Phase II clinical study of concurrent Pazopanib for non-metastatic Sarcoma patients to be treated with Radiotherapy, localized in the extremities, trunk and chest wall or the head and neck region.

Published: 20-10-2015
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Primary Objective:To investigate the proportion of patients with resection specimens demonstrating induction of a pathological (near) complete remission (* 95% tumor regression)Secondary Objectives:To study tumour changes to pre-operative pazopanib...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Musculoskeletal and connective tissue neoplasms
Study type	Interventional

Summary

ID

NL-OMON47205

Source
ToetsingOnline

Brief title
PASART-2

Condition

- Musculoskeletal and connective tissue neoplasms

Synonym
sarcoma, soft tissue tumor

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: Novartis,van de firma Novartis

Intervention

Keyword: pazopanib, radiotherapy, sarcoom, soft tissue tumor

Outcome measures

Primary outcome

The resection specimen of each patient will evaluated for the individual percentage of tumor regression. For the analysis of this primary endpoint, a patient is either a *success* (a pathological (near) complete remission being * 95% tumor regression) or a *failure* (< 95% tumor regression). The proportion of patients with resection specimens demonstrating a pathological (near) complete remission will be calculated. The percentage tumor regression is the proportion of the tumor mass replaced with other tissue where the tumor has regressed, usually fibrous or fibro- inflammatory tissue, necrosis, calcifications or acellular mucin pools

Secondary outcome

* Proportion of patients completed radiotherapy without delay (By definition for this protocol, any lengthening of the overall treatment time by * 3 days is not a delay. Any increase in the overall treatment time of * 4 days will be registered as a delay, including the reason for delay (e.g. machine down-time, public holidays, toxicity etc.)

* Rate of response as measured by RECIST v 1.1 at 4 weeks after completing radiotherapy

* Incidence of toxicities measured by NCI-CTCAE v4.0

* Incidence of acute post-operative wound complications up to 3 weeks (+/- 1 week) after surgery as defined in section 6.1.3 and reference 29 (see also appendix XII)

* local control rate at 2 years , defined as the absence of sarcoma at the original site, counted from day of surgery

* Rate of R0 resections

* Rate of R1 resections

* Disease free survival at 2 and 5 years

* Overall survival at 2 and 5 years

Study description

Background summary

Radiotherapy (RT) alone is able to induce a clinically significant effect with a variable pathologic response (a pathological complete remission, pCR, defined as * 95%, or * 5% remaining visible tumour cells) in only about 10% of cases. A prior phase I study (PASART-1; NCT01985295) suggested that 25 x 2 Gy preoperative RT in combination with once daily 800mg oral pazopanib is feasible, while inducing tissue replacing tumor that can consist of fibrosis and necrosis in 40% of thus treated patients.
An interim analysis showed a 30% pathologic response. In part II the radiotherapy will be reduced tot 18 fractions of 2 Gy.

Uit de interim analyse blijkt dat in 30% van de studiepopulatie een pathologische respons is bereikt en wordt in deel II de radiotherapie dosering naar beneden bijgesteld naar 18 x 2 Gy.

Study objective

Primary Objective:
To investigate the proportion of patients with resection specimens demonstrating induction of a pathological (near) complete remission (* 95% tumor regression)

Secondary Objectives:
To study tumour changes to pre-operative pazopanib and radiotherapy measured by diffusion-weighted and/or blood oxygenation level-dependent MR imaging (DW-MRI or BOLD-MRI), to assess tolerability and toxicity profile of pazopanib with radiotherapy in the pre-operative setting, to determine response to pazopanib and radiotherapy by RECIST 1.1. criteria, to describe any pathological evidence of tumor regression after pre-operative pazopanib and radiotherapy, to determine local control rates, to investigate the rate of R0 and R1 resections, to investigate the incidence of post-operative wound complications, to investigate recurrence rate at 5 years (local and/or distant disease)

Exploratory Objectives:
To study changes in diffusion weighted characteristics; correlation between diffusion weighted MRI characteristics and histopathological response evaluation; correlation between pazopanib plasma and PK tumor tissue; PK and PD correlations as between pazopanib exposure and changes in tumor characteristics on MRI and between pazopanib exposure (plasma PK and tumour PK) and induction of a pathological (near) complete remission (* 95% tumor regression) as measured in the resection specimen; to characterize gene expression, proteomic and and phospho-proteomic, exome targeted sequencing and copy number aberation tumour signatures before and after treatment with pazopanib; to examine changes in angiogenesis makers in tumour tissue after neo-adjuvant treatment with pazopanib using standard immunohistochemistry; to explore the feasibility of measuring gene expression changes both in tumour tissue and peripheral blood after neo-adjuvant treatment with pazopanib and radiotherapy; to explore the potential relationships between changes in radiological, blood and tumour biomarkers changes and any observed anti-tumour activity with neo-adjuvant pazopanib and radiotherapy; to explore the relationship between changes in tumour vasculature assessed by functional MRI with steady-state pazopanib plasma concentrations. To explore changes in tumour proliferation markers and potential predictors for wound complications.

Study design

A prospective Simon two-stage phase II clinical trial.

Intervention

Radiotherapy in combination with pazopanib.
In part I 25 x 2 Gy was delivered in combination with pazopanib. In part II the radiation dose will be reduced to 18 x 2 Gy (in combination with pazopanib).

Study burden and risks

Possible burden and risks associated with study participation comprise the systemic toxicity profile of pazopanib, the extra blood samples for safety

tests and PK and the extra tumour biopsy. Also extra MRI scans.
The possible benefit is a more effective neoadjuvant therapy prior to definitive surgery

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 confirmed newly diagnosed non-metastatic intermediate to high grade soft tissue sarcoma localized to the extremities, trunk and chest wall or the head and neck area, for which the standard treatment is a combination of radiotherapy and surgery (deep seated and/or > 5cm according to the RECIST 1.1 criteria and/or an anticipated close resection margin and/or grade II/III according to the FNCLCC definition)
* Age * 18 years
* WHO performance status of * 1

* Able and willing to undergo blood sampling for PK and PD analysis
* Able to swallow and retain oral medication
* Able and willing to undergo MRI scanning
* Able and willing to undergo tumor biopsies
* Adequate organ functions as described by the laboratory findings in table 1. For thyroid function, the T4 and TSH values must be within normal values of the range of the participating centers
* Written informed consent

Exclusion criteria

* Prior malignancies; except another malignancy and disease-free for * 5 years, or completely resected non-melanomatous skin carcinoma or successfully treated in situ carcinoma
* Patients with recurrent sarcomas (even without prior radiotherapy)
* Ewing sarcoma and other PNET family tumors, rhabdomyosarcomas (both pediatric and adult), osteosarcomas
* Clinically significant gastrointestinal abnormalities which might interfere with oral dosing diagnosed as:
* Active peptic ulcer disease
* Inflammatory bowel disease, ulcerative colitis, or other gastrointestinal conditions with increased risk of perforation
* History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days prior to beginning study treatment
* Major resection of the stomach or small bowel
* Poorly controlled hypertension [defined as systolic blood pressure (SBP) of * 140 mmHg or diastolic blood pressure (DBP) of * 90mmHg]
* Unstable or serious concurrent condition (e.g., active infection requiring systemic therapy)
* Prolongation of corrected QT interval (QTc) > 480 msecs on ECG
* History of any one of more of the following cardiovascular conditions within the past 6 months:
* Cardiac angioplasty or stenting
* Myocardial infarction
* Unstable angina
* Symptomatic peripheral vascular disease
* Coronary artery by-pass graft surgery
* Class II, III or IV congestive heart failure as defined by the New York Heart Association (NYHA)
* History of cerebrovascular accident, pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months
* Macroscopic hematuria
* Hemoptysis that is clinically relevant within 4 weeks of first pazopanib
* Evidence of active bleeding or bleeding diathesis
* Prior major surgery or trauma within 28 days prior to first dose of study medication and/or presence of any non-healing wound, fracture, or ulcer
* Chemotherapy or radiation therapy within 2 weeks prior to the first dose of study

medication
* Biological therapy or treatment with an investigational agent within 28 days or 5 half-lives, whichever is longer prior to the first dose of study medication
* Prohibited medications listed in the protocol for 14 days or five half-lives of a drug (whichever is longer) prior to visit 1 and for the duration of the study
* Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to pazopanib
* 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
* Female patients who are pregnant, breast-feeding or male or female patients of reproductive potential who are not employing an effective method of birth
Note: Lactating females who discontinue nursing prior to the first dose of study drug and agree to refrain from nursing throughout the treatment period and for 14 days following the last dose of study drug are eligible.
AND:
Evidence of post-menopausal status, or negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered postmenopausal if they are amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:
* Women <50 years old would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and with luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution
* Women *50 years of age would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, radiation-induced oophorectomy with last menses >1 year ago, chemotherapy-induced menopause with >1 year interval since last menses, or surgical sterilisation (bilateral oophorectomy or hysterectomy).

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-03-2016
Enrollment:	27
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	20-10-2015
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	10-12-2015
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	30-03-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-09-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-04-2017
Application type:	Amendment
Review commission:	METC NedMec

Approved WMO Date:	14-04-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-09-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-02-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-05-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-05-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-06-2018
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2015-004134-95-NL
ClinicalTrials.gov	NCT02575066
CCMO	NL55004.031.15