A MULTICENTER, PROSPECTIVE, OBSERVATIONAL STUDY TO ASSESS THE CLINICAL ACTIVITY AND THE IMPACT ON SYMPTOM BURDEN AND PATIENTS' QUALITY OF LIFE OF TREATMENT WITH TRABECTEDIN IN ADVANCED SOFT TISSUE SARCOMAS IN A REAL-WORLD SETTING IN GREECE. THE 'BEYOND-STS' STUDY

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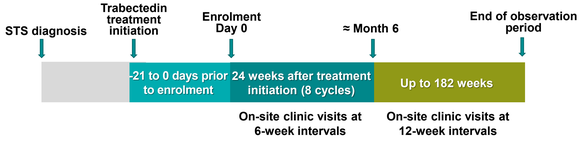
INTRODUCTION

- Advanced soft tissue sarcomas (aSTS) represent a heterogeneous group of rare neoplasms with limited treatment options.[1]
- For locally advanced or metastatic STS, sequential use of doxorubicin-based chemotherapy and ifosfamide as single agents or a combination of these agents is the mainstay approach in Europe.[1] Response rates with these treatment options range from 21% to 56%,[2] while their use is further limited by toxic side effects.[3]
- Trabectedin is indicated for the treatment of patients with aSTS who have failed or are unsuited to receive anthracycline/ifosfamide.[4]
- The aim of 'BEYOND-STS' was to generate real-world evidence on trabectedin effectiveness in aSTS and its impact on symptom burden and quality of life in routine settings in Greece.

STUDY DESIGN

- This was a non-interventional, multicenter, prospective cohort study which included patients with aSTS initiated on trabectedin under routine care conditions in Greece.
- Patients were consecutively enrolled by 13 hospital-based oncologists (of the private and public sector) specializing in the sarcoma care and practicing in geographically diverse locations throughout Greece.
- Each participant was treated with trabectedin, and followed-up in the context of this study, until the last patient enrolled plus up to 54 weeks of treatment or until disease progression, death, withdrawal of consent, unacceptable toxicity, study completion, or physician's decision whichever occurred earlier. Patients who discontinued treatment were followed for up to 24 weeks post-treatment discontinuation.

Figure 1: 'BEYOND-STS' study design



Key Inclusion Criteria
- Adult outpatients (18 years and older) of either gender
- Patients with a histologically confirmed diagnosis of advanced (locally advanced or metastatic) STS who had failed treatment with anthracyclines and ifosfamide or who were unsuited to receive these agents

Key Exclusion Criteria
- Patients who had received >1 cycle of trabectedin at the time of enrolment into the study

Primary endpoint †
- PFSR at 6 months post-treatment initiation

Secondary endpoints
- PFSR at 3 months post-treatment initiation; PFS [‡]; OS [‡]; ORR and DCR [‡]

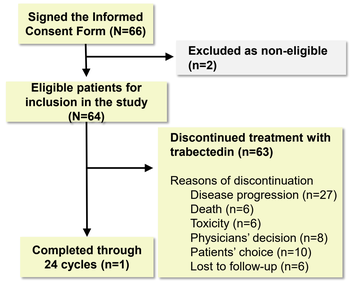
Other endpoints
- Impact of treatment with trabectedin on HRQoL and on the cancer-related symptom burden and symptom interference with function using the Greek validated versions of EQ-5D-3L and MDASI

† Tumor response to trabectedin was evaluated by the participating physicians according to local and institutional common practice, and the response evaluation criteria in solid tumors (RECIST) v1.1.
‡ For PFS, patients who were alive and progression-free at the time of study completion were censored 30 days post treatment discontinuation, while for OS analysis, patients who were alive were censored at their last follow-up date.
‡ DCR was defined as the proportion of patients achieving a BOR of PR or CR per RECIST, or stable disease for at least 24 weeks (i.e., ≥24 weeks have elapsed from first to last response assessment or the patient had been on treatment for at least 24 weeks).
BOR, best overall response; CR, complete response; DCR, disease control rate; EQ-5D-3L, EuroQoL 5-Dimensions, 3-Levels; HRQoL, Health-Related Quality of Life MDASI, M.D. Anderson Symptom Inventory; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFSR, Progression-free survival rate; PR, partial response; PRO, patient-reported outcome; STS, soft tissue sarcoma

RESULTS

Patient disposition, and patient, disease and treatment characteristics

Figure 2: Patient disposition in the study



- From 21 December 2015 to 06 June 2018, 64 eligible patients were enrolled and comprised the full analysis set (Figure 2). At the end of study, one patient (1.6%) was still on treatment and had received 24 cycles.
- Patient characteristics at enrolment are shown in Table 1.
- At enrolment, median (interquartile range, IQR) disease duration was 15.3 (7.8–35.6) months; L-sarcomas were the most prevalent histological subtypes (50.0%) (Figure 3); the majority of the patients had metastatic disease (43, 67.2%).
- Prior to trabectedin treatment initiation, 82.8% (53/64) of the patients had received chemotherapy; 53.1% had received only one, and 29.7% ≥2 prior treatment lines (Figure 3). Among patients with available data, 41.3% (26/63) and 24.6% (15/61) had received prior surgery and prior radiotherapy, respectively.

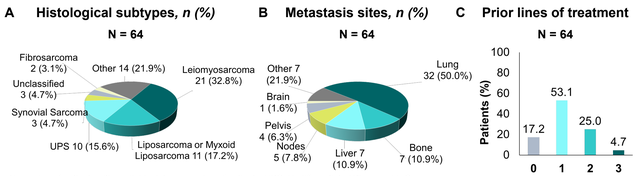
- Over a median (IQR) treatment duration of 1.8 (0.8–3.9) months [mean (standard deviation, SD): 3.7 (4.6) months], the median number of trabectedin cycles received was 3 (IQR: 2.0–6.0; range 1-27).
- Of the patients, 45 (70.3%) received ≥ 3 trabectedin cycles, 19 (29.7%) ≥ 6 cycles, and 11 (17.2%) ≥ 12 cycles.

Table 1: Patient characteristics at enrolment

Characteristic	Full Analysis Set (N=64)
Age, median (IQR)	58.3 (46.9-64.8)
Gender, n (%)	
Female	40 (62.5)
Male	24 (37.5)
BMI classification	
<18.5	4 (6.3)
18.5 - 24.9	24 (37.5)
25.0 – 29.9	23 (35.9)
≥30.0	13 (20.3)
Educational level, n (%)	
No education	7 (10.9)
Primary education	14 (21.9)
Secondary education	26 (40.6)
Tertiary education	17 (26.6)
Employment status, n (%)	
Unemployed	10 (15.6)
Employed	27 (42.2)
Retired	13 (20.3)
Household duties	11 (17.2)
Other	3 (4.7)
PS (ECOG), n (%)	
0	38 (59.4)
1	22 (34.4)
2	2 (3.1)
3	2 (3.1)
Presence of at least one comorbidity, n (%)	34 (53.1)

BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; N, number of patients; PS, Performance Status

Figure 3: Disease characteristics at enrolment



N, number of patients with available data; n, number of patients; UPS, Undifferentiated Pleomorphic Sarcoma

Outcomes

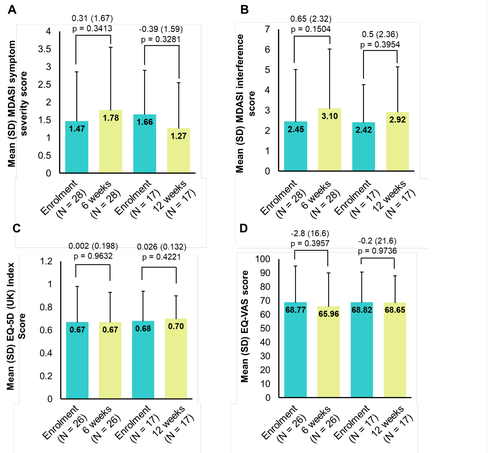
- 3- and 6-month progression-free survival rates (PFSRs) after treatment initiation were 67.9% (95% CI: 54.4%–78.2%) and 51.2% (95% CI: 37.1%–63.7%), respectively.
- Median PFS was 6.6 (95% CI: 3.5–10.1) months.
- Median overall survival (OS) was 13.1 (95% CI: 5.5–18.8) months.
- OS rates at various time points are shown in Table 2.
- The objective response rate (ORR) was 7.8% (95% CI: 1.2%–14.4%).
- The disease control rate (DCR) was 21.9% (95% CI: 11.8%–32.0%).
- Baseline M.D. Anderson Symptom Inventory (MDASI) and EuroQoL 5-Dimensions, 3-Levels (EQ-5D-3L) scores did not significantly change from enrolment at post-enrolment visits among patients with available data (Figure 4).

Table 2: Landmark OS analysis

Analysis timepoint (exact timepoint), *months*	Survival rate (95% CI), %
3 (2.95)	75.33 (62.44-84.33)
6 (5.54)	62.62 (48.87-73.64)
12 (10.69)	50.65 (36.8-62.95)
24 (21.48)	27.57 (15.11-41.53)
36 (30.39)	7.75 (0.80-25.83)

CI, confidence interval; OS, overall survival

Figure 4: Change in HRQoL and symptom burden from enrolment at Weeks 6 and 12



EQ-5D, EuroQoL 5-Dimensions; HRQoL, Health-Related Quality of Life; MDASI, M.D. Anderson Symptom Inventory; N, number of patients; SD, standard deviation; UK, United Kingdom; VAS, Visual Analogue Scale. Mean difference (SD) and p-value are shown for paired data; p-values were calculated with Wilcoxon signed-rank test

Safety

- 79.7% (51/64) patients experienced ≥1 adverse event (AE), and 39.1% (25/64) ≥1 serious AE.
- 46.9% (30/64) patients experienced ≥1 trabectedin-related AE (adverse drug reaction, ADR), and 14.1% (9/64) ≥1 serious ADR (Table 3).
- 18.8% (12/64) patients experienced AEs (other than disease progression) leading to trabectedin discontinuation.

Table 3: Trabectedin-related adverse events

		Full Analysis Set (N=64)			
		Overall	Serious	Grade 1-2	Grade 3-4
	n_{events}	n_{pt} (%)	n_{pt} (%)	n_{pt} (%)	n_{pt} (%)
Total	**87**	**30 (46.9)**	**9 (14.1)**	**20 (31.3)**	**18 (28.1)**
Occurring in ≥2% of patients (>1 patient)					
Fatigue	17	14 (21.9)	1 (1.6)	4 (6.3)	10 (15.6)
Anemia	17	11 (17.2)	5 (7.8)	9 (14.1)	4 (6.3)
Neutropenia	8	6 (9.4)	-	3 (4.7)	4 (6.3)
Nausea	6	6 (9.4)	-	6 (9.4)	-
Thrombocytopenia	5	5 (7.8)	2 (3.1)	3 (4.7)	2 (3.1)
Vomiting	5	5 (7.8)	-	4 (6.3)	1 (1.6)
Leukopenia	3	3 (4.7)	-	3 (4.7)	-
Febrile neutropenia	2†	2 (3.1)	2 (3.1)	-	1 (1.6)
Hepatitis	2†	2 (3.1)	2 (3.1)	-	1 (1.6)
Pancytopenia	2	2 (3.1)	2 (3.1)	-	2 (3.1)

† One event of febrile neutropenia and one event of hepatitis, experienced by 1 patient each, had fatal outcome.
AE, adverse event; n_{events}, number of events; n_{pt}, number of patients with ≥1 event of the respective category

CONCLUSIONS

- The findings of this study support that trabectedin offers a clinical benefit in aSTS patients who have failed or are unsuited to receive anthracycline/ifosfamide, without imposing additional burden on patients' quality of life and symptom interference with daily functioning.
- The safety profile was consistent with the drug class, with no new safety signals emerging.
- Patients were enrolled from geographically diverse locations throughout Greece with non-limiting eligibility criteria apart from those indicated by the European Summary of Product Characteristics of trabectedin,[4] thus enhancing the generalizability of the findings.

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DISCLOSURES

SK: GENESIS Pharma SA: Honoraria, Research Funding; **IB:** GENESIS Pharma SA: Honoraria, Investigator Fees, Advisory Board; **ES:** GENESIS Pharma SA: Honoraria, Investigator Fees, Advisory Board; **PP:** GENESIS Pharma SA: Honoraria, Investigators Fees; **IA:** GENESIS Pharma SA: Advisory Board, Investigator Fees, Research Funding; **ChA:** GENESIS Pharma SA: Honoraria, Investigator Fees, Advisory Board; **PM:** GENESIS Pharma SA: Investigator Fees; **GS:** Nothing to disclose; **ET:** GENESIS Pharma SA: Honoraria, Research Funding, Advisory Board; **GV:** GENESIS Pharma SA: Honoraria, Investigator Fees, Advisory Board, Research Funding; **ChP:** NOVARTIS/ASTRA ZENECA, GENESIS, MSD, AMGEN, MERCK AND ROCHE: Speaker Honoraria and Honoraria for consultancy in advisory boards, BMS/ROCHE: Research grants; **DT:** GENESIS Pharma SA: Investigator Fees; **AA:** GENESIS Pharma SA: Honoraria, Investigator Fees, Advisory Board; **IK:** GENESIS Pharma SA: Honoraria; **KK-M:** GENESIS Pharma SA employee; **TT:** GENESIS Pharma SA employee; **AP:** GENESIS Pharma SA: Honoraria, Investigator Fees, Advisory Board

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