The Potential Role for Immunotherapy in Biochemically Recurrent Prostate Cancer

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KEYWORDS

• Systemic therapy • Immunotherapy-based treatment • Prostate cancer • Biochemically recurrent

KEY POINTS

- Currently, there is no clear standard of care for patients with biochemically recurrent prostate cancer and no systemic therapy has been shown to improve survival.
- Immunotherapy-based treatments are potentially attractive options relative to androgen deprivation therapy due to the generally more favorable side-effect profile.
- Biochemically recurrent prostate cancer patients have a low tumor burden and likely lymph node–based disease, which may make them more likely to respond to immunotherapy.
- As modern immunotherapeutic strategies converge with emerging imaging platforms, immunotherapy may find more opportunities for clinical success in biochemically recurrent prostate cancer than in more advanced disease states.

INTRODUCTION

Approximately 191,930 men will be diagnosed and 33,330 will die from prostate cancer in the United States in 2020.[1] Although the majority of patients can be cured with definitive local therapies, 20% to 40% of patients undergoing radical prostatectomy (RP) and 30% to 50% of those undergoing radiation therapy (RT) at some time point will experience treatment failure, known as biochemical recurrence (BCR) or nonmetastatic castration–sensitive prostate cancer.[2] This common disease state, with more than 25,000 new cases annually, is defined by a rising prostate-specific antigen (PSA) in the absence of visible metastases on conventional imaging (computed tomography [CT] or and technetium Tc 99m [Tc99] bone scan).[3,4] The PSA threshold is dependent on the type of local therapy. PSA value greater than 0.2 ng/mL, measured between 6 weeks and 13 weeks after RP, followed by a repeated test confirming a persistent PSA greater than 0.2 ng/mL, is consistent with BCR.[5] On the other hand, BCR after RT is defined as a PSA rise of 2 ng/mL or more above the nadir, with or without androgen deprivation therapy (ADT) (Phoenix definition).[6] The Phoenix definition frequently has been used in clinical practice and has shown improved accuracy over the American Society for Radiation Oncology definition of BCR (defined as 3 consecutive PSA rises after a nadir) in predicting patient outcomes.[7]

In this asymptomatic phase, in a generally healthy population, the most effective management is still uncertain because no intervention has been shown to prolong survival. Consequently, there is no consensus on when to start

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treatment. BCR is a heterogeneous disease with a variable clinical course: some patients have an indolent course for years and may never die from prostate cancer; others may have a rapid progression to metastatic disease with increased risk of mortality from prostate cancer. In a study evaluating BCR after RP, the median time from BCR to clinical progression was noted to be 8 years and from development of metastasis to prostate cancer–specific mortality (PCSM) was 5 years, indicating that median overall survival (OS) from the diagnosis of BCR was approximately 13 years.[8] Based on retrospective studies, BCR patients do have shorter survival (88% 10-year OS rate compared with the 93% 10-year OS rate in men without BCR).[9] This emphasizes the importance of a personalized treatment approach, assessing the risks of developing metastatic disease balanced against the treatment toxicity and efficacy. Currently, there are several acceptable treatment options: (1) local salvage options, which provide last chance for possible cure (salvage radiation therapy for BCR after RP and salvage prostatectomy in selected patients after RT); (2) close surveillance; (3) intermittent or continuous ADT; and (4) clinical trials.

PATIENT SELECTION AND TIMING OF THERAPY

ADT is a standard systemic therapy for BCR patients who are not candidates for or who have failed or refused salvage treatment. Although ADT overall is manageable, it has a variety of side effects, mostly affecting quality of life as well as having an impact on other morbidities, such as sarcopenia, cardiovascular disease, osteoporosis, and diabetes.

The critical yet still somewhat ambiguous question for patients with BCR is whether earlier ADT treatment is beneficial for BCR patients. Retrospective studies demonstrated that early ADT has no significant effect on OS because it may decrease PCSM but increases non–PCSM.[10–12] Garcia-Albeniz and colleagues[13] presented a retrospective study of 2012 BCR patients from CaPSURE registry at the 2014 annual American Society of Clinical Oncology meeting. Patients who underwent immediate ADT (within 3 months of relapse) had no significant advantage in PCSM (hazard ratio [HR] 1.15) and all-cause mortality (HR 0.94). The immediate ADT arm had an estimated 5-year OS rate of 85.1% whereas the deferred ADT arm (>2 years after relapse) had 87.2%. The estimated 10-year OS was 71.6% in both arms, again demonstrating no significant advantage of early ADT treatment.[13] More recently, an analysis of 2 phase 3 trials evaluating early ADT in BCR was presented together in a preplanned analysis of 339 patients who were prospectively evaluated. Although an initial publication (including some metastatic patients who were castration sensitive) suggested a benefit of ADT, the studies demonstrated that early ADT did not improve survival in this BCR population.[14,15]

One of the key prognostic markers for potentially predicting outcomes in patients with BCR is PSA doubling time (PSADT), because several studies have reported the association between PSADT and risk of disease progression and development of metastatic disease, PCSM, and all-cause mortality.[3,16,17] Klayton and colleagues[18] analyzed 432 BCR patients treated with 3-dimensional conformal radiotherapy or intensity-modulated radiotherapy from 1989 to 2005 and demonstrated that PSADT is a significant predictor of prostate cancer–specific survival. Early initiation of ADT in patients with PSADT less than 6 months was significantly associated with improved prostate cancer–specific survival, although the survival benefit was less apparent in patients with longer PSADT.[18] Another retrospective study of 8669 patients with prostate cancer treated with RT (5918 patients) or RP (2751 patients) found that a PSADT less than 3 months also was significantly associated with PCSM.[16] Choueiri and colleagues[19] reported a retrospective study of 3071 prostate cancer patients at Duke University (between 1988 and 2008) who underwent RP. After a median follow-up of 7.4 years, BCR was diagnosed in 17.8% patients and 14.8% had died of all causes. The median follow-up after PSA failure was 11.2 years. In patients with BCR, a PSADT less than 6 months was associated with a significantly increased risk of overall death from any cause (HR 1.55).[19] D'Amico and colleagues[16] have reported that patients with PSADT greater than 15 months after RP are at minimal risk for prostate cancer metastasis or PCSM, whereas those with a PSADT of 3 months or less are at very high risk. In addition to these studies, a natural history study of 1997 patients who underwent RP and were followed for a mean of 5.3 years was reported by Pound and colleagues.[8] They found that 315 patients (15%) developed BCR, and 103 patients (34%) were not treated with immediate ADT developed metastatic disease. Those who developed metastatic disease more rapidly had PSADT less than 10 months, a Gleason score of greater than or equal to 8, and BCR onset within 2 years after RP.

For patients and providers who elect to treat BCR with ADT, questions remain about the type of ADT and treatment duration. Limited

data exist on the utility of monotherapy with gonadotropin-releasing hormone agonist or antagonist, antiandrogens, or combined androgen blockade. Intermittent ADT (8 months of ADT followed by treatment break until PSA >10 ng/mL) is the preferred option for many clinicians and is based on results of a large randomized phase III, noninferiority study randomly assigning 1386 men with BCR after RT to intermittent or continuous ADT. Intermittent ADT was noninferior (HR 1.02; 95% CI, 0.86–1.21) and quality of life was significantly superior compared with the continuous ADT.[20]

THE ROLE OF IMMUNOTHERAPY IN PROSTATE CANCER

At this point, the role for immunotherapy in prostate cancer is somewhat limited compared with other genitourinary malignancies, such as urothelial cancer and renal cell cancer. Furthermore, most immunotherapy trials have been conducted in men with advanced prostate cancer who already have progressed on ADT, that is, metastatic castration–resistant prostate cancer (mCRPC). In a phase 3 study, sipuleucel-T showed a survival benefit in minimally symptomatic men with mCRPC.[21] Sipuleucel-T is activated cellular therapy (or vaccine) that is derived from a patient's own peripheral blood mononuclear cells (PBMCs). Once removed from a patient's circulation using apheresis, these PBMCs are exposed to the prostate cancer antigen prostatic acid phosphatase (PAP) as well as the cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF) for approximately 48 hours ex vivo. The cells then are reinfused back into the patient every 2 weeks for total of 3 doses.

Despite these findings, the role of sipuleucel-T has been limited for several reasons. First and foremost, the clinical trial demonstrating an improvement in OS did not show a short-term improvement in progression-free survival (PFS). These findings predated the robust clinical development of checkpoint inhibitors; thus, practitioners were not accustomed to the potential delayed clinical impact seen with immune-based therapies. This led to some degree of discomfort using a therapy that showed an OS benefit without a benefit in PFS. This was complicated only further by the lack of substantial PSA declines, even though the Prostate Cancer Clinical Trials Working Group (PCWG) guidelines state that PSA responses should not be used to determine clinical benefit in mCRPC.[22] Thus, although sipuleucel-T remains available today, the treatment by providers is limited based at least partially on dogma that has roots before the modern immune-oncology era as well as subsequent approvals of more conventional antiandrogens like enzalutamide and abiraterone.

Immune checkpoint inhibitors have a limited role in subpopulations of mCRPC patients. Patients with specific genetic mutations, such as microsatellite instability and CDK12 inactivation[23,24] (seen in approximately 5%–10% of prostate cancer patients), appear to respond to PD-1 and PD-L1 inhibition. Response rates to those forms of immunotherapies in mCRPC, however, are approximately 50% based on a small amount of data available thus far. In the largest experience reported to date of PD-1/PD-L1 inhibition, pembrolizumab was reported to have a minimal impact in an unselected population.[25]

Ipilimumab, an anti–CTLA-4 antibody, has been evaluated in 2 large phase 3 trials in mCRPC, both before and after chemotherapy. The first trial, done in the more advanced, postchemotherapy setting after 8-Gy radiotherapy to 1 site of metastatic disease, was nearly positive for its OS endpoint, 11.2 months versus 10.0 months with placebo (HR 0.85; $P = 0{\cdot}053$).[26] These findings raised hopes for a concurrent trial being done in patients who were chemotherapy-naïve and thus potentially had more time to benefit from an immune-based therapy. This trial failed, however, to meet its primary endpoint of OS.[27] These findings, coupled with the toxicity of anti–CTLA-4 inhibition, reduce enthusiasm for testing ipilimumab in patients with BCR.

RATIONALE FOR IMMUNOTHERAPY IN BIOCHEMICALLY RECURRENT PROSTATE CANCER

There are several potentially important biologic characteristics that differentiate the BCR patients compared with patients with advanced mCRPC, where several studies, including those with immune checkpoint inhibitors, have been negative[25–27] (**Table 1**). Patients with BCR have microscopic metastatic disease, not seen on conventional imaging. Thus, compared with patients with macroscopic tumors in advanced disease, it is likely that tumor-related immune suppression (possibly related to increased immunosuppressive cytokines) would be decreased.[28] Furthermore, those micrometastatic foci in BCR appear to be more likely present in lymph nodes as opposed to the bone microenvironment, where 90% of men with mCRPC have substantial disease burden.[29] Biologically speaking, the lymph node may be more conducive to an immune response than the metastatic bone microenvironment.[30]

Table 1
Important biologic differences between patients with biochemically recurrent prostate cancer and metastatic castration–resistant prostate cancer

	Biochemically Recurrent Prostate Cancer	Metastatic Castration–Resistant Prostate Cancer
Testosterone levels	Normal physiologic levels	Castrate levels of testosterone
Predominant Sites of Disease	Lymph nodes (based on early PET imaging)	Bone
Tumor Burden	Minimal—not seen on conventional CT or Tc99 bone scan	Variable—but substantial enough to be seen on conventional imaging

Finally, the impact of long-term testosterone suppression and androgen receptor–targeted therapies on the immune microenvironment has been inadequately studied, although studies of immune checkpoint inhibitors in lung cancer have suggested that men may respond better than women.[31] Furthermore, castration may have an impact on the immune microenvironment by increasing suppressive factors, such as myeloid-derived suppressor cells.[32] Although it remains unclear if any of these factors truly potentiate immunotherapy in BCR over mCRPC, these could be reasons why clinical outcomes with immunotherapy may be different in BCR compared with advanced prostate cancer.

Another key aspect for any therapy in BCR is toxicity. ADT is already available and, although it has unclear benefits, the short-term impact on PSA usually is positive and often allays anxiety in this population of men with rising PSA values. For many BCR patients, the limiting aspect of ADT is toxicity. This highlights an important treatment consideration for men with BCR because these patients have no symptoms from their disease. As data from cancer prevention trials show, patients without symptoms often are reluctant to take therapies that have substantial toxicity.[33,34] Thus, relative to ADT or chemotherapy, immunotherapy (especially vaccine-based strategies) often carries minimal side effects and thus is more likely to be acceptable in the population.

Although ADT has not been shown to improve survival in this population, nonhormonal treatments that can alter PSADT may delay the morbidity associated with the development and treatment of metastatic disease, as reported by a retrospective study of BCR patients who were enrolled in trials at Johns Hopkins University.[35] For 146 patients treated in 4 clinical trials, there was a benefit when therapies were able to improve PSA kinetics 6 months after therapy. For patients who had prolongation of PSADT, the metastasis-free survival (MFS) was 63.5 months compared with 28.9 months in those whose PSADT was unchanged.

These findings could highlight the potential opportunity and benefits for immunotherapy in this population as means to delay metastatic progression and perhaps improve long-term outcomes. Data from previous studies, including sipuleucel-T, suggest that immunotherapy in prostate cancer may slow the growth rate of the disease. This could explain why sipuleucel-T demonstrated a survival advantage in a phase 3 study in mCRPC without showing a short-term benefit in PFS or PSA.[21,36] This benefit may be especially valuable in BCR patients who may live a decade or more whereas mCRPC patients may progress in months and die within years. The potential to allow time for an immune response to develop may be critical for strategies that have an impact on the immune microenvironment beyond simple immune checkpoint inhibition.

SELECTED STUDIES OF IMMUNOTHERAPY IN BIOCHEMICALLY RECURRENT PROSTATE CANCER

Several trials previously have explored the potential role of immunotherapy in BCR prostate cancer (**Table 2**). Therapeutic cancer vaccines generally have minimal toxicity and thus they are viable candidates for the asymptomatic men with BCR. Several studies have explored the potential role for therapeutic cancer vaccines of having an impact on prostate cancer in this disease state, often paired with ADT.

Sipuleucel-T was administered in patients with BCR in a randomized trial in patients who developed a rising PSA after RP within 2 years after surgery.[37] This multicenter trial randomized patients in a 2:1 fashion to either placebo or sipuleucel-T, administered at what has become the standard schedule of infusions, at weeks 0, 2, and 4. ADT was given prior to sipuleucel-T by 3 months to

Table 2
Selected trials of immunotherapy in biochemically recurrent prostate cancer

Treatment	Design and Key Results	Citation
Sipuleucel-T	• Patients: rising PSA within 2 y after surgery • ADT followed by sipuleucel-T • Sipuleucel-T was associated with improved PSADT after testosterone recovery	Beer et al,[37] 2011
Sipuleucel-T	• Patients: PSADT less than or equal to 12 mo • Evaluated sequence of ADT and sipuleucel-T • Better immune responses seen with sipuleucel-T followed by ADT but no difference in PSA recovery	Antonarakis et al,[38] 2017
PROSTVAC	• PROSTVAC followed by ADT • PROSTVAC alone improved PSADT from 5.3 mo to 7.7 mo • PROSTVAC + ADT resulted in complete responses in 20 of 27 patients (74%)	DiPaola et al,[40] 2015
PROSTVAC	• Prostvac in patients with PSADT 5–15 mo • Subset of patients had delayed but sustained PSA declines (range 10%–99%)	Madan et al,[43] 2018
TARP vaccine	• Patients with BCR and HLA-A*0201 • Patients treated with vaccine had slowing of slope log(PSA) in 72% of patients at 24 wk	Wood et al,[46] 2016
pTVG-HP	• Patients with BCR and a PSADT <12 mo • No difference in PSADT or MFS vs GM-CSF control • Improvements seen in 23% of vaccine patients on NaF PET imaging	McNeel et al,[49] 2019

Data from Refs.[37,38,40,43,46,49]

4 months. The primary endpoint of the trial was time to biochemical failure, but the study did not show a clear impact of sipuleucel-T (18 months) relative to the control group (15.4 months; HR 0.936; $P = .737$). Despite these findings, sipuleucel-T had an impact on increasing (ie, improving) PSADT in patients after testosterone recovery of 48%, or 155 days versus 105 days ($P = .038$).

A subsequent trial using sipuleucel-T sequenced with ADT evaluated sequences of ADT before and after sipuleucel-T in BCR patients. Although the study found no difference in mean time of PSA recurrence between the sequences, there were greater immune responses (antigen-specific T-cell proliferation and humoral responses) among patients who received vaccine followed by ADT. These data perhaps suggest an optimal sequence of immunotherapy when paired with ADT in BCR.[38]

PROSTVAC is a viral vector–based immunotherapy that is composed of 2 recombinant viral

vectors, each encoding transgenes for PSA, and a triad of costimulatory molecules (B7.1, ICAM-1, and LFA-3). PROSTVAC initially was studied in a phase I trial, showing safety and feasibility in 15 patients who received recombinant fowlpox-PSA (triad of costimulatory molecules alone or recombinant vaccinia-PSA/triad of costimulatory molecules followed by recombinant fowlpox-PSA/triad of costimulatory molecules on a prime and boost schedule with or without recombinant GM-CSF protein or recombinant fowlpox- GM-CSF vector).[39] A further phase II trial in the form of E9802 was launched with an aim of determining safety and effectiveness of PROSTVAC-V (vaccinia)/TRICOM on cycle 1 followed by PROSTVAC-F (fowlpox)/triad of costimulatory moleculaes (TRICOM) for subsequent cycles in combination with GM-CSF as a first step followed by additional ADT in step 2 in patients with PSA progression without visible metastasis.[40] The primary endpoint for step 1 was to characterize the PSA velocity but also to determine PSA progression at 6 months, and the endpoint for step 2 was to determine PSA response in combination with ADT. The trial results were promising, with a majority of patients, at 63% (25 of 40 patients in step 1), achieving PFS at 6 months with potential slowing of logarithmic PSA velocity translating to a delay in PSADT from 5.3 months to 7.7 months. Furthermore, there were complete responses in 20 patients of 27 patients (74%; 90% CI, 57–87) who were eligible to be evaluated for step 2 (the additional ADT arm). The use of PROSTVAC was supported in other populations of prostate cancer, including that of mCRPC, where phase II data showed an 8.5-month improvement in OS and 44% reduction in the risk of death,[41] although a follow-up phase III trial of PROSTVAC in asymptomatic and minimally symptomatic mCRPC patients unfortunately showed no improvement in OS.[42]

Another study of PROSTVAC in BCR evaluated patients with a PSADT between 5 months and 15 months and treated them with 6 months of PROSTVAC and no ADT compared with surveillance. Preliminary data indicated that a subpopulation of patients (approximately 20%) had delayed PSA declines after an initial rise. The decline often occurred after completing vaccine and while on no ADT or additional therapy. Declines ranged from 10% to 99%, and many declines were sustained for many months. These data highlight the potential to for late effects in this population that otherwise would be surveilled.[43]

T-cell receptor alternate reading frame protein (TARP) is a novel immunogenic protein that is abundantly expressed by prostate cancer epithelial cells, initially described in 1999,[44] that is up-regulated by androgens and variably expressed in different states, including in the aggressive prostate cancers, metastatic prostate cancer,[45] and both hormone-sensitive and castration-resistant disease, making it an attractive antigenic target for prostate cancer vaccine therapy. A first-in-human pilot study involved 41 patients with hormone-sensitive BCR prostate cancer with HLA-A*0201 who were randomized in a 1:1 ratio to either cohort A, where patients received 1 mg of each peptide emulsified together with GM-CSF in Montanide ISA51VG and GM-CSF given subcutaneously, or cohort B patients, who were given autologous dendritic cells pulsed with each peptide plus keyhole limpet hemocyanin intradermally.[46] The study aimed at determining safety of the vaccine approach and measuring the immunogenicity of the TARP peptide vaccination because it has an impact on the PSA velocity (as expressed as slope log[PSA]) or the PSADT and tumor growths. Given a schedule of every 3 weeks for a total of 5 vaccinations with an optional sixth dose of vaccine at 36 weeks, the study showed a majority of patients had a statistically significant slowing in the postvaccination slope log(PSA) (equivalent to an increase/lengthening in PSADT), with declines seen in 72% of patients reaching 24 weeks and 74% reaching 48 weeks ($P = .0012$ and $P = .0004$, respectively, for comparison of overall changes in slope log [PSA]). Although TARP vaccination also showed a 50% decrease in median tumor growth rate, only 15% of patients exhibited decrease in serum PSA levels.

PAP has been shown to be an effective target for sipuleucel-T and there are additional strategies to target PAP. Alternatives, such as using a DNA vaccine encoding PAP that can elicit antigen-specific $CD8^+$ T cells, were studied in early phase I/II trials utilizing DNA vaccine (pTVG-HP [MVI-816]) that encodes PAP in men with non-mCRPC (nmCRPC); 22 patients were enrolled in this study and 3 (14%) developed PAP-specific interferon gamma–secreting $CD8^+$ T cells.[47] Another trial in nmCRPC patients established safety and showed early potential of a plasmid DNA vaccine. Vaccines are given as 6 injections at 2-week intervals and then either quarterly (arm 1) or as determined by multiparameter immune monitoring (arm 2). At 2 years, 6 of 16 patients (38%) remained metastasis-free.[48] A phase II trial, that utilized the same DNA vaccine, enrolled 99 patients with hormone-sensitive prostate cancer and PSADT of less than 12 months, with treatment either with pTVG-HP coadministered intradermally, with 200-mg GM-CSF, or 200-mg GM-CSF alone 6 times biweekly and

then quarterly for 2 years.[49] The primary endpoint was 2-year MFS, which showed no difference between the study arms (41.8% vaccine vs 42.3%, respectively; $P = .97$). Changes in PSADT and median MFS were not different between study arms (18.9 months vs 18.3 months, respectively; HR 1.6; $P = .13$). Decreases in standardized uptake value were seen on sodium fluoride (NaF) PET/CT scan in 23% of vaccine patients versus increases in 50% of controls ($P = .07$).

Selected Current Trials of Immunotherapy in Biochemically Recurrent Prostate Cancer

Although prostate cancer is generally thought to be non-responsive to immune checkpoint inhibitors because of low tumor mutational burden (TMB) and limited T cell immune infiltration, several ongoing studies are evaluating immune checkpoint inhibitors based on immune potential synergies or patient selection.[50] Several studies, however, have reported notable expression of PD-L1, which is up-regulated by interferon-gamma signaling,[51,52] in primary prostate cancer specimens (up to approximately 60%) and CRPC tissue (up to approximately 20%), implying active inflammatory signaling. Inflamed tumors are associated with particularly high risk of recurrence.[52] In a study of RP specimens, PD-L1 expression in greater than or equal to 1% of tumor cells ranged from 13.8% in tumors of any grade to 26.5% of Gleason score 8 to 10 tumors.[53] Moreover, PD-L1 expression was associated with $CD8^+$ T-cell infiltration. This is remarkably similar to the 17% of primary prostate cancers in a separate study that were found to have a DNA damage repair and inflammation gene expression signature predictive of Stimulator of interferon genes (STING) activation as well as increased risk of BCR.[54]

Thus, 1 hypothesis is that patients with BCR could be particularly enriched for having immunogenic tumors and that checkpoint inhibition could be more effective in the micrometastatic and precastration settings. This is being tested in a phase 2 study of nivolumab monotherapy for patients with high-risk BCR prostate cancer based on a PSADT of less than 10 months (NCT03637543). Diagnostic core biopsies (for patients who received primary radiation) or prostatectomy specimens are assessed for tumor PD-L1 expression greater than or equal to 5% by the E1L3N clone, and patients then are assigned to a PD-L1–positive or PD-L1–negative cohort. Once enrolled, if patients experience PSA stabilization or responses, then they can continue to receive nivolumab for up to 2 years in the absence of progression to metastatic disease or unacceptable toxicity. Patients who have isolated PSA progression at 12 weeks can be continued on treatment at investigator's discretion if they are believed to be clinically benefitting (for example, if they experience decreased PSADT time) and have not demonstrated symptomatic or radiographic evidence of metastatic disease.

The primary endpoint is disease control, defined as PSA after 12 weeks of nivolumab that is less than 10% above baseline, or below baseline, and with no symptomatic/radiographic progression. This is more stringent than the PCWG3 definition, which considers PSA progression to be a rise of at least 25% of baseline, because if patients enter the study with a 10-month PSADT, then they would be expected to have a 23% increase in PSA without any intervention.

A variety of planned correlative studies will allow assessment of tumor-based and blood-based biomarkers, including genomics, gene expression, immune tumor microenvironment, T-cell clonality, and soluble biomarkers. These also will help advance understanding of additional mechanisms of resistance to checkpoint inhibition to form the basis for future trials in this space.

Given the promising results of this trial in advanced disease, the combination of pTVG-HP with PD-1 blockade pembrolizumab in patients with castration-sensitive, PSA-recurrent prostate cancer currently is under way (NCT02499835). The combination offers a better concurrent and synergistic approach, rather than a sequential approach, as seen in a combination trial.[55] This therapeutic strategy serves to capitalize on improving antineoplastic activity of the DNA vaccine theoretically by increasing up-regulation and T-cell activation at the time of PD-1 blockade[56] and that PD-1–regulated T-cell activation also was seen in patients treated with a DNA vaccine encoding PAP.[57]

A similar combination strategy is being evaluated at the National Cancer Institute, building on the late PSA declines seen with PROSTVAC alone in BCR patients.[43] In this follow-up study, patients will be surveilled for 4 months before starting multiple vaccines (PROSTVAC and the CV-301 targeting CEA/MUC1). Then, after 4 months of both vaccines, patients will be treated with bintrafusp alfa, a bifunctional fusion protein targeting transforming growth factor β and PD-L1. Immune correlates will evaluate the impact of multiple vaccines in this population compared with one in the previous study and evaluate changes after bintrafusp alfa is added (NCT03315871).

The Future Perspective of Biochemically Recurrent Prostate Cancer in the Age of Modern Imaging

CT scans are considered standard for staging of many solid tumors, including prostate cancer. Although they are not perfect and can miss nodal metastases if size is less than 1.5 cm, they are effective for evaluation of visceral and bone metastases. The gold standard for detection of bone metastases remains Tc99 bone scan; however, its utility is limited in BCR patients with lower PSA values. Both CT and Tc99 bone scans have been utilized for decades in BCR patients; however, the question is whether earlier identification of metastatic disease can influence treatment decisions.

Many efforts have been made to develop novel imaging modalities. One of the most commonly used novel imaging tools is fludeoxyglucose F 18–PET scan; however, this scan has limited sensitivity for detection of lymph node metastases.[58] The most promising novel imaging modalities for the BCR include choline C 11–PET (choline metabolism is impaired in prostate cancer), ^{68}Ga/^{18}F–prostate-specific membrane antigen (transmembrane protein highly expressed in prostate cancer), and anti–fluorocyclobutane F 18–1-carboxylic acid (Axumin) a synthetic L-leucine analog that demonstrates uptake in prostate cancer. Those new modalities have entered into clinical practice, with higher detection of metastatic disease at low PSA levels; however, more prospective studies are needed to define utility of novel scans in making treatment decisions.[58]

Although one point of view may suggest that modern imaging studies will make the disease state of BCR obsolete, that probably is a limited perspective. Some proponents of modern imaging in BCR may suggest that once metastatic sites are identified, the patients have de facto metastatic castration–sensitive disease and thus lifelong ADT is indicated along with docetaxel or antiandrogen therapy. But none of the trials in metastatic castration–sensitive prostate cancer allowed molecular or PET imaging to be the sole mechanism to detect metastatic disease.[59–61] In addition, these studies predominantly evaluated newly diagnosed patients and less frequently in patients with disease recurrence. Furthermore, the natural history of BCR is so variable that over-treatment of patients with BCR would be inevitable. It is unclear if patients would live longer starting ADT for PET-positive metastatic disease compared with waiting until conventional imaging detects their cancer. The toxicity would be magnified if chemotherapy or antiandrogens are added, not to mention the financial ramifications of such choices for the more than 25,000 men a year with BCR.

The alternative strategy would be to treat oligometastatic PET-positive sites in patients with BCR (based on conventional imaging). Although is increasingly is being done in the community, often with the goal of cure, emerging data suggest that it is most effective in patients with limited sites of disease.[62] Furthermore, when different modern (ie, PET) strategies are compared, the metastatic sites do not always overlap.[63] Thus, even with modern imaging, technology still may limit the oligometastatic sites that could be seen and then targeted.

The evolution of modern imaging actually may open up a new therapeutic front in prostate cancer in the BCR space or facilitate patient selection for treatment escalation/de-escalation. The terms may be different (eg, PET-positive disease or PET metastatic, castration sensitive) but once imaging can detect the disease, one of the greatest constraints on large-scale therapeutic development in BCR will have been removed—a lack of an intermediate endpoint that can demonstrate efficacy. All trials in BCR, whether or not they include immunotherapy, now should require molecular imaging to define their clinical impact beyond just PSA values or PSA kinetics. If immunotherapy strategies can demonstrate delayed progression on modern imaging or even improvements on scans, then that could certainly open the door to clinical development, applying the same logic that has been utilized in developing the ICECaP approach for MFS as an endpoint.[64] In this way, modern imaging is not the end of BCR; it actually opens a new frontier in prostate cancer research, much like CHAARTED and STAMPEDE did with metastatic, castration-sensitive disease. In some ways, this disease state will be more complicated because treatments will be required to balance long-ranging, life-altering impact with short-term effects on quality of life. If immunotherapy strategies can have an impact on the disease in this space (perhaps because of smaller tumor burden, anatomic location, or less castration-related immune suppression) and demonstrate that impact on modern imaging, they may have advantages in this asymptomatic population compared with ADT-centric regimens with immediate and long-term side effects. This is a unique time in prostate cancer, where imaging and immunotherapy may evolve symbiotically in the BCR population to better define how both can be used in the future.

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