Prospective observational Study of

localized angiosarcoma of any site: ProStars

version 1.0, 1st September 2023

Sponsor
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This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements.

PRINCIPAL INVESTIGATORS

A full list of Investigators will be available as a separate document

PROTOCOL SIGNATURES PAGE

Sponsor: Italian Sarcoma Group ISG ETS
Study Title: Prospective observational Study of localized angiosarcoma of any site: ProStars

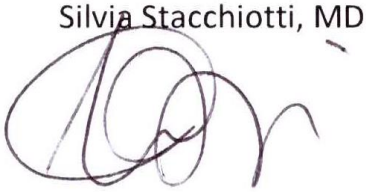
Protocol Version: 1.0

Protocol Date: 01 September 2023

I read this protocol and I accept to conduct this trial in accordance with the protocol stipulations, GCP guidelines and the Declaration of Helsinki.

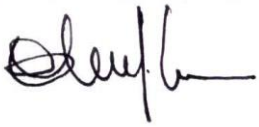
Sponsor Signature:

Silvia Stacchiotti, MD



Investigator Coordinator signature:

Elena Palassini, MD



I have read this protocol and I accept to lead this study following all protocol stipulations, Regulatory Requirements, Good Clinical Practices and adhering to The Declaration of Helsinki.

Site…….

Principal Investigator……

Signature……..

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1. Background

Angiosarcoma (AS) is a malignant vascular neoplasm belonging to the family of mesenchymal tumors, that variably recapitulates the morphological and immunohistochemical features of endothelial cells [Tan PH, 2019].

With an incidence of 2.7/1.000.000/year, AS is a very rare sarcoma. However, it that does not fall into the group of ultra-rare sarcomas, which encompasses sarcomas with an incidence ≤1/1,000,000/year, as recently defined [Stacchiotti S, 2021; de Pinieux G, 2021]. There is a male predominance, with a peak incidence in the seventh decade of life, and a wide age range, although the disease is very rare in children [Lahat J, 2010].

Roughly 60% of ASs arise in the skin and superficial soft tissues, with approximately 50% of cutaneous ASs involving the head and neck region, particularly the scalp [Mark JR, 1996]. Deep soft tissues and breast represent other common sites of origin of AS [Fury MG, 2005]. The remaining ASs can arise from bones and visceral organs such as liver, spleen and heart [Mark JR, 1996].

The etiology is unknown in most cases (primary AS). Nevertheless, in a minority of cases AS may be associated to risk factors such as previous radiation therapy, exposure to vinyl chloride, and chronic lymphedema (secondary AS) [Young RJ, 2010]. Lymphedema-associated AS is also known as Stewart-Treves syndrome. Moreover, a smaller number of ASs occurs in association with implanted foreign materials, in pre-existing vascular malformation, in region of prior trauma or surgery, and in the context of genetic syndromes (e.g. neurofibromatosis and Maffucci syndrome) [Young RJ, 2010].

AS is typically highly aggressive and the prognosis is poor, with a 5-year overall survival (OS) ranging from 30% to 50%, although there is some prognostic variability across presentations [Fayette 2007; Lindet 2013; Lahat 2010; Fury 2005]. The risk of local recurrence is higher than in other sarcomas, ranging from 20% to 40%, and distant metastases may affect lungs, bone, liver and soft tissues, with a possibly higher systemic attitude, e.g. with cases of local regional lymph node metastases (unlike most sarcomas), as well as central nervous system metastases (much rarer in other soft tissue sarcoma histotypes) [Meis-Kindblom JM, 1998].

With regard to prognostic factors, larger tumors (>5 cm) and the presence of an epitheliod component have been associated with a worse outcome [Fayette J, 2007; Lindet C, 2013; Conforti F, 2022; Lahat G, 2010]. As far as grading is concerned, most AS have a high-grade appearance. For those with a low-grade aspect, its prognostic role is controversial, and well-differentiated tumors may still have an aggressive behavior [Morgan MB, 2004; Holden CA, 1987]. In this context, primary breast AS represents the only subgroup of ASs in which the value of grading has been traditionally correlated to prognosis and its prognostic significance has been recently re-assessed [Kuba MG, 2023].

Surgery represents the standard of care in localized AS. Building on the experience of extremity soft tissue sarcomas (STS), radiation therapy is generally added to surgery [Gronchi A, 2021]. However, prospective data on the role of (neo)adjuvant radiation therapy in AS are lacking. In addition, in radiation-associated angiosarcoma (RAAS), out of concern of severe toxicities with re-irradiation, the use of (neo)adjuvant radiation therapy is limited.

With regard to (neo)adjuvant chemotherapy, there are marked variations in practice amongst institutions in this histological type. In STS, (neo)adjuvant chemotherapy is not considered standard treatment, since conflicting results were provided by the several randomized clinical trials performed in the last decades on (neo)adjuvant chemotherapy in STS. However, in the most common STS hystological types of extremities and superficial trunk, there is some evidence that patients at higher risk of death may benefit from (neo)adjuvant chemotherapy with anthracycline and ifosfamide in terms of relapse free survival (RFS) and OS [Frustaci S, 2001; Gronchi A, 2016; Gronchi A, 2020; Pasquali S, 2019; Pasquali S, 2018; Pasquali S, 2022]. On this basis, there is a consensus amongst sarcoma experts that a (neo)adjuvant chemotherapy with anthracycline and ifosfamide for three cycles can be proposed to fit patients with localized STS at higher risk [Gronchi A, 2021]. Considering the high risk of recurrence and the sensitivity to chemotherapy of AS, several sarcoma centers tent to offer a (neo)adjuvant chemotherapy with anthracycline plus ifosfamide to patients with localized AS. However, this policy is not shared by others in the lack of prospective data in AS.

Moreover, in the context of several Italian Sarcoma Group (ISG) centers, in recent years, after the report of intriguing activity and efficacy of paclitaxel and gemcitabine in metastatic AS [Penel N, 2008; Stacchiotti S, 2012], the use of gemcitabine with/without taxanes in the (neo)adjuvant setting in AS was implemented. This is all the more important in patients having a RAAS, who likely have already received anthracyclines for previous cancer. As a result of this policy, in many ISG centers, fit patients with localized AS, in (neo)adjuvant setting receive both the combination of anthracycline and ifosfamide for 3 cycles and the combination of gemcitabine and docetaxel for 3 further cycles. Unfit patients or patients pre-treated with anthracycline for previous breast carcinoma are treated with a gemcitabine-based regimen for 6 cycles, while patients with lower risk of recurrence are treated only with surgery +/- radiation therapy.

Finally, since evidence on the role of (neo)adjuvant chemotherapy in bone AS are even more scarce then in STS, some centres privilege the use of osteosarcoma-like regimens in patients with bone AS.

2. Rationale

The management of localized AS remains a clinical challenge and needs to be better defined and standardized, especially with regards to the role of radiation-therapy and systemic treatment. Several questions about the best treatment approach to some clinical presentations remain open and would need to be answered by clinical studies. Unfortunately, the rarity of this histology among sarcomas makes it challenging to carry out clinical studies in all such presentations. Moreover, prognostic factors are lacking and differences in epidemiological, pathological and clinical aspects between primary AS and secondary AS need to be better characterized.

These issues may be addressed with a prospective multi-institutional observational study, through the collection of clinical and pathological data of patients with localized AS.

Involving all reference centres for sarcoma in Italy, the Italian Sarcoma Group (ISG) will be the ideal network for this study, with the collaboration of the Italian Rare Cancer Network (RTR), a

collaborative network among Italian centres focusing on improving the quality of care of patients with rare tumors.

3. Objectives

This study has the following objectives:

- to provide new data on the natural history of AS of any site and describe prognosis of patients with localized disease, on a relatively large sample of patients, through the collaboration of several Italian centers;
- to identify clinical and pathological prognostic factors, through the correlation of clinical and pathological features of included cases with patient outcome;
- to describe treatment received in localized disease and after recurrences;
- to describe epidemiological, pathological and clinical differences across different sites of origin and different etiologies;
- to generate hypothesis and ideas for future clinical trials.

4. Study design

This study will be a multi-institutional, prospective, observational study of patients with localized primary AS of any site within ISG and RTR centers. Patients will be treated according to clinical practice of the center and according to ISG clinical recommendations on localized AS.

4.1 Clinical assessments and data collection

At baseline the following information will be collected:

- demographic and clinical characteristics of patient, including comorbidities, with a special focus on previous cancer (with details on diagnosis and treatments received);
- clinical characteristics of the tumor: site of origin, size, and multifocality;
- pathological characteristics of the tumor: morphological aspects, proliferative index, tumor cell phenotype, and molecular aspects.

With regard to treatment received for localized disease the following information will be recorded:

- data on surgery: type of surgery, surgical margins, aspects on reconstruction, and post-operative complications according to Clavien Dindo classification;
- data on radiation therapy: setting, dose, dose reductions/interruptions, and related toxicities;
- data on chemotherapy: chemotherapy regimens, setting, number of cycles, doses, dose reductions/interruptions, and related toxicities;
- pathological data on surgical specimen, with the collection of data on residual stainable tumor, necrosis, sclerosis, sclerohyialinosis, and fibrohistiocitic reaction in case of pre-operative treatment;

- radiological and clinical response assessment in case of pre-operative treatments, with the collection of data at baseline, basically every 2 cycles in case of chemotherapy, and before surgery;
- physician's motivation of treatment choice and adherence to clinical recommendations.

Follow-up visit will be visits will be scheduled every 3-6 months. The following information will be collected during follow-up:

- date of last clinical follow-up, date of local recurrence/distant recurrence and site of distant recurrence, status (dead/alive); and date of death;
- data on treatment received for local recurrence and for distant recurrence.

Data will be collected and stored online through an Electronic CRF system, that will run on a secure server and will allow the researchers to enter and store data in an encrypted system. Data will be pseudonymized and no patient identifiable data will be collected.

4.2 Pathological review

A panel of pathologists with recognized experience in STS and bone sarcomas will be set up in order to examine periodically all cases at University of Padova (prof. Paolo dei Tos, prof. Marta Sbaraglia). For this purpose, pathological material from the biopsy and/or from the surgical specimen will be sent to University of Padova.

5. Study population

This study will be addressed to a population of adult and pediatric patients with localized AS, seen at one of the participating centers from ISG and RTR centers. Patient with locally advanced and/or metastatic disease will be excluded. Patient with recurrent disease will be excluded as well.

Eligibility criteria will include:

- pathological diagnosis of AS;
- any site of origin;
- any age;
- primary, localized, resectable disease.

6. Duration of the study and number of patients

An estimated number of 50 patients will be included on yearly basis. The accrual of patients will be open over a 5-year period from the entry of the first patient or until a number of at least 250 patients will be achieved. Follow-up will be extended to additional 5 years. The accrual of the patients will be monitored on yearly basis.

7. Statistical analysis

All analyses will be of descriptive nature and no formal statistical hypotheses will be tested. Continuous variables will be summarized by descriptive statistics (n, missing, mean, standard deviation, minimum, median, interquartile range, maximum) while categorical variables by counts and relative frequencies (%). Percentages for categorical variables will be based on all non-missing values. These descriptive analyses will regard: patient and tumor characteristics, treatment indication, patterns and variation in treatment patterns (i.e., dosing, regimen); treatment-related adverse events and their management; treatment response. Descriptive tables will be presented overall and according to subgroups of interest.

Concerning the survival end-points, OS and RFS curves will be estimated using the Kaplan-Meier method; median OS and RFS time will be derived through the curves together with the 95% two-sided CI. OS and RFS time will be computed from the date of treatment start. Kaplan-Meier curves will be estimated overall and according to subgroups based on putative prognostic factors of interest. Moreover, univariable Cox models will be fitted to study the association between the survival end-points and the putative prognostic factors; multivariable models will be implemented consistently with the number of OS and RFS events, in order to control model overfitting and keep high estimate accuracy.

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