

## Doxorubicin–Trabectedin with Trabectedin Maintenance in Leiomyosarcoma

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### ABSTRACT

#### BACKGROUND

The addition of trabectedin to doxorubicin, followed by trabectedin maintenance, may have superior efficacy to doxorubicin alone as first-line treatment in patients with advanced leiomyosarcoma.

#### METHODS

We conducted a phase 3 trial involving patients with metastatic or unresectable leiomyosarcoma who had not received chemotherapy previously. Patients were randomly assigned to receive either single-agent doxorubicin (six cycles) or doxorubicin plus trabectedin (six cycles), with continued trabectedin as maintenance therapy in patients in the doxorubicin–trabectedin group who did not have disease progression. Surgery to resect residual disease was allowed in each group after six cycles of therapy. Analyses of progression-free survival (primary end point) and overall survival (secondary end point) were adjusted for two stratification factors: tumor origin site (uterine vs. soft tissue) and disease stage (locally advanced vs. metastatic). The primary end-point results were reported previously.

#### RESULTS

A total of 150 patients underwent randomization. At a median follow-up of 55 months (interquartile range, 49 to 63), a total of 107 patients had died (47 in the doxorubicin–trabectedin group and 60 in the doxorubicin group). The median overall survival was longer in the doxorubicin–trabectedin group (33 months; 95% confidence interval [CI], 26 to 48) than in the doxorubicin group (24 months; 95% CI, 19 to 31); the adjusted hazard ratio for death was 0.65 (95% CI, 0.44 to 0.95). In a finding consistent with earlier reports, progression-free survival was longer in the doxorubicin–trabectedin group (12 months; 95% CI, 10 to 16) than in the doxorubicin group (6 months; 95% CI, 4 to 7); the adjusted hazard ratio for progression or death was 0.37 (95% CI, 0.26 to 0.53). The incidence of adverse events and the percentage of patients with dose reductions were higher with doxorubicin plus trabectedin than with doxorubicin alone.

#### CONCLUSIONS

Combination therapy with doxorubicin and trabectedin induction, followed by trabectedin maintenance, was associated with improved overall survival and progression-free survival, as compared with doxorubicin alone, among patients with metastatic or surgically unresectable uterine or soft-tissue leiomyosarcoma. (Funded by PharmaMar and others; LMS04 ClinicalTrials.gov number, NCT02997358.)

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**L**EIOMYOSARCOMAS, WITH AN INCIDENCE of 9.7 per 1 million person-years in France,<sup>1</sup> account for nearly one quarter of all soft-tissue sarcomas,<sup>2</sup> which occur predominantly in uterine locations.<sup>3</sup> Characterized by a bleak prognosis in metastatic or locally advanced stages, leiomyosarcomas vary in terms of their clinical behavior and individual genetic variants. Despite this heterogeneity, the systemic chemotherapy regimen for metastatic soft-tissue sarcoma subtypes has remained largely unchanged, with doxorubicin monotherapy continuing as the standard first-line treatment since its efficacy was first shown in 1973, particularly with regard to sarcomas (with a response observed in 33% of patients).<sup>4</sup> Subsequent trials exploring various drug combinations, including those with doxorubicin, showed that combination therapies have yet to surpass doxorubicin monotherapy in terms of overall survival<sup>5-8</sup>; trials that have been conducted in the past decade have shown overall survival to be approximately 20 months.<sup>9,10</sup>

For metastatic leiomyosarcoma, second-line treatment such as trabectedin, gemcitabine, or dacarbazine has led to an objective response in 4 to 10% of patients, with a median progression-free survival of 3 to 5 months and a median overall survival of approximately 12 months.<sup>11,12</sup> Few studies have investigated first-line treatment in trial populations that included only patients with metastatic leiomyosarcoma. The LMS02 and LMS04 clinical trials<sup>13,14</sup> investigated doxorubicin plus trabectedin as first-line therapy in patients with metastatic or relapsed leiomyosarcoma, and another trial<sup>15</sup> investigated combination therapy with gemcitabine, docetaxel, and bevacizumab in patients with uterine leiomyosarcoma.

The LMS02 trial, which was a phase 2 trial of doxorubicin plus trabectedin as first-line treatment for metastatic or locally advanced leiomyosarcoma, showed promising outcomes in terms of response, disease control, progression-free survival, and overall survival, with a median progression-free survival of 10.1 months and a median overall survival of 34.4 months, given a median follow-up of 7.2 years.<sup>16</sup> The results of the T-DIS trial supported the continued use of trabectedin until disease progression in patients with metastatic soft-tissue sarcoma who did not have disease progression after six cycles.<sup>17</sup>

Prompted by these findings, we initiated the multicenter, phase 3 LMS04 trial to compare doxorubicin alone with doxorubicin plus trabectedin followed by maintenance trabectedin as first-line therapy in patients with metastatic or unresectable uterine or extrauterine leiomyosarcomas who had not received chemotherapy previously. As previously reported, progression-free survival as assessed on the basis of independent central review (the primary end point) was significantly longer with the combination therapy than with doxorubicin alone (median, 12.2 vs. 6.2 months; adjusted hazard ratio for progression or death, 0.41; 95% confidence interval [CI], 0.29 to 0.58;  $P < 0.001$ ); the incidence of toxic effects was higher with the combination therapy, although these effects were manageable.<sup>14</sup> Long-term follow-up data are now available, and we report here the findings of the final analysis in the LMS04 trial, with data on overall survival and survival free from second progression and updated data on progression-free survival.

## METHODS

### TRIAL OVERSIGHT

This investigator-initiated trial was led by Institut Gustave-Roussy, funded in part by the manufacturer of trabectedin (PharmaMar), and designed by members of the French Sarcoma Group, who reviewed and approved the protocol (available with the full text of this article at NEJM.org). PharmaMar had no role in the data collection or analysis or in the writing, editing, review, or approval of the manuscript. One of the authors, a biostatistician in the clinical research department of Institut Gustave-Roussy, developed the statistical analysis plan and analyzed the data. The authors vouch for the accuracy and completeness of the data and for the adherence of the trial to the protocol, as confirmed by the monitoring of each case at every participating center. As defined in the protocol, the manuscript was written by the first author and was reviewed and approved by all the authors. The trial adhered to Good Clinical Practice guidelines and to the principles of the Declaration of Helsinki. Ethics approval was received from all involved centers. Written informed consent was obtained from all the participants.

**RANDOMIZATION AND TREATMENT**

Details of this multicenter, open-label, randomized, phase 3 trial have been published previously.<sup>14</sup> In brief, patients with untreated locally advanced or metastatic leiomyosarcoma were recruited across 20 French Sarcoma Group centers (see the Supplementary Appendix, available at NEJM.org). Patients were randomly assigned in a 1:1 ratio either to receive doxorubicin alone (at a dose of 75 mg per square meter of body-surface area, administered intravenously over a period of 10 to 15 minutes) once every 3 weeks, with lenograstim (at a dose of 150 µg per square meter per day administered subcutaneously from day 3 to day 9) for up to six cycles (doxorubicin group), or to receive doxorubicin (at a dose of 60 mg per square meter, administered intravenously over a period of 10 to 15 minutes) followed by trabectedin (at a dose of 1.1 mg per square meter, administered intravenously over a 3-hour period) once every 3 weeks, with pegylated filgrastim (pegfilgrastim; at a dose of 6 mg administered subcutaneously on day 2), for up to six cycles (doxorubicin–trabectedin group). Treatment with trabectedin alone (1.1 mg per square meter) was continued for up to 17 cycles in patients without disease progression in the doxorubicin–trabectedin group only. Post-treatment surgery to resect residual disease was permissible in each group. Pegfilgrastim was used in the doxorubicin–trabectedin group as recommended in a previous phase 1 study<sup>18</sup> and as performed in the phase 2 LMS02 trial,<sup>13</sup> given that it is more effective as prophylaxis for a high risk of febrile neutropenia than lenograstim or filgrastim, which are usually used in the prevention of the moderate risk of febrile neutropenia that is associated with doxorubicin alone.<sup>19</sup>

Randomization was stratified according to tumor origin site (uterine vs. soft tissue) and disease stage (locally advanced vs. metastatic), without consideration of the resectability of metastases. Patients were required to be 18 years of age or older and to have received a diagnosis of leiomyosarcoma that had been histologically confirmed by expert pathologists within the RRePS (Réseaux de Référence en Pathologie des Sarcomes [Sarcoma Pathology Reference Network]). Eligible patients also had not received chemotherapy previously and had at least one measurable lesion as assessed by the Response

Evaluation Criteria in Solid Tumors (RECIST), version 1.1; an Eastern Cooperative Oncology Group performance-status score of less than 2 (on a 5-point scale, with higher scores indicating greater disability); and adequate organ function. Patients with a recent cancer in remission for less than 3 years or with central nervous system metastases were excluded. Detailed inclusion and exclusion criteria are provided in the protocol.

Tumor evaluations were performed the use of RECIST, version 1.1, every 6 weeks during treatment, every 9 weeks during maintenance or follow-up, and then every 3 months for 1 year, with a transition to evaluation every 6 months until disease progression, death, or last follow-up among patients who did not have progression. Progression of disease was confirmed by means of blinded independent central radiologic review. Randomization was performed by means of an interactive Web-response system (TENALEA [Trans European Network Alea for Clinical Trials Services], version 2.2), with stratification according to tumor origin site and disease stage and with the use of permuted blocks of varying sizes.

**END POINTS AND ASSESSMENTS**

The primary end point was progression-free survival, as assessed on the basis of blinded independent review, which was defined as the time from randomization to progression or death from any cause. Secondary end points included disease control, response, and response duration (all assessed with the use of RECIST, version 1.1), as well as safety (as assessed with the use of the Common Terminology Criteria for Adverse Events, version 4.0, of the National Cancer Institute), overall survival, and second progression-free survival. Receipt of second-line therapy was an additional end point. Results for all the end points except overall survival and second progression-free survival have been published previously.<sup>14</sup>

**STATISTICAL ANALYSIS**

To evaluate the primary end point, we planned for 150 patients to be included in the trial. The median progression-free survival was expected to be 6.0 months in the doxorubicin group and 9.7 months in the doxorubicin–trabectedin group (corresponding hazard ratio, 0.62). We calculated that 136 events (including local relapse, metastases

progression, new metastasis, and death) would be needed to provide the trial with 80% power, with a two-sided alpha level set to 5%. With an enrollment period of 24 months, an assumption that patients would enter the trial in a uniform distribution over the enrollment period, a minimum follow-up of 24 months, and an expectation that 3% of the patients would be enrolled but not undergo randomization in the trial, we calculated that 75 patients in each group would be required (nQuery software, version 7.0).

Efficacy analyses were performed in the intention-to-treat population, which included all the patients who had undergone randomization. The median follow-up and associated interquartile range were estimated by the reversed Kaplan–Meier method. The treatment effect on the basis of updated data for progression-free survival and overall survival was assessed by means of the Cox proportional-hazards model, with adjustment for the stratification factors used for randomization. Hazard ratios from the Cox model, as well as 95% confidence intervals, were calculated. The proportionality-of-hazards assumption was graphically assessed by plotting  $\log(-\log[S(t)])$ , where  $S(t)$  is the probability of survival beyond time  $t$ . Because the statistical analysis plan did not include a provision for the correction for multiplicity, results of secondary end-point analyses and subgroup analyses are reported as point estimates with 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive treatment effects. Statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

## RESULTS

### CHARACTERISTICS OF THE PATIENTS

Trial enrollment began in January 2017, with the final data cutoff for analysis in January 2023. A total of 150 participants underwent randomization: 76 to the doxorubicin group and 74 to the doxorubicin–trabectedin group. Of these patients, 67 had uterine leiomyosarcoma, and 83 had soft-tissue leiomyosarcoma. The demographic and clinical characteristics of the patients are shown in Table 1. Information on race distribution was not collected, because this is not allowed in France.

The median number of cycles was 6 in each group for the induction phase and 10.5 for the maintenance phase in the doxorubicin–trabectedin group (Table 1). A total of 17 patients (23%) in the doxorubicin–trabectedin group did not receive maintenance treatment: 5 because of progression, 5 because of toxic effects, and 2 because the patient declined; in addition, data were missing for 5 patients.

### EFFICACY END POINTS

On extended follow-up (median, 55 months; interquartile range, 49 to 63), the median progression-free survival was longer in the doxorubicin–trabectedin group (12 months; 95% CI, 10 to 16) than in the doxorubicin group (6 months; 95% CI, 4 to 7); the hazard ratio for progression or death was 0.37 (95% CI, 0.26 to 0.53) (Fig. 1). Progression-free survival at 2 years was 30% (95% CI, 21 to 42) in the doxorubicin–trabectedin group, as compared with 3% (95% CI, 1 to 9) in the doxorubicin group.

With 107 deaths (47 in the doxorubicin–trabectedin group and 60 in the doxorubicin group) at the time of the analysis, the median overall survival was 33 months (95% CI, 26 to 48) in the doxorubicin–trabectedin group, as compared with 24 months (95% CI, 19 to 31) in the doxorubicin group; the hazard ratio for death was 0.65 (95% CI, 0.44 to 0.95) (Fig. 2). Overall survival at 2 years was 68% (95% CI, 57 to 78) in the doxorubicin–trabectedin group and 49% (95% CI, 38 to 60) in the doxorubicin group. The majority of deaths in each group were due to disease progression (in 96% of the patients in the doxorubicin–trabectedin group and in 97% of those in the doxorubicin group).

In the doxorubicin group, 28 of 76 patients (37%) received trabectedin as second-line treatment (Table S1 in the Supplementary Appendix), with an additional 17 patients receiving trabectedin in subsequent lines of therapy (totaling 59% of the patients in the doxorubicin group who received trabectedin). Despite these interventions, the time to second disease progression was longer in the doxorubicin–trabectedin group (26 months; 95% CI, 19 to 30) than in the doxorubicin group (13 months; 95% CI, 12 to 15) (hazard ratio, 0.46; 95% CI, 0.32 to 0.65) (Fig. 3).



**ADVERSE EVENTS**

Safety analyses included all the adverse events that occurred between randomization and the date of first progression, death, or withdrawal from the trial. A total of 149 patients (74 in the doxorubicin–trabectedin group and 75 in the doxorubicin group) received at least one cycle of treatment and were included in the safety population. Adverse-event profiles showed increased toxicity with the doxorubicin–trabectedin combination, with a higher incidence and severity of adverse hematologic events in this group than in the doxorubicin group (Table S2). The incidence of grade 3 or 4 adverse events was significantly higher in the doxorubicin–trabectedin group than in the doxorubicin group (97% vs. 56%,  $P < 0.001$ ).

The percentages of patients with neutropenia, anemia, thrombocytopenia, and febrile neutropenia were notably higher in the doxorubicin–trabectedin group than in the doxorubicin group. With respect to liver toxic effects, 34 patients (46%) in the doxorubicin–trabectedin group and 2 patients (3%) in the doxorubicin group had cytolysis of grade 3 or 4. The grade of cytolysis, except in 2 patients (1 in each group) for whom we have no follow-up data, reversed to a maximum of grade 2 (to grade 0 in 79% of the patients in the doxorubicin–trabectedin group, grade 1 in 15%, and grade 2 in 3%). No chronic liver dysfunction has been reported.

Serious adverse events occurred more often in the doxorubicin–trabectedin group (in 37 patients) than in the doxorubicin group (in 20). Despite toxic effects, 60 patients (81%) in the doxorubicin–trabectedin group received six cycles of the doxorubicin–trabectedin combination and 54 patients (71%) in the doxorubicin group received six cycles of doxorubicin. No treatment-related deaths were reported in the doxorubicin–trabectedin group, and one treatment-related death due to cardiac failure was reported in the doxorubicin group.

Surgical intervention after the initial six planned chemotherapy cycles was undertaken in 20% of the patients in the doxorubicin–trabectedin group and in 8% of those in the doxorubicin group. A total of 15 patients with nonuterine sarcomas underwent surgical intervention, as compared with 6 patients with uterine sarcomas. Across the two

trial groups, surgeries targeted the primary tumor in 8 patients (with complete resection in 7) and metastases in 13 patients.

**DISCUSSION**

The randomized, phase 3 LMS04 trial showed a benefit in progression-free survival and improved overall survival with a doxorubicin-based combination regimen (doxorubicin plus trabectedin, followed by maintenance trabectedin) as compared with standard doxorubicin monotherapy. Earlier evidence from the phase 2 LMS02 trial highlighted the potential of this combination therapy, with a response observed in 48% of the patients<sup>13</sup> and with promising survival outcomes despite the occurrence of considerable toxic effects.<sup>16</sup> The current LMS04 trial has now confirmed these findings while also showing the superior efficacy of the combination therapy over treatment with doxorubicin alone — given that an objective tumor response was seen in 36% of the patients in the doxorubicin–trabectedin group, as compared with 13% of those in the doxorubicin group,<sup>14</sup> and that the median progression-free survival nearly doubled, from 6.2 months with the monotherapy to 12.2 months with the combination therapy.

Although there have been numerous attempts to surpass the efficacy of doxorubicin with the use of various agents and combinations, the 2022 National Comprehensive Cancer Network guidelines still endorse doxorubicin as first-line therapy for advanced soft-tissue sarcomas with a level I grade A recommendation.<sup>20</sup> This recommendation, which has stayed the same for decades, underscores the challenge in finding superior treatment options and highlights the clinical relevance of our trial results. Regarding the toxicity of the combination therapy, an accurate selection of the patients needs to be performed (with consideration of their performance status, including, for example, geriatric evaluation).

In contrast to other phase 3 trials that combined various sarcoma subtypes without showing overall survival benefits (median overall survival, 16 to 20 months with combination therapy vs. 18 to 20 months with doxorubicin alone),<sup>8–10,21</sup> our trial not only showed improved survival outcomes but also had a specific focus on leiomyosarcoma.

**Table 1. Characteristics of the Patients.\***

Characteristic	Doxorubicin Alone (N=76)	Doxorubicin + Trabectedin (N=74)
Median age (range) — yr	64 (53–69)	59 (52–68)
Female sex — no. (%)	59 (78)	53 (72)
ECOG performance-status score — no./total no. (%) <sup>†</sup>		
0	45/74 (61)	47/70 (67)
1	29/74 (39)	23/70 (33)
Disease grade — no./total no. (%) <sup>‡</sup>		
1	8/42 (19)	11/41 (27)
2	16/42 (38)	11/41 (27)
3	10/42 (24)	12/41 (29)
Missing data	8/42 (19)	7/41 (17)
Site of primary tumor — no. (%)		
Uterus	34 (45)	33 (45)
Soft tissue	42 (55)	41 (55)
Metastatic disease — no. (%)		
Yes	67 (88)	68 (92)
No	9 (12)	6 (8)
Site of metastasis — no. (%)		
Lung	54 (71)	54 (73)
Liver	23 (30)	24 (32)
Bone	17 (22)	7 (9)
Cutaneous tissue	1 (1)	4 (5)
Other	26 (34)	32 (43)
No. of metastases — no. (%) <sup>§</sup>		
1	7 (9)	8 (11)
≥2	60 (79)	60 (81)
Median no. of cycles received (interquartile range)		
Induction therapy	6 (4–6)	6 (6–6)
Maintenance therapy	NA	10.5 (4–17)
Dose reduction — no. (%)		
Induction therapy	17 (22)	32 (43)
Maintenance therapy	NA	16 (22)
Therapy completed — no. (%)		
Induction therapy for 6 cycles	54 (71)	60 (81)
Maintenance	NA	21 (28)
Disease progression during therapy — no. (%)		
Induction therapy for 6 cycles	17 (22)	5 (7)
Maintenance	NA	23 (31)
Withdrawal due to toxic effects — no. (%)		
Induction therapy for 6 cycles	3 (4)	7 (9)
Maintenance	NA	10 (14)

**Table 1. (Continued.)**

Characteristic	Doxorubicin Alone (N = 76)	Doxorubicin + Trabectedin (N = 74)
Surgery after 6 cycles of therapy — no. (%)	6 (8)	15 (20)
Treatment with trabectedin after the trial — no./total no. (%)		
In second line of therapy	28/74 (38)	2/66 (3)
In subsequent line of therapy	17/74 (23)	NA

\* IQR denotes interquartile range, and NA not available.

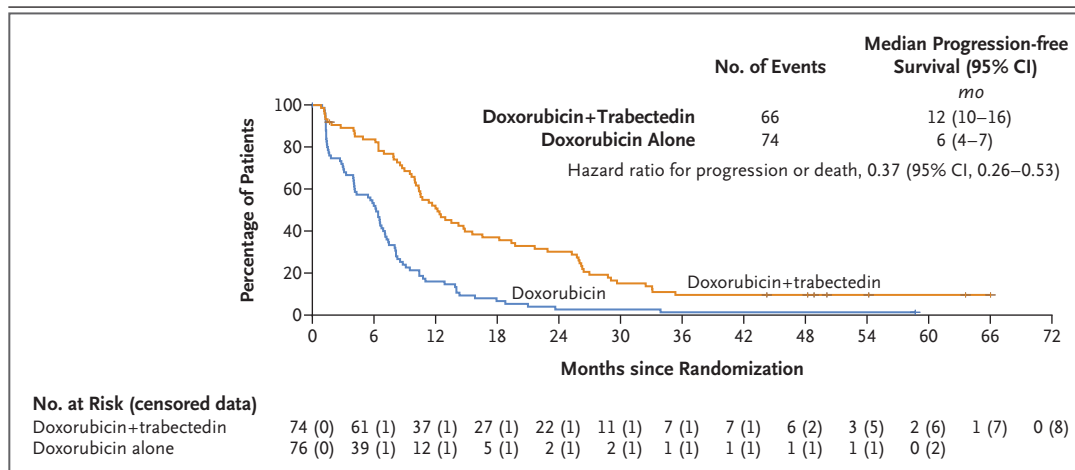
† Eastern Cooperative Oncology Group (ECOG) performance-status scores are assessed on a 5-point scale, with higher scores indicating greater disability. Patients were required to have an ECOG performance-status score of less than 2. Data were missing for two patients in the doxorubicin group and for four in the doxorubicin–trabectedin group.

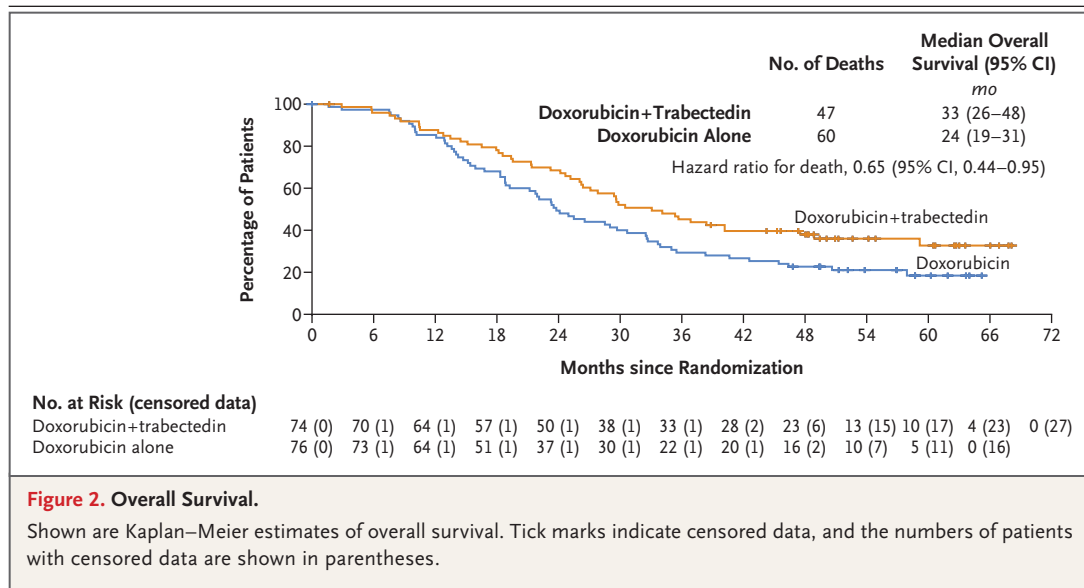
‡ Data were available only for patients with soft-tissue leiomyosarcoma because the grading system is not applicable to uterine sarcoma.

§ The percentages are based on the complete trial groups rather than on the numbers of patients with metastatic disease to show the extent of advanced disease in the trial population.

This specificity is relevant because trials involving patients with mixed histologic characteristics often dilute the potential benefits in distinct sarcoma subtypes. For instance, despite their stratification efforts, the SARC021 (Sarcoma Alliance for Research through Collaboration 021), GeDDiS (Gemcitabine and Docetaxel versus Doxorubicin), and ANNOUNCE trials did not show a survival advantage in patients with leiomyosarcoma when comparing combination therapies with doxorubicin alone (Table S3).<sup>8–10</sup> In a propensity-score–matching analysis based on a retrospective observational study that was focused on leiomyosarcoma only,

investigators compared the results of different doxorubicin-based regimens as first-line treatment for advanced leiomyosarcoma; among 303 patients, 39% received doxorubicin plus dacarbazine, 23% received doxorubicin plus ifosfamide, and 38% received doxorubicin alone.<sup>22</sup> Treatment with doxorubicin plus dacarbazine showed favorable activity in terms of objective response, progression-free survival, and overall survival; however, the adjusted analyses retained an effect on progression-free survival but not on overall survival.<sup>22</sup> No data on toxic effects were reported.





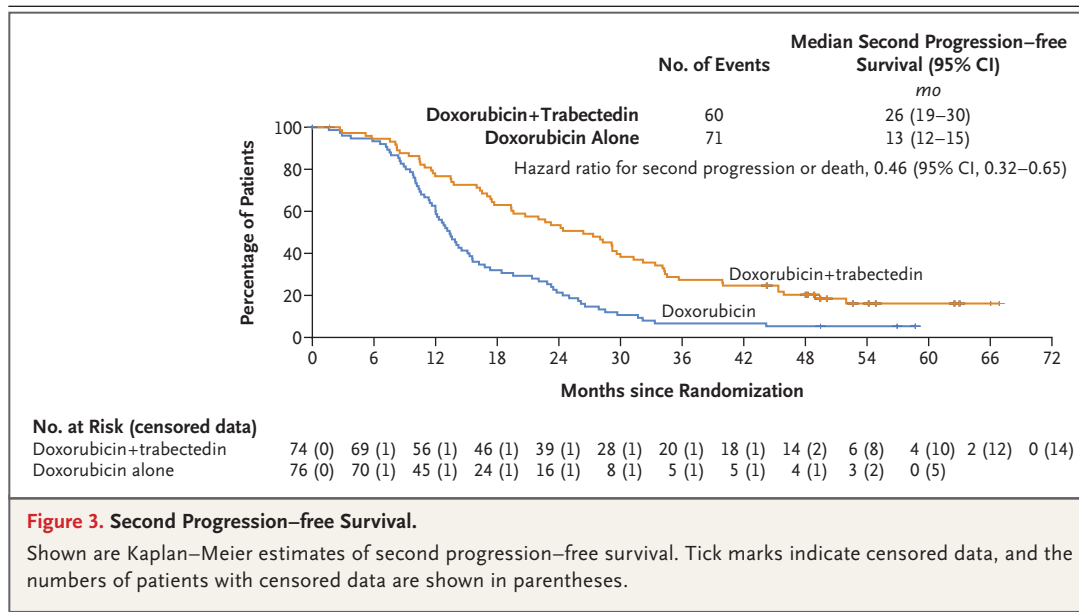
The median overall survival of 33 months that was observed in the doxorubicin–trabectedin group of our trial establishes a benchmark. This outcome may be a result of the efficacy of the initial chemotherapy regimen as well as the effects of subsequent treatments, including surgery, which was more feasible after combination therapy than after monotherapy owing to an apparently higher percentage of patients with a response,<sup>14</sup> and maintenance treatment with trabectedin. The stratification factor of disease stage (locally advanced vs. metastatic) was used in this trial, and the analysis was adjusted for stratification factors. Moreover, the number of metastases (1 vs.  $\geq 2$ ) was well balanced between the two trial groups (Table 1), which suggests that tumor burden does not explain the observed differences in outcome.

Furthermore, the continuation of trabectedin maintenance therapy after the planned initial cycles of combination chemotherapy, as supported by the findings in the T-DIS trial,<sup>17</sup> probably contributed to the observed survival benefits by allowing for extended control of the disease. This approach underscores the importance of studying the effect of continuous treatment in the effective management of advanced sarcomas, given that the contribution of the maintenance phase could have been substantial in the survival results; however, its real effect is unknown.

Some trials have already tested maintenance treatment after combination therapy and were negative. In the SARC021 trial, for example, 46% of 317 patients received evofosfamide monotherapy after the receipt of six cycles of the combination of doxorubicin and evofosfamide (as compared with follow-up after the receipt of six cycles in the doxorubicin group), and no benefit in progression-free survival or overall survival was apparent.<sup>8</sup> In the SUCCEED (Sarcoma Multicenter Clinical Evaluation of the Efficacy of Ridaforolimus) trial, maintenance treatment with a mammalian target of rapamycin (mTOR) inhibitor after one to four lines of chemotherapy marginally delayed tumor progression,<sup>23</sup> but the observed difference was not considered to be sufficiently clinically relevant to allow for approval by the regulatory authorities. The EREMISS trial (data for which have not yet been published; ClinicalTrials.gov number, NCT03793361) is evaluating maintenance treatment with regorafenib after a response to or stabilization after six cycles of first-line doxorubicin-based therapy in patients with soft-tissue sarcoma, with stratification according to histologic subtype (including leiomyosarcoma); the results may help in the interpretation of the effect of maintenance treatment after chemotherapy.

The longer time to second disease progression with the combination therapy than with monotherapy, despite a substantial percentage





of patients in the doxorubicin group receiving trabectedin after disease progression (59% of the patients in the context of second-line or subsequent treatment), reinforces the potential benefits of using an effective combination therapy as early as possible in the disease course rather than waiting for sequential treatment to manage progressing sarcoma. This finding challenges the prevailing paradigm of sequential drug use in the treatment of sarcoma and suggests that a reevaluation of treatment strategies may be warranted. An ongoing trial of a combination of doxorubicin and lurbinectedin induction followed by lurbinectedin maintenance, as compared with doxorubicin alone (NCT06088290), will perhaps confirm the strategy with a lower incidence of toxic effects.

Other strategies of combination therapy with doxorubicin and immune checkpoint inhibitors are being tested (e.g., doxorubicin with APX005M [NCT03719430], and ontropacept [also called TTI-621] plus doxorubicin followed by ontropacept monotherapy [NCT04996004]) to enhance the control of the disease in patient populations with certain histologic subtypes, such as leiomyosarcomas. Options that are being tested in the context of second-line and later therapies as deregulation in DNA damage–repair pathways, especially homologous recombination repair, or phosphoinositide 3-kinase (PI3K) inhibitors may

be more specifically active in leiomyosarcomas than in other subtypes and could perhaps be tested later in the context of first-line therapy for metastatic disease.<sup>24</sup> In the context of the development of drugs to treat sarcoma, the results of our trial advocate for a more nuanced approach, on the basis of histologic features, to the treatment of sarcoma.

In this phase 3 trial, combination therapy with doxorubicin and trabectedin induction, followed by trabectedin maintenance, was associated with improved overall survival and longer progression-free survival among patients with metastatic or surgically unresectable uterine or soft-tissue leiomyosarcoma. The trial results support the use of doxorubicin plus trabectedin for the first-line treatment of advanced or metastatic leiomyosarcomas, offering hope for improved outcomes in this challenging disease area.

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#### APPENDIX

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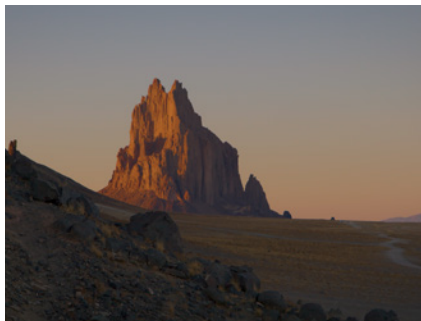
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## Double Take Video: Healing within Kinship



Many physicians rotate through Navajo Nation, but few put down roots. In this video, physicians at the Northern Navajo Medical Center discuss patients' anxieties regarding the lack of continuity of care. They describe efforts to combat the doctor shortage with a local residency program and to build trust through community engagement.

