PRECISION for medicine®

Dose Optimization

A Strategic Lever in Oncology Drug Development

Table of Contents

Introduction

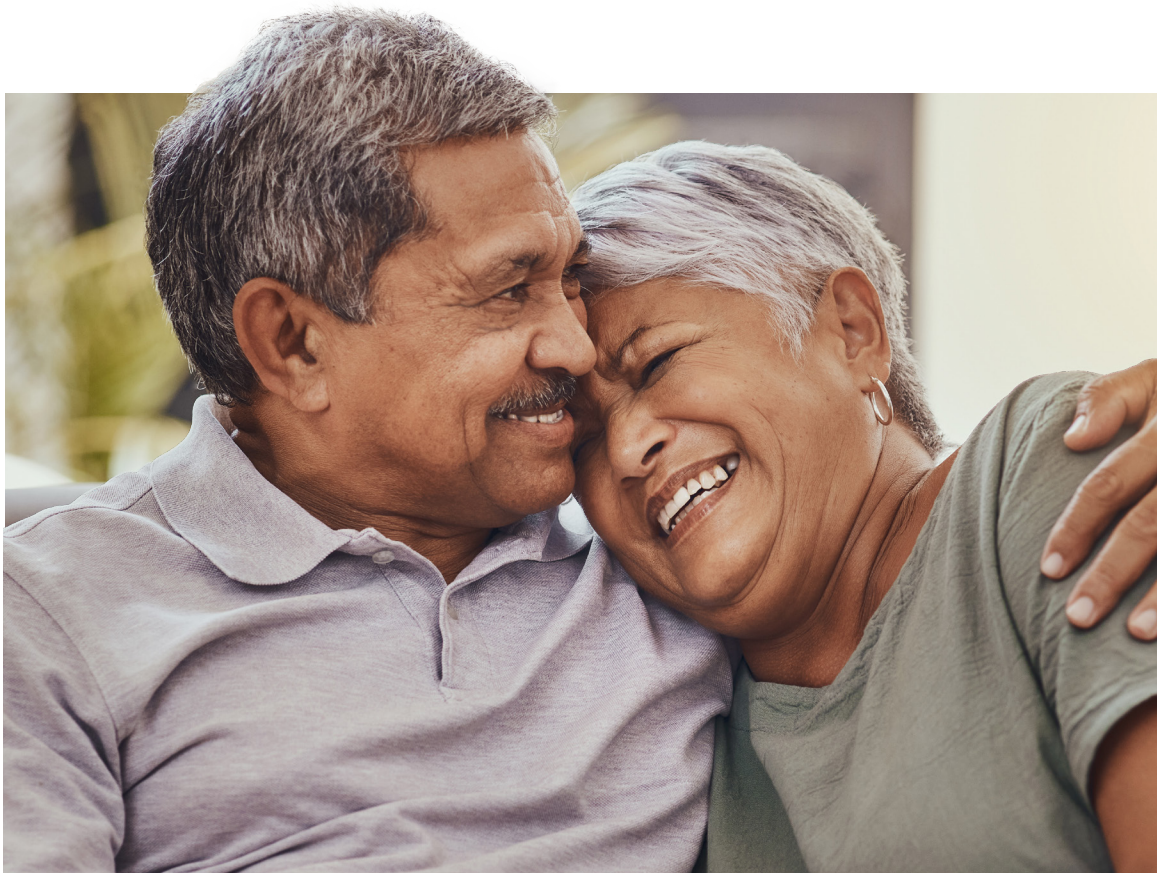
The future of oncology drug development hinges on a critical question: Are we dosing patients efficiently enough to help them thrive?

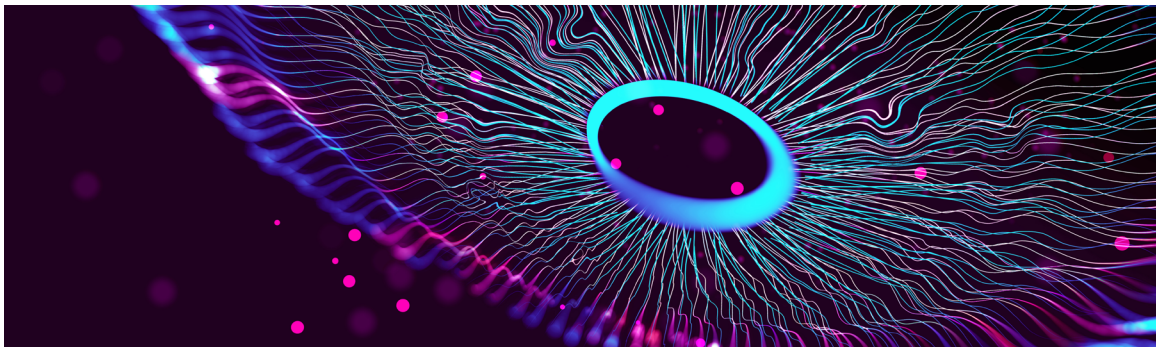
For decades, the oncology field relied on the identification of maximum tolerated dose (MTD) as the dose for further development of new therapies. But today's reality – defined by targeted drugs, immunotherapies, and complex biologics demands a more innovative and patient-centered approach.

Enter Project Optimus, the U.S. Food and Drug Administration's (FDA) initiative that redefines regulatory expectations and elevates the process of identifying the most appropriate dose of an oncology drug that balances efficacy, safety, and tolerability for patients, as a core component of clinical strategy in oncology. This process is known as dose optimization.

The FDA has emphasized that inadequate dose characterization can result in 'more toxicity without additional efficacy,' driving higher rates of dose reductions, treatment discontinuation, and missed opportunities for sustained clinical benefit. This insight underscores why many sponsors are prioritizing dose optimization early in development.

Under Project Optimus, oncology sponsors must justify dose selection with scientific rigor, using pharmacokinetics, pharmacodynamics, and patient outcomes to identify the Optimal Biological Dose (OBD), meaning the dose that delivers maximum therapeutic benefit with acceptable safety.





Sponsors who commit to identifying the OBD in alignment with FDA expectations under Project Optimus are often rewarded with:

- Smarter trial design
- Improved safety/efficacy profiles
- Stronger regulatory positioning
- Long-term cost savings and competitive differentiation

In addition, exposure–response modeling, Bayesian trial designs, and real-time analytics are accelerating a new era of dose finding defined by greater agility, precision, and the ability to deliver more robust, patient-centric, and cost-effective outcomes, all of which are desirable. One study found that integrating dose refinement into trial design increased the probability of success by up to 73 percent, while seamless Phase II/III dose-optimization strategies reduced sample sizes by ~22 percent compared to traditional models.

This e-book offers oncology sponsors and clinical development professionals a strategic view of the changing development landscape, with a focus on the key factors shaping dose optimization, including regulatory trends, emerging methodologies, and operational drivers.

Specifically, it highlights:

- FDA's Project Optimus and global alignment
- Strategic and economic ROI
- Modern trial designs and tools
- Modality-informed strategies
- Patient experience and real-world data

The goal is clear. Integrate dose optimization early in clinical development to minimize regulatory friction and enhance the likelihood of developing safer, more effective therapies rather than risking delays and reactive adjustments later in the process.

At the center of this transformation is Precision for Medicine, a true end-to-end clinical development partner equipped to help sponsors manage the complexity of modern dose strategies. As part of its broader, integrated offering, Precision combines translational insight, adaptive trial execution, and data-driven modeling to help oncology teams make smarter dose decisions earlier, faster, and with greater confidence.

Inside FDA's Push for Smarter Oncology Dosing

Launched by the FDA in 2021, Project Optimus represents a fundamental shift in how early phase oncology dose evaluation is approached, moving away from MTD toward evidence-based, patient-centered dosing.[4,5,6] The goal is to identify the OBD, defined as the dose that achieves a clinically meaningful therapeutic effect with acceptable safety and tolerability.

Key regulatory elements under Project Optimus include:

- Randomized dose-ranging cohorts in early-phase trials to compare efficacy and safety across doses.
- Pharmacokinetic/Pharmacodynamic (PK/PD) modeling to clarify exposure–response relationships.
- Use of validated biomarkers to guide dose selection and improve outcomes for patients.
- Proactive FDA engagement via formal meetings such as EOP1/II and Type D meetings to align dose strategy and trial design.
- Extended safety monitoring, including follow-up beyond the traditional dose-limiting toxicity period (i.e., 1 cycle), to detect cumulative or delayed adverse events in immunotherapy and biologics.[10]

These elements are codified in the FDA's August 2024 draft guidance on dose optimization in oncology, which calls for comparative dose evaluation and mechanistic justification in combination regimens.[4]

As the guidance notes: *"Dose selection must be supported by evidence that each dose under evaluation is pharmacologically active and falls within a therapeutic window that balances efficacy and safety."* The guidance also emphasizes the inclusion of randomized dose-ranging studies and exposure–response modeling in early-phase development to better define the therapeutic window.

Across key industry events, FDA leaders have reiterated that studies incorporating dose optimization have demonstrated superior outcomes compared to traditional MTD-driven approaches, including reduced adverse events and improved median progression-free survival.[7,8] To appreciate why Project Optimus represents a fundamental shift, it is helpful to revisit the legacy strategies it aims to replace.

Precision for Medicine Insight | Translating Project Optimus Principles into Action

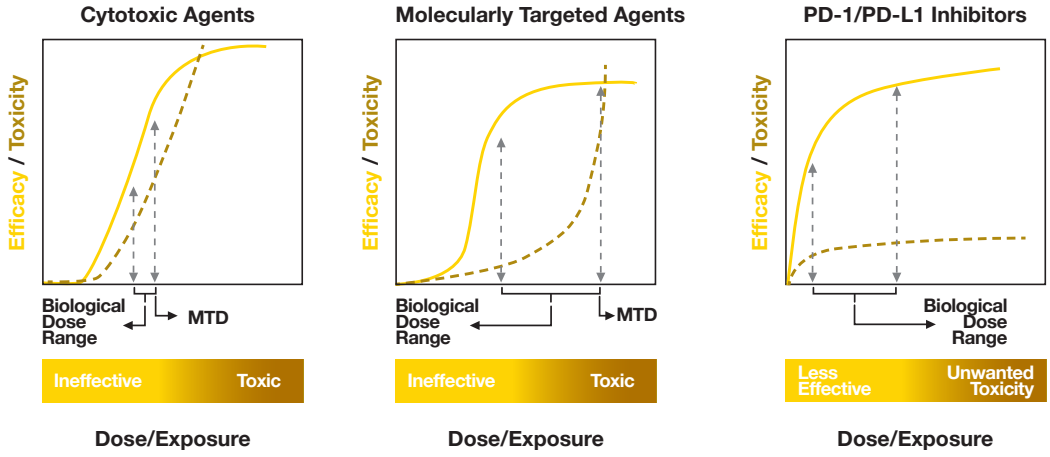
We help sponsors put the principles of Project Optimus into practice by designing trials that prioritize scientific rigor, patient safety, and regulatory alignment. Through integrated biomarker strategies, PK/PD modeling, and adaptive trial design, we enable data-driven dose optimization that meets FDA expectations and supports long-term therapeutic success.

The Shift from Dose Intensity to Dose Intelligence in Modern Oncology

The Maximum Tolerated Dose paradigm emerged during the era of cytotoxic chemotherapy, when higher doses were correlated with greater tumor lethality. Traditional 3+3 dose-escalation designs were used to identify the highest dose patients could tolerate without unacceptable toxicity, regardless of whether that dose offered the most clinical benefit.

However, the therapeutic landscape has shifted. Today's oncology therapeutics, such as molecularly targeted agents, immune checkpoint inhibitors, and antibody–drug conjugates (ADCs), often exhibit non-linear dose–response relationships (See Figure 1). For many of these therapies, efficacy plateaus while toxicity escalates, making the MTD an insufficient benchmark.[9]

Figure 1. **Efficacy and Safety Relationships for CTAs, MTAs, PD/PD-L1 Inhibitors**[10]



That said, MTD remains relevant for specific modalities (e.g., cytotoxic agents and some combination regimens) where therapeutic benefit still correlates with dose intensity. In these cases, MTD serves as a necessary boundary within a broader dose optimization toolkit that also includes OBD and exposure–response modeling. Here, OBD refers to the dose that achieves the intended biological or clinical effect while minimizing toxicity. It prioritizes patient benefit, long-term tolerability, and biological plausibility over sheer dose intensity.

Examples that highlight the rationale for dose optimization include:

- Pembrolizumab (anti–PD-1): Early trials showed comparable efficacy at both 2 mg/kg and 10 mg/kg, with fewer adverse events at the lower dose, illustrating that higher doses did not necessarily confer additional benefit.11
- Sotorasib (KRAS G12C inhibitor): Although initially approved at 960 mg daily, post-marketing studies demonstrated similar efficacy at 240 mg, sparking discussion about the optimal dosing strategy even though the approved dose remains unchanged.[12,13]

Table 1 summarizes key data illustrating the clinical, regulatory, and operational impact of dose selection strategies in oncology drug development.

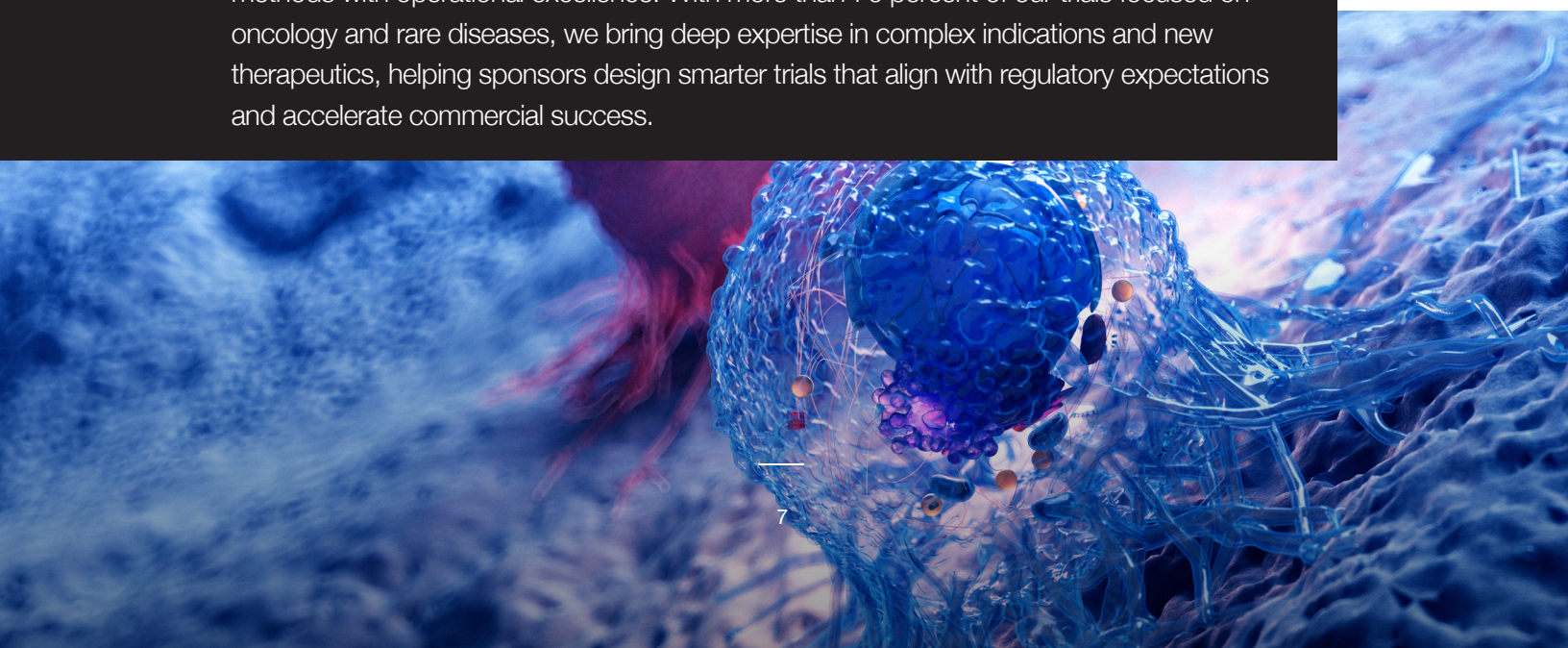
Table 1. **Impact of Dose Selection Strategies in Oncology Drug Development**

Category	Data/Example	Key Insight
FDA Post-Marketing Requirements[14,15]	• 2010–2015: 33% of oncology new molecular entities (NMEs) had dose optimization post-marketing requirements (PMRs) • 43% of these resulted in product label changes • 2016–2022: ~16% of NMEs had dose-related PMRs	Late-stage dose optimization is a challenge, with regulatory and commercial consequences.
Benefits of Early Investment[16]	• Exposure–response modeling • PK/PD integration • Patient-centered trial design	Enables precision, supports rational dose selection, and improves development efficiency and cost-benefit.
MTD-Based Dosing: Tolerability Impact[17]	• Capmatinib, tepotinib, & ensartinib approved at or near MTD • Dose interruptions: up to 54% • Dose reductions: ~24%	High rates of modification indicate poor tolerability and suboptimal initial dose selection

The transition from MTD to OBD is a clinical and economic imperative. Designing trials around OBD ensures safer and more effective treatments for patients, as well as more responsible and sustainable development paths for sponsors.

Precision for Medicine Insight | Advancing Dose Optimization in Oncology

We are driving the evolution of modern dose optimization by combining advanced research methods with operational excellence. With more than 70 percent of our trials focused on oncology and rare diseases, we bring deep expertise in complex indications and new therapeutics, helping sponsors design smarter trials that align with regulatory expectations and accelerate commercial success.



The Economic Case for Model-Informed Dose Strategies in Oncology

Integrating dose optimization upfront can enhance both clinical outcomes and capital efficiency. According to the Tufts Center for the Study of Drug Development, the cost to bring a new drug to market averaged $2.87 billion in 2013 dollars, comprising $1.40 billion in out-of-pocket expenses, $1.16 billion in time costs, and $0.31 billion in post-marketing surveillance.

Targeted strategies, such as precision dosing and exposure–response, model-informed drug development have demonstrated measurable benefits in oncology drug development. Model-informed precision dosing (MIPD) for agents such as busulfan and high-dose methotrexate has been shown to substantially reduce inter patient variability in exposure, diminish toxicity risk, and improve therapeutic precision, all benefits documented in prospective validation studies.

While not conducted in early-phase trials, real-world applications of MIPD, such as PK-guided dosing of busulfan and high-dose methotrexate, demonstrate how model-based approaches can significantly improve target attainment, reduce variability, and enhance outcomes. These examples underscore the potential benefits of shifting dose optimization earlier in development, as advocated by the FDA's Project Optimus initiative.

At a time when R&D returns are shrinking and the cost per pipeline asset continues to rise, early investment in dose optimization can significantly enhance patient outcomes while reducing downstream costs. By minimizing the need for label revisions, additional trials, or the management of preventable toxicities, sponsors can avoid costly late-stage failures, saving potentially hundreds of millions of dollars per program. By avoiding even a small proportion of late-stage failures, drug developers could save hundreds of millions per program.

Realizing these benefits means sponsors need to operationalize dose optimization through the use of modern, adaptive, and data-driven methodologies that accelerate learning and reduce risk. In this environment, deploying the right tools and trial structures (i.e., exposure–response modeling, MIPD, and innovative trial designs) is critical to unlocking both clinical and commercial value.

Faster, Smarter, and Safer Approaches to Dose Selection in Oncology

Legacy dose-escalation models (e.g., the ubiquitous 3+3 trial design) do not meet the demands of today's complex therapies because they are rigid and statistically underpowered. Innovators are changing the equation by adopting updated, flexible trial designs that support faster, more accurate dose selection (Figure 2).

Two approaches are gaining ground with drug development professionals:

- Bayesian designs, such as the Continual Reassessment Method (CRM) and Bayesian Optimal Interval (BOIN), apply Bayesian principles to improve dose selection in early-phase trials. CRM is a model-based approach that uses real-time probability modeling to update a prior hypothesis as patient data accrue, allowing for continuous refinement of dose decisions. In contrast, BOIN is a model-assisted Bayesian design that establishes decision rules before the trial begins, enabling efficient implementation without ongoing model updates. Both methods support greater flexibility, are well-suited to small-sample studies and those leveraging historical or real-world data and improve ethical balance by reducing patient exposure to subtherapeutic or toxic doses.[27]

Figure 2. **Comparison of Legacy vs. Modern Trial Designs**

- Adaptive dose-expansion cohorts enable simultaneous evaluation of multiple doses following initial safety signals. This design allows for rapid identification of a recommended Phase 2 dose, thereby reducing overall timelines and development risk.

A comparative simulation study found that while the interval 3 + 3 (i3+3) design identified the maximum tolerated dose faster than the Bayesian optimal interval (BOIN) design, it did so at the expense of statistical rigor, resulting in lower accuracy and higher patient exposure to excessive dosing. In contrast, BOIN and other model-assisted designs improve dose selection precision and reduce the risk of overdosing compared to rule-based methods, such as i3+3.

Operational innovation is also driving improvements:

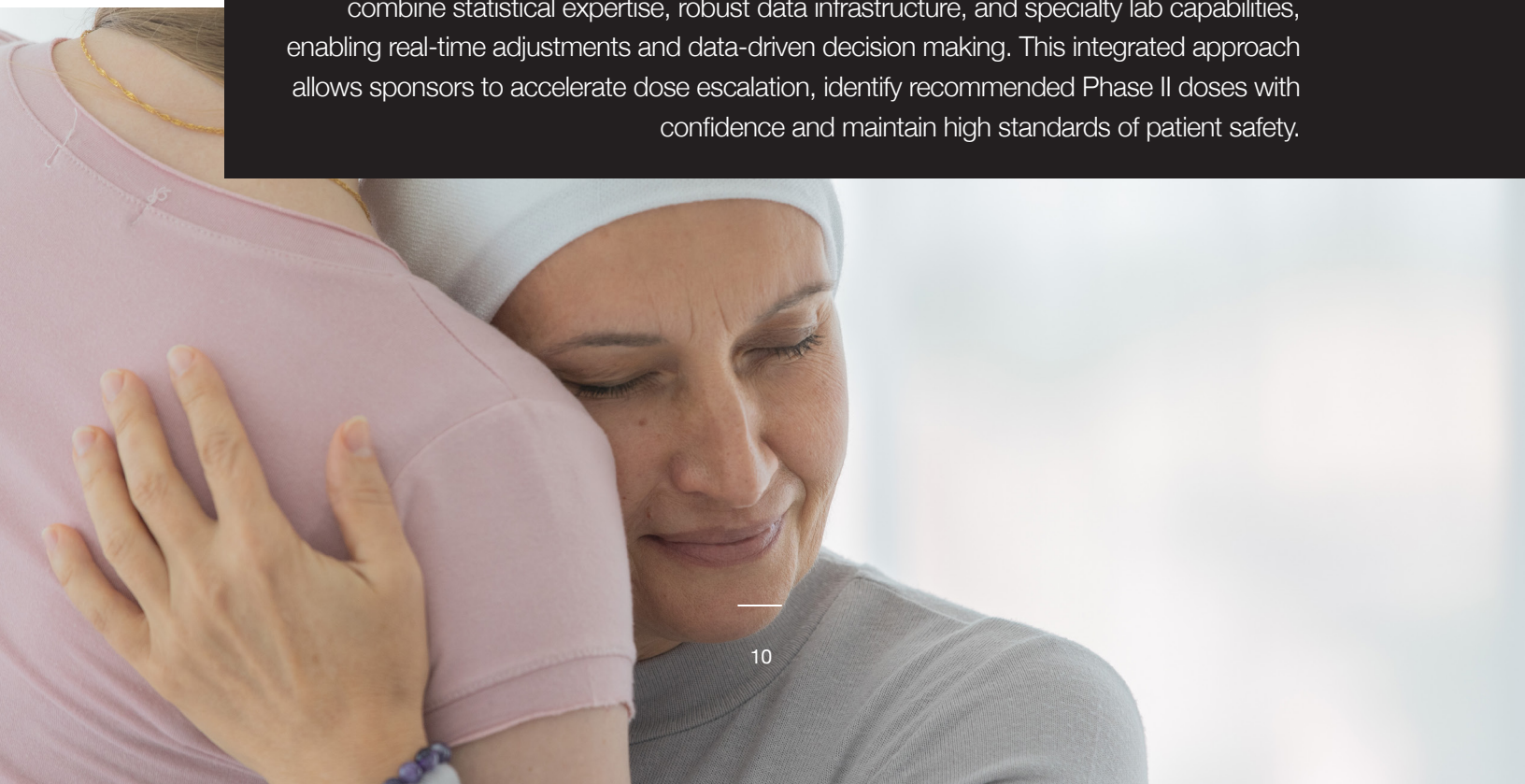
- Backfill enrollment allows new patients to join expansion cohorts at promising doses as they emerge.
- Rolling cohorts integrate ongoing safety reviews with protocol adaptations, increasing the pace of iteration.
- Built-in translational analysis tools track how the body responds to treatments, such as immune activity or biomarker changes, helping researchers adjust the dose in real time.

The following example highlights how adaptive design and centralized oversight can enhance trial resilience and accelerate dose optimization. In 2024, Precision for Medicine managed two Phase I trials for solid tumors using a Bayesian backfill design. When one trial was paused due to funding constraints, the team maintained central biostatistical oversight and preserved core infrastructure. Once funding resumed, the study restarted without data loss, enabling accelerated dose selection and more confident regulatory engagement. This reduced projected timelines by 22 percent and decreased patient enrollment in subtherapeutic arms by 38 percent, improving both trial efficiency and safety outcomes.

These methodologies are valuable for oncology agents, which may demonstrate delayed efficacy or unique toxicity kinetics that traditional designs struggle to capture. While modern trial designs are essential, effective dose optimization also depends on tailoring the right strategy to the unique challenges of each therapeutic modality.

Precision for Medicine Insight | Re-engineering Oncology Trial Designs

We are redefining early-phase oncology by advancing adaptive trial strategies that move beyond the limitations of the traditional designs. Our cross-functional research teams combine statistical expertise, robust data infrastructure, and specialty lab capabilities, enabling real-time adjustments and data-driven decision making. This integrated approach allows sponsors to accelerate dose escalation, identify recommended Phase II doses with confidence and maintain high standards of patient safety.



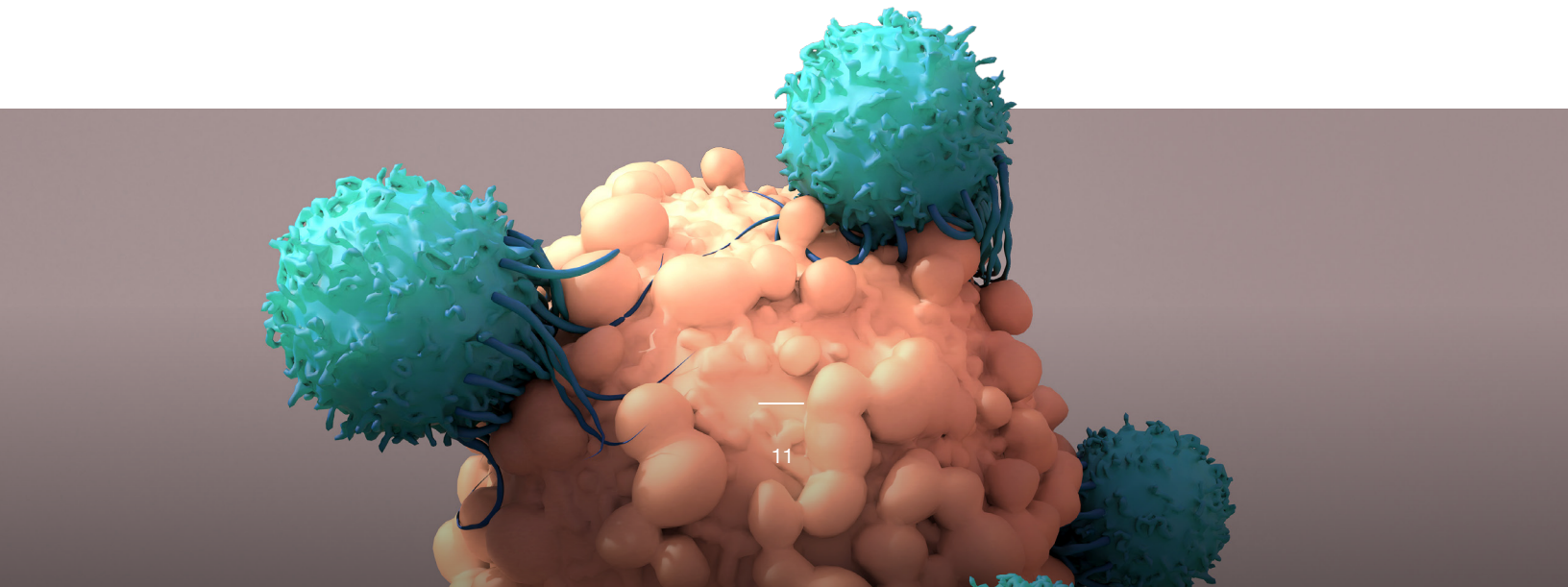
Case Examples in Modality-Specific Dose Optimization

By shifting from reactive corrections to proactive optimization, sponsors can reduce clinical risk, regulatory issues, and downstream costs. Achieving this shift requires a nuanced approach that considers the biological behavior and therapeutic profile of each modality.

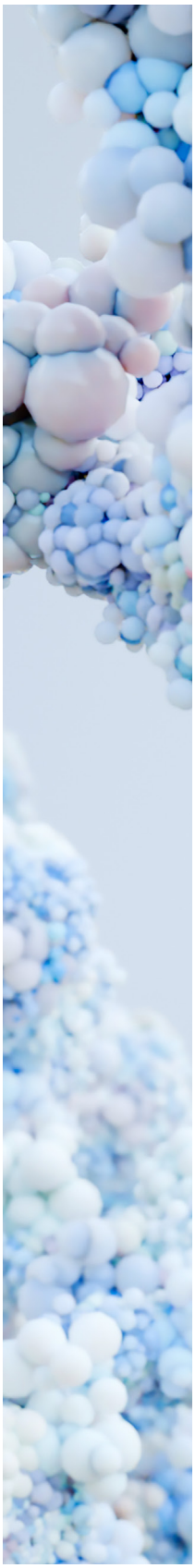
This is true for drug classes where conventional dose-escalation frameworks fall short, such as immune checkpoint inhibitors, antibody–drug conjugates (ADCs), and other modern agents that present modality-specific challenges, demanding tailored strategies. Rather than seeking a universal dosing algorithm, sponsors should align dose selection with pharmacodynamics, pharmacokinetics, mechanism of action, and patient variability. Table 2 presents two case examples demonstrating how modality-specific dose optimization can enhance safety, maintain efficacy, and accelerate time to value.

Table 2. **Case Examples**

Modality	Drug	Dose Optimization Approach	Key Findings	Impact on Development
Immunotherapy	Nivolumab	Exposure–response and efficacy analysis across the dose range in pooled data from Phase 1–3 trials	Similar efficacy across 0.1–10 mg/kg; no additional benefit above ~1 mg/kg; higher doses associated with greater toxicity[28]	Informed use of lower, fixed dosing regimens; supported label dose simplification
Benefits of Early Investment[16]	Trastuzumab Deruxtecan	Comparative safety/efficacy analysis in randomized clinical studies	5.4 mg/kg showed fewer interstitial lung disease events than 6.4 mg/kg with a comparable >60% response rate[29]	Lower dose selected for approval to improve safety profile without compromising efficacy



Balancing Synergy, Safety, and Regulatory Expectations



Dosing complexities are further magnified in the context of combination therapies, where multiple agents interact to shape safety and efficacy. As combination therapies become a cornerstone of modern oncology, —particularly those involving checkpoint inhibitors, monoclonal antibodies, tyrosine kinase inhibitors, antibody–drug conjugates (ADCs), T-cell engagers, and bispecific or trispecific molecules—dose optimization becomes more complex and critical. Each drug in a regimen should be evaluated in isolation and the context of potential pharmacokinetic and pharmacodynamic interactions, synergistic efficacy, and overlapping toxicity.

Case in point: The combination of nivolumab and ipilimumab in melanoma demonstrated vigorous clinical activity but triggered high rates of Grade ≥3 immune-related adverse events. Subsequent trials found that reducing the ipilimumab dose while maintaining nivolumab exposure preserved efficacy while improving tolerability. This adjustment informed the approved dosing schedule and reduced clinical and commercial risk.

Emerging strategies for optimizing drug combinations include:

- Emerging strategies for optimizing drug combinations include adaptive dose-finding frameworks that evaluate multiple dose pairs in parallel, with real-time safety and efficacy monitoring. Examples include CRM and BOIN, which adjust dosing based on ongoing toxicity and response data.
- PK/PD modeling to simulate and predict interactions between agents, reducing reliance on trial-and-error methods.
- Biomarker stratification to identify patient subgroups based on genetic, molecular, or clinical markers most likely to benefit from specific dose combinations or treatment schedules.

A real-world example is the I SPY 2 Phase I/II adaptive immuno-oncology trial. It used rolling cohort expansion, early biomarker-driven enrollment (via magnetic resonance imaging and tissue markers), and integrated translational analytics. This approach enabled dosing decisions up to six months earlier than conventional designs, reduced patient exposure to suboptimal doses, and generated actionable biomarker insights such as early prediction of treatment response based on MRI tumor volume changes and gene expression profiles. It also accelerated regulatory interactions by providing real-time evidence of efficacy signals in defined patient subgroups.

Regulators are also responding to changing strategies, with the FDA's 2024 draft guidance recommending exposure-matching data and mechanistic justification for each drug in a combination regimen.[21] Similar expectations are emerging globally, too.

In the era of combination drug regimens, dose selection is a multi-dimensional problem that requires advanced modeling, adaptive protocols, and early engagement with regulatory authorities. As combination therapies become more personalized, the use of predictive biomarkers will play an important role in determining the optimal dose.

Precision for Medicine Insight | Global Regulatory Acumen and Experience

We help sponsors unify dose optimization efforts across regions by combining global operational reach with worldwide regulatory expertise. Our dedicated consultants guide sponsors through complex requirements from bridging studies and PK/PD modeling to biomarker validation, ensuring alignment with evolving expectations from the FDA, EMA, and other agencies. This proactive approach strengthens compliance and increases the likelihood of timely, successful regulatory reviews internationally.

Opportunities and Limitations of Biomarker-Informed Dose Optimization

Oncology drug dosing is no longer solely determined by safety and pharmacokinetics; biomarkers are helping to inform and optimize it. Molecular genomic signatures that guide patient selection are now being used to refine dose decisions, enabling more tailored and effective treatment strategies (Table 3).

Table 3. **Emerging Applications of Biomarker-Guided Dosing**

Biomarker Type	Example(s)	Application in Dosing	Clinical Status
Predictive Expression Markers	PD-L1, Tumor Mutational Burden (TMB)	Stratify patients for checkpoint inhibitor dosing	Widely used in practice
Molecular Response Markers	Circulating tumor DNA (ctDNA) dynamics	Investigational use to guide dose escalation/de-escalation based on early treatment response	Emerging; not FDA-validated
Pharmacogenomic Markers	CYP450 variants, TPMT, UGT1A1	Predict metabolism-related toxicity or variable efficacy across patient subgroups	Accepted in specific contexts

In recent clinical studies, plasma ctDNA has emerged as a powerful tool for guiding treatment intensity. A 2025 review article highlighted ctDNA's accuracy in monitoring response across lung, colorectal, and breast cancers, supporting its potential use in dynamic, personalized dosing strategies.

That said, implementation challenges persist, as many biomarkers lack harmonized assays or standardized thresholds, while others are dynamic, changing in response to disease progression or treatment exposure. Regulators remain cautious, requiring that biomarkers used in dose justification be validated and supported by a mechanistic rationale. While biomarker-informed dosing is a promising frontier, it is not yet universally applicable and must be implemented within a broader evidence framework.

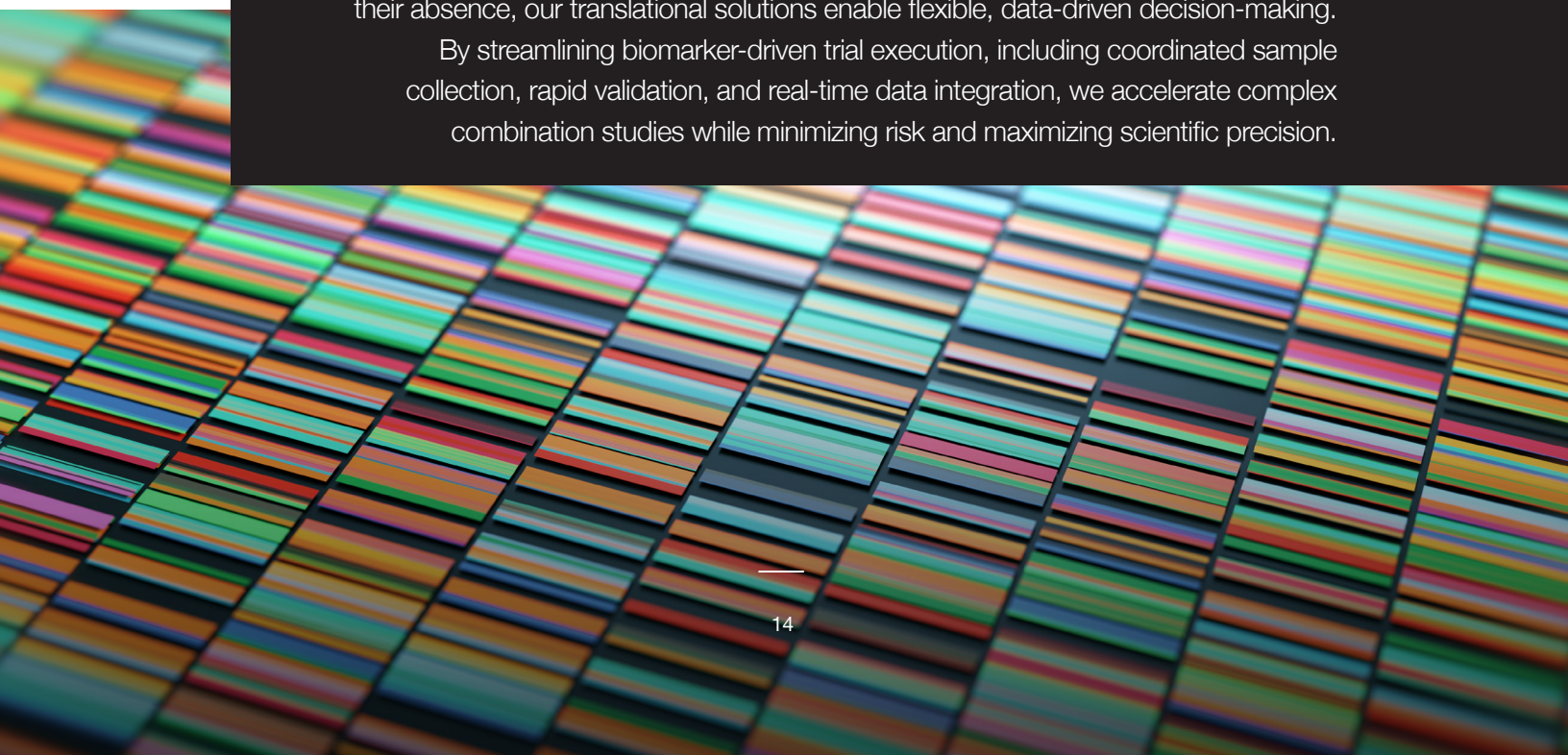
To advance biomarker-guided dosing, sponsors must:

- Invest in early assay validation and standardization across global trial sites.
- Incorporate biomarker endpoints into dose-ranging studies as secondary or exploratory objectives.
- Engage regulators to discuss the evidentiary role of biomarkers in dose justification.

The FDA's Project Optimus supports the integration of validated biomarkers into dose-selection strategies, provided the data are robust and the biomarkers are fit-for-purpose.1 As such, biomarker-informed dosing is evolving from an aspirational concept to a regulatory and commercial differentiator. Biomarkers refine our understanding of drug response at the molecular level, while patient-centered dosing ensures that treatments remain tolerable and sustainable.

Precision for Medicine Insight | Accelerating Biomarker-Informed Strategies

We help sponsors advance programs across the full spectrum of biomarker maturity. Whether integrating validated biomarker insights or building dose-selection strategies in their absence, our translational solutions enable flexible, data-driven decision-making. By streamlining biomarker-driven trial execution, including coordinated sample collection, rapid validation, and real-time data integration, we accelerate complex combination studies while minimizing risk and maximizing scientific precision.



Integrating Patient Experience and Real-World Data into Sustainable Dosing

As oncology care shifts toward chronic disease management, patient experience and quality of life have become central to dosing decisions. Clinical development teams must look beyond pharmacokinetics and tumor response and account for the patient experience, short-term and long-term.

One insight is that patients often prioritize quality of life over marginal gains in efficacy. According to the 2024 Patient-Centered Dosing Initiative (PCDI) survey, 79 percent of individuals with metastatic breast cancer reported that they would prefer a lower dose if it meant experiencing fewer side effects, even if it came with a modest reduction in efficacy. PCDI also found that 63 percent reported better adherence when receiving reduced-dose regimens.22

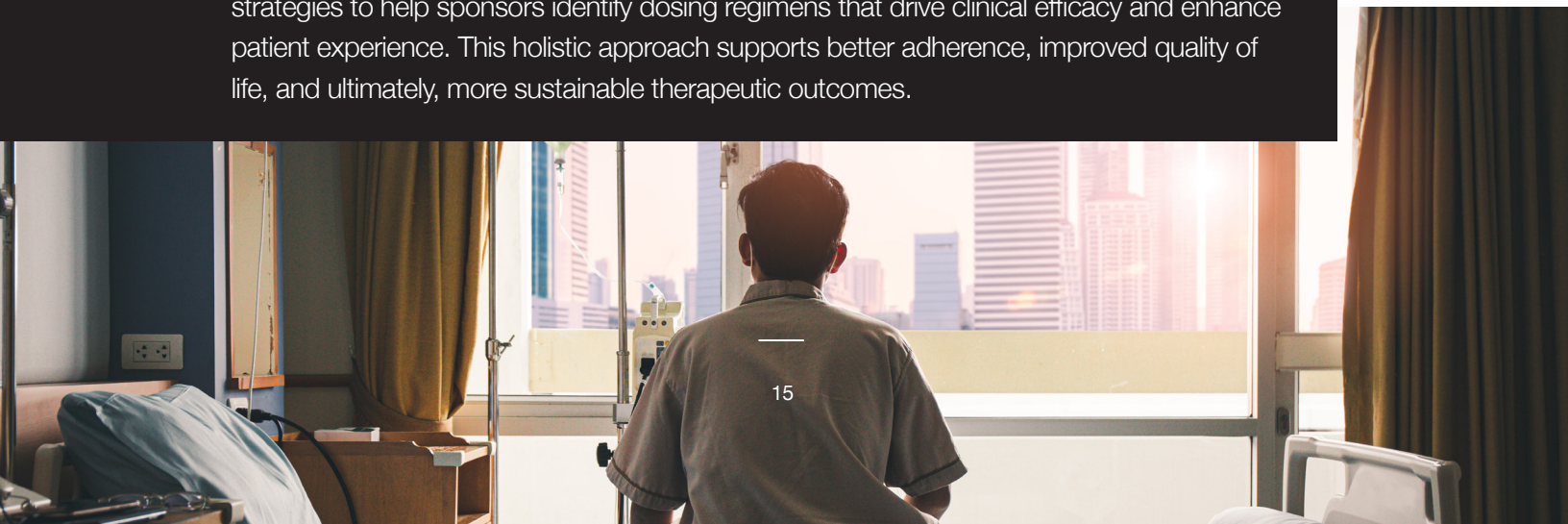
The patient perspective has important implications:

- Dose optimization studies that incorporate patient-reported outcomes and quality-of-life metrics are appreciated by regulators and payers.
- Flexible dosing protocols that allow for real-time titration based on tolerability can improve adherence and reduce discontinuation rates in clinical trials and commercial settings.
- Post-approval dose refinement, informed by real-world data (e.g., electronic health records, wearable devices, and pharmacy claims), supports ongoing optimization and expanded label flexibility.

Digital health platforms enable the tracking of side effects, symptom burden, and adherence in near real-time. When integrated with clinical and PK data, these technologies allow continuous dose optimization beyond the trial setting. As patient preferences and scientific rigor reshape dose strategy, regulators worldwide are responding with new expectations and guidance.

Precision for Medicine Insight | Balancing Dose with Patient Outcomes

We integrate central lab services, biostatistical modeling, and patient engagement strategies to help sponsors identify dosing regimens that drive clinical efficacy and enhance patient experience. This holistic approach supports better adherence, improved quality of life, and ultimately, more sustainable therapeutic outcomes.



Meeting the Rising Bar for Dose Optimization Across Regulatory Jurisdictions

Regulatory momentum is expanding beyond the United States, signaling a global shift toward harmonized expectations in dose optimization.[34] Agencies across major markets are converging around the principles of model-informed, patient-centered, and evidence-driven development, requiring sponsors to align across geographies to mitigate rework, delays, and approval risk.

- The European Medicines Agency (EMA) accelerated support for model-informed drug development through its Adaptive Pathways and Priority Medicines (PRIME) programs, favoring submissions that integrate exposure–response modeling and translational biomarker data.[35] In 2024 alone, seven oncology products advanced through EMA review in part due to dose-justified filings supported by adaptive designs.
- Japan's Pharmaceuticals and Medical Devices Agency (PMDA) revised early development expectations, mandating cross-study PK/PD modeling and exposure-bridging requirements for combination regimens, aligning its guidance with the Project Optimus framework.[36]
- Health Canada and Australia's Therapeutic Goods Administration (TGA) are incorporating Project Optimus principles into regulatory guidance and sponsor engagement protocols.[17]

Dose selection is a global strategic requirement; however, harmonization challenges remain. Biomarker thresholds, assay platforms, and exposure-response modeling assumptions may vary by jurisdiction, requiring thoughtful consideration.

To succeed globally, sponsors must:

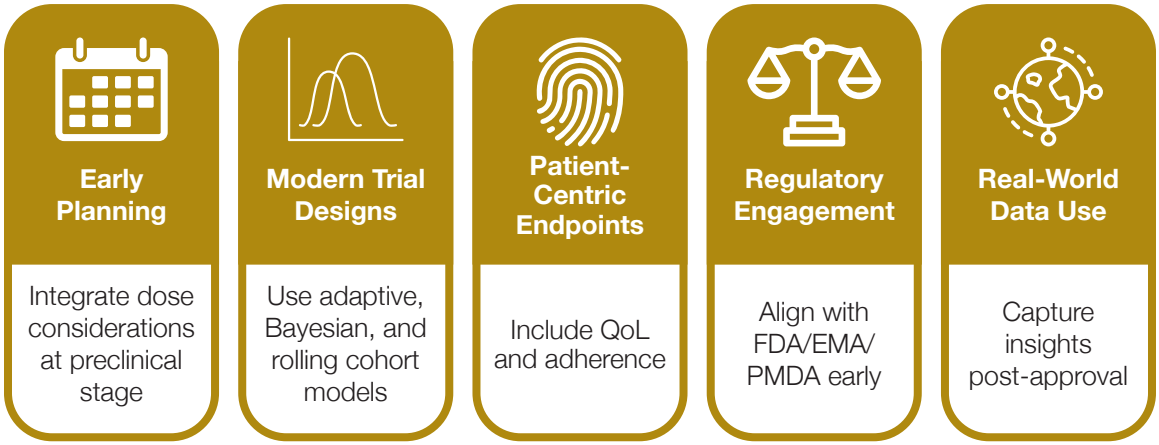
- Develop adaptable dose-justification dossiers with consistent core data and localized assumptions.
- Align biomarker strategies and PK models with input from regulatory science teams.
- Pursue simultaneous health authority engagement (e.g., parallel scientific advice with FDA and EMA) to streamline alignment and avoid redundant studies.

Five Imperatives for Smarter Dose Strategy and Competitive Advantage

Dose optimization is a core strategic differentiator in the current drug development landscape. Given this convergence of science, policy, and patient priorities, what does it take to lead in this new era of oncology drug development?

Sponsors who approach dose selection as an integrated, cross-functional priority are achieving faster development timelines, improved regulatory outcomes, and greater long-term commercial success.[37,38]

Figure 3. **Five Pillars of Modern Dose Optimization**



There are five strategic imperatives for sponsors seeking to lead in this new paradigm:

1. From early on, treat dose selection as a strategic asset, not a technical milestone. Begin dose optimization planning as soon as feasible, at the preclinical and first-in-human stages, rather than as an afterthought at Phase II. Align cross-functional teams (clinical, regulatory, pharmacometrics, commercial) on the importance of dose as a differentiator.
2. Exploit modern trial designs and modeling capabilities. Use adaptive and Bayesian frameworks, rolling cohorts, and real-time analytics to expedite dose finding while ensuring patient safety. Develop or partner for a robust PK/PD and biomarker modeling infrastructure.
3. Prioritize patient-centric endpoints. Include quality-of-life metrics and patient-reported outcomes in early-phase trials. Recognize that patient preference can influence regulatory review and payer acceptance.

4. Engage regulators early and often. Seek pre-IND and scientific advice meetings with multiple agencies to align on modeling assumptions, trial designs, and biomarker use. Global coordination reduces work and accelerates approvals.
5. Leverage real-world data and AI tools post approval. Design systems and tools (e.g., DoseOpt™) that capture dosing, adherence, and safety through electronic health records, digital platforms, and wearables. AI-driven models analyzing ctDNA, metabolomics, and patient-reported outcomes can identify optimal dosing in real time.[39,40,41]

Sponsors that integrate these principles will differentiate their programs, improve patient experiences, and create more durable commercial value.

Precision for Medicine Insight | Think Globally, Act Locally
Our global network of 100+ sites accelerates study start-up, while flexible, client-focused processes ensure that dose strategies are tightly aligned with regulatory milestones, streamlining development and maximizing downstream success.

How Forward-Thinking Sponsors Are Gaining the Dose Advantage

The oncology drug development landscape is dynamic, and legacy paradigms no longer meet the demands of modern therapeutics. Regulatory expectations are rising, patient preferences are evolving, and clinical and commercial outcomes are dependent on administering the correct dose. Leading organizations are making wise investments in translational modeling, adaptive trial design, and biomarker-driven strategies. However, execution with the right clinical development partner matters.

Throughout the uncertainty, Precision for Medicine brings the experience, service, and expertise to help you design smarter trials that bring life-changing therapies to those with the greatest need.

Precision for Medicine Insight | Your Partner of Choice for Oncology Clinical Trials
Precision for Medicine is the preferred partner for oncology innovators who want to move faster and smarter. Our integrated capabilities, spanning AI-powered tools, comprehensive assay support and expertise, global infrastructure including lab facilities, and regulatory insight, help sponsors to accelerate dose selection with scientific confidence and strategic clarity.

Authors

Harpreet Singh, MD
Chief Medical Officer

Nick Richardson, DO, MPH
Vice President,
Clinical Development

Kurt Preugschat
Director,
Biostatistics

Vandana Sundaram
Principal Biostatistician

References

1. U.S. Food and Drug Administration. (2024). Project Optimus: Draft guidance for industry.

2. LThall, P. F., Zang, Y., Chapple, A. G., Yuan, Y., Lin, R., Marin, D., & Msaouel, P. (2023). Novel clinical trial designs with dose optimization to improve long-term outcomes. Clinical Cancer Research, 29(22), 4549–4554.

3. Jiang, L., & Yuan, Y. (2023). A seamless Phase II/III design: A useful strategy to reduce the sample size for dose-optimization. Journal of the National Cancer Institute, 115(16), 1092–1098. https://doi.org/10.1093/jnci/djad103

4. Gao, W., Liu, J., Shtylla, B., et al. (2024). Realizing the promise of Project Optimus: Challenges and emerging opportunities for dose optimization in oncology drug development. CPT: Pharmacometrics & Systems Pharmacology, 13, 691–709.

5. U.S. Food and Drug Administration. (2024, August). Guidance for Industry: Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases.

6. Hojouj, M. I., Cruz, R., & Stuart, M. (2025). Project Optimus: Principles, challenges, and a paradigm shift in dose optimization for cancer therapies. Journal of Clinical Oncology, 43(16_suppl), e23019.

7. SABCS Meeting News. (2024, December 9). Clinical Workshop to review dosage, regimen optimization in breast medical oncology.

8. Oncodaily. (2024, December 24). Mediamedic - SABCS 2024: Clinical Symposium on Dose Optimization and Regimen Design in Breast Oncology.

9. Friends of Cancer Research. (2024). 2024 impact report: Powering advances. Friends of Cancer Research.

10. Soltantabar, P., Lon, H.-K., Parivar, K., Wang, D. D., & Elmeliegy, M. (2023). Optimizing benefit/risk in oncology: Review of post marketing dose optimization and reflections on the road ahead. Critical Reviews in Oncology/Hematology, 182, 103913.

11. Garon, E. B., Rizvi, N. A., Hui, R., et al. (2015). Pembrolizumab for the treatment of non-small-cell lung cancer. New England Journal of Medicine, 372(21), 2018–2028.

12. Food and Drug Administration. (2020). Lumakras (sotorasib) NDA 214665 multi-disciplinary review and evaluation [PDF]. FDA.

13. Aung, W. Y., Neumann, M. F., Wang, K., Chukkalore, D., Morales, J., & Seetharamu, N. (2025). Impact of standard vs reduced dosing of sotorasib on efficacy and toxicity in KRAS G12C–mutated advanced non small cell lung cancer: A systematic review and meta analysis. Journal of Clinical Oncology, 43(16_suppl), 8593.

14. Gendy, J. M., Nomura, N., Stuart, J. N., & Blumenthal, G. (2024). US FDA's dose optimization postmarketing requirements and commitments of oncology approvals and the impact on product labels from 2010 to 2022: An emerging landscape from traditional to novel therapies. Therapeutic Innovation & Regulatory Science, 58(2), 380–386.

15. Collins, G., McKelvey, B., Andrews, H. S., Allen, J. D., & Stewart, M. D. (2024). An analysis of dosing-related postmarketing requirements for novel oncology drugs approved by the U.S. Food and Drug Administration, 2012–2022. Clinical Cancer Research, 30(5), 937–941.

16. Ruiz García, A., Baverel, P., Bottino, D., Dolton, M., Feng, Y., González García, I., … Bonate, P. (2023). A comprehensive regulatory and industry review of modeling and simulation practices in oncology clinical drug development. Journal of Pharmacokinetics and Pharmacodynamics, 50(2), 147–172.

17. Collins KP, Yin D, Pithavala YK, Mittapalli RK. Landscape analysis of adverse events and dose intensity for FDA approved oncology small molecules. Cancer Chemother Pharmacol. 2025 Jan 4;95(1):17.

18. DiMasi, J. A., Hansen, R. W., & Grabowski, H. G. (2016). Innovation in the pharmaceutical industry: New estimates of R&D costs. Journal of Health Economics, 47, 20–33.

19. Agema, B. C., Koch, B. C. P., Mathijssen, R. H. J., & Koolen, S. L. W. (2025). From prospective evaluation to practice: Model informed dose optimization in oncology. Drugs, 85(4), 487–503.

20. Davis JM, Ivanova A, Chung Y, et al. Evaluation of a Test Dose Strategy for Pharmacokinetically-Guided Busulfan Dosing for Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant. 2019 Feb;25(2):391-397

21. Philippidis, A. (2023, February 28). The unbearable cost of drug development: Deloitte report shows 15% jump in R&D to $2.3 billion. GEN Edge.

22. Agema, B. C., Koch, B. C. P., & Mathijssen, R. H. J. (2025). From prospective evaluation to practice: Model-informed dose optimization in oncology. Drugs, 85(7), 1123–1138.

23. Zhou H, Lee JJ, Yuan Y. BOP2: Bayesian optimal design for phase II clinical trials with complex and straightforward endpoints. Stat Med. 2017 Sep 20;36(21):3302-3314.

24. Cytel. (n.d.). Bayesian clinical trial designs. Cytel. Retrieved August 5, 2025, from Cytel website

25. U.S. Food and Drug Administration. (2022, March). Expansion cohorts: Use in first-in-human clinical trials to expedite development of oncology drugs and biologics.

26. Zhou, Y., Li, R., Yan, F., Lee, J. J., & Yuan, Y. (2021). A comparative study of Bayesian optimal interval (BOIN) design with interval 3 + 3 (i3 + 3) design for phase I oncology dose finding trials. Statistics in Biopharmaceutical Research, 13(2), 147–155.

27. Precision for Medicine. (2024). Case study: Operational resilience in Bayesian Phase I trials. Internal publication.

28. Brahmer, J. R., Tykodi, S. S., Chow, L. Q. M., Hwu, W.-J., Topalian, S. L., Hwu, P., Drake, C. G., ... Wigginton, J. M. (2012). Safety and activity of anti–PD-L1 antibody in patients with advanced cancer. The New England Journal of Medicine, 366(26), 2455–2465.

29. Modi S, Jacot W, Yamashita T, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. N Engl J Med. 2022 Jul 7;387(1):9-20.

30. Larkin, J., Chiarion-Sileni, V., Gonzalez, R., Grob, J. J., Cowey, C. L., Lao, C. D., ... & Wolchok, J. D. (2015). Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. New England Journal of Medicine, 373(1), 23–34.

31. Esserman, L. J., Berry, D. A., DeMichele, A., Carey, L., Davis, S. E., Buxton, M., ... & Woodcock, J. (2012). The I-SPY 2 trial: A clinical trial design for efficiently screening multiple drugs and drug combinations in neoadjuvant breast cancer. Clinical Trials, 9(1), 68–80

32. Bartolomucci, A., Nobrega, M., Ferrier, T. et al. Circulating tumor DNA to monitor treatment response in solid tumors and advance precision oncology. npj Precis. Onc. 9, 84 (2025).

33. Loeser, A., Kim, J. S., Peppercorn, J., Burkard, M. E., Niemierko, A., Juric, D., Kalinsky, K., ... Bardia, A. (2024). The right dose: Results of a patient advocate–led survey of individuals with metastatic breast cancer regarding treatment-related side effects and views about dosage assessment to optimize quality of life. JCO Oncology Practice, 20(7).

34. Murphy R, Halford S, Symeonides SN. Project Optimus, an FDA initiative: Considerations for cancer drug development internationally, from an academic perspective. Front Oncol. 2023 Mar 3;13:1144056.

35. EMA. (2024). Evaluation of anticancer medicinal products – Scientific guideline. European Medicines Agency.

36. Pharmaceuticals and Medical Devices Agency. (2020, June 8). Guideline for exposure response analysis of drugs (PSEHB/PED Administrative Notice, June 8, 2020).

37. Friends of Cancer Research. (2021). Optimizing dosing in oncology drug development.

38. Ruiz-Garcia, A., et al. (2023). Application of exposure–response analysis in dose selection. Journal of Pharmacokinetics and Pharmacodynamics, 50, 123–138.

39. Maier, C., Hartung, N., Kloft, C., Huisinga, W., & de Wiljes, J. (2020). Reinforcement learning and Bayesian data assimilation for model-informed precision dosing in oncology (arXiv:2006.01061).

40. Adashek JJ, Subbiah IM, Subbiah V. Artificial Intelligence Systems Assisting Oncologists? Resist and Desist or Enlist and Coexist. Oncologist. 2019 Oct;24(10):1291-1293.

41. Parikh, R., & Hippensteele, A. (2025, May 2). Real world data, real time decisions: AI at the front lines of oncology. Pharmacy Times.

Download your digital copy

For more information please visit us at:
precisionformedicine.com

Rev. 01

PRECISION for medicine®