

# Synopsis

**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

## Objectives

### Primary objectives

- To compare the effect on disease-free survival of full-dose standard chemotherapy vs 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 full-dose standard chemotherapy vs histotype-tailored chemotherapy
- To determine the objective response rate, as defined by RECIST and Choi criteria, induced by preoperative full-dose standard chemotherapy vs histotype-tailored chemotherapy in each different histotype
- To determine the pathological response rate induced by preoperative full-dose standard chemotherapy vs histotype-tailored chemotherapy in each different histotype
- To study the feasibility of combining preoperative chemotherapy and local-regional treatments (radiotherapy)
- To evaluate the potential role of PET in predicting the response to chemotherapy in the neoadjuvant setting

### Surrogacy objective

- To validate the response (both radiological and pathological) to preoperative chemotherapy as a surrogate endpoint of DFS and OS

## Eligibility

### Inclusion criteria

- 1) Soft tissue sarcoma of adults, primary or locally recurrent, with spindle-cell or pleomorphic histology, belonging to one of the following for the randomization (Group 1):
  - Myxoid-round cell liposarcomas (cellular component >5 %)
  - Leiomyosarcoma
  - Synovial sarcoma
  - Malignant peripheral nerve sheath tumor (MPNST)
  - Undifferentiated pleomorphic sarcoma (ex MFH)

Or belonging to one of the following for the registration (Group 2):

- 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 and will have to be centrally reviewed before randomization

- 2) High malignancy grade: grade 3 of 3, according to Coindre, 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  $\leq 1$
- 7) Adequate bone marrow function:
  - WBC  $> 3.500/\text{mm}^3$
  - neutrophil  $> 1.500/\text{mm}^3$
  - platelets  $> 150.000/\text{mm}^3$
  - hemoglobin  $> 11$  g%
- 8) Adequate renal (creatinine  $< 1.3$  mg%) and hepatic function (bilirubin  $< 1.5$  mg% and transaminases  $< 2 \times \text{n.v.}$  If ALP  $> 2.5 \times \text{ULN}$ , ALP LF and/or GGT  $\leq \text{ULN}$ )
- 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  $> 2$
- 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.

The randomization will be performed in five histotype's groups (representing 80% of the cases) identified as follows (**Group 1**):

1. Undifferentiated pleomorphic sarcoma (ex MFH)
2. Myxoid liposarcoma with hypercellularity (round cell MLPS) (cellular component > 5%)
3. Synovial sarcoma
4. Malignant peripheral nerve sheath tumor (MPNST)
5. Leiomyosarcoma

The two arms of treatment are:

**A. Standard chemotherapy based on full-dose epirubicin + ifosfamide**

**B. Histotype-tailored chemotherapy which differs according to the histotype:**

**B<sub>1</sub>:** gemcitabine + docetaxel for histotype 1

**B<sub>2</sub>:** trabectedin for histotype 2

**B<sub>3</sub>:** ifosfamide for histotype 3

**B<sub>4</sub>:** ifosfamide + etoposide for histotype 4

**B<sub>5</sub>:** gemcitabine + dacarbazine for histotype 5

**Arm A foresees, in sequence:**

- 3 cycles of preoperative chemotherapy every 21 days with full dose epirubicin 60 mg/m<sup>2</sup>/day, days 1 and 2 + ifosfamide 3 g/m<sup>2</sup>/day, days 1, 2, 3;
- adequate surgery of the primary or recurrent tumor;
- radiotherapy.

**Arm B<sub>1</sub> foresees, in sequence:**

- 3 cycles of preoperative chemotherapy every 21 days with gemcitabine 900 mg/m<sup>2</sup> on days 1 and 8 and docetaxel 75 mg/m<sup>2</sup> on day 8;
- adequate surgery of the primary or recurrent tumor;
- radiotherapy.

**Arm B<sub>2</sub> foresees, in sequence:**

- 3 cycles of preoperative chemotherapy every 21 days with trabectedin 1.3 mg/m<sup>2</sup>/day;
- adequate surgery of the primary or recurrent tumor;
- radiotherapy.

**Arm B<sub>3</sub> foresees, in sequence:**

- 3 cycles of preoperative chemotherapy every 28 days with high dose continuous infusion ifosfamide 14 g/m<sup>2</sup>, given in 14 days;
- adequate surgery of the primary or recurrent tumor;
- radiotherapy.

**Arm B<sub>4</sub> foresees, in sequence:**

- 3 cycles of preoperative chemotherapy every 21 days with ifosfamide 3g/m<sup>2</sup>/day, days 1, 2, 3 + etoposide 150 mg/m<sup>2</sup>/day, days 1, 2, 3;
- adequate surgery of the primary or recurrent tumor;
- radiotherapy.

**Arm B<sub>5</sub> foresees, in sequence:**

- 3 cycles of preoperative chemotherapy every 14 days with gemcitabine 1800 mg/m<sup>2</sup> on day 1 and dacarbazine 500 mg/m<sup>2</sup> on day 1;
- adequate surgery of the primary or recurrent tumor;

- radiotherapy.

Radiation therapy will be delivered in the post-operative setting, unless otherwise indicated for clinical needs.

If the tailored regimen was not combinable with preoperative RT, patients will be excluded from group 1 and included in Group 2.

The following histotypes will also be included and registered, but treated only by standard chemotherapy (**Group 2**):

- a. Myxofibrosarcoma
- b. Unclassified spindle cell sarcoma
- c. Pleomorphic liposarcoma
- d. Pleomorphic rhabdomyosarcoma

Patients belonging to Group 2 will receive conventional chemotherapy as detailed for Arm A. Radiation therapy will be delivered either in the preoperative or in the post-operative setting. Group 1 patients, who need preoperative radiotherapy, that could not be associated with the specific tailored regimen, will be excluded from the randomization. They will be registered and simply treated by standard CT (Arm A), as reported above.

Patients already undergone definitive surgery will receive all treatment in the post-operative setting and patients needing a re-excision after inadequate surgery will be allowed to receive the treatment as patients in group 1 and 2, but will not be evaluable for response (**Group 3**). If by histology belonging to group 1, they will be randomized to receive either standard chemotherapy (Arm A) or histology tailored chemotherapy (Arm B). If belonging to group 2, they will be registered and treated by standard chemotherapy as in Arm A. Radiation therapy will also be delivered in the post-operative setting as appropriate.

**Number of patients**

350 patients will be randomized over a 3-years period, from a pool of 500 registered patients.

**Staging and tumor assessment procedures**

**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) Chest and upper abdomen CT scan with contrast
- 4) Total body bone scintigraphy in case of clinical suspicion
- 5) PET or PET/CT (optional)
- 6) Double Contrast Enhanced Ultrasound of local lesion (optional)

**Tumor assessment after 1 cycle of CT (just before the 2<sup>nd</sup> 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) PET or PET/CT if performed before study entry.
- 6) 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. 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.

### **Statistical analysis**

The histotype-tailored approach is considered clinically worthwhile if associated, overall, with a 1/3 reduction in the hazard of relapse (HR=0.667), corresponding, for instance, to a reduction in the long term risk of relapse from 40% to 27%. In order to assess such an effect with 80% power at the 5% (1-sided) significance level, 150 events (relapses or deaths) need to be observed. It is expected that the study will be able to recruit approximately 350 patients over a 3-years period, from a pool of 500 registered patients. The final analysis will take place after the observation of the 150th event, which should occur 4-5 years after the recruitment of the 1st patient.

A crucial question in this study relates to the possible different effect of histotype-tailored chemotherapy, as compared to standard chemotherapy, in different histotypes. First, a standard subgroup analysis according to histotype will be conducted, based on the tests for histotype-by-treatment interaction and on the inspection of the appropriate Forrest plot. It is acknowledged that, due to the limited sample size and to the rarity of some of the subgroups, this subgroup analyses have very low power.

Second, should the validation study on radiological and pathological response as surrogate endpoints provide positive indications, response rate will be modeled as a binary variable and by means of a logistic regression model the interaction between treatment arm and histological subtype will be assessed. Due to the well known relationship between the effects of a treatment on the true and on a surrogate endpoint, this analysis is expected to have much more power than the one based on DFS.

A validation study will evaluate overall tumor response (both radiological and pathological) as a surrogate of DFS/OS. The present randomized trial is largely underpowered for a formal validation study according to Prentice's criteria. However, the currently available evidence indicating the validity of tumor response as a surrogate of DFS/OS in various solid tumors, provides the ideal setting for developing and applying an original approach to surrogate endpoints validation based on Bayesian concepts.

No interim analysis is planned with the aim to stop patients' accrual in the presence of positive results (demonstration of superiority of histotype-tailored), because of the extremely low power of these analyses in this generally underpowered study. Conversely, yearly interim futility analyses will be conducted to assess if the study hypothesis that histotype-tailored chemotherapy is associated with a 1/3 reduction in the hazard of relapse is still viable, both in the overall randomized population and in each histological subgroups. It is useful to underline that these analyses do not affect that type I error level, and therefore do not require any correction of the significance level. These analyses will focus both on the relapse-free survival and on the response rate, and will be based on the Bayesian methodology described by Parmar.

Due to the small numbers involved, it is expected that the study will be stopped for futility only in the presence of evidence supporting inferiority (though not significantly so) of the histotype-tailored as compared to standard chemotherapy in the whole study or in a specific subgroup, and as a consequence, these futility analyses can be considered equivalent to safety analyses.