A pilot presurgical trial of nezastomig (costimulatory PSMAxCD28 bispecific antibody) in patients with high-risk, localized prostate cancer followed by radical prostatectomy

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Abstract:

Background: The prostate tumor microenvironment (TME) harbors few intratumoral effector T cells, leading to low response rates with single-agent immune checkpoint therapies. Nezastomig (REGN5678) is a first-in-class PSMAxCD28 bispecific antibody that co-targets prostate specific membrane antigen (PSMA) and the CD28 costimulatory domain on T cells. Clinical responses have been observed in patients with 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: (1) optimize dosing and schedule; (2) identify patient selection biomarkers and (3) develop rational combinations to improve efficacy. To address this, we designed a presurgical "window-of-opportunity" clinical trial for comprehensive evaluation of the prostate TME upon exposure to nezastomig.

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

Methods: This is a single center, open-label, presurgical study to determine the safety and tolerability of nezastomig 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 objective is to evaluate safety and tolerability. The secondary objectives of the study are to assess the proportion of patients who achieve pathological complete response with nezastomig. The exploratory objectives include evaluation of: immune responses in the prostate TME and peripheral blood after treatment with nezastomig compared to untreated control samples and exploratory imaging biomarkers by PSMA PET/CT. Nezastomig is dosed intravenous weekly for a total of six doses prior to surgery. The study employs a Time-to-event Bayesian optimal interval (TITE-BOIN) design to guide treatment level escalation and de-escalation. The maximum enrollment is up to 42 patients.

Results: Twelve patients have been enrolled across two treatment levels (30 mg nezastomig: n=6; 100 mg nezastomig: n=6). All patients have completed surgery. At the 30 mg treatment level, no adverse events >Grade 1 were observed, and no pathologic complete responses were observed. At the 100 mg treatment level, one dose-limiting toxicity was observed: grade 3 hepatitis requiring delay in surgery, which was reversed. The patient safely completed surgery. Efficacy analyses for the 100 mg cohort are in process. Additional patients are now being evaluated at the 100 mg treatment level. Initial immune monitoring analyses revealed alterations in T cell transcriptional states and localized changes in the immune microenvironment in PSMA-expressing regions.

Conclusion: In the initial treatment levels, presurgical treatment with nezastomig is feasible in patients with high-risk localized prostate cancer planned for radical prostatectomy. The comprehensive evaluation of the prostate tumor microenvironment may enable future biomarker-driven development of nezastomig alone and in combination.

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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