Molecular and Clinical Activity of CDX-3379, an Anti-ErbB3 Monoclonal Antibody, in Head and Neck Squamous Cell Carcinoma: A Preoperative "Window-of-Opportunity" Study

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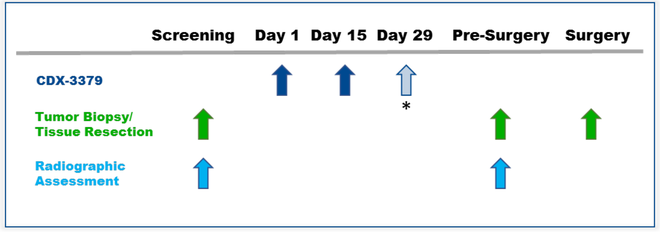
BACKGROUND

- 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, a central enabler for multiple RTKs including EGFR and HER2, may provide a path of resistance to targeted therapies [3,4]
- CDX-3379, an anti-ErbB3 monoclonal antibody with a half-life-extending Fc region YTE mutation, binds a unique epitope with high affinity, blocking both ligand-dependent and independent signaling
- In preclinical HNSCC models, CDX-3379 results in significant tumor reduction and reduced tumor ErbB3 signaling, and antitumor activity is enhanced when combined with cetuximab [5]
- A previous Phase 1 clinical study showed:
  - Favorable pharmacologic profile, with longer half-life and slower clearance than other anti-ErbB3 agents in the clinic
  - Single-agent CDX-3379 (up to 20 mg/kg every 3 weeks) well-tolerated
  - In combination with targeted therapies; acceptable and manageable safety profile consistent with other ErbB3-targeting therapies
  - Patient with cetuximab-refractory HNSCC experienced a durable complete response to CDX-3379 and cetuximab [6]

STUDY DESIGN

Open label "window of opportunity" study in patients with newly diagnosed, operable HNSCC

- Up to 3 CDX-3379 doses (1000 mg IV) at a 2-week interval prior to tumor resection
- Primary objective: Effect on ErbB3 signaling as measured by fit-for-purpose assay of tumor phosphorylated ErbB3 (pErbB3)
  - 29 patients planned to provide 80% power to determine if ≥ 30% of patients have ≥ 50% reduction in pErbB3
- Secondary objectives included assessment of other potential biomarkers, toxicity, pharmacokinetics, immunogenicity, and tumor measurements
- Study closed after enrollment of 12 patients; final results are presented



* 3rd CDX-3379 dose allowed if surgery planned > 14 days after 2nd dose of CDX-3379 (no patient received 3 doses)

RESULTS

Baseline Disease Characteristics

	Enrolled Patients (N=12)
Male, n (%)	10 (83)
Age, median (years), range	56.5 (45, 61)
Squamous cell histology, n (%)	12 (100)
Tumor HPV status, n (%)	
Positive	3 (25)
Negative	9 (75)
Primary tumor location, n (%)	
Oral cavity	5 (42)
Oropharynx	4 (33)
Larynx	3 (25)
Cancer stage, n (%)	
IVA	10 (83)
III	1 (8)
II	1 (8)

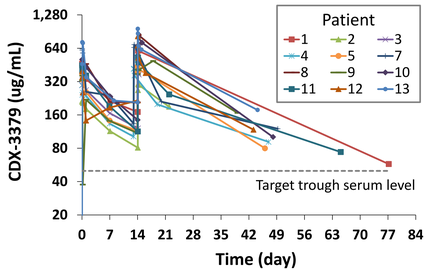
HPV, Human papilloma virus

Exposure and Tolerability

- All patients received two doses of CDX-3379
- Treatment-related toxicity all grade 1-2; most common were diarrhea (n=6), fatigue (n=2), and dermatitis acneiform (n=2)
- No treatment-related serious adverse events

Pharmacokinetics and Immunogenicity

- Target trough CDX-3379 serum levels (50 µg/ml based on mouse xenograft models) achieved
- Mean half-life from first dose: 11.5 days
- 1 patient transiently positive for anti-CDX-3379 antibodies; did not correlate with changes in PK

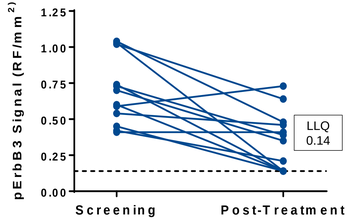


Tumor Biomarker Studies

- All patients underwent tumor resection at a median of 27.5 (range: 18-35) days (equivalent to 13.5 days [range 4 to 21] after 2nd CDX-3379 dose)
- Post-treatment analyses included change in pErbB3 (VeraTag®[7]) and Ki67; expression of ErbB3, NRG (quantitative in situ hybridization); and phosphatase and tensin homolog (PTEN) (quantitative immuno-fluorescence)

Primary endpoint: pErbB3

- 7/12 (58%) patients with > 50% decrease in pErbB3 (p=0.04)
- 4/12 (33%) with pErbB3 below detection level
- 10/12 (83%) with any reduction
- 2 patients without decrease had samples taken at 20 & 21 days post last CDX-3379 dose



Additional biomarker studies

- NRG1 is widely expressed in HNSCC; data did not support a cut-point for CDX-3379 treatment
- Loss of, or low, PTEN reported in 25-30% of HNSCC and potentially prognostic for cetuximab treatment [8,9,10]
- No correlation of post-treatment NRG1, ErbB3 and PTEN expression with changes in pErbB3, Ki67 or tumor measurements (in this small sample size)

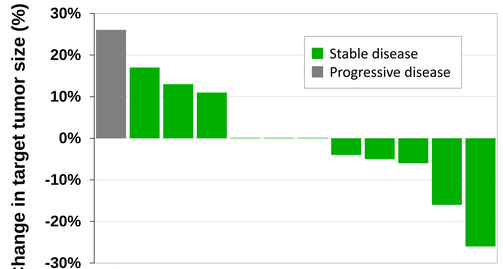
Patient Number	HPV status	% Change, Pre to Post-Treatment		Post Treatment Tumor Resection Samples				Tumor Measurement (% Change)
		pErbB3	Ki67	NRG1	NRG2	ErbB3	PTEN +/Loss	
10	-	-86%	-92%	+	-	+	+	0
11	-	-81%	-17%	+	-	+++	Loss	-4
8[b]	+	-77%	-26%	+	-	+	Loss	-6
12	-	-69%	+34%	++	-	+	+	-26
9	+	-54%	+8%	+	-	+++	+	26
4[a]	-	-51%	+14%	+	+	+	+	0
13	-	-50%	+752%	++	-	-	+	17
1	-	-47%	+125%	+++	-	+	+	-5
7	-	-37%	-47%	+	-	++	+	0
2[a]	+	-15%	-95%	++	++	++++	+	-16
5	-	0%	+43%	+	-	++++	+	13
3[a]	-	+22%	+100%	+	-	+	+	11

a. NRG1, NRG2, ErbB3, PTEN assessments completed using baseline biopsy samples
b. Insufficient post-treatment biopsy tumor tissue available; surgical resection sample used for pErbB3 assessment

- not different from the negative control
+ expression level of 1.2 - 2.5
++ expression level of 2.6 - 3.8
+++ expression level of 3.9 - 5.2
++++ >5.2 (values 18.5 and 17.5)

Tumor Response

- 11/12 (92%) patients had RECIST stable disease prior to resection



Radiographic assessments performed at a median (range) of 20.5 (15-26) days from first CDX-3379 dose.

Patient with marked clinical response:

- Recently diagnosed HPV-negative squamous cell carcinoma of the floor of the mouth
- Large, fungating tumor associated with eating difficulties and significant pain requiring analgesics
- Tumor regression observed within 24 hours of 1st CDX-3379 dose, with the majority of decrease occurring within 48 hours. Pain decreased markedly (from 8/10 to 2/10) in same timeframe.
- 92% decrease in primary tumor by physical exam; 26% decrease in nodal metastasis radiographically
- pErbB3 reduced from 0.45 to <0.14

CONCLUSIONS

- CDX-3379 is associated with molecular and clinical activity in HNSCC
- CDX-3379 administration was well-tolerated and induced a significant decrease in pErbB3
- In this small study of 2 CDX-3379 doses over 14 days, one patient experienced a marked clinical effect including reduced tumor size and symptomatology, and 92% had stable disease pre-resection
- A Phase 2 study has been initiated to evaluate the combination of CDX-3379 and cetuximab for patients with progressive HNSCC after prior cetuximab and checkpoint inhibition

1. Shames 2013
2. Takikita, 2011
3. Arteaga, 2003
4. Arteaga, 2014
5. Alvarado, 2017
6. Falchook, 2016
7. Mukherjee, 2011
8. da Costa, 2015
9. Snietura, 2012
10. Psyrri, 2014

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