A Soluble LAG-3 Protein (Eftilagimod Alpha) with an Anti-PD-1 Antibody (Pembrolizumab): Results of a Phase II Study in NSCLC

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Non-Small Cell Cancer Drug Development Summit

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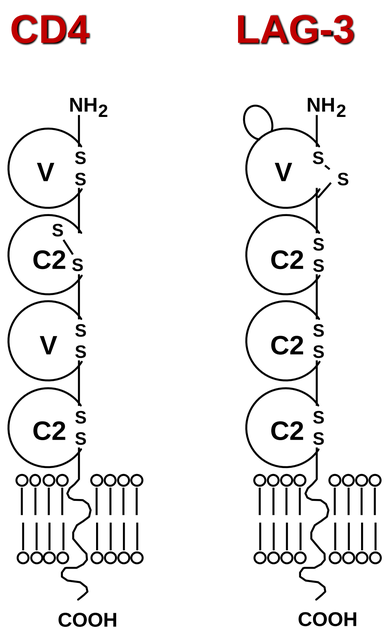
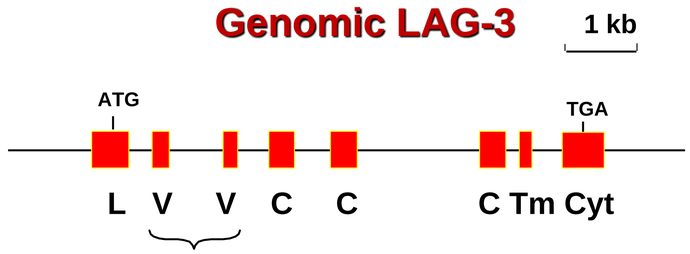
LAG-3 IMMUNOTHERAPY

What is LAG-3?

Lymphocyte Activation Gene-3

(LAG-3 or CD223)

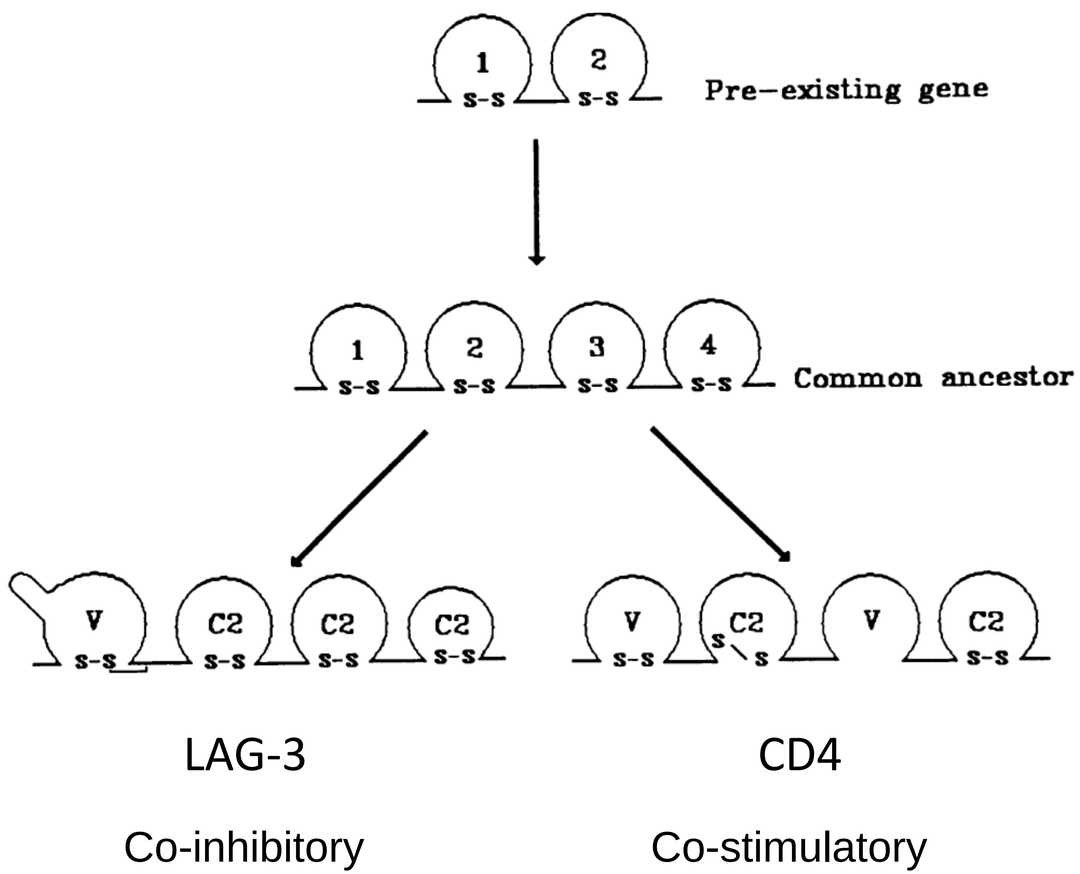




- 4-IgSF domain transmembrane proteins.
- Same genomic organization
  (intron in D1, duplication event D1D2 vs D3D4).
- Close proximity on 12p13.
- Share the same ligands (MHC class II)

J. Exp. Med. 171:1393-1405, 1990

Proposed evolutionary pattern for LAG-3/CD4

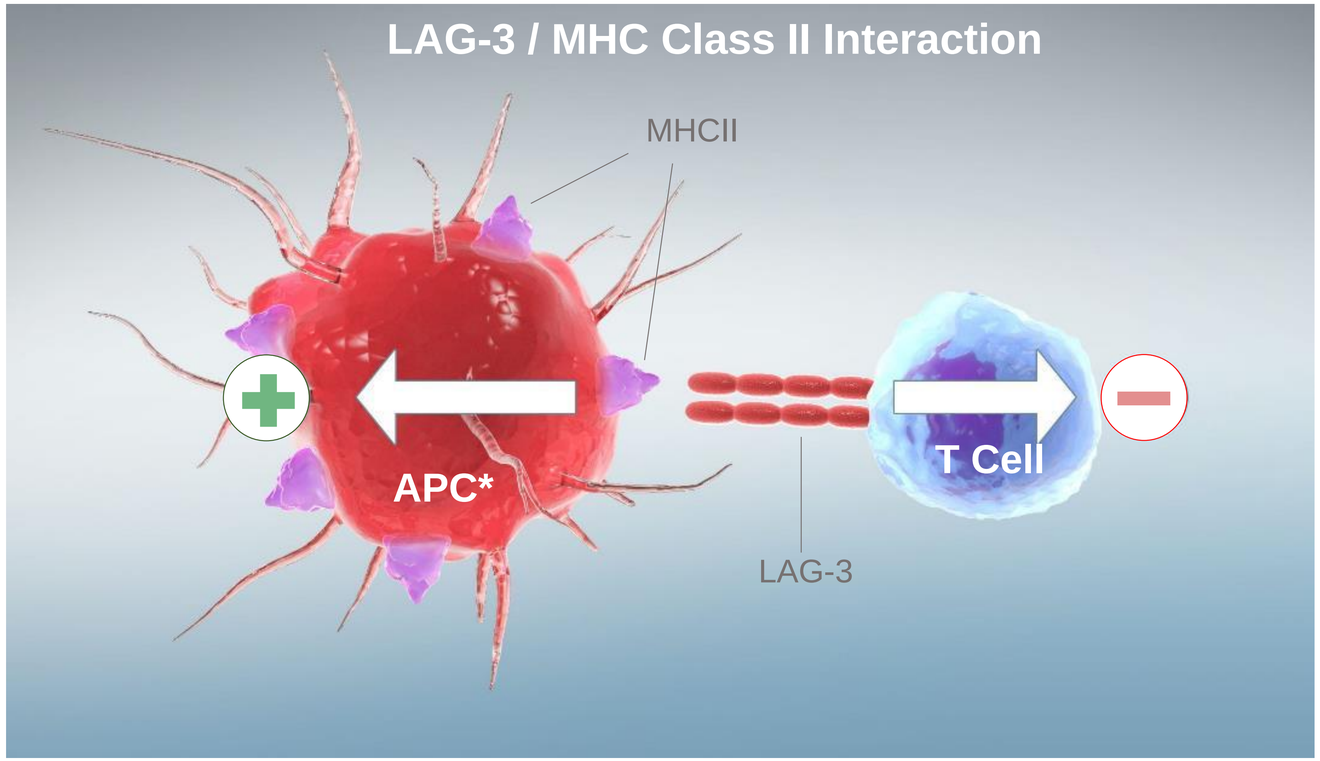


- Duplication of a 2-IgSF domain ancestor
- The LAG-3/CD4 subfamily has evolved like the CTLA-4/CD28 subfamily: one inhibitory and one stimulatory receptor modulating TCR signaling
- A yin/yang modulatory machinery on T cells

Immunogenetics 39:213-217, 1994

LAG-3/MHC-II interaction is a Clinically Validated Therapeutic Target Central to Immune Activation

LAG-3, an immune checkpoint, is widely expressed on tumor infiltrating lymphocytes (TILs) and cytotoxic T cells, and interacts with MHC class II molecules on APCs



Positive regulation of antigen presenting cells (**APCs**) → increase in antigen presentation to cytotoxic $CD8^+$ T cells

Negative regulation of $LAG\text{-}3^+$ T Cells

- Relatlimab and ~25 more products globally
- **3rd validated checkpoint in immuno-oncology**

Notes:
* APC: antigen presenting cell

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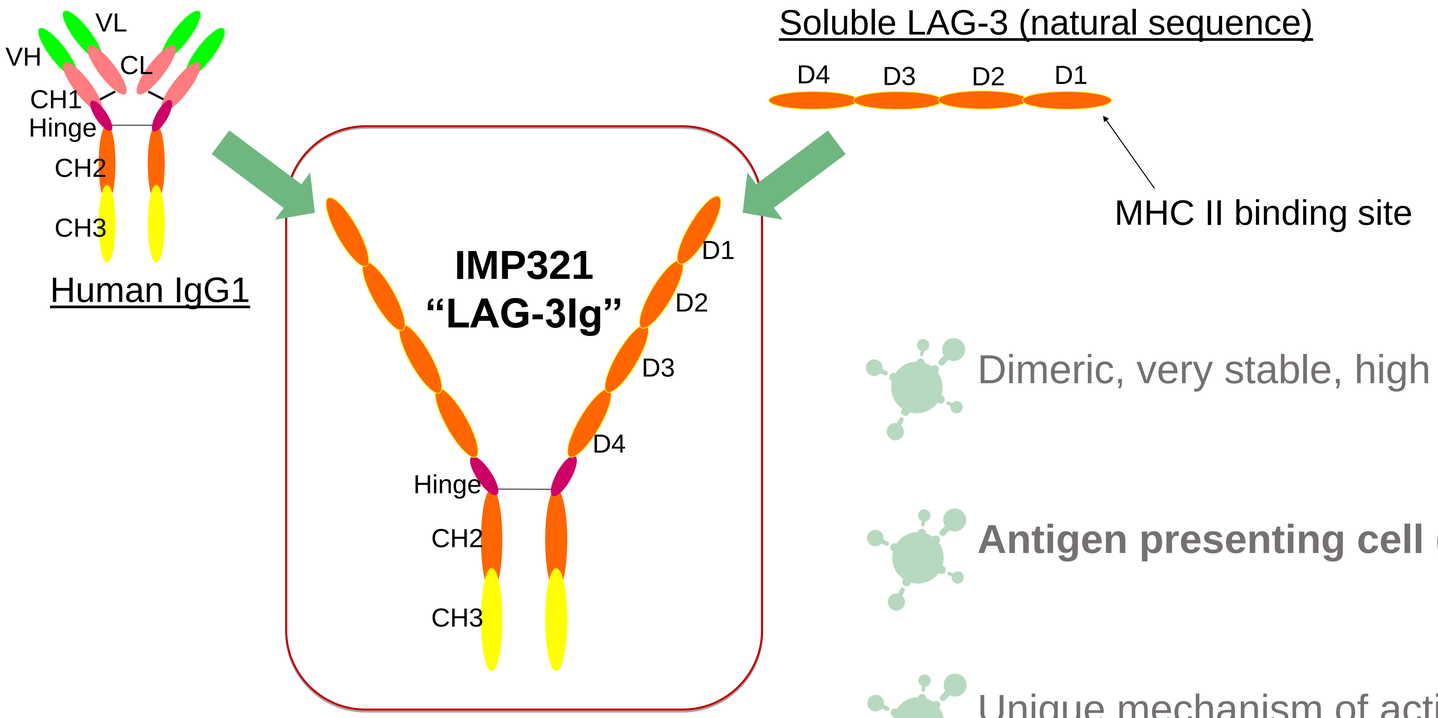
LAG-3 IMMUNOTHERAPY

Eftilagimod Alpha (efti or IMP321)

Eftilagimod Alpha (efti / IMP321)

Efti is a soluble recombinant fusion protein consisting of the Fc portion of a human antibody and the four extracellular domains of human LAG-3



- Dimeric, very stable, high affinity for dendritic cells
- **Antigen presenting cell (APC) activator**
- Unique mechanism of action and first-in-class

Two endogenous non-TLR ligands (sLAG-3 and sCD40L) that induce DC maturation and migration

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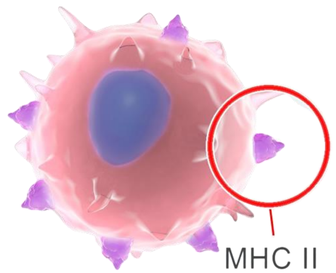
LAG-3 IMMUNOTHERAPY

Peripheral tissues

Immature DC

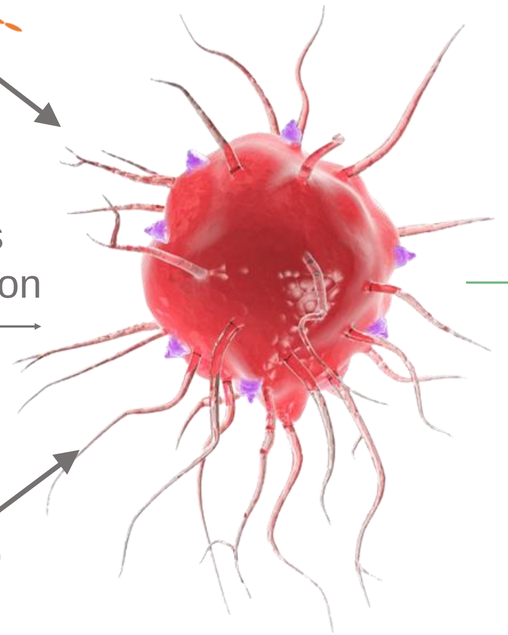


CD80 $^{+}$ CD86 $^{+}$ CD40^{+}
MHC I-II^{+} CD83^{-}
Antigen capture^{+}
CCR5^{+} CCR4^{-}

Maturation & Migration

efti

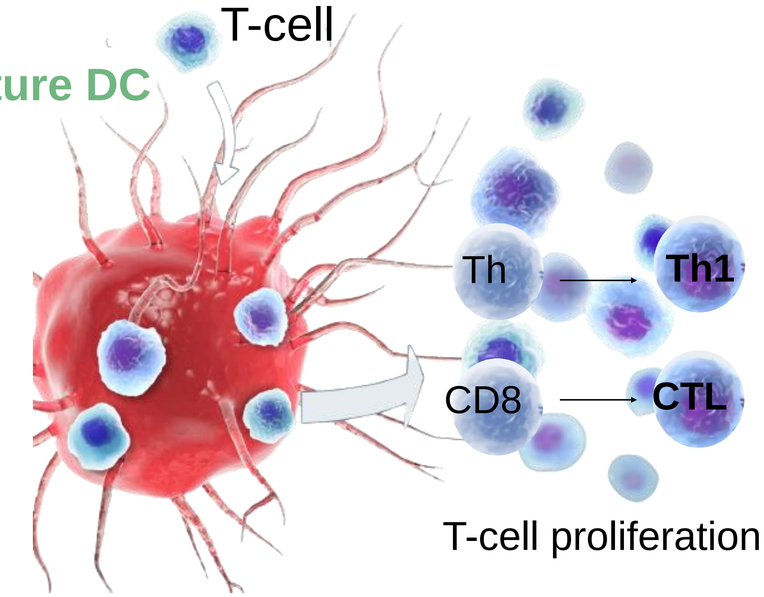
Pathogens
Inflammation



sCD40L

sCD40L and **sLAG-3** are non-TLR ligands that activate DCs

Lymphoid organs



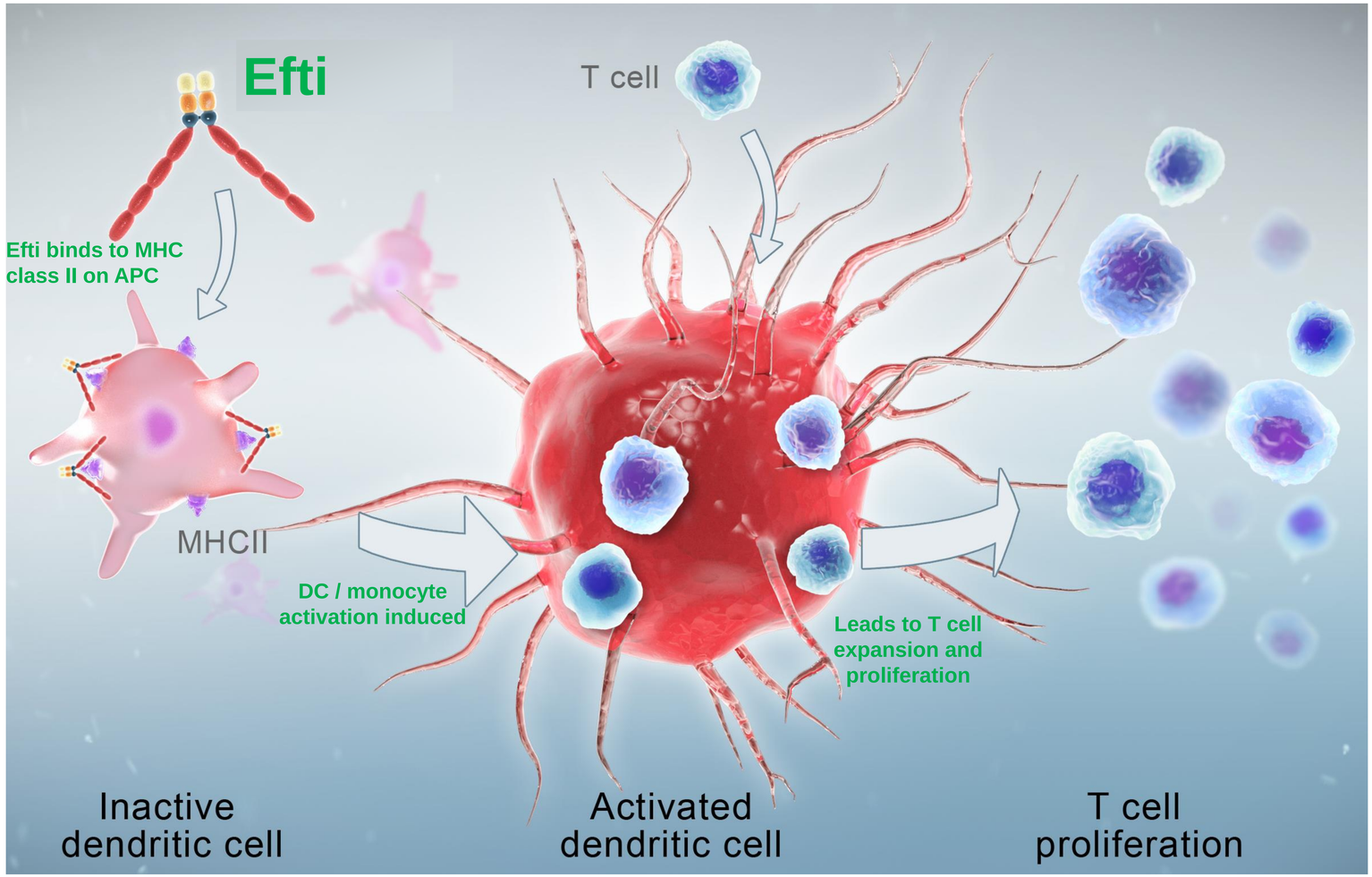
T-cell proliferation

CD80 $^{++}$ CD86 $^{++}$ CD40 $^{++}$
MHC I-II $^{++}$ CD83 $^{+}$
Antigen capture $^{-}$
CCR5^{-} CCR7 $^{+}$
Lymphoid chemokines, IL-12

Efti: Mechanism of Action (MoA)

Efti's unique agonistic MoA leads to T cell expansion and proliferation

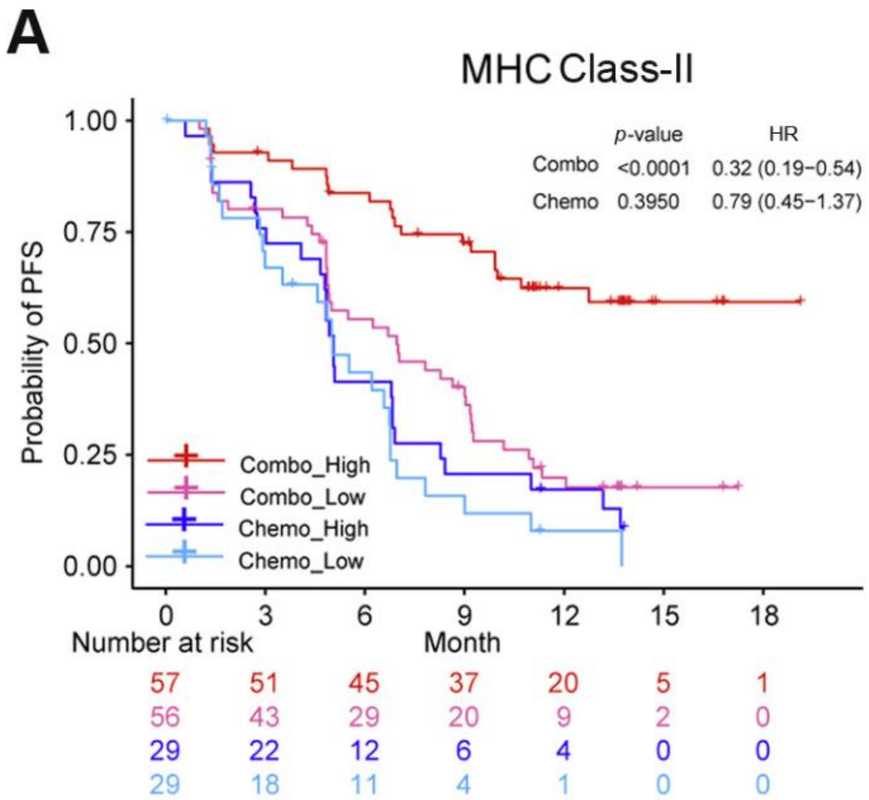
→ **"Pushing the gas pedal" on the immune response!**



Notes:

https://www.youtube.com/watch?v=6EISCGYAGQw

Synergistic benefit of APC activation in combination with ICI in NSQ NSCLC



Phase III ORIENT-11 trial – Biomarker analysis of chemo vs- chemo + PD-1 antagonist in 1st line NSQ NSCLC (Yang et al 2021)

- *Molecules associated with antigen presentation like MHC class II – if enriched in the tumor microenvironment – are predictive for PFS for PD-1 antagonists, but not for chemo.*
- *This holds true irrespective of PD-L1 expression.*

→ APC activation and increased antigen presentation may be key for more responses to PD-1/PD-L1 antagonists.

Figure 4. Association between PFS and gene expression of antigen presentation pathways. PFS correlation of high and low (*A*) MHC class II-related gene signatures, (*B*) MHC class I-related gene signature, (*C*) class II antigen presentation pathway signature, and (*D*) class I antigen presentation pathway signature is revealed for the combo and chemo treatment groups with respective *p* value, HR, 95% confidence interval, and sample size. Chemo, chemotherapy treatment; Chemo_high (or Chemo_low), chemotherapy treatment and high (or low) RNA expression level; Combo, sintilimab plus chemotherapy combination treatment; Combo_high (or Combo_low), sintilimab plus chemotherapy combination treatment and high (or low) RNA expression level; HR, hazard ratio; MHC, major histocompatibility complex; PFS, progression-free survival.

Notes:

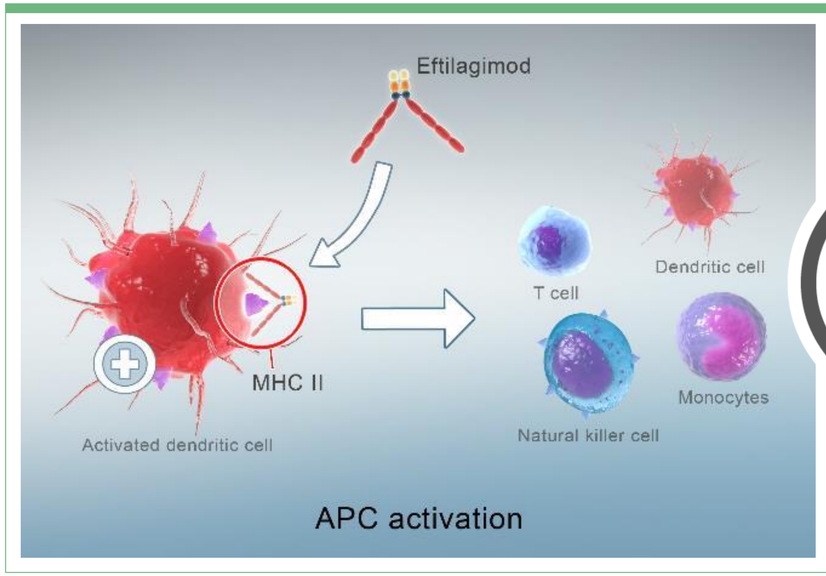
Y Yang et al. Updated Overall Survival Data and Predictive Biomarkers of Sintilimab Plus Pemetrexed and Platinum as First-Line Treatment for Locally Advanced or Metastatic Non-squamous NSCLC in the Phase 3 ORIENT-11 Study. 2021 *J Thor Onc.*
DOI:https://doi.org/10.1016/j.jtho.2021.07.015

Efti is an Innovative LAG-3 IO Product

Not a Checkpoint Inhibitor

- The only APC (MHC II) targeting LAG-3 product candidate currently in development
- A unique approach (“turning cold tumors into hot tumors” with LAG-3)
- Synergistic with other therapeutic agents and modalities e.g. IO agents and chemotherapy

“PUSHING THE ACCELERATOR ON IMMUNE RESPONSES”

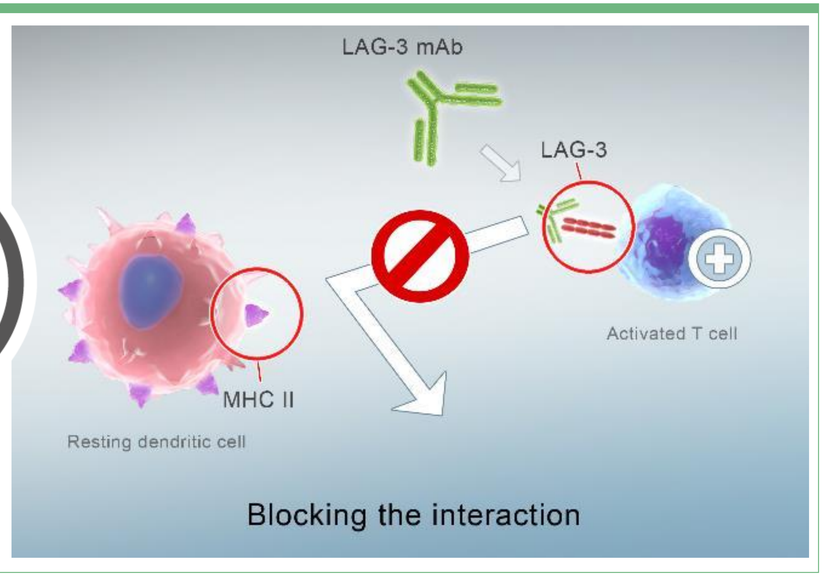


Efti is an **MHC II agonist**

APC activator

- Boosts and sustains cytotoxic T cell responses
- Activates multiple immune cell subsets

“RELEASING THE BRAKE ON THE T CELL”



LAG-3 antagonist, or blocking, antibodies:

Immune checkpoint inhibitor

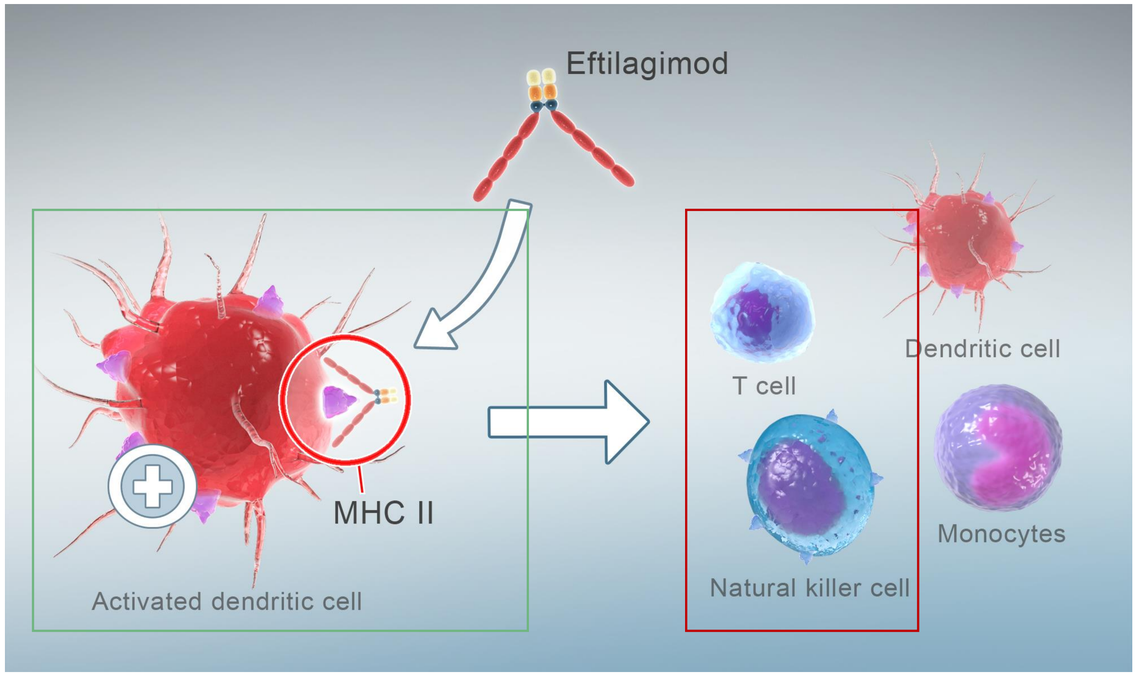
- Increases cytotoxicity of pre-existing CD8 T cell response

Efti Pharmacodynamic Activity

Pharmacodynamic effects observed in different clinical trials

PD Activity in Clinical Trials

Primary and Secondary Target Cells of **efti**



Additional Biomarkers

- Increase of soluble factors of type-1 immune response

→ **IFN-γ**

- Increase of IFN-induced chemokines

→ **CXCL10**

Key factors for T cell infiltration and generation of „hot“ tumor microenvironment

Reschke & Gajewski, *Sci. Immunol.* 2022

Primary Target Cells of efti

- Cells expressing MHC-II
- Dendritic Cells
- Macrophages / Monocytes

Measurement

- Increase in target cell count
- Expression of activation markers on the surface of APCs

Secondary Target Cells of efti

- Cells activated by APCs
- T Cells ($CD4^+$, $CD8^+$)
- Natural Killer Cells (NK)

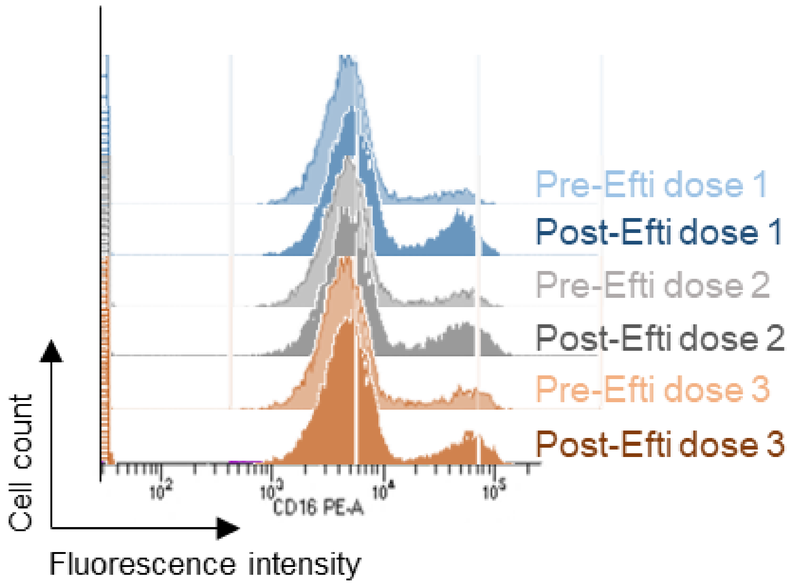
Measurement

- Increase in target cell count
- Increased activation status
- Shift to effector-memory phenotype

PD Activity in Clinical Trials

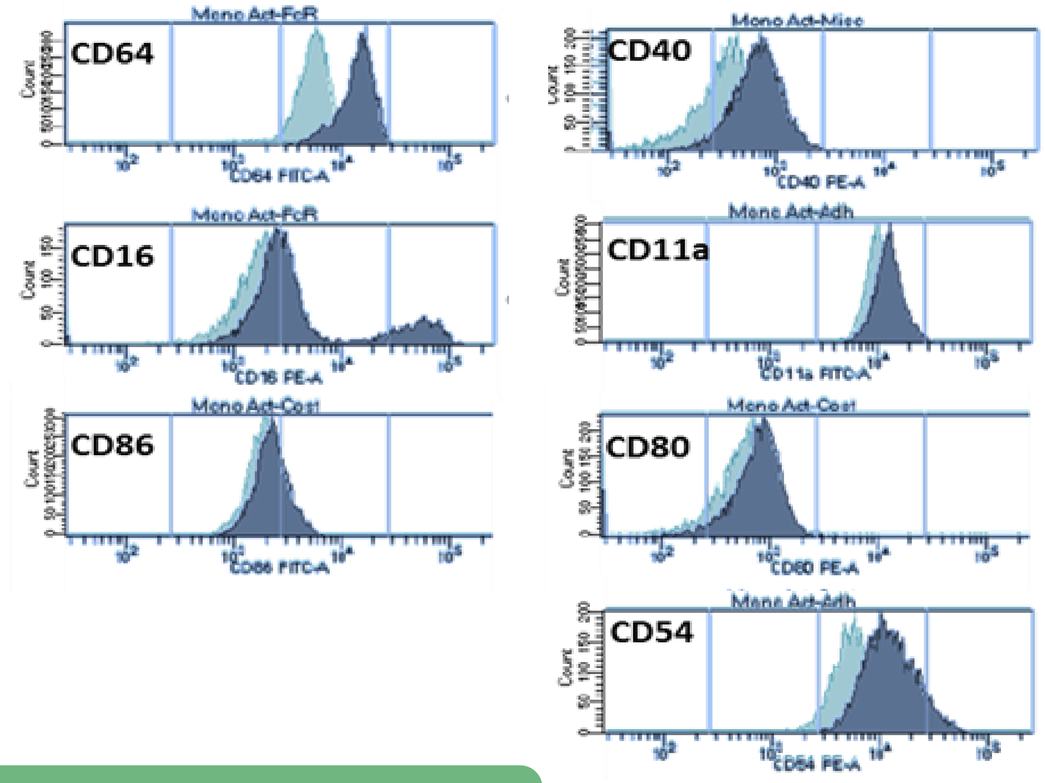
On Primary Target Cells

CD16 expression(1)



Monocyte activation marker expression(2)

Pre-efti dose 1
Post-efti dose 1

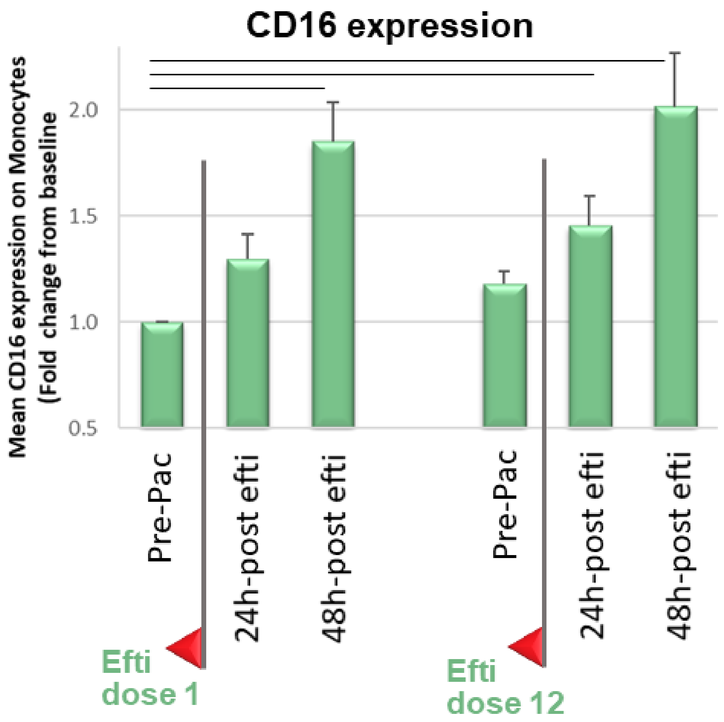


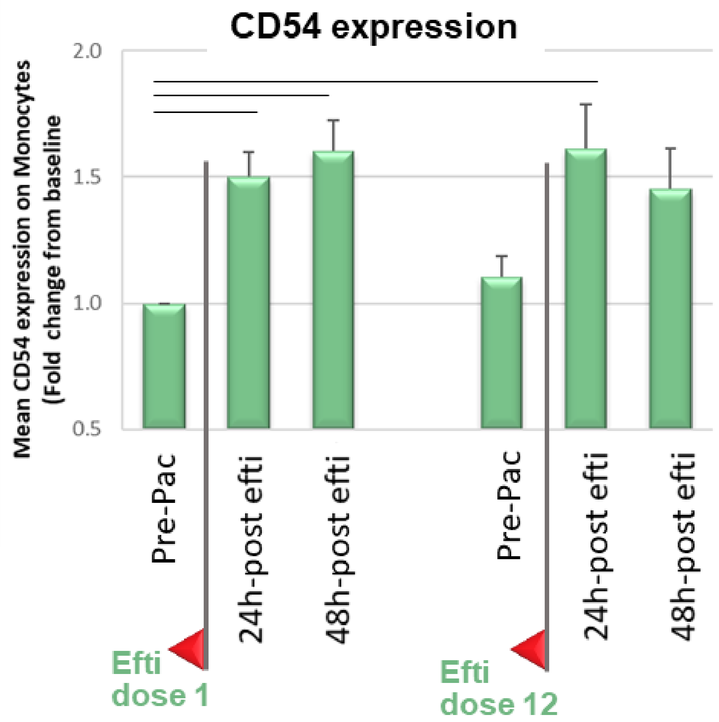
Monocytes increase their activation marker expression following efti administration

Notes:
Blood sample collected pre-efti and 48h-post efti. Ex vivo expression of activation marker on monocytes. Examples of markers expression profiles on monocytes are shown.
(1) Samples collected in INSIGHT-001 trial. Intratumoral injection of Eftilagimod monotherapy.
(2) Samples collected in INSIGHT-002 trial. Intraperitoneal injection of Eftilagimod monotherapy

PD Activity in Clinical Trials

On Primary Target Cells: Increased Activation Markers(1)





Blood samples collected pre-Pac (pre-Paclitaxel in AIPAC), pre-efti and 24h and 48h-post-efti at Cycle 1 (n=14) and Cycle 6 (n=9).
Ex vivo expression of activation markers on monocytes, shown as mean of fold change to baseline of fluorescence intensities (±SEM) for CD16 and CD54.
***p values <0.001** to the baseline (paired Wilcoxon) are displayed as black bars.*

Notes:
(1) Samples collected in run-in stage of AIPAC trial. Efti + Paclitaxel treatment in patients with metastatic breast cancer

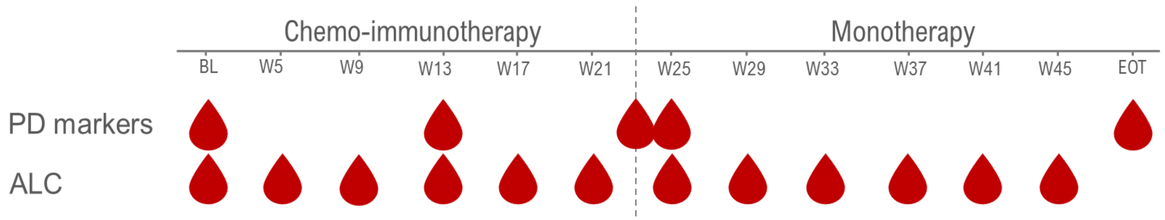
Pharmacodynamic Activity

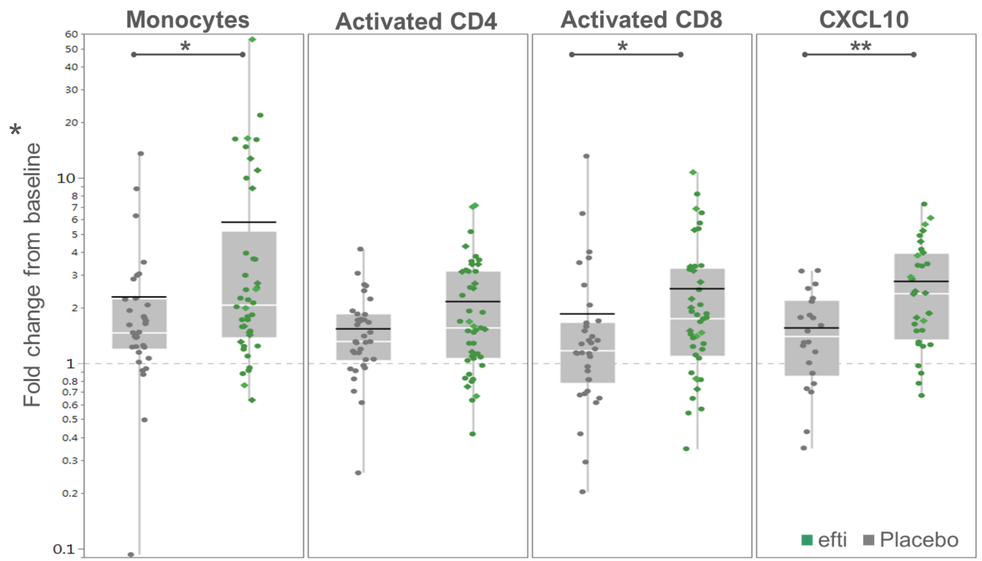
Long-term, significant increase of target cell numbers vs. placebo

PD biomarkers such as monocytes, activated CD4 and CD8 T cells and CXCL10 (IP10) were assessed by flow cytometry at a central lab.

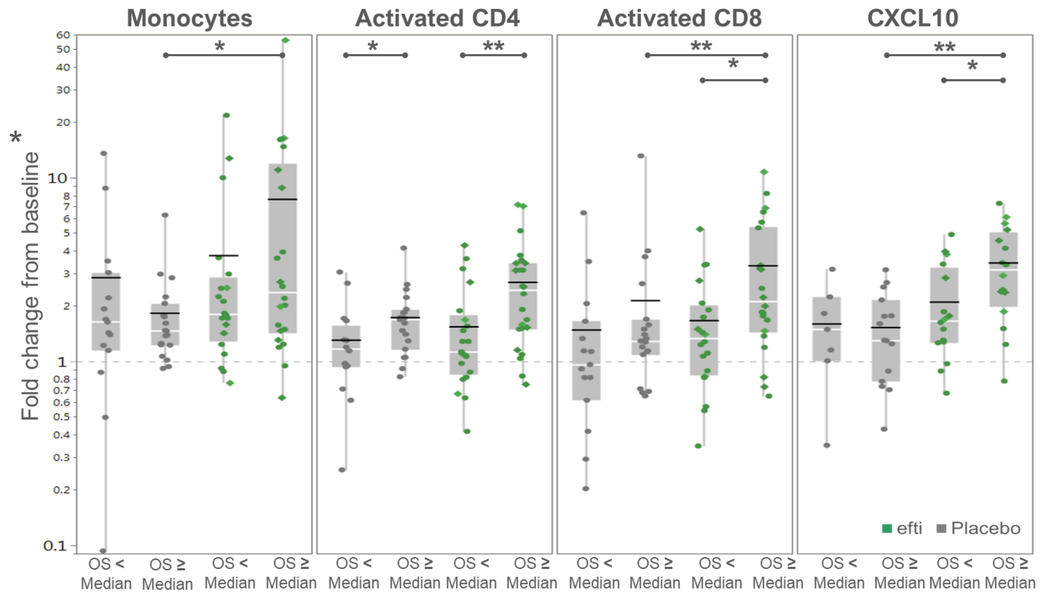
ALC measured locally at clinical sites.

Blood sampling schedule: always prior to next efti administration (D14) → minimal residual effect measured → ***Any increase means a long-term effect as efti is injected again.***





*p<0.05, ** p<0.01.



Median OS= 18.2 months; *p<0.05, ** p<0.01.

Proof of Principle

PD biomarkers significantly increased in the efti group but not in the placebo.

Proof of Concept

PD biomarkers significantly associated with improved OS in the efti group but not in the placebo.

Notes:

These results were presented at ESMO Breast 2022. Database cut-off date was May 14, 2021. Up to 80 pts included.

*The shown Fold Change are the max at any post-treatment timepoint. In Stage 1 there were samples collected shortly post dosing at C1 and at C6.

For trial design and further details on the clinical trial, please look up the AIPAC trial. Treatment: Efti + Paclitaxel vs. Placebo + Paclitaxel

Efti + anti-PD-1 Combination

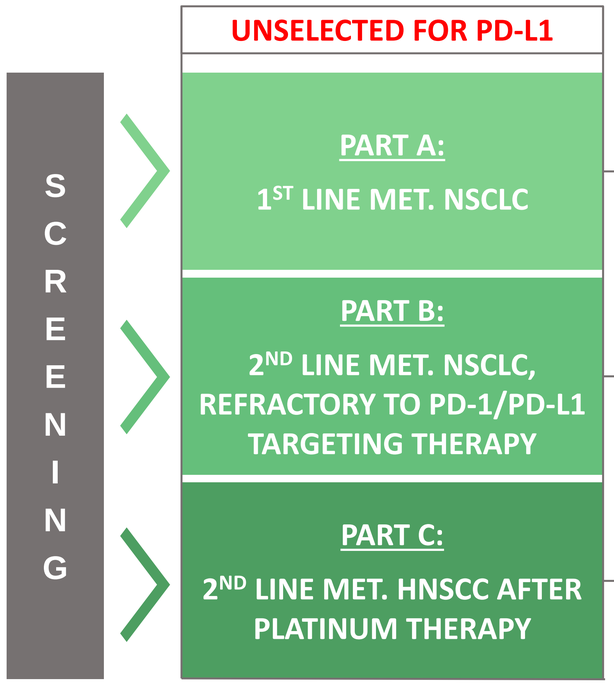
TACTI-002

“Two ACTive Immunotherapies”

Key Clinical Trials

TACTI-002 (Phase II) design & status

TACTI-002: Two ACTive Immunotherapeutics in NSCLC and HNSCC



Treatment	30 mg efti (IMP321) s.c. 200 mg pembrolizumab (Keytruda®) i.v.

COMBINED IMMUNOTHERAPY
PEMBROLIZUMAB + EFTI FOR 12 MONTHS + 12 MONTHS PEMBROLIZUMAB MONO

ORR, PFS, OS, PK, biomarker, safety and tolerability

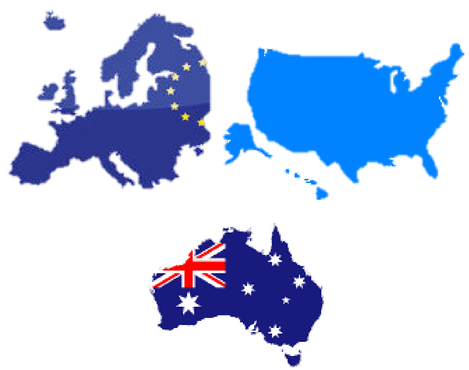
In collaboration with

MERCK
INVENTING FOR LIFE

Recruitment Status Report

- ✓ Fully approved in all countries
- ✓ Up to 189 patients in three indications
  - ✓ Part A (N=114) completed
  - ✓ Part C (N=39) completed
  - ✓ Part B (N=36) completed

Sites in Europe / US / Australia



Notes:
ORR – overall response rate, DCR – disease control rate, PFS – progression free survival, OS – overall survival, QoL – Quality of life

TACTI-002 Results(*)

1st line NSCLC (Part A) - Baseline Characteristics

- **PD-L1 distribution as expected (~70% with PD-L1 TPS < 50% expression) → PD-L1 all comer trial**
- **114 1st line NSCLC patients enrolled with expected disease characteristics**

Baseline parameters		Part A (N=114)
Age, median (range), years		67 (44-85)
Sex, n (%)	Female / Male	30 (26.3) / 84 (73.7)
ECOG PS score, n (%)	0 / 1	43 (37.7) / 71 (62.3)
Smoking status, n (%)	Current or Ex-smoker / Non-smoker	108 (94.7) / 6 (5.3)
Histology, n (%)	Squamous / Non-squamous / Unknown	40 (35.1) / 72 (63.2) / 2 (1.8)
Metastatic disease, n (%)	Yes / No	106 (93.0) / 8 (7.1)
PD-L1 expression TPS[1], n (%)	< 1% 1-49% ≥ 50% Not evaluable	37 (32.5) 40 (35.1) 31 (27.2) 6 (5.3)
Previous therapy, n (%)	Radiotherapy Surgery Systemic therapy for non-metastatic disease	38 (33.3) 23 (20.2) 25 (21.9)

[1] Central assessment of PD-L1 TPS using Dako PD-L1 IHC 22C3 pharmDx for 87 pts. For 21 pts, local assessment was used due to non evaluable central assessment results
TPS: tumor proportion score.

Notes:
(*) Preliminary data, cut-off Apr 15, 2022
ECOG… Eastern Cooperative Oncology Group
iRECIST… Immune Response Evaluation Criteria In Solid Tumors
BICR… Blinded Independent Central Review

Clinical Data

Safety Profile: efti + pembrolizumab(1)

Exposure and Safety Overview

Summary

- ISS database informing on the administration of efti 30 mg in combination with pembrolizumab comprised 110 subjects until data cut-off[1]
- Most common TEAEs were cough (26.4%) and asthenia (25.5%) which generally occurred at Grades 1 and 2.
- Most frequent Grade 3 or 4 severity TEAEs occurring in >5% of subjects were dyspnea (8.2%).
- In total, 86 local injection-site reaction events were reported in 25 subjects (22.7%).
- Immune induced adverse events appear to be not more frequent and not more severe than as with pembrolizumab monotherapy.

General safety parameters TACTI-002 Part A (1st line NSCLC) N=114

	n (%)
Any AR	80 (70.2 %)
ARs Leading to Discontinuation	**11 (9.6 %)**
ARs Leading to Death	3 (2.6 %)
ARs Grade 3 – 5	12 (10.5 %)

Treatment - Benchmarking	Toxicity AEs leading to disc.(2)
Efti + Pembro	**< 10%**
Pembro mono	**1-14%**
Doublet Chemo	**8-22%**
Doublet Chemo + Pembro	**14%**
Doublet Chemo + Atezo + Beva	**33%**
Ipi + Nivo	**18%**

Patients discontinuing in line with rate expected for pembrolizumab alone

Notes:

(1) 110 pts in the ISS safety database, cut-off Dec 2021 – IB 9.0 Mar2021

(2) For Non-small cell lung cancer. Frequencies were taken from respective publications of registrational trials.

TACTI-002 Results

1st line NSCLC (Part A)(1) - ORR

ORR – PD-L1 all comer

Response(5)	iRECIST n (%), N=114	RECIST 1.1 n (%), N=114
Complete Response	**2 (1.8)**	**2 (1.8)**
Partial Response	42 (36.8)	41 (36.0)
Stable Disease	40 (35.1)	39 (34.2)
Progression	19 (16.7)	21 (18.4)
Not Evaluable[2]	11 (9.6)	11 (9.6)
ORR, (ITT=114); [95% CI][3]	**44 (38.6); [29.6-48.2]**	**43 (37.7); [28.8-48.3]**
DCR (ITT=114); [95% CI][3]	84 (73.7); [64.6-81.5]	82 (71.9); [62.7-80.0]
ORR (EVAL[4]=103); [95% CI][3]	**44 (42.7) [33.0-52.9]**	**43 (41.8); [32.1-51.9]**
DCR (EVAL[4]=103); [95% CI][3]	84 (81.5); [72.7-88.5]	82 (79.6); [70.5-86.9]

- ORR (iRECIST - primary endpoint) of 38.6% in the ITT
- RECIST 1.1 comparable with 37.7%
- ORR of 42.7% (iRECIST) and 41.8% (RECIST 1.1) in the EVAL[4] population
- ORR (iRECIST) of 35.0% in squamous and 38.9% in non-squamous tumors

Primary Objective (ORR > 35%) achieved

[2] patients with no on-study post baseline tumor staging for any reason; [3] 95% CIs calculated using Clopper-Pearson method; [4] all patients with ≥ 1 on-study post baseline tumor staging 5- local investigator read, unconfirmed; ITT: intention-to-treat population; EVAL: evaluable population

Notes:

(1) Data cut-off Apr 15, 2022

iRECIST… Immune Response Evaluation Criteria In Solid Tumors

ORR by PD-L1 status for N=108 has also been published at ASCO22 according to local + central reed: TPS <1%: 24.3%; TPS 1-49%: 40%; TPS ≥50%: 51.6%; TPS ≥1%: 45.1%; TPS <50%: 32.5%

TACTI-002 Results

1st line NSCLC (Part A)(*) - ORR

- ORR (iRECIST) by PD-L1 (central only):
  - 28.1% in PD-L1 negative
  - 41.7% in PD-L1 1-49%
  - 52.6% in PD-L1 ≥ 50%
  - 45.5% in PD-L1 ≥ 1%
- DCR (iRECIST) with a range of 68.8-78.9% across all PD-L1 subgroups

Favourable ORR in PD-L1 low and PD-L1 negative tumors

ORR – by PD-L1 status

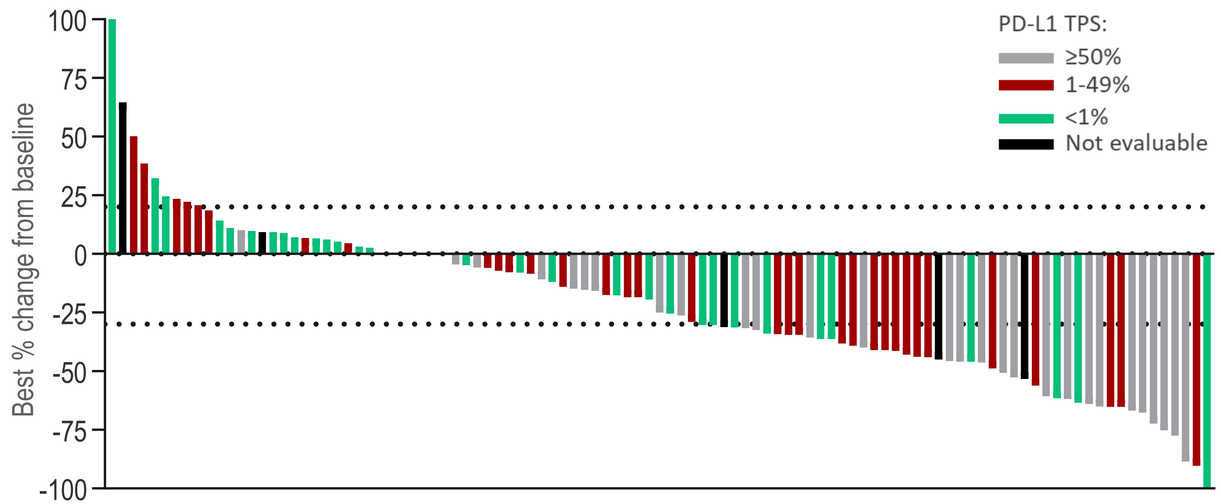
Tumor Response by central PD-L1 status (iRECIST, unconfirmed)[5], N=87	PD-L1 <1% n (%), N=32	PD-L1 1-49% n (%), N=36	PD-L1 ≥50% n (%), N=19	PD-L1 ≥1% n (%), N=55	PD-L1 <50% n (%), N=68
ORR [95% CI][6]	**9 (28.1)** [13.8-46.8]	**15 (41.7)** [25.5-59.2]	**10 (52.6)** [28.9-75.6]	**25 (45.5)** [32.0-59.5]	**24 (35.3)** [24.1-47.8]
DCR [95% CI][6]	**22 (68.8)** [50.0-83.9]	**28 (77.8)** [60.9-89.9]	**15 (79.0)** [54.4-94.0]	**43 (78.2)** [65.0-88.2]	**50 (73.5)** [61.4-83.5]

[5] Central assessment of PD-L1 TPS using Dako PD-L1 IHC 22C3 pharmDx for 87 patients.
[6] 95% CIs calculated using Clopper-Pearson method.

Notes:
* Data cut-off Apr 15, 2022
iRECIST… Immune Response Evaluation Criteria In Solid Tumors

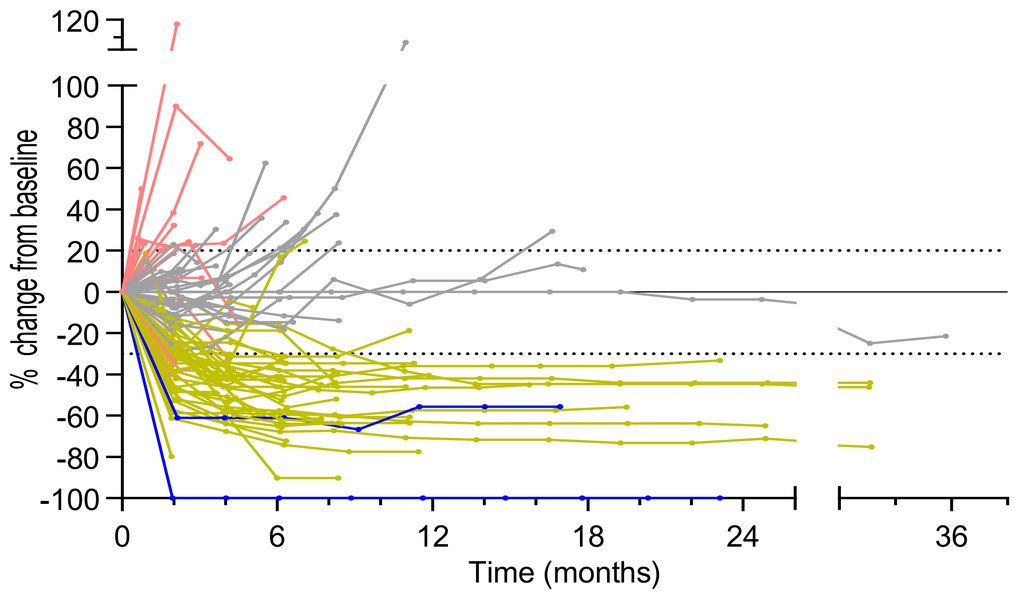
TACTI-002 Results

1st line NSCLC (Part A)(*) - Waterfall & Spider Plot



- 2 complete responses and 19.4% of patients with a target lesion decrease ≥ 50%
- 68/103 (66.0%) of patients with a post-baseline assessment had a decrease in target lesions

[1]All patients with ≥1 post-baseline CT scan n=103; [2] PD-L1 assessed by central assessment (Dako kit); n=79; [3] local assessment included due to non evaluable central assessment results, n=19; [4] no results available for neither central nor local testing, n=5.



- 80% (35/44) of responses[1] already confirmed & 5 (11.4%) pending confirmation
- 95% of patients having a response < 4 months after study start
- Responses are deep and long-lasting
- Only 8.6% of patients with confirmed response[2] progressed ≤ 6 months until data cut-off
- Median DoR not yet reached

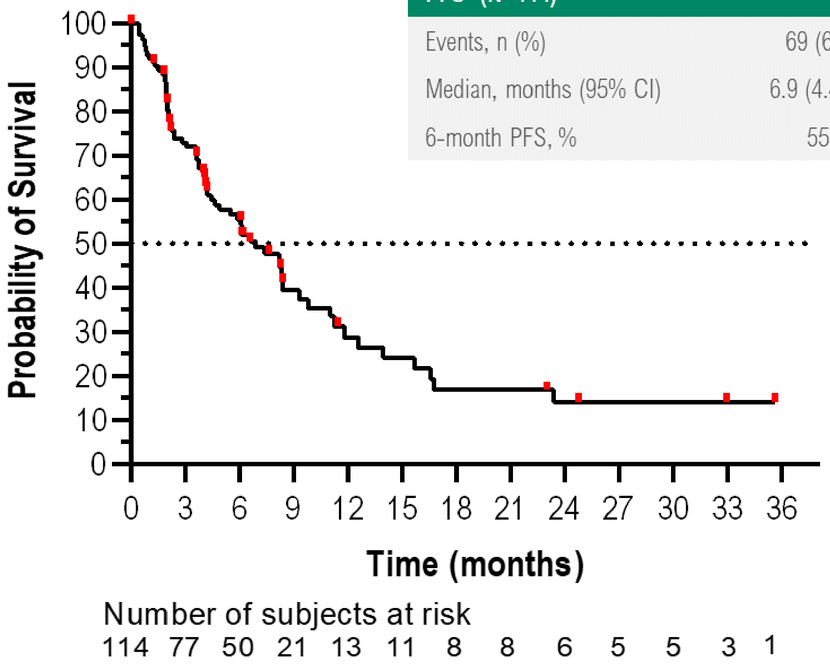
All patients with ≥1 post-baseline CT scan; n=103; iUPD: unconfirmed progressive disease; iCPD: confirmed progressive disease; iPR: partial response; iCR: complete response.
[1] by iRECIST
[2] all patients with confirmed response by iRECIST

Notes:
* Data cut-off Apr 15, 2022
iRECIST… Immune Response Evaluation Criteria In Solid Tumors

TACTI-002 Results

1st line NSCLC (Part A)(*) - PFS

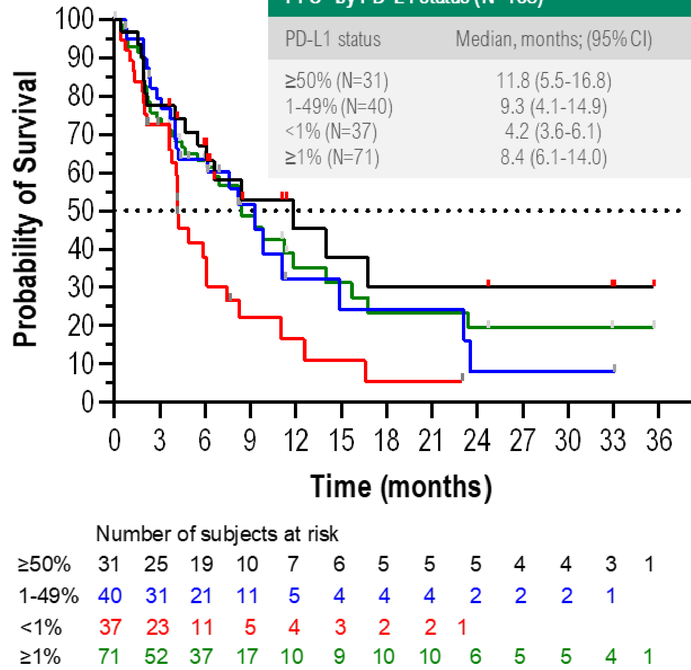
PFS ITT population (N=114)(*)



PFS[1] (N=114)	
Events, n (%)	69 (60.5)
Median, months (95% CI)	6.9 (4.4-8.4)
6-month PFS, %	55.4

- Interim median PFS(*) in the ITT (unselected for PD-L1) was 6.9 (95% CI: 4.4-8.4) months

PFS by PD-L1 status (N=108)(*, 1)



PFS[1] by PD-L1 status (N=108)		
PD-L1 status	Median, months; (95% CI)	Events, n (%)
≥50% (N=31)	11.8 (5.5-16.8)	16 (51.6)
1-49% (N=40)	9.3 (4.1-14.9)	23 (57.5)
<1% (N=37)	4.2 (3.6-6.1)	27 (73.0)
≥1% (N=71)	8.4 (6.1-14.0)	39 (54.9)

- Interim median PFS(1) in PD-L1 ≥ 1% was 8.4 (95% CI: 6.1-14.0) months and 11.8 (5.5-16.8) months in PD-L1 ≥ 50%

Notes:

* Data cut-off Apr 15, 2022; *By iRECIST… Immune Response Evaluation Criteria In Solid Tumors*

(1) Central assessment as per footnote 1 for 87 patients. For 21 patients, local assessment was used due to non evaluable central assessment results.

Summary & Conclusion

- ORR (iRECIST) of 38.6% (95% CI: 29.6-48.2) in 1st line NSCLC patients (ITT) unselected for PD-L1.
- Comparable results acc. to RECIST 1.1 for ORR with 37.7% (95% CI: 28.8-48.3) in the ITT.
- Promising ORR compared to historical control (KN-042[1]).
- Responses are deep and durable (< 10% of confirmed PRs progressed ≤ 6 months).
- In a PD-L1 unselected (incl. PD-L1 neg. + PD-L1 low tumors) population median PFS of 6.9 months [95% CI 4.4-8.4] is promising.
- Treatment with efti plus pembrolizumab is safe and well-tolerated (< 10% discontinuing due to study treatment-related TEAEs).

Conclusion: efti + pembrolizumab shows encouraging efficacy in 1st line PD-L1 unselected NSCLC patients and warrants late-stage clinical investigation

Notes:

(1) Mok et al, The Lancet 2019, http://dx.doi.org/10.1016/S0140-6736(18)32409-7

immutep
LAG-3 IMMUNOTHERAPY

Thank You

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Non-Small Cell Cancer Drug Development Summit

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