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Graaf, P.H. van der

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First-in-Human Dose Selection for T-Cell Engaging Bispecific Antibodies

Piet H. van der Graaf^{1,2,*}

Although bispecific antibodies (“bispecifics,” antibodies that can bind to two different antigens at the same time) are typically coined as novel modalities,¹ they were already reported in 1960 by Nisonoff and colleagues.² However, it was only three decades later for the first clinical investigation to happen and then it took another two to the approval of the first bispecific antibody for human therapeutic use.³ There are now more than 10 bispecific antibodies approved by the US Food and Drug Administration (FDA), the majority for the treatment of cancer (Figure 1).⁴

The initial steps and milestones in the development of bispecific therapeutics were mainly fueled by advances and breakthroughs in biotechnology and antibody engineering. More recently biology, translational medicine as well as clinical pharmacology have played an increasingly important role. The most exciting properties of bispecifics are called obligate, since they are dependent on the physical linkage of the two “arms” and cannot be obtained by combining separate antibodies with the same individual binding properties.³ An example is avidity (sometimes referred to as functional affinity), which quantifies the synergy due to multiple simultaneous binding interactions.^{3,5} These unique properties of bispecifics offer potential therapeutic advantages but also raise significant drug development challenges. For example, the dose/concentration-response relationship for bispecifics can be bell-shaped, which makes dose-finding more challenging.⁵ Second, due to highly

system-dependent pharmacology, the translation of pharmacokinetics-pharmacodynamics (PKPD) of bispecifics is complex and traditional minimal anticipated biological effect level (MABEL) concepts to define first-in-human (FIH) starting dose for conventional monoclonal antibodies do not apply.⁶ Last but not least, how do we predict and manage between-patient variability, which due to the multifactorial mechanism of action may be more pronounced for bispecifics than what is typically observed with conventional monoclonal antibodies.⁵

A series of recent white papers, reviews, and research articles published in *Clinical Pharmacology & Therapeutics* (CPT) reflects the significant interest of drug developers in this area and provides overviews of current clinical pharmacology best practices and innovation.^{4,7–11} In this issue of CPT, a working group from the *American Association of Pharmaceutical Scientists* (AAPS) presents learnings and recommendations for FIH starting dose selection, early clinical development, and recommended Phase 2 dose (RP2D) selection and bioanalytical and biomarkers strategies for T-cell engaging bispecific antibodies.¹² What sets this White Paper apart from somewhat similar recent reviews is that it provides detailed recommendations on *in vitro* pharmacological assays to determine clinically relevant MABEL, and the authors “recommend defining MABEL at EC₅₀ using pharmacologically relevant MABEL assay setup.”¹² In a second paper, in this issue of CPT, Zhou,

¹Certara, Applied BioSimulation, Canterbury, UK; ²Leiden Academic Centre for Drug Research, Leiden, The Netherlands. *Correspondence: Piet H. van der Graaf (piet.vandergraaf@certara.com)

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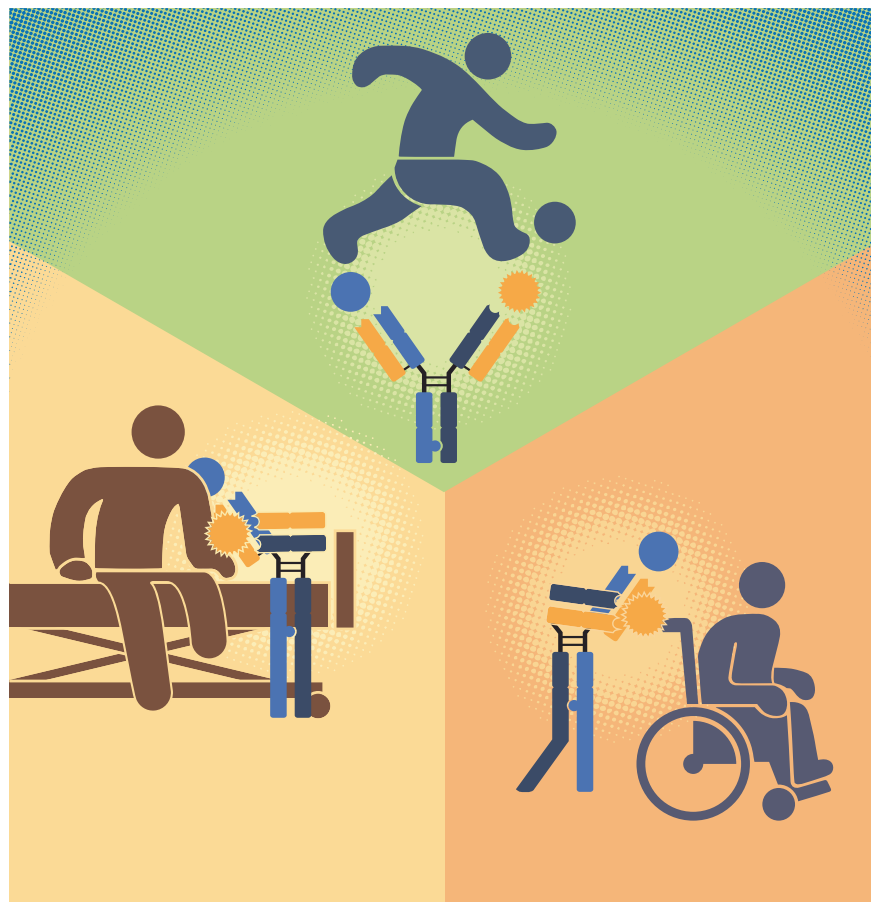


Figure 1 *Clinical Pharmacology & Therapeutics* January 2025 cover image: “First-in-human dose selection for T-cell engaging bispecific antibodies.”

and coworkers try to address what a “pharmacologically relevant MABEL assay setup” is.¹³ To guide FIH dose selection for the bispecific AMG 199, they lowered the effector to target (E:T) ratio in the most sensitive MABEL assay to better reflect the physiological circumstances of the gastric tumor microenvironment in patients. As a result, a 10-fold higher starting dose was selected compared to the one derived from the original assay, and the former was accepted by regulatory agencies. The higher starting dose saved at least two cohorts in FIH and the first clinical observations confirmed it was safe and well tolerated. The novel approach has now been validated across similar programs and the authors propose it can be applied to other bispecifics for both solid and hematological tumors.¹³ An alternative strategy to optimize FIH starting dose for multi-specific biologics and avoid exposing cancer patients to sub-efficacious is the use of quantitative systems pharmacology (QSP) modeling, as discussed in a recent Editorial in this

journal.¹⁴ For example, Carretero-Iglesia *et al.* recently reported that a QSP approach resulted in a 50–100-fold higher starting dose for the trispecific ISB 2001 in multiple myeloma patients.¹⁵ Similar examples¹² demonstrate that innovation in clinical pharmacology has a direct and tangible impact on the speed and cost of the development of bispecific therapeutics, and most importantly on patient lives.

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CONFLICT OF INTEREST

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