Profiling Anti-tumor Immunity in High-Risk Localized Prostate Cancer after Treatment Targeting the B7-H3 Checkpoint

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Background: While CTLA-4 and PD-L1 are infrequently expressed in PCa, B7-H3 (another B7 superfamily member) is highly expressed in many PCas, may modulate anti-tumor immune responses, and is associated with worse prognosis. Binding B7-H3 is now clinically possible with the recent development of enoblituzumab (MacroGenics), a humanized Fc-optimized (for antibody-dependent cell-mediated cytotoxicity [ADCC]) monoclonal antibody that binds B7-H3 with high affinity and specificity. Here we describe a study to test the hypothesis that *neoadjuvant enoblituzumab treatment in patients with localized PCa will lead to partial pathological responses and reduced biochemical recurrence following prostatectomy, initially by modulating T cell immunity in the tumor microenvironment (TME) and also through direct tumor killing via ADCC*.

Methods: Thirty two (32) men with intermediate- and high-risk localized prostate cancer (Gleason sum 7-10) were consented on an IRB-approved single-center, single arm, phase 2 study evaluating the safety, anti-tumor effect, and immunogenicity of neoadjuvant enoblituzumab given prior to radical prostatectomy at Johns Hopkins. Participants receive enoblituzumab at a dose of 15 mg/kg IV given weekly for 6 doses prior to radical prostatectomy. Two weeks after the last dose of enoblituzumab, prostates are harvested at radical prostatectomy, and examined for secondary and correlative endpoints.

Results: The trial has completed enrollment of 32 patients with clinical endpoints maturing and correlatives being explored. Preliminary analysis using single and multiplexed protein IHC, compared to age- and stage-matched untreated prostatectomy controls, indicates statistically significant CD8 infiltration displaying Granzyme B upregulation, unchanged FOXP3+ infiltrate, and PD-L1 and PD-1 upregulation.

Conclusions: This study aims to explore the impact of B7-H3 blockade on PSA recurrence following prostatectomy and the effects on the prostate gland TME. The described finding of enhanced CD8 infiltration and Granzyme B activation with likely adaptive upregulation of PD-L1 and PD-1 *suggests that Enoblituzumab alters the TME in a fashion that results in enhanced CD8+ T cell infiltration and activation – a hallmark of immunotherapy responsiveness.*

Conflict of Interest: Francine Chen, Paul Moore, Jon Wigginton, and Jan Davidson-Moncada are employees of MacroGenics. All other authors report no conflict of interest.

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