Received: 11 May 2023 | Revised: 20 October 2023 | Accepted: 30 October 2023

DOI: 10.1002/psp4.13079

REVIEW

Realizing the promise of Project Optimus: Challenges and emerging opportunities for dose optimization in oncology drug development

Wei Gao[1] | **Jiang Liu**[2] | **Blerta Shtylla**[3] | **Karthik Venkatakrishnan**[1] | **Donghua Yin**[4] | **Mirat Shah**[2] | **Timothy Nicholas**[5] | **Yanguang Cao**[6]

[1]Quantitative Pharmacology, EMD Serono Research & Development Institute, Inc., Billerica, Massachusetts, USA

[2]Food and Drug Administration, Silver Spring, Maryland, USA

[3]Quantitative Systems Pharmacology, Pfizer, San Diego, California, USA

[4]Clinical Pharmacology, Pfizer, San Diego, California, USA

[5]Pharmacometrics, Pfizer, Groton, Connecticut, USA

[6]Division of Pharmacotherapy and Experimental Therapeutics, Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

Correspondence
Wei Gao, EMD Serono Research & Development Institute, Inc., 45A Middlesex Turnpike, Billerica, MA 01821, USA.
Email: wei.gao@emdserono.com

Jiang Liu, US Food and Drug Administration, 10903 New Hampshire Ave, Silver Spring, MD 20993, USA.
Email: jiang.liu@fda.hhs.gov

Timothy Nicholas, Pfizer, 280 Shennecossett Rd, Groton, CT 06340, USA.
Email: timothy.nicholas@pfizer.com

Yanguang Cao, The University of North Carolina at Chapel Hill, 301 Pharmacy Lane, Chapel Hill, NC 27599, USA.
Email: yanguang@unc.edu

Abstract

Project Optimus is a US Food and Drug Administration Oncology Center of Excellence initiative aimed at reforming the dose selection and optimization paradigm in oncology drug development. This project seeks to bring together pharmaceutical companies, international regulatory agencies, academic institutions, patient advocates, and other stakeholders. Although there is much promise in this initiative, there are several challenges that need to be addressed, including multidimensionality of the dose optimization problem in oncology, the heterogeneity of cancer and patients, importance of evaluating long-term tolerability beyond dose-limiting toxicities, and the lack of reliable biomarkers for long-term efficacy. Through the lens of Totality of Evidence and with the mindset of model-informed drug development, we offer insights into dose optimization by building a quantitative knowledge base integrating diverse sources of data and leveraging quantitative modeling tools to build evidence for drug dosage considering exposure, disease biology, efficacy, toxicity, and patient factors. We believe that rational dose optimization can be achieved in oncology drug development, improving patient outcomes by maximizing therapeutic benefit while minimizing toxicity.

INTRODUCTION

Dose optimization in oncology drug development, as in many other therapeutic areas, demands multidisciplinary approaches, making cross-functional commitment vital for success. A Totality of Evidence (ToE) approach would ideally be applied, which involves proactively embedding relevant translational and clinical data generation and integration via iterative modeling and simulation approaches to decrease uncertainty and increase confidence over the development lifecycle progressively.

Project Optimus is an initiative launched by the US Food and Drug Administration (FDA) Oncology Center of Excellence in 2021, aimed at reforming the dose selection and optimization paradigm in oncology.[1–3] According to the FDA, the initiative aims to "educate, innovate, and collaborate with companies, academia, professional societies, international regulatory authorities, and patients 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." The mission of this initiative is to ensure patients are treated with safe and efficacious cancer therapeutics with dosages that are optimized to maximize efficacy while minimizing toxicity.

The conventional paradigm of dose selection for oncology products has typically been a safety-driven approach based on identifying the maximum tolerated dose (MTD; Figure 1), which is generally determined based on assessment of the safety especially dose limiting toxicities (DLTs) within limited numbers of patients and short durations that may not reflect the long-term treatment goals and the tolerability of the drug in clinical practice with contemporary non-cytotoxic mechanisms and modalities. Importantly, emerging immuno-oncology and targeted therapies may achieve desired therapeutic effects at doses lower than the MTD because they often possess different dose/exposure–response (E–R) relationships and potentially wider therapeutic indices compared to cytotoxic chemotherapeutics.[4] In many cases, an MTD is not reached.[5,6] Additionally, newer agents with better safety and tolerability profiles may allow for longer treatment duration. As a result, a lower dose than the MTD may offer a superior benefit–risk profile for patients, particularly for adverse events (AEs) that significantly affect a patient's quality of life and drug compliance. Recognizing the gaps in current practices, stakeholders in the oncology drug development community, including the FDA, have been discussing the

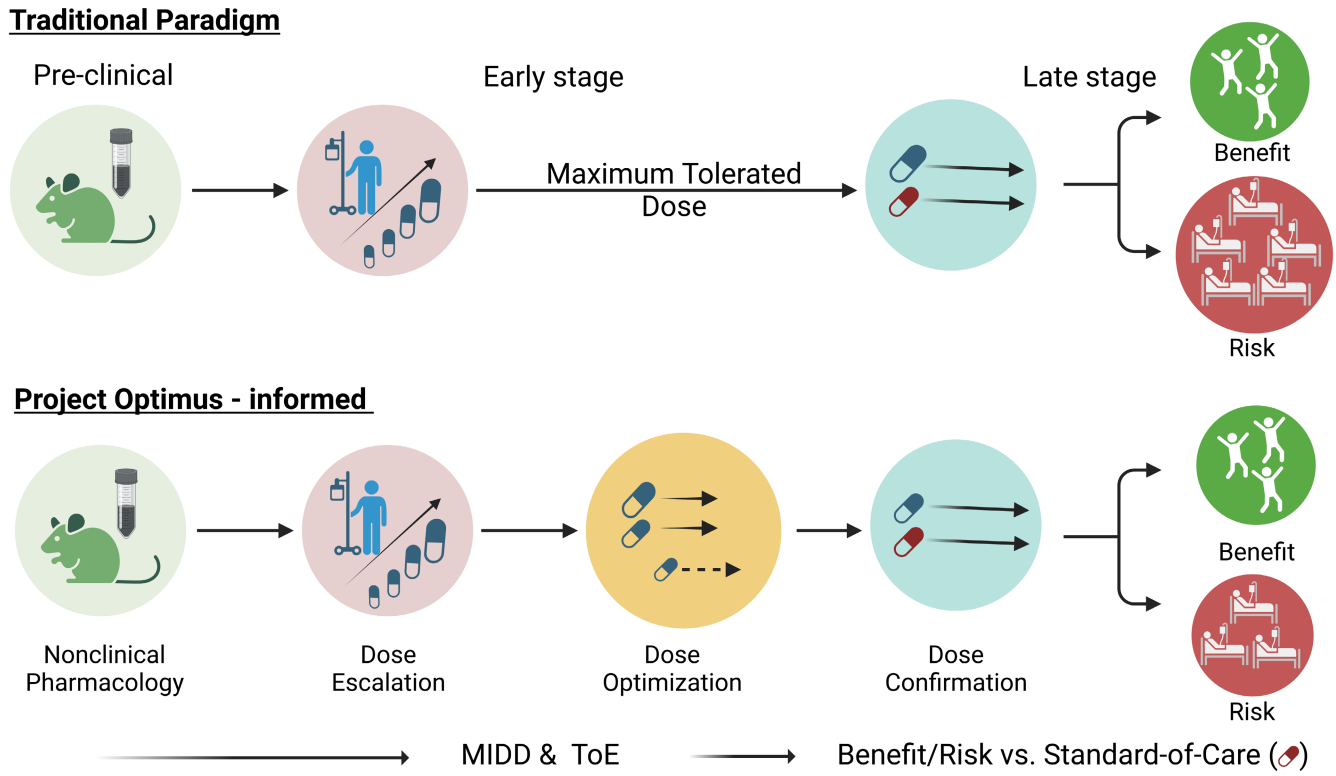

FIGURE 1 Traditional MTD paradigm vs. rational dose optimization approach under Project Optimus for oncology drug development. MIDD, model-informed drug development; ToE, totality of evidence; red pill, control arm, that is, the standard of care.

need for novel approaches to dose optimization over the last decade. Project Optimus provides a unique opportunity for stakeholders in the field to prepare for the new era of a more rational, model-informed drug development-driven approach to dose optimization in oncology clinical development. As quantitative drug developers, it is important to proactively take steps toward readiness for this paradigm shift with progressive changes in the design, conduct, and interpretation of clinical trials.

At the recent American Conference on Pharmacometrics (ACoP) Annual Meeting in 2022, a scientific symposium (*Oncology Drug Development – Getting Ready for Project Optimus*) was held to discuss the opportunities and challenges related to oncology drug development from the pharmaceutical industry, academic, and regulatory perspectives.[7] The symposium highlighted ongoing efforts and complementary perspectives, and put forth strategies for addressing the challenges in implementing Project Optimus. This review delves into this subject matter, drawing inspiration from the presentations and dialogues that took place during the ACoP session.

CHALLENGES

The field of oncology faces unique challenges in the development of new drugs, particularly in rational dose optimization.[1] One of the primary challenges is the heterogeneity of cancer itself, leading to high variations in patient response and safety profiles.[8] Interpatient variability is particularly high within early-phase trials, where participants have often undergone multiple lines of prior therapy which can impact both the safety and antitumor activity measured during treatment with the investigational agent.[9] Factors, such as genetic variability, concomitant drug use, frailty, and cachexia, heterogeneous dose modification/interruption patterns, potential salvage or risk mitigation treatment, and time-variant changes in pharmacokinetics (PK) or pharmacodynamics (PD) can all contribute to high variability, further complicating dose optimization. Without a sufficiently large sample size, establishing robust dose–response and dose-safety relationships in early phase trials becomes challenging because of the diverse patient responses and safety profiles inherent in oncology.

Furthermore, early-phase trials are usually constrained by their short observation periods, limiting the ability to provide a complete picture of the longer-term safety and tolerability that can have a significant impact on patients' with cancer quality of life and treatment compliance.[10] These trial designs typically are not optimized to precisely determine a dose that considers the later-cycle dose adjustments, discontinuations, or milder AEs experienced over an extended duration by a larger patient group. In a thorough analysis of 59 newly approved oral molecular entities from 2010 to 2020, registration trials exhibited median dose reduction, interruption, and discontinuation rates of 28%, 55%, and 10%, respectively.[11] However, acquiring long-term tolerability data usually requires late-phase trials. Additionally, patients enrolled in early-phase trials are frequently heavily pretreated, with limited life expectancies and differing risk tolerances compared to the phase III or intended-use population. These variations in tolerance for immediate and lasting toxicities introduce extra complexities to the selection of optimal oncology drug doses in early-phase trials.

Another challenge of determining the optimal dosage during oncology drug development is the constantly evolving nature of cancer as a disease.[12–15] Cancer cells undergo continuous mutations and genetic changes, leading to time-dependent variations in response to treatments and tumor progression.[16–18] This dynamic variation makes cancer a highly heterogeneous group of diseases, where treatment responses are heavily influenced by the tumor's genetic makeup both before and during the treatment process. As a result, early efficacy readouts may not always consistently translate to long-term clinical outcome or survival benefit.[19] Even within individual patients, early responses might not offer a full projection of long-term survival duration. Finding PD markers that are related to clinical efficacy pose a critical and challenging task within dose optimization studies, necessitating in-depth data analysis and rigorous verification of biomarkers.

Pharmacologically informed modeling and simulation approaches, as reflected in the model-informed drug development (MIDD) framework, have the potential to greatly improve dose optimization practices in oncology drug development.[20] Within the scope of Project Optimus, the utility of MIDD strategies is underscored in their support for more adaptive study designs, integration of preclinical insights, real-time assimilation of PK and PD data, validation of PD markers, and the comprehensive utilization of all available data to delineate an appropriate dose range for further exploration. Nevertheless, it is important to acknowledge that developing and calibrating these models can be complex and computationally demanding, requiring significant amounts of data, expertise, time, and resources. Also crucial for successful implementation is an enterprise-wide commitment of the patient-focused value proposition of investing in a model-informed dose optimization approach and commitment that transcends beyond the clinical pharmacology and pharmacometric communities of practice.

ONCOLOGY DOSE SELECTION/ OPTIMIZATION: A MULTI-DIMENSIONAL PROBLEM REQUIRING A TOTALITY OF EVIDENCE APPROACH COUPLED WITH MODEL-INFORMED DRUG DEVELOPMENT MINDSET

A multidimensional problem

Dose selection and optimization in oncology is a complex task that requires careful consideration of a range of factors, with multiple challenging issues mentioned above. Dose optimization is often a nested problem and needs to be considered in the context of multidimensional optimization of the patient population (cancer type, line of treatment, and predictive biomarker for patient selection) and combination, which includes not only the identification of the right combination partner but importantly its dose, schedule, and, for some mechanisms, the sequence of co-administration.[21] However, there are several opportunities associated with these challenges. For example, small patient populations and high variability of diseases and patients in early clinical trials can lead to opportunities for adaptive trial designs, contextualization in reference to real-world data, Bayesian approaches, patient stratification, and biomarker-assisted trials.[22–26] Moreover, the evolving mindset of oncologists, which places greater emphasis on patient safety and the need for rigorous evaluation of drug benefit–risk profiles, highlights the importance of optimizing doses and treatment regimens to ensure the best possible outcomes for patients.[27,28] Poor dose optimization can lead to adverse consequences for patients, primarily due to toxicity, resulting in a reduced quality of life, frequent dose adjustments at the approved dose, diminished treatment efficacy due to patients' inability to continue therapy or receive subsequent treatment because of toxicities, and challenges in developing combination regimens. Adaptive trial designs enable the real-time or interim analysis of PK, PD biomarkers, and safety data, allowing for the identification of arms with suboptimal dosages for elimination or arms exhibiting favorable efficacy and safety profiles to be supplemented. These trials can incorporate stopping rules based on efficacy, safety, or a combination of both. A notable illustration is presented by study BLC2001, a multicenter, open-label investigation assessing various dosing regimens of erdafitinib in patients with metastatic or surgically unresectable urothelial cancer.[29] The primary objective involved evaluating the overall response rate (ORR) of the selected dosing regimens within a randomized and adaptive design framework. Several prespecified interim analyses were based on ORR, PK, and PD modeling, providing support for discontinuing an inferior dosage arm (10 mg once daily 7 days on/7 days off, with a potential dose increase to 12 mg once daily 7 days on/7 days off beginning in cycle 2). Subsequent PK/PD analysis and clinical data revealed an alternative dosing regimen (8 mg once daily, with a dose increase to 9 mg once daily if serum PO4 level is <5.5 mg/dL) that could optimize the number of patients with serum PO4 levels within the desired range while minimizing treatment interruptions and dose reductions. This alternative dosing regimen was introduced through a protocol amendment and subsequently expanded in subsequent studies, ultimately becoming the approved dosage.

The strategy for selection of dosage (which is comprised of the dose and dosing schedule) of a drug in a general or specific population requires careful consideration of various factors.[30] As shown in Figure 2, those factors can be generally grouped into four major domains: disease-related factors, drug-related factors, patient-related factors, and trial-related factors. It is important to appreciate that dose selection and optimization is an iterative process with different goals at various stages of drug development and should be updated continually as new data become available. When designing the preclinical and clinical development plan at each stage, one common question to ask is how the evidence generated in this stage can fill the knowledge gaps and reduce pertinent uncertainties in the next stage. The primary objective of early drug development, with limited data to define the therapeutic index, is to identify the safe dose and understand the mechanism of action (MoA) and other properties (e.g., modality, PK, PD, etc.) of the novel molecule. Information from preclinical models and the same modality or class of drugs can be leveraged to potentially help fill in where clinical data are lacking. As illustrated in the asciminib case, target asciminib concentrations used for dose optimization were identified using tumor cell lines and xenograft models.[31]

During phase I/II expansion and proof-of-concept stage, important questions include: clinical antitumor activity and safety/tolerability profile in the targeted patient population(s) and dose(s) to be taken forward for confirmatory trials. This is the most critical stage for data generation to inform dose selection, with adequate sample size and treatment duration, and ideally more than one dose level evaluated with a sufficient number of subjects. Notably, dose-expansion trials, which aim to compare different dosages, are typically not designed to provide primary evidence of safety and efficacy for future regulatory approval. In such trials, which strive to further refine dose optimization, the stringent control of type I error may not be essential, given that the trial's main objective is not to definitively establish effectiveness. Additionally, when more than two dosages are under consideration, the design does not necessarily mandate the power to detect pairwise

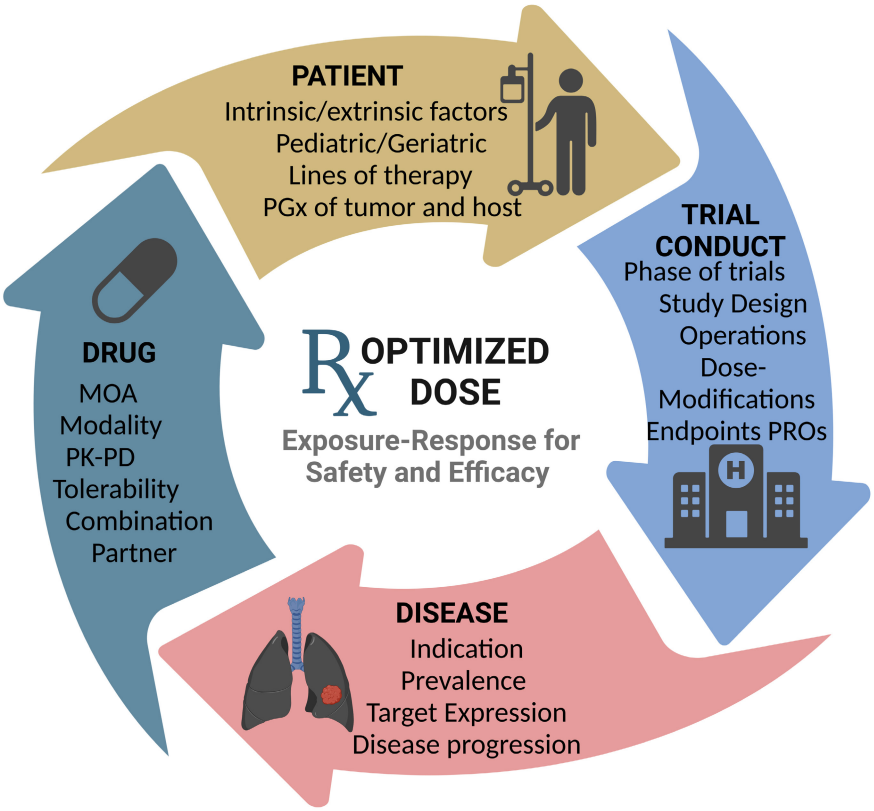

FIGURE 2 Factors impacting optimal dose for oncology treatment. MOA, mechanism of action; PK-PD, pharmacokinetics-pharmacodynamics; PGx, pharmacogenetics; PROs, patient-reported outcomes.

comparisons if a meaningful dose–response trend can be ascertained across arms.[1]

A patient-centric approach in drug development takes into account both intrinsic and extrinsic factors, such as genetic variability, comorbidities, and concomitant medications, which can impact drug exposure, efficacy, and safety.[32] As an example, ceritinib was originally dosed at 750 mg once daily in a fasting state, based on phase I escalation and expansion trials that led to this initially approved posology.[33] However, significant dose reduction/interruption (>60%) was observed primarily due to adverse reactions related to gastrointestinal toxicities, such as diarrhea, nausea, vomiting, and abdominal pain. Of note, a positive food effect was also uncovered at a later stage of drug development, leading to an additional clinical trial evaluating the benefit/risk profile of fed dosing in patients. The totality of these findings led to an update in ceritinib's posology, with the currently approved dosage of 450 mg dose once daily with food, given that dosing with food resulted in better gastrointestinal tolerability.[34] This example emphasizes the critical importance of timely assessment of the role of intrinsic and extrinsic factors so that dosing and administration conditions can be optimized before pivotal development.

The dosing strategy may vary depending on the indication and the benefit–risk assessments for each indication. Information regarding drug PK, PD, antitumor activity, and toxicities across the cancer types or disease settings of interest is critical to consider when selecting and optimizing the dose for a specific indication or patient population. For instance, trastuzumab deruxtecan was first approved at a dose of 5.4 mg/kg every 3 weeks (q3w) based on the results of the DESTINY-Breast01 trial for HER2-positive metastatic breast cancer.[35] Based on results from the DESTINY-Gastric01 trial, which evaluated the drug in patients with HER2-positive gastric cancer, a higher dose of 6.4 mg/kg q3w was approved for gastric cancer. Trastuzumab deruxtecan received further approval recently for patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have an activating human epidermal growth factor receptor 2 HER2 mutation. The recommended dosage for NSCLC is 5.4 mg/kg q3w, the same dosage for the first approved indication of breast cancer, despite the initially focused dosage in the drug development for NSCLC of 6.4 mg/kg q3w in the DESTINY-Lung01 (NCT03505710) trial that demonstrated favorable outcome. Intensive dose selection efforts for NSCLC were implemented under Project Optimus with a focus on mitigating risk for the specific drug-related safety concerns of interstitial lung disease and pneumonitis that were particularly relevant in this population. Thus, the randomized two-arm phase II dose optimization trial DESTINY-Lung02 (NCT04644237) was further conducted. The lower dose of 5.4 mg/kg demonstrated consistent response rates but favorable safety compared to that at the originally

focused 6.4 mg/kg. It was reported that the confirmed ORR in the prespecified early cohort of the DESTINY-Lung02 trial was 53.8% (95% confidence interval [CI], 39.5%–67.8%) at the lower dose group and 42.9% (95% CI, 24.5%–62.8%) at the higher dose group.[36] Patients in the lower dose also experienced a lower frequency of drug-related AEs, including a lower rate of interstitial lung disease. Further population PK evaluation indicated comparable trastuzumab deruxtecan clearance in NSCLC to those in patients with breast cancer.

An illustrative example of dose optimization across patient populations is seen in the case of asciminib.[37] Using PK/PD modeling and simulation, the dose for asciminib, an allosteric inhibitor targeting the BCR-ABL1 protein, was optimized in patients with Philadelphia chromosome-positive chronic myeloid leukemia. Two distinct dosages (40 mg and 200 mg twice a day) were selected for patients in the chronic phase and those with the T315I mutation, respectively. Population PK and PD predictions indicated that both dosages would maintain nearly all patients above the target threshold during the dosing interval. These optimized dosages were then used in the pivotal registration trial and larger expansion cohort, demonstrating efficacy and safety for the initial approval. The above examples illustrate timely, continuous, and iterative knowledge management and data analysis are essential to inform dose selection for optimizing the benefit–risk profile of investigational oncology therapeutics throughout the drug development process.

Totality of evidence approach

The complexity of oncology dose selection and optimization truly highlights the need for a holistic approach with a ToE mindset by leveraging all relevant data to build evidence toward rational dose selection and optimization.[38] MIDD represents a valuable approach to integrate multidimensional evidence, including biology knowledge, in vitro and in vivo animal studies, early phase clinical trials, PK and PD data, patient-specific factors, such as genetics and comorbidities, and knowledge about the competitor compounds, increasingly bolstered by the integration of real-world data. A tangible example of this ToE approach is seen in the case of selpercatinib, an inhibitor of the RET receptor tyrosine kinase, which was obtained accelerated approval for multiple indications, including metastatic RET fusion–positive NSCLC.[39] The approved dosage was optimized through a dose-escalation trial using continuously updated PK/PD models and simulated tumor inhibition profiles based on prior knowledge and emerging clinical data. The 160 mg twice a day dosage was selected considering tumor inhibition models and potential safety concerns related to concentration-dependent QTc interval prolongation. Subsequent PK/PD modeling and simulation further confirmed that tumor size reduction correlated with improved survival probability in patients with RET fusion NSCLC and RET-mutant medullary thyroid cancer, thus supporting the approved dosage.

Additionally, the learn-confirm MIDD paradigm promotes cross-functional collaboration among clinical pharmacologists, pharmacometricians, system pharmacologists, oncologists, statisticians, biomarker scientists, and other stakeholders and ensures that the right questions are being asked and answered throughout the drug development process. The integration of an MIDD approach and a ToE mindset supports a more integrated approach that is importantly purpose-oriented, pivoting to the questions that matter – which in the case of dose optimization pertains to finding the right dosage across clinical contexts of use to maximize benefit versus risk for all patients.

Generate right data package

Drug development is a highly dynamic process, and questions related to dose selection and optimization evolve with the different goals and available knowledge at each phase, as the drug development process progresses from preclinical studies to clinical trials to regulatory submissions and postmarketing activities. Thus, the experiment/trial design and analysis tools must be customized accordingly (Figure 3). This requires a thoughtful and strategic approach to nonclinical and clinical experimental design and execution, including careful consideration of study end points, patient selection criteria, dosing strategies, data collection, and risk management in clinical trials.

In general, collecting data from multiple dose levels, prior to the confirmatory trials, is critical to characterizing the dose/E–R relationships both for efficacy and safety, and to informing dose optimization.[1] The FDA Draft Guidance recommends use of randomized, parallel dose–response trial for comparison of multiple dosages.[3,40] The purpose of these trials is not to demonstrate statistical superiority of one dosage. Rather, it is important that the trial sample size is adequate for assessment of activity, safety, and tolerability for more than one dosage. Additionally, collection of long-term safety and tolerability data is integral to understand the potential for late onset toxicity and the impact of low-grade toxicity, throughout the clinical development process, beginning in the early phases of development, to ensure the proper characterization of the safety and tolerability profile of the drug.

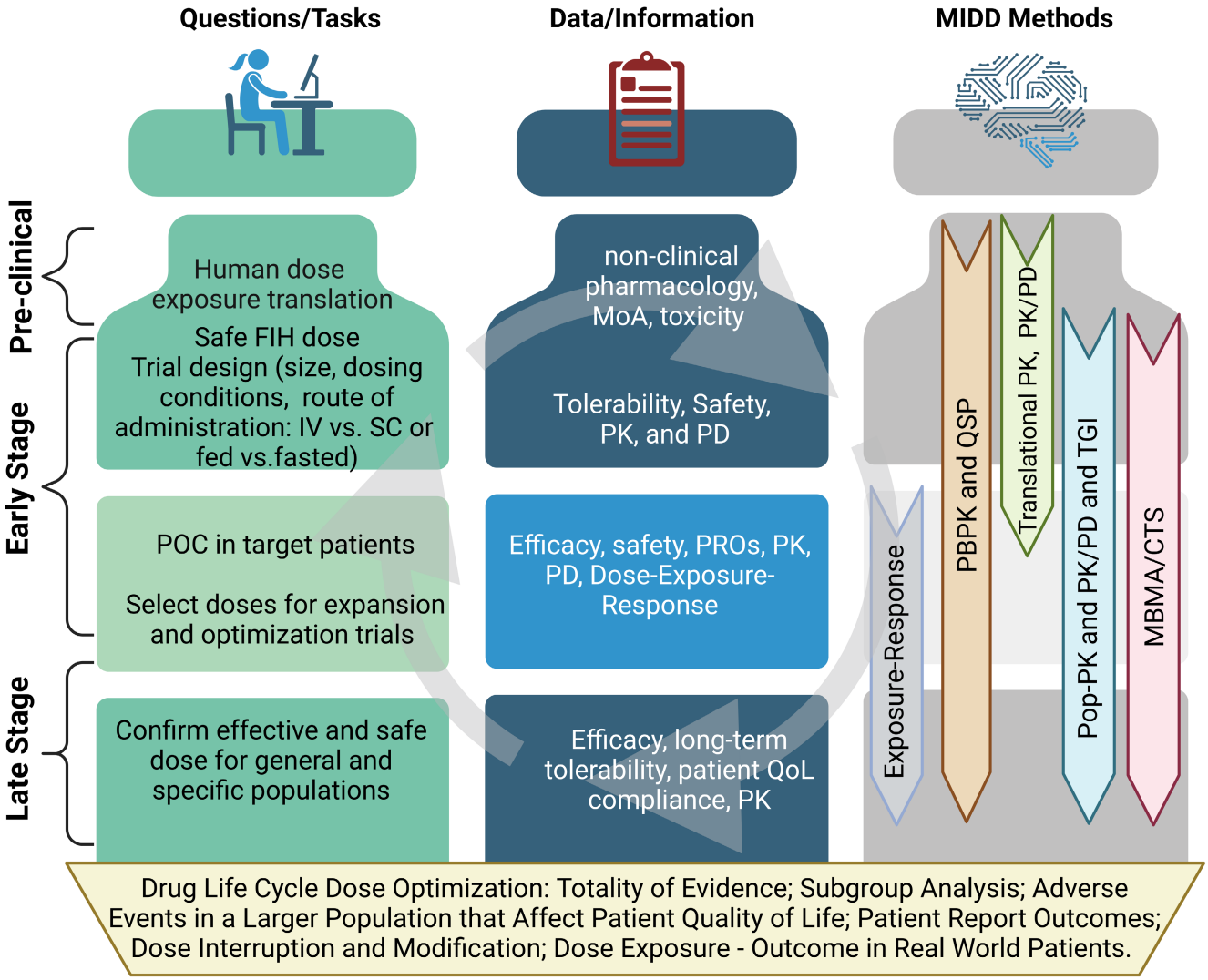

FIGURE 3 The evolving and interactive questions, evidence, and MIDD tools for oncology dose optimization. Dose optimization entails a longitudinal integration of modeling and simulation tools and approaches to address the evolving questions from the early translational stage of oncology research and development to the post-approval phase. CTS, clinical trial simulation; FIH, first-in-human; MBMA, model-based meta-analysis; MIDD, model-informed drug development; MoA, mechanism of action; ORR, overall response rate; OS, overall survival; PBPK, physiologically-based pharmacokinetic; PD, pharmacodynamic; PFS, progression-free survival; PK, pharmacokinetic; POC, proof-of-concept; PRO, patient-reported outcomes; QoL, quality of life; QSP, quantitative systems pharmacology; TGI, tumor growth inhibition.

Generating key evidence early in the development process, such as proof of mechanism, is critical for informing dose selection and optimization and maximizing the chances of success in the later phase. Whereas some decision-making frameworks (e.g., 3 Pillar and 5R) have been widely appreciated and deployed across therapeutic areas, the consistent application of these principles can be challenging in oncology due to the complexity of the disease and patient populations, as well as the accelerated development timelines often required, as reviewed earlier.[41–43] Engaging in discussions with the FDA regarding dose selection strategies in early development can be important for a successful application. Sharing all relevant information used to support dosing decisions will facilitate FDA's ability to provide specific recommendations. This approach fosters a concerted and united effort to consistently apply these principles to enable rational oncology drug development with a focus on timely dose optimization.

Apply right MIDD approaches

To maximize the value of MIDD tools, it is essential to build the quantitative knowledge base proactively by integrating the best available knowledge into mathematical

models designed for evidence generation.[44] It also requires proactively identifying opportunities and actively utilizing relevant MIDD tools throughout the research and development (R&D) process. MIDD tools together with experiments can be used, not only to inform dose selection and optimization, but also to generate hypotheses, identify and fill in gaps in knowledge, and inform clinical trial(s) design, as well as program development strategy. A model development lifecycle relies on iterative steps of data collection, synthesis, estimation, and simulation to fill the modeling and simulation (M&S) toolbox and the learn-confirm cycle. These MIDD tools are expected to evolve throughout a program, and can be utilized for decision making at key steps. As model objects (quantitative knowledge), they can also be adapted or repurposed for other programs being developed. Examples include (1) the borrowing of relevant biological system parameters in mechanistic models that describe the time course of pharmacological activity and associated dose–response for a bispecific T-cell engager development program and for a CAR-T development program that may both be directed toward the same tumor antigen, and (2) the borrowing of drug-related platform knowledge regarding the exposure–toxicity relationships of a common payload that may be a component of antibody-drug conjugates directed at different tumor antigens.

Disease progression modeling (DPM) in neurological diseases represents a good inspirational example how MIDD tools can be used to inform drug development in oncology.[45] DPM has been developed and validated over several decades and integrated multiple types of data, including clinical end points, biomarkers, and imaging, to provide a comprehensive understanding of disease progression and treatment effects. The modeling platform has been leveraged to inform dose selection and optimization, optimize trial design, and identify patient subgroups more likely to respond to treatment.[46] For oncology, indication-specific disease models relating the time course of tumor size (or other measures of tumor burden, such as circulating tumor markers) to survival outcomes can serve as valuable knowledge priors for MIDD in oncology.[47] Such platform model-based priors, together with population PK tumor size analysis of emerging longitudinal tumor size data in dose-ranging expansion cohorts can in principle help forecast the potential relationships between dose and efficacy when applied as part of a Bayesian forecasting framework. Such an approach could help inform the probability that a higher dose (e.g., near-MTD) may offer clinically meaningful improvement in efficacy outcomes compared to a lower, potentially more tolerable dose level. Whereas initial oncology disease models were driven by landmark measures of tumor shrinkage as the predictor of survival hazard, longitudinal models that dynamically link the time course of tumor size to survival hazard are increasingly used, including the emergence of multistate modeling frameworks that can powerfully integrate the totality of tumor size, response categories, and overall survival (OS) states in a longitudinal dataset while also protecting from the impact of immortal time bias.[48–54]

Translational PK/PD (tPK/PD) and Quantitative Systems Pharmacology (QSP) modeling facilitates integration of ToE, including pathophysiology and mechanistic understanding of tumor biology, pharmacology, information from competitor compounds, preclinical and clinical data, to provide a mechanism-based efficacy and toxicity evaluation in silico. Here, we are using the term QSP to more broadly represent both tPK/PD or QSP models. QSP models have been increasingly applied to mechanistically inform drug development and guide regulatory decisions, especially in supporting dose selection in early clinical trials (e.g., first-in-human [FIH]).[55,56] The bottom-up modeling approach of QSP is particularly valuable in oncology, where early clinical trials often lack predictive biomarkers and indication-specific efficacy data, and translation of E–R from preclinical in vivo models is fraught with challenges, particularly for immuno-oncology compounds and modalities.[57] In cases where significant uncertainties exist due to extrapolation into a new MoA, or new indication, a sequential iterative calibration approach can be adopted to gain confidence in QSP model projections. In Kiruac et al., a QSP model linking cell surface receptor (EGFR) activation, the MAPK signaling pathway, and tumor growth of BRAV600 melanoma was converted to BRAV600 CRC through calibration with in vitro (cell line), in vivo (cell- and patient-derived xenograft) studies, tumor response data from three phase I clinical trials testing combinations of EGFR, BRAF, and MEK inhibitors.[58] The model was used to accurately predict phase I clinical response for a new ERK inhibitor and prospective simulations were then used to evaluate potential drug combinations and predictive biomarkers for increasing responsiveness to MEK/ERK inhibitors in the relevant patients with colorectal cancer (CRC) population. Most tumors are highly heterogeneous in terms of clonal composition and molecular phenotypes requiring expansion of classical QSP toolset to include innovative mathematical modeling approaches that can incorporate tumor heterogeneity and resistance development into model-informed dose optimization. A promising example in this space is the work of Poels et al., that used a tumor clonal prevalence model parameterized using in vitro dose–response data in addition to incorporating tumor heterogeneity and intersubject PK variability to predict tumor evolution under different dosing schedules of already approved osimertinib and dacomitinib.[59] This model was validated using cell line data and used to identify an optimal combination dosing schedule used to

support the design for a dose-escalation phase I clinical trial in patients with advanced EGFR mutant lung cancer for study NCT03810807. Continued innovation in QSP virtual trial simulation strategies, as well as more recent efforts using new QSP digital twins workflows has enabled systematic exploration and mapping of biological heterogeneity onto treatment response heterogeneity.[55,55,60–65]

QSP modeling has become an important tool to address questions concerning target selection/validation, human efficacious dose projection, rational combination strategies, patient stratification, and response variability.[60] Continued use of QSP to support dose optimization after the start of FIH studies has been enabled from rapid calibration of models with emerging FIH clinical data and methodological improvements enabling quantitative end-to-end integration from target engagement all the way to key clinical end points of therapeutic response, such as ORR and progression-free survival. Mosunetuzumab (CD20/CD3 bispecific) provides two case studies to illustrate the potential of QSP to support dose optimization in early clinical development. First, a QSP model of Cytokine Release Syndrome using non-human primate data was used to inform the phase Ia/Ib dose escalation design of study NCT02500407 in patients with relapsing/refractory non-Hodgkin's lymphoma (NHL) by proposing pharmacologically plausible step-up dosing regimens to reduce the risk of cytokine release syndrome (CRS) by balancing efficacy considerations.[56] Clinical data generated from NCT02500407 has since confirmed the CRS mitigation of the QSP model-informed step-up dosing regimen. Second, QSP simulated digital twins calibrated with phase I data from NCT02500407 were used to support the characterization of dose/E–R relationships and subsequent dose expansion.[55] Clinically calibrated QSP models, as illustrated here, can help explore through incorporation of totality of clinical and preclinical data across mechanistic sources of patient heterogeneity especially when clinical data are limited, as in the case for mosunetuzumab and other phase I studies, and when different dosing regimens are used across cohorts (fixed and step-up dosing administration of mosunetuzumab). We anticipate that similar examples will continue to emerge, given the recent landscape analysis of the FDA regulatory submissions involving QSP by Bai et al., where the primary use of QSP since 2013 was identified to be in support of dosing questions, including supporting phase III dose selection and pediatric study plans, supporting the dosing regimens in new drug application/biologics license application/biologics license application submissions and supplements for supporting dose selection in new indications.[66]

Whereas the use of QSP as part of the MIDD toolset has been steadily expanding over the years, it will be important for the QSP community to identify key future opportunities, through continued engagement of key pharma stakeholders, academic and regulatory communities, and key use-cases that showcase how QSP can be further engaged in support with dose optimization activities. A few areas of potential future opportunities for QSP to support dose optimization activities are being outlined below. One area of future use of QSP models to support dose optimization would be through early evaluation of optimization dose/regimen strategies for combinations using monotherapy dose optimization data (through assessment of the contribution of components), thereby streamlining and prioritizing doses/regimens that require prospective clinical evaluation. In addition, another area for further evaluation is the use of QSP models to allow early evaluation and continued support of dose/regimens finding activities in different patient populations through bottom-up integration of mechanistic basis for disease progression (e.g., resistant vs. nonresistant virtual patients, early vs. late treatment line patients through use of virtual trials and digital twins). QSP models that contain sufficient biological resolution to project efficacy and toxicity end points can serve a unique role for early evaluation of the therapeutic index, which can then be refined as more clinical data becomes available. Finally, the burst of many novel and complex modalities (e.g., bispecifics, tri-specific antibodies, ADCs, and PROTACs) in oncology requires a deeper and quantitative understanding of the distribution and delivery of active moiety to the site of action and the patient's systemic (including immune) response, QSP modeling could provide an in silico hypothesis testing strategy based on preclinical data, when clinical data are lacking or sparse to enable traditional population PK/PD or E–R analyses to inform dose selection.[67–70] QSP models have demonstrated their utility in amalgamating information from in vitro, preclinical, and early clinical investigations to optimize dosages and regimens for these innovative modalities, especially in the realm of bispecific T-cell engaging biologics; we anticipate that more examples will emerge in the future that illustrate expanded use of QSP in dose optimization.

Physiologically-based pharmacokinetic (PBPK) modeling is another tool widely used in drug development. PBPK incorporates physiological factors, including tissue composition and blood flow, together with drug-specific factors and provides a bottom-up mechanistic characterization of the PK and/or PD behaviors of a drug.[71–74] PBPK analyses have been extensively applied to exploring the effects of extrinsic factors (e.g., concomitant medications and food intake) and intrinsic factors (e.g., age, organ dysfunction, and disease status) on drug exposures and to support dosing recommendations in product labeling. Here, we are focusing on the specific applications of PBPK in addressing general dose selection and

optimization questions in oncology. By adjusting input parameters, such as the dose and dosing regimen, PBPK models can be used to predict the concentration of the drug in different tissues and organs over time. This information can be used to achieve sufficient target concentrations in the tumor while minimizing exposure in normal tissues. A minimal PBPK model for pembrolizumab was used to justify an optimal dose, taking into account the biodistribution of the antibody and the heterogeneity of the tumor in terms of blood perfusion.[75] The model was able to predict tumor and serum concentrations of pembrolizumab, as well as the extent of receptor occupancy at the tumor site, based on different dosing regimens. PBPK model simulations showed that a dose of 200 mg q3w (the recommended phase I dose [RP2D]) could achieve a target receptor occupancy of at least 90% in clinically relevant scenarios. Although the modeling work was done retrospectively and there are some lingering concerns regarding the model assumptions, it provides a modeling framework to predict pharmacology at the site of action.[76]

PBPK modeling could incorporate the binding properties of biologics to target cells, such as T-cells, throughout the human body, and quantify drug disposition in various tissues, including the site of action, and make reasonable predictions of receptor occupancy. The limited distribution of drugs to certain tissues or organs can be a challenge in cancer therapy. Many primary and metastatic lesions have poor vascularization and often reside in tissues with limited drug distribution, leading to incomplete tumor coverage and suboptimal treatment outcomes. PBPK modeling can help predict the dose that can achieve adequate exposure and receptor occupancy in poorly vascularized lesions or tissues with limited drug distribution. Specific opportunities include primary central nervous system tumors and brain metastases.[77,78] This information can be used to guide dose selection in the early stages of drug development when rich exposure–response data may not yet be available. Incorporating PBPK modeling to forecast drug exposure within tumors could offer more reliable forecasts of target engagement. A case in point is the development of cetuximab, an EGFR antagonist antibody approved for metastatic colorectal and head and neck cancer, where the determination of dosing was backed by target engagement as an indicator of effectiveness. Instead of directly measuring target engagement, the saturation of cetuximab clearance, as inferred from PK modeling, was used to estimate target engagement.[79] Analysis of PK data and modeling demonstrated that cetuximab clearance diminished with escalating doses, reaching a plateau at ~200 mg/m^2. Based on the concept of target saturation, a weekly dose of 200 mg/m^2 was recommended for phase II trials. Cetuximab's approval was granted with a maintenance dose of 250 mg/m^2 weekly (initial dose of 400 mg/m^2).

In addition, PBPK models, coupled with QSP models, have been used to optimize the dosing of BiTEs, which are bispecific antibodies that activate T-cells to kill cancer cells. A QSP and PBPK model were used to predict the exposure–response relationship of AMG420, a BiTE used in the treatment of acute lymphoblastic leukemia.[80] The model predicted the optimal dose and schedule of the drug based on factors such as T-cell activation, target expression levels, and PK data. PBPK models can provide a valuable starting point for predicting drug exposure and target engagement and establishing the exposure–response relationship, which in turn can inform dose selection and optimization and support clinical decision making.

Population PK/PD/tumor growth inhibition (TGI) modeling and dose/exposure–response modeling have been widely used in oncology drug development to characterize the variability of drug PK, target occupancy and PD biomarkers, tumor kinetics, clinical efficacy, and safety/tolerability end points. These approaches typically require sufficient sample size and particularly are useful to inform RP2D. These top-down methods, coupled with other statistical techniques and covariate models, provide direct illustration of dose-dependent effectiveness and toxicity, supporting dose expansion and confirmation. The TGI models are mostly used to quantify treatment effects in tumor xenograft experiments and have become well adopted for characterizing drug effects in patients.[49] An example above was for the BCR::ABL1 inhibitor asciminib in chronic phase – chronic myeloid leukemia where the application of tumor dynamic modeling of BCR::ABL1 transcript dynamics elucidated the E–R relationship in this biologically heterogeneous disease. This analysis was vital in informing selection of substantially different doses depending on tumor biology (i.e., presence vs. absence of the T315I mutation) for pivotal development, also serving as a reminder of the importance of pharmacologically informed and multidimensional dose optimization where a single dosage may not be appropriate for all target indications. Although TGI models have been applied for many cytotoxics as well as targeted agents, the model formulations are often semimechanistic and may not contain the level of resolution to infer a biological mechanism, such as whether the drug inhibits growth or directly induces cytotoxicity. Therefore, additional experimental data and more complex model formulations may be needed to elucidate the underlying biological mechanisms and improve the predictive performance of TGI models.

Over the past decade, encouraging progress has been made in the development and application of pharmacostatistical methodology for joint modeling, linking TGI and survival analysis along with certain baseline characteristics in solid tumors, which suggest that longitudinal tumor dynamics data and TGI-survival modeling could

help support early decision making. In their publication, Zheng et al.[81] demonstrated the utility of a population TGI-OS model for durvalumab to identify potential predictive or prognostic biomarkers for tumor growth, shrinkage, and OS in patients with urothelial carcinoma. Chan et al.[82] developed a TGI-OS modeling framework using tumor size data from 10 phase II/III atezolizumab studies across five solid tumor types. The TGI-OS models were able to adequately describe the OS distribution and to predict treatment effect with various atezolizumab monotherapy or combination regimens. Here, population PK/PD/TGI models can assume pivotal roles for establishing relationships among dose (exposure), target engagement, tumor shrinkage, and clinical efficacy.

Regardless of whether the application is in oncology or non-oncology, the MIDD toolbox should include both bottom-up mechanistic modeling and top-down data-driven approaches.[83–86] These approaches, despite having a different algorithm in utilizing data, information, and knowledge for model building, are not mutually exclusive, and may be used in a complementary manner. MIDD tools provide complementary value, and it is essential to use them collaboratively to maximize their potential. Integration of all relevant data, information, and evidence assembled and continuous updates to the quantitative knowledge base throughout the drug discovery and development process are essential for dose selection and optimization. Often, the quantitative knowledge base can be rapidly repurposed for new therapies and enable quantitative assessment of potential combination therapies. Synergy stimulated by applying all relevant tools not only requires technical integration but talents with diverse modeling expertise and cross-disciplinary knowledge.

Machine learning and other advanced analytical techniques have shown promise in improving the accuracy and efficiency of cancer diagnosis, prognosis, and treatment.[87,88] These techniques use algorithms to analyze large datasets of patient and tumor information, allowing for more personalized treatment approaches. One example of machine learning in cancer treatment is the use of predictive models to identify patients who are most likely to benefit from a particular therapy. By analyzing a patient's genomic, proteomic, and other molecular data, these models can help predict how well a patient will respond to a given treatment, and inform the selection of the most appropriate therapy.[89,90] Artificial intelligence techniques are also being used to analyze medical imaging, such as computed tomography (CT) scans and magnetic resonance imaging (MRI) scans, to improve the accuracy of cancer detection and diagnosis. These techniques can identify subtle changes in tissue structure and help distinguish between cancerous and non-cancerous tissue.

Despite their promise, these advanced techniques have yet to be widely adopted in dose optimization studies. Nonetheless, they hold significant potential for using patient-specific data to dissect sources of variability and establish robust dose–response and dose-toxicity relationships. One example of a machine learning approach is a dose-finding algorithm called Model-based Iterative Search and Evaluation of Dose (MISED). MISED uses Bayesian optimization based on preclinical data and early-phase clinical trial data. The algorithm learns from each dose level and adjusts the subsequent doses based on the response to previous doses, ultimately identifying the MTD and the RP2D. Machine learning has also been applied to predict the long-term survival of patients with CRC based on their metastatic locations and heterogeneity of response across metastatic lesions.[18,91] These analyses could be potentially applied to extend our methods for better patient stratification when assessing E–R relationships and finding optimal doses.

Recently, there has been an exploration of agent-based modeling (ABM) approaches to uncover the connections between doses and tumor evolution and patient response across different anatomic sites in the context of bispecific T cell antibodies.[92] It is worth noting that higher doses could potentially exert excessive selective pressures, resulting in rapid tumor evolution and subsequent relapse. Another valuable use of ABM is seen in optimizing the design and analysis of tumor biopsies by modeling spatiotemporal dynamics and leveraging advanced in vitro systems to emulate immune cell infiltration, which could be useful for finding early biomarkers of biological activity and treatment effectiveness.[93,94] Overall, we believe machine learning and artificial intelligence, and many other advanced analytical techniques, hold promise in the development of more accurate and personalized dose–response relationships in oncology drug development.[95–97] However, these techniques must be carefully validated and integrated with traditional pharmacological and clinical approaches to ensure their reliability and applicability in clinical practice.

Because large-scale modeling takes time and interdisciplinary knowledge to develop and validate, early investment and close collaboration are warranted. In fact, striving for clinical deployment of mechanism-rich (biologically contextualizable) model structures to describe population variability in disease dynamics (e.g., tumor evolution and resistance) and dose/exposure relationship to antitumor effects is a future state that should help improve the fidelity in model applications for precision medicine, including but not limited to dose optimization. Furthermore, the availability of open-source models and publicly accessible data are crucial for promoting collaboration, transparency, and innovation.[98,99] Although some

models, such as mosunetuzemab QSP model, have been made openly available, many others remain proprietary and inaccessible to the broader drug development community.[56] This limited access can impede progress in the field, hindering our ability to build upon existing knowledge and develop new therapies. By embracing open science and publicly accessible models, we can facilitate collaboration and accelerate progress toward more effective oncology dose optimization and drug development. We therefore urge our colleagues in the field to support open science and make their models and data publicly accessible, for the benefit of patients and the wider scientific community.

LEVERAGE ALTERNATIVE METHODS AND DATA TO ENABLE EFFICIENT DECISION MAKING

Enhancing value of PD biomarkers

Within drug optimization studies, the identification and validation of PD and response biomarkers for anticipating long-term clinical outcomes, encompassing both efficacy and safety, stands as a crucial endeavor. As illustrated earlier, the scope of response biomarkers ranges broadly, spanning from distantly relevant clinical indicators (e.g., target engagement) to presumed mechanistic impacts (e.g., kinase inhibition) to early clinical endpoints (e.g., ORR). Prior to the maturation of long-term outcome or patient survival data, these biomarkers merit consideration in dose optimization. Commonly, dose optimization trials base efficacy assessments on ORR, which can be assessed earlier and often with a smaller patient cohort, and the attainment of a response directly indicates drug activity. However, in scenarios where ORR inadequately predicts the ultimate clinical outcome, alternative end points like tumor growth inhibition duration could be explored. Biomarker research carries significant value even in situations where the predictive value for long-term outcomes is to be established or unclear at the current stage. Using a biomarker for dose selection is to be supported by our best understanding of physiology and may need to be validated iteratively, sometimes beyond one clinical program. It is a critical component of ToE for dose selection/optimization, particularly during early phase of drug development.

Evaluating PD effects of investigational anticancer agents at the site of action is not a trivial problem and is often considered an important component of providing clinical proof of mechanism in the context of a pharmacological audit trail.[100,101] When justified appropriately, this may require invasive imaging-guided tumor biopsies, which are not without potential risks.[102] Accordingly, it is important to carefully consider the design of pre- and on-treatment tumor biopsies in early phase development with a commitment to maximize the totality of data to inform decision making and dose selection. Careful analytical planning of such studies is a responsibility in keeping with clinical guidelines and best practice recommendations for research biopsies in clinical trials.[27,103] Unlike PD measurements in blood, tumor biopsies cannot be performed serially, and in most cases will provide data on PD effects at a single point of time per patient. Analyzing sparse clinical tumor PD data in the context of QSP or preclinical PK/PD structural models of the PD end point developed on richer data of the time course of drug effect in nonclinical models represents an approach to maximize and enhance the value of clinical PD measurements in tumor tissue.[104] In one recent example, the RP2D of the MET inhibitor Tepotinib was established using such a translational PK/PD modeling and simulation approach, with the selected dosage qualified through stochastic simulations as providing greater than 95% tumor target inhibition in greater than 90% of the patient population.[105] Other examples of using pathway suppression as PD biomarkers include idelalisib and vismodegib. In both cases, phase I trials did not establish an MTD, and instead, the extent of pathway suppression, indicated by phospho-AKT (T308) and GLI1 expression, respectively, guided the selection of doses for their subsequent registration trials.[106]

Cancer is a constantly evolving disease, which invariably leads to therapeutic failure and disease relapse. Tumor evolutionary theory studies the process by which a tumor undergoes genetic and phenotypic changes over time, leading to the emergence of subclones with distinct characteristics.[107,108] Tumor evolution strongly affects the E–R relationships of oncology drugs, which may be considered during clinical development to facilitate the selection of doses that confer durable response. Due to the constantly evolving nature of tumors, the initial tumor is not a reliable indicator of long-term patient survival, and dose selection based solely on early tumor responses may not result in the most effective tumor control. Assessment of PD biomarkers, such as the target engagement and target expression in the biopsy samples or circulating tumor cells where scientifically appropriate, can inform the understanding of pharmacology (MoA and drug specific) and the degree to which tumor resistance develops to treatment.[100,101] PD biomarkers can provide important information about how a drug is working and whether it is having the intended effect on the underlying disease. By measuring the expression or activity of a target protein or

other biomolecules, researchers can gain insight into the MoA of the drug and how it is affecting disease pathology. Coupling evolutionary theory with conventional PK/PD modeling approaches can provide valuable insights into the E–R relationships of oncology drugs and support the selection of doses and regimens that deliver long-term clinical benefit.

Therefore, discovering and validating PD biomarkers that predict long-term tumor response and patient survival should be prioritized as a future area of research as it is relevant to the overall dose optimization roadmap for improving the fidelity of quantitative translation from early to late-stage clinical development.

It is important to note that drug doses and schedules are just one aspect affecting tumor response and that other factors, such as the biological and genetic characteristics of the tumor and the patient population being treated, must also be taken into account when evaluating clinical efficacy and patient survival. Molecularly targeted therapies are designed to target specific genetic variations, and certain genetic variations may make an individual more or less sensitive to a particular drug. Therefore, tumor genetic variations and molecular features may play an important role when finding optimal doses and regimens.

ctDNA: Longitudinal and mechanistic model to inform dose optimization

Circulating tumor DNA (ctDNA) is DNA shed by cancer cells into the bloodstream.[109–111] Measuring ctDNA levels in the blood can be a noninvasive way to monitor tumor response and changes in genetic variants during anticancer treatment and can be used as a biomarker to assist solid tumor drug development.[112] In the context of early-stage cancer setting, ctDNA can serve several purposes, such as detecting specific targetable alteration, enriching high- or low-risk populations for study in a clinical trial, reflecting a patient's response to treatment, or potentially serving as an early marker of treatment efficacy. In recent years, the FDA has granted approval to several ctDNA-based companion diagnostic assays, enabling the safe and effective use of targeted therapies.[113] For early-stage solid tumor cancers, ctDNA may help detect molecular residual disease. By comparing ctDNA composition and variant abundance before and during treatment, we can explore if the cancer cells with certain variants continue to grow and divide and if there is a dose-dependent tumor shrinkage.

There is intense interest and ongoing research of ctDNA to determine whether it possesses the necessary attributes of being quantitative, sensitive, specific, and reproducible as well as the potential for use as an early end point. A potential early application of ctDNA could include utilizing ctDNA clearance, combined with results from target engagement or tumor shrinkage, as early evidence of activity. This information could then inform decisions about backfilling dose arms or escalating doses, allowing for the inclusion of more patients and leading to time and resource savings.[27]

Although promising, there are several challenges to using ctDNA to monitor treatment response.[114] One challenge is the amount of ctDNA in the blood can vary widely between patients, and it can be difficult to detect at low levels.[112] Additionally, ctDNA may not accurately represent the full spectrum of genetic changes present in the tumor, as the ctDNA may only come from certain tumor subclones. Despite these challenges, ctDNA is an area of active research, permitting potentially more rapid prediction of anticancer response early during treatment make it a promising area of research that can inform dose selection and optimization. Of note, proof-of-principle is available for the application of pharmacometric tumor kinetic models to longitudinal ctDNA data, indicating the potential for future integration of exposure-effect relationships into such frameworks to enable learning of dose/exposure–response relationships in early development to inform dose optimization.[115]

Functional imaging and tumor biopsy

The current criteria to estimate the effect of therapy, such as the Response Evaluation Criteria in Solid Tumors, rely primarily on tumor size measurements.[116] However, tumor size may not always be the best predictor of treatment efficacy and long-term patient survival. Therefore, there is growing interest in developing alternative biomarkers and imaging techniques that can provide a more comprehensive and accurate assessment of treatment response. Tumor biopsies have shown application for studying tumor biology and genetic characteristics, which are crucial for patient selection and treatment response prediction. However, it is important to recognize the challenges associated with using post-treatment tumor biopsies to demonstrate proof of principle or PD effects.[102] Factors like biopsy collection time, assay quality, missing data, and other sources of variability can affect the interpretation and application of post-treatment biopsies.

Functional imaging techniques can provide additional information beyond tumor size and can reveal the metabolic activity of the tumor. This can be particularly useful in situations where tumor size does not necessarily correlate with treatment response, such as in some cases of immunotherapy.[117] Additionally, radiomic analysis of

imaging data can extract quantitative features that can be used as biomarkers of treatment response. These features can include textural, shape, and intensity characteristics of the tumor, which can provide insights into tumor biology and heterogeneity.[118] There are various types of functional imaging techniques, including positron emission tomography, functional MRI, and single photon emission CT. Readouts of tumor response using these functional imaging and radiomic data hold high potential to predicting drug efficacy and establishing more robust E–R relationships.

Patient-reported outcomes

Patient-reported outcomes (PROs) are measurements based on a report that comes directly from the patient about the status of a patient's health condition.[119] Although PRO measurement might not be feasible in every cancer trial, when properly defined and implemented, it can offer systematic and quantitative insights into a patient's feelings and functionality during treatment, as well as detailed data on symptomatic AEs associated with the therapy. Complementary to the standard well-defined clinical end points, fit-for-purpose PRO data help inform benefit–risk assessment of cancer therapy from the patient's perspective, aligned with the FDA Oncology Center of Excellence Patient-Focused Drug Development program.[120,121] Better understanding of patients' needs, preferences, and experiences can support dose optimization and also lead to improved adherence to a drug post-approval.

Although there are limited examples of using PROs in early phase dose optimization as of today, there is an increasing interest in collecting PRO data in early dose evaluation trials to inform early benefit–risk assessment, particularly with respect to symptomatic toxicities.[122] Systematically collecting well defined fit-for-purpose PRO data in early phase trials has the potential to provide valuable information that can inform tolerability and later phase trial design.[123] For example, for multiple EGFR-targeting drugs, clinical trials have recorded up to 60% of patients requiring dose modifications (either dose reduction or interruption) due to tolerability issues. Further follow-up and analysis of these PROs data regarding patient tolerance could offer valuable insights for dose selection and refinement, ultimately aiding in the optimization of treatment regimens. The development of ruxolitinib for myelofibrosis, a combined PRO measure encompassing six symptoms specific to the disease was used. This PRO was a pivotal secondary end point that, in conjunction with the primary end point of spleen volume reduction, contributed to the approval of ruxolitinib in 2011.[124]

Moreover, incorporating PRO data collected in dose expansion studies in the ToE can provide a comprehensive understanding of the relationship between drug exposure, biomarker response, antitumor activities, safety and tolerability, and a patient's health-related quality of life. This information can help interpret overall benefit–risk and inform dose selection and optimization, leading to doses and schedules that maximize efficacy while minimizing adverse effects and maintaining patient-reported outcomes. If the PROs indicate that a higher dose is associated with increased side effects or decreased quality of life, then a lower dose may be preferred to balance efficacy and tolerability.[1] Conversely, if the PROs indicate that a lower dose is not providing adequate symptom control or quality of life, then a higher dose may be needed to achieve the desired therapeutic effect. As highlighted by the FDA, using PRO frameworks like PRO-Common Terminology Criteria for Adverse Events could be useful in elucidating the E–R relationships for patient-reported assessment of the impact of AEs, such as diarrhea, on overall quality of life.[3]

Whereas the potential of using PRO assessments as a component of dose optimization in early clinical development is promising, there are certain considerations that need to be taken into account. Incorporating PRO assessments in the dose escalation phase may be challenging, as the proper PRO and systematic collection approach may not be well-defined yet, especially before the AE profile of the investigational agent (principal toxicities of potential relevance to patient quality of life) and before the potential targeted population is identified. In addition, dose escalation is typically conducted in late-line disease settings with small numbers of patients per dose level and in heterogeneous patient populations and their experiences may differ from patients in the intended population for drug approval and clinical use. PRO assessments may be considered in the expansion phase, particularly where there is a prospective comparative evaluation of multiple dosages for dose optimization. Overall, PROs are a valuable addition to the oncology dose optimization toolbox. Although the use of PROs in early phase oncology drug development and dose optimization is a relatively new concept, continued research on PRO methodologies and real-world applications will help to fully realize their potential for improving oncology dose optimization and patient outcomes. Here, a coordinated effort (such as a consortium effort) may be needed to understand quantitatively if and how PROs can be used for dose selection and confirmation.[120]

CONCLUSIONS

The challenges of rational dose optimization in oncology are multifaceted, arising from multidimensionality of

the dose optimization problem in oncology, the heterogeneity of cancer and patients, importance of evaluating long-term tolerability beyond DLTs, and the lack of reliable biomarkers for long-term efficacy. By integrating various sources of data and using quantitative models, MIDD can help researchers and clinicians gain a more complete understanding of drug exposure, efficacy, and toxicity in the context of heterogeneity in disease biology and patient characteristics. Coupled with advances in trial design, novel biomarkers, tumor kinetic methods including consideration of tumor evolution, and integrated databases, modeling and simulation has the potential to enhance dose selection and optimization strategies for cancer treatments. We should proactively build the quantitative knowledge base, including collecting the right data and developing the M&S toolbox, starting in the early phases of R&D to enable science- and data-driven oncology dose optimization strategy and timely decision making, thereby enabling realization of the promise of Project Optimus.

ACKNOWLEDGMENTS

The authors would like to express our gratitude to Timothy Qi at University of North Carolina at Chapel Hill for his assistance in organizing the references for this manuscript.

FUNDING INFORMATION

No funding was received for this work.

CONFLICT OF INTEREST STATEMENT

The opinions expressed in the manuscript are those of the authors and should not be interpreted as the position of their organizations/employers. The opinions expressed in the manuscript are those of the authors and should not be interpreted as the position of the US Food and Drug Administration. W.G. and K.V. are employees of EMD Serono. J.L. and M.S. are employees of the FDA. B.S., D.Y., and T.N. are employees of Pfizer. Y.C. is an employee of UNC.

ORCID

Wei Gao https://orcid.org/0009-0004-3149-8486
Karthik Venkatakrishnan https://orcid.org/0000-0003-4039-9813
Yanguang Cao https://orcid.org/0000-0002-3974-9073

REFERENCES

1. Fourie Zirkelbach J et al. Improving dose-optimization processes used in oncology drug development to minimize toxicity and maximize benefit to patients. *J Clin Oncol*. 2022;40:3489-3500.
2. Shah M, Rahman A, Theoret MR, Pazdur R. The drug-dosing conundrum in oncology – when less is more. *N Engl J Med*. 2021;385:1445-1447.
3. Getting the Dose Right: Optimizing Dose Selection Strategies in Oncology – An FDA-ASCO Virtual Workshop. 2022. https://www.fda.gov/news-events/fda-meetings-conferences-and-workshops/getting-dose-right-optimizing-dose-selection-strategies-oncology-fda-asco-virtual-workshop-05032022
4. Jardim DL, De Melo Gagliato D, Giles FJ, Kurzrock R. Analysis of drug development paradigms for immune checkpoint inhibitors. *Clin Cancer Res*. 2018;24:1785-1794.
5. Mittapalli RK, Guo C, Drescher SK, Yin D. Oncology dose optimization paradigms: knowledge gained and extrapolated from approved oncology therapeutics. *Cancer Chemother Pharmacol*. 2022;90:207-216.
6. Jardim DL, Hess KR, LoRusso P, Kurzrock R, Hong DS. Predictive value of phase I trials for safety in later trials and final approved dose: analysis of 61 approved cancer drugs. *Clin Cancer Res*. 2014;20:281-288.
7. Oncology Drug Development – Getting Ready for Project Optimus. 2022. https://www.fda.gov/about-fda/oncology-center-excellence/project-optimus
8. Meacham CE, Morrison SJ. Tumour heterogeneity and cancer cell plasticity. *Nature*. 2013;501:328-337.
9. Sachs JR, Mayawala K, Gadamsetty S, Kang SP, de Alwis DP. Optimal dosing for targeted therapies in oncology: drug development cases leading by example. *Clin Cancer Res*. 2016;22:1318-1324.
10. Sullivan KM, Dores GM, Nayernama A, et al. Postmarketing colitis cases associated with Alpelisib use reported to the US Food and Drug Administration. *JAMA Oncol*. 2022;8:1503-1505.
11. McCabe C, Bryson E, Harvey RD. Dose derivation of oral anticancer agents: tolerability in late phase registration trials. *Eur J Cancer*. 2020;138:S51.
12. Burrell RA, McGranahan N, Bartek J, Swanton C. The causes and consequences of genetic heterogeneity in cancer evolution. *Nature*. 2013;501:338-345.
13. McGranahan N, Swanton C. Clonal heterogeneity and tumor evolution: past, present, and the future. *Cell*. 2017;168:613-628.
14. Greaves M, Maley CC. Clonal evolution in cancer. *Nature*. 2012;481:306-313.
15. Zhou J, Liu Y, Zhang Y, Li Q, Cao Y. Modeling tumor evolutionary dynamics to predict clinical outcomes for patients with metastatic colorectal cancer: a retrospective analysis. *Cancer Res*. 2020;80:591-601.
16. Zhou J, Li Q, Cao Y. Spatiotemporal heterogeneity across metastases and organ-specific response informs drug efficacy and patient survival in colorectal cancer. *Cancer Res*. 2021;81:2522-2533.
17. Qi T, Dunlap T, Cao Y. Embracing project Optimus: can we leverage evolutionary theory to optimize dosing in oncology? *Pharm Res*. 2022;39:3259-3265.
18. Zhou J, Cipriani A, Liu Y, Fang G, Li Q, Cao Y. Mapping lesion-specific response and progression dynamics and inter-organ variability in metastatic colorectal cancer. *Nat Commun*. 2023;14:417.
19. Merino M, Kasamon Y, Theoret M, Pazdur R, Kluetz P, Gormley N. Irreconcilable differences: The divorce between response rates, progression-free survival, and overall survival. *J Clin Oncol*. 2023;41:2706-2712. doi:10.1200/JCO.23.00225
20. Ruiz-Garcia A, Baverel P, Bottino D, et al. A comprehensive regulatory and industry review of modeling and simulation practices in oncology clinical drug development. *J*

Pharmacokinet Pharmacodyn. 2023;50:147-172. doi:10.1007/s10928-023-09850-2
21. Venkatakrishnan K, Van Der Graaf PH. Toward project Optimus for oncology precision medicine: multi-dimensional dose optimization enabled by quantitative clinical pharmacology. *Clin Pharmacol Ther*. 2022;112:927-932.
22. Korn EL, Freidlin B. Adaptive clinical trials: advantages and disadvantages of various adaptive design elements. *JNCI J Natl Cancer Inst*. 2017;109(6):djx013. doi:10.1093/jnci/djx013
23. Arondekar B, Duh MS, Bhak RH, et al. Real-world evidence in support of oncology product registration: a systematic review of new drug application and biologics license application approvals from 2015–2020. *Clin Cancer Res*. 2022;28:27-35.
24. Nie L, Rubin EH, Mehrotra N, et al. Rendering the 3 + 3 design to rest: more efficient approaches to oncology dose-finding trials in the era of targeted therapy. *Clin Cancer Res*. 2016;22:2623-2629.
25. Garcia VM, Cassier PA, De Bono J. Parallel anticancer drug development and molecular stratification to qualify predictive biomarkers: dealing with obstacles hindering Progress. *Cancer Discov*. 2011;1:207-212.
26. Collignon O, Posch M, Schiel A. Assessment of tumour-agnostic therapies in basket trials. *Lancet Oncol*. 2022;23:e8.
27. Araujo D, Greystoke A, Bates S, et al. Oncology phase I trial design and conduct: time for a change – MDICT guidelines 2022. *Ann Oncol*. 2023;34:48-60.
28. Groenland SL, Ratain MJ, Chen LS, Gandhi V. The right dose: from phase I to clinical practice. *Am Soc Clin Oncol Educ Book*. 2021;41:92-106.
29. BALVERSA (erdafitinib) Drug Approval Package. 2019 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212018Orig1s000TOC.cfm
30. Minasian L, Rosen O, Auclair D, Rahman A, Pazdur R, Schilsky RL. Optimizing dosing of oncology drugs. *Clin Pharmacol Ther*. 2014;96:572-579.
31. SCEMBLIX (asciminib) Drug Approval Package. 2021 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/215358Orig1s000,Orig2s000TOC.cfm
32. Li BT, Daly B, Gospodarowicz M, et al. Reimagining patient-centric cancer clinical trials: a multi-stakeholder international coalition. *Nat Med*. 2022;28:620-626.
33. ZYKADIA (ceritinib) Tablets Drug Approval Package. 2017 https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/211225s004lbl.pdf
34. Cho BC, Obermannova R, Bearz A, et al. Efficacy and safety of Ceritinib (450 mg/d or 600 mg/d) with food versus 750-mg/d fasted in patients with ALK receptor tyrosine kinase (ALK)-positive NSCLC: primary efficacy results from the ASCEND-8 study. *J Thorac Oncol*. 2019;14:1255-1265.
35. Yin O, Iwata H, Lin CC, et al. Exposure-response relationships in patients with HER2-positive metastatic breast cancer and other solid tumors treated with trastuzumab deruxtecan. *Clin Pharmacol Ther*. 2021;110:986-996.
36. Li BT, Smit EF, Goto Y, et al. Trastuzumab deruxtecan in *HER2* -mutant non-small-cell lung cancer. *N Engl J Med*. 2022;386:241-251.
37. Combes FP, Li YF, Hoch M, Lorenzo S, Ho YY, Sy SKB. Exposure-efficacy analysis of Asciminib in Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase. *Clin Pharmacol Ther*. 2022;112:1040-1050.
38. Venkatakrishnan K, Cook J. Driving access to medicines with a totality of evidence mindset: an opportunity for clinical pharmacology. *Clin Pharmacol Ther*. 2018;103:373-375.
39. RETEVMO (selpercatinib) drug approval package. 2020 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/213246Orig1s000TOC.cfm
40. Optimizing the dosage of human prescription drugs and biological products for the treatment of oncologic diseases. 2023 https://www.fda.gov/media/164555/download
41. Morgan P, van der Graaf PH, Arrowsmith J, et al. Can the flow of medicines be improved? Fundamental pharmacokinetic and pharmacological principles toward improving phase II survival. *Drug Discov Today*. 2012;17:419-424.
42. Wu SS, Fernando K, Allerton C, Jansen KU, Vincent MS, Dolsten M. Reviving an R&D pipeline: a step change in the phase II success rate. *Drug Discov Today*. 2021;26:308-314.
43. Morgan P, Brown DG, Lennard S, et al. Impact of a five-dimensional framework on R&D productivity at AstraZeneca. *Nat Rev Drug Discov*. 2018;17:167-181.
44. Madabushi R, Seo P, Zhao L, Tegenge M, Zhu H. Review: role of model-informed drug development approaches in the lifecycle of drug development and regulatory decision-making. *Pharm Res*. 2022;39:1669-1680.
45. Cook SF, Bies RR. Disease progression modeling: key concepts and recent developments. *Curr Pharmacol Rep*. 2016;2:221-230.
46. Rogers JA, Polhamus D, Gillespie WR, et al. Combining patient-level and summary-level data for Alzheimer's disease modeling and simulation: a β regression meta-analysis. *J Pharmacokinet Pharmacodyn*. 2012;39:479-498.
47. Bruno R, Bottino D, de Alwis DP, et al. Progress and opportunities to advance clinical cancer therapeutics using tumor dynamic models. *Clin Cancer Res*. 2020;26:1787-1795.
48. Chen T, Zheng Y, Roskos L, Mager DE. Comparison of sequential and joint nonlinear mixed effects modeling of tumor kinetics and survival following Durvalumab treatment in patients with metastatic urothelial carcinoma. *J Pharmacokinet Pharmacodyn*. 2023;50:251-265. doi:10.1007/s10928-023-09848-w
49. Al-Huniti N, Feng Y, Yu JJ, et al. Tumor growth dynamic modeling in oncology drug development and regulatory approval: past, present, and future opportunities. *CPT Pharmacomet Syst Pharmacol*. 2020;9:419-427.
50. Bruno R, Chanu P, Kågedal M, et al. Support to early clinical decisions in drug development and personalised medicine with checkpoint inhibitors using dynamic biomarker-overall survival models. *Br J Cancer*. 2023;129:1383-1388. doi:10.1038/s41416-023-02190-5
51. Krishnan SM, Friberg LE, Mercier F, et al. Multistate pharmacometric model to define the impact of second-line immunotherapies on the survival outcome of the IMPOWER131 study. *Clin Pharmacol Ther*. 2023;113:851-858.
52. Street S, Chute D, Strohbehn I, et al. The positive effect of immune checkpoint inhibitor-induced thyroiditis on overall survival accounting for immortal time bias: a retrospective cohort study of 6596 patients. *Ann Oncol*. 2021;32:1050-1051.
53. Khandelwal A, Grisic A-M, French J, Venkatakrishnan K. Pharmacometrics golems: exposure–response models in oncology. *Clin Pharmacol Ther*. 2022;112:941-945.
54. Liu H, Milenković-Grišić AM, Krishnan SM, et al. A multistate modeling and simulation framework to learn dose–response

of oncology drugs: application to bintrafusp alfa in non-small cell lung cancer. *CPT Pharmacomet Syst Pharmacol*. 2023:1-13. doi:10.1002/psp4.12976
55. Susilo ME, Li CC, Gadkar K, et al. Systems-based digital twins to help characterize clinical dose–response and propose predictive biomarkers in a phase I study of bispecific antibody, mosunetuzumab, in NHL. *Clin Transl Sci*. 2023;16:1134-1148. doi:10.1111/cts.13501
56. Hosseini I, Gadkar K, Stefanich E, et al. Mitigating the risk of cytokine release syndrome in a phase I trial of CD20/CD3 bispecific antibody mosunetuzumab in NHL: impact of translational system modeling. *NPJ Syst Biol Appl*. 2020;6:28.
57. Bayless NL, Bluestone JA, Bucktrout S, et al. Development of preclinical and clinical models for immune-related adverse events following checkpoint immunotherapy: a perspective from SITC and AACR. *J Immunother Cancer*. 2021;9:e002627.
58. Kirouac DC, Schaefer G, Chan J, et al. Clinical responses to ERK inhibition in BRAF V600E-mutant colorectal cancer predicted using a computational model. *Npj Syst Biol Appl*. 2017;3:14.
59. Poels KE, Schoenfeld AJ, Makhnin A, et al. Identification of optimal dosing schedules of dacomitinib and osimertinib for a phase I/II trial in advanced EGFR-mutant non-small cell lung cancer. *Nat Commun*. 2021;12:3697.
60. Chelliah V, Lazarou G, Bhatnagar S, et al. Quantitative systems pharmacology approaches for immuno-oncology: adding virtual patients to the development paradigm. *Clin Pharmacol Ther*. 2021;109:605-618.
61. Lemaire V, Bassen D, Reed M, et al. From cold to hot: changing perceptions and future opportunities for quantitative systems pharmacology modeling in cancer immunotherapy. *Clin Pharmacol Ther*. 2023;113:963-972.
62. Kumar R, Thiagarajan K, Jagannathan L, et al. Beyond the single average tumor: understanding IO combinations using a clinical QSP model that incorporates heterogeneity in patient response. *CPT Pharmacomet Syst Pharmacol*. 2021;10:684-695.
63. Gadkar K, Kirouac DC, Mager DE, van der Graaf PH, Ramanujan S. A six-stage workflow for robust application of systems pharmacology. *CPT Pharmacomet Syst Pharmacol*. 2016;5:235-249.
64. Allen RJ, Rieger TR, Musante CJ. Efficient generation and selection of virtual populations in quantitative systems pharmacology models. *CPT Pharmacomet Syst Pharmacol*. 2016;5:140-146.
65. Qi T, Cao Y. Virtual clinical trials: a tool for predicting patients who may benefit from treatment beyond progression with pembrolizumab in non-small cell lung cancer. *CPT Pharmacomet Syst Pharmacol*. 2023;12:236-249.
66. Bai JPF, Earp JC, Florian J, et al. Quantitative systems pharmacology: landscape analysis of regulatory submissions to the US Food and Drug Administration. *CPT Pharmacomet Syst Pharmacol*. 2021;10:1479-1484.
67. Betts A, van der Graaf PH. Mechanistic quantitative pharmacology strategies for the early clinical development of bispecific antibodies in oncology. *Clin Pharmacol Ther*. 2020;108:528-541.
68. Abrams RE, Pierre K, el-Murr N, et al. Quantitative systems pharmacology modeling sheds light into the dose response relationship of a trispecific T cell engager in multiple myeloma. *Sci Rep*. 2022;12:10976.
69. Lam I, Pilla Reddy V, Ball K, Arends RH, Mac Gabhann F. Development of and insights from systems pharmacology models of antibody-drug conjugates. *CPT Pharmacomet Syst Pharmacol*. 2022;11:967-990.
70. Haid RTU, Reichel A. A mechanistic pharmacodynamic modeling framework for the assessment and optimization of proteolysis targeting chimeras (PROTACs). *Pharmaceutics*. 2023;15:195.
71. U.S. Food and Drug Administration. Physiologically based pharmacokinetic analyses — format and content guidance for industry. 2018 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/physiologically-based-pharmacokinetic-analyses-format-and-content-guidance-industry
72. European Medicines Agency. Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation. 2018 https://www.ema.europa.eu/en/reporting-physiologically-based-pharmacokinetic-pbpk-modelling-simulation-scientific-guideline
73. Jones H, Rowland-Yeo K. Basic concepts in physiologically based pharmacokinetic modeling in drug discovery and development. *CPT Pharmacomet Syst Pharmacol*. 2013;2:e63.
74. Jean D, Naik K, Milligan L, et al. Development of best practices in physiologically based pharmacokinetic modeling to support clinical pharmacology regulatory decision-making-a workshop summary. *CPT Pharmacomet Syst Pharmacol*. 2021;10:1271-1275.
75. Li TR, Chatterjee M, Lala M, et al. Pivotal dose of pembrolizumab: a dose-finding strategy for Immuno-oncology. *Clin Pharmacol Ther*. 2021;110:200-209.
76. Ratain MJ, Peer CJ, Figg WD, Goldstein DA. Dose optimization of pembrolizumab: less may be more. *Clin Pharmacol Ther*. 2022;111:993.
77. Li J, Jiang J, Bao X, et al. Mechanistic modeling of central nervous system pharmacokinetics and target engagement of HER2 tyrosine kinase inhibitors to inform treatment of breast cancer brain metastases. *Clin Cancer Res*. 2022;28:3329-3341.
78. Li J, Jiang J, Wu J, Bao X, Sanai N. Physiologically based pharmacokinetic modeling of central nervous system pharmacokinetics of CDK4/6 inhibitors to guide selection of drug and dosing regimen for brain cancer treatment. *Clin Pharmacol Ther*. 2021;109:494-506.
79. Baselga J, Pfister D, Cooper MR, et al. Phase I studies of anti-epidermal growth factor receptor chimeric antibody C225 alone and in combination with cisplatin. *J Clin Oncol*. 2000;18:904-914.
80. Yoneyama T, Kim M-S, Piatkov K, Wang H, Zhu AZX. Leveraging a physiologically-based quantitative translational modeling platform for designing B cell maturation antigen-targeting bispecific T cell engagers for treatment of multiple myeloma. *PLoS Comput Biol*. 2022;18:e1009715.
81. Zheng Y, Narwal R, Jin CY, et al. Population modeling of tumor kinetics and overall survival to identify prognostic and predictive biomarkers of efficacy for durvalumab in patients with urothelial carcinoma. *Clin Pharmacol Ther*. 2018;103:643-652.
82. Chan P, Marchand M, Yoshida K, et al. Prediction of overall survival in patients across solid tumors following atezolizumab treatments: a tumor growth inhibition-overall survival modeling framework. *CPT Pharmacomet Syst Pharmacol*. 2021;10:1171-1182.
83. Trame MN, Riggs M, Biliouris K, et al. Perspective on the state of pharmacometrics and systems pharmacology integration: state of pharmacometrics and systems pharmacology integration. *CPT Pharmacomet Syst Pharmacol*. 2018;7:617-620.

84. Musante C, Abernethy D, Allerheiligen S, Lauffenburger D, Zager M. GPS for QSP: a summary of the ACoP6 symposium on quantitative systems pharmacology and a stage for near-term efforts in the field: GPS for QSP. *CPT Pharmacomet Syst Pharmacol*. 2016;5:449-451.
85. Helmlinger G, Sokolov V, Peskov K, et al. Quantitative systems pharmacology: an exemplar model-building workflow with applications in cardiovascular, metabolic, and oncology drug development. *CPT Pharmacomet Syst Pharmacol*. 2019;8:380-395.
86. Graaf PH. Pharmacometrics and/or systems pharmacology. *CPT Pharmacomet Syst Pharmacol*. 2019;8:331-332.
87. Silvestri GA, Jett JR. The intersection of lung cancer screening, radiomics, and artificial intelligence: can one scan really predict the future development of lung cancer? *J Clin Oncol*. 2023;41:2141-2143.
88. Vasey B, Nagendran M, Campbell B, et al. Reporting guideline for the early-stage clinical evaluation of decision support systems driven by artificial intelligence: DECIDE-AI. *Nat Med*. 2022;28:924-933.
89. Rakaee M, Adib E, Ricciuti B, et al. Association of machine learning–based assessment of tumor-infiltrating lymphocytes on standard histologic images with outcomes of immunotherapy in patients with NSCLC. *JAMA Oncol*. 2023;9:51-60.
90. Swanson K, Wu E, Zhang A, Alizadeh AA, Zou J. From patterns to patients: advances in clinical machine learning for cancer diagnosis, prognosis, and treatment. *Cell*. 2023;186:1772-1791.
91. Vera-Yunca D, Girard P, Parra-Guillen ZP, Munafo A, Trocóniz IF, Terranova N. Machine learning analysis of individual tumor lesions in four metastatic colorectal cancer clinical studies: linking tumor heterogeneity to overall survival. *AAPS J*. 2020;22:58.
92. Liu C, Zhou J, Kudlacek S, Qi T, Dunlap T, Cao Y. Population dynamics of immunological synapse formation induced by bispecific T cell engagers predict clinical pharmacodynamics and treatment resistance. *Elife*. 2023;12:e83659.
93. Hutchinson LG, Grimm O. Integrating digital pathology and mathematical modelling to predict spatial biomarker dynamics in cancer immunotherapy. *NPJ Digit Med*. 2022;5:92.
94. Lewin TD, Avignon B, Tovaglieri A, Cabon L, Gjorevski N, Hutchinson LG. An in silico model of T cell infiltration dynamics based on an advanced in vitro system to enhance preclinical decision making in cancer immunotherapy. *Front Pharmacol*. 2022;13:837261.
95. Chan P, Zhou X, Wang N, Liu Q, Bruno R, Jin JY. Application of machine learning for tumor growth inhibition – overall survival modeling platform. *CPT Pharmacomet Syst Pharmacol*. 2021;10:59-66.
96. McComb M, Bies R, Ramanathan M. Machine learning in pharmacometrics: opportunities and challenges. *Br J Clin Pharmacol*. 2022;88:1482-1499.
97. Liu G, Lu J, Lim HS, Jin JY, Lu D. Applying interpretable machine learning workflow to evaluate exposure–response relationships for large-molecule oncology drugs. *CPT Pharmacomet Syst Pharmacol*. 2022;11:1614-1627.
98. Lippert J, Burghaus R, Edginton A, et al. Open systems pharmacology community—an open access, open source, open science approach to modeling and simulation in pharmaceutical sciences. *CPT Pharmacomet Syst Pharmacol*. 2019;8:878-882.
99. Rostami-Hodjegan A, Bois FY. Opening a debate on open-source modeling tools: pouring fuel on fire versus extinguishing the flare of a healthy debate. *CPT Pharmacomet Syst Pharmacol*. 2021;10:420-427.
100. Banerji U, Workman P. Critical parameters in targeted drug development: the pharmacological audit trail. *Semin Oncol*. 2016;43:436-445.
101. Pal A, Shinde R, Miralles MS, Workman P, de Bono J. Applications of liquid biopsy in the pharmacological audit trail for anticancer drug development. *Nat Rev Clin Oncol*. 2021;18:454-467.
102. Sweis RF, Drazer MW, Ratain MJ. Analysis of impact of post-treatment biopsies in phase I clinical trials. *J Clin Oncol*. 2016;34:369-374.
103. Levit LA, Peppercorn JM, Tam AL, et al. Ethical framework for including research biopsies in oncology clinical trials: American Society of Clinical Oncology research statement. *J Clin Oncol*. 2019;37:2368-2377.
104. Venkatakrishnan K, Ecsedy JA. Enhancing value of clinical pharmacodynamics in oncology drug development: an alliance between quantitative pharmacology and translational science. *Clin Pharmacol Ther*. 2017;101:99-113.
105. Xiong W, Friese-Hamim M, Johne A, et al. Translational pharmacokinetic-pharmacodynamic modeling of preclinical and clinical data of the oral MET inhibitor tepotinib to determine the recommended phase II dose. *CPT Pharmacomet Syst Pharmacol*. 2021;10:428-440.
106. Rudin CM. Vismodegib. *Clin Cancer Res*. 2012;18:3218-3222.
107. Mazzocca A. The systemic-evolutionary theory of the origin of cancer (SETOC): a new interpretative model of cancer as a complex biological system. *Int J Mol Sci*. 2019;20:4885.
108. Bozic I, Wu CJ. Delineating the evolutionary dynamics of cancer from theory to reality. *Nat Cancer*. 2020;1:580-588.
109. Chakrabarti S, Michor F. Pharmacokinetics and drug interactions determine optimum combination strategies in computational models of cancer evolution. *Cancer Res*. 2017;77:3908-3921.
110. Tie J, Cohen JD, Lahouel K, et al. Circulating tumor DNA analysis guiding adjuvant therapy in stage II colon cancer. *N Engl J Med*. 2022;386:2261-2272.
111. Dasari A, Morris VK, Allegra CJ, et al. ctDNA applications and integration in colorectal cancer: an NCI colon and Rectal–anal task forces whitepaper. *Nat Rev Clin Oncol*. 2020;17:757-770.
112. U.S. Food and Drug Administration. Use of circulating tumor DNA for earlystage solid tumor drug development guidance for industry. 2022.
113. List of cleared or approved companion diagnostic devices (In Vitro and Imaging Tools).
114. Vellanki PJ, Ghosh S, Pathak A, et al. Regulatory implications of ctDNA in immuno-oncology for solid tumors. *J Immunother Cancer*. 2023;11:e005344.
115. Janssen JM, Verheijen RB, van Duijl TT, et al. Longitudinal nonlinear mixed effects modeling of EGFR mutations in ctDNA as predictor of disease progression in treatment of EGFR-mutant non-small cell lung cancer. *Clin Transl Sci*. 2022;15:1916-1925.
116. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer Oxf Engl*. 2009;1990(45):228-247.
117. Hodi FS, Ballinger M, Lyons B, et al. Immune-modified response evaluation criteria in solid tumors (imRECIST): refining guidelines to assess the clinical benefit of cancer immunotherapy. *J Clin Oncol*. 2018;36:850-858.

118. Lambin P, Rios-Velazquez E, Leijenaar R, et al. Radiomics: extracting more information from medical images using advanced feature analysis. *Eur J Cancer*. 2012;48:441-446.
119. U.S. Food and Drug Administration. Patient-focused drug development glossary.
120. Friends of Cancer Research Annual Meeting 2022. Supporting a patient-centric approach to dose optimization in oncology: the essential role of patient-reported outcomes (PROs). https://friendsofcancerresearch.org/wp-content/uploads/Supporting_Patient-Centric_Approach_Dose_Optimization_Oncology-PROs.pdf
121. U.S. Food and Drug Administration. FDA patient-focused drug development guidance series for enhancing the incorporation of the patient's voice in medical product development and regulatory decision making. https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical
122. U.S. Food and Drug Administration. Core patient-reported outcomes in cancer clinical trials guidance for industry. 2021 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/core-patient-reported-outcomes-cancer-clinical-trials
123. Lee SM, Lu X, Cheng B. Incorporating patient-reported outcomes in dose-finding clinical trials. *Stat Med*. 2020;39:310-325.
124. Basch E. Toward patient-centered drug development in oncology. *N Engl J Med*. 2013;369:397-400.

How to cite this article: Gao W, Liu J, Shtylla B, et al. Realizing the promise of Project Optimus: Challenges and emerging opportunities for dose optimization in oncology drug development. *CPT Pharmacometrics Syst Pharmacol*. 2024;13:691-709. doi:10.1002/psp4.13079