elcc European Lung Cancer Congress 2023

Final data from a phase II study (TACTI-002) of eftilagimod alpha (soluble LAG-3) & pembrolizumab in 2nd line metastatic NSCLC patients resistant to PD-1/PD-L1 inhibitors

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DECLARATION OF INTERESTS

Margarita Majem

Consulting or Advisory Role - AstraZeneca; Boehringer Ingelheim; Bristol-Myers Squibb; Helsinn Therapeutics; Lilly; Merck Sharp & Dohme; Novartis; Pfizer; Roche; Takeda; Sanofi, Jannsen, Amgen.

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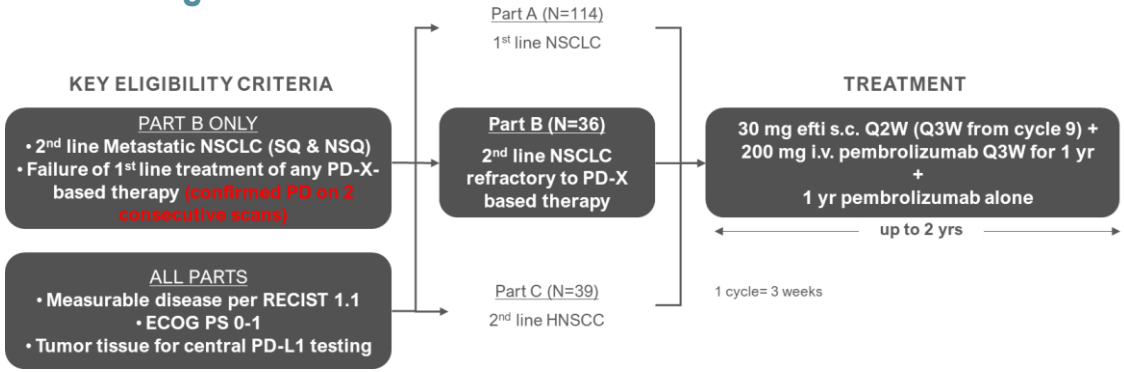
Travel, Accommodations, Expenses - AstraZeneca; Roche.

Eftilagimod alpha (efti) – soluble LAG-3

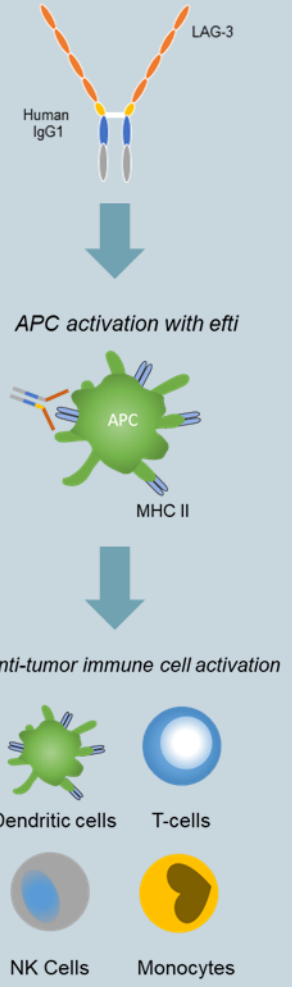
- **Efti: soluble LAG-3 protein** (LAG-3 domains fused to human IgG backbone) **targeting** a subset of **MHC class II molecules** to mediate antigen presenting cell (APC) and subsequent CD8 T-cell activation.
- **Unique from anti-LAG-3:** efti is an MHC-Class II agonist and not a LAG-3 antagonist.
- **Rationale:** efti activates APCs, leading to an increase in activated T cells, which may revert PD-1 resistance.

Trial Design



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

Secondary Endpoints:
Progression free survival, overall survival, safety and tolerability, PK/PD and exploratory biomarkers.



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Baseline Characteristics, Exposure & Adverse Events

Baseline parameters		Part B (N=36)
Age	Median (range), years	67 (46-84)
Sex, n (%)	Female / Male	14 (38.9) / 22 (61.1)
ECOG PS score, n (%)	0 / 1	12 (33.3) / 24 (66.7)
Smoking status, n (%)	Current or Ex-smoker Non-smoker	31 (86.1) 5 (13.9)
Histology, n (%)	Squamous Non-squamous Not specified	7 (19.4) 28 (77.8) 1 (2.8)
PD-L1 expression[1] TPS, n (%)	<1% 1-49% ≥50% NE	13 (36.1) 14 (38.9) 6 (16.7) 3 (8.3)
Last previous therapy, n (%)	Anti-PD-X alone / + ICI Anti-PD-X + chemo	12 (33.3) 24 (66.7)
Resistance in advanced disease setting[2], n (%)	Primary Secondary Other	9 (25.0) 25 (69.4) 2 (5.6)

- All (100%) patients with confirmed PD on previous anti-PD-X.
- 66.7% pre-treated with chemo + anti-PD-X.
- 75% of patients had low or negative PD-L1 expression.

Exposure & Adverse Events[3]

- Median efti exposure was 2.8 mo (range: 0.5-12.5) and 2.8 mo for pembrolizumab (range: 0.7-23.6).
- No treatment discontinuation due to adverse reactions and no unknown irAEs reported; no G5 toxicity.
- Most common (≥10%) TEARs[4]: asthenia (13.9%, G1-2 only) and pruritus (11%, one G3 case).

[1] Central PD-L1 assessed with Dako IHC 22C3 pharmDx for 27 pts. Local results of 6 pts were included due to non evaluable (NE) central assessment results.
[2] Defined according to SITC Immunotherapy Resistance Taskforce Consensus: *Primary: drug exposure at least 6 wks with best response of progressive disease or stable disease (SD) lasting <6 mo. Secondary: drug exposure at least 6 mo with best response as complete response, partial response or SD for over 6 mo. Other: not meeting primary or secondary definitions.*
[3] rated according to NCI CTCAE (v5.0).
[4] relationship to efti and/or pembrolizumab could not be ruled out.
G: grade; ICI: immune checkpoint inhibitor; irAE: immune related adverse event; PD: progressive disease; TEAR: treatment-emergent adverse reaction.

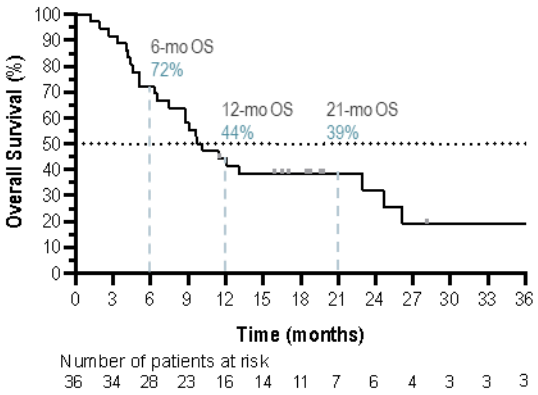
Efficacy – Primary & Secondary Objectives

Efficacy Overview[1]

Response parameter (N=36)	
Partial Response, n (%)	3 (8.3)
Stable Disease, n (%)	9 (25.0)
Progression, n (%)	23 (63.9)
Not Evaluable[2], n (%)	1 (2.8)
ORR[3], n (%) [95% CI][4]	3 (8.3) [1.8-22.5]
DCR, n (%) [95% CI][4]	12 (33.3) [18.6-51.0]

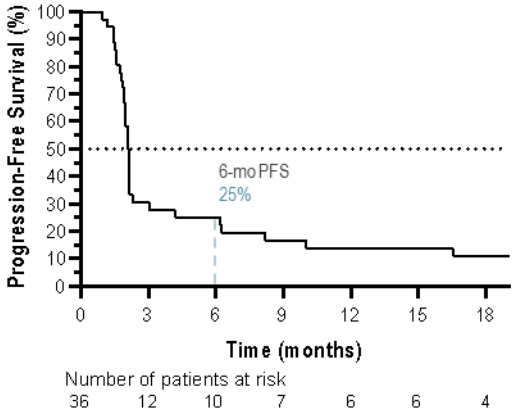
Overall Survival ITT

OS (N=36)	
Events, n (%)	25 (69.4)
Median, months [95% CI][5]	9.9 [6.5-23.0]



Progression Free Survival[1] ITT

PFS (N=36)	
Events, n (%)	34 (94.4)
Median, months [95% CI][5]	2.1 [1.9-2.1]



DCR: disease control rate; ITT: intent to treat population; ORR: overall response rate.
[1] by iRECIST.
[2] Pts with no on-study post-baseline radiological assessment for any reason.
[3] Confirmed ORR.
[4] 95% CIs calculated using Clopper-Pearson method.
[5] 95% CIs calculated using Kaplan Meier survival analysis method.
Note: ORR of evaluable population (N=35) of 8.6%.
Figures have been cropped for visualisation purposes.

- 6-mo PFS rate of 25% and OS rates at 12-mo and 21-mo of 44% and 39%, respectively.

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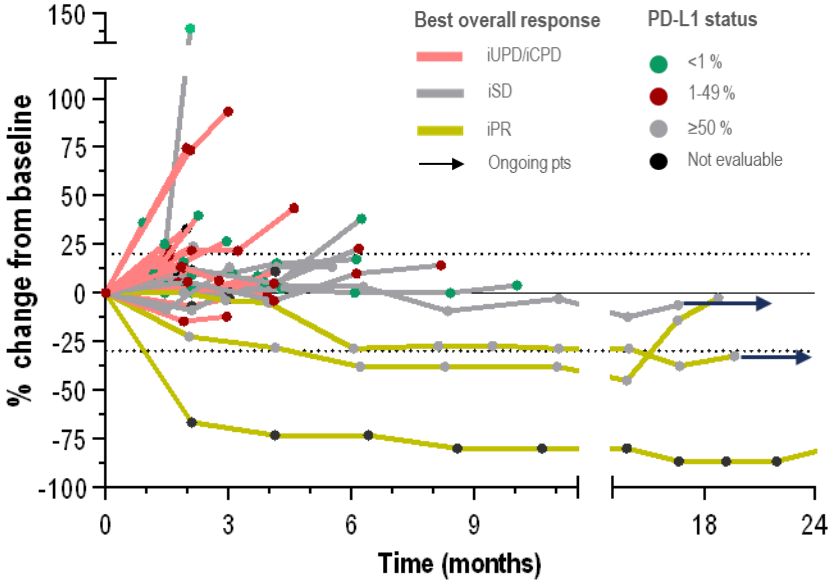
Data cut-off: December 31, 2022

Efficacy – Exploratory Subgroup Analysis

Spider Plot by Response[1] and PD-L1



- 2/3 ongoing responses, staying on treatment 19-24 mo.
- PRs/SDs are long-lasting (see spider plot above).

Efficacy by PD-L1/Resistance to 1st Line I-O

Efficacy parameter	PD-L1		Resistance to first line I-O	
	≥50%, N=6	≥1% N=20	Primary, N=9	Secondary, N=25
ORR[1], n (%)	2 (33.3)	2 (10.0)	0 (0.0)	3 (12.0)
mPFS[1] (% events)	10.4 (66.7)	2.1 (90.0)	1.8 (100)	2.1 (88.0)
3-mo, %	83.3	35.0	22.2	36.0
6-mo, %	50.0	25.0	22.2	28.0
mOS (% events)	NR (33.3)	10.8 (65.0)	7.5 (88.9)	11.4 (64.0)
12-mo, %	66.7	45.0	33.3	48.0
18 mo, %	66.7	33.8	33.3	39.3

- Patients with high PD-L1 expression and with secondary resistance had better ORR, PFS and OS compared to patients with PD-L1 negative expression and primary resistance.

[1] by iRECIST.
I-O: immuno-oncology therapy; NR: not reached.
Note: Figure has been cropped for visualisation purposes.

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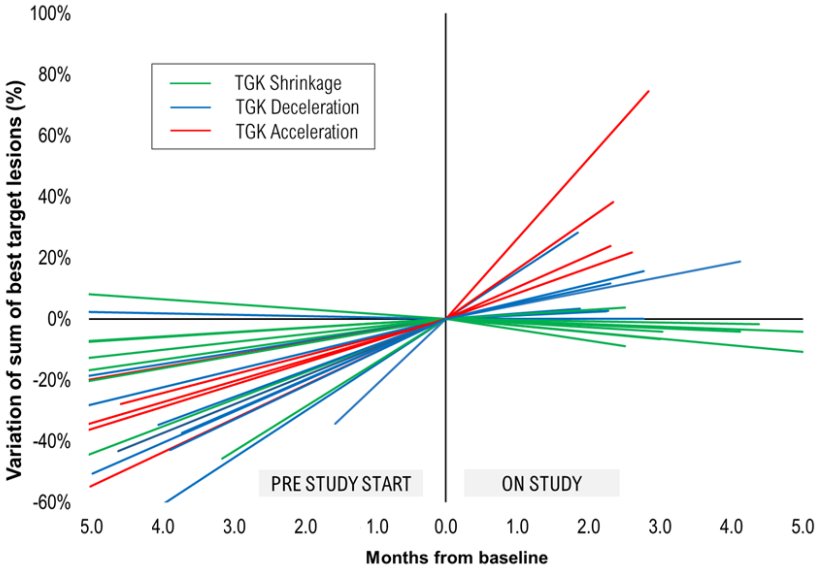
Efficacy – Exploratory Analysis

Tumour Dynamics[1]



- After addition of efti, **83.3% of patients had post-efti treatment initiation tumour growth kinetic shrinkage or deceleration after previous PD**.

Tumor dynamics (N=24)	n (%)
Shrinkage	8 (33.3)
Deceleration	12 (50.0)
Acceleration	4 (16.7)

[1] Tumour growth kinetics (TGK): comparative ratio of the difference of the sum of the largest diameters of target lesions in the pre- & post-baseline setting.
Ref: Saâda-Bouzid E et al, Ann Oncol. 2017 Jul 1;28(7):1605-1611. doi: 10.1093/annonc/mdx178.

Summary & Conclusion

- Efti + pembrolizumab show signs of efficacy with ORR of 8.3%; DCR of 33% and PFS (6-mo landmark PFS of 25%) in patients with predominantly PD-L1 neg/low (82%) 2nd line NSCLC after confirmed progression on 1st line PD-X therapy (67% in combination with chemotherapy).
- Effects are durable with all 3 responders on treatment for 18+ mo and 39% OS rate at 21-mo comparing favorably to historical data (e.g. docetaxel with median OS of 6-9 mo and 10-15% OS rate at 21-mo[1,2]).
- Effects (ORR, PFS, OS) more pronounced in patients with high PD-L1 expression or who were secondary resistant (e.g. mOS not reached for TPS ≥50%).
- Combination of efti + pembrolizumab was well-tolerated without any new safety signals.

Conclusion: The addition of the APC activator eftilagimod alpha administered subcutaneously with anti-PD-1 therapy may revert resistance to anti-PD-X therapy. This data supports further clinical investigation of this innovative chemo-free I-O/I-O combination targeting both APCs (efti) and T cells (anti-PD-1) in an anti-PD-X refractory patient population.

[1] N Engl J Med. 2015 Jul 9;373(2):123-35. doi: 10.1056/NEJMoa1504627.
[2] N Engl J Med. 2015 Oct 22;373(17):1627-39. doi: 10.1056/NEJMoa1507643.

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