ASPEN-03: A Randomized Phase 2 Study of Evorpacept in Combination with Pembrolizumab in Patients with Recurrent, Unresectable or Metastatic (R/M) PD-L1 Positive Head and Neck Squamous Cell Carcinoma (HNSCC)

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B. Keam[1], L. Michel[2], J.-P. Machiels[3], S. Oosting[4], B.G.M. Hughes[5], J.C. Park[6], A. Forgie[7], D. Brickman[7], C. Zhang,[7] A.C. Tsiatis[7], A. Sandler[7], K. Harrington[8]

[1]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea, [2]Department of Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, United States of America, [3]Department of Medical Oncology, Cliniques universitaires Saint-Luc (UCLouvain), Brussels, Belgium, [4]Medical Oncology Department, UMCG – University Medical Center Groningen, Groningen, Netherlands, [5]Cancer Care Services, Royal Brisbane and Women's Hospital and University of Queensland, Brisbane, Australia, [6]Department of Medicine, Massachusetts General Hospital Cancer Center, Boston, MA, United States of America, [7]Department of Clinical Development, ALX Oncology Inc., South San Francisco, CA, United States of America, [8]Dept. Of Radiotherapy and Imaging, The Institute of Cancer Research and The Royal Marsden Hospital, London, United Kingdom

Disclosure / Conflicts of Interest

Bhumsuk Keam

- Consultancy/advisory role: Handok, Trialinformatics, Yuhan, TiumBio, BeOne
- Patents and royalties: nothing
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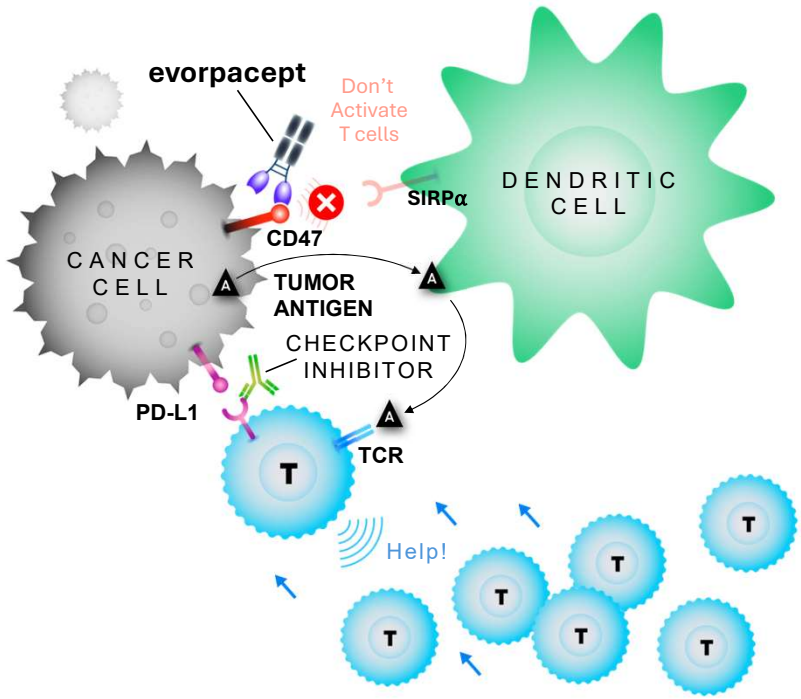
- Employee: nothing
- Other remuneration: nothing

Evorpacept: A CD47 Inhibitor with an Inactive Fc Domain that Enables Anticancer Immune Activation

- Evorpacept blocks the immune evasive 'don't eat me' signal transmitted by CD47 on the surface of cancer cells
- Primary validated mechanism:
  - Evorpacept was designed with an inactive Fc domain to selectively target cancer cells and not healthy cells when combined with anti-cancer antibodies through ADCP
  - This mechanism has been validated in HER2-positive advanced Gastric/GEJ and metastatic breast cancer
- Potential secondary mechanism:
  - CD47 blockade may enhance T-cell priming by activating dendritic cells and stimulating the adaptive immune system
- CD47 expression **may** identify cancers that are responsive to evorpacept

Secondary CD47 Mechanism Investigated in ASPEN-03



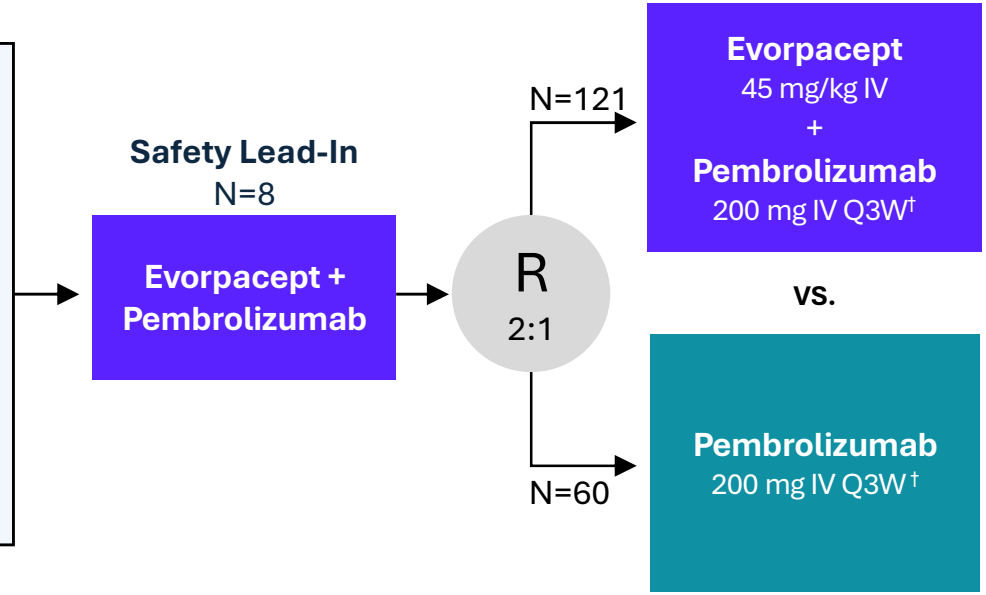
Hypothesis: CD47 blockade may enhance benefit from PD-1 inhibition

ADCP – Antibody dependent cellular phagocytosis.

ASPEN-03 is a Global, Randomized Phase 2 Study in Patients with Recurrent, Unresectable or Metastatic PD-L1 Positive HNSCC (NCT04675294)

Key Eligibility Criteria

- Metastatic or unresectable, recurrent (R/M) HNSCC
- PD-L1 CPS ≥1
- No prior systemic therapy for advanced disease
- Measurable disease
- ≥18 years old
- ECOG PS 0-1



†max of 35 cycles (up to 24 months)

Minimization Factors

- Geography: Asia Pacific, Europe, North America
- PD-L1 CPS: CPS 1-19, CPS ≥20
- HPV (p16) Status: positive, negative, unknown
- Tobacco Habits: Current, Past, Non-user
- ECOG PS: 0, 1

Primary Endpoints

- Objective response rate (BICR)

Primary Analysis

- Compare ORR to historical control ORR 20%

Key Secondary Endpoints

- ORR, DCR, DOR, PFS, TTP, OS, 12-month OS rate, Safety

Exploratory Endpoints

- Preplanned biomarker analysis of CD47 vs efficacy endpoints

BICR – Blinded independent central review; **CPS** – Combined positive score; **DCR** – Disease control rate; **DOR** – Duration of response; **ECOG PS** – Eastern cooperative oncology group performance status; **HNSCC** – Head and neck squamous cell carcinoma; **HPV** – Human papilloma virus; **IV** – Intravenous, **PD-L1** – Programmed death ligand 1; **PFS** – Progression free survival; **ORR** – Objective response rate; **OS** – Overall survival; **Q3W** – Every three weeks; **TTP** – Time to progression.

ASPEN-03: Patient Demographics and Baseline Characteristics

	Evorpacept + Pembrolizumab (n=121)	Pembrolizumab (n=60)
Median Age (range), Yrs	65 (44-87)	66 (31-87)
Male	76%	80%
Race: White, Asian, Other	66%, 25%, 9%	57%, 33%, 10%
Region: North America, Europe, Asia	41%, 24%, 36%	43%, 18%, 38%
ECOG PS 0	40%	40%
Former or Current Smoker	74%	77%
PD-L1 CPS		
1-19	49%	50%
≥20	51%	50%
Disease Status		
Recurrent	38%	38%
Metastatic	62%	62%
Primary Tumor Location		
Oropharynx	41%	40%
Lip or Oral Cavity	36%	30%
Larynx	12%	15%
Hypopharynx	7%	8%
Other	4%	7%
HPV Positive	31%	32%

CPS – Combined positive score; **ECOG PS** – Eastern cooperative oncology group performance status; **HPV** – Human papilloma virus.

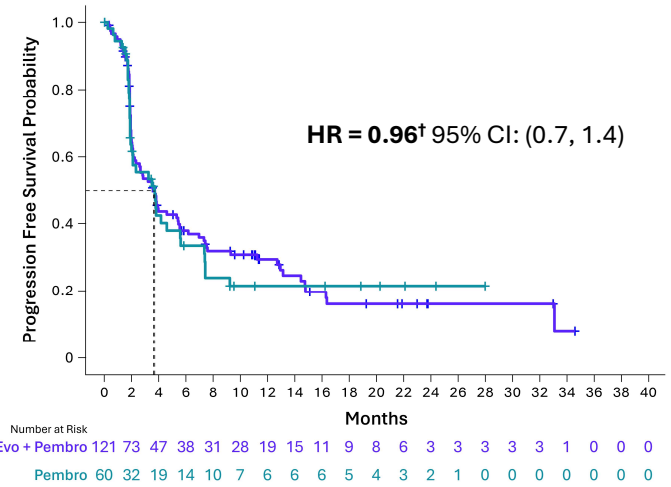
ASPEN-03: Overall Efficacy

ORR and DOR by BICR

	Evorpacept + Pembrolizumab (n=121)	Pembrolizumab (n=60)
ORR, % (95% CI)	26.4 (18.8, 35.2)	18.3 (9.5, 30.4)
CR,%	15.7	13.3
PR, %	10.7	5.0
SD, %	21.5	26.7
PD, %	39.7	36.7
Other*, %	12.4	18.3
Median DOR, mo (95% CI)	31.2, (12.6, NE)	NR, (5.7, NE)
Median Follow Up, mo	19.5	17.9

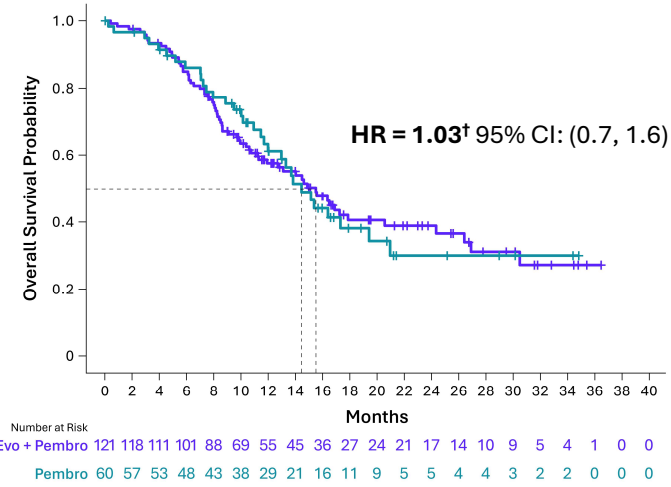
Progression-Free Survival by BICR

	Events	Median, mo
Evo + Pembro	87/121	3.6 (2.2, 5.4)
Pembro	38/60	3.7 (1.9, 5.6)



Overall Survival

	Events	Median, mo
Evo + Pembro	67/121	15.5 (11.3, 20.6)
Pembro	32/60	14.5 (11.7, 19.4)



- ORR for evorpacept + pembrolizumab (26.4%) was not statistically different from ORR for historical control[1] (20%; 1-sided p = 0.038 vs. α = 0.025)
- No evidence of difference in ORR, PFS, or OS between treatment arms

*includes patients without measurable disease at baseline that did not meet criteria for CR or PD, not evaluable, or had no post-baseline assessment available; , †HR (Evo + Pembro vs. Pembro) is from a stratified Cox proportional hazards model stratified by PD-L1 CPS per IRT. **BICR** – Blinded independent central review; **CR** – Complete response; **DOR** – Duration of response; **Evo** – Evorpacept; **mo** – Months; **NR** – Not reached; **NE** – not estimable; **ORR** – Objective response rate; **OS** – Overall survival; **Pembro** – Pembrolizumab; **PD** – Progressive disease; **PFS** – Progression free survival; **PR** – Partial response; **SD** – Stable disease;

1. Burtness *et al.* *Lancet* 2019;394:1915-28.

ASPEN-03 Treatment-Emergent Adverse Events Occurring in >10% in Either Treatment Arm

	Evorpacept + Pembrolizumab (n=122)		Pembrolizumab (n=58)	
n (%)	Any Grade	≥Grade 3	Any Grade	≥Grade 3
Any TEAE	116 (95.1%)	55 (45.1%)	55 (94.8%)	18 (31%)
Fatigue	35 (28.7%)	1 (0.8%)	14 (24.1%)	0
Pruritus	27 (22.1%)	0	7 (12.1%)	0
ALT Increased	29 (23.8%)	6 (4.9%)	7 (12.1%)	3 (5.2%)
AST Increased	24 (19.7%)	4 (3.3%)	7 (12.1%)	0
Hypothyroidism	19 (15.6%)	0	10 (17.2%)	0
Constipation	19 (15.6%)	0	10 (17.2%)	0
Cough	20 (16.4%)	0	6 (10.3%)	0
Dysphagia	17 (13.9%)	1 (0.8%)	6 (10.3%)	1 (1.7%)
Nausea	15 (12.3%)	0	8 (13.8%)	1 (1.7%)
Dizziness	16 (13.1%)	0	5 (8.6%)	0
Dyspnea	17 (13.9%)	4 (3.3%)	4 (6.9%)	0
Alk Phos Increased	16 (13.1%)	0	2 (3.4%)	0
Diarrhea	16 (13.1%)	0	2 (3.4%)	1 (1.7%)
Rash	16 (13.1%)	0	2 (3.4%)	0
Pneumonia	14 (11.5%)	9 (7.4%)	2 (3.4%)	1 (1.7%)
Arthralgia	12(9.8%)	0	6 (10.3%)	1 (1.7%)
Hyponatremia	10 (8.2%)	3 (2.5%)	6 (10.3%)	2 (3.4%)

- EP was generally well tolerated, and no new safety signals were identified
- Treatment-emergent SAEs: 36% vs 17% EP vs P respectively (EP similar to P in historical control[1])
- TEAEs leading to permanent DC or delays were similar:
  - DC: 15.6% vs 12.1% EP vs P
  - Dose delays: 33.6% vs 29.3% in EP vs P
- Grade 5 TEAEs: 11 (9%) vs 3 (5.2%) EP vs P†
  - One grade 5 TRAE in patient on EP (pericardial effusion) considered related to both

†All Treatment Emergent Fatal Events: Evo+Pembro (N=11; 9.0%): Tongue neoplasm malignant stage unspecified N=1; Pneumonia N=1; Pneumonia aspiration N=1; Hemorrhage N=1; tumor hemorrhage N=1; septic shock N=1; pericardial effusion N=1; acute myocardial infarction N=1; Disease progression N=2; Death N=1; Pembro (N=3; 5.2%) : Malignant neoplasm progression N=1; Hemorrhage N=1; Death N=1. DC, discontinuation; E, evorpacept; P, pembrolizumab; 1. Keytruda® EPAR Assessment Report Reference number EMA/CHMP/591139/2019/corr 17 October 2019.

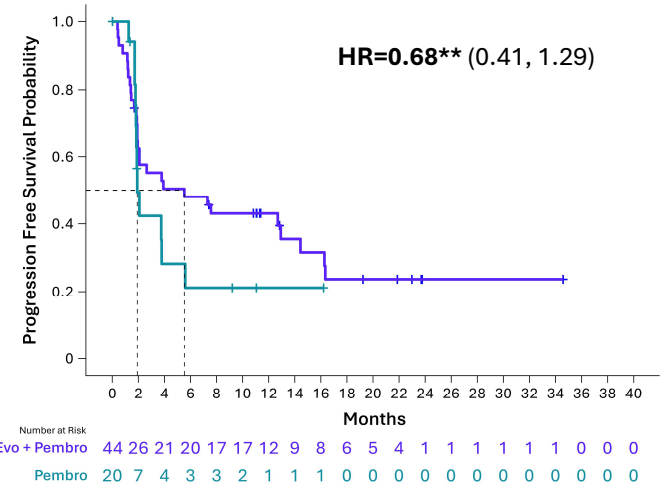
CD47 High May Enrich for Benefit from Combination Therapy

ORR and DOR by BICR

	Evorpacept + Pembrolizumab (n=44)	Pembrolizumab (n=20)
ORR, % (95% CI)	38.6 (24.4, 54.5)	10.0 (1.2, 31.7)
CR,%	22.7	10.0
PR, %	15.9	0
SD, %	15.9	25.0
PD, %	38.6	45.0
Other†, %	6.8	20.0
Median DOR, mo (95% CI)	NR (12.6, NE)	NR (NE, NE)
Median Follow Up, mo	19.5	16.6

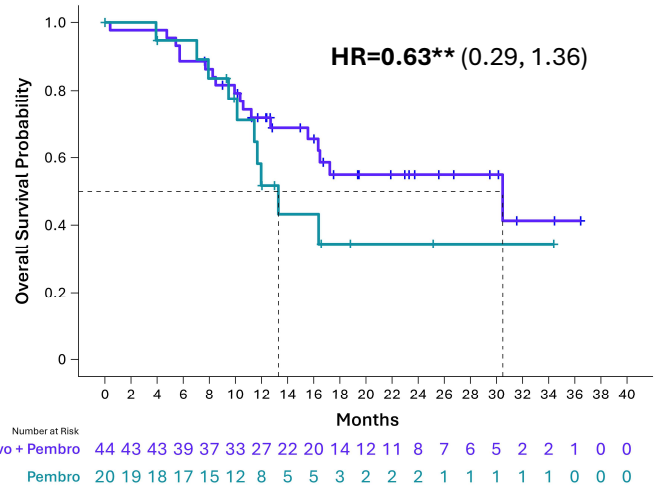
Progression-Free Survival by BICR

	Events	Median, mo
Evo + Pembro CD47 High*	29/44	5.6 (1.9, 14.5)
Pembro CD47 High*	12/20	1.9 (1.8, 5.6)



Overall Survival

	Events	Median, mo
Evo + Pembro CD47 High*	18/44	30.5 (15.6, NE)
Pembro CD47 High*	10/20	13.3 (10.2, NE)



*CD47 high defined as IHC 3+ CD47 membrane staining intensity in ≥25% of tumor cells

† includes who were not evaluable or had no post-baseline assessment available; **HR (Evo + Pembro vs. Pembro) is from a Cox proportional hazards model. **BICR** – Blinded independent central review; **CR** – Complete response; **DOR** – Duration of response; **Evo** – Evorpacept; **mo** – Months; **NE** – Not estimable; **NR** – Not reeached; **ORR** – Objective response rate; **OS** – Overall survival; **Pembro** – Pembrolizumab; **PD** – Progressive disease; **PFS** – Progression free survival; **PR** – Partial response; **SD** – Stable disease.

Conclusions

- ASPEN-03 did not meet the primary endpoint with objective response rate of evorpacept and pembrolizumab (26.4%) compared to historical control of pembrolizumab alone (20%)
- No difference in the overall population observed between the two treatment arms for ORR, PFS, OS
- Evorpacept + pembrolizumab was generally well tolerated and no new safety signals were identified
- High CD47 expression may enrich for benefit from combination therapy with evorpacept and pembrolizumab
- The potential role of CD47 expression in predicting clinical benefit of evorpacept should be considered for future studies

Thank you.

We would like to thank all the participating patients and their families as well as site research staff.

Contact email: info@alxoncology.com