593

**PI3K γ δ INHIBITOR COMBINED WITH RADIATION
ENHANCES THE ANTITUMOR IMMUNE EFFECT OF PD-1
BLOCKADE IN SYNGENIC MURINE BREAST CANCER
MODEL AND HUMANIZED PATIENT-DERIVED
XENOGRAFT MODEL**

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Background Breast cancer is viewed as immunologically cold, imposing an immune-suppressive tumor microenvironment and responding poorly to lone immune checkpoint blockade. As an adjunct to ICB, radiation therapy holds promise in terms of in situ tumor vaccination effect, although it is known to promote immune suppression, increasing regulatory T cells, myeloid-derived suppressor cell, and M2 tumor-associated macrophages. It was our contention that combined use of RT and a PI3K γ δ inhibitor to combat immune suppression might enhance the efficacy of ICB.

Methods Murine breast cancer cells (4T1) were grown in both immune-competent and -deficient BALB/c mice, and tumors were irradiated by 3 fractions of 24 Gy. A PD-1 blockade and a PI3K γ δ inhibitor were then administered every other day for 2 weeks. Tumors from humanized patient-derived breast cancer xenograft model was sequenced to identify immune-related pathways and to profile infiltrated immune cells. Transcriptomic and clinical data were acquired from The Cancer Genome Atlas pan-cancer cohort, and the deconvolution algorithm was used to profile immune cell repertoire.

Results In the immune-competent syngenic 4T1 murine tumor model, PD-1 blockade alone led to tumor hyperprogression, whereas a three-pronged strategy of PI3K γ δ inhibitor, RT, and PD-1 blockade significantly delayed primary tumor growth, boosted abscopal effect, and improved animal survival by comparison. The immune-deficient syngenic 4T1 murine tumor model failed to show this synergism in delaying tumor growth and the abscopal effect. According to FACS analysis, RT significantly increased not only CD8+cytotoxic T-cell fractions but also immune-suppressive Treg cells, MDSCs, and M2 TAMs. However, PI3K γ δ inhibitor significantly lowered proportions of Treg, MDSCs, and M2 TAMs, achieving dramatic gains in splenic, nodal, and tumor CD8+ T-cell populations after triple combination therapy. There were significantly decreased tumor expressions of p-AKT, PD-L1, and HIF1 α by PI3K γ δ inhibition. Triple combination therapy significantly delayed primary tumor growth in humanized PDX model as well and analyses of RNA sequencing data of humanized PDX samples showed decreased immune suppressive pathways with decreased and M2 macrophage and increased CD8+ T-cell by triple combination therapy. In the TCGA pan-cancer cohort, high Treg/CD8+T-cell and M2/M1 TAM ratios and poor overall patient survival was associated with high PIK3CG (PI3K γ) or PIK3CD (PI3K δ) gene expression.

Conclusions These findings collectively indicate that PI3K γ and PI3K δ are clinically relevant targets in an immunosuppressive TME. Combining PI3K γ δ inhibitor, RT, and PD-1 blockade may thus be a viable approach, helping to overcome the therapeutic resistance of immunologically cold tumors such as breast cancer.

<http://dx.doi.org/10.1136/jitc-2021-SITC2021.593>