Solid Tumor Patients Require Higher Cyclophosphamide Dose than Multiple Myeloma Patients to Achieve Adequate Lymphodepletion Necessary to Enable Allogeneic CAR-T Expansion

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BACKGROUND

Poseida Therapeutics is developing innovative allogeneic T cell memory-rich CAR-T therapeutics for both hematologic malignancies and solid tumors. These include P-MUC1C-ALLO3 which targets MUC1 for multiple myeloma, and P-MUC1C-ALLO2 targeting MUC1C for epithelial-derived solid tumors.

Optimal lymphodepletion for allogeneic CAR-T therapy remains to be established. Most allogeneic CAR-T clinical trials have focused on hematologic malignancies, where patients have likely undergone hematopoietic stem cell transplantation and are, therefore, lymphodepleted experienced in contrast to solid tumor patients. Consequently, solid tumor patients treated with allogeneic CAR-T may require higher doses of conditioning chemotherapy to achieve lymphodepletion depth comparable to patients with hematologic malignancies.

This retrospective analysis sought to compare lymphodepletion characteristics and CAR-T cell kinetics with multiple cyclophosphamide doses across our two phase 1 trials (NCT02393814/NCT09055775) which are enrolling solid tumor and multiple myeloma patients, respectively.

Proprietary, non-viral approach to produce TCR-rich, fully allogeneic CAR-T from healthy donors

piggyBac® Gene Insertion

Gene Editing

Cas-CRISPR® Gene Editing

High-yield Clinical Manufacturing

CT070

Design of two phase 1 studies evaluating the safety of Poseida’s TCR-rich allogeneic CAR-T cells

Molecule technology likely for...BCMA viral approach to produce TCR KO chemotherapy - was received by lower WBC nadirs. A: WBC nadir and AUD for the treatment window (day 1 to day 7) in the For treatment window lower and for P-MUC1C-ALLO3 patients treated with CY500 compared to CY300. The reduction of WBC nadirs and AUD was observed for P-MUC1C-ALLO3 patients treated with CY500 compared to CYB. This indicates that CY500 is required to produce comparable lymphodepletion between solid tumor patients and multiple myeloma patients. All patients received the same fluorodeoxy-benz.

CONCLUSIONS

• Solid tumor patients had numerically higher WBC counts prior to conditioning chemotherapy than multiple myeloma patients.

• Increasing CY dose from 300 mg/m² to 500 mg/m² or 1,000 mg/m² did not improve LD and there was no improvement in CAR-T cell expansion for patients treated with CY 500 mg/m² compared to those treated with CY 300 mg/m².

• P-MUC1C-ALLO3 patients treated with CY 3000 mg/m² demonstrated improved lymphodepletion compared to those treated with CY 300 mg/m². There was a trend towards improved P-MUC1C-ALLO3 expansion in patients receiving CY 1000 mg/m² compared to those who received CY 500 mg/m².

• CAR-T cell product attributes are unlikely responsible for the distinct LD requirement for the two patient populations. Because P-MUC1C-ALLO3 cells and P-MUC1C-ALLO3 cells utilize the same transgene, gene editing and manufacturing techniques and both products are produced using the same screened, healthy donor pool.

• A major difference between these two patient populations is the prior exposure of multiple myeloma patients to lymphodepleting chemotherapy associated with prior CAR-T therapy or hematopoietic stem cell transplantation.

• Preliminary data suggest that solid tumor patients may require higher CY doses to achieve adequate LD to enable allogeneic CAR-T expansion.

Continued evaluation of LD regimen is needed as part of developing investigational allogeneic CAR-T in solid tumors.

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LYMPHODEPLETION WITH CY500 DID NOT IMPROVE CAR-T CELL EXPANSION IN P-MUC1C-ALLO3 PATIENTS

Peak IL-15 was increased & Cmax delayed in both solid tumor and multiple myeloma patients with CY1000

LYMPHODEPLETION WITH CY500 DID NOT IMPROVE CAR-T CELL EXPANSION IN P-MUC1C-ALLO3 PATIENTS

Cmax

WBC (x10^3/µL)

P = >0.9999

Figure 4. Lymphodepletion in P-MUC1C-ALLO3 (A) or P-MUC1C-ALLO2 (B) patients presented by cyclophosphamide dose. Peak expansion Cmax is shown for patients treated with a single dose level of 2 x 10^6 cells. 100 mg/m² cyclophosphamide as part of lymphodepleting regimen did not impair P-MUC1C-ALLO3 expansion in solid tumor patients. Cellular kinetics have been assessed by qPCR measuring transcript copies per µg DNA. All patients received the same fluorodeoxy-benz.