Pharmacodynamic (PD) characterization of BGB-24714, a second mitochondrial-derived activator of caspases (SMAC) mimetic, in a first-in-human study in solid tumors

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ABSTRACT

Background:
Inhibitor of apoptosis proteins (IAPs) are key regulators that suppress programmed cell death and are frequently overexpressed in cancer, contributing to tumor survival, drug resistance, and poor prognosis. Inhibition of IAPs restores apoptotic sensitivity and activates the NF-κB pathway, leading to induction of inflammatory cytokines and chemokines. SMACs, when released from mitochondria, naturally antagonize IAPs. BGB-24714 is a potent and selective SMAC mimetic that binds and inhibits IAPs, demonstrating robust antitumor activity across multiple xenograft models. This study presents the first translational PD biomarker evaluation of BGB-24714 in patients with solid tumors; safety and efficacy outcomes are reported separately.

Methods:
PD biomarkers were developed and validated in preclinical models to assess target engagement and downstream pathway modulation. In the monotherapy dose escalation cohorts of BGB-24714 first-in-human study (NCT05381909), blood samples were collected at baseline (pre-dose on cycle 1 day 1) and at serial post-dose timepoints. Cellular IAP1 (cIAP1) levels in PBMCs were quantified to assess target engagement. Caspase-cleaved cytokeratin-18 (ccCK18) was measured as a circulating marker of apoptosis, and cytokine/chemokine profiles were analyzed to evaluate inflammatory signaling.

Results:
In a human breast cancer xenograft model, BGB-24714 induced dose-dependent antitumor activity accompanied by rapid and sustained degradation of cIAP1, with maximal effects at 100 mg/kg. cIAP1 inhibition occurred within 1 hour post-dose and persisted at least for 24 hours, indicating that rapid and durable cIAP1 degradation is required for optimal efficacy. Similar levels and kinetics of cIAP1 degradation were observed in PBMCs and tumor tissue in mice at a clinically relevant dose, validating PBMCs as a suitable surrogate for PD assessment. In the phase 1 study, BGB-24714 induced rapid, sustained, and dose-dependent cIAP1 degradation in PBMCs. Approximately 50% degradation was observed on Day 2 at the 60 mg dose, near

complete cIAP1 degradation was achieved by Day 2 and maintained thereafter at doses ≥ 200 mg. Dose-dependent increases in ccCK18 at Day 15 from 200 mg onward indicated apoptosis induction, while dose-dependent elevations in circulating cytokines and chemokines at Day 15 from doses 200 mg or 300 mg, with a more pronounced trend at 450 mg and above, were consistent with NF-κB pathway activation. Collectively, these PD findings confirm the on-mechanism biological activity of BGB-24714.

Conclusion:
BGB-24714 demonstrated potent, sustained target engagement, apoptosis induction, and immune-inflammatory modulation consistent with its SMAC mimetic mechanism of action. These translational PD results support the biological activity of BGB-24714 in patients with solid tumors.