Preliminary efficacy and safety of the Bruton tyrosine kinase degrader BGB-16673 in patients with relapsed or refractory (R/R) indolent NHL: Results from the phase 1 CaDAnCe-101 study

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Introduction: Bruton tyrosine kinase (BTK) inhibitors have significantly advanced the treatment of patients with B-cell malignancies. However, disease progression can still occur, sometimes due to BTK mutations, necessitating the development of therapies that can inhibit BTK-mediated signaling via an alternative mechanism. BGB-16673 is a bivalent small molecule that induces BTK degradation by binding specifically to BTK and the E3 ligase. The E3 ligase catalyzes the transfer of ubiquitin molecules to BTK which marks BTK for destruction by the proteasome. In preclinical models, BGB-16673 degraded wild-type and mutant forms of BTK associated with resistance to covalent (cBTKi) and noncovalent BTK inhibitors (ncBTKi), leading to tumor suppression. CaDAnCe-101 (BGB-16673-101, NCT05006716) is an ongoing, open-label, first-in-human, phase 1/2 study designed to evaluate BGB-16673 monotherapy in patients with

B-cell malignancies. Here, updated results in patients with follicular lymphoma (FL) and marginal zone lymphoma (MZL) enrolled in the phase 1 portion are presented.
Methods: Eligible patients had R/R NHL (≥2 prior therapies), an ECOG performance status of 0-2, and adequate organ function. All patients with FL must have received an anti-CD20 antibody. Patients with MZL must have previously received an anti-CD20 antibody in the EU and both an anti-CD20 antibody and a cBTKi in the US. BGB-16673 was dosed once daily orally in 28-day cycles. Dose escalation used a Bayesian optimal interval design (6 planned dose levels, 50-600 mg once daily). Primary objectives were to assess safety/tolerability (CTCAE v5.0) and to establish the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D). Dose-limiting toxicities (DLTs) were assessed in the first 4 weeks (cycle 1). A secondary objective was to evaluate the overall response rate (ORR, 2014 Lugano criteria), with the first assessment occurring after 12 weeks of treatment.

Results: As of May 24, 2024, 20 patients with FL (n=8) or MZL (n=12) were treated (100 mg, n=1; 200 mg, n=11; 350 mg, n=8). The median age was 68 years (range, 57-75 years) in patients with FL and 76 years (range, 66-88 years) in those with MZL. The median number of prior therapies for FL and MZL was 4.5 (range, 2-9) and 3.0 (range, 1-8), respectively. Prior therapies included cBTKis (1/8 [13%] in FL and 10/12 [83%] in MZL), BCL2 inhibitors (5/12 [42%] in MZL), and ncBTKis (1/8 [13%] in FL and 1/12 [8%] in MZL). The median follow-up was 11.1 months (range, 2.5-20.6 months) for FL and 3.2 months (range, 0.3-15.8 months) for MZL.

Sixteen patients (80%) reported any-grade treatment-emergent adverse events (TEAEs; grade ≥3, 25%), of which, the most common (≥20%) were upper respiratory tract infection (25%; grade ≥3, 5%), fatigue (25%; no grade ≥3), and contusion (20%; no grade ≥3). Five patients (25%) experienced a grade ≥3 TEAE. One patient experienced hypertension (history of hypertension that worsened to grade 3 on study, monitored without treatment), and 1 patient experienced atrial fibrillation (grade 1), both in the MZL group. One patient experienced major hemorrhage. No febrile neutropenia was seen. No TEAEs led to dose reduction and 1 patient with MZL had a TEAE that led to treatment discontinuation (pleural effusion related to disease progression). No DLTs occurred and the MTD was not reached. No deaths due to TEAEs occurred.

In the 14 response-evaluable patients, the ORR (partial response or better) was 50% (4/8) for FL (CR, n=1; time to CR 3.3 months) and 67% (4/6) for MZL (CR, n=2; time to CR 3.6 and 13.7 months), with 6 of the 8 responses still ongoing at the data cutoff. Median time to first response was 2.7 months (range, 2.6-3.3 months) for FL and 2.9 months (range, 2.8-3.6 months) for MZL. Responses were seen in patients previously treated with a cBTKi (2/4 in MZL and 0/1 in FL with prior cBTKi) and a ncBTKi (0/1 in MZL and 1/1 in FL with prior ncBTKi).

Conclusions: Emerging data from this ongoing, first-in-human study demonstrate that the novel BTK degrader BGB-16673 has a tolerable safety profile and shows clinically meaningful, durable responses in heavily pretreated patients with FL and MZL, including those with prior BTK inhibitor treatment.