# Using clinical utility index (CUI) to determine the optimal biological dose (OBD) of a nonfucosylated anti-TIGIT antibody: A proposed alternative to maximum tolerated dose (MTD)

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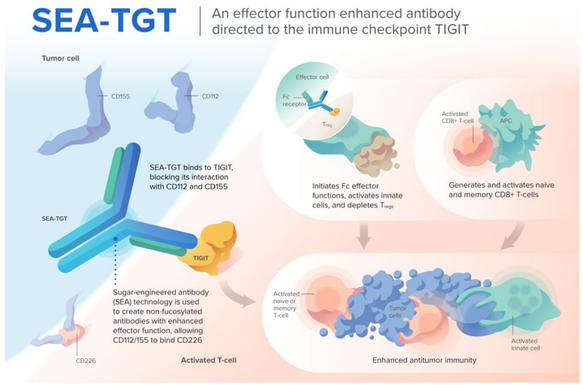
## Background

- SEA-TGT is an investigational, human nonfucosylated monoclonal antibody (mAb) targeting the T cell immunoreceptor with immunoglobulin (Ig) and ITIM domains (TIGIT) protein.
- TIGIT is an immunoregulatory receptor expressed on activated and memory T cells, Tregs, and NK cells.
- SGNTGT-001 (NCT04254107) is a phase 1 clinical trial evaluating the safety and tolerability of SEA-TGT as monotherapy in solid tumors and lymphomas at doses ranging from 0.01 to 6 mg/kg administered intravenously every three weeks (presented in poster CT265)[1]. Because an MTD was not identified in dose escalation, pharmacokinetic (PK) and pharmacodynamic (PD) endpoints were measured to assess biological activity and inform dose selection.

## Proposed SEA-TGT Mechanisms of Action (MOA)




SEA-TGT is an investigational agent, and its safety and efficacy have not been established. Proposed mechanism of action based on preclinical data.

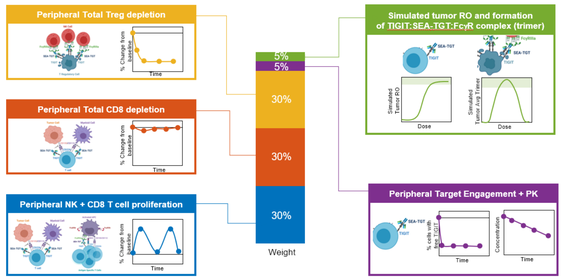

- Releases inhibitory signals driven by TIGIT:CD122 and TIGIT:CD155 binding[2]
- Drives Treg depletion[2]
- Activates innate immune cells (APCs, NK cells) [2]
- Generates and activates naïve and memory CD8+ T cells[2]
- Enhances antitumor immune responses[2]

## References

1. Garralda Cabanas E, et al. Phase 1 Dose-Escalation Study of SEA-TGT Monotherapy in patients with Advanced Malignancies. Poster CT265 presented at: American Association for Cancer Research; April 14-19, 2023.
2. Smith AJ, et al. SEA-TGT is a nonfucosylated antibody with distinct and amplified effector function activity that leverages the dependencies of anti-TIGIT anti-tumor activity upon $Fc\gamma R$ engagement. Poster presented virtually at: Society for Immunotherapy of Cancer Annual Meeting; Nov. 12, 2020.
3. Freise KJ, et al. Moving Beyond Maximum Tolerated Dose for Targeted Oncology Drugs: Use of Clinical Utility Index to Optimize Venetoclax Dosage in Multiple Myeloma Patients. Clin Pharmacol Ther. 2017 Dec;102(6):970-976
4. de Greef-van der Sandt I, et al. A quantitative benefit-risk assessment approach to improve decision making in drug development: Application of a multicriteria decision analysis model in the development of combination therapy for overactive bladder. Clin Pharmacol Ther. 2016 Apr;99(4):442-51.

## Methods

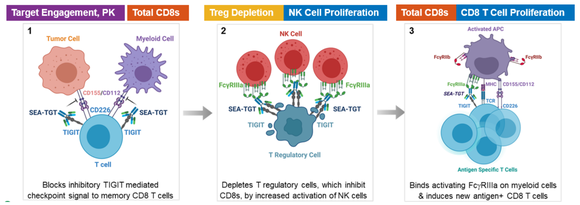
### Clinical Utility Index (CUI) to Compare Biological Activity Across Dose Cohorts




- Clinically meaningful PK and PD endpoints were mathematically integrated into a single output in an objective, quantitative, and weighted manner via a Clinical Utility Index (CUI) model to compare biological activity across dose cohorts. CUI is the sum of the weighted (w) average utility functions (U) for all endpoints of interest (i)[3,4].

$$CUI = \sum_{i=1}^{n} w_i U_i$$

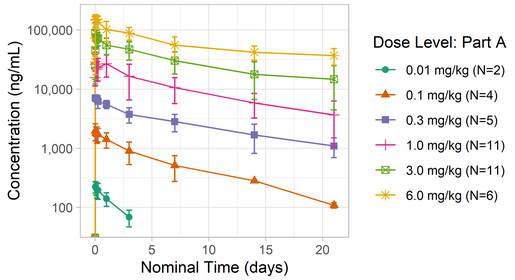
- Given the multiple proposed MOAs of SEA-TGT, PD endpoints in the CUI model included: NK and CD8+ T cell proliferation, maintenance of overall peripheral CD8+ T cell numbers, depletion of peripheral regulatory T cells, and peripheral target engagement, as assessed via flow cytometry.
- PK endpoints in the CUI model included pharmacokinetic linearity, as assessed via SEA-TGT concentrations-time profiles in plasma. Predicted tumor surrogate efficacy metrics included predictions of tumor target engagement and formation of SEA-TGT:TIGIT:$Fc\gamma$RIIIA trimer per Treg complexes in the tumor, as assessed via a semi-mechanistic PK/PD model.




- Utility functions were created using categorical scoring that identified ranges of no (utility score=0), limited (utility score between 0 and 1), or strong (utility score=1) evidence of biological activity.
- All selections were prespecified using SEA-TGT preclinical and literature-based data to limit bias. Endpoints weights were based on a priori consensus that balanced relevant biological activity with variability and/or uncertainty in output.

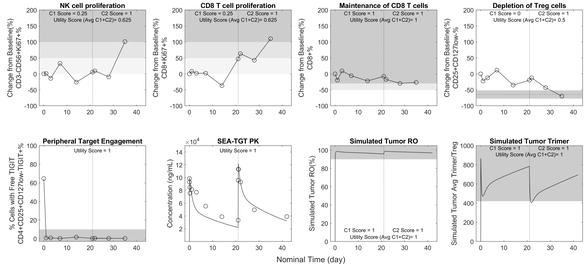
## Results

### SEA-TGT PK Profiles



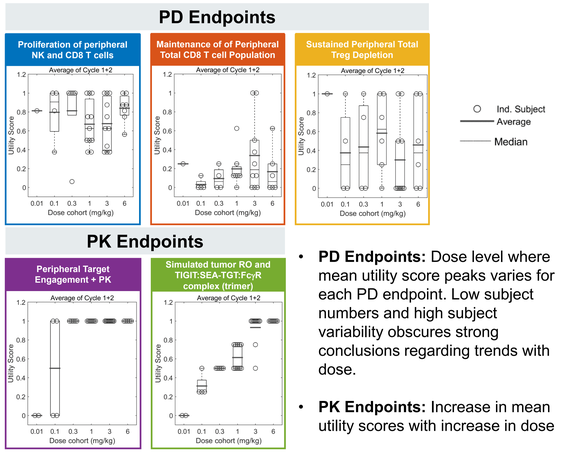

SEA-TGT pharmacokinetics were approximately dose-proportional from 0.3 to 6.0 mg/kg, with dose levels 0.1 and 0.01 mg/kg being within the nonlinear pharmacokinetic range.

### Illustration of the PD and PK Profiles for the CUI Endpoints and Resulting Utility Scores for a Representative Subject



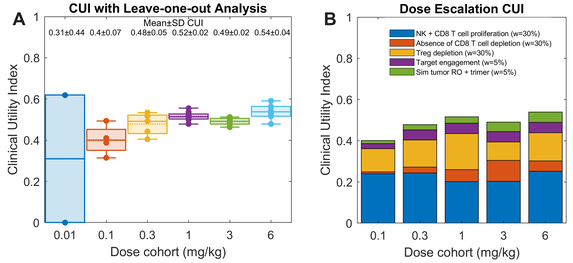

The shaded areas are defined by the utility function categorical cutoffs and represent areas of no biological activity (white, score=0), limited biological activity (light to medium gray, score 0.25 to 0.5), strong biological activity (dark gray, score=1).

### Dose Level with the Highest Utility Score Varies for Each CUI Endpoint




- **PD Endpoints:** Dose level where mean utility score peaks varies for each PD endpoint. Low subject numbers and high subject variability obscures strong conclusions regarding trends with dose.
- **PK Endpoints:** Increase in mean utility scores with increase in dose

### Final Monotherapy SEA-TGT CUI




A) Mean CUI scores show an increase in biological activity from 0.01 to 0.3 mg/kg, with an apparent plateau between CUI scores across 0.3 to 6.0 mg/kg. B) Due to differential weighting, the contribution of each endpoint to the mean CUI score varies with dose level since endpoints are optimized at different doses.

## Conclusions

- A CUI model incorporating PK and PD endpoints was built to help inform dose selection in the absence of a clear dose-safety/response relationship in SEA-TGT monotherapy
- SEA-TGT pharmacokinetics were approximately dose-proportional at doses ranging from 0.3 to 6.0 mg/kg
- SEA-TGT at 1 and 3 mg/kg showed biological activity that was within desirable ranges and had similarly high overall CUI scores relative to all doses evaluated
- Based on monotherapy CUI, 1 mg/kg represents the lowest biologically active dose that ensures PK linearity and has acceptable tolerability

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