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MIDD In Early Oncology Clinical Development: Dose Optimization & Beyond

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Clinical development in oncology is expanding rapidly, with innovation driving the industry on multiple fronts. The explosion of new targets and novel modalities has led to many advancements in treatment including immunotherapies, precision targeted medicines and combination treatment, which continue to increase the scale and complexity of oncology clinical trials. Leading discovery in these areas are emerging biopharmaceutical companies, who originated 70% of new oncology drugs in 2022 and were responsible for 71% of the oncology drug pipeline that same year.[1] It seems like the industry is making a necessary leap forward in life-saving oncologic treatments, but how are life sciences organizations keeping up with this fast-paced evolution?

115 novel active substances in oncology were launched globally in the last five years – an indication of continued success and growth in this space. On top of that, nine out of the ten new US oncology medicines released in 2022 were orphan-designated, demonstrating the desire to address rare and unmet needs, and thus further expanding the market. However, while spending on oncology medicines is expected to reach $375 billion by 2027, the clinical trial success rate in oncology has been trending downward since 2015.[1]

"The probability of trial success in the field of oncology is still really low, despite all the advances that we're making," says Dr. Alex MacDonald, vice president of model-informed drug development (MIDD) at Allucent. There is a large gap between discovery science and the reality of clinical development in oncology, he emphasizes.

Competing factors impacting trial success, such as molecule complexity and global discrepancies in development, are constantly working against one another amid the pressures of accelerating timelines and heightened competition. Sponsors want faster routes to market and earlier indicators of clinical activity, whereas regulatory reviewers want more evidence that dosing has been optimized in support of sponsor product development and study plans, Dr. Vanessa Beddo, vice president and global head of biostatistical consulting at Allucent, points out.

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These two ideas are not necessarily divergent, however, and there may be a way to synergize these priorities. Nevertheless, life sciences companies are finding it challenging to plan and manage the inclusion of dose optimization features into oncology clinical trials and development plans in the presence of sample size constraints. When balancing safety and efficacy considerations, "It's a huge challenge for sponsors to decide when to pull the trigger to more fully characterize the safety and efficacy of an individual dose via expansion, especially for small biotechs aiming to be as efficient as possible with their resources," Beddo adds. Dose optimization is both a necessary means for ensuring that patients receive the right amount of treatment and a key complexity to consider as part of a long and costly development process. With the help of MIDD, dose optimization can serve as a guiding light for keeping oncology clinical trials on track from an early stage.

Optimizing Dose For Novel Modalities

As more next-generation therapies and novel combinations of drugs are explored in oncology, dose optimization becomes an increasingly challenging, but necessary task. Dose-finding clinical trial paradigms have remained largely the same to those developed over 50 years ago for the initial cytotoxic chemotherapeutic drugs, where acute toxicity was considered synonymous with efficacy, says MacDonald. Dose regimen finding was limited to establishing a so-called 'maximum-tolerated dose' (MTD) in a small cohort of refractory patients, and this dose and regimen was typically the only one taken forward in larger efficacy trials. Drug-related adverse events were managed by empiric dose reductions or treatment interruptions.

Further dose optimization and establishing safe and effective dose regimens in combination were left to the medical community rather than the drug innovators, evolving over years and years. While statistical trial design improvements have been introduced to better estimate the MTD, the underlying principle of MTD and the old dose finding paradigm has been successfully challenged by US regulators, resulting in the recent initiative, Project Optimus. This has significant implications for oncology drug innovators, potentially requiring changes to clinical trial design and development plans.

It is now imperative for organizations to address dose optimization early in oncologic therapy development so that they can avoid setbacks further down the road, but there are many critical elements to consider in this specific field of study. "We want to take into account preliminary indicators of efficacy to determine the right dose, as the paradigm for dose justification has changed," says Beddo. "However, by default, efficacy dose-ranging studies can involve a large number of subjects, pairwise comparisons, and the use of inferential methods; these designs are not suitable for patient-sparing oncology studies."

"Historically, and seemingly conversely," Beddo continues, "in the context of cytotoxic therapies as the industry standard, the goal was simply to maximize the dose level in a manner which sufficiently balanced the safety-efficacy tradeoff within a short and acute toxicity period of surveillance—for example, identification of an MTD." The added complexity of additional dose exploration requirements for cancer treatments may, upon initial consideration, seem a bit daunting.

Pharmacological principles dictate for many drugs' mode of actions that there will be a dose-efficacy relationship for a given drug, says MacDonald, and this may be separable from a safety-dose relationship. Until companies recognize this and address it in their early oncology trials, low-grade toxicities associated with targeted therapies will continue to interfere with

administration over longer periods of time, patients will have trouble adhering to dosing schedules and doses will be administered in excess which may lead to disease progression.

Given the complicated considerations for new oncologic therapies, there needs to be an evolving paradigm to identify optimal dosage for non-chemotherapeutics. "I think that it's the oncology environment catching up with the rest of the medical community rather than a new idea," MacDonald notes. Once that is more widely recognized, companies will save time on approval processes and reduce instances of dose reductions and patient dropouts in later trial phases. If life sciences organizations keep performing the same old dosing methods in their oncology clinical trials, innovation will be stalled.

The FDA draft guidance supports the reinvention of the dose selection paradigm by stating that MTD-based methods are not appropriate for newer modalities in oncology, as they have dose responses that may exhibit fewer toxicities and similar efficacy below the MTD, and "the MTD may never be reached in certain situations."[2] The acknowledgement of differences between cytotoxic chemotherapies and new complex therapies is promising, along with future focus on a more seamless development process combining dose-finding and registration trials which was also expressed in the draft. The FDA recommendations for dose optimization additionally include guidance on pharmacokinetic (PK) and pharmacodynamic (PD) components, dose comparability and unique patient populations, among other relevant topics.

Anticipating Regulatory Hurdles

Prior to the launch of Project Optimus in 2021 by the FDA's Oncology Center of Excellence, MacDonald recalls a time when life sciences companies were reluctant to employ dose-finding strategies due to "the desire to make oncology drugs rapidly available to patients who have limited options and the belief that higher drug doses will have better therapeutic activity."[3] Therefore, clinical trials had extremely high rates of risk and attrition that made it hard for novel drugs to progress to more comprehensive investigative studies, he says. Project Optimus' ongoing efforts to transform the dose selection paradigm have changed perceptions of dose-finding practices in the industry, forcing companies to incorporate those practices in early development to allow them to move on to further phases.

While some oncologic drug developers remain unmotivated to comprehensively investigate dose selection more in early development, there may be clinical development plan risks related to differing regional processes used to handle this issue. For example, should a company want to expand study activity to additional regions, and the recommended dose has not been well justified, a regulatory body could ask for additional dose testing and consequently disrupt the assumed development timeline, says Beddo.

Similarly, exploring multiple doses could cause delays if companies assume the initial dose approval in one region will apply to the rest, adds MacDonald, thus dose optimization practices could prevent financial and logistical burdens at every stage of development. In practice, this means investigating at least two dose arms in a Phase I expansion, if not a randomized Phase II study. Additional dose investigation may be required when investigating new indications, depending on the similarity of the disease. One of the main challenges here is the selection of the dose regimens for these investigations.

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For companies that are not prioritizing dose selection, global regulators are growing less and less tolerant of the inconsistencies arising in dosing success

throughout the product's lifecycle. There have been many occasions where dose investigations were required and adjustments made after drug approval, or a product was pulled out of the market entirely due to toxicities being found in real-world patients. It has become subsequently harder to investigate combination therapies because companies are submitting protocols with reduced starting doses to prevent regulatory bodies from derailing dose-escalation plans.

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While Project Optimus has improved these outcomes somewhat, there is still work to do. Beddo suggests that companies "design a plan that's risk-averse downstream, so that at a minimum, doses can be investigated in small amounts as early as possible in the product lifecycle." Since global harmonization on dose-finding has not yet been achieved, it is important to be prepared with evidence as soon as possible or to talk about an evidence generation plan with regulatory reviewers.

Having a plan will allow organizations to move forward as quickly as possible once the efficacy of a therapy is proven. "We're going to need constant contact and re-evaluation to inform safety review committees on where we think things should go next. They're looking at the totality of the evidence between the adverse events, the PK results, and early indicators of efficacy, including pharmacodynamic surrogates and tumor dynamics," she says.

Embracing A Holistic Approach With MIDD

The global clinical trial market is expected to grow at a compound annual growth rate (CAGR) of 5.4% between 2020 and 2027, with the US having the largest single market share, followed by Europe and Asia Pacific.[4] As market competition increases, the use of digital solutions for operational efficiency across all stages of drug development is gaining popularity. Life sciences organizations are looking to transform the standard of care in pressing oncologic indications; therefore, they need the support of adaptive and trusted models to inform their decision-making. MIDD is a way for companies to quantitatively evaluate efficacy and safety throughout oncology clinical trials to improve patient outcomes in the long run.

Successful oncology clinical development requires a holistic approach, Beddo and MacDonald conclude, with multiple data sources to provide PK-PD safety and efficacy evidence. For many novel modalities, translating pre-clinical pharmacology to a clinical setting is not trivial, and traditional animal toxicity methods for setting starting dose are not appropriate. In an initial part of a Phase I study, it is rare that efficacy, biomarker or safety data from an individual study will be definitive enough to make expansion dose selections straightforward. In this context, MIDD can be of major benefit to organizations by giving them the ability to make more precise judgements on starting dose, trial design, expansion dose selection and sample size through data augmentation.

Combining clinical data such as PK, PD, tumor size reduction, or adverse events with pharmacological properties such as pre-clinical potency/efficacy via modeling also allows sponsors to meet Project Optimus expectations by selecting doses that are pharmacologically distinct. This type of quantitative modeling can also provide more information on how a product will be tolerated in a real-world environment, which is especially advantageous for researching new modalities.

"Part of the problem that we have in oncology is that the preclinical promise is optimistic, but the reality is a lot less optimistic," says MacDonald. "So, the only real way to form a realistic prediction of what would

happen in the clinic is to use modeling." Translational modeling of in vitro and animal efficacy data is particularly important in a field where efficacy is king, he adds, and accurate translation to cancer patients is no easy feat.

When MIDD is used to leverage existing data from modalities that have similar mechanisms, companies can use data to inform initial investigation before getting to Phase III and realizing that the evidence needed for approval is unattainable or, for example, that optimal dose is much smaller than anticipated. Pembrolizumab is a prime case where estimates of optimal dose were blown out of proportion in the absence of early-stage modeling. Luckily, in that instance, Merck did not have to start from scratch, but in many other instances, life sciences organizations are not as lucky.

Moreover, MIDD can allow companies to adapt to oncology clinical trials that have endpoints or adverse events that are harder to measure or correlate with tolerability. Most organizations use disease progression indicators such as image scanning to determine dose efficacy, but by ignoring lower-level reactions that are not considered 'clinically meaningful', there could be valuable information that is not factored into dose optimization or other safety and efficacy assessments. "Models can potentially illustrate a dose or an exposure response that would be completely missing if companies are only looking at traditional endpoints," says MacDonald.

While MIDD can both serve as a guide at the start of a clinical development path as well as confirm a treatment approach to an oncologic disease, it cannot replace clinical experimentation. However, therein also lies an opportunity to alter the course of a trial to be more effective with modeling when conducted during early trials, with the totality of emerging clinical data steering the direction of further dosing investigations.

"We can't necessarily overfit dose escalation decisions prospectively," Beddo stresses, "meaning that when we start off with the chore of figuring out what the best dosing regimen is going to be, including absolutely everything into a singular dose escalation decision model may not result in a fully informed optimal dosing decision. Ideally, in the background, we want an adaptive design that allows us to build a holistic picture as to where to go next, usually in tandem with decision-making by a reviewing committee and additional modeling as data allows, while simultaneously operating within prespecified safety parameters for the best interests of the patient."

The Future of Early Oncology Development

The number of cancer cases is expected to reach 1.9 million in 2023 in the US alone, with over 600,000 estimated cancer-related deaths anticipated for the same year.[5] As the urgency in this industry rises, it is becoming increasingly imperative that life sciences organizations prioritize early oncology clinical development as they plan and manage their clinical trials. Dose optimization and other early operational efforts will ensure that companies generate indisputable evidence so that regulatory bodies can approve oncologic drugs faster and deliver patients safe and efficacious treatments earlier on in their diagnoses.

Without the niche expertise to navigate the ongoing challenges of oncology clinical development, organizations may be lost in their journey towards evidence generation or expend massive amounts of resources trying to make up for unplanned toxicities. Allucent's clinical pharmacology modeling simulation enables companies to collaborate with experts in translational, animal efficacy, PK and PD modeling to manage regulatory compliance while continuously adjusting trial design for molecule complexity and competitive obstacles.

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Incorporating Bayesian methods and dose optimization considerations as part of early clinical development may ultimately help move a program to Phase III faster given the growing consensus around the need to dose optimize, by reducing regulatory risks associated with proposing an unjustified dosing paradigm for further development downstream.

MIDD has a lot of potential in an ever-changing oncology landscape, as it can inform decision making on multiple levels, allowing companies to maximize innovation in breakthrough areas. Looking ahead, liquid biopsy and circulating tumor DNA are two areas advancing rapidly that may revolutionize early oncology trial design and decision making, and modeling will be necessary to maximize their promise as endpoints, MacDonald notes.

The use of new surrogate endpoints such as these, Beddo adds, where the increased amount of study, confirmation and validation of these within various cancer types may allow organizations to identify a path to early signal detection so that trial designs may be performed in a seamless manner. Regardless of how modeling is used to accelerate oncology clinical trials in the future, it is clear that MIDD is a necessary part of early oncology clinical development and can help serve millions of patients who are suffering from debilitating oncologic conditions.

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