pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

pERC Final Recommendation
This pERC Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Sonidegib (Odomzo)

Submitted funding request: For the treatment of adult patients with histologically confirmed laBCC that is not amenable to radiation therapy or curative surgery

Submitted By: Sun Pharma Canada Inc.	**Manufactured By:** Sun Pharma Canada Inc.
NOC Date: June 12, 2020	**Submission Date:** June 19, 2020
Initial Recommendation: March 4, 2021	**Final Recommendation:** April 29, 2021

Approximate per patient drug costs, per28 days	Sonidegib is available as a 200 mg capsule at a submitted price of $267.35 per capsule. The recommended dose of 200 mg daily results in a 28-day cost of $7,486 per patient.

pERC RECOMMENDATION

☐ **Reimburse**
☐ **Reimburse with clinical criteria and/or conditions[a]**
☒ **Do not reimburse**

[a] If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.

pERC does not recommend the reimbursement of sonidegib (Odomzo) for the treatment of adult patients with histologically confirmed locally advanced basal cell carcinoma (laBCC) that is not amenable to radiation therapy or curative surgery.

pERC made this recommendation because it was unable to conclude, based on the available evidence, that there was a net clinical benefit of sonidegib in adult patients with laBCC. pERC acknowledged that there is a need for effective treatment options in this setting, although the degree of need was uncertain given the availability of vismodegib. While sonidegib was associated with reasonable response rates, the committee noted that there are marked limitations in the available non-comparative phase II trial resulting in considerable uncertainty in the impact of sonidegib on progression-free survival (PFS) and overall survival (OS). pERC also noted that there was considerable uncertainty around the magnitude of the clinical benefit due to the lack of direct or convincing indirect comparative evidence to vismodegib, which is the only relevant comparator for these patients in Canadian practice.

pERC concluded that sonidegib aligned with patient values of delaying progression, causing less scarring or disfigurement than surgery or radiation, oral option, manageable side effect profile, and no apparent detriment in quality of life. However, pERC noted that the impact of sonidegib on patient outcomes and quality of life compared with vismodegib is uncertain.

The committee noted that due to the limitations associated with the indirect comparative clinical evidence for sonidegib compared to vismodegib, the cost-effectiveness of sonidegib could not be estimated.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Possibility of Resubmission to Support Reimbursement** pERC noted that new clinical data comparing sonidegib with best supportive care in patients with laBCC who are not amenable to radiation therapy or curative surgery and are intolerant to vismodegib could form the basis of a resubmission if comparative efficacy data important to decision-making, such as PFS, OS, and quality of life, are available with an appropriate economic evaluation.

SUMMARY OF pERC DELIBERATIONS

Non-melanoma skin cancer (NMSC) represents 30% of all new cancer cases in Canada. Basal cell carcinoma (BCC) is the most prevalent form of NMSC, accounting for 74% of all cases in Canada.

Various therapeutic options are used to treat BCC, which include surgery, photodynamic therapy, radiotherapy, and approved topical treatments. While BCCs are usually amenable to local therapy, a small proportion of BCCs may progress to an advanced state that is no longer amenable to available treatments, which can result in considerable morbidity and cause severe disfigurement. Locally advanced BCC (laBCC) and metastatic BCC (mBCC) account for up to 10% and 0.5%, respectively, of all BCC cases. pERC agreed with the Clinical Guidance Panel (CGP), the registered clinicians, and the patient groups that there is a need for effective treatment options for patients with laBCC.

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on 4 main criteria:

CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

pERC deliberated on the results of 1 randomized, double-blind, phase II trial (BOLT), which assessed the efficacy and safety of 2 doses of sonidegib in adult patients with histologically confirmed laBCC not amenable to radiotherapy or curative surgery, or mBCC for whom all existing available treatment options had been exhausted. pERC noted the drug reimbursement request was for the subgroup of patients with laBCC in the BOLT trial. In the laBCC subgroup, sonidegib showed an objective response rate (ORR) that exceeded the predefined threshold for a clinically meaningful response (i.e., 30%) in both the 200 mg and 800 mg dose groups, with ORR being slightly higher in the 200 mg group than the 800 mg group. The ORR results in the laBCC subgroup were consistent with the overall study population (i.e., laBCC and mBCC). However, pERC discussed that the laBCC subgroup was not the focus of the primary analysis of the BOLT trial; thus, the efficacy results meeting the 30% threshold may be a spurious result as the sample size was not calculated to provide power for the laBCC subgroup. pERC also noted that the recommended dose of sonidegib was 200 mg; however, 800 mg was considered to be the more efficacious dose in the BOLT trial, resulting in a smaller number of patients assigned to the 200 mg dose group (due to a 1:2 randomization ratio). pERC noted that progression-free survival (PFS) was reported to be clinically meaningful for the laBCC patient population. However, the committee commented that the PFS estimate was uncertain in this patient subgroup as it was neither appropriately powered to test for the treatment effect in the laBCC subgroup nor was it controlled for multiple testing. pERC further acknowledged that the OS estimates were highly uncertain due to the high proportion of censoring for loss to follow-up (43.3%). pERC noted that the BOLT trial included 2 study groups evaluating 2 doses of sonidegib and that there were no placebo or active control groups included in the trial. The committee noted that the currently funded treatment for patients with laBCC is vismodegib. pERC discussed the results of the matching-adjusted indirect comparison (MAIC) and meta-analysis submitted by the sponsor and noted that the submitted indirect treatment comparisons (ITCs) of sonidegib versus vismodegib were poorly conducted and had several limitations, including a lack of statistical comparisons between the treatments, minimal adjustment for potential effect modifiers and prognostic factors in MAIC, lack of assessment for residual confounding, and no description of literature search and data extraction methodology that precluded evaluation of evidentiary completeness. Therefore, pERC concluded that the comparative efficacy of sonidegib to vismodegib was unknown.

Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback from the sponsor, registered clinician group (Ontario Health/ Cancer Care Ontario [CCO] Drug Advisory Committee DAC), and patient advocacy groups (Melanoma Network Canada [MNC], Save Your Skin Foundation [SYSF], and Canadian Skin Patient Alliance [CSPA]) regarding the similar efficacy and toxicity profiles of sonidegib and vismodegib. The sponsor acknowledged that single-arm, non-comparative trials of sonidegib and vismodegib did not permit indirect comparisons adequate to establish the superiority of either drug; however, based on clinical experience and response data from the BOLT trial, sonidegib is expected to be at least as efficacious as vismodegib, and the BOLT trial met its prespecified definition of clinical benefit. The sponsor also highlighted that compared to the ERIVANCE trial, the BOLT trial used more rigorous definitions of response, conducted centrally reviewed outcome assessment, and assessed health-related

quality of life (HRQoL). The registered clinician group also noted that sonidegib has demonstrated similar efficacy to vismodegib based on the ORR reported in the phase II BOLT trial, which was similar to the ERIVANCE trial of vismodegib in terms of trial design, and number and characteristics of enrolled patients. pERC considered feedback from the registered clinician group, and patient advocacy groups regarding the unmet need in patients who experience intolerance to vismodegib. The registered clinicians noted that patients often do not tolerate vismodegib, which can lead to dose interruptions or stopping treatment since dose reductions are not possible due to the lack of different capsule strengths. Although it was recognized by the clinicians that the toxicity profiles of the two drugs are similar, they noted that reimbursement of sonidegib would provide patients the opportunity for dose reduction, and consequently, patients could be maintained on treatment longer and achieve greater clinical benefit. Feedback from the patient advocacy groups also highlighted an unmet need for patients who might not tolerate vismodegib, based on the toxicity profile of vismodegib. The patient groups also identified a need for alternative oral options for elderly patients. Based on similar efficacy data from comparably conducted trials (i.e., BOLT and ERIVANCE) and the need for an effective treatment in the context of vismodegib toxicity, pERC agreed that, sonidegib may have a reasonable place as an alternative therapy for patients who are intolerant to vismodegib. However, pERC noted that there is a lack of evidence to support sequential use of sonidegib in patients who have progressed on vismodegib.

pERC considered the possibility of resubmission to support reimbursement of sonidegib for patients who are intolerant to vismodegib and discussed that best supportive care (BSC) would be the most relevant comparator in this setting. However, based on re-deliberation of the available data, pERC agreed that there is insufficient comparative evidence to support a decision on the reimbursement of sonidegib for this restricted indication. Therefore, pERC noted that new clinical data comparing sonidegib against BSC could form the basis of a resubmission if comparative efficacy data important to decision-making, such as PFS, OS or HRQoL, are available.

pERC discussed patient-reported outcomes from the BOLT trial and noted that the majority of trial participants (both laBCC and mBCC) either maintained or had a nominal improvement in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and EORTC QLQ Head and Neck Cancer module (H&N35) scales for health status, functioning, and disease-related symptoms. pERC agreed with the CGP that there was no apparent detriment to HRQoL based on the available data. However, pERC discussed that in the absence of a direct comparator and a clear definition of clinical improvement, the interpretation of HRQoL may be limited. pERC also noted that outcomes related to HRQoL were not analyzed in the available indirect comparisons and, therefore, no conclusions could be drawn comparing sonidegib to vismodegib for these outcomes.

pERC deliberated on the safety profile of sonidegib in adult patients with advanced BCC and noted that, in the BOLT trial, the most common grade 3 to grade 4 adverse events (AEs) in patients receiving the 200 mg daily dose included an increase in blood creatine phosphokinase (CK) and lipase, asthenia, muscle spasms, hypertension, and weight decrease. Serious AEs (SAEs) in the 200 mg dose group included pneumonia, angina pectoris, bipolar disorder, blood CK increase, and rhabdomyolysis. pERC discussed that the frequency of AEs was higher in the 800 mg dose group and that all of the four treatment-related deaths had occurred within the 800 mg sonidegib group. Overall, pERC agreed that sonidegib is reasonably safe with no unexpected or unmanageable toxicities, and that its safety profile is consistent with other Hedgehog (Hh) inhibitors. However, pERC noted that, due to the limitations of the available evidence, the comparative safety of sonidegib versus vismodegib remains unknown.

Overall, pERC was unable to conclude, based on the available evidence, that there was a net clinical benefit of sonidegib in adult patients with laBCC. The committee agreed with the Clinical Guidance Panel (CGP) that laBCC commonly develops in the elderly population, which increases the potential for treatment toxicity due to the presence of significant comorbid illnesses and can lead to significant morbidity in patients. Therefore, there is a need to have therapeutic choices that have comparable efficacy to existing options in elderly patients. pERC also discussed that sonidegib might represent a potential alternative treatment choice when vismodegib is contraindicated or cannot be tolerated by patients. However, pERC noted that there was considerable uncertainty related to its PFS and OS benefits, and with the comparative efficacy of sonidegib versus the currently funded standard of care, vismodegib. In addition, clinically meaningful quality of life data were not available from the BOLT study. pERC concluded that sonidegib does not meet a clear unmet need in the patient population included in the funding request.

During deliberations, pERC considered the patient advocacy group input received that indicated patients with advanced BCC who are not amenable to radiation therapy or curative surgery experience serious scarring and disfigurement, fear, and anxiety. The committee discussed the patient values on the available treatments and noted that the treatment side effects can lead to significant emotional and physical scaring and social isolation as well as negatively impact patients' quality of life. pERC also noted that input received from patients indicated that there were long wait times for successive surgeries and radiation therapy and an unavailability of more advanced surgery practices in all provinces and regions. They discussed that patients are seeking effective and less invasive options that can stop disease progression, and that patients who had taken sonidegib reported that the benefits of the treatment outweighed the side effects, and that they were pleased with the option of oral treatment. Patients also indicated that oral treatments can be easily administered for elderly patients and lessen burden for caregivers. Therefore, pERC concluded that sonidegib aligned with patient values of delaying progression, causing potentially less scarring or disfigurement, oral option, manageable side effect profile, and no apparent detriment in quality of life. However, pERC noted that the impact of sonidegib on patient outcomes and quality of life compared with vismodegib is uncertain.

pERC deliberated on the cost-effectiveness of sonidegib compared with vismodegib for patients with laBCC. pERC noted substantial limitations with the comparative clinical evidence which led to an assessment of unknown cost-effectiveness of sonidegib compared with vismodegib. Upon reconsideration of the pERC Initial recommendation and based on feedback received from the sponsor, registered clinician group, and the patient groups, pERC discussed whether a funding recommendation could be made for sonidegib in patients who are intolerant to vismodegib. pERC noted that an economic analysis specific to this patient population was not submitted, thus an assessment of the cost-effectiveness of sonidegib in this population was not possible.

pERC also discussed the budget impact analysis. pERC considered the estimated budget impact to be associated with some uncertainty but noted that there may be cost savings dependent on the drug acquisition cost of sonidegib being no more costly than vismodegib. This assessment of the budget impact is based on the assumption that sonidegib and vismodegib will not be used sequentially. If these treatments are used sequentially, the addition of sonidegib will result in an incremental budget impact.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report that provided clinical context
- an evaluation of the sponsor's economic model and budget impact analysis
- guidance from the pCODR clinical and economic review panels
- one joint input on behalf of 2 patient advocacy group(s): MNC and SYSF
- input from registered clinicians: 1 from an individual oncologist from Canadian Dermatology Association (CDA) and 1 group input on behalf of 5 oncologists from Ontario Health- CCO
- input from CADTH's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- Three patient advocacy group: MNC, SYDF, and Canadian Skin Patient Alliance (CSPA)*
- one clinician group: Ontario Health-CCO
- CADTH's PAG
- the sponsor: Sun Pharma Canada Inc.

* Note: CSPA was not part of the joint patient advocacy group input submitted for this submission.

The pERC Initial Recommendation was to not recommend reimbursement of sonidegib (Odomzo) for the treatment of adult patients with histologically confirmed laBCC that is not amenable to radiation therapy or curative surgery.

Feedback on the pERC Initial Recommendation indicated that PAG agreed with pERC's Initial Recommendation to not reimburse sonidegib and supported early conversion to a Final Recommendation, and registered clinician group, patient advocacy groups, and the sponsor disagreed with the pERC Initial Recommendation and did not support early conversion. The sponsor, registered clinician group, and patient advocacy groups all commented on the comparable efficacy and safety of sonidegib and vismodegib and stated that there remains an unmet need for additional effective treatment options for patients who are intolerant to vismodegib.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of sonidegib for the treatment of adult patients with histologically confirmed laBCC that is not amenable to radiation therapy or curative surgery.

Studies included: One phase II trial that randomized patients to two doses of sonidegib

The pCODR systematic review included 1 trial, the BOLT trial, an international, phase II trial that evaluated the efficacy and safety of 2 doses of sonidegib in adult patients with histologically confirmed laBCC not amenable to radiotherapy or curative surgery, or mBCC for which all existing available treatment options had been exhausted. Only a description of the study and results as relevant to the indication (i.e., the laBCC subgroup) under review are discussed.

Eligible patients were randomized in a 1:2 ratio to receive either a 200 mg once-daily dose of sonidegib or a 800 mg once-daily dose of sonidegib. The 200 mg dose was investigated in the trial as it represented the lowest dose level tested that had demonstrated evidence of antitumour activity, and the 800 mg dose was investigated as it represented the highest well-tolerated biologically active dose of sonidegib. It was hypothesized that an 800 mg dose would be more efficacious than 200 mg; therefore, the 1:2 ratio was planned to ensure that more patients would be randomized to the 800 mg dose. However, the 200 mg dose was shown to have better tolerability and similar efficacy to the 800 mg dose in the BOLT trial, thus the study results relevant to the laBCC 200 mg dose subgroup are discussed.

Patient populations: Adult patients with laBCC not amenable to radiotherapy or curative surgery

Key eligibility criteria in the BOLT trial included age 18 years or older, histologically confirmed laBCC not amenable to radiotherapy or curative surgery, a ECOG PS grade of less than or equal to 2, and adequate bone marrow, liver, and renal function. Key exclusion criteria included previous treatment with systemic sonidegib or other Hh pathway inhibitors; current treatment with medications known to be moderate or strong inhibitors or inducers of cytochrome P450 (CYP) 3A4/5 or drugs metabolized by CYP2B6 or CYP2C9 that have a narrow therapeutic index and could not be discontinued before starting treatment with sonidegib; neuromuscular disorders or concurrent treatment with drugs that could cause muscle damage; and patients who are planning on starting a new strenuous exercise regimen after initiation of study treatment.

A total of 230 patients were enrolled in the BOLT trial, of which 194 patients had laBCC. Out of the 194 laBCC patients, 66 were enrolled in the 200 mg group. In the laBCC 200 mg dose subgroup, the median age was 67.0 years (range = 25.0 to 92.0 years) with 57.6% of patients aged 65 years or older. Most patients were White (89.4%) and had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 (66.7%). A total of 74.2% of patients had received any type of prior antineoplastic therapy, with 72.7% having received prior surgery and 7.6% having received prior radiotherapy in the laBCC 200 mg subgroup. A total of 39.4% had infiltrative BCC, 36.4% had nodular BCC, and 13.6% had superficial BCC; 50% had aggressive (high-risk) histology and/or cytology in the 200 mg laBCC subgroup.

Key efficacy results: Clinically meaningful and durable response rates and prolongation of PFS; OS uncertain

The primary outcome in the BOLT trial was ORR assessed by an independent review committee (IRC), which was defined as the proportion of patients with a confirmed best overall response of complete response (CR) or partial response (PR). Treatment was considered to be efficacious if the observed ORR in any treatment arm was greater than or equal to 30% and clinically meaningful if the lower bound of the 95% confidence intervals (CIs) exceeded 20%. At the time of the primary data cut-off, 42.9% (95% CI, 27.7 to 59.0) of laBCC patients in the 200 mg sonidegib group had achieved an objective response, which exceeded the clinically meaningful threshold as defined per protocol. In the 200 mg laBCC sonidegib group, a total of 18 patients achieved a CR or PR, which included 2 (4.8%) patients who achieved a CR and 16 (38.1%) patients who achieved a PR.

Secondary outcomes included OS and IRC-assessed duration of response and PFS. As of the 42-month data cut-off, the median duration of response was 12.9 (95% CI not estimable) months, the median PFS was 19.0 months (95% CI not estimable), and the OS was not estimable in the 200 mg laBCC subgroup.

Patient-reported outcomes: Uncertain HRQoL benefit in the absence of a comparator

HRQoL was evaluated using the EORTC QLQ-C30, EORTC QLQ-H&N35, and the Short Form (36) Health Survey (SF-36). Compliance rates for the overall trial population were more than 90% at baseline but dropped to less than 50% by 7.6 months. In laBCC patients treated with 200 mg of sonidegib, there were noted improvements in EORTC QLQ-C30 scales of physical functioning, social functioning, pain, and fatigue; and for the EORTC QLQ-H&N35 scales, improvements in trouble with social contact, head and neck pain, and weight loss. However, the sponsor did not provide a definition of what constituted an improvement; thus, it is unclear if improvements met clinically meaningful thresholds as defined in the literature. For patients treated with 200 mg of sonidegib (both laBCC and BCC patients), deterioration was seen for fatigue and weight loss, with median times to deterioration being 13.7 months (95% CI, 9.3 to not estimable) and 16.6 months (95% CI, 13.9 to not estimable), respectively, based on EORTC QLQ-C30 scales. Based on SF-36 data, median time to deteriorations in the 200 mg sonidegib group (both laBCC and mBCC patients) were reported to be 7.6 months for bodily pain, 8.5 months for physical component, 11.3 months for role physical, and not estimable for all other components.

Limitations: Decision-making based on a subgroup analysis of the full trial population and small sample size; statistical concerns regarding the risk of type I error and biased censoring rules; lack of comparator

The indication under review (i.e., laBCC patients treated with 200 mg dose) is a subgroup of the full trial, thus both the dose and disease type were not the main consideration in the overall trial sample size calculation. The sample size is further limited as the 800 mg was hypothesized to be the more efficacious dose without compromising safety during the design of the study, and randomization was planned in a 2:1 ratio for the 800 mg to 200 mg groups, respectively. While the results of the laBCC 200 mg subgroup are consistent with the overall trial population, the efficacy results meeting the threshold may be a spurious result due to these reasons.

Furthermore, the subgroup analyses (including those for the laBCC 200 mg subgroup) and secondary efficacy outcomes were not adjusted to account for multiple testing to control the risk of type I error, thus many outcomes of clinical interest should be interpreted as exploratory. In addition, OS estimates were highly uncertain as 43.3% of patients were censored due to loss to follow-up, and OS could have been confounded by subsequent therapies.

Finally, the BOLT trial did not include a comparator, and comparative effectiveness of sonidegib and vismodegib was assessed through ITCs. However, this indirect treatment comparison had a number of limitations and no conclusions can be firmly drawn from the evidence.

Safety: Manageable toxicities that are consistent with other Hh inhibitors

The safety analyses were performed on all patients who received at least 1 dose of study medication and had at least 1 post-baseline safety assessment. As of the primary analysis, median treatment exposure time was 8.9 (range = 1.3 to 21.4) months in the 200 mg sonidegib group and 7.4 (range = 0.3 to 19.1) months in the 800 mg sonidegib group. As of the 42-month analysis, median treatment exposure time was 11.0 (range = 1.3 to 53.2) months in the 200 mg sonidegib group and 6.6 (range = 0.3 to 53.9) months in the 800 mg sonidegib group. All patients treated with the 200 mg dose (n = 79) were included in the safety analysis.

At the primary analysis, 94.9% of patients in the 200 mg group had experienced at least one AE, with 30.4% of patients experiencing grade 3 or grade 4 AEs. Additionally, 13.9% of patients experienced an SAE. There was a slight increase in the incidence of events of the safety outcomes at subsequent data analysis time points, with a notable increase of grade 3 AEs to grade 4 AEs at the 12-month data cut-off to 38.0% of patients. The most common AEs of any grade, irrespective of causality, that occurred in the 200 mg group as of the primary data cut-off and the 42-month data cut-off, respectively, were muscle spasms (49.4% and 54.4%), alopecia (43.0% and 49.4%), dysgeusia (38.0% and 44.3%), and nausea (32.9% and 39.2%). The most common grade 3 or grade 4 AEs that occurred in the 200 mg group at the primary data cut-off and the 42-month data cut-off, respectively, were blood creatine phosphokinase increase (6.3% and 6.3%), lipase increase (5.1% and 6.3%), asthenia (2.5% and 3.8%), muscle spasms (2.5% and 2.5%), hypertension (2.5% and 2.5%, and weight decrease (1.3% and 5.1%). SAEs included pneumonia, angina pectoris, bipolar disorder, blood CK increase, and rhabdomyolysis. As of the primary data analysis, 21.5% of patients in the 200 mg group and 36.0% of those in the 800 mg group had discontinued treatment due to an AE. As of the 42-month data cut-off, 30.4% of patients in the 200 mg group and 40.0% of those in the 800 mg group had discontinued due to AEs. In the 200 mg group, AEs that led to discontinuation at the primary data cut-off included muscle spasms, dysgeusia, weight loss, and nausea. Four on-treatment deaths occurred, all within the 800 mg sonidegib group, with 2 deaths in the laBCC subgroup, which were attributed to pre-existing conditions at baseline.

Comparator information: Comparative effectiveness of sonidegib to vismodegib uncertain

In the absence of a direct head-to-head comparison of sonidegib with vismodegib, the sponsor submitted 1 published and publicly available unanchored MAIC, and 1 published and publicly available meta-analysis (MA) that included vismodegib and other comparators. Two trials were included in the MAIC: the BOLT trial, which provided individual patient data for sonidegib, and the ERIVANCE trial, which provided aggregate data for treatment with vismodegib. No statistical comparisons between the treatments were provided and minimal adjustment for potential effect modifiers and prognostic factors was provided. Further, no assessment of residual confounding was performed. As such, no conclusions can be made regarding the comparative efficacy of sonidegib and vismodegib based on the submitted unanchored MAIC.

A published MA was identified that aimed to determine and compare the efficacy and safety of sonic Hh inhibitors as a class for treating BCC. The publication included 4 treatments: sonidegib, vismodegib, itraconazole, and TAK-441. Only sonidegib and vismodegib are approved in Canada for the treatment of patients with laBCC. Numerous critical limitations to the analyses were identified, which limited the generalizability of the results in the Canadian context. Therefore, the results of the MA should be interpreted with caution.

pERC agreed that the comparative effectiveness was uncertain, and limited conclusions could be drawn from the submitted ITC.

Need and burden of illness: Unmet need to have therapeutic choices with comparable efficacy to existing options that offer improved tolerability and reduced toxicities, and are accessible at a lower cost

pERC noted that laBCC is relatively uncommon, accounting for up to 10% of all BCCs, and that the outcomes of patients with advanced BCC are not as favourable. LaBCC may not be amenable to surgery. While surgery is preferred and may provide improved disease control rates, in some cases of laBCC, surgery may not be an acceptable treatment option as the required procedure may lead to significant deformity or disfigurement or cause detrimental impact on quality of life. Although radiotherapy remains an option for advanced BCC patients not amenable to surgery, its ability to achieve disease control is limited, and it can cause irreversible damage to involved or surrounding organs such as the eyes and nerves. Additionally, radiotherapy cannot be provided to anatomical sites which had previously received maximal radiation doses. Chemotherapy may be used when surgery and/or radiation are contraindicated; however, no standard chemotherapy regimen exists and there is not sufficient evidence supporting its use. Although cisplatin alone, or in combination with other agents such as paclitaxel, 5-fluorouracil, and doxorubicin, have been used, the tumour responses are variable and long-term survival and improvement in quality of life have not been documented. In Canada, vismodegib is the only currently approved systemic treatment option for patients with laBCC who are not amendable to curative surgery or radiation therapy. Vismodegib is funded across most jurisdictions.

Locally advanced BCC commonly develops in the elderly population increasing the potential for treatment toxicity due to the presence of significant comorbid illnesses, and it can lead to significant morbidity in patients. Therefore, there exists an unmet need to have therapeutic choices that have comparable efficacy to existing options, to offer improved tolerability and reduced toxicities, and to be accessible at a lower cost.

Registered clinician input: Clinicians endorse the reimbursement of sonidegib for laBCC

A total of two registered clinician inputs were provided for the review of sonidegib for treatment of adult patients with laBCC that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy: one from an individual oncologist from the CDA and one group input on behalf of five oncologists from CCO. Although both groups of clinicians agreed with inclusion and exclusion criteria of the BOLT trial, the clinician from CDA noted that the trial did not include patients who had been previously treated with, were intolerant to, or progressed with vismodegib. The clinician stated that sonidegib should be made available to patients with laBCC and mBCC patients. The clinician from CDA also noted that sonidegib would be a desirable option for elderly patients and patients who are physically active. Both groups of clinicians noted that currently there is no evidence to inform sequencing; however, the clinicians from CCO stated that there may be evidence to inform the use of sunitinib after failure on sonidegib. Both groups of clinicians stated that currently there is no evidence supporting the use of sonidegib for prevention of recurrence after surgery or radiation therapy. All clinicians responded that it is reasonable for patients to take a drug holiday with sonidegib and resume treatment upon progression.

PATIENT-BASED VALUES

Values of patients with locally advanced and mBCC: Disease control to improve quality of life and lessen the burden of care for caregivers

One joint input from 2 patient advocacy groups, MNC and SYSF, was provided. The input indicated that, from the patients' perspective, living with BCC was significantly challenging caused by debilitating physical and emotional symptoms. The most challenging symptoms of the disease reported by patients were scarring and disfigurement, fear and anxiety, and a negative impact on self-image as well as family and social life. Due to the burdensome nature of the disease, caregivers also reported a lot of physical and emotional stress from their caregiving duties.

Patient values on treatment: Treatments that are less invasive, more tolerable, and can effectively stop disease progression

The patient groups providing input stated that current treatments for BCC, including surgery, topical creams, cryotherapy, and radiation, can result in significantly impairing side effects and significant emotional and physical scarring leading to social isolation, depression, and a negative impact on quality of

life. The patient group input also indicated that treatments can affect patients' ability to eat, swallow, breathe, speak, and sleep. Patients and caregivers were also concerned that successive surgeries and radiation are associated with long wait times and excess travel, which can be time intensive and financially draining. Three patients who had experience with sonidegib reported a positive experience with the drug. One patient did not experience any side effects, while 1 patient experienced alopecia and another experienced mild dysgeusia. The patients reported that the benefits of the treatment outweighed the side effects and that they were pleased with having the option of an oral treatment. BCC patients and caregivers of patients with BCC value treatments that are less invasive and can effectively stop the progression of the disease, and treatments that are more tolerable and cause less pain, scarring, and disfigurement to ultimately improve quality of life.

ECONOMIC EVALUATION

Sonidegib is available as a 200 mg capsule at a submitted price of $267.35 per capsule. The recommended 200 mg daily dose results in a per patient 28-day cost of $7,486 and an annual cost of $97,649.
The sponsor submitted a cost-utility analysis that modelled adult patients with histologically confirmed laBCC that is not amenable to radiation therapy or curative surgery, which aligns with the Health Canada-indicated population. The analysis compared treatment with sonidegib to vismodegib. The sponsor's partitioned survival model consisted of 4 health states: stable disease on treatment, stable disease off treatment, progressed disease (off treatment), and dead. Transitions between the stable disease states and the progressed disease states were treatment dependent, whereas transitions to stable disease (off treatment) state and dead state were assumed to be the same for all patients. Baseline characteristics for all patients in the model were informed by the BOLT trial, and this study was also used to inform the efficacy (i.e., PFS and time to discontinuation) and safety of sonidegib. The efficacy (i.e., PFS and time to discontinuation) and safety of patients receiving vismodegib was derived from the ERIVANCE trial.

CADTH identified the following key limitations with the sponsor's submitted economic analysis:

- The sponsor used a naive comparison to estimate the comparative efficacy of sonidegib compared to vismodegib due to limitations they identified with their indirect comparison (ITC). CADTH clinical reviewers deemed the sponsor's ITC evidence to be inconclusive and therefore could not be used to inform the economic evaluation.
- The sponsor assumed that sonidegib would be associated with cost savings due to averted wound care over the entire 10-year time horizon, which was considered a substantial overestimation based on feedback from clinical experts consulted by CADTH, who noted typical wound care may last a year at most.
- The sponsor assumed a difference between sonidegib and vismodegib in relative dose intensity. The assumed difference is uncertain as it was based on a naive comparison of trial data. According to the clinical experts consulted by CADTH, relative dose intensity is not expected to be different between sonidegib and vismodegib.
- Feedback from clinical experts consulted by CADTH identified limitations with mortality assumptions informing the model.

Due to the lack of robust clinical evidence on the comparative clinical effectiveness of sonidegib compared with vismodegib, CADTH could not determine an estimate of the cost-effectiveness, and thus the cost-effectiveness of sonidegib is unknown.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact

Not applicable.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member
Dr. Jennifer Bell, Bioethicist
Dr. Kelvin Chan, Oncologist
Dr. Michael Crump, Oncologist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Cameron Lane, Patient Member
Dr. Christopher Longo, Health Economist
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Dr. Maureen Trudeau who did not vote due to her role as Committee chair.

All members participated in deliberations and voting on the Final Recommendation, except:

- Dr. Maureen Trudeau, who did not vote due to her role as pERC Chair.

Avoidance of conflicts of interest

All members of the CADTH pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the CADTH website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of sonidegib for the treatment of adult patients with histologically confirmed laBCC that is not amenable to radiation therapy or curative surgery, through their declarations, no members had a real, potential, or perceived conflict based on application of the CADTH *pCODR Conflict of Interest Guidelines*.

Information sources used

pERC is provided with a pCODR Clinical Guidance Report and a pCODR Economic Guidance Report, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the CADTH website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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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.