T1230-02-08

Reverse translational modeling for early benchmarking of clinically active doses from in vitro cell killing and T-cell activation data for BCMAxCD3 T-cell engagers

Eshita Khera[1], Lipi Mukherjee[2], Alex Ferguson[1], Arthur Van De Vyver[1], Meelim Lee[1], Ryan Polli[3], Andrew Stein[4], Stan Ye[2], Suzanne Gaudet[1], Jan-Frederik Schlender[1]

[1] Novartis Biomedical Research, Translational Medicine, Pharmacokinetic Sciences, Modeling & Simulation, [2] Novartis Biomedical Research, Oncology, Drug Discovery, Biotherapeutics, [3] Novartis Biomedical Research, Translational Medicine, Pharmacokinetic Sciences, Oncology, [4]Novartis Development, Early Development Analytics

CONTACT INFORMATION: Presenting author: meelim.lee@novartis.com, Corresponding author: jan-frederik.schlender@novartis.com

aaps National Biotechnology CONFERENCE

PURPOSE

- Project Optimus necessitates early dose rationalization strategies. This is challenging for T-cell engaging bispecifics (TCEs) which exhibit a complex mechanism of action. While several strategies have evolved for selecting a safe first-in-human (FiH) starting dose (*e.g.*, MABEL), fewer efforts have focused on early benchmarking of active doses for expansion [1].
- **This work outlines and qualifies a simple model-informed drug development (MIDD) translational strategy for early approximation of clinically relevant dose ranges using *in vitro* data and historical clinical data analysis.**
- We present a three-step reverse translation strategy leveraging new *in vitro* data and published *ex vivo* data with teclistamab, a bispecific targeting B-cell maturation antigen (BCMA) and CD3 for relapsed/refractory multiple myeloma (RRMM). Using *in vitro* redirected T-cell cytotoxicity (RTCC) data and teclistamab-derived potency scaling factors, we apply our framework to elranatamab and WVT078, two other BCMA bispecifics, and attempt to recapitulate clinically active doses.

METHODS

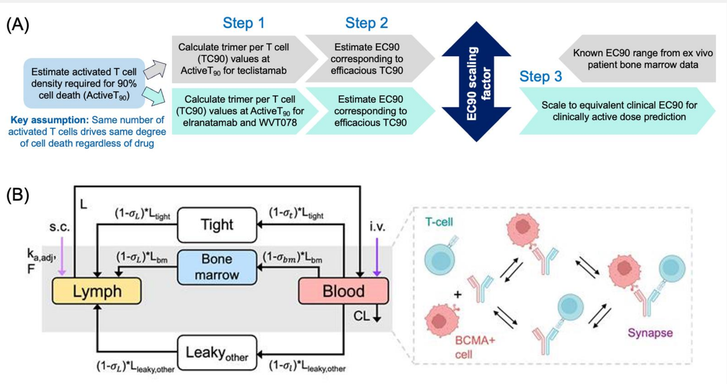

Figure 1. Reverse translation modeling strategy
(A) Schematic of three-step reverse translation framework to calculate (top row) and apply (bottom row) potency scaling factors. (B) Schematic of minimal physiologically-based pharmacokinetic (mPBPK) and target engagement model used to simulate plasma and bone marrow PK. mPBPK model modified and calibrated from [9].

General Strategy. Teclistamab RP2D selection was based on plasma PK achieving maximum EC90 from *ex vivo* RTCC cell killing [2]. In the absence of such *ex vivo* data from healthy donor T cells and MM patient bone marrow (BM) samples with other candidates, we devised a reverse translation strategy using QSP modeling and *in vitro* RTCC data.

***In vitro* RTCC data** for teclistamab, elranatamab, and WVT078 were generated using healthy donor PBMCs and the KMS11-Fluc-mCherry tumor cell line (5:1 E:T ratio) by Incucyte. Immunophenotyping to measure T-cell activation (CD25+ CD4+/CD8+) was evaluated by FACS.

Published literature and internal analysis values. We extracted teclistamab T-cell activation and cell killing data from patient samples [2], teclistamab clinical pharmacokinetics (PK) and RP2D [3], WVT078 clinically active doses [4], elranatamab clinical PK parameters [5], and elranatamab RP2D [6] from literature. WVT078 clinical PK parameters were from internal analysis.

Trimer number calculations and trimer modeling. Bispecific activity depends on ability to bind, activate, and kill. Accordingly, our analyses account for degree of target engagement (depending on BCMA and CD3 affinity and expression), T-cell activation from target engagement, and tumor cell death sensitivity. Immunological synapse ("trimer") modeling was performed according to [7] using published and in-house measured binding kinetics. Using the trimer model, we converted concentration-based EC90 potency to trimer number per T cell (TC90) values under a quasi-equilibrium assumption as described in [8].

RESULTS

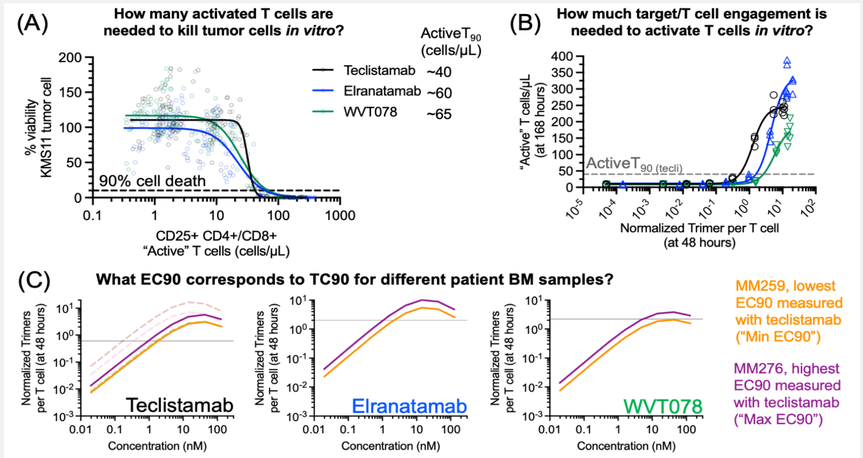

Figure 2. Determining teclistamab *in vitro*-to-*ex vivo* EC90 scaling factors
(A) *In vitro* tumor cell killing and activated T-cell count data used to estimate T cell density required for 90% tumor cell death (ActiveT90).
(B) Correlation plot of measured active T cell count and calculated trimers per cell (TCx).
(C) *Ex vivo* TCx used to translate from *in vitro* TC90 to an "expected" EC90. *Ex vivo* calculations used published affinity and BM expression data in MM patients MM259 and MM276 [2].

The central hypothesis of the reverse translation strategy is that tumor cell killing by activated T cells is bispecific drug-agnostic. Based on this, we reverse translated teclistamab's RP2D from *ex vivo* clinical potency for *in vitro* scaling (*Figure 1A*).

We benchmarked the number of active T cells required for 90% tumor cell death *in vitro* (ActiveT90) and observed **tumor cell killing from activated T cells was essentially BCMA bispecific drug-agnostic for the candidates evaluated** *(Figure 2A)*. We next benchmarked teclistamab TC90 (*Figure 2B*) to determine the "expected" clinical EC90, assuming similar intrinsic sensitivity as KMS11 tumor cells.

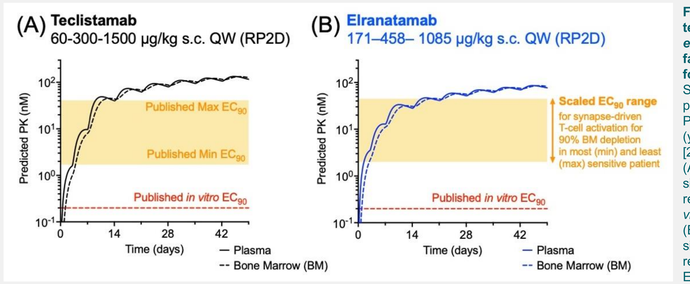

Figure 3. Applying teclistamab *in vitro*-to-*ex vivo* EC90 scaling factor to elranatamab for model qualification
Simulated population plasma and bone marrow PK relative to *ex vivo* (yellow) and *in vitro* (red [2,10]) EC90.
(A) Teclistamab RP2D simulations shown relative to measured *ex vivo* EC90 range.
(B) Elranatamab RP2D simulations shown relative to scaled *ex vivo* EC90 range.

***In vitro*-to-*ex vivo* scaling factors were derived from the fold-difference between the expected EC90 from *in vitro* data and measured maximum and minimum EC90s from *ex vivo* MM patient sample data.** We attributed fold-difference in EC90 to intrinsic sensitivity differences because affinity and expression were accounted for in TC calculations and both teclistamab RTCC datasets use healthy donor T cells.

With our *in vitro* RTCC assay data with teclistamab, elranatamab, and WVT078 as a bridge for translation, teclistamab fold-difference scaling factors were applied to elranatamab for model qualification. We estimated an equivalent clinical EC90 range for elranatamab using the scaling factors. We then leveraged a mPBPK/target engagement model to identify doses with predicted plasma and bone marrow PK that covered the scaled EC90 range. **The resulting predictions that achieved maximum EC90 aligned with the clinically active dose range reported for elranatamab** (*Figure 3B*).

Applying our estimation approach to WVT078, PK predictions for 250 µg/kg (highest monotherapy dose reported in [4]) overlap with the scaled EC90 range *(Figure 4)*. This suggests drug-agnostic value of our reverse translation strategy for early estimation of a clinically-relevant, active dose range.

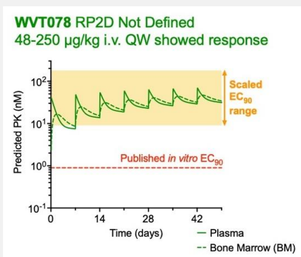

Figure 4. Exploratory application of scaling factors to WVT078
Simulated population plasma and bone marrow PK for 250 µg/kg dose relative to scaled *ex vivo* EC90 range (yellow) and *in vitro* EC90 threshold (red [4]).

CONCLUSIONS

Our three-step reverse translation analysis of three BCMA bispecifics paired *in vitro* RTCC data with published clinical data analyses. When target-specific historical clinical data are available, generating *in vitro* data can enable early and rapid estimation of clinically active dose ranges. This context is significant for TCEs, as the FiH starting dose is often low for safety and requires lengthy escalation.

- Step 1: We benchmarked the number of active T cells required for 90% tumor death *in vitro* and observed that tumor cell killing from activated T cells was essentially BCMA bispecific drug-agnostic for the candidates evaluated.
- Step 2: We derived scaling factors from the difference between "expected" (*in vitro* RTCC) and measured (*ex vivo* RTCC using MM patient samples) clinical EC90 values for teclistamab.
- Step 3: We applied our translational strategy to elranatamab and WVT078, using our *in vitro* RTCC data and teclistamab-derived scaling factors as a bridge. Elranatamab dose predictions covering the scaled EC90 range aligned with clinically active doses. For WVT078, our predictions overlapped with the scaled EC90 range. These results suggest drug-agnostic value of this tool for early benchmarking of clinically active dose ranges.

DISCLOSURES: All authors are shareholders and/or employees of Novartis.

ACKNOWLEDGMENTS: The authors would like to acknowledge the PK Sciences Modeling & Simulation team and project teams for their scientific consultation.

REFERENCES

[1] Shastri, P.N., et al. "Industry Perspective on First-in-Human and Clinical Pharmacology Strategies to Support Clinical Development of T-Cell Engaging Bispecific Antibodies for Cancer Therapy", CPT, 2024.
[2] Pillarisetti, K., et al. "Teclistamab is an active T cell-redirecting bispecific antibody against B-cell maturation antigen for multiple myeloma", Blood Adv, 2020.
[3] Girgis, S., et al. "Translational Modeling Predicts Efficacious Therapeutic Dosing Range of Teclistamab for Multiple Myeloma", Target Oncol, 2022.
[4] Raab, M.S., Cohen, Y.C., Schjesvold, F. et al. Preclinical discovery and initial clinical data of WVT078, a BCMA × CD3 bispecific antibody. Leukemia 37, 1349–1360 (2023).
[5] European Medicines Agency. Elrexfio: EPAR - Public Assessment Report. 2023. European Medicines Agency.
[6] Bahlis, N.J., Costello, C.L., Raje, N.S. et al. Elranatamab in relapsed or refractory multiple myeloma: the MagnetisMM-1 phase 1 trial. Nat Med 29, 2570–2576 (2023).
[7] Betts, A., et al. "A Translational Quantitative Systems Pharmacology Model for CD3 Bispecific Molecules: Application to Quantify T Cell-Mediated Tumor Cell Killing by P-Cadherin LP DART®", AAPS J, 2019.
[8] Schropp, et al. "Target-Mediated Drug Disposition Model for Bispecific Antibodies: Properties, Approximation, and Optimal Dosing Strategy", CPT Pharmacometrics Syst Pharmacol, 2019.
[9] Jiang, X., et al. "Development of a Minimal Physiologically-Based Pharmacokinetic/Pharmacodynamic Model to Characterize Target Cell Depletion and Cytokine Release for T Cell-Redirecting Bispecific Agents in Humans." Eur J Pharm Sci, 2020.
[10] Panowski, S.H., et al. "Preclinical Efficacy and Safety Comparison of CD3 Bispecific and ADC Modalities Targeting BCMA for the Treatment of Multiple Myeloma." Mol Cancer Ther.