

A PHASE 2 STUDY OF VUDALIMAB, A PD-1 X CTLA-4 BISPECIFIC ANTIBODY, PLUS CHEMOTHERAPY OR TARGETED THERAPY IN PATIENTS WITH MOLECULARLY DEFINED SUBTYPES OF METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

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Background Immune checkpoint inhibitor (ICI) monotherapy generally has shown limited clinical benefit in unselected patients with metastatic castration-resistant prostate cancer (mCRPC); thus, strategies to improve response and/or identify patients more likely to respond to treatment are being investigated. Combination anti-PD-1/CTLA-4 therapy has shown better outcomes than either therapy alone. Altering the tumor microenvironment to promote antitumor immunity by combining ICIs with chemotherapy or targeted agents also has potential to increase clinical benefit. Finally, tumors with selected molecular characteristics, including those associated with aggressive variant disease, CDK12 inactivation, and microsatellite instability high (MSI-H) status, have shown increased sensitivity to ICIs. 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. In a Phase 1 study, vudalimab monotherapy was generally well-tolerated and associated with complete and partial responses in patients with multiple tumor types, including mCRPC.¹ This Phase 2 study is designed to evaluate the safety and antitumor activity of vudalimab in combination with other anticancer agents or alone in mCRPC patients with and without specific tumor molecular subtypes.

Methods This multicenter, open-label study is being conducted at approximately 20 sites in the United States. Patients with mCRPC that progressed following treatment with ≥ 2 lines of therapy are enrolled into parallel cohorts based on the presence or absence of molecular abnormalities from prior sequencing reflecting the metastatic state: aggressive variant (Cohort 1), homologous recombination deficient or CDK12 mutation positive PARP inhibitor progressor (Cohort 2) or PARP inhibitor naïve (Cohort 3), MSI-H or mismatch repair deficient (Cohort 4), and no targetable mutation (Cohort 5). Patients receive vudalimab 10 mg/kg intravenously every 2 weeks plus either carboplatin AUC 4/cabazitaxel 20 mg/m² (or docetaxel 60 mg/m², if chemotherapy naïve) every 3 weeks (Cohorts 1, 2, 5; n=20 each) or olaparib 300 mg 2x/day (Cohort 3; n=20), or as monotherapy (Cohort 4; n=5). The study includes review of data from a subset of combination chemotherapy patients by a safety review committee. The primary objective of the study is to evaluate the safety/tolerability of treatment based on adverse events. Secondary objectives include evaluating objective response (RECIST 1.1, as modified by PCWG3), radiographic progression-free survival, and PSA response. Exploratory objectives include assessing pharmacodynamic activity in peripheral blood and tumor, and

correlations of response with cohort-specific molecular tumor characteristics.

Results Enrollment is underway, and initial safety data review has been completed. Preliminary safety and activity data will be presented.

Trial Registration NCT05005728

REFERENCE

1. Shum E, Reilley M, Najjar Y, et al. Preliminary clinical experience with XmAb20717, a PD-1 x CTLA-4 bispecific antibody, in patients with advanced solid tumors. *J Immunother Cancer*. 2021;9: doi: 10.1136/jitc-2021-SITC2021.523.

Ethics Approval The study was approved by each institution's IRB.

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