# Management of Biochemically Recurrent Prostate Cancer After Local Therapy: Evolving Standards of Care and New Directions

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**Abstract:** Among men treated with prostatectomy or radiation therapy for localized prostate cancer, the state of an increasing prostate-specific antigen (PSA) level is known as biochemical recurrence (BCR). BCR can be predictive of the development of subsequent distant metastases and ultimately death, but BCR often predates other signs of clinical progression by several years. Although patients may be concerned about their rising PSA levels, physicians attempting to address patient anxiety must inform them that BCR is not typically associated with imminent death from disease, and that the natural history of biochemical progression may be prolonged. Misinterpretation of the significance of early changes in PSA may cause patients to receive androgen deprivation therapy (ADT) prematurely, especially in settings where the disease is unlikely to impact survival. In addition, knowledge of the morbidities associated with ADT (hot flashes, impotence, sarcopenia, metabolic syndrome, bone loss, and increased risk of vascular disease) has accelerated the search for alternative treatment options for these patients. Clinical trials investigating when and how to best use and supplement hormonal therapies in this patient population are under way, as are trials of novel nonhormonal targeted agents, immunotherapies, natural products, and other pharmaceuticals that have been approved by the US Food and Drug Administration (FDA) for other indications. This review will summarize the acceptable standards of care for the management of biochemically recurrent prostate cancer, and will also outline some novel experimental approaches for the treatment of this disease state.

## Introduction

Fewer than 12% of the 241,700 men expected to have been diagnosed with prostate cancer in the United States in 2012 will die from this disease.[1] Many more patients will experience rising prostate-specific antigen (PSA) levels following local therapy, a condition known as biochemical recurrence (BCR; Figure 1). Physicians treating patients with BCR face a difficult set of decisions in attempting to delay the onset of metastatic disease and death while avoiding over-treating patients whose disease may

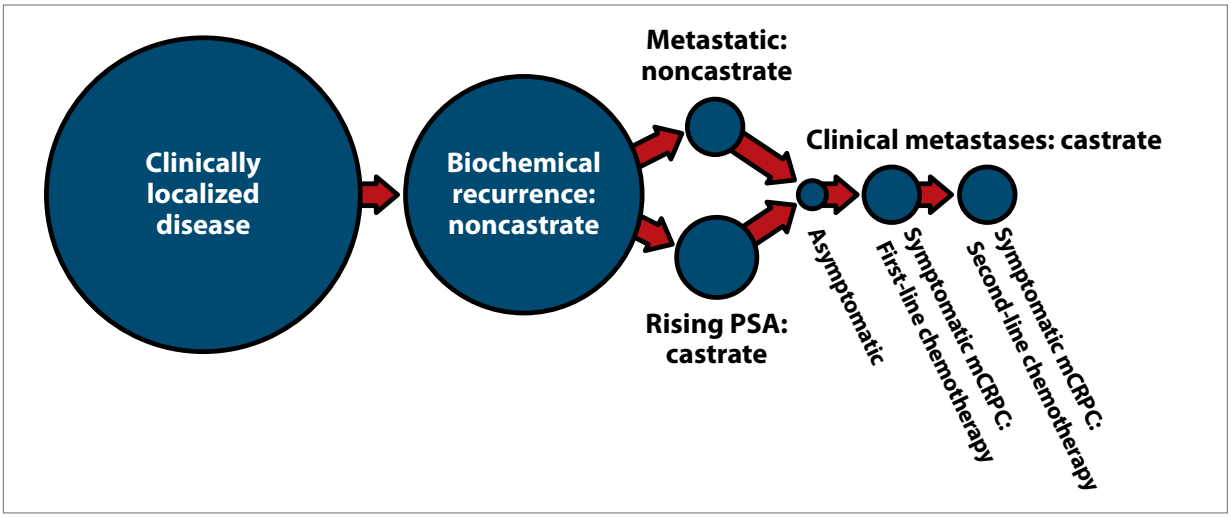


**Figure 1.** Proportional prostate cancer clinical states model. The circles represent the proportional prevalence of each disease state. Adapted from the prostate cancer clinical states model[43] and the prostate cancer clinical states prevalence model.[44] mCRPC=metastatic castration-resistant prostate cancer; PSA=prostate-specific antigen.

never affect their overall survival or quality of life. In this generally healthy population, effective management requires that physicians evaluate PSA levels, as well as clinical and radiologic indicators, in order to balance the morbidity and efficacy of proposed treatments against the risks of metastatic progression.

Radical prostatectomy (RP), which is used in approximately 75,000 newly diagnosed prostate cancer cases each year (30% of those diagnosed),[2] can cure appropriately-selected patients with localized disease, as can external-beam radiation therapy (RT) and brachytherapy, which are used in approximately 60,000 newly diagnosed cases (25% of those diagnosed).[3] However, 20–40% of patients undergoing RP[4,5] and 30–50% of patients undergoing RT will experience biochemical recurrence within 10 years.[6] There is currently no consensus regarding optimal management of this disease state. Reasonable options include: 1) salvage radiation therapy, if progression has occurred after prostatectomy; 2) observation with close surveillance; 3) androgen deprivation therapy (ADT), either intermittent or continuous, initiated upon PSA recurrence or deferred until after clinical/radiographic progression; or 4) enrollment in investigational clinical trials.[7]

Not all patients with BCR prostate cancer have the same prognosis, and stratification of patients into appropriate risk groups is essential. One of the strongest predictors of metastasis and death is the PSA doubling time (PSADT), a mathematical determination of the length of time (in months) needed for the PSA level to double in a given patient. BCR patients with a PSADT greater than 9 months, for example, have a high probability of long-term, metastasis-free survival and overall survival.[8] In addition, among patients with a slow PSADT, radiographic evidence of metastatic disease is likely to be discovered before patients experience clinical symptoms from their metastatic disease. Thus, the value of early ADT is unknown in this population, and research is needed to determine the optimal initiation point of ADT (early vs deferred and continuous vs intermittent) before physicians and patients can act with confidence. Similar questions about optimal treatment and best timing of treatment arise with other stratification factors, such as time-to-BCR, patient age and comorbidities, Gleason score, and pathologic stage. Therefore, multiple clinical factors must be taken into consideration when planning the optimal course of treatment for a particular patient with PSA-recurrent prostate cancer.

In recent years, the search for alternatives to chronic ADT for BCR prostate cancer patients has intensified. A wealth of clinical trials have focused on alternative (ie, non-castrating) hormonal agents, timing of conventional ADT, supplementing ADT with novel agents, or using hormone-sparing treatments in these patients (novel biologic agents, immunotherapies, natural products, and pharmaceuticals that have been approved by the FDA for other diseases but have demonstrated preclinical activity in hormone-sensitive prostate cancer). This review outlines the results of some of the pivotal trials that guide our practice, as well as relevant retrospective analyses describing the natural history of PSA-recurrent prostate cancer. We will conclude by discussing the status of several ongoing investigational trials focusing on treatment of patients with BCR prostate cancer.

## Defining Biochemical Recurrence

Precision in defining BCR is important in order to identify patients at risk of disease progression, to determine the timing for additional treatment options (such as ADT),

and to compare the efficacy of different treatments in the setting of clinical trials. Absent a common definition of BCR, predictions of metastatic progression and mortality would remain unreliable. Of note, the definition of PSA recurrence is dependent upon the type of local therapy received: prostatectomy or radiation therapy. To describe biochemical recurrence after RP, a panel of experts from the American Urological Association (AUA) evaluated 53 different definitions of BCR following RP observed in the literature, and recommended adoption of a single definition. This involved the presence of a PSA greater than 0.2 ng/mL measured 6–13 weeks after RP, followed by a confirmatory test showing a persistent PSA greater than 0.2 ng/mL.[9] Ultra-sensitive PSA assays have recently improved detection levels down to 0.01 ng/mL, and may possibly lead to better treatment outcomes through earlier adoption of salvage radiation therapy following RP.[10,11] However, false positives occurring because of trace amounts of PSA produced by residual benign prostatic tissue, along with uncertainty about whether ultra-low levels of PSA will be followed by continued PSA increases, have led practitioners to continue to rely on the AUA definition for determining when clinically-relevant biochemical recurrence has occurred after prostatectomy.

The definition of BCR following RT is more problematic. The AUA panel found 99 different definitions of BCR following RT, among which the American Society of Therapeutic Radiology and Oncology (ASTRO) definition was the most common. This was defined as the midpoint between PSA nadir and the first of 3 consecutive rises in PSA.[9] Although the AUA recommends that the ASTRO definition be adopted, it has several weaknesses, including failure to use the PSA level at nadir as a risk factor and the requirement to backdate the time of biochemical recurrence. An alternative definition of "nadir +2 ng/mL" (Phoenix definition) has shown improved accuracy over ASTRO in predicting clinical failures.[12-14] However, the nadir-based definition results in substantially lower estimates of BCR at 5 years, and substantially higher estimates of BCR at 10 years than the ASTRO definition.[6] Pending more information on development of distant metastases and prostate-specific mortality, the AUA continues to recommend the ASTRO definition of BCR following RT.

## Prognostic Factors in PSA-Recurrent Prostate Cancer

Pre- and post-treatment prognostic factors allow physicians to assign risk levels and use those risk groupings to help determine whether to start treatment immediately or to defer it. Pretreatment factors that have shown prognostic value include absolute baseline PSA, tumor stage (T-stage), and pathologic findings (including Gleason score, surgical margin status, and lymph node status). All of these parameters are prognostic of development of distant metastases and prostate-specific mortality, with Gleason score providing the greatest prognostic value with advanced T-stage and absolute PSA value also contributing to accuracy of prognosis.[15] Gleason score continues to have prognostic value following local therapy but it is joined by other factors, of which PSADT is likely the most important prognostic factor for metastasis-free survival and overall survival.[8] Time to biochemical recurrence has been shown to be a prognostic factor in some studies[16,17] but not in others.[8] In a landmark study, Pound and associates found that time to biochemical recurrence after RP was as effective as PSADT and Gleason score as a prognostic factor for metastasis.[16] However, a recent multivariate analysis using updated information from these same patients showed that time to biochemical recurrence does not add measurably to the prognostic value of PSADT and Gleason score.[8] Finally, changes in PSADT after initiation of therapy in the setting of clinical trials has also been shown to be prognostic of metastasis-free survival in patients with BCR disease following local therapy.[7]

PSA kinetics have long been known to be prognostic for metastasis-free survival, prostate cancer–specific survival, and overall survival. However, the exact cut-off points for defining high-risk disease have varied. In a study of 3,903 men who had undergone prostatectomy, PSADT less than 12 months corresponded with significantly increased risk of clinical failure.[18] Another study of 8,669 patients with prostate cancer treated with surgery (5,918 patients) or radiation (2,751 patients) found that a PSADT of less than 3 months was significantly associated with prostate cancer–specific mortality.[19] More recently, a series of 3 PSADT cut-off points have been chosen in defining 4 risk groups (<3 months vs 3–9 months vs 9–15 months vs >15 months).[5,8] In addition, the number and timing of PSA measurements needed to accurately estimate PSADT has led to uncertainty about its reliability as a prognostic marker. In the authors' opinion, 3 PSA measurements obtained 3 months apart is considered a reliable foundation for calculation of PSADT.

Finally, a retrospective study of patients with rising PSA following local therapy who were enrolled in 4 clinical trials of nonhormonal agents found that changes in PSADT after treatment initiation were prognostic for metastasis-free survival.[7] Data on overall survival from this cohort are not yet mature. These data suggest that the onset of metastasis may be delayed if an experimental agent is capable of significantly lengthening the PSADT. If these preliminary findings are confirmed in prospective trials using metastasis-free survival as a primary endpoint,

changes in PSADT could become a reasonable intermediate endpoint of future studies in this patient population.[7]

## Diagnostic Evaluation After PSA Recurrence

No formal guidelines have been published defining the frequency of diagnostic evaluations for patients following BCR who choose to undergo surveillance rather than initiating early hormonal therapy. In the authors' opinion, it is reasonable to monitor serum PSA every 3 months and to perform annual technetium-99 bone scans and biannual computed tomography (CT) scans in patients at high risk of metastatic progression as determined by PSA levels (≥5 ng/mL) and/or a rapid PSADT of 9 months or less. In one retrospective study describing the natural history of untreated PSA-recurrent prostate cancer after prostatectomy, it was observed that men with a PSADT of 9 months or less had a median metastasis-free survival of 2 years after biochemical recurrence.[8] Another analysis from this same population reported that the median PSA value at the time of first radiographic metastasis was 31.4 ng/mL (interquartile range, 8.8–87.5 ng/mL).[20] These figures may help to determine whether a particular patient might be at a more imminent risk of metastasis, allowing for more frequent PSA evaluations or imaging tests to be obtained at the treating physician's discretion.

## Salvage Radiation for PSA-Recurrent Prostate Cancer

Three large retrospective studies provide evidence that early salvage radiation therapy, delivered to patients with rapid PSADT, or while the PSA levels remain below 2.0 ng/mL, impacts survival of prostate cancer patients with BCR. A study at Duke University examined 519 patients who experienced BCR after prostatectomy, of which 219 patients received salvage radiation therapy. That study stratified the patients by PSADT (<6 months vs ≥6 months). Salvage radiation therapy significantly improved overall survival in both groups at a median follow-up of 11.3 years, with all-cause mortality hazard ratios (HR) for death of 0.53 and 0.52 for those with faster and slower PSADT, respectively.[21]

A second study of 635 patients with PSA-recurrence after prostatectomy at Johns Hopkins Hospital compared salvage radiation therapy (either alone or with ADT) against observation.[22] In that study, salvage radiation was associated with a 3-fold increase in prostate-cancer specific survival after a median follow-up of 6 years after biochemical recurrence as compared with observation, but this improvement was limited to men with PSADT less than 6 months. Interestingly, salvage radiotherapy was still associated with significant improvement in prostate-specific survival when administered to patients with PSA above 2 ng/mL, only if those patients also had PSADT less than 6 months. No significant increase in prostate cancer–specific survival was seen in patients who were administered salvage radiation more than 2 years after PSA recurrence. In addition, ADT did not significantly improve prostate-cancer specific survival in this patient population.[22] The greater impact of salvage radiation on prostate-specific survival in patients with PSADT less than 6 months was supported by an analysis of a subset of the Duke patients who had comorbidities at the time of PSA recurrence. Significant reduction in all-cause mortality was associated with salvage radiation in both patients with a PSADT less than 6 months (HR, 0.35; $P$=.042) and a PSADT greater than 6 months (HR, 0.60; $P$=.04), but the reduction in all-cause mortality was nearly 60% greater in the patients with PSADT less than 6 months.[21]

Although another large retrospective trial has not shown overall survival benefits from salvage radiation treatment after prostatectomy,[23] the 2 studies described above provide adequate evidence that salvage radiation therapy may positively alter the progression of the disease when administered within 2 years of BCR and while the absolute PSA remains below 2 ng/mL (although even lower PSA values may further increase the chance of cure with salvage radiotherapy). The finding of improved prostate cancer–specific survival in men with PSADT less than 6 months is provocative (and perhaps counterintuitive), and should be confirmed by additional studies.

## Hormonal Therapy For PSA-Recurrent Prostate Cancer

### *Selection of Hormonal Agents*

Androgen deprivation therapy, either through chemical castration or, far more rarely, through orchiectomy, is one reasonable standard of care for BCR prostate cancer after maximal local therapy.[24] Gonadotrophin-releasing hormone (GnRH) agonists, including leuprolide and goserelin, have been the primary medical castration therapies in the Western world. Recently, a GnRH antagonist, degarelix, has been gaining momentum in the first-line setting because clinical trial data suggest that it results in more rapid reduction of testosterone and marginally longer PSA progression-free survival intervals than leuprolide.[25] In addition, patients on degarelix do not experience clinical flare and therefore do not require a short course of androgen receptor antagonists (such as bicalutamide or nilutamide) that are often prescribed for patients initiating leuprolide or goserelin. One potential disadvantage of degarelix is the requirement for monthly administration, since longer formulations of this compound do not exist at the present time. However, both GnRH agonists and antagonists remain reasonable options for initial hormonal treatment of patients with BCR prostate cancer.

### *Timing and Duration of ADT*

Physicians wishing to treat BCR prostate cancer patients with ADT face 2 key timing questions: 1) whether to initiate ADT immediately upon PSA recurrence or to defer its use until after clinical/radiographic progression occurs, and 2) whether to use continuous administration of ADT or intermittent cyclic administration of ADT. As of December 2012, the American Society of Clinical Oncology (ASCO) had not provided definitive guidelines addressing either of these questions. We will review the relevant clinical trial data that may guide clinicians with respect to these 2 issues.

### *Immediate Versus Deferred ADT*

When BCR patients experience clinical/radiographic metastatic disease, immediate initiation of ADT reduces further metastatic progression, improves pain (if present), and reduces the development of skeletal-related events (eg, pathological fracture and spinal cord compression). Immediate ADT in the metastatic setting also reduces prostate cancer–specific mortality, but does not necessarily improve overall survival (compared to initiating ADT at the time of symptomatic progression) because of increases in deaths from other causes.[24,26] For nonmetastatic BCR patients, timing of ADT is controversial. Many men in the BCR setting choose to defer the initiation of hormonal therapy and prefer to allow their physician to monitor their PSA kinetics, bones scans, and CT scans on a regular basis. Two ongoing clinical trials are exploring the timing of ADT initiation after BCR following radiation, the Australian and New Zealand Timing of Androgen Deprivation trial (TOAD; NCT00110162) and the Canadian Early vs. Late Androgen Ablation Therapy trial (ELAAT; NCT0043975).

Until results of these studies are available, uncertainty about the overall survival benefits of immediate ADT initiation, combined with serious adverse effects and quality-of-life issues that may accompany ADT treatment, has led many patients to defer ADT initiation and to opt instead for observation. Their choice to defer ADT is supported by a recently published retrospective review of surgical patients in a single institution,[8] and confirmed by a second study in an independent patient population.[27] These studies reported median metastasis-free survival intervals of 10 years among men with BCR following prostatectomy, even in the absence of ADT and salvage radiation. In addition, another retrospective analysis of BCR prostate cancer patients found that PSADT rose approximately 4 months over 5 years, even without ADT or other therapies, in patients whose PSADT was greater than 15 months at the beginning of the period.[28] These data support earlier findings that BCR patients with PSADT 15 months or greater often enjoy prolonged progression-free survival.[8] At the authors' institution, given the lack of a clear overall survival advantage with the use of immediate ADT, it is generally recommended to defer ADT in patients at low risk of metastatic progression (eg, PSADT >9 months; absolute PSA <10 ng/mL), while early initiation of ADT remains a reasonable choice for those at high risk of developing metastatic disease (eg, PSADT <6 months; absolute PSA >20 ng/mL).

### *Continuous Versus Intermittent ADT*

Once the decision to use ADT has been made, a second controversial decision for BCR prostate cancer patients is whether to use intermittent or continuous administration of androgen deprivation. Intermittent androgen deprivation (IAD) is a cyclic process in which induction treatment continues until maximal PSA response. ADT is then temporarily withdrawn until serum PSA levels rise to a predetermined level, agreed upon by patient and physician (often between 4 and 10 ng/mL), at which point ADT is reinitiated. IAD can allow testosterone levels to recover during each off-treatment cycle, lessening sexual dysfunction and loss of bone mass often associated with continuous androgen deprivation.[29] The lower cost and improved quality of life, combined with noninferiority of IAD in overall survival, have led many patients to choose IAD for treatment of BCR prostate cancer.

Two large phase III trials have attempted to determine whether IAD was noninferior to continuous androgen deprivation (CAD) in patients with recurrent prostate cancer. In an international trial involving 1,386 men with BCR following radiation therapy (with or without prior prostatectomy), patients were randomized into CAD or IAD arms. The IAD group received 8 months of hormonal therapy followed by treatment withdrawal until PSA reached 10 ng/mL or higher during the off-treatment period. After a median follow-up of 6.9 years, the endpoint of overall survival was shown to be noninferior for IAD compared to CAD (8.8 years vs 9.1 years, HR, 1.02; 95% confidence interval [CI], 0.86–1.21). Prostate cancer–related deaths were greater in the IAD group (122 vs 97 deaths), while non-prostate deaths were lower in the IAD group (134 vs 146 deaths). In addition, men in the IAD arm reported reduced hot flashes, although no other differences in adverse effects were reported.[29] Based on the results of this large and well-conducted study, the authors now view intermittent ADT as a very reasonable standard of care for the management of patients with BCR prostate cancer.

A second phase III trial studied 626 southern European patients with locally advanced prostate cancer (some had also developed metastatic disease) and

**Table 1.** Selected Completed and Ongoing Clinical Trials for Patients With PSA-Recurrent Prostate Cancer After Local Therapy

| Trials of ADT Plus Additional Experimental Agents | Findings | Phase/Identifier |
|---|---|---|
| Sequencing of sipuleucel-T and ADT in men with non-metastatic biochemically-recurrent prostate cancer | Ongoing | II - NCT01431391 |
| ADT with or without bevacizumab for PSA-recurrent prostate cancer after definitive local therapy | Ongoing | II - NCT00776594 |
| Oral thalidomide versus placebo in addition to ADT in patients with stage D0 androgen-dependent prostate cancer | Trend toward increased PSADT with thalidomide versus placebo[45] | III - NCT00004635 |
| Bicalutamide with or without MK-2206 (Akt inhibitor) in patients with previously treated prostate cancer | Ongoing | II - NCT01251861 |
| Bicalutamide and RO4929097 in patients with previously treated prostate cancer | Ongoing | II - NCT01200810 |
| Tremelimumab (CTLA4-blocking antibody) plus short-term bicalutamide in patients with stage D0 prostate cancer | Significant prolongation of PSADT was observed in 18% of patients[46] | I - NCT00702923 |
| **Trials of Other Nonhormonal Pharmaceuticals** | **Findings** | **Phase/Identifier** |
| Celecoxib versus placebo in patients with BCR prostate cancer | Despite significant improvements in PSA velocity with celecoxib, study terminated early due to cardiovascular concerns[47] | II - NCT00136487 |
| Celecoxib in treating patients with relapsed prostate cancer following radiation therapy or radical prostatectomy | Significant slowing in PSADT with celecoxib at 3, 6, and 12 months[48] | II - NCT00073970 |
| Rosiglitazone versus placebo for androgen-dependent recurrent prostate cancer | No increase in PSADT or time-to-PSA-progression with rosiglitazone vs placebo[49] | II - NCT00182052 |
| Disulfiram in patients with recurrent prostate cancer as evidenced by a rising PSA | Ongoing | II - NCT01118741 |
| Valproic acid in treating patients with progressive nonmetastatic prostate cancer | Ongoing | II - NCT00670046 |
| Atorvastatin and celecoxib for patients with rising PSA levels after local therapy for prostate cancer | Ongoing | II - NCT01220973 |
| Imatinib in prostate cancer patients with rising PSA following radical prostatectomy | Median PSA did not decrease significantly and trial was halted early due to toxicities[50] | II - NCT01316458 |
| Calcitriol in treating patients with a rising PSA level following local therapy for prostate cancer | Significant but small increase in PSADT from baseline (7.8 to 10.3 months)[51] | II - NCT00004043 |
| Calcifediol for patients with PSA-recurrent prostate cancer | 80% of patients had increases in PSADT[52] | II - NCT00018538 |
| Study of 2 different doses of lenalidomide in biochemically-relapsed prostate cancer | Significant dose-dependent improvement in PSA slope[53] | I/II - NCT00348595 |
| Hydroxychloroquine in treating patients with rising PSA levels after local therapy for prostate cancer | Ongoing | II - NCT00726596 |
| Lapatinib for patients with PSA-recurrent prostate cancer | No PSA responses but significant reduction in mean PSA slope (log PSA/mo)[54] | II - NCT00103194 |
| Sulforaphane in treating patients with PSA-recurrent prostate cancer | Ongoing | II - NCT01228084 |
| pTVG-HP (prostatic acid phosphatase DNA-plasmid vaccine) in patients with recurrent prostate cancer | Significant but small increase in PSADT from baseline (6.5 to 8.5 months)[55] | I - NCT00582140 |
| Fenretinide in patients with BCR, hormone-naïve prostate cancer | Did not meet primary endpoint of PSA response[56] | II - NCT00080899 |

| Trials of Other Nonhormonal Pharmaceuticals | Findings | Phase/Identifier |
|---|---|---|
| Sipuleucel-T versus placebo for the treatment of hormone-sensitive PSA-recurrent prostate cancer | Sipuleucel-T patients had a 48% increase in PSADT [57] | III - NCT00779402 |
| Metformin with simvastatin for patients with BCR prostate carcinoma | Ongoing | II - NCT01561482 |
| ATN-224 (copper/zinc superoxide dismutase inhibitor) at 2 dose levels in patients with PSA-recurrent prostate cancer | Significant mean PSA slope decrease ($P$=.006) and mean PSADT increase ($P$=.032) in the low-dose arm only [58] | II - NCT00405574 |
| **Trials of Nonhormonal Natural Products** | **Findings** | **Phase/Identifier** |
| Pomegranate juice in treating patients with PSA-recurrent prostate cancer (single-arm study) | Significant increase in median PSADT from baseline (11.5–28.7 months) [38] | II - NCT00060086 |
| POMx capsules (pomegranate extract) in patients with PSA-recurrent prostate cancer: 18-month dose-finding study | Significant 6-month PSADT improvement from baseline, no dose effect [42] | II - NCT01220817 |
| Pomegranate extract versus placebo in treating patients with rising PSA after surgery or radiation therapy | Ongoing | II - NCT00336934 |
| Two doses of MPX capsules (muscadine grape skin extract) on rising PSA levels in patients following local therapy for prostate cancer (placebo-controlled trial) | Ongoing | I/II - NCT01317199 |
| Acai juice in prostate cancer patients with rising PSA after local therapy (single-arm study) | Ongoing | II - NCT01521949 |
| Kanglaite (Chinese grass seed oil) gelcaps in PSA-recurrent prostate cancer (dose-finding study) | Ongoing | I/II - NCT01483586 |
| Brassica vegetable diet or indole-3-carbinol pills for patients with PSA recurrence after prostatectomy (2-arm study) | Ongoing | II - NCT00607932 |
| Combination herbal therapy (vitamins $D_3$ and E, selenium, green tea extract, saw palmetto, lycopene, soy derivatives) for PSA recurrence after local therapy (single-arm study) | Ongoing | II - NCT00669656 |

found no difference in overall survival between the IAD and CAD arms, because the reduction in prostate cancer–specific deaths in the CAD arm was offset by a larger number of deaths from cardiovascular disease in the CAD arm. Patients in the IAD arm reported better sexual function, although there was no significant difference in reported quality of life between the treatment arms.[30] Thus, the benefit of avoiding prostate cancer–related death using CAD is balanced by the benefit of avoiding death from other causes, such as cardiovascular disease, using IAD. The risks and benefits must be weighed in each patient, paying particular attention to cardiovascular disease history and risk factors for metabolic syndrome.

## Experimental Approaches For PSA-Recurrent Prostate Cancer

The current treatment landscape for prostate cancer patients experiencing biochemical recurrence offers no ideal systemic approach. Benefits of early initiation of continuous ADT or intermittent ADT are offset by the risk of osteopenia and cardiovascular disease, in addition to the bothersome and common side effects, including hot flashes and erectile dysfunction. Patients with slower PSADT, for whom ADT may not be immediately indicated, face years of anxiety and often seek treatments that delay PSA progression and development of metastases. To this end, researchers are investigating 3 approaches to complement or replace those described earlier in this review for the management of BCR patients: 1) the use of novel agents or vaccination approaches to enhance and/or supplement ADT; 2) the use of pharmaceutical agents or combinations of agents that may already be approved by the US FDA for treatment of other diseases and have demonstrated preclinical activity against hormone-sensitive prostate cancer; and 3) the use of natural products that have shown preclinical activity against hormone-sensitive prostate cancer. Table 1 shows a selected list of completed or

ongoing clinical trials investigating a number of such therapeutic strategies in patients with BCR, nonmetastatic prostate cancer.

### *Selected Trials of ADT Plus Additional Experimental Agents*

The effectiveness of sipuleucel-T (Provenge, Dendreon), the first immunotherapy approved for the treatment of metastatic castration-resistant prostate cancer, is being evaluated in BCR patients who have not yet received hormonal therapy to determine whether administration at an earlier disease state will improve antitumor immune responses and clinical outcomes. It has been suggested that the effectiveness of the vaccine may be enhanced by ADT-induced, T-cell–mediated responses that target prostate cancer cells.[31] Preclinical research in animal models demonstrated ADT enhancement of immunotherapy efficacy,[32,33] and human studies combining hormonal therapy with immunotherapy confirmed the additive effect.[34] A randomized phase II trial is seeking to determine the optimal sequencing for ADT and sipuleucel-T (NCT01431391) in men with PSA-recurrent prostate cancer.

Bevacizumab (Avastin, Genentech/Roche), an anti-angiogenesis monoclonal antibody approved in the United States for multiple tumor types (but not prostate cancer), inhibits vascular endothelial growth factor (VEGF), a major mediator to angiogenesis. ADT induces an 80% reduction in VEGF content in hormone-sensitive prostate cancer cells.[35] In LNCaP xenograft studies, VEGF inhibition combined with ADT demonstrates an increase in tumor necrosis, when compared with either ADT alone or VEGF inhibition alone.[36] A randomized phase II trial is evaluating the effect on time-to-PSA-progression when adding bevacizumab to 6 months of ADT in BCR patients (NCT00776594). In this trial, all patients receive a short course of ADT, and two-thirds also receive 8 doses of intravenous bevacizumab, administered 3 weeks apart.

Reciprocal negative feedback between the androgen receptor and PI3-kinase/Akt/mTOR pathways enables combined pathway inhibition that results in profound apoptosis in preclinical prostate cancer models.[37] In this model, inhibition of the PI3-kinase pathway alone induces overactivation of the androgen receptor pathway, while inhibition of the androgen receptor alone promotes overactivation of the PI3-kinase/Akt/mTOR pathway. Following from this preclinical work, a translational randomized phase II study is combining MK-2206 (an Akt inhibitor) with the anti-androgen bicalutamide in patients with BCR prostate cancer (NCT01251861). During the first 12 weeks of the study, patients are randomized to receive either MK-2206 or to undergo observation. Thereafter, bicalutamide is added to both study arms and continued until evidence of PSA progression.

### *Selected Trials of Other Nonhormonal Agents*

More than 20 clinical trials have been launched in BCR patients, evaluating agents previously approved by the FDA for other diseases that may show benefit in prostate cancer (Table 1). Although many of these trials have been completed, none have resulted in further evaluation in phase III trials. Among the agents that have completed testing are celecoxib (Celebrex, Pfizer), rosiglitazone (Avandia, GlaxoSmithKline), imatinib (Gleevec, Novartis), vitamin D derivatives, lenalidomide (Revlimid, Celgene), lapatinib (Tykerb, GlaxoSmithKline), fenretinide, ATN-224, and the pTVG-HP vaccine. One trial (using celecoxib) was halted early because of excessive cardiovascular toxicities. Other trials completed their accrual but found little or no benefit from the experimental drug, with observed PSADT increases that were not much larger than the increases found in BCR patients who were managed with observation/placebo.[28] Most of the trials were of insufficient duration to measure accepted clinical outcomes, such as radiologic evidence of metastases or survival. It should be emphasized that PSADT changes alone do not provide sufficient justification for major investments in phase III trials, especially in light of side effects and costs associated with many of the compounds being tested for this relatively healthy population.

### *Selected Trials of Natural Products*

A large proportion of patients with BCR prostate cancer who are concerned about their rising PSA but also want to avoid the side effects of ADT and other pharmaceuticals are actively self-medicating with natural products in an attempt to lower their PSA. However, there is little documented evidence that these products are effective and they may not be safe in the quantities or formulations being sold, despite having been consumed for decades by thousands of people in their natural plant forms.

A series of clinical trials seeking to evaluate the safety and efficacy of natural products, including pomegranate juice and extract, muscadine grape skin extract, Chinese grass seed oil, acai berry, and brassica vegetables (eg, broccoli), are now under way. Preclinical rationale supporting these studies focuses on inhibition of nuclear factor-κB and Akt (pomegranate products,[38] muscadine grape skin extract,[39] acai berry,[40] and brassica vegetables[41]). To date, 2 pomegranate trials have been published and both demonstrated significant improvement in PSADT.[38,42] However, these trials are difficult to interpret in the absence of a placebo comparator group. To this end, placebo-controlled trials are now under way for pomegranate (NCT00336934), brassica vegetables (NCT00607932), and muscadine grape skin extract (NCT01317199) in order to compare changes in PSA kinetics between the active treatment arm and the placebo arm.

## Conclusions

Although the treatment landscape for patients with BCR prostate cancer remains challenging, new research is helping to identify patient populations suitable for specific therapies. Clinical trials of pharmaceutical agents, vaccines, and natural products, as well as new approaches to timing and combining hormonal treatments, are currently ongoing. In addition, several trials are now stratifying their patient populations into different risk categories based on the natural history of their disease as well as their age and comorbidities. As more stratified evidence emerges, physicians and their patients may look forward to a time when they can choose treatment strategies that delay the onset of metastatic lesions while avoiding or minimizing the costs and side effects associated with ADT.

The ultimate goal in treating patients with BCR prostate cancer is to identify a safe and effective nonhormonal therapy that is able to delay metastasis and death without the need for pharmacologic castration. An alternative attractive strategy would be one in which a limited course of androgen deprivation (eg, 6 or 12 months) is given together with an additional hormonal or nonhormonal agent in an attempt to eradicate micrometastatic disease before the development of clinical/radiographic metastases. However, designing these types of clinical trials is challenging. For example, if investigating a nonhormonal agent for patients with BCR prostate cancer, the time to first metastasis and time to death are very prolonged, even if selecting only high-risk patients (those with PSADT <6 months). In addition, time to metastasis will be affected by subsequent treatments (including hormonal treatments) that patients may opt to receive if they come off study due to further rises in their PSA. Finally, metastasis-free survival has not been shown to be associated with overall survival in patients with PSA-recurrent prostate cancer, so it is unclear whether it could be used as a surrogate endpoint without adequate follow-up for overall survival. Even more questionable is the significance of treatment-induced changes in PSA kinetics as they relate to metastasis-free survival and overall survival.

Rather than focusing on noncastrating approaches, an alternative strategy would be to investigate the efficacy of short-course androgen suppression combined with other nonhormonal (eg, immunotherapies, antiangiogenics) or novel hormonal agents. A potential relevant endpoint in this setting could be the achievement of an undetectable PSA after a finite course of ADT and after testosterone levels have recovered to the noncastrate range. An undetectable PSA after testosterone recovery in this setting could be interpreted as a "cure" for these patients, although the significance of this has not been tested or validated. With an ever increasing range of novel hormonal agents, the question has emerged as to whether a short course of more complete/maximal androgen signaling inhibition (androgen annihilation) may be able to eradicate micrometastatic disease in this setting. Trials are currently being designed to test this intriguing hypothesis.

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