Interim Results of a Phase 1 Study of TNB-486, a Novel CD19xCD3 T-Cell Engager, in Patients with Relapsed / Refractory (R/R) B-cell Non-Hodgkin lymphoma (B-NHL)

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Background

- Despite treatment advances, substantial **unmet need** remains for patients with R/R diffuse large B cell lymphoma (DLBCL) and follicular lymphoma (FL).

- **CD19** is a **validated target** in B cell lymphoid malignancies with multiple drugs approved by regulatory agencies, including CAR T-cell therapy (CART), antibody drug conjugates (ADCs), Bi-specific T-cell engagers (BiTEs), and naked antibody. These treatments are limited by **toxicity**, access, and/or modest anti-tumor **efficacy**.

- T-cell engagers (TCEs) targeting CD20 have demonstrated clinical efficacy with an acceptable safety profile. Treatment is associated with on-therapy and post-therapy **CD20 antigen loss**.

- The development of a **novel, safe, effective, and widely accessible** anti-CD19 therapy remains of high interest for the treatment of B cell malignancies:
  - Address CD20 antigen loss
  - Induce deeper remissions: CD19 is expressed earlier than CD20 in B cell development
  - Improve efficacy in combination with anti-CD20 therapy
TNB-486: a Second Generation TCE Targeting CD19

- Asymmetric, fully human IgG4 TCE rationally designed to maintain high efficacy while reducing toxicity
  - Unique αCD3 binding site to reduce cytokine release
  - High affinity heavy chain only αCD19 domain
- Silenced IgG4 Fc tail to prevent nonspecific binding and antibody-dependent cellular toxicity
- Long half-life (9-11 days) supports dosing every 2 to 4 weeks
- Off-the-shelf

Interim data from the ongoing Phase 1 study (NCT04594642) in R/R B-NHL are presented

4. NCT04594642. Available at: https://clinicaltrials.gov/ct2/show/NCT04594642

CD19, cluster of differentiation 19; B-cell NHL, B-cell non-Hodgkin lymphoma; R/R relapsed/refractory; Q2W every 2 weeks; Q4W every 4 weeks
Study Overview

Phase 1, global, multicenter dose-escalation and dose-optimization trial

Key Inclusion Eligibility

- Age ≥ 18 years
- CD19+ R/R B-NHL
- ≥ 2 prior lines of therapy (anti-CD19 directed regimens allowed)
- ECOG PS ≤ 2
- ≥ 1 measurable lesion
- No active CNS disease
- Adequate hematologic and organ function

TNB-486 Administration

- Q2W IV dosing (28-day cycle) → Q4W dosing if CR after Cycle 6
- Hospitalization limited to Cycle 1 (Days 1 and 15)

Study Endpoints

- Primary: safety, tolerability, PK
- Secondary: anti-tumor activity (RECIL 2017), OS

Study Design

- Cohort 5a: 2.4 mg
- Cohort 4a: 0.80 mg
- Cohorts 1, 2, 3: 0.03–0.27 mg
- Cohort 4b: 0.27 / 2.4 mg
- Cohort 4c*: 0.27 / 7.2 mg
- Cohort 5b: 0.27 / 2.4 mg
- Cohort 6a: 1.0 / 7.2 mg
- Cohort 6c*: 1.0 / 7.2 mg
- Cohort 7a*: 1.0 / 10 mg

Fixed Dose Cohorts

- Target Dose or First priming dose 0.03 mg – 2.4 mg
- Target Dose 0.8 – 10 mg
- Target Dose 0.8–10 mg

x1 SUD Cohorts

* Cohorts 7a and 6c are no longer enrolling. B-NHL, B-cell non Hodgkin lymphoma; CD19, cluster of differentiation 19; CNS, central nervous system; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance status; IV, intravenous; OS, overall survival; PK, pharmacokinetics; Q2W, every 2 weeks; RP2D, recommended Phase 2 dose; RECIL, Response evaluation criteria in lymphoma; SUD, step-up dosing; R/R, relapsed/refractory. 1. Younes, et al. Ann Onc 2017.
Patient Disposition and Baseline Characteristics

30 patients received ≥ 1 dose of TNB-486

16 active on treatment

14 discontinued due to
Progressive disease (n = 11)
Achieved CR and received allo-HSCT (n = 1)
Other (n = 2)

25 efficacy evaluable

- Median treatment duration of 101 days (6-306)

<table>
<thead>
<tr>
<th>Clinical cut-off date: August 8, 2022</th>
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<table>
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<tr>
<th>N =30</th>
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<tbody>
<tr>
<td>Median age, years (range)</td>
</tr>
<tr>
<td>ECOG PS 0/1/2</td>
</tr>
<tr>
<td>DLBCL</td>
</tr>
<tr>
<td>FL</td>
</tr>
<tr>
<td>MCL</td>
</tr>
<tr>
<td>MZL</td>
</tr>
<tr>
<td>Richter transformation</td>
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<tr>
<td>CD20 negative disease at study entry</td>
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<tr>
<td>Ann Arbor stage, n (%)</td>
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</table>
  ▪ I-II | 4 (13%) |
  ▪ III-IV | 23 (77%) |
  ▪ Missing | 3 (10%) |
| Median lines of prior therapy, n (range) | 4 (2-21) |
| Prior CART-19 | 7 (23%) |
| Prior auto-HSCT | 3 (10%) |
| Prior allo-HSCT | 1 (3%) |

Auto-HSCT, autologous hematopoietic stem cell transplant; Allo-HSCT, allogeneic hematopoietic stem cell transplant; CART, chimeric antigen receptor T-cell therapy; CD20, cluster of differentiation 20; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance status; DLBCL, Diffuse large B-cell lymphoma; FL, Follicular lymphoma; MCL, Mantle cell lymphoma; MZL, Marginal zone lymphoma
High Response Rate to TNB-486 Observed at Low Doses by IRC

- **ORR 81.2% (CR 68.7%)** in B-NHL at doses ≥ 2.4 mg
  - DLBCL: ORR 75% (3/4); CR 50% (2/4)
  - FL: ORR 87.5% (all CRs, 7/8)
  - 2/4 (50%) responses in patients with CART failure
- Majority of responses achieved at the first response assessment (week 8)
- Responses observed irrespective of prior lines of therapy

Responses assessed by RECIL 2017; IRC, Independent Radiological Review Committee; ORR, overall response rate
Complete Responses are Seen Across All B-NHL Subtypes

69-yr-old female with MZL and 6 prior lines of therapy

Disease response assessed by RECIL 2017. DLBCL, diffuse large B-cell lymphoma; HGBL, high-grade B-cell lymphoma; MCL, mantle cell lymphoma; MZL, Marginal zone lymphoma; CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease.
Durable Responses with No Relapses from CR

- 16 of 30 patients remain on treatment
- Loss of CD19 expression could not be examined as no relapses from CR have been observed to date

CR complete response; DC, discontinued; PR, partial response; PD, progressive disease; DLBCL, Diffuse large B-cell lymphoma; HGBL, High-grade B-cell lymphoma; MCL, Mantle cell lymphoma; MZL, Marginal zone lymphoma; RT, Richter transformation. Disease response assessed by RECIL 2017.
## Safety Summary

<table>
<thead>
<tr>
<th>Event</th>
<th>All patients, N = 30</th>
<th>All patients, N = 30</th>
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<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td><strong>AE Grade 3+</strong></td>
<td>16 (53.3)</td>
<td>13 (43.3)</td>
</tr>
<tr>
<td>• Treatment related</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Serious AE</strong></td>
<td>13 (43.3)</td>
<td>5 (16.7)</td>
</tr>
<tr>
<td>• Treatment related</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AE leading to discontinuation</strong></td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>• Treatment related</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AE leading to death</strong></td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>• Treatment related</td>
<td></td>
<td></td>
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- **Infections (any grade)**: 11 (36.6)
- **Tumor Lysis Syndrome**: 0
- **Hypogammaglobulinemia**: 3 (10)
- **Infusion-related reaction**: 2 (6.6)
- **Febrile neutropenia**: 1 (3.3)
- **G3+ neutropenia (related)**: 3 (10)
Cytokine Release Syndrome (CRS)

- All CRS events occurred during Cycle 1, all **rapidly resolved**
- CRS events were predominantly **low-grade** and short in duration (1 day)
- No Grade 3 CRS in patients with FL

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<tr>
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<tr>
<td>Patients that experienced CRS</td>
<td>18 (60%)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>11 (37%)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Onset, median days (range)</td>
<td>2 (0 - 2)</td>
</tr>
<tr>
<td>Duration, median days (range)</td>
<td>2 (0 - 7)</td>
</tr>
<tr>
<td>Tocilizumab use for CRS</td>
<td>9 (30%)</td>
</tr>
<tr>
<td>Resolved</td>
<td>18 (100%)</td>
</tr>
</tbody>
</table>

CRS grade based on ASTCT Consensus Grading (Lee, et al. Biol Blood Marrow Transplant 2019); ASTCT, American Society for Transplantation and Cellular Therapy
Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

- Events classified as ICANS* reported by 10/30 (33%), all resolved
- Grade 3 events occurred in 4 patients with other potential risk factors (e.g. age $\geq$ 80 yrs, prior Grade 4 ICANS post-CART)$^1$
  - Main clinical manifestation was confusion (n=3)
  - 3 of 4 were re-challenged, without recurrence

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<thead>
<tr>
<th>Patients that experienced ICANS*</th>
<th>N= 30</th>
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<tr>
<td></td>
<td>10 (33%)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Resolved</td>
<td>10 (100%)</td>
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</table>

*TNB-486-related neurological AEs potentially consistent with ICANS

$^1$ one subject 84 yrs/MCL; one subject 79 yrs/MZL; one subject 71 yrs/DLBCL with history of G4 ICANS following CART; one subject 49 yrs/Richter transformation
Preliminary Analyses of Cytokines Support Evaluation of Double Step-up Doses

IL-8

No priming (2.4mg)
Cohort 5a (n=6)

0.27 mg priming dose
Target 2.4 mg and 7.2 mg
Cohorts 5b and 6c (n=5)

1 mg priming dose
Target 7.2 mg and 10 mg
Cohorts 6a and 7a (n=10)

Data show group median with Interquartile Range (IQR)

Clinical cut-off date: August 8, 2022
Conclusions

• Results from ongoing Phase 1 study demonstrate **high anti-tumor activity** in R/R B-NHL, even at low doses (≥ 2.4 mg)
  • DLBCL: **ORR 75%; CR 50%**
  • FL: **ORR 87.5% (all CRs)**

• **Deep and durable responses** achieved in heavily pre-treated patients; follow-up is ongoing
  • No patients relapsed after achieving CR

• **Predictable and tolerable safety profile**: transient ICANS and CRS events primarily limited to **Cycle 1**, majority were low grade, all rapidly resolved

• **Double-step up dosing is being implemented** to further reduce the risk of ICANS
Acknowledgements

• The patients and their caregivers
• The study investigators, study coordinators and nurses
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