Initial results from a Phase II study (TACTI-002) in non-small cell lung cancer, or head and neck cancer patients receiving eftilagimod alpha (LAG-3 fusion protein) and pembrolizumab

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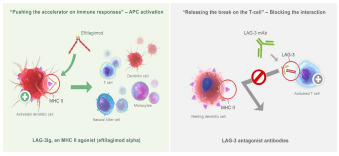
Background



Eftilagimod alpha (efti; previously IMP321) is a **soluble LAG-3 protein** that binds to a subset of MHC class II molecules to **mediate antigen presenting cell (APC)** and then **CD8 T-cell activation**.

Efti is a first-in-class APC activator.

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.

Previous clinical trial experience with the same combination used in metastatic melanoma patients (TACTI-mel study, IMP321-P012, NCT02676869) suggests that the combination is safe and shows encouraging signs of efficacy.

We hereby report initial results of stage 1 of a phase II trial (TACTI-002).

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 (MSD code), 2018-001994-25 (EudraCT) and NCT03625323 (ClinicalTrials.gov).
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Trial Design

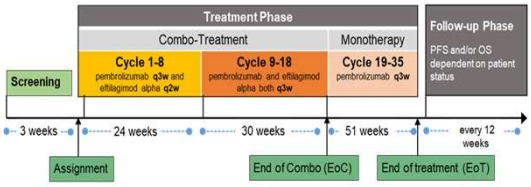
Part A: 1st line, PD-X naïve NSCLC;
Part B: 2nd line, PD-X refractory NSCLC;
Part C: 2nd line PD-X naive HNSCC

- Simon's optimal two-stage design
- Primary endpoint: objective response rate (ORR) as per iRECIST
- Secondary endpoints: progression free survival (PFS) and overall survival (OS)
- Blood samples for PK/PD assessments and anti-drug antibody evaluation are collected

During the first stage, the N1 patients are recruited. Additional patients (N2) will be recruited for each part if the pre-specified threshold for ORR is met. In total, 109 patients are planned to be enrolled.

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

Efti is administered as 30 mg subcutaneous injection every 2 weeks for the first 8 cycles and every 3 weeks for 9 following cycles. Pembrolizumab is administered at a standard dose of 200 mg intravenous infusion every 3 weeks for maximum 2 years.



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

Exposure and Safety[1]

Summary - Exposure:

- In total 33 pts were enrolled until data cut-off[1]. Part A (N=17) stage 1 enrollment was completed in June 2019. Recruitment into part B + C stage 1 and into part A stage 2 is ongoing
- Pts received median 7 (range 1-14) IMP321 injections and median of 5 (range 1-10) pembrolizumab infusions

Safety Parameters	N of patients (%)
Pts with any TEAE	29 (87.9)
Pts with any SAE	10 (30.3)
thereof rel. to IMP321 / pembrolizumab	1 (3.0) / 1 (3.0)
Pts with any grade ≥3 TEAE	15 (45.5)
thereof rel. to IMP321 / pembrolizumab	2 (6.1) / 2 (6.1)

Adverse events ≥ grade 3 and related to either pembrolizumab or efti

Adverse event (PT)	Grade 3 N (%)	Grade 4 N (%)	Serious
Atrial fibrillation	1 (3)	-	Yes
Hepatitis	-	1 (3)	Yes
Diarrhea	1 (3)	-	No

Overview - Safety:

- **1 fatal TEAE** (Hemoptysis, grade 5) unrelated to both study treatments
- **1 patient with SAEs** related to both study drugs (see table left)
- **2 AEs leading to discontinuation:**
  - Hepatitis grade 4 – both study drugs discontinued
  - Diarrhoea grade 3 – pembrolizumab discontinued

Adverse events occured in ≥ 10 % of pts (N=33 in total)

Adverse event (PT)	Any Grade N (%)	Grade 3 N (%)	Grade 4 N (%)	Grade 5 N (%)
Asthenia	9 (27.3)	-	-	-
Cough	12 (36.4)	-	-	-
Decreased appetite	6 (18.2)	-	-	-
Diarrhoea	5 (15.2)	1 (3.0)	-	-
Dyspnoea	6 (18.2)	3 (9.1)	-	-
Fatigue	5 (15.2)	-	-	-
Nausea	4 (12.1)	-	-	-

[1] - Data cut-off date: 9th Oct 2019

APC…antigen-presenting cell
AE…adverse event
BOR…best overall response
DCR…disease control rate
DMC…Data Monitoring Committee
ECOG…Eastern Cooperative Oncology Group
HNSCC…head and neck squamous cell cancer
ICI…immune checkpoint inhibitor
iRECIST…Immune Response Evaluation Criteria In Solid Tumors
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
PFS…progression-free survival
ORR…objective response rate
SAE…serious adverse event
TEAE…treatment emergent adverse event

Initial Efficacy Part A stage 1 - PD-X naive NSCLC[2]

Baseline Characteristics:

- Non-small cell lung cancer stage pts with stage IIIB not amenable to curative treatment or stage IV not amenable to EGFR/ALK based therapy who were treatment naïve for advanced/ metastatic disease were enrolled
- Majority of pts male and had ECOG of 0
- 58 % of pts previously treated for NSCLC with surgery, radiochemo or radiotherapy
- Patients with different PD-L1 status enrolled (< 1 %; 1-49 %; ≥ 50 %); data not yet available for all pts
- 58 % ≥ 65 yrs

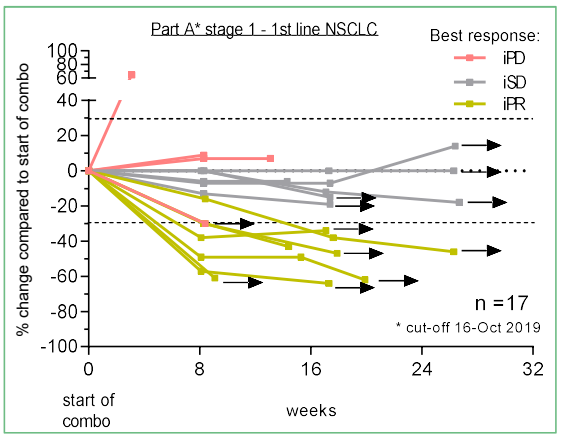
Baseline Parameters (n=17)	N (%)
Median age, yrs (range)	65 (53 – 76)
Sex	
Female	6 (35.3)
Male	11 (64.7)
ECOG	
0	12 (70.6)
1	5 (29.4)
Smoking status	
Never	1 (5.9)
Current / former	16 (94.1)
Histology	
Squamous	10 (58.8)
Non-squamous	7 (41.2)
Location of disease at study entry	
Lung	8 (47.1)
Bone	5 (29.4)

Tumor response - BOR as per iRECIST	N (%) Total (N=17)
Complete Response (iCR)	0 (0)
Partial Response (iPR)	7 (41.2)
Stable Disease (iSD)	6 (35.3)
Progressive Disease (iPD)	4 (23.5)
Objective Response Rate (ORR)	**7 (41.2)**
Disease Control Rate (DCR)	**13 (76.5)**

Summary – Results:

- All 17 patients enrolled to part A stage 1 were evaluable for efficacy
- Median time of FU was 5.6 months (0.7 - 7.4)
- At data cut-off 12 pts (71 %) were still under treatment thereof 9 pts (53 %) reached 24-week landmark already → median PFS not yet reached
- ORR (iRECIST) observed: 41.2 % → stage 2 allowed to be opened
- Target lesions decrease in pts with iPR as BOR was between 38 % and 64 %
- None of the pts with response progressed thus far

[2] - Data cut-off date: 16th Oct 2019



Conclusion

- **Combination of efti and pembrolizumab in PD-X naïve or refractory NSCLC, and in HNSCC patients is safe and well tolerated -> 2nd stage for part A opened by DMC**
- **ORR of 41.2 % in PD-L1 all comer in 1st line NSCLC → 12/17 (71%) still under treatment → encouraging signs of clinical activity in a PD-L1 all comer trial (Pembrolizumab alone in 1-49 % PD-L1 ORR of 16.7 % in KN-042)**
- **Initial results are encouraging that combining the APC activator efti with the checkpoint inhibitor pembrolizumab may result in synergistic therapeutic activity**
- **Recruitment of part B and C stage 1 and part A stage 2 are ongoing**