Approval After Phase I: Ceritinib Runs the Three-Minute Mile

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Disclosures of potential conflicts of interest may be found at the end of this article.

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Thirteen years ago, I wrote an editorial applauding discovery, development, and marketing approval of imatinib for chronic myelogenous leukemia (CML), a signal event in the history of targeted therapy, and the oncology equivalent of the four-minute mile [1]. It took 3 years from the start of trials and required the confirmatory evidence of two phase II studies to receive the U.S. Food and Drug Administration’s (FDA) stamp of conditional approval. A decade later, these pages called attention to the rapid 3-year development of crizotinib for ALK-translocated non-small cell lung cancer (NSCLC), again based on a highly positive phase I and a confirmatory phase II [2]. In that editorial, I predicted that, someday soon, the FDA would approve a new targeted agent after phase I. That day has come to pass with the approval of ceritinib for ALK-rearranged NSCLC.

The strategy for targeted drug development is now radically different from the equivalent trials of cytotoxic drugs. In the case of ceritinib, the research team knew the drug’s target, were able to select the patients that have tumors expressing the target, and could quickly expand the phase I study to include large numbers of patients, thereby accumulating convincing data on efficacy and safety in phase I. The old saw that phase I is all about safety and phase II is all about efficacy no longer applies. Phase I is all about Proof of Principle and efficacy, once a safe dose is reached.

As described by Shaw and colleagues in the New England Journal of Medicine, ceritinib has striking activity in ALK-rearranged NSCLC, both in treatment-naïve patients and in those who experienced tumor progression on crizotinib [3]. Response rates were 58% in the former and 56% in the latter groups, and included responses in patients with central nervous system tumors? An additional 20% of patients, both treatment-naïve and progressing on crizotinib, had stable disease. The median progression-free survival for patients receiving ≥400 mg/m² per day exceeded 7 months.

The drug has clear pharmacological advantages over crizotinib. Its surprising level of activity in crizotinib-resistant tumors may be explained by its greater potency and its particular ability to inhibit ALK with gatekeeper mutations that confer resistance to crizotinib. In this trial, mechanisms of resistance were characterized in a subset of 19 crizotinib-resistant tumors prior to ceritinib treatment, and responses to the new drug were observed in settings where gatekeeper mutations were present, where ALK was amplified, or where no obvious mechanism was identified. While activation of alternative pathways is suspected of contributing to resistance, particularly when tumors fail to show amplification or mutation on biopsy at the time of progression, these results imply that most crizotinib-resistant patients remain ALK-dependent.

The success of this trial has far-reaching implications. As previously shown in CML and now in ALK-rearranged NSCLC, it is possible to design a superior drug based on knowledge of common mechanisms of resistance to the first-in-class inhibitor. Specifically, drugs that evade gatekeeper mutations are of particular value in both diseases. Secondly, a well-designed phase I trial, even if it requires the participation of multiple institutions, can readily attract sufficient patients with uncommon tumors to prove efficacy and safety sufficient for accelerated approval.

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There is much still to be learned about ceritinib. One of the few disadvantages of early approval is often the lack of precise information about optimal dose and the influence of organ dysfunction and feeding on pharmacokinetics and bioavailability. The recommended
earlier trials. It should be noted that the relative effectiveness and safety of ceritinib versus the value of similarly potent new ALK inhibitors from Chugai, Pfizer, and Ariad also remains to be established. Additionally, the optimal use of ceritinib (as first line versus as salvage therapy after crizotinib) has not been resolved. Thus, despite its early approval and its clear promise as a more potent and effective drug, much remains to be learned about both efficacy and toxicity.

With these cautions in mind, there is no escaping the conclusion that this is an important new drug, filling a void for crizotinib-resistant disease, and its accelerated approval AFTER PHASE I, is well justified. This decision by the FDA marks the beginning of a new era of cancer drug development for industry, for its academic partners, and for patients.

Disclosures
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