COMBINING AN ANTI-HER2 MAB WITH TLR-3 AND -9 AGONISTS

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Introduction. Trastuzumab (Herceptin^{TM}) is a humanized monoclonal antibody targeting HER2/ErbB-2. This receptor is overexpressed in approximately 30% of breast cancer, hence being a good target for therapy. Trastuzumab is approved since 1998 and has considerably improved the standard care of breast cancer, but unfortunately 15-20% of patients eventually relapse and develop a metastatic disease. Trastuzumab inhibits tumor cell proliferation and promotes anti-tumor immunity through mechanisms such as antibody-dependent cellular cytotoxicity (ADCC). Studies have shown that both innate and adaptive immune responses are important for trastuzumab activity. In mice, anti-ErbB2 mAb therapy requires IFN-γ-producing T CD8+ cells, type I IFN responses and MyD88-dependent Toll-like receptor (TLR) signaling. PolyI:C and CpG are well-known agonists of TLR-3 and TLR-9, respectively, and as such are potent inducers of type I IFN, IFN-γ, and IP-10 resulting in activation of NK cells and T cells. TLR-3 and TLR-9 agonists have also been shown to enhance ADCC and the recruitment of tumor-specific T cells.

Hypothesis. Administration of the TLR agonists CpG and polyI:C will synergistically act with the anti-ErbB2 mAb to improve the antitumor immune responses against ErbB2+ breast cancer.

Results. In two mouse models of ErbB2+ breast cancer, we demonstrated that combined administration of anti-ErbB2 mAb and CpG/polyI:C resulted in synergistic anti-tumor effects. Treatment of well-established ErbB2+ breast tumors with the combination regimen resulted in complete responses in the majority of mice, in contrast to single agent treatments. Mice were also protected against a re-challenge of tumor cells and had more effective CTL. Depletion assays revealed that NK cells are major mediators compared to CD8 T cells and pDC. Furthermore, qPCR have shown a dramatic upregulation of IFN-γ, TNF-α, IP-10 and IL-12 within the tumors treated with the combination of antibodies and TLR agonists.