

ORIGINAL ARTICLE

Trabectedin—olaparib combination or trabectedin in advanced soft tissue sarcomas after failure of anthracycline-based treatment (TOMAS2): a randomized phase II study from the Italian Sarcoma Group[☆]

L. D'Ambrosio^{1,2*†}, A. Merlini^{1,2†}, A. Brunello³, V. Ferraresi⁴, A. Paioli⁵, B. Vincenzi⁶, M. A. Pantaleo⁷, T. M. De Pas^{8,9}, L. Gurrieri¹⁰, R. Sanfilippo¹¹, A. Buonadonna¹², G. G. Baldi¹³, G. Badalamenti¹⁴, C. Marchiò¹⁵, Y. Pignochino¹⁵, E. Berrino¹⁵, S. E. Bellomo¹⁵, M. Sbaraglia^{16,17}, L. Righi^{1,2}, M. Rabino^{1,2}, F. Tolomeo¹⁵, S. Aliberti¹⁵, D. Sangiolo^{1,15}, A. P. Dei Tos^{16,17}, S. Stacchiotti¹¹ & G. Grignani^{15*}

¹Department of Oncology, University of Torino, Orbassano, Torino; ²AOU San Luigi Gonzaga, Orbassano, Torino; ³Medical Oncology 1 Unit, Department of Medical Oncology, Istituto Oncologico Veneto IOV IRCCS, Padova; ⁴Department of Sarcomas and Rare Tumors Departmental Unit, IRCCS Regina Elena National Cancer Institute, Rome; ⁵Osteoncolony, Bone and Soft Tissue Sarcomas and Innovative Therapies, IRCCS Istituto Ortopedico Rizzoli, Bologna; ⁶Department of Medical Oncology, Policlinico Universitario Campus Bio-Medico and Università Campus Bio-Medico, Roma; ⁷Department of Medical Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, University of Bologna, Bologna; ⁸Department of Medical Oncology, IRCCS Istituto Europeo Oncologia, Milano; ⁹Division of Medical Oncology, Cliniche Humanitas Gavazzeni, Bergamo; ¹⁰Experimental and Clinical Oncology of Immunotherapy and Rare Cancers, Biobank Unit, IRCCS Istituto Romagnolo per la Studio dei Tumori Dino Amadori, Meldola; ¹¹Medical Oncology Unit 2, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano; ¹²Medical Oncology, IRCCS Centro di Riferimento Oncologico di Aviano, Aviano; ¹³Department of Oncology, Hospital of Prato, Azienda USL Toscana Centro, Prato; ¹⁴Department of Precision Medicine in Medical, Surgical and Critical Care (Me.Pre.C.C.), Section of Medical Oncology, University of Palermo, Palermo; ¹⁵Candiolo Cancer Institute, FPO — IRCCS, Candiolo; ¹⁶Department of Integrated Diagnostics, Azienda Ospedale-Università Padova, Padova; ¹⁷Department of Medicine, University of Padova School of Medicine, Padova, Italy



Available online 5 December 2025

Background: Advanced/metastatic soft tissue sarcomas (STSs) remain an unmet clinical need. We previously reported the feasibility and preliminary activity of trabectedin—olaparib combination in patients with advanced STS progressing after anthracycline-based regimens.

Patients and methods: In this investigator-initiated, open-label, phase II randomized trial, adult patients with advanced STS progressing after one or more prior lines of therapy, including at least one anthracycline-based regimen, were randomly assigned 1 : 1 to trabectedin 1.1 mg/m² every 21 days (q21d) intravenous (i.v.) plus olaparib tablets 150 mg twice a day, or trabectedin 1.5 mg/m² q21d i.v. Randomization stratified patients by histology (L-sarcoma, i.e. leiomyosarcoma and liposarcoma versus non-L-sarcoma) and number of prior therapies (one versus two or more). The primary endpoint was progression-free survival (PFS) rate at 6 months (PFS6m) per RECIST1.1. Secondary endpoints included PFS, overall survival (OS), RECIST1.1 overall response rate (ORR), and safety. Exploratory endpoints encompassed biomarker/molecular analyses.

Results: Between 25 May 2020 and 2 November 2022, 130 patients were enrolled at 13 Italian Sarcoma Group centers (81 female; 67 L-sarcoma; 93 one prior line). With a median follow-up of 37.4 months, PFS6m and median PFS were 32% [95% confidence interval (CI) 22% to 46%] and 3.9 months (95% CI 2.7–5.2 months) with trabectedin—olaparib versus 28% (95% CI 19% to 42%) and 2.9 months (95% CI 2.2–3.6 months) with trabectedin [hazard ratio (HR) 0.722, 95% CI 0.501–1.041, *P* = 0.081]. Among 126 assessable patients, ORR was 12.7% (95% CI 6.1% to 22.7%) versus 7.9% (95% CI 3.0% to 16.7%), respectively (odds ratio 1.60, 95% CI 0.50–5.16, *P* = 0.43). In the uterine leiomyosarcoma subgroup, 12-month PFS was 42.9% with trabectedin—olaparib versus 0% with trabectedin. *PARP1* expression significantly correlated with improved PFS with trabectedin—olaparib (PFS6m and median PFS were 41.5% and 4.3 months versus 27.8% and 2.5 months; HR 0.537, 95% CI 0.337–0.855, *P* = 0.009). Grade ≥3 hematological toxicities were significantly more frequent with trabectedin—olaparib.

*Correspondence to: Dr Lorenzo D'Ambrosio, Department of Oncology, University of Turin, San Luigi Gonzaga University Hospital, Regione Gonzole 10, 10043 Orbassano, Torino, Italy. Tel: +390119026105; Fax: +390119026992
E-mail: lorenzo.dambrosio@unito.it (L. D'Ambrosio).

Dr Giovanni Grignani, Division of Medical Oncology, Candiolo Cancer Institute, FPO — IRCCS, Strada Provinciale 142, Km 3.95, 10060 Candiolo, Torino, Italy. Tel: +390119933623

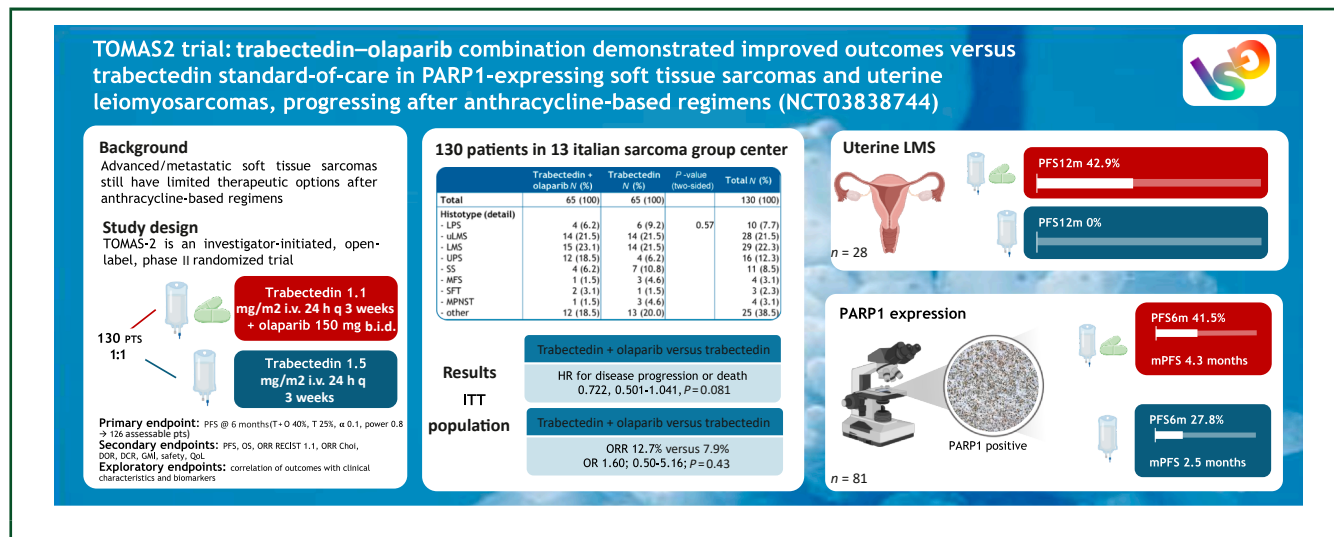
E-mail: giovanni.grignani@ircc.it (G. Grignani).

[†]Shared co-first authorship, both previously at Candiolo Cancer Institute, FPO — IRCCS, Strada Provinciale 142, Km 3.95, 10060 Candiolo, Torino, Italy.

[☆]Note: Preliminary results from this study were presented at the European Society for Medical Oncology 2023 Annual Meeting (proffered paper session—Sarcoma LBA91).

0923-7534/© 2025 The Authors. Published by Elsevier Ltd on behalf of European Society for Medical Oncology. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

GRAPHICAL ABSTRACT



Conclusions: Although trabectedin–olaparib combination reached the prespecified threshold for statistical significance for PFS ($P < 0.10$), the benefit was marginal in the all-comers STS population. Nonetheless, patients affected by PARP1-expressing STS and uterine leiomyosarcoma derived substantial benefit from the combination, supporting further histology- and biomarker-driven investigation in these settings.

Key words: PARP1, biomarker, sarcoma, trabectedin, olaparib, leiomyosarcoma

INTRODUCTION

Soft tissue sarcoma (STS) represents a heterogeneous group of >100 rare malignant tumors sharing a mesenchymal origin.¹ STS management is multidisciplinary, but surgery remains the cornerstone of treatment for localized disease.² With the noteworthy exception of gastrointestinal stromal tumor, prognosis is still dismal and only marginally affected by current medical therapies in advanced, inoperable STS patients.^{3–6} In this field, some improvements have been observed, mainly with combination strategies, although at the price of increased toxicity.^{7–12} In addition, the absence of validated predictive biomarkers contributes to the observed disappointing results.

Trabectedin is a drug registered in Europe for the treatment of advanced STS after failure of anthracycline-based therapy and is characterized by a unique mechanism of action: it binds the minor groove of DNA, forming stable covalent adducts that interfere with DNA damage response and repair (DDR) machinery, resulting in DNA single- and double-strand breaks, and exerting a selective toxicity on tumor-associated macrophages involved in tumor angiogenesis and progression.^{4,13} Given these properties, we explored its combination with poly-ADP-ribose-polymerase-1 (PARP1) inhibitors (PARPi), hypothesizing that PARP1 inhibition might perpetuate trabectedin-induced DNA damage. Indeed, the particular type of DNA damage induced by trabectedin is a crucial priming event to engage PARP1 activity to exploit its subsequent inhibition.¹⁴

In robust STS preclinical models, we demonstrated that trabectedin-induced PARP1 activation can be blocked by the PARPi olaparib, significantly boosting the combined antitumor activity compared with either treatment alone.¹⁴ Namely, trabectedin and olaparib synergism was investigated in several bone and STS histological types both *in vitro* and *in vivo*, with subcutaneous and orthotopic tumor xenografts in mice. Synergism *in vitro* was shown by demonstrating an increase in double-strand breaks in bone and STS cell lines treated with trabectedin and olaparib combination with respect to single-agent activity, resulting in enhanced apoptotic rates in the experimental versus control groups. In the *in vivo* models, trabectedin and olaparib combination effectively reduced tumor growth and prevented metastatic spread, which did not occur with either monotherapy.¹⁴

Consequently, we ran a phase Ib trial in patients with metastatic bone and soft tissue sarcomas progressing after standard anthracycline-based treatments demonstrating the feasibility of trabectedin–olaparib combination.¹⁵ The identified recommended phase II dose was trabectedin 1.1 mg/m² as 24-h continuous i.v. infusion every 3 weeks (q21d) plus olaparib tablets 150 mg orally twice daily (b.i.d.). Furthermore, this phase Ib study showed promising combination activity in STS, especially in leiomyosarcomas.¹⁵

On these bases, within the frame of the Italian Sarcoma Group, we ran a phase II randomized study to test trabectedin–olaparib combination versus trabectedin standard of care in STS.

METHODS

Study design and participants

This was an investigator-initiated, open-label, multicenter, phase II randomized clinical trial (NCT03838744) conducted at 13 Italian Sarcoma Group sites in adult patients affected by advanced/metastatic STS deemed unresectable according to institutional multidisciplinary tumor board evaluation, with measurable RECIST 1.1 disease progression after at least one anthracycline-containing regimen. Informed consent signature was required before any study-related procedure, and all diagnoses were centrally reviewed (Angelo Paolo Dei Tos and Marta Sbaraglia). Previous treatment with trabectedin, olaparib, or their analogues was not allowed. See [Supplementary Material S1](https://doi.org/10.1016/j.annonc.2025.11.019), available at <https://doi.org/10.1016/j.annonc.2025.11.019>, for detailed inclusion and exclusion criteria.

The institutional ethics committee and institutional review board at each study center approved the protocol and the study-related documents (protocol number 201/2019 for coordinating center).

Procedures

Patients were randomly assigned in a 1 : 1 ratio to receive trabectedin 1.1 mg/m² as 24 h continuous i.v. infusion q21d plus olaparib 150 mg orally b.i.d. or trabectedin 1.5 mg/m² as continuous i.v. infusion q21d. All patients received dexamethasone premedication starting from the day before trabectedin infusion ([Supplementary Table S1](https://doi.org/10.1016/j.annonc.2025.11.019), available at <https://doi.org/10.1016/j.annonc.2025.11.019>). Olaparib was administered continuously b.i.d. Treatment continued until progression, unacceptable toxicity, investigator's decision, or patient withdrawal.

Patients were stratified according to histological type (L-sarcoma versus non-L-sarcoma) and number of previous chemotherapy lines for advanced disease (one versus two or more). The L-sarcoma group included patients affected by either liposarcoma (LPS) or leiomyosarcoma, according to previous studies with trabectedin and to the different expected activity of trabectedin monotherapy in L-sarcomas versus non-L-sarcomas. This stratification also reflects the differences in trabectedin approval labels worldwide.^{4,16-20} Randomization used permuted blocks of six patients each according to the stratification factors.

In addition, subgroup analyses were preplanned for age (<65 years versus ≥65 years), sex (males versus females as assigned at birth), histotype [uterine leiomyosarcoma (uLMS), non-uterine leiomyosarcoma (LMS), myxoid LPS, MDM2-amplified LPS, synovial sarcoma, undifferentiated pleomorphic sarcoma, other STS], Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1), *PARP1* expression on formalin-fixed, paraffin embedded tumor samples evaluated by means of anti-PARP1 antibody (positive versus negative; clone EPR18461, Abcam, Rome, Italy; representative stainings and additional details on immunohistochemistry protocol are provided in [Supplementary](https://doi.org/10.1016/j.annonc.2025.11.019)

[Material S1](https://doi.org/10.1016/j.annonc.2025.11.019) and [Figure S1A-C](https://doi.org/10.1016/j.annonc.2025.11.019), available at <https://doi.org/10.1016/j.annonc.2025.11.019>), and homologous recombination deficiency (HRd) status (present versus absent).

HRd status was defined as the presence of impairment in at least one gene from a prespecified DDRR list, and genomic instability score (GIS) was computed using Myriad algorithm. ([Supplementary Material S2](https://doi.org/10.1016/j.annonc.2025.11.019), available at <https://doi.org/10.1016/j.annonc.2025.11.019>). All these analyses were carried out on next-generation sequencing data generated with the TruSight™ Oncology 500 Illumina panel.

Clinically relevant adverse events (AEs) grade >2 according to Common Terminology Criteria for Adverse Events v4.03 (CTCAE v4.03) caused study drug delay (trabectedin) or interruption (olaparib) until recovery or grade ≤1. Dose reductions followed predefined rules ([Supplementary Material S1](https://doi.org/10.1016/j.annonc.2025.11.019), available at <https://doi.org/10.1016/j.annonc.2025.11.019>). In the case of dose reduction, patients were allowed to continue the treatment at dose level -1. In the combination arm, a single dose reduction was permitted and re-escalation was not allowed, but multiple dose interruptions of olaparib were allowed in the case of hematological toxicities. Dose reductions in the trabectedin monotherapy arm followed clinical practice.

Toxicity was monitored weekly by means of both blood tests and clinical examination. Tumors were assessed by computed tomography scans at baseline and every 6 ± 1 weeks afterward.

Outcomes

The primary endpoint of the study was the progression-free survival (PFS, the day-count between therapy start and either disease progression or death) rate at 6 months (PFS6m) according to RECIST 1.1 as per investigator assessment. Secondary endpoints included PFS; overall survival (OS, the day-count between first dose and death from any cause); overall response rate [ORR, the proportion of patients who achieved RECIST 1.1 confirmed complete (CR) or partial response (PR)]; disease control rate [DCR, the proportion of patients who reached CR, PR, or stable disease (SD) state ≥12 weeks]; duration of response (DOR, the day-count between the date of RECIST 1.1 response and progression or death); safety (CTCAE v 4.03), quality of life (QoL, assessed using QLQ C30 and EQ-5D questionnaires); and pain evaluation assessed by means of numerical rating scale (NRS) scores. Pain and QoL were assessed at least at baseline, day 1 of each cycle, and at the end of treatment visit ([Supplementary Material S1](https://doi.org/10.1016/j.annonc.2025.11.019), available at <https://doi.org/10.1016/j.annonc.2025.11.019>). The different outcomes were correlated with clinical characteristics and biomarkers.

Statistical analyses

The sample size was computed assuming a 1 : 1 randomization and a PFS6m of 40% for trabectedin–olaparib versus 25% for trabectedin [hazard ratio (HR) 0.67]. Setting alpha error at 0.1 (one-sided log-rank test) and power at 80%, the

primary analysis was carried out when at least 110 PFS events were observed. Assuming a 24-month accrual, a follow-up ≥ 12 months after the last patient was enrolled, and a 10% rate of non-assessable patients, we planned to enroll a total of 126 patients to observe the expected 110 PFS events. In case one patient was not assessable for response, an additional patient was allowed to be enrolled up to a maximum of 130 patients.

A futility analysis was conducted after enrollment of 60 patients (according to Parmar et al., [Supplementary Material S1](https://doi.org/10.1016/j.annonc.2025.11.019), available at <https://doi.org/10.1016/j.annonc.2025.11.019>). This futility analysis did not affect the type I error level, thereby not requiring any correction of the significance level. Following evaluation by the clinical trial monitoring committee, the trial was recommended to continue to full target accrual.

Activity and safety outcomes were assessed in all patients who received at least one dose of the study drugs (intention-to-treat population).

Descriptive statistics summarized patient demographics and AE frequencies. Qualitative variables were compared using the χ^2 and Fisher's exact tests and/or the Mantel–Haenszel odds ratio (OR) estimates when indicated. Estimates of ORR and DCR are reported with the corresponding two-sided exact binomial 95% confidence intervals (95% CI)

calculated by means of the Clopper–Pearson method. The Kaplan–Meier method estimated median PFS (mPFS), PFS6m, PFS12m, PFS24m, DOR, and OS with their respective 95% CI or inter-quartile ranges (IQRs), and were compared using log-rank test and/or HR estimates calculated by Cox regression when indicated. All statistics were computed using IBM SPSS Statistics (v.29; SPSS Inc., Chicago, IL) and/or R Jamovi, version 2.3.26.0 (R Foundation for Statistical Computing). This study is registered with [ClinicalTrials.gov](https://clinicaltrials.gov), number NCT03838744.

RESULTS

Between 25 May 2020 and 2 November 2022, a total of 149 patients were screened for inclusion and 130 were enrolled and randomly assigned in the TOMAS2 study ([Figure 1](#)). Sixty-five patients were enrolled in each arm. Patients were well balanced across the two arms in terms of baseline characteristics without statistically significant differences. Patient demographics and baseline characteristics are summarized in [Table 1](#).

At data cut-off (31 March 2025), the median follow-up in the overall study population was 37.4 months (95% CI 34.6–40.1 months). One patient was still on treatment in the combination arm.

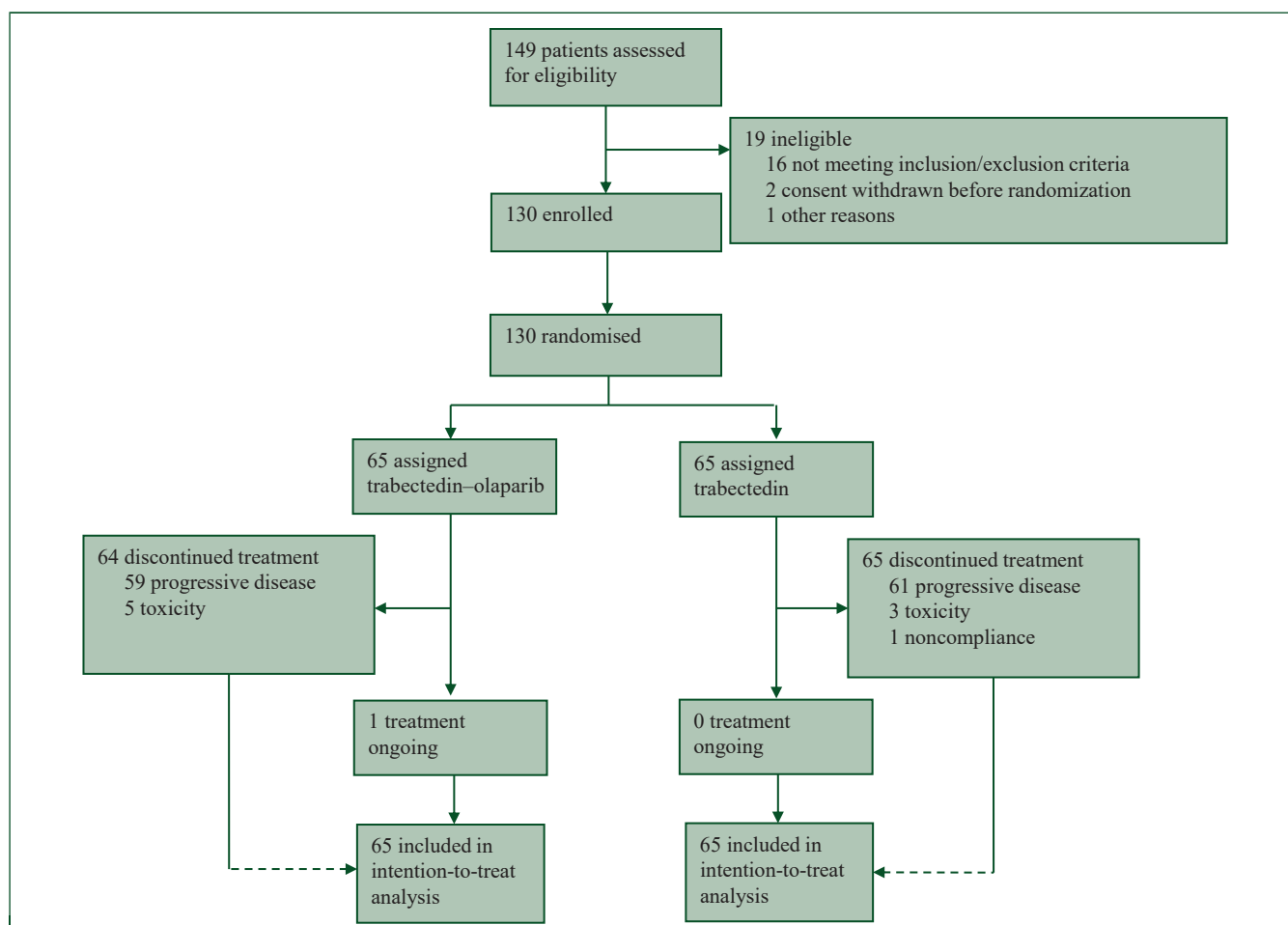


Figure 1. CONSORT diagram.

Table 1. Patient baseline characteristics				
	Trabectedin— olaparib n (%)	Trabectedin, n (%)	P value (two-sided)	Total, n (%)
Total	65 (100)	65 (100)		130 (100)
Sex				
Male	30 (46.2)	19 (29.2)	0.07	49 (37.7)
Female	35 (53.8)	46 (70.8)		81 (62.3)
Age, years				
Median (range)	56 (28-80)	58 (18-79)	1.00	57 (18-80)
<65	44 (67.7)	45 (69.2)		89 (68.5)
≥65	21 (32.3)	20 (30.8)		41 (31.5)
Previous lines				
1	45 (69.2)	48 (73.8)	0.70	93 (71.5)
≥2	20 (30.8)	17 (26.2)		37 (28.5)
Histotype				
L-STS	33 (50.8)	34 (52.3)	1.00	67 (51.5)
Non-L-STS	32 (49.2)	31 (47.7)		63 (48.5)
Histotype (detail)				
LPS	4 (6.2)	6 (9.2)	0.57	10 (7.7)
uLMS	14 (21.5)	14 (21.5)		28 (21.5)
LMS	15 (23.1)	14 (21.5)		29 (22.3)
UPS	12 (18.5)	4 (6.2)		16 (12.3)
SS	4 (6.2)	7 (10.8)		11 (8.5)
MFS	1 (1.5)	3 (4.6)		4 (3.1)
SFT	2 (3.1)	1 (1.5)		3 (2.3)
MPNST	1 (1.5)	3 (4.6)		4 (3.1)
Other	12 (18.5)	13 (20.0)		25 (38.5)
ECOG PS				
0	45 (69.2)	37 (56.9)	0.34	82 (63.1)
1	19 (29.2)	27 (41.5)		46 (35.4)
2	1 (1.5)	1 (1.5)		2 (1.5)

ECOG PS, Eastern Cooperative Oncology Group performance status; LMS, non-uterine leiomyosarcoma; LPS, liposarcoma; L-STS, L-sarcoma (i.e. liposarcoma and leiomyosarcoma); MFS, myxofibrosarcoma; MPNST, malignant peripheral nerve sheath tumor; SFT, solitary fibrous tumor; SS, synovial sarcoma; uLMS, uterine leiomyosarcoma; UPS, undifferentiated pleomorphic sarcoma.

Estimated PFS6m and mPFS were 32% (95% CI 22% to 46%) and 3.9 months (95% CI 2.7-5.2 months) with trabectedin—olaparib versus 28% (95% CI 19% to 42%) and 2.9 months (95% CI 2.2-3.6 months) with trabectedin (log-rank $P = 0.079$; HR 0.722, 95% CI 0.501-1.041, $P = 0.081$).

In an exploratory *post hoc* analysis, PFS12m was 21% (95% CI 13% to 34%) versus 5% (95% CI 2% to 16%) with trabectedin—olaparib versus trabectedin, respectively (Figure 2A).

PFS did not differ significantly between the two groups according to the stratification factors used at time of randomization. Though not statistically significant, a trend toward an improved PFS with the combination was observed in the non-L-sarcoma subgroup (PFS6m 29.0% and mPFS 4.1 months, 95% CI 2.5-5.8 months, versus PFS6m 18.8% and mPFS 2.2 months, 95% CI 1.2-3.1 months; log-rank $P = 0.070$), and in patients treated in second line after for advanced disease (PFS6m 32.8% and mPFS 4.1 months, 95% CI 3.3-5.0 months, versus PFS6m 25.9% and mPFS 2.7 months, 95% CI 1.3-4.1 months, log-rank $P = 0.091$, respectively). (Supplementary Figure S2, available at <https://doi.org/10.1016/j.annonc.2025.11.019>).

In the uLMS subgroup, PFS6m was 42.9% (95% CI 23.4% to 78.5%) with trabectedin—olaparib versus 28.6% (95% CI 12.5% to 65.4%) with trabectedin, while mPFS was 4.0 months and 3.9 months, respectively (HR 0.501, 95% CI 0.203-1.236, $P = 0.134$). Notably, a significant proportion of patients derived a long-term benefit with the combination, achieving a PFS12m of 42.9% (6 out of 14 patients, 95% CI 23.4% to 78.5%) versus 0% with trabectedin alone (Figure 2B).

With 98 death events observed at data cut-off, OS did not differ between the two arms, with a median OS of 17.5 months (95% CI 13.0-22.0 months) with trabectedin—olaparib and 18.2 months (95% CI 12.2-24.1 months) with trabectedin alone (HR 1.157, 95% CI 0.775-1.726, $P = 0.475$) (Supplementary Figure S3, available at <https://doi.org/10.1016/j.annonc.2025.11.019>).

Among 126 patients assessable for response (63 patients in each arm), an ORR of 12.7% (8 PRs, 95% CI 6.1% to 22.7%) was observed with the combination compared with 7.9% (5 PRs, 95% CI 3.0% to 16.7%) with trabectedin alone

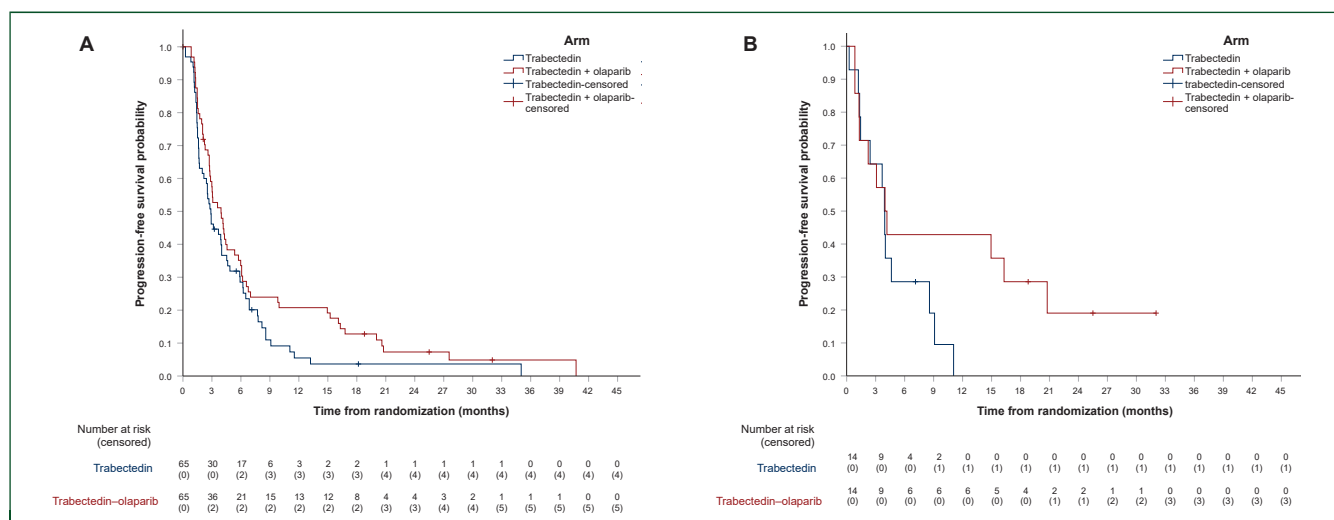


Figure 2. Progression-free survival according to treatment arm. (A) All patients; (B) patients affected by uterine leiomyosarcoma. Red line, trabectedin—olaparib; blue line, trabectedin.

(OR 1.60, 95% CI 0.50-5.16, $P = 0.43$). (Supplementary Figure S4, available at <https://doi.org/10.1016/j.annonc.2025.11.019>).

In a preplanned analysis, PARP1 expression was evaluable for 105 out of 130 samples (80.8%) and correlated with outcome in the trabectedin–olaparib arm but not in the trabectedin arm. Namely, patients with absence of PARP1 expression (24 patients, 22.9%) did not benefit from the addition of olaparib (log-rank $P = 0.347$, Figure 3A), while patients with PARP1 expression of $\geq 1\%$ ($n = 81$, 77.1%) showed a significant benefit with the combination compared with trabectedin (PFS6m 41.5% versus 27.8%; mPFS 4.3 months, 95% CI 2.8-5.8 months, versus 2.5 months, 95% CI 1.7-3.4 months; HR 0.537, 95% CI 0.337-0.855, $P = 0.009$; Figure 3B). Disease response was evaluable in 103 out of 105 patients. In patients with PARP1-negative tumors, we observed no responses among 14 patients in the trabectedin–olaparib arm and one PR out of 10 patients (10%) in the trabectedin arm. Among patients with PARP1-positive tumors, 8/41 patients (19.5%) in the trabectedin–olaparib arm and 2/38 (5.3%) in the trabectedin arm achieved a PR, corresponding to an OR for response of 4.36 (95% CI 0.86-22.05, $P = 0.074$). To further assess the predictive role of PARP1 expression, we

evaluated its impact in the two treatment arms. In patients treated with trabectedin, PARP1 expression did not show any meaningful impact on PFS ($P = 0.503$, Figure 3C), whereas it was associated with a significantly improved PFS in the trabectedin–olaparib arm with a PFS6m of 41.5% and an mPFS of 4.3 months (95% CI 2.8-5.8 months) in PARP1-positive versus 21.4% and 2.0 months (95% CI 0.8-3.2 months) in PARP1-negative patients, respectively (log-rank $P = 0.007$; Figure 3D).

In the uLMS subgroup, PARP1-positive patients ($n = 16$) derived a significant benefit with trabectedin–olaparib combination with an mPFS of 13.7 months (95% CI 0-41.5 months) versus 2.4 months with trabectedin (95% CI 0-5.0 months) (HR 0.251, 95% CI 0.072-0.879, $P = 0.027$; Supplementary Figure S5B, available at <https://doi.org/10.1016/j.annonc.2025.11.019>).

In another preplanned analysis, we explored the impact of HRd on observed outcomes. GIS values were available for 110/130 patients (84.6%). Median GIS value in this population was 21 (IQR 10-33), being higher in LMS and uLMS compared with other histological types [median 26 (IQR 20-33) versus 15 (IQR 4-31), respectively; $P = 0.005$]. When patients were stratified using the median GIS value of 21 (GIS <21 = GIS-low; GIS ≥ 21 = GIS-high), we did not

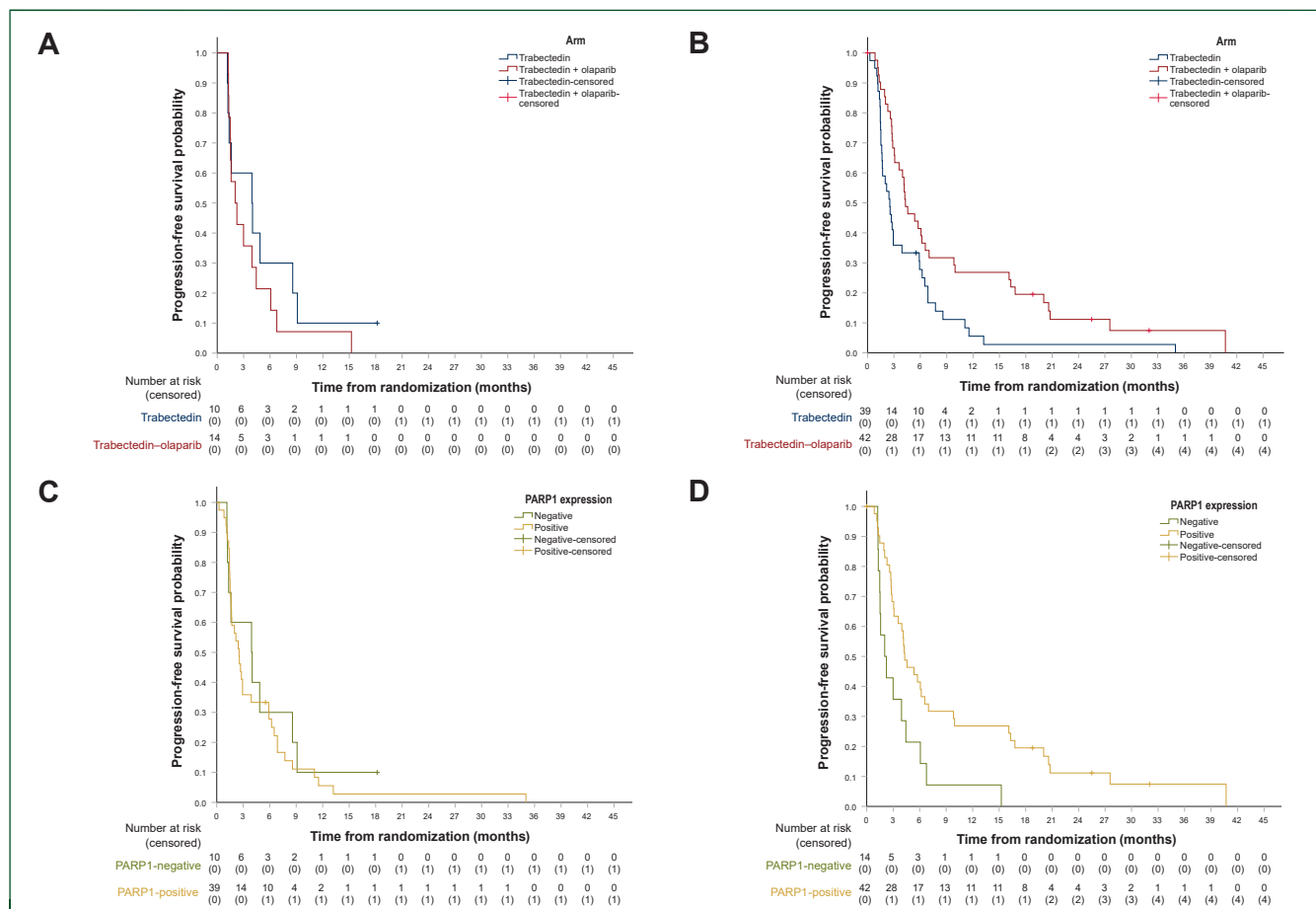


Figure 3. Progression-free survival according to PARP1 expression. (A) PARP1 negative population; red line, trabectedin–olaparib; blue line, trabectedin. (B) PARP1 positive population, red line, trabectedin–olaparib; blue line, trabectedin. (C) Progression-free survival in trabectedin arm according to PARP1 expression; green line, PARP1-negative patients; yellow line, PARP1-positive patients. (D) Progression-free survival in trabectedin–olaparib arm according to PARP1 expression; green line, PARP1-negative patients; yellow line, PARP1-positive patients.

observe a statistically significant benefit with the addition of olaparib in the GIS-low subgroup [median PFS 4.2 months (95% CI 2.8-5.7 months) and PFS6m 29.6% versus 2.8 months (95% CI 1.3-4.3 months) and PFS6m 32.3%; log-rank $P = 0.483$]. In the GIS-high subgroup, we observed a PFS6m of 38.7% and mPFS of 3.9 months (95% CI 2.7-5.2 months) with the combination, versus PFS6m 35.2% and mPFS of 2.9 months (95% CI 0.6-5.3 months) with trabectedin monotherapy, log-rank $P = 0.171$. Remarkably, in the GIS-high subgroup we observed a higher proportion of patients deriving a long-term benefit with the addition of olaparib with a PFS12m of 25.8% versus 0% with trabectedin alone (Supplementary Figure S6, available at <https://doi.org/10.1016/j.annonc.2025.11.019>).

Overall, most relevant grade ≥ 3 AEs were neutropenia, anemia, and thrombocytopenia with trabectedin–olaparib, and aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) increase with trabectedin. Table 2 details all AEs occurring in $>10\%$ of patients. During the entire study, 17 serious AEs (SAEs) were reported in 11 patients. Of these SAEs, two were related to trabectedin–olaparib (grade 3 febrile neutropenia and grade 4 thrombocytopenia occurring in the same patient) and six were attributed to trabectedin (grade 3 neutropenia, leucopenia, and hypokalemia, along with grade 2 diarrhea all reported in one patient; grade 4 AST increase and grade 3 ALT increase in another patient). No treatment-related death was observed. Five patients (7.7%) in combination arm and three (4.6%) in trabectedin arm permanently discontinued treatment due to AEs (OR 1.722, 95% CI 0.394-7.526, $P = 0.470$).

Dose reductions or dose delays were more frequent with trabectedin–olaparib than trabectedin. Namely, in the combination arm trabectedin dose was reduced in 23 (35.4%) and delayed (i.e. delay >3 days due to clinical reasons) in 42 (64.6%) patients, and olaparib dose was reduced in 28 (43.1%) and delayed/interrupted in 54 (83.1%) patients, while in the trabectedin arm dose reductions and/or delays were needed in 25 (38.5%) and 32 (49.2%) patients, respectively.

Finally, no statistically significant changes in QoL or pain scores were observed between baseline and on-treatment assessments in either treatment arm. In the trabectedin arm, there were no significant differences in NRS scores (two-sided paired samples t -test, $P = 0.568$), QLQ-C30 Global Health Status scores ($P = 0.331$), or EQ-5D scores ($P = 0.662$). Similarly, in the trabectedin–olaparib arm, no significant changes were observed in NRS ($P = 0.471$), QLQ-C30 Global Health Status ($P = 0.174$), or EQ-5D ($P = 0.328$) scores. In Supplementary Table S2, available at <https://doi.org/10.1016/j.annonc.2025.11.019>, further details and graphs on QoL assessments are reported.

DISCUSSION

This is the first, multicenter, investigator-initiated, phase II randomized study exploring the combination of trabectedin with the PARP1i olaparib versus standard-of-care

Adverse event	Trabectedin–olaparib (n = 65)						Trabectedin (n = 65)					
	Any grade, n (%)	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Grade 4, n (%)	Grade 5, n (%)	Any grade, n (%)	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Grade 4, n (%)	Grade 5, n (%)
Neutrophil count decreased	43 (66.2)	2 (3.1)	3 (4.6)	17 (26.2)	21 (32.3)	0	25 (38.5)	1 (1.5)	4 (6.2)	7 (10.8)	13 (20.0)	0
Fatigue	38 (58.5)	18 (27.7)	15 (23.1)	4 (6.2)	1 (1.5)	0	34 (52.3)	19 (29.2)	15 (23.1)	0	0	0
Anemia	31 (47.7)	4 (6.2)	15 (23.1)	12 (18.5)	0	0	14 (21.5)	2 (3.1)	11 (16.9)	1 (1.5)	0	0
Platelet count decreased	25 (38.5)	3 (4.6)	9 (13.8)	10 (15.4)	3 (4.6)	0	10 (15.4)	1 (1.5)	4 (6.2)	5 (7.7)	0	0
White blood cell decreased	19 (29.2)	0	6 (9.2)	7 (10.8)	6 (9.2)	0	14 (21.5)	1 (1.5)	5 (7.7)	4 (6.2)	4 (6.2)	0
Nausea	17 (26.2)	14 (21.5)	3 (4.6)	0	0	0	20 (30.8)	16 (24.6)	4 (6.2)	0	0	0
Alanine aminotransferase increased	16 (24.6)	7 (10.8)	4 (6.2)	5 (7.7)	0	0	28 (43.1)	3 (4.6)	8 (12.3)	16 (24.6)	1 (1.5)	0
Fever	14 (21.5)	9 (13.8)	5 (7.7)	0	0	0	5 (7.7)	5 (7.7)	0	0	0	0
GGT increased	12 (18.5)	3 (4.6)	5 (7.7)	4 (6.2)	0	0	11 (16.9)	2 (3.1)	4 (6.2)	5 (7.7)	0	0
Constipation	12 (18.5)	9 (13.8)	3 (4.6)	0	0	0	14 (21.5)	11 (16.9)	2 (3.1)	1 (1.5)	0	0
Diarrhea	11 (16.9)	7 (10.8)	3 (4.6)	1 (1.5)	0	0	9 (13.8)	7 (10.8)	2 (3.1)	0	0	0
Dyspepsia	10 (15.4)	4 (6.2)	4 (6.2)	2 (3.1)	0	0	7 (10.8)	5 (7.7)	2 (3.1)	0	0	0
Creatinine increased	7 (10.8)	3 (4.6)	4 (6.2)	0	0	0	4 (6.2)	4 (6.2)	0	0	0	0
Aspartate aminotransferase increased	7 (10.8)	4 (6.2)	1 (1.5)	2 (3.1)	0	0	17 (26.2)	11 (16.9)	2 (3.1)	4 (6.2)	0	0
Anorexia	7 (10.8)	4 (6.2)	2 (3.1)	1 (1.5)	0	0	2 (3.1)	2 (3.1)	0	0	0	0
Alkaline phosphatase increased	6 (9.2)	5 (7.7)	1 (1.5)	0	0	0	10 (15.4)	4 (6.2)	4 (6.2)	2 (3.1)	0	0
Pain	5 (7.7)	4 (6.2)	0	0	1 (1.5)	0	10 (15.4)	7 (10.8)	3 (4.6)	0	0	0
CPK increased	5 (7.7)	2 (3.1)	1 (1.5)	2 (3.1)	0	0	9 (13.8)	4 (6.2)	2 (3.1)	2 (3.1)	1 (1.5)	0
Febrile neutropenia	5 (7.7)	2 (3.1)	1 (1.5)	2 (3.1)	3 (4.6)	0	2 (3.1)	4 (6.2)	2 (3.1)	1 (1.5)	1 (1.5)	0

CPK, creatine phosphokinase; GGT, γ -glutamyl transpeptidase.

trabectedin in patients affected by advanced STS. Overall, although the combination met the predefined criterion for statistical significance in terms of PFS ($P < 0.10$), this did not translate into a clinically meaningful advantage in the unselected population of patients affected by STS. On the contrary, PARP1 expression was confirmed as a predictive biomarker that identified a subset of patients who derived a statistically significant and clinically relevant benefit from trabectedin—olaparib combination. Moreover, an improved and meaningful long-term PFS was observed with the combination in patients affected by uLMS and/or bearing homologous recombination defects.

Dysregulation of DDR pathways is common in cancer cells, thus representing an attractive therapeutic target.²¹ Among the different agents tested so far, PARP1i were the first to demonstrate efficacy in a relatively broad set of tumors. These compounds were initially explored as potentiators of chemotherapy-induced cytotoxicity following the rationale of impairing the repair of the DNA damage induced by chemotherapy to increase tumor cell death. However, the clinical application of PARP1i and chemotherapy combinations was limited by hematological toxicity. Therefore, PARP1i were primarily developed as single agents or in combination with targeted therapies in patients harboring defects in the homologous recombination pathway.^{22–24}

We tested the combination of PARP1i with trabectedin to take advantage of its unique mechanism of action and lower hematological toxicity compared with other cytotoxic agents. In preclinical studies, we had demonstrated a strong correlation between PARP1 expression and activity of the combination.¹⁴ Consistently, in the TOMAS study, high basal (before treatment start) PARP1 expression was associated with a significantly higher activity of the combination (ORR 27% versus 8% in PARP1-high versus -low). This positioned PARP1 expression as a putative predictive biomarker,¹⁵ which is particularly notable in the light of prior evidence suggesting that PARP1 expression might represent a negative prognostic factor in STS.^{25,26} In the TOMAS2 study, PARP1 expression was associated with an incremental advantage from trabectedin—olaparib combination. This effect was absent in the trabectedin monotherapy arm, reinforcing the role of PARP1 expression as a predictive biomarker. Furthermore, in this STS population, PARP1 expression showed a better correlation with PFS than homologous recombination pathway alterations. However, defining HRd remains challenging, especially in mesenchymal tumors. For instance, although *ATRX* alterations are commonly included in HRd scoring algorithms, their predictive role for PARP1i activity remains debated. Additionally, *ATRX* alterations have been found in up to one-third of uLMS and are associated with poor prognosis in leiomyosarcomas.^{27,28} Moreover, scores mirroring HRd, like GIS, have shown weaker predictive value in STS compared with their performance in epithelial malignancies.²⁹ In our study, we used a GIS of 21 as threshold, corresponding to the median value observed in our population. This was lower than the one used in ovarian cancer

or other carcinomas. Nonetheless, it should be noted that GIS thresholds greatly differ across studies also in epithelial tumors.^{24,30}

Not surprisingly, our study substantiates sarcoma heterogeneity and confirms that homologous recombination alterations are quite common in uLMS, regardless of the method used to detect such genetic defects.^{28,31} Consistently, the uLMS population derived the greatest benefit from trabectedin—olaparib with outcomes similar to a phase II single-arm study with temozolomide—olaparib combination in advanced uLMS. Indeed, in that study, temozolomide—olaparib combination yielded an ORR of 27% and mPFS of 6.9 months, with PFS6m, PFS12m, and PFS24m of 65%, 38%, and 22%, respectively.²⁹ Interestingly, mPFS was significantly better for patients harboring defects in homologous recombination detected by means of RAD51 foci (mPFS 11.2 months versus 5.4 months in HRd and homologous recombination-proficient, respectively) making this assessment more promising in predicting combination activity than HRd scores calculated by scarHRD.²⁹ Similarly, in the uLMS population of the TOMAS2 study treated with trabectedin—olaparib, we observed an ORR of 23% with a PFS12m and a PFS24m of 42.9% and 19.0%, respectively. Altogether, these data support further investigation of PARP1i—chemotherapy combinations in advanced uLMS and STS selected on the basis of *PARP1* expression. The key role of patient selection was further highlighted by the recently reported data of a phase II/III study that explored temozolomide—olaparib combination versus physician's choice in patients with advanced uLMS.³²

The extent to which the observed activity is driven by PARP1i alone or the synergy with chemotherapy remains an open question. However, hints from preclinical and clinical evidence support the superiority of the combination strategy in this disease setting. A recent retrospective analysis of 13 patients affected by uLMS harboring *BRCA1/2* alterations treated with PARP1i showed RECIST 1.1 responses in 17% (1/6) and 71% (5/7) of the patients treated with PARP1i monotherapy and in combination with different compounds, respectively. These data further highlight the role of this class of drugs in the uLMS population and suggest a clinically relevant rationale for the use of combination strategies.³³ However, patient selection remains a key factor. In a phase II study of olaparib—durvalumab combination in an unselected leiomyosarcoma cohort, activity was observed only in a few cases (1 PR and 5 SD as best overall response in 14 assessable patients), further emphasizing the need to identify reliable biomarker/s.³⁴

This is particularly crucial considering the need to spare unnecessary toxicity associated with combinations. Indeed, in the TOMAS2 study, the trabectedin—olaparib arm showed the expected increase in hematological AEs compared with trabectedin alone. Nonetheless, the combination toxicity was manageable with dose modifications or short olaparib interruptions. Data on AEs were similar to those reported in a phase II single-arm study with trabectedin—olaparib in advanced STS.³⁵ The higher rate of

treatment discontinuation due to AEs observed in this study (19% versus 7.7% in the TOMAS2 study) might be related to a different use of dexamethasone premedication and a more restrictive olaparib temporary interruption management. Similar toxicities were observed in the temozolomide—olaparib study, wherein ~50% of patients required dose reductions.²⁹ Upcoming new PARP1i characterized by higher target selectivity and presumably less hematological toxicity may increase interest in exploiting the inhibition of this pathway in combination with chemotherapy, including new synthetic ecteinascidin derivatives.^{23,36,37} Furthermore, our findings suggest that future studies should be guided by biomarker-based patient selection and sarcoma histotypes. Furthermore, given the unique mechanism of action and pharmacokinetic profile of trabectedin, which allows also for extended intervals between drug administrations, together with the potential suitability of PARP1i for intermittent or pulsed dosing, future studies should explore alternative scheduling strategies for combining chemotherapy with PARP1i to minimize toxicity.³⁸

Overall, with the limitations of cross-study comparisons and of the populations enrolled, the combination of trabectedin—olaparib in the TOMAS2 study slightly underperformed compared with the phase Ib study considering patients treated at least at the third dose level in that trial (trabectedin ≥ 0.920 mg/m² q21d; olaparib ≥ 150 mg b.i.d.). Indeed, in the phase Ib study, we had observed a PFS6m of 42% and an ORR of 18% compared with 32% and 12.7% in the phase II study, respectively. Nonetheless, the TOMAS2 results are in line with the few other available data on trabectedin—olaparib combination in STS.³⁵

The performance of the trabectedin monotherapy arm in TOMAS2 aligns with historical data both in L-sarcomas and in non-L-sarcomas, supporting the reliability of the control arm and the representative nature of the enrolled population.^{4,19,39}

Interestingly, in the trabectedin monotherapy arm homologous recombination pathway alterations did not predict drug activity. This partially differs from retrospective series that reported a better outcome with trabectedin in patients harboring alterations in DDRR pathways.^{40–42} This may reflect differences in study design (prospective versus retrospective), biomarker assessment, and the definition of HRd and/or of the DDRR alterations tested across studies.

Our study has some limitations. Indeed, randomization stratified patients according to histotype and the distribution was well balanced in the two arms, but the intrinsic heterogeneity of STS enrolled in the non-L-sarcoma group might have jeopardized the assessment of combination activity in this subgroup. As mentioned in the Methods section, we stratified patients by 'L-sarcoma' and 'non-L-sarcoma' according to previous data on differential activity of trabectedin monotherapy in these two subgroups and to reflect previous registration studies that enrolled patients affected by L-sarcomas only.^{4,17–19,43} To deepen into STS heterogeneity, in the study protocol we had foreseen a preplanned exploratory analysis according to the main

histological subtypes (Supplementary Material S1, available at <https://doi.org/10.1016/j.annonc.2025.11.019>). That said, randomization and the relevant number of patients affected by leiomyosarcoma enrolled in the trial may help to generate hypotheses for future trials in this STS subtype and allow for a deeper evaluation of results coming from translational analyses.

Finally, it is worth acknowledging that the trial was conducted during the coronavirus disease 2019 (COVID-19) pandemic. Nonetheless, accrual was successfully completed in ~2 years.

In conclusion, this is the first prospective randomized trial investigating the combination of trabectedin and olaparib in patients with advanced STS. The trial emphasizes that uLMS is the most promising candidate for further evaluation of PARP1i in combination with chemotherapy. Moreover, *PARP1* expression predicted trabectedin—olaparib activity representing a definite biomarker for future trials leveraging on this inhibitor class of drugs. Finally, improving the assessment of DDRR defects in STS could provide valuable insights and guide more effective therapeutic approaches.

ACKNOWLEDGEMENTS

The authors deeply thank patients and their families for participating in this trial, Gianluca Ignazzi and Viviana Appolloni for data management support, and Laura Abate-Daga and Giuseppe Bianchi for their administrative support.

FUNDING

The research leading to these results has received funding from the Italian Association for Cancer Research (AIRC) [grant numbers IG-17226, IG-23104] to GG, and under Next Gen Clinician Scientist [grant number ID.31761] to LDA; the Foundation for Research on Musculoskeletal and Rare Tumors (FTMSR) to GG; Italian Ministry of Health (Ricerca corrente 2017 and 2025) to GG and Piedmont Foundation for Cancer Research (FPRC 5 per mille 2014) to GG (no grant number); Associazione DaRosa 2023 Award to AM; and by an unrestricted grant from PharmaMar to the Italian Sarcoma Group. AM's research activity was partially supported by [grant numbers Programma Operativo Nazionale 2014–2020 Decreto Ministeriale 1062/2021 Piano Nazionale per la Ricerca 2021–2027. PharmaMar and AstraZeneca provided the study drugs free of charge but were not involved in trial management or results evaluation.

ROLE OF THE FUNDER

Funding sources had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication. All authors had full access to the study data, shared the decision to submit for publication, were involved in writing the report, and agreed upon the report content. The corresponding authors had final responsibility to submit the report for publication.

DISCLOSURE

LDA reports advisory board: PSI CRO Italy, GSK, AstraZeneca, and Boehringer Ingelheim; invited speaker: Boehringer Ingelheim, Gentili, AstraZeneca, GSK, Deciphera, and PharmaMar; meeting participation: PharmaMar, AstraZeneca, Amgen, GSK, Deciphera, and AstraZeneca; and research funding: PharmaMar (to institution). AM reports invited speaker: Boehringer Ingelheim, BeiGene, Sanofi, and Regeneron; and research funding: PharmaMar (to institution). ABr reports advisory board: PharmaMar, Boehringer Ingelheim, Deciphera, and GSK; and invited speaker: Boehringer Ingelheim. AP reports meeting participation: PharmaMar. BV reports advisory board: Abbot, GSK, and Lilly; speaker's bureau: PharmaMar and Deciphera; and institutional funding: BD Bard. RS reports advisory board: Boehringer Ingelheim, Rain Therapeutics; meeting participation: PharmaMar; and research funding (all to institution): Advenchen Laboratories, Amgen/Dompé, AORG Pharmaceuticals, Bayer, Blueprint Medicines, Boehringer Ingelheim, Daiichi-Sankyo, Deciphera, Eisai, Epizyme, Foghorn Therapeutics, GSK, Hutchison MediPharma, InhibRx, Karyopharm Therapeutics, Novartis, Pfizer, PharmaMar, PTC Therapeutics, RAIN, and SpringWorks Therapeutics. GGB reports advisory board or consulting fee: Deciphera, GSK, Merck Sharpe & Dohme (MSD), Eli Lilly, PharmaMar, and Boehringer Ingelheim; invited speaker: PharmaMar, Eli Lilly, GSK, MSD, and Gentili; and meeting participation: Eli Lilly, PharmaMar, and Gentili. CM reports advisory board: Roche, AstraZeneca, Bayer, and Daiichi-Sankyo. MR reports meeting participation: Gentili. SA reports advisory board or consulting fees: MEDENDI; invited speaker: Eisai, Gentili, and Deciphera; and meeting participation: PharmaMar, Gentili, and Deciphera. SS reports advisory board: Agenus, Astex Pharmaceuticals, Bayer, Boehringer Ingelheim, Bavarian Nordic, Daiichi, Deciphera, GSK, Ikena, Ipsen, NEC Oncolmmunity AS, Novartis, Pharmaessentia, Rain Therapeutics, Regeneron, and Servier, invited speaker: GSK, PharmaMar, Aadi, and Gentili; meeting participation: PharmaMar; and research funding (all to institution): Abbisko Therapeutics, Advenchen Laboratories, Amgen, Ayala Pharmaceuticals, Bayer, Blueprint Medicines, Boehringer Ingelheim, Daiichi-Sankyo, Deciphera, Epizyme, GlaxoSmithKline, Hutchison MediPharma, InhibRx, Karyopharm Therapeutics, Novartis, Pfizer, PharmaMar, Rain Therapeutics, and SpringWorks Therapeutics. GG reports invited speaker or consulting role: Boehringer Ingelheim, Incyte, Merck, Novartis, Gentili, Bayer, Lilly, Springworks, AstraZeneca, Deciphera, PharmaMar, and GSK; and research funding (to institution): Bayer and PharmaMar. All other authors have declared no conflicts of interest.

DATA SHARING

The datasets generated and analyzed during this study are not publicly available due to the presence of information that could compromise participant privacy and informed consent. In accordance with Italian and European

regulations, any reuse of the data requires prior approval from the ethics committees of the participating centers. Qualified researchers affiliated with academic institutions may request access to the data by submitting a detailed proposal outlining the intended use. Requests should be directed to the corresponding authors within 24 months from the publication of the article and will be reviewed within the data and safety monitoring board.

REFERENCES

1. WHO Classification of Tumours. *Soft Tissue and Bone Tumours*. 5th ed. IARC; 2020.
2. Gronchi A, Miah AB, Dei Tos AP, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN-GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2021;32(11):1348-1365.
3. Judson I, Verweij J, Gelderblom H, et al. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. *Lancet Oncol*. 2014;15(4):415-423.
4. Demetri GD, von Mehren M, Jones RL, et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of a phase III randomized multicenter clinical trial. *J Clin Oncol*. 2016;34(8):786-793.
5. van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2012;379(9829):1879-1886.
6. Tawbi HA, Burgess M, Bolejack V, et al. Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial. *Lancet Oncol*. 2017;18(11):1493-1501.
7. Pautier P, Italiano A, Piperno-Neumann S, et al. Doxorubicin-trabectedin with trabectedin maintenance in leiomyosarcoma. *N Engl J Med*. 2024;391(9):789-799.
8. D'Ambrosio L, Touati N, Blay JY, et al. Doxorubicin plus dacarbazine, doxorubicin plus ifosfamide, or doxorubicin alone as a first-line treatment for advanced leiomyosarcoma: A propensity score matching analysis from the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. *Cancer*. 2020;126(11):2637-2647.
9. Maki RG, Wathen JK, Patel SR, et al. Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002 [corrected]. *J Clin Oncol*. 2007;25(19):2755-2763.
10. García-Del-Muro X, López-Pousa A, Maurel J, et al. Randomized phase II study comparing gemcitabine plus dacarbazine versus dacarbazine alone in patients with previously treated soft tissue sarcoma: a Spanish Group for Research on Sarcomas study. *J Clin Oncol*. 2011;29(18):2528-2533.
11. D'Angelo SP, Mahoney MR, Van Tine BA, et al. Nivolumab with or without ipilimumab treatment for metastatic sarcoma (Alliance A091401): two open-label, non-comparative, randomised, phase 2 trials. *Lancet Oncol*. 2018;19(3):416-426.
12. Wilky BA, Schwartz GK, Gordon MS, et al. Botenslimab (Fc-enhanced anti-cytotoxic lymphocyte-association protein-4 antibody) Plus Balmstilimab (anti-PD-1 antibody) in Patients With Relapsed/Refractory Metastatic Sarcomas. *J Clin Oncol*. 2025;43(11):1358-1368.
13. Germano G, Frapolli R, Belgiovine C, et al. Role of macrophage targeting in the antitumor activity of trabectedin. *Cancer Cell*. 2013;23(2):249-262.
14. Pignochino Y, Capozzi F, D'Ambrosio L, et al. PARP1 expression drives the synergistic antitumor activity of trabectedin and PARP1 inhibitors in sarcoma preclinical models. *Mol Cancer*. 2017;16(1):86.
15. Grignani G, D'Ambrosio L, Pignochino Y, et al. Trabectedin and olaparib in patients with advanced and non-resectable bone and soft-tissue sarcomas (TOMAS): an open-label, phase 1b study from the Italian Sarcoma Group. *Lancet Oncol*. 2018;19(10):1360-1371.

16. Le Cesne A, Cresta S, Maki RG, et al. A retrospective analysis of antitumour activity with trabectedin in translocation-related sarcomas. *Eur J Cancer*. 2012;48(16):3036-3044.
17. Blay JY, Leahy MG, Nguyen BB, et al. Randomised phase III trial of trabectedin versus doxorubicin-based chemotherapy as first-line therapy in translocation-related sarcomas. *Eur J Cancer*. 2014;50(6):1137-1147.
18. Kawai A, Araki N, Sugiura H, et al. Trabectedin monotherapy after standard chemotherapy versus best supportive care in patients with advanced, translocation-related sarcoma: a randomised, open-label, phase 2 study. *Lancet Oncol*. 2015;16(4):406-416.
19. Demetri GD, Chawla SP, von Mehren M, et al. Efficacy and safety of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of prior anthracyclines and ifosfamide: results of a randomized phase II study of two different schedules. *J Clin Oncol*. 2009;27(25):4188-4196.
20. Barone A, Chi DC, Theoret MR, et al. FDA Approval summary: trabectedin for unresectable or metastatic liposarcoma or leiomyosarcoma following an anthracycline-containing regimen. *Clin Cancer Res*. 2017;23(24):7448-7453.
21. Hanahan D. Hallmarks of cancer: new dimensions. *Cancer Discov*. 2022;12(1):31-46.
22. Yap TA, Sandhu SK, Carden CP, et al. Poly(ADP-ribose) polymerase (PARP) inhibitors: exploiting a synthetic lethal strategy in the clinic. *CA Cancer J Clin*. 2011;61(1):31-49.
23. Bhamidipati D, Haro-Silerio JL, Yap TA, et al. PARP inhibitors: enhancing efficacy through rational combinations. *Br J Cancer*. 2023;129(6):904-916.
24. Hage Chehade C, Gebrael G, Sayegh N, et al. A pan-tumor review of the role of poly(adenosine diphosphate ribose) polymerase inhibitors. *CA Cancer J Clin*. 2025;75(2):141-167.
25. Bertucci F, Finetti P, Monneur A, et al. PARP1 expression in soft tissue sarcomas is a poor-prognosis factor and a new potential therapeutic target. *Mol Oncol*. 2019;13(7):1577-1588.
26. Kim KM, Moon YJ, Park SH, et al. Individual and combined expression of DNA damage response molecules PARP1, γ H2AX, BRCA1, and BRCA2 predict shorter survival of soft tissue sarcoma patients. *PLoS One*. 2016;11(9):e0163193.
27. Dermawan JK, Chiang S, Singer S, et al. Developing novel genomic risk stratification models in soft tissue and uterine leiomyosarcoma. *Clin Cancer Res*. 2024;30(10):2260-2271.
28. Nacev BA, Sanchez-Vega F, Smith SA, et al. Clinical sequencing of soft tissue and bone sarcomas delineates diverse genomic landscapes and potential therapeutic targets. *Nat Commun*. 2022;13(1):3405.
29. Ingham M, Allred JB, Chen L, et al. Phase II study of olaparib and temozolomide for advanced uterine leiomyosarcoma (NCI Protocol 10250). *J Clin Oncol*. 2023;41(25):4154-4163.
30. Ray-Coquard I, Pautier P, Pignata S, et al. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. *N Engl J Med*. 2019;381(25):2416-2428.
31. Planas-Paz L, Pliego-Mendieta A, Hagedorn C, et al. Unravelling homologous recombination repair deficiency and therapeutic opportunities in soft tissue and bone sarcoma. *EMBO Mol Med*. 2023;15(4):e16863.
32. Van Tine BA, Allred JB, Hensley ML, et al. Alliance A092104: A randomized phase 2/3 study of olaparib plus temozolomide versus investigator's choice for the treatment of patients with advanced uterine leiomyosarcoma after progression on prior chemotherapy. *J Clin Oncol*. 2025;43(suppl 16):11507.
33. Rao M, Merrill M, Troxel M, et al. Retrospective analysis of BRCA-altered uterine sarcoma treated with poly (ADP-ribose) polymerase inhibitors. *JCO Precis Oncol*. 2025;9:e2400765.
34. Salawu A, Wang BX, Han M, et al. Safety, immunologic, and clinical activity of durvalumab in combination with olaparib or cediranib in advanced leiomyosarcoma: results of the DAPPER clinical trial. *Clin Cancer Res*. 2023;29(20):4128-4138.
35. Siontis BL, Rice JD, Schuetze SM, et al. A phase II multicenter trial of trabectedin in combination with olaparib in patients with advanced unresectable or metastatic sarcoma. *Clin Cancer Res*. 2025;31(14):2919-2925.
36. Ngoi NYL, Leo E, O'Connor MJ, Yap TA. Development of next-generation poly(ADP-ribose) polymerase 1-selective inhibitors. *Cancer J*. 2021;27(6):521-528.
37. Cote GM, Haddox CL, Choy E, et al. Safety and efficacy of the combination lurbinectedin plus doxorubicin from a phase 1b trial in patients with advanced/metastatic soft-tissue sarcoma. *Clin Cancer Res*. 2024;30(13):2702-2708.
38. Poitureau S, Le Deley MC, Brahmi M, et al. Relative dose intensity of trabectedin and outcome of advanced L-sarcomas. *Cancer Med*. 2025;14(16):e71131.
39. Le Cesne A, Blay JY, Cupissol D, et al. A randomized phase III trial comparing trabectedin to best supportive care in patients with pre-treated soft tissue sarcoma: T-SAR, a French Sarcoma Group trial. *Ann Oncol*. 2021;32(8):1034-1044.
40. Moura DS, Peña-Chilet M, Cordero Varela JA, et al. A DNA damage repair gene-associated signature predicts responses of patients with advanced soft-tissue sarcoma to treatment with trabectedin. *Mol Oncol*. 2021;15(12):3691-3705.
41. Schöffski P, Taron M, Jimeno J, et al. Predictive impact of DNA repair functionality on clinical outcome of advanced sarcoma patients treated with trabectedin: a retrospective multicentric study. *Eur J Cancer*. 2011;47(7):1006-1012.
42. Italiano A, Laurant A, Laroche A, et al. ERCC5/XPG, ERCC1, and BRCA1 gene status and clinical benefit of trabectedin in patients with soft tissue sarcoma. *Cancer*. 2011;117(15):3445-3456.
43. Samuels BL, Chawla S, Patel S, et al. Clinical outcomes and safety with trabectedin therapy in patients with advanced soft tissue sarcomas following failure of prior chemotherapy: results of a worldwide expanded access program study. *Ann Oncol*. 2013;24(6):1703-1709.