Abstract Submission

25. Gene therapy, cellular immunotherapy and vaccination - Clinical

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SAFETY AND PRELIMINARY EFFICACY FINDINGS OF AUTO4, A TRBC1-TARGETTING CAR, IN RELAPSED/REFRACTORY TRBC1 POSITIVE SELECTED T CELL NON-HODGKIN LYMPHOMA

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Background: Peripheral T cell lymphomas (PTCL) are typically aggressive, treatment resistant and associated with poor prognosis. Clinical application of immunotherapy is limited by a lack of target antigens that discriminate malignant from normal T cells. Unlike B cell depletion, pan–T cell aplasia is prohibitively toxic. We recently described a targeting strategy based on the mutually exclusive expression of T cell receptor beta-chain constant domains 1 and 2 (TRBC1 and TRBC2) (Maciocia, PM. et al, Nat Med 2017) which can spare a proportion of the normal T cell compartment.

Aims: Here we describe early clinical findings of AUTO4, a TRBC1 directed autologous CAR T cell therapy, tested against relapsed/refractory (r/r) TRBC1+ PTCL.

Methods: NCT03590574 is multi-centre, single-arm study of AUTO4 with a phase I dose escalation component and a phase II expansion cohort. Here we report the initial findings of the phase I component. Biopsies from patients >18 years of age were screened for TRBC1-positive PTCL using next-generation sequencing. Four flat dose levels were explored: 25 x 10^6, 75 x 10^6, 225 x 10^6, and 450 x 10^6 CAR T cells administered as a single dose. CAR T-cell products are generated using a semi-automated closed process. Patients received lymphodepletion with fludarabine (30mg/m^2 x4, day-6 to day-3) and cyclophosphamide (500mg/m^2 x2 on day-6 and day-5) (Flu/Cy) prior to AUTO4 infusion on Day 0. Primary endpoints were incidence of Grade 3 to 5 toxicity occurring within 60 days of AUTO4 infusion and the frequency of dose limiting toxicities within 28 days of AUTO4 infusion (DLT period). Overall response (CR+PR) rate post AUTO4 infusion by PET-CT (Lugano 2014 criteria) was a secondary endpoint.

Results: As of 09-FEB-2022, n=64 patients consented for screening of TRBC1-positive PTCL. N=24 samples were TRBC1-positive; 7 patients were screen failures including 1 patient who died during screening. 11 products were manufactured; one patient relapsed prior to AUTO4 infusion, and one patient screen failed after product manufacture. To date 9 patients have been treated with AUTO4. The median age in these 9 patients was 57 years (range 34 to 63 years). The T-cell lymphoma subtypes treated were PCTL-NOS (n=4), ALCL (n=1), and AITL (n=4). Two patients had prior stem cell transplantation. The median number of prior treatment lines was 3 (range 1-5). After lymphodepletion with Flu/Cy, 3 patients received 25 × 10^6 CAR T cells, 2 patients received 75 × 10^6 CAR T cells, 1 patient received 225 × 10^6 CAR T cells and 3 patients received 450 × 10^6 CAR T cells. No patient experienced any dose limiting toxicities. The median (range) number of CD3+ T-cells/µl in blood prior to lymphodepletion and at the end of the DLT period (Day 28) was 204 (94-698) and 123 (19-458), respectively. 3 patients (33%) experienced CRS (1 patient with Grade 1, 1 patient with Grade 2, and 1 patient with Grade 3). None of the patients experienced neurotoxicity/ICANS. The most common treatment-emergent adverse events were cytopenias (anemia and neutropenia). Of the 9 patients treated, 5 patients had achieved complete metabolic responses (CMR) by PET-CT at Month 1, one patient remains with a PR 6 months post AUTO4 infusion, and 3 patients did not respond. All 3 patients at the 450x10^6 cell dose achieved a CMR at Month 1.

Summary/Conclusion: AUTO4 has a tolerable safety profile in patients with r/r TRBC1+ peripheral T-cell lymphoma. Early data shows encouraging response rates. Updated data and longer follow up will be presented.

Keywords: Autologous, CAR-T, Peripheral T-cell lymphoma