Characterization of the safety/tolerability profile of zanubrutinib and comparison with the profile of ibrutinib in patients with B-cell malignancies: post hoc analysis of a large clinical trial safety database

Authors: Constantine Tam[12], Jennifer R. Brown[3], Barbara Eichorst[45], Paolo Ghia[6], Wojciech Jurczak[7], Brad S. Kahl[8], Nicole Lamanna[9], Tadeusz Robak[10], Mazyar Shadman[1112], Lugui Qiu[13], Aileen Cohen[14], Meng Zhang[14], Tommi Salmi[15], Jason Paik[14], Liping Wang[14], Jun Zhang[14], Han Ma[14], Alessandra Tedeschi[16]

Institutions: [1]Alfred Health, Melbourne, VIC, Australia; [2]Monash University, Melbourne, VIC, Australia; [3]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [4]Department I of Internal Medicine, University Hospital Cologne, Cologne, Germany; [5]Center for Integrated Oncology, University Hospital Cologne, Cologne, Germany; [6]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milan, Italy; [7]Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland; [8]Siteman Cancer Center, Washington University School of Medicine, St Louis, MO, USA; [9]Herbert Irving Comprehensive Cancer Center, Columbia University, New York, NY, USA; [10]Medical University of Lodz, Lodz, Poland; [11]Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [12]Department of Medicine, University of Washington, Seattle, WA, USA; [13]Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences, Tianjin, China; [14]BeiGene USA, Inc, San Mateo, CA, USA; [15]BeiGene International GmbH, Basel, Switzerland; [16]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy

Aim: To characterize the overall safety and tolerability of zanubrutinib, a potent and selective next-generation Bruton tyrosine kinase inhibitor (BTKi), in patients with B-cell malignancies and compare its profile with that of the first-generation BTKi, ibrutinib.

Method: In the post hoc analyses, safety data were pooled from 10 zanubrutinib monotherapy clinical trials in patients with CLL/SLL, MCL, MZL, WM, FL, and other B-cell malignancies (N=1550), including 2 (ASPEN, ALPINE) that compared zanubrutinib head-to-head with ibrutinib. Incidence rates and exposure-adjusted incidence rates (EAIRs) of treatment-emergent adverse events (TEAEs; summarized in MedDRA preferred terms) and adverse events of special interest (AESIs; defined in grouped terms) were assessed.

Results: Median zanubrutinib exposure was 34.4 months. The most common nonhematologic any-grade TEAEs with zanubrutinib were upper respiratory tract infection (29.7%), diarrhea (21.1%), contusion (19.5%), cough (18.1%), and rash (16.6%). Grade ≥3 TEAEs in ≥5% of patients included pneumonia (8.4%) and hypertension (8.1%). The only serious TEAE in ≥5% of patients was pneumonia (8.2%). In ASPEN/ALPINE, patients treated with zanubrutinib had lower rates of discontinuation (14.1% vs 22.0%), dose reduction (13.9% vs 19.2%), and death (8.7% vs 10.2%) due to TEAEs than those treated with ibrutinib. EAIRs of AESIs were numerically lower with zanubrutinib vs ibrutinib, except for neutropenia (**Table**). With longer follow-up, the prevalence of AESIs with zanubrutinib generally remained constant or decreased.

Conclusion: These pooled safety analyses in patients with B-cell malignancies showed that zanubrutinib is well tolerated, with generally mild to moderate TEAEs and low discontinuation rates due to TEAEs. AESI prevalence generally decreased over time, with no new safety signals

emerging. Long-term tolerability and low discontinuation rates with BTKis are important because continuous treatment is required for better outcomes. These analyses support zanubrutinib as an appropriate long-term treatment option for patients with B-cell malignancies.

Table. Exposure-Adjusted Incidence Rates for Adverse Events of Special Interest

	Zanubrutinib (N=1550)	ASPEN/ALPINE[a]	
		Zanubrutinib (n=425)	Ibrutinib (N=422)
Median exposure, mo	34.4	32.6	25.7
Exposure-adjusted incidence rate, person/100 person-months			
Infections	6.01	5.40	6.64
Opportunistic infections	0.07	0.07	0.13
Hemorrhage	3.00	2.49	3.00
Major hemorrhage	0.17	0.17	0.24
Neutropenia	1.21	1.32	1.05
Thrombocytopenia	0.59	0.49	0.65
Hypertension	0.57	0.82	1.08
Anemia	0.51	0.57	0.75
Second primary malignancies	0.52	0.47	0.58
Skin cancers	0.30	0.27	0.38
Atrial fibrillation/flutter	0.15	0.20	0.64

[a] Head-to-head trials of zanubrutinib vs ibrutinib.