TUTORIAL

Developing Exposure/Response Models for Anticancer Drug Treatment: Special Considerations

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Anticancer agents often have a narrow therapeutic index (TI), requiring precise dosing to ensure sufficient exposure for clinical activity while minimizing toxicity. These agents frequently have complex pharmacology, and combination therapy may cause schedule-specific effects and interactions. We review anticancer drug development, showing how integration of modeling and simulation throughout development can inform anticancer dose selection, potentially improving the late-phase success rate. This article has a companion article in *Clinical Pharmacology & Therapeutics* with practical examples.
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This tutorial provides guidance on various aspects of modeling for anticancer drugs, and references the companion article provided in *CPT*[1] for examples demonstrating the importance of this approach in anticancer drug development. In this tutorial, examples are presented showing the utility of translational modeling for rational dose selection for first-in-human (FIH) studies and continued model-based evaluations to refine dosing as well as determining drug efficacy and safety.

The low approval rate of new therapeutic agents has been reviewed previously. DiMasi *et al.*[2] reported that anticancer agents had an average success rate, but that nearly half the anticancer/immunologic drugs moved from phase II trials to more expensive phase III testing. After reaching phase III, there was a 55% probability of a successful marketing approval application, supporting the need for more efficient, effective approaches to anticancer drug development. The 2006 U.S. Food and Drug Administration Critical Path Opportunities document supported modeling and simulation to evaluate clinical trial designs, as well as the use of innovative trial designs.[3] Model-based drug development develops and utilizes models describing disease progression, pharmacokinetics (PK), and pharmacodynamics (PD) to improve study designs and facilitate quantitative decision-making. Among its key components are improved and innovative trial designs, establishment of quantitative decision criteria, and assessment of trial performance metrics relative to these criteria.[4] However, owing to the common practice of dosing to a maximum tolerated dose, model-based drug development is generally given less consideration when making development decisions for anticancer agents.

Modeling anticancer drugs often presents difficulties not seen in other therapeutic areas. In particular, owing to practical considerations, many clinical trials have limited (or no) PK sampling, resulting in poor understanding of the clinical pharmacology necessary to better understand trial results. Biomarkers of clinical benefit, such as tumor size, are often ignored or oversimplified (e.g., RECIST[5]), or show high between-subject variability (BSV), such as is seen with evaluations of tumor growth.[6] Given the high cost of phase III failures, it is important to identify metrics predictive of longer-term therapeutic success for use in proof-of-concept studies.

PHARMACOKINETIC CONSIDERATIONS

PK evaluations are routinely carried out for anticancer agents. However, many anticancer agents exhibit high BSV, and PK evaluations in clinical trials are often sparse. Thus, population-based approaches are often the best option and can identify covariates that may be useful to guide dose individualization. These agents can generally be described using standard model-based approaches[7] or through application of physiologically based pharmacokinetic (PBPK) approaches. PBPK modeling requires an iterative approach starting with model building based on *in vitro* and *in vivo* data, followed by model verification. For model verification, information on model plausibility regarding physiology and drug absorption, distribution, metabolism, and excretion is considered as important as the demonstration of visual inspection of the simulation results against observed data.[8] Prediction of human PK is important to reduce PK treatment failure and to assess suitability of proposed dose regimens for novel compounds. For small molecules, PBPK models have successfully been used to predict human exposure and to design phase I studies.[9]

In addition to identification and quantification of predictive factors for PK, these models can be implemented in study design optimization[10] to minimize sampling necessary for PK, to reduce the number of subjects needed to undergo these evaluations, improving information obtained from clinical trials. Because many oncology trials have limited sampling or take samples from a limited patient population, the use of optimal design methods, such as D-optimization, would potentially improve trial informativeness.

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Pharmacokinetic drug interactions

Many anticancer agents are administered with other drugs with similar toxicity; thus, relative contribution of a new agent to dose-limiting toxicity needs to be estimated before testing new combinations, and confirmed during clinical trials. Combination therapy based on drug action synergy has improved clinical outcomes, but results in more complex issues for safety and efficacy assessments. Typically, when two or more anticancer agents are first given concomitantly, a dose escalation trial of the combined agents is conducted.[11] This is because of commonly identified schedule- and sequence-dependence of pharmacological effects of anticancer combination treatments. Sequence dependence is well known for phase-specific drugs, such as taxanes, where combination with different anticancer agents can result in cytotoxic synergism or antagonism depending on administration sequence of the drugs.[12] Vigano *et al.*[13] provides an excellent reference detailing sequence and schedule interactions for taxanes.

Drug-drug interactions (DDIs) constitute a serious problem in oncology because of the narrow TI for most anticancer drugs. DDIs can be attributed to PK or PD. Many anticancer drugs are metabolized by cytochrome P450 (CYP). As some act as inducers or inhibitors of one or more CYP isoenzymes, changes in concentrations of concomitant drugs are possible. Anticancer drugs can act not only as victims but as perpetrators in DDI. For example, *in vitro* inhibition of docetaxel clearance via CYP3A4 is seen with concomitant administration of vinorelbine, vinblastine, and doxorubicin.[14] Even drugs used in premedication regimens, such as dexamethasone and ketoconazole, should be considered.

P-glycoprotein, an efflux transporter, can also be involved in DDIs. Oral administration, which is becoming more common, increases the risk of DDIs because oral anticancer drugs are usually administered daily, and can affect interactions via the oral route that were not seen with parenteral administration. A review of DDI prevalence with oral anticancer agents[15] found DDIs are very common with oral cancer therapy (46% of patients had potential DDIs and 16% had a major DDI). Thus, altered PK or PD can affect toxicity or efficacy. Investigation of underlying mechanisms of DDIs is essential during development of novel agents, and implementation of systems pharmacology models is an important component.

Traditional designs to evaluate single DDIs are often not feasible with anticancer agents. Thus, innovative approaches are necessary to evaluate the pharmacology of these agents. Model-based drug development provides tools to evaluate data accumulated during drug development, helping to identify appropriate dose metrics and determining the risk/benefit of treatment with these agents. Ethical issues and/or the difficulty of testing anticancer agents in volunteers may preclude formal DDI studies. However, modeling and simulation can be used to evaluate the PK of various anticancer agents to evaluate the probability of DDIs.

PBPK modeling is increasingly used to evaluate DDIs by integrating *in vitro* information, and is often included in submission documents to the health authorities.[8,16] For example, ibrutinib, developed for treatment of mantle cell lymphoma and chronic lymphocytic lymphoma, is predominantly metabolized by CYP3A4. In healthy volunteers, ibrutinib exposure increased 30-fold with ketoconazole (strong inhibitor) and was more than 10-fold reduced with rifampicin (strong inducer). Dose adjustments for coadministration with weak CYP3A4 inducers or inhibitors were justified with PBPK predictions without conducting further DDI studies.[17] Similarly, additional DDI studies were successfully avoided for ceritinib (a time-dependent CYP3A4 inhibitor), which was developed for treatment of patients with anaplastic lymphoma kinase-positive, metastatic non-small cell lung cancer.[18] In both cases, PBPK modeling was successfully applied to assess various untested clinical situations.

Pharmacodynamic modeling

During anticancer drug development, PD evaluations are often conducted on a variety of efficacy or safety metrics. PK-PD modeling of anticancer drugs involves a wide range of approaches, including evaluation of continuous biomarkers of response (including tumor growth), evaluation of categorical responses, and time-to-event (TTE) modeling. These evaluations are a part of model-based drug development for anticancer agents.

Translational PK-PD modeling and early clinical development

PK-PD modeling provides robust support to a drug development program when implemented in early stage development, and is conducted throughout all phases. In the discovery phase, modeling provides insights into mechanism of action, and enables selection of clinical candidate molecules based on PK properties and the predicted human TI. Translational PK-PD modeling can support the design of FIH studies by providing estimates of efficacious target exposures, associated dose regimens, and guidance in selection of biomarker and optimal sampling time points for exposure and biomarkers.[19]

Oncology phase 1 studies differ from other phase I studies in that they are mainly evaluated in patients whose disease condition is progressive and fatal. The Food and Drug Administration guideline for anticancer pharmaceuticals states "the goal of selecting a starting dose is to identify a dose that is expected to have pharmacological effects and is reasonably safe." Preclinical PK-PD modeling helps project the pharmacological response in humans by quantifying the exposure–response relationship in nonclinical species and subsequently accounting for the species differences. Moreover, profiling the TI in preclinical studies with subsequent prediction to humans is a critical step, particularly owing to the narrow TI of most anticancer drugs. Translational PK-PD modeling offers a rational approach to select the most favorable dose and dosing regimen in early clinical development.

Translational PK-PD models are important tools to project preclinical efficacy to human response. The *in vivo* evaluation of anticancer drugs is mainly done in immune-deficient mice (athymic nude or severe combined immunodeficient mice) transplanted s.c. with human tumor cell lines or patient-derived tumor material.[20] In addition to xenograft

models, syngeneic or genetically engineered mouse models are used in anticancer drug development. During the translational process, it is important to remember the limitations of the preclinical models in representing the pathophysiological phenotype of patients with cancer, particularly regarding immune competence, tumor heterogeneity, tumor microenvironment, and stromal components.[20]

For translation to humans, models must account for species differences between animals and humans, including PK and drug tolerability.[21] For biological agents, such as monoclonal antibodies, cross-reactivity, target affinity, target expression patterns between mouse and man, and the interference by the mouse immune system (e.g., antibody-dependent cell-mediated cytotoxicity, complement activation, and targeting of natural killer cells) are important considerations and must be accounted for as far as possible.[22] For many monoclonal antibodies, the interaction with its target can impact PK. Thus, PK can be used to derive important information on drug-target interaction. This phenomenon, target-mediated drug disposition, leads to saturable distribution and elimination kinetics, with substantial BSV.[23] Preclinical target-mediated drug disposition models can explore potential impacts of disease-related target load on PK variability[24] or be scaled to humans to guide dose selection of FIH.[25] Daydé *et al.*[24] conducted preclinical PK-PD studies to better understand the clinically observed interpatient variability of rituximab, a monoclonal antibody targeting CD20. The impact of tumor burden on PK and efficacy was tested in a murine syngeneic model of lymphoma expressing human CD20 sharing characteristics of the human disease. PK-PD modeling suggested high tumor burden increases rituximab clearance, reducing efficacy. In another study, Tabrizi and Roskos[25] approximated target saturation of anti-mUC18 monoclonal antibody based on the predicted nonlinear elimination and scaled it to humans. For the FIH study, a minimal anticipated biological effect level dose was justified based on the projected 10% target saturation as well as a PK-based dose-escalation scheme[25] illustrating the utility of target-mediated drug disposition models to guide early clinical development. This approach assumes that the target is highly accessible. For less accessible targets, or targets with high turnover, the approximation of target saturation from the clearance may be misleading. Lammerts van Bueren *et al.*[26] explored *in vitro* and *in vivo* receptor-mediated elimination of an anti-epidermal growth factor receptor antibody 2F8 in cynomolgus monkeys and tumor-bearing mice. They concluded that epidermal growth factor receptor saturation in normal tissue does not predict saturation in tumor tissue, as local drug concentration may be more rapidly reduced without impacting the PK. Grimm[27] provided a theoretical explanation why saturation of clearance can greatly underpredict receptor occupancy of poorly accessible targets.

Multiscale PK-PD models to improve translation to humans
Using biomarkers to drive tumor growth inhibition enables a quantitative assessment of the relationship between biomarker and tumor growth inhibition, which may guide dose regimen selection in the clinic if similar biomarker data can

be obtained. Multiscale PK-PD models can simultaneously incorporate different processes to bridge multiple temporal and spatial scales that are relevant in cancer (**Figure 1**). These models allow the modeler to quantitatively relate events on the molecular level to events on cellular and/or tissue levels. The additional value of multiscale models is in biomarker selection to monitor drug response and to improve translatability of the nonclinical PK-PD relationship to humans (**Figure 1**). Such models relate the biomarker profile to efficacy, which also promotes identification of adequate tissue exposure.

Figure 1 illustrates how multiscale information can be exploited to increase confidence in human projections and improve the interpretive value of early phase I clinical data. This approach was applied to everolimus, a mammalian target of rapamycin inhibitor.[28,29] The mammalian target of rapamycin regulates mRNA translation via serine/threonine kinase p70S6 kinase (S6K), which subsequently regulates protein translation through phosphorylation of ribosomal protein S6. Everolimus blocks the mammalian target of rapamycin pathway and inhibits the downstream signal S6K1. The preclinical PK-PD model described the relationship between inhibition of S6K1 and antitumor effects of different concentrations of everolimus in tumor-bearing rats. Once corrected for interspecies PK differences, the model provided indication of which dose and regimens should be investigated in a phase I dose escalation trial. The preclinical model predicted *a priori* that, in humans, everolimus doses of 5 or 10 mg/day would demonstrate a more profound and sustained effect on S6K1 inhibition than weekly doses of 20, 30, 50, or 70 mg. The authors found that 20–30 mg would be the minimal weekly dose for efficacy based on mammalian target of rapamycin inhibition, but increasing the weekly dosage to 50 or 70 mg/wk would not increase the durability of S6K1 inhibition. It also showed the kinetics of downstream effects in peripheral blood mononuclear cells correlated well with antitumor effect. This supported incorporation of PD measurements collected in peripheral blood mononuclear cells and has the potential to predict the optimal dosing schedule.[29] In line with this simulation, a subsequent phase III trial in renal cell carcinoma showed that progression-free survival and overall survival (OS) were significantly improved ($P < 0.001$) with daily 10 mg dosing.[30]

MODELING TUMOR GROWTH

The most common marker of response in oncology is tumor growth, which can be evaluated in numerous ways. Measurements of tumor volume and other tumor-related biomarkers have been used to describe the progression of disease and the response to treatment. Tumor growth models used to describe the time course of tumor growth inhibition typically utilize ordinary differential equations, and the conceptual framework has recently been summarized.[6] Frequently, a temporal delay is observed between PK and response, which requires a mathematical model similar to an indirect response model to account for this delay. **Table 1** provides examples of the application of PK-PD modeling to
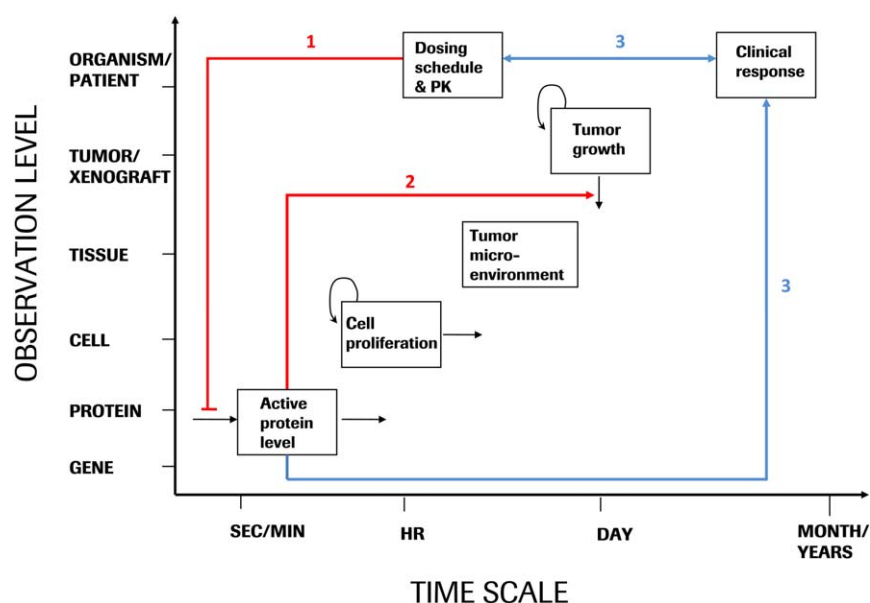
Figure 1 Multiscale pharmacokinetic-pharmacodynamic (PK-PD) models relate quantitatively events on molecular to cellular and/or on tissue levels to support selection of biomarker to monitor drug response. These models increase the confidence in projecting translational PK-PD relationship from animal to man, as illustrated in the example. The steps include (1) establish PK-PD model to quantitatively understand the pharmacological activity of the drug in preclinical species; (2) link biomarker response to anticancer effect to define required pharmacological activity to obtain tumor regression in preclinical model; and (3) scale model to humans to select dose/dosing schedule and monitor biomarker profile in patients in early clinical trial to find the "right" dose and dosing schedule.

tumor growth inhibition for a range of targets and xenografts.

Changes in tumor volume over time can be represented by terms describing net growth and drug-induced tumor shrinkage, as shown in the following equation:

$$\frac{dTV}{dt} = \text{net growth-drug induced shrinkage.} \tag{1}$$

Because of the semimechanistic nature of these models, they can be useful to characterize PK-PD properties of anticancer drug treatments in preclinical models. This approach has advantages over empirical approaches, which do not make use of the effect over time, but instead attempt to correlate an exposure metric, such as area under the concentration-time curve (AUC) or steady-state average concentration with tumor growth inhibition at a single timepoint. Drug potency estimates from a single timepoint will be time-dependent, and therefore not useful for translation to the clinic.

Tumor growth models in control groups of preclinical species

Empirical models are commonly used to describe tumor growth in the absence of the drug treatment in xenograft experiments. For preclinical evaluations, the focus is to obtain quantitative predictions of drug effect in mechanistic terms — not to predict future tumor volume beyond the observation period. A good description of tumor growth in the untreated group is an important prerequisite to appropriately capture drug effect. Tumors are expected to grow exponentially during early growth phases, followed by a linear phase before reaching a plateau. However, tumor-

bearing mice are euthanized for ethical reasons when tumor volume reaches the maximal allowable tumor mass, which often occurs before a plateau phase is observed. Model selection is therefore based on parsimony principles, which means providing a sufficient goodness-of-fit of observed data while using the fewest number of parameters (**Supplementary Material S1**).

In the absence of effective drug treatment, net tumor growth (the balance of growth and natural cell death) can be described by an exponential function,[31] exponential growth that can be inhibited by tumor volume,[32] or some combination of linear and exponential functions.[33–35] First order (exponential) net growth is represented in the following equation:

$$\frac{dTV}{dt} = k_{ng} \cdot TV(t) \tag{2}$$

where k_{ng} is the first order rate constant (days^{-1}). For tumor growth data showing a plateau phase, various models have been proposed.[6] Kogame *et al*.[32] proposed a model including first order growth and inhibition of tumor growth by its tumor volume, which is described as:

$$\frac{dTV}{dt} = k_{ng} \cdot \left(1 - \frac{TV(t)}{TG_{50} + TV(t)}\right) \cdot TV(t) \tag{3}$$

where TG_{50} is the tumor size that inhibits tumor growth by 50% and is based on the underlying physiology where local conditions can limit tumor growth.[32]

In the absence of a plateau phase, an alternative growth model allowing the tumor growth function to switch between

Table 1 Summary of PK-PD models used to describe tumor growth inhibition in xenograft models

Reference	Target	Xenograft model	Objectives	Model
Simple growth models				
Bueno, 2008[34]	Transforming growth factor-β	Calu6, MX1	To develop a semimechanistic PK-PD model to integrate PK and PD with tumor growth inhibition.	$\frac{dTV}{dt} = \frac{K_{grw1} \times (1 - Effect) \times TV(t)}{\left[1 + \left(\frac{K_{grw1}}{K_{grw0}} \times TV(t)\right)^{\gamma}\right]^{1/\gamma}}$ (1) $Effect = f(\text{biomarker})$
Kogame, 2013[32]	Hedgehog pathway	PAN-04	To characterize PK and antitumor effects to support dosing regimen selection in the clinic.	$\frac{dTV}{dt} = k_{in} \cdot \left(1 - \frac{TV(t)}{TG_{50} + TV(t)}\right) \cdot (1 - Effect) \cdot TV(t)$ (1) $Effect = \frac{I_{max} \cdot C}{IC_{50} + C}$
Phase-specific models				
Yamazaki, 2008[93] Yamazaki, 2012[94]	ALK and cMET	GTL16 H3122, Karpas299	To characterize the PK and antitumor effects to support dosing regimen selection in the clinic.	$\frac{dTV}{dt} = k_{ng} \cdot (1 - Effect) \cdot TV(t) - k_{out} \cdot TV(t)$ (1) $Effect = \frac{E_{max} \times C^n}{EC_{50}^n + C^n}$
Wong, 2009[36] Gong, 2013[95] Wong, 2013[96]	B-Raf kinase inhibitor Endoxifen Inhibitor of apoptosis	A375 MCF7 MDA-MB-231-X1.1	To characterize *in vitro* and *in vivo* potency and PD properties. To define the *in vivo* potency. To characterize PK-PD to support a second-generation molecule.	$\frac{dTV}{dt} = k_{ng} \cdot TV(t) - K \cdot TV(t)$ (1) $K = \frac{K_{max} \times C^n}{KC_{50}^n + C^n}$
Salphati, 2010[37] Wong, 2011[38]	Phosphatidylinositol 3-kinase inhibitor Hedgehog pathway	MCF7.1 Medulloblastoma allograft, D5123	To characterize *in vivo* efficacy and investigate PK-PD relationships. To characterize PK-PD to support dosing regimen selection in the clinic.	$\frac{dTV}{dt} = k_{ng} \cdot TV(t) - K \cdot TV(t)$ (1) $K = \frac{K_{max} \times (\%I)^n}{K(\%I)_{50}^n + (\%I)^n}$
Phase nonspecific models incorporating transit compartments				
Cell distribution models				
Simeoni, 2004[33] Rocchetti, 2007[42] Rocchetti, 2009[97] Shah, 2012[98] Fetterly, 2013[99]	Cytotoxic agents Cytotoxic agents Combination therapies Antibody drug conjugate VEGF and docetaxel	A2780, HCT116 A2780 Bx-pc3, HT29, KM-12 L540cy, Karpas299 Acute myeloid leukemia	To develop a minimal PK-PD model. To explore the use of drug-specific parameters in predicting human responses. To develop a PK-PD model for combination therapy. To develop a multiscale mechanism-based PK-PD model. To determine the most effective *in vivo* combination using a PK-PD approach.	$\frac{dx_1(t)}{dt} = \frac{\lambda_0 \cdot x_1(t)}{\left[1 + \left(\frac{\lambda_0}{\lambda_1} \cdot w(t)\right)^{\psi}\right]^{1/\psi}} - k_2 \cdot c(t) \cdot x_1(t)$ $\frac{dx_2(t)}{dt} = k_2 \cdot c(t) \cdot x_1(t) - k_1 \cdot x_2(t)$ $\frac{dx_3(t)}{dt} = k_1 \cdot [x_2(t) - x_3(t)]$ $\frac{dx_4(t)}{dt} = k_1 \cdot [x_3(t) - x_4(t)]$ $w(t) = x_1(t) + x_2(t) + x_3(t) + x_4(t)$ $x_{1(t=0)} = w(0)$ $x_{2(t=0)} = x_{3(t=0)} = x_{4(t=0)} = 0$
Koch, 2009[35]	Combination therapies	PC3, HCT116	To demonstrate the feasibility of empirical PK-PD modeling for combination drugs.	$\frac{dx_1(t)}{dt} = \frac{2 \cdot \lambda_0 \cdot \lambda_1 \cdot x_1(t)^2}{[\lambda_1 + 2 \cdot \lambda_0 \cdot x_1(t) \cdot w(t)]} - TI \cdot x_1(t)$ $\frac{dx_2(t)}{dt} = TI \cdot x_1(t) - k_1 \cdot x_2(t)$ $\frac{dx_3(t)}{dt} = k_1 \cdot [x_2(t) - x_3(t)]$ $\frac{dx_4(t)}{dt} = k_1 \cdot [x_3(t) - x_4(t)]$ $w(t) = x_1(t) + x_2(t) + x_3(t) + x_4(t)$ $TI(t) = k_2^a \cdot c_a(t) + k_2^b \cdot c_b(t) \cdot \psi$ $x_{1(t=0)} = w(0)$ $x_{2(t=0)} = x_{3(t=0)} = x_{4(t=0)} = 0$

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Table 1. *cont.*

Reference	Target	Xenograft model	Objectives	Model
Terranova, 2013[50]	Combination therapies	A278, HT29, BxPC3 human pancreatic adenocarcinoma cell lines	PK-PD model to mechanistically describe combo drug treatment.	$\frac{dx_{00}(t) \rightarrow}{dt} = f_p(w(t)) - k_{2a} \cdot c_a(t) + k_{2b} \cdot c_b(t) + v_{11}) * x_{00}$ $\frac{dx_{ij}(t)}{dt} = u_{aij} + u_{bij} + v_{ij}$ $w_{(0)} = \sum_{i=0}^{3}\sum_{j=0}^{3} x_{ij}(t)$ $x_{00}(0) = w_0$ $x_{ij}(0) = 0$ $i + j > 0$ $\frac{dx_1(t)}{dt} = \frac{\lambda_0 \cdot x_{00}(t)}{\left[1 + \left(\frac{\lambda_0}{\lambda_1} \cdot w(t)\right)^{\psi}\right]^{1/\psi}}$ $u_{aij} = \begin{cases} 0 & i=0 \\ k_{2a}c_a(t)x_{i-1,j} - k_{1a}x_{ij} & i=1 \\ k_{1a}x_{i-1_j} - k_{1a}x_{ij} & i=2 \end{cases}$ $u_{bij} = \begin{cases} 0 & i=0 \\ k_{2b}c_b(t)x_{i,j-1} - k_b x_{ij} & i=1 \\ k_{1a}x_{i-1_j} - k_{1a}x_{ij} & i=2 \end{cases}$ $v_{aij} = \begin{cases} \gamma c_a(t)x_{i-1,j}c_b(t)x_{00} & i=j=1 \\ 0_{ij} & otherwwise \end{cases}$
Jumbe, 2010[100]	Antibody-drug conjugate	Fo5, BT474EEI	To develop a PK-PD model to describe antitumor activity as a function of dose and schedule.	$\frac{dV_1(t)}{dt} = kGn - kK \cdot Effect \cdot V_1(t)$ $\frac{dV_2(t)}{dt} = kK\left(Effect \cdot V_1(t) - V_2(t)\right)$ $\frac{dV_3(t)}{dt} = kK \cdot \left(V_2(t) - V_3(t)\right)$ $TV(t) = V_1(t) + V_2(t) + V_3(t)$ $Effect = \frac{K_{max} \times C(t)}{KC_{50} + C(t)}$ $V_{1(t=0)} = TV_{(0)}$ $V_{2(t=0)} = V_{3(t=0)} = 0$
Signal distribution models				
Yang, 2010[41]	Paclitaxel	Colon-26	To compare the properties of two promising transduction models.	$\frac{dR}{dt} = g \cdot R - K_4 \cdot R, \quad R(0) = w(0)$ $\frac{dK_1}{dt} = \frac{1}{\tau} \cdot \left(\frac{K_{max} \cdot C}{IC_{50} + C} - K_1\right), \quad K_1(0) = 0$ $\frac{dK_2}{dt} = (K_1 - K_2)/\tau, \quad K_2(0) = 0$ $\frac{dK_3}{dt} = (K_2 - K_3)/\tau, \quad K_3(0) = 0$ $\frac{dK_4}{dt} = (K_3 - K_4)/\tau, \quad K_4(0) = 0$
Higgins, 2014[68]	MDM2	SJSA osteosarcoma	To determine the scheduling requirements for optimal antitumor activity using a PK-PD approach.	$\frac{dR}{dt} = g \cdot R - K_4 \cdot R, \quad R(0) = w(0)$ $\frac{dK_1}{dt} = \frac{1}{\tau} \cdot (k_2 \cdot C - K_1), \quad K_1(0) = 0$ $\frac{dK_2}{dt} = \frac{1}{\tau} \cdot (K_1 - K_2), \quad K_2(0) = 0$ $\frac{dK_3}{dt} = \frac{1}{\tau} \cdot (K_2 - K_3), \quad K_3(0) = 0$ $\frac{dK_4}{dt} = \frac{1}{\tau} \cdot (K_3 - K_4), \quad K_4(0) = 0$

This table provides a summary reference of published tumor growth and drug effect models. (1) Initial condition: $TV_{(t=0)} = TV_{(0)}$.
ALK, anaplastic lymphoma kinase; PD, pharmacodynamics; PK, pharmacokinetics; VEGF, vascular endothelial growth factor.

exponential and linear growth[33] is described in the following equation:

$$\frac{dTV}{dt} = \frac{\lambda_0 \cdot TV(t)}{\left[1 + \left(\frac{\lambda_0}{\lambda_1} \cdot TV(t)\right)^{\psi}\right]^{1/\psi}} \quad (4)$$

Koch *et al*.[35] suggested an empirical tumor growth model with a smooth transition between exponential to linear

growth phases that are represented in the following equation:

$$\frac{dTV}{dt} = \frac{2 \cdot \lambda_0 \cdot \lambda_1 \cdot TV(t)}{\lambda_1 + 2 \cdot \lambda_0 \cdot TV(t)} \quad (5)$$

where λ_0 and λ_1 are first-order and zero-order rate constants characterizing exponential and linear growth, respectively, and in Eq. 4, ψ is a parameter that allows the system
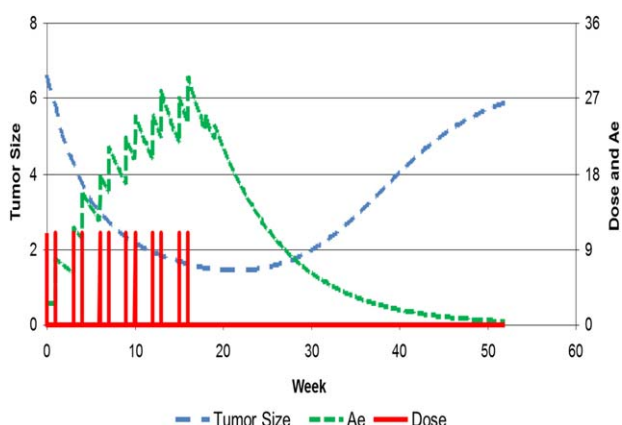
Figure 2 Response of non-small cell lung cancer during and after six cycles of treatment with gemcitabine (red bars). The predicted accumulation of the nominal amount of active substance during treatment and washout after treatment (dotted green line) determines the effect on inhibition of tumor growth. The time course of tumor size (dashed blue line) reaches a minimum some weeks after stopping treatment (adapted from ref. 45 with permission).

to sharply switch from exponential to linear growth. A fixed value of 20 was suggested for ψ.[33] For these equations, the initial condition is given as $TV_{(t = 0)} = TV_0$.

Tumor growth models in drug treatment groups
The addition of anticancer drug treatment is expected to inhibit tumor growth. In a simple growth model, the model assumes that the exponential growth of the xenograft can be reduced by a drug effect either directly or through inhibition of the target.[32,34] The cell cycle phase nonspecific model assumes exponential growth, and that drug acts by a first-order rate constant.[31] In the cell cycle phase-specific model, the drug affects the sensitive cells that can cycle between sensitive and resistant pools. Drug effect can be incorporated by including a sigmoid Emax equation. For example, a first-order growth model with the drug effect included as a sigmoid Emax model[36] is shown in the following equation:

$$\frac{dTV}{dt} = k_{ng} \cdot TV(t) - K \cdot TV(t) \tag{6}$$

where the initial condition $TV_{(t = 0)} = TV_0$, k_{ng} is a first-order growth rate constant, K is a function describing drug effect is shown in the following equation:

$$K = \frac{K_{max} \cdot C^n}{KC_{50}^n + C^n} \tag{7}$$

where K_{max} describes the maximum drug effect, KC_{50} is the concentration at half-maximal response, and n is the hill coefficient. An alternate parameterization was proposed where biomarker response is used in lieu of drug concentration.[37–39]

The response of anticancer drugs is typically delayed relative to the time course of drug exposure. Tumor size is determined by the net effect of growth and shrinkage because of cell death. Many current anticancer drug treat-

ments reduce the rate of growth, for example by modifying DNA replication. Thus, although the drug effect on growth is related to exposure, tumor shrinkage because of inhibition of growth and death of damaged cells is a secondary effect. The time course of response to treatment depends primarily on the factors influencing the delay between drug administration and eventual effects on tumor growth. These delays arise from distribution to the site of action, binding to the target receptor, and the turnover of physiological mediators leading to an observable response.

Transit compartment models, originally developed to describe kinetics of signal transduction processes, were shown to describe time delay.[40] Transduction models were proposed based on the phase nonspecific models, but make use of transit compartments to describe a delay between PK and tumor growth inhibition.[31,33,39,41] In the cell distribution model, tumor volume is assumed to represent the population of cycling cells plus additional cells that are in various stages of cell death and removal.[33,41] In contrast, the signal distribution model assumes the drug acts on a receptor, and the resulting signal is cascaded through a series of transit compartments.[31,41] Lobo and Balthasar[31] proposed a signal distribution model describing tumor growth dynamics of *in vitro* data assuming a delayed drug effect because of signal transduction processes.

Simeoni *et al*.[33] developed a semimechanistic PK-PD model to assess antitumor effect in xenograft mice assuming a delay in tumor response because of the duration of drug-induced cell death. As a secondary parameter, a threshold concentration was derived that defines the predicted concentration at which the drug-induced tumor kill rate equals the tumor growth rate and, as a result, net tumor stasis is achieved. Thus, threshold concentration can be regarded as reference concentration above which relevant anticancer activity is expected in patients. Rocchetti *et al*.[42] demonstrated that predicted threshold concentration derived from xenograft experiments correlated with the active dose in humans for several marketed drugs.

Tumor growth models have been used to evaluate treatment effect with various anticancer agents in clinical trials to quantify individual sensitivity and response to anticancer drugs. Many of the translational models can be applied to clinical data. A simple function that can be used to describe the growth of a tumor as an exponential increase in cell count with time is given in the following equation[43]:

$$\frac{dTumor}{dt} = k_{growth} \cdot Tumor - k_{death} \cdot Tumor \cdot C_{e,A}. \tag{8}$$

The effect of drug treatment may be to slow tumor growth rate (k_{growth}) or increase cell death rate (k_{death}). The delayed effect of drug concentration can be handled using an effect compartment model ($C_{e,A}$).[44]

A model describing the non-small cell lung cancer response to gemcitabine treatment in humans used a semimechanistic model based on the principles of delayed response to treatment.[45] The response time course is slow in relation to the PK of gemcitabine (**Figure 2**). This delay was explained by a combination of slow onset of drug effect

and slow turnover because of tumor cell shrinkage and loss using the following equation:

$$\frac{dSize}{dt} = \left(RateIn * Effect - \frac{1}{TTurnover} * Size \right) * Size. \quad (9)$$

where Size is the tumor size, RateIn is the rate of tumor growth, Effect is the drug effect on tumor growth, and TTurnover is tumor turnover. A second size parameter was included to describe a simplified form of feedback to describe an asymptote for tumor size. This model is limited owing to the inability to predict tumor regrowth in the presence of treatment, something that is often observed in clinical settings.

A more realistic tumor growth model should take resistance to drug, such as may occur through mutation, into account. The change of cell characteristic from a responsive to an unresponsive state can be either reversible or irreversible. The equations below describe reversible transition between sensitive phases ($Tumor_S$) and phases that are not sensitive to therapeutic intervention ($Tumor_R$)[46]:

$$\frac{dTumor_S}{dt} = k_{growth} \cdot Tumor_S - k_{SR} \cdot Tumor_S$$
$$+ k_{RS} \cdot Tumor_R - k_{death} \cdot Tumor_S \quad (10)$$
$$\frac{dTumor_R}{dt} = k_{SR} \cdot Tumor_S - k_{RS} \cdot Tumor_R$$

where the rates of transformation to and from the resistant state are indicated by kSR and kRS, respectively.

Claret *et al*.[47] developed a model describing tumor size based on RECIST criteria as a function of time and drug exposure that accounts for tumor growth and drug action. The model incorporates a first-order tumor growth rate. A resistance process was incorporated to describe tumor regrowth as shown in the equation below:

$$\frac{dy(t)}{dt} = K_L - K_D \cdot Exposure(t) \cdot y(t) \quad y(0) = y_0$$
$$K_D(t) = K_{D,0}.e^{-\lambda t} \quad (11)$$

where y(t) is the tumor size at time t, y(0) is the baseline tumor size, K_L is the tumor growth rate, $K_D(t)$ is the drug-constant cell kill rate that decreases exponentially with time (according to λ) from an initial value of $K_{D,0}$ to account for the progressive development of resistance, and Exposure(t) is the drug exposure at time t. Thus, this model can describe regrowth of tumors but has no tumor size limitations.

Tumor growth and response exhibits high BSV, with some patients responding to treatment and others showing continued tumor growth. In settings with highly variable response to therapy, a mixture of model approaches[48] allows development of functions describing separate trajectories for responders and nonresponders may provide a useful approach to reduce BSV in parameter estimates. Primarily, mixture models are used when data yield a multimodal distribution for a random effect (η) that cannot be removed or made symmetric by inclusion of a covariate, or transformation of the η distribution. Mixture models are always the second choice to using an appropriate covariate. However, mixture models can provide insight into the data, improving the structure of a nonmixture model. This approach was used to describe tumor growth relative to MK-3475, in which different tumor growth patterns were identified.[49] For illustration, simulated tumor growth profiles are shown in **Figure 3** (see **Supplementary Material S2**):

This approach simplifies identification of predictive factors for responders or nonresponders. By allowing the model to identify what sort of tumor growth each patient experiences under treatment, covariates within each responder category can be scrutinized.

Tumor growth drug interactions
Combination therapies are widely used to treat patients with cancer. Model-based approaches can be applied in preclinical development to characterize pharmacological drug interaction. For example, Koch *et al*.[35] proposed an empirical model of tumor growth to look at the effect of combination therapy, whereas Terranova *et al*.[50] suggested a mechanistic PK-PD model to characterize combination therapies in xenograft experiments. Both approaches include an interaction term to score the synergistic/antagonistic interaction. However, utility of the Koch model to describe tumor growth DDIs is restricted to drugs with similar mechanisms of action. Furthermore, because only one drug potency is modulated through the interaction term, requires be made about assumptions on the interaction effect. The more physiologic Terranova model does not have these limitations.

Timing of administered agents can play an important role in effectiveness of combination therapy. Harrold *et al*.[51] developed a multiscale pharmacological model linking drug exposure, receptor occupancy, and signal transduction events to changes in tumor burden. This translational modeling approach enables the ability to select the optimal drug combinations and optimal dosing regimen for further exploration.

Measuring tumor response to treatment
Developing PK-PD models necessitates understanding the limitations of methods evaluating response. Tumors can be measured directly through visualization or indirectly through assessment of biomarkers of tumor growth. These methods are described below.

Direct measurements of tumor growth
Traditional RECIST criteria for categorizing response to treatment are largely based on changes in tumor size described by the sum of the longest diameters of tumor visible on computed tomography (CT) or magnetic resonance imaging scans. RECIST categories have been criticized because they discard much of the quantitative information included in measurements.[5,52]

Although RECIST is the most common metric of tumor size, alternative assessments are becoming available. Combined positron emission tomography/CT, an imaging method combining positron emission tomography functional imagery with anatomic information of CT, allows visualization of tumor response. Positron emission tomography/CT is able to provide more precise evaluations of tumor growth
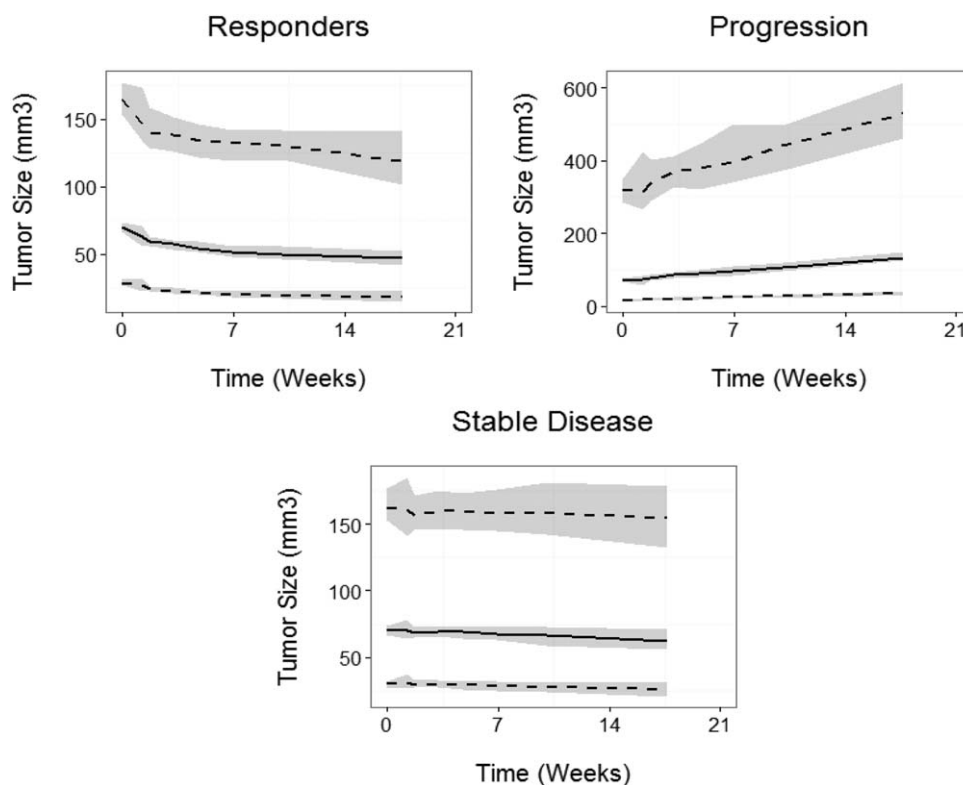
Figure 3 Simulated tumor responses using a mixture of models. In each panel, the overall range of tumor growth over time for subjects who have responded to therapy (responders), remained stable (stable disease), and not responded (progression). The solid lines represent the median tumor trajectory, the dashed lines represent the lower 2.5 percentile and the upper 97.5 percentile of expected tumor growth, and the shaded gray regions are 95% confidence intervals of the percentiles. Defining separate functions for different subpopulations can help to determine the effect of the drug in a sensitive patient population.

and response than RECIST, and precise information is crucial to development of useful models. The ability to measure early treatment response makes positron emission tomography/CT useful during anticancer drug development, allowing visualization of tumor metabolism, cellular proliferation, specific cell surface receptors, angiogenesis, and tumor hypoxia.[53] Standardized uptake values provide quantitative measures of tissue accumulation of ^{18}F-fluorodeoxyglucose by normalizing measured tissue radioactivity to the injected dose and body weight.[54] Standardized uptake values represent the ratio of image-derived radioactivity concentration in a selected body part at a certain time to radioactivity across the whole body.

Tumor biomarkers

The use of image-based measurements of tumor size has a variety of limitations. It can be difficult to reliably identify the same primary tumor or metastasis in order to describe overall tumor size in a consistent fashion. Tumors may be diffuse and not identifiable by traditional imaging methods. An alternative to direct measurement of tumor size is to use a biomarker produced by the tumor in proportion to its size. The biomarker concentration is typically measured in blood. Changes in concentration are assumed to be due to changes in tumor size rather than changes in biomarker clearance.

Biomarkers can predict tumor growth, as was shown with sunitinib.[55] The authors examined several biomarkers (vascular endothelial growth factor, soluble vascular endothelial growth factor receptor-2, soluble vascular endothelial growth factor receptor-3, and soluble stem cell factor receptor) to ascertain their ability to predict tumor response and ultimately survival. A similar approach was used with CA-125 as a biomarker for ovarian tumors. Imaging methods were used to link the time courses of CA-125 and tumor size.[56] CA-125 changes after treatment were used to predict tumor size time course. CA-125 was a better predictor of progression-free survival than models based on observed tumor size, which may reflect the ability of CA-125 to describe a tumor that is not visible with standard imaging methods.

SAFETY EVALUATIONS

Safety is commonly evaluated to establish appropriate doses of anticancer agents. Adverse events are broadly divided into categorical evaluations (e.g., mucositis grade), and continuous evaluations (e.g., absolute neutrophil count). When events are reported in terms of occurrence (e.g., a binary event where a subject experienced an event

or did not) or grade of occurrence (e.g., an ordered categorical event where increasing severity is associated with higher event grades), the relationship between exposure and events should be conducted using logistic regression because intermediate grades or occurrences cannot occur. However, caution must be used when attempting to extrapolate logistic models to other dose regimens, as these models are largely empirical, with little or no mechanistic basis, and lack usefulness when applied to conditions (e.g., schedules, or routes of administration) different from those from which they were originally derived. In general, if the probability of an event is related to AUC, suggesting the same toxicity will occur regardless of how the drug is administered (e.g., a high dose infused twice weekly will produce the same toxicity as lower doses infused 5 times weekly), which is not always true.

In a logistic model, the probability of an event occurring in an individual (p_i) is represented as follows:

$$\text{Probability } p_i = \frac{e^{\lambda i}}{(1+e^{\lambda i})}. \quad (12)$$

where λ_i is a function of covariates (X_i), scale factors (θ) and BSV (η_i) ($\lambda_i = f(X_i, \theta, \eta_i)$.

$$\text{Odds ratio } e^{\lambda i} = \frac{p_i}{(1+p_i)}. \quad (13)$$

The odds ratio is one way to quantify how strongly covariates are associated with the occurrence of an event in a given population. Exponentiating the odds ratio to isolate λ_i gives the logit:

$$\text{Logit } Log\left(\frac{p_i}{(1+p_i)}\right) = \lambda i. \quad (14)$$

In binary logistic regression, we relate factors, such as drug exposure, to the probability of a patient experiencing an event. However, when the events are graded by severity, this approach must be modified to take into account that the events are ordered:

$$g[P(Y_{i,j} \geq m | \eta_i)] = log\left[\frac{p}{1-p}\right] = \sum_{k=1}^{m} \beta_k + f_d + \eta_i. \quad (15)$$

where $Y_{i,j}$ is the ith observation of the jth individual, m is the number of grades of an event (1 mild, 2 moderate, etc.), f_d is a function of drug exposure, and β_k is an underlying baseline probability such that:

$$\beta_1 \text{ is } 1 \geq m, \quad \beta_2 \text{ is } 2 \geq m, etc. \quad (16)$$

$$\text{Probability } p = \frac{e^{\sum_{m}^{k=1} \beta_k + f_d + \eta}}{(1+e^{\sum_{m}^{k=1} \beta_k + f_d + \eta})}. \quad (17)$$

Adverse events can be dependent on prior occurrences. For instance, a patient who has experienced a high-grade adverse event usually undergoes dose reduction owing to

the likelihood that this patient will have the same or worse grade of event on subsequent doses. Thus, it may be important to account for past events when predicting future occurrences. In such cases, the use of a transition or Markov model should be considered.[57] With Markov models, the probability of observing the data ($Y_{i,j}$) depends on the previous observation ($Y_{i,j-1}$) such that:

$$g[P(Y_{i,j} \geq m | Y_{i,j-1} = h, \eta_i)] = log\left[\frac{p}{1-p}\right] = \sum_{k=1}^{m} \beta_{k,h} + f_{d,h} + \eta_i. \quad (18)$$

Examples of logistic regression models are in **Supplementary Material S3**.

Logistic regression is frequently used for graded safety assessments. An evaluation of pralatrexate[58] found drug exposure and folate levels were predictive of mucositis, requiring folate pretreat before pralatrexate administration. A pooled retrospective evaluation of topotecan identified several factors predictive of high drug exposure (weight, renal function, performance status, and drug formulation), and other factors, such as previous treatment with platinum-based drugs, that would potentially increase patient sensitivity to neutropenia.[59] This work used an ordered categorical evaluation of common toxicity criteria-graded neutropenia after infusions of 1.5 mg/m^2 administered daily for 5 days every 3 weeks. The model identified drug exposure (AUC) and the number of courses of prior treatment with platinum-based regimens as predictive factors for neutropenia.

A more elegant solution with broader applicability was proposed by Friberg *et al.*,[60] who described the delayed transient decrease and rebound of neutrophils after varying anticancer regimens in the rat model. This model was subsequently tested across a range of drugs in humans,[61] identifying drug effect parameters for several anticancer agents and showing good consistency of system parameters across all drugs evaluated. Puisset *et al.*[62] applied this model to docetaxel, where prior chemotherapy was again identified as a predictor of neutropenia. The model was also evaluated as a predictive tool for myelosuppression[63] with good results, suggesting that semiphysiologic models are useful to identify maximum tolerated doses during drug development. Finally, the Friberg model was linked to the probability of febrile neutropenia,[64] suggesting the further benefit of identification of patients who are at high risk for developing febrile neutropenia based on predictive factors and/or drug exposure.

Because anticancer agents are usually administered as combination therapy, PK or PD interactions can increase toxicity. Consequently, the model for neutrophil time course proposed by Friberg *et al.*[60] was adapted by Soto *et al.*[65] to predict the neutropenia arising from concomitant administration of several anticancer agents. However, the assumption that the actions of both agents are additive in effect is usually made, which may underestimate the combined effect. This same model can be modified to describe effects of anticancer drugs on platelet and red blood cell counts.

Estimating the TI in preclinical species and projecting it to humans based on a dynamic translational PK-PD model
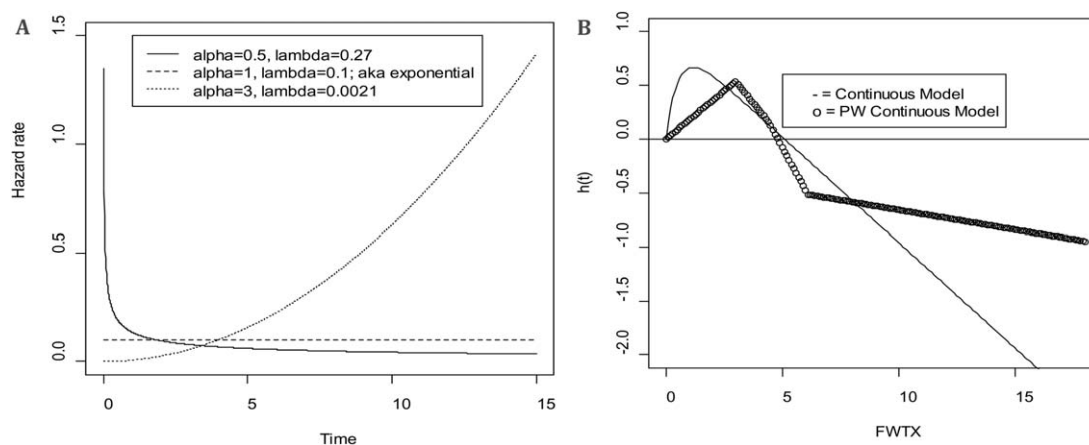
Figure 4 Hazard functions. (a) A Weibull hazard function showing the impact of varying α (the shape parameter) and λ (the scale parameter). Weibull functions can therefore account for increasing or decreasing hazards. (b) Piecewise continuous and continuously differentiable hazard functions. Although the piecewise hazard function is not easily related to physiology, the use of such functions, if appropriately supported by the data, can improve the ability of the time-to-event (TTE) model to describe the reduction in hazard because of drug exposure. In this figure, the continuous model would provide a biased estimate of hazard reduction at high first week of treatment (FWTX) if the piecewise hazard function were derived from observed data.

has become feasible with the development of scalable semiphysiologic models of myelosuppression. For example, a translational PK-PD model was developed to describe the time-course of the drug-induced thrombocytopenia by separating system-specific (platelet baseline level, maturation time, rate of progenitor production, feedback regulation) and drug-specific (e.g., drug potency) parameters.[61,66] The model was scaled to humans by accounting for system-specific differences while assuming drug potency to be the same across species.[67] Human PK was predicted by a PBPK model and linked to the scaled thrombocytopenia model to predict the time-course of drug-induced thrombocytopenia in humans.[66] Simulations suggested dosing regimens projected to provide similar anticancer effect based on a semimechanistic PK-PD model developed to predict tumor growth inhibition in tumor-bearing xenograft mice.[68] The most favorable dosing regimen that allowed differentiation of antitumor effect from drug-induced thrombocytopenia was selected and implemented in the FIH trial.

MODELING OUTCOMES (TTE)

TTE models find many uses in pharmacometrics and have been recently reviewed.[69] Examples for anticancer agents include OS and progression-free survival, dropout from a clinical trial, and time to the occurrence of a treatment-emergent adverse event. A noteworthy feature of such data is that it may not be observed (censored) during the observation period. Theoretically, if one could follow the subject long enough, the event might be observed. TTE models describing the distribution of event times, such as time to death, are commonly used to test hypotheses about treatment effectiveness.

A common approach is to use parametric hazard functions, which can be parameterized to describe the hazard

for an event with and without treatment, as shown in the equation below:

$$\text{Constant} \quad h(t) = \alpha \quad \alpha > 0. \quad (19)$$

This function, a constant hazard, is uncommon, but it has been used under the assumption that as long as the absolute neutrophil count is below some critical level, there is a constant hazard of developing febrile neutropenia.

$$\text{Gompertz} \quad h(t) = \theta \cdot e^{\alpha \cdot t}\theta, \quad \alpha > 0 : t \geq 0 \quad (20)$$

$$\text{Weibull} \quad h(t) = \alpha \cdot \lambda \cdot t^{\alpha-1}\alpha, \quad \lambda > 0 : t \geq 0 \quad (21)$$

where t is time, α is the shape parameter, and λ is the scale parameter. Example hazard curves for the Weibull function are shown in **Figure 4a**. The Weibull function can be reparameterized in terms of α, and the median of the Weibull distribution (TM) as shown in the equation below:

$$\text{Weibull} \quad 2h(t) = \frac{0.693\alpha}{TM} \cdot \left(\frac{t}{TM}\right)^{(\alpha-1)}\alpha > 0 \quad (22)$$

$$\text{Parametric} \quad h(t) = e^{\alpha + \beta \cdot t + \gamma \cdot X1}\alpha > 0. \quad (23)$$

Where α is the log of the baseline hazard (at t = 0), β is a scale factor for time 't', γ is a scale factor for the covariate effect, and X1 is a measure of drug exposure (or other covariate). Parametric approaches are often used as they are interpretable (see **Supplementary Material S4**).

TTE analysis commonly uses factors assessed at baseline (e.g., prognostic factors) as covariates to account for between-subject differences in outcome. These factors can be incorporated into hazard functions and tested to identify their impact. If important, such covariates can be useful for determining appropriate treatment strategy (commonly referred to as "staging" in oncology).
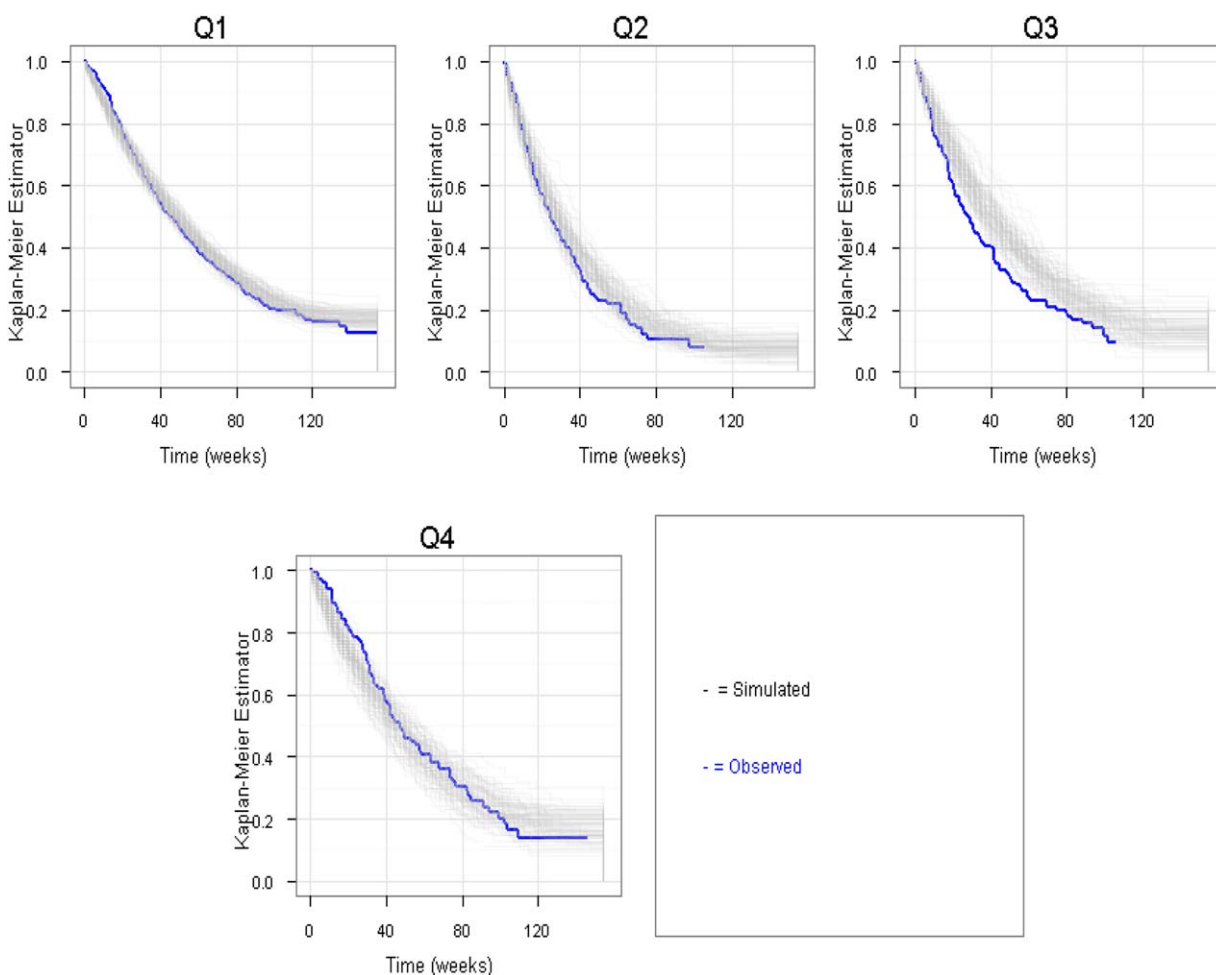
Figure 5 Example Visual Predictive Check of a time-to-event model. In the example below, the final TTE model was used to simulate multiple replicates of the study, and Kaplan–Meier plots of the simulated data (shaded area) were overlaid on the observed data (blue lines). In such evaluations, it is common to generate these figures stratified by predictive covariates; here, the data were stratified by drug exposure. In this example Visual Predictive Check, the model performs well for most exposure quantiles but slightly underestimates survival benefit in the third quantile.

Often after a model is fitted to data, it is desirable to see if the model contradicts the data. The model monitoring distribution, or posterior predictive check, is one approach to evaluate model performance.[72] This involves simulating from the final TTE model incorporating parameter uncertainty and plot nonparametric survival (i.e., Kaplan–Meier) or hazard estimators based upon the simulated data and then overlay the estimators based upon the observed data, as shown in **Figure 5**.[70,73] Several issues deserve attention when simulating with TTE models. The first involves the simulation technique. It is well known that the cumulative distribution function, $F(t)$, is distributed unit uniform. Because of the survival function, $S(t)$ is $1-F(t)$, it is also distributed unit uniform. To simulate a survival curve, one can simulate a unit uniform variate, u, and plot u vs. $t = S^{-1}(u)$. If S is invertible, this is trivial; otherwise other methods may be required to compute "t."[74] This approach is cogent if one is working with a known density (i.e., one that integrates to unity, such as Gompertz).

EXPOSURE–RESPONSE CONSIDERATIONS

Consider the common case in which survival data are to be modeled from a cohort of patients with cancer, all of whom received either the same dosing regimen or placebo. A number of predictors of survival are available from baseline or very early in treatment. A measure of drug exposure is available from the first week of treatment (FWTX), but BSV in FWTX is substantial. When Kaplan–Meier plots are generated by exposure quartile, a nonmonotone pattern is evident. Subjects in the two lowest FWTX quartiles have worse survival than subjects receiving placebo, with subjects in the highest two quartiles having improved survival relative to placebo. It is important to ensure that these comparisons are made with subjects whose underlying covariates are similar.[75] If key covariates are imbalanced in the exposure quartiles, modeling the impact of the underlying covariates and using simulation to compare to simulated placebo outcomes may be appropriate.

After establishing that the nonmonotone exposure-survival pattern is not due to covariate imbalance, and keeping in mind that subjects were not randomized to FWTX (exposure in this case is observed), it is decided to model the data. Two possible approaches with such apparent relationships are piecewise continuous and continuously differentiable hazards. For the piecewise continuous approach, the change points (knots) for h(t) must be manually selected or estimated. Likewise, coming up with a continuous h(t) that in nonmonotone is challenging. One possible continuous h(t) is described in the equation below. A comparison of a continuous and piecewise continuous hazard functions are depicted in **Figure 4b**.

$$h(t) = e^{\frac{-FWTX \cdot e^{\alpha}}{1 + e^{\beta}}} - e^{-e^{\alpha \cdot FWTX} \cdot e^{\gamma \cdot FWTX}} \tag{24}$$

Another potential situation might be a monotone relationship with higher levels of exposure associated with worse survival. This might be explained by an unobserved dichotomous covariate that is associated with both poorer survival and lower drug elimination (which is referred to as a latent confounder). Examples include poor performance status, which is often negatively associated with survival and slower clearance, and dose reductions because of mechanism-based toxicities. Unexpected relationships between survival and drug exposure have been described for angiogenesis inhibitors.[76] Bortezomib has been reported to stimulate angiogenesis at low concentrations, while inhibiting angiogenesis at higher exposure (i.e., bell-shaped dose-response).[77]

TIME-DEPENDENT COVARIATES

Using a single evaluation of tumor size to predict outcome can cause problems because the observed time course of tumor size may be confounded with survival.[78] The use of time-varying factors, such as tumor size or biomarkers,[55] can be included as covariates in TTE models to account for disease progression or remission on outcome. However, covariate misclassification often biases parameter estimates for data-analytic models. Misclassification could be recording the wrong category for an ordinal or nominal covariate, or measurement error for a continuous covariate. If a time-varying covariate is fixed to a baseline value in a TTE analysis, the degree of misclassification may increase with time and result in underestimation of the covariate effect. An often cited example is mortality among liver failure patients who have a model of end-stage liver disease scores recorded longitudinally. Using a model of end-stage liver disease as a time-varying covariate results in a larger model of end-stage liver disease effect than just using the baseline value.[79] Thus, when covariates vary over time, including more than just the baseline, value is an important means of reducing bias.

However, using time-varying covariates in TTE models requires careful consideration. Even if the covariate is time invariant, its effect on outcome may change with time. A lag effect may be needed for events having long incubation periods. Given a history of a changing covariate value up to the time of event, or censoring, there are concerns on how to use this information. One could use the covariate value at the event time, the maximum value up to the event time, or some sort of average. Time-varying covariates could be allowed to interact with baseline covariates (e.g., larger baseline tumor may grow faster and be less likely to respond).

Broadly speaking, covariates may be classified as external or internal. External or internal covariates are generated by a stochastic process external or internal to the subject, respectively.[71] External covariates are further subclassified as fixed, fixed path, or ancillary. A fixed covariate is time invariant (e.g., sex at randomization), a fixed path covariate changes with time in a predictable way (e.g., attained age), and an ancillary covariate is generated by a random process external to the subject (e.g., circadian effects).

Internal covariates can only be observed if the subject is alive and uncensored. From a modeling perspective, it is optimal if the internal covariate affects the TTE, as opposed to the converse. Consider a randomized study of placebo vs. a novel anticancer agent. Serial measures on tumor size are recorded. Also presume tumor size is on the causal pathway to death. If the time-varying tumor size and treatment arm are included in the TTE model as simple independent covariates, the treatment effect may be underestimated, as the drug effect may be absorbed into the tumor size effect. If the primary goal of modeling is to quantify treatment benefit, inclusion of time-varying tumor size along with treatment coded as dichotomous is suboptimal. Inclusion of time-varying tumor size could minimize the apparent treatment effect, if the treatment effect is via tumor size attenuation. An option to avoid this would be to model TTE as a function of tumor size, which is modeled via a separate function as depending on drug exposure.[71] It is important to include appropriate relationships between time-varying covariates within the TTE model.

Wang *et al*.[80] developed a model linking drug levels to tumor growth, which was subsequently linked to OS. The model was used to identify a metric (tumor size change at week 8) as an early covariate of patient response to treatment, and was subsequently used to examine the potential OS benefit for cytostatic vs. cytotoxic agents.[81] A simplified version of this approach was also used by Claret *et al*.,[47] using individual predicted tumor trajectory to evaluate survival. However, Wang and Claret were not using time-varying covariates for individuals, and did not integrate the hazard over time. Linking drug exposure to tumor growth and then ultimately linking time-varying tumor growth to OS provides important information about appropriate exposure for novel anticancer agents, as was shown with sunitinib.[55]

Bruno *et al*.[82] reviewed various approaches to modeling tumor growth and its impact on OS. The authors suggested jointly modeling the drug effect on tumor growth and OS, or serially modeling tumor growth, then using *post hoc* estimates tumor size as predictors of OS. They also recommended considering D-optimization to help identify informative times to evaluate tumor size.

DOSE SELECTION

The goal of optimal dose selection is to maximize the likelihood of producing therapeutic response while minimizing

unacceptable toxicity. For drugs that produce therapeutic effects at doses not associated with adverse events (i.e., a wide therapeutic index), the incentive for precisely determining dose is lower than for drugs with a narrow TI. Most anticancer agents have a narrow TI, requiring careful evaluation of optimal dosing schedules and individualized dosing to minimize the BSV in drug exposure.

Historically, many anticancer agents are dosed based on body surface area (BSA), which was initially proposed as a metric for individualizing dose. Egorin[83] noted that using BSA-based dosing was initially implemented as a means to derive safe starting doses for phase I anticancer studies from preclinical animal toxicology data based on its theoretical ability to predict metabolic rate. The limitations of using BSA as the primary size metric is based on the fact that the PK of many anticancer agents are not related (or are not linearly related) to BSA (e.g., a prospective study of epirubicin evaluating fixed dosing found no correlation with body size for either PK or neutropenia) and on difficulties in treating obese patients.[84] Despite numerous articles questioning the value of BSA-based dosing,[85] the practice is still common today.[86]

Variables for dose selection include the amount of drug delivered, frequency of administration, and treatment duration. Ideally, these should be selected based on knowledge of the relationship between the dose, the concentration time course, and the subsequent effects and likelihood of beneficial and adverse consequences resulting from these concentrations. PK-PD models relate doses to concentrations and then describe concentration-effect relationships, facilitating the prediction of the time course of the drug effects. Population-based evaluations identify patient factors predictive of exposure and response,[7,87] making simulating with these models useful in developing appropriate dose regimens. In 1988, Canal *et al*.[88] suggested implementation of adaptive dose adjustment, based on PK and PK-PD models, to allow revision of the dosage after measurement of drug concentration and comparison of exposure metrics based on known PK-PD relationships. Ten years later, Evans *et al*.[89] reported that individualizing the dose of methotrexate to account for the patient's ability to clear the drug improved the 5-year survival from 66% to 76% in children with B-lineage acute lymphoblastic leukemia. Taking the concept of individualized therapy further, Barrett *et al*.[90] developed a dashboard system (user interactive decision support software) to fully individualize methotrexate dosing in pediatric patients, potentially further improving outcomes. Although a fully powered prospective clinical trial evaluating the outcomes with dashboard-guided dosing vs. standard care has never been reported, the expectation is that this approach would further reduce toxicity and improve efficacy.

The identification of novel targets increased the opportunity to individualize therapy. For trastuzumab, tumors expressing high HER-2/neu are more likely to respond than those with low or no HER-2/neu expression.[91] In several studies comparing disease-free survival in patients with HER-2/neu-positive breast cancer, treatment with trastuzumab was found to offer benefit.[92] Identification of more sensitive subpopulations of patients using PK-PD modeling could allow enrichment of patient populations in early phase studies, leading to higher response rates or earlier discontinuation of failing drug candidates.

CONCLUSIONS

There are a number of special considerations that anticancer drug development often faces: a narrow TI, complex pharmacology, combination therapy, lack of data from healthy subjects, sparse PK sampling, and high BSV for PK and PD. Currently, new anticancer agents have a high failure rate in late-stage development, which is partly attributable to these considerations, suggesting that anticancer drug development would benefit from systematic model-based evaluations of the data across all phases of drug development. PK-PD modeling can provide information about new anticancer agents, improving mechanistic understanding of the drug and identifying exposures associated with response and toxicity. When tumor models are developed during preclinical evaluations, results can be scaled to humans, providing important information for rapid identification of the TI in humans, facilitating selection of dose regimens for testing during clinical development. Updating models with human data as it becomes available can support appropriate dose metrics, and may reduce the number of late-state development failures.

A wide variety of models are routinely developed during anticancer drug development, including PK, disease progression, and exposure-response modeling. Exposure-response modeling can include TTE models and models relating exposure to adverse events. Such models can be applied to investigate DDI. Simulation can help identify safe starting doses for combination therapy. Models can also be used to determine informative times to assess exposure or response.

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