OUTCOMES OF RELAPSED/REFRACTORY MCL PATIENTS TREATED WITH ZANUBRUTINIB MONOTHERAPY IN THE SECOND LINE AND IN LATER LINES: A POOLED ANALYSIS FROM 2 STUDIES

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Background

Zanubrutinib is a highly specific, potent BTK inhibitor with minimal off-target inhibition of other kinases. It has showed complete and sustained 24-hour BTK occupancy in both blood and lymph node biopsies and is associated with durable responses in patients with mantle cell lymphoma (MCL). In a phase 2 study conducted in patients with relapsed/refractory (R/R) MCL, treatment with zanubrutinib resulted in an overall response rate (ORR) of 84%, with a complete response rate (CRR) of 78%, and median progression free survival (PFS) was not reached.

Aims

We presented the pooled analysis trying to answer question of the optimal schedule of zanubrutinib dosing in patients with R/R MCL.

Methods

Our analysis was based on a pooled data including R/R MCL patients treated with zanubrutinib in a phase 1 study (ClinicalTrials. gov NCT02343120) and a phase 2 study (ClinicalTrials. gov NCT03206970), corresponding median study follow-up 18.3 and 18.4 months.

Inverse propensity score weighting method was used to create a weighted sample leading to a conservative analysis compared to a randomized controlled trial, in which R/R MCL patients who finished first line of therapy are randomized into two arms. The patients in Arm A are treated by zanubrutinib, while those in Arm B are treated by any anti-cancer therapies other than BTK inhibitors and followed by zanubrutinib if progress from prior lines of therapy. The efficacy outcomes of zanubrutinib in the two arms were examined, including CRR, ORR, PFS and overall survival (OS). The difference between arms in CRR and ORR were investigated by logistic regression, and the difference between arms in time-to-event endpoints by the Cox proportional hazards model. The considered endpoints were adjusted by study. The landmark analysis of duration of response (DOR), PFS and OS at 6 and 12 months was reported for the whole population as well as the subpopulation of complete responders and partial responders. The safety profile in each arm was summarized.

Results

Forty-one R/R MCL patients received second line treatment with zanubrutinib (Arm A) and seventy-one received treatment with zanubrutinib in later lines (Arm B). In the weighted sample, all baseline covariates were balanced between arms and the prevalence of prior medication use in each arm were preserved; the median follow-up time were 17.2 vs. 16.8 CRR was significantly higher in Arm A than in Arm B, while ORR was higher in Arm A but not statistically significant. There was no significant difference in PFS and OS curves between two arms, but the PFS rates and OS rates at 6 and 12 month were higher in Arm A (Table 1). In Arm A, efficacy was better in complete responders in terms of DOR rates, PFS rates and OS rates at 6 and 12 months.

In general, safety profile in Arm A was also better in extent of exposure and adverse events, especially in adverse events of special interest including diarrhea, major hemorrhage and atrial fibrillation/flutter.

Table 1: Summary of Efficacy Endpoints

	Weighted Pooled Sample		
	Arm A	Arm B	Total
CRR, % (95% CI)	74.6 (58.2, 87.0)	61.1 (47.3, 74.0)	66.0 (55.1, 76.0)
ORR, % (95% CI)	90.7 (78.1, 97.3)	83.5 (71.0, 92.2)	86.1 (77.3, 92.5)
PFS Rate at, % (95% CI) [a]			
6 Month	89.0 (80.6, 98.6)	76.2 (66.2, 88.2)	80.9 (73.8, 88.6)
12 Month	82.5 (71.7, 95.2)	66.4 (55.6, 80.1)	72.3 (64.3, 81.3)
OS Rate at, % (95% CI) [a]			
6 Month	96.2 (91.0, 100)	92.1 (86.5, 98.0)	93.6 (89.1, 98.3)
12 Month	87.5 (78.1, 98.5)	83.6 (75.7, 92.6)	85.0 (78.5, 92.2)

Abbreviations: CI, confidence interval; OS, overall survival; PFS, progression free survival.
Notes: [a] The PFS rate and OS rate at 6 month and 12 month are calculated by the Kaplan-Meier method with 95% CI constructed by the Greenwood's formula.

Conclusion

Patients with R/R MCL who receive zanubrutinib as second line appear to respond more favorably than when administered as later lines. Treatment was well tolerated in both arms with lower rates of bleeding and atrial fibrillation in those receiving second line treatment.