Efficacy and Safety of Zanubrutinib vs. Venetoclax+Ibrutinib in the Treatment-naïve (TN) Chronic Lymphocytic Leukemia (CLL): A Matching-Adjusted Indirect Comparison (MAIC)

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Background: Zanubrutinib (zanu) is a highly effective Bruton tyrosine kinase inhibitor (BTKi) approved for the treatment of CLL. The phase 3 SEQUOIA trial (NCT03336333) evaluated the efficacy and safety of zanu in TN CLL patients with no del17p mutations (arm A, zanu; arm B, bendamustine+ rituximab), and with del17p mutations (arm C, zanu). The combination of fixed duration BCL-2 inhibitor venetoclax (V) plus the BTKi ibrutinib (I) was approved by the European Medicine Agency (EMA) for the treatment of TN CLL. V+I has been evaluated in GLOW (NCT03462719) including older/comorbid patients and excluding the del17p/TP53 population and in CAPTIVATE (NCT02910583) including younger/fitter patients and no restrictions on del17p and TP53. As no head-to-head clinical study comparing zanu vs. V+I exists, an indirect comparison is required to evaluate the efficacy and safety of the two treatments.

Aim: To conduct a population adjusted indirect comparison between zanu and V+I and reduce potential bias due to differences in study populations.

Methods: Since SEQUOIA and the V+I studies cannot be linked through a common control arm, two unanchored MAICs were conducted, matching individual patient data (IPD) from arm A of SEQUOIA vs. the V+I arm of GLOW, and pooled arm A+C of SEQUOIA vs. the V+I arm of CAPTIVATE. Adjustments for age, sex, geographic region, CLL stage, cancer type, cytogenetic mutations, complex karyotype, ECOG, bulky disease, time from diagnosis, beta2-microglobulin, and creatinine clearance were considered based on availability and magnitude of imbalance between populations. Weighted Cox regression was used to derive relative treatment effect estimates. Given that matching variables mainly impact efficacy and not safety, the primary safety comparison did not apply weights used in the efficacy comparison; naïve comparison was carried out as the primary approach.

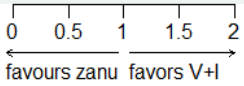
Results: For PFS, unadjusted comparison between zanu in SEQUOIA arm A (n=241) and V+I in GLOW (n=106) indicated potential treatment benefit in favor of zanu (HR=0.71 [95%CI: 0.39-1.28, p=0.2578]). After matching, the two treatments were similar (HR=0.84 [95%CI: 0.45-1.59, p=0.5977]). The unadjusted comparison between zanu in SEQUOIA arm A+C (n=352) and V+I in CAPTIVATE (n=159) also indicated a similar treatment effect for zanu and V+I (HR=1.00 [95%CI: 0.65-1.52, p=0.9874]). After matching, the HR=0.78 (95%CI: 0.38-1.62, p=0.5099) showed a potential benefit for zanu. For safety, significantly lower incidence was indicated for zanu vs. V+I in both GLOW and CAPTIVATE with regards to multiple adverse events (AEs) (figure). Sensitivity analyses exploring the impact of using different sets of matching factors in the efficacy comparisons and population matching in safety comparisons showed consistent results.

Summary/Conclusion: Due to low sample size of V+I studies and the high variability in population characteristics, the relative treatment effect estimates had a wider probability range. However, the

adjusted estimates of the relative treatment effect suggest a potential trend for PFS benefit in favor of zanu vs. V+I. Comparison of AE incidence rates across SEQUOIA and V+I studies identified a significantly better safety profile for zanu vs. V+I, despite longer treatment exposure for zanu (median 44 months) compared to V+I (median 13.8 months in both trials) and no adjustment for differences in treatment exposure were made in the safety comparisons. The observed safety differences between zanu and V+I suggest considerable impact on patients quality of life, that should be weighted at the time of treatment decision-making in TN CLL.

Figure. Forest plot of AEs of any grade or grade 3+ with a p-value <0.2 in the safety comparison against the GLOW and CAPTIVATE studies.

Adverse Events	Comparator Study	Zanu (n / N)	V+I (n / N)	OR (95% CI)	p-value
Diarrhea, any grade	GLOW	41/240	54/106	0.20 (0.12, 0.33)	<0.001
	CAPTIVATE	63/351	99/159	0.13 (0.09, 0.20)	<0.001
Diarrhea, grade 3+	GLOW	4/240	11/106	0.15 (0.05, 0.47)	0.001
Neutropenia*, any grade	GLOW	32/240	44/106	0.22 (0.13, 0.37)	<0.001
	CAPTIVATE	45/351	66/159	0.21 (0.13, 0.32)	<0.001
Neutropenia*, grade 3+	GLOW	24/240	37/106	0.21 (0.12, 0.37)	<0.001
	CAPTIVATE	36/351	52/159	0.24 (0.15, 0.38)	<0.001
Nausea, any grade	GLOW	31/240	28/106	0.41 (0.23, 0.73)	0.003
	CAPTIVATE	51/351	68/159	0.23 (0.15, 0.35)	<0.001
Anemia, any grade	GLOW	16/240	19/106	0.33 (0.16, 0.67)	0.002
UTI, any grade	GLOW	24/240	17/106	0.58 (0.30, 1.14)	0.112
Edema peripheral, any grade	GLOW	23/240	16/106	0.60 (0.30, 1.18)	0.138
Atrial fibrillation, any grade	GLOW	10/240	15/106	0.26 (0.11, 0.61)	0.002
Atrial fibrillation, grade 3+	GLOW	2/240	7/106	0.12 (0.02, 0.58)	0.009
Decreased appetite, any grade	GLOW	7/240	14/106	0.20 (0.08, 0.50)	0.001
Thrombocytopenia, any grade	GLOW	12/240	12/106	0.41 (0.18, 0.95)	0.038
Thrombocytopenia, grade 3+	GLOW	4/240	6/106	0.28 (0.08, 1.02)	0.054
Arthralgia, any grade	CAPTIVATE	63/351	53/159	0.44 (0.29, 0.67)	<0.001
Epistaxis, any grade	GLOW	13/240	12/106	0.45 (0.20, 1.02)	0.056
Cough, any grade	GLOW	35/240	9/106	1.84 (0.85, 3.98)	0.121
Hyponatremia, grade 3+	GLOW	5/240	6/106	0.35 (0.11, 1.19)	0.093



*Comparison against GLOW includes “neutrophil count decreased”.

Abbreviations: AE, adverse event; CI, confidence interval; OR, odds ratio; UTI, urinary tract infection.