What Clinical Trials Are Needed for Treatment of Leiomyosarcoma?

Bernd Kasper, MD, PhD¹,*
Lorenzo D’Ambrosio, MD²
Elizabeth J. Davis, MD³
Matthew Ingham, MD⁴
Javier Martin Broto, MD⁵
Jonathan C. Trent, MD, PhD⁶
Winan J. van Houdt, MD⁷
Brian A. Van Tine, MD, PhD⁸

Address
*¹Mannheim University Medical Center, University of Heidelberg, Theodor-Kutzer-Ufer 1-3, D-68167, Mannheim, Germany
Email: bernd.kasper@umm.de
²Department of Oncology, University of Turin, Turin, Italy
³Department of Internal Medicine, Division of Hematology/Oncology, Vanderbilt University Medical Center, Nashville, USA
⁴Columbia University School of Medicine, New York, USA
⁵Medical Oncology Department, University Hospital Fundacion Jimenez Diaz, Madrid, Spain
⁶Syvlester Comprehensive Cancer Center, University of Miami, Miami, USA
⁷Department of Surgical Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands
⁸Siteman Cancer Center, Washington University in St. Louis, St. Louis, USA

© The Author(s) 2022. This article is an open access publication

This article is part of the Topical Collection on Sarcoma

Keywords Leiomyosarcoma · Clinical trials · NLMSF · Treatment · Research

Opinion statement
Leiomyosarcoma is one of the most common subtypes of soft tissue sarcomas accounting for approximately 20% of sarcomas. As leiomyosarcoma patients frequently develop metastatic disease, effective systemic therapies are needed to improve clinical outcomes. The overall activity of the currently available conventional systemic therapies and the prognosis of patients with advanced and/or metastatic disease are poor. As such, the treatment of this patient population remains challenging. As a result, there is a clear
unmet medical need, and designing and performing meaningful clinical studies are of utmost importance to improve the prognosis of this patient group. Therefore, the aim of this review is to briefly summarize state-of-the-art treatments for leiomyosarcoma patients and to describe trial characteristics needed for informative clinical studies.

Introduction

Soft tissue sarcomas (STS) represent a highly heterogeneous group of mesenchymal malignancies comprising more than 150 histological subtypes. Leiomyosarcoma (LMS) is one of the most frequent subtypes accounting for approximately 20% of patients. LMS occurs in middle-aged or older adults with a female predominance. LMS originates from the smooth muscle or their precursor cells, and thus can arise anywhere in the body with a predilection for the retroperitoneum, the extremities, and the uterus [1]. LMS can be divided into “extrauterine” (retroperitoneal, gastrointestinal, extremity, or subcutaneous) and “uterine” LMS, each with distinct clinicopathological characteristics [2, 3]. Diagnosis and staging of patients with LMS are in line with the general recommendations for STS and visceral sarcomas [4] and overall management of LMS patients should be part of a multidisciplinary team in a high-volume sarcoma reference center. Despite complete resection of the primary tumor, LMS patients frequently develop metastatic disease; therefore, effective systemic therapies are needed. However, the overall activity of the currently available conventional systemic therapies and the prognosis of patients with advanced or metastatic disease are still poor, making the treatment of LMS patients challenging. Having clearly identified an unmet medical need, designing and performing meaningful clinical studies are of utmost importance to improve the prognosis of this patient population. Therefore, the aim of this review is to briefly summarize state-of-the-art treatments for LMS patients and to describe trial characteristics for the optimal design of clinical studies in this patient group. This work is based on a recent joint white paper from the National LeioMyoSarcoma Foundation (NLMSF) in collaboration with Sarcoma Patients EuroNet (SPAEN) and has been supported by the NLMSF [5–].

Treatment paradigms for leiomyosarcoma patients

Surgery remains the cornerstone in the management of patients with localized LMS and the standard surgical procedure is a wide excision with negative margins (R0) [4]. In the case of R1 or R2 resections, re-operation in experienced centers is considered following possible preoperative treatments. Significant independent predictors for local recurrence are size and margin, whereas predictors for distant recurrence are size and grade [6]. In patients with extremity high-risk LMS (G2-3, deep ≥ 5 cm lesions), adjuvant or neoadjuvant radiation therapy is administered in addition to surgery. In patients with retroperitoneal and pelvic LMS, especially if low grade and borderline resectable, consideration should be given to neoadjuvant radiation based upon the results of the European Organisation for Research and Treatment of Cancer (EORTC) STRASS trial [7–]. Adjuvant chemotherapy is not globally accepted as the standard treatment strategy for the postoperative therapy of adult patients with LMS but can be considered in high-risk patients to reduce the risk of local recurrence and increase survival rates [4]. Neoadjuvant chemotherapy may have the same potential benefits as adjuvant chemotherapy, but similarly universal consensus
Neoadjuvant chemotherapy does have the advantage to allow for early response evaluation, to potentially prevent subsequent adjuvant chemotherapy, to treat micro-metastatic disease, and to downsize tumors allowing for less extensive surgical procedures. As of today, neoadjuvant chemotherapy as well as radiation therapy may be considered for patients with high-risk extremity/trunk LMS (lesion diameter $\geq 5$ cm, tumor deep to fascia, adjacent to bone or neurovascular structures, invasion of skin, or based on prediction models such as Sarculator) [8]. The efficacy of neoadjuvant chemotherapy in retroperitoneal LMS (and liposarcomas) is currently being evaluated in the EORTC/Soft Tissue and Bone Sarcoma Group (STBSG) STRASS-2 trial in patients with resectable retroperitoneal sarcomas (NCT04031677), which hopefully may settle the long-lasting controversial debate about this topic. Unfortunately, there are no biomarkers available predicting responses to the different neoadjuvant chemotherapy regimens, preventing optimized patient selection for perioperative treatment strategies.

Standard first-line chemotherapy for STS consists of anthracycline-based regimens, and doxorubicin is the first-line chemotherapy of choice in patients with advanced LMS [4]. Doxorubicin plus ifosfamide demonstrated a significantly higher response rate and longer progression-free survival (PFS) compared to single-agent doxorubicin, but no significant difference in overall survival (OS) in a trial including all STS subtypes [9]. Interestingly, the addition of ifosfamide was not found to be beneficial in the LMS subgroup in a post hoc analysis of this trial. In patients with LMS, the combination of doxorubicin plus dacarbazine is another option for multi-agent first-line chemotherapy [10]. Although ifosfamide might still retain some efficacy in women with uterine LMS, it appears to be less effective for patients with extra-uterine LMS [11, 12]. In a randomized phase 3 trial in first-line advanced STS, no significant difference in response rate, PFS, and OS was observed between single-agent doxorubicin and gemcitabine plus docetaxel, although doxorubicin was better tolerated with similar findings for the LMS cohort [13]. Promising data have been reported for the first-line combination of doxorubicin plus trabectedin in LMS [14]; however, final results from the randomized phase 3 trial comparing this combination versus doxorubicin alone are awaited (NCT02997358). In second line or later, trabectedin is a standard option for the treatment of advanced STS (including LMS) after failure of doxorubicin with or without ifosfamide, or for patients “unsuited” to receive these agents. Chemosensitivity to trabectedin has been noted in different STS subtypes, but best responses have been observed in LMS and liposarcomas [15, 16, 17]. Dacarbazine is a reasonable choice to consider in the refractory setting for LMS, and can be combined with gemcitabine. This combination is generally well tolerated and given on a convenient schedule [18]. Additionally, uterine LMS has an unusual sensitivity to dacarbazine. Two randomized studies comparing the efficacy of gemcitabine plus docetaxel versus gemcitabine alone reported divergent findings in patients with relapsed or metastatic LMS [19, 20]. In a subsequent pooled analysis, no significant improvement of response rate and PFS could be demonstrated by the addition of docetaxel for LMS [21]. Pazopanib is recommended for selected subtypes of advanced STS including LMS after prior chemotherapy for advanced and/or metastatic disease. The PALETTE trial included 165 patients with LMS. Pazopanib was shown to significantly prolong PFS; however, this did not translate into a statistically significant OS difference compared to placebo [22,
It should be highlighted that the phase 3 eribulin trial included LMS and liposarcoma patients. Interestingly, higher response rates and rates of disease control were seen with dacarbazine for the LMS cohort in comparison to liposarcoma patients; this may have been the reason that eribulin was deemed ineffective for the LMS population [24]. Table 1 illustrates key studies on the current management of advanced/metastatic patients with STS/LMS.

What clinical trials are needed for LMS?

The overall effectiveness of the currently available systemic treatment options for patients with LMS in the advanced and/or metastatic setting is limited; thus, patients’ overall prognosis remains poor. Therefore, designing and performing clinically meaningful and promising studies are of utmost importance to improve the prognosis of this patient population. The aim of this section is to describe trial characteristics for designing effective clinical studies in this distinct patient group.

1. Studies should be LMS-specific: Evidence-based data for LMS mainly comes from clinical trials open for the recruitment of a variety of heterogeneous STS subtypes; there are few prospective trials exclusively designed for the inclusion of LMS or even uterine LMS patients. Here are a few positive examples: (1) The North Eastern German Society of Gynaecological Oncology is currently evaluating the role of pazopanib versus pazopanib plus gemcitabine in the treatment of advanced or metastatic uterine LMS in an ongoing prospective randomized controlled phase 2 trial (PazoDoble; NCT02203760). (2) The French Sarcoma Group has conducted a randomized phase 3 study comparing the efficacy of doxorubicin plus trabectedin followed by trabectedin versus doxorubicin alone in LMS patients; final results are eagerly awaited (LMS-04; NCT02997358). (3) The EORTC/STBSG is currently developing an open label, randomized, phase 2 study on

| Agent(s)                                      | Phase | n   | Line   | ORR    | PFS (months) | OS (months) |
|-----------------------------------------------|-------|-----|--------|--------|--------------|-------------|
| Doxorubicin vs doxorubicin + ifosfamide [9•]  | III   | 455 | 1st    | 14%    | 26%          | 4.6 7.4 12.8 14.3 |
| Doxorubicin vs gemcitabine + docetaxel [13]  | III   | 257 | 1st    | 19%    | 20%          | 5.4 5.5 17.6 15.5 |
| Gemcitabine vs gemcitabine + docetaxel [19]  | II    | 122 | 1st–3rd| 8%     | 16%          | 3.0 6.2 11.5 17.9 |
| Dacarbazine vs gemcitabine + dacarbazine [18] | II    | 113 | 2nd+   | 25%    | 49%          | 2 4.2 8.2 16.8 |
| Pazopanib vs placebo [22]                     | III   | 372 | 2nd+   | 6%     | 0%           | 4.6 1.6 12.5 10.7 |
| Gemcitabine + docetaxel [25]                  | II    | 45  | 1st    | 25%    |              | 7.1 17.9     |
| Trabectedin vs dacarbazine [26]               | III   | 403 | 3rd+   | 10%    | 7%           | 4.8 1.5 14.1 13.6 |
| Temozolomide [27]                             | II    | 60  | 3rd+   | 9%     | 15%          | 2.3 13.8     |

ORR, overall response rate; PFS, progression-free survival; OS, overall survival. *Clinical benefit rate including stable disease
doxorubicin, doxorubicin plus dacarbazine, or gemcitabine plus dacarbazine for first-line treatment of advanced LMS patients (DODECANESEO) based on a retrospective STBSG analysis [28]. Without doubt, international collaboration is essential to perform LMS-specific trials. The importance of including reference centers and reference networks for recruiting more patients into clinical trials is critical in this context.

2. **Studies should focus on certain clinical settings:** The majority of clinical studies are currently being conducted in the metastatic disease setting, mainly in later treatment lines (3rd/4th/5th line) potentially prolonging patients’ lives for only a few months. Other important scenarios where clinical trials are needed include the following: (1) Performing clinical studies in the neo-adjuvant setting especially in high-risk localized LMS has the potential to actually cure patients, if the appropriate perioperative systemic regimen is administered. (2) When performing clinical studies in the (neo-)adjuvant setting, biomarkers are needed for response prediction as described below in more detail. Moreover, this is also the case for the metastatic disease setting. (3) The potential of performing “window-of-opportunity” studies should be emphasized to allow for fast response evaluation, to analyze biological processes, and to include more patients into clinical studies. Patients that are undergoing surgery, either in the primary, locally recurrent, or even metastatic setting, are excellent candidates to study new drugs or drug combinations with the opportunity to study both radiological and pathological mechanisms of response and resistance.

3. **Studies should explore new therapeutic avenues:** Besides the evaluation of the activity of conventional chemotherapeutic agents for LMS, new treatment avenues need to be explored. There are a number of ongoing trials exploring the possible value of immunotherapy in STS [29], including anti-PD1/PD-L1 monotherapy [30, 31], combined PD1/CTLA4 inhibition [32], or PD1 therapy combined with cyclophosphamide [33] or anti-VEGF tyrosine kinase inhibitor (TKI) axitinib [34], although the numbers of LMS patients included in these all-comer studies are small. Obviously, single-agent PD1 blockade does not seem to be the optimal LMS strategy, but hopefully combination therapies with other agents will be more promising. Multiple retrospective studies have suggested that STS/LMS do have underlying immunogenicity [35, 36, 37], but the exact therapeutic strategy to exploit this remains elusive. A large study of ~1000 LMS tissue samples suggests in a very small number of patients tumors harbor classic immunotherapy response markers. Additionally, this study found most tumor microenvironments had markers associated with low T cell but high for fibroblast abundance. This observation suggests clinical trials for LMS patients should include strategies to increase T cell abundance in the tumor microenvironment [38]. Ongoing clinical trials are combining cytotoxic chemotherapy, including doxorubicin, gemcitabine, and trabectedin, with checkpoint blockade, which may help to increase tumor immunogenicity of “cold” tumors: (1) A phase 2 study from the German Interdisciplinary Sarcoma Group (GISG) testing the combined treatment with nivolumab plus trabectedin in patients with metastatic or inoperable STS has a dedicated LMS cohort (GISG-15; NiTraSarc; NCT03590210). (2) Cabozantinib is being explored in a randomized study with or without dual PD1/CTLA4...
checkpoint blockade, with a broader spectrum TKI potentially more impactful to the tumor microenvironment than narrow VEGF inhibitors (NCT04551430). (3) Anlotinib is being evaluated in a randomized phase 3 trial with a specific LMS cohort (APROMISS; NCT03016819).

4. Studies should follow a clear biological rationale: Based on recent research suggesting that LMS may harbor characteristic defects in the homologous recombination DNA repair pathway [39, 40, 41, 42], a number of trials are currently evaluating PARP inhibitor–based approaches: (1) One trial is evaluating olaparib plus trabectedin versus doctor's choice in various solid tumors harboring deficiency in DNA repair but is not sarcoma-specific (GISG-16; TopArt; NCT03127215). (2) A phase 1B trial of the combination of olaparib plus trabectedin in patients with previously treated advanced/metastatic STS has shown activity especially in LMS patients [43]. A phase 2 randomized study comparing standard trabectedin versus the combination of trabectedin plus olaparib is currently ongoing with a dedicated stratification for L-sarcomas (NCT03838744). A phase 2 single-arm trial of the same treatment combination in patients with advanced sarcomas has a LMS-specific cohort (NCT04076579). (3) Another phase 2 study is testing the combination of olaparib plus temozolomide specifically in patients with advanced metastatic or unresectable uterine LMS (NCT038880019) and could demonstrate promising results with an overall response rate of 27%, a median PFS of 6.9 months, and a median duration of response of 12 months [44], a perfect example for a successful bench-to-bedside approach. In this context, correlative studies are critical such as the example of three current GEIS (Spanish Sarcoma Research Group) studies in a selected group of STS histologies including LMS: In an upfront phase 2 trial, the compound LB100 will be explored in combination with doxorubicin versus doxorubicin alone in advanced L-sarcomas. In a second line trial, selinexor is combined with gemcitabine in a LMS-specific cohort (NCT04595994). Additionally, LMS patients will be enrolled in a new cohort of IMMUNOSARC-2 exploring immune mechanisms of tumor cell death for the combination of doxorubicin, dacarbazine, and nivolumab (NCT03277924). For all these trials, correlative studies with compulsory tumor blocks at baseline will be performed.

5. Studies should evaluate the role of biomarkers: Circulating tumor DNA (ctDNA) offers a rapid and noninvasive method of next-generation sequencing (NGS) that could be used for diagnosis, prognostic assessment, disease-response assessment to therapy, and detection of recurrence [45, 46, 47]. This strategy is worth exploring also in tumors not harboring a clear-cut gene driver like LMS. NGS of ctDNA allows identification of somatic and potentially germline genomic alterations in plasma from LMS patients [48, 49]; however, further validation and prospective evaluation are warranted to investigate the clinical utility of ctDNA especially for LMS patients: (1) A Sarcoma Alliance for Research Through Collaboration (SARC)–funded pilot study is evaluating ctDNA as a biomarker of relapse-free survival and response to therapy in patients with high-grade, high-risk, localized LMS. (2) A SARC-supported study of ctDNA as biomarker of sarcoma response to chemotherapy in patients with metastatic LMS is currently being planned. (3) Perhaps a molecular “signature” could serve as a better prognostic and predictive
biomarker than the anatomic location. Data from several retrospective studies in LMS have shown that the Complexity INdex in SARComas (CINSARC) has utility in predicting risk of relapse [50, 51]. CINSARC is currently undergoing prospective evaluation in the perioperative setting (NCT03805022, NCT02789384, and NCT04307277).

6. Studies should capture Patient-Reported Outcomes (PROs): There is growing recognition of the potential value offered by PROs fostered by patient involvement in clinical research. The work to develop a multidimensional sarcoma-specific scale is underway; however, there is some distance still to go to have a LMS-specific one. Validated composite tools to gather multidimensional data which enable a Health-Related Quality-of-Life (HRQoL) to be assessed are available with the weakness that they measure a “moment in time” rather than give a full picture of patient experience. It is now possible to construct questionnaires exploring detailed aspects of the patient experience opening to individual PROs. Item libraries are available such as the one of the EORTC Quality of Life Group containing over 900 PRO items, each of them in many languages and validated [52]. An important development has been the PRO Common Terminology Criteria for Adverse Events (CTCAE) from NCI [53]. The CTCAE has been a mainstay of cancer clinical trial practice and reporting for many years, but the grading relies on clinician observation of patients’ experience. The PRO version calls for patients to report their experience first-hand. Gathering these data using smartphones and internet reporting opens the way for a more sensitive and often more accurate reporting of adverse events in clinical studies.

**Fig. 1.** Trial characteristics for designing clinical studies in LMS.
Conclusions

In summary, there is a clear need for large international randomized or single-arm LMS-specific clinical trials, with an underlying biological rationale. It is strongly advisable to seek therapeutic advice of a high-volume reference center or to enroll patients in suitable subtype-specific clinical studies, factors clearly linked to a superior outcome for this patient group [54, 55]. Figure 1 summarizes trial characteristics for designing meaningful clinical studies for LMS patients which will deliver novel therapies and help better understand important biological as well as clinical questions.

Declarations

Funding
Open Access funding enabled and organized by Projekt DEAL.

Conflict of interest
BK declares personal fees from Ayala, Bayer, Blueprint, Boehringer Ingelheim, GSK, PharmaMar, Roche, and SpringWorks. EJD receives research funding from Bristol-Myers Squibb, Incyte, Five Prime, Karyopharm, Top Alliance BioSciences, Actuate, and Genentech and personal fees from Karyopharm and Deciphera. JCT serves as a consultant for Deciphera, Blueprint, Cogent Biosciences, Epizyme, C4 Therapeutics, and Daiichi-Sankyo. BAVT declares grants from Merck; grants and personal fees from Pfizer; grants from TRACON Pharmaceuticals; grants, personal fees, and others from GlaxoSmithKline; personal fees from Polaris Inc.; personal fees from Lilly; personal fees from Caris Life Sciences; personal fees from Novartis; personal fees from CytRx; personal fees from Plexxikon; personal fees from Epizyme; personal fees from Daiichi Sankyo; personal fees from Adaptimmune; personal fees from Immune Design; personal fees from Bayer; personal fees from Cytokinetics; and personal fees from Deciphera; and has a patent issued for the use of ME1 as a biomarker and ACXT3102.

Open Access

This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.
References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. Martin-Liberal J. Leiomyosarcoma: principles of management. Intractable Rare Dis Res. 2013;2:127–9.

2. Fletcher B, Hogendoorn PC, Mertens F. WHO Classification of Tumours of Soft Tissue and Bone. World Health Organisation 2013:467.

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

4. Casali PG, Abecassis N, Aro HT, Bauer S, Biagini R, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29(Suppl 4):iv51–67.

5. Kasper B, Achee A, Schuster K, Wilson R, van Oortmerssen G, Gladdy RA, et al. Unmet medical needs and future perspectives for leiomyosarcoma patients-a position paper from the National Leiomyosarcoma Foundation (NLMSF) and Sarcoma Patients EuroNet (SPAEN). Cancers (Basel). 2021;13:886.

This joint white paper from the National Leiomyosarcoma Foundation (NLMSF) in collaboration with Sarcoma Patients EuroNet (SPAEN) summarizes state-of-the-art treatments for leiomyosarcoma patients in order to identify knowledge gaps and current unmet needs, thereby guiding the community to design innovative clinical trials and basic research to close this research gap.

6. Gladdy RA, Qin LX, Moraco N, Agaram NP, Brennan MF, Singer S. Predictors of survival and recurrence in primary leiomyosarcoma. Ann Surg Oncol. 2013;20:1851–7.

7. Bonvalot S, Gronchi A, Le Péchoux C, Swallow CJ, Strauss D, Meeus P, et al. Preoperative radiotherapy plus surgery versus surgery alone for patients with primary retroperitoneal sarcoma (EORTC-62092; STRASS): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2020;21:1366–7.

This is an important academic phase III study evaluating the impact of neoadjuvant radiotherapy in retroperitoneal sarcomas including LMS.

8. Gronchi A, Ferrari S, Quagliuolo V, Martin-Broto JM, Pousa AL, Grignani G, et al. Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-STS 1001): an international, open-label, randomised, controlled, phase 3, multicentre trial. Lancet Oncol. 2017;18:812–22.

9. Judson I, Verweij J, Gelderblom H, Hartmann JT, Schöffski 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;15:415–2.

This paper describes the results of a large phase III EORTC study comparing doxorubicin versus doxorubicin plus ifosfamide in first-line therapy for advanced or metastatic STS patients highlighting the remaining gold standard of a doxorubicin-based first-line chemotherapy.

10. Rahal C, Mir O. Doxorubicin plus dacarbazine (DD) in advanced leiomyosarcoma. A retrospective review of Gustave Roussy Institute. Presented at The European Cancer Congress, Amsterdam, The Netherlands. 2013.

11. Penel N, Italiano A, Isambert N, Bousquet G, Duffaud F, French Sarcoma Group (Groupe Sarcome Français/Groupe d’Etude des Tumeurs Osseuses). Factors affecting the outcome of patients with metastatic leiomyosarcoma treated with doxorubicin-containing chemotherapy. Ann Oncol. 2010;21:1361–5.

12. Sleijfer S, Ouali M, van Clabbeke M, Kranup-Hansen A, Rodenhuis S, Le Cesne A, et al. Prognostic and predictive factors for outcome to first-line ifosfamide-containing chemotherapy for adult patients with advanced soft tissue sarcomas: an exploratory, retrospective analysis on large series from the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG). Eur J Cancer. 2010;46:72–83.

13. Seddon B, Strauss SJ, Whelan J, Leahy M, Woll P, Cowie F, et al. Gemcitabine and docetaxel versus doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft-tissue sarcomas (GeDDiS): a randomised controlled phase 3 trial. Lancet Oncol. 2017;18:1397–410.

14. Pautier P, Floquet A, Chevreau C, Penel N, Guillemet C, Delambre C, et al. Trabectedin in combination with doxorubicin for first-line treatment of advanced uterine or soft-tissue leiomyosarcoma (LMS-02): a non-randomised, multicentre, phase 2 trial. Lancet Oncol. 2015;16:457–64.

15. 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;27:4188–96.

16. 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;34:786–93.

17. Hensley ML, Patel SR, von Mehren M, Ganjoo K, Jones RL, Staddon A, et al. Efficacy and safety of trabectedin or dacarbazine in patients with advanced uterine leiomyosarcoma after failure of anthracycline-based chemotherapy: Subgroup analysis of a phase 3, randomized clinical trial. Gynecol Oncol. 2017;146:531–7.

18. García-Del-Muro X, López-Pousa A, Maurel J, Martín J, Martínez-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;29:2528–33.

19. 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;25:2755–63.

20. Pautier P, Flocquet A, Penel N, Piperno-Neumann S, Isambert N, Roy A, et al. Randomized multicenter and stratified phase II study of gemcitabine alone versus gemcitabine and docetaxel in patients with metastatic or relapsed leiomyosarcoma: a Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) French Sarcoma Group Study (TAXOGEM study). Oncologist. 2012;17:1213–20.

21. Duffaud F, Bui-Nguyen B, et al. A pooled analysis of the final results of two randomised phase II studies comparing gemcitabine vs. gemcitabine plus docetaxel in patients with metastatic/relapsed leiomyosarcoma. Presented at the 16th Annual Meeting of the Connective Tissue Oncology Society (CTOS), Paris. 2010.

22. Van der Graaf WTA, Blay JY, Chawla SP, Kim DW, Bui-Nguyen B, Casali PG, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2012;79:1879–86.

23. Benson C, Ray-Coquard I, Sleijfer S, Litière S, Blay JY, Le Cesne A, et al. Outcome of uterine sarcoma patients treated with pazopanib: a retrospective analysis based on two European Organisation for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group (STBSG) clinical trials 62043 and 62072. Gynecol Oncol. 2016;142:89–94.

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

25. Seddon B, Scurr M, Jones RL, Wood Z, Propert-Lewis C, Fisher C, et al. A phase II trial to assess the activity of gemcitabine and docetaxel as first line chemotherapy treatment in patients with unresectable leiomyosarcoma. Clin Sarcoma Res. 2015;5:13.

26. Patel S, von Mehren M, Reed DR, Kaiser P, Charlson J, Ryan CW, et al. Overall survival and histology-specific subgroup analyses from a phase 3, randomized controlled study of trabectedin or dacarbazine in patients with advanced liposarcoma or leiomyosarcoma. Cancer. 2017;123:3285–9.

27. Trent JC, Beach J, Burgess MA, et al. A two-arm phase II study of temozolomide in patients with advanced gastrointestinal stromal tumors and other soft tissue sarcomas. Cancer. 2003;98:2693–9.

28. D’Ambrosio L, Touati N, Blay JY, Grignani G, Flippot R, Czarnecka AM, et al. Doxorubicin plus dacarbazine, doxorubicin plus ifosfamide, or doxorubicin alone as a first-line treatment for advanced leiomyosarcoma: a propensity score matching analysis from the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. Cancer. 2020;126:2637–47.

29. Italiano A, Bellera C, D’Angelo S. PD1/PD-L1 targeting in advanced soft-tissue sarcomas: a pooled analysis of phase II trials. J Hematol Oncol. 2020;13:55.

30. Tawbi HA, Burgess M, Bolejack V, Van Tine BA, Schuetze SM, Hu J, et al. Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial. Lancet Oncol. 2016;17:183–93.

31. Ben-Ami E, Baryauskas CM, Solomon S, Talhil K, Malley R, Hohos M, et al. Immunotherapy with single agent nivolumab for advanced leiomyosarcoma of the uterus: results of a phase 2 study. Cancer. 2017;123:3285–90.

32. D’Angelo SP, Mahoney MR, Van Tine BA, Atkins J, Milhem MM, Jahagirdar BN, et al. Nivolumab with or without ipilimumab treatment for metastatic sarcoma (Alliance A091401): two open-label, non-comparative, randomised, phase 2 trials. Lancet Oncol. 2018;19:416–26.

33. Touloumde M, Penel N, Adam J, Chevreau C, Blay JY, Le Cesne A, et al. Use of PD-1 targeting, macrophage infiltration, and IDO pathway activation in sarcomas: a phase 2 clinical trial. JAMA Oncol. 2016;2:493–7.

34. Wilky BA, Trucco MM, Subhawong TK, Florou V, Park W, Kwon D, et al. Axitinib plus pembrolizumab in patients with advanced sarcomas including alveolar soft-part sarcoma: a single-centre, single-arm, phase 2 trial. Lancet Oncol. 2018;19:837–48.

35. Pollack SM, He Q, Yearley JH, Emerson R, Vignali M, Petitprez F, de Reyniès A, Keung EZ, Wei-Wu Chen T, Zhang Y, et al. T-cell infiltration and clonality correlate with programmed cell death protein 1 and programmed death-ligand 1 expression in patients with soft tissue sarcomas. Cancer. 2017;123:3291–304.

36. Petiprez F, de Reyniès A, Keung EZ, Wei-Wu Chen T, Sun CM, Calderaro J, et al. B cells are associated with survival and immunotherapy response in sarcoma. Nature. 2020;577:556–60.
What Clinical Trials Are Needed for Treatment of Leiomyosarcoma?  Kasper et al.

37. Cancer Genome Atlas Research Network. Comprehensive and integrated genomic characterization of adult soft tissue sarcomas. Cell. 2017;171:950–65.

38. Lagos G, Groisberg R, Dizon DS, et al. Large scale multiomic analysis suggests mechanisms of resistance to immunotherapy in leiomyosarcoma. J Clin Oncol. 2021;39(suppl 15):abstr 11512.

39. Chudasama P, Mughal SS, Sanders MA, Hübschmann D, Chung I, Deeg KI, et al. Integrative genomic and transcriptomic analysis of leiomyosarcoma. Nat Commun. 2018;9:14.

This Nature publication is the preclinical background for a number of clinical studies currently evaluating PARP inhibitors in combination with chemotherapies in LMS patients.

40. Pignochino Y, Capozzi F, D'Ambrosio L, Dell’Aglio C, Basiricò M, Canta M, et al. PARP1 expression drives the synergistic antitumor activity of trabectedin and PARP1 inhibitors in sarcoma preclinical models. Mol Cancer. 2017;16:86.

41. Oza J, Doshi SD, Hao L, Musi E, Schwartz GK, Ingham M. Homologous recombination repair deficiency as a therapeutic target in sarcoma. Semin Oncol. 2020;47:380–9.

42. Rosenbaum E, Jonsson P, Seier K, Xuan Qin L, Chi P, Dickson M, et al. Clinical outcome of leiomyosarcomas with somatic alteration in homologous recombination pathway genes. JCO Precis Oncol. 2020;4:PO.20.00122.

43. Grignani G, D'Ambrosio L, Pignochino Y, Palmerini E, Zucchetti M, Boccone P, et al. Trabectedin and olaparib in patients with advanced and non-resectable bone and soft-tissue sarcomas (TOMAS): an open-label, phase 1b study from the Italian Sarcoma Group. Lancet Oncol. 2018;19:1360–71.

44. Ingham M, Allred JB, Gano K, et al. NCI protocol 10250: a phase II study of temozolomide and olaparib for the treatment of advanced uterine leiomyosarcoma. J Clin Oncol. 2021;39(suppl 15):abstr 11506.

45. Mas A, Simón C. Molecular differential diagnosis of uterine leiomyomas and leiomyosarcomas. Biol Reprod. 2019;101:1115–23.

46. Przybyl J, Spans L, Lum DA, Zhu S, Vennam S, Forgó E, et al. Detection of circulating tumor DNA in patients with uterine leiomyomas. JCO Precis Oncol. 2019;3:PO.18.00409.

47. Przybyl J, Chabon JJ, Spans L, Ganjoo KN, Vennam S, Newman AM, et al. Combination approach for detecting different types of alterations in circulating tumor DNA in leiomyosarcoma. Clin Cancer Res. 2018;24:2688–99.

48. Hemming ML, Klega KS, Rhoades J, Ha G, Acker KE, Andersen JL, et al. Detection of circulating tumor DNA in patients with leiomyosarcoma with progressive disease. JCO Precis Oncol 2019;PO.18.00235.

49. Arshad J, Barreto-Coelho P, Jonczak E, Espejo A, D’Amato G, Trent JC. Identification of genetic alterations by circulating tumor DNA in leiomyosarcoma: a molecular analysis of 73 patients. Journal of Immunotherapy and Precision Oncology. 2020;3:64–8.

50. Chibon F, Lagarde P, Salas S, Péro G, Brouste V, Tirole F, et al. Validated prediction of clinical outcome in sarcomas and multiple types of cancer on the basis of a gene expression signature related to genome complexity. Nat Med. 2010;16:781–187.

51. Italiano A, Lagarde P, Brulard C, Terrier P, Laë M, Marques B, et al. Genetic profiling identifies two classes of soft-tissue leiomyosarcomas with distinct clinical characteristics. Clin Cancer Res. 2013;19:1190–6.

52. EORTC Quality of Life Item Library. https://qol.eortc.org/item-library.

53. Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™). https://healthcaredelivery.cancer.gov/proctcae.

54. Blay JY, Soibinet P, Penel N, Bompas E, Duffaud F, Stoeckle E, et al. Improved survival using specialized multidisciplinary board in sarcoma patients. Ann Oncol. 2017;28:2852–9.

55. Keung EZ, Chiang YJ, Cormier JN, Torres KE, Hunt KK, Feig BW, Roland CL. Treatment at low-volume hospitals is associated with reduced short-term and long-term outcomes for patients with retroperitoneal sarcoma. Cancer. 2018;124:4495–503.

Publisher’s Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.