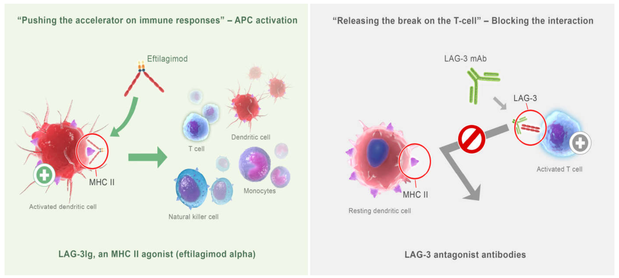
TACTI-002 (Two ACTive Immunotherapeutics): A multicenter, open label, Phase II study in patients with previously untreated unresectable or metastatic non-small cell lung cancer (NSCLC), or recurrent PD-X refractory NSCLC or with recurrent or metastatic squamous head and neck cancer (HNSCC) receiving the soluble LAG-3 fusion protein eftilagimod alpha (IMP321) in combination with pembrolizumab (PD 1 antagonist)

Martin Forster[1], Christian Mueller[2], Chrystelle Brignone[3], Tatsiana Skrahina[2], Frederic Triebel[3]

[1] UCL Cancer Institute , London, United Kingdom
[2] Clinical Development, Immutep GmbH, Leipzig, Germany
[3] Research & Development, Immutep S.A.S., Orsay, France

Background



Eftilagimod alpha (efti, IMP321) is a recombinant LAG-3Ig fusion protein that binds to MHC class II and mediates antigen-presenting cell (APC) activation followed by CD8 T cell activation.

Pembrolizumab binds to the PD-1 receptor, blocking both immune-suppressing ligands, PD-L1 and PD-L2, from interacting with PD-1 to help restore effector T cell responses. The rationale to combine efti and pembrolizumab comes from their complementary mechanisms of action. Efti activates APCs and leads to an increase in activated T cells which effect potentially reduces the number of non-responders to pembrolizumab.

Combining an APC activator like efti to pembrolizumab is therefore fundamentally different from many other trials combining two checkpoint inhibitors like an anti-LAG-3 mAb with an anti-PD-1 mAb.

For more information, please visit http://www.immutep.com/investors-media/presentations.html or use the following:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA provided pembrolizumab for the study.
The trial identifiers are IMP321-P015 (Sponsor code), Keynote-PN798 (Merck code), 2018-001994-25 (EudraCT) and NCT03625323 (ClinicalTrials.gov).
Corresponding author: Frederic Triebel, frederic.triebel@immutep.com

Objectives

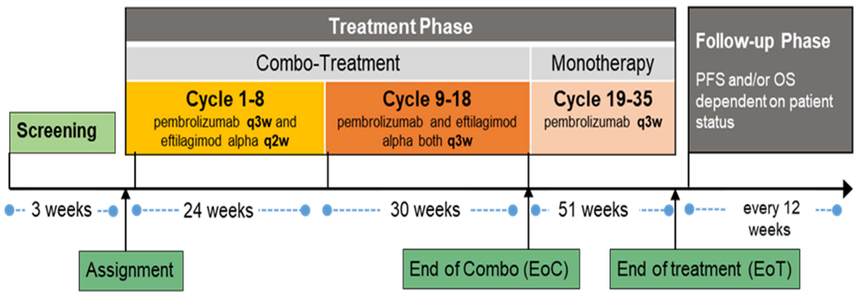
- To evaluate the response rate of eftilagimod alpha given in combination with pembrolizumab in patients with advanced / metastatic NSCLC (PD-X naïve, 1st line and PD-X refractory, 2nd line) and recurrent HNSCC
- To further evaluate the safety, tolerability and antitumor activity of eftilagimod alpha when combined with pembrolizumab
- To assess the pharmacokinetic and immunogenic properties of eftilagimod alpha

Treatment

The treatment consists of an immuno-immunotherapy combo phase followed by a monotherapy phase.

- **combo phase**: **8 cycles** of 3 weeks with pembrolizumab (200 mg iv.) q3w and eftilagimod alpha (30 mg sc.) q2w; followed by **10 cycles** of 3 weeks with pembrolizumab (200 mg iv.) and eftilagimod alpha (30 mg sc.) both given q3w

- **monotherapy phase**: 17 cycles of 3 weeks with pembrolizumab (200 mg iv.) q3w



Legend: 1 cycle = 3 weeks; q2w – every 2 weeks, q3w every 3 weeks

Other key inclusion and exclusion criteria

Inclusion:

- Submission of formalin-fixed diagnostic tumor tissue
- ECOG performance status 0-1
- Expected survival longer than three months

Exclusion:

- Part A 1st line, PD-X naïve NSCLC amenable for curative standard of care, received systemic therapy for stage IV or amenable to EGFR/ALK based therapy
- Part B 2nd line, PD-X refractory NSCLC with symptomatic ascites or pleural effusion or >1 line of chemotherapy for metastatic disease
- Part C 2nd line PD-X naive HNSCC amenable to curative treatment or >1 systemic regimen for recurrent and/or metastatic disease
- Prior anti-PD-X therapy or other immunotherapy targeting T cell co-stimulation or chekcpoint pathways (Part A and C only)
- Prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T cell receptor (e.g., CTLA-4, OX 40, CD137) and was discontinued from that treatment due to a Grade 3 or higher irAE (Part B only)
- Systemic anti-cancer therapy, major surgery or any other investigational agent within 4 weeks prior to first dose of study treatment
- Known cerebral or leptomeningeal metastases
- Any condition requiring continuous systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 7 days prior to first dose of study treatment.

APC…antigen-presenting cell
ECOG…Eastern Cooperative Oncology Group
efti…Eftilagimod alpha
HNSCC…head and neck squamous cell cancer
LAG-3…Lymphocyte Activation gene-3
MHC…major Histocompatibility Complex
NSCLC…non-small cell lung cancer
PD-L1, PD-L2…Programmed Death ligand-1, -2
PD-X…PD-1 or PD-L1 targeted therapy

Study population

- Part A (1st line, PD-X naïve NSCLC): histologically- or cytologically-confirmed diagnosis of non-small cell lung carcinoma stage IIIB not amenable to curative treatment or stage IV not amenable to EGFR/ALK based therapy, treatment naïve for systemic therapy given for advanced/metastatic disease (previous palliative radiotherapy for advanced/metastatic disease acceptable)
- Part B (2nd line, PD-X refractory NSCLC): histologically- or cytologically-confirmed diagnosis of NSCLC after failure of first-line treatment (for metastatic disease) with at least 2 cycles of any PD-1/PD-L1 containing based therapy alone, or in combination with any other immunotherapeutic or chemotherapy
- Part C (2nd line PD-X naive HNSCC): 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, and larynx that is considered incurable by local therapies after failure of prior platinum-based therapy

Trial design

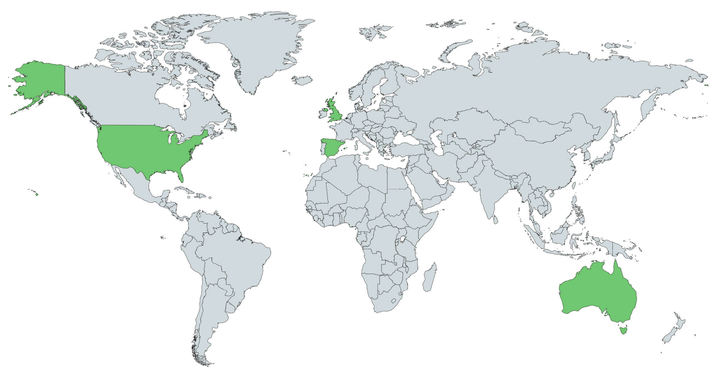
A multicenter, open-label, Phase II clinical trial applying Simon's 2-stage design.

During the first stage, the number of N1 patients will be recruited. In case there are more responses than threshold r1 observed in patients recruited in Stage 1 (N1), additional patients (N2) will be recruited in Stage 2.

Indication	Threshold r1	Initial No. of pts (N1)	Add. No. of pts (N2)	N total
Part A: NSCLC 1st line	4	17	19	36
Part B: NSCLC 2nd line	1	23	13	36
Part C: HNSCC	2	18	19	37

Involved countries

- The Tacti-002 trial was submitted and approved in 4 countries and 13 sites:
  - Australia
  - Spain
  - United Kingdom
  - United States of America



Study duration

- Status: first approvals from competent authorities and ECs/IRBs received
- Estimated study start date: November 2018
- Estimated primary completion date: June 2020
- Estimated study completion date: June 2021

Statistical analysis

- N = 58 (Stage 1) + 51 (Stage 2)
- All efficacy analyses will be based on Investigator's assessment acc. to iRECIST