COMMENTARY

Is it Time to Change the Control Placebo Arms in Phase III Trials of Metastatic Castration Resistant Prostate Cancer?

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Abstract

Prostate cancer is common all around the world. Hormonal therapy is the mainstay of therapy, however castration-resistant prostate cancer (CRPC) becomes a serious problem and needs further clinical trials with novel agents. Novel agents like cabazitaxel, abireterone acetate or enzalutamide are encouraging but we do not know which one is the best in metastatic CRPC. In here, treatment modalities for metastatic CRPC are discussed witha mini-review of the literature.

Keywords: Castration-resistant prostate cancer - abiraterone acetate - cabazitaxel - enzalutamide

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Introduction

Prostate cancer is the most prevalent cancer in the male population in Western countries. According to recent evidence, it is the second leading cause of cancer-related death among men in the US (Iranikhah et al., 2014). The incidence increases in parallel to the increase in geriatric population.

Bone is the most common site for metastasis. Hormonal therapy is the main treatment modality with a median response duration of 12-33 months in metastatic prostate cancer, but most of them become castration resistant after a while (Lee et al., 2014). Docetaxel-based chemotherapy is the first choice of chemotherapy in metastatic castration-resistant prostate cancer (CRPC). However, treatment of those progressed under docetaxel-based chemotherapy led the investigators to use novel agents like cabazitaxel, abiraterone acetate or enzalutamide in metastatic CRPC (de Bono et al., 2010; 2011; Beer et al., 2014) (see Table 1).

Enzalutamide is an androgen receptor inhibitor which

Table 1. Phase III Trials of Metastatic Castration Resistant Prostate Cancer

Trial Name	Study design/population Phase	Drug dose Primary Endpoint	Results	OS
Published Results				
De Bono et al, 2010. TROPIC study	R, OL, M	C+P*: C 25 mg/m^2 q 3 wk + P* MP*: M 12 mg/m^2 q 3 wk + P*	Median OS: 12.7 mo MP*, 15.1 mo CP*; HR: 0.7; p<0.0001; 30% reduction in the risk of death Median PFS: 1.4 mo MP*, 2.8 mo CP*; HR: 0.7; p<0.0001 Safety profile was predictable and manageble	2.4 mo
	Patients with mCRPC following docetaxel therapy.	OS		
	M+P*(n:377)			
	C+P* (n:378)			
	Phase III			
De Bono et al., 2011. COU-AA-301	R (2:1), DB, M, PC	A+P*: Abiraterone 1 gr/d+ P* P+P.*: Placebo daily+ P*	OS: 14.8 mo A+P*, 10.9 mo P+P*; HR: 0,65; p<0.001	3.9 mo
	Failed 1 or 2 chemotherapy regimens, one of which contained docetaxel	OS		
	A+P* (n:797) P+P* (n: 398)			
	Phase III			

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Table 1. (continued) Phase III Trials of Metastatic Castration Resistant Prostate Cancer

Scher et al 2012 AFFIRM	R (2:1), DB, M, PC	Enzalutamide 160 mg/d Placebo	Median OS: 18.4 mo E, 13.6 mo P; HR:0.63; p<0.001	4.8 mo
	Patients with mCRPC following docetaxel therapy.	OS	ORR: 29% E, 4% P	
	E (n: 800) P (n:399)		PSA PFS: 8.3 mo E, 3 mo P	
	Phase III			
Beer et al (Beer et al., 2014). PREVAIL study İnterim analysis	R, DB, OL, M, PC	E 160 mg/d Placebo (no Prednisone)	rPFS: 65% E, 14% P 81% risk reduction; HR: 0.19; p<0.001	2.2 mo (est)
	Pre chemo	rPFS OS	OS: 29% reduction in the risk of death; HR: 0.71; p<0.001	
	E (n:872) P (n:845)		Median time until initiation of cytotoxic chemotherapy: 28 mo E, 10.8 mo P	
	Phase III		OR: 59% E, 5% P; p<0.0001	
Lee at al (Lee et al., 2014).	Patients with mCRPC following docetaxel therapy.	CP*: C 25 mg/m² q 3 wk + P*	PSA response: 32%	
	CP* (n:26)	Safety Efficacy	Median time to treatment failure: 4.2 mo	
			Median time to progression: 8.5 mo	
			Median OS: 16.5 mo	

AP*; abtaterone+prednisone, CP*; cabazitaxel+prednisone, d; day, DB; double-blind, E; enzalutamide, est; estimated, HR; hazard ratio, mCRPC; metastatic castration-resistant prostate cancer, mo; months, M; multicenter, MP*; mitoxantrone+ prednisone, PC; placebo-controled, PFS; progression-free survival, OL; open-label, OR; objective response, OS; overall survival, P; placebo, PP*; placebo+prednisone, R; randomized, rPFS; radiographic progression-free survival, wk; week; *Prednisone 5 mg BID

was shown to have survival benefit in prostate cancer (Scher et al., 2012; Beer et al., 2014). Beer et al reported that enzalutamide has significantly decreased death rate & radiological progression in metastatic CRPC recently (Beer et al., 2014). The results are encouraging. However, enzalutamide was compared with placebo as a standard

Table 2. Ongoing Phase II Clinical Trials of Enzalutumab (Enzalutamide) in Prostate Cancer

Trial Name	Study design/population	Drug dose	Primary End-point	Comment
Ongoing phase II studies with enzalutamide in prostat cancer				
Efstathiou et al 2014	OL	E 160 mg/d and Abiraterone 1 gr/d+ P*	Safety Efficacy PK DDI	Active arm PSA RR
	Histologically/cytologically confirmed CRPC Bone metastases Ongoing androgen deprivation therapy			Maximum PSA decline ≥50% (37/49 [76%]) ≥ 90% (22/49 [45%]) PSA ≤ 0.1ng/ml (5/49 [10%])
	E+A (n:60)			E+ A combination has a favorable safety profile, without clinically meaningful PK DDI.
				11/60 (18%) patients progressed within 4 months
Alliance	OL, R	E 160 mg/d	OS	ClinicalTrials.gov Identifier:
	Arm A: Enzalutamide	E+A+P: E 160 mg/d and Abiraterone 1 gr/d+ P*		NCT01949337
	Arm B: Emzalutamide (Enzalutamide)+ Abirateron+Prednisone (E+A+P)			
M.D. Anderson Cancer Center	R, OL	Abiraterone 1 gr/d P*E 160 mg/d LHRHa monthly injection or three-month injection	Safety	ClinicalTrials.gov Identifier:
	Arm A: Abiraterone Acetate + Prednisone + Enzalutamide + LHRHa		Efficacy	NCT01946165
	Arm B: Abiraterone Acetate + Prednisone + LHRHa			

*CRPC; castration-resistant prostate cancer, DDI; drug-drug interactions, d; day, E; enzalutamide, E+A; enzalutamide+ abiraterone asetat, OL; open label, OS; overall survival, PK; pharmacokinetic, R; randomized, RR; response rate, LHRHa; luteinizing hormone-releasing hormone analog;

arm in this phase III trial. In this study, enzalutamide not only delayed initiation of subsequent chemotherapy but also led to a significant reduction in soft-tissue disease from baseline in 59% of the patients. It was well tolerated with similar rates of leaving study due to adverse events (6%) in enzalutamide and placebo arms (Beer et al., 2014).

Cabazitaxel is a novel taxane which is effective even in metastatic taxane-resistant prostate cancer. Cabazitaxel had statistically and clinically significant overall survival benefit over mitoxantrone (de Bono et al., 2010). Abiraterone acetate was also shown to have activity in MPC by inhibiting androgen biosynthesis enzyme, CYP17. Increased survival was observed in all subgroups with a low rate of additional treatment-related toxicity in experimental arm (de Bono et al., 2011; Zhou et al., 2014).

In phase III trials of these novel agents, the standard arms were designed as mitoxantrone for cabazitaxel and placebo for both abiraterone acetate and enzalutamide (de Bono et al., 2010; de Bono et al., 2011; Beer et al., 2014). There was no statistically significant difference in overall survival of mCRPC patients in an indirect comparison of enzalutamide with abiraterone acetate (Tan et al., 2014). However, enzalutamide had significant benefits over abiraterone acetate for secondary outcomes, such as time to PSA progression, radiographic progression free survival and PSA response rates. Ongoing phase II clinical trials are listed in Table 2.

We consider that it is time to compare these novel agents with each other instead of placebo since they were shown to have statistically significant activity in previous phase III trials. So, it might contribute to the choice of optimal treatment for metastatic CRPC.

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