1. REGISTRY SYNOPSIS

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TITLE OF STUDY	*A cooperative investigation of the AIO, ARO and CAO to optimize either neo – or adjuvant treatment strategies adult patients with large sized, high grade non-rhabdomyo (soft tissue) sarcoma (NRSTS)*
CONDITION	*Cancer, Soft tissue sarcoma (non-rhabdomyosarcoma, high grade)*
OBJECTIVE(S)	*Primary:* to examine whether concomitant chemotherapy with doxorubicin and ifosfamide and radiation (RXT) improves disease-free survival for patients with large (>5cm), high grade (G2/3) adult-type soft tissue sarcoma (NRSTS) compared to standard procedures alone (surgery and radiotherapy if applicable). *Secondary:* to examine whether chemoradiation improves overall survival, to establish a close cooperation between pediatric and adult oncologists, radiooncologist and surgeons in order to develop specialised reference and study centres as well as to improve recruitment and evaluation of data in adult type NRSTS, to evaluate prognostic and predictive factors (f.e. age, different subtypes) for treatment failure, to assess short- and long-term toxicity, quality of life (acc. to EORTC QLQ-C30, PEDQOL questionnaire for children).
INTERVENTION (S)	Experimental intervention: neoadjuvant *IFO-DOXO x 3(4) - IFO x 2 + RXT 50.4 Gy** – or adjuvant *IFO-DOXO x 4 - IFO x 2 + RXT 50.4 Gy** (*if indicated/applicable, otherwise IFO-DOXO x 5) Control intervention: historical controls (registry data: patients not treated with chemotherapy (surgery alone and RXT if applicable)
KEY INCLUSION AND EXCLUSION CRITERIA	Key inclusion criteria: Age up to 65 years at date of biopsy histopathologically confirmed NRSTS (R0/I) Size ≥ 5 cm No evidence of metastatic disease No previous treatment except for primary surgery Key exclusion criteria: Low grade (G1)
OUTCOME(S)	Primary efficacy endpoint: Disease-free survival Key secondary endpoint(s): survival, factors for treatment failure, biology of different subtypes of NRSTS, to establish a national cooperation between adult and pediatric oncology groups, medical oncologists, surgeons/orthopaedic surgeons, and radiation oncologists. Assessment of safety: Short- and long-term toxicity (AE, SAE , lab assessment,
STUDY TYPE	*Multi-center, prospective, controlled, cooperative Registry of parallel groups with the intention to optimize therapy for patients with large sized, high grade NRSTS*

STATISTICAL ANALYSIS	Efficacy: Primary endpoint is the disease-free survival (DFS). Description of the primary efficacy analysis and population: Efficacy analysis will be based on the intention to treat [ITT] population. The treatment arm will be compared with historical controls (registry data, patients not treated with neo- or adjuvant chemotherapy) by applying the two-sided Log rank test on the significance level α = 0.05. 274 patients will be assessed for eligibility to get 249 patients. The accrual period will be 2.5 years. The sample size was calculated to achieve a power of 80% to detect a hazard ratio of 1.388, which corresponds to the difference of 65% vs. 55 % DFS 3 years. Secondary endpoints: Multivariate Cox regression model with stepwise variable selection will be applied as an exploratory analysis to study prognostic factors for DFS. As a secondary endpoint the overall survival (ITT – population) will be analysed using the same methods of analysis. Further endpoints will be QOL, frequency of SAE, AE (toxicity).
SAMPLE SIZE	To be assessed for eligibility (n = 274), to be allocated to trial (n = 249), to be analysed (n = 249)
PARTICIPATING CENTERS	AIO – Internistische Onkologie, CAO – Chirurgische AG Onkologie, ARO – AG Radiologische Onkologie of the German Cancer Society and the Cooperative Weichteilsarkom-Studiengruppe (GPOH). Further centers: tbd. (planned no. approx. 25-30).

2. THE MEDICAL PROBLEM

2.1 EVIDENCE

Soft tissue sarcomas are malignant tumors that arise from tissue with mesodermal and rarely (neuro-) ektodermal origin. More than 50 different histological subtypes of soft tissue tumors have been described, which are often associated with unique clinical, prognostic and therapeutic features. The annual clinical incidence of soft tissue sarcoma is around 30/million population, i.e. less than 1 percent of all malignant tumors in adults (predominantly non-rhabbdomyosarcoma/NRSTS) and appr. 8% in children (predominantly rhabdomyosarcoma/RMS). Soft tissue sarcomas may occur anywhere and at any age (*Hartmann, 2005*).

The role of chemotherapy in the treatment of adult and childhood ´so-called´ NRSTS continues to be controversial in pediatric as well as adult oncology community. Several randomized adjuvant chemotherapy trials have been performed over the years in adult type soft tissue sarcomas. At present only a minority of them have shown a significant survival advantage for chemotherapy. Nevertheless, more recent data seem to suggest different considerations. In fact, 14 randomized trials comprising 1,568 adult patients with NRSTS were included in a meta-analysis. This study demonstrated a reduction in the risk of local and distant failures at 10 years in the group treated with intensified doxorubicin-based chemotherapy, with an advantage of 10% in recurrence free survival and of 4% in overall survival (*Sarcoma Meta-analysis Collaboration, 1997).* Moreover, a small Italian randomized trial on adjuvant full-dose doxorubicin + ifosfamide was closed in advance due to an early striking benefit in overall survival in favour of the chemotherapy arm. Long-term results of this trial are still consistent with a benefit *(Frustaci S, 2001)*. This trial has been defined by George Demetri as the first "modern" study on adjuvant chemotherapy in NRSTS (*Demetri, 2002*).

In pediatric patients only a few studies reported data on the efficacy of chemotherapy in NRSTS. These patients were generally treated with the same chemotherapy regimens adopted for RMS (cyclophosphamide/ifosfamide, vincristine, actinomycin D as standard treatment). The role of adjuvant chemotherapy was explored by a POG trial which compared a regimen with cyclophosphamide, vincristine, doxorubicin and actinomycin D to observation. The study failed in its aim because 51 out of 81 patients refused randomization (*Pratt, 1999)*.

Therefore, though adjuvant (neo-)chemotherapy is yet not currently standard treatment for adult soft tissue sarcomas, more hints of efficacy have been provided. Chemotherapy often is suggested in high-risk cases (high grade, large sized) or considered as a shared decision-making in conditions of uncertainty *(Clark MA, 2005).* In particular, the role of chemotherapy seems more relevant if a precise selection of high risk and high grade cases is provided and, moreover, if a higher dose intensity chemotherapy including the most active drugs is delivered.

2.2 THE NEED

Patients with locally advanced NRSTS have been reported to have a 5-year survival rate of less than 50%. The problems to be addressed by AIO/ARO/CAO-CWS-1 are thus the following:
a) Given the low incidence of NRSTS and the results currently achieved, even the largest centers need unacceptably long recruitment periods to complete randomized trials.
- *to be addressed by* National cooperation between adult and pediatric oncology groups, medical oncologists, surgeons/orthopaedic surgeons, and radiation oncologists and by using historical controls as comparator.
b) The results of the published prospective trials apply to a limited subgroup of patients only, especially adult and prediatric patients with NRSTS have always been treated in different protocols.
- *to be addressed by* Extension of eligibility criteria to include adult and pediatric sarcomas and prospective analysis of prognostic factors for the whole cohort.
c) The impact for patients whose high grade, large sized tumors were treated with pre- or postoperative chemoradiotherapy is unknown.
- *to be addressed by* Prospective inclusion of large sized, high grade NRSTS to pre- or postoperative chemoradiotherapy (consisting of ifosfamide plus doxorubicin).
d) No further improvement can be expected from modifications of standard dose chemotherapy for locally advanced NRSTS but half of these patients will still die from their disease.
- *to be addressed by* Dose intensified ifosfamide added to doxorubicin.

3. JUSTIFICATION OF DESIGN ASPECTS

3.1 CONTROL(S)/COMPARATOR(S)

AIO/ARO/CAO-CWS-1 is a controlled clinical trial aiming to optimize sarcoma therapy. Blinding or placebo controls are not feasible due to the setting in which the trial is performed and the drugs used. The results of the trial will be both generalizible and representative. The control group is appropriate as they are derived from a national registry and is therefore representative of the whole cohort. A 1:1 randomisation would prolong the study period up to 8 years despite national wide cooperation.

3.2. INCLUSION CRITERIA

1. Age up to 65 years (64 years + 364 days) at date of biopsy
2. histopathologically confirmed NRSTS (R0/I)
3. Tumor size ≥ 5 cm
4. Neutrophils ≥ 1.5 x 10^9/L (or WBC ≥ 3.0 x 10^9/L, platelet ≥ 100 x 10^9/L
5. Glomular filtration rate according to Cockroft-Gault formula ≥ 50 ml/min
6. Serum bilirubin ≤ 1.5 ULN
7. No evidence of metastatic disease
8. No previous treatment except for primary surgery
9. Maximum of a 6 week interval between the definitive surgical approach and the start of protocol
10. No pre-existing illnesses preventing treatment
11. Sufficient shortening fraction [≥ 28%] and/or ejection fraction [(47%])
12. Adequate performance status (Karnofsky score (60 or WHO (2)
13. Diagnostic material available for pathology review
14. Written informed consent
15. Available for long term follow up

3.2.1 Exclusion criteria

1. Evidence of distant metastases
2. Low grade NRSTS (G1)
3. previous malignancy except of in situ cervical cancer or basal cell cancer of the skin, unless treated with curative intent and without evidence of disease (5 years
4. previous chemotherapy or radiation; recurrent NRSTS is allowed when no previous adjuvant treatment had been applied
5. any medical condition precluding treatment with protocol (f.e. HIV, psychiatric disorders)
6. pregnant or lactating women

3.3 Outcome measures

Primary endpoint is DFS, secondary endpoints are overall survival and toxicity. Events are defined as death or relapse. Toxicity endpoints include renal and cardiac function. In addition, quality of life measures will be introduced as a secondary endpoint. Toxicity will be assessed using the CTCAE 3.0 toxicity scale. Quality of life according to the EORTC QLQ-30 and PEDQOL.

3.4 Methods against bias

In order to deal with assurance of quality and consistency, AIO/ARO/CAO-CWS-1 will form a Coordinating Center for quality matters, located at the Koordinierungszentrum Klinische Studien (KKS) Tübingen, Germany. The office is responsible for the development and implementation of the trial's Quality Assurance Program, including routine monitoring procedures, on-site visits, and adverse events reporting, as well as other good clinical practice techniques. It is responsible for the development of standard operational procedures relating to quality assurance issues, based on the ICH/GCP guidelines and EU directive 2001/20/EC, which are then to be implemented for the trial as a whole.

Data Consistency

Standardized reporting of toxicity will be according to the CTCAE Version 3.0. Data consistency will be checked at the appropriate Trials Centers by comparing information from CRFs with that from pathology reports and surgery reports and submitted progress notes.

Review of Trial Quality Indicators

An IDMC, independent of trial leadership, free of conflicts of interest, will be formed. The main objectives of the IDMC are to ensure that patients in the clinical trial are protected, ensure that evaluation of interim results and decisions about continuing, modifying, or terminating the clinical trial and reporting results are made competently and independently; and ensure that the credibility of clinical trial reports and the ethics of clinical trial conduct are maintained

Issues surrounding accrual, eligibility criteria, and compliance with the protocol will be reviewed during the regular meetings of the IDMC. A CDC and KKS Tübingen will supply the IDMC with all necessary information.

Reference Panels

Panels of each group shall check the protocol for content, consistency and accuracy on all topics (Pathology, Radiology, Surgical, Oncology and Radiotherapy Panel). AIO/ARO/CAO-CWS-1 is served by a number of reference panels. The pathology panel's purpose is to ensure uniform histopathological criteria for admission to the trial. The surgery and radiotherapy panels' purposes are to assess operability and to ensure optimal local treatment for all patients. The radiology panel's purpose is to review imaging studies in order to determine the metastatic status of individual patients.

3.5 PROPOSED SAMPLE SIZE/POWER CALCULATIONS

Sample size calculations for this trial have been calculated using the method of nQuery Advisor 6.0 (Lakatos, 1992). Analysis of DFS is planned to take place three years after the closure of the trial, analysis of OS is planned for four years after closure. Based on the previous experience, 3-year DFS for the standard arm is expected to be 55%. Assuming a two-sided significance level of 5%, 80% power and 100 patients registered per year, it is proposed that 249 patients be included into AIO/ARO/CAO-CWS-1. This will require 274 patients to be registered. Inclusion of 249 patients will allow an increase of 10%, from 55% to 65%, to be detected in 5-year DFS. The total number of events required is 146. Hazard ratio is 1.388.

3.6 FEASIBILITY OF RECRUITMENT

AIO/ARO/CAO-CWS-1 is a collaboration of four national groups within the German Cancer Society involved in clinical research in soft tissue sarcoma: AIO, ARO, CAO and CWS and its associated centers. Each of these centers has experience in participating in large, multi-center studies in the disease. Based on experience in previous trials, the four disciplines and associated centers expect to include approximately 100 patients per year in total. Thus, accrual is expected to take 2.5 years. Further centers will be invited to participate within the trial to a maximum center no. of 25 to 30. Participating investigators/centers must fulfill a set of basic criteria of a AIO/ARO/CAO-CWS-1 Commitment Form.

4. STATISTICAL ANALYSES

Efficacy:

Primary endpoint of the study is the disease-free survival (DFS). DFS will be measured as the time from inclusion to the date of recurrence or the last date the patient was known to be recurrence-free. Efficacy analysis will be based on the intention to treat [ITT] population. The treatment arms will be compared by applying the two-sided Log rank test on the significance level $\alpha = 0.05$.

Secondary analysis:

The multivariate Cox regression model with stepwise variable selection will be applied as an exploratory analysis to study prognostic factors for overall survival and DFS.

Secondary endpoints:

As a secondary endpoint the overall survival (ITT – population) will be analysed using the same methods of analysis. QOL SA and SAE assessment will be reported per treatment arm and analysed

using methods of longitudinal analysis (mixed models). Proportions of patients experiencing grade 3 and 4 toxicities will be compared using chi-square tests or Fisher's exact tests where appropriate.

Sample size:

274 patients will be registered for eligibility to get 249 patients included. The accrual period will be 2.5 years, followed by a 3 years follow-up period. The sample size was calculated to achieve a power of 80% to detect a hazard ratio of 1.388, which corresponds to the difference of 65% vs. 55 %-DFS at 3 years after inclusion.

5. ETHICAL CONSIDERATIONS

AIO/ARO/CAO-CWS-1 will be conducted in full accordance with the Declaration of Helsinki, last revised by 52nd WMA General Assembly, Edinburgh, Scotland, October 2000. Before being activated, the protocol, patient information sheets, and consent forms must have been reviewed and accepted by the appropriate Ethics Committee of the centers.

The Ethics Committee will also be informed about all severe or unexpected adverse events made known to the Chief Investigator. Before entering patients into the trial, clinicians must, therefore ensure that they have ethical approval to participate in the trial according to their national and, where applicable, European laws and regulations. It may be necessary to await the vote of the local Ethical Committee and to inform that board about protocol amendments, adverse events, and termination of the trial, as detailed above.

References

Hartmann, JT and Bauer S. Adult type soft tissue sarcoma - locally advanced and metastatic. Curr Opin Hem Oncol (2005) in press

Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data. Sarcoma Meta-analysis Collaboration. Lancet (1997) 350:1647-54

Frustaci S, Gherlinzoni F, De Paoli A, et al: Adjuvant chemotherapy for adult soft tissue sarcomas of extremities and girdles: results of the Italian randomized cooperative trial. J Clin Oncol (2001) 19:1238-47

Demetri G.D. Highlights of sarcoma research. J Clin Oncol Classic Papers and Current Comments (2002) 7:681-684

Pratt CB, Pappo AS, Gieser P, et al. Role of adjuvant chemotherapy in the treatment of surgically resected pediatric nonrhabdomyosarcomatous soft tissue sarcomas: a Pediatric Oncology Group Study. J Clin Oncol (1999) 17:1219-26

Clark MA, Fisher C, Judson I, et al. Soft-tissue sarcomas in adults. N Engl J Med (2005) 353:701-11

Lakatos, E and Lan KKG. A comparison of sample size methods for the logrank statistic. Statistics in Medicine 1992 11: 179-91