A Phase 1b/2 Study of AMG 655 in Combination With Doxorubiicn for the First-Line Treatment of Locally Advanced or Metastatic, Unresectable Soft Tissue Sarcoma

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Part 1 (phase 1b): to identify a dose of AMG 655 in combination with doxorubicin that is safe and tolerated as determined by the incidence of dose limiting toxicity Part 2 (phase2): To estimate the efficacy, as measured by progression-free survival...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON32142

Source
ToetsingOnline

Brief title
Treatment of Locally Metastatic, Unresectable Soft Tissue Sarcoma

Condition

- Other condition

Synonym
Soft Tissue Sarcoma

Health condition

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Research involving
Human

Sponsors and support

Primary sponsor: Amgen
Source(s) of monetary or material Support: Amgen

Intervention

Keyword: AMG 655, Phase Ib/II, Soft Tissue Sarcoma, Unresectable

Outcome measures

Primary outcome

Part 1 (phase 1b): To identify a dose of AMG 655 in combination with doxorubicin that is safe and tolerated as determined by the incidence of dose limiting toxicity.

Part 2 (phase 2): To estimate the efficacy, as measured by progression-fee survival, AMG 655 at the dose selected in part 1, in combination with doxorubicin.

Secondary outcome

To estimate the clinical benefit of AMG 655 in combination with doxorubicin, as measured by objective response rate, time to response, duration of response, clinical benefit rate (complete response, partial response, and disease stabilization more or equal to 12 weeks, as measured by modified response evaluation criteria in solid tumors, progression-free survival (part 1), and overall survival.

To evaluate the safety and tolerability of AMG 655 in combination with doxorubicin (part 2)

To evaluate anti-AMG 655 antibody formation

To evaluate the pharmacokinetics of AMG 655 (part 1; selected sites in part 2)

Exploratory:

To investigate the objective response rate and progression fee survival in subjects treated with AMG 655 monotherapy, after disease progression on doxorubicin plus placebo (part 2, arm B)

To investigate the relationship between AMG 655 pharmacokinetics and treatment outcomes (including tumor response and pharmacodynamic endpoints)

To investigate the pharmacodynamics response to AMG 655 in combination with doxorubicin, as assessed by apoptosis biomarkers (caspase 3/7, genomic DNA levels; part 1; selected sites in part 2), and correlate with treatment outcomes

To investigate other potential biomarker development (e.g., biochemical levels and abundance of drug targets) by biochemical analysis of blood and/or tumor tissue, and correlate with treatment outcomes

To investigate the genetic variation in drug metabolism genes, cancer genes, and drug target genes, and correlate with treatment outcomes (optional; requires separate informed consent)

To estimate the effect of AMG 655 on patient reported outcomes pertaining to cancer-related and treatment-related symptoms and health-related quality of life based on European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30.

To estimate the time to improvement in cancer-related symptoms based on European Organization for Research and Treatment of Cancer Quality of Life

Questionnaire - Core 30.

To estimate health utilities associated with unresectable soft tissue sarcoma

using the European Organization for Research and Treatment of Cancer Quality

of Life Questionnaire - Core 30

Study description

Background summary

In this study, the study medication AMG 655 is evaluated for the treatment of patients with Soft Tissue Sarcoma (STS). Doxorubicin chemotherapy, alone or in combination, is a standard of care in the management of unresectable soft tissue sarcoma. The tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) pathway is a potential therapeutic target for cancer. Several lines of evidence support developing AMG 655 in combination with chemotherapy to treat sarcoma. Sarcoma tumor samples express high levels of TRAIL receptor 1 and TRAIL receptor 2 by immunohistochemistry. With in vitro models, including human cell lines, primary tissue culture, and human tumor xenograft models, TRAIL has been shown to induce apoptosis in multiple sarcoma subtypes, and its activity is enhanced in combination with chemotherapy, in particular doxorubicin. The TRAIL receptor 2 targeted antibody lextumumab achieved prolonged disease stabilization in a number of subjects with refractory soft tissue sarcoma. This protocol is the first study of AMG 655 in combination with doxorubicin. Based on the safety profile observed in the AMG 655 first in human study, and the mechanism of action and drug product characteristics of doxorubicin and AMG 655, overlapping toxicities between AMG 655 and doxorubicin are not expected.
Approximately 30 sites will participate in this study and will be distributed across the United States and Europe. The approximately sample size for this study is 117. Approximately 5 to 27 subjects in part 1 and approximately 90 subjects part 2.

Study objective

Part 1 (phase 1b): to identify a dose of AMG 655 in combination with doxorubicin that is safe and tolerated as determined by the incidence of dose limiting toxicity
Part 2 (phase2): To estimate the efficacy, as measured by progression-free survival, of AMG 655 at the dose selected in part 1, in combination with doxorubicin.

Study design

This is a multi-center, 2-part phase 1b/2 study of AMG 655 in combination with doxorubicin as first-line therapy for subjects with locally advanced or metastatic, unresectabel soft tissue sarcoma (STS).

Part 1: is an open label phase 1b segment to identify a dose of AMG 655 in combination with doxorubicin that is safe and tolerable as determined by the incidence of dose limiting toxicity. Approximately 6 subjects will initially be enrolled to receive the target dose of AMG 655 (15mg/kg Q3W) in combination with doxorubicin (75 mg/m2 Q3W). The first 3 subjects will be enrolled at a rate of 1 or less then 1 subject per week. If the target dose regimen is safe based on the incidence of dose limiting toxicity, part 2 will open for enrollment. If it is not safe, alternate lower dose levels will be explored (e.g., 5mg/kg; 1.5 mg/kg), to identify the maximum tolerated dose of AMG 655 in combination with doxorubicin.

Part 2: is a randomized double-blind placebo-controlled phase 2 investigation of doxorubicin in combination with AMG 655 at the target dose, the maximum tolerated dose (if lower than the target dose; as determined in part 1), or an alternate lower dose. Part 2 will randomize subjects (n=90) in a 2:1 ratio to receive AMG 655 (arm A; n=60), or placebo (arm B; n=30), in combination with doxorubicin. Subjects will be stratified according to histological cell type (liposarcoma versus leiomyosarcoma versus other), and Eastern Cooperative Oncology Group performance status (ECOG 0 versus ECOG 1)

Intervention

In both parts of the study, doxorubicin will be administered on day 1 of each 21-day cycle, followed by AMG 655 (part 1; part 2, arm A) or placebo (part 2 arm B). No more than 6 cycles of doxorubicin will be given. AMG 655 or placebo monotherapy may continue after doxorubicin has been discontinued, until disease progression, death unacceptable toxicity, consent withdrawal, or administrative decision, for up to 30 months from the first administration of study treatment.

In part 2 of the study, subjects in the placebo group (arm B) may have the opportunity to receive open label single agent AMG 655 ('roll over treatment') upon disease progression.

Study burden and risks

Subjects will receive doxorubicin and AMG 655 (part 1; part 2, arm A) or placebo (part 2, arm B), for up to 6 cycles, followed by AMG 655 or placebo alone, until disease progression, death, AMG 655 or placebo intolerability, consent withdrawal, or administrative decision, for up to 30 months from the first administration of study treatment. Eligible subjects on arm B may then

receive single Agent AMG 6565 roll over treatment until subsequent disease progression, death, unacceptable toxicity, consent withdrawal, or administrative decision, for up to 30 months from the first administration of study treatment. The median survival on the control arm, not including a treatment effect from potential subsequent AMG 655, is anticipated to be approximately to 12 months (van Glabdeke et al, 1999).

The maximum duration of the study is approximately 52 to 60 months (from the first subject enrolled in part 1 until approximately 36 months form the last subject randomized in part 2).

The safety follow-up visit will occur 30 days (+ 3 days) after the last dose of investigational treatment. The day 60 follow-up visit will occur 60 days (+14 days) after the last dose of investigational treatment. Subject will be contacted every 3 months (+/- 2 weeks) in the long-term follow-up, until 36 months after the last subject has been randomized, to assess survival and disease progression, if not documented previously.

Contacts

Public
Amgen

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Scientific
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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 or cytologically confirmed soft tissue sarcoma
Locally advanced, recurrent, or metastatic, unresectable disease
Intermediate or high grade disease (grade 2 or 3 according to the Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grading sysem)

Exclusion criteria

The following tumor types ar not eligible: Alveolar soft part sarcoma, Clear cell sarcoma (melanoma of soft parts), Chondrosarcoma, Desmoid tumor, Desmoplastic small round cell tumor, Embryonal rhabdomyosarcoma, Ewing sarcoma / Primitive neuroectodermal tumor (PNET), Gastrointestinal stroma tumor (GIST), Kaposi sarcoma, Mesothelioma, Mixed mesodermal tumor, Neuroblastoma, Osteosarcoma.
History or known presence of uncontrolled central nervous system (CNS) metastasis
Prior Chemotherapy or investigational agent(s) for the treatment of locally advanced or metastatic, unresectable soft tissue sarcoma (prior neo-adjuvant or adjuvant therapy is allowed, provided there was no disease progression with 6 months after completion of treatment)

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-10-2008
Enrollment:	5
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	21-01-2008
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	24-07-2008
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	22-04-2009
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	25-02-2010
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	EUCTR2007-04409-81-NL
CCMO	NL20273.058.07