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:
Olaratumab (Lartruvo)

Submitted Funding Request:
In combination with doxorubicin for the treatment of adult patients with advanced soft tissue sarcoma (STS) not amenable to curative treatment with radiotherapy or surgery and for whom treatment with an anthracycline-containing regimen is appropriate.

Submitted by:
Eli Lilly Canada Inc.

Manufactured by:
Eli Lilly Canada Inc.

NOC Date:
November 23, 2017

Submission Date:
October 26, 2017

Initial Recommendation Issued:
March 29, 2018

Approximate per Patient Drug Costs, per Month (28 Days)	Olaratumab costs: $788.12 per 190 mg and $2,074.00 per 500 mg vials At the recommended dose, olaratumab costs: • no wastage (500 mg): $414.80 per day and $11,614.40 per 28-day • with wastage (500 mg): $493.81 per day and $13,826.67 per 28-day.

pERC RECOMMENDATION

pERC conditionally recommends the reimbursement of olaratumab (Lartruvo) plus doxorubicin (Olara + DOX) for patients with advanced soft tissue sarcoma (STS) not amenable to curative treatment with radiotherapy or surgery and for whom treatment with an anthracycline-containing regimen is appropriate only if the following conditions are met:

- cost-effectiveness being improved to an acceptable level
- time- limited reimbursement until more robust clinical data are made available for a future reassessment.

If the aforementioned conditions cannot be met, pERC does not recommend reimbursement of olaratumab. Eligible patients should have a good performance status and treatment should be continued until disease progression or unacceptable toxicity.

pERC made this recommendation because it was satisfied that there may be a net clinical benefit of Olara + DOX based on clinically meaningful improvements in overall survival (OS) and a manageable toxicity profile in a patient population with an unmet need. However, pERC acknowledged there was considerable uncertainty about the OS benefit due to limitations in the evidence from the available phase II clinical trial. pERC agreed that Olara + DOX aligned with patient values to the extent that it may prolong survival and has a manageable toxicity profile; however, the Committee was unable to

	determine olaratumab's impact on patients' quality of life as it was not measured in the trial. pERC noted at the submitted estimates and the Economic Guidance Panel's re-analysis estimates Olara + DOX could not be considered cost-effective in this population compared with DOX alone. Additionally, there is uncertainty in the available clinical data informing the economic model.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Ensuring Evidence-Based Clinical Effectiveness and Cost-effectiveness** pERC noted that the final results for the phase III trial ANNOUNCE are estimated to be available in 2020. Given the uncertainty in the magnitude of clinical benefit and cost-effectiveness, jurisdictions should consider a time-limited reimbursement of Olara + DOX, with a reassessment of the efficacy, safety, and cost-effectiveness when the final results of the ANNOUNCE trial are available from the submitter. pERC noted that this approach would help facilitate the equitable and timely access to promising treatments for patients while ensuring that treatments considered for public reimbursement adhere to a level of rigour that sufficiently demonstrates effectiveness, safety, and cost-effectiveness. **Pricing Arrangements to Improve Cost-Effectiveness** Given pERC was satisfied that there may be a net clinical benefit of Olara + DOX in patients with advanced or metastatic soft tissue sarcoma, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of olaratumab to an acceptable level. **Smaller Vial Size to Reduce Drug Wastage** pERC noted that the availability of smaller vial sizes will be important to reduce drug wastage. Currently, only the 500 mg vial is available while the smaller 190 mg vial is anticipated to be available in Q4 2018. pERC agreed on the importance of the timely availability of the smaller vial size to a meaningful impact on the ICER, as the larger 500mg vial contributes to considerable wastage. **Time-Limited Need for Olaratumab** When implementing a funding recommendation for Olara + DOX, jurisdictions may want to consider addressing the time-limited need for the addition of olaratumab to DOX monotherapy in patients with advanced STS who have not had disease progression and are eligible for treatment as per study criteria. **Please note:** Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

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

Soft tissue sarcoma (STS) is a heterogeneous group of malignant tumours derived from mesenchymal tissue outside the skeleton and having differing sites of origin and metastasis, histologic and molecular variants. This heterogeneous aspect of STS increases the risk of imbalance in prognostic factors, known and unknown, in small prospective studies. In the metastatic situation, this is compounded by varying intervals between primary tumour diagnosis and metastasis (disease-free interval) reflecting sarcoma aggressiveness. The most common histological types of STS are liposarcoma, leiomyosarcoma, and undifferentiated pleomorphic sarcoma. STS comprise less than 1% of all malignancies and the latest Canadian statistics for 2013 show 1,255 cases and 765 deaths. Primary STS is treated by surgery alone, or surgery plus radiotherapy with or without (neo) adjuvant chemotherapy. Most patients who develop metastases are not suitable for surgery, and if they are medically fit they will receive palliative chemotherapy. Standard first-line treatment in Canada is doxorubicin (DOX) monotherapy. Although a variety of agents have been studied over the last 20 years, none have demonstrated an overall survival (OS) advantage. Median survival from diagnosis in patients requiring palliative chemotherapy is poor, in the range of 12 to18 months, with less than 10% surviving five years. pERC agreed that there is a considerable need for additional effective treatment options in this setting.

pERC deliberated upon the results of one two-part, open-label, phase 1b and randomized phase 2 trial, JGDG. The Phase 1b portion evaluated the safety of Olara+DOX, while Phase 2 evaluated efficacy and safety. Based on the phase II portion of the JGDG study, pERC concluded that there may be a net clinical benefit with the use of Olara + DOX compared to DOX monotherapy. Despite the limitations in the design of the trial, namely the small sample size and the use of a two-sided alpha level of 0.2 which increased the probability of detecting a false positive in the primary outcome, pERC agreed with the Clinical Guidance Panel (CGP) that the large magnitude of benefit observed for overall survival (OS) (absolute improvement of 11.8 months) was clinically meaningful in this population. However, the Committee further acknowledged that the early separation of the Kaplan Meier curves for survival highlighted the possibility of a biological effect or difference between the treatment arms as opposed to treatment effect. This concern was highlighted by the CGP in their interpretation. pERC noted that the impact of Olara + DOX on patients' quality of life (QoL) is unknown as it was not measured in the trial. pERC discussed that Olara + DOX had increased toxicities compared with DOX monotherapy; however, the toxicities were noted to be mild and manageable. pERC further discussed that the conclusions that can be drawn from phase II data are not as robust as those that can be drawn from a phase III randomized controlled trial (RCT), making it difficult to determine the magnitude of long-term benefit with Olara + DOX. pERC further noted that phase II trials are hypothesis-generating and their intent is to determine whether there is sufficient promise to proceed to a phase III confirmatory trial. pERC considered that the ongoing phase III RCT, ANNOUNCE, comparing Olara + DOX to DOX monotherapy in patients with metastatic STS has completed enrolment of 460 patients, and that the final results are expected to be available in 2020. The primary outcome of the ANNOUNCE trial is OS, in addition, QoL data are also being collected. As this study has not been closed early for ethical reasons to make Olara + DOX available to both treatment groups, pERC agreed that clinical equipoise still remains. Given the limitations in the phase II JGDG trial and uncertainty in the magnitude of OS benefit reported, pERC agreed that additional clinical and safety data should be made available for a reassessment once the final results are reported for the ANNOUNCE trial.

pERC considered the generalizability of the JGDG trial results and noted that over half of the patients in the trial were previously treated. Based on the opinion of the Clinical Guidance Panel (CGP) and input from registered clinicians, pERC noted that the majority of Canadian patients are likely to be first line and agreed that the JGDG trial results are generalizable to the Canadian setting. However, there will be some patients in the Canadian setting who are expected to receive Olara + DOX in the second-line setting (e.g., patients with uterine leiomyosarcoma among others). pERC agreed that eligibility for treatment should not be restricted based on histological subtype except in patients with Kaposi sarcomas who were

excluded from the JGDG trial and patients with gastrointestinal stromal tumours (GIST) as no patients with GIST were enrolled in the JGDG trial and there is no evidence for the use of Olara + DOX in this population.

pERC deliberated on input from one patient advocacy group and noted that patients with STS value having treatments that help stop disease progression, prolong survival, improve QoL, and have a manageable toxicity profile. Patients indicated that available therapies can be harsh and reduce their quality of life. Patients also reported that they experienced several symptoms associated with the location of their tumour including pain, sleeplessness, exhaustion and various difficulties. pERC noted that the clinically meaningful improvement in OS and manageable toxicity profile, aligned with patients' values. pERC further noted that QoL, which is greatly affected in patients with STS, was not measured in the trial therefore it is unclear if Olara + DOX provides any meaningful improvement in this important patient outcome. pERC agreed that the results of the ANNOUNCE trial will provide data that will help answer important questions related to the magnitude of benefit and other outcomes which patients value, like QoL. Overall, pERC concluded that even though there were no data on QoL available, the meaningful improvements in OS and manageable toxicity in a group of patients with a considerable unmet need, aligned with patient values.

pERC deliberated on the cost-effectiveness of Olara + DOX compared with DOX alone and concluded that, at the submitted price, Olara + DOX is not cost-effective. pERC noted that the clinical effect estimates used to inform the model created a large amount of uncertainty in the incremental cost-effectiveness ratio (ICER). Based on this, the assumption made in the submitted results about the number of years patients live and benefit from treatment with Olara + DOX (time horizon) had the largest impact on the ICER. pERC agreed that the prognosis of patients with advanced or metastatic STS is poor and therefore it is not realistic to expect patients would survive an additional 25 years. Given this clinical rationale and the uncertainty in the magnitude of OS benefit with Olara + DOX, pERC agreed with the Economic Guidance Panel's (EGPs) re-analysis which shortened the time horizon to five years. pERC also noted that the methods used to extrapolate long-term benefit (parametric model) and the source of patient data used to determine the drug acquisition costs had an impact on the incremental cost-effectiveness (ICER). pERC agreed with the changes made by the EGP to these additional two inputs and when all three inputs are combined, the ICER increased substantially. pERC therefore concluded that Olara + DOX is not cost-effective at the submitted price. pERC agreed that results from the ongoing phase III ANNOUNCE trial will be important to address the uncertainty in the magnitude of OS benefit with Olara + DOX and resulting cost-effectiveness. Although not included in the EGP's re-analysis estimates, pERC discussed that the potential availability of the smaller 190mg vial size later in 2018 would have a meaningful impact on the ICER, as the larger 500mg vial is the only currently available vial size and could therefore result in considerable wastage..

pERC discussed the feasibility of implementing a reimbursement recommendation for Olara + DOX and noted several factors identified by PAG. pERC agreed that a time-limited availability of Olara + DOX for patients who are currently receiving single agent DOX and have not had disease progression is reasonable. pERC also agreed it is reasonable for patients to continue treatment with the single agent Olara following the end of fixed DOX treatment as this is in alignment with the trial protocol. Furthermore, pERC agreed that the eligible reimbursement population should not be restricted based on histological subtype except for patients with Kaposi sarcoma who were excluded from the JGDG trial and patients with GIST as no patients with GIST were enrolled in the JGDG trial and there is no evidence for the use of Olara + DOX in this population.

pERC noted that the availability of smaller vial sizes will be important to reduce drug wastage. Currently, only the 500 mg vial is available while the smaller 190 mg vial will be available in Q4 2018. pERC agreed on the importance of the timely availability of the smaller vial size to reduce wastage and impact of the added cost on the ICER. pERC noted that the budget impact analysis is sensitive to the number of patients who will be eligible for Olara + DOX treatment and the availability of the smaller 190 mg vial size. pERC therefore re-iterated the importance of making smaller vial sizes available to jurisdictions to minimize wastage.

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 the pCODR clinical and economic review panels
- input from one patient advocacy group (Sarcoma Cancer Foundation of Canada (SCFC))
- input from registered clinicians
- input from pCODR's Provincial Advisory Group (PAG).

OVERALL CLINICAL BENEFIT

pCODR Review Scope

The purpose of the review is to evaluate the safety and efficacy of olaratumab (Lartruvo) in combination with doxorubicin for the treatment of patients with advanced STS not amenable to curative treatment with radiotherapy or surgery, and for whom treatment with an anthracycline-containing regimen is appropriate.

Studies Included: Small Phase II Randomized Study

The pCODR systematic review included one open-label, phase Ib and randomized phase II trial, JGDG. The phase Ib part of the study was non-randomized, and all patients (n=15) received a combination of olaratumab (Olara) and doxorubicin (DOX). In the phase II portion of the JGDG trial, patients were randomly assigned, on a 1:1 basis, to combination therapy with Olara + DOX (n = 66), or doxorubicin (n = 67). pERC noted that the sample size of the study was small.

Olara was dosed at 15 mg/kg on day 1 and day 8 and DOX was dosed at 75 mg/m^2 on day 1 of each 21-day cycle for up to eight cycles. To minimize the risk of DOX-related cardiotoxicity, patients who received more than four cycles of doxorubicin were allowed to receive dexrazoxane at the investigator's discretion on day 1 of cycles 5 to 8 in both Olara + DOX and DOX groups. Dexrazoxane was administered at a ratio of 10:1 to the administered dose of doxorubicin. Dexrazoxane was administered to 38 (59.4%) and 29 (44.6%) of patients in the Olara + DOX and DOX groups, respectively.

pERC noted that the JGDG trial allowed for a significance level of 0.20 (nominal significance level of 0.1999 adjusted for the interim analysis). However, the key efficacy result in the main publication is reported based on the 95% CIs (which correspond to a 0.05 level of significance). This is based on a post hoc change to the planned statistical analysis plan. Based on this post hoc change to the analysis plan, there is a considerable overlap of the 95% CIs between the median progression free survival (PFS) rates reported for Olara + DOX and DOX groups. Furthermore, the 95% CI for the reported stratified hazard ratio (HR) for PFS contains 1.0 (null hypothesis value). The authors also reported results based on the original analysis plan (a significance level of 0.2) where a statistically significant PFS improvement in favour of the Olara + DOX group was achieved. pERC agreed that there is considerable uncertainty in the results of the JGDG trial given that it allowed for a 20% risk for concluding a statistical difference in PFS where there is none. Notably the study did not define any method for assessing the significance of secondary outcomes.

The pCODR review also provided contextual information on a manufacturer submitted indirect treatment comparison (ITC) of Olara versus available treatment options in patients with advanced STS. pERC noted that the JGDG trial compared with DOX, which is considered to be the most relevant comparison in the Canadian setting. Based on this, the ITC was not discussed further or used to inform any of pERC's conclusions.

Patient Populations: Potential for Unknown Confounding Factors

Key eligibility criteria for both the phase Ib and phase II required that patients be 18 years of age or older, and have: a histologically confirmed diagnosis of locally advanced or metastatic STS not previously treated with an anthracycline, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and available tumour tissue to determine platelet-derived growth factor receptor α (PDGFRα) expression by immunohistochemistry. Key exclusion criteria included Kaposi's sarcoma, untreated central

nervous system metastases, or previous treatment with anthracyclines and anthracenediones (mitoxantrone).

A total of 133 patients were enrolled in the phase II part of the JGDG trial, of which 66 were randomly assigned to the Olara + DOX group and 67 to the DOX group. Baseline characteristics were well balanced except for a slightly higher proportion of women in the Olara + DOX versus DOX group (61% versus 51%, respectively). The majority of patients in the Olara + DOX and DOX groups were white (83% and 90%) and had an EGOG PS of 0 to 1 (94% in both groups). Six percent of patients in both treatment groups had an ECOG PS of 2. More than half of patients had one or more previous therapies in the two groups (59% and 54%, respectively). pERC noted discussions from the CGP indicating there was limited information on the primary site of metastasis and histological type comparison was restricted to leiomyosarcoma versus non-leiomyosarcoma. Given the small sample size of the study, pERC agreed that such an imbalance of prognostic factors between groups could lead to false-positive or negative results.

There was a total of 17(26%) and 16(24%) major protocol violations in the Olara + DOX and DOX groups, respectively. The most frequent reasons for major protocol violations were issues with informed consent (both groups), protocol procedures/visits not performed/missing (Olara + DOX) and inclusion/exclusion criteria violated (DOX).

Key efficacy results: Large but uncertain magnitude in overall survival, reassessment once ANNOUNCE results are reported

The key efficacy outcome deliberated on by pERC included investigator-assessed PFS, the primary outcome of the phase II portion of the trial, defined as the time from the date of randomization to the earliest date of documented tumour progression or death from any cause. Key secondary outcomes included OS, ORR and safety. The key efficacy outcome of the phase I portion of the study was safety. The phase I aspect of the study is not discussed any further in this recommendation as it was not used to inform pERC's discussions or recommendation. As of the August 15, 2014 data cut-off, the median PFS was 6.6 and 4.1 months in the Olara + DOX compared with DOX groups, respectively (stratified HR 0.672; 95% CI, 0.442 to 1.021, $P = 0.0615$). Although the results are reported using a significance level of 0.05, pERC noted that significance is met only at an alpha level of 0.2 which aligns with the original trial design. pERC agreed that a 20% chance of detecting a false positive is high and makes the PFS results uncertain. For secondary outcomes, OS was improved in favour of the Olara + DOX compared with DOX group (26.5 versus 14.7, HR 0.463 (0.301, 0.710) p=0.0003). ORR was also improved in favour of the Olara + DOX versus DOX group, 18.2% versus 11.9%, respectively ($P = 0.3421$).

Despite the limitations due to the phase II nature of the trial, namely the small sample size and the use of a two-sided alpha level of 0.2 in the analysis of the primary outcome, pERC agreed that the magnitude of benefit observed for overall survival (OS) was large (absolute improvement of 11.8 months) and clinically meaningful in a population with considerable unmet need. pERC acknowledged that these results are very promising but uncertain and require confirmatory data. Notably, the early separation of the Kaplan Meier curves for survival indicates a potential biological effect as opposed to treatment effect. pERC agreed that such a biological effect is plausible considering the heterogeneous nature of STS and the small sample size of the study which could have resulted in an imbalance of unknown prognostic factors.

Although over half of the patients in the trial were previously treated, pERC agreed that the trial results can be generalized into the Canadian population, the majority of whom are likely to be first line. However, some patients in the Canadian setting are expected to receive Olara + DOX in the second-line setting (e.g., patients with uterine leiomyosarcoma among others). pERC also agreed that eligibility for treatment should not be restricted based on histological subtype except in patients with Kaposi sarcomas who were excluded from the trial and patients with gastrointestinal tumours (GIST) as no patients with GIST were enrolled on the trial and there is no evidence on the use of Olara + DOX in this population.

pERC discussed the ongoing phase III RCT, ANNOUNCE, comparing Olara + DOX to DOX monotherapy in patients with metastatic STS and noted that it has completed enrolment of 460 patients and that final results are expected to be reported in 2020. The primary outcome of this trial is OS, and QoL data are also being collected. As this study has not been closed early for ethical reasons (that is, to make Olara + DOX available to both treatment groups), pERC agreed that clinical equipoise still remains. Given the very promising OS results with the JGDG trial, pERC agreed it was reasonable to make treatment available to patients. pERC however agreed that the limitations in the phase II JGDG trial and uncertainty in the magnitude of OS benefit remain and confirmatory clinical and safety data should be made available for a

reassessment once the final results are reported for the ANNOUNCE trial. pERC also noted that Health Canada issued a Notice of Compliance with conditions pending results of clinical trials to verify the anticipated benefit of Olara + DOX in this patient population.

Patient-reported Outcomes: Not Measured

pERC noted that the JGDG trial did not measure QoL. Based on input from patient advocacy groups, pERC agreed that QoL is an important outcome for patients however the committee was unable to assess the impact of Olara + DOX on patients' quality of life. pERC further stressed the importance of a reassessment once the results of the ANNOUNCE trial are available as it is collecting QoL data.

Safety: Greater Toxicities With Olaratumab

pERC discussed the toxicity profile of olaratumab observed in the JGDG trial. A similar proportion of patients in Olara + DOX and DOX groups experienced grade 3 adverse events (AEs) (38% in each group). However, a higher percentage of the patients in Olara + DOX compared with DOX group experienced grade 4 AE's (42% versus 31%) and treatment related grade 3 or higher adverse events (67% versus 55%). The proportion of patients experiencing serious adverse events (42% and 38%, respectively) and treatment related serious adverse events (22% and 20%, respectively) was similar between the two groups. Infusion-related reactions were only observed in the Olara + DOX group (13%). Although toxicity with Olara + DOX was greater than with DOX alone, it did not result in an increased number of febrile neutropenia events, hospital admissions, treatment discontinuations or deaths, the clinical guidance panel also felt that these toxicities were manageable. pERC noted that toxicities were increased in the Olara + DOX compared with DOX monotherapy groups however the Committee agreed that the toxicities were mild and manageable.

Need and Burden of Illness: Heterogeneous Disease

Soft tissue sarcomas (STS) are a heterogeneous group of malignant tumours derived from mesenchymal tissue outside the skeleton. STS is not organ specific and can have differing sites of origin and metastases as well as differing histologic and molecular variants. The most common primary sites of metastasis are the lower limb, buttock and intra-abdominal. The heterogeneous aspect of STS increases the risk of imbalance in prognostic factors, known and unknown, in small prospective studies. In the metastatic situation, this is compounded by varying intervals between primary tumour diagnosis and metastasis (disease-free interval) reflecting sarcoma aggressiveness. The most common histological types of STS are liposarcoma, leiomyosarcoma, and undifferentiated pleomorphic sarcoma.

STS comprise less than 1% of all malignancies and the latest Canadian statistics for 2013 show 1,255 cases and 765 deaths. Excluding pediatric sarcomas, the peak age of incidence is between 60 and 80 years, but with a significant spread that includes adolescents and young adults. Primary STS are treated by surgery alone, surgery plus radiotherapy with or without (neo)adjuvant chemotherapy. Most patients who develop metastases are not suitable for surgery, and if medically fit, will receive palliative chemotherapy. Although a variety of agents have been studied over the last 20 years, none have demonstrated an overall survival (OS) advantage and DOX remains the standard Canadian treatment option. Median survival from diagnosis in patients requiring palliative chemotherapy is poor, in the range of 12 to 18 months, with less than 10% surviving five years. Based on clinical opinion, pERC noted that a reasonable estimate of the number of patients who would be eligible for treatment with Olara + DOX is 500 to 600 patients a year. pERC therefore agreed that there is a need for new and more effective treatment options in this setting.

Registered Clinician Input: Meaningful Overall Survival Benefit

Registered clinicians agreed that DOX monotherapy is the standard treatment option for Canadian patients. Input indicated that the magnitude of OS benefit observed with Olara + DOX was large, a benefit that has not been seen in many decades among a variety of agents studied in STS. pERC agreed that Olara + DOX has demonstrated very promising OS improvements, however the results need to be confirmed based on the final results from the randomized phase III ANNOUNCE trial. Based on the results of the JGDG trial, registered clinician input indicated that all patients who would be eligible for DOX monotherapy should qualify for Olara + DOX treatment regardless of histology. pERC noted that eligibility should only be restricted in patients with Kaposi sarcoma as they were excluded from the trial and patients with GIST as there were no patients with GIST enrolled.

Registered clinicians also noted that Olara + DOX was associated with increased myelosuppression, mucositis, vomiting, and abdominal and musculoskeletal pain compared with doxorubicin alone.

PATIENT-BASED VALUES

Values of Patients with Soft Tissue Sarcoma: Quality of Life Improvement, Effective Treatment Options

pERC deliberated upon input from one patient advocacy group describing the experience of four patients and caregivers with STS. Patients described a significant impact on their quality of life due to STS. Patients also described being unable to conduct daily living activities beyond their own treatment. Patients live with considerable, sleeplessness, exhaustion, and various difficulties depending on the location of the tumour. Caregivers indicated that it can be a crushing experience to watch a loved one battle cancer, especially without the ability to access proper treatments.

Patients also expressed that available treatments for STS can be harsh and have a negative impact on their QoL. Despite the availability of chemotherapy patients often need to stop treatment due to disease progression or toxicities associated with treatment. Patients also noted the difficulty in treating their disease given the many subtypes and lack of a "gold standard" treatment.

Patient Values on Treatment: Improvement in Survival, Disease Progression, Quality of Life and Manageable Toxicity Profile.

Patients indicated that any treatment that halts disease progression or increases the length of their lives is very exciting as progression is typically quick after diagnosis of STS. New treatment options that will improve quality of life, stop disease progression, and have a manageable side effect profile are valuable as patients feel this will ultimately improve their outcomes.

One patient and one caregiver with direct experience with olaratumab provided input. This patient indicated that disease progression had stopped, and side effects were not significant. The caregiver indicated that there was less for them to manage and support with positive results and fewer side effects due to olaratumab treatment.

pERC noted that the clinically meaningful improvement in OS and manageable toxicity profile, aligned with patients' value. pERC however noted that QoL, which is greatly impacted in patients with STS, was not measured in the trial; therefore it is unclear if Olara + DOX provides any meaningful improvement in this important patient outcome. pERC agreed that the results of the ANNOUNCE trial will provide data that will help answer important questions related to the magnitude of benefit and other outcomes which patients value such as QoL. Overall, pERC concluded that Olara + DOX aligned with patient values.

ECONOMIC EVALUATION

Economic Model Submitted: Cost-effectiveness and Cost-utility Analysis

The EGP assessed cost-effectiveness and cost-utility analyses comparing Olara + DOX to DOX monotherapy in patients with advanced STS.

Basis of the Economic Model: Small Phase II Trial for Clinical Effect Estimates

Costs included were drug acquisition cost, administration costs, cardiac monitoring costs, AE management costs, subsequent treatment costs and costs due to wastage.

Key clinical effect estimates considered in the analysis include OS, PFS, utilities, and disutilities associated with adverse events. pERC noted that there was uncertainty in the clinical effect estimates given the source of the clinical trial data. Furthermore, extrapolating this uncertain survival benefit over 25 years had a large impact on the ICER. Utility estimates were also based on a literature review and not based on direct measurement from the trial. pERC noted that the ICER was sensitive to utility estimates; however, in the absence of alternative sources, the EGP did not include alterations to utilities in their re-analysis. pERC agreed that results from the ongoing phase III ANNOUNCE trial, which is collecting QoL data, may provide better estimates for QoL in patients treated with Olara + DOX.

Drug Costs: Vial Wastage

Olaratumab costs $788.12 and $2,074.00 per 190 mg and 500 mg vials, respectively. This amounts to $4.15 per mg. The recommended dose of olaratumab is 15 mg/kg on days 1 and 8 of a 21-day cycle. Based on the availability of the 190 mg and 500 mg vials (Q4 and Q1 of 2018, respectively), the cost of olaratumab

will vary. Using 190mg and assuming no wastage olaratumab costs $414.7000per day and $11,614.64 per 28-day course. Using 190 mg and assuming wastage of unused vials, olaratumab costs $450.35 per day and $12,609.92 per 28-day course. Using 500 mg and assuming no wastage olaratumab costs $414.80 per day $11,614.40 per 28-day course. Using the 500 mg vial and assuming wastage of unused vials, olaratumab costs $493.81 per day and $13,826.67 per 28-day course.

Doxorubicin costs $7.21 per mg. At the recommended dose of 75mg/m^2 IV on day 1 of 21-day cycle, doxorubicin costs $43.75 per day and $1,225.33 per 28-day course.

Cost-effectiveness Estimates: Uncertain Clinical Effect Estimates and Long Time Horizon
pERC deliberated on the cost-effectiveness of Olara + DOX compared with DOX and concluded that, at the submitted price, Olara + DOX is not cost-effective. pERC made this conclusion because there is uncertainty in the clinical effect estimates used to inform the model. pERC noted that the number of years patients are anticipated to live and benefit from treatment with Olara + DOX (time horizon) had the largest impact on the ICER. pERC agreed that the prognosis of patients with advanced or metastatic STS is poor therefore, it is not realistic to expect patients would survive an additional 25 years. Given this clinical rationale and the uncertainty in the magnitude of OS benefit with Olara + DOX, pERC agreed with the Economic Guidance Panel's (EGP) re-analysis, shortening the time horizon to five years. pERC also noted that the methods used to extrapolate long-term benefit (parametric model) and the source of patient data used to determine the drug acquisition costs impacted the ICER. pERC agreed with these changes made by the EGP and when all three inputs are changed, the ICER increased substantially. pERC therefore concluded that Olara + DOX is not cost-effective at the submitted price. pERC agreed that results from the ongoing phase III ANNOUNCE trial will be important to determine the magnitude of OS benefit with Olara + DOX and resulting cost-effectiveness. Although not included in the EGP's re-analysis estimates, pERC discussed that the anticipated availability of the smaller 190 mg vial size will minimize wastage and has a meaningful impact on the ICER if only the larger 500 mg vial is available.

ADOPTION FEASIBILITY

Considerations for Implementation and Budget Impact: Time-limited Reimbursement
pERC discussed the feasibility of implementing a reimbursement recommendation for Olara + DOX and noted several factors identified by PAG. pERC noted that the final results for the phase III trial ANNOUNCE is estimated for 2020. Given the uncertainty in the magnitude of clinical benefit and cost-effectiveness, jurisdictions should consider a time-limited reimbursement of Olara + DOX, with a reassessment of the efficacy, safety, and cost-effectiveness when the final results of the ANNOUNCE trial are available from the submitter. pERC noted that this approach would help facilitate the equitable and timely access to promising treatments for patients while ensuring that treatments considered for public reimbursement adhere to a level of rigour that sufficiently demonstrates effectiveness, safety, and cost-effectiveness.

In discussing the patient population that should be eligible for treatment pERC agreed with a time-limited availability of Olara + DOX for patients who are currently receiving single agent DOX and have not had disease progression. pERC also agreed it is reasonable for patients to continue treatment with single agent Olara following the end of fixed DOX treatment as this is in alignment with the trial protocol. Further, pERC agreed that the eligible reimbursement population should not be restricted based on histological subtype except for patients with Kaposi sarcoma who were excluded from the JGDG trial and patients with gastrointestinal stromal tumours (GIST) as no patients with GIST were enrolled in the JGDG trial and there is no evidence for the use of Olara + DOX in this population.

pERC noted that the availability of smaller vial sizes will be important to reduce drug wastage. Currently, only the 500 mg vial is available while the smaller 190 mg vial is anticipated to be available in Q4 2018. pERC agreed on the importance of a timely availability of the smaller vial size to reduce wastage and impact of the added cost on the incremental cost-effectiveness ratio. pERC noted that the budget impact analysis is sensitive to the number of patients who will be eligible for Olara + DOX treatment and the availability of the smaller 190 mg vial size. pERC therefore re-iterated the importance of making smaller vial sizes available to jurisdictions to minimize wastage.

DRUG AND CONDITION INFORMATION

Drug Information	• Monoclonal antibody • 190 mg and 500 mg vials. The 190 mg vial size is anticipated to be available Q$ 2018 • 15 mg/kg on days 1 and 8 of a 21-day cycle
Cancer Treated	• Advanced soft tissue sarcoma
Burden of Illness	• Latest Canadian statistics for 2013 show 1,255 cases and 765 deaths • Median survival of 12 to 18 months with less than 10% surviving five years • Heterogeneous group of malignant tumours
Current Standard Treatment	• Doxorubicin
Limitations of Current Therapy	• No gold standard among various typed of histological subtypes of STS • No major advances in treatment in over 20 years

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

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

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Craig Earle, Oncologist
Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Cameron Lane, Patient Member Alternate
Christopher Longo, Economist
Valerie McDonald, Patient Member
Carole McMahon, Patient Member
Dr. Marianne Taylor, Oncologist

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

- Dr. Kelvin Chan and Dr. Craig Earle who were not present for the meeting
- Cameron Lane who did not vote due to his role as a patient member alternate.

Avoidance of Conflicts of Interest

All members of the 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 olaratumab (Lartruvo) for soft tissue sarcoma (STS), through their declarations, four members had a real, potential, or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, none of these members were excluded from voting.

Information Sources Used

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 the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*.

Use of This Recommendation

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

Disclaimer

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APPENDIX 1: CADTH PAN-CANADIAN ONCOLOGY DRUG REVIEW EXPERT REVIEW COMMITTEE RESPONSES TO PROVINCIAL ADVISORY GROUP IMPLEMENTATION QUESTIONS

PAG Implementation Questions	pERC Recommendation
• PAG noted that the current submission is based on a phase IIb trial while there is an ongoing phase III trial, the ANNOUNCE trial. • The ANNOUNCE trial is evaluating the efficacy and safety of olaratumab plus doxorubicin compared with placebo plus doxorubicin in the same patient population and PAG would like information on this trial, if available.	• pERC noted that the final results for the phase III trial ANNOUNCE is estimated for 2020. Given the uncertainty in the magnitude of clinical benefit and cost-effectiveness, jurisdictions should consider a time-limited reimbursement of Olara + DOX, with a reassessment of the efficacy, safety, and cost-effectiveness when the final results of the ANNOUNCE trial are available from the submitter.
• PAG is requesting information to guide the sequencing of olaratumab and its place in therapy.	• Although over half of the patients in the trial were previously treated, pERC agreed that the trial results can be generalized into the Canadian population, the majority of whom are likely to be first line. Some patients in the Canadian setting are however expected to receive Olara + DOX in the second-line setting (e.g., patients with uterine leiomyosarcoma among others).
• As there are many types of sarcomas, PAG is also requesting clarity on which subtypes of sarcomas would be eligible for treatment with olaratumab and which subtypes should be excluded.	• pERC agreed that the eligible reimbursement population should not be restricted based on histological subtype except for patients with Kaposi sarcoma and GIST.
• PAG would like guidance on any time-limited need for patients who have failed treatment with doxorubicin and for patients who are on doxorubicin but have not yet progressed.	• pERC agreed with a time-limited availability of Olara + DOX for patients who are currently receiving single agent DOX and have not had disease progression.
• PAG noted concern for drug wastage given the low patient numbers and vial sizes (500 mg and 190 mg vials). • Wastage will be very significant if only the 500 mg vial size is initially available. • PAG noted that vial sharing would be difficult with the small number of patients. PAG is requesting information on cost with wastage when only the 500 mg vial size is available and when both the 500mg and 190 mg vial sizes are available.	• pERC noted that both the ICER and BIA are sensitive to the cost associated with the vial size available. • pERC agreed on the importance of a timely availability of the smaller vial size to reduce wastage and impact of the added cost on the incremental cost-effectiveness ratio and minimize wastage.

PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee.