6 Critical Factors for Achieving Success on the Accelerated Approval Pathway for Oncology Drugs

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Cancer drug development is changing fast. Biotech and pharmaceutical organizations are leveraging genomic insights and enhanced computing power to create precision medicines that challenge cancer's defenses through distinct mechanisms of action. Based on the genomic profiles of patients and their tumors, oncologists can now select from an increasing range of targeted treatments that attack cancer and minimize adverse effects.

To keep pace with this unprecedented acceleration in oncology research and development, the regulatory landscape is evolving rapidly. The number of US Food and Drug Administration (FDA) approvals of novel new oncology drugs has doubled over the past 2 years,[1] in part due to the expansion of expedited approval programs to include the breakthrough therapy designation that provides opportunities to interact with regulators early in the clinical trial process.[2,3] In 2015 alone, 16 of the 45 novel new drugs (NNDs) approved by the FDA's Center for Drug Evaluation and Research (CDER) were oncology treatments (see Figure 1).[1,3]

Figure 1.

**Rise in Oncology Novel New Drug Approvals**[1]
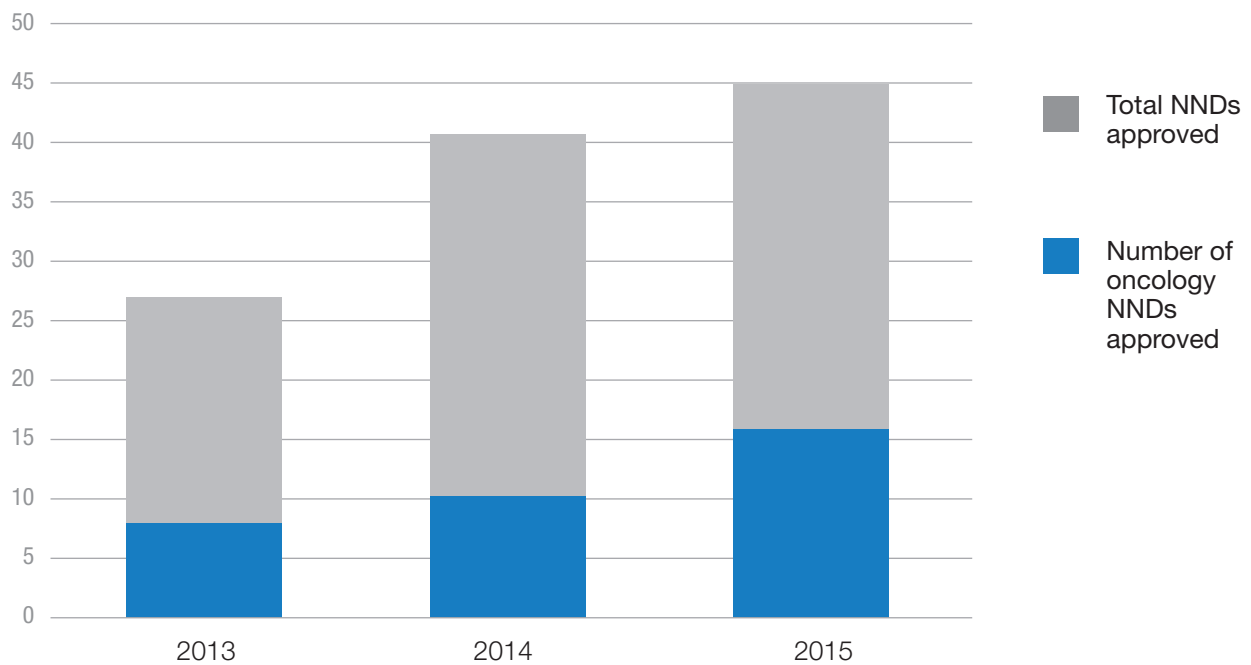
In this high-stakes, high-velocity environment of oncology drug development and regulatory approval, biotech companies face significant competitive pressure to move quickly from first-in-human to proof-of-concept. It is imperative to design smarter clinical trials that deliver both speed and strength. From the outset, trials must be designed to ensure collecting the best evidence in the right patients, at the right time, more cost-effectively than ever before. Here are 6 critical factors for achieving success on the accelerated approval pathway.

1. Develop custom biomarkers and assays.

Scientists who focus exclusively on developing novel molecules may not have the bandwidth or expertise to develop robust biomarker strategies. However, they should strongly consider outsourcing that development, since integrating custom biomarkers into drug trials greatly improves the probability of success. From 2006 to 2015, drug applications with biomarkers had a higher likelihood of approval across all phases of development. Overall, from phase 1 to approval, applications with biomarkers achieved a 3-times greater probability of approval (25.9%) compared with applications without biomarkers (8.4%) (Figure 2).[4]

Figure 2.

Probability of Success With or Without Biomarkers[4]

Without biomarkers | With biomarkers
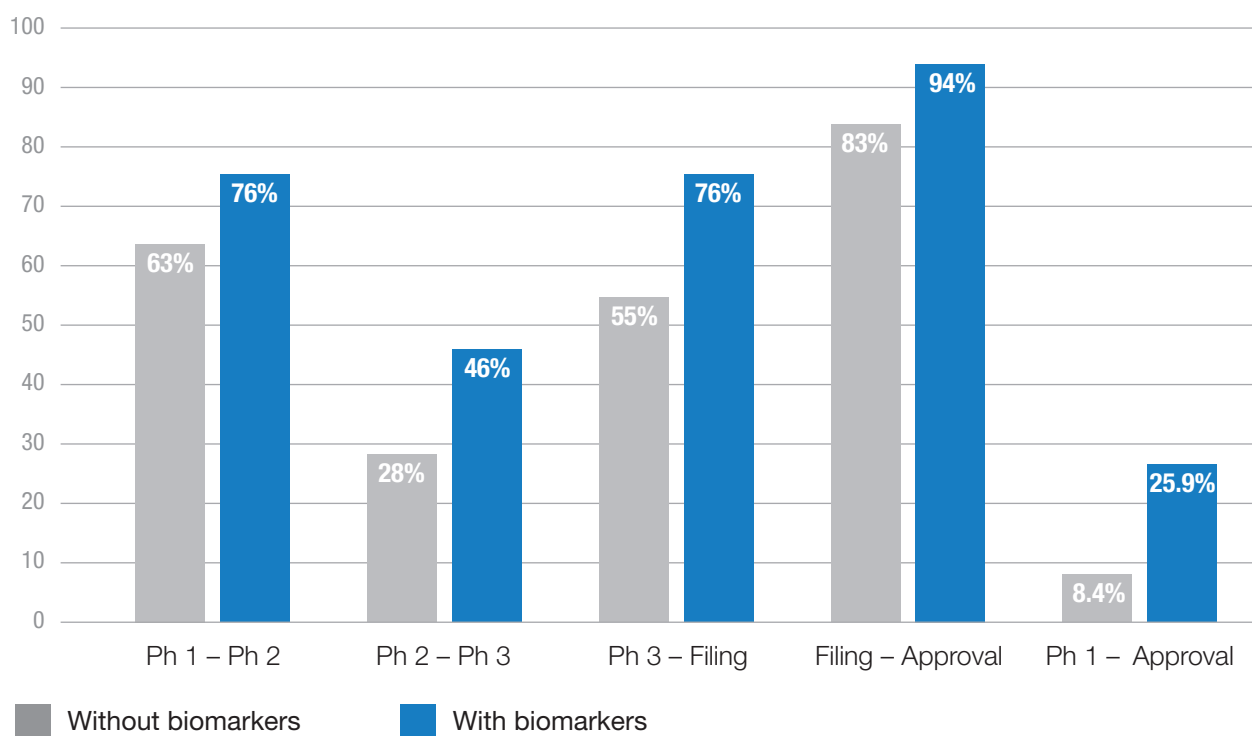
The FDA approved 39 oncology drugs from 2011 to 2015. Of these, 15 included biomarker evidence, more than triple the 4 cancer drugs approved with biomarker evidence in the 5-year span from 2005-2009.[5]

Whether the ideal measurements include taking blood, serum, or tissue samples, the right biomarkers and assays need to be developed before clinical trials begin. Incorporating biomarker strategies into clinical trial design allows researchers to identify responders, optimize doses, and narrow results for further study, facilitating regulatory review and maximizing return on investment.

It's also important to begin thinking about the downstream regulatory implications for potential companion and complementary diagnostics. "Drug developers need to decide if the biomarker will be a lab-based test, a companion diagnostic, or only used as a research-based assay for premarket approval, and evaluate which approach is worth investing in," says Deborah Phippard, PhD, Vice President, Research Services with Precision for Medicine. A good example of a drug that achieved accelerated approval with a companion

diagnostic is Xalkori® (crizotinib), which was approved by the FDA in August 2011 for late-stage non–small cell lung cancer, together with the Vysis ALK Break Apart FISH Probe Kit that identifies patients with the abnormal ALK gene.[6]

2. Measure the right patient population with an optimized trial design.

By identifying the patients most likely to respond in advance, trials require fewer patients, saving time and money. "Preselecting participants so that only those with certain molecular subtypes of cancer are included in a trial significantly improves the opportunity of achieving response rates in a greater number of patients, in a shorter time frame," says Patricia Devitt, PharmD, President of Precision Oncology.

Conventional studies with sequentially planned phases 1, 2, and 3 are "old school." With modern adaptive trial design, one or more of the study aspects are modified as the trial progresses. By combining insights from clinical outcomes and biomarkers, seamless transitions between "phases" can be built into fewer protocols from the beginning. Researchers can discontinue groups that are not responding and focus on the ones that are. Drug developers gain improved insight into a compound's effect early and can move quickly from proof-of-concept to potential approval with a much smaller number of participants compared to conventional studies.

A recent oncology drug approval that illustrates the benefits of adaptive trial design is Venclexta™ (venetoclax), which received approval in April 2016 based on a single-arm study of 106 patients. The drug targets the B-cell lymphoma 2 (BCL-2) protein that supports cancer growth in patients with relapsed or refractory chronic lymphocytic leukemia who have the chromosome 17p deletion and had received at least one other therapy. In the initial dose-escalation phase, 56 patients received 1 of 8 treatment doses. Learning from this phase informed adjustments to the dose-escalation schedule for an expansion cohort of 60 patients. Study results showed that 79% of participants experienced partial or complete cancer remission.[7,8]

3. Build economic analysis into trial design from the start.

While novel cancer therapies can provide improvements in patient outcomes, patients and payers alike want to know if they are worth the increased cost compared to standard of care. Economic analysis speeds market acceptance and improves acquisition potential after regulatory approval. "Collecting the appropriate economic and clinical data in parallel with clinical trial development can lead to rapid payer acceptance," says Gerry Messerschmidt, Chief Medical Officer of Precision Oncology. By incorporating pricing and reimbursement metrics into the protocol earlier in the process, drug developers can avoid finding out after regulatory approval that payers will not cover a novel compound, even if it performed well in trials or if it comes with a companion diagnostic.

Consider the right valuation metrics before trials begin. "In the pretrial phase, drug developers need to know which end points are relevant to payers and providers for the particular disease area, and what additional evidence payers need to make a decision to pay for the drug," says Jason Shafrin, Director of Healthcare Quality and Value-Based Research Methods at Precision Health Economics. For example, a trial with an end point of overall survival takes longer but earns more ratings points than a trial with an end point of progression-free survival in the American Society of Clinical Oncology Value Framework, one of several decision-making tools that various organizations have developed to help determine the net health benefit for available alternatives.[9,10]

The cost-offset evidence that payers need to see to make a decision to pay for a drug varies by disease and by therapeutic format. It's important to look for disease-specific cost offsets from a healthcare system perspective. For example, a new multiple myeloma drug may reduce the number of stem cell transplants, which are relatively expensive procedures.

4. Tap into an established clinical trial network.

A common challenge to trial completion is getting sites up and running quickly. "If developers partner with a research organization that already has an established clinical trial network with agreements and site leadership teams in place, they can bypass red tape and achieve site activation in a predictably rapid fashion, ideally within a 90-day period," says Devitt.

Beyond rapid start-up, partnering with a contract research organization (CRO) that has an established clinical trial network with a proven track record of consistent patient enrollment and quality performance ensures smooth execution from start to finish. Experienced clinical trial monitors ensure trials achieve enrollment goals and can resolve any issues that arise with rigorous attention to detail.

In one example, a phase 3 registrational trial in relapsed, refractory multiple myeloma, patients needed rescuing when it became evident that the first clinical research associates had little or no experience with multiple myeloma. The study start was delayed, and only minimal monitoring had taken place. A seasoned team, highly experienced in the area of multiple myeloma, was quickly transitioned onto the program to reengage and activate sites, putting the trial back on track.

As a result of Precision Oncology's experience and the clinical monitor's proactive approach around study start-up and patient enrollment activities, the enrollment goal was realized 1 month earlier than the originally projected completion date.[11]

5. Use a translational informatics platform to crunch data in real time.

The emergence of cost-efficient, high-throughput biomarker assays and dramatic advances in computing power are improving and accelerating the ability to develop and test tailored therapeutics in defined patient populations.

Smart machine-learning algorithms can identify variants, genes, and pathways responsible for driving disease severity and treatment response that ultimately can be translated into tailored therapeutics and the associated diagnostics. With advances in biomarker-guided adaptive designs, prespecified biomarker strategies can be employed to adjust a trial at an interim look. "Looking at genomic and immunomic data together with clinical outcome data, in real time, provides faster, prospective insights into treatment response," says Devitt. "Researchers can identify which trial arms are worth pursuing further or stopping early. This helps reduce the risk of late-stage failure and disappointment."

For example, Precision for Medicine's PATH™ Analytics Platform is a predictive analytics engine and knowledge-generation solution that provides researchers with a cloud-based tool to advance research and inform decisions in real time, at all stages of biomarker-guided drug development. PATH provides dynamic, interactive charts that combine genomic and immunomic data with clinical data, allowing developers to interrogate scientific findings at the click of a mouse.

To understand the benefit of real-time decision-making, consider the case of a 2-part, phase 1 study looking at the safety and efficacy of a novel agent—a recombinant, humanized monoclonal antibody that targets a specific receptor, resulting in potent antibody-dependent cellular cytotoxicity. Samples for biomarker activity were collected, but not analyzed until the final cohort was completed and without demonstration of adverse events, leaving unanswered the question of whether the optimal dose had been identified. By analyzing the flow-cytometry data to learn more about the drug's impact on T-cell response, together with the clinical data, the drug developer discovered that the maximum dose had in fact not been reached. With this critical insight, the protocol was revised to pursue higher doses in further phases of research. Had this integrated evaluation not taken place, the researchers would not have had that chance (see Figure 3).[12]

Figure 3.

T-Reg Cell Populations—Sample Display[12]
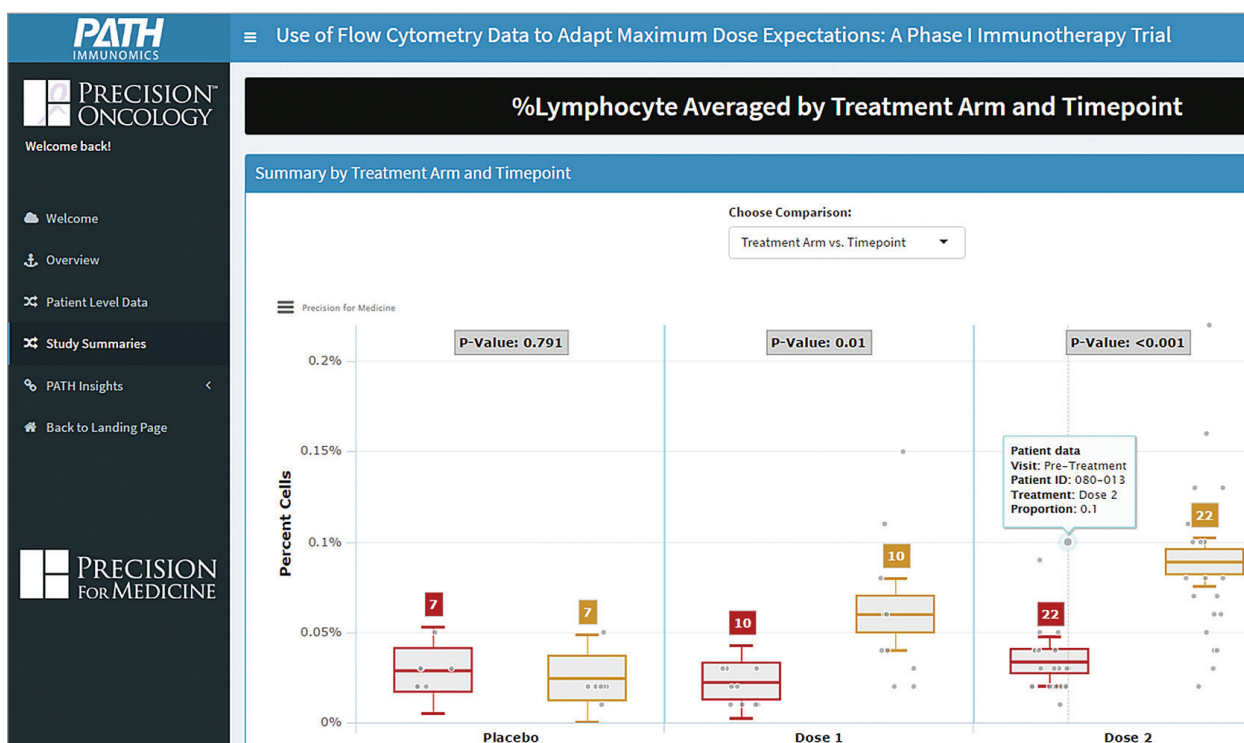
For the full interactive experience, go to www.precisionformedicine.com/path-analytics-platform/.

## 6. Meet the criteria for FDA expedited approval programs.

Drug sponsors need to ensure that applications meet qualifying criteria for one or more of the FDA's 4 expedited approval programs: Fast Track, Breakthrough Therapy, Accelerated Approval, and Priority Review. Ibrance® (palbociclib), for example, a first-in-class drug for the treatment of metastatic breast cancer in combination with letrozole, received breakthrough therapy designation and accelerated approval in February 2015, more than 2 months ahead of the prescription drug user fee goal date.[13]

"The FDA is approving drug applications with biomarker data at much higher rates than those without biomarker data," says Messerschmidt. "They have also been very clear about being willing to look at smaller

clinical trials that have dramatic responses in precisely defined populations." The Xalkori approval in 2011, for example, was based on a trial that consisted of 2 multicenter, single-arm studies that enrolled 255 patients with late-stage, ALK-positive non–small cell lung cancer. In one study, the objective response rate (ORR) was 50% with a 42-week median response duration; in the other, ORR was 61% with a 48-week median response duration.[6]

Conclusion

There are many critical considerations and decisions to make along the pathway to drug approval and commercialization. Addressing as many as possible upfront with smart, adaptive trial designs that incorporate biomarker, clinical, and economic data, and get trials up and running fast with the right patients at the right sites, can significantly accelerate the timeline and maximize investment in R&D.

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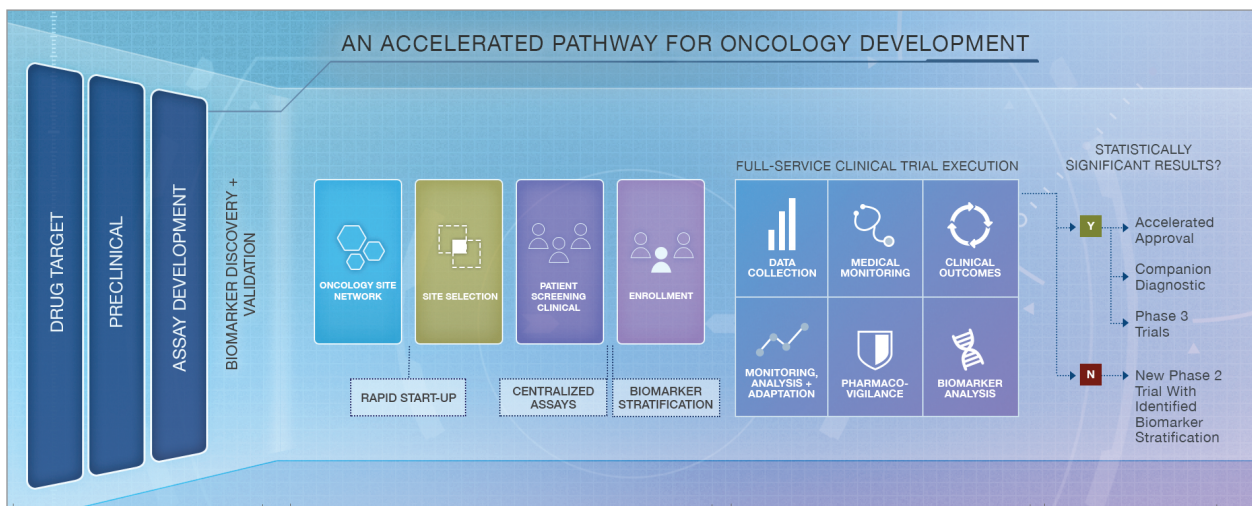
About Precision Oncology

Precision Oncology is exclusively devoted to oncology innovation. As one of the first precision medicine research organizations, Precision Oncology integrates novel biomarker approaches with excellence in oncology clinical trial execution. From preclinical assay development and patient stratification to first patient in and all the way through registration, our approach addresses every aspect of drug development. By helping developers identify and validate relevant biomarkers, Precision Oncology is optimizing therapeutic insights and accelerating development pathways. Learn more at precisionforoncology.com.

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