2 Synopsis

Name of product: ^{177}Lu-PSMA-617 (lutetium (^{177}Lu) vipivotide tetraxetan) [^{177}Lu]Lu-PSMA-617 and ^{68}Ga-PSMA-11 (gallium (^{68}Ga) gozetotide) [^{68}Ga]Ga-PSMA-11

Protocol identification number: PSMA-617-01, EudraCT no. 2018-000459-41, NCT03511664

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

Investigators: Oliver Sartor, MD, Tulane University Medical School, USA and Bernd Joachim Krause, MD, Rostock University Medical Center, Germany

Study centers: Belgium (3); Canada (7); Denmark (3); France (6); Netherlands (4); Sweden (5); UK (9); US (45); Germany (4, for the sub-study only).

Publication (reference): None

Study period

Study initiation date: 29-May-2018 (first patient first visit)

Data cut-off date: 27-Jan-2021 - The required number of overall survival (OS) events was reached to trigger the final OS analysis and primary analysis of rPFS of this study. Enrollment has ended but the study is still ongoing.

Phase of development (phase of this clinical study): III

Primary objective

The primary objective of this study was to compare the 2 alternate endpoints of radiographic-progression-free survival (rPFS) and OS in patients with progressive prostate-specific membrane antigen (PSMA)-positive mCRPC who received ^{177}Lu-PSMA-617 in addition to best supportive/best standard of care (BSC/BSoC) versus patients treated by BSC/BSoC only.

The statistical design of the study was such that, to be declared positive, the study would be required to reach statistical significance on either rPFS or OS at the respective allocated alpha level.

Key secondary objectives

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

- Response evaluation criteria in solid tumours (RECIST) response:
  - Overall response rate (ORR) as measured by RECIST v1.1
  - Disease control rate (DCR) as measured by RECIST v1.1
- Time to a first symptomatic skeletal event (SSE)

Key secondary endpoints were assessed using the Hochberg closed test procedure at the alpha level applicable to the successful OS endpoint. This procedure is reasonable given the positive correlation between the key secondary endpoints.

Additional secondary objectives

- Safety and tolerability of ^{177}Lu-PSMA-617
- Periodic assessment of health-related quality of life (HR QoL) to evaluate impact of intervention on patient well-being (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))
- Health economics
- Progression-free survival (PFS) (radiographic, clinical, or PSA)

- Biochemical response as measured by prostate-specific antigen (PSA). Alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) levels were also collected

Methodology: This is a Phase III, open-label, international, randomized study to evaluate the efficacy and safety of ^{177}Lu-PSMA-617 in patients with progressive PSMA-positive mCRPC, when administered in addition to BSC/BSoC as compared to BSC/BSoC only. Randomized patients were stratified on the following factors: LDH level (≤ or > 260 UI/L), presence of liver metastases (Yes or No), eastern cooperative oncology group (ECOG) score (0-1 or 2) and inclusion of NAAD in the BSC/BSoC (at time of randomization, Yes or No).

Number of patients (planned and analyzed): Planned to be randomized: N=814; Assessed for eligibility: N=1179; Received ^{68}Ga-PSMA-11 positron emission tomography/ computed tomography (PET/CT): N=1003; Total Randomized: N=831 (on or after 05-Mar-2019: N=581); Randomized to ^{177}Lu-PSMA-617+BSC/BSoC: N=551 (on or after 05-Mar-2019: N=385); Randomized to BSC/BSoC only: N=280 (on or after 05-Mar-2019: N=196).

Diagnosis and main criteria for inclusion: Adult male patients who had a histological, pathological, and/or cytological confirmation of PC, progressive mCRPC (based on any one of the following as defined by the prostate cancer clinical trials working group 3 (PCWG3) criteria for clinical trial entry: serum PSA progression, soft-tissue progression, or progression of bone disease), had received at least 1 novel androgen axis drug (NAAD), were previously treated with at least 1 but no more than 2 prior taxane regimens and had a positive ^{68}Ga-PSMA-11 PET/CT scan, as determined by the Sponsor's central reader.

Patients with previous treatment with any of the following within 6 months of randomization: strontium-89, samarium-153, rhenium-186, rhenium-188, radium-223, or hemi-body irradiation or previously treated with PSMA-targeted targeted radioligand therapy (RLT), or any systemic anti-cancer therapy (e.g. chemotherapy, immunotherapy or biological therapy) within 28 days prior to day of randomization were excluded.

Duration of treatment: For the Test arm (^{177}Lu-PSMA-617+BSC/BSoC), at least 4 cycles and up to a maximum of 6 cycles of ^{177}Lu-PSMA-617, the patients could continue BSC/BSoC until they met one of the criteria for treatment discontinuation. For the Reference arm (BSC/BSoC only), there was no pre-defined number of cycles and the patients could continue BSC/BSoC until they met one of the criteria for treatment discontinuation.

Test and reference therapies, dose and mode of administration, batch number:

^{177}Lu-PSMA-617 was administered as a slow i.v. injection at a dose of 7.4 GBq (±10%) once every 6 weeks (±1 week) for a maximum of 6 cycles. It was administered only by qualified/authorized personnel. Treatment with ^{177}Lu-PSMA-617 was performed in accordance with national and/or local radiation safety requirements.

Due to nature of this drug product there was 1 batch number for each patient dose. The list of batch numbers is available in the appendices of the clinical study report.

BSC/BSoC was prescribed by each patient's physician and reflected standard interventions available to clinicians. BSC/BSoC regimen could be adapted during the study to the best interest of the patient at the discretion of the Investigator, however investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radio isotopes (e.g. radium-223), or hemi-body radiotherapy treatment were not allowed during the study.

Criteria for evaluation

Efficacy:

Radiographic imaging for tumor assessments: images were evaluated in accordance with both RECIST 1.1 and PCWG3 criteria. Periodic radiographic imaging included both:

- Computed tomography (CT) with contrast/ Magnetic resonance imaging (MRI)

- CT with contrast/MRI tumor assessments included evaluations of the chest, abdomen, and pelvis.
- The responses of soft tissue, lymph node, and visceral lesions to treatment were characterized using the RECIST v1.1 criteria with caveats outlined in the PCWG3 recommendations.

- Bone scans with ^{99m}Tc labeled diphosphonates
  - Disease progression by bone scan was characterized using the PCWG3 criteria for bone lesions.

Radiographic imaging for tumor assessment was done every 8 weeks (±4 days) after C1D1, for the first 24 weeks (independent of dose delays), then every 12 weeks (±4 days).

An imaging contract research organization was responsible for the collection, quality control, archival, and blinded independent central review of imaging for the study. The results of the central evaluations were used for the analysis of rPFS and ORR. The local Investigator's assessment was used for patient management, and was also utilized in sensitivity analyses.

Survival: all patients who consented to be in the long-term follow-up were to be followed for OS status every 3 ±1 months regardless of randomized treatment discontinuation reason.

Symptomatic skeletal events: the time to the first SSE measured the time from randomization to the first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, requirement for radiation therapy to relieve bone pain or death from any cause, whichever occurred first.

ECOG performance status: the ECOG Performance Status scale was used to assess patients' ability to perform daily living tasks and their range of basic physical ability.

Patient-reported outcomes: The BPI-SF was used to assess the severity of pain and the impact of pain on daily functions. The FACT-P questionnaire was administered to specifically assess the HR QoL of PC patients. The FACT-P is made up of 2 parts: the FACT-G questionnaire with 27 questions, and the PCS comprising an additional 12 questions. The PCS is designed specifically to measure PC-specific quality of life. The EQ-5D-5L questionnaire was administered to assess a patient's self-reported health status.

Clinical progression: Clinical progression was assessed by the Investigator. The following criteria were used to determine when a patient had met the standard for unequivocal evidence of clinical progression:

- Marked escalation in cancer-related pain that was 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 score to ≥ 3 and a finding of the Investigator that the deterioration indicated clinical progression
- In the opinion of the Investigator, it was in the best interest of the patient to discontinue randomized treatment due to clinical progression

Biochemical responses: PSA, LDH and ALP levels were measured by the local laboratory. Changes in PSA levels were used to assess PSA responses as per PCWG3 criteria.

Safety:

Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), with their severity and causality, and pregnancies of partners. This also included the regular monitoring of hematology, blood chemistry, serum/plasma testosterone, urinalysis, and regular assessments of vital signs. During long-term follow-up, limited safety data were collected: hematology, blood chemistry, and AE assessment.

Statistical methods:

Analysis sets

Full Analysis Set (FAS): All randomized patients. Patients were included in the treatment arm to which they were randomized regardless of actual treatment received. This is an intent to treat (ITT) analysis set. This analysis set is used for the analysis of OS.

PFS Full Analysis Set (PFS-FAS): All patients randomized on or after 05-Mar-2019. Patients were included in the treatment arm to which they were randomized regardless of actual treatment received. This analysis set is used for the primary analyses of rPFS and all secondary endpoints except ORR and DCR.

Response Evaluable Analysis Set: The subset of patients in the PFS-FAS with evaluable disease by RECIST at baseline (i.e. at least one target and/or non-target lesion per independent central review radiologist assessment used as the final radiology assessment). Patients were included in the treatment arm to which they were randomized. Soft tissue response as measured by RECIST was assessed in this dataset. This analysis set was used for the primary analyses of ORR and DCR.

FAS Safety Analysis Set: The subset of patients in the FAS who received at least one dose of randomized treatment. Patients were included in the treatment arm corresponding to the actual treatment received.

PSMA-11 Safety Analysis Set: All patients who received a dose of ^{68}Ga-PSMA-11. This included screened patients who were not randomized. Randomized patients were included in the treatment arm to which they were randomized.

Alternate primary endpoints

rPFS was defined as the time (in months) from the date of randomization to the date of radiographic disease progression based on the central review assessment per the PCWG3 criteria or death due to any cause. Patients who were alive without radiographic progression at the analysis data cut-off were censored for rPFS at the time of their last evaluable radiographic assessment. The null hypothesis for rPFS, assumed the median rPFS was 4 months on active treatment for a HR of 1.00. Under the alternative hypothesis, median rPFS on active treatment was assumed to be 6 months for a HR of 0.67.

The null hypothesis, was tested at a one-sided level of significance. The primary analysis was to test the null hypothesis and compare the two treatment arms using a stratified log-rank test stratifying for the randomization stratification factors. The primary analysis of rPFS was based on the PFS-FAS population. The rPFS distribution was estimated using the Kaplan-Meier method, and Kaplan-Meier curves (including number at risk and confidence limits), median, 25th percentile, and 75th percentile and associated 99.2% confidence intervals (CIs) are presented for each treatment arm. The rPFS Kaplan-Meier estimate along with 99.2% CIs are presented at different time points (e.g. 3, 6, and 12 months) for each treatment arm. The one-sided p-value from the log-rank test is presented.

OS was defined as the time (in months) from the date of randomization to the date of death due to any cause. If the patient was not known to have died, then OS was censored. The censoring date was date of the last study visit, or contact, until the cut-off date. The cut-off date was not used for last contact date, unless the patient was seen or contacted on that date. The null hypothesis for survival, assumed median OS was 10 months on active treatment for a HR of 1.00. Under the alternative hypothesis, median OS on active treatment was assumed to be 13.7 months for a HR of 0.7306. The null hypothesis was tested at a one-sided level of significance. The primary analysis was to test the null hypothesis and compare the two treatment arms using a stratified log-rank test stratifying for the randomization stratification factors. The primary analysis of OS was based on the FAS population. The OS distribution was estimated using the Kaplan-Meier method, and Kaplan-Meier curves (including numbers at risk and confidence limits), median, 25th percentile, and 75th percentile and associated 95% CIs are presented for each treatment arm. The OS Kaplan-Meier estimate along with 95% CIs are presented at different time points (e.g. 6, 12, and 18 months) for each treatment arm. The one-sided p-value from the log-rank test is presented.

Key secondary endpoints (ORR, DCR and Time to first SSE)

To control the overall Type I error rate, key secondary endpoints were assessed using the Hochberg closed test procedure at the alpha level applicable to the successful alternate primary endpoint. This procedure is reasonable given the positive correlation between the key secondary endpoints. The 3 key secondary endpoints were controlled for multiplicity using the Hochberg closed test procedure and used the alpha level from the successful OS results (as specified in the statistical analysis plan) for testing.

Summary - Results

Demographic and background characteristics: Demographics and disease characteristics at baseline were well balanced between the 2 randomized arms and representative of mCRPC patients with advanced disease who were previously treated with NAAD and taxanes.

831 patients were randomized in the study, 551 to the ^{177}Lu-PSMA-617+ BSC/BSoC arm and 280 to the BSC/BSoC only arm. All randomized patients, except for 3 patients randomized in error, were positive for eligibility ^{68}Ga-PSMA-11 scans. 96.7% of patients randomized to ^{177}Lu-PSMA617+BSC/BSoC and 71.8% of patients randomized to BSC/BSoC received at least one dose of treatment. The relatively high proportion of patients randomized but never treated in the BSC/BSoC only arm was related to patients who withdrew consent from treatment early in the study because they were not randomized to receive ^{177}Lu-PSMA-617 (in addition to BSC/BSoC). Enhanced study site education measures were implemented to curtail this phenomenon and a sufficient number of patients in both arms could be evaluated for all primary and key secondary endpoints of the study, as well as for safety evaluation.

Efficacy results: The study met both alternate primary efficacy objectives. The primary endpoint rPFS was statistically significant in favor of the ^{177}Lu-PSMA-617+BSC/BSoC arm (stratified Log-rank test $p < 0.001$, one-sided), with an estimated 60% risk reduction of radiographic disease progression or death in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. the BSC/BSoC only arm (HR=0.40; 99.2% CI: 0.29, 0.57, $p < 0.001$). The median rPFS was prolonged by 5.3 months in the ^{177}PSMA617+BSC/BSoC arm. The median rPFS (99.2% CI) was 8.7 months (7.9, 10.8) in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 3.4 months (2.4, 4.0) in the BSC/BSoC only arm. The primary endpoint OS was statistically significant in favor of the ^{177}Lu-PSMA-617+BSC/BSoC arm (stratified Log-rank test $p < 0.001$, one-sided), with an estimated 38% risk reduction of death in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. the BSC/BSoC only arm (HR=0.62; 95% CI: 0.52, 0.74). The median OS was prolonged by 4.0 months in the ^{177}PSMA617+BSC/BSoC arm. The median OS (95% CI) was 15.3 months (14.2, 16.9) in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 11.3 months (9.8, 13.5) in the BSC/BSoC only arm. Sensitivity analyses and subgroup analyses of the primary endpoints, although not adjusted for statistical significance, were consistent with and supportive of the results observed for the primary endpoints. The COVID-19 pandemic had minimal impact on the conduct of this study, and sensitivity analyses showed that the pandemic had no impact on the alternate primary efficacy endpoints evaluations.

The study also met all of its key secondary efficacy objectives. All key secondary endpoints were statistically significant and clinically meaningful in favor of the ^{177}Lu-PSMA-617+BSC/BSoC arm. The ORR was statistically significant in favor of the ^{177}Lu-PSMA-617+BSC/BSoC arm ($p < 0.001$). ORR was 29.8% in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 1.7% in the BSC/BSoC only arm. The response was durable with a median (95% CI) Duration of response (DoR) in responders of 9.8 months (9.1, 11.7) in ^{177}Lu-PSMA-617+BSC/BSoC arm. The median DoR in the BSC/BSoC only arm was not reliable since only 1 of the 2 patients who responded had a RECIST radiographic progression or death. The DCR was also statistically significant in favor of the ^{177}Lu-PSMA-617+BSC/BSoC arm ($p < 0.001$). DCR was 89.0% in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 66.7% in the BSC/BSoC only arm. Time to first SSE was also statistically significant in favor of the ^{177}Lu-PSMA-617+BSC/BSoC arm ($p < 0.001$), with an estimated 50% risk reduction of SSE or death in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. the BSC/BSoC only arm (HR=0.50; 95% CI: 0.40, 0.62). The median time to first SSE (95% CI) was 11.5 months (10.3, 13.2) in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 6.8 months (5.2, 8.5) in the BSC/BSoC only arm. Other secondary efficacy analyses, including progression-free survival,

biochemical response and PRO (including prostate specific FACT-P and pain specific BPI analyses), although not adjusted for statistical significance, were in favor of the ^{177}Lu-PSMA-617+BSC/BSoC arm.

Safety results:

Patients received a single administration of ^{68}Ga-PSMA-11 in the pre-randomization screening period with a mean dose of 167 MBq (4.5 mCi), ranging from 92.8-287.5 MBq (2.5-7.8 mCi). The ^{68}Ga-PSMA-11 administration was well tolerated, with fatigue (1.2%) as the most frequent AE and other AEs were reported in less than 1.0% of patients. Although the treatment-emergent AE reporting was potentially confounded by new or ongoing BSC/BSoC medication, analysis confirms a favorable safety profile in line with published experience with ^{68}Ga-PSMA-11.

Safety of ^{177}Lu-PSMA-617 was consistent with what was previously reported, and was tolerable and manageable with appropriate intervention. Based on the mechanism of action of ^{177}Lu-PSMA-617 and the safety profile from previously published studies, it was already known that treatment with ^{177}Lu-PSMA-617 tend to increase the risk of fatigue, dry mouth, myelosuppression (including anemia, thrombocytopenia, lymphopenia, leucopenia) and nausea and/or vomiting; but these events were manageable with supportive care and with occasional delays in treatment cycles. Renal toxicity was not an important safety concern, and was predominantly low grade with creatinine increases that were reversible. Serious renal events were infrequent and no more common in ^{177}Lu-PSMA-617+BSC/BSoC than in BSC/BSoC only arm. Overall, 11.9% of patients who received ^{177}Lu-PSMA-617 at least once discontinued treatment with ^{177}Lu-PSMA-617 due to an AE. No patient had an interruption due to an AE during the administration of ^{177}Lu-PSMA-617. The main reason to discontinue ^{177}Lu-PSMA-617 was myelosuppression (7.0% of patients), all other events, including fatigue, led to permanent discontinuation of ^{177}Lu-PSMA-617 in < 0.5% of patients each.

Safety data that was collected from patients in the long-term follow-up, after end-of-treatment, did not reveal any new safety concerns. The increased risk of fatigue, dry mouth, myelosuppression and nausea and/or vomiting observed during treatment in the ^{177}Lu-PSMA-617+BSC/BSoC arm were transient. The nature, rate and severity of AEs in the long-term follow-up were similar to the background experience seen in the BSC/BSoC only arm during randomized treatment, and did not provide any evidence of long-term toxicity.

Conclusion:

The results of the study demonstrated superior clinical efficacy and a favorable risk/benefit profile of ^{177}Lu-PSMA-617+BSC/BSoC when compared to BSC/BSoC only in PSMA-positive mCRPC patients previously treated with taxanes and NAADs.

Analysis of efficacy demonstrated a statistically significant improvements in the primary endpoints (OS and rPFS) and the key secondary endpoints (ORR, DCR, and time to first SSE):

- The median rPFS was prolonged by 5.3 months with an estimated 60% risk reduction of radiographic disease progression or death
- The median OS was prolonged by 4.0 months with an estimated 38% risk reduction in death
- The OS and rPFS data was supported by improvements in:
  - ORR of 29.8% in the ^{177}Lu-PSMA-617+BSC/BSoC arm that was durable (median (95% CI) DoR of 9.8 months (9.1, 11.7)) vs. 1.7% in the BSC/BSoC only arm
  - DCR of 89.0% in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 66.7% in the BSC/BSoC only arm
  - Time to first SSE with an estimated 50% risk reduction of SSE or death and a median time to first SSE delayed by 4.7 months

This was further supported by:

- PFS improvement and PSA response. PSA response as ≥ 50% decrease from baseline occurred in 46.0% (95% CI: 40.9, 51.1) of patients in ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 7.1% (95% CI: 4.0, 11.7) of patients in BSC/BSoC only arm.

- Efficacy analyses were consistent across all pre-specified subgroups that included NAAD as part of BSC/BSoC at baseline, LDH level at baseline, liver metastasis at baseline, ECOG score at baseline, age at baseline and race
- QoL data further supported the aforementioned clinical benefit, in particular BPI-SF, a pain-measuring instrument and FACT-P, an instrument which is specific to prostate cancer patients.

Analysis on safety profiles for both ^{68}Ga-PSMA-11 and ^{177}Lu-PSMA-617 were consistent with what was previously reported that was tolerable and manageable with appropriate intervention.

When taken as a whole, the study findings demonstrate a clinically meaningful improvement for men with advanced stage mCRPC over current therapeutic options, where “clinically meaningful” is defined as:

- An HR ≤ 0.8 corresponding to an improvement in median OS within the range of 2.5 to 6 months
- Incremental gains in other efficacy and key secondary endpoints (e.g. rPFS, time to SSE)
- The incremental gains is accompanied by little increase in toxicity compared to prevailing therapies (i.e. taxane- or platinum-based regimens).

The study results suggest that ^{177}Lu-PSMA-617 plus BSC/BSoC represents a novel, efficacious and well tolerated regimen in ^{68}Ga-PSMA-11 PET/CT scan selected patients with mCRPC who were previously treated with 1-2 taxane-based chemotherapy regimens and at least 1 NAAD.

History of changes to the synopsis			
Version	Date (content final)	Summary of Changes	Change to overall conclusion
1.0	28-Jun-2021	Original version	