STS 10.01 Synopsis

Amendament 3.1 14Sep2017

Title	LOCALIZED HIGH-RISK SOFT TISSUE SARCOMAS OF THE EXTREMITIES AND TRUNK WALL IN ADULTS: AN INTEGRATING APPROACH COMPRISING STANDARD VS HISTOTYPE-TAILORED NEOADJUVANT CHEMOTHERAPY (ISG-STS 10-01)
Primary objectives	▪ To compare the effect on disease-free survival of full-dose standard chemotherapy with histotype-tailored chemotherapy within the context of an integrated strategy for high risk soft tissue sarcomas typical of the adult.
Secondary objectives	▪ To compare the effect on overall survival of full-dose standard chemotherapy vs histotype-tailored chemotherapy. ▪ To compare the probability of response of standard vs histotype-tailored chemotherapy in the whole population receiving primary chemotherapy. ▪ To determine the objective response rate, as defined by RECIST and Choi criteria induced by preoperative full-dose standard chemotherapy vs tailored chemotherapy in each different histotype. ▪ To determine the pathological response rate induced by preoperative full-dose standard chemotherapy vs tailored chemotherapy in each different histotype. ▪ To study the feasibility of integration of preoperative chemotherapy with preoperative local-regional treatments (radiotherapy). ▪ PET response.
Surrogacy objective	▪ To validate the response to preoperative chemotherapy (both radiological and pathological) as a surrogate endpoint by showing that disease free survival and overall survival depend on response status and are independent of the treatment arm.
Inclusion according Amendament 3	Soft tissue sarcoma of adults, primary or locally recurrent, with histology, belonging to Myxoid-Round Cell Liposarcoma (cellular component >5 %) (Group 1) Or belonging to one of the following for the registration (Group 2): ▪ Leiomyosarcoma ▪ Synovial sarcoma ▪ Malignant Peripheral Nerve Sheat Tumor ▪ Undifferentiated Pleomorphic Sarcoma (ex Malignant fibrous histiocytoma) ▪ Myxofibrosarcoma ▪ Unclassified Spindle Cell Sarcoma ▪ Pleomorphic Liposarcoma ▪ Pleomorphic Rhabdomyosarcoma Or belonging to either group but not being evaluable for response (re-excision after previous inadequate resection or primary definitive surgery) (Group3).

	The histological diagnosis must be made according to the WHO criteria (19) and will have to be centrally reviewed before randomization. 2) High malignancy grade: grade 3 of 3, according to Coindre (20), or grade 2 at biopsy with a radiological evidence of more than 50% of necrosis in the tumor mass. 3) Deep seated extremities, girdles and/or superficial trunk (thoracic or abdominal wall) lesion. 4) Size of primary tumor (visible or previously inadequately resected) $\geq$5 cm at instrumental staging (CT, MRI), or locally recurrent of any size. 5) Age $\geq$ 18 years. 6) ECOG performance status $\leq$1 (21). 7) Adequate bone marrow function: WBC >3.500/mm^3 neutrophil >1.500/mm^3 platelets >150.000/mm^3 hemoglobin >11 g%. 8) Adequate renal (creatinine <1.3 mg%), and hepatic function (bilirubin <1.5 mg% and transaminases <2 x n.v. If ALP > 2.5 x ULN, ALP LF and/or GGT ≤ ULN). 9) Adequate cardiac function (FE $\geq$50%). 10) Signed informed consent. 11) Complete compliance of the participating center with the protocol requirements.
Exclusion Criteria	1) Pregnancy or lactation. 2) Distant metastasis. 3) Other malignancies within past 5 years, with the exception of carcinoma in situ of cervix and basocellular skin cancers treated with eradicating intent. 4) Sarcoma histotypes other than those mentioned in the inclusion criteria. 5) Prior CT and/or RT. 6) Serious psychiatric disease that precludes informed consent or limits compliance. 7) Medical disease limiting survival to less than two years, limiting compliance or which in the physician's opinion might interfere significantly with the toxicity of the treatments. 8) Cardiovascular diseases resulting in a New York Heart Association Functional Status >2 (22). 9) Uncontrolled bacterial, viral or fungal infection. 10) Impossibility of ensuring adequate follow-up. 11) Failure to comply with the requirements of the present protocol leading to exclusion of the participating center.
Study design	This is a prospective, controlled, phase III randomized study comparing full-dose standard chemotherapy with histotype-tailored chemotherapy within the context of an integrated strategy for high risk soft tissue sarcomas typical of the adult **RANDOMIZATION PRIOR AMENDMENT 3.0** **Randomized patients (Group 1)**

	Patients belonging to Group 1 were then randomized to receive standard *versus* histotype-tailored chemotherapy. The randomization was to be performed before starting the first cycle of chemotherapy. The only stratifications was the administration of preoperative radiation therapy or not, for those histological subtypes for which the combination between the HT CT and RT is doable. For each histotype group there were two arms of treatment: **A**: **standard chemotherapy based on full-dose epirubicin + ifosfamide** **B**:**histotype-tailored chemotherapy which differs according to the histotype**. Five different regimens of histotype-tailored chemotherapy have been identified. **B_1:** gemcitabine + docetaxel for histotype **1** **B_2:** trabectedin for histotype **2** **B_3**: ifosfamide for histotype **3** **B_4:** ifosfamide + etoposide for histotype **4** **B_5:** gemcitabine + dacarbazine for histotype **5** **Arm A foresees, in sequence**: ▪ 3 cycles of preoperative chemotherapy with full dose epirubicin + ifosfamide; ▪ adequate surgery of the primary or recurrent tumor, according to the modalities described in the proper paragraph; ▪ radiotherapy according to the indications and modalities described in the proper paragraph. **Arm B_1 forsees, in sequence:** ▪ 3 cycles of preoperative chemotherapy with gemcitabine + docetaxel; ▪ adequate surgery of the primary or recurrent tumor, according to the modalities described in the proper paragraph; ▪ radiotherapy according to the indications and modalities described in the proper paragraph . **Arm B_2 forsees, in sequence:** ▪ 3 cycles of preoperative chemotherapy with trabectedin; ▪ adequate surgery of the primary or recurrent tumor, according to the modalities described in the proper paragraph; ▪ radiotherapy according to the indications and modalities described in the proper paragraph. **Arm B_3 forsees, in sequence:** ▪ 3 cycles of preoperative chemotherapy with high dose continuous infusion ifosfamide; ▪ adequate surgery of the primary or recurrent tumor, according to the modalities described in the proper paragraph; ▪ radiotherapy according to the indications and modalities described in the proper paragraph. **Arm B_4 forsees, in sequence:** ▪ 3 cycles of preoperative chemotherapy with ifosfamide + etoposide; ▪ adequate surgery of the primary or recurrent tumor, according to the modalities described in the proper paragraph; ▪ radiotherapy according to the indications and modalities described in the proper paragraph.

	Arm B_5 forsees, in sequence: ▪ 3 cycles of preoperative chemotherapy with gemcitabine + dacarbazine; ▪ adequate surgery of the primary or recurrent tumor, according to the modalities described in the proper paragraph; ▪ radiotherapy according to the indications and modalities described in the proper paragraph. Radiation therapy was delivered in the post-operative setting, unless otherwise indicated for clinical needs. If the tailored regimen was not combinable with preoperative RT, patients were excluded from group 1 and included in Group 2 (just registration and treatment by conventional chemotherapy). **Registered patients (Group 2)** Patients belonging to Group 2 received conventional chemotherapy as detailed for Arm A. Radiation therapy was deliverable either in the preoperative or in the post-operative setting. Patients belonging to Group 1 but needing preoperative radiotherapy, not combinable with the tailored regimen, were excluded from the randomization: they were registered and simply treated by standard CT (Arm A), as reported above. **Patients included after definitive surgery (Group 3)** Patients already undergone definitive surgery received all treatment in the post-operative setting. Patients needing a re-excision after inadequate surgery were allowed to receive the treatment as patients in group 1 and 2, but were not evaluable for response. If by histology belonging to group 1, they were randomized to receive either standard chemotherapy (Arm A) or histology tailored chemotherapy (Arm B). If belonging to group 2, they were registered and treated by standard chemotherapy as in Arm A. Radiation therapy was delivered in the post-operative setting as appropriate **RANDOMIZATION ACCORDING AMENDMENT 3.0** According to the results of the 3rd futility analysis carried out on May 10th 2016 it is not ethically acceptable to enroll additional patients into the original study, due to the presence **of a significantly worse DFS and OS in the experimental arm.** However, a strong rationale (ref) suggests the efficacy of the experimental therapy (trabectedin) in the Myxoid Liposarcoma subgroup. While confirming a markedly reduced toxicity of this regimen as compared to the standard, the analysis support the hypothesis of an equivalent efficacy. As a consequence, patients with a histological diagnosis of Myxoid liposarcoma with hypercellularity (round cell MLPS) (cellular component > 5 %) will be randomized to receive either standard chemotherapy (Arm A) or trabectedin (Arm B2). All patients with other histotypes they will be registered and treated by standard chemotherapy as in Arm A. Radiation therapy will be also delivered in the post-operative setting as appropriate.

Randomized patients (Group 1)

Myxoid liposarcoma with hypercellularity (round cell MLPS) (cellular component > 5 %)
will be randomized to receive standard (Arm A) versus histotype-tailored chemotherapy (Arm B2)

A: standard chemotherapy based on full-dose epirubicin + ifosfamide
B2: trabectedin

Registered patients (Group 2)

Patients with the following histotypes:

Undifferentiated pleomorphic Sarcoma (ex MFH)
Synovial sarcoma
Malignant Peripheral Nerve Sheath Tumor (MPNST)
Leiomyosarcoma
Myxofibrosarcoma
Unclassified Spindle Cell Sarcoma
Pleomorphic Liposarcoma
Pleomorphic Rhabdomyosarcoma

will registered into the study and will received conventional chemotherapy (Arm A)

Arm A: standard chemotherapy based on full-dose epirubicin + ifosfamide

Radiation therapy will be delivered either in the preoperative or in the post-operative setting.

Patients included after definitive surgery (Group 3)
Patients already undergone definitive surgery received all treatment in the post-operative setting. Patients needing a re-excision after inadequate surgery were be allowed to receive the treatment based according their histotypes but will not be evaluable for response.

If by histology is **Myxoid liposarcoma with hypercellularity (round cell MLPS) (cellular component > 5 %)** they will be randomized to receive either standard chemotherapy (Arm A) or trabectedin (Arm B2).

If belonging to other histotypes they will be registered and treated by standard chemotherapy as in Arm A.
Radiation therapy will be also delivered in the post-operative setting as appropriate.

Arm A foresees, in sequence:
- 3 cycles of preoperative chemotherapy with full dose epirubicin + ifosfamide;
- adequate surgery of the primary or recurrent tumor, according to the modalities described in the proper paragraph;

	▪ radiotherapy according to the indications and modalities described in the proper paragraph. **Arm B_2 forsees, in sequence:** ▪ 3 cycles of preoperative chemotherapy with trabectedin; ▪ adequate surgery of the primary or recurrent tumor, according to the modalities described in the proper paragraph; radiotherapy according to the indications and modalities described in the proper
Statistical Design and Sample Size	Based on considerations regarding the lower toxicity associated with the use of Trabectidine and the clinical relevance of DFS endpoint, the non-inferiority margin has been set at a HR of relapse = 1.25, corresponding, for example, to an absolute decrease in the projected probability of DFS at 3 years from 70% to 64%. To this aim, a Bayesian monitoring approach will be used. The (posterior) probability that the true HR is ≥1.25 will be continuously updated, using as prior the probability distribution of the HR computed on the first 64 patients with 8 events. Randomization may continue until the (posterior) probability that the true HR is higher than 1.25 will be greater than 80% or smaller than 5%. In the first instance, which is equivalent to stopping a study for futility, Trabectidine will be confirmed to be less effective than standard chemotherapy. In the second instance, the hypothesis of inferiority will be rejected and Trabectidine will be declared not inferior to standard chemotherapy. As a consequence, the present trial has no fixed sample size, and, in theory, randomization might continue indefinitely (unless external circumstances occur, such as, for instance, new promising drugs become available for trial). The results of this analyses will be submitted yearly to the IDMC. Considering the rate of accrual (64 ML patients) and of events (8 relapses/deaths) recorded so far during the 5 yrs duration of this trial, it can at best be projected that during the next 5 years a similar number of patients will be randomized and 20-24 events will be observed (8 among the newly randomized patients and 12-16 among the previously randomized patients). As a consequence, with a total of 28-32 events, the estimated HR will have a Confidence Interval equivalent to the point estimated multiplied/divided by 2. For instance, if the observed HR is 0.9 (favouring trabectedine) the confidence interval will be 0.45-1.8 (insufficient to reject the null hypothesis of inferiority). Inclusion in the prior of external evidence may be helpful to reduce this uncertainty, but it is clear that it will be possible to stop the trial only if extreme results are observed in favour or against trabectidine. Yet, this trial will provide much more robust evidence than presently available on which treatment decisions in these patients can be based, while allowing to stop randomization timely should it become unacceptable from an ethical viewpoint
Staging and tumor assement procedure	**Staging procedures before study entry (Group 1-3)** 1) Physical examination with measurement in cm of at least the largest tumor diameter and definition of the site, anatomical compartment, margins, mobility, consistency, relationship with vessel, nerve and bone structures, presence of satellite lymph

	node involvement 2) Conventional and dynamic contrast enhanced MRI (contrast enhanced CT only if MRI is contraindicated) of local lesion with evaluation of tumor extension and necrosis 3) Chet and upper abdomen CT scan with contrast 4) Total body bone scintigraphy in case of clinical suspiction 5) PET or PET/CT(optional) 6) 6) Double Contrast Enhanced Ultrasoun of local lesion (optiona) **Tumor assessment after 1 cycle of CT (just before the 2nd cycle) (Group 1-2)** 1) Conventional and dynamic contrast enhanced MRI (contrast enhanced CT only if MRI is contraindicated) of local lesion with evaluation of tumor extension and necrosis 2) PET or PET/CT if performed before study entry. 3) Double Contrast Enhanced Ultrasound of local lesion if performed before study entry **Staging and tumor assessment before surgery (Group 1-2)** 1) Physical examination with measurement in cm of at least the largest tumor diameter and definition of the site, anatomical compartment, margins, mobility, consistency, relationship with vessel, nerve and bone structures, presence of satellite lymph node involvement. 2) Conventional and dynamic contrast enhanced MRI (contrast enhanced CT only if MRI is contraindicated) of local lesion with evaluation of tumor extension and necrosis 3) Chest and upper abdomen CT scan with contrast 4) Total body bone scintigraphy in case of clinical suspicion. 5) Double Contrast Enhanced Ultrasound of local lesion if performed before study entry
Translational Research	Frozen material as well as formalin-fixed paraffin embedded material will be made available for translational research provided specific IRB is obtained. Areas of research will include identification and validation of the potential predictive markers for each histological subgroups and attention will be posed on the analysis of the immune contexture and on its interaction with the different chemotherapy regimens Investigation of potential novel therapeutic targets will be also one of the aims of the transitional research (TR) program. Genomic, epigenomic and proteomic approaches will be used. Molecular techniques will be applied whenever relevant, including expression profiling and ex vivo investigations of drug sensitivity. Molecular analysis of methylation of *MGMT* promoter will be performed on those specimen belonging to patients treated with alkylating agents to assess its predictive value. TR program will include storage of paraffin embedded material as well frozen material both from pre and post chemotherapy specimen. TR program will focus of prospective validation of the CINSARC prognostic signature. As well as on identification of new prognostic/predictive signatures. Specific genomic and/or expression profiles will also be investigated in each of the five histotypes if numerous enough. When feasible a tissue microarray (TMA) will be generated from both pre and post chemotherapy material. TMA will be used for testing immunohistochemically candidate markers in the perspective of investigating the main mechanisms of tumor progression, namely: resistance,cell cycle regulatory proteins, angiogenesis, metastasis/invasion markers and senescence markers.