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Review Article

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Rational Second-Generation Antiandrogen Use in Prostate Cancer

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Abstract

The second-generation antiandrogens have achieved an ever-growing list of approvals and indications in subsets of prostate cancer. Here, we provide an overview of second-generation antiandrogen trials and FDA approvals and outline a rational sequencing approach for the use of these agents as they relate to chemotherapy and other available treatment modalities in advanced prostate cancer. All published phase II-III randomized controlled trials reporting outcomes with the use of second-generation antiandrogens in prostate cancer are included as well as all published trials and retrospective studies of second-generation antiandrogen sequencing and/or combinations. Complete tabular and graphical representation of all available evidence is provided regarding the use and sequencing of second-generation antiandrogens in prostate cancer. In metastatic castration-resistant prostate cancer, evidence suggests prioritization of abiraterone before chemotherapy, chemotherapy after second-generation antiandrogen failure, and postchemotherapy enzalutamide in select patients to maximize agent efficacy and tolerability. We conclude that a rational, optimized sequencing of second-generation antiandrogens with other treatment options is feasible with present data.

Key words: castration resistance; enzalutamide; abiraterone; darolutamide; apalutamide.

Implications for Practice

Second-generation antiandrogens target CYP17A or the androgen receptor to augment androgen-deprivation therapy and provide an important modality in advanced prostate cancer. Cross-trial comparison allows a rational sequential use of these cancer-directed therapies in metastatic castration-sensitive and both nonmetastatic and metastatic castration-resistant prostate cancer.

Introduction

Prostate cancer is the most common cancer in men and kills over 100,000 men each year in the US and Europe.[1,2] Prostate cells depend on androgens for survival, which has shaped the treatment of prostate cancer over the last 75 years. Androgen-deprivation therapy (ADT) limits the systemic availability of androgens and, by extension, prostate cancer cell survival. This is most commonly achieved with gonadotropin-releasing hormone (GnRH) agonists (eg, goserelin, leuprorelin) or GnRH antagonists (eg, degarelix) that modulate the gonadotropin-releasing hormone receptor (GnRHR). An alternative method of ADT is bilateral orchiectomy, the technique whereby the relationship between lowering testosterone and control of prostate cancer was first understood.[3] Historically, ADT has been the initial therapy for high risk or metastatic castration-sensitive prostate cancer (CSPC) and biochemically recurrent prostate cancer after failure of local therapy. The efficacy of ADT alone generally subsides after 18-24 months of treatment, leading to castration-resistant prostate cancer (CRPC).[4] Distinct from and complementary to ADT, first-generation antiandrogens such as bicalutamide directly inhibit androgen receptor (AR) translocation and activity. These agents may be used to prevent GnRH agonist-related PSA flares; however, they have uncertain utility in improving survival over ADT alone[5] and have been replaced by second-generation antiandrogens.

Second-generation antiandrogens have 2 main mechanisms to overcome the limitations of first-generation antiandrogens (Fig. 1). First, abiraterone acetate (abiraterone) is a pregnenolone analog that effectively inhibits 17α-hydroxylase/C17,20-lyase (CYP17A1)-mediated androgen synthesis in testicular, prostate, and adrenal tissues. Second, the direct AR inhibitors enzalutamide, darolutamide, and apalutamide exhibit increased specificity and potency in blocking AR activity. Each has demonstrated survival benefit beyond ADT alone in randomized clinical trials (Table 1, Supplementary Fig. S1 and Table S1). Together, they have dramatically changed the landscape of prostate cancer treatment (Supplementary Figs. S2-3 and Table S2). The emergence of these newer second-generation antiandrogens with improved activity raises questions on how effectively to apply these agents in advanced prostate cancer. Beginning with Food and Drug Administration (FDA) and European Medicines

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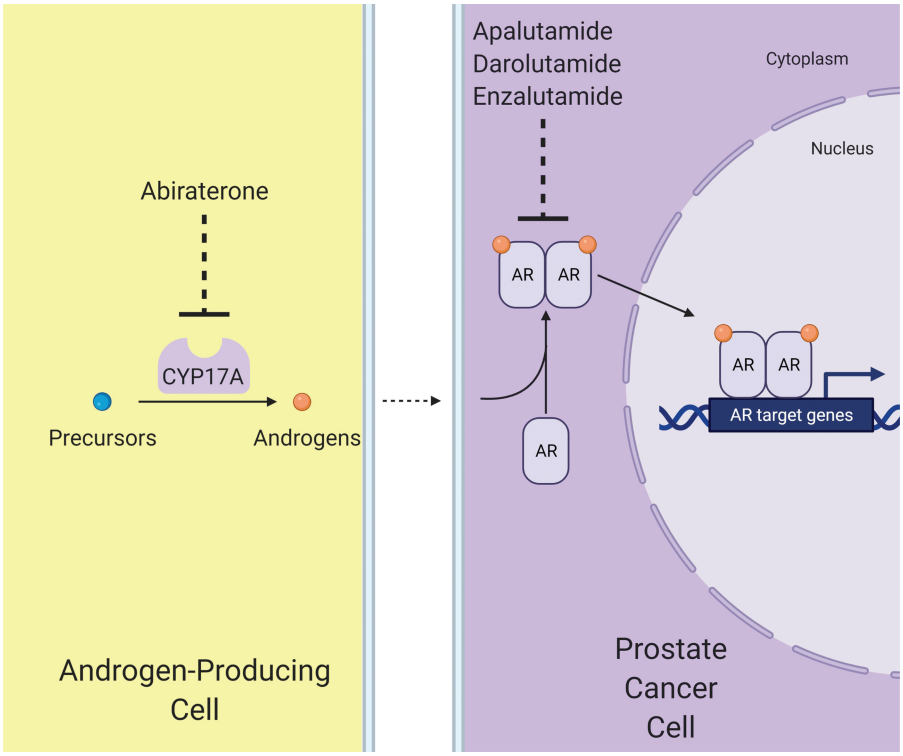

Figure 1. Mechanisms of action for second-generation antiandrogens. Abiraterone inhibits CYP17A1-mediated conversion of precursors pregnenolone and progesterone to DHEA and androstenedione, respectively. Enzalutamide, apalutamide, and darolutamide directly bind and inhibit AR.

Agency (EMA) approval of abiraterone in 2011 and 2012 in the postchemotherapy metastatic CRPC setting, these therapeutics have become a mainstay in the treatment of men with prostate cancer in a variety of clinical settings and resulted in a completely new treatment paradigm in prostate cancer. Here, we discuss the rational use of second-generation antiandrogens in prostate cancer given available data.

Evidence Acquisition

A systematic search of the AACT Clinical Trials Transformation Initiative (CTTI) database was performed 1/2021 to find all registered trials with any treatment arm containing abiraterone, CB-7630, JNJ-212082, enzalutamide, MDV-3100, apalutamide, ARN-509, JNJ-927, darolutamide, ODM-201, or BAY1841788. Trial identifiers were then used to query PubMed/Medline for all indexed publications reporting results of these trials. In cases where updated reports of outcomes in a trial have been reported in different publications, data from the most recent publication were used. Pre-identified outcomes of biochemical progression-free, radiographic/metastasis-free, skeletal event-free, chemotherapy-free, and overall survival as well as response rate and adverse event rates by CTCAE (Common Terminology Criteria for Adverse Events) were reported for each available arm. Trial identifiers and publication information are listed in Supplementary Table S1.

Evidence Synthesis

Second-generation Antiandrogens in Metastatic Castration-Resistant Prostate Cancer

Initially, abiraterone was approved in docetaxel-progressive mCRPC after showing an overall survival (OS) benefit in the placebo-controlled phase III COU-AA-301 trial in 2011.[6] The median survival benefit of abiraterone versus placebo in this heavily treated population was nearly 5 months with a median OS of 15.8 months (95% CI 14.8-17.0 months) versus 11.2 months (95% CI 10.4-13.1; hazard ratio [HR] 0.74 [95% CI 0.64-0.86], $P < .0001$). Enzalutamide performed similarly in the phase III AFFIRM trial with median survival benefit of nearly 5 months versus placebo (median OS 18.4 months [95% CI 17.3-NR] versus 13.6 months, [95% CI 11.3-15.8], HR 0.63, [95% CI 0.53-0.75], $P < .001$).[7] Based on these studies, enzalutamide and abiraterone were approved in progressive mCRPC after docetaxel in 2011 and 2012, respectively.

Given that antecedent chemotherapeutic regimens provided a comparatively smaller survival advantage of around 2 months,[8-10] second-generation antiandrogens were then tested in chemotherapy-naïve mCRPC. Abiraterone with prednisone again showed an approximate 5 month median survival advantage versus placebo with prednisone in the phase III COU-AA-302 trial (34.7 months [95% CI 32.7-36.8] versus 30.3 months [95% CI 28.7-33.3], HR 0.81 [95% CI 0.70-0.93], $P = .003$).[11,12] The co-primary endpoint of radiographic progression-free survival (rPFS) was similarly improved by approximately 5 months over placebo (Supplementary Table S2). In addition, abiraterone significantly improved the prespecified secondary endpoint of median time to opiate use for cancer pain (33.4 months [95% CI 30.2-39.8] versus 23.4 months [95% CI 20.3-27.5]). Adverse events (AEs) of abiraterone and prednisone included hypertension, hypokalemia, and cardiac complications, but grade 3-5 AEs were only slightly more common versus placebo and prednisone (53.5% vs 43.7%, cardiac complications 7.6% vs 3.7%).

Table 1. Approved second-generation antiandrogens and key trials. A table of key trials leading ot the approval of second-generation antiandrogens in prostate cancer, listed by indication.

			Biochemical Progression			Radiographic/Metastatic Progression			Skeletal Event			Chemotherapy			Death				
	Study and agents	Patients (no.)	Median EFS (95% CI)	HR (95% CI)	*P* value	Median EFS (95% CI)	HR (95% CI)	*P* value	Median EFS (95% CI)	HR (95% CI)	*P* value	Median EFS (95% CI)	HR (95% CI)	*P* value	Median OS (95% CI)	HR (95% CI)	*P* value	RR (%)	AE3+ (%)
Post-chemotherapy mCRPC	**COU-AA-301 (NCT00638690)[6] phase III[a]**																		
	Abiraterone	797	8.5 (8.3-11.1)	0.63 (0.52-0.78)	<.0001		0.66 (0.58-0.76)	<.0001							15.8 (14.8-17.0)	0.74 (0.64-0.86)	<.0001	15%	
	Placebo	398	6.6 (5.6-8.3)												11.2 (10.4-13.1)			3%	
	AFFIRM (NCT00974311)[7] phase III[a]																		
	Enzalutamide	800	8.3 (5.8-8.3)	0.25 (0.20-0.30)	<.001		0.4 (0.35-0.47)	<.001	16.7 (14.6-19.1)	0.69 (0.57-0.84)	<.001				18.4 (17.3-NR)	0.63 (0.53-0.75)	<.001	29%	45%
	Placebo	399	3 (2.9-3.7)						13.3 (9.9-NR)						13.6 (11.3-15.8)			4%	34%
Chemotherapy-naïve mCRPC	**COU-AA-302 (NCT00887198)[12] phase III[b]**																		
	Abiraterone	546	11.1	0.49 (0.42-0.57)	<.001		0.53 (0.45-0.62)	<.001				25.2	0.58 (0.49-0.69)	<.001	34.7 (32.7-36.8)	0.81 (0.70-0.93)	.0033		54%
	Placebo	542	5.6									16.8			30.3 (28.7-33.3)				44%
	PREVAIL (NCT01212991)[13] phase II[b]																		
	Enzalutamide	626	11.2	0.17 (0.15-0.20)	<.001		0.19 (0.15-0.23)	<.001	31.1	0.72 (0.61-0.84)	<.001	28	0.35 (0.30-0.40)	<.001	32.4	0.71 (0.60-0.84)	<.001	59%	
	Placebo	532	2.8						31.3			10.8			30.2			5%	
	TERRAIN (NCT01288911)[14,c] phase II																		
	Enzalutamide	184	19.4 (16.6-NR)	0.28 (0.20-0.39)	<.0001		0.51 (0.36-0.74)	0.0002											31%
	Bicalutamide	191	5.8 (5.6-8.3)																24%
	STRIVE (NCT01664923)[19,c] mCRPC cohort (65%) phase II																		
	Enzalutamide	128	24.9 (16.6-NR)	0.19 (0.13-0.28)	<.001		0.32 (0.21-0.50)	<.001											36%
	Bicalutamide	129	5.7 (5.6-8.3)																36%
nmCRPC	**PROSPER (NCT02003924)[21,22] phase III[a]**																		
	Enzalutamide	933	37.2 (33.1-NR)	0.07 (0.05-0.08)	<.001		0.29 (0.24-0.35)	<.0001				39.6	0.21 (0.17-0.26)	<.001	67.0 (64.0-NR)	0.73 (0.61-0.89)	0.0011		48%
	Placebo	468	3.9 (3.8-4.0)									17.7			56.3 (54.4-63.0)				27%
	STRIVE (NCT01664923)[19,c] phase II metastatic and nonmetastatic																		
	Enzalutamide	198	NR (19.4-NR)	0.19 (0.14-0.26)	<.001		0.32 (0.21-0.50)	<.001							NR			60%	36%
	Bicalutamide	198	8.3 (5.7-8.5)												NR				36%

Table 1. Continued

	Study and agents	Patients (no.)	Biochemical Progression			Radiographic/Metastatic Progression			Skeletal Event			Chemotherapy			Death			RR (%)	AE3+ (%)
			Median EFS (95% CI)	HR (95% CI)	*P* value	Median EFS (95% CI)	HR (95% CI)	*P* value	Median EFS (95% CI)	HR (95% CI)	*P* value	Median EFS (95% CI)	HR (95% CI)	*P* value	Median OS (95% CI)	HR (95% CI)	*P* value		
	- nmCRPC cohort (35%)																		
	Enzalutamide	70	NR (19.4-NR)	0.18 (0.10-0.34)	<.001		0.24 (0.10-0.56)	<.001											
	Bicalutamide	69	11.1 (8.4-13.9)																
	ARAMIS (NCT02200614)[20] phase III[a]																		
	Darolutamide	955	NR	0.13 (0.11-0.16)	<.001		0.41 (0.34-0.5)	<.001	NR	0.43 (0.22-0.84)	.01	73	0.43 (0.31-0.60)	<.001	NR	0.71 (0.50-0.99)	.045		25%
	Placebo	554							NR			38.2			NR				19%
	SPARTAN (NCT01946204)[23,24] phase III[a]																		
	Apalutamide	806	NR	0.06 (0.05-0.08)	<.0001		0.28 (0.23-0.35)	<.001				NR	0.6 (0.45-0.80)	.0001	NR	0.75 (0.59-0.96)	.0197		45%
	Placebo	401	3.7									NR			39				34%
CSPC	STAMPEDE (NCT00268476)[26] phase III metastatic and nonmetastatic[a]																		
	Abiraterone	960								0.46 (0.37-0.58)	<.001					0.63 (0.52-0.76)	<.001		33%
	Placebo	948																	47%
	- nonmetastatic cohort (48%)																		
	Abiraterone	455								0.56 (0.27-1.18)	.123					0.75 (0.48-1.18)	.21		
	Placebo	460																	
	-metastatic cohort (52%)																		
	Abiraterone	502								0.45 (0.36-0.58)	<.001					0.61 (0.49-0.75)	.027		
	Placebo	500																	
CSPC	Latitude (NCT01715285)[25] phase III metastatic CSPC[b]																		
	Abiraterone	597	33.2	0.3 (0.26-0.35)	<.001		0.47 (0.39-0.55)	<.001	NR	0.7 (0.54-0.92)	.009	NR	0.44 (0.35-0.56)	<.001	NR	0.62 (0.51-0.76)	<.001		63%
	Placebo	602	7.4						NR			38.9			34.7				48%
	ARCHES (NCT02677896)[31] phase III metastatic CSPC[a]																		
	Enzalutamide	574	NR (NR-NR)	0.19 (0.13-0.26)	<.001		0.39 (0.30-0.50)	<.001	NR (NR-NR)	0.52 (0.33-0.82)	.002	30.2	0.28 (0.20-0.40)	<.001	NR	0.81 (0.53-1.25)	.3361	83%	24%
	Placebo	576	NR (NR-NR)						NR (NR-NR)			NR			NR			64%	26%
	ENZAMET (NCT02446405)[30] phase III metastatic CSPC[a]																		
	Enzalutamide	933	37.2 (33.1-NR)	0.07 (0.05-0.08)	<.001		0.29 (0.24-0.35)	<.001				39.6	0.21 (0.17-0.26)	<.001	NR	0.67 (0.58-0.86)	.002		31%
	Placebo	468	3.9 (3.8-4.0)									17.7			NR				23%

Table 1. Continued

Study and agents	Patients (no.)	Biochemical Progression			Radiographic/Metastatic Progression			Skeletal Event			Chemotherapy			Death				
		Median EFS (95% CI)	HR (95% CI)	*P* value	Median EFS (95% CI)	HR (95% CI)	*P* value	Median EFS (95% CI)	HR (95% CI)	*P* value	Median EFS (95% CI)	HR (95% CI)	*P* value	Median OS (95% CI)	HR (95% CI)	*P* value	RR (%)	AE3+ (%)
TITAN (NCT02489318)[17] phase III metastatic CSPC[b]																		
Apalutamide	525	NR	0.26 (0.21-0.32)	<.0001		0.48 (0.39-0.60)	<.001	NR	0.8 (0.56-1.15)	.23	NR	0.39 (0.27-0.56)	<.001	NR	0.67 (0.51-0.89)	.005		42%
Placebo	527	12.9						NR			NR			NR				41%

[a]Primary outcome.
[b]Co-primary outcomes.
[c]A different primary outcome. See also Supplementary Table S2 for median overall survival, PSA, progression-free survival, and metastatic/radiographic progression-free survival benefit as well as hazard ratio for death versus placebo.

The benefit of enzalutamide in prechemotherapy mCRPC was similar in the phase II PREVAIL trial, which demonstrated an approximate 2 month median survival benefit (median OS 32.4 months vs 30.2 months, HR 0.71 [95% CI 0.60-0.84], $P < .001$) versus placebo, similar to that of chemotherapy.[13] Enzalutamide demonstrated a biochemical progression-free survival (median 19.4 months [95% CI 16.6-NR] versus 5.8 months [95% CI 5.6-8.3], HR 0.28 [95% CI 0.20-0.39]) and radiographic progression-free survival (HR 0.52 [95% CI 0.36-0.74]) benefit over bicalutamide in the phase II TERRAIN study.[14]

A direct comparison of abiraterone and enzalutamide was performed in a pivotal trial including patients with metastatic CRPC reported by Khalaf et al (NCT02125357).[15] In this phase II crossover study, 202 patients mCRPC were given abiraterone and prednisone (Arm A) or enzalutamide (Arm B) until biochemical progression. On progression, 148 patients then crossed over to the opposing arm. In an interim analysis prior to crossover, time to biochemical progression was equivalent (7.4 months versus 8.0 months, HR = 0.88 [95% CI 0.61-1.27]), although initial measures of PSA reduction slightly favored enzalutamide.[16] A quality-of-life interim analysis similarly favored abiraterone with improved FACT-P scores in the abiraterone arm (worsening FACT-P in 8% vs 16% of patients, $P = .09$).[17]

Nonmetastatic Castration-Resistant Prostate Cancer

Up to one-third of patients with optimally-treated localized CSPC develop local recurrence or biochemical recurrence without detectable metastases despite castrate-levels of testosterone (ie, under 50 ng/dL).[18] The phase II STRIVE trial of enzalutamide, although mostly in men with mCRPC, also included a sizeable cohort of 139 men (35%) with nonmetastatic CRPC (nmCRPC).[19] While not powered to detect differences in overall survival, it did show favorable biochemical progression-free survival of enzalutamide versus bicalutamide in men with nmCRPC (hazard ratio 0.19 [95% CI 0.14-0.26], $P < .001$) which also held for nonmetastatic disease (nmCRPC hazard ratio 0.18 [95% CI 0.1-0.34], $P < .001$). Radiographic progression-free survival among patients in the nmCRPC subset analysis of STRIVE was also substantially improved (HR 0.24, [95% CI 0.10-0.56], $P < .001$). These observations led to additional trials with significantly larger enrollment to test second-generation antiandrogens in nmCRPC.

Of the second-generation antiandrogens, darolutamide was the first to show statistically significant benefit in overall survival in nmCRPC in the ARAMIS study (HR 0.71, [95% CI 0.50-0.99], $P = .045$).[20] Later, enzalutamide in the PROSPER trial and apalutamide in the SPARTAN trial showed similar significantly reduced hazard ratios for death (HR 0.73 [95% CI 0.0.61-0.89], $P = .0011$ and HR 0.75, [95% CI 0.50-0.99], $P = .0045$, respectively).[21-24] All 3 therapeutics are approved for use in nmCRPC on the basis of similar and significantly improved outcomes in biochemical PFS (HR ranging 0.06-0.13), radiographic or metastatic PFS (HR ranging 0.28-0.41), and time to chemotherapy (HR ranging 0.23-0.44) in these phase III trials.

Grade 3 and greater AEs in ARAMIS were similar in patients receiving darolutamide or placebo (25% vs 19%).[20] Both apalutamide and enzalutamide are associated with increased grade 3 and greater AEs in comparable studies.[21-24] Specific medication side-effects and limitations are well-reviewed

elsewhere, but enzalutamide should be used carefully in patients with ischemic heart disease and high seizure risk as cardiac events and seizures have been reported in prior studies. Patients with a history or high risk of seizures were excluded from PROSPER, but neither ARAMIS nor SPARTAN excluded these patients. Despite this, patients with nmCRPC receiving darolutamide did not experience increased seizure risk in ARAMIS (0.2% in both arms) and patients receiving apalutamide appeared to experience only a slightly increased risk of seizure in SPARTAN (0.2% vs 0%). In all, patients taking darolutamide reported relatively few skin complaints (3%) or fatigue (16%) that are seen in one quarter to one-third of patients taking enzalutamide or apalutamide. It is believed these differences may relate to the diminished blood-brain barrier penetration of darolutamide.

Metastatic Castration-Sensitive Prostate Cancer

All second-generation antiandrogens target androgen-mediated prostate cancer cell survival. Thus, the exploration of these agents in metastatic CSPC (mCSPC) in phase III trials was a natural step.

Abiraterone with ADT showed significant improvement in overall survival for castration-naïve (STAMPEDE, arm G, HR 0.63 [95% CI 0.52-0.76], $P < .001$) and castration-sensitive (LATITUDE HR 0.62 [95% CI 0.51-0.76], $P < .001$) prostate cancer.[25,26] STAMPEDE included both metastatic and nonmetastatic disease, and the overall survival benefit was most clearly present in patients with metastases (HR 0.61 [95% CI 0.49-0.75], $P = .027$). Notably, only patients with high-risk disease were enrolled in LATITUDE and this group also formed the bulk of patients in STAMPEDE. As a result, FDA approval of abiraterone in CSPC was conditioned on 2 or 3 defined high-risk factors (ie, Gleason score 8-10, 3 or more bone metastases, and/or visceral metastases).

In contrast to abiraterone, both apalutamide and enzalutamide are approved in mCSPC without regard to risk. Apalutamide showed significantly improved overall survival versus placebo in the phase III TITAN trial (HR 0.67, [95% CI 0.51-0.89], $P = .005$).[27] Importantly, mCSPC does not include pelvic lymph node metastases, and FDA approval in this setting stipulates distant lymph node or extranodal involvement. This benefit has persisted even after unblinding and crossover (OS HR 0.65, [95% CI 0.53-0.79], $P < .0001$).[28] The ongoing LACOG-0415 may offer clues about the relative merits of apalutamide versus abiraterone in this setting.[29] Enzalutamide showed significant overall survival benefit in ENZAMET (HR 0.67, [95% CI 0.58-0.89], $P = .002$), particularly in patients with low-volume disease (HR 0.43 [95% CI 0.26-0.72], $P = .0012$).[30] This benefit was not seen in the ARCHES trial, although this phase III trial met its endpoint of radiographic progression-free survival by a significant margin (HR 0.39 [95% CI 0.30-0.50], $P < .001$).[31] Given STAMPEDE and CHAARTED data suggesting efficacy of docetaxel in high-volume mCSPC, some clinicians prefer chemotherapy in select patients in this setting.[32,33]

While cross-trial comparison is not reliable, the reported biochemical progression-free survival, radiographic progression-free survival, and time to next chemotherapy appear equivalent for second-generation antiandrogens in these studies. There are no phase III randomized trials comparing docetaxel and anti-androgens in this setting.

Non-Metastatic Castration-Sensitive Prostate Cancer

Fewer trials thus far have evaluated second-generation antiandrogens specifically in nonmetastatic castration-sensitive or castration-naïve disease. STAMPEDE included a sizeable cohort of patients with nonmetastatic disease, but abiraterone did not significantly improve overall survival in these patients (HR 0.75 [95% CI 0.48-1.18], $P = .21$) in contrast to those with metastatic disease (HR 0.61 [95% CI 0.49-0.75], $P = .027$). However, these data are not sufficiently mature to exclude OS benefit in nmCSPC and the study was not powered for this endpoint. An early phase II study of abiraterone in the neoadjuvant setting showed few pathological responses (10% in patients receiving 24 weeks of abiraterone versus 4% in patients receiving 12 weeks of abiraterone prior to prostatectomy),[34] which has dampened hopes for earlier use of second-generation antiandrogens. Nevertheless, several ongoing studies may offer additional clues for the use of these agents in early disease. LACOG-0415 is currently testing apalutamide and abiraterone in CSPC and includes patients with locally advanced disease.[29] NCT02268175 is further testing enzalutamide with or without abiraterone in CSPC prior to radical prostatectomy. Second-generation antiandrogens should not be used in nonmetastatic CSPC outside of a clinical trial.

Combinations

Previously, chemotherapy with docetaxel was the sole standard of care in mCRPC (see Supplementary Table S3).[9,10] While the CHAARTED trial established docetaxel chemotherapy as a valid option in high-volume mCSPC[32] and recent phase II study NCT02254785 shows benefit to cabazitaxel before second-generation antiandrogens in patients with certain high-risk features in mCRPC,[35] most clinicians and patients prefer to minimize exposure to cytotoxic agents. Indeed, quality of life deteriorates significantly with chemotherapy—even if only temporarily—without conferring significantly different survival improvement over antiandrogens in this setting (see also Supplementary Tables S2-3).[32,33,36]

Concurrent antiandrogen and chemotherapy treatments are associated with significant adverse events that may exceed clinical utility. The phase II ENZAMET study included patients who received early docetaxel after enzalutamide, which did not seem to improve survival (HR 0.9 [95% CI 0.62-1.31]) but was associated with significant toxicities including increased seizures.[30] Interestingly, the ongoing phase III PEACE-1 study (NCT01957436) has shown overall survival and radiographic progression-free survival benefit in de novo metastatic CSPC by combining abiraterone and standard-of-care ADT and docetaxel (OS HR 0.75 [95% CI 0.59-0.95], $P = .017$) versus standard-of-care docetaxel and ADT alone.[37,38] This benefit may be limited to patients with high-volume disease (ie, visceral metastases or 4 or more bony lesions with at least one metastasis outside the vertebral bodies and pelvis) on this interim analysis (OS HR 0.72 [95% CI 0.55-0.95], $P = .019$).[38] Final results of PEACE-1 and those of the phase III ARASENS trial (NCT02799602) testing the addition of darolutamide to docetaxel and ADT will provide additional key data on the efficacy of such combinations in metastatic CSPC.

The combination of 2 second-generation antiandrogens has not improved outcomes (Table 2). In the Alliance A031201

Table 2. Combinations of antiandrogens by trial. All published combination phase II-III trials involving combinations with second-generation antiandrogens in prostate cancer.

		Biochemical progression			Radiographic/metastatic progression			Skeletal event			Chemotherapy			Death				
Study and agents	Patients (no.)	Median EFS (95% CI)	HR (95% CI)	*P* value	Median EFS (95% CI)	HR (95% CI)	*P* value	Median EFS (95% CI)	HR (95% CI)	*P* value	Median EFS (95% CI)	HR (95% CI)	*P* value	Median OS (95% CI)	HR (95% CI)	*P* value	RR (%)	AE3+ (%)
Alliance A031201 (NCT01949337)[39] metastatic CRPC (chemotherapy-naïve and post-docetaxel), phase III																		
Abiraterone + Enzalutamide	654													32.7 (29.9-35.4)	1.03	.53	76%	69%
Enzalutamide	657													33.6 (30.5-36.5)			80%	56%
PLATO (NCT01995513)[40] chemotherapy-naïve metastatic CRPC after enzalutamide, phase IV																		
Abiraterone + Enzalutamide	126	2.8	0.87 (0.62-1.24)	.45		0.83 (0.61-1.12)	.22				10.3	0.86 (0.62-1.20)	.38				68%	45%
Abiraterone	125	2.8									8.6						57%	37%
ACIS (NCT02257736)[41] chemotherapy-naïve metastatic CRPC, phase III																		
Abiraterone + apalutamide	492	13.8		.076	22.6 (19.5-27.4)	0.69 (0.58-0.83)	<.0001				36.1		.51	36.2		.498		63%
Abiraterone	490	12.0			16.6 (13.9-19.3)						34.2			33.7				56%
Clarke et al (NCT01972217)[44] CRPC after progression on docetaxel, phase II																		
Abiraterone + olaparib	71					0.65 (0.44-0.97)	.034					0.78 (0.54-1.13)	.19	22.7 (17.4-29.4)	0.91 (0.60-1.38)	.66		54%
Abiraterone	71													20.9 (17.6-26.3)				28%
ERA 223 (NCT02043678)[45] metastatic CRPC with bone metastases, phase III																		
Abiraterone + Radium-223	57	9.6 (8.2-10.8)	0.94 (0.79-1.11)	.46		1.15 (0.96-1.38)	.129	25.5 (20.6-NR)	0.91 (0.50-1.64)	.76	29.5	1.03 (0.82-1.31)	.80	30.7 (25.8-NR)	1.2 (0.95-1.51)	0.128	72%	63%
Abiraterone	57	9.0 (7.9-10.1)						28.7 (19.7-NR)			28.5			33.3 (30.2-41.1)			67%	57%

Table 3. Sequencing studies of second-generation antiandrogens in prostate cancer. A table of studies evaluating second-generation antiandrogens post-chemotherapy, post-second-generation antiandrogen, and in the third line after second-generation antiandrogen and chemotherapy.

			Biochemical Progression			Radiographic/Metastatic Progression			Skeletal Event			Chemotherapy			Death				
	Study and Agents	Patients (no.)	Median EFS (95% CI)	HR (95% CI)	p value	Median EFS (95% CI)	HR (95% CI)	p value	Median EFS (95% CI)	HR (95% CI)	p value	Median EFS (95% CI)	HR (95% CI)	p value	Median OS (95% CI)	HR (95% CI)	p value	RR (%)	AE3+ (%)
Post-chemotherapy abiraterone or enzalutamide	COU-AA-301 (NCT00638690)[6] phase III																		
	Docetaxel → Abiraterone	797	8.5 (8.3-11.1)	0.63 (0.52-0.78)	<.0001		0.66 (0.58-0.76)	<.0001							15.8 (14.8-17.0)	0.74 (0.64-0.86)	<.0001	15%	
	Placebo	398	6.6 (5.6-8.3)												11.2 (10.4-13.1)			3%	
	Satoh et al (NCT01795703)[65] phase II																		
	Docetaxel → Abiraterone	47	108.5 (85-114)												NR			28%	36%
	AFFIRM (NCT00974311)[7] phase II																		
	Docetaxel → Enzalutamide	800	8.3 (5.8-8.3)	0.25 (0.20-0.30)	<.001		0.4 (0.35-0.47)	<.001	16.7 (14.6-19.1)	0.69 (0.57-0.84)	<.001				18.4 (17.3-NR)	0.63 (0.53-0.75)	<.001	29%	45%
	Placebo	399	3 (2.9-3.7)						13.3 (9.9-NR)						13.6 (11.3-15.8)			4%	34%
Second-line 2nd Generation Antiandrogen or Chemo after Antiandrogen	Khalaf et al pre-crossover (NCT02125357)[16] phase II																		
	Abiraterone	101	11.2 (8.3-15.0)	0.95 (0.66-1.36)	.78													68%	
	Enzalutamide	101	10.2 (7.5-14.7)															82%	
	Khalaf et al post-crossover (NCT02125357)[15] phase II																		
	Abiraterone → Enzalutamide	73	19.3 (16.0-30.5)	0.42 (0.28-0.65)	<.0001										28.8 (25.4-NR)	0.79 (0.54-1.16)	.23	36%	
	Enzalutamide → Abiraterone	75	15.2 (11.9-19.8)												24.7 (18.8-34)			4%	
	Suzman et al[48]																		
	Abiraterone → Enzalutamide	30	4.1	1.35 (0.53-3.66)	.502			.252											
	Abiraterone → Docetaxel	31	4.1s																
Second-line 2nd Generation Antiandrogen or Chemo after Antiandrogen	PLATO (NCT01995513)[40] phase IV																		
	Enzalutamide → Abiraterone + Enzalutamide	126	2.8	0.87 (0.62-1.24)	.45		0.83 (0.61-1.12)	.22				10.3	0.861 (0.616-1.204)	.3818				68%	45%
	Enzalutamide → Abiraterone	125	2.8									8.6						57%	37%
	Noonan et al[47]																		
	Docetaxel → Abiraterone	30	3.6 (2.5-4.7)												11.6 (6.5-16.6)			3.3%	

Table 3. Continued

	Study and Agents	Patients (no.)	Biochemical Progression			Radiographic/Metastatic Progression			Skeletal Event			Chemotherapy			Death			RR (%)	AE3+ (%)
			Median EFS (95% CI)	HR (95% CI)	p value	Median EFS (95% CI)	HR (95% CI)	p value	Median EFS (95% CI)	HR (95% CI)	p value	Median EFS (95% CI)	HR (95% CI)	p value	Median OS (95% CI)	HR (95% CI)	p value		
Third-line 2nd Generation Antiandrogen	CARD (NCT02485691)[49] phase IV																		
	Docetaxel + enzalutamide/ abiraterone → abiraterone/ enzalutamide	126				3.7	1.85 (1.37-2.5)	<.001	16.7	1.7 (0.99-2.9)	.051				11.0	1.56 (1.1-2.17)	.008	14%	52%
	Docetaxel + enzalutamide/ abiraterone → cabazitaxel	129				8.0			NR						13.6			36%	56%
	Azad et al[50]																		
	Docetaxel + abiraterone → enzalutamide	68				4.6	1.15 (0.66-2.0)	0.6							10.6	0.63 (0.33-1.2)	.2		
	Abiraterone → enzalutamide	47				6.6									8.6				
	Loriot et al[51]																		
	Docetaxel/ Enzalutamide → Abiraterone	38	2.7 (2.3-4.1)												7.2 (5.0-NR)			18%	
	Badrising et al[52]																		
	Docetaxel/ Abiraterone → enzalutamide	33	4.0 (3.7-NR)												7.3 (6.6-NR)				

trial comparing enzalutamide and abiraterone versus enzalutaimde alone, an interim analysis showed equivalent median overall survival (32.7 months [95% CI 29.9-35.4] vs 33.6 months [95% CI 30.5-36.4], P = .53) but increased grade 3-5 adverse events (68.8% vs 55.6%).[39] Likewise, in the PLATO study adding abiraterone to enzalutamide after PSA progression did not improve subsequent biochemical PFS (median 2.8 months in each arm, HR 0.87 [95% CI 0.62-1.24], P = .45), radiographic PFS (median 5.7 months vs 5.6 months, HR 0.83 [95% CI 0.61-1.12], P = .22), or time to chemotherapy (median 10.3 months vs 8.6 months, HR 0.861 [95% CI 0.616-1.204], P = .3818).[40] Recently reported outcomes of the ACIS trial combining apalutamide and abiraterone in mCRPC point toward an additive effect of apalutamide in addition to abiraterone for radiographic progression-free survival versus abiraterone alone (22.6 vs 16.6 months, HR 0.69 [95% CI 0.58-0.83], P < .0001) but no difference in median overall survival (36.2 months vs 33.7 months, P = .498).[41] Adverse effects from the addition of apalutamide were present (AE grade 3 and greater in 63% vs 56%).

An ongoing arm of the STAMPEDE trial is further testing the combination of abiraterone and enzalutamide, but early reports suggest increased toxicity without clinical benefit.[42] LACOG-0415 is further testing the combination of apalutamide and abiraterone in CSPC.[43] Other combinations of abiraterone with apoly ADP ribose polymerase (PARP) inhibitor, olaparib, or radium-223 have shown increased toxicity.[44,45] Apalutamide combined with PARP inhibitor niraparib has been similarly disappointing with high toxicity.[46] Multiantiandrogen therapy and other combinations should not be prescribed outside of a clinical trial at this time.

Sequences

Given the poor efficacy and tolerability of combination therapies, further trials have focused on therapy sequencing (Table 3). In the final analysis of the phase II crossover study NCT02125357 by Khalaf et al in mCRPC discussed briefly above, an abiraterone-to-enzalutamide sequence resulted in superior time to second biochemical progression compared to an enzalutamide-to-abiraterone sequence (19.3 months [95% CI 16.0-30.5] vs 15.2 months [95% CI 11.9-19.8], HR 0.42 [95% CI 0.28-0.65], P < .0001).[15] Enzalutamide also showed a significantly improved response rate of 36% after biochemical progression on abiraterone compared to a 4% response rate to abiraterone after enzalutamide. OS was not significantly different (median 28.8 months [95% CI 25.4-NR] vs 24.7 months [95% CI 18.8-34.0], HR 0.79 [95% CI 0.54-1.16], P = .23) but the study was not powered for this endpoint. While these data suggest that abiraterone may best precede enzalutamide, the efficacy of a second agent is profoundly reduced in either case with second antiandrogen response rates more than halved for enzalutamide (82% vs 36%) and reduced by an order of magnitude for abiraterone (68% vs 4%). The effectiveness of abiraterone after enzalutamide in mCRPC in one retrospective series by Noonan *et al* is also clearly reduced (median OS 11.6 months [95% CI 6.5-16.6]).[47] These observations suggest cross-tolerance among second-generation antiandrogens.

Given that immediate sequential antiandrogen therapy performs poorly, could chemotherapy serve to sensitize tumors to antiandrogen in mCRPC? Most of the data in this space come from retrospective analyses rather than controlled trials (Table 3, Supplementary Fig. S4). Post-abiraterone enzalutamide or docetaxel provided equivalent biochemical progression-free survival in a retrospective study by Suzman et al (median 4.1 months in each arm, HR 1.35 [95% CI 0.53-3.66, P = .502]).[48] As previously discussed, side effect profiles for these medications generally favor nonchemotherapeutic agents like second-generation antiandrogens. Conversely, both abiraterone and enzalutamide showed impressive efficacy after chemotherapy in the COU-AA-301 and AFFIRM trials, respectively (median survival 15.8 months [95% CI 14.8-17.0], HR 0.74 [95% CI 0.64-0.86], P < .0001 and 18.4 months [95% CI 17.3-NR], HR 0.63 [95% CI 0.53-0.75], P < .001).[6,7]

Third-line systemic treatment with a second-generation antiandrogen (ie, after failure of both chemotherapy and another second-generation antiandrogen) is expected to perform poorly. One striking, practice-changing comparison in the third-line setting was made in the CARD study.[49] In this study, patients with poor previous response to second-generation antiandrogen (ie, progression within 12 months) and progression on docetaxel were randomized to cabazitaxel or to alternative second-generation antiandrogen (abiraterone or enzalutamide after enzalutamide or abiraterone, respectively). In this selected group of patients, cabazitaxel improved overall survival (median overall survival 11 months with second-generation antiandrogen versus 13.6 months with cabazitaxel, HR 1.56 [95% CI 1.1-2.17], P = .008). In this setting, second-generation antiandrogens enzalutamide and abiraterone behave similarly to placebo.

Data for unselected patients with prior effective chemotherapy and second-generation antiandrogen therapy are retrospective. Azad et al found a reasonable survival benefit for enzalutamide after both docetaxel and abiraterone.[50] Single-arm studies by Loriot et al and Badrising et al similarly affirm acceptable performance of third-line abiraterone and enzalutamide, respectively.[51,52] The lack of control arms in these studies hinders agent selection, but NCT02125357 reported by Khalaf et al suggest that abiraterone may perform best prior to enzalutamide.[15]

Conclusions

A Rational Sequence of Treatment

These observations taken together posit a rational approach for second-generation antiandrogens in mCRPC (Fig. 2, right upper quadrant). If no immediate response is required (eg, in low-volume, nonvisceral disease) and the patient does not have diabetes, severe hepatic impairment, or severe cardiovascular disease (ie, relative contraindications), abiraterone may be an ideal first choice for metastatic CRPC. In patients with contraindications, enzalutamide is also a viable option. At progression (median 11 months), where comorbidities and performance status allow, chemotherapy with docetaxel (75 mg/m^2 every 3 weeks for up to 10 cycles) or an alternative treatment based on genetics (eg, olaparib or rucaparib in DNA damage repair-deficient [DDR] tumors)[53] or metastatic pattern (eg, Radium-223 in the absence of visceral metastases or radiotherapy in oligometastatic disease)[54,55] may be offered for mCRPC. At next progression, multiple options including second-generation antiandrogens emerge. Postchemotherapy enzalutamide is reasonable for eligible patients who have previously received clinical benefit from abiraterone (ie, over 12

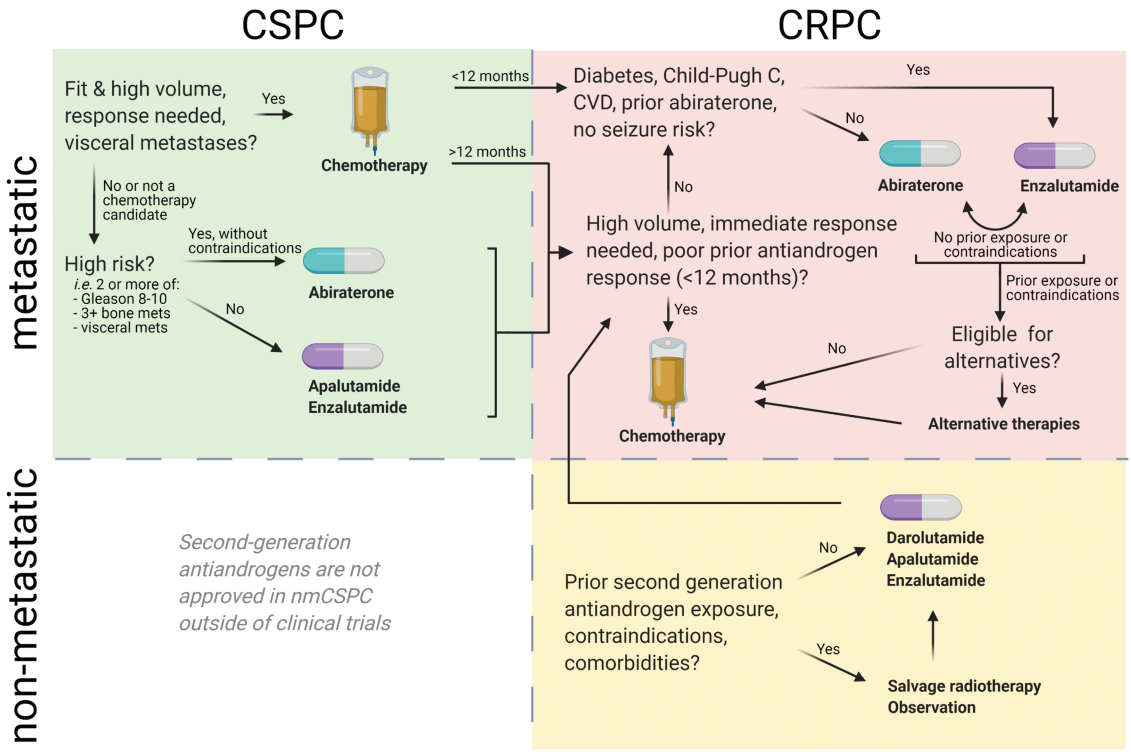

Figure 2. A rational approach to second-generation antiandrogens in mCRPC and nmCRPC. In patients with mCSPC or CRPC, second generation antiandrogen therapy is reasonable as outlined. Faded lines indicate decision points. Solid lines indicate progression.

months). Otherwise, cabazitaxel is clearly superior to a second second-generation antiandrogen. In patients unable to receive enzalutamide, some clinicians prefer an alternative direct AR inhibitor off-label. In patients who previously received second-generation antiandrogen with poor response (ie, under 12 months), third-line chemotherapy with cabazitaxel is definitively superior to second-generation antiandrogen. It is recommended that genetic alterations should be sought early in prostate cancer evaluation, as patients with mutations in genes involved in homologous recombination repair (eg, BRCA1) should be considered for PARP inhibitor treatment[56] and additional alternative therapies targeting known pathogenic mutations in clinical trials. Lastly, ^{117}Lu-PSMA-617 radionuclide therapy has shown promise in addition to standard treatments (ie, third-line abiraterone, enzalutamide, or palliative nonchemotherapy options) in the phase III VISION trial (NCT03511664) in the third-line setting (after both second-generation antiandrogen and chemotherapy) in mCRPC.[57] Overall survival in this setting clearly exceeded that of standard of care therapies alone (HR 0.62 [95% CI 0.52-0.74], P < .001), and regulatory approvals are pending at this time.

For nonmetastatic CRPC (Fig. 2, right lower quadrant), multiple medications are approved (ie, apalutamide, darolutamide, or enzalutamide) and may be suitable depending on patient characteristics. We prefer darolutamide given its proven OS benefit and lower apparent grade 3 and greater AEs. Abiraterone is not approved in this setting, although it is sometimes used off label in patients for whom direct androgen inhibitors are contraindicated. While data are not sufficient to recommend a specific sequence, patients with nmCRPC after second-generation antiandrogen may also benefit from localized therapies (eg, salvage radiation to the pelvic lymph nodes and/or prostatectomy bed).[58]

In metastatic CSPC (Fig. 2, left upper quadrant), up-front treatment with docetaxel chemotherapy may be preferred in young patients with high-volume disease (as defined by CHAARTED, ie, visceral metastases or 4 or more bony lesions with at least one outside vertebral bodies and pelvis) and in patients needing rapid response. This preference is based on observed response rates for chemotherapy in this setting as well as the time-limited nature of chemotherapy treatment. For others with mCSPC, a second-generation antiandrogen is an appropriate choice. Abiraterone (high-risk disease only), enzalutamide, and apalutamide are approved agents in this setting. Concurrent use of second-generation antiandrogen and chemotherapy is associated with significantly increased toxicities and should be avoided outside of clinical trials. It is unknown whether there is a survival benefit from earlier addition of second-generation antiandrogen after docetaxel chemotherapy or in switching from one antiandrogen to another based on PSA progression in this setting.

Future Directions

While the above approach is rational based on available data, direct comparisons are lacking and clinical judgment with patient-specific consideration is essential. Furthermore, the prostate cancer landscape continues to shift as these agents are tested earlier in prostate cancer progression and in increasingly complex combinations (Table 4). STAMPEDE included a significant subset of patients with high-risk localized CSPC that may indicate possible benefit in this population (HR 0.75, 95% CI 0.48-1.18, P = .21).[26] It is possible that second-generation antiandrogen therapy may reach further into intermediate-risk non-metastatic CSPC once the final results of LACOG-0415 comparing apalutamide and abiraterone in the absence of ADT are reported.[29] Similar

Table 4. Ongoing key trials of second-generation antiandrogens. A table of important ongoing studies evaluating second-generation antiandrogens in combination with other therapies.

	Study and agents	Patient population	Primary endpoint(s)	Secondary endpoints
CSPC	**STAMPEDE (NCT00268476)**[43]	Metastatic and nonmetastatic CSPC	Overall survival	PSA progression
	ADT + Enzalutamide			Radiographic PFS
	ADT + Enzalutamide + Abiraterone			Time to skeletal events
	LACOG-0415 (NCT02867020)[29]	Metastatic and nonmetastatic CSPC	PSA response	PSA progression Radiographic PFS
	Abiraterone + ADT			
	Apalutamide			Safety
	Abiraterone + Apalutamide			Time to pain progression
				FACT-P
				Time to resistance
				Metastasis-free survival
	EA8183 (NCT04484818)	High-risk CSPC after surgery	Metastasis-free survival	Recurrence-free survival
	ADT + Darolutamide			Overall survival
	ADT alone			Testosterone kinetics
				Safety, FACT-P
	NCT02268175	Neoadjuvant CNPC	pCR/MRD	Residual cancer burden
	ADT + Enzalutamide + Abiraterone			Biochemical PFS
	ADT + Enzalutamide			
	ARASENS (NCT02799602)	Metastatic CSPC	OS	Time to mCRPC
	ADT + Docetaxel + Darolutamide			Subsequent therapy
	ADT + Docetaxel			SSE
				Pain-related outcomes
	TALAPRO-3 (NCT04821622)	Metastatic CSPC with DDR deficiency	Radiographic PFS	OS
	ADT + Talazoparib + Enzalutamide			Response rates and duration
	ADT + Enzalutamide			Subsequent therapy
				Adverse events
	PEACE-1 (NCT01957436)[37,38]	Metastatic CSPC	Radiographic PFS	Time to CRPC
	ADT + Docetaxel + Abiraterone +/- RT		OS	EFS, SSE
				PSA response rate
	ADT + Docetaxel +/- RT			Time to next therapy/QOL
	KEYNOTE-991 (NCT04191096)	Metastatic CSPC	Radiographic PFS	Time to events
	ADT + Enzalutamide + Pembrolizumab		OS	Time to progression
	ADT + Enzalutamide			Response rates
CRPC	**TALAPRO-1 (NCT03148795)**	Metastatic CRPC with DDR deficiency	ORR	Duration of response
	ADT + Enzalutamide + Talazoparib			Time to progression
	ADT + Enzalutamide			QOL measures
	TALAPRO-2 (NCT03395197)	Metastatic CRPC	Radiographic PFS	OS
	ADT + Enzalutamide + Talazoparib			ORR, PSA response
	ADT + Enzalutamide			Time to progression
				Time to next therapies
	KEYNOTE-365 (NCT02861573)	Metastatic CRPC	Safety	PSA response
	Pembrolizumab + Abiraterone			Overall response rate (ORR)
	Other pembrolizumab combinations			

Indications are listed for each trial.

trials of other combinations are ongoing. Testing is also under way in the neoadjuvant setting for enzalutamide or combination abiraterone and enzalutamide in prostate cancers prior to initial resection (NCT02268175).[59]

Additional agents are being tested for augmentation of second-generation antiandrogens. While Clarke et al show improved radiographic progression-free survival with the addition of PARP inhibitor olaparib to abiraterone after

chemotherapy (median 17.8 months [95% CI 2.9-27.6] vs 6.5 months [2.7-NR], HR 0.65 [95% CI 0.44-0.97], P = .034), reported grade 3 adverse events were nearly doubled (54% vs 28%) and no overall survival benefit has yet been shown with such a combination (median 22.7 months [95% CI 17.4-29.4] vs 20.9 months [95% CI 17.6-26.3], P = .28).[44] Multiple phase III studies are underway for PARP inhibition in various prostate cancer contexts.

One intriguing concept is the use of high-dose testosterone to restore antiandrogen sensitivity after failure of enzalutamide.[60] This "bipolar androgen therapy" (BAT) showed efficacy in the large TRANSFORMER trial, where it significantly improved response rates to enzalutamide, and pre-enzalutamide BAT may provide an OS benefit in future appropriately-powered studies (HR 0.68, [95% CI 0.36-1.28], P = .225).[61] Furthermore, BAT appears to increase the response rates to either abiraterone or enzalutamide.[62] Future phase III trials, particularly in selected patients with TP53 or DDR, will help determine where BAT will be most clinically useful.[63]

Results from KEYNOTE-365 (NCT02861573) and KEYNOTE-995 (NCT04191096) combining abiraterone or enzalutamide with pembrolizumab, which as a monotherapy has poor activity in prostate cancer, are also anticipated. However, a smaller study has failed to find benefit for enzalutamide added to ipilimumab and nivolumab in patients with AR-V7-expressing mCRPC.[64] Additional antiresistance agents are needed and may be suitable in clinical trials either (1) during initial antiandrogen treatment or (2) at initial progression on antiandrogen treatment.

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Conflict of Interest

The authors indicated no financial relationships.

Author Contributions

Conception/design: B.C. Collection and/or assembly of data: J.J.O. Data analysis and interpretation: J.J.O., L.C.P., F.Q., S.S.P., B.C. Manuscript writing: J.J.O. Final approval of manuscript: All Authors.

Data Availability

No proprietary data were used in this manuscript.

Ethics Statement

No additional human or animal subjects were used in the generation of this manuscript.

Supplementary Material

Supplementary material is available at *The Oncologist* online.

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