

ONCOLOGY

Driving Product Development and Finding the Fast Track in Early-Phase Oncology Programs

ABSTRACT

Small- to mid-sized biotech and pharma companies face many challenges when planning and executing an early-phase oncology trial, from performing a regulatory gap analysis and developing a target product profile to identifying the right patients and selecting efficacy endpoints.

Often, early-phase trials involve a class of drug or target that has never been tested in a clinical trial.



Introduction

Sponsors of first-in-human trials of novel oncology compounds face significant challenges. Beyond the typical circumstances of limited budget, compressed timeline, scarcity of skilled clinical trial professionals, and limited knowledge of regulatory hurdles, for many innovative biotech and specialty pharma sponsors, the success of the company depends heavily on the outcome of the trial.

Often, these early-phase trials involve a class of drug or target that has never been tested in a clinical trial. For the purposes of this white paper, we will focus on the following development scenario: Your target is a newly validated mutated receptor that is only present in a limited number of patients with cancer, with no diagnostic test yet approved. And the compound is an antibody-like molecule that inhibits the receptor's activity but also stimulates a potent immune response.

To further complicate matters, much of the preclinical data suggests the compound will synergize with unapproved newer molecules that are in later-stage trials. In this situation, you are co-developing – at a very early stage – biomarkers and diagnostic kits to define those patients who will best respond to your investigative therapy.

In this white paper, we explore the many aspects a company must consider in planning and executing an early-phase oncology trial of this hypothetical compound, from performing a regulatory gap analysis and developing a target product profile to identifying the right patients and selecting efficacy endpoints.

Optimizing regulatory strategy

For emerging and small- to mid-sized biotech and pharma companies with a novel oncology product, the first major goal of clinical development is a first-in-human study – often a Phase I safety, tolerability, and pharmacokinetics study in a limited number of targeted patients with cancer. Unfortunately, these sponsors can be faced with a shortage of skilled clinical trial professionals and limited regulatory knowledge and experience.

Sponsors should keep in mind that various U.S. Food and Drug Administration (FDA) guidance documents are available, summarizing the FDA's current thinking on a broad range of clinical trial-related matters. While these guidance documents are not legally binding, the FDA generally expects the guidance to be followed. However, the FDA is willing to discuss alternative approaches to process management, and sponsors are encouraged to initiate these discussions early in the clinical development program.

Leading with a regulatory gap analysis

A regulatory gap analysis is a subject matter technical review of data content and adequacy to support pre-clinical meetings with the FDA or with regulatory authorities outside of the U.S. The analysis typically includes pharmacology, Good Laboratory Practices (GLP) non-clinical safety, and Good Manufacturing Practices (GMP) information leading to original Investigational New Drug Applications (INDs) or Clinical Trial Applications (CTAs).

Identification of gap analysis differences provides high-level guidance for additional work that may be necessary to resolve data limitations and deficiencies.

Meeting with regulators

In the scenario of a first-in-human trial of a novel oncology compound, a pre-investigational new drug application (pre-IND) meeting with the appropriate oncology team at the FDA is the optimal path to early interaction with FDA reviewers. A pre-IND meeting affords sponsors the opportunity to provide critical background on pharmacology, manufacturing, and non-clinical safety information, as well as to propose in the form of a clinical synopsis their IND-enabling trial.

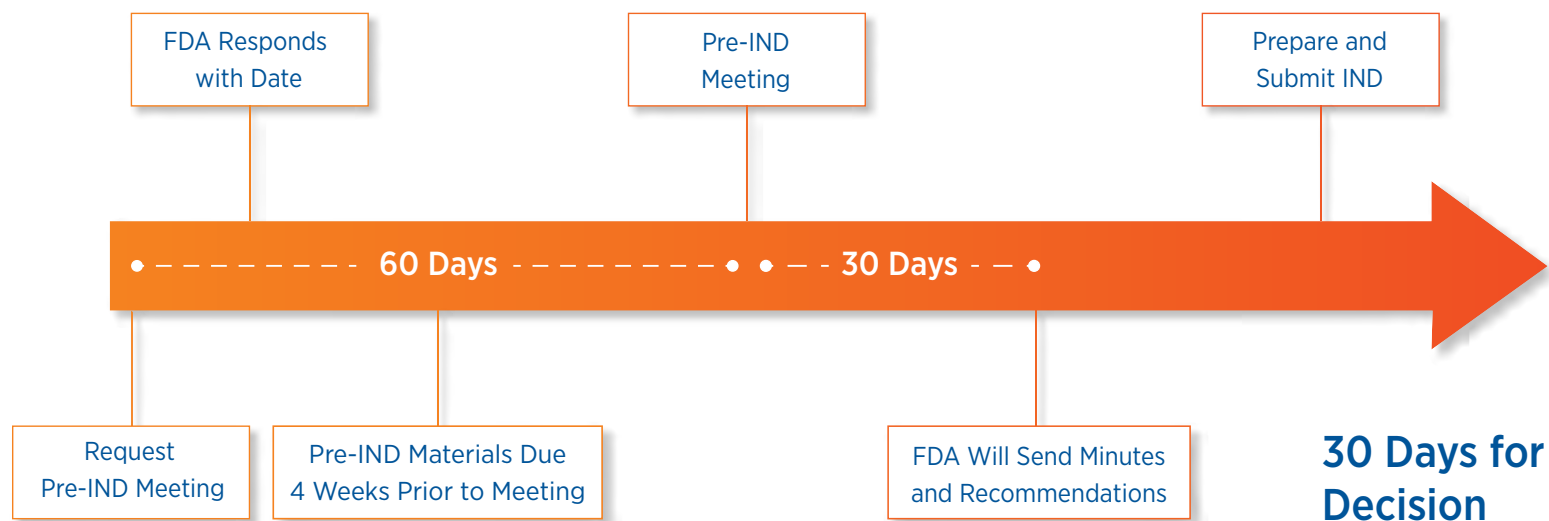
All of this information is included in a pre-IND briefing package and is subject to further review at a later date under the 30-day IND safety review after submission of the actual IND. The FDA Draft Guidance on *Formal Meetings Between the FDA and Sponsors or Applicants* outlines the structure, format, content, and timelines for a pre-IND meeting request as well as the briefing package for submission to support the meeting.¹

Sponsors are advised to expect at least 60 days to elapse between the request for a pre-IND meeting and the meeting itself (see Figure 1). The FDA is allowed 21 days to respond to a meeting request and, in recent years, our experience is that the FDA has typically taken those full 21 days to respond.

The FDA's response may be to grant a face-to-face meeting, to schedule a teleconference, or to provide a written response only. Sponsors should note that pre-IND materials are due four weeks prior to the scheduled meeting, regardless of meeting format, and the FDA will dictate the date of delivery for that pre-IND briefing package.

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Figure 1. Pre-IND Timeline



Generally, 24 to 48 hours prior to the pre-IND meeting, the FDA issues its preliminary comments, giving the sponsor an opportunity to digest the FDA's thinking for further discussion. The purpose of the pre-IND meeting is to obviate any issues that may arise in the context of an IND submission.

Within 30 days after the meeting, the FDA will send both the meeting minutes and its recommendations to the sponsor in hard copy. From there, the timeline for preparing and submitting an IND is contingent upon the extent of additional work that may be required. Once an IND has been submitted, the 30-day safety review clock begins. At the end of 30 days, the FDA is required to render its decision.

Following IND submission and approval, sponsors will need to plan for future milestone meetings with the FDA, such as:

- End of Phase I (EOP1) meetings to discuss the outcomes of a Phase I study, which may create an opportunity to negotiate a shortening of the Phase II/III program
- Type C meetings to discuss the progress of Phase II/III studies and gain further direction from the FDA with regard to specific outcome, endpoint, safety, or efficacy findings or even overall strategy
- Type B meetings, also known as pre-New Drug Application (pre-NDA) or End of Phase II (EOP2) meetings, to present information to support a Phase III program

Optimizing the regulatory pathway

There are several options for accelerating the regulatory pathway for novel oncology programs. In its guidance on *Expedited Programs for Serious Conditions—Drugs and Biologics*, the FDA describes the qualifying criteria for Fast Track, Breakthrough Therapy, and Regenerative Medicine Advanced Therapy designations.²

Some of these accelerated pathways use a surrogate clinical endpoint to receive conditional approval with the requirement to demonstrate adequate and well-controlled data, following approval, that the surrogate endpoint was indeed representative of a beneficial outcome to the patient. The FDA guidance also includes criteria for manufacturing, product quality, and non-clinical considerations as well as guidelines on submission content, structure, and processes.

In the EU, there are similar expedited approval programs for serious conditions, namely the PRiority MEdicines (PRIME) program and the advanced therapy medicinal products (ATMPs) classification – the latter a relatively new initiative on the part of the European Medicines Agency to provide for expedited development of groundbreaking opportunities for the treatment of disease or injury.³

Understanding other relevant regulatory guidance

Other useful FDA guidance documents include:

- **Qualification process for drug development tools.** This guidance describes the qualification process for biomarkers that may be used as endpoints in clinical studies intended to support product labeling. Biomarkers may be used in two different ways in clinical studies. The first way is in Phase II to gather presumptive evidence of clinical efficacy such that there is a rationale to move forward with product development. The second way is in Phase III, where the process has been validated and can be used to support product labeling. This guidance also describes clinical outcome assessments intended to support the demonstration of clinical benefit for product labeling. These assessments include patient-reported, clinician-reported, and observer-reported outcomes, which are discussed at length in a separate FDA guidance, *Patient-Reported Outcomes Measures: Use in Medical Product Development to Support Labeling Claims*.⁴
- **In vitro companion diagnostic devices.** This guidance defines an in vitro companion diagnostic device as one that provides information essential for the safe and effective use of a corresponding therapeutic product. The guidance also describes certain statutory regulatory approval requirements relevant to therapeutic product labeling that stipulates concomitant use of an in vitro companion diagnostic device when its use is essential to the safe and effective use of the therapeutic product.⁵

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- **Co-development of two or more new investigational drugs for use in combination.** In the development scenario on which this white paper centers, the investigational product has the potential to provide additional clinical benefit when co-administered with another late-stage clinical development product. The conditions under which this additional clinical benefit may be explored are described in this guidance, either pre-approval of both products or post-approval of the late-stage product under an IND for expanded labeling claims. This guidance describes processes for determining the appropriateness of co-development and provides guiding principles for both nonclinical and clinical co-development.⁶



Designing a clinical development plan

The clinical development plan is an important document that details the entire clinical research strategy for a drug and, as such, requires multi-disciplinary stakeholder input. A well-designed clinical development plan is crucial for guiding regulatory thinking and should include:

- **Target product profile for labeling**, including desired efficacy and safety profiles, dosage and administration, and how the drug will be supplied
- **Scientific rationale for development**, including chemical and physical composition, nonclinical pharmacology, and toxicology
- **Commercial rationale for development**, including indications, medical need, and marketing opportunity
- **A clinical trial plan**, including all activities from Phase I to Phase IV
- **Regulatory considerations**, including milestone meetings, regulator negotiations, and IND/CTA submission and maintenance
- **Strategic planning**, including key decision points and go/no-go decisions

Sponsors should keep in mind that the clinical development plan is a living document that can and should be revised to address evolving thinking over the course of a clinical development program.

Developing a rational clinical development strategy

Developing a target product profile

When developing a target product profile and considering what is needed to ensure that a product is successful, there are five key technical factors that are substantial contributors (see Figure 2). A sixth factor to consider is the right culture, one that encourages effective decision-making and has the flexibility to adapt as the clinical development program moves forward.

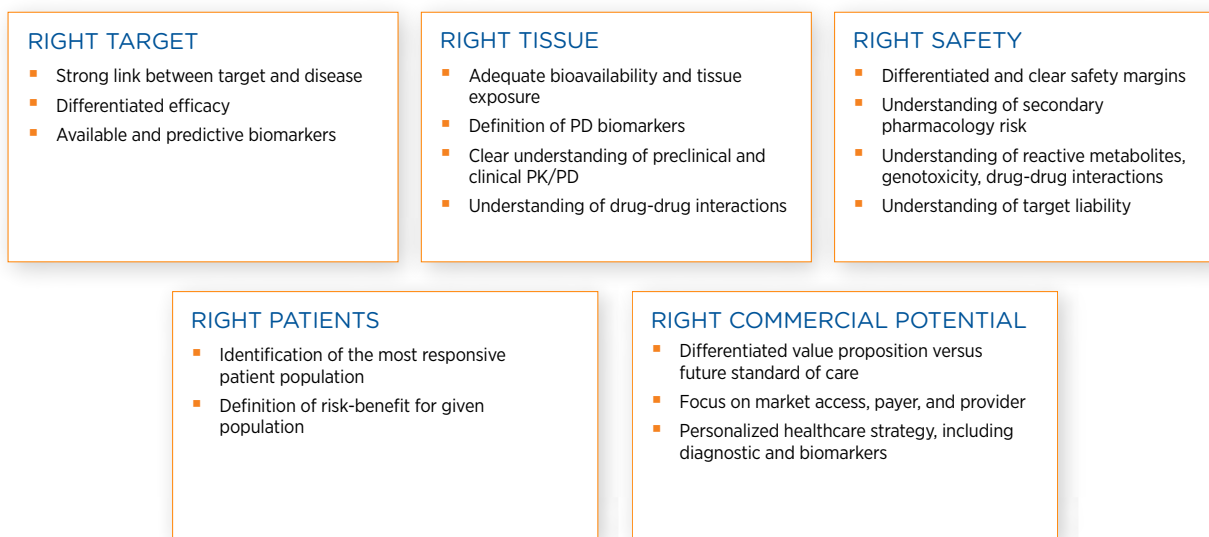
Preparing for additional indications

Increasingly, we are finding that among innovative biotech and specialty pharma companies, early-phase studies are going beyond proof of concept and enrichment cohorts are being conducted in expansion Phase I or Phase II studies. Organizations are using efficacy data to expand their Phase I/II designs and initiate discussions with the FDA regarding accelerated pathways. For small- and mid-sized companies, it is important to understand not only what the budget allows but also how to be nimble enough within study designs to explore additional indications in parallel if the investigative drug demonstrates efficacy in other tumor types during early-phase studies.

Optimizing novel dose combinations

Combination therapy is becoming more common in early-phase studies of immuno-oncology products. Unlike monotherapies, the maximum tolerated dose (MTD) for a combination therapy is not a single number. Instead, it is a space on the dose curve between the two drugs, and the recommended Phase II dose (RP2D) is the point within that space which is predicted to give maximum tumor growth rate inhibition.

Figure 2. The five R's: A five-dimensional framework for predicting product success



Selecting study design

Unlike studies of cytotoxic chemotherapies, which often rely on a traditional 3+3 design, investigations of immuno-oncology products that target tumor mutations may be better suited to a basket-study design. While traditional clinical trials focus on a particular cancer type, basket studies are concentrated on a specific mutation found in the tumor, regardless of where the cancer originated. As such, if the interest is in studying the effect of a specific treatment within a particular biomarker-positive group of patients, a basket study may be an appropriate option.

Another study design to consider is an adaptive dose-escalation design, where a single-dose regimen is used to determine MTD before switching to a multiple-dose regimen to determine RP2D. Adaptive dose-escalation studies may include multiple cohorts and multiple tumor types.

Identifying investigators and sites

It is critical to adopt a data-driven approach to recruitment modeling, which will drive investigator and site selection. In this age of precision medicine, the evaluation criteria for site selection often needs to go beyond simply the availability of – and ability to recruit – patients to include the site’s experience in handling the nuances of early-stage oncology trials.

Medical perspectives in operationalizing early-phase studies

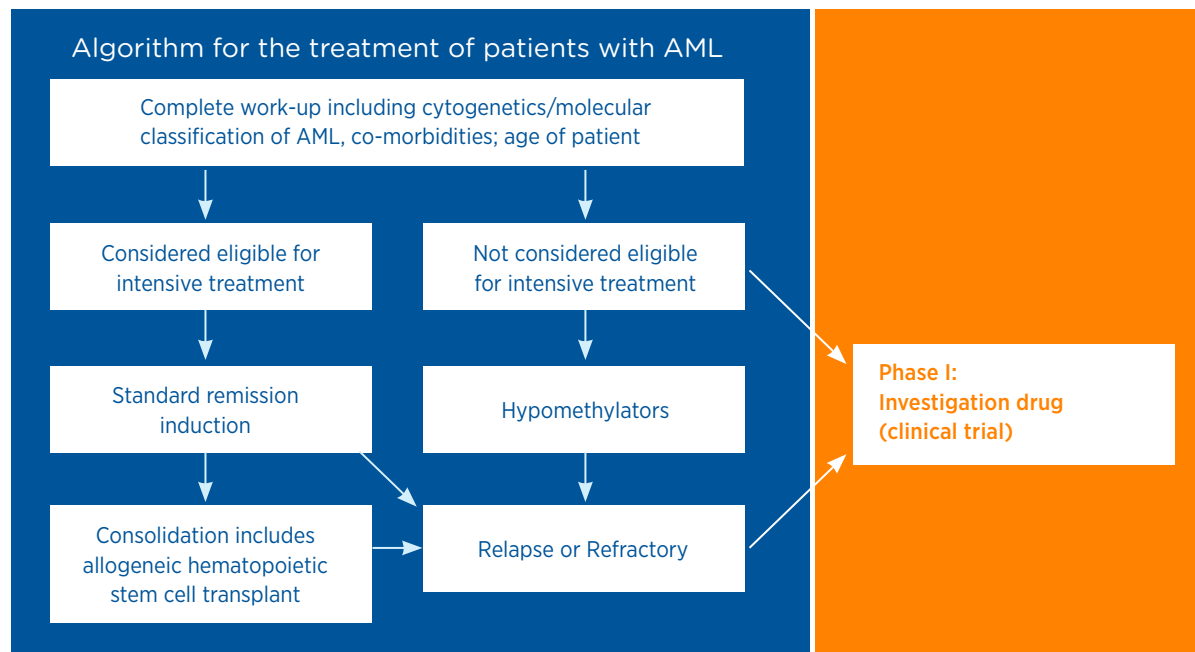
Identifying subjects for Phase I oncology studies

Defining a patient population for a Phase I oncology trial can be challenging due to complexities associated with previous treatment regimens or co-morbidities. The standard treatment algorithm for the indication can serve as a guideline for identifying appropriate subjects and should be applied with thoughtful consideration of individual circumstances. See Figure 3 for an example of how the treatment algorithm for patients with acute myeloid leukemia (AML) may inform identification of subjects for a Phase I study.

The algorithm may be more straightforward in other tumor types where there are standard frontline, second-line, and third-line therapies. In these cases, the novel agent would either be introduced as a last-line therapy or as a third-line therapy, alone or in combination with standard of care.

Of note, healthy volunteers have been included in some first-in-human trials using molecularly targeted agents due to their considerably lower toxicity profiles. Important factors

Figure 3. Identifying subjects for a Phase I AML trial⁷



to consider in the design of oncology trials that include healthy volunteers include careful observation of effects on major organ systems, early detection of adverse effects, limited exposure to the drug, a conservative dosing scheme, and immediate cessation of exposure at the first evidence of toxicity.

The advantages of conducting studies in healthy volunteers include rapid enrollment, investigation of bioavailability/pharmacokinetics, metabolic profiling, dose finding, and the ability to acquire data

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not confounded by diseases. However, extrapolation of results from these studies to patients with cancer might be limited, and the low-dose pharmacokinetics in healthy volunteers may differ from therapeutic-dose pharmacokinetics in patients with cancer. As a result, a careful risk-benefit assessment should be made when planning trials that include healthy volunteers.⁸

Performing an eligibility review

For the purposes of a clinical study, it is important to make sure the patient population is as consistent as possible and exhibits the appropriate marker(s) for treatment. Performing a real-time eligibility review helps ensure that the patient population selected is consistent with the defined disease and the criteria outlined in the protocol.

Typically, subjects in early Phase I studies have limited further-treatment options. Real-time review of eligibility at the time of enrollment will help sponsors:

- Develop an eligibility or slot assignment document to be used by study staff
- Identify critical source documents for medical review to confirm key eligibility criteria
- Establish processes for querying the site regarding eligibility criteria
- Limit turnaround time between submission and approval

The key to this process is communication between the sponsor, contract research organization (CRO), and the sites to ensure that appropriate, eligible patients are available when a slot opens up for enrollment.

Managing cohorts

Cohort management is more art than science, and having a CRO in place that is experienced with cohort management can mean the difference between success and failure. Cohort management involves mission-critical activities related to subject registration, cohort assignment, and dose escalation data review. Cohort assignment is an essential activity, especially for multi-center, global dose-escalation studies, which are typical for Phase I oncology trials. Dose-escalation data review and codification prior to enrolling into the next dose cohort is also essential, not only for subject safety but also for data appropriateness and quality.

Conducting safety reviews and managing dose escalations

Safety review can be conducted in a number of ways, but generally a committee is established and defined in the protocol to oversee all safety aspects of the study. All available safety data in a cohort or across the study, including cumulative information from all dosed patients and any relevant new preclinical information, must be presented to the committee for review. This committee will determine whether it is appropriate to move to the next dose, open up a cohort for the next dose, and comment on any other safety aspects of the study.

The type of safety review committee needed will depend on study design. While independent safety or data monitoring committees are typical for later-stage, blinded, randomized-controlled trials, they may be less appropriate for early-stage, open-label Phase I studies that are not placebo controlled. In Phase I oncology trials, it may be more reasonable and efficient to put together a safety review committee consisting

of medical personnel from the sponsor or CRO, investigators, and other relevant study staff. This allows for more rapid, nimble decision-making.

Dose escalation goes hand-in-hand with safety reviews. Typically, a dose escalation/safety review meeting is convened just after the end of the dose-limiting toxicity (DLT) observation period for the last patient enrolled into the cohort. The purpose of the meeting is to evaluate all the safety data and determine whether to expand the cohort or move on to the next dose. Data reports that might be reviewed include:

- Adverse events, including serious adverse events and deaths
- Toxicity events
- De-escalation events and dose modifications
- Vital signs and physical examinations
- Safety laboratory data and electrocardiograms
- Pharmacokinetic data, if relevant
- Patient profiles

With regard to data management for dose escalation, if the protocol is written in an adaptive fashion, it is best to have a somewhat flexible database design that allows additional cohorts to be entered into the study. While not typical, in some trials efficacy is considered in the determination of dose escalation.

Selecting clinical efficacy endpoints

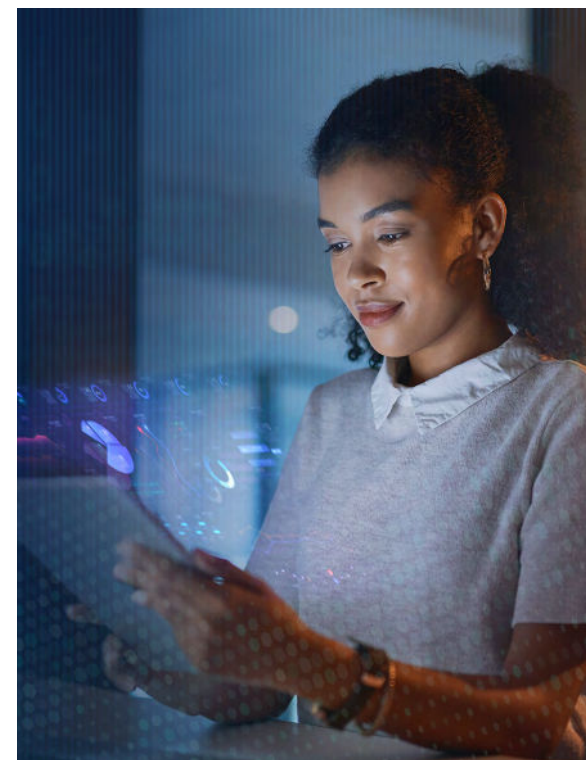
Often, the objective of an early-phase study is more than just safety and dose-finding. Sponsors are interested in getting an early readout on the investigative drug's effect in a particular indication or across a number of indications. To that end, it is important to be consistent in obtaining and reviewing efficacy data.

There are a number of published efficacy endpoint review criteria, for example the Lugano criteria for Non-Hodgkin's lymphoma. These published criteria can help guide investigators in assessing patients. For study participants, the use of efficacy endpoints can inform decisions around when to withdraw from experimental therapy and consider other lines of treatment.

If efficacy endpoints are to be considered as part of a go/no-go decision, sponsors may consider convening an endpoint adjudication committee. These types of committees are tasked with helping to interpret data in a consistent fashion or to limit confounding of more sophisticated or more complicated endpoint assessment. Typically, endpoint adjudication involves central reading of some component of the endpoint – often radiographic imaging studies – to provide consistency.

Conclusion

There are a multitude of factors to consider and challenges to overcome when developing early-phase oncology programs. However, biotech and specialty pharma sponsors are not alone. There are many highly skilled individuals and organizations available to help plan and execute studies of novel oncology compounds. Some contract research organizations specialize in these scenarios and can help sponsors meet their goals, ideally getting involved immediately after – if not before – sponsors meet critical funding milestones. Adopting a one-team approach and an agreed-upon definition of attainable objectives combined with a strategic clinical development plan not only improves the likelihood of meeting study objectives but also sets the stage for successful development of more advanced trials.



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About Premier Consulting

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Our end-to-end solutions in strategy, regulatory, nonclinical, clinical, CMC, quality, and commercial help sponsors build and execute development plans that meet regulatory requirements and deliver results for sponsors and the patients they serve.”