Background Chimeric antigen receptor (CAR) T cells have shown remarkable results in hematological malignancies but limited efficacy in the setting of solid tumors. GD2 is a tumor antigen expressed on neuroblastoma and osteosarcoma, and previous studies of T cells expressing 1st generation GD2-CAR were shown to be safe and mediated modest antitumor activity in patients with refractory neuroblastoma. Myeloid cells orchestrate immune responses with the ability to either activate or limit T cell responses. In the setting of solid tumors, myeloid-mediated immune suppression is known to play an important role in dampening antitumor activity. We hypothesized that myeloid cells impact CAR T cell expansion in patients with solid tumors.

Methods A phase I trial (NCT02107963) was performed to determine the feasibility and safety of administering 3rd generation GD2-CAR (GD2-CAR.OX40.28.z.ICD9) T cells in children and young adults with GD2+ neuroblastoma and osteosarcoma. Peripheral blood patient samples were analyzed retrospectively by qPCR for CAR expansion, multiplex ELISA for cytokine levels, mass cytometry (CyTOF) for phenotype analysis, ATAC-seq for epigenetic determination, and RNA-seq for transcriptomic evaluation.

Results 15 patients were enrolled on four dose levels, of which 13 patients were infused. While 76.9% of patients had stable disease by day 28, eventually all patients had disease progression. GD2-CAR T cells expanded in all patients receiving treatment, half of whom had expansion similar to that seen in clinically active CD19 and CD22 CAR T cells, but with limited persistence. To gain insight into the immune compartment in patients with good versus poor CAR T cell expansion, we evaluated immune profiles in patient pre-treatment apheresis and post-treatment peripheral blood samples. The main findings of this study indicate that a higher proportion of monocytes in pre-treatment apheresis was associated with poor CAR T cell expansion and post-treatment peripheral blood samples. The longitudinal analysis demonstrated that CXCR3+ monocytes were low following treatment in both good and poor CAR T cell expanders, demonstrating a transition in myeloid populations in response to GD2-CAR T cell treatment.

Conclusions Together, these data suggest that GD2-CAR T cell administration is associated with changes in the myeloid cell compartment in solid tumor patients. This study provides evidence of novel myeloid-based pre-treatment biomarkers of CAR T cell expansion and rationale for the combination of CAR T cells with myeloid-modulating therapies as a strategy to improve outcomes for patients with solid tumors.

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Trial Registration NCT02107963

Ethics Approval The phase I study protocol conformed to the Declaration of Helsinki, Good Clinical Practice guidelines, and was approved by the NCI Institutional Review Board (14-C-0059) and the FDA. All patients or their legal guardians signed a document of informed consent indicating their understanding of the investigational nature and risks of this study.