Combination of Neuregulin with EGFR Activation Signatures are Potential Biomarkers of Activity of KTN3379, an Anti-ErbB3 Antibody, in HNSCC

Summary

- KTN3379 is an IgG1 monoclonal antibody that binds to a unique epitope in ErbB3 and locks the receptor in its inactive state
- KTN3379 potently inhibits both NRG-dependent and independent ErbB3 activation
- YTE substitutions in the Fc region of KTN3379 enhance serum half life and target exposure

Here we demonstrate that:
- NRG, an activating ErbB3 ligand is overexpressed in HNSCC tumors
- ErbB receptors (EGFR, HER2, and ErbB3) are widely expressed in HNSCC
- ErbB3 activation requires HER2 but not EGFR
- Dual ERK and AKT pathway inhibition requires combined EGFR and ErbB3 inhibition
- EGFR activation signatures (AREG, TGFα, and EGFR homodimers) enrich for KTN3379 activity

Results

3 KTN3379 Enhances Cetuximab Activity in a Subset of HNSCC Models

- Combination of KTN3379 with cetuximab enhances single agent activity in vitro and in vivo

6 High Levels of AREG and TGFα Enrich for KTN3379 Activity in HNSCC Models

- High levels of secreted AREG and TGFα in HNSCC cell lines correlate with KTN3379 activity

9 Ongoing Phase 1b Evaluation of KTN3379 Combinations in Selected Tumors

- MTD not established with KTN3379 monotherapy up to maximum administered dose of 20 mg/kg
- Most common toxicities for KTN3379 alone or in combination have included diarrhea and rash
- KTN3379 can be combined with vemurafenib, cetuximab, erlotinib, trastuzumab at 15 to 20 mg/kg QW
- All patients achieved serum concentration above those required for maximal antitumor activity in animal tumor models
- Pharmacodynamic biomarker analyses showed soluble circulating ErbB3 levels were increased in all patients at all doses
- Preliminary tumor response (HNSCC, NSCLC, CRC) data support Phase 2 studies in HNSCC and BRAF mutant tumors:
  - 1 CR in cetuximab-resistant HNSCC patient
  - 2 PR in BRAF mutant HSCC
  - Durable SD in BRAF mutant CRC
- Ongoing biomarker-oriented Window of Opportunity clinical study in HNSCC patients
- Plans for Phase 2 trial in HNSCC

**Table 1:**

- NRG is most highly overexpressed in HNSCC tumors.
- Higher NRG expression in HPV- and PDX cell subsets within HNSCC.

**Table 2:**

- ErbB receptors are widely expressed in HNSCC.
- HER2 (H2T) is detectably expressed in most HNSCC tumors and cell lines.
- Widespread expression of EGFR (H1T) and HER2 (H2T) in HNSCC tumors and cell lines.

**Table 3:**

- Treatment with pan-erbB (anti-HER) inline, but not cetuximab, inhibits ErbB3 phosphorylation.

**Table 4:**

- Combination of KTN3379 with cetuximab enhances single agent activity in vitro and in vivo.