Fortrea

WHITE PAPER

A new era of the clinical trial: How immuno-oncology advances are reshaping traditional clinical development paradigms

The traditional paradigm for clinical trial design is being upended, driven by an explosion in our understanding of cancer biology and the promise of an ever-growing array of advanced immunotherapy candidates. In this article, we will describe the key recent advancements in oncology clinical trial design and execution, exploring the challenges and opportunities they present in the push to get more effective therapies to patients as quickly as possible.

The rocky road to immunotherapy success

Approaches to systemic anti-cancer therapy have shifted significantly in recent decades. The non-specific cytotoxic agents that once dominated the oncotherapy space first gave way to more targeted agents in the 1980s and 1990s, following that advanced, novel immunotherapeutic strategies took center stage. The potential of such immunotherapies to address untreatable malignancies is generating momentum: from 2017 to 2020 alone, the number of immunotherapy candidates grew by 223%, with 4,700 therapies now in development.[1]

Although curiosity has grown, it has not been matched by an increase in drug development success. Indeed, most candidate immunotherapies still fail at a significant cost to developers and patients.

Several factors have impeded the road to clinical success. One of the most important has been the difficulty of effectively predicting a candidate's efficacy in humans using available in vitro models. Impressive progress has been made in this arena in recent years though, particularly with the refinement of several mouse models, propelling us towards optimized preclinical strategies.

Similarly, developers have faced significant hurdles in clinical development. Unprecedented challenges at this stage have fueled a stark departure from traditional clinical trial paradigms. Today, researchers are leveraging biomarkers as well as novel statistical and design methodologies to conduct smaller, shorter and more efficient trials.

In this article, we discuss the key drivers of this paradigm shift, the resultant advancements in clinical trial design and execution and the challenges and opportunities these present in the push to get more effective therapies to patients as quickly as possible.

New knowledge spawns new clinical development requirements

In the last decade, oncology, and indeed, medicine in general, has been defined by the transition to precision therapies. Key to this is the broader accessibility of individual-level molecular profiling, thanks to cheaper and more readily available next-generation genomic sequencing technologies that deliver higher-quality data.

Through such advances, researchers have gained a deeper understanding of the genetic drivers of malignancy and the molecular pathways involved in tumorigenesis and disease progression. Accordingly, cancers that were once anatomically or histologically defined are now understood to be underpinned by genomic and molecular diversity. Naturally, this has driven the development and validation of a variety of biomarkers and with them, a growth of diverse targeted and precision candidate immunotherapies and their combinations.

While this rapidly expanding knowledge is a move in the right direction for better cancer treatment, it is placing an increased demand on clinical development. To be fit-for-purpose, today's immunotherapy clinical trials must be able to accommodate the vast molecular heterogeneity of cancer, knowledge that changes at pace, increasing societal and patient expectations of faster drug approvals and the mechanistic idiosyncrasies for immuno-oncology (IO) therapies relative to earlier therapeutic modalities. This, of course, is no easy task.

The birth of the biomarker-driven trial

Deeper molecular-level knowledge of cancers and more accessible patient-level molecular profiling is enabling the use of biomarkers in clinical development. Where evidence suggests that a treatment will only be effective in a population expressing a specific molecular marker, for example, trials can be set up to selectively recruit those patients (a so-called enrichment design). Aside from the obvious ethical appeal of testing candidate therapies in only those patients most likely to benefit, these trials can (and often do) use much smaller patient populations, as the treatment effect is expected to be greater.

Accordingly, the average number of patients in oncology trials dropped from 429 to 129 between 2014 and 2019—a reduction of 72%.[2] For developers, this means reduced clinical development costs and less clinical trial complexity, alongside a potentially expedited clinical trial.

While these trials offer attractive benefits, they present challenges, both in terms of experimental design and execution. For example, for new biomarker-specific therapies, researchers often need to simultaneously validate a companion in vitro diagnostic (IVD) device via prospective phase II and phase III studies.[3] Sample collection in biomarker trials also adds to the resource, logistical and analytical complexity of the trial, especially where biopsy samples from primary, circulating and metastasized tumor are needed to identify a biomarker.[3]

Absorb, adapt and thrive

Both the need to accelerate trials and quickly absorb new knowledge is driving the increasing adoption of the adaptive clinical trial. In contrast to the traditional clinical trial paradigm, adaptive clinical trials use accumulating data to make pre-defined protocol modifications while preserving experimental integrity and validity. Such modifications can span trial and statistical procedures and have given rise to a variety of different adaptive trial design types (table 1).

Table 1: Types of adaptive designs appropriate for phases II and III of drug development.
(Based on ref: Nitulescu, Roy, Agnihotram V Ramanakumar and Vatche Bartekian. "A Synthesis of Adaptive Designs in Clinical Trials." 2016)

Type of Adaptive Design	Advantages	Disadvantages
Sample Size Re-estimation	Fewer subjects than planned may be sufficient; sample size can be increased during the trial to maintain statistical power	Too few subjects at interim analysis may lead to lack of statistical significance; adaptations based on interim analysis can be misguided if study sample is too small
Adaptive Randomization	Increases probability of identifying the most effective treatment; decreases maintaining subjects on inefficient treatments	May not be feasible for trials with longer follow-ups or treatment duration; therapy impact assessment is difficult due to the complicated statistical structure
Hypothesis-Adaptive Design	Allows to test the most likely hypotheses	Statistical analysis is complicated by the structure of hypothesis-dependent randomization
Adaptive Group Sequential Design	Trials can be stopped early to save resources and avoid exposing subjects to known ineffective or unsafe treatments; various stopping schemes are available to control Type I error	May increase the size of the trial in case of equivocal results from early analysis; may affect control of Type I error if there is a shift of the target population
Biomarker-Adaptive Design	Methods to assess and control Type I error rates are well established; the design may identify responsive patient populations and understand the disease; it helps in the development of personalized interventions and diagnostic tools	Predicting the relationship between biomarker and outcome is not straightforward and advanced analyses may be required
Adaptive Seamless Phase II/III	Speeds up Phase III studies - time and costs savings; simplified planning of Phase III due to the availability of data from the Phase lib; sample size for the Phase III trials can be reduced.	Study endpoints may change at different stages of a study; methodological validity and accuracy will be challenged in different settings; FDA does not currently recognize these designs as being valid

In practice, these adaptions open various avenues for optimization, benefitting both therapy developers and patients alike. For example, sample sizes can be expanded to preserve statistical power (or reduced while still maintaining that power), which means it's more feasible to identify and abandon futile treatments and doses; in fact entire trials may be stopped if therapy success or failure is demonstrated early. As such, developers benefit from shorter and smaller trials, optimized resource use, and the power to recognize and act as early as possible if a poorly performing therapy fails.

Similarly, as with some biomarker-driven trials, patients in adaptive trials are less likely to be exposed to ineffective therapies and can be assigned to effective interventions with greater likelihood of success. Moreover, broader patient populations, beyond those recruited to trials, also benefit, because researchers can reach efficacy conclusions sooner, speeding a therapy's path to market. Despite the potential benefits, designing and implementing adaptive clinical trials has its challenges. Adaptive trials are more statistically complex and computationally intensive to design than traditional trials, and so deeper statistical expertise and access to suitable technology is required from the get-go. This complexity, combined with the industry's general lack of familiarity with adaptive trials, also means researchers can struggle to obtain stakeholder buy-in and funding for their trial. Once buy-in is secured, researchers can then face difficulties in trial execution—drug supply, data capture and data management are all more difficult in a trial that is dynamic. Finally, interim data analyses can be complex and time-consuming, even if appropriately skilled personnel are on hand.

Short and seamless

The traditional paradigm for clinical trials of cytotoxic agents has typically comprised three distinct phases progressing sequentially: phase I determined dose and safety; phase II confirmed dose, noted side-effects and determined efficacy; and phase III confirmed efficacy, comparing the novel treatment against the standard of care. Only then, following successful phase III results, would regulators grant approval. Understandably, this approach is lengthy, averaging 10 years from first-in-human studies to market approval. Now, the transition to targeted and then precision therapies, together with the growing expectations and needs of patients, has meant upending this long and arduous development approach. This has been achieved via several routes.

First, regulators have created mechanisms to expedite the development of therapies targeting serious diseases. One of the most important is the accelerated approval (AA) framework, which has been used heavily in the oncology space, particularly during the targeted therapy era. In this approach, if there is a severely unmet medical need, researchers can use promising phase II trial results to secure early approval of a therapy (although later confirmatory phase III results are still required). Importantly, if granted AA, developers can potentially cut their time-to-market from approximately 10 years to fewer than five years, giving patients access to a larger pool of promising interventions much earlier.[4]

The era of precision immunotherapies has seen further trial-shortening innovation, perhaps the most notable being the seamless clinical trial. In a seamless clinical trial, otherwise known as a combined-phase study, two or more trial phases are merged into a single trial. In the case of immunotherapies, seamless trials typically begin with a small phase I trial, where expansion cohorts are added progressively. Using this approach, AA is possible, and developers can shorten their time-to-approval significantly, as was the case in the KEYNOTE-001 trial investigating the monoclonal antibody pembrolizumab. Pembrolizumab received accelerated approval for two different indications in 2014 and 2015, respectively, following investigational new drug application submission in 2010.[5]

These (and other) trial-shortening advancements have had a drastic impact on average clinical development times. Indeed, median drug development times have dropped greatly, from 113 months for cytotoxic agents to 87 months and 65 months for targeted and precision oncology agents, respectively.[6]

That said, and while the benefits of shorter trials are certainly attractive, developers should be aware of the drawbacks involved. For seamless trials in particular, these include the additional care and statistical expertise needed to create a sound statistical plan, alongside the logistical complexity of extra interim analyses. If a seamless trial involves biomarkers, the implementation and decision-making process is even more complex. Ensuring adequate stakeholder communication is also especially challenging in seamless trials given the lack of stops between trial phases.

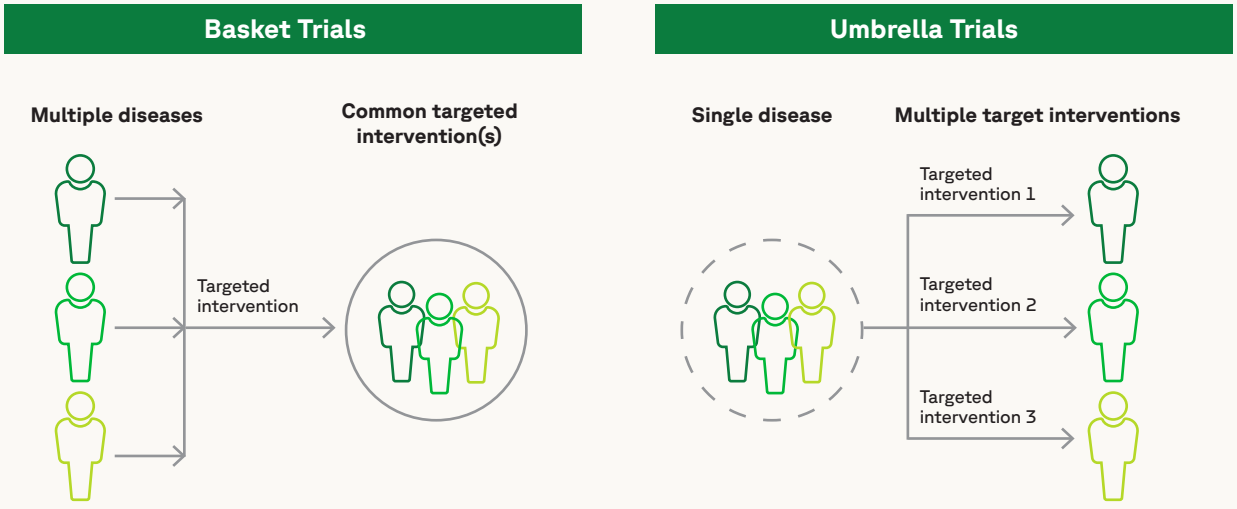
For researchers with their sights set on AA more generally (whether using a seamless design or not), there is the challenge of recruiting patients for later confirmatory trials once the therapy in question is already on the market.

Mastering molecular heterogeneity

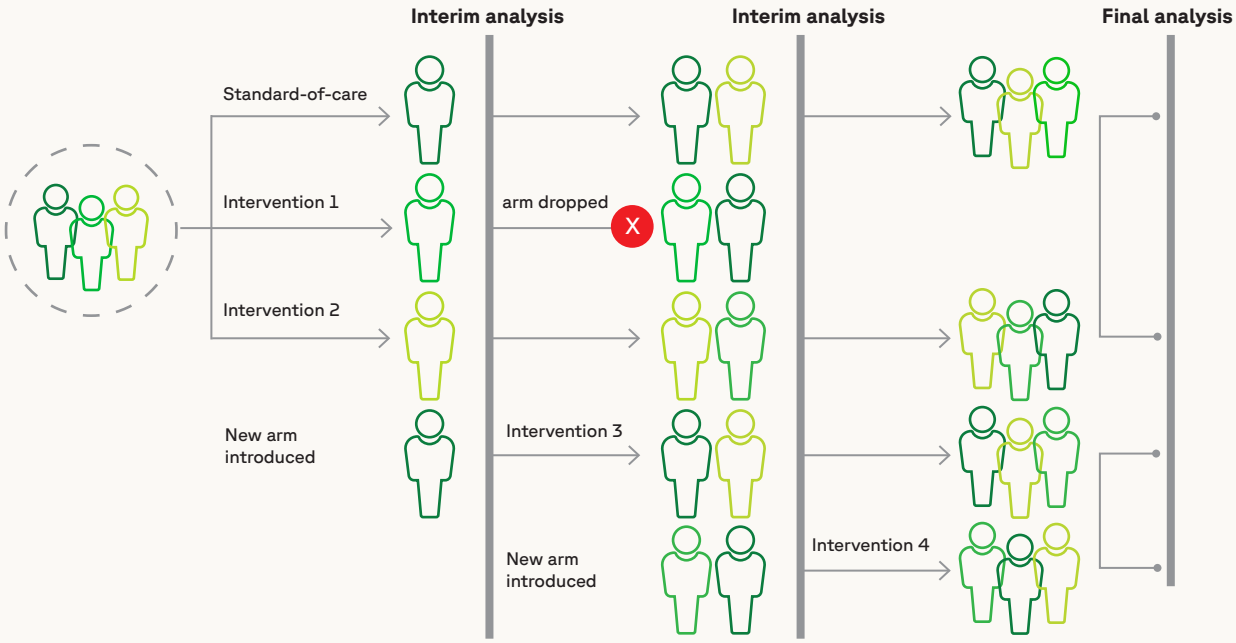
As mentioned above, researchers are discovering an array of cancer-specific molecular mechanisms, and several candidate drugs have emerged targeting those mechanisms. It is impossible, however, to efficiently test all these possible candidates and combinations using traditional trial designs. This scenario has driven the creation of the master protocol.

Master protocols are clinical trials that concurrently test multiple drugs or molecularly defined sub-populations in a single protocol. While the term encompasses a multitude of clinical trial designs, master protocols are commonly divided into umbrella, basket and platform trials (figure 2).[7] With the ability to simultaneously explore multiple therapies and multiple sub-populations under a unified clinical trial infrastructure, researchers can design and implement more efficient, flexible and faster trials. Perhaps most importantly, some master protocols allow investigators to add new therapies to an established trial, which dramatically speeds evaluation and means researchers can react flexibly to emerging knowledge. The large, multi-site nature of such trials also offers greater opportunities for collaboration among researchers, and stratifying patients by molecular features means patients can access more personalized therapies.

Figure 2: Diagrammatic representation of the three main master protocol types: basket trials, umbrella trials and platform trials.



Platform Trials



Master protocols, despite their widely acknowledged ability to get precision therapies to patients faster, are not without their challenges. First is their sheer complexity, which influences trial design, implementation, data collection and results interpretation. Because of this, master protocols are often not feasible without expertise from a partner well-versed in such designs. Second is the challenge of securing funding, complicated by the fact that master protocols often have evolving goals and no clear, predefined end. Moreover (and possibly paradoxically), while these trials can be more resource efficient, they are generally very expensive to set up and maintain.

Accommodating the idiosyncrasies of immunotherapies

In addition to the need to expedite development and better cater to the molecular heterogeneity of cancers, researchers have had to contend with the divergent therapeutic behavior of novel immunotherapies relative to cytotoxic agents.

Perhaps one of the most interesting examples of such a difference between immunotherapies and traditional cytotoxic agents is that seen when comparing their Kaplan-Meier curves (See Figure 2).[7] The curves display a late yet sustained separation, indicative of long-term immunotherapy benefit in select patients. While this is exciting, the statistical challenges it presents have required researchers to use new, more appropriate statistical tools and ways of evaluating therapeutic success. More specifically, researchers are now exploring novel clinical endpoints, such as milestone survival and landmark analysis, as alternatives to progression-free survival.

Then there is the challenge of late, severe and unusual toxicity sometimes observed in immunotherapies beyond the dose-limiting toxicity period. This has meant conducting longer pharmacovigilance studies, which can significantly increase the cost of a trial.

Immune checkpoint inhibitors pose a particular challenge in this regard, as late-onset, long-lasting immune-related adverse events are common. Worryingly, they are also widely underreported. Faced with this challenge, some researchers have suggested using time-dependent survival analysis as a way to effectively assess the impact of these events on overall survival. Additionally, greater use of real-world data has been put forward as an option to better capture late and long-lasting adverse event data, without the need for costly trial extensions.[8]

Finally, novel immunotherapies can trigger patterns of radiological response not typically seen with more traditional interventions. In a small number of patients, so called 'pseudo-progression' or 'hyper-progression' is observed. Current or more traditional response-monitoring approaches, however, may not be best suited to objectively identify, track and evaluate these. For this reason, working groups have developed approaches such as iRECIST and itRECIST[9,10] which aim to better measure systemic and intertumoral immunotherapy response, respectively. Crucially, though, and despite significant industry collaboration and effort, there is still no consensus on how best to approach response criteria for different immunotherapies.[11]

In pursuit of clinical development success

Developments in tools, technology and biological understanding have propelled cancer therapies beyond cytotoxic agents and into the current era of targeted and precision immunotherapies. The scientific and market focus accompanying these advances is evident. But taking this vast pool of candidate therapies and getting the most effective ones to patients has proved difficult.

To bolster success rates, effectively capitalize on emerging knowledge, and drive therapies to patients sooner, the traditional clinical trial paradigm has had to undergo a tremendous shift. This shift, while offering unique opportunities for developers and cancer patients, has brought about a host of new challenges and considerations for pharmaceutical companies. In such a dynamic and complex landscape, collaborating with the right partner—one that possesses the necessary experience and knowledge—can help maximize your chances of clinical development success.

References

1. https://www.nature.com/articles/d41573-020-00166-1
2. https://www.nature.com/articles/d41573-019-00167-9
3. https://vantagebiotrials.com/wp-content/uploads/2016/06/CTP2016_White_Paper_Adaptive-Design_F.pdf
4. https://www.annalsofoncology.org/article/S0923-7534(19)31353-5/fulltext
5. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5452070
6. https://www.oncotarget.com/article/10588/text
7. https://pubmed.ncbi.nlm.nih.gov/32661115
8. https://www.ejcancer.com/article/S0959-8049(21)00169-6/fulltext
9. https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(17)30074-8/fulltext
10. https://ascopubs.org/doi/10.1200/JCO.19.02985
11. https://jitc.bmj.com/content/jitc/10/6/e004849.full.pdf

LEARN MORE at fortrea.com

Fortrea

WP_0024_ONCO_A New Era_0524