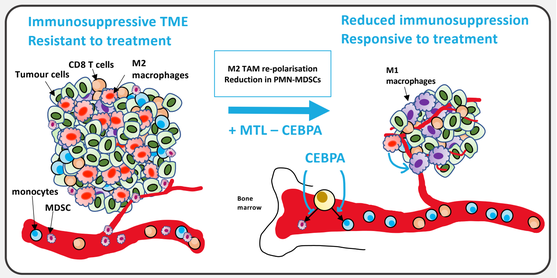
TIMEPOINT, a Phase 1 study of MTL-CEBPA in combination with pembrolizumab, confirms the immunomodulatory effect of MTL-CEBPA in solid tumours

LB192

Plummer R[1], Sodergren MH[2], Ryan BM[3], Tchakov I[3], Hodgson R[3], Raulf N[3], Tan CP[3], Nicholls JP[2,3], Adderkin A[3], Vassiliadou N[3], Reebye V[2,3], Voutila J[3], Sinigaglia L[3], Meyer T[4], Pinato D[2], Sarker D[5], Basu B[6], Blagden S[7], Cook N[8], Evans J[9], Yachnin J[10], Chee CE[11], Li D[12], El-Khoueiry A[13], Diab M[14], Huang K-W[15], Spalding D[2], Noel MS[16], Keenan B[17], Mahalingam D[18], Song MS[19], Zacharoulis D, Storkholm J[2], McNeish I[2], Habib R[3], Rossi JJ[19], Habib NA[2,3]

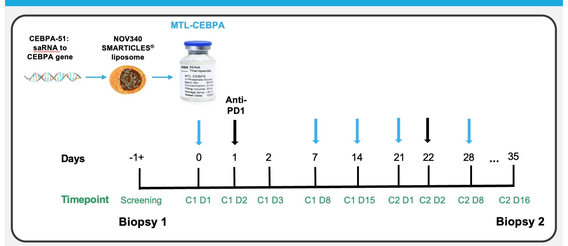
[1]The Northern Centre for Cancer Care, Freeman Hospital, Newcastle NE7 7DN, UK; [2]Department of Surgery & Cancer, Imperial College London, London W12 0NN, UK; [3]MiNA Therapeutics Ltd, London, W12 0BZ, UK; [4]Research Department of Oncology, UCL Cancer Institute, University College London, London WC1E 6DD, UK; [5]Department of Research Oncology, Guys Hospital, Kings College London, London SE1 9RT; [6]Oncology Centre, Addenbrooke's Hospital, Cambridge, CB2 0QQ, UK; [7]Department of Oncology, Oxford University, Churchill Hospital, Oxford OX3 7LE, UK; [8]Clinical Trials Unit, The Christie NHS Foundation Trust, Manchester M20 4BX; [9]The Beatson West of Scotland Cancer Centre, Glasgow G12 0YN, Scotland; [10]Centrum Kliniska Cancerstudier, Karolinska University Hospital, Stockholm, 17176, Sweden; [11] National University Hospital, National University Cancer Institute Singapore, Singapore 11928; [12]Department of Medical Oncology & Therapeutics Research, City of Hope Comprehensive Cancer Center, Duarte, CA 91010, USA; [13]Norris Comprehensive Cancer Centre, Keck Medicine, University of Southern California, Los Angeles, CA 90089, USA; [14]Winship Cancer Institute, Emory University, Atlanta, GA 30322, USA; [15]National Taiwan University Hospital, Taipei, Taiwan; [16]Medstar Georgetown University Hospital, Washington DC 20007, USA; [17]University of California San Francisco, San Francisco, CA 94143, USA; [18]Robert H Lurie Comprehensive Cancer Centre, Northwestern University, Chicago, IL 60611, USA; [19]Beckman Research Institute, City of Hope, CA, USA; [20] Department of General Surgery, University Hospital of Larissa, Larissa, Greece

Background



- Most cancer patients do not benefit from currently approved immune checkpoint inhibitors (ICI), suggesting that additional immunomodulation is required to improve outcomes (1).
- Immature myeloid cells such as myeloid-derived suppressor cells (MDSCs) are immunosuppressive and contribute to tumour progression and treatment resistance (2).
- The transcription factor CCAAT enhancer binding-protein alpha (CEBPA) is essential for myeloid differentiation, thereby promoting effector activity and proliferation (3).
- MTL-CEBPA is a small-activating (sa) RNA targeting CEBPA, formulated within a lipid nanoparticle, with key trophism for myeloid cells and myeloid precursor populations.
- In a phase I trial of patients with hepatocellular carcinoma (HCC) of viral aetiology, MTL-CEBPA treatment combined with sorafenib (SOR) showed significant anti-tumour activity (NCT02716012), with response to MTL-CEBPA associated with a reduction in peripheral MDSC levels and diminished intratumoural levels of M2 macrophages (4).
- TIMEPOINT is a 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.

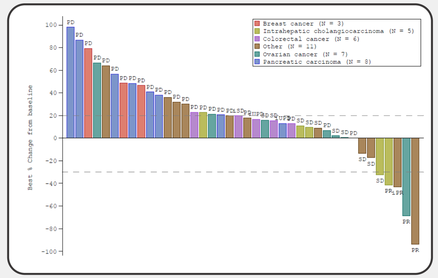
TIMEPOINT Schedule



Dosing schedule of MTL-CEBPA/pembrolizumab in TIMEPOINT trial; C1 D1 = cycle 1 day 1

References: (1) Ueno, M *et al*., Annals of Oncology, 2020 (2) Veglia *et al*., Nat Rev Immunol, 2021 (3) Avellino R, Delwel R. Blood, 2017 (4) Sarker, D *et al*., Clin. Cancer. Res 2020

Best objective response of MTL-CEBPA and pembrolizumab

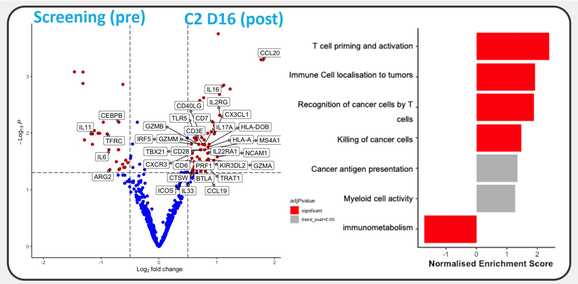


Waterfall plot illustrating patient best objective tumour response assessed by RECIST criteria in Phase 1a and Phase 1b.

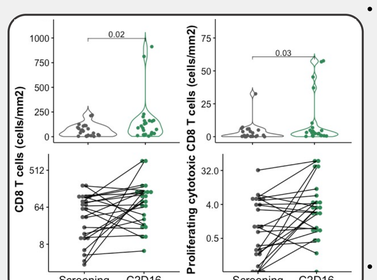
iRECIST= immune RECIST
irRECIST= immune-related RECIST
PD= progressive disease
PR= partial response
SD= stable disease
UPD= unconfirmed progressive disease

- MTL-CEBPA in combination with pembrolizumab shows anti-tumour activity with responses in solid organ malignancies considered usually resistant to ICIs.
- MTL-CEBPA was considered safe and tolerable at all dose levels studied, with no TEAEs leading to discontinuation of MTL-CEBPA.

Treatment-associated increases in intratumoural immune activity



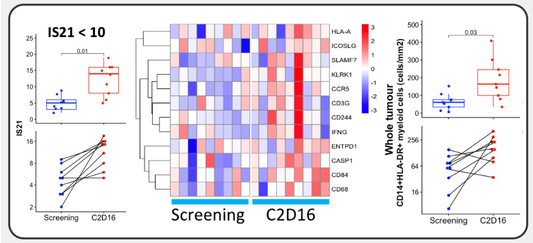
Gene expression analyses of 24 pre- and post- treatment paired patient biopsies by Nanostring PanCancer IO 360 platform, analysed by DESeq2 with genes of interest labelled (left). FGSEA analysis of differentially expressed Pan-cancer IO gene sets between pre- and post-treatment across all patients (right). Red = P adjust < 0.05, grey pathways = P <0.05 (right)



Intratumoural CD3+ CD8+ T cells and CD3+CD8+Ki67+GZMB+ T cells between timepoints (IHC).

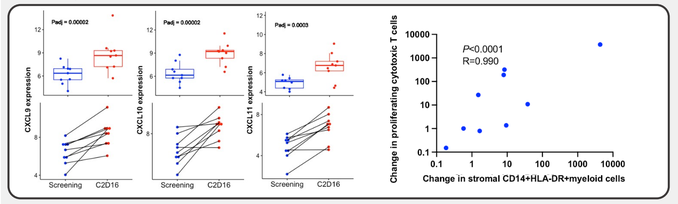
- MTL-CEBPA and pembrolizumab combination treatment is associated with profound positive gene expression changes in the tumour microenvironment (TME) towards immune activation and reduced immunosuppression
- Gene expression changes validated by concurrent significant increases in T cell populations post-treatment

Treatment associated switch of immune desert to inflamed



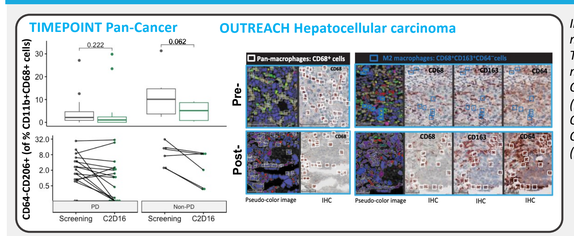
In patients with an immune-desert (Immunoscore21®; IS21<10) TME pre-treatment; changes in IS21 gene expression (left), T cell memory gene expression (GSE10239; middle) and numbers of intratumoural CD11b+ CD14+CD15-HLA-DR+ cells with treatment (IHC; right)

- Post-treatment, there is increased influx of inflammatory APC myeloid cells into the TME, increased secretion of T cell chemoattractants and enhanced migration, priming and activation of T cells
- Data suggest MTL-CEBPA combination with pembrolizumab can convert it a cold TME to hot, or immune inflamed.



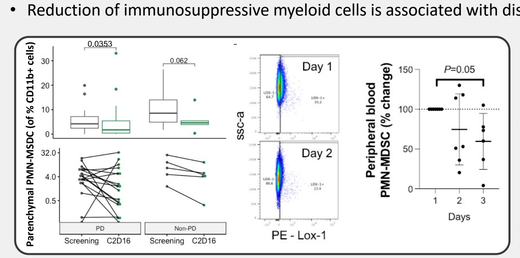
In patients with an immune-desert TME pre-treatment; changes in T cell chemokines by Nanostring with treatment (top) and correlation of cell type changes (bottom)

MTL-CEBPA reduces immunosuppression via PMN-MDSCs and M2 TAMs



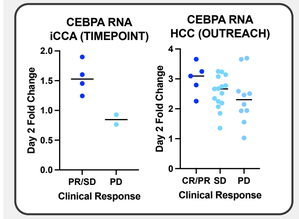
Intratumoural M2 macrophages in TIMEPOINT measured by CD206 expression (left) and OUTREACH by CD163 expression (right) by IHC.

- MTL-CEBPA treatment is associated with myeloid cell differentiation, with reduced M2 macrophages and PMN-MDSCs in the tumour and periphery in two patient cohorts
- Reduction of immunosuppressive myeloid cells is associated with disease stabilisation



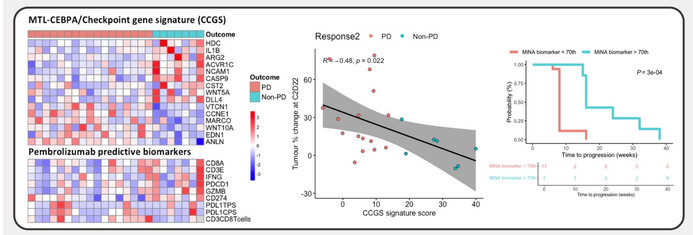
Intratumoural polymorphonuclear (PMN)-MDSC populations pre-treatment (left), peripheral blood PMN-MDSC populations detected by flow cytometry (right)

Transcriptional-based biomarkers of clinical response



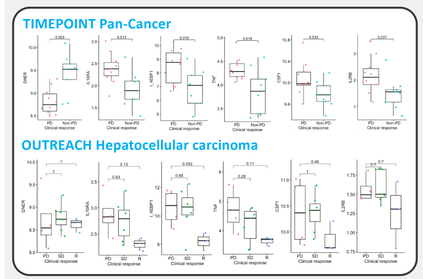
CEBPA RNA at C1 D2 compared to C1-D1 in patient peripheral WBCs by qPCR

- Increased CEBPA RNA post-MTL-CEBPA predicts response in patients with intrahepatic cholangiocarcinoma (iCCA; TIMEPOINT), and hepatocellular carcinoma (HCC; OUTREACH) in two independent clinical trials
- Intratumoural MTL-CEBPA and Checkpoint Gene Signature (CCGS) significantly predicts clinical response across cancer types
- CCGS genes relate to myeloid-driven immunosuppression, linking mechanism of action of MTL-CEBPA



Intratumoural Nanostring gene expression of CCGS genes at Screening (left; top) and pembrolizumab-associated biomarkers (left; bottom); Pearson correlation of CCGS at pre-treatment with tumour change post-treatment (middle); Kaplan Meier plot of time to PD with CCGS score, splitting patients by 70th percentile of CCGS (right)

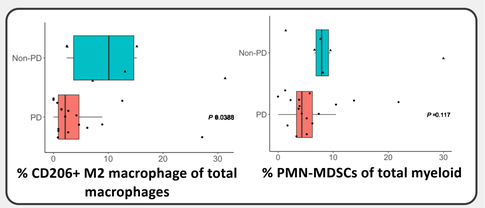
Protein and cellular biomarkers of clinical response



OLINK pre-treatment serum analysis, NPX values Inflammation panel

- Circulating protein analysis can predict outcome to MTL-CEBPA combination treatments, across multiple tumour types and combination drugs
- Patients with enrichment of M2 macrophages and PMN-MDSCs, MTL-CEBPA target cells, are more likely to have disease stabilisation post-treatment

Intratumoural M2 macrophage and PMN-MDSC proportions of macrophage and total myeloid cells, respectively at Screening (IHC)



Collectively, these data suggest a positive immunomodulatory TME effect of the combination of MTL-CEBPA with pembrolizumab, driven by modulation of MTL-CEBPA-target immunosuppressive myeloid cells, a predictive biomarker of clinical response