Five strategies for meeting the requirements of Project Optimus and improving the chances of approval

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The study designs and dose-finding strategies that have dominated decades of oncology drug development are becoming obsolete as the FDA's Project Optimus takes full effect. The agency is now heavily scrutinizing Phase 1 and 2 studies to see whether they identify the safest and most effective dose—while this change seems abrupt, it's loomed over the field for a long time.

Developers in other therapeutic areas have always had to conduct extensive dose-finding programs. After an era of extraordinary flexibility in evidentiary standards for cancer drugs, the FDA is returning to a more rigid interpretation of requirements (Table 1). The result is that early-stage cancer trials will likely take longer and cost more.

Companies that don't collect enough data to justify their dosing strategy could face significant regulatory delays. The FDA may issue clinical holds, refuse to file (RTF) decisions, and complete response (CR) letters requesting additional studies to explore alternative doses or regimens.

Table 1. How Project Optimus reprioritizes early-stage cancer trials

Old Framework	Project Optimus
Safety is the primary objective. Test the highest tolerable dose for maximal tumor suppression.	**Safety and efficacy are interconnected.** Find a well-tolerated dose that still achieves adequate efficacy. Look beyond DLTs.
Find the maximum tolerated dose (MTD). Once you determine the MTD, proceed directly to Phase 1b/2 or possibly a pivotal trial with a single dose.	**Identify a range of active doses.** Test them in subsequent dose expansion cohorts or, preferably, randomized dose optimization studies before proceeding to the pivotal trial.
Characterize short-term (28-day) toxicities.	**Characterize long-term toxicities.** Look for side effects associated with chronic administration of the drug.
Utilize a static, rules-based 3+3 dose escalation design. Enroll as few patients as possible in 3-person increments to reach the recommended Phase 2 dose (RP2D).	**Use flexible and efficient trial designs.** Capture efficacy and safety across a range of doses, enrolling patients as needed and expanding cohorts to find the optimal dose.
Analyze results at the end of the study. Trial data is available only after the database lock.	**Plan for prespecified interim analyses.** An independent DMC can analyze data from an ongoing trial based on a prospective statistical plan. These analyses can enhance the "learning" phase of development.
Advance swiftly. Proceed from dose escalation to a single expansion cohort as soon as possible.	**Explore dose- and exposure-response relationships deliberately.** In multiple cohorts, examine safety (including conventional safety endpoints and clinical events), pharmacodynamics (PD) (including target-engagement and pathway-related biomarkers), and efficacy (including radiographic and blood-based tumor-related biomarkers).
Focus on severe and life-threatening toxicities. Dose-limiting toxicities (Grade 3 AEs or higher) are the most important. Collect patient-reported outcome (PRO) data later in development, if at all.	**Focus on overall toxicities.** Collect patient experience data early in development with tools such as CTCAE-PRO. Consider all AEs, including low-grade events such as mild diarrhea or pain. Assess general safety and tolerability using objective and subjective tools at each dose level. Consider the totality of the data in the context of PD and efficacy to refine the dose.
Advance all cancer drugs as quickly as possible. Late-stage trial failures are the "cost of doing business."	**Advance only the most promising molecules.** Invest in a sophisticated Phase 1b/2a study and "fail fast" rather than rush into a Phase 2b/3 trial with incomplete evidence.
Expedited regulatory mechanisms have lower evidence requirements. For example, Breakthrough Therapy and Accelerated Approval drugs require fewer trials.	**Evidence-based dose selection is essential for all drugs.** Sponsors must conduct adequate dose-finding studies regardless of a drug's regulatory designations.
Post-marketing requirements and commitments are commonplace. Let physicians sort out the dosing details once a drug is approved.	**Pre-market evaluation should characterize the relationship between exposure, safety, and response.** Sorting out dosing details is a pre-market activity.
The pre-IND meeting is a perfunctory milestone. Initiate a Phase 1 trial as quickly as possible.	**The pre-IND meeting is a valuable one-time opportunity.** Use it to pressure test your dose-finding plan.

SOURCES: Parexel expert analysis and Friends of Cancer Research Q&A [April 7, 2022] Optimizing Dosing in Oncology Drug Development. Key to acronyms: AE=Adverse Event; CTCAE=Common Terminology Criteria for Adverse Events; DMC=Data Monitoring Committee.

We've helped our clients adapt to the new standards with five best practices.

1. Conduct an in-depth preclinical evaluation

An extensive preclinical data package can help companies identify the most promising doses to test clinically. Companies developing cancer therapies have traditionally studied a narrower range of doses preclinically for translation into human trials.

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Preclinical data should be robust enough to help establish the maximum recommended starting dose (MSRD) and predict the efficacious dose range. Choose an animal model that predicts the human response and set aggressive goals to weed out product candidates that may not induce an adequate response. This can be complicated because preclinical models do not reliably predict activity in the clinic. If preclinical results don't indicate significant activity, companies can consider terminating an asset early and investing in a better one.

2. Run data-rich early dosing studies

Traditional first-in-human (FIH) trials have utilized the inflexible 3+3 rules-based design, wherein three or six patients are enrolled at each dose level until the maximum tolerated dose (MTD) is reached. Although alternative designs, such as adaptive trials, have existed for many years, companies have been reluctant to adopt them because these model-based designs can be more complex operationally and statistically, often requiring a multidisciplinary team of experts.

But there are significant advantages to flexible designs. They can allow for additional cohorts and multiple dosages in the expansion phase of a dose-finding trial. They can incorporate a randomized dose-finding trial based on emerging clinical data over the dose range studied. Data-rich early studies may well need to enroll more patients. FIH studies for targeted cancer therapies should resemble a typical FIH study in healthy volunteers, where the study's primary objective is not MTD, but the evaluation of safety, tolerability, and PK of a new molecular entity (NME).

The FDA is pushing for a more extended period of "learning" in cancer drug development, including Phase 2 studies that randomize patients to two or more different doses. We advise clients to investigate dosing regimens that will result in different exposures with minimal overlap. Moreover, companies must enroll sufficient numbers of patients per regimen to achieve a more realistic signal of the exposure-response relationship. A recent Friends of Cancer Research white paper covers this topic in depth.

The goal should be to select a dosing regimen for pivotal efficacy trials based on multiple data readouts, including safety and tolerability (beyond dose-limiting toxicities and including dose modifications), anti-tumor activity, exposure, and other pharmacodynamic effects.

3. Add dynamic biomarkers to help identify the optimal dose

Project Optimus will likely spur sponsors and regulators to develop and validate endpoints more informative of a drug's activity. For example, overall response rate (ORR) is the most common surrogate endpoint to measure early efficacy. Simply put, ORR indicates whether the drug destroys or shrinks tumors below a pre-defined threshold. However, ORR can be a blunt tool for quantifying dose- and exposure-response relationships to identify the optimal dose.

While ORR may remain the primary surrogate endpoint to measure clinical benefit, more diverse endpoints can broaden the data that companies have to justify the optimal dose.

Dynamic biomarkers, such as tumor growth rate (TGR), tumor growth kinetics (TGK), and circulating tumor DNA (ctDNA), could be used to measure the depth and intensity of response at different doses and exposures. These may yield richer evidence to identify the effective dose and how responses may change as the dose increases. Other clinically relevant, novel biomarkers include minimal residual disease (MRD) in blood cancer, pathologic complete response (pCR) in neoadjuvant breast cancer, and metastasis-free survival (MFS) in prostate cancer.

Because early clinical trials enroll a small number of highly heterogenous patients, sponsors should collect pathway- and disease-related biomarker data starting in Phase 1. Biomarker data is critical to optimal dose-finding strategies and robust PK/PD modeling. Oncology drug development often accelerates due to expedited regulatory mechanisms and trial designs that progress seamlessly from safety to efficacy. Biomarker analyses should thus be prioritized and performed in real-time to have a timely impact on dose selection at subsequent stages.

4. Understand the toxicities that matter to patients

Traditionally, cancer drug developers have focused on escalating the dose until severe toxicities such as Grade 3 vomiting and neutropenia occur. While this approach worked for chemotherapeutic agents—designed to kill as many cancer cells as possible over a limited number of administration cycles—this will no longer be acceptable for immuno-oncology drugs that will be administered continuously for two years or more.

One solution is to gather toxicity data directly from patients using tools such as the National Cancer Institute's Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Combined with conventional clinician-reported CTCAE data, PROs can help developers understand how a drug impacts patients' daily activities.

Often, sponsors are wary of collecting patient-reported data on adverse events because some research suggests that patients report greater severity of symptoms than clinicians. However, not having patient perspectives and preferences could handicap companies as they select tolerable dosing regimens that boost compliance. For example, targeted cancer therapies might produce fewer acute (Grade 3 or higher) toxicities in the first cycle or two. But during medium- and long-term treatment, patients may still experience drug-related "low-grade" toxicities such as mild pain and chronic fatigue. This is essential information for sponsors to have.

Regulators are increasingly interested in cancer PROs, so a globally relevant development program must include longitudinal and cumulative toxicity data. Recent research shows PROs remain relatively rare in early-stage dose-finding cancer trials (about 5.3% of studies), but their use is increasing.

5. Use FDA meetings to de-risk your dose-finding strategy

The FDA has clarified that discussions about dose-finding strategies do not necessarily need to be tied to milestone meetings. That said, the pre-investigational new drug (pre-IND) meeting is a valuable opportunity for companies to vet plans for an innovative trial design or novel efficacy biomarker.

There is no official guidance on how to comply with Project Optimus. While the FDA has launched a webpage, the agency's Oncology Center of Excellence is still working on a document to guide dose optimization. In the meantime, three existing FDA guidance documents outline model-informed drug development. They include:

- Population Pharmacokinetics (February 2022);
- Exposure-Response Relationships—Study Design, Data Analysis, and Regulatory Applications (April 2003); and
- E4 Dose-Response Information to Support Drug Registration (July 1996).

Companies preparing for a meeting with the FDA on dose-finding strategies should be familiar with these documents.

Well-designed dose-finding studies will pay off later

Justifying a dosing strategy chosen years ago—before Project Optimus—is a difficult challenge, but some sponsors with late-stage products may find themselves in this situation. Recently, Parexel helped a client who was in this situation after they filed a new drug application (NDA). Data from their early-stage studies were heavily weighted toward a single dose (the MTD), but this dose was poorly tolerated and required dose modifications in most patients within the first few months of treatment. We used modeling and simulation (M&S) techniques to quantify the exposure-response relationships and explore and consider other possible dosing regimens. In general, M&S techniques can support a dose selected under the MTD paradigm but may not be adequate if the data are lacking. In the past, sponsors often made post-marketing commitments (PMCs) to address data gaps, but the FDA is moving away from that solution. In the current environment, conducting well-designed dose-finding trials from the start is more efficient and compliant.

The added time and cost of collecting comprehensive dose- and exposure-response data at the early stages of development will pay off for developers. Products with a more precise risk-benefit profile, a smoother regulatory path, fewer PMCs, and better patient compliance will achieve faster uptake and sustained market share.

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