Retrospective Analysis of *BRCA*-Altered Uterine Sarcoma Treated With Poly(ADP-ribose) Polymerase Inhibitors

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ABSTRACT

PURPOSE Uterine sarcomas are rare, aggressive tumors with limited chemotherapy responsiveness. Poly(ADP-ribose) polymerase inhibitors (PARPis) have emerged as targeted therapies for patients with *BRCA* mutations across multiple cancer types, with anecdotal responses in uterine sarcoma. This retrospective, single-center study aims to describe relevant genomic and clinical features of patients with *BRCA*-altered uterine sarcoma and the efficacy of PARPis in this population.

METHODS Eligible patients included all histopathologically confirmed uterine sarcoma with pathogenic *BRCA* alterations identified through Memorial Sloan Kettering Cancer Center-integrated mutation profiling of actionable cancer targets, excluding carcinosarcoma. Genomic, pathologic, and treatment information was extracted from the cBioPortal database and chart review.

RESULTS Thirty-five patients were identified with uterine sarcoma harboring pathogenic *BRCA* alterations, including 33 *BRCA2* alterations (70% homozygous deletions, 3% structural variants, 27% mutations) and two *BRCA1* mutations. Leiomyosarcoma (LMS) was the most common histology (86%). Thirteen patients with uterine LMS were treated with PARPis in the recurrent/metastatic therapy setting (54% combination therapy regimens) with an overall response rate (ORR) of 46% (1 of 6 for PARPi monotherapy, 5 of 7 for PARPi combination regimens), a clinical benefit rate (CBR) of 62%, and a median progression-free survival (PFS) of 13.2 months (range, 1.0-71.9). The median PFS ratio compared with previous systemic therapy was 1.9 (range, 0.4-53.9), and 58% had a PFS ratio of ≥1.3. The median time on PARPi was 14.5 months (range, 1.3-71.9). The ORR for patients with somatic *BRCA2* deletions was 60% (n = 6 of 10), with a CBR of 80% (n = 8 of 10). One patient with metastatic disease and progression on previous hormonal and chemotherapy demonstrated a complete response to PARP/PD-L1 inhibitor combination therapy, ongoing for 70+ months.

CONCLUSION PARPis demonstrate promising efficacy in patients with uterine LMS with somatic *BRCA2* deletions.

ACCOMPANYING CONTENT

Appendix

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INTRODUCTION

Uterine sarcomas are rare gynecologic malignancies representing 1% of all cancers of the female reproductive tract and 3%-7% of all uterine malignancies.[1] Uterine leiomyosarcoma (LMS), which arises from the smooth muscle of the myometrium, is the most common uterine sarcoma. Uterine LMS demonstrates aggressive behavior and is associated with high rates of progression and recurrence, regardless of stage at diagnosis.[2] Five-year survival rates range from 65% for early-stage disease to 15% for patients with metastatic disease.[3]

The mainstay of treatment for uterine LMS is complete surgical resection.[1] There are a number of systemic treatment options for control of metastatic disease. For advanced and/or recurrent uterine LMS, doxorubicin plus trabectedin or gemcitabine/docetaxel is the preferred first-line regimen, with reported median progression-free survival (PFS) of 12 months and 4-6 months, respectively.[4-7]

Poly(ADP-ribose) polymerase inhibitors (PARPis) have emerged as an effective targeted therapy across different cancer types.[8] PARPis interfere with the repair of single-strand breaks in DNA, inducing synthetic lethality in cells with loss-of-function alterations in *BRCA* and other homologous recombination repair genes.[9] PARPis are currently US Food and Drug Administration–approved for treatment of *BRCA*-altered breast, ovarian, prostate, and pancreatic

CONTEXT

Key Objective

What is the efficacy of poly(ADP-ribose) polymerase inhibitors (PARPis) in patients with recurrent/metastatic *BRCA*-altered uterine sarcoma?

Knowledge Generated

In this small retrospective study, PARPi monotherapy and combination therapy regimens showed an overall response rate of 46%, a clinical benefit rate of 62%, and a median progression-free survival of 13.2 months (range, 1.0-71.9 months) for patients with *BRCA*-altered uterine leiomyosarcoma, with responses observed only in patients with *BRCA2* homozygous deletions. These clinical end points appeared to largely outperform standard chemotherapies currently used for non–first-line uterine sarcoma treatment.

Relevance

PARPis should be considered as a treatment option for patients with uterine sarcoma harboring *BRCA2* deep deletions.

cancers, and studies continue to investigate their efficacy in other cancers, including a recent trial of talazoparib in patients with 20 different *BRCA1/2*-mutated tumor types.[10]

Uterine sarcomas exhibit high rates of somatic mutations in homologous recombination DNA damage response (DDR) genes (15%-28%), which has been associated with lower PFS on standard first-line chemotherapy and lower overall survival compared with wild-type DDR gene status.[11,12] Particularly, enrichment in *BRCA2* homozygous deletions (5%) has been identified in uterine LMS,[13] indicating potential for use of PARPis in this population. Favorable results have recently been noted for small sample sizes of *BRCA*-altered uterine sarcomas treated with PARPis. In 2023, Schram et al[14] reported the results of a phase IIb tumor-agnostic trial of PARPi in combination with PD-L1 inhibitors, which found that 3 of 3 patients with *BRCA1/2*-altered uterine LMS included in the study demonstrated prolonged objective responses. On continuous follow-up, we found that one of these patients—who had metastatic disease and previous progression on letrozole and gemcitabine/docetaxel—has had a 70-month ongoing complete response (CR) and currently remains on talazoparib with no significant toxicities (Fig 1). Given these promising initial findings, we performed a retrospective analysis of all patients with *BRCA*-altered uterine sarcoma treated with PARPis at our institution to further describe the efficacy of PARPi therapy in this patient population.

METHODS

Eligible Patients

This study retrospectively analyzed all patients with histopathologically confirmed uterine sarcoma at the Memorial Sloan Kettering Cancer Center (MSK) with *BRCA* alterations identified through MSK-integrated mutation profiling of actionable cancer targets (IMPACT) next-generation sequencing (NGS).[15] The study was approved by the Institutional Review Board. The cBioPortal database MSK Clinical Sequencing Cohort was queried for patients with cancer type listed as uterine sarcoma from January 2014 through June 18, 2024.[16,17] Carcinosarcoma was excluded as this histology is considered a metaplastic carcinoma in which the sarcomatous component is derived from the carcinoma in most cases.[18] From these results, all patients with copy number alterations (CNA), mutations, or structural variants (SVs) in *BRCA1* and/or *BRCA2* were reviewed; *BRCA* amplifications and missense mutations or SVs with unknown oncogenic effects per OncoKB annotations were removed. Finally, three patients with *BRCA*-altered uterine sarcoma treated with PARPis whose cancer types were misclassified in cBioPortal and one who received external genetic testing were identified and added to the cohort.

Demographic, Genomic, Pathology, and Treatment Information

For each patient, age at diagnosis and self-reported ancestry and race were extracted from the MSK tumor registry, cBioPortal results, and electronic medical records.

BRCA1 and/or *BRCA2* alteration type (pathogenic CNA, mutation, or SV), somatic versus germline status, and coaltered genes were identified from the cBioPortal database. For the patient with external genetic testing, the *BRCA* mutation type and somatic versus germline status were determined from the outside genetic testing report; coalterations were not available.

Uterine sarcoma histology was identified from surgical pathology reports. Mitotic rate was identified as the maximum mitoses per 10 high-power fields (HPFs) listed in surgical pathology reports for the primary tumor or specimens from metastatic sites if unavailable for the primary tumor. Estrogen receptor (ER) positivity and progesterone

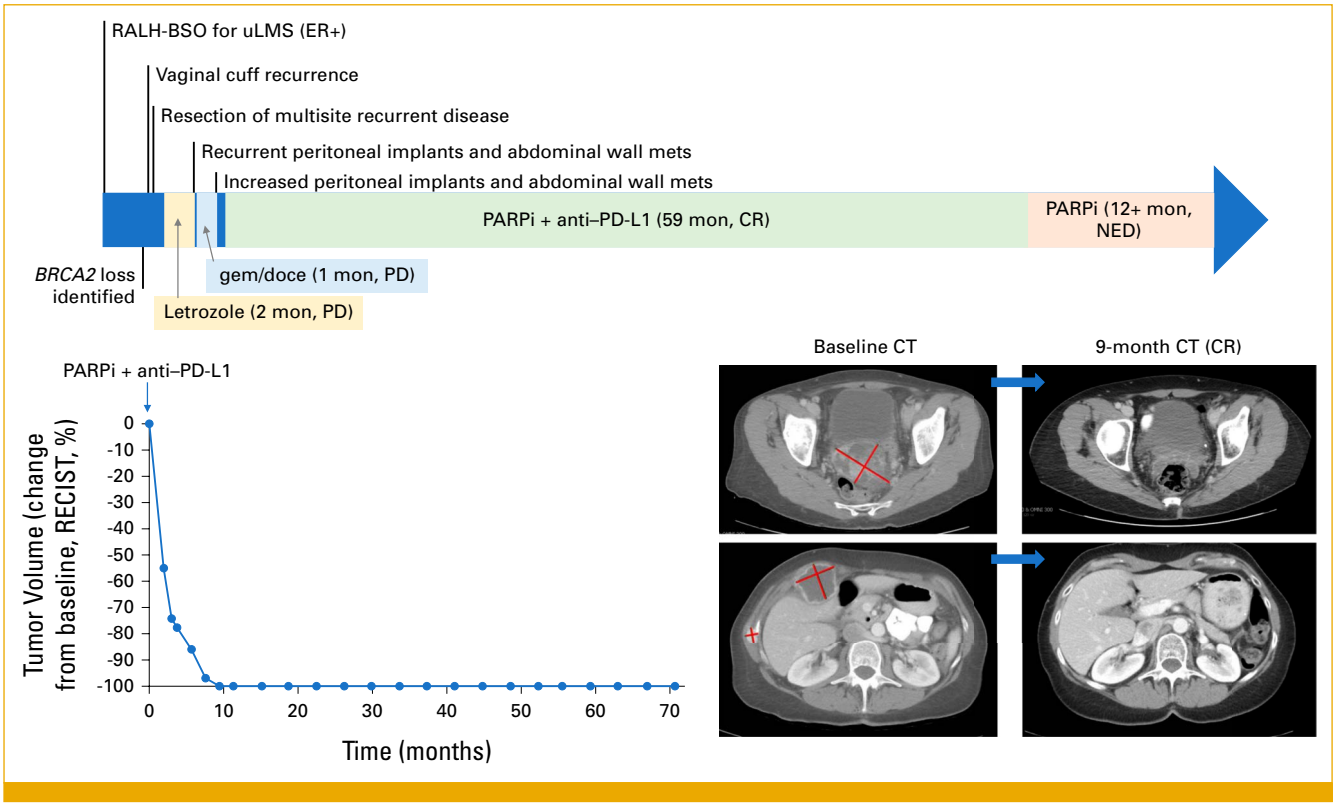

FIG 1. Oncology history, tumor volume measurements, and pre- and post-treatment CT scans of a 67-year-old woman with metastatic uterine LMS with *BRCA2* deep deletion treated with PARPi in combination with PD-L1 inhibitor. ER, estrogen receptor; CR, complete response; CT, computed tomography; LMS, leiomyosarcoma; NED, no evidence of disease; PARPi, poly(ADP-ribose) polymerase inhibitor; PD, progressive disease; RALH-BSO, robotic-assisted laparoscopic hysterectomy and bilateral salpingo-oophorectomy; uLMS, uterine leiomyosarcoma.

receptor (PR) positivity were determined by immunohistochemistry. Any staining for ER and PR (>0%) was considered a positive result. The extent of disease at primary diagnosis was stratified into uterine-confined, nonmorcellated; uterine-confined, morcellated; and non–uterine-confined because of the limited prognostic utility of International Federation of Gynecology and Obstetrics and American Joint Committee on Cancer staging systems for uterine LMS.[19] The extent of disease at the time of study or death was stratified into no evidence of disease, uterine-confined, and non–uterine-confined.

Previous treatment data regarding whether each patient had received surgery, radiation, and systemic therapy were extracted. Systemic therapies were categorized into chemotherapy, immunotherapy, hormonal therapy, PARPis, and other targeted therapies.

PARPi Information

For patients treated with PARPis in the recurrent/metastatic therapy setting, the regimen, date of first dose, date of last dose, date of first response, date of progression, and reason for discontinuation of PARPis were extracted. Responses to PARPis (CR, partial response [PR], stable disease [SD], or progressive disease [PD]) were determined using RECIST v1.1 when tumor response assessments were available.[20] Clinical information and radiology reports were used to determine responses when RECIST was not reported. Confirmed responses on two consecutive scans were required for CR or PR. Overall response rate (ORR) for the PARPi-treated group was calculated as the percentage of patients who had partial or CRs of all patients treated with PARPis. Clinical benefit rate (CBR) was calculated as the percentage of patients who had partial or CRs, or SD for at least 16 weeks, of all patients treated with PARPis.

For treatment intervals, time to response was calculated using the duration between first dose of PARPi and first partial or CR. Duration of response was calculated using the duration between the date of first response and the date of progression, censored with a data cutoff of July 2, 2024, for patients with ongoing responses. Time to progression was calculated using the duration between the date of first dose of PARPi and the date of progression, censored with the same data cutoff for patients with ongoing responses or SD. Time on therapy was calculated using the duration between the date of first dose of PARPi and the date of last doses of PARPi, censored with the same data cutoff for patients with ongoing treatment.

PFS ratios were calculated by dividing the time to progression on PARPis by the time to progression on the most recent previous line of systemic therapy. One patient who received radiation therapy concurrently with the previous line of systemic therapy was excluded from this calculation. A PFS ratio of at least 1.3 was considered to represent a benefit for the patient.[21] Patients treated in the maintenance setting were excluded from analysis of best response to PARPi, current PARPi status, ORR and CBR, treatment intervals, and PFS ratios.

RESULTS

Patient Selection

We initially identified 534 patients with uterine sarcoma, of whom 40 had *BRCA* alterations. After removal of one patient with carcinosarcoma, removal of eight patients with *BRCA* alterations of unknown oncogenic effect, and addition of four patients who were misclassified or received outside genetic testing, our cohort contained 35 patients with uterine sarcoma with pathogenic *BRCA* alterations.

Demographic, Genomic, Pathologic, and Treatment Information

The demographic and genomic information of this population is detailed in Table 1. The median age at diagnosis was 54 years (range of 34-74), and the majority of patients were White (77%). Our cohort was found to have 35 total pathogenic alterations in *BRCA2* (33) and *BRCA1* (2). Of the *BRCA2* alterations, homozygous deletions were most common (70%), followed by mutations (27%) and SVs (3%). Three of the *BRCA2* alterations were germline (9%), all of which were frameshift mutations. The *BRCA1* alterations were both somatic mutations, with one frameshift and one missense. Several coalterations in other cancer-related genes were identified on MSK-IMPACT NGS panel testing (Fig 2). The most frequently coaltered genes were *TP53* (62%), *RB1* (62%), *CYSLTR2* (54%), *ATRX* (44%), and *PTEN* (29%).

Pathology and treatment-related information for the uterine sarcoma cohort is shown in Table 2. LMS was the most common tumor histology (86%), followed by adenosarcoma (6%). The median mitotic rate was 25 mitoses per 10 HPFs (range of 5-63, n = 33). Twenty-five of these tumors (76%) had a mitotic rate above 15 mitoses/10 HPFs, which has been associated with worse overall survival and disease-free survival.[22] All LMS cases fulfilled histologic criteria for conventional LMS, with malignancy defined as the presence of at least two of the following features: diffuse moderate to severe atypia, tumor necrosis, and a mitotic index of ≥10 mitotic figures/10 HPFs. Most remaining tumors were considered histologically high grade. With regard to hormone receptor expression, 69% and 57% of tumors were ER-positive and PR-positive, respectively. At the time of initial diagnosis, 19 patients had disease confined to the uterus (54%), of which two underwent morcellation (6%), which has been associated with increased risk of abdominal or pelvic recurrence and shorter recurrence-free survival because of dissemination of cancer cells during surgery.[23] Finally, at the time of study or death, 26 patients had disease disseminated beyond the uterus (74%), eight patients had no evidence of disease on computed tomography scan (23%), and one patient had unknown disease extent (3%).

TABLE 1. Demographic and Genomic Information for Patients With Uterine Sarcoma Harboring Pathogenic *BRCA* Alterations (N = 35)

BRCA-Altered Uterine Sarcoma	N = 35
Demographic information	
Age at diagnosis, years, median (range)	54 (34-74)
Ancestry, No. (%)	
European (excluding Ashkenazi Jewish)	20 (57)
African	3 (9)
Ashkenazi Jewish European	3 (9)
East Asian	1 (3)
Admixed/other	4 (11)
Not available	4 (11)
Race, No. (%)	
White	27 (77)
Black	4 (11)
Asian	2 (6)
Other	1 (3)
Not available	1 (3)
Genomic information, No. (%)	
BRCA2 alterations, n = 33	
Inheritance	
Somatic	30 (91)
Germline	3 (9)
Alteration type	
Homozygous deletion	23 (70)
Structural variant	1 (3)
Mutation	9 (27)
Nonsense	1 (11)
Frameshift	7 (78)
Splice	1 (11)
Missense	0
BRCA1 alterations, n = 2	
Inheritance	
Somatic	2 (100)
Germline	0
Alteration type	
Homozygous deletion	0
Structural variant	0
Mutation	2 (100)
Nonsense	0
Frameshift	1 (50)
Splice	0
Missense	1 (50)

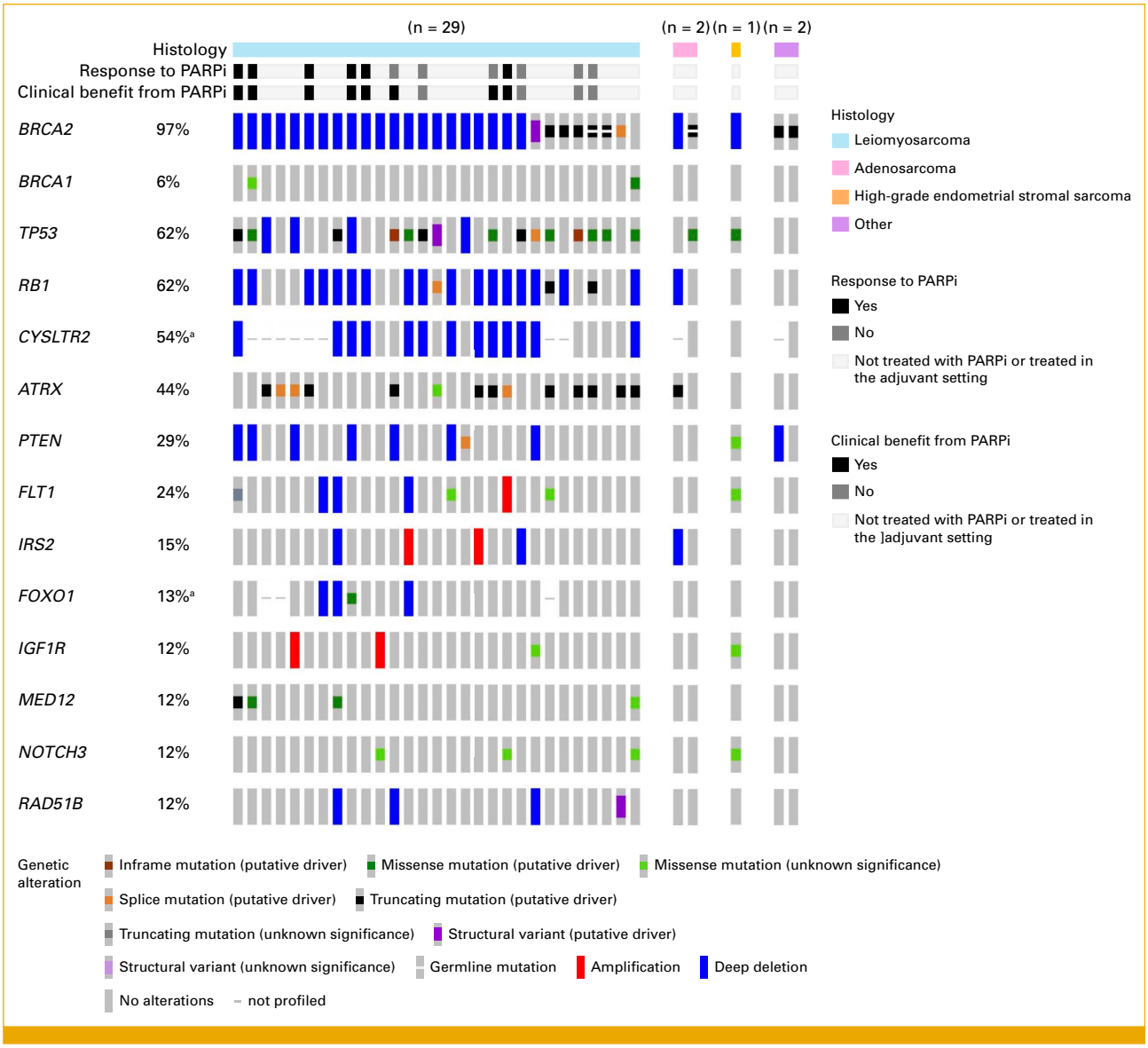

FIG 2. *BRCA* alterations and coalterations with at least 10% frequency identified via MSK-IMPACT in the uterine sarcoma cohort, by tumor histology (n = 34). One patient with leiomyosarcoma with outside genetic testing who had *BRCA1* frameshift mutation and no response or clinical benefit with PARPis is not shown. Other histology included (left to right) one patient with uterine tumor resembling ovarian sex cord tumor versus dedifferentiation of low-grade stromal sarcoma and one patient with uterine sarcoma with myogenic differentiation. [a]*CYSLTR2* and *FOXO1* were not sequenced in all cases, and the reported percentages reflect only those cases that were tested. IMPACT, integrated mutation profiling of actionable cancer targets; MSK, Memorial Sloan Kettering Cancer Center; PARPi, poly(ADP-ribose) polymerase inhibitor.

All patients with *BRCA*-altered uterine sarcoma underwent surgery, 17 received radiation (49%), and 30 received one or more systemic therapies (86%), with a median of three lines of systemic therapy (range 0-13, n = 30). Twenty-nine patients received chemotherapy (83%), most commonly gemcitabine/docetaxel (69%) and doxorubicin (43%). Examining other classes of systemic treatment, 17 patients received hormonal therapy (49%), with letrozole as the most common drug (34%); six patients received immunotherapy (17%), all immune checkpoint inhibitors as part of combination regimens with PARPis; 15 patients received PARPis (43%); and eight patients received other targeted therapies (23%), with olaratumab (14%) and pazopanib (11%) as the most common drugs.

PARPi Treatment Information and Outcomes

Of the 15 patients with uterine sarcoma who received PARPi therapy, 14 had LMS (Fig 3; Table 3) and one had adenosarcoma with sarcomatous overgrowth. For the LMS group, four PARPi drugs (olaparib, talazoparib, niraparib, and rucaparib) were represented, with olaparib being the most common (50%). Eight patients received PARPi initially in combination with another drug (57%), including five

TABLE 2. Pathology and Treatment Information for Patients With Uterine Sarcoma Harboring Pathogenic *BRCA* Alterations (N = 35)

BRCA-Altered Uterine Sarcoma	N = 35
Pathology information	
Sarcoma histology, No. (%)	
LMS[a]	30 (86)
Adenosarcoma	2 (6)
Adenosarcoma with sarcomatous overgrowth	1 (3)
Adenosarcoma without stromal overgrowth	1 (3)
High-grade endometrial stromal sarcoma	1 (3)
Other[b]	2 (6)
Mitotic rate, mitoses/10 HPFs, n = 33, median (range)	25 (5-63)
ER and PR expression, No. (%)	
ER+/PR+	20 (57)
ER+/PR−	3 (9)
ER−/PR+	0
ER−/PR−	5 (14)
ER+, PR not reported	1 (3)
Not reported	6 (17)
Extent of disease at primary diagnosis, No. (%)	
Uterine-confined, nonmorcellated	17 (49)
Uterine-confined, morcellated	2 (6)
Non–uterine-confined	13 (37)
Unknown	3 (9)
Extent of disease at the time of study or death, No. (%)	
No evidence of disease	8 (23)
Uterine-confined	0
Non–uterine-confined	26 (74)
Unknown	1 (3)
Treatment information	
Treatment modalities, No. (%)	
Surgery	
Yes	35 (100)
No	0
Unknown	0
Radiation therapy	
Yes	17 (49)
No	16 (46)
Unknown	2 (6)
Systemic therapy	
Yes	30 (86)
No	2 (6)
Unknown	3 (9)
Total lines of systemic therapy, n = 30,[c] median (range)	3 (0-13)
Classes of systemic therapy, No. (%)	
Chemotherapy	29 (83)
Hormonal therapy	17 (49)
Immunotherapy	6 (17)
Other targeted therapy (not including PARPis)	8 (23)
PARPi	15 (43)

Abbreviations: ER, estrogen receptor; HPFs, high-power fields; LMS, leiomyosarcoma; NGS, next-generation sequencing; PARPi, PARP inhibitor; PR, progesterone receptor; TSC, tuberous sclerosis complex.
[a]Two cases were diagnosed at outside institutions as uterine LMS. Review of submitted slides at our institution read these cases as PEComa on the basis of histology and immunohistochemistry stains; subsequent NGS did not identify *TSC* alterations in these cases, and NGS findings are consistent with LMS. We have elected to include these two cases with the uterine LMS cohort.
[b]Other histology included one patient with uterine tumor resembling ovarian sex cord tumor versus dedifferentiation of low-grade stromal sarcoma and one patient with uterine sarcoma with myogenic differentiation.
[c]Statistics for the number of lines of systemic therapy excluded five patients who were lost to follow-up because of receiving treatment at an outside facility (n = 2) or for whom it was unknown whether they received systemic therapy (n = 3).

patients treated as part of clinical trials of PARPi with the immune checkpoint inhibitors avelumab or nivolumab[14,24] and two treated in a trial of PARPi with a Wee1 inhibitor.[25] The cohort was pretreated, with a median of two previous lines of systemic therapy (range, 1-9).

Thirteen of the patients with LMS were treated with PARPi in the recurrent/metastatic therapy setting, and one was treated with PARPi in the maintenance setting. For patients treated in the recurrent/metastatic therapy setting, analysis of PARPi outcomes indicated that one patient had a best response of CR (8%), five patients had a best response of PR (38%), five patients had a best response of SD (38%), and two patients had a best response of PD (15%). The ORR was 46%, and the CBR was 62%. One patient received PARPi maintenance therapy with pembrolizumab and later with temozolomide and was therefore not evaluable for efficacy. The median time to first response and duration of response were 1.7 months (range, 1.6-5.9) and 37.0 months (range, 12.8-70.2), respectively, for the six patients who exhibited CR or PR. The median time to progression was 13.2 months (range, 1.3-71.9; median 2.0 for PARPi monotherapy [n = 6]; median 40.9 for PARPi in combination with immune checkpoint inhibitors [n = 5]). The median PFS ratio comparing PARPis with the previous line of systemic therapy was 1.9 (range, 0.4-53.9; n = 12). Seven patients exhibited a PFS ratio of at least 1.3 (58%), which was considered to indicate benefit from the PARPi; the previous lines of therapy in these

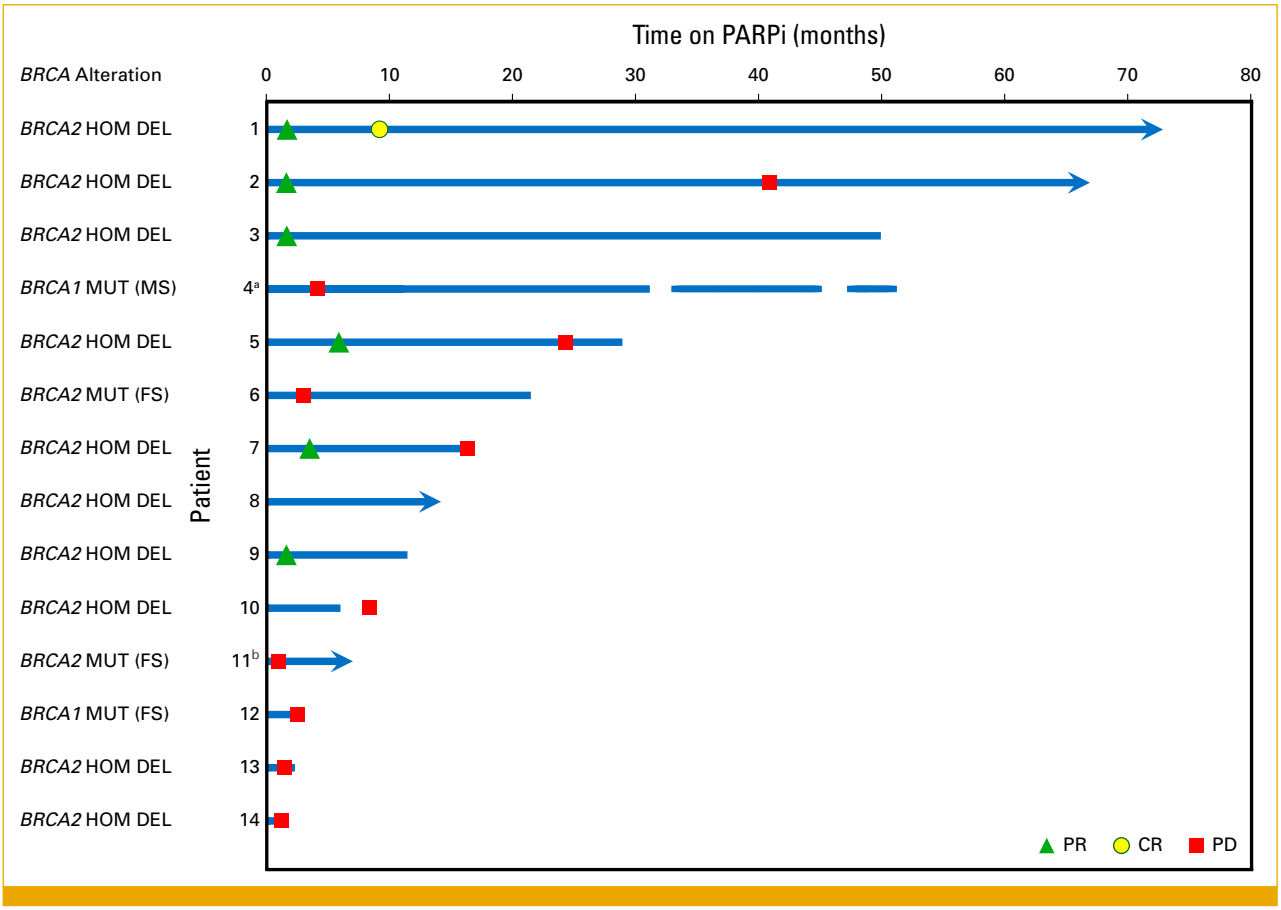

FIG 3. PARPi treatment duration and outcomes for patients with *BRCA*-altered uterine LMS. [a]Patient 4 was initially treated with PARPis in the maintenance setting and stopped and restarted multiple PARPis. [b]Patient 11 was censored at 6 months because of outside treatment/loss to follow-up. CR, complete response; FS, frameshift; HOM DEL, homozygous deletion; LMS, leiomyosarcoma; MS, missense; MUT, mutation; PARPi, poly(ADP-ribose) polymerase inhibitor; PD, progressive disease; PR, partial response.

patients were gemcitabine docetaxel (43%), liposomal doxorubicin (29%), gemcitabine monotherapy (14%), or an mTOR kinase inhibitor (14%).

All six patients with responses had somatic *BRCA2* deep deletions. The ORR for patients with *BRCA2* homozygous deletions was 60% (n = 6 of 10), with a CBR of 80% (n = 8 of 10). For the three patients with *BRCA1* or *BRCA2* frameshift mutations, the median time to progression was 2.6 months (range, 1.0-3.0). Given the cohort size, it was not possible to determine the impact of *TP53*, *RB1*, or *ATRX* coalteration status on PARPi responses (Appendix Fig A1). By treatment regimen, responses were observed in 1 of 6 patients treated with PARPi monotherapy (four *BRCA2* homozygous deletions, one *BRCA2* frameshift mutation, one *BRCA1* frameshift mutation), 4 of 5 patients treated with PARPi in combination with immune checkpoint inhibitors (five *BRCA2* homozygous deletions), and 1 of 2 patients treated with PARPi in combination with Wee1 inhibitors (one *BRCA2* homozygous deletion, one *BRCA2* frameshift mutation).

The median time on PARPi therapy was 14.5 months (range, 1.3-71.9; n = 12), and the most common cause of discontinuation was eventual disease progression (six patients, 46%). Two patients (15%) experienced severe adverse effects that required discontinuation of PARPis: one patient had persistent cytopenias because of myelosuppression, which has been a documented risk of PARPi use,[26] and another had autoimmune nephritis likely because of administration of the immunotherapy, nivolumab, with PARPi. The former patient, who experienced SD on PARPi therapy, progressed 2 months after discontinuation, whereas the latter patient, who experienced a PR on PARPi therapy, remains with SD. In addition, one patient with a durable PR discontinued PARPi therapy after 4 years to mitigate the risk of secondary myeloid malignancy because of prolonged PARPi use[27] and has remained progression-free over 1 year later at the time of study. Three patients with LMS (23%) remained on PARPi therapy at the time of study (one with an ongoing CR, one with ongoing SD, and one being treated postprogression with clinical benefit). One patient had unknown PARPi treatment status because of loss to follow-up.

DISCUSSION

To our knowledge, this retrospective study represents the largest investigation of patients with *BRCA*-altered uterine sarcoma to date. Most patients had LMS, and coalterations

TABLE 3. PARPi Treatment Information and Outcomes for Patients With Uterine LMS Harboring Pathogenic *BRCA* Alterations

BRCA-Altered Uterine LMS Treated With PARPis	
PARPi treatment information	n = 14
PARPi regimen, No. (%)	
PARPi drug[a]	
Olaparib	7 (50)
Talazoparib	3 (21)
Niraparib	3 (21)
Rucaparib	2 (14)
Initial PARPi regimen type	
Monotherapy	6 (43)
Combination therapy[b]	8 (57)
Drug given in combination with PARPi	
Avelumab	3 (21)
Investigational Wee1 inhibitor	2 (14)
Nivolumab	2 (14)
Pembrolizumab	1 (7)
Temozolomide	1 (7)
Lines of systemic therapy before PARPi, median (range)	2 (1-9)
PARPi efficacy	n = 13[c]
Treatment outcome, No. (%)	
Best response to PARPi	
Complete response	1 (8)
Partial response	5 (38)
Stable disease	5 (38)
Duration ≥16 weeks	2 (15)
Duration <16 weeks	3 (23)
Progressive disease	2 (15)
Current PARPi status	
Ongoing treatment with PARPi	3 (23)
Discontinuation of PARPi	9 (69)
Reason for discontinuation	
Disease progression	6 (46)
Myelosuppression	1 (8)
Autoimmune nephritis (from combination with immunotherapy)	1 (8)
Ongoing partial response with no progression	1 (8)
Unknown	1 (8)
Treatment intervals, months, median (range)	
Time to first response	1.7 (1.6-5.9), n = 6
Duration of response	37.0 (12.8-70.2), n = 6
Time to progression	13.2 (1.0-71.9), n = 13
Time on therapy[d]	14.5 (1.3-71.9), n = 12
Clinical end points	
Overall response rate, %	46
Clinical benefit rate, %	62
PFS ratio, median (range)	1.9 (0.4-53.9), n = 12[e]
PFS ratio ≥1.3, No. (%)	7 (58), n = 12

(continued in next column)

TABLE 3. PARPi Treatment Information and Outcomes for Patients With Uterine LMS Harboring Pathogenic *BRCA* Alterations (continued)

Abbreviations: LMS, leiomyosarcoma; PARPi, PARP inhibitor; PFS, progression-free survival.
[a]One patient received olaparib and niraparib in different combination regimens.
[b]One patient received PARPi with pembrolizumab and temozolomide in different lines of therapy.
[c]One patient excluded from PARPi efficacy statistics because of treatment in the maintenance setting.
[d]One patient was censored at 6 months because of outside treatment and was excluded from the statistics for time on therapy.
[e]One patient received radiation therapy concurrently with the previous line of systemic therapy before the PARPi and was excluded from the statistics for PFS ratio.

were present most commonly in *TP53* (62%), *RB1* (62%), and *CYSLTR2* (54%) on the basis of NGS panel testing. These findings are in line with a previous genomic analysis of 80 patients with uterine LMS, which also reported highest alteration frequencies in *TP53* (56%) and *RB1* (51%).[28] Notably, we observed that *RB1* and *CYSLTR2* alterations were most commonly homozygous deletions and both reside on chromosome 13 (13q12.2), just downstream of *BRCA2* (13q13.1). It is therefore not surprising that these three genes are commonly codeleted. Although the frequency of *BRCA2* somatic deletions may be explained, in part, by a selective pressure to alter *RB1*, *RB1* loss is not universal in our cohort with a rate consistent with the non–*BRCA*-selected uterine sarcoma population.[28]

Our cohort of pretreated patients showed remarkable outcomes with an ORR of 46%, a CBR of 62%, and a median PFS of 13.2 months (range, 1.3-71.9 months) on PARPi monotherapy or combination therapy. Although these results should be interpreted with caution because of our study's limited sample size and retrospective design, PARPi therapy appeared to largely outperform standard chemotherapies and hormonal therapies currently used for non–first-line uterine sarcoma treatment (Appendix Table A1). Gemcitabine/docetaxel, a preferred regimen for recurrent uterine sarcoma, had an ORR of 16%-53%, a CBR of 32%-77% (SD cutoff 24 weeks or not reported), and a median PFS of 5.6-6.2 months when studied in pretreated metastatic or unresectable LMS and soft tissue sarcoma.[29-31] Other regimens used as non–first-line therapy for uterine sarcoma and soft tissue sarcoma include gemcitabine monotherapy (ORR, 8%-20.5%; median PFS, 3.0 months),[30,32] gemcitabine/dacarbazine

(ORR, 12%; median PFS, 4.2 months),[33] trabectedin (ORR, 9.9%-23.5%; median PFS, 3.3-4.2 months),[34-36] temozolomide (ORR, 8%-15.5%; median PFS, 2.2 months),[37,38] and doxorubicin/ifosfamide/mesna (ORR, 22.2%; median PFS, 6.0 months).[39] Additional treatment options such as dacarbazine monotherapy,[33,35,40] eribulin,[40] pazopanib,[41] and aromatase inhibitors[42-44] have comparably modest response rates in this population with reported ORRs below 10%. In the first-line setting, doxorubicin/trabectedin followed by trabectedin maintenance has recently been shown to have an ORR of 36% and a median PFS of 12.2 months, with improved overall survival and PFS compared with doxorubicin alone for patients with metastatic or unresectable LMS.[4,45]

PARPis have previously been studied in LMS without *BRCA* selection, with lower levels of clinical efficacy reported. A phase II study of rucaparib/nivolumab in patients with pretreated advanced LMS, which did not require loss of DDR pathways for eligibility, found minimal therapeutic activity.[24] Of the 20 patients enrolled, there was one PR which occurred in a patient with a *BRCA2* deletion, and the median PFS was 7.8 weeks. Therefore, our findings further support the design of trials with appropriately selected patients for PARPis on the basis of *BRCA* status.

Our results also raise the question of whether *BRCA* alteration type plays a role in the response to PARPi therapy in uterine sarcoma. Eight of 10 patients with LMS with *BRCA* homozygous deletions treated with PARPis exhibited clinical benefit, compared with 0 of 3 patients with LMS without homozygous deletions treated with PARPis in the recurrent/metastatic therapy setting. These findings may be explained by one of the major mechanisms of resistance to PARPis, reversion mutations that restore *BRCA* protein function,[46] which would not be possible in the case of homozygous deletions. Similarly, a genomic analysis of extraordinary responders on the phase II TOPARP-B trial of olaparib in metastatic castration-resistant prostate cancer identified somatic *BRCA2* deletions as the strongest predictor of prolonged benefit with patients experiencing substantially longer response durations compared with those with other genomic alterations.[47] Notably, the majority of patients with *BRCA*-altered uterine sarcoma had *BRCA2* alterations. Only one *BRCA1*-altered patient was treated with PARPi in the recurrent/metastatic therapy setting, and she did not have a response. It was therefore not possible to analyze the influence of *BRCA1* versus *BRCA2* alteration status PARPi treatment outcomes.

It remains an ongoing question whether the addition of immunotherapy improves PARPi treatment outcomes in *BRCA*-altered uterine LMS. Four of five efficacy-evaluable patients with LMS who received PARPis in combination with immune checkpoint inhibitors exhibited responses, and 5 of 5 exhibited clinical benefit, compared with responses in 1 of 6 and clinical benefit in 2 of 6 patients who received PARPi monotherapy. Preclinical studies have shown synergy between PARPis and immune checkpoint inhibitors, with proposed mechanisms including that PARPi leads to (1) increased tumor mutational burden and neoantigen load, (2) activation of the cGAS-STING pathway, and (3) upregulation of PD-L1, thereby increasing sensitivity to immune checkpoint blockade.[48] However, reported clinical data in advanced solid tumors have not clearly demonstrated synergy with the combination of PARP and checkpoint blockade.[14,49] Consistent with this, no responses were observed in a small study of 11 genomically unselected patients with LMS treated with the PD-L1 inhibitor, durvalumab, in combination with olaparib.[50] Because of the limited sample size of our study, we are not able to determine the added benefit of immunotherapy to PARP inhibition in *BRCA*-altered uterine sarcoma.

Historically, the benefit of PARPis has been largely limited to disease types characterized by a high rate of germline *BRCA* mutations, including breast, ovarian, prostate, and pancreatic cancers.[51-54] Basket trials of PARPis enrolling a range of tumor types have consistently demonstrated the greatest efficacy in these *BRCA*-associated tumor types with anecdotal responses in other tumor types.[10,14,55] Our results in patients with somatic *BRCA* alterations support consideration of PARPis for *BRCA*-altered uterine sarcoma and therefore also highlight the importance of NGS testing in this population to guide treatment decisions.

In conclusion, our study describes the activity of PARPi treatment in a cohort of patients with *BRCA*-altered uterine sarcoma. We demonstrate significant efficacy of PARPi therapy in this difficult-to-treat population, with clinical end points that largely outperformed standard therapies and notable cases of prolonged responses. Additional data are needed to improve understanding of optimal PARPi treatment regimens, particularly the role of combination therapy, and patient genomic profiles to maximize therapeutic benefit in uterine sarcomas.

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APPENDIX

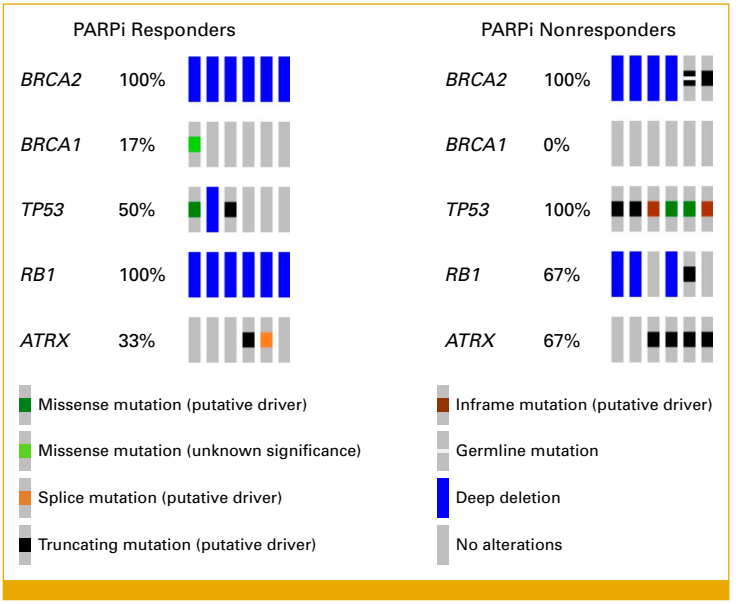

FIG A1. *BRCA* alterations and coalterations in *TP53*, *RB1*, and *ATRX* for patients with uterine leiomyosarcoma treated with PARPis in the recurrent/metastatic setting, by response to PARPis (n = 12). One patient with outside genetic testing who had *BRCA1* frameshift mutation and did not respond to PARPis not shown. PARPi, PARP inhibitor.

TABLE A1. Comparison of PARPi Treatment Outcomes With Standard Chemotherapies and Hormonal Therapies in the Non–First-Line Setting

Regimen	Patient Population	Previous Therapy	No. of Patients Analyzed	Overall Response Rate (%)	Clinical Benefit Rate (%)	Median Progression-Free Survival (months)	Reference
PARPis							
PARPis (olaparib, talazoparib, niraparib, rucaparib)	*BRCA*-altered uterine LMS	Median 2 previous systemic therapies	13	46	62, SD cutoff 16 weeks	13.2	Current study
Gemcitabine/docetaxel							
Gemcitabine (days 1 and 8)/docetaxel (day 8) every 3 weeks	Metastatic uterine LMS	One previous line of chemotherapy (90% doxorubicin)	48	27	77, SD cutoff not reported	5.6+	Hensley et al[29]
Gemcitabine (days 1 and 8)/docetaxel (day 8) every 3 weeks	Metastatic soft tissue sarcoma	Zero to three previous lines of chemotherapy (median 1 prior)	69	16	32, SD cutoff 24 weeks	6.2	Maki et al[30]
Gemcitabine (days 1 and 8)/docetaxel (day 8) every 3 weeks	Unresectable LMS	Zero to two previous lines of chemotherapy (47% doxorubicin)	34	53	Not available[a] (SD 7/34)	5.6	Hensley et al[31]
Gemcitabine							
Gemcitabine (days 1 and 8) every 3 weeks	Metastatic soft tissue sarcoma	Zero to three previous chemotherapies (median 1 prior)	48	8	27, SD cutoff 24 weeks	3.0	Maki et al[30]
Gemcitabine (days 1, 8, and 15) every 4 weeks	Persistent or recurrent uterine LMS	One previous chemotherapy or radiotherapy	42	20.5	Not available[a] (SD 15.9%)	Not reported	Look et al[32]
Gemcitabine/dacarbazine							
Gemcitabine (day 1)/dacarbazine (day 1) every 2 weeks	Advanced soft tissue sarcoma	Previous treatment with anthracyclines and ifosfamide or contraindication for their use	57	12	49, SD cutoff 12 weeks	4.2	Garcia-del-Muro et al[33]
Dacarbazine							
Dacarbazine (day 1) every 3 weeks	Metastatic liposarcoma or LMS	At least one previous chemotherapy (87% at least two prior)	173	6.9	19, SD cutoff 18 weeks	1.5	Demetri et al[35]
Dacarbazine (day 1) every 3 weeks	Advanced or metastatic liposarcoma or LMS	At least two previous systemic regimens for advanced disease	224	5	48, SD cutoff 11 weeks	2.6	Schoffski et al[40]
Dacarbazine (day 1) every 3 weeks	Advanced soft tissue sarcoma	Previous treatment with anthracyclines and ifosfamide or contraindication for their use	52	4	25, SD cutoff 12 weeks	2.0	Garcia-del-Muro et al[33]
Trabectedin							
Trabectedin (day 1) every 3 weeks	Persistent, recurrent, or metastatic uterine LMS	At least one previous systemic therapy (63% one prior, 37% two to three prior)	108	23.5	Not available[a] (SD 37.4%)	4.1	Gadducci et al[34]
Trabectedin (day 1) every 3 weeks	Metastatic liposarcoma or LMS	At least one previous chemotherapy (89% at least two prior)	345	9.9	34, SD cutoff 18 weeks	4.2	Demetri et al[35]
Retrospective study: trabectedin (day 1) every 3 weeks	Advanced uterine LMS	One to five previous chemotherapies (median 3 prior)	66	16	Not available[a] (SD 35%)	3.3	Sanfilippo et al[36]
Temozolomide							
Temozolomide 6-week continuous oral regimen	Advanced soft tissue sarcoma	One previous chemotherapy (96% previous doxorubicin)	45	15.5 (5/11 for GYN sarcoma)	Not available[a] (SD 18.6%)	2.2	Garcia-del-Muro et al[38]

(continued on following page)

TABLE A1. Comparison of PARPi Treatment Outcomes With Standard Chemotherapies and Hormonal Therapies in the Non–First-Line Setting (continued)

Regimen	Patient Population	Previous Therapy	No. of Patients Analyzed	Overall Response Rate (%)	Clinical Benefit Rate (%)	Median Progression-Free Survival (months)	Reference
Retrospective study: temozolomide 6-week continuous oral regimen	Recurrent or metastatic unresectable LMS	Two to five previous chemotherapies (100% previous doxorubicin)	12	8	Not available[a] (SD 4/12)	Not reported	Anderson et al[37]
Retrospective study: temozolomide bolus dose (days 1-5) every 4 weeks	Recurrent or metastatic unresectable LMS	Two to six previous chemotherapies (100% previous doxorubicin)	7	14	Not available[a] (SD 4/7)	Not reported	Anderson et al[37]
Other chemotherapies							
Eribulin (days 1 and 8) every 3 weeks	Advanced or metastatic liposarcoma or LMS	At least two previous systemic regimens for advanced disease	228	4	46, SD cutoff 11 weeks	2.6	Schoffski et al[40]
Pazopanib once daily oral regimen	Metastatic soft tissue sarcoma	At least one regimen containing anthracycline, maximum of four previous lines of systemic therapy	246	6	Not available[a] (SD 67%)	4.6	van der Graaf et al[41]
Retrospective study: doxorubicin (day 1)/ifosfamide + mesna (days 1-3) every 3 weeks	Recurrent uterine LMS	One previous chemotherapy (100% gemcitabine/docetaxel)	9	22.2	66.7, SD cutoff not reported	6.0	Niu et al[39]
Hormonal therapies							
Anastrozole once daily oral regimen	Hormone receptor–positive uterine LMS	No previous hormonal therapy, 28% previous chemotherapy	31	3.2	35.5, SD cutoff 12 weeks	2.8	Edmondson et al[42]
Letrozole once daily oral regimen	Unresectable uterine LMS with ER and/or PR expression	No previous hormonal therapy, zero to nine previous chemotherapies (median 2 prior)	26	0	Not available[a] (SD 54%)	3	George et al[43]
Retrospective study: aromatase inhibitors (letrozole, anastrozole, exemestane)	Advanced or recurrent uterine LMS	68% at least one previous chemotherapy, 21% previous hormonal therapy	34	9	Not available[a] (SD 32%)	2.9	O'Cearbhaill et al[44]

Abbreviations: ER, estrogen receptor; GYN, gynecologic; LMS, leiomyosarcoma; PARPi, PARP inhibitor; PR, progesterone receptor; SD, stable disease.

[a]Duration of SD not reported.