pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Olaratumab (Lartruvo) for Soft Tissue Sarcoma

April 18, 2018

DISCLAIMER

Not a Substitute for Professional Advice

This report is primarily intended to help Canadian health systems leaders and policymakers make well-informed decisions and thereby improve the quality of health care services. While patients and others may use this report, they are made available for informational and educational purposes only. This report should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision making process, or as a substitute for professional medical advice.

Liability

pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report.

Reports generated by pCODR are composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR report).

FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories with the exception of Quebec, which does not participate in pCODR at this time.

INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: info@pcodr.ca
Website: www.cadth.ca/pcodr

TABLE OF CONTENTS

1 GUIDANCE IN BRIEF

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 olaratumab (Lartruvo) for soft tissue sarcoma (STS). 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 CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding olaratumab (Lartruvo) for soft tissue sarcoma (STS) conducted by the Sarcoma Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; 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. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on olaratumab (Lartruvo) for soft tissue sarcoma (STS), a summary of submitted Provincial Advisory Group Input on olaratumab (Lartruvo) for soft tissue sarcoma (STS), and a summary of submitted Registered Clinician Input on olaratumab (Lartruvo) for soft tissue sarcoma (STS), and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the effectiveness and safety of olaratumab (Lartruvo) in combination with doxorubicin for the treatment of 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. This is similar to the Health Canada regulatory approval.

Olaratumab is a recombinant human immunoglobulin IgG1 monoclonal antibody that specifically binds PDGF-alpha, blocking PDGF-AA, PDGF-BB and PDGF-CC binding and receptor activation. The PDGF signaling pathway is important in cancer cell proliferation, metastasis, and the tumour microenvironment. The recommended dose of olaratumab is 15 mg/kg administered by intravenous infusion over 60 minutes on days 1 and 8 of each 21-day cycle, until disease progression or unacceptable toxicity. For the first 8 cycles, olaratumab is co-administered with doxorubicin, which is given on day 1 of each cycle following the olaratumab infusion.

Olaratumab has received regulatory approval from a number of international agencies. The NICE review approved the use of olaratumab in patients have not had any previous systemic chemotherapy for advanced soft tissue sarcoma and cannot have curative treatment with surgery or their disease does not respond to radiotherapy.[1]

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one randomized controlled trial. The results of JGDG trial are presented below.

JGDG trial

Study JGDG was a two-part open-label, phase 1b and randomised phase 2 trial which was conducted at 16 clinical sites in the United States. The trial included adult patients with a histologically confirmed diagnosis of locally advanced or metastatic STS, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, who were not previously treated with an anthracycline. Phase 1b part of the study was non-randomized, and all patients (n=15) received a combination of olaratumab (15 mg/kg) on day 1 and day 8 plus doxorubicin (75 mg/m²) on day 1 of each 21-day cycle for up to eight cycles. In phase 2, patients were randomly assigned, on a 1:1 basis, to receive either combination therapy with olaratumab and doxorubicin (as described for phase 1b; n=66), or doxorubicin (75 mg/m²) on day 1 of each 21-day cycle for up to eight cycles (n=67). The phase 1b primary outcome was safety. The phase 2 primary outcome was investigator-assessed progression-free survival (PFS), defined as the time from the date of randomization to the earliest date of documented tumour progression or death from any cause. A blinded independent retrospective review of radiographic scans was conducted following the final PFS database lock. The secondary outcomes included overall survival (OS), objective response rate (ORR), safety, and pharmacokinetics.[2]

Efficacy

The key efficacy outcomes of JGDG trial are presented in Table 1.1. As of 15-Aug-2014 data cut-off, 55 (83.3%) progression events had occurred in the Olara+DOX arm and 48 events (71.6%) in the DOX arm. The median PFS was 6.6 months (95% CI 4.1, 8.3) in the Olara+DOX arm and 4.1 months (95% CI 2.8, 5.4) in the DOX arm (stratified HR 0.672; 95% CI 0.442–1.021, p=0.0615).[2] The 3- and 6-month investigator-assessed PFS rates were 69.0%, and 53.9%, respectively, for the Olara+DOX arm. The corresponding rates were 59.9% and 31.1%, respectively, for the DOX arm.[2] An independent review showed a median PFS of 8·2 months (95% CI 5·5, 9·8) in the Olara+DOX arm, and 4·4 months (95% CI 3·1, 7·4) in the DOX arm.[2] The PFS HR estimated by the independent review (stratified HR 0.67; 95% CI 0.40, 1.12, p=0.1208) was nearly equal to the HR that was estimated by the investigators. Subgroups analyses did not suggest any significant between-group differences with respect to the histological tumor type, age, gender, duration of disease and site of metastasis.[2-6]

The median overall survival was 26.5 months (95% CI 20.9, 31.7) in the Olara+DOX arm, as compared to 14.7 months (95% CI 9.2–17.1) in the DOX arm (stratified HR, 0·46, 95% CI 0·30–0·71, p=0·0003).[2,4] The 3- and 6-month survival rates were 95.2% and 90.5%, respectively, in the Olara+DOX arm and 87.6% and 73.3%, respectively in the DOX arm.[2]

ORR was 18.2% (95% CI 9.8, 29.6) in the Olara+DOX group and 11.9% (95% CI 5.3, 22.2) in the Dox group (p=0.3421). The ORR for the independent assessment was reported to be 18.2% (95% CI 9.8, 29.6) with Olara+DOX and 7.5% (95% CI 2.5, 16.6) with doxorubicin (p=0·0740). The median duration of response was 8.3 months (95% CI 2.7, 12.7) in the Olara+DOX arm, and 8.2 months (95% CI 2.8, 14.5) in the DOX arm.[2]

Quality of life

Quality of life outcomes were not reported in JGDG trial.

Harms

Adverse events (AEs) reported in phase 1b and phase 2 of JGDG trial are presented in Table In phase 1b, treatment related AEs of any grade occurred in 93.3% (14/15) of the

patients. Grade 3 or 4 treatment-related AEs, and three patients and treatment-related serious AEs were reported in 60% (9/15) and serious AEs in 20% (3/15) of the study participants. In phase 2, similar proportions of patients in Olara+DOX and DOX arms experienced AEs of any grade (98% of patients in each group), or grade 3 AEs (38% in each group). However, a higher percentage of the patients in Olara+DOX arm (42%) experienced grade 4 AEs, when compared with those in the DOX arm (31%). Treatment-related adverse events of grade 3 or higher were also more frequently reported in Olara+DOX group (67%) than in those in the DOX group (55%). The most common adverse events of all grades experienced by the Olara+DOX group were nausea (73%), fatigue (69%), neutropenia (58%), and mucositis (53%). In the DOX group, the most common AEs were fatigue (69%), nausea (52%), alopecia (40%), and neutropenia (35%). Doxorubicin-related toxicities (including neutropenia, mucositis, nausea, vomiting, and diarrhoea) were more frequent in the Olara+DOX arm, but did not result in an increased number of febrile neutropenia events, hospital admissions, treatment discontinuations, or deaths.[2]

Thirteen percent of patients in the Olara+DOX group and 18% of those in the DOX group discontinued treatment because of an AE. Mortality was reported in 61% (39/64) of patients in the Olara+DOX group and 79% (51/65) of those in the DOX group.[4]

Table 1.1: Highlights of Key Outcomes of JGDG Trial

Efficacy outcomes		
	Olara+DOX (N=66)	**DOX (N=67)**
Primary Outcome		
PFS (as assessed by the investigators)		
Number of events, n (%)	55 (83.3)	48 (71.6)
Median PFS, months (95% CI)	6.6 (4.1, 8.3)	4.1 (2.8, 5.4)
Stratified HR* (95% CI)	0.672 (0.442, 1,021)	
3-month PFS rate (95% CI)	69.0 (55.7, 78.9)	59.9 (45.9, 71.4)
6-month PFS rate (95% CI)	53.9 (40.6, 65.4)	31.1 (18.9, 44.1)
Secondary Outcomes		
OS		
Number of deaths, n (%)	39 (59.1)	52 (77.6)
Median survival, months (95% CI)	26.5 (20.9, 31.7)	14.7 (9.2, 17.1)
Stratified HR* (95% CI)	0.463 (0.301, 0.710)	
3-month OS rate (95% CI)	95.2 (86.0, 98.4)	87.6 (76.8, 93.6)
6-month OS rate (95% CI)	90.5 (80.0, 95.6)	73.3 (60.6, 82.5)
ORR (as assessed by the investigators)		
Number of events, n (%)	12 (18.2)	8 (11.9)
Best Overall response		
Complete remission	2 (3.0)	1 (1.5)
Partial remission	10 (15.2)	7 (10.4)
Stable disease	39 (59.1)	34 (50.7)
Progressive disease	11 (16.7)	15 (22.4)
Not evaluable	4 (6.1)	10 (14.9)
Harm Outcomes		
	Olara+DOX (N=64)	**DOX (N=65)**
Phase 1b		
AEs (any grade), n (%)	**15 (100)**	**9 (60)**
Treatment-related AEs	**14 (93.3)**	**8 (53.3)**
SAEs (any grade), n (%)	**7 (46.7)**	**6 (40.0)**
Treatment-related SAEs	**3 (20.0)**	**3 (20.0)**

Table 1.1: Highlights of Key Outcomes of JGDG Trial		
Efficacy outcomes		
WDAE	0 (0)	0 (0)
Phase 2		
AEs (any grade), n (%)	63 (98)	64 (98)
Treatment-related AEs	63 (98)	63 (97)
SAEs (any grade), n (%)	27 (42)	25 (38)
Treatment-related SAEs	14 (22)	17 (26)
WDAE	8 (13)	12 (18)
AE = adverse event, CI = confidence interval, HR = hazard ratio, HRQoL = health-related quality of life, N = number randomized; n = number of events; SAEs = serious adverse events; WDAE = withdrawal due to an adverse event *HR < 1 favours Olara+DOX		

Limitations

- The JGDG trial is a phase-1b/phase 2 open-label trial that provided preliminary results on the efficacy of olaratumab as an add-on to doxorubicin in patients with advanced STS. The study allowed for a significance level of 0.20 (nominal significance level of 0.1999 adjusted for the interim analysis). However, uncertainty around the key efficacy results is reported based on the 95% CIs (which correspond to a 0.05 level of significance). Therefore, although the authors reported a protocol-defined statistically significant PFS improvement in the Olara+DOX arm, there is a considerable overlap of the 95% CIs between the median PFS rates reported for Olara+DOX and DOX arms. Furthermore, the 95% CI for the reported stratified HR for PFS contains 1.0 (null hypothesis value). Therefore, the results should be judged with attention to the fact that, for a given sample size, an extended significance level (i.e., increased type I error rate) can increase the risk of drawing a false-positive conclusion (rejecting the null hypothesis when it is true).
- The open label nature of the study might introduce the risk of reporting and performance biases, as the study participants and the investigators were aware of the treatment assignments. This could particularly be important in reporting of subjective outcomes (e.g., AEs) by the patients and care providers.
- There were more patients who required doxorubicin dose adjustments in the Olara+DOX arm than in the DOX arm. In addition, the rate of censoring was higher in the DOX arm. The investigators performed sensitivity analyses using different censoring/event definition scenarios, to show the robustness of their primary analysis. The results of the sensitivity analyses should be taken into account when interpreting the results.
- After completion of 8 cycles of DOX, patients in the Olara + DOX group could receive Olara monotherapy until disease progression, while patients in the DOX group were observed and could receive Olara monotherapy after documented disease progression. The OS rates might be confounded because the patients in the DOX arm who crossed over to olaratumab were not analysed in their assigned treatment group.
- The study showed an improvement in PFS and OS in patients who received olaratumab as an add-on to doxorubicin, However, the treatment effect size was greater for OS (11.8 months; p=0·0003) than for PFS (2.5 months; p=0.0615); i.e., the longer OS is not sufficiently explained by an increased delay in tumor progression. This disparity between the magnitude of estimates of PFS and OS should be addressed in future confirmatory trials.
- Patient-reported quality of life outcomes were not measured in the JGDG trial.[5]

- An ongoing randomized, double-blind, placebo-controlled, phase 3 —ANNOUNCE— trial is expected to clarify some of the uncertainties surrounding survival outcomes (OS and PFS) in JGDG, and address limitations that arise from the lack of allocation concealment and QoL measures in this phase 2 trial. The results of the ANNOUNCE trial are anticipated in 2019.

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

From a patient perspective soft tissue sarcoma is an aggressive disease where there is no cure. Available treatments, such as chemotherapies for the disease can be harsh and provide low quality of life for patients. Patients live in considerable pain, sleeplessness, exhaustion and various difficulties depending on the location of the tumour. Additionally, caregivers have lost employment, lost homes, and generally live in difficulty for long periods of time as they miss out on day to day activities and being part of their family and community. SFCF noted that the currently available treatments present challenges as STS has many different subtypes, it is difficult to find "gold-standard" treatments that will work across all patients. SFCF hopes for a new treatment that will improve quality of life, "halt disease progression", increase length of life and provide a manageable side effect profile. The one patient who had direct experience with olaratumab reported that he was able to see a "halt in disease progression" and the side-effects were not significant.

Please see Section 3 for details.

Provincial Advisory Group (PAG) Input

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

Clinical factors:

- Place in therapy and sequencing with chemotherapy
- Submission is based on Phase 2b trial with an ongoing Phase 3 trial

Economic factors:

- Potential for wastage due to small patient numbers and available vial sizes

Please see Section 4 for details.

Registered Clinician Input

Treatments for STS include single agent doxorubicin, single agent gemcitabine, gemcitabine/ docetaxel combination, and pazopanib. Olaratumab plus doxorubicin demonstrated superiority in overall survival compared with doxorubicin alone with patients living a median of 12 months longer. This is the first time in decades that a drug has demonstrated survival benefit in adults with advanced STS and represents a necessity for Canadian patients. Olaratumab plus doxorubicin would be considered first-line for patients with advanced/metastatic STS. Clinicians don't anticipate any patients would be ineligible based on histology.

Please see Section 5 for details.

Summary of Supplemental Questions

Summary of a Manufacturer-submitted indirect treatment comparison of olaratumab versus available treatment options in patients with advanced STS

The results of the Manufacturer-submitted systematic review and NMA[7,8] suggested that Olara+DOX had a significantly greater OS benefit than DOX, GemDoc, and three IfoDOX regimens. The hazard ratio NMA method demonstrated a significant PFS benefit for

Olara+DOX compared with GemDoc, while the results of the fractional polynomial NMA showed a significantly greater PFS for Olara+DOX when compared with IfoDOX (12.5 g/m2, 90 mg/m2), DOX, and GemDoc. No significant differences were identified between Olara+DOX and other treatments of interest in terms of objective tumor response rate. Discontinuation rate due to AEs was significantly lower for Olara+DOX, when compared with GemDoc and three of the four IfoDOX regimens.

Overall, the results of the NMAs should be treated with caution because there were no closed loops in the network and there was only one study for each comparison.

See section 7 for more information.

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.

1.2.3 Factors Related to Generalizability of the Evidence

Table 1.2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

[Table 2]: Assessment of generalizability of evidence for [drug name in indication]

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td rowspan="3">Population</td><td>Performance status</td><td>JGDG trial limited eligibility to patients with an ECOG performance status of 0-2. Ninety four percent of patients in both arms had an ECOG score of 0 or 1.

<table><tr><td>ECOG</td><td colspan="2">Study Cohorts</td></tr><tr><td></td><td>Olara+DOX</td><td>DOX</td></tr><tr><td>0-1</td><td>62 (94%)</td><td>63 (94%)</td></tr><tr><td>2</td><td>4 (6%)</td><td>4 (6%)</td></tr></table></td><td>Does performance status limit the interpretation of the trial results (efficacy or toxicity) with respect to the target population (e.g., Canadian clinical practice)?</td><td>The CGP recognize that few patients in the JGDG trial had an ECOG PS of 2. Given that these patients were not excluded from the trial, the CGP agree that the use of olaratumab in patients with ECOG PS of 2 should be at the discretion of the treating physician.</td></tr>
<tr><td>Age</td><td>JGDG trial limited eligibility to patient’s ≥18 years. The median age was 58.5 (range: 22-85) years in Olara+DOX group and 58.0 (range: 29-86) years in DOX group.</td><td>Does the age restriction in the trial limit the interpretation of the trial results with respect to the target population?</td><td>The CGP agree the overall trial results are generalizable to the different age groups represented in the JGDG trial.</td></tr>
<tr><td>Previous anti-cancer treatments</td><td>Thirty nine patients (59%) in the Olara+DOX arm and 36 patients (54%) in the DOX arm had received prior systemic anti-cancer treatments before entry to the phase 2 trial. The number and type of previous systemic treatments are listed below

<table><tr><td>Lines of therapy, n (%)</td><td>Olara+DOX (n=66)</td><td>DOX (n=67)</td></tr><tr><td>1st line</td><td>14 (21.2)</td><td>12 (17.9)</td></tr><tr><td>2nd line</td><td>8 (12.1)</td><td>7 (10.4)</td></tr><tr><td>3rd line</td><td>2 (3.0)</td><td>1 (1.5)</td></tr><tr><td>4th line</td><td>2 (3.0)</td><td>0 (0)</td></tr></table>
<table><tr><td>Previous regimens, n (%)</td><td>Olara+DOX (n=66)</td><td>DOX (n=67)</td></tr><tr><td>Gemcitabine/ Docetaxel</td><td>25 (37.9)</td><td>27 (40.3)</td></tr><tr><td>Other</td><td>24 (36.4)</td><td>19 (28.4)</td></tr></table></td><td>Are the pre-trial treatments used by the trial participants relevant in the Canadian setting?</td><td>In Canada, most patients presenting with metastatic STS would be chemotherapy-naive. Those who received (neo)adjuvant DOX containing regimens would not be eligible for Olara+DOX treatment. A small number of patients, mainly with leiomyosarcomas often of uterine origin, may already have received gemcitabine/docetaxel chemotherapy before being considered for Olara+DOX.</td></tr>
<tr><td>Outcomes</td><td>Appropriateness of primary and Secondary Outcomes</td><td>Primary: PFS by the investigators
Secondary: OS, PFS by independent review panel, ORR by investigator and independent review panel, safety</td><td>Were the primary and secondary outcomes appropriate for the trial design?</td><td>The CGP agree the outcomes used in the trial are relevant and clinically appropriate.</td></tr>
<tr><td rowspan="2">Setting</td><td>Countries participating in the trial</td><td>The trial was conducted in 16 centres in the United States.</td><td>Is there any known difference in the practice pattern between those countries and Canada?</td><td>The CGP agree that there are difference in treatment sequence patients would get between Canadian and US patients. It is unclear how this would impact the overall trial results.</td></tr>
<tr><td>Location of the participating centres</td><td>The vast majority of the study sites (14 of 16) were academic centres.</td><td>Are the results of the trial generalizable to community practice setting in Canada??</td><td>The CGP agree the setting in which the trial was conducted is generalizable to the Canadian context.</td></tr>
<tr><td colspan="5">CGP = Clinical Guidance Panel; DOX = doxorubicin monotherapy; ECOG = Eastern Cooperative Oncology Group; Olara+DOX = combination therapy with olaratumab and doxorubicin; ORR = objective response rate; PFS = progression-free survival; OS = overall survival</td></tr>
</table>

1.2.4 Interpretation

Burden of Metastatic Soft Tissue Sarcoma (STS)

Soft tissue sarcomas (STS) are malignant tumours, derived from mesenchymal tissues outside the skeleton that are not organ specific and can arise anywhere in the body. Excluding pediatric sarcomas, the peak age incidence is between 60 and 80 years, but with a significant spread that include adolescents and young adults. The most common primary sites of metastasis are the lower limb, buttock and intra-abdominal. STS are rare comprising of less than 1% of all malignancies. The latest Canadian statistics for 2013 show 1,255 cases and 765 deaths.[9] The majority of deaths occur as a result of distant metastases or unresectable disease (particularly for non-extremity sites). Median survival from diagnosis in patients requiring palliative chemotherapy is poor, in the range of 12-18 months, with less than 10% surviving 5 years. If Olara+DOX becomes available, a reasonable estimate of patients who would be eligible for this treatment is 500-600 patients/year.

Feedback from patient advocacy groups emphasizes the high mortality rate, and the burden of disease related to pain, exhaustion and local functional disabilities that often limit activities of daily living. Treatment options are limited and multiple toxicities impact quality of life. The CGP agree that this experience described by patients is representative of what is seen with patients in clinical practice.

Effectiveness of Olaratumab (in combination with DOX)

As outlined in Section 2.1, for the past 20 years single agent DOX has been the standard of care for palliative treatment of advanced/metastatic STS in Canada (CCO Guideline), and is an appropriate comparator for any new systemic treatment. For fitter, younger patients, the combination of IfoDOX (IFOS) may be used based on the results of multiple studies, but most definitively on the large EORTC trial[10] which showed significant improvement in RR (p=0.0006) and median PFS (HR 0.74, p=0.0003) but not OS (HR 0.83, p=0.076). The CGP agree that in the majority of instances DOX is used in the Canadian setting and DOX+IFOS would have limited use.

Currently available clinical data on olaratumab are limited to the results of a single prospective phase 1b/II trial, JGDG. A follow up study, JGDJ (ANNOUNCE), is a randomized, double-blind, placebo-controlled, phase 3 trial comparing Olara+DOX with placebo + DOX in patients with metastatic STS. Enrollment of 460 patients is complete, and first results are expected in early 2019. ANNOUNCE 2 is a phase 1b (open label) leading into a phase 2, double-blind study of Olara + Docetaxel/Gemcitabine vs Placebo + Docetaxel/Gemcitabine, enrolling 310 patients with first results expected at the end of 2019.

Study JGDG (Tap-W, 2016) was a two-part open-label, phase 1b and randomized phase 2 trial, conducted at 16 sites in the United States (no Canadian participants). Eligibility criteria included histologically confirmed diagnosis of locally advanced/metastatic STS (excluding Kaposi sarcoma) not previously treated with an anthracycline, age 18 years or above, ECOG performance status 0-2, and accessible tumour to determine platelet derived growth factor alpha (PDGFα) expression. In phase 1b, all 15 patients received DOX 75 mg/m2 IV + olaratumab 15 mg/kg IV days 1 and 8 every 21 days for up to 8 cycles (Olara+DOX). In phase 2, patients were randomly assigned 1:1 to Olara+DOX (66 patients) and standard DOX (67 patients). Dexrazoxane could be administered with DOX (ratio 10:1) at investigator discretion on day 1, cycles 5-8.

The phase 1b primary endpoint was safety and the phase 2 primary endpoint was PFS, using a 2-sided alpha level of 0.2 and statistical power of 0.8. Secondary endpoints included OS, objective response rate (ORR), safety and pharmacokinetics. The analysis population for efficacy was changed from randomized and treated to all randomized patients (intention-to-treat [ITT] population). The original statistical analysis plan presented 90% CIs for efficacy outcomes but this was changed to 95% CIs, thought to be more appropriate and conventional for regulatory submissions. Additional ad-hoc sensitivity exploratory analyses were performed to evaluate the robustness and internal consistency of OS results to any potential impact of baseline and post-baseline variables.

The baseline characteristics (age, race, ethnic origin, ECOG PS) were balanced except for a slightly higher proportion of women in the Olara+DOX arm (61%) vs the DOX arm (51%). Distribution of histological type, when divided between leiomyosarcoma (36% vs 40%) and non-leiomyosarcoma (64% vs 60%), was similar, but there were 25 different subtypes represented in the latter group, making it impossible to ensure balance. Prior systemic therapy was administered in 38 (58%) vs 37 (55%) of patients, with neo-/adjuvant chemotherapy given to 20 in each arm, and up to 4 lines of chemotherapy for advanced disease used in 26 vs 20 patients. Drugs involved were mainly ifosfamide, docetaxel and gemcitabine, and it is difficult to evaluate extent and type of chemotherapy delivered and assess the possibility of chemo-resistance. Details of duration of disease from primary diagnosis to trial entry, disease–free interval (DFI), which could indicate the proportion of slow vs rapidly growing tumors, was not broken down for each arm. There were no obvious imbalances of sites of metastatic disease between the 2 arms, but no measurement of disease burden (multiple sites/bulky disease).

As of the 15 August 2014 data cut-off, 55 (83.3%) progression events had occurred in the Olara+DOX arm and 48 (71.6%) in the DOX arm. The median PFS was 6.6 months (95% CI 4.1-8.3) vs 4.1 (95% CI 2.8-5.4), with a stratified HR 0.672; 95 % CI 0.442-1.021, p=0.0615). Subgroup analyses for PFS did not suggest any significant between-group differences with respect to histological subtype, age, gender, duration of disease and site of metastasis. Final analysis of OS was performed as planned after 91 (71%) patients died in the ITT population. The median OS was 26.5 months (95% CI 20.9-30.1) for Olara+DOX vs 14.7 months (95% CI 9.2-17.1) for DOX, with a stratified HR 0.46; 95% CI 0.30-0.71; p=0.0003). It is notable that the Kaplan-Meier OS curves separated early in therapy, within the first 2 months, and remained stable over time. A stratified Cox multivariate model of OS was performed, adjusting for multiple potential prognostic factors, and was consistent with the primary analysis. There seemed to be more benefit for Olara+DOX for those having a shorter duration of disease (split at 14.95 months) before study entry. PDGFα was analyzed twice, because a more specific assay was developed. With the latter assay, 33% of tumors in patients treated with Olara+DOX and 34% with DOX were positive but the interaction effect between PDGFα expression (positive vs negative) and treatment was not significant for either OS (p=0.3209) or PFS (p=0.5924). ORR, defined as the proportion of patients achieving a best overall response of CR or PR, was 18.2% (95 % CI 9.8-29.6) in the Olara+DOX group and 11.9% (95% CI 5.3-22.2) in DOX group (p=0.3421). Results of a blinded independent review produced respective ORR of 18.2% vs 7.5% (p=0.0740).

Safety of Olara+DOX

The addition of olaratumab to DOX was generally well tolerated, although there were more grade 4 AEs (42% vs 31%). Treatment-related AEs of grade 3 or higher were also more frequent (67% vs 55%). The most common AEs of all grades on Olara+DOX were nausea (73%), fatigue (69%) neutropenia (58%) and mucositis (53%). In the DOX group, these were fatigue (69%), nausea (53%), alopecia (40%) and neutropenia (35%). The percentage of

patients who discontinued Olara+DOX was lower (13%) than on DOX (18%). DOX-related toxicities (including neutropenia, mucositis, nausea, vomiting diarrhea) were more frequent in the Olara+DOX arm, but did not result in an increased number of febrile neutropenia events, hospital admissions, treatment discontinuations or deaths. Data were not collected on quality of life (QoL) or patient reported outcomes (PRO).

Limitations of Evidence

- The evidence is based on a single small RCT, in which a large and highly significant improvement in median OS of 11.8 months is reported. Although the difference in PFS is only 2.5 months, as the statistical plan allowed for a significance level of 0.20, in the manuscript (Tap-W, 2016). Based on this analysis plan, the current results would be described as a significant improvement. However, the 95% CI (corresponding to 0.05 significance) reported for regulatory purposes overlapped 1.0, increasing the risk of drawing a false-positive conclusion.
- The greater treatment effect size for OS is unusual, and the small size of the study in a heterogeneous tumour such as STS with many different subtypes raises the possibility of imbalance of prognostic factors between the arms leading to a false-positive result. Although the sensitivity analyses did not show any obvious differences with respect to histological subtype, age, gender, duration of disease and site of metastasis, these have limitations within the compared groups. For example, histological type comparison was restricted to leiomyosarcoma vs non-leiomyosarcoma, and there was limited information about sites of primary metastases and disease free interval. The CGP acknowledge that to fully address concerns related to potential imbalance among multiple sub-types of STS, very large trials (accrual numbering in the thousands) would be needed. Given the very low incidence of STS these trials have never been done. The CGP anticipate that the number of patients recruited in the ANNOUNCE trial would be sufficient to clarify this limitation.
- The very early separation (by 2 months) of the OS curves could suggest a biological rather than treatment effect.
- The open label nature of the study could increase the risk of reporting and performance biases. This was addressed by a blinded independent assessment of treatment response and disease progression, which did not significantly alter the conclusions. The OS results are not subject to this type of bias.
- After completion of eight cycles of DOX, patients on Olara+DOX were permitted to remain on Olara monotherapy (maintenance) until disease progression, while patients on the DOX arm were allowed to cross-over to Olara monotherapy after documented disease progression. The OS rates might be confounded as the ITT analysis was performed with no adjustment for cross-over; i.e., the patients in the DOX arm who crossed over to olaratumab were kept in the DOX monotherapy group.
- Patients were not chemo-naïve on entry to the study, with 55-58% having received previous chemotherapy with a variety of drugs, increasing the risk of variable drug resistance in patients on the trial.
- There is no clear evidence of a specific targeted mechanism of action for olaratumab in this study as PDGFα expression in the STS was not related to outcome.
- The increase in toxicity in the Olara+DOX arm, compared with DOX alone, was relatively mild and importantly did not result in an increased number of febrile neutropenia events, hospital admissions, treatment discontinuations or deaths. However, no data were collected on QoL or PRO, a deficiency that has been addressed in the phase 3 trial, ANNOUNCE.

With the results of the ANNOUNCE trial the CGP anticipate that the response and survival (PFS, OS) outcomes observed in the JGDG trial would have a more firm basis in a properly constructed phase III trial powered for these outcomes. This would also apply to sub-group analyses.

Need and Therapeutic Options

Therapeutic options are limited for patients with STS. DOX with/without IFOS has remained the standard first-line therapy for more than 30 years, and second-line therapies have limited efficacy. Survival rates for patients with metastatic disease remain dismal.

Patient input emphasizes that "…there are few effective new treatments and any new treatments are extremely welcome in the patient community…" and "…any treatment that halts disease progression or increases the length of a patient's life is very exciting". Other comments include "…less targeted treatment have considerable side effect profiles, so a new development like Olaratumab is extremely positive and long-awaited by our community" and "access to treatments remains a critical issue for sarcoma patients, as those without private insurance or a plan that will cover certain treatments have difficulty paying the high cost of treatments not funded publicly". Information is only available from one Canadian patient who received Olaratumab "…we were thrilled to hear that he was able to see a halt in disease progression and did not feel that the side effects were significant. This gives us great hope that as more Canadian patients are able to access this treatment, they too will show positive results. The benefit to patients and families is immeasurable – essentially positive results give them hope and a future where they had terminal diagnosis before."

The CGP noted that registered clinicians are equally excited about olaratumab, stating that "this is the first time in decades that a drug has demonstrated survival benefit in adults with advanced STS and represents a necessity for Canadian patients." An additional comment is that "olaratumab in combination with doxorubicin is now considered standard treatment for adults with soft tissue sarcoma in the US…" The Provincial Advisory Group (PAG) poses some questions about subtypes of STS which would be eligible for treatment with Olara+DOX, and requests guidance on any time-limited need for Olaratumab in patients who have failed treatment with DOX, and those on DOX who have not yet progressed. PAG also raised concerns about drug wastage given the vial sizes (500 mg and 190 mg) and the extra personnel resources needed and costs of delivering an intravenous treatment twice every 3 weeks.

1.3 Conclusions

The Clinical Guidance Panel concludes that there is a net overall clinical benefit to the addition of Olaratumab to DOX chemotherapy in the treatment of advanced/metastatic STS, based on data from one phase 2 RCT that has shown a clinically and statistically significant improvement in median OS of 11.8 months for patients receiving Olara + DOX compared with those receiving DOX alone. Olaratumab was well tolerated, although toxicity (nausea, fatigue, mucositis, neutropenia) was greater than with DOX alone, but did not result in an increased number of febrile neutropenia events, hospital admissions, treatment discontinuations or deaths.

The Clinical Guidance Panel also considered a number of caveats to this conclusion:

- The small size of the study (133 patients) in a heterogeneous tumour means that there are risks of imbalance of prognostic factors (known and unknown) across the arms, and confounding by previous and subsequent chemotherapies.

- An unusually high proportion (55-58%) of patients had received previous chemotherapy before trial entry, reflecting practice in US centres, but increasing the risk of variable drug resistance across the arms. In contrast, it is likely that most Canadian patients would receive DOX +/- Olaratumab as first-line therapy for metastatic STS, although some might have received (neo)adjuvant chemotherapy.
- The early separation of the OS curves could suggest a biologic (variation in tumor aggressiveness across the arms) rather that a treatment effect, and this is consistent with the modest median PFS difference of 2.5 months.
- There is no clear evidence of a specific targeted mechanism of action for Olaratumab, as PDGFα expression in the STS was not related to outcome.
- Although side-effects of the combination were only slightly worse that on DOX alone, QoL and PRO were not collected in this study.
- Administration of Olaratumab IV days 1 and 8, every 3 weeks will be more inconvenient for patients and providers, unless it replaces use of IFOS in combination with DOX. Notably, IFOS+DOX is not widely used in Canada
- ANNOUNCE – a randomized, double-blind, placebo-controlled, phase 3 trial comparing Olara+DOX with Placebo + DOX in patients with metastatic STS - has completed enrollment of 460 patients, and first results are expected in early 2019. The primary outcome is OS, and QoL data are being collected.
- Sarcoma patient groups and registered clinicians are excited by the potential of this treatment to prolong survival in clinical practice, although there is virtually no Canadian experience reported to date (Canadian sites are participating in the ANNOUNCE phase 3 trial).
- If the use of Olara+DOX is recommended on the basis of the JGDG phase II RCT, eligibility for this treatment should closely follow the trial criteria.
- All histological types of STS should be eligible, with the exception of Kaposi sarcoma and GIST (although the latter was trial eligible, no cases were entered).
- It should be left to clinician discretion whether to give Olara+DOX to patients with ECOG PS of 2 (only 6% of trial patients were in this category).
- Although it may be reasonable to add Olaratumab to treatment for patients who have already started single agent DOX therapy (or have completed this treatment but not relapsed), the CGP does not recommend this strategy until more data are available from the completed ANNOUNCE trial.
- Olaratumab should not be given with chemotherapies other than DOX.

2 BACKGROUND CLINICAL INFORMATION

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

2.1 Description of the Condition

Soft tissue sarcomas (STS) are malignant tumors derived from mesenchymal tissue outside the skeleton. As this tissue is ubiquitous throughout the body, STS are not organ specific and can arise in any site. Commonest primary locations are lower limb, 29%, particularly the thigh, and intra-abdominal, 36%, including 15% retroperitoneal and 21% visceral.[11] The median age at diagnosis is 65 years. Pathological classification is complex, and conventionally is based on features of histological differentiation characteristic of normal mesenchymal tissues such as striated/smooth muscle, fat, nerve sheath, blood vessels etc. with the commonest histological types being liposarcoma, leiomyosarcoma and undifferentiated pleomorphic sarcoma.

Immunohistochemical markers are used to distinguish STS from carcinomas, melanomas, lymphomas and other malignancies, and may assist in characterization of subtypes. Increasing knowledge of molecular biology has allowed the identification of some rare types of sarcoma that are associated with specific types of chromosomal translocation (e.g., Ewing's sarcoma, synovial sarcoma, myxoid liposarcoma, alveolar rhabdomyosarcoma), although understanding of the molecular changes that drive growth is still imperfect.[12,13] Our knowledge improved with the discovery that growth of gastrointestinal stromal tumors (GIST), previously known as leiomyosarcomas of bowel, is frequently driven by mutations of the KIT gene, and targeted therapy with imatinib is highly effective in producing durable remissions in recurrent and metastatic GIST.[14] Unfortunately, similar dramatic successes in other adult STS have been elusive, as tumor growth is usually driven by complex molecular alterations.[12,13] However, as our knowledge and understanding of the biology of STS has improved, targeted agents developed for use in commoner cancers have been evaluated in STS with putative targets.

It should be emphasized that the extreme heterogeneity of STS (differing sites of origin and metastasis, histologic and molecular variants) increases the risk of imbalance of prognostic factors, known and unknown, in small prospective studies. In the metastatic situation, this is compounded by varying intervals between primary tumor diagnosis and metastasis (disease-free interval) reflecting sarcoma aggressiveness. These factors are of particular concern in phase II evaluations, but also can be a source of bias in small randomized trials (RCT). Logistically, it is difficult in a rare tumor to conduct RCT accruing thousands of patients, but adequate trial size is important.

As many cancer registries collect organ specific data, it is difficult to find accurate information on incidence and mortality. Many textbooks and reviews give vague figures, e.g., STS are <1% of all cancers, incidence rates range from 1.5 - 5 per 100,000 population.[11] The American Cancer Society[15] estimates that in 2017 there will be 12,390 cases of STS with 4,990 deaths. The latest statistics from the Canadian Cancer Society[9] are 1,255 new cases and 765 deaths (2013). Most deaths occur as a result of distant metastases which develop in approximately one-third of patients. Extremity STS have a predilection for metastasis to lung and, except for a few subtypes (e.g., epithelioid, synovial, rhabdomyosarcomas) rarely spread to lymph nodes. Intra-abdominal sarcomas often metastasize to liver.[11]

2.2 Accepted Clinical Practice

Primary STS are treated by surgery alone, surgery plus radiotherapy with or without (neo)adjuvant chemotherapy. Locally recurrent tumors are managed in a similar way. In a highly selected group of patients, resection of metastases (usually in lung or liver) may be curative.[11]

Most patients who develop metastases are not suitable for surgery, and if medically fit will receive palliative chemotherapy. Standard first-line regimens have included doxorubicin (DOX) alone, DOX combinations such as mesna/adriamycin/ifosfamide/dacarbazine (MAID), DOX + ifosfamide (IFOS) and adriamycin + dacarbazine (ADIC) with/without cyclophosphamide (CYVADIC).[11,16] A meta-analysis of RCT comparing DOX with DOX combinations formed the basis for a Cancer Care Ontario (CCO), Program in Evidence-Based Care, Practice Guideline 11.2.8[17] This was first published in 1999, with updated literature searches in 2004 and September 2011. In the original meta-analysis, eight RCT including 2,281 patients were reviewed. Objective response rates (RR) ranged from 16-27% for DOX and 14-34% for DOX combinations. There was a trend for improved RR with combination chemotherapy, but this did not reach statistical significance (OR 0.79; 95% CI 0.60-1.05; p=0.10). Survival (OS) data could only be abstracted from 6 studies involving 2,097 patients, and showed no significant advantage for DOX combination therapy (OR 0.84; 95% CI 0.67-1.06; p=0.13). Nausea, vomiting and myelosuppression were more frequent with combination chemotherapy. Other common toxicities occurring with DOX alone or in combination include alopecia, mucositis and the risk of cardiotoxicity with cumulative doses of DOX □550 mg/m2. Two additional RCT were identified in the CCO 2011 search. In the first, two different schedules of high dose IFOS (9 g/m2 continuous infusion over 3 days and 3 g/m2 over 3 hours daily x 3) were compared with DOX 75 mg/m2.[18] In this study 326 patients were randomized, and similar RR, progression-free (PFS) and OS were seen in the 3 arms. Although high RR (up to 50%) have been reported in many phase II studies of DOX/IFOS combinations, these have not been confirmed in RCT. For example, in the second study reviewed by CCO,[19] which was stopped at interim analysis for futility, DOX 75 mg/m2 x 6 cycles (Arm A, n=67) was compared with a sequential combination of DOX 30 mg/m2 daily x 3 every 3 weeks for 3 cycles followed by IFOS 12.5 g/m2 by continuous infusion over 5 days every 3 weeks x cycles (Arm B, n=65). RR were 23.4 % in Arm A and 24.1% in Arm B, with no significant differences in PFS (p=0.88) and OS (p=0.14). The results of these two studies did not alter the Guideline conclusions, and the 2004 recommendation was endorsed "Single agent doxorubicin is an appropriate first-line chemotherapy option for advanced or metastatic STS. Some combination chemotherapy regimens, given in conventional doses, produce only marginal increases in response rates at the expense of increased toxic effects, with no improvement is overall survival." This Guideline is no longer maintained, and was archived in October 2014, available for Education and Information purposes.

The largest and probably most definitive RCT of a DOX/high-dose IFOS combination,[10] similarly showed disappointing results. DOX 75 mg/m2 (n=228) was compared with DOX 75 mg/m2 + IFOS 10 g/m2 over 4 days (n=227). The RR, 14% vs 26%, p< 0.0006, and median PFS, 4.6 vs 7.4 months, HR 0.74, p=0.003, were better for the combination, but median OS was not significantly different, 12.8 vs 14.3 months, HR 0.83, p=0.076. Toxicities were substantially greater for the combination treatment. Interpretation of these results has varied, but in Canada and many European countries, single agent DOX has remained the standard of care for palliative chemotherapy in advanced/metastatic STS.

The remainder of this review will focus on studies conducted over the last 20 years, evaluating new drugs or combinations particularly where these have been compared in RCT with single agent DOX, which is generally accepted as the standard of care for first-line chemotherapy for

metastatic STS. Unless stated otherwise, "standard DOX" refers to DOX 75 mg/m2 given IV every 3 weeks until progression, or for 6-8 cycles.

IFOS is one of the more active drugs in STS but has significant side effects. In addition to myelosuppression, specific toxicities include bladder irritation with hematuria, and at higher doses renal damage, and rarely unpredictable neurotoxicity causing confusion/coma. Mesna and extensive hydration reduce these risks. Thus some more recent studies have focused on analogues of IFOS that may be more active and/or have less toxicity. Palifosfamide is an active metabolite of IFOS that does not require prodrug activation, avoiding the generation of toxic metabolites. However, in a large RCT[20] standard DOX + placebo (n=221) was compared with standard DOX + palifosfamide 150 mg/m2 (n=226), and respective median PFS were 5.2 vs 6.0 months, HR 0.86, p=0.19, with more toxicities in the combination arm. Median OS rates were 16.9 vs 15.9 months, HR 1.05, p=0.74. Similarly, no benefit was demonstrated for evofosfamide, a hypoxia-activated prodrug of bromo-isophosphamide mustard. In a large RCT[21] median OS rates, 19.0 vs 18.4 months, HR 1.06, p=0.527, were similar for arms comparing standard DOX (n=323) vs standard DOX + Evofosfamide 300 mg/m2 days 1, 8 (n=317).

The benefits of second-line chemotherapy are even more limited, and few RCT have been performed in this setting. The most commonly used agents in Canada are IFOS (if not used first line), dacarbazine13 and gemcitabine (GEM) +/- docetaxel (DOC). In selected patients, high dose (12-14 g/cycle) IFOS may be used in patients who have failed conventional doses of the drug. RR are usually in the range 10-20% with PFS in the range of 3-6 months. More recently, based on promising phase II data[22,23] use of a combination of GEM/DOC has been advocated for treatment of leiomyosarcomas (particularly those in the uterus). However, in an RCT (vs GEM alone) in an unselected group of STS, the results of this combination were disappointing.[24] Not surprisingly, when the DOC/GEM combination was compared with DOX as first line chemotherapy, it was not superior and toxicities were similar. In this UK/Swiss trial,[25] comparing standard DOX (n=129) with GEM 675 mg/m2 days 1,8 + DOC 75mg/m2 (n=128), median PFS rates were 23.3 vs 23.7 weeks, HR 1.28, p=0.06.

Eribulin, a new microtubule-dynamic inhibitor, 1.4 mg/m2 days 1,8, was compared to dacarbazine, 850-1200 mg/m2, in patients with liposarcoma or leiomyosarcoma who had received at least 2 prior chemotherapy regimens for advanced STS. Interestingly, survival was significantly improved in patients receiving eribulin (n=228) vs dacarbazine (n=224) with median OS rates of 13.5 vs 11.5 months, HR 0.77, p=0.0169.[26] Somewhat puzzlingly, median PFS was similar for the two arms, 2.6 vs 2.6 months, HR 0.88, p=0.23). Although not a comparison with standard DOX as first-line therapy, this RCT of eribulin in STS provides an interesting example of extension of OS in the setting of limited effects on PFS, a phenomenon observed in the olaratumab/DOX study under review.

Trabectedin is a novel agent binding to the minor groove of DNA inducing single- and double-strand breaks. It has been approved in Europe for some time for treatment of STS. In a large RCT comparing trabectedin (n=354) to dacarbazine (n=173) in patients with advanced liposarcoma or leiomyosacoma who had received prior therapy including an anthracycline, median PFS 4.2 vs 1.5 months, HR 0.55, p<0.001 was superior, but at interim analysis, OS was similar, 12.4 vs 12.9 months, HR 0.87, p=0.37.[27] However, when two schedules of trabectedin, a 3 hour infusion (T3h, n=47) and a 24 hour infusion (T24h, n=43), were compared with standard DOX (n=43) as first-line therapy in advanced STS, respective median PFS were 2.8, 3.1 and 5.5 months (HR 1.13, p=0.675 for T3h vs DOX and HR 1.50, p=0.944 for T24h vs DOX). The trial was terminated early for lack of superiority.[28] In July 2011, trabectedin was approved by Health Canada. It was evaluated by pCODR, and the final recommendation by pERC, 5 August 2016, was not to reimburse trabectedin in the treatment of metastatic liposarcoma or leiomyosarcoma after failure of prior anthracycline and ifosfamide chemotherapy.

There are some data to suggest that certain chemotherapy agents are more active in specific histologic types of STS, e.g., IFOS in synovial sarcoma, GEM (□ DOC) in leiomyosarcomas, paclitaxel in angiosarcomas, trabectedin in myxoid liposarcomas and leiomyosarcomas, pazopanib in non-adipocytic sarcomas). However, this is low level evidence from phase II studies, and usually these associations lack a "targeted" mechanism of action.[29]

Oral targeted agents such as imatinib, sunitinib, sorafenib, palbociclib and pembrolizumab have produced low objective response rates and modest prolongations in PFS, based on limited phase II data. These agents, which are marketed in the US and Canada for other indications, are used in STS. They are not approved by Health Canada for STS, and most provincial cancer drug plans will not fund these expensive agents. Thus they are used infrequently, mainly in patients with private drug plans, or in those individuals willing to pay.

Pazopanib (a multitargeted tyrosine kinase inhibitor) was evaluated in an RCT (PALETTE) in patients with non-adipocytic advanced STS previously treated with chemotherapy that included an anthracycline.[30] There was an improvement in PFS for pazopanib (n=246) vs placebo (n=123), 4.6 vs 1.6 months, HR 0.31, p<0.0001, but no significant difference in OS, 12.5 vs 10.7 months, HR 0.86, p=0.25. Pazopanib received Health Canada approval in July 2012, and was reviewed by pCODR. The final recommendation by pERC, 29 November 2012, was not to fund pazopanib for patients with STS. Another targeted agent, the oral mTOR inhibitor ridaforolimus, has been evaluated as maintenance therapy for STS in an RCT (SUCCEED). A total of 711 patients, who achieved stable disease or better response to standard chemotherapy, were randomized to ridaforolimus vs placebo as maintenance treatment.[31] The study met its primary end-point of improved median PFS, 17.7 vs 14.6 weeks, HR 0.72, p=0.0001. Median OS rates were 90.6 vs 85.3 weeks, HR 0.93, p=0.46. To date, the manufacturer has not submitted ridaforolimus to pCODR for consideration of funding for advanced STS.

2.3 Evidence-Based Considerations for a Funding Population

Platelet-derived growth factor (PDGF) and PDGFR receptor (PDGFR) signalling plays a significant role in mesenchymal biology. Olaratumab is a recombinant human immunoglobulin IgG1 monoclonal antibody that specifically binds PDGF-alpha, blocking PDGF-AA, PDGF-BB and PDGF-CC binding and receptor activation. Preclinical studies of olaratumab alone or in combination with DOX have shown anti-tumor activity in human sarcoma xenograft models, and provided the rationale for the phase Ib and randomized phase II study of Olara+DOX.[2]

Olaratumab, if approved, will be indicated as first-line chemotherapy in combination with DOX in patients with metastatic (stage IV) STS, excluding GIST (eligible but none actually enrolled in the phase Ib/II study). Absolute numbers of patients eligible for treatment annually are more difficult to estimate. Most patients dying of STS are likely to be candidates for palliative chemotherapy (765 in Canada in 2013), but factors such as advanced age and/or comorbidity, as well as patient interest and referral patterns may reduce that number. A reasonable estimate is 500-600 patients/year may be eligible for treatment with Olara+DOX.

2.4 Other Patient Populations in Whom the Drug May Be Used

If olaratumab is approved to be given with DOX for metastatic STS, during a brief overlap period, clinicians may wish to add olaratumab for patients who have already started palliative single agent DOX, or even use it as maintenance therapy in those who are in stable remission following completion of DOX treatment. Also, although there are no data to support it, some clinicians may wish to use olaratumab (with/without other chemotherapy agents) as a second-line treatment in patients who have already received anthracycline–based chemotherapy in the neo/adjuvant setting, or for metastatic STS.

Other situations, not supported by data, where clinicians may seek to use olaratumab could include adding it to DOX used as a radiosensitizer for neoadjuvant treatment of primary limb and retroperitoneal STS.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Sarcoma Cancer Foundation of Canada (SCFC) provided input on olaratumab (Lartruvo) for the treatment of 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.

Sarcoma Cancer Foundation of Canada (SCFC) gathered information through interviews as well as included collective experience of their Board of Directors, which is made up of sarcoma survivors, family members and caregivers. This was a total of four participants, two of whom were SCFC Board of Directors. SCFC spoke to one patient and one family member/caregiver who had direct experience with olaratumab. The information was gathered in Canada.

From a patient perspective soft tissue sarcoma is an aggressive disease where there is no cure. Available treatments, such as chemotherapies for the disease can be harsh and provide low quality of life for patients. Patients live in considerable pain, sleeplessness, exhaustion and various difficulties depending on the location of the tumour. Additionally, caregivers have lost employment, lost homes, and generally live in difficulty for long periods of time as they miss out on day to day activities and being part of their family and community. SFCF noted that the currently available treatments present challenges as STS has many different subtypes, it is difficult to find "gold-standard" treatments that will work across all patients. SFCF hopes for a new treatment that will improve quality of life, "halt disease progression", increase length of life and provide a manageable side effect profile. The one patient who had direct experience with olaratumab reported that he was able to see a "halt in disease progression" and the side-effects were not significant.

Please see below for a summary of specific input received from SCFC. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that was reported have also been reproduced as is according to the submission, without modification.

Please see below for a summary of specific input received from the patient advocacy groups.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Soft Tissue Sarcoma (STS)

SFCF reported that sarcoma cancer is difficult to treat and the mortality rate is high. SFCF noted that there are few effective new treatments for soft tissue sarcoma and are welcomed by the patient community. SCFC also noted that sarcoma cancer often renders patients unable to conduct daily life activities beyond their treatment. Patients live in considerable pain, sleeplessness, exhaustion, and various difficulties depending on where in the body the tumour is located.

3.1.2 Patients' Experiences with Current Therapy for Soft Tissue Sarcoma (STS)

SFCF noted that many of the available treatments can be harsh to a patient's system and give them a low quality of life, and a negative outcome. Additionally, SFCF also noted that there are a range of chemotherapies and treatments currently available for sarcoma patients; however, a large number of them are not highly effective in soft tissue sarcoma and physicians may use a variety of treatments for patients. Despite this, SFCF noted that the mortality rate for STS is still high. Patients who are able to find effective treatments for a period of time often end up having to stop due to ineffectiveness or due to side effects that they are experiencing. SFCF reported that STS patients have been desperately waiting for new, effective treatments.

3.1.3 Impact of Soft Tissue Sarcoma and Current Therapy on Caregivers

SFCF reported that caregiver are impacted by STS as they have heard many stories from families who have lost employment, lost homes and lived in considerable pain and with great difficult for long periods of time, generally missing out on day to day activities and being a part of their family or community.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for Olaratumab (Lartruvo)

SFCF noted that as patients often progress quickly when diagnosed with a soft tissue sarcoma cancer, any treatment that halts disease procession or increases the length of a patient's life is very exciting. SFCF noted that sarcoma cancer ravages a patient's body and some of the older treatments have considerable side effect profiles, a new development like olaratumab is long awaited by the community. SFCF reported that though the mortality rate in STS is high, the community has hope that the development of new treatments such as olaratumab will provide a brighter future ahead. SFCF also noted that the currently available treatments present challenges as STS has many different subtypes, it is difficult to find "gold-standard" treatments that will work across all patients. SFCF hopes for a new treatment that will improve quality of life, "halt disease progression" and provide a manageable side effect profile, ultimately increasing the outcomes of patients.

3.2.2 What Experiences Have Patients Had to Date with olaratumab (Lartruvo)?

SFCF noted that there were challenges in finding members in their community with specific experience with olaratumab as it is not widely available in Canada, though they were able to interview one patients and one caregiver with direct experience. The patient was able to access the drug through paying out of pocket and was not certain if insurance will cover any of the costs. The patient is still receiving treatment and long term data was not available. SFCF did report that the patient was able to see a "halt in disease progression" and did not report that side effects were significant. SFCF is hopeful that as more Canadian patients are able to access the treatment there will be more positive results giving patients hope.

Caregivers indicated that with positive results for the patient and less side effects due to olaratumab treatment, there was less for the caregiver to manage and support. The caregiver also spoke extensively about how a positive experience with a treatment can change a patient's whole outlook and it is so critical to keep spirits up and think positively for the future. The effect on the caregiver is also one of creating an environment of hope and positive spirits, allowing them to resume more everyday tasks and routines associated with "regular" life before their life supporting a cancer patient. This particular caregiver ran their own business and spoke of the positive difference it made mentally and financially in being able to have the time and energy to participate again in daily activities associated with that. Caregivers indicated that it can be a crushing experience to watch a loved one battle cancer, especially without the ability to access proper treatments. The caregiver expressed that they were grateful that the patient was able to access this treatment and hoped that it would soon be readily available to all Canadian patients and that they could share in the positive experience.

3.3 Additional Information

SFCF noted that soft tissue sarcoma is an aggressive disease for which there is no cure and olaratumab gives patients in Canada hope for a "halt in disease progression" and extended life. There are a number of young people who are also affected by this disease and treatments are needed for patients of all ages. SFCF also noted that access to treatments remains a critical issue for sarcoma patients and those without private insurance or a plan that will cover treatments have difficulty paying the high cost of treatments not funded publically.

4 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. PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

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

Clinical factors:

- Place in therapy and sequencing with chemotherapy
- Submission is based on Phase 2b trial with an ongoing Phase 3 trial

Economic factors:

- Potential for wastage due to small patient numbers and available vial sizes

Please see below for more details.

4.1 Factors Related to Comparators

PAG noted that current treatments for soft tissue sarcomas include doxorubicin, doxorubicin plus ifosfamide, and gemcitabine plus docetaxel. Pazopanib and trabectedin are not funded for soft tissue sarcoma in any provinces.

PAG noted that the current submission is based on a Phase 2b trial while there is an ongoing Phase 3 trial, the ANNOUNCE trial. The ANNOUNCE trial is evaluating the efficacy and safety of olaratumab plus doxorubicin compared to placebo plus doxorubicin in the same patient population and PAG would like information on this trial, if available.

4.2 Factors Related to Patient Population

PAG is requesting information to guide the sequencing of olaratumab and its place in therapy. 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.

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.

4.3 Factors Related to Dosing

PAG noted concern for drug wastage given the low patient numbers and vial sizes (500 mg and 190 mg vials). With a recommended dose of 15 mg/kg a 70 kg patient requires 1050 mg, an 80 kg patient requires 1200 mg and a 90 kg patient requires 1350 mg. Wastage will be very significant if only the 500 mg vial size is initially available. Strategies to minimize waste, such as rounding doses or scheduling multiple patients on same day may not be very helpful as rounding down often does not exceed 5-7% of the prescribed dose (even availability of the 190 mg vial size in the above scenarios would not be sufficient for rounding) and outside of very large centres, there would unlikely be opportunity for sufficient numbers of patients on therapy to economize on vial sharing.

4.4 Factors Related to Implementation Costs

PAG anticipates drug wastage with the implementation of olaratumab given availability of only the 500 mg vial size initially, with the smaller vial size being available at a later time. 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 500mg vial size is available and when both the 500mg and 190mg vial sizes are available.

4.5 Factors Related to Health System

Olaratumab would be administered in an outpatient chemotherapy center for appropriate administration and monitoring of toxicities. As olaratumab is a high cost drug, PAG noted that smaller outpatient cancer centres may not have the resources to administer olaratumab. This is a barrier for those patients who will need to travel to larger cancer centres with the resources and expertise to administer olaratumab.

PAG noted that olaratumab administration will require additional chemotherapy chair time and nursing resources, since two doses are administered in a 21 day cycle compared to treatment with single agent doxorubicin.

4.6 Factors Related to Manufacturer

PAG noted that the 190mg vial size is anticipated to be available at the end of 2018, but indicates that the 190mg would minimize drug wastage, but not as much as would introduction of a smaller vial size (e.g. 100 mg and 50 mg).

5 SUMMARY OF REGISTERED CLINICIAN INPUT

One clinician input was provided as group input from two individual oncologists in Ontario. Please see below for details from the clinician input.

Treatments for STS include single agent doxorubicin, single agent gemcitabine, gemcitabine/ docetaxel combination, and pazopanib. Olaratumab plus doxorubicin demonstrated superiority in overall survival compared with doxorubicin alone with patients living a median of 12 months longer. This is the first time in decades that a drug has demonstrated survival benefit in adults with advanced STS and represents a necessity for Canadian patients. Olaratumab plus doxorubicin would be considered first-line for patients with advanced/metastatic STS. Clinicians don't anticipate any patients would be ineligible based on histology.

Please see below for a summary of specific input received from the registered clinician(s).

5.1 Current Treatment(s) for Soft Tissue Sarcoma

The clinicians providing input indicated that current treatments for STS include single agent doxorubicin, single agent gemcitabine, gemcitabine/docetaxel combination, and pazopanib.

5.2 Eligible Patient Population

The clinicians providing input indicated that olaratumab in combination with doxorubicin is now considered standard treatment for adults with soft tissue sarcoma in the US based on the randomized phase II study comparing the combination against doxorubicin alone.

5.3 Identify Key Benefits and Harms with olaratumab

The clinicians providing input noted that any patient for whom single agent doxorubicin would be considered, combination with olaratumab would also be indicated. They also noted that there are no patients with STS that would be considered ineligible based on histology alone.

The clinicians providing input noted that olaratumab plus doxorubicin was associated with increased myelosuppression, mucositis, vomiting, abdominal and musculoskeletal pain compared with doxorubicin alone.

5.4 Advantages of Olaratumab Over Current Treatments

Olaratumab plus doxorubicin demonstrated superiority in overall survival compared with doxorubicin alone with patients living a median of 12 months longer. According to the clinicians providing input, this is the first time in decades that a drug has demonstrated survival benefit in adults with advanced STS and represents a necessity for Canadian patients.

The number of therapeutic options for adults with advanced STS are extremely limited in Canada as compared to the US with many drugs including, but not limited to, eribulin, trabectedin, pazopanib, and doxorubicin, not covered by government funding. Unlike these agents, olaratumab has demonstrated improved survival for patients, and, according to the clinicians providing input, should be accessible to all patients.

5.5 Sequencing and Priority of Treatments with Olaratumab

Olaratumab plus doxorubicin would be considered first-line for patients with advanced/metastatic STS. The combination would replace single agent doxorubicin as first-line therapy for adults with advanced/metastatic STS.

5.6 Companion Diagnostic Testing

No companion diagnostic testing is required.

5.7 Additional Information

None

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effect of olaratumab on patient outcomes compared to standard therapies or placebo in the treatment of 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.

A supplemental question most relevant to the pCODR review and to the Provincial Advisory Group was identified while developing the review protocol and is outlined in section 7.

- Summary of the a Manufacturer-submitted indirect treatment comparison of olaratumab versus available treatment options in patients with advanced STS

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 Table 6.1. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy used by the pCODR Methods Team is provided in Appendix A.

[Table 6.1]. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished RCTs In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of olaratumab for STS will be included.	Adult (aged ≥18 years) patients with advanced STS who are not amenable to curative treatment with radiotherapy or surgery <u>Subgroups:</u> • Histological tumor type (leiomyosarcoma, fibrosarcoma, liposarcoma, neurofibrosarcoma, pleomorphic undifferentiated sarcoma, angiosarcoma, synovial sarcoma, other) • Age (18-65 years vs. ≥65 years) • Duration of disease (<15 months vs. ≥15 months) • Primary site of metastasis (Liver, lung, other)	Doxorubicin + Olaratumab	Doxorubicin Doxorubicin + Ifosfamide (not widely used or available in Canada) Doxorubicin + Placebo	Efficacy • OS • PFS • ORR • CR • PR Safety • AE • SAE • WDAE QoL
AE = adverse events; CR = complete response; ORR=objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; QoL = quality of life; RCT = randomized controlled trial; SAE = serious adverse events; STS = soft tissue sarcoma; WDAE = withdrawal due to adverse events				

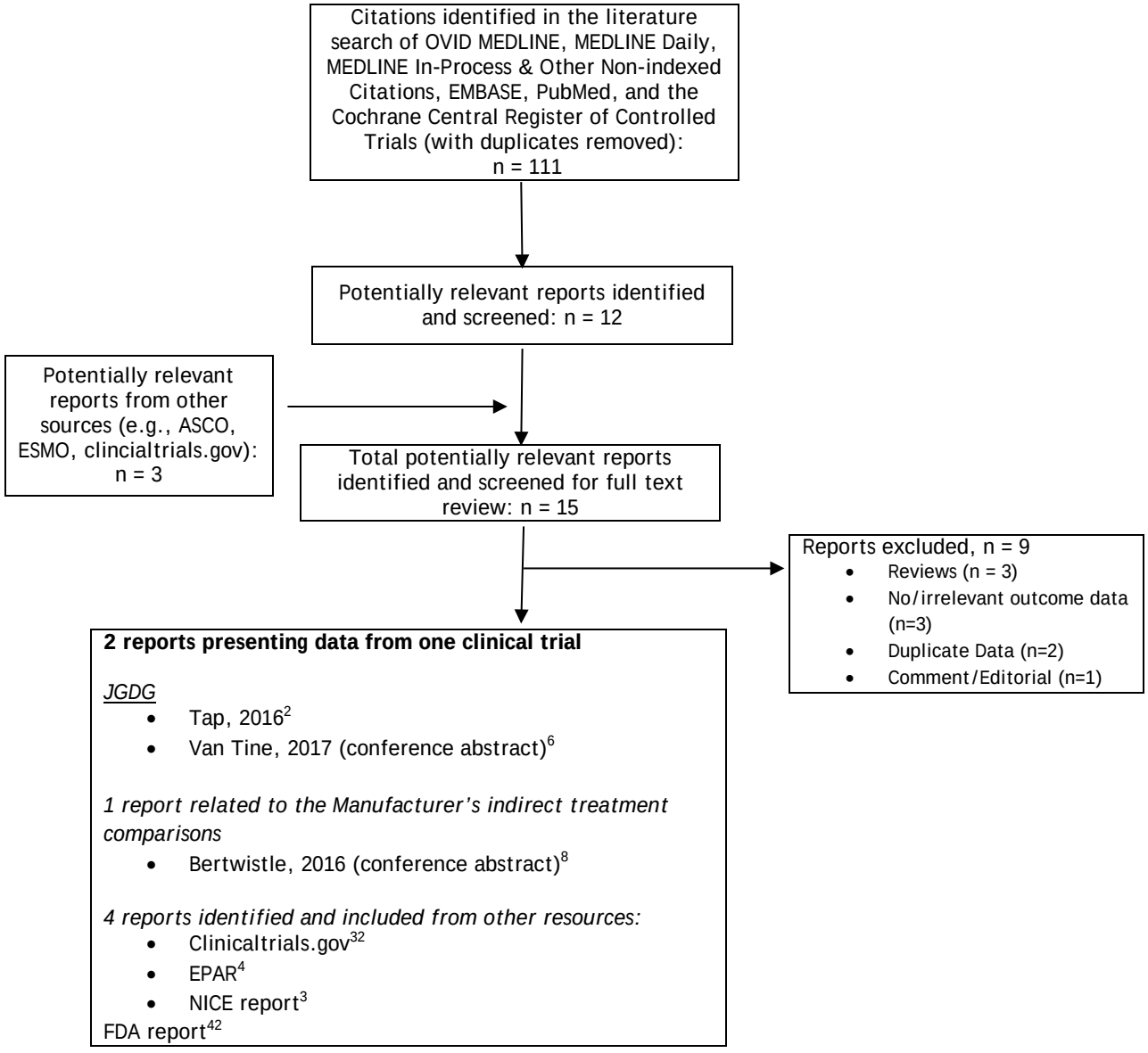
** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.3 Results

6.3.1 Literature Search Results

Of the 15 potentially relevant reports identified, four reports reporting data from one clinical trial were included in the pCODR systematic review,[2-4,32] and 9 studies were excluded. Studies were excluded because they were published as review articles[33-35] or commentaries,[36] reported no or irrelevant study outcomes,[37-39] or included duplicate data.[40,41] Figure 6.1 illustrates the PRISMA flow Diagram for the study selection process.

Figure 6.1: PRISMA Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to studies were also obtained through requests to the Submitter by pCODR: Eli Lilly's submission documents,[7] Eli Lilly's Checkpoint Response(13-Dec-2017)[5] and copies of poster presentations for Van Tine, 2017[43] and Bertwistle, 2016[44]

6.3.2 Summary of Included Studies

One phase 1b/phase 2 trial was included in this review (Table 6.2).[2]

6.3.2.1 Detailed Trial Characteristics

Table 6.2: Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study: JGDG[2] NCT01185964[32] Phase 1b/2, randomized Phase 2, multicenter, open-label study with active control Number randomized: (n = 133) Number treated: (n = 129) Number of centres and number of countries: 16 centres in the United States. Patient Enrolment Dates: 06-Oct-2010 to 14-Jan-2013 Data cut-off Primary PFS analysis: 15-Aug-2014 Secondary OS and ORR analyses: 16-May-2015 Final Analysis Date: 16-May-2015 Funding: Eli Lilly and Company	Key Inclusion Criteria: • Age at study entry ≥ 18 years • Histologically- or cytologically-confirmed locally advanced or metastatic STS, including uterine leiomyosarcoma, not amenable to treatment with surgery or radiotherapy • Measurable disease based on (RECIST v1.1) • ECOG performance status 0-2 • Adequate hepatic, hematologic and renal function. • LVEF ≥50% • Available tumour tissue from either the primary or metastatic tumour for determination of PDGFRα expression. Key Exclusion Criteria: • Kaposi's sarcoma • Previous treatment with doxorubicin, daunorubicin, idarubicin, and/or other anthracyclines and anthracenediones • previous therapy with any agent that targets the PDGF or PDGFR • untreated CNS metastases	**Phase 1b** Olaratumab 15 mg/kg, Days 1 and 8, Q3W (n=15) **Phase 2** Arm 1: Olaratumab 15 mg/kg, Days 1 and 8 + doxorubicin 75 mg/m^2, Day 1, Q3W up to 8 cycles (n=66) In the absence of disease progression or other withdrawal criteria, olaratumab can be continued beyond 8 cycles at 15mg/kg until disease progression. Arm 2: doxorubicin 75 mg/m^2, Day 1, Q3W (n=67)	**Phase 1b** Primary: Safety **Phase 2** Primary PFS (by investigator) Secondary: PFS (by BIRR) OS ORR Pharmacokinetics Safety • SAE • AE • WDAE

AE = adverse events; **BIRR** = blinded independent radiologic review; **CNS** = central nervous system; **ECOG** = Eastern Cooperative Oncology Group; **Jan** = January; **LVEF**=left ventricular ejection fraction; mg/kg = milligram per kilogram of body weight; **mg/m^2** = milligram per square meter of body surface; **Oct**= October; **ORR** = objective response rate; **OS**= overall survival; **PFS** = progression-free survival; **PDGF** = platelet-derived growth factor; **PDGFR** = platelet-derived growth factor receptor; **Q3W** = once every three weeks; **RECIST v1.1**: Response Evaluation Criteria in Solid Tumors, version 1.1; **SAE** = serious adverse events; **STS** = soft tissue sarcoma; **WDAE** = withdrawal due to adverse events

Table 6.3: Select quality characteristics of included studies of olaratumab in patients with advanced soft tissue sarcoma

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
JGDG	olaratumab+ doxorubicin vs doxorubicin	PFS	130	133	Dynamic Minimization Method	None	None	Yes	Yes	No	Yes

a) Trials

Study JGDG was a two-part open-label, phase 1b and randomised phase 2 trial which was conducted at 16 clinical sites, in 16 cities and 15 states, in the United States.

To be eligible for both the phase 1b and phase 2, patients had to 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 0-2, and available tumour tissue to determine platelet-derived growth factor receptor α (PDGFRα) expression by immunohistochemistry. Patients were excluded if they had Kaposi's sarcoma, untreated central nervous system metastases, or if they had received one of the following treatments: doxorubicin, daunorubicin, idarubicin, or other anthracyclines and anthracenediones (mitoxantrone); previous therapy with any drug that targets the platelet-derived growth factor (PDGF) or PDGFR; received; previous radiation therapy to the mediastinal or pericardial area; concurrent treatment with other anticancer therapy including other chemotherapy, immunotherapy, hormonal therapy, radiotherapy, chemo-embolisation, targeted therapy, an investigational agent, or the non-approved use of a drug or device within 4 weeks before study entry. Patients with a known allergy to any of the treatment components, unstable angina pectoris, angioplasty, cardiac stenting, or myocardial infarction 6 months before study entry; and those who were infected by HIV were also excluded.[2,3]

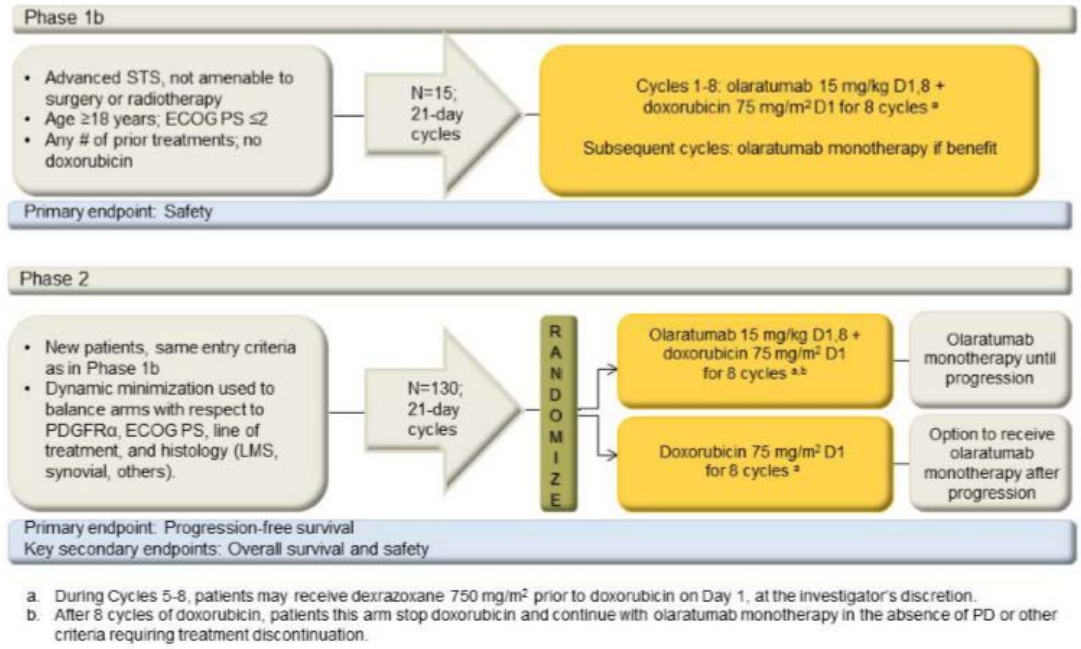
Figure 6.2 illustrates the study design of the JGDG trial. Phase 1b part of the study was non-randomized, and all patients received a combination of olaratumab and doxorubicin (Olara+DOX)(scheduling and dosing details are described under Intervention). In phase 2, patients were randomly assigned, on a 1:1 basis, to receive either Olara+DOX or doxorubicin (DOX), as described below (scheduling and dosing details are described under Intervention).[2] Random allocation was conducted through an interactive system (IVRS, accessed by voice or world-wide web), using a dynamic-minimization algorithm according to the following stratification factors: ECOG performance status (0-1 vs. 2), histological tumour type (leiomyo-sarcoma vs. synovial sarcoma vs. other), immunohistochemical PDGFR expression (positive vs negative), and number of previous lines of treatments (0 vs. ≥1).[2]

The phase 1b primary outcome was safety. The phase 2 primary outcome was progression-free survival (PFS), and secondary outcomes included overall survival (OS), objective response rate (ORR), safety, and pharmacokinetics.[2]

For phase 1b, the sample size was not determined based on statistical considerations, but on a pragmatic determination of enrolling 10-15 patients to evaluate the safety profile of

olaratumab in combination with doxorubicin. For phase 2, a sample size of 130 patients was pre-specified in order to attain 80% power to detect a 50% improvement in median PFS (hazard ratio [HR] 0·67, when comparing patients treated with olaratumab plus doxorubicin (Olara+DOX arm) versus patients treated with doxorubicin alone (DOX arm) [two-sided significance level (α) = 0·20]. The analyses of PFS and OS were based on Kaplan-Meier curves and Mantel's log rank test.[2] Additional analyses were performed using Cox proportional hazards models to estimate HRs. A pre-planned interim analysis of PFS was performed with a minimal nominal α level of 0.0001, which would result in a final nominal adjusted α level of 0·1999 (two-sided).[2]

Figure 6.2 JGDG Study Design[4]



a. During Cycles 5-8, patients may receive dexrazoxane 750 mg/m² prior to doxorubicin on Day 1, at the investigator's discretion.
b. After 8 cycles of doxorubicin, patients this arm stop doxorubicin and continue with olaratumab monotherapy in the absence of PD or other criteria requiring treatment discontinuation.

Source: Lartruvo public assessment report, EMA[4]

There were five protocol amendments for JGDG trial. The most important amendments included an increase in the sample size from 120 to 130 patients to better account for censoring in the analyses of PFS and OS, institution of pre-specified interim analysis (after occurrence of 80 PFS events), and adding sensitivity and supportive analyses.[4] The following post hoc changes were made to planned statistical analysis after the final PFS database lock (16-May-2015):[4]

- The analysis population for efficacy was changed from a randomized and treated population to all randomized patients (intention-to-treat [ITT] population).
- The original statistical analysis plan presented 90% CIs for efficacy outcome. It was decided that 95% CIs would be more appropriate and conventional for the purpose of regulatory submissions.
- A blinded independent review of radiologic assessments was performed.
- Pre-planned subgroup analyses (as per original statistical analysis plan) were changed based on a review of literature.
- Subgroups for subgroup analyses were based on case report forms, unless otherwise noted.

- Additional post hoc sensitivity analyses were performed to evaluate the robustness and internal consistency of the overall survival results to any potential impact of baseline and post-baseline covariates.
- An additional ad hoc exploratory sensitivity analysis was conducted, which did not censor for death or progression that occurred after 2 or more missed visits.

b) Populations

The baseline characteristics of patients in JGDG trial (phase 2) are summarised in Table 6.4A. As shown in the table, the baseline characteristics of the study participants were well-balanced between the two arms, except for a slightly higher proportion of women in the Olara+DOX arm. Thirty nine patients (59%) in the Olara+DOX arm and 36 patients (54%) in the DOX arm had received prior anti-cancer treatments before entry to the phase 2 trial. The baseline disease characteristics along with the types and frequencies of pre-trial anti-cancer therapies in the study groups are summarized in Table 6.4B and Table 6.4C.

Table 6.4: Baseline Characteristics of Participants in Phase 2 JGDG trial (ITT Population), as of 16-May-2015 data cut-off date

A. General Characteristics of study participants[2]

	Olaratumab plus doxorubicin (n=66)	Doxorubicin (n=67)
Age (years)		
Median (range)	58·5 (22–85)	58·0 (29–86)
Sex		
Men	26 (39%)	33 (49%)
Women	40 (61%)	34 (51%)
Race		
White	55 (83%)	60 (90%)
Black	6 (9%)	5 (8%)
Asian	2 (3%)	2 (3%)
Native Hawaiian or other Pacific Islander	1 (2%)	0
Other	2 (3%)	0
Ethnic origin		
Hispanic or Latino	6 (9%)	2 (3%)
Not Hispanic or Latino	60 (91%)	64 (96%)
Missing	0	1 (2%)
ECOG performance status		
0–1	62 (94%)	63 (94%)
2	4 (6%)	4 (6%)
PDGFRα status*		
Stratification assay		
Positive	58 (88%)	59 (88%)
Negative	8 (12%)	8 (12%)
Exploratory assay (post hoc)†		
Positive	18 (33%)	19 (34%)
Negative	37 (67%)	37 (66%)
Histological type		
Leiomyosarcoma	24 (36%)	27 (40%)
Non-leiomyosarcoma‡	42 (64%)	40 (60%)
Previous treatments		
0	27 (41%)	31 (46%)
≥1	39 (59%)	36 (54%)

Source: Reprinted from The Lancet, Vol. 388(10043), Tap WD, Jones RL, Van Tine BA, Chmielowski B, Elias AD, Adkins D et al., Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial, Pages 488-97 Copyright (2016), with permission from Elsevier.[2]

B. Pre-treatment Disease characteristics[4]

	Number of Patients (%)	
	Investigational Arm N = 66	Control Arm N = 67
Duration of Disease (months)[a]		
Mean (SD)	31.9 (41.44)	34.7 (53.07)
Median	15.0	14.9
Minimum – Maximum	0.5 – 233.5	0.3 – 258.6
Grade		
Grade 1	7 (10.6)	8 (11.9)
Grade 2	5 (7.6)	7 (10.4)
Grade 3	29 (43.9)	29 (43.3)
Grade Cannot Be Assessed	6 (9.1)	5 (7.5)
Unknown	19 (28.8)	18 (26.9)
Histological Tumour Type (reclassified from eCRF)		
Angiosarcoma	4 (6.1)	3 (4.5)
Fibrosarcoma	1 (1.5)	0
Leiomyosarcoma	24 (36.4)	27 (40.3)
Liposarcoma	8 (12.1)	15 (22.4)
Neurofibrosarcoma	1 (1.5)	0
Synovial sarcoma	1 (1.5)	2 (3.0)
Undifferentiated Pleomorphic Sarcoma	10 (15.2)	14 (20.9)
Other		
Alveolar Soft Part Sarcoma	1 (1.5)	0
Chondrosarcoma Bone	0	2 (3.0)
Clear Cell Sarcoma	1 (1.5)	0
Endometrial Stromal Sarcoma	1 (1.5)	0
Epithelioid Sarcoma	2 (3.0)	0
Extraskeletal Chondrosarcoma	0	1 (1.5)
Extraskeletal Myxoid Chondrosarcoma	1 (1.5)	0
Fibromyxoid Sarcoma	1 (1.5)	1 (1.5)
Fibrosarcomatous Transformation in a Recurrent Dermatofibrosarcoma	1 (1.5)	0
Hemangiopericytoma	1 (1.5)	1 (1.5)
Malignant Glomus Tumour	1 (1.5)	0
Malignant Peripheral Nerve Sheath Tumour	1 (1.5)	0
Malignant Solitary Fibrous Tumour	1 (1.5)	0
Myxofibrosarcoma	1 (1.5)	0
Myxoid Chondrosarcoma	1 (1.5)	0
Myxoid Sarcoma	0	1 (1.5)
Soft Tissue Undifferentiated Round Cell Sarcoma Negative For Ews	1 (1.5)	0
Undifferentiated Neoplasm	1 (1.5)	0
Undifferentiated Uterine Sarcoma	1 (1.5)	0
Site of Metastatic Disease		
Lung	42 (63.6)	42 (62.7)
Liver	26 (39.4)	22 (32.8)
Soft Tissue	22 (33.3)	33 (49.3)
Lymph Nodes	16 (24.2)	21 (31.3)
Peritoneal	15 (22.7)	23 (34.3)
Bone	10 (15.2)	18 (26.9)
Pleural	10 (15.2)	9 (13.4)
Other[b]	8 (12.1)	16 (23.9)
Skin	3 (4.5)	0

C. Prior anti-cancer therapries[4]

	Number of Patients (%)	
	Investigational Arm N = 66	Control Arm N = 67
Previous Surgery	55 (83.3)	57 (85.1)
Previous Radiotherapy	31 (47.0)	32 (47.8)
Prior Systemic Therapy[a]	38 (57.6)	37 (55.2)
Neoadjuvant	3 (4.5)	10 (14.9)
Adjuvant	17 (25.8)	10 (14.9)
Lines of Therapy[a]		
1st line[b]	14 (21.2)	12 (17.9)
2nd line[b]	8 (12.1)	7 (10.4)
3rd line[b]	2 (3.0)	1 (1.5)
4th line[b]	2 (3.0)	0
Regimen		
Gemcitabine/Docetaxel	25 (37.9)	27 (40.3)
Other	24 (36.4)	19 (28.4)

ECOG PS = Eastern Cooperative Oncology Group Performance Status; **Ews** = Ewing's Sarcoma**; ITT** = intent-t
treat; **N** = number of randomized patients; **SD** = standard deviation; **STS** = soft tissue sarcoma.

Duration of disease is the time from date of histology/pathology confirmation of STS to date of informed consent.
Other sites of metastatic disease included lung, liver, kidney, abdomen, pancreas, spleen, pelvic organs, small bowel, rectum, pelvis, chest, knee, retroperitoneal, other mesenteric masses, mediastinum, thyroid gland, adrenal gland.
Patients may have received more than one type of therapy.
If a patient received more than one line of therapy among 1st, 2nd, 3rd, and 4th line, the patient was counted in the highest line only.

Source: Lartruvo public assessment report, EMA[4]

The CGP identified uterine leiomyosarcoma (LMS) as an important prognostic factor. Based on the NICE committee papers, data as to whether or not patients had uterine LMS were not collected in Study JGDG. However an exploratory retrospective review of pathology reports

for randomised patients in Study JGDG was conducted. Based on this review, a similar distribution of patients with uterine LMS was identified between treatment arms (8 and 7 patients respectively, in the Olara+DOX vs DOX arms). The number of randomised patients with uterine LMS was deemed too small to conduct meaningful subgroup analyses of efficacy. Of note, the study arms were well balanced with respect to retrospectively identified uterine LMS, such that this subgroup could not have substantially biased efficacy outcomes.[3]

The majority of patients in each of the two treatment arms received subsequent therapy after disease progression. Table 6.5 summarizes the frequency of the post-treatment anti-cancer therapies in the study groups.

Table 6.5 Post-Treatment Anticancer Therapies Received by Participants in Phase 2 JGDG trial (ITT Population)[2]

Post-treatment regimen – no. pt (%)	Olaratumab + Doxorubicin (N=66)	Doxorubicin[a] (N=67)
Regimens		
Doxorubicin	1 (1.5)	6 (9.0)
Gemcitabine/Docetaxel	14 (21.2)	8 (11.9)
Other[a]	40 (60.6)	43 (64.2)
Single Agents		
Gemcitabine	15 (22.7)	11 (16.4)
Pazopanib	15 (22.7)	10 (14.9)
Docetaxel	14 (21.2)	8 (11.9)
Dacarbazine	12 (18.2)	8 (11.9)
Trabectedin	11(16.7)	3 (4.5)
Investigational Drug	8 (12.1)	2 (3.0)
Ifosfamide	8 (12.1)	8 (11.9)
Eribulin	3 (4.5)	2 (3.0)

Source: Reprinted from The Lancet, Vol. 388(10043), Tap WD, Jones RL, Van Tine BA, Chmielowski B, Elias AD, Adkins D et al., Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial, Pages 488-97 Copyright (2016), with permission from Elsevier.[2]

c) Interventions

In phase 1b, patients received combination therapy with olaratumab (15 mg/kg) intravenously on day 1 and day 8 plus doxorubicin (75 mg/m²) on day 1 of each 21-day cycle for up to eight cycles. After eight cycles of combination, if disease progression or unacceptable toxicities had not occurred, patients continued to receive olaratumab monotherapy until disease progression. During cycles 5–8, dexrazoxane was allowed on day 1 of each cycle to reduce the potential for doxorubicin -related cardiotoxicity.[2]

In phase 2, patients were randomized to receive one of the following treatments: combination therapy with olaratumab and doxorubicin (as described for phase 1b), or doxorubicin (75 mg/m²) on day 1 of each 21-day cycle for up to eight cycles. After completion of eight cycles of doxorubicin, patients in the Olara+DOX arm continued to receive olaratumab monotherapy until disease progression, and patients in the DOX arm were observed and could cross over to olaratumab monotherapy after documented disease progression, development of unacceptable toxicity, noncompliance or withdrawal of consent by the patient, or the investigator made the decision to stop treatment.[2,4] The median number of doxorubicin infusions was seven (range 1 to 8) in the Olara+DOX arm and four infusions (range 1 to 8) in the DOX arm. The median number of olaratumab infusions in the Olara+DOX arm was 16.5 (range 1.0 to 83). Thirty one of 64 patients in the Olara+DOX arm completed the eight cycles of doxorubicin plus olaratumab, when compared with 17 of 64 patients who completed the eight cycles of doxorubicin only in the DOX arm.[2]

To minimize the risk doxorubicin-related cardiotoxicity, patients who received more than four cycles of doxorubicin were allowed to receive dexrazoxane at investigator's discretion on Day 1 of Cycles 5-8 in both Olara+DOX and DOX arms. Dexrazoxane was administered at a

ratio of 10:1 to the administered dose of doxorubicin.[4] All patients who received 5 or more cycles of doxorubicin were administered dexrazoxane prior to each doxorubicin infusion during Cycles 5 to 8, per protocol (38 patients [59.4%] in Investigational Arm and 29 patients [44.6%] in the Control Arm). One patient in the Investigational Arm received dexrazoxane in Cycle 1. This patient did not receive dexrazoxane in Cycles 2 through 4; dexrazoxane was administered to this patient again prior to doxorubicin in Cycles 5 through 7.[5]

Dose Modifications

The majority of Olaratumab dose modifications (i.e., dose delays, dose reductions, doses held, and infusion rate modifications) were due to AEs.[4] Table 6.6 shows the type and frequency of dose modifications. If olaratumab was discontinued, or its dose was altered, due to drug-related toxicity, the planned doxorubicin schedule and dose was maintained. Similarly, a doxorubicin-related toxicity did not require alteration or discontinuation of olaratumab. However, if doxorubicin was altered or discontinued, dexrazoxane dose should be altered accordingly to maintain a dexrazoxane:doxorubicin dosage ratio of 10:1. All dose reductions were permanent.[2]

Olaratumab Discontinuation

Patients with Grade 3 or 4 infusion-related reactions were immediately and permanently discontinued from olaratumab, in accordance with study protocol.[4] For patients who received Olara+DOX, discontinuation of olaratumab due to drug toxicity did not require discontinuation of doxorubicin. In this case, the patient could continue to receive doxorubicin for a maximum of eight cycles as long as all other study criteria were met.[2]

Table 6.6: Dose modifications in Phase 2 JGDG trial (safety population), as of 16-May-2015 data cut-off date[4]

A. Olaratumab dose modifications

	Investigational Arm N = 64 n (%)	Control Arm: Olaratumab Monotherapy after Doxorubicin Treatment[a] N = 30 n (%)
Patients with Dose Delay	37 (57.8)	8 (26.7)
Patients with Dose Reduced	16 (25.0)	1 (3.3)
Patients with Dose Held	20 (31.3)	2 (6.7)
Patients with Infusion Interrupted	8 (12.5)	4 (13.3)

Abbreviations: N = number of treated patients; n = number of patients in category.
Note: Dose delays and dose reductions could have occurred in the same patient.
a Patients initially randomized to the Control Arm who received olaratumab monotherapy after discontinuation of doxorubicin.

B. **Doxorubicin dose modifications**

	Investigational Arm N = 64 n (%)	Control Arm N = 65 n (%)
Patients with Dose Delay	16 (25.0)	12 (18.5)
Patients with Dose Reduced	16 (25.0)	10 (15.4)
Patients with Dose Held	8 (12.5)	3 (4.6)
Patients with Infusion Interrupted	0	1 (1.5)

Abbreviations: N = number of treated patients; n = number of patients in category.
Note: Dose delays and dose reductions could have occurred in the same patient.

Investigational arm = olaratumab + doxorubicin
Control arm = doxorubicin (olaratumab monotherapy after disease progression)

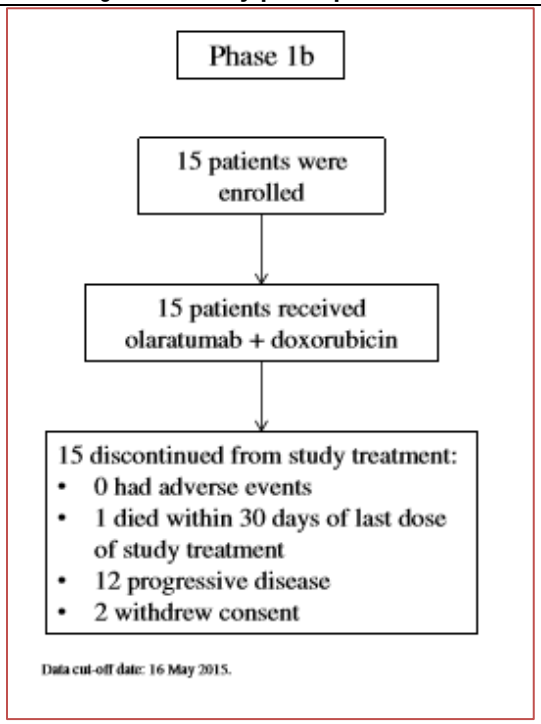
Source: Lartruvo public assessment report, EMA[4]

d) Patient Disposition

Between 06-Oct-2010 and 14-Jan-2013, 15 patients were enrolled and treated in the phase 1b part of the JGDG trial (Figure 6.3).[2] A total of 133 patients were enrolled in the phase 2 part of the JGDG trial, of whom 66 were randomly assigned to the Olara+DOX arm and 67 to the DOX arm (Figure 6.4).[2,4] All 133 patients (ITT population) were included in the efficacy analysis. One hundred and twenty nine (97%) patients (64 in the Olara+DOX arm and 65 in the DOX arm) who received at least one dose of study treatment were included in the analysis of safety outcomes (safety population). Two patients in each study arm were not treated.

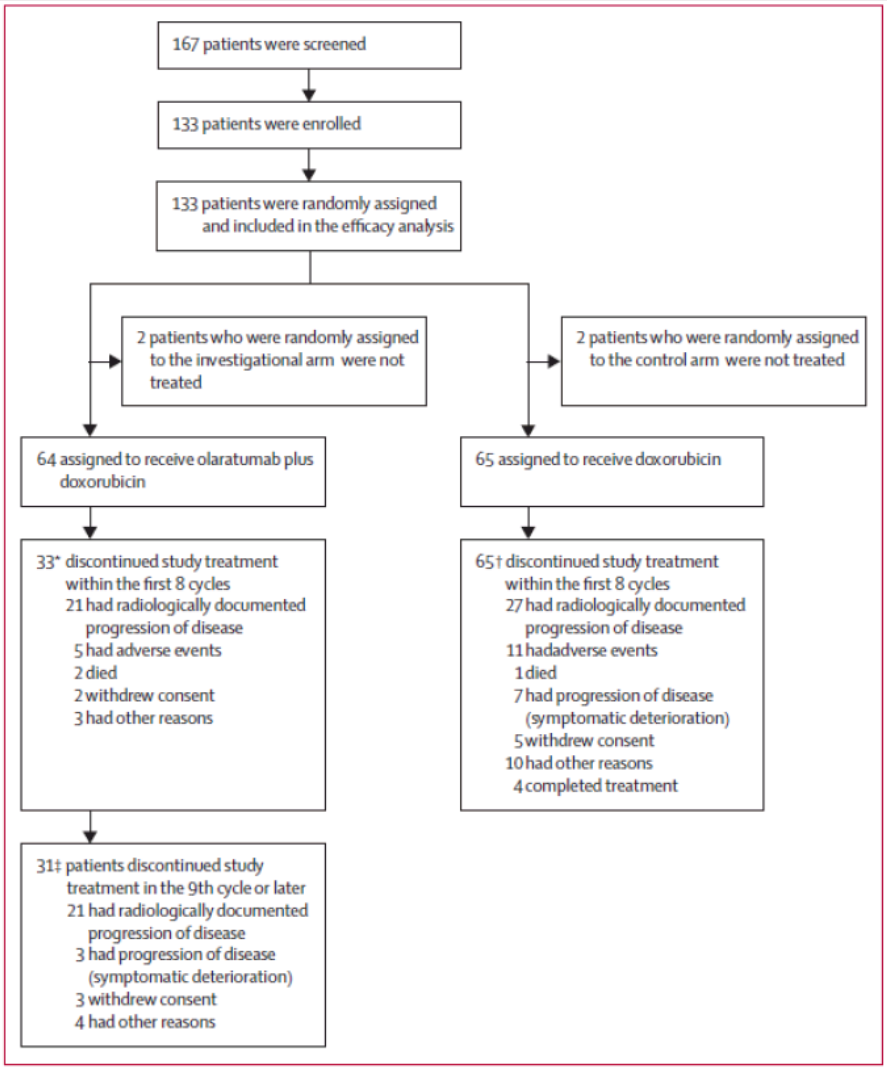
Of the 64 olaratumab-treated patients, 33 (51.5 %) discontinued study treatment within the 8-cycle combination treatment period due to documented disease progression (21/64; 33.0%), AEs (5/64; 8.0%), withdrawal of consent (2/64; 3.0%), death (2/64; 3.0%), or other reasons (3/64; 4.5%). The remaining 31 (48.5%) patients discontinued study treatment in the 9th treatment cycle or later due to documented disease progression (21/64; 33.0%), deterioration of symptoms (3/64; 4.5%), withdrawal of consent (3/64; 4.5%), or other reasons (4/64; 6.5%). Of the 65 patients who were randomly assigned to and treated in the DOX arm, four patients (6.0%) completed the 8-cycle study treatment, and the remaining patients discontinued treatment for the following reasons: documented disease progression (27/65; 41.5%), AEs (11/65; 17.0%), symptomatic deterioration (7/65; 11.0%), withdrawal of consent (5/65; 8.0%), death (1/65; 1.5%), or other reasons (10/65; 15.0%).[2]

Figure 6.3: Consort Diagram of study participants in JGDG trial (Phase 1b)[2]



Source: Reprinted from The Lancet, Vol. 388(10043), Tap WD, Jones RL, Van Tine BA, Chmielowski B, Elias AD, Adkins D et al., Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial, Pages 488-97 Copyright (2016), with permission from Elsevier.[2]

Figure 6.4: Consort Diagram of study participants in JGDG trial (Phase 2)[2]



*Four of the 33 patients received eight cycles of doxorubicin and three of the 33 patients received at least one dose of olaratumab monotherapy. † 17 of the 65 patients received eight cycles of doxorubicin and 30 of the 65 patients received at least one dose of olaratumab monotherapy (following discontinuation of single-drug doxorubicin). ǂ 27 of the 31 patients received eight cycles of doxorubicin and all 31 patients received at least one dose of olaratumab monotherapy.

Source: Reprinted from The Lancet, Vol. 388(10043), Tap WD, Jones RL, Van Tine BA, Chmielowski B, Elias AD, Adkins D et al., Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial, Pages 488-97 Copyright (2016), with permission from Elsevier.[2]

There were 39 major protocol deviations in 33 study participants (17 and 16 patients in the Olara+DOX and DOX arms, respectively). Reasons for protocol deviations in each study arm are described in Table 6.7.

Table 6.7: Major protocol deviations in JGDG trail[42]

Protocol Violation	Olaratumab + Doxorubicin N=66	Doxorubicin N=67
Patients with major protocol violation (%)	17 (25.8)	16 (23.9)
Total number of major protocol violations	20	19
Issues with informed consent	7 (35)	7 (36.8)
Protocol procedures/visits not performed/missing[a]	7 (35)	4 (21.1)
Inclusion/Exclusion criteria violated[b]	2 (10)	5 (26.3)
Incorrect response assessment[c]	2 (10)	1 (5.3)
Out of window visits/procedure	0	2 (10.5)
Medication errors	1 (5)	0
Other[d]	1 (5)	0

(Source: DV.xpt, RS.xpt, TU.xpt)
[a] doxorubicin: patient CP15-0806/001-1007 had liver ablation to target lesion #2 and continued on therapy, doxorubicin + olaratumab: Patient CP15-0806/015-1011 end of treatment date was 2/5/2013 when investigator (INV) determined PD/PFS event date was 11/9/2012
[b] Includes two patients in the doxorubicin arm who had chondrosarcoma. Sponsor stated in CSR these were identified during the submission preparation and not included in the table in the CSR
[c] Olaratumab + doxorubicin: Patient CP15-0806/011-1001 end of treatment date 12/19/2011 when INV determined PD/PFS date was 10/27/2011, Patient CP15-0806/012-1012 had PD by protocol measurements on 11/2/2011 and INV PFS date was 12/19/2011 (BICR did not agree with PD and censored the patient on 12/19/2011); doxorubicin: Patient CP15-0806/004-1007 had INV PD/PFS date recorded on 4/24/2013, but by protocol recorded measurements should have been SD; however, BICR agreed with PD on 4/24/2013.
[d] Other: patient found to be pregnant while in survival follow-up period

Source: FDA report[42]

e) Limitations/Sources of Bias

- The JGDG trial is a phase-1b/phase 2 open-label trial that provided preliminary results on the efficacy of olaratumab as an add-on to doxorubicin in patients with advanced STS. The study allowed for a significance level of 0.20 (nominal significance level of 0.1999 adjusted for the interim analysis). However, uncertainty around the key efficacy results is reported based on the 95% CIs (which correspond to a 0.05 level of significance). Therefore, although the authors reported a protocol-defined statistically significant PFS improvement in the Olara+DOX arm, there is a considerable overlap of the 95% CIs between the median PFS rates reported for Olara+DOX and DOX arms. Furthermore, the 95% CI for the reported stratified HR for PFS contains 1.0 (null hypothesis value). Therefore, the results should be judged with attention to the fact that, for a given sample size, an extended significance level (i.e., increased type I error rate) can increase the risk of drawing a false-positive conclusion (rejecting the null hypothesis when it is true).
- The open label nature of the study might introduce the risk of reporting and performance biases, as the study participants and the investigators were aware of the treatment assignments. This could particularly be important in reporting of subjective outcomes (e.g., AEs) by the patients and care providers. In open-label trials, the reporting behavior of patients may be influenced by their information about the new drug and its side effects. The investigators and assessors may measure and report the AEs of the new drug more frequently and consider the AEs of the comparators as normal or acceptable, or vice versa. To decrease the impact of this bias, a blinded independent assessment of treatment response and disease progression was conducted, after the final PFS database lock, to evaluate the impact of these biases on the assessment of PFS.
- There were more patients who required doxorubicin dose adjustments in the Olara+DOX arm than in the DOX arm. In addition, the rate of censoring was higher in

the Dox arm. The investigators performed sensitivity analyses using different censoring/event definition scenarios, to show the robustness of their primary analysis. The results of the sensitivity analyses should be taken into account when interpreting the results.

- After completion of 8 cycles of DOX, patients in the Olara + DOX group could receive Olara monotherapy until disease progression, while patients in the DOX group were observed and could receive Olara monotherapy after documented disease progression. The OS rates might be confounded because the ITT analysis was performed with no adjustment for cross-over; i.e., the patients in the DOX arm who crossed over to olaratumab were kept in the DOX monotherapy group. The impact of the unadjusted data is to be against the Olara+DOX arm as patients in the DOX arm may be getting benefit from the Olara+DOX when received post progression.
- The study showed an improvement in PFS and OS in patients who received olaratumab as an add-on to doxorubicin, however, the treatment effect size was greater for OS (11.8 months; p=0·0003) than for PFS (2.5 months; p=0.0615); i.e., the longer OS is not sufficiently explained by an increased delay in tumor progression. During the Checkpoint Meeting (13-Dec-2017) the Manufacturer noted that similar pattern (i.e, greater magnitude of benefit for OS than for PFS) had been reported in a recent trial of eribulin for STS, and a number of immunotherapy trials.[5] The Manufacturer hypothesized that olaratumab may have [redacted], "[redacted]". [5] (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed*.)
- Patient-reported quality of life outcomes were not measured in the JGDG trial.[5] Quality of life was identified as an important outcome for patients with advances STS by the Clinical guidance Panel.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Tumour response was assessed every 6 weeks according to the Response Evaluation Criteria in Solid Tumours (version 1.1). Survival was assessed every 2 months until the completion of the study. The overall survival analysis included all randomly assigned patients (ITT analysis). Safety was assessed for all patients who received at least one dose of study treatment. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). Post-hoc sensitivity analyses were performed to show the robustness of primary analysis of PFS, using different censoring or event definition scenarios.[2]

Efficacy Outcomes

Progression-free survival

PFS was the primary efficacy outcome in JGDG trial, and was defined as the time from the date of randomization to the earliest date of documented tumour progression or death

from any cause, whichever was first. Tumour progression was assessed by the investigators based on the Response Evaluation Criteria in Solid Tumours (RECIST) criteria Version 1.[2]

Table 6.8A shows the PFS results as assessed by the investigators. As of the 15-Aug-2014 data cut-off, 55 (83.3%) progression events had occurred in the Olara+DOX arm and 48 events (71.6%) in the DOX arm. The median PFS was 6.6 months (95% CI 4.1, 8.3) in the Olara+DOX arm and 4.1 months (95% CI 2.8, 5.4) in the DOX arm (stratified HR 0.672; 95% CI 0.442–1.021, p=0.0615).[2] Tap et al reported that this 2.5 improvement in median PFS, favouring Olara+DOX, met the protocol-defined significance level of 0.1999 for PFS.[2] However, because the authors chose to report the 95% CIs to estimate the uncertainty around the observed rates (which correspond to a 0.05 level of significance), there is an overlap in the CIs between the reported median PFS rates as well as a 95% CI for the stratified HR that contains 1.0 (null hypothesis value). Therefore, the significance of the results should be interpreted with this consideration (ie. the results would change from statistically significant at a significance level of 0.1999 [~0.20]) to not statistically significant at a significance level of 0.05). The higher rate of censoring observed in the DOX arm (28.4% versus 16.7% in Olara+DOX arm; Table 6.8A) should also be taken into account, when interpreting the results.

The 3- and 6-month investigator-assessed PFS rates were 69.0%, and 53.9%, respectively, for the Olara+DOX arm. The corresponding rates were 59.9% and 31.1%, respectively, for the DOX arm.[2] The Kaplan–Meier curves for investigator assessed PFS for both study arms are shown in Figure 6.5.

A blinded independent retrospective review of radiographic scans was conducted following the final PFS database lock, to evaluate any potential systematic bias favoring either of the treatment arms with respect to PFS assessment (Table 6.8B). Fewer progression events (37 versus 55 events in the Olara+DOX arm and 34 versus 48 events in DOX arm), and higher rates of censoring (43.9% versus 16.7% in the Olara+DOX arm and 49.3% versus 28.4% in the DOX arm) were identified in the independent review versus the investigator assessment, respectively. The independent review showed a larger magnitude of difference in PFS between treatment arms compared to the investigator assessed results with a median PFS of 8·2 months (95% CI 5·5, 9·8) in the Olara+DOX arm, and 4·4 months (95% CI 3·1, 7·4) in the DOX arm. The PFS HR estimated by the independent review (stratified HR 0.67; 95% CI 0.40, 1.12, p=0.1208) was nearly equal to the HR that was estimated by the investigators. The 3-month and 6-month independently reviewed PFS rates were 76.4%, and 60.8%, respectively, for the Olara+DOX arm; and 66.7% and 39.3%, respectively, for the DOX arm.[2]

Table6.8: Progression-Free Survival in JGDG trial(Phase 2, ITT Population), as of 15-August-2014 data cut-off date

A. Investigator-Assessment[2]

	Investigational Arm N = 66	Control Arm N = 67
Number of Events, n (%)	55 (83.3)	48 (71.6)
Number Censored, n (%)	11 (16.7)	19 (28.4)
No Baseline Tumour Assessments	1 (1.5)	2 (3.0)
No Post-Baseline Tumour Assessments	2 (3.0)	2 (3.0)
Death or Progression After Two or More Missed Visits	1 (1.5)	3 (4.5)
Start of New Anticancer Therapy	5 (7.6)	5 (7.5)
No Documented Progression	2 (3.0)	6 (9.0)
Withdrew Consent	0	1 (1.5)
Median[a] (months)	6.6	4.1
95% CI[a]	(4.1, 8.3)	(2.8, 5.4)
Q25 - Q75[a]	2.7 – 10.2	1.6 – 7.4
3 months PFS Rate[a] (%)	69.0	59.9
95% CI[a]	(55.7, 78.9)	(45.9, 71.4)
6 months PFS Rate[a] (%)	53.9	31.1
95% CI[a]	(40.6, 65.4)	(18.9, 44.1)
Stratified Log-rank p-value[b,d]	0.0615	
Stratified Hazard Ratio[c,d]	0.672	
95% CI[c]	(0.442, 1.021)	
Unstratified Log-rank p-value[b,d]	0.1112	
Hazard Ratio[c,d]	0.730	
95% CI[c]	(0.494,1.079)	

B. Independent Review[4]

	Investigational Arm N = 66	Control Arm N = 67
Number of Events, n (%)	37 (56.1)	34 (50.7)
Number Censored, n (%)	29 (43.9)	33 (49.3)
No Baseline Tumour Assessments	7 (10.6)	10 (14.9)
Death or Progression After Two or More Missed Visits	2 (3.0)	5 (7.5)
Start of New Anticancer Therapy	18 (27.3)	6 (9.0)
No Documented Progression	2 (3.0)	11 (16.4)
Withdrew Consent	0	1 (1.5)
Median[a] (months)	8.2	4.4
95% CI[a]	(5.5, 9.8)	(3.1, 7.4)
Q25 - Q75[a]	3.0 – 11.6	1.5 – 8.6
3 months PFS Rate[a] (%)	76.4	66.7
95% CI[a]	(62.8, 85.6)	(51.8, 77.9)
6 months PFS Rate[a] (%)	60.8	39.3
95% CI[a]	(45.8, 72.9)	(24.0, 54.2)
Stratified Log-rank p-value[b,d]	0.1208	
Stratified Hazard Ratio[c,d]	0.670	
95% CI[c]	(0.401, 1.117)	
Unstratified Log-rank p-value[b,d]	0.2157	
Hazard Ratio[c,d]	0.743	
95% CI[c]	(0.464, 1.190)	

Control Arm = Doxorubicin monotherapy; **CI** = confidence interval; **Investigational Arm** = olaratumab + doxorubicin combination therapy; **ITT** = intent-to-treat; **N** = number of randomized patients; **n** = number of patients in category; **PFS** = progression-free survival; **Q** = quartile.

[a] Estimated by the Kaplan-Meier method.

[b] Derived from a two-sided test.

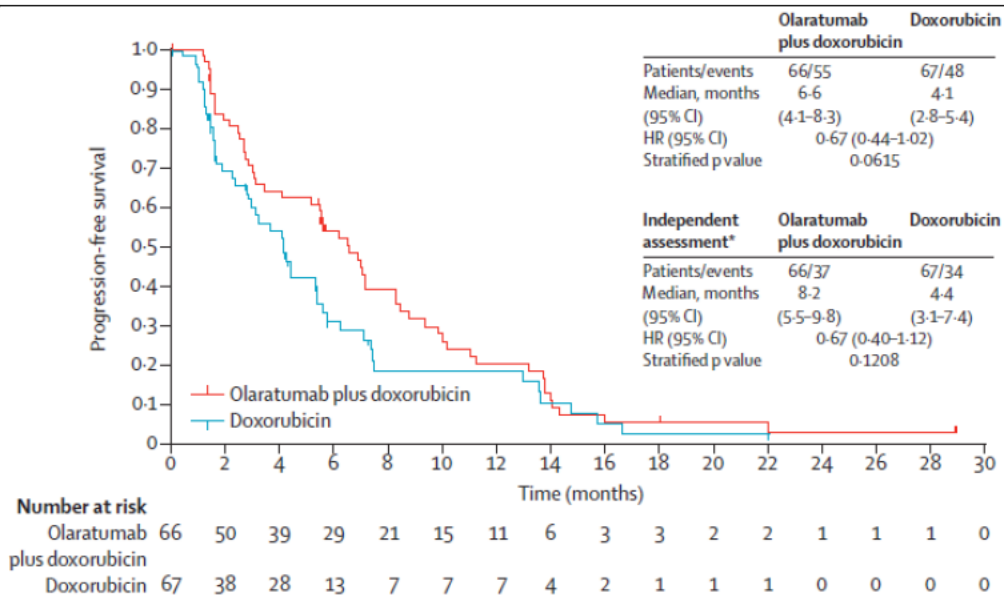
[c] Hazard ratio is expressed as olaratumab + doxorubicin/doxorubicin and estimated from Cox model.

[d] Between olaratumab + doxorubicin arm and doxorubicin arm.

Source Part A: Reprinted from The Lancet, Vol. 388(10043), Tap WD, Jones RL, Van Tine BA, Chmielowski B, Elias AD, Adkins D et al., Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial, Pages 488-97 Copyright (2016), with permission from Elsevier.[2]

Source Part B: Lartruvo public assessment report, EMA[4]

Figure 6.5: Kaplan-Meier curves for the investigator-assessment progression-free survival in JGDG trial (Phase 2, ITT Population)[2]



CI= confidence interval; HR = hazard ratio
*the independent assessment of progression-free survival is included as an insert for comparison.

Source: Reprinted from The Lancet, Vol. 388(10043), Tap WD, Jones RL, Van Tine BA, Chmielowski B, Elias AD, Adkins D et al., Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial, Pages 488-97 Copyright (2016), with permission from Elsevier.[2]

PFS subgroup analyses

The results of the subgroup analyses of PFS data are summarized in Table 6.9. The subgroups analyses did not suggest any significant between-group differences with respect to the histological tumor type, age, gender, duration of disease and site of metastasis.

Table 6.9: Progression-free survival in JGDG trial by subgroups

	Olaratumab + Doxorubicin (n=66)	Doxorubicin (n=67)	Hazard Ratio (95% CI)
Subgroup	Median PFS, months (95% CI) [# Randimized]	Median PFS, months (95% CI) [# Randimized]	
Histological Tumor Type[3]			
Leiomyosarcoma	6.5 (3.0, 9.8) [n=24]	4.1 (1.6, 7.4) [n=27]	0.795 (0.411, 1.540)
Other	6.6 (3.0, 8.4) [n=42]	4.2 (2.2, 5.4) [n=40]	0.702 (0.429, 1.148)
Age Group[4]			
18-65	5.5 (2.8, 8.3) [n=48]	4.1 (1.6, 5.4) [n=43]	0.711 (0.442, 1.144)
≥65 years	7.0 (3.0, 13.7) [n=18]	4.4 (2.2, 5.7) [n=24]	0.563 (0.273, 1.162)
Gender Group[EPAR, page 76][4]			
Male	5.1 (2.4, 9.3) [n=26]	4.1 (2.2, 5.6) [n=33]	0.761 (0.428, 1.354)

Female	7.0 (5.5, 8.8) [n=40]	4.1 (1.6, 12.9) [n=34]	0.787 (0.456, 1.357)
Duration of Disease[Checkpoint][5]			
[redacted]			
Liver Metastases[5]			
[redacted]			
Lung Metastases[5]			
	N=42	N=42	
[redacted]			
Uterine Leiomyosarcoma[6]			
Yes	2.7 (1.1, NE) [n=8]	3.6 1.0, NE [n=7]	0.930 0.245. 3.541

CI= confidence interval; n = number of randomized patients; NR = not reported

Source: NICE, EPAR, Checkpoint, Van Tine 2017[3-6]

(Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until April 2, 2019 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier).

PFS sensitivity analyses

To show the robustness of the primary analysis of PFS, four sensitivity analyses were performed using different censoring/event definition scenarios. Table 6.10 summarizes the results of these sensitivity analyses.

Table 6.10: Sensitivity analysis of progression-free survival in JGDG trail (phase 2, ITT population)[4]

Analysis	Stratified HR (95% CI)	p-Value
Primary analysis	0.672 (0.442,1.021)	0.0615
Sensitivity analyses		
#1 Censored at the start date of any new anti-cancer treatment*	0.623 (0.426,0.910)	0.0135
#2 Used the actual reported date of progression or death (regardless of missing assessments, drug discontinuation, or new anti-cancer treatment)	0.734 (0.497,1.085)	0.1208
#3 Added clinical progression (symptomatic deterioration) as progressive events to the primary analysis	0.631 (0.417,0.953)	0.0280
#4 Did not censor patient whose death or progression occurred after 2 or more missed visits (ad hoc)	0.664 (0.439,1.005)	0.0514

CI= confidence interval; HR = hazard ratio; ITT = intent-to-treat

* If new anticancer treatment started before progression, the patient was considered to have disease progression at the date of the new cancer treatment; if death or progression occurred after 2 or more missed visits, the date of death or progression was used; and if lost to follow-up without progression, the patient was considered to have disease progression at the date of the last adequate assessment.

Source: Lartruvo public assessment report, EMA[4]

Overall Survival

OS was the key secondary outcome in JGDG trial, and was defined as the time from randomization to the date of death from any cause.[2] Final analysis of overall survival was performed as planned after 91 (71%) patients died in the intention-to-treat population. The hazard ratio and 95% confidence limit for OS was estimated from the Cox regression model, stratified by two randomization balancing variables: number of lines of prior therapy, and histologic subtype of the disease.[2]

Table 6.11 shows the OS results as assessed by the investigators. The median overall survival was 26.5 months (95% CI 20.9, 31.7) in the Olara+DOX arm, as compared to 14.7 months (95% CI 9.2–17.1) in the DOX arm (stratified HR, 0·46, 95% CI 0·30–0·71, p=0·0003).[2,4] The 3- and 6-month survival rates were 95.2% and 90.5%, respectively, in the Olara+DOX arm and 87.6% and 73.3%, respectively in the DOX arm.[2] The Kaplan–Meier OS curves for both study arms are shown in Figure 6.6. As can be seen in the figure, OS curves separate relatively early in therapy (within the first two months) and the OS benefit remained stable over time.

Table 6.11: Overall Survival Study JGDG Phase 2; ITT Population, as of 16-May-2015 data cut-off date[4]

	Investigational Arm N = 66	Control Arm N = 67
Number of Deaths, n (%)	39 (59.1)	52 (77.6)
Number Censored, n (%)	27 (40.9)	15 (22.4)
Alive, n (%)	25 (37.9)	12 (17.9)
Lost to follow-up, n (%)	0	1 (1.5)
Withdrawal of Consent, n (%)	2 (3.0)	2 (3.0)
Median Survival (months)	26.5	14.7
95% CI[a]	(20.9, 31.7)	(9.2, 17.1)
Q25 - Q75[a]	13.8 – NE	5.5 – 26.0
3 months Survival Rate[a] (%)	95.2	87.6
95% CI[a]	(86.0, 98.4)	(76.8, 93.6)
6 months Survival Rate[a] (%)	90.5	73.3
95% CI[a]	(80.0, 95.6)	(60.6, 82.5)
Stratified Log-rank p-value[b,d]	0.0003	
Stratified Hazard Ratio[c,d]	0.463	
95% CI[c]	(0.301, 0.710)	
Unstratified Log-rank p-value[b,d]	0.0017	
Hazard Ratio[c,d]	0.517	
95% CI[c]	(0.341, 0.786)	

CI = confidence interval; ITT = intent-to-treat; N = number of randomized patients; n = number of patients in category; NE = not evaluable; Q = quartile.
a Estimated by the Kaplan-Meier method.
b Derived from a two-sided test.
c Hazard ratio is expressed as olaratumab + doxorubicin/doxorubicin and estimated from Cox model.
d Between olaratumab + doxorubicin arm and doxorubicin arm.

Source: Lartruvo public assessment report, EMA[4]

OS subgroup analyses

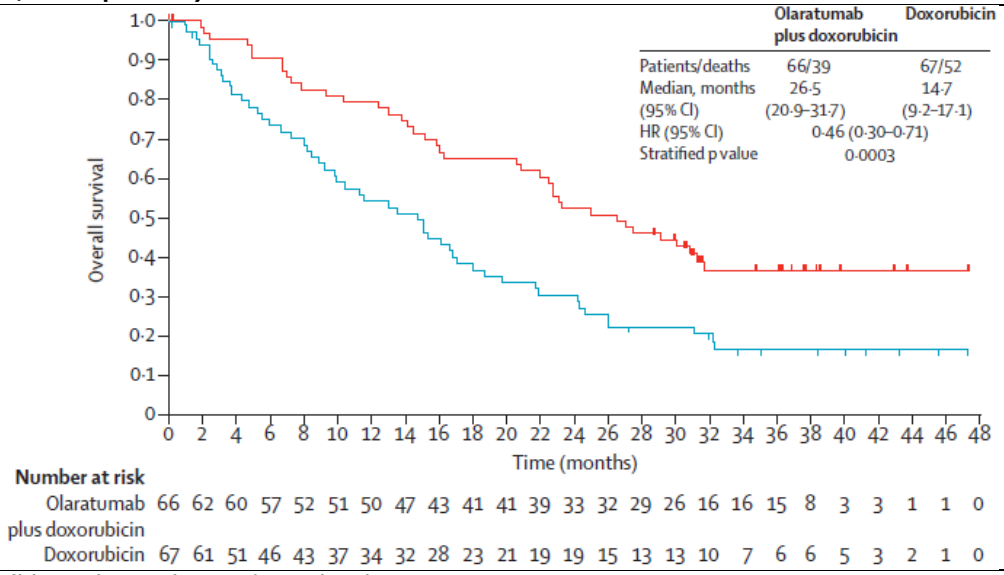
The results of the subgroup analyses of OS data are illustrated in Figure 6.7. A stratified Cox multivariate model of OS was performed, to adjust for potential prognostic factors, including PDGFRα status, number of lines of previous treatment,histological tumour type, liver metastasis, sex, age, weight, duration of disease since diagnosis, grade at diagnosis, albumin level, and ECOG performance score.[4] The adjusted OS HR of 0.429 (95% CI: 0.267,

0.690) was consistent with the stratified univariate OS HR of 0.463 (95% CI 0.301, 0.710) observed in the primary analysis.[4]

In addition to the subgroup analyses presented in Figure 6.7, the Manufacturer provided the results of lung metastases sub-group analysis (42 patients in each of the Olara+DOX x and DOX groups). [redacted].[5] (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed*.)

A retrospective analysis of data from 15 JGDG participants with uterine leiomyosarcoma (8 patients in the Olara+DOX group and 7 in the DOX group) showed that the median OS was 25.0 months (95% CI 4.9, not reached) with Olara+DOX and 11.4 months (95% CI 3.6, not reached) with DOX. The HR was reported to be 0.610 (95% CI 0.175, 2.144).[6]

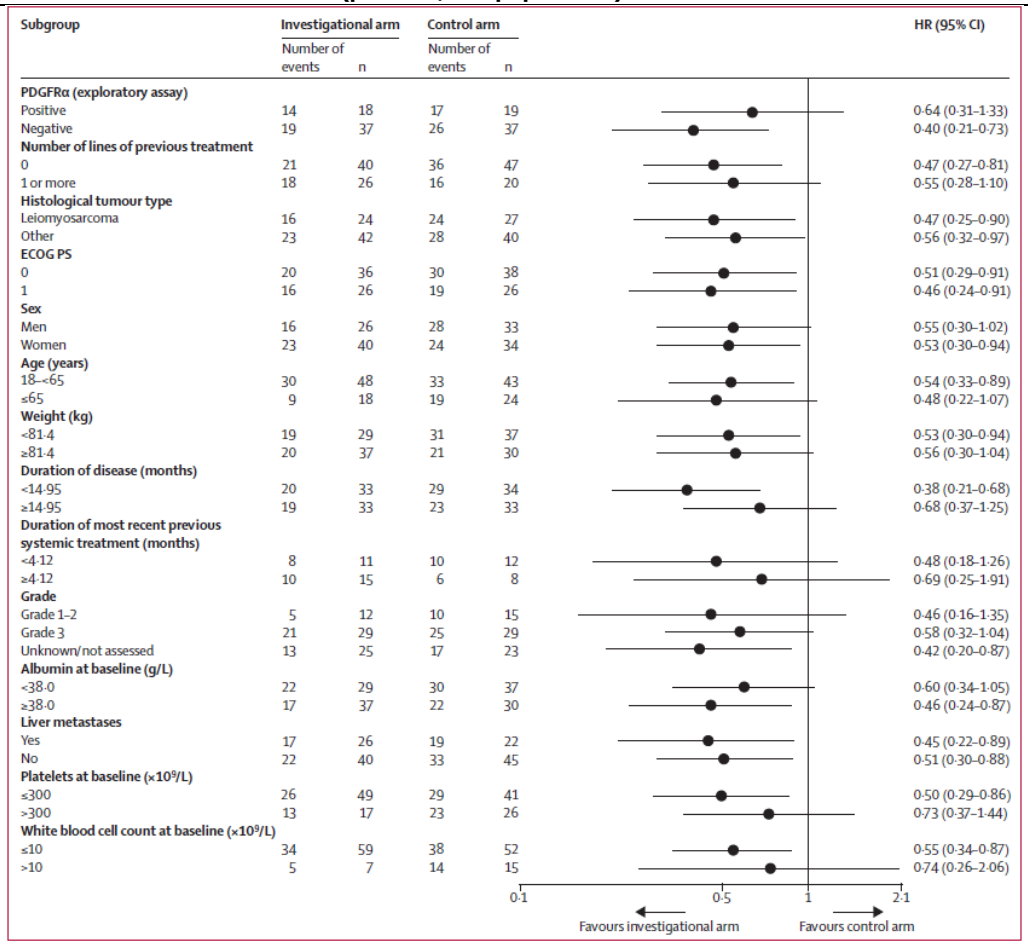
Figure 6.6: Kaplan-Meier curves for the investigator-assessment overall survival **in JGDG trial (Phase 2, ITT Population)**[2]



CI= confidence interval; **HR** = hazard ratio

Source: Reprinted from The Lancet, Vol. 388(10043), Tap WD, Jones RL, Van Tine BA, Chmielowski B, Elias AD, Adkins D et al., Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial, Pages 488-97 Copyright (2016), with permission from Elsevier.[2]

Figure 6.7: Forest plot of overall survival hazard ratios by subgroups defined based on potentially prognostic factors in in JGDG trail (phase 2, ITT population)[2]



Subgroup	Investigational arm		Control arm		HR (95% CI)
	Number of events	n	Number of events	n	
PDGFRα (exploratory assay)					
Positive	14	18	17	19	0·64 (0·31–1·33)
Negative	19	37	26	37	0·40 (0·21–0·73)
Number of lines of previous treatment					
0	21	40	36	47	0·47 (0·27–0·81)
1 or more	18	26	16	20	0·55 (0·28–1·10)
Histological tumour type					
Leiomyosarcoma	16	24	24	27	0·47 (0·25–0·90)
Other	23	42	28	40	0·56 (0·32–0·97)
ECOG PS					
0	20	36	30	38	0·51 (0·29–0·91)
1	16	26	19	26	0·46 (0·24–0·91)
Sex					
Men	16	26	28	33	0·55 (0·30–1·02)
Women	23	40	24	34	0·53 (0·30–0·94)
Age (years)					
18–<65	30	48	33	43	0·54 (0·33–0·89)
≥65	9	18	19	24	0·48 (0·22–1·07)
Weight (kg)					
<81·4	19	29	31	37	0·53 (0·30–0·94)
≥81·4	20	37	21	30	0·56 (0·30–1·04)
Duration of disease (months)					
<14·95	20	33	29	34	0·38 (0·21–0·68)
≥14·95	19	33	23	33	0·68 (0·37–1·25)
Duration of most recent previous systemic treatment (months)					
<4·12	8	11	10	12	0·48 (0·18–1·26)
≥4·12	10	15	6	8	0·69 (0·25–1·91)
Grade					
Grade 1–2	5	12	10	15	0·46 (0·16–1·35)
Grade 3	21	29	25	29	0·58 (0·32–1·04)
Unknown/not assessed	13	25	17	23	0·42 (0·20–0·87)
Albumin at baseline (g/L)					
<38·0	22	29	30	37	0·60 (0·34–1·05)
≥38·0	17	37	22	30	0·46 (0·24–0·87)
Liver metastases					
Yes	17	26	19	22	0·45 (0·22–0·89)
No	22	40	33	45	0·51 (0·30–0·88)
Platelets at baseline (×10⁹/L)					
≤300	26	49	29	41	0·50 (0·29–0·86)
>300	13	17	23	26	0·73 (0·37–1·44)
White blood cell count at baseline (×10⁹/L)					
≤10	34	59	38	52	0·55 (0·34–0·87)
>10	5	7	14	15	0·74 (0·26–2·06)

CI = confidence interval; **ECOG** PS = Eastern Cooperative Oncology Group performance status; **HR** = hazard ratio; **ITT** = intention-to-treat; **PDGFRα** = platelet-derived growth factor receptor α

Source: Reprinted from The Lancet, Vol. 388(10043), Tap WD, Jones RL, Van Tine BA, Chmielowski B, Elias AD, Adkins D et al., Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial, Pages 488-97 Copyright (2016), with permission from Elsevier.[2]

OS Sensitivity Analysis

Two OS sensitivity analysis were performed to examine the influence of post-discontinuation new anti-cancer treatments on the primary OS analysis, both of which were consistent with the primary overall survival analysis: one sensitivity analysis censored at the time of starting any new anticancer treatment, (HR 0.425; 95% CI 0.193, 0.933), and the second censored at the start date of selected anti-cancer treatments ((HR 0.353; 95% CI 0.192, 0.647) (Table 6.12). Similarly, no discrepancies were found in additional post-hoc sensitivity analyses which were performed to examine the impact of the number of cycles of therapy on OS. No additional details were found related to the number of patients censored for these sensitivity analyses.

Table 6.12: Sensitivity analysis of overall survival in JGDG trail (phase 2, ITT population)[2]

Overall Survival	Stratified HR (95% CI)[b,c]	p Value[a,c]
Primary Analysis	0.463 (0.301, 0.710)	0.0003
Censoring at the date		
of starting any new anticancer treatment	0.425 (0.193, 0.933)	0.0284
Censoring at the date of starting selected post-study anticancer therapies		
pazopanib, eribulin, gemcitabine + docetaxel, doxorubicin, and trabectedin	0.353 (0.192,0.647)	0.0005

HR = hazard ratio

a. Derived from a two–sided test.

b. Hazard ratio is expressed as olaratumab + doxorubicin/doxorubicin and estimated from Cox model.

c. Between olaratumab + doxorubicin arm and doxorubicin arm.

Source: Reprinted from The Lancet, Vol. 388(10043), Tap WD, Jones RL, Van Tine BA, Chmielowski B, Elias AD, Adkins D et al., Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial, Pages 488-97 Copyright (2016), with permission from Elsevier.[2]

Objective Response Rate

ORR was a secondary outcome in the JGDG trial, and was defined as the proportion of patients achieving a best overall response of partial response or complete response, according to RECIST, from randomization until disease progression or recurrence.[2] A blinded independent review was conducted following the final database lock (16-May-2015), to evaluate any potential systematic bias favoring either of the treatment arms with respect to the assessment of ORR.[2]

ORR was 18.2% (95% CI 9.8, 29.6) in the Olara+DOX group and 11.9% (95% CI 5.3, 22) in the DOX group (p=0.3421). The ORR for the independent assessment was reported to be 18.2% (95% CI 9.8, 29.6) with Olara+DOX and 7.5% (95% CI 2.5, 16.6) with doxorubicin (p=0·0740). The median duration of response was 8.3 months (95% CI 2.7, 12.7) in the Olara+DOX arm, and 8.2 months (95% CI 2.8, 14.5) in the DOX arm (Table 6.13).[2]

Table 6.13: Response to treatment in JGDG trial (Phase 2; ITT Population), as of 15-August-2014 data cut-off date[2]

Characteristic	Investigator Assessment		Independent Assessment	
	Olaratumab + Doxorubicin (N=66)	Doxorubicin (N=67)	Olaratumab + Doxorubicin (N=66)	Doxorubicin (N=67)
Best overall response—no. (%)				
Complete response	2 (3.0)	1 (1.5)	3 (4.5)	1 (1.5)
Partial response	10 (15.2)	7 (10.4)	9 (13.6)	4 (6.0)
Stable disease	39 (59.1)	34 (50.7)	37 (56.1)	36 (53.7)
Progressive disease	11 (16.7)	15 (22.4)	11 (16.7)	15 (22.4)
Not evaluable	4 (6.1)	10 (14.9)	6 (9.1)	11 (16.4)
Disease control[a]				
No. of patients (%)	51 (77.3)	42 (62.7)	49 (74.2)	41 (61.2)
95% CI	65.3, 86.7	50.0, 74.2	62.0, 84.2	48.5, 72.9
Objective response[b]				
No. of patients (%)	12 (18.2)	8 (11.9)	12 (18.2)	5 (7.5)
95% CI	9.8, 29.6	5.3, 22.	9.8, 29.6	2.5, 16.6
P value (Fisher's exact test)	0.3421		0.0740	
Duration of response—mo.				
Median	8.3	8.2		
95% CI	2.7, 12.7	2.8, 14.5		

CI = confidence interval;; ITT = intent-to-treat; N = number of randomized patients;

Source: Reprinted from The Lancet, Vol. 388(10043), Tap WD, Jones RL, Van Tine BA, Chmielowski B, Elias AD, Adkins D et al., Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial, Pages 488-97 Copyright (2016), with permission from Elsevier.[2]

Quality of Life

Quality of life outcomes were not reported in the identified trial.

Harms Outcomes

Safety was the primary outcome in phase 1b, and a secondary outcome in phase 2 JGDG trial. AEs reported in phase 1b and phase 2 of JGDG trial are presented in Table 6.14 and Table 6.15, respectively.

In phase 1b, treatment related AEs of any grade occurred in 93.3% (14/15) of the patients. Grade 3 or 4 treatment-related AEs were reported in 53.3% (8/15) of patients, and any grade treatment-related serious AEs were reported in 20% (3/15) and grade 3 treatment related serious AEs in 20% (3/15) of the study participants.[2]

In phase 2, similar proportions of patients in Olara+DOX and DOX arms experienced AEs of any grade (98% of patients in each group), or grade 3 AEs (38% in each group). However, a higher percentage of the patients in Olara+DOX arm (42%) experienced grade 4 AEs, when compared with those in the DOX arm (31%). Treatment-related adverse events of grade 3 or higher were also more frequently reported in Olara+DOX group (67%) than in those in the DOX group (55%). The most common adverse events of all grades experienced by the Olara+DOX group were nausea (73%), fatigue (69%), neutropenia (58%), and mucositis (53%). In the DOX group, the most common AEs were fatigue (69%), nausea (52%), infections and infestations (42%) and alopecia (40%), and neutropenia (35%). Serious adverse events were experienced by 42% of patients in the Olara+DOX arm and 38% of those in the DOX arm. Infusion-related reactions were observed in eight (13%) patients in the Olara+DOX arm and no patients (0%) in the DOX arm.[2]

The percentage of patients who discontinued treatment because of an AE was lower in the Olara+DOX group (13%) than in the DOX group (18%).[2] Commonly reported (in >5% of patients) AEs which led to olaratumab dose modifications were: neutropenia in 48.4% (31/64), thrombocytopenia in 12.5% (8/64), febrile neutropenia in 6.3% (4/64), and infusion related reactions in 6.3% (4/64) of patients in the Olara+DOX arm.[4] The most commonly reported (in >5% of patients) AEs which led to DOX dose modifications in the investigational compared to control group respectively, were: neutropenia in 20.3% (13/64) and 9.2% (6/65) and febrile neutropenia in 4.7% (3/64) and 6.2 (4/65).[4]

Mortality was reported in 60.9% (39/64) of patients in the Olara+DOX group and 78.5% (51/65) of those in the DOX group. In the Olara+DOX arm, the cause of death was attributed to disease progression in 38 patients and an unknown cause in one patient. In the DOX group, the cause of death was attributed to disease progression in 44 patients, AEs in six patients, and an unknown cause in one patient.[4] Doxorubicin-related toxicities (including neutropenia, mucositis, nausea, vomiting, and diarrhoea) were more frequent in the Olara+DOX arm, but did not result in an increased number of febrile neutropenia events, hospital admissions, treatment discontinuations, or deaths.[2]

Table 6.14 Adverse events reported in JGDG trial (phase 1b)[2]

	Olaratumab + Doxorubicin (N=15)		
Event	**A11 Grades**	**Grade 3**	**Grade 4**
Any adverse event—no. of patients (%)[b]	15 (100.0)	9 (60.0)	3 (20.0)
Anemia[c]	11 (73.3)	5 (33.3)	0
Fatigue[d]	10 (66.7)	1 (6.7)	0
Nausea	8 (53.3)	2 (13.3)	0
Leukopenia[e]	7 (46.7%)	3 (20.0%)	0
Vomiting	6 (40.0)	2 (13.3)	0
Neutropenia[f]	5 (33.3%)	3 (20.0%)	1 (6.7%)
Abdominal pain[g]	4 (26.7)	3 (20.0)	0
Back pain	3 (20.0)	2 (13.3)	0
Febrile neutropenia[h]	2 (13.3)	2 (13.3)	0
Treatment-related adverse event—no. of patients (%)	14 (93.3)	8 (53.3)	1 (6.7)
Adverse event leading to discontinuation of treatment—no. of patients (%)	0		
Serious adverse event—no. of patients (%)			
Any event	7 (46.7)	6 (40.0)	1 (6.7)
Treatment-related event	3 (20.0)[i]	3 (20.0)[i]	0

[a] Adverse events and clinical laboratory toxicity were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.
[b] The adverse events listed here were reported in at least 15% of patients in the Phase 1b group, except as noted in footnote h. Included are individual preferred terms from the Medical Dictionary for Regulatory Activities [MedDRA] and certain consolidated terms combining clinically synonymous MedDRA preferred terms.
[c] Consolidated term comprising the following preferred terms: anemia, hemoglobin decreased.
[d] Consolidated term comprising the following preferred terms: fatigue, asthenia.
[e] Consolidated term comprising the following preferred terms: leukopenia, white blood cell count decreased.
[f] Consolidated term comprising the following preferred terms: neutropenia, neutrophil count decreased.
[g] Consolidated term comprising the following preferred terms: abdominal pain upper, abdominal pain, abdominal pain lower.
[h] These events are included here because they were associated with Grade ≥3 events and considered clinically important.
[i] Two patients with febrile neutropenia, 1 patient with nausea, and 1 patient with vomiting

Source: Reprinted from The Lancet, Vol. 388(10043), Tap WD, Jones RL, Van Tine BA, Chmielowski B, Elias AD, Adkins D et al., Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial, Pages 488-97 Copyright (2016), with permission from Elsevier.[2]

Table 6.15 Adverse events reported in JGDG trial (phase 2; Safety Population)[2]

	Olaratumab plus doxorubicin (n=64)			Doxorubicin (n=65)		
	Any Grade	Grade 3	Grade ≥4	Any Grade	Grade 3	Grade ≥4
Patients with any adverse event†	63 (98%)	24 (38%)	27 (42%)	64 (98%)	25 (38%)	20 (31%)
Nausea	47 (73%)	1 (2%)	0	34 (52%)	2 (3%)	0
Fatigue‡	44 (69%)	6 (9%)	0	45 (69%)	2 (3%)	0
Neutropenia§¶	37 (58%)	12 (19%)	22 (34%)	23 (35%)	5 (8%)	16 (25%)
Mucositis‖	34 (53%)	2 (3%)	0	23 (35%)	3 (5%)	0
Alopecia	33 (52%)	0	0	26 (40%)	0	0
Vomiting	29 (45%)	0	0	12 (18%)	0	0
Anaemia**	26 (41%)	8 (13%)	0	24 (37%)	6 (9%)	0
Leucopenia††¶	26 (41%)	14 (22%)	9 (14%)	12 (18%)	5 (8%)	6 (9%)
Constipation	22 (34%)	0	0	21 (32%)	1 (2%)	0
Diarrhoea	22 (34%)	2 (3%)	0	15 (23%)	0	0
Decreased appetite	20 (31%)	1 (2%)	0	13 (20%)	0	0
Abdominal pain‡‡	15 (23%)	2 (3%)	0	9 (14%)	0	0
Pyrexia	15 (23%)	0	0	12 (18%)	0	0
Musculoskeletal pain§§	41 (64%)	¶¶	¶¶	16 (25%)	‖‖	‖‖
Febrile neutropenia***	8 (13%)	7 (11%)	1 (2%)	9 (14%)	9 (14%)	0
Infections and infestations***†††	27 (42%)	5 (8%)	0	27 (42%)	4 (6%)	3 (5%)
Infusion-related reaction***‡‡‡	8 (13%)	0	2 (3%)	0	0	0
Treatment-related adverse event	63 (98%)	18 (28%)	25 (39%)	63 (97%)	19 (29%)	17 (26%)
Adverse event leading to discontinuation of treatment	8 (13%)	1 (2%)	3 (5%)	12 (18%)	3 (5%)	5 (8%)
Serious adverse event						
Any event	27 (42%)	20 (31%)	7 (11%)	25 (38%)	14 (22%)	8 (12%)
Treatment-related event	14 (22%)	8 (13%)	6 (9%)	17 (26%)	11 (17%)	5 (8%)
Cardiac dysfunction§§§¶¶¶	15 (23%)	1 (2%)	0	11 (17%)	0	0
Oedema peripheral	10 (16%)	0	0	7 (11%)	0	0
Ejection fraction decreased	5 (8%)	1 (2%)	0	4 (6%)	0	0
Congestive cardiac failure	1 (2%)	1 (2%)	0	0	0	0
Hepatojugular reflux	1 (2%)	0	0	0	0	0
Jugular vein distension	1 (2%)	0	0	0	0	0
Left ventricular dysfunction	1 (2%)	0	0	0	0	0
Cardiac dysfunction (excluding peripheral oedema) ‖‖‖‖	5 (8%)	1 (2%)	0	4 (6%)	0	0
LVEF (lowest post-baseline)						
n****	51	..	..	32	..	..
LVEF <50%	6 (12%)	..	..	3 (9%)	..	..

Data are n (%). LVEF=left ventricular ejection fraction. *Adverse events and clinical laboratory toxicity were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). †The adverse events listed here were reported in at least 15% of patients in the olaratumab plus doxorubicin group, except as noted in footnote ¶¶. These included individual preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA) and specific consolidated terms combining clinically synonymous MedDRA preferred terms. ‡Consolidated term comprising the following preferred terms: fatigue and asthenia. §Consolidated term comprising the following preferred terms: neutropenia and neutrophil count decreased. ¶Some patients reported both neutropenia and leucopenia. ‖Consolidated term comprising the following preferred terms: mucosal inflammation, oropharyngeal pain, and stomatitis. **Consolidated term comprising the following preferred terms: anaemia and haemoglobin decreased. ††Consolidated term comprising the following preferred terms: leucopenia and white blood cell count decreased. ‡‡Consolidated term comprising the following preferred terms: abdominal pain upper, abdominal pain, and abdominal pain lower. §§Preferred terms reported were: arthralgia, back pain, spasms, musculoskeletal chest pain, myalgia, and pain in extremity. ¶¶5 (7·8%) patients (%) had musculoskeletal pain of grade ≥3 in the olaratumab plus doxorubicin group. ‖‖‖ 1 (1·5%) patient had musculoskeletal pain of grade ≥3 in the doxorubicin group. ***These events are included here because they were considered clinically important. †††Includes all preferred terms within the MedDRA system organ class of infections and infestations. ‡‡‡Consolidated term comprising the following preferred terms (from AESI): hypersensitivity, infusion-related reaction, and face oedema. §§§Includes individual preferred terms from MedDRA. ¶¶¶Some patients reported more than one cardiac dysfunction event term. ‖‖‖‖‖No patients with reported adverse events of peripheral oedema had any reported adverse events to suggest cardiac dysfunction. ****Number of patients assessed at baseline and at least one post-baseline timepoint.

*Table 3: Adverse events (phase 2)**

Source: Reprinted from The Lancet, Vol. 388(10043), Tap WD, Jones RL, Van Tine BA, Chmielowski B, Elias AD, Adkins D et al., Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial, Pages 488-97 Copyright (2016), with permission from Elsevier.[2]

6.4 Ongoing Trials

Two ongoing trials, evaluating the efficacy and safety of olaratumab in patients with advanced or metastatic STS, were identified.

JGDJ, also known as ANNOUNCE, is a randomized, double-blind, placebo-controlled, phase III trial of doxorubicin plus olaratumab versus doxorubicin plus placebo in patients with advanced or metastatic soft tissue sarcoma. The ongoing phase III trial is fully enrolled. Estimated study completion date is January 2020 and a primary completion date of January 2019. The primary outcome of the trial is OS, with PFS, ORR, and quality of life being collected as secondary outcomes.

ANNOUNCE 2 trial is a phase 1b (open-label) / phase 2 (randomized, double-blinded) study evaluating gemcitabine and docetaxel with or without olaratumab in the treatment of advanced STS. Estimated study completion date is December 2020 and a primary completion date of December 2019. The primary outcome of the phase 2 trial is OS, with PFS, ORR and quality of life being collected as secondary outcomes.

More details about these trials are presented in Table 6.16.

[Table 6.16]: Ongoing trials of olaratumab in patients with soft tissue sarcoma

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
ANNOUNCE Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Doxorubicin Plus Olaratumab Versus Doxorubicin Plus Placebo in Patients With Advanced or Metastatic Soft Tissue Sarcoma Number of Patients: 460 Start date: September 2015 Estimated Study Completion Date: January 2020 Estimated Primary Completion Date: January 2019 (Final data collection date for primary outcome measure) Study location: Argentina, Australia, Austria, Belgium, Brazil, Canada, Denmark, Finland, France, Germany, Hungary, Israel, Italy, Japan, Korea, Republic of, Mexico, Netherlands, Poland, Russian Federation, Spain, Sweden, Switzerland, Taiwan, United Kingdom, United States	Key Inclusion Criteria: ≥18 years of age Histologically confirmed diagnosis of advanced unresectable or metastatic soft tissue sarcoma not amenable to curative treatment with surgery or radiotherapy. Presence of measurable or non-measurable but evaluable disease as defined by the RECIST 1.1. ECOG performance score of 0-1. No previous history of treatment with anthracyclines Key Exclusion Criteria: - GIST or Kaposi sarcoma. - active or leptomeningeal CNS metastasis - Prior radiotherapy of the mediastinal/pericardial area or whole pelvis radiation. - active fungal, bacterial, and/or known viral infection	Intervention **DOX + Olaratumab** DOX 75 mg/m2 administered IV on day 1 of each 21 day cycle for 8 cycles plus Olaratumab 20 mg/kg administered IV on day 1 and day 8 of cycle 1 and 15 mg/kg Olaratumab administered IV on day 1 and day 8 of cycles 2-8. Beginning with cycle 9, 15 mg/kg Olaratumab administered IV on day 1 and day 8 of each subsequent 21 day cycle until documented progressive disease or discontinuation for any other reason. Placebo Comparator **DOX + Placebo** DOX 75 mg/m2 administered IV on day 1 of each 21 day cycle for 8 cycles plus placebo (equivalent volume) administered IV on day 1 and day 8 for 8 cycles. Beginning with cycle 9, placebo (equivalent volume) administered on days 1 and 8 of each subsequent 21 day cycle until disease progression or discontinuation for any other reason.	Primary: OS Secondary: PFS; ORR; health status on EQ-5D-5L; pharmacokinetics; and others
ANNOUNCE 2 Phase 1b (Open-Label) / Phase 2 (Randomized, Double-Blinded) Study Evaluating Gemcitabine and Docetaxel With or Without Olaratumab in the Treatment of Advanced STS	Key Inclusion Criteria: - ≥18 years of age - ≤ 2 prior lines of systemic therapies (neoadjuvant and adjuvant therapies is not considered as a prior line of therapy) for advanced or metastatic disease. In the	**Phase 1b** Intervention **Olaratumab + Gemcitabine + Docetaxel** (Dose Escalation) Olaratumab IV on day 1 and day 8 of each cycle (1 cycle = 21 days) with gemcitabine IV on day 1 and 8	Primary: - Phase 1b: Recommended Phase 2 dose of Ola - Phase 2: OS

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Number of Patients: 310 Start date: March 2016 Estimated Study Completion Date: December 2020 Estimated Primary Completion Date: December 2019 (Final data collection date for primary outcome measure) Study Location: Australia, France, Germany, Hungary, Israel, Italy, Poland, Spain, United Kingdom, United States Funding: Eli Lilly and Company	Phase 2 part, prior olaratumab/doxorubicin combination therapy in 1 prior treatment line is allowed - Suitable to receive gemcitabine and docetaxel therapy. <u>Key Exclusion Criteria:</u> - GIST or Kaposi sarcoma. - active CNS or leptomeningeal metastasis - active fungal, bacterial, and/or known viral infection	and docetaxel IV on day 8. Participants may continue to receive treatment until discontinuation criteria are met. **Phase 2** <u>Intervention</u> **Olaratumab + Gemcitabine + Docetaxel** Olaratumab IV on day 1 and day 8 of each cycle (1 cycle = 21 days) with gemcitabine IV on day 1 and 8 and docetaxel IV on day 8. Participants may continue to receive treatment until discontinuation criteria are met. <u>Placebo Comparator</u> Placebo + Gemcitabine + Docetaxel Placebo IV on day 1 and day 8 of each cycle (1 cycle = 21 days) with gemcitabine IV on day 1 and 8 and docetaxel IV on day 8. Participants may continue to receive treatment until discontinuation criteria are met.	<u>Secondary:</u> Pharmacokinetics; PFS; ORR; health status on EQ-5D-5L, and others
CNS = central nervous system; DOX= doxorubicin; ECOG = Eastern Cooperative Oncology Group; GIST = gastrointestinal stromal tumor; IV= intravenous; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST: Response Evaluation Criteria in Solid Tumors			

7 SUPPLEMENTAL QUESTIONS

The following supplemental question was identified during development of the review protocol as relevant to the pCODR review of olaratumab in the treatment of patients with advanced STS.

- Summary of the Manufacturer-submitted indirect treatment comparison (ITC) of olaratumab versus available treatment options in patients with advanced STS.

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Summary of a Manufacturer-submitted indirect treatment comparison of olaratumab versus available treatment options in patients with advanced STS

7.1.1 Objective

The pCODR-conducted literature search identified a phase1b/2 randomized trial that compared olaratumab used in combination with doxorubicin with doxorubicin monotherapy in advanced STS. The search did not identify any head-to-head RCTs that assessed the efficacy of olaratumab mono- or combination-therapies with other interventions. The pCODR clinical guidance panel confirmed that doxorubicin is the most appropriate comparator in the Canadian setting and use of other agents is not common.

Within the submission dossier, the pCODR review team identified a Manufacturer conducted a systematic review of clinical trials investigating treatments for advanced STS and a meta-analysis identified to be relevant comparators of olaratumab.[8]

The objective of this section is to summarize the methods and results of the manufacturer-submitted systematic review and meta-analysis that provides evidence for the efficacy of olaratumab versus other treatment options in patients with advanced STS.

7.1.2 Findings

Review of Manufacturer's ITC

7.1.2.1 Objectives

The objectives of the manufacturer-submitted ITC were to perform a systematic review of clinical trials of treatments and combinations of treatments for advanced STS, and to provide quantitative relative measures of the efficacy and safety of olaratumab in comparison with other treatments for advanced STS by therapy line, based on meta-analyses.

7.1.2.2 Overview of Methods

Systematic Review

The Manufacturer conducted a systematic review to identify publications reporting clinical trials that evaluated the efficacy and safety of treatments for STS.[7,8]

The following medical literature databases were searched (during January and February, 2015): MedLine, EMBASE and Cochrane databases, using a predefined search protocol. Additional searches were conducted to identify information on recent trials by searching abstracts from the previous two years of relevant conferences (American Society of Clinical Oncology,

European Society for Medical Oncology, Connective Tissue Oncology Society) and Clinicaltrials.gov. The study results from the JGDG trial were published by Tap et al.[2] published in 2016 were also included. Search terms were designed to capture studies of any systemic treatments for advanced STS in any line of therapy, with no limitations regarding publication date or language.[8]

The study selection criteria are summarized below.

- Population: Aged ≥ 18 years with advanced STS, excluding bone sarcomas, Kaposi sarcoma and gastrointestinal stromal tumour (GIST)
- Intervention and comparators: 53 single or combination agents including doxorubicin, ifosfamide, gemcitabine and olaratumab.
- Outcomes: Overall survival (OS), Progression-free survival (PFS), safety
- Study Type: Phase 2, 3, and 4 clinical trials

An independent double screening and data extraction process was used for study selection

Assessment of Study Quality

Assessment of the methodological quality of included randomized controlled trials (RCTs) was performed by two independent reviewers, using the quality criteria presented in the NICE single technology appraisal guidance (2012) and the Centre for Reviews and Dissemination (2009).[8]

Indirect Treatment Comparisons

Network meta-analyses (NMAs) were conducted on data for OS, PFS, ORR, and discontinuation due to AEs.

- OS and PFS were analyzed using two different approaches: 1) a Bayesian NMA of hazard ratios according to the methods proposed by Woods et al. (2010);[45] and 2) modelling reconstructed patient-level data using an NMA with Bayesian fractional polynomial models based on Jansen's method (2011).[46] Fractional polynomial models of OS curves from trials in the network were extrapolated up to the longest follow-up period in the network (47 months for Tap et al.)[2] to allow mean survival to be compared over the same time period.[8]
- Discontinuation due to AEs was modeled using Bayesian binomial models.

Consideration of heterogeneity or inconsistency in the network was not possible using standard tests (such as Higgins' I^2 and Cochran's test) because there were no closed loops in the networks. As such, the Manufacturer suggested that the results should be interpreted with caution, as they were based on a limited network of evidence.

7.1.2.3 Results of ITC

Systematic Review

The literature searches identified 3555 citations; of which, 222 publications met the inclusion criteria. Out of the 222 publications, 216 citations were excluded as they were based on single-arm trials, or RCTs not linking to Olara+DOX, or RCTs studying interventions that were not of primary interest.[44] As a result, 6 studies (four phase 3 and two phase 2 trials) were included in the meta-analysis. Available comparators for the meta-analysis were doxorubicin

(DOX), gemcitabine + docetaxel (GemDoc), and four different ifosfamide + doxorubicin (IfoDOX) regimens.[44]

Indirect Treatment Comparisons

The six studies that included in the meta-analysis all included anthracycline-naïve patient populations.

Figure 7.1 illustrates the network of clinical trials that were used to perform the NMA.[8] As the figure shows, Olara+DOX is compared with DOX monotherapy in the Tap study;[2] DOX monotherapy is linked to three different regimens of IfosDOX in three trials;[10,19,47] and to - gemcitabine+docetaxel in one trial.[48] One of the three IfosDOX regimens is compared to an additional IfoDOX regimen in one trial.[49] Overall, this network indirectly links Olara+DOX combination to four different IfoDOX regimens as well as GemDoc via a common comparator (DOX).The results of NMAs of efficacy and safety outcomes are shown in Table 7.1A, and Table 7.1B.

Table 7.1: Results of network meta-analyses of treatments for advanced Soft Tissue Sarcoma[44]

Efficacy

Comparison: OlaDox (Tap et al., 2016)[4] vs	Sample Size	HR analysis[b]			Fractional Polynomial analysis[c]		
	(ITT)[a]	HR	95% Cr Int	p value	Mean difference (months)	95% Cr Int	p value
Overall Survival							
Dox	525	0.46	0.30 – 0.71	<0.001	8.59	4.47 – 13	<0.001
$Ifo^{12.5}Dox^{90}$ (Maurel, et al)[12]	59	0.65	0.35 – 1.22	0.184	3.45	-2.46 – 9.38	0.262
$Ifo^{5}Dox^{50}$ (LeCesne, et al; Santoro, et al)[11,13]	(65,149)	0.51	0.31 – 0.83	0.006	7.49	2.95 – 12	<0.001
$Ifo^{10}Dox^{75}$ (Judson, et al)[3]	211	0.56	0.34 – 0.90	0.016	7.05	2.52 – 12	0.002
$Ifo^{5}Dox^{75}$ (LeCesne, et al)[11]	145	0.52	0.30 – 0.91	0.022	7.74	2.52 – 13	0.002
GemDoc (Seddon, et al)[14]	128	0.43	0.25 – 0.74	0.002	9.17	3.99 – 14	< 0.001
Progression-free Survival[d]							
Dox	469	0.67	0.44 – 1.02	0.063	2.81	0.05 – 7.71	0.044
$Ifo^{12.5}Dox^{90}$ (Maurel, et al)[12]	59	0.66	0.38 – 1.15	0.143	3.90	0.12 – 9.01	0.042
$Ifo^{10}Dox^{75}$ (Judson, et al)[3]	211	0.91	0.57 – 1.44	0.701	1.33	-1.72 – 6.40	0.452
GemDoc (Seddon, et al)[14]	128	0.53	0.32 – 0.86	0.012	4.88	1.80 – 9.86	0.001

Cr Int = credible interval; Doc = docetaxel; Dox = doxorubicin; Gem = gemcitabine; HR = hazard ratio; Ifo = ifosfamide; ITT = intention-to-treat; Ola = olaratumab; p-values relate to the probability of equivalence, which can be used in the same way as traditional significance tests and are calculated using the empirical cumulative distribution function, which is the inverse of the method used to calculate credible confidence intervals (see van der Vaart[15]).
Note that all trials in the network were conducted in a first-line population except Tap et al.[4] for which 65% of patients were first-line.
[a] The ITT population considered for efficacy analysis by Tap et al.[4] included a total of 133 patients (OlaDox, n=66, and Dox, n=67)
[b] The HRs from Tap et al.[4] were from the stratified analysis of the ITT population. Note that a HR < 1.0 reflects a lower risk for patients receiving OlaDox
[c] Note that a positive mean difference reflects a lengthening of PFS or OS for patients receiving OlaDox. For OS, these estimates were based on restricting the analysis period to the longest follow up of the trials in the network, which was Tap et al.[4] at 47 months, to allow mean survival to be compared over the same time period. OS for the trials with shorter follow-up periods was extrapolated out to 47 months, based on the FP models
[d] Judson et al.[3] and Maurel et al.[12] report investigator-assessed PFS, while Seddon et al.[14] does not specify PFS assessment method. For consistency, analyses presented here use the investigator-assessed PFS from Tap et al.[4] (which also reports independent assessed PFS). PFS HRs were not reported for the trials using the $Ifo^{5}Dox^{75}$ and $Ifo^{5}Dox^{50}$ regimens[11,13]

Safety

Comparison: OlaDox (Tap et al)[4] vs	Odds Ratio[a]	95% Cr Int
Dox	0.62	0.22 – 1.64
$Ifo^{12.5}Dox^{90}$ (Maurel, et al)[12]	0.06	0.00 – 0.51
$Ifo^{5}Dox^{50}$ (LeCesne, et al; Santoro, et al)[11,13]	0.34	0.10 – 1.13
$Ifo^{10}Dox^{75}$ (Judson, et al)[3]	0.07	0.02 – 0.27
$Ifo^{5}Dox^{75}$ (LeCesne, et al)[11]	0.11	0.03 – 0.44
GemDoc (Seddon, et al)[14]	0.10	0.02 – 0.45

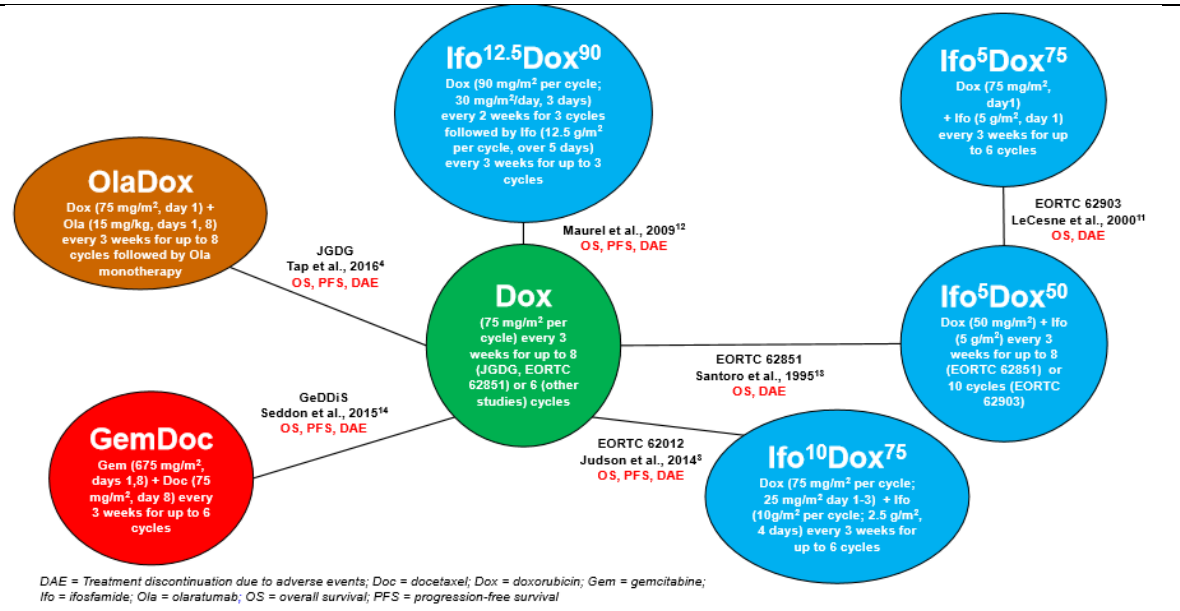
Cr Int = credible interval; Doc = docetaxel; Dox = doxorubicin; Gem = gemcitabine; Ifo = ifosfamide; Ola = olaratumab
[a] Note that an OR < 1.0 reflects a lower risk of discontinuation due to AEs for patients receiving OlaDox

Source: Bertwistle et al. 2016[44] Poster provided by Eli Lilly

In summary:

- Olara+DOX resulted in a significantly greater OS when compared with DOX, GemDoc, and three of the four different IfoDOX regimens.
- Olara+DOX resulted in significantly greater PFS when compared with GemDoc.
- No significant differences were identified between Olara+DOX and other treatments in terms of ORR.
- Olara+DOX showed a significantly lower discontinuation rate due to AEs than GemDoc and three of the four IfoDOX regimens.
- Results from the Bayesian fractional polynomials analysis showed similar results for OS (i.e., Olara+DOX resulted in significantly greater OS when compared with DOX, GemDoc, and three of the IfoDOX regimens). However, the results of the Bayesian fractional polynomials analysis for PFS was different those from the hazard ratio analyses (i.e., Olara+DOX resulted in significantly greater PFS when compared with IfoDOX (12.5 g/m2, 90 mg/m2), DOX, and GemDoc). This discrepancy in the results from the two methods might be related to the fact that in the Bayesian fractional polynomials approach anchoring of distributions using long-term survival data was not required for PFS.
- Olara+DOX showed a significantly lower discontinuation rate due to AEs compared with GemDoc and three of the four IfoDOX regimens

Figure 7.1: Network of clinical trials used in the network meta-analysis[44]



Source: Bertwistle et al. 2016[44] Poster provided by Eli Lilly

7.1.3 Summary

The results of the Manufacturer-submitted systematic review and NMA suggested that Olara+DOX had a significantly greater OS benefit than DOX, GemDoc, and three IfoDOX regimens. The hazard ratio NMA method demonstrated a significant PFS benefit for Olara+DOX compared with GemDoc, while the results of the fractional polynomial NMA showed a significantly greater PFS for Olara+DOX when compared with IfoDOX (12.5 g/m^2, 90 mg/m^2), DOX, and GemDoc. No significant differences were identified between Olara+DOX and other treatments of interest in terms of objective tumor response rate. Discontinuation rate due to AEs was significantly lower for Olara+DOX, when compared with GemDoc and three of the four IfoDOX regimens.

Overall, the results of the NMAs should be treated with caution because there were no closed loops in the network and there was only one study for each comparison.

8 COMPARISON WITH OTHER LITERATURE

No comparisons with other literature were addressed in this review.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Sarcoma 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 olaratumab (Lartruvo) for soft tissue sarcoma (STS). 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 CADTH 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. The manufacturer, as the primary data owner, did not agree to the disclosure of some clinical information which was provided to pERC for their deliberations, and this information has been redacted in this publicly posted Guidance Report.

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 Sarcoma Clinical Guidance Panel is comprised of three oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH 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 AND DETAILED METHODOLOGY

1. Literature search via OVID platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials September 2017, Embase 1974 to 2017 November 02, Ovid MEDLINE(R) ALL 1946 to November 02, 2017

#	Searches	Results
1	(olaratumab* or Lartruvo* or IMC3G3 or IMC 3G3 or TT6HN20MVF or 1024603-93-7 or LY-3012207 or LY3012207).ti,ab,ot,kf,kw,hw,rn,nm.	225
2	1 use medall	47
3	1 use cctr	20
4	*olaratumab/ or (olaratumab* or Lartruvo* or IMC3G3 or IMC 3G3 or TT6HN20MVF or LY-3012207 or LY3012207).ti,ab,kw.	137
5	4 use oemezd	73
6	5 and conference abstract.pt.	28
7	limit 6 to yr="2012 -Current"	23
8	5 not 6	45
9	2 or 3 or 8	112
10	remove duplicates from 9	66
11	10 or 7	89
12	Limit to English language	87

2. Literature search via PubMed

A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#2	Search **#1 AND publisher[sb] Filters: English**	3
#1	Search **olaratumab[Supplementary Concept] OR olaratumab*[tiab] OR Lartruvo*[tiab] OR IMC3G3[tiab] OR IMC 3G3[tiab] OR TT6HN20MVF[rn] OR 1024603-93-7[rn] Filters: English**	40

3. Cochrane Central Register of Controlled Trials (Central)
   Searched via Ovid

4. Grey Literature search via:

Clinical Trial Registries:

U.S. NIH ClinicalTrials. gov
http://www.clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: Lartruvo/olaratumab, soft tissue sarcoma

Select international agencies including:

Food and Drug Administration (FDA):
http://www.fda.gov/

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search: Lartruvo/olaratumab, soft tissue sarcoma

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

Search: Lartruvo/olaratumab, soft tissue sarcoma

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 (1946-2017 Nov 2) with in-process records & daily updates via Ovid; Embase (1974-2017 Nov 2) via Ovid; The Cochrane Central Register of Controlled Trials (September 2017) via Ovid; 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 Lartruvo and olaratumab.

No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, but not limited by publication year.

The search is considered up to date as of March 1, 2018.

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 – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) were searched manually for conference years not available in Embase. 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 additional information as required by the pCODR Review Team.

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.

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

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.

Data Analysis

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

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 clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

REFERENCES

1. Olaratumab in combination with doxorubicin for treating advanced soft tissue sarcoma: final appraisal determination [Internet]. London: National Institute for Health and Care Excellence (NICE); 2017 Jun. [cited 2018 Mar 6]. Available from: https://www.nice.org.uk/guidance/ta465/documents/final-appraisal-determination-document

2. Tap WD, Jones RL, Van Tine BA, Chmielowski B, Elias AD, Adkins D, et al. Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial. Lancet [Internet]. 2016 Jul 30 [cited 2017 Nov 16];388(10043):488-97. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5647653

3. Olaratumab in combination with doxorubicin for treating advanced soft tissue sarcoma: committee papers [Internet]. London: National Institute for Health and Care Excellence (NICE); 2017 Jun 13. [cited 2018 Jan 15]. (Single technology appraisal). Available from: https://www.nice.org.uk/guidance/TA465/evidence

4. Lartruvo: public assessment report [Internet]. London: European Medicines Agency; 2016 Sep 15. [cited 2017 Nov 16]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004216/WC500216871.pdf

5. Eli Lilly Canada response to pCODR checkpoint meeting questions on olaratumab (Lartruvo) in combination with doxorubicin for the treatment of patients with advanced soft tissue sarcoma [additional manufacturer's information]. Toronto (ON): Eli Lilly Canada; 2017 Dec 13.

6. Van Tine BA, Peterson P, Shahir A, Ilaria R, Jones RL. Analysis of efficacy and safety of olaratumab + doxorubicin or doxorubicin alone in patients with uterine leiomyosarcoma: retrospective assessment of the phase 1b/2 study JGDG [abstract]. Int J Gynecol Cancer. 2017;27(Suppl 4):490. (Presented at 20th International Meeting of the European Society of Gynaecological Oncology; 2017 Nov 4-7; Vienna, Austria).

7. pan-Canadian Oncology Drug Review manufacturer submission: Lartruvo (olaratumab) intravenous injection, 10 mg/mL vial. Company: Eli Lilly. Toronto: Eli Lilly Canada; 2017 Oct 25.

8. Bertwistle D, D'Yachkova Y, Vickers AD, Hawe E, Fernandez M, Drove N, et al. Comparative efficacy and saftey of interventions in the treatment of advanced soft tissue sarcoma: a systematic review and network meta analysis [abstract]. Value Health. 2016;19(7):A712. (Presented at ISPOR 19th Annual European Congress; 2016 Oct 29-Nov 2; Vienna, Austria).

9. Soft tissue sarcoma statistics [Internet]. Ottawa (ON): Canadian Cancer Society; 2017. [cited 2017 Nov 8]. Available from: http://www.cancer.ca/en/cancer-information/cancer-type/soft-tissue-sarcoma/statistics/

10. Judson I, Verweij J, Gelderblom H, Hartmann JT, Schoffski P, Blay JY, et al. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. Lancet Oncol. 2014 Apr;15(4):415-23.

11. Singer S, Maki R, O'Sullivan B. Soft tissue sarcoma. In: DeVita VT, Heilman S, Rosenberg SA, editors. Cancer: principles and practice of oncology. 9th edition. Philadelphia (PA): Wolters Kluwer; Lippincott Williams & Wilkins; 2011. p. 1533-77.

12. Singer S, Maki R, O'Sullivan B. Molecular biology of soft tissue sarcoma. In: DeVita VT, Heilman S, Rosenberg SA, editors. Cancer: principles and practice of oncology. 9th edition. Philadelphia (PA): Wolters Kluwer; Lippincott Williams & Wilkins; 2011. p. 1522-32.

13. Borden EC, Baker LH, Bell RS, Bramwell V, Demetri GD, Eisenberg BL, et al. Soft tissue sarcomas of adults: state of the translational science. Clin Cancer Res. 2003 Jun;9(6):1941-56.

14. Gastrointestinal Stromal Tumor Meta-Analysis Group (MetaGIST). Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumors: a meta-analysis of 1,640 patients. J Clin Oncol [Internet]. 2010 Mar 1 [cited 2017 Nov 8];28(7):1247-53. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2834472

15. Estimated new cases and deaths by sex, US. In: Cancer facts & figures 2012. Atlanta (GA): American Cancer Society; 2012.

16. Casali PG, Blay JY, ESMO/CONTICANET/EUROBONET Consensus Panel of experts. Soft tissue sarcomas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010 May;21 Suppl 5:v198-v203.

17. Doxorubicin-based chemotherapy for the palliative treatment of adult patients with locally advanced or metastatic soft tissue sarcoma [Internet]. Version 2. Toronto (ON): Cancer Care Ontario; 2014 Oct. [cited 2017 Nov 8]. (Evidence-based care evidence-based series no.: 11-1). Available from: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/2501

18. Lorigan P, Verweij J, Papai Z, Rodenhuis S, Le Cesne A, Leahy MG, et al. Phase III trial of two investigational schedules of ifosfamide compared with standard-dose doxorubicin in advanced or metastatic soft tissue sarcoma: a European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Study. J Clin Oncol. 2007 Jul 20;25(21):3144-50.

19. Maurel J, Lopez-Pousa A, de Las Penas R, Fra J, Martin J, Cruz J, et al. Efficacy of sequential high-dose doxorubicin and ifosfamide compared with standard-dose doxorubicin in patients with advanced soft tissue sarcoma: an open-label randomized phase II study of the Spanish group for research on sarcomas. J Clin Oncol. 2009 Apr 10;27(11):1893-8.

20. Ryan CW, Merimsky O, Agulnik M, Blay J-Y, Schuetze SM, Van Tine BA. PICASSO III: a phase III, placebo-controlled study of doxorubicin with or without palifosfamide in patients with metastatic soft tissue sarcoma. J Clin Oncol. 2017;34(32):3898-905.

21. Tap WD, Papai Z, Van Tine BA, Attia S, Ganjoo KN, Jones RL, et al. Doxorubicin plus evofosfamide versus doxorubicin alone in locally advanced, unresectable or metastatic soft-tissue sarcoma (TH CR-406/SARC021): an international, multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2017 Aug;18(8):1089-103.

22. Hensley ML, Maki R, Venkatraman E, Geller G, Lovegren M, Aghajanian C, et al. Gemcitabine and docetaxel in patients with unresectable leiomyosarcoma: results of a phase II trial. J Clin Oncol. 2002 Jun 15;20(12):2824-31.

23. Seddon BM, Scurr MR, Jones RL, Wood C, Propert-Lewis RA, A'Hern RA, et al. Phase II study of gencitabine and docetaxel as first-line chemotherapy in advanced/metastatic leiomyosarcoma [abstract]. J Clin Oncol [Internet]. 2009 [cited 2017 Nov 7];27(15s):10528. Available from: http://ascopubs.org/doi/abs/10.1200/jco.2009.27.15s.10528 (Presented at 45th American Society of Clinical Oncology Annual Meeting; 2009 May 29-Jun 2; Orlando, FL).

24. Maki RG, Wathen JK, Patel SR, Priebat DA, Okuno SH, Samuels B, et al. Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue

sarcomas: results of sarcoma alliance for research through collaboration study 002 [corrected]. J Clin Oncol. 2007 Jul 1;25(19):2755-63.

25. Seddon B, Strauss SJ, Whelan J, Leahy M, Woll PJ, Cowie F, et al. Gemcitabine and docetaxel versus doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft-tissue sarcomas (GeDDiS): a randomised controlled phase 3 trial. Lancet Oncol [Internet]. 2017 Oct [cited 2017 Nov 8];18(10):1397-410. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5622179

26. Schoffski P, Chawla S, Maki RG, Italiano A, Gelderblom H, Choy E, et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. Lancet. 2016 Apr 16;387(10028):1629-37.

27. Demetri GD, von Mehren M, Jones RL, Hensley ML, Schuetze SM, Staddon A, et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of a phase III randomized multicenter clinical trial. J Clin Oncol [Internet]. 2016 Mar 10 [cited 2017 Nov 8];34(8):786-93. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5070559

28. Bui-Nguyen B, Butrynski JE, Penel N, Blay JY, Isambert N, Milhem M, et al. A phase IIb multicentre study comparing the efficacy of trabectedin to doxorubicin in patients with advanced or metastatic untreated soft tissue sarcoma: the TRUSTS trial. Eur J Cancer. 2015 Jul;51(10):1312-20.

29. Verweij J, Baker LH. Future treatment of soft tissue sarcomas will be driven by histological subtype and molecular aberrations. Eur J Cancer. 2010 Mar;46(5):863-8.

30. van der Graaf WT, Blay JY, Chawla SP, Kim DW, Bui-Nguyen B, Casali PG, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2012 May 19;379(9829):1879-86.

31. Demetri GD, Chawla SP, Ray-Coquard I, Le Cesne A, Staddon AP, Milhem MM, et al. Results of an international randomized phase III trial of the mammalian target of rapamycin inhibitor ridaforolimus versus placebo to control metastatic sarcomas in patients after benefit from prior chemotherapy. J Clin Oncol. 2013 Jul 1;31(19):2485-92.

32. A study of olaratumab in soft tissue sarcoma. 2017 Apr 14 [cited 2017 Nov 16]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/NCT01185964 NLM Identifier: NCT01185964.

33. Deshpande HA, Cecchini M, Ni CS, Jones R. Olaratumab for the treatment of soft tissue sarcoma. Drugs Today (Barc). 2017;53(4):247-55.

34. Tikhonova IA, Jones-Hughes T, Dunham J, Warren FC, Robinson S, Stephens P, et al. Olaratumab in combination with doxorubicin for the treatment of advanced soft tissue sarcoma: an evidence review group perspective of a National Institute for Health and Care Excellence single technology appraisal. PharmacoEconomics. 2017 Sep 15. E-pub ahead of print.

35. Fala L. Lartruvo (olaratumab) a novel first-line treatment approved for patients with advanced soft-tissue sarcoma. Am Health Drug Benefits. 2017;10(Special Issue):67-9.

36. van der Graaf WT. Olaratumab in soft-tissue sarcomas. Lancet. 2016;388(10043):442-4.

37. Redondo A, Valverde Morales C, Hindi N, Lopez-Martin JA, Honigschmidt G, Zeng Y, et al. ANNOUNCE 2: an open-label phase 1b, and a randomized, double-blind phase 2 study of olaratumab with gemcitabine plus docetaxel in the treatment of patients with advanced soft tissue sarcoma (STS)

[abstract]. Ann Oncol [Internet]. 2016 [cited 2017 Nov 15];27(Suppl 6). Available from: https://academic.oup.com/annonc/article/27/suppl_6/1420TiP/2800314 (Presented at 41st European Society for Medical Oncology Congress; 2016 Oct 7-11; Copenhagen, Denmark).

38. Jones R, Mo G, Baldwin JR, Nichols RD, Ilaria RL, Conti I, et al. Exposure-response of olaratumab for survival outcomes and safety when combined with doxorubicin in soft tissue sarcoma (STS) patients [abstract]. Ann Oncol [Internet]. 2016 [cited 2017 Nov 15];27(Suppl 6). Available from: https://academic.oup.com/annonc/article/27/suppl_6/1402PD/2800295 (Presented at 41st European Society for Medical Oncology Congress; 2016 Oct 7-11; Copenhagen, Denmark).

39. Tap WD, Van Tine BA, Elias AD, Livingston MB, Agulnik M, Cooney MM, et al. A phase Ib/II study evaluating the efficacy of doxorubicin (D) with or without a human anti-PDGFRalpha monoclonal antibody olaratumab (IMC-3G3) in the treatment of advanced soft tissue sarcoma (STS) [abstract]. J Clin Oncol. 2012;30(15 Suppl 1). (Presented at 48th American Society of Clinical Oncology Annual Meeting; 2012 Jun 1-5; Chicago, IL).

40. Tap W, Jones RL, Chmielowski B, Elias AD, Adkins D, Van Tine BA, et al. A randomized phase 1b/2 study evaluating the safety and efficacy of doxorubicin (dox) with or without olaratumab (imc3G3), a human anti-platelet-derived growth factor alpha (pdgfrα) monoclonal antibody, in advanced soft tissue sarcoma (STS) [abstract]. Oncol Res Treat. 2016;39:174. (Presented at German Cancer Congress; 2016 Feb 24-27; Berlin, DE).

41. Tap WD, Jones RL, Chmielowski B, Elias AD, Adkins D, Van Tine BA, et al. A randomized phase Ib/II study evaluating the safety and efficacy of olaratumab (IMC-3G3), a human anti-platelet-derived growth factor alpha (PDGFRalpha) monoclonal antibody, with or without doxorubicin (Dox), in advanced soft tissue sarcoma (STS) [abstract]. J Clin Oncol [Internet]. 2015 [cited 2017 Nov 15];33(15 Suppl 1). Available from: http://ascopubs.org/doi/abs/10.1200/jco.2015.33.15_suppl.10501 (Presented at 51st American Society of Medical Oncology Annual Meeting; 2015 May 29-Jun 2; Chicago, IL).

42. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Multi-discipline review/summary, clinical, non-clinical. In: Lartruvo (olaratumab). Company: Eli Lilly. Application no.: BLA 761038. Approval date: 19/10/2016 [Internet]. Rockville (MD): FDA; 2016 Feb 1 [cited 2018 Jan 15]. (FDA drug approval package). Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/761038Orig1s000MultiDisciplineR.pdf

43. Van Tine BA, Peterson P, Shahir A, Ilaria R Jr, Jones RL. An analysis of efficacy and safety of olaratumab + doxorubicin or doxorubicin alone in patients with uterine leiomyosarcoma: a retrospective assessment of the phase 1b/2 study JGDG [poster]. In: pan-Canadian Oncology Drug Review manufacturer submission: Lartruvo (olaratumab) intravenous injection, 10 mg/mL vial. Toronto: Eli Lilly Canada; 2017 Oct 25. 2017; Mar 12-15.

44. Bertwistle D, D'Yachkova Y, Vickers A, Hawe E, Fernandez M, Drove N, et al. Comparative efficacy and saftey of interventions in the treatment of advanced soft tissue sarcoma: a systematic review and network meta analysis [poster]. In: pan-Canadian Oncology Drug Review manufacturer submission: Lartruvo (olaratumab) intravenous injection, 10 mg/mL vial. Toronto: Eli Lilly Canada; 2017 Oct 25. 2016.

45. Woods BS, Hawkins N, Scott DA. Network meta-analysis on the log-hazard scale, combining count and hazard ratio statistics accounting for multi-arm trials: a tutorial. BMC Med Res Methodol [Internet]. 2010 Jun 10 [cited 2018 Jan 16];10:54. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2906500

46. Jansen JP. Network meta-analysis of survival data with fractional polynomials. BMC Med Res Methodol [Internet]. 2011 May 6 [cited 2018 Jan 16];11:61. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3112194

47. Santoro A, Tursz T, Mouridsen H, Verweij J, Steward W, Somers R, et al. Doxorubicin versus CYVADIC versus doxorubicin plus ifosfamide in first-line treatment of advanced soft tissue sarcomas: a randomized study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. J Clin Oncol. 1995 Jul;13(7):1537-45.

48. Seddon BM, Whelan J, Strauss SJ, Leahy MG, Woll PJ, Cowie F, et al. GeDDiS: a prospective randomized controlled phase III trial of gemcitabine and docetaxel compared with doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft tissue sarcomas (EudraCT 2009-014907-29) [abstract]. J Clin Oncol [Internet]. 2015 [cited 2018 Jan 16];33(Suppl 15):10500. Available from: http://ascopubs.org/doi/abs/10.1200/jco.2015.33.15_suppl.10500 (Presented at 51st American Society of Medical Oncology Annual Meeting; 2015 May 29-Jun 2; Chicago, IL).

49. Le Cesne A, Judson I, Crowther D, Rodenhuis S, Keizer HJ, Van Hoesel Q, et al. Randomized phase III study comparing conventional-dose doxorubicin plus ifosfamide versus high-dose doxorubicin plus ifosfamide plus recombinant human granulocyte-macrophage colony-stimulating factor in advanced soft tissue sarcomas: a trial of the European Organization for Research and Treatment of Cancer/Soft Tissue and Bone Sarcoma Group. J Clin Oncol. 2000 Jul;18(14):2676-84.