# Randomized Phase II Trial of Ficlatuzumab with or without Cetuximab in Pan-Refractory, Advanced Head and Neck Squamous Cell Carcinoma (HNSCC)

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Abstract 6015

## BACKGROUND

**Background:**

- Cetuximab, an anti-EGFR IgG1 monoclonal antibody (mAb), is approved for patients with platinum-resistant, recurrent/metastatic (R/M) HNSCC but only a minority benefit, with overall response rate (ORR) of 10-13%.[1]
- Crosstalk between EGFR and HGF/cMet pathways is a known tumor-intrinsic resistance mechanism.
- HGF is immunosuppressive within tumor microenvironment.
- Our phase Ib trial showed safety and preliminary efficacy of cetuximab and ficlatuzumab, a potent humanized IgG1 anti-HGF mAb, in cetuximab-resistant, advanced HNSCC.[2]
  - The recommended phase II dose was ficlatuzumab 20 mg/kg and cetuximab 500 mg/m$^2$ q 2 weeks.
  - Overall response rate (ORR) and median progression-free survival (mPFS) were 17% and 5.4 months.
  - An increase in peripheral T cells, particularly the CD8+ subset, was associated with treatment response whereas expansion of a distinct myeloid population was associated with progression (**Figure 1**).

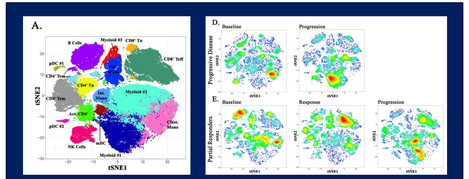
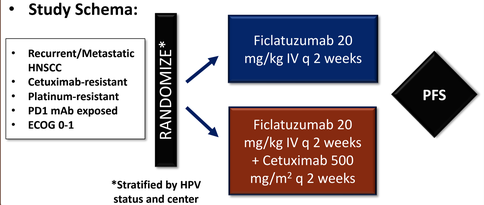



**Figure 1.** Immunophenotyping of PBMCs by spectral cytometry. Selected phenotypic markers correspond to cell subsets denoted in Rphenograph t-SNE **(A)**. t-SNE density plots illustrate the increased proportion of cell subsets corresponding to Rphenograph for **(D)** rapid progressors and **(E)** responders.[2]

## STUDY DESIGN

- **Design:**
  - Randomized non-comparative phase II
  - $\alpha = 0.1$ one-sided; $\beta = 0.9$
  - Arm deemed worthy of further study if lower bound of 90% 1-sided confidence interval (CI) for mPFS excluded historical control of 2 months, as estimated from platinum-resistant[1,3] and partially cetuximab-resistant[4] populations
  - Intent to treat; subjects receiving ≥ 1 dose were evaluable
  - Bayesian continuous monitoring rule for futility
- **Primary Objective:** Efficacy as measured by mPFS
- **Key Secondary Objectives:**
  - ORR, overall survival
  - ORR and mPFS in HPV-stratified populations
  - Toxicity
- **Key Eligibility Criteria:**
  - Adults with recurrent/metastatic HNSCC
  - If oropharynx or unknown primary, p16 status known
  - ECOG performance status 0-1
  - Platinum-resistant or ineligible
  - Cetuximab-resistant (progression on or within 6 months of exposure in the definitive or R/M setting)
  - Prior treatment with anti-PD1 mAb (or ineligible)
  - No significant medical comorbidity
- **Study Schema:**




***Stratified by HPV status and center**

## BASELINE PATIENT CHARACTERISTICS

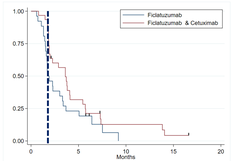
| | Ficlatuzumab N=27 | Combination N=33 | Comparison p-value |
|---|---|---|---|
| **Sex** | | | 0.28 |
| **Female** | 6 (22%) | 3 (9%) | |
| **Male** | 21 (78%) | 30 (91%) | |
| **Age: Median (Range)** | 65 (37-83) | 63 (46-75) | 0.66 |
| **Ethnicity**[a] | | | 1.00 |
| **Hispanic or Latino** | 3 (12%) | 3 (9%) | |
| **Non-Hispanic** | 23 (88%) | 29 (91%) | |
| **Race**[a] | | | 1.00 |
| **White** | 24 (92%) | 30 (94%) | |
| **Black or African American/Asian** | 2 (8%) | 2 (6%) | |
| **Primary Site** | | | 0.58 |
| **Oral Cavity** | 8 (30%) | 6 (18%) | |
| **Oropharynx** | 11 (41%) | 19 (58%) | |
| **Larynx** | 3 (11%) | 4 (12%) | |
| **Other**[b] | 5 (19%) | 4 (12%) | |
| **HPV Positive** | 10 (37%) | 16 (48%) | 0.44 |
| **Months since Last Cetuximab** | | | |
| **Median (Range)** | 2.7 (0-62.6) | 3.6 (0.4-47.9) | 0.66 |
| **Previous Anti-PD1 mAb** | 23 (85%) | 31 (94%) | 0.39 |
| **Platinum Resistant** | 19 (70%) | 24 (73%) | 0.84 |
| **ECOG** | | | 0.18 |
| **Asymptomatic [0]** | 9 (33%) | 6 (18%) | |
| **Symptomatic [1]** | 18 (67%) | 27 (82%) | |

a. 2 Unknown Excluded
b. Other: EBV- Nasopharynx, Paranasal Sinus, External Auditory Canal, Unknown Primary

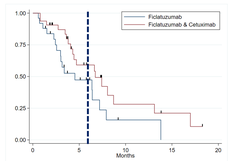
## RESULTS

- 60 subjects were randomized and 58 treated from 2018-2020
- The ficlatuzumab single agent arm stopped for futility after 26 evaluable subjects accrued
  - mPFS 1.8 months (lower bound 90% CI: 1.7 months)
  - ORR 1/26 (4%) – 1 PR (1 PR in HPV- subject)
- **The ficlatuzumab + cetuximab combination arm completed accrual with 32 evaluable subjects and met primary endpoint**
  - **mPFS 3.6 months (lower bound 90% CI 2.3 months; p=0.04)**
  - **ORR 6/32 (19%) – 2 CR and 4 PR**
  - **All responses in HPV- subjects**

## RESULTS




**Progression Free Survival**




**Overall Survival**

Historical Control (mPFS 2 months)[1,3,4]
Historical Control (mOS 6 months)[1,3,4]

## TOXICITY [a]

| | Ficlatuzumab N=26 | | Ficlatuzumab + Cetuximab N=32 | |
|---|---|---|---|---|
| | Grade 1-2 | Grade ≥ 3 | Grade 1-2 | Grade ≥ 3 |
| **Cardiovascular** | | | | |
| Edema | | | | |
| Peripheral | 4 (15%) | 0 | 5 (16%) | 1 (3%) |
| Facial/HN | 2 (8%) | 1 (4%) | 1 (3%) | 0 |
| Cardiopulmonary Arrest | 0 | 0 | 0 | 1 (3%)[b] |
| **Constitutional** | | | | |
| Fatigue | 2 (8%) | 0 | 0 | 1 (3%) |
| Weight Loss | 0 | 0 | 1 (3%) | 0 |
| **Dermatologic** | | | | |
| Acneiform Rash | 1 (4%) | 0 | 14 (44%) | 6 (19%) |
| Maculopapular Rash | 0 | 1 (4%) | 1 (3%) | 0 |
| Paronychia | 0 | 0 | 2 (6%) | 1 (3%) |
| Skin Infection | 1 (4%) | 0 | 1 (3%) | 0 |
| **Gastrointestinal** | | | | |
| Anorexia | 0 | 0 | 1 (3%) | 0 |
| Diarrhea | 0 | 0 | 0 | 1 (3%) |
| Elevated AST/ALT | 0 | 0 | 0 | 1 (3%) |
| Oral mucositis | 0 | 0 | 3 (9%) | 0 |
| **Metabolic** | | | | |
| Hypoalbuminemia | 8 (30%) | 0 | 10 (31%) | 0 |
| **Pulmonary** | | | | |
| Pneumonitis | 0 | 2 (8%)[b] | 1 (3%) | 0 |

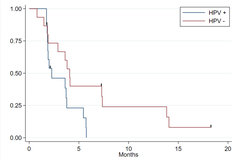
a. Toxicities attributed to protocol treatment
b. Two treatment-related deaths occurred: pneumonitis (ficlatuzumab arm) and cardiopulmonary arrest (combination arm)

## HPV-STRATIFIED ANALYSIS

- An exploratory comparison of ORR and mPFS in the HPV+ and HPV- subgroups was performed in the combination arm. HPV- subjects had superior ORR (p=0.02) and mPFS (p=0.03).

| | Ficlatuzumab + Cetuximab (N=32) | p-value |
|---|---|---|
| **ORR**[a] | | 0.02 |
| **HPV+** | 0/16 (0%) | |
| **HPV-** | 2CR + 4PR/16 (38%) | |
| **mPFS** | | 0.03 |
| **HPV+** | 2.3 (1.9) | |
| **HPV-** | 4.1 (2.9) | |

a. ORR: CR+PR/n
b. mPFS: Months (lower bound of 90% 1-sided CI)




**Progression Free Survival by HPV Status**
**Ficlatuzumab + Cetuximab Arm**

## CONCLUSIONS

- The ficlatuzumab + cetuximab combination met the primary PFS endpoint in pan-refractory, advanced HNSCC
- All responses, including 2 complete and 4 partial responses, occurred in HPV- subjects
- **Notable activity in pan-refractory, HPV- disease warrants phase III investigation**
- The combination was well tolerated with expected class toxicities from HGF/cMet inhibitors including common AEs edema and hypoalbuminemia and uncommon AE pneumonitis

## ACKNOWLEDGMENTS

**References:**

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