Background CDK4/6 inhibitors are approved in combination with hormonotherapy as a first-line intervention against advanced/metastatic hormone receptor (HR)+ HER2 breast cancer, reflecting their ability to extend progression-free survival (PFS) and overall survival (OS) in this patient population. Nonetheless, >50% of women with HR+ breast cancer receiving CDK4/6 inhibitors ultimately progress and succumb to their disease, owing to hitherto poorly characterized mechanisms of acquired resistance. While CDK4/6 inhibitors have been conceived to inhibit the proliferation of cancer cells, accumulating preclinical and clinical evidence indicates that they also mediate numerous immunostimulatory effects that may contribute to efficacy. These observations suggest that hitherto unidentified immunological mechanisms may promote resistance to CDK4/6 inhibitors in patients with HR+HER2 breast cancer.

Methods We harnessed a unique immunocompetent mouse model that closely recapitulates the immunobiology of human HR+HER2 breast cancer — including a cold tumor microenvironment (TME) coupled to poor sensitivity to PD-1 blockers — along with scRNAseq, functional assays and blocking/neutralization experiments to dissect the immunological mechanisms underlying resistance to CDK4/6 inhibitors. The Cancer Genome Atlas (TCGA) was interrogated by in silico analysis. Moreover, immunohistochemistry, multispectral immunofluorescence, and circulating immunophenotyping were performed on samples from 3 independent cohorts of patients with HR+HER2 breast cancer (including longitudinal samples obtained before, during and after CDK4/6 inhibition).

Results Interleukin 17 (IL17)-producing γδ T cells are recruited to mouse HR+HER2 mammary tumors upon CDK4/6 inhibition through a CCL2-dependent mechanism. In this model, circulating IL17 levels correlate with poor OS, and blocking the γδ TCR, neutralizing IL17 or CCL2 equally improve the therapeutic activity of CDK4/6 inhibitors. Patients from the TCGA with a signature of IL17 signaling have poor OS and signs of immunosuppression in the TME. In diagnostic biopsies from patients with HR+HER2 breast cancer, γδ T cell infiltration correlate with tumor grade, and γδ T cells reside in the proximity of PD-L1+ tumor cells and macrophages. Patients with high activated γδ T cells in the circulation have reduced PFS on CDK4/6 inhibitors as compared to their low counterparts. Circulating CCL2 levels augment during CDK4/6 therapy in progressing patients. Finally, tumor-infiltrating γδ T cells increase as compared to baseline in patients relapsing on CDK4/6 inhibitors.

Conclusions Our findings prompt the initiation of clinical trials comparing standard-of-care CDK4/6 inhibition plus letrozole vs CDK4/6 inhibition plus letrozole and an IL17 blocker (at least three of which are currently approved for psoriasis treatment) in patients with HR+HER2 breast cancer.

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