FIERCE-HN: A multicenter, randomized, placebo-controlled, phase 3 study of ficlatuzumab + cetuximab in pts w/ recurrent or metastatic (R/M) HPV-negative head and neck squamous cell carcinoma (HNSCC)

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Background and Rationale

- Squamous carcinoma of the head and neck (HNSCC) make up ~90% of head and neck cancers with 900,000 new cases and 400,000 deaths annually.[1]
- For patients with recurrent/metastatic (R/M) HNSCC, current treatments are palliative with anti-PD-1 checkpoint inhibitor +/- platinum and 5-fluorouracil chemotherapy for first-line followed by taxanes, methotrexate, and cetuximab as later-line options.[2]
- While there have been modest improvements in HPV-associated HNSCC, little improvement in outcomes has been seen in HPV-negative HNSCC.
- The median overall survival (OS) for R/M patients is 10-13 months, and those with HPV-negative HNSCC face the worst outcomes.[2]

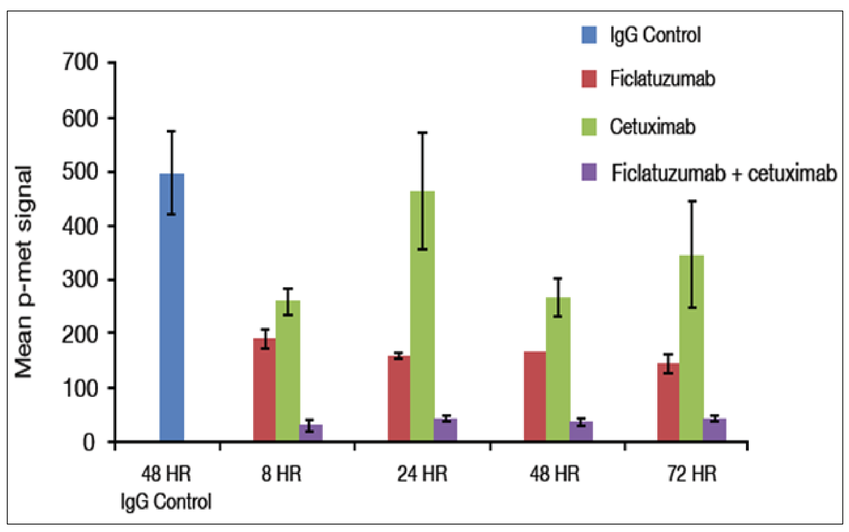
EGFR and cMET Pathway

- Endothelial growth factor receptor (EGFR) is over expressed in up to 90% of HNSCC and sits on the surface next to the cMET receptor.[3]
- The cMET pathway dysregulation is frequently observed in HPV-negative HNSCC.
- The hepatocyte growth factor (HGF)/cMET pathway is an escape mechanism for EGFR blockade.[4]
- When EGFR is blocked, a cross linking effect results in increased expression of cMET receptors and therefore increase binding of the ligand HGF to cMET.
- When HGF binds to the cMET receptor, a downstream cascade of events promotes cell proliferation, cell growth, and cell division.

Rationale for ficlatuzimab

- Ficlatuzimab is an IgG1 monoclonal antibody targeting the ligand HGF, which indirectly blocks cMET signaling.
- Ficlatuzumab has demonstrated differentiated inhibition of HGF/cMET downstream signaling and has a strong combinatory effect with the EGFR inhibitor cetuximab (**Figure 1)**.[5]
- Blocking both cMET and EGFR has the additive effect of blocking resistance and the two main drivers for HPV-negative R/M HNSCC.
- A phase 2 study assessed ficlatuzumab 20mg/kg plus cetuximab 500mg/m^2 every 2 weeks in R/M HNSCC patients that were anti-PD-1, cetuximab, and platinum-resistant. All responses occurred in the HPV-negative population with a median PFS of 4.2 months and ORR of 38% (including 2 CRs)[6]

Figure 1: Inhibition of cMet Activation[5]



Study Protocol and Procedures

Objectives

- **Primary:** Compare the efficacy by overall survival of ficlatuzumab plus cetuximab vs placebo plus cetuximab in participants with R/M HNSCC.
- **Secondary:** Evaluate additional endpoints of efficacy, compare the safety and tolerability of ficlatuzumab plus cetuximab vs placebo plus cetuximab in participants, to evaluate the pharmacokinetics (PK) of ficlatuzumab and cetuximab, and to assess the immunogenicity of ficlatuzumab via antidrug antibodies (ADAs) and neutralizing antibodies (nAB).

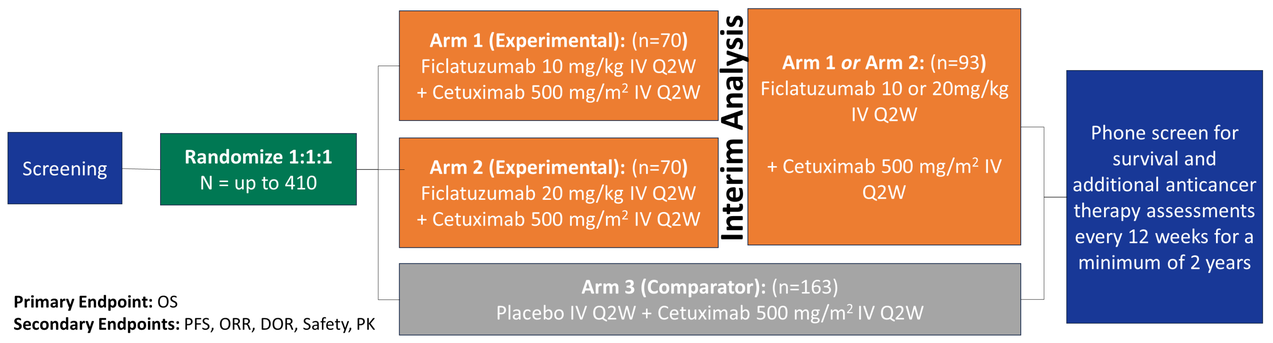
Study Design

- Phase 3, randomized, double-blind, international, multicenter study.
- Approximately 410 total participants will be randomized 1:1:1, with an interim analysis (IA) of efficacy and safety conducted of ficlatuzumab Arm 1 and Arm 2 when 70 randomized participants in each of these arms have completed their first restaging scan (**Figure 2**).
- Purpose of IA is to determine the optimal dose for further progression in the study as the single investigational arm.
- Radiology studies will be performed to evaluate target lesions and response per RECIST v1.1 at screening and then every 8 weeks following Cycle 1 Day 1 for the first year, every 12 weeks for years 2 and 3, and then every 6 months thereafter until disease progression or the start of subsequent anticancer therapy.

Figure 2: Study schema

FIERCE-HN

Screening	Randomization	Treatment Period	Safety Follow-Up
30 days	Within 3 days of first dose	Treat until disease progression, toxicity, withdrawal of consent, or start of new anti-cancer therapy	Minimum 2 years for all patients from first dose



Enrollment Criteria

- Key enrollment criteria are shown in **Table 1**

Table 1. Key Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion criteria
Patients ≥18 years with histologically and/or cytologically confirmed primary diagnosis of R/M HNSCC. a. Primary tumor locations of oropharynx (p16 negative), oral cavity, hypopharynx, or larynx Participants with oropharyngeal cancer will be required to have proof of HPV-negative status submitted based on a pathology report.	Participants may not have received >2 prior lines of anticancer therapy or prior treatment with cetuximab/alternative EGFR inhibitors for the treatment of R/M HNSCC
At least 1 measurable lesion by contrast CT or MRI scan according to RECIST v.1.1. Such lesions must not have been previously irradiated; if the measurable lesion(s) has been irradiated, clear progression must be documented.	Known untreated and uncontrolled brain metastases or leptomeningeal carcinomatosis Note: Participants with locally treated brain metastases are eligible provided 2 weeks have elapsed since local therapy. Participants are allowed to continue steroid taper during the start of study treatment.
Participants must have failed prior therapy with an anti-PD-1/PD-L1 ICI and with platinum-based chemotherapy administered in combination or sequentially, in either the locally advanced or R/M setting.	Significant cardiovascular disease, including: a. Cardiac failure New York Heart Association class III or IV b. Myocardial infarction, severe or unstable angina within 6 months prior to randomization c. History of serious ventricular arrhythmia
ECOG PS 0-1 with life expectancy of at least 12 weeks.	History of severe allergic or anaphylactic reactions or hypersensitivity to recombinant proteins or excipients in the investigational agent or cetuximab.
Patients with feeding tubes are eligible for the study.	

Summary

- R/M HPV-negative HNSCC continues to have poor outcomes for patients, despite advances in the HPV-positive HNSCC population.
- The phase 2 trial of ficlatuzumab plus cetuximab in HPV-negative patients has shown activity in the difficult to treat HPV-negative cohort, including 2 complete responses.[6]
- The FIERCE-HN trial is designed to determine whether the addition of ficlatuzumab to cetuximab will provide clinically meaningful benefit to patients with R/M HPV-negative HNSCC who have progressed after ICI and platinum-based therapy.

This phase 3 randomized, double blinded, placebo-controlled study will evaluate efficacy by overall survival of ficlatuzumab plus cetuximab vs placebo plus cetuximab in participants with R/M HPV-negative HNSCC.

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