A Phase 2 Trial of Prostate Specific Membrane Antigen Antibody Drug Conjugate (PSMA ADC) in Taxane-Treated Metastatic Castration-Resistant Prostate Cancer (mCRPC)

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Abstract

Background: The abundant expression of PSMA on prostate cancer cells provides a rationale for antibody therapy. PSMA ADC is a fully human antibody to PSMA linked to the microtubule disrupting agent monomethyl auristatin E (MMAE) that binds PSMA. And is internalized and cleaved by lysosomal enzymes releasing free MMAE causing cell cycle arrest and apoptosis.

Methods: Seventy-five patients with progressive mCRPC progressing after taxane treatment and ECOG PS 0 or 1 were treated. PSMA ADC was administered Q3 wk IV for up to 8 cycles. Safety, tumor response by PSA, circulating tumor cells (CTC), imaging, biomarkers and clinical progression were assessed. Dosing was initiated at 2.5 mg/kg and adjustment for tolerability was allowed.

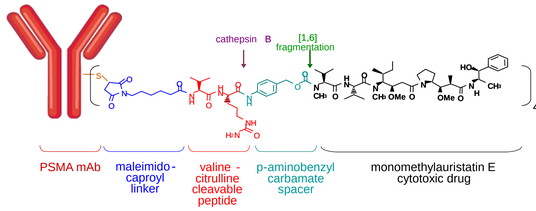
Results: 35 pts initiated treatment at 2.5 mg/kg. Due to neutropenia, the remaining 35 pts began at 2.3 mg/kg. All pts had received prior docetaxel and abiraterone and/or enzalutamide. 41% had also received cabazitaxel. Adverse events (AEs) were consistent with those seen in phase 1; most common significant AEs were neutropenia (grade 4, 6.7% and 11.4% at 2.3 and 2.5 mg/kg, respectively) and peripheral neuropathy (grade ≥3, 6.7% (2.3) and 5.7% (2.5)). Two pts at 2.5 mg/kg died of sepsis associated with neutropenia. 47% of pts at 2.3 and 53% of pts at 2.5 had declines in CTC from ≥5 to <5 cells/7.5 ml blood and 57.1% (2.3) and 74.1% (2.5) had ≥50% CTC declines. Thus far, 26.1% (2.3) and 16.1% (2.5) have had PSA declines of ≥30%. PSA and CTC responses were associated with higher PSMA expression on CTC and lower neuroendocrine (NE) markers (NSE and CgA). The CTC conversion rate (≥5 to <5) was ~80% in pts with low NE markers. Prior cabazitaxel or abiraterone and/or enzalutamide did not appear to affect response. Centralized assessments of images by RECIST of all pts are under evaluation and will be presented.

Conclusions: PSMA ADC at 2.3 mg/kg was generally well tolerated in pts with progressive mCRPC previously treated with taxanes. Antitumor activity, CTC and PSA reductions were observed at 2.3 and 2.5 mg/kg. Updated safety, tumor response and radiographic assessments from the full cohorts of 2.3 and 2.5 mg/kg will be presented. A docetaxel naïve cohort is currently accruing patients.

Introduction

- Prostate cancer is the second leading cause of cancer death in American men
- PSMA is a 750 amino acid, type II transmembrane glycoprotein highly expressed in prostate cancer cells with limited expression in normal non-prostatic tissues
- Treatment of mCRPC has changed dramatically and includes multiple FDA-approved agents
- Progression after taxanes and novel anti-androgens represents a major unmet medical need, which is partly attributed to neuroendocrine differentiation
- The identification of biomarkers can facilitate the tailored development of molecularly targeted new therapies to address this need

PSMA: Target for ADC Therapy



Study Schema

Each cycle last 3 weeks unless there is a dose delay

Study Objectives & Key Eligibility Criteria

Objectives:

- To assess the anti-tumor activity of PSMA ADC in patients with progressive mCRPC
- To assess the tolerability of PSMA ADC in these patients

Inclusion:

- mCRPC progressed on abiraterone and/or enzalutamide,
- Prior history of treatment with at least one taxane-containing chemotherapeutic regimen (e.g., docetaxel, cabazitaxel)
- ECOG PS of 0, 1, or 2
- Hepatic, renal, and hematological laboratory parameters within normal limits

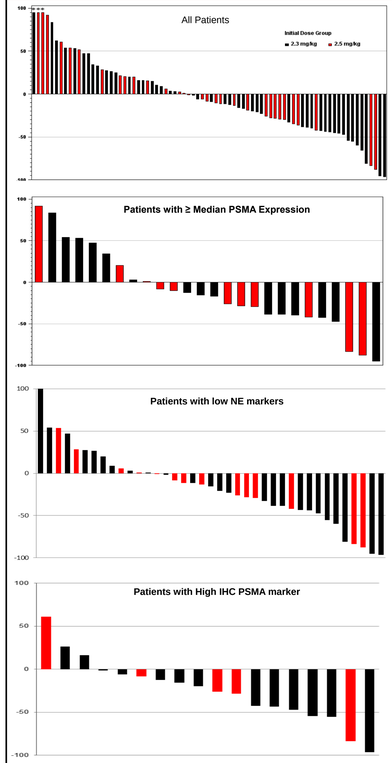
Exclusion:

- Treatment with >2 prior cytotoxic chemotherapies
- Predominant histological or cytological confirmation of neuroendocrine prostate cancer

Demographics and Baseline Characteristics

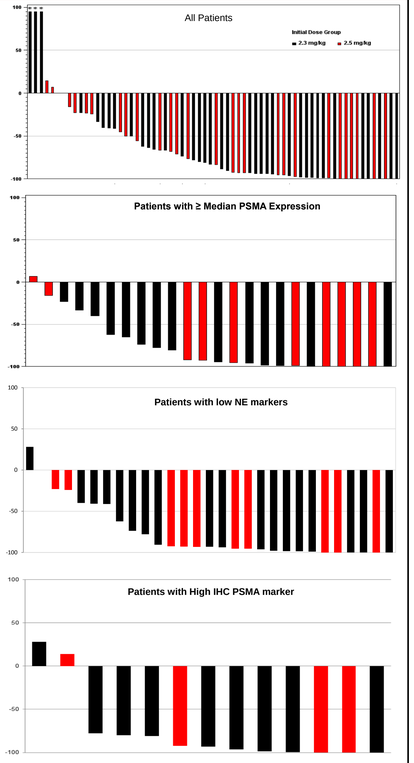
	Dose, (n)		
	2.3 mg/kg (49)	2.5 mg/kg (34)	All Subjects
Age	70	71.5	71
Race			
White	43 (88%)	32 (94%)	75 (90%)
African American	4 (8%)	2 (6%)	6 (8%)
Other	2 (4%)	0	2 (2%)
PS 0	17	13	30
PS 1	28	20	48
PS 2	4	1	5
Baseline PSA	166.5 (7.5-17459.6)	312.8 (11.2-2520.2)	189.3 (7.5-17459.6)

PSA Results



PSA Responses		
Initial Dose Level (n)	**≥30% Decline (n)**	**≥50% Decline (n)**
2.3 mg/kg (47)	36.17% (17)	14.89% (7)
2.5 mg/kg (31)	16.13% (5)	6.45% (2)
PSMA Expression (26)	34.62% (9)	11.54% (3)
Low NE (39)	35.9% (14)	17.95% (7)
High IHC PSMA (18)	38.89% (7)	22.22% (4)
Total (78)	28.21% (22)	10.26% (9)

CTC Results



CTC Responses		
Initial Dose Level (n)	**≥50% Decline**	**Conversion ≥5 CTC at baseline to < 5 CTC Following Treatment**
2.3 mg/kg (39)	74.36% (29)	45.45% (15/33)
2.5 mg/kg (27)	74.07% (20)	45.83% (11/24)
PSMA Expression (24)	79.17% (19)	52.38% (11/21)
Low NE (29)	75.86% (22)	55.17% (16/29)
High IHC PSMA (13)	84.62% (11)	53.85% (7/13)
Total (66)	74.24% (49)	45.61% (26/57)

Additional Results

Marker	Response	Correlation Coefficient (n=41)	p-value
NSE	Best PSA pct chg	-0.0023	0.9842
NSE	Best CTC pct chg	0.0620	0.6467
CgA	Best PSA pct chg	0.1066	0.3796
CgA	Best CTC pct chg	0.0497	0.7237
PSMA Expression	Best PSA pct chg	-0.1720	0.2424
PSMA Expression	Best CTC pct chg	-0.3517	0.0192*
Low NE	Best PSA pct chg	-0.2999	0.0116*
Low NE	Best CTC pct chg	-0.0811	0.5639
Low NE & PSMA Expression	Best PSA pct chg	-0.3878	0.0093*
Low NE & PSMA Expression	Best CTC pct chg	-0.2615	0.0986

* P <.05

Patients Beyond 4 Cycles	
Dose	**Percent**
2.3 mg/kg	38.8%
2.5 mg/kg	23.5%

Best Overall Response (RECIST 1.1)		
Total Evaluable Patients n=50	n	Percent
Progressive Disease	8	16%
Stable Disease	42	84%

- At 6 months follow-up, overall survival is 86% (Kaplan Meier analysis)

Reason for Discontinuation	2.3 mg/kg (n=46)	2.5 mg/kg (n=34)
Adverse event	14 (28.6%)	8 (23.5%)
Disease progression	23 (46.9%)	15 (44.1%)
Patient request	4 (8.2%)	8 (23.5%)

Adverse Events Grade 3 and Above*

	2.3 mg/kg (n=49) Grades 3 and above		2.5 mg/kg (n=34) Grades 3 and above	
Event	n	%	n	%
Fatigue	9	18.4	7	20.6
Neutropenia	9	18.4	11	32.4
Decreased electrolytes	5	10.2	7	20.6
Neuropathy peripheral	4	8.2	2	5.9
Anaemia	4	8.2	3	8.8
Dehydration	3	6.1	1	2.9
Asthenia	3	6.1	2	5.9
Muscular weakness	2	4.1	1	2.9
Nausea	2	4.1	0	0.0
Diarrhoea	2	4.1	0	0.0
Dyspnoea	1	2.0	2	5.9
Abdominal pain	1	2.0	1	2.9
Sepsis/Septic Shock‡	0	0.0	2	5.9
Myalgia	0	0.0	1	2.9
Pain	0	0.0	1	2.9
Arthralgia	0	0.0	1	2.9

* Possibly related or greater

‡ 2 deaths occurred at 2.5 mg/kg from sepsis associated with neutropenia

Conclusions

- In taxane-experienced mCRPC treated with PSMA ADC at doses of 2.3 mg/kg, reductions of PSA ≥30% are seen in ~36% and reductions of ≥50% are seen in ~15% of patients
- CTC conversion from unfavorable to favorable occurs in ~45% of patients
- PSMA expression both by IHC and CTC correlates well to PSA and CTC response
- Low NE markers correlate well to PSA response with CTC reduction of >50% in 76% of patients
- 2.3 mg/kg is generally well tolerated and appears to be better tolerated than 2.5 mg/kg; most common AE's are fatigue and neutropenia
- A taxane-naïve cohort is ongoing

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