Expert Review of Anticancer Therapy

ISSN: 1473-7140 (Print) 1744-8328 (Online) Journal homepage: http://www.tandfonline.com/loi/iery20

Preserving quality of life as a key treatment goal in advanced soft tissue sarcoma

Robin L Jones, Axel Le Cesne, Tony Ibrahim, Xavier Garcia del Muro & Franka Menge

To cite this article: Robin L Jones, Axel Le Cesne, Tony Ibrahim, Xavier Garcia del Muro & Franka Menge (2018): Preserving quality of life as a key treatment goal in advanced soft tissue sarcoma, Expert Review of Anticancer Therapy, DOI: 10.1080/14737140.2018.1524298

To link to this article: https://doi.org/10.1080/14737140.2018.1524298

Accepted author version posted online: 17 Sep 2018.

Publisher: Taylor & Francis

Journal: *Expert Review of Anticancer Therapy*

DOI: 10.1080/14737140.2018.1524298

Preserving quality of life as a key treatment goal in advanced soft tissue sarcoma

Robin L Jones[a], Axel Le Cesne[b], Tony Ibrahim[b], Xavier Garcia del Muro[c], Franka Menge[d]

[a]Sarcoma Unit, Royal Marsden Hospital, Institute of Cancer Research, London, United Kingdom robin.jones4@nhs.net

[b]Department of Medical Oncology, Gustave Roussy, Villejuif, France
Axel.LECESNE@gustaveroussy.fr; TONY.IBRAHIM@gustaveroussy.fr

[c]Medical Oncology Department, Institute Catalan of Oncology, Barcelona, Spain
garciadelmuro@iconcologia.net

[d]Division of Surgical Oncology & Thoracic Surgery, Mannheim University Medical Center, Mannheim, Germany franka.menge@umm.de

Corresponding author:

Dr RL Jones, Sarcoma Unit, Royal Marsden Hospital/Institute of Cancer Research, Fulham Road, London, SW3 6JJ, UK.

Email: robin.jones4@nhs.net

Funding

This paper was funded by PharmaMar SA, Madrid, Spain.

Writing assistance was provided by Content Ed Net (Madrid, Spain) with funding from PharmaMar SA, Madrid, Spain.

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Preserving quality of life as a key treatment goal in advanced soft tissue sarcoma

Robin L Jones[a], Axel Le Cesne[b], Tony Ibrahim[b], Xavier Garcia del Muro[c], Franka Menge[d]

[a]Sarcoma Unit, Royal Marsden Hospital, Institute of Cancer Research, London, United Kingdom robin.jones4@nhs.net
[b]Department of Medical Oncology, Gustave Roussy, Villejuif, France
Axel.LECESNE@gustaveroussy.fr; TONY.IBRAHIM@gustaveroussy.fr
[c]Medical Oncology Department, Institute Catalan of Oncology, Barcelona, Spain
garciadelmuro@iconcologia.net
[d]Division of Surgical Oncology & Thoracic Surgery, Mannheim University Medical Center, Mannheim, Germany franka.menge@umm.de

Corresponding author:
Dr RL Jones, Sarcoma Unit, Royal Marsden Hospital/Institute of Cancer Research, Fulham Road, London, SW3 6JJ, UK.
Email: robin.jones4@nhs.net

Funding
This paper has received funding from PharmaMar SA, Madrid, Spain

Declaration of interest
Writing assistance was provided by Content Ed Net (Madrid, Spain) with funding from PharmaMar SA, Madrid, Spain.
The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer Disclosures
Peer reviewers on this manuscript have no relevant financial or other relationships to disclose

Abstract

Introduction: Health-related quality of life (HRQoL) is a patient-reported outcome that addresses patients' perceptions of symptoms across physical, emotional, cognitive and social domains. As HRQoL is currently rarely measured outside clinical trials in oncology, it must be inferred from patients' everyday performance during treatment. To gain insight into the HRQoL of advanced STS patients receiving palliative treatment in clinical practice, three case studies of patients treated with trabectedin are examined.

Areas covered: The patient in Case 1 has maintained complete remission for more than 8 years after receiving 9 cycles of second-line trabectedin followed by secondary surgery for recurrent myxoid liposarcoma, and was able to resume normal activities during trabectedin treatment. Case 2 describes 10 years' follow-up of a patient with myxoid liposarcoma who remains well after many lines of chemotherapy including extended use of trabectedin in the second line. The third case illustrates the feasibility of extending survival time in an elderly patient with metastatic leiomyosarcoma who was able to maintain a busy and active lifestyle while receiving second-line trabectedin.

Expert commentary: Owing to its relatively benign safety profile, trabectedin frequently permits prolonged therapy and is generally well tolerated, often allowing patients to carry on with normal daily activities.

Key words: health-related quality of life; soft tissue sarcomas; trabectedin

1. Introduction

Disease management is increasingly becoming patient-centric. A patient's own report of a response to treatment or health care that is not subject to interpretation by a clinician or healthcare professional is known as a patient-reported outcome (PRO). PROs typically deal with aspects of the patient's health, functional status or quality of life (QoL) [1]. An important PRO in the oncological setting is health-related quality of life (HRQoL) which addresses patients' perceptions of symptoms across physical, emotional, cognitive and social domains [2,3]. HRQoL data, along with sociodemographic variables and clinical measures, are prognostic indicators for overall survival in a range of cancers [3–5].

Multiple instruments, either disease-specific or generic, have been used to measure HRQoL in oncology. The cancer-specific European Organization for Research and Treatment of Cancer 30-item core QoL questionnaire (EORTC QLQ-C30) [7] is widely used, for example by Quinten and colleagues [3–5], to demonstrate the prognostic value of HRQoL domain data. For patients with soft tissue sarcomas (STS) and extremity bone sarcomas, the Toronto Extremity Salvage Score (TESS) is a disease-specific PRO to evaluate physical function [8]. Generic instruments used to assess HRQoL in cancer patients include the 36-item Short Form 36 (SF-36) [9]. A standardized instrument for measuring generic health status is the five-dimensional instrument (EQ-5D) developed by the EuroQol Group. Alongside condition-specific PROs, there is growing use of the EQ-5D as part of routine, administrative data collection in healthcare systems to generate real-world insights into treatment and provider effectiveness [11].

Although only few studies in patients with sarcomas have included QoL as an endpoint, they indicate that HRQoL deteriorates with disease progression. In patients with metastatic STS or bone sarcomas, application of the EORTC QLQ-C30 and EQ-5D instruments showed that disease progression had a significant negative impact on HRQoL, with patients receiving second-line treatment reporting lower health utility than those receiving first-line therapy [12]. Application of the EORTC QLQ-C30 tool in the PALETTE trial for patients with

advanced STS receiving pazopanib or placebo for second-line or later therapy showed no statistically significant between-group differences in QOL-C30 global health status and a trend towards a decline in mean global health status over time in both treatment arms [13]. In the randomized phase III SAR-3007 trial comparing trabectedin and dacarbazine in patients with advanced leiomyosarcoma or liposarcoma [14], patients completed the MD Anderson Symptom Inventory, a self-reported 19-item questionnaire that captures experience across 13 symptom measures and six measures of physical and mental functions. No clinically meaningful differences between treatment arms were observed, although symptom burden at baseline was relatively low and minimal symptom and functional interference was maintained for the duration of both treatments.

HRQoL is rarely formally measured in oncology clinical studies, and much less frequently if at all in routine clinical practice. In clinical practice, patients' QoL must be inferred by other means such as their everyday performance during or after local or systemic treatment.

Chemotherapy is the mainstay of treatment for patients with advanced or metastatic STS. Selecting the best chemotherapeutic regimen for an individual patient requires evaluation of various patient- and tumor-related factors as well as the patient's goals and expectations of treatment [15]. Certain clinical situations demand an aggressive treatment approach to reduce tumor burden or alleviate symptoms, whereas other situations call for a palliative approach with the aims of long-term disease control and preservation of QoL [15]. To gain insight into the QoL of patients with advanced STS receiving chemotherapy in routine clinical practice, we present three case studies of patients treated with trabectedin in the second line, with a focus on patients' ability to perform usual daily activities under treatment.

2. Case studies

2.1 . Case 1

In July 2008, a 23-year-old female presented a bulky mediastinal and intra-thoracic right side tumor manifested by dyspnea and weight loss. Diagnosis was grade (G) 1 myxoid liposarcoma. Three cycles of neoadjuvant doxorubicin + ifosfamide led to stable disease but with severe associated adverse effects, mainly febrile neutropenia. Computed tomography (CT) scans showed a mixed (fat + fleshy) lesion in the right thoracic hemisphere with a left side mediastinal shift (Figure 1). Following agreement by surgeons that complete resection was feasible in this patient, R0 surgery was performed followed by adjuvant radiotherapy 50 Gy / 25 fraction which was standard protocol at the time of treatment. In September 2009 (6 months after adjuvant radiotherapy), the patient had a symptomatic intrathoracic recurrence confirmed by biopsy. Trabectedin commenced at a dose of 1.5 mg/m^2 although had to be reduced due to elevated liver enzymes (10 $\times$ upper limit of normal); bilirubin remained normal and clinical symptoms were absent. Major clinical improvement was observed during trabectedin treatment and, in the absence of symptomatic adverse events, the patient was able to resume normal activities. After 9 cycles of trabectedin, CT scan showed complete remission of the first lesion and a major response in the second lesion in the right lobe of the thymus (Figure 2). Positron-emission tomography (PET) indicated no disease activity. In May 2010, the thymus was surgically resected. Pathological examination indicated no tumor cells and only fibrosis. For 8 years since, the patient has undergone regular surveillance with no signs of recurrence.

2.2. Case 2

Case 2 involves a male patient aged 37 years at the time of diagnosis (July 2008) with antecedents of an appendectomy in 1987. He was diagnosed with a 10 cm soft tissue tumor located in the thoracic wall, in the right posterior costophrenic sinus. Core needle biopsy

indicated myxoid liposarcoma. A right thoracotomy was performed on 31 July 2008. Pathology was reported as a G2 myxoid liposarcoma, $10 \times 7 \times 3$ cm in size, with vascular invasion. Resection was marginal. Post-surgery, the patient received external radiotherapy combined with brachytherapy in the thoracic wall (66 Gy).

CT scan in December 2011 detected a right apical pulmonary mass which was confirmed by biopsy as relapsed myxoid liposarcoma. In February 2012, the patient underwent surgical resection by cervico-sterno-thoracotomy. Pathology indicated G2 myxoid liposarcoma, 6 cm in diameter. Post-operative radiation (66 Gy) was administered.

In March 2013, the patient presented a right paratracheal mediastinal mass of 4 cm, a right paravertebral retrocrural mass of 6.6 cm and four liver metastases (the largest being 2.8 cm). He was enrolled in the phase III randomized clinical trial of doxorubicin ± evofosfamide (TH-CR-406) [16], and allocated to doxorubicin 75 mg/m^2 monotherapy which commenced in April 2013. Several episodes of G4 neutropenia, without associated fever, necessitated delay of subsequent cycles to every 4 weeks instead of every 3 weeks. After 2 cycles of doxorubicin, stable disease was observed and, after 4 cycles, CT scan showed a partial response. The patient completed 6 cycles of chemotherapy in July 2013.

In July 2014 the patient presented with progression of the retrocrural lesion (9 cm) and liver metastases, the largest being 2.1 cm. Treatment commenced with trabectedin 1.5 mg/m^2 in a 24 h infusion every 3 weeks, with good tolerability. Adverse events were limited to mild asthenia, sporadic nausea, and asymptomatic G3 neutropenia which was managed by administering prophylactic granulocyte-colony stimulating factor (G-CSF) for 5 days in subsequent cycles. During treatment, he maintained an active life, taking care of his two young children and travelling with them between cycles. After four cycles of trabectedin, a CT scan showed a partial response in the liver metastases and retrocrural mass. CT images before and after 6 cycles of trabectedin are shown in Figure 3. Ten cycles of trabectedin were delivered, ending in April 2015. During the two last cycles, asthenia worsened (still G1 but more prolonged). The patient was weary of chemotherapy and requested a break. The partial

response was maintained until February 2016, when a CT scan showed an increase in the size of the liver metastases (largest 4.5 cm) and retrocrural lesion. Trabectedin rechallenge (1.5 mg/m^2 in 24 h) commenced and 6 cycles were delivered, ending in August 2016 due to worsening asthenia. Treatment was well tolerated, although asymptomatic G3 neutropenia despite prophylactic G-CSF led to frequent 1-week delays in administration of the next cycle. After 3 cycles of trabectedin, a CT scan revealed a new partial response which was maintained until January 2017. CT images pre- and post-rechallenge with trabectedin (6 cycles) are shown in Figure 4.

There was no response to third-line therapy with gemcitabine + dacarbazine (× 3 months). Eribulin led to stable disease but treatment was stopped after 3 cycles due to polyneuropathy; disease progressed within 3 months. Ifosfamide was initiated and was ongoing at the time of writing.

2.3. Case 3

Case 3 involves a 65-year-old female patient who presented in June 2013 to her general practitioner with diffuse intra-abdominal pain. Initially the pain occurred only in the morning but worsened over ensuing months; at first presentation to hospital it was described as occurring after every meal. Symptoms such as night sweats, weight loss or loss of appetite were absent. Medical history included arterial hypertension, hypothyroidism and a tubal pregnancy more than 30 years ago. She had no history of a previous serious illness, nor any intra-abdominal operations.

A thoracic and abdominal CT scan showed a large (13.5 × 12.0 × 10 cm) right retroperitoneal mass presumably related to the adrenal gland. Liver infiltration was suggested, and two suspicious intrapulmonary lesions were described. Ultrasound-guided core needle biopsy led to a diagnosis of a G2 (French Federation of Comprehensive Cancer Centers) leiomyosarcoma.

Explorative laparoscopy identified three small, previously unknown liver lesions which were diagnosed as metastases by instantaneous section. Infiltration of the caudate lobe precluded opportunity for a reasonable tumor resection.

Following the patient's recovery from surgery, first-line doxorubicin 75 mg/m^2 was administered every 3 weeks for 6 cycles. G-CSF support was required after the third cycle due to a low neutrophil count. The doxorubicin dose was reduced to 60 mg/m^2 for the last 2 cycles due to worsening of her general condition, especially asthenia and progressive thrombocytopenia. She tolerated doxorubicin reasonably well and, after 6 cycles, the unresectable intra-abdominal tumor was reduced in size to 9.0 cm. Fractionated radiotherapy (total dose of 54 Gy) given to consolidate the tumor was well tolerated.

A follow-up CT scan a year later showed growing intrahepatic and intrapulmonary metastases although, clinically, the patient was in good condition. Second-line trabectedin was initiated and 12 cycles were delivered. Pulmonary metastases during and at the end of trabectedin therapy are shown in Figure 5. The trabectedin dose had to be reduced gradually from 1.5 mg/m^2 (24 h) to 1.0 mg/m^2 (24 h) due to elevated liver enzymes (>10 × upper limit of normal), although bilirubin remained normal and clinical symptoms were absent. G-CSF support due to transient afebrile G4 neutropenia was required for cycles in which the trabectedin dose was above 1.0 mg/m^2. The best outcome under trabectedin was stable disease. During the entire course of therapy, the patient maintained normal daily activities: she managed the household, cared for herself, looked after her grandchildren, travelled in her mobile home for holidays, went on bicycle tours; and managed support services for her mother who had also been diagnosed with sarcoma.

After 12 cycles of trabectedin, the patient presented again with growing intrahepatic and intrapulmonary metastases while the irradiated intra-abdominal tumor remained stable. Third-line therapy with pazopanib was started but stopped when she developed an acute infarction of the medial cerebral artery with transient paresis of her right hand. As the patient remained in reasonably good general health she agreed to fourth-line therapy with gemcitabine +

dacarbazine. After two cycles, the tumor progressed with rapid onset of growing intrahepatic and intrapulmonary lesions, as well as diffuse intramuscular and subcutaneous metastases. As her general condition deteriorated quickly, the therapeutic strategy was switched to best supportive care. The patient died 28 months after first diagnosis of leiomyosarcoma. Figure 6 shows an intra-abdominal mass and liver metastases during and at the end of treatment with trabectedin, and under third-line (pazopanib) and fourth-line (gemcitabine + dacarbazine) therapy.

3. Expert commentary

Consistent with the results of previous phase II [17] and phase III [18] clinical trials and real-life studies [19–21] reporting on second-line use of trabectedin in advanced liposarcoma and leiomyosarcoma, trabectedin showed good efficacy in these patients. To provide some perspective on the distinguishing features of trabectedin in the palliative setting in advanced sarcoma, key elements of each case are summarized below.

The patient in Case 1 received 9 cycles of second-line trabectedin followed by secondary surgery for a recurrent G1 myxoid liposarcoma, achieving a complete response in one lesion and a major response in the other lesion which facilitated curative surgery (Figure 7). In the absence of symptomatic adverse events, she was able to resume normal activities, although a dose reduction was required due to the presence of elevated liver enzymes [22]. Transient elevations in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) tend to be more common during the first two cycles of trabectedin then decline in subsequent cycles and, as indicated, can be managed with dose reductions [17,18,21].

In Case 2, standard first-line doxorubicin monotherapy for metastatic myxoid liposarcoma produced a partial response despite 1-week delays in the dosing interval due to G4 neutropenia. At recurrence, treatment commenced with second-line trabectedin which was mainly well tolerated with G-CSF support for asymptomatic G3 neutropenia. The patient

maintained an active life during treatment including taking care of two young children. Ten cycles of trabectedin were administered, resulting in a partial response after 4 cycles and a progression-free interval of approximately 19 months. Trabectedin rechallenge (× 6 cycles) at recurrence resulted in a new partial response. Clinical benefit with trabectedin rechallenge has been reported in patients with responding myxoid liposarcomas [23]. Around the time that the patient had completed his first course of trabectedin, it was reported that treatment continuation is superior to treatment interruption in terms of 6-month progression-free survival (51.9 *vs* 23.1%; p = 0.02) in patients with advanced doxorubicin-refractory STS who have not progressed after receiving 6 cycles of trabectedin [24]. Nevertheless, despite the treatment interruption, the patient achieved a new partial response to trabectedin rechallenge which was maintained for approximately 9 months. He remains alive approximately 10 years after initial diagnosis (Figure 8).

Case 3 illustrates the feasibility of extending survival time in an elderly patient with metastatic leiomyosarcoma (Figure 9). Standard first-line doxorubicin therapy resulted in a partial response, although G-CSF support and dose reductions were required to manage various toxicities. At disease recurrence, second-line treatment with trabectedin commenced which was maintained for 12 cycles. Adverse events were managed by dose reductions and G-CSF support as required. During trabectedin treatment, the patient maintained an active and busy lifestyle including managing her own affairs as well as support services for her seriously ill mother. A retrospective pooled analysis of phase II trials of trabectedin involving 350 STS patients indicated that trabectedin is a feasible option regardless of patient age (< 60 years, ≥ 60 years), providing meaningful clinical benefit with an acceptable and manageable safety profile [25].

For most patients with refractory STS, the main therapeutic goal is long-term disease stabilization with good QoL [15]. Collectively, these case studies highlight several features of trabectedin that set it apart from other chemotherapeutic agents for palliative treatment of advanced STS. The relatively benign safety profile of trabectedin compared with other chemotherapeutic agents frequently allows for prolonged treatment and makes trabectedin

suitable for use in the elderly. Adverse effects that do occur with trabectedin can generally be readily managed with dose reductions and G-CSF support. In the event of treatment interruption (e.g. a patient requests a 'drug holiday'), trabectedin rechallenge is a feasible and effective approach. During treatment with trabectedin, many patients are able to carry out normal daily activities, with inferred less detriment to their HRQoL compared with other chemotherapeutic options for use in advanced sarcoma. Indeed, until such time as PROs are integrated into daily clinical practice, a few simple questions about a patient's everyday life might serve as a useful surrogate measure of HRQol. Importantly, the good tolerability of trabectedin does not come at the cost of compromised efficacy as patients can benefit from an active treatment capable of producing prolonged stable disease.

4. Five-year view

In the palliative setting of advanced STS, understanding the effectiveness of treatment from a patient's perspective is essential to inform the selection of options that adequately address his/her individual needs. As such, interest in incorporating PROs into clinical research and routine practice is growing. PRO provide first-hand insight into patients' health status, treatment satisfaction, well-being, and HRQoL.

Leading the way in this regard is YonLife (ClinicalTrials.gov identifier: NCT02204111), a prospective study designed to explore the effect of a multidisciplinary expert consensus on QoL in patients with metastatic STS [26,27]. The study involved seven sites in Germany and was completed in September 2017. Adult patients under treatment with trabectedin were randomized to receive multidimensional intervention or usual supportive treatment (control group). The intervention group received individualized treatment proposals compiled by an expert panel based on a patient's self-assessed HRQoL using a standard online questionnaire (FACT-G) and supplemented with clinical data derived from the patient file. Despite

methodological uncertainties regarding the choice of PROs for assessment as well as the practicality of proposing treatment for patients not encountered in person, this ambitious study has the potential to provide a platform for future patient-directed research. At minimum, the study will provide greater insight into HRQoL in patients with advanced STS receiving treatment with trabectedin. The results are awaited with interest.

Key issues

A patient's own report of a response to treatment or health care that is not subject to interpretation by a clinician or healthcare professional is known as a patient-reported outcome (PRO).

PROs typically deal with aspects of a patient's health, functional status or health-related quality of life (HRQoL).

HRQoL is rarely formally measured in oncology clinical studies and much less so in clinical practice; thus, it must be inferred by other means such as the ability of a patient to carry out usual daily activities during or after treatment.

This review presents three case studies of patients with advanced STS under treatment with trabectedin.

The patient in Case 1 has maintained complete remission for more than 8 years after receiving 9 cycles of second-line trabectedin followed by secondary surgery for a recurrent myxoid liposarcoma. In the absence of symptomatic adverse events during trabectedin treatment, she was able to resume normal activities.

The second case describes 10 years' follow-up of a patient with myxoid liposarcoma who remains well after many lines of chemotherapy. He achieved partial responses during second-line treatment with trabectedin and subsequent rechallenge and maintained an active life during treatment.

The third case illustrates the feasibility of extending survival time with trabectedin in an elderly patient with metastatic leiomyosarcoma. During the entire course of trabectedin (12 cycles), the patient was able to maintain a busy and active lifestyle.

Owing to its relatively benign safety profile, trabectedin frequently permits patients to benefit from an active treatment for prolonged periods and is generally well tolerated, often allowing patients to carry on with normal daily activities.

References

1. Weldring T, Smith SM. Patient-reported outcomes (PROs) and patient-reported outcome measures (PROMs). Health Serv Insights. 2013;6:61–68.
   ***Provides an overview of patients' involvement in clinical research and service evaluation along with the benefits and limitations.**

2. Bottomley A. The cancer patient and quality of life. Oncologist. 2002;7(2):120–125.

3. Osoba D. Health-related quality of life and cancer clinical trials. Ther Adv Med Oncol. 2011;3(2):57–71.

4. Quinten C, Coens C, Mauer M, et al. Baseline quality of life as a prognostic indicator of survival: a meta-analysis of individual patient data from EORTC clinical trials. Lancet Oncol. 2009;10(9):865–871.

5. Quinten C, Maringwa J, Gotay CC, et al. Patient self-reports of symptoms and clinician ratings as predictors of overall cancer survival. J Natl Cancer Inst. 2011;103(24):1851–1858.

6. Quinten C, Martinelli F, Coens C, et al. A global analysis of multitrial data investigating quality of life and symptoms as prognostic factors for survival in different tumor sites. Cancer. 2014;120(2):302–311.

7. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365–376.

8. Davis AM, Wright JG, Williams JI, Bombardier C, Griffin A, Bell RS. Development of a measure of physical function for patients with bone and soft tissue sarcoma. Qual Life Res. 1996;5(5):508–516.

9. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473–483.

10. EuroQol Research Foundation [Internet]. EQ-5D. 2017; Available at https://euroqol.org/

11. Devlin NJ, Brooks R. EQ-5D and the EuroQol Group: past, present and future. Appl Health Econ Health Policy. 2017 Apr;15(2):127-137.
***Examines potential future uses of the EQ-5D for measuring and valuing health status.**

12. Reichardt P, Leahy M, Garcia Del Muro X et al. Quality of life and utility in patients with metastatic soft tissue and bone sarcoma: the Sarcoma Treatment and Burden of Illness in North America and Europe (SABINE) study. Sarcoma. 2012;2012:740279.

13. Coens C, van der Graaf WT, Blay JY, et al. Health-related quality-of-life results from PALETTE: a randomized, double-blind, phase 3 trial of pazopanib versus placebo in patients with soft tissue sarcoma whose disease has progressed during or after prior chemotherapy—a European Organization for Research and Treatment of Cancer soft

tissue and bone sarcoma group global network study (EORTC 62072). Cancer. 2015;121:2933–2941.

14. Demetri GD, von Mehren M, Jones RL et al. Patient-reported outcomes from randomized, phase-3 study of trabectedin (T) vs. dacarbazine (D) in advanced leiomyosarcoma (LMS) or liposarcoma (LPS) [abstract]. J Clin Oncol. 2016;34(Suppl):11061.

15. Reichardt P. Soft tissue sarcomas, a look into the future: different treatments for different subtypes. Future Oncol. 2014;10(8 Suppl):s19–27.

16. Tap WD, Papai Z, Van Tine BA, et al. Doxorubicin plus evofosfamide versus doxorubicin alone in locally advanced, unresectable or metastatic soft-tissue sarcoma (TH CR-406/SARC021): an international, multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2017;18(8):1089–1103.

17. Demetri GD, Chawla SP, von Mehren M, 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;27(25):4188–4196.

18. Demetri GD, Von Mehren M, Jones LR, et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcomas after failure of conventional chemotherapy: results of a phase III randomized multicenter clinical trial. J Clin Oncol. 2016;34(8):786-793.

19. Grosso F, Jones RL, Demetri GD, et al. Efficacy of trabectedin (ecteinascidin-743) in advanced pretreated myxoid liposarcomas: a retrospective study. Lancet Oncol. 2008;8:595–602.

20. Grosso F, Sanfilippo R, Virdis E, et al. Trabectedin in myxoid liposarcomas (MLS): a long-term analysis of a single-institution series. Ann Oncol. 2009;20(8):1439–1444.

21. Le Cesne A, Ray-Coquard I, Duffaud F, et al. Trabectedin in patients with advanced soft tissue sarcoma: a retrospective national analysis of the French Sarcoma Group. Eur J Cancer. 2015;51(6):742–750.

22. Yondelis®. Summary of Product Characteristics. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000773/WC500045832.pdf

23. Sanfilippo R, Grosso F, Virdis E, Morosi C, Tercero JC, Gronchi A, et al. Rechallenge with trabectedin in patients with responding myxoid liposarcoma [abstract]. J Clin Oncol. 2009;27(Suppl):10575.

24. Le Cesne A, Blay JY, Domont J, et al. Interruption versus continuation of trabectedin in patients with soft-tissue sarcoma (T-DIS): a randomised phase 2 trial. Lancet Oncol. 2015;16(3):312–319.

25. Cesne AL, Judson I, Maki R, Grosso F, Schuetze S, Mehren MV, et al. Trabectedin is a feasible treatment for soft tissue sarcoma patients regardless of patient age: a retrospective pooled analysis of five phase II trials. Br J Cancer. 2013;109(7):1717–1724.

26. ClinicalTrials gov. Patient directed intervention towards a multidimensional recommendation guideline to improve the quality of life for patients with soft tissue sarcoma under palliative treatment with trabectedin. https://clinicaltrials.gov/ct2/show/NCT02204111

27. Schuler M, Richter S, Ehninger G, Bornhäuser M, Hentschel L. A cluster-randomised, controlled proof-of-concept study to explore the feasibility and effect of a patient-directed intervention on quality of life in patients with advanced soft tissue sarcoma. BMJ Open. 2017;7(6):e014614.

Figure Legends

Figure 1. Case 1: Computed tomography (CT) scans after 3 cycles of neoadjuvant doxorubicin + ifosfamide showing a 20 cm mixed (fat + fleshy) lesion in the right thoracic hemisphere with left side mediastinal shift: a) coronal CT scan; b) axial CT scan.

Figure 2. Case 1: Computed tomography scan showing a) recurrence of two hypodense lesions in the thymus, the first in the left superior lobe and the second in the right lobe; and b) a complete response in the first lesion and a major response in the second lesion after 9 cycles of trabectedin.

Figure 3. Case 2: Axial computed tomography scans in a patient with recurrent myxoid liposarcoma: a) before trabectedin; b) after 6 cycles of trabectedin.

Figure 4. Case 2: Axial computed tomography scans in a patient with recurrent myxoid liposarcoma a) before rechallenge with trabectedin; b) after rechallenge with 6 cycles of trabectedin.

Figure 5. Case 3: Computed tomography scans showing pulmonary metastases in a patient with leiomyosarcoma a) during treatment with trabectedin (June 2015); b) at the end of treatment with trabectedin (February 2016).

Figure 6. Case 3. Computed tomography scans showing an intra-abdominal mass and liver metastases in a patient with leiomyosarcoma a) during treatment with trabectedin; b) at the end of treatment with trabectedin; c) under third-line (pazopanib) and fourth-line (gemcitabine + dacarbazine) therapy.

Figure 7. Case 1 timeline. AE, adverse event; G, grade.

Figure 8. Case 2 timeline. DTIC, dacarbazine; G, grade; Gem, gemcitabine; mo, months; NR, no response; PR, partial response; SD, stable disease.

Figure 9. Case 3 timeline. BSC, best supportive care; DTIC, dacarbazine; G, grade; Gem, gemcitabine; PR, partial response; SD, stable disease.

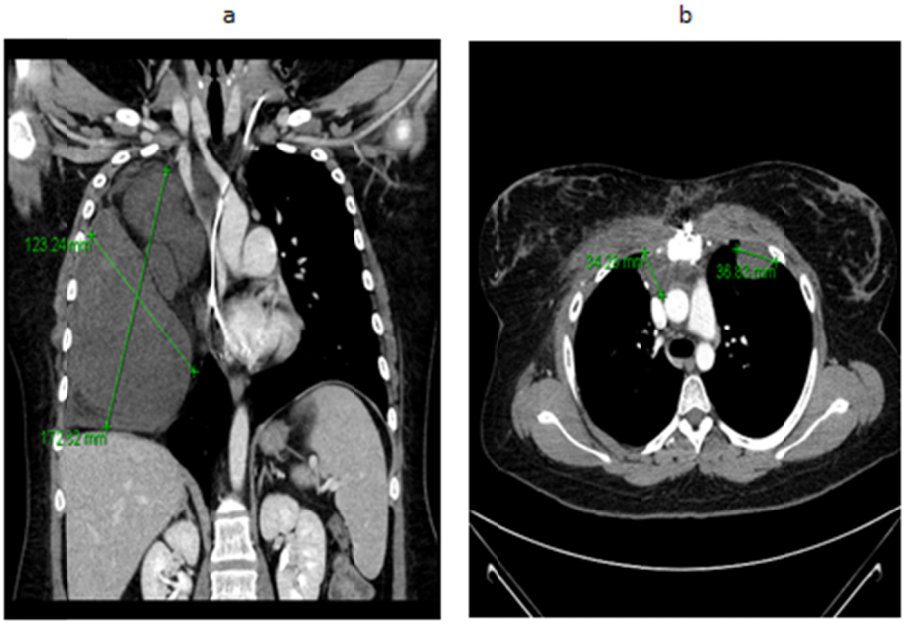

Figure 1

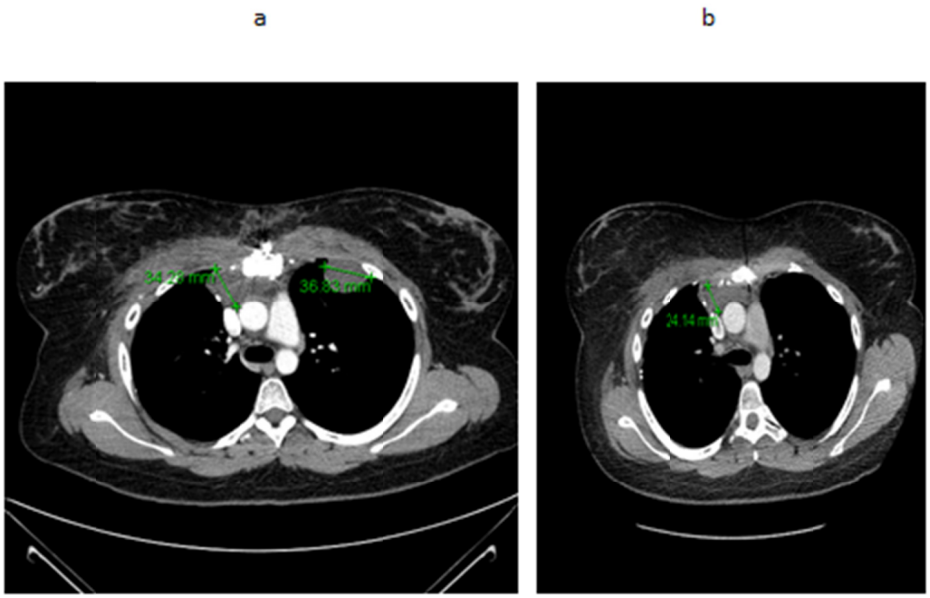

Figure 2

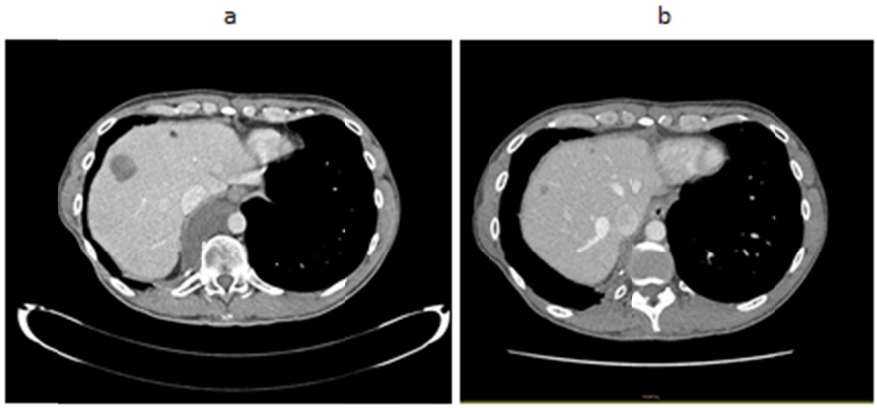

Figure 3

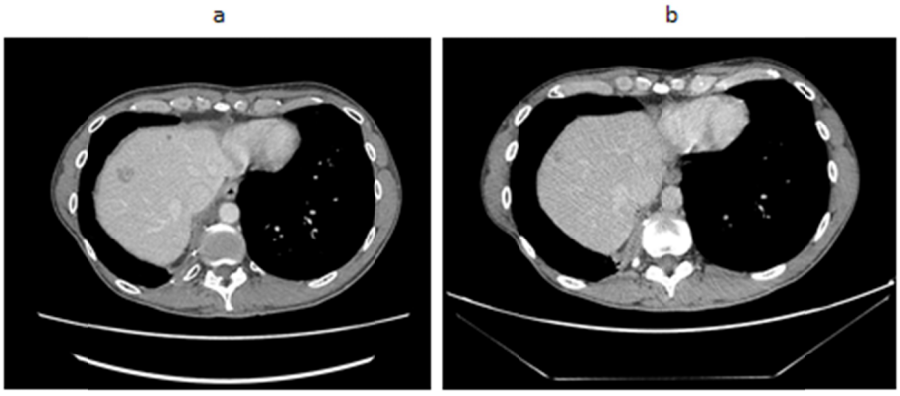

Figure 4

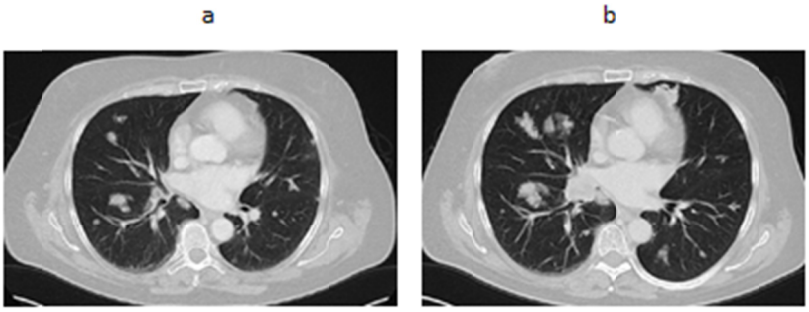

Figure 5

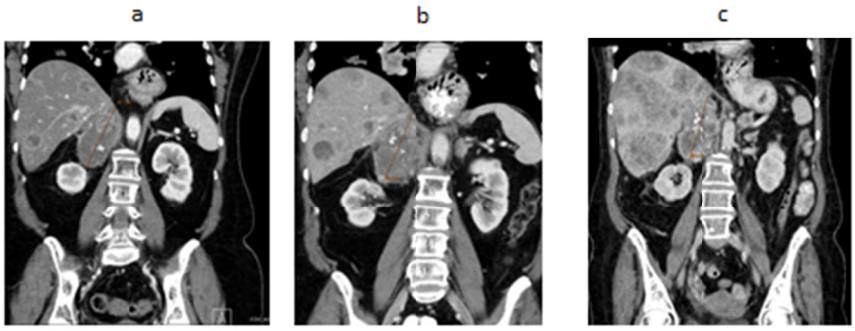

Figure 6

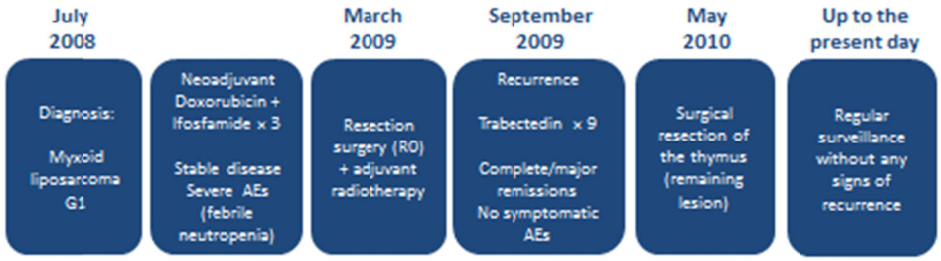

Figure 7

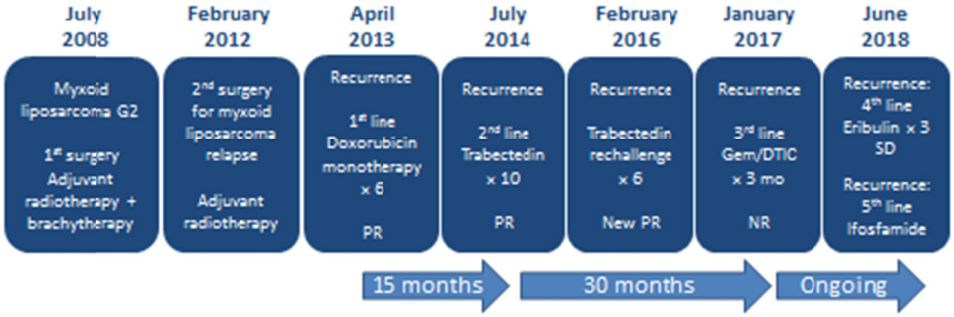

Figure 8

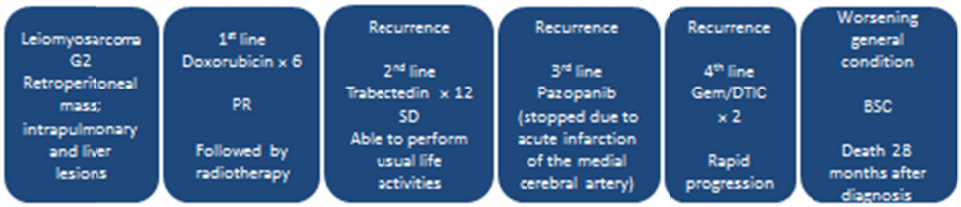

Figure 9