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

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Background: 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).

Aims: 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 (**Table**), the incidence of grade 3/4 infections (excluding COVID-19), neutropenia, thrombocytopenia, and febrile neutropenia and TEAEs leading to discontinuation was lower with zanubrutinib vs VenO (nominal $P<.05$ for all). With longer zanubrutinib exposure at the 61.2-month median treatment duration for zanubrutinib, the incidence rate of infection was higher with zanubrutinib vs VenO but similar after excluding COVID-19. 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%).

Summary/Conclusion: 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.

Table. AEIs in SEQUOIA vs CLL14

	Zanubrutinib up to 104 weeks	**Zanubrutinib DCO: April 30, 2024**
	SEQUOIA zanubrutinib (n=351) vs CLL14 VenO (n=212)	**SEQUOIA zanubrutinib (n=351) vs CLL14 VenO (n=212)**
Median treatment exposure, months	23.9 vs 11.1	61.2 vs 11.1
Grade 3/4 infections and infestations (system organ class), %	12.5 vs 17.5; *P*=.109	27.1 vs 17.5; *P*=.010
Excluding COVID-19	11.1 vs 17.5; *P*=.034	20.2 vs 17.5; *P*=.418
Grade 3/4 neutropenia, %	9.1 vs 52.8; *P*<.001	10.3 vs 52.8; *P*<.001
Grade 3/4 thrombocytopenia, %	1.1 vs 13.7; *P*<.001	1.7 vs 13.7; *P*<.001
Grade 3/4 febrile neutropenia, %	0.6 vs 5.2; *P*=.004	0.9 vs 5.2; *P*=.005
Any TEAE leading to discontinuation, %	7.4 vs 15.6; *P*=.003	18.8 vs 15.6; *P*=.329
Excluding COVID-19	6.6 vs 15.6; *P*=.001	16.2 vs 15.6; *P*=.833

All *P* values are nominal.