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Initial results from a Phase II study (TACTI-002) of eftilagimod alpha (soluble LAG-3 protein) and pembrolizumab as 2nd line treatment for PD-L1 unselected metastatic head and neck cancer (HNSCC) patients

immutep
LAG-3 IMMUNOTHERAPY

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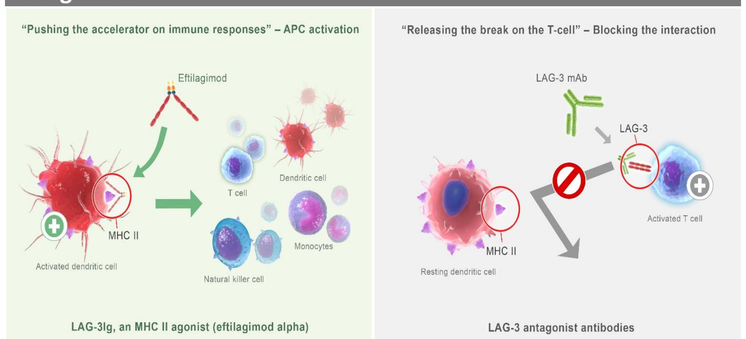
Background



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 cells (APC)** and then **activation of CD8 T-cells**.

Efti is a first-in-class APC activator.

The rationale for **combining efti and pembrolizumab** comes from their complementary mechanisms of action. Efti activates APCs, leading to an increase in activated T cells, modulating the tumor micro-environment and potentially increasing the likelihood of responding to pembrolizumab.

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

Previous clinical trial experience with the combination of efti and pembrolizumab in patients with metastatic melanoma (TACTI-mel; NCT02676869) demonstrated the combination to be safe and showed encouraging signs of efficacy.

We hereby report results from stage 1 part C of a phase II umbrella trial (TACTI-002, NCT03625323).

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

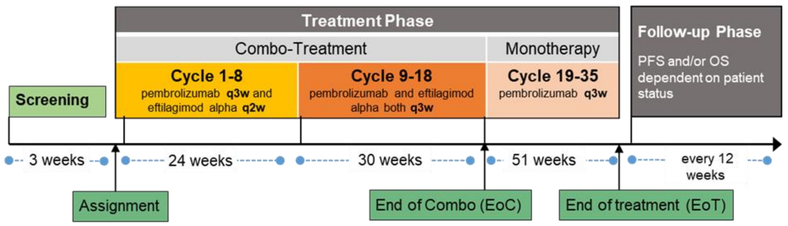
Part C: 2nd line PD-X naive HNSCC; Recurrent disease not amenable to curative treatment, or metastatic disease incurable by local therapies after failure of prior platinum-based therapy

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 enrolment
- Blood samples for PK/PD assessments and anti-drug antibody evaluation are collected

The study has a Simon's two-stage design:
N1 patients are recruited into the first stage. 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 2nd line	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 the following 9 cycles. Pembrolizumab is administered at a standard dose of 200 mg intravenous infusion every 3 weeks for maximum of 2 years.



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

Enrolment to Part A + C stage 1 was completed in 2019, while Part B stage 1 and Part A stage 2 were completed in 2020. Recruitment in Part C stage 2 is ongoing.

Exposure and Safety[1]

Summary - Exposure:
- In total, 88 pts were enrolled in all three parts and stages until data cut-off[1].
- Pts received median 5.5 (range 1-22) efti injections and median of 4 (range 1-25) pembrolizumab infusions

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

Safety Parameters	No. of patients (%)
Pts with any TEAE	80 (90.9)
Pts with any SAE	27 (30.7)
thereof related to efti / pembrolizumab	5 (5.7) / 6 (6.8)
Pts with any grade ≥3 TEAE	42 (47.7)
thereof related to efti / pembrolizumab	8 (9.1) / 9 (10.2)

Further safety data can be found on poster 1266P:

[1,2] - *Data cut-off date: 21th Aug 2020*

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

- 18 patients enrolled, treated and evaluated (16 with ≥ 1 post baseline scan)
- Different types of HNSCC:
  - Oropharynx n=6; 33.3 %
  - Hypopharynx n=5; 27.8 %
  - Oral cavity n=5; 27.8 %
  - Larynx n=2; 11.1%

Tumor response - iBOR as per iRECIST	N (%) Total (N=18)
Complete Response (iCR)	**2 (11.1)**
Partial Response (iPR)	5 (27.8)
Stable Disease (iSD)	2 (11.1)
Progressive Disease (iUPD/ICPD)	7 (38.9)
Not Evaluable*	2 (11.1)
Objective Response Rate (iORR) [95 % CI interval]	**7 (38.9) [17.3 – 64.3]**
Disease Control Rate (iDCR)	9 (50.0 %)

* - pt dropped out prior to first re-staging

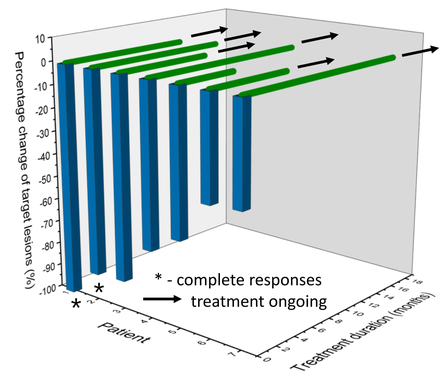
Baseline Parameters (n=18)	N (%)
Age [yrs]	Median 66 (48-78)
Female / Male	1 (5.6) / 17 (94.4)
ECOG 0 / 1	10 (55.6) / 8 (44.4)
Current / Ex-smokers	17 (94.4)
Previous chemotherapy	18 (100 %)
Previous cetuximab	9 (50 %)

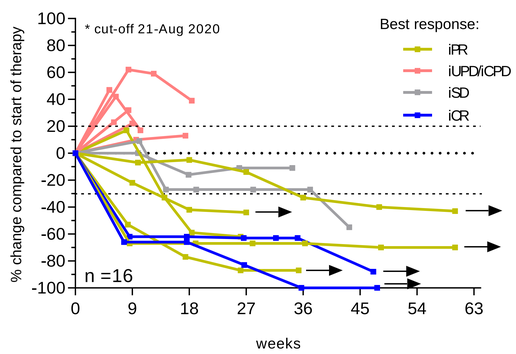
- Patients with all different PD-L1 subgroups (by CPS) enrolled → PD-L1 all comer trial

PD-L1 distribution*	N (%)	Historically expected**	Pts with iPR/iCR
CPS < 1 %	3 (16.7 %)	15 %	0
CPS 1-19 %	5 (27.8 %)	45 %	1
CPS ≥ 20 %	7 (38.9 %)	40 %	6
NE	3 (16.7%)		0

*Centrally assessed by Dako PD-L1 IHC 22C3 pharmDx
** - Burtness et al (2019); https://doi.org/10.1016/S0140-6736(19)32591-7

Summary:
- iORR of 38.9 % [95 % CI 17.3%, 64.3%]
- 11.1 % (2 pts) with complete response
- 6 of 7 responses confirmed
- 1 response at CPS of 2 %
- 1 response after pseudo-progression
- 6 of 7 responders continue therapy at 6+ months → median duration of response not reached
- Median PFS is 4.26 months [95 % CI 1.48; NE]
- 47.1 % and 39.2 % of patients are progression-free at 6 and 9 months, respectively
- 66.7 % of patients alive at 6 and 9 months with a minimum follow-up of 8+ months → median not yet reached





Conclusion

HNSCC
- iORR of 38.9 % in PD-L1 all comer 2nd line HNSCC, including 2 complete responses → encouraging if referenced to pembrolizumab alone in comparable patient population (KN-040)
- Response seen in < 20 % PD-L1 CPS group
- Median PFS of 4.26 months and durability of responses are encouraging

Overall
- Combination of efti and pembrolizumab in NSCLC and HNSCC patients is safe and well-tolerated
- Results underlining the potential synergy of the APC activator efti with the checkpoint inhibitor pembrolizumab may result in synergistic therapeutic activity with an excellent safety profile
- Data from the NSCLC part A stage 1 is presented on *poster 1266P*