Nonclinical studies addressing the mechanism of action of trastuzumab (Herceptin).

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HER2 is a ligand-less member of the human epidermal growth factor receptor or ErbB family of tyrosine kinases. In normal biological systems, HER2 functions as a co-receptor for a multitude of epidermal growth factor-like ligands that bind and activate other HER family members. HER2 overexpression is observed in a number of human adenocarcinomas and results in constitutive HER2 activation. Specific targeting of these tumors can be accomplished with antibodies directed against the extracellular domain of the HER2 protein. One of these antibodies, 4D5, has been fully humanized and is termed trastuzumab (Herceptin; Genentech, San Francisco, CA). Treatment of HER2-overexpressing breast cancer cell lines with trastuzumab results in induction of p27KIP1 and the Rb-related protein, p130, which in turn significantly reduces the number of cells undergoing S-phase. A number of other phenotypic changes are observed in vitro as a consequence of trastuzumab binding to HER2-overexpressing cells. These phenotypic changes include downmodulation of the HER2 receptor, inhibition of tumor cell growth, reversed cytokine resistance, restored E-cadherin expression levels, and reduced vascular endothelial growth factor production. Interaction of trastuzumab with the human immune system via its human immunoglobulin G1 Fc domain may potentiate its antitumor activities. In vitro studies demonstrate that trastuzumab is very effective in mediating antibody-dependent cell-mediated cytotoxicity against HER2-overexpressing tumor targets. Trastuzumab treatment of mouse xenograft models results in marked suppression of tumor growth. When given in combination with standard cytotoxic chemotherapeutic agents, trastuzumab treatment generally results in statistically superior antitumor efficacy compared with either agent given alone. Taken together, these studies suggest that the mechanism of action of trastuzumab includes antagonizing the constitutive growth-signaling properties of the HER2 system, enlisting immune cells to attack and kill the tumor target, and augmenting chemotherapy-induced cytotoxicity.