Combining the antigen-presenting cell activator eftilagimod alpha (soluble LAG-3) and pembrolizumab: efficacy results from the 1st line non-small cell lung cancer cohort of TACTI-002 (Phase II)

Abstract # 1470

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BACKGROUND

- **Mechanism of action**: eftilagimod alpha (efti) is soluble LAG-3 protein (LAG-3 domains fused to human IgG backbone [**Figure 1**] (1)) targeting a subset of MHC class II molecules to mediate activation of antigen presenting cells (APC: dendritic cells & monocytes), natural killer (NK) and T-cells (**Figure 2**). Efti is an MHC class II agonist.
- **Difference to anti-LAG-3 mAbs**: efti is an MHC-Class II agonist and not a LAG-3 antagonist.
- **Rationale for study**: Stimulation of the dendritic cell network and the resulting T cell recruitment/activation may overcome resistance to anti-PD-1 (programmed cell death protein 1) therapy.

Figure 1. Structure of efti

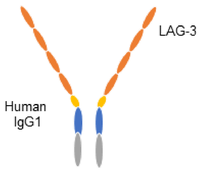
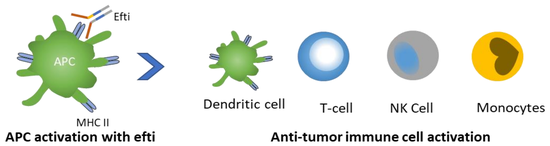


Figure 2. Mechanism of action of efti



METHODS

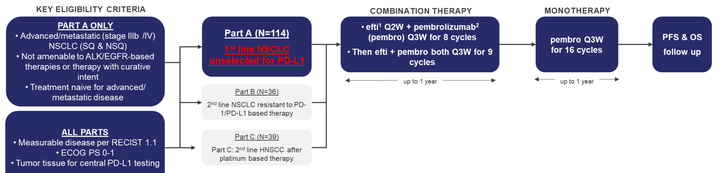
Study Design and Patients

- Non-randomized, multinational, open-label, trial for **1st line advanced/metastatic NSCLC** patients **unselected for PD-L1 expression**.
- Efti is administered as a 30 mg subcutaneous injection every 2 weeks for the first 8 cycles (1 cycle: 3 weeks) and every 3 weeks for the following 9 cycles. Pembrolizumab (pembro) is administered at a standard dose of 200 mg intravenous infusion every 3 weeks for maximum of 2 years (**Figure 3**).
- Statistical considerations (Part A): Powered (80%; 1-sided alpha 0.025) to show an increase in ORR from 23% to ≥35% (2).

Assessments and Statistical Analyses:

- Central assessment of tumor cell PD-L1 expression (by Dako PD-L1 IHC 22C3 pharmDx), performed retrospectively.
- Imaging performed every 9 weeks and reported according to iRECIST and RECIST 1.1.
- Safety and efficacy analyzed in all patients who received at least one dose of study drug.
- Data cut-off date was July 1, 2022; minimum follow-up of 7+ months.

Figure 3. Study design



Primary Endpoint: Objective response rate (ORR), as per iRECIST.

Secondary Endpoints: Progression free survival (PFS), overall survival (OS), safety and tolerability, pharmacokinetic/ pharmacodynamic and exploratory biomarkers.

RESULTS

BASELINE CHARACTERISTICS

- In Part A, 114 patients were recruited in 18 sites across 6 countries between Mar 2019-Nov 2021. Baseline characteristics are reported in **Table 1**.
- ~75% of patients presented with PD-L1 low (1-49% tumor proportion score [TPS]) or PD-L1 negative tumors.

Table 1. Baseline characteristics

Baseline parameters, n (%)	Part A (N=114)	
Age (years), median (range)	67 (44-85)	
Female Male	30 (26.3) 84 (73.7)	
ECOG 0 ECOG 1	43 (37.7) 71 (62.3)	
Current or Ex-smoker Non-smokers	108 (94.7) 6 (5.3)	
Squamous Non-squamous pathology Not otherwise specified	40 (35.1) 72 (63.2) 2 (1.8)	
Metastatic disease	113 (99.1)	
Previous radiotherapy Previous surgery Previous systemic therapy for non-metastatic disease	38 (33.3) 23 (20.2) 26 (22.8)	
PD-L1 (TPS) <1% 1-49% ≥50%	Central only[1]: 32 (35.6) 38 (42.2) 20 (22.2)	Central + local[2]: 37 (34.3) 42 (38.9) 29 (26.9)

[1] N=90; Central assessment of PD-L1 TPS using Dako IHC 22C3 pharmDx.
[2] N=108; Central assessment as per footnote 1 for 90 patients. For 18 patients, local assessment was used for non evaluable central assessment results.

EXPOSURE

- Median efti exposure was 24.7 weeks (range 1-58.0) and 24.2 weeks for pembro (range 0.1-103.3).
- 6 patients completed 2 years of treatment and 24 patients still on therapy at data cut-off.

SAFETY

- irAEs[1] >2%: hypothyroidism (6.1%), pneumonitis (4.4%), hyperthyroidism (3.5%), and myositis (2.6%).
- 26.3% of patients had any type of local injection site reactions[2] G1+2. No reactions ≥G3 were reported.

[1] relationship to efti and/or pembrolizumab could not be ruled out
[2] any PT containing injection site

Table 2. General overview of AEs

Safety parameter[1]	n (%)
Adverse reactions with fatal outcome[2]	3 (2.6)
Serious adverse reactions[2]	*12 (10.5)*
Grade ≥3 adverse reactions[2]	*14 (12.3)*
Adverse reactions leading to discontinuation of treatment[2]	*11 (9.6)*

[1]AEs rated according to NCI CTCAE (v5.0)
[2]relationship to efti and/or pembrolizumab could not be ruled out

Table 3. Frequent AEs (incidence ≥10%) related to study treatment[2]

Adverse event (PT)[1]	Any grade N (%)	Grade 3 N (%)	Grade 4/5 N (%)
Pruritus	23 (20.2)	*N/A*	*N/A*
Asthenia	22 (19.3)	*N/A*	*N/A*
Rash	15 (13.2)	*N/A*	*N/A*
Diarrhoea	12 (10.5)	*1 (0.9)*	*N/A*
Fatigue	12 (10.5)	*1 (0.9)*	*N/A*

[1] AEs rated according to NCI CTCAE (v5.0)
[2] relationship to efti and/or pembrolizumab could not be ruled out

EFFICACY

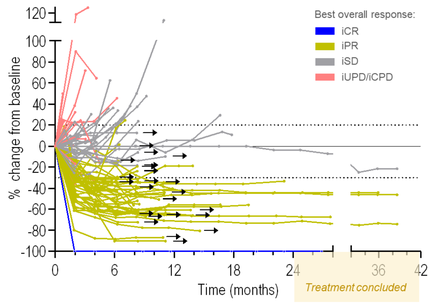
- ORR (iRECIST) of 40.4% (95% CI: 31.3-50.0) in the ITT population (**Table 4**). Results are comparable with RECIST 1.1.
- Responses confirmed in 87% of cases (confirmed ORR by iRECIST: 35.1% (95% CI: 26.4-44.6).
- ORR for PD-L1 negative patients of >30%. ORR for patients with 1-49% TPS of 45% (**Table 5**).
- Comparable ORR for squamous (37.5% [95% CI: 22.7-54.2]) and non-squamous (40.3% [95% CI: 28.99-52.5]) histologies.
- Response onset is early, and responses are long lasting with <10% of patients with response progress within 6 months (**Figure 4**).
- Median interim PFS of 6.6 months [95% CI: 4.6-9.3] (**Figure 5**).
- 40 confirmed responses with a median interim duration of response of 21.6 months (95% CI: 17.3-30.0) (**Figure 6**).

Table 4. Best overall response, ITT (N=114)

Response	iRECIST[4] n (%)	RECIST 1.1[4] n (%)
Complete Response	1 (0.9)	1 (0.9)
Partial Response	45 (39.5)	43 (37.8)
Stable Disease	37 (32.5)	37 (32.5)
Progression	18 (15.8)	20 (17.5)
Not Evaluable[1]	13 (11.4)	13 (11.4)
ORR, (ITT=114); [95% CI][2]	46 (40.4); [31.3-50.0]	44 (38.6); [29.6-48.2]
ORR (EVAL[3]=101); [95% CI][2]	46 (45.5); [35.6-55.8]	44 (43.6); [33.7-53.8]

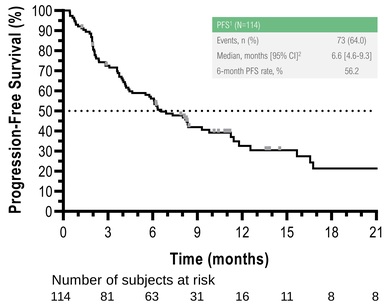
1. Patients with no on-study post-baseline tumor staging for any reason.
2. 95% confidence intervals calculated using Clopper-Pearson method.
3. All patients with ≥1 on-study post-baseline tumor staging.
4. unconfirmed

Figure 4. Spider plot (N=101*)



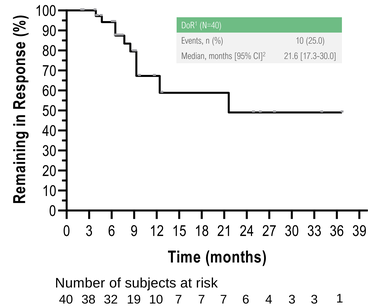
*all patients with ≥1 post-baseline CT scan with evaluable response; n=101. Patients are listed with iPR / iCR whether confirmed or unconfirmed.
→ ongoing patients remaining on study at data cut-off (N=24).

Figure 5. Progression free survival[1], ITT (N=114)



[1] by iRECIST.
[2] 95% confidence intervals calculated using Clopper-Pearson method.
Note: figure has been cropped for visualization purposes.

Figure 6. Duration of response[1] (N=40)



[1] by iRECIST including only patients with confirmed response.
[2] 95% confidence intervals calculated using Clopper-Pearson method.

Table 5. Overview of efficacy endpoints (iRECIST)

PD-L1 TPS[1]	ITT (N=114)	<1% (N=32)	1-49% (N=38)	≥50% (N=20)	≥1% (N=58)
ORR					
ORR, % [95% CI][2]	40.4 [31.3-50.0]	31.3 [16.1-50.0]	44.7 [28.6-61.7]	55.0 [31.5-76.9]	48.3 [35.0-61.8]
Progression-free survival					
Median, months [95% CI][2]	6.6 [4.6-9.3]	4.2 [3.6-6.1]	8.3 [4.4-15.7]	16.7 [4.0-16.8]	9.3 [6.1-15.7]
% of events	64.0	81.3	60.5	50.0	58.6

Note: ORR results for combined central + local PD-L1 (N=108): ORR for PD-L1 TPS <1% of 27%; ORR for TPS 1-49% of 42.9%; ORR for TPS ≥50% of 51.7%; ORR for TPS ≥1% of 46.5%.

1. Central assessment of PD-L1 TPS using Dako IHC 22C3 pharmDx for 90 patients.
2. 95% confidence intervals calculated using Clopper-Pearson method.

BIOMARKERS

- Blood samples collected pre-efti dosing at baseline (n=85), after 3 months (n=70) and 6 months (n=38), always 2 weeks after the previous efti dosing, ensuring only minimal residual effect was measured (**Figure 7**).
- IFN-γ and CXCL10/IP10 (markers for TH1 response) are significantly elevated at 3 and 6 months compared to baseline (**Figure 8**).
- Increase is seen early (<24 hours) after first efti administration (data not shown).

Figure 7. Blood sampling schedule

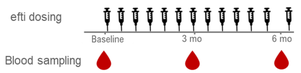
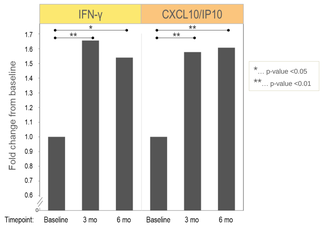


Figure 8. Biomarkers



Plasma levels of IFN-g and CXCL10/IP10 are shown as mean of concentration.
Two-sided Wilcoxon matched-pair signed rank test on timepoint versus baseline are shown.

SUMMARY & CONCLUSION

- Encouraging ORR (iRECIST) of 40.4% (95% CI: 31.3-50.0) in 1st line NSCLC patient population not amenable to targeted therapy, comprising ~75% of patients with PD-L1 TPS <50%.
- Responses seen across all PD-L1 subgroups and histology types.
- Responses are deep and durable with interim median DoR of 21.6 months.
- Interim PFS of 6.6 months [95% CI 4.6-9.3] in this PD-L1 unselected patient population is promising.
- ORR and PFS compared to historical control is encouraging especially for patients with PD-L1 negative / PD-L1 low (1-49%) tumors.
- Treatment with efti plus pembrolizumab is safe and well-tolerated with no new safety signals.

Conclusion: efti + pembrolizumab shows encouraging efficacy across all PD-L1 levels, including in PD-L1 low (1-49% TPS) and PD-L1 negative (<1% TPS) patients and is very well tolerated, warranting further late-stage development.

ABBREVIATIONS

(i)CR…complete response
ECOG…Eastern Cooperative Oncology Group
irAE…immune-related adverse events
ITT…intention-to-treat
LAG-3…Lymphocyte Activation Gene-3
MHC…Major Histocompatibility Complex
(i)PR…partial response
PT…preferred term
(i)RECIST…(Immune) Response Evaluation Criteria In Solid Tumors
(i)SD…stable disease
(i)UPD…unconfirmed progressive disease

REFERENCES

1. Brignone C, Clin Cancer Res. 2009;15: 6225- 6231.
2. True response rates sources/assumptions: KN-001 &-042 (KN-001: NB Leighl et al, Lancet Respir Med, 2019; 7(4): 347-357; KN-042: TSK Mok et al, Lancet 2019;393(10183:1819-1830), expecting that ~70% of patients will have PD-L1 TPS <50%.

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DISCLOSURES

The following represents disclosure information provided by the presenter of this abstract:
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