A Phase 2 Study of Vudalimab (XmAb®20717), an Anti-PD-1/CTLA-4 Bispecific Antibody, in Patients With Selected Gynecological Malignancies and High-Risk Metastatic Castration-Resistant Prostate Cancer

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Background

Vudalimab (XmAb20717) is a humanized bispecific monoclonal antibody (Figure 1) that simultaneously targets programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) and binds preferentially to PD-1/CTLA-4 dual positive cells

In a Phase 1 study of vudalimab, the recommended Phase 2 dose was 10 mg/kg intravenously every 2 weeks, which was generally well tolerated, with rash, pruritus, and increased transaminases being the most frequently reported immune-related adverse events. The overall response rate (ORR) for patients receiving 10 mg/kg (n = 78; efficacy evaluable) was 14.1%, with responses seen in several solid tumor types, primarily in checkpoint inhibitor–experienced patients. Responses were also seen in metastatic castration-resistant prostate cancer (mCRPC; 2 partial responses) and ovarian cancer (1 complete response)[1]

These tumor types are typically not responsive to single-agent immune check point inhibitor (ICI) therapy, but responses have been observed when anti–PD-1 and anti–CTLA-4 therapies have been combined

Blocking both PD-1 and CTLA-4 may be an effective treatment strategy for patients with advanced epithelial ovarian cancer, including high-grade serous ovarian cancer (HGSOC), clear cell carcinoma (CCC),[2] advanced cervical cancer,[3,4] and mCRPC[5]

Objectives

Primary Objective

- To assess the preliminary antitumor activity of vudalimab using ORR per Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1 and Prostate Cancer Working Group 3 for the mCRPC cohort

Secondary Objectives

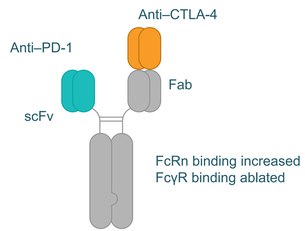
- To assess antitumor activity based on best observed response, duration of response (DOR), progression-free survival, and overall survival, as well as biochemical response in the mCRPC cohort
- To characterize the pharmacokinetics of vudalimab
- To evaluate the safety and tolerability of vudalimab

Exploratory Objectives

- To establish potential biomarkers associated with clinical response
- To explore pharmacodynamic effects in peripheral blood and tumor tissue and their association with clinical response

Background and Study Schema

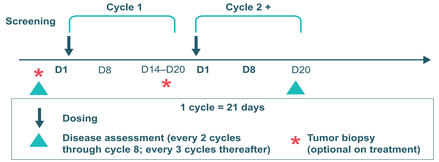
Figure 1. Vudalimab-PD-1 × CTLA-4 bispecific monoclonal antibody



Fab, fragment, antigen-binding; Fc, fragment, crystallizable; FcγR, Fc gamma receptor; FcRn, neonatal Fc receptor; scFv, single-chain variable fragment (immunoglobulin fusion protein).

- Pharmacokinetic modeling of Phase 1 study data was used to establish a flat-dose regimen of vudalimab that extends dosing to 3-week intervals
  - 1200 mg (body weight ≥ 80 kg) or 1000 mg (body weight < 80 kg) every 3 weeks (Q3W; **Figure 2**)

Figure 2. Study schema



Vudalimab is administered intravenously at 1200 mg (body weight ≥ 80 kg) or 1000 mg (body weight < 80 kg) Q3W until disease progression, unacceptable toxicity, or consent withdrawal. A starting dose of 1000 mg may be increased to 1200 mg starting with the fourth dose at the investigator's discretion in the absence of Grade ≥ 2 immune-related adverse events. D, day.

Acknowledgments

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References

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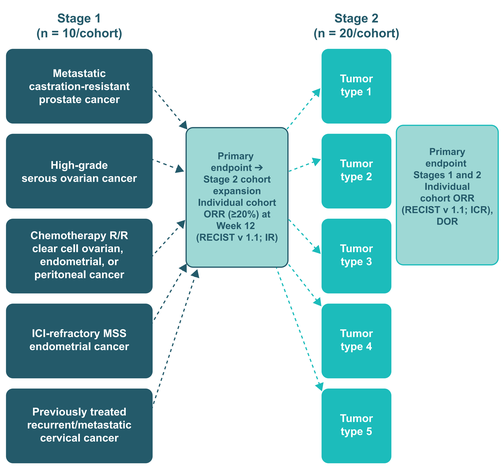
Study Details

This Phase 2, multicenter, 2-stage, parallel-group, open-label study (NCT05032040) is designed to evaluate the safety and antitumor activity of vudalimab in selected gynecologic tumor types and high-risk mCRPC (**Figure 3**)

Figure 3. Study design



ICR, independent central review; IR, investigator review; R/R, relapsed or refractory.

Study Status and Sites

- Approximately 13 sites in the United States will participate
- Enrollment is currently ongoing at the following sites:
  - Columbia University Irving Medical Center: June Y. Hou, MD
  - Valkyrie Clinical Trials: David Berz, MD, PhD, MPH
  - Emory University School of Medicine: Jacqueline Brown, MD
  - Comprehensive Cancer Centers of Nevada: Oscar Goodman, MD
  - Karmanos Cancer Institute: Ira Winer, MD, PhD, FACOG

Table 2. Key Inclusion and Exclusion Criteria

Inclusion Criteria

Histologically confirmed diagnosis of one of the following tumor types:
• Persistent or recurrent HGSOC or CCC after treatment with platinum-based systemic chemotherapy
• Microsatellite stable (MSS)/mismatch repair proficient advanced endometrial cancer (EC; not eligible for curative surgery or radiation) that has progressed following 1 line of systemic therapy and combination therapy (ICI and a targeted agent)
• Recurrent or metastatic cervical carcinoma previously treated with chemotherapy and immunotherapy
• High-risk mCRPC
  ◦ Castration resistance defined as progressive disease after surgical castration, or medical androgen ablation with testosterone level < 50 ng/dL
  ◦ High risk defined as presence of any visceral, soft tissue, or lymph node metastases with or without bone metastases

Measurable disease by RECIST v 1.1
Adequate archival tumor tissue or pre-dose fresh tumor biopsy tissue
Eastern Cooperative Oncology Group performance status of 0 or 1
Exclusion Criteria
Patients currently receiving anticancer therapies other than luteinizing hormone-releasing hormone in patients with mCRPC
More than 2 prior chemotherapy regimens for patients in the cervical cancer, CCC, HGSOC, or mCRPC cohorts
Prior treatment with CTLA-4, PD-1, programmed death-ligand 1– or programmed death-ligand 2–directed therapy (except for MSS EC or cervical cancer)
Other anticancer therapy within 2 weeks prior to start of study treatment
Grade 4 immune-mediated adverse event associated with prior immunotherapy
Failure to recover from any immunotherapy-related toxicity related to prior anticancer therapy to Grade ≤ 1
Failure to recover (to Grade ≤ 2) from any toxicity related to previous anticancer treatment
Known, active central nervous system metastases and/or carcinomatous meningitis
Active known or suspected autoimmune disease
Active infection
Laboratory tests indicating inadequate bone marrow, liver, or kidney function

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