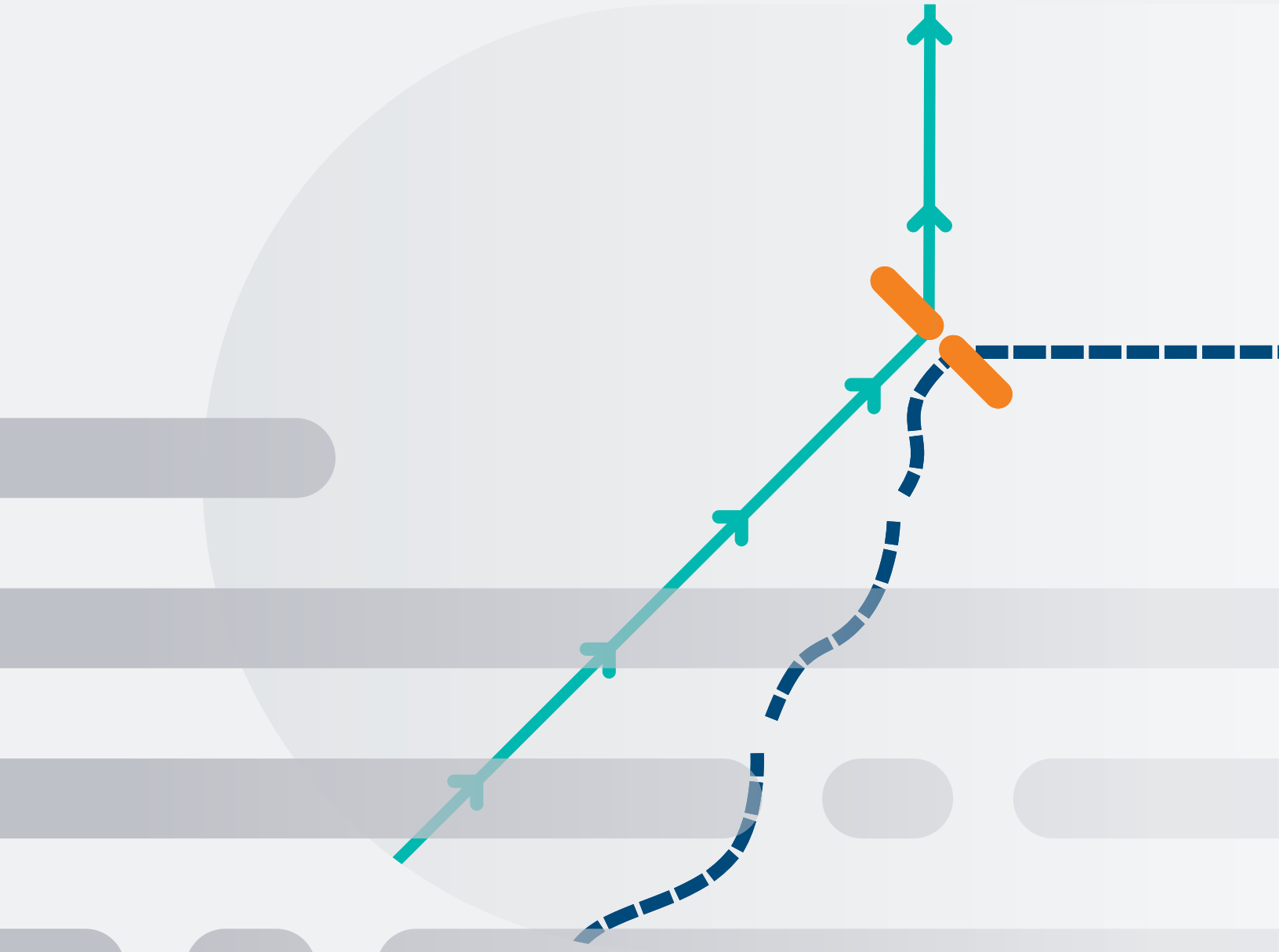
IQVIA™ BIOTECH

White Paper

A DIFFERENT ROUTE TO FASTER APPROVALS

Embracing innovative designs in early phase oncology studies



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INTRODUCTION

Advancements in science and technology combined with unmet patient needs are driving accelerated timelines and creative pathways for oncology drug development. This white paper explores several aspects during protocol design to ensure the best way forward, including how a seamless clinical trial strategy requires a different mindset than traditional pathways.

Advancements in science and technology, combined with unmet patient needs, driving accelerated timelines and creative pathways for oncology drug development. While public desire for novel and effective treatments understandably remains high, precision medicine and immunotherapeutic achievements have shifted the goals. Researchers and clinicians want to develop transformative medicines with less toxicity than traditional chemotherapies that curtail progression of cancers and their recurrences, if not eradicate them. With such treatments in mind, oncology sponsors and regulators alike seek new ways to efficiently move promising therapies from the clinic to approval, and have started to embrace a seemingly seamless path that bypasses the traditional development paradigm of stand-alone sequential Phase I, II and III trials. Today, when sponsors see strong responses during early development, they may consider a faster path to approval via single-arm studies or early phase expansion cohort trials conceived to gather pivotal data. Regulatory authorities have embraced these innovative approaches. As a specialty oncology clinical research organization, IQVIA™ Biotech counsels sponsors considering these routes to consider several aspects during protocol design to ensure the best way forward, including how a seamless clinical trial strategy requires a different mindset than traditional pathways.

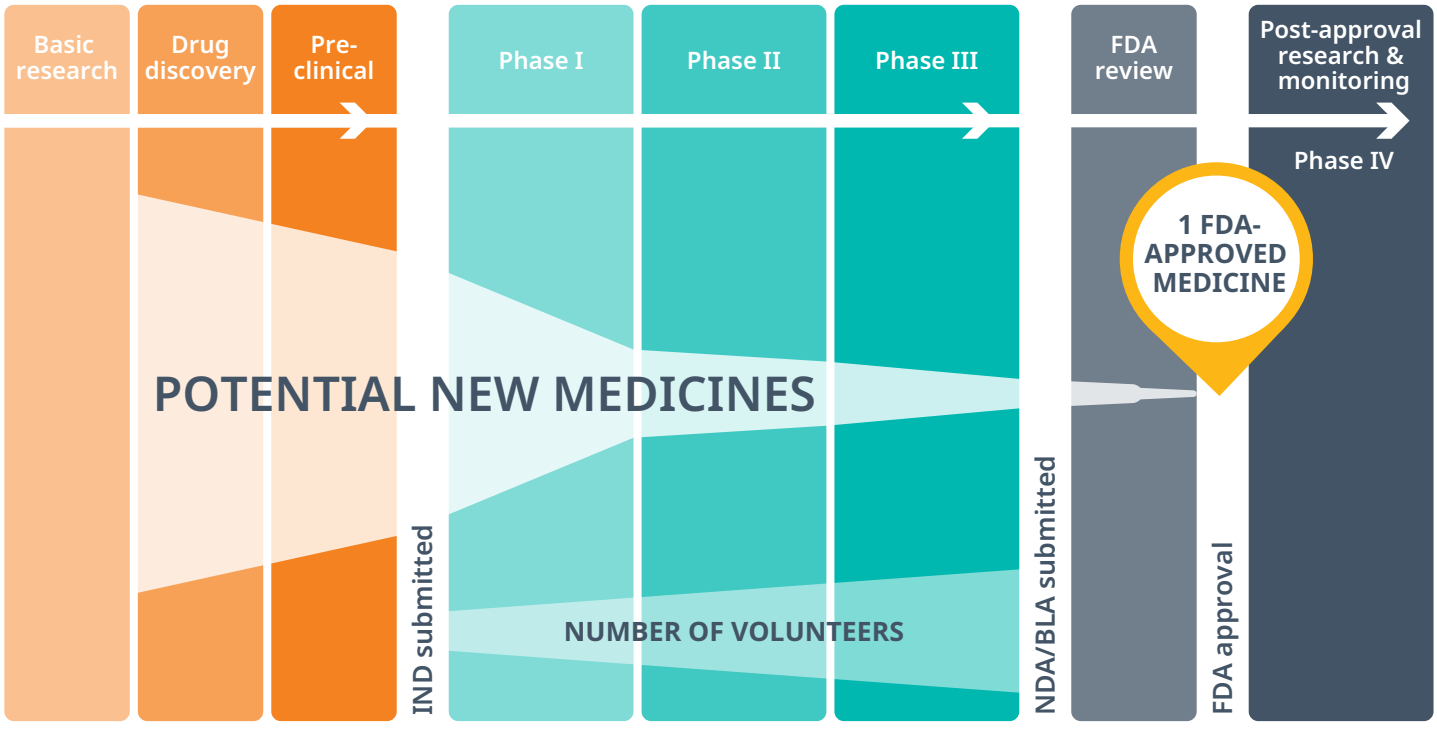
> ***"The function of the formal controlled clinical trial is to separate the relative handful of discoveries which prove to be true advances in therapy from a legion of false leads and unverifiable clinical impressions, and to delineate in a scientific way the extent of and the limitations which attend the effectiveness of drugs."***
>
> *— William Thomas Beaver, M.D., drafter of the initial regulations defining "adequate and controlled" clinical studies.[1]*

DEMANDING DATA: CREATION OF MODERN CLINICAL TRIAL DESIGN

The well-defined clinical investigation process to characterize and document a medicine's safety and efficacy has roots in the U.S. Federal Food, Drug, and Cosmetic Act of 1938, which was the first to require sponsors to provide evidence of a drug's safety before marketing. The Kefauver–Harris Amendment in 1962 strengthened and expanded the requirements to include the provision of efficacy data from "adequate and well-controlled investigations" before U.S. marketing approval. Consequently, the U.S. Food and Drug Administration (FDA) regulations established formal definitions for the traditional sequential and distinct Phase I (safety and dose optimization), Phase II (efficacy and side effects) and Phase III (efficacy and adverse reactions) clinical trials now used for more than 50 years.

The continual evolution of the clinical development process has since yielded two additional phases. Since 2001, the FDA has required manufacturers to report outcomes of some Phase IV post-marketing studies, which often focus on increased monitoring of a drug's efficacy and safety in real world settings among large patient populations. Then in 2006, new guidance from the FDA established what is now called a Phase 0 trial to help sponsors gather pharmacokinetic (PK) and pharmacodynamic (PD) data in minimal numbers of patients using subtherapeutic doses of investigational new drugs. The results of such exploratory studies help shape follow-on trials and development.

Traditional phased clinical trial design



Key: IND-Investigational New Drug Application, NDA-New Drug Application, BLA-Biologics License Application
Source: Graphic adaptation of Phrma, "The Biopharmaceutical Research & Development Process."
https://www.phrma.org/advocacy/research-development/clinical-trials

The pace of traditional trial phases, however, can be both slow and inflexible, and access to clinical trial participants often is competitive. In response, the FDA created a formal accelerated path for certain drugs in 1992. Yet, unmet patient needs and economics remain long-term impetuses for further trial time improvements, given that "a 10 percent improvement in cycle time and success rates can shave $634 million off the total capitalized cost of $2.6 billion required, on average, to bring a new drug to market."[2]

> Of note, the FDA considers surrogate endpoints used for accelerated approval as markers, not a measure of clinical benefit. These markers can be, for example, lab measurements, radiographic images or physical signs while an intermediate endpoint is "a measure of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on irreversible morbidity and mortality."

Speedier Drugs: Four FDA Approaches[3]

While the relatively recent adoption of innovative designs for early trials can speed the regulatory road for new oncology treatments, the FDA has had a faster path for certain drugs for 25 years. There are four approaches for sponsors to consider.

ACCELERATED APPROVAL:
A regulation established in 1992 and revised in 2012 that allows drugs for serious conditions that fill an unmet medical need, to be approved based on a surrogate or intermediate clinical endpoints.

BREAKTHROUGH THERAPY:
A process created in 2012 designed to expedite the development and review of drugs that may demonstrate substantial improvement compared to available therapies. The criteria include the use of preliminary clinical evidence.

FAST TRACK:
A process created in 1997 to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need.

PRIORITY REVIEW:
A designation established in 1992 indicating the FDA's goal is to take action on an application within six months.

The FDA offers as an oncology example that rather than tracking if a treatment extends survival, approvals may be based on shrinkage of solid tumors because of the likelihood this measure predicts clinical benefit. Such criteria take less time to establish, and potentially shorten a trial, although the agency will require additional Phase IV studies to confirm this benefit. If a trial fails outright to verify the predictions or the treatment risks outweigh its benefits, the FDA may withdraw approval.

Of note, the FDA approved the first two chimeric antigen receptor T-cell (CAR-T) therapies after conferring both breakthrough designations and priority reviews: Novartis' Kymriah™ (tisagenlecleucel) in August 2017 for pediatric and young adult patients with relapsed or refractory B-cell acute lymphoblastic leukemia;[4] and, in October 2017, Kite's Yescarta® (axicabtagene ciloleucel) as a treatment for patients with relapsed/refractory aggressive B-cell non-Hodgkin lymphoma who are ineligible for autologous stem cell transplant.[5]

The Agency's 2014 *Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics*[6] provides additional information and the threshold criteria generally used by the agency to conclude whether a drug qualifies for one or more of these four expedited development and review programs.

Enter a new driver of trial design and timeline changes: the multitude of scientific and technological advancements known as precision medicine, the tailoring of medical treatment to the individual characteristics of each patient. The uptake of genetic sequencing and other precision medicine tools in the oncology research and development space and the gains in resulting knowledge has many sponsors using or considering new and rapidly evolving pathways to speed drug development creatively. These new paths already have realized approvals in about five years rather than the 10 or more of traditional trials.[7] Genetic sequencing, dropping in cost per genome to $1,121 in 2017 from nearly $100,000 in 2001,[8] has significantly stimulated trial design change because of its capability to rapidly identify mutations and hence druggable targets in individual patients. Since the approval of the first drug developed to block a known oncogene, Novartis' kinase inhibitor Gleevec® (imatinib) in 2001 for use in patients with chronic myelogenous leukemia, the sector's R&D focus on driver mutations has spawned new classes of molecularly targeted agents (MTAs).

The MTA approach has made trials more complicated in several ways. Most cancers have a variety of mutations that can evolve during the course of the disease, resulting in a heterogeneity of targets that trials historically treated as homogeneous. Moreover, sampling methods by their nature offer examples, not comprehensive accounts, of tumor mutations. Pre-personalized medicine methods of detecting mutations had been an "attendance test" of sorts – are they present or not. Today, sponsors must consider a more biologically based assessment that recognizes mutations may be continuously evolving based on therapeutic interventions, and that their proportional variations within a trial timeline have significance.

This mix of mutations also forces sponsors to decide which therapeutic approach to pursue: should their MTA be a mono- or combination therapy? The choice impacts the trial protocol's design, data collection, patient selection and timeline, as a first-in-human combination therapy often needs a monotherapy escalation first to demonstrate dosing safety, while combination analyses must address the challenge of delineating the novel treatment's dosing, scheduling and effects.

The protocol also must consider the identification of patients most likely to respond to an investigative MTA based on their tumors' mutation expression, a challenge akin to finding patients with a sub-type of an already rare disease. When successful, the resulting cohort homogeneity can permit powering for analyses using smaller populations, realizing potential resource efficiencies for sponsors. But the hunt for such trial participants requires sponsors to select appropriate companion diagnostics. The FDA-approval of genomic profiling diagnostics has led to adoption by many academic medical centers and other research institutions for evaluations of patients' tumor mutations, while smaller and community hospitals may not offer comprehensive panels. More frequently, with the emergence of new targets, sponsors may need to consider using or developing investigational diagnostics, which bring their own, separate regulatory journeys. Often, sponsors of early stage oncology trials choose to examine both general and biomarker-specific patient populations within the same protocol to determine or validate expression levels and their correlations with drug performance, data that will help shape expansion cohorts. For example, the design of many checkpoint inhibitor trials examines how the expression of the programmed death-1 ligand 1 (PD-L1) correlates to patient response to anti-PD-1/L1 antibodies. Tumor mutation burden also has emerged recently as a possible biomarker sponsors are examining as a response measure for checkpoint inhibitor therapies.

The uptake of genetic sequencing and other precision medicine tools in the oncology research and development space and the gains in resulting knowledge has many sponsors using or considering new and rapidly evolving pathways to speed drug development creatively.

TRANSFORMING TRIALS: ADOPTION OF SEAMLESS EXPANSION-COHORT DESIGNS

The direct acceleration of promising new therapies proven in Phase I studies into registrational studies often takes on "a seamless approach of adding cohorts to a first-in-human (FIH) trial to investigate doses and activity in a variety of cancers."[9] This blurred approach features coinciding pharmacology and early assessment of efficacy in a proof-of-concept stage. This design permits establishing dosing followed by further efficacy testing via therapeutically aligned or mutation-defined patient cohort expansion that is either single-arm or randomized. Seamless designs often retain the original cohort for safety analyses. Depending on the strength of the data and the rarity of the patient population, sponsors can directly seek approval.

> *"Compared with traditional cytotoxic chemotherapies, new targeted therapies for cancer may demonstrate early evidence of clear benefit that make the traditional approach to drug development inefficient and even unethical if equipoise is lost."*
>
> — *Description of December 2016 Drug Development Paradigm in Oncology Workshop planned by U.S. government, industry, academic and patient advocacy stakeholders, focused and hosted by the National Cancer Policy Forum in collaboration with the National Academies of Sciences, Engineering, and Medicine.*[10]

Seamless trial design is increasingly popular with sponsors. An October 2017 analysis examined 1,786 Phase I / II studies enrolling 100 or more patients presented at ASCO from 2010 to 2017. The findings, reported at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, revealed that 65 percent of the 51 identified seamless studies presented data in 2015 or later.[11] Of note, these 51 trials accounted for 15 percent of patients, had up to 13 expansion cohorts and involved 50 investigational new drugs (INDs), including targeted therapies, immunotherapies, antibody-drug conjugates and chemotherapies.[6] In 2016, the FDA Office of Hematology and Oncology Products (OHOP) reported having received more than 40 active commercial IND applications for large FIH oncology trials using seamless strategies.[7]

The seamless design appears to increase the likelihood of approval. The analysis reported at the 2017 AACR-NCI-EORTC found that of the 50 INDs in such trials, 14 percent (eight) received accelerated approval from the FDA and one, a priority review.[11] The investigators noted that such performance could be considered as a high success rate given that an estimated 5 percent of oncology drugs entering human testing ultimately receive FDA approval.[6] An April 2017 analysis addressed the role of expansion cohorts in this success. The investigators' review of 533 Phase I trials evaluating 381 drugs, of which 112 drugs had at least one expansion cohort, revealed that those with cohort size of two to 20 had twice the odds of successful Phase II trials.[8] Moreover, drugs in the reviewed Phase I trials with expansion cohorts had a 95 percent[6] higher five-year probability rate of approval.[12]

TRANSFORMING CANCER TRIAL DESIGN

Susan E. Bates, M.D., now director of Translational Cancer Medicine at Columbia University Medical Center, and colleagues offer a roster helpful in reviewing the new oncology trial landscape.[13]

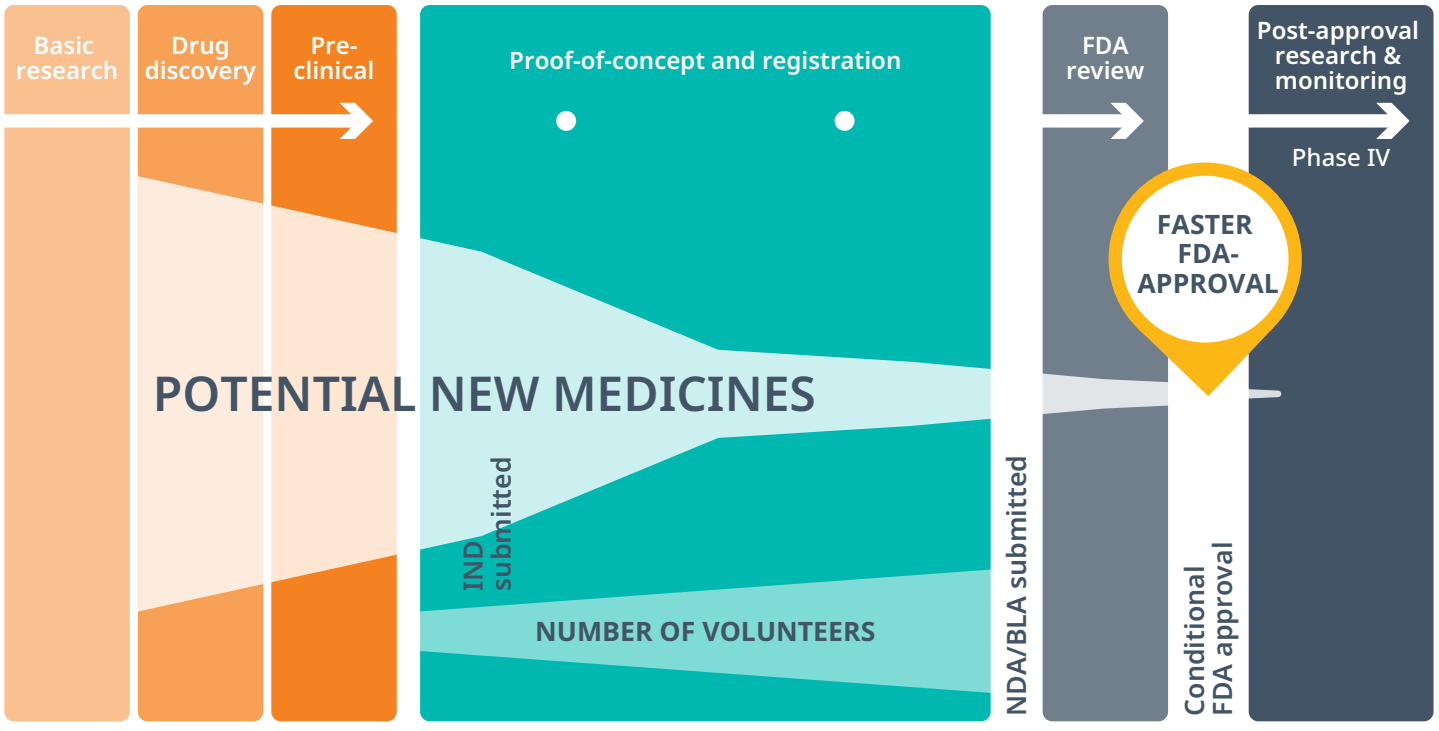
This new seamless oncology trial landscape can incorporate a variety of designs, including platform and basket studies. Merck's checkpoint inhibitor Keytruda® (pembrolizumab) provides a pioneering oncology example of a seamless indication finder trial. The company began a single Phase I FIH study, KEYNOTE -001, focused on safety and dosing in patients with advanced solid tumors in 2011,[9] but it had six parts.[14] Based on positive and early response rates and duration of response results, notably in patients with metastatic melanoma or non-small cell lung cancer (NSCLC), the company added more than 20 cohorts[15] to evaluate efficacy, alternative dosing regimens and a potential predictive biomarker.

TRIAL DESIGN	DESCRIPTION
PLATFORM TRIAL	Evaluates many therapies in a particular disease or group of diseases. Therapies usually have different sponsors and may be combinations or sequences.
STANDING TRIAL	Platform trial in which therapies enter and leave over time.
MASTER PROTOCOL	A trial with multiple treatment options requiring separate protocols but under the same aegis. Informed consent is usually required for both the master protocol and the respective individual protocol.
INDICATION FINDER	Evaluates a particular therapy across multiple cancers that are defined by organ type or across subtypes within a specific organ type. The goal is to determine which diseases or which biomarker subtypes are appropriate for further development.
BASKET (OR BUCKET) TRIAL	Evaluates the effect of a particular targeted therapy on a particular genetic or molecular aberration across cancer organ types. Variant of indication finder but the therapy is not evaluated for its off-target effects.
UMBRELLA TRIAL	This term may be useless because it is used for very different designs by different researchers and reporters. Bates, et al uses it for platform trials (many therapies) that are indication finders for each therapy.
ADAPTIVE TRIAL	Trials in which unblinded data are monitored and used to determine the future course of the trial based on prospectively defined decision rules.
SEAMLESS PHASES	A particular kind of adaptive trial that moves from one phase of drug development to another without pausing accrual. Decisions at the phase switch usually involve greater focus. Examples include dropping arms, dropping doses or schedules, dropping patient subsets, changing randomization proportions, estimating the sample size for the next phase, and there are many possibilities. Bates, et al do not include changing primary endpoints. They also noted that the FDA's 2010 draft "Guidance for Industry, Adaptive Design Clinical Trials for Drugs and Biologics" focused on Phase III trials and avoids the term "seamless Phase II/III" because the term provides "no additional meaning beyond the term adaptive."[16]

- **Part A:** Escalation of doses - to determine the maximum tolerated dose (MTD) and recommended Phase II dose (RP2D) for patients with carcinoma or melanoma. Then:
- **Part B:** Explored safety, tolerability and efficacy in patients with advanced or metastatic melanoma and comparison of dosing schedules.
- **Part C:** Examined safety, tolerability and efficacy in patients with advanced or metastatic NSCLC.
- **Part D:** Explored Part A's low and high dosing in patients with advanced or metastatic melanoma.
- **Part E:** Examined low, medium and high doses in combination with chemotherapy in patients with locally advanced or metastatic NSCLC.
- **Part F:** Investigated low and high doses in treatment-naive and previously treated patients with NSCLC with programmed cell death 1 ligand (PD-L1) gene expression.

This expansion design resulted in a total trial enrollment of more than 1,200 patients,[9] yet the results of a single-arm cohort of 173 patients with melanoma supported the FDA approval of Keytruda as the first anti-PD-1 therapy, in September 2014.[9] The indication, for patients with advanced, unresectable or metastatic malignant melanoma with disease progression after prior treatment with Yervoy® (ipilimumab), also included use of the BRAF V600 mutation as a biomarker to select additional melanoma patients.[17] Since this approval, Keytruda has received approval for additional indications globally, six of which the FDA made conditional pending verification in confirmatory trials.

Seamless Single Arm Trial Design



Key: IND-Investigational New Drug Application, NDA-New Drug Application, BLA-Biologics License Application

Single-arm studies have been the basis of other accelerated FDA approvals. An assessment of the 24 such approvals between 2011 and early 2015, found 54 percent (13) used data from single-arm clinical trials, of which nine involved targeted or molecularly selected patient populations, with Keytruda being the only one of these 24 to receive subsequent full approval.[7] Among these accelerated approvals: additional checkpoint inhibitors and drugs with other mechanisms of action, including Tecentriq® (atezolizumab, anti-PD-L1) from a Phase II trial in 2016; Bavencio® (avelumab, anti-PD-L1) from a Phase II study in 2017; and Imfinzi® (durvalumab) from a Phase I/II study in 2017. The first FDA-approved poly (ADP-ribose) polymerase (PARP) inhibitor, AstraZeneca's Lynparza® (olaparib), used a Phase II single-arm study less than five years after the trial began,[18,19] and the anaplastic lymphoma kinase (ALK) inhibitor Zykadia® (ceritinib), from Novartis, received approval in less than four years after launching a single-arm study.[20]

CHOOSING COMPRESSED DESIGN: CONSIDERATIONS

The choice to forgo a traditional separate, sequential phased trial design is not for all INDs. Sponsors evaluating whether their candidate is suitable for registrational single-arm studies might well contemplate the following four questions, set forth by members of NIH, the FDA, industry, patient advocacy groups and academia.[21]

Does an agent have:

1. Strong scientific rationale or preclinical data supporting its mechanism of action?
2. A well-defined patient population?
3. Substantial, durable tumor responses distinctly exceeding available therapies?
4. Favorable benefit–risk profile?

Sponsors also should weigh distinct design advantages against several disadvantages. The essential benefits are those shared with traditional trials: delivering a therapeutic solution that can stabilize or reverse disease and improve quality of life to patients whose serious illnesses have no current alternatives. First-in-class medicines establish long-term brand recognition and an embedded sales force that serve additional indications and line extensions, and a compressed, seamless protocol brings efficiencies that could result in earlier access for patients, faster time to market, and possibly a significant competitive edge, longer patent protection and greater revenue.

Among the limitations of compressed trials is that drug approvals based just on early expansion trial data have less understood survival and safety profiles. The lack of a comparative data set for historical controls, particularly for narrow mutation-defined patient populations, can be a hurdle. Many single-arm studies use the response rate as a surrogate endpoint for long-term clinical benefit and require validation in randomized trials. Subsequent, long-term, multi-year follow-up data can reveal drug efficacies in wider populations. Such data also may help differentiate the effects of the medication and that of the cancer, comorbidities or age, particularly for adverse events involving the circulatory or respiratory systems.

Of course, failure in confirmatory studies can occur. For example, in May 2017, the Phase 3 IMvigor211 study evaluating TECENTRIQ® (atezolizumab) in people with locally advanced or metastatic urothelial cancer whose disease progressed during or after treatment with a platinum-based chemotherapy did not meet its primary endpoint.[22] The drug had received an accelerated approval for this indication from the FDA in April 2017. Then in late July 2017, Keytruda failed to meet the primary endpoint of overall survival in the pivotal Phase III KEYNOTE-040 trial in patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC), an indication approved in August 2016 by

> *"...the issue we're trying to reimagine today, in a sense, is when do we acquire all that information in the drug-development process, how do we acquire it, and how quickly can we apply this information?"*[23]
>
> — *Richard Schilsky, MD, Senior Vice President and Chief Medical Officer of ASCO, in a February 2017 ASCO Post.*

the FDA. Merck stated at the time that the "indication remains unchanged and clinical trials continue,"[24] including another Phase III clinical trial of Keytruda in patients with recurrent or metastatic HNSCC.

Of note, a failed confirmatory study is not necessarily the end of a drug's therapeutic life. Iclusig® (ponatinib) is a case in point. The FDA approved this tyrosine kinase inhibitor for two rare blood and bone marrow cancers, chronic myeloid leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia, using a single-arm study in 2012, but long-term follow up showed high rates of thrombotic events leading to the FDA rescinding the approval in 2013.[25] The drug was approved again in 2014 with a restricted indication, and the label later expanded in 2016 based on 48-month data from a Phase II trial.[26]

Sponsors who decide to purse seamless designs must address several aspects of single-arm expansion cohort trials.

PROTOCOLS

In supporting the adoption of seamless expansion-cohort trials, the FDA OHOP suggests the incorporation of traditional trial design features to ensure patient protection. For example, it offers "greater attention to the statistical rationale and analysis plan for additional cohorts, establishment of external oversight committees, and more frequent, real-time communication among sponsors, investigators, Institutional Review Boards (IRBs), regulators, and patients."[9] To aid sponsors, OHOP offers nine questions about standard elements routinely found in sequential-phase drug development that expansion-cohort designs should incorporate.[9]

Certainly, expansion protocols must provide the criteria and scientific basis for their approach, including the statistical justification of how the quantity and size of cohorts will address objectives of each group and the overarching trial. The AACR-NCI-EORTC-reported analysis found that 69 percent of the 29 studies published from the 51 identified seamless studies lacked a statistical analysis plan to calculate the expansion cohorts sample sizes.[11] The investigators stated that such a deficiency could limit the value of data to descriptions requiring subsequent validation. Because seamless trials usually employ multiple non-randomized cohorts and study design amendments, the risk of false-positive or -negative errors increases "compared with later-phase trials, thus affecting the validity and interpretation of the data."[11]

> ***Sponsors need to be clear about the intent of expansion plans to seek, for example, new indications across tumor types or to create randomized or single-arm confirmatory arms.***

Sponsors need to be clear about the intent of expansion plans to seek, for example, new indications across tumor types or to create randomized or single-arm confirmatory arms. IQVIA Biotech has seen sponsors draft flexibility into protocols, providing inclusion/exclusion criteria as well as processes descriptions for some arms of expansion with the understanding that commitment to additional arms, based on emerging data with indications, to be determined later. Sponsors may also keep the window open for future cohorts based on potential competitors going after the same indication or build in triggers for the FDA's Breakthrough Designation based on the array and quantity of patient responses.

IQVIA Biotech advises sponsors to structure several go/no-go indicators into their expansion decision requirements, such as engagement of the target at a high enough rate with safety and response rates at or above acceptable minimum thresholds. Protocols should include the criteria for and methods to stop a cohort or trial if toxicity or lack of efficacy occurs. These determinations require the capture and evaluation of data for detailed PK, PD and safety and tolerability analyses, and will inform the expansion dosing formulation, levels and scheduling plans.

This information also permits assessment of one or more biomarkers in predicting initial antitumor activity as well as therapeutic responses. Biomarker testing is not yet standardized industry-wide and may confound results. For example, Bristol-Myers Squibb's immuno-oncology agent Opdivo® (nivolumab) recently did not meet its primary endpoint of progression-free survival (PFS) in the CheckMate 026 trial evaluating the therapy as a first-line in patients with untreated stage IV or recurrent NSCLC with a PD-L1 expression level of 5 percent or more.[27] This outcome may have been the result of "a PD-L1 assay that discriminates poorly at certain values."[28] Therefore, the protocol must delineate how the role of the biomarker will be measured. If a biomarker is determined to influence patient outcomes, sponsors

QUESTIONS FOR LARGE FIH TRIAL DESIGNS[9]

From the FDA's Office of Hematology and Oncology Products, Center for Drug Evaluation and Research.

1. Is there a compelling rationale for including multiple expansion cohorts?
2. Is the sample-size range consistent with the stated objectives and endpoints?
3. Is there an appropriate statistical analysis plan for all stated endpoints?
4. Are the eligibility criteria appropriately tailored to the expansion cohorts?
5. Is there a defined end to the trial, in terms of both efficacy and futility?
6. Is there a system in place to communicate with all investigators in a timely fashion?
7. Does the informed consent reflect the current knowledge of safety and efficacy of the investigational drug and other agents in the same class?
8. If the trial may be used for regulatory approval, is there an independent oversight committee?
9. If the trial may be used for regulatory approval, has there been communication with regulatory agencies?

may need to expand the trial size to provide data for acceptable statistical power.

Patient outcomes usually are evaluated in a context of comparison, which single-arm studies by their nature do not have. Therefore, the use and analysis of historical efficacy and safety data as controls for comparing and interpreting prognosis, response and progression should be specified in the protocol. A source for such historical data is the independent, not-for-profit initiative Project Data Sphere, LLC of the CEO Roundtable on Cancer's Life Sciences Consortium that is "a free digital library-laboratory that provides one place where the research community can broadly share, integrate and analyze historical, patient-level data from academic and industry Phase III cancer clinical trials."[29]

IRBs and other reviewers should approach their evaluations of seamless trials as they would a traditional phased trial, but with the recognition that collected data and analyses will generate amendments to the protocol as the trial continues, but before activating key steps. Several best practices can help mitigate sponsor subjectivity without hindering a multi-site expansion trial. Sponsors might use a pause between a trial's dose escalation and expansion parts to allow each site's IRB and regulators to review the totality of trial data so that no one site suspends accrual activity because of a wait for data review. To aid this effort, sponsors should make every effort to provide standardized data and its statistical analyses in a timely matter, preferably via electronic formats, not just scans, which expedite collection and extraction.

Standard practice is to anticipate changes to informed consent documentation with new safety information gleaned from the initial dose-escalation period trial. However, in the adaptive setting of expanded cohorts, early stages might also inform changes to the drug's efficacy profile, so sponsors should plan accordingly, including the updating of patients and if the trial changes significantly, revision of consent.

Additionally, some accelerated early phase study designs include adaptive, or Bayesian model, strategies. These approaches can frequently include interim analyses that use probabilities to evaluate treatment safety, efficacy, trial futility or success, as well as explicit rules regarding subsequent decisions based on the results. Modeling of doses and response correlations and of relationships between proximate endpoints and the primary endpoint also are useful during interim analyses. Investigators also might apply participant response data to adapt future patient randomization.

ENDPOINTS AND IMAGING

Endpoints provide the means to determine the strength and certainty of patients' responses and symptom control. Single-arm studies use objective response as an endpoint because it frequently is the first efficacy signal, permitting a shorter time for analyses compared to endpoints based on events such as progression-free or overall survival (PFS, OS) that may take more time to realize.[15] Sponsors may find clinical value in using durable response rate, which evaluates a pre-specified time frame based on the expected timing of disease progression, and disease control rate because of the relationship between stable disease and OS.

For studies with immuno-oncology therapies, the limits of traditional standards for tumor response evaluation are well known. The clinical meaningfulness of post-therapy changes depends on the response size, duration and type. The regulatory-accepted Response Evaluation Criteria In Solid Tumors (RECIST 1.1) criteria permit categorizations into complete or partial response, but not necessarily the full range of differences. While the FDA permits the use of RECIST 1.1 for trials using PFS or response-based endpoints, these benchmarks are inadequate to characterize the patterns of responses seen in patients treated with immunotherapies. For example, early tumor enlargement due to flare could be inaccurately marked as progressive disease, possibly resulting in premature halting of treatment

before a patient exhibits an objective response or disease stabilization.[24] An evaluation of Keytruda in patients with advanced melanoma in the KEYNOTE-001 trial determined reliance on RECIST 1.1 to delineate progressive disease likely undervalued the drug's efficacy in about 15 percent of patients.[30]

Therefore, sponsors should consider other imaging techniques, data representation and validated patient-reported outcomes for context to tumor response. Specifically, IQVIA Biotech advises sponsors exploring immuno-oncology therapies to consider the merits of using an immune-related version of RECIST 1.1, in addition to RECIST 1.1. These include the immune-related response criteria (irRC), an adaptation of irRC known as the irRECIST (or the iRECIST), published in 2017 by the RECIST working group.

These criteria all make predictions of response using overall tumor burden calculations and acknowledge the occurrence of flare in judging the manifestation of progressive disease. The iRECIST defines disease progression as unconfirmed and confirmed (iUPD, iCPD), while providing the criteria for confirmation and how atypical responses might be identified, characterized and interpreted. iRECIST also considers the clinical status of the patient for treatment decisions after confirmed progression. IQVIA Biotech recommends that sponsors consider indication-specific measures, such as Response Assessment in Neuro-Oncology Criteria (RANO), which can aid in translation of findings to clinical practice.

Additionally, sponsors must consider the methods and timing of imaging processing. Typically, a site's radiology team manages imaging for FIH trials, but the use of expanded protocols might require sponsors to engage a central laboratory, as the uniformity of quality control and adjudication is critical. Such prospective collection and processing also may optimize the regulatory submission process because of related reductions in time, costs and of risks and challenges of retrospective image collection, such as image loss or impaired review due to compressed formats. IQVIA Biotech has advised some sponsors to a "collect and hold" approach that ensures images are taken and stored but does not engage central reads, and the related costs, until data suggests that level of rigor is necessary.

COMPANION DIAGNOSTICS

IQVIA Biotech has found the vast majority of oncology INDs require companion diagnostics for approval, either commercially available or sponsor-developed. Many sponsors while testing in FIH trials permit a site's local CLIA lab to conduct the testing until proof-of-concept warrants investment in the development of a diagnostic, which requires a separate regulatory path. Protocol planning discussions with regulatory agencies certainly should address the nature of diagnostics to meet their eventual approval criteria. For global trials, sponsors should understand that outside of the United States, the number of sites experienced and conducting extensive genetic screening and next-generation sequencing is limited.

Increasingly in the United States, cancer patients have opportunities to try immuno-oncology therapies, so sponsors who require naïve patients may need to enroll in regions of the world with less consistent access to cutting-edge treatments.

SITES

Large academic medical centers perform dose-escalation studies because they can later accommodate large recruitment expansions. However, sponsors may also need to consider the selection of sites based on where certain cancers are common, like China for patients with gastric cancer or Australia for those with melanoma. Increasingly in the United States, cancer patients have opportunities to try immuno-oncology therapies, so sponsors who require naïve patients may need to enroll in regions of the world with less consistent access to cutting-edge treatments, such as Eastern Europe, Latin America and Asia Pacific.

Growth to such global levels can then bring a challenge of identifying sites where investigators and teams have prior experience with the candidate drug class. A clinical development team with oncology experience understands the current competitive landscape and can help identify the best locations and execute training to ensure staff development to the appropriate level for safe and efficient trial conduct.

During dose-escalation, traditional trials usually execute at one to three sites, but IQVIA Biotech has seen early expansion-cohort trials involve 10 or more sites, particularly when enrolling patients with rare or mutation-defined cancers or using multiple or large cohorts. Later, such trials can have cohorts grow to the size of smaller traditional trials, or even with overall totals rivaling those frequent in cardiology studies.

Timing is a critical issue related to trial scale. Dose escalation can take up to a year, so half-way through that effort may be a good time for sponsors to begin opening sites in preparation for screening to enroll expansion cohorts, given site preparation can take at least four months. Trial momentum can be impacted by the transition from dose-escalation, typically done within one department by one team, to expansion, involving one or more departments within the same site. The use of different treatment combinations may also influence intricacies of expansion timing.

Efficient and effective communication and end-to-end coordination and feedback are essential to multi-site trials to create accountability without siloing information, particularly early safety or atypical response signals. Where a FIH trial has multiple sites and not just one PI generating the understanding of the candidate therapy, a CRO can advise sponsors on the best vertical and horizontal infrastructure for optimal communications, such as ensuring that protocol summaries and investigator materials are revised regularly to reflect current trial experience.

SAFETY

The FDA OHOP advises that expansion-cohort designs feature patient safeguards to help mitigate potential risks. The concern is even greater for trials that examine combinations of novel drug candidates with standard-of-care chemotherapy or radiation treatments because of potential for increased or unpredicted toxicities.

Therefore, the OHOP proposes leveraging the FDA's Breakthrough Therapy designation to determine if an IND exhibits the early evidence of efficacy that warrants a seamless development program. OHOP reasons this criterion enables sponsors to have "more intensive, real-time interaction with the FDA throughout the course of drug development, which would ensure a

The OHOP proposes leveraging the FDA's Breakthrough Therapy designation to determine if an IND exhibits the early evidence of efficacy that warrants a seamless development program.

high level of regulatory oversight and frequent, timely communication between sponsors and regulators from all disciplines."[9]

The OHOP also recommends sponsors use an independent data and safety monitoring committee with a sizeable group of independent members, not only to evaluate safety and efficacy data from cohorts at planned intervals, but also to counsel on whether to add, pause or close cohorts. The independence of such a committee affords the integrity of transparency practices and statistical analyses while permitting discussion with sponsors and principal investigators.

REGULATORY RELATIONSHIPS

Sponsors of all trial types are advised to plan meetings with the FDA to receive oversight, discuss guidance and raise concerns, particularly if considering accelerated pathways. Traditional trials have such milestone meetings built in, usually at planning, before enrollment and as Phase II ends. OHOP encourages seamless trials sponsors to pursue and schedule meetings for feedback from the agency early in the planning and before any significant cohort expansions. Of note, OHOP counsels that the FDA regulatory oversight of trials with a range of tumor types may not be the same team to review the subsequent marketing application, so sponsors cannot assume agency familiarity when they make their formal submissions. In practice, IQVIA Biotech has found that these meetings can delay the initiation of clinical trials. Therefore, sponsors must weigh the risk of a delay in initiation vs. the risk of clinical hold upon review of the IND submission when choosing a regulatory strategy.

BUDGET AND RESOURCING

Scaling up from a fast-moving dose-escalation activity into cohorts has anticipated expenses in staff, resources and time. Sponsors can optimistically plan from the start to do it all, or begin with a small proof-of-concept trial and potentially amend it based on results and their desire to license or sell their development rights. For those planning to manage their own expansion, a partnership with the right CRO can make a difference.

Another budget consideration is the cost of any additional treatments participants need, such as supportive care. Typically, outside of the United States the use of approved, standard-of-care treatments is not covered by payers because of the investigational nature of the trial setting or lack of national reimbursement. On-label use of such treatments is usually, but not always, covered in the United States. Sponsors may wish to negotiate with the manufacturers of any additional treatments to lower costs.

Comparator cohorts can provide efficacy and safety data, but sponsors should also collect quality-of-life data to aid in creating a robust profile for their INDs.

PAYERS

Increasingly, the hurdle for pharmaceuticals and biotechs is not regulatory approval, but payer approval. Receiving reimbursement and getting on formulary, unless a drug is first-in-class, increasingly requires a sponsor to anticipate the competitiveness of the market and the drug's demonstrated benefits. To that end, superiority of outcomes data may be needed particularly in countries where single-arm studies traditionally have not reached the approval and reimbursement threshold, a consequence that could delay global access. Comparator cohorts can provide efficacy and safety data, but sponsors should also collect quality-of-life data to aid in creating a robust profile for their INDs.

For example, in 2014 the United Kingdom's National Institute for Health and Care Excellence (NICE) declined to reimburse Roche's antibody-drug conjugate Kadcyla® (trastuzumab emtansine) as a treatment for patients with HER2-positive metastatic breast cancer, citing that the cost was too high for the per-patient benefit. However, NICE modified its decision in June 2017 to cover the drug after changing the comparator of care to Herceptin® plus capecitabine, which the agency now considers the standard, and after Roche offered to discount the drug's cost.

With regulators in mind, sponsors might employ comparator cohorts to garner efficacy and safety data. Additionally, collecting quality-of-life data will aid in creating a robust profile for their INDs and reimbursement processes.

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