

NEOADJUVANT NIVOLUMAB COMBINED WITH CCR2/5 INHIBITOR OR ANTI-IL-8 ANTIBODY IN NON-SMALL CELL LUNG CANCER AND HEPATOCELLULAR CARCINOMA

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Background Immune checkpoint blockade (ICB) has revolutionized cancer treatment; however, most patients fail to achieve the full clinical benefit of ICB. Although anti-PD-1 agents are FDA-approved for non-small cell lung cancer (NSCLC) and hepatocellular carcinoma (HCC), only a minority of patients respond clinically.^{1,2} This limited response is likely due, in part, to immunosuppressive factors within the tumor microenvironment (TME). Myeloid cells, specifically monocyte-derived macrophages (mo-Macs) and immature granulocytes (iPMNs), make up the majority of leukocytes in the TME and suppress anti-tumor immunity; pre-clinical work has revealed that tumor-derived CCR2 ligands and interleukin-8 (IL-8) play a key role in recruiting mo-Macs and iPMNs, respectively, to the TME.³⁻⁷ Disrupting these signaling pathways appears to potentiate the role of PD-1 blockade in mouse models, although only modest clinical benefit has been demonstrated to date in metastatic cancer models. In this “window-of-opportunity” trial, patients will receive neoadjuvant nivolumab monotherapy or neoadjuvant nivolumab in conjunction with a CCR2/5 inhibitor or an anti-IL8 antibody prior to surgical resection, providing a unique opportunity to elaborate the specific effects of these agents on the TME and to identify factors that may allow clinicians to better predict response in the future.

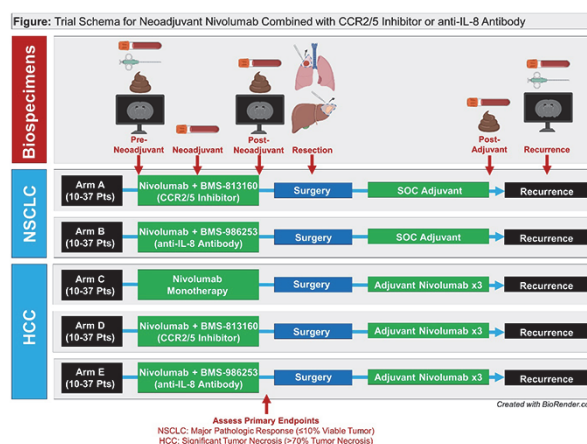
Methods This phase IIa multi-cohort, two-stage trial was designed to assess the clinical efficacy of BMS-813160 (CCR2/5 inhibitor) and BMS-986253 (anti-IL8 antibody) in patients with resectable NSCLC and HCC. The trial contains 2 cohorts (NSCLC and HCC) consisting of 5 arms (figure 1); arms A and B will enroll patients with NSCLC and arms C, D, and E will enroll patients with HCC. Patients will be treated with neoadjuvant nivolumab either alone (arm C) or in combination with BMS-813160 (arms A and D) or BMS-986253 (arms B and E). The patients will then undergo surgical resection, followed by standard-of-care adjuvant therapy in the NSCLC cohort or adjuvant nivolumab therapy in the HCC cohort. The primary endpoint for the NSCLC cohort is major pathologic response, defined as $\leq 10\%$ viable tumor at time of surgery. The primary endpoint for the HCC cohort is significant tumor necrosis, defined as $>70\%$ tumor necrosis at time of surgery. The secondary endpoints are time to surgery, safety and tolerability, radiographic response, progression-free survival, and overall survival. Tissue, blood, and stool will be collected prior to treatment and at the time of surgery. Deep immune monitoring will be performed using multiplex and single-cell analysis platforms to define the immunodynamic effects of the therapies.

Trial Registration NCT04123379

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Ethics Approval This trial obtained approval from the Icahn School of Medicine at Mount Sinai Institutional Review Board (#18-2375); all patients gave informed consent before participating in this trial.



Abstract 629 Figure 1: Trial Schema

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