Biomarkers to personalize treatment with 177Lu-PSMA-617 in men with metastatic castration-resistant prostate cancer – a state of the art review

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***Abstract*:** Radioligand therapy with Lutetium-177 (177Lu)-Prostate-specific membrane antigen (PSMA) has shown to prolong survival in metastatic castration resistant prostate cancer (mCRPC). One of the major challenges for clinicians in the future is to select those patients who would benefit most from this therapy to position it in the treatment landscape of mCRPC. This, in turn, will lead to the delivery of personalized therapies. In this narrative review article we summarize recent studies investigating both predictive and prognostic clinical, imaging-based, and molecular biomarkers to predict treatment response to 177Lu-PSMA-617 radioligand therapy with the aim of identifying men who should be considered for this approach. Of note, the evidence on the role of biomarkers currently relies on small retrospective trials and their validation in larger prospective cohorts is necessary before these results can be translated in the clinical practice.

Keywords: 177Lu-PSMA-617 radioligand therapy, biomarkers, mCRPC

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Introduction

Metastatic castration resistant prostate cancer

Prostate cancer (PC) is one of the most prevalent malignancies in the world and is the third most common cause of cancer-related mortality in men.[1] While most cases are diagnosed in localized stage and are managed expectantly or cured by local therapy such as surgery or radiotherapy, a considerable number of patients with intermediate or high-risk localized, locally advanced or metastatic cancer die from the disease itself each year.[1] Although therapeutic advances have been introduced in the field of metastatic PC in the past years, androgen deprivation therapy (ADT) remains the leading therapeutic backbone for metastatic PC.[2,3] However, patients managed with ADT would ineluctably develop a castration resistant state during follow-up. As such, additional therapies are needed. The exact mechanisms driving progression from androgen-dependent PC to castration resistance prostate cancer (CRPC) are not completely understood and might involve androgen receptor signaling despite depletion of circulating androgens and androgen receptor blockade is thought to be central to the development of CRPC.[4,5]

Over the past years, the treatment landscape of metastatic CRPC (mCRPC) has substantially improved due to the availability of different agents, including taxane-based chemotherapeutics (e.g. docetaxel, cabazitaxel), androgen receptor signaling inhibitors (ARSI) (e.g. abiraterone acetate, enzalutamide, apalutamide), radium-223 in the third line therapy setting, poly-ADP-Ribose-Polymerase (PARP) inhibition in patients with DNA damage repair (DDR) alterations (BRCA1, 2) or immune based

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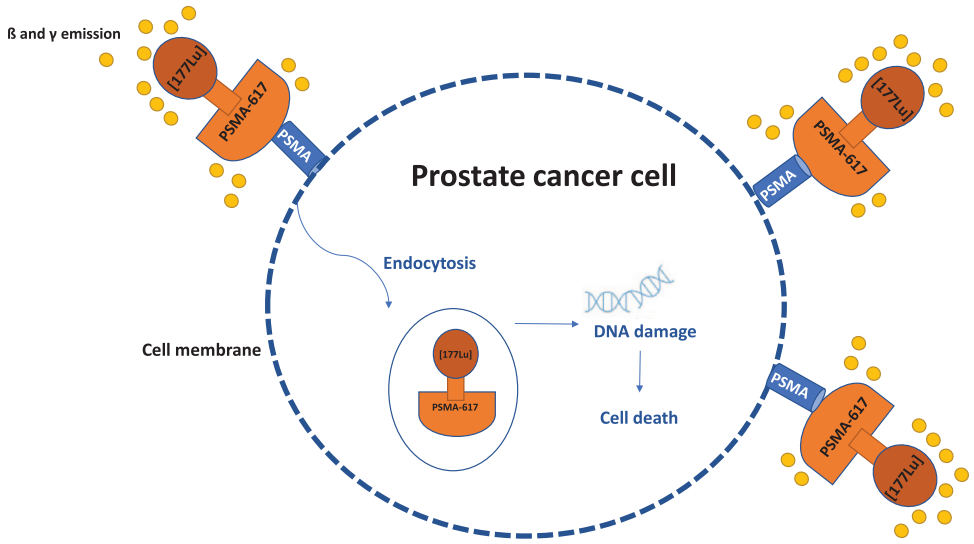

Figure 1. Mechanism of action of lutetium-177-labeled prostate-specific membrane antigen: PSMA-617 targeting ligand radiolabeled with [177Lu] binds to PSMA molecule on the prostate cancer cell membrane →177Lu-atom releases ß and γ particles → DNA damage → cell death.
[177Lu], lutetium-177; PSMA, prostate-specific membrane antigen.

strategies like the autologous vaccine sipuleucel T and the PD-1-inhibitor pembrolizumab which have been approved in selected patients in the Unites States only.[6]

However, fast tumor progression, cross-resistance, the use of these substances in earlier (hormone-sensitive) stage of the disease and patient related factors (e.g. performance status, co-morbidities) should be taken into account when assessing which is the optimal treatment sequencing in the setting of mCRPC.

PSMA in diagnostic and therapy

Prostate-specific membrane antigen (PSMA), also known as glutamate carboxypeptidase II or folate hydrolase I, is a prostate membrane specific bound protein on the epithelial cells of the prostate.[7] PSMA is also over-expressed physiologically in other organs including kidney, salivary gland, lacrimal gland and duodenal mucosa.[8] The exact role of PSMA over-expression on PC cells is not completely understood. Preclinical evidence shows that PC cells demonstrate increased glutamine utilization and therefore may in part depend on PSMA for nucleotide biosynthesis and metabolism, which in turn influences cell proliferation and invasiveness.[9]

Basically, PSMA-targeting tracers can be labeled with different radionuclides for diagnostic purposes, among them positron emission tomography (PET) imaging of PC with either Gallium-68 or Flourine-18 are the most common ones.[10] Due to its superiority to conventional imaging (bone scan/computer-tomography) or other PET radiopharmaceuticals, PSMA PET imaging of biochemically recurrent PC (BCR) is currently implemented in routine management in many countries and recommended by several guidelines including the European Association of Urology (EAU) or the American Society of Clinical Oncology (ASCO) guidelines[11–13].

Beside its diagnostic role, in the last decade, PSMA radioligand therapy (RLT) gained prominence in treating mCRPC in late stages in the last decade. In particular, the Lutetium-177 conjugated small molecule peptide, 177Lu-PSMA-617 is the most used PSMA-targeted radionuclide therapy in clinical development (Figure 1). 177Lu has favorable physical characteristics with a short-range medium-energy β particle for crossfire to surrounding tumor cells, relatively long half-life of 6.7 days and low energy γ emission. Promising antitumor activity and modest toxicity of 177Lu-PSMA RLT were reported in multiple retrospective studies in the past years.

Recently, the randomized multicenter phase II trial TheraP evaluated 200 mCRPC patients for whom cabazitaxel was considered the next appropriate standard treatment and demonstrated that

177Lu-PSMA-617 led to a higher prostate specific antigen (PSA) response (⩾50%) (66% vs 37%) compared to chemotherapy. In addition, 177Lu-PSMA-617 delayed radiographic and PSA progression compared to cabazitaxel (hazard ratio (HR) 0.63). At 12 months (mo), 19% had not progressed with 177Lu-PSMA-617 compared to 3% with cabazitaxel, although the median progression-free survival (PFS) was similar at 5.1 months, with a greater benefit for 177Lu-PSMA-617 emerging after 6 months. The objective response rate (ORR) defined by RECIST 1.1 was higher with 177Lu-PSMA-617 (49% vs 24%).[14] Of note, grade 3–4 adverse events occurred in 33% in the 177Lu-PSMA-617 group versus 53% in the cabazitaxel group suggesting that this novel therapy option is superior to chemotherapy in terms of side effects.

Furthermore, the multicenter randomized phase III VISION trial included 831 patients progressed on at least one ARSI and one or two taxane to receive 177Lu-PSMA-617 plus standard-of-care (SOC) vs SOC alone. Both primary endpoints overall survival (OS) (median 11.3 to 15.3 mo, HR: 0.62) and radiologic progression-free survival (fPFS) (median: 3.4 to 8.7 mo, HR: 0.4) were reached in the 177Lu-PSMA-617 arm.[15]

In conclusion, two randomized trials evaluated the role of 177Lu-PSMA-617 in the setting of mCRPC and provide complementary evidence: the VISION study demonstrated a survival benefit in men who have exhausted current therapeutic options while TheraP trial places PSMA theranostics once step earlier by comparing it to cabazitaxel showing greater efficacy, lower toxicity and better patient reported outcomes.

Currently, 177Lu-PSMA-617 therapy is investigated even in earlier stage of disease (locally advanced, primary metastatic), prior to chemotherapy and/or ARSI as well as in combination with PARP inhibitors (olaparib), hormonal therapy (enzalutamide) or immunotherapy (pembrolizumab) (reviewed in Sandhu et al.[16]).

Despite promising findings, better understanding of optimal patient selection for PSMA based RLT, sequencing of the available therapies and therapeutic resistance remain key ongoing challenges. Therefore, there is an unmet need for both predictive and prognostic biomarkers to use RLT at the optimal time point for the optimal patient in order to pursue a personalized treatment concept.

This review article provides an overview of the current literature on image based, blood based and patient /tumor characteristics-based biomarkers and discuss their impact in daily practice. In addition, we report first findings from preclinical or early phase clinical studies.

Clinical biomarkers

Ferdinandus *et al.*[17] analyzed 40 mCRPC patients with distant metastases and progressive disease who underwent 177Lu-PSMA-617 therapy and found that younger age (cutoff 65 years, $p < 0.001$) had a negative impact on any PSA decline during therapy. In line with this finding, patients' age >77 years has been demonstrated as significant predictor for a PSA decrease $>20\%$ during 177Lu-PSMA-617 therapy in another cohort.[18]

Several studies revealed that asymptomatic patients have better OS rates compared to symptomatic patients when treated with 177Lu-PSMA-617 (reviewed in von Eyben et al.[19]). For example, the regular use of pain medication ($p = 0.0018$) as well as high Gleason Score ($p = 0.01$) were related to a PSA decline of more than 50% during therapy.[17] Patients with pain and high Gleason score may comprise a selection of patients who have a poor prognosis and may respond poorly to any therapy. Ahmadazedehfar *et al.*[20] also reported that both PSA decline and OS were worse in patients with regular need for analgesics. In addition, poor performance status was reported to be associated with lower therapy response.[21,22]

Generally, the presence of visceral metastatic load is associated with poor OS in mCRPC. Concerning its prognostic impact during RLT, Heck and colleagues reported in 100 patients treated by 177Lu-PSMA-617 that median PFS was 3.1 mo in patients with visceral metastasis diagnosed by Gallium-PSMA PET CT versus 5.9 mo in those without visceral metastasis (HR: 1.7, $p = 0.02$).[23] This finding is in line with another German trial reporting that liver metastasis are associated with decreased OS ($p = 0.001$).[24]

Beside its impact on OS, a recent meta-analysis including 1504 177Lu-PSMA-617 treated mCRPC patients confirmed that the presence of

visceral metastasis is associated with low biochemical response rate and worse PFS.[25]

Furthermore, Kessel *et al.*[26] reported that patients with liver metastases have worse outcomes compared to those with lung or lymph node metastases. The WARMTH multicenter study evaluated the impact of the extent of the bone involvement on OS mCRPC patients receiving 177Lu-PSMA-617 and found that the extent of bone involvement correlated negatively with the OS after RLT.[27]

Notably, biochemical progressive disease after 1–2 courses of 177Lu-PSMA-617 was an independent predictor of shorter OS in the recently published REALTY study investigating 254 mCRPC patients treated with RLT everyday academic practice.[28]

Concerning the impact of previous antineoplastic treatment on response to RLT current literature reports conflicting data. A retrospective study including 167 177Lu-PSMA-617 treated mCRPC patients evaluated clinical outcomes stratified according to previous taxane chemotherapy. Median OS was 10.7 mo for taxane-retreated patients and 27.1 mo for taxane-naïve patients. Median radiographic PFS (rPFS) was 6.0 mo for taxane-pretreated patients and 8.8 mo for taxane-naïve patients. Further, PSA response was 40% in taxane-pretreated patients vs 57% in taxane naïve patients.[21] In addition, second line cabazitaxel chemotherapy was reported in a retrospective trial as indicator for poor survival.[26] This finding was confirmed by the multicenter WARMTH trial, where significant negative prognosticators of OS were prior chemotherapy in patients with <6 bone lesions. Furthermore, patients with prior radium-223-therapy showed longer OS in the WARMTH trial.[27] Further prior treatment with ARSI for less than 12 months has been reported to be associated with worse OS during treatment of Lu-PSMA-617 with the radiosentitizer idronoxil (NOX66).[29] In contrast, there exist data that neither pre-treatments with abiraterone/enzalutamide nor docetaxel/cabazitaxel nor distribution of metastases affected survival and rate of response to PSMA-RLT.[30]

FDG uptake

Overall, fluorodeoxyglucose (FDG) uptake is a reliable marker to assess tumor burden in various tumors including PC. Suman *et al.*[31] demonstrated in a cohort of 35 177Lu-PSMA-617 treated patients, that high FDG uptake ($SUV_{max}>15$) correlates with lack of response, progressive disease and short PFS. In addition, PET imaging analyses were conducted using whole-body segmentation quantifying molecular tumor volume. Interestingly, this analysis identified FDG-positive tumor volume and mean intensity of PSMA- avid tumor uptake as biomarker for OS.[32] Very recently, FDG positive/PSMA negative lesions have claimed as predictor for short OS during RLT as a significantly lower OS rates were observed in patients with at least one FDG + /PSMA- lesion at baseline PET/CTs with a median OS of 6.0 ± 0.5 months. In comparison, patients without any FDG + / PSMA-lesions had a median OS of 16.0 ± 2.5 months.[33] However, there exists also one small trial with 18 patients, where intensity of activity on FDG PEt alone was not predictive of a treatment response.[34]

A representative picture of a patient with FDG + / PSMA + liver lesions who did not respond (PSA, imaging) to 177Lu-PSMA RLT is illustrated in Figure 2.

Imaging biomarkers

PSMA total tumor volume and PSMA tumor intensity

Generally, total tumor volume (TTV) is calculated by summarizing the volumes of segmented lesions to obtain the whole-body tumor volume ager subtracting physiologic PSA accumulation in the liver, bladder, spleen, kidn.ey, tear, small bowel and salivary glands from foci with pathological PSMA uptake.[35]

There exist several studies reporting that the PSMA TTV is associated with OS and/or PSA response during 177Lu-PSMA-617 treatment.[17,36–38] Complementary or as alternative to TTV, the intensity of PSMA activity on screening imaging correlated strongly to treatment response. Mean PSMA standard uptake value (SUV) was 6 ± 4 in those without response versus 10 ± 4 in those with response ($p<0.04$).[34]

A recently published phase I/II study combining Lu-PSMA-617 with the radiosensitizer idronoxil (NOX66) observed that higher PSMA SUVmean correlated with treatment response, while higher PSMA tumor volume was associated with worse OS.[29]

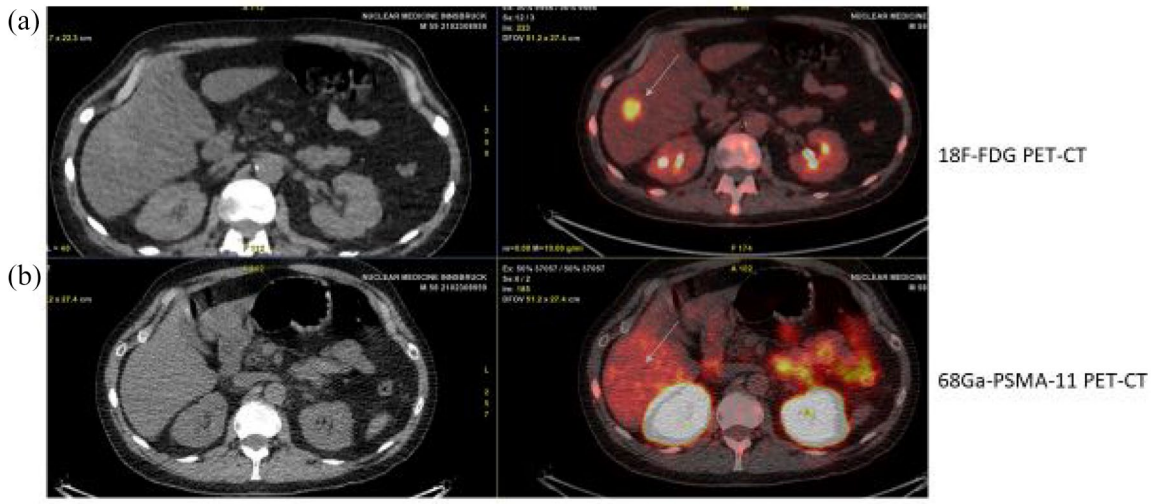

Figure 2. 18 F-FDG PET-CT (a) and 68Ga-PSMA-11 PET-CT (b) images show an high uptake of FDG (SUV Max 9,25) in the liver metastasis with no relevant 68Ga-PSMA uptake.

Furthermore, molecular imaging-based response using tumor-to-liver ratio (TLR) was independently associated with PFS suggesting that molecular imaging-based response assessment with PSMA PET using normalization of the total lesion PSMA over healthy liver tissue uptake could be an appropriate biomarker to monitor RLT in mCRPC patients and to predict PFS of this treatment modality.[12]

Bone scan index (BSI)

Bone scintigraphy is still one of the first-line imaging modalities for the screening of bone metastasis in patients with PC. The amount (%) of bone metastasis can be calculated using a bone scan index thanks to recent advances in quantitative bone scintigraphy. Since an artificial neural network was applied for hot-spot characterization and quantitation, BSI has become a simple, reproducible and practical means of quantifying bone metastasis. Thus, BSI is presently considered as an imaging biomarker of bone metastasis.[39]

Ferdinandus *et al.*[32] recently described in 50 patients treated by 177Lu-PSMA-617 in the ANZCTR trial (NCT12615000912583) where patients underwent baseline PSMA-PET, FDG-PET, and planar 99mTc-bone scan imaging that BSI is a significant biomarker prognostic of OS. Thus, BSI can be considered as biomarker in only bone metastatic disease, but admittedly most mCRPC present also with lymph node and/or visceral metastatic load.

Nomograms to predict outcomes

Gafita *et al.*[40] were able to develop nomograms to predict outcomes in patients who are candidates for 177Lu-PSMA using mCRPC patients who had received 177Lu-PSMA as part of the previous phase II trials (NCT03042312, ACTRN 12615000912583) or compassionate access programs. Summarizing, three different nomograms to predict OS, PSA-PFS and PSA response $\geqslant 50\%$ were developed and externally validated incorporating prognostic variables like tumor PSMA expression, number of PSMA-positive metastatic lesions, and disease site based on molecular imaging TNM classification system. Interestingly, nomograms support preclinical findings and suggest that high levels of tumor PSMA expression is a prerequisite for favorable outcome following 177Lu-PSMA. In addition, bone disease is less likely to be adequately controlled with 177Lu-PSMA.

Blood based biomarkers

PSA and PSA doubling time

Measurement of PSA is the most common serum marker to detect PC as well as to predict tumor recurrence and therapy response in patients with PC.[41–43] Even during 177Lu-PSMA-617 treatment, PSA decline after the first and the second therapy cycle was reported in few studies as predictor for therapy response as well as for prolonged OS.[26,30,37,38,44] For example PSA changes 6 weeks after 177Lu-PSMA-617 initiation has

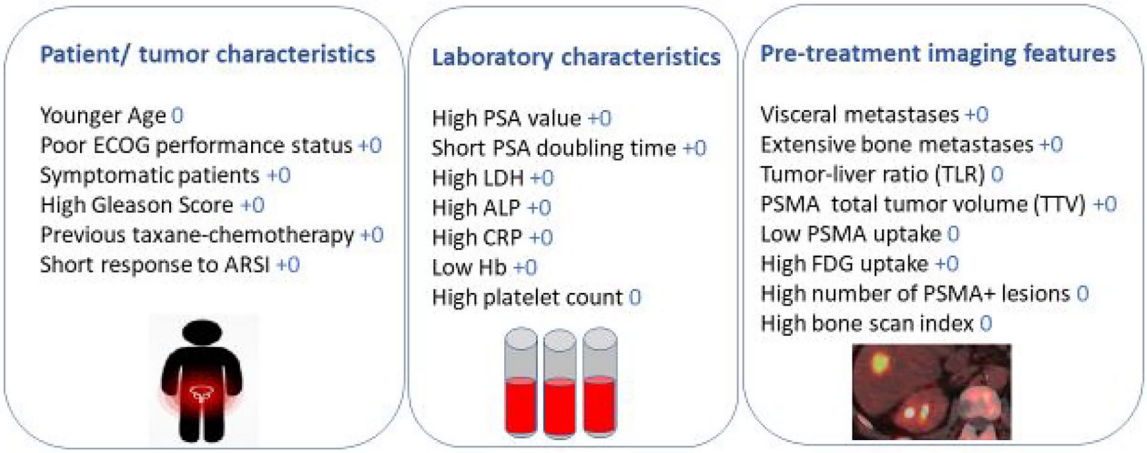

Figure 3. Biomarkers associated with no/short response to 177Lu-PSMA-617 therapy.
+ indicates prognostic biomarker, **0** indicates predictive biomarker, + **0** indicates prognostic and predictive biomarker-; ARSI, androgen receptor signaling inhibitors.

been proposed as an early indicator of long-term clinical outcome as a PSA decline ⩾30% at 6 weeks was associated with longer OS (16.7 mo) compared to stable PSA (11.8 mo) or PSA progression (6.5 mo).[44] In addition, it has been demonstrated that patients with negative serum PSA doubling time (PSA-DT) harbored superior 1-year PFS compared to those with positive serum PSA-DT (52.5 vs 47.5%) ($p = 0.029$).[31]

Lactate dehydrogenase (LDH)

Next, the presence of high LDH levels was associated with poor OS in several trials assessing its predictive impact during RLT.[23,32,45,46] Moreover, LDH kinetics within two to three months during therapy has been reported as predictive biomarker in a retrospective trial including 137 patients.[46] However, another trial did not confirm this finding.[37]

C-reactive protein (CRP)

The pretreatment CRP value was also associated with OS (HR: 1.07, $p = 0.02$) in a retrospective trial comprising 38 patients treated by 177Lu-PSMA-617.[37] Further a CRP value of >20 mg/L had a negative impact on any PSA decline during therapy ($p = 0.006$).[17]

Hemoglobin (Hb)

A multicenter trial including data of 61 patients pretreated by with abiraterone/enzalutamide (75.4%) and docetaxel/cabazitaxel (68.9%) who received three cycles of PSMA-RLT depicted that the levels of basal Hb were able to predict survival of patients.[30] Similarly, normal pre-treatment Hb levels were predictive for a ⩾50% PSA decline during therapy, while lower pre-treatment Hb levels were associated with a lack of PSA declines.[17,30] However, the trial from Grubmüller and colleagues did not confirm this finding possibly caused by the relatively low patient number included in this trial.[37]

Platelet count

Ferdinandus and collegues reported already four years ago that platelet counts (>300 G/L; $p < 0.001$) have a negative impact on any PSA decline.[17]

Alkaline phosphatase (ALP)

Retrospective analyses reported a combined predictive and prognostic impact of ALP levels <200 concerning PSA PFS (41 versus 18 wks) and OS (56 vs 28 weeks).[47] Even other studies reported similar findings.[32,46,48]

Summarizing, Figure 3 illustrates an overview on clinical, blood-based and imaging-based biomarkers that can be adopted in daily routine stratified according to its predictive or prognostic value.

Molecular biomarkers

Due to rapid technological developments, diverse types of biomarkers have been detected at genomic,

transcriptomic, proteomic, metabolomic, immunomic, and cellular levels claiming to investigate its significance also in the field of RTL.

Recently, an Austrian trial assessed by immunohistochemistry the association of tissue PSMA expression in PSMA PET positive metastatic biopsies of 10 mCRPC patients among them 9 patients were treated by 177Lu-PSMA-617. They found that assessment of PSMA presence at biopsy is not a reliable predictor of response to 177Lu-PSMA-617.[49] Similarly, to the negative study on protein levels in tissue, also on mRNA level PSMA does not display strong prognostic ability.[48] However, in our hand, when interpreting the results of these trials, apart from the small patient collective, tumor heterogeneity among both patients and different metastases must be taken into consideration claiming to further investigation of the prognostic impact of tissue based PSMA expression.

PSMA expression measured on circulating tumor cells (CTC) (using the ADNA test) has been reported from a Japanese study group to be predictive of poorer treatment response, shorter PSA PFS and OS during 177Lu-PSMA-617 treatment suggesting that PSMA expression in CTC may be a novel poor prognostic marker for CRPC.[50] In addition, Kessel *et al.*[48] conducted a study performing molecular analysis of CTC (Dynabeads™ mRNA DIRECT™ Purification Kit) of 19 mCRPC patients receiving177Lu-PSMA-617 demonstrating that that full length androgen receptor (AR-FL) and its splice variant AR-V7 might serve as prognostic biomarkers displaying high tumor burden in mCRPC patient prior to PSMA-RLT.

Genomic instability is mostly associated with defects in the DNA repair system suggesting that DDR alterations may be predictive also for response to RLT. Indeed, one study found higher PSMA expression in patients with deleterious aberrations in BRCA2 and ATM than in molecularly unselected mCRPC biopsies.[51]

Conclusion

Recently, 177Lu-PSMA-617 therapy has shown to prolong PFS and OS in mCRPC patients leading to a possible FDA/EMA approval that is expected in the next few months. In this setting, RLT compete with alternative therapeutic strategies such as cabazitaxel. In addition, combinational studies of 177Lu-PSMA-617 with standard treatments or with additional experimental substances not only in mCRPC but also in earlier therapy lines are currently ongoing. Different biomarkers are available that are associated with response to therapy.

One of the major challenges for clinicians is to select those patients who would best benefit from this therapy and to precociously change to alterative therapeutic strategies in non-responders to propose a personalized treatment approach. However, markers to reliably help selection of a specific therapy or sequence in the setting of mCRPC with different previous lines of treatment are not yet available.

Author contributions

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Giorgio Gandaglia: Conceptualization; Data curation; Investigation; Project administration; Writing – original draft; Writing – review & editing.

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