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Randomized, Phase II Study of Ficlatuzumab With or Without Cetuximab in Patients With Cetuximab-Resistant, Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma

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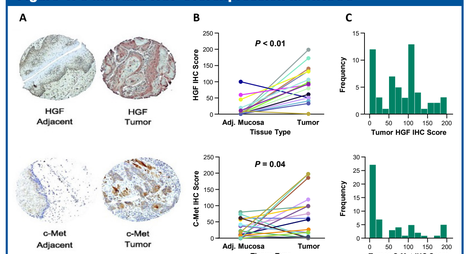
Background

- Roughly 90% of all head and neck cancers are squamous cell carcinomas (HNSCC), which is the sixth leading cancer by incidence worldwide[1]
  - Despite advances in multimodality therapy, 5-year overall survival (OS) is approximately 60% and has increased only incrementally in the past 2 decades[2]
  - Patients with recurrent/metastatic (R/M) HNSCC have a particularly poor prognosis, with a median OS of 6 to 10 months[2]
- To date, the only targeted therapy to treat HNSCC is cetuximab, an anti-epithelial growth factor receptor (EGFR) monoclonal antibody (mAb)[3]
  - EGFR is a transmembrane glycoprotein receptor kinase (RTK) that initiates a pleiotropic network of downstream signaling cascades, effecting cellular proliferation and angiogenesis
  - Despite aberrant signaling in HNSCC, primary or acquired resistance to cetuximab is inevitable, initiating interest in understanding resistance mechanisms by which to drive novel therapeutic options for this patient population
- An established resistance mechanism to anti-EGFR therapy is activation of alternative RTKs, including c-Met, the hepatocyte growth factor (HGF) receptor
  - c-Met and/or HGF are overexpressed in approximately 80% of HNSCC[4] (**Figure 1**)
  - Data have shown that HGF/c-Met inhibition may overcome resistance to anti-EGFR therapy in R/M HNSCC[5-9]

Figure 1. c-Met and HGF overexpression in HNSCC[4]



c-Met and HGF protein levels were assessed by immunohistochemistry (IHC) in HNSCC tumors and paired normal adjacent mucosa (n = 26). Intensity (integer scale 0 to +3) and percentage of tumor stained were evaluated. A weighted score of intensity times percentage of tumor stained was calculated. (A) Tumor tissues showed increased HGF and c-Met staining compared with paired normal adjacent mucosal tissues. (B) A two-tailed Wilcoxon signed-rank test for paired samples indicated significant differences in weighted HGF and c-Met intensity in tumor versus paired normal adjacent mucosa (HGF, $P < 0.001$; c-Met, $P = 0.04$). (C) HGF and c-Met IHC score frequency distributions indicated that higher levels of HGF were more frequently present in HNSCC tumors than c-Met tumors. Adapted from *Clinical Cancer Research*, 2009, 15(11), 3740-3750, Knowles LM et al, HGF and c-Met Participate in Paracrine Tumorigenic Pathways in Head and Neck Squamous Cell Cancer, with permission from AACR.

- **Combined EGFR/HGF/c-Met inhibition has also shown promising clinical activity in a phase 1b study of cetuximab in combination with a humanized HGF-inhibitory immunoglobulin G1 mAb, ficlatuzumab, in patients with cetuximab-resistant, R/M HNSCC[10]**
  - No dose-limiting toxicities were observed, and the recommended phase 2 dose (RP2D) was determined to be ficlatuzumab 20 mg/kg and cetuximab 500 mg/m^2 every 2 weeks (Q2W)
  - **Median progression-free survival (PFS) at the RP2D was 5 months (90% confidence interval [CI]; 2-not reached), and the clinical benefit rate was 67%**
  - Based on these findings, further study into this poor prognosis population is warranted

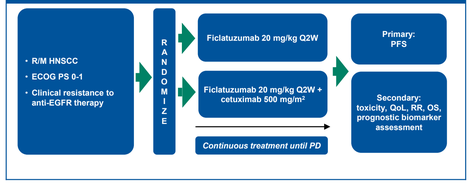
Study Hypothesis

- Inhibition of the HGF/c-Met pathway may overcome resistance to EGFR therapy and provide an important clinical benefit in patients with R/M HNSCC
- The cetuximab and ficlatuzumab combination or ficlatuzumab alone can improve the median PFS from the historical control of 2 months to 3.3 months (a 60% improvement) in patients with R/M HNSCC

Study Design

- This study (NCT03422536) is an investigator-sponsored, randomized, noncomparative, multicenter, 2-arm phase 2 trial of ficlatuzumab monotherapy and ficlatuzumab plus cetuximab combination therapy in patients with R/M HNSCC after failure of cetuximab (**Figure 2**)

Figure 2. Study design



ECOG PS, Eastern Cooperative Oncology Group performance status; RR, response rate; PD, progressive disease; QoL, quality of life.

- Patients will be randomized in a 1:1 ratio (ficlatuzumab/ficlatuzumab and cetuximab) and stratified by
  - Human papillomavirus (HPV) status: HPV-positive HNSCC will be assessed by p16 status performed per standard of care at the local site; patients must meet both of the following criteria: 1) either oropharynx or unknown primary site; and 2) p16+ by IHC where ≥70% of tumor cells demonstrate diffuse nuclear and cytoplasmic staining with p16 antibody
  - Study center
- Cetuximab will be administered first as an intravenous (IV) infusion at a dose of 500 mg/m^2 Q2W (± 3 days) beginning on the same day as the first dose of ficlatuzumab
- Ficlatuzumab will be administered as an IV infusion at a dose of 20 mg/kg Q2W (±3 days) beginning on the same day as the first dose of cetuximab
- Treatment will continue until disease progression or until one of the following criteria applies:
  - Intercurrent illness that prevents further administration of treatment
  - Unacceptable adverse events (AEs)
  - Patient election to withdraw from the study for any reason
  - General or specific changes in the patient's condition that would render the patient unacceptable for further treatment in the judgement of the investigator
- Up to 2 dose reductions will be allowed for patients with grade ≥3 hematologic toxicity or treatment-related AEs, and dose interruptions will be allowed for the management of persistent AEs
- Patients will be followed for survival every 3 months for 2 years after removal from the study or death (whichever occurs first); patients removed from the study for unacceptable AEs will be followed until resolution or stabilization of the AE
- Toxicity will be graded via the National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE) version 4.0
- Response assessment will be as follows:
  - Response and progression will be evaluated every 8 weeks using the revised Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
  - Measurable disease (**Table 1**) will be defined by the presence of ≥1 measurable lesion that can be accurately measured in ≥1 dimension as ≥20 mm (for neck lymph nodes; ≥15 mm)
  - Changes in the largest diameter (unidimensional measurement) of tumor lesions and the shortest diameter in the case of malignant lymph nodes will be used
  - Target lesions will be identified as all measurable lesions (up to a maximum of 2 per organ, and 5 lesions in total) and evaluated as complete response (CR), partial response (PR), PD, or stable disease (SD)
  - Measurement of non-target lesions will not be required, but the presence or absence of each will be noted throughout the duration of follow-up

Table 1. Evaluation for patients with measurable disease (ie, target disease)

Target lesions	Non-target lesions	New lesions	Overall response	Best overall response when confirmation is required
CR	CR	No	CR	≥4 weeks confirmation[a]
CR	Non-CR/non-PD	No	PR	≥4 weeks confirmation[a]
CR	Not evaluated	No	PR	
PR	Non-CR/non-PD/ not evaluated	No	PR	
SD	Non-CR/non-PD/ not evaluated	No	SD	Documented at least once ≥4 weeks from baseline
PD	Any	Yes or no	PD	
Any	PD[b]	Yes or no	PD	No prior SD, PR, or CR
Any	Any	Yes	PD	

[a]Only for nonrandomized trials with response as the primary endpoint. [b]In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

- Before initiation of treatment, all patients will undergo a mandatory research biopsy to investigate the relationship between candidate tumoral, genomic, peripheral, and immune biomarkers and clinical outcomes (PFS and response) in each arm, including:
  - HGF/c-Met; EGFR and EGFR/HER2 dimers; mutations in *PIK3CA*, *PTEN*, and *HRAS*; peripheral serum biomarkers including VeriStrat, HGF, soluble HGF, and interleukin 6; peripheral lymphocyte populations; and archived and baseline immune infiltrate
- Three mechanistic biomarkers will be prioritized for specialized alpha spending
  - Baseline VeriStrat
  - Baseline HGF/c-Met dimers
  - Baseline pMet

Study Objectives

Primary Objective

- To assess the efficacy of ficlatuzumab, with or without concurrent cetuximab, in patients with cetuximab-resistant, R/M HNSCC as measured by PFS

Secondary Objectives

- To describe toxicity and patient-reported QoL
- To evaluate RR and OS in both treatment arms
- To evaluate the relationship between clinical outcomes (PFS, RR) and candidate tumoral, genomic, peripheral, and immune biomarkers

Inclusion/Exclusion Criteria

Key Inclusion Criteria

- Adults aged 18 years
- Consent to a research biopsy of tumor tissue at baseline
- ECOG PS 0 or 1 at the time of informed consent
- Measurable disease per RECIST version 1.1 criteria
- Histologically confirmed HNSCC from any primary site
- R/M disease, fulfilling ≥1 of the following criteria:
  - Incurable disease (as assessed by surgical or radiation oncology)
  - Metastatic disease
  - Persistent or progressive disease following curative-intent radiation
- Cetuximab resistant, fulfilling ≥1 of the following criteria:
  - Disease persistence or recurrence within 6 months of completing definitive radiotherapy for locally advanced disease (radiation must have included concurrent cetuximab; induction chemotherapy may or may not have included cetuximab)
  - Disease progression during or within 6 months of cetuximab treatment in the R/M setting
  - Prior cetuximab exposure (any line of therapy)
- Platinum-resistant or platinum-ineligible, fulfilling ≥1 of the following criteria:
  - Disease persistence or recurrence within 6 months of completing definitive radiotherapy for locally advanced disease, where platinum chemotherapy was administered as a component of induction and/or concurrent systemic treatment
  - Disease progression within 6 months of treatment with platinum chemotherapy
  - Deemed as an unacceptable candidate for platinum chemotherapy (as assessed by the local investigator)
  - Prior platinum exposure (any line of therapy)
- If eligible for immunotherapy, patients must have prior immunotherapy exposure (anti-PD-1 or anti-PD-L1)
  - Prior exposure to investigational immunotherapies (including anti-CTLA-4, anti-OX40, anti-CD40, anti-CD27, and anti-TNFR antibodies) is also considered acceptable
- Within 28 days of registration, the following laboratory values must be measured:
  - Absolute neutrophil count ≥1500/mm^3
  - Platelet count ≥75,000/mm^3
  - Creatinine clearance ≥40 mL/minute
  - Serum bilirubin ≤1.5 times the upper limit of normal (ULN)
  - Aspartate aminotransferase and alanine aminotransferase ≤3× ULN

Key Exclusion Criteria

- Nasopharyngeal primary site (if World Health Organization type III [nonkeratinizing and positive for Epstein-Barr virus], as assessed by investigator at the local site)
- History of severe allergic or anaphylactic reactions or hypersensitivity to recombinant proteins or excipients
- Prior treatment with an HGF/c-Met inhibitor (rilotumumab, crizotinib, MetMAb, or ARQ197) or systemic antibiotics or antifungals within 7 days before study day 1
- Uncontrolled central nervous system metastases
- Failure to recover to grade 1 or baseline from all AEs from previous therapy
- Significant pulmonary disease (including pulmonary hypertension or interstitial pneumonitis), electrolyte imbalance, cardiovascular disease, or thrombotic or embolic events
- Decreased serum albumin <30 g/L (<3 g/dL)
- Peripheral edema grade ≥2 (per NCI-CTCAE version 4.0)
- History of second malignancy within 2 years before study day 1 (with the exception of excised and cured non-melanoma skin cancer, carcinoma in situ of breast or cervix, superficial bladder cancer, stage I differentiated thyroid cancer that is resected or observed, or pT1a /pT1b prostate cancer comprising <5% of resected tissue with normal prostate-specific antigen since resection, or cT1a/cT1b prostate cancer treated with brachytherapy or external beam radiation therapy with normal PSA since radiation)
- Major surgery within 6 weeks before study day 1
- HIV-positive patients receiving combination antiretroviral therapy
- Pregnant or breastfeeding women

Statistical Methods

- The primary objective is to estimate PFS in both study arms compared with an historical control of 2 months represented by dealer's choice chemotherapy in the phase 3 trial of nivolumab in platinum-refractory HNSCC; both arms will be tested for a 60% increase of PFS from a median of 2 months to 3.33 months
  - PFS will be tested using a log-rank test with 90% power while assuming a 0.10 one-sided type 1 error rate
  - 66 patients (33 for ficlatuzumab, 33 for ficlatuzumab/cetuximab) with a total of 33 events per arm will be required
  - Assuming a dropout percentage of 10%, 74 patients in total will be accrued to obtain the necessary 66 eligible randomized patients
  - Enrollment will take 24 months, with an additional follow-up of 6 months (making the study duration approximately 2.5 years)
  - If both arms achieve the hypothesized PFS, the numerically superior arm will be advanced to phase 3 testing
- PFS and OS will be estimated for each arm using a Kaplan-Meier estimates
- Toxicity and RR will be reported with an exact 95% CI
- The relationship between PFS and candidate biomarkers will be assessed using Cox proportional hazards
  - Baseline VeriStrat, HGF/c-Met dimers, and baseline pMet will be tested at $\alpha = 0.05$ in order to guarantee a maximum 15% false discovery rate
- Other candidate biomarkers will be quantitatively measured and evaluated as predictors of PFS and/or tumor response in generalized linear models
  - Calculated *P* values for testing the significance of prediction models will be adjusted for false discovery using the Benjamini and Hochberg method
- The study will include a continuous Bayesian monitoring rule for futility

References

1. Global Burden of Disease Cancer Collaboration, et al. *JAMA Oncol.* 2017;3:524-548.
2. Howlander N, et al. SEER cancer statistics review, 1975-2013. http://seer.cancer.gov/csr/1975_2013/.
3. Vermorken JB, et al. *N Engl J Med.* 2008;359:1116-1127.
4. Knowles LM, et al. *Clin Cancer Res.* 2009;15:3740-3750.
5. Seiwert TY, et al. *Cancer Res.* 2009;69:3021-3031.
6. Wilson TR, et al. *Nature.* 2012;487:505-509.
7. Takahashi N, et al. *Br J Cancer.* 2014;110:2716-2727.
8. Yamada T, et al. *J Thorac Oncol.* 2012;7:272-280.
9. Tanaka H, et al. *Int J Cancer.* 2011;129:1410-1416.
10. Bauman JE, et al. *J Clin Oncol.* 2017;35(15_suppl):6038.

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