An Open-Label, Phase Ib, Dose*Escalation Study of the Safety and Pharmacology of the Anti-CD40 Monoclonal Antibody SGN-40 Administered in Combination with Bortezomib (Velcade®, PS-341) in Patients with Relapsed or Refractory Multiple Myeloma.

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Plasma cell neoplasms
Study type	Interventional

Summary

ID

NL-OMON31502

Source
ToetsingOnline

Brief title
GNE ACF4375g

Condition

- Plasma cell neoplasms
- Plasma cell neoplasms

Synonym
M. Kahler; Plasma Cell dyscrasia

Research involving
Human

Sponsors and support

Primary sponsor: Genentech
Source(s) of monetary or material Support: Farmaceutische Industrie

Intervention

Keyword: anti-CD40, Multiple Myeloma, safety, SGN-40

Outcome measures

Primary outcome

Occurrence and nature of DLT

Secondary outcome

Secondary Study Parameters / Outcome of the Study:

• Occurrence, nature, and severity of treatment-emergent adverse events graded according to the NCI CTCAE v3.0

• Changes in vital signs, physical examination findings, ECOG performance score, and clinical laboratory results

• Additional laboratory safety assessments, including serum immunoglobulin levels and immunogenicity assays (HAHA)

Diagnostic Exploratory Endpoints

• CD40 expression levels in bone marrow multiple myeloma cells pre-treatment

• Gene expression analysis of bone marrow multiple myeloma cells pre-treatment

• Frequency of polymorphisms in Fc*R DNA (optional)

Pharmacodynamic Exploratory Endpoints

• Changes in the characteristics of B- and T-cells, NK cells, monocytes, and other lymphocyte subsets

• Changes in the levels of a panel of cytokines and chemokines assessed from peripheral blood

Activity Endpoints

• Objective response as determined by both the IMWG criteria and EBMT/IBMTR criteria

• Event-free survival, defined as the time from Day 1 to the first occurrence of progression, relapse, death from any cause, or initiation of new multiple myeloma therapies

• Duration of objective response, defined as the interval of time from the first occurrence of a documented objective response until progressive disease, start of another therapy for multiple myeloma, or death from any cause

• Time to objective response, defined as the interval of time from Day 1 to the first occurrence of a documented objective response

Study description

Background summary

CD40 is a type I transmembrane protein of the tumour necrosis receptor superfamily. CD40 is expressed on cells with high proliferative potential and plays important roles in B-cell proliferation and differentiation, immunoglobulin isotype switching, and cell viability. CD40 is highly expressed on several types of B-cell hematologic malignancies, including multiple myeloma (MM). With > 90% of tumour specimens testing positive, CD40 is an attractive potential target for antibody-based cancer therapy.
Multiple myeloma (MM) is an incurable, malignant B cell disorder of unknown aetiology, characterized by uncontrolled proliferation of monoclonal plasma cells in bone marrow and presence of monoclonal immunoglobulin (M-protein or

paraprotein) in serum and/or urine except the 1%-2% of patients with non-secretory MM. MM is often associated with multiple osteolytic lesions, bone pain, hypercalcemia, anaemia, renal insufficiency, and increased susceptibility to infections.
MM constitutes 1% of all cancers with an estimated 19,900 new cases of multiple myeloma diagnosed in the United States during 2007, of which approximately 50% are unresponsive to chemotherapy. Without treatment life expectancy is less than 1 year; with treatment at least 2*3 years. Current treatment regimens have improved remission rates and survival and include high-dose chemotherapy followed by autologous stem cell transplantation; allogeneic transplantation; and dosing regimens incorporating recently approved agents: thalidomide, bortezomib, and lenalidomide. Despite these advances, all MM patients do succumb to the disease. Novel therapeutic strategies are needed to improve the outcome for these patients.
SGN-40 is a humanized IgG1 form of S2C6, a murine anti*human CD40 monoclonal antibody, developed by Seattle Genetics. Phase I clinical research takes place since 2004; Phase II from 2006. SGN-40 binds to CD40 expressed on cell surfaces and functions as a partial agonist in vitro and has demonstrated several mechanisms of action in MM and NHL cell lines, including apoptosis induced by growth-inhibitory signalling, antibody dependent cellular cytotoxicity, and antibody-dependent cellular phagocytosis.

Study objective

The primary objective of the study is to determine the MTD (Maximally Tolerated Dose) of SGN-40 from among three possible dose levels when combined with a standard dose of bortezomib and to determine the safety and adverse event profile for combination therapy with SGN-40 and bortezomib.

Study design

The study will be conducted in two parts: Part 1, dose escalation to establish the MTD and to select a dose for further evaluation, and Part 2, cohort expansion up to 20 MM patients treated at a single dose level at or below the MTD to define the safety and PK profile and to obtain a preliminary estimate of anti myeloma activity.
Patients will receive 2 to 8 cycles (21-days) of therapy. All patients will undergo safety assessments, tumor response determinations, PK studies, and correlative biomarker testing. Patients who do not progress, nor achieve a response will receive a maximum of 8 cycles of therapy. Upon treatment completion patients who have not progressed will be followed for 6 weeks for safety, pharmacokinetics, and disease status, visiting the clinic every 2 weeks. After which the patients will be followed every 6 weeks until disease progression, initiation of another MM therapy, or death, up till all patients completing * 52 weeks or have discontinued the study, if that occurs sooner.

Part 1: Dose Escalation
Starting with Cohort 1, 3 patients will be enrolled initially. If no dose-limiting toxicity (DLT) occurs up till Day 15 of Cycle 2 (i.e. 8 doses of bortezomib and 6 doses of SGN-40), the next cohort will begin enrolment. If 1 DLT occurs among the first 3 patients, 3 more patients will be enrolled at the same dose level. If only 1 DLT is observed among the 6 patients in this expanded dose group, the next cohort starts. When * 2 DLTs occur at any dose level, that level is determined to be not tolerated. All dose-escalation and de-escalation decisions will be made by the Medical Monitor and investigators. Additional patients may be enrolled to replace patients who discontinue the study prior to Day 15/Cycle 2 (except for DLT). Patients who experience a DLT will stop dosing and, in general, will receive no further SGN-40 administration in combination with bortezomib. However, if a objective clinical benefit is demonstrated and if toxicity is adequately managed, Medical Monitor and regulatory authorities may discuss on a case-by-case basis whether dosing might be allowed to continue.

Part 2: Expanded Dose Cohorts
After the MTD is determined, a dose level at or below the MTD will be chosen for the expanded cohort by the Medical Monitor after consultation with the investigators and review of all available safety and PK data and formed by enrolling additional patients until a total of 20 MM patients are treated at the chosen dose. If no dose cohort completes treatment with fewer than two DLTs and no MTD can be determined, then no additional patients will be enrolled.

Intervention

The administration of SGN-40 and bortezomib according to protocol

Study burden and risks

Burden for the subjects is mainly related to the infusion of both SGN-40 and/or bortezomib on days 1, 4, 8, 11, 15 (cycle 1) or days 1, 4, 8, 11 (cycles 2 - 8) and blood sampling for trial purposes.
Risks involved are the occurrence of anaphylaxis related events
Potential drug-related adverse events include: cytokine-release syndrome (first dose-headache accompanied by fever and muscle ache), asymptomatic elevation of hepatic transaminases, conjunctivitis/eye inflammation. Other, also potentially cancer related, adverse events include: fatigue, headache, nausea, pyrexia, diarrhoea, back pain, anaemia, chills, constipation, dyspnoea, decreased appetite, vomiting, hypercalcemia, cough, hypotension, peripheral oedema, thrombocytopenia, ocular hyperaemia and rash.
Events not related or unlikely to be related to SGN-40 include: disease progression, renal failure and deep venous thrombosis.

Contacts

Public
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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

• Documented pathologic diagnosis of multiple myeloma that has relapsed or failed to respond after treatment with at least one prior systemic therapy (other than corticosteroid monotherapy)
• Measurable disease, defined as follows:
Serum M-protein >= 1 g/dL (>= 10 g/L)
Urine M-protein >= 200 mg/24 hr urine collection
Involved FLC level >= 10 mg/dL (>= 100 mg/L, provided serum FLC ratio is abnormal)
• At least one prior systemic therapy other than single-agent corticosteroids
• European Union patients must have had prior bone marrow transplant (autologous) or be ineligible for transplant (note: the requirement for prior transplant is based on the approved indication for bortezomib in the European Union at the time the protocol was finalized).
• If previously received bortezomib, demonstration of clinical response of any duration or

stable disease with progression free interval of >= 6 months from the start of that therapy
• If previously received bortezomib, must have recovered from bortezomib related toxicities and must have a peripheral neuropathy score of Grade <= 1, according to the NCI CTCAE v3.0
• If applicable, completion of autologous transplant >= 12 weeks prior to Day 1
• Discontinuation of previous anticancer or investigational therapy for >= 21 days prior to treatment, or >= 90 days prior to treatment for previous monoclonal antibody administration
• ECOG performance status of 0 or 1 (see Appendix F)
• Life expectancy of > 3 months

Exclusion criteria

• Prior treatment with a monoclonal antibody directed against CD40
• Prior allogeneic bone marrow transplant
• Concurrent systemic corticosteroid therapy (except corticosteroid therapy <= 20 mg/day prednisone or equivalent used to treat an illness other than lymphoma)
• clinical laboratory values:
ANC < 1000/µL
Platelet count < 75,000/µL
Total bilirubin > 1.6 mg/dL AST or ALT greater than the upper limit of normal (ULN) Serum creatinine > 1.5 times upper limit of normal or calculated creatinine
clearance < 50 mL/min
Hemoglobin < 9 g/dL (may be transfused to maintain or exceed this level) ;• Other invasive malignancies within 3 years prior to Day 1 except for adequately treated basal cell or squamous cell skin cancer; carcinoma in situ of the cervix, breast, or prostate; or other cancer of which the patient has been disease-free for >= 3 years
• Prior anaphylactic reaction to human immunoglobulin administration
• Symptomatic hyperviscosity syndrome
• Known intracranial disease or epidural disease
Patients with lytic lesions of the cranium secondary to myeloma are eligible to enroll.
• Active infection requiring parenteral antibiotics within 14 days of Day 1
• Major surgical procedure or significant traumatic injury within 28 days prior to Day 1, or anticipation of need for major surgical procedure during the course of the study
• Serious, nonhealing wound, ulcer, or bone fracture
• Clinically significant cardiac disease (New York Heart Association, Class III or IV), including preexisting arrhythmia, congestive heart failure, or cardiomyopathy
• Any contraindication to bortezomib treatment, including hypersensitivity to bortezomib, boron, or mannitol

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	10-11-2008
Enrollment:	26
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Bortezomib
Generic name:	Velcade
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	SGN-40
Generic name:	NA

Ethics review

Approved WMO

Date:	12-02-2008
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	21-04-2008
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	24-07-2008
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-05-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-10-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-10-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2007-006213-17-NL
CCMO	NL21130.029.08