

TARGET MODULATION WITHIN THE TUMOR MICROENVIRONMENT (TME) BY DARATUMUMAB (ANTI-CD38) BUT NOT EDICOTINIB (CSF-1R INHIBITOR) IN MEN WITH HIGH-RISK LOCALIZED PROSTATE CANCER

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Background Prostate cancer is "immunologically cold," with enrichment of myeloid populations, immunosuppressive cytokines, and few T cells within the tumor microenvironment (TME). CD38 is expressed on myeloid cells, T cells, plasma B cells, and NK cells. Macrophage colony-stimulating factor-1 receptor (CSF-1R) controls macrophage differentiation and function. We hypothesized that either anti-CD38 (daratumumab) or CSF-1R inhibitor (edicotinib) would be safe and well-tolerated for primary prostate cancer, with successful target modulation on immune populations within the TME.

Methods In this single-center, open-label, presurgical study, patients were enrolled into Arm A (daratumumab, four weekly doses pre-surgery) or Arm B (edicotinib, orally daily for four weeks pre-surgery). Patients had high-risk localized or locally advanced prostate cancer (at least 1 core Gleason ≥ 8) appropriate for radical prostatectomy (RP), ≥ 3 biopsies involved with cancer, and no radiographic evidence of metastatic disease. Treated and untreated (Gleason-matched) fresh and formalin-fixed paraffin-embedded prostatectomy specimens and paired blood (PBMCs), bone marrow biopsies (BMBx) and aspirates (BMA) were evaluated for target modulation using IHC (prostate, BMBx) and flow cytometry (prostate, BMA, PBMCs). The primary endpoint was incidence of adverse events (AEs). The secondary endpoint was pathologic complete remission (pCR) rate.

Results Twenty-five patients were treated (Arm A, n=15; Arm B, n=10) and completed four doses of daratumumab or four weeks of edicotinib prior to RP. The most common AEs were Arm A: daratumumab infusion reaction (33%, 5/15); Arm B: increased aspartate aminotransferase (40%, 4/10). Grade 3 related AEs in Arm A occurred in 3 patients (12%; infusion reaction, n=2; urticaria, n=1), with no Grade 4/5 related events. No \geq Grade 3 related AEs occurred in Arm B. All patients completed surgery, however no patients achieved pCR. IHC revealed lower density of CD38+ cells in daratumumab-treated vs. untreated prostate tumors and in patient-matched post-treatment vs. pre-treatment BMBx. Similarly, flow cytometry showed decreased frequency of CD38+ T cells and macrophages in daratumumab-treated vs. untreated prostate tumors and patient-matched post-treatment vs. pre-treatment PBMCs and BMAs. Edicotinib did not demonstrate an impact on CSF-1R+ immune cells in prostate, bone marrow, or PBMCs.

Conclusions Daratumumab and edicotinib were safe and well-tolerated as presurgical therapy for high-risk localized prostate cancer, with no pCRs. Evidence of target modulation was consistently observed in prostate tumors, bone marrow, and PBMCs for daratumumab, but not edicotinib. Myeloid-targeted agents such as daratumumab alone are insufficient to generate anti-tumor responses in prostate cancer.

Trial Registration NCT03177460

Ethics Approval This study was approved by MD Anderson Cancer Center Institutional Review Board; protocol numbers 2017-0103 and PA13-0291.

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