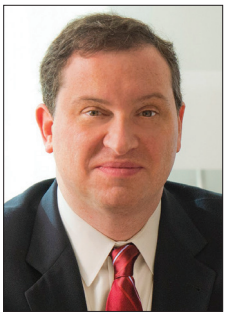
I Wish I Knew . . .



On April 6, 2023, AbbVie announced its intent to voluntarily withdraw its accelerated approval for ibrutinib in mantle cell lymphoma and marginal zone lymphoma in the United States. We have had quite a few withdrawals of accelerated approvals recently. Perhaps the FDA is attempting to clean house and make up for some of its past shortcomings. This announcement struck me as particularly impactful, however, because it was associated with the results of the SHINE trial. Ibrutinib's accelerated approval in mantle cell lymphoma and marginal zone lymphoma was based on overall response data from phase 2 studies and was contingent upon the results from confirmatory phase 3 trials: SHINE and SELENE.

The SHINE trial investigated ibrutinib vs placebo in combination with six cycles of bendamustine plus rituximab, followed by rituximab maintenance, in patients with untreated mantle cell lymphoma aged 65 years or older. The primary endpoint for the trial was investigator-assessed PFS, with OS and safety assessed as secondary endpoints. A total of 523 patients were randomized to one of the two treatment arms. After a median follow-up of 84.7 months, the median PFS was 80.6 months in the ibrutinib group and 52.9 months in the placebo group, with a hazard ratio for disease progression or death of 0.75 (P=.01). These results were published in the *New England Journal of Medicine* by Wang and colleagues on June 30, 2022. The OS at 7 years was similar in the two groups, at 55.0% in the ibrutinib group and 56.8% in the placebo group, with a hazard ratio of 1.07. The incidence of grade 3 or 4 adverse events during treatment was 81.5% in the ibrutinib group and 77.3% in the placebo group.

At first glance, a trial meeting its primary endpoint with such a great margin should be considered a successful trial. The results of the SHINE trial, a pivotal phase 3 registration trial using PFS as the primary endpoint, should have translated into a full approval. However, not only did ibrutinib fall short of obtaining full approval in mantle cell lymphoma, it, in essence, ended up losing its accelerated approval. This raised an immediate question: How could a successful trial lead to the failure of a drug? I initially became concerned that the denial of ibrutinib's full approval for this indication was based on it not achieving a statistical benefit in OS in the trial. Although this might represent the FDA "moving the goal posts" after the trial was undertaken by deciding to require an improvement in OS and not just PFS, my real concern is that the reason behind the shift in desired endpoint is an error in thinking by the FDA that an improvement in PFS must translate into an improvement in OS. Was this going to be a new standard, given the advances made with our novel therapies in lymphoma that are moving us out of the "unmet need" arena? For most lymphomas, we have excellent second-line therapies that enable us to adequately salvage patients but avoid hitting the OS endpoint. Requiring an OS benefit would prevent much novel drug development.

After much thought, I have another hypothesis. As noted, OS in SHINE was similar in the two arms, with 39.8% of patients in the ibrutinib group and 40.8% of patients in the placebo group dying. Although the rate of death due to disease progression favored ibrutinib (11.5% vs 20.6%), the rate of death due to adverse events favored placebo (10.7% vs 6.1%). What might now be emerging is the possibility that any benefit in PFS is negated by the increased mortality associated with the use of the drug. On the other hand, I would have expected the increase in deaths to be apparent on the PFS curve, as the PFS definition includes progression or death.

How are we supposed to interpret the FDA's actions? On the one hand, the FDA may be posturing to make up for past mistakes by now holding approvals to higher standards, possibly denying patients access to effective therapies. Given that ibrutinib remains on the market and off-label prescribing is ubiquitous, its use may continue unimpeded. But what if the FDA's decision is based upon a safety signal they saw? What if there are concerns that the benefits are outweighed by harm? Does this signal extend to other BTK inhibitors with chemotherapy for mantle cell lymphoma? What about patients currently on ibrutinib?

I take issue with how this process has played out. Although the decision to withdraw ibrutinib for approval in mantle cell and marginal zone lymphoma was voluntarily made by the pharmaceutical company, it is based on data generated from clinical trials and has implications far beyond the patients in those clinical trials. The FDA has an obligation to disseminate this information to everyone involved in the care of patients impacted by these data. Knowledge is power. If disseminating it benefits patients, withholding it is negligence. I want to see an FDA that better educates physicians and advocates for patients!

Sincerely,

Richard R. Furman, MD