to activate tumor-associated plasmacytoid dendritic cells, inducing an interferon-rich tumor microenvironment and anti-tumor CD8+ T cell responses.

**Methods** CMP-001-001 is an ongoing Phase 1b trial evaluating the safety and efficacy of CMP-001 in combination with pembrolizumab (Part 1; N = 144) or alone (Part 2; N = 23) in patients with advanced melanoma resistant to prior anti-PD-1 therapy (Tables 1). CMP-001 is administered IT into accessible lesion(s) either with, or without on-site saline dilution (table 1), and response assessed by RECIST v1.1. Monotherapy patients who progress can be rolled over onto combination therapy and continue on study. Baseline and on-therapy serum is analyzed for cytokines, and immunohistochemistry and RNA-Seq are performed on available tumor biopsies.

**Results** Adverse events (AEs) attributed to CMP-001 in combination with pembrolizumab or as monotherapy consisted predominately of transient low-grade flu-like symptoms and injection site reactions: Grade 3+ related AEs were reported in 33% of patients treated with combination therapy and 22% of patients with monotherapy.

The Objective Response Rate (ORR) with undiluted CMP-001 in combination with pembrolizumab was 24% (18/75; 95% confidence interval: 15%-35% (table 1); on-site dilution of CMP-001 was associated with a substantial decrease in ORR to 12% (7/61; 95% confidence interval: 5%-22% (table 1). Three additional patients had a delayed partial response after an initial period of disease progression. Anti-tumor response was comparable between injected and uninjected lesions. The median duration of response to combination therapy has not been reached. The ORR to CMP-001 monotherapy was 22% (5/23; 95% confidence interval: 7%-44% (table 1); time from last anti-PD-1 therapy before CMP-001 was 1.5 to >20 months in responders; 3 of the patients responding to CMP-001 monotherapy achieved PR at the first evaluation, but progressed by the second evaluation.

Serum and tumor biopsy translational studies in the patients receiving combination therapy supported the proposed mechanism of TLR9 activation and identified a possible association between induction of serum CXCL10 and response.

**Conclusions** IT CMP-001 alone and in combination with pembrolizumab appears well tolerated, can reverse resistance to anti-PD-1 therapy, and can produce deep and durable clinical responses in patients with advanced melanoma.

**Ethics Approval** CMP-001-001 was centrally approved by the WCG-WIRB, WIRB approval tracking number 20152597.

**Poster Presentations**

**Biomarkers, immune monitoring, and novel technologies**

**P851** IDENTIFYING POTENTIAL PREDICTIVE BIOMARKERS FROM PLASMA EXOSOMES AND ADOPTIVE T CELLS THAT DIFFERENTIATE SHORT AND LONG-TERM METASTATIC NASOPHARYNGEAL CANCER SURVIVORS TREATED WITH CHEMOTHERAPY AND VIRUS-SPECIFIC T CELLS

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Background The identification of biomarkers predicting a better outcome to adoptive T cell therapy is an emerging, still nascent field. We previously completed a phase 2 clinical trial of autologous adoptive EBV-specific cytotoxic T lymphocyte (CTL) immunotherapy following gemcitabine + carboplatin chemotherapy as first-line treatment in 35 advanced incurable stage 4c nasopharyngeal carcinoma (NPC) patients. Here, we aim 1) to evaluate exosome proteins for potential specific predictive biomarkers of benefit to adoptive T cell therapy and 2) to investigate if a specific immunophenotype of our generated EBV targeting CTLs correlates with survival benefit.

Methods We isolated exosome from plasma samples by size exclusion chromatography and magnetic-based isolation technology, followed by fluorescence-activated cell sorting (FACS) analysis, Western blot analysis for immune-related checkpoint molecules, or mass spectrometry for exosomal peptide detection. All the generated CTLs were analyzed by gene expression microarray as well as a FACS system with the use of T cell-specific 23-antibody panel for comprehensive immunophenotyping. The representative CTL samples were also subject to single-cell (sc) RNA-Seq with DNA barcoded antibodies for comprehensive integrated transcriptomics and immunophenotyping analysis.

Results Patients with overall survival longer than 2 years were grouped as long survivors and the remaining patients were grouped as short survivors. Differentially expressed immune-related checkpoint molecules, such as PD1, ICOS, and CD137, were detected in in pre-treatment exosome of long and short survivors. Furthermore, more than 13,000 high confident and unique peptides which belong to 1,500 unique proteins were identified and quantified by mass spectrometry from the purified plasma exosome. Pathway enrichment analysis further showed that plasma exosome of the short survivors had significantly higher innate immune response-activating signal transduction-related peptides detected (p-value = 4.81 x 10^-5). The transcriptomic analysis revealed that statistically lower expressions of SELL (CD62L) and LEF1 were found in the EBV CTL of the short survivors, suggesting that the EBV CTL of short survivors were characterized by a lesser central memory T cell phenotype.

Conclusions Our data reports that specific pre-treatment plasma exosome proteins, and separately, transcriptomic profile of the generated baseline EBV CTLs prior to infusion into the patients correlate with patient survival, suggesting that they could be used together as biomarkers to predict outcome in the advanced NPC patients treated with this chemo-immunotherapy combination. More in-depth analysis of the immunophenotyping of all the CTLs and the representative CTLs’ scRNA-Seq data will be presented at the meeting.

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