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Abstract CT264: Mutant KRAS peptide vaccine combined with ipilimumab/nivolumab in advanced mismatch repair proficient/microsatellite stable (MMRp/MSS) colorectal cancer: Preliminary analysis from a phase I study FREE

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Abstract

Background:

Colorectal cancer (CRC) is the second leading cause of cancer death in the United States. Immune checkpoint inhibitors (ICIs) have minimal activity in the ~95% of metastatic CRC that are MMRp/MSS, largely due to significantly lower expression of neoantigens. Combining neoantigen vaccines targeting mutant KRAS (mKRAS), an oncogenic driver found in ~40% of CRC, with ICIs, may sensitize metastatic mKRAS MMRp/MSS CRC to immunotherapy.

Methods:

This is a first-in-human Phase 1 trial (NCT 04117087) of mKRAS-VAX - a pooled synthetic long peptide (SLP) vaccine targeting the six most common KRAS mutations (G12D, G13D, G12V, G12C, G12A, G12R) - in combination with ipilimumab/nivolumab (ipi/nivo) in patients with heavily pretreated MMRp/MSS CRC (progression on 2 or more lines of chemotherapy). Key inclusion criteria included tumor expression of a KRAS mutation included in mKRAS-VAX and prior 5-fluorouracil, oxaliplatin, and irinotecan exposure. In the priming phase, patients received 4 weekly doses of mKRAS-VAX as well as ipilimumab (1mg/kg every 6 weeks for 2 doses) and nivolumab (3mg/kg every 3 weeks for 4 doses). In the boost phase, patients received mKRAS-VAX every 8 weeks and nivolumab (480mg every 4 weeks) up to 1 year total. Primary endpoints are safety and mKRAS-specific T cell response. Secondary endpoints are overall response rate (ORR), progression-free survival (PFS), and overall survival (OS).

Skip to Main Content

Results:

At the time of data cutoff (December 13, 2024), 12 patients have been treated. Most adverse events were grade 1 (61.2%) or grade 2 (29.6%). 31.6% of AEs were immune-related including three that were grade 3 (2 adrenal insufficiency, 1 arthralgia). There was one grade 4 adverse event (sepsis), which was not treatment related. 8/12 (75%) patients achieved a mKRAS-specific T cell response to their tumor specific KRAS mutation as assessed by serial IFNγ ELISpot, with a median 9-fold increase from baseline. There was one RECIST partial response (8.3%) and 2/7 (29%) patients with active liver metastases had tumor shrinkage, a phenotype which is increasingly recognized as refractory to immunotherapy in MMRp/MSS CRC. The disease control rate (DCR) was 41.7% (5/12) with a median PFS was 3.7 months and median OS of 24.9 months.

Conclusions:

mKRAS-VAX and ipi/nivo is well-tolerated and induced mKRAS-specific T-cell responses. Moreover, this strategy resulted in meaningful clinical responses in chemorefractory metastatic mKRAS MMRp/MSS CRC with OS that was provocative. Ongoing studies of the T cell repertoire in blood and tumor tissue will be used to identify biomarkers that predict response to mKRAS-targeted immunotherapy. A Phase 1b clinical trial (NCT06411691) investigating mKRAS-VAX with ICIs balstilimab and botensilimab in advanced MMRp/MSS CRC and pancreatic ductal adenocarcinoma is underway.

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