A Phase 2 Study of Vudalimab, a PD-1 × CTLA-4 Bispecific Antibody, Plus Chemotherapy or Targeted Therapy in Patients With Molecularly Defined Subtypes of Metastatic Castration-Resistant Prostate Cancer

Mark N. Stein,[1] Oscar B. Goodman Jr,[2] Tanya B. Dorff,[3] Vivek Narayan,[4] Jose Avitia,[5] Rana R. McKay,[6] Luke Nordquist,[7] Matthew Rettig,[8] Michael T. Schweizer,[9] Roby A. Thomas,[10] Michael H. Silverman,[11] Li Yao,[12] Raphael Clynes,[12] Jolene S Shorr[12]

[1]Division of Hematology and Oncology, Herbert Irving Comprehensive Cancer Center, Columbia University Irving Medical Center, New York, NY; [2]Comprehensive Cancer Centers of Nevada, Las Vegas, NV; [3]City of Hope Comprehensive Cancer Center, Duarte, CA; [4]Hospital of the University of Pennsylvania, Philadelphia, PA; [5]New Mexico Oncology Hematology Consultants, Albuquerque, NM; [6]University of California, San Diego, La Jolla, CA; [7]Urology Cancer Center, Omaha, NE; [8]VA Greater Los Angeles Healthcare System, Los Angeles, CA; [9]University of Washington/Fred Hutchinson Cancer Center, Seattle, WA; [10]University of Pittsburgh Medical Center, Hillman Cancer Center, Pittsburgh, PA; [11]Biostrategics, Ltd., Marblehead, MA; [12]Xencor, Inc., Monrovia, CA

Background

- Vudalimab (XmAb20717) is a humanized bispecific monoclonal antibody that simultaneously targets PD-1 and CTLA-4, and binds preferentially to PD-1/CTLA-4 dual-positive cells
- Preliminary data from a Phase 1 study of vudalimab monotherapy in patients with advanced solid tumors[1] indicate a dose of 10 mg/kg Q2W was
  - Generally well tolerated – rash, pruritus, and increased transaminases were the most common irAEs
  - Associated with complete and partial responses (PRs) in patients with melanoma, RCC, and NSCLC, as well as mCRPC, a tumor type not typically responsive to single-agent checkpoint inhibition
- The durability of responses in the mCRPC patients (PRs in 2 of 4 mCRPC patients with measurable disease) was notable – 41.3 and 27 weeks
  - Both patients were without progression on bone scans, and had confirmed PSA decreases ≥ 50% following treatment
- Dual PD-1/CTLA-4 blockade previously has been shown to improve outcomes in patients with mCRPC relative to those observed for agents directed at a single checkpoint[2]
- Additional strategies to optimize response to immune checkpoint inhibitor (ICI) therapy in patients with mCRPC include
  - Selection of patients with tumor molecular characteristics that sensitize to ICIs, including those associated with aggressive variant disease,[3] CDK12 inactivation,[4,5] and microsatellite instability-high (MSI-H) or mismatch repair-deficient (MMRD) status[6]
  - Altering the tumor microenvironment to promote antitumor immunity by combining ICIs with chemotherapy or targeted agents[7]
- This Phase 2, multicenter, parallel-group, open-label study (NCT05005728) is designed to evaluate the safety and antitumor activity of vudalimab in combination with other anticancer agents in subgroups of mCRPC patients with and without specific tumor molecular subtypes
- We report preliminary data on the first 9 patients enrolled in the study, with a focus on safety in the first 8 patients treated with vudalimab in combination with carboplatin and either cabazitaxel or docetaxel

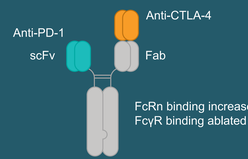


Figure 1. Vudalimab PD-1 × CTLA-4 bispecific monoclonal antibody

Scan the QR code to download an electronic version of the poster. The QR code is intended to provide scientific information for individual reference. The PDF should not be altered or reproduced in any way.

Methods

Study Objectives

- Primary
  - Evaluate the safety and tolerability of vudalimab alone and in combination with other anticancer therapies in patients with mCRPC
- Secondary
  - Characterize PK and immunogenicity of vudalimab
  - Assess antitumor activity of vudalimab alone and in combination with other anticancer agents, based on biochemical response, rPFS (RECIST v 1.1, as modified by PCWG3), objective response rate, duration of response
- Exploratory
  - Characterize pharmacodynamics, based on cell surface markers on selected immune system cells in peripheral blood
  - Assess changes in immune cell density and intratumoral and juxta-tumoral immune and tumor cell expression of PD-L1, PD-1, and other immune checkpoint markers
  - Correlate clinical response with tumor and circulating tumor DNA mutation profiles, interferon transcriptional signature, and immune profiling characteristics of cells in the tumor microenvironment by transcriptomic analysis of tumor tissue
  - Correlate clinical responses with specific genetic defects of molecularly defined cohorts

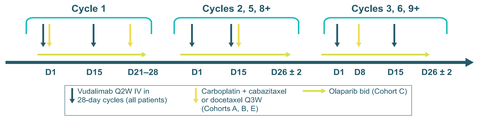
Figure 2. Molecular Cohorts and Treatment

Study Population	Cohort	Treatment
• mCRPC with documented progression (PSA, soft-tissue, or bone disease) after ≥ 2 prior lines of anticancer therapy in metastatic setting • Documented targeted or whole exome sequencing of metastatic tumor	**Cohort A (n = 20)** Aggressive Variant Prostate Cancer (≥ 2 RB1, TP53, PTEN Alterations)	**Vudalimab + Carboplatin + Cabazitaxel**
	Cohort B (n = 20) Prior PARPi Progressor ≥ 1 Homologous Recombination Deficiency or CDK12	**Vudalimab + Carboplatin + Cabazitaxel**
	Cohort C (n = 20) PARPi Naïve ≥ 1 Homologous Recombination Deficiency or CDK12	**Vudalimab + Olaparib**
	Cohort D (n = 5) MSI-High or MMRD Cohort E (n = 20) No Targetable Mutations	**Vudalimab Monotherapy**
	Cohort E (n = 20) No Targetable Mutations	**Vudalimab + Carboplatin + Cabazitaxel**

Cohorts A, B, and E – vudalimab 10 mg/kg Q2W + carboplatin AUC4 IV Q3W + cabazitaxel 20 mg/m² (or docetaxel 60 mg/m², if docetaxel naïve) Q2W
Cohort C – vudalimab 10 mg/kg Q2W + olaparib 300 mg twice daily
Cohort D – vudalimab 10 mg/kg Q2W

- Treatment may continue until patient no longer deriving clinical benefit or adverse event warranting treatment withdrawal
- Dose reductions of chemotherapy for adverse events per standard practice
- Maximum 8 cycles of carboplatin permitted
- Planned safety review of subset of patients across vudalimab + chemotherapy cohorts

Figure 3. Study Schema



- CT/MRI and bone scan at screening, every 8 weeks for 28 weeks, and every 12 weeks thereafter
- PSA at baseline, end of Cycle 1, and every 8 weeks thereafter
- Tumor biopsy at screening (optional if archival tissue available) and end of Cycle 1 (optional)

bid, twice daily; CT, computed tomography; D, day; IV, intravenous; MRI, magnetic resonance imaging; Q2W, every 2 weeks; Q3W, every 3 weeks.

Table 1. Key Entry Criteria

Inclusion	Exclusion
• Histologically confirmed diagnosis of carcinoma of the prostate	• Currently receiving anticancer therapies, other than ADT
• Documented progressive mCRPC based on ≥ 1 of the following – PSA progression (≥ 2 rises with a ≥ 1-week interval)* – Soft-tissue progression per RECIST 1.1 – Progression of bone disease or ≥ 2 new bone lesions by bone scan	• Other anticancer therapy within 2 weeks prior to start of study treatment • Prior treatment with any CTLA-4, PD-1, • PD-L1, or PD-L2-directed immunotherapy (except Cohort D) • Grade 4 immune-mediated adverse event related to prior immunotherapy (Cohort D only) • Failure to recover from any toxicity related to previous anticancer treatment to Grade 2 or lower • Known, active CNS metastases and/or carcinomatous meningitis • Active known or suspected autoimmune disease • Active infection • Hemoglobin ≤ 9.0 g/dL, platelet count < 100 × 10^9/L, ANC < 1.0 × 10^9/L (≤ 1.7 × 10^9/L for patients who will receive cabazitaxel)
• Disease progression after ≥ 2 prior lines of anticancer therapy approved for treatment of metastatic prostate cancer[8]	
• In the absence of surgical orchiectomy, must be on and continue androgen suppression treatment throughout the study	
• Documented cohort-specific genetic features in metastatic tissue	
• Evaluable disease, based on PCWG3 criteria	
• Adequate archival metastatic tumor tissue or agree to biopsy of metastatic tumor site	
• ECOG 0 or 1	

Conclusions

- Review of safety data from 8 patients treated with vudalimab + carboplatin + cabazitaxel or docetaxel indicated tolerability issues with this combination
- The protocol will be amended to restrict carboplatin and taxane in combination with vudalimab to patients with aggressive variant disease, and use single-agent taxane therapy in combination with vudalimab in the remaining chemotherapy cohorts
- Enrollment into chemotherapy cohorts will restart following implementation of the amended protocol with the revised regimens
- The vudalimab + olaparib and vudalimab monotherapy cohorts remain open for enrollment

Acknowledgments

With gratitude to the patients, their families, and caregivers and the XmAb20717-04 investigational study teams for support in the conduct of this research. This study is sponsored by Xencor, Inc. Medical writing and editorial support was provided by Parexel and funded by Xencor, Inc.

References

1. Shum E, et al. *J Immunother Cancer*. 2021;9:A553.
2. Sharma P, et al. *Cancer Cell*. 2020;38:489–499.
3. Aparicio AM, et al. *Clin Cancer Res*. 2016;22:1520–1530.
4. Antonarakis ES, et al. *JCO Precis Oncol*. 2020;4:370–381.
5. Wu YM, et al. *Cell*. 2018;173:1770–1782.
6. Abida W, et al. *JAMA Oncol*. 2019;5:471–478.
7. Picardo SL, Hansen AR. *Ann Transl Med*. 2019;7:346.

Results

Table 2. Demographics and Baseline Characteristics

Patient	Cohort	Age (years)	Mt at Diagnosis	ECOG PS	> 3 Lines Prior Systemic Therapy	Prior Chemotherapy	Prior Radiation Therapy
40101	AVPC	68	Yes	1	Yes	Yes	Metastasis
40102	AVPC	58	Yes	0	No	No	None
40201	PARPiP HRD	53	Yes	0	Yes	Yes	None
40301	PARPiN HRD	69	No	1	NR	NR	NR
40501	NTM	69	Yes	0	Yes	Yes	Metastasis
40502	NTM	68	No	0	Yes	Yes	Primary
40503	NTM	68	No	0	No	No	Primary
40504	NTM	65	No	1	No	Yes	Metastasis
40505	NTM	63	Yes	1	No	No	Primary

Data cut September 7, 2022.
AVPC, aggressive variant prostate cancer; PARPiN HRD, PARPi-naïve homologous recombination deficient; PARPiP HRD, PARPi progressor homologous recombination deficient; NR, not recorded in database; NTM, no targetable mutation.

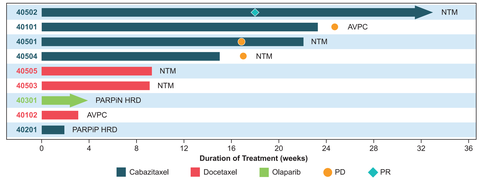
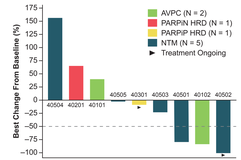


Figure 4. Time on treatment with vudalimab + carboplatin + cabazitaxel (blue lines) or + docetaxel (red lines) or vudalimab + olaparib (green lib).

Arrows indicate treatment ongoing as of the data cut. Data cut September 7, 2022.
AVPC, aggressive variant prostate cancer; PARPiN HRD, PARPi-naïve homologous recombination deficient; PARPiP HRD, PARPi progressor homologous recombination deficient; NTM, no targetable mutation; PD, progressive disease; PR, partial response.

Preliminary Clinical Activity



3 patients have had decreases in PSA from baseline ≥ 50%

- 40102 – 27.9 to 4.7 ng/mL at end of Cycle 1 and 9.2 ng/mL ~8 weeks after end of treatment
- 40501 – 110.8 to 23.2 ng/mL at end of Cycle 3, increasing to 83.4 ng/mL at ~24 weeks
- 40502 – 828.9 to 90.5 ng/mL at end of Cycle 1, and persistently low (0.97 ng/mL) through continuing treatment at ~35 weeks

Figure 5. Best percentage change from baseline in prostate specific antigen over time.

Data cut September 7, 2022.

Table 3. Investigator Assessment of Best Overall Response

Patient	Cohort	Best Overall Response (RECIST v 1.1)
40101	AVPC	SD
40102	AVPC	SD
40201	PARPiP HRD	Non-CR/non-PD
40501	NTM	SD
40502	NTM	PR
40503	NTM	SD
40504	NTM	SD

Note: Patient 40301 had insufficient follow-up at the time of the data cut for response assessment; response assessment not available for Patient 40505. Data cut September 7, 2022. AVPC, aggressive variant prostate cancer; CR, complete response; NTM, no targetable mutation; PARPiP HRD, PARPi progressor homologous recombination deficient; PD, progressive disease; PR, partial response; SD, stable disease.Dx

Safety

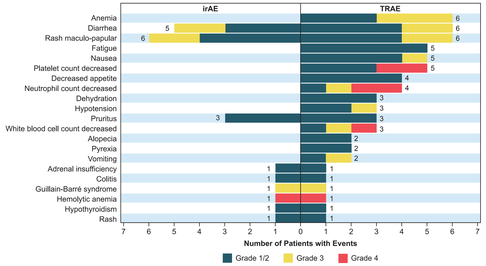


Figure 6. Treatment-related adverse events (TRAE; i.e., events attributed by the investigator to any component of combination therapy) reported for ≥ 2 of the 8 patients treated with vudalimab + chemotherapy or any immunotherapy-related adverse event (irAE; as determined by the sponsor) by maximum CTCAE grade.

No irAEs or TRAEs were reported for the patient who received vudalimab + olaparib. Data cut September 7, 2022. CTCAE, Common Terminology Criteria for Adverse Events.

- Treatment-related serious adverse events (SAEs) occurring within the first cycle of therapy were reported for 5 of the 8 patients treated with vudalimab + chemotherapy
  - Vomiting (Grade 3), maculopapular rash (Grade 2), and colitis (Grade 2) in 1 patient, and sepsis (Grade 3), Guillain-Barré syndrome (Grade 3), nausea (Grade 3), and diarrhea (Grade 2) in 1 patient each
  - An additional patient had Grade 3 maculopapular rash, diarrhea, and leukocytosis (not meeting SAE criteria) within the first cycle of therapy
  - Other treatment-related SAEs included decreases in platelet and neutrophil counts (Grade 4), sinusitis, febrile neutropenia, and anemia (Grade 3) in 1 patient, and hemolytic anemia (Grade 4) in 1 patient
- All events resolved with medical management, including steroids where appropriate, and/or interruption or cessation of study therapy
- Overall, 4 patients had adverse events resulting in discontinuation of study treatment
- With the exception of Guillain-Barré syndrome (a rare event associated with ICI therapy), the types of irAEs observed in these patients generally are consistent with vudalimab experience at a dose of 10 mg/kg from the Phase 1 monotherapy study (n = 110)[1]
- A decision to change the vudalimab + chemotherapy regimen was prompted by the frequency, severity, and incidence in these 8 patients of treatment-related serious and/or severe adverse events leading to discontinuation of treatment
- The investigators and sponsor agreed to retain the vudalimab dose, and modify the chemotherapy regimen before proceeding with further enrollment into chemotherapy cohorts

Table 4. Treatment by Cohort With Revised Chemotherapy Regimens

Cohort	Regimen	Vudalimab Dose	Combination Therapy Dose
A: Aggressive variant (≥ 2 RB1, TP53, PTEN alterations)	Vudalimab + carboplatin + taxane	10 mg/kg Q2W	**Starting dose** Carboplatin AUC3 Cabazitaxel 15 mg/m² or docetaxel 50 mg/m²* **Target dose (Cycle 2+) Q3W†** Carboplatin AUC4 Cabazitaxel 20 mg/m² or docetaxel 60 mg/m²*
B: PARPi progressor - HRD/CDK12 biallelic loss E: No targetable mutation	Vudalimab + taxane	10 mg/kg Q2W	Cabazitaxel 20 mg/m² or docetaxel 75 mg/m²* Q3W†
C: PARPi Naïve – HRD/ CDK12 biallelic loss	Vudalimab + olaparib	10 mg/kg Q2W	Olaparib 300 mg twice daily
D: MSI-H or MMRD	Vudalimab monotherapy	10 mg/kg Q2W	

*If docetaxel naïve. †Dose reductions of chemotherapy for adverse events per standard practice; for patients in Cohort A, maximum 8 cycles of carboplatin permitted.

Presented at the Society for Immunotherapy of Cancer Annual Meeting; November 8–12, 2022; Boston, MA and Virtual