Phase I clinical study of a combined modality treatment of sarcomas of the extremities or in head and neck area with radiotherapy (RT) and dose-escalation of Pazopanib

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To study the safety and feasibility of adding 6 weeks of orally administered Pazopanib to 25 x 2Gy in 5 weeks preoperative radiotherapy in soft tissue sarcoma patients (to identify the Dose Limiting Toxicity (DLT) and the Recommend Phase II Dose (...

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

Summary

ID

NL-OMON39288

Source
ToetsingOnline

Brief title
PASART-1

Condition

- Musculoskeletal and connective tissue neoplasms

Synonym
sarcoma, soft tissue tumor

Research involving
Human

Sponsors and support

Primary sponsor: Nederlands Kanker Instituut
Source(s) of monetary or material Support: GlaxoSmithKline,GSK

Intervention

Keyword: Pazopanib, radiotherapy, sarcoma

Outcome measures

Primary outcome

To study the safety and feasibility of adding 6 weeks of orally administered

Pazopanib to 25 x 2Gy in 5 weeks preoperative radiotherapy in soft tissue

sarcoma patients.

Secondary outcome

The secondary objective is to explore the feasibility to perform perfusion

weighted MRI imaging regarding tumor response to RT and neoangio genesis

inhibitor by pazopanib.

Study description

Background summary

Soft tissue sarcomas represent less than 1 % of all newly diagnosed malignant tumors, predominantly in the extremities. For most patients presenting with localized disease the combination of surgery and radiotherapy is considered standard of care. Pre-operative irradiation is supplied to a lower dose (50 Gy versus 60-66 Gy) and to a smaller volume, thereby probably reducing the risk of late and often irreversible complications. Myxoid liposarcomas showed marked necrosis after 50 Gy preoperative radiotherapy probably by a shutdown of the tumor vasculature.

Study objective

To study the safety and feasibility of adding 6 weeks of orally administered Pazopanib to 25 x 2Gy in 5 weeks preoperative radiotherapy in soft tissue

sarcoma patients (to identify the Dose Limiting Toxicity (DLT) and the Recommend Phase II Dose (RPTD) if pazopanib is added to 50 Gy pre-operatively)
To explore the feasibility of performing data acquisition for translational research regarding tumor response and normal tissue toxicity. This should be considered as a feasibility study for future trials in larger patient groups.

Study design

This Phase I study will be performed in 3 centers experienced in the treatment of sarcomas (Antoni van Leeuwenhoek Hospital-Netherlands Cancer Institute, Erasmus University Medical Center, Leiden University Medical Center).
The starting dose is 400 mg/day since Phase I and II studies revealed that the well tolerated dose was 800 mg/day. Besides the potential synergistic effect or additive anti-tumor effect, also the toxicity might be potentiated by the combination treatment. Therefore, 50 % of the dose given in Phase I, II and III monotherapy trials is a conservative starting dose level for the combination treatment.

The protocol will follow a 3 + 3 design (see Figure 1 and Table 1 in Protocol):
Per cohort, 3 patients will be treated according to the treatment protocol (section 4.1.1). The time interval between the start of treatment of the first patient of one cohort and the third patient of the similar cohort has to be equal to or larger than 3 weeks to avoid that 3 patients of the same cohort will start simultaneously. The dose is allowed to be escalated if the third patient of the last cohort did not show any DLT within 3 weeks after the end of the treatment protocol. If one patient is experiencing a DLT, an additional cohort of 3 patients will be added within the similar dose level (again the time interval between the start of treatment of the first patient of one cohort and the third patient of the similar cohort has to be equal to or larger than 3 weeks to avoid that 3 patients of the same cohort will start simultaneously).
If only 1 of the 6 patients experienced a DLT the dose will be escalated to the next dose level. If 2 (or more) patients of the 6 patients experienced DLT the previous dose level is the Recommend Phase II Dose (RPTD) (the current dose level is considered as the maximum administered dose (MAD).

The protocol will NOT follow a 3 + 3 design concerning wound complication after surgery; the reason for this is the baseline risk of wound complication after surgery with preoperative irradiation alone. O*Sullivan reported in a phase III trial randomizing between pre-operative and post-operative radiotherapy of extremity sarcoma patients a 35% incidence (31/88 patients) wound complications {O'Sullivan, 2002} after 4 months of follow up. Since the decision of further dose escalation will be made only after 3 weeks a smaller wound complication probability can be expected. Assuming a 25 % incidence of wound complications, the probability that 0, 1, 2 or 3 patients in one cohort will experience wound complications is 42%, 42%, 14% and 2% respectively (according to a binomial distribution with n=3 and P(wound complication)=0.25). Therefore, the DLT for wound complications after surgery is defined as if more than 2 out of 3 (or

more than 3 out of 6) patients experience wound complications.

Intervention

25 x 2Gy preoperative radiotherapy concurrent with and 1 week preceded by Pazopanib in escalating dosages.

Study burden and risks

• the known side effects for Pazopanib
• the repeated tumor biopsies
• the repeated MRI scans
• the psychological burden of participation in a clinical trial

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

1. Histologically confirmed newly diagnosed intermediate to high grade soft tissue sarcoma of and localized to the extremities or head and neck for which the treatment is a combination of both surgery and radiotherapy (deep seated, > 5cm according to the RECIST criteria, grade II/III according to the WHO definition).
2. Age >= 18 years
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.
4. 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
5. Before patient registration/randomization, written informed consent must be given according to ICH/GCP, and national/local regulations.
6. No prior malignancies; except subjects who have had another malignancy and have been disease-free for 5 years, or subjects with a history of completely resected non-melanomatous skin carcinoma or successfully treated in situ carcinoma are eligible.
7. No clinically significant gastrointestinal abnormalities which might interfere with oral dosing diagnosed as:
• Active peptic ulcer disease
• Known intraluminal metastatic lesion/s with suspected bleeding
• 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
• Malabsorption syndrome
• Major resection of the stomach or small bowel
8. No uncontrolled hypertension
9. No unstable or serious concurrent condition (e.g., active infection requiring systemic therapy).
10. No poorly controlled hypertension
11. No prolongation of corrected QT interval (QTc) >480 msecs.
12. No history of any one of more of the following cardiovascular conditions within the past 6 months:
a. Cardiac angioplasty or stenting
b. Myocardial infarction
c. Unstable angina
d. Symptomatic peripheral vascular disease
e. Coronary artery by-pass graft surgery
f. Class II, III or IV congestive heart failure as defined by the New York Heart Association (NYHA)
g. History of cerebrovascular accident, pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months.
13. No history of cerebrovascular accident, pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months.
Note: Subjects with recent DVT who have been treated with therapeutic anti-coagulant agents (excluding therapeutic warfarin) for at least 6 weeks are eligible.

14. No macroscopic hematuria
15. No hemoptysis that is clinically relevant within 4 weeks of first dose of study drug.
16. No evidence of active bleeding or bleeding diathesis.
17. No known endobronchial lesions or involvement of large pulmonary vessels by tumour
18. No prior major surgery or trauma within 28 days prior to first dose of study drug and/or presence of any non-healing wound, fracture, or ulcer.
19. No chemotherapy or radiation therapy within 2 weeks prior to the first dose of study drug.
20. No biological therapy, hormonal therapy or treatment with an investigational agent within 28 days (for bevacizumab, 60 days) or 5 half-lives, whichever is longer prior to the first dose of study drug.
21. No 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 should be taken
22. No known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to pazopanib
23. Possibility for venous access for PK sampling.
24. Able to swallow and retain oral medication.
25. A life expectancy of at least 12 weeks.
26. Adequate Organ Function as defined in Table 1 of Protocol

Exclusion criteria

1. Patients with recurrent sarcomas (even without prior radiotherapy) are not eligible. Ineligible sarcoma subtypes as well are: Ewing sarcoma and other PNET family tumors, rhabdomysarcomas (both pediatric and adult), osteosarcomas.
2. Patient should not be pregnant or lactating.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-04-2012

Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Pazopanib
Generic name:	Pazopanib

Ethics review

Approved WMO Date:	11-11-2009
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	02-06-2010
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	21-11-2011
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	18-12-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-01-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	14-05-2014

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	EUCTR2009-014901-15-NL
CCMO	NL29294.031.09