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ORIGINAL RESEARCH

TRAbectedin in adVanced rEtroperitoneal well differentiated/dedifferentiated Liposarcoma and Leiomyosarcoma (TRAVELL): results of a phase II study from the Italian Sarcoma Group

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Background: This is a multicentre, single-arm, phase II study aimed at further exploring the activity of trabectedin as second-/further-line treatment in retroperitoneal leiomyosarcoma (LMS) and well-differentiated/dedifferentiated liposarcoma (LPS).

Materials and methods: The primary endpoint was the growth modulation index (GMI) defined as the ratio between PFS under trabectedin (PFS) and during previous chemotherapy treatment: time to progression (TTP-1). Secondary endpoints were objective response rate (ORR) and PFS. As per protocol, patients were considered responders if the GMI was >1.33, non-responders if <0.75 and neither if 0.76-1.32.

Results: Overall 91 patients were assessable for the primary endpoint (32 patients with LMS and 59 patients with LPS): the median number of cycles received was 6.0 (Q1-Q3 3.0-12.0), and the main reason for treatment discontinuation was disease progression in 72% of patients. The median PFS was 6.0 months, while the median TTP1 was 7.5 months (8.1 and 6.4 months for LMS and LPS, respectively). Thirty-three patients [52%, 95% confidence interval (CI) 36% to 58%, $P = 0.674$, odds of response 1.1] had a GMI >1.33 (LMS 46%, 95% CI 26% to 67%, odds of response 0.85; LPS 56%, 95% CI 40% to 72%, odds of response 1.3). Overall, in LPS we observed 15/47 patients with a GMI <0.5 and 15/47 patients with a GMI >2. Among LMS patients, 9/26 had a GMI <0.5 and 10/26 had a GMI >2. Overall, ORR (complete response + partial response) was 16% (24% for LMS and 12% for LPS).

Conclusions: While the primary endpoint of the study was not met, we noticed a subgroup of patients with a markedly discrepant TTP with trabectedin in comparison to previous therapy (GMI <0.5 or >2, the latter including some patients with a long TTP with trabectedin). A mismatch between PFS and overall survival was observed, possibly due to the natural history of the two different histologies and the availability of further lines in LMS.

Key words: sarcoma, liposarcoma, leiomyosarcoma, trabectedin, chemotherapy

INTRODUCTION

Retroperitoneal soft-tissue sarcomas (R-STSs) are rare neoplasms, accounting for 10%-15% of STSs, which represent 1%-3% of all cancers. R-STSs may have different histological types, but the most frequent are leiomyosarcoma (LMS) and well-differentiated/dedifferentiated liposarcoma (LPS).[1,2] Both histologies, when arising from the retroperitoneum, have a worse outcome than those arising in the limbs. Indeed, because of its anatomical peculiarities (lack of boundaries and abdominal compliance to tumour growth in the absence of symptoms), the retroperitoneal space poses huge challenges for treatment. The only potentially curative treatment for primary R-STSs is surgery; however, since anatomical constraints limit the achievement of wide resection margins, local recurrence is much more frequent than at

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any other anatomic site and this is the leading cause of death.[3-5] This explains why R-STSs have a worse outcome when compared with sarcomas at most other sites, despite a relatively indolent biology. This is particularly true for cases of low- and intermediate-grade LPS, which account for approximately one-half of sarcomas arising in the retroperitoneum. Other subtypes, such as high-grade LMS, pose a significant risk of developing distant metastases, while local recurrence after complete resection is less common.[6-8] Treatment options for recurrent/advanced retroperitoneal sarcomas are limited. In locally recurrent disease, surgery can still play a role, with an evaluation of disease-free interval. If technically feasible, surgery can be carried out to obtain a macroscopically complete resection, although the anticipated rate of further local regional failure can be relatively high. Patients with unresectable or metastatic disease usually receive chemotherapy. The use of chemotherapy may also be reasonable in patients with a local recurrence after a short disease-free interval.[9]

In the advanced setting, first-line chemotherapy usually consists of doxorubicin and/or ifosfamide in LPS and doxorubicin alone or with dacarbazine in LMS, with a dose—response relationship and objective response rates (ORRs) between 20% and 50% for LMS, while the ORRs reported in LPS are lower.[10-12] Other medical options are very limited, particularly in patients with LPS, where gemcitabine and pazopanib, often used as a later-line treatment in LMS, are not active.[13-17]

Furthermore, targeted therapies such as MDM2 inhibitors and CDK4 inhibitors are still under clinical evaluation and are not currently available in clinical practice.

Trabectedin, an anticancer agent derived from a natural marine product, binds to the minor groove of DNA and interacts with DNA repair enzymes and transcription factors, resulting in interference with several cell-cycle processes.[18,19] Trabectedin is active in LMS and LPS and has been approved by the European Medicines Agency as second-line chemotherapy for STSs and by the Food and Drug Administration for LPS and LMS. Although the response rate observed in pre-registration studies did not exceed 10%, trabectedin provided disease control, with progression arrest rates exceeding 50% and PFS under trabectedin (PFS) rates exceeding 20% at 6 months.[20-22] Thus, the activity of trabectedin may be expressed by a reduction in tumour growth.

In this perspective, to investigate the activity of cytostatic cancer treatment (such as trabectedin), firstly in 1998, Von Hoff proposed the use of an intra-patient comparison of successive time to progression (TTP). The growth modulation index (GMI) was the result of the ratio of the TTP with the second or later treatment divided by the TTP with the first-line treatment.[23] Subsequently, the GMI has been retrospectively evaluated in patients with advanced STS treated with trabectedin, describing a longer overall survival (OS) (24 months) for patients with a GMI >1.33.[24] Evidence from retrospective studies suggests that tumour growth rate may be an independent predictor of disease-specific survival (DSS) in locally recurrent retroperitoneal LPS. Patients with a local recurrence growth rate of >0.9 cm/month had a significantly worse DSS, and re-resection of the recurrence did not alter their poor outcome. On the contrary, patients with slower-growing tumours seem to benefit from iterative surgery.[25] If these results were confirmed, the growth rate could be the first useful tool to guide surgical decision making in this patient setting.

Thus, the main focus of the current study was to investigate whether this growth reduction could be exploited in the multidisciplinary management of patients with R-STSs.

MATERIALS AND METHODS

Study design

This Italian, multicentre, single-arm, phase II study, with an intra-patient comparison endpoint, was conducted to confirm the activity of trabectedin as a second-/later-line treatment in patients with retroperitoneal LMS and well-differentiated/dedifferentiated LPS, and to investigate the peculiar benefit provided by trabectedin in typical R-STSs, in order to help refine the multidisciplinary clinical decision-making process.

Outcomes

The study primary endpoint was the proportion of responders to trabectedin, based on the ratio, in every single patient, between PFS and time to progression after previous chemotherapy treatment (TTP1). The primary endpoint was calculated in the overall sample. Secondary endpoints were ORR, pathological tumour response in patients undergoing surgery after treatment, PFS and safety profile.

Study population and treatment

Patients with previously treated, histologically confirmed, retroperitoneal LMS and well-differentiated/dedifferentiated LPS were eligible for enrolment. Patients could either be amenable to or unsuitable for surgery, but the addition of medical treatment was considered clinically advisable. Main eligibility criteria were as follows: >18 years of age; Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2; measurable disease (as defined by RECIST); adequate haematological, renal and liver functions; ≥ 1 previous systemic treatment employing anthracyclines with or without ifosfamide (unless both were clinically contraindicated). Patients were ineligible if they had: known central nervous system metastases; prior exposure to trabectedin; other malignancies within the past 5 years, except for basal cell carcinoma or cervical carcinoma *in situ* that was adequately treated.

After being assessed for eligibility and signing informed consent, patients were treated with trabectedin at a dose of 1.3-1.5 mg/m^2, up to a maximum total dose of 2.6 mg per cycle; investigators decided the appropriate dose taking into account several parameters such as age, adverse reactions to previous treatments, ECOG performance status, alkaline

phosphatase greater than the upper limit of normal (ULN) and creatinine clearance >ULN. Trabectedin was administered as a 24-h continuous infusion via central venous access, until progressive disease (PD), major toxicity, patient's intolerance or unwillingness to continue treatment or medical decision by the responsible physician. Dose reductions were foreseen any time the following severe toxicities occurred during the previous cycles: neutrophil count <500/mm^3; platelet count <25 000/mm^3; bilirubin or aminotransferases [alanine aminotransferase (ALT) or aspartate aminotransferase (AST)] >2.5 × ULN; any grade (G) 3 or 4 trabectedin-related adverse reactions (such as nausea, vomiting, fatigue). Two reductions were allowed: level -1 with the starting dose reduction to 1.2 or 1.1 mg/m^2 and level -2 with a further decrease to 1 or 0.9 mg/m^2. After reduction, escalation was not permitted.

The study was conducted at 20 investigational centres in Italy. All toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0.

The trial protocol was registered with the EudraCT number 2012-005428-14 and was approved by the appropriate institutional review board or independent ethics committee at each trial centre. All patients provided written informed consent before enrolment.

Statistical analysis

The per-protocol population comprised all registered patients, with no major violations of eligibility criteria, for whom the tumour response could be evaluated at least once while on treatment.

The PFS was calculated in each patient as the time from treatment start to the date of first observed progression or death. Subjects who had not progressed or died while in the study were censored at the last evaluable radiographic assessment date.

TTP1 was defined as the time from the previous line of treatment start to the date of the previous progression. PFS was analysed descriptively in terms of medians, 25% and 75% quartiles, using the Kaplan—Meier methods.

Where possible, objective responses were evaluated according to RECIST criteria and the best overall response obtained during the study was provided.

Given the high heterogeneity of results in this treatment setting, an intra-patient comparison was adopted. For each patient, the PFS under trabectedin was compared with TTP observed in the previous line of chemotherapy (TTP1), and the PFS/TTP1 ratio (GMI) was calculated. The following algorithm was used:

- if PFS/TTP1 was ≥1.33, the patient was considered a responder;
- if PFS/TTP1 was ≤0.75, the patient was considered a non-responder; and
- if PFS/TTP1 was 0.76-1.32, the patient was considered as neither a responder nor a non-responder.

A generalised sign test was used. Assuming a proportion of patients assessable for response (defined as responders or non-responders according to the rules described above) of ∼50%, no more than 80 patients were required to be included in the study in order to have an 80% power to detect an odds of trabectedin response of ≥2.5, with an alpha error of 2.5% (one-sided). An odds of response >2.5 corresponds to a minimum percentage of responder patients equal to 72; therefore, with 40 assessable patients, the study had to reach at least 29 responders (29 responders out of 40 assessable patients; odds = 29/11 = 2.6).

Table 1. Patient characteristics at baseline

	Leiomyosarcoma (*n* = 32)	Liposarcoma (*n* = 59)	Overall (*n* = 91)
Number of patients with baseline visit, *n* (%)	32 (100)	59 (100)	91 (100)
Age, years			
Median (Q1-Q3)	60.0 (48.9-69.3)	67.7 (54.9-73.3)	64.4 (53.1-72.4)
Min-max	34.1-85.4	34.9-79.9	34.1-85.4
Race, *n* (%)			
Caucasian	32 (100)	58 (98.3)	90 (98.9)
Asian	0 (0.0)	1 (1.7)	1 (1.1)
Sex, *n* (%)			
Male	10 (31.3)	39 (66.1)	49 (53.8)
Female	22 (68.8)	20 (33.9)	42 (46.2)
Missing	1	0	1
ECOG PS, *n* (%)			
0	19 (61.3)	41 (70.7)	60 (67.4)
1	12 (38.7)	15 (25.9)	27 (30.3)
2	0 (0.0)	2 (3.4)	2 (2.2)
Missing	1	1	2
Patients amenable to surgery at the time of enrolment, *n* (%)			
No	27 (87.1)	49 (84.5)	76 (85.4)
Yes	4 (12.9)	9 (15.5)	13 (14.6)
Missing	1	1	2

Liposarcoma refers to well-differentiated/dedifferentiated liposarcoma.
ECOG PS, Eastern Cooperative Oncology Group performance status; Min-max, minimum-maximum values; Q1-Q3, first-third quartile; SD, standard deviation.

Safety analysis was carried out on the safety population, defined as all registered patients who received at least one dose of study treatment. Safety information was registered from the time of the informed consent signature until 30 days after the last trabectedin administration date. Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities. The maximum toxicity grade experienced by each patient, for each toxicity, was graded according to NCI-CTCAE version 4.0. The chi-square test for trend was used to compare the maximum grade for each standard of care by histological type.

RESULTS

From July 2014 to February 2019, 104 patients were enrolled in the study and 91 patients were assessable for the primary endpoint. Of 13 patients excluded, 4 patients did not have any disease assessment, 1 patient did not start trabectedin, 1 patient did not have TTP1 and 7 patients were ineligible for the study (6 patients were chemo-naive and 1 patient had sarcoma mixoide histotype). Among the assessable patients, 32 had LMS and 59 had LPS. Patient baseline characteristics are summarised in Table 1.

A description of previous therapy received by the patient population is reported in Table 2. Of note, 10% of patients underwent surgery after progression to previous treatment before study entry, 15% underwent surgery after preoperative chemotherapy before study entry and only 4% of patients (4/91, all with a diagnosis of LPS) underwent surgery during or after trabectedin. Unfortunately, for these latter four patients, the pathologist was not able to detect the pathological response.

Overall, the median number of cycles received was 6.0 (interquartile range 3.0-12.0 cycles). Thirty-one patients received >10 cycles and five patients received >30 cycles of treatment. One patient received a total of 58 cycles. The median dose administered in the first three cycles was 2.2 mg (2.0-2.4 mg). Forty-four percent of patients had to reduce the dose; the main reason for drug reduction was medical decision in 35% of patients and G3-4 AEs in 29% of patients. A further 10% of patients needed a second dose reduction, the majority of them (57%) due to medical

Table 2. Previous therapy: first endpoint population

	Leiomyosarcoma (n = 32)	Liposarcoma (n = 59)	Overall (N = 91)
Number of lines of previous chemotherapy before enrolment, *n* (%)			
One	20 (62.5)	47 (79.7)	67 (73.6)
Two	8 (25.0)	11 (18.6)	19 (20.9)
Three	4 (12.5)	1 (1.7)	5 (5.5)
Characteristics of last chemotherapy before enrolment			
Regimen, *n* (%)			
Anthracyclines	17 (53.1)	27 (45.8)	44 (48.4)
Anthracyclines + other	3 (9.4)	0 (0.0)	3 (3.3)
Ifosfamide	1 (3.1)	7 (11.9)	8 (8.8)
Ifosfamide + anthracyclines	7 (21.9)	21 (35.6)	28 (30.8)
Other	4 (12.5)	4 (6.8)	8 (8.8)
Total number of cycles			
Median (Q1-Q3)	4.0 (3.0-6.0)	4.0 (3.0-6.0)	4.0 (3.0-6.0)
Min-max	2.0-21.0	1.0-19.0	1.0-21.0
Time from first administration of last chemotherapy to enrolment, months			
Median (Q1-Q3)	10.4 (4.7-24.8)	9.2 (3.4-18.8)	10.1 (3.9-20.3)
Min-max	1.5-100.6	1.6-147.5	1.5-147.5
Time from last administration of last chemotherapy to enrolment, months			
Median (Q1-Q3)	6.7 (1.3-22.2)	5.4 (1.2-13.8)	6.2 (1.3-14.3)
Min-max	0.5-99.1	0.4-144.8	0.4-144.8
Time from progression with last chemotherapy to enrolment, months			
Median (Q1-Q3)	0.8 (0.4-2.3)	1.0 (0.5-2.8)	0.9 (0.4-2.8)
Min-max	0.0-98.8	0.0-45.7	0.0-98.8
Reason for discontinuation of last chemotherapy, *n* (%)			
Disease progression	14 (45.2)	37 (62.7)	51 (56.7)
Patient decision	7 (22.6)	9 (15.3)	16 (17.8)
Medical decision	2 (6.5)	3 (5.1)	5 (5.6)
Surgery	6 (19.4)	5 (8.5)	11 (12.2)
Treatment completed	2 (6.5)	5 (8.5)	7 (7.8)
Missing	1	0	1
Time to progression with last chemotherapy (TTP1), months			
Median (Q1-Q3)	8.1 (2.8-13.8)	6.4 (2.5-14.2)	7.5 (2.5-14.2)
Min-max	1.2-70.7	0.6-138.0	0.6-138.0
Surgery before study entry, *n* (%)			
No	24 (75.0)	44 (74.6)	68 (74.7)
After progression	2 (6.3)	7 (11.9)	9 (9.9)
Before progression (neoadjuvant chemotherapy)	6 (18.8)	8 (13.6)	14 (15.4)

Liposarcoma refers to well-differentiated/dedifferentiated liposarcoma.
Min-max, minimum-maximum values; Q1-Q3, first-third quartile; SD, standard deviation.

Table 3. Treatment compliance

	Leiomyosarcoma (n = 32)	Liposarcoma (n = 59)	Overall (N = 91)
Number of cycles of trabectedin			
Mean (SD)	8.8 (6.3)	9.4 (10.6)	9.2 (9.3)
Median (Q1-Q3)	7.0 (3.0-13.0)	5.0 (3.0-11.0)	6.0 (3.0-12.0)
Min-max	1.0-25.0	1.0-58.0	1.0-58.0
Number of cycles of trabectedin, *n* (%)			
≥2	31 (96.9)	55 (93.2)	86 (94.5)
≥6	22 (68.8)	28 (47.5)	50 (54.9)
≥9	12 (37.5)	23 (39.0)	35 (38.5)
≥19	4 (12.5)	8 (13.6)	12 (13.2)
37	—	2 (3.4)	2 (2.2)
58	—	1 (1.7)	1 (1.1)
Treatment discontinued, *n* (%)	32 (100)	59 (100)	91 (100)
Reason for discontinuation, *n* (%)			
Disease progression	25 (78.1)	42 (71.2)	67 (73.6)
Medical decision	2 (6.3)	4 (6.8)	6 (6.6)
Death	0 (0.0)	1 (1.7)	1 (1.1)
Worsening of PS	2 (6.3)	2 (3.4)	4 (4.4)
Intercurrent severe illness	0 (0.0)	1 (1.7)	1 (1.1)
Toxicity	1 (3.1)	4 (6.8)	5 (5.5)
Subject refusal	2 (6.3)	0 (0.0)	2 (2.2)
Surgery	0 (0.0)	3 (5.1)	3 (3.3)
Other	0 (0.0)	2 (3.4)	2 (2.2)
Progression type			
1: Radiological disease progression	23 (92.0)	42 (100)	65 (97.0)
2: Symptomatic disease progression	2 (8.0)	0 (0.0)	2 (3.0)

Histology A, leyomiosarcoma; Histology B, well-differentiated/dedifferentiated liposarcoma.
Min-max: minimum-maximum values; PS, performance status; Q1-Q3, first-third quartile; SD, standard deviation.

decision. The main reason for treatment discontinuation was disease progression in 72% of patients, followed by medical decision (8%) (Table 3).

Overall 85 patients experienced progression or death (31 patients—96.9% of LMS; 54 patients—90.0% of LPS) and 18 died (6 patients—18.8% of LMS; 12 patients—20.0% of LPS). The median PFS was 6.0 months (6.2 and 6.0 months for LMS and LPS, respectively), while the median TTP1 was 7.5 months (8.1 and 6.4 months for LMS and LPS, respectively). Thirty-three patients (52%, 95% CI 36% to 58%, $P = 0.674$, odds of response 1.1) had a GMI >1.33 (LMS 46%, 95% CI 26% to 67%, odds of response 0.85; LPS 56%, 95% CI 40% to 72%, odds of response 1.3). Overall, in LPS we observed 15/47 patients with a GMI <0.5 and 15/47 patients with a GMI >2. Among LMS patients, 9/26 had a GMI <0.5 and 10/26 had a GMI >2. Six patients with well-differentiated/dedifferentiated LPS had a GMI >5.

PFS and OS Kaplan—Meier curves of both groups are reported in Figures 1 and 2, respectively.

The ORR (complete response + partial response) to trabectedin was 16% (24% for LMS and 12% for LPS), while PD as the best response was observed in 17% of LMS patients and slightly less than 40% of LPS patients. Previous treatment had been based on anthracyclines and/or ifosfamide in 85% of patients (91% in the LPS population).

Safety evaluation

One hundred and one patients were included in the safety analysis. Sixteen patients (49.5%) with LMS and 41 patients (66.1%) with LPS experienced at least one trabectedin-related AE, leading to treatment discontinuation in 5 patients. The main adverse drug reactions (ADRs) included blood and lymphatic disorders, liver enzyme increase and gastrointestinal disorders and fatigue. The majority of these ADRs were mild/moderate in severity; in particular, we observed neutropenia G1-2 and G3-4, respectively, in 11% and 12% of patients; anaemia G1-2 in 7% and G3-4 in 3% of patients; thrombocytopenia G1-2 in 4.5% of patients; and febrile neutropenia in 2% of patients. G1-2 AST and ALT increased were reported, respectively, in 27% and 22% of patients, while G3-4 in 2% and 1% of patients. Nineteen percent of patients had G1-2 γ-glutamyltransferase increase and 3% had a G3-4 increase. The reported gastrointestinal disorders were only G1-2 and included nausea, vomiting and diarrhoea, respectively, in 17%, 4.5% and 7% of patients. Asthenia G1-2 was reported in 23% of patients and G3-4 in 2% of them.

Nine serious adverse events (SAEs) experienced by five patients were reported. Out of these, three SAEs (neutropenia, febrile neutropenia and urinary tract infection) were assessed by the investigator as possibly related to trabectedin. No SAEs with fatal outcomes were registered during the study.

All ADRs reported were expected and in line with the safety profile of trabectedin.

DISCUSSION

In this phase II study on 91 patients with advanced pretreated retroperitoneal LMS and well-differentiated/dedifferentiated LPS, the median PFS was in the range of

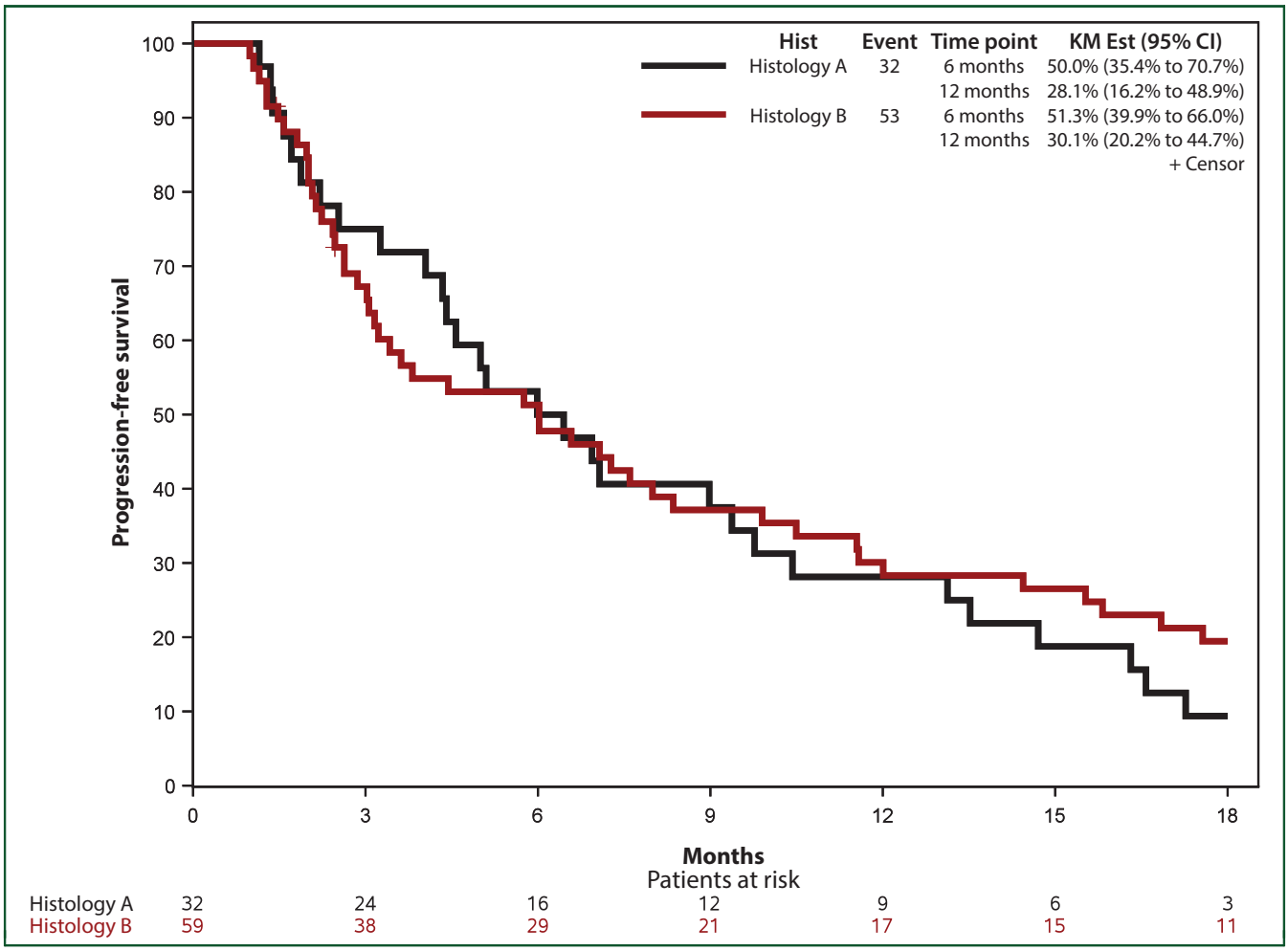

Figure 1. **Kaplan–Meier estimate (KM) of progression-free survival: per-protocol population.**

6 months for both LMS and LPS, with an ORR of 24% for LMS and 12% for LPS. The study did not meet its primary endpoint, i.e. >50% of responders according to GMI (PFS/TTP1 ≥1.33) resulting in an odds of response of 0.88, lower than expected (odds = 2.5). Intriguingly, in patients with LPS, six had a GMI >5, all having a low-grade disease (well-differentiated LPS or low-grade dedifferentiated LPS).

A weakness of this study is the limited number of patients. However, it only included patients with retroperitoneal sarcomas, which represent ∼10% of all sarcomas. This may add to the homogeneity of this patient population. Indeed, retroperitoneal sarcomas have distinct characteristics just due to their anatomical location.

Overall, the activity and efficacy of trabectedin were in the range of published trials, namely slightly better although this population was less selected.[21] Indeed, they were also slightly better than those from a real-world population of patients with advanced sarcoma of multiple histologies treated with trabectedin (6-month PFS: ∼45%).[26,27]

Actually, in this study, the activity of trabectedin was formally assessed through GMI, and in this sense, it did not meet its primary endpoint. However, GMI is strictly related to the response to the previous line of therapy, being the ratio between PFS on the last and PFS on the previous therapy. In other words, GMI has much to do with both the response to the current line of therapy and the previous one, being affected by both. Indeed, it is worth observing that GMI was >5 in the subgroup of patients with a low-grade LPS, thus suggesting a mismatch between sensitivity to anthracyclines and sensitivity to trabectedin in this particular histological type, as already reported in a retrospective series in literature.[27,28] Furthermore, 25% of patients underwent surgery before being enrolled in this study, and this may have affected TTP1, too.

With regard to surgery after treatment in this study, only 4% of our patients were operated on. Overall, 85% of patients were not amenable to surgery at baseline. As a matter of fact, however, trabectedin was apparently not able to change surgical indications.

OS in this study was better than in the published literature.[16,21] This probably reflects a selection bias, with 40% of patients with LPS (65% of the study population) having a low-grade disease. Moreover, most patients in this study

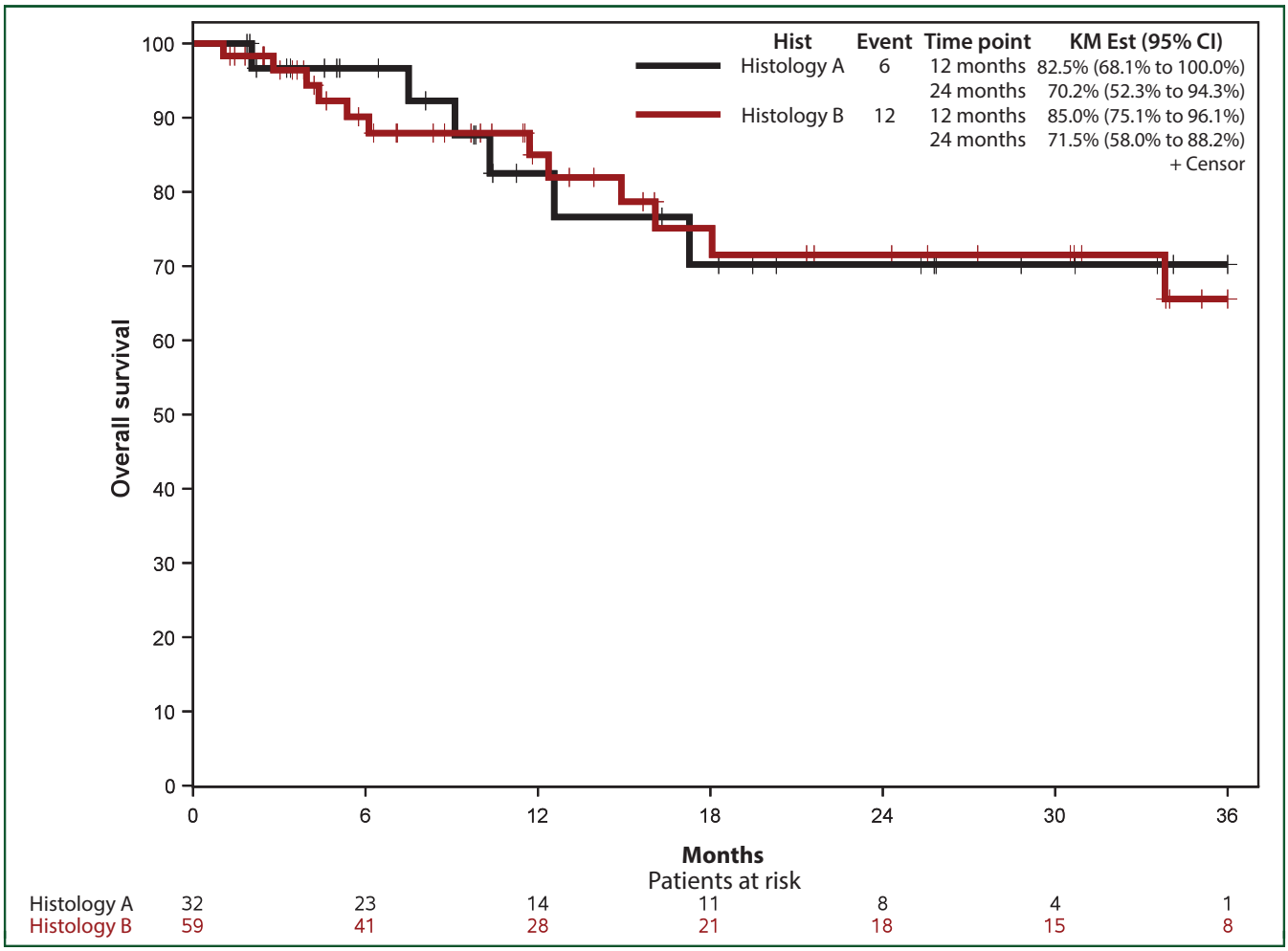

Figure 2. Kaplan–Meier estimate of overall survival: per-protocol population.
CI, confidence interval; KM, Kaplan–Meier.

(75%) received trabectedin as second-line treatment, thus at an initial phase of the disease, while literature data refer to patients who mainly received trabectedin in further lines. Finally, today LMS patients may be treated effectively with several lines of medical therapy, which may have favourably affected OS.

In conclusion, this study confirms that trabectedin has limited activity in LPS and LMS, but not trivial. There was a mismatch between PFS and OS, which might be due to the natural history of disease in LPS patients enrolled in this study and to the availability of further-line therapies in LMS.

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DISCLOSURE

The authors have declared no conflicts of interest.

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