# Proteasome inhibitors overcome lapatinib resistance by downregulation of HER family

*Chi-Hua Tsai[1], Wei-Chien Huang[1, 2].*

*[1]Graduate Institute of Cancer Biology, [2]Center for Molecular Medicine, China Medical University and Hospital*

## Abstract

**Backgrounds:**
Lapatinib, a dual EGFR/HER2 tyrosine kinase inhibitor, have shown significant clinical benefits in advanced HER2-positve breast cancer Patients, but the response is not durable. Therefore, development of alternative therapeutic strategies is urgently needed for the patients failed to lapatinib treatment. Proteasome inhibitors have been reported to possess anti-tumor activity by modulating cell surface receptors and inducing apoptosis.Therefore, this study aims to examine whether proteasome inhibitor bortezomib can overcome lapatinib resistance and its underlying molecular mechanisms.
**Materials and Methods:**
Lapatinib-resistant cells were established by chronic treating HER2-positive breast cancer cell lines with increasing doses of lapatinib. The inhibitory effects of bortezomib on cell viability of these breast cancer cells were examined by using MTT assays. The regulation of HER family protein and mRNA expression by bortezomib was examined in Western blot and reverse-transcription quantitative polymerase chain reaction (RT-qPCR) analyses, respectively.
**Results:**
Treatment of bortezomib suppressed cell viability of parental and lapatinib-resistant breast cancer cells equally, suggesting that proteasome inhibitors can circumvent lapatinib resistance. Furthermore, bortezomib suppressed the protein levels of all HER family members in a dose-dependent manner, but only reduced the mRNA levels of HER2, HER3 and HER4 but not EGFR. HER family members and Akt were known to be the client proteins of HSP90 for protein folding, and inhibition of HSP90 caused these client proteins degradation via the ubiquitin-proteasome pathway. Our data further showed that treatment with bortezomib reduced the protein-folding function of HSP90 and that proteasome inhibitor- and HSP90 inhibitor-induced the protein degradation of HER family members but not Akt was prevented by pretreatment with autophagy-lysosome inhibitor bafilomycin A1.

## Results

***Fig. 1. Growth inhibition of lapatinib-resistant breast cancer cells by Bortezomib.***

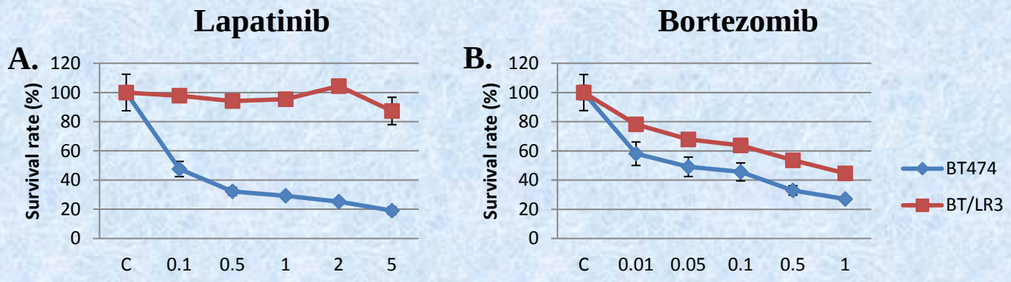



***Fig. 2. Bortezomib suppresses clonogenic growth of lapatinib-resistant breast cancer cells.***

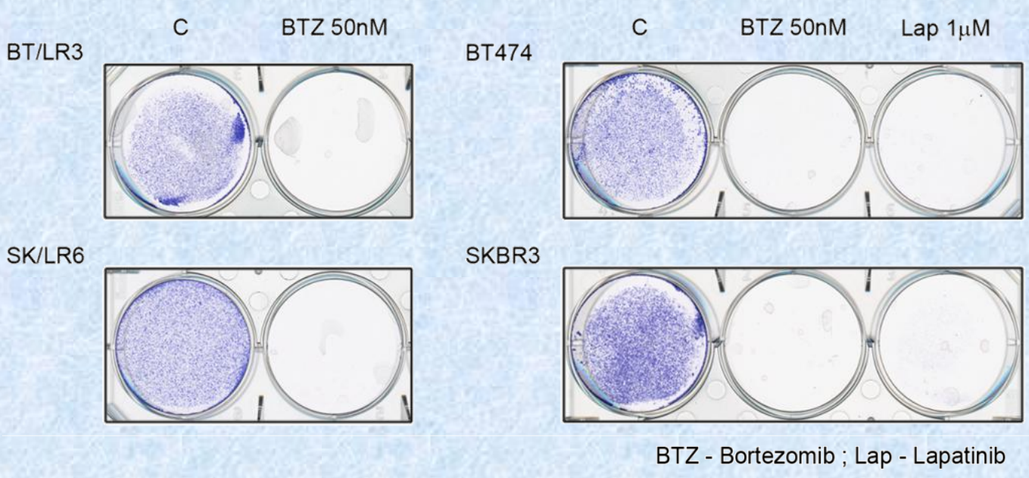



***Fig. 3. Proteasome inhibitors down-regulated HER family expression in breast cancer cells.***

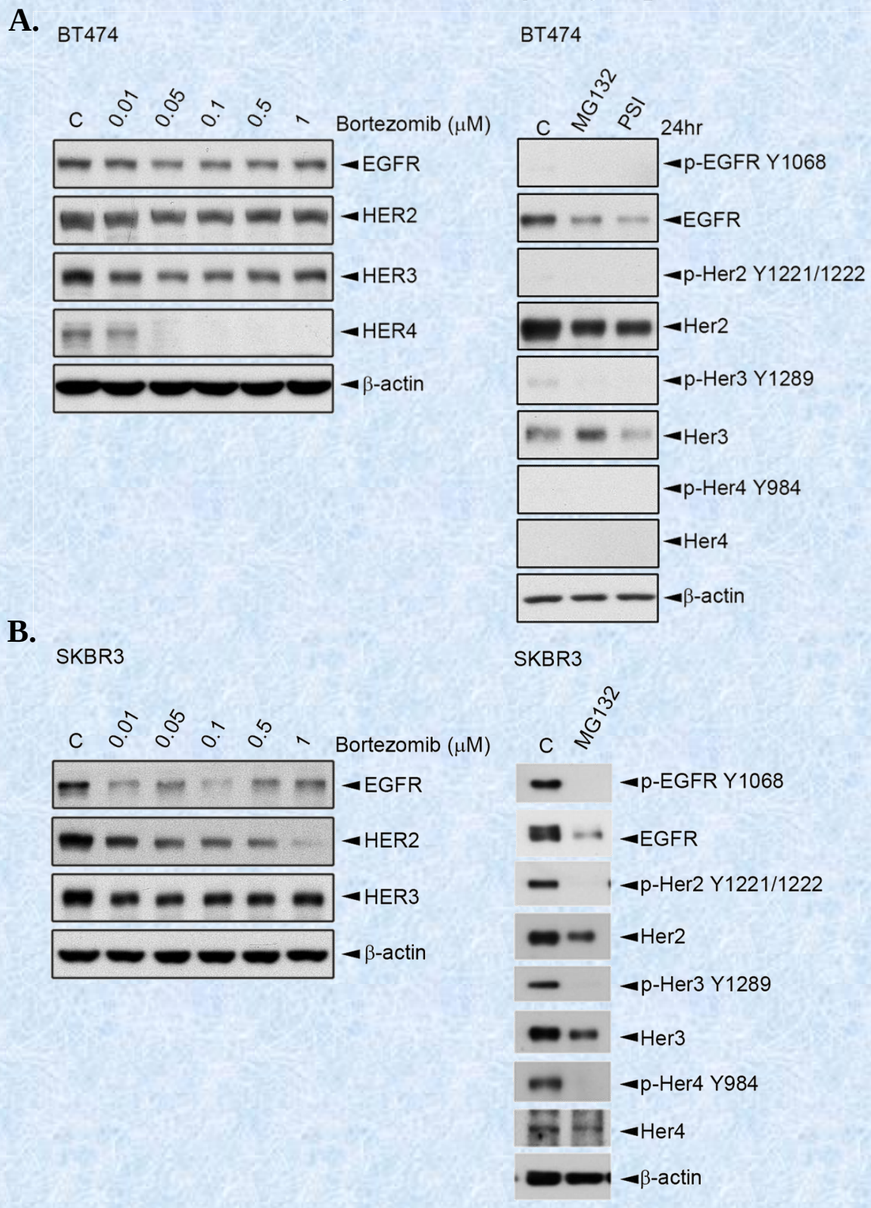



***Fig. 4. Bortezomib down-regulated HER family expression in lapatinib-resistant breast cancer cells.***

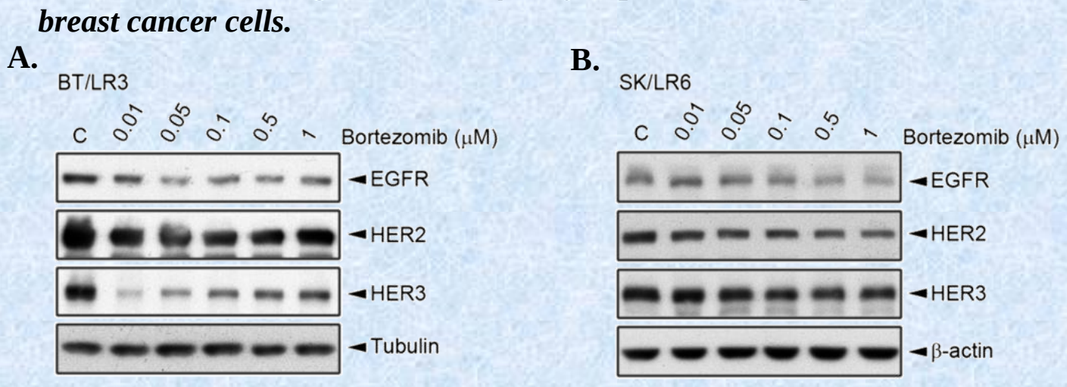



***Fig. 5.The inhibitory effect of Bortezomib on HER family mRNA expression in BT474 cell.***

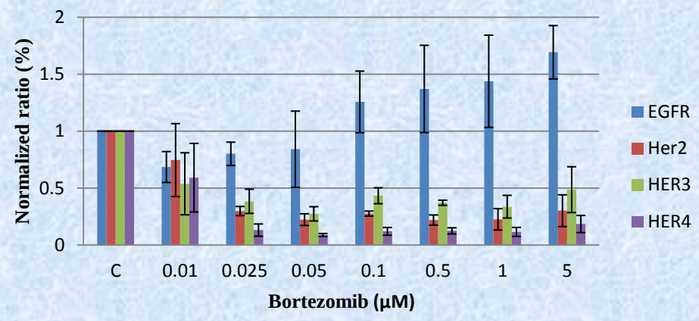



***Fig. 6. Bortezomib suppresses Hsp90α activity***

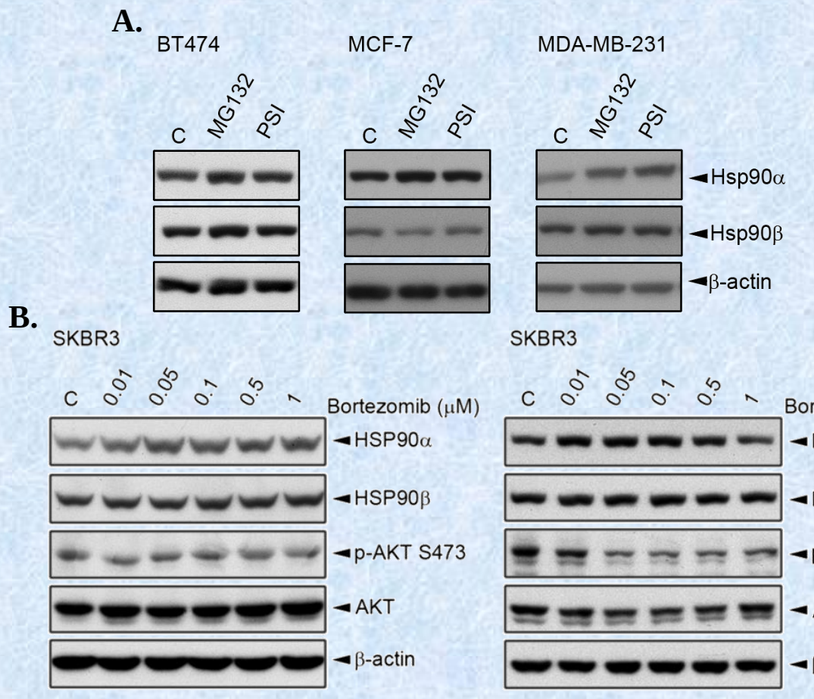
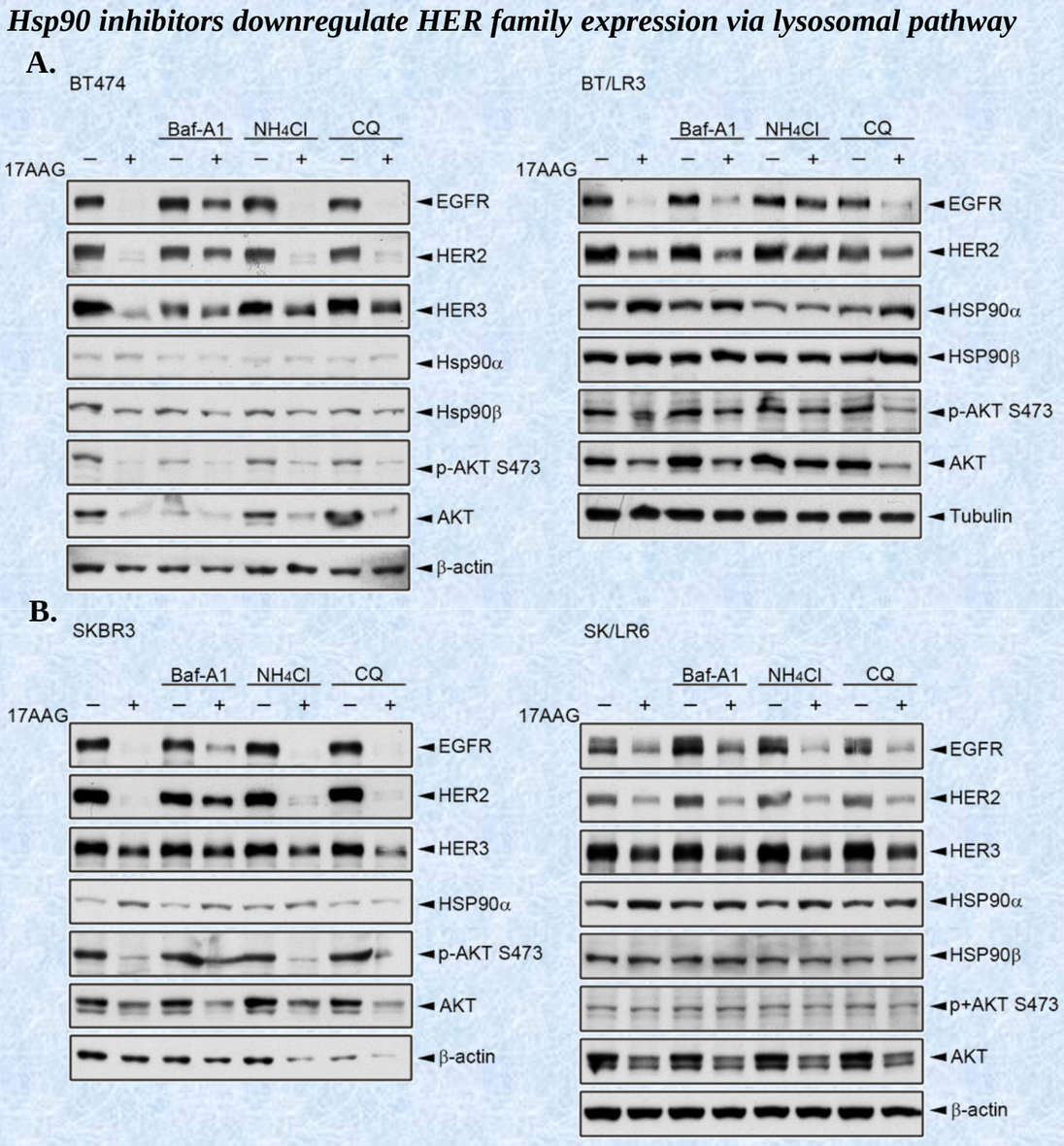



***Fig. 7. Bortezomib downregulates HER family expression via lysosomal pathway.***




***Fig. 8. Hsp90 inhibitors downregulate HER family expression via lysosomal pathway***




## Conclusion

Proteasome inhibitors may overcome lapatinib resistance by inducing the lysosomal protein degradation of HER family via impairing the function of HSP90.