MTL-CEBPA is a novel immunotherapy targeting the myeloid cell lineage which has shown promising clinical activity as monotherapy and combination therapy with tyrosine kinase inhibitors in hepatocellular carcinoma (HCC). Immunosuppressive myeloid cells are associated with worse outcomes to checkpoint inhibitors. Pre-clinical data have shown that MTL-CEBPA potentiates the oncological effect of PD-1 inhibitors (Figure 1A below). Further, following reprogramming by MTL-CEBPA, co-culturing MDMSCs with T cells leads to enhanced T cell proliferation (Figure 1B below).

MTL-CEBPA comprises SMARTICiLE® liposomal nanoparticle encapsulating CEBP-31, a 21-mer small activating 2′-O-Me RNA oligonucleotide duplex designed to specifically target and up-regulate transcription of the CEBPA gene.

Methods

This phase 1A/B, first-in-human, open-label, multicenter study evaluates the safety, tolerability, PK, and efficacy of MTL-CEBPA in combination with a pembrolizumab in adult patients with advanced solid tumours across 3 dose cohorts (70mg/380mg/330mg/m2 MTL-CEBPA via IV infusion once weekly for 3 consecutive weeks with final week break per cycle, with 200mg pembrolizumab every 3 weeks) between November 2019 and 7 April 2021. This study comprises a dose escalation of 3 staged cohorts in a 3 + 3 design. The primary endpoint is safety (1A) and ORR (RECISt1.1) (1B); key secondary endpoints include PK, CR rate & DCR. Key inclusion criteria: Patients with advanced solid tumours who have progressed on standard of care therapy or for whom no standard therapy is available, measurable disease, ECOG PS ≤2, life expectancy >5 months. A dose exploration will determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D). MTL-CEBPA dosing was preceded by prednisolone/hydrocortisone and anti-histamine administration to minimise the risk of infusion reactions.

A phase 1 study of saRNA myeloid modulating agent MTL-CEBPA in combination with pembrolizumab in adult patients with advanced solid tumours

Results

Pathways predicted to be inhibited (z-score leads)

CEBPA
Leukocyte extravasation signaling
Ephrin receptor signaling

Pharmacokinetics

Individual CEBP-31 plasma concentration vs time profiles after co-administration of either AJ 30 (0) or R8 (9) mg/m2 MTL-CEBPA on D1 and D8 and 200 mg pembrolizumab on D2 (indicated by an arrow). Plasma CEBP-31 concentration vs time profiles were collected over 7 days after the first dose (D1) and over 3 days after the second dose (D8).

Treatment Outcomes

C) Spider plot illustrating each patient and primary tumour

D) Retrospective analysis of patient outcomes a) pembrolizumab monotherapy b) pembrolizumab + MTL-CEBPA

Conclusion

MTL-CEBPA in combination with pembrolizumab demonstrated manageable toxicity at the dose levels tested and has shown antitumour activity. MTD was not reached and RP2D was determined at 130mg/m2 on day 1, 8, and 15 of a 28 day cycle. Enrolment into the dose expansion is ongoing.