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 CD8α 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 CD8α co-receptor with the engineered MAGE-A4\(^{1,2}\) 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\(^{1,2}\) TCR and CD8α 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\(^2\)/day for 4 days and cyclophosphamide 600 mg/m\(^2\)/day for 3 days.

Results As of 16 July 2020, 5 pts (1 with MRCLS, 2 with esophageogastric 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 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+ cells in the final MP varied (range 45 to 84%). Co-expression of the MAGE-A4 TCR and CD8α in the patient MP enabled CD4+ 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 CD8α co-receptor on CD4+ 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 iPS cell 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.

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: NCT03844110). Treatment consists of 2 days lympho conditioning (fludarabine 25 mg/m\(^2\) and cyclophosphamide 300 mg/m\(^2\)) 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 1×10\(^8\) cells, 6 with 3×10\(^8\) cells) and 6 with FT500 (3 each with 1×10\(^8\) and 3×10\(^8\) cells) combined with ICI. No dose limiting toxicities, Grade \(^3\) related adverse events (AEs), Grade \(^3\) related serious AEs, or related AEs leading to treatment discontinuation were reported. No graft-versus-host disease (GvHD), cytotoxic 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 3×10\(^8\) FT500 cells is safe and tolerable without evidence of GvHD, CRS, NT, or host immune rejection. Enrollment of advanced