PHASE 1/2 STUDY OF SINGLE-AGENT ZANUBRUTINIB IN PATIENTS WITH RELAPSED/REFRACTORY MARGINAL ZONE LYMPHOMA

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Background

Marginal zone lymphoma (MZL) is the third most common lymphoma and represents approximately 5% to 15% of all non-Hodgkin lymphomas. Improved understanding of the disease biology, including genetic and molecular characteristics, has changed the therapeutic landscape of MZL, and there is increasing evidence that targeted therapies, including Bruton tyrosine kinase inhibitors, have improved efficacy and have shown tolerable toxicity profiles over chemotherapy-based approaches. Zanubrutinib, a potent and selective Bruton tyrosine kinase inhibitor, has established therapeutic activity in B-cell malignancies including chronic lymphocytic leukemia, mantle cell lymphoma, and Waldenström macroglobulinemia.

Aims

To examine the safety and preliminary efficacy of single-agent zanubrutinib in a phase 1/2 study of patients with relapsed/refractory MZL.

Methods

Treatment consisted of oral zanubrutinib at 160 mg twice daily (n=17) or 320 mg once daily (n=3) until disease progression or unacceptable toxicity. Efficacy end points included the proportion of patients achieving a complete or partial response in accordance with Lugano classification (*J Clin Oncol.* 2014;32:3059).

Results

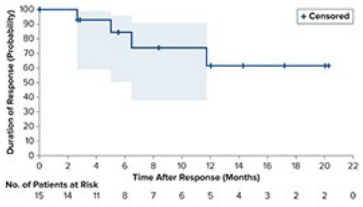
Between September 2014 and August 2018, 20 patients with relapsed/refractory MZL started treatment with zanubrutinib; 65% of patients were aged >65, and 15% were aged >75 years. Patient distribution across MZL subtypes was as follows: extranodal (mucosa-associated lymphoid tissue), 45%; splenic, 30%; and nodal, 25%. The median number of prior therapies was 2, with RCVP (rituximab, cyclophosphamide, vincristine, and prednisone) being the most common type of therapy. At a median follow-up of 22.16 months, 60% of patients remained on treatment. Reasons for treatment discontinuation included disease progression (25%), adverse events (AEs) in 5% of patients (with 1 patient having treatment-related diarrhea), patient's withdrawal of consent (5%), and other (5%). Therapy was well-tolerated, with the most commonly reported AEs (≥20%) being contusion (35%), diarrhea (35%), upper respiratory tract infection (30%), rash (30%), pyrexia (25%), sinusitis (20%), nausea (20%), and nasopharyngitis (20%). AEs of interest included neutropenia (30%), major hemorrhage (1 patient), and grade 3 diarrhea (1 patient). No patients experienced atrial fibrillation/flutter. Investigator-assessed overall response rate was 75%, and complete response rate was 10% (Table). Median time to response was 2.9 months. Median duration of response (complete or partial response) was not reached (95% CI, 6.47 months to not evaluable) at a median response follow-up of 12 months. Rates of progression-free survival at 12 and 18 months were 77% and 69.3%, respectively. Rate of overall survival at both 12 and 18 months was 100%.

Table. Efficacy and Safety Outcomes.

Baseline Patient Characteristics	R/R MZL (n=20)
Age, median (range), y	70 (52-85)
No. of prior therapies, median (range)	2 (1-5)
Safety Assessment, n (%)	
AEs leading to discontinuation	1 (5)
Grade ≥3 AEs	10 (50)
Grade 5 AEs	0
Atrial fibrillation/flutter	0
Major hemorrhage	1 (5)
Grade ≥3 infections	4 (20)
Response Assessment, n (%)	
ORR	15 (75)
CR	2 (10)
PR	13 (65)
SD	4 (20)
PD	1 (5)

AE, adverse event; CR, complete response; MZL, marginal zone lymphoma; ORR, overall response rate; PD, progressive disease; PR, partial response; R/R relapsed/refractory; SD, stable disease.

Figure. Duration of Response



Conclusion

Zanubrutinib treatment demonstrated deep and durable responses in patients with MZL. Treatment discontinuation from AEs was uncommon, with no grade 5 AEs. The safety profile of zanubrutinib therapy in these patients was favorable and consistent with that in prior studies.