Three-year follow-up of treatment-naïve and previously treated patients with Waldenström macroglobulinemia (WM) receiving single-agent zanubrutinib.

Authors:
Constantine Si Lun Tam, Stephen Opat, Paula Marlton, David Gottlieb, David Simpson, Gavin Cull, David Ritchie, Emma Verner, Javier Munoz, Alessandra Tedeschi, Jane Huang, William Novotny, Ziwen Tan, Eric Holmgren, Siminder K. Atwal, John Francis Seymour, Andrew Warwick Roberts, Judith Trotman; Peter MacCallum Cancer Centre, Melbourne, St Vincent's Hospital, Fitzroy, University of Melbourne, Parkville and Royal Melbourne Hospital, Parkville, Victoria, Australia; Monash Health, Monash University, Clayton, Victoria, Australia; Princess Alexandra Hospital and University of Queensland, Brisbane, Queensland, Australia; Faculty of Medicine and Health, University of Sydney, Westmead Hospital, Sydney, Australia; North Shore Hospital, Auckland, New Zealand and BeiGene USA, Inc., San Mateo, CA; Sir Charles Gairdner Hospital and University of Western Australia, Perth, WA, Australia; Peter MacCallum Cancer Centre, Melbourne, University of Melbourne, Parkville, Victoria, Australia; Concord Repatriation General Hospital and University of Sydney, Concord, Australia; Banner MD Anderson Cancer Center, Gilbert, AZ; ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; BeiGene USA, Inc., San Mateo, CA; BeiGene (Beijing) Co., Ltd., Beijing, CA, China

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.

Methods:
Patients had TN or R/R WM and required treatment as per International Workshop on WM (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 73 patients evaluable (24 TN, 49 R/R).

Results:
Between September 2014 and August 2018, 77 patients with WM (24 TN and 53 R/R) began treatment with zanubrutinib (55% aged > 65 years; 21% aged > 75 years). At a median follow up of 32.7 months, 73% remain on treatment. Reasons for treatment discontinuation included adverse events (AE) in 13% (only one related), disease progression (10.4%), and other (3.9%). Results are presented for TN and R/R combined. The overall response rate was 96% and VGPR/CR rate was 45%. The rates of VGPR/CR increased over time; 22% at 6 mos, 33% at 12 months and 45% at 24 months. Three-year progression-free survival (PFS) was 81%, and overall survival (OS) was 85%. The most commonly reported AEs were upper respiratory tract infection (52%), contusion (33%, 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%).

Conclusions:
Long-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. Clinical trial information: NCT02343120.

Efficacy and safety outcomes.

Assessment	TN WM (n = 24), %	R/R WM (n = 53), %	Total (n = 77), %
VGPR/CR rate	33.3	51.0	45.2
36-mo PFS	91.5	76.2	80.5
Assessment	TN WM (n = 24), %	R/R WM (n = 53), %	Total (n = 77), %
36-mo OS	100.0	80.2	84.8
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
≥Grade 3 infections	8.3	35.9	27.3

Assessment	TN WM (n = 24), %	R/R WM (n = 53), %	Total (n = 77), %
36-mo OS	100.0	80.2	84.8
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
≥Grade 3 infections	8.3	35.9	27.3