VISION: An international, prospective, open label, multicenter, randomized Phase 3 study of 177LU-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)

Published: 23-08-2018
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The primary objective of this study is to compare overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive 177Lu-PSMA-617 in addition to best supportive/best standard of care versus patients treated with best supportive/...

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

Summary

ID

NL-OMON52710

Source
ToetsingOnline

Brief title
VISION

Condition

- Reproductive neoplasms male malignant and unspecified
- Prostatic disorders (excl infections and inflammations)

Synonym
mCRPC, prostate cancer

Research involving
Human

Sponsors and support

Primary sponsor: Endocyte, Inc., a Novartis Company
Source(s) of monetary or material Support: Endocyte;Inc.

Intervention

Keyword: 177LU-PSMA-617, best supportive care/best standard of care, metastatic castration-resistant prostate cancer

Outcome measures

Primary outcome

One of the primary endpoints is OS and is defined as the time from

randomization to the date of death from any cause. The 2nd now added primary

endpoint is rPFS (radiographic Progression Free Survival).

Secondary outcome

The key secondary endpoints include the following:

1.

2. RECIST response to include:

a. Objective response rate (ORR) (CR + PR) as measured by RECIST v1.1 response

in soft tissue, lymph node and visceral lesions. Duration of Response (DOR)

will also be measured in patients with a CR or PR from date of first response

to the date of RECIST progression or death.

b. Disease Control Rate (DCR) (CR + PR + stable disease [SD]) as measured by

RECIST v1.1 response in soft tissue, lymph node and visceral lesions.

3. The time to a first SSE defined as date of randomization to the date of

first new symptomatic pathological bone fracture, spinal cord compression,

tumor-related orthopedic surgical intervention, or requirement for radiation therapy to relieve bone pain or death from any cause, whichever occurs first.

Additional Secondary endpoints

1. To evaluate the safety and tolerability of 177Lu-PSMA-617

2. Aspects of HRQoL will be reported using the EuroQol 5-dimensions 5-level [EQ-5D-5L] questionnaire, Functional Assessment of Cancer Therapy - Prostate [FACT-P] questionnaire and Brief Pain Inventory - Short Form [BPI-SF]

3. Health economics

4. Progression-free survival is defined as the date of randomization to the date of first evidence of radiographic progression, clinical progression, PSA progression, or death from any cause, whichever occurs first.

a. Radiographic progression is defined as the date of radiographic disease progression as outlined in the Prostate Cancer Working Group 3 (PCWG3) Guidelines.

b. Unequivocal clinical progression. Unequivocal evidence of clinical progression is defined as:

* - Marked escalation in cancer related pain that is assessed by the investigator to indicate the need for other systemic chemotherapy

*- Immediate need for initiation of new anticancer treatment, surgical or radiological intervention for complications due to tumor progression even in the absence of radiological progression

*- Marked deterioration in ECOG performance status to >= Grade 3 and/or in the opinion of the investigator ECOG deterioration indicates clinical progression

*- In the opinion of the investigator, it is in the best interest of the

patient to discontinue treatment due to clinical progression

c. PSA progression is defined as the date that a >= 25% increase in PSA and an absolute increase of 2 ng/mL or more from the nadir is documented and confirmed by a second consecutive value obtained 3 or more weeks later. Rises in PSA within the first 12 weeks will be ignored in the absence of other evidence of disease progression (PCWG3 Guidance). Where no decline from baseline is documented, PSA progression is defined as a 25% increase from the baseline value along with an increase in absolute value of 2 ng/mL or more after 12 weeks of treatment.

5. Biochemical response endpoints:

a. Proportion of subjects who are PSA responders, defined as a patient who has achieved a >=50% decrease from baseline that is confirmed by a second PSA measurement >=4 weeks.

b. Alkaline phosphatase [ALP] and lactate dehydrogenase [LDH] levels will also be collected.

Study description

Background summary

The novel therapeutic drug 177Lu-PSMA-617 was developed by the German Cancer Research Center, Deutsches Krebsforschungszentrum (DKFZ) in collaboration with University Hospital Heidelberg for the treatment of patients with metastatic prostate cancer (Kratochwil et al 2015, Hillier et al 2009). Based on preclinical data that demonstrated high PSMA binding affinity and compound internalization, prolonged tumor uptake, rapid kidney clearance, and high tumor-to-background ratio, 177Lu-PSMA-617 proceeded into clinical development at investigative sites in Germany.
Over 20 compassionate use publications and prospective Phase 2 clinical trial data describe the use of 177Lu-PSMA-617 in patients who have been exposed to

approved agents. In the post-taxane, post-androgen axis inhibitor setting 177Lu-PSMA-617 has demonstrated a well-established, predictable, well tolerated safety profile. Clinical series have confirmed 8% incidence of Grade 1 to 2 xerostomia, less than 10% asymptomatic hematological of Grade 3 to 4 toxicity and no significant renal toxicity. Efficacy has been demonstrated on multiple clinically significant endpoints, including PSA response, soft tissue lesion response measured by RECIST, PFS, OS, pain and quality of life. No standard dose and schedule have been developed.
The preliminary clinical evidence indicates 177Lu-PSMA-617 may demonstrate clinical benefit in patients with mCRPC in a setting where patients had been exposed to chemotherapy and NAADs and there is no recommended standard of care. This Phase 3 study will assess the efficacy of 177Lu-PSMA-617 in patients with progressive PSMA-positive mCRPC by measuring overall survival in a randomized, prospective, open-label trial.

Study objective

The primary objective of this study is to compare overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive 177Lu-PSMA-617 in addition to best supportive/best standard of care versus patients treated with best supportive/best standard of care alone. A 2nd endpoint, radiographic progression free survival - rPFS - has been added as alternative primary endpoint.

Key secondary objectives are an arm-to-arm comparison of the following:

• Response Evaluation Criteria in Solid Tumors (RECIST) response
• Time to a first symptomatic skeletal event (SSE)
Additional Secondary Objectives:
• Safety and tolerability of 177Lu-PSMA-617
• Health-related quality of life (HRQoL; EQ-5D-5L, FACT-P and Brief Pain Inventory - Short Form (BPI-SF))
• Health economics
• Progression-free survival (PFS) (radiographic, clinical, or prostate-specific antigen [PSA] progression-free survival)
• Biochemical response as measured by PSA. Alkaline phosphatase [ALP] levels and lactate dehydrogenase [LDH] levels will also be measured.

Study design

Patients with PSMA positive scans will be randomized in a 2:1 ratio to receive either 177Lu-PSMA-617 plus best supportive/best standard of care or to receive best supportive/best standard of care only. Best supportive/best standard of care will be determined by the treating physician/investigator but will exclude investigational agents, cytotoxic chemotherapy, other systemic radioisotopes, and hemi-body radiotherapy. Novel androgen axis drugs [NAADs] (such as

abiraterone or enzalutamide) are allowed.
The study is open-label and patients will be monitored throughout the 6 to 10-month treatment period for survival, disease progression, and adverse events. A long-term follow-up period will include the collection of survival and treatment updates, adverse events assessment, as well as blood for hematology and chemistry testing. During follow-up, patients will be contacted every 3 months (±1 month) via phone, email, or letter for 24 months or until the the overall censoring rate for survival reduces to a level identified in the SAP.
An End of Treatment visit should occur once a patient is to enter the long term follow up. This visit should occur approximately 30 days from the last dose of 177Lu-PSMA-617 or best supportive/best standard of care, but before the initiation of subsequent anti-cancer treatment, outside of what is allowed on study.

Intervention

Patients randomized to receive the investigational product will receive 7.4 GBq (±10%) 177Lu-PSMA-617 intravenously every 6 weeks (±1 week) for a maximum of 6 cycles. After 4 cycles, patients will be assessed for (1) evidence of response, (2) residual disease, and (3) tolerance to 177Lu-PSMA-617. If the patient meets the criteria above, and agrees to continue with additional treatment of 177Lu-PSMA-617 radioligand therapy, the investigator may administer 2 additional cycles. A maximum of 6 cycles of radioligand therapy is allowed.
After the last cycle of 177Lu-PSMA-617, patients can continue best supportive/best standard of care alone.
If the patient does not meet all of the criteria or does not agree to additional 177Lu-PSMA-617 treatment, then no additional doses of 177Lu-PSMA-617 will be administered after Cycle 4. These patients can continue on best supportive/best standard of care alone after Cycle 4.
Radiographic imaging will be done every 8 weeks (±4 days) during the first 24 weeks of treatment and every 12 weeks (± 4 days) thereafter, regardless of treatment delays, through the End of Treatment visit.
The previous 2 PSA values will be noted before randomization. Serum testosterone and PSA levels will be measured within 3 days prior to Day 1 of each cycle. Hematology and chemistry will be done weekly during Cycle 1 (within 3 days prior to each time point) and within 3 days prior to Days 1, 15, and 29 in Cycles 2 to 6 (i.e. every two weeks). After Cycle 6, hematology and chemistry will be done every 8 weeks (±1 week) until the patient starts long term follow up.
Patients will complete the BPI-SF, EQ-5D-5L and FACT-P questionnaires about their pain level and HRQoL during screening and prior to treatment on Day 1 of each cycle and through the End of Treatment visit. Patients will be monitored throughout the study for SSEs.

Study burden and risks

Patients will be randomized to 1 of 2 treatment arms. Randomization will be stratified to avoid bias in treatment selection. Treatment will be open-label. Patients may experience side effects related to the 177LU-PSMA-617 and radiation. For full list of side effects please refer to Appendix E of the ICF. In addition to side effects patients may experience discomforts and risks associated with the study procedures and visits.

Contacts

Public
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US
Scientific
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East Hanover NJ 07936-1080
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Patients must have the ability to understand and sign an approved ICF.
2. Patients must have the ability to understand and comply with all protocol requirements.
3. Patients must be >=18 years of age.

4. Patients must have an ECOG performance status of 0 to 2.
5. Patients must have a life expectancy >6 months.
6. Patients must have histological, pathological, and/or cytological confirmation of prostate cancer.
7. Patients must be 68Ga-PSMA-11 PET/CT scan positive, and eligible , as determined by the sponsor's central reader.
8. Patients must have a castrate level of serum/plasma testosterone (<50 ng/dL or <1.7 nmol/L).
9. Patients must have received at least one NAAD (such as enzalutamide and/or abiraterone).
10. Patients must have been previously treated with at least 1, but no more than 2 previous taxane regimens. A taxane regimen is defined as a minimum exposure of 2 cycles of a taxane. If a patient has received only 1 taxane regimen, the patient is eligible if: a. The patient's physician deems him unsuitable to receive a second taxane regimen (e.g. frailty assessed by geriatric or health status evaluation, intolerance, etc.)
11. Patients must have progressive mCRPC. Documented progressive mCRPC will be based on at least 1 of the following criteria:
a. Serum / plasma PSA progression defined as 2 consecutive increases in PSA over a previous reference value measured at least 1 week prior. The minimal start value is 2.0 ng/mL.
b. Soft-tissue progression defined as an increase >=20% in the sum of the diameter (SOD) (short axis for nodal lesions and long axis for non-nodal lesions) of all target lesions based on the smallest SOD since treatment started or the appearance of one or more new lesions.
c. Progression of bone disease: evaluable disease or new bone lesions(s) by bone scan (2+2 PCWG3 criteria, Scher et al 2016).
12. Patients must have >=1 metastatic lesion that is present on baseline CT, MRI, or bone scan imaging obtained <=28 days prior to beginning study therapy.
13. Patients must have recovered to <= Grade 2 from all clinically significant toxicities related to prior therapies (i.e. prior chemotherapy, radiation, immunotherapy, etc.).
14. Patients must have adequate organ function:
a. Bone marrow reserve:
• White blood cell (WBC) count >=2.5 × 109/L (2.5 × 109/L is equivalent to 2.5 × 103/µL and 2.5 × K/µL and 2.5 × 103/cumm and 2500/µL) OR absolute neutrophil count (ANC) >=1.5 × 109/L (1.5 × 109/L is equivalent to 1.5 × 103/µL and 1.5 × K/µL and 1.5 × 103/cumm and 1500/µL)
• Platelets >=100 × 109/L (100 × 109/L is equivalent to 100 × 103/µL and 100 × K/µL and 100 × 103/cumm and 100,000/µL)
• Hemoglobin >=9 g/dL (9 g/dL is equivalent to 90 g/L and 5.59 mmol/L)
b. Hepatic:
• Total bilirubin <=1.5 x the institutional upper limit of normal (ULN). For patients with known Gilbert*s Syndrome <=3 × ULN is permitted
• Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) <=3.0 × ULN OR <=5.0 × ULN for patients with liver metastases
c. Renal:

• Serum plasma creatinine <=1.5 x ULN or creatinine clearance >=50 mL/min
15. Albumin >3.0 g/dL (3.0 g/dL is equivalent to 30 g/L)
16.
17. HIV-infected patients who are healthy and have a low risk of AIDS-related outcomes are included in this trial.
For patients who have partners of childbearing potential:
18. Partner and/or patient must use a method of birth control with adequate barrier protection, deemed acceptable by the principle investigator during the study and for 6 months after last study drug administration.
19. The best standard of care/ best supportive care options planned for this patient: a. Are allowed by the protocol b. Have been agreed to by the treating investigator and patient c. Allow for the management of the patient without 177Lu-PSMA-617.

Exclusion criteria

1. Previous treatment with any of the following within 6 months of randomization: Strontium-89, Samarium-153, Rhenium-186, Rhenium188, Radium-223 hemi-body irradiation. Any of the listed radio ligand therapies and hemi-body irradiation require a 6 month wash out period. PSMA-targeted radioligand therapy is not allowed.
2. Any systemic anti-cancer therapy (e.g. chemotherapy, immunotherapy or biological therapy [including monoclonal antibodies]) within 28 days prior to day of randomization.
3. Any investigational agents within 28 days prior to day of randomization.
4. Known hypersensitivity to the components of the study therapy or its analogs.
5. Other concurrent cytotoxic chemotherapy, immunotherapy, radioligand therapy, or investigational therapy.
6. Transfusion for the sole purpose of making a subject eligible for study inclusion.
7. Patients with a history of CNS metastases must have received therapy (surgery, radiotherapy, gamma knife) and be neurologically stable, asymptomatic, and not receiving corticosteroids for the purposes of maintaining neurologic integrity. Patients with epidural disease, canal disease and prior cord involvement are eligible if those areas have been treated, are stable, and not neurologically impaired. For patients with parenchymal CNS metastasis (or a history of CNS metastasis), baseline and subsequent radiological imaging must include evaluation of the brain (MRI preferred or CT with contrast).
8. A superscan as seen in the baseline bone scan.
9. Symptomatic cord compression, or clinical or radiologic findings indicative of impending cord compression.
10. Concurrent serious (as determined by the Principal Investigator) medical conditions, including, but not limited to, New York Heart Association class III or IV congestive heart failure, history of congenital prolonged QT syndrome, uncontrolled infection, active hepatitis B or C, or other significant co-morbid

conditions that in the opinion of the investigator would impair study participation or cooperation. This applies to known active Hep B or C - screening is not required.
11. Diagnosed with other malignancies that are expected to alter life expectancy or may interfere with disease assessment. Patients with adequately treated non-melanoma skin cancer, superficial bladder cancer and patients with prior history of malignancy who have been disease free for more than 3 years are eligible.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-12-2018
Enrollment:	38
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	177LU-PSMA-617
Generic name:	177LU-PSMA-617
Product type:	Medicine
Brand name:	68Ga-PSMA-11 prepared using PSMA-11 sterile kit
Generic name:	68Ga-PSMA-11 prepared using PSMA-11 sterile kit

Product type:	Medicine
Brand name:	68Ga-PSMA-11-HBED-CC
Generic name:	68Ga-PSMA-11-HBED-CC
Product type:	Medicine
Brand name:	best supportive care/best standard of care
Generic name:	best supportive care/best standard of care
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	23-08-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-12-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-05-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-07-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-09-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-09-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	31-10-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-07-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-10-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-11-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-12-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-05-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-06-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-07-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-08-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	25-10-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-10-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-04-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2018-000459-41-NL
ClinicalTrials.gov	NCT03511664
CCMO	NL66744.091.18