

# ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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## Recent Data for Acalabrutinib in Chronic Lymphocytic Leukemia



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### H&O What type of drug is acalabrutinib?

**PG** Acalabrutinib (Calquence, AstraZeneca) is a so-called next-generation Bruton's tyrosine kinase (BTK) inhibitor. The first-generation BTK inhibitor, ibrutinib (Imbruvica, Pharmacyclics/Janssen), is a covalent inhibitor. Acalabrutinib covalently binds to C481. Acalabrutinib inhibits very few kinases other than BTK. In contrast, ibrutinib inhibits several other kinases. This difference might explain the fact that acalabrutinib has fewer off-target effects than ibrutinib.

Acalabrutinib and ibrutinib are both oral agents. The typical daily dose of acalabrutinib is two 100-mg capsules. Ibrutinib is administered once daily, at a dose of 420 mg for chronic lymphocytic leukemia (CLL).

### H&O What clinical trial data led to the approval of acalabrutinib in CLL?

**PG** The US Food and Drug Administration (FDA) approved acalabrutinib based on 2 different trials. The ELEVATE-TN trial enrolled treatment-naïve patients with CLL. The patients were elderly and/or had comorbidities. The patients were randomly assigned to acalabrutinib monotherapy, acalabrutinib plus the anti-CD20 monoclonal antibody obinutuzumab (Gazyva, Genentech), or the standard treatment regimen of chlorambucil plus obinutuzumab. The study showed an improvement in progression-free survival (PFS) for acalabrutinib alone and in combination with obinutuzumab as compared

with chlorambucil plus obinutuzumab. Acalabrutinib also decreased the risk of death and progression. There were no significant differences in overall survival, likely because patients who developed relapsed disease during treatment with chlorambucil plus obinutuzumab were permitted to switch to acalabrutinib monotherapy for rescue therapy.

The benefit in PFS was evident among patients with high-risk genetic features, such as *TP53* aberrations, deletion 17p, or an unmutated immunoglobulin heavy chain variable region (IGHV) gene. The combination of acalabrutinib plus obinutuzumab appeared to be somewhat more effective than acalabrutinib alone, although the total number of patients in these arms was too low to confirm the significance of the difference. In addition, the study was not designed or powered to detect any differences between the acalabrutinib arms.

The ASCEND trial evaluated acalabrutinib in patients with relapsed or refractory CLL. The patients were randomly assigned to treatment with either acalabrutinib monotherapy or the physician's choice of the phosphoinositide 3-kinase (PI3) delta inhibitor idelalisib (Zydelig, Gilead) plus the anti-CD20 monoclonal antibody rituximab (Rituxan, Genentech/Biogen) or traditional chemotherapy with bendamustine (Bendeka, Teva) plus rituximab. Most patients in the physician's choice arm received idelalisib plus rituximab. Therefore, the ASCEND trial is perhaps the first study to compare 2 new chemotherapy-free treatments: acalabrutinib in one arm and idelalisib plus rituximab in the other arm.

The trial reached the primary endpoint of PFS. The median PFS was not reached with acalabrutinib monotherapy vs 16.5 months in the physician's choice arm.

### **H&O** What was learned about acalabrutinib in studies presented at the 2021 American Society of Clinical Oncology (ASCO) annual meeting?

**PG** At the 2021 ASCO meeting, my colleagues and I presented a 4-year update of data from the ELEVATE-TN study. In the initial analysis that led to FDA approval, the follow-up was approximately 2 years. The long-term update showed that the efficacy results were maintained. There were no new safety signals. A difference between acalabrutinib alone vs acalabrutinib plus obinutuzumab was still apparent. Future data may show that acalabrutinib plus obinutuzumab is superior to acalabrutinib alone. The patient numbers from the ELEVATE-TN trial are too low to provide confirmation.

Another important study in CLL presented at the 2021 ASCO meeting was the ELEVATE-RR trial. This noninferiority, head-to-head trial compared acalabrutinib monotherapy vs ibrutinib monotherapy in patients with relapsed or refractory disease. The trial enrolled a high-risk population with either deletion 17p or deletion 11q because these patients are difficult to treat with chemotherapy. With approximately 4 years of follow-up, the study showed that acalabrutinib was not inferior to ibrutinib in terms of efficacy. There was no difference in PFS, the primary endpoint, with a hazard ratio of 1.00. Secondary endpoints consisted of atrial fibrillation/flutter, grade 3 or higher infection, incidence of Richter transformation, and overall survival. The frequency of any-grade atrial fibrillation was lower with acalabrutinib compared with ibrutinib. There were no statistically significant differences for the other secondary endpoints.

Treatment with acalabrutinib was associated with lower rates of hypertension, minor bleeding, arthralgia, and myalgia (although these events were not secondary endpoints). The ELEVATE-RR trial therefore showed that acalabrutinib had similar efficacy to ibrutinib, but caused less atrial fibrillation and had a safety profile that was more tolerable overall.

### **H&O** What are the main toxicities associated with acalabrutinib, and how are they managed?

**PG** Acalabrutinib, being a BTK inhibitor, is associated with some cardiovascular toxicity, although less than that reported with ibrutinib. It appears that acalabrutinib is not associated with ventricular arrhythmia or sudden death. The most common adverse event associated with acalabrutinib is headache, which typically arises a few

hours after the first intake of the drug. The headaches last for a median of 3 weeks. Patients report that these headaches are similar to others they have experienced. Typically, the headaches can be managed with standard treatments, such as anti-inflammatory drugs. They also respond to caffeine. Some doctors advise patients with headaches to drink soda or coffee, as they contain caffeine.

In the United States, clinical use suggests that acalabrutinib is well tolerated and associated with fewer adverse events than ibrutinib, confirming the evidence generated in the clinical trials.

The other adverse events can be managed following protocols established for BTK inhibitors. For example, the patient can take 1 capsule of acalabrutinib rather than 2 capsules. In addition, treatment can be stopped for a short period, perhaps a few days, so that the patient can recover from the event. Treatment can then start again.

### **H&O** Are there patients who are better or worse candidates for acalabrutinib?

**PG** When a physician has identified a BTK inhibitor as the treatment strategy, acalabrutinib might be a preferable choice based on the more tolerable safety profile, particularly in terms of cardiovascular toxicity. The risk of cardiovascular toxicity is lower with acalabrutinib than ibrutinib, but it still remains. Therefore, if a physician is especially concerned about cardiovascular risk, including atrial fibrillation, bleeding, or hypertension, treatment with a BTK inhibitor will not be initiated. Instead, another strategy, such as a BCL-2 inhibitor, might be considered.

### **H&O** Has anything been learned as acalabrutinib moved from trials to use in the clinic?

**PG** The approval of acalabrutinib was earlier in the United States than in Europe, and thus there is currently

more experience in the former. In the United States, clinical use suggests that acalabrutinib is well tolerated and associated with fewer adverse events than ibrutinib, confirming the evidence generated in the clinical trials. The use of acalabrutinib in the United States is increasing. Acalabrutinib is also administered in combination with obinutuzumab, as this combination might reduce lymphocytosis or achieve more profound responses, which might be a goal in certain settings, such as younger patients.

### H&O Are there ongoing studies of acalabrutinib?

**PG** Studies are evaluating the combination regimen of acalabrutinib plus the BCL-2 inhibitor venetoclax (Venclexta, Genentech/AbbVie). The ongoing, randomized phase 3 AMPLIFY trial is evaluating the combination regimen of acalabrutinib and venetoclax, with or without obinutuzumab, in patients with untreated CLL. Patients in the comparator arm will receive fludarabine, cyclophosphamide, and rituximab (FCR) or bendamustine plus rituximab, depending on their age. Treatment will last a fixed duration of 1 year. Data regarding a fixed-duration regimen will be helpful. Currently, acalabrutinib is administered indefinitely until the patient develops disease progression or intolerable adverse events. The AMPLIFY trial should help determine whether combining acalabrutinib with other drugs in a fixed duration will be safe and will allow patients a treatment holiday, in order to decrease the possibility of long-term adverse events and the occurrence of drug resistance.

### H&O Does acalabrutinib have the potential for use in other malignancies?

**PG** The BTK pathway is also relevant in other diseases. In the United States, acalabrutinib is approved for the treatment of mantle cell lymphoma. (This indication is not yet approved in Europe.) BTK inhibitors are approved in other diseases, such as Waldenström macroglobulinemia and marginal zone lymphoma, in the United States. In

the future, the approval of acalabrutinib may encompass these conditions, as well as other lymphomas.

### Disclosure

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### Suggested Readings

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