Interim results for Phase 1b dose expansion of MTL-CEBPA in combination with pembrolizumab in patients with advanced solid tumour malignancies

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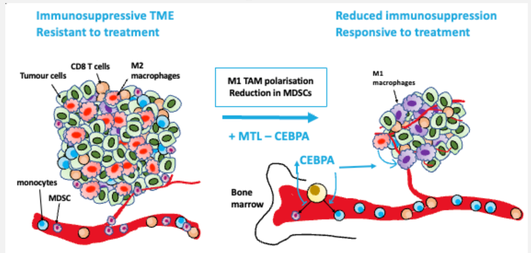
Background

Most cancer patients do not benefit from currently approved immune checkpoint inhibitors (ICI), suggesting that additional immunomodulation is required to improve outcomes. MTL-CEBPA is a novel immunotherapy targeting the myeloid cell lineage that has shown promising clinical activity in hepatocellular carcinoma and preclinical activity in models of solid tumour cancers in combination with ICIs. We previously reported dose escalation data for MTL-CEBPA in combination with ICI from TIMEPOINT, an ongoing multi-centre phase 1/1b study (NCT-04105335) evaluating the safety, PK, immunomodulation and clinical activity of MTL-CEBPA in combination with pembrolizumab in patients with anti-PD(L)1 naïve advanced solid tumours for whom no standard therapy is available. MTL-CEBPA comprises SMARTICLES® liposomal nanoparticle encapsulating CEBPA-51, 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/98mg/130mg/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 15 March 2022. This study comprises a dose escalation of 3 planned cohorts in a 3 + 3 design followed by a dose expansion. 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 >3 months. MTL-CEBPA dosing was preceded by prednisolone/hydrocortisone and anti-histamine administration to minimise the risk of infusion reactions. In the dose expansion part of TIMEPOINT, patients were treated at RP2D 130mg/m2 MTL-CEBPA QW for 3 consecutive weeks and 1 week off (28-day cycle) and 200mg pembrolizumab Q3W. Analysis was undertaken of plasma cytokine and complement profiles; gene expression (qPCR and Nanostring I/O 360) and immune landscape (multiplex IHC) from core tumour biopsies taken at baseline and cycle 2. Adverse events (AEs) were assessed by CTCAEv5.0.

Results

Patient Demographics

	Phase 1a (Escalation) n=10 (n=9 Eval for RECIST)	Phase 1b (Expansion) n=40 (n=31 Eval for RECIST)	All Patients n=50 (n=40 Eval for RECIST)
Age (Mean/Median)	47.5/50.5	60.4/62.5	57.8/58.5
Gender (M/F%)	30/70	35/65	34/66
ECOG (0/1%)	60/40	42.5/57.5	46/54
Median Prior Lines of Therapy	2	3	3
Tumor types	Colorectal (n=9), Pancreatic (n=9), Ovarian(n=8), Cholangiocarcinoma (n=7), Breast (n=4), Others* (n=13)		
RECIST response Partial Response (PR)	2 (22%) (1 x Ovarian; 1 x Mesothelioma)	2 (6.5%) (1 x Intrah. Cholangioca; 1 x Neuroendocrine)	4 (10%)
Stable Disease (SD)	3 (33.3%)	8 (25.8%)	11 (27.5%)
Progressive Disease (PD)	4 (44.4%)	21 (67.7%)	25 (62.5%)

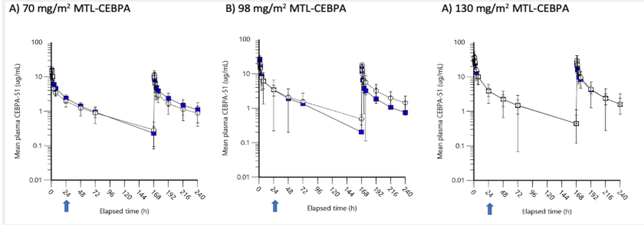
Table 1. Demographics, clinical characteristics and clinical response
"Other" category contains epithelioid mesothelioma, thymic cancer metastatic, hepatocellular carcinoma, eccrine carcinoma, adenocarcinoma, lung neoplasm malignant, extrahepatic cholangiocarcinoma, neuroendocrine tumour, leiomyosarcoma, malignant peritoneal neoplasm, anal squamous cell carcinoma and mesothelioma

Overview of Adverse Events

	Phase 1a MTL-CEBPA 70 mg/m² QW (N=4)	Phase 1a MTL-CEBPA 98 mg/m² QW (N=3)	Phase 1a MTL-CEBPA 130 mg/m² QW (N=3)	Phase 1b MTL-CEBPA 130 mg/m² QW (N=40)	MTL-CEBPA overall (N=50)
All AEs	4 (100.0)	3 (100.0)	3 (100.0)	39 (97.5)	49 (98.0)
Pre-treatment AE	2 (50.0)	1 (33.3)	1 (33.3)	10 (25.0)	14 (28.0)
All TEAEs	4 (100.0)	3 (100.0)	3 (100.0)	39 (97.5)	49 (98.0)
MTL-CEBPA only related TEAE	3 (75.0)	1 (33.3)	3 (100.0)	13 (32.5)	20 (40.0)
Serious TEAE	0	0	0	0	0
CTCAE grade ≥3	0	0	0	0	0
Pembrolizumab only related TEAE	1 (25.0)	2 (66.7)	1 (33.3)	8 (20.0)	12 (24.0)
Serious TEAE	0	0	0	0	0
CTCAE grade ≥3	1 (25.0)	0	0	1 (25.0)	2 (4.0)
MTL-CEBPA and pembrolizumab-related TEAE	4 (100.0)	2 (66.7)	3 (33.3)	19 (47.5)	26 (52.0)
Serious TEAE	0	0	0	1 (2.5)	1 (2.0)
CTCAE grade ≥3	1 (25.0)	0	0	3 (7.5)	4 (8.0)
Serious TEAE	0	0	0	7 (17.5)	7 (14.0)
CTCAE grade ≥3 TEAE	2 (50.0)	0	1 (33.3)	17 (42.5)	20 (40.0)
TEAE by worst CTCAE grade					
CTCAE 1	1 (25.0)	1 (33.3)	0	4 (10.0)	6 (12.0)
CTCAE 2	1 (25.0)	2 (66.7)	2 (66.7)	18 (45.0)	23 (46.0)
CTCAE 3	2 (50.0)	0	1 (33.3)	16 (40.0)	19 (38.0)
CTCAE 4	0	0	0	1 (2.5)	1 (2.0)
TEAE leading to discontinuation of MTL-CEBPA	0	0	0	0	0
TEAE leading to discontinuation of pembrolizumab	1 (25.0)	0	1 (33.3)	1 (2.5)	3 (6.0)
TEAE leading to discontinuation of MTL-CEBPA and pembrolizumab	0	0	0	2 (5.0)	2 (4.0)
TEAE leading to interruption of MTL-CEBPA	0	0	0	5 (12.5)	5 (10.0)
TEAE leading to interruption of pembrolizumab	0	0	0	2 (5.0)	2 (4.0)
TEAE leading to interruption of MTL-CEBPA and pembrolizumab	1 (25.0)	0	0	6 (15.0)	7 (14.0)
TEAE leading to dose reduction of MTL-CEBPA	0	0	0	0	0
TEAE leading to dose reduction of pembrolizumab	0	0	0	0	0
TEAE leading to dose reduction of MTL-CEBPA and pembrolizumab	0	0	0	0	0
TEAE leading to death	0	0	0	0	0

- No TEAEs leading to death were seen during the study and no TEAEs leading to discontinuation of MTL-CEBPA alone with only 2 participants discontinuing both study drugs due to TEAEs

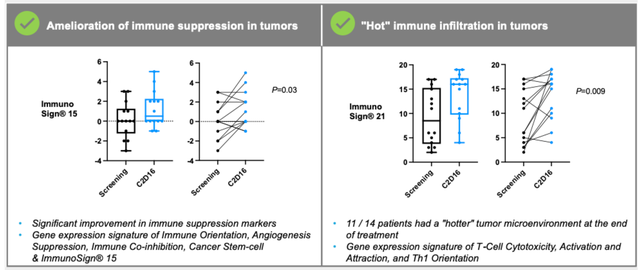
Co-administration with pembrolizumab does not effect PK of MTL-CEBPA



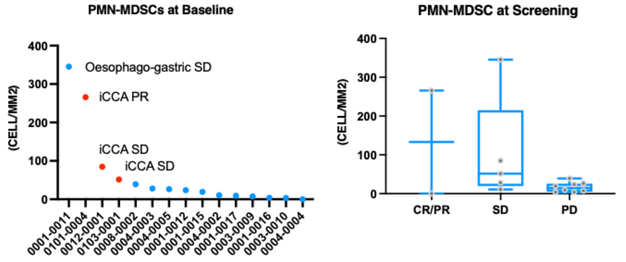
Mean plasma CEBPA-51 concentration vs time profiles – combination vs monotherapy
Comparison of mean plasma CEBPA-51 concentration vs time profiles after once-weekly administration of MTL-CEBPA, given either as monotherapy (open symbols) or in combination with 200 mg pembrolizumab, administered 24 h after the first dose of MTL-CEBPA, (closed symbols). A) 70 mg/m2 MTL-CEBPA combination with pembrolizumab (n=4); monotherapy (n=6) B) 98 mg/m2 MTL-CEBPA combination with pembrolizumab (n=3); monotherapy (n=3) C) 130 mg/m2 MTL-CEBPA combination with pembrolizumab (n=9); monotherapy (n=3). For the combination therapy cohorts, administration of pembrolizumab is shown by the blue arrow

Changes observed in TME

Analysis of paired biopsies (stroma and parenchyma) in 14 pts from TIMEPOINT Ph1b

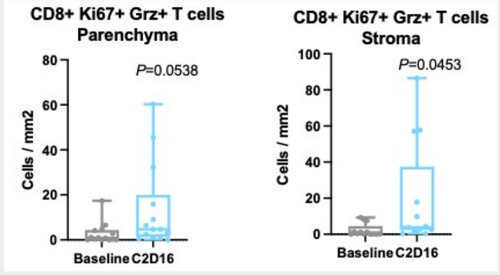


Patients with best clinical responses were those that had the highest number of MDSCs in their tumours at baseline



The combination treatment decreased PMN-MDSCs in 8/14 patients both in circulation and in the TME, and we observed that patients with a low baseline PMN-MDSC did not achieve a clinical response.

Multiplex IHC analysis demonstrates significant increase in proliferating granzyme producing T cells at C2D16

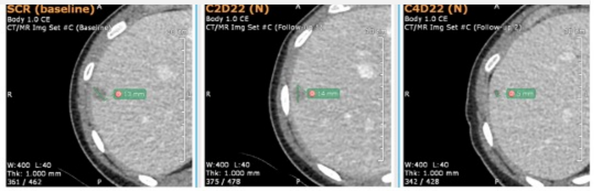


Case Study

Baseline characteristics:

- Age 30. Female; Neuroendocrine cancer 2019. TNM Stage T3N1M1. ECOG 0
- 5 TLs (lung, liver, l.n., other), 4NTLs (lung, liver, bone, other)
- No prior surgery.
- Prior anti-cancer systemic treatment: Carboplatin/Etoposide (Jan20 - Jun20), Everolimus (Jul20 – Mar21); Capecitabine/Temozolomide (May21 – Jul21)

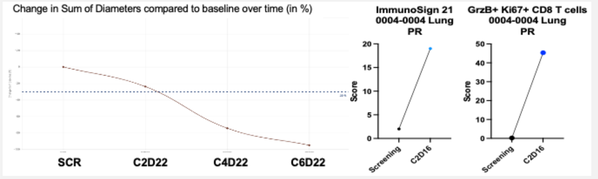
Tumour assessments at response



Baseline | C2 D22 | C4 D22 – PR (Lesion disappeared at next scan C6D22)

Treatment and outcomes:

- ICF July 2021, Started study treatment Aug 2021 – ongoing treatment at DCO (after PD and oligometastasis surgery)
- Dose level: MTL-CEBPA 130 mg/m2 QW
- Achieved PR in C4, DoR 58 days, PFS 161 days
- Surgery to ovarian lesions C8 – bilateral oophorectomy and salpingectomy
- Continued ongoing study treatment



Conclusion

MTL-CEBPA in combination with pembrolizumab is safe and well tolerated, with encouraging early signs of activity in heavily pre-treated patients across multiple tumour types. Treatment was associated with intratumoural changes supporting the hypothesis of immunomodulation by MTL-CEBPA and further investigation in combination with ICI is warranted.