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TRIAL IN PROGRESS: AN INTRAVENOUSLY ADMINISTERED SECOND-GENERATION STING AGONIST, BI 1703880 WITH A NOVEL LEAD-IN DESIGN IN COMBINATION WITH EZABENLIMAB

¹Kevin Harrington*, ²Elizabeth Dowling, ³Robert Latek, ³Michael Schmohl, ⁴Patricia Lorusso. ¹The Royal Marsden NHS Foundation Trust, Sutton, UK; ²Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT, USA; ³Boehringer Ingelheim International GmbH, Ingelheim, Germany; ⁴Yale Cancer Center, New Haven, CT, USA

Background The prognosis for cancer patients diagnosed with advanced-stage disease or who have experienced disease progression is poor. STING (stimulator of interferon genes) is an intracellular nucleic acid sensor, which has a key role in innate immunity and detects the presence of cytosolic cyclic dinucleotides indicative of pathogen invasion and cellular disruption. BI 1703880 is a synthetic second-generation STING agonist, which induces a type 1 interferon response and transient secretion of interferon β and proinflammatory cytokines. Interferon receptor signaling upregulates PD-L1 expression, which reduces T-cell functionality and facilitates immune evasion through interaction with PD-1, suggesting that the combination of BI 1703880 with an anti-PD-1 antibody, such as ezabenzimab, may synergize to overcome tumor resistance.

Methods The 1480-0001 study is a first-in-human Phase Ia, open-label, dose-escalation trial of BI 1703880 monotherapy and in combination with ezabenzimab. In this innovative trial design, all patients will receive intravenous BI 1703880 as monotherapy followed by BI 1703880 in combination with ezabenzimab. The primary objective is to characterize the dose-toxicity curve for escalating doses of BI 1703880 in combination with ezabenzimab. Secondary objectives are to determine the safety profile of escalating doses of BI 1703880 (dose-limiting toxicities), to characterize its pharmacokinetics and pharmacodynamics, and to assess efficacy.

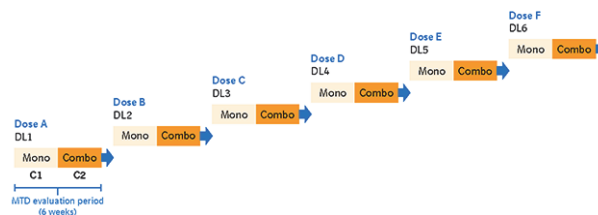
The lead-in dose escalation of BI 1703880 will be tested through six consecutive cohorts (figure 1) guided by a Bayesian 5-parameter logistic regression model with fitted overdose control. This will determine the maximum tolerated dose estimate. BI 1703880 will be administered intravenously for up to 18 cycles, or unacceptable toxicity or disease progression, at increasing dose levels (figure 2). Patients can continue to receive treatment if there is clinical benefit. Ezabenzimab 240 mg will be administered intravenously from Cycle 2 (figure 2). Approximately 36 patients will be enrolled.

Key eligibility criteria include an advanced, unresectable and/or metastatic malignant solid tumor, Eastern Cooperative Oncology Group performance score of 0–1, exhausted established treatment options and at least one lesion amenable to pre- and on-treatment biopsy.

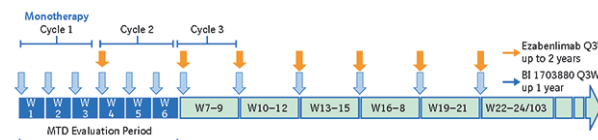
Peripheral and tumor biomarkers will be analyzed to assess the BI 1703880 mode of action. Peripheral cytokine analysis will supplement clinical safety profiles for informing dose escalation decisions, since cytokine release syndrome is a potential risk for STING agonists.

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Abstract 626 Figure 1



Abstract 626 Figure 2

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