Enzalutamide for the treatment of metastatic castrate resistant prostate cancer before chemotherapy

National Drug Monograph Addendum

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VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

This addendum provides information on the use of enzalutamide for men with metastatic castrate resistant prostate cancer prior to receiving chemotherapy. The original drug monograph can be found at:
Enzalutamide Drug Monograph

Introduction

Enzalutamide was initially approved in 2012 for the treatment of patients with metastatic castrate resistant prostate cancer who previously received chemotherapy containing docetaxel. In June of 2014 results of the PREVAIL comparing enzalutamide to placebo in the treatment of patients with metastatic castrate resistant prostate cancer who have not received chemotherapy were published. This addendum will review the data from the PREVAIL trial in patients with asymptomatic or minimally symptomatic metastatic castrate resistant prostate cancer who had not received previous chemotherapy.

The optimal treatment of patients with asymptomatic or minimally symptomatic metastatic castrate resistant prostate cancer who are medically or surgically castrate is undefined.[1] Older second-line hormonal therapies produce short-lived PSA responses but have not demonstrated a survival advantage in comparative trials.[2] Cytotoxic chemotherapy is generally reserved for patients who are symptomatic. In this context, the American Society of Clinical Oncology has endorsed the Cancer Care Ontario Practice Guidelines for nonhormonal therapy for men with metastatic castration-resistant prostate cancer that recommend consideration of the timing of docetaxel therapy in men with evidence of metastases but without symptoms based on individualized discussions with patients based on their clinical status and preferences.[3] Sipuleucel-T was shown in a phase III clinical trial to provide a modest survival benefit without affecting tumor regression, symptoms, or disease progression in patients who were asymptomatic or minimally symptomatic.[4] In a phase III trial compared to placebo plus prednisone, abiraterone plus prednisone significantly prolonged radiograph progression free survival. While overall survival was numerically prolonged with abiraterone plus prednisone, it did not reach statistical significance by pre-specified boundaries for significance.[5]

Efficacy in patients who have not received previous chemotherapy

Phase III trial (PREVAIL Trial)[6]

Efficacy Measures

Primary Endpoint(s):

Co-primary endpoints of radiographic Progression Free Survival (rPFS) (blinded review) and Overall Survival (OS)

- rPFS definition: the time from randomization to the first objective evidence of radiographic disease progression assessed by the blinded independent central review facility or death due to any cause within 168 days after treatment discontinuation, whichever comes first (soft tissue progression defined according to modified Response Evaluation Criteria in Solid Tumors [RECIST] criteria[7]; or progression on bone scanning according to criteria adapted from the Prostate Cancer Working Group 2 [PCWG2])[8].
- Overall Survival definition: the time from randomization to death from any cause.

Secondary Endpoints:

- time to initiation of cytotoxic chemotherapy
- time to first skeletal-related event
- best overall tissue response
- time to PSA progression
- time to decline in PSA level of 50% or more from baseline

Exploratory Endpoints

- Quality of life using the Functional Assessment of Cancer Therapy-Prostate (FACT-P)
- Decline in PSA o 90% or more from baseline

Study Design (see Table 3)
Phase III, multinational, randomized, double-blinded, placebo controlled trial in patients with metastatic castration resistant prostate cancer with PSA progression, radiographic progression in soft tissue or bone or both who are asymptomatic with an ECOG Performance Status of 0 or1, and were asymptomatic (score 0 or 1) or mildly symptomatic (score of 2 or 3 on Brief Pain Inventory Short Form question 3) despite ongoing androgen deprivation with serum testosterone levels less than 50 ng/mL who have not received previous cytotoxic chemotherapy. Patients with visceral disease, including lung or liver metastases, or New York Heart Association class I or II heart failure were eligible. Patients with a seizure history or co-morbidity conferring a predisposition to seizures were excluded. Patients receiving medications that lower the seizure threshold were eligible. Coprimary Endpoints were Radiographic Progression Free Survival (rPFS) and Overall Survival.

Treatment: Enzalutamide 160 mg orally once a day or Placebo once a day.

Summary of Efficacy

Table 1 Results of phase III trial in patients without previous chemotherapy treatment

Outcome	Enzalutamide N=872	Placebo N=845
rPFS		
Hazard ratio	**0.19**	**-**
95%CI	**0.15-0.23**	**-**
P value	**<0.001**	**-**
Median PFS	**Not yet reached**	**3.9 months**
Rate of PFS at 12 months	**65%**	**14%**
Overall Survival (interim analysis)		
Hazard ratio	**0.71**	**-**
95%CI	**0.60-0.84**	**-**
P value	**<0.001**	**-**
Median OS estimated	**32.4 months**	**30.2 months**
Overall Survival (updated analysis)		
Hazard ratio	**0.73**	**-**
95%CI	**0.63-0.85**	**-**
P valude	**<0.001**	**-**
Median OS estimated	**Not yet reached**	**31 months**
Percent alive at 18 month	82	73
Subsequent therapies		
Any postbaseline antineoplastic therapy- %	43.8	76
Taking at least one of the following postbaseline antineoplastic therapies- %	40.3	70.3
Docetaxel plus prednisone	32.8	56.7
Abiraterone plus prednisone	20.5	45.6
Cabazitaxel plus prednisone	5.8	13.0
Sipuleucel-T	1.4	1.2
Enzalutamide	1.0	4.4
Selective Secondary and Pre-specified Exploratory Endpoints		
Median time to start of cytotoxic chemotherapy Hazard ratio P value	28 mos 0.35 <0.001	10.8 mos
Median time to decline in FACT-P Hazard ratio P value	11.3 mos 0.63 <0.001	5.6 mos
Median time to 1st skeletal related event Hazard ratio P value	31.1 mos 0.72 <0.001	31.3 mos

Baseline patient characteristics were well balanced in each group. The median time on study drug was longer in the enzalutamide group (16.6. months vs 4.6 months). 68% of patients in the enzalutamide group received therapy for at least 12 months versus 18% of

patients in the placebo arm. The effect of enzalutamide treatment on rPFS was consistent in all pre-specified subgroups with point estimates and 95% Confidence Intervals favoring enzalutamide. The point estimates in all pre-specified subgroups for overall survival all favored enzalutamide; however the upper bound of the 95% Confidence Interval crossed 1.0 in the following subgroups: Geographic region-North America, Visceral Disease at screening-Yes, and Baseline PSA value ≤median. Objective response in patients with measureable soft-tissue disease was seen in 59% of patients receiving enzalutamide and 5% of patients receiving placebo.

Safety

Table 2: Adverse events occurring in at least 10% of enzalutamide patients and events of special interest

	Enzalutamide (N=871)		Placebo (N=844)	
	All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)
Fatigue	36	2	26	2
Back pain	27	3	22	3
Constipation	22	<1	17	<1
Arthralgia	20	1	16	1
Decreased appetite	18	<1	16	1
Hot flush	18	<1	8	0
Diarrhea	16	<1	14	<1
Hypertension	13	7	4	2
Asthenia	13	1	8	1
Fall	12	1	5	1
Weight loss	11	1	8	<1
Peripheral edema	11	<1	8	<1
Headache	10	<1	7	<1
Special Interest				
Any cardiac event	10	3	8	2
Atrial Fib	2	<1	1	1
Acute coronary syndrome	1	1	<1	<1
Acute renal failure	4	1	5	1
Ischemic or hemorrhagic stroke	1	1	1	<1
Elevation in alanine aminotransferase	1	<1	1	<1
Seizure	1	<1	<1	0

A grade 3 or higher adverse event was reported in 43% of enzalutamide patients versus 37% of placebo patients.
Any serious adverse event: 32% enzalutamide versus 27% placebo
Adverse event leading to discontinuation: 6% enzalutamide versus 6% placebo
Adverse event leading to death: 4% enzalutamide versus 4% placebo

Seizures were previously reported with enzalutamide therapy in patients who had previously received chemotherapy. In this trial, seizure was observed in 1 patient in each group, and both patients had a history of seizures unknown to the study investigator at the time of enrollment. Hypertension was more common in the enzalutamide group and occurred more often in patients with a history of hypertension. It was not associated with an increased risk of cardiovascular events or renal events and was managed with standard therapies. Enzalutamide therapy did not result in hepatotoxicity.

Conclusions

In men with metastatic, castrate-resistant prostate cancer with castrate levels of testosterone who were asymptomatic or mildly symptomatic and who had not received previous chemotherapy, enzalutamide significantly prolonged radiograph progression free survival and overall survival compared to placebo. The adverse event profile was similar to that seen when enzalutamide was used after chemotherapy. There were no new safety signals.

Outcome in clinically significant area	rPFS: Not yet reached versus 3.9 months, HR 0.19 Overall Survival: Not yet reached vs 31 months, HR 0.73 Delay in time to start cytotoxic chemotherapy, delay in decline in performance status (FACT-P), delay in time to PSA progression
Effect Size	HR for progression: 0.19 (95%CI 0.15-0.23) HR for survival: 0.73 (95%CI 0.63-0.85)
Potential Harms	Grade 3 or 4 adverse events all less than or equal to 7%; no increased risk for seizures, hepatoxocity
Net Clinical Benefit	Moderate

Table 3. Summary of Clinical Trials Investigating Use of Enzalutamide in patients with metastatic castrate resistant prostate cancer without previous chemotherapy

Citation Design Analysis type Setting	Eligibility Criteria	Interventions	Patient Population Profile			Efficacy Results
Beer TM et al. 2014 multinational, randomized, double-blind, placebo-controlled, phase 3 Supported by Medivation and Astellas Pharma	• PSA progression according to Prostate Cancer Clinical Trials Working Group 2 criteria • Or radiographic progression in soft tissue or bone with or without PSA progressions • Ongoing androgen deprivation with a serum testosterone level less than 50 ng/dL • ECOG performance status 0-1 • No symptoms or mild symptoms as defined by the Brief Pain Inventory-Short Form (BPI-SF)(0-1 = asymptomatic; 2 or 3=mildly symptomatic) • Hematologic and chemical labs meet pre-defined criteria • Previous therapy with an antiandrogen and concurrent glucocorticoids permitted but not required • Visceral disease including lung or liver mets were eligible • New York Heart Association class I or II heart failure eligible Excluded:	• Enzalutamide 160mg orally once daily with or without food OR • Placebo daily with or without food		Enzalutamide N=872	Placebo N=845	Co-primary: Radiographic Progression Free Survival (rPFS) and Overall Survival (OS): 1st interim analysis rPFS median: not reached versus 3.9 mos HR 0.19 (95%CI 0.15-0.23)) Interim analysis for OS OS median: 32.4 mos versus 30.2 months HR 0.71 (95%CI 0.60-0.84) P<0.001) Updated analysis OS med: not yet reached versus 31 months HR 0.73 (95%CI 0.63-0.85) P<0.001 Secondary Med time to initiate chemo 28mos vs 10.8 mos HR 0.35 P<0.001 Med time to decline in FACT-P 11.3 mos vs 5.6 mos HR 0.63 P<0.001 Med time to 1st SRE 31.1 mos vs 31.3 mos HR 0.72 P<0.001 Med time to PSA progression 11.2 mos vs 2.8 mos HR 0.17 P<0.001 Decline in PSA ≥50% from baseline 78% vs 3 % P<0.001
			Age (%)			
			<65	20.5	21.2	
			65-74	43.1	44.3	
			≥75-84	31.4	28.4	
			≥85	4.9	6.2	
			Race (%)			
			Asian	9.7	9.7	
			African-American	2.4	1.5	
			White	76.7	77.5	
			Disease (%)			
			Bone only	39.9	39.6	
			Soft tissue	14.2	17.6	
			Bone+ST	45.1	42	
			Disease progression at entry (%)			
			PSA only	43	43.7	
			Rad/c PSA	40	40.7	
			Rad/w/o PSA	14.4	12.7	
			None	2.5	3.0	
			ECOG PS (%)			
			0	67	69.2	
			1	33	30.8	
			≥2	0	0	
			Baseline PSA			
			Median	54.1	44.2	
			BPI-SF base %			
			0-1	66.2	67.5	
			2-3	32	31.2	
			≥4	1.7	1.3	

Citation Design Analysis type Setting	Eligibility Criteria	Interventions	Patient Population Profile	Efficacy Results
	• Patients with history of seizure or condition pre-disposing to seizure; patients taking meds known to lower seizure threshold were eligible.			Decline in PSA ≥90% from baseline 47% vs 1% P<0.001 Objective response 59% vs 5% P<0.001

References

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