CDX3379-04: Phase 2 Evaluation of CDX-3379 in Combination with Cetuximab in Patients with Advanced Treatment-Refractory Head and Neck Squamous Cell Carcinoma

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BACKGROUND

- ErbB3 signaling may contribute to resistance to targeted therapies such as cetuximab
- CDX-3379 is a fully human anti-ErbB3 monoclonal IgG1λ antibody with extended serum half-life and a potent inhibitor of ErbB3 activation via a unique mechanism of action that locks ErbB3 in an inactive configuration[1]
- CDX-3379 antitumor activity has been observed in patients with head and neck squamous cell carcinoma (HNSCC) patients in previous clinical studies:
  - In a phase 1b study, a durable complete response (CR) with CDX-3379 and cetuximab in a patient with cetuximab-refractory HPV(-) HNSCC[2]
  - In a window of opportunity study, an exceptional clinical response in a patient with HPV(-) HNSCC[3]

CDX3379-04 STUDY DESIGN

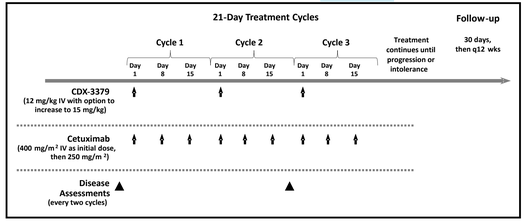
NCT03254927 is a phase 2, multicenter, open-label, single-arm clinical trial to evaluate safety and efficacy of CDX-3379 in combination with cetuximab in patients with advanced HNSCC

Key Eligibility Criteria

- **Recurrent/metastatic HPV(-) HNSCC, not curable with local treatment (eg, 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 OBJECTIVES

Primary Objective: Objective Response Rate (ORR): CR or PR (RECIST 1.1)
Secondary Objectives: Clinical benefit rate, duration of response, progression-free survival, overall survival, safety, pharmacokinetics, immunogenicity
Exploratory Objectives: Biomarker analysis

STAGE 1 RESULTS

Patient Demographics (N=15)

Median Age, years (range)		61 (46-68)
Male:		11 (73%)
Race:	White	13 (87%)
	Black	1 (7%)
	Asian	1 (7%)
ECOG at Baseline:	0	1 (7%)
	1	14 (93%)
Smoking or Tobacco Use:	Prior Smoker	13 (87%)
Site of Primary Tumor:	Oral Cavity	8 (53%)
	Pharynx	5 (33%)
	Larynx	1 (7%)
	Other	1 (7%)
P16 Status: (only required for pts with oropharyngeal tumors)	Negative	7 (47%)
	Positive	1 (7%)
	Not Done	7 (47%)
# Prior Regimens, median (range)		3 (2-6)
Prior Treatment with Cetuximab		14* (93%)
Prior Checkpoint Inhibitor		15 (100%)

Exposure to Study Drug

CDX-3379 Median # doses (min, max)		3 (1, 16)
Cetuximab Median # doses (min, max)		6 (1, 46)
Duration of treatment	< 3 months	12 (80%)
	3 - 6 months	2 (13%)
	≥12 months	1 (7%)
Dose Reductions, Delays and/or Holidays		10 (67%)
Reasons for Discontinuing Study Treatment	Disease Progression	7 (47%)
	Clinical Progression	4 (27%)
	Adverse Event	2 (13%)
	Death	1 (7%)
Ongoing Treatment		1 (7%)

Safety

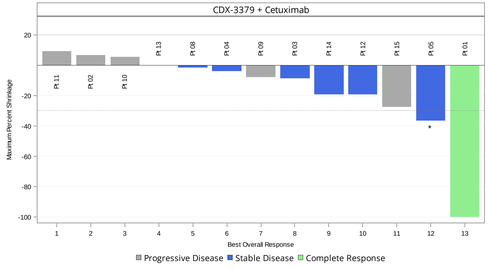
CDX-3379 Treatment-Related AEs (N=15) ≥10% or ≥G3 in ≥ 2 patients	Overall N (%)	Grade 3-5 N (%)
Diarrhea	10 (67)	4 (27)
Fatigue	2 (13)	-
Hypokalemia	4 (27)	3 (20)
Hypomagnesemia	3 (20)	2 (13)
Electrocardiogram QT prolonged	2 (13)	1 (7)
Mucositis	3 (20)	2 (13)
Palmar-plantar erythrodysesthesia syndrome	2 (13)	-
Rash	2 (13)	1 (7)

AEs, adverse events. Three patients experienced serious treatment-related AEs including diarrhea, QT prolongation and mucosal inflammation.

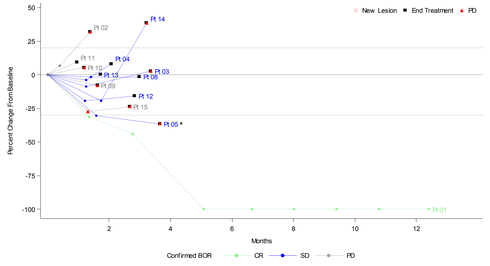
Efficacy

Best Overall Response (BOR) (N=15)	n (%)
Complete Response (CR)	1 (7%)
Partial Response (PR)	0 (0%)
Stable Disease (SD)	7 (47%)*
Progressive Disease (PD)	6 (40%)
Not Evaluable (NE)	1 (7%)
Clinical Benefit Rate (N=14)	
SD ≥ 12 weeks	3 (21%)
Clinical Benefit Rate (Objective Response or SD ≥12 wks)	4 (29%)

Best Overall Response – Response Evaluable Population**



Spider Plot of Tumor Burden – Response Evaluable Population**



* Includes one cetuximab-naïve patient, who experienced a single-timepoint PR
**Two patients did not have a post-baseline disease assessment

EXPLORATORY BIOMARKER ANALYSIS

- Next-generation sequencing was performed targeting >1400 cancer-related genes
- The analysis included 18 HNSCC tumor samples from three CDX-3379 clinical studies:
  - CDX3379-01 Phase 1b (CDX-3379 + cetuximab): one patient with cetuximab-refractory, HPV(-) HNSCC with a durable complete response
  - CDX3379-02 (CDX-3379 monotherapy; window of opportunity study): 3 patients, including a patient with an exceptional clinical response (92% tumor shrinkage assessed by physical examination after 2 doses of CDX-3379 every 2 weeks)[3]
  - CDX3379-04 (CDX-3379 + cetuximab): 14 patients, one ongoing, durable complete response (11+ months) and one unconfirmed partial response

	Responders																	
Study	*3379-01*	3379-04	3379-04	*3379-02*	3379-04	3379-04	3379-04	3379-04	3379-04	3379-04	3379-04	3379-04	3379-04	3379-04	3379-04	3379-04	*3379-02*	*3379-02*
Patient ID	*Pt A*	Pt 01	Pt 05*	*Pt B*[†]	Pt 04	Pt 08	Pt 12	Pt 14	Pt 03	Pt 13	Pt 02	Pt 09	Pt 10	Pt 15	Pt 11	Pt 06	*Pt C*[†]	*Pt D*[†]
Primary Tumor	*Oral Cavity*	Oral Cavity	Oral Cavity	*Oral Cavity*	Oro-pharynx	Oral Cavity	Hypo-pharynx	Oral Cavity	Larynx	Oro-pharynx	Naso-pharynx	Oral Cavity	Oral Cavity	Oral Cavity	Hypo-pharynx	Oral Cavity	*Oral Cavity*	*Pharynx*
HPV Status	*Negative*	Negative	Not tested	*Negative*	Negative	Not tested	Not tested	Negative	Not tested	Negative	Not tested	Negative	Negative	Not tested	Negative	Positive	*Negative*	*Positive*
Best Response	***CR***	**CR**	uPR	*Exceptional Response*	SD (≥12 wks)	SD (≥12 wks)	SD (≥12 wks)	SD	SD	SD	PD	PD	PD	PD	PD	PD	*0% Shrinkage*	*-16% Shrinkage*
TP53																		
PIK3CA																		
FAT1																		
NOTCH1																		
NOTCH2																		
NOTCH3																		
NOTCH4																		

CR: complete response; uPR: unconfirmed partial response; SD: stable disease; PD: progressive disease
Tumor samples from the CDX3379-01 and CDX3379-02 studies are italicized
[†]Per protocol, surgery was conducted following 2nd dose of CDX-3379

- FAT1 mutations were identified in all patients considered responders in this analysis
- NOTCH1, NOTCH2 or NOTCH3 mutations also appeared to be enriched in patients in whom clinical activity was observed
- Inactivating mutations in the FAT1 and NOTCH genes have been identified in 32% and 26% of HPV(-) HNSCC tumors, respectively[4]
- Loss of FAT1 function results in activation of the transcriptional cofactor YAP1[5]; YAP1 has been shown to upregulate components of ErbB signaling pathways[6,7], including the ErbB3 ligand NRG1[8]
- Preclinical studies investigating the association of CDX-3379 sensitivity and inactivating mutations of FAT1 and other genes are ongoing

CONCLUSIONS AND FUTURE DIRECTIONS

- Clinical activity has been observed in the CDX3379-04 study, including a durable complete response (11+ months) and tumor shrinkage, in patients with advanced, recurrent, HPV(-) HNSCC, where treatment options are limited
  - Clinical Benefit Rate of 29% was achieved
  - Dose reductions and/or delays to the combination therapy in the majority of patients may have impacted the magnitude of antitumor activity; dose modifications are being considered for future studies
  - CDX-3379 in combination with cetuximab was associated with the expected target-mediated adverse events of diarrhea and rash
- Across the CDX-3379 studies, mutations in FAT1 and NOTCH1, NOTCH2, or NOTCH3 and primary tumor site of oral cavity were associated with clinical activity in HNSCC
  - All 4 responding patients had FAT1 mutations and primary tumor site of oral cavity
  - Three of the responding patients also had NOTCH1, NOTCH2, or NOTCH3 mutations
- Future CDX-3379 development will focus on the clinical utility of biomarker-driven patient selection

References
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