**Phase II Neoadjuvant and Immunologic Study of B7-H3 Targeting with Enoblituzumab in Localized Intermediate- and High-Risk Prostate Cancer**

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**KEY STUDY ENDPOINTS**

**SUMMARY**

This study aims to understand the impact of B7-H3 targeting/blockade on PSA recurrence following prostatectomy, impact on the prostate gland tumor microenvironment (TME), and assess whether (like PD-L1 status) B7-H3 IHC staining can be used to predict response or resistance to B7-H3–targeted therapies.

**REFERENCES**

Kim et al. BJU International. 2016 May;85:93.

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**BACKGROUND**

- Prostate cancer (PCa) is the second-most common cause of cancer-related death in men, killing approximately one in 50 American males.
- Immune-checkpoint blockade has resulted in unprecedented treatment advances in multiple tumor types, despite yielding modest results in PCa.

**STUDY DESIGN**

- This is a single-center, single-arm, phase 2 study evaluating the safety, anti-tumor effect, and immunogenicity of neoadjuvant Enoblituzumab (MGA271) given prior to radical prostatectomy in men with intermediate and high-risk localized prostate cancer.
- Eligible patients (n=32) will receive Enoblituzumab at a dose of 15mg/kg IV given weekly for 6 doses beginning 50 days prior to radical prostatectomy.
- Follow-up evaluation for adverse events will occur 30 days and 90 days after surgery.

**PRELIMINARY RESULTS**

**Figure 4:** Prostatectomy immunohistochemistry staining from two patients (I and II) following neoadjuvant Enoblituzumab treatment. Small malignant glands lined by enlarged atypical epithelial cells show clear membrane staining by both anti-B7-H3 (A and F) and anti-Enoblituzumab (anti-MGA271, C and H). Adjacent non-malignant prostatic ducts show relatively negative membrane staining (B-E and D-G).

**Figure 5:** Prostatectomy immunohistochemistry (IHC) staining from a patient following neoadjuvant Enoblituzumab treatment. Shown are CD8+ T cell infiltrates (arrows) which are in close proximity to atypical malignant glands (arrows).

**CD8+ T cell quantitation in the Enoblituzumab-treated prostatectomy samples indicates a statistically significant increase in infiltrate compared to age- and stage-matched untreated prostatectomy controls** (via direct ADCC or indirectly via T cell killing) using TUNEL staining and cleaved Caspase 3 staining.

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**KEY STUDY ENDPOINTS**

- Primary endpoints: Clinical activity and severity of adverse events
- Estimation of clinical benefit based on the PSA, response rate (PSA <0.1 ng/mL) at 12 months after radical prostatectomy, as well as time to PSA recurrence and pathologic response

**Correlative endpoints:**
- Quantification of Enoblituzumab-induced tumor cell death (via direct ADC or indirectly via T cell killing) using TUNEL staining and cleaved Caspase 3 staining
- To assess the immune response to Enoblituzumab using quantification of CD8 T cell infiltration into the tumor/SF tumor areas, determining the effect of Enoblituzumab treatment on the CD8/Treg ratio, and quantifying the extent of PD-L1+ cell density in the prostate from harvested prostate gland tissue of treated patients

**SUMMARY**

This study aims to understand the impact of B7-H3 targeting/blockade on PSA recurrence following prostatectomy, impact on the prostate gland tumor microenvironment (TME), and assess whether (like PD-L1 status) B7-H3 IHC staining can be used to predict response or resistance to B7-H3–targeted therapies.

**STUDY HYPOTHESIS**

- Neoadjuvant Enoblituzumab treatment in patients with high-risk localized PCa will lead to partial pathological responses and reduce biochemical recurrence following prostatectomy, initially by modulating T cell immunity in the tumor microenvironment (TME) and also direct tumor killing via ADCC.
- Additionally, the proposed immunologic analyses from these patients are expected to test the hypothesis that Enoblituzumab treatment enhances PCA-specific T cell responses systemically, and further, to identify additional immunologic targets for combinatorial immunotherapies.

**STUDY AIMs**

1. To determine Fc receptor genotype (CD16A, CD32A, CD64) and TIM3, all of which are targets for existing clinical antibodies in pre- and post-treatment tumor tissue
2. To determine Fc receptor genotype (CD16A, CD32A, CD32B), which could affect Enoblituzumab’s ADC activity as it does with Rituximab
3. To analyze the tumor-specific repertoire using TCRTseq-based technologies, testing the hypothesis that successful anti-tumor responses modulate the TCR repertoire in peripheral and tumor-infiltrating lymphocytes and assessing relative responses to mutation-associated neoantigens (MANAs) vs PCa tumor-associated antigens (TAAs).

**PRELIMINARY RESULTS**

**SPECIAL AIMS**

- To determine whether Enoblituzumab mediated B7-H3 inhibition is safe, effective and immunologically active in the pre-surgical PCa setting by conducting a phase II neoadjuvant clinical trial in 32 men with high-risk localized PCa scheduled for prostatectomy.
- To determine whether Enoblituzumab results in pathologic anti-tumor responses and will improve prostatectomy outcomes in patients with localized PCa.
- To interrogate mutation-associated neoantigen-specific T cell responses induced by anti-B7-H3 therapy, analyze targetable immune-checkpoints adaptively-induced upon Enoblituzumab treatment, as well as elucidate the repertoire and gene-expression profiles of tumor-specific tumor-infiltrating T cells (TILs) utilizing multi-parameter flow cytometry and RNAseq. This first-in-field translational study of Enoblituzumab in PCa will allow concurrent exploration of its clinical efficacy and anti-tumor immunity.

**Figure 3.** Schema for the neoadjuvant Enoblituzumab clinical trial (NCT02923180).