Zanubrutinib safety/tolerability profile and comparison with ibrutinib profile in B-cell malignancies: Post hoc analysis of a large clinical trial safety database

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Introduction: Bruton tyrosine kinase inhibitors (BTKi) block B-cell receptor pathway signaling, leading to growth inhibition and cell death in malignant B-cells. First-generation BTKi, ibrutinib (ibr) revolutionized treatment; however, inhibition of off-target kinases such as EGFR, HER2, TEC, and CSK may be associated with toxicities, including diarrhea, rash, bleeding, and atrial fibrillation (Afib), that limit its use. Zanubrutinib (zanu), a potent and selective next-generation BTKi, maximizes BTK occupancy and minimizes off-target effects. Here, we characterized the overall safety/tolerability of zanu and compared it with ibr in patients (pts) with B-cell malignancies using the zanu clinical safety database.

Methods: Safety data were pooled from 10 clinical trials of zanu monotherapy; 2 of the included studies (ASPEN; ALPINE) compared zanu head to head with ibr. Pts 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; adverse events of special interest (AESI) were defined using pooled terms. Rates of TEAEs, exposure-adjusted incidence rates (EAIRs), and prevalence over time of AESI were assessed.

Results: Pooled analyses included 1550 pts treated with zanu. Median zanu exposure was 28.6 months with 31.2% of pts having treatment exposure of ≥36 mo. Most common nonhematologic AEs were upper respiratory tract infection (29.0%), diarrhea (19.9%), contusion (19.4%), cough (17.2%), and rash (16.2%); grade ≥3 nonhematologic AEs occurring in ≥5% of pts included pneumonia (7.9%) and hypertension (7.4%). The most common serious AE was pneumonia (7.5%). Zanu discontinuation due to 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, and most (3.2%) were due to infections including COVID-19-related AEs.

The most common AESI in the pooled zanu population and in ibr-treated pts from ASPEN and ALPINE (N=422) were infections and hemorrhage **(Table)**. With the exception of neutropenia, EAIRs were numerically lower for zanu vs ibr, 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 zanu AESI tended to remain constant or decrease with longer follow-up.

Conclusions: As BTKi therapy requires continuous treatment, long-term tolerability and low treatment discontinuation rates are needed for successful outcomes. zanu was well tolerated, with generally mild-to-moderate AEs that tended not to lead to treatment discontinuation. Prevalence of AESI generally trended down over time without emergence of new safety signals, supporting zanu as a good option for long-term treatment.

Table. Overall and EAIR 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)	6.18	287 (68)	6.67
Opportunistic infections	*36 (2)*	*0.08*	*13 (3)*	*0.14*
Hemorrhage	785 (51)	3.26	191 (45)	3.44
Major hemorrhage	*81 (5)*	*0.17*	*26 (6)*	*0.28*
Neutropenia	458 (30)	1.32	97 (23)	1.19
Thrombocytopenia	265 (17)	0.64	66 (16)	0.75
Hypertension	235 (15)	0.57	91 (22)	1.15
Anemia	236 (15)	0.54	2 (17)	0.84
Secondary primary malignancies	228 (15)	0.53	49 (12)	0.55
Skin cancers	*136 (9)*	*0.31*	*34 (8)*	*0.38*
Atrial fibrillation/flutter	72 (5)	0.15	62 (15)	0.70

EAIR, exposure-adjusted incidence rate.