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12 Sep 2023 | **Analysis**

Project Optimus Is Coming To Cancer Combination Therapy Development

by Sue Sutter

FDA initiative aimed at optimizing cancer drug dosage earlier in development started with single-agent therapies, but moving into combinations is 'a natural progression,' Oncology Center of Excellence's Richard Pazdur says. At a recent workshop, experts discuss considerations for combination product dosage optimization and review case studies that reflect Optimus principles.

The US Food and Drug Administration's Project Optimus, which has changed how sponsors approach dosage optimization for single-agent oncology agents, is coming to combination therapies.

During a recent two-day workshop sponsored by the agency and American Society of Clinical Oncology, FDA officials made clear that sponsors should be prepared to apply the principles of Project Optimus in the combination therapy setting.

Agency officials, along with representatives from academia and industry, discussed how this might be accomplished given the added complexity of studying multiple drugs together. They also reviewed case studies of combination therapy approvals that predated Optimus but for which the design of the clinical programs reflected some of the principles subsequently embraced under the initiative.

'Logical Progression'

One of the Oncology Center of Excellence's many "projects," Optimus is aimed at reforming the oncology drug dosing paradigm by moving away from the maximum tolerated dose approach. Under Optimus, the agency wants sponsors to identify a range of potentially therapeutic doses that could be evaluated in a randomized trial, which would then inform the dose to be studied in a registrational trial. (Also see "*US FDA Uses PI3K Inhibitor Experience To Spell Out What It Wants*

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In Dose Optimization Studies" - Pink Sheet, 29 Apr, 2022.)

In June, an advisory committee discussed how the Optimus principles could be applied to pediatric cancer drug development. (Also see "*Project Optimus For Kids: US FDA Aims To Improve Dosage Optimization For Pediatric Cancer Drugs*" - Pink Sheet, 20 Jul, 2023.)

> ***"Although the initial portion of the project Optimus was to look at single drugs, a logical progression of this discussion in oncology would be in drug combinations, since most drugs in oncology are used in combination." – FDA's Richard Pazdur***

The agency now is making clear that it has combination therapies in the sites of Project Optimus' scope.

"Although the initial portion of the Project Optimus was to look at single drugs, a logical progression of this discussion in oncology would be in drug combinations, since most drugs in oncology are used in combination," OCE Director Richard Pazdur said.

Pazdur noted the concept for Optimus grew out of the agency's review work, including looking at clinical trials and development programs that failed.

"Many times if one doesn't have the right dose of a drug you're building a house on really what I call quicksand," Pazdur said. "We noticed that many development plans rushing through drug development, not paying really adequate attention to what is the dosing of a drug, can have really deleterious and sometimes very disastrous consequences for the development of the drug and the future of the drug."

"This could be observed by a heavy excess of toxicities, which are obviously of concern to patients and the prescribers but also to the future of the drug when one takes it into randomized studies where, because of excessive toxicities, because of a selection of dose, one may actually have the observation of ... inferior survival of patients that are entered on a drug where one is observing excess of toxicities. So this was kind of the genesis of Project Optimus."

Revised Guidance And 'Dosing Took Kit' Coming

In a January draft guidance, the FDA laid out its expectations for sponsors to do more dosage optimization work early in the development process, rather than waiting to conduct such studies

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postapproval.

The guidance discussed combination therapies in the context of subsequent indications and usages, stating that strong rationale for choice of dosage should be provided before initiating a registration trial to support a subsequent indication and usage, especially for oncologic diseases not adequately represented in completed dose-finding trials or for new combination regimens. (Also see "*No Excuses: US FDA Wants Early, Thorough Dosage Optimization For Cancer Drugs*" - Pink Sheet, 18 Jan, 2023.)

In comments on the guidance, stakeholders sought more clarity on dosage optimization recommendations for combination therapies and requested the agency explicitly state it would take a case-by-case approach to evaluating dosage optimization in combinations. (Also see "*US FDA Cancer Drug Dosage Optimization Guidance Will Increase Exposure To Ineffective Agents, NCI Says*" - Pink Sheet, 7 Apr, 2023.)

> ***The agency is developing a "dosing tool kit" to help companies in providing information on all the different factors they considered when picking their proposed doses, FDA's Stacy Shord said.***

Stacy Shord, deputy director of the Division of Cancer Pharmacology II, said the agency is in the process of revising the guidance and is trying to address some of the concerns raised in the public comments.

In addition, the agency is developing a "tool kit" that will help ensure it has all the information it needs from sponsors on dose selection and optimization for cancer drugs earlier in a development program.

"We're also working on what we want to call a dosing tool kit, which will be hopefully published at some point too," Shord said. This tool kit will reflect all the questions the FDA asks about a product's dose, including safety and efficacy by dose.

The agency is looking for "high level summaries from the company of all the different factors that they kind of considered when they picked their dosages, even for a dose escalation trial," Shord said. "Why did they pick these dose levels? What are they anticipating in these different dose levels? What are their expectations?"

“By having all of that information available and knowing what our expectations are … ahead of the time helps because when we get into the meeting packages and companies are asking for advice on their dose or the acceptability of the dosing program, it's really hard sometimes because we're missing a lot" of critical information, Shord said.

“And then we end up in this kind of Catch-22, where we're saying, based on the available information, this is kind of what our thought process is. But then we don't necessarily have the full picture. And then when we do get the full picture, you know, we're waiting another couple of months until the company gets all the information to us, and we have another meeting.”

“Starting to have those conversations earlier about all the different pieces that kind of go into making a dose selection and having that information readily available, whether it's in a protocol or a meeting package, and having those open conversations across the company that's sponsoring the drug [or] within our own cells within the FDA” is helpful, Shord said.

‘Landmark Changes’ Ahead

Julie Bullock, senior VP with *Certara* Drug Development Solutions, discussed the historical approach to combination therapy development and its limitations, and how this will evolve in the era of Optimus, which she said will result in “landmark changes” for how sponsors approach combination clinical studies.

She described the typical approach where the dose-finding process begins with the investigational agent given at a lower dose or a few dose levels below a target dose, and once drug-limiting toxicity criteria have passed the next dose cohort is enrolled. After safety and drug interaction potential have been confirmed, a dose level is chosen for expansion and then proof of concept is established. This dose is then often taken into a Phase III trial.

“While this approach is efficient it only gives us a very limited understanding of pharmacokinetic safety and drug interactions and assumes a few things,” Bullock said. “First, that we have optimized the investigational dose and know that this is the target that was needed for efficacy. This is often not the case with combination development. It started in parallel to monotherapy expansion and before efficacy or an optimized dose is established.”

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> *combination development. Taken together, all of this will determine how simple or complex your combination dose-finding approach will need to be." – Certara's Julie Bullock*

Second, it is usually assumed that the approved drug in a combination "has a prescribed dose that has been determined to be optimal and doesn't need adjusting for efficacy or toxicity when given in combination. While that may be the case for drugs approved in the future under Project Optimus, many of our currently approved drugs were approved with inadequate dose finding," she said.

Furthermore, dose should take into account mechanism of action, and some synergistic models may necessitate further dose-finding even for approved agents.

"The bottom line is that this approach, while efficient, does not evaluate the interplay between combination mechanism, dose and activity or efficacy, and the overall understanding of dose and safety can also be limited," Bullock said. "While this approach may still be an option for well-characterized drugs, the future of combination development will look a bit more complex and should incorporate additional dose ranging in order to better understand the contributions of dosage to activity and safety."

The burden of proof with regard to dose for a combination will vary and depend upon the certainty one has in going into the combination, she said. Programs with investigational assets or those with novel mechanisms will require more data and more complex trial designs to understand the balance of safety, efficacy and activity of the combination.

"There are multiple factors driving how we will approach the combination development – the mechanism scenarios for efficacy as well as toxicity, whether the NME monotherapy dose has been optimized, and what we're combining it with," Bullock said. "Many approved drugs are not optimized or being used in indications outside of their approved label. In these cases, these approved drugs are more like new molecular entities for combination development. Taken together, all of this will determine how simple or complex your combination dose-finding approach will need to be."

Considerations Moving Forward

Mirat Shah, the FDA's clinical lead for Project Optimus, said stakeholders should keep two key questions in mind when it comes to combination therapy development.

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“One, are all components of the combination needed? I think that's come up over and over again in our discussions, particularly with patients and patient advocates. Do I need to be taking all of these products?”

“And if the answer is yes, how can we best optimize the dosages of those products to maximize benefit-risk of the combination?” Shah said.

Project Optimus’ initial focus on single agents provides an opening for better optimization of dosages used in combination therapies going forward, Shah said.

Usually there is information on each of the products as monotherapy before the combination is put together, Shah said. “One of the goals of course of Project Optimus is that going forward, more and more products will be optimized for their dosages, including as monotherapies earlier on. And I think that that will also make it a little bit easier to put these products in combination.”

Shord also noted opportunities to leverage data from same-in-class products to “help us figure out a better starting point” in combination therapy development and “and maybe not expose patients to some of the inactive dosages that aren't necessary.”

Lower Doses, Alternative Schedules

Nicole Gormley, director of the FDA’s Division of Hematologic Malignancies II, said more attention needs to be paid to investigating lower doses of approved agents that are used in combination.

“I think in a clinical trial or other investigational setting like that it can be really helpful to look at lower doses and to gain more information,” Gormley said.

> *“Anything that we can do to make a schedule of a drug more tolerable for patients in terms of time toxicity is really good … while we're addressing also the physical side effects as well.” – Patient-Centered Dosing Initiative’s Janice Cowden*

“Oftentimes there's a dose that's developed in monotherapy, but when you're thinking about combining it with other therapeutics the dose that works best may actually be a lower dose in terms of improving tolerability, even if allowing for greater administration long-term of the

dose, and it might even have better efficacy."

Panelists discussed the need to look not just at lower doses to optimize efficacy and tolerability, but also at alternative dosing schedules. For instance, less frequent dosing schedules potentially could reduce patient burden in terms of time and cost.

"I think anything that we can do to make a schedule of a drug more tolerable for patients in terms of time toxicity is really good ... while we're addressing also the physical side effects as well," said Janice Cowden, a patient advocate with the Patient-Centered Dosing Initiative.

Opdualag Case Study

The workshop featured presentations on use of nonclinical approaches and modeling to inform dosage optimization for combinations, as well as the use of flexible clinical study designs and different statistical approaches.

The meeting also included several case studies of combination therapy regimens based on development programs that pre-dated, but nevertheless align with, the Optimus principles.

The most recent approval case study was that of *Bristol Myers Squibb Company*'s Opdualag, which combines the PD-1 inhibitor nivolumab and the lymphocyte activation gene-3 blocking antibody relatlimab. It was approved in March 2022 for treatment of adult and pediatric patients ages 12 years and older with unresectable or metastatic melanoma. The approved dose is 480 mg nivolumab and 160 mg relatlimab given intravenously every four weeks.

Preclinical data indicated the combined blockade of LAG-3 and PD-1 was likely to lead to higher anti-tumor activity than blocking each receptor alone, said Akintunde Belllo, senior VP and head of clinical pharmacology, pharmacometrics, disposition and bioanalysis at BMS.

> ***"This was all conducted in a pre-Project Optimus era, so you very much seem to have anticipated the direction of where things were headed." – IGM Biosciences' Chris Takimoto***

He noted BMS already had an understanding of nivolumab as monotherapy treatment for melanoma and in combination with Yervoy (ipilimumab). Consequently, the company anchored the nivolumab dose for the combination product on the existing monotherapy dose of 240 mg every two weeks or 480 mg every four weeks.

The clinical development program for Opdualag included an assessment relatlimab as monotherapy as well as an extensive evaluation of the combination dose and regimen (every two weeks versus every four).

A Phase I/IIb study spanned tumor types and included randomized components in melanoma patients previously treated with a PD-1 inhibitor as well as those who were PD-1 naïve. One of these randomized portions comprised dose-response cohorts in melanoma patients using a higher dose of relatlimab in the combination.

In the pivotal Phase III study, a regimen of nivolumab 480 mg/relatlimab 160 mg every four weeks was compared against nivolumab 480 mg, with the combination demonstrating better progression-free survival in previously untreated patients. (Also see "*Keeping Track: Pluvicto Boosts Novartis In Radiotherapy; BMS Builds Out IO Estate With Opdualag*" - Pink Sheet, 25 Mar, 2022.)

Efficacy and acceptable safety seen in the clinical trials, plus clinical pharmacology and pharmacometrics analyses, supported the fixed-dose combo regimen of 480/160 every four weeks in adults with metastatic or unresectable melanoma, Bello said.

“What really stands out is the thoroughness of the dose exploration that you all undertook, particularly in the initial Phase I” study, Chris Takimoto, chief medical officer of *IGM Biosciences, Inc.*, said to Bello. “This was all conducted in a pre-Project Optimus era, so you very much seem to have anticipated the direction of where things were headed.”