ORIGINAL ARTICLE

Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer

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ABSTRACT

BACKGROUND

Metastatic castration-resistant prostate cancer remains fatal despite recent advances. Prostate-specific membrane antigen (PSMA) is highly expressed in metastatic castration-resistant prostate cancer. Lutetium-177 (^{177}Lu)–PSMA-617 is a radioligand therapy that delivers beta-particle radiation to PSMA-expressing cells and the surrounding microenvironment.

METHODS

We conducted an international, open-label, phase 3 trial evaluating ^{177}Lu-PSMA-617 in patients who had metastatic castration-resistant prostate cancer previously treated with at least one androgen-receptor–pathway inhibitor and one or two taxane regimens and who had PSMA-positive gallium-68 (^{68}Ga)–labeled PSMA-11 positron-emission tomographic–computed tomographic scans. Patients were randomly assigned in a 2:1 ratio to receive either ^{177}Lu-PSMA-617 (7.4 GBq every 6 weeks for four to six cycles) plus protocol-permitted standard care or standard care alone. Protocol-permitted standard care excluded chemotherapy, immunotherapy, radium-223 (^{223}Ra), and investigational drugs. The alternate primary end points were imaging-based progression-free survival and overall survival, which were powered for hazard ratios of 0.67 and 0.73, respectively. Key secondary end points were objective response, disease control, and time to symptomatic skeletal events. Adverse events during treatment were those occurring no more than 30 days after the last dose and before subsequent anticancer treatment.

RESULTS

From June 2018 to mid-October 2019, a total of 831 of 1179 screened patients underwent randomization. The baseline characteristics of the patients were balanced between the groups. The median follow-up was 20.9 months. ^{177}Lu-PSMA-617 plus standard care significantly prolonged, as compared with standard care, both imaging-based progression-free survival (median, 8.7 vs. 3.4 months; hazard ratio for progression or death, 0.40; 99.2% confidence interval [CI], 0.29 to 0.57; P<0.001) and overall survival (median, 15.3 vs. 11.3 months; hazard ratio for death, 0.62; 95% CI, 0.52 to 0.74; P<0.001). All the key secondary end points significantly favored ^{177}Lu-PSMA-617. The incidence of adverse events of grade 3 or above was higher with ^{177}Lu-PSMA-617 than without (52.7% vs. 38.0%), but quality of life was not adversely affected.

CONCLUSIONS

Radioligand therapy with ^{177}Lu-PSMA-617 prolonged imaging-based progression-free survival and overall survival when added to standard care in patients with advanced PSMA-positive metastatic castration-resistant prostate cancer. (Funded by Endocyte, a Novartis company; VISION ClinicalTrials.gov number, NCT03511664.)

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Metastatic castration-resistant prostate cancer remains incurable and fatal, despite the availability of multiple classes of therapy that delay disease progression and prolong life.[1,2] The most recent drug approvals in prostate cancer have brought clinical benefit to subgroups of patients who had been selected on the basis of genomic factors.[3-6] Radioligand therapies such as lutetium-177 (^{177}Lu)–PSMA-617 can target prostate cancer cells while sparing most normal tissues in patients who have been selected with the use of imaging to confirm radionuclide binding.[7]

Prostate-specific membrane antigen (PSMA) is a transmembrane glutamate carboxypeptidase that is highly expressed on prostate cancer cells.[8,9] High PSMA expression is an independent biomarker of poor prognosis throughout the course of prostate cancer and across anatomical sites.[10-12] Metastatic lesions are PSMA-positive in most patients with metastatic castration-resistant prostate cancer,[13,14] and high expression has been independently associated with reduced survival.[15]

^{177}Lu-PSMA-617 delivers beta-particle radiation selectively to PSMA-positive cells and the surrounding microenvironment.[16-18] This radioligand therapy has been associated with encouraging biochemical and radiographic response rates, reduced pain, and low toxicity in multiple early-phase studies involving patients with progression of metastatic castration-resistant prostate cancer after standard therapy.[19-25] Here, we report the results of VISION, a phase 3 trial investigating the efficacy and safety of ^{177}Lu-PSMA-617 plus protocol-permitted standard care in a specific population of previously treated patients with metastatic castration-resistant prostate cancer who were selected for PSMA positivity on the basis of PSMA positron-emission tomographic (PET) imaging.[26]

METHODS

TRIAL OVERSIGHT

We conducted this prospective, open-label, randomized, international, phase 3 trial in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. All the patients provided written informed consent. Independent ethics review boards approved the trial protocol, which is available with the full text of this article at NEJM.org, at each trial site. An independent committee monitored safety throughout the trial.

The trial was designed, interpreted, and reported as a collaboration between the lead investigators and employees of Endocyte (the sponsor) and Advanced Accelerator Applications, both of which are Novartis companies. Data were analyzed by the sponsor and provided confidentially to the authors. Four authors who are employees of Novartis vouch for the accuracy and completeness of the data. All the authors had full access to all the trial data, made the decision to submit the manuscript for publication, and vouch for the fidelity of the trial to the protocol. All the authors critically reviewed and approved the manuscript; medical writing and editing assistance was funded by Advanced Accelerator Applications.

PATIENTS

Eligible patients were adults who had castration-resistant prostate cancer and at least one metastatic lesion on baseline computed tomography (CT), magnetic resonance imaging (MRI), or bone-scan imaging. Disease progression after the receipt of previous treatment both with one or more approved androgen-receptor–pathway inhibitors and with either one or two taxane regimens was required. There was no upper limit on the permitted number of previous androgen-receptor–pathway inhibitors (e.g., abiraterone and enzalutamide).

Eligible patients had PSMA-positive metastatic castration-resistant prostate cancer, which was defined as at least one PSMA-positive metastatic lesion and no PSMA-negative lesions that would be excluded according to the protocol criteria; PSMA-positive status was determined with the use of centrally read gallium-68 (^{68}Ga)–labeled PSMA-11 (^{68}Ga-PSMA-11) PET–CT imaging at baseline.[27] Diagnostic-grade CT scans were also available for all the patients. The presence of PSMA-positive lesions was defined in the protocol as ^{68}Ga-PSMA-11 uptake greater than that of liver parenchyma in one or more metastatic lesions of any size in any organ system. The presence of PSMA-negative lesions was defined in the protocol as PSMA uptake equal to or lower than that of liver parenchyma in any lymph node with a short axis of at least 2.5 cm, in any metastatic solid-organ lesions with a short axis of at least 1.0 cm, or in any metastatic bone

lesion with a soft-tissue component of at least 1.0 cm in the short axis. Patients with any PSMA-negative metastatic lesion meeting these criteria were ineligible.

An Eastern Cooperative Oncology Group performance-status score of 0 through 2 (on a scale from 0 to 5, with higher numbers indicating greater disability),[28] a life expectancy of at least 6 months, and adequate organ and bone marrow function were also required. Full eligibility criteria are provided in the trial protocol.

TRIAL DESIGN AND INTERVENTIONS

The trial was conducted at 84 sites (52 in North America and 32 in Europe). All the patients received protocol-permitted standard care. Patients were randomly assigned in a 2:1 ratio to receive either ^{177}Lu-PSMA-617 plus protocol-permitted standard care (^{177}Lu-PSMA-617 group) or standard care alone (control group). Details regarding randomization are provided in the Supplementary Methods section in the Supplementary Appendix, available at NEJM.org.

Standard-care therapy that was permitted by the trial protocol had to be agreed on and assigned by the physician–investigator before randomization, but it could be modified at the discretion of the treating physician. Standard-care therapies could not include cytotoxic chemotherapy, systemic radioisotopes (e.g., radium-223 [^{223}Ra]), immunotherapy, or drugs that were investigational when the trial was designed (e.g., olaparib). These constraints were used because of a lack of safety data on combining the investigational drug with these agents. Permitted treatments included but were not restricted to the approved hormonal treatments (including abiraterone and enzalutamide), bisphosphonates, radiation therapy, denosumab, or glucocorticoid at any dose. Castrate testosterone levels had to be maintained throughout the trial.

In addition to protocol-permitted standard-care treatments, which were received by all patients, those in the ^{177}Lu-PSMA-617 group received intravenous infusions of ^{177}Lu-PSMA-617 at a dose of 7.4 GBq (200 mCi) once every 6 weeks for four cycles. Two additional cycles (up to six cycles in total) could be administered, at the discretion of the treating physician, in patients who had evidence of response. Details are provided in the Supplementary Methods section.

Patients continued to receive standard care, with or without ^{177}Lu-PSMA-617, until imaging-documented disease progression was detected, an unacceptable level of toxic effects occurred, a determined lack of clinical benefit was recognized, or a prohibited treatment was deemed to be necessary. Follow-up CT or MRI and technetium-99m (^{99m}Tc)–labeled methylene diphosphonate bone scans were scheduled to take place every 8 weeks for 24 weeks and then every 12 weeks thereafter (see the Supplementary Methods section and Fig. S1 in the Supplementary Appendix). Patients whose condition was deemed to be appropriate for additional chemotherapy could discontinue the trial treatment and receive chemotherapy at the discretion of their physician. Treatment could also be discontinued because of nonadherence to the trial regimen or withdrawal of consent or at the discretion of the investigator or sponsor. Postprotocol therapies were those that were received after progression or after the discontinuation of randomly assigned treatment for the other reasons given above.

END POINTS

Imaging-based progression-free survival and overall survival were alternate primary end points, which meant that the trial would be deemed to be positive if the results with respect to either or both of these primary end points were significant at the allocated significance level (alpha) with the use of the stratified log-rank test (see below). Imaging-based progression-free survival was defined as the time from randomization to independently centrally reviewed disease progression (defined according to the Prostate Cancer Clinical Trials Working Group 3 criteria[29]) or death. Overall survival was defined as the time from randomization to death from any cause.

A protocol amendment added imaging-based progression-free survival as an alternate primary end point after discussions with the Food and Drug Administration (FDA) (see the Revision History section in the protocol). At the time of this amendment, a minority of patients had undergone randomization, and no primary endpoint events had occurred.

Key secondary end points were objective response and disease control (which were defined according to the Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1, with the use

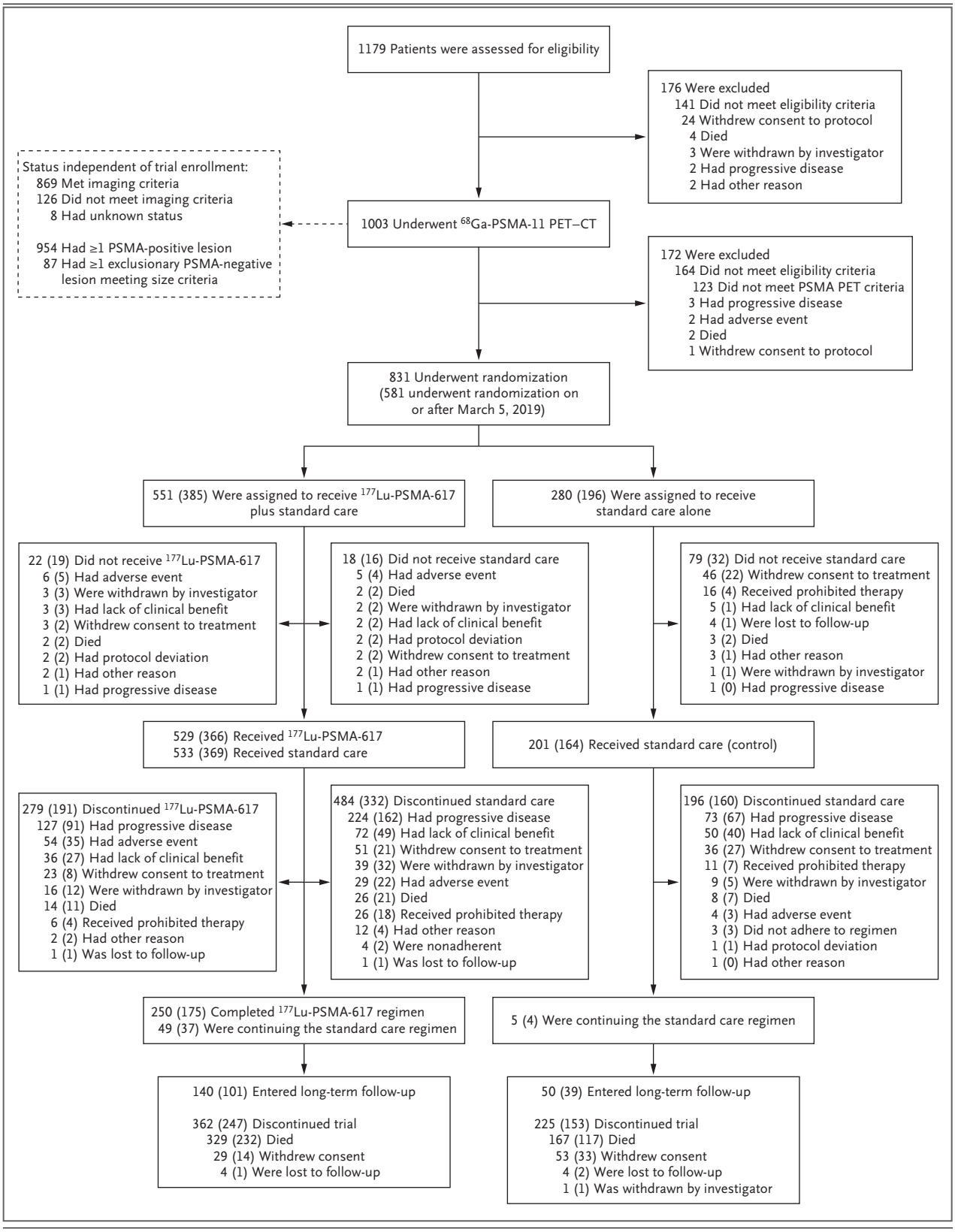


Figure 1 (facing page). Screening, Randomization, and Follow-up of the Patients.

The numbers in parentheses indicate the numbers of patients who underwent randomization on or after March 5, 2019, which was the date on which trial-site education measures were implemented to reduce the incidence of withdrawal from the trial in the control group (see the Supplementary Methods section). In the ^{177}Lu-PSMA-617 group, the reasons for withdrawal of consent to receive ^{177}Lu-PSMA-617 were the following: noted as "no reason given" on the case-report form (in 1 patient), unknown (in 1), and treatment "fatigue" due to travel or protocol procedures (in 1). In the same group, the reasons for withdrawal of consent to receive standard care were the following: noted as "no reason given" on the case-report form (in 1) and treatment "fatigue" due to travel or protocol procedures (in 1). In the control group, the reasons that patients withdrew consent to treatment were the following: an assessment that the patient was receiving best care without ^{177}Lu-PSMA-617 (in 31), noted as "no reason given" on the case-report form (in 7), a decision to pursue treatment outside the trial (in 5), treatment "fatigue" due to travel or protocol procedures (in 2), and a perceived lack of benefit (in 1). CT denotes computed tomography, PET positron-emission tomography, and PSMA prostate-specific membrane antigen.

of a time frame of >6 weeks for nonprogressive disease) and the time to first symptomatic skeletal event (as previously defined)[30,31] or death. Additional secondary end points included the safety profile of ^{177}Lu-PSMA-617 and health-related quality-of-life, pain, and biomarker outcomes, including prostate-specific antigen (PSA) response (Table S1). Adverse events during treatment were defined as those occurring from the first dose of treatment up to and including 30 days after the last dose or before the receipt of subsequent anticancer treatment, whichever came first. Health-related quality of life was assessed with the use of the Functional Assessment of Cancer Therapy–Prostate (FACT-P; the total score is the sum of the scores of 39 items of the questionnaire and ranges from 1 to 156, with higher scores indicating better quality of life), and pain with the use of the Brief Pain Inventory–Short Form (BPI-SF; scores range from 0 to 10, with lower scores representing lower levels of pain intensity).

ANALYSIS SETS

All the efficacy outcomes were analyzed in intention-to-treat populations. The analysis of overall survival included all the patients who had undergone randomization, whereas imaging-based progression-free survival and key secondary efficacy outcomes were analyzed in a subgroup of patients who had undergone randomization, for the following reason. After the trial started (May 29, 2018), a high incidence of withdrawal from the trial was noted in the control group at certain sites and was attributed principally to patient disappointment (see the Supplementary Methods section). After discussion with regulatory authorities, we implemented enhanced trial-site education measures on March 5, 2019 to reduce the incidence of withdrawal. The high incidence of withdrawal could have affected the interpretability of radiographic end points. Therefore, the primary analysis of imaging-based progression-free survival and the analyses of key secondary end points were amended to include only the patients who had undergone randomization on or after March 5, 2019. To maintain statistical power for the analysis of imaging-based progression-free survival, a planned sample of 557 patients who had been enrolled on or after March 5, 2019, was required. To ensure that this number was reached, the planned total sample size was increased from 750 to 814 in the protocol amendment on July 8, 2019 (see the protocol).

Key secondary efficacy outcomes were analyzed in patients who had disease that could be evaluated according to RECIST, version 1.1, at baseline and who had undergone randomization on or after March 5, 2019. The safety of the randomized trial treatments was assessed according to treatment received in all the patients who received at least one dose.

STATISTICAL ANALYSIS

The overall significance level for the trial was 0.025 (one-sided), which was allocated between the alternate primary end points (Table S2). This approach provided the trial with 84% power to detect a hazard ratio of 0.67, at a one-sided significance level of 0.004, in the analysis of imaging-based progression-free survival after the occurrence of 364 events in 557 patients and also provided the trial with 90% power to detect a hazard ratio of 0.73, at a one-sided significance level of 0.025 (or 0.021 if the result in the analysis of imaging-based progression-free survival was not significant), in the analysis of overall survival after 508 deaths in 814 patients.

The principal method of statistical comparison for the primary and key secondary time-to-

event end points was the log-rank test, with stratification according to the randomization factors. The method for all other time-to-event end points was the Wald chi-square test from the stratified Cox proportional-hazards model. The stratified Cox model was used to estimate hazard ratios and associated confidence intervals. Medians, percentiles, and associated confidence intervals were estimated with the use of the Kaplan–Meier method. All the confidence intervals were two-sided, and one-sided P values from the analyses of the primary efficacy outcomes were converted to two-sided P values for this article. The Hochberg procedure[32] was used to adjust for multiple testing of the key secondary efficacy end points, with the use of the two-sided alpha from the final overall survival analysis, if it was positive (Table S2). The analysis methods for health-related quality-of-life and pain outcomes are provided in the Supplementary Appendix. Full details of the statistical analysis plan are provided in the protocol.

RESULTS

PATIENTS

Of the 1179 patients screened, 1003 (85.1%) underwent ^{68}Ga-PSMA-11 PET–CT scanning (Fig. 1). Of these 1003 patients, 954 (95.1%) had at least one PSMA-positive metastatic lesion, and 87 (8.7%) had at least one exclusionary PSMA-negative metastatic lesion. The eligibility criteria for PSMA imaging were not met in 126 patients (12.6%; those with no PSMA-positive lesions or ≥1 exclusionary PSMA-negative lesion) and were met in 869 patients (86.6%; those with ≥1 PSMA-positive lesion and no exclusionary PSMA-negative lesions); 8 patients (0.8%) had unknown status.

Of the 1003 patients who underwent scanning, 831 (82.9%) were judged to have met all the trial eligibility criteria, including the PSMA imaging criteria, and were randomly assigned, between June 4, 2018, and October 23, 2019, to receive either ^{177}Lu-PSMA-617 plus protocol-permitted standard care (551 patients) or standard care alone (280) (Fig. 1). Of these 831 patients, 581 were randomly assigned to the ^{177}Lu-PSMA-617 group (385 patients) or the control group (196) after the enhanced trial-site education measures were implemented (on or after March 5, 2019). The percentage of patients in the control group who discontinued the trial without receiving the randomly assigned treatment was 56% (47 of 84 patients) before the implementation of these measures and 16.3% (32 of 196 patients) after implementation, as compared with 1.2% (2 of 166 patients) and 4.2% (16 of 385 patients), respectively, in the ^{177}Lu-PSMA-617 group. The data-cutoff date for the final analyses was January 27, 2021. The median follow-up was 20.9 months. The demographic and disease characteristics of the patients at baseline and their previous treatments were balanced between the trial groups and between the randomization periods (Tables 1 and S3).

EFFICACY

Primary End Points

Among the 581 patients in the analysis set, the median imaging-based progression-free survival was 8.7 months in the ^{177}Lu-PSMA-617 group, as compared with 3.4 months in the control group (hazard ratio for progression or death, 0.40; 99.2% confidence interval [CI], 0.29 to 0.57; P<0.001 [significance level, 0.008]) (Fig. 2A). Results were similar in an ad hoc analysis that included all the patients who had undergone randomization (Fig. S2).

The median overall survival among all 831 patients who had undergone randomization was 15.3 months in the ^{177}Lu-PSMA-617 group, as compared with 11.3 months in the control group (hazard ratio for death, 0.62; 95% CI, 0.52 to 0.74; P<0.001 [significance level, 0.05]) (Fig. 2B). The median follow-up was 20.3 months (95% CI, 19.8 to 21.0) in the ^{177}Lu-PSMA-617 group and 19.8 months (95% CI, 18.3 to 20.8) in the control group.

The results regarding overall survival were similar in a prespecified supplementary analysis involving the 581 patients who were in the analysis set for imaging-based progression-free survival (hazard ratio for death, 0.63; 95% CI, 0.51 to 0.79) (Fig. S3). After ad hoc adjustment of this analysis for postprotocol chemotherapy, the hazard ratio was 0.64 (95% CI, 0.51 to 0.80). Overall, in this analysis set, 108 of 581 patients (18.6%) received postprotocol taxane therapy and 40 (6.9%) received postprotocol platinum-containing compound therapy; the incidence was somewhat higher in the control group than in the ^{177}Lu-PSMA-617 group (Table S4). Prespecified subgroup analyses of the primary efficacy end points are shown in Figure S4.

Table 1. Characteristics of the Patients at Baseline, According to Analysis Set.*

Characteristic	Analysis Set for Imaging-Based Progression-free Survival (N=581)		All Patients Who Underwent Randomization (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)
Median age (range) — yr	71.0 (52–94)	72.0 (51–89)	70.0 (48–94)	71.5 (40–89)
ECOG performance-status score of 0 or 1 — no. (%)†	352 (91.4)	179 (91.3)	510 (92.6)	258 (92.1)
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)
Median PSA level (range) — ng/ml	93.2 (0–6988)	90.7 (0–6600)	77.5 (0–6988)	74.6 (0–8995)
Median alkaline phosphatase level (range) — IU/liter‡	108.0 (26–2524)	96.0 (34–1355)	105.0 (17–2524)	94.5 (28–1355)
Median LDH (range) — IU/liter‡	230.5 (119–5387)	232.0 (105–2693)	221.0 (88–5387)	224.0 (105–2693)
Median time since diagnosis (range) — yr	7.3 (0.9–28.9)	7.0 (0.7–26.2)	7.4 (0.9–28.9)	7.4 (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 androgen-receptor–pathway inhibitor — no. (%)‖				
One regimen	213 (55.3)	98 (50.0)	298 (54.1)	128 (45.7)
Two regimens	150 (39.0)	86 (43.9)	213 (38.7)	128 (45.7)
More than two regimens	22 (5.7)	12 (6.1)	40 (7.3)	24 (8.6)
Previous taxane therapy — no. (%)**				
One regimen	207 (53.8)	102 (52.0)	325 (59.0)	156 (55.7)
Two regimens	173 (44.9)	92 (46.9)	220 (39.9)	122 (43.6)
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)

* The analysis set for imaging-based progression-free survival included patients who underwent randomization on or after March 5, 2019, which was the date on which trial-site education measures were implemented to reduce the incidence of withdrawal in the control group (see the Supplementary Methods section). Percentages may not total 100 because of rounding. LDH denotes lactate dehydrogenase, and PSA prostate-specific antigen.

† Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher numbers indicating greater disability.

‡ Data were missing for a very small number of patients (Table S3).

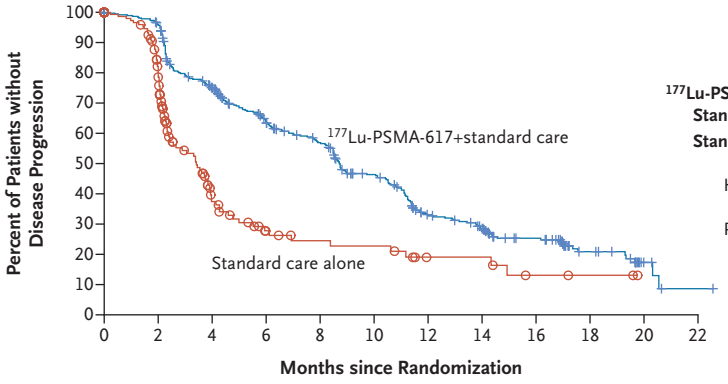
§ Scores on the Gleason scale range from 2 to 10, with higher scores indicating a worse prognosis. A score of 8 to 10 indicates high-grade cancer. In the remaining patients whose score was known, the Gleason score was 2 to 7 (intermediate or low-grade cancer).

¶ Data exclude biopsy and include prostatectomy, radical prostatectomy, transurethral prostatectomy, cystoprostatectomy, and retropubic prostatectomy.

‖ Androgen-receptor–pathway inhibitors were defined as enzalutamide, abiraterone, and apalutamide.

** Taxanes were defined as cabazitaxel, docetaxel, and paclitaxel. Of the 831 patients, 8 (1.0%) had received more than two taxanes previously. Overall, the reasons for the last taxane therapy were the following: therapeutic use in 559 of 831 patients (67.3%), adjuvant therapy in 109 (13.1%), unknown in 106 (12.8%), neoadjuvant therapy in 33 (4.0%), maintenance therapy in 17 (2.0%), other in 5 (0.6%), and prophylaxis in 2 (0.2%). The use of taxanes was well balanced between treatment groups in both analysis sets.

A Imaging-Based Progression-free Survival



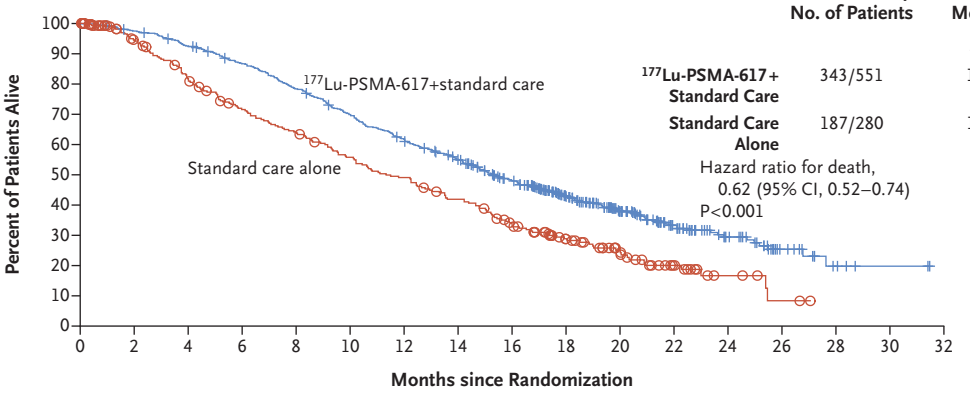
	No. of Events/ No. of Patients	Median (mo)
^{177}Lu-PSMA-617+ Standard Care	254/385	8.7
Standard Care Alone	93/196	3.4

Hazard ratio for progression or death, 0.40 (99.2% CI, 0.29–0.57)
P<0.001

No. at Risk

^{177}Lu-PSMA-617+standard care	385	362	272	215	182	137	88	71	49	21	6	1
Standard care alone	196	119	36	19	14	13	7	7	3	2	0	0

B Overall Survival



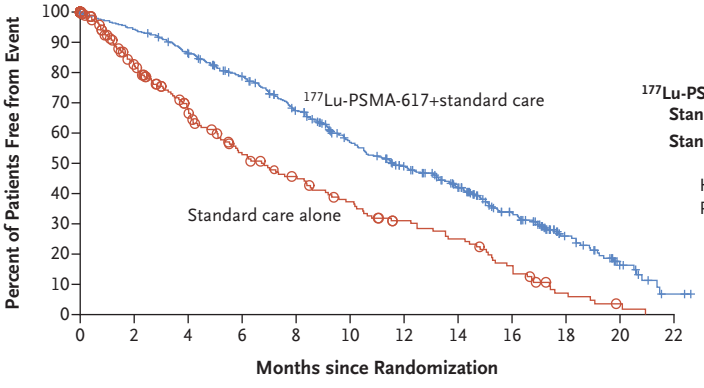
	No. of Events/ No. of Patients	Median (mo)
^{177}Lu-PSMA-617+ Standard Care	343/551	15.3
Standard Care Alone	187/280	11.3

Hazard ratio for death, 0.62 (95% CI, 0.52–0.74)
P<0.001

No. at Risk

^{177}Lu-PSMA-617+standard care	551	535	506	470	425	377	332	289	236	166	112	63	36	15	5	2	0
Standard care alone	280	238	203	173	155	133	117	98	73	51	33	16	6	2	0	0	0

C Time to First Symptomatic Skeletal Event



	No. of Events/ No. of Patients	Median (mo)
^{177}Lu-PSMA-617+ Standard Care	256/385	11.5
Standard Care Alone	137/196	6.8

Hazard ratio, 0.50 (95% CI, 0.40–0.62)
P<0.001

No. at Risk

^{177}Lu-PSMA-617+standard care	385	363	329	290	240	189	153	117	73	34	12	2
Standard care alone	196	141	104	75	61	48	36	29	15	6	2	0

Figure 2 (facing page). Imaging-based Progression-free Survival and Overall Survival (Primary Efficacy Outcomes) and Time to the First Symptomatic Skeletal Event (Key Secondary Outcome).

Panel A shows imaging-based progression-free survival among the 581 patients who had been randomly assigned to receive either ^{177}Lu-PSMA-617 plus standard care or standard care alone after the implementation of enhanced trial-site education measures. Imaging-based progression-free survival, defined as the time to imaging-documented disease progression according to criteria of the Prostate Cancer Clinical Trials Working Group 3 or death, was independently centrally reviewed. Panel B shows overall survival among all 831 patients who had undergone randomization. Panel C shows the time to first symptomatic skeletal event or death in the same population as was used in the analysis of imaging-based progression-free survival. Plus signs and circles indicate censored data in the ^{177}Lu-PSMA-617 group and control group, respectively; information on data censoring is provided in Table S5.

Sensitivity Analyses of Primary End Points

A panel of exploratory ad hoc analyses investigated the sensitivity of the primary end points to data censoring that was due to withdrawal (Table S5), with the use of four different methods.[33,34] The results were consistent with the primary analyses of imaging-based progression-free survival and overall survival (Table S6).

Key Secondary End Points

Among the 581 patients in the analysis set, the median time to the first symptomatic skeletal event or death was 11.5 months in the ^{177}Lu-PSMA-617 group, as compared with 6.8 months in the control group (hazard ratio, 0.50; 95% CI, 0.40 to 0.62; P<0.001 [significance level, 0.05]) (Fig. 2C). Among the 248 patients who had measurable target lesions according to RECIST, version 1.1, on independent central review at baseline, a complete response was noted in 17 of 184 patients (9.2%) in the ^{177}Lu-PSMA-617 group and in none of the 64 patients in the control group. A partial response was noted in 77 patients (41.8%) in the ^{177}Lu-PSMA-617 group and in 2 (3%) in the control group (Table S7).

Other Secondary End Points

The proportions of patients with confirmed decreases in the PSA level of at least 50% and 80% from baseline were higher in the ^{177}Lu-PSMA-617 group than in the control group; a waterfall plot of the PSA data is shown in Figure S5. The time to deterioration in the FACT-P total score and BPI-SF pain intensity score also favored the ^{177}Lu-PSMA-617 group over the control group (Fig. S6). Details of the health-related quality-of-life and pain results are not reported here.

SAFETY

Drug Exposure

The median duration of exposure to ^{177}Lu-PSMA-617 was 6.9 months (range, 0.3 to 10.2), with patients starting a median of 5 cycles (range, 1 to 6) and with a median cumulative dose of 37.5 GBq (range, 7.0 to 48.3) (Table S8). With regard to standard care, the median treatment exposure was 7.6 months (range, 0.3 to 31.3) in the ^{177}Lu-PSMA-617 group and 2.1 months (range, 0.0 to 26.0) in the control group, with patients starting a median of 5 cycles (range, 1 to 16) and 2 cycles (range, 1 to 14), respectively. The standard-care therapies that were received are shown in Table S9, and the postprotocol therapies in Table S10.

Adverse Events

The incidence of adverse events of grade 3 or higher during treatment was higher in the ^{177}Lu-PSMA-617 group than in the control group (Table 2). Fatigue, dry mouth, and nausea were the most common adverse events in the ^{177}Lu-PSMA-617 group, and these adverse events were nearly all of grade 1 or 2 (Tables 2 and S11 [see footnote regarding dry eye]). Groupings of adverse events according to topics of interest are shown in Table S12. Details regarding serious treatment-related adverse events and grade 5 adverse events are provided in the Supplementary Results section.

DISCUSSION

VISION was a phase 3 trial of targeted radioligand therapy in patients with prostate cancer. The PSMA-targeted radioligand ^{177}Lu-PSMA-617 prolonged overall survival and delayed imaging-based progression when added to standard care in patients with PSMA-expressing metastatic castration-resistant prostate cancer. Secondary efficacy outcomes also favored the addition of ^{177}Lu-PSMA-617 to standard care. Treatment with

Table 2. Adverse Events.*

Event	^{177}Lu-PSMA-617 plus Standard Care (N=529)		Standard Care Alone (N=205)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Any adverse event	519 (98.1)	279 (52.7)	170 (82.9)	78 (38.0)
Adverse event that occurred in >12% of patients				
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)
Anemia	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)
Adverse event that led to reduction in ^{177}Lu-PSMA-617 dose	30 (5.7)	10 (1.9)	NA	NA
Adverse event that led to interruption of ^{177}Lu-PSMA-617†	85 (16.1)	42 (7.9)	NA	NA
Adverse event that led to discontinuation of ^{177}Lu-PSMA-617†	63 (11.9)	37 (7.0)	NA	NA
Adverse event that led to death‡	19 (3.6)	19 (3.6)	6 (2.9)	6 (2.9)

* Shown are data for all the patients who underwent randomization and received at least one dose of their assigned treatment (standard care, with or without ^{177}Lu-PSMA-617). Adverse events during the treatment period were those that occurred on or after the start of randomized treatment and up to 30 days after the last administration of the randomized treatment (standard care or ^{177}Lu-PSMA-617, whichever was later) or before subsequent anticancer treatment. Adverse events were coded with the use of Common Terminology Criteria for Adverse Events, version 5.0, and terms from the *Medical Dictionary for Regulatory Activities*, version 23.1. NA denotes not applicable.

† Patients who had been randomly assigned to receive ^{177}Lu-PSMA-617 plus standard care and who did not receive ^{177}Lu-PSMA-617 but did receive standard care were included in the control group (standard care alone) of the safety population; 3 patients had adverse events during cycle 1 of ^{177}Lu-PSMA-617 therapy that led to the interruption (in 2 of 205 patients [1.0%]) or discontinuation (in 1 [0.5%]) of that therapy.

‡ Five adverse events that led to death in the ^{177}Lu-PSMA-617 group were considered by the investigators to be related to the drug: pancytopenia (in 2 patients), bone marrow failure (in 1), subdural hematoma (in 1), and intracranial hemorrhage (in 1).

^{177}Lu-PSMA-617 was associated with a low incidence of adverse events that led to dose reduction, interruption, or discontinuation, which is consistent with the safety profile in early-phase studies.[19-25]

Treatment with ^{177}Lu-PSMA-617 prolonged overall survival in a population of patients with disease that was refractory to androgen-receptor–pathway inhibitors (at least one regimen) and taxane chemotherapy (one or two regimens). Nearly all the enrolled patients (≥97%) had already received docetaxel, and 38% had already received cabazitaxel. Ongoing phase 3 trials (ClinicalTrials.gov numbers, NCT04689828 and NCT04720157) are investigating whether ^{177}Lu-PSMA-617 can provide therapeutic benefit earlier

in the treatment sequence than was used in our trial, as compared with other treatment options.

This trial did not compare ^{177}Lu-PSMA-617 with another specific treatment, as was done in the phase 2 TheraP trial. In the TheraP trial, this radioligand therapy led to a significantly higher proportion of patients with a PSA response than second-line cabazitaxel chemotherapy.[25] Rather, in this trial, we investigated the use of ^{177}Lu-PSMA-617 as an addition to existing standard care at the time the trial was designed. The rationale for the exclusion of certain treatments was that the safety profile of these therapies had not been established in combination with ^{177}Lu-PSMA-617. The trial aimed to assess the efficacy of ^{177}Lu-PSMA-617 plus standard-care therapies that could safely be combined in order to provide physicians with a broad permitted range of concomitant treatment options. Patients who had received only one taxane were ineligible if they were deemed at baseline to be candidates for receiving a second taxane. Approximately one fifth of the patients in the imaging-based progression-free survival analysis set received a second taxane postprotocol, with a slightly higher percentage in the control group than in the ^{177}Lu-PSMA-617 group. Although the TheraP trial of ^{177}Lu-PSMA-617 as compared with cabazitaxel did not include overall survival as a primary end point, the findings of our trial and the TheraP trial complement each other in showing the efficacy of this radioligand therapy in patients for whom cabazitaxel was the next treatment option and in those who had already received two taxanes or had not been candidates at baseline for receiving a second taxane.

A possible advantage of the imaging criteria that were used in our trial is that they allow patients with PSMA-positive metastatic castration-resistant prostate cancer to receive life-extending therapy on the basis of only one PET scan plus conventional imaging. Imaging of metabolic activity with ^{18}F-fluorodeoxyglucose PET was coupled with ^{68}Ga-PSMA-11 PET in some previous trials, including the phase 2 TheraP trial.[24,25] Further studies, including various post hoc analyses of the present trial, may be necessary to improve the criteria for selecting patients.

The lack of a placebo control and of a double-blind design are limitations of clinical trials of radiopharmaceuticals in general, owing to the challenges associated with radiation protection regulations and the ease of detecting radioactivity in the smartphone era. Another potential limitation of the trial is the upgrading of imaging-based progression-free survival from a key secondary end point to an alternate primary end point in a protocol amendment, on the basis of discussions with the FDA soon after the trial started. However, the allocation of the significance level (alpha) between the alternate primary end points maintained a trial-wide type I error at the conventional level, which meant that the trial was no more likely to return a false positive result than it would have been with a single primary end point.

Another limitation is that adverse events were defined as occurring during the treatment period for only up to 30 days after the last dose of protocol-permitted standard-care treatment or ^{177}Lu-PSMA-617, whichever was later. Among patients in the ^{177}Lu-PSMA-617 group who continued to receive standard care after their last cycle of the radioligand therapy, adverse events during the treatment period were therefore assessed for longer than 30 days after the last dose of ^{177}Lu-PSMA-617. Nevertheless, the 30-day post-dose period for such adverse events may have led to an underestimation of toxicity, given the 7-day half-life of ^{177}Lu. The incidence of toxic effects may also have been overestimated relative to the control group because patients in the ^{177}Lu-PSMA-617 group had a longer treatment time than those in the control group (median exposure, 7.6 months and 2.1 months, respectively).

In this trial, the addition of ^{177}Lu-PSMA-617 to standard care significantly extended survival among patients with metastatic castration-resistant prostate cancer and progressive disease who had received previous treatment with one or more androgen-receptor–pathway inhibitors and one or two taxanes. Treatment with ^{177}Lu-PSMA-617 was associated with toxic effects that were mainly of grade 3 or lower, and this therapy also extended the time to symptomatic skeletal events, prolonged the time to worsening of health-related quality of life and pain, and delayed biochemical progression.

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APPENDIX

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