Short Study Report for Health Authorities

Name of Sponsor/Company: EORTC	Individual study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of the finished product: Doxorubicin / Cyclophosphamide / Prednisolone	Volume:	
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Title of the Study	TOLERANCE: a 3 arm randomized study on healTh-related quality Of Life of ElderRly pAtients with advaNced soft tissue sarComa undergoing doxorubicin every three weeks or doxorubicin weekly or cyclophosphamide plus prednisolone treatment EORTC-1976-STBSG-QLG-ETF Protocol version 2.0	

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Investigators & Study Centres

A total of 14 patients were randomized by 9 sites from 5 countries:

Investigator	Insitution	Address	Nbr of patients randomized
Nin Johanna	Academisch Ziekenhuis Maastricht	P. Debyelaan 25 - P.O. Box 5800 NL 6202 AZ Maastricht Netherlands	2
Oosten Astrid	Erasmus MC	Dr. Molenwaterplein 40, PO box 2040 NL 3015 GD Rotterdam Netherlands	1
Sebio Garcia Ana	Hospital De La Santa Creu I Sant Pau	C/ Sant Quintí 89 ES 08041 Barcelona Spain	1
Vaz Salgado Maria Angeles	Hospital Universitario Ramon y Cajal	Carretera de Colmenar Viejo Km 9,100 ES 28034 Madrid Spain	2
Salah Samer	King Hussein Cancer Center	2020 Queen Rania Al Abdullah St. P.O. Box 1269, Al-Jubeiha 11941 Amman Jordan	2
Benson Charlotte	Royal Marsden Hospital - Chelsea, London	Fulham Road 203 GB London SW3 6JJ United Kingdom	2
Lee Alexander	The Christie NHS Foundation Trust	Wilmslow Road GB Manchester M20 4BX United Kingdom	1
van der Graaf Winette	The Netherlands Cancer Institute-Antoni Van Leeuwenhoekziekenhuis	Plesmanlaan 121 NL 1066 CX Amsterdam Netherlands	2
Dileo Palma	University College Hospital	235 Euston Road GB London NW1 2BU United Kingdom	1

Publication (reference)	Not applicable: no publication on the study results is expected due to the premature closure of the trial.

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Phase of development	Phase 3	
Studied period	First patient randomized: 19 July 2022 Last patient enrolled: 4 September 2023 Date of study termination: 22 September 2023 Database lock: 23 February 2024	
Substantial changes to the protocol	*The study protocol was approved on 11 March 2021.* *During the course of the study, one amendment was made which was approved on 7 March 2022. This amendement was implemented to add prednisone as study treatment to allow the use of both prednisone and prednisolone in experimental arm 2.* *In May 2023, only 5 patients had been randomized in the study compared to the expected yearly accrual of 74 patients. At that time, 17 of the anticipated 30 sites were activated. The study was considered to be in a critical state, failing to achieve its accrual target. An action plan was put forward and a survey launched to identify obstacles to recruitment. On September 22nd 2023, the decision was made to close the trial effective immediately and participating sites were informed of the immediate closure of the trial.*	

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Objective(s)	Primary objectives: The primary objective of this study is to assess whether a higher HRQoL, in terms of impact of the disease and its treatment on physical and role functioning, is achieved with metronomic schedules of doxorubicin or cyclophosphamide plus predniso(lo)ne versus the standard doxorubicin treatment. Secondary objectives • To assess whether there is an improvement in quality of life, in terms of impact of the disease and its treatment on social, emotional and cognitive functioning as well as self-reported symptoms and overall quality of life/health perception, among patients treated with metronomic doxorubicin, patients treated with metronomic cyclophosphamide plus predniso(lo)ne and patients treated with standard doxorubicin regimen. • To assess whether there is a difference in the progression free survival, overall survival and tumour response among patients treated with metronomic doxorubicin, patients treated with metronomic cyclophosphamide plus predniso(lo)ne and patients treated with standard doxorubicin regimen. • To assess the toxicity profile of the three treatment arms • To assess the tolerability of the three treatment arms	

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Methodology	This is a multi-centre, open label, randomized phase 3 study (1:2:2 randomization). After confirmation of the eligibility criteria, 185 patients will be randomized 1:2:2 to either - control arm: doxorubicin 60-75 mg/m² IV every 3 weeks - experimental arm 1: doxorubicin 12 mg/m2 IV every week - experimental arm 2: cyclophosphamide tablets 100 mg twice a day (morning and evening) plus prednisolone/prednisone tablets 10 or 20 mg once a day (in the morning), on day 1 to day 7 of each 14 day cycle. HRQoL assessment will be performed every 3 weeks during the first 12 weeks and every 12 weeks thereafter until 1 year after start of treatment. Disease evaluation will be performed every 12 weeks until progression. The primary endpoint of the study is difference among the study arms in physical and role functioning at 12 weeks.	
Number of patients Number planed (Statistical design) Number analysed	Planned: 185 randomized Achieved: 14 randomized	

Diagnosis and main criteria for inclusion	Inclusion criteria • Histologically proven advanced unresectable or metastatic soft tissue sarcoma (STS) • Representative formalin fixed, paraffin embedded tumour blocks or slides, either from the primary tumour or a metastatic lesion, must be available for central review. Note: Local histopathological diagnosis will be accepted for entry into this trial but it is mandatory to collect tumour tissue for retrospective central review of tumour histology and grade. • Age ≥ 65 years of age (patients between 65 and 69 years old are eligible if G8 score ≤ 14; patients ≥ 70 years old are eligible independent of G8 score) • WHO performance status 0 – 2 • Life expectancy based on other significant morbidity of ≥ 6 months • Presence of measurable disease (according to RECIST 1.1), as confirmed by imaging within the 28 days prior to randomization. CT with IV contrast is the preferred imaging modality. In case of any contra-indications (medical or regulatory), it is allowed to perform a non-contrast CT + MRI. • Progressive disease at entry based on RECIST 1.1 • Adequate haematological and organ function assessed prior to randomization • Completion of EORTC QLQ-C30 and EORTC QLQ-ELD14. • Assessment of G8 geriatric screening tool • Before patient registration/randomization, written informed consent must be given according to ICH/GCP, and national/local regulations including commitment to completing questionnaires during the course of the study.
Treatment Test product, dose and mode of administration (batch number if applicable)	**Experimental arm 1** Patients randomized to the experimental arm 1 will be treated with doxorubicin 12 mg/m2 administered weekly intravenously (bolus or short infusion as per local standard practice) for a maximum of 450 mg/m2 until disease progression, unacceptable toxicity, patient's refusal or occurrence of concomitant disease requiring intervention that interferes with the study treatment, whichever comes first.

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	Experimental arm 2 Patients randomized to the experimental arm 2 will be treated with oral cyclophosphamide 100 mg BD (at approximately 8:00 and 19:00) plus prednisolone/prednisone 10 or 20 mg daily (in the morning) on day 1 to day 7 of each 14-day cycle until disease progression, unacceptable toxicity, patient's refusal or occurrence of concomitant disease requiring intervention that interferes with the study treatment, whichever comes first.	
Duration of treatment	See description above	
Reference therapy, dose and mode of administration (batch number if applicable)	**Control arm** Patients randomized to the control arm will be treated with doxorubicin 60 to 75 mg/m² administered intravenously every 3 weeks (short or continuous infusion as per local standard practice) for a maximum of 6 cycles or until disease progression, unacceptable toxicity, patient's refusal or occurrence of concomitant disease requiring intervention that interferes with the study treatment, whichever comes first.	
Criteria for evaluation		

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Efficacy	Difference in physical and role functioning at 12 weeks. • Physical functioning (PF) is one of the functional scale scores of the EORTC QLQ-C30 questionnaire. The scale score is based on the mean score of 5 items measuring patients' self-reported ability to perform physical activities. The scale score can range from 0-100 with higher scores indicating better functioning. • Role functioning (RF) is one of the other functional scale scores of the EORTC QLQ-C30 questionnaire. The scale score is based on the mean score of 2 items measuring patients' self-reported ability to perform daily tasks related to household, work or recreation. The scale score can range from 0-100 with higher scores indicating better functioning. Secondary endpoints(s): • Difference in all other EORTC QLQ-C30 scales at 12 weeks • Sensitivity: Difference in physical and role functioning at 24 weeks • Difference in progression free survival (PFS) at 12 weeks according to the RECIST 1.1 • Other efficacy: PFS, overall survival (OS), tumour response (RECIST 1.1) • Tolerability: treatment discontinuation, delay and/or reduction.	
Safety	Safety: Adverse Events (AEs) according to CTCAE v5.0	

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Statistical methods	Each experimental arm will have demonstrated superiority to the control arm if it shows superiority in at least one of the two primary scales: PF or RF. A superiority test will be performed by fitting a mixed-model-repeated-measures (MMRM) to the ITT population. Each MMRM will include treatment, a time effect, a time-treatment interaction, the baseline score, as well as age and gender as fixed effects and a patient specific random effect fitted. The main test will be obtained by contrasting the scores in the two treatment arms at week 12 (F-test). For this test, HRQoL data will be limited to those questionnaires completed prior to starting any post-protocol anti-cancer therapy. The estimated mean scores per treatment arm and the control arm will be presented together with associated 95% confidence interval. Graphs will display the mean score by treatment group with their 99% confidence intervals. In addition, the proportion of patients achieving a clinical relevant change from baseline at week 12 will also be summarized. The primary tests will be repeated on the per-protocol population to assess the robustness of the results with respect to eligibility and/or protocol deviations. In addition, the primary tests will be repeated including all HRQoL data (i.e., including data collected after start of further anti-cancer therapy). Randomization will be stratified according to: Institution, Baseline QLQ-C30 physical functioning score (≤80 vs > 80), Baseline QLQ-C30 role functioning score (≤80 vs > 80).	

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<tr><td>Summary of Results
Efficacy Results</td><td colspan="2">At the time of database lock (23 February 2024), only 14 patients out of the planned 185 were randomized (ie. 7.6%) between 19 July 2022 (first patient randomized) and 4 September 2023 (last patient randomized). The 14 patients were allocated as follows:
- 3 in Control arm: doxorubicin 60-75 mg/m² IV every 3 weeks
- 5 in Experimental arm 1: doxorubicin 12 mg/m2 IV every week
- 6 in Experimental arm 2: cyclophosphamide tablets 100 mg twice a day plus predniso(lo)ne tablets 10/20 mg once a day, on day 1 to day 7 of each 14 day cycle.

The trial was closed prematurely due to the low accrual rate. Due to the limited number of patients randomized and the incomplete data cleaining, no formal analyses can be done on the data.

A total of three deaths were observed: 1 in the control arm and 2 in the experimental arm 1. However, it should be noted that follow-up for the patients in this study was very limited due to closure for poor accrual.</td></tr>
<tr><td>Safety Results</td><td colspan="2">Ony one AE related to study treatment was reported, which was in the control arm.</td></tr>
<tr><td>Conclusions</td><td colspan="2">At time of study closure, efficacy and safety data reported in the EORTC study database were very limited. No reliable conclusions can be drawn from this study.</td></tr>
<tr><td>Date of Report</td><td colspan="2">28 May 2025</td></tr>
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