A pilot presurgical trial of REGN5678 (Anti-PSMAxCD28) in patients with high-risk, localized prostate cancer followed by radical prostatectomy

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Abstract:

Background: The prostate tumor microenvironment (TME) is highly immunosuppressive, characterized by a low tumor mutational burden and neoantigen load associated with few intratumoral effector T cells. Accordingly, low response rates have been observed with single-agent immune checkpoint therapies. The T cell bispecific antibody REGN5678, which co-targets the prostate specific membrane antigen (PSMA) on tumor cells and the CD28 costimulatory domain on T cells, has demonstrated promising efficacy in metastatic castration-resistant prostate cancer (mCRPC) in combination with cemiplimab (anti-PD-1), with grade ≥3 immune-mediated adverse reactions observed in participants with anti-tumor activity (NCT03972657). There are unmet needs to understand mechanisms of response and resistance to REGN5678 within the prostate TME to: (1) identify predictive biomarkers to optimize patient selection and (2) develop rational combinatorial approaches to improve efficacy. To achieve these goals, we designed a presurgical clinical trial to enable evaluation of whole tumor specimens for immune monitoring analyses.

Hypothesis: In patients with high-risk, localized prostate cancer appropriate for surgery, REGN5678 monotherapy will have an acceptable safety profile.

Methods: This is a single center, open-label, presurgical study to determine the safety and tolerability of REGN5678 in patients with high-risk localized prostate cancer appropriate for radical prostatectomy, with no evidence of distant metastatic disease by technetium-99m bone scan and computed tomography. The primary objectives of the study are to evaluate safety and tolerability of REGN5678 in patients with high-risk, localized prostate cancer. The secondary objectives of the study are to assess the proportion of patients who achieve pathological complete response with REGN5678. The exploratory objectives include evaluation of: immune responses in the prostate TME and peripheral blood after treatment with REGN5678 compared to untreated control samples and exploratory imaging biomarkers by PSMA PET/CT. REGN5678 will be dosed IV weekly for a total of six doses prior to surgery. The study will employ a Time-to-event Bayesian optimal interval (TITE-BOIN) design to guide treatment level escalation and de-escalation.

Results/Conclusion: The study is currently open and enrolling. The first 6 patients have been treated at an initial starting dose of REGN5678 and completed surgery. No adverse events >Grade 1 have been observed. The study has escalated to enroll an additional 6 patients at the next treatment level based on prespecified safety rules. Based on safety signals from this study and the ongoing first-in-human Phase 1/2 study of REGN5678 in mCRPC (NCT03972657), an amendment may be introduced to expand total enrollment to 42 patients. Immune monitoring analyses from prostate tissue specimens is ongoing.

Ethics Approval: This study was approved by the MD Anderson Cancer Center Institutional Review Board; protocol number 2023-0135. ClinicalTrials.gov Identifier: NCT06085664.

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