ErbB3 (HER3) and its ligand, neuregulin-1 (NRG1), are widely expressed in head and neck squamous cell carcinoma (HNSCC) and associated with tumor progression. ErbB3 may provide a key mechanism of resistance to therapies targeting EGFR and HER2. Human papillomavirus negative (HPV-) tumors, typified by poorer prognosis, have shown favorable response to ErbB3-targeted therapy.

CDX-3379: A Novel, Fully Human IgG1 Anti-ErbB3 Monoclonal Antibody

Characteristics and mechanism of action:
- Half-life-extending Fc region YTE mutation, binds to a unique epitope in ErbB3, locks the receptor in an inactive configuration.
- Blocks both ligand-dependent and ligand-independent ErbB3 signaling.

CDX-3379 Prevents ErbB Dimer Formation

CDX-3379 and cetuximab combined inhibit AKT and ERK pathways.

CDX-3379 Improves Anti-Tumor Activity in Combination with Cetuximab in Preclinical Model of HNSCC

CDX-3379 demonstrated significant single agent activity and enhanced cetuximab anti-tumor activity in HNSCC xenograft FaDu model. Animals dosed 2X/wk at 10 mg/kg. Asterisks denote statistical significance; *** p-value <0.001.

Previous Phase 1 clinical studies in 82 patients have shown:
- Favorable pharmacologic profile, with slower clearance than other anti-ErbB3 agents in the clinic.
- Single-agent CDX-3379 (up to 20 mg/kg every 3 weeks) was generally well tolerated.
- In combination with targeted therapies:
  - Acceptable and manageable safety profile consistent with other ErbB3-targeting therapies.
  - Durable complete response (CR) with CDX-3379 and cetuximab in a patient with previous cetuximab-refractory HPV-HNSCC.
  - Two patients with BRAF-mutant non-small cell lung cancer (NSCLC), one dabrafenib-resistant, experienced partial responses (PR) to CDX-3379 and vemurafenib.
  - As monotherapy (two 1000 mg doses at a 2-week interval) prior to planned HNSCC resection:
    - Phosphorylated ErbB3 decreased in post-treatment tumor samples for 10/12 (83%) patients.
  - 11/12 (92%) patients experienced RECIST stable disease pre-resection.
  - Exceptional clinical response: one patient with large, fungating floor-of-mouth tumor experienced 92% shrinkage of primary tumor by physical exam, with marked improvement in pain and ability to eat.

NCT02524927 is a Phase 2, multi-center, open-label, single-arm clinical trial to determine whether the combination of CDX-3379 and cetuximab can overcome resistance to cetuximab.

Key Eligibility Criteria:
- Recurrent/metastatic HPV-negative HNSCC, not curable with local treatment (e.g., surgery, radiation).
- Cetuximab resistance (progression within 6 months).
- Prior PD-1 targeted checkpoint inhibition, unless not a candidate.
- RECIST 1.1 measurable disease.
- ECOG 0 or 1; life expectancy ≥ 12 weeks.
- No active brain metastases.
- No nasal, paranasal sinus, or nasopharyngeal WHO Type III carcinoma.

STUDY DESIGN

NCT02014909 Phase IIb of CDX-3379 Alone and in Combination with Targeted Therapy in Advanced Solid Tumors N = 64

NCT02473371 Phase I Preoperative Window-of-Opportunity Study in Resectable HNSCC N = 12

NCT02456701 Phase I Pilot Study of CDX-3379 and Vemurafenib in BRAF Mut Radioiodine-refractory Thyroid Cancer N = 6

STUDY ASSESSMENTS

- Tumor response (MRI/CT): Every 6 weeks during treatment.
- Tumor biopsy: Screening, Cycle 2, and at progression.
- Safety and toxicity assessments.
- CDX-3379 pharmacokinetics and immunogenicity.

STUDY ENDPOINTS / HYPOTHESIS

Primary Objective:
- Objective Response Rate (ORR): CR or PR, per RECIST 1.1.
- Study hypothesis: H0 = ORR ≤ 5%, HA = ORR 20%, 80% power, α = 0.05 (threshold for positive study ≥ 4 PR/CR in 27 patients).

Secondary Objectives:
- Clinical benefit response (PR/CR or SD ≥ 4 months), duration of response, progression-free survival, overall survival, safety, pharmacokinetics, immunogenicity.

Exploratory Objectives:
- Biomarkers (HER3, NRG1, AREG and TGF-α) in pre- and post-treatment tumor samples.

STUDY STATUS

- Open to enrollment: November 2017.
- 4 active, enrolling clinical sites.
- Approximately 10 U.S. sites planned.

References:
1. Shames D, 2013
2. Takikita M, 2011
3. Arteaga C, 2003
5. Jiang N, 2014
8. Vermorken J, 2013
12. Duvvuri U, 2018