The application of a PI3K inhibitor and an AKT inhibitor in HER2-positive breast cancer cells with resistance to HER2-directed antibody-drug conjugates

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**Purpose**

There is no standard approach for resistance to trastuzumab deruxtecan in HER2-positive breast cancer. We aim to develop strategies using both PI3K and AKT inhibitors in cells that have *PIK3CA* mutations and are resistant to antibody-drug conjugates (ADCs).

**Materials and Methods**

We developed five breast cancer cell lines with resistance to ADCs from HCC1954 cells. Cells were subjected to varying doses of trastuzumab emtansine or trastuzumab deruxtecan. The response was assessed by cell counting. HER2 status was analyzed using western blotting and immunofluorescence labeling, while gene mutation patterns were examined by next-generation sequencing. The efficacy of two PI3K inhibitors, alpelisib and inavolisib, and one AKT inhibitor, capivasertib, was tested in ADCs-resistant cells. Compounds were employed either as monotherapy or in combination. Their effectiveness was evaluated by antiproliferative assays. A mouse model with an ADC-resistant breast cancer cell line has been established, in which we assessed anti-xenograft effects of alpelisib or capivasertib.

**Results**

All five ADCs-resistant cell lines showed HER2 downregulation. After ADC treatments, *PIK3CA* mutations remained. In these cells and their parental HCC1954 cells, PI3K and/or AKT inhibitors demonstrated efficacy. The combination of PI3K and AKT inhibitors contributed to a prominent down-regulation of phospho-S6. Alpelisib or capivasertib showed anti-xenograft effects in the mouse model.

**Conclusion**

For HER2-positive ADCs-resistant breast cancer cell lines with *PIK3CA* mutations and HER2-downregulation, a combination of PI3K and AKT inhibitors provides an effective approach. Either alpelisib or capivasertib can hinder the growth of xenografts. The combination strategy will be imminently evaluated *in vivo*.