KTN3379 is an IgG1 monoclonal antibody against ErbB3 that inhibits both ligand-dependent and independent activation.

- Three point mutations (YTE) in the Fc region of KTN3379
- Treatment of BRAF mutant cell lines with trametinib or vemurafenib for 24 hours results in cell-surface upregulation of ErbB3, as determined with an anti-ErbB3 antibody (left), or fluorescently-labeled NRG1 (right)

**Results**

- NRG1 and NRG2 are highly expressed in BRAF Mutated Thyroid Cancer and Melanoma, Respectively
- NRG1 and NRG2 RNA expression was surveyed in different BRAF mutated tumor types
- NRG1 is highly expressed in thyroid cancer, whereas NRG2 is highly expressed in melanoma

**Conclusions**

- Targeting ErbB3 with KTN3379 hampers adaptive resistance to BRAF/MEK inhibitors in tumors with an oncogenic MAPK signaling drive
- ErbB3 is upregulated in response to BRAF/MEK inhibition
- NRG-stimulated activation of ErbB3 and AKT is potentiated dose dependently with trametinib or vemurafenib treatment of BRAF mutant tumor cell lines
- NRG attenuates the antiproliferative effects of BRAF/MEK inhibitors, however treatment with KTN3379 resensitizes the tumor cells to inhibitors
- Tumors with a high prevalence of BRAF mutation express NRG1 (thyroid) and/or NRG2 (melanoma) which may provide autocrine stimulation of ErbB3 and contribute to adaptive resistance to BRAF/MEK inhibitors
- NRG1 is the most potent ErbB3 ligand tested
- An ongoing Phase 1b study combining KTN3379 with vemurafenib in BRAF mutated tumors support further development in BRAF mutant cancer and other settings (eg., Head & Neck cancer)