related AE leading to treatment discontinuation. Infusion reactions occurred at a much lower rate, with only 1.2% of patients experiencing any infusion-related reaction. The incidence of notable harms was unchanged at the updated analysis.

Critical Appraisal

The most notable limitations of Study 1620 relate to the single-arm, open-label design. Due to this, it is impossible to draw any conclusions about efficacy with any level of certainty. The clinical experts consulted by CADTH agreed with the clinically meaningful ORR threshold of 20%, and it was also noted that this threshold is consistent with what was used in previous single-arm trials in patients with laBCC. Rejection of the null hypothesis (ORR = 20%) required the lower bound of the 95% CI to exclude 20%, and this was not achieved at the time of the primary analysis (ORR = 28.6%; 95% CI, 19.2% to 39.5%). Additionally, 2 patients did not meet the inclusion criterion requiring enrolled patients to have at least 1 measurable lesion. They were enrolled in the study despite this which, according to clinical experts consulted for this review, would likely bias the results by increasing the ORR. Important protocol deviations occurred in 23.8% of all patients in the laBCC group of Study 1620, although the observed protocol deviations were considered acceptable for a second-line oncology clinical trial. The most common important protocol deviations were related to enrolling patients despite inclusion criteria (15.5%) and exclusion criteria (3.6%) deviations. There was a relatively high number of patients that discontinued the study for reasons other than progressive disease or death (19.0% at the primary analysis data cut). These reasons included AEs, loss to follow-up, noncompliance with the protocol, withdrawal of consent, patient decision, and sponsor decision. In the case of noncompliance with the protocol and sponsor decision, the CADTH review team did not believe that these were valid reasons to discontinue the study and this was likely to bias the results in favour of cemiplimab.

According to the study protocol, for a patient to have achieved complete response or partial response, a response must have been confirmed at least 4 weeks following the initial documented response. If the response was not confirmed, the patient was reported as having stable disease. The sponsor presented an unplanned sensitivity analysis in which the pre-specified threshold to reject the null hypothesis was reached, which included the responses from 2 patients who had unconfirmed initial responses at the time of primary analysis. Both patients ultimately had their responses confirmed; however, these results were based on an ad hoc redefinition of the primary outcome that differs from the study protocol. There is an increased risk of type I error because there was no adjustment for multiplicity in this analysis; therefore, the obtained results should be interpreted with caution. The sponsor also provided the results of an unplanned updated analysis [redacted] the reported ORR at this data cut was 32.1% (95% CI, 22.4% to 43.2%). The same limitations regarding no adjustment for multiplicity and increased risk of type I error apply to the updated analysis and results.

According to the clinical experts consulted by CADTH, the demographic and disease characteristics of the Study 1620 population were reflective of the Canadian population with laBCC. The dosage of cemiplimab in Study 1620 was aligned with the Health Canada–approved dosing and with clinical practice. In the study, treatment with cemiplimab was administered until progressive disease, unacceptable toxicity, or up to 93 weeks duration. The protocol allowed for re-treatment of patients who had completed the full treatment course but experienced progressive disease during the follow-up period. The sponsor confirmed that 1 patient had entered re-treatment with cemiplimab. Given the lack of data, data from this trial may not be generalizable to treatment beyond the 93-week treatment course or within a re-treatment setting for patients who experience progressive disease following discontinuation of cemiplimab.

Indirect Comparisons

No indirect evidence was identified for this review.

Other Relevant Evidence

No other relevant evidence was identified for this review.

Economic Evidence

Table 4: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Adult patients with locally advanced basal cell carcinoma previously treated with a hedgehog pathway inhibitor, consistent with the reimbursement request
Treatment	Cemiplimab
Submitted price	Cemiplimab, 350 mg vial: $8,200
Treatment cost	The cost for cemiplimab is $10,933 per 28 days
Comparator	BSC in the context of palliative care (no active therapy, palliative radiotherapy, wound management, and physician visits)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (35 years)
Key data source	Clinical efficacy for patients receiving cemiplimab was modelled using OS and PFS observed in Study 1620. Clinical efficacy for patients receiving BSC was modelled using OS from Cowey et al. (2021).

Component	Description
Key limitations	• There was no direct or indirect evidence comparing cemiplimab to BSC, and evidence derived from the single-arm trial on cemiplimab was associated with significant limitations. Therefore, the impact of cemiplimab is highly uncertain, and the relative impact vs. BSC is unknown. • The sponsor's model assumed 100% of patients who receive cemiplimab start pre-progression and 100% of patients who receive BSC start post-progression. Progression in the trial was defined as "recurrent or progressive disease," which could still occur in an untreated cohort. This model structure overestimated the benefit of cemiplimab for 2 reasons. First, it assumed 100% of patients benefit immediately from receiving cemiplimab, although the response rate in the trial was only 32% and no patients responded before 2 months. Second, the definition of "progression" in the trial included patients with new lesions or lesions that increased in size. The assumption that all patients receiving BSC had the same outcomes as these patients at the start of the model is inappropriate. • The sponsor's choice of parametric survival functions overestimated the survival benefit and delay of progression associated with cemiplimab when extrapolating beyond the trial period. The sponsor assumed a survival benefit from cemiplimab relative to BSC (4.42 additional LYs), which was not expected by the clinical experts. • The sponsor overestimated resource utilization associated with BSC (dermatologist, general practitioner, and oncology visits) relative to those who receive cemiplimab. • The sponsor underestimated the frequency of wound dressings required for patients receiving cemiplimab, therefore underestimating costs for those who receive cemiplimab. • Utility decrements associated with AEs were inappropriately applied as a 1-time multiplier for 1 cycle length vs. the total treatment duration.
CADTH reanalysis results	• Given the lack of reliable clinical data to inform comparative effectiveness and the highly uncertain model structure, CADTH was unable to derive a base case. Instead CADTH performed an exploratory reanalysis which used a Weibull parametric function to extrapolate OS, assumed OS is similar for both treatments, used a gamma parametric function to extrapolate PFS, adjusted the frequency of post-progression health care visits, increased the frequency of wound dressings based on objective response rates from the clinical trial, and applied utility decrements for AEs annually for the total treatment duration. • The CADTH exploratory reanalysis found that cemiplimab is associated with an ICER of $2,259,421 per QALY and the probability of cost-effectiveness at a WTP threshold of $50,000 per QALY is 0%. A price reduction of 97% is necessary to achieve cost-effectiveness at this threshold. Given that CADTH could not change the model structure, these results are based on the assumption that 100% of patients benefit from receiving cemiplimab, which is likely an underestimation of the true ICER. • A scenario analysis was performed to assess the uncertainty in utility values for the post-progression state, which increased the ICER to $3,331,586 per QALY.

AE = adverse event; BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life-year; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life-year; WTP = willingness to pay; vs. = versus.

Budget Impact

CADTH reanalysis increased the market shares for cemiplimab and applied the mean treatment duration to calculate costs. In the CADTH base case, the budget impact is expected to be $6,481,980 in year 1, $13,433,342 in year 2, and $20,290,516 in year 3, with a 3-year total budget impact of $40,205,838. CADTH found the budget impact of cemiplimab to be sensitive to market shares and medical eligibility. This budget impact also assumes there is no re-treatment.

CADTH

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Catherine Moltzan, Dr. Christopher Longo, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: January 12, 2022

Regrets: None

Conflicts of interest: None