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Abstract CT265: KRAS^{G12D}targeting using engineered exosomes in pancreatic cancer: Results from the iEXPLORE phase 1 trial FREE

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Abstract

Despite its pivotal role in pancreatic ductal adenocarcinoma (PDAC), oncogenic Kras has eluded pharmacological targeting design, albeit with more recent and promising development. Given the preponderance of Kras^{G12D} mutation in PDAC, we engineered exosomes from allogenic bone marrow derived mesenchymal cells with incorporation of Kras^{G12D}siRNA payload. We report on a comprehensive preclinical toxicology and biodistribution analysis of clinical grade iExosomes in mice and rhesus macaques, which informed on their safety as therapeutic agents in patients. We report on the clinical testing of iExosomes in a Phase 1 study that employed a classical 3+3 dose escalation design. Patients with metastatic disease were enrolled after multiple lines of therapy failure. No dose limiting toxicities (DLTs) were encountered for all 3 dose levels tested, and no DLT were noted for the 3 of the 9 patients who had stable disease after completing the first 3 cycles and allowed to undergo an additional 3 consecutive cycles. A follow up accelerated dose titration trial enrolled an additional 3 patients. The maximum tolerated dose was not reached, with no DLT encountered at the highest dosage used. Stable disease of target lesions was observed in 6 of the 12 patients treated with iExosomes, permitting their enrollment in additional iExosomes doses, with no DLT encountered. All patients eventually demonstrated PD. Target engagement was studied with down regulation of circulating Kras^{G12D} DNA and pre- and post-biopsy tissue analysis for Kras signaling. Immune profiling revealed opportunistic synergy with immune checkpoint blockade (ICB). Murine studies confirmed synergy of iExosomes with anti-CTLA4 antibodies specifically, with iExosomes reprograming the tumor immune microenvironment and recruiting Tregs susceptible to anti-CTLA4 co-treatment. This trial is the first-in-human therapeutic trial utilizing engineered exosomes from bone marrow derived mesenchymal cells, and we report on the safety of exosomes as well as target engagement in pancreatic cancer with a payload suppressing oncogenic Kras. The trial informed on the

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opportunistic and future combination therapy with ICB. ClinicalTrials.gov identifier: NCT03608631.

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