A phase 1 study of BGB-24714, a second mitochondrial-derived activator of caspases (SMAC) mimetic, as monotherapy or in combination with chemotherapy or concurrent chemoradiotherapy in solid tumors

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ABSTRACT

Background: Apoptosis modulation may enhance the efficacy of standard-of-care chemotherapy (CT) and concurrent chemoradiotherapy (cCRT) in solid tumors. BGB-24714, a selective SMAC mimetic that antagonizes Inhibitor of Apoptosis Proteins (IAPs), has demonstrated promising preclinical antitumor activity. This open-label, multicenter, first-in-human Phase (Ph) 1 study evaluated BGB-24714 as monotherapy or in combination with CT or cCRT in patients (pts) with advanced or metastatic solid tumors (NCT05381909).

Methods: The study included dose-escalation (1a) and -expansion (1b) Phs. Ph1a Part A assessed BGB-24714 monotherapy; Part B: BGB-24714 + weekly paclitaxel; Parts C/D: BGB-24714 + cCRT in NSCLC and esophageal squamous cell carcinoma (ESCC), respectively. Ph1b enrolled pts with second-line or later metastatic NSCLC and platinum-resistant ovarian cancer (PROC) to receive BGB-24714 + docetaxel or paclitaxel,

respectively. Primary endpoints were safety/tolerability (Ph1a) and preliminary antitumor activity (Ph1b).

Results: As of July 25, 2025, 157 pts were enrolled and treated (132 in Ph1a; 25 in Ph1b [11 NSCLC; 14 PROC]). 9 dose levels (DLs; 30 mg to 900 mg QD) of BGB-24714 were assessed (n=68) in Ph1a Part A and 7 DLs (60 mg to 650 mg QD) in Ph1a Parts B to D (n=64). No MTD was reached in Ph1a monotherapy or combination dose escalation.

The most common BGB-24714-related TEAEs varied by study part and were predominantly low grade: nausea (33.8%) in Ph1a Part A, diarrhea (25%) in Part B, neutrophil count decreased (43.8%) in Parts C/D, diarrhea and fatigue (45.5% each) in Ph1b-NSCLC, and stomatitis, ALT/AST increased (28.6% each) in Ph1b-PROC. The most common Grade ≥3 BGB-24714-related TEAEs were ALT increased (5.9%) in Ph1a Part A, lipase increased and fatigue (6.3% each) in Part B, neutrophil count decreased (31.3%) in Parts C/D, anemia (27.3%) in Ph1b-NSCLC, and neutrophil count decreased (28.6%) in Ph1b-PROC. The most common serious BGB-24714-related TEAEs (≥5%) were pneumonitis (6.3%) in Ph1a Part B, diarrhea (18.2%) in Ph1b-NSCLC, and febrile neutropenia and fatigue (7.1% each) in Ph1b-PROC. Treatment discontinuation due to BGB-24714-related TEAEs occurred in 12.1% of Ph1a and 24.0% of Ph1b pts.

Confirmed ORRs in Ph1a were 0% (Part A), 12.8% (Part B), 54.5% (Part C), and 66.7% (Part D); DCRs were 40.0%, 59.6%, 81.8%, and 100.0%, respectively. In Ph1b, confirmed ORRs were 0% in NSCLC and 28.6% in PROC; DCRs were 70.0% and 85.7%, respectively; median PFS was 162 days for both NSCLC and PROC. Pharmacodynamics showed rapid and sustained cIAP1 degradation in a dose-dependent manner, demonstrating strong target engagement in apoptosis regulatory pathway.

Conclusion: BGB-24714 demonstrated antitumor activity with a manageable safety profile in pts with advanced or metastatic solid tumors.