pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The 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-funding decisions. The pCODR process brings consistency and clarity to the cancer drug assessment process 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: Vismodegib (Erivedge) **Submitted Funding Request:** For the treatment of adult patients with histologically confirmed metastatic basal cell carcinoma or with locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy	
Submitted By: Hoffmann-La Roche Limited	**Manufactured By:** Hoffmann-La Roche Limited
NOC Date: July 12, 2013	**Submission Date:** June 14, 2013
Initial Recommendation: October 31, 2013	**Final Recommendation:** January 10, 2014

pERC RECOMMENDATION

The pCODR Expert Review Committee (pERC) recommends funding vismodegib in patients with metastatic basal cell carcinoma (BCC) or with locally advanced BCC (including patients with basal cell nevus syndrome, i.e. Gorlin syndrome, who are 18 years of age or older) who are inappropriate for surgery or radiotherapy conditional on the cost-effectiveness being improved to an acceptable level. Funding should be for patients with ECOG performance status ≤ 2 who have measurable metastatic disease or locally advanced disease, which is considered inoperable or inappropriate for surgery and inappropriate for radiotherapy. The Committee made this recommendation because it was satisfied that there may be a net clinical benefit of vismodegib based on meaningful objective response rates. pERC also considered that this is a population with few effective therapeutic options and vismodegib aligns with patient values. However, pERC acknowledged that because of the non-randomized, non-comparative phase two study design, there was considerable uncertainty around the magnitude of the clinical benefit and the cost-effectiveness of vismodegib. This led to a wide range of incremental cost-effectiveness estimates, all of which pERC considered unacceptable. Therefore, vismodegib could not be considered cost-effective at the submitted price.

pERC noted that there were insufficient data available to make a recommendation on the use of vismodegib in a broader population less than 18 years old.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Pricing Arrangements to Improve Cost-Effectiveness
Given that pERC was satisfied that there may be a net clinical benefit of vismodegib in patients with metastatic or locally advanced BCC who are inappropriate for surgery or radiotherapy, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of vismodegib to an acceptable level. Because of the considerable uncertainty in the magnitude of the clinical effect estimates, pERC determined that a substantial reduction in drug price would likely be required to offset this and improve cost-effectiveness.

Collecting Evidence to Reduce Uncertainty in Cost-Effectiveness
Given the considerable uncertainty in the magnitude of clinical benefit of vismodegib in patients with metastatic or locally advanced BCC who are inappropriate for surgery or radiotherapy, pERC concluded that any additional prospective evidence that could be collected to decrease the uncertainty in the incremental effect would be of benefit in understanding the true cost-effectiveness of vismodegib. Information on efficacy, quality of life and strategies for long-term control in patients who may receive vismodegib long-term would be of particular value.

Avoiding Use of Vismodegib in a Broader Patient Population
pERC noted that drug price was a key driver of the incremental cost-effectiveness estimates and there is a potential for vismodegib to be used outside of the recommended population. Because the prevalence of BCC is high, indication creep could have a large budget impact. Therefore, to prevent indication creep, provinces may want to consider additional measures to encourage high quality prescribing of vismodegib to the recommended population of those evaluated in the ERIVANCE study. pERC determined that, as one measure to limit budget impact and achieve high quality prescribing, decisions on the use of vismodegib should be made by a multi-disciplinary team that would include one or more dermatologists, surgeons, radiation oncologists and medical oncologists.

Additional Resources Required Due to Controlled Distribution
pERC noted that currently vismodegib can only be obtained through a controlled distribution program that may require additional pharmacy and human resources to manage the controlled distribution.

SUMMARY OF pERC DELIBERATIONS

pERC noted that there is currently no standard treatment for patients with metastatic and locally advanced basal cell carcinoma who are inappropriate for surgery or radiotherapy. Although chemotherapy with drugs such as cisplatin is sometimes used, there is limited evidence that these treatments improve patient outcomes. Many patients do not receive any other treatments when surgery and radiotherapy are not options. pERC also discussed that basal cell carcinoma is very common but that the number of patients who are inappropriate for surgery and radiotherapy is likely very small, which may have impacted the feasibility of conducting a randomized controlled trial. However, pERC further discussed that because there have been no effective treatment options for these patients to date, they may not be seeking treatment within the healthcare system and their true numbers are unknown. With the availability of vismodegib, there may be more patients with BCC seeking treatment and, therefore, a larger patient population to treat. pERC discussed the burden of metastatic and locally advanced BCC and considered that morbidity is a substantial concern. In extreme cases, patients may experience severe disfigurement and surgery could result in the loss of essential structures or organs such as eyes or ears. For patients, such disfigurement may lead to loss of function, extreme social isolation and decreased quality of life.

pERC's Deliberative Framework for drug funding recommendations focuses on four main criteria:	
CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

One non-randomized, non-comparative study was included in the pCODR systematic review, the ERIVANCE study (Sekulic 2012), which evaluated vismodegib in patients who were inappropriate for surgery or radiotherapy. pERC deliberated upon the results of the ERIVANCE study and determined that there may be a net clinical benefit of treatment with vismodegib. pERC noted that a substantial proportion of patients (43% metastatic and 30% locally advanced) experienced a response as assessed by an independent review committee. pERC noted that historical treatment response rates in this population were not available for comparative purposes. However, pERC discussed that the minimum expected response rates of 10% (metastatic) and 20% (locally advanced), which were established at the outset of the ERIVANCE study, were exceeded by a wide margin. pERC considered this to be a meaningful outcome for a condition in which there were previously few treatment options. pERC discussed the limitations of relying on non-randomized, non-comparative evidence and concluded that there is considerable uncertainty surrounding the exact magnitude of the clinical benefit of vismodegib. pERC further discussed the challenges of assessing the efficacy of vismodegib in the absence of comparative data and noted that a study involving retrospective or historical controls could have helped inform pERC's deliberations. Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback from pCODR's Provincial Advisory Group on the uncertainty of the clinical benefit associated with vismodegib. pERC acknowledged the uncertainty in the magnitude of the benefit. Despite this, pERC was confident that there may be a net clinical benefit associated with vismodegib. pERC also noted that in exceptional circumstances, non-randomized, non-comparative evidence is acceptable to support funding recommendations. pERC confirmed that due to the small patient population, a randomized controlled trial may not have been feasible and that equipoise no longer exists for vismodegib in this population. Therefore, a randomized controlled trial is unlikely to be undertaken in the future.

pERC also noted that 22% of patients in the ERVIANCE study had basal cell nevus syndrome (Gorlin syndrome) or suspected Gorlin syndrome and achieved a response rate of 67% . It was noted that BCC in patients with Gorlin syndrome is a result of a genetic mutation and is a lifelong condition that would require long-term treatment. pERC noted that the patients with Gorlin syndrome in the ERIVANCE study all had locally advanced BCC and met all of the other trial inclusion criteria such as being 18 years or older and having lesions ineligible for surgery. Therefore, pERC considered that it would be reasonable to use vismodegib in Gorlin syndrome patients, but only if patients met these other trial inclusion criteria.

pERC reviewed the safety evidence for vismodegib from the ERIVANCE study. The most common adverse events observed were muscle spasms and alopecia. pERC also noted that vismodegib is a teratogen and that there are prescribing restrictions in place to limit exposure to the risks associated with vismodegib.

Given these restrictions and the high clinical need for treatments in this select population, pERC generally considered that the toxicity of vismodegib was acceptable for the narrow population of patients who are clearly ineligible or inappropriate for surgery as defined in the ERIVANCE study. There were 12% of patients who discontinued vismodegib due to an adverse event. Furthermore, pERC noted that because there is only one tablet size available for vismodegib, dose reductions were not an option for these patients and there is uncertainty in the appropriateness of alternative dosing schedules. Considering all of these factors, pERC discussed the need for strategies to monitor disease control and to acquire more experience with vismodegib with regard to the side effects of long-term use.

pERC reviewed patient advocacy group input and concluded that vismodegib aligns with patient values. pERC noted that patients with BCC who are inappropriate for surgery or radiotherapy experience serious deformity and social isolation, which has a debilitating impact on their quality of life. pERC noted that meaningful quality of life data were not available from the ERIVANCE study. However, pERC considered the objective response rates from the clinical trial were a measure of tumor regression and that patients who experienced such a response have less disfigurement and, therefore, would likely have an improved quality of life. pERC also noted that patient advocacy group input indicated patients with the extent of disease of those in the trial have often tried multiple other therapies but none are effective and patients are seeking effective treatment options. pERC also considered that vismodegib demonstrated a meaningful and durable response, which aligns with patient values of accessing effective treatment options. pERC noted that patients are prepared to accept the risks and side effects of new treatments if the treatment is effective. Therefore, although there are serious risks associated with a teratogen such as vismodegib, pERC considered that patients appeared willing to accept this risk if vismodegib is effective.

pERC deliberated upon the cost-effectiveness of vismodegib compared with best supportive care. It was noted that due to the limitations of relying on non-randomized, non-comparative evidence from the ERIVANCE study, there was substantial uncertainty in the magnitude of clinical benefit associated with vismodegib. This made it challenging to estimate the incremental effect of treatment with vismodegib and the resulting incremental cost-effectiveness estimates for vismodegib reflect this uncertainty. pERC further discussed that the utility estimates were a key driver and further uncertainty was created because meaningful quality of life data were not available from the ERIVANCE study and there was a wide range of utility estimates in the literature that could be used. This considerable uncertainty led to a wide range of incremental cost-effectiveness estimates, all of which pERC considered unacceptable. Therefore, vismodegib could not be considered cost-effective at the submitted price. pERC further noted that any prospective evidence regarding clinical efficacy and quality of life that could be collected to decrease the uncertainty in the incremental effect and provide better utility estimates would be of benefit to inform the true cost-effectiveness of vismodegib. Upon reconsideration of the pERC initial recommendation, pERC discussed feedback received from the manufacturer regarding the uncertainty in their submitted incremental cost-effectiveness estimates. pERC noted that the uncertainty in an economic analysis like vismodegib's that is based on non-randomized, non-comparative evidence is large and is inherently different from the type of uncertainty observed in economic analyses based on a randomized controlled trial. Therefore, pERC confirmed that additional prospective clinical data would be required to decrease the uncertainty in the cost-effectiveness of vismodegib. In addition, because of the considerable uncertainty in the magnitude of the clinical effect estimates, pERC concluded that a substantial reduction in drug price would likely be required to offset this and improve cost-effectiveness.

pERC discussed the feasibility of adoption and noted that the budget impact of vismodegib is uncertain and has the potential to be large. Although the number of patients with metastatic or locally advanced BCC who are ineligible for surgery and radiotherapy may currently be small, the number of patients who may seek treatment once vismodegib is accessible may increase. It was also noted that vismodegib will be an additional treatment and will not be replacing another treatment in this setting. In addition, because vismodegib is a teratogen and is only available through a controlled distribution programme, additional pharmacy resources will be required. Also, it was noted that vismodegib is an oral treatment and may be more easily accessible than surgery or radiotherapy for some patients, which could also contribute to indication creep. Considering these factors, pERC noted that the budget impact of vismodegib could be large and provinces may want to consider additional measures to limit budget impact and encourage high quality prescribing of vismodegib to the recommended population (as defined by inclusion criteria in the ERIVANCE study). pERC also determined that, as one measure to control prescribing, decisions on the use of vismodegib should be made by a multi-disciplinary team that would include one or more dermatologists, surgeons, radiation oncologists and medical oncologists. pERC noted that in the ERIVANCE study patients with metastatic BCC had measurable disease according to RECIST

criteria. Patients with locally advanced BCC had ~~or~~ at least one lesion 10 mm or more that was considered either inoperable or inappropriate for surgery as confirmed by a specialist in Mohs dermatologic, head and neck or plastic surgery. Acceptable reasons for surgery or radiotherapy to be considered inappropriate included an inoperable tumour, previous radiotherapy, radiotherapy inappropriate or contraindicated; surgery inappropriate due to recurrence after 2 or more surgeries and curative resection unlikely; or surgery inappropriate due to substantial morbidity or expected deformity. pERC considered that it would be important to limit the use of vismodegib to these patients in order to prevent use of vismodegib in those patients who are appropriate or eligible for surgery or radiotherapy. However, pERC also discussed that lesion size is not the best criterion to use when deciding to prescribe vismodegib, rather it is the extent of surgery and potential for disfigurement that is most important.

Upon reconsideration of the pERC initial recommendation, pERC discussed feedback received from pCODR's Provincial Advisory Group regarding the need for testing for the Hedgehog status in this patient population. pERC noted that testing will not be necessary as at least 90% of patients are positive for this acquired aberrant activation pathway. pERC also noted that vismodegib can only be obtained currently through a controlled distribution program that may require additional pharmacy and human resources to manage the controlled distribution.

EVIDENCE IN BRIEF

pERC deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report providing clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis
- guidance from pCODR clinical and economic review panels
- input from two patient advocacy groups (Melanoma Network of Canada and Save Your Skin Foundation)
- input from pCODR's Provincial Advisory Group.

Feedback on the pERC Initial Recommendation was also provided by:

- pCODR's Provincial Advisory Group.
- one patient advocacy group (Save Your Skin Foundation)
- the Submitter (Hoffmann-La Roche Limited)

The pERC initial recommendation was to recommend funding vismodegib in patients with metastatic basal cell carcinoma (BCC) or with locally advanced BCC (including patients with Gorlin syndrome 18 years of age or older) who are inappropriate for surgery or radiotherapy conditional on the cost-effectiveness being improved to an acceptable level. Feedback on the pERC Initial Recommendation indicated that the manufacturer and patient advocacy group agreed with the pERC Initial Recommendation while pCODR's Provincial Advisory Group disagreed with the initial recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The pCODR review evaluated the safety and efficacy of vismodegib on patient outcomes compared to standard therapies or best supportive care in patients with metastatic or locally advanced basal cell carcinoma (BCC) who were inappropriate for surgery or radiotherapy.

Studies included: one single-arm study

The pCODR systematic review included one non-randomized, non-comparative Phase 2 trial, the ERIVANCE study (Sekulic 2012), which assessed the safety and efficacy of vismodegib (150mg orally once daily) in patients with metastatic BCC or locally advanced BCC who were inappropriate for surgery or radiotherapy (N=99).

No randomized controlled trials were identified that met the eligibility criteria of this systematic review. pERC discussed the feasibility of conducting a randomized controlled trial in this population and noted

that currently there is no standard of care for patients with locally advanced BCC and metastatic BCC in whom surgery or radiotherapy is not an option. Therefore, there is no appropriate comparator. In addition, pERC noted that, although BCC is very common, the number of patients currently known to be inappropriate for surgery or radiotherapy is small, which may have impacted the feasibility of conducting a randomized controlled trial in this population. However, pERC noted that a study providing comparative data by including retrospective or historical controls could have helped inform pERC's deliberations.

The pCODR review also provided contextual information on an ongoing non-randomized non-comparative safety study, STEVIE, which has only been reported in conference abstracts (Hansson 2012, Grob 2013).

Patient populations: inappropriate for surgery or radiotherapy

pERC discussed the patient population included in the ERIVANCE study. It was noted that there were 33 patients with metastatic BCC and 63 patients with locally advanced BCC who were inappropriate for surgery or radiotherapy.

Patients with metastatic BCC had measurable disease (including nodal metastases) according to RECIST criteria. Patients with locally advanced BCC had at least one lesion of at least 10 mm that was considered inoperable or for which surgery was considered inappropriate as confirmed by a specialist in Mohs dermatologic, head and neck or plastic surgery. Acceptable reasons for surgery or radiotherapy to be considered inappropriate included an inoperable tumour, previous radiotherapy, radiotherapy inappropriate or contraindicated; surgery inappropriate due to recurrence after 2 or more surgeries and curative resection unlikely; or surgery inappropriate due to substantial morbidity or deformity expected. pERC discussed that it would be very important to limit the use of vismodegib to patients defined to be inappropriate for surgery or radiotherapy as outlined in the ERIVANCE study because there is considerable potential for indication creep if patients who are appropriate for surgery prefer an oral therapy over surgery or want to delay surgery.

There were also 21 patients (22%) in ERIVANCE with Gorlin syndrome or suspected Gorlin syndrome, all of whom had locally advanced BCC. pERC noted that BCC in patients with Gorlin syndrome is a result of a genetic mutation and is a lifelong condition that would require long-term treatment. pERC discussed that the patients with Gorlin syndrome in the ERIVANCE study all had locally advanced BCC and met all of the other trial inclusion criteria such as being 18 years or older and having lesions ineligible for surgery. pERC considered that the use of vismodegib in a broader population less than 18 years of age would not be appropriate. It was noted that this would be most relevant for patients with Gorlin syndrome, which is a lifelong condition, because other types of BCC predominantly affect an older population.
All patients included in the study had an ECOG performance status of 2 or less.

Key efficacy results: meaningful and durable tumour response

Key efficacy outcomes deliberated upon by pERC included overall survival, progression-free survival, response rate and duration of response. Objective response rate, when assessed by independent review committee, was the primary outcome of the ERIVANCE study.

pERC noted that morbidity is a substantial concern for these patients. Therefore, measures of disease control such as response rate are very important. In patients with locally advanced BCC, although death is rare, morbidity is common. In the ERIVANCE study, tumours were assessed using physical examination documented by photography. For each individual patient, a response was defined as a ≥30% reduction in the externally visible or radiographic dimension. pERC noted that a substantial proportion of patients experienced a response as assessed by an independent review committee. There were 43% of metastatic patients (95%CI: 16 to 48%) and 30% of locally advanced patients (95%CI: 30 to 56%) who had a response. pERC noted the historical treatment response rates in this population were not available. Therefore, it was difficult to place these responses in context. However, pERC noted that in the overall study population, the minimum expected response rates of 10% (metastatic) and 20% (locally advanced), which were pre-defined at the outset of the ERIVANCE study, were exceeded by a wide margin. pERC discussed that obtaining a substantial response would likely lead to less morbidity for patients. Therefore, pERC agreed with the pCODR Clinical Guidance Panel that this was a meaningful outcome for a condition in which there were previously no effective treatment options available. However, pERC decided that there is considerable uncertainty surrounding the exact magnitude of the clinical benefit of vismodegib because of the limitations of relying on non-randomized, non-comparative evidence. pERC also noted that none of the patients with metastatic BCC had a complete response, while 21% of patients with locally advanced

BCC had a complete response. The duration of response was 7.6 months in both the metastatic BCC and locally advanced BCC populations, when assessed by independent review. pERC considered this evidence of a durable response.

Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback from pCODR's Provincial Advisory Group on the uncertainty of clinical benefit associated with vismodegib. pERC acknowledged the uncertainty in the magnitude of the benefit Despite this, pERC was confident that there may be a net clinical benefit associated with vismodegib. pERC also noted that in exceptional circumstances, non-randomized, non-comparative evidence is acceptable. pERC confirmed that due to the small patient population, a randomized controlled trial may not have been feasible and that equipoise no longer exists for vismodegib in this population. Therefore, a randomized controlled trial is unlikely to be undertaken in the future.

pERC also discussed that 22% of patients in the ERVIANCE study had Gorlin syndrome or suspected Gorlin syndrome. In a post-hoc subgroup analysis, these patients achieved a response rate of 67% (95%CI: 45% to 85%) compared to 30% (95% CI: 19% to 46%) in the remaining patients with locally advanced BCC. It was noted that BCC in patients with Gorlin syndrome is a result of a genetic mutation and is a lifelong condition that would require long-term treatment. pERC discussed that the patients with Gorlin syndrome in the ERIVANCE study, all had locally advanced BCC and met all of the other trial inclusion criteria such as being 18 years or older and having lesions ineligible for surgery. Therefore, pERC considered that it would be reasonable to use vismodegib in Gorlin syndrome patients but only if patients met these other trial inclusion criteria. There were insufficient data available to make a recommendation on the use of vismodegib in a broader population with Gorlin syndrome, such as those less than 18 years or who may have been eligible for surgery.

pERC noted that the proportion of patients surviving at one year in the ERIVANCE study was high (78% metastatic, 93% locally advanced). Median progression-free survival as assessed by independent review was 9.5 months in both metastatic patients and locally advanced patients. pERC discussed that progression of BCC is slow, therefore, without a control group, it is uncertain how overall survival and progression-free survival may have compared with patients who received no treatment during the same period of time.

Quality of life: no meaningful quality of life data available but tumour response suggests improvement

pERC acknowledged that morbidity is a substantial concern for patients with BCC, especially those with locally advanced disease. Therefore, quality of life and functional outcomes are very important in this population. Patients with BCC who are inappropriate for surgery may experience severe disfigurement, leading to extreme social isolation and decreased quality of life. However, pERC noted that meaningful quality of life data were not available from the ERIVANCE study due to the type of instrument and the quality of the data collected. While SF-36 was measured in the ERIVANCE study, more specific quality of life instruments are available both for cancer and dermatology, and would have been more appropriate. However, pERC considered that response rates documented in the ERIVANCE study would likely result in patients experiencing less morbidity and having improved quality of life as a result of the tumour regression.

Safety: high withdrawals and restrictions due to teratogenicity

pERC reviewed the safety evidence for vismodegib from the ERIVANCE study. Serious adverse events were experienced by 25% of patients, and there was no clear pattern of serious events. The most common grade 3 or 4 events were weight loss (5%), muscle spasms (4%) and fatigue (4%). The most common adverse events observed were muscle spasms (68% of patients) and alopecia (63% of patients). There were 7 deaths but it was reported that they were thought to be unrelated to drug. pERC also noted that vismodegib is a teratogen and that there are prescribing restrictions in place to limit exposure to the risks associated with vismodegib. Given that these restrictions are in place and there is a high clinical need for treatments in this select population, pERC considered that the toxicity of vismodegib was acceptable for the restricted population of patients who are clearly ineligible or inappropriate for surgery or radiotherapy, or who had failed prior radiotherapy as defined in the ERIVANCE study. There were 12% of patients in ERIVANCE who discontinued vismodegib due to adverse events. pERC noted that because there is only one tablet size available for vismodegib, dose reductions were not an option for these patients and there is uncertainty concerning the appropriateness of alternative dosing schedules. In

addition, approximately half of patients discontinued treatment. The most common reason for discontinuation in metastatic patients was disease progression while in locally advanced patients, it was due to the patients' decision. pERC further noted that patient discontinuations from the study were high, despite there being no other treatment options available. Considering all of these factors, pERC discussed that strategies to monitor disease control and the effects of long-term use of vismodegib were required as more experience is obtained with vismodegib.

Limitations: no comparative data or meaningful quality of life data

pERC discussed the limitations of relying on non-randomized, non-comparative evidence and concluded that there is considerable uncertainty surrounding the exact magnitude of the clinical benefit of vismodegib. pERC further discussed the challenges of assessing the efficacy of vismodegib in the absence of comparative data and noted that a study including retrospective or historical controls could have helped informed pERC's deliberations. In addition, pERC considered that there was a need for a better understanding of the impact of vismodegib on the morbidity and functional outcomes of patients with advanced BCC. However, quality of life was not measured in a meaningful way in the ERIVANCE study.

Need: effective treatments for patients with no other therapeutic options

Basal cell carcinoma is the most common cancer in North America and affects about 50,000 to 60,000 Canadians per year. pERC noted that BCC typically affects older patients but is becoming more common in younger patients. It is a lifelong condition for patients who are born with Gorlin syndrome. pERC discussed the burden of metastatic and locally advanced BCC and considered that morbidity is a substantial concern. Although metastatic BCC is rare, it was noted that locally advanced BCC can be invasive, with tumours causing significant tissue destruction, resulting in significant morbidity. In extreme cases, patients may experience severe disfigurement and surgery could result in the loss of essential structures or organs such as eyes or ears. Such disfigurement may lead to extreme social isolation and decreased quality of life for patients.

pERC noted that there is currently no standard treatment for patients with metastatic and locally advanced basal cell carcinoma who are inappropriate for surgery or radiotherapy. Although chemotherapy with drugs such as cisplatin is sometimes used, there is limited evidence that these treatments improve patient outcomes and many patients do not receive other treatments when surgery and radiotherapy are not an option. Therefore, there is a distinct need for effective treatment options in these patients. pERC noted that although basal cell carcinoma is very common, the number of patients who are inappropriate for surgery and radiotherapy is likely very small, which may have impacted the feasibility of conducting a randomized controlled trial. However, pERC further discussed that, because there have been no effective treatment options to date for these patients, they may not be seeking treatment within the healthcare system and their true numbers are unknown. With the availability of vismodegib, it is possible that there may be more patients with BCC seeking treatment and, therefore, a larger patient population to treat.

PATIENT-BASED VALUES

Values of patients with locally advanced and metastatic basal cell carcinoma: disease control to improve quality of life and deformities

pERC reviewed patient advocacy group input and noted that patients with BCC who are inappropriate for surgery or radiotherapy experience serious deformity and social isolation, which has a debilitating impact on their quality of life. Aspects of this disease that were important to respondents to control include the side effects of radiation and the scars from surgery to remove BCC, as these greatly impacted the physical appearance of the patient. Patients are greatly impacted by the physical appearance of the scars. Patients indicate that they face the certainty of disease progression including ongoing advancement of basal cell carcinomas despite repeated surgeries, radiation and courses of medication. pERC noted that meaningful quality of life data were not available from the ERIVANCE study. However, pERC considered that the objective response rates observed with vismodegib in the ERIVANCE study were a measure of tumor regression and that patients who experienced such responses would have less disfigurement and, therefore, would likely have an improved quality of life. Therefore, pERC concluded that vismodegib aligns with patient values.

Patient values on treatment: willing to tolerate serious risks if therapy is effective

Current therapies have proven to be ineffective at stopping disease progression and have severe side-effects leading to decreased quality of life, loss of income and mental health challenges, including the negative impact on their caregivers and children. pERC also noted that input received from patients indicated that they had tried multiple therapies but none were effective. Patients are seeking effective treatment options and patients who had taken vismodegib reported that their condition had stabilized without progression, many for the first time in their lives. pERC also considered that vismodegib demonstrated a meaningful and durable response, which aligns with the patient value of accessing effective treatment options.

Patients who had experience with vismodegib reported that the side effects were mild or moderate and included muscle cramps, some hair loss, weight loss, abnormal liver function test results and change in taste. Patients indicated that they were willing to accept side effects and the serious risks associated with a new drug, such as vismodegib, if they knew that the side-effects can be appropriately managed and the treatment is effective. Therefore, although there are serious risks associated with a teratogen such as vismodegib, pERC considered that patients appeared willing to accept this risk if vismodegib is effective.

Patients also reported that the benefits of vismodegib included ease of administration as it was taken at home and allowed the patients to avoid repeated surgeries and visits to the hospital.

ECONOMIC EVALUATION

Economic model submitted: cost-effectiveness

The pCODR Economic Guidance Panel (EGP) assessed a cost-effectiveness analysis of vismodegib (Erivedge) vs. Best Supportive Care (BSC) for the treatment of adult patients with histologically confirmed metastatic basal cell carcinoma (mBCC) or locally advanced basal cell carcinoma (laBCC) who were inappropriate for surgery or radiotherapy.

Basis of the economic model: clinical and economic inputs

Costs included treatment with vismodegib, wound care and healthcare visit costs. The factors that mainly influence incremental cost are the unit price of vismodegib and the weekly supportive care cost after progression.

Key clinical effects were quality of life, as represented by the utility estimates and the assumption of a difference in overall survival between the progression-free and progressed state.

Drug costs: one tablet size does not allow for dose reductions

Based on the list price, vismodegib costs $294.22 per 150 mg. At the recommended dose of 150mg per day, the cost of vismodegib is $294.22 per day or $8,238.24 per 28-day cycle.

pERC noted that because there is only one tablet size available for vismodegib, dose reductions were not an option for these patients and there is uncertainty in the appropriateness of alternative dosing schedules.

Cost-effectiveness estimates: highly dependent on quality of life benefit and utilities

pERC deliberated upon the cost-effectiveness of vismodegib compared with best supportive care. It was noted that due to the limitations of relying on non-randomized, non-comparative evidence from the ERIVANCE study, there was substantial uncertainty in the magnitude of clinical benefit associated with vismodegib. This made it challenging to estimate the incremental effect of treatment with vismodegib and, therefore, the resulting incremental cost-effectiveness estimates for vismodegib. pERC further discussed that the utility estimates were a key driver and further uncertainty was created because meaningful quality of life data were not available from the ERIVANCE study. In addition, there was a wide range of utility estimates from the literature that could be used. pERC noted that these estimates were similar to those provided by the manufacturer. This considerable uncertainty led to a wide range

of incremental cost-effectiveness estimates, all of which pERC considered unacceptable. Therefore, vismodegib could not be considered cost-effective at the submitted price.

pERC further noted that any prospective evidence regarding clinical efficacy and quality of life that could be collected to decrease the uncertainty in the incremental clinical effect and better understand the utility estimates would be of benefit in informing the true cost-effectiveness of vismodegib.

Other factors that influenced the EGP's estimates included the time horizon and the costs of wound care. However, the impact of these factors was relatively small compared with the impact of the utility estimates and the EGP was able to adjust the time horizon and wound care costs in their re-analyses.

Upon reconsideration of the pERC initial recommendation, pERC discussed feedback received from the manufacturer regarding the uncertainty in the submitted incremental cost-effectiveness estimates. pERC discussed that the uncertainty in an economic analysis that is based on non-randomized, non-comparative evidence is large and is inherently different from the type of uncertainty observed in economic analyses based on a randomized controlled trial. Therefore, pERC confirmed that additional prospective clinical data would be required to decrease the uncertainty in the cost-effectiveness of vismodegib. In addition, because of the considerable uncertainty in the magnitude of the clinical effect estimates, pERC concluded that a substantial reduction in drug price would likely be required to offset this and improve cost-effectiveness.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: uncertainty in budget impact and limiting indication creep

pERC discussed the feasibility of adoption and noted that the budget impact of vismodegib is uncertain because the number of patients with metastatic or locally advanced BCC who are ineligible for surgery and radiotherapy and who may seek treatment once vismodegib is available is uncertain. It was noted that vismodegib will be an additional treatment and will not be replacing another treatment in this setting. In addition, because vismodegib is a teratogen and is only available through a controlled distribution program, additional pharmacy resources would be required. Also, it was noted that vismodegib is an oral treatment and may be more easily accessible than surgery or radiotherapy for some patients, which could also contribute to indication creep. Because the prevalence of BCC is high, indication creep could have a large budget impact. Therefore, to prevent indication creep, pERC noted that provinces may want to consider additional measures to encourage high quality prescribing of vismodegib to the recommended population (as defined by inclusion criteria in the ERIVANCE study).
Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the Provincial Advisory Group regarding the potential for indication creep with vismodegib. Because the decision to not use conventional treatment methods for basal cell carcinoma is complex, pERC determined that, as one measure to achieve high quality prescribing, decisions on the use of vismodegib should be made by a multi-disciplinary team that would include one or more dermatologists, surgeons, radiation oncologists and medical oncologists.
pERC also confirmed that the inclusion criteria of the ERIVANCE study should be followed but also discussed that lesion size (an eligibility criterion of the study) is not the best criterion to use when deciding to prescribe vismodegib. The key issue is whether the lesion's removal would result in major disfigurement if treated by surgery or serious side effects if treated by radiotherapy.

Upon reconsideration of the pERC initial recommendation, pERC discussed feedback received from pCODR's Provincial Advisory Group regarding the need for testing for the Hedgehog status in this patient population. pERC noted that testing will not be necessary as at least 90% of patients are positive for this acquired aberrant activation pathway.

DRUG AND CONDITION INFORMATION

Drug Information	• Hedgehog inhibitor • Available as 150 mg tablets • Recommended dose of 150 mg orally once daily
Cancer Treated	• Basal cell carcinoma, locally advanced or metastatic • Patients ineligible or inappropriate for radiotherapy or surgery
Burden of Illness	• Most common cancer in North America and affects about 50,000 to 60,000 Canadians per year (75% of all non-melanoma skin cancers and 25% of all cancers in North America) • Basal cell carcinomas rarely metastasize but are locally invasive and can cause significant tissue destruction and result in significant morbidity and decline in functional outcomes and quality of life • Gorlin's Syndrome patients have a genetic mutation and lifelong hereditary nevoid basal cell syndrome
Current Standard Treatment	• No effective treatment options available when ineligible for surgery and radiotherapy • Chemotherapy is used sometimes but has no proven benefit
Limitations of Current Therapy	• Current therapies not effective and need for new treatments

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee (pERC)

Recommendations are made by the pCODR Expert Review Committee following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Anthony Fields, Oncologist (Chair)
Dr. Maureen Trudeau, Oncologist (Vice-Chair)
Dr. Chaim Bell, Economist
Dr. Scott Berry, Oncologist
Bryson Brown, Patient Member
Mario de Lemos, Pharmacist
Dr. Sunil Desai, Oncologist
Mike Doyle, Economist
Dr. Bill Evans, Oncologist
Dr. Allan Grill, Family Physician
Dr. Paul Hoskins, Oncologist
Danica Wasney, Pharmacist
Carole McMahon, Patient Member Alternate
Jo Nanson, Patient Member
Dr. Peter Venner, Oncologist
Dr. Tallal Younis, Oncologist

All members participated in deliberations and voting on the initial recommendation except:

- Dr. Bill Evans who was not present for the meeting
- Carol McMahon who did not vote due to her role as a patient member alternate

All members participated in deliberations and voting on the final recommendation except:

- Carol McMahon who did not vote due to her role as a patient member alternate

Avoidance of conflicts of interest

All members of the 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 pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of vismodegib (Erivedge) for basal cell carcinoma, through their declarations, six members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, none of these members were excluded from voting.

Information sources used

The pCODR Expert Review Committee 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 their deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR 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*. There was no non-disclosable information in this recommendation document.

Use of this recommendation

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