

pCODR EXPERT REVIEW COMMITTEE (pERC) INITIAL RECOMMENDATION

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

Providing Feedback on this Initial Recommendation

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

Drug:
Trabectedin (Yondelis)

Submitted Funding Request:
For the treatment of patients with metastatic liposarcoma or leiomyosarcoma after failure of prior anthracycline and ifosfamide chemotherapy

Submitted by:
Janssen Inc.

Manufactured by:
Janssen Inc.

NOC Date:
July 14, 2011

Submission Date:
December 22, 2015

Initial Recommendation Issued:
June 3, 2016

pERC RECOMMENDATION

pERC does not recommend reimbursement of trabectedin (Yondelis) for the treatment of patients with metastatic liposarcoma or leiomyosarcoma after failure of prior anthracycline and ifosfamide chemotherapy.

pERC made this recommendation because it concluded there is no net clinical benefit of trabectedin compared with dacarbazine. pERC considered that, compared with dacarbazine, trabectedin had only a very modest progression-free survival benefit, no detectable overall survival benefit, moderate but not insignificant toxicities, and that quality of life data is lacking. pERC noted that trabectedin partially aligned with patient values as there is substantial need for more effective treatment options.

The Committee also noted that compared with dacarbazine, trabectedin was not cost-effective in this population.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

No next steps were identified.

SUMMARY OF pERC DELIBERATIONS

Soft tissue sarcomas (STS) are rare type of cancers, comprising approximately 1% of all cancers diagnosed in Canada. Leiomyosarcoma and liposarcoma account for about 40% of all STS diagnosed. Most patients with localized STS will have disease relapse that is not curable and the prognosis is poor. There is currently no standard of care for patients with metastatic liposarcoma or leiomyosarcoma after prior therapy with an anthracycline and ifosfamide chemotherapy. In the third-line setting, treatments include gemcitabine with or without docetaxel and dacarbazine. These treatment options are associated with limited efficacy and considerable toxicity. pERC noted that the goals of treatment for patients with metastatic liposarcoma or leiomyosarcoma are primarily palliative; namely, to prolong life while maintaining or improving quality of life (QoL). pERC concluded that there is a need for more effective treatments with less toxicity that improve QoL and extend overall survival (OS).

[pERC's Deliberative Framework](#) for drug reimbursement recommendations focuses on four main criteria:

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated upon the results of the SAR-3007 study, which compared trabectedin with dacarbazine. pERC considered that, although dacarbazine is a reasonable comparator, it is not a commonly used treatment option in Canada. pERC noted that the difference in median OS (the primary end point) between trabectedin and dacarbazine in the SAR-3007 study was small and not statistically significant. pERC acknowledged that the pCODR Clinical Guidance Panel (CGP) felt that subsequent therapies following progression may have affected the potential to observe an OS benefit with trabectedin. However, pERC disagreed with the CGP as these therapies have not previously shown OS benefits. In addition, crossover from dacarbazine to trabectedin was not allowed in the study. pERC noted that the magnitude of the absolute benefit in progression-free survival (PFS) was modest for trabectedin compared with dacarbazine (median 4.2 months versus 1.5 months, respectively). Patients in the trabectedin group had a longer time from initial diagnosis to starting treatment than patients in the dacarbazine group (a median difference of approximately seven-months). pERC noted that more patients in the trabectedin group may have had a better prognosis (i.e., slower disease progression), which could have made results more favourable for the trabectedin group compared with the dacarbazine group. Overall response rates were very low in both the trabectedin and dacarbazine groups and all were partial responses.

pERC also considered patient-reported outcomes of symptom burden and impact of treatment on symptom change or stability to be similar between trabectedin and dacarbazine up to cycle 8 in the SAR-3007 study. pERC noted that, while symptoms are directly related to the disease and effect of treatment, QoL is multidimensional and includes symptoms, side effects of treatment, and functional scales (physical, role, emotional, social, and cognitive). pERC felt that having additional data on QoL would have been useful in understanding patients' experience with trabectedin.

pERC discussed the toxicity profile of trabectedin and noted that overall, there were similar rates of all grade adverse events (AEs) with trabectedin compared with dacarbazine. However, more patients in the trabectedin group experienced grade 3 to 4 AEs than the dacarbazine group (81% versus 57%, respectively). These included clinical rhabdomyolysis, nausea, vomiting, fatigue, diarrhea, constipation, anorexia, dyspnea, headaches, fever, cough, elevation of liver function tests, and elevation of creatine kinase. pERC noted that these AEs could be managed in clinical practice, but additional monitoring of patients would still be required. pERC highlighted that trabectedin had more frequent and higher grades of AEs compared with dacarbazine, a drug with a well-documented high toxicity profile. pERC noted that there was a very modest PFS benefit in favour of trabectedin. However, given the absence of an OS benefit, the lack of robust QoL data, and the potential for substantial toxicities with trabectedin, pERC concluded that there was no overall net clinical benefit with trabectedin compared with dacarbazine.

pERC discussed patient advocacy group input, which indicated that there are currently limited treatment options available and that patients were willing to tolerate side effects when treatment delayed or stopped disease progression. pERC acknowledged that there is no standard of care in metastatic

liposarcoma or leiomyosarcoma after prior anthracycline and ifosfamide chemotherapy and that there is an unmet need for effective treatment options. However, pERC noted that in the SAR-3007 study, trabectedin was associated with a modest PFS benefit, no survival benefit, and no difference in symptom outcomes. On balance, therefore, pERC considered that trabectedin only partially aligned with patient values.

pERC deliberated upon the cost-effectiveness of trabectedin and concluded that it is not cost-effective when compared with dacarbazine for patients with metastatic liposarcoma or leiomyosarcoma who were previously treated with at least either a combination of an anthracycline and ifosfamide or an anthracycline plus additional chemotherapy regimen. pERC noted that the cost and proportion of subsequent therapies following disease progression on trabectedin or dacarbazine was a large driver of both the cost and the incremental cost-effectiveness ratio. Overall, neither the submitter's nor the pCODR Economic Guidance Panel's (EGP's) best estimates for trabectedin compared with dacarbazine could be considered cost-effective in this setting.

pERC discussed the feasibility of implementing a reimbursement recommendation for trabectedin and noted that the budget impact may increase due to the potential for wastage (as vial sharing is unlikely) and due to the indefinite treatment duration of trabectedin. pERC also discussed the resource intensity of trabectedin, noting the additional monitoring of toxicities that would be required and that not all jurisdictions would be able to administer trabectedin in outpatient chemotherapy centres, and therefore would administer trabectedin in inpatient hospitals. On the other hand, liposarcoma and leiomyosarcoma are uncommon cancers, and so the absolute budget impact is likely modest.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon a pCODR systematic review, other literature in the Clinical Guidance Report that provided clinical context, an evaluation of the manufacturer's economic model and budget impact analysis, guidance from pCODR clinical and economic review panels, input from one patient advocacy group (Sarcoma Cancer Foundation of Canada), and input from pCODR's Provincial Advisory Group (PAG).

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of this review is to evaluate the safety and efficacy of trabectedin (Yondelis) compared with an appropriate comparator for the treatment of patients with metastatic liposarcoma or leiomyosarcoma after failure of prior anthracycline and ifosfamide chemotherapy.

Studies included: One open-label phase 3 randomized controlled trial

The pCODR systematic review included one international, multi-centre, open-label, phase 3 randomized controlled study (SAR-3007) that compared the efficacy and safety of trabectedin with dacarbazine. Patients received trabectedin at a dose of 1.5 mg/m², via continuous intravenous infusion over 24 hours, administered on day 1 of each 21-day cycle. Dacarbazine was given at a dose of 1 g/m² intravenous infusion over 20 to 120 minutes, administered on day 1 of each 21-day cycle. Both treatments were administered until disease progression or intolerable toxicity. Patients in the dacarbazine group with progressive disease were not allowed to crossover to the trabectedin group in the study. pERC noted that four patients in the dacarbazine group received trabectedin as a subsequent anticancer therapy.

Patient populations: Previously treated patients with performance status 0 or 1

The SAR-3007 study included patients aged 15 years and older with unresectable locally advanced or metastatic liposarcoma or leiomyosarcoma. All patients were previously treated with either a combination of anthracycline and ifosfamide or an anthracycline and at least one or more additional cytotoxic chemotherapy agents. Patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 (50%) or 1 (50%). The median age of patients was approximately 57 years and the majority of patients had two or more prior lines of chemotherapy (89% and 87% in the trabectedin and dacarbazine groups, respectively). pERC noted that compared with the dacarbazine group, the trabectedin group had a longer time from initial diagnosis to starting treatment (median of 34 versus 27 months, respectively). Five (1%) patients in the trabectedin group did not receive trabectedin compared with 18 (10%) patients in the dacarbazine group.

Key efficacy results: No overall survival benefit and modest progression-free survival benefit

The primary end point of the SAR-3007 study was overall survival (OS), which was not statistically significantly different between trabectedin and dacarbazine (13.7 versus 13.1 months, respectively; hazard ratio [HR] = 0.93, 95% confidence interval [CI]: 0.75 to 1.15, $P = 0.49$). pERC acknowledged that the pCODR Clinical Guidance Panel felt that subsequent therapies post-progression on trabectedin or dacarbazine may have impacted the OS results. pERC disagreed that the differences in the subsequent therapies may have confounded the OS results, as none of the subsequent therapies have previously shown an OS benefit in this patient population. pERC also discussed the progression-free survival (PFS) results observed in the SAR-3007 study. Trabectedin was associated with a 2.7-month improvement in PFS compared with dacarbazine (4.2 months versus 1.5 months, respectively; HR = 0.55, 95%CI, 0.44 to 0.70, $P < 0.0001$). pERC considered there to be an absence of an OS benefit, and the PFS benefit observed was modest. pERC noted that overall response rates, which were all partial responses, were very low in both the trabectedin and dacarbazine groups (9.9% versus 6.9%, respectively).

Quality of life: No significant difference in symptom outcomes

While symptom-specific symptoms were assessed in the SAR-3007 study, patients' overall health-related quality of life was not. Patient-reported symptom burden and the impact of treatment on symptom change or stability was assessed using the MD Anderson Symptom Inventory. Results suggested that the majority of patients in both groups were asymptomatic or minimally asymptomatic. There were no

significant differences from baseline to cycle 8 in both groups, with the exception of cycle 2, in which 9.4% and 3.3% of patients in the trabectedin and dacarbazine groups, respectively, reported nausea. Results were based on 71 and 14 patients in the trabectedin and dacarbazine groups, respectively, who were still on treatment by cycle 8. pERC emphasized the importance of quality-of-life (QoL) data to inform its deliberations, given the modest clinical effect of trabectedin on PFS.

Safety: More frequent and higher-grade adverse events compared with dacarbazine

Almost all patients in the SAR-3007 study experienced a treatment-emergent adverse event (AE). More patients in the trabectedin group experienced grade 3 to 4 AEs than the dacarbazine group (81% versus 57%, respectively). Grade 3 to 4 AEs were reported in a higher proportion of patients treated with trabectedin compared with dacarbazine for clinical rhabdomyolysis, nausea, vomiting, fatigue, diarrhea, constipation, anorexia, dyspnea, headaches, fever, cough, elevation of liver function tests, and elevation of creatine kinase. Withdrawals due to AEs were reported in 26% and 22% of patients treated with trabectedin and dacarbazine, respectively. Three patients (12%) and no patients had a treatment-related death in the trabectedin and dacarbazine groups, respectively. pERC discussed the side effect profile of the comparator dacarbazine and noted that it is associated with substantial toxicities. Furthermore, pERC noted that trabectedin had more frequent and higher grades of AEs than dacarbazine.

Need and burden of illness: Current therapies have limited effectiveness and substantial toxicities

Sarcomas comprise about 1% of all cancers diagnosed in Canada. About 40% of sarcomas are liposarcoma or leiomyosarcoma. There is no standard of care for patients with metastatic liposarcoma or leiomyosarcoma after prior therapy with an anthracycline and ifosfamide chemotherapy. Treatments include, but are not limited to gemcitabine with or without docetaxel, dacarbazine, clinical trials, and best supportive care/palliative care. pERC noted that the goals of treatment for patients with metastatic liposarcoma or leiomyosarcoma are primarily palliative; namely, to prolong life while maintaining or improving QoL. Overall, pERC considered that there is a need for new and effective therapies for patients with metastatic liposarcoma and leiomyosarcoma that provide prolong survival, improve QoL, and have more favourable toxicity profiles.

PATIENT-BASED VALUES

Values of patients with metastatic liposarcoma or leiomyosarcoma: Delayed progression

pERC deliberated upon patient advocacy group input for trabectedin for metastatic liposarcoma or leiomyosarcoma and discussed the values of patients with metastatic liposarcoma or leiomyosarcoma. Patients indicated that the key symptoms to control were severe pain, fatigue, difficulty breathing, difficulty sleeping, cough, constipation, and inability to complete daily tasks. pERC acknowledged that patients indicated that there are currently limited treatment options and that they were willing to tolerate side effects for treatments that delay or stop disease progression. pERC noted that patient advocacy input was based on six conversations with patients, caregivers, and physicians in the Canadian sarcoma community. The patient advocacy group also mentioned having insight into the experience of the disease from calls to the organization's 1-800 line and email support service. pERC acknowledged the difficulty that patient advocacy groups have in accessing patients, especially those with late-stage liposarcoma or leiomyosarcoma.

Patient values on treatment: Disease control with acceptable toxicities

pERC noted that two patients who provided input had direct experience with trabectedin. These patients reported that trabectedin was able to slow disease progression and was tolerable in terms of side effects such as fatigue, nausea, vomiting, and iron deficiency. In discussion, pERC stated that based on the current evidence, trabectedin was associated with a modest PFS benefit, no survival benefit, no difference in symptom outcomes, and a potential for substantial toxicities. pERC acknowledged the importance of having more treatment options in this patient population. On balance, therefore, pERC considered trabectedin to be only partially aligned with patient values.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility analysis

The pCODR Economic Guidance Panel (EGP) assessed a cost-utility analysis of patients with metastatic liposarcoma or leiomyosarcoma who were previously treated with at least either a combination of an anthracycline and ifosfamide or an anthracycline plus additional chemotherapy regimen. Trabectedin was compared with dacarbazine. A comparison was based on the results of the SAR-3007 study.

Basis of the economic model: Clinical and economic inputs

Costs considered in the model provided by the submitter included drug costs, drug administration costs, AE costs, subsequent treatment costs, palliative care costs, and end of life costs. The key clinical outcomes considered in the model provided by the submitter were OS and PFS estimates from the SAR-3007 study. Utilities were determined from the literature.

Drug costs: Very high drug cost compared with other treatment options

Trabectedin costs \$3,061.33 per milligram. At the recommended dose of 1.5 mg/m² intravenous infusion over 24 hours every 21 days, trabectedin costs \$371.73 per day and \$10,408.52 per 28-day course.

Dacarbazine costs \$0.3852 per mg. At the recommended dose of 1 g/m² intravenous infusion over 20 to 120 minutes every 21 days, dacarbazine costs \$80.59 per day and \$2,266.67 per 28-day course.

Cost-effectiveness estimates: Not cost-effective at submitted price

pERC deliberated upon the cost-effectiveness of trabectedin and noted that the EGP's estimate of the incremental cost-effectiveness ratios (ICERs) was higher than the submitter's estimate, primarily because of different assumptions regarding the cost of subsequent treatments post-progression and proportion of patients receiving subsequent treatment post-progression. pERC reviewed the ICERs provided by both the submitter and the EGP and determined that trabectedin was not cost-effective, at the submitted price, when compared with dacarbazine in either analysis.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Small patient population

pERC discussed the feasibility of implementing a reimbursement recommendation for trabectedin and noted that trabectedin provides another treatment option for a very small number of patients. Key challenges to implementation include the indefinite treatment duration of trabectedin, drug wastage due to the very small number of patients, and 24-hour continuous infusion, which would increase resource impact. Trabectedin would be given in an outpatient chemotherapy centre or in-patient hospital. For the administration of trabectedin in inpatient hospitals, hospital resources are required for appropriate administration and monitoring of toxicities.

DRUG AND CONDITION INFORMATION

Drug Information	<ul style="list-style-type: none"> Alkylating agent that is in the class of DNA-binding agents 1.5 mg/m² intravenous infusion over 24 hours, administered on day 1 of each 21-day cycle
Cancer Treated	<ul style="list-style-type: none"> Metastatic liposarcoma or leiomyosarcoma after failure of prior anthracycline and ifosfamide chemotherapy
Burden of Illness	<ul style="list-style-type: none"> Sarcomas comprise about 1% of all cancers diagnosed in Canada Leiomyosarcoma and liposarcoma account for about 40% of all sarcomas diagnosed (second and third most common sarcomas diagnosed after gastrointestinal stromal tumour)
Current Standard Treatment	<ul style="list-style-type: none"> Therapeutic options are limited for patients with metastatic liposarcoma or leiomyosarcoma There is no standard of care; treatment includes gemcitabine with or without docetaxel, dacarbazine, best supportive care/palliative care
Limitations of Current Therapy	<ul style="list-style-type: none"> Current therapeutic options after failure of doxorubicin and ifosfamide are associated with limited efficacy and significant toxicity

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

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

Dr. Anthony Fields, Oncologist (Chair)	Don Husereau, Health Economist
Dr. Maureen Trudeau, Oncologist (Vice-Chair)	Dr. Anil Abraham Joy, Oncologist
Dr. Scott Berry, Oncologist	Karen MacCurdy-Thompson, Pharmacist
Dr. Kelvin Chan, Oncologist	Valerie McDonald, Patient Member Alternate
Dr. Matthew Cheung, Oncologist	Carole McMahon, Patient Member
Dr. Craig Earle, Oncologist	Dr. Catherine Moltzan, Oncologist
Dr. Allan Grill, Family Physician	Jo Nanson, Patient Member
Dr. Paul Hoskins, Oncologist	Danica Wasney, Pharmacist

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

- Matthew Cheung and Jo Nanson, who were not present for the meeting
- Paul Hoskins, who was excluded from voting due to a conflict of interest.

Avoidance of conflicts of interest

All members of pERC must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of trabectedin (Yondelis) for metastatic liposarcoma or leiomyosarcoma, through their declarations, four members had a real, potential, or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, one of these members was excluded from voting.

Information sources used

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

Consulting publicly disclosed information

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

Use of this recommendation

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

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