The impact of depth of response on long-term clinical outcomes: Exploratory analyses from multiple expansion cohorts of a phase 1/1b study of ficerafusp alfa plus pembrolizumab in first-line recurrent/ metastatic HPV-negative head and neck squamous cell carcinoma

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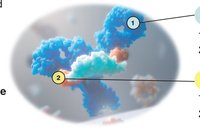
BACKGROUND

- **Ficerafusp alfa** is a first-in-class bifunctional EGFR-targeted antibody designed to trap TGF-β, thereby enabling **tumor penetration** and driving deep and durable responses[1,2]
- An ongoing Phase 1/1b study is evaluating ficerafusp alfa in combination with pembrolizumab as first-line (1L) treatment for PD-L1 combined positive score (CPS) ≥1, recurrent or metastatic (R/M), human papillomavirus (HPV)-negative head and neck squamous cell carcinoma (HNSCC)[3]
- Initial findings have demonstrated high objective response rates (ORRs); rapid, deep and durable responses; prolonged overall survival (OS), and a manageable safety profile[4-6]
- Depth of response (maximum percentage reduction in sum of target lesion diameters from baseline recorded prior to disease progression) is an emerging indicator of long-term benefit; however, data are limited in R/M HPV-negative HNSCC[7]
- Retrospective analyses of pembrolizumab-treated patients suggest that a depth of response ≥45% predicts longer OS and progression-free survival (PFS)[8]
- **The objective of the current analysis was to evaluate whether deep responses (defined as depth of response ≥80%) with ficerafusp alfa plus pembrolizumab correlate with longer duration of response (DOR), PFS, and OS in this 1L cohort**

Additional data from this study, including an integrated clinical summary with long-term outcomes, are presented concurrently in this session. Please see **Abstract #6040 (poster board #497)**

FICERAFUSP ALFA: A BIFUNCTIONAL TGF-β LIGAND-TRAPPING × EGFR-TARGETED ANTIBODY[1]

TGF-β trapping combined with **EGFR targeting** remodels the fibrotic **TME,** enhances **tumor penetration** of immune cells, and may synergize with ICIs for **deep, durable** responses



Targeting EGFR
1. Direct antitumor effect
2. Drives tumor targeting

Trapping TGF-β
1. Enables **tumor penetration**
2. Prevents resistance

PHASE 1/1B STUDY OF FICERAFUSP ALFA IN 1L CPS ≥1 R/M HPV-NEGATIVE HNSCC (NCT04429542)

Part A: Dose escalation (3+3 design)[3]

Ficerafusp alfa + **pembrolizumab**

R/M HNSCC

Ficerafusp alfa 240-1500 mg QW IV
Pembrolizumab 200 mg Q3W IV

MTD not reached

Part B: Dose expansion in 1L R/M HPV-negative HNSCC (Simon 2-stage design)[4-6]

Expansion cohorts

- **Ficerafusp alfa 750 mg QW** + **Pembrolizumab 200 mg Q3W**
- **Ficerafusp alfa 1500 mg QW*** + **Pembrolizumab 200 mg Q3W**
- **Ficerafusp alfa 2000 mg Q2W** + **Pembrolizumab 400 mg Q6W**

Primary objective: Safety/tolerability

Secondary objectives: PK/PD, immunogenicity, preliminary efficacy

Key inclusion criteria:
- 1L R/M HNSCC
- Primary tumor in oral cavity, oropharynx, larynx, or hypopharynx
- PD-L1 CPS ≥1†
- ECOG PS 0-1

- **As of March 31, 2026**, 91 patients received the study drug (safety analysis [SA] set) and 85 were evaluable for efficacy (efficacy evaluable [EE] set)
- In the 750 mg QW, 1500 mg QW, and 2000 mg Q2W cohorts, respectively:
  - Patient numbers in the SA/EE populations were 31/30, 30/28, and 30/27
  - **Median (95% CI) follow-up was 20 (20-22), 36 (36-43) and 24 (12-27) months**
- A pooled analysis of the EE population across all three dose cohorts evaluated whether a deep response (≥80% shrinkage) predicted prolonged DOR, PFS, and OS compared with standard partial response (PR <80%). Patients with stable disease (SD) and progressive disease (PD) were included in survival plots for context
- **A cutoff of ≥80% tumor shrinkage was established to define deep response,** representing the observed radiographic threshold that serves as a biological proxy for 'near-complete clearance' of target lesions, **capturing profound tumor reduction despite limited residual disease or scar tissue**
- Limitations
  - This was a post hoc exploratory analysis limited by small sample sizes in each subgroup
  - Depth of response categories are not validated and a unified standard threshold for deep response has not been established[7,8]

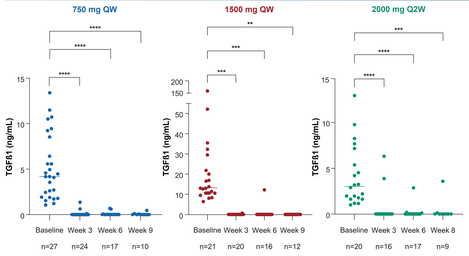
CI, confidence interval; **ECOG PS,** Eastern Cooperative Oncology Group performance status; **IV,** intravenous; **MTD,** maximum tolerated dose; **PK/PD,** pharmacokinetics/pharmacodynamics; **Q2W,** every 2 weeks; **Q3W,** every 3 weeks; **Q6W,** ever 6 weeks; **QW,** once weekly
*The 1500 mg QW cohort also enrolled HPV-positive patients, who were not included in the current analysis.
†PD-L1 CPS was assessed locally in archival or fresh samples using the 22C3 immunohistochemistry or other validated assay.

BASELINE CHARACTERISTICS

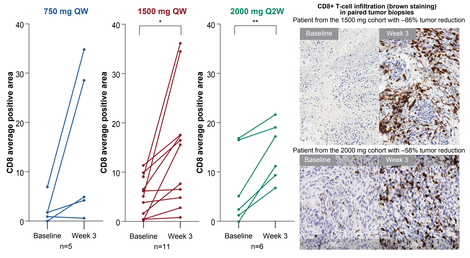
	750 mg QW (N=31)	1500 mg QW (N=30)	2000 mg Q2W (N=30)
Age, median (min-max)	64 (28-78)	63 (31-84)	63 (32-94)
Sex, n (%)			
Male	20 (65)	19 (63)	20 (67)
Female	11 (35)	11 (37)	10 (33)
Primary disease site, n (%)			
Oral cavity	19 (61)	14 (47)	19 (63)
Oropharynx (HPV negative)	4 (13)	8 (27)	6 (20)
Hypopharynx	5 (16)	4 (13)	2 (7)
Larynx	3 (10)	4 (13)	3 (10)
CPS, n (%)			
1-19	12 (39)	15 (50)	15 (50)
≥20	19 (61)	15 (50)	15 (50)
LR vs DM disease, (%)			
LR only	16 (52)	9 (30)	19 (63)
DM only	5 (16)	7 (23)	5 (17)
LR + DM	10 (32)	14 (47)	6 (20)
Target lesion diameter (mm) at baseline, median (min-max)	41 (11-131)	49 (10-133)	33 (10-187)
Sum of target lesion diameters at baseline, n (%)			
>50 mm	10 (32)	14 (47)	11 (37)
>70 mm	4 (13)	8 (27)	7 (23)
ECOG PS, n (%)			
0	11 (35)	11 (37)	10 (33)
1	20 (65)	19 (63)	20 (67)

DM, distant metastatic; **LR**, locoregional.

TGF-β1 NEUTRALIZATION IN PLASMA AND CD8+ T CELL INFILTRATION IN TUMORS



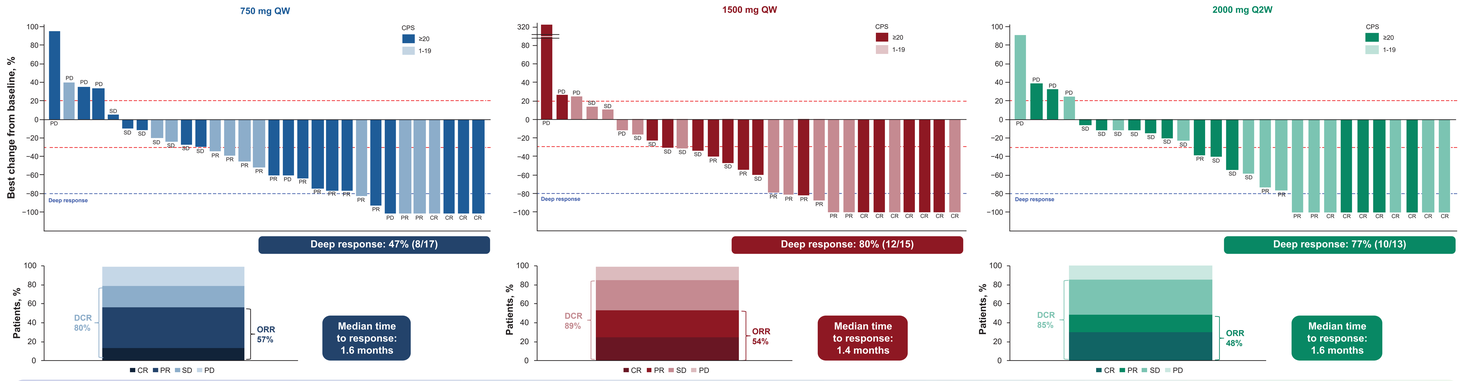
TGF-β neutralization was performed on pre- and post-treatment plasma samples using the Meso Scale Discovery platform. ****p<0.0001, ***p<0.001, **p<0.01, *p<0.05 (1-way ANOVA [analysis of variance]).



- Sustained TGF-β neutralization in plasma was observed across all dose groups
- Increased CD8 T cell tumor infiltration was observed in all dose groups, reaching statistical significance in the 1500 mg QW and 2000 mg Q2W dose groups

Paired tumor biopsies were analyzed by immunohistochemistry for CD8+ T cells. **p<0.01, *p<0.05 (paired T-test).

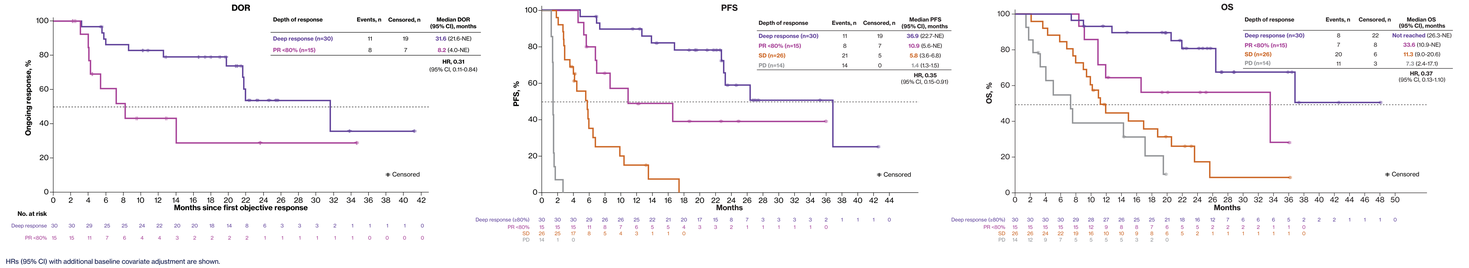
BEST OVERALL RESPONSE, OBJECTIVE RESPONSE RATES, AND DEEP RESPONSES IN FICERAFUSP ALFA DOSE COHORTS



- High ORRs were demonstrated across all three evaluated dose levels; **DCRs were ≥80% across all doses**
- **Responses occurred rapidly (~1.5 months),** with higher dose intensities driving maximal tumor shrinkage
- **More than two-thirds of responders at higher doses achieved deep responses (≥80% tumor shrinkage)**

CR, complete response; **DCR**, disease control rate; **PD**, progressive disease; **PR**, partial response; **SD**, stable disease.

CORRELATION BETWEEN DEPTH OF RESPONSE AND LONG-TERM OUTCOMES IN POOLED FICERAFUSP ALFA DOSE COHORTS



HRs (95% CI) with additional baseline covariate adjustment are shown.

Deep response (≥80% tumor shrinkage) was associated with substantially prolonged DOR compared with **PR <80%** (HR, 0.31 [95% CI, 0.11-0.84])

Patients achieving **deep response (≥80% tumor shrinkage)** had a clinically meaningful 65% reduction in the risk of disease progression or death compared with **PR <80%** (HR, 0.35 [95% CI, 0.15-0.91)

Achieving a **deep response (≥80% tumor shrinkage)** substantially improved OS vs **PR <80%**, reducing the risk of death by 63% (HR, 0.37 [95% CI, 0.13–1.10])

KEY TAKEAWAYS

- **Rapid, deep, and durable responses** were observed across all evaluated doses and schedules following **1L treatment with ficerafusp alfa plus pembrolizumab** in patients with **HPV-negative HNSCC**
  - **Confirmed ORR of 54% at the optimal biological dose of ficerafusp alfa 1500 mg QW**
- Clinical outcomes are supported by paired biopsy data demonstrating robust CD8+ T-cell tumor penetration, confirming that **neutralizing TGF-β-mediated immune exclusion** provides a clear biological mechanism for the deep and durable responses observed
- Responses occurred rapidly and continued to deepen over time; notably, high rates of **deep response (≥80% shrinkage)** were observed in responders:
  - **80%** of responders treated at the Phase 3 optimal biological dose (**1500 mg QW**)
  - **77%** of responders treated with an alternate biweekly regimen (**2000 mg Q2W**)
- Achieving a **deep response was strongly associated with better long-term efficacy outcomes**, including substantially prolonged DOR, PFS, and OS compared with a PR <80%
- In R/M HPV-negative HNSCC, >70% of patients present with locoregional recurrence and bulky, highly symptomatic tumors, thus rapid and profound tumor clearance are critically important; data reported here suggest **depth of response may serve as a clinically meaningful surrogate for long-term outcomes** in patients with this difficult-to-treat disease
- The **consistent depth and durability of responses** observed across all cohorts provide a strong clinical rationale for utilizing **ORR as a predictive surrogate endpoint in the planned Phase 3 FORTIFI-HN01 trial interim analysis**

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