A HER3 antibody that blocks ligand-independent HER2-HER3 dimerization inhibits growth of HER2-dependent tumors and sensitizes to HER2 and PI3K inhibitors

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Introduction

- Inappropriate HER2/HER3 dimerization as a result of HER2 over-expression in cancer results in HER3-mediated activation of the oncogenic PI3K pathway.
- HER2-targeted agents such as trastuzumab, pertuzumab or lapatinib inefficiently inhibit HER3-mediated HER3 activation allowing persistent HER3 signaling that is speculated to limit clinical responses.
- Consequently, the combination of a HER2 targeted agent with HER3 agents may be of clinical benefit.
- Furthermore, HER3 activation has recently been implicated in the relief of a feedback loop induced by PI3K inhibitors.
- This compensatory phosphorylation of HER3 counteracts the pharmacological inhibition of PI3K/Akt and limits the full activity of PI3K/HER3.
- We hypothesize that complete inhibition of HER3 is required for the full effect of PI3K/Akt inhibitors against HER2+ tumors.

HER3 antibody sensitizes cells to PI3Kα inhibitor

Cells were plated at 10,000 to 50,000 cells per well in 6-well plates and treated in triplicate with DMSO, 10 µg/ml LJM716, and/or 1 µm BYL719. Media was replenished every 3-4 days with replenishment of LJM716. Cells were stained with crystal violet when control treated cells were confluent, ranging from 14-21 days. Representative images and quantification of integrated intensity (% control) are shown. *, P < 0.05, t-test.

HER3 antibody in combination with dual blockade of HER2 improves survival in vivo

Female athymic mice were injected with BT474 cells and randomized to vehicle or the indicated combinations of 20 mg/kg LJM716, 20 mg/kg trastuzumab, and 100 mg/kg lapatinib. Treatment was administered for 35 days. Tumors were measured two to three times a week with calipers. Each data point represents the mean tumor volume ± S.E.M. of triplicate samples. *, P < 0.05, t-test.

HER3 antibody in combination with PI3Kα inhibitor completely eliminate PI3K mutant tumors in vivo

Left panel: Female athymic mice were injected with NCI-N87 or MDA435 cells and randomized to vehicle or 20 mg/kg LJM716 and/or 12.5 to 30 mg/kg BYL719. Treatment was administered for 21 to 48 days. Tumors were measured two to three times a week with calipers. Each data point represents the mean tumor volume ± S.E.M. of triplicate samples. *, P < 0.05, t-test.

Conclusions

- Treatment with LJM716 inhibited HER2/HER3 dimers, P-HER2 and P-Akt in HER2+ breast cancer cell lines with PI3K pathway mutations.

- As a single agent, the HER3 antibody markedly inhibited HER2+ xenograft growth. Treatment with LJM716 in combination with lapatinib and trastuzumab improved survival of mice with HER2+ xenografts compared to lapatinib and trastuzumab.

- LJM716 sensitized breast cancer cells and xenografts to a PI38066-specific inhibitor.

- The HER3 antibody in combination with trastuzumab inhibited PI3K/Akt and xenograft growth as well as the combination of pertuzumab and trastuzumab.