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WHITE PAPER

Finding the optimal dose in Project Optimus: Understanding your oncology asset and defining your possibilities

Project Optimus was first announced by the U.S. Food and Drug Administration's (FDA) Oncology Center of Excellence in 2021. Underpinning Project Optimus, the FDA describes its initiative to promote the adoption of "a dose-finding and dose optimization paradigm across oncology that emphasizes selection of a dose or doses that maximizes not only the efficacy of a drug but the safety and tolerability as well."[1] The initiative gained momentum as the FDA provided further clarifications around the guidance and began working closely with biotech and pharmaceutical companies through scientific engagement meetings to partner with industry in both the interpretation and implementation of optimal biological dose (OBD)-finding strategies.

While Project Optimus has now become more widely established in oncology trials, implementing this initiative still requires overcoming several operational obstacles. To support oncology drug developers, this white paper will discuss the challenges of implementing Project Optimus, the role of dose modeling and simulation, strategies for studying advanced and combination oncology therapies and how Fortrea can provide expertise to navigate complex designs.

Recognizing inherent operational challenges

Several significant operational challenges are associated with Project Optimus. These include:

- **Evolving clinical trial designs:** Historically, dose-finding studies with assets altering a biological pathway in oncology focused on determining the maximum tolerated dose (MTD) in Phase I trials before advancing to later phases. Under Project Optimus, sponsors assess the pharmacokinetic and pharmacodynamic profiles of the asset to determine the optimal biological dose (OBD). This requires close monitoring of blood samples and, in many cases, tumor tissue samples with real-time analysis and interpretation

- **Increasing the number of study arms:** While adaptive multi-arm trials can enable flexible dose adjustments based on real-time patient data, these require additional cancer patient cohorts based on type and/or biological profile of the cancer, drug supply logistics, clinical monitoring and data management as well as analysis. For emerging biotechs, this process can present challenges in prioritizing cohorts based on available finances. Securing investments may also be difficult, given that investors typically prioritize opportunities for accelerated regulatory approval to maximize market exclusivity and return on investment
- **Extending Phase I timelines:** A more thorough dose exploration potentially lengthens the early phase study duration, delaying early approval opportunities and confirmatory trials. This can increase trial duration and costs, delaying the path to approval and potentially leading to a competitive disadvantage. Leveraging preclinical data, where possible, to justify the starting dose and using starting dose data from similar assets can save months in clinical development
- **Introducing further regulatory complexity:** Sponsors must design trials aligning with evolving FDA expectations. However, given that FDA guidelines are not yet fully standardized, there can be uncertainty in how much dose-finding data is needed. Therefore, early and ongoing dialog with the regulatory agency is essential. New dose selection approaches require enhanced dossier submission complexity, with increased data volume and justification for dose choices. Finally, sponsors face challenges aligning with FDA expectations and regulatory expectations from European Medicines Agency (EMA), Pharmaceuticals and Medical Devices Agency (PMDA), National Medical Products Administration (NMPA) and other regulatory bodies

A Project Optimus primer

Project Optimus aims to reform dose optimization and selection strategies in oncology drug development. Traditionally, oncology drug trials have favored maximum tolerated dose (MTD) strategies, which often result in significant toxicity without necessarily improving efficacy.

Project Optimus encourages early dose exploration and optimization, ensuring that the selected dose maximizes therapeutic benefit while minimizing adverse effects.

Understanding the importance of preclinical data

The successful implementation of Project Optimus begins in the preclinical phase, where rigorous evaluation of dose-response relationships is essential to inform clinical trial design. Unlike traditional studies focused on identifying the MTD, preclinical toxicology studies under Project Optimus will evaluate lower doses that may still achieve pharmacodynamic efficacy with reduced toxicity.

These studies must integrate pharmacokinetic/pharmacodynamic (PK/PD) modeling to predict optimal dose ranges. In this stage, *in vivo* and *in vitro* models can bridge preclinical findings with human outcomes, ensuring that dose selection strategies predict clinical success.

Additionally, integrating preclinical data can help address formulation considerations for chemistry, manufacturing and controls (CMC), such as oral or IV administration and dose scheduling, while deepening understanding of the drug and its mechanism.

Focusing on modeling and simulation in FDA's Project Optimus

Modeling and simulation (M&S) is considered the natural framework for incorporating and contextualizing information derived from many informational sources. It plays a crucial role in facilitating drug development under the Project Optimus paradigm. M&S has many potential benefits; top among these are integrating information across multiple data sources, optimizing clinical dose-ranging trial designs and facilitating the dose selection and optimization process.

Weighing the totality of evidence through modeling and simulations

In its guidance document "Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases," the FDA states: "Relevant nonclinical and clinical data (such as PK, PD, safety, tolerability, dosage convenience and activity), as well as the dose- and exposure-response relationships should be evaluated to select a dosage(s) for clinical trial(s)."[2]

For example, physiologically based PK (PBPK) models routinely integrate data from *in vitro* and animal experiments to predict *in vivo* human drug exposures in both the blood pool and tissues or organs associated with a drug's effects, both intended and unintended. Similarly, in 2009, Claret et al. reported an integrated PK/PD approach that quantified the relationships between the dose of a drug, its systemic exposure and its impact on both tumor growth and patient outcome (overall survival) in colorectal cancer.[3] The methodology pioneered by these authors has since become a standard component of the dose justification for any oncology compound.

Modeling and simulation offer a powerful toolset for addressing the challenges posed by FDA's Project Optimus. By empowering decisions based on the totality of evidence, improving the efficiency of clinical trials, and facilitating dose selection and optimization, M&S can significantly contribute to the development of safer and more effective oncology drugs. As Project Optimus continues to evolve, the ongoing integration of M&S will be essential in advancing the field of oncology drug development.

Study design in Project Optimus

Several statistical and design considerations can help support Project Optimus studies, such as accelerated titration or other study designs using escalation rules, like Bayesian optimal interval (BOIN) design or modified toxicity probability interval (MTPI-2). Sponsors must consider when to start their randomized dose optimization, when to switch from all solid tumors to targeted populations and when to stop randomizing.

Several approaches can be incorporated, such as estimating the starting dose or applying step-up dosing for an immuno-oncology study. Due to the requirement for significant PD and PK data, incorporation of additional patients at or around the optimal dose is essential through a process of "backfilling," which includes additional patients at the specified dose while simultaneously progressing as appropriate with the next dose.

Another consideration is moving from monotherapy—which is the starting point in multiple ascending (MAD) dose studies leading to OBD with the asset—to combination therapy. This is becoming more frequent with the speed of innovations in cancer clinical trials. Working with a combination therapy requires dose re-titration with the combination and the starting dose again being informed by monotherapy dosing, as well as preclinical data evaluation and modeling simulations.

At the European Society for Medical Oncology (ESMO) Targeted Anticancer Therapies Congress 2025, Timothy A. Yap, MBBS, PhD, FRCP, of MD Anderson Cancer Center presented considerations for developing novel-novel drug combinations. He shared that study design should be based on robust preclinical data, which involves conducting detailed PK/PD/efficacy modeling to determine the potential activity of each component as monotherapy and in combination with the potential simultaneous dose escalation of both drugs. However, he noted that questions from the regulators will be expected, such as: "Will the FDA expect monotherapy optimization for each compound and, if so, to what extent? Does it matter if both investigational drugs are expected to contribute equally, or if one is contributing significantly less?" These questions re-emphasize the need for close discussions with the authorities at every step of the process.

Supporting patient retention and recruitment

The increasing focus on precision oncology emphasizes the need for patient selection as early as possible in multiple dose-finding cohorts and dose expansion-designed trials driven by Project Optimus. Sponsors face additional pressure to identify the profile of high-responders as early as possible. They can then enroll sufficient numbers to establish OBD and expand as early as possible, which can be challenging in rare cancer or biomarker-driven studies. This approach requires a site-centric strategy around patient identification and recruitment.

Sponsors should consider solutions that support patient identification and referrals such as data-enabled patient recruitment, the use of genomic and/or electronic medical records to identify potential patients in real-time, and engagement with their treating physician to refer or directly recruit them into a relevant study. Building these types of solutions globally will become increasingly important for feasibility evaluations and direct patient engagement and recruitment.

From the patient perspective, patients may be less willing to participate in prolonged dose exploration studies compared to traditional Phase I dose-escalation trials. A lower-dose cohort may be perceived as resulting in suboptimal efficacy as compared to higher dose levels in systemic chemotherapies. However, with new molecular targeted agents (MTAs) and immunotherapies, a lower dose may have similar efficacy and potentially fewer side effects and it is essential that this is communicated thoughtfully to patients.[4]

With extensive site engagement and patient inclusion strategies, sponsors and CROs can provide valuable education about the dosing levels. By highlighting the benefit of study participation, they can address recruitment and retention challenges.

Addressing more precise patient selection with biomarkers

Given the evolution of the understanding of the functional mutational drivers for many cancers, Project Optimus requires a more precise focus on patient selection in an effort to ensure that the most appropriately defined patient group is incorporated as early as possible to determine the OBD. Biomarkers (genetic mutations and expressed proteins detected in cancer or blood) support this patient stratification process based on response potential or baseline disease burden rather than a "one-size-fits-all" approach. Regulators have drafted guidance in an effort to provide industry with more information.[5]

Patients can also be stratified by their baseline disease burden to avoid overdosing in low-risk patients. In contrast, high-risk patients may be excluded if they are more likely to experience severe toxicity if using immune-stimulating combinations. For example, a trial using a chimeric antigen receptor (CAR T) and interleukin-2 (IL-2) may need to exclude patients with high baseline inflammation, as they could face excessive immune activation.

It's important to note that using exploratory biomarkers to inform dose selection may require additional validation and regulatory negotiation. Further, not all oncology drugs have well-defined biomarkers, complicating dose selection.

Phase II: Optimizing the dose-ranging trial designs

In Phase II, the dose-ranging phase of drug development represents a critical juncture in the process. Here, the optimal biological dose(s) are identified and will be carried forward into the pivotal confirmatory trials. Approximately 30% of drugs fail during Phase II, and of those that progress to Phase III, 58% will fail.[6] Ill-posed dose-ranging strategies contribute to these failures, as they may fail to identify the dosage and/or scheduling that achieves the desired level of efficacy without unacceptable safety risk.

Clinical trial simulation (CTS) can help de-risk the dose-ranging process. In CTS, researchers can conduct *in silico* trials that mimic the conditions of actual clinical trials. In doing so, a variety of clinical trial designs may be considered. Generally, each design is simulated many times over. By summarizing these trial replications, an estimate of the success probability for each design is provided, and the best-performing design may be selected.[7]

Facilitating dose selection and optimization

One of the key goals of Project Optimus is to minimize the toxicity associated with oncology drugs while maintaining their efficacy. Ideally, the results of dose-ranging clinical trials clearly indicate which dose(s) satisfy the acceptance criteria. Unfortunately, the results of dose-ranging trials do not always prove to be so definitive. Sponsors may find themselves in the unenviable situation in which none of the doses studied in Phase II satisfy both the safety and efficacy criteria.

For example, consider a hypothetical scenario in which only the highest dose studied surpasses the minimal efficacy threshold but with unacceptable toxicity. In such instances, PK/PD models may provide the means to explore *in silico* alternative dosing regimens capable of maintaining exposures in the therapeutic range. M&S also provides the capability to personalize doses based on patient characteristics, an approach that has been shown to improve therapeutic performance in many instances.[8]

Another challenge of dose selection that may be addressed through M&S is that posed by complex exposure-response relationships. For example, the bispecific class of molecules is known to exhibit a "bell-shaped" exposure-response. If the therapy is dosed either too low or too high, sub-optimal efficacy is the result. Hitting the "sweet spot" between these two extremes would be exceedingly difficult without a model-based dosing paradigm.[9]

Advanced therapies and Project Optimus

Advanced therapies and precision medicine influence dynamic biological processes. With Project Optimus, sponsors need to understand how the drug performs in the clinical space—beyond the starting dose—as more data becomes available.

For CAR T therapies, the traditional maximum tolerated dose (MTD) model is ill-suited for several reasons:

- **Nonlinear PK:** Higher initial doses do not always mean higher long-term exposure, given that CAR T-cells expand upon infusion
- **Serious side effects:** Higher doses of a CAR T therapy increase the risk of Cytokine Release Syndrome (CRS) & Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)
- **Inherent variability:** T-cell persistence and response are patient-specific, making it difficult to define an "optimal" dose or employ fixed-dose strategies using traditional paradigms

To enable CAR T dose optimization, an adaptive trial design can refine the initial dose based on real-time functional cell assay data and apply biomarker-driven dose selection (e.g., baseline cytokine levels, tumor burden or immune status). Finally, lower starting doses with a step-up dosing strategy can help manage the risk of CRS.

Bispecific Antibodies (BsAbs)

Bispecific antibodies, for example, CD3/CD20 or CD3/BCMA, redirect T-cells to tumors, leading to potent cytotoxic activity. Similar to CAR T, BsAbs present unique PK/PD and safety challenges with CRS. Other concerns include:

- **Short half-life:** Many bispecifics have shorter half-lives, requiring chronic dosing optimization
- **Tailored dosing regimens:** Clearance mechanisms vary between bispecific platforms, such as IgG-like vs. fragment-based designs

Here, step-up dosing regimens can mitigate the risk of CRS, model-informed drug development (MIDD) can balance efficacy/toxicity and exposure-response modeling can determine the minimum effective dose (MED) rather than just the MTD.

Reflecting on lessons learned in oncology studies

As our teams at Fortrea have supported sponsors in their Project Optimus-driven studies, we have gathered several lessons learned, which include:

- **Delivering thorough site and investigator training:** Research sites and investigators must adapt to new trial methodologies, stressing the importance of extensive training and engagement
- **Addressing the need for early regulatory consultation and engagement while recognizing global regulatory variability:** Sponsors running international trials must balance FDA expectations with differing guidelines from other regulatory agencies, such as the EMA, and embrace early and ongoing dialog with multiple agencies to ensure a consensus on requirements are met. Working with regulators early in development can help align expectations and inform dose-optimization strategies
- **Navigating longer dose-finding phases:** A seamless Phase I/II (evaluation phase) design can accelerate dose selection, for implementation in the registrational intent studies (confirmation phase). For studies with high toxicity risks where overlapping adverse effects could limit dose flexibility including scheduling, step-up dosing and intra-patient dose adjustments may be necessary
- **Employing model-informed drug development (MIDD):** To reduce patient burden, modeling and simulation (M&S) technology can help inform decision-making and reduce unnecessary patient exposure by integrating data from *in vivo/in vitro* studies to predict drug effects[10]

Evolving oncology drug development requires a collaborative effort among industry sponsors, investigators and site staff, regulators and patients. This level of coordination is especially important when studying acquired resistance, tumor-agnostic treatments and combination therapies, which require more complex early phase studies and careful patient selection.

Fortrea is committed to helping sponsors pursue Project Optimus implementation. Our dedicated team of preclinical and modeling experts applies specialized knowledge to design and refine pharmacokinetic and pharmacodynamic models based on initial data, providing the most informative insights for protocol development. Additionally, our regulatory strategy and consultancy team offers expert guidance in compiling comprehensive dossiers and preparing for meetings with agencies in collaboration with your teams.

From integrating preclinical data and modeling to providing regulatory strategy, protocol design and statistical expertise, sponsors need comprehensive support to advance Project Optimus studies. By optimizing trial designs, prioritizing patient-centric approaches and leveraging innovative data analysis techniques, we help the oncology community navigate evolving challenges. Together, we can successfully adapt to this new regulatory landscape and enhance therapeutic outcomes for individuals living with cancer.

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