850 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.[1]

Methods 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. Clinical activity was assessed by RECIST v1.1/iRECIST.

Results At data cut-off 15 March 2022, 50 patients across a wide range of tumour types reported to have primary resistance to anti-PD(L)1 therapy have been enrolled. Patient demographics, clinical characteristics are in table 1. The most frequent AEs in at least 5 patients (10%) are listed in table 2. 20 patients (40%) experienced an AE Gr $^{3}3$, 1 pt (2%) had a Gr4 AE, and there were no Gr 5 AEs. 7 pts (14%) had a SAE, however there were no AEs leading to dose modification or treatment discontinuation of MTL-CEBPA. Pharmacokinetic profile of MTL-CEBPA was not affected by pembrolizumab. Cytokine/complement analysis did not suggest cytokine release syndrome. Paired tumour biopsies during treatment suggested significant increase in Immunosign21 (figure 1) and proliferation of granzyme-producing T cells. 4 (10%) patients had confirmed PR (table 1). A 30-year-old NET patient with primarily lung involvement (failed 3 prior lines of therapy) achieved PR (43% reduction) in cycle 4, associated with a transformation from cold to hot TME (Immunosign21 from 2/21 to 19/21).

Conclusions 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.

REFERENCE

1. Plummer R, Sodergren M, Pinato D, *et al.* 515 A phase 1 study of myeloid modulating agent MTL-CEBPA in combination with pembrolizumab in adult patients with advanced solid tumours *Journal for ImmunoTherapy of Cancer* 2021;**9**:doi: 10.1136/jitc-2021-SITC2021.515.

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

Abstract 850 Table 1 Demographics, clinical characteristics and clinical response

	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

Abstract 850 Table 2 Most common AEs in order of decreasing incidence in at least 5 patients (10%)

TEAE (MedRA PT)	All Patients (n=50)	All Patients CTC Gr >=3 (n=50)
Anaemia	17 (34%)	1 (2%)
Fatigue	17 (34%)	1 (2%)
Abdominal pain	14 (28%)	2 (4%)
ALT increased	12 (24%)	1 (2%)
AST increased	12 (24%)	2 (4%)
Decreased appetite	11 (22%)	0
Nausea	11 (22%)	0
Back pain	9 (18%)	0
Constipation	9 (18%)	0
Diarrhoea	9 (18%)	0
GGT increased	8 (16%)	2 (4%)
Vomiting	8 (16%)	1 (2%)
AP increased	7 (14%)	1 (2%)
Arthralgia	6 (12%)	0
Cough	6 (12%)	0
Lethargy	6 (12%)	0
Abdominal pain upper	5 (10%)	1 (2%)
Hyponatraemia	5 (10%)	1 (2%)
Lower respiratory tract infection	5 (10%)	0

Table 2. Most common AEs in order of decreasing incidence in at least 5 patients (10%)

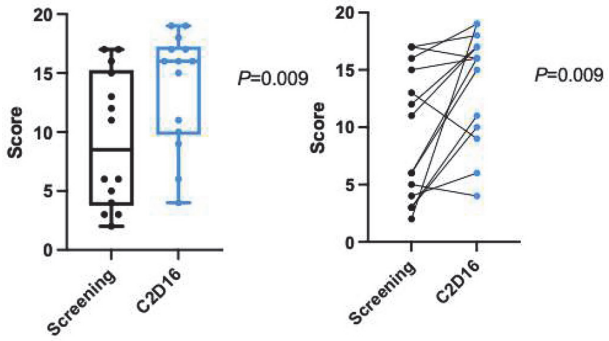

Figure 1. Change in Immunosign21 score (Veracyte) following combination treatment with MTL-CEBPA and pembrolizumab

Abstract 850 Figure 1 Change in Immunosign21 score (Veracyte) following combination treatment with MTL-CEBPA and pembrolizumab

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