Introduction to Biological and Small Molecule Drug Research and Development: Chapter 9. Targeting HER2 by monoclonal antibodies for cancer therapy

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HER2 (ErbB-2) is a member of the human epidermal growth factor receptor tyrosine kinase family which is involved in the regulation of cell proliferation, survival and differentiation. Soon after its discovery, HER2 was shown frequently to be overexpressed in breast cancer and was associated with a worse prognosis. It was identified as a target for drug development and molecular cloning of the gene and expression in cell lines provided a vehicle for the selection of HER2-specific antibodies. The monoclonal antibody trastuzumab is the first HER2-targeting drug approved for cancer treatment. By significantly extending the time to disease progression and overall survival of patients, it has become established in all treatment lines of early and metastatic HER2-positive breast cancer, as well as in HER2-positive advanced metastatic gastric or gastroesophageal junction cancer. Combination of trastuzumab with pertuzumab, a second antibody binding to a distinct epitope on HER2 which implies a different mode of action, took the treatment of HER2-positive metastatic breast cancer to the next level of success. Finally, trastuzumab emtansine is an antibodydrug conjugate that retains all pharmacodynamic activities of trastuzumab and delivers a toxic maytansinoid directly to the tumour cells. Current clinical results indicate that trastuzumab emtansine may be more efficacious and less toxic than trastuzumab plus chemotherapy, and further improvement is expected in combination with pertuzumab.

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