

CLL IN FOCUS

Current Developments in the Management of Chronic Lymphocytic Leukemia

Six-Year Update of the ELEVATE-TN Study on Acalabrutinib



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H&O Could you describe the impetus for and design of the ELEVATE-TN trial?

JS The ELEVATE-TN study was conducted to seek regulatory authorization for acalabrutinib (Calquence, AstraZeneca) in the frontline setting. Acalabrutinib is a selective, covalent Bruton tyrosine kinase (BTK) inhibitor with efficacy in chronic lymphocytic leukemia (CLL). The initial study compared 2 regimens of acalabrutinib vs an existing standard of care, obinutuzumab (Gazyva, Genentech) and chlorambucil (Leukeran, Aspen Global), in an older CLL patient population. The control arm had been used in 5 different registration studies, and this was 1 of those 5 studies. The 2 acalabrutinib arms were acalabrutinib monotherapy and acalabrutinib in combination with obinutuzumab. The primary endpoint was progression-free survival (PFS). Key secondary endpoints included overall response rate, overall survival, safety, and toxicity.

H&O What were the initial findings of the trial, and how have they evolved over the past 6 years?

JS The most important initial finding was that both acalabrutinib-containing regimens beat the control arm of obinutuzumab and chlorambucil to a statistically significant and clinically meaningful extent. The way that the data have evolved over the last 6 years has been interesting because the addition of anti-CD20 antibodies to BTK inhibitors has been a subject of controversy in the field. Specifically, prior studies, including ALLIANCE and another from MD Anderson, involved the addition of rituximab,

an anti-CD20 antibody, to ibrutinib (Imbruvica, Pharmacyclics/Janssen), a BTK inhibitor, and showed no clinically meaningful improvement; however, in this study, we saw that the addition of obinutuzumab to acalabrutinib led to further improvements in PFS. In our first report, which was based on less than 4 years of follow-up, the difference was relatively small. The magnitude of the PFS benefit has continued to increase over time and is now quite substantial. One of the challenges is that acalabrutinib, being a pill, is often considered for monotherapy based on its simplicity; patients may prefer it to avoid infusions. Secondly, during the COVID pandemic, anti-CD20 antibodies fell out of favor owing to concerns about interference with the effectiveness of the COVID vaccine. Despite the improvement in PFS with the addition of obinutuzumab to acalabrutinib, there remains a reasonable measure of both practice variation and uncertainty as to whether to include the anti-CD20 antibody.

H&O What role do genomic markers play in this trial?

JS In this study, we looked at traditional high-risk markers, including *IGHV* mutation status and deletion 17p (del[17p]) and/or *TP53* mutation. What we saw was that the presence or absence of the *IGHV* mutation did not appear to have a clinically significant impact on either of the acalabrutinib-containing regimens; however, it did have the predicted adverse impact on patients treated with obinutuzumab and chlorambucil.

The del(17p) or *TP53*-mutated population was a bit

more interesting. Specifically, we found that the benefit of adding obinutuzumab occurred only in patients who had normal 17p status or wild-type *TP53*. If patients had del(17p) or mutated *TP53*, they did not receive additional benefits by adding obinutuzumab.

H&O What were the adverse events?

JS Adverse events for both agents are well-characterized within the field at this point, and this study led to no surprises. Some bruising and bleeding were reported, but these were relatively mild. Neutropenia and infections were also observed. When obinutuzumab was added, the rates of grade 3/4 neutropenia increased, along with a slight increase in infectious complications. In all, BTK inhibitors are currently well-established and considered to be a safe and effective class of drugs.

H&O How do BTK inhibitors contribute to the treatment paradigm for CLL, and what distinguishes their role in this context?

JS Right now, BTK inhibitors are the most commonly utilized frontline therapy in the management of CLL. There are 3 BTK inhibitors used in this space, including acalabrutinib, zanubrutinib (Brukinsa, BeiGene), and ibrutinib. Ibrutinib, as the first agent in this class, played a pivotal role in establishing the superiority of BTK inhibitors vs various chemoimmunotherapy regimens that were previously standard; however, the second-generation BTK inhibitors, acalabrutinib and zanubrutinib, have been compared with ibrutinib and found to have fewer overall side effects. Consequently, second-generation BTK inhibitors, particularly acalabrutinib and zanubrutinib, are being utilized more frequently among patients initiating BTK inhibitor therapy. The role of obinutuzumab is somewhat less clearly defined, and its use depends on both patient and physician preferences.

H&O What is the next step for this combination therapy?

JS Currently, acalabrutinib stands as the most used BTK inhibitor in the frontline setting, often as a monotherapy. However, in terms of what is coming ahead, there is considerable interest in combining acalabrutinib with existing BCL2 inhibitors, such as venetoclax (Venclexta, AbbVie/Genentech). The results of a registration study examining this combination are forthcoming, and I would not be surprised to witness the emergence of an all-oral regimen becoming more commonly used. Despite these developments, acalabrutinib as monotherapy or in combination with obinutuzumab remains a good treatment option for patients.

H&O What other CLL treatment options exist?

JS The other treatment strategy involves fixed-duration obinutuzumab in combination with venetoclax. This option is appealing because patients receive 6 months of infusions and 12 months of pills, followed by a period off therapy. Although this combination poses a logistical challenge and requires more monitoring, it serves as a favorable alternative for motivated and medically suitable patients.

Finally, there are chemoimmunotherapy regimens, although recent evidence has shown the superiority of novel targeted agents to chemoimmunotherapy. Therefore, chemoimmunotherapy may be limited to geographic locations where targeted agents are unavailable, such as in some international settings, or individuals lacking access to novel agents owing to financial or other social constraints.

H&O Beyond ELEVATE-TN, what other studies support acalabrutinib's efficacy and safety?

JS ELEVATE-TN focused on treatment-naïve patients, but 2 additional studies looked at it in the relapsed or refractory (R/R) population. One was ELEVATE-RR, in which acalabrutinib was compared head-to-head against ibrutinib. The second, the ASCEND trial, compared acalabrutinib vs an investigator's choice of either a phosphoinositide 3-kinase inhibitor or traditional chemoimmunotherapy, where it had demonstrated superiority. Together, this trio of studies firmly established the role of acalabrutinib in both the frontline and R/R settings.

Disclosures

Dr Sharman has consulted for AbbVie, AstraZeneca, BeiGene, Lilly, Janssen, and Merck.

Suggested Readings

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