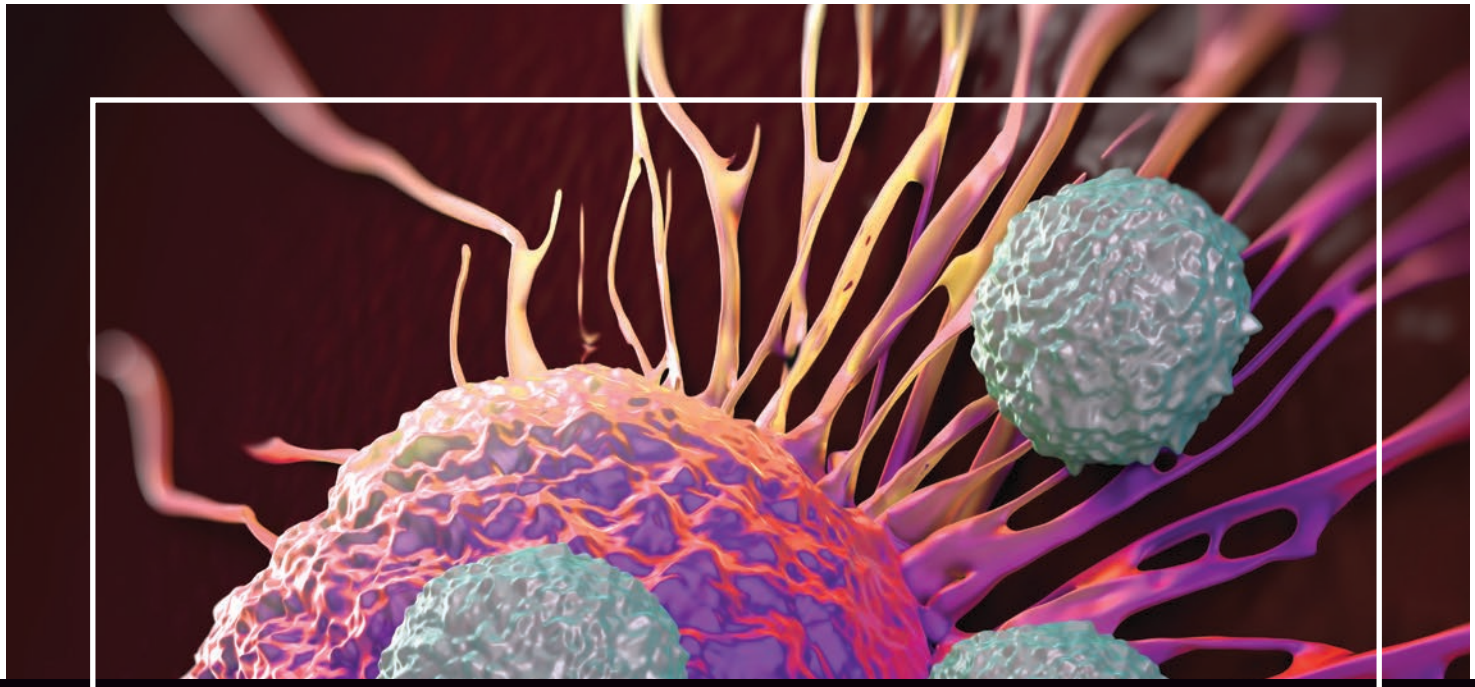
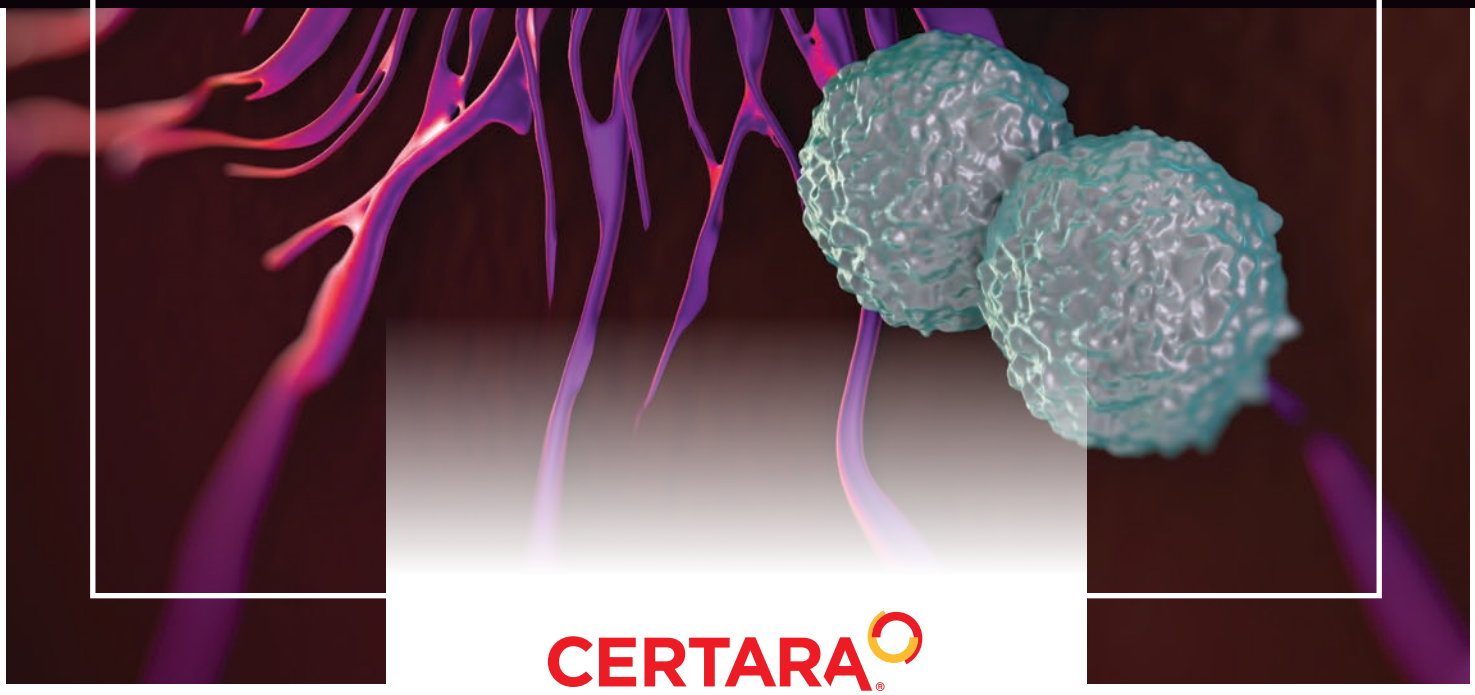


THE MODEL-INFORMED DRUG DEVELOPMENT IMPERATIVE IN ONCOLOGY R&D



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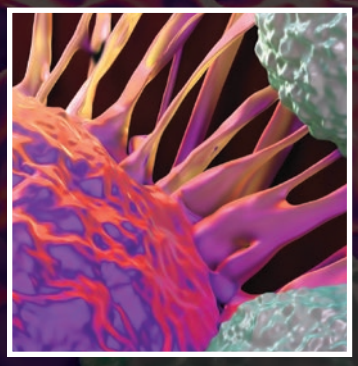


THE **MODEL-INFORMED DRUG DEVELOPMENT** IMPERATIVE IN **ONCOLOGY R&D**

Executive summary

Model-informed drug development (MIDD) leverages a range of quantitative methods (modeling and simulation or *in silico* tools) to inform critical R&D decisions such as dose regimen, evaluation of safety and efficacy, understanding mechanism of action, clinical trial design, including cohort selection and analysis of special populations, as well as the commercial probability of success as compared with existing therapies or those in development. It provides value across the development cycle, for informing internal decisions, including "go/no go" based on probability of regulatory and technical success, and/or regulatory and label decision support.

The impact of MIDD is especially powerful in oncology, where numerous cases demonstrate its enormous value in streamlining and accelerating the development cycle and supporting breakthrough therapy options for these fragile patients. MIDD is used to elucidate the complexities of oncology development, including those related to combination therapies, drug-drug interactions and other safety issues, and identifying more informative endpoints. However, despite exponential uptake in recent years and increasing bullishness on the part of the regulators, MIDD is still being underutilized—signaling a missed opportunity for many stakeholders.

Background

Cancer is the second leading cause of death globally and was responsible for 8.8 million deaths in 2015, according to the World Health Organization.[1] By 2030, the number of persons diagnosed with cancer is projected to reach 22 million. Fortunately, thanks to ongoing advances in diagnostic testing, earlier diagnosis and prevention programs, and innovation in drug development, the overall cancer death rate declined by 13% between 2004 and 2013, according to the National Institutes of Health's National Cancer Institute (NCI),[2] and the number of long-term survivors continues to grow.

Due to the critical nature of oncology and the pressing unmet need it presents, both the pipeline for new oncology therapies and the pace of approvals have been strong. For instance, from 2011 through 2016, 68 novel oncology therapies were approved and are now being used to treat more than 22 different types of cancer, among them leukemia, lung cancer, multiple myeloma, melanoma, and lymphoma.[3]

Meanwhile, the global R&D pipeline for new oncology therapy options remains robust, with more than 600 unique molecules in late-phase development, of which 90% are targeted therapies including immuno-oncology agents.[3]

Still, due to its inherent variability and complexity, oncology drug development remains the therapeutic area with the highest clinical attrition rate, with up to 80% of all investigational drugs failing in Phase 2, creating a tremendous waste of resources.

Clearly, the strong drug pipeline in oncology is great news for patients. But it has also created unprecedented competition—and a greater-than-ever sense of urgency—for drug-development companies that are striving to discover, validate, and launch promising new medications in the most streamlined, time-efficient, and cost-effective manner possible, ahead of their competitors.

The challenges in oncology drug development

Unlike drug developers targeting other disease states, investigators pursuing novel oncology therapies face a distinct set of challenges. Oncology drugs are often very toxic, which precludes conducting clinical trials in healthy volunteers. In addition, patients with cancer differ from healthy people in terms of their demographics and physiology.

These factors can significantly alter the pharmacokinetic profile of drugs in this population compared to healthy volunteers. Furthermore, cancer patients often take multiple medications concurrently to treat not just their cancer, but comorbidities and treatment-associated side effects as well. As a result, this already fragile and highly medicated patient population faces an increased risk of drug-drug interactions (DDIs) and other safety issues.

The historic approach to cancer care has relied heavily on classical chemotherapy drugs. Because these agents are cytotoxic, efforts to identify the maximum tolerated dose and use toxicity-guided treatment regimens became standard operating practice. By comparison, many of today's advanced therapies no longer rely exclusively on the use of cytotoxic chemotherapy drugs, but on targeted therapies. These include both small-molecule agents and monoclonal antibodies, a growing number of immuno-oncology options that harness the body's immune system to destroy cancer cells, and countless combinations of all of these methodologies.

The method of developing these new drugs is not the same as that for the previous cytotoxic paradigm, which relied on toxicity-guided dose determination and identification of maximum tolerated dosing. Instead, the paradigm for targeted oncology therapies is driven by the targeted activity of the therapy option (Figure 1).[4]

The traditional approach to drug development in oncology was heavily based on empirical and descriptive investigation techniques. Following this approach, late-phase clinical trials were used to confirm appropriate dosing and identify the complex interplay between efficacy and toxicity. From a practical standpoint, separate clinical trials were typically conducted only to evaluate a small sub-set of proposed patient sub-populations and dosing schemes.

Today, oncology drug development efforts are being increasingly supplemented by a more mechanistic and predictive approach that benefits from today's many modeling and simulation techniques. The growth of MIDD has rapidly evolved in recent years due to advances in computational power, the development of user-friendly software platforms, and a deeper understanding of both how the underlying biology impacts the ways in which investigational drugs impact the body and how the body reacts to different drug therapies.

Today, MIDD is supporting the development and approval of targeted cancer therapies by better characterizing the risk-benefit profile of a drug while supporting accelerated development and regulatory-approval pathways.

Figure 1: Example Factors that Inform Dose Regimens for Oncology

Blending real-world and virtual trials

The classic approach to evaluating drug delivery, safety, and efficacy relies heavily on *in vivo* and *in vitro* testing, animal-based toxicity testing, and clinical trials for humans to evaluate the overall pharmacokinetic (PK) and pharmacodynamic (PD) profile of the compound. But during the evaluation of any candidate drug therapy, clinical trials alone simply cannot evaluate all potential scenarios for an investigational drug once it is used in real-world settings. This is especially true in oncology, where healthy volunteer testing is not part of the process, and the combination of urgent unmet medical need and the opportunity to leverage accelerated pathways places a strong time pressure on the clinical development work.

Today, MIDD is being used to plan, inform, and analyze *in vivo* clinical trials and to conduct standalone virtual trials. As carrying out an endless array of clinical trials to evaluate the therapy in multiple patients is not practical from a cost or patient-enrollment standpoint, MIDD can be used to "fill in the gaps" and answer more "what if" questions.

Further, dosing and efficacy data developed for an oncology drug in one indication cannot simply be applied to other indications, which may have different tumor genotypes or molecular stratifications. Instead, the strategic use of MIDD can help sponsors augment the clinical findings and create expanded insight—to elucidate efficacy and safety mechanisms, optimize the dosing strategy, and fine-tune label claims for their drug programs.

MIDD can also be used to inform commercial options, assess go/no go decisions, determine comparator effectiveness, evaluate potential alternative drug pricing strategies, support and streamline regulatory filings, and demonstrate to payers that the ROI exists once the product is commercially available.

The dose matters

With newer targeted therapy options in oncology, the dosing strategy is no longer dictated solely by the maximum tolerated dose or toxicity limits. Instead, determining the optimal administration of these novel oncology options requires a deeper understanding of several key factors:

- The underlying biology of the malignancy
- The drug's particular mechanism of action (MOA)
- The patient's likely PK/PD response to the administered therapy

In general, oncology drugs tend to have relatively narrow therapeutic indices (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. A robust dosing strategy will also include potential adjustments that account for the impact of co-medications or patient factors, such as genotype or organ function. A variety of models are routinely developed during oncology drug development to establish the optimal dosing strategy, including PK, disease progression, and exposure-response models.

MIDD helps identify safe starting doses for combination therapies as the clinical testing of all combinations of drugs and doses is not feasible. For example, physiologically-based pharmacokinetic (PBPK) models are applied to investigate DDIs and can be used to support dose and formulation recommendations.

Meanwhile, requirements for dedicated clinical trials to evaluate drug performance in patients with other health issues, such as renal or hepatic impairment, can add years to the process. By contrast, virtual organ impairment studies are already being conducted and accepted today by regulators for dosing justifications.

In addition, an emerging contribution of MIDD is the use of model-based estimates of drug-mediated tumor growth inhibition using longitudinal tumor size data to elucidate the drugs' dose-response relationships. These models link drug-mediated tumor growth inhibition to overall survival using historical data.

These models can then be leveraged to predict outcomes based on early clinical studies (Phase 1 or Phase 2) with new investigational treatments, including combinations. These models can also help inform dose refinement as a drug moves from early to late clinical development.

Such insights are critical to characterize the efficacy profile of the drug, to optimize dosing strategies, and to evaluate how the drug performs when combined with other cancer-treatment modalities in the face of other co-administered medications.

The ability to perform fewer clinical trials—but create deeper understanding by adding modeling-derived insight and predictions—not only helps to strengthen and streamline the drug-development process, but also helps demonstrate a more robust case for the candidate therapy to take into regulatory review.

Putting MIDD to work in oncology

The opportunities to leverage MIDD to answer crucial questions span the oncology drug development cycle.

- In the translational stage, from pre-clinical to early clinical, the focus is on optimal first-in-human (FIH) dosing, concomitant medications, and pharmacodynamic (PD) endpoints to help guide dose schedule options
- In early clinical development, MIDD is used to assess dosing and dose schedules with more precision, study formulation options, assess potential DDIs, and study more cohort- or patient-specific factors
- In the late clinical stage, it is leveraged to select the pivotal clinical trial dose that will provide optimum risk-benefit, perform bridging studies, and further study adverse event (AE) potential

Specific opportunities for MIDD in pre-clinical to c

1

Predict and characterize PK—semi-physiological approaches can be used to predict PK at the site of action in a greater number of patient sub-populations than were included in the actual clinical trials.

PBPK modeling provides a powerful tool to understand the exposure at the site of action (ie, the tumor). The comprehensive summary of the underlying "system knowledge" enables extrapolations between species (ie, from mouse to man) or between patient populations (ie, between adult and pediatric patients).

4

Characterize variation in drug exposure (intrinsic/ extrinsic factors)—in the absence of dedicated clinical pharmacology studies, population PK analysis of sparsely sampled patient data can help to bridge the gap.

In many recent oncology drug approvals, the characterization of the pharmacokinetics and the impact of demographic and disease factors was based solely on integrated population PK analyses across the available patient data, rather than through dedicated Phase 1 studies. As a result, approved regulatory label statements relative to the pharmacokinetics for these drugs are purely model-based.

7

Characterize biomarker response in early clinical studies—help define biologically effective doses and determine dose ranges for further clinical testing.

When an early clinical efficacy biomarker is available, PK/PD models for that biomarker allow the characterization of target engagement and help establish the dose regimens associated with pharmacological activity.

clinical translation include:

2

Translate pre-clinical data—use mouse xenograft data to (further) support clinical dose regimen setting.

An alternative or adjunct to clinical biomarkers for early clinical dose setting is the translation of pre-clinical efficacy data. For example, in the clinical development of the anti-PD1 antibody pembrolizumab, the selection of the lowest and, ultimately, approved dose was largely built on a translational model framework through which mouse xenograft data were leveraged to predict clinically efficacious dose regimens.

3

Assess downstream biochemical or cellular effects of target/pathway modulation—quantitative systems pharmacology (QSP) is an emerging technology that sits at the interface between pharmacometrics modeling and simulation and systems biology.

QSP allows investigators to predict the effects of multiple therapeutic interventions in combination. QSP can provide a framework to evaluate these potential combinations prior to clinical testing, by providing a quantitative understanding of how different mechanisms will interact.

5

Characterize tumor-size responses to therapy—helps to establish the optimal dose regimen and therapeutic window, and allow the use of the relationship as an early marker for survival (eg, to use the tool for patient stratification during clinical trial design and/or treatment).

Several promising oncology drug products have received their initial approval on the basis of tumor size in response to therapy (objective response data)—rather than survival outcomes. This places further emphasis on developing a thorough understanding of tumor-size dynamics and the effects of investigational drugs on tumor growth or shrinkage. As a result, novel approaches to tumor-size modeling are being developed and applied to support both drug development and regulatory decision-making.

6

Characterize safety profile—establish exposure-safety relationship, optimize dose regimen from a safety perspective, and help establish the therapeutic window.

As for all drugs, the therapeutic window is determined by the balance between efficacy and safety. Exposure-response evaluations of safety data (including adverse events or specific safety findings such as neutropenia) are a crucial element in the regulatory-submission package to complement the analyses performed on efficacy. Through application of PBPK, a prospective DDI risk-management strategy can be developed. PBPK models created in pre-clinical or early clinical development are updated iteratively with clinical data.

8

Optimize trial designs—determine dose regimen selection, streamline patient selection and enrollment, and determine the optimal assessment scheme.

While most oncology modeling focuses on characterizing drug responses to support development decisions, the potential for MIDD to optimize clinical trial designs is still underappreciated. By optimizing PK/PD, investigators can often minimize the burden on patients.

9

Understand the competitive landscape—using model-based meta-analysis of (publicly available) clinical trial data for competitor therapies for the same indication.

Especially in immuno-oncology investigations, compounds are tested across a broad range of tumor types. Model-based meta-analyses enable up-to-date quantification of the competitive landscape in different indications and can help bridge efficacy and/or safety information across indications to support dose setting in a new indication prior to actual clinical testing.

Case studies: Leveraging MIDD from development to approval

MIDD allows drug developers to cost-effectively perform exposure-response analyses to explore relationships between drug exposure and clinical response. Such relationships cannot be observed by analyzing PK or clinical markers of efficacy and toxicity in isolation.

For example, ibrutinib (see Case 1) is a cytochrome P450 3A4 substrate. Dedicated clinical trials with a strong CYP3A4 inhibitor (ketoconazole) and a strong CYP3A4 inducer (rifampin) were conducted, concurrently with PBPK modeling, to predict exposure alterations when ibrutinib was administered in the presence of moderate and weak CYP3A4 inhibitors and inducers. The results of the trials and modeling together were used to derive the most appropriate dose modifications to inform physicians when prescribing ibrutinib with CYP3A4 modulators.

Another well regarded use of PK/PD and exposure-response modeling and simulation for determining dose justification is pembrolizumab (see Case 2 on page 10). In the Phase 1b study patients received 2 mg/kg or 10 mg/kg every 3 weeks. Exposure-response analyses for both safety and efficacy were conducted,[5] and no exposure trends were identified across the 2 to 10 mg/kg dose range. As documented in FDA reviews, these exploratory analyses were used to support the dose regimen of 2 mg/kg every 3 weeks for pembrolizumab in the treatment of patients with advanced non-small cell lung cancer.

Modern approaches can also be used during the approval phase. For example, last May, FDA granted the first approval of a cancer treatment based on a tumor's biomarker without regard to the tumor's original location. Pembrolizumab is indicated for the treatment of adult and pediatric patients with unresectable or metastatic solid tumors that have been identified as having a biomarker known as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), abnormalities that affect the proper repair of DNA inside the cell. Rather than requiring separate development programs for each disease site, a single therapeutic approach was created for patients with different tumor types, allowing extrapolation of the observed treatment effect to diverse tumors.[6]

Case 1

Using PBPK modeling to inform dose, dose regimen, and characterize DDI risk for ibrutinib (Imbruvica)

Ibrutinib is now available to treat B cell cancers such as mantle cell lymphoma, chronic lymphocytic leukemia, and Waldenström's macroglobulinemia (a form of non-Hodgkin's lymphoma). It is both a tyrosine kinase inhibitor and a CYP3A substrate. Because of its very high clearance rate, ibrutinib is particularly susceptible to drug-drug interactions. During the development of ibrutinib, PBPK modeling, using the Simcyp Simulator™, provided critical insights on DDI liability.

PBPK models were developed using *in vitro* and clinical data, verified using known inhibitors and inducers of CYP3A, an Imbruvica substrate, and applied to untested clinical DDI scenarios. Then, PBPK modeling was used to understand the mechanisms for drug metabolism to provide critical insights on DDI liability across different patient populations.

The modeled results helped clarify the most appropriate dosing regimens and streamline the regulatory-approval process. The modeled findings now appear within the drug's approved label to inform the dose-optimization strategy when this CYP3A substrate oncology agent is co-administered with other CYP3A inhibitor medications. The goal was to optimize dosing to prevent the plasma concentration of the drug from rising to potentially adverse levels.[7]

The PBPK model was then used to interpolate DDI effects of mild, moderate, and strong CYP3A4 inducers and inhibitors and used to inform dosing guidance in the drug label with appropriate drug-response information, including 24 individual claims for untested DDI scenarios (without the need for clinical trials), and provided a dose optimization strategy aligned to individuals with different metabolic profiles. ■

Regulators are bullish on MIDD

In recent months, the Commissioner of the US FDA has stated the agency's commitment to these technologies in several statements:[8]

"I want to highlight one example of these steps, which we're investing in, and will be expanding on, as part of our broader Innovation Initiative. It's the use of in silico tools in clinical trials for improving drug development and making regulation more efficient.

FDA's Center for Drug Evaluation and Research (CDER) is currently using modeling and simulation to predict clinical outcomes, inform clinical trial designs, support evidence of effectiveness, optimize dosing, predict product safety, and evaluate potential adverse event mechanisms. We'll be putting out additional, updated guidance on how aspects of these in silico *tools can be advanced and incorporated into different aspects of drug development."*

Figure 2 shows the rapid acceptance of these methods by FDA.[9] The use of MIDD has been included in many key regulatory mandates and guidance documents, including the 21st Century Cures Act and the current PDUFA and GDUFA. Parallel paths exist at other major regulatory agencies, including EMA and PMDA.

With regard to oncology, and as part of its PDUFA VI commitment, FDA held a workshop on the topic[10] on February 1, 2018, stating:

"Over the past few decades, there has been extensive investment in oncology drug discovery and development. Despite greater understanding of disease biology and drug mechanisms of action, further progress in model-informed strategies is needed to continue advancements in oncology drug development.

As more effective and complex combination strategies and novel targets for cancer treatment evolve, exploring more informative and predictive endpoints to assess treatment response has become an active area of research. Alternative metrics that require shorter periods of observation or provide more precise assessment of treatment effects could lead to more rapid completion of clinical trials and require fewer patients. Model-informed approaches can help satisfy a need to optimize dosing regimens for patients. Investigations to refine dosing regimens often occur after new drug approval and/or are driven by pharmacometric modeling approaches. There is growing interest in using model-informed approaches to help balance the risks and benefits of oncology products by identifying optimal dosing regimens and broad stakeholder engagement and discussion around this topic can be beneficial."

Figure 2: Evolution of MIDD at OCP

Adapted from Zineh & Woodcock, *CPT 2013;* PMID: 23571772

Case 2

The role of MIDD in the development of pembrolizumab (Keytruda)

Historically, cancer has been categorized by the anatomical origin of the tumor—eg, breast cancer, lung cancer, leukemia, and so on. Typically, the anatomical origin of cancer then dictated the approach to treatment.

However, in recent years, this framework has been changing. In June 2017, *Science* published a paper reporting that a wide range of different cancer types with loss-of-function mutations in the mismatch repair pathway have favorable responses to PD-1 blockade immunotherapy.[11] The FDA has approved the anti-PD-1 immuno-oncology drug pembrolizumab (Keytruda) for patients whose cancers have this genetic abnormality. These cancers include melanoma, non-small cell lung cancer (NSCLC), classical Hodgkin's lymphoma, head and neck cancer, and urothelial cancer.

Pembrolizumab (Keytruda, Merck & Co.) is a potent, humanized monoclonal antibody. This checkpoint inhibitor targets programmed death-1 (PD-1) receptors whose ligands (PD-L1 and PD-L2) bind to PD-1 receptors and prevent the immune system from recognizing them. Tumor cells that express PD-1 ligands are able to avoid the body's natural T-cell-mediated cancer-killing capabilities. By binding to PD-1 receptors on T-cells, pembrolizumab helps to remove this "cloak of invisibility," thereby inducing elimination of cancer cells by the immune system.[12]

The mechanism of action of pembrolizumab—binding to PD-1 receptors on T-cells—does not depend on direct engagement of the drug with tumor cells. For this reason, substantial differences in exposure-response and dose-response are not expected across different tumor types. This makes it an immuno-oncology therapeutic option that holds promise in many cancer types.

Pembrolizumab was first evaluated in pre-clinical mouse experiments. To identify the dose range to be used in first-in-man clinical studies, a translational PK/PD modeling approach was used. The model structure combined a compartmental PK model with a published physiologically-based tissue compartment.

This model was then linked to receptor occupancy to show how pembrolizumab binding to PD-1 receptors drives tumor-growth inhibition. Simulations using this model framework allowed quantification of the mechanism of action of pembrolizumab in mice and extrapolation of dosing to humans.

Once the drug entered the clinic, a population PK (PopPK) model (defined below), as well as exposure-response results from patients with advanced melanoma or NSCLC, were used to evaluate a fixed dosing regimen with the aim of maintaining pembrolizumab exposures within the range demonstrated to provide near maximal efficiency and acceptable safety. Individual predicted PK exposures were within the target range.

PopPK analysis is a model-based approach to describe the time course of a drug exposure across individuals in a population by estimation of both population-level typical PK parameters (eg, clearance, volume of distribution) and explicit terms to describe variability, including inter-subject variability, underlying the distribution of drug exposures. It is the preferred method for interpreting sparse concentration data.[13]

The Freshwater et al. study aimed to demonstrate that the fixed dose selected was able to maintain exposures within the existing safety/efficacy target range that had been established for melanoma and NSCLC. The study results found that doses of 200 mg and 2 mg/kg provide similar exposure distributions, with no advantages to either dosing approach with respect to controlling PK variability. These findings are important because they suggest that weight-based and fixed-dose regimens are appropriate for pembrolizumab—and this was borne out by modeling and simulation efforts. ■

Adoption of MIDD manifested in oncology drug labels

In recent years, MIDD has become an established practice in biopharmaceutical drug-development and regulatory-approval efforts to inform drug label claims.

Analysis of peer review publications using PK modeling in oncology development, based on the modeling approach (Figure 3), showed that a majority of studies employed population modeling approaches in the data analysis (75%).[14]

In terms of areas of application of PK modeling (Figure 4), the most prominent area of application was investigation of internal and external factors that influence PK variability.[14] This was followed by studies investigating dosing issues (22%), including dose finding and clinical practice-based dosing issues. The most studied special populations were pediatric patients.

Figure 3: PK Modeling Approaches in Oncology

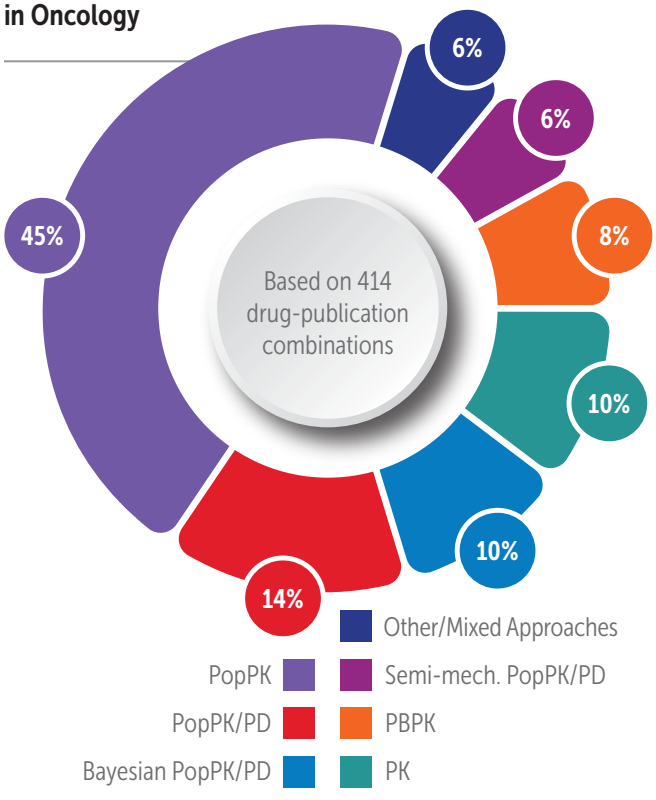
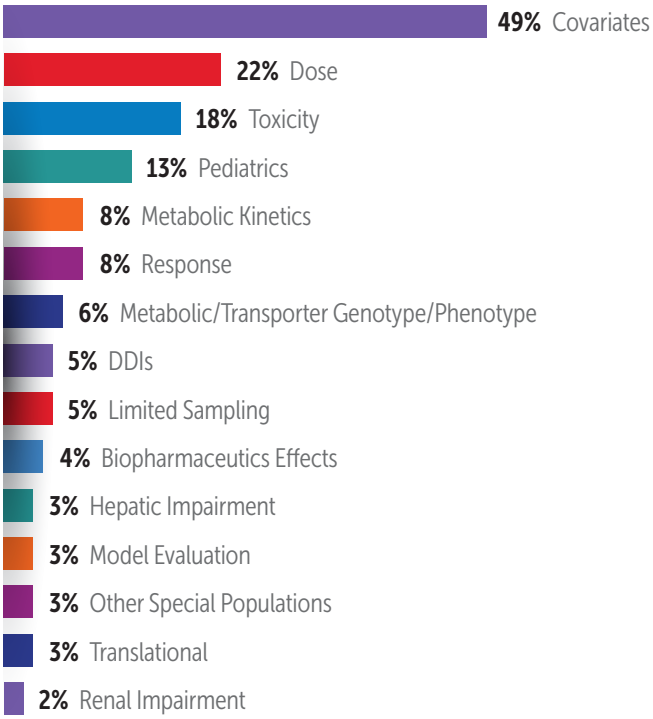


Figure 4: Applications of PK Modeling in Oncology



Closing thoughts

The value in today's rapidly advancing MIDD capabilities comes from their ability to integrate complex, detailed information about the drug's MOA with growing understanding about the underlying biology that drives both cancer proliferation and the patient's response to various oncolytic therapies. Today's advanced understanding of human physiology and pharmacology have helped to make these models very robust and trustworthy, able to make useful, hypothesis-generating predictions that can then be experimentally verified. Increasingly, global regulatory agencies have been receptive to the findings and willing to consider modeled results and clinical insights during the regulatory-approval process and to incorporate modeled clinical findings into the approved product labeling.

A growing body of evidence shows that the use of MIDD to support drug-discovery and drug-development efforts—particularly in oncology—can save time and money, help investigators to make better decisions, and focus their efforts on those investigational therapies that will yield the greatest clinical and marketing advantage while minimizing risk to patients.

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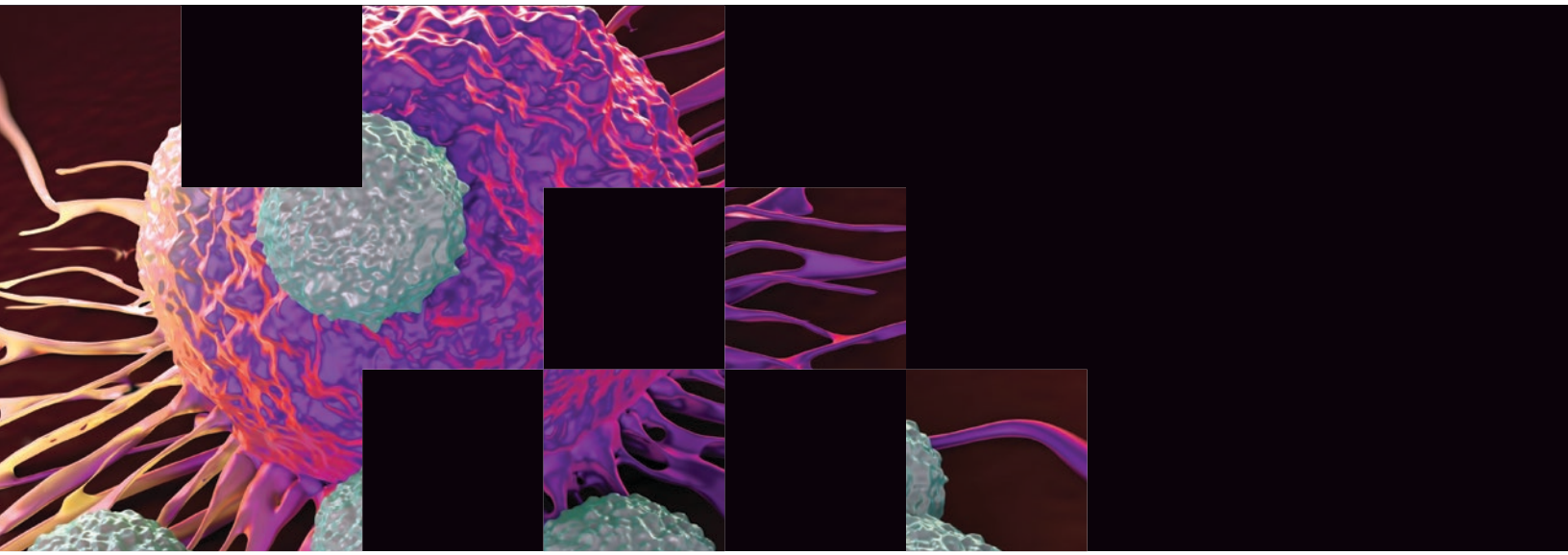

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