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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immutep elcc
LAG-3 IMMUNOTHERAPY

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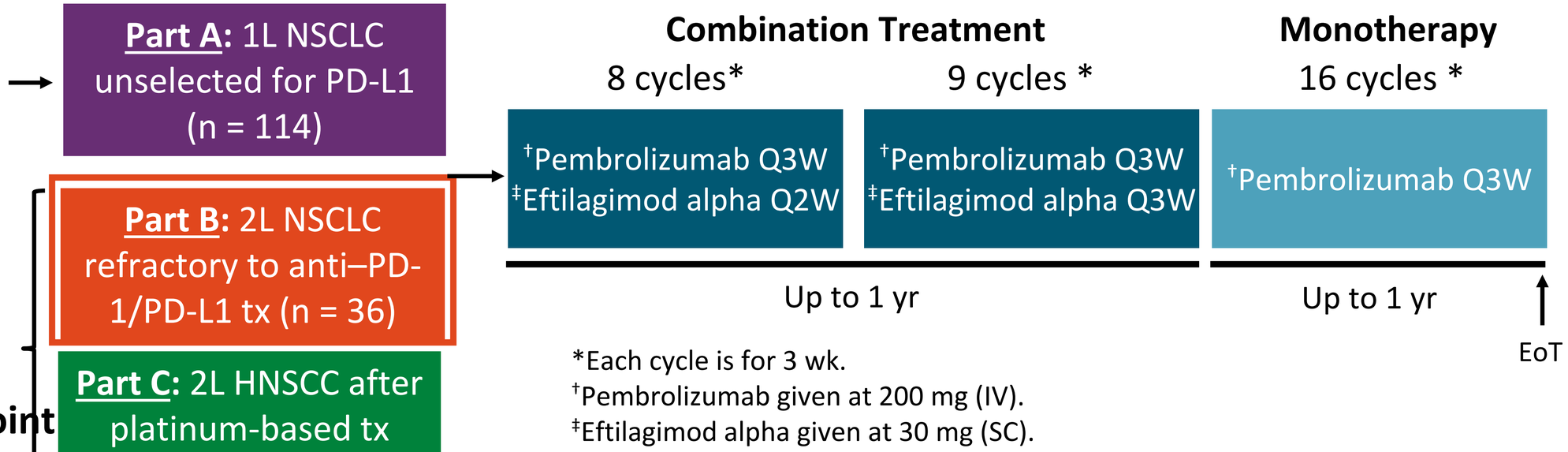
TACTI-002: Eftilagimod Alpha Plus Pembrolizumab in NSCLC or HNSCC[1-4]

- Nonrandomized, parallel assignment, open-label phase II trial

Part A:
Patients with newly diagnosed locally advanced or metastatic NSCLC, not amenable to ALK/EGFR inhibitor tx or tx with curative intent, ECOG PS 0/1, availability of tumor tissue

Parts B and C:
Patients with previously treated NSCLC or HNSCC, ECOG PS 0/1, availability of tumor tissue



- **Primary endpoint**
- **Secondary endpoi** 1, PFS, OS, DoR, safety and PK/PD (including potential biomarkers)

1. Peguero. ASCO 2019. Abstr TPS2667. 2. Clay. ASCO 2021. Abstr 9046. 3. Felip. ASCO 2022. Abstr 9003. 4. NCT03625323.

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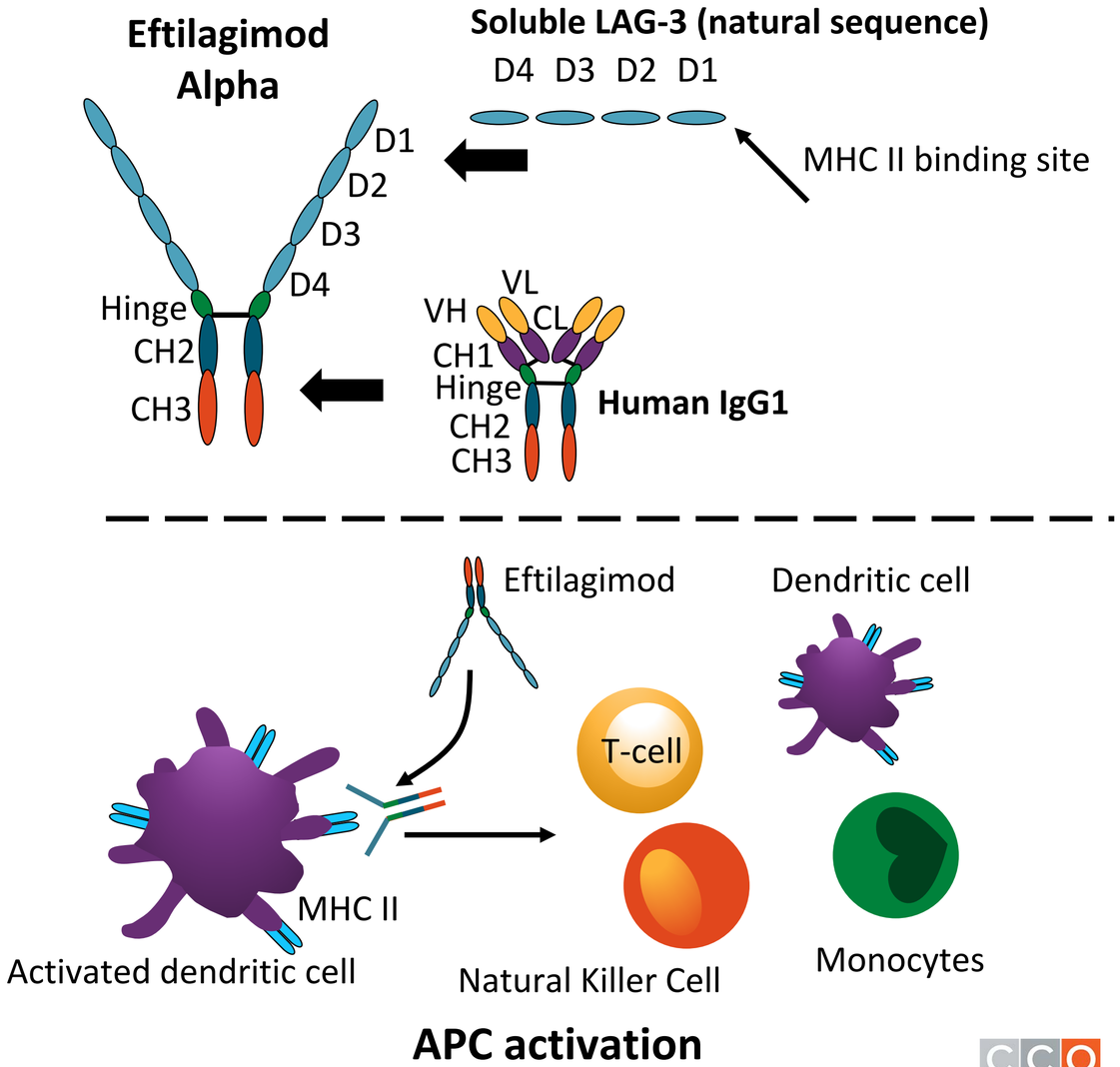
LAG-3: Varied Biologic Effects

- Negatively regulates cellular proliferation and activation[1,2]
  - Similar to, but not redundant with PD-1, CTLA-4
- LAG-3 is expressed on multiple cell types including CD4+ and CD8+ T-cells and T-regulatory cells, and helps maintain self and tumor tolerance[3,4]
- The major ligand for LAG-3 is MHC class II[5]

1. Workman. J Immunol. 2004;172:5450. 2. Workman. J Immunol. 2005;174:688. 3. Huang. Immunity. 2004;21:503.
4. Grosso. J Clin Invest. 2007;117:3383. 5. MacLachlan. Eur J Immunol. 2021;52:331.

Eftilagimod Alpha Dimeric Recombinant LAG-3

- Recombinant, soluble LAG-3 fusion protein
- Mechanism of action is different from antibodies or bispecific antibodies targeting LAG-3
- MHC class II agonist
  - Binds to MHC class II on APC leading to APC activation
- Activated APCs leads to increased T-cell activation



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Felip. ASCO 2020. Abstr 3100. Clay. ASCO 2021. Abstr 9046.

Figure 1. efti‘s mechanism of action

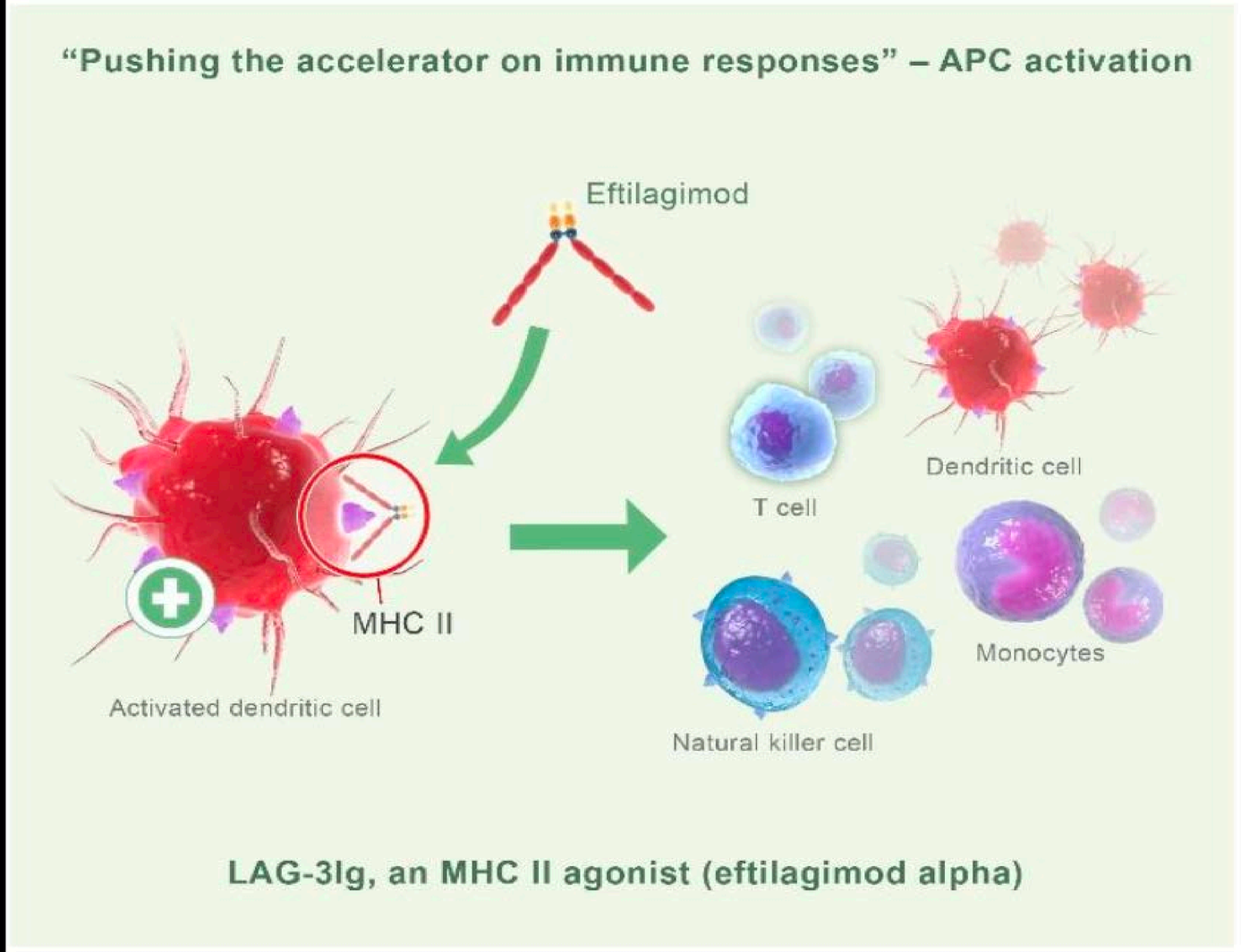
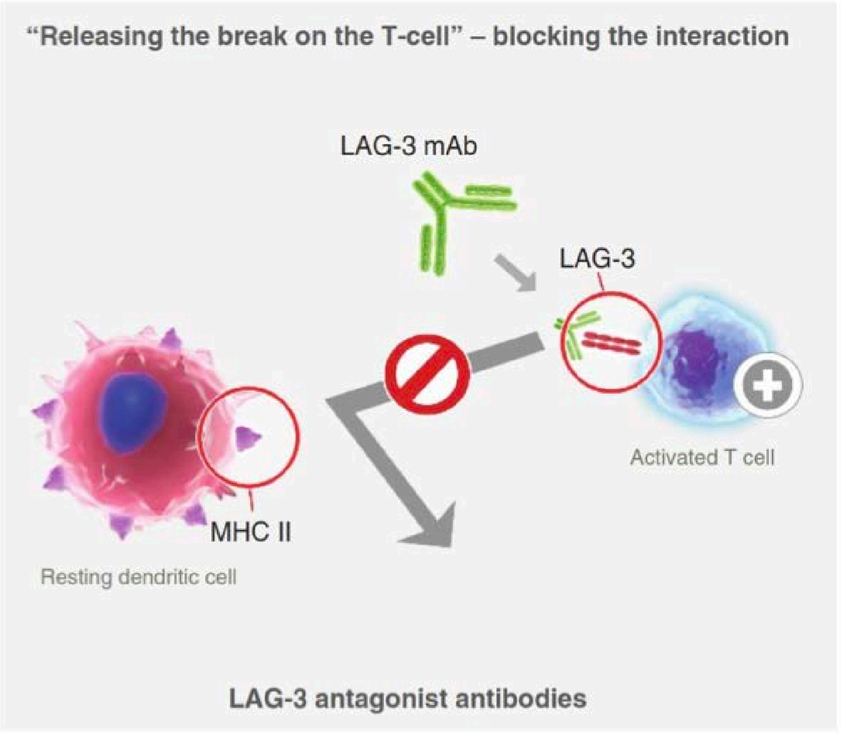


Figure 3. Difference to anti-LAG-3



Rationale ?

- In combination with pembrolizumab, which is more of a cytotoxic T-cell stimulatory agent at the site of cytotoxic T-cell tumor interactions, eftilagimod alpha works upstream at the antigen-presenting cell and T-cell interface to increase the overall immune response

- Stimulation of the dendritic cell network and the subsequent T-cell recruitment caused by eftilagimod alpha could help combat resistance to anti–PD-1 agents

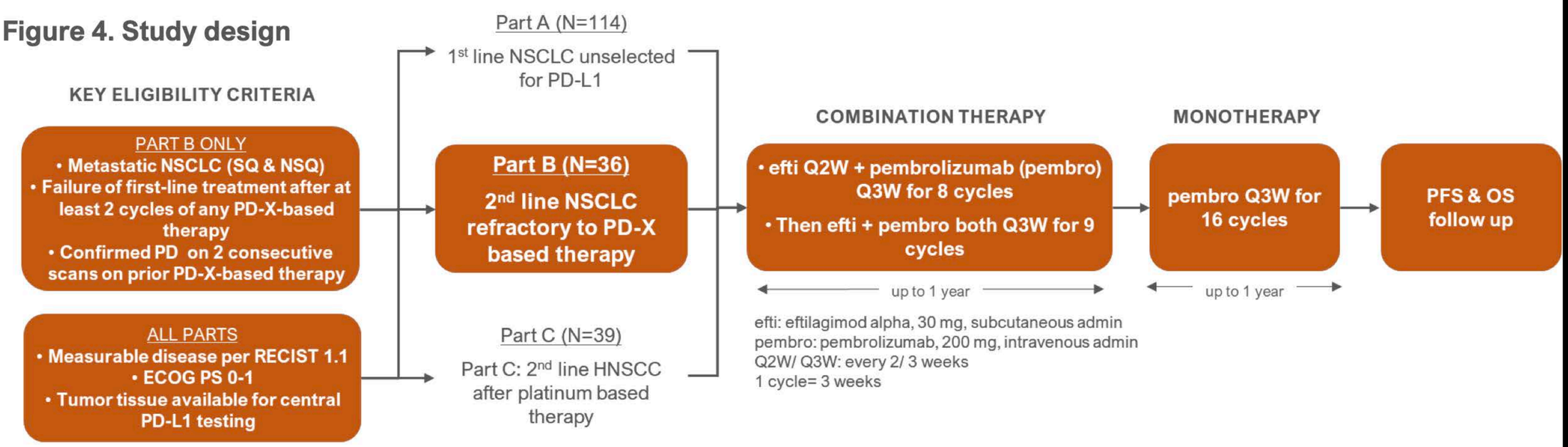
- Synergistic in combination with pembrolizumab

Methods

Study design and patients

- *Non randomised, Phase II, open label, multinational trial*

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.

Assessment and Statistical analysis

- *Primary Endpoint : ORR as per iRECIST*
- *Secondary Endpoints: PFS and other efficacy parameter, safety and tolerability and other exploratory biomarkers*
- *Central assessment of PDL-1 after enrollment*
- *Imaging performed every 9 weeks and reported according to iRECIST and RECIST v1.1*
- *Safety and efficacy analysed based on intent to treat principle*
- *Data cut off Jan 21, 2022 (min 5 months of follow-up)*

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)

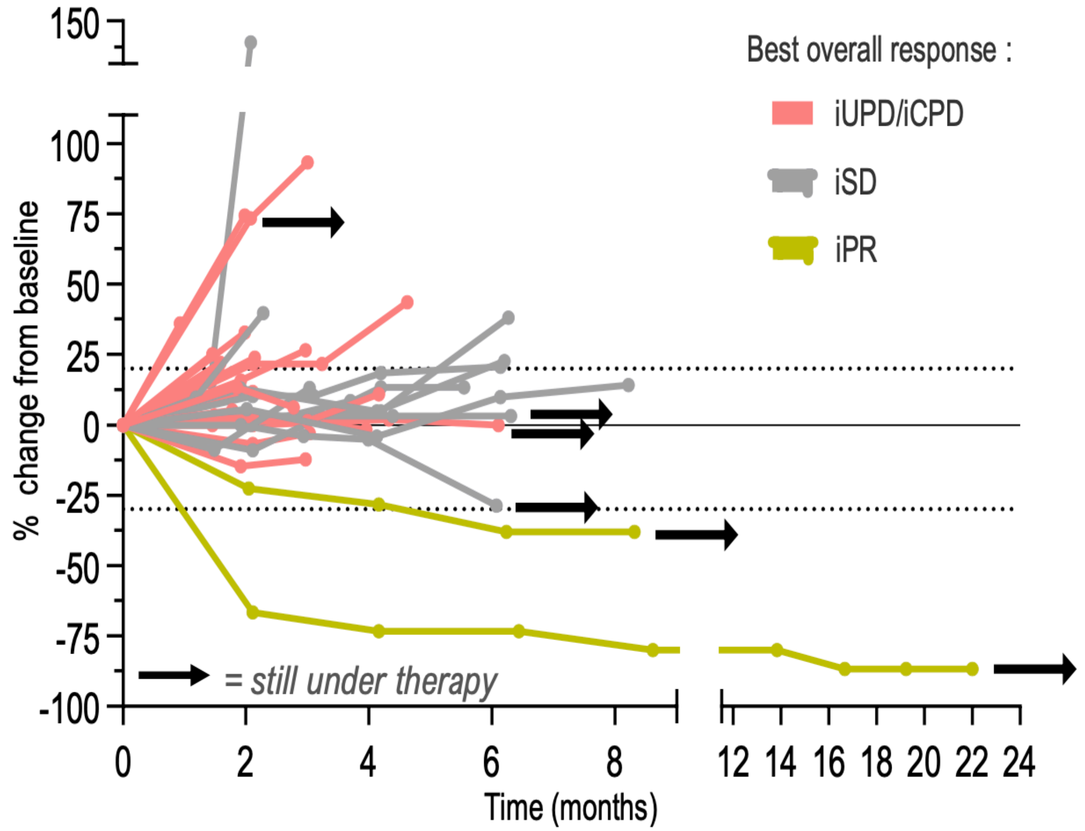
Efficacy

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)

Efficacy

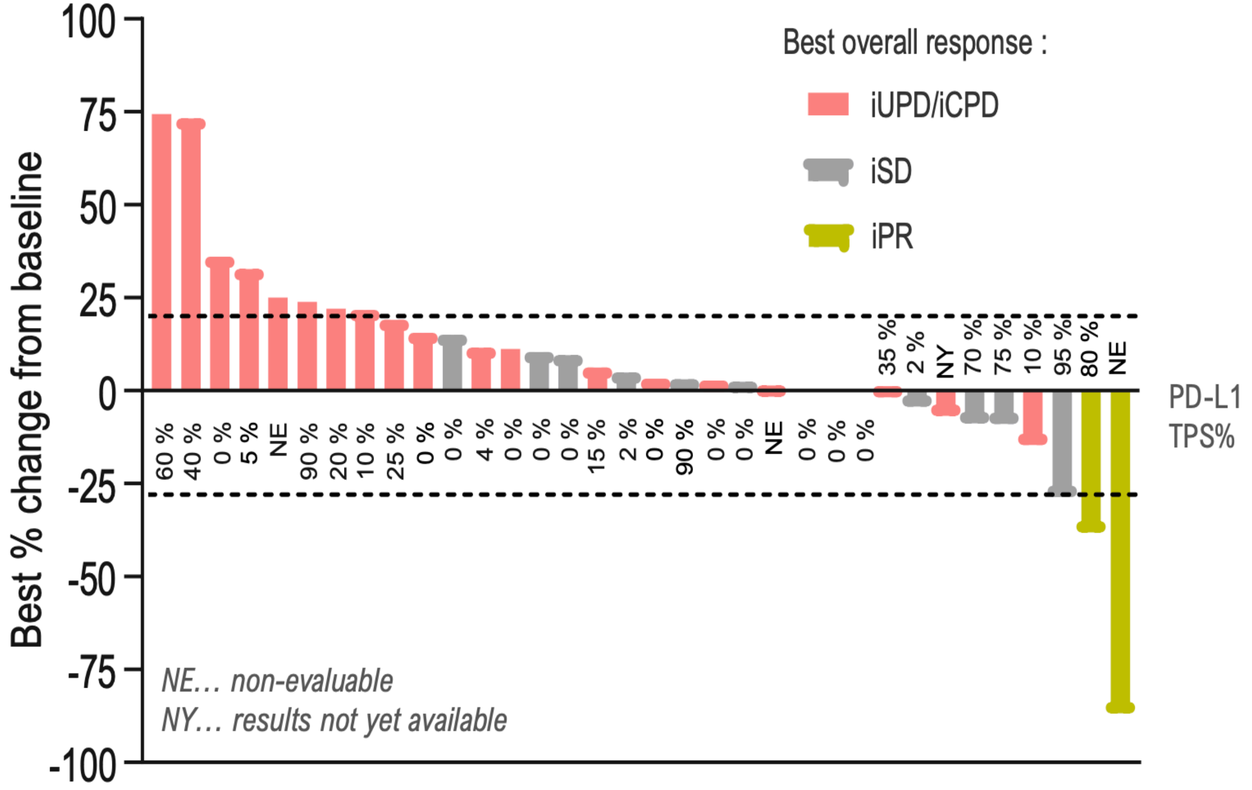
Figure 3. Spider plot (N=34)**



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

- *26 % progression free at 6 months*

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



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

- *73 % alive at 6 months*

Tumour growth kinetics (TGK)

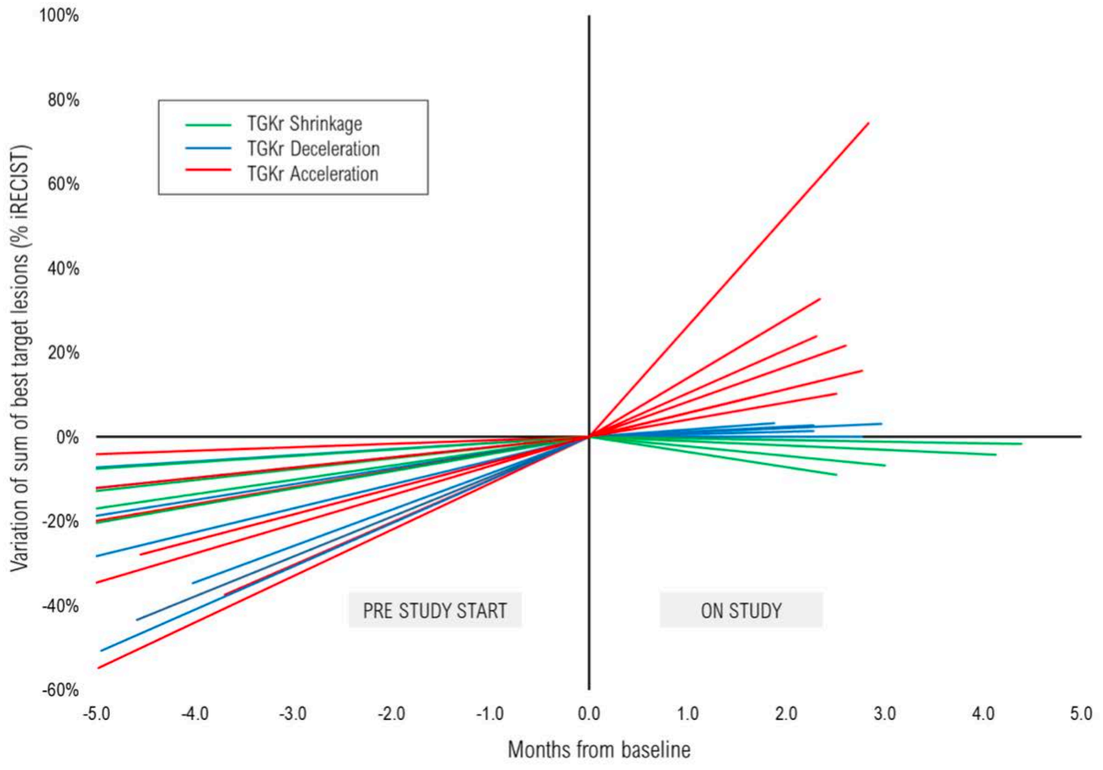
- *Obtained as comparative ratio of the difference of the sum of the largest diameters of the target lesions in the pre and post baseline settin*
- *73.7% of evaluable patients had post-treatment TGK shrinkage or deceleration*

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 5. Tumor growth kinetics (N=19)*



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

Common TEAE

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)	-	-

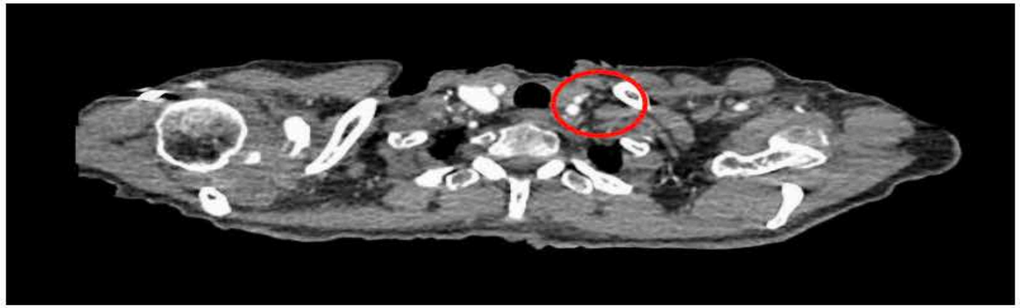
Case 1

Figure 6. Single case #1

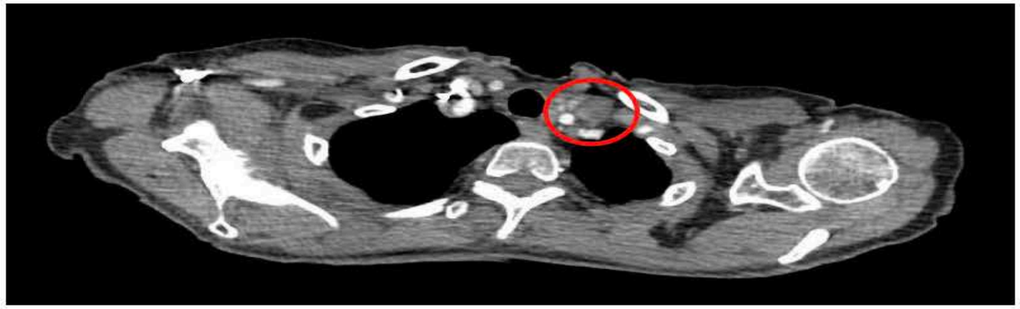
- 71-year-old female diagnosed with metastatic NSCLC (NSQ) in Sep 2016.
- Received 1st line carboplatin + pemetrexed + pembrolizumab for 18 months → stopped due to PD.
- At study entry: ECOG 1, non-evaluable PD-L1 TPS, EGFR/ALK negative, ex-smoker
- Started TACTI-002 in Feb 2020 and is still on therapy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

Lymph Node Lesion

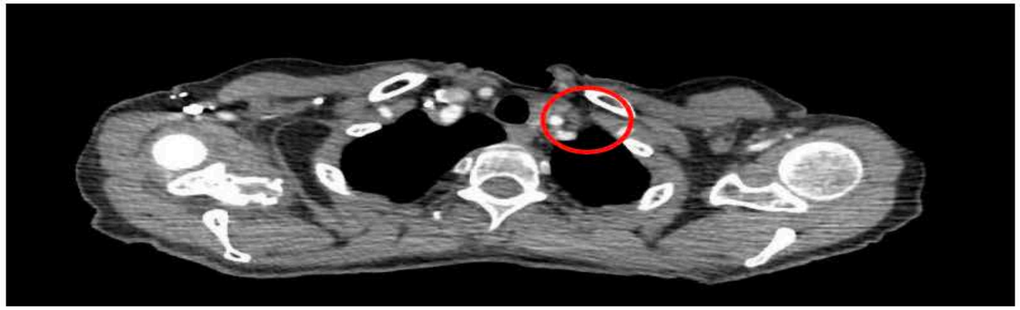
PRE-STUDY (DEC 2019)
PD on basis of skeletal metastases. No supraclavicular lymphadenopathy seen at this point



BASELINE (FEB 2020)
Further PD confirmed with new left supraclavicular lymph node measuring 1.5cm

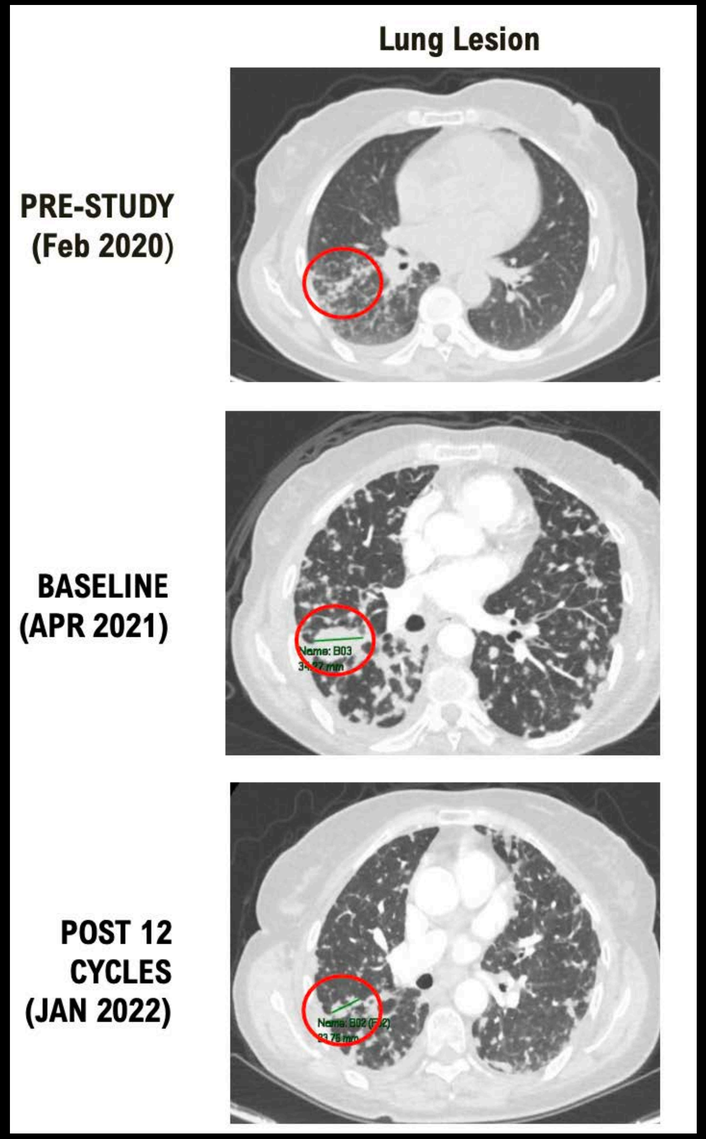


POST 3 CYCLES (APR 2020)
Left supraclavicular node shrunk to 5mm (-67%)



Case 2

- 67 years old female, mNSCLC, Diagnosed in Aug 2019
- Received Pembrolizumab + Cisplatin + Pemetrexed for 8 months, discontinuing after progression
- At study enrolment, 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 %)



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.

Update-Aug 2022

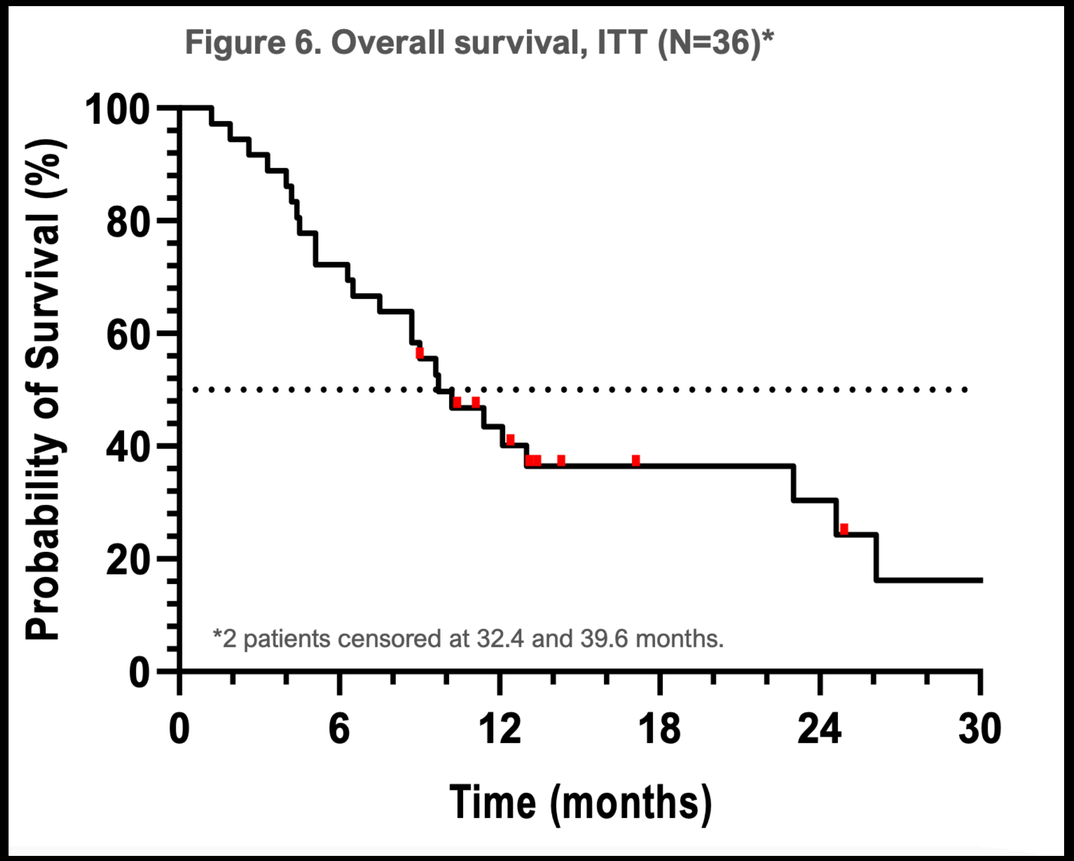
Median OS was 9.7 months

18-month OS rate was 36.5%

6-month PFS rate was 25%

Response comparable across PDL-1 expression

Response irrespective of primary or secondary resistance



My take

- *Patients with post progression on immunotherapy, unmet need*
- *Efti gives an option to continue chemotherapy free treatment for a longer period - beyond progression*
- *First line or second line - randomised, larger trials in both the settings with comparative arms*

- *Thankyou :)*