BACKGROUND

Background: Cetuximab, an anti-EGFR monoclonal antibody, is approved for patients with recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC), but only a minority benefit. Median progression-free survival (PFS) and overall response rate (ORR) for cetuximab monotherapy are 2.3 months and 1.5% respectively. Activation of c-Met, the receptor for hepatocyte growth factor (HGF), overcomes EGFR inhibition in preclinical models and high serum HGF is associated with cetuximab resistance in patients. We conducted a phase I trial evaluating the combination of cetuximab and ficlatuzumab, an anti-HGF monoclonal antibody, in patients with recurrent/metastatic R/M HNSCC.

METHODS

Study Design: N pazinac-a-k-in-a adaptive phase I design with k set to 2 for a target DLT rate of ≤ 33%. If 8 patients are treated without DLT (2 out of 1 and 3), the upper 90% confidence bound for the estimated DLT rate at dose tier 2 is 6.32.

Key Eligibility Criteria

• Recurrent/Metastatic HNSCC
• Cetuximab-resistant (expansion phase)
• Disease progression during or within 6 months of cetuximab therapy, and “poor” indicates resistance and poor prognosis.

Primary Objective: To establish the recommended phase II dose (RP2D) of ficlatuzumab and cetuximab.

Key Secondary Objectives

• To evaluate preliminary clinical efficacy of RP2D
• To evaluate the relationship between efficacy of 1) baseline tumor p-Met expression and 2) serum Veristrat, a proteomic classifier where “good” predicts benefit from anti-EGFR therapy, and “poor” indicates resistance and poor prognosis.

RESULTS

• No DLTs were observed at any dose tier.
• Any ≥ Grade 3 non hematologic toxicity except the following:
• Grade 1 neutropenia with fever
• Grade 3 thrombocytopenia with bleeding
• Grade 4 neutropenia or thrombocytopenia

• Median PFS at RP2D was 6.0 months (90% CI=2 months).

• The confirmed ORR was 17% (1 PR at tier 1; 1 at tier 2).

• Median OS at RP2D was 8.2 months (90% CI=2.7 months).

• From Sept 2015, June 2016, 12 patients enrolled and were treated at (3 at dose tier 1; 9 at dose tier 2).
• No DLTs were observed at any dose tier.
• The RP2D is ficlatuzumab 20 mg/kg and cetuximab 500 mg/m² every 2 weeks.

• Supported by the Investigator Initiated Trials Programs of Aveo Oncology and the Shared Resources of the University of Pittsburgh Cancer Institute (P50CA076984).

ACKNOWLEDGMENTS

HGF and c-Met protein levels were assayed by IHC on HNSCC tumors and paired adjacent mucosa in 38 N. A. tumors showed increased staining for HGF and c-Met staining vs. paired adjacent mucosa. B. 2nd and Wilcoxon signed-rank test indicated significant differences in weighted HGF and c-Met intensity in tumor vs. paired adjacent mucosa (HGF: P = 0.01; Met: P = 0.04). C. HGF and Met IHC score frequency distributions.

PHENOTYPIC CHARACTERIZATION

Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
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<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>11 (92%)</td>
</tr>
<tr>
<td>Male</td>
<td>1 (8%)</td>
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<td>Age (Average, St)</td>
<td>75.8 years</td>
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TOXICITY

Constitutional

- Flu-like Symptoms: 5 (42%) 0

Dermatologic

- Acne: 9 (75%) 0

Hematologic

- Neutropenia: 5 (42%) 1 (9%) 0

- Thrombocytopenia: 4 (33%) 0

Vascular

- Thromboembolism: 0 (0%) 2 (17%) 0

DEFINITION OF DOSE LIMITING TOXICITY

- Any ≥ Grade 3 non hematologic toxicity except the following:
- Grade 1 neutropenia with fever
- Grade 3 thrombocytopenia with bleeding
- Grade 4 neutropenia or thrombocytopenia

- Disease progression during or within 6 months of cetuximab therapy

• Disease recurrence within 6 months of completing definitive radiation therapy
• Disease progression during or within 6 months of cetuximab in patients with recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) but only a minority benefit.

- Median progression free survival (PFS) and overall response rate (ORR) for cetuximab monotherapy are 2.3 months and 1.5% respectively.

- Activation of c-Met, the receptor for hepatocyte growth factor (HGF), overcomes EGFR inhibition in preclinical models and high serum HGF is associated with cetuximab resistance in patients.

- Supported by the Investigator Initiated Trials Programs of Aveo Oncology and the Shared Resources of the University of Pittsburgh Cancer Institute (P50CA076984).

CONCLUSIONS

- The RP2D is ficlatuzumab 20 mg/kg and cetuximab 500 mg/m² IV every 2 weeks.

- This well-tolerated combination demonstrated promising activity in patients with poor prognosis recurrent/metastatic R/M HNSCC.

- A randomized, phase II, multicenter, investigator-initiated trial evaluating ficlatuzumab +/- cetuximab in cetuximab-resistant recurrent/metastatic HNSCC will start enrollment in Q4 2017.