A phase II multicenter study comparing the efficacy of the oral angiogenesis inhibitor nintedanib with the intravenous cytotoxic compound ifosfamide for treatment of patients with advanced metastatic soft tissue sarcoma after failure of systemic non-oxazaphosporine-based first line chemotherapy for inoperable disease "ANITA"

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Ethical review	Approved WMO
Status	Completed
Health condition type	Soft tissue neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON50681

Source
ToetsingOnline

Brief title
Phase II study comparing nintedanib with ifosfamide in soft tissue sarcoma

Condition

- Soft tissue neoplasms malignant and unspecified

Synonym
Cancer, Soft tissue sarcoma

Research involving
Human

Sponsors and support

Primary sponsor: European Organisation for Research in Treatment of Cancer (EORTC)
Source(s) of monetary or material Support: EORTC

Intervention

Keyword: Ifosfamide, Nintedanib, Phase II, sarcoma

Outcome measures

Primary outcome

Primary endpoint: Progression free survival (RECIST 1.1)

Secondary outcome

Secondary endpoints:

· Progression-free rate at 12 weeks (binary)

· Overall survival

· Objective response rate

· Clinical benefit rate

· Response duration

· Total duration of treatment with nintedanib (including treatment beyond

RECIST progression)

Study description

Background summary

Soft tissue sarcoma (STS) is a very heterogeneous family of rare malignant tumors. In the case of localized disease, surgery is the most important and potentially curative treatment option. Patients with inoperable primary tumors or local relapses of STS, or metastatic disease are commonly treated with systemic therapy. Systemic therapy is primarily based on chemotherapy. The anthracycline cytotoxic compound doxorubicin is the most commonly applied first-line treatment in STS. In case of progression after an anthracycline, the few approved chemotherapy options include ifosfamide (all STS subtypes, but preferential activity in synovial sarcoma), dacarbazine (all subtypes, mainly active in leiomyosarcoma) and trabectedin (selected STS subtypes, available in most countries only after failure of both anthracyclines and ifosfamide for patients with leiomyosarcoma and liposarcoma). The oral angiogenesis inhibitor pazopanib, a multi-targeted tyrosine kinase inhibitor against vascular endothelial growth factor receptors [VEGFR] -1,-2,-3, platelet-derived growth factor receptor [PDGFR] and KIT, is approved after failure of anthracyclines and ifosfamide and can prolong progression-free survival after multiple lines of cytotoxic therapy.

Nintedanib is an oral tyrosine kinase inhibitor that acts on platelet derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR) and vascular endothelial growth factor receptor (VEGFR), which all are potentially relevant and in part clinically validated targets in STS. The drug is generally well tolerated and approved by regulatory agencies for treatment of idiopathic pulmonary fibrosis and for adult patients with locally advanced metastatic or locally recurrent non-small cell lung cancer after first-line chemotherapy. The angiogenesis inhibitor nintedanib has not yet been studied in patients with STS.

The oral angiogenesis inhibitor pazopanib has already become part of the treatment of STS after failure of chemotherapy and there is a good rationale to test this or similar compounds in earlier lines of sarcoma treatment. The current study will compare the efficacy of the oral angiogenesis inhibitor nintedanib with ifosfamide in patients with advanced, inoperable and/or metastatic STS in second line.

Study objective

The primary objective of the trial is to evaluate whether nintedanib given as second-line therapy for advanced, inoperable and/or metastatic STS prolongs progression-free survival when compared with ifosfamide.

Secondary objectives are to evaluate the efficacy of nintedanib as compared to ifosfamide in terms of progression-free rate at 12 weeks, overall survival,

objective response rate, patient benefit rate, response duration, total duration of treatment with nintedanib safety, Health related Quality of Life and Health Economics.

Exploratory objectives include an analysis of putative predictive biomarkers for the anti-tumor effects of the treatment.

Study design

This is a prospective, multicentric, randomized, open label Phase II trial investigating whether the oral angiogenesis inhibitor nintedanib, as compared to the intravenous cytotoxic compound ifosfamide, given for patients with advanced, inoperable and/or metastatic STS after failure of first line chemotherapy prolongs progression-free survival.

Intervention

Experimental arm (A):
Nintedanib 200 mg twice daily orally.

Nintedanib will be given continuously until clinically relevant disease progression according to the investigator's assessment or until other criteria for treatment discontinuation are met as specified in the protocol. Dosing beyond RECIST 1.1 progression is allowed for the oral agent if the patient still derives benefit from the treatment.

Standard Arm:
Ifosfamide 3 g/m2 intravenously on days 1, 2 and 3 every 21 days for up to a maximum of 6 cycles.

Study burden and risks

-possible side effects from the treatment with nintedanib
-patients are asked to complete questionnaires, prior to start of treatment, during treatment, and possibly up to a year after treatment.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

SELECTION CRITERIA, *Written informed consent
*Histologically proven advanced, inoperable (medical or surgical) and/or metastatic malignant STS of intermediate or high grade, excluding the following tumor types:
* Well-differentiated liposarcoma/atypical lipoma
* Embryonal rhabdomyosarcoma
* Chondrosarcoma (extraskeletal myxoid chondrosarcoma is eligible)
* Osteosarcoma (extraskeletal osteosarcoma is eligible)
* Ewing family of tumors/primitive neuroectodermal tumor
* Gastro-intestinal stromal tumor
* Dermatofibrosarcoma protuberans
* For STS where no established grading system exists, or sarcoma subtypes which are very indolent or have an unpredictable clinical behavior, patient entry requires prospective approval in writing, on a case-by-case basis by the Study Coordinator of this trial and EORTC Headquarters (HQ).
*Representative formalin fixed, paraffin embedded tumor blocks or unstained tissue slides, either from the primary tumor or a metastatic lesion, must be available for histological central review.
* One (and no less or more than one) line of previous systemic chemotherapy for

advanced, inoperable and/or metastatic malignant STS. Note: Patients treated in first line with doxorubicin/olaratumab or doxorubicin/placebo +/- olaratumab/placebo maintenance qualify for the trial and such treatment will be considered as one line according to the protocol.
* Prior neoadjuvant, adjuvant and or first-line maintenance systemic chemotherapy for locally advanced or metastatic STS is allowed and does count as zero lines of treatment, provided that the disease did not progress during neoadjuvant and/or adjuvant therapy or within 12 weeks after completion of the perioperative treatment. In case the disease progressed during neoadjuvant, adjuvant and or first-line maintenance systemic chemotherapy or within 12 weeks after its
completion, the treatment is counted as one line and the patient can theoretically participate in the trial, provided all other selection criteria are met.
* Prior to study enrolment, all patients need to have confirmed RECIST 1.1 disease progression based on local investigator's assessment.
* Presence of measurable disease according to RECIST 1.1.
* Age 18 years or older.
* WHO performance status (PS) 0-2.
* Life expectancy of at least 3 months.
Adequate bone marrow, liver and renal function and coagulation parameters:
* neutrophils >= 1.5 x 10^9/L;
* hemoglobin >= 9 g/dL (or >= 5.6 mmol/L). Blood transfusions or the administration of hematopoietic growth factors are allowed to achieve these baseline values;
* platelets >= 100 x 10^9/L. Platelet transfusions or the administration of hematopoietic growth factors are allowed to achieve these baseline values;
* Total bilirubin <= ULN;
* Patients with Gilbert syndrome and/or bilirubin < 2xULN and normal AST/ALT are eligible;
* SGPT/ALT and SGOT/AST <= 2.5 x ULN for patients with liver metastasis;
* SGPT/ALT and SGOT/ AST <= 1.5x ULN for patients without liver metastasis;
* Serum creatinine or creatinine clearance/eGFR within normal limits to baseline assessed as per local standard method;
* International normalized ratio (INR) <= 2;
*Prothrombin time (PT) and partial thromboplastin time (PTT) <= 1.5x ULN
*Normal cardiac function (left ventricular ejection fraction (LVEF)
* Absence of serious illnesses or medical conditions, including a history of chronic alcohol abuse, active and chronic hepatitis B or C, chronic infection with HIV or clinically relevant liver cirrhosis.
* Absence of active gastrointestinal disorders or abnormalities that interfere with absorption of the study drug.
* Women of childbearing potential (WOCBP) must have a negative serum pregnancy test within 72 hours prior to randomization., *No history of central nervous system metastasis or leptomeningeal tumor spread.
* No active brain metastases (e.g. stable for <4 weeks, no adequate previous treatment with radiotherapy, symptomatic, requiring treatment with

anti-convulsants; dexamethasone
* No prior exposure to an oxazaphosphorine agent, including but not limited to ifosfamide, cyclophosphamide, trofosfamide or evofosfamide (TH-302).
* No prior exposure to oral or intravenous angiogenesis inhibitors, including but not limited to tyrosine kinase inhibitors such as pazopanib, sunitinib, sorafenib, axitinib or similar or monoclonal antibodies targeting angiogenesis.
* No other anti-cancer therapy (systemic therapy, radiotherapy (except for brain and extremities), surgery, limb perfusion, immunotherapy) within 28 days prior to randomization.
* No treatment with another investigational agent within 28 days prior to randomization.
* No treatment with another investigational agent concomitantly with the trial.
* No known hypersensitivity to or known specific contraindications for the use of nintedanib or ifosfamide.
No uncontrolled arterial hypertension defined at baseline as blood pressure >= 150/100 mmHg despite adequate medical therapy.
* No use of therapeutic anticoagulation (except low-dose heparin and/or heparin flush as needed for maintenance of an indwelling intravenous devise) or anti-platelet therapy (except for low-dose therapy with acetylsalicylic acid < 325 mg per day).
* No known inherited predisposition for bleeding or thromboembolism.
* No history of clinically significant hemorrhagic or thromboembolic event in the past 6 months.
* No persistence of clinically relevant therapy-related toxicity from previous chemotherapy and/or radiotherapy. Grade 1 or 2 adverse events (AEs) are acceptable.
* No history, within the past five years, of malignancies other than STS (except: basal or squamous cell carcinoma of the skin, in situ carcinoma of the cervix, resected prostate cancer staged pT1-2 with Gleason Score <= 6 and postoperative PSA < 0.5 ng/ml). Patients with a history of other malignancies who are disease-free from that condition for more than 5 years are eligible.

Exclusion criteria

See section D4a

Study design

Design

Study phase: 2

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	15-02-2018
Enrollment:	22
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ifosfamide
Generic name:	Ifosfamide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Nintedanib
Generic name:	Nintedanib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	25-04-2017
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	11-10-2017
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van

	Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	10-10-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	11-02-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-12-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	10-12-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2016-002093-12-NL

Register	ID
ClinicalTrials.gov	NCT02808247
CCMO	NL60208.031.17

Study results

Date completed: 01-01-2022

Results posted: 06-05-2022

First publication
03-05-2022