Lu-177 PSMA Therapy for Metastatic Prostate Cancer

1. The aim of this presentation is to evaluate the current status of Lu-177 PSMA (prostate specific membrane antigen) therapy for metastatic castration-resistant prostate cancer (mCRPC) in light of the current literature. Also addressed are patient preparation, therapy administration and side effect profiles, internal radiation dosimetry, and related topics.

2. Lu-177 PSMA therapy efficacy was assessed by using prospective trials, meta-analyses and major retrospective trials. Predictors of efficacy were also mentioned. Although there are some different approaches regarding the use of Lu-177 PSMA therapy in different countries, this type of therapy is generally safe, with a low toxicity profile.

3. From the oncological point of view, a PSA decline of ≥50% was seen in 10.6–69% of patients with mCRPC; progression-free survival (PFS) was reported to be 3–13.7 months in different studies. Consequently, Lu-177 PSMA therapy is a promising treatment in patients with mCRPC, with good clinical efficacy, even in heavily pretreated patients with multiple lines of systemic therapy. Currently, there are ongoing clinical trials in the United States, including a phase III multicenter FDA registration trial. The drug has already been approved in several other countries.

4. Prostate cancer (PCa) is the most common cancer in men and the second cause of death related to cancer in the United States. For 2020, it was estimated that 191,930 new cases would be diagnosed, whereas a total of 33,340 cases would have resulted in death due to PCa.

5. Depending on the relationship between serum PSA levels and applied treatment according to the location of the disease, the natural course of PCa might be evaluated in four distinct disease states. In the initial state, disease is localized to the prostate and curative treatment options such as radical prostatectomy (RP) or radiotherapy (RT) are available.

    - If the patient was not cured at the initial phase, a non-castrate rising PSA phase follows.
    - The third state is non-castrate metastatic and
    - The fourth state is metastatic castration-resistant PCa (mCRPC).

6. It is estimated that the metastatic state of PCa leads to death in 30% of the patients within 5 years, whereas the survival of patients with mCRPC is only 14 months. For the metastatic disease state, the backbone treatment option is hormonal. Briefly, androgen deprivation therapy (ADT) leads to the inhibition of progression of PCa for a period of 18–24 months.

7. Despite appropriate ADT, if the disease progresses, it is defined as mCRPC. For this disease state, many agents given in conjunction with ADT are available with different survival benefits, e.g., abiraterone, enzalutamide and apalutamide interfere with androgenic stimulation of the PCa growth by blocking androgen synthesis.

    - Systemic taxane-based chemotherapies, such as docetaxel for patients with high metastatic burden, or cabazitaxel after treatment with docetaxel, are also available.

    - Immunotherapy with sipueleucel-T and bone-targeted radiopharmaceutical therapy with radium-223 (^{223}Ra) are also in use, although less frequent.

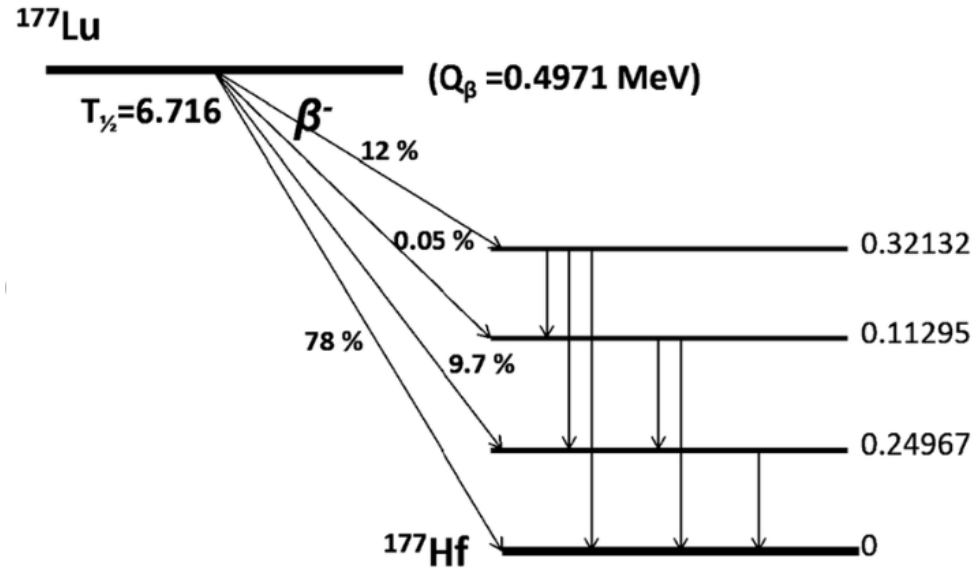
    - The use of theranostic agents such as ^{177}Lu -PSMA or ^{225}Ac-PSMA is an emerging therapy in patients with mCRPC. These compounds are available in many countries outside North America; a multicenter phase III clinical trial is underway in the United States.

8. Our goal is to summarize the theranostic benefits of ^{177}Lu PSMA in mCRPC.

    - The drug was approved by the US FDA on March 24, 2022.
    - Prostate-specific membrane antigen (PSMA) is a type II membrane glycoprotein that is physiologically expressed in several tissues. This protein is over-expressed in PCa.
    - Currently, ^{68}Ga-labelled PSMA imaging shows a high diagnostic accuracy in staging and also the detection of early biochemical recurrence with very promising performances at very low PSA.
    - Overexpressed in a majority of PCa cells, PSMA can allow effective use as a molecular imaging target and for targeted radioligand therapy of CRPCa.
    - A beta emitter, e.g., ^{177}Lu, bound to a PSMA molecule, was deemed to be an emerging radionuclide as a theranostics agent. It might also be used as a theranostic radiotracer in combination with ^{225}Ac to locate PCa cells and specifically destroy them. This approach, using alpha or beta emitter agents, came into practice with favorable outcomes as a part of personalized medicine, enabling early decision-making and monitoring of therapy.

Physical Properties of Lu-177

- Decay Scheme



- Half-life: 6.716 d
- Gamma rays emitted by ^{177}Lu (all are imageable)

E_γ (keV)
71.646
112.95
136.724
208.366
249.67
321.312

10. Patient Selection

Summary of patient selection, preparation and cautionary considerations.

Patient selection	Patients with mCRPC who are ineligible or finalized the approved alternative options and with adequate uptake of PSMA ligands on the basis of a pre-therapy imaging study can be considered for treatment [13].
	Uptake of tumors > liver uptake (at least 1.5 times the SUV_{mean}) [16]. Liver metastases negative on PSMA-ligand PET should be ruled out, even if the remainder of the disease demonstrates intense PSMA expression [13].
	Life expectancy > 6 months ECOG performance status > 2 Unless the main objective is alleviating suffering from disease-related symptoms [13].

11. Patient Preparation

Patient preparation and cautionary considerations	Complete blood tests need to be performed within the two weeks before the ^{177}Lu-PSMA therapy
	White blood cells > 2500/L Platelet > 75,000/L Hemoglobulin > 8 mg/dL If blood cell counts were below the suggested thresholds, blood cell transfusion can be considered to avoid adverse effects [13].
	Myelosuppressive therapies should be discontinued for protecting bone marrow reserves [14].
	Patients with obstructive urinary disorders which might be evaluated with 99m Tc-MAG3 or 99m Tc-DTPA scintigraphy should be resolved before the therapy to reduce the radiation exposure to the kidneys [15].
	Creatinine level should <2× upper limit of normal GFR > 30 mL/min [13].
	Liver transaminase levels should be <5× upper limit of normal [13].

Radionuclide Preparation and Dosing Regimens

- The ^{177}Lu PSMA-617 labeling protocols are described in the literature.

- The standard administered activity of ^{177}Lu PSMA therapy is variable across the published literature. Administered doses can vary by 2–8 GBq for each therapy, up to 4–6 cycles at 6–12 weekly intervals. A standard empiric dose of 6–7.4 GBq is mostly administered to patients due to the reported low rates of adverse events unless any risk factor is present for toxicity.

- Tumor burden affects the cumulative dose of non-target organs, which was described earlier as the "tumor sink effect". Depending on this idea, Violet et al. used an algorithm and reported the safety results of ^{177}Lu PSMA-617 therapy when increasing the injected dose by 1 GBq if there were >20 sites of disease, decreasing dose by 1 GBq if <10 sites.

- In addition, they increased dose by 0.5 GBq per factor if weight > 90 kg or GFR (glomerular filtration rate) > 90 mL/min and decreased dose by 0.5 GBq if weight < 70 kg or GFR < 60 mL/min

- Finally, there is an ongoing dose escalation study with ^{177}Lu PSMA-617 using a dose fractionation regimen, presuming that the dose-escalation of ^{177}Lu PSMA-617 is safe up to 22.2 GBq per cycle with fractionated dosing, with promising early efficacy and tolerability signals. Up to six cycles have been described without any serious adverse events. Dosimetry can be used to calculate the cumulative dose of non-targeted organs such as kidneys, salivary/lacrimal glands or bone marrow to avoid the radiation toxicity.

12. Performing Therapy

- At the start of therapy, patients are advised to be well hydrated by oral intake. Oral hydration before, on the day of and two days after therapy is encouraged. Injection of ^{177}Lu PSMA is administered intravenously over one to two minutes. Meanwhile, in patients with low cardiovascular risk, 1-2 liters of 0.9% NaCl can be given after the therapy.

- Corticosteroids and antiemetics can be used. Despite being controversial, ice-packs could be used for the external cooling of salivary glands, 30 min before and up to four hours after the therapy.

- Due to the renal excretion of ^{177}Lu PSMA, patients should follow the radiation safety rules for contamination risk. To reduce radiation exposure, patients are advised to void frequently or are catheterized if necessary.

13. Release of Patients

- After the administration of ^{177}Lu PSMA, the patient-specific radiation dose decreases below 2.5 mR/hour at 1 m from the patient's chest, well below the US NRC release criterion of 7 mR/hr in the US, which allows treatment in outpatient settings.

- Patients are warned to stay away from children, and especially pregnant women, for approximately 3 days after the therapy, to follow the hygiene rules for contamination risk, and are encouraged to maintain hydration, void frequently and shower daily.

- In the US, ^{177}Lu PSMA treatments are usually performed in outpatient settings, with home release exposure below 7 mR/hour and guidance given to patients.

14. Post-Therapy Imaging

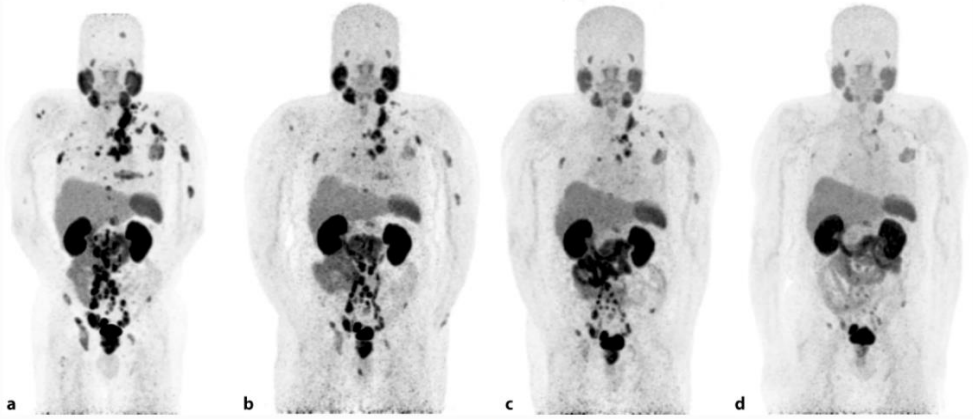
- A whole-body scan can be performed 24-48 h post-injection to confirm tumoral uptake. SPECT/CT can be added to whole body imaging (4, 24 and 96 h post-injection) for dosimetry analysis.

- In addition to PSA response, patients may be evaluated for interim therapy response with ^{68}Ga-PSMA imaging after two cycles of ^{177}Lu PSMA therapy, for determining lesion response. The patients can be evaluated with ^{68}Ga-PSMA imaging after finishing four cycles of therapy, for evaluating therapy response.

Lu-177 Scans: baseline; after 2, 4, and 6 cycles

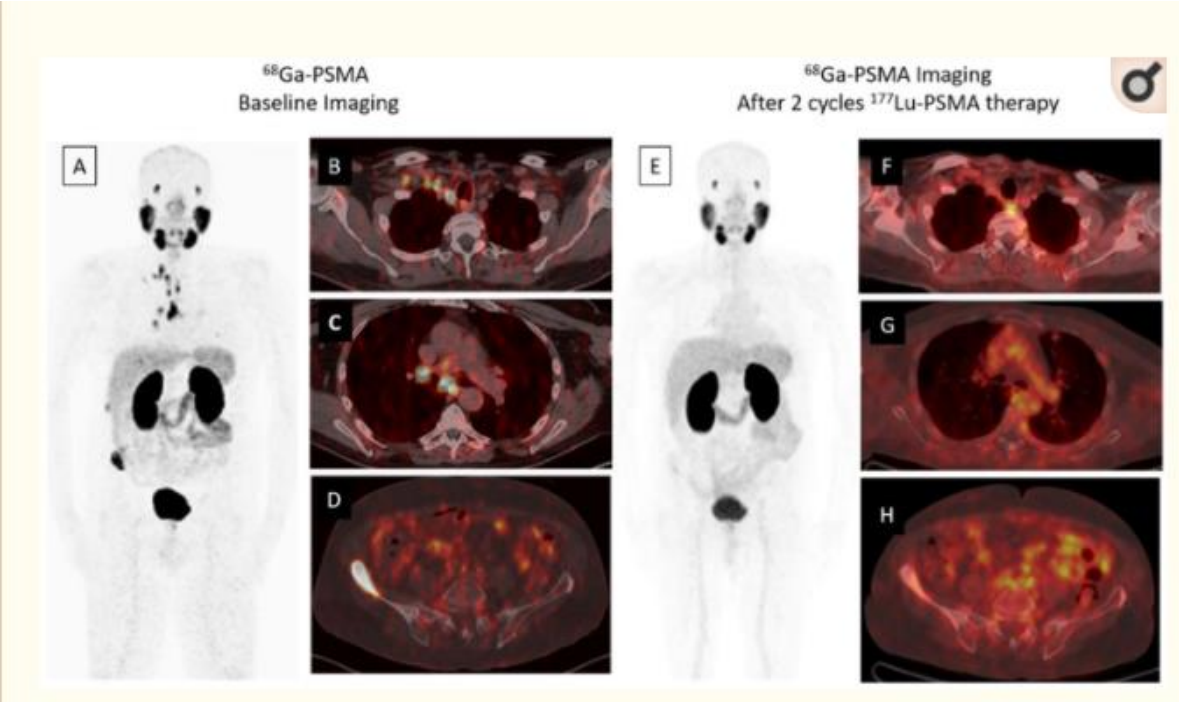
Fig. 1

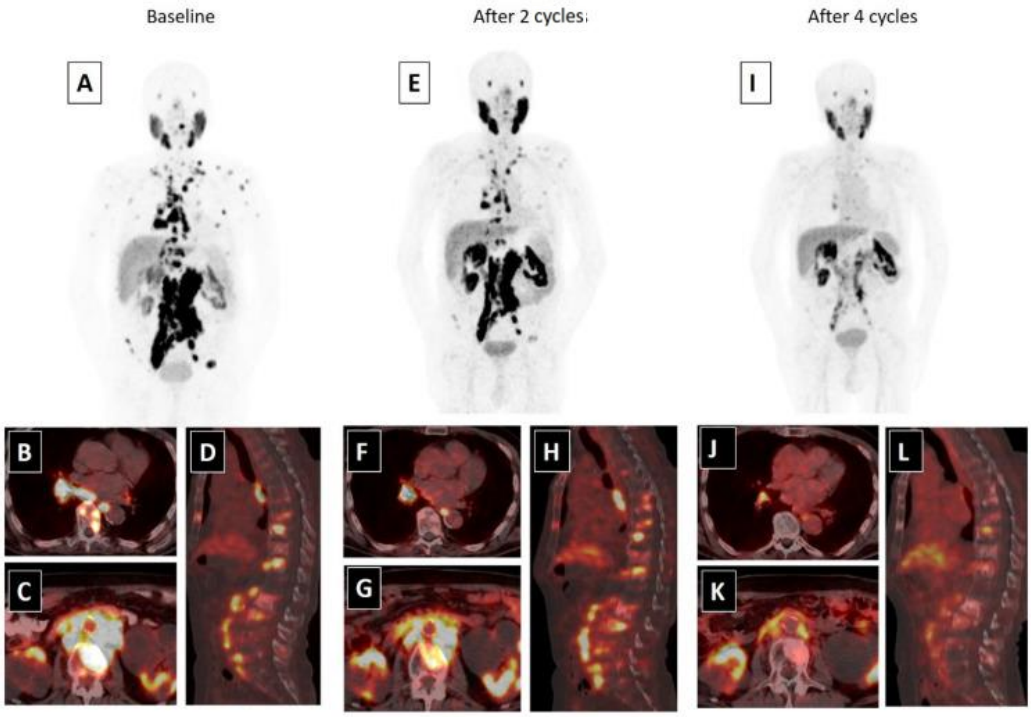
From: Lutetium-177-PSMA therapy for prostate cancer patients—a brief overview of the literatureLutetium-177 PSMA therapie voor patiënten met prostaatkanker – een kort overzicht van de literatuur



Baseline (**a**) and follow-up (**b** after 2 cycles; **c** after 4 cycles; **d** after 6 cycles) [^{68}Ga]Ga-PSMA PET/CT of a patient with mCRPC, who was treated with 6.0 GBq [^{177}Lu]Lu-PSMA-617 (Novartis, Basel, Switserland). Prostate-specific antigen (PSA) response was as follows: 100 ng/ml (baseline), 190 ng/ml (after 2 cycles), 52 ng/ml (after 4 cycles) and 19 ng/ml (after 6 cycles)

Post-Therapy Imaging





An 80-year-old male with mCRPC, having a Gleason score of 4 + 5 = 9 and a serum PSA value of 293.5 ng/mL, was not responsive to the systemic therapies, such as docetaxel, abiraterone and cabazitaxel. He was also suffering from pain (5/10) and fatigue

15. Internal Radiation Dosimetry

Several investigators have published radiation dosimetry results of Lu-177 PSMA-617 therapy, the most commonly used radiopharmaceutical in multiple centers.

Tumor doses were approximately 3.2-13.1 Gy/GBq

Table 2: Estimated Radiation Absorbed Dose

	Absorbed dose per unit activity (Gy/GBq) N = 29		Calculated absorbed dose for 7.4 GBq administration (Gy)		Calculated absorbed dose for 6 x 7.4 GBq (44.4 GBq cumulative activity) (Gy)	
Organ*	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Adrenals	0.033	0.025	0.24	0.19	1.5	1.1
Brain	0.007	0.005	0.049	0.035	0.30	0.22
Esophagus	0.025	0.026	0.18	0.19	1.1	1.1
Eyes	0.022	0.024	0.16	0.18	0.99	1.1
Gallbladder wall	0.028	0.026	0.20	0.19	1.2	1.1
Heart wall	0.17	0.12	1.2	0.83	7.8	5.2
Kidneys	0.43	0.16	3.1	1.2	19	7.3
Lacrimal glands	2.1	0.47	15	3.4	92	21
Left colon	0.58	0.14	4.1	1.0	26	6.0
Liver	0.090	0.044	0.64	0.32	4.0	2.0
Lungs	0.11	0.11	0.76	0.81	4.7	4.9
Pancreas	0.027	0.026	0.19	0.19	1.2	1.1
Prostate	0.027	0.026	0.19	0.19	1.2	1.1
Rectum	0.56	0.14	4.0	1.1	25	6.2
Right colon	0.32	0.078	2.3	0.58	14	3.4
Salivary glands	0.63	0.36	4.5	2.6	28	16
Small intestine	0.071	0.031	0.50	0.23	3.1	1.4
Spleen	0.067	0.027	0.48	0.20	3.0	1.2
Stomach wall	0.025	0.026	0.18	0.19	1.1	1.1
Testes	0.023	0.025	0.16	0.18	1.0	1.1
Thymus	0.025	0.026	0.18	0.19	1.1	1.1
Thyroid	0.26	0.37	1.8	2.7	11	16
Total body	0.037	0.027	0.27	0.20	1.6	1.2
Urinary bladder wall	0.32	0.025	2.3	0.19	14	1.1
*Estimated radiation absorbed dose for bone marrow is not included *[see Warnings and Precautions (5.2)]*.						

Toxicity associated with these organs is rarely seen in clinical practice. Supporting this view, previous studies which used SPECT/CT for dosimetry reported lower doses for non-targeted organs, and showed that PSMA ligand therapy is a safe treatment option with a lack of significant toxic effects. Violet et al. published that the SUV (standardized uptake value) max and absorbed dose in salivary glands and kidneys decreased significantly if a greater disease burden existed; thus, tumor burden may be relevant in predicting salivary gland and renal toxicity.

The current thresholds of absorbed organ doses were defined based on external beam radiotherapy (EBRT) literature. The accepted absorbed dose is 23 Gy for kidneys, 34 Gy for lacrimal glands, 26 Gy for parotid glands and 2 Gy for bone marrow.

Due to the differences between EBRT and systemic radionuclide therapy, organs can tolerate higher doses in radionuclide therapy compared to EBRT. Depending on previously mentioned dosimetry results, the absorbed doses to critical organs will be below the accepted doses, even in repeated cycles of Lu-177 PSMA-617 therapy. Specific absorbed dose estimates for critical organs under Lu-177 PSMA-617 or Lu-177 PSMA-I&T therapy are summarized in Table 2.

Due to the nature of the PSMA ligand therapy, unintentional radiation exposure is delivered to PSMA-expressing non-targeted tissues. However, limited side effects can be observed related to the absorbed dose. Kidneys, salivary glands, lacrimal glands and bone marrow are the most exposed organs. Reported adverse events were mild or transient related to Lu-177 PSMA therapy. Hematotoxicity is the most common serious adverse event due to the bystander effect, which is described in 12% of patients undergoing Lu-177 PSMA-617 therapy with high tumor burden in bone.

16. Adverse Events

Grade 3–4 toxicities, anemia (10%), leukopenia (3%) and thrombocytopenia (4%) were reported in the multicenter trial, whereas the rates were similar to the placebo group (1–14%) or ^{223}Ra therapy group (3–13%) in the ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) trial. Xerostomia is the second most common adverse effect and was reported in 8 and 11% in two different studies. However, mild xerostomia was found to be in 87% of patients in whom external cooling of salivary glands was not administered. Grade 3–4 nephrotoxicity was not reported in current studies.

Efficacy

A few prospective trials demonstrate the efficacy of Lu-177 PSMA therapy in the treatment of mCRPC with progressive disease. In a dual-center phase II trial, Tagawa et al. used Lu-177 PSMA therapy in a cohort of 47 patients in whom 55.3% had also received prior chemotherapy. Briefly, 10.6, 36.2 and 59.6% of the patients had a PSA decline of ≥50%, ≥30% and any PSA decline, respectively, after a single dose of Lu-177 PSMA therapy. Meanwhile, 66.7% of the patients had a ≥50% decline in circulating tumor cell (CTC) counts.

The median time for progression was 12 (8–47) weeks. When the authors made a comparison between maximum tolerated dose and survival, they found that survival was longer (21.8 months vs. 11.9 months) with maximum tolerated dose (70 vs. 65 mCi/m^2).

Efficacy

In a phase II proof of concept trial, Hofman et al. recruited 30 patients with mCRPC with progressive disease who previously used standard therapy options such as docetaxel (87%), cabazitaxel (47%) and abiraterone, and/or enzalutamide (83%) [16]. Patients received 1 to 4 cycles of intravenous Lu-177 PSMA-617 at six weekly intervals. Disease progression status and adverse reactions were assessed. In addition to the primary study endpoint of PSA response rate

(50% decline from the baseline), other endpoints such as progression-free survival (PFS) and overall survival (OS), as well as imaging responses and quality of life (QOL), were also evaluated. Briefly, 17 (57%) patients met the PSA response criteria and 29 (97%) of the patients had some degree of PSA response.

Meanwhile, 3 months after the last injection, 40, 37, and 37% of the patients had the non-progressive disease (complete response, partial response and stable disease) according to ^{68}Ga PSMA-11, FDG (fluorodeoxyglucose), and bone scanning, respectively. During follow-up, PSA progression was encountered in 27 (90%) patients and the median PFS and OS were calculated as 7.6 and 13.5 months, respectively. Lu-177 PSMA-617 therapy was well-tolerated with minimal adverse events, such as dry mouth, in 87% of the patients. Moreover, the pain level of the study participants (27 patients (90%)) improved in all study time points that significantly contributed to the quality of life. Even though this study had no control group for comparison, a randomized multicenter study comparing the activity and safety of Lu-177 PSMA-617 therapy in comparison with cabazitaxel was recently published (TheraP trial). The primary endpoint was PSA response, defined by a reduction of at least 50% from the baseline [41]. The authors showed that this PSA reduction was higher in the assigned Lu-177 PSMA-617 group than the cabazitaxel group (65/99 vs. 37/101 patients). Meanwhile, PFS at 12 months was shown to be better in the Lu-177 PSMA-617-treated group (19 vs. 3%). Additionally, Grade 3–4 adverse events occurred more frequently in the cabazitaxel group (33 vs. 53%), whereas Grade 3–4 thrombocytopenia was more common (11 vs. 0%) and Grade 3–4 neutropenia was less commonly seen in the Lu-177 PSMA-617-treated group (4 vs. 13%). Accordingly, despite this data providing strong evidence that Lu-177 PSMA-617 is more efficient than cabazitaxel, OS data was not given.

Efficacy

Recently, Yadav et al. reported the outcomes of Lu-177 PSMA-617 therapy in a prospective single arm, in a single-center study. They recruited 90 mCRPC patients with progressive disease on second-line hormonal therapy and/or docetaxel chemotherapy [38]. After the first cycle of Lu-177 PSMA-617 therapy and at the end of the therapy (up to seven cycles), a greater than 50% decline in PSA was shown in 32.2 and 45.5% of patients, respectively. Tumor response such as partial remission, stable disease, and progressive disease were seen in 27.5, 43.5, and 29% of patients, respectively. Additionally, improvement in the pain score was observed in 54% of patients after the first cycle of therapy, with a corresponding reduction in the analgesic score. The median OS and median PFS were 14 and 11.8 months, respectively. Similarly, a randomized phase III VISION trial was developed to compare overall survival (OS) in patients with progressive PSMA-positive mCRPC. The study group was randomized to receive either Lu-177 PSMA-617 in addition to the best supportive and best standard of care, or the best supportive and best standard of care alone. The estimated study completion is May 2021 (NCT03511664). The sample size was calculated as 750 patients who received at least one novel

androgen axis drug, as well as having been previously treated with one to two taxane regimens.

Meta- Analysis

A recent systematic review compared Lu-177 PSMA therapy with third-line treatments such as abiraterone, enzalutamide and cabazitaxel [45]. The median serum PSA values were comparable between groups. Despite variations in terms of Lu-177 PSMA therapies and the number of cycles performed, overall, 44% (95% CI 31–51%) of the patients had a PSA decline of ≥50%. This was 21% (95% CI 16–27%) in patients receiving third-line treatment (overall 44 vs. 22%, p = 0.002). Individually, the rate of PSA decline of ≥50% was 4, 20 and 29% with abiraterone, enzalutamide and cabazitaxel, respectively. In available articles, OS was 14 months for Lu-177 PSMA therapy and 11 months for third line treatment alternatives (p = 0.32). Discontinuation due to adverse events was more common in patients receiving third-line treatment alternatives.

Major Retrospective Trials

Rahbar et al. retrospectively reported results from 12 therapy centers for 145 patients with serial PSA levels at baseline, and follow-up for 99 of 145 patients (68%) [21]. The response was determined as the lowest PSA level measured at follow-up and at least 8 weeks after the start of the first Lu-177 PSMA-617 cycle. As the major finding, 45% of patients showed a PSA decline of at least 50%. These patients were considered as biochemical responders. Accordingly, a PSA decline of any amount occurred in 60% of patients. Most responders showed a PSA decline of 50% after the first cycle. Visceral metastases and high alkaline phosphatase (ALP) levels (more than 220 U/L) were predictors of a poor outcome. Patients with three or more cycles of Lu-177 PSMA-617 therapy responded better. Of 47 patients, 21 (45%) had a partial response and 13 (28%) had stable disease in the follow-up period according to imaging assessments. Grade 3 and Grade 4 hematologic toxicity occurred in 12% of the patients and no therapy-related deaths were reported.

In terms of patient-reported outcomes, Lu-177 PSMA-617/I&T therapy was reported to lead to pain relief in 33–70% of patients, improved quality of life in 60% and improved performance status in 74% [55]. Overall, 30–70% of patients showed a PSA decline of 50% or more with Lu-177 PSMA therapy. The response rate compares well with the response of chemotherapy agents (cabazitaxel and docetaxel). Efficacy results due to RECIST (response evaluation criteria in solid tumors), PERCIST (PET response criteria in solid tumors) and EORTC (European Organisation for Research and Treatment of Cancer) criteria, percentage of symptom relief and PSA decline, PFS and OS are shown in Table 3.

Future Perspectives

Currently, Lu-177 PSMA therapy is used as the last resort in the treatment of mCRPC. In almost all studies, patients had increased survival time, including different alternatives such as; docetaxel, cabazitaxel, abiraterone, enzalutamide and ^{223}Ra. However, it is currently not well-known whether treatment response could be better if Lu-177 PSMA therapy was used in the first-line or earlier settings. Comparative studies are urgently needed.