Phase 2 Neoadjuvant Trial of the anti-B7-H3 Antibody, Enoblituzumab, in Men with Localized Prostate Cancer: Safety, Efficacy, and Immune Correlates

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BACKGROUND

- B7 homolog 3 (B7-H3), a member of the B7 superfamily, is highly expressed (relative to PD-L1 and PD-L2) in prostate cancer, and is associated with rapid biochemical recurrence and early metastases.
- B7-H3 may play immune suppressive and tumor-autonomous roles that favor cancer growth
- Enoblituzumab (MacroGenics, Inc.) is an investigational humanized Fc-optimized B7-H3–targeting antibody that induces antibody-dependent cellular cytotoxicity (ADCC).

STUDY HYPOTHESIS

- Neoadjuvant enoblituzumab treatment in patients with high-risk localized PCa will lead to reduced biochemical recurrence following prostatectomy, by modulating T cell immunity in the tumor microenvironment (TME) and also direct tumor killing via ADCC.

STUDY DESIGN

- Phase 2 single-center, single-arm, neoadjuvant trial, men with operable intermediate- and high-risk localized prostate cancer (Grade Groups 3-5) were enrolled to evaluate the safety, anti-tumor efficacy, and immunogenicity of enoblituzumab when given prior to prostatectomy. Patients received enoblituzumab (15 mg/kg IV weekly x 6) prior to surgery. Prostate glands were harvested 2 weeks after the last enoblituzumab dose, and were examined for pathologic and immunologic endpoints. The co-primary outcomes were safety and PSA0 at 1 year post-op.

Key Inclusion Criteria:

- Histological adenocarcinoma; clinical stage T1c–T3b, N0, M0; Gleason sum 7-10; at least 2 positive cores; prior decision to undergo radical prostatectomy; adult male >18 years of age; ECOG performance status 0-1

Key Exclusion Criteria:

- Prior hormones, biologics, or chemotherapy for prostate cancer; prior immunotherapy/vaccine therapy for prostate cancer; history of autoimmune disease requiring systemic immunosuppression

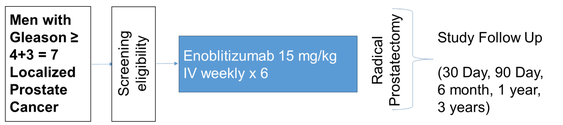


Figure 1. Study schema for the neoadjuvant enoblituzumab clinical trial (**NCT02923180**).

RESULTS

Table 1. Baseline patient demographics and clinical characteristics

	Overall (N=32)
Age (years)	
Mean (SD)	63.1 (6.95)
Median [Min, Max]	64.0 [48.0, 74.0]
Age >= 65 (years)	
Yes	15.0 (46.9%)
No	17.0 (53.1%)
Race	
White	30.0 (93.8%)
Black	1.00 (3.1%)
Asian	1.00 (3.1%)
Other	0 (0%)
Smoking History	
Yes	9.00 (28.1%)
No	23.0 (71.9%)
Family Prostate Cancer History	
Yes	7.00 (21.9%)
No	25.0 (78.1%)
PSA > 10 at Diagnosis (ng/mL)	
Yes	15.0 (46.9%)
No	17.0 (53.1%)
Median Time From Study Entry to Prostatectomy (weeks)	
Mean (SD)	7.00 (0.392)
Median [Min, Max]	6.86 [6.57, 8.29]
ECOG	
0	31.0 (96.9%)
1	1.00 (3.1%)
BMI	
Normal (BMI 18.5 – 24.9)	6.00 (18.8%)
Overweight (BMI 25.0 – 29.9)	14.0 (43.8%)
Obese (>= 30.0)	12.0 (37.5%)
Grade Group / Gleason sum at biopsy	
Grade Group 2	0 (0%)
Grade Group 3	5.00 (15.6%)
Grade Group 4	11.0 (34.4%)
Grade Group 5	16.0 (50.0%)
Gleason Sum at biopsy	
7	5.00 (15.6%)
8	11.0 (34.4%)
9-10	16.0 (50.0%)
Previous Therapy	
Yes	0 (0%)
No	32.0 (100%)
Stage >= T3 at Initial Diagnosis	
Yes	23.0 (71.9%)
No	9.00 (28.1%)
High-risk localized PCa	
Yes	31.0 (96.9%)
No	1.00 (3.1%)
Very high-risk (VHR) localized PCa	
Yes	23.0 (71.9%)
No	9.00 (28.1%)

[1] High-risk localized PCa: Gleason sum 8-10 at biopsy, or clinical stage ≥ T3, or screening PSA > 20 ng/ml.
[2] Very high-risk (VHR) localized PCa: primary Gleason pattern of 5 at biopsy, ≥ 5 biopsy cores with Gleason sum 8-10, or multiple individual high-risk features (i.e. Gleason sum 8–10 and PSA >20)

Table 2. Pathology outcomes post treatment

	Overall (N=32)
Grade Group / Gleason sum at Prostatectomy	
Grade Group 2	8.00 (25.0%)
Grade Group 3	9.00 (28.1%)
Grade Group 4	0 (0%)
Grade Group 5	15.0 (46.9%)
Gleason Sum at Prostatectomy	
7	17.0 (53.1%)
8	0 (0%)
9-10	15.0 (46.9%)
Pathological (surgical) stage	
Yes	24.0 (75.0%)
No	8.00 (25.0%)
Presence of intraductal or ductal histology (Prostatectomy)	
Yes	1.00 (3.1%)
No	31.0 (96.9%)
Presence of lymphovascular invasion (Prostatectomy)	
Yes	2.00 (6.3%)
No	30.0 (93.8%)
Presence of extraprostatic extension (Prostatectomy)	
Yes	19.0 (59.4%)
No	13.0 (40.6%)
Presence of Seminal Vesicle invasion (Prostatectomy)	
Yes	8.00 (25.0%)
No	24.0 (75.0%)
Positive margins (Prostatectomy)	
Yes	10.0 (31.3%)
No	22.0 (68.8%)
Positive lymph nodes (Prostatectomy)	
Yes	4.00 (12.5%)
No	28.0 (87.5%)
pCR	
Yes	0 (0%)
No	32.0 (100%)
Previous Therapy	
Yes	0 (0%)
No	32.0 (100%)
CAPRA-S Score	
0-2	4.00 (12.5%)
3-5	12.0 (37.5%)
>= 6	16.0 (50.0%)

Table 3. Gleason Group Change of Treated and 1:1 Matched (grade group, stage, margins, block age [within 2 years], age [within 2 years], and self reported race) Untreated Prostatectomy Controls

	Control Prostatectomy 1:1 Matched (N=32)	Treated Prostatectomy (N=32)	Overall (N=64)
Net Group Grade Change (RP-Biopsy)			
< 0 (Downgrade)	7.00 (21.9%)	16.0 (50.0%)	23.0 (35.9%)
= 0 (No Change)	13.0 (40.6%)	12.0 (37.5%)	25.0 (39.1%)
> 0 (Upgrade)	12.0 (37.5%)	4.00 (12.5%)	16.0 (25.0%)

Table 4. McNemar Test of Association Between Treatment and Gleason Grade Group Change. P=0.0159.

	Treated Prostatectomy	
	< 0 (Downgrade)	>= 0 (No Change or Upgrade)
Control Prostatectomy 1:1 Matched		
< 0 (Downgrade)	6	1
>= 0 (No Change or Upgrade)	10	15

Figure 2. Waterfall plot of PSA percentage change from screening prior to radical prostatectomy. PSA = prostate-specific antigen

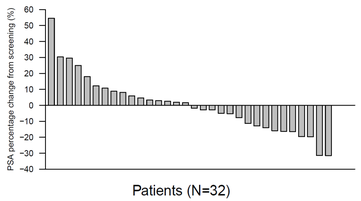
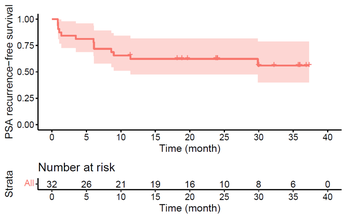


Figure 3. Kaplan-Meier curve showing median time-to-PSA-recurrence (PSA ≥ 0.2 ng/mL) after radical prostatectomy. 95% confidence intervals for point estimates shown in pink shading.



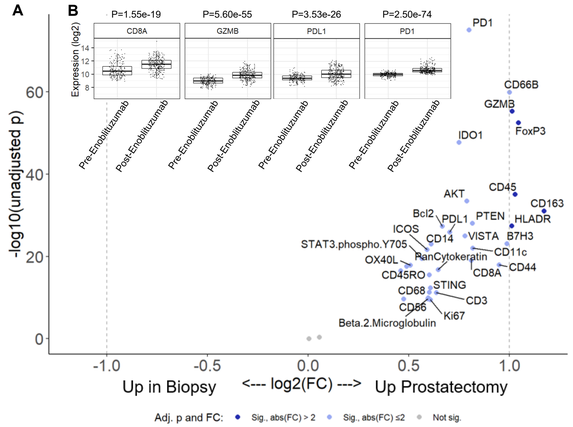
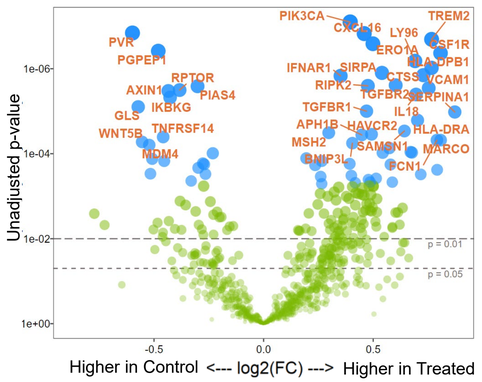


Figure 4. (A) **Volcano plot of tumor region protein expression changes pre-treatment (biopsy) versus post-treatment (prostatectomy) by Nanostring GeoMx Digital Spatial Profiling. X-axis shows the log2-transformed fold-change (FC) in expression and y-axis shows –log10-transformed unadjusted p-values. Proteins that remain significant after Benjamini Hochberg (BH) (adjusted *p <0.01*) are in shades of blue, with dark blue indicating absolute value of FC > 2 and light blue indicating absolute value of FC ≤ 2.** (B) **CD8A, GZMB, PD-L1, and PD1 biopsy (pre-enoblituzumab) versus prostatectomy (post-enoblituzumab) protein expression. P values shown are from a mixed linear model post BH adjustment.**

Figure 5. Volcano plot of tumor region mRNA expression changes of matched untreated control prostatectomies versus post-treatment prostatectomies by Nanostring PanCancer IO 360 analysis. Genes that remained significant after Benjamini and Yekutieli False Discovery Rate (FDR, adjusted *p < 0.01*) are in blue and labeled).



SUMMARY

- A total of 32 patients were enrolled.
- Grade 3/4 drug-related adverse events occurred in 12% of patients; no surgical delay due to AEs.
- One patient developed a grade-3 infusion reaction, and one had immune myocarditis that improved with steroids.
- Pre-prostatectomy PSA declines of >10% were observed in 34% of patients (95% CI: 20-52%).
- PSA0 at 1 year post-op was seen in 66% of men (95% CI: 48-80%).
- Median time to PSA recurrence was not reached (95% CI: 9.4 months – NE).
- Gleason grade group changes were significantly associated with treatment compared to 1:1 matched controls.
- Exploratory tumor microenvironment profiling by NanoString GeoMx spatial proteomics and PanCancer IO 360 mRNA expression analysis revealed evidence of post-treatment upregulation of CD8+ T cells, PD-1/PD-L1, and immune activation (granzyme B, interferon signaling, myeloid inflammation).

Overall, inhibition of B7-H3 with enoblituzumab demonstrated favorable safety and encouraging activity in prostate cancer patients. Preliminary data suggest robust intratumoral induction (adaptive upregulation) of immune checkpoints, T cell activation, and myeloid inflammation

LIMITATIONS

- Small sample size
- Short treatment time of 6 weeks of therapy
- Preliminary correlative data still being analyzed

REFERENCES

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- Roth et al. Cancer Res 2007 Aug 15;67(16):7893-900.

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Disclosures

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