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

Abstract # 82

Forster M[1]; Krebs M.G[2]; Majem M[3]; Peguero J[4]; Clay T[5]; Felip E[6]; Iams W[7]; Roxburgh P[8]; Dodger B[9]; Bajaj P[10]; Kefas J[11]; Scott JA[12]; Mueller C[13]; Triebel F[14]

[1]UCL Cancer Institute / University College London Hospitals NHS Foundation, London, UK; [2]Division of Cancer Sciences, The University of Manchester and The Christie NHS Foundation Trust, Manchester, UK; [3]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [4]Oncology Consultants, P.A., Houston, USA; [5]St John of God Subiaco Hospital, Perth, Australia; [6]Vall d'Hebron University Hospital, Barcelona, Spain; [7]Vanderbilt Ingram Cancer Center Division of Hematology/Oncology, Tennessee, United States; [8]Wolfson Wohl Cancer Research Centre, Institute of Cancer Sciences, University of Glasgow and Beatson West of Scotland Cancer Centre, Scotland, United Kingdom; [9]Fundación Jiménez Diaz, Madrid, Spain; [10]Tasman Oncology, Queensland, Australia; [11]University College London Hospitals NHS Trust, London, United Kingdom; [12]The Christie NHS Foundation Trust, Manchester, United Kingdom; [13]Clinical Development, Immutep GmbH, Berlin, Germany; [14]Research & Development, Immutep S.A.S., Orsay, France

IASLC 2022 World Conference on Lung Cancer
AUGUST 6-9, 2022 | VIENNA, AUSTRIA

BACKGROUND

- **Mechanism of action**: eftilagimod alpha (efti) is soluble LAG-3 protein (LAG-3 domains fused to human IgG backbone [**Figure 1**]) targeting a subset of MHC class II molecules to mediate activation of antigen presenting cells (APCs: 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 does not bind to LAG-3 on T cells like anti-LAG-3 antagonists (**Figure 3**).
- **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

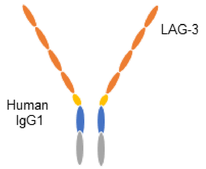


Figure 2. Mechanism of action of efti

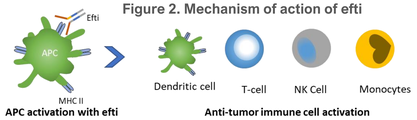
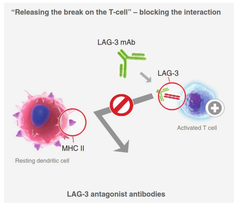


Figure 3. Difference to anti-LAG-3



METHODS

Study Design and Patients

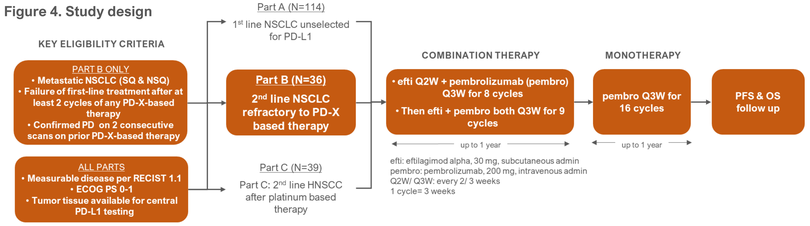
- Non-randomized, multinational, open-label, trial for **2nd line, PD-X refractory* metastatic NSCLC** patients **unselected for PD-L1 expression**.
- Simon's optimal two-stage designed trial.
- Efti is administered as a 30 mg subcutaneous injection every 2 weeks for the first 8 cycles (1 cycle: 3 weeks) 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 4**).

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.
- Database cut-off date was July 1, 2022; minimum follow-up of 10+ months.

*failure of first-line treatment with confirmed disease progression (by 2 scans 4 weeks apart) after at least 2 cycles of any PD-X-based therapy.

Figure 4. 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

- 36 patients (pts) were recruited in 10 sites across 4 countries between Apr 2019-Aug 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.
- 66.7% received the combination of doublet chemo + anti-PD-1/anti-PD-L1 prior to inclusion.
- 41.7% did not respond (no PR or CR acc. RECIST 1.1) to 1st line therapy.

Table 1. Baseline characteristics

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-smokers	31 (86.1) 5 (13.9)
Squamous Non-squamous pathology Unknown	7 (19.4) 28 (77.8) 1 (2.8)
Prior PD-L1 therapy with chemotherapy	36 (100) 24 (66.7)
Tumor resistance* Primary resistance Secondary resistance	 10 (27.8) 24 (66.7)
PD-L1 (TPS) <1% 1-49% ≥50% Not evaluable	 13 (36.1) 14 (38.9) 6 (16.7) 3 (8.3)

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

SAFETY

- The most common adverse events (AEs) were decreased appetite (33.3%), dyspnea (30.6%), and cough (27.8%) (**Table 3**).
- No treatment-related deaths or discontinuations occurred (**Table 2**).

Table 2. General overview of AEs

Safety parameter*	n (%)
Any AE	35 (97.2)
Any serious AE	7 (19.4)
thereof related to study treatment**	3 (8.3)
Patients with any Grade ≥3 AE	12 (33.3)
thereof related to study treatment**	3 (8.3)
Patients with fatal AEs	2 (5.6)
thereof related to study treatment**	0
Patients with AEs leading to discontinuation of study treatment**	1 (2.8)
thereof related to study treatment**	0

*AEs rated according to National Cancer Institute Common Terminology Criteria for Adverse Events (v5.0)[2]
**Study treatment= efti and/or pembro

Table 3. Frequent AEs (incidence ≥15%) irrespective of relationship to study treatment

Adverse event (PT)	Any grade N (%)	Grade 3 N (%)	Grade 4/5 N (%)
Decreased appetite	12 (33.3)	-	-
Dyspnoea	11 (30.6)	1 (2.8)	1 (2.8)
Cough	10 (27.8)	-	-
Asthenia	8 (22.2)	1 (2.8)	-
Fatigue	7 (19.4)	1 (2.8)	-
Arthralgia	6 (16.7)	1 (2.8)	-
Weight decreased	6 (16.7)	-	-

Table 4. Frequent AEs (incidence ≥10%) related to study treatment

Adverse event (PT)	Any grade N (%)	Grade 3 N (%)	Grade 4/5 N (%)
Asthenia	5 (13.9)	-	-
Injection site erythema	5 (13.9)	-	-
Injection site reaction	4 (11.1)	-	-

EFFICACY

By Intention-to-treat (ITT) population

- 2 patients (5.6%) with durable PRs (**Figure 5**).
- Overall response rate (ORR) of 5.6 % and disease control rate (DCR) of 36.1% according to iRECIST (**Table 5**).
- iRECIST results comparable to RECIST 1.1 (**Table 5**).
- 25% of patients progression-free at 6 months (**Table 6**) with median progression free survival (PFS) of 2.1 months.
- Survival rates showing 72% and 37% of patients alive at 6 and 18 months, respectively (**Table 6**) with **median overall survival (OS) of 9.7 months** (**Figure 6**).

By PD-L1/ Resistance Level

- Comparable PFS and OS results for PD-L1 subgroups (**Table 6**).
- PD-L1 results of the two confirmed responses (TPS= 50%; TPS= unknown).
- Comparable PFS (25-30% at 6 months) and OS rates (70% at 6 months) for pts with primary or secondary resistant tumors, respectively.
- Both responses were observed in secondary resistant pts.

Figure 5. Spider plot (N=34*)

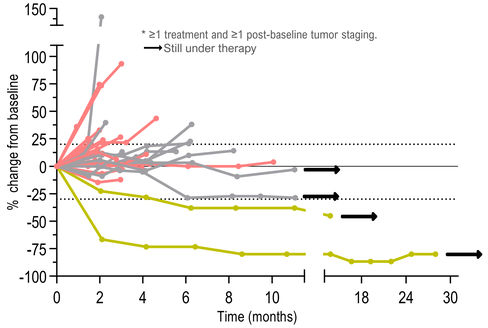


Table 5. Best overall response, ITT

Tumor response* (N=36)	iRECIST n (%)	RECIST 1.1 n (%)
Partial Response	2 (5.6)	2 (5.6)
Stable Disease	11 (30.6)	10
Progression	22 (61.1)	23
Not Evaluable**	1 (2.8)	1 (2.8)
Overall Response Rate (ITT)	2 (5.6)	2 (5.6)
Disease Control Rate (ITT)	13 (36.1)	12 (33.3)
ORR (EVAL)	2/35 (5.7)	2/35 (5.7)

*local investigator read, confirmed; **no post-baseline scan available

Figure 6. Overall survival, ITT (N=36)*

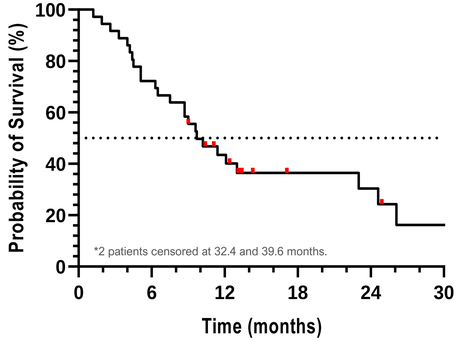


Table 6. ORR, PFS and OS for ITT and PD-L1 subgroups

PD-L1 TPS	ITT (N=36)	<1% (N=13)	1-49% (N=14)	≥50% (N=6)
ORR (iRECIST)				
ORR, %	5.6	-	-	16.7
Overall survival				
Median, months	9.7	8.7	9.6	NR
No. of events	25	10	11	2
6-month OS, %	72.2	61.5	71.4	100
12-month OS, %	43.4	46.2	32.7	66.7
18-month OS, %	36.5	46.2	16.3	NR
Progression-free survival (iRECIST)				
Median, months	2.1	2.1	1.9	7.6
No. of events	32	13	14	3
3-month PFS, %	30.6	23.1	14.3	66.7
6-month PFS, %	25.0	15.4	14.3	50.0

CONCLUSION

- Anti-tumor activity of an anti-PD-1 plus an APC activator (soluble LAG-3, efti) after confirmed progression on anti-PD-X based therapy in a very challenging 2nd line NSCLC population with limited treatment options:
  - *75% PD-L1 TPS of <50%, 67% pre-treated with doublet chemo + anti-PD-1 and 42% with no objective response to first line therapy.*
  - *Confirmed & durable (10+ months) responses in 2 pts (5.6%).*
  - *Long-term (6+ months) disease control in 25% of pts.*
  - *36.5% alive at 18 months.*
- Combination is well tolerated without any new safety signals.
- The data supports further clinical investigation of efti + pembrolizumab in PD-X refractory patients.

ABBREVIATIONS

CR…complete response
ECOG…Eastern Cooperative Oncology Group
(i)RECIST…(Immune) Response Evaluation Criteria In Solid Tumors
ITT…intention-to-treat
LAG-3…Lymphocyte Activation Gene-3
MHC…Major Histocompatibility Complex
NR…not yet reached
PD-X…PD-1 or PD-L1 targeted therapy
PR…partial response
PT…preferred term
ORR…objective response rate

REFERENCES

1. Kluger HM et al, J Immunotherapy Cancer. 2020 Mar;8(1):e000398. doi: 10.1136/jitc-2019-000398
2. Common Terminology Criteria for Adverse Events (CTCAE) Version 5. Published: November 27. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute.

ACKNOWLEDGEMENTS

- We thank all the participating patients & their families.
- We thank the dedicated clinical trial investigators & their team members.
- Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA provided pembrolizumab for the study.
- This study is sponsored by Immutep. Corresponding author: Frederic Triebel, frederic.triebel@immutep.com

DISCLOSURES

The following represents disclosure information provided by the presenter of this abstract
Consulting or Advisory Role - Achilles Therapeutics; AstraZeneca; Bayer; Bristol-Myers Squibb; Celgene; Guardant Health; Lilly; Merck; Nanobiotix; Novartis; Oxford VacMedix; Pfizer; PharmaMar; Roche
Research Funding - AstraZeneca (Inst); Boehringer Ingelheim (Inst); Merck (Inst)
Travel, Accommodations, Expenses - AstraZeneca; Bristol-Myers Squibb; Celgene; Guardant Health; MSD Oncology