Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Sartor O, de Bono, J, Chi KN, et al. Lutetium-177–PSMA-617 for metastatic castration-resistant prostate cancer. N Engl J Med. DOI: 10.1056/NEJMoa2107322

Supplementary Appendix

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SUPPLEMENTARY METHODS

Randomization

Patients were randomly allocated using an interactive response system. Randomization was stratified by baseline lactate dehydrogenase level (≤260 U/mL or >260 U/mL), presence of liver metastases (yes or no), ECOG Performance Status (0–1 or 2) and inclusion of androgen receptor pathway inhibition in protocol-permitted standard care at the time of randomization (yes or no).

Drug nomenclature

The official term for ^{177}Lu-PSMA-617 is [^{177}Lu]Lu-PSMA-617 and the international non-proprietary name is lutetium (^{177}Lu) vipivotide tetraxetan. The official term for ^{68}Ga-PSMA-11 is "[^{68}Ga]Ga-PSMA-11 and the international non-proprietary name is gallium (^{68}Ga) gozetotide.

Measures to reduce withdrawal rate

In February 2019, the sponsor noted unexpectedly unequal rates of patients starting on their randomly assigned treatment between the ^{177}Lu-PSMA-617 and control arms, following anecdotal reports raised by investigators in October 2018. Investigations identified the root cause of this disparity as disappointment among those not randomly assigned to receive ^{177}Lu-PSMA-617. It was also noted that PSMA-targeted radiopharmaceuticals were available off-protocol in some countries. In October 2018, the sponsor updated the study site training materials to clarify the eligibility criteria, mandated involvement of multidisciplinary teams in the provision of care, and emphasized the importance of retaining patients in the control arm. In March 2019, the sponsor: initiated regular investigator meetings and sent a letter to investigators stressing these points and discouraging enrolment of patients who self-referred with the intention of simply accessing ^{177}Lu-PSMA-617; initiated regular contact with sites to discuss management of patients in the control arm; produced a patient information tool to guide pre-screening discussions of expectations; and limited reimbursement for patients to discourage long-distance travel. Protocol amendments were also made to clarify these points (available at NEJM.org).

^{177}Lu-PSMA-617 administration

Patients randomized to the ^{177}Lu-PSMA-617 arm received protocol-permitted standard care plus a maximum of six cycles of ^{177}Lu-PSMA-617 7.4 GBq (200 mCi) every six weeks. After four cycles, patients were re-assessed before receiving further cycles. Only patients with

evidence of response, signs of residual disease and good tolerance could receive cycles five and six.

At the discretion of the investigator, ^{177}Lu-PSMA-617 doses could be delayed by up to 4 weeks or reduced by 20% (without further reduction or re-escalation) to manage toxicity or adverse events. See Table 1 in section 5.1.4 of the protocol for details (available at NEJM.org). Results of physical examinations, toxicity assessments, and hematology and blood biochemistry results were evaluated before each cycle.

^{177}Lu-PSMA-617 was administered slowly via the intravenous route, preceded and followed by saline flush. Vital signs were monitored before and 30 and 60 minutes after administration. Patients were encouraged to maintain good fluid intake. Treatment procedures followed applicable national and local radiation and safety requirements, and varied among study sites.

Supportive care for ^{177}Lu-PSMA-617 infusions was determined by the treating physician according to clinical practice at the study site. Recommended treatments included sodium bicarbonate mouthwash and prophylactic oral or intravenous anti-emetics (e.g. ondansetron, dexamethasone). Optional treatments included allopurinol in patients with gout or high tumor burden, cooling of the salivary glands before and/or during administration, and infusion of 0.9% saline 500mL after administration.

Assessments

Baseline PSMA PET/CT scans were performed 1–6 weeks before the start of treatment using the 2017 procedural guidelines and a [^{68}Ga]Ga-PSMA-11 dose of 111–185 MBq (3–5 mCi).[1]

Patients' tumors were imaged at baseline, every 8 weeks for 24 weeks after starting treatment, then every 12 weeks until end of treatment, and every 3 months during the subsequent follow-up period (for patients who discontinued treatment for reasons other than imaging-based progression and consented to further assessment). Radiological evaluations comprised diagnostic-grade CT scans with contrast or MRI of the chest, abdomen and pelvis and ^{99m}Tc-diphosphonate bone scans, all performed according to the PCWG3 guidelines.[2] The follow-up period continued for up to 24 months or until 508 patients had died (Figure S1).

Patients underwent other assessments at baseline, at the beginning of each six-weekly treatment cycle, then six weeks after the last cycle, then every 12 weeks, at end of

treatment, then every 3 months during the follow-up period (Figure S1). These included ECOG performance status; EuroQol 5-dimension 5-level (EQ-5D), Functional Assessment of Cancer Therapy – Prostate (FACT-P) and Brief Pain Inventory – Short Form (BPI-SF) questionnaires; physical examinations; and measurements of weight, vital signs and testosterone and PSA levels. Hematology and biochemistry were assessed at the same times as above, plus every week during cycle one and every other week during subsequent cycles, and every 3 months during the follow-up period. Adverse events and treatments were monitored throughout the study, including the follow-up period (Figure S1).

Definition of treatment-emergent adverse events

In the ^{177}Lu-PSMA-617 plus protocol-permitted standard care arm, treatment-emergent adverse events were defined as those occurring from the first dose of ^{177}Lu-PSMA-617 up to and including 30 days after the last dose of standard care treatment or of ^{177}Lu-PSMA-617 treatment, whichever was later, or until subsequent anti-cancer treatment. In the protocol-permitted standard care alone arm, treatment-emergent adverse events were defined as those occurring from the first dose of standard-of-care treatment up to and including 30 days after the last dose of standard-of-care treatment, or until subsequent anti-cancer treatment. Further details are provided in the protocol (available at NEJM.org).

RECIST v1.1 response rate definitions

RECIST v1.1. response rates were assessed per PCWG3 guidelines[2] in patients with measurable disease at baseline, defined as the presence of at least one target lesion. RECIST v1.1 responses were also assessed among patients with evaluable disease at baseline, defined as the presence of at least one target lesion or at least one non-target lesion. Patients with target lesions or both target and non-target lesions were classified as complete response (CR), partial response (PR), stable disease (SD), progressive disease or non-evaluable (NE). Patients with non-target lesions only were classified as CR, PR, non-CR/non-PD, or NE. Overall response rate was the proportion of patients with evaluable disease at baseline who had a best overall response of CR or PR. Disease control rate was the proportion of patients with evaluable disease at baseline who had a best overall response of CR, PR, SD or non-CR/non-PD.

Approaches to censoring and missing assessments

For imaging-based progression-free survival, patients without disease progression were censored at the date of their last evaluable scan, patients with no evaluable scans were censored at the date of randomization, and patients with two or more consecutive missed

scans immediately before disease progression or death were censored at the date of their last evaluable scan before the two missed scans. For overall survival, patients not known to have died were censored at the date of last contact. Details of censoring for other time-to-event endpoints and approach to missing data for other endpoints are provided in the statistical analysis plan (available at NEJM.org).

Sensitivity analyses of primary endpoints accounting for censoring

Exploratory *ad hoc* analyses were performed to assess sensitivity of the primary statistical comparisons of imaging-based progression-free survival and overall survival to imbalance of censoring between the study arms. The censoring events of principal interest for analysis were 'adequate assessment not available' for imaging-based progression-free survival, and 'lost to follow-up' and 'withdrawal of consent' for overall survival. The four types of analyses used published and accepted methods.[3,4]

The extreme-case analysis considered all drop-outs in the ^{177}Lu-PSMA-617 arm as events. The two best-case analyses imputed data for drop-outs in the control arm based on the hazard rate in the 20% of patients with the longest survival either overall or in the control arm only. 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 or control arm that would make the primary analysis lose statistical significance.

Statistical analyses for HRQoL and pain outcomes

HRQoL and pain were analyzed in patients randomized after 5 March 2019 who had a baseline and at least one post-baseline assessment. Time to worsening in FACT-P total score was defined as the time from randomization to a decrease of 10 points or more, clinical disease progression (excluding imaging-based and PSA progression), or death. Time to worsening in BPI-SF pain intensity was defined as time from randomization to an increase of 30% or more, an increase of 2 points or more, clinical disease progression (excluding imaging-based and PSA progression), or death. The stratified Cox regression model was used to estimate hazard ratio and associated confidence interval (CI). Median, percentiles and associated confidence interval were estimated using the Kaplan-Meier method.

SUPPLEMENTARY RESULTS

Grade 5 treatment-related adverse events.

Grade 5 treatment-related adverse events occurred in 5/529 patients (0.9%) in the ^{177}Lu-PSMA-617 plus standard care arm and none in the control arm (pancytopenia, n=2; bone-marrow failure, n=1; subdural hematoma, n=1; intracranial hemorrhage, n=1).

Serious treatment-related adverse events

Serious drug-related treatment-emergent adverse events reported in the ^{177}Lu-PSMA-617 plus standard care arm (Table 2) were: grade 2–3 anemia in 11/529 patients (2.1%), grade 3–5 pancytopenia in 5 (0.9%; two grade 5), grade 3–4 thrombocytopenia in 3 (0.6%), grade 3 leukopenia in 2 (0.4%), grade 5 bone marrow failure in 1 (0.2%), grade 1 febrile neutropenia in 1 (0.2%), grade 3 neutropenia in 1 (0.2%); grade 3 cardiac failure in 1 (0.2%), grade 3 ventricular tachycardia in 1 (0.2%); grade 2–3 nausea in 2 (0.4%), grade 2–3 vomiting in 2 (0.4%); grade 3 abdominal pain in 1 (0.2%), grade 3 constipation in 1 (0.2%), grade 3 upper gastrointestinal hemorrhage in 1 (0.2%); grade 3 fatigue in 1 (0.2%), grade 3 generalized edema in 1 (0.2%), grade 3 peripheral edema in 1 (0.2%), grade 3 pain in 1 (0.2%), grade 1 pyrexia in 1 (0.2%); grade 3 pneumonia in 2 (0.4%), grade 3 herpes zoster in 1 (0.2%), grade 3 infection in 1 (0.2%), grade 4 sepsis in 1 (0.2%), grade 3 septic shock in 1 (0.2%), grade 3 urinary tract infection in 1 (0.2%), grade 3 wound infection in 1 (0.2%); grade 5 subdural hematoma in 1 (0.2%); grade 3 dehydration in 1 (0.2%), grade 4 hypocalcemia in 1 (0.2%), grade 3 hypokalemia in 1 (0.2%), grade 3 tumor lysis syndrome in 1 (0.2%); grade 3 arthralgia in 1 (0.2%); grade 1 or 5 intracranial hemorrhage in 2 (0.4%), grade 2 cerebral infarction in 1 (0.2%), grade 2 seizure in 1 (0.2%); grade 3 syncope in 1 (0.2%); grade 2 delirium in 1 (0.2%); and grade 3 acute kidney injury in 2 (0.4%), grade 3 hematuria in 2 (0.4%); and grade 3 pulmonary embolism in 1 (0.2%).

Serious drug-related treatment-emergent adverse events reported in the standard care alone arm (Table 2) were: grade 4 inappropriate antidiuretic hormone secretion in 1 (0.5%); grade 3 lower gastrointestinal hemorrhage in 1 (0.5%); grade 2 hepatocellular injury in 1 (0.5%); grade 3 hypervolemia in 1 (0.5%), grade 4 hyperphosphatemia in 1 (0.5%); and grade 3 spinal cord compression in 1 (0.5%).

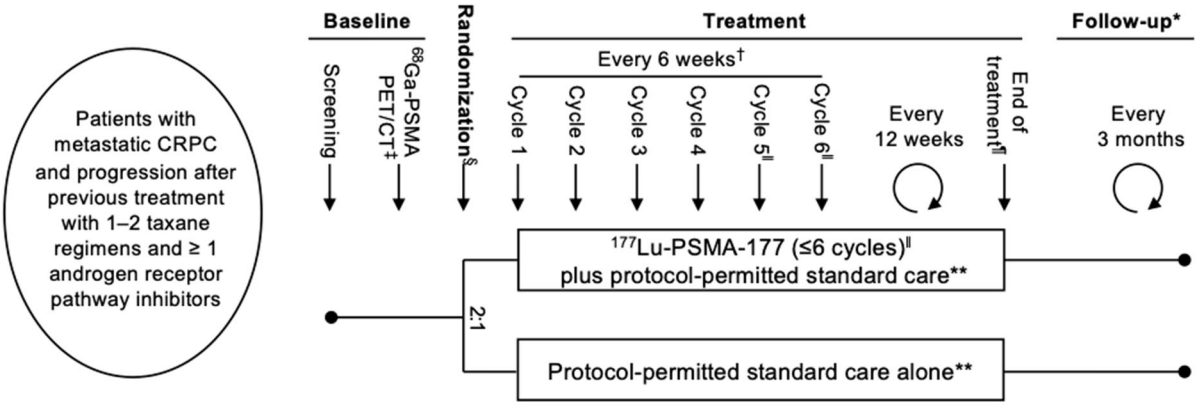
^{68}Ga-PSMA-11 population, exposure and safety

Baseline characteristics of the 1003 patients who received ^{68}Ga-PSMA-11 for PET/CT, including those not enrolled, are shown in Table S13. They received a median decay-

corrected dose of 166.60 MBq (range, 92.8–287.5), or 1.92 MBq/kg (0.9–3.7) when corrected for body weight. ^{68}Ga-PSMA-11 treatment-emergent adverse events are shown in Table S14.

SUPPLEMENTARY FIGURES

Figure S1. Study design



CT/MRI and ^{99m}Tc bone scans	x……x††		…..Every 8 weeks for 24 weeks…..						x			(x)††
ECOG performance status	x……x§§		x	x	x	x	x	x	x	x		
HRQoL and pain scores‖‖	x……x§§		x	x	x	x	x	x	x	x		
Physical examination	x……x§§		x	x	x	x	x	x	x	x		
Weight and vital signs	x……x§§		x	x	x	x	x	x	x	x		
Testosterone and PSA	x……x§§		x	x	x	x	x	x	x	x		
Hematology and biochemistry	x……x§§		x¶¶	x¶¶	x¶¶	x¶¶	x¶¶	x¶¶	x	x		x
Adverse events and treatments	x***……											x†††

*Follow-up for 24 months or until 508 patients had died.

†Within 1 week of scheduled ^{177}Lu-PSMA-617 treatment unless delayed by ≤4 weeks for toxicity or adverse events.

‡PET/CT with ^{68}Ga-PSMA-11 performed 1–6 weeks before start of treatment in patients meeting all other enrolment criteria (except presence of metastatic lesions).

§Randomization up to 28 days before start of treatment; stratified by baseline LDH level (≤260 U/mL or >260 U/mL), presence or absence of liver metastases, ECOG Performance Status (0–1 or 2) and inclusion or non-inclusion of androgen receptor pathway inhibition in protocol-permitted standard care at randomization.

‖Cycles 5 and 6 of ^{177}Lu-PSMA-617 only in patients with evidence of response, radiological signs of residual disease and good tolerance.

¶Randomly assigned study treatment continued until imaging-based disease progression, unacceptable toxicity, requirement for a prohibited treatment, non-compliance, lack of clinical benefit, or withdrawal by the patient, investigator or sponsor; patients continued on protocol-permitted standard care while and after receiving ^{177}Lu-PSMA-617.

**Planned before randomization; prohibited treatments were investigational agents, cytotoxic chemotherapy, immunotherapy, systemic radioisotopes and hemi-body radiotherapy.

††Baseline imaging up to 28 days before start of treatment.

‡‡In patients who did not discontinue treatment because of imaging-based disease progression.

§§Baseline assessments up to 4 weeks before start of treatment.

‖‖EQ-5D, FACT-P and BPI-SF.

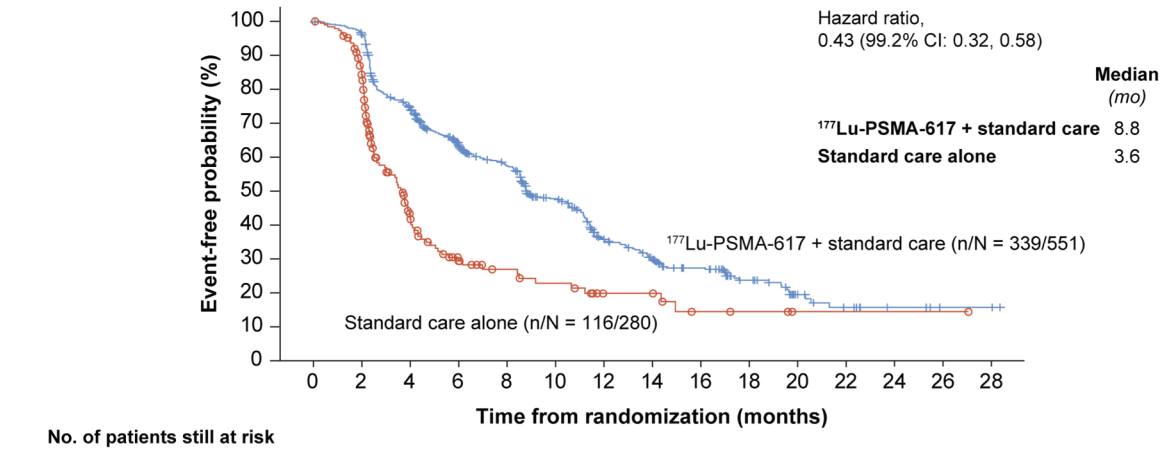
¶¶Every week during cycle 1 and every other week during cycles 2–6.

***Adverse events and serious adverse events were monitored from consent onwards; treatment-emergent adverse events were those occurring from the first dose of randomized treatment up to and including 30 days after the last dose.

†††Adverse events were self-reported in the follow-up period and serious adverse events were not included.

BPI-SF, Brief Pain Inventory – Short Form; CRPC, castration-resistant prostate cancer; CT, computed tomography with contrast; ECOG, Eastern Cooperative Oncology Group; EQ-5D, EuroQol 5-dimension 5-level; FACT-P, Functional Assessment of Cancer Therapy – Prostate; HRQoL, health-related quality of life; PSA, prostate specific antigen; PSMA, prostate specific membrane antigen; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PET, positron emission tomography.

Figure S2. Imaging-based progression-free survival in all randomized patients (*ad hoc* analysis)



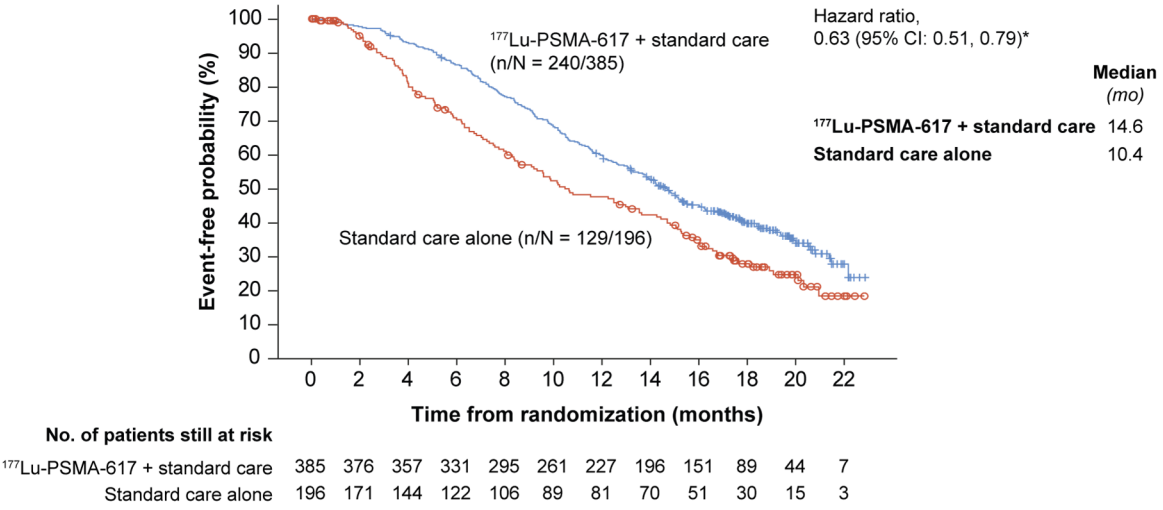
No. of patients still at risk

^{177}Lu-PSMA-617 + standard care	551	510	382	289	246	180	118	92	68	38	18	11	5	2	2
Standard care alone	280	150	50	27	20	16	9	9	4	3	1	1	1	1	0

Shown is imaging-based progression-free survival in patients allocated to ^{177}Lu-PSMA-617 plus standard care or standard care alone, in all randomized patients (N=831). Imaging-based progression-free survival was independently centrally reviewed and defined as the time to imaging-documented disease progression per PCWG3 criteria or death.

CI, confidence interval; PCWG3, Prostate Cancer Working Group 3.

Figure S3. Overall survival in the analysis set used for imaging-based progression-free survival (prespecified supplementary analysis with *ad hoc* adjustment)



*Hazard ratio of 0.64 (95% CI: 0.51, 0.80) after *ad hoc* adjustment for post-protocol chemotherapy using a time-dependent covariate; chemotherapy includes taxanes and platinum-based compounds (see Table S4).

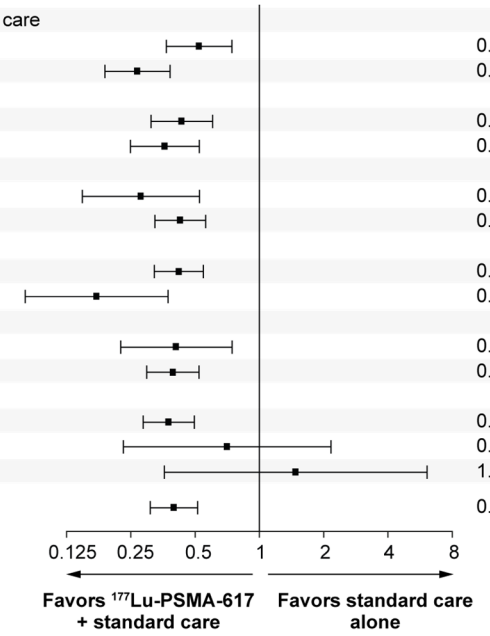
Data are from patients randomized after implementation of enhanced study site education measures, n=581 (see Supplementary Methods).

CI, confidence interval.

Figure S4. Prespecified subgroup analyses of imaging-based progression-free survival and overall survival

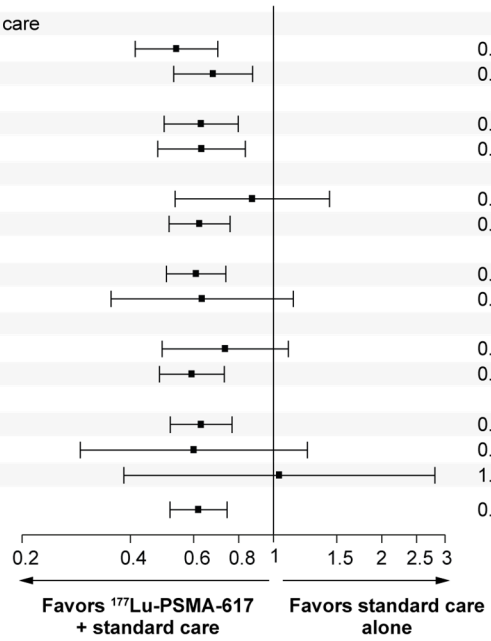
A Imaging-based progression-free survival (n=581)

Subgroup	^{177}Lu-PSMA-617 + standard care (N=385) n/N	(%)	Standard care alone (N=196) n/N	(%)	Hazard ratio (95% CI)
Androgen receptor pathway inhibitors as part of planned standard care					
Yes	107/70	(62.9)	46/107	(43.0)	0.53 (0.37, 0.76)
No	147/215	(68.4)	47/89	(52.8)	0.27 (0.19, 0.39)
LDH					
≤260 IU/L	149/244	(61.1)	49/120	(40.8)	0.44 (0.32, 0.61)
>260 IU/L	104/140	(74.3)	44/75	(58.7)	0.37 (0.25, 0.53)
Liver metastases					
Yes	33/37	(89.2)	17/22	(77.3)	0.28 (0.15, 0.53)
No	221/348	(63.5)	76/174	(43.7)	0.43 (0.33, 0.57)
ECOG score					
0 or 1	228/352	(64.8)	83/179	(46.4)	0.43 (0.33, 0.56)
2	26/33	(78.8)	10/17	(58.8)	0.18 (0.08, 0.38)
Age					
<65 years	62/96	(64.6)	15/39	(38.5)	0.42 (0.23, 0.76)
≥65 years	192/289	(66.4)	78/157	(49.7)	0.40 (0.30, 0.53)
Race					
White	224/336	(66.7)	80/166	(48.2)	0.38 (0.29, 0.50)
African American or Black	15/29	(51.7)	4/14	(28.6)	0.72 (0.23, 2.20)
Asian	4/6	(66.7)	4/9	(44.4)	1.50 (0.36, 6.19)
All patients	254/385	(66.0)	93/196	(47.4)	0.40 (0.31, 0.52)



B Overall survival (N=831)

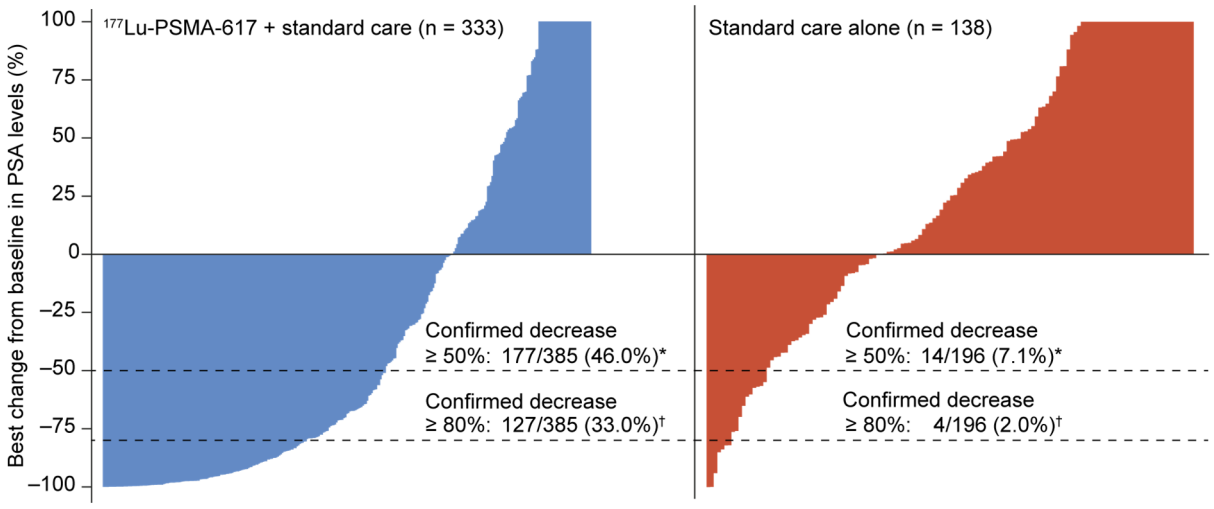
Subgroup	^{177}Lu-PSMA-617 + standard care (N=551) n/N	(%)	Standard care alone (N=280) n/N	(%)	Hazard ratio (95% CI)
Androgen receptor pathway inhibitors as part of planned standard care					
Yes	135/243	(55.6)	96/146	(65.8)	0.54 (0.41, 0.70)
No	208/308	(67.5)	91/134	(67.9)	0.68 (0.53, 0.87)
LDH					
≤260 IU/L	202/368	(54.9)	107/182	(58.8)	0.63 (0.50, 0.80)
>260 IU/L	140/182	(76.9)	80/97	(82.5)	0.63 (0.48, 0.84)
Liver metastases					
Yes	40/48	(83.3)	28/34	(82.4)	0.87 (0.53, 1.43)
No	303/503	(60.2)	159/246	(64.6)	0.62 (0.51, 0.76)
ECOG score					
0 or 1	305/510	(59.8)	170/258	(65.9)	0.61 (0.50, 0.74)
2	38/41	(92.7)	17/22	(77.3)	0.63 (0.35, 1.13)
Age					
<65 years	82/145	(56.6)	38/60	(63.3)	0.73 (0.49, 1.10)
≥65 years	261/406	(64.3)	149/220	(67.7)	0.59 (0.48, 0.73)
Race					
White	300/486	(61.7)	159/235	(67.7)	0.63 (0.52, 0.77)
African American or Black	20/34	(58.8)	12/21	(57.1)	0.60 (0.29, 1.24)
Asian	9/9	(100)	7/11	(63.6)	1.04 (0.38, 2.81)
All patients	343/551	(62.3)	187/280	(66.8)	0.62 (0.52, 0.74)



Panel A data are from patients randomized after implementation of enhanced study site education measures (see Supplementary Methods). Panel B data are from all randomized patients. The vertical line indicates the point of no effect at a hazard ratio of unity; hazard ratios below unity favor ^{177}Lu-PSMA-617. Error bars indicate 95% CI.

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group, LDH, lactate dehydrogenase

Figure S5. Prostate specific antigen responses (additional secondary outcome)

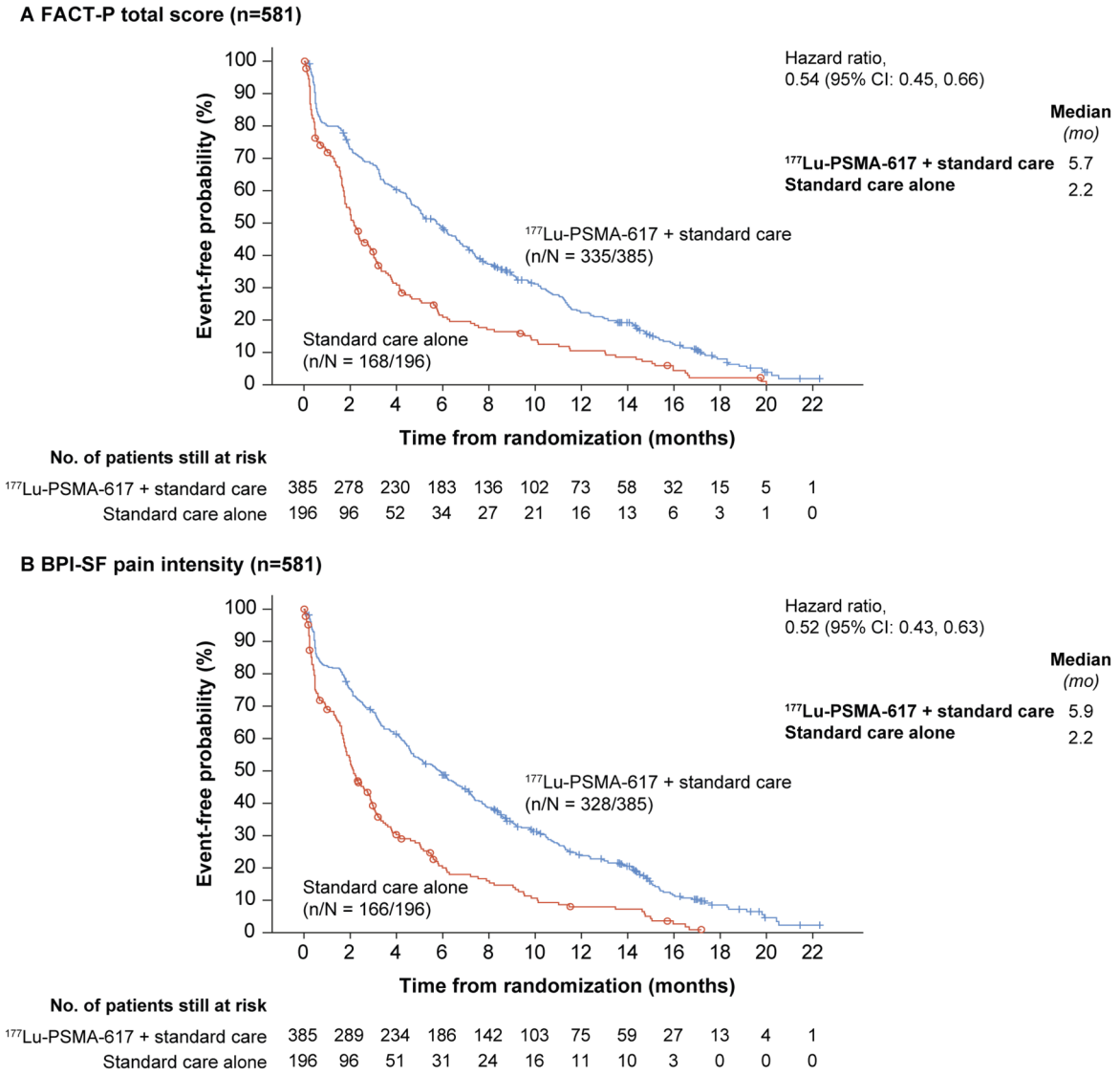


*Odds ratio, 11.19 (95% CI: 6.25, 20.04)
†Odds ratio, 23.62 (95% CI: 8.57, 65.11)

Data are from patients with available PSA data allocated to ^{177}Lu-PSMA-617 plus standard care or standard care alone. The proportion of patients with any decrease in best percentage change from baseline was 71.5% in the ^{177}Lu-PSMA-617 arm and 35.5% in the control arm. Data are from patients randomized after implementation of enhanced study site education measures, n=581 (see Supplementary Methods). Increases greater than 100% are truncated to 100%.

PSA, prostate specific antigen.

Figure S6. Top-line health-related quality of life and pain outcomes



Panel A shows time to worsening of 10 points or greater in FACT-P total score, clinical disease progression, or death. Panel B shows time to worsening of 30% or greater or 2 points or greater in BPI-SF pain intensity, clinical disease progression, or death. Data are from patients randomized after implementation of enhanced study site education measures (see Supplementary Methods) who had a baseline assessment and at least one post-baseline assessment.

BPI-SF, Brief Pain Inventory – Short Form; CI, confidence interval; FACT-P, Functional Assessment of Cancer Therapy – Prostate.

SUPPLEMENTARY TABLES

Table S1. Prespecified study endpoints and definitions

Endpoint	Definition
Alternate primary endpoints	
Imaging-based progression-free survival*	Time from randomization to centrally reviewed imaging-documented disease progression, defined according to PCWG3 guidelines,[2] or death.
Overall survival†	Time from randomization to death.
Key secondary endpoints	
Overall response rate*	RECIST v1.1 complete response or partial response in soft tissue, lymph node or visceral lesions.
Disease control rate*	RECIST v1.1 complete response, partial response or stable disease in soft tissue, lymph node or visceral lesions.
Time to first symptomatic skeletal event*	Time from randomization to first new pathological bone fracture, spinal cord compression, tumor-related orthopedic surgery, radiation therapy for bone pain, or death.
Additional secondary endpoints	
Safety and tolerability‡	Results of clinical laboratory evaluations, vital signs, adverse event monitoring.
Health-related quality of life*	Patient responses on EQ-5D, FACT-P and BPI-SF instruments.
Health economics*	Defined in separate analysis plan.
Progression-free survival*	Time from randomization to first evidence of centrally reviewed imaging-based progression (defined according to PCWG3 guidelines),[2] clinical progression (defined as marked increase in pain warranting chemotherapy; immediate need for new intervention due to progression; ECOG performance status grade 3 or higher or marked deterioration; and discontinuation of treatment due to progression), PSA progression (confirmed increase in levels of both 25% and 2 ng/mL from baseline or nadir, whichever is lower, occurring after 12 weeks of treatment) or death.
Biochemical response*	PSA response, defined as ≥50% or ≥80% decrease from baseline, duration of response, PSA doubling time, changes from baseline in PSA, ALP and LDH levels.

*Assessed in patients randomized on or after the date when enhanced study site education measures were implemented to reduce the drop-out rate in the control arm (See Supplementary Methods).

†Assessed in all randomized patients

‡Assessed in all randomized patients who received treatment (at least one dose).

See original and most recent versions of the study protocol for further details (available at NEJM.org with the full text of this article).

BPI-SF, Brief Pain Inventory – Short Form; ECOG, Eastern Cooperative Oncology Group; EQ-5D-5L, EuroQoL 5-domain 5-level; FACT-P, Functional Assessment of Cancer Therapy – Prostate; PCWG3, Prostate Cancer Working Group 3; RECIST, Response Evaluation Criteria in Solid Tumors; PSA, prostate-specific antigen.

Table S2. Alternate primary endpoints and overall type 1 error control

Endpoint	Prespecified final analysis
A: Imaging-based 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 imaging-based 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 imaging-based 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 imaging-based progression free survival nor overall survival is met.

Table S3. Characteristics of patients at baseline (expanded)

Characteristic	Imaging-based progression-free survival analysis set (n=581)*		All randomized patients (N=831)	
	^{177}Lu-PSMA-617 plus standard care (n=385)	Standard care alone (n=196)	^{177}Lu-PSMA-617 plus standard care (n=551)	Standard care alone (n=280)
Age				
Median (range) – years	71.0 (52–94)	72.0 (51–89)	70.0 (48–94)	71.5 (40–89)
≥65–84 years – no (%)	282 (73.2)	152 (77.6)	398 (72.2)	214 (76.4)
≥85 years – no. (%)	7 (1.8)	5 (2.6)	8 (1.5)	6 (2.1)
Race – no. (%)				
White	336 (87.3)	166 (84.7)	486 (88.2)	235 (83.9)
Black or African-American	29 (7.5)	14 (7.1)	34 (6.2)	21 (7.5)
Asian	6 (1.6)	9 (4.6)	9 (1.6)	11 (3.9)
Other†	2 (0.5)	0	2 (0.4)	0
Missing	12 (3.1)	7 (3.6)	20 (3.6)	13 (4.6)
ECOG performance status – no. (%)				
0 or 1	352 (91.4)	179 (91.3)	510 (92.6)	258 (92.1)
2	33 (8.6)	17 (8.7)	41 (7.4)	22 (7.9)
Site of disease – no. (%)				
Lung	35 (9.1)	20 (10.2)	49 (8.9)	28 (10.0)
Liver	47 (12.2)	26 (13.3)	63 (11.4)	38 (13.6)
Lymph node	193 (50.1)	99 (50.5)	274 (49.7)	141 (50.4)
Bone	351 (91.2)	179 (91.3)	504 (91.5)	256 (91.4)
RECIST v1.1 lesions‡				
Sum of target lesion diameters in mm – median (range)	44.0 (10–351)	43.5 (10–209)	45.0 (10–351)	46.2 (10–249)
Target lesions – no. (%)	203 (52.7)	100 (51.0)	279 (50.6)	140 (50.0)
Non-target lesions – no. (%)	303 (78.7)	144 (73.5)	429 (77.9)	212 (75.7)
Prostate-specific antigen doubling time§				
No.	182	82	269	131
Median (range) – months	2.40 (0.0–37.3)	2.82 (0.0–93.1)	2.37 (0.0–74.4)	2.60 (0.0–93.1)
≤6 months – no. (%)	167 (91.8)	70 (85.4)	245 (91.1)	115 (87.8)
Prostate-specific antigen – ng/mL				
Median (range)	93.2 (0–6988)	90.7 (0–6600)	77.5 (0–6988)	74.6 (0–8995)
Alkaline phosphatase – IU/liter				
No.	383	195	547	278
Median (range)	108.0 (26–2524)	96.0 (34–1355)	105.0 (17–2524)	94.5 (28–1355)
Lactate dehydrogenase – IU/liter				
No.	384	195	550	279
Median (range)	230.5 (119–5387)	232.0 (105–2693)	221.0 (88–5387)	224.0 (105–2693)
Prostate cancer history				
Time since diagnosis – years				
Median (range)	7.26 (0.9–28.9)	7.01 (0.7–26.2)	7.42 (0.9–28.9)	7.37 (0.7-26.2)
Gleason score at diagnosis – no. (%)				
8–10	226 (58.7)	118 (60.2)	324 (58.8)	170 (60.7)
Unknown	28 (7.3)	19 (9.7)	42 (7.6)	24 (8.6)
Previous prostatectomy – no. (%)‖	159 (41.3)	82 (41.8)	240 (43.6)	130 (46.4)
Previous radiotherapy – no. (%)	286 (74.3)	152 (77.6)	415 (75.3)	217 (77.5)
Previous systemic therapy¶				
1 regimen	1 (0.3)	0	1 (0.2)	0
2 regimens	16 (4.2)	13 (6.6)	22 (4.0)	15 (5.4)
3 regimens	74 (19.2)	33 (16.8)	95 (17.2)	41 (14.6)
≥3 regimens	294 (76.4)	150 (76.5)	433 (78.6)	224 (80.0)

Previous androgen receptor pathway inhibitor – no. (%)**				
1 regimen	213 (55.3)	98 (50.0)	298 (54.1)	128 (45.7)
2 regimens	150 (39.0)	86 (43.9)	213 (38.7)	128 (45.7)
>2 regimens	22 (5.7)	12 (6.1)	40 (7.3)	24 (8.6)
Abiraterone	157 (40.8)	85 (43.4)	187 (33.9)	106 (37.9)
Abiraterone acetate	110 (28.6)	62 (31.6)	210 (38.1)	114 (40.7)
Enzalutamide	280 (72.7)	145 (74.0)	395 (71.7)	206 (73.6)
Apalutamide	8 (2.1)	5 (2.6)	13 (2.4)	5 (1.8)
Previous taxane therapy – no. (%)††				
1 regimen	207 (53.8)	102 (52.0)	325 (59.0)	156 (55.7)
2 regimens	173 (44.9)	92 (46.9)	220 (39.9)	122 (43.6)
>2 regimens	5 (1.3)	2 (1.0)	6 (1.1)	2 (0.7)
Docetaxel	377 (97.9)	191 (97.4)	534 (96.9)	273 (97.5)
Cabazitaxel	161 (41.8)	84 (42.9)	209 (37.9)	107 (38.2)

*Patients randomized on or after the date when enhanced study site education measures were implemented to reduce the drop-out rate in the control group (see Supplementary Methods).

†Other includes native Hawaiian or other Pacific islander, American or Alaskan native, and more than one race reported.

‡In patients with disease evaluable by RECIST v1.1 at baseline.

§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 (months). Patients with at least 3 PSA values prior to and at the time of screening were included in the model. Negative values were set to zero. Patients not included in the ≤6-month category had stable, non-increasing or decreasing PSA levels, or doubling time >6 months (data not shown).

‖Excludes biopsy; includes prostatectomy, radical prostatectomy, transurethral prostatectomy, cysto-prostatectomy and retro-pubic prostatectomy.

¶Includes radium-223 dichloride in 145/831 (17.4%) and sipuleucel-T in 158/831(19.0%) patients overall, well balanced between arms.

**Androgen receptor pathway inhibitors defined as enzalutamide, abiraterone, and apalutamide.

††Taxane defined as cabazitaxel, docetaxel or paclitaxel. Reasons for the last taxane therapy were: therapeutic in 559/831 (67.3%), adjuvant in 109/831 (13.1%), unknown in 106/831 (12.8%), neo-adjuvant in 33/831 (4.0%), maintenance in 17/831 (2.0%), other in 5/831 (0.6%) and prophylaxis in 2/831 (0.2%) patients overall, well balanced between arms.

ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen; RECIST, response evaluation criteria in solid tumors; SD, standard deviation.

Table S4. Cancer-related therapy after discontinuation of randomized treatment in the imaging-based progression-free survival analysis set

Treatment*	^{177}Lu-PSMA-617 plus standard care (n=385)	Standard care alone (n=196)	Overall (n=581)
Radiotherapy – no. (%)	25 (6.5)	22 (11.2)	47 (8.1)
Medication – no. (%)	97 (25.2)	63 (32.1)	160 (27.5)
Medications received by ≥1% of patients overall – no. (%)†			
Taxanes	64 (16.6)	44 (22.4)	108 (18.6)
Cabazitaxel	51 (13.2)	38 (19.4)	89 (15.3)
Docetaxel	17 (4.4)	8 (4.1)	25 (4.3)
Paclitaxel	2 (0.5)	2 (1.0)	4 (0.7)
Paclitaxel albumin	1 (0.3)	0	1 (0.2)
Platinum compounds	24 (6.2)	16 (8.2)	40 (6.9)
Carboplatin	22 (5.7)	16 (8.2)	38 (6.5)
Cisplatin	3 (0.8)	1 (0.5)	4 (0.7)
Monoclonal antibodies	8 (2.1)	14 (7.1)	22 (3.8)
Nivolumab	3 (0.8)	2 (1.0)	5 (0.9)
Ipilimumab	2 (0.5)	1 (0.5)	3 (0.5)
Pembrolizumab	2 (0.5)	7 (3.6)	9 (1.5)
Atezolizumab	1 (0.3)	3 (1.5)	4 (0.7)
Durvalumab	1 (0.3)	0	1 (0.2)
Jnj 63723283	1 (0.3)	0	1 (0.2)
Tremelimumab	1 (0.3)	0	1 (0.2)
Bevacizumab	0	3 (1.5)	3 (0.5)
Anti-androgens	12 (3.1)	9 (4.6)	21 (3.6)
Enzalutamide	6 (1.6)	4 (2.0)	10 (1.7)
Apalutamide	3 (0.8)	2 (1.0)	5 (0.9)
Darolutamide	2 (0.5)	3 (1.5)	5 (0.9)
Proxalutamide	1 (0.3)	0	1 (0.2)
Bicalutamide	0	1 (0.5)	1 (0.2)
Investigational drug	7 (1.8)	12 (6.1)	19 (3.3)
Other anti-neoplastic agents	9 (2.3)	8 (4.1)	17 (2.9)
Olaparib	5 (1.3)	6 (3.1)	11 (1.9)
Niraparib	2 (0.5)	0	2 (0.3)
CDX 301	1 (0.3)	0	1 (0.2)
Estramustine	1 (0.3)	0	1 (0.2)
Rucaparib	0	1 (0.5)	1 (0.2)
Talazoparib	0	1 (0.5)	1 (0.2)
Therapeutic radiopharmaceuticals	7 (1.8)	9 (4.6)	16 (2.8)
Radium Ra-223 dichloride	7 (1.8)	6 (3.1)	13 (2.2)
Lutetium (^{177}Lu) PSMA-617	0	1 (0.5)	1 (0.2)
Various	0	2 (1.0)	2 (0.3)
Other hormone antagonists	11 (2.9)	2 (1.0)	13 (2.2)
Abiraterone	9 (2.3)	1 (0.5)	10 (1.7)
Abiraterone acetate	2 (0.5)	1 (0.5)	3 (0.5)
Nitrogen mustard analogues	4 (1.0)	3 (1.5)	7 (1.2)
Cyclophosphamide	3 (0.8)	3 (1.5)	6 (1.0)
Chlorambucil	1 (0.3)	0	1 (0.2)
Etoposide	6 (1.6)	1 (0.5)	7 (1.2)

*Data are from patients randomized after implementation of enhanced study site education, n=581 (see Supplementary Methods).

†Overall; ranked by overall frequency; coded using WHODrug Global version March 2020 B3.

Table S5. Events and censoring in imaging-based progression-free survival and overall survival endpoint primary analyses

	Imaging-based progression-free survival analysis set (n=581)*		All randomized patients (N=831)	
	^{177}Lu-PSMA-617 plus standard care (n=385)	Standard care alone (n=196)	^{177}Lu-PSMA-617 plus standard care (n=551)	Standard care alone (n=280)
Imaging-based progression-free survival – no. (%)				
Imaging-based progression	171 (44.4)	59 (30.1)	NA	NA
Death	83 (21.6)	34 (17.3)	NA	NA
Censored	131 (34.0)	103 (52.6)	NA	NA
Ongoing without event	90 (23.4)	24 (12.2)	NA	NA
Event documented after ≥2 tumor assessments missed	36 (9.4)	44 (22.4)	NA	NA
Adequate assessment not available*	5 (1.3)	35 (17.9)	NA	NA
Overall survival – no. (%)				
Death	NA	NA	343 (62.3)	187 (66.8)
Censored	NA	NA	208 (37.7)	93 (33.2)
Alive†	NA	NA	189 (34.3)	55 (19.6)
Lost to follow-up‡	NA	NA	4 (0.7)	5 (1.8)
Withdrew consent	NA	NA	15 (2.7)	33 (11.8)

*Patients without adequate baseline or post-baseline assessments.
†Patients without event and still on study at data cut-off date.
‡Patients who discontinued the study for reasons other than withdrew consent.

Table S6. Exploratory sensitivity analyses of imaging-based progression-free survival and overall survival

Analysis	Scenario	
Imaging-based progression-free survival		**HR (99.2% CI)**
Analysis per protocol	No adjustment	0.40 (0.29, 0.57)
Extreme case	Consider censoring as events in treatment arm	0.42 (0.30, 0.60)
Multiple imputation under best patients overall	Hazard in control arm based on best 20% of patients across both arms	0.77 (0.55, 1.07)
Multiple imputation under best patients in control arm	Hazard in control arm based on best 20% of patients in the control arm	0.56 (0.40, 0.79)
Multiple imputation under non-informative censoring	Hazard unchanged after censoring	0.40 (0.29, 0.56)
Multiple imputation under informative censoring	Hazard decrease by 60% in control arm after censoring*	0.54 (0.38, 0.77)
Tipping point: upper 99.2% CI = 1	Hazard decrease by 85% in control arm after censoring*	0.71 (0.50, 1.01)
Tipping point: extreme case	Hazard decrease by 11% in control arm after censoring*	0.42 (0.30, 0.59)
Overall survival		**HR (95% CI)**
Analysis per protocol	No adjustment	0.62 (0.52, 0.74)
Extreme case	Consider censoring as events in treatment arm	0.66 (0.55, 0.79)
Multiple imputation under best patients overall	Hazard in control arm based on best 20% of patients across both arms	0.80 (0.67, 0.96)
Multiple imputation under best patients in control arm	Hazard in control arm based on best 20% of patients in the control arm	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 control arm after censoring*	0.68 (0.56, 0.82)
Tipping point: upper 95% CI = 1	Hazard decrease by 99% in control arm after censoring*	0.84 (0.70, 1.00)
Tipping point: extreme case	Hazard decrease by 27% in control arm after censoring*	0.66 (0.55, 0.79)

*Risk remains unchanged after censoring in the ^{177}Lu-PSMA-617 arm

Table S7. RECIST v1.1 response rates per independent central review

	^{177}Lu-PSMA-617 plus standard care (n=385)	Standard care alone (n=196)
In patients with measurable disease at baseline*		
Number of patients	184	64
Best overall response – no. (%)		
Complete response	17 (9.2)	0
Partial response	77 (41.8)	2 (3.1)
Stable disease	65 (35.3)	30 (46.9)
Progressive disease	24 (13.0)	29 (45.3)
Unknown	1 (0.5)	3 (4.7)
In patients with evaluable disease at baseline†		
Number of patients	319	120
Best overall response – no. (%)		
Complete response	18 (5.6)	0
Partial response	77 (24.1)	2 (1.7)
Stable disease	68 (21.3)	30 (25.0)
Non-complete response / non-progressive disease‡	121 (37.9)	48 (40.0)
Progressive disease	33 (10.3)	35 (29.2)
Unknown	2 (0.6)	5 (4.2)
Statistical analysis in patients with evaluable disease at baseline§		
Number of patients	319	120
Overall response rate – no. (%)‖	95 (29.8)	2 (1.7)
Odds ratio (95% CI)	24.99 (6.05, 103.24)	
P value	<0.001	
Disease control rate – no. (%)¶	284 (89.0)	80 (66.7)
Odds ratio (95% CI)	5.79 (3.18, 10.55)	
P value	<0.001	

*Patients with at least one target lesion (per PCWG3 guidance).

†Patients with at least one target lesion or at least one non-target lesion.

‡Category for patients with no target lesions.

§Key secondary endpoint; the statistical analysis plan (available at NEJM.org) defines this as responses among patients with measurable disease at baseline, but also specifies inclusion of non-complete response / non-progressive disease, which is a category reserved for patients with non-measurable disease.

‖Sum of complete response and partial response.

¶Sum of complete response, partial response, stable disease, and non-complete response / non-progressive disease.

CI, confidence interval; RECIST, response evaluation criteria in solid tumors;

Table S8. Exposure to ^{177}Lu-PSMA-617 and standard care treatments

Exposure metric*	^{177}Lu-PSMA-617 plus standard care (n=529)	Standard care alone (n=205)
Standard care		
Duration of exposure – months		
Median (range)	7.56 (0.3–31.3)	2.07 (0.0–26.0)
Cycles started per patient – no.		
Median (range)	5.0 (1–16)	2.0 (1–14)
Average duration of cycle – months		
Median (range)	1.38 (0.2–2.4)	1.12 (0.0–2.0)
Patients with at least one delayed cycle – no. (%)	158 (29.9)	16 (7.8)
^{177}Lu-PSMA-617		
Duration of exposure – months		
Median (range)	6.90 (0.3–10.2)	NA
Cycles started per patient – no.		
Median (range)	5.0 (1–6)	NA
Average duration of cycle – months		
Median (range)	1.37 (0.3–2.4)	NA
Patients with at least one delayed cycle – no. (%)	93 (17.6)	NA
Patients with at least one dose interrupted – no. (%)	16 (3.0)	NA
Patients with at least one dose reduced† – no. (%)	30 (5.7)	NA
Cumulative dose per patient – GBq		
Median (range)	37.53 (7.0–48.3)	NA
Dose intensity – GBq per cycle		
Cycle 1 – median (range)	7.53 (6.1–8.2)	NA
Cycle 2 – median (range)	7.51 (5.7–8.1)	NA
Cycle 3 – median (range)	7.47 (5.7–8.1)	NA
Cycle 4 – median (range)	7.48 (5.8–8.1)	NA
Cycle 5 – median (range)	7.49 (5.3–8.2)	NA
Cycle 6 – median (range)	7.51 (5.8–8.3)	NA
Dose intensity – GBq per month		
Median (range)	5.45 (3.1–25.3)	NA

*Data for all randomized patients who received at least one dose of their assigned treatment (standard care with or without ^{177}Lu-PSMA-617).

†Due to an adverse event.

NA, not applicable.

Table S9. Standard care therapy

Treatment*	^{177}Lu-PSMA-617 plus standard care (n=529)	Standard care alone (n=205)	Overall (n=734)
Medication – no. (%)	529 (100.0)	205 (100.0)	734 (100.0)
Radiotherapy – no. (%)	79 (14.9)	34 (16.6)	113 (15.4)
Other interventions – no. (%)	24 (4.5)	5 (2.4)	29 (4.0)
Standard-care anti-cancer medications† received by ≥1% of patients – no. (%)‡			
Gonadotropin-releasing hormone analogues	468 (88.5)	172 (83.9)	640 (87.2)
Glucocorticoids	335 (63.3)	134 (65.4)	469 (63.9)
Androgen receptor pathway inhibitors	278 (52.6)	139 (67.8)	417 (56.8)
Enzalutamide	157 (29.7)	87 (42.4)	244 (33.2)
Abiraterone	132 (25.0)	72 (35.1)	204 (27.8)
Apalutamide	10 (1.9)	1 (0.5)	11 (1.5)
Darolutamide	2 (0.4)	1 (0.5)	3 (0.4)
Denosumab	184 (34.8)	80 (39.0)	264 (36.0)
Bisphosphonates	45 (8.5)	28 (13.7)	73 (9.9)
Testosterone 5α reductase inhibitors	16 (3.0)	11 (5.4)	27 (3.7)
Degarelix acetate	12 (2.3)	1 (0.5)	13 (1.8)
Degarelix	6 (1.1)	5 (2.4)	11 (1.5)
Estrogens	12 (2.3)	1 (0.5)	13 (1.8)

*Data for all randomized patients who received at least one dose of their assigned treatment (standard care therapy and/or ^{177}Lu-PSMA-617)

†Standard-of-care supportive measures not shown, e.g. pain control, fluid hydration, etc.

‡Overall; ranked by overall frequency; coded using WHODrug Global version March 2020 B3, except for androgen receptor pathway inhibitors, which includes the drugs shown from the codes ‘anti-androgens’ and ‘other hormone antagonists and related agents’.

Table S10. Cancer-related therapy after discontinuation of randomized study treatment

Treatment*	^{177}Lu-PSMA-617 plus standard care (n=551)	Standard care alone (n=280)
Radiotherapy – no. (%)	49 (8.9)	31 (11.1)
Medication – no. (%)	155 (28.1)	97 (34.6)
Medications received by ≥1% of patients – no. (%)†		
Taxanes	99 (18.0)	61 (21.8)
Cabazitaxel	82 (14.9)	53 (18.9)
Docetaxel	27 (4.9)	10 (3.6)
Paclitaxel	2 (0.4)	2 (0.7)
Paclitaxel albumin	2 (0.4)	0
Platinum compounds	40 (7.3)	27 (9.6)
Therapeutic radiopharmaceuticals	16 (2.9)	23 (8.2)
^{223}Ra dichloride	14 (2.5)	15 (5.4)
[^{177}Lu]Lu-PSMA-617	2 (0.4)	3 (1.1)
[^{225}Ac]Ac-PSMA-617	1 (0.2)	0
Other	0	5 (1.8)
Monoclonal antibodies	16 (2.9)	22 (7.9)
Anti-androgens	23 (4.2)	13 (4.6)
Enzalutamide	12 (2.2)	7 (2.5)
Darolutamide	5 (0.9)	3 (1.1)
Apalutamide	4 (0.7)	2 (0.7)
Proxalutamide	2 (0.4)	1 (0.4)
Bicalutamide	1 (0.2)	1 (0.4)
Other antineoplastic agents	17 (3.1)	9 (3.2)
Investigational drug	9 (1.6)	15 (5.4)
Other hormone antagonists and related agents	13 (2.4)	4 (1.4)
Abiraterone	10 (1.8)	1 (0.4)
Abiraterone acetate	3 (0.5)	2 (0.7)
Degarelix acetate	0	1 (0.4)
Protein kinase inhibitors	8 (1.5)	4 (1.4)
Podophyllotoxin derivatives	8 (1.5)	2 (0.7)
Nitrogen mustard analogues	5 (0.9)	3 (1.1)

*Data for all randomized patients

†Overall; ranked by overall frequency; coded using WHODrug Global version March 2020 B3.

Table S11. Treatment-emergent adverse events (expanded)

Treatment-emergent adverse event*	^{177}Lu-PSMA-617 plus standard care (n=529)		Standard care alone (n=205)	
	All grades	Grade ≥3	All grades	Grade ≥3
Any – no. (%)	519 (98.1)	279 (52.7)	170 (82.9)	78 (38.0)
Any drug-related – no. (%)	451 (85.3)	150 (28.4)	59 (28.8)	8 (3.9)
Serious – no. (%)	192 (36.3)	169 (31.9)	57 (27.8)	52 (25.4)
Serious drug-related – no. (%)	49 (9.3)	43 (8.1)	5 (2.4)	5 (2.4)
Leading to death – no. (%)	19 (3.6)	19 (3.6)	6 (2.9)	6 (2.9)
Leading to death, drug-related – no. (%)†	5 (0.9)	5 (0.9)	0	0
Leading to dose reduction – no. (%)				
of ^{177}Lu-PSMA-617	30 (5.7)	10 (1.9)	NA	NA
of standard care	17 (3.2)	0	7 (3.4)	0
Leading to interruption – no. (%)				
of ^{177}Lu-PSMA-617	85 (16.1)	42 (7.9)	NA‡	NA‡
of standard care	50 (9.5)	32 (6.0)	14 (6.8)	9 (4.4)
Leading to discontinuation – no. (%)				
of ^{177}Lu-PSMA-617	63 (11.9)	37 (7.0)	NA‡	NA‡
of standard care	45 (8.5)	25 (4.7)	16 (7.8)	12 (5.9)
Occurring in ≥5% of patients – no. (%)§				
Fatigue	228 (43.1)	31 (5.9)	47 (22.9)	3 (1.5)
Dry mouth	205 (38.8)	0	1 (0.5)	0
Nausea	187 (35.3)	7 (1.3)	34 (16.6)	1 (0.5)
Anaemia	168 (31.8)	68 (12.9)	27 (13.2)	10 (4.9)
Back pain	124 (23.4)	17 (3.2)	30 (14.6)	7 (3.4)
Arthralgia	118 (22.3)	6 (1.1)	26 (12.7)	1 (0.5)
Decreased appetite	112 (21.2)	10 (1.9)	30 (14.6)	1 (0.5)
Constipation	107 (20.2)	6 (1.1)	23 (11.2)	1 (0.5)
Diarrhea	100 (18.9)	4 (0.8)	6 (2.9)	1 (0.5)
Vomiting	100 (18.9)	5 (0.9)	13 (6.3)	1 (0.5)
Thrombocytopenia	91 (17.2)	42 (7.9)	9 (4.4)	2 (1.0)
Lymphopenia	75 (14.2)	41 (7.8)	8 (3.9)	1 (0.5)
Leukopenia	66 (12.5)	13 (2.5)	4 (2.0)	1 (0.5)
Bone pain	59 (11.2)	13 (2.5)	17 (8.3)	5 (2.4)
Urinary tract infection	58 (11.0)	20 (3.8)	2 (1.0)	1 (0.5)
Weight decreased	57 (10.8)	2 (0.4)	18 (8.8)	0
Dyspnea	53 (10.0)	7 (1.3)	20 (9.8)	3 (1.5)
Oedema peripheral	51 (9.6)	2 (0.4)	13 (6.3)	0
Hematuria	45 (8.5)	13 (2.5)	9 (4.4)	1 (0.5)
Neutropenia	45 (8.5)	18 (3.4)	3 (1.5)	1 (0.5)
Pain in extremity	45 (8.5)	3 (0.6)	12 (5.9)	0
Dizziness	44 (8.3)	5 (0.9)	9 (4.4)	0
Cough	42 (7.9)	0	13 (6.3)	0
Hypokalemia	40 (7.6)	5 (0.9)	8 (3.9)	0
Fall	38 (7.2)	1 (0.2)	12 (5.9)	2 (1.0)
Headache	37 (7.0)	4 (0.8)	4 (2.0)	0
Hypocalcemia	36 (6.8)	4 (0.8)	7 (3.4)	1 (0.5)
Pyrexia	36 (6.8)	2 (0.4)	7 (3.4)	0
Asthenia	34 (6.4)	6 (1.1)	16 (7.8)	2 (1.0)
Pain	33 (6.2)	7 (1.3)	9 (4.4)	1 (0.5)
Abdominal pain	32 (6.0)	5 (0.9)	7 (3.4)	1 (0.5)
Hypertension	30 (5.7)	17 (3.2)	12 (5.9)	3 (1.5)
Blood creatinine increased	28 (5.3)	1 (0.2)	5 (2.4)	1 (0.5)
Hypophosphatemia	28 (5.3)	5 (0.9)	7 (3.4)	1 (0.5)
Insomnia	28 (5.3)	0	9 (4.4)	0

*Data for all randomized patients who received at least one dose of their assigned treatment (standard care with or without ^{177}Lu-PSMA-617). Treatment-emergent adverse events were those occurring on or after the start of randomized treatment and up to 30 days after last randomized treatment administration (standard care or ^{177}Lu-PSMA-617 , whichever was later), or before subsequent anticancer treatment. Adverse events were coded using Common Terminology Criteria for Adverse Events v5.0 grading and Medical Dictionary for Regulatory Events v23.1 terms.

†Pancytopenia, n=2; bone-marrow failure, n=1; subdural hematoma, n=1; intracranial hemorrhage, n=1.

‡Patients randomized to ^{177}Lu-PSMA-617 plus standard care who did not receive ^{177}Lu-PSMA-617 but did receive standard care were included in the standard care alone arm of the safety population, including those who experienced treatment-emergent adverse events during cycle 1 of ^{177}Lu-PSMA-617 that led to interruption (2/205 [1.0%]) or discontinuation (1/205 [0.5%]).

§Events of clinical interest to the authors with an incidence lower than this threshold include dry eye, in 16/529 patients (3.0%) in the ^{177}Lu-PSMA-617 arm and 2/205 (1.0%) in the control arm (all grade 1–2); and bone marrow failure, in one patient (0.2%) in the ^{177}Lu-PSMA-617 arm (grade 5; see Supplementary Results) and none in the control arm (see also Table S12).

Table S12. Treatment-emergent safety topics of interest

Safety topic (occurring in more than one patient)*	^{177}Lu-PSMA-617 plus standard care (n=529)		Standard carealone (n=205)	
	All grades – no. (%)	Grade 3 to 5 – no. (%)	All grades – no. (%)	Grade 3 to 5 – no. (%)
Fatigue†	260 (49.1)	37 (7.0)	60 (29.3)	5 (2.4)
Bone marrow suppression‡	251 (47.4)	124 (23.4)	36 (17.6)	14 (6.8)
Dry mouth§	208 (39.3)	0	2 (1.0)	0
Nausea and vomiting‖	208 (39.3)	8 (1.5)	35 (17.1)	1 (0.5)
Hypersensitivity¶	55 (10.4)	5 (0.9)	7 (3.4)	0
Hepatotoxicity**	54 (10.2)	15 (2.8)	16 (7.8)	5 (2.4)
Renal effects††	46 (8.7)	18 (3.4)	12 (5.9)	6 (2.9)
Second primary malignancies‡‡	11 (2.1)	4 (0.8)	2 (1.0)	1 (0.5)
QT prolongation§§	9 (1.7)	7 (1.3)	1 (0.5)	1 (0.5)
Intracranial hemorrhage‖‖	7 (1.3)	5 (0.9)	3 (1.5)	2 (1.0)

*Safety topics of interest are groupings of treatment-emergent adverse events (by Medical Dictionary for Regulatory Events v23.1 terms). Data are for all randomized patients who received at least one dose of their assigned treatment (standard care with or without ^{177}Lu-PSMA-617); not all safety topics of interest defined in the protocol are shown.

†Fatigue includes fatigue, asthenia, malaise, lethargy, cachexia, decreased activity.

‡Myelosuppression includes anaemia, thrombocytopenia, lymphopenia, leukopenia, neutropenia, pancytopenia, febrile neutropenia, bicytopenia, bone marrow failure, normocytic anaemia.

§Dry mouth includes dry mouth, aptyalism, lip dry, dry throat.

‖Nausea and vomiting includes nausea, vomiting and retching.

¶Hypersensitivity includes rash, stomatitis, pruritus, conjunctivitis, eczema, rash maculo-papular, dermatitis, generalized oedema, scrotal oedema, sneezing, swelling face, acute respiratory failure, blister, conjunctival oedema, dermatitis acneiform, dermatitis bullous, erythema, eye swelling, flushing, infusion related reaction, localized oedema, periorbital oedema, pneumonitis, rash erythematous, respiratory distress, swelling of eyelid, swollen tongue, dermatitis contact, erythema multiforme, hypersensitivity, seasonal allergy, skin erosion.

**Hepatotoxicity includes aspartate aminotransferase increased, blood alkaline phosphatase increased, hypoalbuminemia, alanine aminotransferase increased, hyperbilirubinemia, ascites, gamma-glutamyltransferase increased, acute hepatic failure, cholestasis, hepatic encephalopathy, hepatic failure, hepatic lesion, hepatitis, hepatocellular injury, international normalized ratio increased, jaundice, transaminases increased.

††Renal effects includes blood creatinine increased, acute kidney injury, blood urea increased, proteinuria, renal failure, urine output decreased.

‡‡Second primary malignancies includes squamous cell carcinoma, metastases to central nervous system, metastases to meninges, basal cell carcinoma, malignant melanoma, squamous cell carcinoma of skin, extradural neoplasm, squamous cell carcinoma of the tongue.

§§QT prolongation includes syncope, ventricular tachycardia, loss of consciousness, cardio-respiratory arrest.

‖‖Intracranial hemorrhage includes subdural hematoma, hemorrhage intracranial, cerebral hemorrhage, cerebral hematoma.

Table S13. Baseline characteristics of patients who received ^{68}Ga-PSMA-11

Characteristic	Not enrolled (n=172)	^{177}Lu-PSMA-617 plus standard care (n=551)	Standard care alone (n=280)	Overall (n=1003)
Age				
Median (range) – years	70.0 (47–90)	70.0 (48–94)	71.5 (40–89)	70.0 (40–94)
≥65–84 years – no (%)	121 (70.3)	398 (72.2)	214 (76.4)	733 (73.1)
≥85 yr – no. (%)	5 (2.9)	8 (1.5)	6 (2.1)	19 (1.9)
Race – no. (%)				
White	147 (85.5)	486 (88.2)	235 (83.9)	868 (86.5)
Black or African American	11 (6.4)	34 (6.2)	21 (7.5)	66 (6.6)
Asian	4 (2.3)	9 (1.6)	11 (3.9)	24 (2.4)
Other*	2 (1.2)	2 (0.4)	0	4 (0.4)
Missing	8 (4.7)	20 (3.6)	13 (4.6)	41 (4.1)
Prostate-specific antigen doubling time†				
No.	75	269	131	475
Median (range) – months	2.21 (0.9–31.8)	2.37 (0.0–74.4)	2.60 (0.0–93.1)	2.41 (0.0–93.1)
≤6 months – no. (%)	67 (89.3)	245 (91.1)	115 (87.8)	427 (89.9)
Prostate-specific antigen – ng/mL				
No.	172	549	280	1001
Median (range)	65.7 (0–5000)	76.0 (0–6988)	74.4 (0–8995)	73.6 (0–8995)
Alkaline phosphatase – IU/liter				
No.	158	530	264	952
Median (range)	114.0 (40–3005)	105.0 (26–2524)	96.0 (29–1355)	105.0 (26–3005)
Lactate dehydrogenase – IU/liter				
No.	153	527	262	942
Median (range)	263.0 (93–1869)	221.0 (88–1643)	224.5 (105–2693)	227.0 (88–2693)
Prostate cancer history				
Time since diagnosis – years				
Median (range)	6.15 (0.3–26.1)	7.42 (0.9–28.9)	7.37 (0.7–26.2)	7.00 (0.3–28.9)
Gleason score at diagnosis – no. (%)				
8–10	99 (57.6)	324 (58.8)	170 (60.7)	593 (59.1)
Unknown	29 (16.9)	42 (7.6)	24 (8.6)	95 (9.5)

*Other includes native Hawaiian or other Pacific islander, American or Alaskan native, and more than one race reported.

†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 (months). Patients with at least 3 PSA values prior to and at the time of screening were included in the model. Negative values were set to zero. Patients not included in the ≤6-month category had stable, non-increasing or decreasing PSA levels, or doubling time >6 months (data not shown).

PSA, prostate-specific antigen.

Table S14. Treatment-emergent adverse events for ^{68}Ga-PSMA-11

Treatment-emergent adverse event*	Patients who received ^{68}Ga-PSMA-11 (N=1003)†	
	Any grade	**Grade ≥3**
Any – no. (%)	122 (12.2)	21 (2.1)
Any drug-related – no. (%)‡	55 (5.5)	4 (0.4)
Serious – no. (%)	16 (1.6)	15 (1.5)
Serious drug-related – no. (%)	1 (0.1)‖	1 (0.1)‖
Leading to death – no. (%)	3 (0.3)¶	3 (0.3)¶
Occurring in ≥0.5% of patients – no. (%)§		
Fatigue	12 (1.2)	1 (0.1)
Asthenia	9 (0.9)	0
Back pain	8 (0.8)	0
Nausea	8 (0.8)	0
Anaemia	7 (0.7)	0
Lymphopenia	6 (0.6)	2 (0.2)
Oedema peripheral	6 (0.6)	0
Constipation	5 (0.5)	0
Decreased appetite	5 (0.5)	0
Vomiting	5 (0.5)	0

*Treatment-emergent adverse event defined as within 6 days of ^{68}Ga-PSMA-11 dosing (or before first dose of randomize study treatment if >6 days)

†Data for all patients who received a dose of ^{68}Ga-PSMA-11, including those not enrolled

‡Not distinguishable between ^{68}Ga-PSMA-11 and standard care.

§Common Terminology Criteria for Adverse Events v5.0 grading and Medical Dictionary for Regulatory Events v23.1 terms.

‖Hyponatremia (in a patient randomized to the ^{177}Lu-PSMA-617 arm)

¶Cardio-respiratory arrest, n=1 (in a patient randomized to the ^{177}Lu-PSMA-617 arm); left ventricular dysfunction, n=1; subdural hematoma, n=1 (in patients not enrolled).

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