THREE-YEAR FOLLOW-UP OF TREATMENT-NAÏVE AND PREVIOUSLY TREATED PATIENTS WITH WALDENSTRÖM MACROGLOBULINEMIA (WM) RECEIVING SINGLE AGENT ZANUBRUTINIB

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Background

Inhibitors of Bruton tyrosine kinase (BTK) have established therapeutic activity in patients with WM. Zanubrutinib, a potent and selective BTK inhibitor was evaluated in a phase 1/2 study in treatment-naïve (TN) and relapsed/refractory (R/R) patients with WM.

Aims

To examine the safety and preliminary efficacy of single-agent zanubrutinib in patients with TN or R/R WM.

Methods

Patients had TN or R/R WM and required treatment as per IWWM criteria. Treatment consisted of oral zanubrutinib at 160 mg twice daily (n=50) or 320 mg once daily (n=23) until disease progression or unacceptable toxicity. Efficacy endpoints included the proportion of patients achieving a complete response (CR) or very good partial response (VGPR) in accordance with IWWM-6 criteria. Efficacy analyses were conducted on the efficacy evaluable patients.

Results

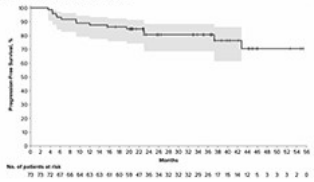
Between September 2014 and August 2018, 77 patients with WM (24 TN and 53 R/R) began treatment with zanubrutinib (54% were aged >65 and 21% >75 years). A total of 73 out of 77 patients were considered efficacy evaluable. At a median follow up of 32.7 months, 73% remain on treatment. Reasons for treatment discontinuation included adverse events (AEs) in 13% of patients (only one treatment-related), disease progression (10.4%) and other (3.9%). Five grade 5 AEs occurred: abdominal sepsis, septic arthritis, scedosporium infection, (patient with prior history of scedosporium abscess) bronchiectasis, and gastric adenocarcinoma (none related). Results are presented for TN and R/R patients combined. The overall response rate was 96% and the VGPR/CR rate was 45% (Table). The rates of VGPR/CR increased over time; 22% at 6 months, 33% at 12 months and 45% at 24 months. The VGPR/CR rate was the highest among patients with the *MYD88^{L265P}/CXCR4^{WT}* genotype (59%). Of the patients with known *MYD88^{WT}*, 62.5% had a major response. The rate of progression-free and overall survival at 3 years were 81% and 85%, respectively. The most commonly reported AEs were upper respiratory tract infection (52%), contusion (32%, all grade 1) and cough (22%). AEs of interest include neutropenia (18.2%), major hemorrhage (4%), atrial fibrillation/flutter (5%), and grade 3 diarrhea (3%).

Figure.

A. Efficacy and Safety Outcomes.

Response Assessment	TN WM (n=24), %	R/R WM (n=49), %	Total (n=73), %
VGPR + CR rate	33.3	51.0	45.2
ORR (MR or better)	100	93.9	96
MRR (PR or better)	88	80	82
36 mo PFS	91.5	76.2	80.5
36 mo OS	100.0	80.2	84.8
Safety Assessment	**TN WM (n=24), %**	**R/R WM (n=53), %**	**Total (n=77), %**
AEs leading to discontinuation	12.5	13.2	13.0
≥Grade 3 AEs	45.8	64.2	58.4
Grade 5 AEs	0	9.4	6.5
Atrial fibrillation/flutter	4.2	5.7	5.2
Major hemorrhage	8.3	1.9	3.9
Hypertension	12.5	17.0	15.6
Neutropenia	16.7	18.9	18.2
≥Grade 3 infections	8.3	35.9	27.3
≥Grade 3 diarrhea	4.2	1.9	2.6

B. Total Progression-free Survival



AE, adverse event; CR, complete response; MR, minimal response; MRR, major response rate; PFS, progression-free survival; PR, partial response; ORR, overall response rate; OS, overall survival; R/R, relapsed/refractory; TN, treatment-naïve; WM, waldenström macroglobulinemia.

Conclusion

Longer-term follow up with continued zanubrutinib treatment demonstrated deep and durable responses in the majority of WM patients. The rates of VGPR/CR increased with prolonged therapy. Disease progression was uncommon. The safety profile of long-term zanubrutinib therapy in these patients was tolerable.