TACTI-003: A randomized Phase IIb study of eftilagimod alpha (soluble LAG-3 protein) and pembrolizumab as first-line treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma

Abstract # 675

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BACKGROUND

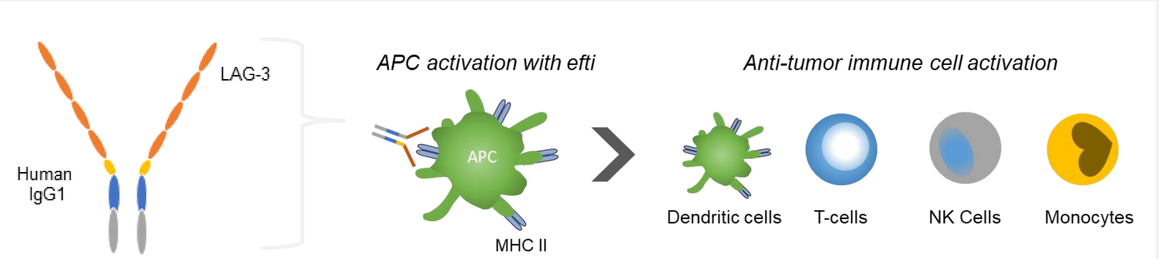
Mechanism of action: eftilagimod alpha (efti) is soluble LAG-3 protein (LAG-3 domains fused to human IgG backbone[1] [**Figure 1**]) targeting a subset of MHC class II molecules to mediate activation of antigen presenting cells (APCs: dendritic cells & monocytes), natural killer (NK) and T-cells (**Figure 1**). Efti is an MHC class II agonist.

Difference to anti-LAG-3 mAbs: efti does not bind to LAG-3 on T cells like anti-LAG-3 antagonists.

Rationale for study: Stimulation of the dendritic cell network and the resulting T cell recruitment/activation may overcome resistance to anti-PD-1 (programmed cell death protein 1) therapy.

Predecessor trial TACTI-002 (NCT03625323) in 2nd line HNSCC had an ORR of 29.7% in the overall population and 40.7% in the PD-L1 CPS ≥1 subpopulation[2]. Results led to fast-track designation of this trial.

Figure 1. Structure and mechanism of action of efti



STUDY SITES

Figure 2. Study sites & expected no. of patients

	Treatment	# of Expected patients
Cohort A (CPS ≥1)	(E + P) & (P Only)	130
Cohort B (CPS <1)	(E + P)	24

RECRUITMENT

Recruitment for TACTI-003 is ongoing. For more info, please visit: https://clinicaltrials.gov/ct2/show/NCT04811027.

ENROLLMENT

This study began October 2021 and is ongoing.

** Treatment is secured for 6 patients who are currently enrolled. Further recruitment is currently on hold.*

METHODS

A multicentre, open label, randomized, Phase IIb trial enrolling patients unselected for PD-L1 expression.

Allocation & stratification will be based on patient PD-L1 expression (**Figure 3**).

Cohort A: CPS score of ≥1

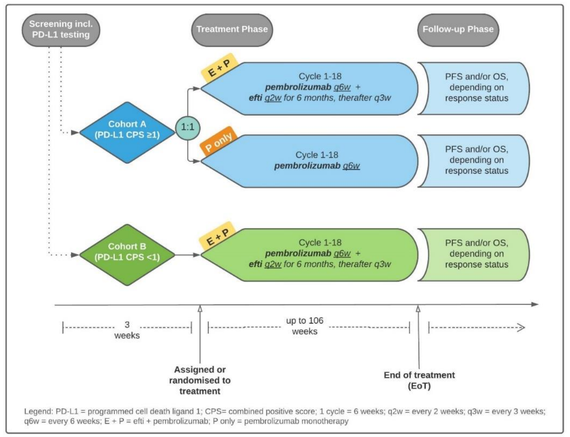
a) **Randomized 1:1** to receive either "**E+P**": **efti + pembrolizumab** or "**P only**": **pembrolizumab alone.**

b) Patients will be stratified for CPS score (1-19 vs. ≥20 and ECOG 0 vs. 1).

Cohort B: CPS score of <1

a) **Non-randomized** to receive a combination of **efti + pembrolizumab "E+P"**.

Figure 3. Study design



Legend: PD-L1 = programmed cell death ligand 1; CPS= combined positive score; 1 cycle = 6 weeks; q2w = every 2 weeks; q3w = every 3 weeks; q6w = every 6 weeks; E + P = efti + pembrolizumab; P only = pembrolizumab monotherapy

Primary objectives:

- **Objective response rate (ORR)** of E + P in **Cohort A** compared to P only in **Cohort A.**
- **ORR** of E + P in **Cohort B**.

Secondary objectives:

- **Overall survival (OS)** and antitumor activity of E + P in **Cohort A** compared to P only in **Cohort A**.
- **OS** and **further antitumor activity** of E + P in **Cohort B**.
- **Safety and tolerability** of E + P compared to P only.
- **Immunogenic properties** of E + P.

Exploratory

- Identify & characterize relevant biomarkers.

Figure 4. Key eligibility criteria

Inclusion Criteria

- Histologically- or cytologically-confirmed recurrent disease unamenable to curative treatment with local or systemic therapy, or metastatic HNSCC of oral cavity, oropharynx, hypopharynx, or larynx that is considered incurable by local therapies and to be treated in the first line palliative setting and who are PD-X naïve.
- Availability of tissue for PD-L1 biomarker analysis from a core or excisional biopsy.
- Availability of PD-L1 biomarker result by using the FDA approved Dako standardized diagnostic test (PD-L1 IHC 22C3 pharmDx).
- Available tissue for testing of human papillomavirus (HPV) status for oropharyngeal cancer (p16 expression testing).
- ECOG performance status 0-1.

Exclusion Criteria

- Disease suitable for curative local therapy.
- ≥1 prior systemic regimen for recurrent and/or metastatic disease.
- Histologically or cytologically confirmed disease of primary anatomic location not specified in inclusion criteria, including HNSCC patients with unknown primary, squamous cell carcinoma originating from skin, or non-squamous histologies.
- Progressive disease (PD) within 6 months of completion of curatively intended systemic treatment.
- Prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody.
- Known active central nervous system metastasis and/or carcinomatous meningitis.
- Received continuous systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 7 days prior to C1D1.

Drug administration:

Pembrolizumab: 400 mg as intravenous infusion over 30 mins every 6 weeks as per **Figure 3**. Max 18 infusions may be administered.

Efti: 30 mg injected ≥30 mins after pembrolizumab infusion (**Figure 3**).

Route of administration is subcutaneous injection (single anatomical site) in anterior face of thigh.

Max 40 injections may be administered.

- Patients will be followed for ORR, PFS and OS. PFS will be radiologically assessed until progressive disease (PD), death, withdrawal of consent, loss to follow-up, or until the end of the trial, whichever occurs first. Radiological assessments will be performed at intervals of 9 weeks until week 36 and every 12 weeks thereafter. OS will be monitored until death, withdrawal of consent, loss to follow-up or until the end of the trial, whichever occurs first.
- Measurability will be assessed according to RECIST 1.1. Treatment decisions will be made according to iRECIST.

ABBREVIATIONS

APC… antigen-presenting cell
CPS… combined positive score
CTLA-4 …anti-cytotoxic T-lymphocyte-associated antigen-4
ECOG… Eastern Cooperative Oncology Group
HNSCC… head and neck squamous cell cancer
HPV…Human papillomavirus
iRECIST/RECIST1.1… Immune Response Evaluation Criteria In Solid Tumors
LAG-3… Lymphocyte Activation gene-3
MHC… Major Histocompatibility Complex
NK… natural killer
ORR… objective response rate
OS… overall survival
PD…progressive disease
PD-L/PD-L1…Programmed Death ligand/-1
PD-X…PD-1 or PD-L1 targeted therapy
PD-X…PD-1 or PD-L1 targeted therapy
PFS… progression-free survival
Th1… T helper type 1

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