TACTI-003 Cohort B: Eftilagimod Alpha (Soluble LAG-3) and Pembrolizumab in First-Line Recurrent or Metastatic Head & Neck Squamous Cell Carcinoma with CPS <1

Poster # 620

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2024 ESMO IMMUNO-ONCOLOGY Annual Congress
GENEVA SWITZERLAND
11-13 DECEMBER 2024

BACKGROUND

Eftilagimod alpha (efti): a soluble LAG-3 protein and MHC Class II agonist that leads to an enhanced immune response by activating antigen presenting cells (APCs), leading to the activation/proliferation of CD8+ T cells[1] (**Figure 1**).

Pembrolizumab: current standard-of-care that antagonizes PD-1 receptor on T cells, enhancing the immune response against cancer cells.

Rationale for study: Efti activates APCs, leading to an increase in activated T cells (CD4/CD8), augmenting responses when combined with PD-(L)1 antagonists such as pembrolizumab.

Encouraging efficacy has been seen when efti was combined with pembrolizumab in 2nd line HNSCC patients after failure of 1st line chemotherapy[2] (**Table 1**) and in 1st line NSCLC regardless of PD-L1 TPS[3] (**Table 2**). Responses were observed irrespective of patients' CPS/TPS level.

Figure 1. Mechanism of action of efti when combined with pembrolizumab

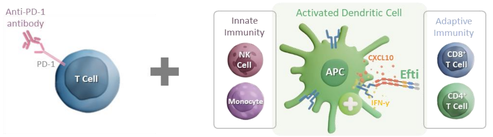


Table 1. Second line HNSCC, presented at ASCO 2023[2]

PD-L1 CPS	ITT, N=37	≥20, N=15	<20, N=17
Objective response rate (iRECIST), %	29.7	60.0	11.8

Table 2. First line NSCLC, presented at ESMO 2023[3]

PD-L1 TPS	<1%, N=32	1-49%, N=38	≥50%, N=20
Objective response rate (iRECIST), %	31.3	44.7	55.0

[1] Brignone C., Clin Cancer Res. 2009;15: 6225- 6231; [2] Doger B. et al, JCO. 2023;41: 6.29-6.29; [3] Carcereny E. et al, Ann of Onc 2023;34:S755-S851.

METHODS

Study Design and Patients

- **TACTI-003** (Two **ACT**ive **I**mmunotherapies-003): Phase IIb, multinational, open label study. We present results from **first-line R/M HNSCC PD-L1 negative (CPS <1), Cohort B**.
- Efti administered as 30 mg subcutaneous injection Q2W for the first 6 months and then Q3W for max 2 years. Pembrolizumab administered as 400 mg intravenous infusion Q6W for max 2 years (**Figure 2**).

Results from Cohort A were published at ESMO 2024 (Kristensen CA et al, Ann of Onc 2024;35:S1227).

Assessments and Statistical Analyses:

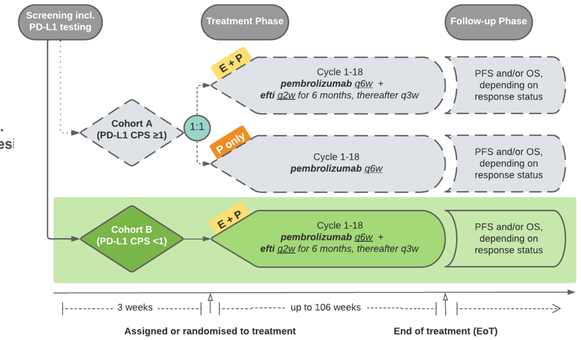
- Prospective assessment of tumor cell PD-L1 expression for enrollment (FDA-approved kit 22C3).
- Imaging performed Q9W (assessed according to RECIST 1.1 and iRECIST).
- Safety was analyzed in all patients who received at least one dose of study drug (N=33). Efficacy was analysed in all patients who were part of the safety population and had at least one evaluable post-baseline scan (N=31).

Safety data cut-off date: June 26, 2024. Efficacy data cut-off date: October 31, 2024.

Endpoints:

Primary Endpoint: ORR by RECIST 1.1.
Secondary Endpoints: ORR by iRECIST, DoR, safety, PFS and OS.

Figure 2. Study des



RESULTS

PATIENT DISPOSITION & BASELINE CHARACTERISTICS

- 33 patients were recruited at 14 sites across 6 countries between April 2022 until October 2023.
- Median age was 64 years (range: 23–83) & 74.2% of patients were male. Of the patients with primary oropharyngeal tumours, 36.4% were HPV positive (**Table 3**).

Table 3. Baseline characteristics

Baseline parameters	N=31
Median age, years (range)	64 (23-83)
Female / Male, %	25.8 / 74.2
ECOG 0 / 1, %	32.3 / 67.7
Current / Ex-smoker / Non-smoker, %	25.8 / 61.3 / 12.9
Primary tumour location, %	
Oral cavity	29.0
Oropharynx	35.5
Hypopharynx	3.2
Larynx	32.3
p16 (HPV) status[1]	
Positive / Negative	36.4 / 63.6
Disease status at study entry[2], %	
Primary only	22.6
Primary + distant	12.9
Distant only	64.5

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

- 25 patients discontinued treatment due to: disease progression (92.0%), adverse event (3.2%) and physician decision (3.2%).

SAFETY

- No treatment-related deaths occurred (**Table 4**).
- Local injection site reactions were observed in 18.2% of patients (all Grade 1).
- The most frequent AEs were fatigue and nausea (**Table 5**).

Table 4. General overview of AEs (N=33)

Safety parameter[1]	N=33
Adverse reactions with fatal outcome[2]	0
Serious adverse reactions[2]	*0*
Grade ≥3 adverse reactions[2]	*15.2*
Adverse reactions leading to discontinuation of treatment[2]	*9.1*[3]

[1] AEs rated according to NCI CTCAE (v5.0).
[2] relationship to efti and/or pembrolizumab could not be ruled out
[3] Immune thrombocytopenia (G4), Immune-mediated hepatitis (G3), Laryngeal obstruction (G4).

Table 5. Frequent AEs (incidence ≥15%) (N=33)

Adverse event (PT)[1]	Any grade, %	Grade 3, %	Grade 4/5, %
Fatigue	21.2	*NA*	*NA*
Nausea	21.2	*NA*	*NA*
Weight decreased	18.2	*NA*	*NA*
Hypothyroidism	18.2	*NA*	*NA*
Constipation	18.2	*NA*	*NA*
Pyrexia	15.2	*NA*	*NA*
Arthralgia	15.2	*NA*	*NA*
GGT increased	15.2	*3.0*	*NA*
Diarrhoea	15.2	*NA*	*NA*
Anaemia	15.2	*NA*	*NA*

[1] AEs rated according to NCI CTCAE (v5.0).
GGT: Gamma-glutamyltransferase.

EFFICACY

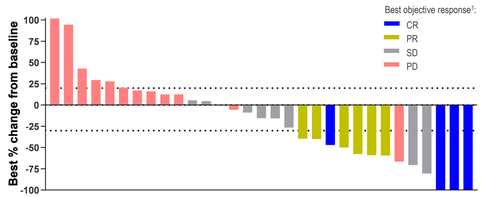
- ORR (RECIST 1.1) of 35.5% (95% CI: 19.2–54.6) and 38.7% (95% CI: 21.8–57.8) by iRECIST (**Table 6**).
- Responses confirmed in 91% of cases with a confirmed ORR by RECIST 1.1 of 32.3% (95% CI: 16.7–51.4).
- Responses were deep, had early onset (median time to response of 2.1 months) and included 4 confirmed complete responses by RECIST 1.1 (**Figure 3**).
- With a median follow up of 16.4 months, median (m) PFS by RECIST 1.1 was 5.8 months with a 6-month PFS rate of 48.4% (**Figure 5**).
- mDoR by RECIST 1.1 was 9.3 months with 50% events. 55% of patients on treatment >6 months and ~30% on treatment >12 months (**Figure 4**).
- mOS was not reached (**Figure 6**) and the 12-month survival rate was 66.8%.

Table 6. Best objective response[1] (N=31)

Response	RECIST 1.1, %	iRECIST, %
Complete Response	12.9	16.1
Partial Response	22.6	22.6
Stable Disease	22.6	25.8
Progressive Disease	41.9	35.5
ORR[1]; [95% CI][2]	35.5 [19.2–54.6]	38.7 [21.8–57.8]
DCR; [95% CI][2]	58.1 [39.1–75.5]	64.5 [45.4–80.8]

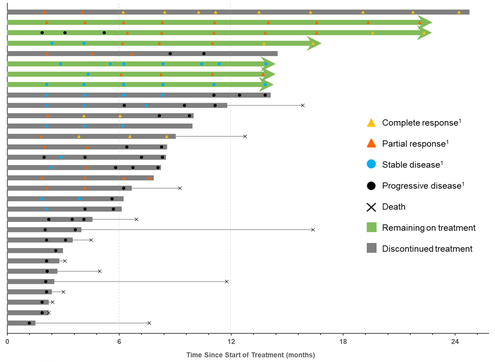
[1] Unconfirmed (local assessment).
[2] 95% confidence intervals calculated using Clopper-Pearson method.
Note:10/11 responses confirmed by RECIST 1.1 and 11/12 by iRECIST.

Figure 3. Waterfall plot (N=31)



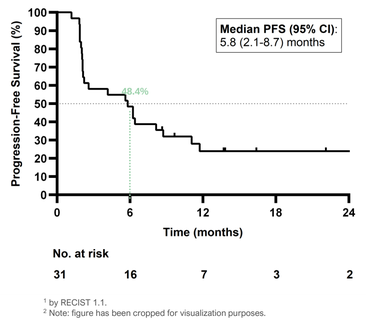
[1] by RECIST 1.1 (local assessment).
Includes one complete response (CR) with a best % change of -47%. This patient had one target lesion of the lymph node, which shrunk to <10 mm.

Figure 4. Swimmer plot (N=31)



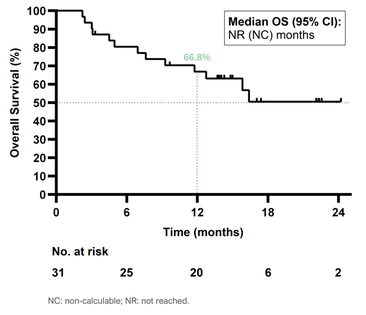
[1] by iRECIST.
Note: treatment decisions were made using iRECIST.

Figure 5. Progression free survival[1,2] (N=31)



[1] by RECIST 1.1.
[2] Note: figure has been cropped for visualization purposes.

Figure 6. Overall survival (N=31)



NC: non-calculable; NR: not reached.

SUMMARY & CONCLUSION

- Efti combined with pembrolizumab led to a high ORR (35.5% [95% CI: 19.2–54.6]) and DCR (58.1% [95% CI: 39.1–75.5]) in this PD-L1 CPS <1 population.
- Promising median PFS of 5.8 months, median DoR of 9.3 months and median OS not yet reached, with 67% of patients alive at 12 months.
- Treatment with efti plus pembrolizumab is safe and well-tolerated with no new safety signals.

Conclusion: Results are promising (mature 12-month OS rate of 67%), especially when considering the expected efficacy of anti-PD-1 alone in this population. Late-stage development is warranted.

ABBREVIATIONS
APC…antigen presenting cell
CPS…combined positive score
CR…complete response
DoR…duration of response
ECOG…Eastern Cooperative Oncology Group
(i)RECIST…(Immune) Response Evaluation Criteria In Solid Tumors
ITT…intention-to-treat
LAG-3…Lymphocyte Activation Gene-3
MHC…Major Histocompatibility Complex
NR…not reached
ORR…objective response rate
OS…overall survival
PD-L1… programmed death-ligand 1
PFS…progression free survival
PR…partial response
PT…preferred term
SD…stable disease
TPS…tumour proportion score
PD…progressive disease

ACKNOWLEDGEMENTS
- We thank all the participating patients & their families.
- We thank the dedicated clinical trial investigators & their team members.
- This study is sponsored by Immutep. Corresponding author: Frederic Triebel, frederic.triebel@immutep.com
- This study is in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

DISCLOSURES
Presenting Author: Dr. Martin Forster.
COI: Advisory board: Bayer, Merck, MSD, Takeda, Ultrahuman, Transgene, Immutep, Amgen, BMS, EQRS, Janssen, Oxford VacMedix, Pharmamar, Regeneron and Syncorp. Research grant: AstraZeneca (Inst), Boehringer Ingelheim (Inst), Merck Serono (Inst) and MSD Oncology (Inst). Invited speaker: Roches, Achilles, Oxford VaxMedix, Apollomics, Takeda, Ellipsis, Moderna, Exscientia, Immutep, ALXOncology; Genmab and Janssen. Advisory role: Ruth Strauss Foundation.