

Bgb-A425, an investigational anti-TIM-3 monoclonal antibody, in combination with tislelizumab, an anti-PD-1 monoclonal antibody, in patients with advanced solid tumors: A phase I/II trial in progress.

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Background:

While immune surveillance plays a critical role in preventing tumor proliferation and metastasis, tumors develop resistance mechanisms to suppress and/or escape the immune system. T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) and programmed cell death protein-1 (PD-1) function as immune checkpoint receptors on tumor-infiltrating lymphocytes. Overlap in expression and function suggests TIM-3 and PD-1 cooperate to maximize effector T-cell exhaustion, leading to a decreased antitumor immune response. Although blockade of TIM-3 alone is unlikely to result in an efficacious antitumor immune response, combined TIM-3/PD-1 blockade may enhance the antitumor properties of anti-PD-1 therapies alone. BGB-A425 is an investigational IgG1-variant monoclonal antibody against TIM-3. Tislelizumab, an anti-PD-1 antibody, was engineered to minimize binding to FcγR on macrophages in order to abrogate antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential resistance to anti-PD-1 therapy. This phase 1/2 study will assess the safety/tolerability, pharmacokinetic (PK) profile, and antitumor activity of BGB-A425 in combination with tislelizumab in patients with advanced solid tumors.

Methods:

This is an open-label phase 1/2 study (NCT03744468) of BGB-A425 in combination with tislelizumab in patients with histologically/cytologically confirmed advanced, metastatic, unresectable solid tumors. Phase 1 will determine the recommended phase 2 dose (RP2D) for combination treatment; phase 2 will assess the antitumor effects of the combination in select tumor types. In phase 1, up to 42 patients will be enrolled into sequential cohorts of increasing doses of intravenous (IV) BGB-A425 in combination with tislelizumab 200 mg IV, based on a 3+3 study design. During Cycle 1, patients will receive BGB-A425 alone on Day 1 followed by tislelizumab alone on Day 8. If no dose-limiting toxicities are observed, patients will receive both BGB-A425 and tislelizumab sequentially on Day 29 and every 21 days thereafter. Once the RP2D is determined, the combination therapy will be evaluated in up to 120 patients with select tumor types in phase 2. Safety/tolerability profile and RP2D determination (phase 1) and objective response rate per RECIST v1.1 (phase 2) are primary objectives; secondary objectives include antitumor activity, PK profile, and immunogenicity of combination therapy. Clinical trial information: [NCT03744468](https://clinicaltrials.gov/ct2/show/study/NCT03744468).