Review Article

Prostate Cancer: Developing Novel Approaches to Castration-Sensitive Disease

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Although androgen-deprivation therapy (ADT) remains the mainstay of castration-sensitive prostate cancer (CSPC) therapy, the disease's heterogeneity and the limited duration of the response have chaperoned the introduction of chemotherapy and the investigation of novel hormonal targeted agents in this setting. Combinations of ADT plus chemotherapy or novel hormonal therapies are being tested at various stages of CSPC with promising results. Furthermore, immunotherapy and experimental drugs are also being actively investigated in this setting. Intriguing multimodality strategies, chiefly deployed for early-stage disease with the aim of maximizing the efficacy and duration of the response, are being explored and may become valid therapeutic options in the future. Ultimately, striking a balance between the clinical gains of these combinations and possibly increased toxicity and reduced quality of life will be necessary. The development of precision medicine and accurate biomarkers is fundamental to progress. ***Cancer* 2016;000:000–000.** © *2016 American Cancer Society.*

KEYWORDS: castration-sensitive, chemohormonal therapy, immunotherapy, novel approaches, prostate cancer.

INTRODUCTION

Prostate cancer (PCa) is the most commonly diagnosed and third most lethal cancer among men in Western countries.[1] The vast majority of patients present with localized disease.[2] If they are treated adequately, most patients have a positive prognosis and a 5-year survival rate approaching 100%.[1] However, a proportion will eventually experience either local or distant recurrence. In addition, metastatic disease accounts for approximately 5% of new diagnoses.[3] The mainstay of treatment for metastatic PCa has been androgen-deprivation therapy (ADT) since Huggins and Hodges first pioneered castration therapy in 1941.[4] Androgens, particularly testosterone and dihydrotestosterone, drive PCa growth. In the modern era, luteinizing hormone-release hormone agonists (LHRHas) and antagonists are used to achieve a castrate level of serum testosterone (by convention defined as a testosterone level < 50 ng/mL). Over the years, many debates have surrounded ADT: early initiation versus deferred initiation, the addition of an androgen receptor (AR) antagonist for combined androgen blockade (CAB) versus monotherapy, LHRHas versus antagonists, and intermittent therapy versus continuous therapy. These issues will not be discussed here because they are not the purpose of this review. It is known that 80% to 90% of patients will initially respond both clinically and biochemically to ADT, and this translates into disease control for several years and improvements in cancer-related symptoms.[5] Nonetheless, hormone therapy is rarely curative, and in the metastatic setting, cancer typically progresses within 2 to 3 years despite castrate levels of serum testosterone.[5] This stage is known as castration-resistant prostate cancer (CRPC) and, despite many more treatment options, commonly leads to death in 2 to 4 years.[6]

Recent breakthroughs in the understanding of the mechanisms of PCa adaptation to ADT, focusing on the AR pathway, have demonstrated that PCa continues to be hormone-dependent even when evolving to castration resistance.[7] This concept allows a refined definition of untreated PCa, which is now termed castration-sensitive prostate cancer (CSPC). This review outlines new developments and investigational strategies for the treatment of CSPC.

THE STATE OF THE ART

ADT can be administered by bilateral orchiectomy or medical castration with LHRHas or antagonists, and although both approaches are equally recommended by the current National Comprehensive Cancer Network (NCCN) guidelines,[3,8] the latter represents the most frequent choice in clinical practice.

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DOI: 10.1002/cncr.30329, **Received:** May 25, 2016; **Revised:** August 9, 2016; **Accepted:** August 12, 2016, **Published online** Month 00, 2016 in Wiley Online Library (wileyonlinelibrary.com)

Lately, the addition of docetaxel to ADT for CSPC has demonstrated a survival advantage, and it is now a validated option for CSPC patients who are considered fit for chemotherapy.[3,8] An understanding of the heterogeneity of PCa cells[9] provided the rationale for 2 large randomized clinical trials that led to the practice change.[10,11] Both the Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED) and the Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) study tested 6 cycles of docetaxel in addition to ADT versus ADT alone in CSPC patients, and they demonstrated an unprecedented survival benefit in favor of the combination.[10,11] CHAARTED recruited only men with metastatic castration-sensitive prostate cancer (mCSPC), whereas STAMPEDE also included men with high-risk, locally advanced, and biochemically recurrent disease. The overall survival (OS) advantage for the metastatic subjects was 13.6 months (hazard ratio [HR], 0.61; 95% confidence interval [CI], 0.47-0.80; $P < .001$) and 15 months (HR, 0.76; 95% CI, 0.62-0.92; $P = .005$) for the CHAARTED and STAMPEDE trials, respectively. In the former, patients were stratified by the metastasis volume (high vs low): a high volume was defined as 4 or more bone metastases with at least 1 metastasis outside the spine and pelvis. The survival benefit was highest in the high-volume cohort (17 months; HR, 0.60; 95% CI, 0.45-0.81; $P < .001$), whereas in the low-volume cohort, the median OS was not reached; longer follow-up is needed, with results expected later in 2016. At present, the CHAARTED data suggest that docetaxel plus ADT should be given only to patients presenting with a high metastatic burden. In contrast, the STAMPEDE study did not stratify by the volume of metastases and achieved a remarkable OS benefit (15 months) for the whole metastatic population.

A meta-analysis of published randomized trials of docetaxel plus ADT in men with mCSPC showed an improvement in the survival at 4 years of 9% (95% CI, 5%-14%).[12] The meta-analysis incorporated low-volume metastatic patients and a smaller trial (GETUG-AFU 15). The latter did not demonstrate a statistically significant OS advantage, likely because of a lack of statistical power.[13] In view of the available data, the updated NCCN guidelines state that despite a less certain benefit for men with lower volume disease, ADT plus docetaxel is recommended for all adequately fit men with newly diagnosed mCSPC, regardless of the disease burden.[3,8] However, until more data for low-volume metastatic patients (specifically long-term follow-up data from CHAARTED) are available, we suggest careful consideration of the risks and possible benefits of chemotherapy in this specific subset of patients. Another caveat applies to men presenting with metastases after the failure of local therapy: they were a minority of participants in these trials in comparison with subjects with newly diagnosed metastatic disease who had not undergone prior local therapy.[10,11] Because the biology of these 2 divergent cancer presentations may differ, it cannot be assumed that chemohormonal therapy will yield equivalent survival benefits for all men with mCSPC, and future trials should analyze these cohorts of mCSPC patients separately.

Other compelling data from the STAMPEDE study presented at the 2015 American Society of Clinical Oncology (ASCO) meeting showed that the addition of 6 cycles of docetaxel to the standard of care (ADT ± radiotherapy [RT]) for men with high-risk M0 PCa resulted in failure-free survival benefits (HR, 0.60; 95% CI, 0.45-0.80; $P = .0003$) in comparison with the standard of care (failure was defined as prostate-specific antigen [PSA] failure or radiographic progression or death due to PCa).[14] These outcomes suggest that docetaxel in combination with ADT and RT can be considered for this subgroup of patients if they are deemed fit. However, it should be noted that the OS data for this subgroup of patients are not yet mature, and thus definitive recommendations cannot be made. Also presented at the 2015 ASCO meeting were the results of the phase 3 Radiation Therapy Oncology Group (RTOG) 0521 trial, which randomized men with high-risk nonmetastatic PCa to receive ADT and RT with or without 6 cycles of adjuvant docetaxel.[15] The study described a OS benefit of 4% (HR, 0.68; 95% CI, 0.44-1.03; 1-sided $P = .03$) and a 5-year disease-free survival advantage of 7% (HR, 0.76; 95% CI, 0.57-1.00; 2-sided $P = .05$) in favor of the adjuvant chemotherapy regimen. Notwithstanding criticisms related to the small survival benefit achieved with docetaxel, the use of a 1-sided statistical analysis, and the prematurity of the analysis (few deaths to date), the current NCCN guidelines list this combination regimen as a valid treatment option for high-risk nonmetastatic PCa patients who are adequately fit.[3,8] Notably, the demonstrated activity of cabazitaxel in metastatic castration-resistant prostate cancer (mCRPC)[16] has also recently prompted its investigation in this setting. The Swedish ongoing phase 3 randomized trial SensiCab (NCT01978873) seeks to assess the efficacy of cabazitaxel in addition to ADT in patients with high-risk/N1/M1 PCa. The hypothesis is that this chemohormonal modality administered early, when the disease burden is null or

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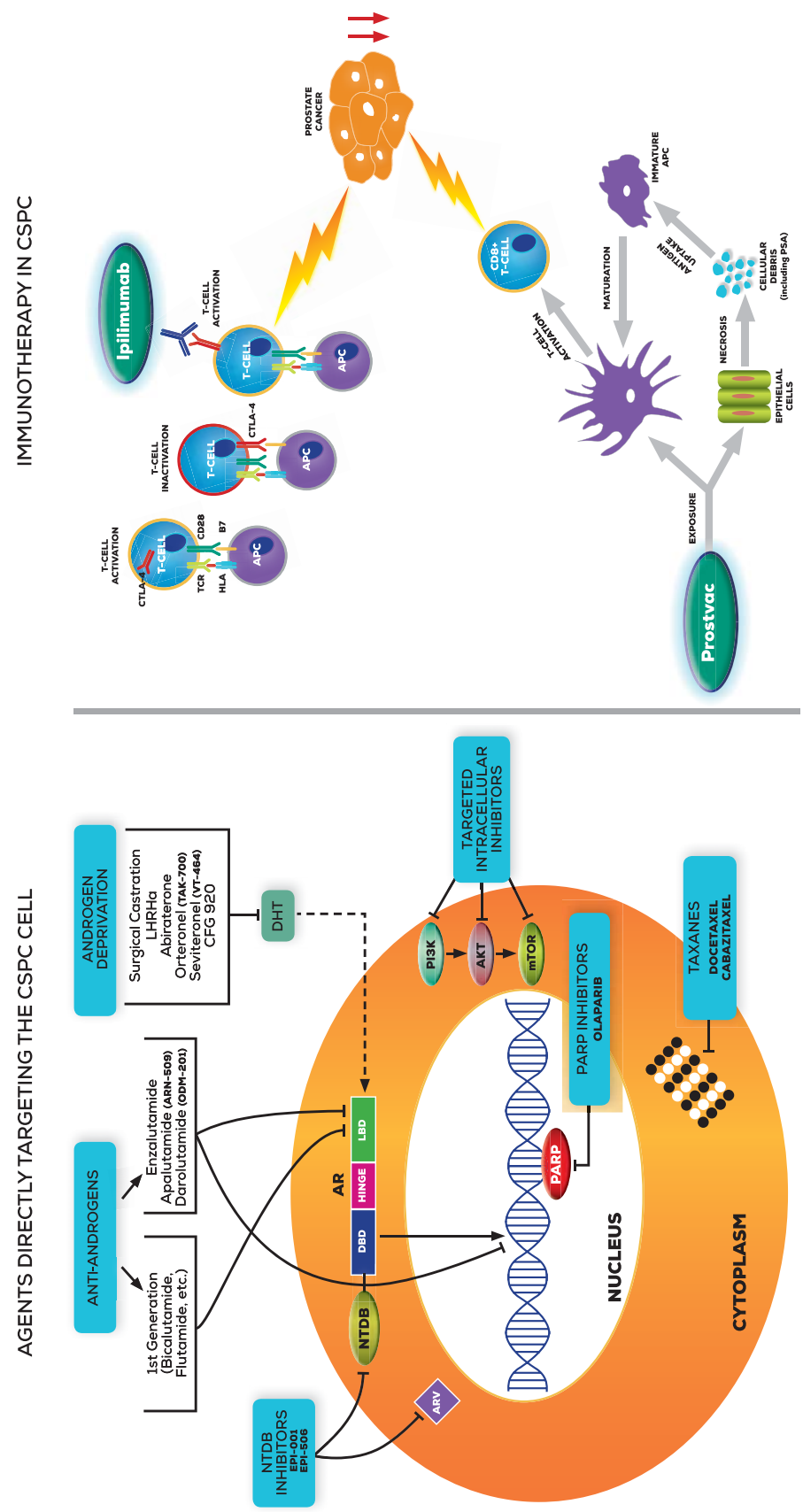

Figure 1. Current and experimental options for the treatment of CSPC. The androgen deprivation approach consists in inhibiting androgen synthesis, particularly the production of DHT. The antiandrogens competitively bind to the AR and thus prevent other agonists, such as DHT, from binding to the AR and promoting signaling. The NTBD inhibitors selectively target the N-terminal domain of the AR and promise efficacy against both normal and aberrant AR splice variants. Several experimental agents inhibit PI3K, AKT, or mTOR pathways which are known to have a key role in cancer survival and progression. PARP inhibitors hinder DNA repair mediated by PARP protein, and, in men with mutated DNA-repair genes such as BRCA1/2, lead to apoptosis. Taxanes bind to β-tubulin and stabilize microtubules, thereby inducing cell death. Both ipilimumab and prostvac work by modulating the immune system against the cancer. Ipilimumab is a human *monoclonal* antibody that targets CTLA-4 and inhibits the downregulation of T-cell activation. Prostvac is a recombinant virus vector vaccine that contains the transgenes for PSA and T-cell co-stimulatory molecules; the immature or mature APCs exposed to prostvac trigger the activation and proliferation of PSA-specific CD8+ T lymphocytes which in turn target tumor cells. APC indicates antigen-presenting cell; AR, androgen receptor; ARV, androgen-receptor splice variants; CSPC, castration-sensitive prostate cancer; CTLA-4, cytotoxic T-lymphocyte antigen 4; DBD, DNA-binding domain; DHT, dihydrotestosterone; HLA, human leukocyte antigen; LBD, ligand-binding domain; LHRHa, luteinizing hormone-release hormone agonists/antagonists; mTOR, mammalian target of rapamycin; NTDB, N-terminal binding domain; PARP, poly(adenosine diphosphate ribose) polymerase; PSA, prostate-specific antigen; TCR, T-cell receptor.

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TABLE 1. Ongoing Trials of Abiraterone or Orteronel (TAK-700) Alone

ClinicalTrials.gov Identifier	Phase	Eligibility	Regimen	Primary Endpoint	Results
NCT01751451	2	BR after RP/RT	Abiraterone vs abiraterone + degarelix vs degarelix	PFS	Estimated complete in October 2017
NCT01786265	2	BR after RP/RT	Abiraterone + LHRH vs LHRH	PSA-free survival	Estimated complete in February 2018
NCT01715285	3	Newly diagnosed mCSPC	Abiraterone + ADT vs placebo + ADT	OS and rPFS	Estimated complete in August 2018
NCT01957436 (PEACE1)	3	mCSPC	Abiraterone + ADT ± docetaxel ± RT vs ADT ± docetaxel ± RT	OS	Estimated complete in October 2023
NCT01546987 (RTOG 1115)	3	High-risk before RP	Orteronel + LHRHa + RT + anti-androgen vs LHRHa + RT + conventional anti-androgen	OS	Estimated complete in June 2020
NCT01809691 (S1216)	3	Newly diagnosed mCSPC	Orteronel + LHRHa vs bicalutamide + LHRHa	OS	Estimated complete in July 2020

Abbreviations: abiraterone, abiraterone acetate plus prednisone; ADT, androgen-deprivation therapy; BR, biochemical relapse; LHRH, luteinizing hormone-releasing hormone; LHRHa, luteinizing hormone-releasing hormone agonist; mCSPC, metastatic castration-sensitive prostate cancer; OS, overall survival; PEACE1, Prostate Cancer Consortium in Europe 1; PFS, progression-free survival; PSA, prostate-specific antigen; RP, radical prostatectomy; rPFS, radiographic progression free survival; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group.

minimal, could result in longer OS, progression-free survival (PFS), and PSA responses for this population.

NOVEL APPROACHES

PCa heterogeneity at all stages and the tendency of that heterogeneity to increase throughout the disease course have been demonstrated.[9] This insight is fostering renewed efforts to evaluate novel drugs and combination regimens, and when these are deployed in the early stages of PCa when the disease is less heterogeneous, these treatments may provide higher and more durable responses (Fig. 1). F1

ADT Combined With Second-Generation Hormonal Agents

Novel AR axis–targeted drugs, particularly abiraterone acetate (abiraterone) and enzalutamide, are being evaluated at various stages of CSPC. The majority of these trials are conducted "per industry agenda," and there has not been an overarching strategic development process based on a biologic rationale. Abiraterone is a potent selective irreversible inhibitor of CYP17A1, a key enzyme in androgen synthesis. Abiraterone is usually administered with prednisone to prevent possible mineralocorticoid excess (hereafter prednisone will not be noted), whereas enzalutamide is a next-generation AR antagonist that binds to AR in competition with androgens and prevents AR translocation to the nucleus and its binding to DNA. Both abiraterone and enzalutamide have demonstrated survival benefits for men with mCRPC.[17-20] The addition of these drugs to gonadal ADT is postulated to effect a more potent type of CAB and result in more efficient suppression of the AR-driven PCa growth pathway.[21]

Abiraterone- or Orteronel-Alone Trials (Table 1) T1

In the last 2 decades, several studies have investigated neoadjuvant ADT for men with early-stage PCa with the aim of decreasing recurrence rates.[22-24] A validated metric of efficacy for neoadjuvant therapy combined with prostatectomy does not exist. However, because local pathological responses in other cancers (breast and bladder) correlate with improved clinical outcomes,[25] pathological responses are also measured in PCa neoadjuvant trials. Overall, despite significant decreases in positive surgical margins, few pathological complete responses (pCRs) and an overall lack of clinical benefit are described in these reports.[22-24] Tissue analyses of prostatectomy specimens provided a partial explanation: they showed that an LHRHa alone fails to elicit deep suppression of tissue androgen levels.[26] Abiraterone, irreversibly inhibiting CYP17A1, potently suppresses androgen synthesis in all tissues, including PCa tissue.[21] In a recent phase 2 trial, patients with localized high-risk PCa were randomly assigned to receive an LHRHa with or without abiraterone with a research prostate biopsy at 12 weeks and radical prostatectomy (RP) at the end of 24 weeks of treatment.[26] At 12 weeks, the abiraterone cohort showed significantly lower levels of intraprostatic dihydrotestosterone ($P < .001$) and testosterone ($P < .05$) in comparison with the cohort receiving an LHRHa alone. At 24 weeks, a 10% pCR rate and a 14% minimal residual disease rate

TABLE 2. Ongoing Trials of Enzalutamide or Apalutamide (ARN-509) Alone

ClinicalTrials.gov Identifier	Phase	Eligibility	Regimen	Primary Endpoint	Results
NCT02023463	1	Intermediate/high-risk before RP	Enzalutamide + LHRHa + RT	Toxicity	Estimated complete in December 2018
NCT02028988	2	Intermediate-risk before RP	Enzalutamide + external-beam RT	PSA $\leq$ 0.2 ng/mL after 6 mo	Estimated complete in June 2021
NCT02508636	2	Very high-risk before RP	Enzalutamide + LHRHa + RT	Toxicity PSA nadir $\leq$ 0.3 ng/mL	Estimated complete in June 2022
NCT02319837 (EMBARK)	3	High-risk localized	Enzalutamide + leuprolide vs enzalutamide vs placebo + leuprolide	MFS	Estimated complete in December 2020
NCT02446444 (ENZARAD/ANZUP)	3	High-risk localized	Enzalutamide + LHRHa + RT vs conventional anti-androgen + LHRHa + RT	OS	Estimated complete in December 2021
NCT02058706	2	mCSPC	Enzalutamide + LHRHa vs bicalutamide + LHRHa	PSA remission after 7 months	Estimated complete in December 2016
NCT02677896	3	mCSPC	Enzalutamide + LHRHa vs placebo + LHRHa	rPFS	Estimated complete in December 2023
NCT02446405 (ENZAMET)	3	mCSPC	Enzalutamide + ADT vs conventional anti-androgen + ADT	OS	Estimated complete in December 2020
NCT02721979	2	Very low/low/low to intermediate	Apalutamide	Negative site–directed and systematic prostate biopsy rate	Estimated complete in April 2017
NCT02531516 (ATLAS)	3	High-risk localized/locally advanced	Apalutamide + bicalutamide placebo + LHRHa vs apalutamide placebo + bicalutamide + LHRHa	MFS	Estimated complete in October 2026
NCT02811809	2	BR after RP/RT	Apalutamide + leuprolide vs leuprolide (until second injection, then apalutamide + leuprolide)	Time to second injection of leuprolide	Estimated complete in March 2021
NCT02489318 (TITAN)	3	mCSPC	Apalutamide + ADT vs placebo + ADT	rPFS OS	Estimated complete in February 2022

Abbreviations: ADT, androgen-deprivation therapy; ANZUP, Australian and New Zealand Urogenital and Prostate Cancer Trials Group; ATLAS, An Efficacy and Safety Study of JNJ-56021927 (ARN-509) in High-Risk Prostate Cancer Subjects Receiving Primary Radiation Therapy; BR, biochemical relapse; EMBARK, Safety and Efficacy Study of Enzalutamide Plus Leuprolide in Patients With Nonmetastatic Prostate Cancer; ENZAMET, Enzalutamide in First Line Androgen Deprivation Therapy for Metastatic Prostate Cancer; ENZARAD, Enzalutamide in Androgen Deprivation Therapy With Radiation Therapy for High Risk, Clinically Localised, Prostate Cancer; LHRHa, luteinizing hormone-releasing hormone analogue; mCSPC, metastatic castration-sensitive prostate cancer; MFS, metastasis-free survival; OS, overall survival; PSA, prostate-specific antigen; RP, radical prostatectomy; rPFS, radiographic progression free survival; RT, radiotherapy.

TABLE 3. Ongoing Trials of Combinations of Novel Androgen Receptor Axis–Targeted Agents

ClinicalTrials.gov Identifier	Phase	Eligibility	Regimen	Primary Endpoint	Results
NCT02268175	2	Intermediate/high-risk localized before RP	Enzalutamide + leuprolide + abiraterone vs enzalutamide + leuprolide	pCR and MRD rates	Estimated complete in February 2022
NCT02789878	2	High-risk localized before RP	Abiraterone + goserelin + apalutamide vs abiraterone + goserelin	pCR and pnCR	Estimated complete in October 2019
NCT02772588	2	Very high-risk localized	Abiraterone + apalutamide + leuprolide + RT	BR rate	Estimated complete in May 2018
NCT02799602 (ARASENS)	3	mCSPC	Darolutamide (ODM-201) + ADT + docetaxel vs placebo + ADT + docetaxel	OS	Estimated complete in January 2022

Abbreviations: abiraterone, abiraterone acetate plus prednisone; ADT, androgen-deprivation therapy; ARASENS, ODM-201 in Addition to Standard ADT and Docetaxel in Metastatic Castration Sensitive Prostate Cancer; BR, biochemical relapse; mCSPC, metastatic castration-sensitive prostate cancer; MRD, minimal residual disease; OS, overall survival; pCR, pathological complete response; pnCR, pathological near complete response; RP, radical prostatectomy; RT, radiotherapy.

(tumor ≤ 5 mm) for patients in the longer exposure abiraterone-LHRHa group were observed. Although some patients with high-risk disease demonstrated remarkably good responses, others had residual high-volume disease.[26] The observed persistence of androgen metabolites within the prostate tissue was postulated as a possible mechanism of resistance for the combined regimen. Investigations of biomarkers of response and resistance, including genomic analyses, are ongoing.

Interestingly, abiraterone was recently proven to have direct bone antiresorptive and anabolic activity.[27] Therefore, with the aim of improving the management of bone metastases and prolonging the time to castration resistance, abiraterone therapy is being evaluated for mCSPC. A randomized phase 3 trial (NCT01715285) is examining the survival benefit of the combination of abiraterone and ADT versus ADT plus a placebo in men with newly diagnosed mCSPC, and similar studies are ongoing (Table 1). Furthermore, orteronel (TAK-700), a reversible nonsteroidal selective inhibitor of 17,20-lyase and thus of androgen synthesis, is being investigated in the same setting. Orteronel, despite showing antitumor activity, failed to demonstrate an OS advantages in CRPC.[28,29] In the phase 3 trial S1216 (NCT01809691), orteronel in addition to an LHRHa for more potent CAB is compared with an LHRHa plus bicalutamide with OS as the primary outcome. Positive outcomes could suggest its use in mCSPC.

Enzalutamide- or Apalutamide-Alone Trials (Table 2)

T2

Many trials have demonstrated that the addition of concomitant and adjuvant ADT to RT is beneficial for the treatment of localized PCa.[30] Subsequently, the possible application of novel AR-targeted agents, particularly enzalutamide, in this setting has garnered much interest. In a phase 3 trial by the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (Enzalutamide in Androgen Deprivation Therapy With Radiation Therapy for High Risk, Clinically Localised, Prostate Cancer [ENZARAD]; NCT02446444), patients with high-risk localized disease are randomized to receive RT with an LHRHa plus enzalutamide or a conventional anti-androgen. The primary outcome is OS, and other relevant endpoints are the cause-specific survival time, biochemical and clinical PFS, and metastasis free-survival time. In addition, an ongoing phase 2 study (NCT02028988) is evaluating the efficacy (PSA response) of noncastrating therapy with enzalutamide alone for 6 months plus RT for intermediate-risk PCa patients.

Moreover, enzalutamide is being explored in mCSPC (Table 2). A multicenter, randomized phase 3 trial (Enzalutamide in First Line Androgen Deprivation Therapy for Metastatic Prostate Cancer [ENZAMET]; NCT02446405) seeks to compare OS and biochemical and clinical PFS with ADT plus enzalutamide versus ADT plus a conventional anti-androgen. Because enzalutamide has been proven both in vitro and more recently in vivo in mCRPC to be a more potent AR blocker and have no AR agonist activity in comparison with bicalutamide, the hypothesis is that enzalutamide will further reduce AR signaling and thus improve outcomes.[31-33]

In addition, the second-generation AR antagonist apalutamide (ARN-509) showed greater potency than first-generation AR inhibitors such as bicalutamide in preclinical models,[34] and it is currently being tested for

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TABLE 4. Ongoing Trials of Chemotherapy Plus ADT

ClinicalTrials.gov Identifier	Phase	Eligibility	Regimen	Primary Endpoint	Results
NCT02494713	2	Intermediate/high-risk before RP	Degarelix + doxorubicin + ketoconazole followed by docetaxel + estramustine	Pathological response	Estimated complete in February 2027
NCT00430183 (CALGB/Alliance 90203/PUNCH)	3	High-risk before RP	Docetaxel + LHRHa + RP vs immediate RP	3-y biochemical progression-free survival rate	Estimated complete in June 2018
NCT00348816	2	BR after RP	Docetaxel + RT	PSA decline and PSA nadir (0 ng/mL rate)	Estimated complete in December 2016
NCT02543255 (ACDC-RP)	2	High-risk before RP	Cabazitaxel + abiraterone + leuprolide vs abiraterone + leuprolide	pCR	Estimated complete in October 2018
NCT01952223 (PEACE2)	3	High-risk localized before RP/RT	Cabazitaxel + ADT + prostate RT vs ADT + prostate RT vs cabazitaxel + ADT + pelvic RT vs ADT + pelvic RT	PFS	Estimated complete in September 2026
NCT01978873 (SensiCab)	3	High-risk/N1/mCSPC	Cabazitaxel + ADT vs ADT	OS	Estimated complete in November 2019

Abbreviations: abiraterone, abiraterone acetate plus prednisone; ACDC-RP, Anti-Androgens and Cabazitaxel in Defining Complete Response in Prostatectomy; ADT, androgen-deprivation therapy; BR, biochemical relapse; CALGB, Cancer and Leukemia Group B; LHRHa, luteinizing hormone-releasing hormone agonist; mCSPC, metastatic castration-sensitive prostate cancer; OS, overall survival; pCR, pathological complete response; PEACE2, Prostate Cancer Consortium in Europe 2; PFS, progression-free survival; PSA, prostate-specific antigen; PUNCH, Preoperative Use of Neoadjuvant Chemohormonal Therapy; RP, radical prostatectomy; RT, radiotherapy.

mCSPC as well as other stages of the disease (Table 2). The randomized phase 3 trial TITAN (NCT02489318) is assessing the efficacy of the combination of apalutamide and ADT versus ADT plus a placebo in patients with low-volume mCSPC. Positive results could provide a new treatment option for this specific subgroup of patients.

AR Axis Combination Trials

The need for improving AR-directed tumor growth inhibition led to the investigation of combinations of hormonal agents (Table 3). In preclinical models of CRPC xenografts, abiraterone exposure in some cases resulted in increased expression of AR, CYP17, and other key enzymes pivotal for testosterone synthesis.[35] Thus, the combination of a potent AR antagonist with abiraterone may inhibit de novo steroidogenesis in the tumor and thus result in more effective therapy. To test this hypothesis, a randomized phase 2 trial (NCT02268175) is currently recruiting intermediate- and high-risk PCa patients for enzalutamide and leuprolide with or without abiraterone before RP. The efficacy of this combination of second-generation hormonal agents is being assessed in terms of pCR and minimal residual disease rates, and the trial includes an analysis of the bone marrow as a niche for resistant tumor clones. Recently, the results of a similar phase 2 trial that randomized high-risk PCa patients to receive abiraterone and an LHRHa with or without enzalutamide before RP were reported (ASCO 2016). The incidence of pathological downstaging ($\leq$pT2N0) was lower (30% vs 52%; $P = .07$) and the detection of androgen-receptor splice variant 7 was more frequent in the combination arm (enzalutamide plus abiraterone and an LHRHa) than the arm receiving abiraterone plus an LHRHa. These data indicate that the addition of enzalutamide to an LHRHa plus abiraterone was not effective in this trial. However, further investigation of the utility of more intense ADT is needed before any definite conclusions are drawn.[36]

Finally, a new generation of AR pathway–targeted agents is going through clinical development.[37-39] Darolutamide (ODM-201) is a novel nonsteroidal antiandrogen that in vitro showed greater potency and a higher affinity for AR than enzalutamide and negligible penetrance of the blood-brain barrier.[40] VT-464 and CFG920 are novel CYP17 inhibitors in early stages of development. Lastly, EPI-001 and its successor EPI-506 are first-in-class selective inhibitors of the N-terminal domain of the AR and thereby promise to be effective against canonical and aberrant AR splice variants. Especially if proven effective against CRPC, some of these agents are likely to be evaluated also for CSPC in the near future. In this respect, a multicenter, randomized phase 3 trial investigating darolutamide in mCSPC (ODM-201 in Addition to Standard ADT and Docetaxel in Metastatic Castration Sensitive Prostate Cancer [ARASENS]; NCT02799602) was recently started (Table 3).

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ADT Combined With Chemotherapy

A plausible reason for the lack of a survival benefit from ADT-only neoadjuvant therapy is that androgen-independent stem cells may already be present at early stages of the disease, and under the selective pressure exerted by ADT, the growth and spread of systemic micrometastases are possible.[9,41] Over the years, several phase 1/2 studies have evaluated the efficacy of neoadjuvant chemotherapy; they have frequently achieved favorable PSA declines and statistically significant rates of tumor reduction and negative surgical margins.[42,43] However, these reports are quite heterogeneous with respect to the cytotoxic agent and dosage used, the analysis of pathological outcomes, the primary outcomes evaluated, and the duration of follow-up.[43] Most importantly, none of these studies have reported pCR rates. Therefore, because neither neoadjuvant ADT nor chemotherapy alone seems to result in improved clinical outcomes, combination regimens of chemotherapy plus ADT have been tested in multiple studies[44,45] and are the focus of ongoing research (Table 4). The vast majority of these trials have investigated some combination of docetaxel and hormonal therapy as neoadjuvant treatment before RP. In the largest phase 2 study, which was led by the Canadian Urologic Oncology group, CAB and docetaxel were given to high-risk patients before RP. Overall, the treatment was well tolerated, and a median PSA decrease before surgery of 98.4% and a pCR rate of 3% were reported.[46] In a contemporary, multicenter phase 3 trial (Groupe d'Etude des Tumeurs Urogénitales [GETUG]) GETUG-12, patients with high-risk localized or N1 disease randomly received an LHRHa plus or minus docetaxel and estramustine. After a median follow-up of 8.8 years, the rate of recurrence-free survival (RFS), which included biochemical, local, and distant relapse, was 62% (95% CI, 55%-69%) in the ADT-chemotherapy group and 50% (95% CI, 44%-57%) in the ADT-alone group.[47] However, because most relapses were biochemical, it has not been ascertained whether the described RFS benefit will translate into an improvement of clinically significant long-term outcomes. Furthermore, per the study design, all patients underwent staging pelvic lymph node dissection after 3 months of treatment, and even though 71% of the patients were N0, the vast majority received RT instead of RP.[47] Therefore, caution should be used in applying these findings to the neoadjuvant prostatectomy setting. Because of the conflicting body of findings between prostatectomy pathological endpoints and long-term outcomes, the current NCCN guidelines do not recommend the use of neoadjuvant therapy for patients with localized or locally advanced PCa. For this reason, there is anticipation for the results of a multicenter, randomized phase 3 trial (Cancer and Leukemia Group B [CALGB]/Alliance 90203/Preoperative Use of Neoadjuvant Chemohormonal Therapy [PUNCH; NCT00430183) comparing the efficacy of 6 cycles of docetaxel in addition to an LHRHa followed by RP with the efficacy of immediate RP alone for high-risk PCa patients. Results are expected in 2017, and genomic analyses to detect differences between chemohormonal responders and nonresponders are under way. Lately, just as for other agents demonstrating survival benefits for mCRPC patients, there is interest in testing the taxane cabazitaxel[16] in the neoadjuvant setting. A 4-arm phase 3 trial (Prostate Cancer Consortium in Europe 2 [PEACE2]; NCT01952223) seeks to evaluate the efficacy of ADT and prostate RT plus or minus cabazitaxel or ADT and prostate and pelvic RT plus or minus cabazitaxel, which are being randomly assigned to men with high-risk disease. These prospective, randomized trials have the potential to change the therapeutic approach to high-risk localized PCa patients by validating the use of neoadjuvant therapy.

Because chemotherapy is postulated to target the androgen-independent cancer clones, which are possibly the cause of distant relapse, assessing chemohormonal therapy in the adjuvant setting is equally rational. Docetaxel and RT may have a synergistic effect because they both induce cell cycle arrest and apoptosis in the G2 and M phases.[48,49] In this respect, the preliminary results of RTOG 0621, a single-arm phase 2 trial of patients with high-risk features treated after surgery with RT plus ADT and docetaxel, were reported at the 2014 ASCO meeting. The rate of freedom from progression (defined as a PSA level < 0.4 ng/mL and no clinical failure or death from any cause) at 3 years was 71% (95% CI, 61%-81%; $P < .001$).[50] Although these results seem interesting, at the moment, phase 3 trials are scarce, and enrollment represents a major challenge in this setting. In this regard, the contemporary Veterans Affairs Cooperative Studies Program 553 trial (NCT00132301) is evaluating the efficacy of 6 cycles of docetaxel versus surveillance until biochemical recurrence (BR) for RP-treated patients with a high risk of relapse. Positive results could potentially lead to extending the chemohormonal approach to the post-RP adjuvant setting.

Similarly, in the past, several phase 2 trials have suggested a possible benefit of chemotherapy with hormone therapy in the BR stage.[51-53] Taplin et al[51] conducted a phase 2 study of men with BR treated with docetaxel and estramustine and 18 months of CAB. After a median of 5 years of follow-up and with recovered testosterone, 11% of the subjects had PSA levels < 0.1 ng/mL, and 24% had

not reinitiated ADT.[52] In a similar fashion, noting that angiogenesis may have a key role in PCa growth and metastasis,[54] a phase 2 trial explored the benefits of early multimodality systemic therapy with the antiangiogenic drug bevacizumab in addition to chemohormonal treatment for men with BR. After a median follow-up of 27.5 months, 20% of men were BR-free, and 46% had not restarted ADT.[53] Although phase 2 data are promising, phase 3 trials are needed to confirm the overall benefits of chemohormonal therapy in the BR setting.

Finally, the recent progress made in the field of next-generation sequencing has resulted in an improved understanding of the genomic landscape of PCa. In particular, recent genomic analyses have demonstrated that approximately 20% of patients with mCRPC have somatic mutations in DNA repair genes (DRGs), including *BRCA1, BRCA2, ATM, FANCA, RAD51B*, and *RAD51C*.[55] The DRG somatic mutation rate is lower in localized PCa versus mCRPC at approximately 8% (The Cancer Genome Atlas), but the prevalence may be higher in select populations and in patients with very high-risk disease. In addition, the prevalence in mCSPC is not known but is under investigation.[56] The rate of DRG germline aberrations in mCRPC is as high as 11%, and this may also be found in high-risk patients with earlier stages of CSPC.[57] Although the prognostic implications of this finding are still unclear, a recent study suggested that *BRCA2* germline mutation carriers are more frequently associated with metastases at diagnosis, a Gleason score ≥ 8, a T3/4 stage, and significantly shorter 5-year metastasis-free survival for those subjects with localized PCa.[58] However, it is known that patients with DRG mutations frequently respond to platinum therapy (cisplatin and carboplatin) and to poly(-adenosine diphosphate ribose) polymerase (PARP) inhibitors; this provides an opportunity to evaluate these therapies in both CRPC and CSPC.[59,60]

A phase 2 trial of the PARP inhibitor olaparib in advanced CRPC (Phase II Trial of Olaparib in Patients With Advanced Castration Resistant Prostate Cancer [TOPARP]) revealed that 88% of the 16 patients found with DRG alterations, including *BRCA1/2*, Fanconi anemia genes, *ATM*, and *CHEK2*, responded to olaparib.[60] This study served as a proof of concept of the efficacy of PARP inhibitors in mCRPC, and it also suggested that the subset of patients who may be sensitive to PARP inhibitors or platinum therapy is not limited to *BRCA1/2* aberrations and most likely also includes somatic mutations in genes involved in the homologous recombination pathway. Such mutations may be responsible for functional defects similar to those of *BRCA*-mutated tumors (BRCAness); this would explain the sensitivity to PARP inhibitors and platinum. In the future, once validated through prospective clinical trials, a large BRCAness panel could be used as a biomarker of responsiveness to platinum therapy and PARP inhibitors and thereby allow precision medicine. Furthermore, the TOPARP study laid the basis for further evaluations of olaparib in earlier stages of the disease and in combination with other agents. For CSPC, a phase 1 study of men with intermediate/high-risk disease before RP (NCT02324998) is assessing the feasibility of degarelix with or without olaparib.

The field of genomics and PCa is rapidly evolving, and in the context of CSPC, we recommend that genomic sequencing analysis be considered in men with a family history of PCa and in men with a young or very aggressive presentation of PCa. In addition, we deem that when men with CSPC harbor DRG abnormalities, despite the lack of prospective data, platinum therapy or PARP inhibitors with ADT can be considered (preferably in a trial).

ADT Combined With Bone-Targeted Therapies

Samarium 153 (Sm153) and radium 223 (Ra223) are radiopharmaceutical β and α emitters, respectively, devised to selectively bind to hydroxyapatite in the bone and thereby result in irradiation of osteoblastic metastases with minimal effect on surrounding normal tissue. Ra223 demonstrated a survival benefit in mCRPC.[61] These findings provide support for investigating these compounds in nonmetastatic CSPC patients in hopes of prolonging the time to metastatic disease. The ongoing phase 2 study RTOG 0622 (NCT00551525) is exploring the safety and efficacy of Sm153 given to post-RP N0/N1 patients with BR, whereas a multicenter, randomized phase 2 trial (NCT02656563) is seeking to assess the efficacy of Ra223 in prolonging the off-treatment interval for men with BR who have received 6 to 8 months of intermittent ADT. Furthermore, an ongoing randomized phase 2 study (NCT02582749) is testing Ra223 with or without ADT for men with newly diagnosed mCSPC. Positive results could lead to a phase 3 trial.

Long-term ADT is associated with a loss of bone mineral density and weight gain, which increase the incidence of fractures in men with PCa.[62,63] Along with calcium and vitamin D supplementation, bisphosphonates (particularly zoledronic acid) and the anti–receptor activator of nuclear factor κB ligand antibody denosumab should be considered for mCRPC patients undergoing ADT according to the fracture risk.[63,64] These compounds have also been proven to decrease bone pain and the rate of skeletal-related events in patients with osseous

TABLE 5. Ongoing Trials of Investigational Immunotherapeutic Drugs

Examined Drug	Mechanism of Action	Eligibility	Regimen	Primary Endpoint	ClinicalTrials.gov Identifier
Prostvac-V (PSA-TRICOM)	V: a recombinant vaccinia virus vector vaccine containing the genes for human PSA and 3 costimulatory molecules	Very low-risk/low-risk and undergoing active surveillance	Prostvac-V vs placebo	Change in CD4 + and CD8 + cell infiltration of prostate biopsies	NCT02326805
Prostvac-VF (PSA-TRICOM)	F: a recombinant fowlpox virus vector vaccine containing the genes for human PSA and 3 costimulatory molecules	Intermediate/high-risk before RP	Prostvac-V as primary vaccination followed by Prostvac-F boost	Change in CD4 + and CD8 + cell infiltration of prostatic tissue	NCT02153918
Prostvac-VF (PSA-TRICOM)	VF: a recombinant vaccinia and fowlpox virus vector vaccine containing the genes for human PSA and 3 costimulatory molecules	Localized before RP	Prostvac-VF vs ipilimumab vs Prostvac-VF + ipilimumab	CD3 + T-cell immune response	NCT02506114
Prostvac-VF (PSA-TRICOM)	VF: a recombinant vaccinia and fowlpox virus vector vaccine containing the genes for human PSA and 3 costimulatory molecules	BR after RP/RT	Prostvac-VF ± enzalutamide	Decrease in regrowth rate	NCT01875250
Prostvac-VF (PSA-TRICOM)	VF: a recombinant vaccinia and fowlpox virus vector vaccine containing the genes for human PSA and 3 costimulatory molecules	Newly diagnosed mCSPC	ADT + simultaneous Prostvac-VF and docetaxel vs ADT + sequential Prostvac-VF and docetaxel	Comparison of immune responses of 2 cohorts	NCT02649855
DCVAC/PCa	Dendritic cell–based vaccine	mCSPC	DCVAC/PCa + ADT vs ADT	PSA progression rate	NCT02107391
GVAX	Immunotherapy comprising LNCaP and PC-3 cell lines genetically modified to produce granulocyte-macrophage colony-stimulating factor	High-risk before RP	GVAX + degarelix vs degarelix	Comparison of intraprostatic CD8 + T-cell infiltration between 2 cohorts	NCT01696877
ProstAtak (PrTK03)	Combination of vector AdV-tk and valacyclovir producing a vaccine effect	Intermediate/high-risk	Prostatak + valacyclovir + RT ± ADT vs placebo + valacyclovir + RT ± ADT	Disease-free survival	NCT01436968
L-BLP25 (tecemotide)	Synthetic lipopeptide used as an antigen to stimulate an immune response against cancer cells such as PCa that overexpress mucin-1	Intermediate/high-risk	L-BLP25 + RT + ADT vs RT + ADT	Measure of mucin-1–specific T cells at baseline vs 2 mo after RT vs 6 mo after RT	NCT01496131

Abbreviations: ADT, androgen-deprivation therapy; AdV-tk, adenovirus thymidine kinase; BR, biochemical recurrence; mCSPC, metastatic castration-sensitive prostate cancer; PCa, prostate cancer; PrTK03, Phase 3 Study of ProstAtak Immunotherapy With Standard Radiation Therapy for Localized Prostate Cancer; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiotherapy; TRICOM, triad of costimulatory molecules.

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mCRPC.[65,66] In the recent multicenter phase 3 trial CALGB 90202 (Alliance), zoledronate, randomly administered to patients with mCSPC, showed no skeletal-related events or OS benefit.[67] Similarly, the STAMPEDE trial reported no survival advantage for the combination of zoledronate and standard of care plus or minus docetaxel for men with high-risk, locally advanced, recurrent or metastatic disease.[10] Therefore, these bone-targeted therapies are not recommended in this setting except for treating osteoporosis. However, it should be noted that denosumab has not been assessed for mCSPC yet.

ADT Combined With Immunotherapy

Another intriguing and developing chapter in the treatment of PCa is immunotherapy.

Because the neoadjuvant setting provides the opportunity to observe the effects of a compound at the tissue level and could ultimately serve as a proof of principle, several experimental immunotherapeutic drugs are currently being explored at this stage as single agents or in combination (Table 5). GVAX-PCa is a cellular vaccine comprising a mixture of 2 irradiated allogeneic PCa cell lines genetically modified to produce granulocyte-macrophage colony-stimulating factor. An interesting phase 2 trial studied the effects of the combination of GVAX and docetaxel in patients undergoing RP. No pCRs were observed; however, downstaging of the Gleason score (significance unknown) was observed in 4 of 6 men after RP.[68] In addition, a phase 1/2 trial (NCT01696877) is currently evaluating the combination of GVAX and degarelix before RP (Table 5).

Moreover, the investigation of ipilimumab, a human monoclonal antibody that binds to cytotoxic T-lymphocyte antigen 4 and inhibits the downregulation of T-cell activation, in CSPC is also ongoing. Although preclinical studies supported its antitumor activity in PCa,[69] the subsequent phase 1/2 studies of ipilimumab in mCRPC yielded quite disappointing results.[70,71] Furthermore, in a randomized phase 3 trial of patients with mCRPC progressing after docetaxel, ipilimumab after RT showed no statistically significant OS difference in comparison with a placebo.[72] However, a subgroup analysis of patients with favorable prognostic features demonstrated a significantly improved survival advantage in comparison with a placebo, and interestingly, the trend was for achieved objective responses to be sustained over the long term.[72] Therefore, ipilimumab is currently being investigated in combination with an LHRHa before RP for men with high-risk PCa in a phase 2 trial (NCT01194271). Moreover, a phase 2 study (NCT02020070) is analyzing the safety and efficacy of the multimodality approach of ipilimumab plus degarelix in men with newly diagnosed oligometastatic disease before and after RP and in men with postsurgical biochemical or distant relapse. Finally, a phase 2 trial (NCT02506114) will evaluate the CD3 + T-cell immune response to ipilimumab or Prostvac-VF, a recombinant virus vector vaccine containing the genes for human PSA and 3 costimulatory molecules, in men with localized PCa before surgery. In this respect, Prostvac-VF is being tested also in several ongoing trials (Table 5).

Despite these trials, immunotherapy for CSPC remains a preliminary approach for which biomarkers and clinical endpoints of efficacy are still needed.

Nonhormonal Approaches With or Without Standard ADT

Preclinical data support the evaluation of a variety of nonhormonal agents in early PCa. In this respect, compounds directed at serum vascular endothelial growth factor and various other tyrosine kinase inhibitors have been and are being investigated in PCa clinical trials and might emerge as future therapeutic options for CSPC. In particular, because tumors cannot grow more than 1 to 2 mm without developing neovasculature,[73] exploiting antiangiogenetic drugs has become an ongoing focus, and trials include evaluations of bevacizumab (NCT00776594), sunitinib, and cabozantinib. In this regard, despite the negative results achieved in mCRPC,[74,75] the combination of cabozantinib and ADT is being tested in a phase 2 study (NCT01630590) of men with mCSPC with PFS as the main outcome measure.

Furthermore, the antidiabetic oral drug metformin is being actively analyzed for various stages of CSPC (NCT01620593 and NCT02420652). The rationale stems from the demonstration in vitro of an antiproliferative effect of metformin and from the observation of ADT being associated with metabolic syndrome, insulin resistance, and hyperinsulinemia. The latter stimulates insulin receptor expression on PCa and possible tumor growth. Metformin has been shown to reduce insulin levels and also to inhibit the mammalian target of rapamycin pathway.[76]

In addition, several agents that target specific cancer genotypes and have shown promising results in preclinical studies are being or could soon be investigated in clinical trials of CSPC. In particular, because both SRC and mitogen-activated protein kinase kinase/extracellular signal-regulated kinase signaling pathways have been shown to be upregulated in CRPC,[77,78] a neoadjuvant

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phase 2 trial (NCT01990196) is comparing the effects of the AR inhibition of degarelix plus enzalutamide with or without the SRC inhibitor dasatinib or the mitogen-activated protein kinase kinase inhibitor trametinib. Furthermore, the pan-AKT inhibitor AZD5363 has shown efficacy in mouse models of phosphatase and tensin homolog–deficient PCa. Because the PI3K/AKT pathway is frequently altered in advanced PCa, mainly because of the functional loss of phosphatase and tensin homolog, this protein is a potential target for personalized therapy.[79] We envisage that the outcomes of these and future trials as well as the broad availability of commercial next-generation DNA sequencing will eventually lead to routine genomic screening of PCa patients to identify actionable mutations and inform optimal individualized therapy.

In conclusion, although ADT remains the cornerstone of CSPC therapy, PCa heterogeneity supports the investigation of chemotherapy, novel AR axis–targeted agents, and other pathway inhibitors in CSPC. In particular, multimodality approaches are being actively explored and are likely to generate future treatment advances. Moreover, these strategies will be explored in the early stages of disease with the aim of maximizing the efficacy and duration of the response. However, striking a balance between the clinical benefits of earlier therapy and increased toxicity and cost will become paramount. To this end, developing biomarkers and precision medicine is a fundamental step toward extending the benefits and reducing the risks of ineffective therapy.

Finally, the advances of genomics and immunotherapy are translating into a multitude of experimental approaches, and ongoing and future trials will explore their efficacy in CSPC patients.

FUNDING SUPPORT

This work was supported by the Fairweather Family Fund and the Fat Boys/Slim Sisters Pan-Mass Prostate Cancer Research Fund.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Edoardo Francini: Writing and editing. **Mary-Ellen Taplin**: Writing and editing.

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Prostate Cancer: Developing Novel Approaches to Castration-Sensitive Disease

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Multimodality approaches including chemotherapy and novel hormonal agents are frequently investigated in early-stage prostate cancer with the aim of maximizing the response efficacy and duration for patients with castration-sensitive disease. Immunotherapy and experimental molecules are also being actively explored in this setting.

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