ELEVATE-RR: ACALABRUTINIB DEMONSTRATES SIMILAR EFFICACY AND BETTER SAFETY COMPARED WITH IBRUTINIB

Presented By

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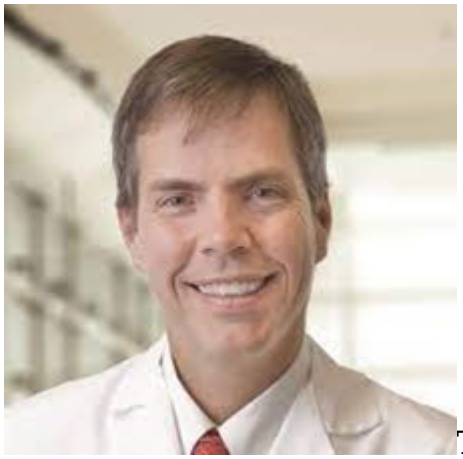
Phase 3, ELEVATE-RR



The phase 3 ELEVATE-RR trial was a head-to-head comparison of acalabrutinib versus ibrutinib in previously treated patients with chronic lymphocytic leukemia. The first results of this study demonstrated that acalabrutinib had better tolerability than ibrutinib with fewer patients experiencing cardiovascular toxicities. Moreover, acalabrutinib had similar efficacy to ibrutinib concerning progression-free survival.

This phase 3 trial was presented at the American Society of Clinical Oncology (ASCO) Annual Meeting, which was held virtually 4-10 June, 2021 [1]. *Medicom's journalist* spoke with principle investigator, the D. Warren Brown Chair of Leukemia Research, Dr. John Byrd (Ohio State University College of Medicine, USA) [1].

Bruton's tyrosine kinase (BTK) plays a critical role in chronic lymphocytic leukemia (CLL) tumor cell migration, adhesion, proliferation, and survival. Ibrutinib was the 1st irreversible BTK inhibitor but is associated with adverse events (AEs), particularly cardiovascular toxicities, that can lead to treatment discontinuation. Acalabrutinib is a next-generation, more selective BTK inhibitor. The first results of the head-to-head phase 3 trial ELEVATE-RR (NCT02477696), which compared safety and efficacy of ibrutinib and acalabrutinib in patients with previously treated CLL and presence of del(17p) or del(11q) [1]. Patients were randomised 1:1 into 2 treatment arms and received either 100 mg acalubritinib twice daily or 420 mg ibrutinib once daily. The primary endpoint was non-inferiority on progression-free survival (PFS), which was then followed by superiority analysis in secondary endpoints of safety and efficacy. Included were 533 patients, 268 received acalabrutinib and 265 received ibrutinib. The median duration of follow up was 40.9 months. More than half of the patients discontinued treatment, mainly due to disease progression, which was to be expected given that the patients were pre-treated. Median PFS was 38.4% in both arms. Thus, the primary endpoint, non-inferiority of PFS with acalabrutinib versus ibrutinib, was

met. First results of secondary endpoints were also presented: the incidence of any-grade atrial fibrillation/flutter was significantly lower with acalabrutinib, the incidence of grade ≥3 infection was similar between treatment arms, the incidence of Richter's transformation was similar, and the hazard ratio of overall survival was comparable. Summarizing safety data revealed fewer adverse events (AEs) leading to treatment discontinuation and fewer deaths due to AEs for acalabrutinib, while any-grade and grade ≥3 AE incidences were comparable.

In summary, acalabrutinib was non-inferior to ibrutinib in the primary endpoint PFS and demonstrated lower frequencies of common AEs. These results demonstrate that acalabrutinib is better tolerated and has similar efficacy to ibrutinib in patients with previously treated CLL.

Medicom interviewed researcher John Byrd to understand the implications:

CAN YOU TELL US WHY THESE DATA ARE IMPORTANT?

"The ELEVATE-RR trial is the first phase 3 study that has compared the first-generation, irreversible Bruton's tyrosine kinase inhibitor ibrutinib to acalabrutinib, a second-generation BTK inhibitor, that is more selective than the first generation molecule in relapsed and refractory CLL. The study was designed as a non-inferiority study and a non-inferiority study typically work to show that, clinically, drugs work similarly in terms of preserving remission and overall survival, while showing other benefits. This study included over 500 patients, at the endpoint of showing non-inferiority, eventually, suggesting that these therapies are very similar in terms of remission duration.

These results also demonstrated for the first time in a randomized setting, that cardiac effects, in particular, atrial fibrillation and hypertension were significantly less frequently noted with acalabrutinib as compared to ibrutinib. Over time, we saw that there was increased therapy cessation with ibrutinib as compared with acalabrutinib, which did increase adverse events in a variety of areas. In balance, acalabrutinib did have more frequent headaches and coughs compared to ibrutinib. Over time, the benefit was seen in these areas, and when one looks at the overall survival of the study, while there was not a significant finding, the hazard ratio of 0.82 for overall survival favored acalabrutinib.

The significance of this for patients with relapsed and refractory CLL, can certainly extend to untreated CLL. Finally, these results suggest that we now have two Bruton's tyrosine kinase inhibitors that are highly effective for CLL. This study showed clearly that one of

these is safer with respect to cardiovascular complications and other adverse events that cause patients to stop therapy."

WHAT WILL THE IMPACT BE ON DAY-TO-DAY CLINICAL PRACTICE?

"When you look at the direct comparison, physicians choose drugs for their patients based upon how well they work, taking the side effects and the cost into account, and this study shows that one therapy works just as well, but with fewer side effects. If the health economics look favorable going forward, then I think we will see substantially broader use of acalabrutinib based on these data."

LIMITATIONS AND NEXT STEPS?

"One of the main limitations of this study, as with all the randomized studies comparing to acalabrutinib, was that it was not blinded. The investigators were not blinded to which therapy the patient was receiving. That was decided in part because of the difference in therapy administration, and the size of tablets. That choice in design can influence side effect reporting perhaps leading to a subjective bias to believe that the acalabrutinib was safer. However, it was notable that the most significant side effect difference between acalabrutinib and ibrutinib was atrial fibrillation and hypertension, which are hard black and white outcomes, not subjective at all. The second limitation is that this study was applied to relapsed and refractory patients and, in general, which facilitated a more rapid response. If this study had been done in previously untreated patients, we would not have the answer to this important question for several more years."

1. Byrd J, et al. First results of a head-to-head trial of acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia. 0.1200/JCO.2021.39.15_suppl.7500 Journal of Clinical Oncology 39, no. 15_suppl (May 20, 2021) 7500-7500.

