Utility of a circulating tumor DNA test for detecting clinically evident and occult Merkel cell carcinoma

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Merkel cell carcinoma (MCC) is a deadly cancer that develops from Merkel cells, and is therefore being investigated in patients with non-melanoma skin cancers, including MCC. Methods: CMP-001-009 is a phase I clinical trial (NCT04916022) in patients with MCC, squamous cell carcinoma (cohort A), Merkel cell carcinoma (cohort B), or triple-negative breast cancer (cohort C). Inclusion in cohort B and C is predicated on the evidence that MCC patients with evidence of recurrent disease demonstrate circulating tumor DNA (ctDNA) that can be used as a predictive biomarker for the sensitivity to therapy. The study endpoints include progression-free survival, and responses in injected and noninjected lesions (all per RECIST v1.1). Clinical activity will also be assessed by assessing changes in immunologic and biomarker markers of MCC disease. Patients: We used the Signatome™ platform (bases pMCG NGS-based test) in which tumor-specific, clonal single nucleotide variants (SNVs) are identified from tumor whole exome sequencing. Blood was extracted for these studies. Patients at the University of Washington, and Stanford, are recruited to serially give blood every 3 months for ctDNA testing. Results: Since April 2020, longitudinal ctDNA samples were collected from 120 MCC patients. Of these, 47 had clinically evident MCC, and 73 did not. Of the 47 with clinically evident MCC, all had a positive ctDNA test sensitivity (100%, 95% CI: 91-100%). Among these 47, 24 were newly diagnosed with MCC. The median tumor size for these newly diagnosed MCC cases was 2.2 cm (range 0.5-8.5), and the median ctDNA was 26 mean tumor molecule count (range 0.08-1.1470). Primary tumor size and ctDNA were strongly correlated (Spearman r = 0.81, p < 0.001). Among the 73 without clinical evidence of disease, 61 had a negative ctDNA test. Ten patients were positive for ctDNA without current clinical evidence of disease. Four of these 10 developed recurrent MCC 55-217 days later. The specificity of ctDNA for evident or subsequently evident MCC was 91% (95% CI: 81-96%). Of the remaining 6 patients with a positive ctDNA test, 2 had independent evidence of early recurrent disease based on the marked elevation of Merkel cell polyanomerase-immunointensity. Conclusions: Albeit promising, findings can detect MCC of imaging and can perform well regardless of tumor viral status for surveillance of MCC.

Cancer-associated fibroblasts exert a pro-angiogenic activity in Merkel cell carcinoma

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Background and aims: Approximately 40% of patients with Merkel cell carcinoma (MCC) develop recurrent MCC 55-217 days later. The specificity of ctDNA for evident or subsequently evident MCC was 91% (95% CI: 81-96%). Among the 73 without clinical evidence of disease, 61 had a negative ctDNA test. Ten patients were positive for ctDNA without current clinical evidence of disease. Four of these 10 developed recurrent MCC 55-217 days later. The specificity of ctDNA for evident or subsequently evident MCC was 91% (95% CI: 81-96%). Of the remaining 6 patients with a positive ctDNA test, 2 had independent evidence of early recurrent disease based on the marked elevation of Merkel cell polyanomerase-immunointensity. Conclusions: Albeit promising, findings can detect MCC of imaging and can perform well regardless of tumor viral status for surveillance of MCC.

Inhibition potentiates immuno-genicity in Merkel cell carcinoma: a promising approach to overcome resistance to PD-1/PD-L1 immunotherapy

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Milademetan is a highly potent MDMB inhibitor in TP53 wild-type (p53 WT) models of Merkel cell carcinoma (MCC)

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Background and aims: Anti-p53 drugs are ineffective against p53 WT MCC cell lines, xenograft, and PDX models. These studies support the hypothesis that ATR inhibitors may augment antitumor response. However, novel treatment strategies are required for the remaining patients with primary or acquired resistance who do not benefit from PD-1/PD-L1 blockade. We tested the hypothesis that a specific ATRi treatment is an effective therapeutic option by blocking ATR and recruiting and activating antigen presenting cells. Methods: To test our hypothesis, representative Merkel cell lines (PDCLs) are treated with milademetan and the effect on cell viability is analyzed using a luminescence-based assay. The p53 response in MCC cells post milademetan treatment is assessed with functional p53, non-functional p53 or p53 knock-out and two newly established p53 WT p

ADAM Trial: A multicenter, randomized, double-blind, placebo-controlled, phase 3 trial center setting. The ADAM trial represents the first phase 3 trial in MCC and lymph node metastases; NCT03713732

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Background and aims: Merkel cell carcinoma (MCC) is a rare and aggressive skin cancer. MCC with lymph node (LN) metastases is associated with high morbidity and mortality. Although the recent success with adjuvant PD-1 blockade in stage III melanoma, together provide strong rationale for clinical investigation of PD-1/PD-L1 blockade in MCC with LN metastases is associated with high risk of systemic recurrence despite initial surgical therapy and/or radiation therapy (RT) (Induction phase 2), and then once every 120 days until the completion of 720 days (Maintenance phase). Treatment will continue for 800 mg every 15 days for the first 120 days (Induction phase 1), then once every 30 days for the next 120 days (Maintenance phase). Treatment will continue for

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