Pink Sheet
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US FDA's 'Project Optimus' Will Encourage Move Away From Conventional Dose-Finding For Modern Cancer Therapies

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Executive Summary

Simply carrying forward the maximum tolerated dose into later-stage trials does not account for the importance of long-term tolerability – and the fact that higher doses are not necessarily better for patients.

FDA'S PREPARES TO TAKE THE WHEEL AND TRANSFORM ONCOLOGY DOSING.

Source: Raymond Boyd/Michael Ochs Archives/Getty Images

The Oncology Center of Excellence's latest "project" under development will investigate strategies for better dose optimization of oncology products and how to best implement them, US Food & Drug Administration Office of Oncologic Diseases medical oncologist Mirat Shah said during a "hot topics" in cancer regulation panel discussion at the American Association for Cancer Research annual meeting on 20 May.

While Shah did not give any specifics on "Project Optimus" itself, promising "there will be more to come," she did outline what a better dose optimization program would look like. In general, she said, FDA's philosophy is that "more of a drug is not necessarily better for patients, and tools

exist to change the dosing paradigm in oncology."

OCE also gave an updated on Project "Beyond Breakthrough" at the AACR meeting. (*See sidebar.*)

The traditional 3x3 dosing finding design used to identify the maximum tolerated dose for cytotoxic chemotherapies is not applicable for modern targeted or immuno-therapeutics, because a higher dose does not necessarily result in greater anti-tumor activity, Shah said. Furthermore, patients may be staying on therapy for much longer than was typical a decade ago, so long-term tolerability in dosing is important.

Those limitations were thoroughly discussed during a 2015 dose-finding workshop co-sponsored by FDA and AACR. The stated goal of the two-day workshop was to promote "a movement away from conventional dose escalation trial design" and move toward more innovative designs. (Also see ""Breakthrough" Dose-Finding In Oncology" - Pink Sheet, 1 Jun, 2015.)

Oncology 'Beyond Breakthrough' Takes Shape: FDA Project Will Create Benefits 'Menu,' Rescission Process

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US FDA's oncology team has come to realize that a better understanding of how to personalize its 'all-hands-on-deck' approach would be even more helpful – especially for first-time sponsors.

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Despite awareness among sponsors of the issues with conventional dose-finding with modern oncologics, "we at FDA frequently see the maximum tolerated dose, or if the MTD is not reached, the maximum administered dose, carried forward for future studies without consideration of tolerability – and even if there is no evidence that the higher dose has a better activity than the lower dose," Shah said.

"One reason for this may be drug makers fearing decreased efficacy at a lower dose, but there also needs to be a focus on patient quality of life," she said. Shah pointed out that the concept of carrying forward the maximum tolerated dose into larger clinical trials is unique to oncology; other therapeutic areas use a "more holistic approach to dose selection."

Shah outlined what a more "holistic approach" in cancer drug development could look like:

Consider the full spectrum of information in determining the optimal dose, including non-clinical data, PK/PD data, and early efficacy and safety data, rather than just automatically carrying forward the maximum tolerated dose. "Data from other products in the same class may provide insight into how to best optimize the dose."

Fully characterize exposure/response relationships early. This includes understanding target engagement, and the relationship to efficacy and safety. "Charactering these relationships early may aid in the development of alternate dosing regimens or combination therapies," Shah said.

Consider information beyond dose-limiting toxicities and from beyond the first treatment cycle. Additional information to consider includes the occurrence of late toxicities, frequency of dose modifications and rates of lower-grade toxicities, which can significantly impact quality of life. Patient-reported outcomes also may be helpful.

Pursue multiple dose expansion cohorts after initial dose escalation, or randomize patients between two or more doses to gain information about preliminary efficacy or safety and tolerability. "These data can help support a more informed decision on which dose or which doses to carry forward to pivotal studies." Shah noted that even in a single-arm study, patients could be randomized to two or more doses.