



From Signal to Standard: *The Rising Structural Role of Biomarkers in Oncology Trials*

From Afterthought to Design Driver

Over the past decade, biomarkers have moved from the margins of oncology clinical trials into their structural core. Where they were once treated as exploratory endpoints or optional correlative work, they now shape who is eligible for a study, how early activity is interpreted and which dose ultimately reaches clinical practice. In the era of precision oncology, trials increasingly ask whether a drug works in a biologically defined subgroup, using biomarkers as the organising framework for design and analysis.

From the perspective of an early-phase oncologist, the most important shift is not simply that biomarkers are used more often, but that they are integrated earlier and more deliberately into development. When a biomarker and a drug are conceived and developed together, sometimes even biomarker first, compound second, the odds of selecting the right patients, demonstrating proof of mechanism and identifying a biologically appropriate dose are significantly better.

Biomarkers at the Gate – Patient Selection

In modern oncology, virtually every targeted agent is developed against a specific gene, protein, or pathway, making biomarker-based patient selection the most visible and consequential use of biomarkers in early-phase trials. Enrichment strategies improve signal detection in small cohorts, but they carry trade-offs; narrow eligibility criteria can hamper recruitment and may exclude patients who might benefit. In practice, broad molecular profiling panels assessing multiple alterations from a single biopsy or blood draw can open several potential trial pathways for each patient while addressing the underlying biological heterogeneity of cancer.

Beyond Inclusion – Biomarkers as Proof of Mechanism

Once a patient is enrolled, biomarkers take on a second critical role: confirming that the drug is doing what it is supposed to do. In early-phase trials, where traditional efficacy endpoints are immature, pharmacodynamic biomarkers are the primary evidence that a compound is engaging its target, modifying relevant pathways and producing measurable biological effects. This proof-of-mechanism work demands repeated blood sampling, extended pharmacokinetics visits and serial biopsies, a significant burden on patients and sites but one that is essential for sound go/no-go decisions. That burden still requires a clear justification for every sample. Each biopsy, blood draw or additional timepoint should answer a defined development question that cannot be addressed through a less invasive approach. Protocol teams must balance the value of richer biological data against procedure-related risk, travel, time in clinic and cumulative fatigue, particularly for patients who are already heavily treated. The value of this approach is well illustrated by the development of pembrolizumab; retrospective analysis of PD-L1 expression in a Phase 1 cohort drove adaptive

redesign of the study and PD-L1 ultimately became a standard first-line treatment biomarker in non-small cell lung cancer, demonstrating how mechanistic evidence generated in early trials can reshape an entire therapeutic class.

Tissue, Liquid Biopsy and the Expanding Biomarker Toolbox

The tools available for biomarker assessment in oncology trials have expanded considerably over the past decade and early-phase studies are at the forefront of integrating them.

Histological assessment of tissue biopsies remains the gold standard for proof of mechanism; regulators expect tissue-based evidence of target engagement in the early-phase setting and this is unlikely to change. Blood-based approaches including circulating tumour DNA, cell-free DNA and whole exome sequencing complement tissue assessment by enabling dynamic monitoring across treatment cycles, capturing resistance mechanisms and tumour heterogeneity that a single biopsy may miss. Complementing tissue-level data with liquid biopsy is now standard practice in many Phase 1 studies. Looking ahead, multi-omics integration, spanning genomics, transcriptomics, proteomics and immune profiling, will create more complete biological portraits of individual tumours. However, realising that potential requires standardised data collection and regulatory frameworks that can keep pace.

Co-Development of Drugs and Diagnostics

Perhaps the most important conceptual shift in modern oncology drug development is the recognition that a drug and biomarker cannot be developed independently. When a biomarker is identified retrospectively, after a compound has already moved through early- and mid-stage development, the result is often a validation gap that delays or undermines the ability to use it at scale. Companion diagnostic platforms, assay cutoffs and validation plans should be defined during Phase 1 design, not after. Yet early assays and cutoffs often need refinement as dose-escalation data reveal which biological signals matter. Waiting for complete validation can make early use impractical, while postponing validation until expansion may leave a promising drug without a dependable way to select patients. Parallel development allows analytical validation, cutoff refinement and regulatory discussion to progress alongside dose escalation. Equally important is practicality: a biomarker that works in a specialist centre but is unaffordable or unavailable in routine practice is of limited value to the field. Regulators, particularly in Europe, need frameworks that support parallel validation during dose escalation so that by the time expansion cohorts open, the tools to identify patients are already fit for purpose.

Project Optimus and Dose Optimisation

One of the most consequential regulatory shifts in recent years is the move away from the assumption that the highest tolerated dose is the best dose. Project Optimus, the US Food and Drug Administration's initiative to reform dose selection in



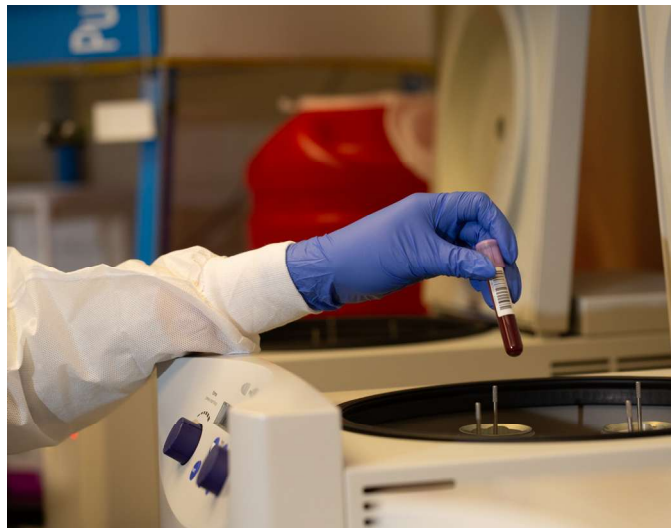
oncology, requires sponsors of targeted therapies to conduct structured dose-optimisation work and justify dose based on a broader evidence base than tolerability alone. Biomarkers are central to this. When two doses appear similarly safe clinically, pharmacodynamic and molecular readouts can reveal whether higher exposure adds meaningful biological activity or whether a lower dose already achieves full target engagement. Nearly every early-phase protocol now includes a formal dose-optimisation cohort following escalation, with biomarker endpoints built in to support the comparison. This approach has significant patient benefit, reducing toxicity levels and improving quality of life without sacrificing efficacy.

Operational Realities of Biomarker Inclusion

Making biomarkers structural to trial design increases operational complexity across screening, testing, logistics and site coordination. Experienced multidisciplinary teams bringing together investigators, pathologists, molecular laboratory staff and sponsors are essential to interpreting biomarker data within clinical context and translating findings into real-time decisions. The challenge intensifies when a target attracts broad simultaneous interest. When multiple sponsors pursue the same biomarker, each may impose different assay platforms, cutoffs or central testing requirements, creating a fragmented landscape for sites trying to screen patients across trials. Trials targeting MTAP are a current example; choosing between expensive central next-generation sequencing and more affordable local immunohistochemistry reflects both scientific and practical pressures. When each sponsor accepts a different method, sites may repeat testing on the same limited tissue, extend turnaround times and increase screening costs. Shared performance standards and broader acceptance of validated local results could reduce duplication while preserving assay quality. MTAP therefore illustrates a wider need to harmonise testing for biomarkers pursued across several competing programmes. The answer lies in collaboration. In an integrated early-phase network, a toxicity signal or biomarker finding at one centre informs and can alter trial management across the network to the benefit of both patients and sponsors. For biomarkers that are clinically important and widely pursued, treating assay development and usage optimisation as a collective priority would benefit all stakeholders considerably.

Toward More Precise, Equitable, Biomarker-Driven Clinical Trials

The number of actionable molecular targets in oncology is growing rapidly and so is the pressure to be precise about which biomarkers and drugs are truly worth pursuing. Artificial intelligence is beginning to contribute to target identification, compound prioritisation and complex data analysis; its near-term impact is strongest in basic research and trial design, though its use across all aspects of trial execution is not too far in the future. Multi-omics integration, combining genomic, transcriptomic, proteomic and immune profiling data, is creating richer pictures of tumour biology and drug response. However, its systematic adoption in early-phase trials requires further standardisation and regulatory clarity. Antibody-drug conjugates add another important test case. As these agents expand across tumour types and into earlier treatment settings, development will need to define not only the target but also the relevant expression threshold, tumour context and changes under treatment. Target expression alone does not consistently predict benefit,



so biomarker strategies must also account for heterogeneity and resistance rather than assume a simple drug-to-target match. The ultimate goal is to use these advances to benefit patients, an outcome that will require sustained commitment to validation, standardisation and equitable access to testing. The structural integration of biomarkers into oncology trials will be the foundation on which more precise, more effective and more equitable cancer care will be built.

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Dr. Tatiana Hernández Guerrero

Tatiana Hernández Guerrero, MD, PhD, is Director of Clinical Research at START Barcelona, part of The START Center for Cancer Research's global network of early-phase oncology clinical trial sites. Dr Hernández's clinical focus is on DNA-repair targeted therapies and immunotherapy, and she has served as Investigator on more than 60 clinical trials. She received her MD from Carabobo State University in Venezuela and a PhD in Medicine and a master's degree in healthcare management from ESADE in Spain.