Molecular and Clinical Activity of CDX-3379, an Anti-ErbB3 Monoclonal Antibody, in Head and Neck Squamous Cell Carcinoma Patients

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Abstract

Purpose: ErbB3 and its ligand neuregulin-1 (NRG1) are widely expressed in head and neck squamous cell carcinoma (HNSCC) and associated with tumor progression. A "window-of-opportunity" study (NCT02473731) was conducted to evaluate the pharmacodynamic effects of CDX-3379, an anti-ErbB3 mAb, in patients with HNSCC.

Patients and Methods: Twelve patients with newly diagnosed, operable HNSCC received two infusions of CDX-3379 (1,000 mg) at a 2-week interval prior to tumor resection. The primary study objective was to achieve ≥50% reduction in tumor ErbB3 signaling (phosphorylation of ErbB3; pErbB3) in ≥30% of patients. Other potential tumor biomarkers, pharmacokinetics, safety, and tumor measurements were also assessed.

Results: pErbB3 was detectable in all tumors prior to treatment and decreased for 10 of 12 (83%) patients following CDX-3379 dosing, with ≥50% reduction in 7 of 12 (58%; P = 0.04; 95% confidence interval, 27.7%–84.8%). Target trough CDX-3379 serum levels were achieved in all patients. CDX-3379 treatment-related toxicity was grade 1–2 and included diarrhea, fatigue, and acneform dermatitis. Five of 12 (42%) patients had shrinkage in tumor burden, including a marked clinical response in a patient with human papillomavirus-negative oral cavity HNSCC. All patients with tumor shrinkage had tumors that expressed both NRG1 and ErbB3 and demonstrated reduced pErbB3 with CDX-3379 treatment.

Conclusion: This study demonstrates that CDX-3379 can inhibit tumor ErbB3 phosphorylation in HNSCC. CDX-3379 was well tolerated and associated with measurable tumor regression. A phase II study (NCT03254927) has been initiated to evaluate CDX-3379 in combination with cetuximab for patients with advanced HNSCC.

Introduction

Despite the advent of EGFR-targeted therapies and immune checkpoint inhibitors, the median overall survival for patients with advanced human papillomavirus (HPV-) head and neck squamous cell carcinoma (HNSCC) remains less than 1 year. The best data to date for first-line palliative therapy is with the use of the EXTREME regimen (cetuximab in combination with platinum plus 5-fluorouracil chemotherapy followed by cetuximab; ref. 1). In 2016, two mAbs (pembrolizumab and nivolumab) targeting the programmed death-1 receptor were approved for the treatment of patients with platinum-refractory, recurrent/metastatic HNSCC (1, 2). Nivolumab improved overall survival compared with single-agent, investigator-choice chemotherapy, with a lower toxicity rate in a randomized phase III trial (3). Despite this exciting therapeutic advance, the response rate is only 13%, with a median progression-free survival of 2 months and median overall survival of 7.5 months. As such, there remains a pressing unmet clinical need to identify novel therapeutic targets.

ErbB3 or HER3 is a member of the EGFR human epidermal growth factor (HER/ErbB) family of receptor tyrosine kinases (RTK), which also includes EGFR, ErbB2 (HER2), and ErbB4 (HER4). The ErbB family of RTKs plays a role in the pathogenesis of many types of cancers, including lung, breast, colorectal, and head and neck. ErbB3 lacks detectable tyrosine kinase activity, and consequently needs to form heterodimers with other ErbB receptors to become active (4). In the presence of the ErbB3 ligand, NRG1, or NRG2, ErbB3 preferentially dimerizes with ErbB2, subsequently undergoing phosphorylation and enabling downstream signaling. NRG1 is expressed in the majority (>80%) of HPV-negative and-positive HNSCC tumors (5) and membranous ErbB3 expression is strongly associated with poor prognosis in HNSCC (6). While EGFR targeting with mAbs such as cetuximab have demonstrated clinical benefit, response rates are modest,
Translational Relevance

ErbB3 signaling is a known resistance mechanism to anti-EGFR therapies including cetuximab. The ErbB3 ligand neuregulin-1 (NRG1) is expressed in the majority of head and neck squamous cell carcinoma (HNSCC), suggesting that ErbB3 signaling is active in this tumor type and may contribute to tumor growth and resistance to therapy. A window-of-opportunity study was conducted in patients with HNSCC to characterize the biologic activity of CDX-3379, a human anti-ErbB3 mAb, and other potential biomarkers of response. Most tumors expressed NRG1 and had detectable ErbB3 phosphor-ylation (pErbB3) prior to treatment. CDX-3379 modulated tumor pErbB3 at target trough concentrations and tumor shrinkage was observed in a subset of patients, including a marked clinical response. These data indicate CDX-3379 inhibits ErbB3 in patients with HNSCC tumors and provide the rationale for further development of CDX-3379 in HNSCC and potentially other ErbB3- and NRG-expressing tumors.

suggesting contribution of additional tumor drivers and/or resistance mechanisms. We and others reported that signaling through ErbB3 stimulates tumor growth and mediates cetuximab resistance in preclinical HNSCC models (7). These data suggest ErbB3 may play a role in the pathogenesis of HNSCC.

CDX-3379 (previously known as KTN3379) is a human anti-ErbB3 mAb engineered with half-life extending YTE substitutions in the Fc region and reduced antibody-dependent cell-mediated cytotoxicity activity (8). Preclinically, significant tumor growth inhibition was observed in response to CDX-3379 treatment in HNSCC xenograft models (5). In a prior phase I/ib study (NCT02014909; ref. 9), CDX-3379 monotherap-y (up to 20 mg/kg every 3 weeks) was well tolerated without identification of a MTD. Target CDX-3379 serum trough levels of 50 μg/mL, which elicited maximal antitumor activity in preclinical models, were achieved with doses >10 mg/kg every 3 weeks. Treatment with the combination of CDX-3379 and cetuximab was associated with a durable complete response in a patient with HNSCC who had previously progressed on cetuximab (9).

The present "window-of-opportunity" study was conducted to evaluate the effect of CDX-3379 on tumor ErbB3 signaling (phosphorylation of ErbB3; pErbB3) in patients with newly diagnosed HNSCC. The CDX-3379 dose level (1,000 mg every 2 weeks) was chosen to exceed the established target serum trough levels that led to maximal antitumor efficacy in preclinical models. Pre- and posttreatment tumor samples were evaluated for changes in ErbB3 phosphorylation and proliferation (Ki67). Additional molecular analyses included expression of NRG1, NRG2, ErbB3, and phosphatase and tensin homolog (PTEN) as potential biomarkers of response to CDX-3379. Clinical assessments within the brief presurgical timeframe included safety and radiographic tumor assessments.

Patients and Methods

Patients

This study was open to adult patients ≥18 years of age with newly diagnosed HNSCC of the oral cavity, oropharynx, hypophasyms, or larynx who were planned for surgical resection. Other criteria included Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, adequate bone and marrow function, and contraceptive requirements. Exclusion criteria for the study included any prior or concurrent therapy for HNSCC, systemic steroids within 7 days of first study dose (allowable exception of inhaled or topical corticosteroids), another invasive malignancy within 2 years prior to enrollment (excepting localized cancers), or uncontrolled intercurrent illness.

The study was conducted at the University of Pittsburgh Medical Center (Pittsburg, PA) and University of California San Francisco Medical Center (San Francisco, CA), was approved by institutional review boards and the FDA, and was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice. All patients gave written informed consent before any protocol-specific procedures. This study is registered with ClinicalTrials.gov (NCT02473731).

Study design, treatments, and procedures

In this single-arm, open-label "window-of-opportunity" study, eligible, consented patients with newly diagnosed, operable HNSCC received treatment with CDX-3379 in the window prior to planned surgical resection. CDX-3379, at a dose of 1,000 mg, was administered as a 60-minute intravenous infusion, at a 2-week interval. Surgery was scheduled as soon as possible and ideally within 14 days after the second dose of CDX-3379. A third dose of CDX-3379 was permitted in the event of a scheduling delay resulting in surgery at ≥2 weeks following the second dose.

Safety assessments performed prior to and throughout study treatment included physical exam, vital signs, electrocardiogram, echocardiogram, or multigated acquisition scan, and routine chemistry, hematology, coagulation, and urinalysis panels. Toxicity was assessed through 30 days posttreatment and graded per National Cancer Institute Common Terminol-ogy Criteria for Adverse Events version 4.03. Radiographic imaging (CT or MRI) was performed pretreatment and posttreatment prior to resection. Tumor measurements were assessed by investigators according to the RECIST 1.1 (10). Blood samples were obtained for pharmacokinetic and immuno-necity analyses prior to each CDX-3379 infusion, on the day of surgery, and at 30 days posttreatment. Pharmacokinetic samples were also obtained at 0, 1, and 4 hours after comple-tion of each infusion, with additional samples after the first infusion at 24 hours and day 8.

Tissue acquisition and correlative studies

Biomarker expression analysis was conducted on pre- and posttreatment biopsy and surgical resection samples. Given the sensitivity of phosphorylated proteins to method preparation, posttreatment biopsy samples were collected on the day of surgery before devascularization or resection of the tumor specimen to provide matched pre- and posttreatment samples with consistent preparation and fixation methods for pErbB3 analysis. Tumor tissue was also obtained from the resection specimens to ensure sufficient amount of tissue for remaining analyses.

Three to 4 tissue samples were taken either by incisional biopsy or punch biopsy, immediately fixed in 10% neutral buffered formalin (NBF) for 6–72 hours, and then paraffin-embedded. Hematoxylin and eosin staining was used to confirm the presence of tumor.
ErbB3 (Tyr1289) mAb; Cell Signaling Technology). Released HER3 antibody (mouse monoclonal, B9A11; Monogram) and pharmaceutical services. Brieﬂey, an anti-YTE antibody is passively adsorbed to a standard MSD plate. Following incubation, washing, and blocking, CDX-3379-Sulfo-Tag was added as the secondary detection reagent. MSD read buffer containing TPA was added to the wells and the plate was read on an MSD Sector Imager 2400. The RLU signal generated from positive controls and test samples was proportional to the amount of anti-CDX-3379 antibody found in the sample. A screening cut-off point was determined from 50 normal human serum samples based on parametric method and a 5% false-positive rate.

Specificity of screened positive samples was conﬁrmed by immunodepletion with drug product using an inhibition cutoff point based on a 1% false-positive rate.

Statistical analysis

The primary study objective was to assess change in pErbB3 in tumor tissue before and after exposure to CDX-3379. Secondary objectives were to assess the effect of CDX-3379 on the Ki67 proliferative index in tumor tissue obtained pre- and posttreatment; identify candidate biomarkers for CDX-3379 pharmacodynamic response or resistance; evaluate the safety, tolerability, pharmacokinetics, and immunogenicity of CDX-3379; and changes in tumor measurements before and after exposure to CDX-3379. The relationship between pErbB3 and the tumor proliferation marker Ki67, tumor measurements, or other biomarker results were also evaluated.

A sample size of 29 patients was calculated to provide 80% power to determine whether ≥30% of patients demonstrated a ≥50% decrease in tumor pErbB3 levels following treatment with CDX-3379. However, enrollment was discontinued after the primary study objective was met in the ﬁrst 12 study patients. Statistical analysis for this measurement was calculated using the Clopper–Pearson exact conﬁdence interval.

Results

Patient characteristics

Twelve patients with newly diagnosed HNSCC were enrolled in this study between October 26, 2015 and June 29, 2016. Of the 12 enrolled patients, 10 were male while 2 were female, and median age was 56.5 years (range 45–61). Nine (75%) had HPV-negative and 3 (25%) had HPV-positive tumors. The most frequent primary tumor site was oral cavity (5; 42%), followed by oropharynx (4; 31%), and larynx (3; 25%). Median time from diagnosis to ﬁrst CDX-3379 dose was 31 days (range 14–48). Stage IVa disease was most prevalent (10; 83%); 1 patient presented with Stage III and 1 with Stage II disease (Table 1).

Study treatments and tolerability

All patients received two doses of CDX-3379. No treatment-related serious adverse events were reported. The most common treatment-related toxicities reported were diarrhea, fatigue, and dermatitis aciform (Table 2), all of which were mild or moderate. No study patients discontinued or required dose modiﬁcations due to toxicity.
Preoperative Study of the Anti-ErbB3 mAb CDX-3379 in HNSCC

NOTE: All treatment-related toxicity was

<table>
<thead>
<tr>
<th></th>
<th>All treated patients (N = 12)</th>
</tr>
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<tbody>
<tr>
<td>Days from diagnosis to treatment, median (range)</td>
<td>31 (14–48)</td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>56.5 (45–61)</td>
</tr>
<tr>
<td>Male</td>
<td>10 (83%)</td>
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<td>ECOG performance status</td>
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</tr>
<tr>
<td>ECOG 0</td>
<td>11 (92%)</td>
</tr>
<tr>
<td>ECOG 1</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Primary head and neck tumor type</td>
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</tr>
<tr>
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<td>5 (41.7%)</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>4 (33.3%)</td>
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<tr>
<td>Larynx</td>
<td>3 (25.0%)</td>
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<tr>
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<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
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<td>1 (8%)</td>
</tr>
<tr>
<td>II</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>III</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>IVA</td>
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</tr>
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<tr>
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<td>9 (75%)</td>
</tr>
<tr>
<td>Positive</td>
<td>3 (25%)</td>
</tr>
</tbody>
</table>

NOTE: Data shown as n (%). The values were rounded to the nearest whole number.

Pharmacokinetics and immunogenicity

On the basis of phase I clinical study data (9) with doses up to 20 mg/kg (comparable with single doses of up to 1,828 mg) every 3 weeks, it was determined that a 1,000 mg dose every 2 weeks would achieve trough serum concentrations of CDX-3379 exceeding those that resulted in maximal antitumor activity in preclinical models (50 ng/mL). As shown in Fig. 1, CDX-3379 serum levels in all patients exceeded the target pharmacokinetic trough levels for up to 77 days. Mean half-life in cycle 1 was calculated as 11.5 days, with mean clearance of 365 mL/day (Supplementary Table S1). A specific anti-CDX-3379 antibody response was observed at day 15 in 1 patient who was negative at baseline, but the preserection sample collected 4 days later was found to be nonspecific. No apparent impact on pharmacokinetic parameters was noted in association with this transient immunogenicity.

Molecular biomarkers in tumor samples

Pretreatment and posttreatment tumor samples were obtained for all 12 patients. Surgical resection occurred at a median of 27.5 days (range 18–35) after first CDX-3379 dose, corresponding to a median of 13.5 days (range 4–21) after last CDX-3379 dose.

Posttreatment tumor biopsy samples collected prior to surgery were used to determine pErbB3 levels, with the exception of patient 108-02, where the surgical resection samples were used because of insufficiency of the posttreatment sample. All pretreatment tumor samples had detectable levels of pErbB3 (range 0.41–1.04 RF/mm²). Decreased pErbB3 was observed in most posttreatment tumor samples, with a ≥50% decrease achieved in 7 of 12 (58%; P = 0.04; 95% confidence interval [CI], 27.7–84.8%) patients and 4 of 12 (33%) having posttreatment pErbB3 levels below the limit of detection of the assay (Fig. 2b; Table 3). The 2 patients (103-02 and 105-01) without a decrease in pErbB3 had posttreatment samples taken at 20 and 21 days post last CDX-3379 dose.

Of the 12 evaluable pre- and posttreatment tumor tissue sample pairs, 5 of 12 (42%) showed a decrease in Ki67 levels posttreatment, with two posttreatment tumor samples (102-02, HPV-positive and 110-01, HPV-negative) showing a ≥90% reduction in Ki67 in response to CDX-3379 treatment (Table 3; Supplementary Fig. S1A). However, this decrease was not statistically significant overall (Supplementary Fig. S1B). Decreases in Ki67 after CDX-3379 treatment did not associate with changes in pErbB3 (Table 3).

Tumor tissue was evaluated for NRG1, NRG2, and ErbB3 mRNA and PTEN protein expression (Table 3). Analysis of NRG1, NRG2, and ErbB3 mRNA expression was deemed more quantitative than IHC and requires less tissue than Western blotting. In addition, the large numbers of NRG1 isoforms are more reliably captured by mRNA-based methods. Furthermore, ErbB3 mRNA and protein expression were shown to correlate in a panel of HNSCC cell lines (Supplementary Fig. S2).

Tumor resection samples were used preferentially, although pretreatment biopsy samples were utilized for 3 patients. ErbB3 mRNA was detectable in 11 of 12 (92%) of tumor samples. One tumor sample (113-02) was negative for ErbB3 mRNA expression, but had detectable pretreatment pErbB3, which may reflect assay limitations. Most patient samples expressed either NRG1 (11/12), or NRG2 (2/12), consistent with the observation that pErbB3 was detectable in all pretreatment tumor samples. Loss of PTEN staining in tumor tissue was observed in 2 of 12 (17%) tumors. No clear relationships between NRG, ErbB3, or PTEN expression and changes in Ki67 or tumor measurements were observed (Table 3; Supplementary Fig. S3).

Tumor assessments and molecular correlations

Posttreatment radiographic assessments were performed at a median of 20.5 (range 15–26) days after the first CDX-3379 dose. At the posttreatment assessment, decreased tumor burden was observed for 5 of 12 (42%) patients, with shrinkage of the sum of target lesion diameters ranging from −4% to −26% (Fig. 3; Table 3). Three patients had no change in tumor size, while 3 had slight tumor growth, for a total of 11 of 12 (92%) of patients with RECIST stable disease during the preoperative period. One patient with HPV-positive disease experienced a 26% increase in target lesion burden, resulting in progressive disease.

Notably, a 14-year-old male patient with stage T4aN1M0 HPV-negative oral cavity HNSCC experienced a marked clinical response in association with CDX-3379 treatment (13). At baseline, the tumor on physical examination was large and fungating and was associated with eating difficulties and significant pain requiring analgesics. Within 48 hours of the first dose, the patient noted tumor shrinkage, a marked decrease in pain (from 8/10 to 2/10), and an improved ability to eat. The primary tumor site was...
not readily evaluable radiographically due to interference of dental amalgam, however nodal metastasis decreased by 26%, and the primary tumor size decreased by 92% as assessed on physical examination on day 16. Tumor pH3 expression decreased below the assay limit of quantification (Table 3). Additional molecular characterization of this patient’s tumor is described in a separate article (13).

Although the magnitude of tumor shrinkage did not clearly associate with changes in tumor pH3 and NRG1 (Table 3), all 5 patients showing a measurable reduction in tumor burden also had a reduction in tumor pH3 with treatment, including 3 (60%) with reductions in pH3 below the limit of quantification. In contrast, a reduction below the limit of quantification was achieved in only 1 (14%) of the remaining 7 patients who had no change in tumor size. Similarly, moderate to high NRG1 expression was detected for 3 (60%) of the 5 patients with tumor regression, and 1 (14%) of the remaining patients (Table 3). No correlations were observed between change in tumor burden and Ki67, HPV status, or other biomarkers (Supplementary Fig. S3).

Discussion

Window-of-opportunity trials provide a powerful model to assess biomarker alterations induced upon drug treatment, by comparing baseline tumor tissue with those obtained after drug treatment. This window-of-opportunity study set out to evaluate whether CDX-3379 would inhibit ErbB3 phosphorylation in human tumors prior to surgery. In addition, we assessed toxicity and any clinical activity prior to tumor resection in these newly diagnosed, operable HNSCC patients. Potential biomarkers of response were also assessed.

There were no treatment-related serious adverse events, and drug treatment was very well tolerated. Treatment with two 1,000 mg doses of CDX-3379 at a 2-week interval achieved trough serum levels above the target level for maximal activity in preclinical models. pH3 was detectable in all tumor samples collected prior to dosing, indicating the ErbB3 signaling pathway was active in these tumors. Consistent with this, either NRG1 or NRG2 mRNA was also detected in all tumors. Following CDX-3379 treatment, the majority of patients’ tumors demonstrated a significant reduction in ErbB3 phosphorylation (Fig. 2b), with 58% (P = 0.04; 95% CI, 27.7%–84.8%) achieving a reduction of ≥50%. These data indicate that, at the dose and schedule used in this study, sufficient concentrations of CDX-3379 were achieved in tumors to inhibit ErbB3 activation. Despite the short treatment duration, we observed tumor shrinkage on posttreatment radiographic assessment in 42% of patients, including 2 of 3 HPV-positive patients. Another HPV-positive patient had progressive disease despite a 54% reduction in pH3, suggestive of an additional tumor driver in addition to ErbB3. Interestingly, 1

![Figure 1](https://example.com/figure1.png)

**Pharmacokinetics.** CDX-3379 serum concentration over time is individually displayed for each patient. All 12 patients received CDX-3379 (1,000 mg) at a 2-week interval for a total of two doses. Dotted line represents target trough concentration of 50 μg/mL, which resulted in maximal antitumor efficacy in preclinical models.

![Figure 2](https://example.com/figure2.png)

**Figure 2.** Phospho-tyrosine T289-ErbB3 expression by VeraTag. A, Change in pH3 level in individual patient tumor samples. Posttreatment pH3 levels were below the assay level of detection for 4 patients (108-01, 110-02, 111-02, and 112-02); values were set at the assay level of detection of 0.14. B, Mean tumor pH3 levels for all patients (n = 12) before and after CDX-3379 treatment.
HPV-negative patient experienced a dramatic clinical response after a single dose. We did not see an obvious relationship between tumor shrinkage and pharmacodynamic changes in pErB3, suggesting that other tumor drivers may compensate for loss of ErbB3 activity. However, all patients with measurable reductions in tumor burden had tumors expressing both NRG1 and ErbB3 and reduced pErB3 with CDX-3379 treatment, consistent with the clinical hypothesis. Comparison of NRG1, NRG2, and ErbB3 expression data with changes in pErB3, Ki-67, or tumor measurements did not reveal significant correlations, although we may be limited by the small sample size and brief duration of treatment (Supplementary Fig. S3). Two patients with PTEN loss showed some of the largest pErB3 reduction changes and measurable tumor shrinkage, which is of potential interest considering that PTEN loss has previously been associated with resistance to cetuximab and functional correlation studies are aimed at understanding how CDX-3379 treatment affects tumor biology, with the ultimate goal of identifying biomarkers that predict response.

Ki67 is a nuclear nonhistone protein expressed in proliferating human tissue and is commonly used as a biomarker of treatment activity in window-opportunity studies. However, a treatment-induced decrease in Ki67 in HNSCC tumors has not been demonstrated to correlate with treatment activity, and Ki67 may not be a surrogate biomarker in all cancers (15–18). In this clinical study, Ki67 decreases were observed in a subset of tumors following CDX-3379 treatment. However, the changes did not correlate with changes in pErB3 or tumor measurements. Hence, the utility of Ki67 as a surrogate endpoint for clinical benefit in HNSCC is not supported by this study.

To our knowledge, this is the first example of an anti-ErbB3 mAb demonstrating meaningful target inhibition in a relevant clinical setting and single-agent activity in HNSCC. One major strength of this study is the ability to evaluate pre- and posttreatment samples on all patients. Limitations of this study include the relatively small number of treated patients, and the short duration of treatment with CDX-3379, which hampers assessment of CDX-3379 antitumor efficacy and duration of response. Overall, this window-of-opportunity study demonstrated the feasibility of this type of trial design in the evaluation of single-agent activity of compounds being developed and explored HNSCC as a target indication for the ErbB3/NRG signaling pathway. This study demonstrated biologic activity of CDX-3379 at the target serum exposure level based on significant decreases in posttreatment pErB3 levels as well as antitumor effects. The current development focus for CDX-3379 is the agent activity of compounds being developed and explored feasibility of this type of trial design in the evaluation of single-agent activity of compounds being developed and explored

| Patient | HPV status | Pre | Post | % change | Pre | Post | % change | NRG1 | NRG2 | ErbB3 | PTEN | Tumor measurement (% change)
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<td>0.48</td>
<td>–54%</td>
<td>6,629</td>
<td>7,160</td>
<td>8%</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>26</td>
</tr>
</tbody>
</table>

Abbreviation: BLQ, below the limit of quantification.

1pErB3 determined using quantitative VeraTag of pre- and posttreatment biopsies for all patients except 108-02 (posttreatment results determined using resection sample). Data represent change from pre- to posttreatment samples.

2Ki67 expression assessed by IHC (AQUA) in pre- and posttreatment samples.

3NRG1, NRG2, ErbB3, and PTEN assessed using posttreatment tumor resection samples for all patients except 102-02, 103-02, and 104-02 (pretreatment biopsy were evaluated). mRNA expression levels of NRG1, NRG2, ErbB3 evaluated by quantitative RNAscope assays (–, not different from the negative control probe; +, expression level of 1.2–2.5; ++, expression level of 2.6–3.8; ++++, expression level of 3.9–5.2; ++++, expression level >5.2). PTEN expression assessed by IHC (AQUA).

4Percent change from pre- to posttreatment in the sum of the longest diameters of RECIST 1.1 target lesions.

Figure 3.
Waterfall plot of change in tumor burden. Percent change from baseline in the sum of longest diameters of target lesion(s) for each study patient. Radiographic assessments were performed at a median (range) of 20.5 (15–26) days from first CDX-3379 dose. HPV status is denoted by + and – signs.
study of combination CDX-3379 and cetuximab treatment in patients with HPV-negative HNSCC has been initiated at multiple clinical sites to further evaluate the potential for clinical benefit in this patient population.

Disclosure of Potential Conflicts of Interest
U. Duvvuri is an employee of VAPHS, and is a consultant/advisory board member for Medtronic and Activo Surgical. D. Alvarado and T. LaVallee hold ownership interest (including patents) in Celldex Therapeutics. V.M. Neu- meister is an employee of Akoya Biosciences. J.E. Bauman is a consultant/ advisory board member for Merck, Astra Zeneca, EMD Serono, and CUE Pharmaceuticals. No potential conflicts of interest were disclosed by the other authors.

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This work does not represent the views of the Department of Veterans Affairs nor the U.S. Government.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J. George, S. Kim, V.M. Neumeister, T. Hawthorne, T. LaVallee, J.E. Bauman
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