

EORTC-STBSG Study **1809 (STRASS 2)**

A randomized phase III study of neoadjuvant chemotherapy followed by surgery versus surgery alone for patient with High Risk RetroPeritoneal Sarcoma

Study coordinator: **Alessandro Gronchi**

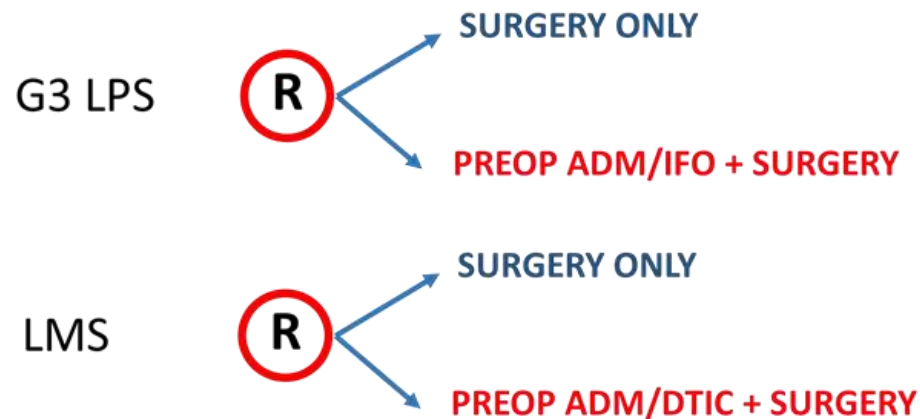
Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy

Study co-coordinator: **Winan van Houdt**

The Netherlands Cancer Institute-Antoni Van Leeuwenhoekziekenhuis, Amsterdam, the Netherlands

Study design

Phase III open label multicenter international clinical trial aiming to assess whether preoperative chemotherapy, as an adjunct to curative-intent surgery, improves the prognosis of high risk DD LPS and LMS patients



Main inclusion criteria

- LMS
 - Grade 2 and 3
 - Size >5cm
- Dedifferentiated LPS
 - Grade 3
 - Grade 2
 - With necrosis on imaging when no necrosis on biopsy
 - With a high cinsarc profile

Study treatment

Control arm:

Large en-bloc curative intent surgery within 4 weeks following randomization

Experimental arm:

- 3 cycles of neoadjuvant chemotherapy starting within 2 weeks from randomization:
 - High grade LPS: ADM 75 mg/m² (or the equivalent EpiADM 120mg/m²) + Ifosfamide 9g/m² Q3 weeks
 - LMS: ADM 75 mg/m² + DTIC 1g/m² Q3 weeks
- Re-assessment of operability
- Large en-bloc curative intent surgery within 3-6 weeks of last cycle of chemotherapy

Study endpoints

➤ Primary endpoint

- Disease free survival (from registration) will include all events progression on neoadjuvant treatment, non-operable tumors, distant metastases and/or local recurrence.

➤ Secondary endpoints

- **Radiological response at time of surgery (post-C3, POST C1 taken out)**
- Pathological response
- Recurrence free survival
- Overall survival
- Metastases-free survival
- Safety and toxicity of neoadjuvant chemotherapy
- Perioperative complications
- Late complications
- Health-Related Quality of life (EORTC QLQ-C30)

Imaging

Primary and some secondary endpoints are imaging based

→ RECIST 1.1 assessment based on 3 monthly contrast enhanced CT scans of thorax, abdomen and pelvis.

Exploratory endpoints might include (not mandatory):

- a comparison of RECIST vs CHOI response
- TBC: response evaluation with MRI, PET-MRI, PET-CT

Quality of Life

QoL assessment will be done by mean of a new questionnaire specific for patients suffering from sarcoma.

The questionnaire will be developed based on the EORTC QLQ-C30 with the addition of specific items.

The questionnaire development and the QoL assessment description in the STRASS-2 protocol will be coordinated by Olga Husson with the support of the QoL unit at EORTC.

Translational research (1)

***To be further defined based on available funding –
tissue samples and blood to be stored in local biobank
for future projects***

Study duration

- 5.5 years enrollment (250 patients)
- 1,5 years FU
- Patients not enrolled in the trial need to be entered into RESAR

Interim analysis

- Two interim looks for futility are foreseen in this design
 - one after approximately 40% of events have occurred (around 4 years after first patient in)
 - one after approximately 66.7% of events have occurred (around 5 years after first patient in).

Study duration

- 5.5 years enrollment (250 patients)
- 1,5 years FU

Current status and timelines

2019

- **Outline v2.0 released:** 28-Jan-2019

2019

- **Protocol v1.0 released:** July 2019

2019

- **First REG submission:** August 2019

2019

- **CFR design and database ready:** November 2019

2019

- **First site active:** December 2019

International collaboration

- Legal sponsor in Europe: EORTC
 - EORTC managing data, general safety event reporting and communication
 - Multi-disciplinary steering committee being formed including surg-oncs, med-oncs, radiologists, pathologist, basic scientists
- Collaboration with US, Canadian, Australian sites
 - US: Dr. Raut coordinating investigator
 - IND exempt drug study so no
 - Most likely only local IRB approval on an institutional level required
- Potential collaboration with sites in Taiwan, Japan, other?

Budget

Fully academic setting

Budget relatively low: low side compensation fee (1000 euro?)

Study partially funded by the STBSG + negotiations ongoing with:

- Companies (Helsinn, TBD)
- Private charity

!! National grants will be explored in collaboration with the participating investigators per country.

Sub-study on Akynzeo

Akynzeo is a combination agent (netupitant / palonosetron) used in the management of chemotherapy-induced nausea and vomiting and it is administered with dexamethasone.

Chemotherapy regimens administered in the STRASS-2 study are of high emetogenic potential and require a triple antiemetic regimen prophylaxis

The aim of the substudy is to obtain data on the use Akynzeo + dex in this indication
→ awaiting feedback from Helsinn on specific objectives and data to be collected

Participation in the sub-study will be optional for sites

Participating sites will take Akynzeo + dex from the shelf

Thank you!

Translational research (1)

To be further defined based on available funding – tissue samples and blood to be stored in local biobank for future projects

To evaluate molecular tumour characteristics and immune-related features relevant to response

- 1. Evaluate the total mutational burden and correlate with treatment response and outcome*
- 2. Evaluate the role of DNA repair mechanisms in drug resistance and tumour growth*
- 3. Evaluate the role of multi-drug resistance genes in drug resistance*
- 4. Evaluate whether immune cells play a relevant role in treatment response and whether neo-adjuvant treatment could be an immunosensitizer*
- 5. Evaluate the use of liquid biopsies for further analysis on potential biomarkers. This also includes germline analysis for pharmacogenomics*

Interim analysis

- Two interim looks for futility are foreseen in this design
 - one after approximately 40% of events have occurred (around 4 years after first patient in)
 - one after approximately 66.7% of events have occurred (around 5 years after first patient in).
- The stopping boundaries will be calculated using gamma spending function (with $\gamma = -4$) thus allowing a very aggressive stopping rule for futility, as illustrated below by the stopping rules
 - At 40% events: $HR > 1.106$ or a one-sided p-value > 0.647
 - At 66.7% events: $HR > 0.877$ or a one-sided p-value > 0.264