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Navigating dose optimization requirements as a small biotech

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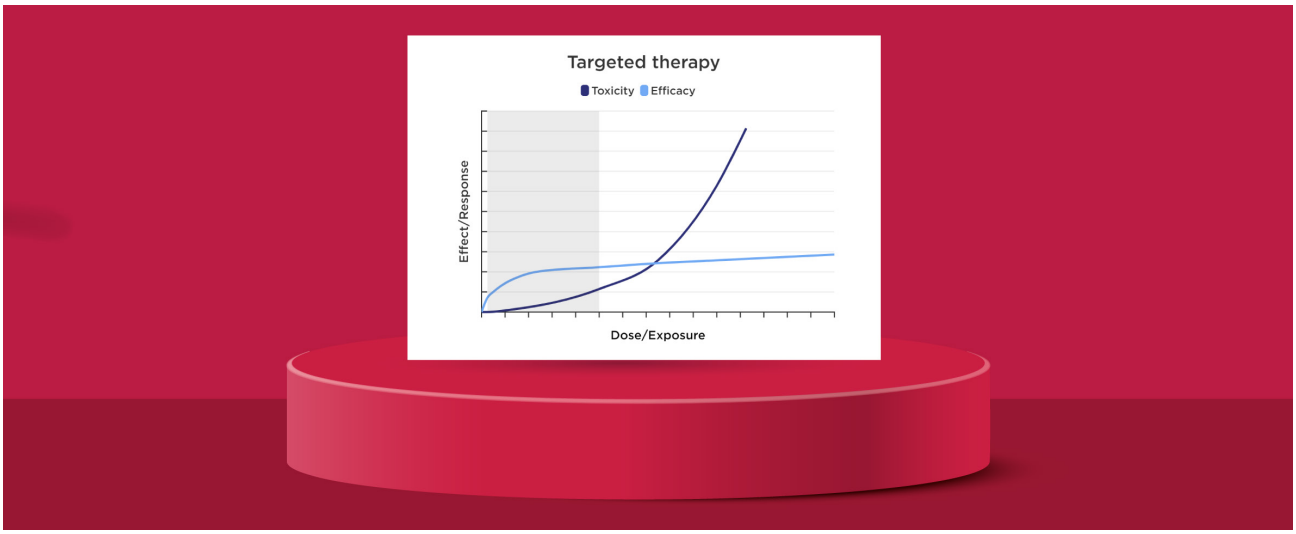

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There's no doubt that FDA's Project Optimus and newly issued dose optimization guidance will benefit patients, but with added resource requirements in the earliest stages of clinical development, it's also creating new challenges for some smaller biotechs.

For any targeted cancer companies that haven't been following Project Optimus, now is the time to take notice and align with FDA on its new dose-finding expectations.

Last week, FDA released draft guidance on dose-optimization studies for targeted oncology therapies, making official the suggestions that Richard Pazdur and his team at FDA's Oncology Center of Excellence have been advocating for nearly two years through Project Optimus. Launched in 2021, Project Optimus aims to revamp dose-finding studies to emphasize safety as well as efficacy from the start.

The guidance directs drug developers away from the dose-finding model that's been the standard in Phase I trials for decades: dose escalation to find the maximum-tolerated dose (MTD). Instead, it recommends a more thorough dose-response and exposure-response analysis to identify doses that optimize both safety and efficacy.

For many programs, that will mean including more patients in dose-finding studies, building in more complex statistical modeling, and bringing randomized trial design — in this case dose randomization — into the earliest stages of clinical development.

With those changes come higher costs.

"Quickly escalating to a dose that is limited by a dose-limiting toxicity criteria, then skipping back one dose to define the maximum-tolerated dose and powering forward, those days are over," Troy Wilson, CEO of Kura Oncology Inc. (NASDAQ:KURA) told BioCentury. "FDA is very focused on what is the totality of data to get the dose optimization right. Any company that doesn't lean into this is probably going to struggle."

The reason behind the shift in FDA's thinking is that a key assumption that held true for older drug classes is no longer valid for newer targeted drugs and immunotherapies.

The MTD paradigm is based on the assumption that the maximum-tolerated dose is going to be more effective than a lower dose. Though that's true for chemotherapies, efficacy often plateaus long before an MTD is reached with newer drug classes, so higher doses often lead to added toxicities without added benefits.

Moreover, the MTD method often misses late-onset toxicities and fails to account for the accumulating effects of low-grade toxicities that can occur with newer therapies, affecting long-term tolerability and outcomes.

The PI3K inhibitor class is the poster child for FDA's dose optimization push. Years after several therapies gained accelerated approvals based on acceptable short-term safety and efficacy data, most indications for many PI3K inhibitors have been pulled from the market. A growing body of evidence suggests accumulation of late-onset toxicities has a detrimental effect that can lead treated patients to have worse overall survival than patients who didn't receive the treatment.

The PI3K case brought the issue to light. Now, limiting patient exposure through modified dose-finding trial designs is a must for FDA across oncology mechanisms and indications.

For some biotechs, dose optimization is becoming an important component of their differentiation strategies, proving just as beneficial for the companies as for patients.

For others, it raises concerns about costs of Phase I studies, possibly putting clinical development out of reach of some smaller companies. This camp is calling for more clarity on how and where the guidance should apply.

One biotech executive who spoke to BioCentury on the condition of anonymity said that with the guidance, "FDA has changed the goal post in the middle of the game." For some companies, it may have been sufficient at the start of their programs to prove that a dose was safe and effective, but the bar has since been raised to identifying the safest effective dose.

Companies most affected by the guidance will likely be those that have already completed dose-finding studies using an MTD approach and may need to repeat or expand studies to meet new expectations.

Guidance details

The new draft guidance builds on previous guidance documents for dose-finding studies in oncology, but with several new recommendations that will change the way cancer studies are conducted.

It was written specifically for targeted therapies and immunotherapies, and does not apply to cell and gene therapies, cancer vaccines, radiopharmaceuticals or cancer vaccines, which require unique dosing considerations.

It does apply broadly, however, to small molecules and biologics. And therapies moving through expedited development or review pathways aren't exempt, according to language in the guidance.

At the core of the new guidance is a recommendation to conduct a randomized, parallel dose-response study — a trial design that has been largely reserved for later-stage studies in the cancer field. The purpose is to gain data directly comparing doses on safety, efficacy, PK and PD.

The guidance suggests that dose randomization can also be done in registrational studies, as long as sufficient, earlier data supporting the selected dose has been collected.

The randomized studies do not need to be statistically powered for dose superiority or non-inferiority. However, the biotech executive who wished not to be named said it is very difficult to determine the number of patients FDA expects in each dose arm. In traditional dose-escalation studies, including three patients is relatively standard, with promising cohorts sometimes expanded to six.

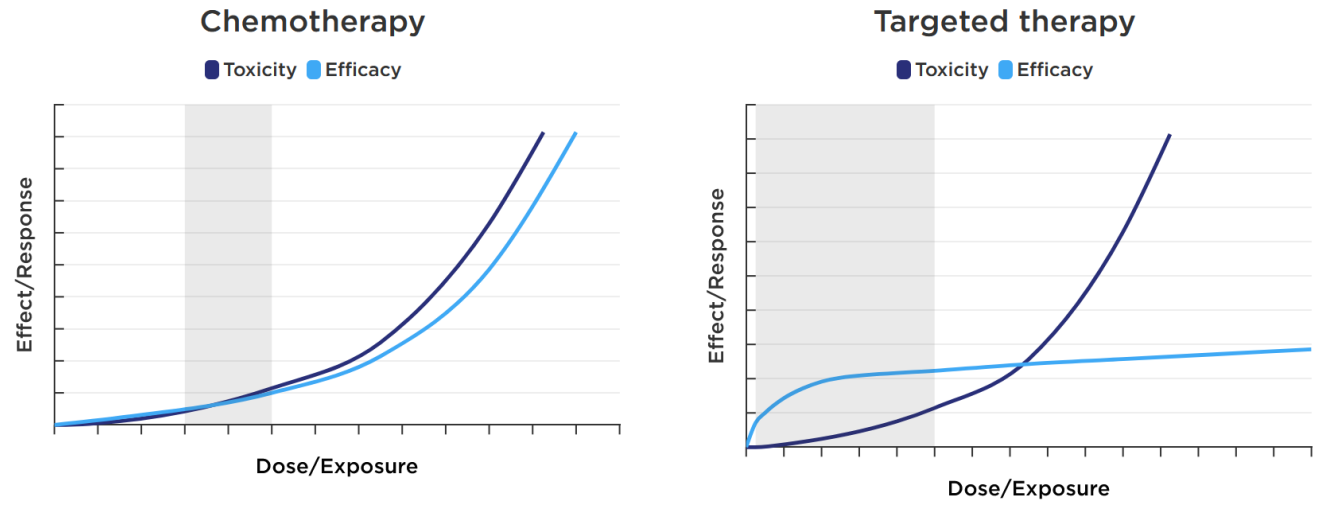
Friends of Cancer Research CEO Jeff Allen agreed. "There have been questions raised about sample size, how many different doses need to be evaluated to differentiate between doses at a feasible level to keep development moving forward. Trying to articulate some of that would help inform those decisions," he told BioCentury.

The guidance also suggests that dose-finding studies should enroll a broad population, consistent with an initiative at FDA to build more diversity into clinical studies and make them better represent the real-world treatment population. Though drug developers see the benefit in optimizing doses, some executives are concerned that the infrastructure doesn't yet exist to satisfy the recommendation to build representative diversity into the earlier-stage dose-finding studies.

Standing up clinical trial sites outside major academic medical centers is a necessary step to increase clinical trial diversity, but most community medical centers still lack the training and systems required for clinical trial participation. Organizing new clinical trial sites sets a high bar for small biotechs, especially for early-stage trials.

Executives also raised concerns about the manufacturing challenges that dose optimization can present for oral therapies. The guidance states, "perceived difficulty in manufacturing multiple dose strengths is an insufficient rationale for not comparing multiple doses in clinical trials." Though trials can be designed to evaluate doses as multiples of available formulations, additional manufacturing burden

Example dose-response curves



Gray shaded area represents range of tolerable effective doses. Model uses data from FDA advisory committee meeting on PI3K inhibitors.

may exist if FDA requests data from specific doses that can't be attained by combining existing tablets or capsules.

Other recommendations in the guidance include considering adaptive trial designs to maximize the data from promising doses, providing clinical and non-clinical evidence for dose decisions in new indications for approved drugs, and incorporating a more thorough analysis of lower-grade toxicities in the dose-finding studies, including through the use of patient-reported outcomes (PROs).

The guidance states that "inclusion of PROs should be considered to enhance the assessment of tolerability in the early phase dose-finding trials."

Allen said Friends of Cancer Research has been examining the roles PROs can play in dose optimization, and he believes they will be an important outcome measure in early studies.

"I think PROs are another tool that can supplement existing clinical reporting. Toxicity measures regularly used may not give the full scope of tolerability," he said.

Dose optimization advantages

The consensus among biotech executives interviewed by BioCentury is that dose optimization requires more resources than traditional MTD studies, but they're split on whether the new expectations will be a net positive or negative for companies.

"This means more cost for small companies, more patients, more analysis, more centers for these rare diseases, and requires really thinking about what you're trying to achieve," said Kura's Wilson.

He noted, however, that dose optimization has been standard for other indications. "Oncology has had the luxury of using MTD and single dose escalation as initial Phase I. Now, we're in line with other targeted therapies and biologics, and dose optimization is de rigueur."

He added that the guidance has "lengthened and complicated the early development path for targeted oncology therapeutics. There's very little that isn't targeted. Nearly every compound is going to have to do this."

That's not necessarily a bad thing, he said. The added upfront effort led Kura to an optimized dose of its menin inhibitor ziftomenib that may improve the therapy's odds of long-term success. Kura was among the first companies to conduct dose-optimization studies, in part due to the leadership of CMO Stephen Dale.

"In our experiments, we kept dose escalating and seeing activity, but we weren't seeing dose-limiting activity. Stephen led the charge to go to FDA and say, 'we would like to do this differently.' We had a couple of doses that might be active, and needed to run head-to-head studies to determine the best dose."

Wilson said FDA "was exactly aligned with our thinking." At the time, he said, "there was no mention of Project Optimus. Investors asked what was wrong with our drug. It took two or three months before one company after another was having similar discussions and investors began to understand."

In addition to altering dose-finding trial designs, Dale told BioCentury there are other steps companies can take to better operate under the new dose-optimization framework.

The first is working with investigators to change how they think about cancer drug dosing.

"The perception from investigators that certainly doesn't feature in FDA guidance is that more is better. The concept of giving patients a lower dose isn't the familiar route, so it's important we work collaboratively with investigators, given the new guidance," he said.

The second is building out preclinical biomarker studies that can gauge activity, toxicity and PK/PD to support clinical dose selection. "The real key is that you want to see a pharmacodynamic marker that can manifest itself as a clinical biomarker," said Dale. "More preclinical data to validate dose optimization and inform clinical biomarker strategy would be extremely helpful. Preclinical development has to be more focused on that aspect than before."

Peter Luo, CEO of Adagene Inc. (NASDAQ:ADAG), told BioCentury dose-optimization studies have been a key part of the company's differentiation strategy designed to overcome the safety challenges and realize the potential efficacy of anti-CTLA-4 therapies. By carefully selecting a dose for its anti-CTLA-4 mAb, the company hopes to reach the market with a drug that's more tolerable than others in the class.

Adagene has a pair of next-generation mAbs against CTLA-4 that each incorporate modifications to improve safety. ADG116 targets a unique epitope to increase antibody-dependent cellular cytotoxicity and regulatory T cell (Treg) depletion, and ADG126 adds a masking technology to restrict activity to the tumor microenvironment.

Luo told BioCentury that CTLA-4 inhibitors are linked to late-onset toxicities that often arise after four treatment cycles. "Only through early randomized trials will you be able to pick up safety and efficacy signals and be more confident about dosing moving forward."

Adagene had also decided before Project Optimus to incorporate dose optimization into its clinical program, and the company has evaluated its therapies in relatively large dose cohorts.

Luo also credits the dose-finding strategy for the company's partnering success, noting that extensive dosing data is important when moving from monotherapy to combination studies, and therefore helped attract Roche (SIX:ROG; OTCQX:RHHBY) for a combination study.

Dose optimization challenges

While dose optimization has been a strategic differentiator for some companies, it means consistently longer, larger Phase I studies.

For some companies, that's been a headache.

In the nearly two years between when Project Optimus was announced and when the draft guidance was released, there have been several examples of companies collecting more dosing data than originally planned before advancing to pivotal trials.

For example, Allarity Therapeutics Inc. (NASDAQ:ALLR) discontinued monotherapy development of receptor tyrosine kinase inhibitor dovitinib last year after reporting that FDA may require a new dose-optimization study before initiating additional Phase III trials. With the cost, delay and shifting competitive landscape, Allarity said the monotherapy program was no longer commercially viable.

The biotech executive who wished to remain anonymous said Project Optimus guidelines have led to delays and backtracking for one of their company's programs. Identifying an appropriate trial design for dose optimization has been difficult, they said.

Dose optimization recommendations may have also contributed to a lengthy Phase I study at Bicycle Therapeutics plc (NASDAQ:BCYC), but CEO Kevin Lee said that was part of the company's clinical trial design strategy from the start.

Lee told BioCentury Project Optimus was "foremost in our minds" when designing the dose-finding study for BT8009, a bicycle-toxin conjugate targeting PRR4.

Bicycle began a Phase I/II trial of BT8009 in September 2020. More than two years elapsed before the company announced the first patient had been dosed in the trial's Phase II component, which is evaluating two doses.

Lee said the new dose optimization process was "burdensome in that it leads to longer Phase I trials." He noted, however, that "ultimately, it forces biotechs to answer questions regarding dosing and schedule that they might never ask. Assuming this leads to better clinical outcomes, this should be in biotechs' best interests."

With the public market downturn dragging on and some biotechs running low on cash, it may be a particularly difficult time for small companies to increase the complexity of early clinical trials. More stories like Allarity's may come

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to light as the industry adapts to the new dose-optimization requirements.

New therapeutic candidates aren't the only products facing increased requirements under Project Optimus; even drugs on the market may be subject to additional dose analyses.

For example, FDA has requested a postmarket, dose-randomization study of Lumakras sotorasib from Amgen Inc. (NASDAQ:AMGN). The results could help guide safe combination trials that incorporate the KRAS inhibitor. Lumakras was approved in 2021 at a once-daily 960 mg dose, which had an acceptable safety profile but some tolerability issues. The post-approval study will compare the approved dose with 240 mg once daily.

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