THERAPEUTICS

PI3K–PARP combination

Breast cancer cells with mutations in *BRCA1* or *BRCA2* have defects in the homologous recombination DNA repair pathway, and this confers sensitivity to inhibitors of poly(ADP) ribose polymerase (PARP). PARP inhibitors are currently being tested in the clinic but, like many targeted therapies, it seems that clinical responses are not durable.

Ibrahim and colleagues showed that treating triple-negative breast cancer (TNBC) cells (that were BRCA proficient) with a PI3K inhibitor decreased BRCA1 expression and sensitized these cells to treatment with PARP inhibitors. This combination synergistically reduced the growth of two different BRCA-proficient xenograft tumours derived from patients with TNBC. Reduced growth was not observed in a xenograft that did not show reduced BRCA1 expression on PI3K inhibition. The authors showed that activation of ERK and the transcription factor ETS1 (in the presence of inhibited PI3K) led to downregulated BRCA1 expression.

Juvekar and colleagues found that PI3K inhibition suppressed RAD51 foci formation, an indicator of homologous recombination repair, in a mouse model of breast cancer that expressed low levels of BRCA1. Combined PARP and PI3K inhibition had a synergistic antiproliferative effect on established BRCA1-defective breast tumours *in vivo* and on patient-derived BRCA1-defective xenograft tumours, one of which had developed resistance to PARP inhibition.

This combination may be effective for treating both BRCA1-defective and BRCA-proficient TNBC.

Gemma K. Alderton

ORIGINAL RESEARCH PAPERS Ibrahim, Y. H. *et al.* PI3K inhibition impairs BRCA1/2 expression and sensitizes BRCA proficient triple negative breast cancer to PARP inhibition. *Cancer Disc.* 22 Aug 2012 (doi:10.1158/2159-8290.CD-11-0348) | Juvekar, A. *et al.* Combining a PI3K inhibitor with a PARP inhibitor provides an effective therapy for a mouse model of BRCA1-related breast cancer. *Cancer Disc.* 22 Aug 2012 (doi:10.1158/2159-8290.CD-11-0336)

> “Combined PARP and PI3K inhibition had a synergistic antiproliferative effect”