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US FDA Uses PI3K Inhibitor Experience To Spell Out What It Wants In Dose Optimization Studies

by Sue Sutter

Advisory committee review of safety issues with the PI3K inhibitor class of drugs for hematologic malignancies served as a platform for the Oncology Center of Excellence's Project Optimus initiative, which emphasizes an earlier and more thorough assessment of different doses, including through randomized trials.

The US Food and Drug Administration's Oncology Center of Excellence used the recent advisory committee review of safety concerns with phosphatidylinositol 3-kinase (PI3K) inhibitors to publicly spell out its expectations for dose optimization studies under Project Optimus.

Those expectations include more comprehensive dose escalation studies with more patients and longer periods of observation, to be followed by randomized, parallel dose response trials and, potentially, inclusion of multiple doses as a part of a registration trial.

For combination therapies, the agency wants sponsors to refrain from simply taking the approved monotherapy dose and applying it in a combination. It also wants the safety, efficacy, pharmacokinetics and exposure-response for efficacy and safety evaluated for each product in the combination alone as an initial step.

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studies." – FDA's Nicole Gormley

OCE's recommended strategies for dose optimization likely will be included in a Project Optimus guidance currently under development. Nevertheless, the oncology office used the PI3K inhibitor experience to highlight shortfalls with the historical approach to dose selection based on maximum tolerated dose.

"Dose optimization does require additional resources, and it does require additional time," said Nicole Gormley, director of the Division of Hematologic Malignancies II. "In our experience, though, and what we're seeing here in the PI3 kinase inhibitors and in other areas, is that it's time well spent. The investments that are made in finding the right dose … improve outcomes for patients, and then it results in a better product in the end. That allows us to have confidence in the results from the studies."

Although the FDA does not have authority to require dose optimization studies, "it's something that we strongly recommend and encourage," Gormley said.

Shortfalls Of The MTD Approach

At its 21 April meeting, the Oncologic Drugs Advisory Committee overwhelmingly agreed with FDA oncology review staff that a new development paradigm is needed for PI3K inhibitors.

The drug class has been the focus of recent withdrawals of accelerated approval indications after several randomized trials demonstrated adverse survival trends. The advisory committee said future approvals in the class for hematologic malignancies should be supported by randomized data, rather than single-arm studies. (Also see "*PI3K Inhibitors For Hematology Indications Need Randomized Data, FDA Panel Says*" - Pink Sheet, 21 Apr, 2022.)

Given beneficial responses on efficacy endpoints in the randomized studies, the FDA has concluded that the adverse survival trends are a safety issue resulting from the drugs' well-recognized toxicities. Although dose optimization is particularly important for drugs like PI3K inhibitors, which have a narrow range between effective and toxic doses, dose optimization was not achieved for this class of drugs, in part, because sponsors were focused on trying to determine maximum tolerated dose. (Also see "*PI3K Inhibitors: Overall Survival, Adverse Events And Dose Optimization Top US FDA's Concerns*" - Pink Sheet, 19 Apr, 2022.)

MTD has been the approach historically used for dose selection in oncology drug development. However, it is out of sync with the highly targeted nature of newer drug classes, the FDA said.

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“With respect to dose selection for oncology, we've generally pursued an MTD approach. However, we have many examples of oncology drugs with significant toxicities, including the PI3K inhibitors, that require dose modifications or dose interruptions in the postapproval setting,” said Brian Booth, director of the Division of Cancer Pharmacology I. “We need to reconsider our approach to dose selection and to think more about dose optimization for oncology drugs, especially with the current therapeutic options that are available such as targeted therapies.”

Cytotoxic chemotherapies typically have parallel curves for toxicity and efficacy. However, for targeted therapies such as the PI3Ks, the curves differ – with an earlier plateau for efficacy followed by a more gradual increase in toxicity. For these drugs, it may be possible to reduce the dose, sparing some toxicities in the process, without significantly impacting efficacy, Booth said.

Project Optimus

OCE’s Project Optimus was initiated based on a recognition that many oncology drugs require dose adjustment, which may lead to suboptimal therapy. The program is aimed at ensuring that cancer drug doses are optimized to maximize efficacy, safety and tolerability. (Also see "*US FDA’s ‘Project Optimus’ Will Encourage Move Away From Conventional Dose-Finding For Modern Cancer Therapies*" - Pink Sheet, 26 May, 2021.)

Under the initiative, the FDA will communicate its expectations for dose finding and dose optimization through guidance documents, workshops and public meetings, and drug developers are encouraged to meet with oncology review divisions early in development to discuss such studies.

Another aim of Project Optimus is to develop strategies for dose finding and optimization that leverage nonclinical and clinical data in dose selection, including randomized evaluations of a range of doses. These studies should be performed as early as possible in the development program.

The traditional 3x3 approach to dose escalation and selection is used to identify an MTD, which is then carried forward into registration studies. However, this approach involves few patients at each dose, a short observation period for dose-limiting toxicities (DLT), and an emphasis on DLTs but not on other safety, Booth said.

An optimized dose selection strategy begins with the same dose escalation design, but with the purpose of better understanding the pharmacokinetics, pharmacodynamics, safety and efficacy at each dose level, Booth said. This will often include expansion of several dose cohorts to generate these additional data at promising dose levels. In addition, longer periods of observation are incorporated to assess adverse events, including the onset of delayed toxicities.

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In addition, consideration should be given to nonclinical data, such as in vitro or in vivo receptor occupancy/target engagement data, Booth said. In early trials, PK sampling in a sufficient number of patients should be performed to characterize the drug's PK after multiple doses, and PK/PD relationships should be considered with biomarker and study outcomes.

This dose escalation phase could be followed by randomized, parallel dose response trials of multiple doses when feasible. In addition, multiple doses could be compared in registration trials.

Combination Strategies

Booth also described some general recommendations on dose optimization strategies for combinations, which he said "can get quite complicated":

- Do not simply use the approved monotherapy dose in the combination;
- Evaluate safety, efficacy, PK and exposure-response for efficacy and safety for each product alone first;
- For two new drugs, study multiple doses of both drugs, especially the more active or toxic drug;
- Use small dose escalation increments in the combination setting;
- Evaluate exposure-response for efficacy and safety for the combination regimen; and
- Assess potential drug-drug interactions that may increase systemic exposures higher than the monotherapy, especially at steady state.

Gormley said dose optimization should be both indication-specific and molecule-specific. A dose that is optimal for an acute myeloid leukemia population may be different from what is needed for an indolent follicular lymphoma population, she said. "When new indications are explored, information from prior studies … should be incorporated into those dose optimization studies."

In the case of the PI3K inhibitors, there are some data for each of the four approved products to suggest that lower doses may have been equally effective to those selected for marketing, Gormley said.

But "the issue that we find ourselves with across the class generally is that we don't have lots of data or robust data at the lower doses. And I think that's where a randomized dose finding trial or randomized Phase II trial could really be helpful, spending a little bit more time at dose

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optimization where you're collecting more robust data at lower doses compared to the higher doses" for efficacy, safety and tolerability.

ODAC Members Weigh In

Louis Diehl, professor of medicine at Duke University, asked how, in a situation where two doses are tested in a parallel dose randomized trial, one would know that the optimal dose is actually one of the two selected for the study.

> *For whatever dose optimization study design is proposed, "I think that some degree of quantification of the uncertainty in the results of that design would be very useful." – University of Virginia's Mark Conaway*

"You may never perfectly know that you have the best dose possible, but I think we would have more information than what we currently have," Gormley said, adding that dose optimization is a process that should continue throughout a drug's lifecycle. "I think we'd be in a much better situation than where we are now."

Mark Conaway, professor and director of translational research at the University of Virginia, said the need for dose optimization is important and "I think really the central issue here is the choice of dose that went into some of the early studies" of the PI3K inhibitors.

Although the FDA cannot mandate specific dose optimization studies, Conaway suggested requiring sponsors to quantify the degree of uncertainty in the study designs that lead to the doses selected for further development. For whatever design is proposed, "I think that some degree of quantification of the uncertainty in the results of that design would be very useful," he said.

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