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Strategic Implications Of Trial Design In Early Phase Oncology Studies

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Oncology has long led the way as the most active therapeutic area (TA) for clinical trials and this shows no sign of changing in the immediate future. Indeed, Citeline's most recent annual Clinical Trials Roundup showed that oncology was the top-ranking TA by some distance, with 3,394 trial initiations, compared to second-place infectious diseases with 1,711.[1]

Notably, oncology has also reclaimed its top spot for disease indications studied, which had for the prior two years been claimed by COVID-19 as industry reacted with speed to overcome the global pandemic. Unspecified solid tumors accounted for 566 clinical trial initiations, just surpassing novel coronavirus which accounted for 563 initiations.

These figures point to the great advancements being made in oncology drug development, substantially improving treatment options through increased efficacy, improved survival rates and fulfilling the unmet needs of many patients across the globe. For the US, by therapeutic area, oncology continues to accumulate the most FDA approvals. CDER gave a green light to 13 (24%) new cancer therapies in 2023.[2]

Neurology came in second, with 9 (16%) approvals, also in line with recent trends. Infectious diseases and hematology tied for third, with 5 (9%) apiece. FDA's CBER only approved a single oncology product in 2023 (Neutrophil recovery in patients with hematologic malignancies).

However, such powerful therapies are also associated with potentially severe or life-threatening adverse events, which much be managed to ensure patient safety. Early phase studies are critical to understanding the balance between safety and efficacy, being the first opportunity to test different dosing regimens amongst smaller cohorts before progressing to later trials with much greater numbers of patients.

New FDA Guidance for Dosage Optimization in Oncology Treatment (i.e., Project Optimus) in 2023,[3] and a changing landscape of therapeutic options warrants sponsors to take a new vision on the early phase development of these therapies. Making the right trial design decisions is key to ensuring they optimize dosing and success prospects, while always keeping a patient-centric mindset.

Ensuring Patient Safety Remains Priority

The key objectives of early phase studies in any indication are to determine safety and efficacy of the treatment on a small cohort of patients. However, Sharon Moore, chief medical officer at global contract research organization (CRO) Caidya, notes that close attention to safety is particularly important in Phase I/II trials in oncology.

"These products have limited safety data, especially when the trial is first in human and only has non-clinical data available. Or they might be entering Phase II, with small amounts of safety data from patients in Phase I," she notes.

This places increased importance on the need for investigators to identify potential safety risks. Moore continues, "physicians seeing these patients will monitor for new potential adverse events and assess if they are related to the study product. In addition to their underlying malignancy, patients may have multiple comorbidities that may require concomitant medications, or receive drugs to mitigate side effects from prior or concomitantly administered anti-cancer agents. To understand the contributions of these symptoms, and the adverse events occurring after administration of often multiple drugs, requires a high degree of expertise that goes along with conducting these types of trials."

The primary objective of selecting the recommended Phase II dose for oncology drugs has historically been to determine the maximum tolerated dose (MTD), or one close to the MTD would be used in subsequent clinical trials without further efforts to optimize the dosage. In contrast to cytotoxic chemotherapy drugs, targeted therapies demonstrate different dose-response relationships. Doses of newer, targeted therapy below the MTD may have similar efficacy to the MTD but with fewer toxicities. Additionally, the MTD may never be reached with some molecules. At the same time, patients may receive targeted therapies for much longer periods, potentially leading to lower grade but persistent symptomatic toxicities, which can be more challenging to tolerate over time, resulting in a recommended dosage that is poorly tolerated, adversely impacts functioning and quality-of-life, and moreover, affects a patient's ability to remain on a drug and thereby derive maximal clinical benefit.

Ultimately, if safety cannot be assured and severity of adverse events is too great, this has a detrimental impact on product prospects. However, the other goal

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of early phase research is to determine efficacy and understand the balance between the risk to benefit ratio. For heavily pre-treated patients, severe adverse events may be somewhat accepted if a drug can show efficacy, due to the lack of alternative options. In these cases, even a smaller improvement in survival rates can lead to approval. One example of this is AstraZeneca and Daiichi-Sankyo's Enhertu, an ADC recently approved for all three subtypes of breast cancer for pre-treated metastatic patients. It has black box warnings on its label and is associated with grade 5 interstitial lung disease but is approved nonetheless as the efficacy is extremely positive and these patients are in an area of unmet need.

The field of oncology treatments has become increasingly complex, with the rise of biologics and personalized therapies often making identifying efficacy more challenging for investigators. Moore outlines that one particular challenge is where combinations of different treatments are studied. For example, chemotherapies, targeted therapies, and immunotherapies may be utilized in a trial to determine if this is a more efficacious route. "Combinations of therapies come in earlier in oncology. After they do the initial single doses and drug assessment, many are used in combination to try and achieve the best efficacy," she says.

Peter Langecker, executive medical director at Caidya agrees with this. "It can be a really hard question to answer, whether the effect comes from the drug or not. Is it the driving force?" he notes.

Nuances Of Early Phase Oncology Studies

According to Langecker, one of the key challenges of early phase oncology trials is the serious prognoses of patients. "These patients are often very sick, have had multiple previous therapies and advanced cancer that has grown through prior attempts to rein it in. They may have had standard chemotherapy, which is very bone-marrow-toxic, and additional targeted therapies that could have affected organ function, as well as autoimmune diseases if the prior treatment was a checkpoint inhibitor," he states.

For these reasons, heavily pretreated patients are often on studies for much shorter durations, and this is particularly the case in Phase I trials where response to therapies in a significant way is rare. Moreover, there are cohorts which receive lower doses and Langecker notes that here, "even a miracle drug may not have much of an effect." Additionally, intrinsic factors resulting from patient conditions – for example, renal or liver impairment – may affect dose and exposure response. Sponsors need to be mindful of this when conducting their early phase studies.

However, the upside of the severity of patient conditions is that they are usually highly motivated to stay in studies, increasing compliance rates. "These are patients that are running out of options," says Langecker. They also tend to experience improved quality of life through relatively rapid symptomatic relief if there is an effect from treatment, rather than just objective response.

"This is very different from, let's say, cardiovascular disease, where patients stay on these treatments for sometimes years and further clinical trials, but other than lower blood pressure measurements there is no significant improvement for them. Compliance can be poor and patients may not continue on a trial simply because they don't realize how high blood pressure can slowly kill them."

The traditional MTD paradigm often does not adequately evaluate other data, such as low-grade symptomatic toxicities (i.e., grade 1-2), dosage modifications, drug activity, dose- and exposure-response relationships, and relevant specific populations (defined by age, organ impairment, concomitant medications or concurrent illnesses).

Therefore, dosage and regimen optimization prior to a product's approval is recommended, because delaying until after approval may result in large numbers of patients being exposed to a poorly tolerated dosage or one without maximal clinical benefit. Furthermore, conducting clinical trials to compare multiple dosages may be challenging to complete once a drug is approved for a given indication.

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Key Oncology Early Phase Considerations

In the strategic development of early phase oncology clinical studies, there are a number of key considerations for sponsors. Firstly, with regards to dosing strategy, using a case study of an antibody-drug conjugate (ADC), Moore states this should be based on differential pharmacokinetics (PK) and pharmacodynamics (PD) of the antibody and payload. PK plays a particularly important role in dose escalations, measuring cytotoxicity of payloads and ultimately determining maximum tolerated dose (MTD).

Langecker notes that PK is key for longer-term follow-up. "Now we use PK much longer to see whether there is an effect from long-term dosing, either in changes in sensitivity or responsiveness, or induction of metabolization, things like that." Moore continues: "We've always considered PK data to be important in looking at the safety of compounds and try to use that as part of the input into determining maximum tolerated dose. If we have dose limiting toxicities (DLT), are those toxicities correlating with the levels we are seeing in PK?"

With regards to determining MTD using PK and PD, the picture is changing as oncology treatments evolve. In more targeted, biologic therapies, Moore emphasizes that the concept of MTD may not be as relevant. "With some compounds, especially the biologics, you may not reach an MTD, but instead may look for an optimal biologic dose. That is something that from a PD perspective you're really beginning to see more as we have more biologic therapeutic options," she states. The relationship between PK and PD provides data that can assist in balancing tolerability with efficacy and finding that optimal dose. Only pursuing the MTD, without exploring lower doses and utilizing PK and PD information, means the study may result in a recommended dosage that is poorly tolerated, adversely impacts functioning and quality-of-life, and moreover, affects a patient's ability to remain on a drug and thereby derive maximal clinical benefit.

Dose Optimization In A Post-Project Optimus Landscape

FDA's Project Optimus goal was devised in order to reform the dose optimization and dose selection paradigm in oncology. While MTD had previously been the goal of early studies, as more targeted therapies entered into first-in-human oncology trials it has become clear that a higher dose does not always result in better antitumor activity. However, MTD may result in longer-term tolerability issues, which are ultimately unnecessary.

As a result of Project Optimus, early phase studies will need to review efficacy of a wider range of doses, demonstrating dose-exposure, -PD, -toxicity and -activity relationships, including randomized evaluations for dose selection.[4] According to Langecker, this reflects a real shift in FDA's approach to oncology dosing.

"Previously, FDA would say "if you can't tell me what the DLT is, then your dose escalation is a failed study, and you must do it again." Now, instead they are saying, "You have to show me the optimal dose of biological activity that you need in order for your drug to be active." That is why PK and PD, measuring markers of the drug's effect in the body, and also companion diagnostics, have become so important," he says.

This shift has real impact on early phase studies and Moore notes the importance of looking at the benefit-risk ratio. "It's so important that we consider the benefits and the risk. Dose optimization ensures that we're looking for best efficacy, but also considering the safety profile of the product and the patient themselves. If the adverse events become so severe that the patient cannot continue the therapy, or doesn't feel like it's worth the benefit, it's important to look at a dose that offers the best benefit-risk ratio," she states.

From a commercial perspective, it is also critical to get dosage right in early phase trials. This is where safety profiles and data are established, and there are many processes and tests that need to be completed. Once the drug has progressed to Phase II or III studies, the dosing regimen cannot simply be changed if it is wrong and needs to be higher or lower. Instead, full dose-escalation studies must be repeated. This greatly hinders progress and can cause significant delays in development, as well as being costly. Additionally, sponsors must be mindful to assess whether different doses are needed for different indications or sub-populations as early as possible to avoid back-tracking at a later stage.

Making Clinical Trial Design Decisions

As objectives shift in light of Project Optimus for early phase oncology studies, trial designs and models must also pivot. Their complexity must be taken into consideration, especially where targeted therapies are looking at specific mutations that may occur across different tumor types. "As a result, you have cohorts of different tumor types, and they are looking for efficacy in these based on mutation in the tumor. This has led to more basket trials and master protocol designs," says Moore.

There are also novel models being used to mitigate the number of patients in Phase I studies that are treated at suboptimal doses, thus reducing their chances of therapeutic benefit. Moore notes that one of these is accelerated titration, which combines elements of the traditional 3+3 design and model-based design.[5] Existing research has already indicated that these designs can effectively reduce the number of patients who are under-treated, and also accelerate completion of Phase I studies while substantially increasing the amount of data obtained.[6]

Another consideration for early-phase trials is the need for de-escalation studies. In key opinion leader (KOL) discussions conducted by Biomedtracker, it was frequently raised that issues can arise where patients are treated with a dose, show improvement in disease, but are required to continue treatment in line with the existing protocol if there are no studies investigating whether dose de-escalation leads to recurrence or disease progression.[7] This can ultimately decrease a patient's quality of life through unnecessary prolonged treatment, and is a particular issue in breast cancer where patients may be treated for years at a time on one drug.

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While complex designs can lead to enhanced information and patient experience, Langecker notes that there are caveats for sponsors that they should be aware of. "It all boils down to time and money. If you have more complicated designs, you may need to enroll more patients, which takes more time, and every patient costs money," he says. This can be particularly difficult to navigate for smaller biotech companies who need to optimize every cost for their investors. It is important for sponsors to understand these tradeoffs and be able to draw the line on what is most beneficial for their development prospects. "At the same time companies should keep in mind that the selection of a dose that ultimately is found to lead to previously undetected toxicities in long-term use may find acceptable use at a lower dose, thus decreasing product revenue and return on the substantial investments made in the development of the molecule" he adds.

A Promising Future For Oncology

Oncology therapies are becoming increasingly complex and targeted, offering new challenges for sponsors, but greatly improving patient prospects. In light of Project Optimus, change is now a requirement, but there is support available to sponsors struggling to adapt to a new environment, in the form of experienced CROs.

"Looking backwards we can say that in the oncology space, and in particular with newer targeted therapies, we've really been doing Project Optimus for years," says Langecker. "When we had those escalations of combinations, the single-agent compound was maybe a couple of steps ahead, but then the dose escalation of the combination followed stepwise on the heels of the single agent. In many clinical trials, there are some where you would start at a dose where you had safety maybe for two or three dose levels, and you would use that as the first dose for the combination, but you would always keep those escalating maybe three or four steps, where the single agent had maybe five or six dose escalation steps," he continues.

Moore concludes that while change is needed, fundamentally there is significant promise for early phase oncology. "The advances therapeutically that are being made, and all the different kinds of therapies that are being investigated, it's not just drugs, it's also biologics. It's cell therapy and vaccines, and all different kinds of approaches with different methods of administration. All of the different approaches that are being used make this a very exciting time."

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