Advances in the Treatment of Metastatic Prostate Cancer

Jong Chul Park, MD, and Mario A. Eisenberger, MD

From the Genito-Urinary Oncology Program, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, The Johns Hopkins University, Baltimore, MD.

CME Activity

Target Audience: The target audience for *Mayo Clinic Proceedings* is primarily internal medicine physicians and other clinicians who wish to advance their current knowledge of clinical medicine and who wish to stay abreast of advances in medical research.

Statement of Need: General internists and primary care physicians must maintain an extensive knowledge base on a wide variety of topics covering all body systems as well as common and uncommon disorders. *Mayo Clinic Proceedings* aims to leverage the expertise of its authors to help physicians understand best practices in diagnosis and management of conditions encountered in the clinical setting.

Accreditation: Mayo Clinic College of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Credit Statement: Mayo Clinic College of Medicine designates this journal-based CME activity for a maximum of 1.0 *AMA PRA Category 1 Credit(s).*™ Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Learning Objectives: On completion of this article, you should be able to (1) describe and discuss the various clinical paradigms of advanced prostate cancer; (2) describe and discuss current treatments for patients with metastatic prostate cancer; and (3) discuss future direction of research in metastatic prostate cancer.

Disclosures: As a provider accredited by ACCME, Mayo Clinic College of Medicine (Mayo School of Continuous Professional Development) must ensure balance, independence, objectivity, and scientific rigor in its educational activities. Course Director(s), Planning Committee members, Faculty, and all others who are in a position to control the content of this educational activity are required to disclose all relevant financial relationships with any commercial interest related to the subject matter of the educational activity. Safeguards against commercial bias have been put in place. Faculty also will disclose any off-label and/or investigational use of pharmaceuticals or instruments discussed in their presentation. Disclosure of this information will be published in course materials so that those participants in the activity may formulate their own judgments regarding the presentation.

In their editorial and administrative roles, William L. Lanier, Jr, MD, Terry L. Jopke, Kimberly D. Sankey, and Nicki M. Smith, MPA, have control of the content of this program but have no relevant financial relationship(s) with industry.

The authors report no competing interests.

Method of Participation: In order to claim credit, participants must complete the following:

1. Read the activity.
2. Complete the online CME Test and Evaluation. Participants must achieve a score of 80% on the CME Test. One retake is allowed.

Visit www.mayoclinicproceedings.org, select CME, and then select CME articles to locate this article online to access the online process. On successful completion of the online test and evaluation, you can instantly download and print your certificate of credit.

Estimated Time: The estimated time to complete each article is approximately 1 hour.

Hardware/Software: PC or MAC with Internet access.

Date of Release: 12/1/2015

Expiration Date: 11/30/2017 (Credit can no longer be offered after it has passed the expiration date.)

Privacy Policy: http://www.mayoclinic.org/global/privacy.html

Questions? Contact dletcsupport@mayo.edu.

Abstract

During the past several years, there has been substantial progress in the development of treatments for advanced prostate cancer with the approval of multiple new life-prolonging agents using different mechanisms of action. Such progress was attainable because of advances in our understanding of the biology behind mechanisms of androgen receptor pathway activation, complex tumor-microenvironment interaction of bone metastasis, antitumor immunology, and new oncogenic pathways. Continuous efforts are being made to develop new therapeutics with novel mechanisms of action, define the optimal sequences and/or combinations of current agents, and identify reliable surrogate end points to facilitate new drug development.

 ■ Mayo Clin Proc. 2015;90(12):1719-1733

Prostate cancer is the most common malignancy in men in the United States, with an estimated 220,800 new cases in 2015.[1] Since the introduction of the serum prostate-specific antigen (PSA) test and the wide acceptance of routine PSA screening, there has been a substantial stage shift with a dramatic decrease in the proportion of advanced stage disease at diagnosis; approximately 80% of prostate cancer cases are diagnosed as localized disease and only 4% as metastatic disease.[1-3]

In the past decade, the landscape of treatments for metastatic prostate cancer had drastic changes from treatments with mostly palliative benefits to a number of new life-prolonging therapeutics approved by the Food and Drug Administration (FDA) (Figure 1). Despite such advances, metastatic prostate cancer remains a lethal disease and accounts for approximately

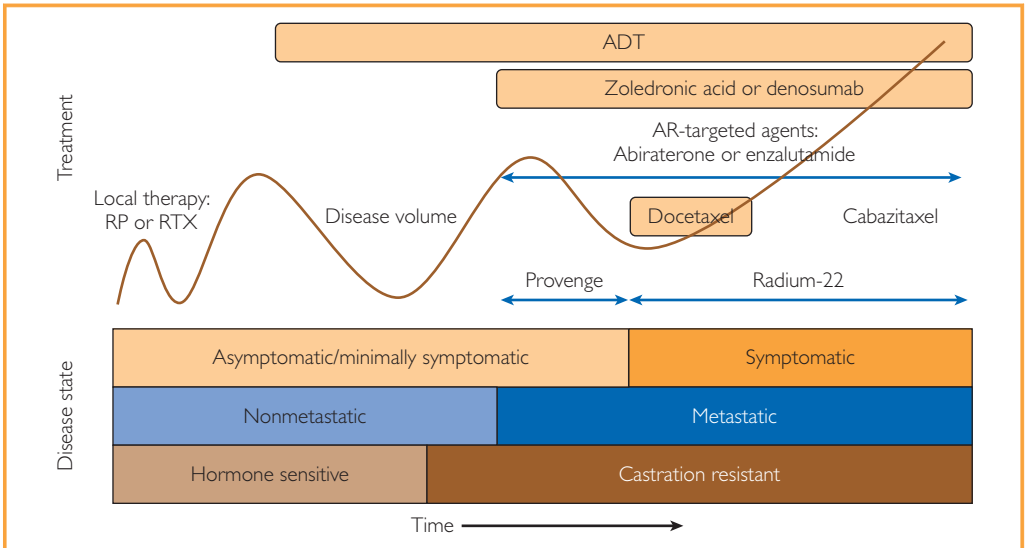

FIGURE 1. Natural history and management landscape of prostate cancer. ADT = androgen deprivation therapy; AR = androgen receptor; RP = radical prostatectomy; RTX = radiation therapy.

27,000 cancer-related deaths annually. In this review, we discuss the treatment of metastatic prostate cancer focusing on recent advances, challenges in new drug development, and promising ongoing research.

TREATMENT OF METASTATIC HORMONE-SENSITIVE PROSTATE CANCER

For patients with newly diagnosed, hormone-naive, metastatic disease, androgen deprivation therapy (ADT) either by bilateral orchiectomy (surgical castration) or by testicular androgen synthesis (medical castration) suppression using luteinizing hormone-releasing hormone agonists or antagonists remains the cornerstone of initial treatment. The ADT of both modalities reduces serum testosterone levels to less than 50 ng/dL and results in PSA and/or radiographic response as well as symptomatic improvement in most patients.[4]

The addition of first-generation antiandrogens to ADT (combined androgen blockade) as the initial therapy has shown minimal clinical benefit at the expense of more toxicity and higher cost in comparison with ADT alone.[5-7] The benefit of combined androgen blockade using more potent second-generation antiandrogens such as enzalutamide and orteronel is under evaluation, but the routine use of combined androgen blockade is not generally recommended.

More recently, multiinstitutional prospective trials evaluating the role of upfront docetaxel chemotherapy in addition to hormone therapy have been reported (Table 1).[8-11] Although the survival benefit did not reach statistical significance in the French Genitourinary Tumor Group (GETUG-AFU) 15 trial,[8] the following 2 larger trials, ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease (CHAARTED)[12] and Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE),[10] found significant survival improvements of early docetaxel use in newly diagnosed metastatic disease. A small sample size with a relatively low proportion of high-volume disease and a higher proportion of patients receiving salvage chemotherapy in the GETUG-AFU 15 trial may have contributed to the negative survival benefit. Subset analysis in the CHAARTED study suggests that patients with high-volume disease derive greater benefits from this combined approach, whereas more follow-up is needed to evaluate the benefits in patients with lower tumor burden.[12] The STAMPEDE study evaluated a mixed population of both high-risk locally advanced and metastatic disease and the specifics on the disease volume status is not available, which may explain the difference in the magnitude of survival benefit between CHAARTED and STAMPEDE studies.[10] At the present time,

Mayo Clin Proc. ■ December 2015;90(12):1719-1733 ■ http://dx.doi.org/10.1016/j.mayocp.2015.10.010
www.mayoclinicproceedings.org

there is an evolving consensus supporting upfront docetaxel treatment for patients with high-volume metastatic prostate cancer, although the definition of high-volume disease used in the trial (presence of visceral metastases and/or ≥4 bone metastases) is arbitrary and requires careful consideration.

TREATMENT OF METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

Despite the initially high response rate to the suppression of gonadal testosterone, the overwhelming majority of patients with metastatic disease eventually experience disease progression and evolve into a new disease state called castration-resistant prostate cancer (CRPC). Before the approval of docetaxel in 2004, the treatment for metastatic castration-resistant prostate cancer (mCRPC) was limited to agents with no evidence of survival benefit such as corticosteroid, estrogen, other weak secondary hormonal agents, mitoxantrone, and palliative bone-targeting agents including radioisotope and bisphosphonates.

Since the approval of docetaxel, there have been a total of 6 therapeutic agents approved by the FDA for mCRPC treatment, all with established survival benefit (sipuleucel-T, cabazitaxel, abiraterone, radium 223, and enzalutamide) (Table 2).

TABLE 1. Phase III Trials Evaluating Early Use of Docetaxel Chemotherapy in Hormone-Sensitive Prostate Cancer[a]

Trial	No. of subjects	No. of cycles	mOS (mo)	HR (*P* value)
GETUG-AFU 15[8]	Total 385	9	60.9 vs 46.5	0.9 (.444)
	HV[b] 47%		39 vs 35.1	0.8 (.35)
	LV 53%		83.1 vs NR	1.0 (.87)
CHAARTED[9,12]	Total 790	6	57.6 vs 44.0	0.61 (.0003)
	HV[b] 65%		49.2. vs 32.2	0.60 (.0006)
	LV 35%		NR in both	0.63 (.1398)
STAMPEDE[10]	Total 1776	6	77 vs 67	0.76 (.003)
	M1[c] 61%		65 vs 43	0.73 (.002)
	M0[c] 39%		NR in both	
RTOG 0521[d,11]	563	6	4-y survival 93% vs 89%	0.70 (.04)

[a]CHAARTED = ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease; GETUG-AFU = French Genitourinary Tumor Group; HR = hazard ratio; HV = high-volume; mOS = median overall survival; NR = not reached; STAMPEDE = Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy.
[b]Definition of HV disease: GETUG-AFU 15: ≥4 bone lesions, 1 beyond axial skeleton, or visceral disease; CHAARTED: ≥4 bone lesions, or visceral disease.
[c]Disease state: M1, metastatic disease; M0, high-risk nonmetastatic disease.
[d]Locally advanced nonmetastatic high-risk patients randomized to androgen suppression and radiation therapy with/without docetaxel.

ANDROGEN RECEPTOR–TARGETED THERAPY

Androgen receptor (AR) is a member of the nuclear steroid hormone receptor family and functions as a DNA-binding transcription factor. It has 4 functional domains: N-terminal domain, DNA-binding domain, hinge region, and ligand-binding domain (LBD). The N-terminal domain is the primary effector region and is responsible for the major transactivation function of AR.[22] In its inactive form, AR resides in the cytoplasm and is stabilized by 2 chaperone heat shock proteins. Upon binding of androgen ligands to the LBD, AR undergoes a conformational change and homodimerizes before it translocates to the nucleus, binds to the DNA, and initiates transcription activity.[22]

The AR pathway is found to be persistently activated in most cases of castration- resistant disease through various mechanisms: maintenance of tissue androgen concentration using adrenal androgen precursors or through intratumoral (de novo) androgen synthesis, AR gene amplification/AR overexpression, AR gene mutations that confer broader ligand specificity to alternative ligands, development of AR isoforms that are constitutively activated in the absence of ligand, and "crosstalk" with other signaling pathways.[23]

Because the AR pathway remains the main driver of disease after the development of castration resistance, AR-directed therapies either by further suppression of androgen synthesis or through blockade of AR have become the main therapeutic strategy. Traditional secondary hormonal manipulations such as first-generation antiandrogens, corticosteroids, ketoconazole, and estrogen provide only modest and relatively short-duration benefit.[24-26]

Suppression of Androgen Biosynthesis

Androgens are synthesized from cholesterol via multiple enzymatic steps. Cytochrome P450 (CYP) 17 is the key enzyme in androgen synthesis and has both 17α-hydroxylase and C17,20 lyase activity.[27]

Ketoconazole has a nonspecific CYP17 inhibitory property and suppresses androgen

TABLE 2. Current Approved Agents With Survival Benefit for mCRPC

Agent	FDA approval		Registration trial				
	Date	Indication	Trial/design	N	PE	Median (mo)	HR (*P* value)
Docetaxel with prednisone	May 19, 2004	mCRPC	TAX 327[13] RCT with mitoxantrone (1:1)	1006	OS	18.9 vs 16.5	0.76 (.009)
Sipuleucel-T	April 29, 2010	mCRPC, no or minimal symptom	IMPACT[14] RCT with placebo (2:1)	512	OS	25.8 vs 21.7	0.78 (.03)
Cabazitaxel with prednisone	June 17, 2010	mCRPC, postdocetaxel	TROPIC[15] RCT with mitoxantrone (1:1)	755	OS	15.1 vs 12.7	0.70 (<.001)
Abiraterone with prednisone	April 28, 2011	mCRPC, postdocetaxel	COU-AA-301[16] RCT with placebo/prednisone (2:1)	1195	OS	14.8 vs 10.9	0.65 (<.001)
	December 10, 2012	mCRPC, predocetaxel	COU-AA-302[17,18] RCT with placebo/prednisone (1:1)	1088	OS rPFS	34.7 vs 30.3 16.5 vs 8.3	0.81 (.0033) 0.53 (<.001)
Enzalutamide	August 31, 2012	mCRPC, postdocetaxel	AFFIRM[19] RCT with placebo (2:1)	1199	OS	18.4 vs 13.6	0.63 (<.001)
	September 10, 2014	mCRPC, predocetaxel	PREVAIL[20] RCT with placebo (1:1)	1717	OS rPFS	32.4 vs 30.2 NR vs 3.9	0.71 (<.001) 0.19 (<.001)
Radium-223	May 15, 2013	mCRPC, symptomatic bone mets, no known visceral mets	ALSYMPCA[21] RCT with placebo (2:1)	921	OS	14.9 vs 11.3	0.70 (.002)

AFFIRM = A study evaluating the Efficacy and Safety of the Investigational drug MDV3100; ALSYMPCA = Alpharadin in Symptomatic Prostate Cancer Patient; COU-AA = COUGAR-Abiraterone acetate; FDA = Food and Drug Administration; HR = hazard ratio; IMPACT = Immunotherapy for Prostate Adenocarcinoma Treatment; mCRPC = metastatic castration-resistant prostate cancer; mets = metastasis; NR = not reached; OS = overall survival; PE = primary end point; PREVAIL = A safety and Efficacy Study of Oral MDV3100 in Chemotherapy-Naive Patients with Progressive Metastatic Prostate Cancer; RCT = randomized controlled trial; rPFS = radiographic progression-free survival; TAX = Taxotere; TROPIC = XRP6258 Plus Prednisone Compared to Mitoxantrone Plus Prednisone in Hormone Refractory Metastatic Prostate Cancer.

biosynthesis when used in high doses. It was approved by the FDA in 1981 as an antifungal agent but has been used off-label for prostate cancer treatment.[28] Because of its nonselectivity, it is associated with modest antitumor efficacy and significant toxicity as well as interaction with a wide range of medications due to its effect on other CYP enzymes.

Abiraterone acetate (AA) is a selective, more potent, and irreversible CYP17 inhibitor. It was first approved in 2011 for use in patients with mCRPC after docetaxel chemotherapy based on significant survival extension[16] and was subsequently approved for chemotherapy-naive patients with mCRPC.[17] Although AA is generally well tolerated, it causes adverse effects such as hypertension, hypokalemia, and fluid retention related to compensatory mineralocorticoid excess from the adrenocorticotropic hormone feedback loop,[29] thus requiring concurrent use of low-dose prednisone.

Orteronel (TAK 700) is a more selective CYP17 inhibitor that suppresses lyase activity with minimal effects on hydroxylase activity. Such selectivity confers a hypothetical advantage over AA of less suppression of the mineralocorticoid pathway and thus no requirement for concomitant corticosteroid administration. Although orteronel failed to meet its primary end point of survival benefit in both chemotherapy-naive and chemotherapy-treated patients with mCRPC,[30,31] it significantly delayed disease progression and is currently under evaluation in patients with metastatic hormone-sensitive prostate cancer.

AR Blockade

The first steroidal antiandrogen, cyproterone acetate, was introduced in 1964 for use in prostate cancer treatment. Despite its use for decades primarily in Europe, it has never been evaluated in large prospective trials and is not approved for use in North America.[32] Flutamide is the first nonsteroidal antiandrogen approved in 1989.[33] However, because of significant gastrointestinal toxicity and an inconvenient thrice-daily schedule, it has been mostly replaced by bicalutamide and

Mayo Clin Proc. ■ December 2015;90(12):1719-1733 ■ http://dx.doi.org/10.1016/j.mayocp.2015.10.010
www.mayoclinicproceedings.org

nilutamide (FDA approval in 1995[34] and 1996,[35] respectively). These first-generation antiandrogens are now being replaced by more potent compounds with greater affinity to AR compared with natural androgens.

Enzalutamide is a second-generation antiandrogen designed to overcome resistance to first-generation antiandrogens and avoid antagonist-to-agonist conversion, which can be seen often with first-generation antiandrogens. Enzalutamide has activity in all 3 steps of the AR signaling pathways: (1) AR binding to androgen, (2) AR nuclear translocation, and (3) AR DNA binding and coactivator recruitment. Enzalutamide was first approved in 2012 for mCRPC after docetaxel chemotherapy,[19] followed by extension of indication for use in chemotherapy-naive patients in 2014.[20] Enzalutamide does not require concurrent corticosteroid treatment, and its absorption is not affected by food intake. However, it is associated with a low risk of seizure (<1%), which is thought to be an off-target effect of gamma-aminobutyric acid A inhibition,[36] and thus should be avoided in patients with underlying conditions that predispose to seizure. Currently, a phase IV postmarketing safety study is ongoing to evaluate the incidence of seizures during enzalutamide therapy.

ARN-509 is another new-generation antiandrogen with higher affinity than enzalutamide to LBD but lower central nervous system penetration, thus theoretically allowing for a higher therapeutic index.[37] It is currently under clinical evaluation in various stages of prostate cancer.

Despite the survival benefit of next-generation AR-targeted agents in mCRPC, approximately one-third of the patients experience no response (primary resistance) and most of the patients who had an initial response eventually progress (acquired resistance) commonly accompanied by PSA rise, indicating persistent activation of AR signaling.[16,17,19] Molecular analyses of resistant tumors revealed that the mechanisms of resistance are extensively heterogeneous including both AR-mediated and non–AR-mediated pathways, which is clearly a critical concept to be included in research strategies moving forward in this disease.[38]

Resistance to AR-Targeted Therapy

The discovery of an AR splice variant (AR-V) and the development of a detection platform exemplifies the principle that specific knowledge of mechanisms of resistance will enhance our ability to plan and design new therapeutic approaches as we embark in the era of personalized medicine. AR-V7 is a truncated AR variant that lacks LBD, leading to ligand-independent constitutive activation of AR.[39] Because the antitumor activity of both ezalutamide and AA depends on direct and indirect interactions with LBD, this variant form confers resistance to both agents. A recent study reported that AR-V7 detected in circulating tumor cells (CTCs) in the blood of patients can predict resistance to both enzalutamide and AA.[40] Currently, a prospective validation study of AR-V7 as a predictive biomarker is ongoing. In addition, the development of therapeutic agents with novel mechanisms that are effective in tumors harboring the AR-V7 variant is warranted.

Galeterone (TOK-001) is a unique compound with triple AR-directed mechanisms: CYP17 inhibition, direct AR blockade, and degradation of AR protein.[41] Galeterone has shown clinical efficacy in patients who had previously been treated with enzalutamide, AA, or both.[42] In addition, galeterone has been shown to induce degradation of AR-V7 protein and antitumor activity in AR-V7–harboring CRPC xenograft model.[43] On the basis of preliminary preclinical data suggesting the possibility of a non–LBD-dependent mechanism, a phase III trial was designed to evaluate galeterone in comparison with enzalutamide in men with AR-V7–expressing mCRPC.

"Bipolar" androgen therapy is a newly investigated strategy to overcome castration resistance where high-dose testosterone and ADT are given together generating an extreme fluctuation in androgen levels. Exposure to supraphysiologic testosterone induces apoptosis of high AR-expressing prostate cancer cells through inhibition of DNA relicensing and induction of double-stand DNA breaks and may resensitize CRPC cells to subsequent AR-directed therapy.[44] This provocative paradoxical approach has shown promising results in a small pilot study[45] and is under clinical trials with various second-generation AR-targeted agents (RE-sensitizing with Supraphysiologic Testosterone to Overcome REsistant (RESTORE) [NCT02090114] and Testosterone Revival Abolishes Negative Symptoms, Fosters Objective Response and Modulate

TABLE 3. Selected Trials of AR-Directed Strategies in Metastatic Prostate Cancer[a]

Agent	MOA	Clinical trial	Phase	Identifier	Target subjects
Enzalutamide	AR antagonist	ADT ± enzalutamide	III	NCT02446405 (ENZAMET)	mHSPC
Enzalutamide Abiraterone	AR antagonist CYP17 inhibitor	Enzalutamide ± AA	III	NCT01949337 (ALLIANCE)	mCRPC
		AA ± enzalutamide	VI	NCT01995513 (PLATO)	mCRPC, postenzalutamide
		Enzalutamide → AA vs AA → enzalutamide	II	NCT02125357	mCRPC
		AA → Cabazitaxel vs enzalutamide Enzalutamide → Cabazitaxel vs AA	II	NCT02379390 (PRIMCAB)	mCRPC
Abiraterone	CYP17 inhibitor	AA ± cabazitaxel	II	NCT02218606	mCRPC
		Docetaxel ± AA	II	NCT02036060	mCRPC, post-AA
ARN-509	AR antagonist	AA ± ARN-509	III	NCT02257736	mCRPC, post-AA
		ARN-509 + everolimus	Ib	NCT02106507	mCRPC
Orteronel (TAK-700)	CYP17 inhibitor	ADT + orteronel vs bicalutamide	III	NCT01809691	mHSPC
Galeterone (TOK-001)	CYP17 inhibitor AR antagonist	Galeterone vs enzalutamide (ARMOR-3)	III	NCT02438007	mCRPC, AR-V7 +
VT-464	CYP17 inhibitor AR antagonist	VT-464	II	NCT02445976	mCRPC, post-AA or enzalutamide
ODM-204	CYP17 inhibitor AR antagonist	ODM-204	I/II		mCRPC
Apatorsen (OGX-427)	Hsp27 inhibitor	AA ± OGX-427	II	NCT01681433	mCRPC, post-AA
Testosterone		Testosterone → AA[b] or enzalutamide	II	NCT02090114 (RESTORE)	mCRPC, post-AA or enzalutamide
		Testosterone vs enzalutamide	II	NCT02286921 (TRANSFORMER)	mCRPC

[a]AA = abiraterone acetate; ADT = androgen deprivation therapy; ALLIANCE = Alliance for Clinical Trials; AR = androgen receptor; AR-V7 = androgen receptor splice variant-7; ENZAMET = Enzalutamide in First Line Androgen Deprivation Therapy for Metastatic Prostate Cancer; mCRPC = metastatic castration-resistant prostate cancer; mHSPC = metastatic hormone-sensitive prostate cancer; MOA = mechanism of action; PLATO = Safety Study of Continued Enzalutamide Treatment in Prostate Cancer Patients; PRIMCAB = Primary Resistant Patients to Abiraterone or Enz; RESTORE = RE-sensitizing with Supraphysiologic Testosterone to Overcome REsistant; TRANSFORMER = Testosterone Revival Abolishes Negative Symptoms, Fosters Objective Response and Modulate Enzalutamide Resistance.

[b]Subsequent posttestosterone abiraterone or enzalutamide is dependent on the pretestosterone treatment history.

Enzalutamide Resistance (TRANSFORMER) [NCT02286921]). Last, the combinational approach with non–AR-directed agents, cytotoxic chemotherapy, or immunotherapy agents is being evaluated in an effort to either enhance AR-targeted agents or overcome resistance.

As our experience has matured, it has become apparent that the benefit of enzalutamide or AA is significantly diminished when either drug is used after the other, suggesting that there may be cross-resistance between the 2 agents.[46-51] Moreover, use of these agents might have a negative effect on subsequent docetaxel activity.[52,53] Several trials addressing the issue of cross-resistance, optimal combination, or sequencing of the current therapeutics are ongoing (Table 3).

CHEMOTHERAPY

Docetaxel is the first therapy that demonstrated survival benefit in metastatic prostate cancer in 2 pivotal trials. Docetaxel plus prednisone (TAX 327) or estramustine (SWOG 99-16) prolonged overall survival (OS) compared with mitoxantrone plus prednisone by around 2 months in patients with mCRPC.[13,54] Nine randomized trials of the docetaxel-based combination regimen compared with docetaxel alone have been completed over the past decade; however, none has resulted in a significant improvement in survival (Table 4).[55-64]

Cabazitaxel is another tubulin-binding taxane that was specifically developed for postdocetaxel use. In a registration phase III trial, cabazitaxel led to improved survival compared

Mayo Clin Proc. ■ December 2015;90(12):1719-1733 ■ http://dx.doi.org/10.1016/j.mayocp.2015.10.010
www.mayoclinicproceedings.org

TABLE 4. Phase III Docetaxel-Based Combination Trials[a]

Combination	Trial	Design	N	PE	Median (mo)	HR (*P* value)	G 3/4 toxicity (%)
Docetaxel ± bevacizumab	CALGB 90401[55]	RDBPC. 1:1	1050	OS	22.6 vs 21.5	0.91 (.181)	75.4 vs 56.2
Docetaxel ± aflibercept	VENICE[56]	RDBPC. 1:1	1224	OS	22.1 vs 21.2	0.94 (.38)	30 vs 8
Docetaxel ± atrasentan	SWOG S0421[57]	RDBPC. 1:1	994	OS	17.8 vs 17.6	1.04 (.64)	57 vs 60
				PFS	9.2 vs 9.1	1.02 (.81)	
Docetaxel ± zibotentan	ENTHUSE M1[58]	RDBPC. 1:1	1052	OS	20.0 vs 19.2	1.00 (.963)	60.7 vs 60.4
Docetaxel ± dasatinib	READY[59]	RDBPC. 1:1	1522	OS	21.5 vs 21.2	0.99 (.90)	60 vs 55
Docetaxel ± GVAX	VITAL-2[60]	ROL. 1:1	408/600[b]	OS	12.4 vs 14.8	1.70 (.0076)	Not reported
Docetaxel ± calcitriol	ASCENT-2[61]	ROL. 1:1	1059	OS	17.8 vs 20.2	1.33 (.002)	31.2 vs 26.4
Docetaxel ± custirsen	SYNERGY[62]	RDBPC. 1:1	1022	OS	23.4 vs 22.2	0.93 (.207)	Not reported
Docetaxel ± lenalidomide	MAINSAIL[63]	RDBPC. 1:1	1059	OS	17.7 vs NR	1.53 (.0017)	22 vs 16

[a]ASCENT = AIPC Study of Calcitriol Enhancing Taxotere; CALGB = Cancer And Leukemia Group B; ENTHUSE = Endothelin A Antagonist in Hormone Resistant Prostate Cancer with Bone Metastases; G = grade; HR = hazard ratio; MAINSAIL = Study to Evaluate Safety and Effectiveness of Lenalidomide in Combination with Docetaxel and Prednisone for Patients with Castration-Resistant Prostate Cancer; OS = overall survival; PE = primary end point; RDBPC = randomized double-blind placebo-controlled; READY = Randomized Study Comparing Docetaxel Plus Dasatinib to Docetaxel Plus Placebo in Castration-resistant Prostate Cancer; ROL = randomized open label; SYNERGY = Comparison of Decetaxel/Prednisone to Docetaxel/Prednisone in Combination with OGX-011 in Men with Prostate Cancer; SWOG = Southwest Oncology Group; VENICE = Aflibercept in Combination with Docetaxel in Metastatic Androgen Independent Prostate Cancer; VITAL-2 = Docetaxel in Combination With GVAX Immunotherapy in Versus Docetaxel and Prednisone in Prostate Cancer Patients.

[b]The study was prematurely terminated after accrual of 408 patients because of an imbalance in deaths: 67 deaths in the GVAX arm and 47 deaths in the docetaxel arm.

with mitoxantrone in patients with mCRPC after docetaxel chemotherapy.[15]

Because cabazitaxel is mostly used after extensive previous therapies, it is often associated with substantial toxicity, particularly neutropenia. Thus, primary prophylaxis with granulocyte colony-stimulating factor should be considered in high-risk patients. Alternative lower dose (20 mg/m^2) and schedules (weekly or biweekly) are being tested to reduce toxicity while maintaining efficacy. Currently, cabazitaxel is being evaluated in a head-to-head trial with docetaxel as first-line chemotherapy.

BONE-TARGETED THERAPY

Prostate cancer has high tropism for bone and 80% to 90% of the patients with mCRPC have bone metastasis.[65,66] Bone metastasis is associated with a collection of complications called skeletal-related events (SREs), which include pathologic fractures, cord compression, and the use of surgery or radiation to treat unstable or painful metastatic lesions in bone. The palliation of bone-related symptoms and prevention of SREs have become an integral part of prostate cancer management. Various systemic therapeutics that directly target bone lesions remain an important therapeutic arsenal for multifocal lesions that are not feasible for local treatment such as radiation or surgery.

Bisphosphonate is a derivative of inorganic pyrophosphate molecules that adhere to the hydroxyapatite crystal-binding site of the bone matrix and inhibit osteoclastic activity. Bisphosphonates have long been used in various conditions including osteoporosis, Paget disease, multiple myeloma, and bone metastasis of solid tumors. Zoledronic acid (ZA) is a third-generation bisphosphonate and is the most potent among its class. It was approved in 2002 for the prevention of SREs in mCRPC based on significant decrease in the risk of SREs (P=.021).[67] However, ZA was not associated with reduced risk of SREs in metastatic hormone-sensitive prostate cancer[68] and failed to prevent or delay the development of bone metastasis in high-risk localized prostate cancer.[69]

Denosumab is a fully human monoclonal antibody against the receptor activator of nuclear factor κB ligand, a cytokine that is essential for the function and survival of osteoclasts.[70] Unlike bisphosphonates, denosumab can be used in patients with renal insufficiency. Denosumab has been shown to be equivalent to ZA in the prevention of SREs but superior in delaying the time to first SRE and reducing the rates of multiple SREs in a head-to-head trial.[71] Adverse event rates were similar, without a significant difference in osteonecrosis of the jaw, which occurs in less than

5% of the patients (P=.09). Denosumab has also been explored for its role in the prevention of bone metastasis in high-risk localized disease. Although denosumab prolonged median bone metastasis–free survival and delayed the time to first bone metastasis compared with placebo,[72] the FDA did not approve denosumab for this indication.

Another bone-directed approach is the use of radioactive isotopes that can localize to regions of enhanced bone turnover by virtue of calcium homology (Ca-mimetic) or through linkage to a phosphate ligand such as ethylenediamine tetra(methylene phosphonic acid). Strontium-89 is a beta particle–emitting calcium-mimetic that is the first radiopharmaceutical approved for prostate cancer bone metastasis in 1993.[73] Samarium-152 is also a beta particle–emitting radionuclide that is chelated by ethylenediamine tetra(methylene phosphonic acid) for bone targeting. It was approved in 1997 for relief from pain in patients with metastatic bone lesions.[74] Although beta particle–emitting agents are effective in relieving symptoms, they are associated with severe bone marrow suppression due to deep tissue penetration and possible increase in the risk of hematologic malignancies.[75,76]

Radium-223 is a calcium-mimetic radioisotope, but its decay results in the emission of alpha particles that have higher linear energy transfer, causing more effective double-strand DNA breaks, but shorter radius of energy transfer, allowing for minimal damage to the surrounding marrow. Radium-223 has been shown to reduce the incidence of SREs and extend survival in patients with bone metastatic CRPC.[21] It was approved in 2013 for the treatment of CRPC with symptomatic bone metastases without known visceral involvement. Currently, an observational cohort study is ongoing to assess pain and bone pain–related quality of life in patients treated with radium-223. Its favorable safety profile with minimal bone marrow suppression makes combinational strategies with other effective systemic agents feasible. Radium-223 is being evaluated in combination with AR-targeted agents, chemotherapy, and immunotherapy.

IMMUNOTHERAPY

Prostate cancer had long been considered intrinsically nonimmunogenic, thus unlikely to respond to immune-based treatment. Early nonspecific cytokine-based trials showed only minimal antitumor activity in prostate cancer. However, advances in understanding of tumor immunogenicity and the mechanisms of immune escape of cancer have led to the development of novel immune-based therapeutic approaches in prostate cancer.

Therapeutic Vaccines

Among various immune-based therapeutic strategies, the therapeutic vaccine approach has been most successful in prostate cancer. Therapeutic cancer vaccines are designed to enhance immune recognition of specific tumor-associated antigens (TAAs), leading to tumor-specific T-cell–mediated destruction. Prostate cancer is an attractive target for vaccine approach because it expresses organ-specific target TAAs such as PSA, prostatic acid phosphatase (PAP), and prostate-specific membrane antigen, and its indolent course allows for sufficient time to generate immune responses.[77]

Sipuleucel-T is an autologous cellular vaccine in which patients' dendritic cells are incubated ex vivo with a fusion protein consisting of prostate antigen PAP and granulocyte macrophage colony-stimulating factor, an immune activator, to generate anti-PAP immune responses. Sipuleucel-T was approved in 2010 on the basis of survival benefit in patients with asymptomatic or minimally symptomatic mCRPC.[14,78] Despite high-level evidence of survival benefit, sipuleucel-T has not been as widely accepted as other approved agents because of lack of measurable clinical response, high cost, and logistical challenges involving leukapheresis, product manufacturing, and delivery.

Prostvac-VF is a poxviral vector-based vaccine that is in the late stage of clinical development. Prostvac-VF consists of a recombinant vaccinia vector (prime) and a recombinant fowlpox vector (boost), both of which are engineered to express PSA and T-cell costimulatory molecules.[79] Unlike sipuleucel-T, Prostvac-VF is an off-the-shelf vaccine and does not require ex vivo processing. It has shown a survival benefit in a randomized phase II study[80] and is currently under a phase III trial in patients with asymptomatic or minimally symptomatic chemotherapy-naive mCRPC (PROSPECT).

Other therapeutic vaccines with different vectors and TAAs are under development including

Mayo Clin Proc. ■ December 2015;90(12):1719-1733 ■ http://dx.doi.org/10.1016/j.mayocp.2015.10.010
www.mayoclinicproceedings.org

TABLE 5. Selective Ongoing Immune Therapy Trials in Metastatic Prostate Cancer

Agent	Clinical trial design	Phase	Identifier
Sipuleucel-T	Sipuleucel-T with concurrent vs sequential AA	Randomized PII	NCT01487863
	Sipuleucel-T with concurrent vs sequential enzalutamide	Randomized PII	NCT01981122
	Sipuleucel-T ± Radium-223	Randomized PII	NCT02463799
	Sipuleucel-T ± XRT	Randomized PII	NCT01807065
	Sipuleucel-T with immediate vs delayed ipilimumab	Randomized PII	NCT01804465
Prostvac-VF	Rrostvac-VF ± GM-CSF vs placebo	Randomized PIII	NCT01322490
	Enzalutamide ± Prostvac-VF	Randomized PII	NCT01867333
	Docetaxel ± Prostvac-VF	Randomized PII	NCT01145508
Ipilimumab	Ipilimumab	Randomized PIII	NCT01057810
	Ipilimumab + AA	Single-arm PII	NCT01688492
	Ipilimumab + ADT	Single-arm PII	NCT01498978
Pembrolizumab	Pembrolizumab + enzalutamide	Single-arm PII	NCT02312557
	ADXS-PSA ± pembrolizumab	Phase I/II	NCT02325557
	Pembrolizumab + cryosurgery	Single-arm PII	NCT02489357

AA = abiraterone acetate; P = phase; XRT = radiation therapy.

a live attenuated *Listeria* bacterium-based vaccine engineered to target PSA (ADXS-PSA) and a DNA vaccine targeting AR LBD (pTVG-AR).

Checkpoint Inhibitors

Among various immune escape mechanisms, inhibitory immune checkpoints such as cytotoxic T-lymphocyte–associated protein 4 and programmed cell death 1 (PD-1) have been found to play critical roles in cancer progression.

Ipilimumab, a monoclonal antibody against cytotoxic T-lymphocyte–associated protein 4, has shown antitumor activity in prostate cancer with a PSA response (PSA decline ≥50%) of 15% to 20%.[81] However, ipilimumab failed to demonstrate survival benefit in patients with mCRPC who had been treated with docetaxel in a phase III trial.[82] Of note, the presence of visceral metastases and poor prognostic clinical factors markedly attenuated the effect of ipilimumab. To this end, a second phase III study of ipilimumab is ongoing in chemotherapy-naive patients with mCRPC with bone-only metastasis and no or minimal symptoms (Table 5).

Programmed cell death 1 is another negative checkpoint receptor expressed on the surface of activated T cells and inhibits cytotoxic T-cell responses when binding to its ligands, programmed cell death ligand 1 (PD-L1) or programmed cell death ligand 2. Several monoclonal antibodies targeting PD-1 (pembrolizumab and nivolumab) and PD-L1 (atezolizumab) have shown promising antitumor activity in various solid tumors. The antitumor activity of PD-1/PD-L1–targeted agents seems to be correlated with PD-L1 expression in tumor cells or tumor-infiltrating immune cells.[83] In prostate cancer, PD-L1 expression in the primary tumor is rare and the early study of nivolumab failed to show antitumor activity in a small subpopulation of patients with prostate cancer.[83,84] However, recent data showed that PD-L1 expression in prostate cancer can be upregulated after antiandrogen and inflammatory cytokine treatment, suggesting that PD-1/PD-L1–targeted therapy may have a role in a subset of patients with prostate cancer.[85,86] The role of anti–PD-1/PD-L1 agents alone or in combination is being tested in various stages of prostate cancer (Table 5).

Combination Immunotherapy

A modest antitumor response with low response rate suggests that therapeutic vaccine or immune checkpoint inhibitor alone may not be sufficient to overcome complex immune escape mechanisms and to elicit effective antitumor activity in advanced prostate cancer. Thus, a combinational approach with immunomodulatory therapies is under active evaluation.

Radiation or chemotherapy-induced cell death stimulates tumor-specific immune responses by an enhanced display of TAAs and upregulation of tumor-suppressive proteins and inflammatory cytokines (immunogenic cell death).[87-89] Several combination trials are ongoing to further validate

TABLE 6. Selected Investigational Agents in Clinical Trials in Metastatic Prostate Cancer[a]

Agent	Target	Clinical trial			
		Design	Phase	Identifier	Target subjects
Tivozanib	VEGF	Tivozanib + enzalutamide	II	NCT01885949	mCRPC
Sunitinib	VEGF	AA ± sunitinib vs dasatinib	II	NCT01254864	mCRPC
Veliparib	PARP 1/2	AA ± veliparib	II	NCT01576172	mCRPC
Olaparib	PARP 1/2	AA ± orlaparib	II	NCT01972217	mCRPC, postdocetaxel
Everolimus	mTOR	Enzalutamide + everolimus	I	NCT02125084	mCRPC
		Docetaxel + everolimus/bevacizumab	Ib/II	NCT00574769	mCRPC
MLN0128	mTOR	MLN0128	II	NCT02091531	mCRPC, postenzalutamide or AA
LY3023414	mTOR/PI3K	Enzalutamide ± LY3023414	II	NCT02407054	mCRPC
BKM120	PI3K	BKM120	II	NCT01385293	mCRPC
		BKM120 + AA	Ib	NCT01741753	mCRPC, postdocetaxel
Aflusertib	AKT	Aflusertib + AA vs enzalutamide	I	NCT02380313	mCRPC
Palbociclib	CDK4/6	ADT ± palbociclib	II	NCT02059213	mHSPC, Rb (+)[b]
LDE225	Hedgehog	LDE225 + docetaxel	Ib	NCT02182622	mCRPC, postdocetaxel
Vismodegib	Hedgehog	Vismodegib	I	NCT02115828	mCRPC
Cixutumumab	IGF-I	ADT + cixutumumab	II	NCT01120236	mHSPC
BI 836845	IGF-I/II	Enzalutamide ± BI 836845	Ib/II	NCT02204072	mCRPC

[a]AA = abiraterone acetate; CDK = cyclin-dependent kinase; IGF = insulin-like growth factor; mCRPC = metastatic castration-resistant prostate cancer; mHSPC = metastatic hormone-sensitive prostate cancer; mTOR = mammalian target of rapamycin; PARP = poly(ADP-ribose) polymerase; PI3K = phosphatidylinositide 3-kinase; Rb = retinoblastoma; VEGF = vascular endothelial growth factor.
[b]Presence of Rb gene mutation.

the augmentation of antitumor immune responses by cytotoxic therapies.

Recently, multiple lines of evidence suggest that androgen possesses immunosuppressive properties and androgen ablation may have positive immunological effects in prostate cancer.[90] In addition, apoptotic release of TAAs by AR-targeted therapies can synergize with immune-based treatment. Immunotherapy with ADT or AR-targeted agents in combination or in different sequences is being tested.

Last, the combination of 2 immunotherapies with distinct and compensatory mechanisms such as TAA-specific therapeutic vaccines and nonspecific immune-stimulating checkpoint inhibitors is a promising strategy to maximize antitumor immune responses. Notable ongoing immunotherapy trials are summarized in Table 5.

NOVEL THERAPEUTIC TARGETS

Although the AR pathway is a key driver in prostate cancer, it is increasingly recognized that advanced prostate cancer is a molecularly heterogeneous disease harboring various molecular alterations. Relevant pathways under investigation as prostate cancer therapeutic targets include those mediated by vascular endothelial growth factor receptor, poly(ADP-ribose) polymerase, phosphatidylinositide 3-kinase, protein kinase B, and mammalian target of rapamycin (phosphatidylinositide 3-kinase/Akt/mammalian target of rapamycin pathway), Hedgehog signaling, protein chaperones (HSP27), and the insulin-like growth factor pathway. Yet, none of the experimental agents targeting alternative pathways has shown survival benefit. A summary depicting the selective targeted agents in various stages of clinical trial development is given in Table 6.

CURRENT ISSUES IN MANAGEMENT AND FUTURE DIRECTIONS

Defining the Optimal Sequence and Outcomes

As a number of new therapeutic agents have been approved for the management of advanced prostate cancer in a relatively short period of time, we are faced with a new challenge of finding the optimal sequence of these agents in this population. With the introduction of new-generation AR-targeted agents that in general have favorable safety profiles compared with cytotoxic chemotherapeutics, new-generation hormonal agents have been established as the

Mayo Clin Proc. ■ December 2015;90(12):1719-1733 ■ http://dx.doi.org/10.1016/j.mayocp.2015.10.010
www.mayoclinicproceedings.org

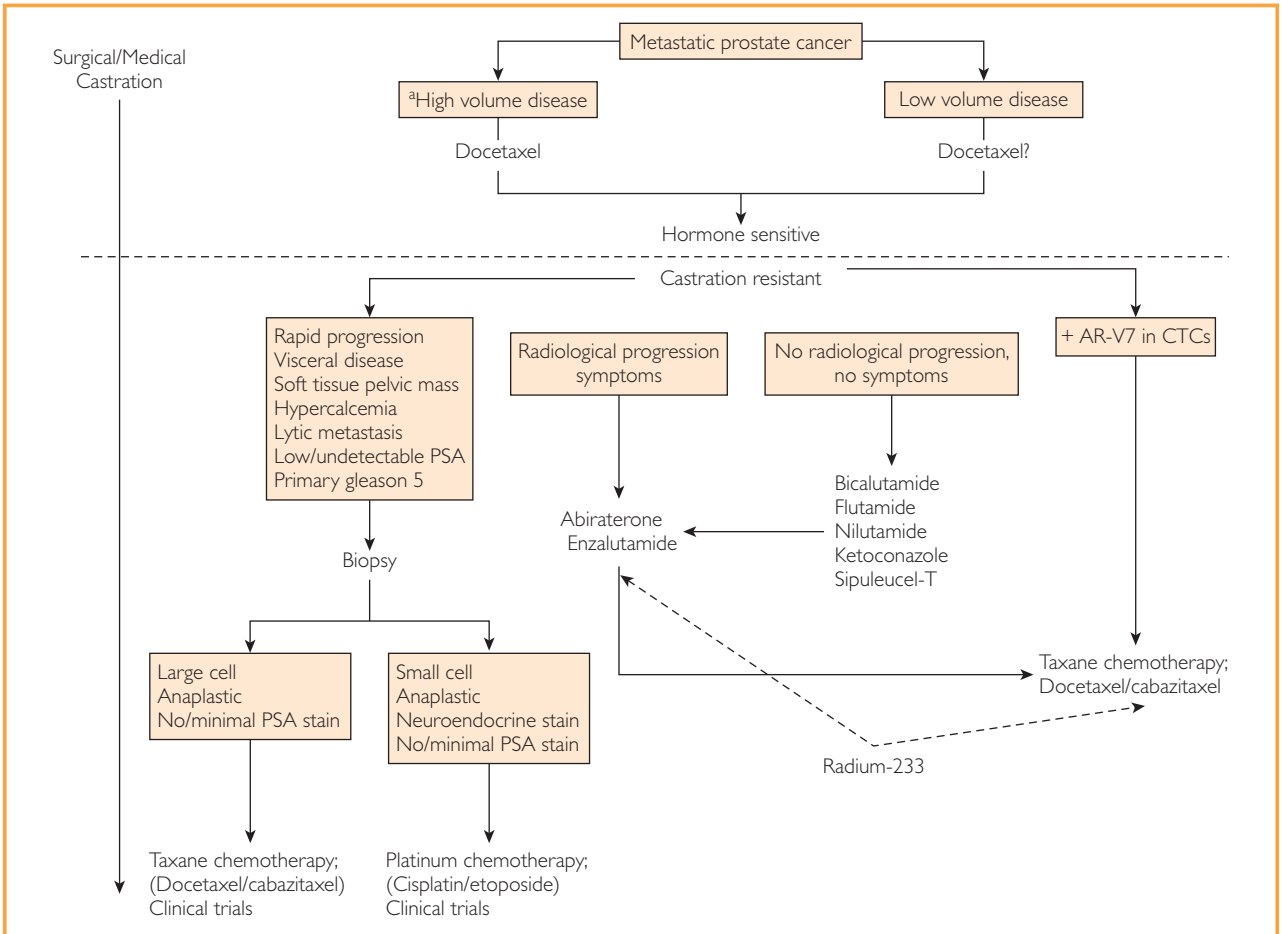

FIGURE 2. Potential strategy for sequencing systemic therapies. [a]High volume disease = ≥4 bone lesions or visceral disease; CTC = circulating tumor cell; PSA = prostate-specific antigen.

preferred first-line therapy after the development of castration resistance. However, no data exist to indicate which of these AR-targeted agents should be used first except that the response of a subsequent AR agent after the other is suboptimal. In addition, recent studies support the use of upfront chemotherapy before the development of castration resistance. Similarly, optimal timing of other therapeutics with different mechanisms of action including sipuleucel-T and radium-223 as well as the second-line chemotherapy cabazitaxel requires further evaluation (Figure 2). There are currently a series of clinical trials attempting to define the optimal sequence as well as explore the role of combination of current therapeutics. Blood and tissue biomarkers may assist in the selection of the most appropriate treatment and the specific evaluation of therapeutic outcomes.

Regulatory Issues in New Drug Development

Since the approval of docetaxel in 2004 based on OS benefit, the FDA has based approval of agents for metastatic prostate cancer on OS except for the bone-targeted agent for which prevention of SREs served for regulatory approval. However, OS as a primary end point in registry trials in prostate cancer has long been a matter of controversy because of the indolent natural history requiring long follow-up periods. With multiple therapeutics with proven survival benefits, the significant prolongation of OS has been increasingly difficult. A series of recent phase III trials in which agents that demonstrated promising efficacy in early phase studies failed to demonstrate survival benefit further fueled the controversy about the optimal regulatory end point.

The commonly used secondary end points, PSA or radiographic progression-free survival (rPFS), have been proposed as potential surrogates for OS for regulatory approval, but they have several limitations. The definition of PFS is dependent on the frequency of measurement, and its definition is complex in prostate cancer. PSA is under direct and exclusive transcriptional control of AR and thus fails to represent disease status when the tumor is not primarily driven by the AR pathway as in tumors with anaplastic or neuroendocrine differentiation. Accurate assessment of treatment response or progression of skeletal lesions, which is the only area of metastasis in most of the patients, is difficult with traditional bone scintigraphy. The Prostate Cancer Working Group 2 has defined rPFS for metastatic prostate cancer using a modified form of RECIST 1.0 for soft tissue lesions, in which only those lymph nodes that are 2 cm or greater in size are considered measurable, and specific criteria for bone lesions.[91] Morris et al[92] reported the correlation of Prostate Cancer Working Group 2—defined rPFS and OS in the phase III trial of AA (COU-AA-302). However, not all agents that may confer OS benefit necessarily result in PSA or radiographic responses, which is often the case with immunotherapeutic agents. Thus, it is imperative to develop a new surrogate end point that can be reliably used in registration trials for timely approval of effective agents and also reduction of cost by avoiding long-term follow-up. A recent analysis of a panel of biomarkers showed that the CTC count is correlated with survival in mCRPC, and independent phase III trials are ongoing to validate the individual patient—level surrogacy of CTC.[93]

CONCLUSION

During the past several years, there has been rapid progress in our understanding of the biology of prostate cancer such as mechanisms of AR pathway activation, complex tumor-microenvironment interaction of bone metastasis, antitumor immunology, and new oncogenic pathways, all of which provide many new opportunities to develop promising prostate cancer therapeutics. Clinical research has evolved from a relatively empiric application of novel therapeutics to a more disease- and patient-targeted specific approach that involves close integration of laboratory and clinical principles. This approach will require a careful review of basic clinical principles of drug development and regulatory guidelines for new drug approval.

Abbreviations and Acronyms: **AA** = abiraterone acetate; **ADT** = androgen deprivation therapy; **AR** = androgen receptor; **AR-V** = AR splice variant; **CRPC** = castration-resistant prostate cancer; **CTC** = circulating tumor cell; **CYP** = cytochrome P450; **FDA** = Food and Drug Administration; **LBD** = ligand-binding domain; **mCRPC** = metastatic castration-resistant prostate cancer; **OS** = overall survival; **PAP** = prostatic acid phosphatase; **PD-1** = programmed cell death 1; **PD-L1** = programmed cell death ligand 1; **PSA** = prostate-specific antigen; **rPFS** = radiographic progression-free survival; **SRE** = skeletal-related event; **TAA** = tumor-associated antigen; **ZA** = zoledronic acid

Correspondence: Address to Mario A. Eisenberger, MD, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, The Johns Hopkins University, Oncology Cancer Research Bldg 1, 1650 Orleans St, Rm 1M51, Baltimore, MD 21231 (eisenma@jhmi.edu). Individual reprints of this article and a bound reprint of the entire Symposium on Neoplastic Hematology and Medical Oncology will be available for purchase from our website www.mayoclinicproceedings.org.

The Symposium on Neoplastic Hematology and Medical Oncology will continue in an upcoming issue.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin*. 2015;65(1):5-29.
2. Sandblom G, Varenhorst E, Löfman O, Rosell J, Carlsson P. Clinical consequences of screening for prostate cancer: 15 years follow-up of a randomised controlled trial in Sweden. *Eur Urol*. 2004;46(6):717-723:discussion 724.
3. Facts F. An interactive tool for access to SEER cancer statistics. *Surveillance Research Program*. 2015. http://seer.cancer.gov/faststats. Accessed September 15, 2015.
4. Oefelein MG, Feng A, Scolieri MJ, Ricchiutti D, Resnick MI. Reassessment of the definition of castrate levels of testosterone: implications for clinical decision making. *Urology*. 2000;56(6):1021-1024.
5. Crawford ED, Eisenberger MA, McLeod DG, et al. A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. *N Engl J Med*. 1989;321(7):419-424.
6. Eisenberger MA, Blumenstein BA, Crawford ED, et al. Bilateral orchiectomy with or without flutamide for metastatic prostate cancer. *N Engl J Med*. 1998;339(15):1036-1042.
7. Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. Prostate Cancer Trialists' Collaborative Group. *Lancet*. 2000;355(9214):1491-1498.
8. Gravis G, Boher J-M, Joly F, et al. Androgen deprivation therapy (ADT) plus docetaxel (D) versus ADT alone for hormone-naive metastatic prostate cancer (PCa): long-term analysis of the GETUG-AFU 15 phase III trial. *J Clin Oncol*. 2015;33(suppl 7):abstr140.
9. Sweeney C, Chen Y-H, Carducci MA, et al. Impact on overall survival (OS) with chemohormonal therapy versus hormonal therapy for hormone-sensitive newly metastatic prostate cancer (mPrCa): an ECOG-led phase III randomized trial. *J Clin Oncol*. 2014;32(5s, suppl):abstrLBA2.

10. James ND, Sydes MR, Mason MD, et al. Docetaxel and/or zoledronic acid for hormone-naive prostate cancer: first overall survival results from STAMPEDE (NCT00268476). *J Clin Oncol*. 2015;33(suppl):abstr5001.
11. Sandler HM, Hu C, Rosenthal SA, et al. A phase III protocol of androgen suppression (AS) and 3DCRT/IMRT versus AS and 3DCRT/IMRT followed by chemotherapy (CT) with docetaxel and prednisone for localized, high-risk prostate cancer (RTOG 0521). *J Clin Oncol*. 2015;33(suppl):abstrLBA5002.
12. Sweeney CJ, Chen Y-H, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med*. 2015;373(8):737-746.
13. Tannock IF, de Wit R, Berry WR, et al; TAX 327 Investigators. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med*. 2004;351(15):1502-1512.
14. Kantoff PW, Higano CS, Shore ND, et al; IMPACT Study Investigators. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med*. 2010;363(5):411-422.
15. de Bono JS, Oudard S, Ozguroglu M, et al; TROPIC Investigators. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet*. 2010;376(9747):1147-1154.
16. de Bono JS, Logothetis CJ, Molina A, et al; COU-AA-301 Investigators. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med*. 2011;364(21):1995-2005.
17. Ryan CJ, Smith MR, de Bono JS, et al; COU-AA-302 Investigators. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med*. 2013;368(2):138-148.
18. Ryan CJ, Smith MR, Fizazi K, et al; COU-AA-302 Investigators. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol*. 2015;16(2):152-160.
19. Scher HI, Fizazi K, Saad F, et al; AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. 2012;367(13):1187-1197.
20. Beer TM, Armstrong AJ, Rathkopf DE, et al; PREVAIL Investigators. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med*. 2014;371(5):424-433.
21. Parker C, Nilsson S, Heinrich D, et al; ALSYMPCA Investigators. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. 2013;369(3):213-223.
22. Gelmann EP. Molecular biology of the androgen receptor. *J Clin Oncol*. 2002;20(13):3001-3015.
23. Mizokami A, Namiki M. Reconsideration of progression to CRPC during androgen deprivation therapy. *J Steroid Biochem Mol Biol*. 2015;145:164-171.
24. Scher HI, Liebertz C, Kelly WK, et al. Bicalutamide for advanced prostate cancer: the natural versus treated history of disease. *J Clin Oncol*. 1997;15(8):2928-2938.
25. Kassouf W, Tanguay S, Aprikian AG. Nilutamide as second line hormone therapy for prostate cancer after androgen ablation fails. *J Urol*. 2003;169(5):1742-1744.
26. Fossa SD, Slee PH, Brausi M, et al. Flutamide versus prednisone in patients with prostate cancer symptomatically progressing after androgen-ablative therapy: a phase III study of the European Organization for Research and Treatment of Cancer Genitourinary Group. *J Clin Oncol*. 2001;19(1):62-71.
27. Attard G, Richards J, de Bono JS. New strategies in metastatic prostate cancer: targeting the androgen receptor signaling pathway. *Clin Cancer Res*. 2011;17(7):1649-1657.
28. Liebertz C, Fox P. Ketoconazole as a secondary hormonal intervention in advanced prostate cancer. *Clin J Oncol Nurs*. 2006;10(3):361-366.
29. Attard G, Reid AH, Yap TA, et al. Phase I clinical trial of a selective inhibitor of CYP17, abiraterone acetate, confirms that castration-resistant prostate cancer commonly remains hormone driven. *J Clin Oncol*. 2008;26(28):4563-4571.
30. De Wit R, Fizazi K, Jinga V, et al. Phase 3, randomized, placebo-controlled trial of orteronel (TAK-700) plus prednisone in patients (pts) with chemotherapy-naive metastatic castration-resistant prostate cancer (mCRPC) (ELM-PC 4 trial). *J Clin Oncol*. 2014;32(5s, suppl):abstr5008.
31. Dreicer R, Jones R, Oudard S, et al. Results from a phase 3, randomized, double-blind, multicenter, placebo-controlled trial of orteronel (TAK-700) plus prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) that has progressed during or following docetaxel-based therapy (ELM-PC 5 trial). *ASCO Meet Abstr*. 2014;32(suppl 4):abstr7.
32. Schroder FH. Cyproterone acetate—mechanism of action and clinical effectiveness in prostate cancer treatment. *Cancer*. 1993;72(12, suppl):3810-3815.
33. Flutamide for prostate cancer. *Med Lett Drugs Ther*. 1989;31(797):72.
34. Bicalutamide for prostate cancer. *Med Lett Drugs Ther*. 1996;38(977):56-57.
35. Nilutamide approved for metastatic prostate cancer. *Am J Health Syst Pharm*. 1996;53(23):2784.
36. Foster WR, Car BD, Shi H, et al. Drug safety is a barrier to the discovery and development of new androgen receptor antagonists. *Prostate*. 2011;71(5):480-488.
37. Rathkopf DE, Morris MJ, Fox JJ, et al. Phase I study of ARN-509, a novel antiandrogen, in the treatment of castration-resistant prostate cancer. *J Clin Oncol*. 2013;31(28):3525-3530.
38. Yuan X, Cai C, Chen S, Chen S, Yu Z, Balk SP. Androgen receptor functions in castration-resistant prostate cancer and mechanisms of resistance to new agents targeting the androgen axis. *Oncogene*. 2014;33(22):2815-2825.
39. Chan SC, Li Y, Dehm SM. Androgen receptor splice variants activate androgen receptor target genes and support aberrant prostate cancer cell growth independent of canonical androgen receptor nuclear localization signal. *J Biol Chem*. 2012;287(23):19736-19749.
40. Antonarakis ES, Lu C, Wang H, et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. *N Engl J Med*. 2014;371(11):1028-1038.
41. Bruno RD, Vasaitis TS, Gediya LK, et al. Synthesis and biological evaluations of putative metabolically stable analogs of VN/124-1 (TOK-001): head to head anti-tumor efficacy evaluation of VN/124-1 (TOK-001) and abiraterone in LAPC-4 human prostate cancer xenograft model. *Steroids*. 2011;76(12):1268-1279.
42. Taplin M, Chi KN, Chu F, et al. Galeterone in 4 patient populations of men with CRPC: results from ARMOR2. *Ann Oncol*. 2014;25(suppl 4):iv257.
43. Kwegyir-Afful AK, Ramalingam S, Purushottamachar P, Ramamurthy VP, Njar VC. Galeterone and VNPT55 induce proteasomal degradation of AR/AR-V7, induce significant apoptosis via cytochrome c release and suppress growth of castration resistant prostate cancer xenografts in vivo. *Oncotarget*. 2015;6(29):27440-27460.
44. Denmeade SR, Isaacs JT. Bipolar androgen therapy: the rationale for rapid cycling of supraphysiologic androgen/ablation in men with castration resistant prostate cancer. *Prostate*. 2010;70(14):1600-1607.
45. Schweizer MT, Antonarakis ES, Wang H, et al. Effect of bipolar androgen therapy for asymptomatic men with castration-resistant prostate cancer: results from a pilot clinical study. *Sci Transl Med*. 2015;7(269):269ra262.
46. Badrising S, van der Noort V, van Oort IM, et al. Clinical activity and tolerability of enzalutamide (MDV3100) in patients with metastatic, castration-resistant prostate cancer who progress after docetaxel and abiraterone treatment. *Cancer*. 2014;120(7):968-975.
47. Noonan KL, North S, Bitting RL, Armstrong AJ, Ellard SL, Chi KN. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. *Ann Oncol*. 2013;24(7):1802-1807.

48. Suzman DL, Luber B, Schweizer MT, Nadal R, Antonarakis ES. Clinical activity of enzalutamide versus docetaxel in men with castration-resistant prostate cancer progressing after abiraterone. *Prostate*. 2014;74(13):1278-1285.
49. Schrader AJ, Boegemann M, Ohlmann CH, et al. Enzalutamide in castration-resistant prostate cancer patients progressing after docetaxel and abiraterone. *Eur Urol*. 2014;65(1):30-36.
50. Cheng HH, Gulati R, Azad A, et al. Activity of enzalutamide in men with metastatic castration-resistant prostate cancer is affected by prior treatment with abiraterone and/or docetaxel. *Prostate Cancer Prostatic Dis*. 2015;18(2):122-127.
51. Azad AA, Eigl BJ, Murray RN, Kollmannsberger C, Chi KN. Efficacy of enzalutamide following abiraterone acetate in chemotherapy-naive metastatic castration-resistant prostate cancer patients. *Eur Urol*. 2015;67(1):23-29.
52. Mezynski J, Pezaro C, Bianchini D, et al. Antitumour activity of docetaxel following treatment with the CYP17A1 inhibitor abiraterone: clinical evidence for cross-resistance? *Ann Oncol*. 2012;23(11):2943-2947.
53. Schweizer MT, Zhou XC, Wang H, et al. The influence of prior abiraterone treatment on the clinical activity of docetaxel in men with metastatic castration-resistant prostate cancer. *Eur Urol*. 2014;66(4):646-652.
54. Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med*. 2004; 351(15):1513-1520.
55. Kelly WK, Halabi S, Carducci M, et al. Randomized, double-blind, placebo-controlled phase III trial comparing docetaxel and prednisone with or without bevacizumab in men with metastatic castration-resistant prostate cancer: CALGB 90401. *J Clin Oncol*. 2012;30(13):1534-1540.
56. Tannock IF, Fizazi K, Ivanov S, et al; VENICE Investigators. Aflibercept versus placebo in combination with docetaxel and prednisone for treatment of men with metastatic castration-resistant prostate cancer (VENICE): a phase 3, double-blind randomised trial. *Lancet Oncol*. 2013;14(8): 760-768.
57. Quinn DI, Tangen CM, Hussain M, et al. Docetaxel and atrasentan versus docetaxel and placebo for men with advanced castration-resistant prostate cancer (SWOG S0421): a randomised phase 3 trial. *Lancet Oncol*. 2013;14(9):893-900.
58. Fizazi K, Higano CS, Nelson JB, et al. Phase III, randomized, placebo-controlled study of docetaxel in combination with zibotentan in patients with metastatic castration-resistant prostate cancer. *J Clin Oncol*. 2013;31(14):1740-1747.
59. Araujo JC, Trudel GC, Saad F, et al. Docetaxel and dasatinib or placebo in men with metastatic castration-resistant prostate cancer (READY): a randomised, double-blind phase 3 trial. *Lancet Oncol*. 2013;14(13):1307-1316.
60. Small E, Demkow T, Gerritsen WR, Rolland F, Hoskin P, Smith DC, et al. A phase III trial of GVAX immunotherapy for prostate cancer in combination with docetaxel vs docetaxel plus prednisone in symptomatic, castration-resistant prostate cancer (CRPC). *Proc Am Soc Clin Oncol*. 2009:abstr 7 http://scholar.google.com/scholar_lookup?title=A%20phase%20III%20trial%20of%20GVAX%20immunotherapy%20for%20prostate%20cancer%20in%20combination%20with%20docetaxel%20versus%20docetaxel%20plus%20prednisone%20in%20symptomatic%2C%20castration-resistant%20prostate%20cancer%20%28CRPC%29&author=E%20Small&author=T%20Demkow&author=WR%20Gerritsen&publication_year=2009. Accessed November 2, 2015.
61. Scher HI, Jia X, Chi K, et al. Randomized, open-label phase III trial of docetaxel plus high-dose calcitriol versus docetaxel plus prednisone for patients with castration-resistant prostate cancer. *J Clin Oncol*. 2011;29(16):2191-2198.
62. Chi KN, Higano CS, Blumenstein BA, et al. Phase III SYNERGY trial: Docetaxel +/- custirsen and overall survival in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) and poor prognosis. *J Clin Oncol*. 2015;33(suppl): abstr5009.
63. Antonarakis ES, Eisenberger MA. Phase III trials with docetaxel-based combinations for metastatic castration-resistant prostate cancer: time to learn from past experiences. *J Clin Oncol*. 2013; 31(14):1709-1712.
64. Petrylak DP, Vogelzang NJ, Budnik N, et al. Docetaxel and prednisone with or without lenalidomide in chemotherapy-naive patients with metastatic castration-resistant prostate cancer (MAINSAIL): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet Oncol*. 2015;16(4):417-425.
65. Saitoh H, Hida M, Shimbo T, Nakamura K, Yamagata J, Satoh T. Metastatic patterns of prostatic cancer. Correlation between sites and number of organs involved. *Cancer*. 1984;54(12): 3078-3084.
66. Jacobs SC. Spread of prostatic cancer to bone. *Urology*. 1983; 21(4):337-344.
67. Saad F, Gleason DM, Murray R, et al; Zoledronic Acid Prostate Cancer Study Group. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst*. 2002;94(19):1458-1468.
68. Smith MR, Halabi S, Ryan CJ, et al. Randomized controlled trial of early zoledronic acid in men with castration-sensitive prostate cancer and bone metastases: results of CALGB 90202 (alliance). *J Clin Oncol*. 2014;32(11):1143-1150.
69. Wirth M, Tammela T, Cicalese V, et al. Prevention of bone metastases in patients with high-risk nonmetastatic prostate cancer treated with zoledronic acid: efficacy and safety results of the Zometa European Study (ZEUS). *Eur Urol*. 2015;67(3):482-491.
70. Delmas PD. Clinical potential of RANKL inhibition for the management of postmenopausal osteoporosis and other metabolic bone diseases. *J Clin Densitom*. 2008;11(2):325-338.
71. Snedecor SJ, Carter JA, Kaura S, Botteman MF. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a cost-effectiveness analysis. *J Med Econ*. 2013;16(1):19-29.
72. Smith MR, Saad F, Coleman R, et al. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. *Lancet*. 2012;379(9810):39-46.
73. Radioactive strontium-89 for painful bone metastases. *Med Lett Drugs Ther*. 1993;35(908):102.
74. Samarium-153 lexidronam for painful bone metastases. *Med Lett Drugs Ther*. 1997;39(1008):83-84.
75. Silberstein EB, Williams C. Strontium-89 therapy for the pain of osseous metastases. *J Nucl Med*. 1985;26(4):345-348.
76. Sartor O, Reid RH, Hoskin PJ, et al; Quadramet 424Sm10/11 Study Group. Samarium-153-Lexidronam complex for treatment of painful bone metastases in hormone-refractory prostate cancer. *Urology*. 2004;63(5):940-945.
77. Gulley JL, Drake CG. Immunotherapy for prostate cancer: recent advances, lessons learned, and areas for further research. *Clin Cancer Res*. 2011;17(12):3884-3891.
78. Higano CS, Schellhammer PF, Small EJ, et al. Integrated data from 2 randomized, double-blind, placebo-controlled, phase 3 trials of active cellular immunotherapy with sipuleucel-T in advanced prostate cancer. *Cancer*. 2009;115(16):3670-3679.
79. Madan RA, Arlen PM, Mohebtash M, Hodge JW, Gulley JL. Prostvac-VF: a vector-based vaccine targeting PSA in prostate cancer. *Expert Opin Investig Drugs*. 2009;18(7):1001-1011.
80. Kantoff PW, Schuetz TJ, Blumenstein BA, et al. Overall survival analysis of a phase II randomized controlled trial of a Poxviral-based PSA-targeted immunotherapy in metastatic castration-resistant prostate cancer. *J Clin Oncol*. 2010;28(7):1099-1105.
81. Slovin SF, Higano CS, Hamid O, et al. Ipilimumab alone or in combination with radiotherapy in metastatic castration-resistant prostate cancer: results from an open-label, multicenter phase I/II study. *Ann Oncol*. 2013;24(7):1813-1821.
82. Kwon ED, Drake CG, Scher HI, et al; CA184-043 Investigators. Ipilimumab versus placebo after radiotherapy in patients with

metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2014;15(7):700-712.

83. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med*. 2012;366(26):2443-2454.
84. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med*. 2012;366(26):2455-2465.
85. Martin AM, Nirschl TR, Nirschl CJ, et al. Paucity of PD-L1 expression in prostate cancer: innate and adaptive immune resistance [published online ahead of print August 11, 2015). *Prostate Cancer Prostatic Dis*.
86. Bishop JL, Sio A, Angeles A, et al. PD-L1 is highly expressed in enzalutamide resistant prostate cancer. *Oncotarget*. 2015;6(1):234-242.
87. Shore ND, Mantz CA, Dosoretz DE, et al. Building on sipuleucel-T for immunologic treatment of castration-resistant prostate cancer. *Cancer Control*. 2013;20(1):7-16.
88. Tesniere A, Panaretakis T, Kepp O, et al. Molecular characteristics of immunogenic cancer cell death. *Cell Death Differ*. 2008; 15(1):3-12.
89. Bernstein MB, Garnett CT, Zhang H, et al. Radiation-induced modulation of costimulatory and coinhibitory T-cell signaling molecules on human prostate carcinoma cells promotes productive antitumor immune interactions. *Cancer Biother Radiopharm*. 2014;29(4):153-161.
90. Drake CG, Doody AD, Mihalyo MA, et al. Androgen ablation mitigates tolerance to a prostate/prostate cancer-restricted antigen. *Cancer Cell*. 2005;7(3):239-249.
91. Scher HI, Halabi S, Tannock I, et al. Prostate Cancer Clinical Trials Working Group. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol*. 2008;26(7): 1148-1159.
92. Morris MJ, Molina A, Small EJ, et al. Radiographic progression-free survival as a response biomarker in metastatic castration-resistant prostate cancer: COU-AA-302 results. *J Clin Oncol*. 2015;33(12):1356-1363.
93. Scher HI, Heller G, Molina A, et al. Circulating tumor cell biomarker panel as an individual-level surrogate for survival in metastatic castration-resistant prostate cancer. *J Clin Oncol*. 2015;33(12):1348-1355.