Abstract 199: Targeting B7-H3 in prostate cancer: Phase 2 trial in localized prostate cancer using the anti-B7-H3 antibody enoblituzumab, with biomarker correlatives

Authors: Eugene Shenderov[1,2], Angelo M. De Marzo MD, PhD[1,3,4], Tamara L. Lotan MD[1,3,4], Hao Wang PhD[5], Sin Chan[1], Su Jin Lim[5], Hongkai Ji[6], Mohamad E. Allaf[4], Carolyn Chapman[1], Paul Moore[7], Francine Chen[7], Kristina Sorg[8], Andrew M. White[8], Sarah E. Church[8], Briana Hudson[8], Paul Fields[9], Shaohui Hu[10], Samuel R. Denmeade[1], Kenneth J. Pienta[1], Christian P. Pavlovich[4], Ashley E. Ross[11], Charles G. Drake[1,12], Drew Pardoll[1,2], Emmanuel S. Antonarakis[1,2,13]

[1]Department of Oncology or [2]The Bloomberg-Kimmel Institute for Cancer Immunotherapy or [3]Department of Pathology or [4]Department of Urology or [5]Department of Oncology Biostatistics and Bioinformatics, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA; [6]Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, 615 North Wolfe Street, Baltimore, Maryland 21205, USA; [7]MacroGenics, Inc, Rockville, MD, USA; [8]NanoString Technologies Inc, Seattle, WA, USA; [9]Adaptive Biotechnologies, Seattle, WA, USA; [10]CDI Labs, Baltimore, MD, USA; [11]Urology, Northwestern, Chicago, IL, USA; [12]Current address: Immuno-Oncology, Janssen, Horsham, PA, USA; [13]Current address: University of Minnesota Masonic Cancer Center, Minneapolis, MN

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 (**Fig. 1**), and is associated with rapid biochemical recurrence and early metastases (**Fig. 2**)[1].

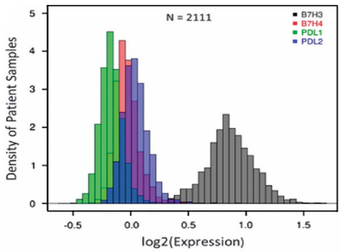


Figure 1: mRNA expression distributions of B7-H3, B7-H4, PD-L1 and PD-L2 from a radical prostatectomy cohort at Johns Hopkins.

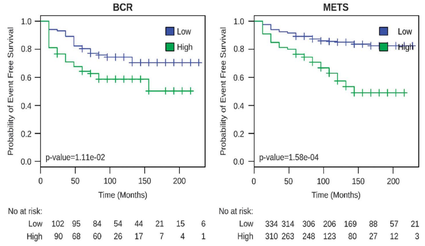


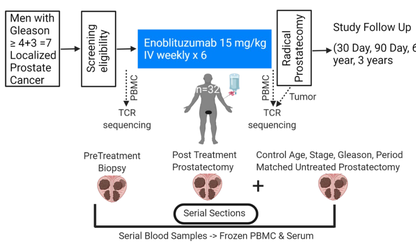
Figure 2. Survival curves for biochemical recurrence (BCR) and metastasis (METS) in a prostatectomy cohort (n=2111) stratified according to low and high B7-H3 mRNA expression.

- Enoblituzumab (MacroGenics, Inc.) is an investigational humanized Fc-optimized B7-H3–targeting antibody that induces antibody-dependent cellular cytotoxicity (ADCC).

METHODS:

- 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.

- 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.



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

6-weeks of anti-B7-H3 treatment with enoblituzumab demonstrated favorable safety and encouraging clinical activity in high risk prostate cancer patients with local disease prior to prostatectomy

- *Investigator initiated trial investigating an anti-B7-H3 monoclonal antibody agent with ADCC activity for Prostate Cancer*
- *Trial results provide rational for further development of enoblituzumab & future B7-H3 targeted agents in prostate cancer*
- *Minimal toxicity noted*

Limitations:
- Small sample size
- Short treatment time of 6 weeks of therapy

References:

- Benzon et al. Prostate Cancer Prostatic Dis. 2016 Nov 1.
- Powderly J, et al. SITC abstract 2015.
- Roth et al. Cancer Res 2007 Aug 15;67(16):7893-900.

Study support provided by:

Correspondence: Eugene Shenderov at Eugene.Shenderov@jhmi.edu

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RESULTS:

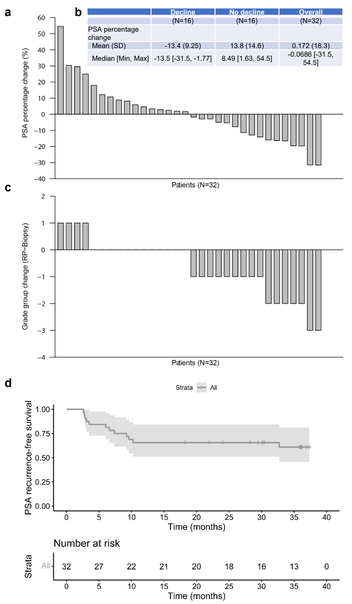

Figure 4. Enoblituzumab demonstrates activity in in the neoadjuvant treatment of prostate cancer patients prior to radical prostatectomy. a, Waterfall plot of percentage change in PSA from screening to prior to radical prostatectomy, computed as [(Day 50 PSA – Screening PSA) / Screening PSA] x 100 (%). **b,** Mean and median PSA percentage change in decliners versus non-decliners. **c,** Waterfall plot of grade group change from biopsy to radical prostatectomy. **d,** 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 gray shading.

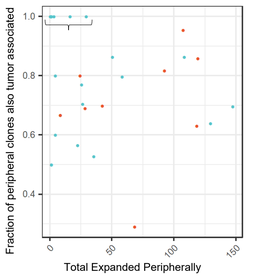

Figure 5. All patients (7/7) whose peripherally expanded T-cell clones were also 100% matching the intratumorally expanded T-cell clones demonstrated PSA0 at 1 year (indicated by bracket). Each point on the scatter plot represents a patient. 1.0 = 100%. Blue dots indicate patients with PSA0 at 1 year and red dots indicate PSA recurrent patients. Immunosequencing of the CDR3 regions of human TCRβ chains was performed using the Adaptive ImmunoSEQ Assay

Table 1 | All treatment-related Adverse-Events (AEs) by type and grade.

AE CTCAE Terminology	All Grade AEs	Grade 1	Grade 2	Grade 3	Grade 4
Total Independent Patients		31/32 (97%)	12/32 (38%)	4/32 (12%)	0/32 (0%)
Fatigue	23 (72%)	22 (69%)	1 (3%)	0 (0%)	0 (0%)
Neurological (headache, dizziness, paresthesia)	14 (44%)	13 (41%)	1 (3%)	0 (0%)	0 (0%)
Flu-like/cold symptoms	13 (41%)	12 (38%)	1 (3%)	0 (0%)	0 (0%)
GI (nausea, vomiting, anorexia, constipation, weight gain)	12 (38%)	10 (31%)	2 (6%)	0 (0%)	0 (0%)
URI, cough, nasal congestion, chills, fever, sore throat	12 (38%)	9 (28%)	3 (9%)	0 (0%)	0 (0%)
Infusion related reaction	7 (22%)	1 (3%)	5 (16%)	1 (3%)	0 (0%)
Arthralgia/Myalgia	6 (19%)	5 (16%)	1 (3%)	0 (0%)	0 (0%)
Amylase/Lipase increased	3 (9%)	1 (3%)	1 (3%)	1 (3%)	0 (0%)
Rash maculo-papular	3 (9%)	2 (6%)	0 (0%)	1 (3%)	0 (0%)
Anemia	2 (6%)	1 (3%)	1 (3%)	0 (0%)	0 (0%)
Dermatitis/Pruritus	2 (6%)	2 (6%)	0 (0%)	0 (0%)	0 (0%)
Edema lower extremities	2 (6%)	2 (6%)	0 (0%)	0 (0%)	0 (0%)
Hypotension	2 (6%)	1 (3%)	0 (0%)	1 (3%)	0 (0%)
Skin subcutaneous tissue disorder (bruising, IV infiltration, flushing)	2 (6%)	2 (6%)	0 (0%)	0 (0%)	0 (0%)
Bilirubin increase	1 (3%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)
CD4 lymphocytes decreased	1 (3%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)
Diarrhea/Colitis	1 (3%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)
Dry mouth	1 (3%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)
Dysgeusia	1 (3%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)
Electrolyte change (hypocalcemia, hypercalcemia, hyponatremia, hypokalemia)	1 (3%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)
Myocarditis/Pericarditis	1 (3%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)
Pericardial effusion	1 (3%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)
Platelet count decreased	1 (3%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)
Vascular disorders	1 (3%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)

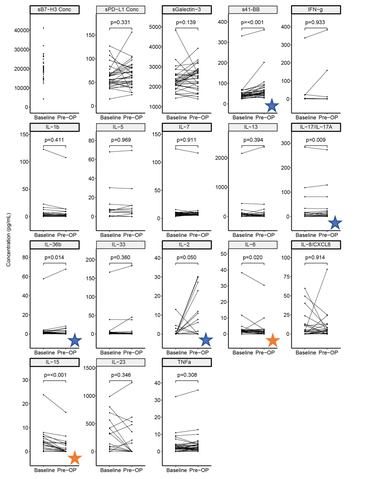

Figure 6. Changes in circulating cytokines, chemokines, and soluble protein levels from baseline to pre-op (D50). Cytokine analysis were performed from n=32 patients using n=64 samples. Only baseline soluble B7-H3 (sB7-H3) levels shown due to post-treatment ELISA interference from enoblituzumab. Wilcoxon signed-rank test utilized to compare cytokine levels between two time points with statistically significant increase (▲) and decrease (▼) shown.