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REVIEW ARTICLE

Soft Tissue and Uterine Leiomyosarcoma

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A B S T R A C T

Leiomyosarcoma (LMS) is one of the most common subtypes of soft tissue sarcoma in adults and can occur in almost any part of the body. Uterine leiomyosarcoma is the most common subtype of uterine sarcoma. Increased awareness of this unique histology has allowed for the development of drugs that are specific to LMS and has begun to shed light on the similarities and possible unique aspects of soft tissue and uterine LMS. In this review, we summarize the current understanding of the epidemiology, diagnosis, genomics, and treatment options for LMS.

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EPIDEMIOLOGY

Leiomyosarcoma (LMS) is one of the most common subtypes of malignant mesenchymal neoplasms and represents approximately 10% to 20% of all newly diagnosed soft tissue sarcomas (STSs).[1] Common locations include the abdomen, retroperitoneum, larger blood vessels, and the uterus. LMS is less common in the extremities compared with other sarcoma subtypes, accounting for 10% to 15% of limb sarcomas, with preference for the thigh. LMS of the uterus (uLMS) is the most common subtype of uterine sarcoma and likely accounts for the single largest site-specific group of LMS.[2]

As in STSs in general, the overall incidence of LMS increases with age and peaks at the seventh decade of life. In contrast, uLMS occurs from the third decade into old age, but is most common in the perimenopausal age group—the fifth decade of life.[3] The sex incidence greatly depends on tumor location, with women comprising a clear majority of patients with retroperitoneal and inferior vena cava LMS, whereas there is a mild male predominance in noncutaneous soft tissue sites and cutaneous LMS.[3]

ETIOLOGY AND PREDISPOSING FACTORS

Most patients have no clear predisposing factors for the development of LMS. Patients with hereditary retinoblastoma have a cumulative risk of 13.1% for developing any STS as a secondary malignancy, including LMS,[4] which is in agreement with the relevance of *RB1* loss in sporadic LMS (see below). Similarly, patients with inherited *TP53* mutations—Li-Fraumeni syndrome—are at risk for developing sarcomas, including LMS, of any site.[5] In one study of patients with Li-Fraumeni syndrome, 7% to 8% developed LMS at a median age of 44 years.

Radiation exposure also increases the risk of developing sarcomas, including LMS.[6] Whereas tamoxifen use is most closely associated with an increased risk for endometrial carcinomas, there are reports of uLMS associated with tamoxifen exposure.[7]

PATHOLOGY AND TUMOR BIOLOGY

Histopathology

LMS is a malignant mesenchymal tumor composed of cells that show distinct features of the smooth muscle lineage. The typical histologic pattern of LMS of any origin is that of intersecting, sharply marginated fascicles of spindle cells with abundant eosinophilic cytoplasm and elongated and hyperchromatic nuclei.[3] Focal pleomorphism is common, and some patients show extensive pleomorphism that resembles any undifferentiated STS.[8] The majority of LMS are reactive for α-smooth muscle actin, desmin, and h-caldesmon on immunohistochemistry, although none of these markers is specific for smooth muscle differentiation.

Stanford criteria are commonly used for histologic diagnosis of uLMS, incorporating the presence of histologic atypia, tumor cell necrosis, and an elevated mitotic rate.[9] Estrogen receptors (ERs) and/or progesterone receptors (PRs) have been reported to be positive in 40% to 70% of patients and may have prognostic significance.[10] Because of the nuances of histologic diagnosis—particularly in light of

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additional complex smooth muscle tumors of the uterus, including atypical leiomyomas and smooth muscle tumors of uncertain malignant potential—expert review by gynecologic and/or sarcoma pathologists is recommended for LMS of any site.

Tumor Biology

Standard karyotyping and fluorescent in situ hybridization techniques as well as more recent DNA copy number variation studies have demonstrated that cytogenetic and molecular changes in LMS are complex.[11,12] The most consistent changes that have been detected across several studies are losses that involve two tumor suppressor genes, *RB1* (10q) and *PTEN* (13q).[11,12] Recent whole-exome sequencing of LMS and uLMS has confirmed this highly heterogeneous genomic landscape and has demonstrated frequent alterations in *TP53*, *RB*, *ATRX*, and *MED12*.[13,14]

Recently, The Cancer Genome Atlas performed a multiplatform molecular characterization of multiple subtypes of soft tissue sarcoma, including 53 soft tissue LMS and 27 uLMS.[60] Overall, sarcomas were noted to have low mutational burdens compared with other tumors in the Cancer Genome Atlas project. In addition, analysis confirmed mutations and deletions in *RB1, p53*, and *PTEN* as common events in LMS of any site. Somatic copy number alterations were commonly observed without clear distinction between sites of LMS; however, distinct methylation and mRNA signatures were noted between uLMS and soft tissue LMS, some of which have prognostic implication. Of interest, uLMS was noted to have a higher DNA damage response score, whereas soft tissue LMS was noted to have a more prominent hypoxia-inducible factor-1α signaling signature. Gene expression studies have been performed previously in LMS and identified three reproducible molecular subtypes that are overall distributed similarly over LMS and uLMS.[15] Subtype I LMS expresses most genes associated with smooth muscle differentiation, tends to be the conventional LMS subtype, and demonstrates improved outcome compared with subtype II LMS, which, in turn, represents a less differentiated form of LMS and partially overlaps in a subset of patients with undifferentiated pleomorphic sarcoma. Subtype III LMS is the only subtype that displays a preference for a specific anatomic site and was more likely to be from the uterus, although uLMS is evenly distributed over the three subtypes. Although intriguing from a research perspective, gene expression remains an investigational technique and has not yet been applied to clinical practice in the care of patients with LMS of any site.[15]

Several pathways and signal intermediates have been investigated in LMS, and the relevance of the activation of the phosphatidylinositol 3-kinase/AKT pathway has been consistently demonstrated throughout several studies.[16] Indeed, genomic deletion of chromosome 10q targets the *PTEN* tumor suppressor gene and leads to the hyperactivation of phosphatidylinositol 3-kinase/AKT, which is a common finding in LMS. Although approximately one half of LMS expresses insulin-like growth factor (IGF)-1R and IGF-II,[13,17] the relevance of IGFR in the proliferation and survival of LMS is yet to be elucidated.

Despite the increase in descriptive knowledge of genomic abnormalities and mutated signaling pathways in LMS, none of these has been proven to serve as effective therapeutic targets. Studies are ongoing to increase our understanding of the complex biologic underpinnings of LMS.

PRINCIPLES OF GENERAL MANAGEMENT

Diagnosis

Clinical presentation of LMS, as with other STSs, is often associated with nonspecific symptoms caused by the displacement of structures, rather than invasion, in specific anatomic locations of the primary tumor and its metastases. Pretreatment biopsy is mandatory in extrauterine sites, with core biopsy the preferred technique. Detailed pathologic evaluation is typically performed after complete resection. Although endometrial biopsy may rarely yield a diagnosis of uLMS, it is far more common to have a negative endometrial biopsy or curettage as LMS is a disease of the myometrium. In many cases the diagnosis of uLMS is made at the time of hysterectomy.

Imaging approaches include magnetic resonance imaging in soft tissue extremity/truncal tumors and uterine masses, and contrast-enhanced computed tomography scan for retroperitoneal lesions. Chest and abdominal computed tomography scan is required in the initial workup, as hematogenous spread is a frequent event in LMS, with the lung and liver as two common sites of metastases.

Unfortunately, in uLMS, no single imaging criterion can reliably distinguish a benign uterine tumor from one that is malignant. Intrauterine masses that had been considered to be benign fibroids, but that continue to increase in size after menopause, should raise suspicion for malignancy. One study of preoperative magnetic resonance imaging for patients with uterine mesenchymal neoplasms demonstrated poor accuracy in distinguishing leiomyomas with atypical features from malignant mesenchymal neoplasms.[18] A more recent study identified combinations of qualitative magnetic resonance features that could accurately differentiate LMS from atypical leiomyoma.[19]

Prognostic Factors

Histologic grade, tumor size, and tumor depth are the three major clinicopathologic prognostic factors for STSs, including extra-uLMS,[20,21] and all are included in the American Joint Committee of Cancer staging system (Table 1). LMS has substantial intrinsic aggressiveness as one of the sarcoma subtypes with the highest risk of distant recurrence and decreased disease-specific survival.[20] In contrast, uLMSs are staged by using the Federation of Gynecology and Obstetrics (FIGO) 2009 staging system (Table 2), which does not include tumor grading. Five-year survival estimates of uLMS by FIGO stage for stage I is 76%; stage II, 60%; stage III, 45%; and stage IV, 29%. Other factors that have been evaluated for their potential prognostic effect include tumor fragmentation,[22] extrauterine spread, mitotic index, and tumor grade, although tumor grade in uLMS remains an area of controversy and is not routinely applied to diagnostic or staging procedures.[23]

TREATMENT OF LMS AND uLMS

Localized Disease

Surgical resection is the cornerstone treatment for patients with localized LMS, independent of the site of origin. The standard surgical procedure involves a complete excision with wide negative margins (R0 resection), which offers the best chance of cure; however, because many LMSs are large and located in the retroperitoneum,

Table 1. American Joint Committee of Cancer Version 7 Staging System for Soft Tissue Sarcoma

Staging System				
Primary tumor (T)				
TX	Primary tumor cannot be assessed			
T0	No evidence of primary tumor			
T1	Tumor ≤ 5 cm in greatest dimension			
T1a	Superficial tumor			
T1b	Deep tumor			
T2	Tumor > 5 cm in greatest dimension			
T2a	Superficial tumor			
T2b	Deep tumor			
Regional lymph nodes (N)				
NX	Regional lymph nodes cannot be assessed			
N0	No regional lymph node metastasis			
N1	Regional lymph node metastasis			
Distant metastases (M)				
M0	No distant metastasis			
M1	Distant metastasis			
Histologic grade (G)				
GX	Grade cannot be assessed			
G1	Grade 1			
G2	Grade 2			
G3	Grade 3			
Anatomic stage				
Stage IA	T1a	N0	M0	G1, GX
	T1b	N0	M0	G1, GX
Stage IB	T2a	N0	M0	G1, GX
	T2b	N0	M0	G1, GX
Stage IIA	T1a	N0	M0	G2, G3
	T1b	N0	M0	G2, G3
Stage IIB	T2a	N0	M0	G2
	T2b	N0	M0	G2
Stage III	T2a, T2b	N0	M0	G3
	Any T	N1	M0	Any G
Stage IV	Any T	Any N	M1	Any G

achieving surgical R0 resection is challenging as a result of anatomic constraints. The ability to perform a complete surgical resection at the time of initial presentation is the most important prognostic factor for survival.[24]

For uLMS, hysterectomy is recommended for patients whose disease seems to be limited to the uterus. Uterine morcellation procedures have been associated with the intra-operative spread of malignant tissue and poorer survival outcomes.[22] Routine lymph node dissection is not generally required because the risk of occult metastatic disease to lymph nodes is low. Lymph nodes that appear enlarged and/or suspicious for malignant involvement should undergo resection.[25] Bilateral salpingo-oophorectomy is reasonable in perimenopausal and postmenopausal women, although it is recognized that there are no data to indicate that oophorectomy improves survival outcomes.[25] For uLMS disease that appears locally advanced but potentially completely resectable, an attempt to resect all visible disease is reasonable. Retrospective data have demonstrated longer overall survival (OS) among women whose disease is completely resected compared with those with residual disease.[26]

Adjuvant Radiotherapy

Radiation therapy, either pre- or postoperatively, leads to improved local control rates in localized STS of the extremity and trunk, but there are no randomized data that address this question in retroperitoneal sarcomas, which leads to institutional variation on the use of radiation in this setting. A large, multinational trial that addresses this question (ClinicalTrials.gov identifier: NCT01344018) has recently completed accrual, and results will inform future practice standards.

Adjuvant pelvic radiation is not recommended for patients with FIGO stage I uLMS as a prospective randomized trial demonstrated no improvement in local recurrence rates and OS outcomes in uterine sarcomas, including uLMS.[27]

Adjuvant Systemic Therapy

Despite complete, intact resection of uterus-limited, high-grade LMS, the risk of recurrence after complete resection of uLMS approaches 50% to 70%,[28] and is approximately 40% in extra-uLMS.[29] Subsequent efforts have been pursued to evaluate adjuvant therapy, although its role remains poorly understood.

There have been no specific trials of adjuvant chemotherapy in LMS that originates outside of the uterus, although LMS has been included in more comprehensive trials of adjuvant chemotherapy in STS. There is institutional variation in the use of adjuvant chemotherapy for LMS on the basis of the interpretation of data from trials of systemic therapy for high-grade, extremity-localized STS in general. Combination docetaxel and gemcitabine has been proven as an effective regimen in patients with metastatic uLMS; therefore, it has been investigated as an adjuvant regimen. A prospective phase II study of adjuvant gemcitabine plus docetaxel for four cycles, followed by doxorubicin for four cycles, in women with uterus-limited uLMS demonstrated a 2-year progression-free survival (PFS) rate of 78% and a 3-year PFS rate of 58%[30]; however, this PFS rate did not seem to be superior to outcomes among women who were observed in informal cross-trial comparison. An international, randomized, phase III trial of observation versus adjuvant chemotherapy failed to recruit patients and definitively closed in 2016. Whether there is benefit from adjuvant docetaxel plus gemcitabine in patients with FIGO stage I uLMS remains unanswered, and observation is a standard approach. Similarly, there are no prospective data that address adjuvant chemotherapy for more advanced, completely resected disease.

Metastatic Disease

Surgery. Patients with metastatic LMS of any site should be evaluated to determine whether the resection of metastases may be

Table 2. Federation of Gynecology and Obstetrics Staging System for Uterine Sarcomas

Stage	Definition
I	Tumor limited to the uterus
IA	Tumor ≤ 5 cm greatest dimension
IB	Tumor > 5 cm in greatest dimension
II	Tumor extends beyond the uterus, within the pelvis
IIA	Tumor involves adnexa
IIB	Tumor involves other pelvic tissues
III	Tumor infiltrates abdominal tissues
IIIA	One site
IIIB	More than one site
IIIC	Regional lymph node metastasis
IV	Invasion of organs and/or distant metastasis
IVA	Tumor invades bladder or rectum
IVB	Distant metastasis

appropriate. In general, resection should be considered for patients with a relatively long disease-free interval and an isolated site of disease that is amenable to complete resection, with an acceptably low risk of morbidity.[31] There are no data that evaluate adjuvant systemic treatment after metastasectomy, and the standard approach is surveillance.

Systemic Treatment of Unresectable Metastatic Disease

Chemotherapy. The different STS subtypes have recognized variable patterns of chemosensitivity, and LMS show moderate sensitivity to chemotherapy, whereas uLMS seems to be overall more responsive.[32] There is no established best first-line chemotherapy treatment. Regimens to consider for first-line therapy are listed in Table 3 and include doxorubicin-based therapies such as doxorubicin plus ifosfamide[33] and doxorubicin plus olaratumab,[34] as well as gemcitabine plus docetaxel.[35-37]

Combination docetaxel plus gemcitabine, unlike other STSs, seems to be particularly effective in LMS as both first-line and second-line treatments in patients who have previously received anthracycline-based therapy. The phase II study, Comparison of Gemcitabine Versus Gemcitabine Plus Docetaxel in Unresectable Soft Tissue Sarcoma (SARC002) demonstrated improved objective response, PFS, and OS with gemcitabine plus docetaxel compared with gemcitabine alone in advanced, previously treated STS.[42] This study also confirmed the higher sensitivity of LMS and uLMS to this regimen, which had been observed previously in nonrandomized clinical trials.[43,44] In contrast, the study, Randomized Multicenter and Stratified Phase II Study of Gemcitabine Alone Versus Gemcitabine and Docetaxel in Patients With Metastatic or relapsed Leiomyosarcomas: A Federation Nationale des Centres de Lutte Contre le Cancer French Sarcoma Group Study (TAXOGEM) only observed benefit of the combination in uLMS, but this was not statistically significant.[45] These encouraging results in second-line treatment and beyond were explored to the first line. The phase III multicenter trial, Gemcitabine and Docetaxel Versus Doxorubicin as First-Line Treatment in Previously Untreated Advanced Unresectable or Metastatic Soft-Tissue Sarcoma (GeDDiS) did not observe differences in response rate and PFS from first-line docetaxel plus gemcitabine treatment compared with single-agent doxorubicin, with both regimens demonstrating activity in both LMS and uLMS.[38] Only doxorubicin in combination with olaratumab has demonstrated an OS benefit; when compared with doxorubicin alone, however, the number of patients with LMS was relatively small, and a confirmatory phase III trial is pending. Given the broad number of regimens with activity in first-line therapy, treatment recommendations for an individual patient should take into consideration individual patient circumstances.

Several regimens have shown activity in LMS as second-line treatment or later and are listed in Table 4. Trabectedin is approved in patients with unresectable or metastatic liposarcoma or LMS/uLMS who received a prior anthracycline-containing regimen on the basis of a phase III trial that demonstrated trabectedin superiority over dacarbazine in PFS, but not in objective response rate (ORR) or OS.[46] The efficacy and safety of trabectedin in patients with uLMS was confirmed in a later subgroup analysis from the phase III trial.[51] Several studies, including data from 431 patients with LMS of any origin who were treated in a trabectedin expanded access program demonstrated an ORR of 7.5% in patients with LMS compared with 5.9% among patients with all-type STS.[52] Likewise, patients with L-sarcomas (LMS and liposarcomas) obtained a higher clinical benefit rate (54%) and median OS (16.2 months) than did patients with non–L-sarcomas (38% and 8.4 months, respectively). Trabectedin also demonstrated activity as a first-line treatment in LMS or uLMS, either alone or in combination with doxorubicin in two nonrandomized phase II trials.[39,40] However, a subsequent randomized trial of trabectedin plus doxorubicin compared with doxorubicin alone demonstrated no improvement in response rates (17% in both arms) or PFS (5.7 months *v* 5.5 months; Table 3).[41]

The small-molecule inhibitor pazopanib also has activity in LMS and uLMS. Pazopanib improved PFS (4.6 months *v* 1.6 months) compared with placebo in STS, although there was no difference in OS, and ORR was observed in only 4% of patients.[47] Pazopanib demonstrated modest efficacy in a subgroup analysis of patients with uLMS (response rate, 11%; PFS, 3 months; OS, 17.5 months; Table 4).[53]

In another phase III trial for L-sarcomas, eribulin demonstrated superior OS benefit compared with dacarbazine, but this was not the case for PFS or response rate.[48] These data led to US Food and Drug Administration approval of eribulin for liposarcoma, but not for LMS on the basis of preplanned subgroup analysis. Finally, other agents or regimens have been reported to have activity in LMS, such as dacarbazine,[46,48] gemcitabine

Table 3. Early-Line Systemic Therapies Evaluated in STS and LMS/uLMS

Regimen	First Author	Phase	No. of Patients	Type of Sarcoma	No. LMS	Line	RR (%)	PFS (months)	OS (months)
Doxorubicin *v* doxorubicin + ifosfamide	Judson[33]	III	455	STS	103	First	14 *v* 26	4.6 *v* 7.4	12.8 *v* 14.3
Doxorubicin *v* doxorubicin + olaratumab	Tap[34]	II-R	133	STS	51	First	11.9 *v* 18.2	4.1 *v* 6.6	14.7 *v* 26.5
Gemcitabine + docetaxel	Hensley[35]	II	42	uLMS	42	First	35.8	4.4	16.1
Gemcitabine + docetaxel	Seddon[36]	II	44	LMS/uLMS	44	First	25	7.1	17.9
Gemcitabine + docetaxel ± bevacizumab	Hensley[37]	III	107	uLMS	107	First	31.5 *v* 35.8	6.2 *v* 4.2	26.9 *v* 23.3
Doxorubicin *v* gemcitabine + docetaxel	Seddon[38]	III	257	STS	NA	First	NA	5.3 *v* 5.5	16.3 *v* 14.5
Trabectedin	Monk[39]	II	22	uLMS	22	First	10	5.8	> 26.1
Doxorubicin + trabectedin	Pautier[40]	II	109	LMS/uLMS	109	First	39.4/59.6	12.9/8.2	34.5/20.2
Doxorubicin *v* doxorubicin + trabectedin	Martín-Broto[41]	II-R	115	STS	35	First	17 *v* 17	5.5 *v* 5.7	13.7 *v* 13.3

NOTE. Slash symbol in outcome columns (RR, PFS, OS) shows separated LMS and uLMS data.
Abbreviations: LMS, leiomyosarcoma; NA, not available; OS, overall survival; PFS, progression-free survival; R, randomized; RR, response rate; STS, soft tissue sarcoma; uLMS, uterine leiomyosarcoma.

Table 4. Later-Line Systemic Therapies Evaluated in STS and LMS/uLMS

Regimen	First Author	Phase	No. of Patients	Type of Sarcoma	No. LMS	Line	RR (%)	PFS (months)	OS (months)
Gemcitabine *v* gemcitabine + docetaxel	Maki[42]	II-R	122	STS	38	> 1	8 *v* 16	3 *v* 6.2	11.5 *v* 17.9
Gemcitabine + docetaxel	Hensley[44]	II	43	LMS/uLMS	43	≥ 1	52.9	5.6	17.9
Gemcitabine + docetaxel	Hensley[43]	II	51	uLMS	51	≥ 1	27.1	6.7	14.7
Gemcitabine *v* gemcitabine + docetaxel	Pautier[45]	II-R	90	LMS/uLMS	90	0-1	14/19 *v* 5/24	6.3/5.5 *v* 3.4/4.7	15/20 *v* 13/23
Trabectedin *v* DTIC	Demetri[46]	III	518	STS	378	> 1	9.9 *v* 6.9	4.2 *v* 1.5	12.4 *v* 12.9
Pazopanib *v* placebo	Van der Graaf[47]	III	369	STS	NA	> 1	6 *v* 0	4.6 *v* 1.6	11.9 *v* 10.4
Eribulin *v* DTIC	Schoffski[48]	III	452	STS	215	> 1	4 *v* 5	2.6 *v* 2.6	13.5 *v* 11.5
DTIC *v* gemcitabine + DTIC	García del Muro[49]	II	113	STS	32	> 1	4 *v* 12	2 *v* 4.2	8.2 *v* 16.8
Liposomal doxorubicin	Sutton[50]	II	32	uLMS	32	> 1	16.1	NA	NA

NOTE. Slash symbol in outcome columns (RR, PFS, OS) shows separated LMS and uLMS data.
Abbreviations: DTIC, dacarbazine; LMS, leiomyosarcoma; NA, not available; OS, overall survival; PFS, progression-free survival; R, randomized; RR, response rate; STS, soft tissue sarcoma; uLMS, uterine leiomyosarcoma.

monotherapy,[42,45] gemcitabine plus dacarbazine,[49] and liposomal doxorubicin.[50]

Antihormone therapies. A small prospective study of the aromatase inhibitor letrozole in patients with ER- and/or PR-positive uLMS demonstrated a 12-week PFS rate of 50% with a median duration of treatment of 2.2 months.[54] Of interest, three patients, all of whom had tumors that expressed ER and PR in > 90% of tumor cells, continued to receive letrozole for > 24 weeks. Thus, hormonal blockade may also be considered for patients with uLMS with low disease burden and indolent disease pace, particularly if their tumors are ER and PR positive.[10] Of importance, prior retrospective data have suggested that high expression of ER/PR in uLMS is associated with an indolent clinical course, and, therefore, the effect of aromatase inhibition on PFS may be confounded by favorable tumor biology.[55]

Immunotherapy. Checkpoint inhibitors have been explored as a therapeutic modality in both uLMS and extra-uLMS. There have been rare case reports of responses to single-agent programmed death-ligand 1 antibodies, although predictive markers of response remain undefined in this patient population.[56] A one-arm study of single-agent nivolumab in patients with advanced uLMS, which closed after the first stage of accrual (12 patients) for lack of efficacy, demonstrated no objective responses and a median PFS of 1.8 months.[57] Similarly, in a single-arm phase II trial that combined pembrolizumab with metronomic cyclophosphamide in STS, no patients with LMS demonstrated predefined clinical benefit, and PFS was only 1.4 months.[58] A randomized phase II study evaluated nivolumab versus nivolumab plus ipilimumab in patients with STS.[59] Patients with LMS comprised approximately one third of 85 enrolled patients. ORR was 3% in the nivolumab arm and 16% in the nivolumab plus ipilimumab arm. Among the eight of 85 patients who achieved a response, three had LMS. Observed PFS was 2.1 months with nivolumab and 4.4 months with nivolumab plus ipilimumab.

Although there may be rare case reports of response to checkpoint inhibition in LMS, use of these agents is not warranted outside of the clinical trial setting. It is hoped that biomarkers of response may be identified that will help to optimize treatment choices for patients with LMS.

SUMMARY

LMS is one of the more common subtypes of soft tissue sarcoma. A multidisciplinary approach is important for the diagnosis and treatment of these rare cancers. Surgery remains the mainstay of therapy for primary, localized disease. Doxorubin-based regimens and gemcitabine-based regimens are the backbone of early-line therapy for metastatic disease, but multiple newer agents have recently been approved for later-line advanced disease. Ongoing efforts to increase our understanding of the biologic underpinnings of the disease are critical to continued progress in improving the lives of patients with this disease. International consortia are essential to collect data and carry out clinical trials in patients with rare cancers.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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