Zanubrutinib in Patients with Relapsed/Refractory Mantle Cell Lymphoma

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Objectives: Zanubrutinib is a selective and irreversible BTK inhibitor that has demonstrated potent inhibition of BTK in prior studies, with minimal, off-target inhibition of other kinases. We present safety and efficacy results from a phase 2 study of zanubrutinib in patients with relapsed/refractory mantle cell lymphoma (R/R MCL) in China.

Methods: In this single-arm, multicenter phase 2 study (ClinicalTrials.gov NCT03206970), oral zanubrutinib (160 mg BID) was given to R/R MCL patients until disease progression (PD) or unacceptable toxicity. Primary endpoint was overall response rate (ORR) assessed by an independent review committee (IRC) according to the 2014 Lugano Classification. Secondary endpoints included progression-free survival (PFS), time to response (TTR), duration of response (DOR), investigator-assessed ORR, and safety.

Results: As of February 15, 2019, 86 R/R MCL patients were enrolled at 13 centers in China. Patient characteristics are summarized in the table. The median study follow-up was 18.4 months (range, 0.3-23.5 months) with 60.5% of patients were continuing to receive study drug and 39.5% had discontinued study drug, primarily due to PD (27.9%) and AE (9.3%). In 86 evaluable patients, investigator-assessed ORR was 83.7%, and 67 (77.9%) patients achieved complete response. The median DOR was 19.5 month, 81.8% (95% CI 70.7% to 89.0%) and 67.4% (95% CI 53.3% to 78.1%) of responders were estimated event (progressive disease/death) free at 12 and 15 months, respectively. The median PFS was 22.1 months, the estimated PFS event free rates at 12 and 15 months were 74.6% (95% CI 63.7% to 82.6%) and 72.1% (95% CI 61.0% to 80.5%), respectively. The ORR was generally consistent across all subgroups analyzed (MIPI [Mantle Cell International Prognostic Index], previous therapy, blastoid variant, etc). The most common (≥10%) treatment-emergent AEs (TEAEs) included decreased neutrophil count (44.2%), upper respiratory tract infection (34.9%), rash (33.7%), decreased white blood cell (WBC) count (31.4%), decreased platelet count (25.6%), hypokalemia (16.3%), diarrhea, anemia (each 15.1%), alanine aminotransferase increased, and hypertension (each 14.0%). Grade 3 or higher TEAEs reported in at least 5% patients included decreased neutrophil count (18.6%), lung infection (7.0%), decreased WBC count, anemia (each 5.8%). The most frequent hemorrhage events were blood urine present, hematuria and petechiae/purpura/contusion (4.7% each, grade 1/2). Major hemorrhage (serious or grade 3 or higher bleeding or central nervous system bleeding of any grade) was reported in 3 patients (3.5%). No cases of atrial fibrillation/flutter, second primary malignancies or tumor lysis syndrome were reported. TEAEs leading to treatment discontinuation in 8 (9.3%) patients included infection, lung infection, pneumonia, road traffic accident, cerebral hemorrhage, interstitial lung disease, decreased platelet count and death (n=1 each).

Conclusions: Zanubrutinib demonstrated high activity in patients with R/R MCL with high ORR and CR rates and durable response documented by PET-based imagine. The safety profile was consistent with previous reports of zanubrutinib treatment.

Table. Patient Characteristics, Efficacy, and Safety

Patient Characteristics	**N = 86**
Median age, y (range)	60.5 (34-75)
Sex, n (%)	
Male	67 (77.9)
Female	19 (22.1)
Time since first diagnosis of MCL (months)	30.1 (3.1-102.4)
Median no. of prior lines of therapy (range)	2 (1-4)
Bulky disease, n (%)	
>10 cm	7 (8.1)
>5 cm	37 (43.0)
Blastic variant form of MCL, n (%)	12 (14.0)
Stage IV disease, n (%)	64 (74.4)
Intermediate/high-risk per MIPI-b, n (%)	72 (83.7)
Efficacy (by Investigator) [a]	**N = 86**
Overall response rate, n (%); (95% CI)	72 (83.7); (74.2, 90.8)
Complete response, n (%)	67 (77.9)
Partial response, n (%)	5 (5.8)
Stable disease, n (%)	1 (1.2)
Progressive disease, n (%)	8 (9.3)
Discontinued prior to first response assessment, n (%)	5 (5.8)
Safety, n (%)	**N = 86**
Any TEAE	83 (96.5)
Any grade ≥3 TEAE	36 (41.9)
TEAE leading to zanubrutinib discontinuation	8 (9.3)
TEAE leading to death	5 (5.8)

[a]IRC-assessed efficacy will be reported later

MIPI-b, Mantle Cell International Prognostic Index-biologic