617 TRASTUZUMAB AND PERTUZUMAB COMBINATION THERAPY ACTIVATES COMPLEMENT-DEPENDENT CYTOTOXICITY AND PHAGOCYTOSIS AGAINST HER2+ BREAST CANCER

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Background Standard-of-care frontline treatment for HER2+ breast cancers (BC) is comprised of two HER2-specific monoclonal antibodies (mAb), Trastuzumab and Pertuzumab with chemotherapy. This combination (T+P) has proven highly effective, however its synergistic mechanism of action is largely unknown. Initial studies demonstrated that Pertuzumab suppressed HER2 hetero-dimerization, thus the T+P mechanism of action (MOA) has been widely reported as due to Pertuzumab-mediated signaling suppression in combination with Trastuzumab-mediated induction of immunity. However, the therapeutic MOA for Pertuzumab remains unclear, especially combination with Trastuzumab. As the only solid cancer effectively treated by a mAb combination, unraveling this MOA may be critical in extending this strategy to other cancers, as well as to improving this treatment modality.

Methods In this study, we used multiple mouse models of human HER2 expressing breast cancer, and an endogenous transgenic HER2+ BC model that is tolerant to human HER2, and by using both novel murine and human versions of Pertuzumab and Trastuzumab, we elucidated the synergistic antitumor immune mechanism of the two antibodies when used in combination.

Results First, we demonstrated that Pertuzumab, just like Trastuzumab [1], can engage with Fc receptors and activate Antibody-Dependent-Cellular-Phagocytosis (ADCP) to elicit antitumor efficacy, as well as inhibit oncogenic signaling of HER2. More importantly, we identified that the combination of Pertuzumab with Trastuzumab synergistically and strongly induced classical pathway complement activation, enabling both direct complement-dependent cytotoxicity (CDC) of tumor cells, as well as anti-tumor complement-dependent cellular phagocytosis (CDCP) by macrophages. Furthermore, tumor expression of C1q was positively associated with survival outcome in HER2+ BC patients, whereas expression of complement regulators CD55 and CD59 were inversely correlated. Accordingly, depletion of C1q in mice abolished the synergistic antitumor effect of T+P therapy, whereas knockdown of CD55 and CD59 expression enhanced T+P therapeutic efficacy.

Conclusions Our study identifies complement activation as a potentially significant antitumor MOA for T+P therapies that may be clinically enabled by complement regulatory blockade to augment therapeutic efficacy.

REFERENCES

1. Tsao L, et al. CD47 blockade augmentation of trastuzumab antitumor efficacy dependent on antibody-dependent cellular phagocytosis. JCI Insight. 2019; 4(24): e131882.

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