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### INITIAL SAFETY, EFFICACY, AND PRODUCT ATTRIBUTES FROM THE SURPASS TRIAL WITH ADP-A2M4CD8, A SPEAR T-CELL THERAPY INCORPORATING AN AFFINITY OPTIMIZED TCR TARGETING MAGE-A4 AND A CD8 $\alpha$ CO-RECEPTOR

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**Background** The ongoing SURPASS trial (NCT04044859) evaluates safety and efficacy of next-generation ADP-A2M4CD8 SPEAR T-cells co-expressing the CD8 $\alpha$  co-receptor with the engineered MAGE-A4<sup>c1032</sup>T cell receptor (TCR).

**Methods** First-in-human trial in HLA-A\*02 positive patients (pts) with advanced cancers expressing MAGE-A4 antigen by immunohistochemistry. Eligible pts undergo apheresis, T-cells are isolated, transduced with a Lentiviral vector containing the MAGE-A4<sup>c1032</sup> TCR and CD8 $\alpha$  co receptor, and expanded. Expansion, transduction level, cellular composition and function of the manufactured product (MP) are assessed in vitro. Prior to infusion, pts receive lymphodepletion with fludarabine 30 mg/m<sup>2</sup>/day for 4 days and cyclophosphamide 600 mg/m<sup>2</sup>/day for 3 days.

**Results** As of 16 July 2020, 5 pts (1 with MRCLS, 2 with esophagogastric junction [EGJ] cancers, 1 with ovarian cancer, and 1 with head and neck cancer) were treated with ADP-A2M4 CD8 (range ~1 to 5.7 billion transduced cells). No DLTs or SAEs have been reported. To date, 1 pt with EGJ cancer had a partial response (PR per RECIST) and has had progression-free survival >6 months. One pt with head and neck cancer also had a PR. All other pts have had best overall response of stable disease. MP expanded by an average of 15.3 fold during manufacturing (range 5.9 to 25.6-fold). On average, 43% of T-cells in the MP expressed the TCR (range 23 to 63%). The fraction of CD4<sup>+</sup> cells in the final MP varied (range 45 to 84%). Co-expression of the MAGE-A4 TCR and CD8 $\alpha$  in CD4<sup>+</sup> T-cells in the patient MP enabled CD4<sup>+</sup> T-cells to kill tumor target cells directly in vitro. MAGE-A4 expression in tumor biopsies varied (H-score range 55 to 300). Transduced T-cells were detected in peripheral blood of all pts. IFN-gamma increased transiently in the serum of 1 pt who responded.

**Conclusions** ADP-A2M4CD8 SPEAR T-cells have shown an acceptable safety profile and pts with EGJ cancer and head and neck cancer have demonstrated evidence of antitumor activity. Translational data and early clinical results indicate that co-expression of the CD8 $\alpha$  co-receptor on CD4<sup>+</sup> SPEAR T-cells may increase the potency of the product by conferring additional killing activity to the helper T-cell subset. This dose escalation trial is ongoing and updated clinical and translational data will be presented.

**Trial Registration** NCT04044859

**Ethics Approval** The trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines and was approved by local authorities. An independent ethics committee or institutional review board approved the clinical protocol at each participating center. All

the patients provided written informed consent before study entry.

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### PRELIMINARY RESULTS OF AN ONGOING PHASE I TRIAL OF FT500, A FIRST-IN-CLASS, OFF-THE-SHELF, INDUCED PLURIPOTENT STEM CELL (IPSC) DERIVED NATURAL KILLER (NK) CELL THERAPY IN ADVANCED SOLID TUMORS

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**Background** FT500 is an investigational, off-the-shelf NK cell cancer immunotherapy derived from a human clonal master iPSC line, a renewable cell source from which innate effector cells can be mass produced and made available off-the-shelf for broad patient access and multiple dose administration. FT500 has potent innate cellular cytotoxicity as compared to NK cells sourced from healthy donors and has been shown to synergize with T cells and anti-PD-1 blockade in preclinical studies.<sup>1</sup>

**Methods** FT500 is being investigated in a Phase I clinical trial as monotherapy and in combination with immune checkpoint inhibitors (ICIs) in patients with advanced solid tumors and lymphomas (ClinicalTrials.gov: NCT03841110). Treatment consists of 2 days lympho conditioning (fludarabine 25 mg/m<sup>2</sup> and cyclophosphamide 300 mg/m<sup>2</sup>) followed by 2 cycles of 3 once weekly doses of FT500 as monotherapy or combined with 1 of 3 approved ICIs (nivolumab, pembrolizumab, or atezolizumab) in patients who have failed prior ICI therapy. Key clinical and translational readouts include FT500 safety and tolerability, including immune mediated toxicities and anti-product immunogenicity.

**Results** 15 patients with relapsed/refractory disease following a median of 4 prior therapies were treated in dose escalation, including 9 with FT500 monotherapy (3 with 1 $\times$ 10<sup>8</sup> cells, 6 with 3 $\times$ 10<sup>8</sup> cells) and 6 with FT500 (3 each with 1 $\times$ 10<sup>8</sup> and 3 $\times$ 10<sup>8</sup> cells) combined with ICI. No dose limiting toxicities, Grade  $\geq$ 3 related adverse events (AEs), Grade  $\geq$ 3 related serious AEs, or related AEs leading to treatment discontinuation were reported. No graft-versus-host disease (GvHD), cytokine release syndrome (CRS), or neurotoxicity (NT) was observed. The most common treatment-emergent AEs in >3 patients were nausea (9), fatigue (7), constipation, decreased appetite, decreased lymphocyte count, decreased white blood cell count (5 each), anemia, and decreased neutrophil count (4 each). Nine of 13 efficacy-evaluable solid tumor patients had best response of stable disease by iRECIST. One patient with classical Hodgkin lymphoma (cHL) refractory to prior experimental anti-PD-1 therapy had a 58% reduction in target lesions size following FT500 plus ICI. No evidence of robust B- or T-cell mediated anti product responses was observed despite endogenous immune cell recovery following lympho-conditioning.

**Conclusions** Administration of 6 doses of up to 3 $\times$ 10<sup>8</sup> FT500 cells is safe and tolerable without evidence of GvHD, CRS, NT, or host immune rejection. Enrollment of advanced

non-small cell lung cancer and cHL patients at 3×10<sup>8</sup> FT500 cells per dose combined with ICI is ongoing.

**Ethics Approval** This study is being conducted in accordance with the Declaration of Helsinki and was approved by all Institutional Review Boards from each clinical site participating in the study. Specific approval numbers can be provided upon request.

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#### ROLE OF CT SCANS OF ABDOMEN AND PELVIS IN MANAGEMENT OF PATIENTS WITH IMMUNOTHERAPY-INDUCED COLITIS

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**Background** Colitis is one of the most common immune-related adverse event in patients who receive immune checkpoint inhibitors targeting cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death-1 (PD-1). Although radiographic changes are reported on computed tomography such as mild diffuse bowel thickening or segmental colitis, the utility of CT in diagnosis of patients with suspected immune-related colitis is not well studied.

**Methods** CT scans of the abdomen and pelvis of 34 patients on immunotherapy with a clinical diagnosis of immunotherapy induced colitis and 19 patients receiving immunotherapy without clinical symptoms of colitis (control) were enrolled in this retrospective study. Segments of the colon (rectum, sigmoid, descending, transverse, ascending and cecum) were assessed independently by two fellowship trained abdominal imaging specialists with 7 and 13 years' experience who were blinded to the clinical diagnosis. Each segment was assessed for mucosal enhancement, wall thickening, distension, peri-serosal fat stranding. Any disagreements were resolved in consensus. The degree of distension and the spurious assignment of wall thickening were the most common causes for disagreement. The presence of any of the signs was considered as radiographic evidence of colitis.

**Results** CT evidence of colitis was seen in 16 of 34 patients with symptoms of colitis. 7 of 19 patients who did not have symptoms of colitis showed signs of colitis on CT. The sensitivity, specificity, Positive Predictive Value and Negative Predictive Value for colitis on CT is 47%, 63.2%, 69.5% and 40%, respectively.

**Conclusions** CT has a low sensitivity, specificity and negative predictive value for the diagnosis of immunotherapy-induced colitis. CT has no role in the diagnosis of patients suspected of having uncomplicated immune-related colitis and should not be used routinely for management.

**Trial Registration** This protocol is not registered on clinicaltrials.gov.

**Ethics Approval** This protocol was IRB approved on: 11/16/2015 - IRB 4 Chair Designee FWA #: 00000363 OHRP IRB Registration Number: IRB 4 IRB00005015

**Consent** This protocol utilizes an IRB approved waiver of consent.

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#### TARGETING INNATE IMMUNITY WITH BXCL701 IN COMBINATION WITH PEMBROLIZUMAB IN PATIENTS WITH ADVANCED SOLID CANCERS: PHASE 2 BASKET STUDY

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**Background** BXCL701 is an oral competitive inhibitor of DPPs, primarily DPP8/9, that activates inflammasome mediated pyroptosis. BXCL701 therefore, can induce an innate immune reaction and tumor inflammation, bridging between innate and adaptive immunity, potentially leading to synergistic anticancer activity when combined with PD-1 antibody pembrolizumab.

**Methods** This is a phase 2, open-label, single-center study (NCT04171219) of oral BXCL701 0.3 mg BID on days 1–14 and intravenous pembrolizumab 200 mg on day 1 of a 21-day cycle with a safety lead-in to evaluate RECIST/iRECIST response rate in patients with advanced solid cancers. After confirming safety and dose limiting toxicities (DLT) in the first 6 patients, additional patients are being enrolled to a PD-1/PD-L1 antibodies (ab) naïve cohort and PD-1/PD-L1 ab pretreated cohort. Each cohort is planned to enroll 9 patients, and if a partial (PR) or complete response (CR) is observed the cohort is expanded to a total of 17 patients. The treatment is considered promising if at least 3 PRs or CRs are observed in a cohort of 17 patients.

**Results** As of August 24, 2020, 14 patients were treated; 5 patients (prostate cancer, endometrial cancer, uveal melanoma, liposarcoma, basal cell carcinoma) were enrolled in the PD-1/PD-L1 ab naïve cohort and 9 patients (leiomyosarcoma, squamous cell carcinoma of unknown primary, melanoma, myxoid sarcoma, pleomorphic sarcoma, colorectal cancer, anaplastic astrocytoma, prostate cancer) were enrolled to PD-1/PD-L1 ab pretreated cohort. Among all 14 patients, there was 1 episode of grade 4 hypotension (recovered) and 1 episode of grade 5 hypotension attributed to BXCL701. In the PD-1/PD-L1 ab naïve cohort, of 3 patients with available imaging, 2 had a PR (uveal melanoma previously treated with PD-1/OX40 fusion protein [-31%] n=1; and microsatellite stable endometrial cancer [-62%], n=1). In the PD-1/PD-L1 ab pretreated cohort, there were no objective responses in 5 patients with available imaging; however, a patient with pleomorphic sarcoma refractory to PD-1 antibody monotherapy demonstrated a tumor shrinkage of -18% on the first restaging imaging.

**Conclusions** BXCL701 in combination with pembrolizumab demonstrated encouraging signals of activity in selected difficult-to-treat cancers. Mitigation strategies to prevent events of high-grade hypotension are being implemented to allow the enrollment continuation.

**Trial Registration** NCT04171219

**Ethics Approval** The study was approved by MD Anderson IRB

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