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Commentary

US Food and Drug Administration Approvals for Bruton Tyrosine Kinase Inhibitors in Patients With Chronic Lymphocytic Leukemia: Potential Inefficiencies in Trial Design and Evidence Generation

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The US Food and Drug Administration granted acalabrutinib approval as the second Bruton tyrosine kinase (BTK) inhibitor to treat patients with chronic lymphocytic leukemia and small lymphocytic lymphoma as monotherapy or in combination with obinutuzumab. This approval was based on 2 phase 3 trials: ELEVATE-TN and ASCEND. There are several concerns with the design of these trials, including suboptimal treatment of patients in the control arm, expansion of the trial population, and lack of data regarding efficacy or tolerability compared with ibrutinib, a first-in-class drug. The Food and Drug Administration approval of acalabrutinib for patients with chronic lymphocytic leukemia and small lymphocytic lymphoma represents concerning drug approval patterns in the United States and a weakness in evidence generation. ***Cancer* 2020;126:4270-4272**. © *2020 American Cancer Society*.

KEYWORDS: acalabrutinib, Bruton tyrosine kinase (BTK) inhibitor, chronic lymphocytic leukemia (CLL), ibrutinib, small lymphocytic lymphoma (SLL), US Food and Drug Administration (FDA) approval.

INTRODUCTION

Bruton tyrosine kinase (BTK) inhibitors have been a standard of care in patients with chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) since 2014. Ibrutinib is a first-in-class BTK inhibitor that irreversibly inactivates the kinase by covalently binding to a cysteine residue near the active site. First approved by the US Food and Drug Administration (FDA) in 2014, ibrutinib initially was authorized for the treatment of patients with CLL with 17p deletion or after first-line therapy. This was based on Study 1102 (ClinicalTrials.gov identifier NCT01105247), a single-arm study of 48 previously treated patients with CLL. Study 1102 was followed by the RESONATE trial, a phase 3 study of 391 patients with previously treated CLL in which ibrutinib was compared with ofatumumab. In this study, approximately 32% of patients had a 17p deletion, which is known to be a predictor of poor survival and resistance to treatment.[1] It is interesting to note that ibrutinib benefit occurred irrespective of chromosome 17p status. The timeline of these events is shown in Figure 1.

On November 21, 2019, acalabrutinib (Calquence; AstraZeneca) was approved in the United States as the second BTK inhibitor for the treatment of patients with CLL and/or SLL as monotherapy or in combination with obinutuzumab. This was based on 2 phase 3 trials, ELEVATE-TN and ASCEND, which demonstrated improved progression-free survival. ELEVATE-TN included previously untreated patients who were considered unfit for intensive therapy and who were aged ≥65 years and with comorbidities. The ASCEND trial (CTCAE - Common Terminology Criteria for Adverse Events) included patients with recurrent or refractory CLL. The design of both trials and the FDA approval of acalabrutinib raise several concerning patterns in trial design and drug approvals in BTK inhibitors.

First, in both trials, the treatment administered to the control arm was suboptimal and not an adequate comparison. The prognostic implications of 17p deletion first were reported in 2000 by Dohner et al.[2] At the time of ibrutinib approval in 2014, it was known that approximately 5% of patients with CLL harbor a 17p deletion at the time of diagnosis and many other patients develop either a 17p deletion or a TP53 mutation later in the course of disease.[3] By 2015, ibrutinib was the standard of care for patients with 17p abnormalities. Nevertheless, TP53 mutations or 17p deletions were noted in approximately 14% of participants in the ELEVATE-TN trial and 28% of participants in the ASCEND trial.[4] In this subgroup of patients, at the start of trial enrollment, ibrutinib was considered to be the most effective agent in both

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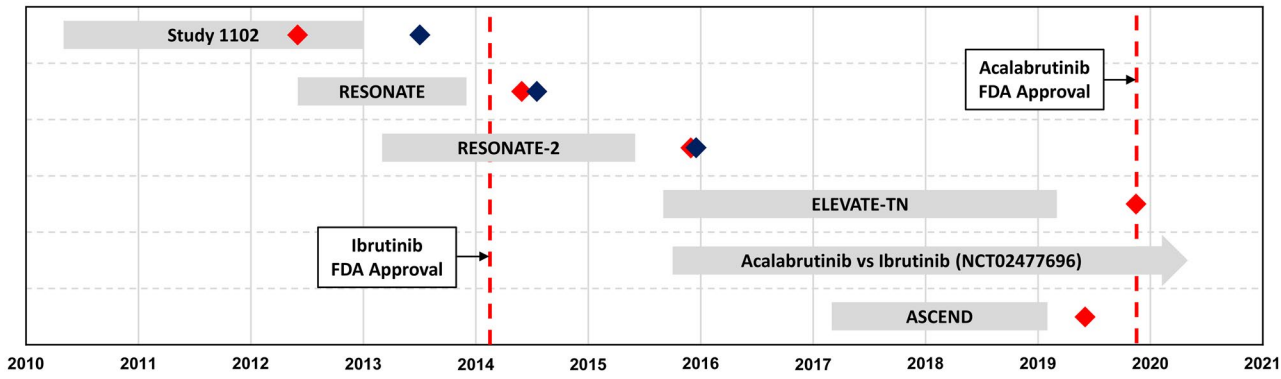

FIGURE 1. Timeline of accrual duration of clinical trials regarding Bruton tyrosine kinase (BTK) inhibitors in patients with chronic lymphocytic leukemia (CLL) and/or small lymphocytic lymphoma (SLL). Blue diamonds indicate the date of publication; red diamonds, the date the first results were reported in an abstract or press release; ASCEND, a phase 3 trial comparing acalabrutinib versus investigator choice (idelalisib plus rituximab or bendamustine plus rituximab) in patients with recurrent refractory CLL; ClinicalTrials.gov identifier NCT02477696, a phase 3 noninferiority study of acalabrutinib versus ibrutinib in previously treated patients with high-risk CLL; ELEVATE-TN, a phase 3 trial comparing acalabrutinib plus obinutuzumab or acalabrutinib versus obinutuzumab plus chlorambucil; FDA, US Food and Drug Administration; RESONATE, a phase 3 trial comparing ibrutinib with ofatumumab in previously treated patients with CLL; RESONATE-2, a phase 3 trial comparing ibrutinib with chlorambucil in untreated patients with high-risk CLL excluding those with a 17p deletion; Study 1102, a single-arm study of ibrutinib in previously treated patients with CLL.

patients who were newly diagnosed with and those with recurrent refractory CLL.

ELEVATE-TN began enrollment in September 2015 and used a control arm of obinutuzumab plus chlorambucil, which was not considered standard therapy in patients with TP53 aberrations. In the ASCEND trial, the control arm was the investigators' choice of either idelalisib and rituximab or bendamustine and rituximab. The ASCEND trial began enrolling patients in February 2017. Neither trial permitted the use of ibrutinib, even for patients with 17p alterations.

Second, the ASCEND trial questionably expanded the trial population. Idelalisib and rituximab were approved in 2014 after a phase 3 trial suggested an improvement in progression-free survival in patients with recurrent CLL who were deemed unfit for chemoimmunotherapy. Therefore, the combination was approved in patients with comorbidities for whom rituximab alone would be considered appropriate therapy.[5] However, the ASCEND trial did not limit participation to patients with comorbidities. Nevertheless, approximately 77% of the control group received idelalisib and rituximab. In 2017, when the study started enrollment, ibrutinib was established as an effective treatment in patients with recurrent refractory CLL. This study was critical for the approval of acalabrutinib in a wider population of patients with CLL who required treatment. Discordance between trial participants and patients who were treated after drug approval has long been a concern. More often, trial participants are younger and have fewer comorbidities, leading to a higher incidence of adverse events in real-world patients. In the ASCEND trial, idelalisib, a treatment that to our knowledge is appropriate only among patients who are ineligible for standard treatment, facilitated acalabrutinib approval within a wider context, when it is likely chemoimmunotherapy should have been offered to at least some patients in the control arm and conferred a greater benefit. The design of the trial with an inadequate control arm[6] failed to generate necessary evidence applicable to patients with recurrent refractory CLL without comorbidities. Trials with inadequate control arms generally fail to provide relevant information for practicing clinicians, namely, is this new drug better than the standard of care I would currently apply? Although at least some blame can be attributed to the study sponsor, investigators, and institutional review board oversight, FDA approval based on this evidence is problematic, because the agency is one of the few safeguards of the public interest.

Third, acalabrutinib was approved without any data regarding its efficacy or tolerability compared with ibrutinib, a first-in-class drug. A phase 3 study comparing acalabrutinib with ibrutinib began enrollment in October 2015, a month after recruitment was initiated for the ELEVATE-TN trial; to our knowledge, it currently has 533 participants with an estimated study completion date of March 2021. However, the FDA approved acalabrutinib for the treatment of patients with CLL prior to the publication of any results from this study. The application by AstraZeneca requesting approval of acalabrutinib for the treatment of CLL cites the

distinct toxicity profile of ibrutinib leading to therapy discontinuation and the need for better tolerated therapeutic agents.[7] Comparison of the observed rates of adverse events across clinical trials is not possible. However, in the intervention arm of the ASCEND trial, patients receiving acalabrutinib monotherapy are reported to have high rates of grade 3 infection, neutropenia, and anemia, as was reported for ibrutinib. There also are increased rates of atrial fibrillation and second primary malignancies, which is considered a class side effect of BTK inhibitors.[4] The available evidence does not suggest any clear improvement in the toxicity profile of acalabrutinib compared with ibrutinib.

The approval of acalabrutinib for the treatment of patients with CLL and/or SLL represents several concerning drug approval patterns in the United States. Both the ELEVATE-TN and ASCEND trials have demonstrated suboptimal treatment of the control arm based on best available therapy at the time of trial design. The majority of patients in the control arm of the ASCEND trial received a treatment indicated for unfit patients; however, acalabrutinib was approved for a general patient population irrespective of comorbidities. Last, to the best of our knowledge, there is no evidence of an advantage of acalabrutinib compared with ibrutinib with regard to either efficacy or safety. Finally, acalabrutinib is not substantively less expensive than ibrutinib. A 28-day prescription of ibrutinib is $13,546 compared with $14,692 for acalabrutinib.[8] The regulatory history of BTK inhibitors suggests weaknesses in the generation of optimum evidence, and problematic regulatory oversight.

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