Reviewer's report

Title: OSU-03012 sensitizes breast cancers to lapatinib-induced cell killing: a role for Nck1 but not Nck2

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Reviewer: Ching-Shih Chen

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In this study, the authors demonstrated the synergistic interaction between lapatinib and OSU-03012 in suppressing the proliferation of MDA-MB-231 and BT474 cells, and attributed this synergistic effect to the ability of this therapeutic combination to enhance ER stress by downregulating Nck1 expression, thereby facilitating eIF2-alpha phosphorylation, in part, by promoting its dissociation from complexes with Nck1 and PP1. Overall, this is a well-prepared manuscript with solid mechanistic data to support the conclusion. However, a few minor issues warrant attention.

1. Fig. 1A-D depict the effects of OSU-03012, lapatinib, and the drug combination on cell death and colony formation in both cell lines at a single concentration, i.e., 2 microM. The authors should present these results at other concentrations, as they have reported in the isobologram analysis in Table 1, to show the general effect of this drug combination.

2. In the clonogenic assay, the synergistic effect of the drug combination is particularly striking in MDA-MB-231 cells relative to BT474 cells (Fig. 1C and D), which warrants elaboration.

3. The Western blot analysis in Fig. 4A, lower panel (i.e., effect on Nck2 expression) should be repeated to make sure that the loading controls are even among different samples.

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

None to declare