Anti-cancer efficacy of an anti-ErbB3 antibody, ISU104, against the cancers with NRG1-overexpression, NRG1-fusion, or oncogenic ErbB3 mutations

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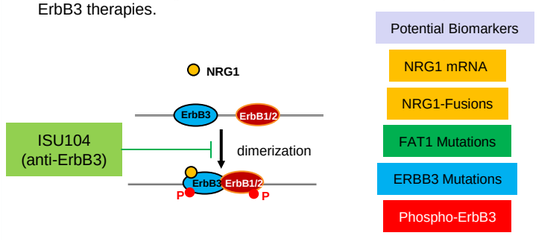
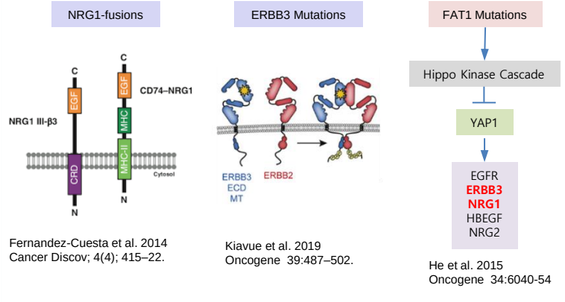
Abstract

- ErbB3, a heterodimeric partner of EGFR or ErbB2, plays important roles in the survival and growth of cancer cells through activation of PI3K/AKT pathway. ErbB3 can be activated by NRG1 expressed either by cancer cells or adjacent mesenchymal cells, or NRG1-fusion proteins produced by genetic alterations in cancer cells. Oncogenic driver mutations in ERBB3 also induce its activation. Previously, we have demonstrated preclinical anti-cancer efficacy of a monoclonal anti-ErbB3 antibody, ISU104 as a monotherapy or in combination with anti-EGFR antibody in various preclinical models. Biomarker analysis of the models demonstrated that there is a significant positive correlation between tumor growth inhibition by ISU104 and NRG1 mRNA/pErbB3 protein expression levels.
- Based on this analysis, anti-cancer efficacy of ISU104 was further explored in the cancer cells and cell line- or patient-derived xenograft cancer models with phospho-ErbB3, NRG1 mRNA overexpression, NRG1-fusion, FAT-1 mutations or oncogenic ErbB3 mutations. ISU104 potently inhibited phosphorylation of ErbB3 and Akt, cell proliferation and tumor growth of such models. Potential impacts of other genetic alterations on the anti-cancer efficacy of ISU104 were also investigated.
- Overall, the presented data suggest that ISU104, and anti-ErbB3 agent at an early stage of clinical development, can be applied for the treatment of the solid tumors expressing high levels of phospho-ErbB3 or NRG1 mRNA or harboring genetic alterations such as NRG1-fusion, FAT1 mutations or oncogenic ERBB3 mutations.

Introduction

- ISU104 is a human monoclonal anti-ErbB3 antibody at an early clinical stage of development.
- It specifically binds to the domain 3 of ErbB3 and inhibits both ligand-dependent and ligand-independent signaling of ErbB3/PI3K pathway.
- ISU104 potently inhibits NRG1 (ligand) binding to ErbB3.
- Several potential biomarkers such as NRG1 mRNA, NRG1-fusions, FAT1 mutations or oncogenic ERBB3 mutations have been propose for anti-ErbB3 therapies.





Fernandez-Cuesta et al. 2014
Cancer Discov; 4(4); 415–22.

Kiavue et al. 2019
Oncogene 39:487–502.

He et al. 2015
Oncogene 34:6040-54

Purpose

- To demonstrate whether ISU104 (anti-ErbB3) has anti-cancer efficacy against the preclinical models with the proposed biomarkers, such as high phospho-ErbB3, NRG1 mRNA overexpression, NRG1-fusions, FAT1 mutations or oncogenic ErbB3 mutations.

Results

NRG1-fusions

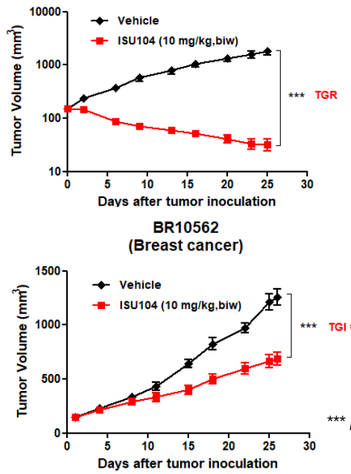


Figure 1. Tumor growth inhibition (TGI) of the PDX-models with NRG-1 fusion by ISU104. Significant TGI were observed in two out of 3 NRG1-fusion models (BR10562, OV6308 and SA10157).

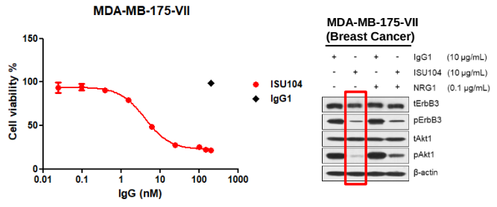


Figure 2. Inhibition of cell proliferation and ErbB3/PI3K signaling of the cancer cells (MDA-MB-175-VII) with NRG-1 fusion by ISU104.

FAT1 mutations

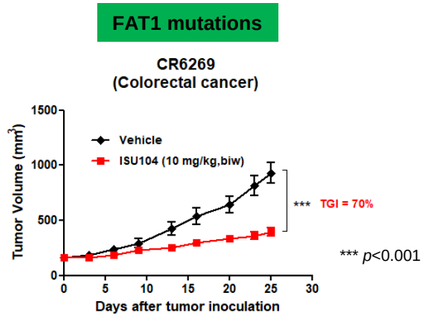
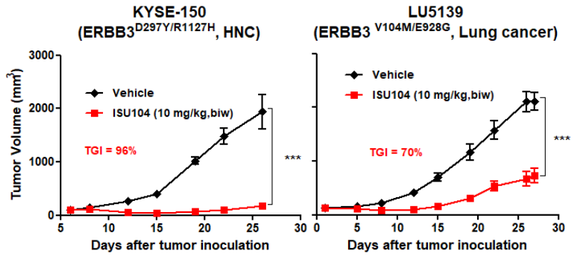


Figure 3. TGI of the PDX-model with FAT1 mutation (CR6269; L1012AfsTer10) by ISU104.

Results

Oncogenic ERBB3 mutations



*** p<0.001

Figure 4. TGI of the CDX- and PDX-tumors with oncogenic ErbB3 mutations by ISU104. Significant TGI were observed in one CDX (KYSE-150) and one out of 3 PDX models with ERBB3 mutation (LU5139, GA6894 and GA0318).

NRG1 mRNA

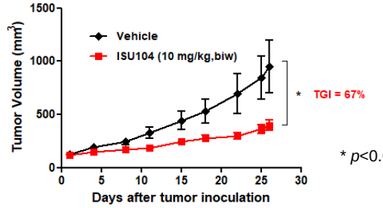


Figure 5. TGI of the PDX-model with high NRG1 expression (CR5038) by ISU104.

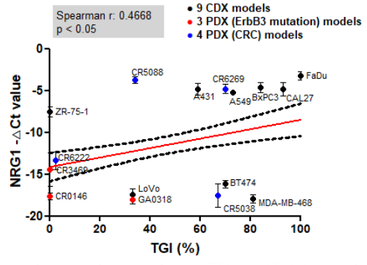


Figure 6. Significant correlations between TGI by ISU104 and the levels of NRG1 mRNA as quantified by real-time RT-PCR, respectively. ΔCt=Ct (NRG1)-Ct (β-actin)

Phospho-ErbB3

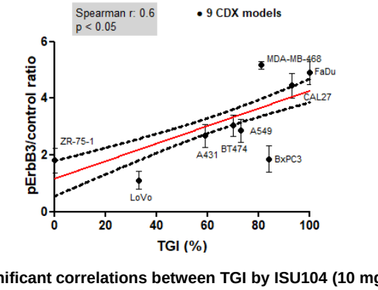


Figure 7. Significant correlations between TGI by ISU104 (10 mg/kg, biw) and the levels of pErbB3 as quantified by western blotting.

Results

Known/Predicted Driver Mutations in the Models

Table 1. Known and predicted driver mutations in the xenograft models evaluated for anti-cancer efficacy of ISU104.

Model	Tumor Type	TGI %	Known and Predicted Driver Mutations (a.a. changes)
FaDu	Head and Neck/Pharynx	Regression	KRAS (Q61H); **FAT1** (K3277NfsTer4)
OV6308	Ovary	Regression	**LOXL2-NRG1 fusion**
KYSE-150	Head and Neck/Esophageal	96	**ERBB3** (D297Y, R1127H)
CAL27	Head and Neck/Tongue	93	TP53 (H193L)
BxPC3	Pancreas	84	TP53 (Y220C)
MDA-MB-468	Breast	81	TP53 (R273H)
A549	Lung	73	KRAS (G12S); **FAT1** (R2567H)
CR6269	Colorectal	70	PIK3CA (H1047R); **FAT1** (L1012AfsTer10)
LU5139	Lung	70	ERBB2 (L755S); ERBB2 (A1216D); **ERBB3** (V104M/E928G)
BT474	Breast	70	TP53 (E285K)
CR5038	Colorectal	67	TP53 (R175H); KRAS (Q61H); ErbB2 (P489L);PIK3CA (E726K); PIK3CA (N1044K)
A431	Skin	59	**FAT1** (Q2494Ter); TP53 (R273H)
BR10562	Breast	52	**CLU-NRG1 fusion**
CR5088	Colorectal	34 (ns)	NRAS (G13R-64.5%)
LoVo	Colorectal	33 (ns)	KRAS (G13D)
GA0318	Gastric	30 (ns)	**ERBB3** (V104L); KRAS (G12D); PIK3CA (H1047R/E545V)
GA6894	Gastric	22 (ns)	ERBB2 (S310A); **ERBB3** (V104M); PIK3CA (R1026Q)
SA10157	Sarcoma	0	**ADAM9-NRG1 fusion**
CR6222	Colorectal	0	TP53 (G245S); TP53(R175H); KRAS (G12D)
CR0146	Colorectal	0	**ERBB3** (G284R), KRAS (K117N), PIK3CA (E545G)
CR3469	Colorectal	0	**ERBB3** (V104M); KRAS (G12D)
ZR-75-1	Breast	0	HRAS (E162K); PTEN (L108R)

Summary

- Potential predictive biomarkers for an anti-ErbB3, ISU104 were evaluated using various preclinical models.
- ISU104 showed anti-cancer efficacy in the models of NRG1-fusions, FAT1 mutations and oncogenic ERBB3 mutations with exceptions.
- NRG1 mRNA expression and the levels of pErbB3 were correlated with the tumor growth inhibition by ISU104.
- The tested biomarkers are planned to be evaluated in the ongoing phase I and subsequent clinical studies of ISU104.

Acknowledgement

- Presenting Author: Seung-Beom Hong (hongsb@isu.co.kr)