Maximizing Success in Early Stage Oncology Trials: Considerations and strategies in the era of molecularly targeted agents

Abstract

Making a meaningful impact on the survival and quality of life of patients with cancer remains a significant challenge. In this white paper, we discuss considerations and strategies for maximizing the likelihood of success in early phase oncology trials and developing significantly improved therapeutics for patients.
Background
The success rate of investigational compounds eventually approved for clinical use in cancer remains the lowest among all diseases. Of the more than 750 drugs currently under development for the treatment of cancer, it is predicted based on past performance that only a few will ultimately demonstrate sufficient efficacy and safety for regulatory approval and clinical use. The likelihood of approval for investigational oncology drugs tested in Phase I trials is only 6.7 percent, the lowest among all therapeutic areas. Furthermore, the drug development process in oncology is estimated to take 1.5 years longer than in other diseases, likely due to slow recruitment and the long study duration needed to assess survival endpoints.

However, progressive regulatory policies, a favorable political climate, increased funding for cancer start-ups, and improved scientific and clinical approaches to developing cancer therapeutics are beginning to alter the status quo. These trends promise to increase approval rates, bringing better and more numerous therapeutic options to cancer patients.

Today, due to a global focus on cancer, most therapeutics are molecularly targeted agents (MTAs) which are less toxic, more effective and tailored toward specific mutations or pathways altered in patients. MTAs comprise a vast array of different molecules and approaches, but all are generally designed to engage specific cancer-dependent targets and specifically kill cancer cells. Advances in our understanding of the molecular pathogenesis of cancer have led to increased interest and use of in MTAs.

The first two MTAs – imatinib and rituximab – were launched in 1997, and now, molecularly targeted agents represent the vast majority of new oncology drug approvals. Over the past decade, the number of novel anticancer drugs in development has risen.
Applying Quality by Design to the Rare Disease Population: Special Considerations

Exponentially, in 2015, the U.S. Food and Drug Administration’s Center for Drug Evaluation and Research (CDER) approved 45 novel drugs, more than the average number approved annually during the past decade.

Enhancing the probability of success using a disciplined framework to assess pipeline quality

A key challenge for every sponsor is maintaining research and development productivity at a sustainable level amidst a changing regulatory landscape, a challenging reimbursement environment, escalating clinical trial costs and the rigor involved in improving existing therapies. A longitudinal review of AstraZeneca’s small-molecule drug pipeline has yielded a framework for assessing pipeline quality and project success, which is still applicable to sponsors of oncology drugs who are seeking to minimize development costs and maximize new drug output. The most critical factors for increasing the probability of successful transitions to later-stage trials include:

**Right target**

Gather the necessary data to demonstrate a clear linkage of the target to the disease. This may include:

- Direct evidence of target linkage to human disease
- A well-validated animal model or good platform of data from preclinical studies
- A strong understanding of the biological underpinnings of the target or disease
- Validated efficacy biomarkers

A high level of confidence in the biological role of the target in human disease is a predictor of successful projects and provides a basis to direct studies to strengthen or invalidate the scientific hypothesis.

**Right tissue**

Establish candidate drug bioavailability and/or pharmacological engagement in the target organ. The probability of success is increased if appropriate pharmacokinetics/pharmacodynamics...
Rightsafety
Develop an appropriate safety profile. There is a crucial need for sponsors to pay attention to preclinical safety signals as these signals typically become more problematic as a project progresses, resulting in project delays - or even closures. Although safety signals may sometimes be unclear or difficult to translate from preclinical models to humans, applying robust criteria for safety will help prevent progression of molecules that are likely to fail in later-stage clinical trials.

Rightrt patients
Test the compound of interest in the correct patient population. High confidence in patient selection positively correlates with molecule progression to later-stage clinical trials, and projects with clear patient stratification plans demonstrate a greater likelihood of success. Development plans should target the optimal patient population based on the current scientific understanding of the disease. Ideally, patients can be identified and stratified using a predictive biomarker. In the absence of a biomarker, patient selection can be based on known markers of disease stratification or a series of potential biomarkers examined during the trial and analysed retrospectively.

Rightsocialpotential
Ensure alignment of scientific opportunity with commercial insight and value. The commercial potential of a molecule - its potential to deliver a medically differentiated and commercially viable product - should be used to guide project development. In order to determine the commercial potential of the compound of interest, it is critical to have a detailed understanding of current and future standards of care, as they dictate what is required for a new medicine with respect to efficacy and safety. It is important to note that it is becoming essential to incorporate Health Economics and Outcomes Research (HEOR) early on in the development of therapeutics. Companies and other stakeholders of a therapeutic must be able to demonstrate both economic and clinical evidence to providers, healthcare decision-makers and payers.

It is also important to define the market opportunity based on the:
+ Unmet medical need
+ Size and geographical distribution of the patient population
+ HEOR
+ Cost of the development program
+ Overall program risk and probability of success

Evaluation of these factors requires the right culture, as well as clear communication among the scientific and commercial teams within the company.
Throughout every phase of early research and development, it is crucial for both scientists and clinicians to gain a confident understanding of the disease biology, the relationship of the target to the disease indication, and the proposed mechanism of action of a potential drug in the context of the right patient. Coupling this understanding with the best regulatory and clinical strategy will also enhance the probability of success. Following this framework may help sponsors ensure that only those molecules with sufficiently promising data and commercial value are taken into, and through, clinical development.

**Target product profile**

In addition to examining your potential therapeutic pipeline, it is also useful to implement a framework that uncovers critical areas of risk and supports success. Creating a target product profile can also help sponsors objectively assess the quality of an investigative compound and its potential for success. A target product profile (TPP) is a multidisciplinary strategic development process tool that summarizes a drug development program in terms of future labelling concepts and facilitates discussion between the FDA and the industry. The TPP is a dynamic document that defines the value proposition and key differentiators of a compound of interest, and used to guide program development strategy.

A well-structured TPP comprises a comprehensive analysis of various aspects of a potential new product in comparison to a competitor product or standard of care, including:

- Desired indications
- Safety and efficacy claims
- Pricing and reimbursement
- Product valuation for each indication
- Differentiating product features and leading claims
- Exclusivity measures

Understanding treatment patterns and market trends, as well as the potential indications, claims and commercial value associated with a product, aids in focusing research and development efforts.

The process of developing a TPP helps align regulatory, preclinical, marketing, and HEOR strategies for a compound of interest from early-stage development to market entry. It also streamlines the research involved in validating a compound for development by leveraging multidisciplinary expertise and facilitating cross-functional communication. In addition, having a TPP in place helps sponsors understand what can be achieved with current financing, as well as key points where additional financing will be needed.

Keep in mind that the TPP should be a living document that is revisited and revised, as needed, throughout the course of product development. Ultimately, the TPP provides the framework for product labelling.

**Regulatory strategy & expedited approval pathways**

Sponsors of oncology compounds may be able to leverage expedited development and review methods designed to help bring important medications to the market as quickly as possible:

- **Fast Track** speeds new drug development and review for drugs with the potential to address unmet medical needs by:
  - Increasing the level of communication the FDA allocates to sponsors
  - Enabling CDER to review portions of a drug application before submission of the complete application, i.e., rolling review
Breakthrough status is designed to help shorten the development time of a potential new therapy. It is applicable to drugs with preliminary clinical evidence demonstrating that the drug may result in substantial improvement on at least one clinically significant endpoint over available therapies. A breakthrough therapy designation includes all of the Fast Track program features, as well as more intensive FDA guidance on an efficient drug development program.

Priority Review is reserved for situations in which CDER has determined that the investigational drug could potentially provide a significant advance in medical care. For priority review, CDER sets a target to review the drug within six months instead of the standard 10 months. Note that, in some instances, priority review is assigned as a result of the sponsor redeeming a voucher under CDER’s Priority Review Voucher Program.

Accelerated Approval allows early approval of a drug for a serious or life-threatening illness that offers a benefit over current treatments, speeding the availability of the drug to patients who need it. This approval is based on a surrogate endpoint or other clinical measure that is reasonably likely to predict a clinical benefit of the drug. Once Accelerated Approval is granted, the drug must undergo additional testing to confirm that benefit.

Orphan Designation enables sponsors to benefit from significant tax incentives, enhanced patent protection and marketing rights, clinical research subsidies, close coordination with the FDA throughout development, and priority FDA review with application fee waivers.

Approximately 60 percent of CDER’s approvals for novel drugs in 2015 were designated in one or more of these expedited approval pathways.

### Trial design strategies

**Phase I trials in oncology**

A Phase I trial represents the critical transition of a novel compound from the preclinical to clinical stage. As such, it serves as the foundation for future development. To accommodate the differences between MTAs and traditional cytotoxic agents, the landscape of Phase I oncology trials is evolving to adapt to these novel, targeted therapies and to improve the efficiency of cancer drug development. Sponsors need to be aware of this changing landscape in order to expedite the clinical translation of their investigative compounds into new cancer therapies and increase the probability of success.

To accelerate drug development, these new expedited approval pathways require demonstration of efficacy in early-phase trials. Conventionally, Phase I oncology trials have been designed to characterize the safety, tolerability and maximal tolerated dose (MTD) of a novel agent by enrolling patients with a wide range of advanced-stage cancers that have been refractory to standard therapy. With the emergence of MTAs, novel approaches related to dose escalation, patient selection and study endpoints are gaining popularity in Phase I studies.
Applying Quality by Design to the Rare Disease Population: Special Considerations

New dose-escalation schemes, including accelerated titration and model-based designs, enable faster dose escalation and/or more precise dose determinations using statistical modelling that incorporates data from all previously treated patients. They may also result in fewer patients enrolled per cohort at sub-therapeutic doses and a higher percent of patients treated at the RP2D (recommended Phase II dose), the maximal dose with acceptable toxicity. With the various dose-escalation schemes now available, selecting the optimal trial design may mean the difference between success and failure in a Phase I trial of a targeted therapy.

### Improved patient selection based on genetic or molecular biomarkers

Most cancers arise from mutations in multiple oncogenes, rather than from alterations in a single gene. As a result, even within the same cancer type, individual tumors are driven by distinct sets of dysregulated pathways. This heterogeneity underlies the observed variability in responses to MTAs, which are typically active only in a sub-group of patients with a predictive biomarker.

Increasingly, Phase I trials are being used as a platform to explore predictive biomarkers and enable early evaluation of an investigative product’s efficacy by selecting patients who are likely to respond based on certain molecular criteria. When used appropriately, this approach can improve the efficiency and safety of drug development.

However, there are challenges inherent to identifying and incorporating biomarkers in early-stage trials since targeted therapies are likely to engage – and be modulated by – several signaling pathways. Thus, establishing a very strong scientific basis for the biomarker with preclinical validation is a prerequisite for using it for patient selection. Many sponsors will include a...
comprehensive series of potential biomarkers and even global “omic” (e.g., proteomic, metabolomic) analyses with the desire of finding a correlative patient selection biomarker(s) from retrospective analysis undertaken after efficacy is determined in clinical trials.

**Changes in study endpoints**

Traditionally, the primary endpoint of a Phase I clinical trial has been toxicity, with efficacy considered only as a secondary outcome. Now, with the breakthrough therapy designation created by the FDA to expedite drug development, obtaining early evidence of efficacy has become a key objective of many Phase I studies. At times, the use of efficacy endpoints with demonstration of clear clinical benefit in the Phase I setting can lead to the direct transition to a Phase III study. In fact, tumor response rate at the recommended Phase II dose (RP2D) as an efficacy endpoint contributed to over 75 percent of accelerated oncology drug approvals by the FDA from 2002 to 2012. Moreover, the use of toxicity as the primary determinant of the RP2D for targeted therapies is controversial. Several studies have shown that, unlike cytotoxic chemotherapy agents, the efficacy of MTAs might not be reliably predicted by either toxicity or dose. When determining the RP2D for MTAs, alternate endpoints that reflect target modulation and downstream molecular effects (e.g., levels of protein expression in tumor tissue or levels of serum proteins) may be more relevant surrogates of activity than toxicity. As such, the PK/PD evaluation of MTAs has become an essential part of Phase I trials and sponsors may also wish to include “omics” analysis to determine the best biomarkers for PD effects.

For sponsors studying immunotherapies, it is important to consider how disease progression is defined, as this may significantly impact whether or not patients are permitted to continue with investigative treatment. Standard Response Evaluation Criteria In Solid Tumors (RECIST) rules define progression as the development of any new lesion and may not be as relevant as immune-related response criteria (irRC), which look at the entire tumor burden and may allow more comprehensive evaluation of response patterns.

**Figure 5. Immune-related response criteria (irRC)**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>New measurable lesions (≥ 5 x 5mm)</td>
<td>Incorporated into tumor burden</td>
</tr>
<tr>
<td>New, nonmeasurable lesions (&gt; 5 x 5mm)</td>
<td>Do not define progression (but preclude irCR)</td>
</tr>
<tr>
<td>Non-index lesions</td>
<td>Contribute to defining irCR (complete disappearance required)</td>
</tr>
<tr>
<td>CR (Complete Response)</td>
<td>Disappearance of all lesions in two consecutive observation not less than four weeks apart</td>
</tr>
<tr>
<td>PR (Partial Response)</td>
<td>≥ 50% decrease in tumor burden compared with baseline in two observations at least four weeks apart</td>
</tr>
<tr>
<td>SD (Stable Disease)</td>
<td>Neither a 50% decrease in tumor burden compared with nadir can be established</td>
</tr>
<tr>
<td>PD (Progressive Disease)</td>
<td>At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least four weeks apart</td>
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Combination studies

Due to the intrinsic heterogeneity of most cancers, combinations of MTAs with another targeted therapy or standard chemotherapy may yield more clinical benefit than monotherapy alone. Hence, Phase I trials of combination therapies are becoming increasingly common. Combination therapy is also an attractive strategy for counteracting the inherent or acquired resistance mechanisms associated with some MTAs. If a sponsor is considering a combination study, it is important to compile evidence supporting the rationale for the drug combination – and the appropriate drug sequencing – prior to designing the trial.

In their guidelines for the design of Phase I trials, the Clinical Trial Design Task Force of the National Cancer Institute’s Investigational Drug Steering Committee (IDSC) recommends:

- A clearly-established pharmacological or biological rationale justifying the drug combination that is supported by preclinical and/or clinical data,
- A sound development plan for future Phase II trials of the combination,
- Careful consideration of overlapping toxicities and PK/PDs, and
- Appropriate selection of a study design based on the probability of interactions

Exploratory or microdosing trials

Also known as Phase 0 trials, exploratory or microdosing trials can potentially reduce development time and cost by informing and accelerating further clinical decision-making. Among other things, Phase 0 trials may be used to refine a biomarker assay using human tissue, develop a novel imaging probe, determine a dose range and administration sequence, or further evaluate human PK/PD prior to Phase I testing. Generally, these trials have lower regulatory hurdles, but it should be noted that they are primarily designed to investigate how preclinical data translate into humans and are not intended to observe response. Nonetheless, they may be useful in preparing to conduct a more comprehensive Phase I/II trial and enhance the probability of success in those trials.

In some instances, healthy volunteers are now being included in First in Man (FIH) trials using MTAs due to their considerably lower toxicity profiles. Important considerations in the design of anticancer 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 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 not confounded by diseases. However, extrapolation of results from these studies to cancer patients might be limited and the low-dose pharmacokinetics in healthy volunteers may differ from therapeutic-dose pharmacokinetics in cancer patients. As a result, a careful risk-benefit assessment should be made when planning trials that include healthy volunteers.
Considerations for the clinical development plan

There are three key areas that should be covered in the clinical development plan for oncology trials of a novel compound:

**Unmet medical need**

One approach for determining unmet need involves evaluating standard treatment algorithms and identifying groups of patients who are not considered eligible for available treatments. For example, in acute myeloid leukemia (AML) – where incidence increases almost fourfold for patients over the age of 65 and 80 percent of patients relapse – there is an unmet medical need for therapeutic alternatives for patients who are not considered eligible for intensive treatment according to the standard treatment algorithm.

**Clinical development timeline and feasibility**

The clinical development timeline may include monotherapy studies and/or combination studies, and should take into account feasibility, eligibility for expedited approval, standard of care, and the larger competitive landscape. The timeline must be data-driven, including anticipated country/site mix and enrollment rates. The timeline should also indicate which studies can be completed with available funding, and which will require additional funding.

When evaluating the clinical development plan, it is useful to consider the following:

- What are the relative advantages and disadvantages of conducting the study through an investigator-initiated trial versus a sponsored study?
- Is there sufficient safety information to proceed to the next phase?
- Is there strong, indication-specific scientific rationale to support the decision to proceed?
- Is there a clear, well-defined biomarker/companion diagnostic strategy?
- Are the timelines and costs realistic?
- What is the return on investment?

As discussed above it is important to think about the entire clinical strategy including pivotal registration trials even before planning your FIH study. Upon Phase I date becoming available the strategy for Phase II can be finalized.
Beginning with the end in mind: planning for Phase I/II trials

If strong, indication-specific safety and efficacy data now exist to support the decision to proceed to a Phase II trial, sponsors must turn their attention to designing a Phase II trial that can most accurately predict the success of later stage studies.

Traditionally, the single-arm Phase II study was the principal mechanism for deciding whether to proceed to a randomized Phase II trial. These Phase II trials frequently used response rate as the primary endpoint and were powered to yield a reasonably low false-negative rate. Due to the relatively small number of patients enrolled and the reliance on historical controls for estimating expected response rate, these single-arm Phase II studies were associated with a fairly high false-positive rate.25

With the emergence of MTAs, many of which show some measure of activity in single-arm Phase II trials, it has become clear that the ability of the standard Phase II platform to accurately predict Phase III is low. In fact, approximately 60 percent of oncology regimens that demonstrate promising activity in single-arm Phase II trials fail to demonstrate superiority in the Phase III setting.26 As such, the rigor with which Phase II trials are conducted must be increased.

The randomized Phase II trial is a well-known platform for testing the efficacy of novel oncology agents and has the potential to minimize some of the pitfalls inherent in the single-arm Phase II design.27 Randomized Phase II trial designs fall into three main categories:

1. Randomized selection, or pick the winner, in which the best of two or more arms is selected for further evaluation. Typically, this design does not involve a standard therapy control. Instead, patients are randomly enrolled into two or more experimental arms, often evaluating different doses or schedules. As there is no formal attempt to compare any of the experimental arms with another, this design may be thought of as conducting several Phase II trials in parallel and can accelerate the transition between Phase II and Phase III testing. Increasingly, sponsors are applying randomized selection designs in the expansion phase of the Phase I setting, rather than waiting till Phase II, to maximize the efficiency and cost-effectiveness of their clinical development program.

2. Randomized comparison, in which a formal statistical comparison is made between the control and experimental groups. For these studies, the control group could be either placebo or standard therapy. The typical goal of this type of study is to identify promising experimental regimens that have a high likelihood of success in the Phase III setting. Given the desirability of making a go/no-go decision earlier and earlier in the development process, the Phase I expansion phase is often used to determine descriptive safety and efficacy information with the aim of identifying the dose and standard for a randomized comparison Phase II study. The hazard ratio requirements need to be set very high at the Phase II stage of a molecule’s development to support a Phase III investment decision.

3. Randomized discontinuation, in which all patients receive the investigative agent. Those who respond continue treatment, those who are clinically adverse or experience toxicity discontinue treatment, and those with stable disease are randomized to continue or discontinue therapy in a double-blind manner.28 This may be useful for evaluating drugs whose major predicted effect is disease stabilization. Randomized discontinuation designs also represent interesting possibilities for the future development of combination therapies using two checkpoint inhibitors or immunomodulators.
In order to maximize the predictive value of a Phase II trial, sponsors should have a prospective statistical plan for evaluating the data from these studies to minimize the false positive rate. Whenever possible, the endpoints of the trial should be tailored to the drug’s anticipated mechanism of action. For example, if a drug is expected to prolong the duration of stable disease, it may be more appropriate to use progression-free survival (PFS) as an endpoint, rather than response rate.

A SWOT analysis may be a useful tool for sponsors and development committees to employ in making the decision of whether or not to proceed to a randomized Phase II trial.

**Partnering with a CRO**

Early-stage oncology drug development presents both challenges and opportunities for sponsors, many of whom are new to the development process. A contract research organization (CRO) partner can help sponsors understand and navigate the changing landscape of Phase I-II oncology trials. The right CRO can assist with many aspects of a clinical trial development program, including:

- **Strategic planning**, to assist the sponsor in creating the best regulatory and clinical plan to meet their short-long term objectives.

**Figure 7. Making the gating decision to invest in Phase II**

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluate PFS, OS, response rate</td>
<td>High bar for success</td>
</tr>
<tr>
<td>Conventional development path</td>
<td>False +ve/-ve Phase III</td>
</tr>
<tr>
<td>Opportunities</td>
<td>Threats</td>
</tr>
<tr>
<td>Biomarker data</td>
<td>Establish predictive biomarker</td>
</tr>
<tr>
<td>Determine CR</td>
<td>High competitive environment for registration path</td>
</tr>
</tbody>
</table>

**Conclusion**

This is an exciting time to be in oncology research and development, as scientific advancements have led to earlier and better cancer detection; improved ways of managing side effects; and increased survival among patients with cancer. From 1975 to 2010, there was a 19 percent improvement in five-year overall survival in patients with cancer. However, today, two out of three patients diagnosed with cancer survive at least five years. From October 2014 through October 2015, the FDA approved 10 new cancer treatments, one new cancer prevention vaccine, 12 new uses for previously-approved cancer therapies, and one new use for a device. In the first quarter of 2016, the FDA already approved two drugs for the treatment of cancer. These facts demonstrate the FDA’s commitment to accelerating the review and approval of medicines likely to enhance patient care. With proper planning, a well-designed development strategy, and the right CRO partner, sponsors can maximize their likelihood of success in early-phase oncology trials.
References

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Premier Research is a leading clinical development service provider that helps highly innovative biotech and specialty pharma companies transform breakthrough ideas into reality. The company has a wealth of experience in the execution of global, regional and local clinical development programs with a special focus on addressing unmet needs in areas such as analgesia, CNS, oncology, pediatric and rare disease. Premier Research operates in 84 countries and employs 1,000 professionals, including a strong international network of clinical monitors and project managers, regulatory, data management, statistical, scientific, and medical experts. They are focused on smart study design for advanced medicines that allow life-changing treatments.