AUGMENTATION OF CD8 T CELL MEMORY VIA CDK4/6 INHIBITION CAN BE SEQUENTIALLY COMBINED WITH PD-1 BLOCKADE TO AVOID TOXICITIES

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Background CDK4/6 inhibitors are approved to treat breast cancer and are in trials for other malignancies. We examined CDK4/6 inhibition in mouse and human CD8 T cells during early stages of activation. Mice receiving tumor-specific CD8 T cells treated with CDK4/6 inhibitors displayed increased T cell persistence and immunologic memory. CDK4/6 inhibition upregulated Mxd4, a negative regulator of Myc, in both mouse and human CD8 T cells. Silencing of Mxd4 or Myc in mouse CD8 T cells demonstrated the importance of this axis for memory formation. We used single cell transcriptional profiling and TCR clonotype tracking to evaluate recently activated human CD8 T cells in breast cancer patients before and during treatment with either palbociclib or abemaciclib. CDK4/6 inhibitor therapy in humans increases the frequency of CD8 memory precursors and downregulates their expression of MYC target genes, suggesting that CDK4/6 inhibitors in cancer patients may augment long-term protective immunity (Heckler and Ali et al. Cancer Discovery 2021).

Methods We will present unpublished data on samples collected from a Phase I trial of combination ribociclib with PD-1 blockade (NCT03294694). Unfortunately, combination of CDK4/6i and PD-1 blockade leads to high rates of adverse events, as seen in several clinical trials. To better understand the mechanism of action of CDK4/6i versus PD-1 blockade on tumor-specific CD8 T cells, we performed single-cell RNA-sequencing and T-cell receptor clonotype tracking of breast and ovarian cancer patients treated with the CDK4/6 inhibitor ribociclib and PD-1 blockade.

Results We confirmed our observation of increased memory skewing of peripheral CD8 T cells, and we identified TCR clonotypes that matched tumor-infiltrating T cells. We highlight evidence of two orthogonal treatment-associated phenomena: expansion of T cell effector populations and promotion of T cell memory formation. Augmentation of the antitumor memory pool by ribociclib boosts the efficacy of subsequent PD-1 blockade in a mouse models of melanoma and breast cancer.

Conclusions We therefore demonstrate that PD-1 blockade and CDK4/6 inhibition augment nonoverlapping features of CD8 T cell activation in metastatic cancer, pointing toward sequential therapy as a potentially safe and synergistic strategy in patients.

Ethics Approval For breast and ovarian cancer patients, we obtained written informed consent from the patients, and the studies were conducted in accordance with the Declaration of Helsinki and the Belmont Report. Patient peripheral blood samples were obtained via Dana-Farber Cancer Institute Institutional Review Board protocols 18-258, 13-364, and/or 17-024. Animals were housed at the Dana-Farber Cancer Institute and were maintained according to protocols approved by the DFCI IACUC (#14-019 and #14-037).