pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review Final Clinical Guidance Report

Trabectedin (Yondelis) for Metastatic Liposarcoma or Leiomyosarcoma

August 5, 2016

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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.

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1 GUIDANCE IN BRIEF

1.1 Background

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

Trabectedin is a natural marine tetrahydroisoquinoline compound with antitumour properties that is now produced by chemical synthesis and is in the class of DNA-binding agents. Trabectedin has a Health Canada indication that is similar to the funding request, for the treatment of patients with metastatic liposarcoma or leiomyosarcoma after failure of prior anthracycline and ifosfamide chemotherapy. For the treatment of liposarcoma or leiomyosarcoma, Health Canada's recommended starting dose is 1.5 mg/m^2 body surface area, administered as an intravenous infusion over 24 hours with a three week interval between cycles. Continuous treatment is recommended whilst clinical benefit (measured with progression-free survival and objective response rate) is noted; in addition, certain criteria are required prior to each treatment cycle (see section 2.1.1).

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one open-label randomised controlled trial, ET743-SAR-3007, comparing trabectedin (n=384) to dacarbazine (n=193) in patients with unresectable locally advanced or metastatic L-sarcomas. Patients were aged 15 years or older, had an ECOG performance status of 0 or 1, and had received previous anthracycline and ifosfamide or an anthracycline and at least 1 or more additional cytotoxic chemotherapy.

Patient characteristics were reported to be balanced between groups in terms of demographics, disease severity, and prior treatments received.

Efficacy

The primary outcome was overall survival (OS) in the ET743-SAR-3007 study, select secondary endpoints included progression-free survival (PFS), symptom severity/interference, and tumour response rates.

At the time of the PFS analysis (interim analysis of OS), the median number of cycles of treatment received by patients in the trabectedin group was 4.0 cycles, and the median number of cycles of treatment received by patients in the dacarbazine group was 2.0 cycles. At the data cut-off date of January 5, 2015, the median OS was 13.7 versus 13.1 months in the trabectedin and dacarbazine groups, respectively (HR=0.93, 95%CI: 0.75-1.15, p=0.49). At the data cut-off date of September 16, 2013, the median PFS was 4.2 versus 1.5 months in the trabectedin and dacarbazine groups, respectively (HR=0.55, 95%CI: 0.44-0.70, p <0.0001). For symptom outcomes, there were no meaningful changes from baseline to cycle 8 observed in either treatment group assessed using the M.D. Anderson Symptom Inventory. Tumor response rates were higher in the trabectedin versus the dacarbazine group, however, a statistically significant between-group difference was not detected.

Harms

The most common adverse events (AEs) reported in the trabectedin group included nausea, fatigue, vomiting, diarrhea, constipation, decreased appetite, dyspnea, headache, fever and cough. Almost all patients in both groups experienced an AE with 99.7% versus 98.8% of patients in the trabectedin and dacarbazine groups, respectively. More patients in the trabectedin group (9.9%) compared to the dacarbazine group (6.4%) stopped treatment due to AEs. Overall, 220 (58%) and 102 (59%) patients in the trabectedin and dacarbazine group died.

1.2.2 Additional Evidence

pCODR received input on trabectedin for metastatic Liposarcoma or leiomyosarcoma from one patient advocacy group Sarcoma Cancer Foundation of Canada (SCFC). Provincial Advisory Group (PAG) input was obtained from nine of the nine provinces participating in pCODR.

1.2.3 Interpretation and Guidance

Sarcomas comprise of about 1% of all cancers diagnosed in Canada, approximately 1,000 cases per year in Canada. Leiomyosarcoma and liposarcoma account for 40% of all sarcomas, they are the second and third most common sarcomas diagnosed after gastrointestinal stromal tumour. Current therapeutic options after failure of doxorubicin ± ifosfamide are limited, these include dacarbazine, pazopanib in non-liposarcomas, and gemcitabine ± docetaxel in leiomyosarcoma. All of these treatments have limited efficacy and some toxicity.

Effectiveness

In SAR-3007 trial, trabectedin was not associated with an improvement in OS, the primary endpoint of the trial. However, 71% and 69% of patients treated with trabectedin and dacarbazine, respectively, received at least one subsequent line of systemic therapy this may have led to the absence of OS benefit. PFS was clinically and statistically significant with trabectedin when compared with dacarbazine. Other secondary endpoints of overall response rate, clinical benefit rate, and treatment termination due to lack of efficacy, favoured trabectedin. Quality of life indicated no difference between the two groups despite a higher incidence of toxicities with trabectedin. The trial enrolled patients who were ECOG 0-1 or asymptomatic/minimally symptomatic, therefore it would be very unlikely to observe improvement in disease-related symptoms with therapy.

Safety

There was no difference in the incidence of adverse events in both groups in the SAR-3007 study; however, there were more all grades and grade 3-5 toxicity associated with trabectedin compared with dacarbazine. These included: nausea, vomiting, fatigue, diarrhea, constipation, anorexia, dyspnea, headaches, fever, cough, elevation of AST/ALT, elevation of creatine kinase (CK) and clinical rhabdomyolysis. Treatment-related death was observed in 2.1% of patients in the trabectedin group. Drug-related adverse events were higher in the trabectedin compared with dacarbazine group.

1.3 Conclusions

Overall, there is a net clinical benefit of trabectedin compared with dacarbazine in advanced or metastatic leiomyosarcoma and liposarcoma patients who have progressed on prior doxorubicin and/or ifosfamide. Trabectedin did not improve the median OS when

compared to dacarbazine; this may be complicated by at least 70% of patients receiving post-study therapy with active agents. However, a clinically and statistically important improvement in median PFS and clinical benefit rate in this patient population was seen. This was observed in all predefined and post-hoc subgroups. Trabectedin was associated with an increase in all grades and grade 3-5 non-haematological toxicity, particularly elevation of AST/ALT, CK and rhabdomyolysis. The latter required stringent monitoring during therapy. Thus, more patients discontinued trabectedin due to toxicity; however, such increase in toxicity did not translate to detriment in quality-of-life. Overall, based on the meaningful improvement in median PFS and maintenance of quality of life, despite an increase in toxicity, trabectedin represents an option for recurrent or metastatic liposarcoma and leiomyosarcoma patients who have progressed after prior doxorubicin ± ifosfamide in either the curative or recurrent/metastatic settings. The CGP also considered:

- The appropriateness of dacarbazine as the comparator group is not universally accepted. The NCCN guidelines in 2009 considered dacarbazine as a recommended treatment option in this patient population but this is not widely accepted in the Canadian context.
- OS is considered as the most unbiased endpoint in any randomized phase III clinical trials as compared to PFS. This is increasingly being challenged as the most appropriate endpoint both by academia and the regulatory agencies. Cross-over to other potentially effective agents can potentially minimize the OS benefit. Any difference in OS is impossible when subsequent lines of therapy are then offered to patients on study. There is no control once patients progress as to how their care differs between the two groups.[12] Furthermore, a meta-analysis by Sharma E et al.[13] did not show any OS benefit of second-line or later palliative chemotherapy in this setting; however, a clinically and statistically meaningful improvement in median PFS was seen. This was further supported by the regulatory approval of pazopanib in the PALETTE study by Van der Graaf et al. throughout the world based on an improvement of median PFS without any improvement in median OS. All in all, an improvement in PFS is a clinically acceptable endpoint for metastatic sarcomas.

2 CLINICAL GUIDANCE

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding trabectedin (Yondelis) for metastatic liposarcoma or leiomyosarcoma after failure of prior anthracycline-based chemotherapy. 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 Report is based on: a systematic review of the literature regarding trabectedin conducted by the Sarcoma Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; and supplemental issues relevant to the implementation of a funding decision.

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

2.1 Context for the Clinical Guidance

2.1.1 Introduction

For patients who fail first line therapy for the treatment of liposarcoma or leiomyosarcoma, the treatment options are limited.[1,2] Trabectedin, also called ET-743, is a marine-derived cytotoxic alkaloid which causes DNA damage and subsequently results in perturbation of the cell cycle and induction of apoptosis.[3-5] In 2011, Health Canada approved the use of trabectedin for the treatment of patients with metastatic liposarcoma and leiomyosarcoma after failure of prior anthracycline-based chemotherapy.[5,6] The recommended dose of trabectedin is 1.5 mg/m^2 administered via a 24-hour central venous infusion, every three weeks. In the product monograph of trabectedin, duration of treatment was not specified. Continuous treatment with trabectedin is recommended whilst clinical benefit (measured with progression-free survival and objective response rate) is noted. In addition, the following criteria are required prior to each treatment cycle:

- Absolute neutrophil count (ANC) ≥ 1,500/mm^3
- Platelet count ≥ 100,000/mm^3
- Hemoglobin ≥ 9 g/dL
- Bilirubin ≤ upper limit of normal (ULN)
- Alkaline phosphatase of non-osseous origin ≤ 2.5 x ULN (consider hepatic isoenzymes 5 nucleotidase or GGT, to distinguish if the elevation could be osseous in origin)
- Albumin ≥ 25 g/L
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x ULN
- Creatinine clearance ≥ 30 mL/min (monotherapy)
- Creatine phosphokinase (CPK) ≤ 2.5 x ULN

The same criteria as above must be met prior to initiation of next cycles. Otherwise treatment must be delayed for up to 3 weeks until the criteria are met.

If these toxicities (myelosuppression, hepatoxicity and renal toxicity) persist beyond 3 weeks, treatment discontinuation should be considered. The same dose should be given for all cycles provided that no Grade 3-4 toxicities are seen and the patient fulfills the re-treatment criteria.

2.1.2 Objectives and Scope of pCODR Review

To evaluate the effect of trabectedin (Yondelis) compared with standard therapies on patient outcomes in patients with metastatic liposarcoma or leiomyosarcoma (L-sarcomas) who have failed prior anthracycline-based chemotherapy.

2.1.3 Highlights of Evidence in the Systematic Review

The efficacy and safety of trabectedin at a starting dose of 1.5 mg/m^2 as a 24-hour intravenous infusion (N=384) was compared with dacarbazine at 1 g/m^2 (N=193) in an international, multicentre, open-label RCT (ET743-SAR-3007).[7] The study recruited patients aged ≥ 15 years with unresectable locally advanced or metastatic L-sarcomas, with an ECOG performance status of 0 or 1, and who had received previous anthracycline and ifosfamide or an anthracycline and at least 1 or more additional cytotoxic chemotherapy. The median age of the study participants was 56 - 57 years (range 17 to 81 years), and patients were predominantly white (72% - 78%). Patients who had central nervous system metastasis or had an ECOG performance status score of 2 were excluded from this study; therefore the generalizability of the study results to these subgroups is uncertain.

As of the clinical cut-off date of January 5, 2015 (within a time frame of three years and eight months), 322 patients had died, 220 (58%) from the trabectedin group and 102 (59%) from the dacarbazine group. The difference in the primary endpoint, overall survival (OS), was not statistically significant between the two treatment arms: 13.7 months in the trabectedin group versus 13.1 months in the dacarbazine group (hazard ratio [HR] = 0.93, 95% confidence intervals [CI]: 0.75 – 1.15, p = 0.49). Progression-free survival (PFS), one of the secondary endpoints of the study, was assessed with a clinical cut-off date of September 16, 2013 (within a time frame of two years and four months). The median PFS was 4.2 months in the trabectedin arm versus 1.5 months in the dacarbazine arm (HR = 0.55, 95% CI: 0.44 - 0.70, p < 0.0001). Results of OS and PFS in subgroups of liposarcoma versus leiomyosarcoma were consistent with those reported in the overall population. Symptom severity and symptom interference were assessed using the M.D. Anderson Symptom Inventory (MDASI) up to cycle 8. There were no meaningful changes from baseline to cycle 8 observed in either treatment group. The tumour response rates (partial response) were higher in patients treated with trabectedin than dacarbazine, however, a statistically significant between-group difference was not detected.

The most common all grade adverse events (AEs) (≥ 20%) reported in the trabectedin group included nausea, fatigue, vomiting, diarrhea, constipation, decreased appetite, dyspnea, headache, fever and cough. The most common laboratory abnormalities (≥ 20%) were increases in AST or ALT, neutropenia, thrombocytopenia and anemia. They were all more frequent in patients receiving trabectedin than in patients receiving dacarbazine. Most of these AEs were graded

1 or 2. Treatment discontinuation was more common in the trabectedin group. The main reasons for early discontinuation were disease progression and AEs. Compared to the dacarbazine group (6% as of September 16, 2013; 22% as of January 5, 2015), more patients in the trabectedin group (10% as of September 16, 2013; 26% as of January 5, 2015) stopped treatment due to AEs. As of September 16, 2013, more patients in the dacarbazine group (61%) stopped treatment due to lack of efficacy, compared to the trabectedin group (54%).

Table 1. Key Efficacy and Safety Outcomes from ET743-SAR-3007

Efficacy		
	Trabectedin (N=384)	Dacarbazine (N=193)
Overall Survival (data cut-off: January 5, 2015)		
Median (months)	13.7 (12.2 - 16.0)	13.1 (9.1 - 16.2)
Hazard Ratio (95% CI)	0.93 (0.75 - 1.15)	
P-value	0.49	
Progression-Free Survival (data cut-off: September 16, 2013)		
Median (months)	4.2	1.5
Hazard Ratio (95% CI)	0.55 (0.44 - 0.70)	
P-value	< 0.0001	
Objective Response Rate (data cut-off: September 16, 2013)		
n (%)	34 (9.9)	12 (6.9)
Odds Ratio	1.47	
P-value	0.33	
Safety (data cut-off: January 5, 2015)		
	Trabectedin (N=378)	Dacarbazine (N=172)
All deaths, n (%)	220 (58)	102 (59)
Any AEs, n (%)	377 (100)	170 (99)
Any SAEs, n (%)	155 (41)	52 (30)
Withdrawal due to AEs, n (%)	98 (26)	37 (22)
AE=adverse event; CI=confidence interval		

2.1.4 Comparison with Other Literature

Relevant literature identified jointly by the pCODR Clinical Guidance Panel and Methods Team and providing supporting information to the systematic review is summarized below. This information has not been systematically reviewed.

There are no drug class reviews, health technology assessments or other randomized controlled trials available at present to provide more comprehensive insights on the effectiveness and safety of trabectedin on metastatic L-sarcomas.

A systematic review (2013) was conducted by Gupta and colleagues to examine the effectiveness and safety profile of various systemic chemotherapy in women with inoperable, locally advanced, recurrent, or metastatic uterine leiomyosarcoma.[8] This was an update of a 2005 systematic review. Multiple databases were search to identify relevant studies from January 2004 to June 2011. The search was limited to English

language publications only. Studies investigating the effect of gemcitabine, doxorubicin, trabectedin alone, or a combination of gemcitabine plus docetaxel and reporting on tumour response rate, overall survival, toxicity, PFS or quality of life in uterine leiomyosarcoma were eligible. Other types of sarcoma were excluded from this review. Six studies (RCT and single-arm studies) were included. Patients who received prior chemotherapy or no previous chemotherapy were included. Findings of the Gupta review suggested that gemcitabine plus docetaxel had longer median OS (14.7 – 17.9 months) and higher ORR (27% - 53%) than doxorubicin alone (OS 12.1 months; ORR 25%). This combination therapy was also related to more toxicity than doxorubicin alone. Gemcitabine monotherapy had comparable effect on tumour response rate as doxorubicin (21% vs. 25%). Gemcitabine plus docetaxel was not superior to gemcitabine alone on tumour response rate (23% vs. 18%) or PFS (6 months vs. 4.9 months). The authors concluded that doxorubicin, gemcitabine, and gemcitabine plus docetaxel were treatment options in women with inoperable, locally advanced, recurrent or metastatic uterine leiomyosarcoma as first- or second-line therapy. The Gupta review did not identify any trabectedin studies which met their inclusion criteria.

Demetri and colleagues conducted a multicenter, open-label phase II RCT to evaluate the effect of trabectedin administered by two different schedules in adult patients with locally advanced or metastatic liposarcoma or leiomyosarcoma following treatment with anthracycline plus ifosfamide.[9] Patients received trabectedin 1.5mg/m^2 every three weeks (q3) or trabectedin 0.58 mg/m^2 weekly for 3 of 4 weeks. The eligibility criteria of this phase II study were similar to the Demetri 2015 study. Time to progression was the primary efficacy endpoint. In total, 270 patients were enrolled, 136 in the q3 weeks regimen and 134 in the weekly regimen. The study found that the median time to progression was 3.7 months with the q3 weeks regimen versus 2.3 months with the weekly regimen, p=0.03. Results on PFS (3.3 months vs. 2.3 months, p=0.04) and OS (13.9 months vs. 11.8 months, p=0.19) favored the q3 week regimen as well. The q3 week regimen was associated with more neutropenia, elevated AST/ALT, emesis and fatigue. The authors concluded that the q3 week regimen with trabectedin showed superior disease control in liposarcoma and leiomyosarcoma.

The submitter commented on the pCODR Expert Committee's (pERC's) Initial Recommendation that a systematic review and meta-analysis of RCTs investigating systemic therapy in STS found that PFS and RR were appropriate surrogates for OS. The study was performed to investigate the surrogacy of intermediate endpoints including PFS, RR, 3 month PFS, and 6 month PFS with OS as well as time trends in the design and interpretation of trials.[12] Three month PFS and 6 month PFS were extracted based on reported Kaplan-Meier estimates, and when not reported, were estimated from Kaplan-Meier PFS curves as binary proportions. Data on 12-week and 24-week PFS were considered interchangeable with 3 month PFS and 6 month PFS, respectively. Fifty-two RCTS published between 1974 and 2014, comprising 9,762 patients met the inclusion criteria for the review. The standardized ß coefficient for the weighted linear regression of OS with intermediate endpoints indicated a highly significant correlation between PFS and OS (R=0.61) and substantially significant correlation between RR and OS (R=0.51). There were no significant correlations between 3 month PFS and 6 month PFS with OS. There were only two studies with a crossover design that reported HR and CIs for both OS and PFS and a sensitivity analysis to assess the influence of a crossover effect was not possible. OS was the primary endpoint in two studies, both of which were published between 2005 and 2014. Overall, the review suggested that for advanced STS, PFS and RR appeared to be appropriate surrogates for OS. However, there was a poor correlation between OS and both 3 month PFS and 6 month PFS. Relevant limitations identified by the authors included incorporating of data from

studies with variable sample sizes and assuming endpoints for studies lacking a clearly defined primary endpoint.

2.1.5 Summary of Supplemental Questions

No supplemental questions were addressed in this review.

2.1.6 Other Considerations

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

Patient Advocacy Group Input

One patient advocacy group, Sarcoma Cancer Foundation of Canada (SCFC), provided input on the trabectedin (Yondelis) submission as treatment for patients with metastatic liposarcoma or leiomyosarcoma,

From a patient perspective, as current treatments typically result in various side effects, patients stated that they would be willing to tolerate side effects, especially for results in slowing or stopping disease progression. Reported side-effects include fatigue, nausea (with some vomiting), and iron deficiency. These side effects were reported in addition to patients' other sarcoma symptoms.

According to the SCFC, the key symptoms associated with liposarcoma or leiomyosarcoma include severe pain, fatigue, difficulty breathing, difficulty sleeping, cough, constipation and cessation of ability to complete daily tasks. SCFC reported that physicians may try different treatments for patients based on what chemotherapies have been previously tried, and availability of clinical trials, therefore symptoms suffered by individuals may differ. SCFC noted that treatments must be accessed in hospital or in a cancer clinic and therefore some patients, depending on where they live, have to travel to access treatment, often having to stay overnight or for longer periods of time away from their homes, increasing the financial hardship of this disease.

PAG Input

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

Clinical factors:

- Provides another treatment option for a very small number of patients

Economic factors:

- Drug wastage
- Hospital admission and resources required to administer the 24 hour infusion via central line

2.2 Interpretation and Guidance

Effectiveness

Trabectedin did not improve the primary endpoint of median overall survival (OS) as compared to dacarbazine (13.7 month versus 13.1 month, HR=0.93, p=0.49). Seventy-one percent of trabectedin-treated patients and 69% of dacarbazine-treated patients received

at least one subsequent line of systemic therapy; therefore, it is difficult to ascertain if this led to the absence of OS benefit in this trial. However, trabectedin did clinically and statistically improve the median progression-free survival (PFS) compared with dacarbazine (4.2 versus 1.5 months, HR=0.55, p<0.0001) in all predefined and post-hoc clinical and pathological subgroups. PFS is considered a measure of the biological effect of therapy on a cancer and thus an improvement of PFS with at least symptom stabilization can be considered as clinically important.

Other secondary endpoints included overall response rate (ORR) (9.9% versus 6.9%), clinical benefit rate (34% versus 19%) and treatment termination due to lack of efficacy (53.9% versus 61.3%), all favouring trabectedin. Quality of life was measured using the MD Anderson Symptom Index from baseline up to cycle 8; it showed no difference between the two groups despite a higher incidence of various toxicities in the trabectedin-treated group. This finding is particularly important as enrolled patients were ECOG 0-1 or asymptomatic/minimally asymptomatic, therefore, it would be very unlikely to observe improvement in disease-related symptoms with therapy. Patients with liver, bone and retroperitoneal recurrences are often symptomatic, especially if they have progressed while being on therapy. Absence of progression will be able to delay the presentation of symptoms or reduction of symptoms. The absence of symptom deterioration mirrored the absence of progression of sarcoma and can be considered as clinically meaningful to patients and physicians. Overall, the median OS, PFS and ORR were consistent with a prior randomized phase II study comparing trabectedin administered as a 24-hour infusion and weekly 1-hour infusion 3 out 4 weeks in patients with previously treated advanced or metastatic leiomyosarcoma and liposarcoma.

Safety

Overall, there was no difference in the incidence of adverse events (AEs) between the two groups (99.7% for trabectedin and 98.8% for dacarbazine). However, more trabectedin-treated patients experienced all grades and grade 3-5 toxicity than those treated with dacarbazine; particularly, nausea, vomiting, fatigue, diarrhea, constipation, anorexia, dyspnea, headaches, fever, cough, elevation of AST/ALT, elevation of creatine kinase (CK) and clinical rhabdomyolysis. Monitoring of haematological toxicity, AST, ALT, bilirubin, ALKP, CK and creatinine weekly is important for early detection of rhabdomyolysis. The incidence of myelosuppression was similar between the two groups. Treatment-related death was only observed in the trabectedin group at 2.1% and the incidence of treatment termination due to drug-related AEs was 9.9% in the trabectedin-group and 6.4% in the dacarbazine-group. Overall, trabectedin is considered safe and tolerable in this setting.

Burden of illness

Sarcoma comprise of about 1% of all cancers diagnosed in Canada, estimated to be just overall 1,000 cases per annum in Canada. Leiomyosarcoma and liposarcoma were the second and third most common sarcomas diagnosed after gastrointestinal stromal tumour and account for about 40% of all sarcoma. About 50% of patients with localized sarcoma will develop recurrent or metastatic disease that is then deemed incurable. Limited by age, comorbidities and ECOG performance >2, less than 480 patients per annum will be candidates for palliative chemotherapy. Overall, burden of disease is small in comparison to other cancers.

Need

Current therapeutic options after failure of doxorubicin with or without ifosfamide are limited. More effective therapy measured preferably by median OS, followed by median PFS with tolerable toxicity and/or at least neutral impact on quality of life or sarcoma-

associated symptoms are needed. Unfortunately, there are limited options including dacarbazine, pazopanib in non-liposarcomas, and gemcitabine ± docetaxel in leiomyosarcoma. All of these treatments have limited efficacy and some toxicity.

Table 2. Assessment of Factors that May Affect Generalizability (ET743-SAR-3007 study)

Domain	Factor	Evidence	Generalizability question	CGP Assessment of Generalizability
Population	Stage of disease or other subtypes	Unresectable, locally advanced or metastatic liposarcoma (dedifferentiated, myxoid round cell, or pleomorphic) or leiomyosarcoma were eligible	Does stage limit the interpretation of the trial results with respect to the target population?	There is no data to support the use of trabectedin in patients with localized resectable disease or with other subgroups beyond liposarcoma or leiomyosarcoma.
	Performance Status	ECOG PS 0 and 1 were eligible. Planned subgroup analysis by PS (0 vs. 1) was conducted. Progression-free Survival: **ECOG PS 0:** T vs. D: 4.7 months vs. 1.5 months; Hazard ratio 0.51 (95%CI 0.36 - 0.71) **ECOG PS 1:** T vs. D: 2.9 months vs. 1.5 months; Hazard ratio 0.60 (95%CI 0.43 - 0.82)	Does performance status limit the interpretation of the trial results (efficacy or toxicity) with respect to the target population?	The trial included patients with an ECOG PS 0-1. However, the CGP felt based on expert clinical opinion, patients with ECOG = 2 would benefit from trabectedin and are treated similar to ECOG 0-1 in clinical practice.
	Age	Patients ≥ 15 years old were eligible. In the study, > 75% of the participants were < 65 years. A priori subgroup analysis by age on PFS was conducted. Progression-free Survival: **< 65 years:** T vs. D: 4.1 months vs. 1.8 months; Hazard ratio 0.60 (95%CI 0.46 - 0.78) **≥ 65 years:** T vs. D: 4.9 months vs. 1.5 months; Hazard ratio 0.40 (95%CI 0.24 - 0.67)	Does the age restriction in the trial limit the interpretation of the trial results with respect to the target population (patients younger than 15 years old)?	The results are not generalizable to patients <15 years. The CGP recognized that tumours are very rare in these young patients, however, there are dosing guidelines for pediatric patients with this drug.

	Organ dysfunction	Adequate organ functions were required. All side effects from prior therapy had to be resolved to grade 1 or less according to NCI-CTCAE version 4.0. Known significant chronic liver disease, MI within 6 months before enrollment, heart failure, uncontrolled angina or other uncontrolled intercurrent illness were ineligible.[10]	Does the exclusion of patients with organ dysfunction limit the interpretation of the trial results with respect to the target population?	Trabectedin is liver metabolized by CYP 3A4 and glucuronidation. Potential life threatening toxicity such as rhabdomyolysis tends to occur in patients with total bilirubin < q1.5 ULN, AST/ALT and ALKP to be < 2.5 x ULN, although PK of trabectedin did not correlate with AST/ALT. Liver dysfunction study has been performed but the results are still pending. After which, recommended dose for patients with moderate to severe liver dysfunction can be made. No patients were enrolled in any trabectedin studies with creatinine clearance < 30ml/min. Given < 1% of trabectedin is excreted unaltered in urine, it is reasonable to expect that renal adjustment is needed if creatinine clearance $\geq$ 30 ml/min. No recommendation can be made to that with creatinine clearance < 30 ml/min.
	Metastatic Sites	CNS metastasis was excluded.	Did the exclusion of patients with CNS metastatic disease limit the interpretation of the trial results with respect to the target population?	The trial excluded patients with CNS metastases. However, the CGP felt based on expert clinical opinion, patients with treated CNS metastases and found to be stable on CT/MRI of brain and off steroids would benefit from trabectedin. Of note, CNS metastases are not common in these two types of sarcoma.
	Ethnicity	Patients from the US, Brazil, Australia and New Zealand were recruited. No requirements on Ethnicity. In the study, ~95% of the patients were recruited from US. ~75% were White, ~12% were Black or African. American.[10]	If the trial was conducted outside of Canada, is there a known difference in effect based on ethnicity that might yield a different result in a Canadian setting?	We would apply the study to all ethnicities, as that's what the trial included. However, some ethnicities are under-represented.

	Biomarkers	Leiomyosarcoma: ~73% (uterine > 50%) Liposarcoma: ~27% (dedifferentiated > 50%) Planned subgroup analyses by histologic subtype on PFS were conducted. Progression-free Survival: **Leiomyosarcoma:** T vs. D: 4.3 months vs. 1.6 months; Hazard ratio 0.55 (95%CI 0.42 – 0.73) **Liposarcoma:** T vs. D: 3.0 months vs. 1.5 months; Hazard ratio 0.55 (95%CI 0.34 – 0.87	Is there a subgroup analysis based on leiomyosarcoma or liposarcoma or uterine leiomyosarcoma, (i.e., based on histologic subtype)?	The CGP were of the opinion that there was enough phase 2 data to suggest the inclusion of other histologies.
Intervention	Treatment Intent	Palliative treatment.	Are the results of the treatment generalizable to an alternative treatment intent? (i.e., if the trial is palliative in intent, could the therapy also be used in the adjuvant setting or vice versa?)	The current data will not be able to support the use of trabectedin as a single agent or in combination in the adjuvant or treatment-naïve recurrent or metastatic setting. A phase III study failed to show superiority of trabectedin or doxorubicin ± ifosfamide in treatment naïve recurrent or metastatic STS.[11] The first line trial comparing trabectedin ± doxorubicin in the first-line setting has been terminated.
	Line of therapy	Patients received prior chemotherapy, either anthracycline + ifosfamide, or an anthracycline-containing regimen and 1 additional cytotoxic chemotherapy regimen. In this study, ~90% of patients received ≥ 2 lines of prior chemotherapy.	Are the results of the trial generalizable to other lines of therapy?	The CGP were of the opinion that it is possibly generalizable to other lines of therapy. However, it is not known if trabectedin is better than doxorubicin and may be more toxic; a study in first-line therapy is needed. The percentage of patients who received 1 line of prior therapy (~10%) is similar to what is seen in Canadian practice.
	Administration of intervention	Interventions were administered in the same way as the clinical practice.	Are the results of the trial generalizable to a different dose or	The 24-hour continuous infusion administration schedule of trabectedin has been used in the compassionate access program.

			administration schedule?	
Comparator	Standard of Care	Dacarbazine may not be an appropriate comparator for trabectedin in Canada.	If the comparator is non-standard, are the results of the trial applicable in the Canadian setting?	Dacarbazine is a reasonable comparator (opinion by NCCN). Similar option is available in Canada.
	Dose and Schedule	Dacarbazine was administered consistently with the common practice in Canada.	If the dose and/or schedule is not standard, are the results of the trial relevant in the Canadian setting?	Dose/schedule of DTIC was reasonable.
Setting	Countries participating in the Trial	Patients from the US, Brazil, Australia and New Zealand were recruited. No requirements on Ethnicity. In the study, ~95% of the patients were recruited from US. Ra~75% were White, ~12% were Black or African American.[10]	If the trial was conducted in other countries, is there any known difference in the practice pattern between those countries and Canada? Differences in the patterns of care might impact the clinical outcomes or the resources used to achieve the outcomes.	We would apply the study to all ethnicities, as that's what the trial included. However, some ethnicities are under-represented.
	Location of the participating centres	Patients from the US, Brazil, Australia and New Zealand were recruited. No requirements on Ethnicity.	If the trial was conducted only in academic centres are the results applicable in the community setting?	The study was conducted in a mix of academic and community cancer centres. This is generalizable to the Canadian setting.

	Supportive medications, procedures, or care	The supportive medications (corticosteroids), procedures (central IV infusion) or care used with the intervention in the study were the same as those used in Canadian clinical practice.	Are the results of the trial generalizable to a setting where different supportive medications, procedures, or care are used?	Dexamethasone and ondansetron were commonly used for antiemetics for moderately to highly emetogenic chemotherapy. Due to rhabdomyolysis can occur in patients receiving trabectedin, especially during cycles 1-2 in patients who have concurrent maximum increase in AST/ALT and grade 3 or 4 neutropenia. Complete CBC, differential, AST/ALT/ALKP/bilirubin/creatinine/BUN and CK have to be done weekly during at least the first 2 cycles and thereafter prior to each cycle. These laboratory tests are commonly available in all Canadian laboratories.

Assessment of Factors that May Affect Generalizability

- The patient population enrolled in the trabectedin versus DTIC in patients with advanced or metastatic leiomyosarcoma and liposarcoma who have received prior chemotherapy is similar to that of the Canadian setting with the exception that this study included only patients with ECOG 0-1 rather than ECOG 0-2 in the Canadian setting.
- The current evidence only supports the use of trabectedin in patients with leiomyosarcoma and liposarcoma who have received prior chemotherapy in the advanced or metastatic setting. The currently available evidence failed to show superiority of trabectedin over doxorubicin ± ifosfamide in the treatment-naïve, advanced or metastatic setting.
- The 24-hour continuous infusion schedule has been adopted into Canadian practice in both the academic and community setting through the compassionate access program of trabectedin.
- The supportive care and laboratory testing, including AST, ALT, ALKP, bilirubin and CK, can be easily accessed or adopted in the Canadian setting.

2.3 Conclusions

Overall, there is a net clinical benefit of trabectedin compared with dacarbazine in advanced or metastatic leiomyosarcoma and liposarcoma patients who have progressed on prior doxorubicin and/or ifosfamide. Trabectedin did not improve the median OS when compared to dacarbazine; this may be complicated by approximately 70% of patients receiving post-study therapy with active agents. However, a clinically and statistically important improvement in median PFS and clinical benefit rate in this patient population was seen. This was observed in all predefined and post-hoc subgroups. Trabectedin was associated with an increase in all grades and grade 3-5 non-haematological toxicity, particularly elevation of AST/ALT, CK and rhabdomyolysis. The latter required stringent monitoring during therapy. Thus, more patients discontinued trabectedin due to toxicity; however, such increase in toxicity did not translate to detriment in quality-of-life. Overall, based on the meaningful improvement in median PFS and maintenance of quality of life, despite an increase in toxicity, trabectedin represents an option for recurrent or metastatic liposarcoma and leiomyosarcoma patients who have progressed after prior doxorubicin ± ifosfamide in either the curative or recurrent/metastatic settings. The CGP also considered:

- The appropriateness of dacarbazine as the comparator group is not universally accepted. The NCCN guidelines in 2009 considered dacarbazine as a recommended treatment option in this patient population but this is not widely accepted in the Canadian context.
- OS is considered as the most unbiased endpoint in any randomized phase III clinical trials as compared to PFS. This is increasingly being challenged as the most appropriate endpoint both by academia and the regulatory agencies. Cross-over to other potentially effective agents can potentially minimize the OS benefit. Any difference in OS is impossible when subsequent lines of therapy are then offered to patients on study. There is no control once patients progress as to how their care differs between the two groups.[12] Furthermore, a meta-analysis by Sharma E et al.[13] did not show any OS benefit of second-line or later palliative chemotherapy in this setting; however, a clinically and statistically meaningful improvement in median PFS was seen. This was further supported by the regulatory approval of pazopanib in the PALETTE study by Van der Graaf et al. throughout the world based on an improvement of median PFS without any improvement in median OS. All in all, an improvement in PFS is a clinically acceptable endpoint for metastatic sarcomas.

3 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.

3.1 Description of the Condition

Soft tissue sarcoma (STS) arise from any site in the body, but most commonly from the abdominal cavity and the extremities. The most common histological subtypes include undifferentiated pleomorphic sarcoma (previously named malignant fibrous histiocytoma), leiomyosarcoma (LMS), liposarcoma (LPS), fibrosarcoma, synovial sarcoma, malignant peripheral nerve sheath tumour, and angiosarcoma. There are multiple rare subtypes of STS, including but not limited to, alveolar soft part sarcoma, clear cell sarcoma, and dermatofibrosarcoma protuberans.

Pathological diagnosis of STS is traditionally based on morphology and immunohistochemistry. With the identification of chromosomal translocations (e.g., Ewing sarcoma, alveolar soft part sarcoma, synovial sarcoma) and oncogene aberrations (e.g., KIT or PDGFRA mutations in gastrointestinal sarcoma, MDM2 or CDK4 amplification/overexpression in well-differentiated and dedifferentiated liposarcoma),[14,15] molecular diagnostics are increasingly used in the diagnosis of STS.

According to the 2015 Canadian Cancer Statistics, 1,175 new cases of STS were diagnosed in 2010. The 5-year overall survival rates for all stages of STS was 65% in 2010, more specifically, for stage I, II and III STS were 90%, 81% and 56%, respectively. Overall, about 50% of the patients with localized STS will recur with the majority being incurable at relapse. The most common site of metastatic disease is the lung. In those with limited lung metastases, resection can potentially offer a 5-years overall survival rate of 20%.

3.2 Accepted Clinical Practice

In localized STS, primary therapy is surgery and radiation which can be given either pre-operatively or post-operatively. To date, adjuvant chemotherapy using doxorubicin or doxorubicin/ifosfamide combination has failed to demonstrate an improvement in overall survival as compared to observation in any patient subpopulation according to the most recent randomized phase III studies and the meta-analyses by the EORTC and Cancer Care Ontario.[16-18]

Doxorubicin is considered acceptable first-line chemotherapy for metastatic STS. In the updated meta-analysis by Cancer Care Ontario in 2010, combination therapy provided an improvement in overall response rate and median progression-free survival, without a statistically significant improvement in median overall survival over single agent doxorubicin.

Judson et al. reported the randomized phase III trial of doxorubicin (75 mg/m^2) compared with doxorubicin (same dose) plus ifosfamide at 2.5g/m^2/day for 4 days every 3 weeks with G-CSF support which failed to demonstrate an improvement in OS (12.8 months versus 14.3 months, HR=0.83, p=0.076). But both the median PFS and ORR were improved in the combination arm (4.6 versus 7.4 months, HR=0.74, p=0.003 and 14% versus 26%, p<0.0006), at the expense of statistically significant increased incidences of grade 3 or 4 hematological toxicity.[19]

Two randomized phase III trials comparing doxorubicin and doxorubicin in combination with novel ifosfamide prodrug (evofosfamide, TH-302) or metabolites (palifosfamide) failed to show any improvement in PFS or OS.

The randomized phase III trial of pazopanib to placebo (PALETTE study) in patients with at least 1 prior line of chemotherapy in the advanced disease setting demonstrated an improvement of median PFS from 1.6 to 4.6 months (HR=0.31; p<0.001), ORR 4% versus 0% (p=0.019) but no improvement in median OS (12.5 versus 10.7 months; HR=0.86, p=0.15). Quality of life was measured by Global QoL Score, EORTC QLQ-C30 and EQ-5D at baseline, weeks 4, 8 and 12. Overall, there was no difference in Global QoL Score, but patients on pazopanib experienced significantly more diarrhea and anorexia. Overall, 99% of patients treated with pazopanib experienced adverse events (AE) as compared to 89% in the placebo-arm. The most common treatment-related AE were dyspnea, elevation of AST/ALT, anemia, pneumothorax and venous thromboembolic disease. The pazopanib treated patients were more likely to experience fatigue, diarrhea, weight loss and hypertension. Based on the result of this study, pazopanib received regulatory approval from FDA, Health Canada and other jurisdictions. However, pazopanib was not recommended for funding by pCODR for patients with STS.

Gemcitabine/docetaxel was initially reported in a single-arm phase II study in previously treated LMS by Hensley et al. In this study, 34 patients with either uterine or non-uterine LMS, of whom 50% had prior chemotherapy, were treated with gemcitabine at 900 mg/m^2 on days 1 and 8 and docetaxel at 100 mg/m^2 on day 8 every 3 weeks with G-CSF support.[12] Overall response rate was 53% and the median PFS was 5.6 months. Subsequently, single-arm phase II studies in treatment-naïve and previously treated uterine LMS were reported with ORR of 35.8% and 27% respectively, and mPFS of 4.4 months and 5.6 months respectively.[20,21] Maki et al. reported a randomized phase II trial comparing docetaxel/gemcitabine with gemcitabine. Thirty-two percent of patients had LMS. The median PFS in the combination arm was 6.2 months as compared to 3 months in the gemcitabine-arm, and corresponding median OS were 17.9 and 11.5 months. Specifically, the response rates in the LMS patients (N=38) treated with the combination and gemcitabine alone were 27.5% and 11.1%, respectively. Despite G-CSF support, the combination arms treated were more likely to develop febrile neutropenia, neutropenia, anemia and thrombocytopenia.[22]

The French Sarcoma Group reported their randomized phase II study of gemcitabine versus gemcitabine/docetaxel with stratification into uterine and non-uterine LMS. Unfortunately, there were no difference in the response rate (uterine LMS: 19% versus 24% and non-uterine LMS: 14% versus 5%) and PFS (uterine LMS: 5.5 versus 4.7 month and non-uterine LMS: 6.3 versus 3.8 months).[23]

Gupta et al. performed a systemic review of gemcitabine/docetaxel in first and second-line uterine LMS as compared to doxorubicin. The combination treated patients may have a longer median OS and ORR. But the combination may be one option in these patients, amongst doxorubicin and single agent gemcitabine.[24]

In the Annual Meeting of the American Society of Clinical Oncology 2015, the randomized phase III trial comparing doxorubicin with gemcitabine/docetaxel with G-CSF support in patients with treatment naïve advanced uterine LMS (>30% of enrolled patients), synovial sarcoma, pleomorphic sarcoma and other sarcomas (GeDDis trial).[25] Two hundred and fifty-seven patients were randomized in a 1:1 fashion. The primary endpoint of PFS at 24 weeks were similar (46.1% for doxorubicin-arm and 46% in gemcitabine/docetaxel-arm; HR=1.28, p=0.07) and so was the OS at 24 weeks (86.7% versus 82.5%, respectively; HR=1.07, p=0.67). Patients treated in the combination arm had lower dose intensity, more delay and termination of treatment due to toxicity.

Other agents in the previously treated patients include ifosfamide, particularly high-dose ifosfamide, if not used in first-line, dacarbazine and dacarbazine/gemcitabine combination.

Preclinical evidence showed a dose response relationship of ifosfamide in STS. Various phase II studies of single ifosfamide administered at different doses and schedules yielded ORR in previously untreated and treated STS patients of 6-90% and 8-53.8%, respectively.[26-38]

More specifically for advanced well-differentiated and dedifferentiated LPS, ifosfamide administered as 14 g/m^2 as continuous infusion over 14 days every 4 weeks with 80% of patients had prior treatment including 19 had prior doxorubicin/ifosfamide and 2 with doxorubicin and 1 with trabectedin. Seven PR's were observed but all were in dedifferentiated liposarcoma and a median PFS was 7 months. Toxicity included grade 2 or 3 anemia (3/28), grade 3 or 4 neutropenia (4/28), grade 3 thrombocytopenia (1/28), grade 3 nausea (3/28) and grade 3 fatigue (6/28) as well as 1 patient with grade 3 confusion.[39]

A phase II study of dacarbazine administered as 800 mg/m^2 on day 1 or 400 mg/m^2 on days 1 and 2 and 300 mg/m^2 on days 1-3 every 3 weeks reported a combined response rate for all the schedules at 7.5% and median PFS of 2 months in second- or third-line STS. The 3-month progression-free rate was 26%,[32] which is deemed to be an active regimen according to the EORTC criteria.[40]

The Spanish Sarcoma Group reported a randomized phase II trial of gemcitabine versus gemcitabine/dacarbazine in previously treated STS. One hundred and thirteen patients were enrolled and the progression-free rate at 3 months was 56% in the combination arm as compared to 37% (p=0.001). The median PFS (4.2 versus 2 months; HR=0.58, p=0.005), median OS (16.8 versus 8.2 months; HR=0.56; p=0.014), ORR (49% versus 25%, p=0.009) were all superior in the combination. The combination was considered as well tolerated with the most common toxicity being neutropenia, asthenia, vomiting and stomatitis. No patients discontinued therapy in either arm due to toxicity.[41]

CDK 4 is found to be amplified in >90% of well-differentiated and dedifferentiated LPS.[14,15] Dickson et al. reported a phase II study of palbociclib (PD0332991), a CDK4/6 inhibitor, in this patient population. Out of the 51 patients enrolled, 48 patients had CDK4 amplification and 41 had intact Rb gene. Thirty patients were treated and 17% of whom had pure well-differentiated LPS and 63% had prior doxorubicin-based chemotherapy. Overall, 1 patient had a PR and 3 had some reduction in the size of the tumour. The PFR at 3 month was 66% which fulfilled the EORTC criteria for clinical activity, with the corresponding median PFS at 18 weeks. Toxicity was mostly haematological, including grade 3 or 4 anemia (17%), neutropenia (50%) and thrombocytopenia (17%). 24% of patients required dose reduction.[42] A phase III trial is currently being planned.

Schoffski et al. reported in the Annual Meeting of the American Society of Oncology in 2015 the phase III trial of eribulin versus dacarbazine in patients with previously treated LMS and LPS. Eribulin is a halichondrin B analog that primarily disrupts the microtubule dynamic by binding at the plus ends leading to inhibition of the growth phase of microtubules.[43-45] In addition, it also affects the tumour vasculature, reverses epithelial-mesenchymal transition and suppression of migration and invasion by cancer cells.[46-48] The 12-week PFR in the phase 2 study in adipocytic sarcoma was 47% and 32% in LMS exceeded EORTC criteria for acceptable clinical activity for further development in the phase 3 setting.[49] Patients who had at least intermediate grade LPS and LMS, received at least 2 lines of prior chemotherapy in the advanced setting, and ECOG 0-2 were randomized to eribulin at 1.4 mg/m^2 on days 1 and 8 or dacabazine at 850 or 1000 or 1200 mg/m^2 on day 1 every 3 weeks. With 451 patients randomized in a 1:1 ratio, the median OS was 13.5

eribulin) versus 11.5 months (dacarbazine); HR=0.768, p=0.0169, with no difference in PFS at 2.6 months (HR=0.877, p=0.2287) or 12-week PFS rate (OR=0.13, p=0.253). Overall RR was comparable in the 2 arms (3.9% in the eribulin-arm vs. 4.9% in the dacarbazine-arm). Survival benefit was observed in all preplanned subgroups, including grades, baseline ECOG PS, prior therapy, age, sex, number of prior regimens as well as geographical regions. Treatment-related grade 3-5 AEs occurred in 67.3% of eribulin-treated patients and 56.3% of dacarbazine-treated patients. There were more patients withdrawn from therapy and had dose reduction in eribulin-arm but similar proportion of patients had dose interruption between the 2 arms. The most common toxicity included neutropenia, fatigue, nausea, alopecia, constipation, anemia, pyrexia, asthenia and peripheral sensory neuropathy.

3.3 Evidence-Based Considerations for a Funding Population

Trabectedin is being considered for funding in patients with recurrent or metastatic LMS and LPS who have received prior doxorubicin-based chemotherapy. In the study comparing trabectedin and dacarbazine, 88% patients had at least 2 lines of chemotherapy, >90% had prior surgery and 50% had prior radiotherapy. Seventy-three percent were LMS, including both uterine (39%) and non-uterine LMS (34%) and 27% LPS, including myxoid ± round cell, pleomorphic and dedifferentiated subtypes. It is estimated about 480 STS patients died in 2010 in Canada, of whom at most 40% had LMS and LPS. Thus, about 190 patients will potentially be eligible for trabectedin. But due to advanced age, co-morbidity and performance status $\geq$ 2, the number patients who will likely be eligible to receive trabectedin in Canada will be less than 190.

Eligibility to receive trabectedin will be determined by the histological diagnosis by local pathologists and the fulfillment of laboratory criteria regarding AST/ALT, bilirubin, alkaline phosphatise and CK.

3.4 Other Patient Populations in Whom the Drug May Be Used

Based on phase II or retrospective studies, trabectedin demonstrated anti-tumour activity in synovial sarcoma,[50,51] other translocation associated sarcomas,[52,53] undifferentiated sarcoma,[50] and other subtypes.[54,55]

To date, there is no evidence that shows trabectedin to be superior to doxorubicin in the treatment naïve, advanced STS setting.[56]

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Sarcoma Cancer Foundation of Canada (SCFC), provided input on the trabectedin (Yondelis) submission as treatment for patients with metastatic liposarcoma or leiomyosarcoma, and their input is summarized below.

SCFC conducted lengthy one on one conversations with a total of 6 patients, and caregivers in the Canadian Sarcoma community to gather insight into their personal experience.

Questions asked by SCFC included information about respondents' specific tumour type, where their treatment took place, whether they have used trabectedin, what side effects they can describe, their experience with sarcoma, barriers to everyday living, challenges associated with the disease and what type of support they could be offered to ease their burden.

There were 4 female and 2 male respondents. All respondents were Canadian adults ranging in age from mid-30 to close to 70 years of age. Of the 6 respondents, 2 had specific experience using trabectedin, and 2 were caregivers for patients who had experience with trabectedin. SCFC reported that input was also informed by conversations within the Canadian Sarcoma community regarding challenges posed by the disease and patient experience living with sarcoma. SCFC stated that they receive calls and emails on a daily basis at their 1-800 telephone line and to their email and are very involved with clinics across Canada. According to SCFC, these calls and emails have given them substantial insight into the patient experience.

SCFC also noted that sarcoma is a rare cancer and as there are over 50 types, a community search was required in order to find people with the specific tumour types indicated. Consequently, SCFC stated that more input from respondents could have been possible had there been additional time to search for these respondents.

From a patient perspective, as current treatments typically result in various side effects, patients stated that they would be willing to tolerate side effects, especially if it resulted in slowing or stopping disease progression. Reported side-effects include fatigue, nausea (with some vomiting), and iron deficiency. These side effects were reported in addition to patients' other sarcoma symptoms.

According to the SCFC, the key symptoms associated with liposarcoma or leimyosarcoma include severe pain, fatigue, difficulty breathing, difficulty sleeping, cough, constipation and cessation of ability to complete daily tasks. SCFC reported that physicians may try different treatments for patients based on what chemotherapies have been previously tried, and the availability of clinical trials. SCFC noted that treatments must be accessed in hospital or in a cancer clinic and therefore some patients may have to travel to access treatment, often having to stay overnight or for longer periods of time away from their homes, increasing the financial hardship of this disease.

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

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients have with Metastatic Liposarcoma or Leiomyosarcoma

SCFC highlighted that there are currently a limited number of therapies for patients with metastatic liposarcoma or leiomyosarcoma and survival rates are low. SCFC reported that the key symptoms associated with liposarcoma or leimyosarcoma include severe pain, fatigue, difficulty breathing, difficulty sleeping, cough, constipation and cessation of ability to complete daily tasks.

SCFC also found that a lack of sleep, ongoing pain and other physical symptoms can often make everyday tasks, such as, driving or cooking difficult or impossible. Therefore, it was stated that patients need more support than prior to living with these types of sarcoma. SCFC indicated that there are multiple conditions which patients suffer from including acid reflux, cough, and pain, and also find it problematic maintaining nutrition. All of these were stated as possibly affecting sleep, memory, mood and general energy levels of patients.

SCFC indicated that patients are often unable to work while suffering from this disease. This can be due to a combination of factors, which leads patients to lose their ability to financially support themselves or their families, thus causing hardship and depression or feelings of hopelessness.

In addition, patients with this metastatic disease are often confined to bed for periods of time or to their home. Another disadvantage is that treatments can be time consuming involving several trips to the hospital and specialists' office.

4.1.2 Patients' Experiences with Current Therapy for Metastatic Liposarcoma or Leiomyosarcoma

SCFC indicated that surgery or radiation is used in some patients, but where that is not an option, these patients must turn to chemotherapies and medications. Often, these medications are limited for soft tissue sarcomas.

SCFC reported that current treatments include: doxorubicin, ifosfamide, doxorubicin and ifosfamide, doxorubicin and dacarbazine, gemcitabine, gemcitabine and docetaxel, dacarbazine, dacarbazine and gemcitabine, and pazopanib. SCFC submitted that patients would be willing to tolerate side effects, as current treatments also typically result in various side effects. The willingness to tolerate side-effects was most prevalent in cases where results showed slowing or stopping disease progression.

SCFC specified that treatments must be accessed in hospital or in a cancer clinic. Therefore some patients, depending on where they live, may be required to travel to access treatment, often having to stay overnight or for longer periods of time away from their homes, which increases the financial hardship of this disease.

SCFC also reported that knowing the survival outcomes of soft tissue sarcomas are not currently high; therefore it is difficult to keep patients in positive spirits and give them hope for positive outcomes. SCFC indicated that this new treatment under review would be welcome by physicians and patients in order to continue to combat metastatic liposarcoma or leiomyosarcoma.

4.1.3 Impact of Metastatic Liposarcoma or Leiomyosarcoma and Current Therapy on Caregivers

SCFC received input from 2 caregivers and noted their personal experience on caring for a sarcoma cancer patient.

According to SCFC, caring for patients with these types of soft tissue sarcomas is very taxing on both caregivers and families.

SCFC stated that caregivers are often unable to work or have to take extended periods of leave to care for patients, and this is aside from the financial impact already described by the patient being unable to work.

To help illustrate the experience of the caregiver, below are some of the key responses reported by SCFC:

1) Living with pain, difficulty breathing, difficulty sleeping, depression and other symptoms takes a toll not only on the patient but on the caregiver watching them suffer as well.
2) Lengthy and frequent treatment and doctor's appointments for patient and caregivers.
3) It can often be a full time commitment to take care of a patient with this type of cancer as caregivers also have to make up for the patient's inability to undertake daily tasks.

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with Trabectedin

According to SCFC, there are no specific expectations other than the fact that patients and the medical community welcomes access to this treatment. SCFC submits that drug under review is showing positive effects on slowing disease progression for patients; and therefore, both patients and caregivers who do not have experience with this drug are optimistic with potentially having an additional treatment for this cancer.

According to SCFC, there were only 2 patients found who had previous experience with trabectedin. These patients obtained the drug under review through clinical trials, a manufacturer's compassionate supply, by paying for it out of pocket or through private insurance.

However, those who have experience found it to slow disease progression and to be tolerable in terms of reported side-effects such as fatigue, nausea, and iron deficiency.

SCFC reported that when treatment is not a first-line therapy, it is often difficult to separate disease symptoms from side effects of previous treatments, and from side effects of current treatments.

SCFC also indicated that both patients and caregivers reported that trabectedin improved their quality of day to day life and some patients experienced a halt in disease progression while being on treatment.

4.3 Additional Information

SCFC noted that trabectedin was seen as a positive and welcome option in the sarcoma community.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

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

Overall Summary

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

Clinical factors:

- Provides another treatment option for a very small number of patients

Economic factors:

- Drug wastage
- Hospital admission and resources required to administer the 24 hour infusion via central line

Please see below for more details.

5.1 Factors Related to Comparators

There is no standard of care for patients with advanced liposarcoma or leiomyosarcoma after prior therapy with an anthracycline and ifosfamide chemotherapy. In the very small number of patients in Canada, treatment with gemcitabine, pazopanib[1], and dacarbazine has been used.

[1] Pazopanib for soft tissue sarcoma was reviewed by pCODR and pERC did not recommend funding. Pazopanib is not funded in most provinces for this indication; in some provinces, pazopanib is considered for funding on a case-by-case basis.

5.2 Factors Related to Patient Population

PAG noted that liposarcoma and leiomyosarcoma are uncommon cancers. In some provinces, there may only be one or two patients with this subtype of sarcoma. Trabectedin would provide another treatment option for these patients.

PAG noted that trabectedin is provided by the manufacturer's compassionate access program for treatment of sarcomas, not limited to liposarcoma and leiomyosarcoma. Thus, PAG is seeking information on the generalizability of trial results to other soft tissue sarcomas.

In addition, PAG noted that there are ongoing trials for use of trabectedin in combination with docetaxel for first-line treatment of sarcoma but recognizes this would be out of scope for this review.

5.3 Factors Related to Dosing

PAG noted that trabectedin is administered every three weeks until disease progression. Although the every three week administration schedule is an enabler to implementation,

the indefinite treatment duration could be a barrier to implementation because the impact on resources is unknown.

5.4 Factors Related to Implementation Costs

PAG had concerns for incremental costs due to drug wastage, since vial sharing is unlikely possible given the very small number of patients. The dose of trabectedin is based on weight and there is only one vial size (1mg per vial). A dose of 2.55mg (1.5mg/m^2 x 1.7 m^2) would result in drug wastage. This is a barrier to implementation.

PAG indicated that the administration of trabectedin will require admission to hospital for insertion of a central line and for the 24-hour infusion. This would be another barrier to implementation as hospital resources are required and patient access could be limited to a small number of tertiary care centers.

5.5 Factors Related to Health System

Trabectedin, being an intravenous drug, would be administered in an outpatient chemotherapy center or inpatient hospital for appropriate administration and monitoring of toxicities. If recommended for funding, intravenous chemotherapy drugs would be fully funded in all jurisdictions for eligible patients. This would be an enabler as there would be no co-pays or deductibles for patients.

However, PAG noted that trabectedin is administered as a 24-hour infusion via a central line. This would require patients to be admitted to hospital for treatment as an in-patient, and would also have hospital resource implications. This would be a barrier to implementation.

5.6 Factors Related to Manufacturer

Trabectedin was provided by the manufacturer on a compassionate basis for the treatment of sarcoma. PAG is seeking clarity on whether the manufacturer's compassionate program will continue for patients using trabectedin for other soft tissue sarcomas and in the first-line setting.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effect of trabectedin (Yondelis) in the treatment of patients with advanced and/or metastatic liposarcoma or leiomyosarcoma subtypes of soft tissue sarcoma after failure of prior anthracycline-based chemotherapy.

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 3 below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

Table 3. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished RCTs	Patients with metastatic liposarcoma or leiomyosarcoma after failure of prior anthracycline and ifosfamide chemotherapy	Trabectedin monotherapy at recommended dose	Chemotherapy agents (single or combination) for STS: • Dacarbazine • Gemcitabine • Pazopanib • Paclitaxel • Gemcitabine + dacarbazine • Gemcitabine + docetaxel	• OS • PFS • HRQoL • ORR (CR + PR) • SAE • AE • WDAE

AE=adverse event; CR=complete response; HRQoL=health-related quality of life; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PR=partial response; RCT=randomized controlled trial; SAE=serious adverse event; STS=soft tissue sarcoma; WDAE=withdrawal due to adverse event

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

6.2.2 Literature Search Methods

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

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-present) with in-process records & daily updates via Ovid; Embase (1974-2016 January 11) via Ovid; The Cochrane Central Register of Controlled Trials (December 2015) via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were trabectedin, Yondelis, liposarcoma, leiomyosarcoma and sarcoma.

Methodological filters were applied to limit retrieval to randomized controlled trials and controlled clinical trials. 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 May 5, 2016.

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. The search for conference abstracts of the American Society of Clinical Oncology (ASCO) was limited to the last five years. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

6.2.3 Study Selection

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

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

6.2.4 Quality Assessment

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

6.2.5 Data Analysis

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

6.2.6 Writing of the Review Report

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

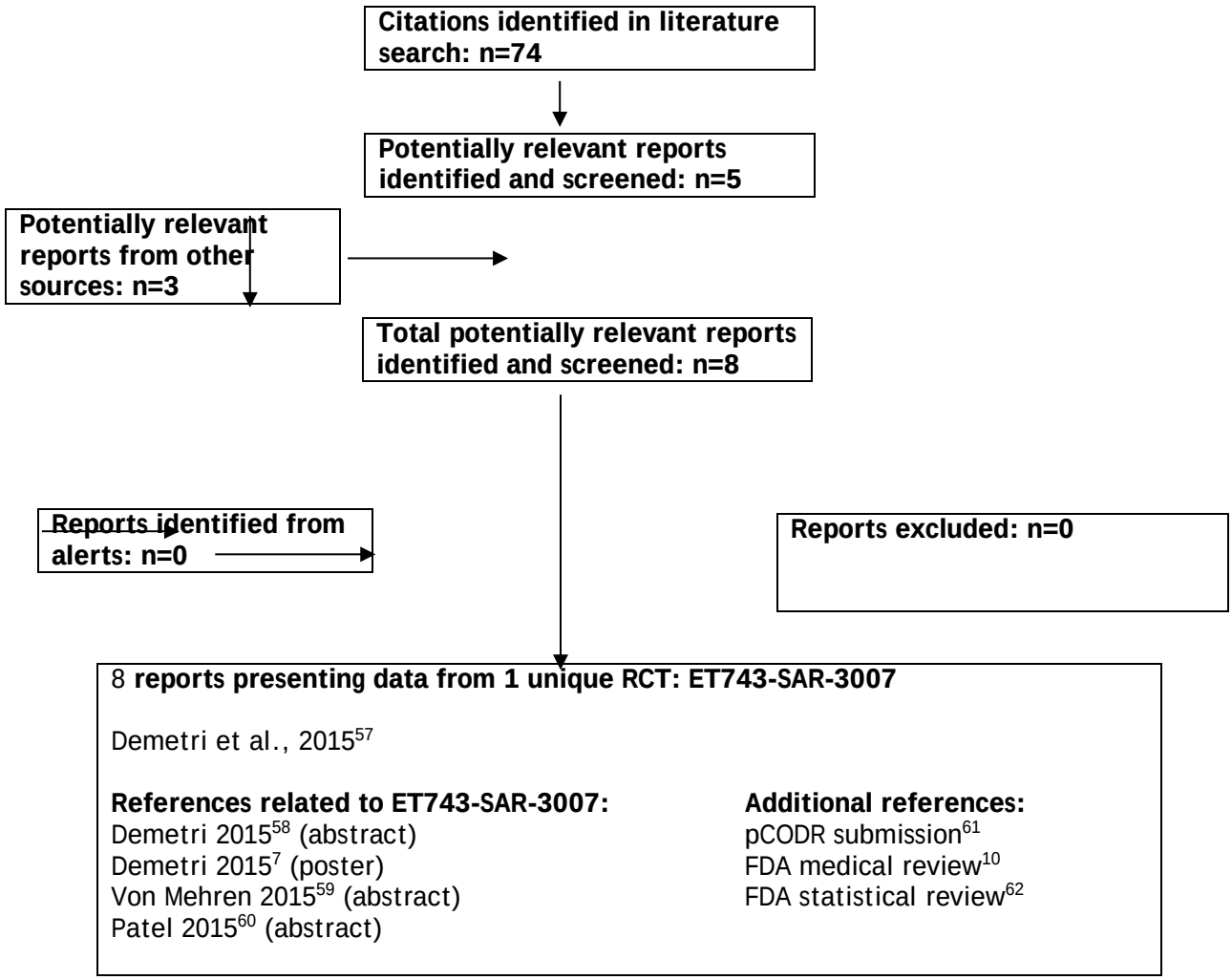
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions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

6.3 Results

6.3.1 Literature Search Results

Of the 74 reports identified in the literature search, eight publications concerning one unique study[57] were included in the pCODR systematic review.

Figure 1. QUOROM Flow Diagram for Inclusion and Exclusion of studies



6.3.2 Summary of Included Studies

6.3.2.1 Detailed Trial Characteristics

a) Trials

One phase III, open-label, multicenter active-controlled RCT (ET743-SAR-3007, NCT01343277) was included in this review (see Table 4 for detailed information).[57] The RCT evaluated the efficacy and safety of trabectedin in patients with advanced/metastatic liposarcoma or leiomyosarcoma after failure of prior anthracycline-based chemotherapy. Patients were randomized to receive either

trabectedin or dacarbazine. The primary efficacy endpoint in this study was overall survival (OS). The secondary endpoints included progression-free survival (PFS), change in symptom severity, objective response rate (ORR), and safety.

Patients and investigators were not blinded during the study. Investigators assessed tumour response by radiographic imaging of the chest, abdomen and pelvis until disease progression, subsequent anticancer therapy or death occurred. The radiographic PFS (rPFS) results from approximately 60% of the study participants (from sites that enrolled nine or more patients at the time of the interim analysis of OS) were retrospectively audited by independent radiologists who were unaware of the treatment assignments.[10] Safety data of the study drugs were assessed based on observed adverse events, clinical laboratory tests, vital sign measurement, physical examination, cardiac function and concomitant medication use by investigators.

With a planned sample size of 570 patients, the study would have 80% power to detect a statistically significant difference between a median OS of 10 months in the dacarbazine group and a median OS of 13.5 months in the trabectedin group (target OS hazard ratio [HR] of 0.74) with 376 events, at a two-sided significance level of 0.05. The interim analysis of OS in this study was planned when 50% of the required number of events (188 deaths) occurred. The analysis of PFS was scheduled at the same time of the OS interim analysis after a projected 331 PFS events, with a power of at least 90% to detect a difference in median PFS between dacarbazine and trabectedin (2.50 months versus 3.75 months, respectively; target HR of 0.667), at a two-sided significance level of 0.05. OS and PFS between trabectedin and dacarbazine were compared using an unstratified log-rank test, with a level of significance of 0.05. The Fisher's exact test was used to detect the difference in ORR between the study drugs. The data cut-off date for the interim analysis of OS was September 16, 2013, while the cut-off date for the final analysis of OS was January 5, 2015. The intention-to-treat (ITT) population, which was defined as all randomized patients, was the primary analysis population for the efficacy analyses.[62]

Table 4. Summary of Trial characteristics of the ET743-SAR-3007 Study

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
Multinational, open-label, active-controlled, phase III RCT 90 sites in 4 countries[a] (Canada not included) Randomization was performed at a 2:1 (trabectedin:dacarbazine) ratio, and stratified by type of sarcoma, ECOG performance status (0 vs. 1), and number of prior chemotherapy regimens (1 vs. ≥2).[10] Study start date: May 27, 2011 Data cut-off for interim analysis of OS: September 16, 2013 Data cut-off for final analysis of OS: January 5, 2015 Funded by: Janssen Pharmaceuticals and non-industry research foundation.	<u>Inclusion criteria:</u> Age ≥ 15 years; with unresectable locally advanced or metastatic L-sarcomas; were previously treated with either a combination of anthracycline and ifosfamide or an anthracycline and at least 1 or more additional cytotoxic chemotherapy agents; adequate bone marrow, renal and liver functions; ECOG PS of 0 or 1. <u>Exclusion criteria:</u> Known CNS metastasis; myocardial infarct ≤ 6 months before enrollment; New York Heart Association class II or greater heart failure; less than 3 weeks from last dose of systemic cytotoxic therapy, radiation therapy, or therapy with any investigational agent; other malignancy within past 3 years.	Trabectedin 1.5 mg/m^2, IV infusion over 24-hr, administered on day 1 of each 21-day cycle. Dacarbazine 1 g/m^2, IV infusion over 20- to 120-minute, administered on day 1 of each 21-day cycle. Both treatment groups were treated until disease progression or intolerable toxicity.[10]	<u>Primary</u> • OS <u>Secondary</u> • PFS • Patient-reported outcome (symptom severity and symptom interference) • ORR • Safety

CNS=central nervous system; ECOG PS= Eastern Cooperative Oncology Group performance status; IV=intravenous; L-sarcoma=liposarcoma and leiomyosarcoma; ORR=objective response rate; OS= overall survival; PFS= progression-free survival; RCT= randomized controlled trial

[a]These countries included Australia, Brazil, New Zealand, and the United States of America (US) with 94% of patients treated with trabectedin enrolled in US sites.

Data sources: Demetri 2015,[57] Patel 2015,[60] Clinicaltrials.gov,[63] FDA medical review[10]

b) Populations

At the clinical cut-off date for final analysis of OS at January 5, 2015, a total of 577 patients were randomized in the ET743-SAR-3007 study, with 384 in the trabectedin group and 193 in the dacarbazine group.

Overall, baseline characteristics were balanced across both trabectedin and dacarbazine groups in terms of demographics, disease severity, and prior treatments received at the time of interim analysis of OS, when 518 patients were enrolled in ET743-SAR-3007, with 345 in the trabectedin group and 173 in the

dacarbazine group (Table 5). There was a higher proportion of white patients in the trabectedin group compared with the dacarbazine group (78% vs. 72%, respectively), and patients with a BMI > 30 kg/m^2 in the trabectedin group compared to the dacarbazine group (41% vs. 35%, respectively). The median time from initial diagnosis to randomization was seven months longer in the trabectedin group compared with the dacarbazine group (34 months vs. 27 months). The demographic characteristics of the 577 patients in the final analysis were consistent with the 518 patients in the interim analysis of OS (data not shown).[10]

Table 5. Baseline Patient Demographics and Disease Characteristics in ET743-SAR-3007 (data cut-off for interim analysis of OS: September 16, 2013)

	Trabectedin (n=345)	Dacarbazine (n=173)
Age, years		
Median (range)	57 (18-81)	56 (17-79)
Sex, n (%)		
Male	107 (31)	47 (27)
Female	238 (69)	126 (73)
Race, n (%)		
White	269 (78)	125 (72)
Non-White	57 (17)	35 (20)
Unknown/not reported	19 (6)	13 (8)
BMI, kg/m^2		
Median (range)	28.11 (14.5-78.1)	27.05 (13.3-66.7)
< 30, n (%)	203 (59)	112 (65)
≥ 30, n (%)	142 (41)	61 (35)
Histology		
Leiomyosarcoma	252 (73)	126 (73)
Liposarcoma	93 (27)	47 (27)
Best response to last line of previous chemotherapy		
CR/PR/SD	146 (42)	68 (39)
Disease progression	198 (57)	103 (60)
Unknown/missing	1 (0)	2 (1)
ECOG performance status, n (%)		
0	171 (50)	86 (50)
1	174 (50)	87 (50)
Number of prior chemotherapy, n (%)		
1	38 (11)	23 (13)
≥ 2	307 (89)	150 (87)
Previous surgery for malignancy, n (%)		

	Trabectedin (n=345)	Dacarbazine (n=173)
Yes	327 (95)	158 (91)
No	18 (5)	15 (9)
Previous radiotherapy for malignancy, n (%)		
Yes	176 (51)	80 (46)
No	169 (49)	93 (54)
Time from initial diagnosis to randomization, months		
Median (range)	33.9 (2.5-318.5)	27.1 (1.6-267.1)
BMI=body mass index; CR=compete response; ECOG=Eastern Cooperative Oncology Group; PR=partial response; SD=stable disease		

Source: Demetri 2015,[57] FDA medical review[10]

c) *Interventions*

Patients received trabectedin at a starting dose of 1.5 mg/m^2 via a central venous catheter as a 24-hour IV infusion or dacarbazine at a starting dose of 1 g/m^2 as a 20- to 120-minute IV infusion. The study drugs were administered at day 1 of each 21-day cycle. Patients in the trabectedin group required premedication of dexamethasone 20 mg IV for hepatoprotective and anti-emetic effects.[5] Dose reduction or dose delay was possible in case of treatment-related toxicities. During the study, patients were not allowed to cross over from the dacarbazine group to the trabectedin group until interim analysis of OS (September 16, 2013).[58] Treatment was continued until the occurrence of unacceptable side effects or disease progression.[63]

The median number of cycles that patients received the study drug was greater in the trabectedin group than in the dacarbazine group, 4 cycles vs. 2 cycles, respectively. As of September 16, 2013, the median total treatment duration was 12 weeks in the trabectedin group and seven weeks in the dacarbazine group, and the median duration of follow-up after the last dose of study drug was 8.6 months in the overall population. Cycle delays or dose reductions were reported in 57% and 35% of patients in the trabectedin group respectively, compared with 40% and 10% of patients in the dacarbazine group. The median dose intensity of trabectedin was 1.37 mg/m^2 per cycle (91% of the target dose), while the median dose intensity of dacarbazine was 0.98 g/m^2 per cycle (98% of the target dose).

Table 6 presents systemic anti-cancer treatments received after progression at the interim analysis. Overall, patients in the dacarbazine group received more antineoplastic therapies compared with the trabectedin group. The most commonly prescribed anti-cancer agent was pazopanib in both treatment groups after progression. Post-progression anti-cancer therapy use was similar at the final analysis for OS, with 71% and 69% of patients treated with trabectedin and dacarbazine, respectively, receiving subsequent anti-cancer therapies.[7]

Table 6. Post Progression Anti-Cancer Therapy Use (ITT Population)

	Trabectedin (n=345)	Dacarbazine (n=173)
Overall anticancer therapy	162 (47%)	97 (56%)
Pazopanib	63 (18%)	48 (28%)
Dacarbazine	60 (17%)	11 (6%)
Gemcitabine	30 (9%)	25 (15%)
Docetaxel	19 (6%)	21 (12%)

	Trabectedin (n=345)	Dacarbazine (n=173)
Ifosfamide	7 (2%)	10 (6%)
Doxorubicin	9 (3%)	5 (3%)
Radiation	35 (10)	25 (15)
Surgery	23 (7)	17 (10)

Data sources: FDA Medical Review,[10] Demetri 2015[57]

d) Patient Disposition

The ITT population (N = 518 as of September 16, 2013) in the ET743-SAR-3007 study was defined as randomized patients, regardless of whether they received the study medication.[62] Safety analyses were performed for all randomized patients who received the allocated intervention (N = 495 as of September 16, 2013). Of the 518 randomized patients, 345 patients were assigned to receive trabectedin and 173 patients were assigned to receive dacarbazine. Five patients from the trabectedin group and 18 patients from the dacarbazine group did not receive the allocated study medication (reasons were not publically reported).

As of the data cut-off date on September 16, 2013, 96 (28%) patients randomized to trabectedin remained on treatment, while 23 (13%) patients randomized to dacarbazine remained on treatment. The primary reason for discontinuation from study drug was disease progression in both arms. Patients in the dacarbazine group were more likely to withdraw from the study due to disease progression, compared with those in the trabectedin group. Other reasons for discontinuation from the study drug included adverse events, withdrawal of consent, or other. Percentage of patients withdrew from the study due to adverse events was higher in the trabectedin arm (9.9%) compared with the dacarbazine arm (6.4%). At the time of final analysis of OS (January 5, 2015), eight patients (2.1%) in the trabectedin arm and two in the dacarbazine arm (1.2%) were receiving ongoing treatment.[10] In total, 322 patients had died, 220 from the trabectedin group and 102 from the dacarbazine group.

A summary of the patient disposition in ET743-SAR-3007 is presented in Table 7.

Table 7. Patient Disposition in the ET743-SAR-3007 Study (as of September 16, 2013)

	Trabectedin	Dacarbazine
Randomized	345	173
Not treated (n, %)	5 (1.4)	18 (10.4)
Treated (n, %)	340 (98.6)	155 (89.6)
Discontinued study (n, %)	244 (70.7)	132 (76.3)
Disease progression	186 (53.9)	106 (61.3)
Adverse events	34 (9.9)	11 (6.4)
Patient withdrawal consent	11 (3.2)	11 (6.4)
Death	9 (2.6)	1 (0.6)
Other	4 (1.2)	3 (1.7)
Still on treatment at data cut-off for interim analysis of OS (n, %)	96 (27.8)	23 (13.3)
ITT population (n, %)	345 (100)	173 (100)
Safety population (n, %)	340 (98.6)	155 (89.6)
ITT=intention-to-treat; NR=not reported; OS=overall survival		

Data sources: Demetri 2015,[57] FDA Medical Review,[10] FDA Statistical Review[62]

e) Limitations/Sources of Bias

ET743-SAR-3007 was an open-label randomized trial. Central randomization was carried out to ensure allocation concealment and balanced patient characteristics at baseline. Cross-over from dacarbazine to trabectedin was not allowed before interim analysis of OS to avoid data contamination. Tumour response measured by radiographic imaging of the chest, abdomen and pelvis was assessed by investigators, while approximately 60% of such results were retrospectively audited by independent radiologists who were unaware of the treatment assignments. An independent Data Monitoring Committee was established to monitor the efficacy and safety data, to ensure patient safety throughout the study and to assess if efficacy objectives had been achieved. Other strengths of the study included an appropriate sample size and power calculation for OS and PFS, ITT analysis and subgroup analyses to adjust for various patient/trial characteristics.

Potential limitations in the ET743-SAR-3007 study include:

- Patients and investigators were not blinded during the study. The impact of an open-label study design on patient-reported outcomes is unknown.
- According to the Clinical Guidance Panel, there is no standard of care in Canada and dacarbazine is a reasonable comparator.
- Three protocol amendments occurred during the study; 58 patients were enrolled at the time of the third amendment (a change to allow anthracycline and ifosfamide containing regimen and one additional cytotoxic chemotherapy; provision for de-bulking surgery and the criteria to be met for such surgery, an update to the definition of PFS, an update to the most recent version of MDASI questionnaire, and minor editorial changes and clarifications). It was unclear how the protocol amendment would change the recruitment procedure, number of participants, inclusion criteria and efficacy assessment.
- Even though in general, the patients' baseline characteristics were similar between the two treatment groups, there were still differences in races, BMI and time since initial diagnosis to randomization, which would have introduced biases into the study. Internal validity of the study was compromised because these imbalanced patient characteristics at baseline had the potential to bias the study results; however, it is unknown how these imbalances have affected the results.
- Various post-progression treatment modalities may bias OS. A higher percentage of patients in the dacarbazine group received chemotherapy, radiotherapy or surgery, compared to those in the trabectedin group. It is challenging to predict the direction that the OS may have been biased, due to the different efficacy and safety profile of the adopted post-progression treatment modalities.
- Patient-reported outcomes were measured using MDASI scores and was insufficiently reported. The results were based on a small group of patients who were still on treatment at the time of completing the questionnaire (20% in the trabectedin group and 8% in the dacarbazine group by Cycle 8). Therefore the results should be interpreted with caution.
- Generalizability of the study results is limited because of the rigorous patient selection criteria. Patients with ECOG performance status score of 2 or with CNS metastasis were excluded. It may be unusual to see a large proportion of patients with good performance status in this population. The effect of high performance status scores on the assessment of the impact of

trabectedin on quality of life and disease symptoms remains uncertain. On the other hand, patients with performance status 2 or greater were excluded when they may benefit from the study drug. However, there is a lack of evidence to assess the effectiveness and safety in such patients.

- The study did not include any Canadian sites. It may be appropriate to extrapolate the study results to the Canadian population given the similar geographical region and races between these two countries.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

The efficacy analyses were conducted in the ITT population, comprised of all randomized patients. The safety population comprised all patients who received at least one dose of study drug. The assessments of efficacy and safety were performed every six weeks during the first 36 weeks on study and every nine weeks thereafter until disease progression, subsequent anticancer therapy or death occurred. The cut-off date for the interim analysis on OS and the final PFS assessment was September 16, 2013, and the cut-off date for the final analysis on OS was January 5, 2015. Results from the final analysis are reported in this review. Results from the interim analysis are presented only when the final analysis results are unavailable. Tables 8 and 9 present the key efficacy and harm outcomes from this study.

Table 8: Summary of Efficacy Outcomes from the ET743-SAR-3007 Study

	Trabectedin (n=384)	Dacarbazine (n=193)
Overall Survival (data cut-off for interim analysis: September 16, 2013, time frame 2 years and 4 months; for final analysis: January 5, 2015, time frame 3 years and 8 months)		
Median (months) (95% CI)	Final: 13.7 (12.2 - 16.0) *Interim: 12.4 (11.2 - 14.6)*	Final: 13.1 (9.1 - 16.2) *Interim: 12.9 (7.8 - 16.4)*
HR (95% CI)	Final: 0.93 (0.75 - 1.15) *Interim: 0.87 (0.64 - 1.18)*	
p-value	Final: 0.49 *Interim: 0.37*	
Subgroups:		
Histological subtype	Liposarcoma: 12.6	Liposarcoma: 13.1
	HR (95% CI): 1.05 (0.69 - 1.60) p-value: 0.826	
	Leiomyosarcoma: 14.1	Leiomyosarcoma: 13.6
	HR (95% CI): 0.89 (0.69 - 1.15) p-value: 0.372	
Progression-Free Survival (data cut-off: September 16, 2013, time frame 2 years and 4 months)		
Median (months) (95% CI)	4.2	1.5
HR (95% CI)	0.55 (0.44 - 0.70)	
p-value	< 0.0001	
Subgroups:		
Histological subtype	Liposarcoma: 3.0 (1.5 - 4.8)	Liposarcoma: 1.5 (1.4 - 2.7)
	HR (95% CI): 0.55 (0.3 - 0.9) p-value: 0.0093	
	Leiomyosarcoma: 4.3 (3.5 - 5.0)	Leiomyosarcoma: 1.6 (1.5 - 2.8)
	HR (95% CI): 0.55 (0.4 - 0.7)	

	Trabectedin (n=384)	Dacarbazine (n=193)
	p-value: < 0.0001	
ECOG performance status	0: 4.7 months	0: 1.5 months
	HR (95% CI): 0.51 (0.36 - 0.71)	
	1: 2.9 months	1: 1.5 months
	HR (95% CI): 0.60 (0.43 - 0.82)	
Age	< 65 years: 4.1 months	< 65 years: 1.8 months
	HR (95% CI): 0.60 (0.46 - 0.78)	
	≥ 65 years: 4.9 months	≥ 65 years: 1.5 months
	HR (95% CI): 0.40 (0.24 - 0.67)	
Health-Related Quality of Life (measured by MDASI scores, time frame not reported)		
Baseline MDASI scores were comparable between trabectedin and dacarbazine. By Cycle 8, no meaningful changes from baseline were observed for either group. No further details were reported.		
Objective Response Rate (data cut-off: September 16, 2013, time frame 2 years and 4 months)		
Overall response rate, n (%)	34 (9.9)	12 (6.9)
Complete response, n (%)	0	0
Partial response, n (%)	34 (9.9)	12 (6.9)
OR	1.467	
p-value	0.33	
CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; HR=hazard ratio; MDASI=MD Anderson Symptom Inventory; OR=odds ratio; OS=overall survival; PFS=progression-free survival		

Sources: FDA medical review,[10] Demetri[7,57,58]

Efficacy Outcomes

1. *Overall Survival (OS)*

OS was defined as the time from randomization to death from any cause. Kaplan-Meier estimates of survival probabilities were used to obtain median survival times and their 95% confidence intervals (CI). The difference in OS between the two treatments was compared using unstratified log-rank test.

In the final analysis of OS performed after 381 deaths had occurred (clinical data cut-off: January 5, 2015; the pre-specified number of death events was reached), the median OS was 13.7 months (95% CI 12.2 to 16.0) for the trabectedin arm and 13.1 months (95% CI 9.1 to 16.2) for the dacarbazine arm; HR = 0.93, 95% CI 0.75 to 1.15, p = 0.49. A pre-specified stratification analysis by ECOG performance status score, subtype of L-sarcoma, and number of prior lines of chemotherapy was consistent with the unstratified analysis of OS (HR=0.939; 95% CI 0.756 to 1.167; p=0.5721).[7,10,60]

An interim analysis of OS was performed when 188 deaths occurred at the date of data cut-off (September 16, 2013).[57] The median OS was 12.4 months in the trabectedin group and 12.9 months in the dacarbazine group (HR = 0.87, p = 0.37). The results were consistent with the final analysis.

2. *Progression-Free Survival (PFS)*

PFS was defined as the time from randomization to disease progression or death due to any cause. Kaplan-Meier median PFS times and their 95% CI were used. The PFS results between treatment groups were compared using unstratified log-rank test.

As of September 16, 2013, the number of pre-specified PFS events in sample size calculation was reached. The median PFS was longer in the trabectedin group (4.2 months), as compared with 1.5 months in the dacarbazine group (HR = 0.55, 95% CI 0.44 to 0.70, p < 0.0001). Compared to dacarbazine, treatment with trabectedin was associated with a statistically significant decrease (45%) in the risk of disease progression or death.

In an ESMO poster (2015) relevant to the Demetri study, the authors reported PFS stratified by histological subtype (liposarcoma and leiomyosarcoma).[7] In the liposarcoma subgroup, the median PFS was 3.0 months in the trabectedin group and 1.5 months in the dacarbazine group, HR = 0.55 (95% CI 0.34 to 0.87, p = 0.009). In the leiomyosarcoma subgroup, the median PFS was 4.3 months in the trabectedin group and 1.6 months in the dacarbazine group, HR = 0.55 (95% CI 0.42 to 0.73, p < 0.0001). All subgroup analyses were pre-planned.

FDA agreed that the independent radiologists' assessment of the rPFS results for approximately 60% of the study participants (4.3 months in the trabectedin group vs. 1.9 months in the dacarbazine group; HR = 0.55, 95% CI 0.40 to 0.75, p=0.0001) appeared consistent with the investigator's assessment of rPFS (HR = 0.58, 95% CI 0.43 to 0.79, p=0.0004).[14]

3. Health-related Quality of Life

M.D. Anderson Symptom Inventory (MDASI) scores were used to assess patients' perceived symptom burden and determine the impact of treatment on symptom change or stability. MDASI is a 19-item self-reported questionnaire in that 13 items are related to symptom severity and six items measure how much these symptoms have interfered with six daily activities. All items are rated from 0 (symptom not present or did not interfere) to 10 (most severe symptom or interfered completely).[10,64]

At baseline, MDASI scores were low in both treatment groups. By Cycle 8, there were no meaningful changes from baseline were observed through 8 cycles for either treatment group, except that at Cycle 2, 9.4% of patients in the trabectedin group reported nausea compared with 3.3% of patients in the dacarbazine group, p = 0.0396. The results were based on the responses from 71 patients in the trabectedin group and 14 patients in the dacarbazine group who were still treated with the study drugs by Cycle 8. No other details were provided on this outcome.[14]

4. Objective Response Rate (ORR)

ORR was defined as partial response or complete response while on study treatment based on investigator assessments of target, non-target, and new lesions using RECIST 1.1. Only patients with measurable soft tissue disease at baseline were included in the analysis.

Higher ORRs, based on partial response as complete response was not observed in either group, were reported in the trabectedin group as compared to the dacarbazine group; however a statistically significant difference between the treatment groups was not detected: 34 patients (9.9%) vs. 12 patients (6.9%) respectively, odds ratio = 1.47, p = 0.33. The median duration of response was 6.5 months with trabectedin and 4.2 months with dacarbazine; however, statistically significant difference between the two groups was not detected, p = 0.14.

Harms Outcomes

The safety analysis population consisted of 550 patients who had received at least one dose of the study drug at the final analysis of OS, 378 from the trabectedin group and 172 from the dacarbazine group. Adverse events were classified using the NCI-CTCAE and monitored by an independent data monitoring committee.

Details of adverse events associated with the use of trabectedin compared with dacarbazine are presented in Tables 9 and 10.

5. Any Adverse Events (AEs)

Treatment-emergent AEs were reported in 377 (100%) patients in the trabectedin group and in 170 (99%) patients in the dacarbazine group. The most common AEs were predominantly of grade 1 to 2 severity. Among the 378 patients who received at least one dose of trabectedin, the most commonly reported adverse reactions (≥ 20%) were nausea (75%), fatigue (69%), vomiting (46%), constipation (37%), decreased appetite (37%), diarrhea (35%), peripheral edema (28%), dyspnea (25%) and headache (25%). The most common laboratory abnormalities (≥20%) were increases in AST (38%) or ALT (49%), neutropenia (31%), and anemia (42%). Patients in the trabectedin group (81%) were more likely to report a Grade 3-4 AE compared to those in the dacarbazine group (57%).Increased AST (16%) and ALT (31%), neutropenia (30%) and anemia (18%) were frequently reported Grade 3-4 AEs (≥ 10%).[10,65]

6. Serious Adverse Events (SAEs)

As of the final analysis of OS in ET743-SAR-3007, a larger proportion of patients treated with trabectedin reported SAEs than those treated with dacarbazine: 155 (41%) vs. 52 (30%), respectively.[66] The most frequent (≥ 2%) non-fatal SAEs in the trabectedin group compared to the dacarbazine group were nausea, vomiting, dyspnea, febrile neutropenia, pyrexia, dehydration, and acute renal failure.[10]

7. Withdrawal due to Adverse Events

A higher percentage of patient withdrawal due to adverse events was observed in the trabectedin group (10%) compared to the dacarbazine group (6%) as of September 16, 2013.[10] As of January 5, 2015, a higher percentage of patient withdrawal due to adverse events was reported in the trabectedin group (26%) compared to the dacarbazine group (22%).[66]

8. Adverse Events of Special Interest

Rhabdomyolysis was reported in four patients (1.2%) of the trabectedin-treated patients, and no patients in the dacarbazine group.[10]

9. Deaths

In total, 220 patients (58%) in the trabectedin group and 102 patients (59%) in the dacarbazine group died during a period of three years and eight months from the start of the study. Twelve patients (3.2%) in the trabectedin died due to treatment-emergent adverse events. None of the patients in the dacarbazine group died due to adverse events.[10]

Table 9. Summary of Harm Outcomes in the ET743-SAR-3007 Study (final analysis cut-off: January 5, 2015)

	Trabectedin (N=378) n (%)	Dacarbazine (N=172) n (%)
Any AEs	377 (100)	170 (99)
Withdrawal due to AEs	98 (26)	37 (22)
Total deaths	220 (58)	102 (59)
Treatment-related death	12 (3)	0
SAEs	155 (41)	52 (30)
AE=adverse event; NR=not reported; SAE=serious adverse event		

Data sources: manufacturer response to checkpoint meeting questions,[66] FDA medical review[10]

Table 10. Incidence of Treatment-Emergent Adverse Events (≥ 20% of Trabectedin-Treated Patients) Reported in the ET743-SAR-3007 Study (as of January 5, 2015)

	Trabectedin (N=378) n (%)	Dacarbazine (N=172) n (%)
Nausea	285 (75)	86 (50)
Vomiting	173 (46)	37 (22)
Constipation	140 (37)	53 (31)
Diarrhea	132 (35)	40 (23)
Decreased appetite	139 (37)	36 (21)
Fatigue	261 (69)	89 (52)
Edema peripheral	107 (28)	22 (13)
ALT increased	186 (49)	12 (7)
AST increased	142 (38)	10 (6)
Neutropenia	119 (31)	31 (18)
Blood alkaline phosphatase increased	85 (22)	15 (9)
Thrombocytopenia	74 (20)	34 (20)
Anemia	157 (42)	48 (28)
Dyspnea	94 (25)	35 (20)
Cough	85 (22)	36 (21)
Headache	93 (25)	32 (19)

Data source: FDA medical review[10]

6.4 Ongoing Trials

At present, clinical trials that compare trabectedin and other chemotherapy agents are ongoing in patients with STS. Details of these ongoing trials are presented in Table 11.

Table 11. Ongoing Trials Comparing Trabectedin and Other Chemotherapy

	Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
NCT01692678	Multi-centre, OL, RCT Estimated enrolment: 141 Estimated study completion date: Feb. 2019 Status: currently recruiting patients	Chinese patients ≥ 15 years, with locally advanced or metastatic L-sarcoma who were previously treated with at least an anthracycline and ifosfaminde containing regimen, or an anthracycline containing regimen and 1 additional cytotoxic chemotherapy regimen. Exclusion criteria: known CNS metastasis	Trabectedin: a dose of 1.5, 1.2 or 1.0 mg/m^2 as a 24-hour intravenous infusion on Day 1 of each 21-day treatment cycle Dacarbazine: a dose of 1 g/m^2 as a longer than 30-minute intravenous infusion on Day 1 of each 21-day treatment cycle	Primary: optimal dose level, OS Secondary: PFS, TTP, ORR, DR,
NCT02247544	Multi-centre, single arm, OL, phase 2 study with intra-patient comparison. Estimated enrolment: 95 Estimated study completion date: Oct. 2020 Status: currently recruiting patients	Patients ≥ 18 years, with retroperitoneal leiomyosarcoma and well differentiated /dedifferentiated liposarcoma expressed in terms of slowing down tumour growth. ECOG performance status ≤ 2. Exclusion criteria: known CNS metastases	Trabectedin: a dose of 1.5 mg/m^2 or 1.3 mg/m^2 (at investigator's discretion, with a top-dose of 2.6 total mg per cycle) as a 24-hour infusion once every 3 weeks (cycle day 1).	Primary: growth modulation rate Secondary: ORR, PFS, number of patients with grade ≥ 3 AEs, SAEs; cancer-related pain
NCT02249702	OL, RCT. Estimated enrolment: 150 Estimated study completion date: Dec. 2017 Status: currently recruiting patients	Females ≥ 18 years of age, with metastatic or locally relapsed uterine leiomyosarcoma pretreated with conventional chemotherapy. ECOG performance status ≤ 2. Exclusion criteria: known CNS metastases	Trabectedin: 1.3 mg/m^2 will be administered via a central venous catheter as a 24-hour infusion on day 1 of 21-days treatment cycles Gemcitabine + docetaxel: Gemcitabine 900 mg/m^2 will be administered via a central venous catheter on days one and eight over 90 min, followed by	Primary: progression free rate Secondary: best response rate, PFS, OS, safety

	Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
			docetaxel 75 mg/m^2 on day eight iv over 1 h	

AE = adverse event; CNS = central nervous system; DR = duration of response; ECOG = European Eastern Cooperative Oncology Group; iv = intravenous; OL = open label; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial; SAE = serious adverse event; TTP = time to progression

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were addressed in this review.

8 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 Trabectedin (Yondelis) for Metastatic Liposarcoma or Leiomyosarcoma. 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. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

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

The 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

See section 6.2.2 for more details on literature search methods.

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** December 2015**, Embase** 1974 to 2016 January 11**, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

Line #	Searches	Results
1	(Yondelis* or trabectedin* or ET743 or ET 743 or ECT 743 or ECT743 or CCRIS 8133 or CCRIS8133 or NSC 648766 or NSC648766 or ID0YZQ2TCP or 114899-77-3 or ecteinascidin-743).ti,ot,ab,rn,hw,nm,kf.	2409
2	exp Liposarcoma/ or Leiomyosarcoma/ or (liposarcoma* or leiomyosarcoma* or leio myosarcoma* or leiomyoplastic sarcoma*).ti,ab.	36852
3	Sarcoma/	61576
4	Smooth Muscle Tumor/ or Neoplasms, Muscle Tissue/ or Neoplasms, Adipose Tissue/	16270
5	((muscle or adipose tissue* or fat tissue* or soft tissue*) and (tumor* or tumour* or cancer* or neoplasm* or sarcoma*)).ti,ab.	160526
6	or/2-5	247420
7	1 and 6	985
8	7 use pmez	267
9	7 use cctr	13
10	8 or 9	280
11	*trabectedin/ or (Yondelis* or trabectedin* or ET743 or ET 743 or ECT 743 or ECT743 or CCRIS 8133 or CCRIS8133 or NSC 648766 or NSC648766 or ecteinascidin-743).ti,ab.	1542
12	exp Liposarcoma/ or Leiomyosarcoma/ or (liposarcoma* or leiomyosarcoma* or leio myosarcoma* or leiomyoplastic sarcoma*).ti,ab.	36852
13	Soft Tissue Sarcoma/	38994
14	Muscle Tumor/ or Muscle Cancer/ or Soft Tissue Tumor/	15458

15	((muscle or adipose tissue* or fat tissue* or soft tissue*) and (tumor* or tumour* or cancer* or neoplasm* or sarcoma*)).ti,ab.	160526
16	or/12-15	216526
17	11 and 16	697
18	17 use oemezd	431
19	10 or 18	711
20	limit 19 to english language	677
21	remove duplicates from 20	456
22	(Randomized Controlled Trial or Controlled Clinical Trial).pt.	925227
23	Randomized Controlled Trial/	795909
24	Randomized Controlled Trials as Topic/	132081
25	"Randomized Controlled Trial (topic)"/	88775
26	Controlled Clinical Trial/	481320
27	Controlled Clinical Trials as Topic/	9531
28	"Controlled Clinical Trial (topic)"/	5636
29	Randomization/	174151
30	Random Allocation/	167805
31	Double-Blind Method/	335678
32	Double Blind Procedure/	127573
33	Double-Blind Studies/	221098
34	Single-Blind Method/	53737
35	Single Blind Procedure/	21272
36	Single-Blind Studies/	55248
37	Placebos/	279980
38	Placebo/	281016
39	Control Groups/	86990
40	Control Group/	86902
41	(random* or sham or placebo*).ti,ab,hw.	3078075

42	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	626285
43	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	1689
44	(control* adj3 (study or studies or trial*)).ti,ab.	1010234
45	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw.	73023
46	allocated.ti,ab,hw.	129679
47	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.	75462
48	or/22-47	3877044
49	20 and 48	124
50	9 or 49	127
51	remove duplicates from 50	94
52	21 not 51	376

2. Literature search via PubMed

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

Search	Query	Items found
#9	Search **#8 AND publisher[sb]**	8
#8	Search **#4 AND (#5 OR #6 OR #7)**	276
#7	Search **(muscle[tiab] OR adipose tissue*[tiab] OR fat tissue*[tiab] OR soft tissue*) AND (tumor*[tiab] OR tumour*[tiab] OR cancer*[tiab] OR neoplasm*[tiab] OR sarcoma*[tiab])**	74020
#6	Search **Sarcoma[mh:noexp] OR Smooth Muscle Tumor[mh] OR Neoplasms, Muscle Tissue[mh:noexp] OR Neoplasms, Adipose Tissue[mh:noexp]**	30123
#5	Search **Liposarcoma[mh] OR Leiomyosarcoma[mh] OR liposarcoma*[tiab] or leiomyosarcoma*[tiab] OR leio myosarcoma*[tiab] OR leiomyoplastic sarcoma*[tiab]**	15942
#4	Search **Trabectedin[Supplementary Concept] OR trabectedin*[tiab] OR Yondelis*[tiab] OR ET743[tiab] OR ET 743[tiab] OR ECT 743[tiab] OR ECT743[tiab] OR CCRIS 8133[tiab] OR CCRIS8133[tiab] OR NSC 648766[tiab] OR NSC648766[tiab] OR ID0YZQ2TCP[tiab] OR ecteinascidin-743[tiab]**	615

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: Yondelis, trabectedin + sarcoma

Select international agencies including:

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

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

Search: Yondelis, trabectedin

Conference abstracts:

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

Search: liposarcoma, leiomyosarcoma + Yondelis, trabectedin

- last 5 years

REFERENCES

1. George S, Demetri GD. Systemic treatment of metastatic soft tissue sarcoma. In: Post TW, editor. UpToDate [Internet]. Waltham (MA): UpToDate; 2015 [cited 2016 Mar 10]. Available from: www.uptodate.com Subscription required.

2. Sarcoma Disease Site Group. Doxorubicin-based chemotherapy for the palliative treatment of adult patients with locally advanced or metastatic soft tissue sarcoma [Internet]. Toronto: Cancer Care Ontario; 2011 Sep 15. [cited 2016 Mar 10]. (Program in Evidence-based Care Evidence-Based Series No.: 11-1 Version 2). Available from: https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=34380

3. Trabectedin: Ecteinascidin 743, Ecteinascidin-743, ET 743, ET-743, NSC 684766. Drugs R D. 2006;7(5):317-28.

4. Martin-Liberal J, Judson I. Safety evaluation of trabectedin in treatment of soft-tissue sarcomas. Expert Opin Drug Saf. 2013 Nov;12(6):905-11.

5. PrYondelis® (trabectedin): 1 mg/vial for injection [product monograph]. Toronto: Janssen; 2015 Nov 26.

6. Notice of compliance information: Yondelis. In: Drugs & health products. Ottawa: Therapeutic Products Directorate, Health Canada; 2011 Jul 14.

7. Demetri G, Patel SR, Thomas S, Livingston M, Undevia SD, Richardson G, et al. Efficacy and safety of trabectedin or dacarbazine for treatment of patients with advanced leiomyosarcoma or liposarcoma after prior chemotherapy. Poster presented at: 18th European Cancer Congress; 2015 Sep; 25-29; Vienna, Austria.

8. Gupta AA, Yao X, Verma S, Mackay H, Hopkins L, Sarcoma Disease Site Group and the Gynecology Cancer Disease Site Group. Systematic chemotherapy for inoperable, locally advanced, recurrent, or metastatic uterine leiomyosarcoma: a systematic review. Clin Oncol (R Coll Radiol). 2013 Jun;25(6):346-55.

9. Demetri GD, Chawla SP, Von Mehren M, Ritch P, Baker LH, Blay JY, et al. Efficacy and safety of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of prior anthracyclines and ifosfamide: results of a randomized phase II study of two different schedules. J Clin Oncol. 2009 Sep 1;27(25):4188-96.

10. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Medical review(s). In: Yondelis (trabectedin). Company: Janssen Application no.: 207953. Approval date: 10/23/2015 [Internet]. Rockville (MD): FDA; 2015 Oct 23 [cited 2015 Dec 23]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207953Orig1s000MedR.pdf

11. Blay JY, Leahy MG, Nguyen BB, Patel SR, Hohenberger P, Santoro A, et al. Randomised phase III trial of trabectedin versus doxorubicin-based chemotherapy as first-line therapy in translocation-related sarcomas. Eur J Cancer. 2014 Apr;50(6):1137-47.

12. Zer A, Prince RM, Amir E, Abdul RA. Evolution of randomized trials in advanced/metastatic soft tissue sarcoma: end point selection, surrogacy, and quality of reporting. J Clin Oncol. 2016 May 1;34(13):1469-75.

13. Sharma S, Takyar S, Manson SC, Powell S, Penel N. Efficacy and safety of pharmacological interventions in second- or later-line treatment of patients with advanced soft tissue sarcoma: a

systematic review. BMC Cancer [Internet]. 2013 [cited 2016 May 6];13:385. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3765173

14. Binh MB, Sastre-Garau X, Guillou L, de Pinieux G, Terrier P, Lagace R, et al. MDM2 and CDK4 immunostainings are useful adjuncts in diagnosing well-differentiated and dedifferentiated liposarcoma subtypes: a comparative analysis of 559 soft tissue neoplasms with genetic data. Am J Surg Pathol. 2005 Oct;29(10):1340-7.

15. Sirvent N, Coindre JM, Maire G, Hostein I, Keslair F, Guillou L, et al. Detection of MDM2-CDK4 amplification by fluorescence in situ hybridization in 200 paraffin-embedded tumor samples: utility in diagnosing adipocytic lesions and comparison with immunohistochemistry and real-time PCR. Am J Surg Pathol. 2007 Oct;31(10):1476-89.

16. Le Cesne A, Ouali M, Leahy MG, Santoro A, Hoekstra HJ, Hohenberger P, et al. Doxorubicin-based adjuvant chemotherapy in soft tissue sarcoma: pooled analysis of two STBSG-EORTC phase III clinical trials. Ann Oncol. 2014 Dec;25(12):2425-32.

17. Woll PJ, Reichardt P, Le Cesne A, Bonvalot S, Azzarelli A, Hoekstra HJ, et al. Adjuvant chemotherapy with doxorubicin, ifosfamide, and lenograstim for resected soft-tissue sarcoma (EORTC 62931): a multicentre randomised controlled trial. Lancet Oncol. 2012 Oct;13(10):1045-54.

18. Pautier P, Floquet A, Gladieff L, Bompas E, Ray-Coquard I, Piperno-Neumann S, et al. A randomized clinical trial of adjuvant chemotherapy with doxorubicin, ifosfamide, and cisplatin followed by radiotherapy versus radiotherapy alone in patients with localized uterine sarcomas (SARCGYN study). A study of the French Sarcoma Group. Ann Oncol. 2013 Apr;24(4):1099-104.

19. 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.

20. Hensley ML, Blessing JA, Degeest K, Abulafia O, Rose PG, Homesley HD. Fixed-dose rate gemcitabine plus docetaxel as second-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II study. Gynecol Oncol [Internet]. 2008 Jun [cited 2016 Jan 14];109(3):323-8. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2692926

21. Hensley ML, Blessing JA, Mannel R, Rose PG. Fixed-dose rate gemcitabine plus docetaxel as first-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II trial. Gynecol Oncol [Internet]. 2008 Jun [cited 2016 Jan 14];109(3):329-34. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2504727

22. 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.

23. Pautier P, Floquet A, Penel N, Piperno-Neumann S, Isambert N, Rey A, et al. Randomized multicenter and stratified phase II study of gemcitabine alone versus gemcitabine and docetaxel in patients with metastatic or relapsed leiomyosarcomas: a Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) French Sarcoma Group Study (TAXOGEM study). Oncologist [Internet]. 2012 [cited 2016 Jan 14];17(9):1213-20. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3448415

24. Gupta AA, Yao X, Verma S, Mackay H, Hopkins L. Chemotherapy (gemcitabine, docetaxel plus gemcitabine, doxorubicin, or trabectedin) in inoperable, locally advanced, recurrent, or metastatic

uterine leiomyosarcoma: a clinical practice guideline. Curr Oncol [Internet]. 2013 Oct [cited 2016 Jan 14];20(5):e448-e454. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3805413

25. Seddon BM, Whelan J, Strauss SJ, Leahy MG, Woll PJ, Cowie F, et al. GeDDiS: A prospective randomised 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 May 20;33(15 Suppl 1):abstr 10500. Available from: http://meetinglibrary.asco.org/content/144877-156 (Presented at Annual Meeting of the American Society of Clinical Oncology; 2015 May 29-June 2; Chicago, Illinois).

26. Antman KH, Ryan L, Elias A, Sherman D, Grier HE. Response to ifosfamide and mesna: 124 previously treated patients with metastatic or unresectable sarcoma. J Clin Oncol. 1989 Jan;7(1):126-31.

27. Bramwell VH, Mouridsen HT, Santoro A, Blackledge G, Somers R, Verweij J, et al. Cyclophosphamide versus ifosfamide: a randomized phase II trial in adult soft-tissue sarcomas. The European Organization for Research and Treatment of Cancer [EORTC], Soft Tissue and Bone Sarcoma Group. Cancer Chemother Pharmacol. 1993;31 Suppl 2:S180-S184.

28. Buesa JM, Lopez-Pousa A, Martin J, Anton A, Garcia del Muro J, Bellmunt J, et al. Phase II trial of first-line high-dose ifosfamide in advanced soft tissue sarcomas of the adult: a study of the Spanish Group for Research on Sarcomas (GEIS). Ann Oncol. 1998 Aug;9(8):871-6.

29. Gullu I, Yalcin S, Tekuzman G, Barista I, Alkis N, Celik I, et al. High-dose ifosfamide by infusion with Mesna in advanced refractory sarcomas. Cancer Invest. 1996;14(3):239-42.

30. Le Cesne A, Antoine E, Spielmann M, Le Chevalier T, Brain E, Toussaint C, et al. High-dose ifosfamide: circumvention of resistance to standard-dose ifosfamide in advanced soft tissue sarcomas. J Clin Oncol. 1995 Jul;13(7):1600-8.

31. Lopez M, Carpano S, Amodio A, Gionfra T, Della GM, Foggi P, et al. Single-agent ifosfamide in the treatment of anthracycline-refractory adult sarcomas. Clin Ter. 1998 Sep;149(5):331-3.

32. Nielsen OS, Judson I, van Hoesel Q, Le Cesne A, Keizer HJ, Blay JY, et al. Effect of high-dose ifosfamide in advanced soft tissue sarcomas. A multicentre phase II study of the EORTC Soft Tissue and Bone Sarcoma Group. Eur J Cancer. 2000 Jan;36(1):61-7.

33. Palumbo R, Palmeri S, Antimi M, Gatti C, Raffo P, Villani G, et al. Phase II study of continuous-infusion high-dose ifosfamide in advanced and/or metastatic pretreated soft tissue sarcomas. Ann Oncol. 1997 Nov;8(11):1159-62.

34. Patel SR, Vadhan-Raj S, Papadopolous N, Plager C, Burgess MA, Hays C, et al. High-dose ifosfamide in bone and soft tissue sarcomas: results of phase II and pilot studies--dose-response and schedule dependence. J Clin Oncol. 1997 Jun;15(6):2378-84.

35. Sutton GP, Blessing JA, Barrett RJ, McGehee R. Phase II trial of ifosfamide and mesna in leiomyosarcoma of the uterus: a Gynecologic Oncology Group study. Am J Obstet Gynecol. 1992 Feb;166(2):556-9.

36. Tursz T. High-dose ifosfamide in the treatment of advanced soft tissue sarcomas. Semin Oncol. 1996 Jun;23(3 Suppl 7):34-9.

37. van Oosterom AT, Mouridsen HT, Nielsen OS, Dombernowsky P, Krzemieniecki K, Judson I, et al. Results of randomised studies of the EORTC Soft Tissue and Bone Sarcoma Group (STBSG) with two

different ifosfamide regimens in first- and second-line chemotherapy in advanced soft tissue sarcoma patients. Eur J Cancer. 2002 Dec;38(18):2397-406.

38. Yalcin B, Pamir A, Buyukcelik A, Utkan G, Akbulut H, Demirkazik A, et al. High-dose ifosfamide with hematopoietic growth factor support in advanced bone and soft tissue sarcomas. Exp Oncol. 2004 Dec;26(4):320-5.

39. Sanfilippo R, Bertulli R, Marrari A, Fumagalli E, Pilotti S, Morosi C, et al. High-dose continuous-infusion ifosfamide in advanced well-differentiated/dedifferentiated liposarcoma. Clin Sarcoma Res [Internet]. 2014 [cited 2016 Jan 14];4(1):16. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4307996

40. Van Glabbeke M, Verweij J, Judson I, Nielsen OS, EORTC Soft Tissue and Bone Sarcoma Group. Progression-free rate as the principal end-point for phase II trials in soft-tissue sarcomas. Eur J Cancer. 2002 Mar;38(4):543-9.

41. Garcia-Del-Muro X, Lopez-Pousa A, Maurel J, Martin J, Martinez-Trufero J, Casado A, et al. Randomized phase II study comparing gemcitabine plus dacarbazine versus dacarbazine alone in patients with previously treated soft tissue sarcoma: a Spanish Group for Research on Sarcomas study. J Clin Oncol. 2011 Jun 20;29(18):2528-33.

42. Dickson MA, Tap WD, Keohan ML, D'Angelo SP, Gounder MM, Antonescu CR, et al. Phase II trial of the CDK4 inhibitor PD0332991 in patients with advanced CDK4-amplified well-differentiated or dedifferentiated liposarcoma. J Clin Oncol [Internet]. 2013 Jun 1 [cited 2016 Jan 14];31(16):2024-8. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3661937

43. Towle MJ, Salvato KA, Budrow J, Wels BF, Kuznetsov G, Aalfs KK, et al. In vitro and in vivo anticancer activities of synthetic macrocyclic ketone analogues of halichondrin B. Cancer Res. 2001 Feb 1;61(3):1013-21.

44. Jordan MA, Kamath K, Manna T, Okouneva T, Miller HP, Davis C, et al. The primary antimitotic mechanism of action of the synthetic halichondrin E7389 is suppression of microtubule growth. Mol Cancer Ther. 2005 Jul;4(7):1086-95.

45. Smith JA, Wilson L, Azarenko O, Zhu X, Lewis BM, Littlefield BA, et al. Eribulin binds at microtubule ends to a single site on tubulin to suppress dynamic instability. Biochemistry [Internet]. 2010 Feb 16 [cited 2016 Jan 14];49(6):1331-7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2846717

46. Funahashi Y, Okamoto K, Adachi Y, Semba T, Uesugi M, Ozawa Y, et al. Eribulin mesylate reduces tumor microenvironment abnormality by vascular remodeling in preclinical human breast cancer models. Cancer Sci [Internet]. 2014 Oct [cited 2016 Jan 14];105(10):1334-42. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4462349

47. Agoulnik SI, Kawano S, Taylor N, Oestreicher J, Matsui J, Chow J, et al. Eribulin mesylate exerts specific gene expression changes in pericytes and shortens pericyte-driven capillary network in vitro. Vasc Cell [Internet]. 2014 [cited 2016 Jan 14];6(1):3. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4016419

48. Yoshida T, Ozawa Y, Kimura T, Sato Y, Kuznetsov G, Xu S, et al. Eribulin mesilate suppresses experimental metastasis of breast cancer cells by reversing phenotype from epithelial-mesenchymal transition (EMT) to mesenchymal-epithelial transition (MET) states. Br J Cancer [Internet]. 2014 Mar

18 [cited 2016 Jan 14];110(6):1497-505. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3960630

49. Schoffski P, Ray-Coquard IL, Cioffi A, Bui NB, Bauer S, Hartmann JT, et al. Activity of eribulin mesylate in patients with soft-tissue sarcoma: a phase 2 study in four independent histological subtypes. Lancet Oncol. 2011 Oct;12(11):1045-52.

50. De Sanctis R, Marrari A, Marchetti S, Mussi C, Balzarini L, Lutman FR, et al. Efficacy of trabectedin in advanced soft tissue sarcoma: beyond lipo- and leiomyosarcoma. Drug Des Devel Ther [Internet]. 2015 [cited 2016 Jan 14];9:5785-91. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4629957

51. Sanfilippo R, Dileo P, Blay JY, Constantinidou A, Le Cesne A, Benson C, et al. Trabectedin in advanced synovial sarcomas: a multicenter retrospective study from four European institutions and the Italian Rare Cancer Network. Anticancer Drugs. 2015 Jul;26(6):678-81.

52. Kawai A, Araki N, Sugiura H, Ueda T, Yonemoto T, Takahashi M, et al. Trabectedin monotherapy after standard chemotherapy versus best supportive care in patients with advanced, translocation-related sarcoma: a randomised, open-label, phase 2 study. Lancet Oncol. 2015 Apr;16(4):406-16.

53. Le Cesne A, Cresta S, Maki RG, Blay JY, Verweij J, Poveda A, et al. A retrospective analysis of antitumour activity with trabectedin in translocation-related sarcomas. Eur J Cancer. 2012 Nov;48(16):3036-44.

54. Le Cesne A, Ray-Coquard I, Duffaud F, Chevreau C, Penel N, Bui NB, et al. Trabectedin in patients with advanced soft tissue sarcoma: a retrospective national analysis of the French Sarcoma Group. Eur J Cancer. 2015 Apr;51(6):742-50.

55. Le Cesne A, Blay JY, Domont J, Tresch-Bruneel E, Chevreau C, Bertucci F, et al. Interruption versus continuation of trabectedin in patients with soft-tissue sarcoma (T-DIS): a randomised phase 2 trial. Lancet Oncol. 2015 Mar;16(3):312-9.

56. 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.

57. 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 2016 Mar 12];34(8):786-93. Available from: http://jco.ascopubs.org/content/early/2015/09/14/JCO.2015.62.4734.full.pdf+html

58. Demetri GD, Von Mehren M, Jones RL, Hensley ML, Schuetze S, Staddon AP, et al. A randomized phase III study of trabectedin (T) or dacarbazine (D) for the treatment of patients (pts) with advanced liposarcoma (LPS) or leiomyosarcoma (LMS) [abstract]. J Clin Oncol [Internet]. 2015 [cited 2016 Jan 26];33(15 Suppl 1). Available from: http://meeting.ascopubs.org/cgi/content/abstract/33/15_suppl/10503?sid=6c858718-c485-419e-ac35-9d744063513e (Presented at Annual Meeting of the American Society of Clinical Oncology; 2015 May 29-June 2; Chicago, Illinois).

59. Von Mehren M, Demetri GD, Schuetze SM, Jones RL, Milhem M, Elias A, et al. Efficacy and safety of trabectedin (T) or dacarbazine (D) in an elderly patient subgroup (>65 years) with advanced

leiomyosarcoma (LMS) or liposarcoma (LPS) after prior chemotherapy [abstract]. Eur J Cancer. 2015;51(Suppl 3):S194. (Presented at European Cancer Congress; 2015 Sept 25-29; Vienna, Austria).

60. Patel S, Von Mehren M, Reed D, Agulnik M, Kaiser P, Charlson J, et al. Final overall survival (OS) analysis of the randomized phase 3 study of trabectedin (T) or dacarbazine (D) for the treatment of patients (pts) with advanced leiomyosarcoma (LMS) or liposarcoma (LPS) [abstract]. Eur J Cancer. 2015;51 Suppl 3:S689. (Presented at European Cancer Congress; 2015; Sept 25-29; Vienna, Austria).

61. pan-Canadian Oncology Drug Review manufacturer submission: Yondelis® (trabectedin), 1 mg/vial sterile lyophilized powder for IV infusion. Company: Janssen Inc. Toronto (ON): Janssen Inc.; 2015 Dec 22.

62. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Statistical review(s). In: Yondelis (trabectedin). Company: Janssen Application no.: 207953. Approval date: 10/23/2015 [Internet]. Rockville (MD): FDA; 2015 Oct 23 [cited 2015 Dec 23]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207953Orig1s000StatR.pdf

63. Janssen Research & Development, LLC. A study of trabectedin or dacarbazine for the treatment of patients with advanced liposarcoma or leiomyosarcoma. 2011 Apr 26 [cited 2016 Mar 10; last updated 2015 Dec 22; results first received 2015 Dec 22]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/NCT01343277?term=NCT01343277 Identifier: NCT01343277.

64. Protocol for: 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. 2016 Mar 10;34(8):786-93. [Internet]. Toronto: Janssen Research & Development; 2014 Nov 12. Document No.: EDMS-ERI-14393045:5.0. [cited 2016 Mar 17]. Available from: http://jco.ascopubs.org/content/suppl/2015/09/14/JCO.2015.62.4734.DC1/Protocol_2015.624734.pdf

65. U.S. FDA approves Yondelis® (trabectedin) for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma, two common subtypes of soft tissue sarcoma [Internet]. New Brunswick (NJ): Johnson & Johnson; 2015 Oct 23. [cited 2016 Mar 17]. Available from: http://www.jnj.com/news/all/US-FDA-Approves-YONDELIS-trabectedin-for-the-treatment-of-patients-with-Unresectable-or-Metastatic-Liposarcoma-or-Leiomyosarcoma

66. Janssen response to pCODR checkpoint meeting questions on trabectedin (Yondelis) for metastatic liposarcoma or leiomyosarcoma [additional manufacturer's information]. Toronto: Janssen; 2016 Mar 1.