ZANUBRUTINIB IN PATIENTS WITH RELAPSED/REFRACTORY MANTLE CELL LYMPHOMA

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Introduction: 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 updated safety and efficacy results from a phase 2 study of zanubrutinib in patients with R/R MCL.

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 September 16, 2018, 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 13.9 months (range, 0.3-18.5 months) with treatment discontinuation in 29 (33.7%) patients, primarily due to PD (19 [22.1%]) and AE (8 [9.3%]). In 85 efficacy evaluable patients, investigator-assessed ORR was 84.7%, and 65 (76.5%) patients achieved complete response. The median DOR was 14.0 months (range, 2.32-14.0 months). The median PFS was 16.7 months (range 0.0+ to 16.7+ months). The ORR was generally consistent across subgroups analyzed (MIPI [Mantle Cell International Prognostic Index], previous therapy, blastoid variant, etc). The most common (≥15%) treatment-emergent AEs (TEAEs) included decreased neutrophil count (41.9%), rash

(33.7%), upper respiratory tract infection (33.7%), decreased white blood cell (WBC) count (26.7%), decreased platelet count (25.6%), hypokalemia (16.3%), and diarrhea (15.1%). Grade 3 TEAEs reported in >2 patients included decreased neutrophil count (16.3%), decreased WBC count, anemia, lung infection (each 5.8%), decreased platelet count (4.7%), and hypertension (3.5%). The most frequent hemorrhage events were hematuria and petechiae/purpura/contusion (4.7% each, grade 1/2). Major hemorrhage (serious or grade 3 bleeding or central nervous system bleeding of any grade) was reported in 2 patients (2.3%). No cases of atrial fibrillation/flutter, second primary malignancies or tumor lysis syndrome were reported. TEAEs leading to treatment discontinuation in nine (10.5%) patients included infection, lung infection, pneumonia, upper gastrointestinal hemorrhage, road traffic accident, cerebral hemorrhage, interstitial lung disease (n=1 each), and decreased platelet count (n=2).

Conclusions: Updated results of this study further substantiated the high activity of zanubrutinib resulting in a high rate of durable response in R/R MCL. 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 (Best Response)[b]	**N = 85[a]**
Overall response rate, n (%); (95% CI)	72 (84.7); (75.3, 91.6)
Complete response, n (%)	65 (76.5)
Partial response, n (%)	7 (8.2)
Stable disease, n (%)	1 (1.2)
Progressive disease, n (%)	8 (9.4)
Discontinued prior to first response assessment, n (%)	4 (4.7)
Safety, n (%)	**N = 86**
Any TEAE	83 (96.5)
Any grade ≥3 TEAE	34 (39.5)
TEAE leading to zanubrutinib discontinuation	9 (10.5)
Grade 5 TEAE	5 (5.8)

[a]One patient was not evaluable for response due to a lack of central pathologic confirmation of MCL.
[b]IRC-assessed efficacy will be reported later.
MIPI-b, Mantle Cell International Prognostic Index-biologic