ISU104, a Fully Human anti-ErbB3 Antibody, Overcomes Acquired Cetuximab-Resistance

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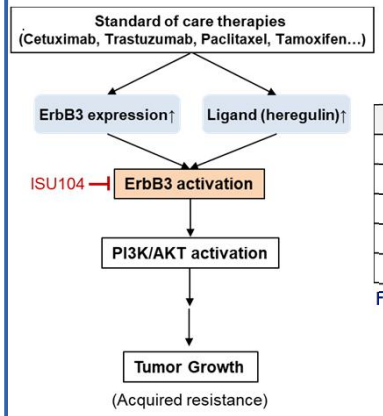
AACR, 2018
#5965

Abstract

- ErbB3 is noted as one of major causes of acquired cetuximab-resistance in colorectal and head and neck cancers. ErbB3 causes activation of alternative signaling pathways that bypass the original target and sustained PI3K/AKT activation, and these are associated with cetuximab-resistance.
- We confirmed the induced ErbB3 activation by the cetuximab-treatment in FaDu head and neck squamous-cell carcinoma (HNSCC) xenograft model. Immunoblot analysis was shown that twice weekly 10 mg/kg of cetuximab treatment upregulated ErbB3 expression and phosphorylation even though tumor growth was well controlled.
- To investigate whether ErbB3 activation by ligand, heregulin (HRG) might induce cetuximab resistance, two cetuximab-sensitive colorectal cancer cell lines, DiFi and LIM1215 were treated 0-25 ng/mL of HRG. HRG induced dose-dependent cetuximab resistance in cell proliferation assay, and those were reversed via ISU104 treatment.
- To evaluate if ISU104 could overcome resistance to cetuximab *in vivo*, acquired cetuximab-resistant FaDu xenograft model was established. Tumors that had acquired resistance to 5 mg/kg of cetuximab treatment were significantly regressed by replaced treatment of ISU104 alone (10 mg/kg) or combination treatment of ISU104 and cetuximab, while mice continued on cetuximab only were shown uncontrolled tumor growth like vehicle-treated group.
- Our results suggest that ISU104 effectively overcomes cetuximab resistance and may provide clinical benefit to cetuximab-resistant patients.

Acquired Resistance to Cetuximab via ErbB3 Activation

- **ErbB1 or ErbB2–targeted therapies or several chemotherapies induced ErbB3 expression and activation, which renders resistance to the therapies**

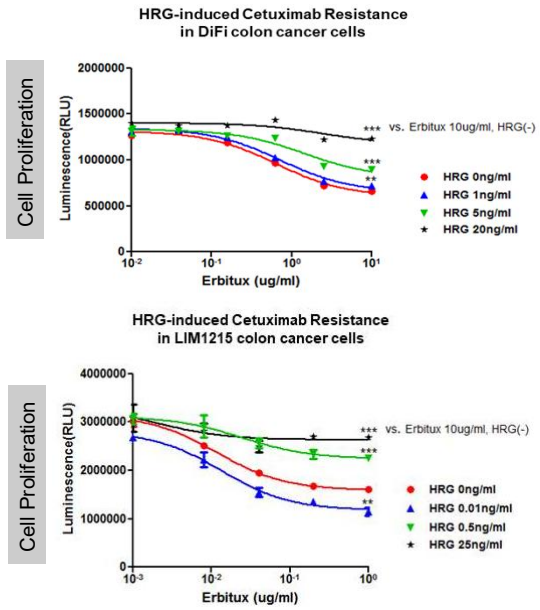


Markers	Vehicle	Cetuximab
pErbB1		
pErbB2		
pErbB3		
tErbB3		
β-Actin		

FaDu head & neck cancer xenograft tissues

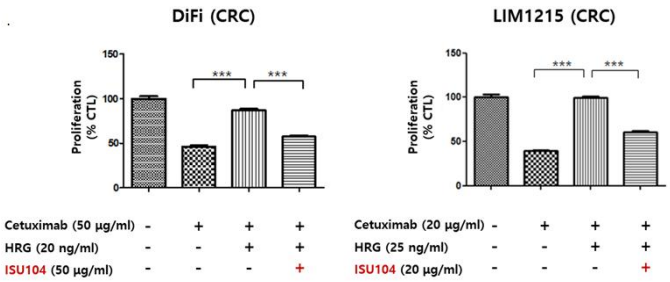
Induction of Cetuximab Resistance by ErbB3 Activation

- **HRG, an activator or ErbB3, suppressed Cetuximab-mediated inhibition of cell proliferation**



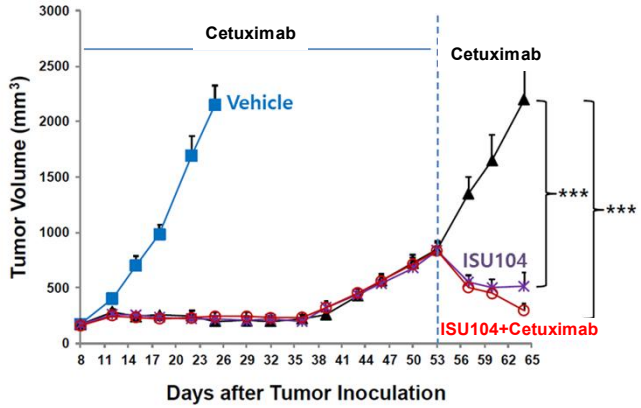
Inhibition of Cetuximab-Resistant Cell Proliferation

- **ISU104 restores anti-proliferation activity of Cetuximab**



Suppression of Cetuximab-Resistant Tumor Growth

- **Co-treatment of ISU104 and Cetuximab regressed tumor in Cetuximab-resistant FaDu HNSCC xenograft model**



Summary

- **ErbB3 activation is one of the key mechanism how cancer cells acquire resistance to Cetuximab (anti-EGFR therapy)**
- **Activation of ErbB3 by HRG suppressed anti-proliferation activity of Cetuximab**
- **ISU104 (anti-ErbB3) restores anti-proliferation activity of Erbitux**
- **Co-treatment of ISU104 and Cetuximab regressed Cetuximab-resistant tumor**
- **ISU104 would give clinical benefits to the patients demonstrating resistance to the current standard treatment, such as anti-EGFR and anti-ErbB2 therapies**

Acknowledgements

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number : HI16C0528)