Sustained depth and durability of response with TGF-β trapping in recurrent or metastatic HPV-negative head and neck squamous cell carcinoma: Long-term results from expansion cohorts of a Phase 1/1b study of ficerafusp alfa plus pembrolizumab

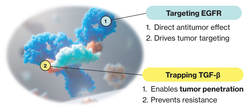
Deborah J. Wong,[1] Christine H. Chung,[2] Glenn J. Hanna,[3] Dan P. Zandberg,[4] Tamara A. Sussman,[5] Eric Sherman,[6] Neal Akhave,[7] Assuntina G. Sacco,[8] Ariel Birnbaum,[9] Susannah Calhoun,[10] Ling Gao,[10] Rita Dalal,[10] Zhao Yang,[10] John Kaczmar[11]

[1]University of California, Los Angeles, CA, USA; [2]Moffitt Cancer Center, Tampa, FL, USA; [3]Center for Head and Neck Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [4]UPMC Hillman Cancer Center, Pittsburgh, PA, USA; [5]Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA; [6]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [7]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [8]UC San Diego Health, Moores Cancer Center, La Jolla, CA, USA; [9]Rhode Island Hospital, Providence, RI, USA; [10]Bicara Therapeutics, Boston, MA, USA; [11]Hollings Cancer Center, Medical University of South Carolina, Charleston, SC, USA

BACKGROUND

- While immune checkpoint inhibitors (ICIs) have shifted the treatment paradigm in recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC), long-term survival remains limited in many patients[1-4]
- Patients with **human papillomavirus (HPV)-negative HNSCC** often exhibit an immune-excluded tumor microenvironment (TME) characterized by overexpression of epidermal growth factor receptor (EGFR) and transforming growth factor (TGF)-β, which is associated with poor prognosis and resistance to ICIs[5-8]
- **Ficerafusp alfa** is a first-in-class bifunctional antibody designed to enable **tumor penetration** by breaking barriers in the TME through simultaneous targeting of EGFR and neutralization of TGF-β[9]
- The safety and efficacy of first-line (1L) ficerafusp alfa in combination with pembrolizumab in PD-L1 combined positive score (CPS) ≥1, R/M HPV-negative HNSCC has been shown in an ongoing Phase 1/1b study[10]
  - Preliminary evaluations of the 750 mg weekly (QW), 1500 mg QW, and 2000 mg every 2 weeks (Q2W) cohorts successfully established early clinical activity and tolerability of the bifunctional mechanism[11-13]
- **Herein we present an integrated analysis of all three dose cohorts with extended follow-up, highlighting TGF-β inhibition, depth of response, long-term survival outcomes, and sustained disease control**

Ficerafusp alfa: A bifunctional TGF-β ligand-trapping × EGFR-targeted antibody[9]



Additional data from this study, including exploratory analyses to evaluate correlation between depth of response and clinical outcomes, are presented concurrently in this session. Please see **Abstract #6058 (poster board #515)**

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

Part A: Dose escalation
(3+3 design)[10]

Ficerafusp alfa + pembrolizumab

R/M HNSCC

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

MTD not reached

Expansion cohorts

Part B: Dose expansion in 1L R/M HPV-negative HNSCC
(Simon 2-stage design)[11-13]

- **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[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**

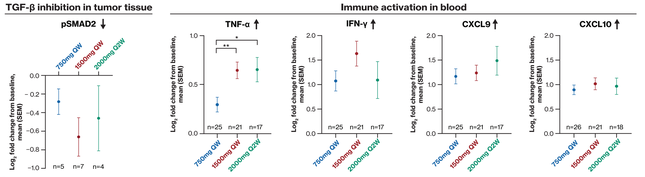
ECOG PS, Eastern Cooperative Oncology Group performance status; **IV**, intravenous; **MTD**, maximum tolerated dose; **PK/PD**, pharmacokinetics/pharmacodynamics; **Q2W**, every 2 weeks; **Q3W**, every 3 weeks; **Q6W**, every 6 weeks; **QW**, once weekly.
*The 1500 mg QW cohort also enrolled HPV-positive 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.

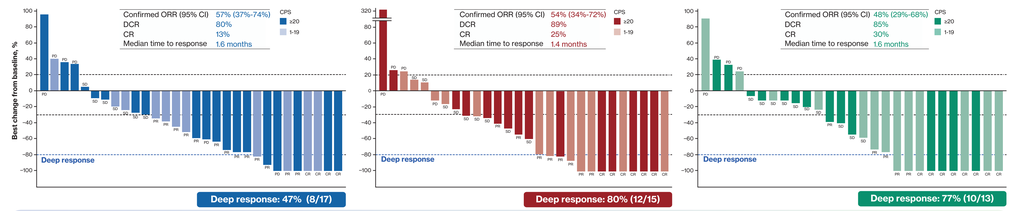
TGF-β INHIBITION AND IMMUNE ACTIVATION ACROSS FICERAFUSP ALFA DOSES



- **Consistent with the observed clinical dose-response**, biomarker analyses demonstrate a trend toward enhanced localized TGF-β pathway inhibition (measured via pSMAD2 reduction in tumor tissue) at the 1500 mg QW and 2000 mg Q2W dose levels
- **Further supporting the sustained clinical benefit**, this optimized target engagement is accompanied by the upregulation of key circulating immune markers (TNF-α, IFN-γ, CXCL9, and CXCL10), reflecting systemic immune activation at higher doses
- **Collectively, these data provide mechanistic validation** that maximizing intra-tumoral TGF-β inhibition elicits the immune activation responsible for the depth and durability of clinical responses observed in these cohorts

Paired tumor biopsies were analyzed by immunohistochemistry for pSMAD2. Cytokine analysis was performed on pre- and post-treatment (QW: 3 weeks, Q2W: 6 weeks) plasma samples using the Meso Scale Discovery platform. *pc.05, **p ≤.01 (Mann-Whitney test).
CXCL9, C-X-C motif chemokine ligand 9; **CXCL10**, C-X-C motif chemokine ligand 10; **IFN-γ**, interferon gamma; **pSMAD2**, phosphorylated SMAD2; **TGF-β**, transforming growth factor beta; **TNF-α**, tumor necrosis factor alpha.

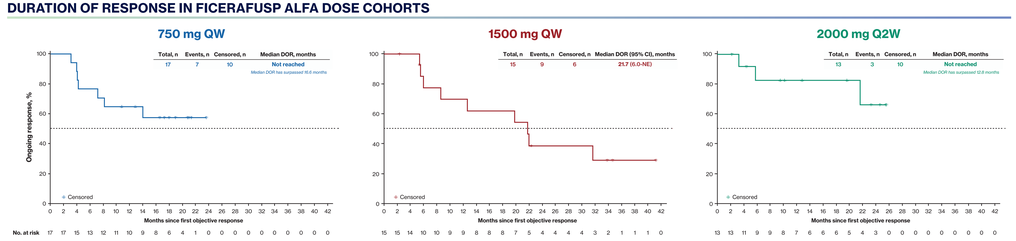
BEST OVERALL RESPONSE, OBJECTIVE RESPONSE RATES, AND DEEP RESPONSES IN FICERAFUSP ALFA DOSE COHORTS



- ORRs were comparable across all three evaluated dose levels and responses occurred rapidly, with higher dose intensities driving maximal tumor shrinkage
- **More than two-thirds of responders achieved deep responses (≥80% tumor shrinkage)**

CI, confidence interval; **CR**, complete response; **DCR**, disease control rate; **ORR**, objective response rate; **PD**, progressive disease; **PR**, partial response; **SD**, stable disease.

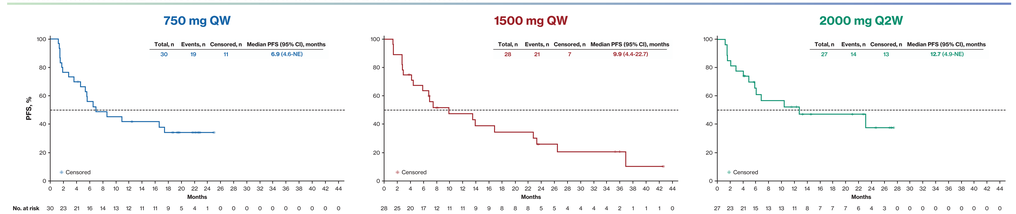
DURATION OF RESPONSE IN FICERAFUSP ALFA DOSE COHORTS



- After a **median follow-up of 36 months, median DOR in the 1500 mg QW cohort was of 21.7 months**, with 10% of patients (n=3) remaining on active treatment. This prolonged durability is consistent with a remodeled TME following ficerafusp alfa-mediated TGF-β trapping
- While DOR data are immature for the 750 mg QW and 2000 mg Q2W cohorts, early trajectories suggest a similar profile of prolonged response durability established at the 1500 mg QW dose

NE, not estimable; **DOR**, duration of response.

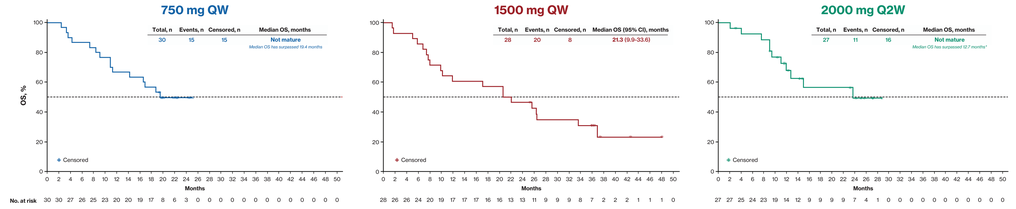
PROGRESSION-FREE SURVIVAL IN FICERAFUSP ALFA DOSE COHORTS



- **All dosing cohorts demonstrated clinically meaningful and consistent disease control in a historically difficult-to-treat 1L HPV-negative population**
- A clear dose-response relationship was observed; escalation from 750 mg (median PFS 6.9 months) to the **1500 mg (median PFS 9.9 months)** and 2000 mg Q2W (median PFS 12.7 months) cohorts illustrates the clinical value of optimized TGF-β neutralization and sustained disease control across varying doses and schedules

PFS, progression-free survival.

OVERALL SURVIVAL IN FICERAFUSP ALFA DOSE COHORTS



- At a median follow-up of 36 months, the **1500 mg QW** cohort achieved a clinically meaningful **median OS of 21.3 months**; the tail of the curve reflects **durable long-term survival**, highlighted by a landmark **3-year OS rate of 31%**
- Early trajectories for the **maturing 750 mg and 2000 mg Q2W cohorts** remain consistent with this profile, **demonstrating efficacy across lower exposures and alternative dose schedules**

OS, overall survival.
*Data maturation reflects a bimodal enrollment distribution: in the initial 15 EE patients (median follow-up, 27 months), median OS was not reached (95% CI, 9-NE, median has surpassed 23.6 months). The remaining 12 EE patients had a median follow-up of 11.7 months.

CONFIRMED ORR BY CPS, TUMOR BURDEN, AND DISEASE SITE IN FICERAFUSP ALFA DOSE COHORTS

		750 mg QW (n=30)	1500 mg QW (n=28)	2000 mg Q2W (n=27)
CPS, % (n/N)	1-19	**73** (8/11)	**54** (7/13)	**57** (8/14)
	≥20	**47** (9/19)	**53** (8/15)	**38** (5/13)
Tumor burden, % (n/N) (sum of target lesion diameters)	≤50 mm	**55** (11/20)	**53** (8/15)	**53** (9/17)
	>50 mm	**60** (6/10)	**54** (7/13)	**40** (4/10)
	>70 mm	**50** (2/4)	**43** (3/7)	**33** (2/6)
Extent of disease, % (n/N)	LR only	**38** (6/16)	**62** (5/8)	**50** (7/14)
	DM only	**100** (5/5)	**29** (2/7)	**40** (2/5)
	LR + DM	**67** (6/9)	**62** (8/13)	**50** (4/8)

Ficerafusp alfa demonstrated high ORRs across all doses, regardless of CPS score, high tumor burden, or metastatic site involvement

SAFETY WITH FICERAFUSP ALFA + PEMBROLIZUMAB IN FICERAFUSP ALFA DOSE COHORTS

Preferred term, n (%)	750 mg QW (N=31)		1500 mg QW (N=30)		2000 mg Q2W (N=30)	
	Any grade*	Grade 3	Any grade†	Grade 3	Any grade*	Grade 3
Any TRAE	31 (100)	11 (35)	28 (93)	15 (50)	29 (97)	16 (53)
Dermatitis acneiform	27 (87)	1 (3)	23 (77)	4 (13)	24 (80)	3 (10)
Pruritus	13 (42)	1 (3)	16 (53)	1 (3)	11 (37)	1 (3)
Anemia	8 (26)	3 (10)	13 (43)	7 (23)	15 (50)	8 (27)
Hypomagnesemia	7 (23)	0	13 (43)	0	6 (20)	0
Fatigue	13 (42)	0 (0)	11 (37)	1 (3)	12 (40)	1 (3)
Dry skin	10 (32)	0	9 (30)	0	9 (30)	0
Hypophosphatemia	10 (32)	0	8 (27)	0	6 (20)	0
Hypokalemia	8 (26)	1 (3)	8 (27)	0	5 (17)	0
Stomatitis	13 (42)	4 (13)	8 (27)	0	11 (37)	3 (10)
Nausea	5 (16)	0	6 (20)	0	9 (30)	1 (3)
Epistaxis	11 (35)	1 (3)	5 (17)	0	12 (40)	0
Skin fissures	10 (32)	0	6 (20)	0	7 (23)	0
Headache	6 (19)	0	4 (13)	1 (3)	10 (33)	0
Infusion-related reaction	6 (19)	1 (3)	4 (13)	1 (3)	7 (23)	0
Lipase increased	7 (23)	1 (3)	6 (20)	1 (3)	2 (7)	1 (3)
Amylase increased	8 (26)	1 (3)	4 (13)	0	1 (3)	0
Mouth bleeding	8 (26)	1 (3)	0	0	4 (13)	0

Most frequently reported (≥20%) TEAEs related to ficerafusp alfa.
Dose discontinuations due to ficerafusp alfa-related TEAEs in the 750mg QW, 1500mg QW and 2000mg Q2W dose cohorts were reported in 2 (6%), 3 (10%) and 2 (7%) patients, respectively. No patient had a grade 5 TEAE related to ficerafusp alfa.

*1 patient had grade 4 hypokalemia. †1 patient had grade 4 pericarditis.
TEAE, treatment-emergent adverse event; **TRAE**, treatment-related adverse event.

- The safety profile was comparable across all doses, with AEs consistent with known drug mechanisms (TGF-β, EGFR, and PD-1 blockade) and underlying HNSCC
- No new safety signals were observed in any dose cohort with longer follow-up
- Most AEs were manageable with standard care guidelines and protocol driven measures. Few patients discontinued ficerafusp alfa because of TRAEs
- PK analysis (data not shown) indicated that exposure increased in an approximately dose-proportional manner and all three dosing regimens maintained target therapeutic levels throughout treatment

KEY TAKEAWAYS

- **With 3 years of median follow-up, 1L ficerafusp alfa 1500 mg QW (optimal biological dose)** plus pembrolizumab continues to demonstrate durable efficacy in CPS ≥1 R/M HPV-negative HNSCC
  - **Survival: Median OS of 21.3 months** with an estimated **31% of patients alive at 3 years**
  - **Response: Confirmed ORR of 54%** (CR in 25%) with a **rapid median time to response of 1.4 months;** notably, this ORR of 54% was consistently maintained in historically difficult-to-treat subgroups, including patients with CPS 1-19 and those with bulky disease
  - **Depth and durability: Median DOR of 21.7 months; 80% of responders achieved deep responses, defined as ≥80% tumor shrinkage**
- **Clinical validation of TGF-β inhibition:** These prolonged clinical benefits – including greater depth and durability of response and extended survival at dose intensities with higher TGF-β inhibition – are consistent with a **remodeled TME following ficerafusp alfa-mediated TGF-β trapping**
- **Safety:** Ficerafusp alfa in combination with pembrolizumab had a manageable safety profile across all dose cohorts, demonstrating a **favorable benefit-risk profile**
- **Future directions:** The established dose-response relationship and broad therapeutic index support evaluation of **alternative ficerafusp alfa dosing regimens;** furthermore, the consistently high ORRs and depth of response **validate the planned ORR-based interim analysis** in the ongoing FORTIFI-HN01 trial

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