A Multicenter, Randomized, Double-Blind, Phase 2/3 Study of Ficerafusp Alfa (BCA101) or Placebo in Combination With Pembrolizumab for First-Line Treatment of PD-L1-Positive, Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma: The FORTIFI-HN01 Study

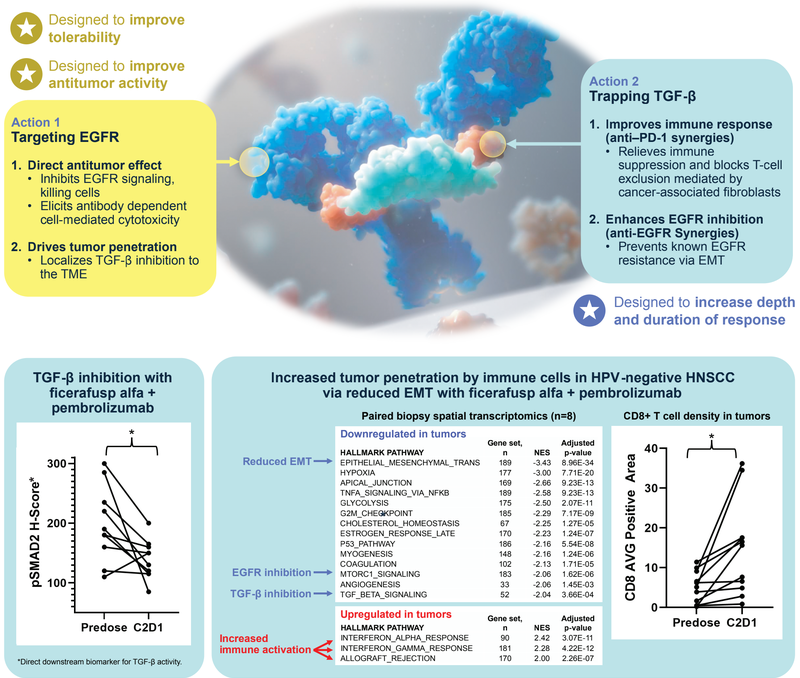
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BACKGROUND

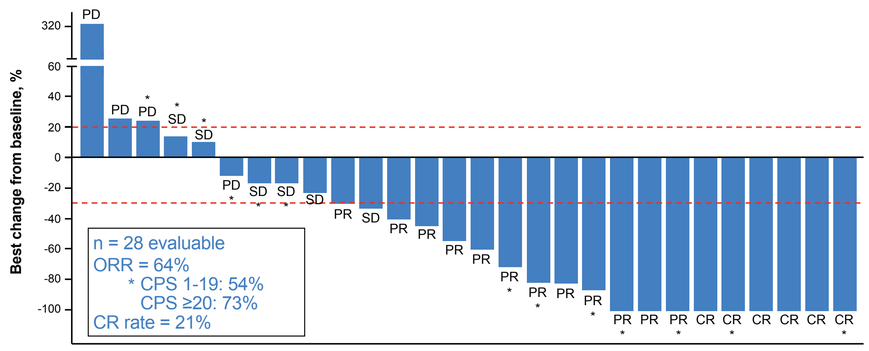
- Inadequate tumor penetration by immune cells has challenged the treatment of many solid tumors[1,2]
- Human papilloma virus (HPV)-negative head and neck squamous cell carcinoma (HNSCC) is an aggressive disease characterized by high levels of epithelial growth factor receptor (EGFR) and transforming growth factor-β (TGF-β) associated with immune cell exclusion, resistance to standard treatments, and poor prognosis[2-6]
- Ficerafusp alfa is a first-in-class bifunctional antibody designed to drive tumor penetration by breaking barriers in the tumor microenvironment (TME) that have challenged the treatment of multiple solid tumors (**Figure 1**)[3]
  - Specifically, ficerafusp alfa combines two clinically validated targets: an EGFR-directed monoclonal antibody with a domain that binds to human TGF-β
  - Through this targeted mechanism, ficerafusp alfa reverses the fibrotic and immune-excluded tumor microenvironment driven by TGF-β signaling to enable tumor penetration that drives deep and durable responses

Figure 1. Ficerafusp alfa mechanism of action[3]



- Ficerafusp alfa-driven tumor penetration results in clinically meaningful treatment benefits
  - A phase 1/1b study (NCT04429542) assessed ficerafusp alfa in combination with pembrolizumab as first-line (1L) treatment for HPV-negative, PD-L1 combined positive score (CPS) ≥1, recurrent or metastatic (R/M) HNSCC[7,8]
  - Ficerafusp alfa treatment resulted in deep and durable responses (**Figure 2**) with prolonged progression-free survival (PFS) and overall survival (OS) compared with historical benchmarks in HPV-negative HNSCC[7,8]
  - Paired biopsies showed inhibition of EGFR and TGF-β, reduced epithelial-mesenchymal transition (EMT), and increased immune activation, demonstrating increased tumor penetration by immune cells (**Figure 1**)[3]
  - This provides a strong rationale for combining ficerafusp alfa with pembrolizumab in tumors where EMT, a known resistance mechanism to immune checkpoint inhibitors, impedes tumor penetration of key immune cells that are needed to generate clinically meaningful responses[3,7-9]

Figure 2. Tumor responses with 1L ficerafusp alfa + pembrolizumab in patients with HPV-negative, PD-L1 CPS ≥1, R/M HNSCC (phase 1b cohort)[9]



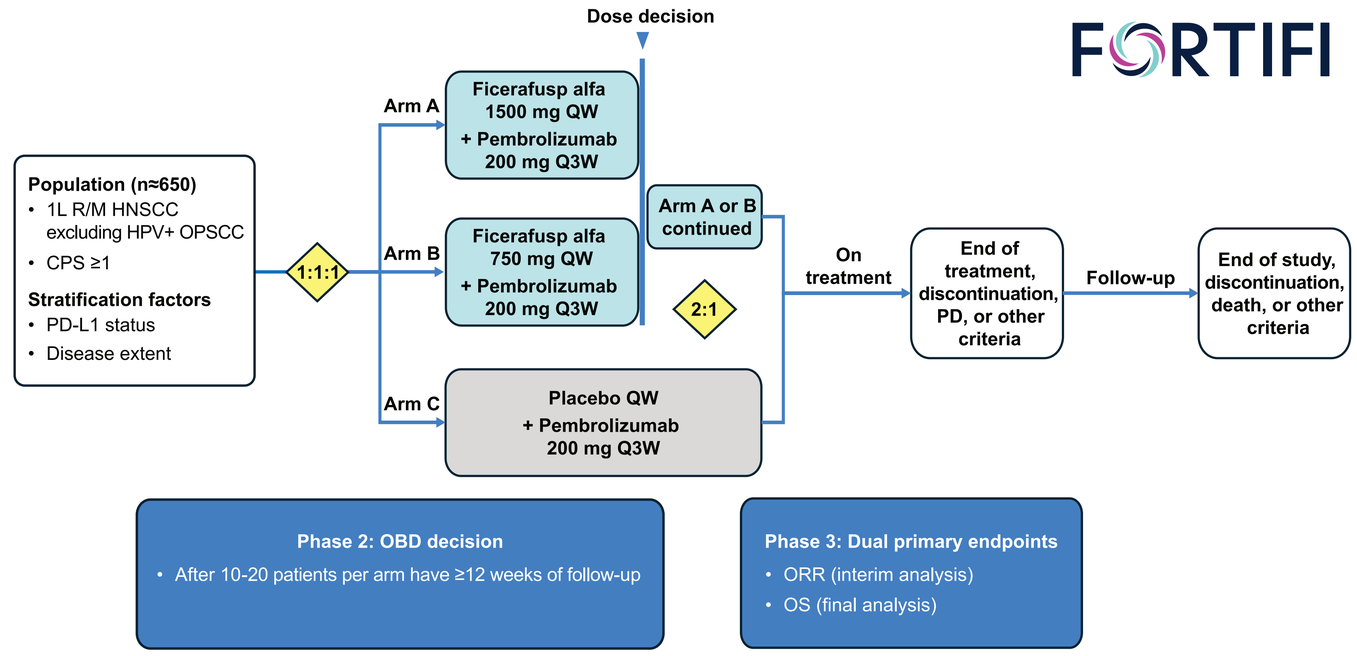
Investigator-assessed best overall response per RECIST 1.1. Includes confirmed and unconfirmed responses. 1 CR was detected via FDG-PET scan.
CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; uPR, unconfirmed partial response.

FORTIFI-HN01 STUDY DESIGN

DESIGN AND OBJECTIVES

- Phase 2/3, seamless, global, multicenter, randomized, placebo-controlled, double-blind study (**Figure 3; Table 1**)
- Phase 2 primary objective:
  - Determine the optimal biological dose (OBD) of ficerafusp alfa, supported by safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy
- Phase 3 objectives:
  - Primary: Compare objective response rates (ORRs) and OS with ficerafusp alfa in combination with pembrolizumab vs placebo in combination with pembrolizumab
  - Secondary: Evaluation of safety, additional efficacy measures, and patient-reported outcomes

Figure 3. FORTIFI-HN01 phase 2/3 study design (NCT06788990)



OPSCC, oropharyngeal squamous cell carcinoma; Q3W, every 3 weeks; QW, weekly.

Table 1. Key eligibility criteria

Key inclusion criteria
Histologically or cytologically confirmed R/M HNSCC
Eligible primary tumor locations: oral cavity, hypopharynx, larynx, or oropharynx (HPV-negative if OPSCC)
PD-L1 CPS ≥1
No prior systemic therapy in the R/M setting, and completed systemic therapy >6 months prior if given as part of multimodal treatment for locoregionally advanced disease
Measurable disease per RECIST 1.1
Eastern Cooperative Oncology Group performance status 0 or 1
Age ≥18 years
Key exclusion criteria
Disease suitable for local therapy administered with curative intent
Prior treatment with therapy targeted to TGF-β
Prior therapy with an anti-EGFR antibody (except for radiosensitizing and multimodal treatment for locoregionally advanced disease)
Prior neoadjuvant and/or adjuvant immune checkpoint inhibitor therapy completed ≤6 months prior to study treatment initiation
History of grade ≥2 intolerance or hypersensitivity reaction to anti-EGFR therapy or other murine proteins

CONTACT

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