AACR-NCI-EORTC Virtual International Conference on
MOLECULAR TARGETS AND CANCER THERAPEUTICS
October 7-10, 2021

# Zenocutuzumab is an effective HER2/HER3 Biclonics® antibody in cancers with NRG1 fusions

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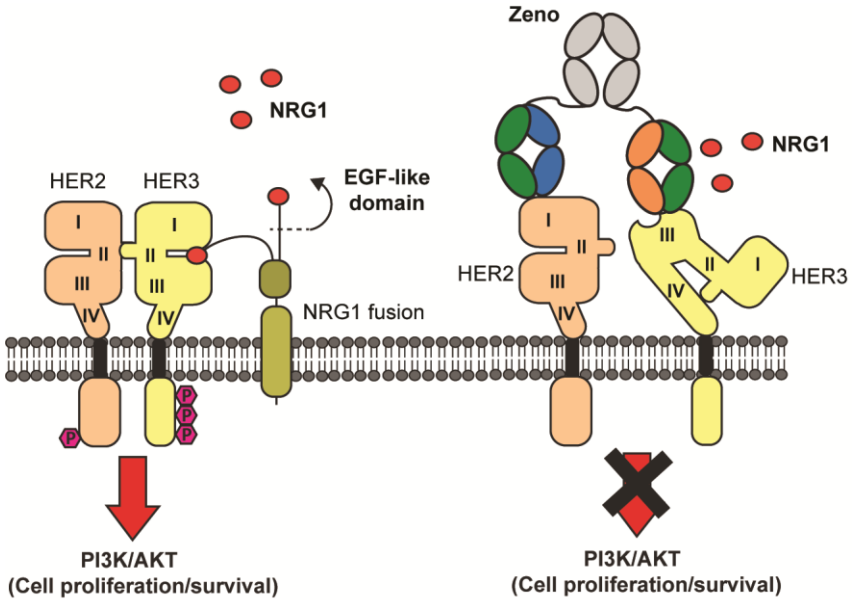
I have the following financial relationships to disclose:

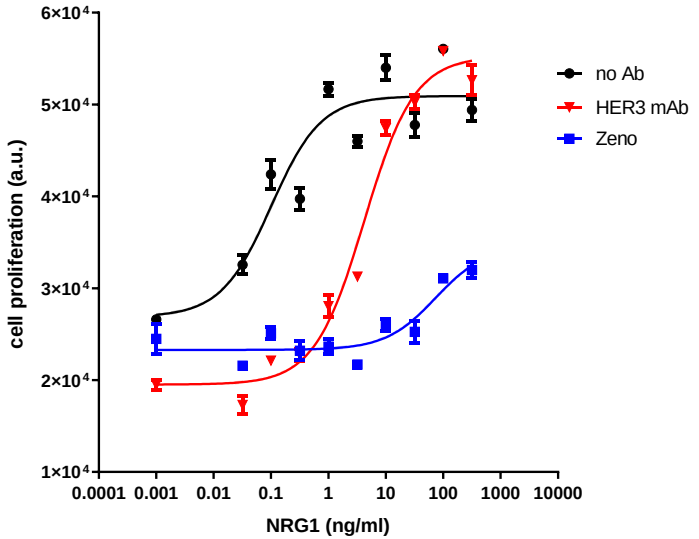
Employee and shareholder of: Merus NV

# Zeno potently inhibits NRG1-mediated signaling by a Dock & Block® mechanism

Zenocutuzumab (Zeno) binds via its anti-HER2 Fab arm to domain I of HER2.

Docking on HER2 increases the potency of the anti-HER3 Fab arm to bind domain 3 of HER3 and block binding of the ligand NRG1.

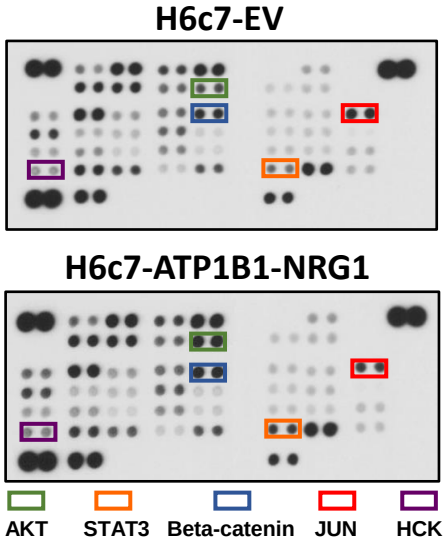


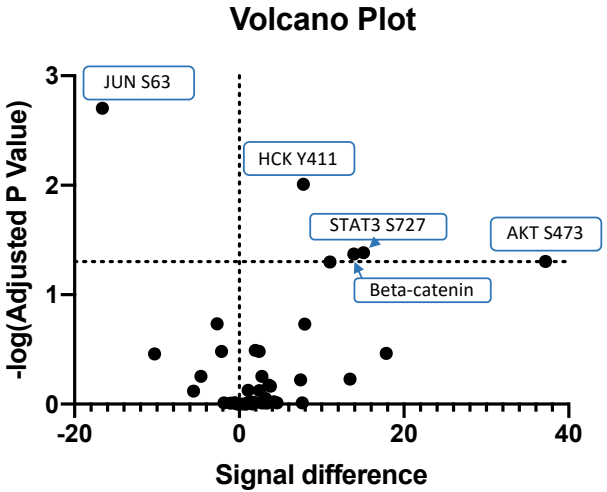



# NRG1 gene fusions drive activation of oncogenic signaling pathways

NRG1 gene fusions are tumorigenic events occurring in patients with certain lung, pancreatic and other cancers.

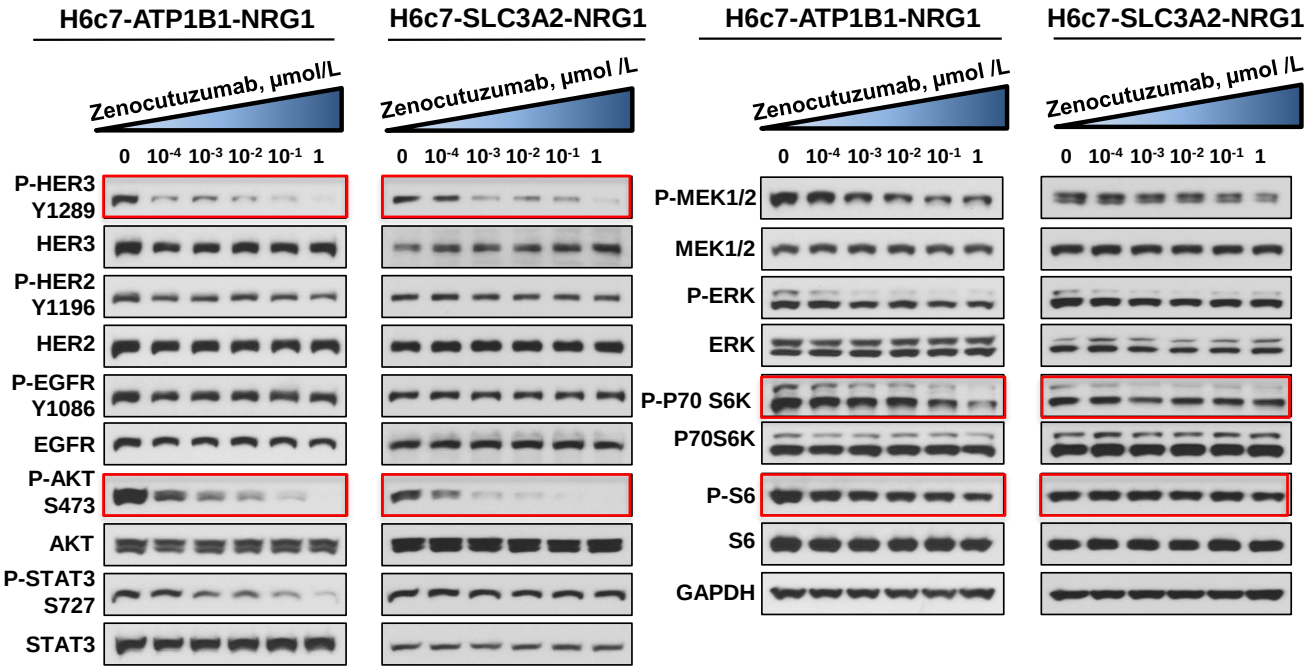
Insertion of the NRG1 fusion ATP1B1-NRG1 into immortalized pancreatic ductal epithelial cells (H6c7) leads to activation of the HER3 oncogenic signaling pathways including AKT.



# Zeno inhibits downstream signaling in NRG1-fusion containing cells

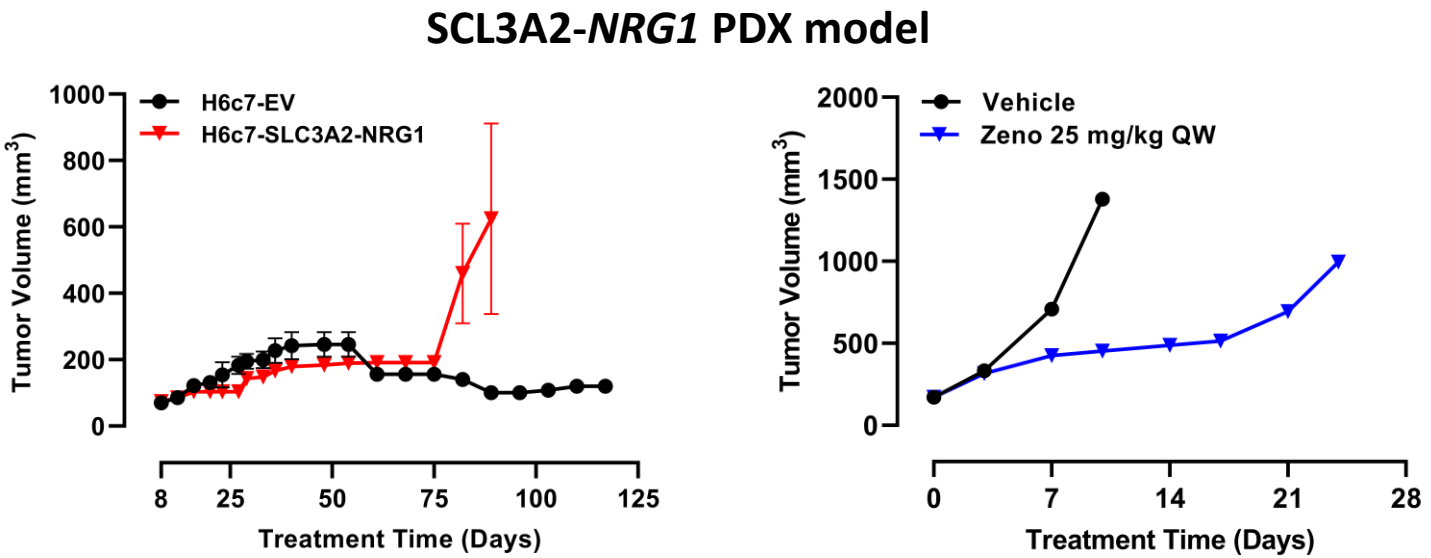
Zeno inhibits HER3 and PI3K/AKT-related downstream signaling pathways in H6c7 cells harboring NRG1 gene fusions in vitro.




Western blots show total protein levels and phosphorylation levels (P-) of signaling proteins 90 minutes after Zeno treatment

# Zeno blocks growth of tumors derived from NRG1 fusion-containing cells

Zeno inhibits the proliferation of SLC3A2-NRG1 fusion transformed H6c7 cells implanted in immunocompromised mice.

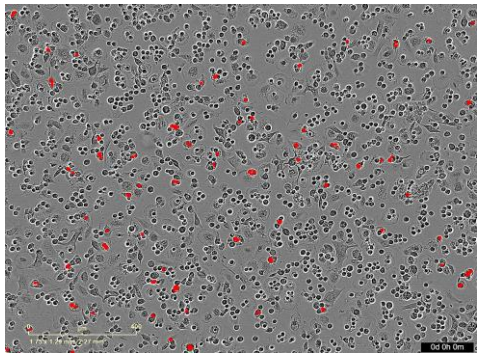


# Zeno mediates phagocytosis of cancer cells (ADCP)

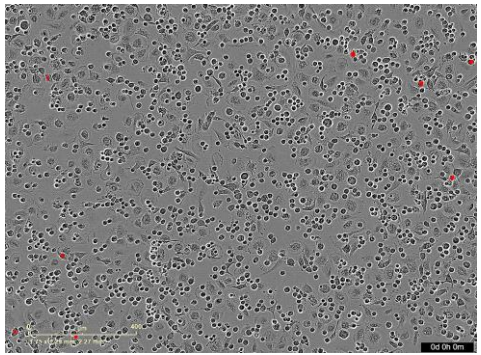
Zeno is an IgG1 and can bind efficiently to the Fc receptors on immune cells, including macrophages.

Zeno effectively induces phagocytosis of SK-BR-3 cells by monocyte derived macrophages.

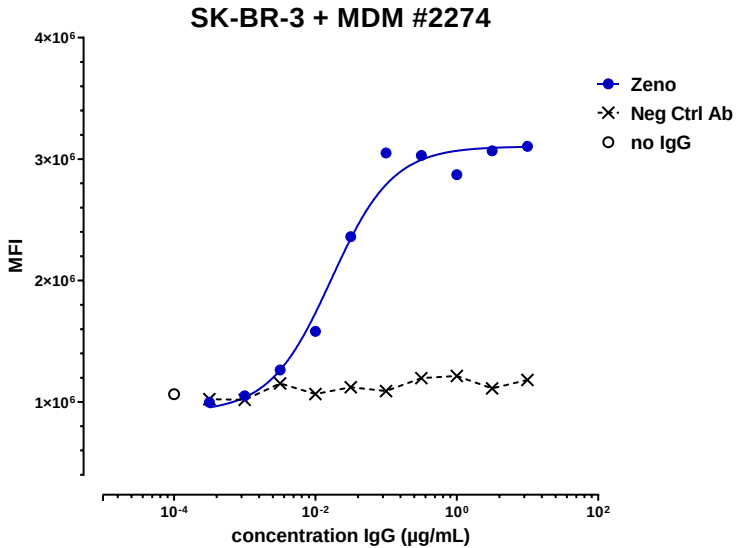
**Zeno (10 µg/mL)**



**Neg Ctrl Ab (µg/mL)**

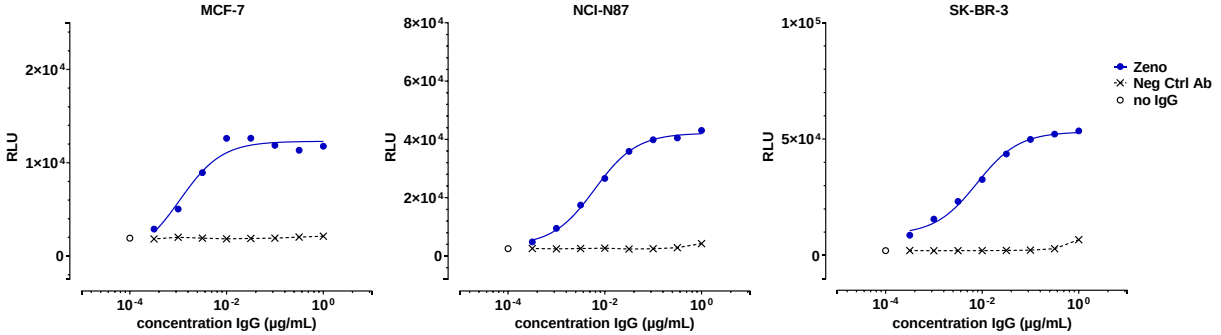


Red cells = cells in phagosomes (pHrodo-Red fluorescence > 10 RCU)

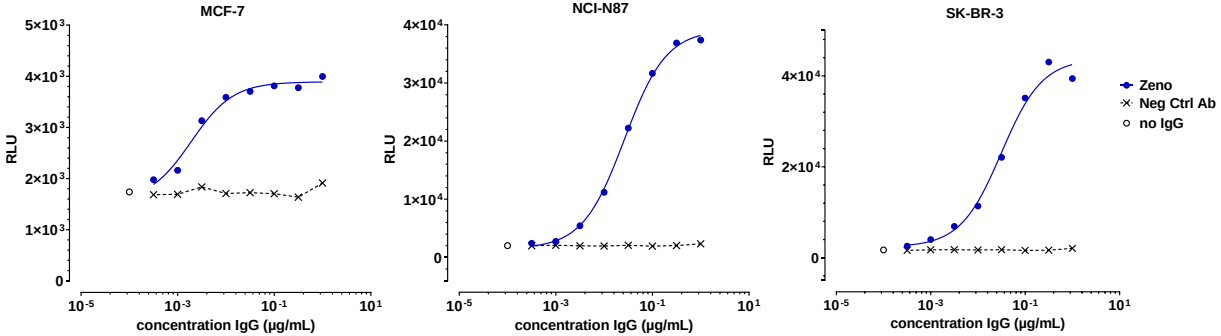


# Zeno mediates antibody dependent cellular toxicity of cancer cells (ADCC)

FcγRIIIa V158 (high affinity)




FcγRIIIa F158 (low affinity)




| | | | |
|---|---|---|---|
| **HER2 expression** | Low | High | High |
| **HER3 expression** | High | Low | High |

**Zeno mediates ADCC with all tested cell lines irrespective of the Fc-gamma receptor polymorphism, or the expression level HER2 or HER3.**

# Summary and conclusions

- Zeno potently blocks NRG1-fusion mediated downstream signaling and growth in vitro and in vivo.
  - The Dock & Block® mechanism enhances the potency of Zeno 100-fold as compared to an anti-HER3 antibody alone.

- Zeno induces immune effector function mediated killing of cancer cells
  - ADCC and ADCP are Fc-mediated dose-dependent.

- The two distinct mechanisms of action of Zeno - inhibition of downstream signaling of HER3 and immune effector function support the clinical efficacy of Zeno demonstrated in patients with NRG1 fusion-driven cancers
  - As of Sept 1 more than 80 patients are enrolled in our clinical program (www.nrg1.com).