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Novel Therapies for Castration-Resistant Prostate Cancer

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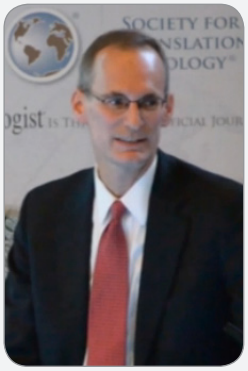

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Historical Progress in the Treatment of Metastatic Prostate Cancer

The treatment of metastatic castration-resistant prostate cancer (mCRPC) has been substantially transformed over the past 2 decades. From traditional palliative treatments aimed at reducing cancer-related symptoms, significant progress has been made with United States Food and Drug Administration (FDA) approval of drugs targeting increased survival. This began with approval of docetaxel in 2004, and since that time, five new therapies have been approved for treatment of mCRPC based on data demonstrating improved survival. However, it is important to note that these drugs were developed in parallel, each one not accounting for the others, leading to significant challenges in understanding optimal sequencing of treatments and combinations of agents in therapy strategies. These new agents possess multiple mechanisms of action (MOAs) including immunotherapy (sipuleucel-T), hormonal therapies (abiraterone acetate, enzalutamide), cytotoxic treatments (cabazitaxel), and bone-directed therapy (alpha emitter Radium-223). These drugs impact different parts of the prostate cancer disease continuum timeline, and while they present promising therapy options, multiple questions remain surrounding timing/sequencing of therapy and the potential for combination therapy.

Drugs in Development for mCRPC

Complicating the future therapy landscape is the fact that many other new drugs are in development, focusing on different therapeutic targets and MOAs (Table 1).

Two of these agents have shown especially promising results in investigational studies: ARN-509, a novel antiandrogen agent focused on targeting disease earlier, and cabozantinib, a tyrosine kinase inhibitor (TKI) targeting more advanced disease.

Cabozantinib (XL184)

Cabozantinib is an orally available TKI, targeting TK receptors MET and RET and vascular endothelial growth factor receptor (VEGFR). The agent was approved to treat medullary thyroid cancer based on data from the EXAM study published in 2013. Studying a patient population with locally advanced or metastatic disease, the results showed a dramatic increase in progression-free survival (PFS), with a median survival difference of 11.2 months in the treatment cohort versus only 4.0 months in those patients who received placebo [1]. The biology behind the rationale for potential use of this drug in mCRPC focuses on the role of MET and VEGFR in tumor-bone interactions in patients with metastatic disease. MET is highly expressed in bone metastases, and both osteoblasts and osteoclasts express MET and VEGFR and also respond to the ligands hepatocyte growth factor (HGF) and VEGF. HGF and VEGF direct the cross-talk between tumor cells, osteoclasts, and osteoblasts, so targeting MET and VEGFR would have interactions on tumor, bone, and tumor-bone interactions.

Table 1. Drugs in development for metastatic prostate cancer

Class/Agent	Status	Trials
Antiandrogen		
OMD-201	Phase II	ARADES
ARN-509	Phase III	SPARTAN
CYP17 Inhibitor		
Orteronel	Phase III	ELM-PC 4, ELM-PC 5
CYP17 inhibitor and antiandrogen		
Galaterone	Phase II	ARMOR2
Immunotherapy		
Ipilimumab	Phase III	CA-184-043, CA-184-095
PROSTVAC	Phase III	PROSPECT
Novel targets		
Custirsen	Phase III	AFFINITY, SYNERGY
Tyrosine kinase inhibitors		
Dasantinib	Phase III	READY
Cabozantinib	Phase III	COMET-1, COMET-2

Cabozantinib has been evaluated in a variety of malignancies, including prostate cancer. One randomized discontinuation study in patients with mCRPC and bone metastases showed marked resolution in activity in bone metastases seen on technetium-99m bone scans after treatment with cabozantinib, something rarely seen with other agents [2]. This study then progressed to a nonrandomized expansion cohort, a more advanced group of patients treated with uninterrupted cabozantinib. All of these patients had bone metastases, with 31% also having visceral disease spread. All had disease progression despite treatment with docetaxel, and some had progression after treatment with other agents (35% following abiraterone acetate, 24% following cabazitaxel, and 54% following bisphosphonate for bone metastases along with 14% who received denosumab and 1% who received Radium-223). These patients had aggressive disease, with median prostate-specific antigen (PSA) of 194 ng/mL. The primary endpoint was bone scan response defined as >30% reduction in bone scan lesion area. The median change in bone scan lesion area was a 60% reduction with cabozantinib.

The study also suggested that the activity of cabozantinib was not cross-resistant with other therapies. There was evidence of tumor regression in 80% of patients and two thirds of patients had improvement in measurable soft tissue disease, although relatively few met criteria for Response Evaluation Criteria In Solid Tumors (RECIST) response. Declines in PSA were observed in 36% of patients although PSA changes did not always correlate with other parameters of clinical benefit. Approximately 92% demonstrated best circulating tumor cell (CTC) decrease ≥30%, and the median best CTC change was an 86% decrease. Conversion to <5 CTCs was 39% at week 6. Pain decreases of ≥30% were found in 64% of patients studied, and 56% decreased narcotics use, including 31% who discontinued narcotics for pain altogether. As predicted from preclinical studies, cabozantinib resulted in a notable response in bone biomarkers, including a median 37% reduction in osteoclast biomarker C-terminal telopeptide (CTx) at week 12 along with reductions in osteoblast biomarker bone-specific alkaline phosphatase (BSAP). The study concluded that cabozantinib (100 mg QD) has clinical activity in men with treatment-refractory mCRPC, including: 67% complete or partial bone scan responses; 80% regression of measurable disease; 46% median pain improvement in patients with pain score ≥4; and substantial reductions in CTCs and bone turnover markers.

Cabozantinib also has been found to have activity at a lower dose (40 mg QD) and has a safety profile similar to other TKIs. Ongoing phase III studies will evaluate the effects of cabozantinib on overall survival (COMET-1, cabozantanib vs placebo plus predinisone) and pain (COMET-2, cabozantinib vs mitoxantrone plus prednisone) [3].

ARN-509

There is an extensive body of evidence supporting the conclusion that androgen receptor (AR) overexpression is a central mechanism in mCRPC. Eighty percent of tumor cells show increased AR messenger ribonucleic acid (mRNA) and protein levels, and 10%-20% show gene amplification. Approximately 10% of cells have a gain-of-function AR gene mutation. Preclinical models have shown that AR overexpression results in resistance to antiandrogens such as bicalutamide, which exhibits agonist activity. Unlike drugs such as bicalutamide, the investigational agent ARN-509 is not an AR agonist. This agent antagonizes and blocks nuclear translocation of AR and prevents binding of androgen response elements on DNA, inhibiting tumor growth. Preclinical studies demonstrate potent activity: ARN-509 shrank tumors in a mouse model of CRPC, showing marked dose-dependent tumor regression at low plasma exposure and substantially greater efficacy than traditional older antiandrogens [4].

ARN-509 has now been evaluated in a phase I study where patients received continuous daily doses of oral ARN-509 until evidence of disease progression was found. Positron emission tomography/computed tomography (PET-CT) imaging was used to monitor [(18)F]fluoro-α-dihydrotestosterone (FDHT) binding to AR in tumors before and during treatment. The primary objective of the study was to determine pharmacokinetics, safety, and recommended phase II dose. Results demonstrated that the majority of patients experienced a PSA decline with most experiencing a >50% decline in PSA. Activity was observed at daily dosing ranges from 30 mg to 480 mg, and these doses achieved plasma levels consistent with projected maximal efficacy seen in preclinical models. Quantitative imaging demonstrated robust target engagement >90%. In terms of safety, maximum tolerated dose (MTD) was not reached as there were no dose-limiting toxicities (DLTs), and none of the patients experienced seizures or grade 3 or 4 fatigue. The most common adverse events included fatigue, back pain, dyspnea, and gastrointestinal symptoms. The data from this study validated 240 mg as the recommended phase II dose, and preclinical projection confirmed an optimal biological dose between 180 and 300 mg per day [5]. Phase II studies have evaluated three different disease cohorts: men with nonmetastatic CRPC; those with mCRPC who are treatment naïve with no prior salvage therapy; and patients with mCRPC that progressed with treatment with abiraterone acetate. Data so far have demonstrated that 91% of patients with nonmetastatic CRPC have shown a PSA response to treatment with ARN-509, as have 88% of those with treatment-naïve CRPC. A degree of response (24%) was seen in the abiraterone acetate cohort, but there was a substantial fall-off in activity in this group [6]. In summary, data to date have demonstrated that ARN-509 is active in men with CRPC, with a robust 12-week PSA response for patients with nonmetastatic disease and treatment-naïve metastatic disease and a lesser response in patients who had progressed while receiving abiraterone acetate. The agent has a manageable safety profile with no treatment-related serious adverse events. Overall, these data support further development and study of ARN-509. The SPARTAN phase III randomized, controlled trial is in the planning stages. This study will include men with nonmetastatic CRPC with rising PSA despite treatment with surgical or medical ADT and particularly high-risk features, specifically a PSA doubling time of ≤10 months. Patients will be randomized to ARN-509 and continuing androgen-deprivation therapy (ADT) or placebo plus ADT, with a primary endpoint of metastasis-free survival (MFS) and key secondary endpoint of overall survival (OS). Additional phase III studies are also planned.

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