Abstract Submission

25. Gene therapy, cellular immunotherapy and vaccination - Clinical

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DUAL ANTIGEN TARGETING WITH CO-TRANSDUCED CD19/22 CAR T CELLS FOR RELAPSED/REFRACTORY ALL

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Background: CD19 negative escape is a major cause of relapse after CD19 CAR T cell therapy for relapsed/refractory (r/r) paediatric ALL and dual targeting of CD19/CD22 may overcome this. We have previously shown that AUTO1, a fast off rate autologous CD19 CAR T cell therapy was highly active in ALL with a favorable safety profile and excellent persistence (Ghorashian *et al* Nat.Med. 2019). Building on these properties, we developed AUTO1/22 in which autologous T cells are co-transduced with 2 different lentiviral vectors encoding our existing CD19 CAR and a novel CD22CAR designed to recognise targets with low antigen density. AUTO1/22 was evaluated in a Phase I study in children/young adults with r/rALL (NCT02443831).

Aims: To determine the safety/biological efficacy of AUTO1/22

Methods: Patients with r/r B-ALL age < 25 ywho were ineligible for/relapsed after Tisagenlecleucel were recruited. Following fludarabine/cyclophosphamide lymphodepletion, patients received $1x10^6$ /kg CAR^+ T cells. The presence of CAR T cells in the blood/bone marrow (BM) was assessed by flow cytometry + qPCR and BM MRD was assessed by IgH qPCR + flow cytometry. Primary end-points were incidence of grade 3-5 toxicity and the proportion of patients achieving MRD negative remission.

Results: Ten patients have been treated and 8 are evaluable with >1 month follow-up. The median age was 12 years and patients had a median of 3.5 prior lines of therapy (range 2-6). Five of 8 patients had relapsed post allogeneic SCT, 4 had received prior Blinatumomab/Inotuzumab and 3 had relapsed after prior Tisagenlecleucel. Prior to lymphodepletion, 2 patients had >5% BM disease, 5 had MRD between 10^{-2} and 10^{-5} and 1 was BM MRD negative. CAR T cell products had a central memory phenotype with predominance of CD19/22 double positive cells (median 59.3%) and balanced populations of CD19 and CD22 single positive cells (16% and 10.9% respectively).Cytokine release syndrome (CRS) occurred in 7/8 patients (grade 1 *n=2*, grade 2 *n=5*) requiring Tocilizumab in 3 cases, but severe (≥ grade 3) CRS was not seen and no patients required ICU admission for CRS. Grade 1-2 ICANS was observed in 3 patients. One patient had delayed grade 4 leucoencephalopathy (MRI/brain biopsy were more indicative of fludarabine toxicity than CAR T related) and has ongoing neurological recovery. 7 patients had grade 3-4 cytopenia persisting beyond/recurring after day 28, requiring a CD34+ stem cell top up in 1 case. 5/8 patients had CD19CAR T cells and 3/8 patients had CD22CAR T cells detectable at last follow-up. 7 of 8 evaluable patients (88%) achieved MRD negative CR/CRi at 1 month post-infusion. One patient did not respond with CD19+ CNS relapse + MRD level BM disease at day 28. Of the 7 responding patients, 1 had frank CD19+CD22+ BM and extramedullary relapse at 3 months and 1 had emergence of MRD level disease at 10.5 months post infusion, in both cases associated with loss of CAR T cells. One other patient had early loss of CAR T cells with B cell recovery but ongoing MRD negative CR at 3 months post-infusion and remains in MRD negative CR on maintenance chemotherapy. Overall, at a median follow-up of 4.8 months, 5/8 patients remain in MRD negative CR at last follow-up.

Summary/Conclusion: We demonstrate that dual CD19/22 targeting CAR T cells generated by co-transduction show an acceptable safety profile, with robust expansion/persistence and early efficacy in a heavily pre-treated cohort. To date with limited follow-up we have not observed antigen negative relapse but longer follow up is needed.

Keywords: CAR-T