First-line treatment of CLL/SLL with the all-oral combination of sonrotoclax and zanubrutinib achieves undetectable minimal residual disease rates of >90%, including in patients with del(17p)/TP53

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Background: Oral, fixed-duration BTKi-BCL2i combinations are effective and convenient options for first-line treatment of CLL. However, current regimens, including those using second-generation BTKi, are limited by low uMRD rates. We hypothesize that upgrading the BCL2i component of BTKi-BCL2i with sonrotoclax, a next generation BCL2i with ~14x pharmacological potency compared with venetoclax, may lead to improved uMRD rates.

Aims: To report updated safety and efficacy results in patients with treatment-naive CLL/SLL treated with zanubrutinib + sonrotoclax (320 mg cohort) in a phase 1/1b study (NCT04277637), with a median follow-up of 30.9 months (range, 3.1-41.9 months).

Methods: Study treatment consisted of lead-in zanubrutinib 320 mg QD for 8-12 weeks, after which sonrotoclax was added with a ramp-up to the target dose of 320 mg QD. Patients were treated until progression, unacceptable toxicity, or protocol-defined elective discontinuation after 96 weeks of combination treatment at target dose. Primary endpoint was safety per NCI-CTCAE v5.0. Secondary endpoints included overall response rate (ORR). Exploratory endpoints

included uMRD4 rates in peripheral blood per flow cytometry and next generation-sequencing (NGS).

Results: Of the 86 patients enrolled in the sonrotoclax 320 mg cohort, 45 (52%) remained on treatment at data cut-off, and 40 (47%) discontinued sonrotoclax, most due to protocol-defined elective discontinuation (85%; n=34). The most common (≥30%) any-grade treatment-emergent adverse events (TEAEs) were neutropenia (38%), contusion (38%), COVID-19 (33%), and upper respiratory tract infection (30%). Neutropenia was the most common grade ≥3 TEAE (29%). No TLS occurred, and no AEs led to death.

In 84 efficacy-evaluable patients, the ORR was 100%, with 46 (55%) achieving complete response. Median time to response was 2.6 months (range, 1.5-9.1 months). No patients in the 320 mg cohort experienced progression with an estimated 30-month PFS of 100%.

The best uMRD4 rate assessed by flow cytometry was 99% (83/84) and 100% (10/10) in patients with *TP53*/del(17p) mutations. Median time from reaching sonrotoclax target dose to uMRD was 3.0 months (range, 2.3-27.4 months), and the best uMRD4 rates by weeks 24, 48 and 96 were 81% (69/85), 91% (63/69) and 98% (55/56), respectively. No patient with uMRD4 reverted to MRD4+. In the NGS evaluable set, best uMRD5 ($<10^{-5}$) was 86% (66/77). Updated results will be presented.

Conclusions: Sonrotoclax + zanubrutinib was well tolerated and achieved uMRD rates of >90%, including in patients with high-risk cytogenetics. The depth and kinetics of uMRD achieved with sonrotoclax + zanubrutinib highlights the improved potency and differentiated profile of this combination versus available combination therapies in first-line CLL. Sonrotoclax + zanubrutinib is being evaluated in two phase 3 clinical trials (NCT06073821, NCT07277231).