Results from a phase II study investigating eftilagimod alpha (soluble LAG-3 protein) and pembrolizumab in 2nd line PD-1/PD-L1 refractory metastatic non-small cell lung carcinoma (NSCLC) patients

 # 11P

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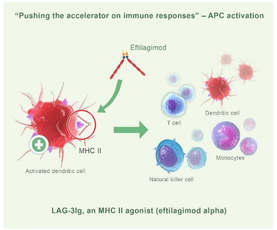
BACKGROUND

Figure 1. efti's mechanism of action



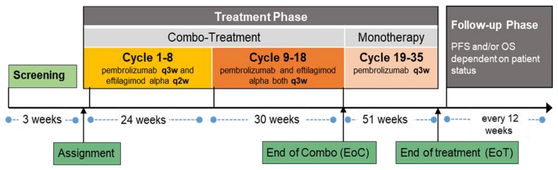
Eftilagimod alpha (efti) is a soluble LAG-3 protein binding to a subset of MHC class II molecules, thus mediating antigen presenting cell (APC) and CD8 T-cell activation (**Figure 1**). Such stimulation of the dendritic cell network and resulting T cell recruitment may lead to stronger anti-tumor responses in combination with pembrolizumab than observed with pembrolizumab alone. We report results from the 2nd line PD-X refractory metastatic non-small cell lung carcinoma (NSCLC) cohort (Part B) of the TACTI-002 study (NCT03625323).

METHODS

Study Design and Patients

- Non-randomized, multinational, open-label, phase II trial.
- 2nd line, PD-X refractory metastatic PD-L1 all-comer NSCLC patients.
- Simon's two stage design.
- Efti is administered as a 30 mg subcutaneous injection every 2 weeks for the first 8 cycles and every 3 weeks for the following 9 cycles (total 1 year). Pembrolizumab is administered at a standard dose of 200 mg intravenous infusion every 3 weeks for maximum of 2 years (**Figure 2**).

Figure 2. Study design



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

Assessments and Statistical Analyses:

- **Primary Endpoint:** Objective response rate (ORR), as per iRECIST.
- **Secondary Endpoints:** Progression free survival (PFS) and other efficacy parameter, safety and tolerability, and exploratory biomarkers.
- Central assessment of tumor cell PD-L1 expression (by Dako PD-L1 IHC 22C3 pharmDx) after enrolment.
- Imaging performed every 9 weeks and reported according to iRECIST and RECIST 1.1.
- Safety and efficacy was analyzed following intent to treat principle (all patients who received at least one dose of study medication).
- Database cut-off date was January 21, 2022 (min. follow up of 5+ months).

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Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA provided pembrolizumab for the study.

BASELINE CHARACTERISTICS

- A total of 36 patients were enrolled and treated into this part of the study. Baseline characteristics are reported in **Table 1**.
- Majority of patients presented with PD-L1 TPS <50% (69.4%) and received prior chemotherapy in combination with PD-1/PD-L1 therapy (72.2%).

Table 1. Baseline characteristics (N=36)

Baseline parameters, n (%)	
Age (years), median (range)	67 (46-84)
Female Male	14 (38.9) 22 (61.1)
ECOG 0 ECOG 1	12 (33.3) 24 (66.7)
Current or Ex-smoker Non-smoker	31 (86.1) 5 (13.9)
Squamous Non-squamous pathology Unknown	7 (19.4) 28 (77.8) 1 (2.8)
Prior PD-1/PD-L1 therapy with chemotherapy	36 (100) 26 (72.2)
Liver metastasis	4 (11.1)
Tumor resistance* Primary resistance Secondary resistance	11 (30.6) 24 (66.7)
PD-L1 (TPS) <1% 1-49% ≥50% Not evaluable/not yet	 13 (36.1) 12 (33.3) 7 (19.4) 4 (11.1)

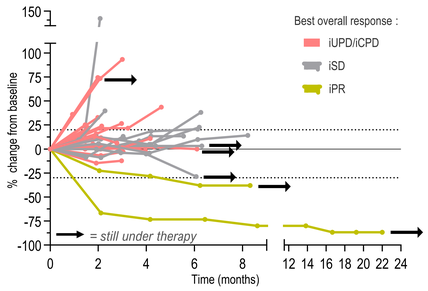
**... Tumor resistance defined according to SITC Immunotherapy Resistance Taskforce consensus[1]*

References:
[1] Kluger HM et al, J Immunotherapy Cancer. 2020 Mar;8(1):e000398. doi: 10.1136/jitc-2019-000398
[2] Saâda-Bouzid E et al, Ann Oncol. 2017 Jul 1;28(7):1605-1611. doi: 10.1093/annonc/mdx178

EFFICACY

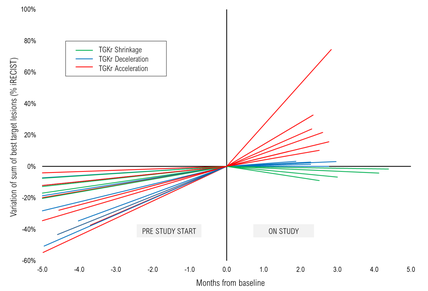
- ORR (iRECIST) of 6% in the intent to treat population(**Table 2**).
- Both responders showed deep (**Figure 4**) and durable partial responses (**Figure 3**).
- 36 % disease control rate and 26% being progression free at 6 months
- Comparable results using RECIST 1.1.
- 6 patients still under therapy (**Figure 3**) and 73% alive at 6 months.

Figure 3. Spider plot (N=34)**



**: ≥1 treatment and ≥1 post-baseline tumor staging + measurable target lesion post baseline

Figure 5. Tumor growth kinetics (N=19)*

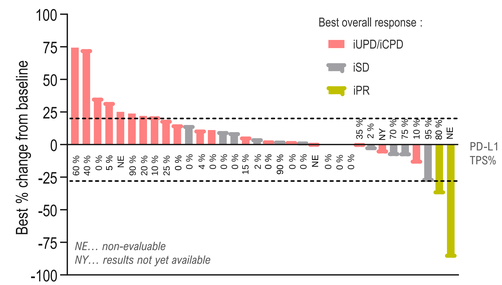


- Tumour growth kinetics (TGK) obtained as a comparative ratio of the difference of the sum of the largest diameters of target lesions in the pre- and post-baseline setting (**Figure 5**)[2].
- 73.7% of evaluable patients had post-treatment TGK shrinkage or deceleration (**Table 3**).

Table 2. Best overall response (iRECIST), N=36

Tumor response (iRECIST)*	Overall n (%)
Complete Response	0 (0)
Partial Response	2 (5.6)
Stable Disease	11 (30.6)
Progression	22 (61.1)
Not Evaluable**	1 (2.8)
Overall Response Rate (ITT)	2/36 (5.6)
Disease Control Rate (ITT)	13/36 (36.1)
Overall Response Rate (evaluable pts)	2/35 (5.7)
Disease Control Rate (evaluable pts)	13/35 (37.1)

Figure 4. Waterfall plot (N=34)**



**: ≥1 treatment and ≥1 post-baseline tumor staging + measurable target lesions post baseline.

Table 3. Tumor growth kinetics, N=19#

Tumor dynamics	n (%)
Shrinkage	4 (21.1)
Deceleration	10 (52.6)
Acceleration	5 (26.3)

 # ...evaluable set (N=19): ≥1 pre- and post-baseline scan following the same tumors

Figure 6. Single case #1

- 71-year-old female diagnosed with metastatic NSCLC (NSQ) in Sep 2016.
- Received 1st line carboplatin + pemetrexed + pembrolizumab for 18 months → stopped due to PD.
- At study entry: ECOG 1, non-evaluable PD-L1 TPS, EGFR/ALK negative, ex-smoker
- Started TACTI-002 in Feb 2020 and is still on therapy (Jan 2022) with confirmed ongoing partial response (-87%)

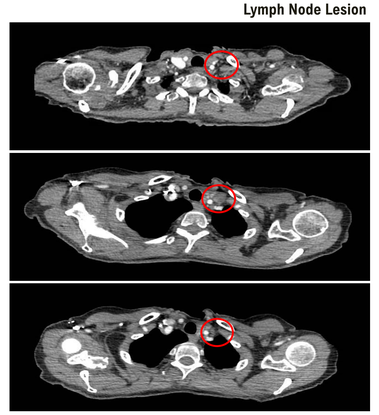
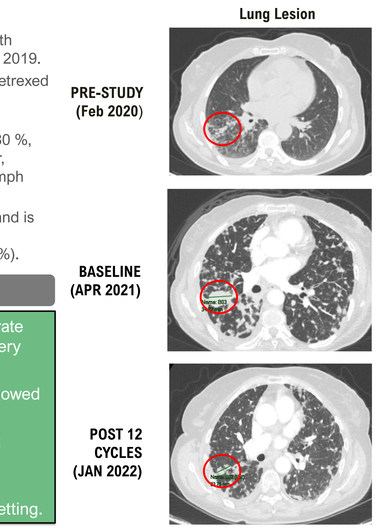


Figure 7. Single case #2

- 67-year-old female diagnosed with metastatic NSCLC (NSQ) in Aug 2019.
- Received 1st line cisplatin + pemetrexed + pembrolizumab for 8 months. discontinuing after progression.
- At study entry: ECOG 0, PD-L1 80 %, EGFR/ALK negative, non-smoker, several metastatic sites (lung, lymph nodes).
- Started TACTI-002 in Apr 2021 and is still on therapy (Jan 2022) with confirmed partial response (-38 %).



EXPOSURE AND SAFETY

Table 4. General overview of adverse events (N=36)

Safety parameter	n (%)
Patients with any TEAE	35 (97.2)
Patients with any SAE	8 (22.2)
thereof related to efti/pembro	1 (2.8)/1 (2.8)
Patients with any grade ≥3 TEAE	13 (36.1)
thereof related to efti/pembro	1 (2.8)/3 (8.3)
Patients with fatal TEAEs*	3 (8.3)*
thereof related to efti /pembro	0
Patients with TEAEs leading to discontinuation of any study treatment	3 (8.3)

**... metastatic neoplasm; dyspnea, acute respiratory failure (each occurring once)*

- Pts received a median of 5 (range 2–31) pembrolizumab and 7 (range 2-22) efti administrations.
- The most common TEAEs were dyspnea (33.3%), decreased appetite (33.3%), and cough (25%) (**Table 5**). No treatment-related deaths occurred (**Table 4**).

Table 5. Frequent treatment-emergent adverse events occurring ≥15% (N=36)

Adverse event (PT)	Any grade N (%)	Grade 3 N (%)	Grade 4/5 N (%)
Dyspnoea	12 (33.3)	2 (5.6)	-
Decreased appetite	12 (33.3)	-	-
Cough	9 (25.0)	-	-
Asthenia	8 (22.2)	1 (2.8)	-
Fatigue	6 (16.7)	1 (2.8)	-
Weight decreased	6 (16.7)	-	-

CONCLUSION

- Two confirmed partial responses (5.6%), 36 % disease control rate leading to 26% with long-term (6+ months) disease control in very difficult to treat (PD-X refractory NSCLC) patient population.
- Encouraging early OS data with 6-months landmark analysis showed 73 % survival rate.
- The combination of an APC activator (efti) plus PD-1 antagonist (pembrolizumab) is well-tolerated and shows signs of antitumor activity in PD-X refractory 2nd line NSCLC patients.
- This combination warrants further clinical investigation in this setting.

ALK…Anaplastic Lymphoma Kinase
APC…antigen-presenting cell
ECOG…Eastern Cooperative Oncology Group
EGFR…Epidermal growth factor receptor
iRECIST…Immune Response Evaluation Criteria In Solid Tumors
ITT…Intent to treat population
LAG-3…Lymphocyte Activation gene-3
MHC…Major Histocompatibility Complex
NSCLC…non-small cell lung cancer
PD-L1…Programmed Death ligand-1
PD-X…PD-1 or PD-L1 targeted therapy
PFS...progression-free survival
PT...preferred term
ORR…objective response rate
SAE…treatment-emergent adverse event
TEAE… treatment-emergent adverse event
TPS…Tumor Proportion Score
TGK…tumor growth kinetics