GUEST EDITORIAL

Optimize the dose: An optimal step forward for FDA

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"We are going to start making this a requirement", stated Richard Pazdur, MD during STAT's ASCO Recap on June 9, 2021.

The "this" may be a watershed moment for patients with cancer and oncology as a field. It was in regard to the FDA's requirement that Amgen conduct a randomized clinical trial comparing the labeled dosage (960 mg daily) of the recently approved KRAS inhibitor sotorasib to a 75% lower dosage (240 mg daily).

Dr. Pazdur elaborated: "What we really want companies to do is—like all other therapeutic areas—is start doing randomized phase II studies *before* they go into their pivotal studies."

We applaud Dr. Pazdur and his FDA colleagues for this historic step, which will reduce toxicities and benefit patients. It is also a wakeup call for the entire oncology drug development enterprise.

Oncology drug development has changed minimally from that used for chemotherapy: it has focused on determining the maximally tolerated dose (MTD) as quickly as possible and using that dose in registration trials to get to market as quickly as possible.

Neither dose nor toxicity were considered important as long as the drug was "tolerated." Oncologists have long believed that "more is always better," and patients have feared the toxicities of anticancer therapy.

Randomized dose-ranging trials, which are performed routinely in all other therapeutic areas, have been eschewed in oncology. Indeed, as Harpreet Singh, MD, director of the FDA's Division of Oncology 2, stated in the same ASCO Recap, "This isn't just an Amgen issue—this is a cultural issue throughout oncology."

With the FDA's focus on dose optimization for drugs in the development pipeline, we are delighted that OCCA can focus its efforts to optimize dosing of marketed drugs.

The FDA's statement is an unambiguously positive step for anticancer drug development.

First, it emphasizes that the primary objective of a phase I study should be to determine a range of doses to be studied in subsequent dose-ranging phase II trial(s), rather than simply identifying the MTD.

Careful analysis of pharmacokinetic data and the inclusion of reliable blood-based pharmacodynamic biomarkers (if available) may enable this vision, although for some drugs like sotorasib, clinical activity may be evident at all dose levels.

Secondly, the phase II program, as for development of non-oncology drugs, will include randomized trials that focus on determining the optimal dose, with study of population pharmacokinetics to assess the relationships of drug exposure with antitumor activity and toxicity.

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For drugs envisioned to be used alone, such studies should include a range of potentially effective doses, up to the MTD. For drugs to be used in combination with a marketed agent, such studies should include a group of patients who receive the marketed agent alone or with a placebo.

A key issue in the design of such trials will be the selection of the most appropriate endpoint to determine activity. While RECIST response rate or decrease in a validated tumor marker will be appropriate for many drugs, other possibilities include progression-free survival or another measure of tumor growth delay or size.

The structure of pivotal phase III trials will be largely unchanged—except for added confidence that the prescribed dose of the new agent is evidence-based and patient-friendly.

Phase III trials should continue to use endpoints that reflect patient benefit, ideally overall survival and a measure of its quality. If the optimal dose of the experimental agent has not been adequately ascertained during phase II, it would be appropriate for the FDA to require a phase III study of two active doses.

New FDA policies regarding oncology drug development will have major implications for companies that are conducting or relying upon phase III trials that only evaluated the MTD of the investigational agent.

If the data are otherwise sufficient for approval, a postmarketing requirement for dose optimization is likely, and should be welcomed by oncologists and their patients as essential to maximizing the ratio of benefit to toxicity.

These companies may face a drug pricing quandary, however: based on dose optimization studies, the label could eventually be modified to a lower dosage, thus impacting sales revenue (or the potential backlash of a massive price increase). And companies planning their "End of Phase II" meeting with the FDA may be surprised to learn that they have not satisfied the requirements of an appropriate, patient-centered randomized dose-ranging phase II trial.

This change in policy is also important for the prescribing of already marketed oncology drugs. The Optimal Cancer Care Alliance (OCCA), formerly the Value in Cancer Care Consortium, was formed in 2016 with the objectives of preserving best outcomes for patients and promoting their safety.

With the FDA's focus on dose optimization for drugs in the development pipeline, we are delighted that OCCA can focus its efforts to optimize dosing of marketed drugs.

The FDA's policy shift is a major tailwind in this effort; guided by FDA-mandated dose-optimization trials, oncologists will increasingly come to reject the notion that "more is always better."

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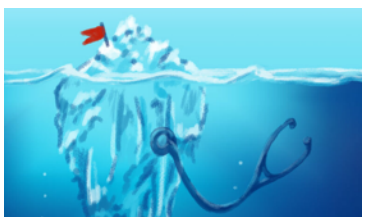

In the days leading up to the 2021 American Society of Clinical Oncology annual meeting, The Cancer Letter published a