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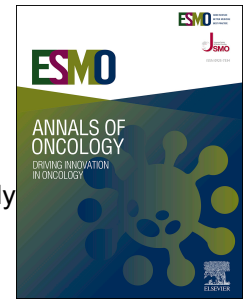

Trabectedin-olaparib combination or trabectedin in advanced soft tissue sarcomas after failure of anthracycline-based treatment (TOMAS2): a randomized phase 2 study from the Italian Sarcoma Group

L. D'Ambrosio, A. Merlini, A. Brunello, V. Ferraresi, A. Paioli, B. Vincenzi, M.A. Pantaleo, T.M. De Pas, L. Gurrieri, R. Sanfilippo, A. Buonadonna, G.G. Baldi, G. Badalamenti, C. Marchiò, Y. Pignochino, E. Berrino, S.E. Bellomo, M. Sbaraglia, L. Righi, M. Rabino, F. Tolomeo, S. Aliberti, D. Sangiolo, A.P.Dei Tos, S. Stacchiotti, G. Grignani

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TOMAS2 trial: Trabectedin-olaparib combination demonstrated improved outcomes versus trabectedin standard-of-care in PARP1-expressing soft tissue sarcomas and uterine leiomyosarcomas, progressing after anthracycline-based regimens (NCT03838744)

BACKGROUND

Advanced/metastatic soft tissue sarcomas still have limited therapeutic options after anthracycline-based regimens

STUDY DESIGN

TOMAS-2 is an investigator-initiated, open-label, phase 2 randomized trial

130 PTS
1:1

- Trabectedin 1.1 mg/m2 i.v. 24h q 3wks + olaparib 150 mg BID
- Trabectedin 1.5 mg/m2 i.v. 24h q 3wks

Primary endpoint: PFS@6m (T+O 40%, T 25%, α 0.1, power 0.8 → 126 evaluable pts)
Secondary endpoints: PFS, OS, ORR RECIST 1.1, ORR Choi, DOR, DCR, GMI, safety, QoL
Exploratory endpoints: correlation of outcomes with clinical characteristics and biomarkers

130 patients in 13 Italian Sarcoma Group center

	Trabectedin + olaparib N (%)	Trabectedin N (%)	p-value (2-sided)	Total N (%)
Total	65 (100)	65 (100)		130 (100)
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)

RESULTS ITT POPULATION

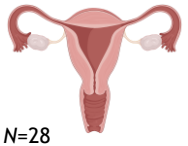
Trabectedin + olaparib vs trabectedin

HR for disease progression or death
0.722, 0.501-1.041, *P*=0.081

Trabectedin + olaparib vs trabectedin

ORR 12.7% vs 7.9%
OR 1.60; 0.50-5.16; P=0.43

UTERINE LMS

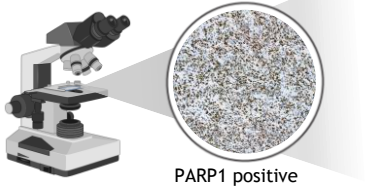


PFS12m 42.9%

PFS12m 0%

N=28

PARP1 expression



PARP1 positive

PFS6m 41.5%

mPFS 4.3 months

PFS6m 27.8%

mPFS 2.5 months

N=81

Original article

Trabectedin-olaparib combination or trabectedin in advanced soft tissue sarcomas after failure of anthracycline-based treatment (TOMAS2): a randomized phase 2 study from the Italian Sarcoma Group

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Figures 3

Tables 2

References 43

Previous presentations: preliminary results from this study were presented at the European Society for Medical Oncology 2023 Annual Meeting (Proffered paper session - Sarcoma LBA91).

Abstract

Background

Advanced/metastatic soft tissue sarcomas (STS) 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 2 randomized trial, adult patients with advanced STS progressing after ≥1 anthracycline-based line of therapy were randomized 1:1 to trabectedin 1.1 mg/m^2 q21d i.v. plus olaparib tablets 150 mg BID, or trabectedin 1.5 mg/m^2 q21d i.v. Randomization stratified patients by histology (L-sarcoma, i.e. leiomyosarcoma and liposarcoma *vs.* non-L-sarcoma) and number of prior therapies (1 *vs.* ≥2). The primary endpoint was progression-free survival (PFS) rate at 6-month (PFS6m) per RECIST1.1. Secondary endpoints included PFS, overall survival (OS), RECIST1.1 overall response rate (ORR), safety. Exploratory endpoints encompassed biomarker/molecular analyses.

Results

Between May 25, 2020, and November 2, 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% (22-46%) and 3.9 months (95%CI 2.7-5.2) with trabectedin-olaparib *vs.* 28% (19-42%) and 2.9 months (2.2-3.6) with trabectedin (HR=0.722, 0.501-1.041, *P*=0.081). Among 126 evaluable patients, ORR was 12.7% (6.1-22.7%) *vs.* 7.9% (3.0-16.7%), respectively (OR=1.60; 0.50-5.16; *P*=0.43). In the uterine leiomyosarcoma subgroup, 12-month PFS was 42.9% with trabectedin-olaparib *vs.* 0% with trabectedin. *PARP1* expression significantly correlated with improved PFS with trabectedin-olaparib (median PFS and PFS6m 4.3 months and

41.5% *vs.* 2.5 months and 27.8% with trabectedin; HR=0.537, 0.337-0.855, *P*=0.009). Grade ≥3 hematological toxicities were significantly more frequent with trabectedin-olaparib.

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.

Keywords

PARP1; biomarker; sarcoma; trabectedin; olaparib; leiomyosarcoma.

NCT No. NCT03838744

Highlights:

- The TOMAS2 study randomized patients with metastatic soft tissue sarcomas (STS) to trabectedin-olaparib or trabectedin
- Trabectedin-olaparib reached the prespecified significance level for PFS (p<0.1) but the benefit was marginal in all-comers
- Trabectedin-olaparib significantly improved progression-free survival in patients with PARP1 expression on tumor tissue
- About 40% of patients with uterine leiomyosarcoma treated with trabectedin-olaparib where progression-free at 12-month
- Trabectedin-olaparib combination deserves further investigation in PARP1-positive STS and in uterine leiomyosarcoma

Main text

Introduction

Soft tissue sarcomas (STS) represent a heterogeneous group of more than 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 GIST, 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, though 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 (DDRR) machinery, resulting into DNA single- and double-strand breaks, and exerts 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 (PARP1i), 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 PARP1i olaparib, significantly boosting the combined antitumor activity compared to 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 (DSBs) 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 *vs.* 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 1b 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-2 dose (RP2D) was trabectedin 1.1 mg/m^2 as 24-h continuous intravenous (i.v.) infusion every 3 weeks plus olaparib tablets 150 mg orally twice daily. Furthermore, this phase 1b study showed promising combination activity in STS, especially in leiomyosarcomas.[15]

On these bases, within the frame of the Italian Sarcoma Group (ISG), we ran a phase 2 randomized study to test trabectedin-olaparib combination vs. trabectedin standard-of-care in STS.

Methods

Study design and participants

This was an investigator-initiated, open-label, multicenter, phase 2 randomized clinical trial conducted at 13 ISG 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 (APDT, MS). Previous treatment with trabectedin, olaparib or their analogues was not allowed. See Protocol pp 29-33 for detailed inclusion and exclusion criteria.

The Institutional Ethic 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 randomized in a 1:1 ratio to receive trabectedin 1.1 mg/m^2 as 24h continuous i.v. infusion every 3 weeks plus olaparib 150 mg orally BID or trabectedin 1.5 mg/m^2 as continuous i.v.

infusion every 3 weeks. All patients received dexamethasone premedication starting from the day before trabectedin infusion (Table S1, appendix p 1). Olaparib was administered continuously twice daily. Treatment continued until progression, unacceptable toxicity, investigator's decision, or patient withdrawal.

Patients were stratified according to histological type (L-sarcoma *vs.* non-L-sarcoma) and number of previous chemotherapy lines for advanced disease (1 *vs.* ≥2). The L-sarcoma group included patients affected by either liposarcoma or leiomyosarcoma, according to previous studies with trabectedin and to the different expected activity of trabectedin monotherapy in L-sarcomas *vs.* non-L-sarcomas. This stratification also reflects the differences in trabectedin approval labels worldwide.[4, 16-20] Randomization used permuted blocks of 6 patients each according to the stratification factors.

In addition, subgroup analyses were pre-planned for age (<65 *vs.* ≥65 years), sex (males *vs.* females as assigned at birth), histotype (uterine LMS, non-uterine LMS, myxoid LPS, MDM2-amplified LPS, synovial sarcoma, undifferentiated pleomorphic sarcoma (UPS), other STS), ECOG performance status (0 *vs.* 1), *PARP1* expression on FFPE tumor samples evaluated by means of anti-PARP1 antibody (positive *vs.* negative; clone EPR18461, Abcam, Rome, Italy; representative stainings and additional details on IHC protocol are provided in Figure S1A-C, appendix p 2), and homologous recombination deficiency (HRd) status (present *vs.* absent).

HRd status was defined in presence of impairment in at least one gene from a pre-specified DDRR list and genomic instability score (GIS) was computed using Myriad algorithm.(appendix p 3) All these analyses were performed on next-generation sequencing data generated with the TruSight™ Oncology 500 Illumina panel.

Clinically relevant adverse events (AEs) above grade 2 (G2) according to Common Terminology Criteria for Adverse Events v4.03 (CTCAE v4.03) caused study drugs delay (trabectedin) or interruption (olaparib) until recovery or grade≤1. Dose reductions followed predefined rules (Protocol pp 34-43). In 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 case of hematological toxicities. Dose reductions in 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 (CT) scans at baseline and every 6 +/- 1 weeks afterwards.

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-month (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 (see Protocol pp 65, 68, 112, and 114 for further details). 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 *vs.* 25% for trabectedin (hazard ratio 0.67). Setting alpha error at 0.1 (one-sided log-rank test) and power at 80%, the primary analysis was performed when at least 110 PFS events were observed. Assuming a 24-month accrual, a follow-up ≥12 months after the last patient was enrolled, a 10% rate of non-evaluable patients, we planned to enroll a total of 126 patients to observe the

expected 110 PFS events. In case one patient was not evaluable 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, Protocol pp 27, 107). 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, OS, with their respective 95% CI or inter-quartile ranges (IQR) and compared using log-rank test and/or hazard ratio (HR) estimates calculated by Cox regression when indicated. All statistics were computed using IBM SPSS Statistics (v.29; SPSS Inc., Chicago, IL, USA) and/or R Jamovi, version 2.3.26.0 (R Foundation for Statistical Computing). This study is registered with ClinicalTrials.gov, number NCT03838744.

Results

Between May 25, 2020, and November 2, 2022, a total of 149 patients were screened for inclusion and 130 were enrolled and randomized 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 (March 31, 2025), the median follow-up in the overall study population was 37.4 months (95%CI 34.6-40.1). One patient was still on treatment in the combination arm.

Estimated PFS6m and mPFS were 32% (95%CI 22-46%) and 3.9 months (95%CI 2.7-5.2) with trabectedin-olaparib *vs.* 28% (95%CI 19-42%) and 2.9 months (95%CI 2.2-3.6) 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% (13-34%) *vs.* 5% (2-16%) with trabectedin-olaparib *vs.* 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 non-L-sarcoma subgroup (PFS6m 29.0% and mPFS 4.1 months, 95%CI 2.5-5.8, *vs.* PFS6m 18.8% and mPFS 2.2 months, 95%CI 1.2-3.1; 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, *vs.* PFS6m 25.9% and mPFS 2.7 months, 95%CI 1.3-4.1, log-rank *P*=0.091, respectively). (Figure S2, appendix p 4).

In the uterine leiomyosarcoma (uLMS) subgroup, PFS6m was 42.9% (95%CI 23.4-78.5%) with trabectedin-olaparib vs. 28.6% (95%CI 12.5-65.4%) with trabectedin, while mPFS was 4.0 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% (six out of 14 patients, 95%CI 23.4-78.5%) *vs.* 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) with trabectedin-olaparib and 18.2 months (95%CI 12.2-24.1) with trabectedin alone (HR 1.157, 95%CI 0.775-1.726; *P*=0.475).(Figure S3, appendix p 5).

Among 126 patients evaluable for response (63 patients in each arm), an ORR of 12.7% (8 PRs, 95%CI 6.1-22.7%) was observed with the combination compared to 7.9% (5 PRs, 95%CI 3.0-16.7%) with trabectedin alone (OR 1.60, 95%CI 0.50-5.16, *P*=0.43). (Figure S4, appendix p 6).

In a preplanned analysis, *PARP1* expression was evaluable for 105 out of 130 samples (80.8%) and correlated with outcome in trabectedin-olaparib but not in 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 1% or higher (81, 77.1%) showed a significant benefit with the combination compared to trabectedin (PFS6m 41.5% *vs.* 27.8%; mPFS 4.3, 95%CI 2.8-5.8, *vs.* 2.5 months, 95%CI 1.7-3.4; 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 among ten 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 a mPFS of 4.3 months (95%CI 2.8-5.8) in PARP1-positive *vs.* 21.4% and 2.0 months (95%CI 0.8-3.2) 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 a mPFS of 13.7 months (95%CI 0-41.5) *vs.* 2.4 months with trabectedin (95%CI 0-5.0) (HR 0.251, 95%CI 0.072-0.879; *P*=0.027; Figure S5B, appendix p 7).

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 to other histological types [median 26 (IQR 20-33) *vs.* 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 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, and

PFS6m 29.6% vs. 2.8 months, 95%CI 1.3-4.3, and PFS6m 32.3%; log-rank *P*=0.483). In the GIS-high subgroup, we observed a PFS6m 38.7% and mPFS of 3.9 months (95%CI 2.7-5.2) with the combination, vs. PFS6m 35.2% and mPFS of 2.9 months (95%CI 0.6-5.3) 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% vs 0% with trabectedin alone (Figure S6, appendix p 8).

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 more than 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 6 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, olaparib dose was reduced in 28 (43.1%) and delayed/interrupted in 54 (83.1%) patients, while in 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 (2-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 appendix pp 9-17 further details and graphs on QoL assessments are reported.

Discussion

This is the first, multicenter, investigator-initiated, phase 2 randomized study exploring the combination of trabectedin with the PARP1i olaparib versus standard-of-care 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 HR defects.

Dysregulation of DDRR 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 HR 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 to 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% *vs.* 8%

in PARP1-high *vs.* -low). This positioned *PARP1* expression as a putative predictive biomarker,[15] which is particularly notable in 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 HR 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 to 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 sarcomas heterogeneity and confirms that HR alterations are quite common in uLMS, regardless 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 2 single-arm study with temozolomide-olaparib combination in advanced uLMS. Indeed, in that study, temozolomide-olaparib combination yielded an ORR of 27%, 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 HR detected by means of RAD51 foci (mPFS 11.2 *vs.* 5.4 months in HR-deficient and HR-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 2/3 study that explored temozolomide-olaparib combination *vs.* 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 thirteen 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 rational for the use of combination strategies.[33] However, patient's selection remains a key-factor. In a phase 2 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 evaluable 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 to 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 2 single-arm study with trabectedin-olaparib in advanced STS.[35] The higher rate of treatment discontinuation due to AEs observed in this study (19% vs. 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 about 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 allow 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 to the phase 1b study considering patients treated at least at the third dose level in that trial (trabectedin ≥0.920 mg/m^2 q21d; olaparib ≥150 mg BID). Indeed, in the phase 1b study, we had observed a PFS6m of 42% and an ORR of 18% compared to 32% and 12.7% in the phase 2 study, respectively. Nonetheless, 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 HR 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 *vs.* 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 which enrolled patients affected by L-sarcomas only.[4, 17-19, 43] To deepen into STS heterogeneity, in the study protocol we had foreseen a pre-planned exploratory analysis according to the main histologic subtypes (protocol p 26). 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 COVID-19 pandemic. Nonetheless, accrual was successfully completed in approximately two 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.

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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 DSMB.

Contributions

LDA conceptualization, study design, data collection, data analysis, methodology, project administration, supervision, writing - original draft

AM data collection, data analysis, methodology, project administration, supervision, writing - original draft

ABr data collection, writing - review & editing

VF data collection, writing - review & editing

AP data collection, writing - review & editing

BV data collection, writing - review & editing

MAP data collection, writing - review & editing

TMDP data collection, writing - review & editing

LG data collection, writing - review & editing

RS data collection, writing - review & editing

ABu data collection, writing - review & editing

GGB data collection, writing - review & editing

GB data collection, writing - review & editing

CM data collection, writing - review & editing

YP data collection, data analysis, supervision, writing - review & editing

EB data collection, data analysis, supervision, writing - review & editing

SEB data collection, data analysis, supervision, writing - review & editing

MS data collection, data analysis, writing - review & editing

LR data collection, data analysis, writing - review & editing

MR data collection, data analysis, writing - review & editing

FT data collection, writing - review & editing

SA data collection, writing - review & editing

DS data collection, data analysis, writing - review & editing

APDT data collection, data analysis, writing - review & editing

SS data collection, funding acquisition, methodology, project administration, supervision, writing - review & editing

GG conceptualization, study design, data collection, data analysis, funding acquisition, methodology, project administration, supervision, writing - original draft

Declaration of interests

LDA reports Advisory Board: PSI CRO Italy, GSK, AstraZeneca, Boehringer Ingelheim; Invited Speaker: Boehringer Ingelheim, Gentili, AstraZeneca, GSK, Deciphera, PharmaMar; Meeting participation: PharmaMar, AstraZeneca, Amgen, GSK, Deciphera, AstraZeneca; Research Funding: Pharmamar (Inst)

AM reports Invited Speaker: Boehringer Ingelheim, Beigene, Sanofi, Regeneron; Research Funding: Pharmamar (Inst)

ABr reports Advisory Board: PharmaMar, Boehringer Ingelheim, Deciphera, GSK; Invited Speaker: Boehringer Ingelheim.

VF reports no clinflict of interest.

AP reports Meeting participation: PharmaMar.

BV reports Advisory Board: Abbot, GSK, Lilly; Speaker's Bureau: PharmaMar, Deciphera; Institutional, Funding: BD Bard.

MAP reports no conflict of interest.

TMDP reports no conflict of interest.

LG reports no conflict of interest.

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FT reports no conflict of interest.

SA reports Advisory Board or Consulting fees: MEDENDI, Invited Speaker: Eisai, Gentili, Deciphera; Meeting participation: PharmaMar, Gentili, Deciphera

DS reports no conflict of interest.

APDT reports no conflict of interest.

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Legends to Figures and Tables

Figure 1. CONSORT diagram

Table 1. Patients baseline characteristics. L-STS, L-sarcoma (i.e., liposarcoma and leiomyosarcoma); LPS, liposarcoma; uLMS, uterine leiomyosarcoma, LMS non-uterine leiomyosarcoma; UPS, undifferentiated pleomorphic sarcoma; SS, synovial sarcoma; MFS, myxofibrosarcoma; SFT, solitary fibrous tumor; MPNST, malignant peripheral nerve sheath tumor; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Figure 2. Progression-free survival according to treatment arm. Panel A, all patients; panel B, patients affected by uterine leiomyosarcoma. Red line, trabectedin-olaparib; blue line, trabectedin.

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

Table 2. Adverse events occurring in ≥10% of the patients. GGT, gamma-glutamyl transpeptidase; CPK, creatine phosphokinase.

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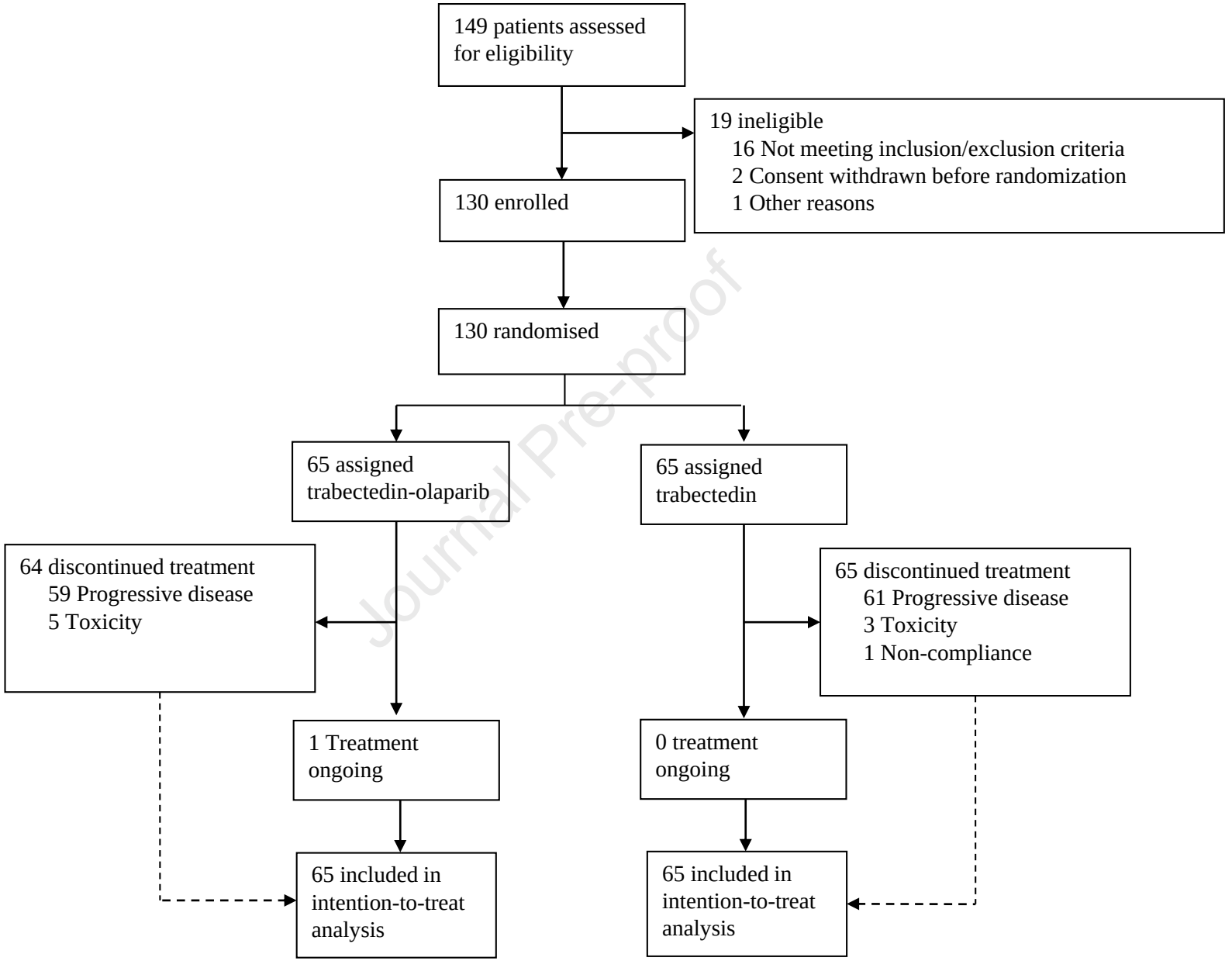
	Trabectedin-olaparib N (%)	Trabectedin N (%)	p-value (2-sided)	Total N (%)
Total	65 (100)	65 (100)		130 (100)
Sex				
- male	30 (46·2)	19 (29·2)	0·07	49 (37·7)
- female	35 (53·8)	46 (70·8)		81 (62·3)
Age				
- Median (range)	56 (28–80)	58 (18–79)	1·00	57 (18–80)
- <65	44 (67·7)	45 (69·2)		89 (68·5)
- ≥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)

Table 1. Patients baseline characteristics. L-STS, L-sarcoma (i.e., liposarcoma and leiomyosarcoma); LPS, liposarcoma; uLMS, uterine leiomyosarcoma, LMS non-uterine leiomyosarcoma; UPS, undifferentiated pleomorphic sarcoma; SS, synovial sarcoma; MFS, myxofibrosarcoma; SFT, solitary fibrous tumor; MPNST, malignant peripheral nerve sheath tumor; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Adverse event	trabectedin-olaparib (n=65)						trabectedin (n=65)					
	Any grade (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Grade 5 (%)	Any grade (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Grade 5 (%)
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)	3 (4·6)		2 (3·1)			1 (1·5)	1 (1·5)	

Table 2. Adverse events occurring in ≥10% of the patients. GGT, gamma–glutamyl transpeptidase; CPK, creatine phosphokinase.



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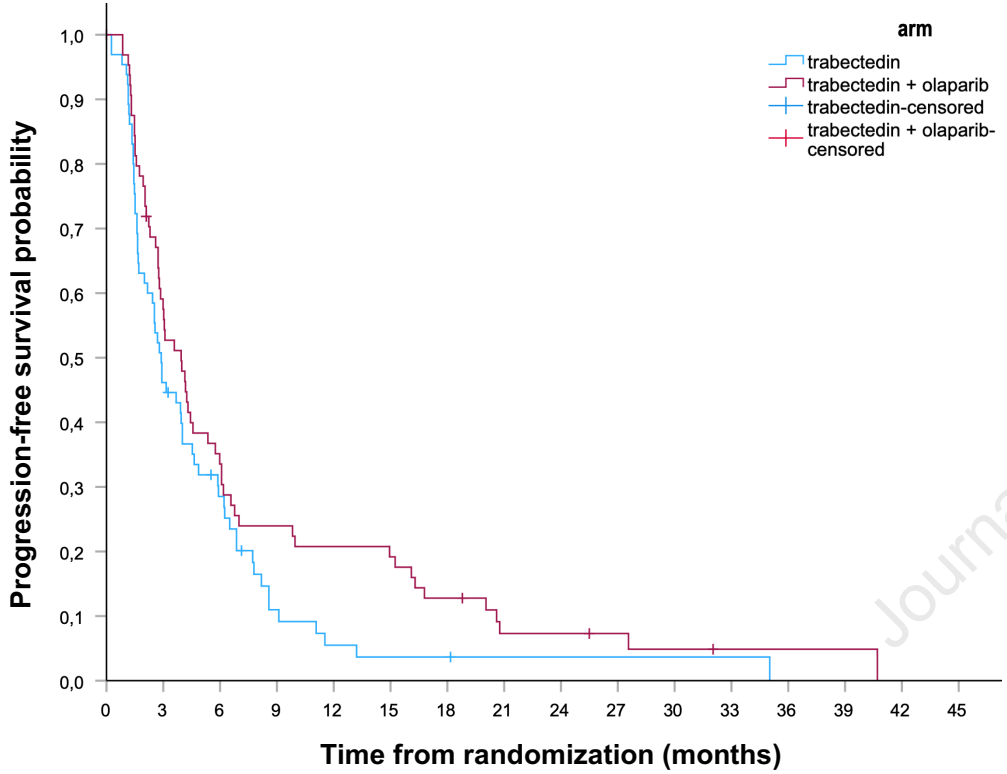
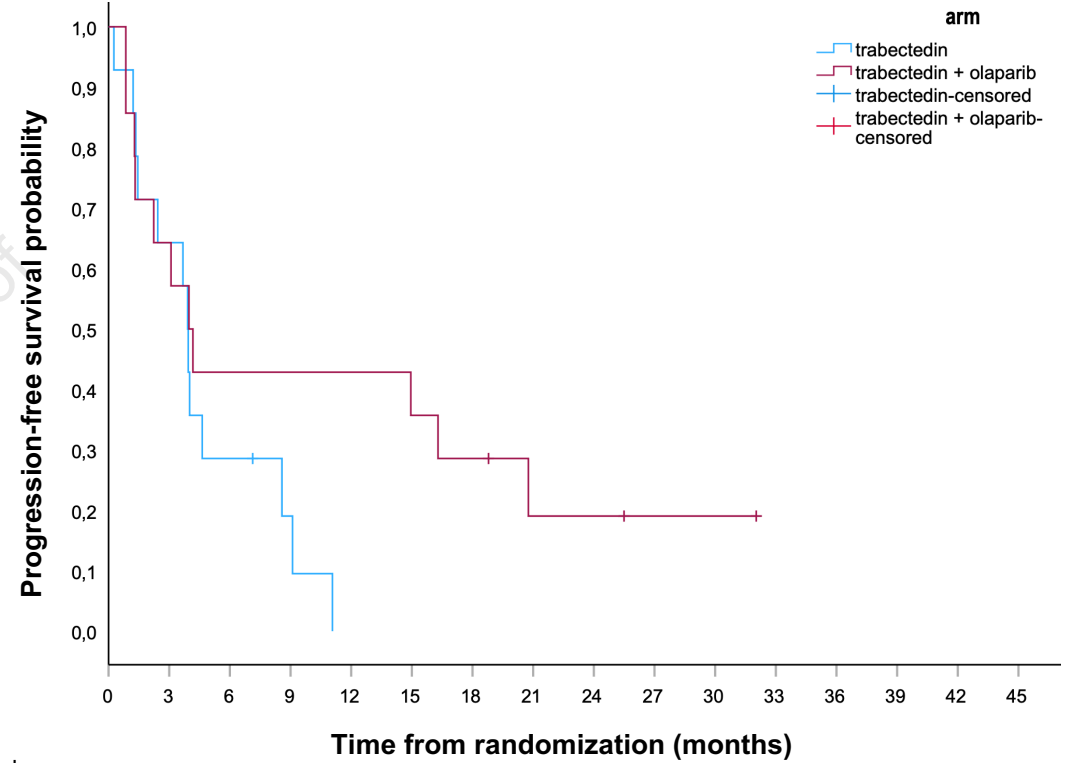


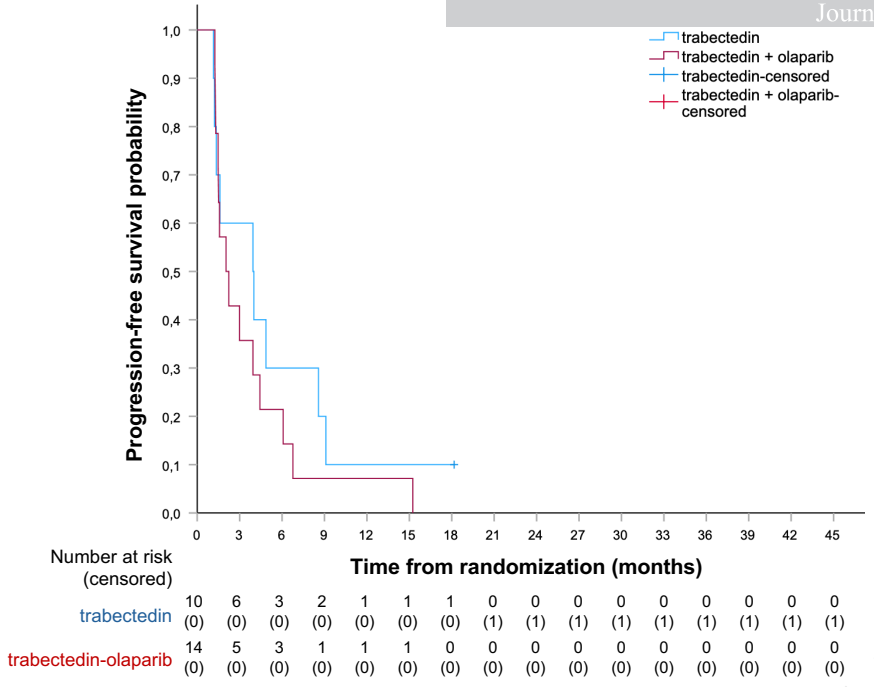
Number at risk (censored)																
trabectedin	65 (0)	30 (0)	17 (2)	6 (3)	3 (3)	2 (3)	2 (3)	1 (4)	1 (4)	1 (4)	1 (4)	1 (4)	0 (4)	0 (4)	0 (4)	0 (4)
trabectedin-olaparib	65 (0)	36 (2)	21 (2)	15 (2)	13 (2)	12 (2)	8 (2)	4 (3)	4 (3)	3 (4)	2 (4)	1 (5)	1 (5)	1 (5)	0 (5)	0 (5)

B



Number at risk (censored)																
trabectedin	14 (0)	9 (0)	4 (0)	2 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)
trabectedin-olaparib	14 (0)	9 (0)	6 (0)	6 (0)	6 (0)	5 (0)	4 (0)	2 (1)	2 (1)	1 (2)	1 (2)	0 (3)	0 (3)	0 (3)	0 (3)	0 (3)

A



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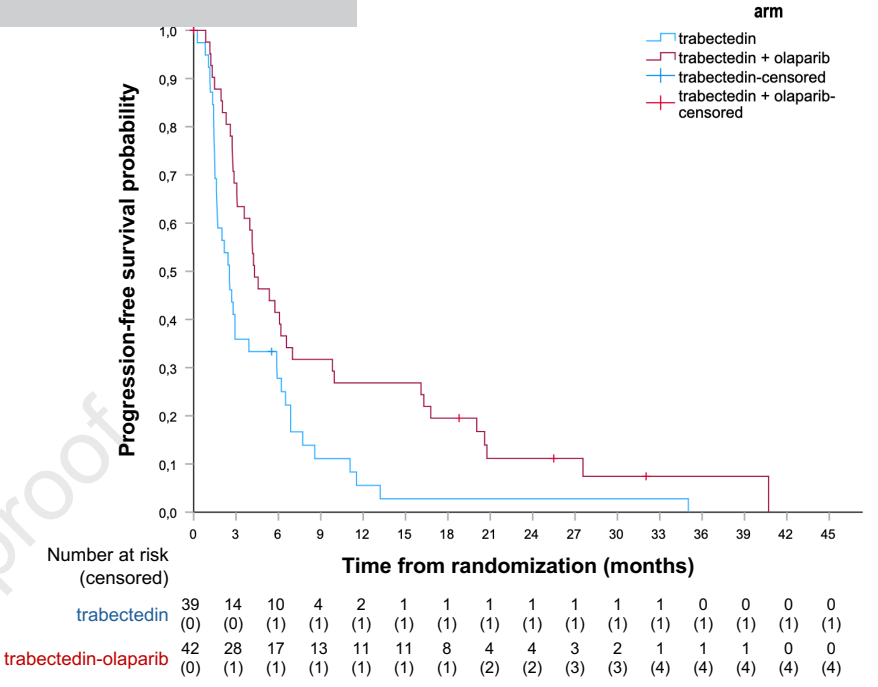

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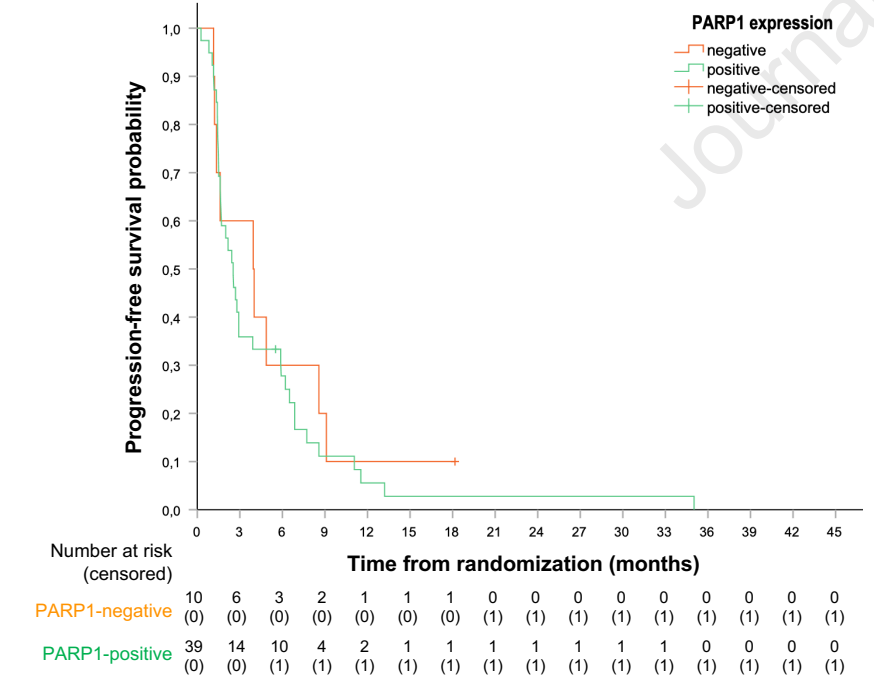

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