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Editorial

# Ponatinib: Accelerated Disapproval

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

Drug development for life-threatening diseases is still a process in evolution. In oncology, as drugs have become more targeted, the regulatory path to drug approval has shortened, with increasing reliance on the Accelerated Approval pathway to provide early access to active agents. However, this approach is not without risks, as illustrated by the recent experience with ponatinib, a promising agent in chronic myeloid leukemia (CML).

In 1992, responding to the need for rapid access to anti-HIV medication, Congress passed legislation creating a new pathway for early drug approval, called "Accelerated Approval" (AA). From its inception, this approval was considered conditional because it relied on a surrogate endpoint, such as response rate, that was considered "reasonably likely to predict a clinical benefit." The law required further proof of safety and efficacy in postmarketing trials, because neither could be fully understood at the time of AA. Nonetheless, AA fulfilled the need to provide promising new medications for serious or potentially fatal conditions.

AA has proven to be a welcome regulatory innovation—especially within oncology. More than 40 anticancer agents have thus far gained AA. In 2014 alone, fully one quarter of *all* Food and Drug Administration (FDA) approvals in hematology/oncology were granted via the accelerated pathway. In an analysis of oncology products granted AA between 1992 and 2010, the median time from AA to full approval was 3.9 years, underscoring the importance of AA in providing early access to promising anticancer agents [1]. Despite this positive impact on drug development, challenges remain.

## Ponatinib

Ponatinib, a highly potent tyrosine kinase inhibitor (TKI), targets the BCR-ABL fusion protein that drives CML. Granted AA in December 2012 for the treatment of patients with CML or Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) that is resistant to or intolerant of prior TKI therapy, ponatinib exhibits striking antitumor activity against *BCR-ABL* mutations that confer resistance to other inhibitors. In particular, ponatinib is the only TKI that consistently overcomes the T315I gatekeeper mutation, found in 15% of patients with drug-resistant CML [2]. In a pivotal phase II study, 70% of T315I-positive CML patients achieved a major cytogenetic response (MCR) on ponatinib, and 51% of patients previously treated with dasatinib or nilotinib also achieved a MCR [3].

## Toxicity

No thrombotic events were initially observed in the phase I study of ponatinib [4]. However, a subsequent phase II trial revealed an 8% incidence of serious arterial thrombotic events—risks that were noted in a black box warning in December 2012 [3]. Additional follow-up from these ponatinib trials has since revealed a high frequency of serious adverse vascular events (48% and 24% in the phase I and II trials, respectively) [5]. This concern led the FDA and Ariad Pharmaceuticals to abruptly withdraw ponatinib from the market in October 2013. Importantly, an ongoing phase III trial (EPIC) comparing ponatinib to imatinib for the first-line treatment of CML was also closed, patients were crossed over to imatinib, and their follow-up was terminated.

Withdrawal of ponatinib from the market presented problems for patients responding to the drug. For many, there was no alternative. Providers were instructed to seek single-patient investigational new drug (IND) applications to permit continued access to the drug. Between November 2013 and January 2014, more than 370 patients applied for single-patient INDs [6]. In January 2014, the FDA allowed reintroduction of ponatinib into the market, but only for patients for whom no other TKI is indicated. Specifically, the use of ponatinib is now limited to treatment of adult patients with T315I-positive CML or T315I-positive, Ph+ ALL regardless of prior TKI therapy, as well as the treatment of adult patients with CML (any phase) or Ph+ ALL for whom no other TKI therapy is indicated. In addition, new safety measures were added, including a risk evaluation and mitigation strategy program and new requirements for postmarketing studies. Important lessons have since become clear surrounding the decisions to grant AA, to withdraw approval, and to reintroduce the drug.

## A Broad Label

Ponatinib's initial AA was based upon data from the phase II PACE study, which included CML patients with either T315I or resistance/intolerance to the second-generation inhibitors dasatinib or nilotinib. However, the approval was broadened to include resistance to, or intolerance of, *any single TKI*. The initial label, allowing use of ponatinib in imatinib-resistant patients not yet treated with second-line TKIs, did not fit the strict definition of an unmet need, because other agents were commercially available for these patients. The lack of a companion diagnostic for the T315I resistance mutation may have led to the broader

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label in the U.S. It should be noted, however, that many National Cancer Institute comprehensive cancer centers have the capability of detecting T315I through "home brew" laboratory developed tests. Had the narrower indication (T315I) been used in the initial approval, withdrawal of ponatinib AA might have been unnecessary.

## Unexpected Toxicity

Preclinical evaluations of ponatinib did not identify signals of vascular toxicity. Accordingly, early trials did not exclude patients with cardiovascular risk factors. Further, clinical protocols did not clearly define vascular occlusive events nor require documentation of such events by imaging and/or laboratory tests. Analyses by FDA subsequently broadened the definition of vascular events (including nonspecific "chest pain"), thereby expanding the apparent frequency of events.

In the phase III EPIC trial, closed after accrual of 307 patients, the incidence of any arterial occlusive event was 7% in the ponatinib arm versus 2% in the imatinib arm [7]. With a median follow-up of 5.1 months, this difference did not reach statistical significance and did not meet predetermined criteria for trial closure. Nevertheless, both the FDA and the sponsor agreed to close the trial based upon the accumulating phase I–II toxicity data. Because toxicity was so important in the regulatory decisions to withdraw ponatinib, consistent and clinically relevant definitions of thrombotic toxicity, with appropriate clinical and radiological documentation, would have helped in reaching regulatory decisions. Only with carefully defined prospective criteria and longer follow-up will it be possible to determine the true risk of thrombosis while also enabling safety comparisons among agents.

## Uncertainties About Dose

Ponatinib's journey through the regulatory process, accelerated because of its activity in refractory CML, illustrates another potential risk of early approval, namely uncertainty about dose. Responses were seen at the lowest dose levels in the phase I trial of ponatinib [4]. Daily doses of 15–45 mg achieved serum drug concentrations predicted to suppress the development of resistance mutations in preclinical studies. Thus, the approved daily dose of 45 mg may not have been optimal in terms of efficacy and safety, particularly because subsequent analyses now suggest an association between dose intensity and risk for vascular adverse events [8]. Additional trials of 15–30-mg doses of ponatinib will therefore be necessary.

## Therapeutic Potential

Following suspension of the EPIC trial, an analysis of the first 307 patients enrolled revealed a consistent and striking two- to threefold improvement in rates of major molecular response at each successive time point [7]. With appropriate dose adjustment and exclusion of patients at high risk of toxicity, ponatinib may yet prove to be a useful first line agent for CML.

## Conclusion

AA has addressed important unmet needs in oncology. The ponatinib experience teaches the important lesson that such approval, although a valuable advance, entails risk and leads to marketing based on incomplete information about toxicity, dose, and therapeutic potential. These aspects of drug evaluation will require extensive study after marketing, and early approval is only justified if the drug fills a serious gap. Thus, the label should be written as specifically and narrowly as possible to address that gap. Furthermore, the policy of requiring companion diagnostics for AA of drugs that target specific mutations needs further discussion, particularly when testing for such mutations is widely available at cancer centers.

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