Accepted Manuscript

Decrease in phosphorylated ERK indicates the therapeutic efficacy of a clinical PI3Kα-selective inhibitor CYH33 in breast cancer

Xue-ling Liu, Yi-chao Xu, Yu-xiang Wang, Yi Chen, Bo-bo Wang, Yi Wang, Lan-ding Hu, Qing-yang Ma, Yu-chao Zhang, Yi-ming Sun, Ying-lei Gao, Chun-hao Yang, Jian Ding, Ling-hua Meng

PII: S0304-3835(18)30469-5

DOI: 10.1016/j.canlet.2018.07.011

Reference: CAN 13985

To appear in: *Cancer Letters*

Received Date: 30 March 2018

Revised Date: 7 June 2018

Accepted Date: 5 July 2018

Please cite this article as: X.-l. Liu, Y.-c. Xu, Y.-x. Wang, Y. Chen, B.-b. Wang, Y. Wang, L.-d. Hu, Q.-y. Ma, Y.-c. Zhang, Y.-m. Sun, Y.-l. Gao, C.-h. Yang, J. Ding, L.-h. Meng, Decrease in phosphorylated ERK indicates the therapeutic efficacy of a clinical PI3Kα-selective inhibitor CYH33 in breast cancer, *Cancer Letters* (2018), doi: 10.1016/j.canlet.2018.07.011.

Abstract

PI3Ks are frequently hyper-activated in breast cancer and targeting PI3Kα has exhibited promising but variable response in preclinical and clinical settings. CYH33 is a novel PI3Kα-selective inhibitor in phase I clinical trial. We investigated the efficacy of CYH33 against breast cancer and explored potential predictive biomarkers. CYH33 potently restrained tumor growth in mice bearing human breast cancer cell xenografts and in R26-Pik3ca^{H1047R};MMTV-Cre transgenic mice. CYH33 significantly inhibited proliferation of a panel of human breast cancer cells, while diversity in sensitivity has been observed. Cells harboring activating *PIK3CA* mutation, amplified *HER2* were more responsive to CYH33 than their counterparts. Besides, cells in HER2-enriched or luminal subtype were more sensitive to CYH33 than basal-like breast cancer. Sensitivity to CYH33 has been further revealed to be associated with induction of G1 phase arrest and simultaneous inhibition of Akt and ERK. Sensitivity of patient-derived xenograft to CYH33 was also positively correlated with decrease in phosphorylated ERK. Taken together, CYH33 is a promising PI3Kα inhibitor for breast cancer treatment and decrease in ERK phosphorylation may indicate its efficacy, which provides useful clues for rational design of the ongoing clinical trials.