

Neoadjuvant Chemotherapy in High-Risk Soft Tissue Sarcomas: Final Results of a Randomized Trial From Italian (ISG), Spanish (GEIS), French (FSG), and Polish (PSG) Sarcoma Groups

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PURPOSE To determine whether the administration of histology-tailored neoadjuvant chemotherapy (HT) was superior to the administration of standard anthracycline plus ifosfamide neoadjuvant chemotherapy (A+I) in high-risk soft tissue sarcoma (STS) of an extremity or the trunk wall.

PATIENTS AND METHODS This was a randomized, open-label, phase III trial. Patients had localized high-risk STS (grade 3; size, ≥ 5 cm) of an extremity or trunk wall, belonging to one of the following five histologic subtypes: high-grade myxoid liposarcoma (HG-MLPS); leiomyosarcoma (LMS), synovial sarcoma (SS), malignant peripheral nerve sheath tumor (MPNST), and undifferentiated pleomorphic sarcoma (UPS). Patients were randomly assigned in a 1:1 ratio to receive three cycles of A+I or HT. The HT regimens were as follows: trabectedin in HG-MLPS; gemcitabine plus dacarbazine in LMS; high-dose prolonged-infusion ifosfamide in SS; etoposide plus ifosfamide in MPNST; and gemcitabine plus docetaxel in UPS. Primary and secondary end points were disease-free survival (DFS) and overall survival (OS), estimated using the Kaplan-Meier method and compared using Cox models adjusted for treatment and stratification factors. The study is registered at ClinicalTrials.gov (identifier [NCT01710176](https://clinicaltrials.gov/ct2/show/study/NCT01710176)).

RESULTS Between May 2011 and May 2016, 287 patients (UPS: n = 97 [33.8%]; HG-MLPS: n = 65 [22.6%]; SS: n = 70 [24.4%]; MPNST: n = 27 [9.4%]; and LMS: n = 28 [9.8%]) were randomly assigned to either A+I or HT. At the final analysis, with a median follow-up of 52 months, the projected DFS and OS probabilities were 0.55 and 0.47 (log-rank $P = .323$) and 0.76 and 0.66 (log-rank $P = .018$) at 60 months in the A+I arm and HT arm, respectively. No treatment-related deaths were observed.

CONCLUSION In a population of patients with localized high-risk STS, HT was not associated with a better DFS or OS, suggesting that A+I should remain the regimen to choose whenever neoadjuvant chemotherapy is used in patients with high-risk STS.

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ASSOCIATED CONTENT

Data Supplement Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Despite optimal local treatment, 50% of patients affected by localized high-risk soft tissue sarcoma (STS) of the extremities or trunk wall die of metastatic disease.^{1,2} Neoadjuvant/adjuvant chemotherapy has been tested in several trials and two meta-analyses,^{3,4} showing a 5% to 10% overall survival (OS) benefit. However these studies and meta-analyses have been weakened by conflicting results of individual trials.⁵

The Italian Sarcoma Group (ISG) studies were characterized by the selection of patients with high-risk STS (tumors ≥ 5 cm and malignancy grade of 3). The first

study^{6,7} preported a benefit in OS and disease-free survival (DFS) after a treatment with five courses of anthracycline plus ifosfamide adjuvant chemotherapy (A+I) versus no additional treatment. However, a drop in dose intensity was observed after the administration of three cycles. A second study in collaboration with the Spanish Sarcoma Group (GEIS) showed that the administration of three courses of the same A+I in the neoadjuvant setting was not inferior to the administration of five courses.⁸

In collaboration with GEIS, the French Sarcoma Group, and the Polish Sarcoma Group, we then compared the

CONTEXT

Key Objective

To investigate whether neoadjuvant histotype-tailored chemotherapy (HT) is superior to standard anthracycline plus ifosfamide chemotherapy (A+I) in five high-risk soft tissue sarcoma (STS) subtypes of the extremities or trunk wall.

Knowledge Generated

In this randomized, multicenter, open-label, prospective trial in which patients affected by high-risk myxoid liposarcoma, malignant peripheral nerve sheath tumor, leiomyosarcoma, synovial sarcoma, or undifferentiated pleomorphic sarcoma were randomly assigned in a 1:1 ratio to A+I or HT, a nonstatistically significant difference in 5-year disease-free survival (DFS; 0.55 v 0.47) and a statistically significant difference in overall survival (OS; 0.76 v 0.66) in favor of A+I were observed.

Relevance

HT was not associated with better DFS or OS, suggesting that A+I should remain the regimen to choose whenever neoadjuvant chemotherapy is used to treat the aforementioned five histologic subtypes, which account for 80% of all high-risk STS of the extremities or trunk wall.

administration of A+I with a histotype-tailored neoadjuvant chemotherapy (HT) in five major STS histologic subtypes, selected because, in the metastatic setting, these subtypes had demonstrated specific sensitivities to drugs different from anthracycline.⁹⁻¹³

This study was terminated slightly early, after the third prespecified futility analysis and after the inclusion of 287 of 350 patients for the observation, at a median follow-up of 1 year, of a hazard ratio (HR) of 2.0 in DFS and 2.7 in OS of the HT approach.¹⁴ We report herein the final results.

PATIENTS AND METHODS

Study Design

This was a prospective, open-label, randomized, controlled study comparing A+I with HT for patients with primary localized high-risk STS. Patients were enrolled in 32 hospitals in one of the following four countries: Italy, Spain, France, and Poland.

The trial protocol and all amendments were approved by the appropriate independent ethics committee at each trial center. The trial was conducted in accordance with the provisions of the Declaration of Helsinki. All patients provided written informed consent before enrollment. The full protocol is available in the Data Supplement.

Participants

Patients were eligible if aged ≥ 18 years; had a histologically proven and centrally reviewed diagnosis (before random assignment) of localized STS originating in an extremity or trunk wall, belonging to high-grade myxoid liposarcoma (HG-MLPS; cellular component $> 5\%$), leiomyosarcoma (LMS), synovial sarcoma (SS), malignant peripheral nerve sheath tumor (MPNST), or undifferentiated pleomorphic sarcoma (UPS); with high malignancy grade (grade 3, according to the Fédération Nationale des Centres

de Lutte Contra le Cancer [National Federation of Cancer Centers] grading system¹⁵); and ≥ 5 cm in the longest diameter at baseline radiologic assessment. Patients were ineligible if they had distant metastases. Other inclusion and exclusion criteria can be found in the Data Supplement.

Randomization and Blinding

Patients were randomly assigned in a 1:1 ratio to receive three cycles of A+I or HT. Random assignment was performed centrally at the clinical trial center in Genova, Italy, stratified by administration of preoperative radiation therapy (RT) versus no preoperative RT and by country of enrollment (Spain v France v Poland v Italy) and was not balanced by histotype or participating site. Computer-generated random lists were prepared using permuted balanced blocks of size 4 and 6 in random sequence. An Internet-based randomization system ensured concealment of the treatment assignment until the patient had been registered in the system. Treatment allocation was communicated electronically to the study center and by the local investigator to the patient. No blinding of treatment assignments was deemed possible because of obvious differences in schedules and modes of administration, as well as in toxicity, across regimens.

Procedures

In the A+I arm, chemotherapy had to be repeated every 21 days and included epirubicin 60 mg/m²/d short infusion on days 1 and 2 plus ifosfamide 3 g/m²/d on days 1, 2, and 3.

In the HT arm, chemotherapy for HG-MLPS had to be repeated every 21 days and consisted of trabectedin 1.3 mg/m², given by 24-hour continuous infusion. Of note, at the start of the study, trabectedin was not yet available and three patients received as a tailored regimen adriamycin 75 mg/m²/d monotherapy short infusion every

3 weeks. Trabectedin was then introduced with the first amendment (November 2011). For LMS, chemotherapy had to be repeated every 14 days and consisted of gemcitabine 1,800 mg/m² on day 1 administered intravenously (IV) over 180 minutes and dacarbazine 500 mg/m² on day 1 administered IV over 20 minutes. For SS, chemotherapy consisted of high-dose ifosfamide 14 g/m², given over 14 days via an external infusion pump, every 28 days. For MPNST chemotherapy had to be repeated every 21 days and consisted of etoposide 150 mg/m²/d on days 1, 2, and 3 and ifosfamide 3 g/m²/d on days 1, 2, and 3. For UPS, chemotherapy had to be repeated every 21 days and consisted of gemcitabine 900 mg/m² on days 1 and 8 administered IV over 90 minutes and docetaxel 75 mg/m² on day 8 administered IV over 1 hour.

Toxic effects were graded using the National Cancer Institute Common Toxicity criteria, version 4.0. Dose reductions were foreseen and are reported in the Data Supplement. Response according to RECIST 1.1¹⁶ and modified Choi criteria¹⁷⁻¹⁹ was assessed after the first cycle and after the third cycle at the time of surgery.

Surgery was planned 3 to 4 weeks after the administration of last preoperative cycle and not before 4 weeks from the end of preoperative RT. Follow-up was conducted every 4 months for the first 2 years after the end of treatment, then every 6 months from the third to the fifth year after the end of treatment, and yearly after the sixth year.

Statistical Analysis

The Kaplan-Meier method²⁰ was used to estimate DFS and OS. For the analysis of DFS, progression before surgery, relapse after surgery, and death without progression or relapse were considered events, whereas patients who were alive and disease free or who were lost to follow-up were censored at the time of the last examination. For the analysis of OS, data for patients who were alive or who were lost to follow-up were censored at the time of the last contact. Between-group differences in DFS and OS were assessed by stratified log-rank test. HRs and associated 95% CIs were assessed by stratified Cox proportional hazards model.²¹ All randomly assigned patients were included in DFS and OS analyses and considered in the treatment group assigned at randomization (the intention-to-treat [ITT] population). SAS, version 9.2 (SAS Institute, Cary, NC) and SPSS, version 22.0 (IBM, Armonk, NY) were the statistical software programs used.

The original sample size estimates were based on the consideration that the HT approach could have been associated, overall, with a one-third reduction in the hazard of relapse (HR, 0.667), corresponding to a reduction in the long-term risk of relapse from 40% to 27%. To assess such an effect with 80% power at the 5% (one-sided) significance level, 150 events (relapses or deaths) had to be observed among 350 randomly assigned patients. The final analysis had been planned after the observation of the

150th event, expected to occur 4 to 5 years after the start of the study.

Yearly interim futility analyses were performed to assess whether the study hypothesis that HT was associated with a one-third reduction in the hazard of relapse was still viable,²² whereas no interim analysis aimed at stopping the study for efficacy was planned or conducted. Therefore, no correction for multiple analyses (α spending) was needed, because the α error was entirely preserved for the final analysis.

An external independent data monitoring committee (IDMC) oversaw the trial and assessed the safety and efficacy at prespecified interim analyses. Committee members are listed in the Data Supplement.

On May 23, 2016, the IDMC recommended the early termination of the study on the basis of the third prespecified futility interim analysis, which showed, at a median follow-up of 1 year, an HR of 2 in DFS of the HT approach. This was also associated with an HR of 2.7 in OS. These results were reported in full, as recommended by the IDMC.¹⁴ The final study analysis was maintained, as planned, 2 years later, but an amendment was introduced, and the one-sided test was replaced by a two-sided test (still at the 5% α level) based on the results of the futility analysis, which suggested a higher risk in the HT arm. The final analysis, therefore, was planned after the observation of 130 events, allowing an 80% power to confirm at the 5% two-sided level the significant difference observed at the third futility analysis.

As a consequence, caution adopted in the interpretation of the interim analysis should be applied also to the present analysis because early study results were used to modify the null hypothesis, which was being tested.

Ancillary Analysis

On the basis of the 10-year OS predicted by the nomogram included in the Sarculator validated tool²³ (<http://www.sarculator.com>), patients were categorized into two groups: those with a 10-year predicted OS < 60% and those with a 10-year predicted OS \geq 60%. The Kaplan-Meier method was used to estimate DFS and OS for patients allocated to each category of Sarculator's predicted 10-year OS. Between-group differences were assessed on the ITT population by using a stratified log-rank test. HRs and 95% CIs were calculated with a stratified Cox proportional-hazards model as described previously in Patients and Methods.

RESULTS

From May 2011 to May 2016, 435 patients were registered and 287 were randomly assigned to the A+I (n = 145) or the HT arm (n = 142). Men made up 177 of the patients; 110 were women (Table 1). The ITT population is depicted in Figure 1.

TABLE 1. Clinical and Pathologic Characteristics of Patients Randomly Assigned to Two Treatment Arms (intention-to-treat population)

Characteristic	Treatment		All (N = 287)
	Standard Chemotherapy (n = 145) ^a	Histotype-Tailored Chemotherapy (n = 142)	
Age, years, mean (SD)	48 (13)	49 (13)	40 (13)
IQR	20	21	20
Sex			
Male	92 (63.45)	85 (59.86)	177 (61.67)
Female	53 (36.55)	57 (40.14)	110 (38.33)
Tumor size, mm, mean (SD)	112 (51)	105 (65)	109 (58)
Minimum to maximum range	26-360	10-680	10-680
IQR	52.00	60.00	55.00
Histology			
High-grade myxoid liposarcoma	37 (25.52)	28 (19.72)	65 (22.65)
Synovial sarcoma	36 (24.83)	34 (23.94)	70 (24.39)
Malignant peripheral nerve sheath tumor	15 (10.34)	12 (8.45)	27 (9.41)
Leiomyosarcoma	12 (8.28)	16 (11.27)	28 (9.76)
Undifferentiated pleomorphic sarcoma	43 (29.66)	50 (35.21)	93 (32.40)
Mixofibrosarcoma ^b	0 (0.00)	2 (1.41)	2 (0.70)
Unclassified spindle cell ^b	1 (0.69)	0 (0.00)	1 (0.35)
Pleomorphic liposarcoma ^b	1 (0.69)	0 (0.00)	1 (0.35)
Site			
Thoracic wall	5 (3.45)	4 (2.82)	9 (3.14)
Abdominal wall	2 (1.38)	2 (1.41)	4 (1.39)
Paraspinal	4 (2.76)	1 (0.70)	5 (1.74)
Shoulder girdle	15 (10.34)	8 (5.63)	23 (8.01)
Upper limb	9 (6.21)	11 (7.75)	20 (6.97)
Pelvic girdle	10 (6.90)	18 (12.68)	28 (9.76)
Lower limb	100 (68.97)	98 (69.01)	198 (68.99)
RT			
Preoperative	17 (11.72)	18 (12.68)	35 (12.20)
Postoperative	96 (66.21)	95 (66.90)	191 (66.55)
Pre and postoperative	2 (1.38)	1 (0.70)	3 (1.05)
None	30 (20.69)	28 (19.72)	58 (20.21)
Microscopic surgical margin ^c			
R0	111 (78.17)	113 (81.29)	224 (79.71)
R1	29 (20.42)	21 (15.10)	50 (17.79)
R2	2 (1.41)	4 (2.87)	6 (2.13)
Unknown	0	1 (0.74)	1 (0.37)
Type of surgery ^d			
Conservative	104 (92.04)	105 (95.45)	209 (93.76)
Amputation	9 (7.96)	5 (4.45)	14 (6.28)

NOTE. Data are No. of patients (%) unless otherwise indicated.

Abbreviations: IQR, interquartile range; RT, radiation therapy; SD, standard deviation.

^aAnthracycline plus ifosfamide.

^bIneligible histology at study entry.

^cSix patients did not undergo surgery (n = 3 [2.1%] of 145 patients in the standard chemotherapy arm; n = 3 [2.1%] of 142 patients in the histotype-tailored chemotherapy [HT] arm) for locally advanced disease (n = 2 cases; one per study arm), occurrence of distant metastases in the preoperative phase (n = 3 cases; n = 2 in the standard chemotherapy arm; n = 1 in the HT arm) and one refusal (HT arm).

^dExcluding abdominal wall, thoracic wall, and paraspinal.

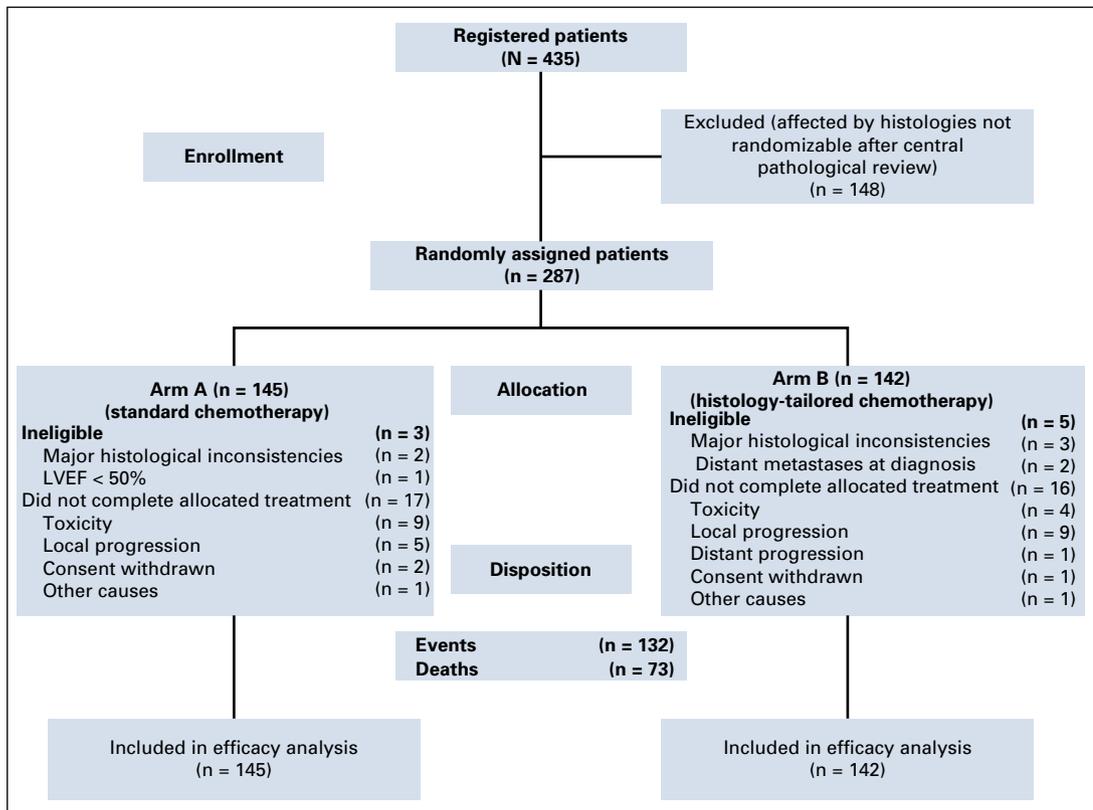


FIG 1. CONSORT diagram. LVEF, left ventricular ejection fraction.

Of the 287 total patients, 281 (97.9%) underwent surgery. The remaining six patients (n = 3 [2.1%] in the A+I arm; n = 3 [2.1%] in HT arm) did not undergo surgery for the following reasons: locally advanced disease (n = 2 cases; one per study arm), occurrence of distant metastases in the preoperative phase (n = 3 cases; n = 2 in the A+I arm; n = 1 in HT arm), and one refusal (HT arm).

At the final analysis, with a median follow-up of 52 months (range, 22 to 88 months; interquartile range, 28), 132 events were observed, 63 in the A+I arm and 69 in HT arm. The corresponding DFS probabilities at 60 months were 0.55 (95% CI, 0.46 to 0.63) in the A+I arm and 0.47 (95% CI, 0.38 to 0.57) in the HT arm (Fig 2A). The HR, estimated in a stratified Cox proportional hazards model, was 1.23 (95% CI, 0.88 to 1.73; $P = .32$). Findings of a per-protocol analysis, excluding ineligible patients, were consistent with those from the Cox proportional hazards model (HR, 1.23; 95% CI, 0.86 to 1.74).

A total of 73 deaths occurred in the total group of patients, 28 in the A+I arm and 45 in the HT arm. The corresponding OS probabilities at 60 months were 0.76 (95% CI, 0.67 to 0.84) in the A+I arm and 0.66 (95% CI, 0.57 to 0.75) in the HT arm (Fig 2B). The HR, estimated in a univariate Cox proportional hazards model, was 1.77 (95% CI, 1.10 to 2.83; $P = .02$). Findings of a per-protocol analysis, excluding ineligible patients, were consistent with

those from the Cox proportional hazards model (HR, 1.69; 95% CI, 1.05 to 2.72).

Of the 287 patients, 240 (83.6%) had measurable disease at the time of study entry and were evaluable according to RECIST 1.1: 121 (83.4%) of 145 patients in the A+I arm and 119 (83.8%) of 142 patients in HT arm, whereas 47 (16.4%) of the total 287 patients (n = 24 [16.5%] of 145 patients in the A+I arm; n = 23 [16.2%] of 142 patients in the HT arm) were included in the study without measurable disease, after prior tumor excision.

Of the 240 patients evaluable for response, 230 (96%), 117 of 121 (96.6%) in the A+I arm and 113 of 119 (94.9%) in the HT arm, were assessed by a local investigator. No complete responses were observed. Of the 230 patients, 23 (10%) had a partial response (n = 16 [13.6%] of 117 patients in the A+I arm; n = 7 [6.2%] of 113 patients in the HT arm), whereas 184 (80%) of the 230 patients had stable disease (n = 93 [79.5%] of 117 patients in the A+I arm; n = 91 [80.5%] of 113 patients in the HT arm). Twenty-three (10%) of 230 patients (n = 8 [6.8%] of 117 patients in the A+I arm; n = 15 [13.3%] of 113 patients in the HT arm) had progressive disease. An analysis of a centralized review of response and outcome will be the subject of a separate report. No toxic deaths were observed in either study arm. Safety and toxicity data are reported in the Data Supplement.

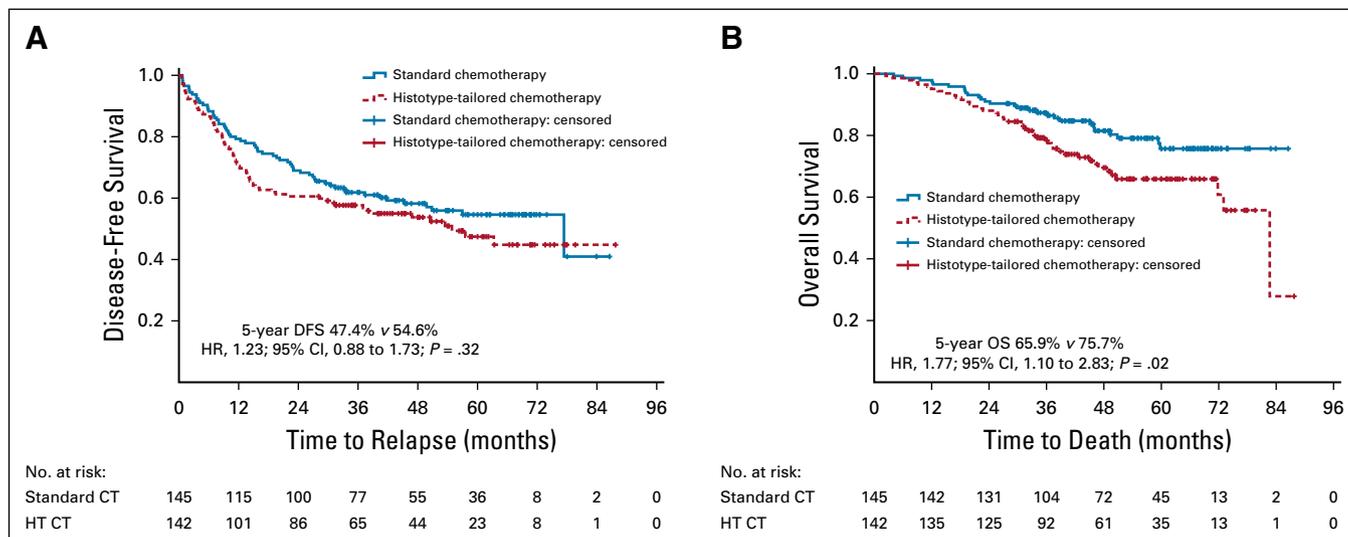


FIG 2. Graphs of (A) disease-free survival (DFS) and (B) overall survival (OS) of standard (anthracycline plus ifosfamide) versus histotype-tailored (HT) chemotherapy (CT). HR, hazard ratio.

Ancillary Analysis

Patients with a Sarculator-predicted OS $\geq 60\%$ had a DFS and OS at 5 years of 0.61 and 0.81, respectively, in the A+I arm and 0.60 and 0.75, respectively, in the HT arm (DFS HR, 1.01 [95% CI, 0.61 to 1.67], $P = .96$; OS HR, 1.51 [95% CI, 0.75 to 3.05], $P = .25$; Fig 3A and 3B). Patients with a predicted OS $< 60\%$ had a DFS and OS at 5 years of 0.45 and 0.66, respectively, in the A+I and 0.34 and 0.55, respectively, in the HT arm (DFS HR, 1.47 [95% CI, 0.92 to 2.37], $P = .11$; OS HR, 1.91 [95% CI, 1.00 to 3.66], $P = .05$; Fig 3C and 3D).

DISCUSSION

This phase III trial in patients with localized, high-risk STS of the extremities and trunk wall did not show a superior DFS (the primary study end point) of HT over A+I. On the contrary, there was a trend in favor of A+I, which was consistent with a parallel OS difference.

Of note, the difference in DFS in favor of the A+I was statistically significant at the third futility analysis, but its magnitude decreased at this final analysis. Indeed, the HT group initially seemed to reproduce the outcome of the no-treatment group of the first ISG trial¹⁴: Its projected 4-year DFS at the time of the third futility analysis was 0.38, whereas the 4-year DFS of the no-treatment arm of the first ISG trial was 0.37.⁶ At the end, the HT group had better results than initially detected (5-year DFS, 0.47), suggesting some effect of HT per se, and this affected the advantage in DFS more than the advantage in OS in favor of A+I at this final analysis. Thus, this trial cannot be interpreted as a formal proof that neoadjuvant chemotherapy is effective as such. Furthermore, the trial was originally designed with a one-sided superiority test, meaning that the alternative hypothesis of superiority of the A+I arm was not contemplated.

Because the switch to the two-sided test was dictated by the results of the interim analysis, caution is needed in the interpretation of hypothesis testing. However, various considerations, including the consistency of the differences in the various analyses and the coherence between the DFS and OS figures reported in our study and in other similar studies,⁵⁻⁷ support the validity of our findings.

Of note, randomization was not stratified by histologic subtype. As a result, as shown in Table 1, the distribution of subtypes was not balanced between the two study arms, with sizably more HG-MLPS and fewer UPS cases in the A+I arm, which may partially explain the observed differences in the survival outcome.

However, it is worth noting that the DFS and OS figures of A+I in the three ISG subsequent trials were superimposable: DFS values were 0.50,^{6,7} 0.57,⁸ and 0.55, respectively, and OS values were 0.69,^{6,7} 0.70,⁸ and 0.76, respectively, at 5 years, suggesting these are the figures that new treatment modalities or agents will have to compare with, provided the study population is truly high risk.

Recently, the largest and negative adjuvant trial (EORTC-62931²⁴) was revisited. Patients were stratified by the predicted OS, using a validated nomogram.²³ The analysis²⁵ showed how the study population was marked by a median predicted OS $> 70\%$. When a cutoff of 60% was used, patients with a predicted OS $< 60\%$ had a significant benefit in DFS and OS by the administration of adjuvant chemotherapy.

Similarly a non-prespecified subgroup analysis using the same predictive nomogram²³ to stratify baseline risk of patients enrolled in this trial suggested the benefit in favor of A+I may be higher when the baseline risk is higher. Interestingly, the proportional (not only the absolute) risk

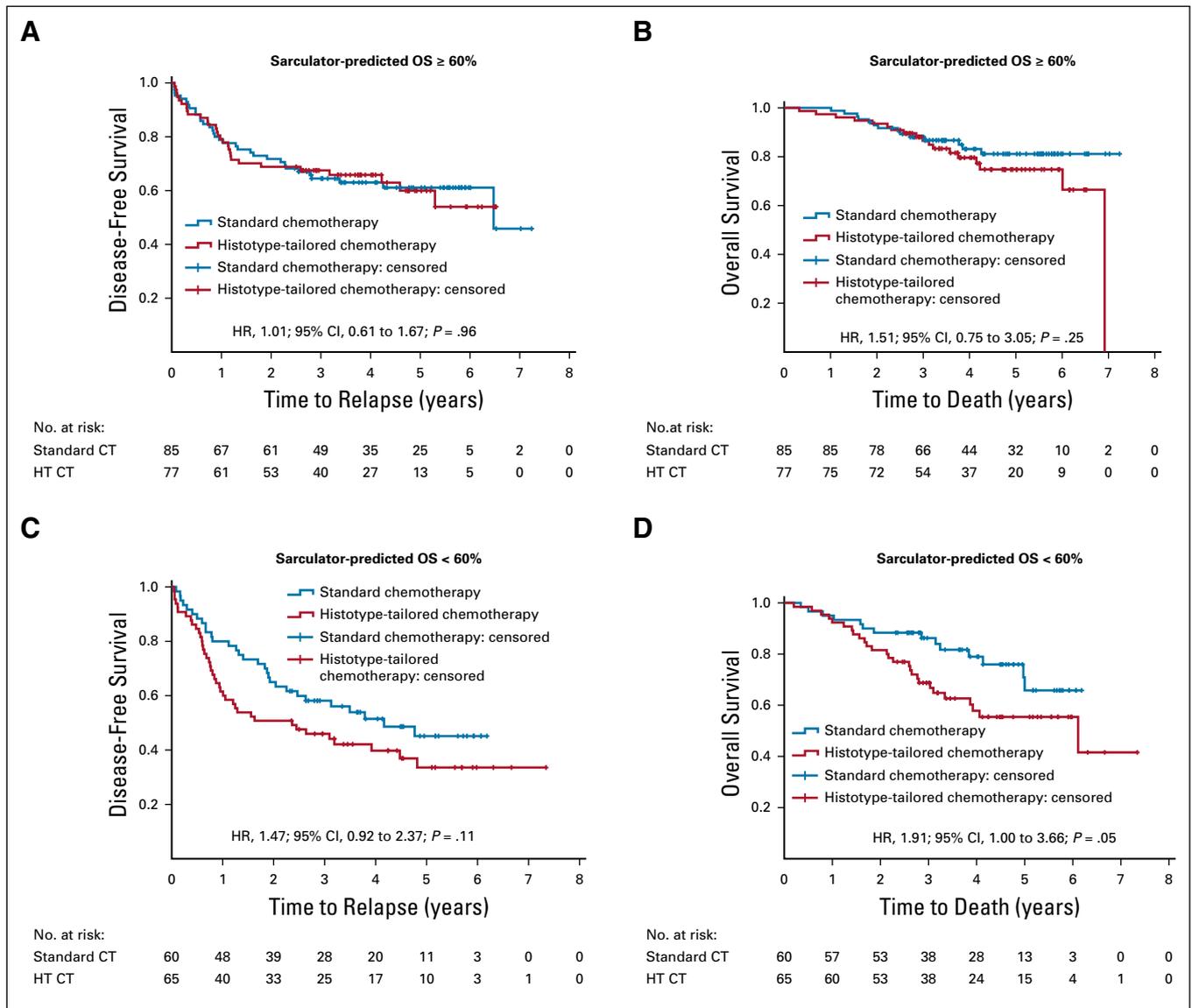


FIG 3. Graphs of (A) disease-free survival and (B) overall survival of standard (anthracycline plus ifosfamide) versus histotype-tailored (HT) chemotherapy (CT) in patients with Sarculator-predicted OS \geq 60%. (C) Disease-free survival and overall survival of standard versus HT chemotherapy in patients with Sarculator-predicted OS < 60%. HR, hazard ratio.

reduction of the administration of chemotherapy looks lower when the baseline risk is lower.¹ One may hypothesize that adjuvant or neoadjuvant chemotherapy should be reserved for patients with STS with a high baseline risk (a cutoff of 40% risk was selected). Clearly, a higher risk corresponds, on average, to a higher malignancy grade and, thus, potentially, to a higher efficacy of chemotherapy.

In this trial, RT was predominantly performed postoperatively. In the previous trial, it was done preoperatively in more than half of patients.⁸ Assuming free surgical margins as an indicator, their proportion was higher in the previous trial and lower in the latter (R0 resections were obtained in 90% of the patients in the previous trial, v 80% in this latter one). We previously showed that the preoperative combination of A+I

with RT is feasible²⁶ and apparently offsets the adverse impact of positive surgical margins.²⁷ In the end, one should not overlook the local impact of preoperative treatments. In other words, although the primary aim of neoadjuvant chemotherapy in operable patients is systemic, a local benefit is likely to occur at least in a proportion of patients. Function preservation may well be part of this benefit.

In this trial, we conceived HT regimens without anthracyclines. In the end, this trial shows that anthracyclines are still an important component of chemotherapy of STS in the eligible histologic subtypes. Even for this reason, we would not conclude that any HT was proven inferior, because HT regimens could have well included an anthracycline. As a matter of fact, HT is widely used in the advanced setting of

STS and in a subgroup, such as LMS, probably the best regimen might combine an anthracycline with dacarbazine.²⁸

In addition, after the third futility analysis, a decision to continue recruitment in the cohort of MLPS was made to test the hypothesis of a possible equivalence between trabectedin and A+I. Trabectedin is combinable with RT²⁹ and this could well become an alternative to anthracycline-based chemotherapy in HG-MLPS. Recruitment of the expansion of this cohort will be completed in June 2020.

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In conclusion, current clinical practice guidelines state that adjuvant or neoadjuvant chemotherapy in adult patients with high-risk localized STS is not standard practice, but it is an option to consider in conditions of uncertainty for shared decision-making. With all the aforementioned caveats, we believe the data provided in the final analysis of this trial may support the choice of an anthracycline-based neoadjuvant chemotherapy whenever an adjuvant treatment is considered and the risk of relapse is high.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Neoadjuvant Chemotherapy in High-Risk Soft Tissue Sarcomas: Final Results of a Randomized Trial From Italian (ISG), Spanish (GEIS), French (FSG), and Polish (PSG) Sarcoma Groups**

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