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# Pharmacodynamic endpoints as clinical trial objectives to answer important questions in oncology drug development

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ABSTRACT

Analyzing the molecular interplay between malignancies and therapeutic agents is rarely a straightforward process, but we hope that this special issue of *Seminars* has highlighted the clinical value of such endeavors as well as the relevant theoretical and practical considerations. Here, we conclude with both an overview of the various high-value applications of clinical pharmacodynamics (PD) in developmental therapeutics and an outline of the framework for incorporating PD analyses into the design of clinical trials. Given the increasingly recognized importance of determining and administering the biologically effective dose (BED) and schedule of targeted agents, we explain how clinical PD biomarkers specific to the agent mechanism of action (MOA) can be used for the development of pharmacodynamics-guided biologically effective dosage regimens (PD-BEDR) to maximize the efficacy and minimize the toxicity of targeted therapies. In addition, we discuss how MOA-based PD biomarker analyses can be used both as patient selection diagnostic tools and for designing novel drug combinations targeting the specific mutational signature of a given malignancy. We also describe the role of PD analyses in clinical trials, including for MOA confirmation and dosage regimen optimization during phase 0 trials as well as for correlating molecular changes with clinical efficacy when establishing proof-of-concept in phase I/II trials. Finally, we outline the critical technological developments that are needed to enhance the quality and quantity of future clinical PD data collection, broaden the types of molecular questions that can be answered in the clinic, and, ultimately, improve patient outcomes.

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## 1. Drug mechanism of action: fundamental knowledge for developing therapeutics

Since the earliest days of oncology drug development, mechanism of action (MOA) has served as a guiding principle for: (1) selecting experimental agents with novel MOAs to advance into clinical trials, (2) setting dose schedules of investigational agents, (3) selecting patients who enrich early clinical trial populations with potential responders, and (4) combining drugs with non–cross-resistant MOAs to generate new regimens. The use of pharmacodynamics (PD) during clinical drug development primarily involves the strategy and timing of using MOA knowledge to complement, but not supplant, clinical information in decision making—a form of "rational drug development" that measures the actual molecular target response instead of predicting it from estimates of drug concentration in the tissue [1–3]. Drug development is generally more likely to succeed if the preclinical MOA has been confirmed in patient tumors, so it seems illogical to accept the preclinical MOA *carte blanche* when clinical confirmation in different genomic contexts is possible. Conversely, development is more likely to stall if the MOA of the investigational agent in human patients and preclinical models is different yet this difference never recognized. Thus, in a wide variety of scenarios, the use of PD tools to confirm the preclinical MOA in patients enhances the drug development process.

Because performing invasive biopsies for MOA and other clinical PD studies is a research activity but not a diagnostic one, this process cannot inform the medical treatment of an individual patient. Thus, it is ethically imperative that the value and utility of the acquired MOA knowledge justify the increased risk to the patient from the research biopsies. The crux of the matter is that this knowledge is valuable and useful only when it answers key questions and correctly informs the development of an investigational agent [4], so the only ethical PD studies are those conducted with methodology of sufficient quality to provide reliable and relevant measurements. The primary ethical responsibility for the clinical PD study lies with the team that will collect and analyze

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the research biopsy samples to obtain this knowledge. As described in detail in the following sections, well-designed PD studies that use robust, fit-for-purpose measurement tools to confirm drug MOA in human tumors create an ever-expanding platform of translational and clinical knowledge that is sufficiently reliable for conceiving, building, and prioritizing new clinical trials and drug regimens.

## 2. High-value applications of clinical PD in oncology drug development

Clinical PD assessment usually begins by seeking proof-of-mechanism (POM) evidence in tumor biopsy samples. This fundamental knowledge of the full PD response can be applied in many ways to advance and enhance oncology drug development, including: (1) optimal scheduling of targeted agents based on molecular response rather than plasma pharmacokinetics or toxicity; (2) using the biologically effective dose (BED) rather than maximum tolerated dose (MTD) to achieve a safe yet maximum effect on the molecular target in tumor; (3) creating new, mechanistically based drug combinations capable of directly and safely treating the multiple signaling defects that drive many malignancies; and (4) developing protein biomarkers as improved diagnostics for patient selection. Building on the preceding articles in this issue of *Seminars in Oncology*, the following sections describe several of the potentially high-impact applications of clinical PD.

### 2.1. Proof of clinical mechanism of action

Clinical POM is usually the first application of PD measurements in oncology developmental therapeutics because verifying the MOA of a new compound as it emerges from preclinical development is a foundational step toward its full pharmacological characterization. The inability to confirm the MOA of an investigational agent—or actually disproving the MOA by observing efficacy in the absence of molecular target modulation—means that further development of the agent must be entirely empirical. Additionally, neither the optimization of dosing schedule nor the discovery and evaluation of candidate drug combinations using PD biomarkers is possible without establishing this fundamental property.

This *Seminars* edition is focused on molecular PD, so POM herein refers to confirming that an investigational agent engages its intended molecular target, resulting in the desired alteration of target function. For first-in-human studies, this will most likely be the mechanism of action assigned to the investigational agent during preclinical development. If efficacious, a drug's action on its molecular target should trigger sequential biochemical, cellular, and, ultimately, multi-cellular physiological responses, with the latter manifesting as a clinical response. The sequential steps of an unfolding PD response can be divided into primary (1°), secondary (2°), and tertiary (3°) PD effects, and each of these effect levels requires different PD biomarkers and likely different time points for study.

The 1° PD effect is the first action of a drug on the biological system; for example, the clinical POM for imatinib was assay-based evidence of reversible inhibition of Bcr-Abl kinase activity [5]. A 1° PD effect is considered evidence of target engagement, ie, proof that the drug is interacting with a target and affecting its function. Without this step, no other molecular, biochemical, or physiological changes should occur; if they do, then one must conclude that there are off-target drug effects, ie, engagement of unintended target(s). The 1° PD effect can be any change in the reaction product of any targeted enzyme: for example, an autophosphorylation site of a receptor tyrosine kinase or a phosphoprotein product of a tyrosine kinase. The National Cancer Institute (NCI) conducted the first phase 0 clinical trial in oncology, under the exploratory investigational new drug (xIND) mechanism, using a measured decrease in the reaction product of poly(ADP-ribose) polymerase (PARP) 1/2 catalytic activity to demonstrate the MOA of veliparib [6].

In addition to examining 1° effects by measuring changes in activity of the drug target, POM studies often include evaluation of predicted drug-induced 2° effects, ie, the biochemical changes occurring immediately downstream of the intended molecular target, such as a reduction in phospho-ERK levels after drug inhibition of Raf kinase activity. Subsequent cell biological or physiological responses to these biochemical consequences of target engagement are termed 3° PD effects and include, for example, drug effects on cell cycle progression, apoptosis, effector T-cell–mediated tumor cell cytolysis, and tumor cell migration/invasiveness.

A foundational principle of dose-response is the reversible binding of an agent to its molecular target, the extent of which is determined in real time by measuring the unbound ("free") drug concentration in the microenvironment surrounding the molecular target. The subject of pharmacokinetics (PK) involves the understanding of this unbound drug concentration at the target as a function of elapsed time since dose administration, and this concentration is determined by the combined effects of absorption, distribution, metabolism, and elimination (ADME). The unbound drug concentration at the molecular target is the variable that connects pharmacodynamics to pharmacokinetics, and because of this connection, establishing a PK/PD relationship is an important breakthrough in the understanding of dose-response. Unfortunately, it is highly impractical to measure unbound drug concentrations in the microenvironment or even at a macroscopic level in tumor biopsies, and it is clinically impossible to apply the dense sampling strategy of systemic PK studies to repeated measurements of drug level in tumor for deriving concentration × time profiles. Thus, PK studies often settle for the much more practical measurement of drug levels in plasma, and then assume that tissue and plasma drug concentrations equilibrate rapidly, without actually measuring drug levels in tumor. There is, however, an alternative approach that balances feasibility with scientific rigor; establishing a relationship between plasma drug concentration and 1° PD biomarker response provides some confidence that plasma concentrations of drug can be used as surrogate measurements of drug concentration in the tumor tissue.

Full characterization of a molecular drug response includes the evaluation of PD biomarkers for each of the 1°, 2°, and 3° effect levels that compose the complete drug response. The PD study of a single dose of an investigational agent will usually reveal a change in molecular target status within minutes to hours of dose administration, with biochemical modulation occurring throughout the window of time that molecular target function is sufficiently inhibited. Cellular consequences may be measurable if the single dose is expected to be potentially therapeutic, but the lower doses used for pharmacology studies might not modulate cellular biochemistry for a long enough duration to affect cell biology or physiology. Multiple doses of a reversible inhibitor may be required to detect changes in 3° PD biomarkers because prolonged, perhaps even continually sustained modulation of molecular target function may be required to alter cellular behavior. There is thus the conundrum that single-dose studies provide a purer profile of PD response over time than multiple-dose studies that superimpose 1°, 2°, and 3° drug effects, but unless the single dose shows clinical efficacy, it should not be expected to elicit a robust 3° biomarker response. This is the most likely explanation for the paucity of successful proof of concept (POC) studies associating molecular target modulation with efficacy. With targeted agents, a successful POC study will need to be built upon multiple milestones: POM from a 1° PD biomarker response shortly after administration of the first dose; reproducing the 1° PD biomarker response after multiple doses; a sustainable and perhaps