A randomized, double-blind, placebo-controlled, multicenter Phase II trial investigating two doses of EMD 525797 in subjects with asymptomatic or mildly symptomatic metastatic castrate-resistant prostate cancer (mCRPC).

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The main objective of this study is to investigate of the drug EMD 525797 is better then no treatment with subjects with metastasized asymptomatic or mild symptomatic mCRPC. The efficacy and safety of the drug EMD 525797 is evaluated.Primary...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Reproductive neoplasms male malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON38307

Source
ToetsingOnline

Brief title
PERSEUS

Condition

- Reproductive neoplasms male malignant and unspecified

Synonym
castrate-resistant prostatecarcinoma; prostate cancer

Research involving

Human

Sponsors and support

Primary sponsor: Merck
Source(s) of monetary or material Support: farmaceutische industrie

Intervention

Keyword: HRPC, mCRPC, Prostatecancer

Outcome measures

Primary outcome

The primary endpoint of the trial is PFS defined as the time from the date of randomization until the first documented sign of objective radiographic disease progression or death from any cause. Death will only be considered as an event when it is reported within 12 weeks after the last tumor assessment without progression.

Objective radiographic disease progression is defined as one of the following conditions:

• Bone lesion progression (appearance of 2 or more new bone lesions compared to baseline) assessed with bone scintigraphy, which must be confirmed by bone scintigraphy 6 weeks later if subjects remain asymptomatic or mildly symptomatic. Assessments based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 modified according to the Prostate Cancer Working Group 2 (PCWG-2).

• Soft-tissue lesion progression according to RECIST 1.0 modified according to PCWG-2 assessed with CT scans.

• Presence of skeletal events defined as cord compression or fracture documented via a scheduled or an unscheduled radiographic assessment triggered

by increasing pain (needing opioids or radiation) or other signs and/or symptoms at Investigator discretion.

Secondary outcome

Efficacy Endpoints:

Overall survival (OS), time to progression (TTP), presence of tumor response in soft tissue lesions, presence of disease control in soft tissue lesions, number of new bone lesions compared to baseline, presence of disease control in bone lesions, bone and soft tissue lesions composite tumor response, TTP in soft tissue lesions, TTP in bone lesions, TTP in bone or soft tissue lesions, presence of skeletal events, time of occurrence of first skeletal related events, presence of prostate specific antigen (PSA) response, duration of PSA response, time to PSA response, percentage change from baseline in PSA serum concentration during treatment, percentage change from baseline in the number of CTCs, percentage change from previous time point in the number of CTCs.

Primary and secondary efficacy endpoints also apply to the open-label cohort (1500 mg EMD 525797) for exploratory evaluation, with the following change to the primary definitions of efficacy endpoints, otherwise indicated: the date of origin will be the first dosing date of EMD 525797 1500 mg received as an open-label treatment.

Safety Endpoints:

Toxicity will be graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0.

The safety endpoints of the trial are considered to be the incidence, severity, and relationship to the trial drug of:

• Treatment-emergent adverse events (TEAEs).

• Treatment-related TEAEs.

• Serious adverse events (SAEs) and related SAEs (including deaths).

• Adverse events leading to permanent treatment discontinuation.

• Clinically significant changes in routine hematology and biochemistry

laboratory tests (according to laboratory reference ranges) from baseline.

• Clinically significant changes in vital signs and physical examination.

• Antibodies to EMD 525797.

• ECG including QT/QTc prolongation.

Pharmacokinetics Endpoints

• Population pharmacokinetics (popPK) of EMD 525797.

• Serum concentrations of EMD 525797.

Study description

Background summary

EMD 525797 is a monoclonalantibody antagonist directed against the αv subunit of integrin receptors and has been developed for the treatment of cancer. These integrin receptors are highly expressed in angiogenic, proliferating tumor blood vessels and on certain types of tumor cells.
In addition, in a limited set of tumors, increased expression of this integrin receptor is associated with increased cell invasion and metastasis. It has been demonstrated that members of the αv-integrin family play a direct role in tumor progression, tumor angiogenesis and metastasis. These receptors are present on the tumor cells of prostate cancer.

Integrins are also involved in bone physiology and pathophysiology and the expression of normal fully functional αvβ3 is required for prostate cancer cell growth within the bone as well as tumor-induced bone remodeling. The clinical and pre-clinical results to date indicate that the αv-integrine receptor

inhibitor may have an affect in subjects with castrate-resistant prostate cancer with bone metastasis and progession of disease before chemotherapy.

Study objective

The main objective of this study is to investigate of the drug EMD 525797 is better then no treatment with subjects with metastasized asymptomatic or mild symptomatic mCRPC. The efficacy and safety of the drug EMD 525797 is evaluated.

Primary Objective:
The primary objective of the trial is to evaluate the clinical anti-tumor activity of EMD 525797 administered as 1-hour intravenous (i.v.) infusion every 3 weeks in terms of progression free survival (PFS) time in subjects with asymptomatic or mildly symptomatic mCRPC.
Secondary Objectives:
• To further evaluate the efficacy of EMD 525797
• To further characterize the safety profile of EMD 525797
• To further evaluate the pharmacokinetic (PK) profile of EMD 525797
• To explore the relationship between number and/or changes of numbers and biomarkers and the clinical outcome (e.g., primary and secondary endpoints).
Other Objectives:
Identify potential predictive markers of response for the treatment under investigation by:
• Exploring the relationship between candidate proteins, candidate cell types, or metabolites circulating in the blood and/or expressed by the tumor and the clinical outcome (e.g., primary and secondary endpoints).
• Exploring the effect of genetic variations in the host genome and/or in the tumor genome on the clinical outcome (e.g., primary and secondary endpoints).
• Exploring the relationship between biomarkers found in urine and the clinical outcome (e.g., primary and secondary endpoints).

Study design

This is a randomized, double-blind, placebo-controlled, multicenter Phase II trial investigating two doses of EMD 525797 in subjects with asymptomatic or mildly symptomatic metastatic castrate-resistant prostate cancer (mCRPC). Symptomatic mCRPC is classified as mild if the symptoms do not require either opioid therapy or chemotherapy.

It is planned to randomize a total of 216 subjects to receive EMD 525797 (750 mg or 1500 mg doses) or placebo. In addition, all subjects will follow the standard of care (SoC) consisting of the continued treatment with luteinizing-hormone-releasing hormone (LHRH) agonists and biphosphonates, because the National Comprehensive Cancer Network (NCCN) and other national treatment guidelines (S3 in Germany, European Association of Urology [EAU] guidelines) recommend additional treatment with biphosphonates.

EMD 525797 will be given i.v. every 3 weeks until disease progression or stop of trial treatment due to toxicity or other reasons. The biphosphonate infusion can also be administered every 3 weeks and, if dosed on the same day, is to be given 1 hour prior to EMD 525797 infusion.

Two dose levels of EMD 525797 were chosen for investigation in this trial based on PK modeling and preliminary results from the trial EMR 62242-002 in subjects with late stage prostate cancer. These 2 dose levels, 750 mg and 1500 mg, are expected to achieve different levels of target saturation over 3 weeks with the underlying assumption that a saturation of the observed non-linear clearance (CL) pathway equals the saturation of the target:
Arm 1 - EMD 525797 1500 mg + SoC: At steady state the serum through concentration of EMD 525797 is expected to be constantly above the IC99 of the non-linear CL pathway.
Arm 2 - EMD 525797 750 mg + SoC: At steady state the serum trough concentration of EMD 525797 is expected to be above the IC95 and to reach the IC99 of the non-linear CL pathway during administration intervals of 3 weeks with the peak concentration.
Arm 3 - Placebo + SoC: The trial will be controlled using placebo (a 0.9% sodium chloride solution) plus SoC, since no approved active comparator is currently available and a placebo plus SoC arm is justifiable. If subjects experience radiographic progressive disease (PD) without symptoms (asymptomatic) or with mild symptoms (mildly symptomatic) not requiring either opioid treatment or chemotherapy, and a second bonescan after 6 weeks confims the progression, then they will be provided a possibility to receive an open-label treatment with 1500 mg of EMD 525797. Until this confirmation the treatment is continued.

As soon as the subject ends the treatment because of progression or another reason, this subject will be followed for survival follow up unless the subject withdraws.

Intervention

EMD 525797 will be administered as 1-hour i.v. infusion. Administration of EMD 525797 will occur on Day 1 of each 3-week cycle. The assignment will be double blind to one of the following treatments:

EMD 525797 1500 mg + SoC

or

EMD 525797 750 mg + SoC

or

Placebo + SoC

If subjects experience radiographic progressive disease (PD) without symptoms (asymptomatic) or with mild symptoms (mildly symptomatic) not requiring either opioid treatment or chemotherapy, and a second bonescan after 6 weeks confims the progression, then they will be provided a possibility to receive an open-label treatment with 1500 mg of EMD 525797.

Study burden and risks

The procedures and treatments per visit are described at page 59-64 and at page 104-108.

The subjects will need to come more frequent to the hospital then normally. There will be more blood sampling, bone scans and CT/MRI then normal. There is a screening visit which can be done in one day or done in more then one day. During the screening visit a bone scan, CT/MRI scan, blood samping (also HIV/Hepatitis testing), chest X-ray, ECG, physical examination will be done. The subject will need to have started biphosphonate treatment 2 days upfront the randomization.
During study day 1 the IMP will be given via infusion, several blood samples, urine test and ECGs will be done.
During the other cycli (every 3 weeks), there will be blood sampling, physical examination, ECGs, urine tests, first an infusion with biphosphonate and thereafter with IMP.
After 12 weeks (cycle 5) a bone scan and a CT/MRI will be done. Thereafter every 6 weeks until cycle 13 a bone scan and CT/MRI scan and after cycle 13 every 12 weeks a bone scan and CT/MRI scan until disease progression.
During the end of treatment visit: physical examination, blood sampling, urine, a CT/MRI and bone scan in case the subject did not progress but stopped for another reason.
During the safety follow up visit: ECGs, blood sampling, urine test.
During survival/progression follow up visits: every 12 weeks bone scan and CT/MRI scan in case the patient did not show progression and PSA assessment. Otherwise only survival follow up.

Estimated risks:
Information on EMD 525797 gained from animal experiments, experience with the use of the EMD 525797 in healthy volunteers and patients as well as experience with other drugs belonging to the same group of drugs indicate that side effects such as feeling of warmth, fever, flush, redness and pain at the injection site, headache, tiredness, changes in blood pressure, nausea, vomiting, constipation, or loose stools may occur in single cases. In addition, allergic reactions and flu-like symptoms as observed for other monoclonal antibodies cannot be excluded.
The possibility for bleeding (as seen in one case) or thromboembolic events as experienced with other anti-angiogenic drugs may be anticipated in association with EMD 525797 treatment. Furthermore, although not observed until now the possible effects of EMD 525797 on thyroid functions cannot be ruled out. Blood

sampling can cause temporary discomfort. The needle sticks may cause local pain, bruising, swelling, lightheadedness, dizziness and rarely, fainting and/or a possible infection from the needle stick. Exposure to ionizing radiation by CT scans and bone scans. In the worse case this can lead to any radiation associated diseases in the future. The contrast substance injected during the CT scan may cause pain, burning feeling, sweating and rarely a serious allergic reaction that can be serious The contrast agent used in the CT scan may cause kidney damage, especially if the subject is diabetic or dehydrated. In addition the thyroid function may be affected. If a CT scan is not recommended by your trial doctor, instead a MRI may be performed which does not use radiation. For your MRIs, you will receive a contrast agent called gadolinium administered intravenously prior to each MR. This contrast agent may occasionally cause nausea and vomiting. Very rarely, it may cause slight warmth or pain at the injection site. Allergic reactions may also occur very rarely, and, in extremely rare instances, these can be potentially serious.
Harm to an unborn child: It is not known whether taking the trial drug will affect sperm or semen, or can result in genetic mutations or other deformities in an unborn child.

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

1. Signed and dated written informed consent prior to any specific trial procedure.
2. Age >=18 years, male.
3. Histologically or cytologically confirmed adenocarcinoma of the prostate (Gleason score).
4. Radiological progression of bone lesions with or without soft tissue lesions within 4 weeks (28 days) prior to randomization.
5. Stable, ongoing adequate testosterone suppression proven by hypogonadal levels of testosterone (<=50 ng/dL) for subjects without surgical castration. Testosterone level will not be documented for subjects who have been surgically castrated.
6. Bisphosphonate treatment has to be initiated at least 2 days prior to start of treatment with EMD 525797.
7. Eastern Cooperative Oncology Group (ECOG) performance status <2.
8. Adequate hematologic function: Absolute Neutrophil Count (ANC) >=1.5 x 109/L; platelets >=100 x 109/L; hemoglobin >=9 g/dL (without transfusion).
9. Adequate hepatic function: total bilirubin <=1.5 x upper limit of normal (ULN); aspartate transaminase (ASAT) <=5 x ULN and alanine aminotransferase (ALAT) <=5 x ULN.
10. Creatinine clearance >=40 mL/min, calculation based on Cockcroft-Gault formula.
11. International Normalized Ratio (INR) and activated partial thromboplastin time (aPTT) within normal range.
12. Effective contraception, e.g., double barrier method, if the risk of conception exists.
13. Ability to comply with the trial and follow-up procedures.
14. Tumor material (from tumor block or punch biopsy) availability must be confirmed at screening. The sample should be collected and sent to the laboratory as soon as possible, ideally by the time of randomization.

Exclusion criteria

1. Acute pathologic fracture, spinal cord compression, or hypercalcemia at Screening.
2. Nonsteroidal antiandrogens, e.g., flutamide and bicalutamide, within 30 days before treatment.
3. Chronic and ongoing treatment with opioids (treatment >10 days).
4. Prior chemotherapy, biologic therapy (targeted therapy), or any experimental therapy for mCRPC.
5. Radiotherapy to bone lesions and/or orthopedic surgery for pathologic fractures. Any kinds of major elective surgery within 30 days prior to trial treatment.
6. Chronic supraphysiologic doses of oral steroids, defined as >10 mg of prednisone equivalents per day.

7. Confirmed or clinically suspected brain metastases.
8. Visceral metastasis.
9. Known hypersensitivity reactions to any of the excipients of the trial medication.
10. History of allergic reactions to any other monoclonal antibody therapy.
11. Uncontrolled hypertension defined as systolic blood pressure >= 160 mmHg and/or diastolic blood pressure >= 100 mmHg under resting conditions for at least 5 minutes.
12. Chronic daily acetylsalicylic acid (ASS) therapy at doses >100 mg.
13. Bleeding disorders and/or history of thromboembolic events (history of superficial thrombophlebitis is not an exclusion criterion).
14. Treatment with thrombolytics or oral or parenteral anticoagulants within 10 days prior to trial treatment.
15. Severe peripheral vascular disease or ulceration; unstable angina pectoris, or myocardial infarction within 6 months before start of trial treatment, clinically significant abnormal ECG at Screening.
16. Known alcohol or drug abuse.
17. Participation in another clinical trial within the past 30 days before start of trial treatment.
18. Dementia, altered mental status, or any psychiatric condition that would prohibit the understanding or rendering of informed consent.
19. Hepatitis B or C, human immunodeficiency virus (HIV) infection, active or chronic.
20. Legal incapacity or limited legal capacity.
21. All other significant diseases which, in the opinion of the Investigator, might impair the subject*s tolerance of trial treatment.
22. Other malignancy if treatment has not been completed within 2 years before start of trial treatment.

Study design

Design

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

Recruitment

NL
Recruitment status: Recruitment stopped

Start date (anticipated):	07-07-2011
Enrollment:	44
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	DI17E6
Generic name:	DI17E6

Ethics review

Approved WMO Date:	24-01-2011
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	21-04-2011
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	30-05-2011
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	12-09-2011
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	26-09-2011
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	19-12-2011
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)

Approved WMO Date:	04-06-2012
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	12-07-2012
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	12-12-2012
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	14-01-2013
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	15-10-2013
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)

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	EUCTR2010-021529-11-NL

Register	ID
ClinicalTrials.gov	NCT01360840
CCMO	NL35473.075.11