Randomized phase II study of brostallicin (PNU-166196A) versus doxorubicin as first line chemotherapy in patients with advanced or metastatic soft tissue sarcoma

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The objective of this trial is to evaluate the activity and safety of Brostallicin used as first line chemotherapy in patients with advanced or metastatic soft tissue sarcoma.

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

Summary

ID

NL-OMON29956

Source
ToetsingOnline

Brief title
BRTA-0100-015

Condition

- Soft tissue neoplasms malignant and unspecified

Synonym
cancer in soft tissue, Softtissuesarcoma

Research involving
Human

Sponsors and support

Primary sponsor: Nerviano Medical Sciences Srl, Italy
Source(s) of monetary or material Support: Nerviano MS

Intervention

Keyword: Brostallicine, Chemotherapy, Metastatic, Soft tissue sarcoma

Outcome measures

Primary outcome

Primary end-point: progression free survival 6 months (26 weeks) after start of

treatment

Secondary outcome

Secondary: overall progression free survival, objective tumor response

(RECIST), duration of response, overall survival

Safety: Safety profile (CTC-AE, version 3.0)

Study description

Background summary

Soft Tissue Sarcoma (STS) is a rare group of heterogeneous mesenchymal cancers originating from connective tissue. The annual incidence of STS is around 2-3/100.000. The 5-year survival in Europe for adult STS (excluding visceral STS) averages 60%, with substantial geographic variations. The median survival time in patients with metastatic STS is usually < 12 months, and only a small subgroup of patients may achieve long term survival.
In advanced soft tissue sarcomas of adults, single agent doxorubicin is still the standard chemotherapy against which more intensive or new drug treatments should be compared.
Combinations of high dose Doxorubicin and Ifosfamide have shown a promising activity (despite an increase of toxicity) and may therefore be used in the frame of clinical trials for young patients with a good performance status.
New treatment options are urgently required. Very few active treatments exist

for the treatment of STS (Doxorubicin, Ifosfamide and DTIC are the only drugs that have shown activity in this disease) and there is a high medical need for new active agents in all lines of chemotherapy. Even though doxorubicin is considered as a standard first line therapy, it induces at best a modest response rate and a modest progression free survival, which justifies using experimental agents up-front.
Brostallicin is a bromoacrylolyl derivative of distamycin A which has shown very promising preclinical activity against a variety of human tumors either in vitro or in vivo. the objective response rate was low but prolonged stable diseases were observed: this is the specific reason for using PFS as the principal end-point for this drug. Elderly patients have been selected for conducting the present study since they are generally not suitable for treatment with aggressive chemotherapy regimens such as high-dose ifosfamide either alone or with doxorubicin, which are
commonly used in younger patients in the frame of clinical trials.

Study objective

The objective of this trial is to evaluate the activity and safety of Brostallicin used as first line chemotherapy in patients with advanced or metastatic soft tissue sarcoma.

Study design

This is a randomized non comparative multicenter phase II trial.
Eligible patients will be randomized at the EORTC Data Center to receive Doxorubicin (standard treatment) or Brostallicin (investigational treatment), with a 1:2 ratio.
Treatment will be given for 6 cycles, unless progression of the disease, unacceptable toxicity or patient*s refusal occurs earlier.
Disease status will be evaluated 6 months (at least 26 weeks) after the start of treatment. Patients alive and progression free at that time will be considered as successes.
Adverse events will be assessed separately for each cycle of therapy.
The one-stage Fleming design will be applied. A total of 108 eligible patients starting protocol therapy are required (36 in the Doxorubicin arm, 72 in the Brostallicin arm).

Intervention

Brostallicin (PNU-166196A), 10 mg/m², 10 min IV infusion, q3w. In case of good tolerance, the dose will be increased to 12,5 mg/m². Maximum 6 cycles, unless the patient withdraws before due to disease progression, drug related event, intercurrent illness or patient refusal

or

Doxorubicin, 75 mg/m², IV bolus, q3w

Study burden and risks

Patients will undergo a full medical examination. An electrocardiogram (ECG) and a scan (MUGA) or cardiac echography (ECHO) to monitor the hartfunstioning, a laboratory blood test, and radiographs, CT scan or Magnetic Resonance Imaging (MRI) to assess the extent of tumor.
A Pregnancy test for women of childbearing capacity will be performed.
To verify the initial diagnosis (done by the pathologist), glass slides or representative images of tumor material (taken at the time of establishing the diagnosis or during surgical procedure) will be reviewed by a pathologist expert in this field.
All patients having chemotherapy will need to have weekly blood samples taken, and there is a risk of bruising or pain, at the site from where the blood was drawn.
Every 3 weeks, patients will be seen at the outpatient*s department, for a physical examination and to take some blood samples.
The cardiac function, if necessary, will be monitored at regular intervals with a MUGA scan or echocardiography. This in any case will happen after 6 cycles.
CT- or MRI scans will be taken every 6 weeks during therapy.
See also protocol page 28, Summary table.

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

• Histologically proven advanced and/or metastatic malignant soft tissue sarcoma of high or intermediate grade, and of one of the following histologies (WHO classification 2002):
• Adipocytic (liposarcoma dedifferentiated, myxoid/round cell, pleomorphic, mixed-type, not otherwise specified)
• Fibroblastic (adult fibrosarcoma, myxofibrosarcoma, sclerosing epithelioid fibrosarcoma)
• So-called fibrohistiocytic (pleomorphic Malignant Fibrous Histiocytoma (MFH), giant cell *MFH*, inflammatory *MFH*)
• Leiomyosarcoma
• Malignant glomus tumors
• Skeletal muscles (rhabdomyosarcoma, alveolar or pleomorphic) excluding embryonal rhabdomyosarcoma
• Vascular (epithelioid haemangioendothelioma, angiosarcoma)
• Uncertain differentiation (synovial, epithelioid, alveolar soft part, clear cell, desmoplastic small round cell, extra-renal rhabdoid, malignant mesenchymoma, perivascular epithelioid cell tumor (PEComa), intimal sarcoma) excluding chondrosarcoma, Ewing tumors / Primitive neuroectodermal tumor (PNET)
• Malignant peripheral nerve sheath tumors
• Malignant solitary fibrous tumors
• Undifferentiated soft tissue sarcomas not otherwise specified
• Other types of sarcoma (not listed as ineligible), if approved by the Study Coordinator (written or e-mail approval needed prior to registration)
• The following tumor types are ineligible:
• Embryonal rhabdomyosarcoma
• Chondrosarcoma
• Osteosarcoma
• Ewing tumors / PNET
• Gastro-intestinal stromal tumors
• Dermatofibrosarcoma protuberans
• Inflammatory myofibroblastic sarcoma
• Neuroblastoma
• Malignant mesothelioma

• Mixed mesodermal tumors of the uterus
• Formalin fixed paraffin embedded tumour blocks and representative H/E (haematoxylin/eosin) slides must be available for histological central review. Histological central review is not required before treatment start but is mandatory within 14 days of registration. Local histopathological diagnosis will be accepted for entry into the study.
• Relapsed, refractory and/or metastatic disease incurable by surgery or radiotherapy.
• Evidence of objective progression within the last 6 months (RECIST) documented by measurements of disease, i.e. appearance of new lesions, increase of 20% in the sum of the diameters of measurable lesions, or progression of non measurable lesions to be confirmed by an external review, without other specific treatment since objective documentation of progression.
• Presence of measurable disease (according to RECIST criteria)
• No prior chemotherapy regimen for advanced or metastatic disease; (neo)adjuvant therapy is allowed.
• At least 60 years of age, or patients at least 18 years of age non suitable for intensive chemotherapy combination treatments
• WHO performance status 0 or 1
• Absence of symptomatic or known CNS metastases
• Adequate bone marrow function (ANC> 2. 109/l, PLA>100 109/l)
• Adequate hepatic function (bilirubin <= 1.5 UNL , SGOT/AST <= 2.5 UNL and SGPT/ALT <= 2.5 UNL, Alk.phos <= 2.5 UNL)
• Adequate renal function: calculated or measured creatinine clearance >= 60 ml/min (see Appendix C)
• Clinically normal cardiac function (LVEF assessed by MUGA or ECHO), normal 12 lead ECG, and in the past 6 months no serious cardiac illness or medical condition including but not confined to:
• History of documented congestive heart failure (CHF)
• High-risk uncontrolled arrhythmias
• Angina pectoris requiring antianginal medication
• Clinically significant valvular heart disease
• Evidence of transmural infarction on ECG
• Poorly controlled hypertension (e.g. systolic >180mm Hg or diastolic greater than 100mm Hg)
• No prior history of malignancies other than sarcoma (except for basal cell or squamous cell carcinoma of the skin, carcinoma in situ of the cervix or breast, or the patient has been free of any other malignancies for > 3 years).
• Women should either not be of childbearing potential (having had a hysterectomy, a bilateral oophorectomy or bilateral tubal ligation), or be post-menopausal with a total cessation of menses of >1 year, or not be pregnant (negative serum pregnancy test at entry);should not be lactating; should agree to use contraceptive methods (with a documented failure rate < 1%, vasectomized partner sterile prior to trial entry and sole sexual partner or double-barrier contraception). Sexually active male participants must use barrier methods of contraception.
• Absence of any serious and/or unstable pre-existing medical, psychiatric or other condition (including lab abnormality) that could interfere with patient safety or obtaining informed consent.
• No active uncontrolled infection including known history of AIDS

• Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial
• Before patient registration/randomization, written informed consent must be given according to ICH/GCP, and national/local regulations.

Exclusion criteria

The following tumor types are ineligible: . Embryonal rhabdomyosarcoma . Chondrosarcoma . Osteosarcoma . Ewing tumors / PNET . Gastro-intestinal stromal tumors . Dermatofibrosarcoma protuberans . Inflammatory myofibroblastic sarcoma . Neuroblastoma . Malignant mesothelioma . Mixed mesodermal tumors of the uterus.

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:	Recruitment stopped
Start date (anticipated):	01-12-2007
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Brostallicin
Generic name:	brostallicin

Product type:	Medicine
Brand name:	Doxorubicin
Generic name:	Doxorubicin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	14-08-2006
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	09-11-2007
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2006-001861-40-NL
CCMO	NL13613.058.06