pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

# pan-Canadian Oncology Drug Review Final Clinical Guidance Report

# Aldesleukin (Proleukin) for In-transit Melanoma

**June 22, 2015**

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# TABLE OF CONTENTS

# 1 GUIDANCE IN BRIEF

## 1.1 Background

In Canada, 6,500 new cases of primary melanoma were diagnosed in 2014 and approximately 1,100 individuals will die from melanoma each year.[1] Although the majority of melanoma patients present with early-stage disease and many are cured by surgery, some will recur with local or distant metastases. Approximately 4.5% of melanoma patients will develop local disease recurrence with multiple in-transit metastases. Treatment options include surgical excision, radiation, isolated limb infusion or perfusion, and local injections to try and stimulate an immune response. Many patients treated with local therapy only are elderly and have multiple comorbidities and are not candidates for systemic therapy. Untreated in-transit metastases can be associated with extensive morbidity requiring analgesia and frequent dressing changes for infected, ulcerated metastases.

The objective of this review was to evaluate the effectiveness and safety of aldesleukin (Proleukin™; Interleukin-2 or IL-2) as second line of therapy for in-transit metastatic melanoma after surgery has failed.

## 1.2 Key Results and Interpretation

### 1.2.1 Systematic Review Evidence

Two open-label, single-arm trials were identified and included in this Clinical Guidance Report. Weide et al conducted a phase II study in Germany and included 51 patients with stage IIIB or IV disease with skin or soft-tissue metastases.[2] Aldesleukin was injected intratumourally, with single doses ranging between 0.3 MIU and 6 MIU, depending on the lesion size. 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.[3] 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.

Both studies were single-arm trials with no comparator. The efficacy of aldesleukin compared with 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. In addition, the two studies administered aldesleukin in different ways. While Weide et al reported treatment guidelines for their study, which included minimal single doses of aldesleukin per lesion based on the size of individual lesions, Boyd et al administered aldesleukin based on the number and size of lesions at the discretion of the investigator. There is a greater potential for bias in the method described by Boyd et al as the lead investigator could have knowingly or unknowingly varied the dosages of aldesleukin. Neither study reported quality of life data.

#### *Efficacy*

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%, partial response rate of 0.7%, stable disease rate of 16.3%, and a progressive disease rate of 4.3%.

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% for patients who had ≥20 treated metastases versus [vs.] 66% for patients who had <20 treated metastases; p=0.7458). After 2 years, the overall survival in 33 stage III patients was 77% and in 15 Stage IV patients it was 53%. Overall survival for 15 patients with ≥20 in-transit metastases was similar to the 33 patients with <20 in-transit metastases.[2]

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%. The response rate by lesion was 76% of 629 treated in-transit metastases. The number of treated in-transit metastases did not predict whether patients would experience a complete local response of all treated lesions (ANOVA, p=0.46). The five-year in-transit metastasis-free survival was 77% in complete responders and 18.5% in partial responders (log-rank, p=0.0005). Five-year overall survival was 80% for 20 patients with a complete response and 33% for 12 patients with a partial response (log-rank p=0.012). In addition, 50% of patients with a partial response died due to their disease within 17.5 months after treatment with aldesleukin.[3]

***Harms***

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. The authors recorded only grade 1 or 2 adverse events, of which the most commonly occurring were fever (58%), fatigue (36%), and nausea (34%). No deaths were reported after 25 months of treatment; however 23% of patients with Stage III disease died as did 50% of Stage IV patients.[2]

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 are were treated with acetaminophen. Three of 20 patients (15%) who had a complete response, died. The mean time to death among the 20 complete responders was 12.8 months. Eight of 12 patients (67%) who had a partial response died. The mean time to death was 12.2 months.[3]

### 1.2.2 Additional Evidence

pCODR received input on aldesleukin for in-transit metastatic melanoma from two patient advocacy groups, Melanoma Network of Canada (MNC) and Save Your Skin Foundation (SYSF). Provincial Advisory group input was obtained from nine of the nine provinces participating in pCODR.

No supplemental issues were identified during the development of the review process.

### 1.2.3 Interpretation and Guidance

Neither of the included studies had a comparator arm; however, there is no standard comparator for the treatment of patients with in-transit metastatic melanoma who have failed surgical therapy. The Weide et al trial demonstrated a complete response rate of 78.7% of 894 evaluable lesions and a partial response rate of 0.7%.[2] In the Boyd et al trial, 82% of 39 patients had a complete or partial response. Of the 629 treated in-transit metastases, 76% had a partial or complete response to treatment. Weide et al demonstrated that complete response of all treated lesions was not dependent on the number of lesions treated, with Boyd et al reporting a similar finding.[3]

Treatment with aldesleukin was well tolerated in both studies, with most toxicity being localized erythema and swelling, followed by necrosis of the tumour but not of the normal

surrounding tissue. Injection pain was controlled with topical analgesia. In the Weide et al study, 85% of patients reported transient minor flulike symptoms such as fevers, chills and fatigue. No study-related deaths were reported after 25 months of treatment in the Weide et al study.

Patients with in-transit metastases live with their disease in constant view, which can be distressing for many patients. They are forced to observe the unrelenting progression of the disease as it tracks more and more proximally. Furthermore, in-transit metastases can also present as open lesions that are unsightly and/or can be painful. These lesions can often ulcerate and become infected, requiring daily medical services, such as home care serviced, daily dressing changes, and topical and sometimes systemic antibiotics. Patients often require narcotic analgesics, which can be associated with complications as these patients are often elderly. When these metastases are located near joints they can severely limit the patient's mobility. Complete or partial responses can eliminate or reduce the size of patients' metastases and lead to improved quality of life through increased mobility, lessened pain, and by removing the metastasis from the patient's view.

The burden of illness is low, with only 4.6% of all patients presenting with local regional recurrence. This is a distinct subpopulation of patients, some of whom will do well long-term with local therapy. Aldesleukin, given as intralesional therapy, can often be given instead of isolated limb infusion or perfusion, which may or may not be feasible depending upon the specific location of the disease. Isolated limb infusion or perfusion often require hospitalization and involve operating room resources to administer. In contrast with intralesional aldesleukin, isolated limb infusion or perfusion are associated with a much higher risk of acute toxicities such as pain, limb swelling and ulceration. Intralesional aldesleukin offers the potential for long-term disease control without the use of systemic therapies, such as BRAF inhibitors or ipilimumab, and the toxicities associated with such therapies. Currently there is no standard therapy for patients with local regional disease.

## 1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net clinical benefit to intralesional IL-2 in patients with in-transit metastatic melanoma who have failed surgical therapy for their in-transit metastases (patients with rapidly developing in-transit metastases i.e., lesions recur within 2-3 weeks of surgical excision) and in patients who present with 6 or more in-transit metastases. Intralesional IL-2 offers an effective local therapy for patients with in-transit metastases. It is well tolerated, with a good safety profile, and no reported patient deaths from treatment, based on results from two non-comparative open-label studies demonstrating that this therapy offers high response rates, good disease control rates, a favorable toxicity profile, and survival. It is a small population of patients with only 4.6% of all melanoma patients presenting with only local regional disease. There is currently an unmet need for this patient population. Currently some patients are referred to specialized centers for consideration of isolated limb perfusion or infusion. As there are only a few centers in Canada offer this treatment, eligible patients may have to travel great distances for this therapy. There is also potential risk of morbidity with isolated limb perfusion or infusion. IL-2 injections are easily taught to health care professionals and treatment could be given at most regional cancer centers.

The Clinical Guidance Panel also considered that there are no randomized, controlled studies, albeit there is no standard therapy for this population. As a consequence the review consists of small open label phase 2 studies. The panel felt that it would not be possible to have randomized studies in this population due to small numbers of patients and a lack of a standardized comparator. Patients may be candidates for re-treatment if

they develop subsequent lesions, provided there is a reasonable chance of disease control. For those lesions that do not respond to initial treatment other options should be considered such as systemic therapy. The CGP could not comment on the maximum number of administrations given a lack of data.

# 2 CLINICAL GUIDANCE

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding aldesleukin for in-transit metastatic melanoma. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the pCODR website www.cadth.ca/pcodr.

This Clinical Guidance is based on: a systematic review of the literature regarding aldesleukin conducted by the Melanoma Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on aldesleukin and a summary of submitted Provincial Advisory Group Input on aldesleukin are provided in Sections 3, 4 and 5 respectively.

## 2.1 Context for the Clinical Guidance

### 2.1.1 Introduction

Although primary melanoma can occur in a variety of sites, skin is the most common comprising 95% of cases. In Canada 6500 new cases of primary melanoma were diagnosed in 2014 and approximately 1100 individuals will die from melanoma each year.[1] The incidence of melanoma has been steadily increasing over the past 60-years. Currently the lifetime probability of developing melanoma for women is 1 in 85 and for men is 1 in 67.[4]

Although the majority of melanoma patients present with early stage disease and many are cured by surgery, some will recur with local or distant metastases. A subset of melanoma patients will develop local disease recurrence, some with multiple in transit metastases. Such patients can do well with local therapy, although the majority will subsequently develop distant metastases. A variety of options have been used to treat local recurrences such as surgical excision, systemic treatment with BCG and IL-2, radiation, isolated limb infusion or perfusion, and local injections to try and stimulate an immune response. At the present time there is no standardized therapy for patients with local regional disease. Many patients treated with only local therapy are elderly and have multiple medical comorbidities and are not candidates for systemic therapy. Therefore there is a need for effective local therapy to control the morbidity of local recurrences. Untreated in-transit metastases can be associated with extensive morbidity requiring analgesia, and frequent dressing changes for infected, ulcerated metastases. The incidence of in transit metastases is estimated to be about 4.3%.

### 2.1.2 Objectives and Scope of pCODR Review

To evaluate the effectiveness and safety of aldesleukin (Proleukin™ or interleukin-2, IL-2) as second line of therapy for in-transit metastatic melanoma after surgery has failed.

See Table 3 in Section 6.2.1 for outcomes of interest.

### 2.1.3 Highlights of Evidence in the Systematic Review

*This section describes highlights of evidence in the systematic review. Refer to section 2.2 for the clinical interpretation of this evidence and section 6 for more details of the systematic review.*

Two open label, single arm trials were identified and included in this Clinical Guidance Report. One was a phase II study from Germany. This study by Weide et al. included 51 patients. The outcomes of interest in this study were response rate (by lesion), overall survival and adverse events.[2] The study by Boyd et al. was conducted in London, Ontario and included 39 patients. This study had two independent observers who completed the assessment of response. The outcomes of interest were response rates (by patient) and side effects.[3] In both studies aldesleukin was injected intratumorally.

For a more detailed description of the trial's designs and patient characteristics, please see Table 4 in the *Systematic Review* (Section 6.3.2.1).

**Response rate**

In the Weide et al study, a total of 894 out of 917 (97.5%) individually treated metastases were available to be evaluated for local tumour response. The results demonstrate a complete response rate of 78.7%; a partial response rate of 0.7% rate, a stable disease rate of 16.3%; and a progressive disease rate of 4.3%.[2] The results can be seen in Table 1.

Thirty-three patients had a complete local response to all treated metastases, of whom more patients with stage III disease had a complete response than patients with stage IV disease (82% vs. 40%; $P = .0067$).[2] Thirty-two of these patients were completely free of recognizable tumour after treatment with aldesleukin. Complete response of all treated metastases was not dependent on the number of lesions treated, 73% for patients who had ≥20 treated metastases vs. 66% for patients who had <20 treated metastases; $P = 0.7458$.[2]

**Table 1: Response to treatment in the Weide study[2]**

| | **No of Metastases (%)** | | | | |
|---|---|---|---|---|---|
| | Complete response | Partial response | Stable disease | Progressive disease | P value between groups |
| Response per metastases (n=894) | 704 (78.7) | 6 (0.7) | 146 16.3) | 38 (4.3) | |
| Stage III metastases (n=509) | 493 (96.9) | 3 (0.6) | 5 (1) | 8 (1.6) | <0.0001 |
| Stage IV metastases (n=385) | 211 (54.8) | 3 (0.8) | 141 (36.6) | 30 (7.8) | |
| Visceral metastases not present (n=732) | 677 (92.5) | 4 (0.5) | 35 (4.8) | 16 (2.2) | <0.0001 |

| | No of Metastases (%) | | | | |
|---|---|---|---|---|---|
| | Complete response | Partial response | Stable disease | Progressive disease | P value between groups |
| Visceral metastases present (n=162) | 22(16.7) | 2 (1.2) | 111 (68.5) | 22 (13.6) | |
| Stage III dermal metastases (n=437) | 428 (97.9) | 3 (0.7) | 4 (0.9) | 2 (0.5) | 0.0034 |
| Stage III subcutaneous metastases (n=72) | 65 (90.3) | 0 | 1 (1.4) | 6 (8.3) | |
| Stage IV dermal metastases (n=353) | 200 (56.7) | 0 | 131 (37.1) | 22 (6.2) | 0.0247 |
| Stage IV subcutaneous metastases (n=32) | 11 (34.4) | 3 (9.4) | 10 (31.3) | 8 (25) | |

In the Boyd et al. study, patient response rates were assessed by two independent observers. Overall the response rate (complete plus partial responses) for treatment with aldesleukin was 82%.[3] In the analysis for response by lesion, aldesleukin treatment showed that of the 629 in-transit metastases 150 showed no response to treatment. Therefore the response rate by lesion was 76%, of which all were complete responses.[3] As in the Weide et al study the number of metastases did not predict a patient's response to aldesleukin treatment. (ANOVA $P = 0.46$).[3] Recurrence of disease occurred in four (20%) of the 20 patients who had a complete response. The mean time to relapse was 11 months (range 8.8-14.5 months). Ten out of 12 patients (83%) who had a partial response developed new lesions. The mean time to relapse was 8 months (range 2.8-20.9 months) in this group.[3] The five-year in-transit-free survival was 77% in complete responders and 18.5% in partial responders (log rank $P = 0.0005$). Progressive in-transit disease was seen in 50% of partial responders by 5 months.[3]

### Overall Survival

After 2 years, overall survival in stage III patients was 77% and 53% in stage IV patients in the Weide et al study.[2] In addition overall survival for the subgroup of patients who had stage IV disease without visceral metastases was comparable to that for patients who had stage III disease.[2] Overall survival for 15 patients who had ≥20 metastases was very similar to 33 patients who had <20 metastases. The survival curves overlap and intertwine at the beginning of the treatment and separate only very slightly at around 30 months with the line for > 20 metastases on top.[2]

In the Boyd et al. study the five-year survival for complete responders was 80% and 33% for partial responders (log rank $P = 0.012$).[3] In addition 50% of patients with a partial response died due to their disease within 17.5 months post-treatment.[3]

### *Harms Outcomes*

#### Adverse events

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. The surrounding tissue was not normally affected.[2] A local topical anaesthetic cream and oral metamizole also managed injection pain.[2]

In the Boyd et al. study minor discomfort with injection was felt in all patients. After treatment flu-like symptoms such as, fever, chills and fatigue were observed in 33 patients (85%). Most patients reported that their symptoms were mild and resolved within 24-48 hours and were treated with acetaminophen. Patients who received a higher dose of aldesleukin reported a longer duration of flu-like symptoms.[3]

#### Deaths

In the Weide study there were no study deaths after 25 months of treatment.[2] However, 23% of patients with stage 3 disease died and 50% of patients with stage 4 died.[5]

In the Boyd et al. study three (15%) out of 20 patients who had a complete response that died of disease. The mean time to death in this group was 12.8 months (range 10.5–15.6 months). In the group of partial responders, eight (67%) of the 12 patients died of disease. The mean time to death was 12.2 months (range 3.3–20.6 months).[3]

## 2.1.4 Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

## 2.1.5 Summary of Supplemental Questions

No supplemental questions were addressed in this review.

## 2.1.6 Other Considerations

*See Section 4 and Section 5 for a complete summary of patient advocacy group input and Provincial Advisory Group (PAG) Input, respectively.*

### *Patient Advocacy Group Input*

The following two patient advocacy groups, Melanoma Network of Canada (MNC) and Save Your Skin Foundation (SYSF), provided input on aldesleukin or IL-2 (Proleukin) administered intra-lesionally, for the treatment of in-transit metastasis from melanoma in patients who have failed or are not candidates for surgery or other treatments, and their input is summarized below.

MNC conducted a confidential on-line survey of patients from across Canada. Patients were recruited through a generic letter and email requesting input from patients that had been treated for in-transit metastasis with IL-2 injections or patients who may see a need for this therapy in the future. MNC received a total of 90 patient respondents, of which 26 respondents had been treated with IL-2. The survey had a combination of multiple choice and open ended questions, as well as

rating and options for comment. MNC has provided selected commentary of respondents that are reflective of various perspectives.

SYSF conducted one-on-one interviews with five (5) patients with late stage melanoma patients some of which have gone through the treatment under review, and three (3) caregivers.

From a patient perspective, the symptoms and side effects of in-transit melanoma greatly impacts a patient's quality of life and survival. Respondents report experiencing severe pain, edema and scarring. What often starts as a few lesions on the skin can multiply daily, resulting in massive tumours protruding from the skin that bleed, ooze, smell and continue to spread and can be horribly debilitating and disfiguring. While there have been several drug therapies approved in the last two years for metastatic melanoma, there is currently nothing available for in-transit melanoma. For those respondents who have not used this therapy, the benefits and expectations of this treatment would be should it slow or stop progression and spread of the disease. Respondents that had experienced with IL-2 reported positive effects in that some observed a complete response and the complete disappearance of all signs of cancer. MNC reported that of the 26 respondents that had undergone treatment with IL-2, only two had progression of the disease since treatment. 25% of respondents were 4 to 5 years out from treatment with no recurrence, remaining disease free. The majority indicated the drug was well tolerated with few side effects. The most common side effects reported by respondents included pain and swelling at the injection site. Some respondents had fever and flu like symptoms and a very few respondents had mild nausea. One respondent indicated they could not tolerate the shots, so would not do it again. Patient advocacy groups believe this treatment could address the bridge between in transit disease and full-blown metastatic melanoma based on the positive response outcomes reported by the respondents.

***PAG Input***

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of aldesleukin (interleukin-2):

Clinical factors:

- Interleukin-2 administered intralesionally is a localized treatment option that is less invasive than limb perfusion and less toxic than systemic chemotherapy
- Lack of clarity on maximum number of administrations

Economic factors:

- Very small patient population

## 2.2 Interpretation and Guidance

The systematic review team identified two open-label, single arm trials, one from Germany reported by Weide et al, and the other by Boyd et al. In total, between the two trials, 90 patients were treated with local injections with IL-2. There were no comparison arms in either trial, and in fact there is no standard comparator. The primary endpoint of the German trial was response rate, with survival and adverse events as secondary endpoints. There were a total of 917 lesions injected of which 894 (97.5%) were evaluable

for response. The complete response rate was 78.7% of 894 evaluable lesions, partial response rate of 0.7%, stable disease rate of 16.3%, and a progressive disease rate of 4.3%. Complete response of all treated lesions is not dependent on the number of lesions treated (73% for patients with ≥20 lesions treated versus 66% for patients with <20 lesions treated; p=0.7548). After two years overall survival in Stage III patients was 77% versus 53% in stage IV disease. Overall survival was similar in the 15 patients who had ≥20 metastases versus the 33 patients with <20 metastases.[2]

The study by Boyd et al. 82% of 39 patients had a partial or complete response; however, of the 629 in transit metastasis injected 150 showed no response to treatment (76% response rate). Again the number of lesions treated (< 20 versus > 20) did not predict response rate.[3]

Treatment in both studies was well tolerated, with most toxicity being localized erythema and swelling. This was followed by necrosis of the tumour but no necrosis of normal surrounding tissue. Injection pain was controlled with topical analgesia. 85% of patients in the Weide et al study complained of transient minor flulike symptoms such as fevers, chills and fatigue. There were no study related deaths after 25 months of treatment; however, 23% of patients with stage III disease died and 50% of patients with stage IV disease died.[2] In the Boyd et al study 15% of patients with a complete response died of disease, and 67% of patients with partial response died of disease.[3]

Patients with in-transit metastases often have to live with their disease in constant view and this can be distressing for many patients. They are forced to observe the unrelenting progression of the disease as it tracks more and more proximately. Furthermore, the in-transit metastases can also present as open lesions that are unsightly and/or can be painful. As these lesions often ulcerate and become infected patients require daily medical services, such as home care services, daily dressing changes, and topical and sometimes systemic antibiotics. The lesions are malodourous and hygienically it is difficult for both the care giver and the patient. Patients often require narcotic analgesia and as many patients are elderly there are associated complications of narcotics. If these metastases are located near joints they can severely limit the patient's mobility. Complete or partial responses can eliminate or reduce the size of patients' metastases and lead to improved quality of life through improved mobility, lessened pain, or simply by removing the metastasis from the patient's view thereby improving the patient's psychological well-being.

Two studies show that local injections of IL-2 are an effective treatment with high response rates, low toxicity rates, and good disease control rates. The burden of illness is low, with only 4.6% of all patients presenting with local regional recurrence. This is a distinct subpopulation of patients, some of whom will do well long-term given local therapy. IL-2, given as intralesional therapy, can often be given instead of perfusion or infusion, which may or may not be feasible depending upon the specific location of the disease. Perfusional or infusionsal treatments often require hospitalization and involve operating room resources to administer. In contrast to intralesional Il-2, they are also associated with a much higher risk of acute toxicities such as pain, limb swelling and ulceration. This treatment offers the potential for long-term disease control without the use of systemic therapies and the potential toxicities associated with these therapies. Recently BRAF inhibitors have been introduced in patients who have a BRAF mutation. These drugs have a high cost are associated with toxicities such as fevers, arthralgias, photosensitivity, and skin rash. Treatment is administered on a twice a day dosing schedule. For those patients who are BRAF mutation negative first-line therapy consists of ipilimumab, a CTLA-4 inhibitor. These treatments are associated with immune related adverse events, such as a 10% incidence of grade III/IV diarrhea. Treatment with intralesional IL-2 may spare a substantial proportion of patients with local regional from

systemic therapy with these agents, and thus spare these patients from the associated toxicities of these agents.

Currently there is no standard therapy for patients with local regional disease.

## 2.3 Conclusions

The Clinical Guidance Panel concluded that there is a net clinical benefit to intralesional IL-2 in patients with in-transit metastatic melanoma who have failed surgical therapy for their in-transit metastases (patients with rapidly developing in-transit metastases i.e., lesions recur within 2-3 weeks of surgical excision) and in patients who present with 6 or more in-transit metastases. Intralesional IL-2 offers an effective local therapy for patients with in-transit metastases. It is well tolerated, with a good safety profile, and no reported patient deaths from treatment, based on results from two non-comparative open-label studies demonstrating that this therapy offers high response rates, good disease control rates, a favourable toxicity profile, and survival. It is a small population of patients with only 4.6% of all melanoma patients presenting with only local regional disease. There is currently an unmet need for this patient population. Currently some patients are referred to specialized centers for consideration of isolated limb perfusion or infusion. As there are only a few centers in Canada offer this treatment, eligible patients may have to travel great distances for this therapy. There is also potential risk of morbidity with isolated limb perfusion or infusion. IL-2 injections are easily taught to health care professionals and treatment could be given at most regional cancer centers.

The Clinical Guidance Panel also considered that there are no randomized, controlled studies, albeit there is no standard therapy for this population. As a consequence the review consists of small open label phase 2 studies. The panel felt that it would not be possible to have randomized studies in this population due to small numbers of patients and a lack of a standardized comparator. Patients may be candidates for re-treatment if they develop subsequent lesions, provided there is a reasonable chance of disease control. For those lesions that do not respond to initial treatment other options should be considered such as systemic therapy. The CGP could not comment on the maximum number of administrations given a lack of data.

# 3 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Melanoma Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

## 3.1 Description of the Condition

Melanoma is a malignancy of melanocytes which are distributed throughout the body. Although primary melanoma can occur in a variety of sites, skin is the most common comprising 95% of cases. In Canada 6500 new cases of primary melanoma were diagnosed in 2014 and approximately 1100 individuals will die from melanoma each year.[1] The incidence of melanoma has been steadily increasing over the past 60-years. Currently the lifetime probability of developing melanoma for women is 1 in 85 and for men is 1 in 67.[4]

Staging of melanoma is based on the current AJCC 7th edition classification.[6] The tumour characteristics principally involve the Breslow height, presence or absence of ulceration, and mitotic rate. The detection of microscopic and macroscopic lymph node involvement, ulceration, mitotic rate, LDH and sites of metastatic disease are also incorporated in the staging classification. All of these prognostic factors have important impact upon patient outcomes and also serve to guide management decisions.

Although the majority of melanoma patients present with early stage disease and many are cured by surgery, some will recur with local or distant metastases. A subset of melanoma patients will develop local disease recurrence, some with multiple in transit metastases. Such patients can do well with local therapy, although the majority will subsequently develop distant metastases. A variety of options have been used to treat local recurrences. Some options include surgical excision, radiation, isolated limb infusion or perfusion, and local injections to try and stimulate an immune response. Many patients treated with local therapy only are elderly and have multiple medical comorbidities and are not candidates for systemic therapy. Therefore there is a need for effective local therapy to control the morbidity of local recurrences. Untreated in-transit metastases can be associated with extensive morbidity requiring analgesia, and frequent dressing changes for infected, ulcerated metastases.

The incidence of in transit metastases is estimated to be about 4.3%. In transit metastases are more common in patients who have thicker primary tumors, and those who have ulcerated primaries.

## 3.2 Accepted Clinical Practice

The current clinical management in transit metastases can include both pharmacologic and nonpharmacologic methods. In the absence of extensive metastatic disease treatment modality of choice is surgical excision. Where surgical excision is not possible, isolated limb perfusion or infusion with melphalan plus or minus TNF has been the modality of choice, provided there is access to a center offering this treatment. Radiation therapy may be used if neither surgery or limb perfusion as possible.

Pharmacologic approaches and include BCG, IL-2, or other destination agents. Donald Morton first demonstrated in 1972 that lesions injected with BCG could respond to local therapies, and in addition some non-injected lesions could also respond.

As a minority of patients who present with very localized disease and potentially can have long-term survival disease control local therapies play an integral part the management of these patients.

Isolated limb perfusion is an invasive procedure with associated morbidities and high costs. It is currently performed in a few specialized centers in Canada. It often necessitates patients traveling some distance to the treatment center. Morbidities include lymphedema, skin ulceration, gangrene, and potential limb amputation.

Local therapies have shown high response rates and good rates of disease control. Most of the experience has been with interleukin-2. This is the treatment that is readily adaptable to most cancer centers. Toxicity is minimal with IL-2 injections and typically consists of flu-like symptoms that usually resolve within 24 to 48 hours. Patient's symptoms are easily managed with acetaminophen. Localized therapy can replace limb perfusion or infusions and possibly systemic therapies. New systemic therapies in melanoma can cost over $100,000 per year, and IL-2 injections are substantially cheaper. At the present time there is no standardized therapy for patients with local regional disease, but physicians can employ any of the above-named options. Injectable IL-2 should add substantial cost savings and simplify patient management as they can be treated at their local cancer center. Those patients who do not respond or who recur distantly may require systemic therapy.

## 3.3 Evidence-Based Considerations for a Funding Population

The patient population under discussion is extremely small, and only 4 to 5% of all patients would present with local regional disease only and therefore be candidates for injectable IL-2.

## 3.4 Other Patient Populations in Whom the Drug May Be Used

No other potential uses of the drug that may impact on its utilization were identified.

# 4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

The following two patient advocacy groups, Melanoma Network of Canada (MNC) and Save Your Skin Foundation (SYSF), provided input on aldesleukin or IL-2 (Proleukin) administered intra-lesionally, for the treatment of in-transit metastasis from melanoma in patients who have failed or are not candidates for surgery or other treatments, and their input is summarized below.

MNC conducted a confidential on-line survey of patients from across Canada. Patients were recruited through a generic letter and email requesting input from patients that had been treated for in-transit metastasis with IL-2 injections or patients who may see a need for this therapy in the future. MNC received a total of 90 patient respondents, of which 26 respondents had been treated with IL-2. The survey had a combination of multiple choice and open ended questions, as well as rating and options for comment. MNC has provided selected commentary of respondents that are reflective of various perspectives.

SYSF conducted one-on-one interviews with five (5) patients with late stage melanoma patients some of which have gone through the treatment under review, and three (3) caregivers.

From a patient perspective, the symptoms and side effects of in-transit melanoma greatly impacts a patient's quality of life and survival. Respondents report experiencing severe pain, edema and scarring. What often starts as a few lesions on the skin can multiply daily, resulting in massive tumours protruding from the skin that bleed, ooze, smell and continue to spread and can be horribly debilitating and disfiguring. While there have been several drug therapies approved in the last two years for metastatic melanoma, there is currently nothing available for in-transit melanoma. For those respondents who have not used this therapy, the benefits and expectations of this treatment would be should it slow or stop progression and spread of the disease. Respondents that had experienced with IL-2 reported positive effects in that some observed a complete response and the complete disappearance of all signs of cancer. MNC reported that of the 26 respondents that had undergone treatment with IL-2, only two had progression of the disease since treatment. 25% of respondents were 4 to 5 years out from treatment with no recurrence, remaining disease free. The majority indicated the drug was well tolerated with few side effects. The most common side effects reported by respondents included pain and swelling at the injection site. Some respondents had fever and flu like symptoms and a very few respondents had mild nausea. One respondent indicated they could not tolerate the shots, so would not do it again. Patient advocacy groups believe this treatment could address the bridge between in transit disease and full blown metastatic melanoma based on the positive response outcomes reported by the respondents.

Please see below for a summary of specific input received from the patient advocacy groups. Cited responses are not corrected for spelling or grammar.

## 4.1 Condition and Current Therapy Information

### 4.1.1 Experiences Patients have with In-transit Melanoma

MNC indicated that the symptoms and side effects, impact the disease has on day-to-day life, as well as limitations imposed by the disease, therapies and surgeries are quite varied for patients with melanoma. As melanoma progresses and travels through lymphatic channels of the skin, it creates painful, frightening tumours that bleed, crust, burst, smell and can be horribly debilitating and disfiguring. Stage II and stage III patients have had

little options to treat spread of the disease, other than surgeries and perhaps skin grafts, occasional radiation or topical chemo creams, most of which are highly ineffective.

MNC asked respondents to identify as many symptoms as they had experienced from a list of common adverse effects associated with the disease and treatments. According to MNC, patients commonly experienced pain, scarring, fatigue, mobility issues and fear, depression and anxiety. Below is a list of the key findings from the survey on symptoms and issues that respondents reported.

| Cancer and the different stages of cancer affect people in different ways. What symptoms and issues have you experienced having melanoma? Please select as many responses as appropriate. | | |
|---|---|---|
| **Answer Options** | **Response Percent** | **Response Count** |
| Pain | 58.6% | 34 |
| Scarring or disfigurement | 75.9% | 44 |
| Edema or fluid retention | 31.0% | 18 |
| Lymphedema | 31.0% | 18 |
| Mobility issues (unable to walk or impaired movement) | 27.6% | 16 |
| Gastrointestinal issues | 13.8% | 8 |
| Fluid around lungs | 3.4% | 2 |
| Diarrhea | 24.1% | 14 |
| Headaches | 31.0% | 18 |
| Peripheral neuropathy (nerve pain or damage) | 20.7% | 12 |
| Disrupted sleep | 44.8% | 26 |
| Appetite loss or weight gain | 31.0% | 18 |
| Bleeding problems | 3.4% | 2 |
| Constipation | 3.4% | 2 |
| Fear or anxiety | 69.0% | 40 |
| Fatigue | 62.1% | 36 |
| Depression | 44.8% | 26 |
| Post traumatic stress | 24.1% | 14 |
| Confusion | 20.7% | 12 |
| Nausea or vomiting | 17.2% | 10 |
| Shortness of breath | 13.8% | 8 |
| Incontinence | 3.4% | 2 |
| Neutropenia (is an abnormally low level of neutrophils, a type of white blood cell) | 3.4% | 2 |
| Infections | 17.2% | 10 |
| Other skin conditions including other skin cancers | 17.2% | 10 |
| Damage to organs, such a lungs, liver, brain | 6.9% | 4 |
| None | 6.9% | 4 |
| Other (please specify) | | 16 |

SYSF also noted that ongoing symptoms from patients include loss of energy, fear, anxiety and depression. All of the patients experienced moderate to severe emotional distress. Some patients suffered fatigue, mood swings, loss of vitality and low energy levels.
In addition to the above, MNC reported that respondents experience severe pain, edema, scarring, ulceration with superficial spreading melanoma. What often starts as a few

lesions on the skin can multiply daily, resulting in massive tumours protruding from the skin that bleed, ooze, smell and continue to spread. The visual impact of these tumours causes extreme distress for patients and caregivers. It causes mobility issues and impacts the daily functioning of many patients.

SYSF also noted some other key impact on patients with this disease, include the inability to mentally and physically return to work, the inability to return to "normal" daily life, and anxiety and depression due to their prognosis. Similar to the response to the MNC survey, some patients have also suffered from loss of mobility due to muscle and tissue removal of surgery or treatment.

MNC reported that controlling the spread of the disease is important to patients. According to SYSF, the aspects of melanoma that are most important to control are pain from tumour growth and the pain from those tumours on the patients' body, especially in the areas of movement (e.g., legs, arms etc.).

According to MNC, when caught early, most melanomas are removed by excision, and may be considered cured. SYSF reported that while surgery is an option, there may be problems with surgery if the tumour is in a difficult location on the body. Moreover, the scars from surgery to remove tumours also greatly impact the physical appearance of the patient.

For patients that end up with recurrent disease or continued spread, MNC indicated that there are limited options to stop the progression. Respondents noted that they are horrified to see the pace of growths daily as the disease creeps along the skin towards vital organs or the brain. Respondents compared it to an unrelenting army that is attacking, and that they are defenseless until the disease has spread to such an extent that they are classified as terminally ill, and are then potentially eligible for clinical trials or some of the newer therapies.

To help illustrate the impact on respondents with this cancer, MNC reported some of the comments taken directly from respondents:

- Never knowing how much longer I had to live and where the cancer would move to.
- I was lucky at first. The primary melanoma was removed surgically and it took 6 months to heal. Two years later I had 26 others in the same area. My life was restricted every other week to being at home because of pain and swelling.
- Uncertainty of future and longevity of life, not sure how hard I should work because of uncertain future. All doctor said to me was 5 year survival of 40 %, no prevention ideas; no ideas to self-monitor; no follow up scans; no treatment other than surgery; no regular follow up. What type of cancer is this that leaves us hanging out there in the wind?
- Socially I felt I didn't want to be out and about among people which simply is not me; having been involved in local theatre groups and working with families daily. Many days I simply didn't feel up to doing much of anything with nausea, fatigue and anxiety. My general outlook and way of thinking overall has changed.
- Less activity, problems walking, less social, anxious, angry, resentful, unable to work.

- I had to step back from being the primary care provider to my two young kids for a period of time, I had to quit my job, I couldn't do some of the day to day things that were "normal" for a 30 year old woman.

- Had anxiety and depression before but it increased to the point of needing medication after the diagnosis. I love the outdoors and loved the sun now I am fearful and have restricted my life to avoid the outdoors. This in itself has increased my depression.

I had tumours everywhere. I refused to see my friends and family. I was a freak – fluid was leaking everywhere and I was in constant pain. It felt like an alien had taken over. I would wake in the morning and there were new growths. I planned to kill myself if this didn't stop.

### 4.1.2 Patients' Experiences with Current Therapy for In-Transit Melanoma

MNC noted that there have been several drug therapies approved in the last two years for metastatic melanoma, but nothing for in-transit disease.

SYSF reported that current drugs used to treat melanoma include interferon, surgery, radiation, dacarbazine (DTIC), temozolomide, stereotactic radiation (used on brainstem tumours), vemurafenib and ipilumumab.

According to SYSF, there were few positive results recorded with any of the respondents interviewed that had experienced with interferon, DTIC and temozolomide. While these respondents felt these treatments probably slowed the spread of disease, but they were not effective in preventing the metastasis. Respondents stated that they experienced fatigue and pain from the cancer while using these therapies. The adverse side effects that were most difficult to tolerate for respondents were extreme fatigue, diarrhea, skin issues, nausea, rash, low sodium levels and colitis. According to SYSF, many side effects have been so severe that patients were not able to perform daily functions.

For patients with locally advanced melanoma, which develop in-transit cutaneous metastases, respondents feel surgery is a temporary measure with new lesions often arising quickly, adjacent to the surgical site. Radiation therapy patients feel only works in the direct area treated.

According to MNC, of those surveyed with metastatic disease, 23% of respondents had more than 5 surgeries to try to control in transit spread of the disease. 46% of respondents had at least two surgeries. 20% of respondents had been treated with radiation. The side effects reported from pre-treatment with surgical excision and radiation included lymphedema, scarring, infection, cellulitis, nerve damage, pain. Respondents also reported having significant psycho social issues, including anxiety, depression and fear that not only go along with the diagnosis, but intensify as they visibly see the disease progressing on their skin – often with new tumours arising daily.

MNC reported that 26% of respondents had been treated with interferon, as the standard adjuvant therapy, and of those patients, 100% of respondents had seen progression of the disease. Previous surveys conducted by MNC have indicated side effects from interferon included extreme flu like symptoms and fatigue, cognitive impairment, nausea, fever, rigours, pain, arthritis, headaches, liver failure, low platelet counts, diarrhea, and severe depression. Many of these side effects last beyond a year, depending on the patient's

ability to tolerate the therapy. Most respondents do not complete the full year treatment due to side effects. One respondent stated: "*I now suffer from clinical depression and have been under medical treatment for that since my interferon treatment ended. My memory has been impacted as well*."

SYSF stated that 90% of the respondents responded "yes" that they would "try anything" to win their fight with this cancer. The other 10% of respondents responded, "yes" depending on the severity of the side of effects.

In addition, SYSF indicated that other challenges that patients face include financial implications (i.e., patients could not work while being administered the drugs and have to travel to specific centres for the IL2 injection).

While current therapies have a better survival rate, getting the right patient to the right treatment in the right centers are issues of concerns for patients. Both SYSF and MNC found that there is a large unmet need for these patients due to lack of treatment, in particular when doctors are unable to control spread of the disease through surgery. MNC reported that for patients with in-transit metastasis where surgery is limited or no longer an option, IL-2 injection may be viewed as a therapeutic option that may address this gap in treatment.

### 4.1.3 Impact of In-transit Melanoma and Current Therapy on Caregivers

SYSF conducted interviews with three caregivers who had a close family member who was diagnosed with melanoma. Respondents reported on the emotional distress due to an uncertain prognosis and unknown treatment plan, cancellation of any long-term plans, and time away from work to assist the patient all impacted the routine of the caregiver.

Respondents indicated that there is a lack of information about the side-effects, which result in confusion and distress. As such, respondents found it difficult to know if the symptoms were treatment related or cancer related. The main challenge for some respondents was finding treatments that might work for their loved ones.

Respondents also reported that the cost to the family to travel to centers for treatment is very difficult.

MNC did not include caregivers in this survey as MNC have surveyed caregivers in past submissions. According to previous surveys, it was found that there were negative impacts such as the loss of income either from the patient's inability to work or from the caregiver having to take time off work or having to leave employment to care for the patient. There are also significant impacts on the family unit – mental health, anxiety, stress, physical demands of caring for an ill family member.

Moreover, additional costs and time for attending appointments, managing home care, taking on additional home and family management responsibilities also greatly impact caregivers. Some of these challenges include having to communicate the situation to children and managing their anxiety as well as other family members and friends. MNC reported that trying to be a caregiver both physically and emotionally while dealing with their own stress and challenges could lead to a breakdown in the marriage.

Below are some key statements from patients and caregivers that MNC has highlighted to help provide context on the outcome when treatments are seen to be effective for the individual patient:

- In addition to the obvious physical benefits of the slowing or elimination of the cancer having access to this therapy plays a big role in the emotional and mental being of a patient in knowing there is something being done beyond a "wait and see"!

- Less invasive, so he was able to return to work quickly and we could all breathe a sigh of relief, believing that this may be it. Maybe we have beaten this thing. Can we have hope?
- More mobility-energy, better quality of living.

It reduced the amount of time this disease was consuming of our lives. No more hospital; no more waiting and we can try to move forward, work and enjoy life again with our family.

## 4.2 Information about the Drug Being Reviewed

### 4.2.1 Patient Expectations for and Experiences To Date with Aldesleukin or IL-2

According to SYSF, the respondents interviewed are hoping that this treatment will help with long-term survival and can add years to a very poor prognosis.

MNC indicated that treatment with IL-2 injections for in-transit metastasis would be considered a significant treatment if it slowed or stopped progression and spread of the disease, if surgery was no longer an option. For those who have not used this therapy, IL-2 injections would fill a gap in treatment that currently does not exist. The statements below represent some of the benefits that respondents expect with this treatment option under review. These include:

- Few side effects would allow for much better quality of life.

- It would be of tremendous benefit if it would control and possibly eliminate the disease. I would try anything that could possibly help me and extend my life.

- As a localized treatment you would not get as sick as I would have if having other chemotherapy; would have had surgery only once rather than attempting to chase and remove each spot

- I would think it would give the patient hope of survival or longer survival rate, instead of sitting and waiting and not doing anything to try to cure it.

- I think survival is a pretty big benefit, anything that slows or stops melanoma growth is beneficial.

According to SYSF, respondents that had experienced with IL-2 noted positive effects in that some observed a complete response and the complete disappearance of all signs of cancer. Other respondents had other tumours appear and went for additional treatment.

MNC reported that of the 26 respondents that had undergone treatment with IL-2, only two had progression of the disease since treatment. 25% of respondents were 4 to 5 years out from treatment with no recurrence, remaining disease free.

The most common side effects reported by SYSF respondents were pain and swelling at the injection site. However, all respondents agreed that the discomfort was mild and short lived. Some respondents had fever and flu like symptoms and a very few respondents interviewed had mild nausea.

MNC also asked their respondents about the side effects experienced with the therapy. The majority indicated the drug was well tolerated with few side effects. Most were able to return to normal functioning relatively quickly. One respondent indicated she could not tolerate the shots, so would not do it again. Below is the list of responses surveyed.

| If you have been treated with IL-2 (interleukin 2) injections to control or eliminate your disease, what side effects of the treatment did you or are you experiencing? | | |
|---|---|---|
| **Answer Options** | **Response Percent** | **Response Count** |
| Pain | 30.0% | 6 |
| Burning | 30.0% | 6 |
| Infection | 20.0% | 4 |
| Joint pain | 10.0% | 2 |
| Fever or flu like symptoms | 40.0% | 8 |
| None | 40.0% | 8 |
| Other (please specify) | | 12 |

Some respondents reported the following comments:

- Itching and a rash
- All symptoms start to occur 3 hrs after injections, disappear 2 to 3 days later.
- Leg had weeping sores which lasted 8 months
- Slight flu like symptoms on the first few treatments which diminished as treatment progressed.
- Slight fever, hot and redness at the injection sights

According to SYSF, all respondents reported much more manageable symptoms of pain and swelling at the injection site and agreed they were short-lived. They were treated with painkillers. In addition, all respondents on this treatment found the side-effects to be manageable compared to current therapies of surgery or radiation.

Similarly, MNC reported that the 24 respondents who answered this question agreed that side effects were manageable.

| Were the side effects of the treatment manageable or worth it in your opinion? | | |
|---|---|---|
| **Answer Options** | **Response Percent** | **Response Count** |
| Yes | 100.0% | 24 |
| No | 0.0% | 0 |

Below are some of the comments reported by these respondents.

- A little pain the next day
- Was well manageable
- I did not drive, but after 2 days able to resume most day to day activities.
- Side effects occurred within 4-5 hours but were gone within 24.
- the discomfort was well worth the end result
- Side effects were minimal and treatment was very successful.
- Absolutely I had hardly any side effects and the results were incredible.

Respondents who were interviewed by SYSF reported the benefits outweighing the risks of IL-2. Generally, the symptoms seem to be much more tolerable than current therapies and it increases the overall survival rate of a patient with melanoma.

## 4.3 Additional Information

According to MNC, this is a unique situation, where a therapy is being used to address a large gap in the treatment protocol for patients. MNC believes this therapy should be used on a broader basis to prevent spread of the disease – at which point impact on quality of life, patient survival, time spent in treatment and costs to the health system. In light of what recently approved therapies for melanoma cost, and the potential adverse side effects as well as the efficacy of the therapies, IL-2 injections would be a positive addition to very slim treatment options. As noted above, patients' responses are very positive that it would truly be a large benefit for those that may be eligible, and few downsides for all stakeholders.

Similarly, SYSF report that many melanoma patients indicated their concerns that there are still not enough treatment options available in a timely fashion. Some had to find this treatment on their own and most had to travel outside of their province to get the treatment. This added emotional and financial stress to an already very stressful diagnosis. There is also concern that their needs are not being met and that their issues are not being heard. SYSF also believes that there should be unified melanoma protocols across the country.

MNC commends the physicians for making such an enormous effort without support of the drug company to pursue this viable option on behalf of patients.

# 5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.pcodr.ca). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

**Overall Summary**

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of aldesleukin (interleukin-2):

Clinical factors:

- Interleukin-2 administered intralesionally is a localized treatment option that is less invasive than limb perfusion and less toxic than systemic chemotherapy
- Lack of clarity on maximum number of administrations

Economic factors:

- Very small patient population

Details of these factors and other factors are outlined below.

## 5.1 Factors Related to Comparators

Patients with in-transit melanoma that have failed surgery (e.g. immediate recurrence or too many lesions) have been treated with interleukin-2 provided through the manufacturer's compassionate program for several years. However, the manufacturer abruptly ceased the compassionate program in January 2014. Alternate treatments may be isolated limb perfusion, systemic chemotherapy or oral BRAF inhibitors. PAG noted that intralesional administration of interleukin-2 provides a less invasive and more tolerable treatment option.

## 5.2 Factors Related to Patient Population

There is a very small number of patients who develop in-transit metastasis from melanoma. Since the closure of the manufacturer's compassionate supply program, there is an unmet need for this small group of patients where intralesional interleukin-2 has become the standard of care.

## 5.3 Factors Related to Dosing

PAG noted that the amount of interleukin-2 used depends on the number of lesions and there is the potential for drug wastage. PAG also noted that intralesional interleukin-2 would be given every two weeks for four to eight administrations and would like clarity on the maximum number of administrations.

## 5.4 Factors Related to Implementation Costs

PAG also noted that interleukin-2 for this patient population would be a small drug budget impact but would likely save the health care resources required for limb perfusion or systemic chemotherapy.

## 5.5 Factors Related to Health System

PAG noted that the intralesional administration of interleukin-2 requires specialized treatment centers but patients can be treated on an out-patient basis. This may be a tertiary hospital's surgical day unit or could be in the chemotherapy clinics. Implementation of this treatment protocol would depend on how each province organizes care for patients with in-transit metastasis from melanoma and under what program they each would administer interleukin-2. In some provinces, these patients are treated out-of-province because of the surgical expertise needed to deliver the treatment.

In three of the provinces, interleukin-2 has been used to treat in-transit metastasis from melanoma with compassionate supply from the manufacturer. Other provinces would need to coordinate the appropriate resources to implement the treatment protocol and health care providers would need to become familiar with the intralesional administration of interleukin-2.

PAG noted that chair time in chemotherapy infusion clinics is not required but time in clinics or day surgery program would be needed.

## 5.6 Factors Related to Manufacturer

No other factors that potentially affect the feasibility of implementing a funding recommendation were identified.

# 6 SYSTEMATIC REVIEW

## 6.1 Objectives

To evaluate the effectiveness and safety of Aldesleukin (Proleukin™ or Interleukin-2, IL-2) as second line of therapy for in-transit metastatic melanoma after surgery has failed.

## 6.2 Methods

### 6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

**Table 2. Selection Criteria**

| Clinical Trial Design | Patient Population | Intervention | Appropriate Comparators* | Outcomes |
|---|---|---|---|---|
| Randomized control trials<br><br>In the absence of RCT data, fully published phase 2 clinical trials investigating the efficacy of aldesleukin should be included. Reports of trials with only a dose-escalation design should be excluded. Reports of trials with a mixed design are to be included only if separate data were reported for the cohort of patients who were included in the efficacy-determining phase of the study. | in-transit metastatic melanoma | Aldesleukin | -Best supportive care<br>- No comparator | -Response rate<br>**-Overall survival**<br>-Grade 3 and 4 adverse events,<br>**-Quality of life** |
| **Notes:**<br>** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)* | | | | |

### 6.2.2 Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946- ) with in-process records & daily updates via Ovid; EMBASE (1980- ) via Ovid; The Cochrane Central Register of Controlled Trials (2010, Issue 2) via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were [Aldesleukin, Proleukin™, or Interleukin-2 or IL-2] and [in-transit- melanoma].

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication. Retrieval was limited to the English language.

The search is considered up to date as of May 7, 2015.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicatrials.gov and Ontario Institute for Cancer Research – Ontario Cancer Trials) and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and [Include other conferences as per the guidance provided in S2 on tumour type, e.g. ESMO, ASH, SABCS] were limited to the last five years. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for information as required by the pCODR Review Team.

### 6.2.3 Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

### 6.2.4 Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

### 6.2.5 Data Analysis

No additional data analyses were conducted as part of the pCODR review.

### 6.2.6 Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

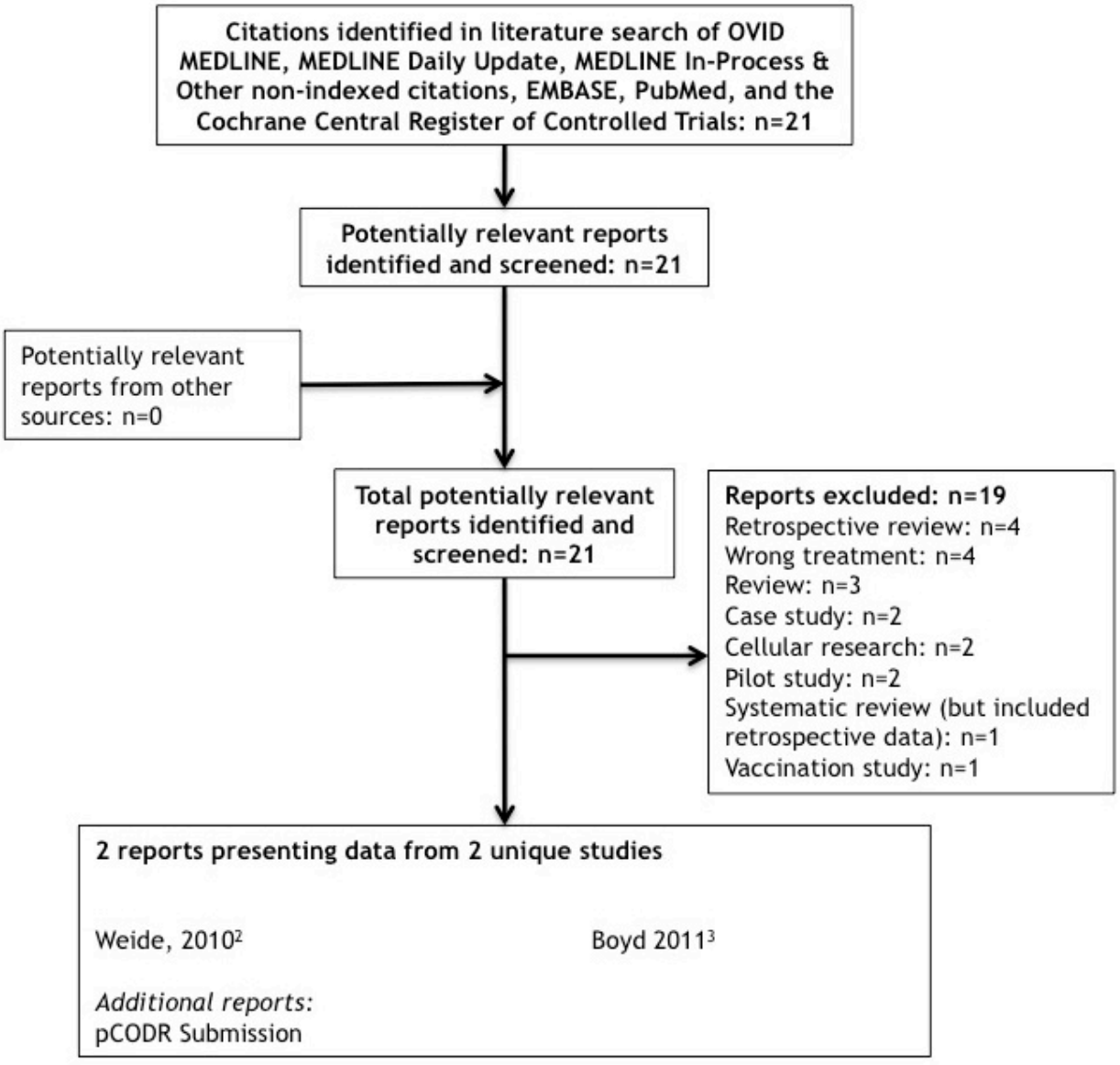
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

## 6.3 Results

### 6.3.1 Literature Search Results

Of the [21] potentially relevant reports identified, [2] studies were included in the pCODR systematic review [2,3] and [11 studies were excluded. Studies were excluded because they were, [retrospective reviews, 7-10 ], [wrong treatments, 11-14], [reviews, 15-17], [case studies, 18,19], [cellular research, 20,21], [pilot studies, 22,23], [systematic review, 24], [vaccination study, 25].

**Figure 1: QUOROM Flow Diagram for Inclusion and Exclusion of studies**




*Note: Additional data related to the studies by Boyd and Weide were also obtained through requests to the Submitter by pCODR*

### 6.3.2 Summary of Included Studies

Two prospective studies were identified that met the eligibility criteria of this systematic review (see Table 3).

#### 6.3.2.1 Detailed Trial Characteristics

**Table 3. Summary of Trial characteristics of the included Studies**

| Trial Design | Key Inclusion Criteria | Intervention and Comparator | Outcomes |
|---|---|---|---|
| NCT00204581 [26 2]<br><br>Phase 2 Open Label study<br><br>Weide et al, 2010<br><br>N=51<br><br>2 sites in Germany<br><br>Start date: August 2003<br><br>Completion date: December 2009<br><br>Funded by: Deutsche Forschungsgemeinschaft grant SFB685 and a research grant from Novartis GmbH | Inclusion Criteria:<br>• Age 18+<br>• Informed consent<br>• Histologically proven melanoma<br>• Have confirmed stage IIIB or stage IV disease (AJCC 2002) with skin or soft-tissue metastases<br><br>Exclusion Criteria:<br>• Pregnant or lactating women<br>• Patients with severe cardiac disease<br>• Patients with severe liver disease or severe renal disease<br>• Simultaneous immunosuppressive treatment (e.g. steroids)<br>• Simultaneous chemotherapy<br>• Pretreated soft-tissue or skin metastases (e.g. cryo-, radiotherapy) | For preparation of aldesleukin, 18 MIU of recombinant human IL-2 were dissolved in 6 mL glucose 5% supplemented with 0.2% human serum albumin. Aldesleukin was injected intratumorally. Single doses ranged between 0.3 MIU and 6 MIU, depending on the lesion size. One injection per lesion was applied for doses per lesion up to 3 MIU, and 2 injections were applied for doses >3 MIU per lesion. | Primary Outcome<br>• Efficacy in regard to complete and partial response<br><br>Secondary Outcomes<br>• Overall survival<br>• Side-effects |
| Open label study [3]<br><br>Boyd et al, 2011<br><br>N=39<br><br>1 centre in Ontario Canada | Inclusion criteria<br>• metastatic in-transit melanoma<br><br>Exclusion Criteria<br>•Patients with local recurrence<br>•Distant metastases (all patients had pre-treatment CT scans of head, chest, abd/ pelvis. CT neck was | Aldesleukin was prepared using a 5 μ/ml solution.<br><br>Injections were conducted biweekly with a goal of four sessions. | • Response rate<br>• Side effects |

| Table 3. Summary of Trial characteristics of the included Studies | | | |
|---|---|---|---|
| **Trial Design** | **Key Inclusion Criteria** | **Intervention and Comparator** | **Outcomes** |
| Funding – No funding part of regular clinical work | performed if indicated (i.e. for head and neck in-transit metastases).[5] | | |
| **MIU** = million international units | | | |

### *a) Trials*

Two trials met the inclusion criteria for this review. One was a phase II study from Germany and the other was a study conducted in London Ontario. The study by Weide et al. from Germany was conducted at two sites. The trial was open labelled and not blinded. Funding was provided by the Deutche Forschungsgemeinschaft grant SFB685 and a research grant from Novartis GmbH. The outcomes of interest in this study were response rate, overall survival and adverse events. The study ran from August 2003 until December 2009.[2] Each treated metastasis was evaluated separately for clinical response between 4 and 8 weeks, after stopping aldesleukin treatment and every 3 months after that.[2] The following definitions were used in the study: "a complete response (CR) of a treated lesion was defined as the disappearance of any evidence of vital tumor and lack of tumor growth after stopping injections over a period of at least 6 months. A partial response (PR) was defined as a decrease ≥30% in the greatest dimension (longest diameter [LD]). Stable disease (SD) was defined as neither sufficient shrinkage to qualify for a PR nor sufficient increase to qualify as progressive disease (PD). PD was defined as an increase ≥20% increase in the LD of the lesion."[2] Study follow-up consisted from the first aldesleukin injection to the date of last contact or death. Only deaths that were caused by melanoma were considered for the survival analyses. The date of last survival update was April 2009. Overall survival estimates were done using Kaplan-Meier analyses and differences in response rates were calculated by using a 2-tailed Fisher exact test."[2]

The study by Boyd et al. was open labelled and two independent observers completed the assessment of response. It was not stated what phase the study was. The study ran from 2005 and 2009 in London, Ontario Canada.[3] There was no funding for the Boyd et al study. Aldesleukin injections were completed as part of clinical care. All research work was done without charge.[5] Response was rated using the Response Evaluation Criteria In Solid Tumors (RECIST) criteria. "The RECIST group defines complete response as the disappearance of all target lesions, partial response as at least a 30% decrease in the sum of the longest diameter of target lesions, progression as at least a 20% increase in the sum of the longest diameter of target lesions, and stable disease as insufficient to qualify as either partial response or progression."[3] However the study simplified these categories is to complete response, partial response, and no response. The no response category captures the stable and progressive disease groups.[3] Response was measured from four weeks from the final IL-2 injection.[3] In addition biopsies were done after treatment to confirm the RECIST classification. All biopsies were reviewed by an independent, blinded pathologist.[3]

### *b) Populations*

In the study by Weide et al. a total of 51 patients were included. The study by Boyd et al. had a total of 39 patients. The patient characteristics are summarized in Table 4.

**Table 4: Patient Characteristics**

| Characteristics | Weide et all N=51 (%)[2] | Boyd et al. N=39 (%)[3] |
|---|---|---|
| Men | 21(44) | 16 |
| Women | 27 (56) | 23 |
| Average age, y(range) | 69 (37-88) | 69 (32-91) |
| Stage | | |
| Stage III | 33 (69) | 39[5] |
| IIIB | 17 | NR |
| IIIC | 16 | 13[5] |
| Stage IV | 15 (31) | NR |
| M1a | 8 | NR |
| M1b | 3 | NR |
| M1c | 4 | NR |
| Visceral metastases present | 5 | NR |
| Site of treated metastases | | |
| Dermal only | 28 (58) | NR |
| Subcutaneous only | 11 (23) | NR |
| Combined | 9 (19) | NR |
| No. of treated metastases | | |
| <20 | 33(69) | NR |
| ≥20 | 15 (31) | NR |
| Previous therapies | | |
| Surgery in stage III/IV | 28 (58) | NR |
| Limb perfusion | 2 (4) | 6 |
| Radiotherapy | 2 (4) | 12 |
| Adjuvant interferon alpha | 14 (29) | NR |
| Systemic chemotherapy | 11(23) | 10 |
| Breslow thickness or original melanoma | NR | 3.5mm (range 0.4-12.0mm) |
| Mean number of in-transit metastases per patient | Nr | 12 (range (1-57) |

| Characteristics | Weide et all N=51 (%)[2] | Boyd et al. N=39 (%)[3] |
|---|---|---|
| Average length of follow-up | NR | 30.4 months (range 2.2-66.6 months) |
| Abbreviations: NR = Not reported | | |

### c) *Interventions*

In the study by Weide et al. "18 MIU of recombinant human aldesleukin were dissolved in 6 mL glucose 5% supplemented with 0.2% human serum albumin. Aldesleukin was injected intratumorally. Single doses ranged between 0.3 MIU and 6 MIU, depending on the lesion size. One injection per lesion was applied for doses per lesion up to 3 MIU, and 2 injections were applied for doses >3 MIU per lesion. Treatment was initiated at 3 MIU aldesleukin daily, and the dose was escalated by 1.5 MIU each treatment day up to the desired total dose according to the number of lesions and treatment guidelines. Up to 25 lesions were treated simultaneously; however, if more lesions were present, then they were treated alternately or subsequently. The treatment schedule was 3 times weekly on an outpatient basis."[2] The treatment guidelines used in the study are below in Table 5.

**Table 5: Study treatment guidelines[2]**

| Size of Individual Lesion, mm | Minimal Single Dose of aldesleukin per Lesion, MIU | Volume Stock Solution, mL | Duration of Treatment, wk |
|---|---|---|---|
| <2 | 0.3 | 0.1 | 2 |
| <5 | 0.6 | 0.2 | 2 |
| <10 | 1.2 | 0.4 | 3 |
| <20 | 3.0 | 1.0 | 4 |
| ≥20 | 6.0 | 2.0 | 4 |

The median duration of aldesleukin treatment was 6 weeks (range, 1-32 weeks) for the Weide study as several patients received a few later treatments for newly developing metastases. The applied median total dose was 68.5 MIU aldesleukin (range, 13.5-548.1 MIU). The median number of metastases treated per patient was 12. The highest daily dose was 16 MIU IL-2.[2]

In the study by Boyd et al. Aldesleukin was prepared using a 5 μ/ml solution. The drug was administered by intra-lesional injection. The drug was distributed among the in-transit metastases based on number and size of lesions at the discretion of the senior author of the study.[3] Proportionately more volume was given to lesions that were larger or more symptomatic than lesions that were flatter and asymptomatic. The total dose was generally kept at or below 2.4 ml (12 μ). Injections were done biweekly with an objective of four sessions.[3] The decision to discontinue aldesleukin treatment was made if the patient had lesions that were growing despite treatment, or if there was no observable response by four injections. Patients that seemed to be responding, or most of their lesions

appeared to be responding, but did not have a complete response by the 4th session, were given more injections to a maximum of seven.[3] The mean number of injection sessions was five (range one to seven) biweekly injections. On average, patients received 2.08 ml (range 0.3–3.2 ml), or 10 µ, of aldesleukin dispersed into their in-transit lesions.[3]

### *d) Patient Disposition*

In the study by Weide et al, two patients were excluded after they provided informed consent because progressive visceral disease was detected at baseline staging and required chemotherapy. Additionally, another patient had no treatment or follow-up data were available.[2] The median follow-up was 25 months from the start of treatment (range, 4-68 months).[2]

In the Boyd et al study all patients were well enough to come to out-patient clinic visits on a regular basis. The patients were followed for an average of 30.4 months (range 2.2-66.6 months).[5] No additional information on patient disposition was available in the study paper or through the checkpoint meeting.

### *e) Limitations/Sources of Bias*

Both studies were single arm open label studies and therefore there was no comparator. Since there is no comparative evidence for aldesleukin the efficacy of it versus 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. In addition, the two studies administered aldesleukin in different ways. While Weide et al reported treatment guidelines for their study, which included minimal single doses of aldesleukin per lesion based on the size of individual lesions, In the study by Boyd et al. aldesleukin was distributed among the in-transit metastases based on number and size of lesions at the discretion of the senior author of the study.[3] There is a greater potential for bias in the method described by Boyd et al as the lead investigator could have knowingly or unknowingly varied the dosages of aldesleukin. In addition the source of funding is not listed for the study and this study was not listed in clinical trials.gov. While this may be because of no external funding it is not transparent. However, the Boyd et al. study did have response rates assessed by independent observers. Neither study reported quality of life data.

## 6.3.2.2 Detailed Outcome Data and Summary of Outcomes

### *Efficacy Outcomes*

#### Response

In the Weide study a total, 894 of 917 (97.5%) individually treated metastases were available to be evaluated for local tumour response. The results can be seen in Table 6. The results demonstrate a complete response rate of 78.7%; a partial response rate of 0.7% rate, a stable disease rate of 16.3%; and a progressive disease rate of 4.3%.[2]

**Table 6: Response to treatment in the Weide study[2]**

| | No of Metastases (%) | | | | |
|---|---|---|---|---|---|
| | Complete response | Partial response | Stable disease | Progressive disease | P value between groups |
| Response per metastases (n=894) | 704 (78.7) | 6 (0.7) | 146 (16.3) | 38 (4.3) | |
| Stage III metastases (n=509) | 493 (96.9) | 3 (0.6) | 5 (1.0) | 8 (1.6) | <0.0001 |
| Stage IV metastases (n=385) | 211 (54.8) | 3 (0.8) | 141 (36.6) | 30 (7.8) | |
| Visceral metastases not present (n=732) | 677 (92.5) | 4 (0.5) | 35 (4.8) | 16 (2.2) | <0.0001 |
| Visceral metastases present (n=162) | 27(16.7) | 2 (1.2) | 111 (68.5) | 22 (13.6) | |
| Stage III dermal metastases (n=437) | 428 (97.9) | 3 (0.7) | 4 (0.9) | 2 (0.5) | 0.0034 |
| Stage III subcutaneous metastases (n=72) | 65 (90.3) | 0 | 1 (1.4) | 6 (8.3) | |
| Stage IV dermal metastases (n=353) | 200 (56.7) | 0 | 131 (37.1) | 22 (6.2) | 0.0247 |
| Stage IV subcutaneous metastases (n=32) | 11 (34.4) | 3 (9.4) | 10 (31.3) | 8 (25.0) | |

Thirty-three patients had a complete local response to all treated metastases. In this group of complete responders, more patients with stage III disease had a complete local response to all treated metastases than patients with stage IV disease (82% vs. 40%; $P = .0067$).[2] Thirty-two complete responders were completely free of any recognizable tumour after treatment with aldesleukin. Complete response of all treated metastases was not dependent on the number of lesions treated, 73% for patients who had ≥20 treated metastases vs. 66% for patients who had <20 treated metastases; $P = 0.7458$.[2]

In the Boyd et al. study, patient response rates were assessed by two independent observers. The response to treatment can be seen in Table 7. Overall, the response rate for treatment with aldesleukin was 82%.[3] In the analysis for response by lesion, of the 629 in-transit metastases, 479 (76%) had a complete response and 150 (24%) showed no response to treatment.[3] This is not broken down into types of response. As in the Weide study the number of metastases (19.1 in complete responders, 13.7 in partial responders, 11.9 in non-responders) did not predict a patient's response to aldesleukin treatment. (ANOVA $P = 0.46$).[3] Moreover, the average duration for in-transit metastases to form after the initial primary melanoma treatment (11.4 months in complete responders, 18.6 months in partial responders and 15 months in non-responders) did not appear to influence the response to aldesleukin treatment (ANOVA $P = 0.33$).[3]

**Table 7: Response rate in the Boyd et al study[3]**

| Complete response n (%) | Partial response n (%) | No response n (%) |
|---|---|---|
| 20 (51) | 12 (31) | 7 (18) |

In the Boyd et al. study, recurrence of disease occurred in four (20%) of the 20 patients who had a complete response. The mean time to relapse was 11 months (range 8.8-14.5 months). Ten out of 12 patients (83%) who had a partial response developed new lesions. The mean time to relapse was 8 months (range 2.8-20.9 months) in this group.[3] The five-year in-transit free survival was 77% in complete responders and 18.5% in partial responders(log rank $P = 0.0005$). Progressive in-transit disease was seen in 50% of partial responders by 5 months.[3]

**Overall Survival**

After 2 years, overall survival in stage III patients was 77% and 53% in stage IV patients in the Weide et al study.[2] In addition overall survival for the subgroup of patients who had stage IV disease without visceral metastases was comparable to that for patients who had stage III disease.[2] Overall survival for 15 patients who had ≥20 metastases was very similar to 33 patients who had <20 metastases. The survival curves overlap and intertwine at the beginning of the treatment and separate only very slightly at around 30 months with the line for ≥ 20 metastases on top.[2]

In the Boyd et al. study the five-year survival for complete responders was 80% and 33% for partial responders (log rank $P = 0.012$).[3] In addition 50% of patients with a partial response died by to their disease by 17.5 months post-treatment.[3]

### *Quality of Life*

Quality of life data were unavailable for both studies.

### *Harms Outcomes*

**Adverse events**

In the Weide study grade 1 and 2 adverse events were collected on 48 patients. 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. The surrounding tissue was not normally affected.[2] A local topical anaesthetic cream and oral metamizole also managed injection pain.[2] Adverse events are summarized in Table 8. Additionally one patient had generalized urticaria. However, this was controlled by prophylactic antihistaminic treatment and did not recur. One patient presented with a worsening of a pre-existing atopic dermatitis, another patients had a single episode of mild cardiac arrhythmia, and another had vitiligo-like depigmentation around the treated metastases.[2]

**Table 8. Adverse events in the Weide study[2]**

| | N= 48 (%) |
|---|---|
| Fever | 28 (58) |
| Fatigue | 17 (36) |
| Nausea | 16 (34) |
| Stomach pain | 4 (8.3) |
| Myalgia | 4 (8.3) |
| Headache | 4 (8.3) |
| Itching exanthema | 3 (6.3) |
| Dry oral mucosa | 2 (4.2) |
| Pruritus | 2 (4.2) |
| Hair loss | 1 (2.1) |
| Diarrhea | 1 (2.1) |

In the Boyd et al. study minor discomfort with injection was felt in all patients. After treatment flu-like symptoms such as, fever, chills and fatigue were observed in 33 patients (85%). Most patients reported that their symptoms were mild and resolved within 24-48 hours and were treated with acetaminophen. Patients who received a higher dose of aldesleukin reported a longer duration of flu-like symptoms.[3]

**Deaths**

In the Weide study there were no study deaths after 25 months of treatment thus showing that there is a good chance for long-term survival in patients who survived the first 2 years.[2] However, 23% of patients with stage 3 disease died and 50% of patients with stage 4 died.[5]

In the Boyd et al. study there was three (15%) out of 20 patients who had a complete response that died of disease. The mean time to death in this group was 12.8 months (range 10.5–15.6 months). In the group of partial responders, eight (67%) of the 12 patients died of disease. The mean time to death was 12.2 months (range 3.3–20.6 months).[3]

## 6.4 Ongoing Trials

No ongoing trials were found.

# 7 SUPPLEMENTAL QUESTIONS

No supplemental questions were addressed in this review

# 8 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Melanoma Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on aldesleukin (Proleukin) for in-transit melanoma Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The pCODR Melanoma Clinical Guidance Panel is comprised of three clinical oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the pCODR website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

# APPENDIX A: LITERATURE SEARCH STRATEGY

1. EBM Reviews - Cochrane Database of Systematic Reviews 2005 to January 2015, Embase 1996 to 2015 Week 08, Ovid MEDLINE(R) Daily Update February 26, 2015, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

1. intransit melanoma.mp
2. * melanoma/dt
3. 1 or 2
4. metastasis.mp
5. 3 and 4
6. *recombinant interleukin-2/
7. IL-2.mp.
8. intra-lesional interleukin-2.mp
9. proleukin.mp.
10. aldesleukin.mp.
11. 6 or 7 or 8 or 9 or 10
12. 5 and 11
13. remove duplicates from 12

**2. Literature Search via PubMed**

1. (melanoma) and ((in transit) OR in-transit))
2. publisher[sb]
3. 1 AND 2

**3. Grey Literature Searches**
**Clinical Trial Registries:**
U.S. NIH ClinicalTrials.gov
www.clinicaltrials.gov
Ontario Institute for Cancer. Ontario Cancer trials
www.ontariocancertrials.ca
Search terms: melanoma and in transit

**Select International Agencies:**
Food and Drug Administration (FDA):
www.fda.gov
Search terms: melanoma and in transit

**Conference Abstracts:**
**American Society of Clinical Oncology (ASCO)**
**via the *Journal of Clinical Oncology* search portal: http://jco.ascopubs.org/search**

Search terms: melanoma and in transit

## REFERENCES


1. Canadian Cancer Society's Steering Committee. Canadian cancer statistics 2014 [Internet]. Toronto: Canadian Cancer Society; 2014. [cited 2014 Oct 3]. Available from: http://www.cancer.ca/~/media/cancer.ca/cw/cancer%20information/cancer%20101/canadian%20cancer%20statistics/canadian-cancer-statistics-2014-en.pdf.

2. Weide B, Derhovanessian E, Pflugfelder A, Eigentler TK, Radny P, Zelba H, et al. High response rate after intratumoral treatment with interleukin-2: results from a phase 2 study in 51 patients with metastasized melanoma. Cancer. 2010;116(17):4139-46.

3. Boyd KU, Wehrli BM, Temple CL. Intra-lesional interleukin-2 for the treatment of in-transit melanoma. Journal of Surgical Oncology. 2011;104(7):711-7.

4. Rigel DS, Russak J, Friedmann R. The evolution of melanoma diagnosis: 25 years beyond the ABCDs. CA Cancer Journal for Clinicians. 2010;60(5):301-16.

5. Cancer Care Ontario. Response to checkpoint meeting questions [internal report]. Toronto (ON): Cancer Care Ontario.

6. American Joint Committee on Cancer. Melanoma of the skin staging. 7th ed. Chicago: The Committee; 2009.

7. Jiang BS, Beasley GM, Speicher PJ, Mosca PJ, Morse MA, Hanks B, et al. Immunotherapy following regional chemotherapy treatment of advanced extremity melanoma. Annals of Surgical Oncology. 2014;21(8):2525-31.

8. Barbour S, Mark Smithers B, Allan C, Bayley G, Thomas J, Foote M, et al. Patterns of Recurrence in Patients with Stage IIIB/C Cutaneous Melanoma of the Head and Neck Following Surgery With and Without Adjuvant Radiation Therapy: Is Isolated Regional Recurrence Salvageable? Ann Surg Oncol. 2015.

9. Hassan S, Petrella T, Kamel-Reid S, Al Habeeb A, Ghazarian D, Wright F. The Role of Intralesional Interleukin-2 for In-Transit Melanoma: A Validation Study. Annals of Surgical Oncology. 2013;1(suppl)(P169):S90.

10. Hassan S, Petrella TM, Zhang T, Kamel-Reid S, Nordio F, Baccarelli A, et al. Pathologic Complete Response to Intralesional Interleukin-2 Therapy Associated with Improved Survival in Melanoma Patients with In-Transit Disease. Ann Surg Oncol. 2014.

11. Green DS, Dalgleish AG, Belonwu N, Fischer MD, Bodman-Smith MD. Topical imiquimod and intralesional interleukin-2 increase activated lymphocytes and restore the Th1/Th2 balance in patients with metastatic melanoma. British Journal of Dermatology. 2008;159(3):606-14.

12. Fitzgerald TL, Gronet EM, Atluri P, Zervos EE, Wong JH. Patterns of node mapping differ for axial and extremity primary cutaneous melanoma: A case for a more selective use of pre-operative imaging. Surgeon. 2015.

13. Moller MG, Salwa S, Soden DM, O'Sullivan GC. Electrochemotherapy as an adjunct or alternative to other treatments for unresectable or in-transit melanoma. Expert Review of Anticancer Therapy. 2009;9(11):1611-30.

14. Read RL, Stalley P, Thompson JF. The Contemporary Role of Major Amputation in the Management of Advanced Limb Melanoma. Ann Surg Oncol. 2015.

15. Triozzi PL, Tuthill RJ, Borden E. Re-inventing intratumoral immunotherapy for melanoma. Immunotherapy. 2011;3(5):653-71.

16. Temple-Oberle CF, Byers BA, Hurdle V, Fyfe A, McKinnon JG. Intra-lesional interleukin-2 therapy for in transit melanoma. Journal of Surgical Oncology. 2014;109(4):327-31.

17. Zbytek B, Carlson JA, Granese J, Ross J, Mihm MC, Jr., Slominski A. Current concepts of metastasis in melanoma. Expert Rev Dermatol. 2008;3(5):569-85.

18. Hutcheon JA, Adams BM, Yang SM. In-transit metastatic melanoma involving a previously fractured patella. ANZ J Surg. 2015.

19. Dehesa LA, Vilar-Alejo J, Valeron-Almazan P, Carretero G. Experience in the treatment of cutaneous in-transit melanoma metastases and satellitosis with intralesional interleukin-2. Actas Dermo-Sifiliograficas. 2009;100(7):571-85.

20. Matsushita S, Tada KI, Kawahara KI, Kawai K, Hashiguchi T, Maruyama I, et al. Advanced malignant melanoma responds to Prunus mume Sieb. Et Zucc (Ume) extract: Case report and in vitro study. Exp Ther Med. 2010;1(4):569-74.

21. Soman N, Marsh J, Lanza G, Wickline S. New mechanisms for non-porative ultrasound stimulation of cargo delivery to cell cytosol with targeted perfluorocarbon nanoparticles. Nanotechnology. 2008;19(18).

22. Radny P, Caroli UM, Bauer J, Paul T, Schlegel C, Eigentler TK, et al. Phase II trial of intralesional therapy with interleukin-2 in soft-tissue melanoma metastases. British Journal of Cancer. 2003;89(9):1620-6.

23. Belli F, Arienti F, Rivoltini L, Santinami M, Mascheroni L, Prada A, et al. Treatment of recurrent in transit metastases from cutaneous melanoma by isolation perfusion in extracorporeal circulation with interleukin-2 and lymphokine activated killer cells. A pilot study. Melanoma Research. 1992;2(4):263-71.

24. Byers BA, Temple-Oberle CF, Hurdle V, McKinnon JG. Treatment of in-transit melanoma with intra-lesional interleukin-2: A systematic review. Journal of Surgical Oncology. 2014;110(6):770-5.

25. Palucka AK, Ueno H, Goldberg G, Israyelyan A, Marches F, Bourdery L, et al. Long-term survival and long-lived immune memory in patients with metastatic melanoma vaccinated with melanoma-antigen loaded dendritic cells. Journal of Clinical Oncology. 2010;1).

26. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT00204581, Intralesional Treatment With Interleukin-2 (Proleukin) in Soft Tissue Melanoma Metastases. A Phase II, Prospective, Open, Multicenter Trial; 2005 September 13[Last updated 2011 August 18; cited 2015 April 14]. Avaliable from: https://clinicaltrials.gov/show/NCT00204581.