Ficerafusp alfa (2000 mg Q2W) and pembrolizumab in HPV-negative first-line recurrent/metastatic head and neck squamous cell carcinoma

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Presenter: Dan P. Zandberg, MD

Disclosure

Dan P. Zandberg

- Consulting or advisory role: Bicara Therapeutics Inc., Blueprint Medicines, Coherus Biosciences, InhibRx, Macrogenics, Merck & Co., Inc., Rahway NJ, USA, Prelude Therapeutics, Seagen
- Research funding: Aduro Biotech, AstraZeneca, AVEO, Bicara Therapeutics Inc., Bristol Myers Squibb, GSK, ISA Pharmaceuticals, Macrogenics, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, Novasenta

Objectives

Upon completion of this activity, attendees will be able to:

- Describe ficerafusp alfa's unique mechanism of action: dual targeting of **TGF-β** and **EGFR** in HPV-negative HNSCC
- Explain how TGF-β neutralization remodels the fibrotic TME to enable **tumor penetration** that **drives deep** and **durable** responses
- Recognize rationale for the feasibility and further exploration of less frequent dosing schedules

EGFR, epidermal growth factor receptor; **HNSCC**, head and neck squamous cell carcinoma; **HPV**, human papillomavirus; **TGF-β**, transforming growth factor-beta; **TME**, tumor microenvironment.

Background and unmet need in HNSCC

HPV-negative R/M HNSCC with CPS ≥1 is characterized by poor clinical outcomes[1-4]

Failing to distinguish HPV status in tumors can mask important efficacy and prognostic signals[2,5]

Confirmatory HPV testing by PCR or RNA ISH is recommended in clinical trials[6]

	Pembrolizumab	Pembrolizumab + Chemotherapy
Any HPV status	**KEYNOTE-048[1]**	
ORR	19%	36%
mDOR	23.4 months	6.7 months
mOS	12.3 months	13.6 months

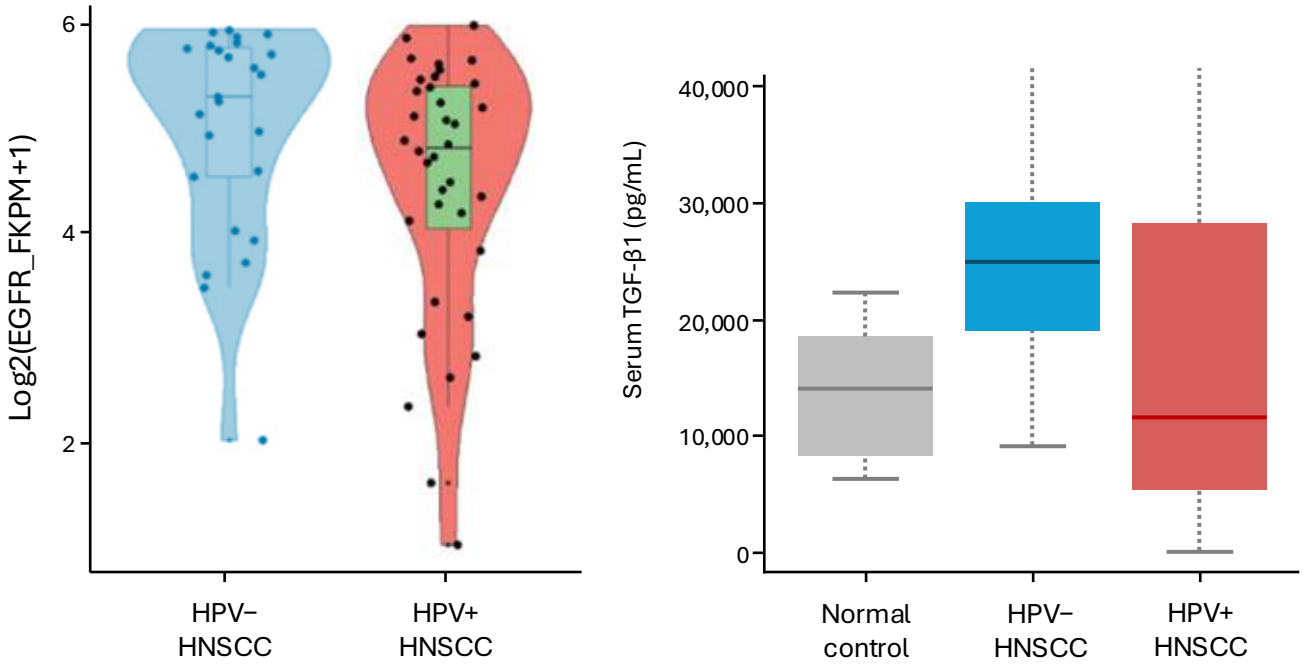
HPV negative	**Real-world data[3,4]**	
mOS	**9 months**	**7 months**

1. Burtness B. et al. *Lancet*. 2019;394:1915-28. 2. Chaudhary R, et al. *Clin Cancer Res*. 2026;32:501-15. 3. Vasiliadou I, et al. *Int J Cancer*. 2024;155(5):883-93. 4. Black CM, et al. *Front Oncol*. 2023;13:1160144. 5. Bedi A et al. *Mol Cancer Ther*. 2012;11(11):2429–39. 6. Lewis JS JR., et al. *Arch Pathol Lab Med* 2025;149:e115-e150.

1L, first line; **CPS**, combined positive score; **HNSCC**, head and neck squamous cell carcinoma; **HPV**, human papillomavirus; **ISH**, in situ hybridization; **mDOR**, median duration of response; **mOS**, median overall survival; **ORR**, objective response rate; **PCR**, polymerase chain reaction; **R/M**, recurrent or metastatic; **RNA**, ribonucleic acid.

HPV-negative R/M HNSCC: a challenging tumor type associated with overexpression of EGFR and TGF-β

Overexpression of EGFR and TGF-β in HNSCC[1]



HPV-negative HNSCC has distinct biological and mutational features that affect prognosis[2-4]

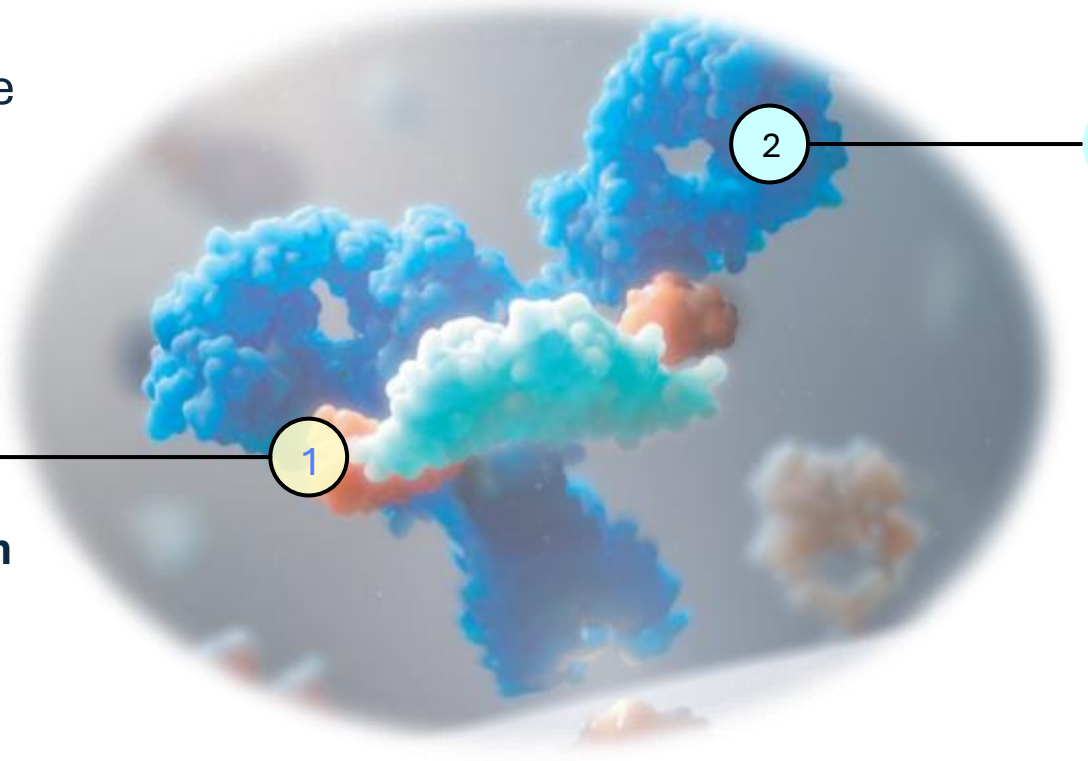
- **Increased EGFR expression**
- **Elevated levels of TGF-β1** in serum
- Convergent **EGFR** and **TGF-β** signaling drives resistance

1. Qiu, J et al. *Front in Oncol*. 2021;11. 2. Bedi A et al. *Mol Cancer Ther*. 2012;11:2429-39. 3. Sabatini ME & Chiocca S. *Br J Cancer*. 2020;122:306-14. 4. The Cancer Genome Atlas Network. *Nature*. 2015;517:576-82.
EGFR, epidermal growth factor receptor; **HNSCC**, head and neck squamous cell carcinoma; **HPV**, human papillomavirus; **R/M**, recurrent or metastatic; **TGF-β**, transforming growth factor-beta.

Ficerafusp Alfa

A bifunctional TGF-β ligand-trapping x EGFR-directed antibody [1,2]

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

1. Herrera M et al. *Trends Cancer*. 2024;10:893-919. 2. Boreddy SR et al. *Cancer Res*. 2023;83:1883–904.
EGFR, epidermal growth factor receptor; **ICI**, immune checkpoint inhibitor; **TGF-β**, transforming growth factor-beta; **TME**, tumor microenvironment.

High response rates observed across doses with ficerafusp alfa + pembrolizumab in HPV-negative, CPS ≥1, 1L R/M HNSCC

- **Deep** and **durable responses** with 750 mg and 1500 mg suggest long-term efficacy
- Complete and prolonged **neutralization of TGF-β1** in plasma
- Manageable safety profile with no treatment-related deaths

	ESMO Asia 2025	*ASCO 2025*
	750 mg QW†	**1500 mg QW‡**
	EE set (N=30)	**EE set (N=28)**
Confirmed ORR	57% (17/30)	54% (15/28)
Disease control rate	83% (25/30)	89% (25/28)
Deep response§	29% (5/17)	80% (12/15)
CR rate	10% (3/30)	21% (6/28)
Median duration of response	NE	21.7 months
Median PFS	NE	9.9 months
Median OS	NE	21.3 months

†Data snapshot: July 9, 2025 (Kaczmar JM, et al. *Ann Oncol.* 2025;36(Suppl 4):667O).
‡Data snapshot: March 20, 2025 (Chung CH, et al. *J Clin Oncol*. 2025;43(16 suppl):6017).
§Deep response is defined as ≥80% tumor regression in target lesions vs baseline.
1L, first line; **CPS**, combined positive score; **CR,** complete response; **EE**, efficacy evaluable**; HPV**, human papillomavirus; **HNSCC**, head and neck squamous cell carcinoma; **NE,** not estimable; **ORR,** objective response rate; **OS,** overall survival; **QW**, weekly; **R/M**, recurrent or metastatic; **TGF-β**, transforming growth factor-beta.

Ficerafusp alfa

Phase 1b dose-expansion cohorts: HPV-negative, CPS ≥1, 1L R/M HNSCC

Dose expansion

Ficerafusp alfa + pembrolizumab

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

NCT04429542

Ficerafusp alfa's **half-life of ~ 8 days** supports the rationale to explore less frequent dosing schedules

Today's focus

Ficerafusp alfa 2000 mg Q2W
+
Pembrolizumab 400 mg Q6W

Dose-expansion cohort (N=30)

1L, first line; **CPS**, combined positive score; **HNSCC**, head and neck squamous cell carcinoma; **HPV**, human papillomavirus; **R/M**, recurrent or metastatic; **Q2W**, every 2 weeks; **Q3W**, every 3 weeks; **Q6W**, every 6 weeks; **QW**, weekly.

Patient characteristics with ficerafusp alfa 2000 mg Q2W + pembrolizumab in HPV-negative, CPS ≥1, 1L R/M HNSCC

Population

- 1L R/M HNSCC
- **HPV negative**
- Oral cavity, oropharynx, larynx, or hypopharynx
- CPS ≥1
- ECOG PS 0-1

Characteristic		Safety set (N=30)
Age, years	Median (range)	63 (28-84)
Sex	Male/female	67%/33%
Primary site of disease	Oropharynx (HPV negative)	20%
	Oral cavity	63%
	Hypopharynx	7%
	Larynx	10%
CPS	1-19	50%
	≥20	50%
Locoregional vs distant metastatic disease	LR only	63%
	LR + DM	20%
	DM only	17%
Sum of target lesion diameters	Median, mm	33
	> 50 mm, %	37%
	> 70 mm, %	23%
ECOG performance status	0/1	33%/67%

Data snapshot: December 16, 2025.
CPS, combined positive score; **DM**, distant metastatic; **ECOG**, Eastern Cooperative Oncology Group; **HNSCC**, head and neck squamous cell carcinoma; **HPV**, human papillomavirus; **LR,** locoregional; **R/M,** recurrent or metastatic.

Safety with ficerafusp alfa 2000 mg Q2W + pembrolizumab in HPV-negative CPS ≥1, 1L R/M HNSCC

- The combination was tolerable with a manageable safety profile
- No treatment-related deaths were reported
- Safety profile at 2000 mg Q2W was consistent with the established safety profile of ficerafusp alfa + pembrolizumab in R/M HNSCC

Most frequently reported TEAEs related to ficerafusp alfa (≥20%)*

	Safety set (N=30)	
	Any grade	Grade 3†
Any TEAE	29 (97%)	16 (53%)
Dermatitis acneiform	24 (80%)	3 (10%)
Anemia	14 (47%)	8 (27%)
Fatigue	12 (40%)	1 (3%)
Epistaxis	12 (40%)	0
Stomatitis	11 (37%)	3 (10%)
Pruritus	11 (37%)	1 (3%)
Headache	10 (33%)	0
Nausea	9 (30%)	1 (3%)
Dry skin	9 (30%)	0
Skin fissures	7 (23%)	0
Infusion-related reaction	7 (23%)	0
Hypophosphatemia	6 (20%)	0
Hypomagnesemia	6 (20%)	0
TRAE leading to ficerafusp alfa discontinuation	3 (10%)	

Data snapshot: December 16, 2025

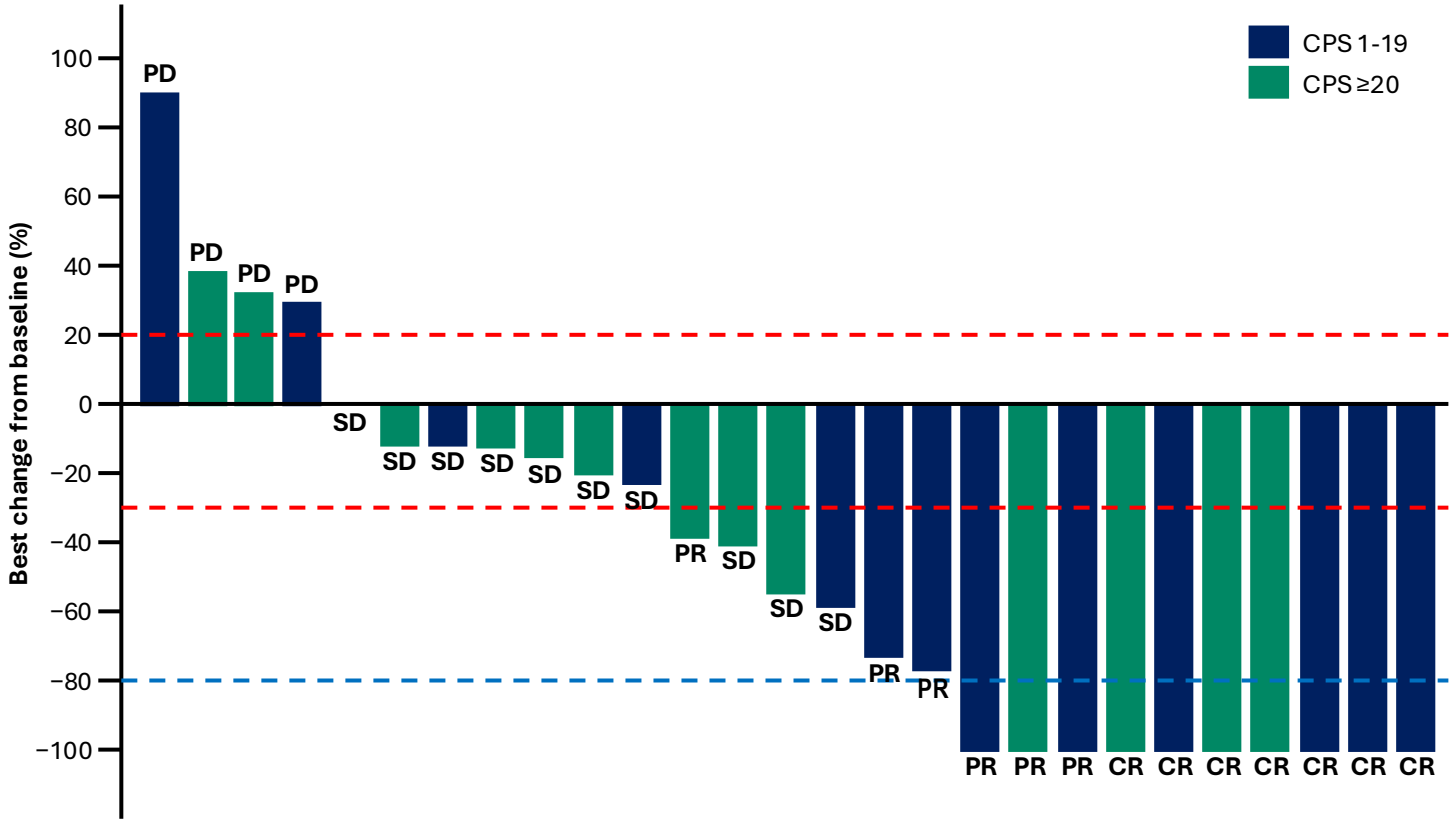
*Related TEAEs are those with relationship of "possibly related", "probably related", and "definitely related" to ficerafusp alfa per investigator assessment, or TEAEs with missing drug relationships (treated as "possibly related").

†1 patient had a grade 4 event (hypokalemia); no grade 5 events occurred.

1L, first line; **CPS**, combined positive score; **HNSCC**, head and neck squamous cell carcinoma; **HPV**, human papillomavirus; **Q2W**, every 2 weeks; **R/M**, recurrent or metastatic; **TEAE**, treatment-emergent adverse event.

Efficacy with ficerafusp alfa 2000 mg Q2W + pembrolizumab in HPV-negative, CPS ≥1, 1L R/M HNSCC

	EE set (N=27)
Confirmed ORR	48% (13/27)
Disease control rate	85% (23/27)
Deep response*	77% (10/13)
CR rate	26% (7/27)
Median time to response	1.6 months

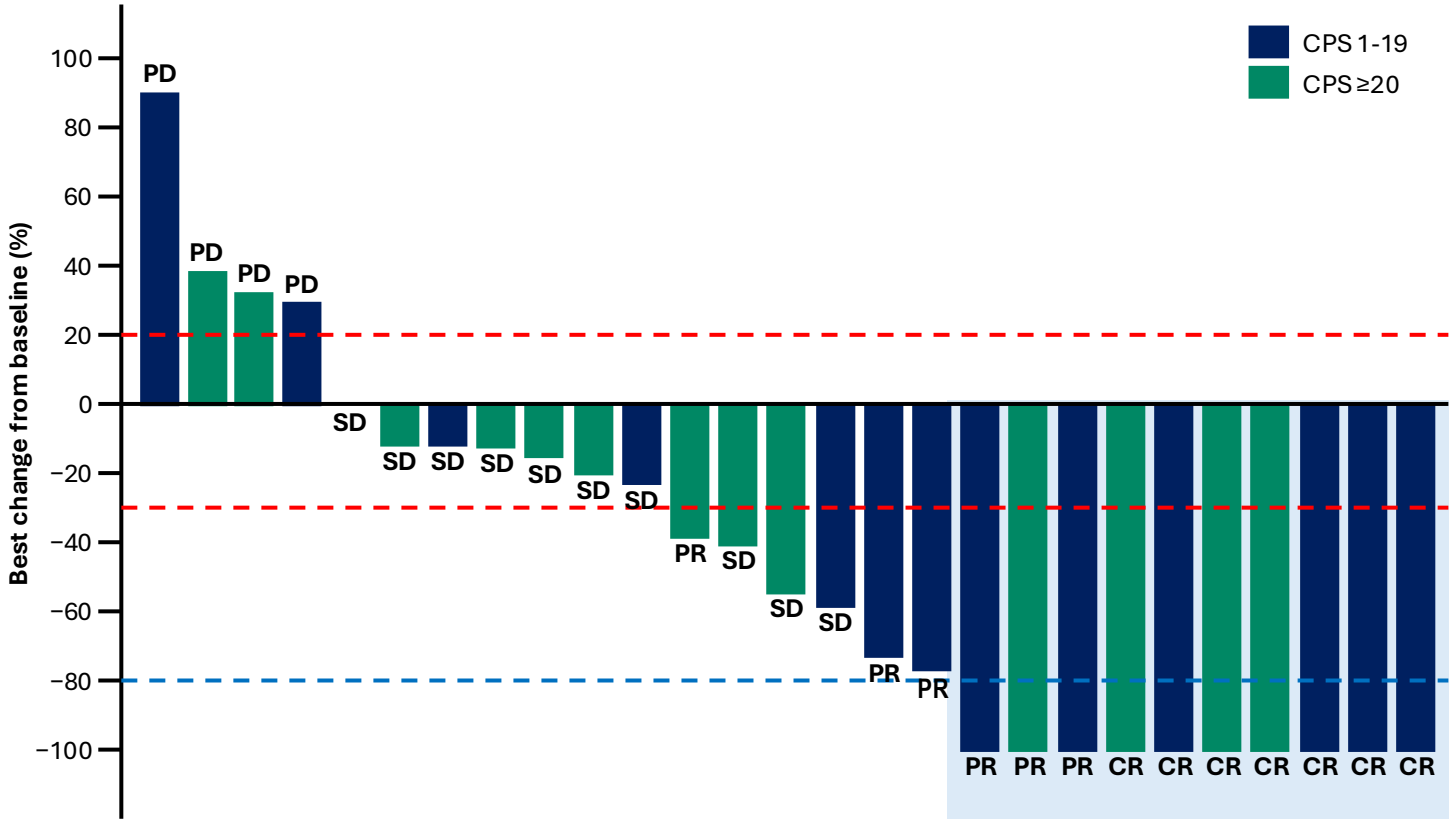


Data snapshot: December 16, 2025.
Table shows investigator-assessed best overall response per RECIST 1.1.
*Deep response is defined as ≥80% tumor regression in target lesions vs baseline.
1L, first line; **CPS**, combined positive score; **CR**, complete response; **EE**, efficacy evaluable; **HNSCC**, head and neck squamous cell carcinoma; **HPV**, human papillomavirus; **ORR**, objective response rate; **Q2W**, every 2 weeks; **PR**, partial response; **R/M**, recurrent or metastatic; **SD**, stable disease.

Efficacy with ficerafusp alfa 2000 mg Q2W + pembrolizumab in HPV-negative, CPS ≥1, 1L R/M HNSCC

	EE set (N=27)
Confirmed ORR	48% (13/27)
Disease control rate	85% (23/27)
Deep response*	77% (10/13)
CR rate	26% (7/27)
Median time to response	1.6 months

		ORR
CPS	1-19	57% (8/14)
	≥20	39% (5/13)
Tumor burden (Sum of target lesion diameters)	≤50 mm	53% (9/17)
	>50 mm	40% (4/10)
	>70 mm	33% (2/6)



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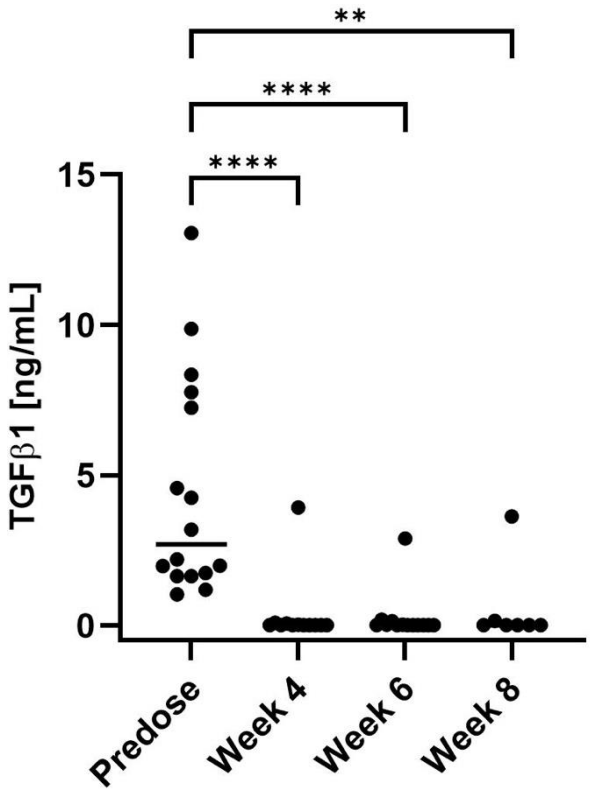
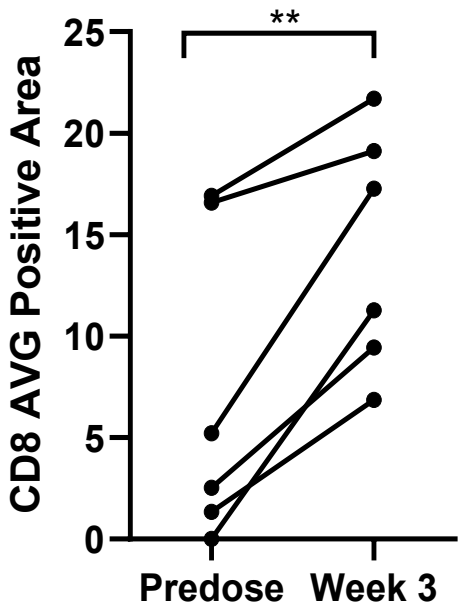
Sustained TGF-β neutralization and tumor penetration of T-cells with ficerafusp alfa 2000mg Q2W + pembrolizumab

TGF-β Neutralization (plasma)



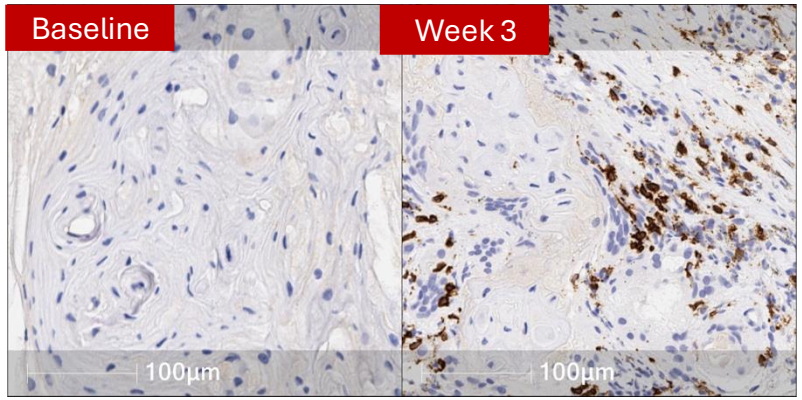
one-way ANOVA ****p<.0001;***p<.001, ** p<.01
Predose N=16, Week 4 N=12, Week 6 N=13, Week 8 N=7
Datapoints collected after a dose hold are excluded

CD8+ T-Cells (paired biopsies)

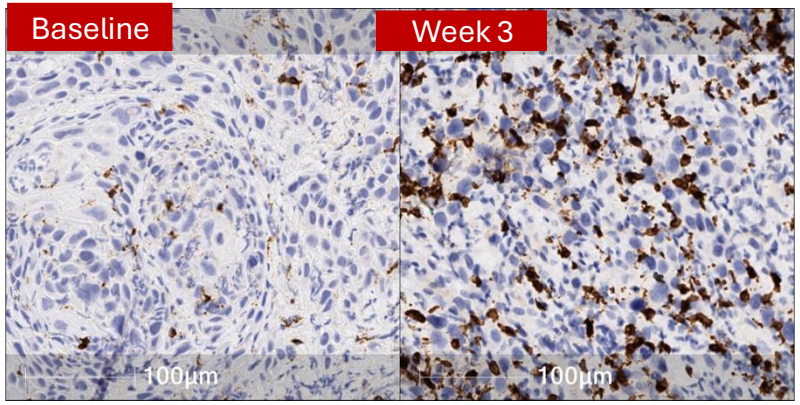


**p<.01 paired t-test, N=6 pairs

Patient with Complete Response



Patient with -58% tumor reduction



In HPV-negative, CPS≥1, R/M HPV-Neg HNSCC.
1L, first line; **CPS**, combined positive score; **HNSCC**, head and neck squamous cell carcinoma; **HPV**, human papillomavirus; **Q2W**, every 2 weeks; **R/M**, recurrent or metastatic; **TGF-β**, transforming growth factor-beta.

Consistency efficacy of ficerafusp alfa + pembrolizumab in HPV-negative, CPS ≥1, 1L R/M HNSCC

	Ficerafusp alfa dose		
	750 mg QW*	1500 mg QW†	2000 mg Q2W
	EE set (N=30)	EE set (N=28)	EE set (N=27)
Confirmed ORR	**57% (17/30)**	**54% (15/28)**	**48% (13/27)**
CPS 1-19	73% (8/11)	54% (7/13)	57% (8/14)
CPS ≥20	47% (9/19)	53% (8/15)	39% (5/13)
CR rate	**10% (3/30)**	**21% (6/28)**	**26% (7/27)**
Disease control rate	**83% (25/30)**	**89% (25/28)**	**85% (23/27)**
Deep response‡	**29% (5/17)**	**80% (12/15)**	**77% (10/13)**
Median DoR	**NE**	**21.7 months**	**NE**
Median OS	**NE**	**21.3 months**	**NE**
Median time to response	**1.6 months**	**1.4 months**	**1.6 months**

- **High response rates** across doses
- Maturing DoR suggests a correlation between **deep** responses and **durability**
- Mechanism of action **consistent** across doses

†Data snapshot: July 9, 2025 (Kaczmar JM, et al. *Ann Oncol*. 2025;36(Suppl 4):667O).
‡Data snapshot: March 20, 2025 (Chung CH, et al. *J Clin Oncol*. 2025;43(16 suppl):6017).
*Deep response is defined as ≥80% tumor regression in target lesions vs baseline.
1L, first line; **CPS**, combined positive score; **CR**, complete response; **DoR**, duration of response; **EE**, efficacy evaluable; **HNSCC**, head and neck squamous cell carcinoma; **HPV**, human papillomavirus; **NE**, not estimable; **ORR**, objective response rate; **OS**, overall survival; **QW**, weekly; **Q2W**, every 2 weeks; **R/M**, recurrent or metastatic.

Ficerafusp alfa 2000 mg Q2W + pembrolizumab in HPV-negative, CPS ≥1, 1L R/M HNSCC: summary

- Efficacy and safety consistent with 1500mg QW, including deep responses

- **Deep responses: 77% of responders had ≥80% tumor shrinkage**
- **26%** had a CR
- Rapid responses: **median 1.6 months**

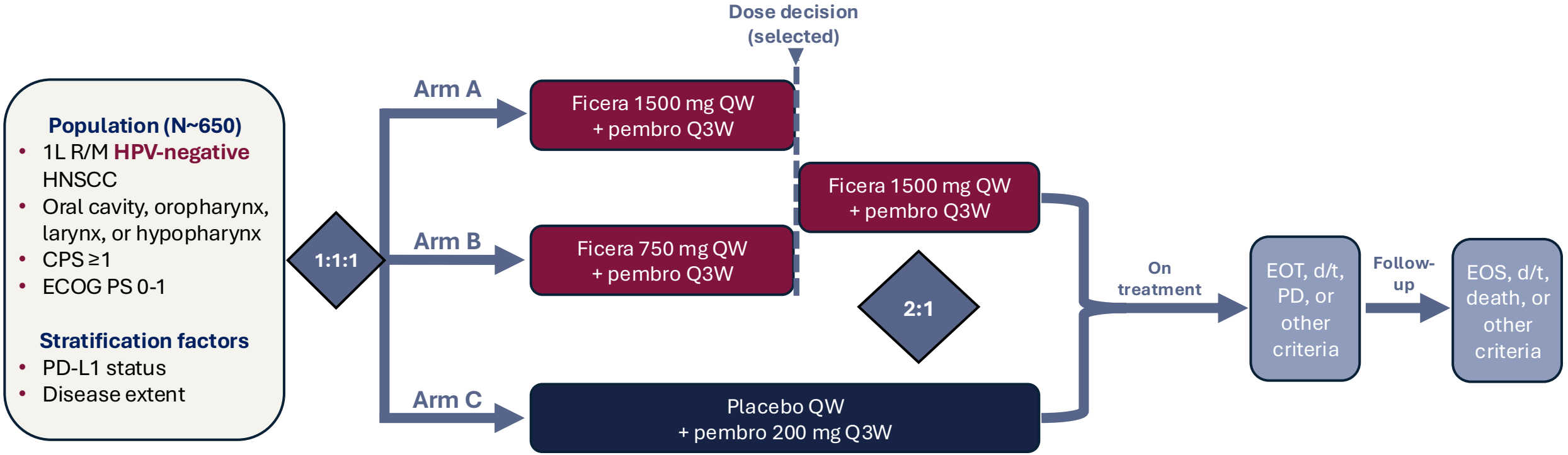
- Consistent safety profile and comparable efficacy, including **deep responses** and rapid response, **justifies further exploration of less frequent dosing schedules**

Ficerafusp alfa was awarded **FDA Breakthrough Therapy Designation** in combination with pembrolizumab for 1L treatment of **HPV-negative** CPS ≥1 R/M HNSCC

1L, first line; **CPS**, combined positive score; **CR**, complete response; **HNSCC**, head and neck squamous cell carcinoma; **HPV**, human papillomavirus; **R/M**, recurrent or metastatic.

FORTIFI-HN01 study:

Global, multicenter, randomized, double-blind, phase 2/3 study of ficerafusp alfa or placebo in combination with pembrolizumab for 1L treatment of PD-L1-positive, R/M HNSCC



Phase 2: ☑
1500 mg QW selected as Optimal Biological Dose

Phase 3:
Dual primary endpoints: ORR and OS

NCT06788990.

1L, first-line; **CPS**, combined positive score; **d/t**, discontinuation; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **EOT**, end of treatment; **EOS**, end of study; **HNSCC**, head and neck squamous cell carcinoma; **HPV**, human papillomavirus; **PD-L1**, programmed death-ligand 1; **Q3W**, every 3 weeks; **QW**, weekly; **OPSCC,** oropharyngeal squamous cell carcinoma; **ORR**, objective response rate; **OS**, overall survival; **PD** progressive disease; **R/M**, recurrent/metastatic.

Acknowledgements

Patients who participated in the study and their families and caregivers

Investigators and clinical trials support staff:
UPMC Hillman Cancer Center, Pittsburgh, Pennsylvania, USA; Hollings Cancer Center, Medical University of South Carolina, Charleston, South Carolina, USA; UC San Diego Health, Moores Cancer Center, La Jolla, California, USA; Center for Head and Neck Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts, USA; Moffitt Cancer Center, Tampa, Florida, USA; Vanderbilt-Ingram Cancer Center, Vanderbilt University, Nashville, Tennessee, USA; Memorial Sloan Kettering Cancer Center, New York, New York, USA; Taussig Cancer Institute, Cleveland Clinic, Cleveland, Ohio, USA; Herbert Irving Comprehensive Cancer Center, Columbia University, New York, New York, USA; UCLA Medical Center, Los Angeles, California, USA

This study was conducted by Bicara Therapeutics Inc. with access to pembrolizumab in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA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