TPS8118 **Poster Session**

Safety, efficacy, and tumor immune microenvironment changes with neoadjuvant chemotherapy and cemiplimab with or without alirocumab in stage 1B-3A non-small cell lung cancer.

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Background: The addition of immune checkpoint blockade to neoadjuvant and adjuvant therapy is now standard of care in early-stage surgically resectable non-small cell lung cancer (NSCLC). However, resistance to immunotherapy limit their benefit for most patients. The pathological complete response (pCR) rate, a surrogate for long term survival, remains close to 20%, leaving many patients at a high risk of recurrence and death. Thus, there is a need to apply strategies to overcome immunotherapy resistance in earlier stages of NSCLC to improve cure. Proprotein convertase subtilisin/kexin type 9 (PCSK9), a major cholesterol regulator, has emerged as an inhibitory modulator of anti-tumor immunity. Preclinical evidence showed that PCSK9 downregulated MHC class I antigen expression on tumor cells. This effect was reversed by genetic or pharmacologic inhibition of PCSK9. PCSK9 inhibitor synergized with immune checkpoint blockade to increase cytotoxic T-cell mediated tumor death. Retrospective clinical analyses of NSCLC patients treated with immune checkpoint inhibitors also showed a correlation between higher PCSK9 levels and poorer survival. **Methods:** TOP 2301 is a multi-center, open label, two-arm, randomized, phase 2 trial of chemotherapy and cemiplimab (350mg IV every 3 weeks) with or without the PCSK-9 inhibitor, alirocumab (150 mg SC every 4 weeks), prior to surgery. Eligible patients will have stage IB-3A NSCLC, deemed surgical candidates, and have no EGFR or ALK mutations. One hundred and twenty-six patients will be randomized 1:1 to receive neoadjuvant SOC chemotherapy and cemiplimab versus SOC chemotherapy, cemiplimab and alirocumab. Approximately 64 participants are required in each arm to have 90% power to reject the null hypothesis. The primary objective is to compare the pCR rates for neoadjuvant chemotherapy plus cemiplimab versus chemotherapy, cemiplimab, and alirocumab. Secondary efficacy objectives for the experimental arm include: the objective response rate (ORR), disease free survival (DFS), and overall survival (OS). A secondary safety objective is to determine the safety and tolerability of neoadjuvant chemotherapy and cemiplimab with alirocumab in early-stage NSCLC. The correlative science objective will evaluate the difference in tumor infiltrating lymphocytes and dendritic cells through IHC, FACs analysis, and bulk RNA-seq with CIBERSORT from postsurgical specimens of patients treated with neoadjuvant chemotherapy and cemiplimab with or without alirocumab. The trial was open to enrollment on 12/15/2024. Clinical trial information: NCT06385262. Research Sponsor: None.