A PHASE 1 STUDY OF MYELOID MODULATING AGENT MTL-CEBPA IN COMBINATION WITH PEMBROLIZUMAB IN ADULT PATIENTS WITH ADVANCED SOLID TUMOURS

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Background 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.

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/98mg/130mg/m² MTL-CEBPA once weekly for 3 consecutive weeks with final week break per cycle, with 200mg pembrolizumab every 3 weeks). The primary endpoint is safety and ORR; 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 >3 months. A dose exploration will determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D).

Results 10 pts (3 men, 7 women; median age 50.5yrs), all with different tumor types (1 each of triple negative breast, methothelioma, squamous thymic, cholangiocarcinoma, eccrine, fibrolamellar hepatocellular, colorectal, pancreatic and 2 platinum resistant high-grade serous ovarian). 4 pts had ≥4 prior lines of treatment. All pts reported treatment-related AEs, 7 pts reported AEs considered related to MTL-CEBPA only and all were grade 1 or 2. The most common was nausea (n=3) followed by anaemia, headache, insomnia, neutropenia, pyrexia, transaminase increase and ventricular extrasystole (all n=1). Five pts reported AEs considered related to pembrolizumab only, 2 AEs in 1 pt only were grade 3 (ALT and AST increases) There were no DLTs, SAEs or AEs leading to discontinuation or to death in the study. Tumor response was evaluated in 9 pts. 2 pts had a PR (epithelioid mesothelioma at 2 months with 83% tumour reduction, pt ongoing at 9 months & serous ovarian cancer at 2 months with 69% reduction in tumour, pt progressed at 6 months). Three pts had SD, 4 pts had PD as BOR, and 4 pts are continuing to receive treatment.

Conclusions MTL-CEBPA in combination with pembrolizumab demonstrated manageable toxicity at the dose levels tested and has shown antitumor 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.

Trial Registration This study was registered with ClinicalTrials.gov, number NCT04105335.

Ethics Approval The study was approved by the North East - Newcastle & North Tyneside 2 Research Ethics Committee, approval number 19/NE/0312.

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