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Abstract # TPS6091

A phase 2, multicenter, open-label study to evaluate the efficacy and safety of CDX-3379 in combination with cetuximab in patients with advanced head and neck squamous cell carcinoma

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BACKGROUND

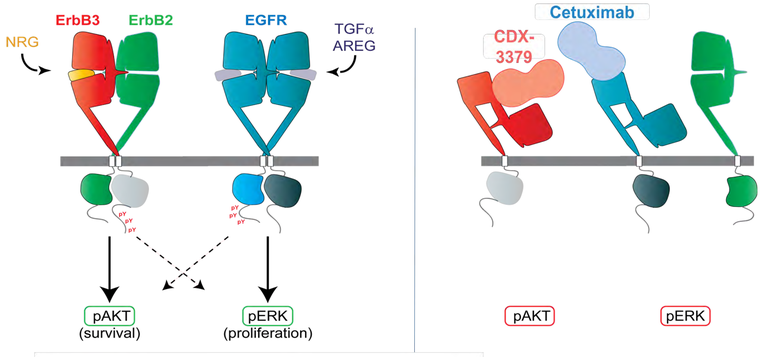
- ErbB3 (HER3) and its ligand, neuregulin-1 (NRG1), are widely expressed in head and neck squamous cell carcinoma (HNSCC) and associated with tumor progression[1,2]
- ErbB3 may provide a key mechanism of resistance to therapies targeting EGFR and HER2[3,4,5,6]
- Human papillomavirus negative (HPV-) tumors, typified by poorer prognosis, have shown favorable response to ErbB3-targeted therapy[7,8]

CDX-3379: A Novel, Fully Human IgG1λ Anti-ErbB3 Monoclonal Antibody

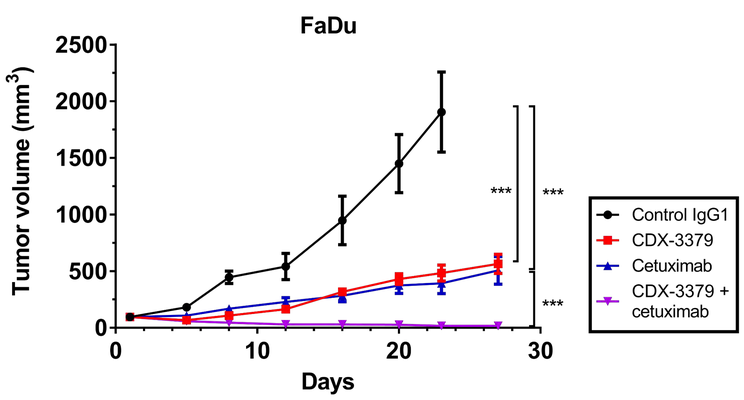
Characteristics and mechanism of action:

- Half-life-extending Fc region YTE mutation, binds to a unique epitope in ErbB3, locks the receptor in an inactive configuration[9]
- Blocks both ligand-dependent and ligand-independent ErbB3 signaling[9]

CDX-3379 Prevents ErbB Dimer Formation



CDX-3379 Improves Anti-Tumor Activity in Combination with Cetuximab in Preclinical Model of HNSCC[10]



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

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PRIOR CLINICAL EXPERIENCE

NCT02014909
Phase 1/1b of CDX-3379 Alone and in Combination with Targeted Therapy in Advanced Solid Tumors[11]
N = 64

NCT02473731
Phase 1 Preoperative Window-of-Opportunity Study in Resectable HNSCC[12]
N = 12

NCT02456701
Phase 1 Pilot Study of CDX-3379 and Vemurafenib in BRAF Mut Radioiodine-refractory Thyroid Cancer
N = 6

Previous Phase 1 clinical studies in 82 patients have shown[11,12]:

- 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

STUDY DESIGN

NCT03254927 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

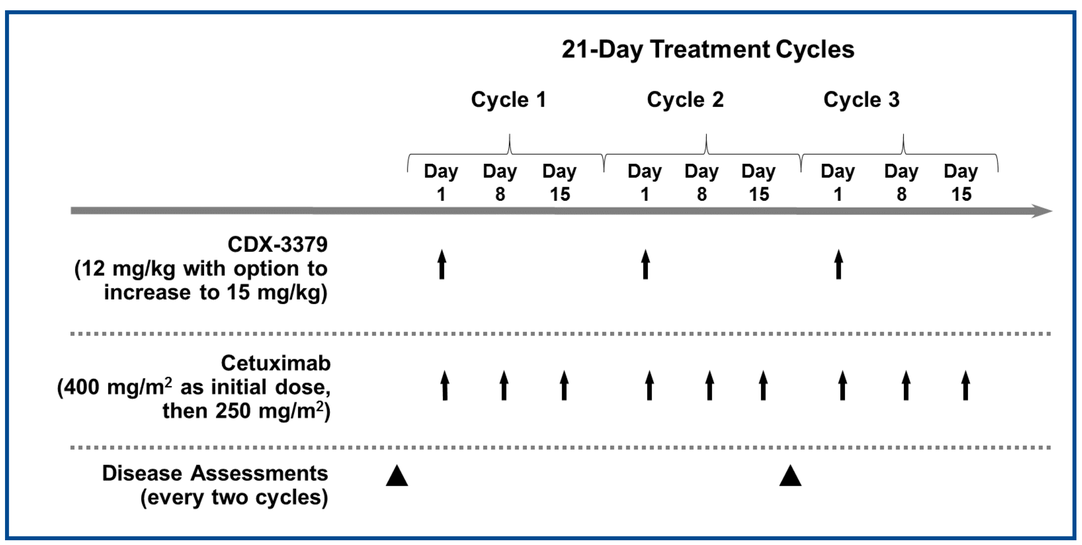
- Recurrent/metastatic HPV-negative HNSCC, not curable with local treatment (e.g., surgery, radiation)
- Cetuximab resistance (progression within 6 months)
- Prior PD-1 targeted checkpoint inhibition, unless not a candidate
- RECIST 1.1 measurable disease
- ECOG 0 or 1; life expectancy ≥ 12 weeks
- No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

Simon's 2-stage design

Stage 1
N = 13

≥1 Response (CR/PR)

Stage 2
N = 14



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: H_0 = ORR ≤ 5%, H_A = 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

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