F6-ABS126

Effects of ADXS-PSA in Combination With Pembrolizumab on Survival in Metastatic,Castration-Resistant Prostate Cancer Patients With or Without Prior Exposure to Docetaxel

Mark N. Stein[1], Lawrence Fong[2], Ronald Tutrone[3], Anthony Mega[4], Elaine T. Lam[5], Surya Vangala[6], Megan Parsi[6], John W. Heyburn[6], Andres Gutierrez[6], Naomi Haas[7]

[1]Columbia University Medical Center, New York, NY; [2]University of California, San Francisco, CA; [3]Chesapeake Urology Research Associates, Towson, MD; [4]Lifespan Oncology Clinical Research, Rhode Island Hospital, Providence, RI; [5]University of Colorado Cancer Center, Aurora, CO; [6]Advaxis, Princeton, NJ; [7]University of Pennsylvania, Philadelphia, PA

INTRODUCTION

PROSTATE CANCER AS A CANDIDATE FOR IMMUNOTHERAPY

- According to estimates by the National Cancer Institute, in 2019 there were approximately 174,650 new cases of prostate cancer (PC) and 31,620 deaths from the disease.
- An estimated 22% of patients in the United States diagnosed with prostate cancer have locally advanced or metastatic disease at presentation.
- Patients with metastatic disease at diagnosis who are treated with androgen deprivation therapy (ADT) often develop a castration-resistant phenotype within 1-3 years (i.e., metastatic castration-resistant prostate cancer, mCRPC). Visceral metastasis is found in approximately 22%-30% of patients with mCRPC and are associated with unfavorable outcomes.
- First-line treatment of mCRPC with visceral metastasis includes the use of chemotherapy (i.e., docetaxel mitoxantrone) or next generation hormonal agents (NGHAs, e.g., enzalutamide, abiraterone). Second-line therapy includes crossover to either one of these agents, cabazitaxel, pembrolizumab for microsatellite instability high (MSI-H) or dMMR, best supportive care (BSC), or clinical trial.
- Clinical outcomes of mCRPC patients who have failed docetaxel include:
  - Median overall survival (mOS) in patients with predominantly bone disease (i.e., ≤ 25% patients with visceral metastasis) who have progressed on NGHA:
    - ~ 8.2-13.6 m with cabazitaxel[1,2,3]
    - 14.1 m with pembrolizumab[4]
  - mOS in patients with predominantly visceral metastasis who:
    - Have not yet received NGHA is 9.5 m with BSC[4] and 13 m with enzalutamide[5]
    - Have progressed on NGHA is 7.9 m and 9.5 m with pembrolizumab alone in PD-LI-negative and -positive, respectively[5]

ADXS-PSA

- ADXS-PSA is a live attenuated *Listeria monocytogenes* (*Lm*)-listeriolysin O (LLO) immunotherapy bioengineered to secrete an antigen adjuvant fusion protein (tLLO-PSA) consisting of a truncated fragment of the listeriolysin (tLLO) fused to human prostate-specific antigen (PSA).[1,2]
  - ADXS-PSA functions as a vector, and is rapidly taken up by antigen-presenting cells (APCs) where expression of full-length human PSA stimulates anti-tumor immune responses.
  - Anti-tumor immunity occurs via several mechanisms, primarily including generation of cytotoxic T lymphocytes (CTLs) targeting PSA. These tumor-specific CTLs can then take advantage of the acute immunologic response to the live vector to facilitate infiltration into the tumor, enabling them to access and destroy tumor cells.
  - In nonclinical studies, ADXS-PSA was found to cause therapeutic regression of tumors that express the PSA antigen. The reduction in tumor growth was directly associated with the induction of PSA-specific immune responses. Furthermore, *Lm*-vectors have shown to exert antitumoral effects at metastatic sites.[6]
  - In this clinical study (Keynote-046), immune correlative analyses in patients with ADXS-PSA monotherapy and with ADXS-PSA + pembrolizumab, have shown T-cell responses against PSA (i.e., 55% and 64% of patients) and antigen spreading (100% and 85% patients, respectively).[7]

PEMBROLIZUMAB

- Checkpoint inhibitor pembrolizumab (Keytruda®) is a high-affinity, IgG4/kappa isotype, humanized anti-PD-1 monoclonal antibody that blocks the binding of programmed cell death protein-1 (PD-1) receptor to its ligands PD-L1 and PD-L2.
- Patient selection by PDL-1 and MSI status and use of pembrolizumab in combination with targeted and hormonal agents are being explored to improve outcomes.

RATIONALE FOR COMBINATION THERAPY WITH ADXS-PSA AND PEMBROLIZUMAB

- Synergistic activity of the combination of ADXS *Lm*-based immunotherapies with PD-1-blocking antibodies has been shown in animal models.[8]
- The magnitude of the PSA-specific T-cell response in ADXS-PSA-treated mCRPC patients is associated with anti-tumor effects, as evidenced by increased T-cell reactivity to PSA and other prostate cancer antigens.[9]
- Correlative immune analyses suggest a broader immune stimulation with ADXS-PSA + pembrolizumab, including T-cell responses against PSA and antigen spreading in most patients.
- Initial results of Part A and Part B of this study were presented at AACR 2019.[10]

OBJECTIVE

- This is a phase 1/2, open-label, multicenter, dose-determining safety and tolerability study with a phase 2 expansion cohort.

PRIMARY

- **Part A:** to evaluate safety and tolerability of ADXS-PSA monotherapy and select the recommended phase 2 dose (RP2D) in patients with mCRPC for use in Part B
- **Part B:** to evaluate safety and tolerability of ADXS-PSA in combination with pembrolizumab and to establish the RP2D for this combination in patients with mCRPC

SECONDARY

- To evaluate anti-tumor activity, overall survival (OS), and progression-free survival (PFS) of ADXS-PSA monotherapy and ADXS-PSA + pembrolizumab combination therapy

EXPLORATORY

- Evaluate correlative immunologic and gene expression profiles

METHODS

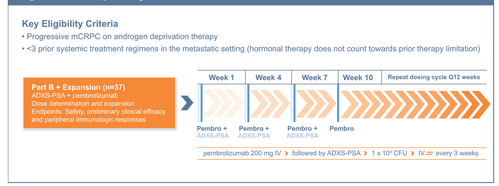
POPULATION

- Patients with progressive mCRPC on androgen deprivation therapy (<3 prior systemic treatment regimens in the metastatic setting) were included. Hormonal therapy did not count towards prior therapy.

PART B COMBINATION THERAPY

- Phase 1/2 dose-determining trial of ADXS-PSA + pembrolizumab
  - Patients were dosed with pembrolizumab 200 mg, IV, followed by ADXS-PSA, 1 x 10^9 CFU, IV, every 3 weeks for up to 24 months or until disease progression or discontinuation.

Figure 1. Study design



RESULTS *

PATIENTS

- A total of 37 patients were treated in Part B with ADXS-PSA + pembrolizumab combination therapy. Table 1 presents information on patient baseline characteristics and prior patient therapies since diagnosis. Of 37 patients in Part B, 36 were negative for microsatellite instability high (MSI-high) status (1 patient was not tested).

Table 1. Patient Population

Baseline Characteristics	(N=37)
Dose, n (%)	RP2D-1 x 10^9 CFU + 200 mg: 37 (100)
Median age, years (min, max)	68.0 (45.0, 92.0)
Time (months) from initial diagnosis to treatment initiation (min, max)	65 (11, 215)
Median Gleason Score (range)	9.0 (6.0, 10.0)
Median PSA, ng/mL (min, max)	41.5 (0.1, 426.3)
ECOG PS, n (%)	
0	18 (48.6)
1	19 (51.4)
Presence of visceral metastases, n (%)	
Yes	11 (30)
No	26 (70)
Prior therapies, n (%)	
1	0 (0)
2	0 (0)
≥ 3	36 (97.3)
Chemotherapy, n (%)	21 (56.8)
Hormonal, n (%)	34 (91.9)
Next generation hormonal agent, n (%)	
Enzalutamide	12 (32.4)
Abiraterone	6 (16.2)
Enzalutamide plus abiraterone	12 (32.4)

* as of January 31, 2020

SAFETY

- Overall, 37 patients (100%) experienced any grade treatment-related adverse events (TRAEs) in Part B.
- The majority of TRAEs consisted of grade 1-2 chills/rigors, fever, hypotension, nausea, and fatigue.
- The combination of ADXS-PSA and pembrolizumab appeared safe and tolerable, with no additive toxicity observed.

Table 2. Treatment-related Adverse Events ≥10% (TRAEs)

TRAE (PT)	All Grades	Grade ≥ 3
Patients with ≥1 TRAE, n (%)	37 (100)	11 (29.7)
TRAEs occurring in ≥10% of patients (Part B), n (%)		
Chills	33 (89.2)	0
Pyrexia	20 (54.1)	1 (2.7)
Nausea	17 (45.9)	0
Fatigue	13 (35.1)	3 (8.1)
Hypotension	8 (21.6)	1 (2.7)
Hypertension	9 (24.3)	6 (16.2)
Anemia	5 (13.5)	3 (8.1)
Decreased appetite	6 (16.2)	0
Hypothyroidism	7 (18.9)	0
Tachycardia	4 (10.8)	0
Vomiting	5 (13.5)	0
Headache	5 (13.5)	0
Diarrhea	4 (10.8)	1 (2.7)
Pain	4 (10.8)	0

Table 3. Treatment-related Serious Adverse Events, Part B (N = 37)

Event, n (%)	All Grades	Grade ≥ 3
Hypertension	2 (5.4)	2 (5.4)
Hypotension	2 (5.4)	0
Acute kidney injury	0	0
Cytokine release syndrome	0	0
Dehydration	1 (2.7)	1 (2.7)
Fatigue	1 (2.7)	1 (2.7)
Infusion-related reaction	1 (2.7)	0
Pneumonitis	1 (2.7)	1 (2.7)
Pyrexia	1 (2.7)	0
Septic shock	0	0
Thrombocytopenia	1 (2.7)	1 (2.7)

EFFICACY

- The best overall response in the evaluable population was stable disease in 21/29 (72.4%) evaluable patients (Table 4)
- The median overall survival observed (mOS) for all patients in Part B was 33.7 months (95% CI, 15.4-NR) (Figures 2-3).
  - mOS for patients with prior docetaxel was 16 months (95% CI, 6.4-34.6); 15/20 patients had received 1 or 2 prior NGHA.
  - mOS for patents with prior visceral metastasis was 16. 4 months (95% 4.0-NR); 10/11 patients had had prior docetaxel and 9 had prior NGHAs (Table 5).
- 14/37 (38%) patients had PSA declines and 9/37 (24%) had ≥ 30% PSA decline from baseline
- 5/11 (45%) patients with visceral metastasis had PSA declines and 3/11 (27%) had ≥ 30% PSA decline from baseline
- Stable disease and/or prolonged overall survival were observed in patients regardless of microsatellite stable status, prior therapies, presence of visceral metastasis, or PSA change <30% or ≥30% (Figure 4, Table 5).

Table 4. Best Overall Response Using RECIST v1.1 With Confirmation of CR and PR

	Part B
Patients treated, N	37
NE, n (%)	6 (17)
ORR population, n	29
CR, n (%)	0 (0)
PR, n (%)	0 (0)
SD, n (%)	21 (72.4)
PD, n (%)	8 (27.5)

CR=complete response; NE=not evaluable; ORR=overall response; PD=progressive disease; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors.

Figure 2. Median overall survival for all patients and those with or without prior exposure to docetaxel.

	N	Events	Median	95% CI
Overall	37	16	33.7	15.4-NR
No docetaxel	17	3	NR	15.1-NR
Post-docetaxel	20	13	16.0	6.4-34.6

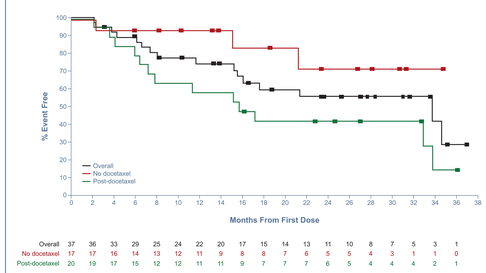


Figure 3. Median overall survival for patients based on prior visceral metastasis status.

	N	Events	Median	95% CI
Overall	37	16	33.7	15.4-NR
Prior visceral metastasis	11	6	16.4	4.0-NR
Without prior visceral metastasis	26	10	33.7	15.1-NR

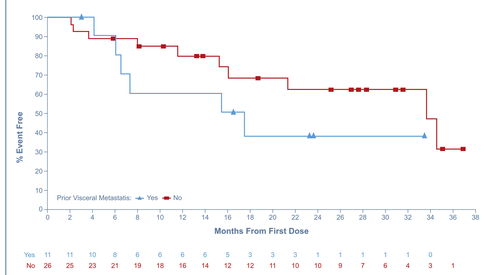


Figure 4. Event chart for tumor response, tumor progression, duration of therapy, and death (all-treated population: ADXS-PSA and pembrolizumab combination therapy).

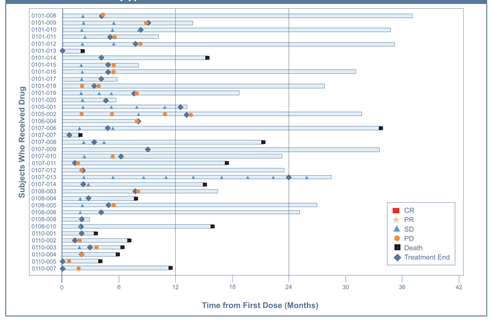


Table 5. Relationship Between Survival, Prior Therapy and PSA Decline in Patients With Visceral Metastasis

		Prior Therapies				
Patient ID	Documented survival, months*	Docetaxel	Enzalutamide	Abiraterone	Enzalutamide and Abiraterone	% PSA change from baseline
0108008	2.9+	Yes	Yes	No	No	1681.8
0110005	4.0	Yes	Yes	No	No	3881.5
0110004	5.9	Yes	No	Yes	No	836.4
0110003	6.4	Yes	No	No	Yes	-11.4
0110002	7.2	Yes	No	Yes	No	-22.2
0101014	15.4	Yes	Yes	No	No	-47.5
0108003	16.4+	Yes	Yes	No	No	-83.0
0107011	17.4	Yes	No	No	Yes	1105.3
0107010	23.3+	Yes	Yes	No	No	244.1
0107012	23.6+	No	No	No	No	140.4
0107009	30.5+	Yes	No	No	No	-55.8

CONCLUSIONS

- The combination of ADXS-PSA and pembrolizumab appeared safe and tolerable in this heavily pretreated, unselected population of patients with MSI-H-negative mCRPC
  - Treatment-related adverse events were mostly grade 1-2 chills/rigors, fever, hypotension, nausea, and fatigue.
  - No additive toxicity was observed with the combination therapy.
- The combination of ADXS-PSA and pembrolizumab appears to show activity in mCRPC and might be associated with prolonged OS in this population, particularly in patients with visceral metastasis:
  - Median OS for all population (95% CI) = 33.7 months (15.4-NR)
    - In patients without prior docetaxel (n=17) = not reached (15.1-NR)
    - In patients with prior docetaxel (n=20) = 16 (6.4-34.6)
    - In patients with prior visceral metastasis (n=11) = 16.4 (4.0-NR)
  - 72% (21/29) of ORR evaluable patients had stable disease
  - 38% (14/37) patients had PSA declines and 24% (9/37) had ≥ 30% PSA decline from baseline
- The potential survival signal seen when using the combination of ADXS-PSA with pembrolizumab in mCRPC patients deserves further evaluation, particularly in those patients with visceral metastasis.

REFERENCES

1. Sella A, et al. Clin Genitourin Cancer. 2014,12:428.
2. Al Nakouzi N, et al. Eur Urol. 2015, 68:228.
3. De Witt R, et al. NEJM. 2019, 381:2506.
4. Loriot Y, et al. Cancer 2017, 123:253.
5. Antonarakis ES, et al. JCO 2019, 38:395.
6. Vitiello M, et.al. Oncogene 2019, 38:375.
7. Hayes SM, et.al. Keystone Symposium. 2019.
8. Bongiorno EK, et al. AACR Conference on Tumor Immunology and Immunotherapy, October 1-4, 2017, Boston, MA. Abstract B15.
9. Hayes SM, et al. Society for Immunotherapy of Cancer Annual Meeting, November 10-12, 2017, National Harbor, MD. Poster P2.
10. Stein MN, et al. American Association Cancer Research (AACR) Annual Meeting. 2019.

DISCLOSURES

Author disclosures are on file and centrally located on the ASCO website.

The authors thank DNA Digital Group LLC for their editorial assistance.

Presented at the Genitourinary Cancers Symposium. February 13-15, 2020, San Francisco, CA.