FIERCE-HN: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Ficlatuzumab (HGF/c-MET MAb) in Combination with Cetuximab in Participants with Recurrent or Metastatic (R/M) HPV Negative Head and Neck Squamous Cell Carcinoma (HNSCC)

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Background

Head and Neck Cancer and Human Papillomavirus (HPV) Status

- In the US, head and neck squamous cell carcinoma (HNSCC) accounts for ~66,000 new cases and 15,000 deaths annually, or 3% of all malignancies[1]
- Global prevalence of head and neck cancers continues to rise and is expected to reach 1 million new cases by 2030[2,3,4,5]

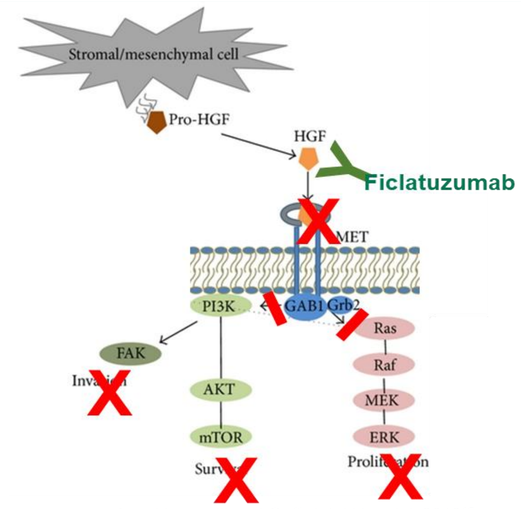
Unmet Medical Need is Significant, Especially Among HPV-Negative Patients

- **Patients with HPV-negative recurrent/metastatic (R/M) HNSCC have median overall survival (mOS) <2 years[6,7]**
- **Treatment options are limited in the R/M setting[7]**
- **Patients with this condition suffer debilitating effects from both their disease and treatment, including disfigurement, physical and functional impairments, and higher incidences of depression and suicide[8]**

Ficlatuzumab and Cetuximab

- Ficlatuzumab is a humanized anti-HGF IgG1 antibody that binds HGF and impacts the c-MET signaling pathway neutralizing the biologic activity of HGF *in vitro* and *in vivo* (**Figure 1**)
  - The HGF/c-MET pathway is frequently up-regulated and functional in HNSCC (paracrine mechanism)[11]
  - Tumor-derived fibroblasts secrete HGF, which then activates c-MET receptors on HNSCC cells[11]
  - HGF promotes cell proliferation, motility, invasion, and angiogenesis via PI3K/Akt, MAPK, and JAK/STAT2 pathway and the associated crosstalk between the EGFR and c-MET pathways[10]
- Cetuximab is an inhibitor of the epidermal growth factor receptor (EGFR) approved in the US and other geographies for the treatment of HNSCC and colorectal cancer[6,7]

Figure 1. Ficlatuzumab Mechanism of Action[12]



Adapted from Venepalli and Goff. *Int J Hepatol.* 2013[12]

Figure 2. Ficlatuzumab plus Cetuximab is More Effective than Either Ficlatuzumab or Cetuximab Alone

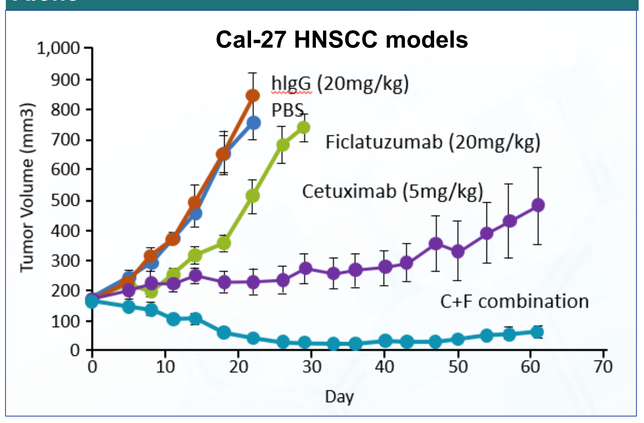


Table 1. HPV Status and Response to Ficlatuzumab-Cetuximab Treatment in a Phase 2 Study of Patients with R/M HNSCC

Parameter	HPV+ N=16	HPV- N=16
CR, n (%)	0 (0%)	2 (13%)
PR, n (%)	0 (0%)	4 (25%)
ORR (CR+PR), n %)	0 (0%)	6 (38%)
mPFS, months	2.3	4.1

Subgroup analysis from:
Bauman, et al. *J Clin Oncol.* 2023;41(22):3851-3862[6].

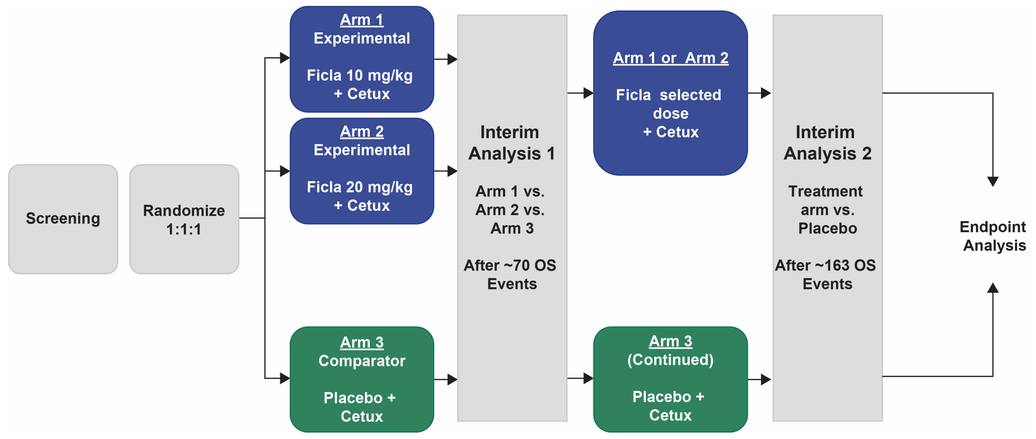
- Activation of the HGF/ c-MET pathway has been implicated in mediating resistance to cetuximab[6]
- Addition of ficlatuzumab to cetuximab has been shown to be more effective than cetuximab alone in preclinical studies (AVEO Pharmaceuticals, Inc., data on file; **Figure 2**)
- The dual targeting of the combination of ficlatuzumab and cetuximab could resensitize the EGFR pathway overcoming cetuximab resistance (**Figure 1**)
- The efficacy of ficlatuzumab alone or in combination with cetuximab was evaluated in a Phase 2 study in patients with pan-refractory HNSCC (resistance to platinum, anti-PD-1 mAb, and cetuximab) who have a very poor historical prognosis[6]
- Targeting both the EGFR and HGF/ c-MET pathways with the combination therapy of ficlatuzumab plus cetuximab was associated with reduced hazard of progression compared to ficlatuzumab alone in HPV-negative patients but not in HPV-positive patients **(Table 1)**
  - Progression-free survival (PFS) was 4.1 months and overall response rate (ORR) was 38% (6/16; 2 complete responses, 4 partial responses)
- These results indicate that dual-EGFR- c-MET antagonism and resensitization to anti-EGFR treatment may be of greater mechanistic importance in HPV-negative disease

Study Design and Eligibility

FIERCE-HN is an ongoing multicenter, randomized, double-blind, placebo-controlled Phase 3 clinical study

- The study compares ficlatuzumab (10 or 20 mg/kg) in combination with cetuximab (500 mg/kg) against placebo plus cetuximab in participants with HPV-negative R/M HNSCC
- Participants will be randomized 1:1:1 into 1 of 3 arms (**Figure 3**). Following the first interim analysis, randomization will continue to be 1:1 for the selected ficlatuzumab dose and placebo arm
- Ficlatuzumab, cetuximab, and/or placebo are administered every 2 weeks by intravenous infusion. Patients remain on treatment until disease progression or unacceptable toxicity
- Statistical analyses will be completed by treatment arm and summarized descriptively. The study has statistical power of 80%, assuming a true OS hazard ratio of 0.667

Figure 3. Overview of Study Design



Key Inclusion Criteria*:

- R/M HNSCC (primary tumor locations of oropharynx, oral cavity, hypopharynx, or larynx) with at least 1 measurable lesion
- Participants with oropharyngeal cancer will be required to have proof of p16 negative status
- Patients must have failed prior therapy with anti–PD-1/PD-L1 ICI and platinum-based chemotherapy
- ECOG PS 0 or 1 and life expectancy ≥12 weeks

Key Exclusion Criteria*:

- Patients who received >2 prior lines of anticancer therapy or prior treatment with cetuximab or other EGFR inhibitors
- Untreated and uncontrolled brain metastases or leptomeningeal carcinomatosis
- Radiographic evidence of interstitial lung disease or idiopathic pulmonary fibrosis

*For more information:

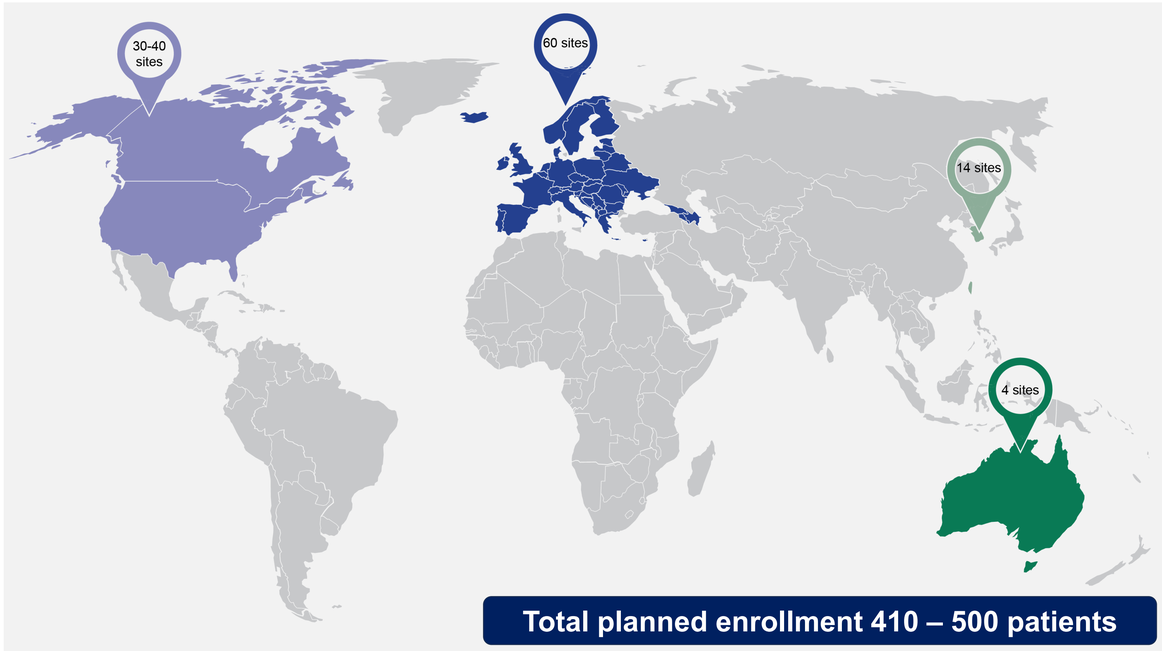
Endpoints

Primary endpoint
- OS

Key secondary endpoints
- PFS
- ORR

Other secondary endpoints
- Disease control rate
- Duration of response
- Incidence and severity of adverse events and laboratory abnormalities
- Ficlatuzumab concentrations in serum samples
- Presence of anti-drug antibodies (ADAs) to ficlatuzumab
- Presence of neutralizing antibodies, as a measure of the immunogenicity of ficlatuzumab
- Quality of life of patients treated with ficlatuzumab plus cetuximab versus placebo plus cetuximab

Active Study Sites



Total planned enrollment 410 – 500 patients

For more information you can contact: clinical@aveooncology.com

Acknowledgements
We express our gratitude to the patients and their caregivers for their invaluable contributions. We also extend our thanks to the clinical study teams and investigators, and steering committee. Collaborator Eli Lilly provided cetuximab. This study is sponsored by AVEO Pharmaceuticals, Inc.

References

[1]Siegel et al. CA Cancer J Clin. 2022;72(1):7-33; [2]Bray et al. CA Cancer J Clin. 2018;68(6): 394-424; [3]Ferlay. Global Cancer Observatory. 2018; IARC; [4]Ferlay et al. Int J Cancer. 2019;144(8):1941-193. [5]Gormley et al. Br Dent J. 2022; 233(9):780-786; [6]Bauman et al. J Clin Oncol. 2023;41(22):3851-3862; [7]Erbitux® (cetuximab) Prescribing Information. 2009; [8] Reike et al. Oral Oncol. 2017;65:76-82; [9]Powell et al. Cancers. 2021;13(20):5206; [10]Raj et al. Mol Cancer. 2022;21(1):31; [11]Knowles et al. Clin Cancer Res. 2009;15(11):3740-3750; [12]Venepalli and Goff. Int J Hepatol. 2013;2013:341636.