Abstract Submission

25. Gene therapy, cellular immunotherapy and vaccination - Clinical

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SAFETY AND EFFICACY FINDINGS OF AUTO1, A FAST-OFF RATE CD19 CAR, IN RELAPSED/REFRACTORY PRIMARY CNS LYMPHOMA

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Background: Relapsed/refractory (r/r) primary central nervous system lymphoma (PCNSL) has a median overall survival of 2-8 months and few therapeutic options. CD19 CAR-T therapy is highly effective for systemic B-cell lymphoma, but associated neurotoxicity has led to exclusion of PCNSL patients from pivotal clinical trials. We have previously described AUTO1, a CD19 CAR with a fast off-rate CD19 binding domain, designed to reduce immune toxicity and improve engraftment. Its clinical activity has been tested in r/r paediatric and adult B-ALL, NHL and CLL, with high remission rates, low incidence of CRS/ICANS despite CAR trafficking into the cerebrospinal fluid (CSF) and long-term CAR-T engraftment.
Aims: Based on these favourable characteristics, we initiated the CAROUSEL study of AUTO1 in PCNSL (NCT04443829), testing both intravenous (IV) and intraventricular (I-VEN) routes of CAR-T delivery. We incorporated anti-PD1 into the conditioning strategy with the aim of enhancing CAR expansion and preventing PD1-mediated CAR silencing in the PCNSL microenvironment.
Methods: ***Manufacturing****:* CAR-T products were generated using a semi-automated, closed process from non-mobilised patient leukapheresate. ***Study Design:*** Subjects>/=16y underwent lymphodepletion with fludarabine (Flu;30mg/m2x3) and cyclophosphamide (Cy;60mg/kgx1) and Pembrolizumab (200mgx1) prior to IV AUTO1 infusion (250x10^6 CAR-T). In the event of failure to achieve PR or a frank relapse event, a 2nd dose of AUTO1 was administered into the CSF via ommaya reservoir (25x10^6 CAR-T) following Flu/Cy at an interval of >/=28d post-IV dosing. Study endpoints include manufacture feasibility, grade 3-5 toxicity and remission rates at 1 and 3 months.
Results: As of 14 February 2022, we enrolled 6 patients, apheresed and manufactured 5 products and infused 5 patients with IV AUTO1 and 1 patient with I-VEN AUTO1. Of enrolled patients, median age was 43y (range 23-50), median ECOG was 1 (range 1-2) and median prior lines of therapy was 2 (range 1-3). All patients had parenchymal disease and all received bridging therapy. Following IV CAR-T, grade 1 and 2 CRS affected 1 and 3 patients respectively and any grade ICANS was observed in 2 patients, with 2 grade 3 events reported. AUTO1 engraftment and response was evaluable in 4 patients at month 1 following IV infusion. Excellent AUTO1 engraftment was observed in all patients in blood and CSF, and all 4 patients had ongoing CAR-T persistence at last follow-up. CSF and blood cytokines were also evaluated.
2/4 evaluable patients had no measurable disease at 2 and 6 months of follow-up respectively. 1 patient had PD at month 1 and was unable to receive further trial treatment. 1 patient had SD at month 1 but progressed at month 2. This patient had an ommaya reservoir implanted to receive I-VEN AUTO1, following which the patient developed grade 2 CRS for 5 days, without overt ICANS. The patient achieved PR at month 1 but progressed at month 2.

Summary/Conclusion: In r/r PCNSL, AUTO1 shows encouraging response rates and excellent CAR-T engraftment/expansion in the blood and CSF. I-VEN administration was well-tolerated and AUTO1 demonstrated activity via direct CSF infusion in a patient who failed IV therapy. Additional patients, updated biological data and longer follow-up will be presented.

Keywords: CAR-T, CNS lymphoma