BGB-11417-203, an ongoing, phase 2 study of sonrotoclax (BGB-11417), a next-generation BCL2 inhibitor, in patients with Waldenström macroglobulinemia

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ABSTRACT

Introduction: Bruton tyrosine kinase (BTK) inhibitors and anti-CD20 antibody-based systemic therapy are included within the preferred treatment algorithms for Waldenström macroglobulinemia (WM). However, to date, no treatments have been approved for patients with WM that are refractory to both BTK inhibitors and anti-CD20 therapy. Venetoclax, the first-generation BCL2 inhibitor, has demonstrated clinical activity in patients with relapsed/refractory (R/R) WM, but it has no regulatory approvals in WM. Sonrotoclax, a next generation BCL2 inhibitor, is more selective and a more pharmacologically potent inhibitor of BCL2 than venetoclax. In a phase 1 trial, sonrotoclax monotherapy was well tolerated at all dose levels tested up to 640 mg and showed promising evidence of antitumor activity in patients with R/R WM. Based on the data from these earlier studies, a phase 2 study of sonrotoclax monotherapy, and sonrotoclax in combination with zanubrutinib, in patients with WM has been initiated and is currently recruiting.

Methods: BGB-11417-203 (NCT05952037) is an open-label, international, phase 2 study among patients with histologically confirmed WM. Approximately 105 patients will be enrolled across 4 cohorts. Patients in Cohort 1 to 3 must have R/R disease with the following requirement: Cohort 1 enrolls patients R/R to both BTK inhibitor therapy and anti-CD20–based systemic therapy combined with chemotherapy or a proteasome inhibitor (PI); Cohort 2 enrolls patients R/R to anti-CD20–based systemic therapy combined with chemotherapy or a PI and who are intolerant to BTK inhibitor therapy; Cohort 3 enrolls patients R/R to a BTK inhibitor and who are unsuitable for chemoimmunotherapy. Patients in Cohorts 1 to 3 will receive sonrotoclax until disease progression, death, unacceptable toxicity, patient withdrawal, loss to follow-up, or study termination. Patients in Cohort 4 are previously untreated and will receive combination therapy with sonrotoclax plus zanubrutinib for up to 20 cycles. The primary endpoint of the study is major response rate (MRR; defined as partial response or better) in Cohort 1 per IWWM-11 criteria, as assessed by independent review committee (IRC). Secondary endpoints include MRR assessed by investigator (INV) in Cohorts 1 to 4, and by IRC in Cohorts 2 and 3; overall response rate and duration of response (INV, Cohorts 1 to 4; IRC, Cohorts 1 to 3); progression-free survival (IRC and INV, Cohorts 1 to 3); time to next treatment (INV, Cohort 4); overall survival (Cohorts 1 to 3); and safety and tolerability. Patient recruitment is ongoing in Australia, the US, China, and Europe.