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Schoffski, P.; Toulmonde, M.; Estival, A.; Marquina, G.; Dudzisz-Sledz, M.; Brahmi, M.; ... ; Gelderblom, H.

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Randomised phase 2 study comparing the efficacy and safety of the oral tyrosine kinase inhibitor nintedanib with single agent ifosfamide in patients with advanced, inoperable, metastatic soft tissue sarcoma after failure of first-line chemotherapy: EORTC-1506-STBSG "ANITA"

Patrick Schöffski [a,b,*], Maud Toulmonde [c], Anna Estival [d], Gloria Marquina [e], Monika Dudzisz-Śledź [f], Mehdi Brahmi [g], Neeltje Steeghs [h], Vasilios Karavasilis [i], Jacco de Haan [j], Agnieszka Wozniak [a,b], Sophie Cousin [c], Marta Domènech [d], Judith V.M.G. Bovée [k], Céline Charon-Barra [l], Sandrine Marreaud [m], Saskia Litière [m], Laura De Meulemeester [m], Christine Olungu [m], Hans Gelderblom [n]

[a] *Department of General Medical Oncology, University Hospitals Leuven, Leuven Cancer Institute, Leuven, Belgium*
[b] *Department of Oncology, KU Leuven, Laboratory of Experimental Oncology, Leuven, Belgium*
[c] *Sarcoma Unit, Institut Bergonié, Bordeaux, France*
[d] *Department of Medical Oncology, Catalan Institute of Oncology (ICO) Badalona | Hospital Germans Trias I Pujol. B-ARGO, Barcelona, Spain*
[e] *Department of General Medical Oncology, Hospital Clinico San Carlos, Madrid, Spain*
[f] *Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland*
[g] *Centre Léon Bérard, Université Cl. Bernard Lyon 1, Lyon, France*
[h] *Department of Medical Oncology, Netherlands Cancer Institute, Amsterdam, the Netherlands*
[i] *University College Hospital, London, United Kingdom*
[j] *University Medical Center, Groningen, the Netherlands*
[k] *Department of Pathology, Leiden University Medical Center, Leiden, the Netherlands*
[l] *Department of Pathology, Centre Georges-François Leclerc, Dijon, France*
[m] *European Organization for Research and Treatment of Cancer, Brussels, Belgium*
[n] *Department of Medical Oncology, Leiden University Medical Center, Leiden, the Netherlands*

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* *Corresponding author*: Department of General Medical Oncology, Leuven Cancer Institute, University Hospitals Leuven, and Laboratory of Experimental Oncology, KU Leuven, Herestraat 49, B-3000 Leuven, Belgium. Fax: +32 16 346901.
E-mail address: patrick.schoffski@uzleuven.be (P. Schöffski).
schoffski (P. Schöffski)

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Fibroblast growth factor receptor;
Vascular endothelial growth factor receptor

Abstract ***Purpose:*** EORTC-1506-STBSG was a prospective, multicentric, randomised, open-label phase 2 trial to assess the efficacy and safety of second-line nintedanib *versus* ifosfamide in patients with advanced, inoperable metastatic soft tissue sarcoma (STS). The primary end-point was progression-free survival.

Patients/methods: Patients with a variety of STS subtypes were randomised 1:1 to nintedanib (200 mg b.i.d. p.o. until disease progression) or ifosfamide (3 g/m^2 i.v. days 1–3, every 21 days for ≤6 cycles). A Korn design was applied aiming to detect an improvement in median progression-free survival (mPFS) from 3 to 4.5 months (HR = 0.667). An interim look was incorporated to stop the trial for futility if <19 of the first 36 patients treated with nintedanib were progression-free at week 12.

Results: At the interim analysis, among the first 36 eligible and evaluable patients randomised for nintedanib, only 13 (36%) were progression-free at week 12. The trial was closed for further accrual as per protocol. In total, 80 patients were randomised (40 per treatment group). The mPFS was 2.5 months (95% CI: 1.5–3.4) for nintedanib and 4.4 months (95% CI: 2.9–6.7) on ifosfamide (adjusted HR = 1.56 [80% CI: 1.14–2.13], $p = 0.070$). The median overall survival was 13.7 months (95% CI: 9.4–23.4) on nintedanib and 24.1 months (95% CI: 10.9–NE) on ifosfamide (adjusted HR = 1.65 [95%CI:0.89–3.06], $p = 0.111$). The clinical benefit rate for nintedanib and ifosfamide was 50% *versus* 62.5% ($p = 0.368$), respectively. Common treatment-related adverse events (all grades) were diarrhoea (35.9% of patients), fatigue (25.6%) and nausea (20.5%) for nintedanib; and fatigue (52.6%), nausea (44.7%) and vomiting, anorexia and alopecia (28.9% each) for ifosfamide.

Conclusion: The trial was stopped for futility. The activity of nintedanib did not warrant further exploration in non-selected, advanced STSs.

1. Introduction

Soft tissue sarcomas (STSs) comprise a heterogeneous group of rare malignant tumours and account for about 1% of all adult cancers [1,2]. Although there are >70 different histological STS subtypes, the most common high-grade STS subtypes include undifferentiated STSs, liposarcomas and leiomyosarcomas [1,3–5]. At diagnosis, 60% of patients present with localised disease; however, about 40% of patients develop metastases within five years, which is associated with very poor survival outcomes [6,7].

In patients with localised STS, surgery is the primary treatment option and is potentially curative [1,4]. Other STS treatment options include radiotherapy and chemotherapy [1,4]. For advanced, unresectable or metastatic STSs, anthracycline-based (e.g., doxorubicin) is the most common first-line chemotherapy regimen [1,8,9]. A median progression-free survival (mPFS) of 4.5 months and a median overall survival (mOS) of 12–18 months have been reported with doxorubicin monotherapy [10]. The doxorubicin-ifosfamide combination has improved the mPFS (7.4 months *versus* 4.6 months) and overall response rate (ORR) (26% *versus* 14%) compared with doxorubicin alone; however, toxicity is increased with doxorubicin-ifosfamide compared with doxorubicin alone and the combination is not associated with an overall survival (OS) benefit as compared with single agent doxorubicin [11].

After progression on an anthracycline regimen, chemotherapy options include ifosfamide (for all STS subtypes, with higher activity in synovial sarcoma), dacarbazine (all STS subtypes, active in leiomyosarcoma, solitary fibrous tumour and other subtypes), trabectedin (selected STS subtypes such as leiomyosarcoma/liposarcoma and translocation-related sarcomas) and eribulin (mainly in liposarcoma) [1,10–15]. Other drugs and drug combinations, such as gemcitabine, docetaxel, paclitaxel etc., are also used as second-line treatments of STS [3,4]. Ifosfamide belongs to the oxazaphosphorine family of cytotoxic agents, has been explored in multiple single agent and combination trials in sarcomas, and is an established standard of care for mesenchymal malignancies since the 1970s. The oral angiogenesis inhibitor pazopanib, a multityrosine kinase inhibitor (TKI) of vascular endothelial growth factor receptor (VEGFR) 1–3; platelet-derived growth factor receptor (PDGFR); and KIT, is indicated in patients with select advanced STS subtypes (excluding liposarcomas) who have failed previous chemotherapy [1,14].

Although there have been significant improvements in the management of patients with STS, the 5-year relative survival for patients with distant metastatic disease was only 15.4% in the United States in 2010–2016 [6]. More effective treatment regimens are needed for patients with locally advanced or metastatic STS.

Angiogenesis is involved in tumour growth and development of metastasis [16,17]. Vascular endothelial growth factor (VEGF) is overexpressed across multiple STS subtypes and is associated with higher tumour grade, vascularity and tumour size [3,18,19]. In addition to VEGF, PDGF is also involved in angiogenesis in STS, and both VEGFR and PDGFR are potential target kinases for the treatment of STS [14,20].

Nintedanib is an oral tyrosine kinase inhibitor targeting PDGFR A/B, fibroblast growth factor receptor 1–3, VEGFR 1–3, and Fms-like tyrosine kinase 3 (FLT3). Nintedanib has been evaluated as a single agent in advanced solid tumours and as a second- or third-line treatment in non-small cell lung cancer (NSCLC) [21,22]. In the European Union and other countries, nintedanib in combination with docetaxel is approved for the treatment of locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma tumour histology after first-line chemotherapy. In the EORTC-1506-STBSG phase 2 trial, the very first trial with this orally bioavailable agent in sarcoma, we investigated the efficacy and safety of nintedanib as a second-line treatment in patients with advanced, inoperable, metastatic STS *versus* standard cytotoxic treatment with ifosfamide.

2. Materials and methods

2.1. Study design

This prospective, multicentric, randomised, open-label phase 2 trial assessed the efficacy and safety of the oral angiogenesis inhibitor nintedanib compared with the intravenous cytotoxic compound ifosfamide in patients with advanced, inoperable and/or metastatic STS after failure of systemic non–oxazaphosphorine-based first-line chemotherapy.

The protocol was approved by ethics committees in all involved institutions and countries as per local legislation, and the study complied with the Declaration of Helsinki, International Conference on Harmonization-Good Clinical Practice, and participating country and institution regulations. The full protocol is available online (see https://www.eortc.be/services/doc/protocols/1506-version4.0.pdf).

2.2. Patients

Eligible patients were ≥18 years old, had a World Health Organization (WHO) performance status (PS) of 0–2, and adequate bone marrow, cardiac, liver and renal function. Patients had histologically proven advanced, inoperable and/or metastatic STS with measurable disease as per response evaluation criteria in solid tumours (RECIST) 1.1 and confirmed disease progression based on local investigator's assessment. One (and no less or more than one) line of previous non–oxazaphosphorine-based systemic chemotherapy for advanced, inoperable and/or metastatic malignant STS was allowed. Patients treated with first-line doxorubicin/olaratumab or doxorubicin/placebo ± olaratumab/placebo maintenance qualified for the trial and such treatment was considered as one line according to the protocol. Prior neoadjuvant, adjuvant and/or first-line maintenance systemic chemotherapy for locally advanced or metastatic STSs was allowed and counted as zero lines of treatment, provided that the disease had not progressed during neoadjuvant and/or adjuvant therapy or within 12-weeks after completion of the perioperative treatment. Patients had no prior exposure to oral or intravenous angiogenesis inhibitors. Patients with Child Pugh B or C hepatic impairment, active brain metastases, central nervous system metastasis or leptomeningeal tumour spread were excluded. Further selection criteria details are provided in the protocol (https://www.eortc.be/services/doc/protocols/1506-version4.0.pdf).

Patients provided written informed consent for all study-related procedures and collection of archival tumour tissue from the primary tumour or a metastatic site for histological central review by one of four involved reference sarcoma expert pathologists of the European Organization for Research and Treatment's Soft Tissue and Bone Sarcoma Group (EORTC STBSG).

After informed consent, potentially eligible patients underwent screening for trial participation and were registered at the EORTC Headquarters. After verification of all eligibility criteria, the patients were centrally randomised to receive one of the study treatments.

2.3. Treatment and procedures

Nintedanib was provided by Boehringer Ingelheim Pharma GmbH as 100 mg and 150 mg soft gelatin capsules. Patients receiving nintedanib took two capsules of 100 mg orally twice daily with a dosing interval of about 12 h at the same time each day, usually in the morning and evening (total dose per day was 400 mg). Ifosfamide and required supportive care agents came from the local pharmacies in the involved institutions, as this treatment is standard of care.

Patients were centrally randomised, and a minimisation technique (variance method) was used for random treatment allocation stratifying by PS (0–1 *versus* 2), histology (leiomyosarcoma or liposarcoma *versus* other histologies), and FNCLCC histopathological grade (grade 2/unknown *versus* grade 3). Patients were randomised 1:1 for treatment with the experimental arm nintedanib (200 mg taken twice daily orally, until clinically relevant disease progression) or the standard arm ifosfamide (3 g/m^2 administered intravenously on days 1–3, every 21 days for up to 6 cycles). Treatment assignment was open labelled. One treatment

cycle was defined as 21 days. Treatment beyond RECIST 1.1 progression was allowed for the oral agent if the patient derived benefit from the treatment, but not in the ifosfamide arm, where a maximum of 6 cycles were administered.

Adverse events (AEs) were managed with supportive care or with dose and schedule modifications (see protocol: https://www.eortc.be/services/doc/protocols/1506-version4.0.pdf).

Safety and tolerability assessments, medical history, physical examinations, vital signs, assessment of the WHO PS and laboratory investigations were performed at the baseline, then every three weeks and at the end of treatment. AEs were rated using common terminology criteria for adverse events version 4.0. Tumour assessments were performed at the baseline, every 6 weeks during the first 48 weeks and every 12 weeks thereafter as per RECIST 1.1 on the basis of computer tomography or magnetic resonance imaging.

2.4. Outcomes

The primary end-point was progression-free survival (PFS) when compared with ifosfamide as assessed by the investigator according to RECIST 1.1.

Secondary end-points included progression-free rate (PFR) at 12 weeks, OS, objective response rate (ORR), clinical benefit rate (CBR), response duration, total duration of treatment with nintedanib and safety. Health-related quality of life and health economics were also assessed but are not reported because of the early closure of the trial for futility.

Exploratory objectives included an analysis of putative predictive biomarkers for the anti-tumour effects of the treatment. Owing to the early closure of the trial and the related smaller sample size, these exploratory analyses will not be performed.

2.5. Statistical analysis

The study applied a Korn design aimed to detect an improvement in mPFS from 3 to 4.5 months (hazard ratio [HR] = 0.667) with nintedanib in the total study population [10,14,23–25]. In total, 158 patients were planned to be entered on the study. The expected mPFS for the control treatment ifosfamide was derived from previous studies in advanced STS with second-line ifosfamide (Van Oosterom *et al.*), phase 3 comparative trial of ifosfamide *versus* doxorubicin (Lorigan *et al.*) and PFR concept as an end-point in STS (Van Glabbeke *et al.*) [2,24,25].

As this trial was the very first clinical study exploring nintedanib in STS, an interim analysis was planned, using the PFR at 12 weeks of the first 36 patients randomised to the experimental arm. This was done with the intention to avoid exposing too many patients to a potentially inactive compound. If <19 of these 36 nintedanib-treated patients were progression-free at the 12-week assessment, the trial was to be stopped early for futility, otherwise the trial was to continue as planned. This interim decision rule originates from a single-arm, single-stage A'Hern design with type I/II errors fixed at $\alpha = 0.1$ and $\beta = 0.15$, testing the null hypothesis H0: $P \leq 40\%$ *versus* H1 $P>40\%$ [26]. This approach ensures that the overall type I error (two-sided alpha of 0.2) is not inflated by the interim look, and the overall power of the design to detect the targeted treatment difference is still maintained at 80%.

The main analysis of the efficacy end-points was assessed in the intention-to-treat (ITT) population. All analyses are performed at the 2-sided 0.2 significance level. Time-to-event end-points (PFS, OS, total treatment duration in the nintedanib arm) are displayed by Kaplan–Meier curves. Median and time point estimates are provided with 95% CI. PFS and OS are compared between the two arms using the score test from a Cox proportional hazards model adjusted for the stratification factors.

The corresponding estimate of the treatment effect (HR) and 80% CI is provided. For patients who achieved a partial response (PR) or complete response (CR), the duration of response was estimated by the Kaplan–Meier method in each therapeutic arm and the analysis was descriptive only.

PFR at 12 weeks, objective response (OR, including CR + PR) and CBR (CR + PR + stable disease [SD]) are reported as proportions with 95% CI (from the exact binomial distribution). The rates were compared between the two arms using a two-sided Fisher exact test. All patients who started the treatment (at least one dose of nintedanib/ifosfamide) were included in the overall safety analysis.

Patient accrual, eligibility and safety were monitored on a regular basis by EORTC and the study coordinator, and a study management group, study steering committee and EORTC's independent data monitoring committee (IDMC) was involved in critical decisions.

2.6. Role of funding source

This study was an investigator-initiated trial proposed by the first author to Boehringer Ingelheim Pharma GmbH (Ingelheim am Rhein, Germany) and EORTC (Brussels, Belgium). EORTC was the legal sponsor. Boehringer Ingelheim Pharma GmbH provided nintedanib and funding but had no role in the study design, data collection, analysis, interpretation, writing of the report or decision to publish this report. The database is held by EORTC, and EORTC statisticians performed the analysis.

3. Results

Between July 26, 2017, and November 21, 2019, a total of 80 patients were randomised (40 patients in each arm) by 18

study centres in 8 countries (Belgium, France, Lithuania, the Netherlands, Poland, Spain, Switzerland and the United Kingdom). The median follow-up at the time of the analysis was 22.2 months overall (interquartile range [IQR] 12.9–27.4).

Patient disposition is shown in Fig. 1. Thirty-nine patients on the nintedanib arm and 38 patients on the ifosfamide arm received treatment and were analysed for safety. The first 36 patients randomised to the nintedanib arm were used to assess the decision rule for futility.

3.1. Patient characteristics

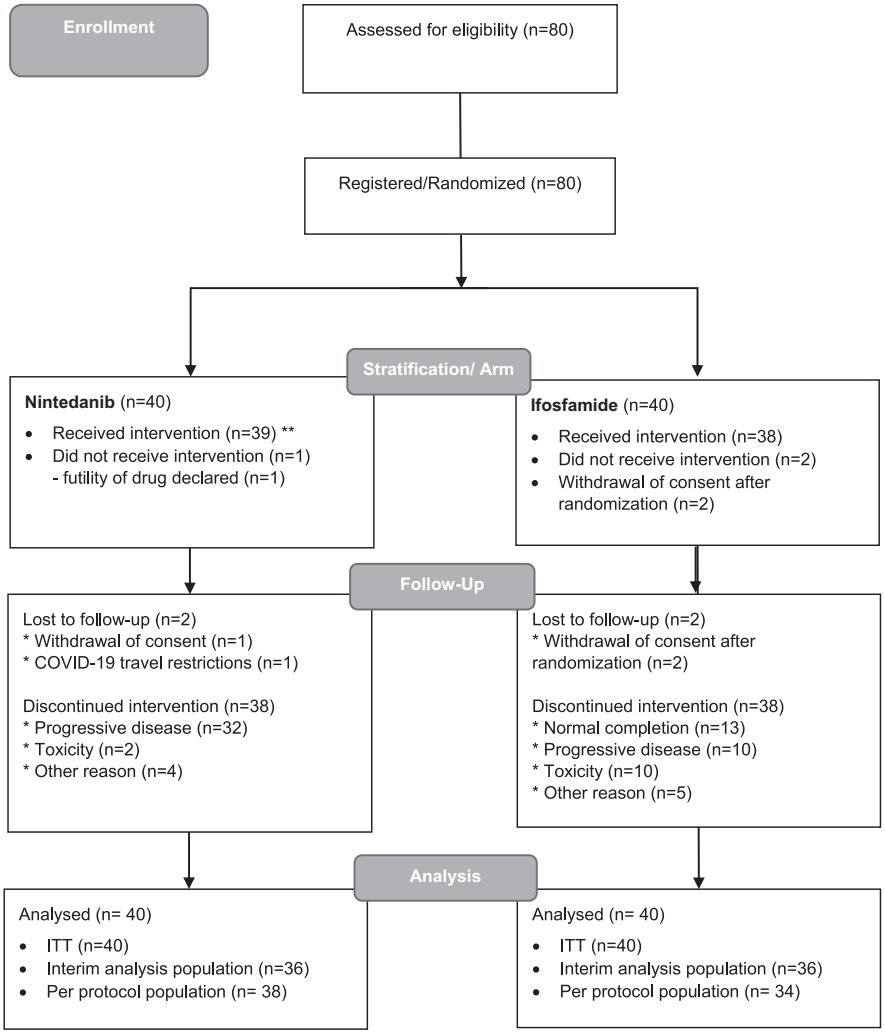
Baseline patient characteristics are shown in Table 1 and were relatively well balanced across the treatment arms. Overall, the median age was 58.5 years (range: 25–75); 52.5% (42/80) and 41.3% (33/80) of patients had WHO PS of 0 and 1, respectively.

Sites provided archival tissue samples for central reference pathology, with four reference pathologists involved. A total of 68 cases were evaluable, and the local histological classification was revised in 11 cases, based on the available material. All cases were confirmed to be STS.

In terms of sarcoma subtype, 27.5% (22/80) of patients had liposarcomas, and 38.8% (31/80) had leiomyosarcomas. Most patients (53.8% [43/80]) had a high-grade tumour as per local pathology. The median tumour size was slightly larger in the nintedanib arm 94.0 mm (2.0–256.0) compared with the ifosfamide arm 72.5 mm (10.0–300.0).

3.2. Exposure to treatment

Of the 80 patients randomised in the study, three patients did not start treatment (two in the ifosfamide arm due to withdrawal of consent, and one in the nintedanib arm due to early suspension of recruitment). Of the 77 patients who started treatment, one patient was still on treatment at the clinical cutoff date (November 3, 2020).



** Includes one patient in the nintedanib arm who was still on treatment at the clinical cut-off date.

ITT, intention to treat; n, number of patients.

Fig. 1. Patient disposition for the randomized phase 2 EORTC-1506-STBSG (ANITA) study.

Table 1
Baseline patient characteristics (ITT population).

	Nintedanib (n = 40) n (%)	Ifosfamide (n = 40) n (%)	Total (N = 80) N (%)
Age			
18–64 years	26 (65.0)	27 (67.5)	53 (66.3)
65–84 years	14 (35.0)	13 (32.5)	27 (33.8)
Median age, years (range)	59.5 (25–75)	56 (28–75)	58.5 (25–75)
WHO performance status (on study)			
0	20 (50.0)	22 (55.0)	42 (52.5)
1	19 (47.5)	14 (35.0)	33 (41.3)
2	1 (2.5)	3 (7.5)	4 (5.0)
Missing	0 (0.0)	1 (2.5)	1 (1.3)
Gender			
Male	20 (50.0)	17 (42.5)	37 (46.3)
Female	20 (50.0)	23 (57.5)	43 (53.8)
History of cardiovascular disease			
No	26 (65.0)	26 (65.0)	52 (65.0)
Yes	14 (35.0)	14 (35.0)	28 (35.0)
Prior or concomitant other malignant diseases			
No	37 (92.5)	36 (90.0)	73 (91.3)
Yes	3 (7.5)	4 (10.0)	7 (8.8)
Any prior or concomitant major medical problem			
No	8 (20.0)	7 (17.5)	15 (18.8)
Yes	32 (80.0)	33 (82.5)	65 (81.3)
Prior treatments for STS			
Prior radiotherapy			
No	22 (55.0)	21 (52.5)	43 (53.8)
Yes	18 (45.0)	19 (47.5)	37 (46.3)
Prior surgery			
No	11 (27.5)	9 (22.5)	20 (25.0)
Yes	29 (72.5)	31 (77.5)	60 (75.0)
Prior adjuvant chemotherapy			
No	40 (100.0)	38 (95.0)	78 (97.5)
Yes	0 (0.0)	2 (5.0)	2 (2.5)
Prior first-line chemotherapy			
No	0 (0.0)	1 (2.5)[b]	1 (1.3)
Yes	40 (100.0)	39 (97.5)	79 (98.8)
Prior first-line maintenance chemotherapy[c]			
No	34 (85.0)	36 (90.0)	70 (87.5)
Yes	6 (15.0)	4 (10.0)	10 (12.5)
Sarcoma subfamily/subtype			
Adipocytic (liposarcoma)	11 (27.5)	11 (27.5)	22 (27.5)
Dedifferentiated	8 (20.0)	11 (27.5)	19 (23.8)
Myxoid/round cell	2 (5.0)	0 (0.0)	2 (2.5)
Pleomorphic	1 (2.5)	0 (0.0)	1 (1.3)
Fibroblastic	5 (12.5)	4 (10.0)	9 (11.3)
Myxofibrosarcoma	1 (2.5)	0 (0.0)	1 (1.3)
Sclerosing epithelioid fibrosarcoma	1 (2.5)	1 (2.5)	2 (2.5)
Solitary fibrous tumour	3 (7.5)	2 (5.0)	5 (6.3)
Low grade fibromyxoid sarcoma	0 (0.0)	1 (2.5)	1 (1.3)
Leiomyosarcoma	14 (35.0)	17 (42.5)	31 (38.8)
Vascular tumours	1 (2.5)	2 (5.0)	3 (3.8)
Epithelioid hemangioendothelioma	1 (2.5)	1 (2.5)	2 (2.5)
Angiosarcoma	0 (0.0)	1 (2.5)	1 (1.3)
Tumours of uncertain differentiation	2 (5.0)	1 (2.5)	3 (3.8)
Synovial sarcoma	1 (2.5)	1 (2.5)	2 (2.5)
Extraskeletal myxoid chondrosarcoma	1 (2.5)	0 (0.0)	1 (1.3)
MPNST	3 (7.5)	2 (5.0)	5 (6.3)
Undifferentiated soft tissue sarcoma	3 (7.5)	3 (7.5)	6 (7.5)
Spindle cell	1 (2.5)	1 (2.5)	2 (2.5)
Pleomorphic (UPS)	0 (0.0)	1 (2.5)	1 (1.3)
NOS	2 (5.0)	1 (2.5)	3 (3.8)
Other[a]	1 (2.5)	0 (0.0)	1 (1.3)
STS tumour grade (FNCLCC)			
Grade 1	0 (0.0)	1 (2.5)	1 (1.3)

(continued on next page)

Table 1 (*continued*)

	Nintedanib (n = 40) n (%)	Ifosfamide (n = 40) n (%)	Total (N = 80) N (%)
Grade 2	19 (47.5)	13 (32.5)	32 (40.0)
Grade 3	20 (50.0)	23 (57.5)	43 (53.8)
Not determined	1 (2.5)	3 (7.5)	4 (5.0)
Median STS tumour size, in mm (range)	94.0 (2.0–256.0)	72.5 (10.0–300.0)	82.5 (2.0–300.0)

[a] Cutaneous leiomyosarcoma.
[b] This patient progressed on adjuvant treatment.
[c] Prior maintenance therapy included trabectedin/doxorubicin, or doxorubicin, or olaratumab/doxorubicin. ITT, intention to treat; MPNST, malignant peripheral nerve sheath tumour, N, n, number of patients; STS, soft tissue sarcoma; WHO, World Health Organization.

The median number of three-weekly treatment cycles was 4 in both treatment arms, and the median relative dose intensity (RDI) was high, with 100.3% in the nintedanib arm and 98.3% in the ifosfamide arm (Table 2). RDI corresponded to the ratio of the total dose received *versus* the total dose expected in a given period. Five patients in the nintedanib arm and eight in the ifosfamide arm had dose reductions, and five patients treated with nintedanib had dose interruptions.

In the nintedanib arm, progressive disease (PD) was the main reason (84.2% of patients) for treatment discontinuation, whereas in the ifosfamide arm, toxicity and/or PD (26.3% of patients each) were the main reasons for early treatment discontinuation.

3.3. Efficacy

For the interim analysis, among the first 36 eligible and evaluable patients randomised to nintedanib, only 13 patients (36%) were progression-free at week 12. Thus, in accordance with the decision rule for the interim analysis (as less than 19 of 36 patients on nintedanib were progression-free at the 12-week assessment) the trial was stopped early, this was endorsed by EORTC's Independent Data Monitoring Committee.

Among the 40 ITT patients in each treatment arm, 14 patients (35%) on nintedanib and 18 patients (45%) on ifosfamide were progression-free at 12-weeks, and the according difference was not statistically significant ($p = 0.494$) (Table 3).

Table 2
Exposure to study treatment, dose modifications and treatment discontinuations.

	Nintedanib	Ifosfamide	Total
Exposure to study treatment	**(n = 38)[a]**	**(n = 38)**	**(N = 76)**
Total dose			
Median	26.1 g	30.5 g/m^2	–
Range	8.4–120.8 g	8.8–54.4 g/m^2	–
Relative dose intensity[b]			
Median	100.3%	98.3%	–
Range	60.9–105.3%	50.5–103.5%	–
Number of treatment cycles, n	**(n = 39)**	**(n = 38)**	**(N = 77)**
Median	4	4	4
Range	1–23	1–6	1–23
Dose modification, n (%)	**(n = 39)**	**(n = 38)**	**(N = 77)**
Dose reduction	5 (12.8)	8 (21.1)	13 (16.9)
Interruption	5 (12.8)	–	5 (6.5)
Major reason for study treatment discontinuation, n (%)	**(n = 38)[a]**	**(n = 38)**	**(N = 76)**
Normal completion	n/a	13 (34.2)	13 (17.1)
Progression of disease/death due to PD	32 (84.2)	10 (26.3)	42 (55.3)
Toxicity (+toxic death)	2 (5.3)	10 (26.3)	12 (15.8)
Patient's decision (not related to toxicity)	1 (2.6)	3 (7.9)	4 (5.3)
Death not due to malignant disease or toxicity	0 (0.0)	1 (2.6)	1 (1.3)
Other	3 (7.9)	1 (2.6)	4 (5.3)

[a] The number of patients in the nintedanib group presented in Table 2 is based on the number of patients who are off treatment and does not include the one patient in the nintedanib arm who was still on treatment at the clinical cutoff date (as shown in the Consort diagram in Fig. 1).
[b] The relative dose intensity (RDI) for a patient corresponded to the ratio of the total dose received *versus* the total dose expected in a given period (thus the RDI could be below, above or equal to 100%). RDI does not take into account treatment discontinuation; it only considered dose reductions and cycle duration modifications. Only one patient in the nintedanib arm could continue treatment beyond cycle 6. N, n, number of patients; PD, progressive disease.

Table 3
Key clinical efficacy end-points.

	Nintedanib (n = 40) n (%)	Ifosfamide (n = 40) n (%)	Total (N = 80) N (%)
Progression-free rate at 12 weeks			
Progression-free at 12 weeks	14 (35.0)	18 (45.0)	32 (40.0)
PFR (80% CI)	35.0% (24.9–46.3%)	45.0% (34.1–56.3%)	–
PFR (95% CI)	35.0% (20.6–51.7%)	45.0% (29.3–61.5%)	–
Response at 12 weeks			
Partial response	2 (5.0)	2 (5.0)	4 (5.0)
Stable disease	12 (30.0)	16 (40.0)	28 (35.0)
Progression	23 (57.5)	12 (30.0)	35 (43.8)
Not evaluable	1 (2.5)	5 (12.5)	6 (7.5)
Not evaluable due to start of new T_x	1 (2.5)	3 (7.5)	4 (5.0)
Early death	1 (2.5)	2 (5.0)	3 (3.8)
Best response and clinical benefit rate			
Best overall response			
Partial response	2 (5.0)	2 (5.0)	4 (5.0)
Stable disease	18 (45.0)	23 (57.5)	41 (51.3)
Progressive disease	19 (47.5)	10 (25.0)	29 (36.3)
Early death	0 (0.0)	2 (5.0)	2 (2.5)
Not evaluable	1 (2.5)	3 (7.5)	4 (5.0)
Objective response (CR + PR)	2 (5.0)	2 (5.0)	4 (5.0)
RR (80% CI)	5.0% (1.3–12.8%)	5.0% (1.3–12.8%)	–
RR (95% CI)	5.0% (0.6–16.9%)	5.0% (0.6–16.9%)	–
Clinical benefit (CR + PR + SD)	20 (50.0)	25 (62.5)	45 (56.3)
CBR (80% CI)	50.0% (38.8–61.2%)	62.5% (51.1–72.9%)	–
CBR (95% CI)	50.0% (33.8–66.2%)	62.5% (45.8–77.3%)	–
Progression-free survival	2.5 mo	4.4 mo	–
(80% CI)	(1.5–2.9 mo)	(3.8–5.6 mo)	
(95% CI)	(1.5–3.4 mo)	(2.9–6.7 mo)	
Overall survival	13.7 mo	24.1 mo	–
(80% CI)	(12.5–17.0 mo)	(15.4 - NE)	
(95% CI)	(9.4–23.4 mo)	(10.9 – NE)	

CBR, clinical benefit rate; CI, confidence interval; CR, complete response; mo, months; NE, not evaluable; PFR, progression-free rate; PR; partial response; RR, response rate; SD, stable disease; T_x, treatment.

The median PFS was 2.5 months (95% CI: 1.5–3.4) on nintedanib and 4.4 months (95% CI: 2.9–6.7) on ifosfamide (Fig. 2A). There was no statistically significant difference in PFS between the treatment groups (adjusted HR = 1.56 [80% CI: 1.14–2.13], $p = 0.070$).

The median OS was 13.7 months (95% CI: 9.4–23.4) on nintedanib and 24.1 months (95% CI: 10.9–NE) on ifosfamide (Fig. 2B). There was no statistically significant difference in OS between the treatment groups (adjusted HR = 1.65 [95% CI: 0.89–3.06], $p = 0.111$).

In terms of best overall response, PRs were reported in 5% of the patients in each treatment group (2 patients per arm), thus there was no difference in response rate (RR) between the groups (i.e., 5.0% [95% CI: 0.6–16.9] $p = 1.000$). Eighteen patients (45%) on nintedanib had SD compared with 23 patients (57.5%) on the ifosfamide arm. The was no significant difference in the CBR between nintedanib compared with ifosfamide (50% [95% CI: 33.8–66.2] *versus* 62.5% [95% CI: 0.6–16.9], $p = 0.368$). PD as best response occurred in 19 patients (47.5%) on nintedanib *versus* 10 patients (25.0%) on ifosfamide (Table 3).

The total treatment duration in the nintedanib arm as estimated by the Kaplan–Meier method was 2.5 months (95% CI: 1.4–3.4).

3.4. Safety

The most common nintedanib-related AEs (all grades) were diarrhoea (35.9% of patients [14/39]), fatigue (25.6% [10/39]) and nausea (20.5% [8/39]) (Table 4). The most common ifosfamide-related AEs (all grades) were fatigue (52.6% [20/38]), nausea (44.7% [17/38]), and vomiting, anorexia and alopecia (28.9% [11/38] each). On the ifosfamide arm, 23.7% (9/38) of patients experienced treatment-related encephalopathy (of which, 10.5% [4/38] were grade 3), 13.2% (5/38) of patients had acute kidney injury (of which, 7.9% [3/38] were grade 3). Grade ≥3 treatment-related AEs occurred in 17.9% (7/39) of patients on nintedanib and 31.6% (12/38) of patients on ifosfamide. Grade 4 treatment-related AEs occurred in one patient on each arm and comprised a small intestinal perforation in the nintedanib arm and a case of sepsis associated with ifosfamide.

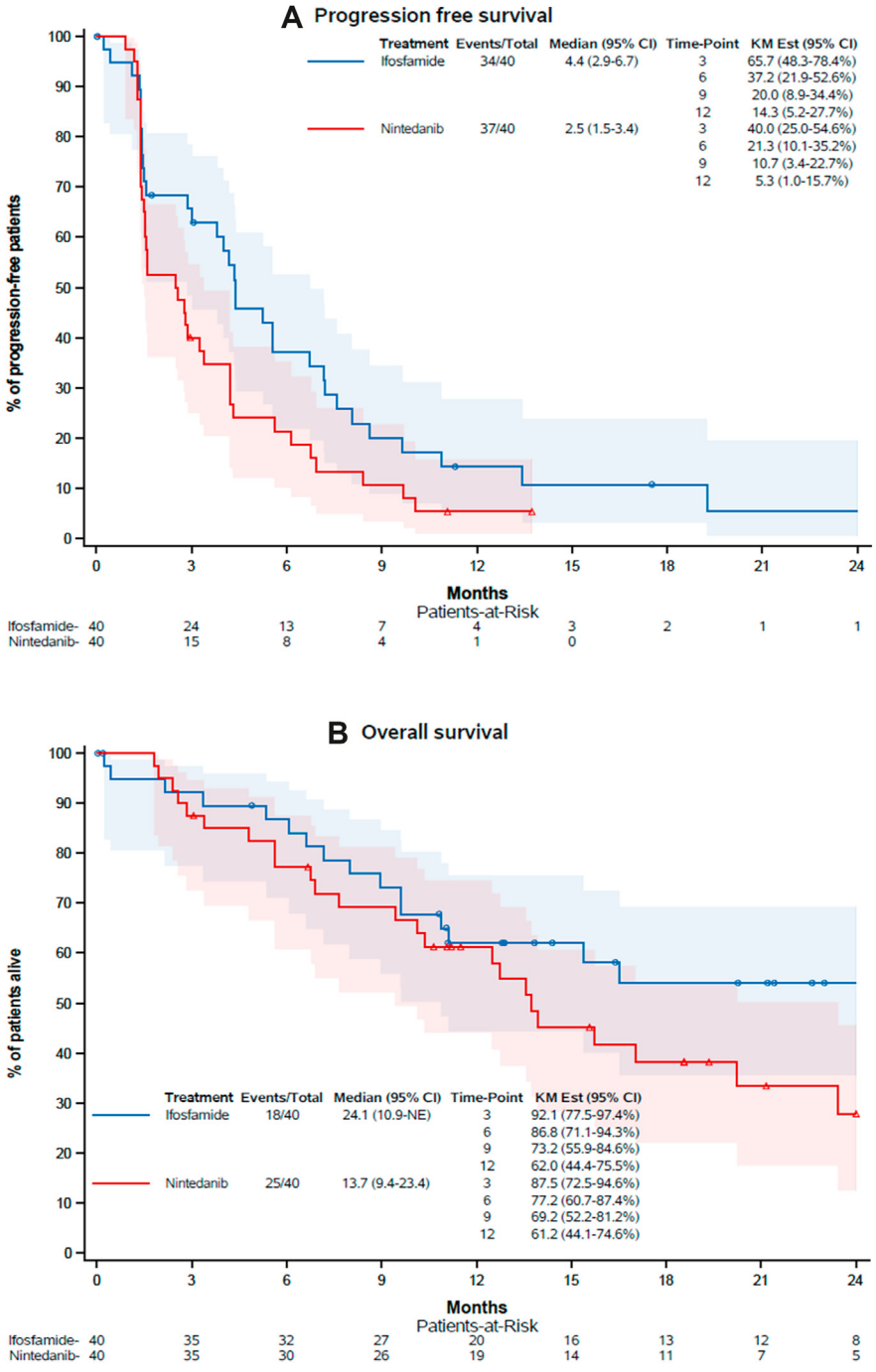


Fig. 2. Kaplan–Meier estimates. **A** Progression-free survival (ITT). **B**. Overall survival. The colour shading around the Kaplan–Meier survival curves represents the 95% CI. CI, confidence intervals; ITT, intention to treat; KM Est, Kaplan–Meier estimate.

A total of 20.5% (8/39) of patients receiving nintedanib and 34.2% (13/38) of patients receiving ifosfamide had serious AEs, regardless of relationship to the study treatment. Serious AEs ≥ grade 4 occurred in 7.7% (3/39) of patients on nintedanib comprising of small intestine perforation (2, one of whom had a previously unknown mesenteric implant) and thromboembolic event (1); and in 7.9% (3/38) of patients on ifosfamide comprising sudden death (1), sepsis (1), thromboembolic event (1).

Table 4
Treatment-related clinical adverse events occurring in ≥10% of patients for all grades (in the safety population).[a]

	Nintedanib (n = 39)					Ifosfamide (n = 38)				
	G 1 n (%)	G 2 n (%)	G 3 n (%)	G 4 n (%)	All G ≥ 1 n (%)	G 1 n (%)	G 2 n (%)	G 3 n (%)	G 4 n (%)	All G ≥ 1 n (%)
All adverse events	9 (23.1)	10 (25.6)	6 (15.4)	1 (2.6)	26 (66.7)	5 (13.2)	12 (31.6)	11 (28.9)	1 (2.6)	29 (76.3)
Diarrhea	8 (20.5)	6 (15.4)	_	_	14 (35.9)	2 (5.3)	2 (5.3)	_	_	4 (10.5)
Fatigue	3 (7.7)	5 (12.8)	2 (5.1)	_	10 (25.6)	7 (18.4)	12 (31.6)	1 (2.6)	_	20 (52.6)
Nausea	6 (15.4)	2 (5.1)	_	_	8 (20.5)	10 (26.3)	5 (13.2)	2 (5.3)	_	17 (44.7)
Vomiting	4 (10.3)	1 (2.6)	1 (2.6)	_	6 (15.4)	7 (18.4)	2 (5.3)	2 (5.3)	_	11 (28.9)
Hypertension	1 (2.6)	2 (5.1)	3 (7.7)	_	6 (15.4)	1 (2.6)	_	_	_	1 (2.6)
Anorexia	1 (2.6)	4 (10.3)	_	_	5 (12.8)	7 (18.4)	2 (5.3)	2 (5.3)	_	11 (28.9)
Dysgeusia	4 (10.3)	1 (2.6)	_	_	5 (12.8)	1 (2.6)	_	_	_	1 (2.6)
Weight loss	2 (5.1)	2 (5.1)	_	_	4 (10.3)	4 (10.5)	_	_	_	4 (10.5)
Constipation[b]	2 (5.1)	_	_	_	2 (5.1)	4 (10.5)	2 (5.3)	_	_	6 (15.8)
Anaemia[b]	_	_	1 (2.6)	_	1 (2.6)	_	5 (13.2)	2 (5.3)	_	7 (18.4)
Alopecia	_	_	n/a	n/a	_	3 (7.9)	8 (21.1)	n/a	n/a	11 (28.9)
Encephalopathy	_	_	_	_	_	1 (2.6)	4 (10.5)	4 (10.5)	_	9 (23.7)
Acute kidney injury	_	_	_	_	_	2 (5.3)	_	3 (7.9)	_	5 (13.2)
Febrile neutropaenia	_	_	_	_	_	_	1 (2.6)	3 (7.9)	_	4 (10.5)

[a] Ranked as per frequency by nintedanib.
[b] ≤10% for nintedanib but included in this table as ≥ 10% for ifosfamide. G, grade; n, number of patients.

Haematological toxicity was mild on the nintedanib arm but was more frequent and of a higher severity on the ifosfamide arm (Table 5). Biochemical adverse events are shown in Table 6.

4. Discussion

EORTC-1506-STBSG was the very first clinical trial exploring the activity of the oral multi-kinase inhibitor nintedanib in patients with advanced, inoperable STS, and used i.v. ifosfamide, an established standard of care with broad activity in this heterogeneous family of malignancies, as comparator. Given the highly experimental character of the oral treatment, the study design incorporated an interim analysis and early stopping rule.

The interim analysis decision rule stated if <19 patients out of the first 36 patients on the nintedanib arm were progression-free at week 12, the trial was to stop for futility. This cutoff was based on experience with another oral agent that is widely used for STS treatment after failure of systemic chemotherapy, pazopanib. Based on the decision rule outlined in the protocol, EORTC-1506-STBSG was stopped early as only 13

Table 5
Grade 2–4 haematological adverse events, all causalities (in the safety population).

		Nintedanib (n = 39)	Ifosfamide (n = 38)	Total (N = 77)
		n (%)	n (%)	N (%)
White blood cell count decreased	Grade 2	2 (5.1)	7 (18.4)	9 (11.7)
	Grade 3	_	2 (5.3)	2 (2.6)
	Grade 4	_	3 (7.9)	3 (3.9)
Neutropaenia	Grade 2	2 (5.1)	5 (13.2)	7 (9.1)
	Grade 3	_	2 (5.3)	2 (2.6)
	Grade 4	_	2 (5.3)	2 (2.6)
Lymphopaenia	Grade 2	11 (28.2)	14 (36.8)	25 (32.5)
	Grade 3	1 (2.6)	16 (42.1)	17 (22.1)
	Grade 4	_	1 (2.6)	1 (1.3)
Thrombocytopaenia	Grade 3	_	1 (2.6)	1 (1.3)
	Grade 4	_	2 (5.3)	2 (2.6)
Anaemia	Grade 2	7 (17.9)	19 (50.0)	26 (33.8)
	Grade 3	_	3 (7.9)	3 (3.9)

N, n, number of patients.

Table 6
Grade 3–4, or > ULN, or < LLN biochemical adverse events, all causalities.

		Nintedanib (n = 39)	Ifosfamide (n = 38)	Total (N = 77)
		n (%)	n (%)	N (%)
BUN abnormality	Below ULN	31 (79.5)	35 (92.1)	66 (85.7)
	Above ULN	8 (20.5)	3 (7.9)	11 (14.3)
Serum creatinine	Grade 2	–	3 (7.9)	3 (3.9)
Total proteins	Above LLN	24 (61.5)	17 (44.7)	41 (53.2)
	Below LLN	14 (35.9)	20 (52.6)	34 (44.2)
	Not reported	1 (2.6)	1 (2.6)	2 (2.6)
Hyperbilirubinaemia	Grade 3	1 (2.6)	–	1 (1.3)
LDH abnormality	Below ULN	23 (59.0)	17 (44.7)	40 (51.9)
	Above ULN	16 (41.0)	19 (50.0)	35 (45.5)
	Not reported	–	2 (5.3)	2 (2.6)
GGT increased	Grade 3	8 (20.5)	1 (2.6)	9 (11.7)
	Not reported	–	1 (2.6)	1 (1.3)
Lipase increased	Grade 3	2 (5.1)	4 (10.5)	6 (7.8)
	Grade 4	1 (2.6)	1 (2.6)	2 (2.6)
	Not reported	1 (2.6)	3 (7.9)	4 (5.2)
Amylase increased	Grade 3	–	1 (2.6)	1 (1.3)
	Not reported	4 (10.3)	4 (10.5)	8 (10.4)
SGPT increased	Grade 3	3 (7.7)	–	3 (3.9)
SGOT increased	Grade 3	1 (2.6)	–	1 (1.3)
	Not reported	–	2 (5.3)	2 (2.6)
Hyponatraemia	Grade 3	1 (2.6)	–	1 (1.3)
Hypokalaemia	Grade 3	–	3 (7.9)	3 (3.9)
Hypercalcaemia	Grade 3	1 (2.6)	–	1 (1.3)
	Not reported	1 (2.6)	–	1 (1.3)
Hypocalcaemia	Grade 4	6 (15.4)	6 (15.8)	12 (15.6)
	Not reported	1 (2.6)	–	1 (1.3)
Bicarbonate	Below LLN	5 (12.8)	7 (18.4)	12 (15.6)
	Above ULN	14 (35.9)	11 (28.9)	25 (32.5)
	Not reported	3 (7.7)	2 (5.3)	5 (6.5)

BUN, blood urea nitrogen; GGT, gamma-glutamyl transferase; LDH, lactate dehydrogenase; LLN, lower normal limit; n, number of patients; SGPT, serum glutamic-pyruvic transaminase; SGOT, serum glutamic oxaloacetic transaminase; ULN, upper normal limit.

patients of the first 36 patients (36%) receiving nintedanib were progression-free at week 12.

EORTC-1506-STBSG did not meet its primary endpoint, as nintedanib given as second-line therapy for advanced, inoperable and/or metastatic STS had a shorter mPFS compared with ifosfamide (2.5 months *versus* 4.4 months, respectively). Furthermore, the PFR at 12 weeks was also lower on the nintedanib arm compared with ifosfamide (35% *versus* 45%). In the PALETTE study with pazopanib *versus* placebo in patients with metastatic STS who progressed despite previous standard chemotherapy, pazopanib significantly improved mPFS compared with placebo (4.6 months *versus* 1.6 months, $p < 0.0001$) [14]. The 2.3 months mPFS on EORTC-1506-STBSG with the oral tyrosine kinase inhibitor nintedanib is lower than the 4.6 months mPFS reported with the oral TKI pazopanib in the PALETTE study. Of note, pazopanib was explored in a more heavily pretreated group of patients (56% of patients had ≥2 lines of previous systemic treatment for advanced STS and 21% had ≥3 lines) [14]. An interesting observation in this trial is that nintedanib was associated with an even shorter PFS than pazopanib in the PALETTE trial. Cross-trial comparisons have always to be interpreted with caution, but this is an unexpected outcome. Nintedanib inhibits VEGFR 1–3, PDGFR A/B, FGFR 1–3, VEGFR 1–3, and FLT3 [21,22,27]. Pazopanib inhibits VEGFR 1–3, PDGFR A/B, FGFR-1 and -3, stem cell factor receptor, interleukin-2 receptor inducible T-cell kinase, leukocyte-specific protein tyrosine kinase and transmembrane glycoprotein receptor tyrosine kinase [28,29]. Nintedanib and pazopanib have a similar mechanism of action as far as VEGFR 1–3, PDGFR A/B, FGFR-1 and -3 are concerned, and these are important targets in STS [27–31]. The potency of the two inhibitors against the individual targets, however, differs to some extent, which could explain some the variation between the two trials. Furthermore, patient selection may have contributed to this. While the patients in the PALETTE study had more lines of prior treatment (56% had ≥ 2+ lines, and 21% had ≥ 3+ lines of treatment) than the patients in

our study, there were also differences between the PALETTE study and our study in the inclusion/exclusion criteria and patient characteristics (for example, the PALETTE study excluded all types of adipocytic sarcoma and chondrosarcoma, while our study included patients with adipocytic sarcoma and extraskeletal myxoid chondrosarcoma) [14]. In addition to these potential explanations for the discrepancy in PFS, we should not underestimate the potential impact of the heterogeneity of the STS family of tumours and the fact that the sample size of patients treated with the oral agents differed between the two studies. This all makes direct comparisons obsolete.

The OS with nintedanib was shorter than that of ifosfamide (13.7 months *versus* 24.1 months). The OS with nintedanib of 13.7 months (95% CI: 9.4–23.4) observed on the EORTC-1506-STBSG study is similar to the 12.3 months (95% CI: 10·6–14·8) observed with pazopanib on the PALETTE study, where typical patients had received more prior lines of treatment (number of lines of previous systemic therapy of 0–1 *versus* 2–4 on the PALETTE study: HR = 0.72 [95% CI: 0.53–0.99]) [14].

In the EORTC-1506-STBSG study, there was a 5% PR on each arm of the study with a CBR of 50% on the nintedanib arm and 62.5% on the ifosfamide arm. The two patients responding to nintedanib had an advanced leiomyosarcoma and an advanced malignant peripheral nerve sheath tumour. Both tissue diagnoses were confirmed by central pathology. The percentage of PRs were similar to those previously reported in other studies with a tyrosine kinase inhibitor or ifosfamide. In the PALETTE study, a 6% PR was reported on the pazopanib arm for best overall response [14]. As a second-line treatment in patients with advanced STS, ifosfamide 5 g/m^2/1-day or 3 g/m^2/3-days had a RR of only 6% or 8% in a historical trial [10]. However, a study with a high-dose ifosfamide regimen (14 g/m^2), as a second- or third-line chemotherapy in STS, was able to achieve a higher ORR (25%) with a 7% CR and 18% PR [10,15].

As expected, nintedanib appeared to have been better tolerated than ifosfamide in the EORTC-1506-STBSG study. Overall, there were 66.7% treatment-related AEs on the nintedanib arm and 76.3% on the ifosfamide arm, of which only 17.9% were grade 3–4 for nintedanib *versus* 31.6% for ifosfamide. Ifosfamide resulted in grade 3–4 treatment-related febrile neutropenia in 4 patients (10.5%) *versus* none in the nintedanib arm.

Recent randomised clinical trials have not used single agent ifosfamide as a comparator, which is multifactorial. Many patients still get anthracycline/ifosfamide-based combinations as upfront treatment; the activity of ifosfamide as a single agent after doxorubicin is perceived by many physicians as marginal as highlighted by the single-digit RRs in historical trials as summarised previously; sarcoma experts have doubt about the efficacy of this agent in some common entities such as leiomyosarcoma; the in-patient administration of this compound is complex and expensive and associated with potential renal, neurological and bladder toxicities. On the ifosfamide arm in the EORTC-1506-STBSG study, 15.8% of patients had treatment-related renal and urinary disorders (13.2% acute kidney injury and 2.6% other), and 23.7% of patients had treatment-related encephalopathy. Acute kidney injury occurs in about 12% of all cancer patients [32]. Ifosfamide-induced nephrotoxicity has been reported to range from 15 to 60% depending on the definition of kidney injury, therapeutic protocols used, and duration of follow-up [33]. A retrospective study in adult patents reported ifosfamide-induced acute kidney injury in 14.4% of patients [33]. In our study, 13.2% of the patients receiving ifosfamide experienced acute kidney injury. The incidence of ifosfamide-related encephalopathy has been reported in 5–40% of patients, the incidence can vary depending on the ifosfamide formulation, and risk factors (such as ECOG PS of 2–4, increased baseline serum creatinine levels, and low albumin levels) [34–36]. In our study, 23.7% of patients had ifosfamide-related encephalopathy. About one-third of our patients were over the age of 65 years and the incidence of ifosfamide-related acute kidney injury and encephalopathy falls within previously reported ranges.

Another reason is that second-line treatment options in STS are more diverse than those in the first-line. Ifosfamide competes in this setting with drugs such as trabectedin, eribulin, dacarbazine, pazopanib and active combinations such as gemcitabine/dacarbazine or gemcitabine/docetaxel. Of note, the objective RR and mPFS observed in the control arm of EORTC-1506-STBSG are very similar to what is achieved in non-selected STS patients with other single agents, albeit at the cost of hospitalisation and clinically relevant, in part severe toxicity of ifosfamide. In the phase 3 randomised trial comparing eribulin with dacarbazine, in previously treated patients with advanced liposarcoma or leiomyosarcoma, the mPFS in all patients was 2.6 months (95% CI: 1.9–2.8) for eribulin *versus* 2.6 months (95% CI: 1.8–2.7) for dacarbazine (HR = 0.88, 95% CI: 0.71–1.09, $p = 0.23$). In the PALETTE phase 3 study, the mPFS was 4.6 months (95% CI: 3.7–4.8) for pazopanib *versus* 1.6 months (95% CI: 0.9–1.8) for placebo (HR = 0·31, 95% CI: 0·24–0·40; $p < 0·0001$) [3,13,14]. Ifosfamide remains an important treatment option for STS patients whose first-line treatment did not contain an oxazaphosphorine derivative, who have a sarcoma subtype known to be potentially sensitive to ifosfamide, e.g., synovial sarcoma and whose general condition and organ function allows to administer this toxic agent [37–39].

It has to be noted that recent attempts to replace ifosfamide by better tolerated, easier to administer and potentially more potent oxazaphosphorine derivatives

have failed [40–42]. In a phase 3 trial, the mPFS was 6.3 months for evofosfamide plus doxorubicin *versus* 6.0 months for doxorubicin alone (HR = 0.85; 95% CI: 0.70–1.03; $p = 0.099$) [41,42]. In the phase 3 PICASSO trial, the mPFS was 6.0 months for doxorubicin plus palifosfamide and 5.2 months for doxorubicin plus placebo (HR = 0.86; 95% CI: 0.68–1.08; $p = 0.19$) [42].

The outcome of EORTC-1506-STBSG highlights once again that clinical studies in sarcoma are at high risk of failure, if the mode of action of the investigational agent is not fully understood and the study population pools a variety of STS subtypes, leading to a suboptimal match between compound and treated tumours [40–43]. Future clinical trials in sarcoma must be based on a thorough understanding of the drug's mechanism of action and the relevance of the drug target in STS, and identification of study populations who would have a considerable chance of benefitting from the treatment.

5. Conclusions

Based on the interim analysis, EORTC-1506-STBSG was stopped for futility as per the protocol. Treatment results achieved with nintedanib in advanced STS do not warrant further exploration of the compound in this setting. Although there was no significant difference between the two treatment arms for mPFS or OS, nintedanib did not prolong the outcome of patients when compared with ifosfamide in non-selected, advanced STS.

Author contributors

Patrick Schöffski had the original idea for this trial, proposed it to EORTC and Boehringer Ingelheim, developed and designed the study, and searched the published works. Protocol writing was a collaboration effort between Patrick Schöffski, EORTC Headquarters staff. Together with Patrick Schöffski, Agnieszka Wozniak coordinated tissue collection and the planned molecular analysis. Patrick Schöffski, Maud Toulmonde, Anna Estival, Gloria Marquina, M Dudzisz-Śledź, Mehdi Brahmi, Neeltje Steeghs, Vasilios Karavasilis, Jacco de Haan and Hans Gelderblom contributed to data collection and patient accrual. Christine Olungu maintained the trial database. Judith V M G Bovée performed pathology review. Saskia Litière did the data analysis, and Patrick Schöffski and Sandrine Marreaud oversaw the management of the clinical trial and data collection. All authors contributed to the interpretation of the data, contributed to revisions of the manuscript, and approved the final version. The corresponding author had full access to the data and was responsible for providing regular information to the relevant committees monitoring this trial, and final responsibility for the decision to submit for publication. This article was reviewed and approved by all authors.

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Prior presentations

None.

Conflict of interest statement

PS has received travel support and institutional funding for participating in an advisory function for Boehringer Ingelheim outside of the scope of the nintedanib project; is an active investigator in multiple recent and ongoing Boehringer Ingelheim clinical trials.

MT, VK, JDH, AW, SC, MB, JB, CC-B, SM, SL, LDM, and **CO** have no competing interests.

AE received honoraria from Roche, MSD and AstraZeneca. Travel expenses and conferences from Pharmamar, Lilly and BMS.

GM provided consultation or attended advisory boards for: GSK/Tesaro, Pharmamar, Lilly. Received honoraria from GSK/Tesaro, Roche, Clovis Oncology, Pharmamar, AstraZeneca, Lilly. Travel expenses from Roche, MSD, GSK/Tesaro, Pharmamar.

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