Prostate Cancer Treatment: ^{177}Lu-PSMA-617 Considerations, Concepts, and Limitations

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Learning Objectives: On successful completion of this activity, participants should be able to describe (1) selection criteria employed in the VISION trial; (2) the VISION trial in the context of other therapies for advanced prostate cancer; and (3) an overview of newer phase III protocols using radiopharmaceuticals in the treatment of advanced prostate cancer.

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The phase III VISION trial using ^{177}Lu-PSMA-617 has significant implications for the field of theranostics and broad repercussions for the clinical management of prostate cancer. Metastatic prostate cancer is a rapidly evolving field with a complex landscape that has multiple established therapies, including chemotherapies, hormonal therapies, immunotherapies, radiopharmaceuticals, and targeted therapies. The current landscape was created by an important series of pivotal phase III trials, typically with an overall-survival endpoint. To best understand the VISION trial (performed on patients with metastatic castration-resistant prostate cancer), it is essential to have a thorough understanding of the key decisions that underpinned the design, as well as the context of those decisions. Here, we describe critical elements of the VISION phase III trial and how those elements will shape regulatory decision making and clinic practice. Inclusion and exclusion criteria were carefully crafted, as were treatments, assessments, and endpoints. The results of the VISION trial were impressive, with clear improvements in survival for patients having few treatment alternatives. Besides the significant progress, there are also significant limitations. ^{177}Lu-PSMA-617 treatments will have far-reaching implications for prostate cancer. Food and Drug Administration approval was granted March 23, 2022, on the basis of the VISION data.

Key words: prostate cancer; castration-resistant; PSMA; theranostics; clinical trials

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The Food and Drug Administration (FDA) approval of ^{177}Lu-PSMA-617 on March 23, 2022, provided an excellent opportunity to understand the context of this new therapy in prostate cancer and to dissect the key design elements for the pivotal phase III VISION trial (*1*).

Prostate cancer has a multiplicity of life-prolonging treatments utilized in the metastatic setting. In general, treatment of metastatic prostate cancer is subdivided into either metastatic castration-sensitive prostate cancer or metastatic castration-resistant prostate cancer (mCRPC) (Fig. 1). For metastatic castration-sensitive prostate cancer, the use of androgen deprivation therapy (ADT) in the form of luteinizing hormone–releasing hormone analogues (e.g., leuprolide, goserelin, triptorelin, degarelix, and relugolix) or orchiectomy has long been utilized, and additional review of older studies is not warranted. More recently, ADT plus docetaxel chemotherapy has been shown to prolong survival in metastatic castration-sensitive prostate cancer (*2,3*), as has ADT plus a novel androgen receptor pathway inhibitor (ARPI): either abiraterone, enzalutamide, or apalutamide (*4–7*). Abiraterone, apalutamide, and enzalutamide are ARPIs that either block the androgen receptor (enzalutamide/enzalutamide) or block androgen synthesis (abiraterone). Today, the use of ADT monotherapy is not typically indicated for those with metastatic castration-sensitive prostate cancer. Two recent phase III studies indicated that ADT plus docetaxel plus abiraterone (*8*) or ADT plus docetaxel plus darolutamide (another androgen receptor antagonist) (*9*) is superior to ADT plus docetaxel.

Table 1 summarizes all life-prolonging trials in men with mCRPC. In 2004, docetaxel was the first agent to prolong survival in phase III mCRPC trials (*10,11*). The androgen axis inhibitors abiraterone and enzalutamide have both been shown to be life-prolonging whether given in the first-line mCRPC setting or in the postdocetaxel mCRPC setting (*12–15*). Cabazitaxel is FDA-approved

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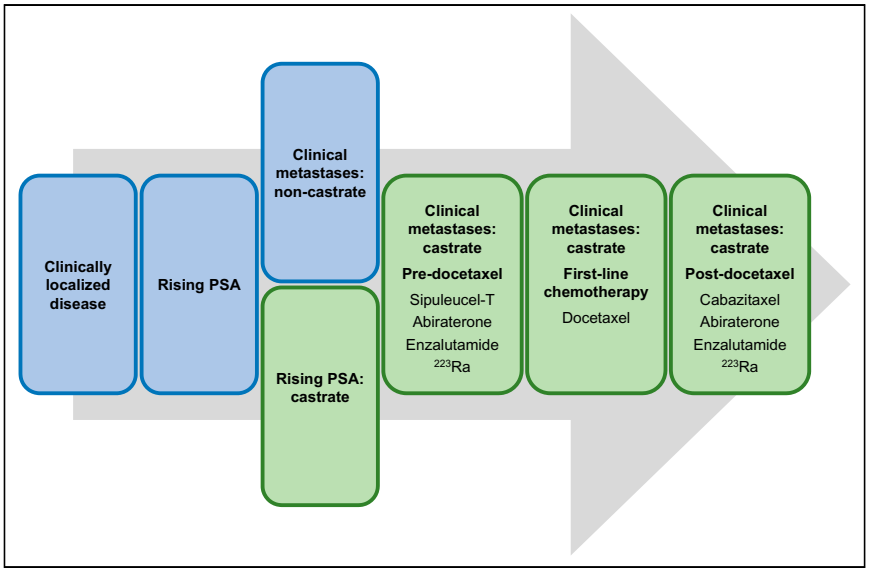

FIGURE 1. Schema of clinical disease state model of prostate cancer before VISION. (Adapted from (*33*).)

in the postdocetaxel setting of mCRPC (*16*) but has also been shown to be active in the post-ARPI and postdocetaxel setting (*17*). The use of ^{223}Ra-dichloride has been shown to be life-prolonging in the pre- or postdocetaxel setting (*18*). Sipuleucel-T, an immunotherapy, has been shown to prolong survival in asymptomatic or minimally symptomatic mCRPC patients (predominantly before chemotherapy) (*19*). Those men with mCRPC and homologous recombination repair defects (such as BRCA1 and BRCA2) live longer after ARPI or after ARPI/docetaxel (*20*).

The VISION trial was clearly conducted in the post-ARPI and posttaxane mCRPC setting, and the recent regulatory approval of ^{177}Lu-PSMA-617 clearly follows the VISION eligibility criteria.

THERANOSTICS

There have been tremendous improvements in theranostics and targeted radiopharmaceuticals over the past decade, and what once was an obscure area of oncology has now emerged as a key component in developmental therapeutics (*21*). Traditional pharmaceutical companies were slow to embrace this field given the early scientific successes that were commercial failures (*22*). It is hard to make investments in a field when the dividends from that investment are difficult to realize. Reasons for commercial failure have been discussed, but reimbursement and the competitive landscape are clearly features of importance.

Though it is debatable when radiopharmaceuticals were embraced in broader cancer circles, the clear success of ^{223}Ra-dichloride in prolonging overall survival (OS) in mCRPC was a catalyst for investment and further research (*18*). Earlier studies leading to FDA approval for ^{89}Sr-chloride and ^{153}Sm-lexidronam demonstrated only palliative benefit (*23–25*). The success of ^{223}Ra-dichloride, followed by success in treating neuroendocrine tumors with ^{177}Lu-DOTATATE (*26*), has been key for commercial involvement (Table 2). Key to regulatory approval is the pivotal trial design and execution. In this article, the design elements for the VISION trial (*1*) will be emphasized, with some explanatory details where controversy existed (Fig. 2). As in any trial design, there are many choices to be made, and these choices as a whole shape the way patients are included, treated, followed, and assessed.

TABLE 1
Anticancer Therapeutic Radiopharmaceuticals Currently Approved by Regulators in United States

Agent	Trade name	Year of FDA approval	Primary endpoint	Indication
^{89}Sr-chloride	Metastron (GE Healthcare)	1993	Pain/analgesics	Painful skeletal metastases
^{153}Sm-lexidronam	Quadramet (Dow Chemical Co.)	1997	Pain/analgesics	Painful osteoblastic metastases
^{90}Y-ibritumomab tiuxetan	Zevalin (Acrotech Biopharma)	2002	Tumor response rate	Low-grade or follicular lymphoma
^{131}I-tositumomab	Bexxar (GlaxoSmithKline)	2003	Tumor response rate	Low-grade or follicular lymphoma
^{223}Ra-dichloride	Xofigo (Bayer)	2013	OS	mCRPC
^{177}Lu-DOTATATE	Lutathera (Advanced Accelerator Applications)	2018	Progression-free survival	Select neuroendocrine tumors
^{131}I-iobenguane	Azedra (Progenics Pharmaceuticals)	2018	Lower blood pressure and tumor response rate	Select pheochromocytoma or paraganglioma
^{177}Lu-PSMA-617	Pluvictoa (Advanced Accelerator Applications)	2022	OS and rPFS	PSMA PET-positive mCRPC after ARPI and taxane

PSMA = prostate-specific membrane antigen.

TABLE 2
Life-Prolonging Phase III Trials in mCRPC

Trial	Front-line mCRPC
TAX 327	Docetaxel/prednisone vs. mitoxantrone/prednisone (*10*)
SWOG 9916	Docetaxel plus estramustine vs. mitoxantrone/prednisone (*11*)
IMPACT	Sipuleucel-T vs. nonactivated immune cell control (*19*)
COU-AA-302	Abiraterone/prednisone vs. placebo/prednisone (*13*)
ALSYMPCA	SOC ± ^{223}Ra (*18*)
PREVAIL	Enzalutamide vs. placebo (*15*)
	After docetaxel
TROPIC	Cabazitaxel/prednisone vs. mitoxantrone/prednisone (*16*)
COU-AA- 301	Abiraterone/prednisone vs. placebo/prednisone (*12*)
AFFIRM	Enzalutamide vs. placebo (*14*)
ALSYMPCA	SOC ± ^{223}Ra (*18*)
	After ARPI or ARPI plus docetaxel in HRR mutated subset only
PROfound	Olaparib vs. abiraterone or enzalutamide (*20*)
	After ARPI and DOCETAXEL)
CARD	Cabazitaxel vs. abiraterone or enzalutamide (*17*)
VISION	SOC ± PSMA-617 ^{177}Lu

HRR = homologous recombination repair.

VISION STUDY DESIGN ENDPOINTS

First, the phase III VISION trial was explicitly designed for regulatory approval. As such, the endpoints were endpoints that the FDA and other regulatory bodies had previously accepted in the course of successful studies on advanced prostate cancer. The trial was originally designed with a single primary endpoint of OS. The OS endpoint is considered to be the gold standard when assessing outcomes in advanced cancer and has a long, successful track record in mCRPC space, having been previously used for approvals of docetaxel, cabazitaxel, sipuleucel-T, ^{223}Ra-dichloride, abiraterone, and enzalutamide (*27*). After the VISION trial had been designed and initiated, a second alternate primary endpoint was added, radiographic progression-free survival (rPFS) or death from any cause. This image-based endpoint was in accordance with guidelines created by the Prostate Cancer Working Group 3 (*28*). This secondary endpoint had been accepted by the FDA as a primary endpoint in the olaparib pivotal trial (*29*). Both the OS and the rPFS endpoints are calculated from the time of randomization (not treatment). The assessment of rPFS is rigorous and must be in accord with clearly defined time lines and methodologies (conventional imaging, not PET scans). The rPFS endpoint, as specified by the Prostate Cancer Working Group 3, was previously found to be strongly associated with OS in mCRPC. PET imaging has not been shown to be a response biomarker, and the relationship between PSMA PET imaging and OS is not validated.

Secondary endpoints in the VISION trial included several traditional analyses favored by the FDA. These endpoints were designed to capture supportive data regarding the activity of the experimental drug relative to the control group. Key secondary endpoints included time to symptomatic skeletal events or death, radiographic objective response using criteria established by RECIST 1.1, and disease control rate as assessed by RECIST 1.1. Symptomatic skeletal events included first use of external-beam radiation therapy to relieve skeletal symptoms, new symptomatic pathologic vertebral or nonvertebral bone fractures, spinal cord compression, or tumor-related orthopedic surgical intervention as previously used in ALSYMPCA (*18*). In addition, other endpoints included a confirmed prostate-specific antigen (PSA) response of 50% or more, and health-related quality-of-life assessments utilizing

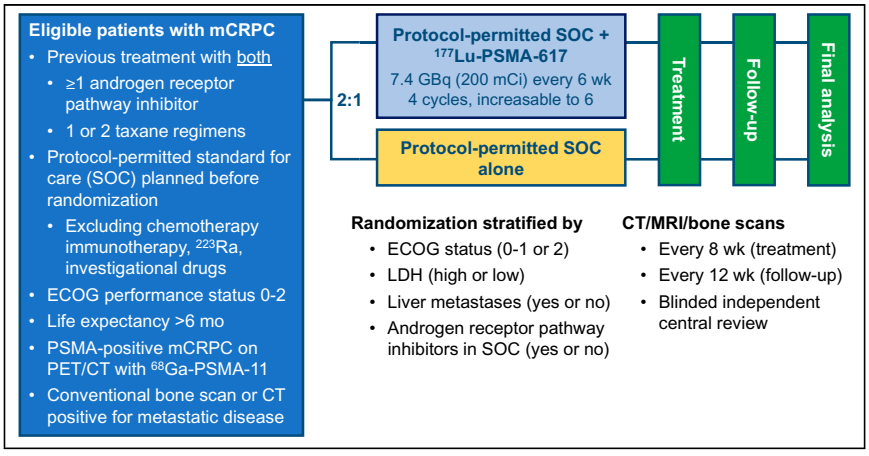

FIGURE 2. Protocol schema for VISION trial. ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase.

the Functional Assessment of Cancer Therapy–Prostate; the Brief Pain Inventory–Short Form; and the EuroQol 5-Dimension, 5-Level Questionnaire. Adverse events were assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Importantly, none of these were unfamiliar endpoints. Symptomatic skeletal events are particularly helpful in bone-dominant cancer such as prostate, and symptomatic skeletal event assessments played a key role in the ^{223}Ra approval. The various additional criteria have been standardized and accepted in multiple phase III trials. The use of familiar endpoints that are clinically relevant and readily interpretable is a key feature in regulatory decision making. Health-related quality-of-life measurements are more key for certain countries than for others, but all regulators want to ensure that health-related quality-of-life parameters are not adversely affected by treatments. Of note, PSA is not sufficient for regulatory action despite being the most commonly reported end point in a multiplicity of trials. PSMA PET is not validated as a surrogate for OS and must be viewed only in exploratory terms.

VISION ELIGIBILITY CRITERIA

All patients enrolled in VISION had to have mCRPC as determined by conventional imaging (i.e., bone scanning and CT or MRI). Progression at the time of trial entry was required to be documented by PSA or imaging-based criteria. The serum PSA minimum was 2.0 ng/mL. All patients were required to have a castration level of testosterone and to have had disease progression after the use of taxane-based chemotherapy (typically docetaxel) and a novel hormone (i.e., abiraterone or enzalutamide). A variety of other prior treatments, such as olaparib, were allowed but not required. Patients were allowed to have up to 2 prior taxane-based chemotherapies. There was no limit to the number of prior hormonal manipulations. The actual patients enrolled had previously received multiple prior therapies, and very few patients had simply received docetaxel and a novel hormone.

The inclusion criteria for the VISION trial also required the use of PSMA PET imaging (using ^{68}Ga-PSMA-11 concomitantly with a nondiagnostic unenhanced CT scan) within 1–4 wk of therapeutic ^{177}Lu-PSMA injection. PSMA PET/CT imaging was allowed only after all other screening criteria for eligibility had been met. The PSMA PET/CT images were read centrally and, importantly, with positive and negative selection criteria. All patients were required to have at least 1 PSMA PET–positive metastatic lesion. No size criteria were specified for the PET-positive lesion. PSMA positivity was determined relative to liver uptake; in other words, the metastatic lesion had to have uptake greater than that in the liver. A diagnostic-grade contrast-enhanced CT scan of the chest, abdomen, and pelvis (or contrast-enhanced MRI) and total-body bone scintigraphy were also required at baseline. A key feature of the selection criteria by PET/CT imaging involved those metastatic lesions that had PSMA uptake less than liver uptake (deemed PSMA PET–negative). Patients were excluded from trial entry if they had PET-negative visceral lesions (liver or lung) at least 1.0 cm in diameter, PSMA PET–negative lytic bone lesions measuring at least 1.0 cm, or PET-negative lymph nodes measuring at least 2.5 cm. Though ^{18}F-FDG PET was not utilized, many of these PSMA-negative lesions conjecturally would have ^{18}F-FDG PET positivity.

The lack of ^{18}F-FDG PET in VISION has met with some discussion. Potentially, the use of ^{18}F-FDG PET would have improved the number of responding patients (*30,31*). In many countries, it is difficult to obtain 2 distinct PET imaging studies, and the requirement of 2 PET imaging studies was debated in the VISION design phase. The decision was made to forego ^{18}F-FDG PET imaging for practical purposes. That decision in retrospect is viewed favorably by many treating physicians, given the unequivocally positive OS outcomes in the VISION trial. That said, there is no question that optimal imaging may eventually prove to have better results. However, optimal imaging is yet to be established in definitive trials with an OS outcome. Thus, until data are presented to the contrary, it is likely that regulators will adopt a PSMA PET–only entry criterion similar to the VISION trial for those being treated with PSMA-targeted radiopharmaceuticals.

In addition to the inclusion criteria for VISION, there were several elements in the exclusion criteria worthy of note. These include patients with bone superscans, poor performance status, and significant degrees of bone marrow suppression. Previous treatment with any of the following within 6 mo of randomization was not allowed: ^{89}Sr, ^{153}Sm, ^{186}Re, ^{188}Re, ^{223}Ra, or hemibody irradiation. Previous PSMA-targeted radioligand therapy was not allowed. Patients with superscans on their bone scintigraphy cannot be evaluated for bone scan progression, hence their exclusion.

Timing of assessments included a PSMA PET scan (^{68}Ga PSMA-11 was used exclusively) 1–4 wk before protocol-defined treatments began; diagnostic CT or MRI (of the chest, abdomen, and pelvis) and total-body bone scintigraphy were conducted within 4 wk of treatment. Investigators were to specify the standard-of-care (SOC) treatment before randomization (given that novel hormone use was a stratification variable). Bone and CT scans were scheduled every 8 wk ($\pm$4 d) after the first dose of isotope for the first 24 wk then every 12 wk thereafter through the end of treatment. It is critical to note that even if the doses of isotope were delayed, tumor assessments were required to stay on the proper imaging schedule.

VISION STRATIFICATIONS, RANDOMIZATION, AND TREATMENTS

Simple randomization can fail when treated patients are unbalanced for critical features known to influence prognosis. The use of stratification overcomes this potential issue. The 4 stratification factors included in the VISION trial were serum lactate dehydrogenase ($>$260 IU/$\leq$260 IU), liver metastases (yes/no), Eastern Cooperative Oncology Group performance status score (0–1/2), and inclusion of a novel hormone (typically enzalutamide or abiraterone), as treatment in the protocol permitted SOC. Lactate dehydrogenase, liver metastatic disease, and Eastern Cooperative Oncology Group performance status are known to be of prognostic importance in multiple phase III mCRPC trials, hence their use here. Life-prolonging hormonal therapy (abiraterone and enzalutamide typically) as a stratification factor was used to ensure balance in this potentially important variable.

Eligible patients were randomized in a 2:1 fashion favoring the isotopic treatment plus SOC over SOC alone. The dose and duration of treatment for ^{177}Lu-PSMA-617 were not a simple decision. Much of the prior data were collected after using various doses for variable durations at variable intervals. The dose for VISION was strongly influenced after evidence was initially provided from a phase II prospective Australian trial (*30*). In that single-arm, single-center trial, a median dose of 7.5 MBq of ^{177}Lu-PSMA-617 was administered every 6 wk up to 4 doses. The outcomes

demonstrated clear efficacy, with manageable toxicity. The VISION trial utilized a planned dosing schema of 7.4 MBq (200 mCi) per dose (fixed dosing being easier to manage logistically than a weight-based dose) given for a planned 4 cycles. However, clinicians at their discretion could administer up to 6 cycles. The criteria for administering 6 cycles included an assessment of response (radiologic and PSA) and clinical benefit after the fourth dose. In addition, the patient should have had residual disease on CT with contrast, MRI, or bone scanning and have shown good tolerance to the prior ^{177}Lu-PSMA-617 treatments. The use of 6 cycles of therapy was controversial to some given the lack of efficacy or safety data in prior trials.

The control group to be utilized in VISION generated considerable discussion at the time of the design. Should an SOC be specified? Should there be an SOC with or without ^{177}Lu-PSMA-617 or an SOC versus ^{177}Lu-PSMA-617? Should chemotherapy be given in the control group? What about ^{223}Ra-dichloride? Was it ethical to allow additional hormonal therapy after prior hormonal therapy had initially failed to control the disease? What control treatment would be acceptable for both clinicians and patients?

A key decision point was to require 1 taxane treatment but allow up to 2 prior taxane treatments in the inclusion criteria. Second-line taxane chemotherapy with cabazitaxel was known to be life-prolonging, but nothing had ever been shown to prolong survival after 2 prior chemotherapies. Thus, every patient who wanted to receive 2 lines of chemotherapy could receive those therapies and still be eligible, unlike the TheraP trial (*31*). There is no effective third-line chemotherapy, thus rendering moot a decision about mandating third-line chemotherapy in the control group. Also, from a practical perspective, most mCRPC patients never receive 2 chemotherapies before they succumb to the disease. In fact, many patients never receive any chemotherapy before they die (*32*). Prostate cancer patient are often chemotherapy-averse, in part because of their advanced age. Thus, to require patients in the control arm to receive a therapy that in real-world settings is not typically utilized seemed inappropriate.

Some data suggested that PSMA expression could be upregulated by the use of hormonal agents such as enzalutamide. Thus, the combination of a novel hormonal agent and the PSMA-targeted agent could potentially have synergistic implications, and novel hormonal agents were allowed as part of SOC. Such synergism had not been proven in clinical trials. In addition, there were no known adverse interactions regarding novel hormones and ^{177}Lu-PSMA-617. Taken together, the use of SOC with or without ^{177}Lu-PSMA-617 was deemed the optimal design. This mirrors the use of SOC with or without ^{223}Ra-dichloride in the phase III ALSYMPCA trial. ALSYMPCA clearly met with regulatory success. Steroids, bisphosphonates, and other bone-health agents, as well as external-beam radiation, were allowed as part of SOC in the final VISION design. Chemotherapy as an SOC was excluded, not only because patients could receive 1 or 2 taxane-based chemotherapies before protocol treatment if they so desired but also because combining ^{177}Lu-PSMA-617 with chemotherapy was not known to be safe. Similar safety concerns excluded use of ^{223}Ra-dichloride or poly(adenosine diphosphate ribose) polymerase inhibitors such as olaparib.

No crossover from the control group to the isotopic group was planned, but after the trial reported positive results, those in the control group meeting eligibility criteria were allowed to receive ^{177}Lu-PSMA-617 in a compassionate-use manner. Few patients were eligible for this compassionate use.

VISION STATISTICAL ANALYSIS PLAN

The statistical analysis plan was originally conceived to be an assessment of OS with 750 patients. The median survival in the control group was estimated to be 10 mo. The experimental group was projected to have a median OS of 13.7 mo (thus generating a hazard ratio [HR] of 0.7306 after 489 events). The trial originally had 2 interim analyses for OS, and rPFS was a secondary endpoint. The statistical plan had 90% power and a 1-sided type 1 error rate of 0.025. A stratified Cox proportional hazards regression model was planned for OS analysis, with a single covariate for randomized treatment and stratification for the 4 variables noted above.

The statistical analysis plan was later revised (effective March 2019) with FDA assent because of high levels of dropout in the control arm at selected sites. At that time, to overcome concerns regarding clinical trial conduct at these locations, certain clinical trial sites were closed to further accrual and additional site-education procedures were implemented at the remaining sites. The control group discontinuation rate was 56% (47/84 patients) before the March 2019 revisions and 16.3% afterward. This rate clearly indicates the importance of the site-culling and education efforts. Of the sites closed to accrual, all site principal investigators were nuclear medicine–focused and had suboptimal multidisciplinary care systems. One of the key missives in the trial site educational enhancements was to incorporate multidisciplinary care for each patient. Multidisciplinary care is optimal for VISION-type patients given the multiplicity of potential complications in caring for those with far-advanced prostate cancer.

The statistical analysis plan invoked after March 2019 assessed both rPFS and OS as coprimary endpoints and allowed for different populations for OS and rPFS assessments given that patients with poor follow-up were not expected to have timely radiographic assessments. Only patients enrolled after March 9, 2019, were assessed for rPFS (n = 557). The estimated sample size was increased to 814. After revisions, the OS assumptions were unchanged (median, 10 and 13.7 mo). The median rPFS assumptions were 4 and 6 mo for the control and experimental arms, respectively. The overall significance level for the trial was 0.025 (1-sided), allocated between the 2 coprimary endpoints. This approach provided the trial with 84% power to detect an HR of 0.67 for rPFS at a 1-sided significance level of 0.004, after 364 events, and also provided the trial with 90% power to detect an HR of 0.73 for OS at a 1-sided significance level of 0.025. The analysis of OS was to occur after 508 deaths. If both rPFS and OS were positive, sequential testing on key secondary endpoints could occur (time to symptomatic skeletal events, RECIST 1.1 response rate, and disease control rate by RECIST 1.1).

VISION PATIENT CHARACTERISTICS

In total, 1,179 patients were screened, and 1,003 (85.1%) had a ^{68}Ga-PSMA-11 PET/CT scan meeting the study-eligibility definition. Of the 1,003 patients, 954 (95.1%) had at least 1 PSMA-positive metastatic lesion, and 87 (8.7%) had at least 1 PSMA-negative metastatic lesion that excluded them from the VISION trial. The eligibility criteria for PSMA imaging were not met in 126 of the 1,003 patients (12.6%), either because there was no PSMA-positive lesions or there was at least 1 exclusionary PSMA-negative lesion. Thus, 869 patients of those scanned with PSMA PET/CT (86.6%) qualified for the study. Eight patients had missing PSMA results and could not be classified. The fact that

nearly 87% of the scanned patients qualified for the study was somewhat surprising and indicates a high level of leniency in determining who was eligible for the study. In the TheraP Australian randomized phase II study, only 68.7% of scanned patients met the criteria for enrollment (*31*). The TheraP group used a double-PET strategy, with both PSMA PET/CT and ^{18}F-FDG PET/CT in the selection criteria.

In total, 831 patients were actually randomized in the VISION trial. Prior treatments were extensively used before the protocol therapy was applied. Of the 831 randomized patients, 342 (41.2%) had received 2 taxane-based chemotherapies (all, of course, had received at least one, as this was an inclusion criterion), and 406 (48.7%) had received 2 or more novel hormonal agents (typically abiraterone and enzalutamide). Use of these agents was well balanced between arms. Median PSA was 74.6 ng/mL in the SOC arm and 77.5 ng/mL in the SOC-plus-isotopic arm. The median time since diagnosis was 7.0 and 7.3 y in the SOC and experimental arms, respectively. Bone metastases were present in 91.4% of SOC patients and 91.5% of experimentally treated patients. Liver metastases were annotated in 13.6% and 11.4% of the randomized patients, respectively.

VISION RESULTS

The median follow-up was 20.9 mo. The endpoints of VISION were well discussed in the primary article (*1*). The OS was clearly positive, with an HR of 0.62 (95% CI, 0.52–0.74; $P < 0.001$). Median survival was 11.3 mo in the SOC arm and 15.3 mo in the SOC–plus–^{177}Lu-PSMA-617 arm. Of the 831 (63.8%) patients, 530 died at the time of the VISION OS analysis, indicating a sufficiently mature trial. For rPFS, the median in the SOC arm was 3.4 mo, versus 8.7 mo in the SOC–plus–^{177}Lu-PSMA-617 arm (HR, 0.40; 99.2% CI, 0.29–0.57; $P < 0.001$). A sensitivity analysis of the rPFS population for OS ($n = 581$) yielded an HR of 0.63 for OS (95% CI, 0.51–0.79). Some have pointed out that the VISION trial likely would have been positive even without PSMA PET/CT selection given the strong HRs and CIs. Analysis of various appropriately powered subsets all revealed positive trends for rPFS and OS. Patients with liver metastases are a special case in which the HR CIs overlapped 1.0 (HR, 0.87; 95% CI, 0.53–1.43), but the subset was clearly underpowered given the small percentage of patients enrolled who had a liver metastasis.

All secondary endpoints analyzed to date have also been positive. Time to symptomatic skeletal events or death was improved by the isotopic treatment (11.5 vs. 6.8 mo; HR, 0.50; 95% CI, 0.40–0.62; $P < 0.001$). RECIST complete response rate by independent central review (among 248 patients with measurable disease at baseline) was 9.2% in the experimental group and 0.0% in the SOC group. Partial responses were annotated in 41.8% of the isotopic-plus-SOC group and 9.2% of the SOC-alone group. Complete-plus-partial responses were 51% versus 9.2%, an impressively high complete response plus partial response rate compared with other mCRPC trials. The CARD trial, similarly conducted on patients progressing after both docetaxel and a novel hormone, reported a RECIST complete response plus partial response of 37.0% for cabazitaxel (*17*). Abiraterone reported a RECIST complete response plus partial response of 14% in the COU-301 trial (postdocetaxel mCRPC) (*12*). PSA responses of at least 50% (confirmed) were found in 46.0% in the experimental arm and 7.1% of the SOC-alone arm. For comparison's sake, in the CARD trial, 35.7% of cabazitaxel patients had a confirmed PSA decline of at least 50%, and 29% of abiraterone patients had a confirmed PSA decline of at least 50%. It is hard to find trials comparable to VISION given the extensive prior treatments administered to these patients. Regardless, the data from these very heavily pretreated patients compare favorably with other postdocetaxel trials on mCRPC.

Health-related quality-of-life (total score for Functional Assessment of Cancer Therapy–Prostate) and pain assessments (pain intensity on Brief Pain Inventory–Short Form) both favor the use of ^{177}Lu-PSMA-617 plus SOC versus SOC alone. The time to deterioration of the Functional Assessment of Cancer Therapy–Prostate total score was 5.7 versus 2.2 mo (HR, 0.54; 95% CI, 0.45–0.66). The time to pain deterioration was 5.9 versus 2.2 mo (HR, 0.52; 95% CI, 0.43–0.63). These patient-centric reports confirm the clinical relevance of the VISION findings. Both OS and health-related quality of life were improved in those treated with ^{177}Lu-PSMA-617 plus SOC.

Treatment-emergent adverse events (Common Terminology Criteria for Adverse Events, version 5.0) were assessed in VISION for an unequal duration when comparing the 2 arms (7.56 mo in the experimental arm vs. 2.07 mo for SOC). An unequal duration of follow-up is known to influence the frequency of adverse events. Some investigators advocate that adverse event rates be corrected for the duration of observation (events per month). The most common adverse events reported in the isotopic arm were fatigue (43.1%), dry mouth (38.8%), nausea (35.3%), anemia (31.8%), and back pain (23.4%). All except dry mouth are potentially disease-related, but there is no doubt that rates were higher in the experimental arm. The control group rates were fatigue (22.9%), dry mouth (0.5%), nausea (16.6%), anemia (13.2%), and back pain (14.6%). Adverse events leading to a reduction in ^{177}Lu dosing were present in 5.7% of patients. Adverse events that led to discontinuation of ^{177}Lu dosing were present in 11.9% of patients. This side effect profile was anticipated given the prior experience with the agent.

LIMITATIONS

The use of ^{177}Lu-PSMA-617 plus SOC compared favorably with SOC at all endpoints. There is no doubt that these patients with far-advanced disease and few choices benefited from the experimental treatment. That said, there is much we do not know. What are the optimal PSMA PET criteria for selection of patients? Do patients with low-SUV lesions respond less favorably than those with high-SUV lesions? Although PSMA PET criteria are debatable, these authors favor keeping the PSMA PET/CT in order to exclude patients unlikely to respond. All patients were planned to have 4 cycles of therapy, and up to 6 were allowed. No PSMA retreatments were allowed. What if there is disease progression during the first 2 or 3 cycles of therapy? Should more be given? Is PSA a reliable marker of response or progression? What about patients with clear pain relief but no PSA decline? Do we give more drug? When should therapies be stopped? How many doses of isotope are optimal? What is the optimal dose of the isotope? What is the optimal frequency of administration? Should we be using PSMA PET/CT as a response criterion? What if the PSMA PET reveals no more disease after 2 cycles? Do we need to give more therapy? What about earlier phases of disease? What is the role of SOC (if any) when given in combination with ^{177}Lu-PSMA-617? Is there a meaningful and clinically relevant

upregulation of PSMA expression when using abiraterone or enzalutamide?

There are many questions that arise despite a positive phase III trial, and many questions remain unanswered. More answers may emerge from additional VISION analyses, and many more analyses will be performed. Many of these questions will require new clinical studies, but pivotal trials are expensive and difficult to execute; definitive answers are not going to be readily forthcoming.

FUTURE PHASE III TRIALS

Additional phase III trials with ^{177}Lu-PSMA-617 are being performed now. These include the PSMAfore trial (NCT04689828) and the PSMAddition trial (NCT04720157). The PSMAfore trial will enroll 450 patients with chemotherapy-naïve mCRPC and has an endpoint of rPFS. Crossover will be allowed. ^{177}Lu-PSMA-617 will be compared with a second novel hormone in those previously treated with at least 1 novel hormone (abiraterone, enzalutamide, apalutamide, or darolutamide). The PSMAddition trial will also have rPFS as a primary endpoint and will enroll patients with metastatic hormone-sensitive prostate cancer. ^{177}Lu-PSMA-617 will be used in combination with ADT and a novel hormone of investigator choice. Docetaxel will not be allowed. PSMAddition will enroll approximately 1,126 patients and will use rPFS as a primary endpoint. Crossover will be allowed.

Other phase III trials with PSMA-targeted therapies will soon have randomization under way. The ^{177}Lu-PSMA I&T agent (also called ^{177}Lu-PNT2002) will be evaluated in SPLASH (NCT04647526) in a setting similar to PSMAfore. Similarly, ^{177}Lu-PSMA I&T will be evaluated in the ECLIPSE trial.

Even more phase III trials are being contemplated. Simply stated, ^{177}Lu-PSMA-617 is an active agent that can provide tumor responses and enhance health-related quality of life in patients with advanced prostate cancer. Additional concepts potentially leading to regulatory approvals are eagerly anticipated. Careful trial design and execution using established endpoints will be key.

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