How the Net Treatment Benefit framework can support dose optimization

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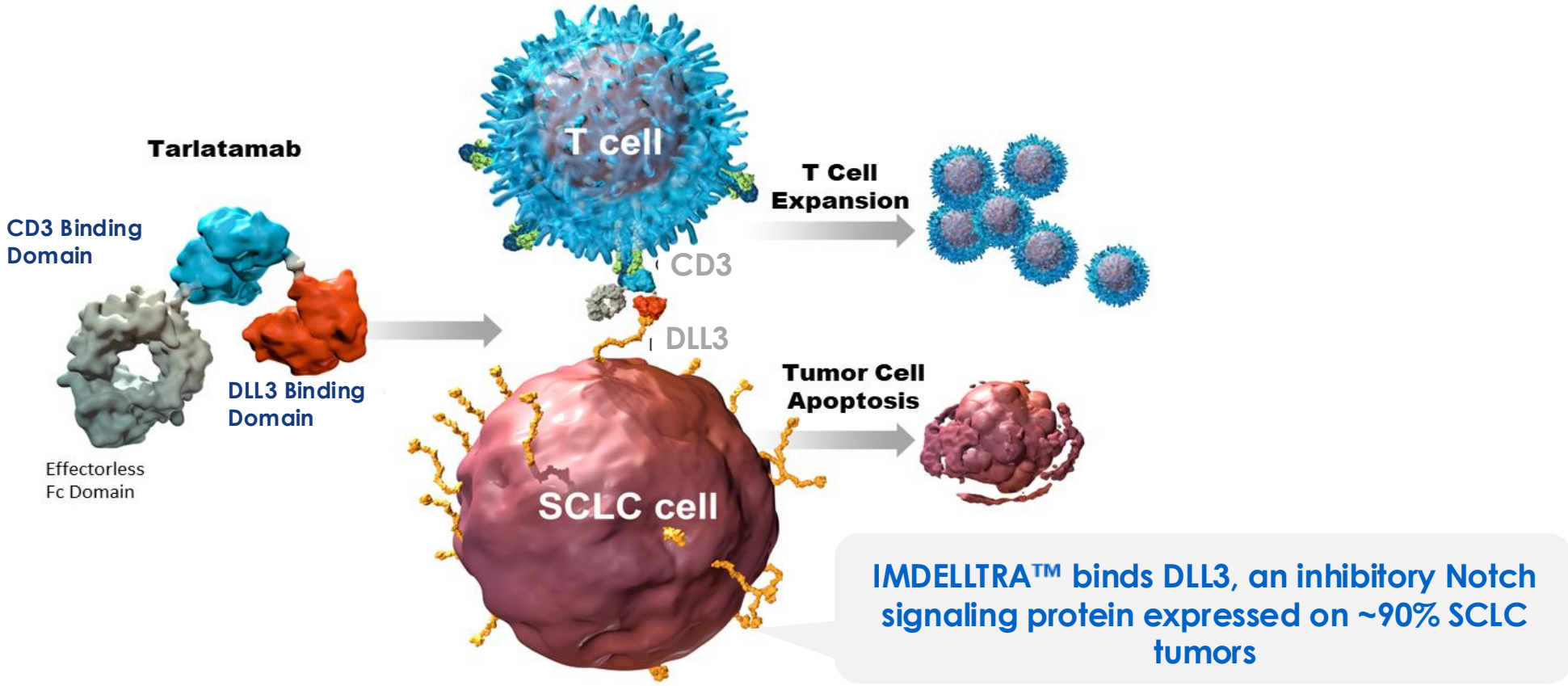
Tarlatamab is an anti-DLL3 x anti-CD3 Bispecific T-cell Engager (Half-Life Extended BiTE® molecule)

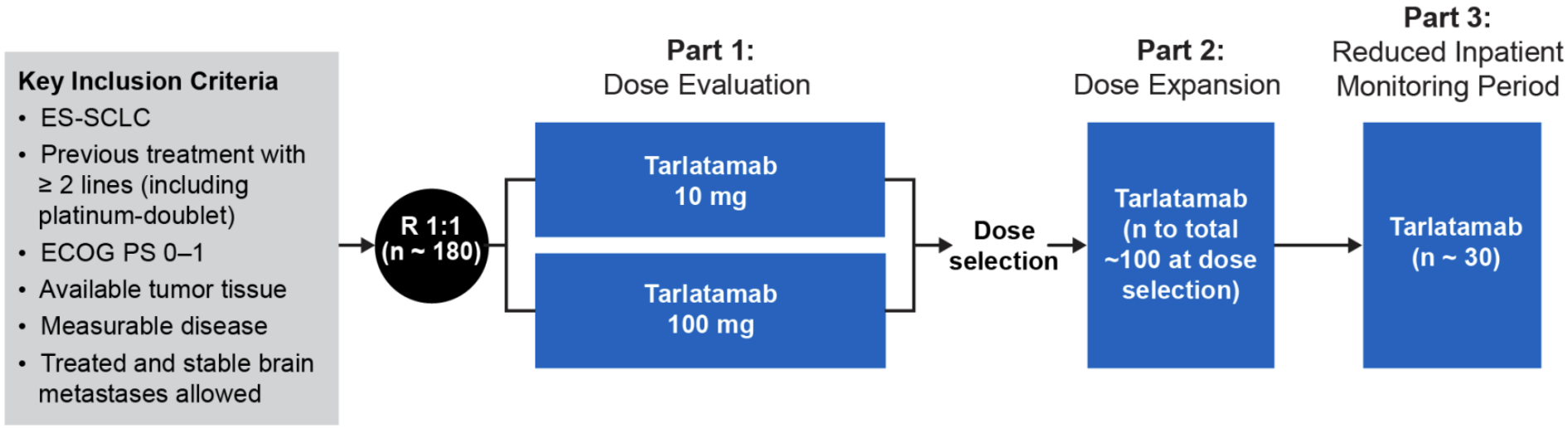


IMDELLTRA™ binds DLL3, an inhibitory Notch signaling protein expressed on ~90% SCLC tumors

Phase 2 DeLLphi-301: Tarlatamab randomized dose optimization

Figures

Figure S1. Study Design



Endpoints

Primary: Objective response rate per RECIST v1.1 by BICR, incidence of adverse events, serum concentrations of tarlatamab

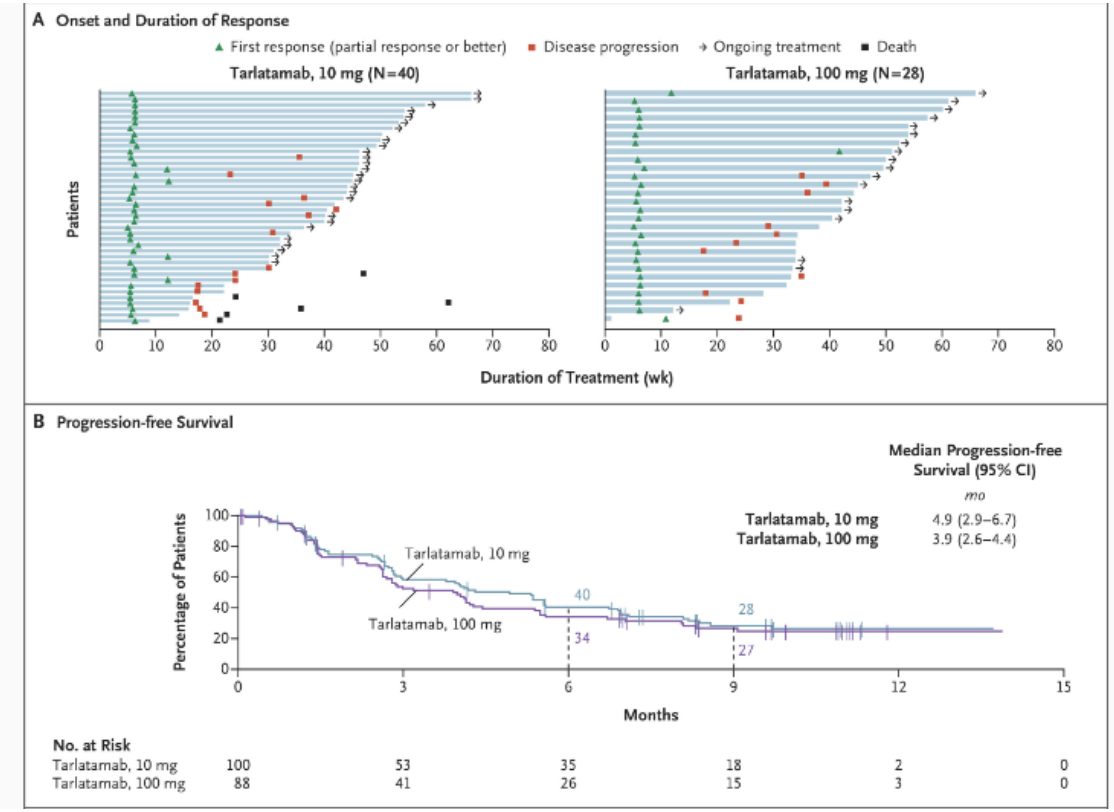
Secondary: Duration of response, disease control rate, duration of disease control, progression-free survival as per RECIST v1.1 by BICR, overall survival; and incidence of anti-tarlatamab antibody formation

BICR: blinded independent central review; ECOG PS: Eastern Cooperative Oncology Group performance status scale; ES-SCLC: extensive stage-small cell lung cancer; R: randomization; RECIST: Response Evaluation Criteria in Solid Tumors.

Ahn et al. 2023, NEJM

Phase 2 DeLLphi-301: Clinical efficacy and safety data supported selection of 10 mg Q2w dose

Objective response rate: **10 mg:** 40% (97.5% CI 29-52)
100 mg: 32% (97.5% CI 21-44)



Ahn et al. 2023, NEJM

Typical way to make a dose decision

- Pivotal decisions are based on primary endpoints and the consideration of secondary endpoints
- It can be challenging as a sponsor to make critical decisions based on one single outcome
- **Net Treatment Benefit framework** was explored more recently via a retrospective review of the PhII Tarlatamab randomized dose optimization data. This analysis supported and reinforced the 10 mg Q2w target dose selection.

NTB used to leverage the totality of the evidence and inform dose selection

Figures

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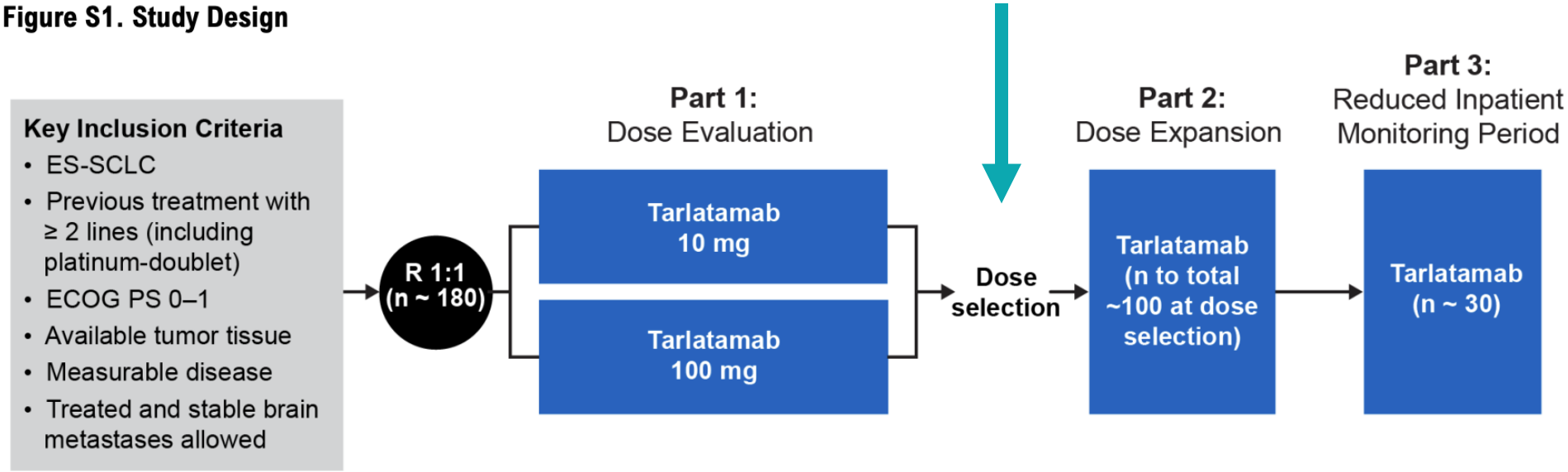

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Dose selection using the totality of evidence approach

Evolving Decision-Making in Phase II

- Integrating efficacy and safety into a unified view
- Making benefit-risk trade-offs explicit and transparent
- Supporting more patient-relevant dose decisions

Collaboration with One2Treat

- Embedded NTB framework within internal decision-making processes
- Enables consistent and scalable use across programs
- Focus on building internal capability with NTB using One2Treat software

Project Optimus

Reforming the dose optimization and dose selection paradigm in oncology

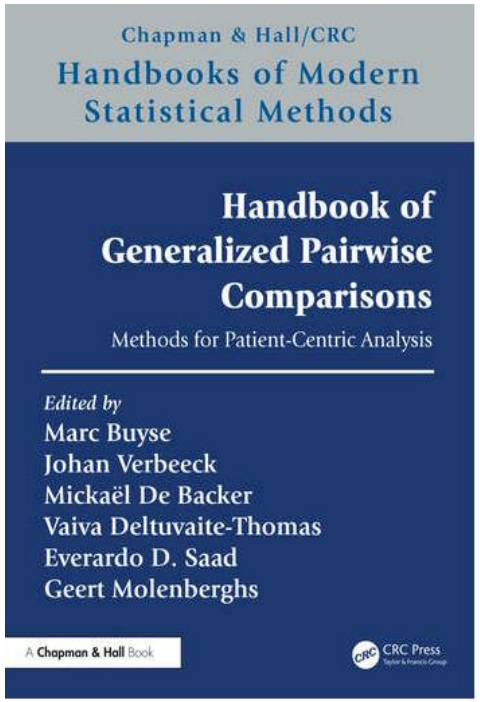
Goals

The goal of Project Optimus is to educate, innovate, and collaborate [...] to move forward with a dose-finding and dose optimization paradigm across oncology that emphasizes selection of a dose or doses that maximizes not only the efficacy of a drug but the safety and tolerability as well.

A robust statistical solution :
The Net Treatment Benefit (NTB)

Comprehensively estimates treatment effects from multiple prioritized outcomes

Produces a single quantitative measure of overall treatment benefit



FDA preface

EMA postface

50+ peer-reviewed publications
1 methodological handbook

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Key principles of the Net Treatment Benefit framework

- **Multiple outcomes** are selected for analysis together (efficacy and safety)
- **Priority order** of outcomes is key
- We can **capture the preferences** of patients and/or clinicians to understand the most relevant outcomes and priority order
- Sensitivity analysis using **all possible permutations**

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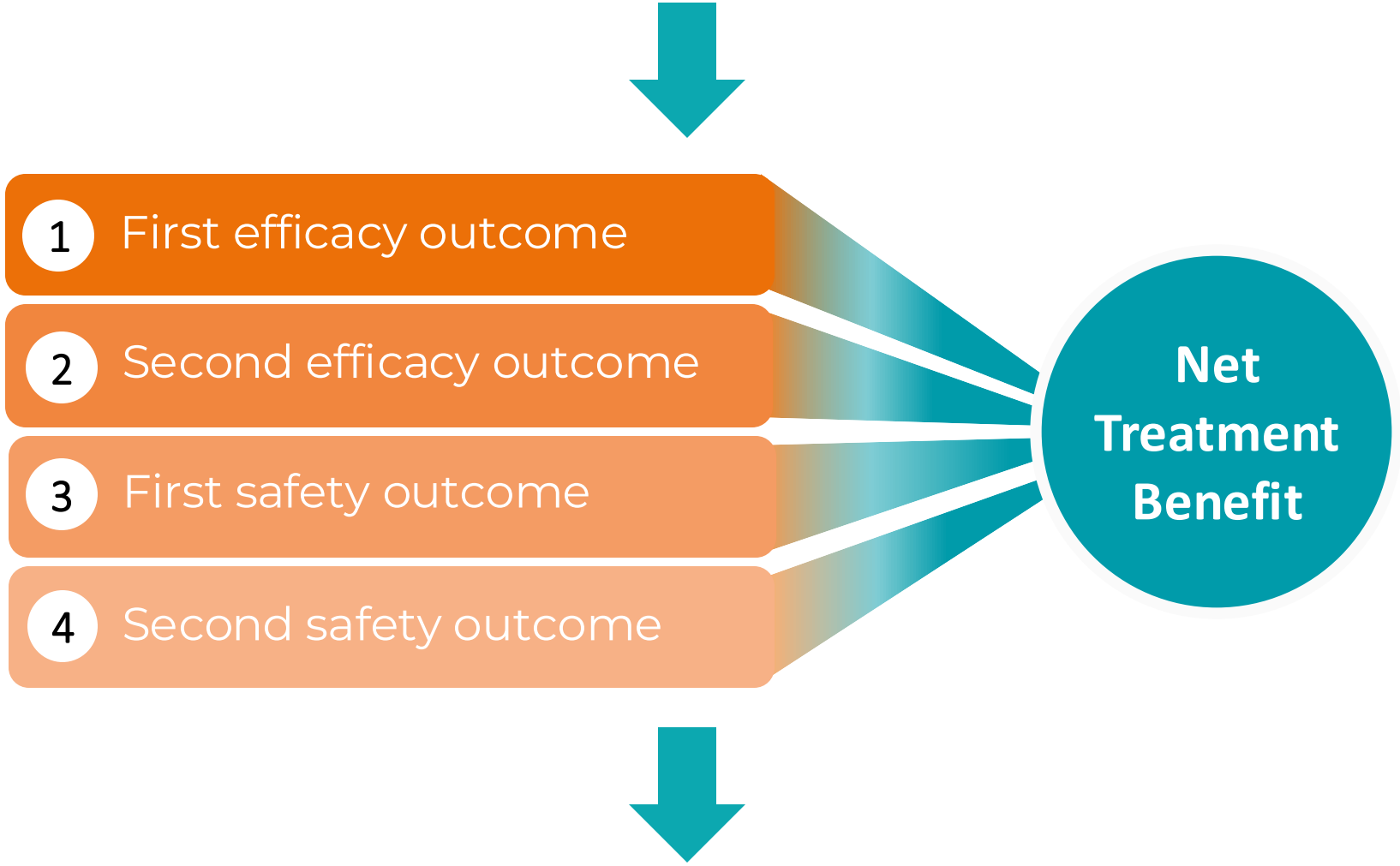

Sensitivity analysis using **all possible permutations**

Article in review…

Tarlatamab Dose in Small-Cell Lung Cancer: Supportive Evidence of Dose Optimization Based on Net Treatment Benefit

Shuang Huang, PhD, Rudradev Sengupta, PhD, Fiona H. Blackhall, MD, PhD Horst-Dieter Hummel, MD Emilie Barré, MSc, Pascal Piedbois, MD, PhD, Marc Buyse, ScD, Mukul Minocha, PhD, Ali Hamidi, MD, Rani Najdi, PhD, Erik S. Anderson, MD, PhD, Suresh S. Ramalingam, MD

Amgen Inc., Thousand Oaks, CA, USA; One2Treat, Louvain-la-Neuve, Belgium; Christie NHS Foundation Trust and University of Manchester, Manchester, UK; Translational Oncology–Early Clinical Trial Unit (ECTU), Bavarian Cancer Research Center, National Center for Tumor Diseases, Comprehensive Cancer Center Mainfranken and University Hospital Würzburg, Würzburg, Germany; I-BioStat, University of Hasselt, Belgium; Winship Cancer Institute of Emory University, Atlanta, GA, USA.

Introduction: Alternative approaches to dose optimization, especially within the oncology landscape, are evolving beyond traditional methods of dose selection. This article provides a comprehensive evaluation of tarlatamab dosing in patients with small-cell lung cancer using the Net Treatment Benefit (NTB) approach.

Methods: NTB was calculated using the benefit-risk profile of the two tarlatamab doses (10 mg, 100 mg) from the randomized phase 2 DeLLphi-301 study based on generalized pairwise comparisons methodology. Seven outcomes (three efficacy and four safety) were included in the total NTB primary analysis. The order of priority for efficacy outcomes was (1) objective response, (2) progression-free survival, and (3) overall survival. The order of priority for safety outcomes was (1) serious adverse events, (2) two events of interest (cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome), (3) grade ≥3 treatment emergent adverse events (TEAEs), and (4) discontinuation due to TEAEs.

Results: For both scenarios (prioritization of efficacy), NTB favored tarlatamab 10 mg dosing [redacted] and 32% by safety prioritization [redacted] tarlatamab 10 mg dosing [redacted] methods. By integrating outcomes into a single measure of benefit, 10 mg dosing of tarlatamab consistently provides superior outcomes (positive NTB) compared with 100 mg dosing, regardless of prioritization of selected outcomes.

Net Treatment Benefit approach

- **Totality of the evidence** approach can be applied across therapeutic areas
- Use of One2Treat software and framework to better **inform decision making**
- **Tangible way** to incorporate clinician and patient perspectives into trial design

01

Clinical trial designs
Integrating prioritized clinical outcomes into trial endpoints

02

Comprehensive benefit and risk analysis of RCT data

03

Communication of medical value for new treatments
(HTA submissions, launch)

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Thank you

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