Clinical Development

lutetium (^{177}Lu) vipivotide tetraxetan

AAA617 ([^{177}Lu]Lu-PSMA-617)

2.7.3 Summary of Clinical Efficacy in prostate-specific membrane antigen-positive metastatic castration-resistant prostate cancer

Document type:	CTD Clinical summary document
Document status:	Final
Release date:	13-Sep-2021

Table of contents

List of tables

List of figures

List of abbreviations used in the text

^{68}Ga-PSMA-11	Gallium-labeled PSMA-11
^{177}Lu-PSMA-617	Lutetium-labeled PSMA-617
ADT	Androgen deprivation therapy
AE	Adverse event
ALP	Alkaline phosphatase
APCCC	Advanced Prostate Cancer Consensus Conference
AR	Androgen receptor
ASCO	American Society of Clinical Oncology
BICR	Blinded independent central review
BPI-SF	Brief pain inventory (short form)
BSC/BSoC	Best supportive care/best standard of care
BOR	Best overall response
C1D1	Cycle 1 day 1
CR	Complete response
CRF	Case Report Form
CRPC	Castration-resistant prostate cancer
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DCR	Disease control rate
DoR	Duration of response
DOTA	Tetraacetic acid
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EOI	End of injection/infusion
EQ-5D-5L	European Quality of Life (EuroQol) – 5 Domain 5 Level scale
ERBT	External beam radiation therapy
ESMO	European Society for Medical Oncology
EudraCT	European Union Drug Regulating Authorities Clinical Trial
FACT-G	Functional Assessment of Cancer Therapy – General
FACT-P	Functional Assessment of Cancer Therapy – Prostate
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
HRQoL	Health-related quality of life
ICH	International Council for Harmonization
IRT	Interactive response technology
i.v.	Intravenous
LDH	Lactate dehydrogenase
mCRPC	Metastatic castration-resistant prostate cancer
NAAD	Novel androgen axis drug (such as abiraterone or enzalutamide)

NCCN	National Comprehensive Cancer Network
ORR	Overall response rate
OS	Overall survival
PARP	Poly ADP-ribose polymerase
PC	Prostate cancer
PCS	Prostate cancer subscale
PCWG	Prostate Cancer Clinical Trials Working Group
PD	Progressive disease
PFS	Progression-free survival
PIS	Pain intensity scale
PR	Partial response
PSA	Prostate specific antigen
PSADT	PSA doubling time
PSI	Prostate symptom index
PSMA	Prostate-specific membrane antigen
PWB	Physical well being
RECIST	Response Evaluation Criteria in Solid Tumors
RLT	Radioligand therapy
rPFS	Radiographic progression-free survival
SAP	Statistical analysis plan
SAWP	Scientific Advice Working Party
SCP	Summary of Clinical Pharmacology
SD	Stable disease
SSE	Symptomatic Skeletal Event
TOI	Trial outcome index
VAS	Visual analog scale

1 Background and overview of clinical efficacy

The purpose of this SCE is to provide an efficacy evaluation of lutetium (^{177}Lu) vipivotide tetraxetan ([^{177}Lu]Lu-PSMA-617), a radioligand therapeutic agent, for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC).

In this SCE, the therapeutic agent lutetium (^{177}Lu) vipivotide tetraxetan ([^{177}Lu]Lu-PSMA-617/ company research code: AAA617) is referred to as ^{177}Lu-PSMA-617, and the radiolabeled compound gallium (^{68}Ga) gozetotide ([^{68}Ga]Ga-PSMA-11/ company research code: AAA517) is referred to as ^{68}Ga-PSMA-11. In addition, AR pathway inhibitors are considered synonymous with and are referred to as NAADs in this document.

1.1 Efficacy aspects of the product or targeted indication

1.1.1 Unmet medical need of target indication

Globally, prostate cancer (PC) is the second most common cancer in men and the fifth most common cause of cancer death among men, with an estimated 1.4 million new cases and 375,304 cancer deaths worldwide in 2020 (Sung et al 2021). In the US, approximately 191,930 new cases of PC and 33,330 deaths were estimated for 2020 (American Cancer Society 2020); in Europe, 473,344 new cases and 108,088 deaths were estimated for 2020 (International Agency for Research on Cancer 2020). Prostate cancer is the second leading cause of cancer-related death among men in the United States, and the third leading cause of cancer-related death among men in Europe (Malvezzi et al 2019, Siegel et al 2020).

The median age at diagnosis of mCRPC is 70 years (Flaig et al 2016) and metastatic prostate cancer has a predilection for bone. As a result, approximately 90% of patients with mCRPC develop bone metastases (Kirby et al 2011), 49% of whom will develop a skeletal-related event within 2 years (Saad et al 2004). Common presentations include bone pain, bone marrow failure, fatigue, or complications such as fractures and spinal cord compression. These presentations typically require radiation or bone surgery, which can significantly impair physical, emotional, and functional well-being (Weinfurt et al 2005).

After an initial response to androgen deprivation therapy (ADT) by chemical and/or surgical castration, most patients with metastatic disease progress to a hormone insensitive stage of the illness, known as metastatic castration-resistant prostate cancer or mCRPC. Ten to 20% of patients with PC become castration-resistant within 5 years, and >50% of those patients die within 3 years with historical standard therapies (Nussbaum et al 2016). The 5-year survival rate is 31% for patients who present with metastatic disease (American Cancer Society 2020). Once patients reach the mCRPC stage, their expected overall survival (OS) is low, as was seen in the randomized Phase III study of cabozantinib vs prednisone in patients with mCRPC who had received prior docetaxel and abiraterone acetate and/or enzalutamide; the median OS of the prednisone control arm was 9.8 months (Smith et al 2016).

Despite therapeutic developments in the last decade, there is a negative impact on quality of life with cytotoxic therapies, and a high humanistic burden remains for patients with mCRPC. Symptomatic skeletal events (SSEs), comorbidities, and bone metastasis further add to the burden for these patients. Almost all patients ultimately progress and exhaust existing treatment

options. High discontinuation rates and toxicities with current treatments along with low survival rates demonstrate there is still a profound need for new treatment options with significant antitumor activity and less toxicity for the treatment of patients with mCRPC.

Targeted radioligand therapy (RLT) offers the possibility to treat prostate cancer lesions in a specific and tumor-selective manner by exploiting cell surface proteins mainly expressed on malignant cells. The prostate-specific membrane antigen (PSMA) is a promising RLT target because it is highly expressed in PC, including mCRPC, but it has low and restricted expression in normal tissues (Bostwick et al 1998, Sokoloff et al 2000, Chang 2004, Ghosh and Heston 2004). This differential in expression provides a mechanism by which targeted therapeutic radiation can be delivered to cancer cells via PSMA while minimizing radiation-related side effects. PSMA-targeted RLT utilizes a radiolabeled small-molecule ligand that targets and binds with high affinity to PSMA, resulting in internalization and retention within the targeted PC cell (Ghosh and Heston 2004, Benešová et al 2015), to treat PSMA-positive mCRPC.

1.1.2 Currently available treatment options for the target population

The current standard of care in metastatic prostate cancer (mPC) is based on chemotherapy, androgen deprivation by different mechanisms of action on the hypothalamic-pituitary-gonadal axis, and adrenal-androgen receptor signaling. Standard ADT and NAADs (i.e. abiraterone acetate or enzalutamide) are commonly well tolerated and can stabilize metastatic castration-sensitive PCs (mCSPC) for many years. However, most patients eventually progress to mCRPC, which remains challenging to treat.

Several agents have been approved for the treatment of mCRPC. NCCN, ASCO, ESMO, and APCCC guidelines provide some consensus and guidance for their use, but there is no proper sequence for delivery of these agents in patients with mCRPC. Regardless, none of these therapies has been proven to prolong survival after NAAD therapies.

Taxane-based chemotherapies and androgen axis inhibitors are the most commonly used agents for patients with mCRPC (Tannock et al 2004, de Bono et al 2010, de Bono et al 2011, Scher et al 2012), and only one study (the CARD study) has demonstrated efficacy after progression has occurred following treatment with these agents (Gillessen et al 2020). In the CARD study, cabazitaxel was more effective than switching from abiraterone to enzalutamide, or vice-versa, in both prolonging imaging based progression-free survival and overall survival of patients with progression after docetaxel and either abiraterone or enzalutamide (de Wit et al, 2019). Other treatment options in this population include bone-directed radiotherapy with ^{223}radium for those with symptomatic bone dominant disease, immunotherapy with sipuleucel-T, and poly ADP-ribose polymerase (PARP) inhibitors in those with specified HRR defects (Kantoff et al 2010, Parker et al 2013, Abida et al 2020, Anscher et al 2020, de Bono et al 2020, Hussain et al 2020).

In clinical practice, NAADs are often used in the first-line mCRPC setting. Sipuleucel-T is most commonly used in mildly asymptomatic small-volume disease, while ^{223}Ra dichloride is used to treat patients with bone-only disease. Taxane-based chemotherapy (i.e. docetaxel and cabazitaxel) is used after abiraterone acetate or enzalutamide and for symptomatic patients, particularly with visceral disease. Docetaxel is used more commonly (Flaig et al 2016), and cabazitaxel was specifically designed for antitumor activity in docetaxel-resistant patients

(de Wit et al 2019). Because both agents have a typical chemotherapy side-effect profile (including bone marrow suppression), they are often not considered due to multiple comorbidities, poor hematological reserve, or patient refusal (Zielinski et al 2014). When the approved second-line treatments (e.g. abiraterone acetate or enzalutamide) are used in the third-line setting, they do not retain the same levels of activity as when used in second line.

NAADs in patients previously exposed to a taxane and either abiraterone acetate or enzalutamide produce only modest activity in terms of PSA decline, and PFS and OS benefit (Loriot et al 2013, Noonan et al 2013, Azad et al 2015, Brasso et al 2015, Cheng et al 2015). As NAADs have been used in earlier lines of therapy, the use of a second NAAD following docetaxel has resulted in diminished efficacy, likely due to cross resistance.

In summary, although the therapeutic landscape of mCRPC has broadened over the last decade, deaths due to mCRPC are still rising in these patients, many of whom are frail and elderly. There are limited options available to patients who fail taxane-based chemotherapy or for whom taxane-based chemotherapy is contraindicated or not appropriate, particularly if alternative agents currently approved in this setting (NAADs) have been used earlier in the disease.

1.1.3 Product and target indication

1.1.3.1 Prostate-specific membrane antigen

PSMA, a type II transmembrane protein, is highly expressed in nearly all prostate cancers, including adenocarcinoma, but has restricted and several hundred-fold lower expression in some normal tissues such as duodenal mucosa, renal proximal tubules, and salivary glands (Bostwick et al 1998, Sokoloff et al 2000, Ghosh and Heston 2004, Chang 2004). Additionally, PSMA overexpression is correlated with advanced, high-grade, metastatic, castration-resistant prostate cancer (Wright et al 1995, Silver et al 1997, Bostwick et al 1998, Murphy et al 1998, Sweat et al 1998, Ross et al 2003, Chang 2004, Queisser et al 2015).

In addition to the expression pattern, the functionality of PSMA plays an equally important role in its value as a tumor-specific targeting mechanism. Specifically, the binding of a high affinity ligand to PSMA, such as the targeting moiety in ^{177}Lu-PSMA-617, leads to internalization through endocytosis and a sustained retention of the ligand and its bound radioactive cargo within the cancer cell (Rajasekaran et al 2003, Benešová et al 2015). This functional feature of PSMA allows for the development of low-molecular-weight targeted radiopharmaceuticals with favorable pharmacokinetic and tumor penetration properties, rather than being restricted to antibody-based targeting strategies (Haberkorn et al 2016).

The result of both selective expression and ligand-based uptake using PSMA as a target is a reduction in background uptake and off-target toxicities as well as an increase in the amount of radioactivity that localizes at the tumor site. These properties make PSMA a promising target for both radioactive imaging as well as radioligand therapeutic intervention.

1.1.3.2 ^{177}Lu-PSMA-617 in prostate cancer

^{177}Lu-PSMA-617 is a novel, small molecule PSMA-targeted RLT that takes advantage of the unique attributes of PSMA described above, and with the recent data, has been shown to deliver clinical benefit and can advance the manner in which prostate cancer is treated. ^{177}Lu-PSMA-

617 was initially developed by the German Cancer Research Center, Deutsches Krebsforschungszentrum (DKFZ) in collaboration with University Hospital Heidelberg (Kratochwil et al 2015).

PSMA-617, the nonradioactive precursor molecule, consists of the PSMA-binding ligand glutamate-urea-lysine and a DOTA-chelator, which are connected by a linker moiety. The drug product ^{177}Lu-PSMA-617 exhibits high PSMA binding affinity and internalization, prolonged tumor retention, and rapid kidney clearance (Benešová et al 2015).

^{177}Lu, the radioactive therapeutic agent being delivered by PSMA-617, has physical properties that make it an ideal radionuclide for the treatment of prostate cancer. ^{177}Lu is a medium-energy β-emitter (497 keV) with a maximal tissue penetration of approximately 2 mm (mean=0.67 mm) and a physical half-life of 6.647 days (Dash et al 2015, Deepa et al 2011). The shorter β-range of ^{177}Lu provides better irradiation of small tumors, in contrast to the longer β-range of ^{90}Y (Emmett et al 2017). The shorter path length also acts to direct the energy within the tumor rather than into the surrounding normal tissues, while the path length is still sufficient to create bystander and crossfire effects within the tumor lesion. The physical half-life combines well with the intratumoral retention of ^{177}Lu-PSMA-617 to reduce the necessary dosing frequency. The biological half-life of PSMA-617 in the tumor lesion has been reported to be between 60-160 hours, which is comparable to the 161-hour physical half-life of ^{177}Lu (Kratochwil et al 2019). The relationship between intratumoral retention and radioactive decay reflects an important attribute of ^{177}Lu-PSMA-617, as a mismatched combination would potentially reduce the effectiveness of each administered dose.

The physical properties and the benefit of PSMA-targeting allow for the delivery of effective activities of ^{177}Lu to PC cells. With regard to therapeutic use, the high PSMA binding affinity and internalization, prolonged tumor uptake, rapid plasma clearance via urinary excretion, and high tumor-to-background ratio contribute to evident clinical potential for ^{177}Lu-PSMA-617 (Benešová et al 2015).

PSMA-11 is another high-affinity PSMA ligand, which when radiolabeled with gallium-68 (^{68}Ga) can be used to identify PSMA expression and determine the local extent of disease by PET imaging. ^{68}Ga-PSMA-11 PET/CT imaging is used as a component of eligibility criteria.

In addition, ^{177}Lu-PSMA-617 has been used experimentally in the clinic since 2013 for the treatment of patients with mCRPC (Ahmadzadehfar et al 2015). As a result, published data on efficacy (and safety) of ^{177}Lu-PSMA-617 in patients with mCRPC is available from many centers. Efficacy results from key publications including prospective and retrospective studies are provided in Table 1-1 and Table 1-2, respectively.

The retrospective studies contain data analyses of ^{177}Lu-PSMA-617 RLT in patients with mCRPC confirming the positive effect on PSA level and showing a ≥50% PSA decline in up to 57% of the patients (Demirci et al 2017, Rahbar et al 2017, Rahbar et al 2018, Rathke et al 2018, van Kalmthout et al 2019). While the efficacy results from the retrospective studies are encouraging, the data from the prospective studies are important as these studies involved well-defined inclusion/exclusion criteria, careful patient selection via ^{68}Ga-PSMA-11 and FDG PET/CT imaging, and prespecified data collection and analysis (Emmett et al 2019, Violet et al 2020, Hofman et al 2021).

Given the promising published data available at the time of PSMA-617-01 study inception, it was hypothesized that treatment with ^{177}Lu-PSMA-617 plus best supportive care/best standard of care (BSC/BSoC) would provide therapeutic benefit for patients with mCRPC who had received at least 1 prior NAAD therapy and no more than 2 prior taxane-based chemotherapeutic regimens, and whose disease expressed PSMA as determined by a ^{68}Ga-PSMA-11 PET/CT scan.

Table 1-1 Efficacy results from prospective studies

Study Number of patients	Median OS (months) (95% CI)	≥50% PSA Response (%)	Median PFS (months) (95% CI)	ORR (CR+PR) (RECIST) (%)
Hofman et al (2021)	-	66% vs. 37%[a]	5.1 vs. 5.1[a]	49 vs. 24[a]
N=200	-	P<0.0001	-	-
Violet et al (2020)	13.3	64[e]	6.9[e]	56[c]
N=50	(10.5, 18.7)	(95% CI: 50-77)	(6.0, 8.7)	
Emmett et al (2019)	11.5[b]	36[f]	NE	40[d]
N=14				

NE = not evaluated.
a: ^{177}Lu-PSMA-617 vs. cabazitaxel
b: Mean
c: Based on 27 patients with measurable soft tissue disease (RECIST v1.1).
d: Based on 10 patients with measurable soft tissue disease (RECIST v1.1).
e: Defined by time to PSA progression as per PCWG2 criteria.
f: Per PCWG2 criteria.

Table 1-2 Efficacy results from retrospective studies

Study Number of patients	Median OS (months) (95% CI)	≥50% PSA Response (%)	Median PFS (months) (95% CI)
Rahbar et al (2018) N=104	12.9 (11.7, 14.2)	33[a]	NE
Rahbar et al (2017) N=145	NE	45[c]	NE
Rathke et al (2018) N=10/group (4-, 6-, 7.4-, and 9.3-GBq groups)	NE	40/30/50/30[d,f]	NE
van Kalmthout et al (2019) N=30	11.3	57[a]	NE
Demirci et al (2017) N=43	15.9 (13.1, 18.7)	53[e,f]	6.5 (4-8.9)

NE = not evaluated.
a: Per PCWG3 criteria.
b: Per PCWG3 criteria; after first cycle, based on serial PSA levels from 99 patients.
c: Per PCWG3 criteria; overall, based on serial PSA levels from 99 patients.
d: >50% PSA response in the 4-, 6-, 7.4-, and 9.3-GBq groups, respectively.
e: >50% PSA response.

1.1.4 Selection and justification of efficacy endpoints

For detailed information regarding the Phase III registration Study PSMA-617-01 (VISION), see Section 1.2.

Primary endpoints

The primary objective of Study PSMA-617-01 utilized two alternate primary endpoints of radiographic PFS (rPFS) as assessed by blinded independent central review (BICR) and OS in patients with progressive PSMA-positive mCRPC who received ^{177}Lu-PSMA-617 in addition to BSC/BSoC compared with patients who received BSC/BSoC only (2:1 randomization ratio). This randomization ratio was used to provide more patients with a potential beneficial treatment over the existing therapies.

Originally, the primary objective of this study was an arm-to-arm comparison of OS. In agreement with the FDA and shortly after study enrollment was initiated, the protocol was amended to implement alternate primary endpoints, meaning rPFS and OS designated as alternate primary endpoints. Because rPFS was a key secondary endpoint at the start of the study, data collection to support rPFS analysis as an alternate primary endpoint was already in place for all randomized patients. Based on this change, 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; it was not required to statistically meet both rPFS and OS to be declared a positive study.

For information regarding health authority agreements/requests for the alternate primary endpoints, see Section 1.1.5.

Alternate primary endpoints are considered multiple primary endpoints, as discussed in the ICH E9 Guideline "Statistical Principles for Clinical Trials" (EMA 1998), the FDA Guidance "Multiple Endpoints in Clinical Trials" (FDA 2017), as well as in the EMA "Guideline on multiplicity issues in clinical trials" (EMA 2017). When using alternate primary endpoints, although demonstration of a treatment effect on at least one of the 2 primary endpoints is sufficient, results for all of the prespecified primary endpoints (rPFS and OS in this case), both positive and negative, are considered in the overall assessment of risks and benefits. Thus, the change to implement alternate primary endpoints does not negatively impact the OS endpoint, and full integrity was maintained for this endpoint and for the study.

As of February 2019, 44 of 61 patients randomized to the control arm had withdrawn consent prior to the first post-baseline radiological assessment (Week 8). Due to the high rate of withdrawal of consent from the control arm early in the study, the Sponsor initiated a set of corrective actions in study conduct at the sites to mitigate this risk. As a result of the corrective actions, withdrawal of consent from treatment with BSC/BSoC subsequently decreased from 28.6% to 11.2% (see Section 3.1.1). To minimize the potential for bias in the analysis of rPFS due to the differential withdrawal of consent rate between the two treatment arms, only patients randomized after full implementation of enhanced study site education measures (05-Mar-2019) were to be included in the confirmatory/primary analysis of rPFS, the allocation of alpha between rPFS and OS was adjusted to allow for analysis of fewer rPFS events while still maintaining the original power for both rPFS and OS, and the total number of patients randomized in the study was increased to ensure sufficient events to maintain power (Table 1-3). The OS analysis still included all randomized patients from the start of the study (FDA Type A 2019; EMA Scientific Advice 2019). These changes maintained all of the assumptions of clinical benefit on which the study was originally powered.

Key secondary and additional secondary endpoints

Key secondary endpoints included an arm-to-arm comparison of ORR and DCR as measured by RECIST v1.1, as well as time to first symptomatic skeletal event (SSE). These endpoints were controlled for multiplicity using the Hochberg closed test procedure using the alpha level from the OS results.

Additional secondary endpoints included PFS (radiographic, clinical, or PSA progression), biochemical response as measured by change over time in PSA, PSA doubling time, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), PSA response and duration of PSA response, and HRQoL.

The endpoints of OS, rPFS, time to first SSE, HRQoL, PFS (radiographic, clinical, or PSA), biochemical response as measured by PSA, and biomarkers ALP and LDH are recommended by PCWG3 (Scher et al 2016). In addition, PFS, OS, ORR, and DCR are all routinely used, accepted and well-recognized endpoints for oncology trials (FDA 2007; EMA 2016). Patients with CRPC with metastatic bone disease are at risk of significant morbidity (including skeletal-related events) with consequential detriment to quality of life and increased mortality. The EQ-5D-5L, generic QoL, required by Health Technology Assessment Agencies, and FACT-P and BPI-SF (both validated in PC) are routinely used patient-reported outcomes (PROs) in clinical studies of patients with mCRPC.

For additional details regarding the secondary endpoints, see Section 1.2.2.

The primary and secondary endpoints were discussed with the health authorities (see Section 1.1.5).

As an addition to Study PSMA-617-01 and based on advice from the EMA during the Scientific Advice Working Party meeting held on 10-April-2019 (EMA Scientific Advice 2019), a sub-study was conducted at sites in Germany in a non-randomized cohort of 30 patients. This sub-study collected dosimetry, PK, urinary metabolites, and ECG data; besides these additional assessments, patients in the sub-study were screened for eligibility, treated, and followed up similarly to patients in the main study. For further details, see [Study PSMA-617-01-Appendix 16.1.1-Protocol-Version 4.1]. For results, see Section 4.2 and [SCP-Section 2.3.1].

1.1.5 Health authority agreements/requests related to efficacy

Health authority (HA) agreement was obtained regarding the proposed study design including primary and secondary endpoints, study population, stratification factors, and statistical analysis plan, as described below (FDA EOP2 Type B 2018, EMA Scientific Advice 2019, BfArM Initial Scientific Advice 2018, BfArM Follow-up Scientific Advice 2020).

Study PSMA-617-01 was discussed with the FDA at the End-of-Phase II meeting held on 30-Jan-2018 (FDA EOP2 Type B 2018). The Study PSMA-617-01 design was revised following the meeting in accordance with FDA input, and randomization began in the US on 04-Jun-2018. A second meeting with the FDA occurred on 16-Aug-2018, where agreement was reached to change rPFS from a key secondary endpoint to an alternate primary endpoint with OS for Study PSMA-617-01 and to assess rPFS via BICR in addition to investigator review for patient management purposes (FDA Type B 2018). On 02-May-2019, a further meeting with the FDA occurred to discuss the high numbers of patients withdrawing consent from the control arm of

the Phase III Study PSMA-617-01. During this discussion, the FDA considered the proposed operational measures and plans to increase enrollment, and to adjust the allocation of alpha between rPFS and OS to allow for analysis of fewer rPFS events to be acceptable (FDA Type A 2019). As a result, the primary analysis of rPFS was planned to be conducted when 364 rPFS events had been observed in patients randomized on or after 05-Mar-2019 with an interim analysis of OS at the time of the rPFS analysis using all patients randomized since study commencement.

In the EU, the design of Study PSMA-617-01 was discussed with BfArM on 13-Sep-2018 and 04-Feb-2020, and with the EMA Scientific Advice Working Party (SAWP) on 10-Apr-2019 (EMA Scientific Advice 2019).

Per discussion with BfArM on 13-Sep-2018, the possibility of introducing rPFS as an alternate primary endpoint was addressed and BfArM acknowledged the possibility of an earlier readout of the study based on a change to alternate primary endpoints of rPFS and OS. It was also agreed that the OS endpoint should be maintained and that the study Sponsor should seek centralized scientific advice (BfArM Initial Scientific Advice 2018).

As a result, the ^{177}Lu-PSMA-617 development plan and PSMA-617-01 study design were discussed with the EMA SAWP on 10-Apr-2019. The SAWP/CHMP emphasized that OS would be the endpoint for regulatory decision-making in the EU, and acknowledged efforts to continue the follow-up for OS. The implementation of corrective actions to reduce the withdrawal of consent in the control arm was considered acceptable and the Sponsor was discouraged from changing the statistical design.

BfArM was further consulted on 04-Feb-2020 on the changes made to the Study PSMA-617-01 protocol and statistical analysis plan. BfArM acknowledged that the potential loss of integrity due to the change to alternate primary endpoints of rPFS and OS seemed negligible (BfArM Follow-up Scientific Advice 2020) and recommended supportive analyses be performed that would mimic as closely as possible those planned in the original protocol.

The FDA, BfArM, and SAWP/CHMP feedback was considered in the prespecified analyses for Study PSMA-617-01 [Study PSMA-617-01-Appendix 16.1.9] and additional analyses presented in this SCE, including an analysis of OS based on the first 750 patients randomized in the FAS in order to mimic the planned OS analysis in the original protocol as closely as possible (for results, see Section 3.2.1.2.1).

1.2 Overview of efficacy studies and data

Randomized clinical trial data

Efficacy claims in this SCE are based on the primary analysis results from the Phase III Study PSMA-617-01 (data cut-off date 27-Jan-2021) [Tabular Listing of All Clinical Studies]. For details regarding Study PSMA-617-01, see Section 1.2.2.

Study PSMA-617-02 (RESIST-PC) is a Phase II study of PSMA-directed endoradiotherapy of mCRPC. This study is not included in this SCE since it does not provide any additional efficacy data to support treatment with ^{177}Lu-PSMA-617 plus BSC/BSoC. This study was ongoing when the Sponsor acquired global development rights to PSMA-617 and to the PSMA-617 IND

application, and was superseded by Study PSMA-617-01. Consequently, Study PSMA-617-02 was terminated early (enrollment ended as of 22-Jun-2018). All patients who were enrolled in Study PSMA-617-02 continued to follow the protocol visit schedule through to completion or discharge, whichever occurred first, and LPLV occurred on 15-Jan-2020.

1.2.1 Study PSMA-617-01

^{177}Lu-PSMA-617 has been developed as a PSMA-targeted RLT for patients with mCRPC.

Registration Study PSMA-617-01 is a randomized, Phase III, international, prospective, open-label, multicenter study to evaluate the efficacy and safety of ^{177}Lu-PSMA-617 plus BSC/BSoC in patients with progressive PSMA-positive mCRPC. Per the inclusion criteria, patients had received at least one NAAD (i.e. abiraterone acetate or enzalutamide) and at least one but no more than 2 previous taxane-based chemotherapy regimens. Patients were randomized in a 2:1 ratio to receive either 7.4 GBq (±10%) ^{177}Lu-PSMA-617 once every 6 weeks (±1 week) for up to 6 cycles (a maximum of 6 cycles) plus BSC/BSoC or BSC/BSoC only. For details regarding the rationale for dose selection, see Section 4.1.

At screening, patients were assessed for eligibility and underwent a ^{68}Ga-PSMA-11 PET/CT scan to evaluate PSMA positivity defined by the central read rules [Study PSMA-617-01-Section 9.5.1]. Only patients with at least one PSMA-positive lesion identified on ^{68}Ga-PSMA-11 PET/CT scan and no negative lesions (as assessed by an independent central reader) were to be enrolled in the study, provided all other inclusion/exclusion criteria were met. An independent central review was utilized to ensure consistency in patient selection as described by the central read rules [Study PSMA-617-01-Appendix 16.1.1-Protocol-Imaging Charter].

Enrolled patients were randomized in a 2:1 ratio to receive either ^{177}Lu-PSMA-617 plus BSC/BSoC (investigational arm) or BSC/BSoC only (BSC/BSoC-only arm) using a permuted block scheme. Randomization was stratified by 4 factors: LDH (≤260 IU/L vs. >260 IU/L); presence of liver metastases (yes vs. no); ECOG performance status score (0 or 1 vs. 2); and inclusion of NAAD in BSC/BSoC at time of randomization (yes vs. no).

The efficacy population (FAS) comprised 831 randomized patients in Study PSMA-617-01 with mCRPC: 551 patients were randomized to ^{177}Lu-PSMA-617 (i.v. 7.4 GBq (±10%) once every 6 weeks (±1 week) for a maximum of 6 cycles) plus BSC/BSoC (investigational arm) and 280 patients were randomized to BSC/BSoC only (control arm). As of the data cut-off date of 27-Jan-2021, the median study follow-up was 20.9 months. Results from this primary analysis provide key efficacy data to support the proposed indication.

The ongoing COVID-19 pandemic had minimal impact on this study. Enrollment was completed on 23-Oct-2019 (prior to the beginning of the pandemic in Europe and North America), and the last dose of ^{177}Lu-PSMA-617 was administered on 26-Jun-2020. Due to the COVID-19 pandemic, changes to the conduct of this study were implemented to ensure the safety and well-being of study participants, and to enable trial oversight and compliance with the study protocol. Six patients discontinued ^{177}Lu-PSMA-617 due to the pandemic, and they all had already received at least 4 cycles of study drug. Missed assessments or procedures due to the pandemic were estimated to represent less than 0.25% of the data to be collected. For OS assessments, 3 deaths were related to COVID-19 infections. Based on results of sensitivity analyses to assess the impact of the COVID-19 pandemic on the evaluation of the alternate

primary endpoints, the pandemic had no impact on the alternate primary efficacy endpoint evaluations [Study PSMA-617-01-Section 11.2.3], (Section 3.2.1.3.1 and Section 3.2.1.3.2).

1.2.2 Summary of Registration Study PSMA-617-01

Study PSMA-617-01 is a randomized (2:1), Phase III, prospective, open-label, multicenter study. An overview of the registration study is presented in Table 1-3 and [Study PSMA-617-01-Figure 9-1]. Patients in Study PSMA-617-01 were representative of the population of patients with progressive PSMA-positive mCRPC. Progressive mCRPC was documented based on one or more of the following criteria as defined per PCWG3: serum PSA progression, soft-tissue progression, or progression of bone disease. Patients were required to have at least one PSMA-positive lesion identified on ^{68}Ga-PSMA-11 PET/CT scan as determined by the central read rules (see Section 1.2.1). In addition, patients were required to have received at least one NAAD (such as enzalutamide and/or abiraterone acetate), and to have received previous treatment with at least 1 but no more than 2 previous taxane-based chemotherapy regimens (with a regimen defined as a minimum exposure of 2 cycles of a taxane). If a patient had received only 1 taxane-based chemotherapy regimen, the patient was eligible if the patient`s physician deemed him unsuitable to receive a second taxane regimen. Patients were also required to have an ECOG performance status of 0 to 2, and ≥ 1 metastatic lesion that was present on baseline CT, MRI, or bone scan imaging.

Shortly after commencement of the trial, a high rate of withdrawal of consent in the BSC/BSoC only arm became evident with the majority of these dropouts withdrawing consent to follow-up. This meant that rPFS data could not be collected for these patients, which consequently could result in bias in the analysis of rPFS. Enhanced study site education measures to curtail this phenomenon were implemented and made effective on 05-Mar-2019 (see Section 1.1.4). As part of the plan to address the high rate of early withdrawal of consent in the BSC/BSoC only arm, the primary analysis of rPFS was altered to focus on patients prospectively randomized on or after 05-Mar-2019; therefore, rPFS was analyzed on an intent- to-treat (ITT) basis in these patients. The OS analysis was also planned on an ITT basis and included all randomized patients (i.e. including those randomized before 05-Mar-2019).

The analysis sets are defined in Section 1.2.3.1.

Table 1-3 Summary of registration Study PSMA-617-01 including statistical methodology for efficacy analyses included in this SCE

Study objective and population	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
No of patients	Total: 831 (2:1 randomization: 551 in ^{177}Lu-PSMA-617 plus BSC/BSoC arm, 280 in BSC/BSoC only arm)
Stratification	Randomization was stratified by the following 4 factors: • LDH (≤ 260 IU/L vs. > 260 IU/L) • Presence of liver metastases (yes vs. no) • ECOG PS score (0 or 1 vs. 2) • Inclusion of NAAD in BSC/BSoC at time of randomization (yes vs. no)

Regimen and treatment duration	^{177}Lu-PSMA-617 was administered i.v. at a dose of 7.4 GBq (±10%) once every 6 weeks (±1 week) for a maximum of 6 cycles. In addition, BSC/BSoC for patients was administered per physician orders and protocol at the institution, and whenever feasible, BSC/BSoC was optimized for all patients prior to randomization. Patients were treated with BSC/BSoC as long as the investigator felt they were clinically benefiting (regardless of radiographic progressive disease based on Investigator's assessment per PCWG3 criteria) or until they required a treatment regimen not allowed on this study.
Tumor assessment	Images were evaluated in accordance with both RECIST v1.1 and PCWG3 criteria. Periodic radiographic imaging included both CT with contrast/MRI imaging and bone scans with technetium-99m (^{99m}Tc) labeled diphosphonates. Radiographic imaging for tumor assessment was done every 8 weeks (± 4 days) after Cycle 1 Day 1 (C1D1), for the first 24 weeks (independent of dose delays), and then every 12 weeks (± 4 days). Both BICR of imaging (for efficacy evaluation) and local Investigator assessment (for patient management) were conducted. For details on the efficacy read process by the Sponsor's central reader, please refer to [Study PSMA-617-01-Appendix 16.1.1-Protocol-Imaging Charter].
Main efficacy endpoints	**Primary:** To compare the 2 alternate endpoints of rPFS and OS in patients with progressive PSMA-positive mCRPC who received ^{177}Lu-PSMA-617 plus BSC/BSoC versus patients treated by BSC/BSoC only. **Key secondary:** arm-to-arm comparison of the following: • Overall Response Rate (ORR; defined as the proportion of patients with a BOR of CR or PR) as measured by RECIST v1.1; duration of response (DoR; defined as duration between date of first documented BOR of CR or PR and date of first documented radiographic progression or death due to any cause) • Disease control rate (DCR; defined as the proportion of patients with BOR of CR, PR, or SD/Non-CR/Non-PD > 6 weeks) as measured by RECIST v1.1 • Time to a first symptomatic skeletal event (SSE; defined as time in months from date of randomization to date of first SSE or death from any cause) For additional details see [Study PSMA-617-01-Section 9.7.6]. **Additional secondary:** • PFS (radiographic, clinical, or PSA progression or death due to any cause) • Biochemical response as measured by change over time in PSA, PSA doubling time, alkaline phosphatase (ALP) and lactate dehydrogenase (LDH), PSA response, and duration of PSA response • HRQoL 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])

Statistical methodology	**Primary:** The primary efficacy analysis was comparison of the 2 alternate endpoints, rPFS and OS, in patients with progressive PSMA-positive mCRPC who received ^{177}Lu-PSMA-617 + BSC/BSoC versus patients treated by BSC/BSoC only. The primary analysis of rPFS was planned to be conducted when 364 rPFS events had been observed in patients prospectively randomized on or after 05-Mar-2019 (PFS-FAS) with an interim analysis of OS at the time of the rPFS primary analysis using all patients randomized (FAS) since study commencement (see Section 1.1.4). A final analysis of OS, using all patients randomized, was planned to take place when 508 deaths had been observed. In order to be declared positive, the study was required to reach statistical significance on either rPFS or OS at the respective allocated alpha level. It was not required to statistically meet both rPFS and OS to be declared a positive study. As stated in the protocol [Study PSMA-617-01-Appendix 16.1.1-Protocol-Section 8.3], the alpha level applicable to OS in the final analysis would depend upon the earlier rPFS and interim OS results. The interim OS analysis was not completed as the targeted number of OS events were observed before the targeted number of rPFS events. Therefore, the alpha level applicable to OS in the final analysis depends upon the final rPFS results as follows: -if $p < 0.004$ 1-sided is achieved for rPFS, then the alpha level for the final analysis of OS is raised to 0.025 1-sided. -if $p < 0.004$ 1-sided is not achieved for rPFS, then the alpha level for the final analysis of OS is 0.021 1-sided Also see [Study PSMA-617-01-Appendix 16.1.9] and Table 8-1. rPFS was defined as the time (in months) from the date of randomization to the date of radiographic disease progression based on the BICR assessment per PCWG3 criteria or death due to any cause. OS was defined as the time (in months) from the date of randomization to the date of death due to any cause. The primary analyses of rPFS and OS compared the treatment arms using stratified log-rank one-sided tests (using the appropriate pre-specified alpha level) stratifying for the randomization stratification factors. Kaplan-Meier (KM) curves, including median rPFS and OS times, hazard ratios and confidence intervals (CIs) estimated from the Cox regression model were provided. **Sensitivity and supportive analyses for rPFS**: Sensitivity and supportive analyses were performed to assess the overall robustness of the rPFS results. For details, see [Study PSMA-617-01-Appendix 16.1.9-Section 8.2.1]. Sensitivity analyses (based on the PFS-FAS) included (1) additional categories of rPFS events, including events regardless of intervening missed assessments; (2) deaths occurring after start of a new anti-cancer therapy were censored at the start date of the new therapy; (3) rPFS was defined from the date of first dose of randomized treatment; (4) rPFS based on Investigator assessment. In addition, sensitivity analyses to assess the impact of COVID-19 included (5) analysis per primary rPFS analysis but censoring COVID-19 related deaths at the last adequate assessment prior to death; and (6) analysis per sensitivity analysis 1 described above but censoring COVID-19 related deaths at the date of death.

	A supplementary analysis of rPFS was also performed using the FAS population. In addition, a comparison of rPFS event type/censor between local radiology review and BICR radiology was performed based on the PFS-FAS. rPFS was also analyzed in the FAS safety analysis set in the ^{177}Lu-PSMA-617 + BSC/BSoC arm by number of ^{177}Lu-PSMA-617 cycles. **Supplementary and sensitivity analyses for OS**: Supplementary and sensitivity analyses were performed to assess the overall robustness of the OS results. For details, see [Study PSMA-617-01-Appendix 16.1.9-Section 8.2.1]. An OS analysis was performed based on the first 750 patients randomized in the FAS (see Section 1.1.5). Supplementary analyses of OS were also performed using the PFS-FAS population. In addition, a sensitivity analysis to assess the impact of COVID-19 included analysis per primary OS analysis but censoring COVID-19 related deaths at the date of death. Lastly, OS was analyzed in the FAS safety analysis set in the ^{177}Lu-PSMA-617 plus BSC/BSoC arm by number of ^{177}Lu-PSMA-617 cycles. **Sensitivity analyses for rPFS and OS:** Additional analyses were also performed to assess sensitivity of rPFS and OS to censoring due to patient drop-out, in which the investigational arm (^{177}Lu-PSMA-617+BSC/BSoC) was compared to the randomized control arm (BSC/BSoC only). In addition, a summary of OS and rPFS events and reasons for censoring as well as a summary of cancer-related (non-radiation) therapy and cancer-related radiotherapy since discontinuation of randomized treatment was provided for patients who withdrew consent to BSC/BSoC and were randomized (1) prior to 5 March 2019, (2) on or after 5 March 2019 (i.e. PFS-Full analysis set) and (3) in the Full analysis set. **Subgroup analysis for rPFS and/or OS:** rPFS and OS were summarized for subgroups as described in [Study PSMA-617-01-Section 9.7.5.4]. Additional subgroup analyses by region, PSADT at baseline, baseline PSA, number of prior NAADs, number of prior immunotherapies, number of prior taxane-based regimens, number of prior non-taxane cytotoxic chemotherapeutic therapies, prior use of bone-sparing agents, prior use of ^{223}Ra dichloride, prior use of PARP inhibitors, concurrent use of NAAD as part of BSC/BSoC treatment, concurrent use of radiation therapy as part of BSC/BSoC treatment, and concurrent use of bone sparing agents as part of BSC/BSoC treatment, were also provided (Section 3.3). **Key secondary endpoints:** For these analyses based on the PFS-FAS, the alpha level applicable to the analysis of the key secondary endpoints ORR, DCR, and time to first SSE depended on the statistically significant results of the final rPFS or on the statistically significant results of OS at either the interim or final analysis based on the Hochberg closed test procedure ([Study PSMA-617-01-Section 9.7.6], Table 8-1). ORR and DCR: ORR and DCR were analyzed using logistic regression with a single covariate for randomized treatment arm and stratification for the randomization stratification factors. ORR was based on RECIST v1.1 response for patients with RECIST evaluable disease at baseline per BICR. The primary analysis of ORR and DCR was on the Response Evaluable Analysis Set. An additional analysis of ORR and DCR was also conducted in patients with measurable disease at baseline (at least one target lesion per BICR). DoR: DoR was also analyzed in the Response Evaluable Analysis Set using mixture distribution methodology (Ellis et al 2008).

	Time to a first SSE: Time to first SSE was summarized and analyzed in the same manner as described for rPFS using the PFS-FAS, except using 2-sided p-values from the stratified log-rank test as the primary comparison. **Secondary:** Analysis of other secondary endpoints was descriptive and included summary statistics (e.g. means, standard deviations, 95% CIs, if applicable). Kaplan-Meier (KM) curves, including median time to event, hazard ratios and 95% CIs estimated from the Cox regression model were presented for time-to-event variables (e.g. PFS etc), if appropriate. A nominal alpha level of 5% was used (there was no alpha level control applied) [Study PSMA-617-01-Table 9-1], Table 8-1. **Additional secondary endpoints:** PFS (radiographic, clinical, or PSA progression): PFS was defined as the time (in months) from the date of randomization to the date of first evidence of radiographic (per BICR), clinical (per Investigator assessment), or PSA progression (as defined in [Study PSMA-617-01-Section 9.7.7.1.1]) or death due to any cause, whichever occurred first. PFS was also analyzed in the FAS analysis set in the ^{177}Lu-PSMA-617 plus BSC/BSoC arm by number of ^{177}Lu-PSMA-617 cycles. Biochemical response: Treatment arm differences of percentage change from baseline in PSA, PSA doubling time, ALP, and LDH across all time points were analyzed using mixed effects general linear models for repeated measures, under the assumption of Missing at Random (MAR). For PSA response, analyses were the same as those for the key secondary endpoint ORR. Duration of PSA response was analyzed using a mixture distribution analysis, as described for DoR. HRQoL: PROs were assessed using the questionnaires FACT-P, BPI-SF, and EQ-5D-5L. Analyses of these additional secondary endpoints were performed based on the PFS-FAS, and all results were reported by randomized treatment arm. Also, FACT-P, FACT-G, BPI-SF pain intensity, and BPI-SF pain interference were analyzed in the FAS safety analysis set in the ^{177}Lu-PSMA-617 plus BSC/BSoC arm by number of ^{177}Lu-PSMA-617 cycles. For more details on all primary and secondary endpoint analyses, please refer to [Study PSMA-617-01-Appendix 16.1.9-Section 8.2].
Data cut-off date	27-Jan-2021
Source: [Synopses of Individual Studies], [Tabular Listing of All Clinical Studies]	

1.2.2.1 Analysis Sets

The following analysis sets were utilized in this study:

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 was 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 was 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 BICR 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.

1.2.3 Efficacy assessments

For further details, see [Study PSMA-617-01-Appendix 16.1.1-Protocol-Section 6.2].

1.2.3.1 Radiographic imaging for tumor assessments

Images were evaluated in accordance with both RECIST v1.1 and PCWG3 criteria. Periodic radiographic imaging included both:

- CT with contrast/MRI imaging
  - 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 RECIST v1.1 with the caveats outlined in the PCWG3 recommendations, see [Study PSMA-617-01-Appendix 16.1.1-Protocol-Appendix 6 and Appendix 7].
- 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 assessments was done every 8 weeks (± 4 days) after C1D1, for the first 24 weeks (independent of dose delays), and then every 12 weeks (± 4 days).

An imaging contract research organization was responsible for the collection, quality control, archiving, and BICR of imaging for the study. The results of the central evaluations were used for the analysis of rPFS and tumor response per RECIST v1.1 criteria. The local Investigator's assessment was used for patient management, and was also utilized in sensitivity/concordance analyses. For details on the efficacy read process by the Sponsor's central reader, please refer to [Study PSMA-617-01-Appendix 16.1.1-Protocol-Imaging Charter].

1.2.3.2 Overall survival

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

1.2.3.3 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.

1.2.3.4 ECOG performance status

The ECOG performance status score was used to assess patients' ability to perform daily living tasks and their range of basic physical ability.

1.2.3.5 Patient-reported outcomes

The FACT-P questionnaire was also administered to specifically assess the HRQoL of patients with PC. 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 BPI-SF was used to assess the severity of pain and the impact of pain on daily functions.

The EQ-5D-5L questionnaire was administered to assess a patient's self-reported health status. EQ-5D was developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. This instrument generates a preference-based health-state utility score (EQ-5D utility index), consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and an overall health-state score based on a visual analog scale (EQ-5D VAS).

1.2.3.6 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 by 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

1.2.3.7 Biochemical responses

PSA, LDH, and ALP levels were measured by the local laboratory. Changes in PSA levels were used to assess PSA responses per PCWG3 criteria; see [Study PSMA-617-01-Appendix 16.1.1-Protocol-Appendix 7].

2 Summary of results of Study PSMA-617-01

This summary presents data from the pivotal Phase III Study PSMA-617-01. Details of the study design and results are presented in Section 1.2.2 and Section 3, respectively. For additional details regarding the study, see [Study PSMA-617-01-Section 2].

Overall, the use of ^{177}Lu-PSMA-617+BSC/BSoC when compared to BSC/BSoC only, in patients with PSMA-positive mCRPC previously treated with taxanes and NAADs, consistently resulted in improvements in key measures of efficacy, including prolongation/risk reduction in rPFS and OS, improvements in ORR, DCR, and delay in time to first SSE, as well as improvements in PFS and PSA, ALP, and LDH levels. In addition, results in favor of treatment with ^{177}Lu-PSMA-617+BSC/BSoC relative to BSC/BSoC only were also observed for PROs associated with stabilization/less deterioration and improved quality of life.

Study population

The planned study population consisted of adult male patients with progressive mCRPC who had received at least 1 prior NAAD therapy and 1-2 prior taxane-based chemotherapy regimens, and who met the eligibility criteria, including PSMA positivity as determined by a ^{68}Ga-PSMA-11 PET/CT scan.

A total of 831 patients were randomized in a 2:1 ratio to receive either ^{177}Lu-PSMA-617 plus BSC/BSoC or BSC/BSoC only. Randomization was stratified by the following 4 factors:

- LDH (≤ 260 IU/L vs. > 260 IU/L)
- Presence of liver metastases (yes vs. no)
- ECOG performance status score (0 or 1 vs. 2)
- Inclusion of NAAD in BSC/BSoC at time of randomization (yes vs. no)

Patients randomized to the investigational arm began ^{177}Lu-PSMA-617 administration within 28 days after randomization (C1D1). These patients received 7.4 GBq (±10%) ^{177}Lu-PSMA-617 once every 6 weeks (±1 week) for a maximum of 6 cycles while receiving BSC/BSoC. After Cycle 4 and prior to Cycle 5 treatment, the Investigator determined whether the patient met the criteria to receive 2 additional cycles of ^{177}Lu-PSMA-617.

BSC/BSoC for each patient in either arm was administered as per physician's orders and protocol at the institution prior to randomization, and continued until the patient came off the randomized treatment period and entered the long-term follow-up. Whenever feasible, BSC/BSoC for each patient was optimized prior to randomization; however, it could be modified over time as needed [Study PSMA-617-01-Section 16.1.1-Protocol-Section 5.2].

Key efficacy results

A high-level summary of the efficacy results reported in this SCE is provided in Table 2-1. For statistical methodology, see Table 1-3, and for additional details, see Section 3.2.

Table 2-1 Results of key efficacy analyses reported in this SCE

Alternate primary endpoints	Study PSMA-617-01 met its primary objectives. Statistically significant improvements were demonstrated for both alternate primary efficacy endpoints in favor of treatment with ^{177}Lu-PSMA-617+BSC/BSoC relative to BSC/BSoC only: • rPFS: estimated 60% reduction in risk of radiographic disease progression or death (HR = 0.40; 99.2% CI: 0.29, 0.57; stratified log-rank test p < 0.001, one-sided) • Median rPFS was prolonged by 5.3 months, from 3.4 months (99.2% CI: 2.4, 4.0) in the BSC/BSoC only arm to 8.7 months (99.2% CI: 7.9, 10.8) in the ^{177}Lu-PSMA-617+BSC/BSoC arm • Results of sensitivity analyses for rPFS were consistent with and supportive of the primary analysis results, with HRs ranging from 0.36 to 0.53; • An analysis of rPFS based on the FAS was also conducted; results were similar to those for the primary analysis based on the PFS-FAS (HR=0.43; 99.2% CI: 0.32, 0.58) • OS: estimated 38% risk reduction of death (HR = 0.62; 95% CI: 0.52, 0.74; stratified log-rank test p < 0.001, one-sided) • Median OS was prolonged by 4.0 months, from 11.3 months (95% CI: 9.8, 13.5) for BSC/BSoC only to 15.3 months (95% CI: 14.2, 16.9) for ^{177}Lu-PSMA-617+BSC/BSoC • Results of a supplementary OS analysis based on the first 750 patients randomized in the FAS were also consistent with the primary analysis results based on the FAS, with an HR of 0.63 (95% CI: 0.52, 0.77) • Results of the supplementary OS analysis conducted on the PFS-FAS were consistent with and supportive of the primary analysis results, with an HR of 0.63 (95% CI: 0.51, 0.79) • Results of additional analyses to assess sensitivity of rPFS and OS to censoring due to patient drop-out were consistent with and supportive of the primary analysis results. • Homogeneity and consistency of the results for rPFS and OS were evident across subgroups; the only exception was subgroups with too few patients to be interpretable

Key secondary endpoints	Statistically significant improvements in favor of treatment with ^{177}Lu-PSMA-617+BSC/BSoC relative to BSC/BSoC only were also demonstrated for all 3 key secondary endpoints (controlled for multiplicity using the Hochberg closed test procedure using the alpha level from the successful OS results):
	• ORR: 29.8% vs. 1.7% (OR=24.99; 95% CI: 6.05, 103.24; stratified Wald's Chi-square test p < 0.001, two-sided); median DOR in responders was 9.8 months (95% CI: 9.1, 11.7) in the ^{177}Lu-PSMA-617+BSC/BSoC arm (median DOR in the BSC/BSoC only arm was not reliable since only 1 of the 2 patients who responded had RECIST radiographic progression or death).
	• DCR: 89.0% vs. 66.7% (OR=5.79; 95% CI: 3.18, 10.55; stratified Wald's Chi-square test p < 0.001, two-sided)
	  • Results of additional analyses of ORR and DCR in patients with measurable disease at baseline (at least one target lesion per BICR) also favored the ^{177}Lu-PSMA-617+BSC/BSoC arm:
	  • ORR: 51.1% vs. 3.1% (OR=37.61; 95% CI: 8.84, 159.99; stratified Wald's Chi-square test p < 0.001, two-sided).
	  • DCR: 86.4% vs. 50.0% (OR=10.03; 95% CI: 4.50, 22.34; stratified Wald's Chi-square test p < 0.001, two-sided).
	• Time to first SSE: estimated 50% risk reduction of SSE or death (HR =0.50; 95% CI: 0.40, 0.62; two-sided p-value: < 0.001)
	  • Median time to first SSE was delayed by 4.7 months, from 6.8 months (95% CI: 5.2, 8.5) to 11.5 months (95% CI: 10.3, 13.2))

Additional secondary endpoints	Improvements in favor of treatment with ^{177}Lu-PSMA-617+BSC/BSoC relative to BSC/BSoC only were also demonstrated for the additional secondary endpoints (no multiplicity adjustment was performed for these analyses):
	• PFS: estimated 70% reduction in risk of radiographic disease progression, clinical progression, PSA progression, or death (HR = 0.30; 95% CI: 0.24, 0.38)
	• Median PFS was prolonged by 3.5 months (from 2.4 months (95% CI: 2.2, 3.0) to 5.9 months (5.2, 6.6))
	• For PSA, ALP, and LDH levels, greater mean and median decreases from baseline were observed for ^{177}Lu-PSMA-617+BSC/BSoC relative to BSC/BSoC only
	    • PSA response as ≥ 50% decrease from baseline occurred in 177/385 (46.0%, 95% CI: 40.9, 51.1) patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 14/196 (7.1%, 95% CI: 4.0, 11.7) patients in the BSC/BSoC only arm.
	Results in favor of treatment with ^{177}Lu-PSMA-617+BSC/BSoC relative to BSC/BSoC only were also observed for PROs, indicating stabilization/slower deterioration while on treatment (no multiplicity adjustment was performed for these analyses). For PRO analyses, worsening also includes clinical progression or death:
	• FACT-P total score: estimated 46% reduction in risk of worsening (HR = 0.54; 95% CI: 0.45, 0.66; Cox two-sided p-value: < 0.001)
	    • Time to worsening was delayed in ^{177}Lu-PSMA-617+BSC/BSoC arm, with median time to deterioration of 5.7 months (95% CI: 4.8, 6.6) in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 2.2 months (95% CI: 1.8, 2.8) in the BSC/BSoC only arm
	• Similar results were observed for the FACT-P total score subscales, including physical well-being, pain-related scale, PSI-8, and TOI, as well as the FACT-G total score
	• BPI-SF pain intensity scale: estimated 48% reduction in risk of worsening (HR = 0.52; 95% CI: 0.43, 0.63; Cox two-sided p-value: < 0.001) in the 177Lu-PSMA-617+BSC/BSoC arm compared to the BSC/BSoC only arm
	    • Time to worsening was delayed by 3.7 months in ^{177}Lu-PSMA-617+BSC/BSoC arm, with median time to deterioration of 5.9 months (95% CI: 4.8, 6.9) in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 2.2 months (95% CI: 1.8, 2.8) in BSC/BSoC only arm
	• Similar results were observed for other BPI-SF scales, including pain interference and worst pain intensity

3 Analysis of results of Study PSMA-617-01

3.1 Study population

The population enrolled in this study reflects the target population of adult patients with progressive PSMA-positive mCRPC who have been treated with NAAD and taxane-based chemotherapy.

3.1.1 Disposition

For a summary of disposition for all screened patients, see [Study PSMA-617-01-Section 10.1.1].

A summary of disposition for all randomized patients (FAS), including treatment disposition, is presented in Figure 3-1 and Table 3-1. For additional information on disposition, including incidence of withdrawal of consent, see [Study PSMA-617-01-Table 14.1.4].

Almost all patients (533 patients, 96.7%) randomized to ^{177}Lu-PSMA-617+BSC/BSoC received at least one dose of randomized treatment (^{177}Lu-PSMA-617 and/or BSC/BSoC). Four patients (0.7%) in this arm received only BSC/BSoC and 18 (3.3%) did not receive any treatment. The main reason for not receiving ^{177}Lu-PSMA-617 was AEs occurring at the time of randomization and prior to the start of ^{177}Lu-PSMA-617 (6 patients, 1.1%); all other reasons were ≤ 0.5%.

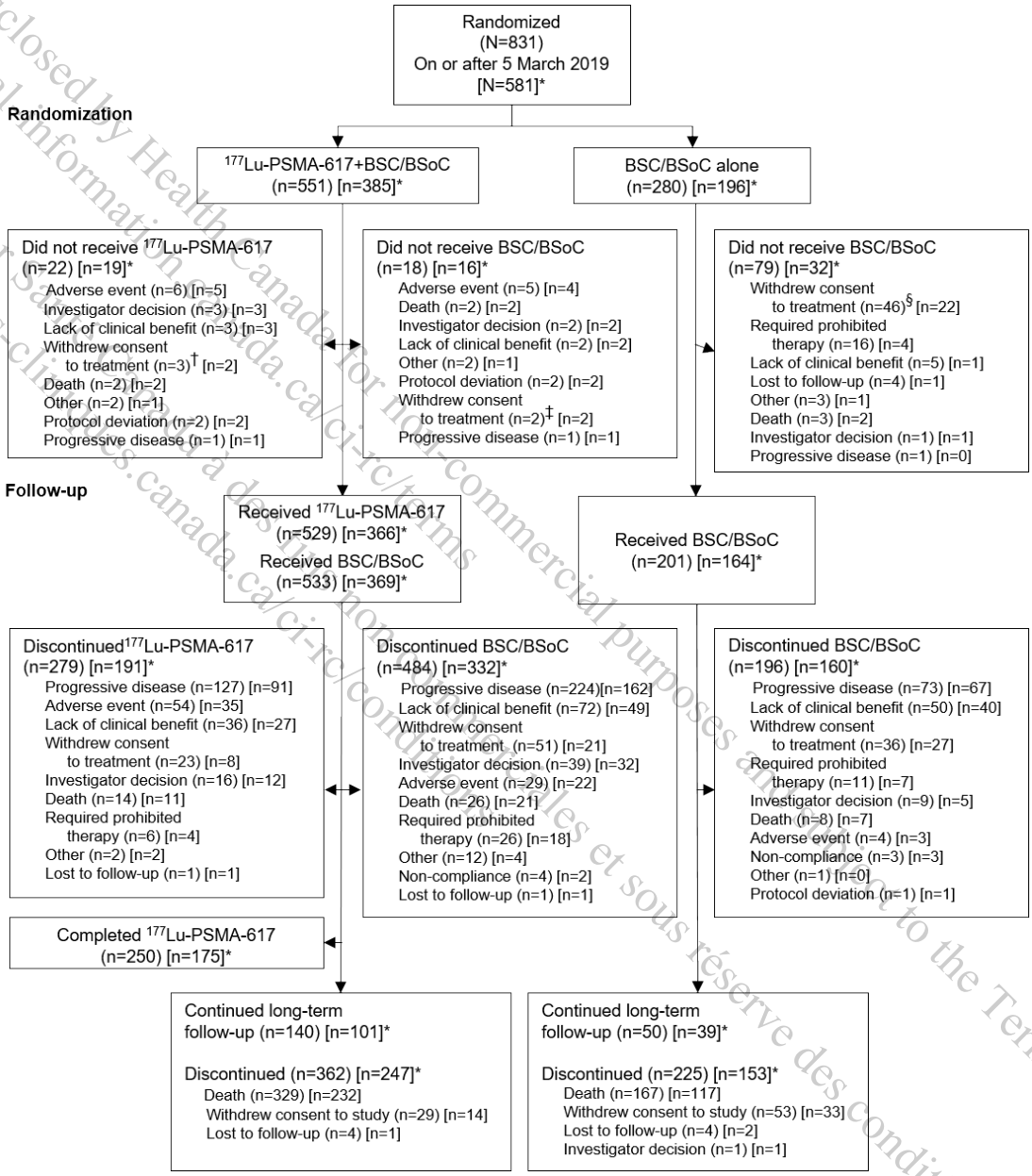
A total of 201 patients (71.8%) randomized to BSC/BSoC only arm received at least one dose of treatment. The majority of patients who were randomized to this arm but were never treated had withdrawn their consent (46 patients, 16.4%), see [Study PSMA-617-01-Table 14.1.4]. The main reason for withdrawing consent from treatment was "because receiving BSC/BSoC only without ^{177}Lu-PSMA-617" (31 patients, 11.1%); enhanced study site education measures were implemented to curtail this phenomenon (see [Study PSMA-617-01-Section 9.2] for further explanations). The incidence of patients withdrawing consent from treatment with BSC/BSoC only decreased from 28.6% (24 patients) for patients randomized prior to 05-Mar-2019, see [Study PSMA-617-01-Table 14.1.4.2], to 11.2% (22 patients) for patients randomized on or after this date; see [Study PSMA-617-01- Table 14.1.4.1].

The main reasons (≥5.0%) for discontinuing ^{177}Lu-PSMA-617 treatment (50.6% of patients) were progressive disease (23.0%), AEs (9.8%), and no longer clinically benefiting (6.5%).

The main reasons for discontinuing BSC/BSoC treatment for ^{177}Lu-PSMA-617+BSC/BSoC vs. BSC/BSoC only were: progressive disease (40.7% vs. 26.1%), no longer clinically benefiting (13.1% vs. 17.9%), and withdrawal of consent for treatment (9.3% vs. 12.9%). The relatively higher incidence of progressive disease in the ^{177}Lu-PSMA-617+BSC/BSoC arm is likely related to the longer period of time in which patients received study-related treatment in this arm; see [Study PSMA-617-01-Section 10.5.1.2].

As of the data cut-off date, 65.7% of patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm and 80.4% in the BSC/BSoC only arm had discontinued from the study. The main reasons for study discontinuation (^{177}Lu-PSMA-617+BSC/BSoC vs. BSC/BSoC only) were death (59.7% vs. 59.6%), withdrawal of consent (protocol; 5.3% vs. 18.9%), patient lost to follow-up (0.7% vs. 1.4%) and investigator decision (0% vs. 0.4%).

Figure 3-1 Patient disposition (All randomized patients)



* Number in square brackets indicate patients randomized on or after 05-Mar-2019; see [Study PSMA-617-01-Section 9.2].
† Reasons for withdrawal of consent to treatment: none given (n=2), travel or procedure "fatigue" (n=1)
‡ Reasons for withdrawal of consent to treatment: none given (n=1), travel or procedure "fatigue" (n=1)
§ Reasons for withdrawal of consent to treatment: receiving BSC/BSoC without ^{177}Lu-PSMA-617 (n=31), none given (n=7), decided to pursue off-study treatment (n=5), travel or procedure "fatigue" (n=2), perceived lack of benefit (n=1)
"Completed ^{177}Lu-PSMA-617" indicates completed at least 4 cycles as reported by the investigator
Source: [Study PSMA-617-01-Table 14.1.1, Table 14.1.4, Table 14.1.4.1, Table 14.1.5.3, Table 14.1.5.4]

Table 3-1 Disposition of randomized patients (FAS)

	^{177}Lu-PSMA-617 +BSC/BSoC N=551	**BSC/BSoC only N=280**	**Overall N=831**
Patients treated	533 (96.7)	201 (71.8)	734 (88.3)
Patients not treated [1]	18 (3.3)	79 (28.2)	97 (11.7)
Patients still on treatment [2]	49 (8.9)	5 (1.8)	54 (6.5)
Patients who discontinued from all study treatments	484 (87.8)	196 (70.0)	680 (81.8)
Patients treated with ^{177}Lu-PSMA-617	**529 (96.0)**		
Patients not treated with ^{177}Lu-PSMA-617	22 (4.0)		
Reason not treated with ^{177}Lu-PSMA-617			
Adverse event	6 (1.1)		
Investigator decision	3 (0.5)		
No longer clinically benefiting	3 (0.5)		
Withdrew consent (treatment)	3 (0.5)		
Death	2 (0.4)		
Other	2 (0.4)		
Protocol deviation	2 (0.4)		
Progressive disease	1 (0.2)		
Patients who completed ^{177}Lu-PSMA-617 [5]	250 (45.4)		
Patients who discontinued from ^{177}Lu-PSMA-617	279 (50.6)		
Reason for discontinuation from ^{177}Lu-PSMA-617			
Progressive disease	127 (23.0)		
Adverse event	54 (9.8)		
No longer clinically benefiting	36 (6.5)		
Withdrew consent (treatment)	23 (4.2)		
Investigator decision	16 (2.9)		
Death	14 (2.5)		
Patient requires care not allowed in the study	6 (1.1)		
Other	2 (0.4)		
Patient lost to follow-up	1 (0.2)		
Patients treated with BSC/BSoC	**533 (96.7)**	**201 (71.8)**	**734 (88.3)**
Patients not treated with BSC/BSoC	18 (3.3)	79 (28.2)	97 (11.7)
Reason not treated with BSC/BSoC			
Withdrew consent (treatment)	2 (0.4)	46 (16.4)	48 (5.8)
Patient requires care not allowed in the study	0	16 (5.7)	16 (1.9)
No longer clinically benefiting	2 (0.4)	5 (1.8)	7 (0.8)
Subject lost to follow-up	0	4 (1.4)	4 (0.5)
Death	2 (0.4)	3 (1.1)	5 (0.6)
Other	2 (0.4)	3 (1.1)	5 (0.6)
Progressive disease	1 (0.2)	1 (0.4)	2 (0.2)
Investigator decision	2 (0.4)	1 (0.4)	3 (0.4)
Adverse event	5 (0.9)	0	5 (0.6)
Protocol deviation	2 (0.4)	0	2 (0.2)
Patients who discontinued from BSC/BSoC	484 (87.8)	196 (70.0)	680 (81.8)
Reason for discontinuation from BSC/BSoC			
Progressive disease	224 (40.7)	73 (26.1)	297 (35.7)

	^{177}Lu-PSMA-617 +BSC/BSoC N=551	BSC/BSoC only N=280	Overall N=831
No longer clinically benefiting	72 (13.1)	50 (17.9)	122 (14.7)
Withdrew consent (treatment)	51 (9.3)	36 (12.9)	87 (10.5)
Investigator decision	39 (7.1)	9 (3.2)	48 (5.8)
Adverse event	29 (5.3)	4 (1.4)	33 (4.0)
Death	26 (4.7)	8 (2.9)	34 (4.1)
Patient requires care not allowed in the study	26 (4.7)	11 (3.9)	37 (4.5)
Other	12 (2.2)	1 (0.4)	13 (1.6)
Patient non-compliance	4 (0.7)	3 (1.1)	7 (0.8)
Patient lost to follow-up	1 (0.2)	0	1 (0.1)
Protocol deviation	0	1 (0.4)	1 (0.1)
Patients continuing in long-term follow-up period [3]	**140 (25.4)**	**50 (17.9)**	**190 (22.9)**
Patients who discontinued from study	362 (65.7)	225 (80.4)	587 (70.6)
Reason for discontinuation from study			
Death	329 (59.7)	167 (59.6)	496 (59.7)
Withdrew consent (protocol) [4]	29 (5.3)	53 (18.9)	82 (9.9)
Subject lost to follow-up	4 (0.7)	4 (1.4)	8 (1.0)
Investigator decision	0	1 (0.4)	1 (0.1)

[1] Patients who did not receive ^{177}Lu-PSMA-617 nor BSC/BSoC. Four patients randomized to ^{177}Lu-PSMA-617+BSC/BSoC did not receive ^{177}Lu-PSMA-617; they only received BSC/BSoC.
[2] Patients still on treatment at the time of the data cut-off date 27-Jan-2021.
[3] Patients in long-term follow-up period are those no longer on treatment and have not discontinued from the study at the time of the data cut-off date.
[4] 34 patients who had withdrew consent (protocol) were later reported as dead through public registry search.
[5] "Completed ^{177}Lu-PSMA-617" indicates completed at least 4 cycles as reported by the investigator.
Source: [Study PSMA-617-01-Table 14.1.4]

3.1.2 Eligibility criteria

^{68}Ga-PSMA-11 was used to determine patient eligibility based on PET imaging patterns defined by the central read criteria. Only patients with at least one PSMA scan-positive lesion identified on PSMA-PET/CT and no PSMA scan-negative lesion fulfilling the exclusion criteria were to be enrolled in the study, provided all other inclusion criteria were met. For details, see [Study PSMA-617-01-Section 10.4.3.1]. A total of 1003 patients underwent a ^{68}Ga-PSMA-11 PET/CT scan; 869 patients (86.6%) met the ^{68}Ga-PSMA-11 eligibility criteria to be enrolled in study. Details of the inclusion and exclusion criteria data resulting in the patient meeting the ^{68}Ga-PSMA-11 PET/CT scan eligibility criteria data for enrollment are presented in [Study PSMA-617-01-Table 10-9].

Of note, 3 patients negative for eligibility by ^{68}PSMA-11 PET/CT scan were randomized in error: 1 in the ^{177}Lu-PSMA-617+BSC/BSoC arm, and 2 in the BSC/BSoC only arm. For further details, see [Study PSMA-617-01-Section 10.4.3.1].

3.1.3 Data sets analyzed

For the definitions of the analysis sets, see Section 1.2.2.1.

The numbers of patients in each analysis set are presented in Table 3-2. In both arms, the main reason for not being enrolled (randomized to one of the treatment arms) was eligibility criteria not met; see [Study PSMA-617-01-Figure 10-1].

The higher proportion of patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm included in the Response evaluable analysis set (57.9% vs. 42.9%) and in the FAS safety analysis set (96.0% vs. 73.2%) may be related to the higher rate of early drop-out in patients randomized to BSC/BSoC only; see Section 3.1.1.

Table 3-2 Analysis sets (All screened patients)

	Not enrolled [1] N=348 n (%)	Lu-PSMA-617 +BSC/BSoC N=551 n (%)	BSC/BSoC only N=280 n (%)	Overall N=1179 n (%)
PSMA-11 safety analysis set	172 (49.4)	551 (100)	280 (100)	1003 (85.1)
Full analysis set (FAS)		551 (100)	280 (100)	831 (70.5)
PFS full analysis set (PFS-FAS)		385 (69.9)	196 (70.0)	581 (49.3)
Response evaluable analysis set		319 (57.9)	120 (42.9)	439 (37.2)
FAS safety analysis set [2]		529 (96.0)	205 (73.2)	734 (62.3)

[1]: Patients who were not randomized to the study.
[2]: For the FAS safety analysis set, the patients were included in the treatment arm corresponding to the actual treatment received (e.g. BSC/BSoC only if they were randomized to ^{177}Lu-PSMA-617+BSC/BSoC but received only BSC/BSoC). See [Study PSMA-617-01-Section 10.1.2] for information on disposition of randomized patients. The definitions for the analysis sets are presented in [Study PSMA-617-01-Section 9.7.2].
Source: [Study PSMA-617-01-Table 14.1.3]

3.1.4 Demographic and other baseline characteristics

3.1.4.1 Demographics at baseline

Demographic and baseline characteristics for all patients randomized (the FAS) are presented in Table 3-3. These characteristics were balanced between the 2 randomized arms. Of note, all sites were localized in Europe or North America (US and Canada) [Study PSMA-617-01-Table 14.1.2], and therefore a majority of patients recruited were White (86.8%), 6.6% were Black or African American, and only 2.4% were Asian. As anticipated for the disease under study, a high proportion of patients were age 65 or over (75.3%).

In addition, demographic and baseline characteristics for the PFS-FAS (all patients randomized on or after the 05-Mar-2019) and the Response evaluable analysis set are presented in [Study PSMA-617-01-Table 14.1.7.2 and -Table 14.1.7.5], respectively. These characteristics were generally balanced between the 2 randomized arms, and similar to those for the FAS.

Table 3-3 Demographic and baseline characteristics (FAS)

	Lu-PSMA-617 +BSC/BSoC N=551	BSC/BSoC only N=280	Overall N=831
Age (years)			
n	551	280	831
Mean (SD)	69.7 (7.4)	70.5 (7.8)	70.0 (7.6)
Median	70.0	71.5	71.0
Min-max	48-94	40-89	40-94
Age (categorized), n (%)			
< 65 years	145 (26.3)	60 (21.4)	205 (24.7)
≥ 65 years	406 (73.7)	220 (78.6)	626 (75.3)
≥ 65-84 years	398 (72.2)	214 (76.4)	612 (73.6)
≥ 85 years	8 (1.5)	6 (2.1)	14 (1.7)
Race, n (%)			
White	486 (88.2)	235 (83.9)	721 (86.8)
Black or African American	34 (6.2)	21 (7.5)	55 (6.6)
Asian	9 (1.6)	11 (3.9)	20 (2.4)
Other [1]	2 (0.4)	0	2 (0.2)
Missing	20 (3.6)	13 (4.6)	33 (4.0)
Ethnicity, n (%)			
Hispanic or Latino	11 (2.0)	3 (1.1)	14 (1.7)
Not Hispanic or Latino	471 (85.5)	240 (85.7)	711 (85.6)
Not reported	69 (12.5)	37 (13.2)	106 (12.8)
Weight (kg)			
n	535	272	807
Mean (SD)	88.0 (17.3)	88.1 (16.5)	88.0 (17.0)
Median	85.3	86.0	85.7
Min-max	54.0-160.0	52.3-147.0	52.3-160.0
Body mass index (kg/m^2)			
n	517	266	783
Mean (SD)	28.4 (5.1)	28.0 (4.7)	28.2 (5.0)
Median	27.7	27.4	27.7
Min-max	17.0-48.4	20.3-44.6	17.0-48.4
ECOG performance status, n (%) [2]			
0-1	510 (92.6)	258 (92.1)	768 (92.4)
2	41 (7.4)	22 (7.9)	63 (7.6)

[1] Other includes Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native and more than one race reported.
[2] ECOG performance status was not collected at the time of screening and was only captured as the categories 0-1 vs. 2 on the enrollment CRF page.
Source: [Study PSMA-617-01-Table 14.1.7.1]

3.1.4.2 Baseline disease characteristics

Baseline disease characteristics for all randomized patients (the FAS) are presented in Table 3-4. Overall, these characteristics were as anticipated for this patient population with mCRPC, and were generally balanced between the 2 randomized arms. Of note, the relatively high frequency of patients with unknown initial histopathological classification, grade, or staging

can be related to the relatively long time since initial diagnosis (mean: 8.5 years (SD=5.6), median: 7.4 years).

Baseline disease characteristics for the PFS-FAS and the Response evaluable analysis set are presented in [Study PSMA-617-01-Table 14.1.8.2 and Table 14.1.8.5], respectively. These characteristics were generally balanced between the 2 randomized arms, and similar to those for the FAS.

Table 3-4 Baseline disease characteristics (FAS)

	Lu-PSMA-617+ BSC/BSoC N=551	BSC/BSoC only N=280	Overall N=831
Time since initial cancer diagnosis (years)			
n	551	280	831
Mean (SD)	8.3 (5.5)	8.9 (5.8)	8.5 (5.6)
Median	7.4	7.4	7.4
Min-max	0.9-28.9	0.7-26.2	0.7-28.9
Initial histopathological classification, n (%)			
Adenocarcinoma	497 (90.2)	258 (92.1)	755 (90.9)
Neuroendocrine	1 (0.2)	0	1 (0.1)
Unknown	47 (8.5)	20 (7.1)	67 (8.1)
Other	6 (1.1)	2 (0.7)	8 (1.0)
Initial histopathological grade, n (%)			
Grade 1	11 (2.0)	2 (0.7)	13 (1.6)
Grade 2	7 (1.3)	5 (1.8)	12 (1.4)
Grade 3	38 (6.9)	11 (3.9)	49 (5.9)
Grade 3-4	15 (2.7)	10 (3.6)	25 (3.0)
Grade 4	53 (9.7)	33 (11.8)	86 (10.4)
Grade 5	63 (11.5)	38 (13.6)	101 (12.2)
Unknown	361 (65.9)	181 (64.6)	542 (65.5)
Initial Gleason score, categorized, n (%)			
2-3	4 (0.7)	0	4 (0.5)
4-7	181 (32.8)	86 (30.7)	267 (32.1)
8-10	324 (58.8)	170 (60.7)	494 (59.4)
Unknown	42 (7.6)	24 (8.6)	66 (7.9)
Staging at initial diagnosis, n (%)			
I	9 (1.6)	3 (1.1)	12 (1.5)
IA	0	1 (0.4)	1 (0.1)
IB	3 (0.5)	4 (1.4)	7 (0.8)
II	26 (4.7)	10 (3.6)	36 (4.4)
IIA	19 (3.5)	8 (2.9)	27 (3.3)
IIB	22 (4.0)	11 (3.9)	33 (4.0)
III	25 (4.6)	11 (3.9)	36 (4.4)
IIIA	23 (4.2)	9 (3.2)	32 (3.9)
IIIB	38 (6.9)	14 (5.0)	52 (6.3)
IIIC	2 (0.4)	5 (1.8)	7 (0.8)
IV	73 (13.3)	44 (15.8)	117 (14.1)
IVA	10 (1.8)	6 (2.2)	16 (1.9)

	Lu-PSMA-617+ BSC/BSoC N=551	BSC/BSoC only N=280	Overall N=831
IVB	21 (3.8)	13 (4.7)	34 (4.1)
Unknown	277 (50.5)	140 (50.2)	417 (50.4)
Baseline target lesions, n (%)			
Yes	279 (50.6)	140 (50.0)	419 (50.4)
No	272 (49.4)	140 (50.0)	412 (49.6)
Baseline non-target lesions, n (%)			
Yes	429 (77.9)	212 (75.7)	641 (77.1)
No	122 (22.1)	68 (24.3)	190 (22.9)
Total sum of target lesion diameters (mm)			
n	279	140	419
Mean (SD)	58.5 (46.4)	58.6 (44.9)	58.5 (45.9)
Median	45.0	46.2	45.0
Min-max	10-351	10-249	10-351
Site of disease (target and non-target lesions), n (%) [1]			
Lung			
Yes	49 (8.9)	28 (10.0)	77 (9.3)
No	502 (91.1)	252 (90.0)	754 (90.7)
Liver			
Yes	63 (11.4)	38 (13.6)	101 (12.2)
No	488 (88.6)	242 (86.4)	730 (87.8)
Lymph node			
Yes	274 (49.7)	141 (50.4)	415 (49.9)
No	277 (50.3)	139 (49.6)	416 (50.1)
Bone			
Yes	504 (91.5)	256 (91.4)	760 (91.5)
No	47 (8.5)	24 (8.6)	71 (8.5)
Baseline PSA doubling time (months) [2]			
n	269	131	400
Mean (SD)	3.2 (5.3)	4.3 (9.1)	3.6 (6.8)
Median	2.4	2.6	2.4
Min-max	0.0-74.4	0.0-93.1	0.0-93.1
Baseline PSA doubling time (categorized), n (%)			
Stable, non-increasing or decreasing	8 (3.0)	4 (3.1)	12 (3.0)
≤ 6 months	245 (91.1)	115 (87.8)	360 (90.0)
> 6 months	16 (5.9)	12 (9.2)	28 (7.0)
Baseline PSA (ng/mL)			
n	551	280	831
Mean (SD)	288.4 (675.8)	387.6 (937.0)	321.8 (774.6)
Median	77.5	74.6	76.0
Min-max	0-6988	0-8995	0-8995
Baseline ALP (IU/L)			
n	547	278	825
Mean (SD)	153.7 (183.7)	150.3 (168.1)	152.6 (178.5)
Median	105.0	94.5	101.0

	Lu-PSMA-617+ BSC/BSoC N=551	BSC/BSoC only N=280	Overall N=831
Min-max	17-2524	28-1355	17-2524
Baseline LDH (IU/L)			
n	550	279	829
Mean	286.4 (283.9)	297.5 (261.7)	290.1 (276.6)
Median	221.0	224.0	223.0
Min-max	88-5387	105-2693	88-5387

[1] Bone site of disease was based on data collected on target and/or non-target lesion or bone scan assessments.
[2] Baseline PSA doubling time was derived for each patient as the natural log 2 divided by the sum of the fixed and random slopes of the random coefficient linear model between natural log of PSA and time of PSA measurement (in months). Patients with at least 3 PSA values prior to and at the time of screening were included in the model.
Source: [Study PSMA-617-01-Table 14.1.8.1]

3.1.5 Stratification factors

Stratification factors per IRT vs. stratification based on values collected on CRF for all randomized patients (FAS) are presented in Table 3-5. In general, there was concordance between the stratification factors per IRT vs. CRF with the exception of minor discordance for NAAD at start of the study. For details, see [Study PSMA-617-01-Section 10.4.3.2].

Stratification factors per IRT vs. stratification based on values collected on the CRF for patients randomized on or after 05-Mar-2019 (PFS-FAS) and the subset of patients in the PFS-FAS with RECIST evaluable disease at baseline (Response evaluable analysis set) are presented in [Study PSMA-617-01-Table 14.1.6.2 and Table 14.1.6.3], respectively. These comparisons demonstrated that stratification factors were generally balanced between the 2 randomized arms, and similar to those for the FAS.

Table 3-5 Stratification factors per IRT vs. stratification based on values collected on CRF (FAS)

Stratification factor Strata reported per IRT Strata reported per CRF	Lu-PSMA-617+ BSC/BSoC N=551	BSC/BSoC only N=280	Overall (N=831)
LDH level			
≤ 260 IU/L	367 (66.6)	185 (66.1)	552 (66.4)
≤ 260 IU/L	364 (66.1)	181 (64.6)	545 (65.6)
> 260 IU/L	2 (0.4)	3 (1.1)	5 (0.6)
Unknown	1 (0.2)	1 (0.4)	2 (0.2)
> 260 IU/L	184 (33.4)	95 (33.9)	279 (33.6)
≤ 260 IU/L	4 (0.7)	1 (0.4)	5 (0.6)
> 260 IU/L	180 (32.7)	94 (33.6)	274 (33.0)
Presence of liver metastases			
Yes	67 (12.2)	36 (12.9)	103 (12.4)
Yes	42 (7.6)	28 (10.0)	70 (8.4)
No	25 (4.5)	8 (2.9)	33 (4.0)
No	484 (87.8)	244 (87.1)	728 (87.6)
Yes	6 (1.1)	6 (2.1)	12 (1.4)

Stratification factor Strata reported per IRT Strata reported per CRF	Lu-PSMA-617+ BSC/BSoC N=551	BSC/BSoC only N=280	Overall (N=831)
No	478 (86.8)	238 (85.0)	716 (86.2)
ECOG score			
0 or 1	511 (92.7)	258 (92.1)	769 (92.5)
0 or 1	510 (92.6)	258 (92.1)	768 (92.4)
2	1 (0.2)	0	1 (0.1)
2	40 (7.3)	22 (7.9)	62 (7.5)
0 or 1	0	0	0
2	40 (7.3)	22 (7.9)	62 (7.5)
Inclusion of NAAD in BSC/BSoC at time of randomization			
Yes	344 (62.4)	173 (61.8)	517 (62.2)
Yes	220 (39.9)	123 (43.9)	343 (41.3)
No	124 (22.5)	50 (17.9)	174 (20.9)
No	207 (37.6)	107 (38.2)	314 (37.8)
Yes	23 (4.2)	23 (8.2)	46 (5.5)
No	184 (33.4)	84 (30.0)	268 (32.3)

Source: [Study PSMA-617-01-Table 14.1.6.1]

3.1.6 Prior, concomitant and post-treatment therapies

3.1.6.1 Medical history

Medical history was balanced between the 2 randomized arms for both the FAS and PFS-FAS.

Medical history for the FAS and PFS-FAS, including past medical conditions/procedures that ended before the time of informed consent, are presented in [Study PSMA-617-01-Table 14.1.9.1 and Table 14.1.9.2], respectively.

3.1.6.2 Prior cancer therapy

Prior cancer therapy, including surgery, radiotherapy, systemic therapy, and prior last taxane therapy, was balanced between the 2 randomized arms for both the FAS and the PFS-FAS, and was as anticipated for a patient population with an advanced disease and a relatively long time since initial diagnosis.

Further information is provided below. For additional details regarding prior cancer therapy, see [Study PSMA-617-01-Section 10.4.4.2].

Prior cancer-related surgery

Overall, almost all patients in the FAS (96.3%) had at least one prostate cancer–related surgery (including biopsies), and 43.2% had therapeutic surgery [Study PSMA-617-01-Table 14.1.11.1].

Likewise, for patients randomized on or after the 05-Mar-2019 (the PFS-FAS), almost all patients (96.2%) had at least one prostate cancer–related surgery (including biopsies), and 39.9% had therapeutic surgery [Study PSMA-617-01-Table 14.1.11.2].

Prior cancer-related radiotherapy

Prior cancer-related radiotherapy for the FAS was balanced between the 2 randomized arms. Overall, a majority of patients (76.1%) had at least one prostate cancer–related radiotherapy, and the most frequent site for radiotherapy was the prostate gland (44.4%) [Study PSMA-617-01-Table 14.1.12.1].

Likewise for the PFS-FAS, a majority of patients (75.4%) had at least one prostate cancer–related radiotherapy, and the most frequent site for radiotherapy was the prostate gland (42.0%) [Study PSMA-617-01-Table 14.1.12.2].

Prior cancer-related systemic therapy

Prior cancer-related systemic therapies for the FAS were balanced between the 2 randomized arms. Overall, the mean number of prior regimens was 5.3 (median=5.0), and the majority of patients (79.1%) had received 4 or more different categories of regimens. The most frequent categories of systemic therapy were therapeutics for 76.9% of patients and adjuvant therapies for 31.3% of patients. All patients had received prior taxane treatment, with 1 regimen in 57.9%, 2 regimens in 41.2%, and more than 2 regimens in 1.0%, as well as prior androgen axis inhibition (NAAD), with 1 regimen in 51.3%, 2 regimens in 41.0%, and more than 2 regimens in 7.7% [Study PSMA-617-01-Table 14.1.13.1].

Prior cancer-related systemic therapies for the PFS-FAS were similar to those for the FAS. Overall, the mean number of prior regimens was 5.1 (median=5.0), and the majority of patients (76.4%) had received 4 or more different categories of regimens. The most frequent categories of systemic therapy were therapeutics for 76.8% of patients and adjuvant therapies for 29.3% of patients. All patients had received prior taxane treatment, with 1 regimen in 53.2%, 2 regimens in 45.6% and more than 2 regimens in 1.2%, as well as prior androgen axis inhibition (NAAD), with 1 regimen in 53.5%, 2 regimens in 40.6%, and more than 2 regimens in 5.9% [Study PSMA-617-01-Table 14.1.13.2].

Prior last taxane therapy

Prior last taxane therapy was defined as the last taxane as part of a taxane-containing regimen, prior to study entry.

For the FAS and PFS-FAS, the last taxane therapies were balanced between the 2 randomized arms [Study PSMA-617-01-Table 14.1.14.1 and Table 14.1.14.2]. For details, see [PSMA-617-01-Section 10.4.4.2.3].

3.1.6.3 Concomitant therapy

Concomitant medications, incidence and site of concurrent radiotherapy, and concurrent surgical and therapeutic procedures were balanced between the 2 randomized arms. For details, see [Study PSMA-617-01-Section 10.4.4.3].

3.1.6.3.1 Concomitant therapies indicated as BSC/BSoC

The BSC/BSoC for the patients in either arm was administered as per physician's orders and protocol at the institution and whenever feasible was optimized prior to randomization; however,

it could be modified over time as needed (see [Study PSMA-617-01-Appendix 16.1.1-Protocol-Section 5.2]).

Concomitant medications indicated as BSC/BSoC

Concomitant medications indicated as BSC/BSoC during randomized treatment for all randomized patients that received at least one dose of randomized treatment (the FAS safety set) are presented in [Study PSMA-617-01-Table 14.3.5.6.1]. All patients (100%) received at least 1 concomitant medication indicated as BSC/BSoC. The most frequent medication was gonadotropin-releasing hormone analogues, reported in 88.5% vs. 83.9% of patients in ^{177}Lu-PSMA-617+BSC/BSoC arm vs. BSC/BSoC only arms, respectively. Concomitant medications were similar in the 2 randomized arms, with differences that were typically < 10%, except for (^{177}Lu-PSMA-617+BSC/BSoC arm vs. BSC/BSoC only arm):

- Serotonin (5HT3) antagonists: 51.0% vs. 17.1% (mainly driven by ondansetron: 49.3% vs. 15.6%)
- Anti-androgens: 34.4% vs. 47.3% (mainly driven by enzalutamide, 29.7% vs. 42.4%)

Concurrent radiotherapies indicated as BSC/BSoC

Incidences and sites of concurrent radiotherapies indicated as BSC/BSoC during randomized treatment for all randomized patients that received at least one dose of randomized treatment (the FAS safety set) were balanced between the 2 arms. Overall, 15.4% received at least one radiotherapy, and the most frequent site of radiotherapy was the back (5.5% vs. 5.4% for ^{177}Lu-PSMA-617+BSC/BSoC arm vs. BSC/BSoC only arm) [Study PSMA-617-01- Table 14.3.5.8.1].

Concurrent surgical and therapeutic procedures indicated as BSC/BSoC

Concurrent surgical and therapeutic procedures indicated as BSC/BSoC during randomized treatment for all randomized patients that received at least one dose of randomized treatment (the FAS safety set) were relatively infrequent in both arms: 4.5% vs. 2.4% in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. BSC/BSoC only arm, respectively [Study PSMA-617-01-Table 14.3.5.7.1].

3.1.6.4 Post-treatment cancer-related therapies

Post-treatment cancer-related non-radiation therapies are presented [Study PSMA-617-01-Table 14.3.12]. The number and types of drugs were generally well-balanced between the 2 randomized arms; therefore, post-treatment cancer-related non-radiation therapy was not considered to have a substantial influence on the OS results; see [Study PSMA-617-01-Section 11.1.2].

A total of 28.1% of patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm and 34.6% in BSC/BSoC only arm had one or more such therapies. The most frequently reported types were taxanes (18.0% vs. 21.8%), platinum compounds (7.3% vs. 9.6%), anti-androgen (4.2% vs. 4.6%), monoclonal-antibodies (2.9% vs. 7.9%), various therapeutic radiopharmaceuticals (2.9% vs 8.2%), and investigational drug (1.6% vs 5.4%). The various therapeutic radiopharmaceuticals were:

- Radium (^{223}Ra) dichloride: 2.5% vs. 5.4%

- Lutetium (^{177}Lu) PSMA-617: 0.4% vs. 1.1%
- Actinium (^{225}Ac) PSMA-617: 0.2% vs. 0%
- Other radiopharmaceuticals: 0% vs. 1.8%

Post-treatment cancer-related radiotherapies (external beam radiation therapy) are presented in [Study PSMA-617-01-Table 14.3.13]; 8.9% of patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm and 11.1% in the BSC/BSoC only arm had one or more radiotherapies, and the most frequent site of radiotherapy was the back (3.1% vs. 3.6%).

3.1.7 Duration of exposure to randomized treatment

Duration of exposure to randomized treatment for the 2 randomized arms is presented in Table 3-6.

Duration of exposure was longer in the ^{177}Lu-PSMA-617+BSC/BSoC arm. This is likely related to the longer time on study for patients randomized to this arm; see Section 3.1.1 and [Study PSMA-617-01-Table 14.1.4].

Table 3-6 Duration of exposure to randomized treatment (FAS safety analysis set)

	Lu-PSMA-617 +BSC/BSoC N=529	BSC/BSoC only N=205
Duration of exposure (months)		
Mean (SD)	7.9 (4.3)	3.5 (3.9)
Median	7.8	2.1
Min-Max	0.3-24.9	0.0-26.0

Source: [Study PSMA-617-01-Table 14.3.5.2.1]

3.1.7.1 Exposure to ^{177}Lu-PSMA-617

3.1.7.1.1 Duration of exposure to ^{177}Lu-PSMA-617 and summary of cycles

Duration of exposure to ^{177}Lu-PSMA-617 and summary of cycles for patients randomized to the ^{177}Lu-PSMA-617+BSC/BSoC arm are presented in Table 3-7. In the ^{177}Lu-PSMA-617+BSC/BSoC arm, 46.5% of the patients had received 6 cycles of ^{177}Lu-PSMA-617, the maximum number of cycles planned per protocol, and 67.7% had received at least 4 cycles of ^{177}Lu-PSMA-617, the minimum number recommended per protocol. The mean (SD) dose intensity was 5.5 (1.2) GBq/month and mean (SD) cumulative dose was 33.4 (12.8) GBq. This is within the published dose intensity range (per cycle) known to have an acceptable toxicity profile for the patients; see [Study PSMA-617-01-Section 9.4.5.2]. Delaying cycles due to AEs was relatively infrequent (7.6%).

For additional details, including dose adjustment of ^{177}Lu-PSMA-617, see [Study PSMA-617-01-Section 10.5.1.2.2].

Table 3-7 Duration of exposure to ^{177}Lu-PSMA-617 and summary of cycles (FAS safety analysis set)

	Lu-PSMA-617 +BSC/BSoC N=529
Duration of exposure (months)	
Mean (SD)	6.3 (2.4)
Median	6.9
Min-Max	0.3-10.2
Number of cycles started by patient	
Mean (SD)	4.5 (1.7)
Median	5.0
Min-Max	1-6
Number of cycles started by patient, n (%)	
1 cycle	33 (6.2)
2 cycles	57 (10.8)
3 cycles	81 (15.3)
4 cycles	69 (13.0)
5 cycles	43 (8.1)
6 cycles	246 (46.5)
Average duration of treatment cycles (months)	
Mean (SD)	1.4 (0.1)
Median	1.4
Min-Max	0.3-2.4
Patients with at least one cycle delayed, n (%)	93 (17.6)
Number of cycles delayed	
n	93
Mean (SD)	1.2 (0.5)
Median	1.0
Min-Max	1-3
Reason for delay of cycle(s), n (%)	
Delayed due to scheduling purposes	56 (10.6)
Delayed due to AE	40 (7.6)
Overall extent of ^{177}Lu-PSMA-617 exposure	
Cumulative dose (GBq)	
Mean (SD)	33.4 (12.8)
Median	37.5
Min-Max	7.0-48.3
Dose intensity (GBq/month)	
Mean (SD)	5.5 (1.2)
Median	5.5
Min-Max	3.1-25.3
Relative dose intensity (%)	
Mean (SD)	104.5 (21.9)
Median	102.6
Min-Max	90.5-471.3

A patient may be counted in more than one row for reason for delay of cycle.
^{177}Lu-PSMA-617 cycles are once every 6 weeks (± 1 week) for a maximum of 6 cycles.
Source: [Study PSMA-617-01-Table 14.3.5.2.1.1, Table 14.3.5.5.1]

3.1.7.2 Exposure to BSC/BSoC

Concomitant therapy indicated as BSC/BSoC is presented in Section 3.1.6.3.1. Duration of exposure to BSC/BSoC is presented in Table 3-8.

Similar to the exposure to overall randomized treatment (Section 3.1.7), the duration of exposure to BSC/BSoC was longer in the ^{177}Lu-PSMA-617+BSC/BSoC arm.

Table 3-8 Duration of exposure to BSC/BSoC (FAS safety analysis set)

	^{177}Lu-PSMA-617+BSC/BSoC N=529	**BSC/BSoC only N=205**
Duration of exposure to BSC/BSoC (months)		
Mean (SD)	8.8 (5.8)	3.5 (3.9)
Median	7.6	2.1
Min-Max	0.3-31.3	0.0-26.0

Source. [Study PSMA-617-01-Table 14.3.5.2.1.2]

Type and duration of exposure to NAADs indicated as BSC/BSoC is presented in Table 3-9. The proportion of patients who received NAADs as BSC/BSoC was lower (52.6% vs. 67.8%) in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. BSC/BSoC only arm. This might be related to an inclination of some Investigators to prescribe more protocol-permitted treatments (NAADs) to the patients who were randomized to receive BSC/BSoC only, as BSC/BSoC could be modified over time as needed; see Section 3.1.1 and Section 3.1.6.3.

Table 3-9 Type and duration of exposure to NAADs indicated as BSC/BSoC (FAS safety analysis set)

	^{177}Lu-PSMA-617+BSC/BSoC N=529	BSC/BSoC only N=205
Number of patients with at least one NAAD indicated as study BSC/BSoC, n (%) [1]	**278 (52.6)**	**139 (67.8)**
Type of NAAD, n (%)		
enzalutamide	157 (29.7)	87 (42.4)
abiraterone	132 (25.0)	72 (35.1)
apalutamide	10 (1.9)	1 (0.5)
darolutamide	2 (0.4)	1 (0.5)
Duration of exposure to NAAD as study BSC/BSoC (months)		
n	278	139
Mean (SD)	8.3 (6.2)	3.6 (4.2)
Median	6.6	2.1
Min-max	0.0-30.9	0.1-26.0

[1] NAADs indicated as BSC/BSoC are all NAAD medications indicated as BSC/BSoC (per sponsor pre-specified list) starting on or after the start of randomized treatment or starting prior to and continuing after the start of randomized treatment but not more than 30 days after end of randomized treatment.
Source: [Study PSMA-617-01-Table 14.3.5.6.7]

3.2 Efficacy results

3.2.1 Primary efficacy results

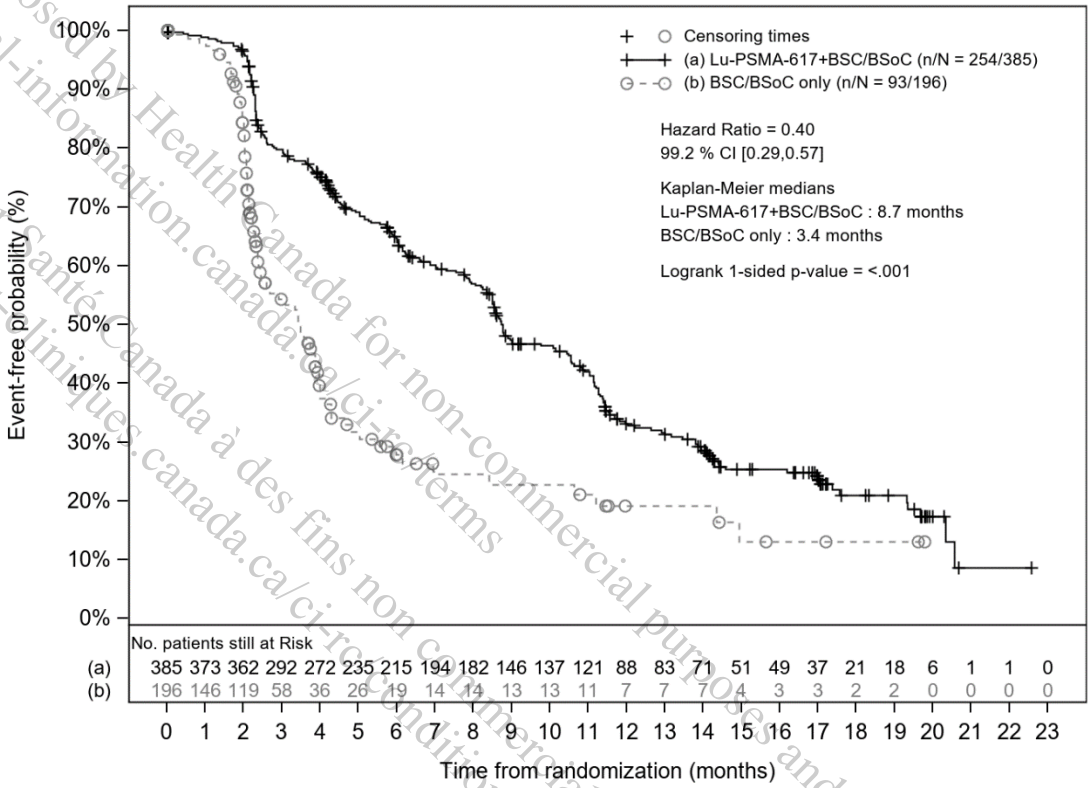
Statistically significant improvements were demonstrated for both alternate primary efficacy endpoints in favor of treatment with ^{177}Lu-PSMA-617+BSC/BSoC relative to BSC/BSoC only:

- rPFS: estimated 60% risk reduction of radiographic disease progression or death (HR = 0.40; 99.2% CI: 0.29, 0.57)
- OS: estimated 38% risk reduction of death (HR = 0.62; 95% CI: 0.52, 0.74)

3.2.1.1 Radiographic progression-free survival (rPFS) per BICR: primary analysis based on PFS-FAS

The study met its primary objective, demonstrating a statistically significant improvement in rPFS based on BICR per PCWG3 criteria for patients receiving ^{177}Lu-PSMA-617+BSC/BSoC compared to patients receiving BSC/BSoC only (PFS-FAS; stratified log-rank test $p < 0.001$, one-sided). There was an estimated 60% risk reduction of radiographic disease progression or death in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared with the BSC/BSoC only arm (HR=0.40; 99.2% CI: 0.29, 0.57; Figure 3-2).

Figure 3-2 Kaplan-Meier plot of rPFS per blinded independent central review (PFS-FAS)



Stratified log-rank test and stratified Cox model using strata per IRT defined by LDH level, presence of liver metastases, ECOG score and inclusion of NAAD in BSC/BSoC at time of randomization.
n/N: number of events/number of patients in treatment arm.
Source: [Study PSMA-617-01-Figure 14.2.2.1]

There were 254 events (66.0%; 171 radiographic progression events and 83 deaths) in the ^{177}Lu-PSMA-617+BSC/BSoC arm and 93 events (47.4%; 59 radiographic progression events and 34 deaths) in the BSC/BSoC only arm. The median rPFS was prolonged by 5.3 months, from 3.4 months (99.2% CI: 2.4, 4.0) in the BSC/BSoC only arm to 8.7 months (99.2% CI: 7.9, 10.8) in the ^{177}Lu-PSMA-617+BSC/BSoC arm (Table 3-10).

The median follow-up time for rPFS in the PFS-FAS differed between the treatment arms (16.4 months in the ^{177}Lu-PSMA-617+BSC/BSoC arm and 3.9 months in the BSC/BSoC arm). The estimated rPFS rates at 6 months were 64.6% vs. 27.8%, in the ^{177}Lu-PSMA-617+BSC/BSoC and BSC/BSoC only arms, respectively (Table 3-10).

The Kaplan-Meier curves for rPFS per BICR diverged after approximately 8 weeks, corresponding to the time of first post-baseline tumor assessment, with the radiographic progression-free probability remaining higher during the entire follow-up period for the ^{177}Lu-PSMA-617+BSC/BSoC arm than for the BSC/BSoC only arm, indicating an early and sustained advantage for ^{177}Lu-PSMA-617 therapy (Figure 3-2).

The censoring rate for rPFS differed between the treatment arms (34.0% vs. 52.6%); there was a greater proportion of patients who were ongoing without an event in the ^{177}Lu-PSMA-

617+BSC/BSoC arm compared to the BSC/BSoC only arm (23.4% vs. 12.2%). Censoring reasons other than 'ongoing without an event' were lower in the ^{177}Lu-PSMA-617+BSC/BSoC arm relative to the BSC/BSoC only arm (Table 3-10).

For results of analyses to assess sensitivity of rPFS to censoring due to drop-outs, see Section 3.2.1.3.3.

Table 3-10 Analysis of rPFS per blinded independent central review using stratified log-rank test and Cox regression model (PFS-FAS)

	^{177}Lu-PSMA-617+BSC/BSoC N=385	BSC/BSoC only N=196
rPFS, n (%)		
Events (progression or death)	254 (66.0)	93 (47.4)
Radiographic progressions	171 (44.4)	59 (30.1)
Deaths	83 (21.6)	34 (17.3)
Censored	131 (34.0)	103 (52.6)
Ongoing without event	90 (23.4)	24 (12.2)
Event documented after 2 or more missed tumor assessments	36 (9.4)	44 (22.4)
Adequate assessment not available [1]	5 (1.3)	35 (17.9)
Kaplan-Meier estimates (months)		
25th percentile [99.2% CI]	4.1 [2.6, 4.9]	2.1 [2.0, 2.3]
Median rPFS [99.2% CI]	8.7 [7.9, 10.8]	3.4 [2.4, 4.0]
75th percentile [99.2% CI]	16.2 [12.9, NE]	7.0 [4.2, NE]
rPFS rates (%)		
3 months (SE) [99.2% CI]	79.8 (2.09) [73.6, 84.7]	54.3 (4.41) [42.0, 65.1]
6 months (SE) [99.2% CI]	64.6 (2.53) [57.5, 70.9]	27.8 (4.51) [16.7, 40.1]
12 months (SE) [99.2% CI]	33.2 (2.67) [26.2, 40.3]	19.1 (4.50) [9.0, 32.1]
HR (stratified Cox PH model)	0.40	
99.2% CI [2],[3]	[0.29, 0.57]	
Stratified Log-rank Test one-sided p-value [3]	< 0.001	
Follow-up time (months) [4]		
Median [95% CI]	16.4 [14.3, 17.0]	3.9 [2.4, 5.4]
Minimum-Maximum	0.0 - 22.6	0.0 - 19.8

[1] Patients censored without adequate post-baseline evaluations or adequate baseline assessment.

[2] Hazard Ratio of ^{177}Lu-PSMA-617+BSC/BSoC vs. BSC/BSoC only.

[3] Both Cox PH model and Log-rank test are stratified for LDH (≤ 260 IU/L vs. > 260 IU/L); presence of liver metastases (yes vs. no); ECOG score (0 or 1 vs. 2); and inclusion of NAAD in BSC/BSoC at time of randomization (yes vs no). IRT data for stratification are used.

[4] Follow-up time = (Date of event or censoring - randomization date + 1)/30.4375 (months) censoring for death or radiographic progression.

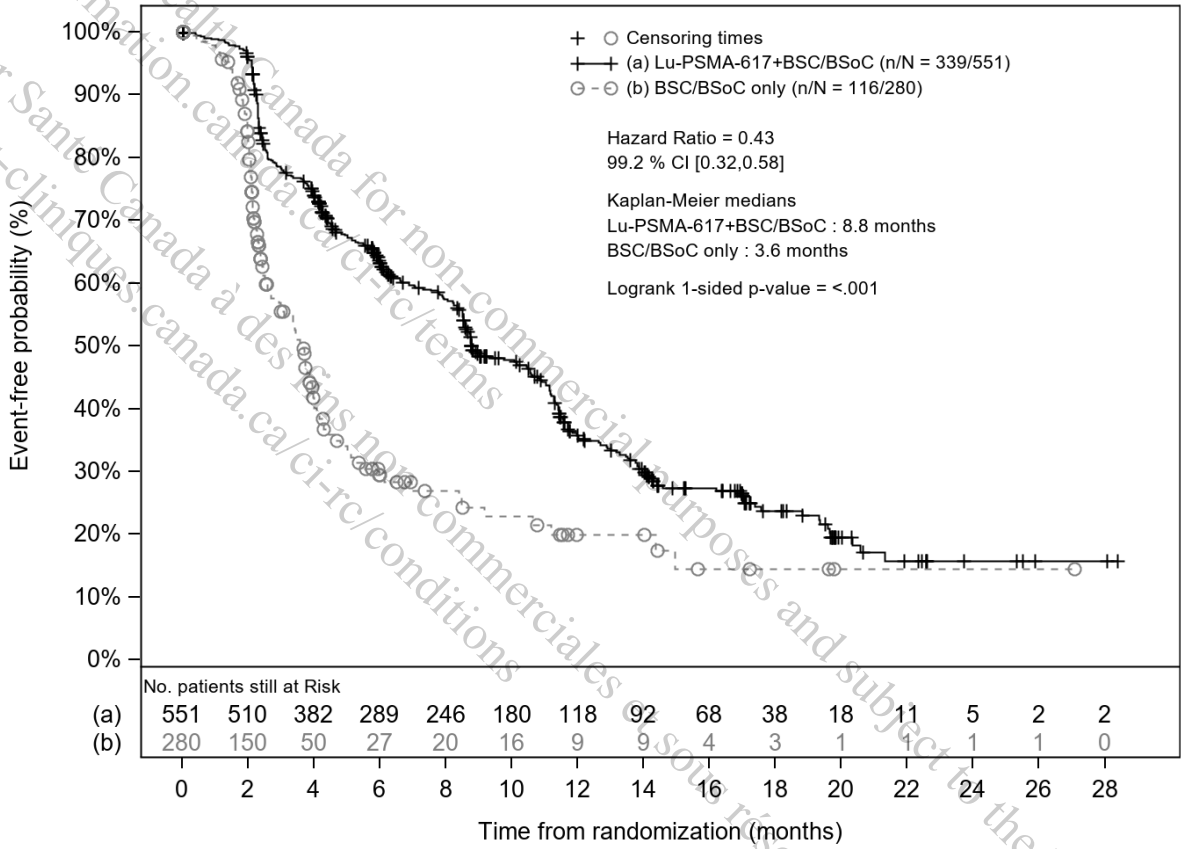
Source: [Study PSMA-617-01-Table 14.2.2.1]

3.2.1.1.1 Analysis of rPFS based on the FAS

In addition to the primary analysis of rPFS based on the PFS-FAS, an analysis of rPFS was also conducted based on the FAS. Similar results were observed to those based on the PFS-FAS, with a statistically significant improvement in rPFS based on BICR per PCWG3 criteria for patients receiving ^{177}Lu-PSMA-617+BSC/BSoC vs. patients receiving BSC/BSoC only

(stratified log-rank test $p < 0.001$, one-sided). There was an estimated 57% risk reduction of radiographic disease progression or death in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared with the BSC/BSoC only arm (HR=0.43; 99.2% CI: 0.32, 0.58; Figure 3-3).

Figure 3-3 Kaplan-Meier plot of rPFS per blinded independent central review (FAS)



Stratified log-rank test and stratified Cox model using strata per IRT defined by LDH level, presence of liver metastases, ECOG score and inclusion of NAAD in BSC/BSoC at time of randomization.
n/N: number of events/number of patients in treatment arm.
Source: [SCE-Appendix 1-Figure 14.2.2.5]

Table 3-11 Analysis of rPFS per blinded independent central review using stratified log-rank test and Cox regression model (FAS)

	^{177}Lu-PSMA-617+BSC/BSoC N=551	BSC/BSoC only N=280
rPFS, n (%)		
Events (progression or death)	339 (61.5)	116 (41.4)
Radiographic progressions	240 (43.6)	66 (23.6)
Deaths	99 (18.0)	50 (17.9)
Censored	212 (38.5)	164 (58.6)
Ongoing without event	131 (23.8)	30 (10.7)
Event documented after 2 or more missed tumor assessments	69 (12.5)	58 (20.7)

	^{177}Lu-PSMA-617+BSC/BSoC N=551	BSC/BSoC only N=280
Adequate assessment not available [1]	12 (2.2)	76 (27.1)
Kaplan-Meier estimates (months)		
25th percentile [99.2% CI]	3.9 [2.6, 4.4]	2.1 [2.0, 2.3]
Median rPFS [99.2% CI]	8.8 [8.3, 11.0]	3.6 [2.5, 4.1]
75th percentile [99.2% CI]	17.1 [13.8, 20.6]	8.5 [4.6, NE]
rPFS rates (%)		
3 months (SE) [99.2% CI]	78.4 (1.80) [73.1, 82.7]	55.5 (3.92) [44.5, 65.1]
6 months (SE) [99.2% CI]	63.5 (2.14) [57.6, 68.9]	29.4 (4.00) [19.3, 40.2]
12 months (SE) [99.2% CI]	35.8 (2.35) [29.6, 42.0]	19.9 (4.04) [10.5, 31.4]
HR (stratified Cox PH model)	0.43	
99.2% CI [2],[3]	[0.32, 0.58]	
Stratified Log-rank Test one-sided p-value	< 0.001	
Follow-up time (months) [4]		
Median [95% CI]	14.3 [13.9, 16.4]	2.6 [2.3, 4.0]
Minimum-Maximum	0.0 – 28.4	0.0 – 27.1

[1] Patients censored without adequate post-baseline evaluations or adequate baseline assessment.

[2] Hazard Ratio of ^{177}Lu-PSMA-617+BSC/BSoC vs. BSC/BSoC only.

[3] Both Cox PH model and Log-rank test are stratified for LDH (≤ 260 IU/L vs. > 260 IU/L); presence of liver metastases (yes vs. no); ECOG score (0 or 1 vs. 2); and inclusion of NAAD in BSC/BSoC at time of randomization (yes vs no). IRT data for stratification are used.

[4] Follow-up time = (Date of event or censoring - randomization date + 1)/30.4375 (months) censoring for death or radiographic progression.

Source: [SCE-Appendix 1-Table 14.2.2.19]

3.2.1.1.2 Withdrawal of consent to BSC/BSoC treatment

Overall, 49 patients (25.0%) in the BSC/BSoC only arm of the PFS-FAS (patients randomized on or after 05-Mar-2019) withdrew consent to BSC/BSoC treatment. Radiographic progression or death information was available for 15 patients (30.6%) (one patient had radiographic progression (2.0%) and 14 patients died (28.6%)), and 34 patients (69.4%) were censored. Of those 34 patients, 2 patients (4.1%) remained on study without an event as of the cut-off date, 8 patients (16.3%) had an event documented after 2 or more missed tumor assessments, and 24 patients (49.0%) were censored without adequate post-baseline evaluations or adequate baseline assessment [SCE-Appendix 1-Table 14.2.2.22].

As expected, withdrawal of consent to BSC/BSoC treatment (33 patients; 39.3%) and censoring (25 patients; 75.8%) were higher for the 84 patients in the FAS randomized to BSC/BSoC only prior to 05-Mar-2019 [SCE-Appendix 1-Table 14.2.2.21] compared with overall patients in the PFS-FAS [SCE-Appendix 1-Table 14.2.2.22]. Results for the FAS are presented in [SCE-Appendix 1-Table 14.2.2.23].

Results of analyses to assess sensitivity of rPFS to censoring due to drop-outs were consistent with the primary analyses of rPFS, and are described in detail in Section 3.2.1.1.3 and Table 3-15. The initial high drop-out rate had no impact on either the interpretation or the robustness of the primary rPFS results.

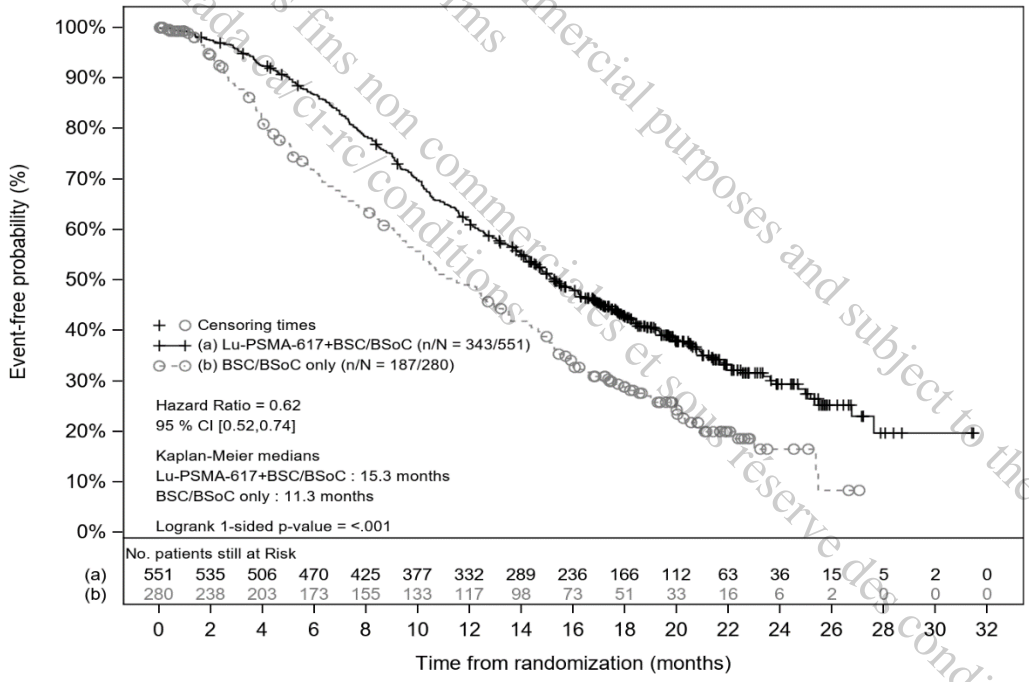
3.2.1.1.3 Analysis of rPFS based on the number of cycles of ^{177}Lu-PSMA-617

In addition, rPFS was analyzed in the ^{177}Lu-PSMA-617 + BSC/BSoC arm of the FAS safety analysis set by number of ^{177}Lu-PSMA-617 cycles. Median rPFS for patients who received 4 cycles of ^{177}Lu-PSMA-617 was 6.4 months (95% CI: 4.3, 7.9), and median rPFS for patients who received 5-6 cycles of ^{177}Lu-PSMA-617 was 13.8 months (95% CI: 12.2, 17.0) [SCE-Appendix 1-Table 14.2.2.20].

3.2.1.2 Overall survival: primary analysis based on the FAS

The study met its primary objective, demonstrating a statistically significant improvement in OS for patients receiving ^{177}Lu-PSMA-617+BSC/BSoC compared to patients receiving BSC/BSoC only (stratified log-rank test $p < 0.001$, one-sided). There was an estimated 38% risk reduction of death in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared with the BSC/BSoC only arm (HR=0.62; 95% CI: 0.52, 0.74; Figure 3-4).

Figure 3-4 Kaplan-Meier plot of OS (FAS)



Stratified log-rank test and stratified Cox model using strata per IRT defined by LDH level, presence of liver metastases, ECOG score and inclusion of NAAD in BSC/BSoC at time of randomization.
n/N: number of events/number of patients in treatment arm.
Source: [Study PSMA-617-01-Figure 14.2.1.1.1]

There were 343 deaths (62.3%) in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 187 deaths (66.8%) in the BSC/BSoC only arm. The median OS was prolonged by 4.0 months, from 11.3 months (95% CI: 9.8, 13.5) in the BSC/BSoC only arm to 15.3 months (95% CI: 14.2, 16.9) in the ^{177}Lu-PSMA-617+BSC/BSoC arm (Table 3-12).

The median follow-up times for OS in the FAS were similar between the treatment arms (20.3 months [95% CI: 19.8, 21.0] vs. 19.8 months [95% CI: 18.3, 20.8] in the ^{177}Lu-PSMA-

617+BSC/BSoC and the BSC/BSoC only arms, respectively). The estimated OS rates at 12 months were 61.7% vs. 49.0%, in the ^{177}Lu-PSMA-617+BSC/BSoC and the BSC/BSoC only arms, respectively (Table 3-12).

The Kaplan-Meier curves for OS diverged after approximately 2 months, remaining higher during the entire follow-up period for the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. the BSC/BSoC arm, indicating an early and sustained advantage for ^{177}Lu-PSMA-617 therapy (Figure 3-4).

The censoring rate for OS differed between the treatment arms (37.7% vs. 33.2%); this appeared to be mainly due to 1) a greater percentage of patients who were alive in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared with the BSC/BSoC only arm, and 2) fewer patients who withdrew consent in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared with the BSC/BSoC only arm (Table 3-11).

For results of analyses to assess sensitivity of OS to censoring due to drop-outs, see Section 3.2.1.3.3.

Table 3-12 Analysis of OS using stratified log-rank test and Cox regression model (FAS)

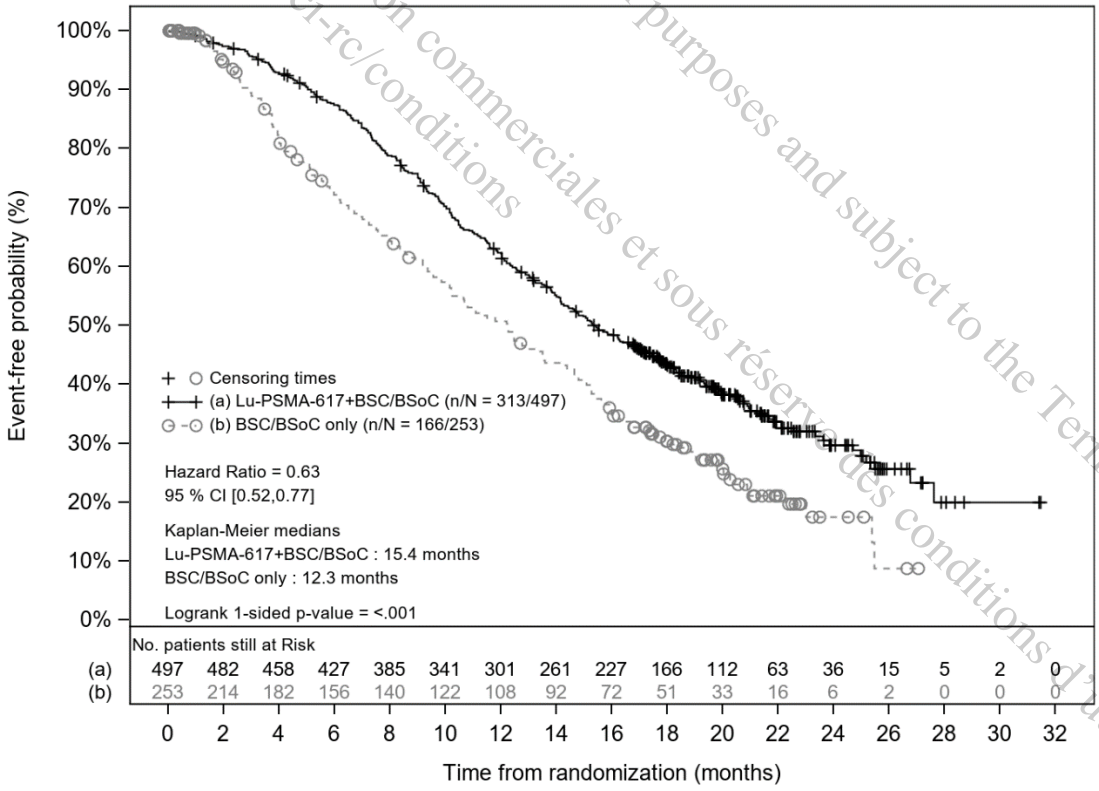
	^{177}Lu-PSMA-617+ BSC/BSoC N=551	BSC/BSoC only N=280
OS, n (%)		
Deaths	343 (62.3)	187 (66.8)
Censored	208 (37.7)	93 (33.2)
Reasons censored, n (%)		
Alive [1]	189 (34.3)	55 (19.6)
Lost to follow-up [2]	4 (0.7)	5 (1.8)
Withdrew consent [3]	15 (2.7)	33 (11.8)
Kaplan-Meier estimates (months)		
25th percentile [95% CI]	9.0 [7.9, 9.7]	5.1 [4.2, 6.3]
Median OS [95% CI]	15.3 [14.2, 16.9]	11.3 [9.8, 13.5]
75th percentile [95% CI]	26.8 [23.9, NE]	19.8 [17.3, 23.0]
OS rates (%)		
6 months (SE) [95% CI]	86.6 (1.46) [83.5, 89.2]	71.5 (2.86) [65.5, 76.7]
12 months (SE) [95% CI]	61.7 (2.09) [57.5, 65.6]	49.0 (3.21) [42.6, 55.1]
18 months (SE) [95% CI]	43.0 (2.18) [38.7, 47.2]	28.8 (2.98) [23.1, 34.7]
Hazard Ratio (Stratified Cox PH model) [4] [5]	0.62	
95% CI	[0.52, 0.74]	
Stratified Log-rank Test one-sided p-value [5]	<0.001	
Follow-up time (months) [6]		
Median [95% CI]	20.3 [19.8, 21.0]	19.8 [18.3, 20.8]
Minimum-Maximum	0.0 - 31.5	0.0 - 27.1

[1] Patients without event and still on study at data cut-off date.
[2] Patients who discontinued the study for reasons other than withdrew consent.
[3] Patients who withdrew consent from the study.
[4] Hazard Ratio of ^{177}Lu-PSMA-617+BSC/BSoC vs. BSC/BSoC only.
[5] Both Cox PH model and Log-rank test are stratified for LDH (≤ 260 IU/L vs. > 260 IU/L); presence of liver metastases (yes vs. no); ECOG score (0 or 1 vs. 2); and inclusion of NAAD in best supportive/standard of care at time of randomization (yes vs no). IRT data for stratification are used.
[6] Follow-up time = (Date of event or censoring - randomization date + 1)/30.4375 (months) censoring for deaths.
Source: [Study PSMA-617-01-Table 14.2.1.1]

3.2.1.2.1 Analysis of OS based on first 750 patients randomized

In addition to the primary analysis of OS, a supplementary OS analysis was conducted based on the first 750 patients randomized in the FAS. The results were similar to those for the primary analysis of OS, with a statistically significant improvement in OS for patients receiving ^{177}Lu-PSMA-617+BSC/BSoC compared to patients receiving BSC/BSoC only (stratified log-rank test $p < 0.001$, one-sided). There was an estimated 37% risk reduction of death in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared with the BSC/BSoC only arm (HR=0.63; 95% CI: 0.52, 0.77; Figure 3-5 and Table 3-13).

Figure 3-5 Kaplan-Meier plot of OS: first 750 patients randomized (FAS)



Stratified log-rank test and stratified Cox model using strata per IRT defined by LDH level, presence of liver metastases, ECOG score and inclusion of NAAD in BSC/BSoC at time of randomization.
n/N: number of events/number of patients in treatment arm.
Source: [SCE-Appendix 1-Figure 14.2.1.1.3]

Table 3-13 Analysis of OS using stratified log-rank test and Cox regression model: first 750 patients randomized (FAS)

	^{177}Lu-PSMA-617+ BSC/BSoC N=497	BSC/BSoC only N=253
OS, n (%)		
Deaths	313 (63.0)	166 (65.6)
Censored	184 (37.0)	87 (34.4)
Reasons censored, n (%)		
Alive [1]	165 (33.2)	50 (19.8)
Lost to follow-up [2]	4 (0.8)	5 (2.0)
Withdrew consent [3]	15 (3.0)	32 (12.6)
Kaplan-Meier estimates (months)		
25th percentile [95% CI]	9.0 [7.9, 9.8]	5.3 [4.1, 6.7]
Median OS [95% CI]	15.4 [14.2, 17.1]	12.3 [10.1, 14.2]
75th percentile [95% CI]	26.8 [23.9, NE]	20.0 [17.5, 25.4]
OS rates (%)		
6 months (SE) [95% CI]	87.4 (1.50) [84.1, 90.0]	72.2 (3.01) [65.8, 77.6]
12 months (SE) [95% CI]	62.2 (2.20) [57.7, 66.3]	50.7 (3.39) [43.9, 57.2]
18 months (SE) [95% CI]	43.5 (2.28) [39.0, 48.0]	30.4 (3.18) [24.3, 36.7]
Hazard Ratio (Stratified Cox PH model) [4] [5]	0.63	
95% CI	[0.52, 0.77]	
Stratified Log-rank Test one-sided p-value [5]	<0.001	
Follow-up time (months) [6]		
Median [95% CI]	20.7 [20.1, 21.5]	19.8 [18.7, 21.2]
Minimum-Maximum	0.0 - 31.5	0.0 - 27.1

[1] Patients without event and still on study at data cut-off date.
[2] Patients who discontinued the study for reasons other than withdrew consent.
[3] Patients who withdrew consent from the study.
[4] Hazard Ratio of ^{177}Lu-PSMA-617+BSC/BSoC vs. BSC/BSoC only.
[5] Both Cox PH model and Log-rank test are stratified for LDH (≤ 260 IU/L vs. > 260 IU/L); presence of liver metastases (yes vs. no); ECOG score (0 or 1 vs. 2); and inclusion of NAAD in best supportive/standard of care at time of randomization (yes vs no). IRT data for stratification are used.
[6] Follow-up time = (Date of event or censoring - randomization date + 1)/30.4375 (months) censoring for deaths.
Source: [SCE-Appendix 1-Table 14.2.1.11]

3.2.1.2.2 Analysis of OS based on PFS-FAS

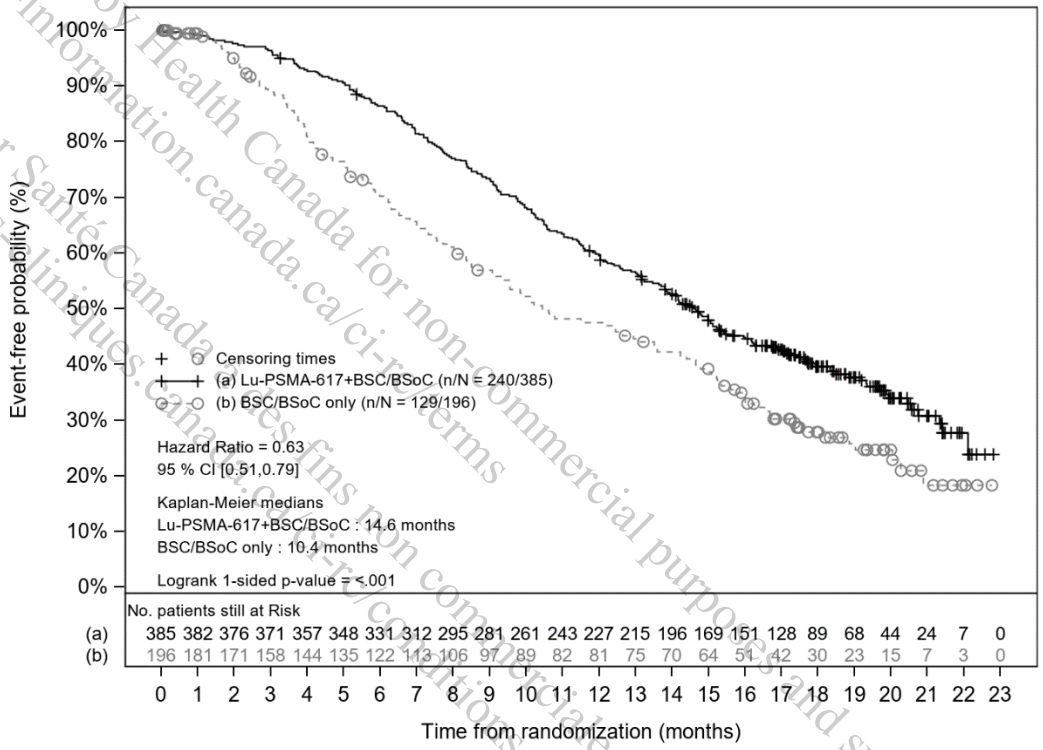
Analysis of OS based on the PFS-FAS (all patients randomized on or after 05-Mar-2019) using a stratified log-rank test and Cox regression model is presented in Figure 3-6 and Table 3-14. Results of this sensitivity analysis are consistent with and support the OS primary endpoint analysis based on the FAS and favor the ^{177}Lu-PSMA-617+BSC/BSoC arm.

The OS analysis on the PFS-FAS was in favor of ^{177}Lu-PSMA-617+BSC/BSoC with an estimated 37.0% risk reduction of death in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. the BSC/BSoC only arm (HR = 0.63; 95% CI, 0.51, 0.79).

There were 240 (62.3%) events in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 129 (65.8%) in the BSC/BSoC only arm. The median OS (95% CI) was 14.6 months (13.2, 16.0) vs.

10.4 months (8.5, 13.6), respectively. The estimated OS rates at 12 months were 59.6% vs. 47.6%, respectively.

Figure 3-6 Kaplan-Meier plot for overall survival (PFS-FAS)



Stratified log-rank test and stratified Cox model using strata per IRT defined by LDH level, presence of liver metastases, ECOG score and inclusion of NAAD in BSC/BSoC at time of randomization.
n/N: number of events/number of patients in treatment arm.
Source: [Study PSMA-617-01-Figure 14.2.1.1.2]

Table 3-14 Analysis of OS using stratified log-rank test and Cox regression model (PFS-FAS)

	^{177}Lu-PSMA-617+BSC/BSoC N=385	BSC/BSoC only N=196
Overall Survival (OS), n (%)		
Deaths	240 (62.3)	129 (65.8)
Censored	145 (37.7)	67 (34.2)
Reasons censored, n (%)		
Alive [1]	138 (35.8)	43 (21.9)
Lost to follow-up [2]	1 (0.3)	3 (1.5)
Withdrew consent [3]	6 (1.6)	21 (10.7)
Kaplan-Meier estimates (months)		
25th percentile [95% CI]	8.5 [7.6, 9.3]	5.1 [4.0, 6.3]
Median OS [95% CI]	14.6 [13.2, 16.0]	10.4 [8.5, 13.6]
75th percentile [95% CI]	22.1 [20.8, NE]	19.0 [16.5, NE]
OS rates (%)		

	^{177}Lu-PSMA-617+BSC/BSoC N=385	BSC/BSoC only N=196
6 months (SE) [95% CI]	86.5 (1.75) [82.6, 89.5]	70.2 (3.43) [62.9, 76.4]
12 months (SE) [95% CI]	59.6 (2.51) [54.5, 64.3]	47.6 (3.79) [40.0, 54.8]
18 months (SE) [95% CI]	39.7 (2.60) [34.6, 44.7]	27.9 (3.54) [21.2, 34.9]
Hazard Ratio (Stratified Cox PH model) [4] [5]	0.63	
95% CI	[0.51, 0.79]	
Stratified Log-rank Test one-sided p-value [5]	< 0.001	
Follow-up time (months)[6]		
Median [95% CI]	18.8 [18.0, 19.6]	18.3 [17.5, 19.6]
Minimum-Maximum	0.0 - 22.8	0.0 - 22.8

[1] Patients without event and still on study at data cut-off date.
[2] Patients who discontinued the study for reasons other than withdrew consent.
[3] Patients who withdrew consent from the study.
[4] Hazard Ratio of ^{177}Lu-PSMA-617+BSC/BSoC vs. BSC/BSoC only.
[5] Both Cox PH model and Log-rank test are stratified for LDH (≤ 260 IU/L vs. > 260 IU/L); presence of liver metastases (yes vs. no); ECOG score (0 or 1 vs. 2); and inclusion of NAAD in best supportive/standard of care at time of randomization (yes vs no). IRT data for stratification are used.
[6] Follow-up time = (Date of event or censoring - randomization date + 1)/30.4375 (months) censoring for deaths.
Source: [Study PSMA-617-01-Table 14.2.1.2]

3.2.1.2.3 Withdrawal of consent to BSC/BSoC treatment

Overall, 82 patients (29.3%) in the BSC/BSoC only arm of the FAS withdrew consent to BSC/BSoC treatment; death information was available for 48 patients (58.5%), 8 patients (9.8%) were alive, and 26 patients (31.7%) withdrew consent from the study as of the cut-off date [SCE-Appendix 1-Table 14.2.1.15]. Of the 82 patients who withdrew consent to BSC/BSoC treatment, following discontinuation of randomized treatment, 13 patients (15.9%) subsequently received one or more non-radiation cancer-related therapies [SCE-Appendix 1-Table 14.3.12.4], and 3 patients (3.7%) subsequently received one or more cancer-related radiotherapies [SCE-Appendix 1-Table 14.3.13.4].

Similar results were observed for patients randomized prior to 05-Mar-2019 in the FAS [SCE-Appendix 1-Table 14.2.1.13] and for patients in the PFS-FAS (randomized on or after 05-Mar-2019) [SCE-Appendix 1-Table 14.2.1.14]. Subsequent therapies following discontinuation of randomized treatment for these patients who withdrew consent to BSC/BSoC treatment, including non-radiation cancer-related therapies and cancer-related radiotherapies, are provided in [SCE-Appendix 1-Table 14.3.12.2, Table 14.3.13.2, Table 14.3.12.3, Table 14.3.13.3], respectively.

Results of analyses to assess sensitivity of OS to censoring due to drop-outs were consistent with the primary analyses of OS, and are described in detail in Section 3.2.1.3.3 and Table 3-15. The initial high drop-out rate had no impact on either the interpretation or the robustness of the primary OS results.

3.2.1.2.4 Analysis of OS based on the number of cycles of ^{177}Lu-PSMA-617

In addition, OS was analyzed in the ^{177}Lu-PSMA-617 + BSC/BSoC arm of the FAS safety analysis set by number of ^{177}Lu-PSMA-617 cycles. Median OS for patients who received 4 cycles of ^{177}Lu-PSMA-617 was 11.0 months (95% CI: 9.6, 12.6), and median OS for patients

who received 5-6 cycles of ^{177}Lu-PSMA-617 was 24.7 months (95% CI: 21.3, 27.6) [SCE-Appendix 1-Table 14.2.1.12].

3.2.1.3 Sensitivity analyses on the primary endpoints

The results of the sensitivity analyses reported in this section were consistent with, and supportive of, the primary analysis results for rPFS and OS.

3.2.1.3.1 Sensitivity analyses of rPFS per BICR

No formal statistical test of hypotheses was performed for these sensitivity analyses.

Sensitivity analyses were conducted as follows for the primary endpoint rPFS:

- Sensitivity analysis 1 [Study PSMA-617-01-Table 14.2.2.8]:
  - Includes events regardless of intervening missed assessments
  - Bone PDs were indicated per PCWG3 guidelines with modified rules for confirmation after Week 16
  - Included all radiographic PD and deaths captured in the study, including scans not centrally read that were captured on the lost to follow-up CRF page
- Sensitivity analysis 2 [Study PSMA-617-01-Table 14.2.2.9]: deaths occurring after start of a new anti-cancer therapy were censored at the start date of the new therapy.
- Sensitivity analysis 3 [Study PSMA-617-01-Table 14.2.2.10]: rPFS was defined from the date of first dose of randomized treatment.
- Sensitivity analysis 4: local investigator assessments were used instead of central reading [Study PSMA-617-01-Table 14.2.2.11].

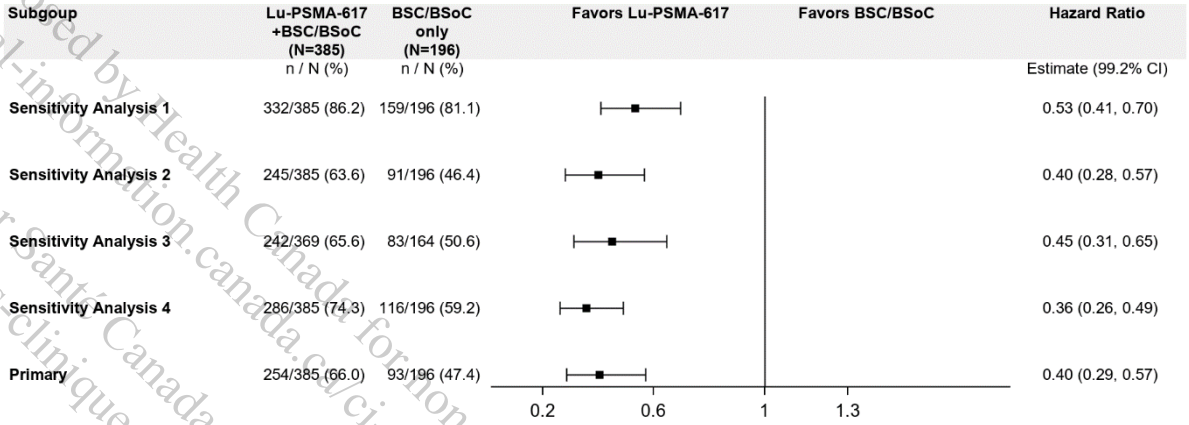
A forest plot of HR with 99.2% CI for the 4 rPFS sensitivity analyses and primary analysis is presented in Figure 3-7. All 4 sensitivity analyses support the rPFS primary endpoint analysis based on the PFS-FAS and favor the ^{177}Lu-PSMA-617+BSC/BSoC arm.

Further information on rPFS assessed by local investigator vs. BICR is presented in [Study PSMA-617-01-Table 14.2.2.16].

In addition, sensitivity analyses of rPFS based on BICR to assess the impact of the COVID-19 pandemic on the evaluation of this alternate primary endpoint was also performed using stratified log-rank test and Cox regression model [Study PSMA-617-01-Table 14.2.2.17 and Table 14.2.2.18]. Results were similar to those for the primary analysis, with similar estimated risk reductions of radiographic disease progression or death in favor of the ^{177}Lu-PSMA-617+BSC/BSoC arm.

Subgroup analyses of rPFS are provided in Section 3.3.

Figure 3-7 Sensitivity analyses of rPFS per blinded independent central review–forest plot of HR with 99.2% CI (PFS-FAS)



n/N: number of events/number of patients in treatment arm.
Vertical line shows no effect point.
Source: [Study PSMA-617-01-Figure 14.2.2.3]

3.2.1.3.2 Sensitivity analyses of OS

The sensitivity analysis of OS related to COVID-19 and using stratified log-rank test and Cox regression model is presented in [Study PSMA-617-01-Table 14.2.1.9]. Results were similar to the primary analysis, with an estimated 38% risk reduction of death in favor of ^{177}Lu-PSMA-617+BSC/BSoC arm.

Subgroup analyses of OS are provided in Section 3.3.

3.2.1.3.3 Analyses to assess sensitivity of rPFS and OS to censoring due to drop-outs

A panel of analyses were performed to assess sensitivity of rPFS and OS to censoring due to drop-outs. The censoring events of principal interest for analysis were "adequate assessment not available" for rPFS, and "lost to follow-up" and "withdrawal of consent" for OS. The four types of analyses that were performed used published and accepted methods (Lu et al 2015; Atkinson et al 2019).

The extreme case analysis considered all drop-outs in the ^{177}Lu-PSMA-617+BSC/BSoC arm as events. The two best case analyses imputed data for drop-outs in the control arm based on the HR in the 20% of patients with the longest survival either overall or in the BSC/BSoC only arm. The event risk inflation/deflation analysis was based on plausible ranges of increased and decreased risk considering possible treatment options after drop-out, with a treatment-specific inflation factor. The tipping-point analysis quantified the increase or decrease in the risk of event in patients dropping out of the ^{177}Lu-PSMA-617+BSC/BSoC arm or BSC/BSoC only arm that would make the primary analysis lose statistical significance.

The results of these sensitivity analyses were consistent with the primary analyses of rPFS and OS (Table 3-15).

Table 3-15 Sensitivity analyses of rPFS and OS assessing impact of censoring due to drop-outs

rPFS (PFS-FAS)	Scenario	HR (99.2% CI)
Analysis per protocol	Censored as it is	0.4 (0.29, 0.57)
Extreme case	The selected extreme case scenario	0.42 (0.3, 0.6)
Multiple imputation under best patients	Hazard in BSC/BSoC arm based on best 20% patients across both arms	0.77 (0.55, 1.07)
Multiple imputation under best BSC/BSoC patients	Hazard in BSC/BSoC arm based on best 20% BSC/BSoC patients	0.56 (0.4, 0.79)
Multiple imputation under non-informative censoring	Hazard remains unchanged after censoring	0.4 (0.29, 0.56)
Multiple imputation under informative censoring	Hazard decrease by 60% in BSC/BSoC arm after censoring*	0.54 (0.38, 0.77)
Tipping point 1: 99.2% CI above 1	Hazard decrease by 85% in BSC/BSoC arm after censoring*	0.71 (0.5, 1.01)
Tipping point 2: Extreme case	Hazard decrease by 11% in BSC/BSoC arm after censoring*	0.42 (0.3, 0.59)
OS (FAS)	**Scenario**	**HR (95% CI)**
Analysis per protocol	Censored as it is	0.62 (0.52, 0.74)
Extreme case	The selected extreme case scenario	0.66 (0.55, 0.79)
Multiple imputation under best patients	Hazard in BSC/BSoC arm based on best 20% patients across both arms	0.8 (0.67, 0.96)
Multiple imputation under best BSC/BSoC patients	Hazard in BSC/BSoC arm based on best 20% BSC/BSoC patients	0.76 (0.64, 0.91)
Multiple imputation under non-informative censoring	Hazard remains unchanged after censoring	0.63 (0.53, 0.76)
Multiple imputation under informative censoring	Hazard decrease by 38% in BSC/BSoC arm after censoring*	0.68 (0.56, 0.82)
Tipping point 1: largest upper 95% CI	Hazard decrease by 99% in BSC/BSoC arm after censoring*	0.84 (0.7, 1.00)
Tipping point 2: Extreme case	Hazard decrease by 27% in BSC/BSoC arm after censoring*	0.66 (0.55, 0.79)

*Risk of event remains unchanged after censoring in the investigational arm (^{177}Lu-PSMA-617+BSC/BSoC arm).
Source: [SCE-Appendix 1-Table 29, Table 30]

3.2.2 Secondary efficacy results

All 3 key secondary efficacy objectives were met:

- ORR was statistically significant in favor of the ^{177}Lu-PSMA-617+BSC/BSoC arm (stratified Wald's Chi-square test $p < 0.001$, two-sided), with ORR of 29.8% in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 1.7% in the BSC/BSoC only arm (odds ratio 24.99; 95% CI: 6.05, 103.24); median DoR in responders was 9.8 months (95% CI: 9.1, 11.7) in the ^{177}Lu-PSMA-617+BSC/BSoC arm (median DoR in the BSC/BSoC only arm was not reliable since only 1 of the 2 patients who responded had RECIST radiographic progression or death).

- DCR was also statistically significant in favor of the ^{177}Lu-PSMA-617+BSC/BSoC arm (stratified Wald's Chi-square test p < 0.001, two-sided), with DCR of 89.0% in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 66.7% in the BSC/BSoC only arm (odds ratio 5.79; 95% CI: 3.18, 10.55).
- Time to first SSE favored the ^{177}Lu-PSMA-617+BSC/BSoC arm with an estimated 50% risk reduction of symptomatic skeletal event or death that was statistically significant (HR= 0.50; 95% CI: 0.40, 0.62; stratified log-rank two-sided p-value: < 0.001)

3.2.2.1 Key secondary efficacy results

The 3 key secondary endpoints presented in this section (ORR, DCR, and time to first SSE) were controlled for multiplicity using the Hochberg closed test procedure and used the alpha level from the successful OS results (as specified in the SAP) for testing; see [Study PSMA-617-01-Table 14.2.4.3].

3.2.2.1.1 Overall response rate and disease control rate

ORR and DCR per BICR (RECIST v1.1) are presented in Table 3-16.

ORR was statistically significant in favor of the ^{177}Lu-PSMA-617+BSC/BSoC arm (stratified Wald's Chi-square test p < 0.001, two-sided). ORR was 29.8% in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 1.7% in the BSC/BSoC only arm, with an odds ratio of 24.99 (95% CI: 6.05, 103.24). Of note, the median DoR in responders was 9.8 months (95% CI: 9.1, 11.7) in the ^{177}Lu-PSMA-617+BSC/BSoC arm (median DoR in the BSC/BSoC only arm was not reliable since only 1 of the 2 patients who responded had RECIST radiographic progression or death). The ratio of the expected DoRs between the treatment arms in all patients with evaluable RECIST disease at baseline is shown in Table 3-16.

The DCR was also statistically significant in favor of the ^{177}Lu-PSMA-617+BSC/BSoC arm (stratified Wald's Chi-square test p < 0.001, two-sided). DCR was 89.0% in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 66.7% in the BSC/BSoC only arm, with an odds ratio of 5.79 (95% CI: 3.18, 10.55).

Table 3-16 Analyses of ORR, DCR, and DoR per blinded independent central review (Response evaluable analysis set)

	^{177}Lu-PSMA-617+BSC/BSoC N=319	BSC/BSoC only N=120
Best overall response (BOR), n (%)		
Complete Response (CR)	18 (5.6)	0
Partial Response (PR)	77 (24.1)	2 (1.7)
Stable Disease	68 (21.3)	30 (25.0)
Non-CR/Non-PD	121 (37.9)	48 (40.0)
Progressive Disease (PD)	33 (10.3)	35 (29.2)
Unknown	2 (0.6)	5 (4.2)
Overall Response Rate (ORR: CR+PR), n (%)	95 (29.8)	2 (1.7)
Odds Ratio [95% CI] [1]	24.99 [6.05, 103.24]	
Two-sided p-value [1]	< 0.001	
Disease Control Rate (DCR CR+PR+Stable Disease+Non-CR/ Non-PD > 6 weeks), n (%)	284 (89.0)	80 (66.7)

	^{177}Lu-PSMA-617+BSC/BSoC N=319	BSC/BSoC only N=120
Odds Ratio [95% CI] [1]	5.79 [3.18, 10.55]	
Two-sided p-value [1]	< 0.001	
Duration of Response (DoR) (months), n (%)		
n	95	2
Events (Progression or Death)	46 (48.4)	1 (50.0)
Radiographic progressions	29 (30.5)	1 (50.0)
Deaths	17 (17.9)	0
Censored	49 (51.6)	1 (50.0)
Ongoing without event	38 (40.0)	1 (50.0)
Event documented after 2 or more missed tumor assessments	11 (11.6)	0
Adequate assessment not available [2]	0	0
Kaplan-Meier estimates (months)		
25th percentile [95% CI]	6.9 [5.9, 8.3]	10.6 [NE, NE]
Median DoR [95% CI]	9.8 [9.1, 11.7]	10.6 [NE, NE]
75th percentile [95% CI]	18.0 [15.5, 18.0]	10.6 [NE, NE]
Mean DoR (months) [3]	12.5	10.6
SE DoR (months) [3]	0.009	0.000
EDoR (months) [3]	3.7	0.2
Ratio of EDoR and 95% CI [3]	21.05 [5.27, 84.05]	
Two-sided p-value [3]	< 0.001	

n: Total number of patients with a CR or PR.
[1] Odds Ratio of ^{177}Lu-PSMA-617+BSC/BSoC vs. BSC/BSoC only based on logistic regression model stratifying for the randomization stratification factors, LDH (≤ 260 IU/L vs. > 260 IU/L); presence of liver metastases (yes vs. no); ECOG score (0 or 1 vs. 2); and inclusion of NAAD in best supportive/standard of care at time of randomization (yes vs no). IRT data for stratification are used. P-value based on Wald's Chi-Square test.
[2] Patient censored without adequate post-baseline evaluations or adequate baseline assessment per RECIST v1.1.
[3] Analyzed using mixture distribution methodology (Ellis et al. 2008). DoR: duration of response in responding patients (months); SE: standard error; EDoR: expected duration of response (months) equals Mean DoR X Overall Response Rate.

Source: [Study PSMA-617-01-Table 14.2.3.1]

Analyses of ORR and DCR in patients with measurable disease at baseline

Results of analyses of ORR and DCR in patients with measurable disease at baseline (at least one target lesion per BICR) also favored the ^{177}Lu-PSMA-617+BSC/BSoC arm (stratified Wald's Chi-square test $p < 0.001$, two-sided). ORR was 51.1% in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 3.1% in the BSC/BSoC only arm, with an odds ratio of 37.61 (95% CI: 8.84, 159.99). DCR also favored the ^{177}Lu-PSMA-617+BSC/BSoC arm, with a DCR of 86.4% in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 50.0% in the BSC/BSoC only arm (odds ratio=10.03; 95% CI: 4.50, 22.34; stratified Wald's Chi-square test $p < 0.001$, two-sided). Median DoR in responders was 9.8 months (95% CI: 9.2, 11.7) in the ^{177}Lu-PSMA-617+BSC/BSoC arm (median DoR in the BSC/BSoC only arm was not reliable since only 1 of the 2 patients who responded had RECIST radiographic progression or death) [SCE-Appendix 1-Table 14.2.3.1.1].

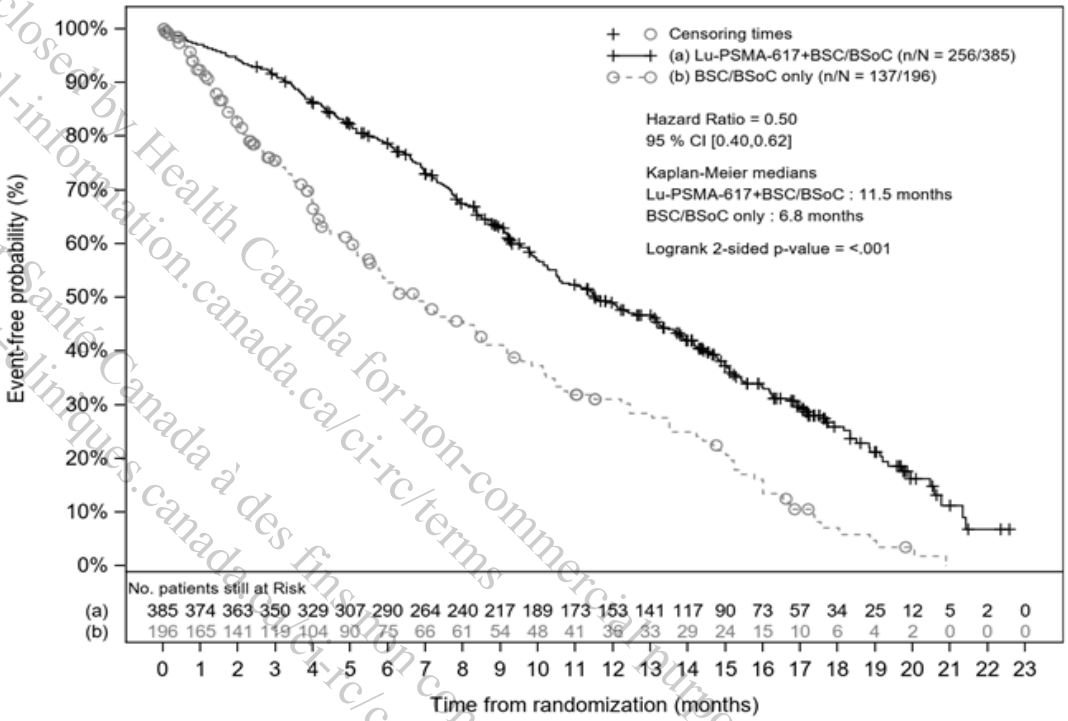
3.2.2.1.2 Time to first symptomatic skeletal event

Time to first SSE (defined as the time from randomization to 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)) is presented in Figure 3-8 and Table 3-17.

Time to first SSE was statistically significant in favor of the ^{177}Lu-PSMA-617+BSC/BSoC arm with an estimated 50% risk reduction of SSE or deaths (HR (95% CI): 0.50 (0.40, 0.62); stratified log-rank two-sided p-value: < 0.001). There were 256 events (66.5%; 60 SSE events and 196 deaths) in the ^{177}Lu-PSMA-617+BSC/BSoC arm and 137 events (69.9%; 34 SSE events and 103 deaths) in the BSC/BSoC only arm. The median time to first SSE was delayed by 4.7 months, from 6.8 (95% CI: 5.2, 8.5) months in the BSC/BSoC only arm to 11.5 months (95% CI: 10.3, 13.2) in the ^{177}Lu-PSMA-617+BSC/BSoC arm.

Delaying the time to first SSE from 6.8 to 11.5 months benefits patients by allowing continued ambulation and freedom of movement. A 50% reduction in risk of SSE or death is an important clinical improvement, especially in the context of providing patient benefit without the addition of the significant toxicity associated with other agents, such as cytotoxic chemotherapy (i.e. taxane- or, platinum-based regimen) or bone-seeking radiopharmaceuticals (i.e. Radium-223) that are often used in the mCRPC setting.

Figure 3-8 Kaplan-Meier plot of time to first SSE (PFS-FAS)



Stratified log-rank test and stratified Cox model using strata per IRT defined by LDH level, presence of liver metastases, ECOG score and inclusion of NAAD in BSC/BSoC at time of randomization.
n/N: number of events/number of patients in treatment arm.
Source: [Study PSMA-617-01-Figure 14.2.3.2]

Table 3-17 Analysis of time to first SSE (PFS-FAS)

	^{177}Lu-PSMA-617+BSC/BSoC N=385	**BSC/BSoC only N=196**
Time to first symptomatic skeletal event (SSE), n (%)		
Events (SSE or Death)	256 (66.5)	137 (69.9)
SSEs	60 (15.6)	34 (17.3)
Deaths	196 (50.9)	103 (52.6)
Censored	129 (33.5)	59 (30.1)
Kaplan-Meier estimates (months)		
25th percentile [95% CI]	6.7 [5.7, 7.6]	3.1 [2.0, 3.9]
Median time to first SSE [95% CI]	11.5 [10.3, 13.2]	6.8 [5.2, 8.5]
75th percentile [95% CI]	18.3 [16.9, 19.4]	13.6 [10.8, 15.3]
First SSE rates (%)		
3 months (SE) [95% CI]	91.4 (1.43) [88.1, 93.8]	75.5 (3.26) [68.4, 81.2]
6 months (SE) [95% CI]	78.7 (2.10) [74.3, 82.5]	52.8 (3.98) [44.7, 60.3]
12 months (SE) [95% CI]	49.0 (2.67) [43.7, 54.1]	31.0 (3.90) [23.6, 38.7]
Hazard Ratio (Stratified Cox PH model) [1] [2]	0.50	
95% CI	[0.40, 0.62]	
Stratified Log-rank Test two-sided p-value	< 0.001	
Follow-up time (months) [3]		

	^{177}Lu-PSMA-617+BSC/BSoC N=385	BSC/BSoC only N=196
Median [95% CI]	17.0 [15.9, 17.3]	16.9 [11.5, NE]
Minimum-Maximum	0.0 - 22.6	0.0 - 20.9

[1] Hazard Ratio of ^{177}Lu-PSMA-617+BSC/BSoC vs. BSC/BSoC only.
[2] Cox PH model is stratified for LDH (≤ 260 IU/L vs. > 260 IU/L); presence of liver metastases (yes vs. no); ECOG score (0 or 1 vs. 2); and inclusion of NAAD in best supportive/standard of care at time of randomization (yes vs no). IRT data for stratification are used
[3] Follow-up time = (Date of event or censoring - randomization date + 1)/30.4375 censoring for death or SSE.
Source: [Study PSMA-617-01-Table 14.2.4.1]

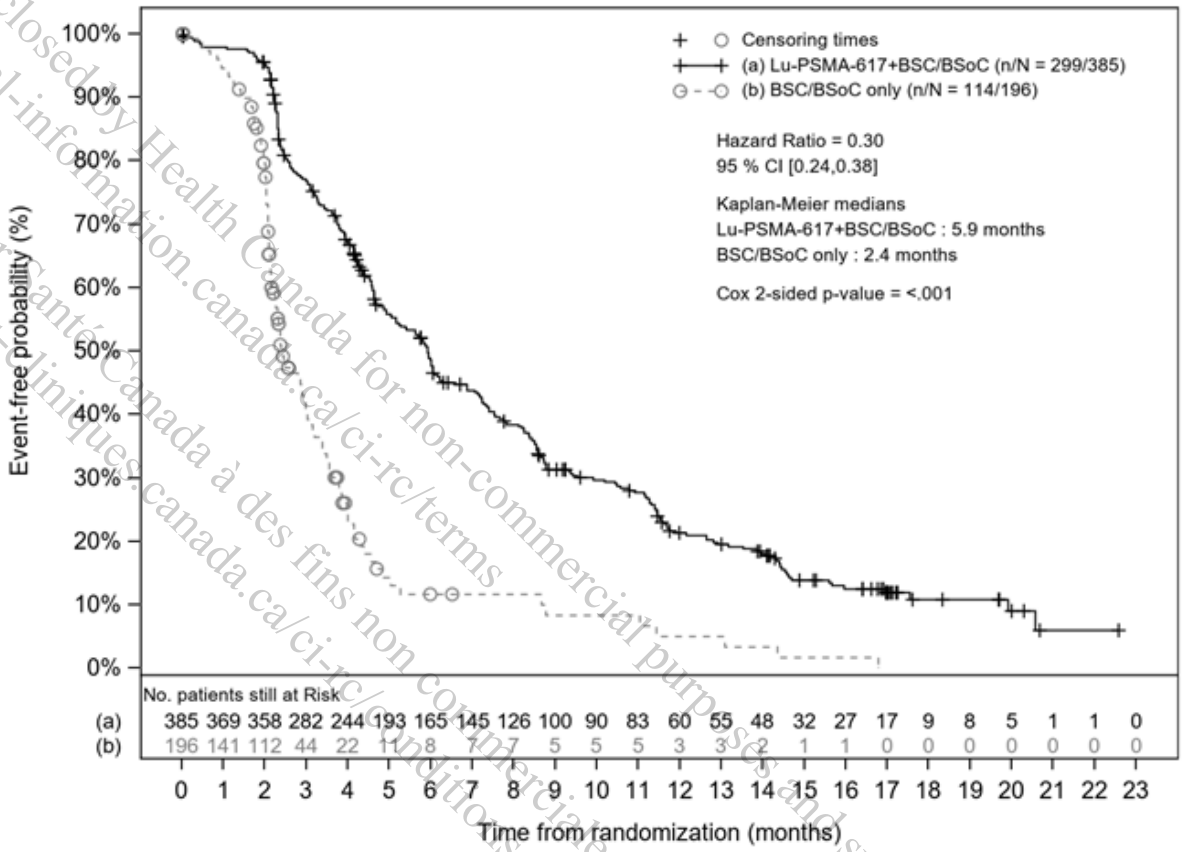
3.2.2.2 Additional secondary efficacy results

No multiplicity adjustment was performed for any of the additional secondary efficacy analyses, thus CIs and p-values should be considered nominal values.

3.2.2.2.1 Progression-free survival

PFS is presented in Figure 3-9 and Table 3-18. There was an estimated 70% risk reduction of radiographic disease progression based on BICR, clinical progression, PSA progression, or death (HR=0.30; 95% CI: 0.24, 0.38) in favor of the ^{177}Lu-PSMA-617+BSC/BSoC arm. Median PFS was 5.9 months (95% CI: 5.2, 6.6) in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 2.4 months (95% CI: 2.2, 3.0) in the BSC/BSoC only arm.

Figure 3-9 Kaplan-Meier plot of PFS (PFS-FAS)



n/N: number of events/number of patients in treatment arm
Source: [Study PSMA-617-01-Figure 14.2.3.4]

Table 3-18 Analysis of PFS (PFS-FAS)

	^{177}Lu-PSMA-617+ BSC/BSoC N=385	BSC/BSoC only N=196
Progression-free survival (PFS), n (%)		
Events (Progression or Death)	299 (77.7)	114 (58.2)
Radiographic progressions	104 (27.0)	41 (20.9)
Clinical progressions	46 (11.9)	32 (16.3)
In the best interest of the patient to discontinue treatment	25 (6.5)	17 (8.7)
Marked deterioration in ECOG performance status to ≥ grade 3	9 (2.3)	3 (1.5)
Immediate need for new anticancer treatment	8 (2.1)	5 (2.6)
Marked escalation in cancer-related pain	4 (1.0)	7 (3.6)
PSA progressions	124 (32.2)	25 (12.8)
Deaths	25 (6.5)	16 (8.2)
Censored	86 (22.3)	82 (41.8)
Ongoing without event	53 (13.8)	14 (7.1)
Event documented after 2 or more missed tumor assessments	28 (7.3)	33 (16.8)
Adequate assessment not available	5 (1.3)	35 (17.9)
Kaplan-Meier estimates (months)		
25th percentile [95% CI]	3.2 [2.6, 3.7]	2.0 [1.9, 2.1]
Median PFS [95% CI]	5.9 [5.2, 6.6]	2.4 [2.2, 3.0]
75th percentile [95% CI]	11.4 [9.9, 12.6]	4.0 [3.5, 4.6]
PFS rates (%)		
3 months (SE) [95% CI]	76.8 (2.19) [72.2, 80.8]	40.1 (4.39) [31.5, 48.6]
6 months (SE) [95% CI]	48.6 (2.65) [43.3, 53.7]	11.7 (3.37) [6.2, 19.2]
12 months (SE) [95% CI]	21.3 (2.28) [17.0, 25.9]	5.0 (2.62) [1.5, 11.9]
Hazard Ratio (Stratified Cox PH model) [1]	0.30	
95% CI	[0.24, 0.38]	
Two-sided p-value	< 0.001	
Follow-up time (months)		
Median [95% CI]	16.6 [14.9, 17.0]	3.9 [2.6, 6.0]
Minimum-Maximum	0.0 - 22.6	0.0 - 16.8

[1] Hazard Ratio of ^{177}Lu-PSMA-617+BSC/BSoC vs. BSC/BSoC only.
Source: [Study PSMA-617-01-Table 14.2.5]

Analysis of PFS based on the number of cycles of ^{177}Lu-PSMA-617

In addition, PFS was also analyzed in the ^{177}Lu-PSMA-617+BSC/BSoC arm of the FAS safety analysis set by number of ^{177}Lu-PSMA-617 cycles. Median PFS was 4.4 months (95% CI: 3.3, 4.7) for patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm who received 4 cycles, and 9.9 months (95% CI: 8.6, 11.3) for patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm who received 5-6 cycles [SCE-Appendix 1-Table 14.2.5.1].

3.2.2.3 Biochemical response

3.2.2.3.1 Prostate-specific antigen levels

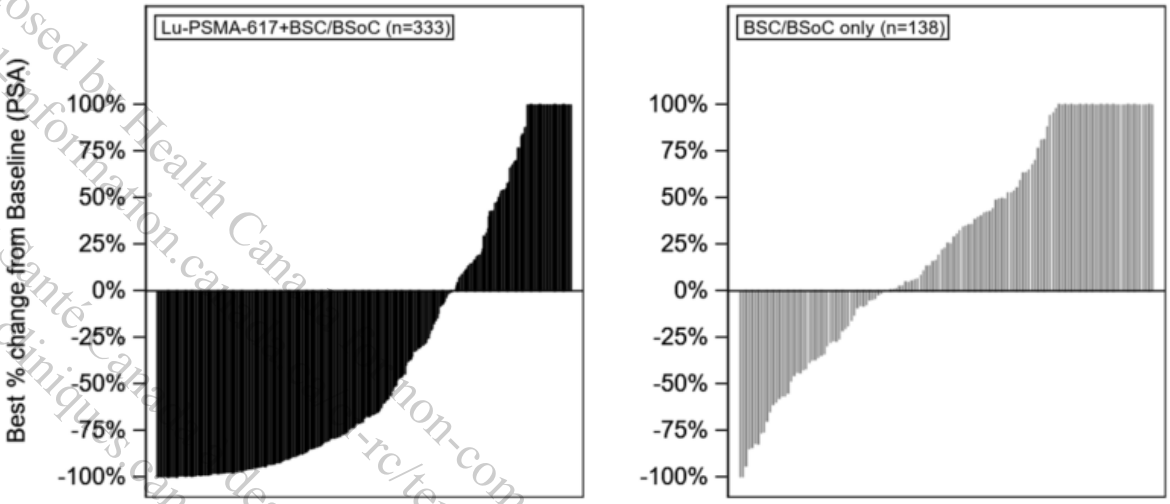
Best percentage change from baseline in PSA level is presented in Table 3-19 and Figure 3-10. Mean and median baseline PSA levels were similar in both arms, while best percentage change from baseline in PSA level favors the ^{177}Lu-PSMA-617+BSC/BSoC arm, with mean and median decreases of 20.9% and 68.6% respectively in this arm, vs. mean and median increases of 50.4% and 24.3% in the BSC/BSoC only arm.

Table 3-19 Best percentage change from baseline in PSA level (PFS-FAS)

	^{177}Lu-PSMA-617+BSC/BSoC N=385	**BSC/BSoC only N=196**
Baseline		
n	353	183
Mean (SD)	339.1 (727.7)	365.8 (798.4)
Median	95.4	91.9
Min, Max	0.9-6360.0	1.1-6600.0
Best % change from baseline [1]		
n	333	138
Mean (SD)	-20.9 (142.6)	50.4 (118.4)
Median	-68.6	24.3
Min, Max	-100-1923	-100-646

[1] Best % change from baseline is the maximum percent decrease at any time post-baseline, including only patients with a baseline value and at least one non-missing post-baseline value (scheduled and unscheduled).
Source: [Study PSMA-617-01-Table 14.2.6.1]

Figure 3-10 Waterfall plot of best percentage change from baseline in PSA level (PFS-FAS)



	Lu-PSMA-617+BSC/BSoC	BSC/BSoC
Decrease in best percentage change from baseline:	71.5%	35.5%
Increase/zero change in best percentage change from baseline:	28.5%	64.5%

Note: Increases greater than 100% have been truncated to 100% to display correctly the figure.
Patients for whom the best percentage change in PSA was not available were excluded from the analysis.
Source: [Study PSMA-617-01-Figure 14.2.5]

PSA response and PSA doubling time during study are presented in Table 3-20. PSA doubling time, proportions of patients with PSA responses (≥ 50% and ≥ 80% decrease from baseline), and duration of PSA response were in favor of the ^{177}Lu-PSMA-617+BSC/BSoC arm. PSA response as ≥ 50% decrease from baseline occurred in 177/385 (46.0%; 95% CI: 40.9, 51.1) patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 14/196 (7.1%; 95% CI: 4.0, 11.7) patients in the BSC/BSoC only arm. It should be noted that the proportion of patients evaluated for PSA doubling time was not balanced between the arms: 284/385 (73.8%) patients randomized to the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 74/196 (37.8%) patients randomized to the BSC/BSoC only arm.

Table 3-20 Analyses of PSA response and PSA doubling time during study (PFS-FAS)

	^{177}Lu-PSMA-617+BSC/BSoC N=385	**BSC/BSoC only N=196**
PSA doubling time (months) [1]		
n	284	74
Stable, non-increasing or decreasing	167 (58.8)	20 (27.0)
Increasing	117 (41.2)	54 (73.0)
Mean	20.1	12.4
[95% CI]	[11.5, 28.6]	[7.9, 16.9]
SD	46.6	16.4
Median	6.6	7.0

	^{177}Lu-PSMA-617+BSC/BSoC N=385	BSC/BSoC only N=196
Min-Max	1.2-344.8	1.8-97.3
PSA Response, n (%) [95% CI] [2]	177 (46.0) [40.9, 51.1]	14 (7.1) [4.0, 11.7]
Odds Ratio [95% CI]	11.19 [6.25, 20.04]	
Two-sided p-value	< 0.001	
PSA ≥ 80% decrease, n (%) [95% CI] [3]	127 (33.0) [28.3, 37.9]	4 (2.0) [0.6, 5.1]
Odds Ratio [95% CI]	23.6 [8.6, 65.1]	
Two-sided p-value	< 0.001	
Duration of PSA Response, n (%)		
n	177	14
Events	98 (55.4)	10 (71.4)
Censored	79 (44.6)	4 (28.6)
Kaplan-Meier estimates (months)		
25th percentile [95% CI]	4.8 [4.1, 5.6]	2.8 [1.4, 4.4]
Median duration of PSA response [95% CI]	8.9 [7.6, 10.7]	4.4 [2.6, 10.8]
75th percentile [95% CI]	14.1 [12.5, NE]	10.8 [3.9, NE]
Mean DoR (months)	12.0	7.7
SE DoR (months)	0.007	0.090
EDoR (months)	5.5	0.6
Ratio of EDoR and 95% CI	9.95 [5.89, 16.79]	
Two-sided p-value	< 0.001	

[1] PSA Doubling Time was derived for each patient as the natural log 2 divided by the sum of the fixed and random slopes of the random coefficient linear model between natural log of PSA and time of PSA measurement (in months). Patients with baseline and at least 3 consecutive post-baseline PSA values were included in the model.
[2] PSA response was defined as the proportion of patients who had a ≥ 50% decrease in PSA from baseline confirmed by a PSA measurement ≥ 4 weeks.
[3] PSA ≥ 80% decrease was defined as the proportion of patients who had a ≥ 80% decrease in PSA from baseline confirmed by a PSA measurement ≥ 4 weeks
Odds Ratio of ^{177}Lu-PSMA-617+BSC/BSoC vs. BSC/BSoC only: based on logistic regression model stratifying for the randomization stratification factors, LDH (≤ 260 IU/L vs. > 260 IU/L); presence of liver metastases (yes vs. no); ECOG score (0 or 1 vs. 2); and inclusion of NAAD in BSC/BSoC at time of randomization (yes vs no). IRT data for stratification are used. P-value based on Wald's Chi-Square test
DoR: analysis using mixture distribution methodology (Ellis et al 2008). DoR: duration of PSA response in responding patients (months); SE: standard error; EDoR: expected duration of PSA response (months) equals Mean DoR X PSA Response Rate
Source: [Study PSMA-617-01-Table 14.2.6.2]

3.2.2.3.2 Alkaline phosphatase levels

Best percentage change from baseline in ALP level is presented in Table 3-21. Mean and median baseline ALP levels were similar in both arms, while best percentage change from baseline in ALP level favors the ^{177}Lu-PSMA-617+BSC/BSoC arm, with mean and median decreases of 14.4% and 17.0% respectively in this arm vs. mean 0.6% increase and median 5.0% decrease respectively in the BSC/BSoC only arm.

Table 3-21 Best percentage change from baseline in ALP level (PFS-FAS)

	^{177}Lu-PSMA-617+ BSC/BSoC N=385	BSC/BSoC only N=196
Baseline		
n	383	195
Mean (SD)	163.4 (205.2)	150.1 (162.5)
Median	108.0	96.0
Min, Max	26-2524	34-1355
Best % change from baseline [1]		
n	372	172
Mean (SD)	-14.4 (46.3)	0.6 (33.8)
Median	-17.0	-5.0
Min, Max	-100-610	-78-132

[1] Best % change from baseline is the maximum percent decrease at any time post-baseline, including only patients with a baseline value and at least one non-missing post-baseline value (scheduled and unscheduled).
Source: [Study PSMA-617-01-Table 14.2.6.3]

3.2.2.3.3 Lactate dehydrogenase levels

Best percentage change from baseline in LDH level is presented in Table 3-22. Mean and median baseline LDH levels were similar in both arms, while best percentage change from baseline in LDH level favors the ^{177}Lu-PSMA-617+BSC/BSoC arm, with mean and median decreases of 23.1% and 23.3% respectively in this arm vs. mean and median decreases of 9.2% of 12.6% respectively in the BSC/BSoC only arm.

Table 3-22 Best percentage change from baseline in LDH level (PFS-FAS)

	^{177}Lu-PSMA-617+ BSC/BSoC N=385	BSC/BSoC only N=196
Baseline		
n	384	195
Mean (SD)	303.5 (326.3)	303.1 (267.8)
Median	230.5	232.0
Min, Max	119-5387	105-2693
Best % change from baseline [1]		
n	371	168
Mean (SD)	-23.1 (23.8)	-9.2 (28.2)
Median	-23.3	-12.6
Min, Max	-100-114	-100-148

[1] Best % change from baseline is the maximum percent decrease at any time post-baseline, including only patients with a baseline value and at least one non-missing post-baseline value (scheduled and unscheduled).
Source: [Study PSMA-617-01-Table 14.2.6.4]

3.2.2.4 Patient-reported outcomes

PRO results confirmed previous findings in prostate cancer where disease-specific measures, such as FACT-P tend to be more sensitive in capturing HRQoL, as well as showing a treatment difference. For PRO analyses, worsening also includes clinical progression or death. FACT-P consistently showed an estimated 46% risk reduction in worsening from baseline in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared to BSC/BSoC only arm across its many subscales and components. Specifically, median time to worsening of the FACT-P total score was delayed by 3.5 months in the ^{177}Lu-PSMA-617+BSC/BSoC arm, with a median time of 5.7 months (95% CI: 4.8, 6.6), compared to 2.2 months (95% CI: 1.8, 2.8) in the BSC/BSoC only arm.

Of note, by Cycle 3, approximately 84% of the patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm and 30% in the BSC/BSoC only arm had PRO data. By Cycle 5, the proportion of patients with data in the BSC/BSoC only arm had dropped to approximately 11%. Therefore, PRO analyses should be interpreted with caution due to the relatively lower proportion of patients with PRO data in the BSC/BSoC only arm and the differential with the ^{177}Lu-PSMA-617+BSC/BSoC arm, especially after Cycle 3. This is related to the relatively shorter period of time on study treatment in the BSC/BSoC only arm; see Section 3.1.7.

3.2.2.4.1 Functional Assessment of Cancer Therapy – Prostate

FACT-P total score

The FACT-P total score (range 0-156) consists of five subscales – a physical well-being, a social/family well-being, emotional well-being, a functional well-being and prostate cancer subscale. As the FACT-P is a prostate cancer-specific HRQoL measure, it is more sensitive to change compared to the EQ-5D-5L due to the range of magnitude. A higher FACT-P score (for all subscales and total scales) correlates with a better HRQoL.

Improvement (≥ 10 point increase) and worsening (≥ 10 point decrease) relative to baseline and time to worsening (earliest occurrence of a ≥ 10-point decrease relative to baseline, clinical progression or death) in FACT-P total score are presented in Figure 3-11 and [Study PSMA-617-01-Table 14.2.8.1.2].

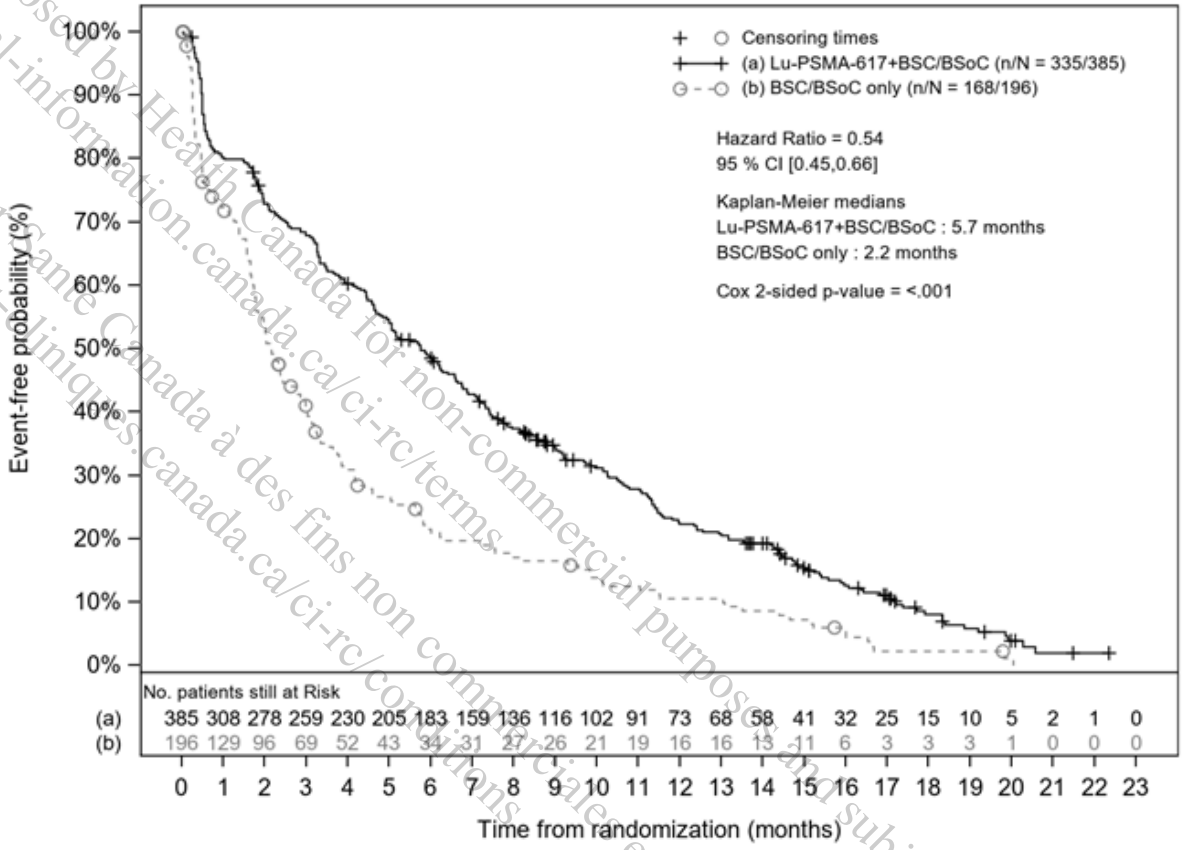
FACT-P total score and change from baseline by visits are presented in [Study PSMA-617-01-Table 14.2.8.1.1]. Mean (108.4 vs. 110.1) and median (109.4 vs. 109.7) FACT-P total score at baseline were similar in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. the BSC/BSoC only arm, respectively.

There was an estimated 46% reduction in risk of worsening, clinical progression or death (HR = 0.54; 95% CI: 0.45, 0.66; Cox two-sided p-value: < 0.001) in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared to the BSC/BSoC only arm (Figure 3-11).

Time to worsening was delayed by 3.5 months in the ^{177}Lu-PSMA-617+BSC/BSoC arm, with median time to deterioration of 5.7 months (95% CI: 4.8, 6.6) in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 2.2 months (95% CI: 1.8, 2.8) in the BSC/BSoC only arm [Study PSMA-617-01-Table 14.2.8.1.2].

Boxplot FACT-P total scores over time are presented in [Study PSMA-617-01-Figure 14.2.6.3].

Figure 3-11 Kaplan-Meier plot of time to worsening in FACT-P total score (PFS-FAS)



Stratified Cox model using strata per IRT defined by LDH level, presence of liver metastases, ECOG score and inclusion of NAAD in BSC/BSoC at time of randomization.
n/N: number of events/number of patients in treatment arm.
Source: [Study PSMA-617-01-Figure 14.2.7.3]

Analysis of FACT-P total score based on the number of cycles of ^{177}Lu-PSMA-617

In addition, FACT-P total score was analyzed in the ^{177}Lu-PSMA-617 + BSC/BSoC arm of the FAS safety analysis set by number of ^{177}Lu-PSMA-617 cycles. Median time to worsening in FACT-P total score for patients who received 4 cycles of ^{177}Lu-PSMA-617 was 5.4 months (95% CI: 4.2, 6.0); for patients who received 5-6 cycles, median time to worsening in FACT-P total score was 9.2 months (95% CI: 8.3, 11.1) [SCE-Appendix 1-Table 14.2.8.1.2.2].

FACT-P total score subscales

FACT-P physical well being

Improvement (≥ 3-point increase) and worsening (≥ 3-point decrease) relative to baseline and time to worsening (earliest occurrence of ≥ 3-point decrease relative to baseline, clinical

progression or death) in FACT-P PWB score are presented in [Study PSMA-617-01-Table 14.2.8.2].

There was an estimated 49% reduction in risk of worsening, clinical progression or death (HR = 0.51; 95% CI: 0.42, 0.62; Cox two-sided p-value: < 0.001) in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared to the BSC/BSoC only arm.

Time to worsening was delayed by 2.9 months in the ^{177}Lu-PSMA-617+BSC/BSoC arm, with median time to deterioration of 4.7 months (95% CI: 3.9, 6.1) in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 1.8 months (95% CI: 1.6, 2.3) in the BSC/BSoC only arm [Study PSMA-617-01-Table 14.2.8.2].

FACT-P prostate cancer subscale-pain-related scale

The FACT-P prostate cancer subscale-pain-related scale comprises 4 questions from the FACT-P, interrogating pain specifically. Improvement (≥ 2 point increase) and worsening (≥ 2 point decrease) relative to baseline and time to worsening in FACT-P PCS pain-related subscale (earliest occurrence of ≥ 2-point decrease relative to baseline, clinical progression or death) are presented in [Study PSMA-617-01-Table 14.2.8.7.2] and graphically presented in [Study PSMA-617-01-Figure 14.2.7.6].

There was an estimated 45% reduction in risk of worsening, clinical progression or death (HR = 0.55; 95% CI: 0.45, 0.66; Cox two-sided p-value: < 0.001) in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared to the BSC/BSoC only arm [Study PSMA-617-01-Figure 14.2.7.6].

Time to worsening was delayed by 2.8 months in the ^{177}Lu-PSMA-617+BSC/BSoC arm, with median time to deterioration of 4.6 months (95% CI: 3.4, 5.0) in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 1.8 months (95% CI: 1.6, 2.1) in the BSC/BSoC only arm [Study PSMA-617-01-Table 14.2.8.7.2].

FACT advanced prostate symptom index-8

The FACT advanced PSI-8 (range 0-32) covers 8 prostate cancer-specific symptom indices: 3 pain-related, one fatigue-related, one weight loss-related, 2 related to urinary difficulties, and one related to concerns about the condition getting worse.

Improvement (≥ 3 point increase) and worsening (≥ 3 point decrease) relative to baseline and time to worsening in FACT advanced PSI-8 (earliest occurrence of ≥ 3 point decrease relative to baseline, clinical progression or death) are presented in [Study PSMA-617-01-Table 14.2.8.8.2] and graphically presented in Figure 3-12.

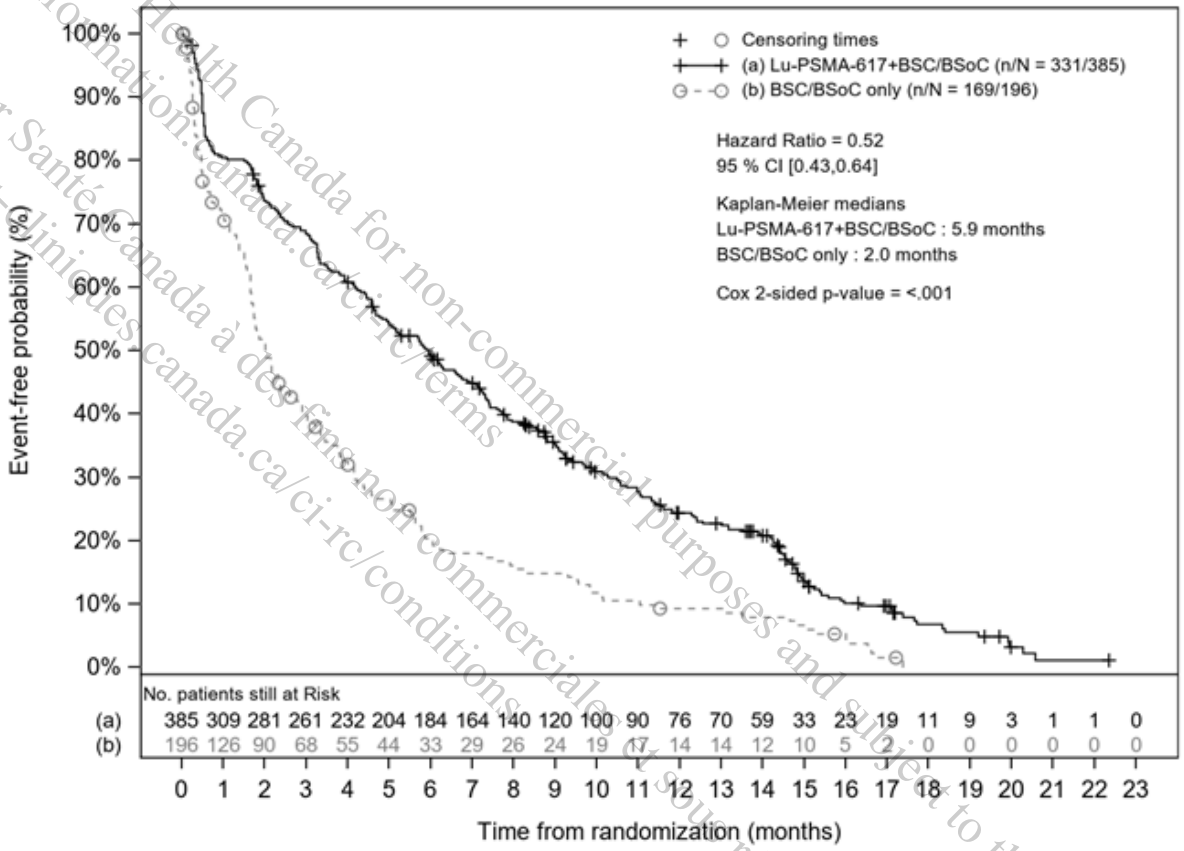
The FACT advanced PSI-8 results suggest overall consistency with the FACT-P total score.

There was an estimated 48% reduction in risk of worsening, clinical progression or death (HR = 0.52; 95% CI: 0.43, 0.64; Cox two-sided p-value: < 0.001) in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared to the BSC/BSoC only arm (Figure 3-12).

Time to worsening was delayed by 3.9 months in the ^{177}Lu-PSMA-617+BSC/BSoC arm, with median time to deterioration of 5.9 months (95% CI: 4.8, 6.9) in the ^{177}Lu-PSMA-

617+BSC/BSoC arm vs. 2.0 months (95% CI: 1.7, 2.6) in the BSC/BSoC only arm [Study PSMA-617-01-Table 14.2.8.8.2].

Figure 3-12 Kaplan-Meier plot of time to worsening in FACT advanced PSI-8 score (PFS-FAS)



Stratified Cox model using strata per IRT defined by LDH level, presence of liver metastases, ECOG score and inclusion of NAAD in BSC/BSoC at time of randomization.
n/N: number of events/number of patients in treatment arm.
Source: [Study PSMA-617-01-Figure 14.2.7.7]

FACT-P Trial Outcome Index

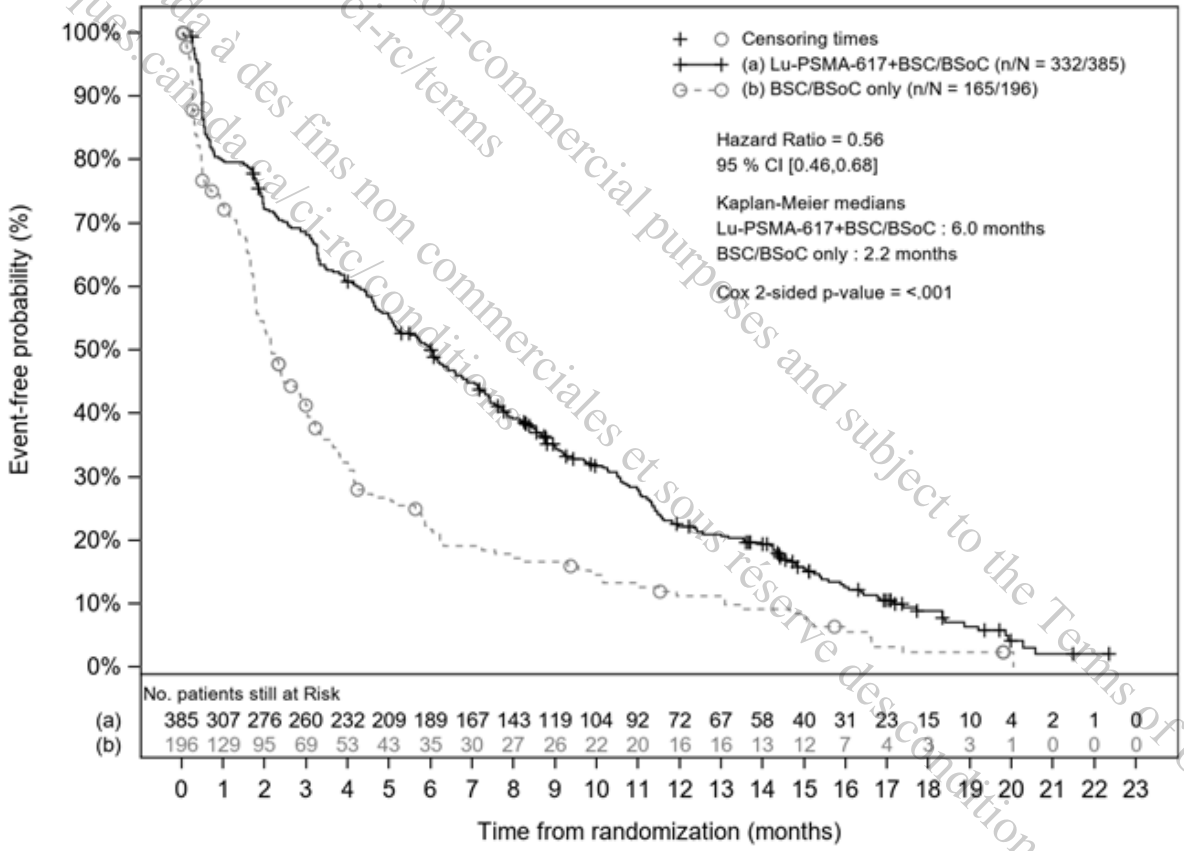
The FACT-P TOI (range 0-104) is based on the physical and functional well-being subscales of the FACT-G and the Prostate Cancer Subscale (PCS). Improvement (≥ 9 point increase) and worsening (≥ 9 point decrease) relative to baseline and time to worsening in trial outcome index (earliest occurrence of ≥ 9 point decrease relative to baseline, clinical progression or death) are presented in [Study PSMA-617-01-Table 14.2.8.9.2], and graphically presented in Figure 3-13.

There was an estimated 44% reduction in risk of worsening, clinical progression or death (HR = 0.56; 95% CI: 0.46, 0.68; Cox two-sided p-value: < 0.001) in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared to the BSC/BSoC only arm (Figure 3-13).

Time to worsening was delayed by 3.8 months in the ^{177}Lu-PSMA-617+BSC/BSoC arm, with median time to deterioration of 6.0 months (95% CI: 5.0, 6.9) in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 2.2 months (95% CI: 1.8, 2.9) in the BSC/BSoC only arm [Study PSMA-617-01-Table 14.2.8.9.2].

Boxplot of FACT-P TOI score over time are presented in [Study PSMA-617-01-Figure 14.2.6.5].

Figure 3-13 Kaplan-Meier plot of time to worsening in FACT-P TOI score (PFS-FAS)



Stratified Cox model using strata per IRT defined by LDH level, presence of liver metastases, ECOG score and inclusion of NAAD in BSC/BSoC at time of randomization.
n/N: number of events/number of patients in treatment arm.
Source: [Study PSMA-617-01-Figure 14.2.7.5]

FACT-G total score

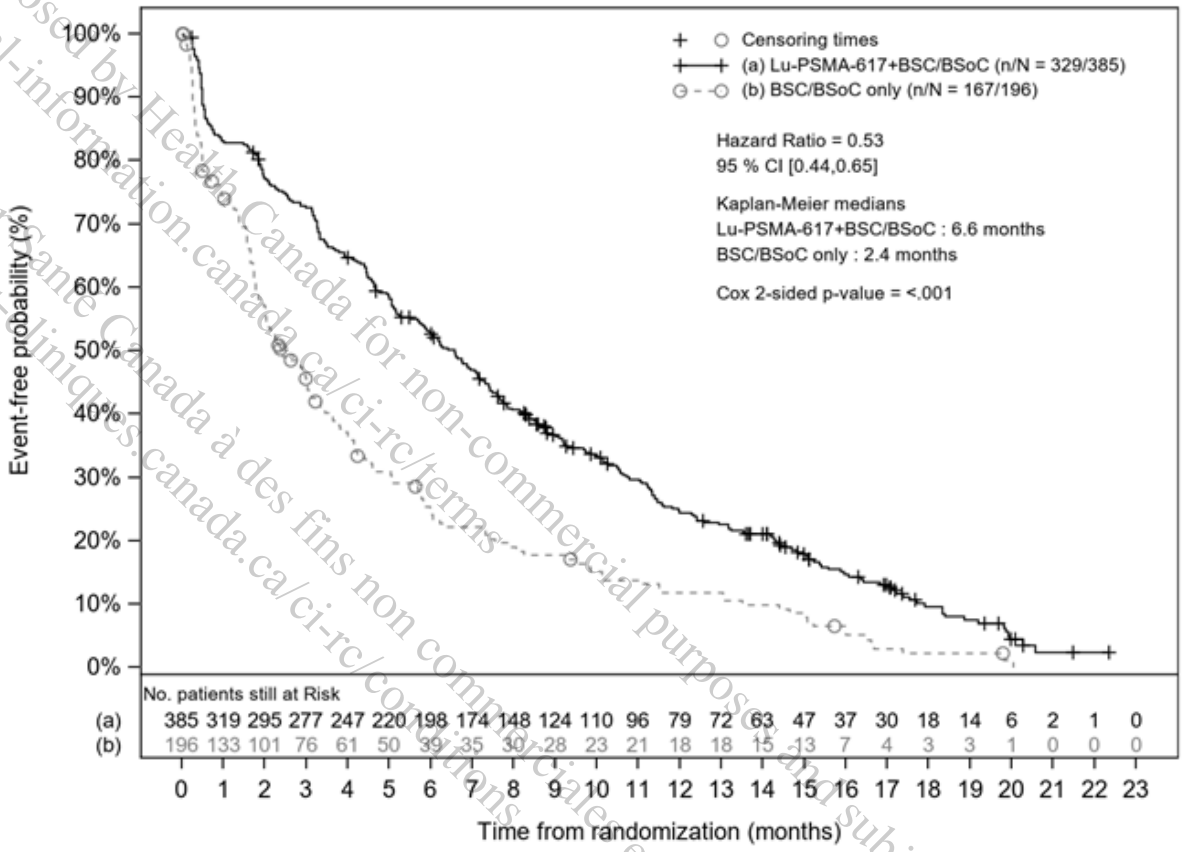
The FACT-G total score (range 0-108) consist of 4 subscales – a physical well-being, a social/family well-being, emotional well-being, and a functional well-being subscale.

Improvement (≥ 9 point increase) and worsening (≥ 9 point decrease) relative to baseline and time to worsening in FACT-G total score (earliest occurrence of ≥ 9 point decrease relative to baseline, clinical progression or death) is presented in [Study PSMA-617-01-Table 14.2.8.10.2] and graphically presented in Figure 3-14.

Consistent with both the FACT-P total score and FACT-P TOI, patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm are more stable than patients in the BSC/BSoC only arm, which can provide a positive indicator of ^{177}Lu-PSMA-617 treatment effect. This is especially encouraging as the FACT-G total score incorporates emotional and social/family well-being as well beyond physical well-being attributes. There was an estimated 47% reduction in risk of worsening, clinical progression or death (HR = 0.53; 95% CI: 0.44, 0.65; Cox two-sided p-value: < 0.001) in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared to the BSC/BSoC only arm (Figure 3-14).

Time to worsening was delayed by 4.2 months in the ^{177}Lu-PSMA-617+BSC/BSoC arm, with median time to deterioration of 6.6 months (95% CI: 5.5, 7.3) in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 2.4 months (95% CI: 2.0, 3.1) in the BSC/BSoC only arm [Study PSMA-617-01-Table 14.2.8.10.2].

Figure 3-14 Kaplan-Meier plot of time to worsening in FACT-G total score (PFS-FAS)



Stratified Cox model using strata per IRT defined by LDH level, presence of liver metastases, ECOG score and inclusion of NAAD in BSC/BSoC at time of randomization.
n/N: number of events/number of patients in treatment arm.
Source: [Study PSMA-617-01-Figure 14.2.7.4]

Analysis of FACT-G total score based on the number of cycles of ^{177}Lu-PSMA-617

In addition, FACT-G total score was analyzed in the ^{177}Lu-PSMA-617 + BSC/BSoC arm of the FAS safety analysis set by number of ^{177}Lu-PSMA-617 cycles. Median time to worsening in FACT-G total score for patients who received 4 cycles of ^{177}Lu-PSMA-617 was 5.6 months (95% CI: 4.6, 6.0); for patients who received 5-6 cycles, median time to worsening in FACT-G total score was 10.3 months (95% CI: 8.8, 11.4) [SCE-Appendix 1-Table 14.2.8.10.2.2].

3.2.2.4.2 Brief Pain Inventory - Short Form

The BPI-SF is a generic pain assessment tool used in research and practice for pain assessment in musculoskeletal conditions, with a higher the BPI-SF score correlating with worse pain. The BPI-SF measures "pain intensity" (range of 0-10 No pain to Worse pain), as well as how the pain "interferes" with daily activities (range 0-10 with 0=no interference to 10=completely interferes).

Time to worsening in Brief Pain Inventory – Short Form pain intensity scale

Pain intensity is an average of the 4 individual scales: worst pain intensity, least pain intensity, average pain intensity and pain right now.

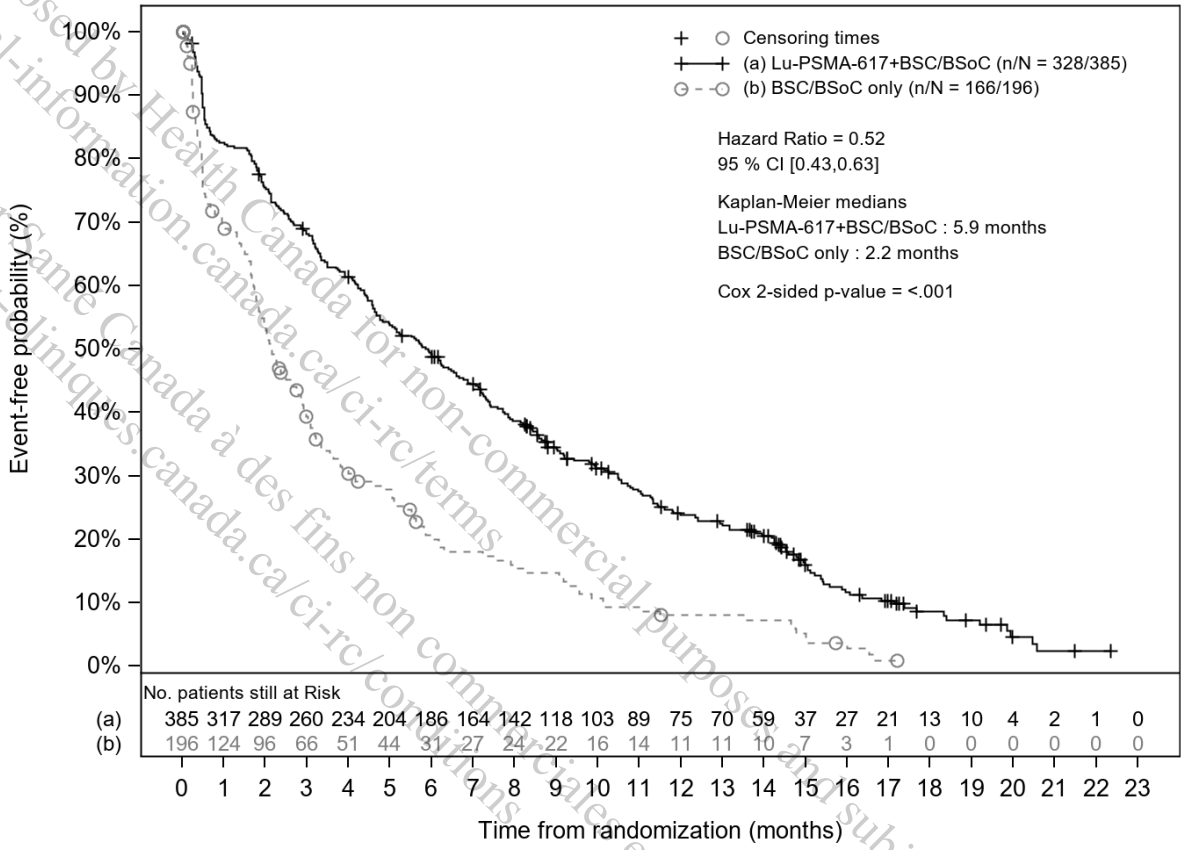
Time to worsening in BPI-SF pain intensity scale (earliest occurrence of ≥ 30% increase or ≥ 2 point increase relative to baseline, clinical progression or death) is presented in [Study PSMA-617-01-Table 14.2.9.1.2], and graphically presented in Figure 3-15. While on treatment, patients appear to be more stable with less pain in the ^{177}Lu-PSMA-617+BSC/BSoC arm, with the BSC/BSoC only arm experiencing a greater degree of variation.

Time to worsening was delayed by 3.7 months in the ^{177}Lu-PSMA-617+BSC/BSoC arm, with median time to deterioration of 5.9 months (95% CI: 4.8, 6.9) in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 2.2 months (95% CI: 1.8, 2.8) in the BSC/BSoC only arm [Study PSMA-617-01-Table 14.2.9.1.2].

There was an estimated 48% reduction in risk of worsening, clinical progression or death (HR = 0.52; 95% CI: 0.43, 0.63; Cox two-sided p-value: < 0.001) in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared to the BSC/BSoC only arm (Figure 3-15).

Boxplot of BPI-SF pain intensity scale over time are presented in [Study PSMA-617-01-Figure 14.2.6.6].

Figure 3-15 Kaplan-Meier plot of time to worsening in BPI-SF pain intensity scale (PFS-FAS)



Stratified Cox model using strata per IRT defined by LDH level, presence of liver metastases, ECOG score and inclusion of NAAD in BSC/BSoC at time of randomization.
n/N: number of events/number of patients in treatment arm.
Source: [Study PSMA-617-01-Figure 14.2.7.13]

Analysis of BPI-SF pain intensity based on the number of cycles of ^{177}Lu-PSMA-617

In addition, BPI-SF pain intensity was analyzed in the ^{177}Lu-PSMA-617 + BSC/BSoC arm of the FAS safety analysis set by number of ^{177}Lu-PSMA-617 cycles. Median time to worsening in BPI-SF pain intensity for patients who received 4 cycles of ^{177}Lu-PSMA-617 was 4.7 months (95% CI: 3.1, 5.7); for patients who received 5-6 cycles, median time to worsening in BPI-SF pain intensity was 9.4 months (95% CI: 8.5, 10.8) [SCE-Appendix 1-Table 14.2.9.1.2.2].

Time to improvement after worsening in Brief Pain Inventory – Short Form pain intensity scale

Time to improvement after worsening in BPI-SF pain intensity scale is presented in [Study PSMA-617-01-Table 14.2.9.1.3] and graphically presented in [Study PSMA-617-01-Figure 14.2.7.16]. Time to improvement after worsening was faster in the ^{177}Lu-PSMA-617+BSC/BSoC arm: the ratio of the expected time to improvement following worsening in all

randomized patients was 0.69 (95% CI: 0.54, 0.87, two-sided p<0.001). The expected time to improvement after worsening for all patients was 2.1 months in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared to 3.0 months in the BSC/BSoC only arm. The Kaplan-Meier median time to improvement after worsening in patients that had worsened relative to baseline was 2.8 months (95% CI: 1.9, 4.2) in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 4.2 months (95% CI: 2.8, 11.3) in the BSC/BSoC arm.

Time to worsening in Brief Pain Inventory – Short Form pain interference scale

Pain interference is an average of the scales of how the pain interferes with daily life. Time to worsening in BPI-SF pain interference scale (earliest occurrence of ≥ 30% increase or ≥ 2 point increase relative to baseline, clinical progression or death) is presented in [Study PSMA-617-01-Table 14.2.9.2.2], and graphically presented in Figure 3-16, with box plot of time to worsening in BPI-SF pain interference scale in [Study PSMA-617-01-Figure 14.2.6.7]. As with the pain intensity scale, the pain interference scale appears to show some variation in the BSC/BSoC only arm, indicating patients were more stable in the ^{177}Lu-PSMA-617+BSC/BSoC arm.

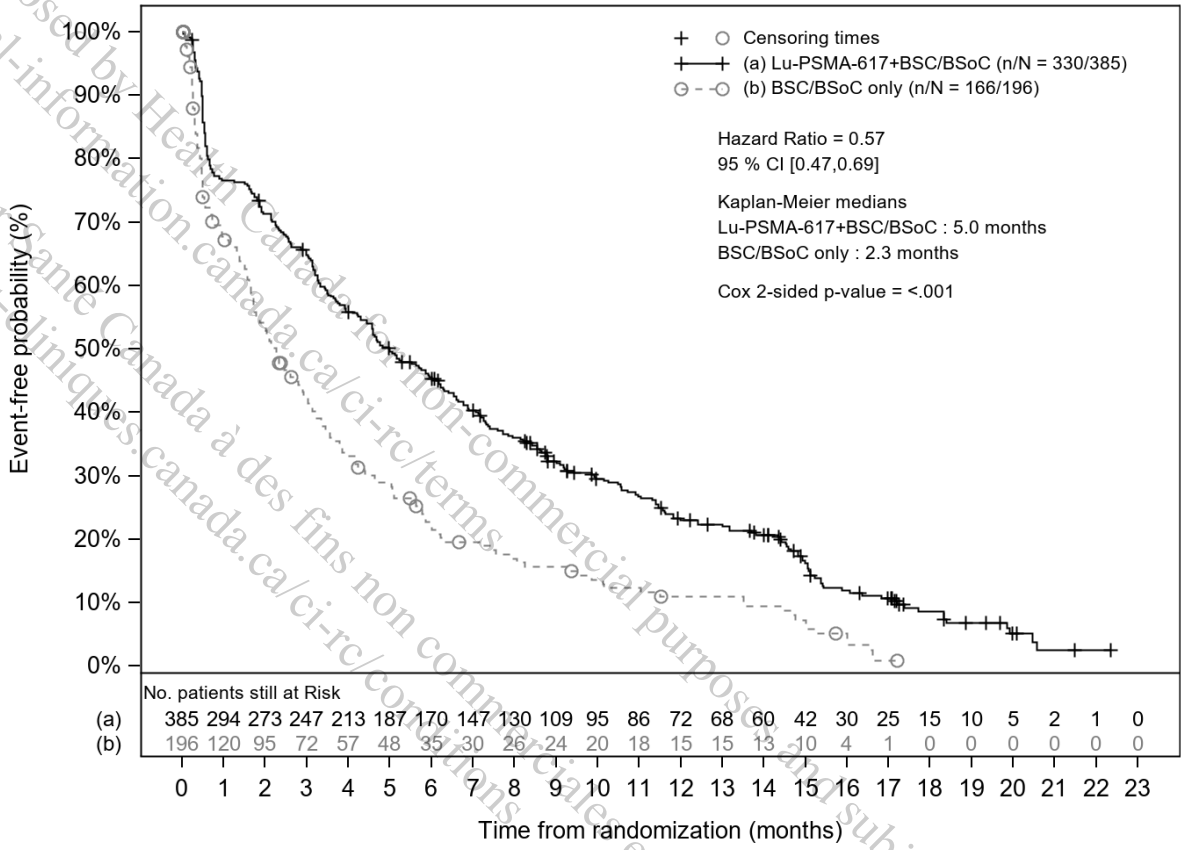
Time to worsening was delayed by 2.7 months in the ^{177}Lu-PSMA-617+BSC/BSoC arm, with median time to deterioration of 5.0 months (95% CI: 4.2, 6.1) in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 2.3 months (95% CI: 1.7, 2.9) in the BSC/BSoC only arm [Study PSMA-617-01-Table 14.2.9.2.2].

There was an estimated 43% reduction in risk of worsening, clinical progression or death (HR = 0.57; 95% CI: 0.47, 0.69; Cox two-sided p-value: < 0.001) in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared to the BSC/BSoC only arm (Figure 3-16).

Analysis of BPI-SF pain interference based on the number of cycles of ^{177}Lu-PSMA-617

In addition, BPI-SF pain interference was analyzed in the ^{177}Lu-PSMA-617 + BSC/BSoC arm of the FAS safety analysis set by number of ^{177}Lu-PSMA-617 cycles. Median time to worsening in BPI-SF pain interference for patients who received 4 cycles of ^{177}Lu-PSMA-617 was 5.6 months (95% CI: 4.4, 6.0); for patients who received 5-6 cycles, median time to worsening in BPI-SF pain interference was 8.8 months (95% CI: 7.4, 10.4) [SCE-Appendix 1-Table 14.2.9.2.2.2].

Figure 3-16 Kaplan-Meier plot of time to worsening in BPI-SF pain interference scale (PFS-FAS)



Stratified Cox model using strata per IRT defined by LDH level, presence of liver metastases, ECOG score and inclusion of NAAD in BSC/BSoC at time of randomization.
n/N: number of events/number of patients in treatment arm.
Source: [Study PSMA-617-01-Figure 14.2.7.14]

Time to improvement after worsening in Brief Pain Inventory – Short Form pain interference scale

Time to improvement after worsening in BPI-SF pain interference scale is presented in [Study PSMA-617-01-Table 14.2.9.2.3] and graphically presented in [Study PSMA-617-01-Figure 14.2.7.17]. The time to improvement after worsening favors the BSC/BSoC only arm: the ratio of expected time to improvement following worsening was 1.37 (95% CI: 1.08, 1.73; two-sided p<0.009). The expected time to improvement after worsening for all patients was 2.7 months in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared to 2.0 months in the BSC/BSoC only arm. The Kaplan-Meier median time to improvement after worsening among patients that worsened was 3.0 months (95% CI: 2.8, 4.4) in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 2.8 months (95% CI: 1.7, NE) in the BSC/BSoC only arm [Study PSMA-617-01-Table 14.2.9.2.3].

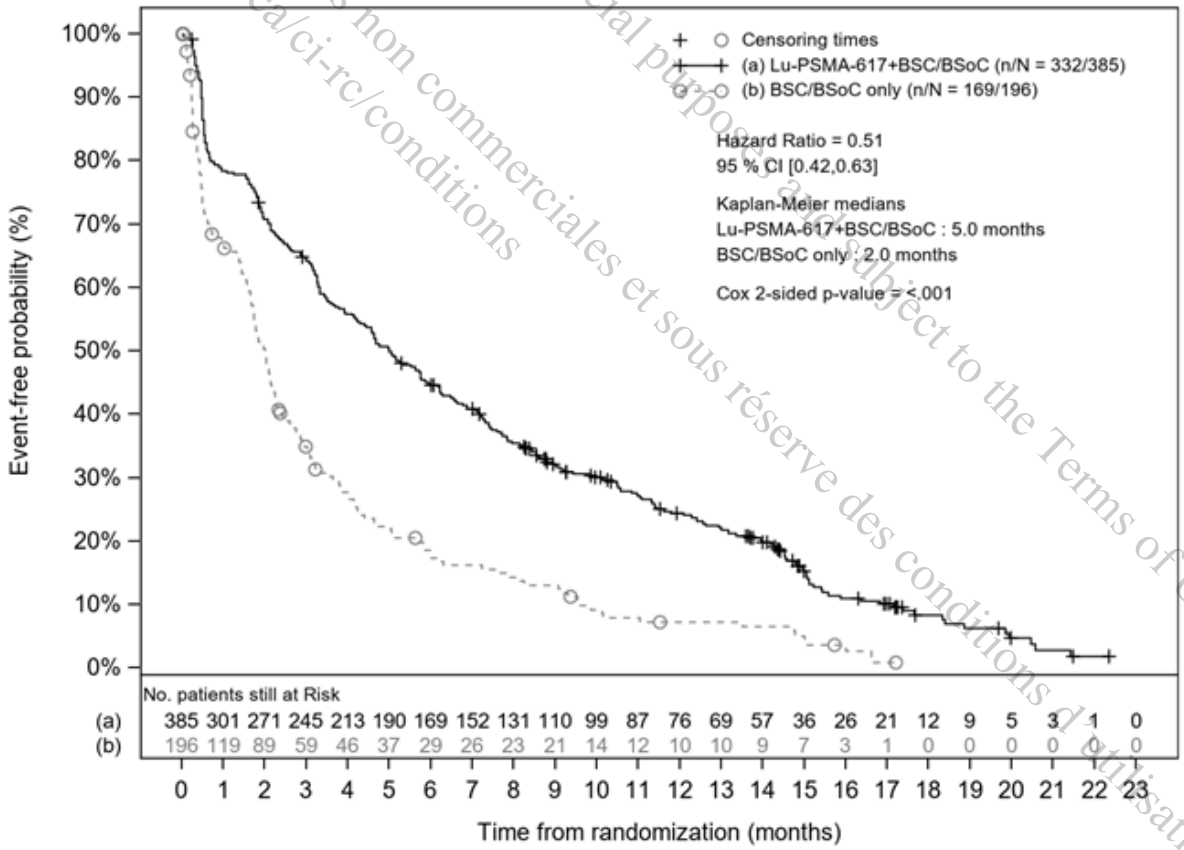
Time to worsening in Brief Pain Inventory – Short Form worst pain intensity scale (time to disease related pain)

Time to worsening in BPI-SF PIS (earliest occurrence of ≥ 30% increase or ≥ 2 point increase relative to baseline, clinical progression or death) is presented in [Study PSMA-617-01-Table 14.2.9.3.2], and graphically presented in Figure 3-17. Time to worsening was delayed by 3.0 months in the ^{177}Lu-PSMA-617+BSC/BSoC arm, with median time to deterioration of 5.0 months (95% CI: 4.2, 5.9) in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 2.0 months (95% CI: 1.7, 2.2) in the BSC/BSoC only arm [Study PSMA-617-01-Table 14.2.9.3.2].

There was an estimated 49% reduction in risk of worsening, clinical progression or death (HR = 0.51; 95% CI: 0.42, 0.63; Cox two-sided p-value: < 0.001) in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared to the BSC/BSoC only arm (Figure 3-17).

Box plot of BPI-SF worst pain intensity scale over time are presented in [Study PSMA-617-01-Figure 14.2.6.8].

Figure 3-17 Kaplan-Meier plot of time to worsening in BPI-SF worst pain intensity scale (PFS-FAS)



Stratified Cox model using strata per IRT defined by LDH level, presence of liver metastases, ECOG score and inclusion of NAAD in BSC/BSoC at time of randomization.
n/N: number of events/number of patients in treatment arm.
Source: [Study PSMA-617-01-Figure 14.2.7.15]

3.2.2.4.3 EuroQoL-5 Dimension-5 Level

The EQ-5D-5L questionnaire is not prostate cancer-specific; instead it is a generic measure, which can lead to ceiling effects in prostate cancer with limited sensitivity, particularly in earlier stages of disease progression.

EQ-5D-5L utility score and change from baseline by visit are presented in [Study PSMA-617-01-Table 14.2.7.2]. At baseline, mean (0.71 vs. 072) and median (0.74 vs. 0.74) values for EQ-5D-5L utility score were similar in both treatment arms.

Improvement (≥ 0.001 increase) and worsening (no change or any decrease) relative to baseline and time to worsening (earliest occurrence of no change or any decrease relative to baseline, clinical progression or death) in EQ-5D-5L utility score is presented in [Study PSMA-617-01-Table 14.2.7.3] and graphically presented in [Study PSMA-617-01-Figure 14.2.7.1].

Despite the differences in drop-out rates between the 2 treatment arms, results suggest that while on randomized treatment, patients reported a more stable health status in the ^{177}Lu-PSMA-617+BSC/BSoC arm. Time to worsening was delayed by 0.5 months in the ^{177}Lu-PSMA-617+BSC/BSoC arm, with median time to deterioration of 1.0 months (95% CI: 0.7, 1.8) in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 0.5 months (95% CI: 0.4, 1.0) in the BSC/BSoC only arm [Study PSMA-617-01-Table 14.2.7.3].

There was an estimated 35% reduction in risk of worsening, clinical progression or death (HR = 0.65; 95% CI: 0.54, 0.78; Cox two-sided p-value: < 0.001) in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared to the BSC/BSoC only arm [Study PSMA-617-01-Table 14.2.7.3].

Boxplot for EQ-5D-5L utility score values over time are presented in [Study PSMA-617-01-Figure 14.2.6.2].

EQ-5D-5L - EQ-VAS

The EQ-5D-5L - EQ VAS records the patient's self-rated health on a vertical visual analogue 0-100 scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. A higher EQ-5D-5L - EQ-VAS score correlates with better health status.

EQ-5D-5L - EQ-VAS values and change from baseline by visit (by cycle) are presented in [Study PSMA-617-01-Table 14.2.7.4] and graphically presented in [Study PSMA-617-01-Figure 14.2.6.2]. Despite the differences in drop-out rates between the 2 treatment arms, especially for the latest cycles, results suggest that while on randomized treatment, patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm were more stable compared to patients in the BSC/BSoC only arm.

3.3 Comparison of results in subpopulations

Homogeneity and consistency of the alternate primary endpoints rPFS and OS were evident across subgroups, including stratification factors, age, region, baseline PSA, prior therapies, and concurrent therapies, demonstrating a consistent beneficial treatment effect. The only exception was subgroups with too few patients to be interpretable.

3.3.1 Methods of subgroup analyses

3.3.1.1 Subgroup definitions

Since the primary efficacy analyses of both alternate endpoints, rPFS and OS, were statistically significant, subgroup analyses for Study PSMA-617-01 were performed using the PFS-FAS for rPFS and the FAS for OS.

The subgroup definitions based on the predefined subgroup analyses in Study PSMA-617-01 are provided in Table 3-23. Additional subgroup analyses were also conducted for this SCE, and the definitions are provided in Table 3-24. Results of analyses for these combined subgroups for rPFS and OS are presented in Figure 3-18 and Figure 3-19, respectively.

No formal statistical testing was performed for any subgroup analyses.

Table 3-23 Subgroup definitions based on predefined analyses for Study PSMA-617-01

Subgroup definitions
• Stratification factor (based on CRF data) – Inclusion of NAADs (e.g., enzalutamide, abiraterone, apalutamide, etc.) as part of assigned BSC/BSoC treatment at start of study (Yes vs. No) as per Investigator assignment
• Stratification factor (based on CRF data) - Baseline LDH (≤ 260 IU/L vs. > 260 IU/L)
• Stratification factor (based on CRF data) - Presence of liver metastases at baseline (Yes vs. No)
• Stratification factor (based on CRF data) - ECOG score at baseline (0 or 1 vs. 2)
• Age (<65 vs. ≥65 years)
• Race (White vs. Black or African American vs. Asian vs. Other (includes "Native Hawaiian or Other Pacific Islander", "American Indian or Alaska Native" or more than one race reported))
Results for these subgroups are also reported in [Study PSMA-617-01-Section 11.1.4].

Table 3-24 Subgroup definitions based on additional subgroup analyses for Study PSMA-617-01

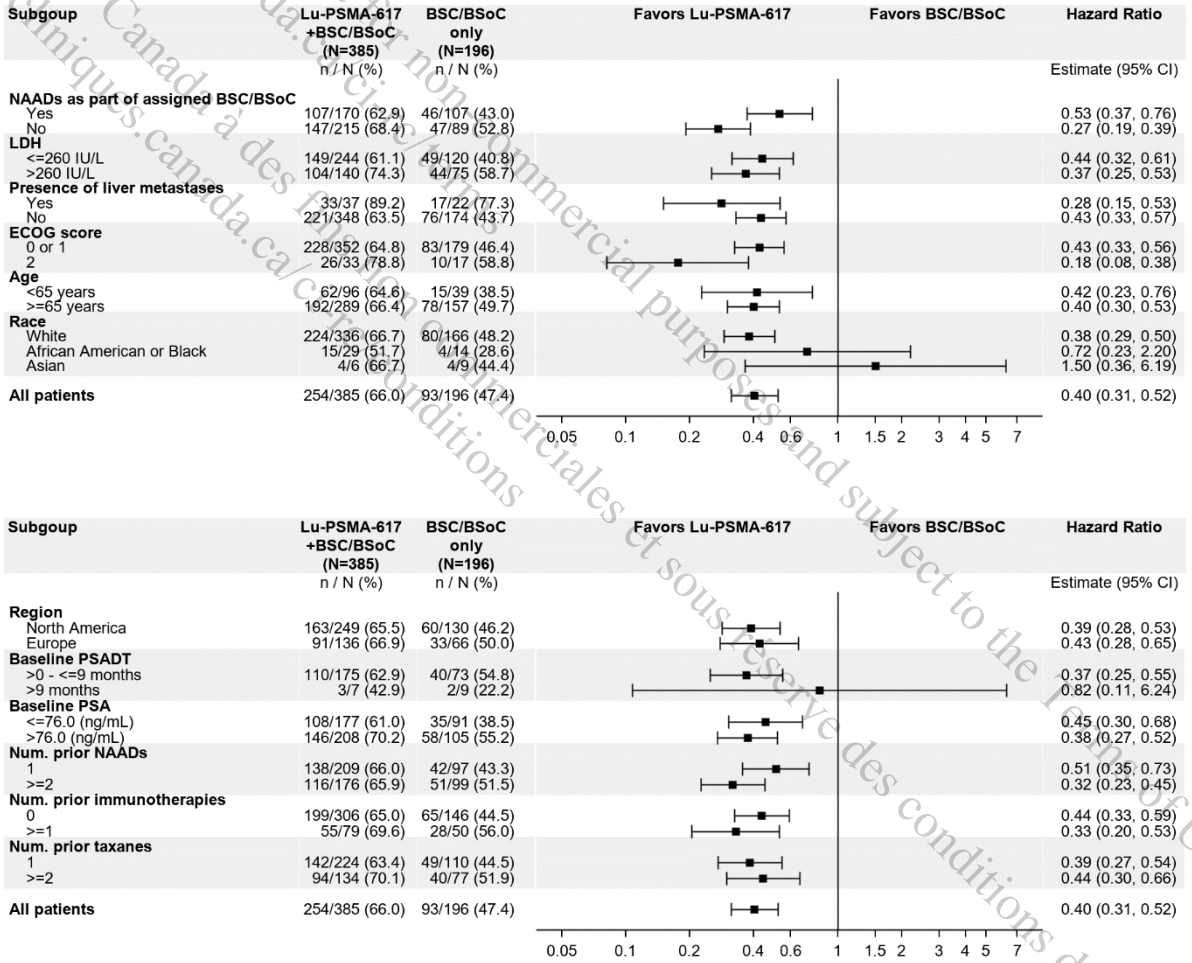
Subgroup definitions
• Region (North America vs. Europe)
• PSA Doubling Time (PSADT) at study baseline (>0 to ≤9 months vs. >9 months)
• Baseline Prostate-Specific Antigen (PSA) (≤median ng/mL vs. >median ng/mL)[a]
• Number of prior NAADs (1 vs. ≥2)
• Number of prior immunotherapies (0 vs. ≥1)
• Number of prior taxane-containing regimens (1 vs. ≥2)[b]
• Number of prior non-taxane cytotoxic chemotherapeutic therapies (0 vs. ≥1)
• Prior use of bone sparing agents (Yes vs. No)
• Prior use of 223-Radium (Yes vs. No)
• Prior use of PARP inhibitors (Yes vs. No)
• Concurrent use of NAADs as part of BSC/BSoC treatment (Yes vs. No)
• Concurrent use of radiation therapy (i.e. external beam) as part of BSC/BSoC treatment (Yes vs. No)
• Concurrent use of bone sparing agents as part of BSC/BSoC treatment (Yes vs. No)
a: Median baseline PSA was derived using the FAS. b: A regimen was defined as administration of ≥2 cycles of a taxane.

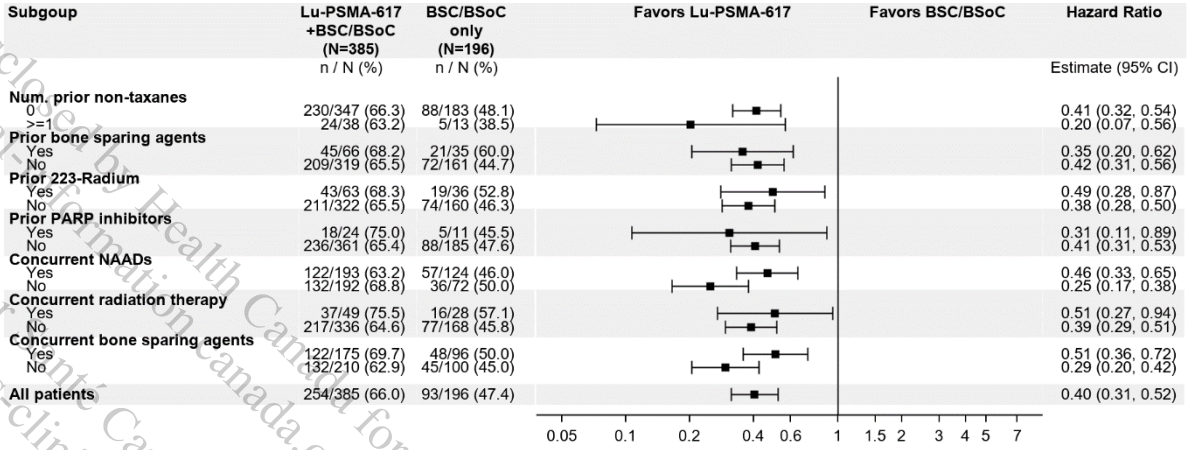
3.3.2 rPFS subgroup analyses per blinded independent central review

A forest plot of HR with 95% CI for subgroup analyses on rPFS per BICR is presented in Figure 3-18.

Subgroup analyses of rPFS were consistent with the primary rPFS analysis and demonstrated homogeneity of the treatment effect across these subgroups, with the exception of subgroups with too few patients to be interpretable (e.g. Asian, African American or Black, and baseline PSADT >9 months).

Figure 3-18 rPFS subgroup analysis per blinded independent central review: forest plot of HR with 95% CI (PFS-FAS)





n/N: Number of events/number of patients in treatment arm. Vertical line shows no effect point.

Note: NAAD: Novel androgen axis drugs, PSADT: Prostate-specific antigen doubling time, PSA: Prostate-specific antigen, PARP: Poly ADP ribose polymerase

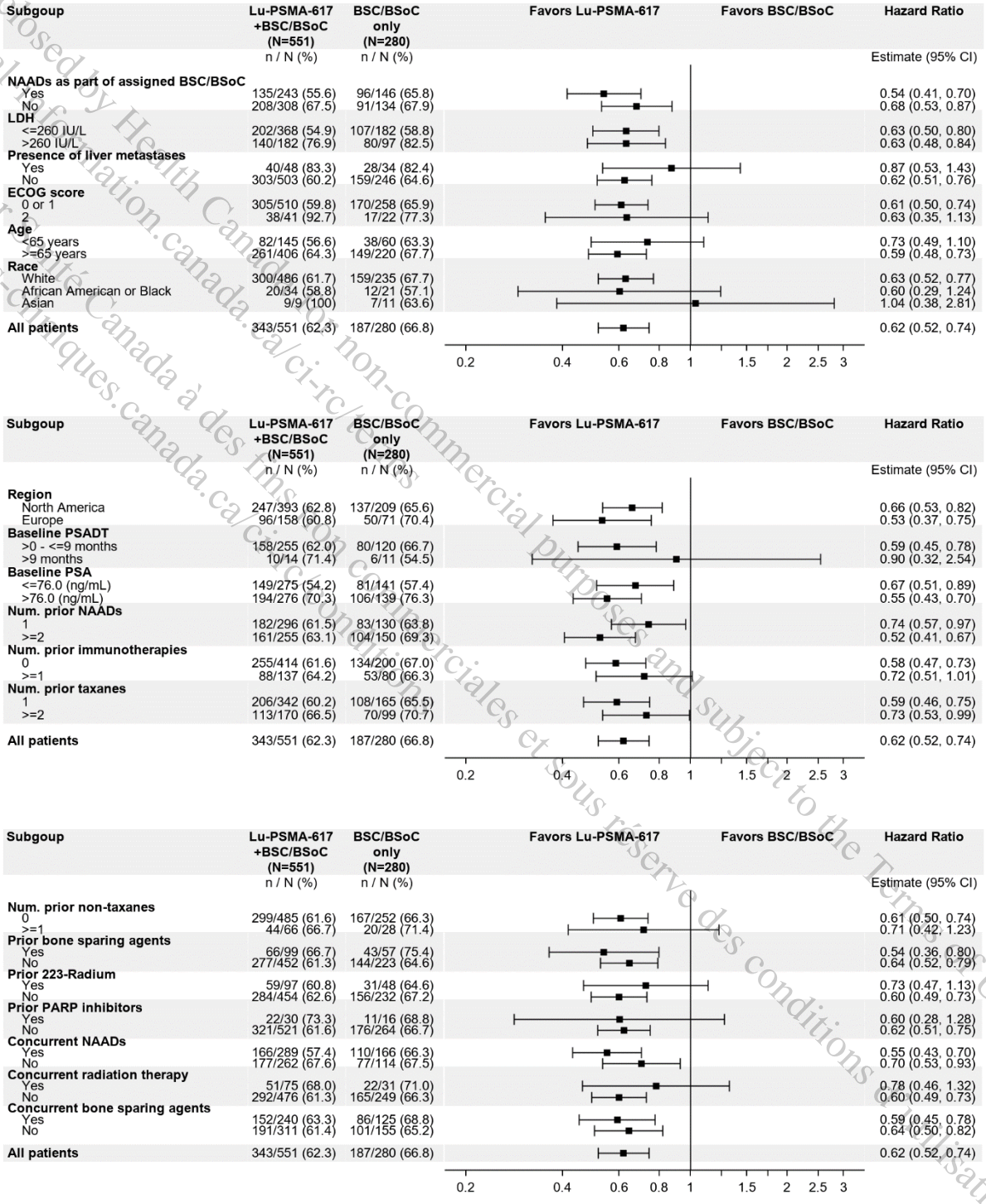
Source: [Study PSMA-617-01-Table 14.2.2.2; Table 14.2.2.3; Table 14.2.2.4; Table 14.2.2.5; Table 14.2.2.6; Table 14.2.2.7]; [SCE-Appendix 1-Figure 2; Table 16; Table 17; Table 18; Table 19; Table 20; Table 21; Table 22; Table 23; Table 24; Table 25; Table 26; Table 27; Table 28]

3.3.3 OS subgroup analyses

A forest plot of HR with 95% CI for OS subgroup analyses are presented in Figure 3-19.

All subgroup analyses of OS were consistent with the primary OS analysis and demonstrate the homogeneity of the treatment effect across these subgroups, with the exception of subgroups with too few patients to be interpretable (e.g. Asian, African American or Black, and baseline PSADT >9 months).

Figure 3-19 OS subgroup analysis: forest plot of HR with 95% CI (FAS)



n/N: Number of events/number of patients in treatment arm. Vertical line shows no effect point.

Note: NAAD: Novel androgen axis drugs, PSADT: Prostate-specific antigen doubling time, PSA: Prostate-specific antigen, PARP: Poly ADP ribose polymerase

Source: [Study PSMA-617-01-Table 14.2.1.3; Table 14.2.1.4]; Table 14.2.1.5; Table 14.2.1.6; Table 14.2.1.7; Table 14.2.1.8]; [SCE-Appendix 1-Figure 1; Table 3; Table 4; Table 5; Table 6; Table 7; Table 8; Table 9; Table 10; Table 11; Table 12; Table 13; Table 14; Table 15]

3.3.4 Efficacy subgroup analyses in the ^{177}Lu-PSMA-617 + BSC/BSoC arm

rPFS, OS, and PFS were also analyzed in the ^{177}Lu-PSMA-617 + BSC/BSoC arm of the FAS safety analysis set by number of ^{177}Lu-PSMA-617 cycles; see Section 3.2.1.1.3, Section 3.2.1.2.4, and Section 3.2.2.2.1, respectively. FACT-P total score and FACT-G total score (see Section 3.2.2.4.1) as well as BPI-SF pain interference and BPI-SF pain intensity (see Section 3.2.2.4.2) were also analyzed in the ^{177}Lu-PSMA-617 + BSC/BSoC arm of the FAS safety analysis set by number of ^{177}Lu-PSMA-617 cycles.

4 Analysis of clinical information relevant to dosing recommendations

4.1 Rationale for dose(s) studied

4.1.1 Summary of dose-selection procedures for Study PSMA-617-01

Prior to the conduct of Study PSMA-617-01, including the sub-study in which dosimetry data were collected for 29 of the enrolled 30 patients, the selection of the ^{177}Lu-PSMA-617 dose and administration schedule was based on published clinical studies characterizing the safety and efficacy experience with ^{177}Lu-PSMA-617. Further, published radiation dosimetry studies, and a consideration of EBRT dose thresholds in organs at risk, provided some general guidance applicable to cumulative radiation exposures. Lastly, experience with the approved ^{177}Lu-radioligand therapeutic Lutathera® provided class-based information.

The determination of the dose regimen for Study PSMA-617-01 was guided by efficacy and safety considerations, with an accounting for the life-threatening nature of the disease. The selected dose of 7.4 GBq every 6 weeks was intended to maximize the probability of efficacy, while maintaining safety parameters which are clinically appropriate for the patient population and advanced disease state.

A high-level summary of the evidence supporting the selected dose and regimen for Study PSMA-617-01 is provided below. Details regarding the dose rationale and dosing recommendations are presented in Section 4.2 and [SCP-Section 3.3.1].

Evaluation of dose and schedule range from published clinical experience

The dose selection for ^{177}Lu-PSMA-617 in Study PSMA-617-01 was supported by the published clinical experience with this agent, documented in 24 publications based on over 500 patients. Across these publications, doses ranged from 2.0-9.3 GBq/cycle, and schedules typically followed an administration schedule of once every 4 to 12 weeks, for 1-8 cycles. Although the German Society of Nuclear Medicine recommended a 6.0 GBq dose every 8 weeks for a maximum of 3 cycles (von Eyben et al 2018), the majority of these publications had used a regimen of 4 cycles of 6 GBq every 8 weeks. The efficacy and safety information from the prospective Phase II "Lu-PSMA" study suggested that dosing of 6-8 GBq every 6

weeks for 4 cycles was well tolerated and efficacious, and this data was a core consideration during the protocol design for Study PSMA-617-01 (Hofman et al 2017). However, there were also reports of more than 4 cycles of ^{177}Lu-PSMA-617 being administered safely as a means to maximize the benefit to the patient (Rahbar et al 2018); therefore, the 2 additional cycles (resulting in a maximum of 6 cycles) were incorporated into the Study PSMA-617-01 protocol under the condition that benefit and tolerability were confirmed following the 4th cycle.

Dosimetry and radiation safety considerations

At present, the absorbed radiation dose thresholds for different organ systems have not been completely defined for RLTs, with existing thresholds being historically based on EBRT. The radiation dose administered during EBRT is frequently limited by the risk of long-term toxicities to adjacent organs as a consequence of treatment with high dose rate radiation, and these limits for EBRT have been estimated and published in the literature (Emami et al 1991, Dawson et al 2010, Marks et al 2010, Emami 2013). However, the application of these EBRT thresholds to RLT is likely too conservative due to the intrinsic differences between external and systemic radiotherapy treatment modalities and thus serves mainly as a guide for RLT dose selection, as opposed to a restrictive limit.

At the time of Study PSMA-617-01 protocol development, 11 dosimetry studies in over 100 patients had been conducted and published. The results were consistent across the studies, and demonstrated exposure that correlated well with the expected rapid clearance of a small molecule, and the limited distribution pattern of a PSMA-targeted RLT. The primary sites of non-tumor uptake reported in these published dosimetry studies were the salivary glands, lacrimal glands, and kidneys, with excretory mechanisms and PSMA expression in the proximal tubules contributing to exposure in the kidneys (see [SCP-Table 5-1] for details). Approximately 50% of the injected dose was shown to be excreted in the urine within the first 48 hours. Additionally normal bone marrow, although PSMA-negative, can be exposed transiently to ^{177}Lu-PSMA-617 while in circulation, or through proximal exposure from the uptake in neighboring PSMA-positive PC bone lesions, a common site of metastasis. The bone marrow also represents a radiosensitive tissue due to its proliferative nature; therefore, the bone marrow radiation absorbed dose was also a consideration.

When determining the dose for Study PSMA-617-01, a more specific consideration of cumulative radiation exposure in these tissues was considered due to multi-cycle treatment with ^{177}Lu-PSMA-617. For details, see [SCP-Section 3.3.1.2].

Class-based evidence (Lutathera)

Lutathera (^{177}Lu-oxodotreotide) was the first approved peptide-based ^{177}Lu-radioligand therapeutic, and utilizes a dose of 7.4 GBq every 8 weeks for a total of 4 cycles, although other doses and schedules have been evaluated in the literature. The published experience with Lutathera informed much of the early development work that has been done with ^{177}Lu-PSMA-617. Comparing dosing schedules with Lutathera is particularly relevant, as the radiation absorbed dose to the kidneys for both agents is comparable, due to both the renal clearance as well as target expression on the renal proximal tubules. Importantly, based on the extensive clinical experience with Lutathera, the radiation absorbed dose thresholds in the kidneys for

RLT were suggested to be higher than the historical EBRT threshold (Bergsma et al 2016, Wessels et al 2008). For further details, see [SCP-Section 3.3.1.3].

4.2 Rationale for recommended dose(s) in the label

The recommended dose of lutetium (^{177}Lu) vipivotide tetraxetan (or ([^{177}Lu]Lu-PSMA-617) is 7.4 GBq (200 mCi) every 6 weeks (±1 week) for a total of 6 doses (total cumulative dose of 44.4 GBq).

This dose recommendation for the label is based on efficacy, dosimetry/radiation safety, and clinical safety results from Study PSMA-617-01, as well as additional published clinical study results since protocol development for Study PSMA-617-01. Further support is provided by published efficacy, safety, and dosimetry data as well as RLT class-based information from Lutathera available at the time of protocol development for Study PSMA-617-01 (see Section 4.1).

The efficacy and safety of ^{177}Lu-PSMA-617+BSC/BSoC are described in this SCE and the [SCS], respectively. Efficacy was demonstrated in the PFS-FAS and FAS (Section 3); in addition, subgroup efficacy analysis results favored 5-6 cycles compared to 4 cycles only. Safety and tolerability remained well tolerated and manageable after 6 cycles [SCS-Section 7].

Efficacy results based on number of cycles of ^{177}Lu-PSMA-617, dosimetry/radiation safety results, and additional published clinical study results since Study PSMA-617-01 initial protocol development presented below provide further support for the recommended dose and regimen.

Study PSMA-617-01 efficacy results based on number of cycles of ^{177}Lu-PSMA-617

Efficacy results from Study PSMA-617-01 support the proposed dose and regimen (Section 3). Support for a total of 6 cycles/doses is provided based on the following efficacy results in the ^{177}Lu-PSMA-617 + BSC/BSoC arm of the FAS safety analysis set by number of ^{177}Lu-PSMA-617 cycles:

- Median rPFS for patients who received 4 cycles of ^{177}Lu-PSMA-617 was 6.4 months (95% CI: 4.3, 7.9); for patients who received 5-6 cycles, median rPFS was 13.8 months (95% CI: 12.2, 17.0) [SCE-Appendix 1-Table 14.2.2.20].
- Median OS for patients who received 4 cycles of ^{177}Lu-PSMA-617 was 11.0 months (95% CI: 9.6, 12.6); for patients who received 5-6 cycles, median OS was 24.7 months (95% CI: 21.3, 27.6) [SCE-Appendix 1-Table 14.2.1.12].
- Median PFS for patients who received 4 cycles of ^{177}Lu-PSMA-617 was 4.4 months (95% CI: 3.3, 4.7); for patients who received 5-6 cycles, median PFS was 9.9 months (95% CI: 8.6, 11.3) [SCE-Appendix 1-Table 14.2.5.1].

Additional support for a total of 6 cycles/doses is provided based on the following PRO results in the ^{177}Lu-PSMA-617 + BSC/BSoC arm of the FAS safety analysis set by number of ^{177}Lu-PSMA-617 cycles:

- Median time to worsening in FACT-P total score for patients who received 4 cycles of ^{177}Lu-PSMA-617 was 5.4 months (95% CI: 4.2, 6.0); for patients who received 5-6 cycles,

median time to worsening in FACT-P total score was 9.2 months (95% CI: 8.3, 11.1) [SCE-Appendix 1-Table 14.2.8.1.2.2].

- Median time to worsening in FACT-G total score for patients who received 4 cycles of ^{177}Lu-PSMA-617 was 5.6 months (95% CI: 4.6, 6.0); for patients who received 5-6 cycles, median time to worsening in FACT-G total score was 10.3 months (95% CI: 8.8, 11.4) [SCE-Appendix 1-Table 14.2.8.10.2.2].
- Median time to worsening in BPI-SF pain intensity for patients who received 4 cycles of ^{177}Lu-PSMA-617 was 4.7 months (95% CI: 3.1, 5.7); for patients who received 5-6 cycles, median time to worsening in BPI-SF pain intensity was 9.4 months (95% CI: 8.5, 10.8) [SCE-Appendix 1-Table 14.2.9.1.2.2].
- Median time to worsening in BPI-SF pain interference for patients who received 4 cycles of ^{177}Lu-PSMA-617 was 5.6 months (95% CI: 4.4, 6.0); for patients who received 5-6 cycles, median time to worsening in BPI-SF pain interference was 8.8 months (95% CI: 7.4, 10.4) [SCE-Appendix 1-Table 14.2.9.2.2.2].

Dosimetry/radiation safety results in PSMA-617-01 sub-study

- A sub-study within PSMA-617-01 evaluated dosimetry in 29 patients and PK in 30 patients from a non-randomized cohort receiving ^{177}Lu-PSMA-617+BSC/BSoC. An overview of these results follows; full details are presented in [SCP-Section 2.3.1] and [SCP-Section 3.3.2].
- Radiation exposures from the PSMA-617-01 sub-study, especially for the organs considered at risk from radiation due to their exposure levels such as salivary glands, lacrimal glands, kidneys and bone marrow, were consistent with the ranges published in literature. Overall, the PSMA-617-01 sub-study dosimetry data indicate minimal risk for patients based on the theoretical calculated cumulative radiation exposure after a total of 6 cycles of 7.4 GBq each [SCP-Section 1.2.2.2]. The sub-study dosimetry data are in line with clinical safety results that indicate adverse events related to these organs at risk are generally of a low-to-moderate severity, tolerable and of a reversible nature [SCS]. Comparison with literature values and detailed comparison with the observed safety profile in Study PSMA-617-01 (main study) per organ at risk are provided in [SCP-Section 3.3.2].

Additional published clinical study results since initial protocol development for Study PSMA-617-01

Since the initial protocol development for Study PSMA-617-01, additional publications summarizing the investigational use of ^{177}Lu-PSMA-617 in mCRPC patient populations with differing prior therapies and concomitant medications suggest low toxicity and encouraging biochemical and radiographic response rates, overall survival and reduced pain using ^{177}Lu-PSMA-617 RLT in patients with mCRPC (Kim et al 2018, von Eyben et al 2018, Yadav et al 2019, Violet et al 2020, Hofman et al 2021, Sadaghiani et al 2021). These publications represent data from retrospective and prospective Phase 1, Phase 2 and dosimetry trials under countries' local regulations using multiple sources of the PSMA-617 precursor and Lu-177 with different preparation processes for ^{177}Lu-PSMA-617. Across these publications, doses have ranged from 1.1-12.0 GBq/cycle, administered once every 4 to 12 weeks, for between 1-9 cycles

(Kulkarni et al 2018b, Grubmüller et al 2019, Sarnelli et al 2019, Yadav et al 2020). Clinical studies also showed that more than 4 cycles of ^{177}Lu-PSMA-617 could be administered safely as a means to maximize the benefit to the patient (Rahbar et al 2018, Kulkarni et al 2018a, Kulkarni et al 2018b, Kulkarni et al 2018c, van Kalmthout et al 2019, Maffey-Steffan et al 2020, Yadav et al 2020, Paganelli et al 2020, Crumbaker et al 2020, Hofman et al 2021, Ahmadzadehfar et al 2021). In the randomized Phase 2 TheraP (ANZUP1603) study in 200 Australian patients, which compared ^{177}Lu-PSMA-617 against cabazitaxel, the starting dose was 8.5 GBq ^{177}Lu-PSMA-617, which was then reduced by 0.5 GBq per cycle, i.e. 8.5, 8, 7.5, 7, 6.5, and 6 GBq. Importantly, the final efficacy and safety information from this randomized Phase 2 study demonstrated that this dosing of 6 cycles, for a total cumulative dose of up to 43.5 GBq, was well tolerated and efficacious (Hofman et al 2021).

4.2.1 Dose modification

Patients should have adequate hematologic function, hepatic function, and renal function. The patient's condition should be assessed by performing laboratory tests before and during treatment with ^{177}Lu-PSMA-617.

4.2.1.1 Effects of intrinsic factors on PK and dosimetry

Demographic factors - body weight, ethnicity, and age

Population PK and dosimetry analyses showed that ^{177}Lu-PSMA-617 exposure and biodistribution are not influenced by body weight or BMI, supporting the use of fixed dosing [SCP-Section 3.4.3].

No information is currently available about the effects of race or ethnicity on biodistribution and PK of ^{177}Lu-PSMA-617 since all patients enrolled in the PSMA-617-01 sub-study were White, and only one patient was Hispanic or Latino [^{177}Lu-PSMA-617 Modeling Report-Section 7.1.1]. Since ^{177}Lu-PSMA-617 is not metabolized by the liver and is eliminated passively through renal excretion, PK is unlikely to be affected by ethnic factors [SCP-Section 3.4.4].

Age in the range of 52 to 80 years (median 67 years) was not found as a statistically significant covariate in the ^{177}Lu-PSMA-617 population PK model [^{177}Lu-PSMA-617 Modeling Report-Section 7.1.4 and Section 7.1.1]; therefore, PK is not affected by age [SCP-Section 3.4.5]. In addition, no overall differences in efficacy were observed between patients ≥ 65 years of age and patients <65 years of age (Figure 3-18 and Figure 3-19).

Renal impairment

No dedicated renal impairment study for ^{177}Lu-PSMA-617 has been conducted. Based on exploration of renal effect in population PK and exposure-dosimetry analyses [SCP-Section 3.4.7], no dose adjustment is recommended in patients with mild (creatinine clearance (CLcr) 60 to 89 mL/min) to moderate (CLcr 30 to 59 mL/min) renal impairment.

The PK profile and safety of ^{177}Lu-PSMA-617 have not been studied in patients with severe renal impairment (CLcr 15 to 29 mL/min) or end-stage renal disease.

Hepatic impairment

As ^{177}Lu-PSMA-617 is not metabolized by, or primarily eliminated through, the liver (Kratochwil et al 2016), hepatic impairment is unlikely to significantly alter the PK of ^{177}Lu-PSMA-617 [SCP-Section 3.4.8]. Hence, no dose adjustment is needed in patients with hepatic impairment.

5 Persistence of efficacy and/or tolerance effects

In Study PSMA-617-01, a statistically significant improvement in rPFS was demonstrated for patients receiving ^{177}Lu-PSMA-617+BSC/BSoC compared to patients receiving BSC/BSoC only (stratified log-rank test $p < 0.001$, one-sided), with an estimated 60% risk reduction of radiographic disease progression or death (HR=0.40; 99.2% CI: 0.29, 0.57). The median follow-up time for rPFS in the PFS-FAS differed between the 2 treatment arms (16.4 months in the ^{177}Lu-PSMA-617+BSC/BSoC arm and 3.9 months in the BSC/BSoC arm) (Table 3-10). Radiographic progression-free probability remained higher during the entire follow-up period for the ^{177}Lu-PSMA-617+BSC/BSoC arm compared with the BSC/BSoC only arm, indicating an early and sustained advantage for ^{177}Lu-PSMA-617 therapy (Figure 3-2).

Likewise, a statistically significant improvement in OS was demonstrated in Study PSMA-617-01 for patients receiving ^{177}Lu-PSMA-617+BSC/BSoC compared to patients receiving BSC/BSoC only (stratified log-rank test $p < 0.001$, one-sided). There was an estimated 38% risk reduction of death in ^{177}Lu-PSMA-617+BSC/BSoC arm compared with the BSC/BSoC only arm (HR=0.62; 95% CI: 0.52, 0.74). The median follow-up times for OS were similar between the 2 treatment arms (20.3 months [95% CI: 19.8, 21.0] vs. 19.8 months [95% CI: 18.3, 20.8] in the ^{177}Lu-PSMA-617+BSC/BSoC and BSC/BSoC only arms, respectively) (Table 3-11). The Kaplan-Meier curves for OS diverged after approximately 2 months, remaining higher during the entire follow-up period for the ^{177}Lu-PSMA-617+BSC/BSoC arm compared with the BSC/BSoC only arm, indicating an early and sustained advantage for ^{177}Lu-PSMA-617 therapy (Figure 3-4).

6 Efficacy conclusions

The results of Study PSMA-617-01 demonstrated that treatment with ^{177}Lu-PSMA-617 consistently resulted in statistically significant and clinically meaningful improvements in key measures of efficacy, including reduced risk of radiographic disease progression or death, a reduced risk of death, increased ORR and DCR, and delay in time to first SSE.

Study PSMA-617-01 met its primary objectives for both alternate primary endpoints. Statistically significant improvements were demonstrated in favor of treatment with ^{177}Lu-PSMA-617+BSC/BSoC relative to BSC/BSoC only:

- For rPFS, there was an estimated 60% risk reduction of radiographic disease progression or death (HR = 0.40; 99.2% CI: 0.29, 0.57; stratified log-rank test $p < 0.001$, one-sided). Median rPFS was prolonged by 5.3 months, from 3.4 months (99.2% CI: 2.4, 4.0) in the BSC/BSoC only arm to 8.7 months (99.2% CI: 7.9, 10.8) in the ^{177}Lu-PSMA-617+BSC/BSoC arm

- Results of sensitivity analyses for rPFS were supportive of the primary analysis results:
  - Sensitivity analysis 1 (including missed assessments, etc): HR=0.53 (99.2% CI: 0.41, 0.70)
  - Sensitivity analysis 2 (censoring of deaths occurring after start of a new anti-cancer therapy): HR= 0.40 (99.2% CI: 0.28, 0.57)
  - Sensitivity analysis 3 (rPFS defined from date of first dose of randomized treatment): HR= 0.45 (99.2% CI: 0.31, 0.65)
  - Sensitivity analysis 4 (local investigator assessments as opposed to central read): HR= 0.36 (99.2% CI: 0.26, 0.49)
- In addition, analysis of rPFS based on the FAS was also supportive of the primary analysis (HR=0.43; 99.2% CI: 0.32, 0.58; stratified log-rank test $p < 0.001$)

- For OS, there was a statistically significant estimated 38% risk reduction of death (HR = 0.62; 95% CI: 0.52, 0.74; stratified log-rank test $p < 0.001$, one-sided). Median OS was prolonged by 4.0 months, from 11.3 months (95% CI: 9.8, 13.5) in the BSC/BSoC only arm to 15.3 months (95% CI: 14.2, 16.9) in the ^{177}Lu-PSMA-617+BSC/BSoC arm
  - Results of a supplementary OS analysis based on the first 750 patients randomized in the FAS, which mimics the OS analysis as planned in the initial protocol, were also consistent with the primary analysis results, with an HR of 0.63 (95% CI: 0.52, 0.77) favoring the ^{177}Lu-PSMA-617+BSC/BSoC arm (stratified log-rank test $p < 0.001$, one-sided)
  - The OS analysis conducted on the PFS-FAS was consistent with and supportive of the primary analysis results, favoring the ^{177}Lu-PSMA-617+BSC/BSoC arm, with an estimated 37% risk reduction of death vs. the BSC/BSoC only arm (HR = 0.63; 95% CI, 0.51, 0.79; stratified Log-rank test $p < 0.001$, one-sided)
- In addition, results of analyses performed to assess sensitivity of rPFS and OS to censoring due to drop-outs were consistent with and supportive of the primary analysis results; as a result, the initial high drop-out rate had no impact on the interpretation or robustness of the primary analysis results.
- Homogeneity and consistency of the alternate primary endpoints rPFS and OS were evident across subgroups, including the baseline stratification factors, age, region, baseline PSA, prior therapies, and concurrent therapies, demonstrating a consistent ^{177}Lu-PSMA-617 treatment effect; the only exception was subgroups with too few patients to be interpretable.

The study met all key secondary efficacy objectives, with statistically significant improvements in favor of treatment with ^{177}Lu-PSMA-617+BSC/BSoC relative to BSC/BSoC only:

- ORR (29.8% vs. 1.7%) was statistically significant in favor of the ^{177}Lu-PSMA-617+BSC/BSoC arm (OR=24.99; 95% CI: 6.05, 103.24; stratified Wald's Chi-square test $p < 0.001$, two-sided); median DoR in responders was 9.8 months (95% CI: 9.1, 11.7) in the ^{177}Lu-PSMA-617+BSC/BSoC arm (median DoR in the BSC/BSoC only arm was not reliable since only 1 of the 2 patients who responded had RECIST radiographic progression or death).

- DCR (89.0% vs. 66.7%) was also statistically significant in favor of the ^{177}Lu-PSMA-617+BSC/BSoC arm (OR=5.79; 95% CI: 3.18, 10.55; stratified Wald's Chi-square test p < 0.001, two-sided)
  - Results of analyses of ORR and DCR in patients with measurable disease at baseline (at least one target lesion per BICR) also favored the ^{177}Lu-PSMA-617+BSC/BSoC arm:
    - ORR: 51.1% vs. 3.1% (OR=37.61; 95% CI: 8.84, 159.99; stratified Wald's Chi-square test p < 0.001, two-sided).
    - DCR: 86.4% vs. 50.0% (OR=10.03; 95% CI: 4.50, 22.34; stratified Wald's Chi-square test p < 0.001, two-sided).
- Time to first SSE was in favor of ^{177}Lu-PSMA-617+BSC/BSoC arm with an estimated 50% risk reduction of a first symptomatic skeletal event or death that was statistically significant (HR =0.50; 95% CI: 0.40, 0.62; two-sided p-value: < 0.001)
  - Median time to first SSE (95% CI) was delayed by 4.7 months (from 6.8 months (95% CI: 5.2, 8.5) to 11.5 months (95% CI: 10.3, 13.2))

For additional secondary efficacy endpoints, improvements in favor of treatment with ^{177}Lu-PSMA-617+BSC/BSoC relative to BSC/BSoC only were also observed (no multiplicity adjustment was performed for these analyses):

- PFS: estimated 70% reduction in risk of radiographic disease progression, clinical progression, PSA progression, or death (HR = 0.30; 95% CI: 0.24, 0.38)
  - Median PFS was prolonged by 3.5 months (from 2.4 months (95% CI: 2.2, 3.0) to 5.9 months (95% CI: 5.2, 6.6))
- For PSA, ALP, and LDH levels, greater mean and median decreases were observed for ^{177}Lu-PSMA-617+BSC/BSoC relative to BSC/BSoC only
  - PSA response of ≥ 50% decrease from baseline occurred in 46.0% (95% CI 40.9, 51.1) of patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 7.1% (95% CI 4.0, 11.7) of patients in the BSC/BSoC only arm.
- Results in favor of treatment with ^{177}Lu-PSMA-617+BSC/BSoC relative to BSC/BSoC only were also observed for PROs, indicating patient stabilization/slower deterioration while on treatment:
  - FACT-P total score: estimated 46% reduction in risk of worsening, clinical progression or death (HR = 0.54; 95% CI: 0.45, 0.66; Cox two-sided p-value: < 0.001) in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared to the BSC/BSoC only arm
    - Time to worsening was delayed by 3.5 months in ^{177}Lu-PSMA-617+BSC/BSoC arm, with median time to deterioration of 5.7 months (95% CI: 4.8, 6.6) in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 2.2 months (95% CI: 1.8, 2.8) in the BSC/BSoC only arm
    - Similar results were observed for the FACT-P total score subscales, including physical well-being, pain-related scale, PSI-8, and TOI
  - BPI-SF pain intensity scale: estimated 48% reduction in risk of worsening, clinical progression, or death (HR = 0.52; 95% CI: 0.43, 0.63; Cox two-sided p-value:

< 0.001) in the 177Lu-PSMA-617+BSC/BSoC arm compared to the BSC/BSoC only arm

- Time to worsening was delayed by 3.7 months in ^{177}Lu-PSMA-617+BSC/BSoC arm, with median time to deterioration of 5.9 months (95% CI: 4.8, 6.9) in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 2.2 months (95% CI: 1.8, 2.8) in the BSC/BSoC only arm

- Similar results were observed for other BPI-SF scales, including pain interference and worst pain intensity

7 References

7.1 Published literature

[Abida W, Patnaik A, Campbell D, et al (2020)] Rucaparib in men with metastatic castration-resistant prostate cancer harboring a BRCA1 or BRCA2 gene alteration. J Clin Oncol; 38:3763-72.

[Ahmadzadehfar H, Rahbar K, Kürpig S, et al (2015)] Early side effects and first results of radioligand therapy with 177Lu-DKFZ-617 PSMA of castrate-resistant metastatic prostate cancer: a two-centre study. EJNMMI Research; 5:36.

[Ahmadzadehfar H, Rahbar K, Baum RP, et al (2021)] Prior therapies as prognostic factors of overall survival in metastatic castration-resistant prostate cancer patients treated with [177Lu]Lu-PSMA-617. A WARMTH multicenter study (the 617 trial). Eur J Nucl Med Mol Imaging; 48(1):113-22.

[American Cancer Society (2020)] Cancer Facts & Figures. No. 500820. Atlanta, GA.

[Anscher MS, Chang C, Gao X, et al (2020)] FDA approval summary: rucaparib for the treatment of patients with deleterious BRCA-mutated metastatic castrate resistant prostate cancer. Oncologist; 26(2):139-46.

[Atkinson A, Kenward MG, Clayton T, et al (2019)] Reference-based sensitivity analysis for time-to-event data. Pharm Stat; 18:645-58.

[Azad AA, Eigl BJ, Murray RN, et al (2015] Efficacy of enzalutamide following abiraterone acetate in chemotherapy-naive metastatic castration-resistant prostate cancer patients. Eur Urol; 67(1):23-9.

[Badrising SK, van der Noort V, van den Eertwegh AJ, et al (2016)] Prognostic parameters for response to enzalutamide after docetaxel and abiraterone treatment in metastatic castration-resistant prostate cancer patients; a possible time relation. Prostate; 76(1):32-40.

[Benešová M, Schäefer M, Bauder-Wüst U, et al (2015)] Preclinical evaluation of a tailor-made DOTA-conjugated PSMA inhibitor with optimized linker moeity for imaging and endoradiotherapy of prostate cancer. J Nucl Med; 56(6):914-20.

[Bergsma H, Konijnenberg MW, van der Zwan WA (2016)] Nephrotoxicity after PRRT with (177)Lu-DOTA-octreotate. Eur j Nucl Med Mol Imaging; 43(10):1802-11.

[Bostwick DG, Pacelli A, Blute M, et al (1998)] Prostate specific membrane antigen expression in prostatic intraepithelial neoplasia and adenocarcinoma: a study of 184 cases. Cancer; 82(11):2256-61.

[Brasso K, Thomsen FB, Schrader AJ, et al (2015)] Enzalutamide antitumour activity against metastatic castration-resistant prostate cancer previously treated with docetaxel and abiraterone: a multicentre analysis. Eur Urol; 68(2):317-24.

[Bräuer A, Grubert LS, Roll W, et al (2017)] ^{177}Lu-PSMA-617 radioligand therapy and outcome in patients with metastasized castration-resistant prostate cancer. Eur J Nucl Med Mol Imaging; 44(10):1663-70.

[Chang SS (2004)] Overview of prostate-specific membrane antigen. Rev Urol; 6 (Suppl 10):S13-S18.

[Cheng HH, Gulati R, Azad A, et al (2015)] Activity of enzalutamide in men with metastatic castration-resistant prostate cancer is affected by prior treatment with abiraterone and/or docetaxel. Prostate Cancer Prostatic Dis; 18(2):122-7.

[Crumbaker M, Pathmanandavel S, Yam AO, et al (2020)] Phase I/II trial of the combination of 177lutetium prostate specific membrane antigen 617 and Idronoxil (NOX66) in men with end-stage metastatic castration-resistant prostate cancer (LuPIN). Eur Urol Oncol; S2588-9311(20)30093-6.

[Dash A, Pillai MRA, Knapp FF (2015)] Production of (177) Lu for targeted radionuclide therapy. Available options. Nucl Med Mol Imaging; 49(2):85-107.

[Dawson LA, Kavanagh BD, Paulino AC, et al (2010)] Radiation-associated kidney injury. Int J Radiat Oncol Biol Phys; 76 (3 Suppl):S108-S115.

[de Bono JS, Oudard S, Ozguroglu M, et al (2010)] Prednisone plus cabazitaxel or mitoxandrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet; 376(7947):1147-54.

[de Bono JS, Logothetis CJ, Molina A, et al (2011)] Abiraterone and increased survival in metastatic prostate cancer. New Engl J Med; 364(21):1995-2005.

[de Bono JS, Mateo J, Fizazi K, et al (2020)] Olaparib for metastatic castration-resistant prostate cancer. New Engl J Med; 382(22):2091-102.

[de Wit R, de Bono J, Sternberg CN, et al (2019)] Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. New Engl J Med; 381(26):2506-18.

[Deepa S, Vijay K, Gowrishankar R, et al (2011)] Precision electron-gamma spectroscopic measurements in the decay of ^{177}Lu. Appl Radiat Isot; 69:869-74.

[Demirci E, Akyel R, Şahin OE, et al (2017)] ^{177}Lu-PSMA-617 treatment of metastatic castration resistant prostate cancer: efficacy and survival [OP-216]. Eur J Nucl Med Mol Imaging; 44 (Suppl 2):S202-S203.

[Ellis S, Carroll KJ, Pemberton K (2008)] Analysis of duration of response in oncology trials. Contemp Clin Trials; 29(4):456-65.

[Emami B, Lyman J, Brown A, et al (1991)] Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys; 21(1):109-22.

[Emami B (2013)] Tolerance of normal tissue to therapeutic radiation. Rep Radiother Oncol; 1(1):35-48.

[Emmett L, Willowson K, Violet J, et al (2017)] Lutetium ^{177} PSMA radionuclide therapy for men with prostate cancer: a review of the current literature and discussion of practical aspects of therapy. J Med Radiat Sci; 64(1):52-60.

[Emmett L, Crumbaker M, Ho B, et al (2019)] Results of a prospective phase 2 pilot trial of ^{177}Lu-PSMA-617 therapy for metastatic castration-resistant prostate cancer including imaging predictors of treatment response and patterns of progression. Clin Genitourin Cancer; 17(1):15-22.

[Flaig TW, Potluri RC, Ng Y, et al (2016)] Treatment evolution for metastatic castration-resistant prostate cancer with recent introduction of novel agents: retrospective analysis of real-world data. Cancer Med; 5(2):182-91.

[Ghosh A and Heston WDW (2004)] Tumor target prostate specific membrane antigen (PSMA) and its regulation in prostate cancer. J Cell Biochem; 91(3):528-39.

[Gillessen S, Attard G, Beer TM, et al (2020)] Management of patients with advanced prostate cancer: report of the Advanced Prostate Cancer Consensus Conference 2019. Eur Urol; 77(4):508-47.

[Grubmüller B, Senn D, Kramer G, et al (2019)] Response assessment using 68Ga-PSMA ligand PET in patients undergoing 177Lu-PSMA radioligand therapy for metastatic castration-resistant prostate cancer. Eur J Nucl Med Mol Imaging; 46(5):1063-72.

[Haberkorn U, Eder J, Kopka K, et al (2016)] New strategies in prostate cancer: prostate-specific membrane antigen (PSMA) ligands for diagnosis and therapy. Clin Cancer Res; 22(1):9-15.

[Hofman MS, Sandhu S, Eu P, et al (2017)] Lutetium-177 PSMA (LuPSMA) theranostics phase II trial: Efficacy, safety and QoL in patients with castrate-resistant prostate cancer treated with LuPSMA. [Abstract 7850]. 2017 European Society for Medical Oncology Annual Meeting; 2017 Sep 8-12; Madrid, Spain. Ann Oncol; 28 Suppl 5:7850.

[Hofman MS, Emmett L, Sandhu S, et al (2021)] [^{177}Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. Lancet; 397(10276):797-804.

[Hussain M, Mateo J, Fizazi K, et al (2020)] Survival with olaparib in metastatic castration-resistant prostate cancer. N Engl J Med; 383(24):2345-57.

[International Agency for Research on Cancer (2020)] Globocan Cancer Today World Fact Sheet, March, 2021. Accessed 21-Jun-2021.

[Kantoff PW, Higano CS, Shore ND, et al (2010)] Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med; 363(5):411-22.

[Kim YJ and Kim Y (2018)] Therapeutic responses and survival effects of 177Lu-PSMA-617 radioligand therapy in metastatic castrate-resistant prostate cancer: a meta-analysis. Clin Nucl Med; 43(10):728-34.

[Kirby M, Hirst C, Crawford ED (2011)] Characterizing the castration-resistant prostate cancer population: a systematic review. Int J Clin Pract; 65(11):1180-92.

[Kratochwil C, Giesel FL, Eder M, et al (2015)] [177Lu]Lutetium-labelled PSMA ligand-induced remission in a patient with metastatic prostate cancer. Eur J Nucl Med Mol Imaging; 42(6):987-8.

[Kratochwil C, Giesel FL, Stefanova M, et al (2016)] PSMA-targeted radionuclide therapy of metastatic castration-resistant prostate cancer with 177Lu-labeled PSMA-617. J Nucl Med; 57(8):1170-6.

[Kratochwil C, Haberkorn U, Giesel FL (2019)] Radionuclide therapy of metastatic prostate cancer. Semin Nucl Med; 49(4):313-25.

[Kulkarni H, Singh A, Schuchardt C, et al (2018a)] Salvage Lu-177 PSMA radioligand therapy in metastatic castration-resistant prostate cancer applying high cumulative radioactivity in repeated cycles. J Nucl Med; 59 Suppl 1:1496.

[Kulkarni H, Schuchardt C, Singh A, et al (2018b)] Early initiation of Lu-177 PSMA radioligand therapy prolongs overall survival in metastatic prostate cancer. J Nucl Med; 59 Suppl 1:529.

[Kulkarni HR, Langbein T, Atay C, et al (2018c)] Safety and long-term efficacy of radioligand therapy using Lu-177 labeled PSMA ligands in metastatic prostate cancer: A single center experience over 5 years. Cancer Research; 78(13):CT015.

[Loriot Y, Bianchini D, Ileana E, et al (2013)] Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). Ann Oncol; 24(7):1807-12.

[Lu K, Li D, Koch GG (2015)] Comparison between two controlled multiple imputation methods for sensitivity analyses of time-to-event data with possibly informative censoring. Stat Biopharm Res; 7:199-213.

[Maffey-Steffan, J, Scarpa L, Svirydenka A, et al (2020)] The 68Ga/^{177}Lu-theragnostic concept in PSMA-targeting of metastatic castration–resistant prostate cancer: impact of post-therapeutic whole-body scintigraphy in the follow-up. Eur J Nucl Med Mol Imaging; 47(3):695-712.

[Malvezzi M, Carioli G, Bertuccio P, et al (2019)] European cancer mortality predictions for the year 2019 with focus on breast cancer. Ann Oncol; 30(5):781-7.

[Marks LB, Ten Haken RK, Martel MK (2010)] Guest editor's introduction to QUANTEC: a users guide. Int J Radiat Oncol Biol Phys; 76 (3 Suppl):S1-S2.

[Murphy GP, Elgamal AAA, Su SL, et al (1998)] Current evaluation of the tissue localization and diagnostic utility of prostate specific membrane antigen. Cancer; 83(11):2259-69.

[Noonan KL, North S, Bitting RL, et al (2013)] Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. Ann Oncol; 24(7):1802-7.

[Nussbaum N, George DJ, Abernethy AP, et al (2016)] Patient experience in the treatment of metastatic castration-resistant prostate cancer: state of the science. Prostate Cancer Prostatic Dis; 19(2):111-21.

[Paganelli G, Sarnelli A, Severi S, et al (2020)] Dosimetry and safety of 177Lu PSMA-617 along with polyglutamate parotid gland protector: preliminary results in metastatic castration-resistant prostate cancer patients. Eur J Nucl Med Mol Imaging; 47(13):3008-17.

[Parker C, Nilsson S, Heinrich D, et al (2013)] Alpha emitter radium-223 and survival in metastatic prostate cancer. New Engl J Med; 369(3):213-23.

[Queisser A, Hagedown SA, Braun M, et al (2015)] Comparison of different prostatic markers in lymph node and distant metastases of prostate cancer. Mod Pathol; 28(1):138-45.

[Rahbar K, Ahmadzadehfar H, Kratochwil C, et al (2017)] German multicenter study investigating ^{177}Lu-PSMA-617 radioligand therapy in advanced prostate cancer patients. J Nucl Med; 58(1):85-90.

[Rahbar K, Boegemann M, Yordanova A, et al (2018)] PSMA targeted radioligandtherapy in metastatic castration resistant prostate cancer after chemotherapy, abiraterone and/or enzalutamide. A retrospective analysis of overall survival. Eur J Nucl Med Mol Imaging; 45(1):12-9.

[Rajasekaran SA, Anilkumar G, Oshima E, et al (2003)] A novel cytoplasmic tail MXXXL motif mediates the internalization of prostate-specific membrane antigen. Mol Biol Cell; 14(12):4835-45.

[Rathke H, Giesel FL, Flechsig P, et al (2018)] Repeated ^{177}Lu-labeled PSMA-617 radioligand therapy using treatment activities of up to 9.3 GBq. J Nucl Med; 59(3):459-65.

[Ross JS, Sheehan CE, Fisher HA, et al (2003)] Correlation of primary tumor prostate-specific membrane antigen expression with disease recurrence in prostate cancer. Clin Cancer Res; 9(17):6357-62.

[Saad F, Gleason DM, Murray R, et al (2004)] Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. J Natl Cancer Inst; 96(11):879-82.

[Sadaghiani MS, Sheikhbahaei S, Werner RA, et al (2021)] A systematic review and meta-analysis of the effectiveness and toxicities of lutetium-177-labeled prostate-specific membrane antigen-targeted radioligand therapy in metastatic castration-resistant prostate cancer. Eur Urol; doi:10.1016/j.eururo.2021.03.004.

[Sarnelli A, Belli ML, Di Iorio V, et al (2019)] Dosimetry of 177Lu-PSMA-617 after mannitol infusion and glutamate tablet administration: Preliminary results of EUDRACT/RSO 2016-002732-32 IRST protocol. Molecules; 24(3):621. doi:10.3390/molecules24030621.

[Scher HI, Fiazai K, Saad F, et al (2012)] Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med; 367(13):1187-97.

[Scher HI, Solo K, Valant J, et al (2015)] Prevalence of prostate cancer clinical states and mortality in the United States: estimates using a dynamic progression model. PLoS ONE; 10(10):e0139440:1-12.

[Scher HI, Morris MJ, Stadler WM, et al (2016)] Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol; 34(12):1402-18.

[Siegel RL, Miller KD, Jemal A (2020)] Cancer statistics, 2020. CA Cancer J Clin; 70(1):7-30.

[Silver DA, Pellicer I, Fair WR, et al (1997)] Prostate-specific membrane antigen expression in normal and malignant human tissues. Clin Cancer Res; 3:81-5.

[Smith M, De Bono J, Sternberg C, et al (2016)] Phase III Study of Cabozantinib in Previously Treated Metastatic Castration-Resistant Prostate Cancer: COMET-1. J Clin Oncol; 34(25):3005-13.

[Sokoloff RL, Norton KC, Gasior CL, et al (2000)] A dual-monoclonal sandwich assay for prostate-specific membrane antigen: levels in tissues, seminal fluid and urine. Prostate; 43(2):150-7.

[Sung H, Ferlay J, Siegel RL, et al (2021)]. Global Cancer Statistics 2020: GLOBOCAN Estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin; 71(3):209-49.

[Sweat SD, Pacelli A, Murphy GP, et al (1998)] Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Urol; 52(4):637-40.

[Tannock IF, de Wit R, Berry WR, et al (2004)]. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. New Engl J Med; 351:1502-12.

[van Kalmthout L, Braat A, Lam M, et al (2019)] First experience with ^{177}Lu-PSMA-617 therapy for advanced prostate cancer in the Netherlands. Clin Nucl Med; 44(6):446-51.

[Violet J, Sandhu S, Iravani A, et al (2020)] Long term follow-up and outcomes of retreatment in an expanded 50-patient single-center phase II prospective trial of ^{177}Lu-PSMA-617 theranostics in metastatic castration-resistant prostate cancer. J Nucl Med; 61:857-65.

[von Eyben FE, Roviello G, Kiljunen T, et al (2018)] Third-line treatment and (177) Lu-PSMA radioligand therapy of metastatic castration-resistant prostate cancer: a systematic review. Eur J Nucl Med Mol Imaging; 45(3):496-508.

[Weinfurt KP, Li Y, Castel LD, et al (2005)] The significance of skeletal-related events for the health-related quality of life of patients with metastatic prostate cancer. Ann Oncol; 16(4):579-84.

[Wessels BW, Konijnenberg MW, Dale RG, et al (2008)] MIRD pamphlet No. 20: The effect of model assumptions on kidney dosimetry and response--implications for radionuclide therapy. J Nucl Med; 49(11):1884-99.

[Wright GL, Haley C, Becket ML, et al (1995)] Expression of prostate-specific membrane antigen in normal, benign, and malignant prostate tissues. Urol Oncol; 1(1):18-28.

[Yadav MP, Ballal S, Sahoo RK, et al (2019)] Radioligand therapy with (177)Lu-PSMA for metastatic castration-resistant prostate cancer: a systematic review and meta-analysis. AJR Am J Roentgenol; 213(2):275-85.

[Yadav MP, Ballal S, Bal C, et al (2020)] Efficacy and safety of ^{177}Lu-PSMA-617 radioligand therapy in metastatic castration-resistant prostate cancer patients. Clin Nucl Med; 45(1):19-31.

[Yordanova A, Becker A, Eppard E, et al (2017)] The impact of repeated cycles of radioligand therapy using [177Lu]Lu-PSMA-617 on renal function in patients with hormone refractory metastatic prostate cancer. Eur J Nucl Med Mol Imaging; 44(9):1473-9.

[Zielinski RR, Azad AA, Chi KN, et al (2014)] Population-based impact on overall survival after the introduction of docetaxel as standard therapy for metastatic castration resistant prostate cancer. Can Urol Assoc J; 8:7-8:E520-E523.

7.2 Minutes of Health Authority meetings

[BfArM Initial Scientific Advice (2018)] Minutes of BfArM Scientific Advice meeting on 13-Sep-2018.

[BfArM Follow-up Scientific Advice (2020)] Minutes of BfArM Scientific Advice meeting on 04-Feb-2020.

[EMA Scientific Advice (2019)] CHMP advice based on discussion meeting on 10-Apr-2019.

[FDA Type B (2018)] Minutes of Type B meeting with the FDA on 16-Aug-2018.

[FDA EOP2 Type B (2018)] Minutes of Type B meeting with the FDA on 30-Jan-2018.

[FDA Type A (2019)] Minutes of Type A meeting with the FDA on 02-May-2019.

7.3 Health Authority guidance

Available upon request.

EMA (1998) Guidance ICH Topic E9: Statistical Principles for Clinical Trials, Step 5. Note for guidance on statistical principles for clinical trials. CPMP/ICH/363/96. September 1998.

EMA (2016) Guideline on the evaluation of anticancer medicinal products in man. EMA/CHMP/205/95 Rev. 5. 25 February 2016.

EMA (2017) Guideline on multiplicity issues in clinical trials. EMA/CHMP/44762/2017. 15 December 2016.

FDA (2007) Guidance for industry: Clinical trial endpoints for the approval of cancer drugs and biologics. US Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). Center for Biologics Evaluation and Research (CBER). May 2007. Clinical/Medical.

FDA (2017) Multiple endpoints in clinical trials: Guidance for industry. Draft guidance. US Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). Center for Biologics Evaluation and Research (CBER). January 2017. Clinical/Medical.

8 Appendix

Table 8-1 Efficacy endpoints and overall type 1 error control

Endpoint	Prespecified final analysis
A: Radiographic progression-free survival*	Inferential test at α=0.004 (one-sided)
*If **A** is positive*	
B: Overall survival*	Inferential test at α=0.025 (one-sided)
*If **B** is positive*	
Key secondary endpoints†	Inferential tests at α=0.05 (two-sided)
Other secondary endpoints	Non-inferential tests at nominal α=0.05 (two-sided)
*If **B** is not met*	
Key secondary endpoints†‡	Non-inferential tests at nominal α=0.05 (two-sided)
Other secondary endpoints	Non-inferential tests at nominal α=0.05 (two-sided)
*If **A** is not met*	
B: Overall survival*	Inferential test at α=0.021 (one-sided)
*If **B** is positive*	
Key secondary endpoints†	Inferential tests at α=0.042 (two-sided)
Other secondary endpoints	Non-inferential tests at nominal α=0.05 (two-sided)
*If **B** is not met*§	
Key secondary endpoints†‡	Non-inferential tests at nominal α=0.05 (two-sided)
Other secondary endpoints	Non-inferential tests at nominal α=0.05 (two-sided)

*Alternate primary endpoints; study would be positive if either radiographic progression-free survival or overall survival were significant at allocated alpha on the prespecified log-rank test stratified by the randomization factors.

†Key secondary endpoints were included in overall type 1 error control using Hochberg closed test procedure.

‡If overall survival is not met but radiographic progression-free survival is positive, the primary endpoint is met but key secondary endpoints are tested non-inferentially at nominal α=0.05 (two sided).

§Primary endpoint not met if neither radiographic progression free survival nor overall survival is met.
Source: [Study PSMA-617-01-Appendix 16.1.9]