Supplement

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On the road to improved outcomes by capturing leiomyosarcoma patients' views

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An international collaborative project set up as a 'priority setting partnership' used a questionnaire to capture the views of patients, carers and clinicians about the sarcoma research agenda. Responses from 25 patients with leiomyosarcoma (LMS) in eight countries provided useful insight from the patient's perspective. Unmet needs identified by patients were in the areas of: LMS-specific trial design; exploring new therapeutic avenues; avoiding morcellation; exploring the immune system in LMS; investigating circulating tumor DNA; implementing molecular characterization of LMS; conducting basic research and a translational pipeline; evaluating imaging modalities; improving early diagnosis; identifying patient-reported outcomes; improving communication, information and support; and addressing survivorship and end-of-life care. Each of the unmet needs is described in more detail.

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In all cases of soft tissue sarcomas (STSs), including leiomyosarcoma (LMS), standard practice should be followed when managing patients. ESMO-EURACAN-GENTURIS guidelines recommend that all STS patients be managed in specialist reference centers [1]. A multidisciplinary team consisting of surgical, orthopedic, radiation, medical and pediatric oncologists as well as pathologists and radiologists is mandatory for all cases; organ-based and nuclear medicine specialists are frequently also required. Management should be carried out in sarcoma reference centers or within reference networks sharing multidisciplinary expertise and treating a high number of patients annually. All patients with an unexplained deep soft tissue mass or a superficial soft tissue lesion measuring $\geq$5 cm in diameter should be referred to a specialist center. Supporting these recommendations, a position paper from the National LeioMyoSarcoma Foundation and Sarcoma Patients EuroNet which presents views about LMS from the patients' perspective emphasizes the need for LMS patients to be managed by a multidisciplinary team in a sarcoma reference center [2].

Current management of LMS

The management of localized STS, and of nonuterine and uterine LMS specifically, is summarized in Table 1 [1,2]. Surgery is standard treatment for most patients with localized STS. This entails wide excision with negative margins (R0) performed by a specifically trained surgeon for nonuterine LMS and *en bloc* total hysterectomy performed by a specifically trained gynecological surgeon for uterine LMS. In the case of grade 2–3 lesions, wide excision and radiotherapy are standard approaches. In nonuterine LMS patients, R1 or R2 resection followed by radiotherapy is recommended in cases where re-resection cannot rescue tumor margins. Radiotherapy is appropriate in selected cases of uterine LMS (local relapse, or cervical, parametral or serosal involvement). Adjuvant or neoadjuvant chemotherapy with anthracyclines and ifosfamide is an option for high-risk STS cases and can be considered in nonuterine LMS if there is risk of recurrence, for borderline resectable tumors or to preserve function. In uterine LMS, adjuvant chemotherapy can be considered in the event of tumor rupture during surgery [1,2]. Unfortunately, a trial evaluating adjuvant chemotherapy in resected uterine LMS was closed due to poor enrollment [3].

Achieving good outcomes while maintaining quality of life is the main goal of treatment for most patients with advanced STS. Anthracycline-based regimens are standard first-line therapy [1]. A propensity score matching analysis retrospectively evaluated doxorubicin plus dacarbazine, doxorubicin plus ifosfamide, and doxorubicin alone

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Table 1. Management of localized disease in soft tissue sarcoma and in nonuterine and uterine leiomyosarcoma.

Category	STS	Nonuterine LMS	Uterine LMS
Surgery	Surgery is standard treatment for all patients	Wide excision with negative margins (R0) by a specifically trained surgeon	*En bloc* total hysterectomy by a specifically trained (gynecological) surgeon
RT	Wide excision & RT are standard in grade 2–3 lesions	R1 and R2 resections followed by RT (if margins cannot be rescued by re-resection)	RT in selected cases (risk factors: local relapse, cervical, parametral or serosal involvement)
Adjuvant/neoadjuvant chemotherapy[†]	An option for high-risk cases	If there is risk for recurrence, in borderline resectable tumors or for function preservation	For cases of tumor rupture during surgery

[†]Anthracycline + ifosfamide.
LMS: Leiomyosarcoma; RT: Radiotherapy; STS: Soft tissue sarcoma.

as first-line treatments for advanced/metastatic LMS. Based on favorable overall response rate and progression-free survival (PFS) outcomes for doxorubicin plus dacarbazine, the authors concluded that the combination warrants further evaluation in prospective trials [4]. ESMO–EURACAN–GENTURIS guidelines position doxorubicin plus dacarbazine as an option for multiagent, first-line chemotherapy for LMS because retrospective evidence points to limited activity of ifosfamide in this subtype [1]. Gemcitabine–docetaxel is generally not recommended as first-line therapy for advanced STS after a phase III trial showed no indication of a superior response compared with doxorubicin (in both nonuterine and uterine LMS subgroups) and greater toxicity, resulting in inferior treatment adherence due to more dose delays and lower dose intensity [5].

Trabectedin is recommended as second-line treatment for patients with STS, including LMS, and also represents a first-line treatment option for patients unsuited to receive standard first-line anthracycline-based therapy [1]. Different histological subtypes of STS exhibit varying chemosensitivity to trabectedin, with the best responses reported in patients with LMS, liposarcoma and translocation-related sarcomas [2]. In a phase III trial in patients with advanced LMS (n = 378) or liposarcoma (n = 140), trabectedin showed superior disease control over dacarbazine, reducing the risk of disease progression or death by 45% (median PFS: 4.2 vs 1.5 months; hazard ratio [HR]: 0.55; $p < 0.001$) [6].

The combination of doxorubicin plus trabectedin is showing promise as first-line treatment for advanced LMS. A multicenter phase II trial (LMS-02) of first-line doxorubicin plus trabectedin for metastatic LMS recorded a median PFS of 10.1 months and median overall survival (OS) of 34.4 months [7]. Based on these encouraging outcomes, a multicenter phase III trial (LMS-04) was conducted which compared doxorubicin plus trabectedin followed by trabectedin (n = 74) with doxorubicin monotherapy (n = 76) as first-line treatment of unresectable or metastatic LMS. After a median follow-up of 37 months, median PFS by blinded, independent, central review (primary end point) was significantly prolonged with the combination regimen versus doxorubicin alone (12.2 vs 6.2 months; adjusted HR: 0.41; $p < 0.0001$). Benefits with doxorubicin plus trabectedin were also observed in overall response rate (38 vs 13%) and median OS (30.5 vs 24.1 months; HR: 0.74). As expected, toxicity with combination therapy was greater than with doxorubicin alone, although manageable [8].

Pazopanib is indicated for use in selected STS subtypes including LMS after previous chemotherapy for advanced or metastatic disease [1]. In a phase III trial of metastatic STS (n = 369) which included 165 patients with LMS, pazopanib significantly prolonged PFS (4.6 vs 1.6 months; HR: 0.31; $p < 0.0001$), but not OS, compared with placebo [9].

Other potential strategies for advanced lines of LMS treatment include gemcitabine monotherapy and combinations such as gemcitabine plus docetaxel, gemcitabine plus dacarbazine or gemcitabine plus vinorelbine [2]. Phase II studies of gemcitabine alone or gemcitabine–docetaxel indicated activity of both regimens in advanced LMS [10–12], although toxicity was greater in the combination arm, with more than 40% of patients discontinuing treatment for a variety of nonhematological toxicities [10]. Gemcitabine–dacarbazine was more effective than dacarbazine alone and was well tolerated in a phase II study of advanced STS (n = 32 with LMS; ~30%) [13]. A phase II trial of gemcitabine–vinorelbine in patients with advanced STS (n = 19 with LMS; 47.5%) reported a clinical benefit rate of 25% at >4 months, with acceptable toxicity [14].

Despite the range of chemotherapeutic choices for LMS, many unmet medical needs remain and there are clear gaps in current treatment standards. The Patient Powered Research Network of Sarcoma Patients EuroNet set up an international project in collaboration with stakeholders to identify priority topics for sarcoma research [15]. A

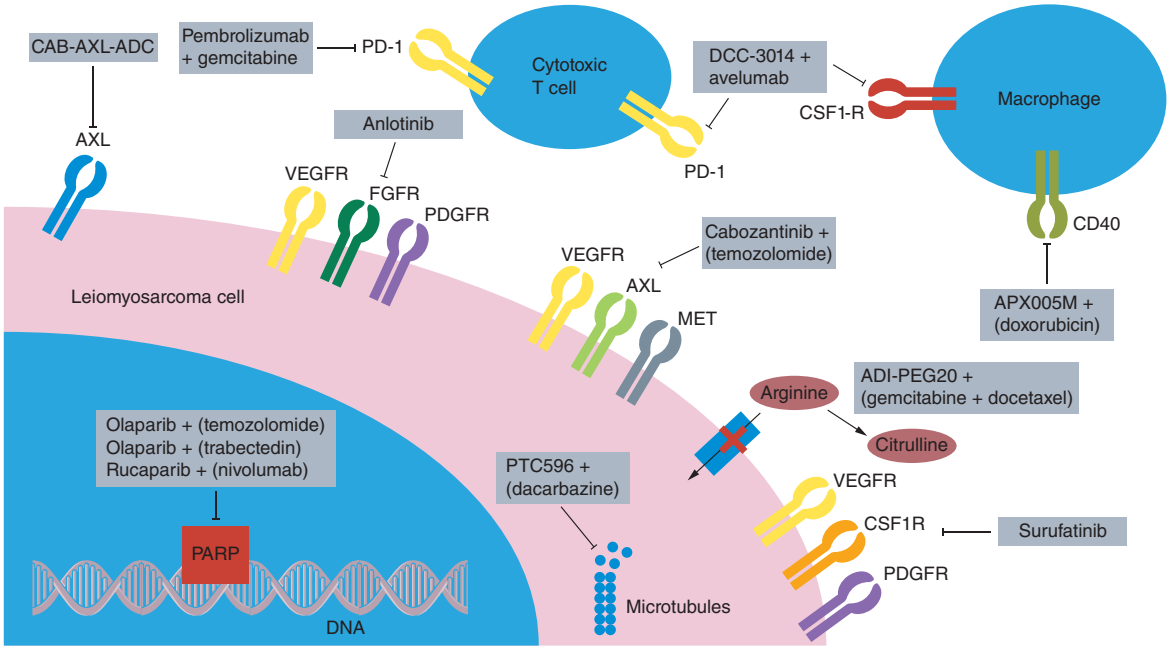

Figure 1. Potential new treatments and therapeutic targets for leiomyosarcoma.
ADI-PEG20: Arginine deiminase with 20,000-molecular-weight PEG; CAB-AXL-ADC: Conditionally active biologic AXL-targeted antibody drug conjugate.

questionnaire was used to capture views on diagnosis, treatment, support, quality of life, survivorship and end-of-life care. A total of 264 sarcoma patients or carers from around the world participated in the online survey. The methodology of the 'Priority Setting Partnership' initiative and respondents' characteristics are reported elsewhere [15]. Initial results identified priority topics for research or advocacy, as well as requests for more information [15]. The responses of a subset of 25 patients with LMS from eight countries (Germany, France, Spain, The Netherlands, UK, USA, Canada and Australia) were compiled separately, providing insight specific to this patient group. The unmet medical needs from the perspective of patients with LMS are summarized by category below [2].

Unmet needs in LMS from the patient perspective

Design LMS-specific studies

From the patient perspective, an unmet medical need is for the design of LMS-specific clinical studies that evaluate treatment sequence and combinations of available systemic therapies. At present, the evidence base for LMS derives mainly from clinical trials which included a range of heterogeneous STS types. Large, international, randomized, comparative and single-arm LMS-specific clinical trials are required, ideally providing an underlying biological rationale for the choice of intervention [2].

Explore new treatments & therapeutic targets for LMS

Patients have identified a need for new treatment avenues and therapeutic targets in LMS. Potential new agents under investigation for LMS include a conditionally active biologic anti-AXL antibody drug conjugate, pembrolizumab (anti-PD-1), anlotinib (anti-VEGF), DCC-3014 (anti-CSF1R) plus avelumab (anti-PD-L1), cabozantinib (inhibitor of multiple tyrosine kinases including RET, MET and VEGFR2), APX005M/sotigalimab (CD40 agonist), PEGylated arginine deiminase, surufatinib (inhibitor of VEGFR1, VEGFR2, VEGFR3, FGFR1 and CSF1R), PTC596 (tubulin binding agent), olaparib (anti-PARP), and rucaparib (anti-PARP) plus nivolumab (anti-PD-1) (Figure 1) [2]. Combining new agents with existing chemotherapeutic agents is also under investigation; for example, pembrolizumab plus gemcitabine [16,17], cabozantinib plus temozolomide [18], PEGylated arginine deiminase plus gemcitabine and docetaxel [19], APX005M/sotigalimab plus doxorubicin [20], and olaparib plus temozolomide [21] or trabectedin (Figure 1) [22–24]. The development of novel agents and new therapeutic targets for LMS requires

collaboration between laboratory and clinical researchers from both academia and industry to identify optimal approaches for individual patients [2].

Avoid morcellation

In cases of undetected uterine malignancy (about 1 in 500 women will have an unexpected diagnosis of uterine LMS) [2], morcellation of the uterus carries the risk of disseminating tumor cells into the pelvis and peritoneal cavity with consequent poorer prognosis [25,26]. Preoperative evaluation to identify a possible malignancy is essential. Total abdominal hysterectomy is a common alternative to morcellation although is not without risks, including blood loss, deep venous thrombosis and, very rarely, death. There is a clear need for greater collaboration between gynecological oncologists and sarcoma experts. The healthcare team should engage the patient in shared decision-making which involves informed consent and thorough explanation of the risks and benefits of each approach, the rationale for a biopsy prior to surgery, and alternatives to morcellation [2].

Explore the immune system in greater depth

Studies have shown that patients with advanced LMS have a poor response to checkpoint inhibitors including anti-PD-1/PD-L1 monotherapy [27,28], combined PD-1/CTLA4 inhibition [29] and PD-1 therapy combined with cyclophosphamide [30] or with the anti-VEGF tyrosine kinase inhibitor axitinib [31]. However, because retrospective studies suggest an underlying immunogenicity in LMS [32–34], clinical trials are underway to explore additional agents that exploit the immune system [2]. Preclinical and translational research is critical toward gaining a better understanding of response and resistance mechanisms in patients with LMS, and to develop biomarkers for specific immune subsets of LMS in order to better tailor combination therapies for patients [2].

Investigate the role of circulating tumor DNA as a means of matching targeted therapy & as a potential biomarker of prognosis, response to therapy & minimal residual disease

Next-generation sequencing (NGS) of circulating tumor DNA (ctDNA) is a rapid and noninvasive method which allows for the identification of genomic alterations in plasma. Uses of NGS include diagnosis, prognostic assessment, assessment of disease response to therapy and detection of recurrence. ctDNA is currently under evaluation in a pilot study as a biomarker of relapse-free survival and response to therapy in patients with localized LMS. A further study is planned of ctDNA as a biomarker of sarcoma response to chemotherapy in patients with metastatic LMS [2].

Implement molecular characterization of LMS to develop prognostic & predictive markers & design molecularly driven clinical trials

Three LMS subtypes with distinct transcriptomic profiles and clinicopathological characteristics have been identified; however, the molecular characteristics differentiating these subtypes are largely unknown. NGS of tumor specimens enables identification of specific gene alterations that can assist in tumor classification and suggest possible mutation-specific therapeutic targets or clinical trials. Molecular markers or genetic signatures could potentially explain the exceptional therapeutic benefit occasionally observed with a specific treatment in a specific patient. Molecular characterization might be achieved by developing a genomic and transcriptomic database containing a large number of diverse LMS tumors and corresponding clinical data [2].

Need for basic research & a translational pipeline

There is a critical lack of fidelity to the human disease in epigenetic and transcriptional programs conducted in established LMS cell lines [35,36]. As such, an urgent need exists for valid laboratory models and more complex preclinical models (e.g., coculture systems, syngeneic models, 'humanized' mice with immune cell engraftment) to identify new agents capable of targeting metabolic vulnerabilities or the immune system. Achieving these goals will require international collaborations within a coordinated research strategy to minimize overlap and maximize funding [2].

Evaluate imaging modalities to better distinguish the features of LMS

Radiomics is a method that uses data characterization algorithms to extract large amounts of quantitative data from medical images, which can be correlated with tumor histology and clinical outcomes. Radiomics entails tumor segmentation using software that analyzes various image features, yielding statistics that describe image signal intensity and spatial heterogeneity. Radiomic features have the potential to reveal tumoral patterns and

characteristics not visible to the naked eye and are known to independently predict OS in STS. In terms of application, radiological response criteria with radiomic features could expedite assessments of drug efficacy. This, in turn, could lead to clinical trials using radiomics to better define response to systemic therapy and improve diagnosis (e.g., LMS vs leiomyoma) [2].

Improve early detection & diagnosis

Given that about 40% of STSs are diagnosed in the locally advanced or metastatic stage, early detection and diagnosis is essential to improve survival. The 5-year survival rate for early-stage disease is currently 81%, compared with 16% for advanced/metastatic disease. Other priorities identified by LMS patients include the need to educate general practitioners to recognize sarcomas and to refer all cases of potential STS to reference centers. Measures to confirm a diagnosis of LMS more readily include improved imaging, education and training of radiologists and identification of innovative ways of detecting LMS, such as blood tests/ctDNA [2].

Identify patient-reported outcomes

The value of patient-reported outcomes (PROs) is increasingly being recognized in oncology. Identifying PROs involves developing a multidimensional scale specific to sarcoma (and to LMS specifically) that meets assessment criteria and provides scores relevant to clinical judgment [37]. Work on a multidimensional scale is underway at the Netherlands Cancer Institute (NKI), European Organisation for Research and Treatment of Cancer and University College London Hospitals. In the interim, patients can identify and share their experience by using individual PROs from item libraries such as the European Organisation for Research and Treatment of Cancer Quality of Life Group Item Library. Another approach may be to establish a consultative patient group to determine the research issues that are of greatest importance to patients and to develop patient input systems for longitudinal assessment via smartphones, tablets and internet links. Ultimately, LMS patients are seeking to have synchronous clinical and patient-reported pathway information that is able to inform physicians and patients throughout the entire diagnostic and treatment journey [2].

Improve communication, information & support

Due to the rarity of LMS, patients often feel 'lonely' with their disease and have a high need for information and support. The treating physician and associated team should be regarded as partners and important sources of information to support patients throughout their journey. At diagnosis, patients may appreciate being given the opportunity for a second opinion and receiving specific information about specialists and expert centers, about how the disease and its treatment will impact on daily life and about how to cope with the disease burden. During treatment, patients may require information about maintaining their quality of life and strengthening their physical and mental well-being through changes to lifestyle, diet or exercise. Other needs include psychosocial support, better physiotherapy and recovery care. As joint decision-making is an integral part of sarcoma care, honest communication and adequate information are essential along the entire treatment trajectory [2].

Address survivorship & end-of-life care issues

Sarcoma survivors often feel alone and insecure when returning to a 'new normal' life. There are no specific follow-up procedures in this regard, and the potential risk of late effects can be a burden to patients and family. End-of-life care is a delicate but important issue that needs to be addressed in a sensitive manner. Questions from patients – what to expect during the last part of the journey, whether there is a choice of where to die and how to communicate clearly with their families – must be answered honestly and transparently [2].

The unmet needs identified by LMS patients are summarized by category in Figure 2.

Conclusion

The management of LMS is evolving, as evidenced by the growing range of treatment options and ongoing research activity dedicated to identifying new therapies and biomarkers of disease and response. Gaining patients' perspectives on unmet needs can assist in the design of new LMS-specific studies to address their concerns. The Priority Setting Partnership project has emphasized the importance of involving patients in the quest for better outcomes.

Figure 2. Unmet needs identified by patients with leiomyosarcoma in an international project sponsored by the Sarcoma Patients EuroNet.
LMS: Leiomyosarcoma.
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Future perspective

Although less rare than other histological subtypes, accounting for up to 25% of all STS cases [38], LMS is nonetheless a major therapeutic challenge. Depending on location, symptoms may be absent until advanced disease, and recurrence is common even after successful primary resection [39]. The effectiveness of currently available systemic treatments for advanced or metastatic LMS is limited and unpredictable, and the overall prognosis is poor [38].

The process of selecting treatment for patients with advanced or metastatic STS involves defining treatment goals and setting individual expectations. Although patient-centric in principle, in practice most of the evidence informing clinical decision-making is based on disease control and survival outcomes. PROs such as general and psychological well-being, health-related quality of life and treatment satisfaction [40], if assessed at all in oncology clinical trials, are generally not the main outcomes of interest. The reasons are myriad and include uncertainty about choice of instrument, perception of importance versus 'hard' end points, staff and participant burden, and concerns about data quality [41].

The current environment underscores the importance of the Priority Setting Partnership initiative, which invited patients, carers, clinicians and industry professionals from around the world to identify uncertainties regarding sarcoma management and to identify ways of involving patients and carers in research. An open-question approach was used to determine which questions participants would most like to see answered by research in the areas of diagnosis, treatment, support, health-related quality of life, survivorship and end-of-life issues. The 264

sarcoma patients and carers in total who participated in the online survey indicated a clear interest in research on better diagnostic techniques, innovative treatments, quality-of-life issues such as long-term side effects, mental and emotional aspects of treatment and end-of-life care [15]. The separate analysis and compilation of responses provided by the 25 participants with LMS has offered first-of-its-kind insight into unmet medical needs from their perspective. LMS patients expressed a clear desire for individualized biology-driven treatment as standard of care, subtype-specific clinical trials and open and honest communication that addresses the psychosocial and physical challenges of living with LMS [2]. As the authors openly acknowledged, the first phase of the Priority Setting Partnership project was limited by the small number of participants and their representativeness of the entire sarcoma population. Strategies have thus been developed to reach under-represented populations in the next phase of the project [15]. At present, the Priority Setting Partnership initiative represents a valuable first step that is useful for investigators, regulatory agencies and, not least, clinicians who may better relate to the needs of their patients with LMS.

The Priority Setting Partnership project is not trivial as it is incumbent on the sarcoma community to adopt new models for trial design and approaches to patient care in clinical practice to improve outcomes. As future therapies increasingly become adapted to clinical and histological molecular subtypes, sarcoma clinicians must be prepared to meet the challenge of selecting the right drug for the right patient at the right time, according to the patient's lifestyle and wishes.

Executive summary

- As with all cases of soft tissue sarcoma, patients with leiomyosarcoma (LMS) should be managed by a multidisciplinary team in a sarcoma reference center.
- Surgery performed by a specifically trained surgeon is standard treatment for most cases of localized LMS; radiotherapy and adjuvant/neoadjuvant chemotherapy can be considered in selected cases.
- Anthracycline-based regimens are standard first-line therapy for advanced LMS.
- Options from second line include trabectedin, pazopanib, and gemcitabine alone or in combination.
- Despite the range of chemotherapeutic choices for LMS, many unmet medical needs remain.
- An international patient network-driven project was conducted to identify priority topics for sarcoma research.
- A separate compilation of responses from 25 patients with LMS has provided first-of-its-kind insight into the needs of this specific group.
- Information gathered from the Priority Setting Partnership initiative can be used to guide the design of innovative clinical trials and basic research to close gaps in the management of LMS and other soft tissue sarcoma subtypes.

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