SNMMI Consensus Statement on Patient Selection and Appropriate Use

of 177Lu-PSMA-617 Radionuclide Therapy

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INTRODUCTION

Prostate-specific membrane antigen (PSMA) is a transmembrane carboxypeptidase that is highly expressed in prostate cancer. Radioligand therapy (RLT) with lutetium-177 (177Lu)-labeled compounds has shown clinical benefit, and the US Food and Drug Administration (FDA) approved 177Lu-PSMA-617 (lutetium Lu 177 vipivotide tetraxetan, Pluvicto; Novartis, Millburn, NJ) 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 177Lu-PSMA RLT.

APPROVED THERAPIES IN PROSTATE CANCER

Androgen Deprivation Therapy

The most commonly administered androgen deprivation therapies (ADTs) are luteinizing hormone-releasing hormone (LHRH) 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 LHRH agonists.

Androgen Receptor Pathway Inhibitors

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 non-castrate (i.e., castration-sensitive) prostate cancer (mCSPC), non-

metastatic CRPC (nmCRPC), and mCRPC. However, only abiraterone and enzalutamide are FDA approved for patients with mCRPC after chemotherapy.

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.

Radium-223

Radium-223 dichloride is an alpha-emitting radionuclide with an 11-day 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 radium-223 compared with the best standard of care (*8*). Radium-223 is generally well tolerated, but its use has been limited, likely due to the rarity of a prostate-specific antigen (PSA) response, preponderance of extra-osseous 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 (PARPis), have shown efficacy in patients with mCRPC who have DNA damage repair (DDR) deficiencies (*9,10*). There remains significant debate about the role of PARPi in patients with mCRPC without documented DDR mutations due to a recent study in which olaparib combined with abiraterone was shown to have a progression-free survival (PFS) benefit versus abiraterone alone in patients irrespective of DDR status (*11*). Sipuleucel-T 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*).

MATERIALS and METHODS

Data Review

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

Scoring of Appropriateness

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 177Lu-PSMA-617

There have been 2 significant randomized prospective trials that evaluated 177Lu-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 177Lu-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 177Lu-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 Lu-177 PSMA-617. The trial had 2 primary endpoints: OS and radiographic PFS

(rPFS) as defined by the Prostate Cancer Working Group 3. In VISION, 177Lu-PSMA-617

demonstrated improved OS (15.3 vs. 11.3 months, p<0.001) and rPFS (8.7 vs. 3.4 months,

p<0.001) compared with the best standard of care, and this trial was the basis of regulatory

approval of 177LuPSMA-617 in the US.

In addition to the VISION and TheraP trials, 2 prospective phase 2 studies have been published. The first was a 50-patient cohort performed at the Peter MacCallum Centre (*16*), which 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 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. Please see **Table 2** for 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 Positron Emission Tomography 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 the liver in all measurable lesions by visual assessment (*18*). Measurable disease was defined as lymph nodes greater than 2.5 cm in the short axis, solid organ metastases greater than 1 cm in the short axis, and bone metastases with

a soft tissue component greater than 1 cm in the short axis. There is limited evidence of the clinical benefit in patients who do not meet the VISION criteria, although in 1 series of patients who did not meet imaging criteria, the reported mean OS was 9.6 months and PSA50 response 21%, lower than the OS of 15 months and 46% in the 177Lu-PSMA-617-treated cohort in VISION (*19*).

The TheraP trial required a single lesion to have a maximum standardized uptake value (SUVmax) greater than 20, and all measurable lesions to have an SUVmax greater than 10. In addition, the TheraP trial excluded patients who had fluorodeoxyglucose (FDG)-positive/PSMA-negative disease (PSMA negative defined as an SUVmax less than 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 positron emission tomography (PET) had a higher PSA response rate with 177Lu-PSMA-617 therapy (*20*), although patients with low PSMA uptake had higher PSA response rates with 177Lu-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 OS benefit in the largest cohort of patients.*

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

The prescribing information for 177Lu-PSMA-617 indicates that patients be selected on the basis of "an approved PSMA-11 imaging agent based on PSMA expression in tumors." Although 68Ga-PSMA-11 was used in both the VISION and TheraP trials to select patients, 68Ga-PSMA-11 PET/computed tomography (CT) (UCSF/UCLA; Illucix, Telix; and Locametz, Novartis) and 18F-DCFPyL (piflufolastat F 18, Pylarify, Lantheus) have similar performance characteristics in prospective clinical trials, have similar labels as diagnostic agents, are regarded as equivalent tracers in clinical practice, and are both used in patient selection for ongoing trials of 177Lu-PSMA RLT (21). It is important to remember that liver activity when using 68Ga-PSMA-11 and 18F-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 18F-DCFPyL or 68Ga-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 TheraP trials has shown that patients with higher whole body (WB) PSMA SUVmeans on baseline PET have better outcomes with 177Lu-PSMA-617 (23,24). In the VISION trial, the highest quartile of SUVmean (SUVmean > 9.9) demonstrated longer OS than for those receiving 177Lu-PSMA-617 with a lower baseline SUVmean (23). Although uptake measured by SUVmean 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 WB SUVmean will become a part of standard clinical work, but currently WB SUVmean 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 magnetic resonance imaging to identify potential PSMA-negative disease, which is particularly important in patients who have known liver disease. In addition, the committee agreed that FDG PET is not required as a standard patient selection tool. If a patient has signs of disease aggressiveness (non-androgen receptor driven or poorly differentiated disease) or suspicion of PSMA-negative disease, use of an FDG PET scan for further disease characterization can be considered.

In a limited setting, it may be appropriate to treat patients who have 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 by using PSMA RLT. It should be noted that the VISION criteria defined PSMA-negative disease in solid organs as greater than 1 cm, and so 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 is 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 at 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 marrow. The group consensus was not to reduce the dose in patients with reduced renal function at baseline, although that 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 hemoglobin ≥ 8 g/dL, white blood cell count ≥ 2.0 x 10^9/L, or absolute neutrophil count ≥ 1.0 x 10^9/L, and platelets ≥ 75 x 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 "superscans" on bone scan. 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 following 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 177Lu-PSMA-617

Castration-Sensitive Prostate Cancer (Score 2 – Rarely Appropriate)

Currently, there is not enough data available to support the use of 177Lu-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 177Lu-PSMA-617 (NCT04720157). The UpFrontPSMA trial is a phase 2 study that compares docetaxel and ADT versus ADT and 177Lu-PSMA-617 with sequential docetaxel (NCT04343885). Until these studies read out, 177Lu-PSMA-617 should not be used in the mCSPC setting.

Castration-Resistant Prostate Cancer Pre-chemotherapy (Score 3 – Rarely Appropriate)

There are no published randomized data to date to support the use of PSMA RLT in the pre-chemotherapy 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 to ARPI switch. Of note, PSMAfore uses 177Lu-PSMA-617, whereas SPLASH and ECLIPSE use 177Lu-PSMA-I&T.

PSMAfore has recently reported positive results, with improvement in rPFS in the PSMA RLT arm compared with second-line ARPI; upon formal publication and approval of this

indication by the FDA, this document may be updated to include the pre-chemotherapy CRPC 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.

Castration-Resistant Prostate Cancer Post-chemotherapy (Score 9 – Appropriate)

The current label for 177Lu-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 177Lu-PSMA-617 after non-taxane-based chemotherapies such as platinum chemotherapy. The panel agreed that chemotherapy in either the CSPC or CRPC setting qualifies patients for treatment with 177Lu-PSMA-617 and that patients should not be required to receive more than 1 line of taxane-based chemotherapy prior to receiving 177Lu-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 177Lu-PSMA-617, treatment of patients after docetaxel and before cabazitaxel is a viable option. The TheraP trial compared the efficacy of 177Lu-PSMA-617 to

that of cabazitaxel and demonstrated improved PSA responses with 177Lu-PSMA-617 (*15*). An important finding was that there was no evidence of improved OS in the 177Lu-PSMA-617 group; further comparative data need to be developed to determine whether sequencing affects outcomes for individual patients or patient groups. When making the decision between using 177Lu-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 (SUVmean < 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 177Lu-PSMA-617 relative to cabazitaxel. Given the similar OS data in the TheraP trial, selecting between 177Lu-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 177Lu-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 Ra-223?

Few data are available to help understand the optimal setting for Ra-223 therapy now that 177Lu-PSMA-617 is FDA approved. The ALSYMPCA trial was performed before the approvals of ARPIs, and the role of Ra-223 after ARPI has not been defined. Clearly patients who have PSMA-avid soft tissue disease should receive 177Lu-PSMA-617 instead of Ra-223. 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 Ra-223 before 177Lu-PSMA-617 without evidence of concerning marrow toxicity (*27,28*), and 17% of patients in the VISION trial had received Ra-223 prior to enrollment (*14*). The committee agreed that patients previously treated with Ra-223 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 weeks. One should consult a hematologist before using these medications. In general, the committee did not recommend dose reductions in order 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 upon approach to minimizing salivary gland toxicity. In patients with symptomatic dry mouth, lubricating rinses such as Biotene (Haleon, Weybridge, UK) 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 that used antiemetic prophylaxis, 34% of patients reported nausea. With or without prophylaxis, antiemetics can be helpful if patients develop treatment-related nausea and vomiting. Pain flare is another potential adverse event, but the routine use of steroids is not recommended. If a patient develops 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 non-opiate 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 weeks and more frequently in patients with lower marrow counts. It is recommended to check lab values 2-3 weeks before the next scheduled therapy to determine whether the treatment should proceed. The PSA level should be checked at least every 6 weeks and is typically checked between each treatment cycle.

When to Consider Cessation of Treatment

There are no defined rules about what should be considered as 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, and/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 is 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 (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 of 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 177Lu-

PSMA single-photon emission CT (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 needs to be performed to understand the role of PSMA RLT beyond 6 cycles.

Imaging During Treatment

In the VISION trial, patients were followed by using bone scans and CT scans every 12 weeks per 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 contrast-enhanced CT at a minimum.

One unique aspect of 177Lu treatment is that the therapy can be imaged by using gamma cameras (either planar imaging or SPECT), and post-treatment 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 post-treatment gamma imaging between cycles 1 and 2 have been shown to correlate with patient outcomes (*30*). In addition, post-treatment gamma 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 by using PSMA PET during therapy to evaluate response. Although PSMA PET may be more accurate in visualizing PSMA-

positive disease compared with post-treatment imaging, there is no evidence that it improves 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 prior to chemotherapy. One is evaluating 177Lu-PSMA-617 (PSMAfore, NCT04689828) and the other 2 are evaluating 177Lu-PSMA-I&T (SPLASH, NCT04647526; ECLIPSE, NCT05204927). PSMAddition is also studying the addition of 177Lu-PSMA-617 in patients with mCSPC being started on ADT and ARPI treatment (NCT04720157). A number of non-registration trials are furthermore evaluating the use of 177Lu-PSMA-617 in combination with other treatments such as immunotherapy (NCT03658447, NCT03805594, and NCT05150236), chemotherapy (NCT04343885), ARPIs (NCT04419402), or DDR pathways (NCT03874884).

CONCLUSION

With the approval of 177Lu-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 ARPI. Patients should be selected by using PSMA PET. On treatment, patients should be followed by using contrast-enhanced CT, and post-treatment gamma 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 pre-chemotherapy mCRPC or other settings pending the full results of ongoing trials.

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. *The 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. *The 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(9). doi: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. [177Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. *The 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 177Lu-PSMA-617 (LuPSMA) versus cabazitaxel in metastatic, castration-resistant prostate cancer (mCRPC) progressing after docetaxel (TheraP ANZUP 1603). *J Clin Oncol*. 2022;40(6)(suppl). https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.6_suppl.010

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 68Ga-PSMA-11 and 18F-DCFPyL normal-organ biodistribution. *Cancer Imaging*. 2019;19:23. doi:10.1186/s40644-019-021

23. Kuo P, Hesterman J, Rahbar K, et al. [68Ga]Ga-PSMA-11 PET baseline imaging as a prognostic tool for clinical outcomes to [177Lu]Lu-PSMA-617 in patients with mCRPC: a VISION substudy. *J Clin Oncol*. 2022;40:5002-5002.

24. Buteau JP, Martin AJ, Emmett L, et al. PSMA and FDG-PET as predictive and prognostic biomarkers in patients given [177Lu]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 177Lu-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 177Lu-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 177Lu-PSMA-617 after radiation exposure to 223Ra-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. [177Lu]-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. 177Lu-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.

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FIGURES and TABLES

Table 1: Use of androgen receptor targeted therapies

Therapy	mCSPC	nmCRPC	mCRPC pre-chemotherapy	mCRPC post-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		

Abbreviations: mCSPC, metastatic castration-sensitive prostate cancer; nmCRPC, non-metastatic castration-resistant prostate cancer; mCRPC, metastatic castration-resistant prostate cancer.

Table 2: Prospective phase 2 and phase 3 studies of 177Lu-PSMA radioligand therapies

registered on clinicaltrial.gov with published results

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

Abbreviations: FDG, fluorodeoxyglucose; OS, overall survival; PFS, progression-free survival; PSA50, 50% decline in prostate-specific antigen; PSMA, prostate-specific membrane antigen; SoC, standard of care; SUVmax, maximum standardized uptake value; SUVmean, mean standardized uptake value.

Table 3: Clinical scenarios for 177Lu-PSMA-617 radioligand therapy

Scenario no.	Description	Appropriateness	Score
1	Treatment of metastatic castration-resistant prostate cancer after chemotherapy and ARPI	Appropriate	9
2	Treatment of metastatic castration-resistant prostate cancer after ARPI and before chemotherapy	Rarely appropriate	3
3	Treatment of patients with metastatic castration-sensitive prostate cancer	Rarely appropriate	2

Abbreviation: ARPI, androgen receptor pathway inhibitor.

Table 4: Baseline laboratory cutoffs

Laboratory value	VISION	TheraP	Recommendations
Kidney function	serum creatinine ≤ 1.5 x ULN or eGFR ≥ 50 mL/min	eGFR ≥ 40 mL/min	eGFR ≥ 30 mL/min
Hgb	Hgb ≥ 9 g/dL	Hgb ≥ 9 g/dL	Hgb ≥ 8 g/dL
WBC count	WBC ≥ 2.5 x 10^9/L or ANC ≥ 1.5 x 10^9/L	ANC ≥ 1.5 x 10^9/L	WBC ≥ 2.0 x 10^9/L or ANC ≥ 1.0 x 10^9/L
Platelets	Platelets ≥ 100 x 10^9/L	Platelets ≥ 100 x 10^9/L	Platelets ≥ 75 x 10^9/L

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