Clinical profile of single-agent modified-release oprozomib tablets in patients with Waldenström's Macroglobulinemia: updated results from a multicenter, open-label, dose-escalation, phase 1b/2 study

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Background: Oprozomib (OPZ) is an oral epoxyketone proteasome inhibitor. Modified-release OPZ tablets have promising antitumor activity in patients (pts) with hematologic malignancies (HM), including Waldenström's macroglobulinemia (WM) (Ghobrial, et al. ASH 2013). Herein, we present updated results from pts with WM enrolled in the ongoing phase (Ph) 1b/2 study (NCT01416428).

Methods: Pts with HM who relapsed after failing ≥1 line of therapy are eligible. The primary objectives of the Ph 1b study are to determine the maximum tolerated dose (MTD) and the safety and tolerability of OPZ. The primary objective of the Ph 2 study is to determine the best overall response rate (ORR; ≥minimal response [MR]). In the Ph 1b study, modified-release OPZ tablets are being administered once daily on Days 1, 2, 8, and 9 of a 14-day cycle (2/7 schedule) or on Days 1–5 of a 14-day cycle (5/14 schedule). The starting dose was 150 mg/day; doses were escalated (30-mg increments) up to 330 mg/day. In the Ph 2 study, pts are receiving 240 mg/day (5/14). Results: As of April 15, 2014, 34 pts with WM were enrolled. Baseline demographic information is included in Table 1. Median treatment duration was 6.3 weeks for all pts (Ph 1 [2/7]: 6.4 weeks; Ph 1 [5/14]: 31.3 weeks; Ph 2 [5/14]: 3.3 weeks). Two pts with WM had a dose-limiting toxicity (Ph 1b, 5/14) at 240 mg and 270 mg, respectively. In the Ph 1b study, the MTD for pts with HM was 300 mg/day (2/7) and 240 mg/day (5/14). Adverse events (AEs) are shown in Table 2. Due to an AE, treatment was held at least once in 8 pts (24%); 13 pts (38%) had their dosage reduced at least once, and 6 pts (18%) discontinued treatment. Of 119 pts with HM enrolled in the study, 2 pts with multiple myeloma (MM) died from upper gastrointestinal (GI) bleeding (5/14, 240 mg/day). In addition, 3 other GI bleeding events were reported in 3 pts with MM (5/14) who received 240 mg/day (GI bleeding [Grade (Gr) 3] and upper GI hemorrhage [Gr 3] that preceded the Gr 5 upper GI hemorrhage in the same patient) or 270 mg/day (Gr 1 rectal bleeding). The bleeding risk of OPZ is under investigation; clinicians should carefully monitor pts. Twenty-nine pts were response-eligible. The ORR in 8 pts on the 2/7 schedule was 37.5%; 1 pt had a partial response (PR) and 2 pts had a MR. In the Ph 1b study (11 pts; 5/14 schedule), the ORR was 90.9% (1 complete response; 6 PR; 3 MR). In the Ph 2 study (10 pts), the ORR was 40.0% (2 PR; 2 MR).

Conclusions: Once-daily modified-release OPZ tablets have promising antitumor activity in pts with WM. Extended-release OPZ tablets will be introduced and safety and tolerability of the new formulation will be assessed. Steps have been taken to prevent further GI bleeding events, including revising the protocol (e.g., change in dose/schedule and formulation, addition of proton pump inhibitors, etc.).