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Review Article

The Value of Phenotypic Precision Medicine in Prostate Cancer

Nathan M. Hawkey,[1] Amanda Broderick,[1] Daniel J. George,[1,2] Oliver Sartor,[3] Andrew J. Armstrong[1,2,*]

[1]Department of Medicine, Division of Medical Oncology, Duke University School of Medicine, Durham, NC, USA
[2]Duke Cancer Institute Center for Prostate and Urologic Cancer, Duke University, Durham, NC, USA
[3]Tulane Cancer Center, Division of Genitourinary Oncology, New Orleans, LA, USA

*Corresponding author: Andrew J. Armstrong, MD, ScM, FACP, Department of Medicine, Surgery, Pharmacology and Cancer Biology, Director of Research, the Duke Cancer Institute Center for Prostate and Urologic Cancers, Divisions of Medical Oncology and Urology, Duke University, DUMC Box 103861, Durham, NC 27710, USA; Email: Andrew.armstrong@duke.edu

Abstract

Prostate cancer is the most common cancer among men and the second leading cause of cancer-related death. For patients who develop metastatic disease, tissue-based and circulating-tumor–based molecular and genomic biomarkers have emerged as a means of improving outcomes through the application of precision medicine. However, the benefit is limited to a minority of patients. An additional approach to further characterize the biology of advanced prostate cancer is through the use of phenotypic precision medicine, or the identification and targeting of phenotypic features of an individual patient's cancer. In this review article, we will discuss the background, potential clinical benefits, and limitations of genomic and phenotypic precision medicine in prostate cancer. We will also highlight how the emergence of image-based phenotypic medicine may lead to greater characterization of advanced prostate cancer disease burden and more individualized treatment approaches in patients.

Key words: phenotypic precision medicine; image-based biomarkers; prostate-specific membrane antigen (PSMA); metastatic castrate-resistant prostate cancer; precision medicine; radiopharmaceuticals.

Implications for Practice

Approximately 20%–40% of men with perceived localized prostate cancer relapse after definitive surgery or radiation therapy with or without androgen deprivation therapy. Subsequent therapies, including those targeting the androgen-signaling axis and taxane chemotherapies, have improved survival in patients with metastatic disease. With the widespread introduction of tumor sequencing, genomic precision medicine has identified genetic alterations in patient subsets who derive additional benefit from targeted therapies. However, few patients will benefit from genomic precision medicine, and alternative approaches are essential. Image-based phenotypic precision medicine has emerged as an additional tool offering therapeutic options for a potentially greater number of patients.

Introduction

Prostate cancer (PC) is the most common cancer among US men, and metastatic PC (mPC) is the second leading cause of cancer-related death, with a 5-year survival near 30% for distant-stage disease.[1,2] Early detection and local therapy have resulted in improved PC–specific survival; however, ~20%–40% of men relapse after surgery or radiation therapy (with or without androgen deprivation therapy).[3,4] For mPC, tissue- and circulating-tumor-cell (CTC)–based molecular/genomic biomarkers have emerged as means of improving outcomes through application of precision medicine.[5,6]

This PC landscape is complicated by vast genotypic and histomorphologic heterogeneity across patients, between tumor sites within individual patients, and among different loci within single tumors.[7,8] These features make prediction of an individual patient's cancer challenging, which is essential for successful application of precision medicine targeting specific genomic features.[9] Despite this, there has been success in the metastatic castration-resistant PC (mCRPC) setting with poly (ADP-ribose) polymerase (PARP) inhibitors (and platinum chemotherapy) for those with loss of homologous recombination genes and immune checkpoint inhibitors (ICIs) for patients with defective DNA mismatch repair.[10-13] However, these agents have been limited to a minority of patients. In this review, we discuss how targeting specific phenotypic features of PC cells via phenotypic precision medicine (PPM) may expand the scope of PC precision medicine.

Genotypic Precision Medicine in PC

Genotypic precision medicine (use of specific and actionable genetic alterations to guide treatment selection) is an important aspect of precision medicine.[14] Increasing availability and

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affordability of tumor molecular testing has allowed more routine germline and somatic genomic evaluation in PC.[14-16] Current clinically validated PC treatments based on genetic biomarkers include ICIs and PARP inhibitors.[17-21]

Pembrolizumab is a programmed death receptor-1/programmed death-ligand 1 (PD-L1) pathway targeted ICI approved for patients with advanced solid tumors, including PC, who have high microsatellite instability (MSI-H), high tumor mutational burden, or are DNA mismatch repair (dMMR) deficient.[17,21,22] The phase II KEYNOTE-199 trial, which included men with docetaxel-refractory mPC, demonstrated similar objective response rates for pembrolizumab regardless of PD-L1 status (PD-L1-positive: 5%; PD-L1-negative: 3%).[20] Responders exhibited a durable response (median duration of response:16.8 months).

Olaparib is a PARP inhibitor approved for mCRPC with genetic alterations involving homologous recombination mediated DNA repair genes (HRR genes). The PROfound trial[17-19] included patients with mCRPC who progressed while receiving novel hormonal therapy and had deleterious or suspected alterations in ≥1 HRR-implicated genes. Patients were separated into cohort A (*BRCA1*, *BRCA2*, or *ATM* alterations) and cohort B (other implicated alterations). Statistically significant benefit in overall survival (OS) was observed for cohort A patients treated with olaparib versus abiraterone or enzalutamide (control) with median OS of 19.1 versus 14.7 months, respectively.[23] There was also a statistically significant improvement in median radiologic progression-free survival (PFS) for the combined A+B cohort (olaparib: 5.8 months; control: 3.5 months).[18,19,21]

Results from the phase II TRITON2 study led to accelerated FDA approval of rucaparib, another PARP inhibitor. This trial included men with mCRPC and deleterious germline or somatic *BRCA* alterations who progressed after 1-2 lines of androgen receptor-directed therapy and 1 line of taxane therapy. Objective response rates of 43.5% (independent radiology review) and 50.8% (investigator review) and a prostate-specific antigen (PSA) response rate (>50% decrease from baseline) of 54.8% were observed.[24] Full FDA approval is anticipated after completion of the phase III TRITON3 trial comparing rucaparib with abiraterone, enzalutamide, or docetaxel in men with HRR mutation-associated mCRPC.[18,19,24]

Genotypic precision medicine for PC has several limitations. Genomic alterations targetable by current therapeutics are present in a small subset of patients; HRR-implicated genes are present in ~23% of men with PC, and MSI-H/dMMR are found in ~3% of men.[21,25] Among men with HRR-implicated genes, those with *ATM* alterations have low rates of response to PARP inhibitors, further limiting the number of patients who may benefit from this approach.[26] Moreover, high degrees of genomic heterogeneity/instability in advanced PC disrupt the identification of other actionable mutations.[7,8,27-29] Biopsy requirements for tumor genotyping generates additional limitations. Biopsies are invasive and can miss alterations due to PC heterogeneity.[29] Bone is the most common site of metastatic disease, affecting >80% of men with mPC.[30,31] Obtaining sufficient tissue for genetic sequencing of bone biopsies has historically been challenging, though changes in biopsy protocols have led to improved yield, with one study indicating a yield of 81.7% for whole exome sequencing.[32] Concordance in genetic alterations between primary tumor specimens and circulating tumor DNA or metastatic tissue has been demonstrated,[33] and the increasing availability of plasma cell–free DNA testing via saliva and blood has mitigated some of the difficulties associated with tumor genotyping. However, plasma cell-free DNA testing has its own drawbacks, including difficulty detecting somatic alterations at low disease burdens.[34]

Despite several potential targets, only a minority of patients benefit from current genotypic precision medicine approaches, which has led to ongoing clinical investigations into the targeting of additional genomic alterations (Table 1). These limitations have also prompted further investigation into PPM.

Phenotypic Precision Medicine in PC

A phenotype is a physical, observable characteristic that is the product of genotype and environment. Clinicians have long relied on PC phenotype for prognosis and management decisions.[35,36] Examples of phenotypic biomarkers validated in advanced PC are shown in Table 2.[37-51]

Histopathologic-Based PPM

Standard of care (SOC) also uses phenotype to inform treatment choices in PC. Current image-based and clinically-based phenotypic biomarkers used in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) include symptomatology, pattern of disease spread, and tumor characteristics such as castration resistance, Gleason score, and neuroendocrine histology.[35] For example, an initial distinction must be made between tumors exhibiting histological features of adenocarcinoma and small cell/neuroendocrine PC (NEPC).[52] This is critical because of NEPC's poor prognosis and high sensitivity to platinum-based chemotherapy.[38,53,54] Based on cellular characteristics suggestive of neuroendocrine or small cell differentiation, a CTC assay has been developed to more easily identify these patients. This CTC neuroendocrine phenotype was found to correlate with poor outcomes after abiraterone or enzalutamide treatment.[38]

Clinical PPM

Disease behavior has prognostic and management value in PC. For example, a meta-analysis demonstrated that clinical phenotype, specifically pattern of spread, has prognostic value in docetaxel-treated men with mCRPC.[31] Patients with lymph node-only disease had the longest median OS (31.6 months). For other metastatic sites, median OS by site was 21.3 months (bone), 19.4 months (lung), and 13.5 months (liver).[31]

Clinically significant pain also has prognostic value in multiple CRPC analyses. A multivariate analysis of prognostic factors in the TAX327 trial identified clinically significant pain as an independent risk factor for death in mCRPC (hazard ratio [HR] 1.48; $P < .001$).[55] Another analysis demonstrated that men with high pain scores (≥17 on the Wisconsin Brief Pain Inventory scale) had a statistically significant lower median OS than did those with low pain scores (<17) (10.2 vs 17.6 months, respectively).[41]

Treatment for progressive, metastatic, prostatic adenocarcinoma is dependent upon chemohormonal therapy exposure. The preferred initial regimen is whichever treatment patients are naïve to (novel hormonal therapy vs taxane) or escalating to cabazitaxel if there has been prior docetaxel exposure.[56,57] Though overall efficacy is reduced with a second-line novel hormonal therapy agent, Khalaf et al demonstrated that enzalutamide showed activity as a second-line novel androgen receptor pathway inhibitor given after progression on

Table 1. Genetic biomarkers in prostate cancer and associated targeted therapies approved or under investigation.

Therapy	Genomic biomarker	Therapy mechanism	FDA approval date or key trials
Pembrolizumab	High microsatellite instability High tumor mutational burden DNA mismatch repair deficiency	PD-1 inhibitor	Approved 2017
Olaparib	HRR-associated gene alterations: most commonly -*BRCA1* -*BRCA2* -*ATM*	PARP inhibitor	Approved 2020
Rucaparib	*BRCA1* *BRCA2*	PARP inhibitor	Approved 2020
Niraparib	*BRCA1* *BRCA2*	PARP inhibitor	GALAHAD trial (NCT02854436) MAGNITUDE trial (NCT03748641) AMPLITUDE trial (NCT04497844)
Talazoparib	DNA damage repair deficiency gene alterations	PARP inhibitor	TALAPRO-2 trial (NCT03395197) TALAPRO-3 trial (NCT04821622)
Ceralasertib (AZD6738)	Deleterious *ATM* alterations	ATR inhibition	PLANETTEtrial (NCT04564027)
Ipatasertib	*PTEN* loss	PIK3/AKT pathway inhibition	IPATential150 trial (NCT03072238)
Capivasertib	*PTEN* loss	AKT inhibitor	CAPItello-281 (NCT04493853)
Dostarlimab	DNA mismatch repair defiency	PD-1 inhibitor	Approved 2021
Tazemetostat	*EZH2* overexpression	EZH2 inhibitor	CELLO-1 (NCT04179864)
Cabozantinib	c-MET VEGFR *AXL*	Multi-targeted tyrosine kinase inhibitor	CONTACT-02 (NCT04446117) NCT04631744
Nivolumab/ipilimumab	*CDK12* loss of function	CTLA4 inhibitor/PD-1 inhibitor	IMPACT (NCT03570619)

Abbreviations: ATM, ataxia-telangiectasia mutated; ATR, ataxia telangiectasia and rad3-related; CDK12, cyclin-dependent kinase 12; c-MET, tyrosine-protein kinase Met; CTLA4, cytotoxic T-lymphocyte associated protein 4; EZH2, enhancer of zeste homolog 2; FDA, Food and Drug Administration; HRR, homologous recombination repair; PARP, poly(ADP-ribose) polymerase; PD-1, programmed death receptor-1; PTEN, phosphatase and tensin homolog; VEGFR, vascular endothelial growth factor receptor.

abiraterone, whereas abiraterone given after enzalutamide did not.[58] Furthermore, Orme and colleagues have outlined a rational sequencing approach of second-generation antiandrogen therapy based on available clinical trial data. Based on their findings, they recommend prioritization of abiraterone prior to chemotherapy, which should be delayed until after second-generation antiandrogen failure, and post-chemotherapy enzalutamide to maximize efficacy.[59]

Subsequent treatment decisions are based on further phenotypic categorization by symptomatology and pattern of spread. For minimally symptomatic/asymptomatic mCRPC, sipuleucel-T, a cellular immunotherapy, has demonstrated OS benefit.[60] However, usage of sipuleucel-T is variable, and many patients who are candidates for therapy will receive taxane-based chemotherapy. One retrospective cohort study of 7272 men who received treatment for mCRPC showed that only 10% of candidates received sipuleucel-T therapy.[61] Men with symptomatic and bone-predominant disease (another phenotypic subset) are candidates for radium-223, a bone-directed alpha emitter, as long as visceral metastases are not present.[62,63] The ALSYMPCA trial demonstrated the benefit of radium-223 versus placebo in OS (median 14.9 vs 11.3 months) and time to first symptomatic skeletal-related event (median 15.6 vs 9.8 months), but only included men with phenotypically symptomatic and painful disease.[62,63] Those who are not candidates for radium-223 or sipuleucel-T would be considered for taxane chemotherapy (though many patients who are candidates for these treatments will receive chemotherapy in place of these options) and potentially platinum-based chemotherapy (for aggressive variant mCRPC).[35,64]

Laboratory-Based PPM

Current prognostic models, such as the PREVAIL prognostic model and CALGB-90401 trial model, incorporate clinical and laboratory data as factors to predict long-term survival in patients with mCRPC.[39,42] These models include PSA, albumin, hemoglobin, lactate dehydrogenase, alkaline phosphatase, and pattern of spread; additionally, the PREVAIL model uses neutrophil-to-lymphocyte ratio, number of bone metastases, presence of pain, and time since diagnosis, while the CALGB-90401 model utilizes Eastern Cooperative Oncology Group performance status and opioid use.[39,42] Both models consider these variables because of their prognostic implications.

CTC count has emerged as another prognostic indicator with the development of validated assays for detection of CTCs in mCRPC. Studies have demonstrated that higher CTC count was adversely related to median OS in men with mCRPC.[45,46] de Bono et al showed a significant decrease in median OS for those with higher CTC count (≥5 CTC/7.5 mL) versus those with lower CTC count (<5 CTC/7.5 mL) (11.5 vs 21.7 months, respectively).[45]

Image-Based Phenotypic Biomarkers

An additional advantage of phenotypic biomarkers is that—in contrast to most genetic biomarkers—some phenotypic

Table 2. Examples of clinically relevant phenotypes in advanced prostate cancer.

Clinical or pathologic phenotype	Example	Implications	References
NEPC/small sell	Histology or CTC Phenotype	Platinum chemotherapy recommendations, anti-NEPC therapies AR indifferent disease	Beltran et al[37] Brown et al[38]
Pattern of metastatic spread	Lymph node vs bone vs lung vs liver	Prognosis Treatment implications for sipuleucel-T, radium-223, AR inhibition in visceral-liver disease	Armstrong et al[39] Halabi et al[31]
Pain	Analgesia score or Brief Pain Inventory	Prognosis Treatment implications for sipuleucel-T, radium, taxane chemotherapy decisions	Armstrong et al[40] Halabi et al[41]
Functional impairment	ECOG, Karnofsky performance status, QoL surveys	Prognostic treatment implications Non-prostate cancer morbidity/mortality	Halabi et al[42] Armstrong et al[39]
PSA levels	Low PSA but bulky disease High PSA progression	AR indifference NEPC/small-cell transformation Aggressive variants may need alternatives to AR inhibition	Corn et al[43] Armstrong et al[39]
Anemia	Transfusion dependence, bone marrow invasion	Prognosis Implications for treatment, safety, pace of disease	Halabi et al[42] Armstrong et al[39]
High alkaline phosphatase levels (bone biomarkers)	Osteoblastic spread, bone metastases	Osteomimicry, risks of fracture and skeletal events, prognostic implications for radium-223 and bone-targeted agents (denosumab, zoledronic acid)	Halabi et al[42] Armstrong et al[39,44]
Circulating tumor cell production	Cellsearch or Epic CTC enumeration	Prognosis pre- and post-treatment in many mCRPC settings Potential intermediate endpoint for efficacy of therapies Biomarker for precision medicine	de Bono et al[45] Scher et al[46,47]
PSMA uptake on PET	High PSMA SUV uptake PSMA heterogeneity	Low PSMA uptake in metastases may indicate AR indifference/NEPC High PSMA update may indicate greater benefit from PSMA-directed therapies	Kuo et al[48] Gafita et al[49,50]
Tc99 bone scan uptake	Automated bone scan index Number of bone lesions	Prognostic associated with pain, fracture risk Targetable with approved therapies in mCRPC	Armstrong et al[51]

Abbreviations: AR, androgen receptor; CTC, circulating tumor cell; ECOG, Eastern Cooperative Oncology Group; mCRPC, metastatic castration-resistant prostate cancer; NEPC, neuroendocrine prostate cancer; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; QoL, quality of life; SUV, standardized uptake value.

biomarkers can be noninvasively visualized with imaging (image-based phenotypic biomarkers). Classically, this has been done with skeletal scintigraphy to help select men with bone-predominant disease for radium-223.[36] More recently, radioligand imaging and therapy has emerged as an image-based PPM strategy for PC. This approach uses molecules that are targeted against a phenotypic biomarker and which can be labeled with a diagnostic imaging or a therapeutic radioisotope (Fig. 1).

One promising example has emerged from the discovery of prostate-specific membrane antigen (PSMA), a prostate-specific protein highly expressed in PC. It has led to the development of PSMA–positron emission tomography (PET) imaging, a novel strategy allowing for noninvasive and accurate PC identification and staging.[65]

Value of Image-Based PPM in PC

Clinical Value of Conventional Imaging

PC is a phenotypically heterogenous disease requiring phenotype identification to select optimal therapies. Although pathology, next-generation sequencing, and biochemical measurements play an important role, cross-sectional and nuclear imaging are central to determining disease phenotype and individualized therapy. The simplest case is diagnosis of early-stage disease, where all patients with unfavorable intermediate, high, or very high-risk PC undergo cross-sectional and bone imaging to rule out regional or distant metastases. Those with non-metastatic disease are offered definitive therapy; patients with mPC receive palliative therapy.

For mPC, additional important phenotypic features on imaging guide treatment selection. Patients with high-volume mPC (visceral metastases and/or ≥4 bone metastases with ≥1 beyond the pelvic vertebral column on technetium-99 bone scan) benefit more from upfront chemohormonal therapy than do those with low-volume disease, who benefit from hormonal therapies and prostate radiation.[66,67] Furthermore, patients with mCRPC with bone-only metastatic disease can be offered radium-223.

Clinical Value of Image-Based PPM

There has been substantial effort to develop tumor-specific nuclear imaging for phenotype differentiation at time of biochemical recurrence (BCR) after definitive therapy, when management strictly depends on whether disease recurrence

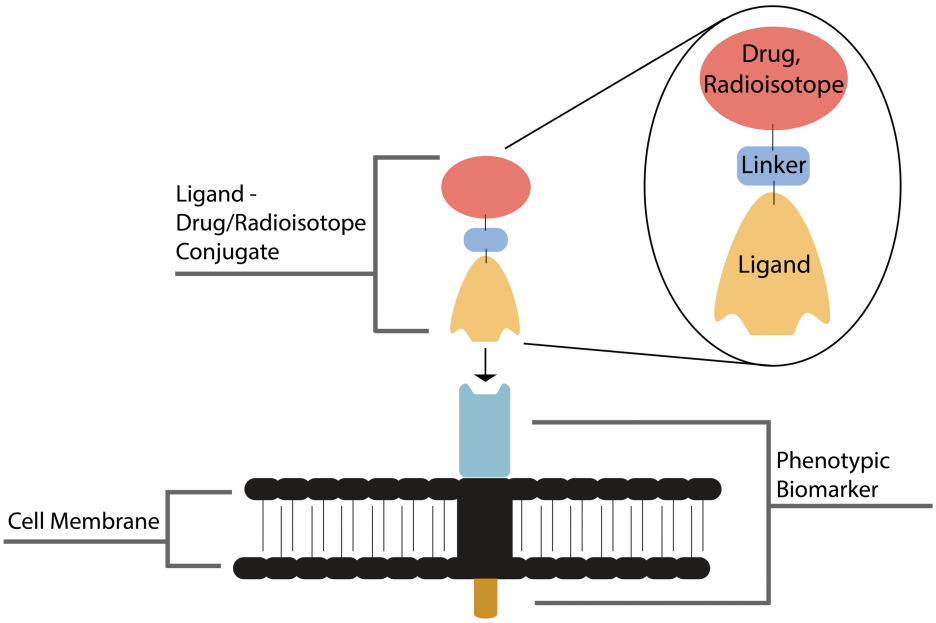

Figure 1. Schema of current ligands that are used in RL theragnostics. The radioligand (RL) theragnostics approach in phenotypic precision medicine uses molecules (ligands) that are targeted against a phenotypic biomarker expressed on cancer cell membranes and which can be conjugated with a diagnostic imaging or a therapeutic radioisotope.

is local, regional, or distant. In 2016, fluciclovine (^{18}F) PET-computerized tomography (CT) was FDA-approved for imaging patients with BCR after initial therapy.[68,69] This radiotracer exploits a phenotype of PC cells in which amino acid transport is significantly upregulated versus most normal tissues.[70]

Schuster et al, in a prospective study (N = 93), compared fluciclovine (^{18}F) PET-CT to indium (^{111}In) capromab pendetide PET-CT (reference standard) for recurrent PC detection.[68] Patients with an initial diagnosis of localized (stage T1c, T2, or T3) prostate adenocarcinoma followed by definitive therapy were included upon suspicion of recurrent PC after negative conventional imaging. Recurrence was based on American Society for Radiation Oncology (ASTRO) criteria or ASTRO/Phoenix criteria.[71,72] Fluciclovine (^{18}F) PET-CT demonstrated an overall (not stratified by PSA value) sensitivity, specificity, and positive predictive value (PPV) in the prostate/prostate bed of 90%, 40%, and 75%, respectively, and in extraprostatic sites of 55%, 97%, and 96%, respectively. Similarly, a subsequent multicenter study of 596 patients demonstrated PPVs for recurrence detection in the prostate/prostate bed and extraprostatic tissue of 72% and 96%, respectively.[73]

Importantly, in the BCR setting, use of fluciclovine (^{18}F) PET-CT versus conventional imaging has led to a personalized approach to therapy selection. A recent prospective randomized trial compared fluciclovine (^{18}F) PET-CT-guided radiation therapy with conventional imaging-guided radiation therapy in 165 patients with BCR after definitive therapy.[74] There was a 35% rate of decision change based on fluciclovine (^{18}F) PET-CT versus conventional imaging. Additionally, 3-year failure-free survival in the fluciclovine (^{18}F) PET-CT and conventional imaging arms were 75% and 63%, respectively (P = .003). The value of fluciclovine (^{18}F) PET-CT-based phenotypic characterization was supported by 2 additional studies that assessed changes in patient management plans based on imaging modality. Overall, 59% and 63% of 213 and 104 patients, respectively, experienced a change in treatment modality.[75,76]

These studies have highlighted the role of fluciclovine (^{18}F) PET-CT in providing personalized image-based therapy selection at BCR and reducing exposure to unnecessary therapeutics. Whether this portends a survival benefit is yet to be determined. Nevertheless, these studies also underline fluciclovine (^{18}F) PET-CT's limited clinical application outside of BCR and low sensitivity when PSA ≤1. Consequently, there remains an unmet need for PC-specific biomarkers that improve diagnostic accuracy and can be used concurrently as a theragnostic target (ie, same target for diagnosis and therapy).

The emergence of PSMA-targeted theragnostics addresses the unmet need for image-based PPM in PC. PSMA, a type II integral membrane glycoprotein, is a glutamate carboxypeptidase highly expressed in PC and an actionable theragnostic target.[77-79] PSMA-based imaging is being increasingly used to individualize therapy at BCR after definitive therapy and upon early biochemical progression in patients with mPC. In 2020, gallium (^{68}Ga) gozetotide became the first FDA-approved PSMA-targeted PET-CT radiotracer for detection of PSMA-positive PC.[80] The FDA also approved another radiotracer in 2021, piflufolastat (^{18}F), for the same indications based on phase II/III clinical data (OSPREY and CONDOR).[81,82] In the OSPREY phase II/III clinical trial, 385 men with high-risk PC undergoing radical prostatectomy with pelvic lymphadenectomy or suspected recurrent or metastatic disease detected on conventional imaging underwent piflufolastat (^{18}F) PET-CT to determine its diagnostic performance versus histopathology. In men with high-risk PC undergoing surgery, median specificity and sensitivity for pelvic node disease was 97.9% and 40.3%, respectively. Median PPV and negative predictive value (NPV) were 86.7% and 83.2%, respectively. Median sensitivity and PPV for detection of metastatic or locoregional disease were 95.8% and 81.9%, respectively.[81] In the phase III CONDOR study, 208 men with BCR underwent piflufolastat

(^{18}F) PET-CT to determine the correct localization rate (CLR). In this study, the overall disease detection rate was 59%–66% and the CLR was 85%–87%.[82]

With the approval of a PSMA-targeted radioligand therapy (RLT), lutetium (^{177}Lu) vipivotide tetraxetan, a new era of image-based PPM will emerge. Lutetium (^{177}Lu) vipivotide tetraxetan is a small-molecule PSMA ligand (vipivotide tetraxetan) linked to a beta-particle emitter, lutetium-177. This RLT demonstrated excellent tolerability and evidence of anti-tumor activity in early phase I and II trials.[83-85] These studies paved the way for the randomized phase III VISION study, which supported FDA approval of lutetium (^{177}Lu) vipivotide tetraxetan on March 23, 2022.[86-88]

In VISION, men with mCRPC and progression on ≥1 androgen-receptor-pathway inhibitor (ARPi) and one-or-more taxane regimens, underwent gallium (^{68}Ga) gozetotide PET-CT screening.[86] Patients were required to have PSMA-positive mCRPC defined by ≥1 PSMA-positive lesion (PSMA uptake greater than the liver parenchyma) as detected by gallium (^{68}Ga) gozetotide PET-CT (see Fig. 2A and Supplementary Online Video S1). Patients with PSMA uptake equal to or lower than the liver parenchyma in any lymph node ≥2.5 cm, any solid-organ lesion ≥1.0 cm, or any bone lesion with soft-tissue component ≥1.0 cm were excluded (sizes in short axis; Fig. 2B). All patients received contrast-enhanced conventional CT for soft-tissue lesion evaluation. Of 1003 patients undergoing PSMA screening, 954 had ≥1 PSMA-positive lesion and 87 had ≥1 PSMA-negative lesion meeting size criteria. 831 patients meeting inclusion criteria were randomized to 4 planned cycles (an additional 2 cycles were permitted for those deemed to have clinical benefit) of lutetium (^{177}Lu) vipivotide tetraxetan at a dose of 7.4 GBq plus SOC versus SOC alone (SOC included hormone therapy, bisphosphonates, denosumab, radiation therapy, or glucocorticoids but did not include chemotherapy, radioisotopes, immunotherapy, or experimental therapy).

Lutetium (^{177}Lu) vipivotide tetraxetan plus SOC significantly improved PFS and OS versus SOC alone (median PFS 8.7 vs 3.4 months, HR 0.40 [99.2% CI 0.29-0.57], $P < .001$; median OS 15.3 vs 11.3 months, HR 0.62 [95% CI

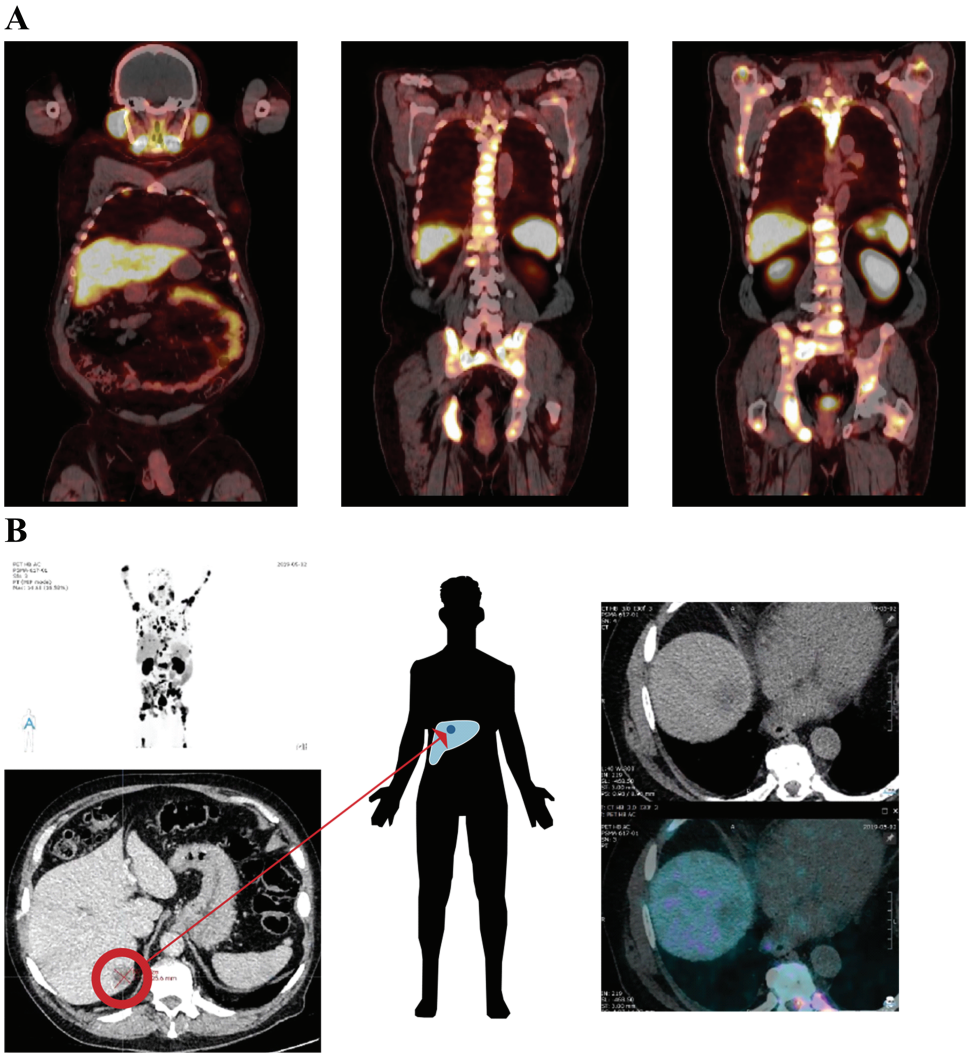

Figure 2. Example imaging from a patient with PSMA-avid disease who would be considered eligible for the VISION study (**A**) and a patient who was not eligible for the VISION study based on the presence of PSMA-negative disease meeting exclusion criteria (**B**) Panel A shows Gallium (^{68}Ga) gozetotide PET images showing PSMA-positive lesions in a patient with high-volume, bone metastatic castration-resistant prostate cancer. Panel B shows a liver metastasis in the right lobe that meets size criteria to assess for exclusion, and uptake is similar or less than liver. Abbreviations: ^{68}Ga, gallium-68; PET, positron emission tomography; PSMA, prostate-specific membrane antigen.

0.52-0.74], $P < .001$).[86] Patients benefited regardless of pattern of spread. However, in a subset of patients with liver metastases, the HR for OS was 0.87 (95% CI 0.53-1.43). The VISION trial highlights the clinical utility of PSMA expression as an image-based, PPM biomarker: patients with PSMA-positive mCRPC on PSMA PET-CT after progression on standard chemohormonal therapy can achieve a survival benefit with PSMA-targeted RLT.

Additionally, TheraP was a randomized phase II trial that evaluated lutetium (^{177}Lu) vipivotide tetraxetan versus cabazitaxel.[89] Participants were men with mCRPC for whom cabazitaxel was considered the next appropriate therapy. Patients were required to undergo a gallium (^{68}Ga) gozetotide PET-CT and concurrent fluorodeoxyglucose (FDG) (^{18}F)-PET-CT. Patients were excluded if there were any lesions positive on FDG PET-CT but negative on PSMA PET-CT. This is a key difference in eligibility criteria versus VISION, where patients were considered PSMA-negative with ≥1 PSMA-negative lesion meeting size criteria on conventional contrast-enhanced CT scans.

Overall, 200 patients were randomized after 291 were screened: 51 were excluded based on discordant positive FDG PET-CT and negative PSMA PET-CT lesions and 29 excluded due to PSMA-negative disease based on low gallium (^{68}Ga) gozetotide uptake. Lutetium (^{177}Lu) vipivotide tetraxetan treatment led to a 23% higher PSA response (PSA decline ≥50% from baseline) and a 16% higher 12-month PFS rate versus cabazitaxel. OS was similar in the lutetium (^{177}Lu) vipivotide tetraxetan group compared with the cabazitaxel group (restricted mean survival time to 36 months was 19.1 vs 19.6 months, 95% CI −3.7 to 2.7).[90] However, lutetium (^{177}Lu) vipivotide tetraxetan treatment yielded a significant improvement in time to cancer-related pain progression and a 20% lower rate of grades 3-4 toxicities versus cabazitaxel.

The VISION and TheraP trials demonstrate the substantial importance of companion diagnostics in the determination of phenotype and appropriate patients for PSMA-targeted therapy. In VISION and TheraP, 12.3% and 27.5% of patients screened, respectively, did not meet PSMA PET criteria.[86,89] While the differences in imaging modality used to determine PSMA eligibility (ie, conventional imaging plus PSMA PET-CT or FDG- and PSMA PET-CT) may play a role in the proportion of PSMA-negative patients seen in these studies, it nonetheless highlights PC as a heterogeneous disease requiring an understanding of PSMA-based imaging interpretation and how it can guide therapy.

PSMA PET-CT can also provide high-value prognostic information. In the INTERIM PET study, 124 men with mCRPC who underwent lutetium (^{177}Lu) vipivotide tetraxetan treatment and received a PSMA PET-CT at baseline and at interim after the completion of 2 cycles of therapy were assessed for OS.[91] Median OS was 13.5 months, and the appearance of ≥1 new lesion on interim PET was found in 59% of patients and associated with poor OS (HR 2.23). Furthermore, the OS of men with progressive disease (increase ≥20% in PSMA-positive tumor volume and appearance of new lesions) was significantly worse versus men with stable disease or partial response (decline ≥20% in PSMA-positive tumor volume and no new lesions) with HRs of 2.52 and 4.16, respectively. Stable disease also was associated with worse OS versus partial response (HR 1.65).

There is emerging evidence that degree of uptake in PSMA-positive lesions strongly correlates with patient outcomes following lutetium (^{177}Lu) vipivotide tetraxetan treatment. In a VISION substudy, investigators assessed pre-enrollment PSMA PET-CT scans of 548 patients who went on to receive lutetium (^{177}Lu) vipivotide tetraxetan in the VISION study.[48] PSMA expression was quantified by PSMA-positive lesions by region, mean standardized uptake value (SUV_{mean}), maximum SUV, PSMA-positive tumor volume, and tumor load (PSMA-positive tumor volume multiplied by SUV_{mean}). Increased whole-body SUV_{mean} was associated with improved clinical outcomes. Patients in the highest quartile for SUV_{mean} had a median radiographic PFS (rPFS) and OS of 14.1 and 21.4 months, respectively, versus patients in the lowest quartile for SUV_{mean} who had a median rPFS and OS of 5.8 and 14.5 months, respectively. Additionally, absence of PSMA-positive lesions in the liver and lymph node and decreased PSMA-positive tumor load were indicators of good prognosis.

Value of Image-Based PPM for the Patient

Conventional imaging plays a crucial role in the determination of disease volume/stage, which guides management and provides prognostic information. The addition of fluciclovine (^{18}F) PET-CT in early BCR after radiation or surgery can help reduce exposure to unnecessary therapies and may improve 3-year failure-free survival, but survival data are lacking.

The ongoing development of PSMA as an image-based biomarker for targeted RLT has created a new paradigm for patient-centered approach to disease management. A patient's disease can now be evaluated for PSMA expression using non-invasive PSMA imaging, which may reduce exposure to more invasive tests and reveal candidates for an additional therapy that offers a survival benefit. Furthermore, PSMA-targeted RLT has consistently shown improved patient-reported quality of life versus standard therapies. In the TheraP trial, patients who received lutetium (^{177}Lu) vipivotide tetraxetan reported meaningful improvements in quality of life and symptoms including fatigue, social functioning, sleep, gastrointestinal and urinary symptoms, and altered sense of taste versus cabazitaxel.[89] Improvements in quality-of-life measures were also seen in the VISION study.[86] Those who received lutetium (^{177}Lu) vipivotide tetraxetan plus SOC versus SOC alone were found to have improvement in time to worsening of their Functional Assessment of Cancer Therapy—Prostate scores (HR 0.54; 95% CI: 0.45-0.66) and their Brief Pain Inventory—Short Form scores (HR 0.52; 95% CI: 0.43-0.63).[86]

Value of Image-Based PPM for the Physician

From the oncologist's perspective, PSMA PET-CT offers an important view of each individual patient's disease phenotype. With information gained from PSMA image-based biomarkers, oncologists are better positioned to offer patient-tailored therapies that maximize benefit. This ranges from tumor localization in early-stage disease and BCR to introducing new systemic therapy in progressive mCRPC. In a recent randomized trial, proPSMA, men with high-risk localized PC underwent first-line imaging with PSMA PET-CT or conventional imaging to compare the accuracy of pelvic node or distant metastatic disease identification.[92] Overall, 30% of the 295 men in the study had pelvic node or distant metastatic disease. The accuracy of PSMA PET-CT versus conventional imaging was 92% versus 65%, respectively. The improved accuracy of PSMA PET-CT led to management changes in 28% of patients versus 15% of patients who received conventional imaging.

Table 3. Ongoing trials evaluating PSMA-targeted RLT for various clinical scenarios in PC.

Trial (NCT#)	Clinical scenario
UpFrontPSMA (NCT04343885)	PSMA-targeted RLT with docetaxel as upfront therapy in high-volume metastatic hormone-sensitive PC
NCT03828838	PSMA-targeted RLT for low-volume metastatic hormone-sensitive PC
PSMAddition (NCT04720157)	PSMA-targeted RLT with standard of care for metastatic hormone-sensitive PC
ENZA-p (NCT04419402)	PSMA-targeted RLT with enzalutamide for metastatic castration-resistant PC
PSMAfore (NCT04689828)	PSMA-targeted RLT versus change in ARDT for metastatic castration-resistant PC
LuTectomy (NCT04430192)	PSMA-targeted RLT for high-risk localized or locoregional disease before prostatectomy
SPLASH (NCT04647526)	PSMA-targeted RLT for metastatic castration-resistant PC that has progressed following ARAT

Abbreviations: ARAT, androgen receptor axis-targeted therapy; ARDT, androgen receptor-directed therapy; PC, prostate cancer; PSMA, prostate-specific membrane antigen; RLT, radioligand therapy.

Thus, PSMA PET-CT has been increasingly adopted for early detection and/or localization of PC at time of BCR. In a prospective survey of physicians who referred patients with BCR at a median PSA of 1.7 ng/mL, physicians were asked to identify intended treatment plans before PSMA PET-CT, after PSMA PET-CT, and again at 3-6 months after imaging.[93] Of 101 evaluable patients, 75% had a positive PSMA PET-CT, resulting in a change in management plan in 61%. Another early analysis of impact on management and outcomes in patients who underwent PSMA PET-CT for BCR detection showed management changes in 60% of 203 patients.[94] Furthermore, there was a 26% decrease in the proportion of patients who were treated with systemic therapy. In patients who received targeted radiotherapy, 45% experienced a complete response.

PSMA PET-CT may also influence management in patients who receive imaging for initial staging (nonsurgical candidates) and restaging after therapy.[95] In a single-center prospective study, PSMA PET-CT changed disease stage in 69% of 197 patients evaluated.[95] Imaging impacted the disease management of patients who were restaged after definitive local therapy (and who did not meet Phoenix criteria for BCR), after other local definitive therapies, and with metastatic disease in 72%, 67%, and 61%, respectively.

Most important, PSMA-targeted image-based biomarkers provide physicians with the ability to offer a life-prolonging treatment that is safe and improves quality-of-life measures versus standard therapies. Patients with progressive mCRPC meeting VISION eligibility criteria will be able to receive PSMA-targeted RLT. Knowledge of the PSMA-expression phenotype can help physicians sequence therapies and reassure patients with a long-term treatment plan. Importantly, there are several ongoing clinical trials that aim to provide survival and outcome data for the use of PSMA-targeted RLT in various clinical scenarios (**Table 3**).

Value of Image-Based PPM to the Healthcare System

Disease assessment with PSMA PET-CT consistently influences treatment decisions and can reduce exposure to unnecessary therapies. For example, patients who are upstaged during their initial evaluation can avoid unnecessary surgery, radiotherapy, or other invasive local therapies. PSMA-targeted imaging and RLT will require a wide range of resources through its implementation in the clinic and ongoing use. These include, but are not limited to, the development of specific quality-control measures, specially trained staff to handle radiolabeled solutions, and clinical staff to administer the medication and monitor patients. At this early stage, analysis of short- and long-term cost-effectiveness is immature and will need to be addressed.

PPM and the Future of Prostate Cancer Management

The role of PPM in the diagnosis, prognostication, and clinical decision making will continue to be a central pillar in PC management in the future. With the recent advancements in phenotypic imaging, namely PSMA PET-CT, the use of PPM in early and late-stage PC will continue to provide important clinical guidance. For example, in early-stage disease, PSMA PET has a higher rate of detection of PC recurrence compared with conventional imaging alone. In a recent prospective study, 44 patients with BCR and negative or equivocal conventional imaging underwent PSMA PET. Among patients with post-PSMA PET treatment decision information available (n=42), PSMA PET-CT led to a change in management (defined as a treatment modality added, switched, or removed) in 71% of patients.[96] Furthermore, a systematic review that included 2639 men with BCR after definitive therapy showed that PSMA PET upon BCR changed management in more than half of the patients and led to a pooled BCR-free survival of 60% at a median follow-up of 20 months.[97]

Despite these observations, further studies are needed to elucidate survival outcomes to guide clinicians on the most appropriate course of action in these patients. One such phase II/III randomized trial, VA STARPORT (NCT04787744), is evaluating CRPC-free survival, radiographic and clinical PFS, and OS among veterans with oligorecurrent PC on PSMA PET-CT who will undergo standard systemic therapy (hormone therapy escalation, salvage local therapy, or chemotherapy) versus PSMA-directed local therapy with surgery or radiation. We are early in our understanding of the wide clinical impacts of PSMA-based PPM, which will likely evolve to be an important clinical tool in all stages of disease.

Summary

Genomic precision medicine has resulted in the ability to predict response to targeted therapies. However, these therapies are limited to a minority of patients. PPM has been an integral part of clinical decision making and therapy selection. Recently, PSMA-targeted imaging and therapeutics has emerged as a new paradigm in the management of men with PC.

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Conflict of Interest

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No proprietary data were used in this manuscript.

Supplementary Material

Supplementary material is available at *The Oncologist* online.

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