Characterization of Zanubrutinib Safety/Tolerability Profile and Comparison with Ibrutinib Profile in Patients With B-cell Malignancies: Post hoc Analysis of a Large Clinical Trial Safety Database

Authors: Jennifer R. Brown,[1] Barbara Eichorst,[2] Paolo Ghia,[3] Wojciech Jurczak,[4] Brad S. Kahl,[5] Nicole Lamanna,[6] Tadeusz Robak,[7] Mazyar Shadman,[8] Constantine Tam,[9] Lugui Qiu,[10] Aileen Cohen,[11] Meng Zhang[11] , Tommi Salmi,[11] Jason Paik,[11] Liping Wang,[11] Jun Zhang,[11] Han Ma,[11]Alessandra Tedeschi[12]

Affiliations: [1]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [2]Department of Internal Medicine, University of Cologne, Center for Integrated Oncology Aachen Bonn Köln Düsseldorf, Cologne, Germany; [3]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milano, Italy; [4]Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland; [5]Siteman Cancer Center, Washington University School of Medicine, St Louis, MO, USA; [6]Herbert Irving Comprehensive Cancer Center, Columbia University, New York; [7]Medical University of Lodz, Lodz, Poland; [8]Fred Hutchinson Cancer Research Center, Seattle, WA, USA; Department of Medicine, University of Washington, Seattle, WA, USA; [9]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; University of Melbourne, Parkville, VIC, Australia; St Vincent's Hospital Melbourne, Fitzroy, VIC, Australia; Royal Melbourne Hospital, Parkville, VIC, Australia; [10]State Key Laboratory of Experimental Hematology, National Clinical Medical Research Center for Blood Diseases, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin; [11]BeiGene USA, Inc., San Mateo, CA, USA; [12]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy

Background: Bruton tyrosine kinase (BTK) is an important regulator of cell proliferation and cell survival in various B-cell malignancies. BTK inhibitors block BCR-induced BTK activation and its downstream signaling, leading to growth inhibition and cell death in malignant B-cells. First-generation BTK inhibitor, ibrutinib, revolutionized treatment; however, inhibition of off-target kinases such as EGFR, HER2, TEC, and CSK may be associated with toxicities, including gastrointestinal side effects, rash, bleeding, and atrial fibrillation, that limit its use. Zanubrutinib, a potent and selective next-generation Bruton tyrosine kinase (BTK) inhibitor, was designed to maximize BTK occupancy and minimize off-target effects.

Aims: To characterize the overall safety/tolerability profile of zanubrutinib monotherapy and compare the zanubrutinib profile with the profile of ibrutinib in patients (pts) with B-cell malignancies using the zanubrutinib clinical safety database.

Methods: In these *post-hoc* analyses, safety data were pooled from 10 clinical trials of zanubrutinib monotherapy; two of the included studies (ASPEN; ALPINE) compared zanubrutinib head-to-head with ibrutinib. Patients with CLL/SLL, MCL, MZL, WM, FL and other B-cell malignancies were included. Treatment-emergent adverse events (TEAEs) were summarized using MedDRA preferred terms (PT);

adverse events of special interest (AESI) were defined using pooled terms. Rates of TEAEs, exposure-adjusted incidence rates (EAIR), and prevalence over time of AESIs were assessed.

Results: Pooled analyses included 1550 pts (median age, 67 yrs) treated with zanubrutinib monotherapy from multiple geographical regions and races. Median zanubrutinib exposure was 28.6 months with 31.2% of pts having treatment exposure of ≥36 mo. The most commonly reported non-hematologic AEs of any grade were upper respiratory tract infection (29.0%), diarrhea (19.9%), contusion (19.4%), cough (17.2%), and rash (16.2%); grade ≥3 non-hematologic AEs occurring in ≥5% of pts included pneumonia (7.9%) and hypertension (7.4%). The most common serious AE was pneumonia (7.5%). Zanubrutinib discontinuation due to any AE occurred in 12.3% of pts; AEs leading to dose reduction occurred in 9.6%. Disease progression was the most common cause of death (7.2%); deaths attributed to AEs occurred in 5.6% of pts, most (3.2%) were due to infections including COVID-19-related AEs.

The most commonly reported AESIs (any grade) in the pooled zanubrutinib population (N=1550) and in ibrutinib-treated pts from ASPEN and ALPINE (N=422) were infections and hemorrhage **(Table)**. With the exception of neutropenia, EAIRs were numerically lower for zanubrutinib vs ibrutinib most notably hypertension (0.57 vs 1.15 person/100 person-months), anemia (0.54 vs 0.84 person/100 person-months), and atrial fibrillation or flutter (0.15 vs 0.70 person/100 person-months). Prevalence of zanubrutinib AESI tended to remain constant or decrease with longer follow-up.

Conclusions/Summary: As BTKi therapy requires continuous treatment, long-term tolerability and low treatment discontinuation rates are needed for successful outcomes. These pooled safety analyses demonstrate that zanubrutinib is well tolerated in pts with B-cell malignancies. Zanubrutinib AEs were generally mild-to-moderate in severity and tended not to lead to treatment discontinuation. Prevalence of AESI generally trended down over time without emergence of new safety signals, supporting zanubrutinib as a good option for long-term treatment.

Table: Overall and Exposure-adjusted Incidence Rates for Adverse Events of Special Interest in the Pooled Zanubrutinib or Ibrutinib Populations

	Pooled Zanubrutinib Population (N=1550)		Pooled Ibrutinib Population (N=422)	
	n (%)	EAIR (person/100 person-months)	n (%)	EAIR (person/100 person-months)
Infections	1096 (70.7)	6.18	287 (68.0)	6.67
Opportunistic infections	*36 (2.3)*	*0.08*	*13 (3.1)*	*0.14*
Hemorrhage	785 (50.6)	3.26	191 (45.3)	3.44
Major hemorrhage	*81 (5.2)*	*0.17*	*26 (6.2)*	*0.28*
Neutropenia	458 (29.5)	1.32	97 (23.0)	1.19
Thrombocytopenia	265 (17.1)	0.64	66 (15.6)	0.75
Hypertension	235 (15.2)	0.57	91 (21.6)	1.15
Anemia	236 (15.2)	0.54	2 (17.1)	0.84
Secondary primary malignancies	228 (14.7)	0.53	49 (11.6)	0.55
Skin cancers	*136 (8.8)*	*0.31*	*34 (8.1)*	*0.38*
Atrial fibrillation/flutter	72 (4.6)	0.15	62 (14.7	0.70
Abbreviations: EAIR, exposure adjusted incidence rate.				