CDX3379-04: Phase II Evaluation of CDX3379 in Combination with Cetuximab in Patients with 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.
- CDX3379 is a fully human anti-ERBB3 monoclonal IgG1 antibody with extended half-life and a patient inhibitory (PI) antibody via a unique mechanism of action that blocks ERBB3 in an active conformation.
- CDX3379 anti-tumor 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 CDX3379 and cetuximab in a patient with cetuximab-refractory HNSCC was observed during an exploratory study, an exclusion of clinical response in a patient with HNSCC.

Consort Study Design

NCT02549287 is a phase 2, multicenter, open-label, single-arm clinical trial to evaluate safety and efficacy of CDX3379 in combination with cetuximab in patients with advanced HNSCC.

Exploratory Biomarker Analysis

- Recurrent/metastatic PI(3,K)HNSCC, not curable with local therapy.
- Cetuximab-resistant (progression within 6 months).
- Prior PI(3,K)HNSCCfailure, unless not a candidate.
- Neutrophil count <5,000/mm3.
- Platelet count <100,000/mm3.
- Hypomagnesemia.
- Hypokalemia.
- Fatigue.
- Hypothyroidism.

Study Assessments

- Tumor Response (RECIST): every 4 weeks.
- Tumor biopsy: Screening, Cycle 2, and at progression.
- Safety and toxicity assessments.
- CDX3379 pharmacokinetics and immunogenicity.

Study Objectives

Primary Objective: Objective Response Rate (ORR); CR or PR (RECIST 1.1).
- Assessment of duration of response, progression-free survival, overall survival, safety, pharmacokinetics, immunochemistry.

Exploratory Objectives: Biomarker analysis.

Exposure to Study Drug

- CDX3379 Median # doses (min, max): 21 (2, 24).
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- Duration of treatment: 3 months (12%); 3 -5 months (33%); >6 months (6%).
- Dose reductions, delayeds, and holidays: 20 (8%)
- Reasons for Discontinuing Study treatment: Disease Progression (74%); Clinical Progression (47%); Advise Event (12%); Death (12%).

Safety

- Grade 5 or higher toxicity: 1 patient.
- Primary safety endpoints: CT toxicity, infusion reactions, and mucositis.

Clinical Benefit Rate, Duration of Response, Progression-Free Survival

- Clinical Benefit Rate: 42% (95% CI: 27% - 57%).
- Duration of response: 6 months (47%).
- Progression-Free Survival: 6 months (27%).

Exploratory Biomarker Analysis

- Three of the responding patients also had NOTCH1, NOTCH2, or NOTCH3 mutations.

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, HNSCC, where treatment options are limited.
- Clinical Benefit Rate of 29% was achieved.
- Dose reductions and delays to the combination therapy in the majority of patients may have impacted the magnitude of anti-tumor activity, dose modifications are being considered for future studies.
- CDX3379 plus cetuximab was associated with the expected targeted-mediated adverse events of diarrhea and rash.
- Across the CDX3379 studies, mutations in PI(3, K)HNSCC, 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 CDX3379 development will focus on the clinical utility of biomarker-driven patient selection.

References

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