Adverse events of interest with zanubrutinib vs fixed-duration combination of venetoclax + obinutuzumab in treatment-naive chronic lymphocytic leukemia

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ABSTRACT

Introduction: The efficacy and safety of BTKi zanubrutinib monotherapy has been evaluated in treatment-naive chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) in SEQUOIA (NCT03336333), while the combination of fixed-duration BCL-2 inhibitor venetoclax + CD20 monoclonal antibody obinutuzumab (VenO) has been evaluated in CLL14 (NCT02242942). This analysis evaluated selective adverse events of interest (AEIs) with zanubrutinib vs VenO.

Methods: The incidence rates of infections, hematologic events, and treatment-emergent adverse events (TEAEs) leading to treatment discontinuation of zanubrutinib in SEQUOIA (n=351) and VenO in CLL14 (n=212) were compared. In this analysis, data for zanubrutinib at median treatment duration of 23.9 months (to match safety follow-up for VenO) and 61.1 months and data for fixed-duration VenO from available publications (median treatment duration, 11.1 months) were compared for AEIs. Zanubrutinib outcomes were adjusted for COVID-19 as SEQUOIA was ongoing during the pandemic while CLL14 was conducted prior to the pandemic.

Results: With a median treatment duration of 23.9 months with zanubrutinib vs 11.1 months with VenO, the incidence of grade 3/4 infections (excluding COVID-19) (11.1% vs 17.5%), neutropenia (9.1% vs 52.8%), thrombocytopenia (1.1 vs 13.7), febrile neutropenia (0.6% vs 5.2%), and TEAEs leading to discontinuation (6.6% vs 15.6%) was lower with zanubrutinib vs VenO (nominal $P<.05$ for all). With longer zanubrutinib exposure of 61.2-months median treatment duration for zanubrutinib, the incidence rate of infection was higher with zanubrutinib (27.1%) vs VenO (17.5%) ($P=.010$) but similar after excluding COVID-19 (20.2% vs 17.5%, $P=.418$). The rates of neutropenia, thrombocytopenia, and febrile neutropenia remained lower with zanubrutinib vs VenO (nominal $P\leq.05$). COVID-19 was the most common TEAE leading to discontinuation of zanubrutinib (1.1% and 1.7% with median treatment duration of 23.9 and 61.1 months, respectively), while neutropenia was the most common TEAE leading to discontinuation of venetoclax (2.4%).

Conclusions: Hematologic toxicity rates were lower with zanubrutinib vs VenO in the analysis time window. Rates of TEAEs leading to discontinuation and infections excluding COVID-19 were lower with zanubrutinib with a median treatment duration of 23.9 months. Continuing zanubrutinib monotherapy does not appear to increase the risk of infection, even with much longer treatment duration, compared with fixed-duration VenO.