# Zenocutuzumab, a HER2 × HER3 bispecific antibody, is effective in cancer models with high NRG1 expression

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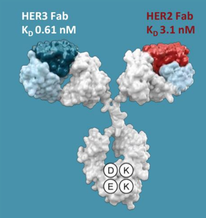
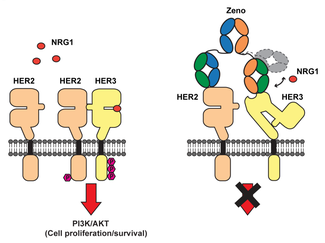
ABSTRACT #1903




## INTRODUCTION

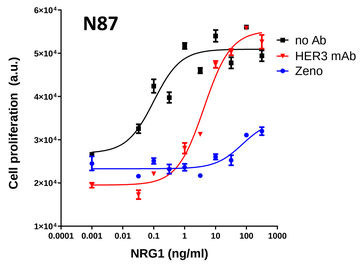
- **Neuregulin 1 (NRG1)** is a ligand that binds to human epidermal growth factor receptor (HER) 3, promoting HER2/HER3 heterodimerization and oncogenesis, leading to tumor growth[1, 2]
- **Zenocutuzumab (Zeno, MCLA-128)** is a bispecific antibody that binds to the extracellular domains of HER2 and HER3 (Figure 1)
  - Anticancer activity is due to blocking NRG1/HER3 binding and HER2/HER3 dimerization, which suppresses tumor cell proliferation and survival via the PI3K-AKT-mTOR oncogenic signaling pathway[3, 4]
- **High NRG1 expression** arising from autocrine signaling or gene amplification is associated with poor prognosis in certain cancers, and resistance to standard therapies[5]
- In this study, we examined the efficacy of Zeno in preclinical models representing multiple tumor types expressing high NRG1 levels

**Figure 1. Zeno "Dock & Block®" mechanism.** Zeno inhibits oncogenesis by docking on the HER2 receptor, which optimally positions the anti-HER3 arm to block the ligand/receptor interaction, and by preventing HER2/HER3 dimerization. Thus, Zeno potently inhibits NRG1-induced HER2/HER3 proliferation and survival signaling of cancer cells. Adapted from Alsina et al. 2017[6]



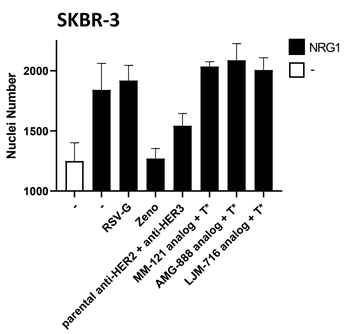

## INHIBITION OF NRG1-DRIVEN PROLIFERATION

- N87 gastric carcinoma cells were stimulated with increasing concentrations of NRG1 and treated with Zeno or the parental HER3 monoclonal antibody (mAb)
- Zeno inhibits NRG1-dependent cell proliferation at higher NRG1 concentrations than the bivalent parental HER3 mAb

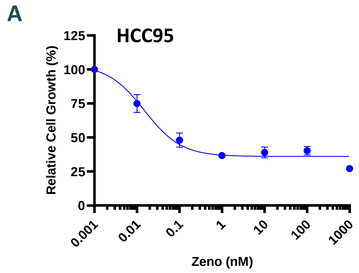


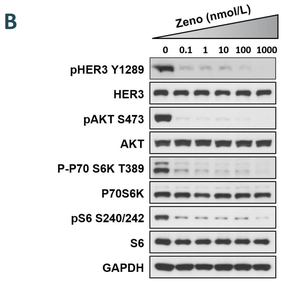

## ZENO BLOCKS HIGH NRG1-INDUCED PROLIFERATION

- SKBR-3 breast cancer cells were stimulated with high NRG1 concentrations (10 ng/ml) and treated with the indicated antibodies
- Analog antibodies targeting HER3 were combined with the HER2 antibody trastuzumab (T*)
- Zeno more potently inhibits high NRG1-driven cell proliferation than the combination of HER2 and HER3 antibodies, including the combination of Zeno's parental monospecific anti-HER2 and anti-HER3 antibodies



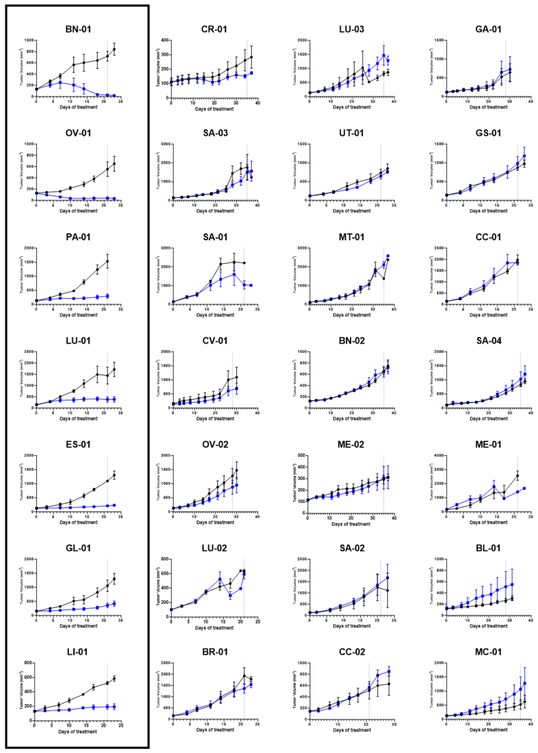

## INHIBITION OF GROWTH AND SIGNALING IN NRG1-AMPLIFIED HCC95 CELLS



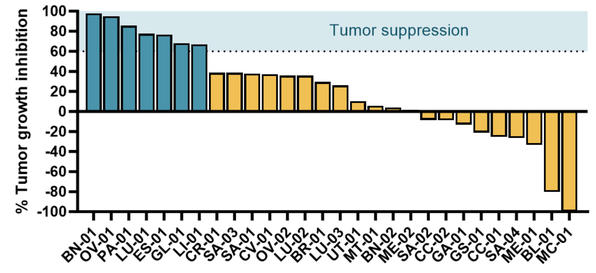

- Lung cancer cell line HCC95 harbors an NRG1 amplification[7]
- Cells were treated with the indicated concentrations of Zeno for 96 hours (A) or 1.5 hours (B)
- Zeno inhibits HCC95 cell proliferation (A) and inhibits signaling pathways involved in the regulation of proliferation and survival, including the PI3K/AKT/mTOR pathway (B)

## EFFICACY IN A DIVERSE PANEL OF PDX MODELS WITH HIGH NRG1 EXPRESSION




- PDX models representing 21 different tumor types were selected based on high NRG1 expression in the respective tumor types
- Weekly treatment with Zeno induced significant tumor growth inhibition in 7 of the 28 PDX models tested (p<0.05; black rectangle)
- Each line represents mean ± SEM of 3 mice per group. Vertical dotted lines indicate the end of the treatment period

## TUMOR SUPPRESSION IN PDX MODELS EXPRESSING HIGH NRG1




- Summary of tumor growth inhibition (% TGI) of 28 PDX models treated weekly with 25 mg/kg Zeno
- Bar colors indicate %TGI >60% (blue) or <60% (yellow). Response is ranked from best to worst

## CONCLUSIONS

- Zeno is observed to:
  - potently inhibit proliferation of N87 gastric cancer and SKBR-3 breast cancer cell lines at high NRG1 concentrations
  - inhibit proliferation of HCC95, an NRG1-amplified lung cancer cell line, and block signaling through pathways involved in the regulation of cell growth and survival
  - significantly inhibit tumor growth in seven high-NRG1-expressing patient-derived xenograft models from diverse tumor types
- These data show that Zeno is effective in tumor cell killing in vitro and in vivo in high NRG1-expressing cancer models representing multiple different tumor types

## METHODS

- **In vivo studies:** Patient-derived xenograft (PDX) models with relatively high NRG1 expression for each tumor type were identified using RNAseq data from Crown Bioscience, Inc. and coded according to tumor type. %TGI = (1-Ti/Vi) × 100%, where T = mean tumor volume of Zeno treatment group, V = mean tumor volume of vehicle group, and i = the last day that all mice/model were measured
- **PDX tumor types:** BL-Bladder Cancer; BN-Brain Cancer; BR-Breast Cancer; CC-Cholangiocarcinoma; CR-Colorectal Cancer; CV-Cervical Cancer; ES-Esophageal Cancer; GA-Gastric Cancer; GL-Gallbladder Cancer; GS-GIST; HN-Head and Neck Cancer; KI-Kidney Cancer; LI-Liver Cancer; LU-Lung Cancer; MC-Metastatic Carcinoma; ME-Melanoma; MT-Mesothelioma; OV-Ovarian Cancer; PA-Pancreatic Cancer; SA-Sarcoma; UT-Uterine Cancer

### References

1 Fernandez-Cuesta et al. Cancer Discov, 2014; 2 Werr et al. Mol Cancer Ther, 2022; 3 Geuijen et al. Cancer Cell, 2018; 4 Schram et al. JClinOncol. 2019; 5 Le Clorennec et al. Mol Cancer Ther, 2017; 6 Alsina et al. ASCO, 2017; 7 Drilon et al. Cancer Discov, 2018

**Presented at:** AACR Annual Meeting; April 5-10, 2024; San Diego, CA, USA

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