

HER2 upregulates PD-L1 expression through PI3K-Akt pathway

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Purpose

Programmed cell death ligand 1 (PD-L1), delivers a signaling to inhibit T proliferation through engagement with its receptor PD-1. Expression of PD-L1 was found in many tumor types, including breast cancer. Blockade of PD-1/PD-L1 interaction by specific antibody is a new therapeutic strategy showing clinical benefits in metastatic renal, lung carcinomas, and melanomas. Expression of oncogenic HER2 is associated with poor prognosis and high histologic grade of breast cancer patients. Lymphocytic infiltration was found to be lower in HER2-positive than in HER2-negative tumors. Furthermore, HER2-positive cancers have higher proportion of PD-L1 positive tumors than other subtypes of breast cancer. Therefore, this study aims to investigate whether HER2 plays a role in modulating tumor immunity through PD-L1 regulation.

Materials & Methods

We measured the expression of HER2 and PD-L1 by western blot and flow cytometry. mRNA level of PD-L1 was determined real-time PCR. Pharmacological inhibitors and siRNA were used to clarify the signal pathways involved in PD-L1 regulation.

Results

The expression of PD-L1 was higher in HER2-high expression cell lines than in HER2-low expression cell lines. PD-L1 expression was increased by ectopic expression of HER2, and decreased by HER2 siRNA and tyrosine kinase inhibitors. However, EGFR TKI or siRNA did not affect PD-L1 expression. Next, we investigated the downstream signal pathway of HER2 involved in PD-L1 regulation. The result showed that expression of PD-L1 was reduced by Akt inhibitors but not Erk inhibitors.

Conclusion

Our results demonstrated that HER2 upregulates PD-L1 expression through PI3K-Akt pathway.

Figure 1

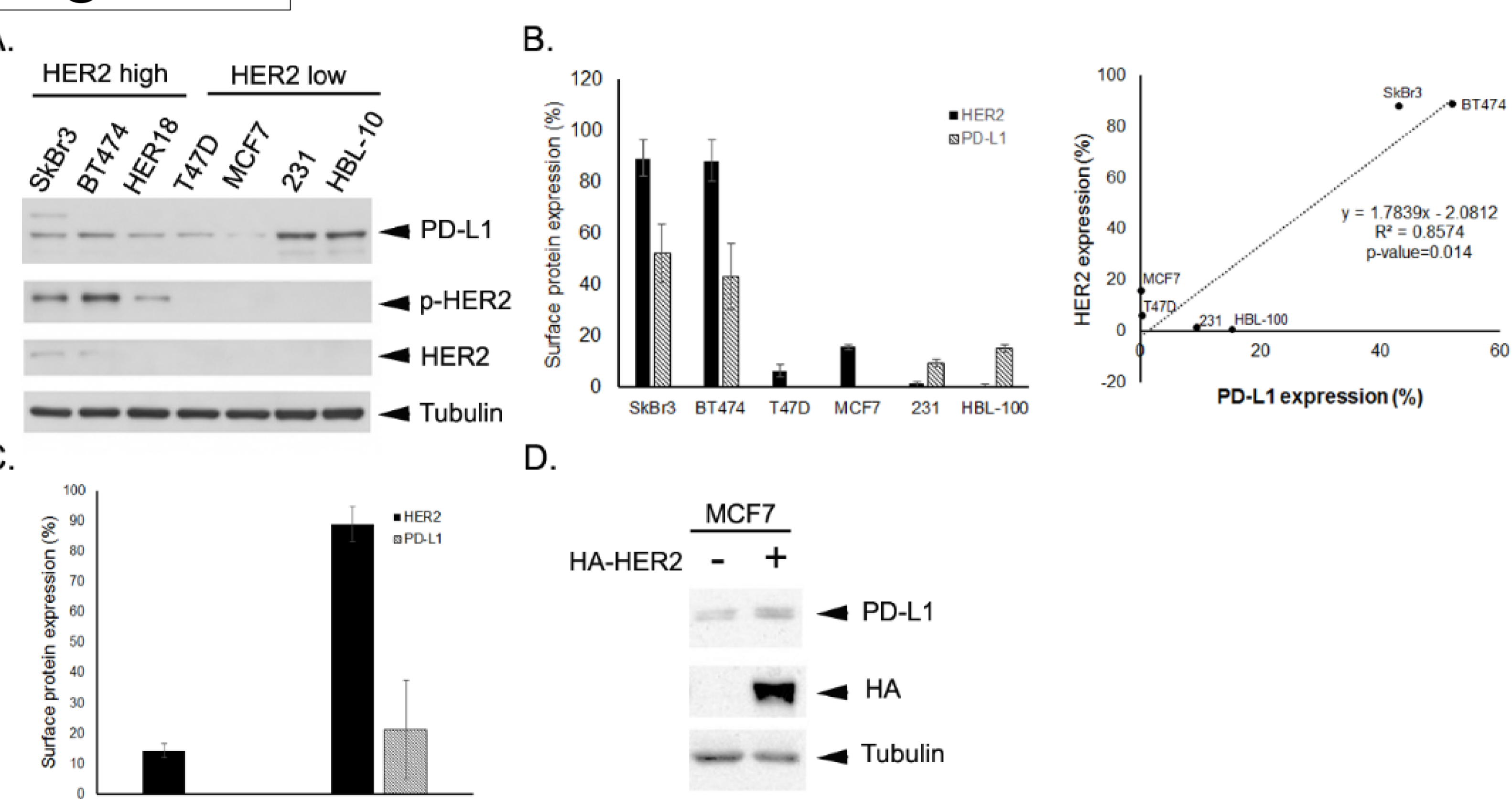


Figure 1. The positive correlation between HER2 and PD-L1 expression.

Figure 3

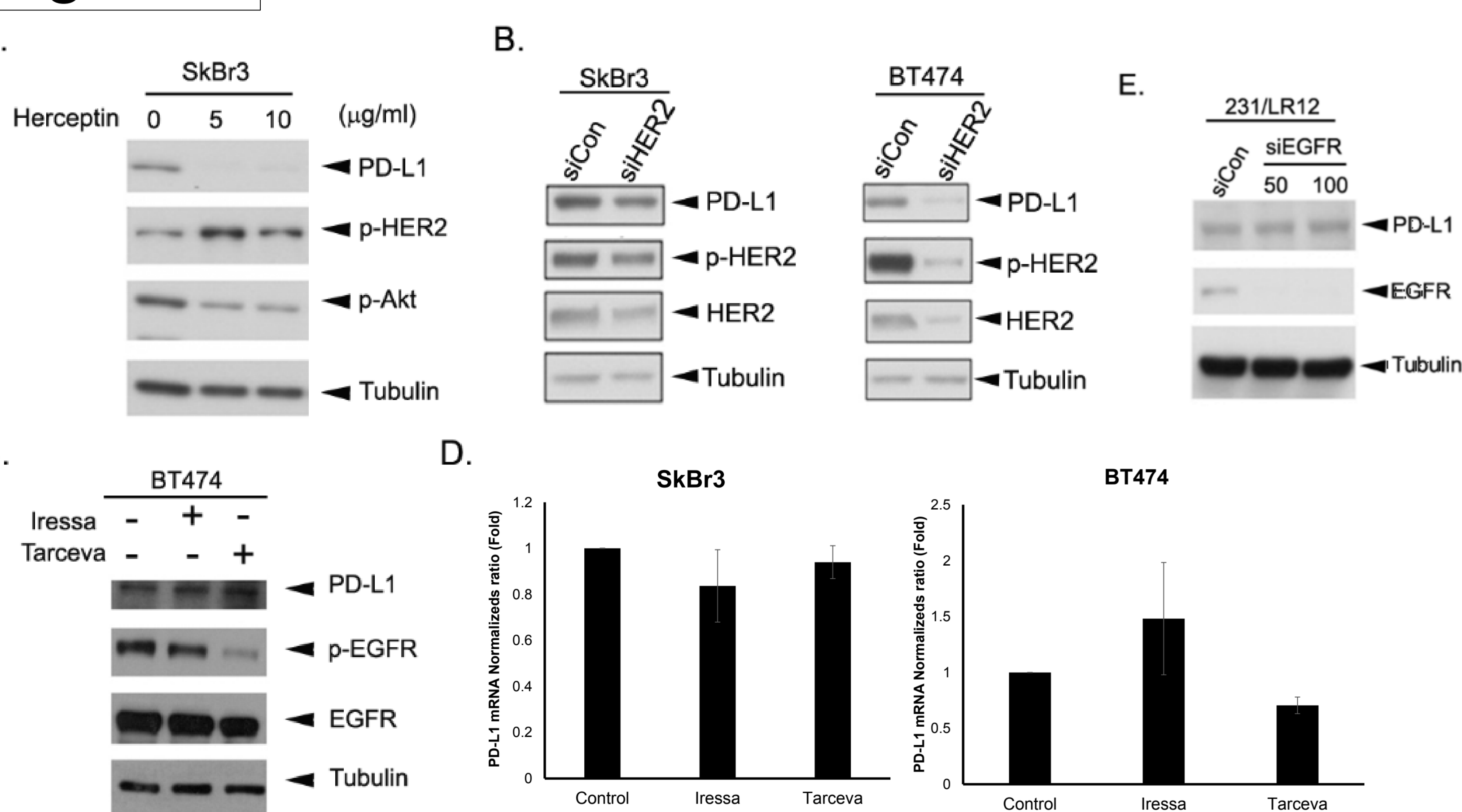


Figure 3. PD-L1 expression was decreased by HER2 down-regulation.

Figure 5

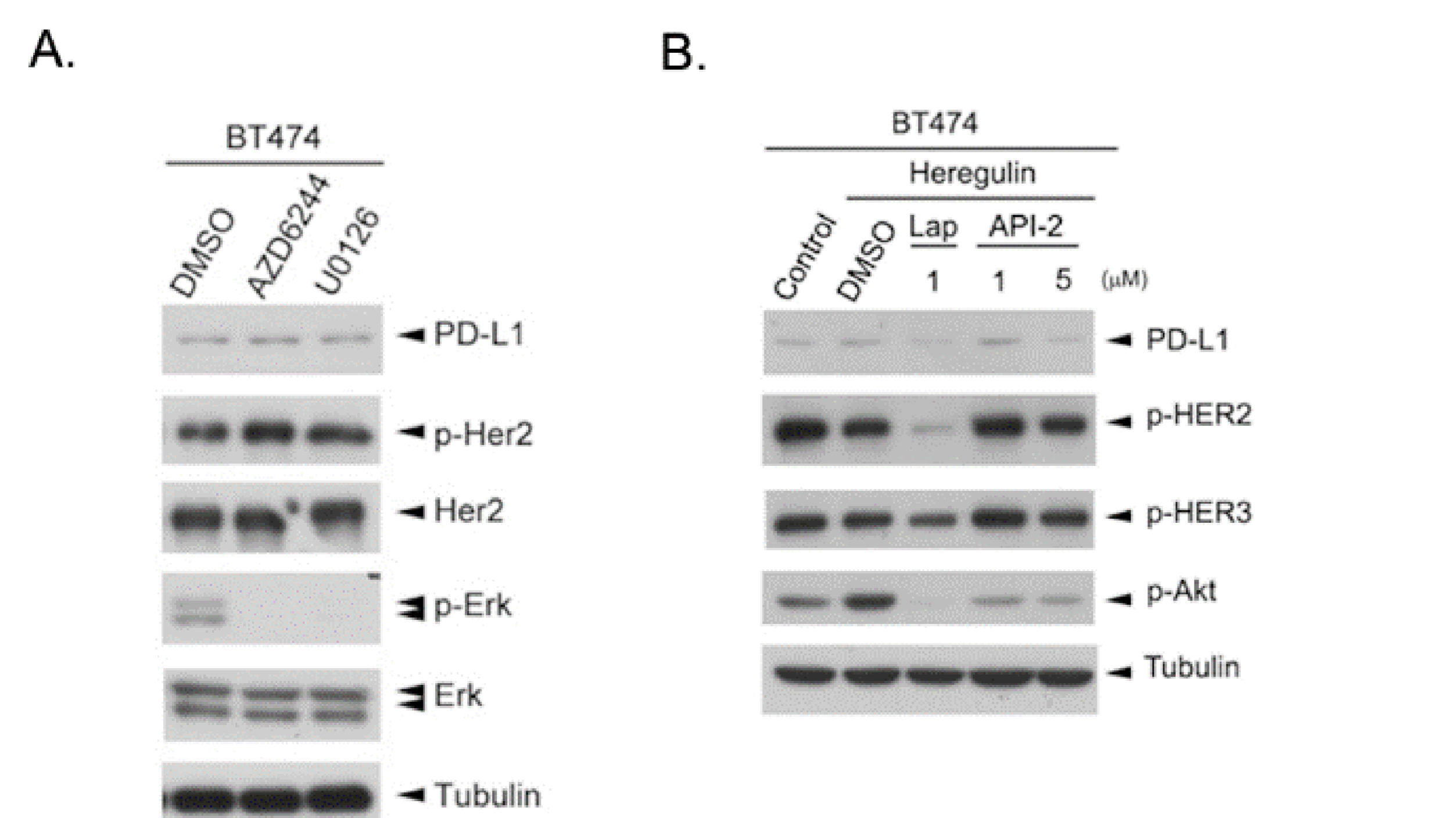


Figure 5. HER2 upregulates PD-L1 expression through PI3K-Akt pathway.

Figure 2

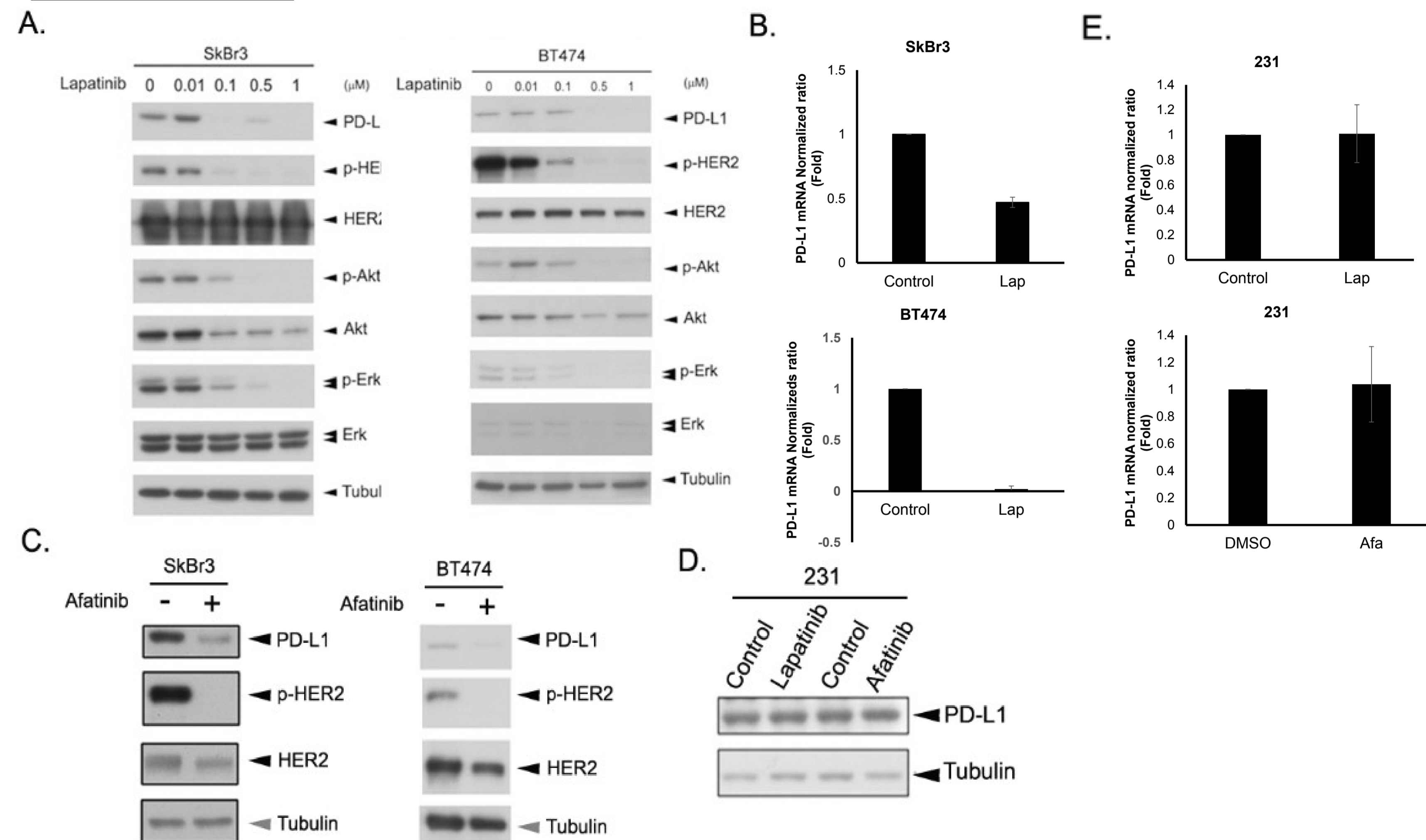


Figure 2. The expression of PD-L1 was reduced by HER2 inhibitors in HER2-high expression cells.

Figure 4

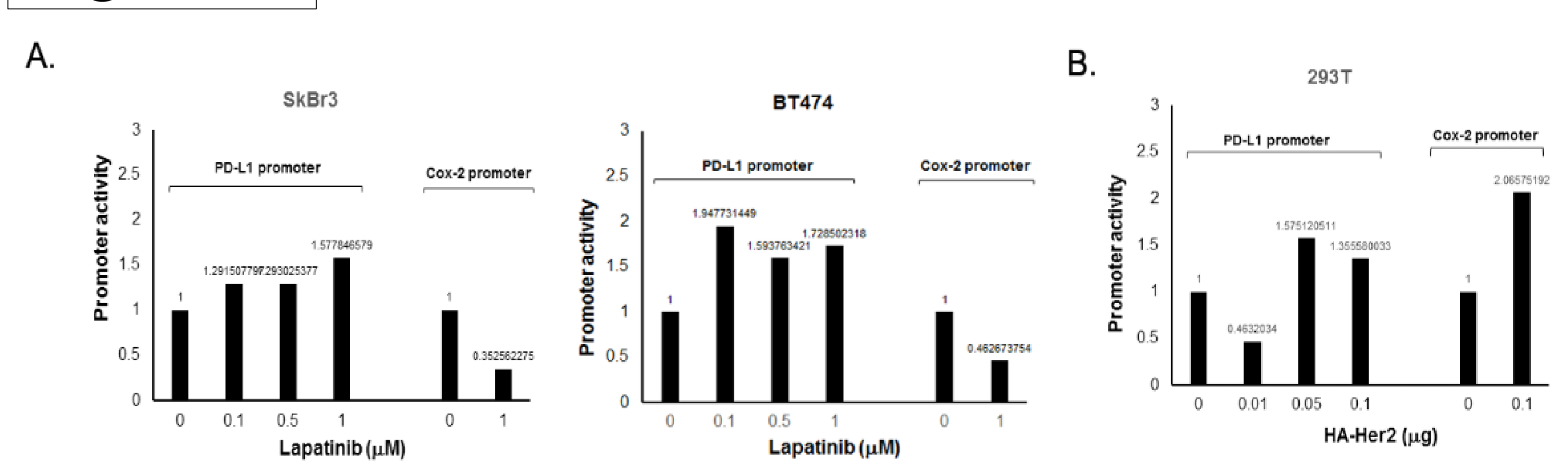


Figure 4. The PD-L1 promoter activity was not effected by Lapatinib treatment or HER2-overexpression.

Figure 6

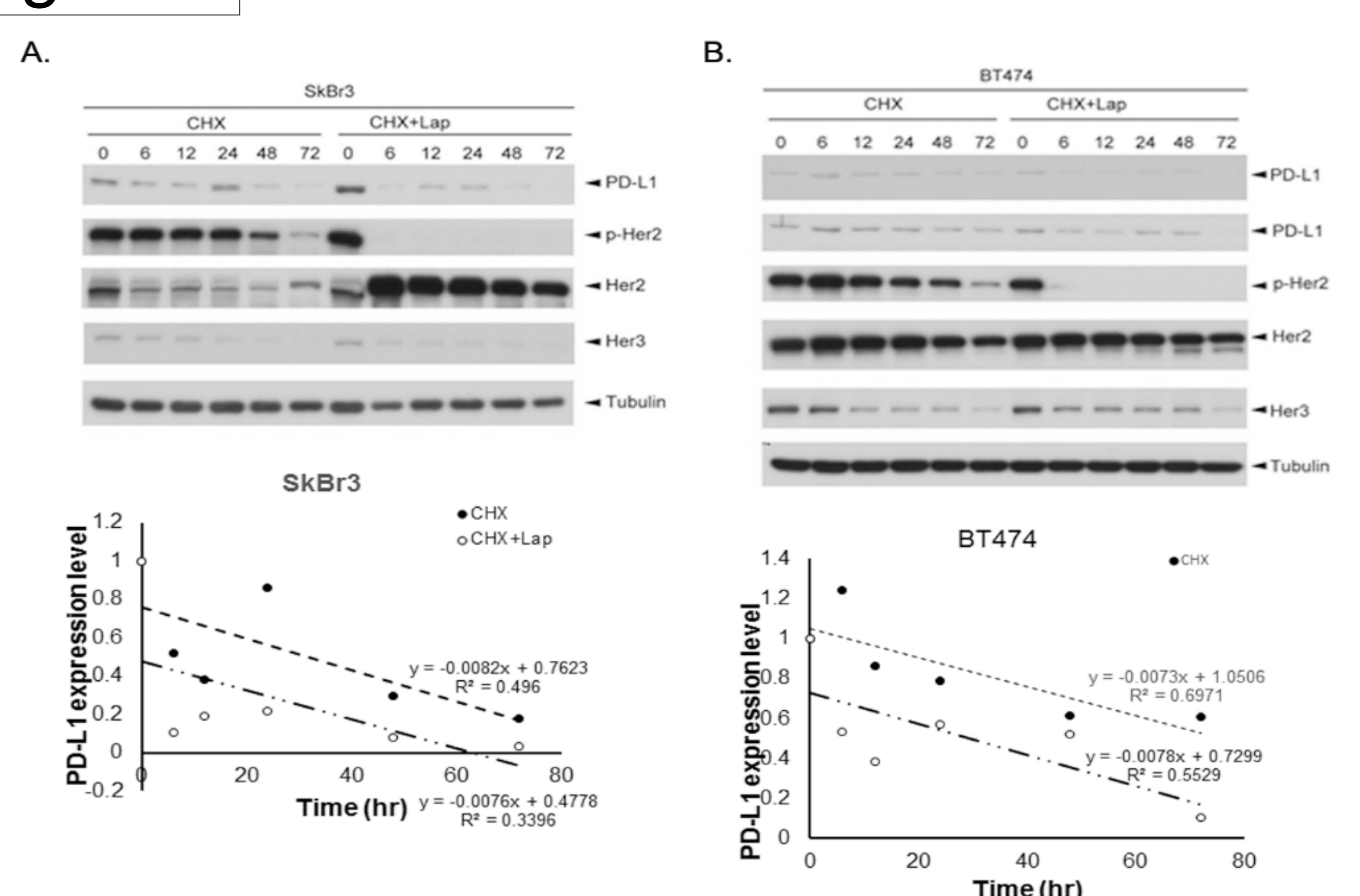


Figure 6. Inhibition of HER2 kinase activity down-regulates PD-L1 expression at post translational level.