Title: Zanubrutinib in Patients with B-cell Malignancies Intolerant to Ibrutinib and/or Acalabrutinib

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Introduction: Bruton tyrosine kinase inhibitor (BTKi) therapy is remarkably effective in a number of B-cell malignancies; however, its continuous use is limited by adverse events (AE) leading to discontinuation. Zanubrutinib is a potent and selective BTKi with the potential to be safe and effective therapy after intolerance to previous BTKi therapy. Here, we report preliminary results of a phase 2 study of zanubrutinib in patients with B-cell malignancies intolerant to ibrutinib and/or acalabrutinib based on a median follow-up of 6 months.

Methods: Patients meeting protocol criteria for intolerance to ibrutinib, acalabrutinib, or both (without documented progressive disease on ibrutinib or acalabrutinib) were given zanubrutinib monotherapy (160 mg twice daily or 320 mg once daily at investigator's discretion). Recurrence of adverse events that

led to intolerance to prior BTKi and additional safety measures were assessed based on the Common Terminology Criteria for AEs v5.0. Investigators determined responses using disease status at study entry as baseline and standard established disease response criteria.

Results: As of March 1, 2021 (cutoff), 64 patients (n=48 chronic lymphocytic leukemia/small lymphocytic lymphoma, n=10 Waldenström macroglobulinemia, n=3 mantle cell lymphoma, n=3 marginal zone lymphoma) were enrolled, received ≥1 dose of zanubrutinib, and were analyzed for safety. The median age was 71 y (range, 49-91); median duration of treatment was 5.9 months (range, 0.6-16.6). The median number of prior regimens was 2 (range, 1-12). Regarding prior BTKi, 55 patients had received ibrutinib monotherapy, 8 had received ibrutinib combination therapy, and 7 had received acalabrutinib monotherapy. The median number of ibrutinib- or acalabrutinib-intolerant adverse events per patient was 2 (range, 1-5). Most ibrutinib- (75%) and acalabrutinib-intolerant events (75%) did not recur with zanubrutinib, **Table**. A majority (90%) of the recurrent ibrutinib-intolerant events were less severe with zanubrutinib than with ibrutinib. Ibrutinib intolerance events present in >1 patient that did not recur on zanubrutinib were alanine aminotransferase increased, aspartate transaminase increased, neutropenia, and pain in extremity. The ibrutinib-intolerant events that recurred were diarrhea, dizziness, insomnia, nausea, constipation, myalgia, stomatitis, arthralgia, headache, muscle spasm, rash, atrial fibrillation, fatigue, hemorrhage, and hypertension. One-third of the recurrent acalabrutinib-intolerant events were less severe with zanubrutinib than with acalabrutinib. The acalabrutinib-intolerant events that recurred were myalgia and arthralgia. Two events of arthralgia that induced acalabrutinib intolerance did not recur with zanubrutinib. No ibrutinib- or acalabrutinib-intolerant events recurred at a higher severity while patients were on zanubrutinib. At cutoff, 57 patients remained on treatment; 1 withdrew consent due to zanubrutinib-unrelated grade 3 syncope. Grade ≥3 adverse events were reported in 14 patients (21.9%), serious adverse events in 5 patients (7.8%; pain in jaw; COVID-19 pneumonia; anemia; febrile neutropenia and salmonella infection [occurred in the same patient]), adverse events requiring dose interruptions in 15 patients (23.4%), and adverse events leading to dose reduction in 3 patients (4.7%). Adverse events led to zanubrutinib discontinuation for 3 patients (4.7%). One death was reported (COVID-19 pneumonia). Among efficacy evaluable patients (n=48), the disease control rate was 89.6% and the overall response rate was 50.0%.

Conclusions: In patients with B-cell malignancies intolerant to ibrutinib and/or acalabrutinib, zanubrutinib therapy was effective and controlled patient's disease or induced responses to therapy,

and was well-tolerated; most adverse events that led to discontinuation of previous BTKi therapy did not recur while patients were on zanubrutinib.

Table:
Recurrence and Severity Change of AEs Leading to Ibrutinib or Acalabrutinib Intolerance

	Adverse events leading to ibrutinib and acalabrutinib intolerance, N	Recurrence on zanubrutinib, n (%)		Severity changes of recurrence on zanubrutinib, n (%)	
		No	Yes	Recurred at lower severity	Recurred at same severity
Ibrutinib	115	86 (75)	29 (25)	26 (90)	3 (10)
Acalabrutinib	12	9 (75)	3 (25)	1 (33)	2 (67)

Note: Multiple events of the same preferred term for a patient are counted once for the event per the worst grade experienced before and after enrollment.