Republic of Iraq

Ministry of Higher Education and Scientific Research

University of Diyala College of Medicine

Efficacy and Safety of Lu-177-PSMA Therapy in Metastatic Prostate Carcinomas

Research presented by

Ali Faisal Taha

Under Supervision of

Professor DR .Suad Muslih _Aldeen abdul _majeed

Department of physiology

بسم الله الرحمن الرحيم

وَقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ عَمَلَكُمْ وَرَسُولُهُ وَالْمُؤْمِنُونَ وَسَتُرَدُّونَ إِلَى عَالِمِ الْغَيْبِ وَالشَّهَادَةِ فَيُنَبِّئُكُمْ بِمَا كُنْتُمْ تَعْمَلُونَ»

صدق الله العظيم

Appreciation

I would like to thank Professor .(Suad Muslih _Aldeen) my teacher and supervisor for guiding me in the article by correcting the mistakes and giving her valuable opinions in many aspect in both scientific facts and literature ones. I hope all the best and successes to her in her career future.

Abbreviations

- **CRPC (castrate-resistance prostatic cancer)**
- **DRE (digital rectal exam)**
- **FDA (Food and Drug Administration)**
- **PSA (prostate-specific antigen)**
- **PSMA (prostate specific membrane antigen)**
- **mCRPC (metastasis castrate-resistance prostatic cancer)**
- **RPT (Radiopharmaceutical therapy)**
- **UBA (urea-based antagonists)**
- **EB-PSMA-617 (Evans blue adapted PSMA-617)**
- **RLT (radioligand treatment)**
- **GBM (Glioblastoma multiforme)**

- **Gbq (Gigabecquerel)**
- **MIRD (Medical Internal Radiation Dose)**
- **VOIs (volumes of interest)**
- **VKC (voxel kernel convolution)**
- **SPECT (Single-photon emission computed tomography)**
- **(PFS) (Progression-free survival)**
- **(OS) (overall survival)**
- **(QOL) (quality of life)**
- **NADH (Nicotinamide adenine dinucleotide)**

Aim of the study

The effectiveness of . ^{177}Lu -PSMA treatment, its administration and side effects

Abstract

This narrative review aims to summarize the present state of . ^{177}Lu -PSMA (prostate specific membrane antigen) treatment for prostate carcinomas and further discusses patient preparation, administration of medication, and side effect profiles. Besides the predictor parameters, the effectiveness of . ^{177}Lu -PSMA treatment was evaluated using prospective studies, meta-analyses, and large retrospective studies. Although . ^{177}Lu -PSMA treatment tend to be used as last options, this type of treatment is typically safe with minimal toxicity. As a result, . ^{177}Lu -PSMA therapy is a viable therapeutic option for individuals with prostate carcinoma, and it showed high clinical effectiveness in patients who were resistant to several lines of systemic therapy. Several clinical studies are now underway in the United States, including a phase III multicenter FDA registration study.

Keywords: *prostate cancer, Lu-177-PSMA, metastasis*

1- Introduction

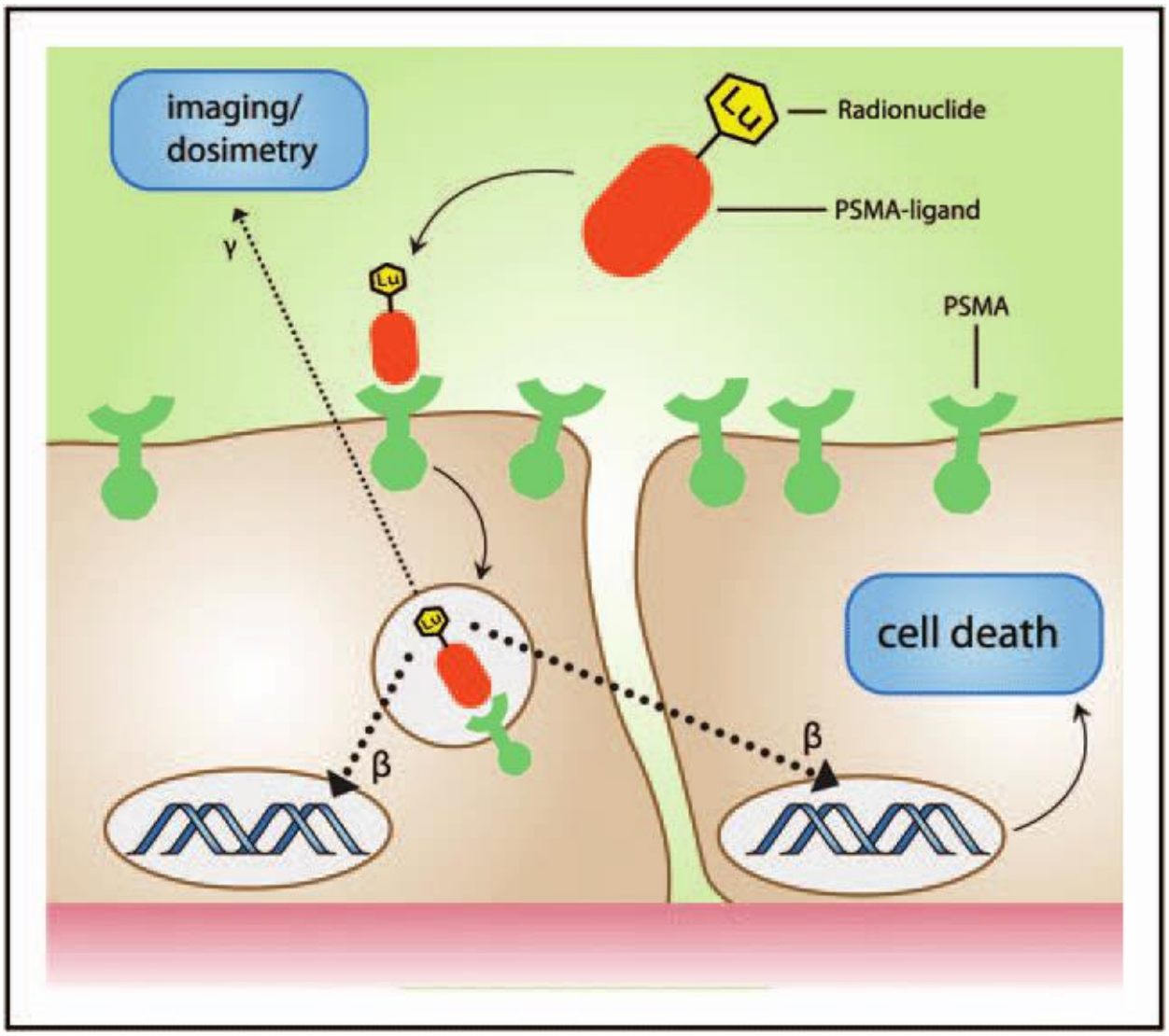
One of the major causes of death across the world is cancer (1-3). After lung cancer, prostate cancer is the second most frequent cancers in males globally. Prostate cancer accounts for around 7.1 percent of newly diagnosed cancer cases and 3.8 percent of cancer mortality worldwide according GLOBOCAN estimation in 2018 (4). Also, a recurrence may occur in one third of male patients with localized treatment. Postoperative recurrence happens in about 15% of patients within 5 years and up to 40% within 10 years. Ultimately, patients with recurrent disease develop androgen ablation-resistant malignant cells. Although these epidemiological data highlights a low death rate among prostate cancer cases, those with advanced prostate cancer may eventually develop castrate-resistance prostatic cancer (CRPC) (5).

With advances in surgical resection, radiotherapy, chemotherapy and hormonal therapy, the ability to diagnose and treat primary prostate cancer has improved (6). Primary diagnosis of prostate cancer is made through digital rectal exam (DRE), increase serum prostate-specific antigen (PSA) levels, and ultrasound guided biopsy of the prostate (6, 7). If the cancer advances, androgen deprivation therapy and chemotherapy are possibilities for individuals who have not undergone radical prostatectomy or primary radiotherapy. Progression to a metastatic CRPC (mCRPC) is still concerned as patients may temporarily response to chemotherapy modality (8, 9). Metastatic type of castrate-resistant prostatic cancer is the last stage of this cancer and it is still a lethal illness (6). In the last decade, radiopharmaceutical agents have been invented to target membrane-specific proteins in some malignancies. Scientists have recently addressed radio-nuclide

therapy using prostate-specific membrane antigen (PSMA) as a safe treatment option for mCRPC patients (9). PSMA belongs to the M28 peptidase family and is a type II transmembrane glycoprotein functioning as glutamate carboxypeptidase on nutrient folate and other substances (6). Membrane of prostate epithelial cells is the major place where PSMA is normally produced, and the involvement of these cells in prostate cancer significantly overexpresses PSMA up 100 to 1000 times of normal level .PSMA expression increases on the surface of malignant prostatic cells with the severity of prostate cancer. This feature makes PSMA an excellent choice for a targeted therapy and cancer imaging (4, 6). Radiopharmaceutical therapy (RPT) is gaining popularity as a safe and effective way to treat a number of cancers and in the case of prostate cancer mainly targets different biophysical properties of PSMA (10). Radiation-induced cell death is the mechanism of action for RPT. In comparison to practically all systemic cancer therapy approaches, RPT has proven effectiveness with low toxicity. RPT engages pharmacological substances binding either selectively to malignant cells or accumulate using physiological pathways to distribute radiation systemically or locally. Almost all of the radionuclides utilized in RPT express imageable photons, allowing for safe simulation of therapeutic substance's biodistribution. Extraordinary promise of this therapy is now being recognized, thanks to the latest FDA approval of multiple RPT substances. Owing to expression of PSMA on the neovasculature of tumors, tiny-molecule PSMA inhibitors have thus been adapted to render radiotherapeutic nuclides in both prostatic cancers and other types. PSMA antagonists are constituted to resemble the neuropeptide N-acetylaspartylglutamate153, 154 and its related substrates, including glutamyl-folic acid derivatives. The small molecule RPT substances can function as urea-based antagonists (such as ^{177}Lu-labelled PSMA-R2 and ^{177}Lu-labelled PSMA-617)[155,156,157,158,159,160,161,162] or phosphoramidate-based antagonists (such as 177Lu-labelled CTT-1403) which

both have been modified to be therapeutic radionuclides[163, 164,165](11). The strongest of these was Lutetium-177-PSMA ([177Lu]-PSMA-617) which attaches to PSMA with an extreme affinity, and destroys PSMA in the cell(10). Many studies have shown that drugs like 177Lu-PSMA are safe and successful for prostate cancer patients. The toxicity of 177Lu-PSMA is mild and 70% of patients respond positively to this procedure with a decrease in PSA levels in their serum (6). Since 177Lu-PSMA is a small molecule that is easily removed from the bloodstream, radiotherapy requires a high level of therapy and regular administrations. Evans blue adapted PSMA-617 (EB-PSMA-617) that binds to both serum albumin and PSMA was synthesized, conjugated to DOTA chelator, and labelled with 177Lu to maximize tumor uptake and boost radiotherapeutic efficacy(12). Lu-PSMA-617 uses -particulate emission with a 0.7 mm mean path duration to expose the prostatic cancerous cell with high radiation. As the radiation conducted with short wavelength, tumors are targeted more precisely, and normal tissues are spared from the damage. Several non-randomized trials of males with metastatic CRPC whose disease progressed after routine treatment encouraged the scientists to study the usage of RPT in prostate cancer (13).

177Lu-PSMA-617 has been utilized in radioligand treatment (RLT) for metastatic castration-resistant prostate cancer (mCRPC) in numerous wide and well-designed trials (4). Hence, this review discusses the efficacy of Lu-177-PSMA treatment and its safety in metastatic prostate carcinomas.



^{177}Lu-PSMA

177Lutetium (177Lu) has gained popularity as the therapeutic radionuclide of choice due to its desirable physical properties. Ideally, the emission characteristics of a therapeutic radionuclide should match the lesion size/volume to be treated to ideally focus energy within the tumour rather than in the tissue surrounding the lesion. ^{177}Lu is a medium-energy β-emitter (490 keV) with a maximum energy of 0.5 MeV and a maximal tissue penetration of <2 mm. The shorter β-range of 177Lu provides better irradiation of small tumours, in contrast to the longer β-

range of 90Y . 177Lu is a reactor produced radiometal that emits low-energy γ-rays at 208 and 113 keV with 10 and 6% abundance respectively. The gamma emission from 177Lu allows for ex vivo imaging and consequently the collection of information pertaining to tumour localisation and dosimetry. Furthermore, 177Lu has a relatively long physical half-life of 6.73 days. It is these physical properties that allow for the delivery of high activities of 177Lu PSMA to prostate cancer cells

2- What is PSMA

Prostate specific membrane antigen is a type II transmembrane glycoprotein encompassing 750 amino acids (14, 15). PSMA has a variety of biological roles and serves as a nutrient-uptake enzyme (folate). Also, it contributes in cell movement, cell viability, and cell proliferation (16). However, PSMA glycoprotein is moderately produced in healthy prostate epithelial cells, but its expression elevates up to 100-1000 times more in most of prostate malignancies, except 5–10% of prostate tumors which do not overexpress PSMA (17). Through an internalization mechanism, PSMA receptors facilitate the endocytosis of the protein bound on them into an endosomal compartment, and thus permit PSMA labeled radioisotopes to

accumulate inside the cell (18). The expression of PSMA is characterized by a tall Gleason score, metastasis, and hormone resistance (18). PSMA is not just found in the prostate; small intestine tract, proximal renal tubules, salivary organs, liver, spleen and other tissues are also other sites where PSMA can be found (17, 19). Although PSMA expression on these cells is substantially lower than that of prostate cancer cells, administration of radionuclide treatment provided for prostatic malignant cell may also influence other nonspecific cells when PSMA is the target of choice(20). Hence, both unfavorable impact of PSMA-targeted treatment and a safe level of radiation are concerned in order to avoid serious radiation harm to non-target organs. (21). PSMA overexpression on the cell surface is not restricted to prostatic cancer and it has also been found in clear cell renal carcinoma. Staging of renal cancer using PSMA was also conducted in some case reports (22). Moreover, detection of other tumors by PSMA-based imaging is possible; however, those cells may not have an overexpression of the PSMA receptor on their cell surface. In fact, PSMA receptor is majorly expressed on the endothelial cells of tumor-related microvessels or in 'neo- angiogenesis'. Glioblastoma multiforme (GBM), colorectal, gastric, and squamous cell malignancies of the head and neck are some tumors showing this feature (23, 24).

3- Why is PSMA tagged with lutetium? The Physical characteristics of Lu177.

Due to its excellent physical properties, lutetium (177Lu) has become a favorable radionuclide (26). A therapeutic radionuclide ought to ideally match in terms of emission properties to the injury size or its volume and focus energy inside the tumor instead of the surrounding tissue (27). Lutetium 177 is characterized as a medium-energy b emitter (490 keV) with a maximum energy of 0.5 MeV and tissue penetration of <2 mm (28). In comparison to 90Y with a longer b-range, 177Lu has

a shorter b-range which allows irradiation exposure of small size tumor better (Table 1). 177Lu is a radio metal created in a reactor that produces low-energy c-rays at 208 and 113 keV with a tenth- and sixth-percent abundance, respectively. Furthermore, 177LU has a physical half-life of 159.6 hours which is a significantly lengthy half-life. These physical features enable 177Lu PSMA to deliver substantial activity levels to malignant prostatic cells (29).

4- PSMA labeling with Lu 177 peptides: diverse small compounds with high affinity to PSMA

A variety of small molecule with high PSMA affinity have been used as therapeutic agents in men with metastatic castrate-resistant prostate cancer in both clinical trials and clinical practice. These include the PSMA–DKFZ-617 molecule, which has been used to treat most patients in the published literature too far. Rather than an antibody, this is a tiny molecule peptide that has been chemically attached with 177Lutetium. It exhibits a high efficiency of internalization into prostate cancer cells in mice, with around 75% of the peptide linked to the cell internalized after 3 hours of incubation (25). In addition, 177Lu PSMA-I&T is a similar small molecule PSMA peptide ending with a different chemical conjugation can be used as a therapeutic drug (26). On the other hand, 177Lu-J591, a monoclonal antibody to the PSMA receptor, has been used to treat prostate cancer with good results; although, it has more limited response and stronger myelosuppression than the smaller PSMA tagged peptides (27).

5- Dosage measurement

The standard given dose of 177Lu PSMA has changed over the experiments conducted by institutions to evaluate safety and toxicity. Infused dose has ranged from 3 to 8 GBq per each injection in males receiving up to 6 injections at a minimum 6-weekly interval (31). Each patient dosage was measured according to a

combination of illness severity, patient's weight, and renal function. A volume of 5 ml Lu PSMA diluted in 0.9% normal saline is slowly and intravenously infused in 30–60 seconds, followed by a flush of 0.9 percent normal saline. Patients should be hydrated with 1-1.5 L of water before and after administration of 177LU PSMA and advised to urinate frequently (31).

6- Dosimetry of the treatment with lutetium 177 PSMA

The safety and effectiveness of a targeted therapy with radionuclide may improve with the use of the patient-specific dosimetry (32). The damage of renal, salivary and lacrimal glands due to radiation is particularly expected in 177Lu PSMA treatment (28, 29). Therefore, each treatment cycle is strongly suggested for image-based dosimetry. In order to assess the activity accumulation and deterioration rate of susceptible organs, dosimetry necessitates patient imaging at several times post-administration (i.e., at 4, 24 and 96 h post-injection). The longer the dosage points are gathered, the more exact the dosage estimations are. In this regard, 3D imaging specifically quantitative SPECT/CT is a favored tool to do dosimetry (30). There are some limitations as planar data may be used to make 2D absorbed dose calculations, especially in the form of structural overlaps, and it most likely cause absorbed dose overestimations (31, 32). Two-dimensional dosimetry requires no software and is usually done in conjunction with the MIRD technique for the complete body geometrically with attenuation and dispersive correction (model-based estimation of the absorbed dose) (8). SPECT may help to prevent the overlapping between planar and MIRD techniques and eliminates tumors in hand-drawn VOIs (volumes of interest) even for the organ- specific metastatic tumors to make an estimation (33). Before the application of an energy sensitivity factor for camera window and collimator, quantitative SPECT needs to be adjusted for scattered and attenuated

photons, dead time and the blurring of remote-dependent detector (34). Nevertheless, without any standardized method to all these, adjustments could also be subjective in the consideration of tiny organs including kidney, lacrimal and salivary glands. 3D data can be also used for dose mapping via voxel kernel convolution (VKC), which measures the deposition of 177Lu particles in the surrounding tissue. VKC depends on the mean volume of a model organ and has the advantage of giving 3D maps and histograms with dose volume for evaluating sub-organ dosage. Any form of dosimetry may be utilized to suggest the safety of further processing cycle and prevent toxicity. The present critical dosage threshold is 23Gy, and 5% of the associated side effects occur in a five-year period (35). The absorbed renal dosage from a targeted radionuclide treatment, particularly 177Lu PSMA, has typically been found to be far below the dose-limiting threshold of 23 Gy(41). Baum et al (42) obtained an average renal dosage of 0.8 m Gy/MBq based on temporal data for the total body in 56 people with castrate-resistant prostate cancer (about 4.6 Gy per cycle based on the reported median activity of 5.76 GBq). This can be comparable to Delker et al.'s study investigating five patients with a novel ligand, 177Lu DFKZ-PSMA-617, with a mean renal absorbed dose of 2.2 Gy (43). In both studies, parotid salivary glands absorbed higher dosage with an average parotid dose of 7,5 Gy compared to than that of kidney with average renal dose of 5,1 Gy in each cycle. Jackson et al (2020) used a single posttreatment SPECT/CT scan and conducted another study to evaluate Radiation Dosimetry in 177 Lu-PSMA-617 treatment. They measured specific dose conversion factors at single time points 11.0, 12.1, 13.6, and 15.2 Gy per MBq/mL for imaging times of 24, 48, 72, and 96 h, respectively. In this regard, parotid demonstrated single-time-point dose factors of 6.7, 9.4, 13.3, and 19.3 Gy per MBq/mL at these intervals, whereas renal factors were 7.1, 10.3, 15.0, and 22.0 Gy per MBq/mL. The most accurate dosage estimations were made when delayed scanning was performed after 72 h. Since,

there is greater degree of tracer elimination at early period, patients should be scanned within the first 2 days in order to assess optimally the dose to healthy tissues. Jackson et al. showed us a way to predict an effective dosage in 177Lu-PSMA-617 treatment. The researchers try to develop dose-response models for this specific treatment area and thus ease and automate the process of radiation dosimetry (36).

7- Current clinical evidence in prostate cancer for use of Lu PSMA

There are few published studies which investigated the use of Lu PSMA in treatment of mCRPC patients (approximately 245 patients). These are mostly modest retrospective studies, but they have demonstrated that there is a substantial percentage of males who are treated with 177 Lu PSMA with a substantial therapeutic response (37-44).

8- Efficacy of the treatment

According to the present research, the proportion of men who have a >50% drop in blood PSA (prostate specific antigen) levels varies from 30% to 70%, which corresponds well to the PSA response rates attained by chemotherapeutic drugs used in mCRPC (Cabazitaxel and Docetaxel)
(45). About 10 to 32% of individuals are resistant to 177Lu PSMA treatment with progressing illness. One of the largest trials with 56 men reported that 80% of their patients had a PSA response to medication. All recently published research investigating 177Lu PSMA therapy in prostate cancer are retrospective, and had employed different of therapeutic interventions, both in dosage (ranging from 3.5 to 8.0 Gbq/injection of Lu PSMA) and number of doses (ranging from one single injection to 4–6 injections 6 weeks apart). This makes it difficult to determine the effectiveness of the therapy at this point. According to the studies conducted to date, a considerable number of males with mCRPC who were managed with all other treatment options faced an unsuccessful therapy. The randomized studies with overall survival power have previously proven survival advantages, hence the next

step must be a prospective investigation of 177Lu PSMA effectiveness. Based on retrospective with one single injection, there is limited data regarding the probable survival advantage of Lu PSMA treatment in males with metastatic CRPC. A trial with 56 patients receiving up to 5 Lu PSMA injection at intervals of six weeks believes that survival improvements may exist (38). The research revealed that 12 individuals died over a 28-month follow-up period (21.4 percent) and the survival rate was 78.6 percent after 28 months with a median progression of 13.7 months. Therefore, any possible survival advantage with 177 Lu PSMA in males with progressed prostate carcinoma must be confirmed by future randomized studies (37-44). Moreover, 30 males with mCRPC were studied who had previously utilized treatment alternatives including docetaxel (87% efficacy), cabazitaxel (47% efficacy) and abiraterone (83% efficacy), and/or enzalutamide (83% efficacy). In this clinical trial, the state of disease development and the presence of side effects were observed in patients receiving 1 to 4 weekly intravenous treatments of 177Lu-PSMA-617. Progression-free survival (PFS) and overall survival (OS), as well as imaging responses along with quality of life (QOL), were other objectives examined in the study in addition to PSA response rate (50% drop from baseline). Almost two-thirds of the patients achieved the PSA response, while the remaining patients had some degree of PSA response. Two third of the prostate cancer cases with complete response, partial response, and stable disease had progressed in healing 3 months after the last injection, while the rest of the patients got better three months after the last. Of the 27 patients who developed PSA progression during follow-up, the average time to PSA elevation and the median overall survival (OS) were 7.6 and 13.5 months, respectively. The majority (87%) of the patients who received 177Lu-PSMA-617 treatment had only mild adverse effects such as dry mouth. Additionally, the pain of research participants had reduced considerably at all study time points that improved the patients' quality of life. In a multicenter research, the activity and

safety of 177Lu-PSMA-617 treatment to cabazitaxel was compared with randomized trials. In this multicentral study, the patients with 177Lu-PSMA-617 therapy demonstrated larger reduction in PSA level than those in the cabazitaxel-assigned group. The PFS results of the study showed that the patients treated with 177Lu-PSMA-617 had better progression-free survival after a year (19 vs. 3 percent). On the other hand, patients of cabazitaxel group experienced more common the grade 3–4 side effects (33% with grade 3 thrombocytopenia, 53% with Grade 4 thrombocytopenia, and 11% with Grade 3–4 neutropenia) In other words, there is no doubt that the evidence favors efficacy of 177Lu-PSMA-617 is more reliable than those of cabazitaxel is reliable, hence these information do not included in the main body of this review for the purpose of conciseness (46, 47). A new meta-analysis published by Kim et al. gathered all previously accessible data including 455 patients from 10 retrospective studies with satisfactory results (48). Kim et al. elucidated that 2/3 of any reduction and 1/3 of reduction of >50% in PSA level can occur by the 1st injection of 177Lu-PSMA-617 treatment. Any time there was a reduction in PSA levels after the cycle of treatment, people lived longer. This result was also corroborated by a more recent meta-analysis by Calopedos et al. with inclusion of 10 studies, as they showed that collectively 68% of patients responded with any decline in serum PSA values, and 37% of patients had a biochemical response of >50% decline in PSA. The authors found that a drop of PSA serum level was noticed in 71% of patients treated with 177Lu-PSMA-617/I&T (49). In the most current study by Von Eyben et al., 2346 patients who had been treated with PSMA radionuclide were reviewed and analyzed. They reported a median overall survival of 16 months for asymptomatic individuals with lymph node metastases only, and showed a shorter survival time for symptomatic patients and those with more advanced cancer (50).

9- Response prediction

On the other hand, 177Lu PSMA response is not satisfactory in all mCRPC cases. Progressive cancer has been reported in 1/3 of the patients treated to date. The heterogeneity in activation of PSMA receptors within the tumor population may result in some cases who are resistant to 177Lu PSMA. Current activity of PSMA is assessed using a 68Ga-PSMA PET/CT method and is a therapeutic prerequisite for all published trials. However, the cutoff value for PSMA intensity using 68Ga-PSMA have not yet been determined to monitor the success of 177Lu PSMA treatment. The most important predictor of poor response to 177 LU PSMA was recently discovered as the platelet level and pain level, possibly reflecting the burden of metastatic bone disease (51). Compared to visceral or nodal lymph node disorders, it was noted that bone metastases seem poorly respond to therapy with Lu PSMA (52). According to Rathke et al. (2018), serum PSA, LDH, and CgA had a baseline and follow-up level and thus can be used as response predictors for 177Lu-PSMA-617 treatment. Baseline level of PSA (a marker for the possible onset of disease) played no prognostic role in prediction of treatment response; in contrast, the findings indicated that baseline serum LDH (a marker for the presence of disease) had the most predictive value and elevated serum LDH levels indicate a greater risk of disease progression when patient are under PSMA ligand therapy. Regarding indicators of poor prognosis, elevated CgA had a modest contribution but was more accurate when the existence of liver metastases was indicated (53).

10- Toxicity and adverse effects

In all published studies, the rate of toxicity in 177Lu PSMA therapy was low. The most vulnerable sites of toxication are kidneys, salivary glands, lacrimal glands and bone marrow.

However, the documented side effects associated with 177Lu-PSMA treatment were modest and reversible (54). Following a treatment, more than thirty pecrcent of

males reported dry mouth or xerostomia. In up to 25% of the men treated, fatigue is the common side effect. Nausea may also be important in up to 10% of males, especially 24-48 hours prior the therapy. Although toxicity in kidneys have not been addressed yet, but this will likely cause a permanent renal dysfunction if it occurs. The most reported serious complication associated with the 177Lu PSMA therapy is haematological toxicity such as grade 3–4 toxicities, anemia (10%), leukopenia (3%) and thrombocylopenia (4%).However, the study of ALSYMPCA (alpharadin in SYMptomatic Prostate Cancer) reported that the patients of placebo group (1–14%) and those treated with 223Ra (3–13%) did not differ significantly in terms of complications rate (55). Despite low rates of hematotoxicity in 177Lu-PSMA-617 therapy, 46.8 (29.8% had platelet transfusions) and 25.5% of patients in the 177Lu-PSMA-J591 Phase 2 trial have been documented with reversible grade 4 thrombocytopenia and grade 4 neutropenia, respectively (42). Hematologic toxicities seem to be an innocent bystander effect in men with severe bone metastases and poor marrow function, rather than a product of direct exposure of bone marrow to radiation. A grade 1-2 reduction of hemoglobin or platelets was observed in 10-25% of the men with massive skeletal metastasis. Also, intoxication at bone marrows is not significant if the patient is free of skeletal metastases. For treatment of severe bone metastasis cases, 177Lu with larger range will likely to have a higher radiant dose than therapies with alpha emitters such as Radium 233. Preliminary studies in men with advanced involvement of bones found that the bone marrow is relatively spared in treatments using a PSMA-labeled alpha emitter using 225 AC(actinium) PSMA-617 (43). The second most frequent adverse effect is xerostomia with a rate of 8-11% (56). In 87% of patients who had no external cooling in the salivary gland, however, minor xerostomia was identified. Current investigations have not demonstrated nephrotoxicity of grade 3–4 (57).

11- Perspectives for the treatment in the future

It seems that in most of the researches on the radionuclides' effectiveness, Lu-PSMA treatment is employed as the main endpoint of the PSA reduction. Even though this endpoint is often recognized as a proxy for response to treatment, its reliability is debated (58). Regarding TAX-327, the researchers found that a same PSA response was achieved with a weekly docetaxel program, and no survival advantage was observed for weekly regimens compared to regimens with 3 injections at a week (59). In a trial by Barber et al., the PSA responseto 177Lu-PSMA-617/I&T treatment was not significant, whereas patients treated with T-pretreated or T-naïve had significantly better survival outcomes (60). Although the relationship between PSA drops and survival benefit is poor, practically all studies examining the effectiveness of 177Lu-PSMA treatment found no correlation between them. Therefore, prospective clinical trials that use objective endpoints are essential to ascertain the survival benefit of 177Lu-PSMA treatment. Nowadays, the clinicians administer 177Lu-PSMA therapy as a last the treatment choice for patients with metastatic CRPC. Our review showed that prostate cancer has remarkably advanced in patients treated with docetaxel, cabazitaxel, abiraterone, enzalutamide, and 223Ra. However, there is no knowledge whether the first line use of 177Lu-PSMA therapy can result in therapeutic response in early scenario. Hence, comparative investigations are required immediately. Despite the limited data yield for 177Lu-PSMA treatment, we feel that the future of theranostics in mCRPC is bright, since theranostics for PCa will almost certainly make an excellent partner for combination treatments. Combination techniques based on the concept of utilizing medications with distinct mechanisms of action are usually considered to be more successful than single drug administrations and have been already utilized in clinical practice for a variety of malignancies, including PCa. In this regard, a randomized trial which compared the efficacy of combined chemo-hormonal with androgen ablation treatment and a study of systemic therapy in mCRPC supported the efficacy of combining therapies in

metastatic PCa (61, 62). Similarly, Murga et al. demonstrated that inhibiting androgen receptor pathways may boost PSMA expression and result in the development of novel combination regimens (63). In consistence, Basu et al. stated that when a second-generation antiandrogen medication, namely abiraterone, was paired with 177Lu-PSMA, the outcomes were favorable. Additionally, the authors advised using a low-dose corticosteroid to avoid any potential symptomatic flare reaction and to avoid abiraterone's mineralocorticoid excess. Finally, idronoxil, an external NADH oxidase type 2 inhibitor, is utilized to radiosensitize patients receiving 177Lu-PSMA treatment. Crumbaker et al. reported no significant toxicity in published phase 1 clinical study in which idronoxil was used in combination with 177Lu-PSMA-617 (64). Considering the low safety profile and strong efficacy of 177Lu-PSMA, it may eventually be used in combination therapy (65).

12- Conclusions

Apparent clinical benefits of 177Lu-PSMA therapy are undeniable, particularly in those patients who had been previously treated with several lines of systemic medication. 177Lu-PSMA therapy seems to be safe and free of toxicity. Also, early research shows that a combination of 177Lu-PSMA treatment prior to other systemic therapies and early in the course of the illness is more beneficial . Therefore, this alternative could be most likely placed somewhere before the final treatment step ofmCRPC in future, but it may be supplemented with other systemic treatments.

1. Mishan MA, Tabari MAK, Parnian J, Fallahi J, Mahrooz A, Bagheri AJG, Chromosomes, et al. Functional mechanisms of miR-192 family in cancer. 2020;59(12):722-35.
2. Mishan MA, Tabari MAK, Zargari M, Bagheri AJEJoP. MicroRNAs in the anticancer effects of celecoxib: A systematic review. 2020:173325.
3. Mishan MA, Tabari K, Mahrooz A, Bagheri AJEJoCPtOJotECPO. Role of microRNAs in the anticancer effects of the flavonoid luteolin: a systematic review. 2021.
4. Kelk E, Ruuge P, Rohtla K, Poksi A, Kairemo K. Radiomics Analysis for 177Lu-DOTAGA-(ly) fk (Sub-KuE) Targeted Radioligand Therapy Dosimetry in Metastatic Prostate Cancer—A Model Based on Clinical Example. Life. 2021;11(2):170.

5. Bansal D, Reimers MA, Knoche EM, Pachynski RK. Immunotherapy and Immunotherapy Combinations in Metastatic Castration-Resistant Prostate Cancer. Cancers. 2021;13(2):334.
6. Ghodsirad MA, Pirayesh E, Akbarian R, Javanmard B, Kaghazchi F, Tavakoli M, et al. Diagnostic Utility of Lutetium-177 (Lu 177) Prostate-Specific Membrane Antigen (PSMA) Scintigraphy In Prostate Cancer Patients With PSA Rise And Negative Conventional Imaging. Urology journal. 2020;17(4):374-8.
7. Lin M, Ta RT, Kairemo K, Le DB, Ravizzini GC. Prostate-Specific Membrane Antigen-Targeted Radiopharmaceuticals in Diagnosis and Therapy of Prostate Cancer: Current Status and Future Perspectives. Cancer Biotherapy & Radiopharmaceuticals. 2020.
8. Emmett L, Willowson K, Violet J, Shin J, Blanksby A, Lee JJJomrs. Lutetium 177 PSMA radionuclide therapy for men with prostate cancer: a review of the current literature and discussion of practical aspects of therapy. 2017;64(1):52-60.
9. Kamaldeep, Wanage G, Sahu SK, Maletha P, Adnan A, Suman S, et al. Examining Absorbed Doses of Indigenously Developed 177Lu-PSMA-617 in Metastatic Castration-Resistant Prostate Cancer Patients at Baseline and During Course of Peptide Receptor Radioligand Therapy. Cancer biotherapy & radiopharmaceuticals. 2020.
10. Gadot M, Davidson T, Aharon M, Atenafu EG, Malki A, Levartovsky M, et al. Clinical variables associated with PSA response to lutetium-177-PSMA ([177Lu]-PSMA-617) radionuclide treatment in men with metastatic castration-resistant prostate cancer. Cancers. 2020;12(5):1078.
11. Sgouros G, Bodei L, McDevitt MR, Nedrow JR. Radiopharmaceutical therapy in cancer: clinical advances and challenges. Nature Reviews Drug Discovery. 2020;19(9):589-608.
12. Zang J, Liu Q, Sui H, Wang R, Jacobson O, Fan X, et al. 177Lu-EB-PSMA radioligand therapy with escalating doses in patients with metastatic castration-resistant prostate cancer. Journal of Nuclear Medicine. 2020;61(12):1772-8.
13. Hofman MS, Emmett L, Sandhu S, Iravani A, Joshua AM, Goh JC, et al. [177Lu] Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. The Lancet. 2021.
14. Kwon H, Lim H, Ha H, Choi D, Son S-H, Nam H, et al. Structure-activity relationship studies of prostate-specific membrane antigen (PSMA) inhibitors derived from α-amino acid with (S)-or (R)-configuration at P1′ region. Bioorganic Chemistry. 2020;104:104304.
15. Bacich DJ, Pinto JT, Tong WP, Heston WD. Cloning, expression, genomic localization, and enzymatic activities of the mouse homolog of prostate-specific membrane antigen/NAALADase/folate hydrolase. Mammalian Genome. 2001;12(2):117-23.
16. Lüttich L, Besso MJ, Heiden S, Baumann M, Krause M, Dubrovska A, et al. Tyrosine Kinase c-MET as Therapeutic Target for Radiosensitization of Head and Neck Squamous Cell Carcinomas. Cancers. 2021;13(8):1865.
17. Pianou NK, Stavrou P, Evangelia Vlontzou M, Phivi Rondogianni M, Demetrios N, Exarhos M, et al. More advantages in detecting bone and soft tissue metastases 18 from prostate cancer using F-PSMA PET/CT. Hell J Nucl Med. 2019;22:6-9.
18. Gupta M, Karthikeyan G, Choudhury P, Babu Koyyala VP, Sharma M, Jain P, et al. A walk with Lu-177 PSMA: How close we have reached from bench to bedside? Cancer Investigation. 2020;38(8-9):486-92.
19. Khawar A, Eppard E, Sinnes JP, Roesch F, Ahmadzadehfar H, Kürpig S, et al. [44Sc] Sc-PSMA-617 biodistribution and dosimetry in patients with metastatic castration-resistant prostate carcinoma. Clinical nuclear medicine. 2018;43(5):323-30.
20. Delker A, Fendler WP, Kratochwil C, Brunegraf A, Gosewisch A, Gildehaus FJ, et al. Dosimetry for 177 Lu-DKFZ-PSMA-617: a new radiopharmaceutical for the treatment of metastatic prostate cancer. European journal of nuclear medicine and molecular imaging. 2016;43(1):42-51.

21. Okamoto S, Thieme A, Allmann J, D'Alessandria C, Maurer T, Retz M, et al. Radiation dosimetry for 177Lu-PSMA I&T in metastatic castration-resistant prostate cancer: absorbed dose in normal organs and tumor lesions. Journal of Nuclear Medicine. 2017;58(3):445-50.
22. Van de Wiele C, Sathekge M, De Spiegeleer B, De Jonghe PJ, Beels L, Maes A. PSMA-targeting positron emission agents for imaging solid tumors other than non-prostate carcinoma: a systematic review. International journal of molecular sciences. 2019;20(19):4886.
23. Evazalipour M, Tehrani BS, Abolhassani M, Morovvati H, Omidfar K. Camel heavy chain antibodies against prostate-specific membrane antigen. Hybridoma. 2012;31(6):424-9.
24. Haffner MC, Kronberger IE, Ross JS, Sheehan CE, Zitt M, Mühlmann G, et al. Prostate-specific membrane antigen expression in the neovasculature of gastric and colorectal cancers. Human pathology. 2009;40(12):1754-61.
25. Kratochwil C, Haberkorn U, Giesel FL, editors. 225Ac-PSMA-617 for therapy of prostate cancer. Seminars in nuclear medicine; 2020: Elsevier.
26. Yusufi N, Wurzer A, Herz M, D'Alessandria C, Feuerecker B, Weber WA, et al. Comparative preclinical biodistribution, dosimetry and endoradiotherapy in mCRPC using 19F/177Lu-rhPSMA-7.3 and 177Lu-PSMA I&T. Journal of Nuclear Medicine. 2020.
27. Sun M, Niaz MJ, Niaz MO, Tagawa ST. Prostate-Specific Membrane Antigen (PSMA)-Targeted Radionuclide Therapies for Prostate Cancer. Current Oncology Reports. 2021;23(5):1-11.
28. Cremonesi M, Ferrari M, Di Dia A, Botta F, De Cicco C, Bodei L, et al. Recent issues on dosimetry and radiobiology for peptide receptor radionuclide therapy. 2011;55(2):155.
29. Ljungberg M, Celler A, Konijnenberg MW, Eckerman KF, Dewaraja YK, Sjögreen-Gleisner KJJonm. MIRD pamphlet no. 26: joint EANM/MIRD guidelines for quantitative 177Lu SPECT applied for dosimetry of radiopharmaceutical therapy. 2016;57(1):151-62.
30. Graves SA, Hobbs RF, editors. Dosimetry for Optimized, Personalized Radiopharmaceutical Therapy. Seminars in Radiation Oncology; 2021: Elsevier.
31. Sandström M, Garske U, Granberg D, Sundin A, Lundqvist HJEjonm, imaging m. Individualized dosimetry in patients undergoing therapy with 177 Lu-DOTA-D-Phe 1-Tyr 3-octreotate. 2010;37(2):212-25.
32. Garkavij M, Nickel M, Sjögreen-Gleisner K, Ljungberg M, Ohlsson T, Wingårdh K, et al. 177Lu-[DOTA0, Tyr3] octreotate therapy in patients with disseminated neuroendocrine tumors: Analysis of dosimetry with impact on future therapeutic strategy. 2010;116(S4):1084-92.
33. Sapienza MT, Willegaignon J. Radionuclide therapy: current status and prospects for internal dosimetry in individualized therapeutic planning. Clinics (Sao Paulo). 2019;74:e835-e.
34. McDougald WA, Miyaoka RS, Alessio AM, Harrison RL, Lewellen TK. A study of SPECT/CT camera stability for quantitative imaging. EJNMMI Phys. 2016;3(1):14-.
35. Emami B, Lyman J, Brown A, Cola L, Goitein M, Munzenrider J, et al. Tolerance of normal tissue to therapeutic irradiation. 1991;21(1):109-22.
36. Jackson PA, Hofman MS, Hicks RJ, Scalzo M, Violet J. Radiation Dosimetry in (177)Lu-PSMA-617 Therapy Using a Single Posttreatment SPECT/CT Scan: A Novel Methodology to Generate Time- and Tissue-Specific Dose Factors. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2020;61(7):1030-6.
37. Ahmadzadehfar H, Essler M, Schäfers M, Rahbar KJNm, biology. Radioligand therapy with 177Lu-PSMA-617 of metastatic prostate cancer has already been arrived in clinical use. 2016;43(12):835-.
38. Baum RP, Kulkarni HR, Schuchardt C, Singh A, Wirtz M, Wiessalla S, et al. 177Lu-labeled prostate-specific membrane antigen radioligand therapy of metastatic castration-resistant prostate cancer: safety and efficacy. 2016;57(7):1006-13.

39. Fendler WP, Kratochwil C, Ahmadzadehfar H, Rahbar K, Baum RP, Schmidt M, et al. 177Lu-PSMA-617 therapy, dosimetry and follow-up in patients with metastatic castration-resistant prostate cancer. 2016;55(3):123-8.
40. Heck M, Retz M, Tauber R, Knorr K, Kratochwil C, Eiber MJDUAA. PSMA-targeted radioligand therapy in prostate cancer. 2017;56(1):32-9.
41. Rahbar K, Schmidt M, Heinzel A, Eppard E, Bode A, Yordanova A, et al. Response and tolerability of a single dose of 177Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer: a multicenter retrospective analysis. 2016;57(9):1334-8.
42. Tagawa ST, Milowsky MI, Morris M, Vallabhajosula S, Christos P, Akhtar NH, et al. Phase II study of lutetium-177–labeled anti-prostate-specific membrane antigen monoclonal antibody J591 for metastatic castration-resistant prostate cancer. 2013;19(18):5182-91.
43. Kratochwil C, Bruchertseifer F, Giesel FL, Weis M, Verburg FA, Mottaghy F, et al. 225Ac-PSMA-617 for PSMA-targeted α-radiation therapy of metastatic castration-resistant prostate cancer. 2016;57(12):1941-4.
44. Zechmann CM, Afshar-Oromieh A, Armor T, Stubbs JB, Mier W, Hadaschik B, et al. Radiation dosimetry and first therapy results with a 124 I/131 I-labeled small molecule (MIP-1095) targeting PSMA for prostate cancer therapy. 2014;41(7):1280-92.
45. Oudard SJFO. TROPIC: Phase III trial of cabazitaxel for the treatment of metastatic castration-resistant prostate cancer. 2011;7(4):497-506.
46. Hofman MS, Emmett L, Sandhu SK, Iravani A, Joshua AM, Goh JC, et al. TheraP: A randomised phase II trial of 177Lu-PSMA-617 (LuPSMA) theranostic versus cabazitaxel in metastatic castration resistant prostate cancer (mCRPC) progressing after docetaxel: Initial results (ANZUP protocol 1603). American Society of Clinical Oncology; 2020.
47. 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. 2018;19(6):825-33.
48. Kim YJ, Kim Y-iJCnm. Therapeutic responses and survival effects of 177Lu-PSMA-617 radioligand therapy in metastatic castrate-resistant prostate cancer: a meta-analysis. 2018;43(10):728-34.
49. Calopedos R, Chalasani V, Asher R, Emmett L, Woo HJPc, diseases p. Lutetium-177-labelled anti-prostate-specific membrane antigen antibody and ligands for the treatment of metastatic castrate-resistant prostate cancer: a systematic review and meta-analysis. 2017;20(3):352-60.
50. von Eyben FE, Bauman G, von Eyben R, Rahbar K, Soydal C, Haug AR, et al. Optimizing PSMA Radioligand Therapy for Patients with Metastatic Castration-Resistant Prostate Cancer. A Systematic Review and Meta-Analysis. 2020;21(23):9054.
51. Ferdinandus J, Eppard E, Gaertner FC, Kürpig S, Fimmers R, Yordanova A, et al. Predictors of response to radioligand therapy of metastatic castrate-resistant prostate cancer with 177Lu-PSMA-617. 2017;58(2):312-9.
52. Kessel K, Seifert R, Schäfers M, Weckesser M, Schlack K, Boegemann M, et al. Second line chemotherapy and visceral metastases are associated with poor survival in patients with mCRPC receiving 177Lu-PSMA-617. 2019;9(17):4841.
53. Rathke H, Holland-Letz T, Mier W, Flechsig P, Mavriopoulou E, Röhrich M, et al. Response prediction of 177Lu-PSMA-617 radioligand therapy using prostate-specific antigen, chromogranin A, and lactate dehydrogenase. 2020;61(5):689-95.
54. Heck MM, Tauber R, Schwaiger S, Retz M, D'Alessandria C, Maurer T, et al. Treatment outcome, toxicity, and predictive factors for radioligand therapy with 177Lu-PSMA-I&T in metastatic castration-resistant prostate cancer. 2019;75(6):920-6.

55. Rahbar K, Ahmadzadehfar H, Kratochwil C, Haberkorn U, Schäfers M, Essler M, et al. German multicenter study investigating 177Lu-PSMA-617 radioligand therapy in advanced prostate cancer patients. 2017;58(1):85-90.
56. Violet J, Sandhu S, Iravani A, Ferdinandus J, Thang S-P, Kong G, et al. Long-term follow-up and outcomes of retreatment in an expanded 50-patient single-center phase II prospective trial of 177Lu-PSMA-617 theranostics in metastatic castration-resistant prostate cancer. 2020;61(6):857-65.
57. Yusufi N, Wurzer A, Herz M, D'Alessandria C, Feuerecker B, Weber WA, et al. Comparative preclinical biodistribution, dosimetry and endoradiotherapy in mCRPC using 19F/177Lu-rhPSMA-7.3 and 177Lu-PSMA I&T. 2020.
58. Scher HI, Morris MJ, Basch E, Heller GJJoco. End points and outcomes in castration-resistant prostate cancer: from clinical trials to clinical practice. 2011;29(27):3695.
59. 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. 2004;351(15):1502-12.
60. Barber TW, Singh A, Kulkarni HR, Niepsch K, Billah B, Baum RPJJoNM. Clinical outcomes of 177Lu-PSMA radioligand therapy in taxane chemotherapy pretreated and taxane chemotherapy naïve patients with metastatic castration resistant prostate cancer. 2019:jnumed. 118.216820.
61. James ND, Sydes MR, Clarke NW, Mason MD, Dearnaley DP, Spears MR, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. 2016;387(10024):1163-77.
62. Sweeney C, Chen Y-H, Liu G, Carducci M, Jarrard D, Eisenberger M, et al. Long term efficacy and QOL data of chemohormonal therapy (C-HT) in low and high volume hormone naïve metastatic prostate cancer (PrCa): E3805 CHAARTED trial. 2016;27:vi244.
63. Murga JD, Moorji SM, Han AQ, Magargal WW, DiPippo VA, Olson WCJTP. Synergistic co-targeting of prostate-specific membrane antigen and androgen receptor in prostate cancer. 2015;75(3):242-54.
64. Basu S, Parghane RV, Joshi A, Prabhash K, Banerjee S. The rationality of combining second-generation antiandrogens with 177Lu-PSMA or its alpha-emitting congeners for better and durable results: will this dominate the therapeutic landscape and be an upfront consideration in metastatic castration-resistant prostate cancer in the coming years? : LWW; 2018.
65. Crumbaker M, Joshua AM, Epstein R, Emmett L. A phase I study of 177Lu-DKFZ PSMA 617 combined with the radiosensitizer idronoxil in men with metastatic castrate-resistant prostate cancer (mCRPC)(LuPin trial). American Society of Clinical Oncology; 2018.