YES1 as a therapeutic target for HER2-positive breast cancer cell after Trastuzumab and Trastuzumab-emtansine (T-DM1) resistance

Abstract: Trastuzumab-emtansine (T-DM1) is a therapeutic agent molecularly targeting human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (MBC), and is especially effective for MBC with resistance to trastuzumab. Although several reports have described T-DM1 resistance, few have examined the mechanism underlying T-DM1 resistance after the development of acquired resistance to trastuzumab. We previously reported that YES1, a member of the Src family, plays an important role in acquired resistance to trastuzumab in *HER2* amplified breast cancer cells. We newly established a trastuzumab/T-DM1-dual resistant cell line and analyzed the resistance mechanisms in this cell line. At first the T-DM1 effectively inhibited the *YES1* amplified trastuzumab resistant cell line, but resistance to T-DM1 gradually developed. *YES1* amplification was further enhanced after acquired resistance to T-DM1 became apparent, and knockdown of *YES1* or administration of the Src inhibitor dasatinib restored sensitivity to T-DM1. Our results indicate that YES1 is also strongly associated with T-DM1 resistance after the development of acquired

resistance to trastuzumab, and continuous inhibition of YES1 is important for overcoming resistance to T-DM1.