Journal of Nuclear Medicine, published on June 8, 2023 as doi:10.2967/jnumed.123.265952

SNMMI Consensus Statement on Patient Selection and Appropriate Use of ^{177}Lu-PSMA-617 Radionuclide Therapy

Thomas A. Hope[1], Emmanuel S. Antonarakis[2], Lisa Bodei[3], Jeremie Calais[4], Amir Iravani[5], Heather Jacene[6], Phillip J. Koo[7], Alicia K. Morgans[8], Joseph R. Osborne[9], Scott T. Tagawa[10], Mary-Ellen Taplin[8], Oliver Sartor[11], and Michael J. Morris[12]

[1]Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, California; [2]University of Minnesota Masonic Cancer Center, Minneapolis, Minnesota; [3]Molecular Imaging and Therapy Service, Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, New York; [4]Ahmanson Translational Theranostics Division, Department of Molecular and Medical Pharmacology, David Geffen School of Medicine, UCLA, Los Angeles, California; [5]Department of Radiology, University of Washington, Seattle, Washington; [6]Department of Radiology, Brigham and Women's Hospital, and Department of Imaging, Dana-Farber Cancer Institute, Boston, Massachusetts; [7]Banner M.D. Anderson Cancer Center, Phoenix, Arizona; [8]Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts; [9]Molecular Imaging and Therapeutics, Department of Radiology, Weill Cornell Medicine, New York, New York; [10]Department of Medicine, Weill Cornell Medical College, New York, New York; [11]Mayo Clinic, Rochester, Minnesota; and [12]Genitourinary Oncology Service, Memorial Sloan Kettering Cancer Center, New York, New York

Prostate-specific membrane antigen (PSMA) is a transmembrane carboxypeptidase that is highly expressed in prostate cancer. Radioligand therapy (RLT) with ^{177}Lu-labeled compounds has shown clinical benefit, and the U.S. Food and Drug Administration (FDA) approved ^{177}Lu-PSMA-617 (^{177}Lu-vipivotide tetraxetan [Pluvicto; Novartis]) for the treatment of men with metastatic castration-resistant prostate cancer (mCRPC) after progressing on taxane-based chemotherapy and at least 1 line of androgen receptor pathway inhibitors (ARPIs). This document aims to provide standardized guidance through expert consensus for the selection and management of patients being treated with ^{177}Lu-PSMA RLT.

APPROVED THERAPIES IN PROSTATE CANCER

Androgen Deprivation Therapy (ADT)

The most commonly administered ADTs are luteinizing hormone–releasing hormone agonists such as leuprorelin. Gonadotropin-releasing hormone antagonists such as degarelix are also used and do not have the short-term symptom flare potentially associated with luteinizing hormone–releasing hormone agonists.

ARPIs

There are 4 FDA-approved ARPIs for the treatment of advanced prostate cancer (Table 1). Abiraterone inhibits the synthesis of androgens, whereas enzalutamide, apalutamide, and darolutamide inhibit androgen receptor signaling at the level of the receptor itself. ARPIs are approved for metastatic noncastrate (i.e., castration-sensitive) prostate cancer (mCSPC), non-mCRPC, and mCRPC. However, only abiraterone and enzalutamide are FDA-approved for patients with mCRPC after chemotherapy.

Received Apr. 27, 2023; accepted Apr. 27, 2023.
For correspondence or reprints, contact Thomas A. Hope (thomas.hope@ucsf.edu)
Published online Jun. 8, 2023.

DOI: 10.2967/jnumed.123.265952

Chemotherapies

There are 2 commonly used taxane chemotherapies in prostate cancer: docetaxel and cabazitaxel. Docetaxel was shown to prolong overall survival (OS) in mCSPC along with ADT in the CHAARTED and STAMPEDE trials (*1,2*) and was superior to mitoxantrone in patients with mCRPC (*3*). More recently, docetaxel was used in the mCSPC setting in combination with abiraterone acetate or darolutamide (*4,5*). Cabazitaxel prolongs survival in the mCRPC setting both before and after docetaxel chemotherapy (*6,7*). Both taxanes are associated with neuropathy and marrow toxicity, as well as other adverse events, which can limit tolerability.

^{223}Ra

^{223}Ra dichloride is an α-emitting radionuclide with an 11-d half-life. It is a bone-seeking calcium mimetic that targets the blastic reactive component of metastatic osseous lesions by substituting radium for calcium in hydroxyapatite formation. In the ALSYMPCA trial, patients with mCRPC had an OS benefit from ^{223}Ra compared with the best standard of care (*8*). ^{223}Ra is generally well tolerated, but its use has been limited, likely because of the rarity of a prostate-specific antigen (PSA) response, the preponderance of extraosseous sites of disease in pretreated mCRPC, and challenges with assessing and following patient response to treatment.

Other Treatments

Rucaparib and olaparib, both poly(adenosine diphosphate–ribose) polymerase inhibitors, have shown efficacy in patients with mCRPC who have DNA damage repair deficiencies (*9,10*). There remains significant debate about the role of poly(adenosine diphosphate–ribose) polymerase inhibitors in patients with mCRPC without documented DNA damage repair mutations because of a recent study in which olaparib combined with abiraterone was shown to have a progression-free survival benefit versus abiraterone alone in patients irrespective of DNA damage repair status (*11*). Sipuleucel-T

TABLE 1
Use of Androgen Receptor–Targeted Therapies

Therapy	mCSPC	Non-mCRPC	mCRPC before chemotherapy	mCRPC after chemotherapy
Abiraterone	LATITUDE NCT01715285		COU-AA-301 NCT00638690	COU-AA-302 NCT00887198
Enzalutamide	ARCHES NCT02677896	PROSPER NCT02003924	TERRAIN NCT01288911; PREVAIL NCT01212991	AFFIRM NCT00974311
Apalutamide		SPARTAN NCT02489318	TITAN NCT02489318	
Darolutamide	ARASENS NCT02799602	ARAMIS NCT02200614		

is an autologous active cellular immunotherapy that prolongs OS in patients with minimally symptomatic mCRPC (*12*). The checkpoint inhibitor pembrolizumab is also used in patients with microsatellite instability-high tumors (*13*).

DATA REVIEW AND SCORING OF APPROPRIATENESS

Given the limited prospective clinical data evaluating ^{177}Lu-PSMA RLTs, a systematic review was not performed. An overview of the 4 prospective phase 2 and 3 trials that used ^{177}Lu-PSMA-617 registered on clinicaltrial.gov and with published results is provided in Table 2.

In developing these guidelines, the workgroup members used the following definition of appropriateness to guide their considerations and group discussions: "The concept of appropriateness, as applied to health care, balances risk and benefit of a treatment, test, or procedure in the context of available resources for an individual patient with specific characteristics." The workgroup scored each scenario as appropriate, may be appropriate, or rarely appropriate on a scale from 1 to 9 (Table 3). Scores 7–9 indicate that the use of the procedure is appropriate for the specific scenario and is generally considered acceptable. Scores 4–6 indicate that the use of the procedure may be appropriate for the specific scenario. This implies that more research is needed to definitely classify the scenario. Scores 1–3 indicate that the use of the procedure is rarely appropriate for the specific scenario and generally is not considered acceptable.

PROSPECTIVE TRIALS OF ^{177}LU-PSMA-617

There have been 2 significant randomized prospective trials that evaluated ^{177}Lu-PSMA-617 in the treatment of patients with mCRPC: VISION and TheraP (*14,15*). TheraP was a randomized phase 2 trial involving 200 patients in which ^{177}Lu-PSMA-617 was randomized against cabazitaxel and a primary endpoint of the percentage of patients with a 50% decline in PSA (PSA50). In TheraP, a large percentage of patients had a PSA50 response with ^{177}Lu-PSMA-617 compared with cabazitaxel (66% vs. 37%, respectively; $P = 0.0016$). VISION was a randomized phase 3 study of 831 patients who were randomized to protocol-defined standard treatments with or without ^{177}Lu-PSMA-617. The trial had 2 primary endpoints: OS and radiographic progression-free survival as defined by the Prostate Cancer Working Group 3. In VISION, ^{177}Lu-PSMA-617 demonstrated improved OS (15.3 vs. 11.3 mo, $P < 0.001$) and radiographic progression-free survival (8.7 vs. 3.4 mo,

TABLE 2
Prospective Phase 2 and Phase 3 Studies of ^{177}Lu-PSMA RLTs Registered on Clinicaltrial.gov with Published Results

Study	Phase	*n*	Design	Primary endpoint	PSMA PET criteria
VISION	3	831	Randomized 1:1, SoC vs ^{177}Lu-PSMA-617+SoC	OS: 15.3 vs. 11.3 mo (HR, 0.62); PFS: 8.7 vs. 3.4 mo (HR, 0.40)	Uptake greater than liver; excluded PSMA-negative measurable disease
TheraP (*15*)	2	200	Randomized 1:1, cabazitaxel vs. ^{177}Lu-PSMA-617	PSA50, best: 66% vs. 44%	$SUV_{max} > 20$ in at least 1 lesion, all measurable disease with $SUV_{max} > 10$; excluded ^{18}F-FDG/PSMA mismatch
RESIST-PC (*17*)	2	64	Single arm: ^{177}Lu-PSMA-617	PSA50 after 2 cycles: 28%	Uptake greater than liver; excluded PSMA-negative soft-tissue lesions
Peter MacCallum (*16*)	2	50	Single arm: ^{177}Lu-PSMA-617	PSA50, best: 64%	$SUV_{max} > 1.5$ times SUV_{mean} of liver; excluded ^{18}F-FDG/PSMA mismatch

SoC = standard of care; HR = hazard ratio; PFS = progression-free survival.

TABLE 3
Clinical Scenarios for ^{177}Lu-PSMA-617 RLT

Scenario	Description	Appropriateness	Score
1	Treatment of mCRPC after chemotherapy and ARPI	Appropriate	9
2	Treatment of mCRPC after ARPI and before chemotherapy	Rarely appropriate	3
3	Treatment of patients with mCSPC	Rarely appropriate	2

$P < 0.001$) compared with the best standard of care, and this trial was the basis of regulatory approval of ^{177}Lu-PSMA-617 in the United States.

In addition to the VISION and TheraP trials, 2 prospective phase 2 studies have been published. The first was a 50-patient cohort at the Peter MacCallum Centre (*16*) and demonstrated a PSA50 in 64% of patients. The second was the RESIST-PC study, which reported results from a 64-patient cohort from UCLA and the Excel Diagnostics & Nuclear Oncology Center (*17*). The primary endpoint of RESIST-PC was the percentage of patients with a PSA50 response after 2 cycles. In the cohort reported, 28% of patients had a PSA50 response after 2 cycles. Given the small sample size and nonrandomized design, conclusions from these studies are limited. Table 2 provides further details.

PATIENT SELECTION

Working group members acknowledge that there has been significant heterogeneity in patient selection across completed trials. The methods of patient selection and their impact on predicting response or outcome to PSMA RLT have not been directly compared. Below are recommendations for patient selection for PSMA RLT. These criteria should be used as guidance rather than as strict rules, and patients with borderline eligibility may benefit from treatment with PSMA RLT. In all cases, multidisciplinary tumor board discussion is recommended.

PSMA PET for Patient Selection

The 2 randomized trials that evaluated PSMA RLT used 2 different criteria for PSMA positivity. The VISION trial required uptake greater than in the liver in all measurable lesions by visual assessment (*18*). Measurable disease was defined as lymph nodes greater than 2.5 cm in short-axis diameter, solid-organ metastases greater than 1 cm in short-axis diameter, and bone metastases with a soft-tissue component greater than 1 cm in short-axis diameter. There is limited evidence of clinical benefit in patients who do not meet the VISION criteria, although in one series of patients who did not meet the imaging criteria, the reported mean OS was 9.6 mo and the PSA50 response was 21%, lower than the 15 mo and 46%, respectively, in the ^{177}Lu-PSMA-617–treated cohort in VISION (*19*).

The TheraP trial required a single lesion to have an SUV_{max} greater than 20 and all measurable lesions to have an SUV_{max} greater than 10. In addition, the TheraP trial excluded patients who had ^{18}F-FDG–positive/PSMA-negative disease (PSMA-negative defined as an $SUV_{max} < 10$). The TheraP criteria resulted in a higher rate of imaging screen failures than reported in the VISION trial (28% vs. 13%, respectively). Secondary analysis of the TheraP trial demonstrated that patients with a higher average uptake on PSMA PET had a higher PSA response rate with ^{177}Lu-PSMA-617 therapy (*20*), although patients with low PSMA uptake had higher PSA response rates with ^{177}Lu-PSMA-617 than with cabazitaxel. Although patients with higher uptake respond better to PSMA RLT, the committee agreed that the VISION criteria (uptake greater than liver) should be used to select patients for PSMA RLT given that these criteria resulted in an OS benefit in the largest cohort of patients.

Preferably, the PSMA PET used for patient selection should be performed within 3 mo of treatment or since progression on the last therapy. It is important that the baseline PSMA PET before ^{177}Lu-PSMA-617 therapy represent the current disease state. If there is evidence of disease progression or intervening therapy, then one should repeat the PSMA PET when feasible.

The prescribing information for ^{177}Lu-PSMA-617 indicates that patients be selected on the basis of "an approved PSMA-11 imaging agent based on PSMA expression in tumors." Although ^{68}Ga-PSMA-11 was used in both the VISION and the TheraP trials to select patients, ^{68}Ga-PSMA-11 (UCSF/UCLA; Illucix [Telix] and Locametz [Novartis]) and ^{18}F-DCFPyL (^{18}F-piflufolastat [Pylarify; Lantheus]) have had similar performance characteristics in prospective clinical trials, have labels similar to those of diagnostic agents, are regarded as equivalent tracers in clinical practice, and are used in patient selection for ongoing trials of ^{177}Lu-PSMA RLT (*21*). It is important to remember that liver activity when using ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL is similar (*22*). Currently, the differences between the 2 radiopharmaceuticals do not appear to affect patient selection. For these reasons, the committee agreed that either ^{18}F-DCFPyL or ^{68}Ga-PSMA-11 can be used to select patients for PSMA RLT. Overall, it is important to have the involvement of a molecular imaging specialist with experience in evaluating PSMA PET imaging.

Secondary analysis of both the VISION and the TheraP trials has shown that patients with a higher whole-body PSMA SUV_{mean} on baseline PET have better outcomes with ^{177}Lu-PSMA-617 (*23,24*). In the VISION trial, patients with the highest quartile of SUV_{mean} ($SUV_{mean} > 9.9$) demonstrated longer OS than patients receiving ^{177}Lu-PSMA-617 with a lower baseline SUV_{mean} (*23*). Although uptake measured by SUV_{mean} appears to correlate well with clinical outcomes, it has thus far been observed in the research setting and not yet applied in routine clinical practice. Moving forward, we hope that the use of whole-body SUV_{mean} will become a part of standard clinical work, but currently whole-body SUV_{mean} is not required to select patients for PSMA RLT.

In addition to imaging with PSMA PET, patients should be imaged with either contrast-enhanced CT or MRI to identify potential PSMA-negative disease, which is particularly important in patients who have known liver disease. In addition, the committee agreed that ^{18}F-FDG PET is not required as a standard patient selection tool. If a patient has signs of disease aggressiveness (disease that is poorly differentiated or not driven by the androgen receptor) or there is suspicion of PSMA-negative disease, use of

an ^{18}F-FDG PET scan for further disease characterization can be considered.

In a limited setting, it may be appropriate to treat patients who show heterogeneous disease on PSMA PET. For example, if there are a limited number of PSMA-negative lesions, it may be appropriate to treat the dominant PSMA-positive disease using PSMA RLT. Because the VISION criteria defined PSMA-negative disease in solid organs as greater than 1 cm, smaller-volume PSMA-negative disease can be considered for treatment, especially if most of the disease is PSMA-positive. This is particularly true in patients who have completed all available therapeutic options. External-beam radiation therapy may be used to treat low-volume PSMA-negative disease and is indicated in symptomatic sites of disease.

Preexisting Renal Dysfunction

Kidney function criteria for VISION and TheraP are provided in Table 4. Although in the VISION trial there was no difference in the rate of renal toxicity in the treatment and control arms, renal toxicity has been reported in patients treated with PSMA RLT (*25*).

The consensus of the panel for renal function was that the baseline estimated glomerular filtration rate should be greater than 30 mL/min. If patients have baseline renal function less than 30 mL/min or are on dialysis, the case should be discussed by a multidisciplinary tumor board. In patients with poorer renal function, the dose to the kidneys decreases, and the main risk is expected to be an increased red marrow dose due to prolonged blood-pool activity. Therefore, in patients with poor renal function, close attention should be paid to the marrow. The group consensus was not to reduce the dose in patients with reduced renal function at baseline, although reduction can be considered in individual cases.

Bone Marrow Dysfunction

Bone marrow inclusion criteria for VISION and TheraP are provided in Table 4. The consensus baseline requirements for marrow function were a hemoglobin level of at least 8 g/dL, a white blood cell count of at least 2.0×10^9/L, or an absolute neutrophil count of at least 1.0×10^9/L and a platelet count of at least 75×10^9/L. Baseline bone marrow dysfunction can be secondary to both disease progression replacing the marrow and marrow injury from prior cytotoxic therapies, and bone marrow biopsies can be helpful to demonstrate diffuse marrow replacement. Marrow replacement in a patient may not be a contraindication for treatment despite poor marrow function, and a multidisciplinary discussion should be undertaken. An important consideration is that, with rapidly progressing marrow disease, one should not wait for recovery of marrow function to start treatment.

Patients with diffuse marrow disease present a unique challenge regarding RLT. The VISION trial excluded patients with bone superscans. How to translate the bone scan finding of diffuse marrow disease to PSMA PET is not well defined. Although not included in the VISION trial, a retrospective pooling of 43 patients across 4 institutions demonstrated that it may be safe to treat patients who have diffuse marrow disease (*26*). In addition, patients with diffuse marrow disease can have significant drops in their counts immediately after treatment, and one should follow these patients more closely and be prepared to transfuse as needed. Overall, the committee agreed that patients with diffuse marrow disease are candidates for PSMA RLT.

CLINICAL SETTINGS FOR ^{177}LU-PSMA-617

mCSPC (Score 2—Rarely Appropriate)

Currently, there are not enough data available to support the use of ^{177}Lu-PSMA-617 RLT in the mCSPC setting. There are 2 ongoing randomized trials evaluating its role in first-line mCSPC. The PSMAddition trial is a phase 3 study that compares ADT and ARPI to ADT, ARPI, and ^{177}Lu-PSMA-617 (NCT04720157). The UpFrontPSMA trial is a phase 2 study that compares docetaxel and ADT versus ADT and ^{177}Lu-PSMA-617 with sequential docetaxel (NCT04343885). Until the findings of these studies are reported, ^{177}Lu-PSMA-617 should not be used in the mCSPC setting.

mCRPC Before Chemotherapy (Score 3—Rarely Appropriate)

There are no published randomized data to date to support the use of PSMA RLT in the prechemotherapy setting. Three similar phase 3 trials are currently evaluating PSMA RLT in this setting. The PSMAfore (NCT04689828), SPLASH (NCT04647526), and ECLIPSE (NCT05204927) trials are all comparing PSMA RLT with ARPI switch. Of note, PSMAfore uses ^{177}Lu-PSMA-617, whereas SPLASH and ECLIPSE use ^{177}Lu-PSMA-I&T.

PSMAfore has recently reported positive results, with improvement in radiographic progression-free survival in the PSMA RLT arm compared with second-line ARPI; on formal publication and approval of this indication by the FDA, this document may be updated to include the prechemotherapy mCRPC setting. Notably, there remain no long-term follow-up data for patients, and caution is warranted for patients with borderline laboratory evaluations in this setting in which they are expected to otherwise have a longer life expectancy than in the heavily pretreated populations reported in the VISION trial.

TABLE 4
Baseline Laboratory Cutoffs

Test	VISION	TheraP	Recommendation
Kidney function	Serum creatinine $\leq 1.5 \times$ ULN or eGFR $\geq$ 50 mL/min	eGFR $\geq$ 40 mL/min	eGFR $\geq$ 30 mL/min
Hgb	Hgb $\geq$ 9 g/dL	Hgb $\geq$ 9 g/dL	Hgb $\geq$ 8 g/dL
WBC count	WBC $\geq 2.5 \times 10^9$/L or ANC $\geq 1.5 \times 10^9$/L	ANC $\geq 1.5 \times 10^9$/L	WBC $\geq 2.0 \times 10^9$/L or ANC $\geq 1.0 \times 10^9$/L
Platelets	Platelets $\geq 100 \times 10^9$/L	Platelets $\geq 100 \times 10^9$/L	Platelets $\geq 75 \times 10^9$/L

ULN = upper limit of normal; eGFR = estimated glomerular filtration rate; Hgb = hemoglobin; WBC = white blood cell; ANC = absolute neutrophil count.

mCRPC After Chemotherapy (Score 9—Appropriate)

The current label for ^{177}Lu-PSMA-617 RLT is for patients with PSMA-avid disease after at least 1 taxane-based chemotherapy course and at least 1 line of ARPI in any advanced disease setting. The most commonly used taxane-based chemotherapies are docetaxel and cabazitaxel; no data exist for using ^{177}Lu-PSMA-617 after non–taxane-based chemotherapies such as platinum chemotherapy. The panel agreed that chemotherapy in either the mCSPC or the mCRPC setting qualifies patients for treatment with ^{177}Lu-PSMA-617 and that patients should not be required to receive more than 1 line of taxane-based chemotherapy before receiving ^{177}Lu-PSMA-617.

One important question is what constitutes prior exposure to chemotherapy. The VISION trial required at least 2 cycles of chemotherapy to qualify. Although there is no requirement on the length of exposure to chemotherapy, the intention is that patients receive chemotherapy until completion, progression, or dose-limiting toxicities.

Since the approved label does not require patients to receive both docetaxel and cabazitaxel before ^{177}Lu-PSMA-617, treatment of patients after docetaxel and before cabazitaxel is a viable option. The TheraP trial compared the efficacy of ^{177}Lu-PSMA-617 with that of cabazitaxel and demonstrated improved PSA responses with ^{177}Lu-PSMA-617 (*15*). An important finding was that there was no evidence of improved OS in the ^{177}Lu-PSMA-617 group; further comparative data need to be developed to determine whether sequencing affects outcomes for individual patients or patient groups. When deciding between using ^{177}Lu-PSMA-617 and cabazitaxel, there are 2 important considerations. The first is the uptake on PSMA PET. Both the TheraP trial and the VISION trial demonstrated that patients with higher uptake respond better to PSMA RLT (*23,24*). Notably, in the lowest quartile of uptake on the TheraP trial ($SUV_{mean} < 6.9$), there was a trend toward an improved PSA50 response rate with cabazitaxel (odds ratio, 0.53) (*24*). The second consideration is tolerability. The TheraP trial demonstrated improved quality of life with ^{177}Lu-PSMA-617 relative to cabazitaxel. Given the similar OS data in the TheraP trial, selecting between ^{177}Lu-PSMA-617 and cabazitaxel on the basis of toxicity profiles is reasonable.

CURRENT CLINICAL STRUGGLES

Role of Androgen Receptor–Targeted Therapies

Patients should be effectively castrate for the duration of PSMA RLT. Patients may also receive treatment with ARPIs such as abiraterone or enzalutamide. In the VISION trial, 53% of patients initiated ARPIs along with ^{177}Lu-PSMA-617, and ARPIs can be safely continued during PSMA RLT treatment (*14*). Currently, there is no evidence for or against using ARPI with PSMA RLT. In addition, if patients start or stop ARPIs during treatment, PSA response may not be reliable, as the androgen receptor controls PSA secretion from tumor cells.

What Is the Role of ^{223}Ra?

Few data are available to help understand the optimal setting for ^{223}Ra therapy now that ^{177}Lu-PSMA-617 is FDA-approved. The ALSYMPCA trial was performed before the approvals of ARPIs, and the role of ^{223}Ra after ARPI has not been defined. Clearly, patients who have PSMA-avid soft-tissue disease should receive ^{177}Lu-PSMA-617 instead of ^{223}Ra. In patients who have bone-only disease, it is not clear how one should sequence the 2 agents. Retrospective data suggest that it is safe to give ^{223}Ra before ^{177}Lu-PSMA-617, without evidence of concerning marrow toxicity (*27,28*), and 17% of patients in the VISION trial had received ^{223}Ra before enrollment (*14*). The committee agreed that patients previously treated with ^{223}Ra are candidates for PSMA RLT.

Treatment-Related Toxicities

There are multiple approaches to the management of treatment-related marrow toxicity. First, one can consider delaying subsequent therapy to allow marrow function to recover. This could be a potential option in a patient who is responding well to treatment. Second, one can administer platelet or red blood cell transfusions during therapy, which is appropriate and was allowed on the VISION trial. Third, one can consider using marrow-stimulating agents such as thrombopoietin for platelets, filgrastim and pegfilgrastim for white blood cells, and erythropoietin for red blood cells. A potential concern is that the use of stimulating agents can potentiate marrow toxicity with subsequent cycles if administered within 2 wk. One should consult a hematologist before using these medications. In general, the committee did not recommend dose reductions to handle treatment-related marrow toxicity.

Dry mouth is a common reported toxicity with PSMA RLT. A careful history should be taken at baseline and subsequent follow-ups to understand the severity of dry mouth to distinguish nighttime dryness from that which limits oral intake and impacts quality of life. Unfortunately, there is no agreed-on approach to minimizing salivary gland toxicity. In patients with symptomatic dry mouth, lubricating rinses such as Biotene (Haleon) can be beneficial. If possible, treatment delays can allow for recovery of salivary gland function.

In general, the panel feels that prophylaxis for nausea and vomiting is not required. However, in the VISION trial, which used antiemetic prophylaxis, 34% of patients reported nausea. With or without prophylaxis, antiemetics can be helpful if patients develop treatment-related nausea and vomiting. A pain flare is another potential adverse event, but the routine use of steroids is not recommended. If a patient develops a significant pain flare or fatigue after therapy, a steroid taper can be considered with subsequent cycles. In addition, patients should receive appropriate supportive medications, such as nonopiate and opiate pain medications, bone-protective agents, bowel regimens, and treatments for emotional distress.

In terms of laboratory evaluation, a complete blood count and metabolic panel should be checked at least every 6 wk and more frequently in patients with lower marrow counts. It is recommended to check lab values 2–3 wk before the next scheduled therapy to determine whether the treatment should proceed. The PSA level should be checked at least every 6 wk and is typically checked between treatment cycles.

When to Consider Cessation of Treatment

There are no defined rules about what should be considered treatment failure for PSMA RLT. Three main factors should be considered: imaging-based progression, PSA progression, and clinical decline. These 3 factors do not always move hand in hand, and patients can have progression on imaging while clinically improving. In the setting of a rising PSA level, the development of worsening clinical symptoms or progression on imaging may indicate it is time to stop therapy. In the setting of a rise in PSA level or minimal radiographic progression, it is reasonable to continue treatment, particularly if no other treatment option is available. When weighing the impact of radiographic progression, the development of new liver lesions on therapy should lead to cessation. If

patients develop focal pain, external-beam radiation therapy can be used for palliative measures during PSMA RLT without requiring cessation of treatment. In general, it is important to administer 2 cycles before assessing response; PSA changes after only 1 cycle are not a reliable marker, and PSA can transiently increase (*17,29*).

In terms of the total number of administered cycles, the VISION trial used 4 cycles, which was expandable to 6 in patients who were benefitting (the median number of cycles on VISION was 5) (*14*). If a patient has evidence of response based on PSA, imaging, or clinical changes, without dose-limiting toxicity, the panel generally recommended continuing on to cycles 5 and 6. The decision on how many cycles to administer should be made on an individual basis for each patient.

Exceptional Responders and Restarting Treatment

A subgroup of patients will have an exceptional response to treatment, with a complete imaging and PSA response. In these patients, cessation of therapy with complete responses on ^{177}Lu-PSMA SPECT was used in TheraP. At the time of subsequent progression, restarting treatment can be considered. Currently, a maximum of 6 cycles can be used. Further work is needed to understand the role of PSMA RLT beyond 6 cycles.

Imaging During Treatment

In the VISION trial, patients were followed using bone scans and CT scans every 12 wk per the protocol. For evaluating response to PSMA RLT, imaging using a bone scan is optional and is primarily used to establish a new baseline after a good response or to confirm progression or response if there is uncertainty based on clinical or biochemical findings. Contrast-enhanced imaging, typically using CT, is valuable in following soft-tissue disease, particularly in the liver. The committee recommends following patients with, at a minimum, contrast-enhanced CT.

One unique aspect of ^{177}Lu treatment is that the therapy can be imaged using γ-cameras (either planar imaging or SPECT), and posttreatment imaging should be considered as a method to follow disease. This allows one to visualize changes in the extent of PSMA-avid disease after each cycle, which can be helpful in tracking patients' disease, particularly in the bones. Changes on posttreatment γ-imaging between cycles 1 and 2 have been shown to correlate with patient outcomes (*30*). In addition, posttreatment γ-imaging can be valuable to evaluate for evidence of residual disease after cycle 4 to inform the need for additional therapies.

Currently, there is no agreed-on role for following patients using PSMA PET during therapy to evaluate response. Although PSMA PET may be more accurate than posttreatment imaging in visualizing PSMA-positive disease, there is no evidence of improved patient management. In addition, PSMA PET has limited sensitivity to the development of PSMA-negative disease. Further research is needed on the role of PSMA PET during treatment with PSMA RLT.

FUTURE DIRECTIONS

Multiple phase 3 trials are evaluating PSMA RLT in patients with metastatic prostate cancer. Three trials are currently evaluating its use in patients with mCRPC before chemotherapy. One is evaluating ^{177}Lu-PSMA-617 (PSMAfore, NCT04689828), and the other two are evaluating ^{177}Lu-PSMA-I&T (SPLASH, NCT04647526; ECLIPSE, NCT05204927). PSMAddition is also studying the addition of ^{177}Lu-PSMA-617 in patients with mCSPC being started on ADT and ARPI treatment (NCT04720157). Several nonregistration trials are furthermore evaluating the use of ^{177}Lu-PSMA-617 in combination with other treatments such as immunotherapy (NCT03658447, NCT03805594, and NCT05150236), chemotherapy (NCT04343885), ARPIs (NCT04419402), or DNA damage repair pathways (NCT03874884).

CONCLUSION

With the approval of ^{177}Lu-PSMA-617, a new class of therapeutics is available to patients with prostate cancer. Currently, PSMA RLT is limited to patients with mCRPC who have progressed on chemotherapy and ARPIs. Patients should be selected using PSMA PET. On treatment, patients should be followed using contrast-enhanced CT, and posttreatment γ-imaging should be considered. How to determine when to stop treatment remains a difficult decision. We look forward to the potential use of PSMA RLT in prechemotherapy mCRPC or other settings pending the full results of ongoing trials.

DISCLOSURE

Emmanuel Antonarakis has served as a paid consultant for Janssen, Astellas, Sanofi, Bayer, Bristol Myers Squibb, Amgen, Constellation, Blue Earth, Exact Sciences, Invitae, Curium, Pfizer, Merck, AstraZeneca, Clovis, and Eli Lilly; has received research support (to his institution) from Janssen, Johnson & Johnson, Sanofi, Bristol Myers Squibb, Pfizer, AstraZeneca, Novartis, Curium, Constellation, Celgene, Merck, Bayer, Clovis, and Orion; and is a coinventor of a biomarker technology that has been licensed to Qiagen. Jeremie Calais receives funding from Astellas, Bayer, Blue Earth Diagnostics, Curium Pharma, DS Pharma, GE Healthcare, Isoray, IBA RadioPharma, Janssen Pharmaceuticals, Lightpointmedical, Lantheus, Progenics, EXINI, Monrol, Novartis, Advanced Accelerator Applications, POINT Biopharma, Radiomedix, Sanofi, and Telix Pharmaceuticals. Phillip Koo receives funding from Bayer, Novartis, Merck, Janssen, AstraZeneca, Astellas, Blue Earth, Lantheus, Clarity, Telix, and GE. Mary-Ellen Taplin receives funding from Propella, Janssen, Clovis, Pfizer, Blue Earth, Arcus Bioscience, and Arvinas. Alicia Morgans receives funding from Astellas, AstraZeneca, AAA, Bayer, Blue Earth, Exelixis, Janssen, Lantheus, Myriad, Myovant, Novartis, Pfizer, Telix, and Sanofi. Michael Morris is a consultant for Lantheus, AstraZeneca, Amgen, Daiichi, Convergent Therapeutics, Pfizer, ITM Isotope Technologies, Clarity Pharmaceuticals, Blue Earth Diagnostics, and POINT Biopharma and receives institutional research funding from Bayer, Corcept, Roche/Genentech, Janssen, Celgene, and Novartis. Thomas Hope receives grant funding to the institution from Clovis Oncology, Philips, GE Healthcare, Lantheus, the Prostate Cancer Foundation, and the National Cancer Institute (R01CA235741 and R01CA212148); receives personal fees from Ipsen, Bayer, and BlueEarth Diagnostics; and receives fees from and has an equity interest in RayzeBio and Curium. Heather Jacene receives funding from Advanced Accelerator Applications (consulting), Blue Earth Diagnostics (consulting; research support to institution), Cambridge University Press (royalties), Spectrum Dynamics (consulting), and Munrol (honoraria). Lisa Bodei is a nonremunerated consultant/speaker for AAA-Novartis, Ipsen, Clovis Oncology, IBA, ITM, and Great Point Partners and received a grant from AAA-Novartis. Scott Tagawa receives research support (to the institution) from Sanofi, Medivation, Astellas, Janssen, Amgen, Progenics, Dendreon, Lilly, Genentech, Newlink, BMS, Inovio, AstraZeneca, Immunomedics, Aveo, Rexahn, Atlab, Boehringer Ingelheim, Millennium, Bayer, Merck,

Abbvie, Karyopharm, Endocyte, Clovis, Seattle Genetics, Novartis, Gilead, POINT Biopharma, and Ambrx and is a consultant for Sanofi, Medivation, Astellas, Dendreon, Janssen, Genentech, Bayer, Endocyte, Eisai, Immunomedics, Karyopharm, Abbvie, Tolmar, Seattle Genetics, Amgen, Clovis, QED, Pfizer, AAA/Novartis, Clarity, Genomic Health, POINT Biopharma, Blue Earth, AIkido Pharma, Telix Pharma, Convergent Therapeutics, EMD Serono, Myovant, Merck, and Daiichi Sankyo. No other potential conflict of interest relevant to this article was reported.

REFERENCES

1. Sweeney CJ, Chen Y-H, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med.* 2015;373:737–746.
2. James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet.* 2016;387:1163–1177.
3. Berthold DR, Pond GR, Soban F, de Wit R, Eisenberger M, Tannock IF. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. *J Clin Oncol.* 2008;26:242–245.
4. Fizazi K, Foulon S, Carles J, et al. Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 × 2 factorial design. *Lancet.* 2022;399:1695–1707.
5. Smith MR, Hussain M, Saad F, et al. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. *N Engl J Med.* 2022;386:1132–1142.
6. de Wit R, de Bono J, Sternberg CN, et al. Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. *N Engl J Med.* 2019;381:2506–2518.
7. Bahl A, Oudard S, Tombal B, et al. Impact of cabazitaxel on 2-year survival and palliation of tumour-related pain in men with metastatic castration-resistant prostate cancer treated in the TROPIC trial. *Ann Oncol.* 2013;24:2402–2408.
8. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med.* 2013;369:213–223.
9. Hussain M, Mateo J, Fizazi K, et al. Survival with olaparib in metastatic castration-resistant prostate cancer. *N Engl J Med.* 2020;383:2345–2357.
10. Abida W, Patnaik A, Campbell D, et al. Rucaparib in men with metastatic castration-resistant prostate cancer harboring a *BRCA1* or *BRCA2* gene alteration. *J Clin Oncol.* 2020;38:3763–3772.
11. Clarke NW, Armstrong AJ, Thiery-Vuillemin A, et al. Abiraterone and olaparib for metastatic castration-resistant prostate cancer. *NEJM Evid.* 2022;1:10.1056/EVIDoa2200043.
12. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med.* 2010;363:411–422.
13. Abida W, Cheng ML, Armenia J, et al. Analysis of the prevalence of microsatellite instability in prostate cancer and response to immune checkpoint blockade. *JAMA Oncol.* 2019;5:471–478.
14. Sartor O, de Bono J, Chi KN, et al. Lutetium-177–PSMA-617 for metastatic castration-resistant prostate cancer. *N Engl J Med.* 2021;385:1091–1103.
15. Hofman MS, Emmett L, Sandhu S, et al. [^{177}Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. *Lancet.* 2021;397:797–804.
16. Violet J, Sandhu S, Iravani A, et al. Long-term follow-up and outcomes of retreatment in an expanded 50-patient single-center phase II prospective trial of ^{177}Lu-PSMA-617 theranostics in metastatic castration-resistant prostate cancer. *J Nucl Med.* 2020;61:857–865.
17. Calais J, Gafita A, Eiber M, et al. Prospective phase 2 trial of PSMA-targeted molecular RadiothErapy with ^{177}Lu-PSMA-617 for metastatic castration-reSISTant Prostate Cancer (RESIST-PC): efficacy results of the UCLA cohort. *J Nucl Med.* 2021;62:1440–1446.
18. Kuo PH, Benson T, Messmann R, Groaning M. Why we did what we did: PSMA PET/CT selection criteria for the VISION trial. *J Nucl Med.* 2022;63:816–818.
19. Hotta M, Gafita A, Czernin J, Calais J. Outcome of patients with PSMA PET/CT screen failure by VISION criteria and treated with ^{177}Lu-PSMA therapy: a multicenter retrospective analysis. *J Nucl Med.* 2022;63:1484–1488.
20. Buteau JP, Martin AJ, Emmett L, et al. PSMA PET and FDG PET as predictors of response and prognosis in a randomized phase 2 trial of ^{177}Lu-PSMA-617 (LuPSMA) versus cabazitaxel in metastatic, castration-resistant prostate cancer (mCRPC) progressing after docetaxel (TheraP ANZUP 1603) [abstract]. *J Clin Oncol.* 2022;40(suppl):10.
21. Jadvar H, Calais J, Fanti S, et al. Appropriate use criteria for prostate-specific membrane antigen PET imaging. *J Nucl Med.* 2022;63:59–68.
22. Ferreira G, Iravani A, Hofman MS, Hicks RJ. Intra-individual comparison of ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL normal-organ biodistribution. *Cancer Imaging.* 2019;19:23.
23. Kuo P, Hesterman J, Rahbar K, et al. [^{68}Ga]Ga-PSMA-11 PET baseline imaging as a prognostic tool for clinical outcomes to [^{177}Lu]Lu-PSMA-617 in patients with mCRPC: a VISION substudy [abstract]. *J Clin Oncol.* 2022;40(suppl):5002.
24. Buteau JP, Martin AJ, Emmett L, et al. PSMA and FDG-PET as predictive and prognostic biomarkers in patients given [^{177}Lu]Lu-PSMA-617 versus cabazitaxel for metastatic castration-resistant prostate cancer (TheraP): a biomarker analysis from a randomised, open-label, phase 2 trial. *Lancet Oncol.* 2022;23:1389–1397.
25. Schäfer H, Mayr S, Büttner-Herold M, et al. Extensive ^{177}Lu-PSMA radioligand therapy can lead to radiation nephropathy with a renal thrombotic microangiopathy–like picture. *Eur Urol.* 2023;83:385–390.
26. Gafita A, Fendler WP, Hui W, et al. Efficacy and safety of ^{177}Lu-labeled prostate-specific membrane antigen radionuclide treatment in patients with diffuse bone marrow involvement: a multicenter retrospective study. *Eur Urol.* 2020;78:148–154.
27. Ahmadzadehfar H, Zimbelmann S, Yordanova A, et al. Radioligand therapy of metastatic prostate cancer using ^{177}Lu-PSMA-617 after radiation exposure to ^{223}Ra-dichloride. *Oncotarget.* 2017;8:55567–55574.
28. Rahbar K, Essler M, Pabst KM, et al. Safety and survival outcomes of lutetium-177–prostate-specific membrane antigen therapy in patients with metastatic castration-resistant prostate cancer with prior radium-223 treatment: the RALU study. *J Nucl Med.* 2023;64:574–578.
29. Hofman MS, Violet J, Hicks RJ, et al. [^{177}Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. *Lancet Oncol.* 2018;19:825–833.
30. John N, Pathmanandavel S, Crumbaker M, et al. ^{177}Lu-PSMA SPECT quantitation at 6 weeks (dose 2) predicts short progression free survival for patients undergoing Lu PSMA I&T therapy. *J Nucl Med.* 2023;64:410–415.