Phase 1 Study of CM24 in Combination with Nivolumab in Patients with Advanced Pancreatic Cancer - Survival, Exploratory Biomarkers and Effect on Neutrophil Extracellular Traps (NETs)

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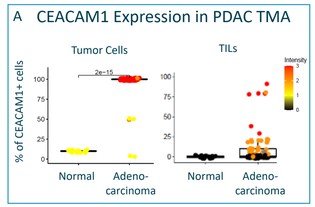
BACKGROUND

- The monoclonal antibody CM24 blocks the activity of carcinoembryonic antigen cell adhesion molecule 1 (CEACAM1), which has important roles in cancer progression, immune evasion, and metastasis. The homophilic interaction of CEACAM1 on tumor cells and tumor infiltrating lymphocytes silences the anti-tumor immunity.
- Enhanced expression of CEACAM1 was demonstrated in pancreatic cancer (Figure 1), both on tumor cells and tumor-infiltrating leukocytes (TILs) in the tumor microenvironment (TME).
- Additionally, CEACAM1 is part of the neutrophil extracellular trap (NET) complex. NETs are regarded as an important member of the tumor microenvironment, which contribute to metastatic dissemination and immune evasion.
- Previously we have demonstrated direct binding of CM24 to NETs, and a significant inhibition of NET-induced cancer cell migration by CM24 (Figure 2)



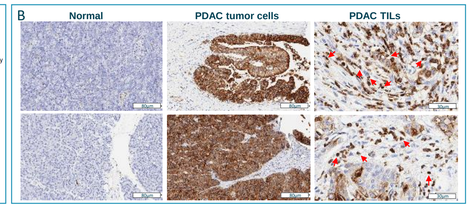
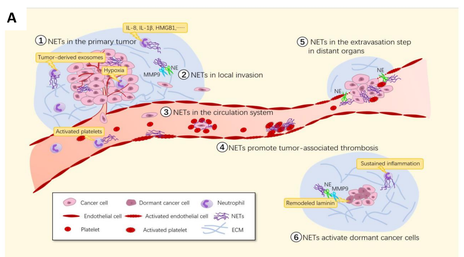


Figure 1: CEACAM1 immunostaining in tumor microarrays (TMA) of pancreatic cancer (PDAC) showed enhanced expression of CEACAM1 on both the tumor cells and tumor infiltrating leukocytes (TILs) as compared to normal tissues. Red arrows indicate CEACAM1+ Tumor-associated myeloid cells. % CEACAM1 positive cells and CEACAM1 intensity analysis included TMA of 38 cases/76 cores of PDAC and 10 cases/20 cores of normal pancreatic tissues (A).



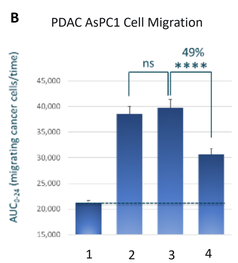


Figure 2. Involvement of NETs in (A) tumor metastasis and immune evasion (adapted from 'Chen, Q et al. Cancers 2021, 13, 2832'). (B) By blocking CEACAM1-CEACAM1 interaction, CM24 inhibits NET-mediated pancreatic cancer cell migration. *Treatments demonstrate AsPC1 cell migration: (1) without NETs (2) with NETs (3) with NETs and Isotype control (4) with NETs and CM24].* High expression of CEACAM1 on AsPC1 cells was measured by FACS.

METHODS

- In the dose escalation part of the study, 11 pancreatic ductal adenocarcinoma (PDAC) patients who received 2 prior lines of therapy were administered CM24 at 10, 15 and 20mg/kg q2w and nivolumab at 480mg q4w (NCT 04731467).
- Levels of the NET marker, myeloperoxidase (MPO), were measured in pretreatment and on-treatment patient serum samples by ELISA.
- Pretreatment biopsies were analyzed for CEACAM1 expression by immunohistochemistry (IHC). CEACAM1 expression in whole blood was measured by FACS analysis.

RESULTS

❖ Efficacy Analysis

11 PDAC patients were evaluable for efficacy assessment with a median OS of 4.5 (95% CI 2.0-11.1) months, including 1 confirmed PR and 3 pts with SD for a disease control rate of 36.4%.

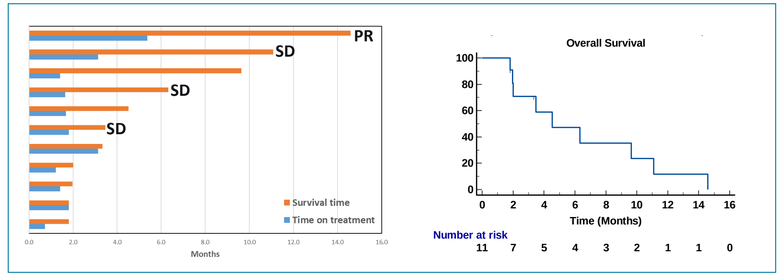


Figure 3: Efficacy analysis of PDAC patients in the dose escalation study of CM24 in combination with nivolumab. (SD- Stable Disease, PR-Partial Response).

❖ High Expression of CEACAM1 on Neutrophils and Neutrophil Extracellular Traps (NETs) Structure

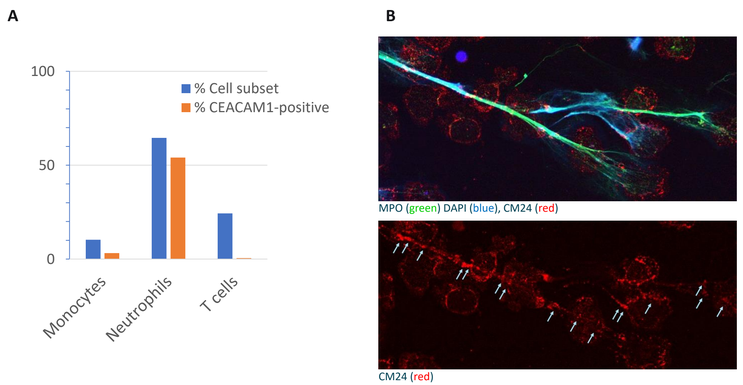


Figure 4: (A) CM24 binding in patients' whole blood using FACS analysis, showed that the most abundant population expressing CEACAM1 in the peripheral blood are the Neutrophils. (B) Co-localization of CEACAM1 (red), extracellular DNA and MPO (myeloperoxidase, NET marker). Fresh Neutrophils were stimulated by PMA to induce NETosis, fixed and stained as indicated above, and imaged using confocal microscopy.

❖ CM24 Treatment Significantly Reduced NET Marker in Patient Serum

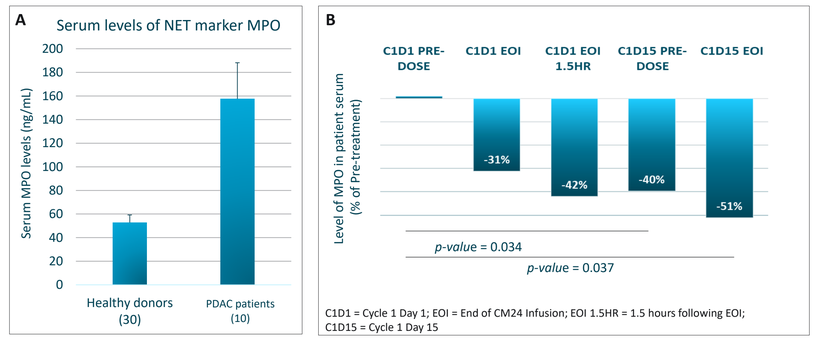


Figure 5: Measurement of MPO in serum. In serum, (A) enhanced levels of the NET biomarker MPO were detected in PDAC patients (n=10) as compared to healthy volunteers (n=30), demonstrating a 3-fold difference in the mean value (p<0.01). (B) MPO levels decreased by an average of 40% (p<0.05) across all dose levels within 2 weeks of CM24 therapy.

❖ High Level of CEACAM1-positive Lymphocytes in the Tumor Microenvironment is Associated with Longer Survival

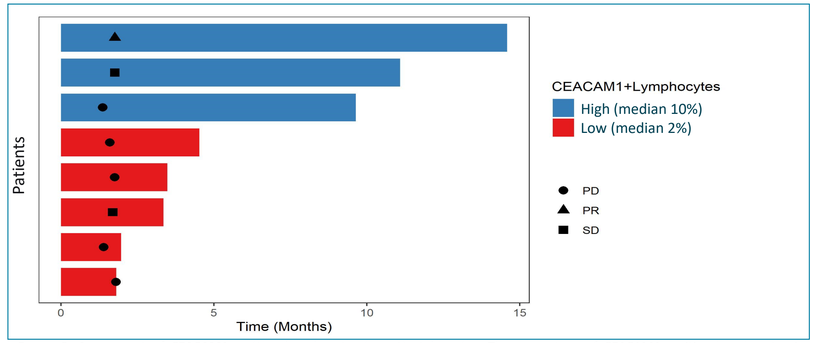


Figure 6: Assessment of CEACAM1-positive lymphocytes in patient biopsies. The percentage of CEACAM1-positive lymphocytes in biopsies of 8 evaluable patients ranged between 0% and 10%, and a cutoff rate to define low (0-5%) vs. high (> 5%) expression was used to stratify the patient survival data. High CEACAM1-positive lymphocytes (median of 10%) were measured in 3/8 PDAC patients with a median survival of 11.1 months (range: 9.6-14.6 months; blue) compared to 5/8 patients with low CEACAM1-positive lymphocytes (median 2%) who exhibited shorter survival (range: 2-4.5 months; red)

CONCLUSIONS

- CM24 in combination with nivolumab shows encouraging data in 2L/3L Pancreatic Ductal Adenocarcinoma (PDAC) patients.
- The positive association between the level of CEACAM1-positive lymphocytes in the patient pretreatment biopsies and patient survival, suggests a potential biomarker for CM24 therapy.
- CM24 effects on NETs demonstrate a novel MOA for CM24, support the role of CM24 in controlling immune evasion and may be used as a pharmacodynamic marker.
- These 2 potential biomarkers are being investigated in the ongoing randomized Phase 2 study.

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