Background CDK4/6 inhibitors are approved in combination with hormone therapy 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 inhibition through a CCL2-dependent mechanism. In this model, circulating IL17 levels correlate with poor OS, 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.

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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REFERENCES


Ethics Approval Mouse experiments were approved by WCM IACUC (#2019-0022). All human studies were on retrospective, fully deidentified samples collected upon informed consent at respective Institutions.