A Phase II study (TACTI-002) of eftilagimod alpha (a soluble LAG-3 protein) with pembrolizumab in PD-L1 unselected patients with metastatic non-small cell lung (NSCLC) or head and neck carcinoma (HNSCC)

Abstract ID: 790

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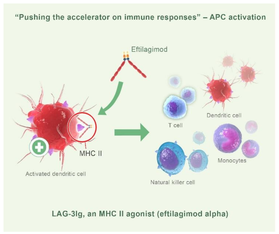
BACKGROUND



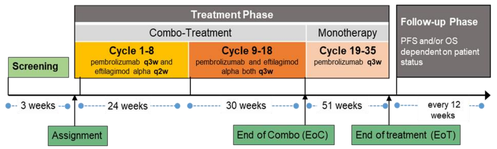
Eftilagimod alpha (efti) is a soluble LAG-3 protein (not an anti-LAG-3 antagonistic antibody) that binds to a subset of MHC class II molecules to mediate antigen presenting cells (APC) and CD8 T-cell activation. The stimulation of the dendritic cell network and subsequent T cell recruitment may lead to stronger anti-tumor responses in combination with pembrolizumab than observed with pembrolizumab alone. We report results from all parts of the TACTI-002 study (NCT03625323).

Non-randomized, multinational, Simon's two stage study consisting of three parts:

Indication	Stage 1 (N) + Stage 2 (N)
Part A: NSCLC 1st line; PD-X-naive	
Stage IIIB (not curable) or IV not amenable to EGFR/ALK based therapy, treatment-naïve for advanced/metastatic disease	17 + 19 = 36
Part B: NSCLC 2nd line; PD-X resistant	
Patients resistant to PD-1/PD-L1 therapy and after failure of 1st line therapy for metastatic disease	23 + 13= 36
Part C: HNSCC 2nd line, PD-X-naïve	
Recurrent disease not amenable to curative treatment, or metastatic disease incurable by local therapies after failure of prior platinum-based therapy	18 + 19 = 37

General Features/Objectives:

- **Primary Endpoint:** Objective Response Rate (ORR), as per iRECIST
- **Secondary Endpoints:** progression free survival (PFS), overall survival (OS) and safety and tolerability as well as PK/PD and exploratory biomarker
- Central assessment of tumor cell PD-L1 expression (by Dako PD-L1 IHC 22C3 pharmDx) after enrolment



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

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. Imaging is performed every 9 weeks and reported according to iRECIST.

Enrolment to Part A (stage 1 and 2) was completed in Q2 2020. Part B stage 1 was completed in Q3 2020. Part C stage 1 was completed in Dec 2019 and 15/19 pts are enrolled in stage 2 (ongoing)

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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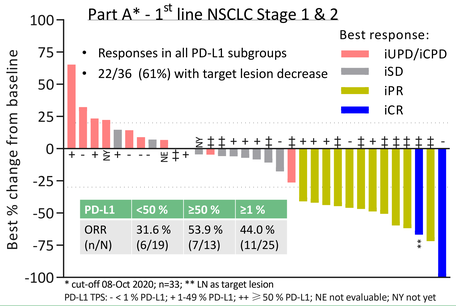
Consulting or Advisory Role - Achilles Therapeutics, Bayer; Janssen, Roche, Seattle Genetics
Research Funding – Roche, BerGenBio
Travel, Accommodation, Expenses - AstraZeneca; BerGenBio

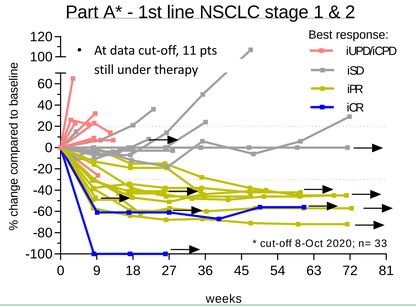
PART A (Stages 1 & 2) – 1st line, PD-X naïve NSCLC; PD-L1 all comer - Patient Characteristics and Efficacy Results

Baseline Characteristics	Stage 1 (N=17) N (%)	Stage 2 (N=19) N (%)	Stage 1+2 (N=36) N (%)
Median age, years (range)	**65 (53 – 76)**	**74 (60-84)**	68.5 (53-84)
Female Male	6 (35.3) 11 (64.7)	5 (26%) 14 (74 %)	11 (30.6) 25 (69.4)
ECOG 0 ECOG 1	12 (70.6) **5 (29.4)**	3 (16 %) **16 (84 %)**	15 (41.7) 21 (58.3)
Never smoker Current or Former smoker	1 (5.9) 16 (94.1)	1 (5.3) 18 (94.7)	2 (6) 34 (94)
Squamous (SQ) Non-squamous (NSQ)	10 (58.8) **7 (41.2)**	5 (26 %) **14 (73 %)**	15 (41.7) 21 (58.3)

- *Different patient population in stage 2 with more ECOG 1, more NSQ and older pts*



Tumor response (iRECIST)	Stage 1 (N=17) N (%)	Stage 2 (N=19) N (%)	Stage 1+2 (N=36) N (%)
Complete Response	**1 (5.9)**	**1 (5.3)**	**2 (5.6)**
Partial Response	8 (47.1)	3 (15.8)	11 (30.6)
Stable Disease	4 (23.5)	7 (36.8)	11 (30.6)
Progression	4 (23.5)	5 (26.3)	9 (25.0)
Not evaluable**	0 (0)	3 (15.8)	3 (8.3)
		Overall Response Rate [95 % CI interval]	**13 (36.1) [20.8-53.8]**
		Overall Response Rate (evaluable pts only)	**13 / 33 (39.4)**
		Disease Control Rate	**24 (66.7)**

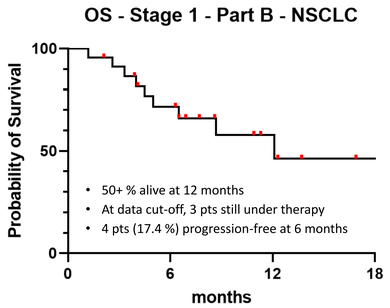


PART B – 2nd line, PD-X refractory NSCLC
Patient Characteristics and Efficacy Results

Baseline Characteristics	Stage 1 (N=23) N (%)
Median age, years (range)	67.0 (46-84)
Female Male	10 (43.5) 13 (56.5)
ECOG 0 ECOG 1	7 (30.4) 16 (69.6)
Current or Former smoker	21 (91.3)
Squamous Non-squamous	5 (21.7) 18 (78.3)
Prior PD-1/PD-L1 with chemotherapy	100 % 61 %

Tumor response (iRECIST)	Stage 1 (N=23) N (%)
Partial Response	**1 (4.4)**
Stable Disease	7 (30.4)
Progression	14 (60.9)
Not Evaluable**	1 (4.4)
Overall Response Rate [95 % CI interval]	**1 (4.4) [0.11 – 21.95]**
Disease Control Rate	8 (34.8)

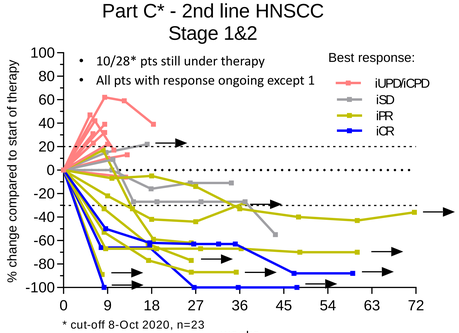
- All pts progressed confirmatively (2 scans) on PD-1/ PD-L1,2 → 100% PD-X resistant/ refractory
- 85 % had PD-L1 of < 50 %
- BOR of 1st line therapy was SD/PD in 61 % of pts → primary resistance

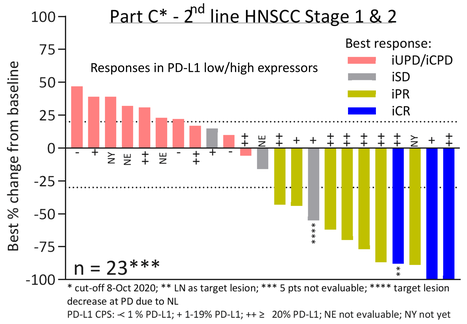


PART C (Stages 1 & 2) – 2nd line, PD-X naïve HNSCC, PD-L1 all comer - Characteristics and Efficacy Results

Baseline Characteristics	Stage 1 + 2 (N=28) N (%)
Median age, years (range)	65.5 (48-84)
Female Male	2 (7.1) 26 (92.9)
ECOG 0 ECOG 1	11 (39.3) 17 (60.7)
Current or Former Smoker	25 (89.3)
Previous chemotherapy	28 (100)
Previous cetuximab	13 (46.4)

- 34/37 pts enrolled; 28 evaluable (≥ 1 post-baseline staging or early drop out)
- Patients with oropharynx (n=7; 25%), hypopharynx (n=6; 21%); oral cavity (n=10; 36%) and larynx (N=5; 18%) → responses in all subgroups





Tumor response (iRECIST)	Stage 1 +2 (N=28) N (%)
Complete Response	**3 (10.7)**
Partial Response	7 (25.0)
Stable Disease	3 (10.7)
Progression	10 (35.7)
Not Evaluable**	5 (17.9)
Overall Response Rate [95 % CI interval]	**10 (35.7) [18.6 – 55.9]**
Overall Response Rate (evaluable pts only)	**10 / 23 (43.5)**
Disease Control Rate	13 / 28 (46.4)

EXPOSURE AND SAFETY*

- 91 patients enrolled and received median of 7 (range 1-22) efti injections and median of 5 (range 1-19) pembrolizumab infusions.
- 28 (30.8 %) pts had an SAE; 5.5 % related to efti; 6.6 % related to pembrolizumab; no fatal treatment-related adverse events

TEAEs with frequency ≥15% in overall population (N=91)

Adverse event (PT)	Any Grade N (%)	Grade 3 N (%)	Grade 4 N (%)	Grade 5 N (%)
Asthenia	27 *(29.7)*	3 *(3.3)*	0	0
Cough	25 *(27.5)*	1 *(1.1)*	0	0
Decreased appetite	23 *(25.3)*	1 *(1.1)*	0	0
Dyspnoea	18 *(19.8)*	7 *(7.7)*	1 *(1.1)*	0
Fatigue	17 *(18.7)*	1 *(1.1)*	0	0
Diarrhoea	15 *(16.5)*	1 *(1.1)*	0	0
Pruritus	15 *(16.5)*	0	0	0

- Five treatment-related AEs led to permanent drug discontinuations in 3 subjects: drug-induced hepatitis G4; ALT elevation G3, ALT elevation G3, diarrhea G1, diarrhea G3
- No new safety signals identified until cut-off*

CONCLUSION

1st line NSCLC – Part A

- In ≥ 1 % PD-L1 ORR is higher (44 %) compared to KEYNOTE studies (ORR ~27 %)[1,2].
- Similar trend in < 50 % PD-L1 expressors with (31.6 %) compared to < 20 % for pembrolizumab alone → important signal for low PD-L1 expressing patients.

NSCLC – PD-1-resistant patients (Part B)

- 1 confirmed partial response and 3 long term (6+ months) SDs in low PD-L1 expressing PD-X resistant patients.
- Favorable (12 vs. 6 months)[5] overall survival compared to chemotherapy.

2nd line HNSCC – Part C

- Durable, deep responses (43.5 % ORR, 3 CRs) in a very challenging patient population; responses in low PD-L1 expressors.
- Trends favorably compared to KEYNOTE studies (ORR ~15 %)[3,4] in a comparable patient population.

Overall

- Combination of efti and pembrolizumab is safe and well-tolerated.
- Data highly supports further clinical late stage development in NSCLC & HNSCC.

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
NL… new lesions
NSCLC…non-small cell lung cancer
PD-L1, PD-L2…Programmed Death ligand-1, -2
PD-X… PD-1 or PD-L1 targeted therapy
Pts … patients
PFS… progression-free survival
ORR… objective response rate
SAE… serious adverse event
TEAE… treatment-emergent adverse event

* data cut-off 8th Oct 2020
** patient dropped out prior to first re-staging and are not evaluable for response
*** PD-L1 testing performed centrally with the DAKO kit

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