A Phase II study of eftilagimod alpha (soluble LAG-3 protein) and pembrolizumab in patients unselected for PD-L1 expression in first line metastatic head and neck squamous cell carcinoma (HNSCC)

Abstract # 440

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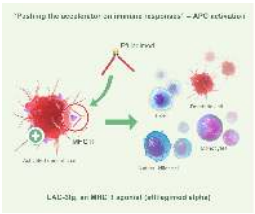
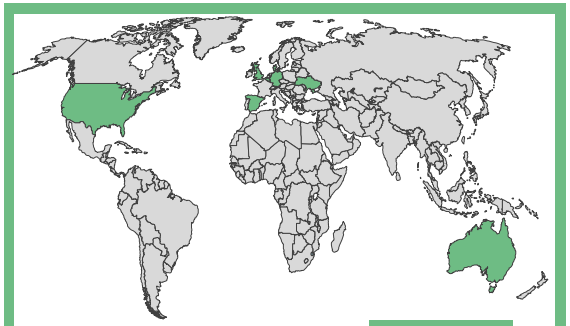
BACKGROUND



Lymphocyte activation gene 3 protein (LAG-3) is a transmembrane protein found on activated T and natural killer (NK) cells and a key mediator of immune responses. Eftilagimod alpha (efti; IMP321) is a recombinant soluble human LAG-3Ig fusion protein which is under development as a cancer immunotherapeutic agent. Like endogenous LAG-3, efti binds to major histocompatibility complex (MHC) class II antigen presenting cells (APCs) such as dendritic cells (DCs) and triggers a T helper 1 (Th1) response and T cell proliferation. Efti is currently investigated in clinical trials in combination with chemotherapy and with PD-1/PD-L1 antagonists in a variety of solid tumors.

INVOLVED COUNTRIES



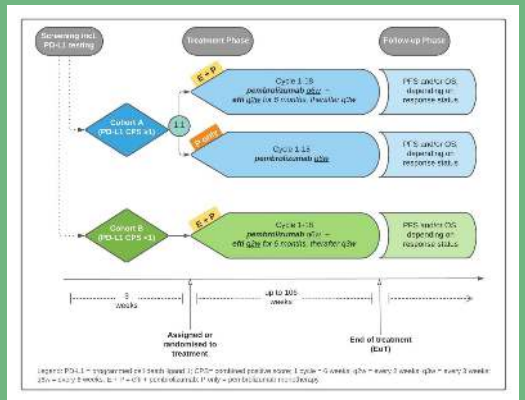
	Treatment	# of Expected Subjects
Cohort A **CPS ≥1**	(E + P) & (P Only)	130
Cohort B **CPS <1**	(E + P)	24

Selected Countries:
- United States
- Australia
- Belgium
- Denmark
- Spain
- United Kingdom
- Ukraine
- Germany

TRIAL DESIGN/ TREATMENT DESIGN

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

Allocation and stratification into Cohort A and Cohort B is based on subject PD-L1 expression.



Cohort A: **CPS score of ≥1**

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

b) Subjects 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"**

- Screening of subjects will be done in the 3 weeks prior to cycle 1 day 1.
- A subject will stay on treatment until disease progression, unacceptable toxicity, completion of 18 cycles (~2 yrs.; completion of trial treatment) or discontinuation for any other reason.
- Four (4) weeks after end of any trial treatment (cycle 18, or earlier if early discontinuation) an end of treatment (EOT) visit will be performed.
- Upon start of trial treatment, subjects will be followed for ORR, PFS and OS. PFS will be radiologically assessed at the trial sites until progressive disease (PD), death, withdrawal of consent, loss to follow-up, or until the end of the trial, whichever occurs first. Radiological assessment will be performed at intervals of 9 weeks until week 36 (i.e. week 9, 18, 27, 36) and every 12 weeks thereafter (week 48, 60, 72, …). 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 RECIST1.1. Treatment decisions will be made according to iRECIST.

DRUG ADMINISTRATION

Pembrolizumab will be given at a dose of 400 mg (flat) using a 30-minute (-5 min/+10 min) i.v. infusion on Day 1 of each 6-week treatment cycles. The maximum number of 18 pembrolizumab infusions may be administered.

Efti will be injected at a dose of 30 mg every 2 weeks for the first app. 6 months (4 cycles), thereafter at a dose of 30 mg every 3 weeks for up to app. 2 years in total (i.e 18 cycles of 6 weeks). The maximum number of 40 efti injections may be administered. Efti is to be given always ≥ 30 minutes after pembrolizumab infusion is finished.

The route of administration for efti will be subcutaneous injection (s.c., single anatomical site) in the anterior face of the thigh. The location of the injection site should be rotated with each injection.

TIMING OF ANALYSIS

Primary analysis will be performed when all subjects in Cohort A complete at least 3 cycles of treatment or discontinued the trial. A final end-of-trial analysis may be performed on cumulative data after all subjects complete the follow up periods.

STUDY TIMELINES

- Study is open for recruitment. For participating sites please refer to clinicaltrials.gov
- Estimated primary completion: April 2023
- Estimated study completion: January 2025

OBJECTIVES

Primary:
- To evaluate the **objective response rate** of efti + pembrolizumab in Cohort A and to compare to pembrolizumab alone in Cohort A.
- To evaluate the **objective response rate** of *efti + pembrolizumab* in Cohort B.

Secondary:
- To evaluate **overall survival (OS)** and further antitumor activity of efti + pembrolizumab in Cohort A and to compare to pembrolizumab alone Cohort A,
- To evaluate the **overall survival** and **further antitumor activity** of efti + pembrolizumab in Cohort B.
- To evaluate the **safety and tolerability** of efti + pembrolizumab compared to pembrolizumab alone.
- To assess the **immunogenic properties** of efti + pembrolizumab.

Exploratory
- To identify and characterize relevant biomarkers.

MAIN INCLUSION CRITERIA

- Histologically- or cytologically-confirmed recurrent disease not amenable to curative treatment with local or systemic therapy, or metastatic (disseminated) HNSCC of the 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).
- Availability of tissue for testing of human papillomavirus (HPV) status for oropharyngeal cancer (p16 expression testing).
- ECOG performance status 0-1.

MAIN EXCLUSION CRITERIA

- Disease is suitable for local therapy administered with curative intent.
- Previously treated with ≥ 1 systemic regimen for recurrent and/or metastatic disease.
- Histologically or cytologically confirmed head and neck cancer of any other primary anatomic location in the head and neck not specified in the inclusion criteria including subjects with HNSCC of unknown primary, squamous cell carcinoma originating from skin, or non-squamous histologies (e.g. nasopharynx, salivary gland or mucosal melanoma).
- Has progressive disease (PD) within 6 months of completion of curatively intended systemic treatment.
- Prior therapy with an 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.
- Receives continuous systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 7 days prior to cycle 1 day 1.

APC… antigen-presenting cell
CPS… combined positive score
DC… dendritic cell
ECOG… Eastern Cooperative Oncology Group
EoT… end of treatment
HNSCC… head and neck squamous cell cancer
iRECIST… Immune Response Evaluation Criteria In Solid Tumors
LAG-3… Lymphocyte Activation gene-3
MHC… Major Histocompatibility Complex
NK… neutral killer
PD… progressive disease
PD-L1… Programmed Death ligand-1
Pts … patients
PFS… progression-free survival
ORR… objective response rate
OS… overall survival
TEAE… treatment-emergent adverse event

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA provided pembrolizumab for the study.
The trial identifiers are IMP321-P022 (Sponsor code), Keynote-PNC-34 (MSD code), 2021-000055-39 (EudraCT) and NCT04811027 (ClinicalTrials.gov).
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