ASPEN: RESULTS OF A PHASE 3 RANDOMIZED TRIAL OF ZANUBRUTINIB VERSUS IBRUTINIB FOR PATIENTS WITH WALDENSTRÖM MACROGLOBULINEMIA (WM)

Author(s): Meletios Dimopoulos, Stephen Opat, Shirley D'Sa, Wojciech Jurczak, Hui-Peng Lee, Gavin Cull, Roger G. Owen, Paula Marlton, Bjorn E. Wahlin, Ramon Garcia Sanz, Helen McCarthy, Stephen Mulligan, Alessandra Tedeschi, Jorge Castillo, Jaroslaw Czyz, Carlos Fernandez De Larrea Rodriguez, David Belada, Edward Libby, Jeffrey Matous, Marina Motta, Tanya Siddiqi, Monica Tani, Marek Trneny, Monique Minnema, Christian Buske, Veronique Leblond, Wai Y. Chan, Jingjing Schneider, Sunhee Ro, Aileen Cohen, Jane Huang, Constantine S. Tam

Background

Bruton tyrosine kinase (BTK) inhibition is an emerging standard of care for Waldenström macroglobulinemia (WM). Zanubrutinib (BGB-3111; ZANU) is an investigational, next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition of TEC-and EGFR-family kinases. ASPEN is a randomized phase 3 study comparing ZANU, a potent and selective BTK inhibitor, versus ibrutinib (IBR), a first generation BTK inhibitor, in patients with WM.

Aims

To compare the efficacy and safety of ZANU versus IBR in patients with WM and *MYD88* mutation.

Methods

Patients with WM and *MYD88* mutation were randomly assigned 1:1 to receive ZANU (160 mg twice daily) or IBR (420 mg once daily). Patients without *MYD88* mutation were assigned to a separate cohort, received ZANU, and are reported separately. Randomization was stratified by CXCR4 mutational status and the number of lines of prior therapy (0 vs 1-3 vs >3). The primary endpoint was the proportion of patients achieving a complete response or very good partial response (CR+VGPR). Sample size was calculated to provide 81% power to detect a difference in CR+VGPR rate of 35% versus 15% in the subset of patients with relapsed or refractory (R/R) WM. Primary analysis was planned to occur at approximately 12 months after the last patient enrolled.

Results

In total, 201 patients were randomized from January 2017 to July 2018. While the treatment groups were well balanced for important baseline factors, in the ZANU arm, there were more elderly patients (aged >75 years, 33.3% vs 22.2%) and more patients with anemia (hemoglobin ≤110 g/L, 65.7% vs 53.5%). At a median follow-up of 19.4 months, the rate of CR+VGPR was 28.4% vs 19.2% with ZANU vs IBR, respectively (2-sided *P*=0.09). Landmark analysis at 12 months showed a trend toward longer progression-free survival and

Table. ASPEN Analyses

Adverse Events, %			ZANU (n=101)	IBR (n=98)
Grade ≥3			58.4	63.3
Leading to dose reduction			13.9	23.5
Leading to discontinuation			4.0	9.2
Leading to death			1.0	4.1
Adverse Events of Interest, %				
Atrial fibrillation or flutter			2.0	15.3
Hypertension			10.9	17.3
Minor haemorrhage			36.6	42.9
Major haemorrhage (any CNS, or grade ≥3 haemorrhage)			5.9	9.2
Neutropenia			29.7	13.3
Grade ≥3 infection			17.8	19.4
Best Overall Response by Independent Central Review, %				
	R/R		Overall	
	ZANU (n=83)	IBR (n=81)	ZANU (n=102)	IBR (n=99)
CR	0	0	0	0
VGPR	**28.9**	**19.8**	**28.4**	**19.2**
PR	49.4	60.5	49.0	58.6
MR	15.7	13.6	16.7	15.2
SD	3.6	2.5	2.9	3.0
PD	1.2	2.5	2.0	2.0
Overall Response Rate, % [95% CI]	94.0 [86.5-98.0]	93.8 [86.2-98.0]	94.1 [87.6-97.8]	92.9 [86.0-97.1]
12-Month PFS, % [95% CI]	92.4 [83.8-96.5]	85.9 [75.9-91.9]	89.7 [81.7-94.3]	87.2 [78.6-92.5]
12-Month OS, % [95% CI]	98.8 [91.6-99.8]	92.5 [84.1-96.6]	97.0 [90.9-99.0]	93.9 [86.8-97.2]

CR and VGPR rates are **bolded** for emphasis of the study primary endpoint.
CR, complete response; MR, minor response; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; R/R relapsed/refractory; SD, stable disease; VGPR, very good PR.

Conclusion

ASPEN is the largest phase 3 trial of BTK inhibitors in WM and the first head-to-head comparison of BTK inhibitors in any disease. Although not statistically significant, ZANU was associated with a higher CR+VGPR response rate, and demonstrated clinically meaningful advantages in safety and tolerability compared with IBR. ClinicalTrials.gov: NCT03053440.