TNB585.001: A Multicenter, Phase 1, Open-Label, Dose-Escalation and Expansion Study of TNB-585, a Bispecific Antibody Targeting PSMA in Subjects with Metastatic Castrate Resistant Prostate Cancer

Abstract TPS5092

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Introduction

- PSMA (Prostate-Specific Membrane Antigen) is a highly prostate-specific surface antigen overexpressed in prostate carcinoma; its expression is correlated with grade and stage and is high in many metastatic castrate-resistant cancers (mCRPC).
- While PSMA is an attractive target for T-cell redirection, such approaches have to date been hampered by significant immune-mediated toxicities such as Cytokine Release Syndrome (CRS).
- We identified a unique αCD3 moiety that induces T-cell dependent cytotoxicity of tumor cells with significantly reduced cytokine secretion using our NGS-based discovery pipeline.
- This αCD3 was incorporated into our novel PSMA x CD3 T-Cell engaging antibody (TCE; TNB-585) that selectively activates effector T-cells over Tregs with reduced cytokine secretion (Figure 1).
- TNB-585 is now being studied in a Phase 1 Clinical Trial, TNB585.001 **(NCT04740034).**

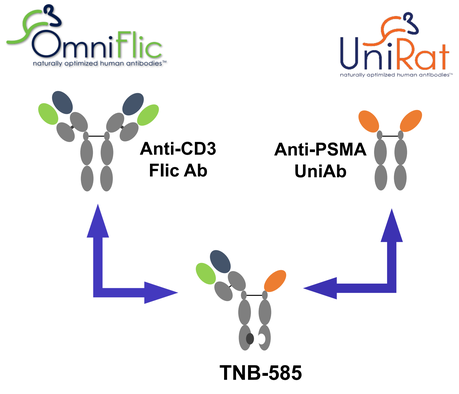


Figure 1: TNB-585 Development
TNB-585 is a fully human TCE combining fixed-light-chain (Flic Ab) and heavy-chain-only (UniAb) arms paired using knobs-in-holes. The FLC arm weakly activates CD3. The HCO arm has a high affinity anti-PSMA moiety.

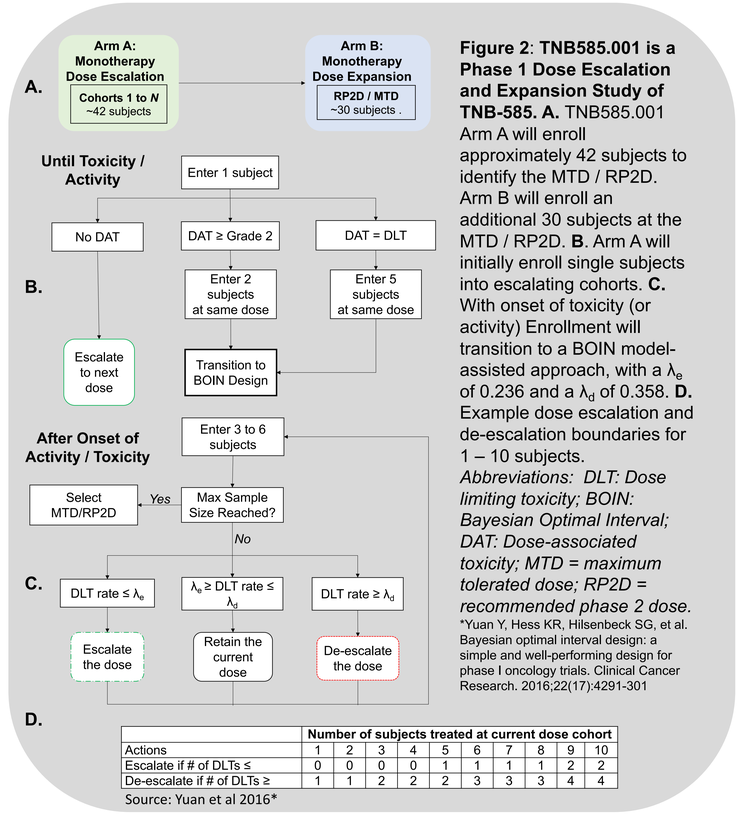
Study Design and Dose Escalation

Table 1: Key Inclusion / Exclusion Criteria in TNB585.001

Key Inclusion Criteria	Key Exclusion Criteria
At least 2 prior lines of Therapy: Taxane exposure permitted but not required	Prior PSMA-targeted Therapy is Permitted
Adequate marrow function: • Absolute neutrophil count (ANC) ≥ 1500/mm^3 • Platelets ≥ 100,000/mm^3 • Hemoglobin ≥ 9.0 g/dL	Other Cancer Drug within 14 days OR 5 half-lives, whichever is shorter (Prior experimental therapy not within 28 days)
eGFR ≥ 30 mL/min	History of CNS involvement / CNS Pathology
AST/ALT ≤ 3 x ULN (except Gilbert or Liver mets: ≤ 5 x ULN)	Other malignancy that may interfere with the study
Well-controlled / Cured HBV, HCV, HIV Permitted	Major Cardiac Disease
ECOG ≤ 2	Chronic Immunosuppressive Therapy

Table 2: Key Design Features of TNB585.001

Key Design Features	Rationale
mCRPC chemo-exposed and -naive	• Broad eligibility • Many subjects chemo-ineligible: high unmet need
Fixed (as opposed to weight-based) Dosing	• Simple dose prep • Error reduction
Every 3 Week (Q3W) Dosing	• Dosing consistent with $T_{1/2}$ • Safety (CRS may set on as late as 2 weeks post-dose)
CT ± Optional PSMA-PET (expansion only)	• PSMA expression important response correlate • PSMA-PET not widely available
Prior PSMA Therapy Permitted	• Published reports suggest sensitivity in these patients • High unmet need in these patients



	Number of subjects treated at current dose cohort									
Actions	1	2	3	4	5	6	7	8	9	10
Escalate if # of DLTs ≤	0	0	0	0	1	1	1	1	2	2
De-escalate if # of DLTs ≥	1	1	2	2	2	3	3	3	4	4

Source: Yuan et al 2016*

Figure 2: TNB585.001 is a Phase 1 Dose Escalation and Expansion Study of TNB-585. A. TNB585.001 Arm A will enroll approximately 42 subjects to identify the MTD / RP2D. Arm B will enroll an additional 30 subjects at the MTD / RP2D. **B**. Arm A will initially enroll single subjects into escalating cohorts. **C.** With onset of toxicity (or activity) Enrollment will transition to a BOIN model-assisted approach, with a λ_e of 0.236 and a λ_d of 0.358. **D.** Example dose escalation and de-escalation boundaries for 1 – 10 subjects.
Abbreviations: DLT: Dose limiting toxicity; BOIN: Bayesian Optimal Interval; DAT: Dose-associated toxicity; MTD = maximum tolerated dose; RP2D = recommended phase 2 dose.
*Yuan Y, Hess KR, Hilsenbeck SG, et al. Bayesian optimal interval design: a simple and well-performing design for phase I oncology trials. Clinical Cancer Research. 2016;22(17):4291-301

Table 3: Sites Enrolling into TNB585.001 Arm A

Site	Location	PI
Tennessee Oncology	Nashville, TN	Dr. Meredith McKean
FCS Sarasota	Sarasota, FL	Dr. Manish Patel
HealthONE Denver	Denver, CO	Dr. Gerald Falchook
Tulane University	New Orleans, LA	Dr. Oliver Sartor
UC San Francisco	San Francisco, CA	Dr. Larry Fong
Jefferson University	Philadelphia, PA	Dr. William Kelly
Mt. Sinai	New York, NY	Dr. Bobby Liaw

Statistical Methods and Study Endpoints

Safety
- Arm A: Dose-Limiting Toxicities (DLTs)
- Arm B: Unacceptable Adverse Events

Activity
- Overall Response Rate (ORR)
- Radiographic Progression-Free Survival (rPFS)
- Overall Survival (OS)
- Rate of subjects with PSA decrease ≥ 50% / 30% (PSA50 / PSA30)
- Duration of Response (DOR)
- Depth of Response

Pharmacokinetic
- C_{max}
- Time to C_{max}
- Area Under the Curve (AUC)
- Clearance (Cl)
- Terminal $T_{1/2}$

Summary:

- TNB-585 clears tumor cells in a PSMA and T-cell dependent manner *in vitro, in vivo,* and *ex vivo.*
- TNB-585 induces less cytokine secretion than a conventional T-cell engaging bispecific *in vitro*, without reduction in tumor cell kill.
- TNB-585 has a predicted half-life of 3 weeks in humans.
- 1 Patient has been enrolled in the Dose Escalation Arm of TNB585.001 and has tolerated treatment well to date.
- The Dose Expansion Arm is anticipated to open Q1 – Q2 2022.

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