TPS2696 **Poster Session**

A phase 1b study of combined treatment with dupilumab (anti-IL-4Ra) and cemiplimab (anti-PD-1) in patients with early-stage, resectable NSCLC.

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Background: For resectable stage II/III non-small cell lung cancer (NSCLC), neoadjuvant chemoimmunotherapy has become standard of care. Patients with Stage I disease (as per AJCC 8) were excluded from chemoimmunotherapy studies given prior data demonstrating no survival benefit from perioperative chemotherapy. However, even patients with Stage 1A (< 2cm) tumors have a 30% chance of recurrence (Altorki *et al*, *NEJM* 2023). Recent research has revealed that tumor-infiltrating myeloid cells express an IL-4 responsive transcriptional signature, and IL-4 signaling within monocyte-derived macrophages plays an essential role in NSCLC progression and tumor microenvironment remodeling. Dupilumab, a monoclonal antibody targeting IL-4 receptor alpha (IL-4Rα), is currently approved for treating asthma and allergic rhinitis, and preclinical studies have demonstrated that blocking IL-4 signaling can significantly reduce lung tumor burden by activating dendritic cells and effector T cells to generate a robust immune response against tumor antigens. These findings are supported by early clinical evidence from a phase 1/2 trial showing that dupilumab can work synergistically with PD-(L)1 inhibition to induce sustained tumor responses in some patients with metastatic NSCLC who had previously progressed on immunotherapy. Whether similar synergy would be seen in the pre-operative setting in patients with Stage 1 tumors, or patients not suitable for chemoimmunotherapy, is not known, though an immunotherapy-alone approach may enable much more brief pre-operative treatment given that T cell changes peak at one week in the metastatic setting, and prior studies show PD-1 blockade alone can cause robust responses in some patients within only a few weeks. **Methods:** This Phase 1b/2a single-arm trial will enroll patients with early-stage (> T1b), resectable NSCLC. Patients will receive one dose each of dupilumab (600mg SC) and cemiplimab (350mg IV) on day 1, followed by surgical resection within 15-21 days, with delays beyond 8 weeks considered a delay of surgery. The trial consists of a 3+3 safety run-in (Phase 1b, up to 6 patients) followed by a Simon's two-stage expansion (Phase 2a, up to 24 total patients). The primary endpoints are safety/feasibility (Phase 1b) and major pathological response rate, defined as ≤10% viable tumor at resection (Phase 2a). Secondary endpoints include time to surgery, pathological complete response rate, event-free survival, and overall survival. Comprehensive correlative studies will characterize the immune response through serial blood sampling (days 1, 4, 8, 15, surgery, and 30 days post-op), matched proteomic and transcriptomic tumor tissue analysis (pre-treatment and operative samples), and stool microbiome profiling to identify potential biomarkers of response. Clinical trial information: NCT06088771. Research Sponsor: Cancer Research Institute.