A Master Protocol Evaluating the Safety and Efficacy of Therapies for Metastatic Castration-resistant Prostate Cancer (mCRPC);- Subprotocol A: A Phase 1b Study Evaluating the Safety and Efficacy of AMG 160 in Combination With Enzalutamide in Subjects With Metastatic Castration-resistant Prostate Cancer (mCRPC)
- Subprotocol B: A Phase 1b Study Evaluating the Safety and Efficacy of AMG 160 in Combination With Abiraterone in Subjects With Metastatic Castration-resistant Prostate Cancer (mCRPC)

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Primary objective: To evaluate the safety, tolerability, and maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) of investigational therapies in subjects with metastatic castration-resistant prostate cancer (mCRPC).Secondary objective:*...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON54909

Source
ToetsingOnline

Brief title
20190505 AMG 160 combination therapy

Condition

- Other condition
- Prostatic disorders (excl infections and inflammations)

Synonym
Metastatic Castration-resistant, prostate cancer

Health condition

prostaat kanker

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Combination therapy, Immunotherapy, Metastatic Prostate Cancer, Prostate-specific membrane antigen

Outcome measures

Primary outcome

The following primary study outcome is applicable for both combination

therapies:

To evaluate the safety, tolerability, and maximum tolerated dose (MTD) or

recommended phase 2 dose (RP2D) of AMG 160 in combination with enzalutamide or

abiraterone in subjects with metastatic castration-resistant prostate cancer

(mCRPC)

* dose-limiting toxicities (DLTs)

* treatment-emergent and treatment-related adverse events

* changes in vital signs and clinical laboratory tests

Secondary outcome

The following secundary study outcome is applicable for both combination therapies:

To evaluate preliminary anti-tumor activity of AMG 160 in combination with enzalutamide or abiraterone

* objective response per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 with Prostate Cancer Working Group 3 (PCWG3) modifications

* circulating tumor cell (CTC) response (CTC0 and CTC conversion)

* prostate-specific antigen (PSA) response

* duration of response (CTC, PSA, conventional radiographic)

* overall survival (OS)

* progression-free survival (radiographic, PSA, clinical)

* time to progression (radiographic, PSA)

* time to subsequent therapy

* 68Gallium (68Ga)-prostate-specific membrane antigen (PSMA)-11 positron emission tomography (PET)/computed tomography (CT) and 18F-fluorodeoxyglucose (FDG) PET/CT based response evaluation

* other PCWG3-recommended endpoints (time to symptomatic skeletal events, alkaline phosphatase [total, bone], lactate dehydrogenase [LDH], hemoglobin, neutrophil to-lymphocyte ratio, urine N-telopeptide)

To characterize the pharmacokinetics (PK) of AMG 160 in combination with

enzalutamide or abiraterone

* PK parameters including, but not limited to, maximum serum concentration

(Cmax), minimum serum concentration (Cmin), area under the concentration-time

curve (AUC) over the dosing interval, accumulation, and half-life (t1/2)

Study description

Background summary

AMG160 is a new half-life extended (HLE) bispecifiic T-cell engager (BiTE®) molecule designed to target T-effector cells to prostate-specific membrane antigen (PSMA) expressing cells.

Disease relapse following enzalutamide / abiraterone is due in part to increased androgen receptor expression (eg. androgen receptor amplification), among other mechanisms. Because these resistance mechanisms do not necessarily confer resistance to immunotherapies like AMG 160, there is a rationale to combine enzalutamide / abiraterone with AMG 160. Furthermore, NHT like enzalutamide or abiraterone have been reported to upregulate PSMA expression on castration-resistant prostate cancer cells, providing additional rationale to combine with PSMA targeted therapies like AMG 160.

This study will evaluate the safety, tolerability and preliminary efficacy of AMG 160 in combination with enzalutamide or abiraterone in subjects with mCRPC.

See section 2.1 in sub protocol A and B for further details.

Study objective

Primary objective:
To evaluate the safety, tolerability, and maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) of investigational therapies in subjects with metastatic castration-resistant prostate cancer (mCRPC).

Secondary objective:
*To evaluate preliminary anti-tumor activity of investigational therapies in subjects with mCRPC
*To characterize the pharmacokinetics (PK) of investigational therapies in

subjects with mCRPC

Study design

Overall study design for both combination therapies:
This is a phase 1b, multicenter, open-label study evaluating the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and efficacy of AMG 160 in combination with enzalutamide or abiraterone. The study will consist of dose exploration (Part 1) and dose expansion (Part 2).
Subjects will be treated until progression (treatment beyond disease progression may be allowed per Prostate Cancer Working Group 3 [PCWG3] guidelines if approved by Amgen medical monitor). Upon permanent discontinuation from the study treatment for any reason, a safety follow-up visit will be performed approximately 30 (+3) days after the last dose of protocol-required therapy or prior to initiation of subsequent therapy, whichever occurs first. After the safety follow-up visit, subjects enter long-term follow-up to assess survival and/or the initiation of subsequent cancer therapy. Long-term follow-up will be conducted every 6 months after the last dose of protocol-required therapy up to 3 years from cycle 1 day 1.
Part 1 (Dose Exploration):
The dose exploration part of the study will estimate the maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) of AMG 160 in combination with enzalutamide or abiraterone using a modified toxicity probability interval (mTPI) design. A RP2D may be identified based on emerging safety, efficacy, and pharmacodynamic data prior to reaching an MTD.
Part 2 (Dose Expansion):
Upon completion of Part 1 of the study, enrollment will commence in Part 2 to confirm the safety and tolerability of the selected dosing regimen and to further evaluate the efficacy of AMG 160 in combination with enzalutamide or abiraterone.

Intervention

Dispension of IP:

Subprotocol A: AMG 160 in combination with enzalutamide
Based on Study 20180101, the AMG 160 starting dose for this study will be 0.09/0.3 mg (MTD/RP2D). This would mean that 0.09 mg of AMG 160 will be administered on cycle 1 day 1 as a 3-day extended IV infusion followed by 0.3 mg maintenance dose starting cycle 1 day 8 and Q2W via short-term infusion. Enzalutamide (160 mg) should be taken once daily.

Depending on observed safety data, the following may occur: additional enrollment to above mentioned dose; or dose de-escalation to 1 dose level below MTD / RP2D of AMG 160 (ie. 0.15 mg). De exploration phase is further explained in 6.2.1.1 of subprotocol A.

Following dose exploration, dose-expansion will be conducted to confirm the safety and tolerability of the selected dose and to further evaluate the efficacy of AMG 160 in combination with enzalutamide.

Subprotocol B: AMG 160 in combination with abiraterone
Based on Study 20180101, the AMG 160 starting dose for this study will be 0.09/0.15 mg (1 dose level below MTD/RP2D). This would mean that 0.09 mg of AMG 160 will be administered on cycle 1 day 1 as a 3-day extended IV infusion followed by 0.15 mg maintenance dose starting cycle 1 day 8 and Q2W via short-term infusion. Abiraterone (1000 mg) should be taken once daily.

Depending on observed safety data, the following may occur: additional enrollment to above mentioned dose (1 dose level below MTD/RP2D); or dose de-escalation to 2 dose level below MTD / RP2D of AMG 160 (ie, 0.09 mg); or dose escalation to MTD / RP2D of AMG 160 (ie. 0.3 mg) De exploration phase is further explained in 6.2.1.1 of subprotocol B.

Following dose exploration, dose-expansion will be conducted to confirm the safety and tolerability of the selected dose and to further evaluate the efficacy of AMG 160 in combination with abiraterone.

Study burden and risks

Next to the key safety risks;
* Cytokine release syndrome (CRS),
* Gastrointestinal toxicities,
* Neurologic toxicities,
* Tumor lysis syndrome,
* Supraventricular arrythmias (related to CRS),
* Thrombocytopenia (related to CRS),
* Eye disorders,

the following should be taken into account in terms of burden to the patient:
* Blood draw: Drawing blood may be painful or cause some bruising.
* Exposure to radiation: CT scan, PET, MUGA and the bone scan involves using X-rays or radioactive markers.
Please refer to Appendix D in ICF for more information about possible side effects, risks, complications and other undesirable effects for all tests and procedures performed in this study.

Disadvantages of participation in the study may be:
- Possible side effects/complications
- Possible adverse effects/discomforts of the evaluations in this study.

Participation in the study also means:
- additional time
- additional or longer hospital stays

- additional tests
- instructions you need to follow.

Contacts

Public
Amgen

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Breda 4817 ZK
NL
Scientific
Amgen

Minervum 7061
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NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Subject has provided informed consent prior to initiation of any study specific activities/procedures.
- Age * 18 years at the time of signing the informed consent.
- Subjects with mCRPC with histologically or cytologically confirmed adenocarcinoma of the prostate without pure neuroendocrine differentiation or small cell features.
- Subjects should have undergone bilateral orchiectomy or should be on continuous androgen deprivation therapy with a gonadotropin releasing hormone

agonist or antagonist.
- Total serum testosterone should be * 50 ng/dL (or 1.7 nmol/L)
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 * 1
- Life expectancy of > 3 months
- Adequate organ function, defined as follows:
* absolute neutrophil count * 1.5 x 10^9/L (without growth factor support within 7 days from screening assessment)
* platelet count * 100 x 10^9/L (without platelet transfusion within 7 days from screening assessment)
* hemoglobin > 9 g/dL (90 g/L) (subprotocol A) / > 10 g/dL (100g/L) (subprotocol B) (without blood transfusion within 7 days from screening assessment)
* estimated glomerular filtration rate based on Modification of Diet in Renal Disease (MDRD) calculation * 30 mL/min/1.73 m2
* AST and ALT < 3 x upper limit of normal (ULN) (or < 5 x ULN for subjects with liver involvement)
* total bilirubin (TBL) < 1.5 x ULN (or < 2 x ULN for subjects with liver metastases)
* left ventricular ejection fraction (LVEF) > 50% (2-D transthoracic echocardiogram [ECHO] is the preferred method of evaluation; multi-gated acquisition scan is acceptable if ECHO is not available)
- Baseline electrocardiogram (ECG) QTc * 470 msec
- Subjects planning to receive enzalutamide (subprotocol A) / abiraterone (subprotocol B) for the first time for mCRPC (subjects who received prior enzalutamide (subprotocol A) / abiraterone (subprotocol B) are not eligible).

Exclusion criteria

Applicable for both subprotocols:
- Pathological finding consistent with pure small cell, neuroendocrine carcinoma of the prostate or any other histology different from adenocarcinoma
- CNS metastases or leptomeningeal disease
- Symptomatic peripheral sensory or motor neuropathy *grade 3
- History or presence of clinically relevant CNS pathology
- Confirmed history/current autoimmune disease or other diseases resulting in permanent immunosuppression or requiring permanent immunosuppressive therapy
- Presence of fungal, bacterial, viral, or other infection requiring IV antimicrobials within 7 days of dosing
- History/evidence of inflammatory bowel disease or any other gastrointestinal disorder causing chronic nausea, vomiting, or diarrhea
- History of arterial or venous thrombosis within 12 months of first dose
- Myocardial infarction, uncontrolled hypertension (Subprotocol A), unstable angina, cardiac arrhythmia requiring medication, and/or symptomatic congestive heart failure (New York Heart Association > class II) within 12 months of first dose of AMG 160

- Unresolved toxicities from prior anti-tumor therapy not having resolved to CTCAE version 5.0 grade 1, with the exception of alopecia or toxicities that are stable and well-controlled AND there is agreement to allow by both the investigator and sponsor
- Known HIV infection, hepatitis C or hepatitis B infection
- History of other malignancy within the past 2 years, with the following exceptions:
* Malignancy treated with curative intent and with no known active disease present for * 3 years before enrollment and felt to be at low risk for recurrence by the treating physician.
* Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
* Adequately treated urothelial papillary noninvasive carcinoma or carcinoma in situ.
- Prior treatment with a taxane for mCRPC.
- Radiation therapy within 4 weeks of first dose (or local or focal radiotherapy within 2 weeks)
- Any anticancer therapy or immunotherapy within 4 weeks of start of first dose, not including LHRH/GnRH analogue. Subjects on a stable bisphosphonate or denosumab regimen for * 30 days prior to enrollment are eligible
- Prior PSMAxCD3 bispecific therapy
- Requiring chronic systemic corticosteroid therapy or any other immunosuppressive therapies. Low dose corticosteroids permitted.
- Prior major surgery within 4 weeks of first dose
- Currently receiving treatment in another investigational device or drug study, or less than 4 weeks since ending treatment on another investigational device or drug study(ies).
- Male subjects with a female partner of childbearing potential or pregnant partner who are unwilling to practice sexual abstinence or use contraception during treatment and for an additional 4 months after the last dose
- Male subjects unwilling to abstain from donating sperm during treatment and for an additional 4 months after the last dose.
- Subject has known sensitivity to any of the products (or components) to be administered during dosing.
- Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures.

Subprotocol A
- Use of strong CYP2C8 inhibitors within 7 days prior to first dose or strong CYP3A4 inducers within 28 days
- Use of narrow therapeutic index drugs that are substrates of CYP3A4, CYP2C9 or CYP2C19 within 28 days.

Subprotocol B
- Baseline moderate and severe hepatic impairment
- Presence of uncontrolled hypertension, hypokalemia, or fluid retention
- History or presence of adrenocortical insufficiency

- Use of concomitant medications that are sensitive substrates for CYP2D6 with a narrow therapeutic index within 7 days
- Use of strong CYP3A4 inducers within 28 days.

Please refer to section 5.2 of subprotocol A and B for the complete list of exclusion criteria.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	AMG 160
Generic name:	AMG 160

Ethics review

Approved WMO Date:	30-07-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-03-2021

Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-06-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2020-001305-23-NL
ClinicalTrials.gov	NCT04631601
CCMO	NL74207.056.20