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Platinum Priority – Collaborative Review – Prostate Cancer

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Castration-Resistant Prostate Cancer: From New Pathophysiology to New Treatment

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Abstract

Context: Until recently, the only approved agent for metastatic castration-resistant prostate cancer (mCRPC) was docetaxel chemotherapy. But over the last 5 years, significant advances in the field have led to the approval of five new agents, each with different mechanisms of action and demonstrating improved overall survival in separate randomized phase 3 trials. Many of these novel agents are now also being evaluated in earlier stages of the disease, which may ultimately lead to even better outcomes.
Objective: To summarize the current literature on the management of mCRPC with a particular focus on novel chemotherapy approaches, hormonal approaches, immunotherapy, and radiopharmaceuticals showing survival benefits in phase 3 clinical trials. Emerging therapies in late stages of development are also discussed briefly.
Evidence acquisition: A comprehensive search of PubMed, identified studies pertaining to novel therapies evaluated in mCRPC since the initial approval of docetaxel in 2004. Abstracts from major international meetings were hand searched to identify studies of novel agents in late stage development in mCRPC. The Clinical Trials.gov database was used to find ongoing clinical trials in the area of mCRPC. A detailed search of each new agent was also performed to ensure that additional trials of these agents in other stages of the disease were included where relevant.
Evidence synthesis: The main agents discussed are the androgen synthesis inhibitor abiraterone acetate, the androgen receptor inhibitor enzalutamide, the novel taxane chemotherapy cabazitaxel, the immunotherapy sipuleucel-T, and the radiopharmaceutical radium 223. Other emerging agents and a brief discussion of negative phase 3 results are also included.
Conclusions: It is a very exciting time in the field of mCRPC, where therapeutic advances have improved outcomes in this disease, although once metastatic overall median survival remains a dismal 2–3 years. The key now will be to understand how best to use these new agents, understand the mechanisms of resistance to them, continue to develop novel treatment strategies, and ultimately test these agents earlier in the disease when cure may be possible.
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1. Introduction

In 2008, GLOBOCAN reported that worldwide prostate cancer (PCa) was the second most common cancer in men, behind lung cancer, accounting for 914 000 new cases and the sixth leading cause of cancer death with 258 000 deaths [1]. Notably, more than half of these cases occurred in developed countries such as Europe, North America and Australia. By 2030, it is estimated there will be 1.7 million new cases annually worldwide [2]. Over the last 5 years, age-adjusted PCa deaths have been decreasing, possibly due to a number of factors including (1) widespread use of prostate-specific antigen (PSA) testing (although highly controversial), (2) improvements in diagnostic testing, and in surgical and radiation techniques, and (3) increased use of androgen-deprivation therapy (ADT) following local treatment for high-risk disease.

Despite our best efforts at early diagnosis, aggressive treatment, and appropriate use of hormonal therapy, many patients eventually relapse. Disease progression despite castrate levels of testosterone is known as castration-resistant prostate cancer (CRPC) and can take the form of biochemical progression (elevated PSA only), radiographic progression (metastatic disease [mCRPC]), or symptomatic progression. In mCRPC, the only treatment until recently to show a survival benefit was docetaxel chemotherapy, but for patients progressing on or after docetaxel, options were limited and the prognosis was poor.

Over the last 5 years, however, several new agents tested in phase 3 clinical trials in mCRPC have not only shown improvements in overall survival (OS) but also symptomatic benefits and have significantly changed the treatment landscape in this disease (Table 1). Some of these new agents have now also been evaluated in the predocetaxel mCRPC setting or even earlier in the disease. It is hoped these new agents will drive death rates from PCa even lower, but in the meantime it is important to remember that none of these new agents are considered curative, strongly underscoring the need for ongoing research. In this review we discuss the main therapeutic advances, emerging agents, and the early sequencing trials aimed at understanding how best to select patients for these agents and how and when these agents should be used given the current data.

2. Evidence acquisition

A comprehensive search of PubMed from 2004 onward was performed. The main search terms were *prostate cancer, castrate-resistant prostate cancer, CRPC, abiraterone acetate, enzalutamide, cabazitaxel, sipuleucel-T, radium 223, phase 2, and phase 3*. In addition, a search of abstracts from all major meetings (European Society of Medical Oncology and American Society of Clinical Oncology) from 2004 onward with the main search term *prostate cancer* was also performed. All papers and abstracts discussing phase 3 trials in mCRPC, novel agents in late stage clinical development,

Table 1 – Key phase 3 trials with new agents in metastatic castration-resistant prostate cancer

Drug	Clinical trial	Mechanism of action	Study design	Main inclusion criteria	Primary end point	Outcome
Abiraterone	COU-AA-301 NCT00638690	Inhibits CYP-17 enzyme	Abiraterone plus prednisone vs placebo plus prednisone	mCRPC Docetaxel pretreated	OS	Improved OS Interim analysis: 13.8 vs 10.9 mo HR: 0.646 Final analysis: 15.6 vs 11.2 mo HR: 0.74
Abiraterone	COU-AA-302 NCT00887198	Inhibits CYP-17 enzyme	Abiraterone plus prednisone vs placebo plus prednisone	mCRPC Asymptomatic or mildly symptomatic No prior chemotherapy	PFS and OS	Improved PFS 16.5 vs 8.3 mo HR: 0.53 Trend to better OS 35.3 vs 30.1 mo HR: 0.79 Not statistically significant
Enzalutamide	AFFIRM NCT00974311	Blocks the androgen receptor	Enzalutamide vs placebo	mCRPC Docetaxel pretreated	OS	Improved OS 18.4 vs 13.6 mo HR: 0.631
Cabazitaxel	TROPIC NCT00417079	Microtubule inhibitor	Cabazitaxel plus prednisone vs mitoxantrone plus prednisone	mCRPC Docetaxel pretreated	OS	Improved OS 15.1 vs 12.7 mo HR: 0.70
Sipuleucel-T	IMPACT NCT00065442	Dendritic vaccine	Sipuleucel-T vs placebo	mCRPC Asymptomatic or mildly symptomatic No prior chemotherapy	OS	Improved OS 25.8 vs 21.7 mo HR: 0.775
Radium-223 (Xofigo)	ALSYMPCA NCT00699751	Radiopharmaceutical α emitter calcium mimetic uptake into bone	Radium-223 vs placebo	mCRPC Symptomatic bone metastases No visceral disease Docetaxel unfit or pretreated	OS	Improved OS 14.0 vs 11.2 mo HR: 0.699

HR = hazard ratio; mCRPC = metastatic castration-resistant prostate cancer; OS = overall survival; PFS = progression-free survival.

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