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

immutep LAG-3 IMMUNOTHERAPY

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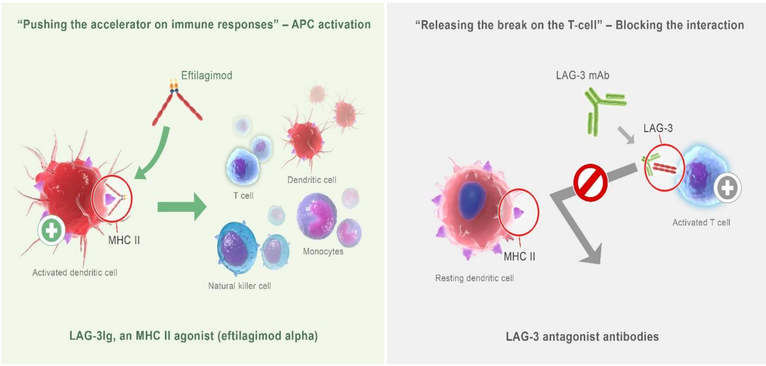
Background



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 from stage 1 of a phase II umbrella trial (TACTI-002, NCT03625323).

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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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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

Trial Design

Part A: 1st line, PD-X naïve NSCLC; stage IIIB not amenable to curative treatment or stage IV not amenable to EGFR/ALK based therapy, treatment naïve for advanced/ metastatic disease

Part B: 2nd line, PD-X refractory NSCLC; pts after failure of 1st line therapy for metastatic disease which incl. at least 2 cycles of PD-X

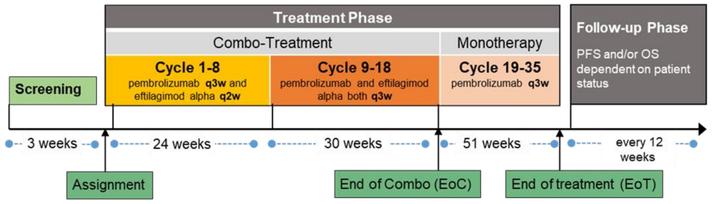
Part C: 2nd line PD-X naive HNSCC; recurrent disease not amenable to curative treatment, or metastatic diseas incurable by local therapies after failure of prior platinum-based therapy

General Features/Objectives:
- Primary endpoint: objective response rate (iORR) as per iRECIST
- Secondary endpoints: progression free survival (PFS) and overall survival (OS)
- Central assessment of tumor cell PD-L1 expression after enrollment
- Blood samples for PK/PD assessments and anti-drug antibody evaluation are collected

The study has a Simon's optimal two-stage design. 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

Part A + C stage 1 enrollment was completed in 2019. Recruitment in part B stage 1 and in part A + C stage 2 is ongoing

Exposure and Safety[1]

Summary - Exposure:
- In total 76 pts were enrolled in all three parts and all stages until data cut-off[1].
- Pts received median 5.5 (range 1-22) efti injections and median of 4 (range 1-20) pembrolizumab infusions

Overview - Safety:
- No treatment related death
- 3 treatment related adverse events leading to permanent discontinuation (hepatitis drug induced G4; ALT & AST elevation G3; diarrhea G1)
- No new safety signals of this new combination identified until cut off

Safety Parameters	N of patients (%)
Pts with any TEAE	71 (93.4)
Pts with any SAE	25 (32.9)
thereof related to efti / pembrolizumab	5 (6.6) / 5 (6.6)
Pts with any grade ≥3 TEAE	31 (40.8)
thereof related to efti / pembrolizumab	6 (7.9) / 6 (7.9)

Treatment emergent adverse events occured in ≥ 10 % of pts (total N=76)

Adverse event (PT)	Any Grade N (%)	Grade 3 N (%)	Grade 4 N (%)	Grade 5 N (%)
Cough	22 (28.9)	-	-	-
Asthenia	18 (23.7)	-	-	-
Decreased appetite	14 (18.4)	-	-	-
Dyspnoe	14 (18.4)	4 (5.3)	1 (1.3)	-
Fatigue	13 (17.1)	1 (1.3)	-	-
Diarrhoea	11 (14.5)	1 (1.3)	-	-
Nausea	9 (11.8)	-	-	-
Constipation	8 (10.5)	1 (1.3)	-	-
Upper respiratory tract infection	8 (10.5)	-	-	-
Anaemia	8 (10.5)	-	-	-

[1] - *Data cut-off date: 4th May 2020*

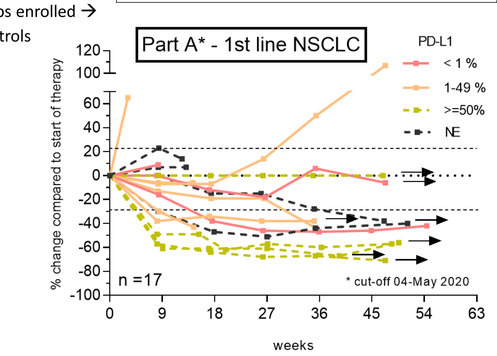
Part A stage 1 - 1st line NSCLC[2], PD-L1 all comer

Baseline Parameters (n=17)	N (%)
Median age, yrs (range)	65 (53 – 76)
Female / Male	6 (35.3) / 11 (64.7)
ECOG 0 / 1	12 (70.6) / 5 (29.4)
Current / former smoker	16 (94.1)
Squamous / Non-squamous	10 (58.8) / 7 (41.2)
PD-L1 (< 1 %/1-49 %/≥50 % TPS)	3 (23 %) / 6 (46 %) / 4 (31 %)

Tumor response - iBOR as per iRECIST	N (%) Total (N=17)
Complete Response (iCR)	0 (0.0)
Partial Response (iPR)	9 (52.9)
Stable Disease (iSD)	5 (29.4)
Progressive Disease (iPD)	3 (17.7)
Objective Response Rate (iORR)	9 (52.9)
Disease Control Rate (iDCR)	14 (82.4)

- Patients with all different PD-L1 subgroups enrolled → proportions comparable to historical controls

Summary:
- 12/17 (71 %) with target lesion decrease
- Responses in all PD-L1 subgroups (4/9 iPRs in < 50 % PD-L1 subgroup)
- 6/9 iPRs confirmed until cut off
- At data cut-off 7 pts (41 %) were still under treatment → estimated median PFS of 9+ months
- Two late responders after 8 and 11 months



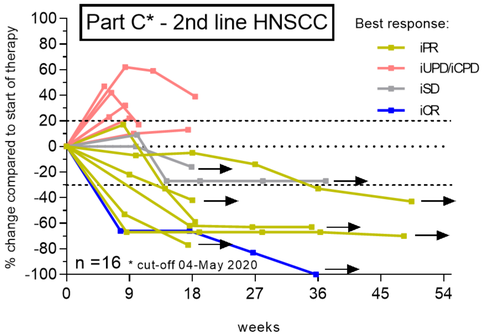
Part C stage 1 – PD-X naive 2nd line HNSCC[2,] PD-L1 all comer

Baseline Parameters (n=18)	N (%)
Median age, yrs	66
Female / Male	1 (5.6) / 17 (94.4)
ECOG 0 / 1	10 (55.6) / 8 (44.4)
PD-L1 (< 1 %/1-20 %/≥20 % CPS)	3 (27.3) / 3 (27.3) / 5 (45.6)

Tumor response - iBOR as per iRECIST	N (%) Total (N=18)
Complete Response (iCR)	1 (5.6)
Partial Response (iPR)	6 (33.3)
Stable Disease (iSD)	2 (11.1)
Progressive Disease (iPD)	7 (38.9)
Not evaluable*	2 (11.1)
Objective Response Rate (iORR)	7 (38.9)
Disease Control Rate (iDCR)	9 (50.0)

- Patients with all different PD-L1 subgroups enrolled → PD-L1 all comer trial

Summary:
- Initial iORR of 38.9 %
- 1 complete response; 1 iPR after pseudo-progression
- 5 responses confirmed
- At data cut-off 8 pts (44 %) still under treatment



Conclusion

NSCLC
- iORR of 53 % in PD-L1 all comer in 1st line NSCLC, encouraging responses in low PD-L1 expressors, majority of pts still on therapy at 8+ months, patients with an unusual late responses
- Encouraging when referenced to Pembrolizumab alone in comparable patient population with ≥1 % PD-L1 expression (KN-024; KN-042)

HNSCC
- iORR of 38.9 % in PD-L1 all comer 2nd line HNSCC including 1 complete response encouraging if referenced to pembrolizumab alone in comparable patient population (KN-040)

Overall
- Combination of efti and pembrolizumab in NSCLC, and HNSCC patients is safe and well tolerated
- Initial results underlining the potential synergy of the APC activator efti with the checkpoint inhibitor pembrolizumab may result in synergistic therapeutic activity without additional toxicity