European Society for Medical Oncology (ESMO) Congress 2024
Proffered Paper Oral Presentation

Primary Results from TACTI-003: A Randomized Phase IIb Trial Comparing Eftilagimod Alpha (soluble LAG-3) Plus Pembrolizumab Versus Pembrolizumab Alone in First-Line Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma with CPS ≥1

Phase IIb study of a soluble LAG-3 protein combined with an anti-PD-1 antibody in R/M 1L HNSCC

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DECLARATION OF INTERESTS

Claus Andrup Kristensen

MSD EMEAC HNSCC Advisory Board
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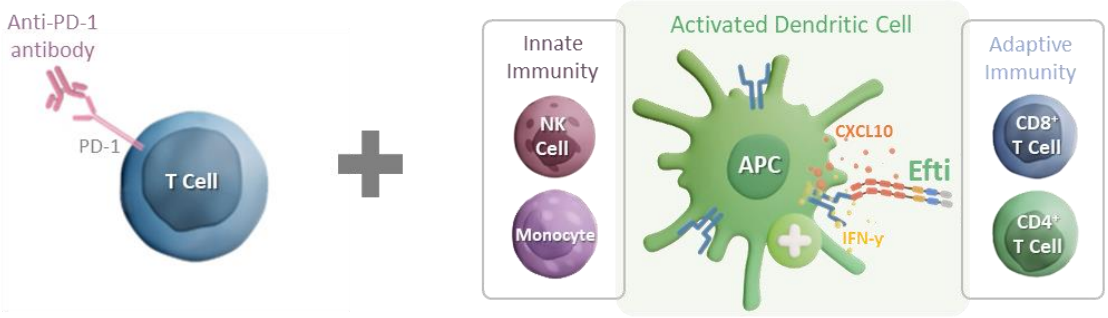
Background

- **Eftilagimod alpha**: a **first-in-class soluble LAG-3 fusion protein** and **MHC Class II agonist** that activates antigen presenting cells (APCs), leading to a broad anti-cancer immune response including but not limited to the activation/proliferation of $CD8^+$ T cells.
- Pembrolizumab: **antibody** that antagonizes the PD-1 receptor on T cells, enhancing the immune response against cancer cells and is **approved for different indications**.



Efti directly targets MHC Class II on APCs, having an agonistic effect, unlike LAG-3 antagonists that target T cells.

MHC: major histocompatibility complex

Rationale

- Efti as an APC activator leads to an increase in activated T cells (CD4/CD8) and stimulates adaptive/innate anti-cancer immunity, augmenting responses when combined with PD-(L)1 antagonists such as pembrolizumab.
- Pembrolizumab is standard-of-care for CPS ≥1 in 1st line HNSCC[1].
- Encouraging efficacy seen in 2nd line R/M HNSCC[2] patients after failure of 1st line chemotherapy, as well as in other indications when efti has been combined with pembrolizumab.

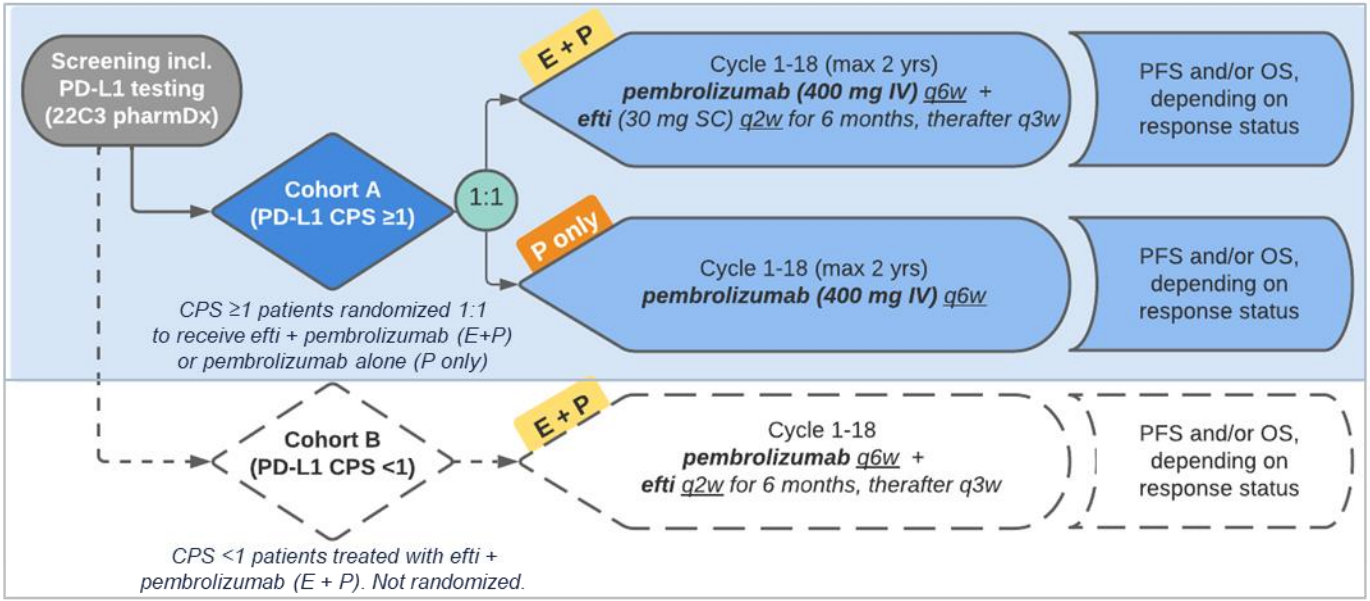
2nd line HNSCC, presented at ASCO 2023[2]

PD-L1 CPS	ITT, N=37	≥20, N=15	<20 N=17
Objective response rate (iRECIST), %	29.7	60.0	11.8
Median duration of response (iRECIST), months	Not yet reached, despite median follow-up of 39 months		

[1] Machiels JP et al, Ann Oncol. 2020 Nov;31(11):1462-1475. doi: 10.1016/j.annonc.2020.07.011.
[2] Doger B. et al, JCO; 41, 6029-6029(2023). https://doi.org/10.1200/JCO.2023.41.16_suppl.6029.

Study Design TACTI-003 (randomized, open label)

Patient Population: R/M HNSCC patients eligible to 1st line therapy with PD-L1 results available[1]



Primary endpoint: ORR* by RECIST 1.1 (imaging Q9W for 36 wks then Q12W) in evaluable patients.

Secondary endpoints: ORR by iRECIST, DoR, TTR, safety, PFS, OS, immunogenicity & QoL.

*Investigator assessment in patients with ≥1 evaluable post-baseline scan.

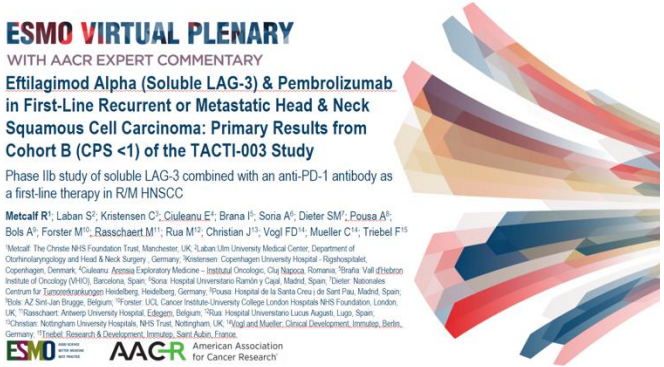
[1] https://clinicaltrials.gov/study/NCT04811027

CPS: combined positive score; OS: overall survival; PD-L1: programmed cell death ligand 1; PFS: progression free survival; Q(2,3..)W: every (2,3..) weeks; Note: 1 cycle = 6 weeks.

Primary Analysis TACTI-003

Cohort B

- Results[1] from 31 evaluable patients were reported in July at ESMO Virtual Plenary with **35.5% ORR** by RECIST 1.1 in 1st line R/M HNSCC with **CPS <1.**



[1] Metcalf, R. et al, Annals of Oncology; 35:8, 754-755(2024). https://doi.org/10.1016/j.annonc.2024.06.012.

Cohort A

- 138 patients enrolled in Cohort A (Oct 2021–Oct 2023) across 9 countries.
- 118 evaluable patients (≥1 post-baseline scan) for primary analysis:
  58 in E+P and 60 in P alone.
- We hereby report the data from the **Primary Analysis of Cohort A** with a data cut-off of March 11, 2024 and minimum follow up of 4 months.

Demographics & Baseline Characteristics

Baseline parameter, %		E+P N=58	P alone N=60
Age	Median age, years (range)	65 (43-87)	66 (38-86)
Sex	Female / Male	20.7 / 79.3	30.0 / 70.0
ECOG	ECOG 0 / ECOG 1	41.4 / 58.6	45.0 / 55.0
Smoking status	Current / Ex / Never	22.4 / 58.6 / 19.0	16.7 / 71.7 / 11.7
Primary tumour	Oral cavity	25.9	31.7
	Oropharynx	41.4	33.3
	Hypopharynx	19.0	13.3
	Larynx	13.8	21.7
p16 (HPV) status[1]	Positive / Negative	29.2 / 70.8	65.0 / 35.0
PD-L1 CPS	1-19 / ≥20	50.0 / 50.0	55.0 / 45.0
Disease status at study entry[2]	Local only	25.9	20.0
	Local and metastatic	24.1	28.3
	Metastatic only	50.0	51.7

[1] In patients with primary oropharyngeal tumours only
[2] local only: local relapse at the site of primary tumor and possibly with or without cervical lymph nodes

- Balanced for CPS and ECOG, which were stratification factors.
- Imbalances were noted including:
  - *Higher number of p16+/HPV+ (known for good prognosis) and female in the P alone arm.*
  - *Primary tumor locations, e.g. lower number of hypopharyngeal cancers (known for poor prognosis) in the P alone arm.*
  - *Lower number of current smokers in the P alone arm.*

Tumour Response Summary

Best Overall Response (BOR); N (%)	E+P N=58	P alone N=60
Complete response	4 (6.9)	3 (5.0)
Partial response	15 (25.9)	13 (21.7)
Stable disease	23 (39.7)	22 (36.7)
Progressive disease	16 (27.6)	22 (36.7)
ORR; N (%) [90% CI][1]	**19 (32.8)**, [22.6–44.3]	**16 (26.7)**, [17.5–37.6]
DCR; N (%)	**42 (72.4)**	**38 (63.3)**
Median DOR; months	**17.5**	**17.1**

[1] Calculated using Clopper-Pearson method.

An additional partial response was reported in E+P arm after data cut-off. Updated ORR of 34.5% (N=20) for E+P.

- Numerically higher ORR[1] & DCR[1] in E+P compared to P alone patients with CPS ≥1.
- Comparable results by iRECIST.
- Excellent median duration of response (DOR) of 17.5 months (E+P) and 17.1 months (P alone).

Data cut-off date: March 11, 2024

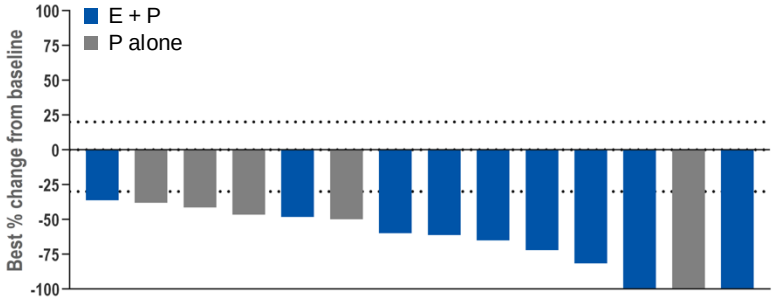
Tumour Response Summary by CPS ≥20

BOR by RECIST 1.1, N (%)	E+P N=29	P alone N=27
Complete response	2 (6.9)	1 (3.7)
Partial response	7 (24.1)	4 (14.8)
Stable disease	13 (44.8)	11 (40.7)
Progressive disease	7 (24.1)	11 (40.7)
ORR [90% CI][1]	**9 (31.0)** [17.2-47.9]	**5 (18.5)** [7.6-35.1]
DCR	**22 (75.9)**	**16 (59.3)**

[1] Calculated using Clopper-Pearson method.

An additional partial response was reported in E+P arm in CPS ≥20 after data cut-off. Updated ORR of 34.5% for E+P.

Waterfall plot of responders CPS ≥20 (N=14)



Clinically meaningful improvement of ORR in E+P (1.7-fold) compared to P alone in patients with CPS ≥20.

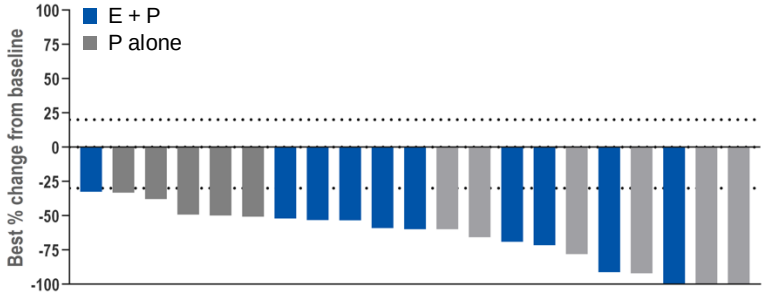
Data cut-off date: March 11, 2024

Tumour Response Summary by CPS 1-19

BOR by RECIST 1.1, %	E+P N=29	P alone N=33
Complete response	2 (6.9)	2 (6.1)
Partial response	8 (27.6)	9 (27.3)
Stable disease	10 (34.5)	11 (33.3)
Progressive disease	9 (31.0)	11 (33.3)
ORR [90% CI][1]	**10 (34.5)** [20.0-51.4]	**11 (33.3)** [19.9-49.1]
DCR	**20 (69.0)**	**22 (66.7)**

[1] Calculated using Clopper-Pearson method.

Waterfall plot of responders CPS 1-19



ORR of 33.3% for P alone in CPS 1-19 atypically higher than CPS ≥20 and well above historical published data.

Data cut-off date: March 11, 2024

Baseline Disease Characteristics by PD-L1 (CPS)

Baseline parameter, %		CPS 1-19		CPS ≥20	
		E+P N=29	P alone N=33	E+P N=29	P alone N=27
Age	Median age, years (range)	66 (43-80)	68 (38-86)	64 (43-87)	64 (49-85)
Sex	Female / Male	17.2 / 82.8	18.2 / 81.8	24.1 / 75.9	44.4 / 55.6
ECOG	ECOG 0 / ECOG 1	41.4 / 58.6	45.5 / 54.5	41.4 / 58.6	44.4 / 55.6
Smoking status	Current / Ex / Never	13.8 / 65.5 / 20.7	15.2 / 78.8 / 6.1	31.0 / 51.7 / 17.2	18.5 / 63.0 / 18.5
Primary tumour	Oral cavity Oropharynx Hypopharynx Larynx	20.7 44.8 17.2 17.2	18.2 39.4 12.1 30.3	31.0 37.9 20.7 10.3	48.1 25.9 14.8 11.1
HPV status*	Positive / Negative	30.8 / 69.2	53.8 / 46.2	27.3 / 72.7	40.7 / 59.3
Disease status at study entry	Local only Local and metastatic Metastatic only	10.3 37.9 51.7	21.2 21.2 57.6	41.4 10.3 48.3	18.5 37.0 44.4

Imbalances by CPS & treatment arm:

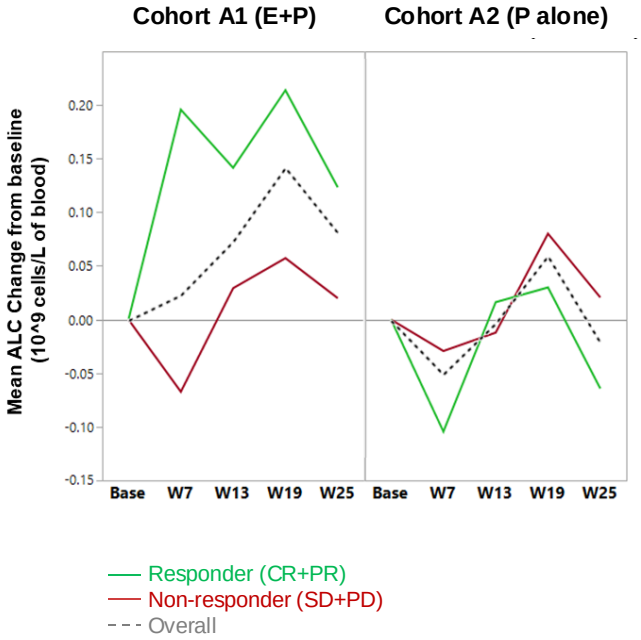
- *Higher number of HPV+ and larynx in CPS 1-19 in P alone arm.*
- *Higher number of female, oral cavity, and lower number of oropharynx in CPS ≥20 in P alone arm.*
- *Higher number of current smokers in CPS ≥20 in E+P arm.*
- *Disease status varied at study entry.*

*In patients with primary oropharyngeal tumours only.
Data cut-off date: March 11, 2024

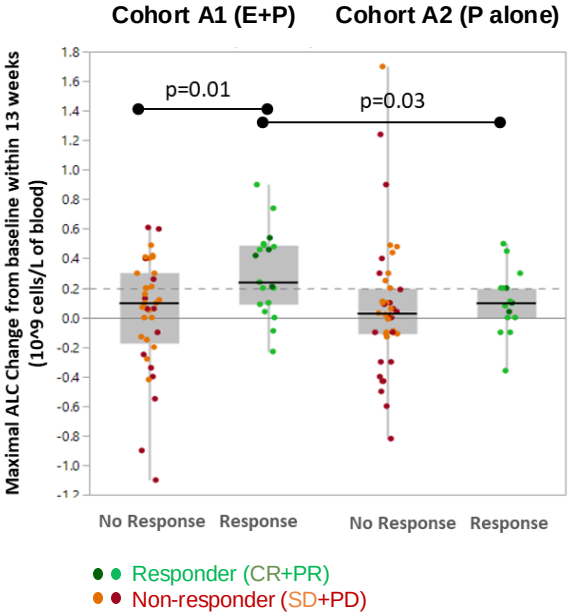
Exploratory Biomarker Analysis

- **Absolute lymphocyte count (ALC)** increase in E+P group on study (left figure).
- ALC increased significantly in responders compared to non-responders (P=0.01) in E+P group and compared to responders (P=0.03) in P alone (right figure).
- Increase of ALC shows the biological activity of efti in this randomized setting.

ALC development on study



ALC change by BOR



Data cut-off date: March 11, 2024

Safety Overview

Summary[5,6]

Safety parameters, n (%)	E+P N=69	P alone N=68
Any TEARs	39 (56.5)	41 (60.3)
Any TEARs with Grade ≥3	7 (10.1)	8 (11.8)
Any TEARs Leading to Discontinuation of Study Treatment[1]	3 (4.3)[2]	3 (4.4)[3]
Any Immune-mediated Adverse Reaction (imAR)	17 (24.6)	29 (42.6)
Any kind of Local Injection Site Reaction (LISR)	9 (13.0)[4]	0

[1] Study treatment: efti and/or pembrolizumab.
[2] Total 5 events: Immune-mediated myositis (G3) & Myasthenic syndrome (G3) in 1 patient; Anaphylactic reaction (G4) and later Immune-mediated enterocolitis (G4) in 1 patient. General physical health deterioration (G2) in 1 patient.
[3] Myocarditis (G3), Erythema multiforme (G3), Rash maculo-papular (G2) in 1 patient each.
[4] All Grade 1-2.
[5] Safety population includes all patients who were treated (N=137). 1 patient was enrolled, but not treated.
[6] TEARs – treatment emergent adverse events at least possibly related to efti and/or pembrolizumab.

Most frequent (≥5%), related adverse events[5,6]

Preferred term, n (%)	E+P N=69	P alone N=68
Hypothyroidism	5 (7.2)	15 (22.1)
Fatigue	9 (13.0)	8 (11.8)
Pruritus	5 (7.2)	5 (7.4)
Diarrhea	5 (7.2)	3 (4.4)
Rash	0	6 (8.8)
Rash maculo-popular	0	4 (5.9)
Injection site reaction	5 (7.2)	0

- No fatal TEARs & no new safety signals.
- Well-balanced Grade ≥3 TEARs between arms.

Conclusions

- E+P led to numerically higher ORR of 32.8% vs 26.7% for P alone in patients with CPS ≥1.
- Effect was largest (1.7-fold increase) in CPS ≥20, with ORR of 31.0% (E+P) vs 18.5% (P alone). No difference observed in CPS 1-19, with unexpectedly high ORR for P alone (33.3%).
- 34.8% ORR (N=89) for E+P regardless of CPS expression (Cohorts A & B), including 31 pts with CPS <1.
- Durability of response maintained by the addition of efti (median >17 mo in both study groups), comparing favorably to historical data from anti-PD-1 with chemotherapy[1-3].
- Absolute lymphocyte count significantly increased (p=0.01) in E+P arm responders (exploratory) only → in line with findings from MBC & NSCLC[4,5] and indicates effective efti-induced immune response.
- E+P is safe with no new safety signals.

→ **E+P is well tolerated with positive efficacy and warrants further investigation. Further updates, including OS, to follow.**

[1] KN-040: Cohen EEW et al. Lancet. 2019 Jan 12;393(10167):156-167. doi: 10.1016/S0140-6736(18)31999-8.
[2] KN-048: Burtness B et al. Lancet. 2019 Nov 23;394(10212):1915-1928. doi: 10.1016/S0140-6736(19)32591-7.
[3] CM-651: Haddad RI et al. J Clin Oncol. 2023 Apr 20;41(12):2166-2180. doi: 10.1200/JCO.22.00332.
[4] AIPAC: Wildiers H et al. Clin Cancer Res. 2024 Feb 1;30(3):532-541. doi: 10.1158/1078-0432.CCR-23-1173.
[5] TACTI-002: Forster M et al. Journal for ImmunoTherapy of Cancer 2023;11:doi: 10.1136/jitc-2023-SITC2023.0595

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