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Hot Topic

Theranostics revolution in prostate cancer: Basics, clinical applications, open issues and future perspectives

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A B S T R A C T

In the last years, theranostics has expanded the therapeutic options available for prostate cancer patients. In this review, we explore this dynamic field and its potential to revolutionize precision medicine for prostate cancer. We delve into the foundational principles, clinical applications, and emerging opportunities, emphasizing the potential synergy between radioligand therapy and other systemic treatments. Additionally, we address the ongoing challenges, including optimizing patient selection, assessing treatment responses, and determining the role of theranostics within the broader landscape of prostate cancer treatment.

Introduction

In the last decade, the therapeutic algorithm of metastatic castration-resistant prostate cancer (mCRPC) has been revolutionized with the advent of various therapeutic strategies that significantly improved patients' outcomes. Systemic options that have demonstrated a survival benefit in this setting include chemotherapy (e.g., docetaxel and cabazitaxel), androgen receptor-signaling inhibitors (ARSI; e.g., enzalutamide and abiraterone acetate), and Poly (ADP-ribose) polymerase (PARP) inhibitors (e.g., olaparib, rucaparib, and talazoparib), either alone or combined with an ARSi, in a selected cohort of tumors harboring HRR, mainly BRCA1/2 alterations) [1]. In metastatic prostate cancer patients, the treatment's sequence is mainly based on clinical criteria and fundamental assumptions: i) chemotherapy with docetaxel is preferable for symptomatic patients [2,3]; ii) in case of visceral metastases, the choice should favor chemotherapy (enzalutamide could be considered an alternative option) [2,4–7]; iii) the sequence of two ARSIs does not provide a survival benefit. The CARD study demonstrated the superiority of cabazitaxel over an ARSI in patients already treated with docetaxel and one ARSI [8]; iv) in the subgroup of patients (around 10 %) with BRCA1/2 mutations, PARP inhibitors prolong survival (even when compared to chemotherapy) [9,10].

Despite significant advances, mCRPC remains a lethal disease with a median survival of approximately 30 months. These patients are often frail due to advanced age and previous therapies. Therefore, offering effective treatments with an acceptable toxicity profile remains a clinical need. Recently, a novel therapeutic strategy - theranostics - has consistently implemented the armamentarium of mCRPC patients. Theranostics represents a novelty due to its unprecedented mechanism of action, combining diagnostic imaging, molecular selection, and personalized targeted treatment. It also constitutes a revolution in terms of the safety profile, logistics, dosimetry, and organizational/accessibility implications. [^{223}Ra]Radium-dichloride and Prostate-Specific Membrane Antigen labeled with 177Lutetium ([^{177}Lu]Lu-PSMA) are already available for mCRPC [11,12]. However, exciting future horizons are opening up to evaluate new combinations, other radioisotopes, and novel potential therapeutic targets.

The present review aims to introduce the basic principles of theranostics, together with a summary of the current clinical evidence, open issues, and future perspectives on its application in mCRPC.

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Basics on theranostics

Although theranostics has been known in nuclear medicine for decades due to the use of radioiodine for differentiated thyroid cancer, only in the last years, with radioligands and instrumentation technological development, this term has become widely used.

Theranostics refers to integrating diagnostic and therapeutic radiopharmaceuticals directed at the same molecular targets [13,14]. In other words, the same molecule can be labelled first with a diagnostic radiopharmaceutical (i.e., gamma or beta + emitter) to precisely demonstrate/assess the presence of a certain disease (cancer cell-expressing target), and then to a therapeutical radiopharmaceutical (i.e., β- or α emitter) treating what we have seen also obtaining simultaneous biodistribution imaging. This integration provides the unique opportunity to optimise patient selection, offering therapeutic radioligands only to the one expressing the molecular targets.

Radioligands are biologically relevant molecules labelled with radioisotopes. The choice of molecule depends on the specific information we want to obtain: labelled substances behave exactly like unlabelled ones, particularly concerning metabolic behaviour.

For diagnostic purposes, the spatiotemporal distribution of the chosen molecule needs to be tracked due to the external emitted radiation. Thus, the energy of decay products must quickly exit the patient's body and be detectable, minimising its biological interaction with healthy tissues. The radioisotopes used for this purpose usually decay by emitting two types of products: (i) gamma radiations (γ emission) or (ii) positrons (β + emission). Diagnostic γ-emitting radionuclides decay by emitting photons used in "conventional nuclear medicine" using gamma cameras (scintigraphy), with bidimensional-planar or tomographic imaging (single-photon emission tomography, SPET). The most widely used γ-emitting radionuclide is Technetium-99 m ([^{99m}Tc]Tc), which is implied for many diagnostic purposes, including bone scans. Differently, total or partial β + emitting radionuclides are used to perform Positron Emission Tomography (PET) imaging. Once emitted, positrons immediately annihilate upon encountering surrounding cells, producing a pair of high-energy gamma photons detected by the PET scanner. Gallium-68 [^{68}Ga]Ga and Fluorine-18 [^{18}F] are the most widely implied β + emitting radionuclides for clinical purposes.

For therapeutic purposes, radioisotopes should deposit high energy within a much more limited range in tissue, from a fraction of a micrometre to a few millimetres at most to spare healthy tissues. This energy deposition within a restricted distance from the emission point should induce radiation damage in the surrounding cells, producing cell damage or death. Radionuclides fitting therapeutic needs include β- emitting, α emitting, and Auger electrons-emitting.

β- particles are high-energy, high-speed electrons. Thus, β- emitting radioisotopes, including [^{177}Lu]Lu, have longer path lengths (maximum penetration around 12 mm) and lower linear energy transfer (LET), which makes them effective against medium to large tumour lesions [15], providing homogeneous radiation dose distribution on the target. On the other hand, the long particle path length can also provide a higher irradiation of the surrounding healthy tissues [16].

By contrast, α particles, including [^{223}Ra]Ra and Actinium-225 ([^{225}Ac]Ac), are helium nuclei, whose mass is 2000 times higher than the mass of β- particles (almost the same difference existing between a bowling ball and a ping pong ball) [17]. When emitted, they release enormous amounts of energy over a very short distance (around 0.1 mm). Consequently, α emitters radionuclides have a moderate path length and high LET. When compared to β- particles, one-cell surface decay of α particles has shown the same degree of cell killing as approximately 1000-cell surface decays of β- particles [18]. Due to these physical properties, α decay provides the ideal characteristics for selectively damaging target tissues, sparing as much as surrounding normal organs and healthy tissues [17]. Smaller lesions, such as micrometastatic sites, may thus be more effectively treated with α than β- irradiation. Fig. 1 visually represents the comparison between β- and α irradiation from the radiobiological point of view.

Notably, some therapeutic radioisotopes (i.e., [^{177}Lu]Lu) can emit even a fraction of gamma rays with favourable energy for scintigraphic detection, allowing post-treatment biodistribution images. These images can be used for dosimetry, calculating the dose delivered to tumour lesions and organs at risk by the therapeutic radioligand. Furthermore,

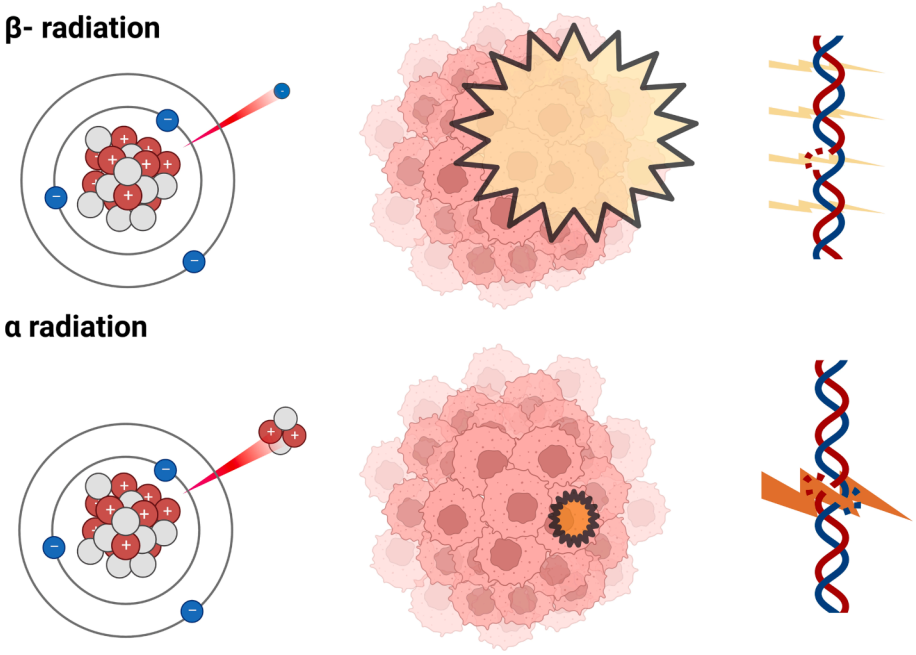

Fig. 1. Major radiobiological differences between β- and α irradiation of cancer lesions. β- irradiation consists of the emission of a single electron with a long radiation range (0.2–12 mm) and low linear energy transfer (LET, 2 KeV/μm). From the radiobiological point of view this results in a higher number of cells receiving low energy damage. The major types of DNA damage induced by β- irradiation are represented by single-stranded breaks. By contrast, α irradiation consists in the emission of helium nuclei, composed of two protons and two neutrons. Due to the higher mass, α particles provide higher LET (100 KeV/μm) in a shorter range (50–80 μm). α particle DNA damage consists of double-stranded DNA breaks. *Created with BioRender.com.*

post-treatment biodistribution images allow prompt simultaneous monitoring of the treatment effects (exploiting the gamma emissions of the therapeutic radiopharmaceutical already injected), providing a dynamic assessment of the outcomes, and achieving enhanced clinical results. For this reason, theranostics not only lead clinicians to treat what they see but also allow them to see what they are treating. Fig. 2 illustrates a compelling example of how post-treatment images are a powerful tool for monitoring the therapeutic effect.

Psma-based theranostics for prostate cancer

PSMA is a type II transmembrane glycoprotein composed of a small intracellular and transmembrane portion, and a relatively ample extracellular domain consisting of 750 amino acids. It is usually located within the cytoplasm in normal prostate cells, being relatively unavailable for binding. By contrast, it is usually overexpressed in cancer cells as its encoding gene (FOLH1) is situated on the short arm of chromosome 11, a region that is not generally deleted in prostate cancer [19]. PSMA is not specific to the prostate gland as it is physiologically expressed by normal cells in several organs [20]. However, it can be promoted as a target for imaging and treatment because of the overexpression by tumours with potentially low impact on healthy tissues.

PSMA expression is increased in the presence of aggressive features, including high Prostate-Specific Antigen (PSA) levels, fast PSA-increasing kinetics, high International Society of Urological Pathology (ISUP) grade, and hormone resistance status [21,22]. Thus, clinically relevant, and highly aggressive prostate cancer can be efficiently targeted by PSMA-based theranostics. For this reason, the largest evidence supporting its therapeutic use is currently focused on the castration-resistant phase of the disease (mCRPC). This aspect represents a singularity for the PSMA theranostic model, as other clinically available theranostics compounds are currently directed to well-differentiated diseases (i.e., in neuroendocrine tumours) [23].

Notably, the relationship between PSMA expression and tumour aggressiveness is not perfectly linear [24], as in a few cases of prostate cancer, PSMA expression can be reduced with the resulting low/absent avidity of PSMA-targeted radiopharmaceuticals [25–27], with consequent poor responses to PSMA-directed therapies [28]. Several studies documented increased [^{18}F]F-Fluorodeoxyglucose ([^{18}F]FDG) avidity by advanced mCRPC low-expressing PSMA lesions, thus supporting the combined use of PSMA and [^{18}F]FDG PET imaging in the selection process of PCa patients for PSMA-based radioligand therapy [29,30].

In recent years, both the intracellular and extracellular domains have been used to target PSMA with monoclonal antibodies, minibodies and small molecules. Due to the larger size of monoclonal antibodies, their use implies slow bloodstream kinetics [31], which results in prolonged diagnostic imaging duration and poor-quality images [31]. For these reasons, PSMA-targeted small molecule ligands have been mainly developed over the last few years. However, the potential therapeutic advantages of PSMA-directed antibodies are still under debate, particularly regarding the possibility of reducing xerostomia and dry eye effects due to the divergent biodistribution compared to small molecules [31].

Clinical evidence of theranostics in mCRPC

Bone scintigraphy based on osteoblastic reaction and targeted radionuclide therapy with the α-particle calcium-mimetic agent, [^{223}Ra]Ra, form a theranostic model for imaging and treatment of osseous metastatic disease. [^{223}Ra]Ra selectively targets areas of increased bone turnover such as bone metastases; it is incorporated into the newly aberrantly formed bone matrix, and emits high-energy α particles with short path-inducing double-stranded DNA breaks with cytotoxic effects [11]. [^{223}Ra]Ra demonstrated a survival advantage over the best standard of care (SOC) in the ALSYMPCA (ALpharadin in SYMptomatic Prostate Cancer patients) trial [32]. This study enrolled 921 mCRPC patients with symptomatic disease, at least two bone metastases identified with skeletal scintigraphy, no known visceral metastases, and

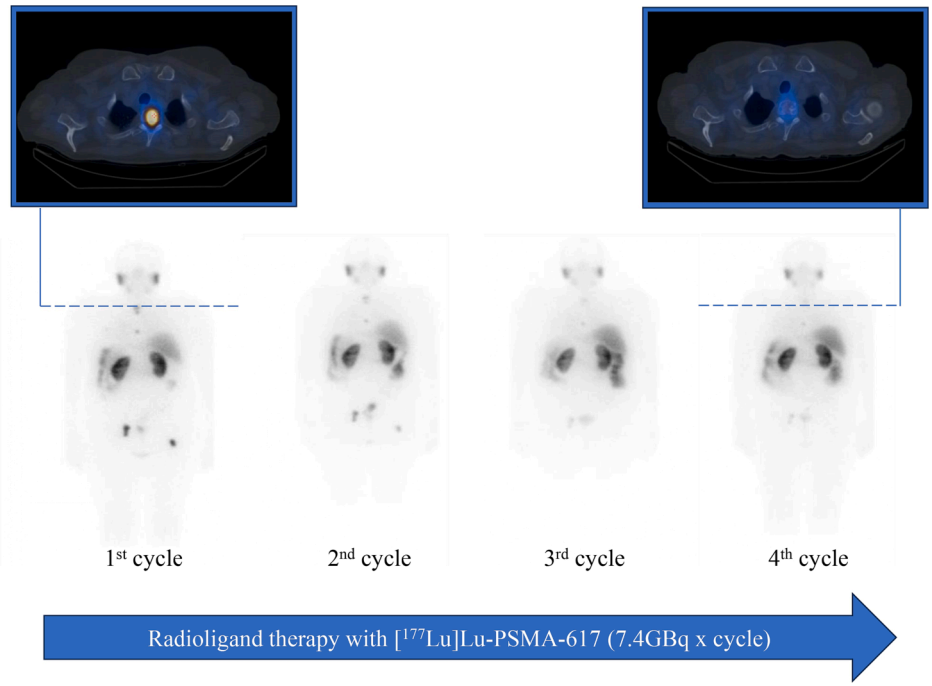

Fig. 2. Emblematic example of treatment monitoring through 24 h SPECT/CT in a patient receiving [^{177}Lu] Lu-PSMA-617. 72-year-old patient with heavily treated prostate cancer. He underwent primary treatment with radical prostatectomy (pT3a, pN0, R +) followed by radiotherapy. Then, he started ARSI (bicalutamide), receiving focal radiotherapy on lumbar spine (L3 to L5). Then he switched to ARSI (enzalutamide) in association with Denosumab and ADT (LH-releasing hormone therapy), followed by a switch to Docetaxel. Afterwards, he received 4 cycles of 7.4 GBq [^{177}Lu]Lu-PSMA-617 (total dose 29.4 GBq) with a good response as demonstrated in this biodistribution post-dose scintigraphic imaging acquired 24 h post radioligand therapy administration (lower panels), further confirmed and magnified by SPECT/CT images on a D3 mainly osteoblastic lesion (upper panels).

prior chemotherapy with docetaxel (patients unsuitable for/who refused chemotherapy were also included). Patients were randomized 2:1 to receive [^{223}Ra]Ra (50 kBq per kilogram of body weight intravenously every 4 weeks for 6 administrations) or a matching placebo. The study met its primary endpoint, showing a prolonged median overall survival (OS) (HR: 0.70, 95 %CI: 0.55–0.88; p = 0.002). Of note, this benefit was maintained regardless of prior docetaxel use (previous docetaxel therapy: HR: 0.70, 95 %CI: 0.56–0.88; p = 0.002; no previous docetaxel use: HR: 0.69, 95 %CI: 0.52–0.92; p = 0.01) [32]. Furthermore, [^{223}Ra]Ra was associated with a greater percentage of patients with an improvement in quality of life (measured through the EQ-5D and FACT-P scores) [10,28]. To date, there are no studies that have compared [^{223}Ra]Ra with other available therapeutic options. However, some trials have been conducted to test the combination of [^{223}Ra]Ra with other systemic treatments in mCRPC. One of them, the ERA-223 study [33] showed that the combination between [^{223}Ra]Ra and abiraterone acetate + prednisone/prednisolone could negatively impact the clinical outcome and increase the risk of fractures. As a consequence, in 2018, a formal warning promoted by the European Medicines Agency (EMA) concerned not only the combination of [^{223}Ra]Ra with ARSI but also restricted its use as monotherapy to mCRPC patients with more than six osteoblastic lesions at bone scan previously treated with at least two systemic therapies or ineligible for any other systemic treatment [34]. This moved [^{223}Ra]Ra treatment to the later stages of mCRPC, with a measurable negative impact on survival outcomes in real-world studies [35].

Differently from the "osteotropic" [^{223}Ra]Ra, [^{177}Lu]Lu-PSMA-617 is an "oncotropic" agent with significant antitumor activity in mCRPC patients, being responsible for tumor objective response, decrease in PSA levels, and remarkable pain reduction [36]. This was further confirmed by the demonstration of radiological Progression Free Survival (rPFS) and OS advantage of [^{177}Lu]Lu-PSMA-617 compared to the SOC (ARSI, steroids, radiotherapy) in PSMA-positive mCRPC men in the VISION pivotal phase III trial [12]. Patients with mCRPC (n = 831) who progressed to at least one ARSI and one or two taxane regimens (i.e. docetaxel and/or cabazitaxel) and who had PSMA-positive [^{68}Ga]Ga-PSMA-11 PET/CT, were randomly assigned (2:1 ratio) to receive [^{177}Lu]Lu-PSMA-617 (7.4 GBq every 6 weeks for four cycles) combined with SOC versus SOC. It is important to underline that protocol-allowed SOC did not include cabazitaxel, other systemic radioisotopes (i.e. [^{223}Ra]Ra), and investigational drugs. Notably, patients were defined PSMA-positive in case of tumor uptake greater than that of the liver in any disease sites; patients were excluded in case of negative PSMA PET/CT (namely, PSMA uptake equal or lower than that of the liver for visceral metastases with a short axis $\geq$ 1 cm, or lymph nodes with short axis $\geq$ 2.5 cm, or lytic bone metastases with a soft tissue component $\geq$ 1 cm). No [^{18}F]FDG PET/CT imaging was required. The study included patients treated with one (55–60 %) or two taxane lines (about 40 %) and patients who received abiraterone and/or enzalutamide (about 90 %). After a median follow-up of 20.9 months, the addition of [^{177}Lu]Lu-PSMA-617 to SOC demonstrated a statistically significant prolongation of imaging-based PFS (HR: 0.40; 95CI%: 0.29–0.57; p < 0.001) and OS (mOS 15.3 vs. 11.3 months; HR: 0.62, 95 %CI: 0.52–0.74, p < 0.001) compared to SOC alone. Fatigue, dry mouth (given to the expression of PSMA in normal salivary glands) and nausea were the most frequent adverse events related to [^{177}Lu]Lu-PSMA-617 therapy; the incidence of grade $\geq$ 3 toxicities was 52.7 % in the experimental arm versus 38 % in the control arm. This higher rate of serious adverse events was however counterbalanced by a prolonged median time to symptomatic skeletal events with [^{177}Lu]Lu-PSMA-617 (11.5 vs. 6.8 months; HR: 0.50, 95 %CI 0.40–0.62, p < 0.001), and an extended time to worsening of health-related quality of life and pain [12].

According to these results, [^{177}Lu]Lu-PSMA-617 represents a feasible option for pretreated mCRPC patients with PSMA-positive disease. However, the VISION study had several limitations concerning patients selection and the trial design. Indeed, although patients treated with cabazitaxel were included, most were cabazitaxel-naïve. For these patients, the systemic therapy received in the control arm, consisting of supportive care or ARSI post-ARSI, could not be considered the most effective standard in this setting. Another prospective study – TheraP – evaluated the activity of [^{177}Lu]Lu-PSMA-617 compared to a more effective comparator. In this phase II trial 200 mCRPC patients, who progressed to prior docetaxel therapy and ARSI, were randomised to receive [^{177}Lu]Lu-PSMA-617 (6–8.5 GBq every 6 weeks for six cycles) or chemotherapy with cabazitaxel (20 mg/m2 every 3 weeks for ten cycles) [37]. Only patients with high PSMA-expression at [^{68}Ga]Ga-PSMA-11 PET/CT, having at least one metastatic site with a maximum standardized uptake value (SUV_{max}) $\geq$ 20 and all other measurable sites with a $SUV_{max} \geq 10$ were included. Mismatched disease on [^{18}F]FDG compared to PSMA PET imaging represented an exclusion criterion. The study met the primary endpoint, with a significant difference in PSA response favouring [^{177}Lu]Lu-PSMA-617 compared to cabazitaxel (66 % vs. 37 % in the intention to treat population). Moreover, [^{177}Lu]Lu-PSMA-617 showed significant improvements in RECIST response rate (49 % vs. 24 %) and radiological/biochemical PFS than chemotherapy (HR: 0.63, CI 95 % 0.46–0.86; p = 0.0028) [37]. The final results, presented at the American Society of Clinical Oncology (ASCO) congress in 2022, revealed no significant difference in OS (HR: 0.92, CI 95 % 0.70–1.4, p = ns) after a median follow-up of 36 months [38]. However, a substantial post-protocol cross-over could have affected the lack of a survival advantage. Moreover, the study was not powered for OS. As expected, [177Lu]Lu-PSMA-617′s toxicity profile radically differed from that of cabazitaxel. Fatigue, nausea, dry mouth, and dry eyes were the common adverse events reported in the experimental groups. However, the PSMA-targeted treatment was well tolerated with a low proportion of grade 3–4 toxicities (33 % vs. 55 %) and less treatment discontinuation (1 % vs. 8 %), compared to chemotherapy. Notably, the extent of bone marrow invasion was not assessed in patients enrolled in the investigational arm. Therefore, it is not possible to determine whether grade 3–4 toxicity was related to the drug or the specific burden of the disease.

Altogether, these results support [^{177}Lu]Lu-PSMA-617 as a new therapeutic strategy in third-line setting for mCRPC patients. However, some issues remain to be stated such as the optimal therapeutic sequence in post-docetaxel setting for patients fit for cabazitaxel and the ideal treatment sequence in the subset of patients carrying BRCA1/2 gene mutation and therefore eligible for PARP inhibitors. At the European Society of Medical Oncology (ESMO) Congress 2023, the results from the PSMAfore study have been presented: PSMAfore is a phase III, multicenter, open-label trial randomizing 450 mCRPC patients, taxanes-naïve and not candidate for a PARP-inhibitor, previously treated with an ARSI (either abiraterone or enzalutamide) to receive [^{177}Lu]Lu-PSMA-617 (7.4 GBq every 6 weeks up to 6 cycles) or a change of the ARSI (enzalutamide or abiraterone) [39]. The primary outcome was rPFS as per PCWG3/RECIST v1.1 criteria (which we could argue as a modest endpoint in this disease setting); secondary endpoints included OS, 50 % or higher reduction of PSA (PSA50), and time to first skeletal event. Of note, crossover to [^{177}Lu]Lu-PSMA-617 was allowed in case of radiographic progression of patients recruited in the control arm (84.3 % of them; it would be interesting to understand why the 15.7 % of patients did not receive [^{177}Lu]Lu-PSMA-617 after disease progression, perhaps due to deterioration of their clinical conditions). Indeed, the control arm can be considered as an "insubstantial" treatment strategy (almost comparable to placebo), given the demonstrated benefit absence from the sequence ARSI to another ARSI, and the demonstrated superiority of chemotherapy over the ARSI re-challenge [8,40,41]. At the primary analysis (median follow-up of 7.3 months, n = 467), the primary endpoint of rPFS was met (HR: 0.41, 95 %CI 0.29–0.56), which was similar to the second interim analysis (HR: 0.43, 95 %CI 0.33–0.54), therefore demonstrating that [^{177}Lu]Lu-PSMA-617 was superior to the "ARSI-change" in terms of reducing the risk of disease progression. Moreover, [^{177}Lu]Lu-PSMA-617 was associated with a higher objective response rate (50.7 % vs. 14.9 %), a greater PSA50 (57.6 % vs. 20.4 %), a

longer time to symptomatic skeletal events (HR: 0.35, 95 %CI 0.22–0.57). No advantage was observed in the pre-specified crossover-adjusted OS analysis (HR: 0.80, 95 %CI 0.48–1.33). The lack of OS benefit (in the metastatic phase of the disease where all the other therapeutic agents demonstrated to significantly prolong OS) together with the weak control arm, and the unavailability of the rate of patients who received chemotherapy in subsequent lines in both treatment arms, raise concerns regarding [^{177}Lu]Lu-PSMA-617 placement in the mCRPC treatment algorithm, being a potential option in those inegible for taxanes chemotherapy.

To better address the best timing for [^{177}Lu]Lu-PSMA-617 within the treatment algorithm of prostate cancer patients, several phase III clinical trials are currently ongoing (Table 1).

Open issues related to patients' selection

Candidates for [^{177}Lu]Lu-PSMA-617 are typically screened with a PSMA PET, as SUV_{max} correlates significantly with tumor PSMA expression measured by immunohistochemistry [42]. Higher PSMA expression results in higher deposition of [^{177}Lu]Lu-PSMA-617 and consequently higher levels of DNA damage in mouse models, which ultimately explains the efficacy of radioligand therapy [43,44]. Thus, baseline PSMA PET is crucial for selecting candidates for the targeted treatment. However, the inter-patients and inter-tumor heterogeneity of PSMA expression [28], together with the lack of a unique and validated imaging threshold that defines PSMA PET positivity, represent unsolved points that could affect the efficacy of radioligand therapy. The current European Association of Nuclear Medicine (EANM) procedural guidelines recommend excluding patients with lesions with diameter $\geq$ 1 cm showing tumor uptake $<$ 0.5-fold of the parotid glands (which approximately equals $<$ 1.0-fold liver-uptake of [^{68}Ga]Ga-PSMA-11 that have been used in the VISION trial [11]) [30]. However, the available clinical trials which used different definitions of positivity [12,37,38], makes patients' selection criteria still a matter of debate. Some considerations must be addressed: the screen failure rate was about 13 % in the VISION [12] compared to 32 % in the TheraP [37], highlighting the more restrictive selection of the latter study. Several data suggested that the degree of baseline PSMA uptake could correlate with response to [^{177}Lu]Lu-PSMA-617. In the VISION trial, SUV_{mean} provided a consistent statistically significant association with improved response across all endpoints assessed [45]. Likewise, a post-hoc analysis of the TheraP showed that the odds of PSA response to [^{177}Lu]Lu-PSMA-617 versus cabazitaxel was significantly higher for men with $SUV_{mean} \geq 10$ [46]. The possible co-existence of a neuroendocrine de-differentiation, has to be considered when facing PSMA-negative tumors, and maybe in these (rare) cases [^{18}F]FDG PET could add something [47]. [^{18}F]FDG PET is not routinely used, but it could be helpful to identify patients who could benefit less from [^{177}Lu]Lu-PSMA-617 therapy, as in the Thera-P [36] and LuPSMA trials [48]. Nevertheless, the discrepancy between [^{18}F]FDG and PSMA PET is pretty low, with less than 5 % of patients with FDG/PSMA mismatch not detected using only PSMA PET (VISION-trial criteria) [49].

Several studies investigated the potential role of baseline clinical characteristics as potential predictors of treatment efficacy to be used in the selection process. Visceral metastasis is the only variable negatively associated with all clinical outcomes (OS, clinical PFS, PSA response) [50]. Moreover, increased lactate dehydrogenase level was found to be an independent predictor of short OS [50]. Further analyses went into more detail to evaluate whether combining baseline clinical and imaging features could predict treatment efficacy [51]. A study combined baseline PSMA PET-derived and clinical parameters in order to develop nomograms for selecting mCRPC candidates for [^{177}Lu]Lu-PSMA-617 therapy [52]. Gafita et al. analysed data from 270 mCRPC patients treated with [^{177}Lu]Lu-PSMA-617 in clinical trials or compassionate access programs, with OS and PSA-PFS representing the endpoints of interest [52]. At multivariate analysis, time since diagnosis of prostate cancer, chemotherapy status, baseline haemoglobin concentration, bone involvement, liver metastasis, number of PSMA-positive metastatic lesions, and tumor SUV_{mean} were predictors selected in the OS model. Using the calculated optimal cut-off for both risk scores, patients could be divided into a high-risk group and a low-risk group. Patients classified as low-risk showed favourable OS (24.9 months vs. 7.4 months, $p < 0.0001$) and PSA-PFS (6.6 vs. 2.5 months, $p = 0.022$) when compared with those in the high-risk group [52]. Furthermore, this analysis identified the bone disease as a negative factor of response to [^{177}Lu]Lu-PSMA-617 [52], in accordance with what has been reported by others [53].

Prospective validation of these biomarkers could help in the future in the selection of patients more likely to benefit from [^{177}Lu]Lu-PSMA-617 treatment with the final goal of a tailored clinical decision-making process. In line with previous experiences with [^{223}Ra]Ra [54], a uniform and validated composite score that integrates different information from diverse morphological-biochemical-clinical-metabolic features of the disease might standardize patients' selection to more tailored therapy and improve patients' outcomes.

Open issues related to treatment response assessment

Another important point that deserves consideration is evaluating tumor response to treatment. The VISION trial had as alternate primary endpoints OS and rPFS determined by CT or MRI and bone scans. PSA response was included in the secondary endpoints. Only one PSMA PET

Table 1
Ongoing phase III prostate cancer trials involving PSMA-directed radioligand therapy.

NCT number	Study Title	Disease setting	Intervention	Comparator arm	Primary outcome
NCT04720157PSMAddition	An International Prospective Open-label, Randomized, Phase III Study Comparing 177Lu-PSMA-617 in Combination With SoC, Versus SoC Alone, in Adult Male Patients With mHSPC (PSMAddition)	mHSPC	[^{177}Lu]Lu-PSMA-617 + ADT + ARPI	ADT + ARPI	rPFS
NCT04647526SPLASH	Study Evaluating mCRPC Treatment Using PSMA [Lu-177]-PNT2002 Therapy After Second-line Hormonal Treatment (SPLASH)	mCRPC previously treated with second-line ARPI	[^{177}Lu]Lu-PNT2002 + ADT	ADT + ARPI	rPFS
NCT05204927ECLIPSE	177Lu-PSMA-I&T for Metastatic Castration-Resistant Prostate Cancer	mCRPC previously treated withARPI, without prior taxane therapy	[^{177}Lu]Lu-PSMA-I&T + ADT	ADT + ARPI	rPFS
NCT04876651PROSTACT	177Lu-DOTA-rosopatamab With Best Standard of Care (SoC) for the Second Line of Treatment for Metastatic Castrate-resistant Prostate Cancer, Which Expresses PSMA (PROSTACT)	mCRPC previously treated with ARPI	[^{177}Lu]Lu-TLX591 + ADT + SoC	ADT + SoC	rPFS

Abbreviation: ADT: androgen deprivation therapy; ARPI: androgen receptor pathway inhibitors; mCRPC: metastatic castration-resistant prostate cancer; mHSPC: metastatic hormonal sensitive prostate cancer; rPFS: radiographic progression-free survival; SoC: standard of care.

was required for trial entry, and only morphological imaging and bone scan were repeated at restaging [11]. The TheraP study restricted the primary endpoint to PSA50 [36]. The radiographic progression was evaluated using CT and bone scanning according to RECIST v1.1 and PCWG3 criteria [37]. Once again, no PSMA PET was required to define progression or response [37].

To notice, since molecular alterations usually precede morphological ones, a higher percentage of progression could be diagnosed earlier by molecular than by morphological criteria. Although not yet validated in the context of clinical trials, several methods have been proposed to assess responses with PSMA PET imaging [55]. The PSMA PET Progression (PPP) criteria have been proposed based on the PCWG3 criteria [56]. PPP suggests that, for progressive disease, two new lesions are sufficient. Unlike bone scans, confirmatory scans are typically not required due to the rarity of the flare phenomenon in PSMA PET. Progression may also be considered when discordant behaviour is observed in other lesions. Another approach combines PSMA PET and PSA measurements, based on the RECIP 1.0 study [57]. This study examined 124 patients before and after 12 weeks of radioligand therapy. It concluded that PSMA volume was the most accurate measure and that a combination of PSA and PSMA volume assessment was the best predictor for OS. The response was defined as a PSA decrease of at least 50 % or RECIP-PR/RECIP-CR, while progression was defined as a PSA increase of at least 25 % or RECIP-PD [57].

In agreement with previous data showing the correlation between tumor-absorbed dose and treatment response in neuroendocrine tumors patients who underwent radioligand therapy [58,59], it has been suggested that tumor-absorbed doses of [^{177}Lu]Lu-PSMA-617 (despite the technical difficulties related to its determination) may be a relevant predictor of disease response as well. Indeed, a good correlation was documented between functional and morphological changes on PSMA PET and the visual uptake in [^{177}Lu]Lu-PSMA-617 at the whole body scans acquired at 24-hour post-infusion (using planar scintigraphy or Single-Photon Emission computed Tomography/CT, SPECT/CT) [60,61]. In a prospective cohort of 30 mCRPC patients, the mean tumor dose of [^{177}Lu]Lu-PSMA-617 correlated with PSA50 [62]. Moreover, 7 % of the patients enrolled in the TheraP trial suspended the treatment because of protocol-defined exceptional PSMA response to therapy evaluated by 24 h SPECT/CT [37]. 24 h SPECT/CT is acquired per protocol in nearly all the main studies, and it represents a rapid and adequate evaluation instrument, without any further administration, using only the gamma emission from the already injected lutetium.

PSA reduction is also important to evaluate tumour response. [^{177}Lu]Lu-PSMA-617 therapy was associated with a PSA50 in nearly 50 % patients in the main randomized prospective trials (around 2/3 in the experimental arm of the TheraP versus 1/3 of patients treated with cabazitaxel [37]; 46 % in the VISION study versus 7 % among patients who received standard of care [11]), confirmed by the *meta*-analysis of Von Eyben and colleagues [63]. PSA trend during [^{177}Lu]Lu-PSMA-617 therapy has also been investigated. A retrospective analysis of 124 patients treated with [^{177}Lu]Lu-PSMA-617 showed that an early decrease in PSA levels higher than or equal to 30 % after 6 weeks from the start of treatment was associated with longer OS compared to that of patients with PSA increase or stability [64]. The association between early biochemical response and patient outcomes was then confirmed by another small analysis conducted in 27 mCRPC patients; a reduction in PSA $\geq$ 30 % 4 weeks after starting [^{177}Lu]Lu-PSMA-617 correlated with persistence of biochemical response at 16 weeks and longer OS [65]. Moreover, sustained PSA50 for over 24 weeks was reported to correlate with radiological response [66], and ultimately could represent a prognostic marker associated with longer OS [63,67]. Of interest, PSA value may help to evaluate morphological or unclear imaging results in case of mixed/discordant response, acting as a precursor of a radiological/metabolic disease progression. To notice, 2–7 % of patients in the TheraP trial showed partial response by molecular and morphological criteria despite PSA progression and resulted in tumor progression in the subsequent disease assessments [37,68]. Notably, the opposite phenomenon may also occur, with PSA reduction in the presence of imaging progression [69].

In summary, a comprehensive assessment of a patient's response to treatment might be achieved by combining various measures, including clinical status, quality of life assessments, PSA values, CT, and MRI. Serial PSA measurements and a 24-hour post-therapy SPECT/CT scan can accurately monitor radioligand therapy. Additionally, PSMA PET/CT may serve as a valuable tool for evaluating treatment response, although its validation in clinical trials is still necessary.

Future perspectives

Given the results of the prospective trials previously seen, [^{177}Lu]Lu-PSMA-617 is currently being evaluated in different therapeutic scenarios, but also in different disease settings such as patients with oligometastatic or metastatic hormonal sensitive prostate cancer (mHSPC). Additionally, other small molecule inhibitors of radiolabelled PSMA, such as [^{177}Lu]Lu-PSMA-I&T or PSMA ligands labelled with other radioisotopes are also under investigation. Table 1 summarises the currently active and recruiting phase III prostate cancer trials involving PSMA-directed radioligand therapy, while Table 2 depicts the main recruiting phase I/II trials.

In the setting of mHSPC, PSMAddition (NCT04720157) is an open-label, phase III clinical trial randomizing more than 1000 patients to determine the efficacy of [^{177}Lu]Lu-PSMA-617 in combination with androgen deprivation therapy (ADT) + ARSI versus ADT + ARSI alone. The primary outcome of the study is rPFS. UpFrontPSMA (NCT04343885) is a phase II trial in patients with newly diagnosed metastatic prostate cancer randomized to receive [^{177}Lu]Lu-PSMA-617 (7.5 GBq every 6 weeks for two cycles) followed by six cycles of docetaxel compared to six cycles of docetaxel. The primary endpoint will be the proportion of patients with undetectable PSA 1 year after starting therapy.

In patients with taxane-naïve mCRPC, two phase III trials are underway with [^{177}Lu]Lu-PSMA-I&T against ARSI: SPLASH and ECLIPSE. SPLASH trial (NCT04647526) involves two parts: a lead-in treatment phase to evaluate safety and dosimetry of [^{177}Lu]Lu-PSMA-I&T, successfully completed [70], and a randomisation phase to either [^{177}Lu]Lu-PSMA-I&T or ARSI. ECLIPSE trial (NCT05204927) is randomizing 400 patients in a 2:1 ratio to either up to four doses of [^{177}Lu]Lu-PSMA-I&T or ARSI. For both studies, the primary endpoint is rPFS. The control arm with ARSI in patients already treated with ARSI could represent the main limitation of these studies, likewise in the PSMAfore trial [39]. On the contrary, NCT04663997 is a phase II trial randomizing patients with mCRPC who have previously received ARSI to receive [^{177}Lu]Lu-PSMA-617 or docetaxel, with PFS as the primary endpoint.

Many studies are ongoing to evaluate combined therapy with [^{177}Lu]Lu-PSMA-617 to enhance anti-tumor activity by exploiting a potential synergistic effect of different agents with diverse mechanisms of action. Pre-clinical data support a cross-talk in the castration-resistant but not in the castration-sensitive phase of disease between the androgen receptor and PSMA receptor pathways. In particular, treatment with enzalutamide could lead to an up-regulation of PSMA receptors in mCRPC [71]. The interim data from the phase 2 ENZA-p study [72] presented at the 2023 ESMO Conference involved mCRPC patients in the first line of treatment, who have not received chemotherapy in the castration-resistant disease phase, with positive PSMA PET screening (considered in the case of $SUV_{max} \geq 15$ at one site and ≥ 10 at all measurable sites), and at high risk of early failure with enzalutamide (defined in case of at least 2 poor risk factors among LDH $\geq$ ULN, ALP $\geq$ ULN, albumin < 35 g/L, de novo metastatic tumor, < 3 years from initial diagnosis, > 5 bone metastases, visceral metastases, PSA doubling time < 84 days, previous treatment with abiraterone, pain requiring opioids). Patients ($n = 162$) were randomized to enzalutamide monotherapy or the combination of enzalutamide + [^{177}Lu]Lu-PSMA-617 (7.5 GBq for 2 up to 4 doses as

Table 2
Ongoing phase I/II prostate cancer trials involving PSMA-directed radioligand therapy.

NCT number	Study Title	Disease setting	Clinicaltrial phase	Intervention	Comparatorarm	Primary outcomemeasure
NCT04343885	In Men With Metastatic Prostate Cancer, What is the Safety and Benefit of Lutetium-177 PSMA Radionuclide Treatment in Addition to Chemotherapy (UpFrontPSMA)	mHSPC	II	[^{177}Lu]Lu-PSMA-617 + ADT + Docetaxel	ADT + Docetaxel	Undetectable PSA rate at 12 months
NCT04443062	Lutetium-177-PSMA-617 in Oligo-metastatic Hormone Sensitive Prostate Cancer (Bullseye)	Oligometastatic mHSPC	II	[^{177}Lu]Lu-PSMA-617	No intervention	Fraction of pts that have PD within 6 months / time to PD
NCT05146973	External Beam Therapy With Theranostic Radioligand Therapy for Oligometastatic Prostate Cancer (ProstACT TARGET)	Biochemically recurrent oligometastatic prostatecancer	II	[^{177}Lu]Lu-TLX591, + EBRT	/	PSA PFS
NCT04419402	ENZA-p: A randomized phase II trial using PSMA as a therapeutic agent and prognostic indicator in men with metastatic castration-resistant prostate cancer treated with enzalutamide (ANZUP 1901).	mCRPC	II	[^{177}Lu]Lu-PSMA-617 + ADT + Enzalutamide	ADT + Enzalutamide	PSA PFS
NCT04663997	^{177}LuPSMA-617 vs Docetaxel in Metastatic Castration Resistant and PSMA-Positive Prostate Cancer	mCRPC previously treated withARPI	II	[^{177}Lu]Lu-PSMA-617 + ADT	ADT + Docetaxel	PFS
NCT05113537	Abemaciclib Before ^{177}Lu-PSMA-617 for the Treatment of Metastatic Castrate Resistant Prostate Cancer (UPLIFT)	mCRPC previously treated withARPI	I/II	Abemaciclib, [^{177}Lu] Lu-PSMA-617	/	DLT MTD RP2D Change in SUV_{max}
NCT05340374	Cabazitaxel in Combination With ^{177}Lu-PSMA-617 in Metastatic Castration-resistant Prostate Cancer (LuCAB)	mCRPC previously treated withdocetaxel and ARPI	I/II	Cabazitaxel + [^{177}Lu]Lu-PSMA-617	/	DLT MTDRP2D
NCT03454750	Radiometabolic Therapy (RMT) With ^{177}Lu PSMA 617 in Advanced Castration Resistant Prostate Cancer (CRPC) (LU-PSMA)	mCRPC	II	[^{177}Lu]Lu-PSMA-617	/	DCR, safety
NCT03874884	^{177}Lu-PSMA-617 Therapy and Olaparib in Patients With MetastaticCastration Resistant ProstateCancer (LuPARP)	mCRPC previously treated withARPI	I	[^{177}Lu]Lu-PSMA + Olaparib	/	DLT MTDRP2D
NCT05150236	EVOLUTION: ^{177}Lu-PSMA Therapy Versus ^{177}Lu-PSMA in Combination With Ipilimumab andNivolumab for Men With mCRPC (ANZUP2001)	mCRPC previously treated withARPI	II	[^{177}Lu]Lu-PSMA-617 + ipilimumab + nivolumab	[^{177}Lu]Lu-PSMA-617	PSA PFS
NCT03658447	PRINCE (PSMA-lutetium Radionuclide Therapy and ImmuNotherapyin Prostate CancEr) (PRINCE)	mCRPC previously treated withARPI	I/II	[^{177}Lu]Lu-PSMA-617 + Pembrolizumab	/	PSA response rateSafety/Tolerability
NCT03805594	^{177}Lu-PSMA-617 and Pembrolizumab in Treating Patients With Metastatic Castration-ResistantProstate Cancer	mCRPC previously treated withARPI	I	[^{177}Lu]Lu-PSMA-617 + Pembrolizumab	/	RP2DORR
NCT05383079	Combination of Radium-223 and Lutetium-177 PSMA-I&T in Men With Metastatic Castration-ResistantProstate Cancer (AlphaBet)	mCRPC previously treated withARPI	I/II	[^{223}Ra]Ra + [^{177}Lu] Lu PSMA-I&T	/	DLT MTD RP2DPSA response rate
NCT04786847	^{177}Lu-DOTA-TLX591 Safety, Biodistribution and Dosimetry Study (ProstACTSelect)	mCRPC previously treated withARPI	I	[^{177}Lu]Lu-DOTA-TLX591	/	Treatment-related adverse events
NCT05496959	^{177}-Lutetium-PSMA Before Stereotactic Body Radiotherapy for the Treatment of Oligorecurrent Prostate Cancer, The LUNAR Study (LUNAR)	Oligorecurrent prostate cancer	II	[^{177}Lu]Lu-PSMA-I&T beforeSBRT	SBRT	PSMA-PET/CT-based PFS
NCT05219500	Targeted Alpha Therapy With 225Actinium-PSMA-I&T of Castration-resISTant Prostate Cancer (TATCIST). (TATCIST)	mCRPC previously treated withARPI	II	[^{225}Ac]Ac-PSMA-I&T	/	Efficacy and safety

Abbreviation: ADT: androgen deprivation therapy; ARPI: androgen receptor pathway inhibitors; DCR, disease control rate; DLTs, dose-limiting toxicities; EBRT: external beam radiation therapy; mCRPC: metastatic castration resistant prostate cancer; mHSPC: metastatic hormonal sensitive prostate cancer; MTD, maximum tolerated dose; ORR, objective response rate; PD: progressive disease; PFS: progression-free survival; PSA, prostate-specific antigen; pts: patients; RP2D: recommended phase II dose; SBRT, stereotactic body radiation therapy.

adaptive dosing based on the response at 24 h SPECT/CT) [73]. The study met its primary endpoint, showing a median PSA-PFS of 13 months with the combination therapy compared to 7.8 months with enzalutamide monotherapy (HR: 0.43, 95 %CI 0.29–0.63, $p = 0.00001$). Further, enzalutamide + [^{177}Lu]Lu-PSMA-617 was associated with a higher PSA response rate (PSA50 93 % vs. 68 %, and PSA90 78 % vs. 37 %, $p < 0.001$). The combination was well tolerated, with a rate of severe adverse events reported in 33 % compared to 35 % in the control arm [73]. ENZA-p is the first randomized study that combined an ARSI with [^{177}Lu]Lu-PSMA-617, and the first study to use an adapted dose of [^{177}Lu]Lu-PSMA-617 based on response, aiming to avoid toxicity in responder patients. The study demonstrated an interesting action of this combination, intended as a biochemical response (questionable endpoint in first-line mCRPC). The issue remains open whether the activity demonstrated by this combination would translate into prolongation of patient OS. However, there is a planned follow-up of PFS and

OS of the study until July 2024. In the future, it will be intriguing to explore whether combining [^{177}Lu]Lu-PSMA-617 with another ARSI could prove effective in patients who have progressed on an ARSI.

Another potential treatment strategy under evaluation involves the combination of [^{177}Lu]Lu-PSMA-617 and PARP inhibitors, exploiting a synergistic effect between these two therapeutic agents on DNA damage. β- irradiation delivered by [^{177}Lu]Lu-PSMA-617 to PSMA-expressing cancer sites, primarily causes single-strand DNA breaks, typically repaired by PARP-dependent pathways [74]. Blocking PARP could convert DNA single-strand breaks into lethal double-strand breaks through replication fork collapse. Indeed, enhanced anti-tumour activity was demonstrated in the LuPARP trial, which hypothesised an increased DNA damage due to the radiosensitization effect of olaparib [75]. LuPARP (NCT03874884) is a phase I trial involving 48 patients with mCRPC, pre-treated with a prior ARSI and docetaxel, and with high PSMA expression (defined as PSMA $SUV_{max} > 15$ at any site, $SUV_{max} > 10$ at other sites, no [^{18}F]FDG discordance). This study followed a 3 + 3 dose escalation design: [^{177}Lu]Lu-PSMA-617 was administered at a dose of 7.4 GBq 6 weekly for 6 cycles, while olaparib was concurrently administered at a dose of 50 to 300 mg twice daily on days 2 to 15, −4 to 14, or −4 to 18 of each 6-week cycle. The primary endpoints were maximum tolerated dose (MTD), dose-limiting toxicities (DLT), and the recommended phase II dose (RP2D). Secondary endpoints included efficacy outcomes: rPFS, PSA-response rate, PSA-PFS, ORR, OS, and safety. The combination of [^{177}Lu]Lu-PSMA-617 and olaparib was well tolerated, with no DLTs reported across the dose levels, and no grade 4 adverse events. In the overall population, the PSA50 and PSA90 response rates were 66 % and 44 %, respectively; PSA response rates were even better at higher olaparib dose levels. The ORR by RECIST v1.1 criteria was 78 %. Dose-expansion phase is currently underway and the recommended phase II dose is 7.4 Gb of [^{177}Lu]Lu-PSMA-617 in conjunction with olaparib 300 mg twice daily on days −4 to 18 of each 6-weekly cycle.

Finally, several clinical trials are now in progress to evaluate the combination of [^{177}Lu]Lu-PSMA-617 and immune checkpoint inhibitors. The assumption is that [^{177}Lu]Lu-PSMA-617 could stimulate the tumor microenvironment immunogenicity to enhance immune checkpoint inhibitors. Namely, the EVOLUTION trial (NCT05150236) aims to determine the activity and safety of ipilimumab and nivolumab in combination with [^{177}Lu]Lu-PSMA-617 in mCRPC patients. Furthermore, the NCT03805594 is a phase Ib/II trial enrolling chemotherapy-naïve mCRPC patients with progression on at least one prior androgen signalling inhibitor; the phase Ib trial showed that the combination of [^{177}Lu]Lu-PSMA-617 and pembrolizumab was well tolerated and leads to durable responses in a subset of mCRPC patients [76]. The phase II study is currently ongoing.

Conclusions

In conclusion, the evolution of theranostics is poised to transform the landscape of precision medicine in prostate cancer. However, many open issues still need to be addressed, including the optimization of patient selection and treatment response assessment, the identification of the correct place in the treatment landscape, as well as the evaluation of potential synergy with other systemic treatments. The journey toward personalized and effective care for prostate cancer patients is just beginning, and the possibilities are boundless.

CRediT authorship contribution statement

Matteo Bauckneht: Conceptualization, Methodology, Supervision, Validation, Methodology, Data curation, Writing – original draft, Project administration, Validation. **Chiara Ciccarese:** Conceptualization, Methodology, Supervision, Validation, Methodology, Data curation, Writing – original draft, Supervision. **Riccardo Laudicella:** Methodology, Data curation, Writing – original draft, Supervision. **Claudia Mosillo:** Methodology, Data curation, Writing – original draft, Supervision. **Francesca D'Amico:** Resources, Investigation. **Annunziato Anghelone:** Resources, Investigation. **Alessandro Strusi:** Resources, Investigation. **Viria Beccia:** Resources, Investigation. **Sergio Bracarda:** Conceptualization, Methodology, Supervision, Validation. **Giuseppe Fornarini:** Conceptualization, Methodology, Supervision, Validation. **Giampaolo Tortora:** Conceptualization, Methodology, Supervision, Validation. **Roberto Iacovelli:** Conceptualization, Methodology, Supervision, Validation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Parker C, Castro E, Fizazi K, Heidenreich A, Ost P, Procopio G, et al. Prostate cancer: ESMO Clinical Practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2020;31(9):1119–34.

[2] Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351(15):1502–12.

[3] Iacovelli R, Ciccarese C, Caffo O, De Giorgi U, Tucci M, Mosillo C, et al. The prognostic value of pain in castration-sensitive prostate cancer. Prostate Cancer Prostatic Dis 2020;23(4):654–60.

[4] Fizazi K, Scher HI, Molina A, Logothetis CJ, Chi KN, Jones RJ, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 2012;13(10):983–92.

[5] Ryan CJ, Smith MR, Fizazi K, Saad F, Mulders PFA, Sternberg CN, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 2015;16(2):152–60.

[6] Cabot RC, Harris NL, Rosenberg ES, Shepard J-A, Cort AM, Ebeling SH, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367(13):1187–97.

[7] Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014;371(5):424–33.

[8] de Wit R, de Bono J, Sternberg CN, Fizazi K, Tombal B, Wülfing C, et al. Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. N Engl J Med 2019;381(26):2506–18.

[9] de Bono J, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med 2020;382(22):2091–102.

[10] Fizazi K, Piulats JM, Reaume MN, Ostler P, McDermott R, Gingerich JR, et al. Rucaparib or physician's choice in metastatic prostate cancer. N Engl J Med 2023;388(8):719–32.

[11] Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fosså SD, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 2013;369(3):213–23.

[12] Sartor O, de Bono J, Chi KN, Fizazi K, Herrmann K, Rahbar K, et al. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. N Engl J Med 2021;385(12):1091–103.

[13] Turner JH. An introduction to the clinical practice of theranostics in oncology. BJR 2018;91(1091):20180440.

[14] Filippi L, Chiaravalloti A, Schillaci O, Cianni R, Bagni O. Theranostic approaches in nuclear medicine: current status and future prospects. Expert Rev Med Devices 2020;17(4):331–43. https://doi.org/10.1080/17434440.2020.1741348. Epub 2020 Mar 19 PMID: 32157920.

[15] Mulford DA, Scheinberg DA, Jurcic JG. The promise of targeted {alpha}-particle therapy. J Nucl Med 2005;46(Suppl 1):199S–204S. PMID: 15653670.

[16] Sofou S. Radionuclide carriers for targeting of cancer. Int J Nanomedicine 2008;3(2):181–99. https://doi.org/10.2147/ijn.s2736. PMID: 18686778; PMCID: PMC2527672.

[17] Poty S, Francesconi LC, McDevitt MR, Morris MJ, Lewis JS. α-Emitters for Radiotherapy: From Basic Radiochemistry to Clinical Studies—Part 1. J Nucl Med 2018;59(6):878–84.

[18] Humm JL. A microdosimetric model of astatine-211 labeled antibodies for radioimmunotherapy. Int J Radiat Oncol Biol Phys 1987;13(11):1767–73. https://doi.org/10.1016/0360-3016(87)90176-3. PMID: 3667382.

[19] O'Keefe DS, Su SL, Bacich DJ, Horiguchi Y, Luo Y, Powell CT, et al. Mapping, genomic organization and promoter analysis of the human prostate-specific membrane antigen gene. Biochim Biophys Acta 1998;1443(1–2):113–27. https://doi.org/10.1016/s0167-4781(98)00200-0. PMID: 9838072.

[20] Hofman MS, Hicks RJ, Maurer T, Eiber M. Prostate-specific Membrane Antigen PET: Clinical Utility in Prostate Cancer, Normal Patterns, Pearls, and Pitfalls.

Radiographics 2018;38(1):200–17. https://doi.org/10.1148/rg.2018170108. PMID: 29320333.
[21] Chang SS. Overview of prostate-specific membrane antigen. Rev Urol. 2004;6 Suppl 10(Suppl 10):S13-8. PMID: 16985927; PMCID: PMC1472940.
[22] Bodar YJL, Veerman H, Meijer D, de Bie K, van Leeuwen PJ, Donswijk ML, et al. Standardised uptake values as determined on prostate-specific membrane antigen positron emission tomography/computed tomography is associated with oncological outcomes in patients with prostate cancer. BJU Int 2022;129(6):768–76.
[23] Fazio N, La Salvia A. Precision medicine in gastroenteropancreatic neuroendocrine neoplasms: Where are we in 2023? Best Pract Res Clin Endocrinol Metab 2023;37(5):101794.
[24] Bauckneht M, Marini C, Cossu V, Campi C, Riondato M, Bruno S, et al. Gene's expression underpinning the divergent predictive value of [18F]F-fluorodeoxyglucose and prostate-specific membrane antigen positron emission tomography in primary prostate cancer: a bioinformatic and experimental study. J Transl Med 2023;21(1). https://doi.org/10.1186/s12967-022-03846-1. PMID: 36600265; PMCID: PMC9811737.
[25] Sartor O. Outcome of Patients with PSMA PET/CT Screening Failure by VISION Criteria and Treated with 177Lu-PSMA: A Multicenter Retrospective Analysis. J Nucl Med 2022;63(10):1482–3. https://doi.org/10.2967/jnumed.122.264128. Epub 2022 May 26 PMID: 35618477.
[26] Laudicella R, La Torre F, Davì V, Crocè L, Aricò D, Leonardi G, et al. Prostate Cancer Biochemical Recurrence Resulted Negative on [68Ga]Ga-PSMA-11 but Positive on [18F]Fluoromethylcholine PET/CT. Tomography 2022 Sep 30;8(5):2471–4. https://doi.org/10.3390/tomography8050205. PMID: 36287804; PMCID: PMC9609559.
[27] Laudicella R, Rüschoff JH, Ferraro DA, Brada MD, Hausmann D, Mebert I, et al. Infiltrative growth pattern of prostate cancer is associated with lower uptake on PSMA PET and reduced diffusion restriction on mpMRI. Eur J Nucl Med Mol Imaging 2022;49(11):3917–28.
[28] Thang SP, Violet J, Sandhu S, Iravani A, Akhurst T, Kong G, et al. Poor Outcomes for Patients with Metastatic Castration-resistant Prostate Cancer with Low Prostate-specific Membrane Antigen (PSMA) Expression Deemed Ineligible for 177Lu-labelled PSMA Radioligand Therapy. Eur Urol Oncol 2019;2(6):670–6.
[29] Jadvar H. The VISION Forward: Recognition and Implication of PSMA-/18F-FDG+ mCRPC. J Nucl Med. 2022; 63(6):812-815. doi: 10.2967/jnumed.121.263274. Epub 2021 Dec 21. PMID: 34933889; PMCID: PMC9157736.
[30] Kratochwil C, Fendler WP, Eiber M, Hofman MS, Emmett L, Calais J, et al. Joint EANM/SNMMI procedure guideline for the use of 177Lu-labeled PSMA-targeted radioligand-therapy (177Lu-PSMA-RLT). Eur J Nucl Med Mol Imaging 2023;50(9):2830–45.
[31] Nauseef JT, Bander NH, Tagawa ST. Emerging Prostate-specific Membrane Antigen-based Therapeutics: Small Molecules, Antibodies, and Beyond. Eur Urol Focus 2021;7(2):254–7. https://doi.org/10.1016/j.euf.2021.02.006. Epub 2021 Feb 27 PMID: 33648895.
[32] Sartor O, Coleman R, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, et al. Effect of radium-223 dichloride on symptomatic skeletal events in patients with castration-resistant prostate cancer and bone metastases: results from a phase 3, double-blind, randomised trial. Lancet Oncol 2014 Jun;15(7):738–46. https://doi.org/10.1016/S1470-2045(14)70183-4. Epub 2014 May 13 PMID: 24836273.
[33] Smith M, Parker C, Saad F, Miller K, Tombal B, Ng QS, et al. Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019;20(3):408–19.
[34] EMA. EMA Restricts Use of Prostate Cancer Medicine XOFIGO. Available online: https://www.ema.europa.eu/en/news/emarestricts-use-prostate-cancer-medicine-xofigo (accessed on 3 novembre 2023).
[35] Bauckneht M, Rebuzzi SE, Ponzano M, Borea R, Signori A, Frantellizzi V, et al. Prognostic Value of the BIO-Ra Score in Metastatic Castration-Resistant Prostate Cancer Patients Treated with Radium-223 after the European Medicines Agency Restricted Use: Secondary Investigations of the Multicentric BIO-Ra Study. Cancers (Basel) 2022 Mar 29;14(7):1744. https://doi.org/10.3390/cancers14071744. PMID: 35406515; PMCID: PMC8996965.
[36] Kim YJ, Kim Y-I. Therapeutic responses and survival effects of 177Lu-PSMA-617 radioligand therapy in metastatic castrate-resistant prostate cancer: a meta-analysis. Clin Nucl Med 2018;43(10):728–34.
[37] 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 randomized, open-label, phase 2 trial. Lancet 2021;397(10276):797–804.
[38] Hofman MS, Shahneen Sandhu LE, Iravani A, et al. TheraP: 177Lu-PSMA-617 (LuPSMA) versus cabazitaxel in metastatic castration-resistant prostate cancer (mCRPC) progressing after docetaxel—Overall survival after median follow-up of 3 years (ANZUP 1603). J Clin Oncol 2022;40(16s) doi : https://doi.org/10.1200/JCO.2022.40.16_suppl.5000.
[39] Sartor O, et al. PSMAfore: A phase III study to compare 177Lu-PSMA-617 treatment with a change in androgen receptor pathway inhibitor in taxane-naïve patients with mCRPC. ESMO Congress 2023:LBA13.
[40] Maines F, Caffo O, Veccia A, Trentin C, Tortora G, Galligioni E, et al. Se quencing new agents after docetaxel in patients with metastatic castration-resis tant prostate cancer. Crit Rev Oncol He matol 2015;96(3):498–506.
[41] Oh WK, Cheng WY, Miao R, Vekeman F, Gauthier-Loiselle M, Duh MS, et al. Real-world outcomes in patients with metastatic castration-resistant prostate cancer receiving second-line chemothera py versus an alternative androgen recep tor-targeted agent (ARTA) following early progression on a first-line ARTA in a US community oncology setting. Urol Oncol 2018;36(11):500.e1–9.
[42] Woythal N, Arsenic R, Kempkensteffen C, Miller K, Janssen JC, Huang K, et al. Immunohistochemical Validation of PSMA Expression Measured by 68Ga-PSMA PET/CT in Primary Prostate Cancer. J Nucl Med 2018;59(2):238–43. https://doi.org/10.2967/jnumed.117.195172. Epub 2017 Aug 3 PMID: 28775203.
[43] Jeitner TM, Babich JW, Kelly JM. Advances in PSMA theranostics. Transl Oncol 2022;22:101450.
[44] Current K, Meyer C, Magyar CE, Mona CE, Almajano J, Slavik R, Stuparu AD, Cheng C, Dawson DW, Radu CG, Czernin J, Lueckerath K. Investigating PSMA-Targeted Radioligand Therapy Efficacy as a Function of Cellular PSMA Levels and Intratumoral PSMA Heterogeneity. Clin Cancer Res. 2020;26(12):2946-2955. doi: 10.1158/1078-0432.CCR-19-1485. Epub 2020 Jan 13. PMID: 31932492; PMCID: PMC7299755.
[45] 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. Journal of Clinical Oncology 40, no. 16_suppl (June 01, 2022) 5002-5002. DOI: 10.1200/JCO.2022.40.16_suppl.5002.
[46] Buteau JP, Martin AJ, Emmett L, Iravani A, Sandhu S, Joshua AM, 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(11):1389–97.
[47] Thang SP, Violet J, Sandhu S, Iravani A, Akhurst T, Kong G, et al. Poor Outcomes for Patients with Metastatic Castration-resistant Prostate Cancer with Low Prostate-specific Membrane Antigen (PSMA) Expression Deemed Ineligible for 177Lu-labelled PSMA Radioligand Therapy. Eur Urol Oncol 2019 Nov;2(6):670–6. https://doi.org/10.1016/j.euo.2018.11.007. Epub 2018 Dec 13 PMID: 31412006.
[48] Hofman MS, Violet J, Hicks RJ, Ferdinandus J, Thang SP, Akhurst T, 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(6):825–33. https://doi.org/10.1016/S1470-2045(18)30198-0. Epub 2018 May 8 PMID: 29752180.
[49] Seifert R, Telli T, Hadaschik B, Fendler WP, Kuo PH, Herrmann K. Is 18F-FDG PET Needed to Assess 177Lu-PSMA Therapy Eligibility? A VISION-like. Single-Center Analysis J Nucl Med 2023;64(5):731–7.
[50] Heck MM, Tauber R, Schwaiger S, et al. Treatment outcome, toxicity, and predictive factors for radioligand therapy with 177Lu-PSMA-I&T in metastatic castration-resistant prostate cancer. Eur Urol 2019; 75: 920–26.
[51] Ferdinandus J, Violet J, Sandhu S, Hicks RJ, Ravi Kumar AS, Iravani A, et al. Prognostic biomarkers in men with metastatic castration-resistant prostate cancer receiving [177Lu]-PSMA-617. Eur J Nucl Med Mol Imaging 2020;47(10):2322–7.
[52] Gafita A, Calais J, Grogan TR, Hadaschik B, Wang H, Weber M, et al. Nomograms to predict outcomes after 177Lu-PSMA therapy in men with metastatic castration-resistant prostate cancer: an international, multicentre, retrospective study. Lancet Oncol 2021 Aug;22(8):1115–25. https://doi.org/10.1016/S1470-2045(21)00274-6. Epub 2021 Jul 8 PMID: 34246328.
[53] Freitag MT, Radtke JP, Hadaschik BA, Kopp-Schneider A, Eder M, Kopka K, et al. Comparison of hybrid (68)Ga-PSMA PET/MRI and (68)Ga-PSMA PET/CT in the evaluation of lymph node and bone metastases of prostate cancer. Eur J Nucl Med Mol Imaging 2016;43(1):70–83.
[54] Bauckneht M, Rebuzzi SE, Signori A, Frantellizzi V, Murianni V, Lodi Rizzini E, et al. The prognostic power of inflammatory indices and clinical factors in metastatic castration-resistant prostate cancer patients treated with radium-223 (BIO-Ra study). Eur J Nucl Med Mol Imaging 2022;49(3):1063–74.
[55] Laudicella R, Bauckneht M, Burger IA. Is There a Role of Interim PSMA PET in Chemotherapy of Prostate Cancer? Is There a Role of Interim PSMA PET in Chemotherapy of Prostate Cancer? Semin Nucl Med 2024;54(1):87–96.
[56] Fanti S, Hadaschik B, Herrmann K. Proposal for Systemic-Therapy Response-Assessment Criteria at the Time of PSMA PET/CT Imaging: The PSMA PET Progression Criteria. J Nucl Med 2020;61:678–82.
[57] Gafita A, Rauscher I, Weber M, et al. Novel Framework for Treatment Response Evaluation Using PSMA PET/CT in Patients with Metastatic Castration-Resistant Prostate Cancer (RECIP 1.0): An International Multicenter Study. J Nucl Med 2022;63:1651–8.
[58] Ilan E, Sandström M, Wassberg C, Sundin A, Garske-Román U, Eriksson B, et al. Dose response of pancreatic neuroendocrine tumors treated with peptide receptor radionuclide therapy using 177Lu-DOTATATE. J Nucl Med 2015 Feb;56(2):177–82. https://doi.org/10.2967/jnumed.114.148437. Epub 2015 Jan 15 PMID: 25593115.
[59] Alipour R, Jackson P, Bressel M, Hogg A, Callahan J, Hicks RJ, et al. The relationship between tumour dosimetry, response, and overall survival in patients with unresectable Neuroendocrine Neoplasms (NEN) treated with 177Lu DOTATATE (LuTate). Eur J Nucl Med Mol Imaging 2023;50(10):2997–3010.
[60] Violet J, Jackson P, Ferdinandus J, Sandhu S, Akhurst T, Iravani A, et al. Dosimetry of 177Lu-PSMA-617 in Metastatic Castration-Resistant Prostate Cancer: Correlations Between Pretherapeutic Imaging and Whole-Body Tumor Dosimetry with Treatment Outcomes. J Nucl Med 2019 Apr;60(4):517–23. https://doi.org/10.2967/jnumed.118.219352. Epub 2018 Oct 5 PMID: 30291192.
[61] Scarpa L, Buxbaum S, Kendler D, Fink K, Bektic J, Gruber L, et al. The $^{68}Ga/^{177}Lu$ theragnostic concept in PSMA targeting of castration-resistant prostate cancer: correlation of SUVmax values and absorbed dose estimates. Eur J Nucl Med Mol Imaging 2017;44(5):788–800. https://doi.org/10.1007/s00259-016-3609-9. Epub 2017 Jan 12 PMID: 28083690.
[62] Maffey-Steffan J, Scarpa L, Svirydenka A, Nilica B, Mair C, Buxbaum S, et al. The 68Ga/177Lu-theragnostic concept in PSMA-targeting of metastatic castration-resistant prostate cancer: impact of post-therapeutic whole-body scintigraphy in

the follow-up. Eur J Nucl Med Mol Imaging 2020 Mar;47(3):695–712. https://doi.org/10.1007/s00259-019-04583-2. Epub 2019 Nov 27.
[63] von Eyben FE, Bauman G, von Eyben R, Rahbar K, Soydal C, Haug AR, Virgolini I, Kulkarni H, Baum R, Paganelli G. Optimizing PSMA Radioligand Therapy for Patients with Metastatic Castration-Resistant Prostate Cancer. A Systematic Review and Meta-Analysis. Int J Mol Sci. 2020 Nov 28;21(23):9054. doi: 10.3390/ijms21239054. PMID: 33260535; PMCID: PMC7730994.
[64] Gafita A, Heck MM, Rauscher I, Tauber R, Cala L, Franz C, et al. Early Prostate-Specific Antigen Changes and Clinical Outcome After 177Lu-PSMA Radionuclide Treatment in Patients with Metastatic Castration-Resistant Prostate Cancer. J Nucl Med 2020;61(10):1476–83. https://doi.org/10.2967/jnumed.119.240242. Epub 2020 Feb 28 PMID: 32111687.
[65] Kind F, Fassbender TF, Andrieux G, Boerries M, Meyer PT, Ruf J. Early PSA Change after [177Lu]PSMA-617 Radioligand Therapy as a Predicator of Biochemical Response and Overall Survival. Cancers (Basel) 2021;14(1):149. https://doi.org/10.3390/cancers14010149. PMID: 35008315; PMCID: PMC8750166.
[66] Kratochwil C, Giesel FL, Stefanova M, Benešová M, Bronzel M, Afshar-Oromieh A, et al. PSMA-Targeted Radionuclide Therapy of Metastatic Castration-Resistant Prostate Cancer with 177Lu-Labeled PSMA-617. J Nucl Med 2016 Aug;57(8):1170–6. https://doi.org/10.2967/jnumed.115.171397. Epub 2016 Mar 16 PMID: 26985056.
[67] Khreish F, Kochems N, Rosar F, Sabet A, Ries M, Maus S, et al. Response and outcome of liver metastases in patients with metastatic castration-resistant prostate cancer (mCRPC) undergoing 177Lu-PSMA-617 radioligand therapy. Eur J Nucl Med Mol Imaging 2021 Jan;48(1):103–12. https://doi.org/10.1007/s00259-020-04828-5. Epub 2020 May 6 PMID: 32378019.
[68] Gupta M, Choudhury PS, Rawal S, Goel HC, Rao SA. Evaluation of RECIST, PERCIST, EORTC, and MDA Criteria for Assessing Treatment Response with Ga68-PSMA PET-CT in Metastatic Prostate Cancer Patient with Biochemical Progression: a Comparative Study. Nucl Med Mol Imaging 2018;52(6):420–9.
[69] Han S, Woo S, Kim YI, Lee JL, Wibmer AG, Schoder H, et al. Concordance between Response Assessment Using Prostate-Specific Membrane Antigen PET and Serum Prostate-Specific Antigen Levels after Systemic Treatment in Patients with Metastatic Castration Resistant Prostate Cancer: A Systematic Review and Meta-Analysis. Diagnostics (Basel) 2021 Apr 7;11(4):663. https://doi.org/10.3390/diagnostics11040663. PMID: 33917006; PMCID: PMC8067707.
[70] Hansen A, Probst S, Tutrone R, et al. Efficacy and safety of 177Lu-PNT2002 prostate-specific membrane antigen (PSMA) therapy in metastatic castration-resistant prostate cancer (mCRPC): initial results from SPLASH Annals of Oncology (2022) 33 (suppl_7): S616 S652.0.1016/annonc/annonc1070.
[71] Rosar F, Dewes S, Ries M, Schaefer A, Khreish F, Maus S, et al. New insights in the paradigm of upregulation of tumoral PSMA expression by androgen receptor blockade: enzalutamide induces PSMA upregulation in castration-resistant prostate cancer even in patients having previously progressed on enzalutamide. Eur J Nucl Med Mol Imaging 2020;47(3):687–94.
[72] Emmett L, Subramaniam S, Joshua AM, Crumbaker M, Martin A, Zhang AY, et al. ENZA-p trial protocol: a randomized phase II trial using prostate-specific membrane antigen as a therapeutic target and prognostic indicator in men with metastatic castration-resistant prostate cancer treated with enzalutamide (ANZUP 1901). BJU Int 2021;128(5):642–51.
[73] Emmet L et al. Enzalutamide and 177Lu-PSMA-617 in poor-risk, metastatic, castration-resistant prostate cancer (mCRPC): A randomised, phase II trial: ENZA-p (ANZUP 1901). ESMO 2023, Abstract LBA84.
[74] Nonnekens J, van Kranenburg M, Beerens CEMT, Suker M, Doukas M, van Eijck CHJ, et al. Potentiation of peptide receptor radionuclide therapy by the PARP inhibitor olaparib. Theranostics 2016;6(11):1821–32.
[75] Sandhu S, Joshua AM, Emmett L, et al. LuPARP: Phase 1 trial of 177Lu-PSMA-617 and olaparib in patients with metastatic castration resistant prostate cancer (mCRPC). J Clin Oncol 41, no. 16_suppl (June 01, 2023) 5005-5005. 10.1200/JCO.2023.41.16_suppl.5005.
[76] Aggarwal RR, Sam SL, Koshkin VS, et al. Immunogenic priming with 177Lu-PSMA-617 plus 10.1200/JCO.2021.39.15_suppl.5053 Journal of Clinical Oncology 39, no. 15_suppl (May 20, 2021) 5053-5053.