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Title: Sonrotoclax monotherapy demonstrates durable clinical activity in relapsed/refractory marginal zone lymphoma: 30-month follow-up from an ongoing phase 1/1b study

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Introduction: Marginal zone lymphoma (MZL) remains incurable with current therapies. Patients with relapsed or refractory (R/R) disease have limited treatment options and there is a significant clinical need for novel and effective therapies. B-cell lymphoma 2 (BCL2) inhibition represents a promising therapeutic approach in multiple B-cell malignancies. Sonrotoclax is a next-generation BCL2 inhibitor designed to have high target selectivity, enhanced pharmacologic potency, and an optimized pharmacokinetic profile characterized by a shorter half-life and minimal drug accumulation. These properties may enable deeper target inhibition while mitigating toxicity. Here, we report updated results for patients with R/R MZL from an ongoing phase 1/1b study evaluating sonrotoclax monotherapy or combination therapies in patients with mature B-cell malignancies (NCT04277637).

Methods: Patients with various non-Hodgkin lymphoma subtypes received oral sonrotoclax 40, 80, 160, 320, or 640 mg once daily with a 3-day daily ramp-up to the target dose followed by expansions at 320 and 640 mg. Patients were treated until progressive disease (PD) or unacceptable toxicity. The primary endpoint was safety per NCI-CTCAE v5.0, including assessment of tumor lysis syndrome (TLS) as defined by Howard 2011 criteria. Overall response rate (ORR) assessed by Lugano 2014 criteria was a secondary endpoint.

Results: As of May 18, 2026, 24 patients with MZL received sonrotoclax 40 mg (n=1), 160 mg (n=2), 320 mg (n=10), and 640 mg (n=11). Patients had a median age of 73 y (range, 54-85 y), 46% were male, and 96% were White. At baseline, patients had a median of 2 prior therapies and 46% had received ≥3 prior lines of therapy. Nine patients (38%) had received prior Bruton tyrosine kinase (BTK) inhibitor treatment, and 7 patients (29%) received a BTK inhibitor as their last prior treatment. All patients had prior anti-CD20 therapy. The median follow-up was 30.2 months (mo; range, 3.5-60.5 mo). As of the data cutoff date, 3 patients in the sonrotoclax 640-mg cohort remained on treatment, while 21 discontinued treatment due to PD (n=14), adverse events (AEs; n=4: neutropenia, progressive multifocal leukoencephalopathy [PML], sepsis, and myelodysplastic syndrome), physician decision (n=2), or patient withdrawal (n=1).

Maximum tolerated dose was not reached at the maximum assessed dose of sonrotoclax 640 mg; one dose-limiting toxicity (febrile neutropenia) occurred in the sonrotoclax 160-mg cohort. The most common (≥20%) all-grade treatment-emergent AEs (TEAEs) were pyrexia (46%), anemia (29%), nausea (29%), neutropenia (25%), constipation (25%), fatigue (25%), headache (25%), cough (21%), and diarrhea (21%). The most common grade ≥3 TEAEs (≥10%) were anemia (17%), neutropenia (17%), and pneumonia (13%). One grade 5 TEAE of PML occurred in a patient with a prior treatment history of rituximab and bendamustine and was deemed not related to sonrotoclax. No cases of clinical TLS occurred. Laboratory TLS was observed in 2 patients in the sonrotoclax 640-mg cohort during ramp-up (patient 1 had lymph nodes measuring 60 mm, spleen measuring 21 cm, and white blood cell [WBC] count of 46.9 × 10^9/L; patient 2 had lymph nodes measuring 28 mm, spleen measuring 20 cm, and WBC count of 352 × 10^9/L); both cases resolved within 24 hours without sequelae or dose modification.

Among 24 response-evaluable patients across dose levels, the ORR was 50% with a complete response (CR) rate of 17%; in the sonrotoclax 640-mg cohort (n=11), the ORR and CR rate were 73% and 36%, respectively. Of 9 patients who experienced progression while on prior BTK inhibitor treatment, six (67%) responded to sonrotoclax. In the sonrotoclax 640-

mg cohort (n=11), median PFS was 27.1 mo (95% CI, 5.6 mo-not estimable), the 24-mo PFS rate was 55% (95% CI, 23%-78%), and median duration of response was not reached.

Conclusions: Sonrotoclax monotherapy demonstrated encouraging response rates and durable disease control in heavily pretreated patients with MZL, with a suggestion of more favorable outcomes observed with sonrotoclax 640 mg. Notably, the clinical activity achieved with sonrotoclax doses up to 640 mg was not associated with new safety signals or clinical TLS. These findings are consistent with the broad clinical activity and favorable safety profile reported for sonrotoclax across hematologic malignancies and support further development of sonrotoclax-based treatment strategies in patients with MZL.