Background

Although colorectal cancer (CRC) is traditionally considered to be immunologically inert, some subsets of colorectal cancer, particularly mismatch repair-deficient (MMRd) tumors, can be highly responsive to immune checkpoint blockade (ICB). Recent studies show that even mismatch repair-proficient (MMRp) tumors can respond to combined PD-1/CTLA-4 ICB. Tumor-associated macrophages (TAMs) are an influential component of the tumor microenvironment (TME), although the exact role of these immune cells in tumor pathogenesis and progression remains enigmatic. TAMs are highly heterogeneous and can be either pro-inflammatory or anti-inflammatory, and thus exhibit anti-tumorigenic or pro-tumorigenic effects respectively. Signal regulatory protein α (SIRPα) is a transmembrane protein expressed on TAMs that binds to CD47 on target cells, eliciting a ‘don’t-eat-me’ signal that inhibits phagocytosis by macrophages. In preclinical studies, anti-SIRPα antibodies have been shown to induce macrophage-dependent anti-tumor activity and skew macrophages towards an anti-tumorigenic phenotype. Since colorectal cancer lesions are often dominated by both T cells and anti-inflammatory TAMs, combination therapy with an anti-SIRPα antibody and an anti-PD-1 antibody may result in synergistic killing of tumor cells by TAMs and T cells.

Methods

This phase I, open-label, parallel-cohort, single-center trial (NCT05444129) was designed to assess the safety, feasibility, clinical efficacy, and biological activity of BI-765063 (an anti-SIRPα antibody) in combination with either ezabenlimab (Cohort A) or pembrolizumab (Cohort B), both anti-PD-1 antibodies, in patients with early-stage, resectable CRC (figure 1). Each cohort will enroll 25 patients. Treatment will be given as a single-dose in the neoadjuvant setting. All patients will then be scheduled to undergo surgical resection 2 to 6 weeks after treatment administration. The primary endpoint is a composite safety and feasibility endpoint, defined as the proportion of patients exhibiting any grade-3 or higher treatment-related adverse event or any treatment-related adverse event delaying surgery more than 6 weeks after treatment administration. The secondary endpoints include pathological response, defined as 50% or greater tumor regression, time from treatment administration to surgery, and radiographic response. Tissue, blood, and stool will be collected prior to treatment administration and at the time of resection. Immune monitoring will be performed using multiplex and single-cell analysis platforms to define the immunodynamic effects of these therapies.

Trial Registration

ClinicalTrials.gov Identifier: NCT05444129

Ethics Approval

On 9/23/2022 an Institutional Review Board of the Mount Sinai School of Medicine, in accordance with Mount Sinai's Federal Wide Assurances (FWA#00005651) to the Department of Health and Human Services approved the human subject research (ID 1502-0001; FWA#00005656, FWA#00005651) to the Department of Health and Human Services approved the human subject research (ID 1502-0001; PRMC-22-037; STUDY-22-00928) from 9/23/2022 to 9/19/2023.

Consent

Written informed consent was obtained from the patient for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

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