# pCODR EXPERT REVIEW COMMITTEE (pERC)
# INITIAL 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.

**Providing Feedback on this Initial Recommendation**
Taking into consideration feedback from eligible stakeholders, the pERC will make a Final Recommendation. Feedback must be provided in accordance with *pCODR Procedures*, which are available on the pCODR website. The Final Recommendation will be posted on the pCODR website once available, and will supersede this Initial Recommendation.

**Drug:**
Aldesleukin (Proleukin)

**Submitted Funding Request:**
Administered intralesionally, for the treatment of in-transit metastases from melanoma in patients who have failed or are not candidates for surgery or other treatments

**Submitted By:**
Cancer Care Ontario Melanoma Disease Site Group

**Manufactured By:**
Novartis Pharmaceuticals Canada Inc.

**NOC Date:**
N/A

**Submission Date:**
January 30, 2015

**Initial Recommendation Issued:**
June 4, 2015

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| **pERC RECOMMENDATION** | The pCODR Expert Review Committee (pERC) recommends funding aldesleukin (Proleukin) in patients with unresectable in-transit metastatic melanoma (i.e., patients with rapidly developing in-transit metastases after surgery or patients who present with multiple in-transit metastases unsuitable for surgical resection). Funding should be for aldesleukin when administered as an intralesional injection.<br><br>pERC made this recommendation because it was satisfied that there is a net clinical benefit of aldesleukin based on meaningful complete response rates, the durability of some of the responses, the potential for improvement in quality of life, and the low toxicity associated with this localized treatment. pERC also considered that this is a small patient population with limited treatment options, all of which have the potential for significant toxicity. However, pERC acknowledged that because of the non-randomized, non-comparative study designs of the available clinical trials, there was considerable uncertainty in the magnitude of the clinical benefit of aldesleukin. pERC was also satisfied that aldesleukin aligns with patient values and that it is cost-effective, at the list price, compared with usual care. |
| **POTENTIAL NEXT STEPS FOR STAKEHOLDERS** | **Optimal Dosing and Stopping Criteria Unknown**<br>pERC acknowledged that there remains uncertainty in the actual dose per lesion, the frequency of intralesional therapy and the optimal duration of treatment with intralesional aldesleukin. pERC recognized that provinces will need to address these issues, and noted that collaboration among provinces, with input from local tumour groups, to develop a common approach would be of value. |

# SUMMARY OF pERC DELIBERATIONS

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

In Canada, the incidence of primary melanoma in 2014 was 6,500, with approximately 1,100 deaths due to melanoma. In-transit metastases are estimated to occur in about 4-5% of patients and occur more frequently in patients with thicker primary tumours or in those with ulcerated primary tumours. In-transit metastatic melanoma lesions are cutaneous or subcutaneous deposits of melanoma that are often painful, disfiguring, malodourous, and unsightly. Lesions can also be located in areas that limit mobility or they can be open and oozing, requiring additional care to prevent infection. Treatment for in-transit melanoma is often surgical excision; however, pERC noted that for patients in whom in-transit metastases rapidly develop after surgery or in whom the number or location of in-transit metastases precludes surgery, there are limited treatment options. Eligible patients may receive therapies such as isolated limb perfusion or infusion, radiation therapy, or systemic therapy with oral or IV chemotherapy or immunotherapy. pERC noted that isolated limb perfusion or infusion is not available to patients in all provinces and that it is a very resource-intense therapy with a risk of substantial adverse events. pERC also noted that not all patients would be eligible to receive systemic therapy, which carries a high risk of toxicity, and that melanomas are often radiation-resistant. pERC discussed that there is a need for localized therapies that are easy to administer, that can be used to treat areas of the body other than the limbs and that can help patients to maintain a reasonable quality of life.

pERC deliberated on two single-arm, non-randomized phase two studies (Boyd et al, 2011 and Weide et al, 2010) that prospectively observed treatment with aldesleukin in patients with in-transit metastatic melanoma. pERC noted that the complete response rates in both studies were high, when measured on a per lesion basis (Boyd study, 76%; Weide study, 79%) or on an individual patient basis (51% and 65%, respectively). pERC also noted that in the Boyd study, the five-year in-transit-metastasis-free survival was 77% in patients with a complete response. pERC discussed the potential for improvement in quality of life for these patients, given the highly localized nature of both the disease and treatment coupled with the high rate of localized complete response. pERC concluded that intralesional aldesleukin is meaningfully effective. However, pERC noted that there is uncertainty in the magnitude of the clinical effect, due to the non-randomized, non-comparative nature of the clinical trials that provide the available evidence. pERC noted that given the small patient population, a randomized controlled trial is highly unlikely to be undertaken in this disease setting.

pERC considered that the toxicity reported in the two studies consisted mostly of fever lasting a few days after injection, pain associated with intralesional injections, and localized swelling and discomfort at the injection site. pERC discussed that the toxicities associated with intralesional aldesleukin are much less than the toxicities associated with currently available therapies such as systemic therapy or isolated limb perfusion or infusion.

pERC reviewed patient advocacy group input from several groups and concluded that intralesional aldesleukin aligns with patient values. pERC noted that patients described in-transit melanoma as an aspect of this disease that can cause a significant reduction in quality of life, loss or reduction in mobility, disfigurement, and unsightliness, depending on the size and location of the in-transit tumours. pERC also noted that patients wanted effective treatments that could stop the local spread of their disease and provide durable remissions. pERC concluded that treatment with intralesional aldesleukin aligns with patient values of arresting disease progression, inducing durable complete remissions in some patients with probable improvement in quality of life, while inducing minimal adverse events.

pERC deliberated upon the cost-effectiveness of intralesional aldesleukin compared with usual care. pERC noted that the pCODR Economic Guidance Panel's (EGP) best estimates of incremental cost-effectiveness and incremental cost-utility indicated that aldesleukin is the dominant strategy compared with usual care. pERC also noted that when the EGP explored a three-fold increase in the cost of aldesleukin, the incremental cost-utility estimates remained cost-effective ($18,441 per QALY gained).

pERC accepted the best estimates of the EGP and concluded that aldesleukin, at the list price, is cost-effective compared with usual care.

pERC discussed the feasibility of adoption of intralesional therapy with aldesleukin and noted that aldesleukin had been in use in this way for this patient population for a number of years as it was previously available through the manufacturer's compassionate program for non-approved indications. pERC noted that although centres in some provinces may not currently have the expertise to administer aldesleukin intralesionally, pERC considered that the appropriate technique can be readily taught to health care professionals and that treatment could likely be offered at most cancer treatment centres. pERC also discussed the potential budget impact and noted that the size of the population that develops in-transit metastases is very small and that the cost of aldesleukin is not substantial. In addition, pERC noted that the submitter's budget impact analysis suggests that if even a conservatively small percentage of patients (5%) are able to avoid systemic therapies, treatment with aldesleukin would be cost-saving.

# EVIDENCE IN BRIEF

pERC deliberated upon a pCODR systematic review, other literature in the Clinical Guidance Report providing clinical context, an evaluation of the submitter'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 [MNC] and Save Your Skin Foundation [SYSF]) and input from pCODR's Provincial Advisory Group.

## OVERALL CLINICAL BENEFIT

### pCODR review scope

The purpose of the review is to evaluate the effectiveness and safety of intralesional aldesleukin for patients with in-transit metastatic melanoma (i.e., cutaneous or subcutaneous deposits of melanoma) after failure of surgery.

### Studies included: Two single-arm phase II studies

The pCODR systematic review did not identify any comparative studies of intralesional aldesleukin in patients with in-transit metastatic melanoma after failure of surgery. The systematic review did identify two non-randomized, non-comparative phase II studies; a German study by Weide et al, 2010 and a Canadian study by Boyd et al, 2011.

Weide et al enrolled 51 patients with Stage III or IV disease with injectable dermal or subcutaneous metastases. Aldesleukin was injected three times weekly with the duration of treatment ranging from 2-4 weeks. The outcomes of interest were response rate, overall survival, and adverse events. Each treated metastasis was evaluated separately for clinical response. Only deaths due to melanoma were considered in the survival analysis.

Boyd et al enrolled 39 patients with metastatic in-transit melanoma. Aldesleukin was injected biweekly with a goal of four sessions. The outcomes of interest were response rate and adverse effects. Response was assessed by two independent observers and evaluated for each patient using the Response Evaluation Criteria in Solid Tumours (RECIST) criteria.

### Study limitations: Non-comparative studies; differences in assessment of response

pERC noted that both studies were non-comparative designs and, therefore, the magnitude of the benefit of aldesleukin compared with no treatment or other treatments is uncertain. The two studies assessed response differently, with Weide et al assessing response for each individual lesion, whereas Boyd et al assessed response at the patient level.

### Patient populations

A similar proportion of female patients were included in both studies (56% in Weide et al and 59% in Boyd et al). The average age of included patients was 69 years in both studies. In the Weide et al study, 69% of patients had Stage III disease and 31% had Stage IV, whereas in the Boyd et al study, all 39 patients had Stage III disease. Weide et al reported that 31% of patients had 20 or more metastases treated.

### Key efficacy results: High complete response rates

In the Weide et al study, a total of 894 of 917 individually treated metastases were evaluable for local tumour response. The complete response rate was 78.7%, the partial response rate was 0.7%, and the stable disease rate was 16.3%. Thirty-three of 51 patients (64.7%) had a complete local response to all treated metastases. The percentage of patients with a complete local response of all treated lesions was not dependent on the number of lesions treated (73% complete response rate for patients who had 20 or more treated metastases versus a 66% complete response rate for patients who had less than 20 treated metastases; p=0.7458). After 2 years, overall survival in the 33 Stage III patients was 77% and in the 15 Stage IV patients, it was 53%.

In the Boyd et al study, 51% of 39 patients had a complete response and 31% had a partial response, for an overall response rate of 82%. Of 629 treated in-transit metastases, 76% had a complete local response but 24% showed no response to treatment. The number of treated in-transit metastases did not predict

whether patients would experience a complete local response to all treated lesions (ANOVA, p=0.46). The five-year in-transit metastasis-free survival rate was 77% in patients with a complete response and 18.5% in patients with a partial response (log-rank, p=0.0005). The 5-year overall survival was 80% for the 20 patients with a complete response and 33% for the 12 patients with a partial response (log-rank, p=0.012). In addition, 50% of patients with only a partial response died due to their disease within 17.5 months after treatment with aldesleukin.

### Quality of life: No data available; disease has obvious detrimental effects

No data on quality of life were available from either the Weide et al or Boyd et al study.

pERC noted that the pCODR Clinical Guidance Panel (CGP) reported that patients with in-transit metastatic melanoma have a distressing disease with unsightly and painful lesions. These lesions often ulcerate and become infected, requiring daily dressing changes and topical, or sometimes systemic, antibiotics. Patients often require narcotic analgesics to cope with the pain and discomfort. If the lesions are located near joints they can severely limit the patient's mobility. pERC discussed that, despite the lack of formal quality of life data, a local complete response could be reasonably expected to lead to improvements in mobility and lessened pain by eliminating or reducing the size of patients' metastases, thereby improving quality of life.

### Safety: Generally mild and manageable toxicity

In the Weide et al study, treatment with aldesleukin usually caused an inflammatory injection site reaction that consisted of local swelling and erythema, followed by selective necrosis of the tumour tissue. pERC noted that only grade 1 or 2 adverse events occurred in the study, with the most common being fever (58%), fatigue (36%) and nausea (34%). No deaths were reported after 25 months of treatment.

In the Boyd et al study, minor discomfort with the injection of aldesleukin was seen in all patients. After treatment, 85% of patients experienced flu-like symptoms. Most patients reported that their symptoms were mild and resolved within 24 to 48 hours. Three of 20 patients (15%) who had a complete response died, with a mean time to death of 12.8 months.

### Comparator information: No standard therapy; toxicity of available therapies

pERC noted that for patients with in-transit metastatic melanoma who have failed surgery, there is no standard therapy and that treatment options are limited. pERC noted that some patients may be referred to specialized centres for consideration of isolated limb perfusion or infusion; however, very few centres in Canada have the expertise and resources to deliver this form of resource-intense treatment and not all patients would be eligible for such treatment. In addition, isolated limb perfusion or infusion is associated with a higher risk of acute and severe toxicities such as pain, limb swelling, and ulceration. pERC noted that other treatment options for these patients include radiation therapy or systemic therapy. pERC considered that radiation therapy has limited effectiveness in the localized setting, that systemic therapy has significant associated toxicities and that many patients with in-transit metastases are not eligible for systemic therapy due to age-related morbidity.

### Need: Additional treatment options are required

pERC noted that patients with in-transit metastatic melanoma have a distressing disease as lesions are unsightly, painful, and can limit mobility. Systemic therapies and isolated limb perfusion or infusion have a significant potential for severe toxic effects and some patients may not be eligible for those treatments. pERC considered that intralesional aldesleukin is a localized treatment with minimal toxicity which would offer those patients who are not eligible to receive systemic therapy an effective treatment option and that it may offer patients an opportunity to enjoy long term durable remission or to delay or avoid systemic therapy.

### Dosing: Differences between studies in administration of aldesleukin; optimal dosing and stopping criteria are unknown

pERC noted that the two studies administered aldesleukin in different ways and that the dosing of aldesleukin was not clearly defined in either study. Weide et al reported treatment administration guidelines that included minimal single doses of aldesleukin based on the size of individual lesions, while Boyd et al administered aldesleukin at the discretion of the investigator based on the number and size of lesions. Given that there remained uncertainty in the actual dose per lesion, the frequency of

intralesional therapy and the optimal duration of treatment with intralesional aldesleukin, pERC recognized that provinces will need to address these issues, and noted that collaboration among provinces, with input from local tumour groups, to develop a common approach would be of value.

## PATIENT-BASED VALUES

### Patient advocacy group input

Input from two patient advocacy groups indicated that patients with in-transit metastatic melanoma value treatments that slow or stop progression of their disease.
The Melanoma Network of Canada (MNC) conducted an online survey of patients across Canada. A total of 90 patients responded, of whom 26 had received treatment with aldesleukin. The Save Your Skin Foundation (SYSF) conducted one-on-one interviews with 5 patients (none of whom had received aldesleukin) and 3 caregivers.

### Values of patients with in-transit metastatic melanoma: Need for treatment options that slow or stop progression and improve patients' quality of life

pERC noted that from the patient's perspective, the symptoms and side effects of in-transit melanoma greatly impact a patient's quality of life. Respondents reported experiencing severe pain, edema and scarring. pERC noted that patients described their disease as horribly debilitating and disfiguring as they could see lesions multiply daily, resulting in tumours protruding from the skin that bleed, ooze, smell, and continue to spread. Patients also described a lack of effective treatment options for in-transit metastatic melanoma.

pERC noted that patients reported receiving various treatments for their disease, including interferon, surgery, radiation, dacarbazine, temozolomide, vemurafenib, and ipilimumab. Respondents felt that these treatments might have slowed the spread of their disease, but were not effective in preventing metastases. Side effects experienced by respondents included fatigue, diarrhea, skin issues, nausea, rash, low sodium levels, and colitis. Respondents indicated that many side effects were so severe that patients were not able to perform daily functions.

### Patient values on treatment: want therapies that are effective at stopping or slowing progression and with less toxicity

pERC noted that of 26 respondents to the MNC survey who received aldesleukin injections, the following side effects of treatment were experienced: fever or flu-like symptoms (n=8), pain (n=6), burning (n=6), infection (n=4), joint pain (n=2), or other (n=12). Eight respondents reported that they experienced no side effects. The most commonly reported side effects by the five patients interviewed by the SYSF were pain and swelling at the injection site, however, that discomfort was mild and short-lived. All of the five respondents to the SYSF survey noted that they felt the side effects of treatment were manageable.

## ECONOMIC EVALUATION

### Economic model submitted: cost-utility (QALY) and cost-effectiveness (life-years) analyses

The pCODR Economic Guidance Panel (EGP) assessed one cost-utility analysis (clinical effects measured by quality-adjusted life-years [QALYs] gained) and one cost-effectiveness analysis (clinical effects measured by life-years [LYs] gained) of aldesleukin compared with usual care (systemic therapy, isolated limb perfusion, or radiation therapy) in patients with in-transit metastatic melanoma after failure of surgery. Both analyses were conducted using the same Markov model.

### Basis of the economic model: clinical and economic inputs

Costs considered in the analysis included the cost of patient assessment, initial consult and follow-up costs, medication/therapy costs, and biopsy costs.

The key clinical outcomes considered in the cost-effectiveness analysis using life-years gained (LYs) as the measure of effect, were response rates and progression rates. Non-comparative data from several sources were used to inform the comparison of intralesional aldesleukin with usual care. The key clinical

outcomes considered in the cost-utility analysis using quality-adjusted life years gained (QALYs) as the measure of effect were response rates, progression rates, and utility data as above.

### Drug costs: Aldesleukin may cost less compared with usual care

At the list price, aldesleukin costs $508.47 per vial at a strength of 5 MIU/mL (22 MIU or 1.3 mg per vial). At the maximum of 22 MIU (5 syringes of 0.8 mL) given every 2 weeks, the average cost per day is $36.32 and the average cost per 28-day course is $1,016.94.

The Submitter assumed that the cost of aldesleukin is $662 per treatment which included the cost of the initial consult and patient assessment, treatment administration and follow-up costs, as well as biopsy costs.

The EGP's best estimate of the extra cost of aldesleukin compared with usual care results in a cost-savings of $5074, in patients with in-transit metastatic melanoma after failure of surgery. The factors that most influence the incremental cost of aldesleukin are the drug cost and the costs of isolated limb perfusion or infusion, systemic therapies, and radiation therapy.

### Clinical effect estimates: Incremental effect in favour of aldesleukin

The EGP's best estimate of the extra clinical effect of aldesleukin compared with usual care was 0.304 QALYs gained or 0.589 life-years gained. The factor that most influenced the incremental clinical effect was the proportion of patients in the usual care arm receiving each type of therapy. pERC noted that the EGP reported that the modeling of survival was assumed to be constant over time, which may be an oversimplification that may have influenced the model results and that the model could have been improved by using time-dependent transition probabilities between health states, provided that the necessary data exist.

### Cost-effectiveness estimates: EGP's best estimate is that aldesleukin is the dominant strategy compared with usual care and is similar to the submitter's estimate

pERC noted that the EGP's best estimates of the incremental cost-effectiveness and incremental cost-utility indicated that aldesleukin is the dominant strategy compared with usual care; that is, aldesleukin resulted in cost-savings compared with usual care while providing superior clinical benefit. pERC also noted that the EGP's best estimate was similar to the submitter's. Finally, pERC noted that even when the EGP explored increasing the cost of aldesleukin 3-fold, the incremental cost-utility ratio was $18,441 per QALY gained, which pERC concluded was still cost-effective.

## ADOPTION FEASIBILITY

### Considerations for implementation and budget impact: familiarity with aldesleukin; method of injection can be easily taught; small size of population would limit budget impact

pERC noted that the factors that most influence the potential budget impact include the small size of the population who develop in-transit metastatic melanoma and might benefit from intralesional therapy and the low cost of aldesleukin. The robustness of the analysis was improved through the use of a conservative assumption that all patients eventually underwent systemic therapy. pERC also noted that the budget impact analysis estimated that if 5% of patients are able to avoid systemic therapy, then treatment with aldesleukin becomes cost-saving.

pERC discussed the feasibility of adoption and noted that there is familiarity with aldesleukin within the healthcare system as it had been in use for this patient population for a number of years as it was previously available through the manufacturer's compassionate program for non-approved indications. pERC also noted that, although the current expertise to administer intralesional aldesleukin is limited to only a few centres, the method of injection can be readily taught to health care professionals and that the treatment could likely be offered in most cancer treatment centres.

# DRUG AND CONDITION INFORMATION

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| Drug Information | • Cytokine<br>• 22 million IU/vial<br>• Dosing varies, commonly given as 1 million units/mL (5 million units divided into 5 syringes) administered via intralesional injections, four to eight times every 2 weeks |
| Cancer Treated | • In-transit metastatic melanoma, after failure of surgery |
| Burden of Illness | • 6,500 new cases of primary melanoma were diagnosed in 2014 and approximately 1,100 individuals will die from melanoma each year<br>• The incidence of in-transit metastases is estimated to be about 4.3% |
| Current Standard Treatment | • Limb perfusion, systemic chemotherapy or immunotherapy, or oral BRAF inhibitors for BRAF mutation-positive disease |
| Limitations of Current Therapy | • Many patients treated with local therapy are elderly and have multiple medical comorbidities, that preclude the use of other forms of therapy<br>• Need for effective local therapy to control the morbidity of in-transit metastases |

# 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. Scott Berry, Oncologist
Bryson Brown, Patient Member
Dr. Matthew Cheung, Oncologist
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. Tallal Younis, Oncologist
Dr. Kelvin Chan, Oncologist

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

- Scott Berry and Kelvin Chan who were not present for the meeting
- Carole McMahon who did not vote due to her role as a patient member alternate
- Maureen Trudeau who was excluded due to a conflict of interest

### 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 aldesleukin (Proleukin) for in-transit melanoma through their declarations, six members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, but 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*.

### Use of this recommendation

This recommendation from the pCODR Expert Review Committee (pERC) is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policymakers 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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