Phase I study of the anti-HGF monoclonal antibody, ficlatuzumab, and cetuximab in cetuximab-resistant, recurrent/metastatic head and neck cancer

Abstract 6038

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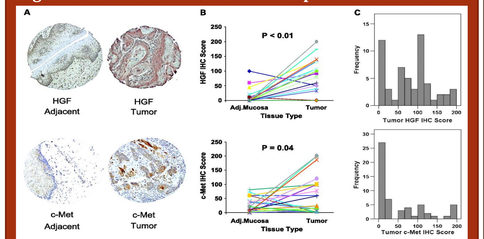
BACKGROUND

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 13% 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 IgG1 anti-HGF monoclonal antibody, in patients with cetuximab-resistant, R/M HNSCC.

Figure 1. HGF and c=Met are over-expressed in HNSCC



HGF and c-Met protein levels were assessed by IHC in HNSCC tumors and paired adjacent mucosa (n = 26). A, tumors showed increased HGF and c-Met staining vs. paired adjacent mucosa. B, 2-sided Wilcoxon signed-rank test indicated significant differences in weighted HGF and c-Met intensity in tumor vs. paired adjacent mucosa (HGF; P < 0.001; c-Met; P = 0.04). C, HGF and c-Met IHC score frequency distributions.[1]

1. Knowles LM, Stabile LP, Egloff AM, et al. HGF and c-Met participate in paracrine tumorigenic pathways in head and neck squamous cell cancer. Clin Cancer Res. 2009;15: 3740-3750.

METHODS

Study Design: Narayana k-in-a-row adaptive phase I design with k set to 2 for a target DLT rate of ≤ 33%. If 8 patients are treated without DLT (2+6 on tiers 1 and 3), the upper 90% confidence bound for the estimated DLT rate at dose tier 2 is 0.32.

Key Eligibility Criteria

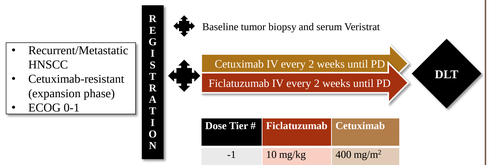
- Recurrent/Metastatic HNSCC
- Cetuximab-resistant (expansion phase)
  - Disease recurrence within 6 months of completing definitive cetuximab-radiation therapy
  - Disease progression during or within 6 months of cetuximab in the recurrent/metastatic setting.

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 and 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.

SCHEMA



Dose Tier #	Ficlatuzumab	Cetuximab
-1	10 mg/kg	400 mg/m^2
1 (Starting)	10 mg/kg	500 mg/m^2
* Dose Tier 1.5 for de-escalation only if needed		
1.5*	15 mg/kg	500 mg/m^2
2	20 mg/kg	500 mg/m^2

DEFINITION OF DOSE LIMITING TOXICITY

- Any ≥ Grade 3 non hematologic toxicity except the following grade 3 toxicities: rash; infusion reaction; nausea, vomiting or diarrhea lasting < 48 hours; isolated AST or ALT elevation; asymptomatic electrolyte abnormality
- Grade 3 neutropenia with fever
- Grade 3 thrombocytopenia with bleeding
- Grade 4 neutropenia or thrombocytopenia
- AST or ALT elevation ≥ 3x ULN with concurrent elevation of bilirubin ≥ 2x ULN
- Ficlatuzumab-related toxicity that requires a dose reduction or results in ≥ 2 missed doses

PATIENT CHARACTERISTICS

Patient Characteristics	N (%)
Age (Average, Range)	60.4 (46.7-75.8 years)
Sex	
Male	10 (83%)
Female	2 (17%)
ECOG Performance Status	
0	7 (58%)
1	5 (42%)
Primary Tumor Site	
Oral Cavity	1 (8%)
Oropharynx	3 (25%)
Hypopharynx	2 (17%)
Larynx	5 (42%)
External Auditory Canal	1 (8%)
Platinum-Refractory	
Yes	11 (92%)
No	1 (8%)
HPV Status	
p16+ oropharynx	1 (8%)
p16- oropharynx and non-oropharynx	11 (92%)
Veristrat Status	
Good	4 (33%)
Poor	8 (67%)

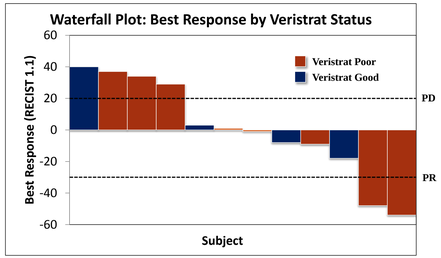
RESULTS

- From Sept 2015-June 2016, 12 patients enrolled and were treated (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/m^2 every 2 weeks.
- The confirmed ORR was 17% (1 PR at tier 1; 1 at tier 2).
- Median PFS at RP2D was 6.0 months (90% CI=2 months-not reached)
- Median OS at RP2D was 8.2 months (90% CI=2.7 months-not reached).

TOXICITY

	NCI CTCAE GRADE Grade 1-2	Grade 3-4
Constitutional		
Flu-like Symptoms	5 (42%)	0
Dermatologic		
Acneiform Rash	9 (75%)	0
Hepatic		
Hypoalbuminemia	5 (42%)	1 (8%)
Infection	0	2 (17%)
Metabolic		
Hypomagnesemia	4 (33%)	0
Hyponatremia	2 (17%)	0
Hypophosphatemia	4 (33%)	1 (8%)
Vascular		
Thromboembolism	0	2 (17%)
Edema		
Peripheral	1 (8%)	1 (8%)
Head and Neck	2 (17%)	0

BIOMARKERS



p-Met expression was measured by IHC (Clone D26) in baseline tumor biopsies and H-Score calculated as % positive cells (0-100) x staining intensity (0-3). Veristrat status (good/poor) was determined in baseline serum samples. There was no association between either biomarker and PFS or best response. The 2 patients with confirmed PR were Veristrat Poor.

CONCLUSIONS

- The RP2D is ficlatuzumab 20 mg/kg and cetuximab 500 mg/m^2 IV every 2 weeks.
- This well-tolerated combination demonstrated promising activity in patients with poor prognosis, cetuximab-resistant 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.

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