TPS2698 Poster Session

A phase Ib study of a pooled synthetic long peptide mutant KRAS vaccine combined with balstilimab/botensilimab in metastatic pancreatic cancer and metastatic MMR-proficient colorectal cancer in the maintenance setting.

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Background: Expressed in > 90% of all patients with pancreatic ductal adenocarcinoma (PDAC) and ~40% in mismatch repair-proficient colorectal cancer (MMRp CRC), the mutated oncoprotein KRAS (mKRAS), is an attractive neoantigen vaccine target. Efforts to sensitize these immunologically 'cold' tumors to immune checkpoint inhibitors have just started to yield encouraging clinical data with novel agents. In an ongoing pilot study in patients with resected PDAC and metastatic MMRp CRC (NCT04117087), we demonstrated that a pooled synthetic long peptide (SLP) mKRAS vaccine in combination with ipilimumab and nivolumab was safe and well tolerated. This combination induced robust de novo mKRAS-specific T cells in peripheral blood associated with improved disease-free survival (Haldar *et al.*, 2023). Recently, the Fc-enhanced anti-CLTA-4 antibody, botensilimab (bot), in combination with balstilimab (bal; anti-PD-1) has been shown to demonstrate clinical activity in metastatic relapsed/refractory MMRp CRC (Bullock *et al.*, 2024). Based on these encouraging data, our study combines mKRAS vaccine with dual checkpoint blockade to assess safety and early clinical efficacy in patients with metastatic PDAC and metastatic MMRp CRC in the maintenance setting. **Methods:** This is a first-in-human, single-arm, open-label phase Ib trial evaluating mKRAS vaccine with bal/bot in patients with metastatic PDAC (Cohort A, n = 21) and metastatic MMRp CRC (Cohort B, n = 21). The vaccine consists of SLPs corresponding to six common mKRAS alleles: G12D, G12V, G12R, G12C, G12A, G13D admixed with poly-ICLC adjuvant. In the priming phase (Cycle 1) the mKRAS vaccine is given on days 1, 8, 15 and 22 along with bal/bot on day 1 and bal on day 15. In the boost phase, (Cycle 2 and beyond), patients receive bal every 2 weeks and boost vaccines starting on Cycle 4 and every other cycle for a maximum of 2 years. Eligible patients must have metastatic PDAC or MMRp CRC and measurable disease per RECIST 1.1 amenable to biopsies at baseline and week 9. Patients must have one of the six KRAS mutations contained in the vaccine. Patients must have received 4-6 months of 1st line standard chemotherapy without disease progression. The primary endpoints are safety and tolerability, 4-month progression free survival (Cohort A), and objective response rate (Cohort B). Secondary endpoints include disease control rate, objective response rate (Cohort A), and progression free survival (Cohort B). Correlative studies will examine T cell receptor (TCR) clonal expansion in peripheral blood and paired tumor specimens pre- and post-vaccination by next generation TCR sequencing. Patient accrual began in October 2024 with the safety run in completed. Enrollment is currently ongoing. Study drug support provided by Agenus. Trial information: NCT06411691. Clinical trial information: NCT06411691. Research Sponsor: U.S. Department of Defense; U.S. National Institutes of Health.