Hyperactivation of mTORC1 drives resistance to the pan-HER tyrosine kinase inhibitor neratinib in HER2-mutant cancers

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Clinical background
- Tumor genomic profiling has identified patients with cancers harboring activating ERBB2 (HER2) mutations that are sensitive to HER2 targeted therapies.
- In the SUMMIT phase II basket trial, a subset of patients with ERBB2-mutant cancers exhibited significant clinical benefit from treatment with the pan-HER irreversible tyrosine kinase inhibitor (TKI) neratinib.
- However, durable responses to neratinib are few, suggesting mechanisms of de novo and acquired drug resistance. Thus, we sought to identify actionable mechanisms of resistance to neratinib.

Identification of mTORC1 as a potential driver of neratinib resistance

- Neratinib-resistant HER2-mutant cells sustain S6 phosphorylation in the presence of mTORC1 inhibitors.
- Combined neratinib and mTORC1 suppression overcomes neratinib resistance.
- mTORC1 activation could be partly attributed to RAS pathway upregulation.

Conclusions
- Neratinib-resistant HER2-mutant cells sustain increased phosphorylation to other mTORC1 targets, which may contribute to resistance to HER2 TKIs.
- Addition of the TORC1 inhibitor everolimus to neratinib as well as inhibition of PI3K/AKT or STAT3 overcomes resistance to neratinib.
- mTORC1 activation in resistant mouse models was associated with increased mTORC1 protein expression and S6 phosphorylation.
- Patients with cancers harboring mTORC1 activating mutations did not exhibit clinical benefit from neratinib, compared to patients with HER2 activating mutations.
- Addition of TORC1 inhibitors may play a role in irreversibly HER2 TKI-resistant cancers with HER2 activating mutations.