# Dose Optimization in Oncology: What is Your Strategy?

Elisabeth Coart, Vaiva Deltuvaite-Thomas, Leandro Garcia-Barrado, Jennifer Menda, Vincent Staggs, Everardo D. Saad, Rudradev Sengupta, Pascal Piedbois, Tomasz Burzykowski, and Marc Buyse

## Introduction

In January 2023, the Food and Drug Administration (FDA) released the draft guidance outlining the key principles of Project Optimus,[1] whose overarching goal is to educate, innovate, and collaborate with all relevant stakeholders to move forward with a dose-finding and dose-optimization paradigm in oncology in a manner that maximizes the relationship between efficacy, safety and tolerability of novel agents.[2] In August 2024, a final guidance was published, taking the comments by various stakeholders into account. In the current article, we summarize key principles and the relevant literature on dose optimization in oncology, also providing our views on the implementation of Project Optimus by biotechnology and pharmaceutical sponsors. Of note, in the FDA document, “dosage” refers to “dose and schedule”,[1] but the term “dose” is frequently used with that same meaning in other places.[2] Moreover, we note that the term "dose-finding" is used with two different meanings in the literature, at times referring to phase 1, dose-escalation trials (often with expansion cohorts),[1,3] and at times to subsequent trials in which at least two doses have already been deemed tolerable and need to be compared before conducting a pivotal trial.[1,4] In this text, we will refer to the former setting as dose finding and to the latter as dose optimization; likewise, we will use “dose” (instead of “dosage”) in the more general sense of the term.

## The emergence of Project Optimus

The story behind Project Optimus can be traced in part to the activity of Friends of Cancer Research, a non-profit organization dedicated to improving cancer research, regulation and policy. They published a white paper on the topic already in 2013. In 2021, Friends of Cancer Research and FDA held a joint meeting that largely crystalized the framework for Project Optimus. But even before 2013, it had been recognized that the maximum tolerated dose (MTD), useful to guide early phases of drug development in the chemotherapy era, may not be as useful for novel anticancer agents, such as targeted therapies and immunotherapies.[5,6] With chemotherapy, there is usually a narrow therapeutic window, a steep dose-response curve, more concern with acute toxicity, and an expectedly short treatment duration. With novel agents, the optimal biological dose depends on the

interplay of aspects such as mechanism of action, target saturation, and chronic administration, typically associated with a wider therapeutic window. The MTD paradigm assumes that "more is better" in terms of efficacy, as long as the higher doses continue to be tolerable. This paradigm tends to disregard the possibility that lower doses may have similar activity with improved tolerability, which may translate into a more favorable relationship between efficacy and safety, as well as more prolonged adherence. Moreover, the MTD paradigm—including the focus on dose-limiting toxicity (DLT)—often does not adequately evaluate low-grade symptomatic toxicity, dose modifications, drug activity, and the relationships between dose/exposure and efficacy/safety.[1] Finally, the DLT/MTD paradigm typically focuses on short-term toxicity, whereas it has been increasingly recognized that long-term toxicity (or late side effects) impairs tolerability and plays a key role with targeted therapies and immunotherapies.[7] For modern oncology drugs, the paradigm "less is more" might be a better fit.[8]

Despite the frequent criticism of the MTD paradigm, there has been relatively little change in trial design for dose finding in oncology over the last two decades. Even in recent trials of novel agents, the MTD (or the maximum administered dose when the MTD was not reached) was often selected for further development.[3] Perhaps as a consequence, there have been many examples of drugs whose doses had to be modified for safety or tolerability concerns after FDA approval.[8,9] Likewise, there have been cases in which post-approval dose modifications were motivated by the opportunity to increase efficacy in particular populations.[9] In these cases, large numbers of patients may have been exposed to a poorly tolerated dose or one without optimal clinical benefit.[1] This is the background against which Project Optimus has emerged, in the attempt to optimize doses before approval, thus bridging a long-standing gap in drug development in oncology. It should be noted that Project Optimus aligns with another recent FDA initiative that has long been in the making, namely the Patient-Focused Drug Development Program, which aims at incorporating the patient's voice in drug development and regulatory decision-making.

The draft guidance related to Optimus Project caused much commotion and received many official comments (these can be consulted in the guidance's docket online https://www.regulations.gov/docket/FDA-2022-D-2827/comments). The US National Cancer Institute raised the concern that oncology drug development would take longer and become (even more) costly due to the expectations associated with Project Optimus. In addition, the ethics of exposing more patients to therapies without established positive benefit/risk ratio was questioned. The Friends of Cancer Research, together with patient-organizations, took the opposite view and endorsed studying tolerability prior to approval as they anticipated that this would result in fewer patients changing therapy due to tolerability issues and hence in more patients benefiting from the therapy. Some pharma companies criticized the overly directive approach to dose optimization, a comment that FDA accommodated by adding that dose optimization is 'multifaceted' and there is no one-size-fits-all approach, together with the invitation to talk to the agency early on in clinical development about dose-selection plans. Most other changes in the final guidance document were clarifications.

**Highlights of the FDA guidance**

*Trial design for dose optimization*

FDA advises that the multiple doses to be compared "should be selected based on the relevant nonclinical and clinical data that provide a preliminary understanding of dose- and exposure-response relationships for activity, safety, and tolerability."[1] This may suggest that dose-finding trials should include evaluation of efficacy in addition to the analysis of toxicity. Dose-escalation designs that used joint assessment of toxicity and efficacy were already a focus of research in the late 1990's and early 2000's.[10] In recent years, coinciding with the FDA's advice, the interest in research on such designs has increased. For instance, attempts to extend the established dose-escalation designs, like the Bayesian Optimal Interval (BOIN) design, by using the so-called "backfilling" (in which additional patients are treated at doses lower than the current escalated dose level but where responses have been seen) have been undertaken.[11] This coincides with the FDA's advice that, before initiating a trial directly comparing multiple doses, it may be reasonable to add a sufficient number of patients to dose-level cohorts in an earlier, dose-escalation trial.[1] Novel designs, which try to combine dose finding with dose optimization, are also being developed.[12]

Clinical trials for dose optimization should be ideally designed as randomized, parallel-group trials that compare at least two doses regarding their activity, safety, and tolerability.[1,3,4] Although these trials do not need to be powered to conduct formal statistical comparisons across doses, they should be sufficiently sized to allow meaningful assessments of activity, safety, and tolerability for each dose. In these trials, it is common to base efficacy on the objective response rate, but other endpoints can be considered.[4] Adaptive designs can also be considered, and trials for dose optimization may be conducted separately or, depending on drug specificities and previous data, embedded in pivotal trials. Methodologically, many options already exist to include an optimal arm-selecting analysis into a pivot trial in the seamless phase 2/3 setting, whether based on long-term[13] or early-available endpoints.[14] More flexible methods exist, for example, in the realm of Multi-Arms Multi-Stage (MAMS) designs.[15] In these cases, rigorous control of type-I error follows the usual principles for pivotal trials, and the statistical analysis plan should specify a multiple-testing procedure when multiple comparisons are planned.[1]

Regarding the assessment of safety and tolerability, paramount metrics are the duration of exposure, the proportion of patients who are able to receive all planned doses, the percentage of patients requiring dosage interruptions, dose reductions, and drug discontinuations for adverse events (AEs), and the percentage of patients with serious AEs.[1,3] Moreover, attention should be given to AEs that are of low grade but persistent, such as grade 1-2 diarrhea. Indeed, having the tolerability endpoints rigorously defined as toxicity endpoints will be a prerequisite to formally evaluating tolerability in trials aiming at dose finding and dose optimization. Likely, tolerability information is already available in the medical records of the—often late-line—patients in early-phase trials that could be captured in the clinical trial database without adding much burden for the patients or study staff. For drugs associated with early-onset, serious, or life-threatening toxicity which may improve with subsequent administration, evaluation of an alternative dosing strategy, such as titration, is encouraged.[1] Likewise, intra-patient dose escalation could be foreseen in these trials.[4] Finally, patient-reported outcomes should be considered for the assessment of tolerability, and early engagement with patients and their representatives is desirable.[1]

*Clinical pharmacology for dose optimization*

Historically, the need to move fast when bringing new oncology drugs to the market meant that the "more-is-better" philosophy was applied to the pharmacokinetic (PK) parameters as well, by assuming the same steep dose-response relationship seen in cytotoxic drugs. This has allowed companies to omit the PK/pharmacodynamic (PD) analyses in the early stages of development. Of note, exposure-response analyses for efficacy and safety are often incorporated in pivotal trials; however, these trials frequently assess a single dose of the experimental agent, something that limits the range of exposure and the utility of these analyses toward informing optimal patient benefit as related to dose.[3] Moreover, typically multiple drugs are incorporated into an oncology treatment. The impact of multiple doses, multiple drugs, and effects like food interactions needs to be taken into account. The PK characteristics of the novel oncology drugs are taken rather as an afterthought, an information required to meet regulatory requirements, but not as an essential part of the dose-optimization strategy as is usually the case in multiple other indications.

In the guidance document, FDA recommends that trials designed to optimize the selection of dose(s) to be tested in pivotal trials include PK sampling and a corresponding statistical analysis plan to be submitted to the agency.[1] These trials should enroll an appropriately broad population to allow assessment across relevant subpopulations likely to derive benefit in the future. Sample collection and the analysis plan should also be sufficient to support population PK and the analyses of dose-response and exposure-response relationships both for safety and efficacy, following the FDA guidance on this topic.[16] This requirement of integrating the PK/PD into the dose-finding strategies of oncology drug development has sparked concerns about delayed access to novel treatment options. However, a large number of recent FDA approvals have led to dose modification/withdrawal,[3] as well as delays, holds, or requests for additional post-marketing studies. Implementing appropriate dose-selection early on can and should address these issues. A slight delay in market access might prove beneficial in post-marketing settings which could become, arguably, a worthy compromise.

Importantly, population PK data should be evaluated to identify specific populations with clinically meaningful differences in exposure. For oral drugs, the effect of food on PK and safety should be evaluated early in the development. A practical recommendation, provided elsewhere, is that the doses selected for comparison in these studies should not have predictably overlapping PK exposures, to allow proper distinction between them.[4] For example, if two doses are compared, the lowest could be the minimum dose expected to provide activity based on previous data, with the highest dose selected within safety constraints with the aim of ascertaining whether dose increases result in increased activity with acceptable toxicity; a practical way to implement this idea has recently been proposed.[12] Moreover, in January 2014 the FDA published the first version of the Study Data Technical Conformance Guide, recently updated,[17] which calls sponsors and contract research organizations to standardize and format PK/PD data in Clinical Data Interchange Standards Consortium (CDISC) standards (https://www.cdisc.org/standards/foundational). This standardized, efficient and effective way to format and transfer PK/PD data provides the FDA and sponsors with consistent and reliable data for integrating PK/PD into joint analyses, along with efficacy and toxicity.

In addition to PK and other data, PD biomarkers could be part of the dose selection. PD provides valuable insight of a drug's effect on the body, for example dose-response relationships, which can lead to a superior dose selection rather MTD by default.[8] This is in line with the current development

practice for immuno-oncology agents, with 50% of phase 1 trials including PD markers reporting that these biomarkers influenced clinical development decisions, including dose selection.[18]

*Additional considerations*

The FDA guidance provides considerations on the formulation and on subsequent indications of the drug under development. The agency recommends that various dose strengths be available to allow evaluation of multiple doses in clinical trials, preempting any perceived difficulty in manufacturing multiple dose strengths as a rationale for not entertaining comparisons of multiple doses. Regarding subsequent indications, it is anticipated that different doses may be needed in different settings because of potential differences in tumor biology, patient population, treatment setting, and concurrent treatments, among other factors. Relevant nonclinical and clinical data can support a proposed dose to be evaluated in a registration trial for a subsequent indication, but a strong rationale for choosing that dose should be provided before initiating such a trial, especially for disease settings not adequately represented in earlier trials or for new combination regimens. Conversely, if sufficient rationale for that choice cannot be provided, additional studies should be conducted for dose optimization in the new indication.

**Implementation of these principles**

The FDA guidance on dose optimization in oncology represents an important step forward and a plea for innovative methods in drug development. Interestingly, the recommendations provided are relatively broad and not particularly prescriptive, leaving considerable room for interpretation and flexibility on the part of sponsors. We surmise that this flexibility has advantages but at the same time creates the need for a development strategy that requires additional methodological input not needed a few years ago.

General methodological principles outlined in the FDA guidance include the desirability of randomized trials, the possibility of foregoing formal comparisons when the intent is only dose optimization, the need to control type-I error only in the setting of definitive efficacy assessments, and the acceptability of adaptive designs. Randomization is a desirable feature of early drug development, as we have argued elsewhere,[19,20] and the FDA has recently emphasized it both in the setting of dose optimization[1] and of accelerated approval (AA).[21] Randomization in early drug development, including for dose optimization, does not entail sample-size calculation in a manner that ensures sufficient statistical power for formal comparisons. Rather, the goal is to minimize selection bias and produce relatively similar groups of patients with regard to prognostic features, which in turn allows for an increased reliance on the interpretation of dose-response and exposure-response relationships.[1] Nevertheless, careful consideration of outcome variables of interest, including those related to PK, activity, and toxicity, may disclose opportunities for formal comparisons using conventional or novel statistical methods that allow the joint analysis of multiple endpoints, particularly the method of Generalized Pairwise Comparisons.[22] Whether such considerations are worthwhile will depend on individual characteristics of the development program, including the availability of previous data, pharmacological issues specific to the drug and disease, and the purpose of the trial beyond dose optimization. For example, in some cases

sponsors have powered specific components of a dose-optimization trial with the aim of increasing the chance of moving an active dose of the agent to its pivotal phase of development.[23]

Beyond these general principles, the FDA document is silent about specific statistical methods, notwithstanding the recognition by the agency of some of these methods as "fit-for-purpose" in the setting of dose optimization.[24] This may be seen as an opportunity to propose trial designs that are in line with sponsors' expectations and capabilities regarding the statistical support needed for dose optimization. In this setting, there is ample opportunity for using Bayesian methods, particularly the BOIN design and its variations.[24,25] Another area not covered by the guidance and offering opportunities for creativity alongside the need for expertise is the integration of dose optimization in the framework of AA. In this case, sponsors must consider the tradeoff between the need to demonstrate activity at an optimal dose (with such activity required for AA) and the need to have this dose determined reliably; in other words, the difficulty in accomplishing these two goals in a single trial aiming at AA needs to be carefully factored into its design. Finally, dose optimization may be challenging in the setting of rare diseases, which will engender the need for additional considerations regarding trial design and objectives.[26] In all these cases, sponsors must carefully weigh the pros and cons of various methods, as well as the perennial tradeoff between moving fast and learning reliably.

## Conclusion

Project Optimus aims at emphasizing the importance of dose optimization as an early and pre-market component of drug development. Sponsors must recognize the importance of dose optimization and consider initiating the relevant discussions with FDA, which is open to providing feedback at various points in the development program. These discussions do not need to be tied to milestone meetings with the agency. Trials for dose optimization do not need to be powered to determine statistical superiority of one dose but should contribute to understanding of the shape of the dose-response curve. The ultimate goal of this exercise is to ascertain whether higher doses, usually associated with greater toxicity, are likely to provide more benefit to patients than lower doses. When the assessment of two or more doses leads to comparable efficacy, the lowest effective dose should be used in the registration trial. Further dose optimization may be required for drugs used in combination and for new indications. In contemporary oncology, dose optimization is essential to ensure that approved agents allow patients to receive treatments that maximize efficacy while minimizing toxicity.

## References

1. U.S. Department of Health and Human Services. Food and Drug Administration. Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases. Guidance for Industry, January 2023. Available at https://www.fda.gov/media/164555/download (Accessed 19 July 2024).

2. U.S. Department of Health and Human Services. Food and Drug Administration. Project Optimus. Available at https://www.fda.gov/about-fda/oncology-center-excellence/project-optimus (Accessed 17 July 2024).

3. Zirkelbach JF, et al. Improving Dose-Optimization Processes Used in Oncology Drug Development to Minimize Toxicity and Maximize Benefit to Patients. J Clin Oncol 2022;40:3489-3500.

4. Friends of Cancer Research White Paper. Optimizing Dosing in Oncology Drug Development. Friends of Cancer Research Annual Meeting 2021. Available at https://friendsofcancerresearch.org/wp-content/uploads/Optimizing_Dosing_in_Oncology_Drug_Development.pdf (Accessed 17 July 2024).

5. Parulekar WR, Eisenhauer E. Phase I trial design for solid tumor studies of targeted, non-cytotoxic agents: theory and practice. J Natl Cancer Inst 2004;96:990-997.

6. Postel-Vinay S, et al. Challenges of phase 1 clinical trials evaluating immune checkpoint-targeted antibodies. Ann Oncol 2016;27:214-224.

7. Biard L. Dose optimization for cancer treatments with considerations for late-onset toxicities. Clin Trials 2024;21:322-330.

8. Shah M, et al. The drug-dosing conundrum in oncology—when less is more. N Engl J Med 2021; 385:1445–1447.

9. Soltantabar P, et al. Optimizing benefit/risk in oncology: Review of post-marketing dose optimization and reflections on the road ahead. Crit Rev Oncol Hematol 2023:182:103913.

10. Sverdlov O, Gao L. Phase I/II dose-finding designs with efficacy and safety endpoints. In: Handbook of Methods for Designing, Monitoring, and Analyzing Dose-Finding Trials. O'Quigley J, Iasonos A, Bornkamp B (eds). Boca Raton: CRC Press, 2017.

11. Zhao, et al. Backfilling Patients in Phase I Dose-Escalation Trials Using Bayesian Optimal Interval Design (BOIN) Clin Cancer Res 2024;30:673–679.

12. Guo B, Yuan Y. DROID: dose-ranging approach to optimizing dose in oncology drug-development. Biometrics 2023;79:2907–2919.

13. Stallard N, Todd S. Sequential designs for phase III clinical trials incorporating treatment selection. Stat Med 2003;22:689-703.

14. Kelly PJ, et al. An adaptive group sequential design for phase II/III clinical trials that select a single treatment from several. J Biopharm Stat 2005;15:641-58.

15. Royston P, et al. Designs for clinical trials with time-to-event outcomes based on stopping guidelines for lack of benefit. Trials 2011;12:81.

16. U.S. Department of Health and Human Services. Food and Drug Administration. Population Pharmacokinetics. Guidance for Industry, February 2022. Available at https://www.fda.gov/media/128793/download (Accessed 19 July 2024).

17. U.S. Department of Health and Human Services. Food and Drug Administration. Technical Specifications Document. Study Data Technical Conformance Guide. Available at https://www.fda.gov/media/153632/download (Accessed 5 November 2024).

18. Salawu Al et al. Impact of pharmacodynamic biomarkers in immunooncology phase 1 clinical trials. Eur J Cancer 2022;173:167-177.

19. Saad ED, et al. Precision medicine needs randomized clinical trials. Nat Rev Clin Oncol 2017;14:317-323.

20. Coart E, Saad ED. Considerations on the mechanics and sample sizes for early trials of targeted agents and immunotherapy in oncology. Exp Rev Precision Med Drug Dev 2021;6:271-280.

21. U.S. Department of Health and Human Services. Food and Drug Administration. Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics. Draft Guidance for Industry, March 2023. Available at https://www.fda.gov/media/166431/download (Accessed 20 July 2024).

22. Buyse M, et al. The Net Benefit of a treatment should take the correlation between benefits and harms into account. J Clin Epidemiol 2021;137:148-158.

23. Ahn MJ, et al. Tarlatamab for Patients with Previously Treated Small-Cell Lung Cancer. N Engl J Med 2023;389:2063-2075.

24. U.S. Department of Health and Human Services. Food and Drug Administration. Drug Development Tools: Fit-for-Purpose Initiative. Available at https://www.fda.gov/drugs/development-approval-process-drugs/drug-development-tools-fit-purpose-initiative (Accessed 19 July 2024).

25. Yuan Y, et al. Model-Assisted Designs for Early-Phase Clinical Trials: Simplicity Meets Superiority. JCO Precis Oncol 2019;3:PO.19.00032.

26. Wesevich A, Ratain MJ. Project Optimus: Is the US Food and Drug Administration Waiving Dose Optimization for Orphan Drugs? JAMA Oncol 2023;9:1489-1490.