A soluble LAG-3 protein (eftilagimod alpha) with an anti-PD-1 antibody (pembrolizumab): results of a phase II study in NSCLC

Frédéric Triebel MD, PhD

Non-Small Cell Cancer Drug Development Summit
Virtual meeting, July 15th 2021

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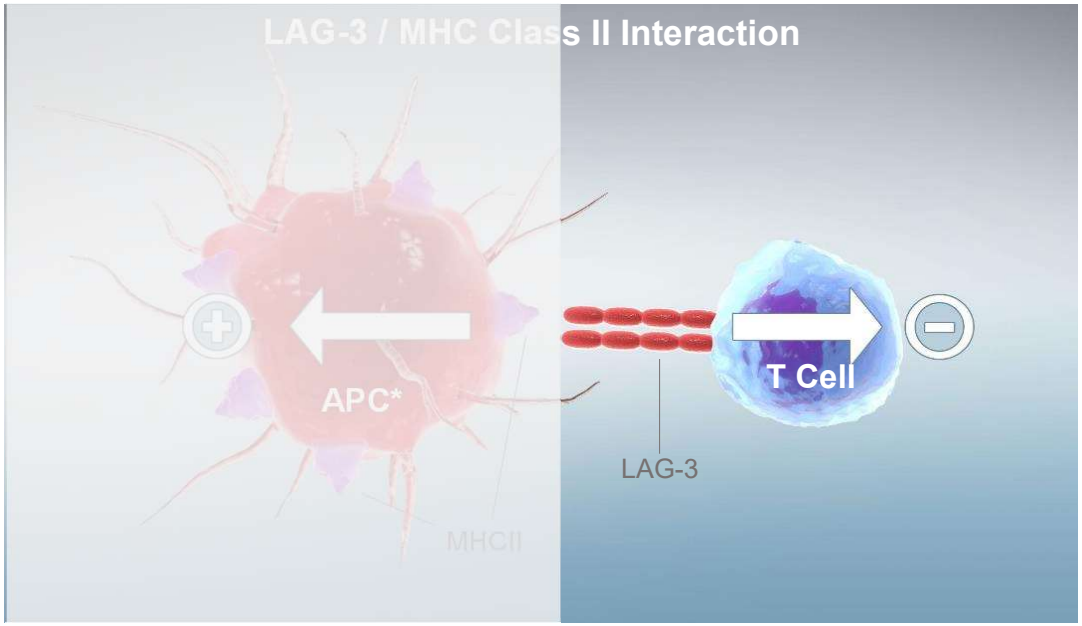
MHC II / LAG-3 Interaction as a Therapeutic Target

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 antigen presenting cells (APCs)

→ **Prime target for immune therapy**



Negative regulation of LAG-3⁺ T Cells

- Relatlimab + 15 more products in clinical development
- Clinical validation at ASCO 2021 (RELATIVITY-047 - relatlimab + nivolumab in melanoma)

Positive regulation of antigen presenting cells (**APCs**) via MHC II transferred activating signals → increase in antigen presentation to cytotoxic CD8⁺ T cells

MHC II (APC) / LAG-3 (T cell) interaction is important for tumor immunology

This APC / T cell interaction is now a validated target since ASCO 2021 → 3rd validated checkpoint in immuno-oncology

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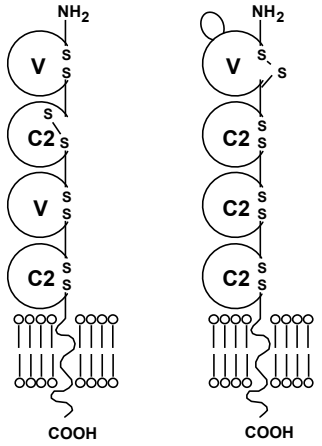
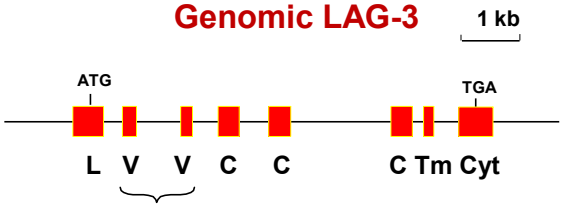
LAG-3 IMMUNOTHERAPY

What is LAG-3?

Lymphocyte Activation Gene-3
(LAG-3 or CD223)





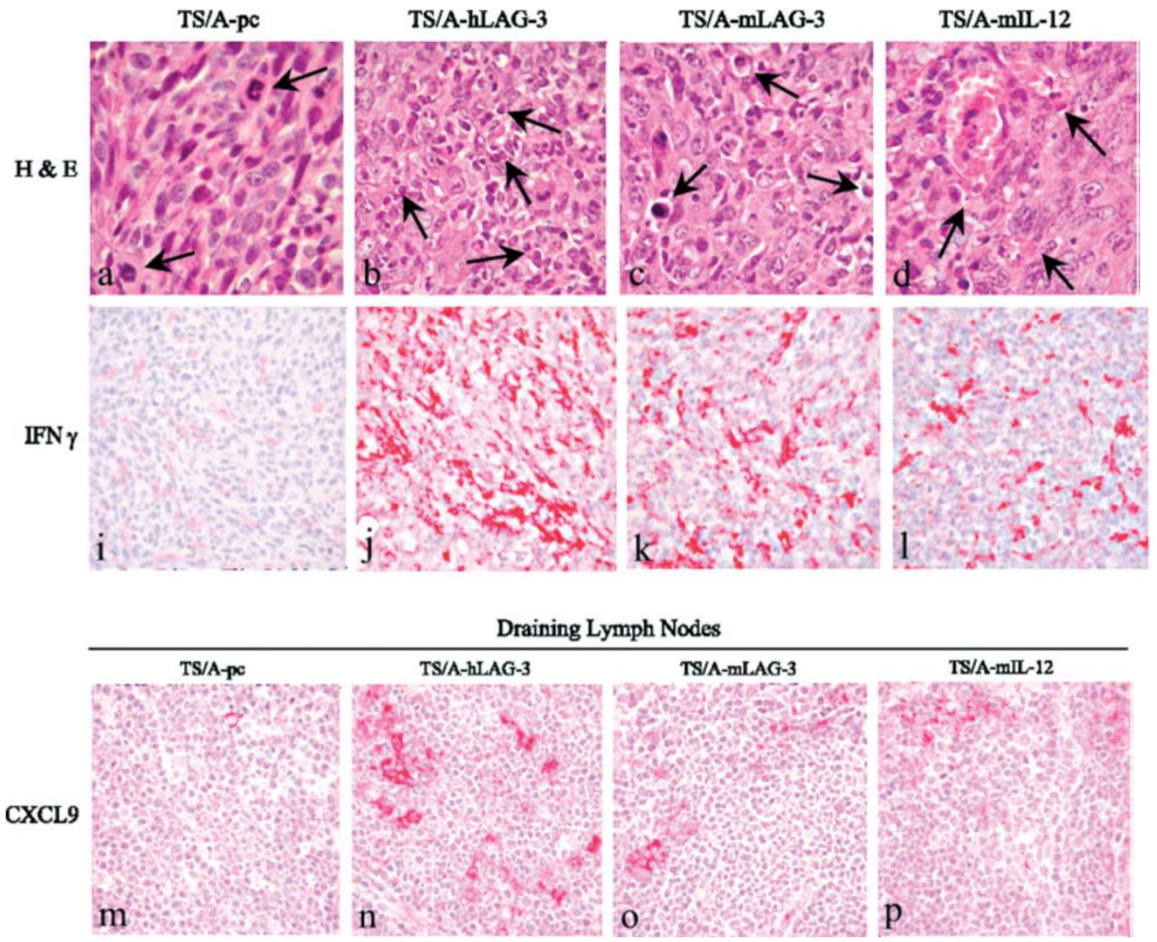
- 4-IgSF domain transmembrane proteins.
- Same genomic organization
  (intron in D1, duplication event D1D2 vs D3D4).
- Close proximity on 12p13.
- Share the same ligands (MHC class II)

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

Immunological mechanisms elicited at the tumour site by LAG-3 versus IL-12: sharing a common Th1 anti-tumour immune pathway

The mammary adenocarcinoma TS/A tumor is rejected in mice when TS/A cells express hLAG-3, mLAG-3 or mIL-12 (positive control).

TS/A-pc: untransfected parental cells (negative control).



J Pathol 2005; 205: 82–91

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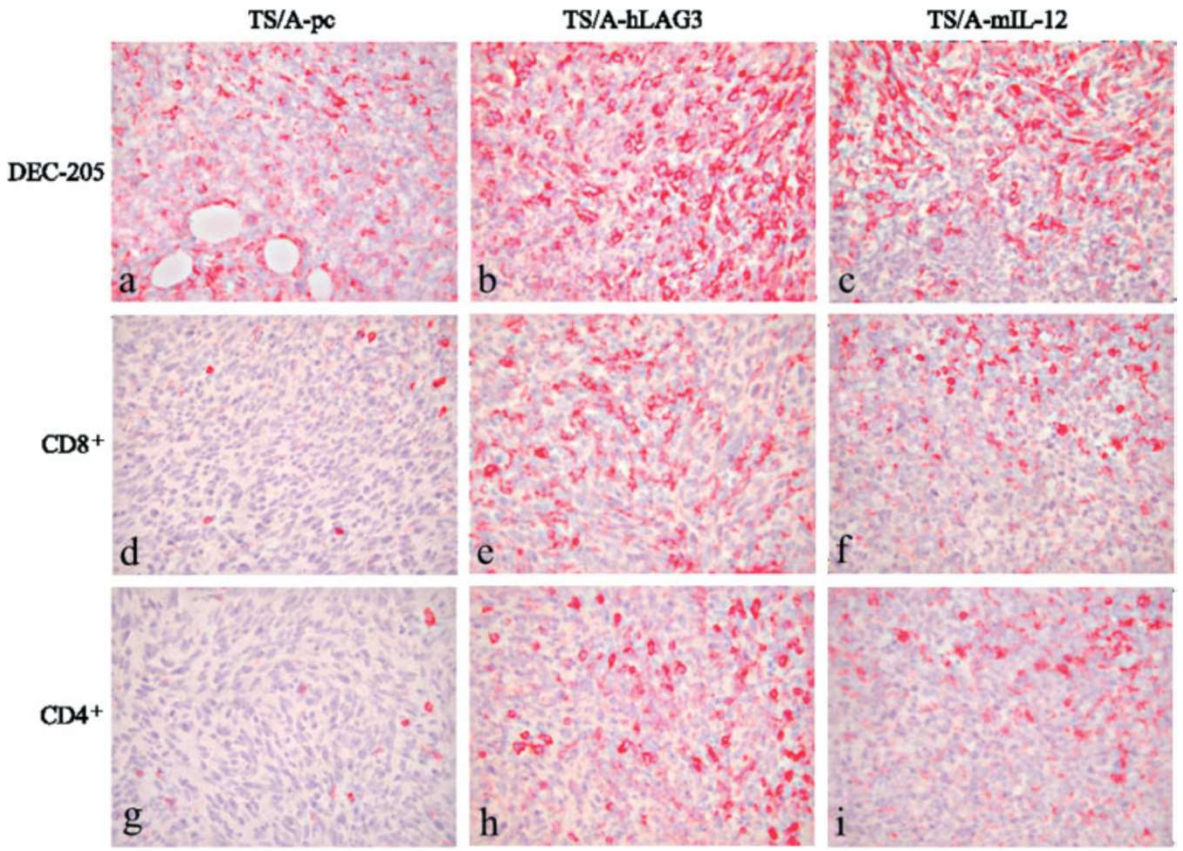

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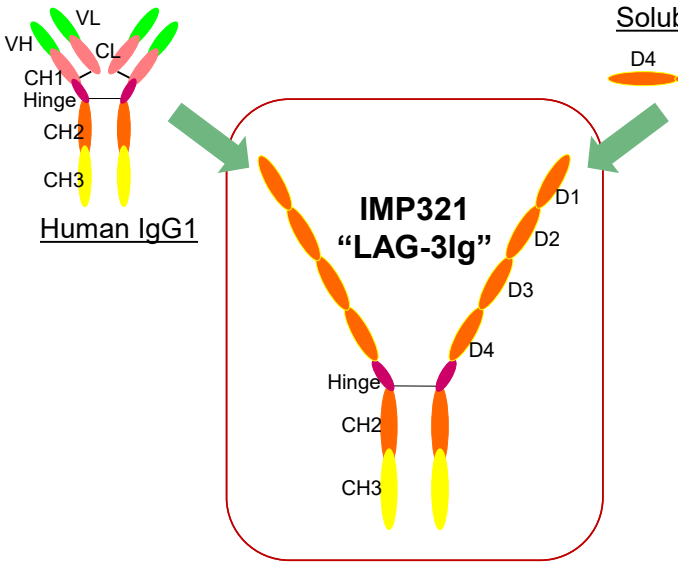
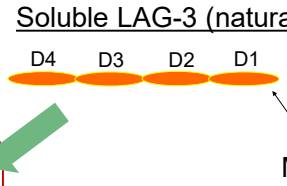
LAG-3 IMMUNOTHERAPY

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

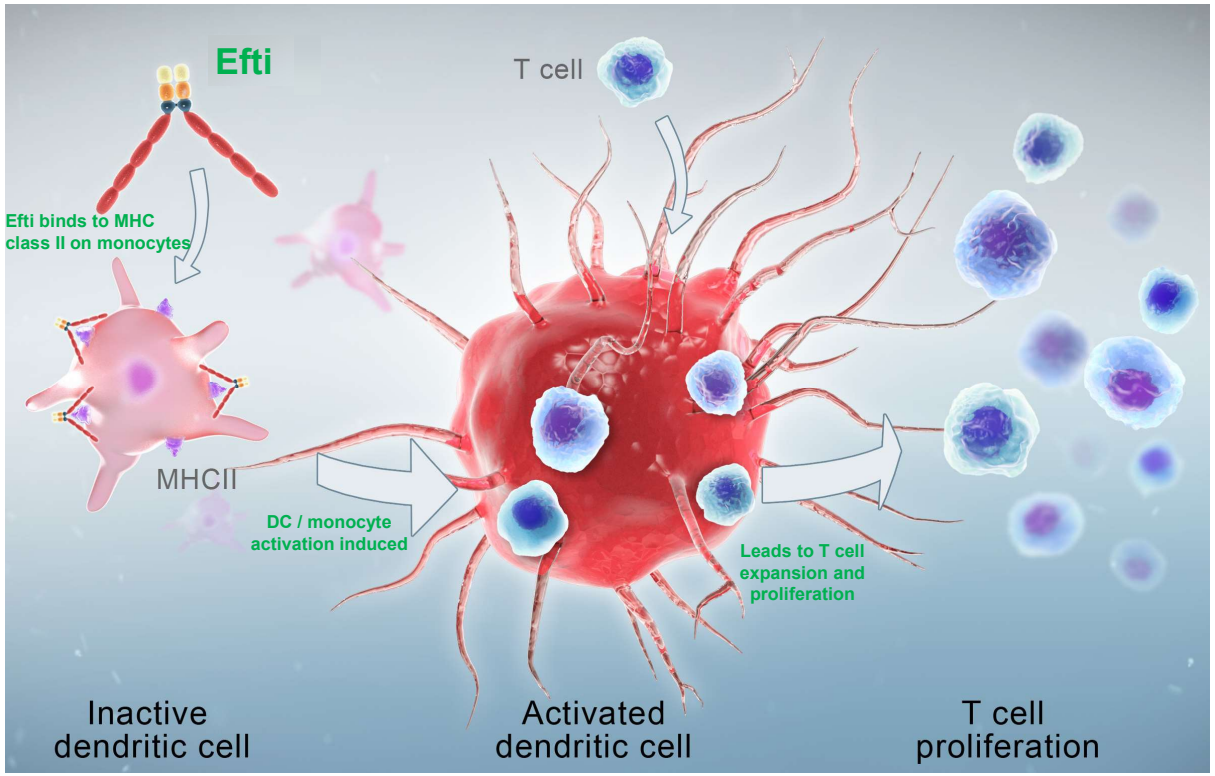




- Dimeric, very stable, high affinity for dendritic cells
- Antigen presenting cell (APC) activator
- Unique mechanism of action and first-in-class

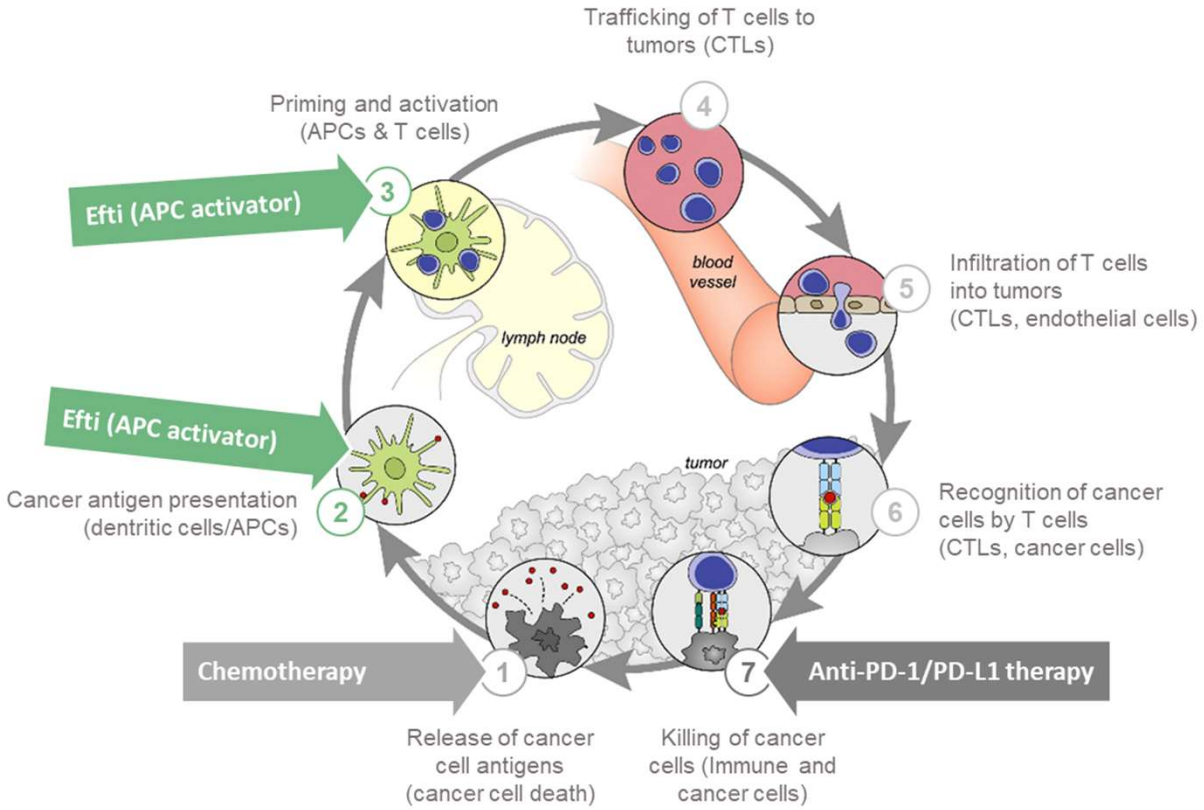
Efti: Mechanism of Action (MoA)

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

The synergistic benefit of APC activation in combination with ICI



Therapeutic interventions leading to increased T cell responses in cancer. The Cancer Immunity Cycle. Adapted from Chen and Mellman (1).

"Pushing the gas pedal"

- Efti induces **sustained APC activation** → boost the effector memory CD8 compartment to a more tumor-aggressive TH1-driven phenotype

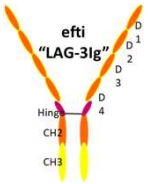
"Releasing the brakes"

- The efti induced **sustained increase of activated CD8 T cells** and elevated **IFNγ** levels → enable ICI (immune checkpoint inhibitors) to exert their effect
- Two active immunotherapies will together create a synergistic benefit to patient groups with cold and tepid tumors

Notes:

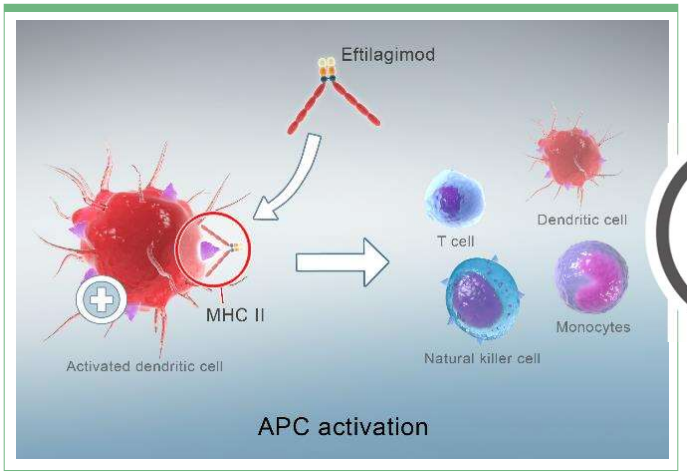
Chen, D. S., and I. Mellman. 2013. Oncology meets immunology: the cancer-immunity cycle. *Immunity* 39: 1-10.

Efti: an Innovative LAG-3 I-O Product Candidate



- Efti is a soluble LAG-3 protein targeting a subset of MHC class II on APC
- Potentially synergistic with other therapeutic agents e.g. immuno-oncology (I-O) agents & chemotherapies

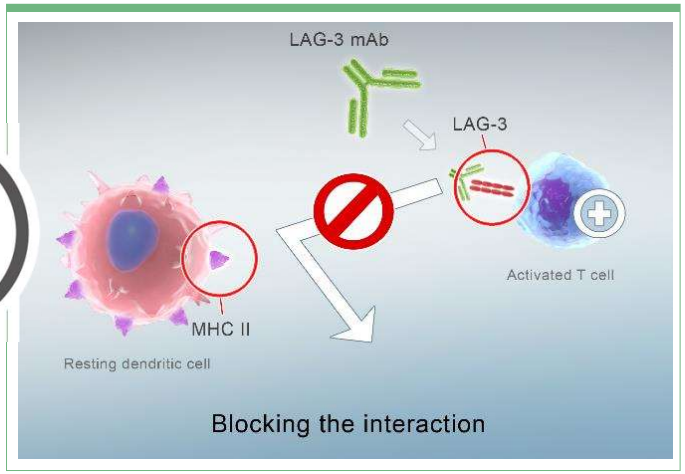
"PUSHING THE ACCELERATOR ON IMMUNE RESPONSES"



Efti is an **MHC II agonist:**
APC activator

- boost and sustain the $CD8^+$ T cell responses
- activate multiple immune cell subsets

"RELEASING THE BRAKE ON THE T CELL"



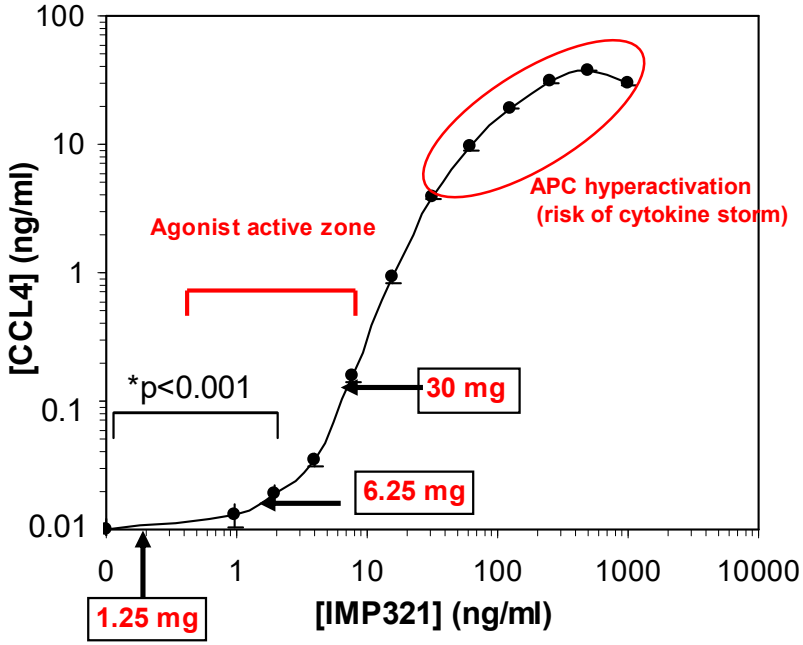
LAG-3 antagonist (blocking) antibodies:
Immune checkpoint inhibitor

- increase cytotoxicity of the pre-existing CD8 T cell response

Efti as an MHC class II agonist

In vitro bioactivity of efti (IMP321). IMP321 potency to induce CCL4 (MIP-1β) secretion was tested using the MHC class II$^+$ human monocytic THP-1 cells. The results are presented as concentration of CCL4 produced in supernatant after 4hrs of culture (mean of 5-plicate determinations ± SD) as a function of IMP321 concentration on a logarithmic scale. The lowest concentration of IMP321 inducing a response statistically different from the baseline is indicated.

The concentrations found in the serum of patients 2hr after s.c. injection of 1.25, 6.25 and 30 mg in patients are indicated by arrows.



Efti: Potential Pipeline in a Product

Potential for use in various combination settings

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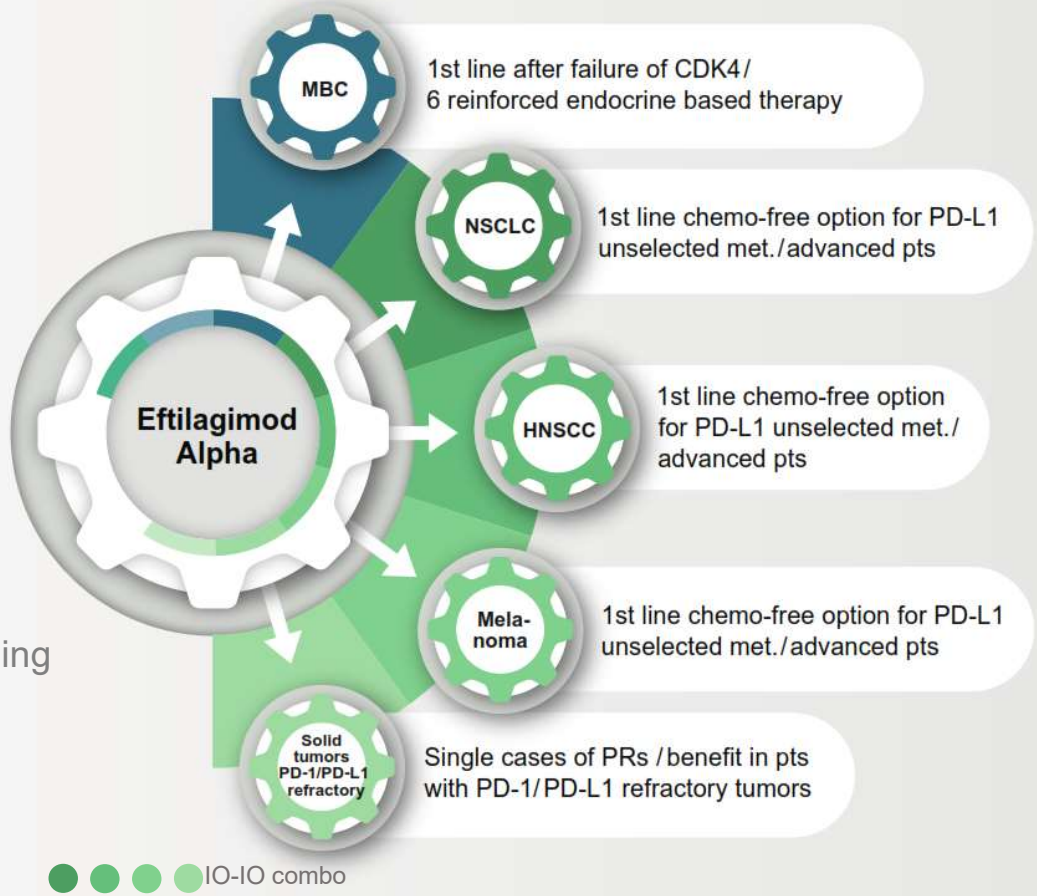
- Unique MHC II agonist
- Excellent safety profile
- Encouraging efficacy data
- Low cost of goods
- Unique protective IP positioning (unlike ICI mAbs)



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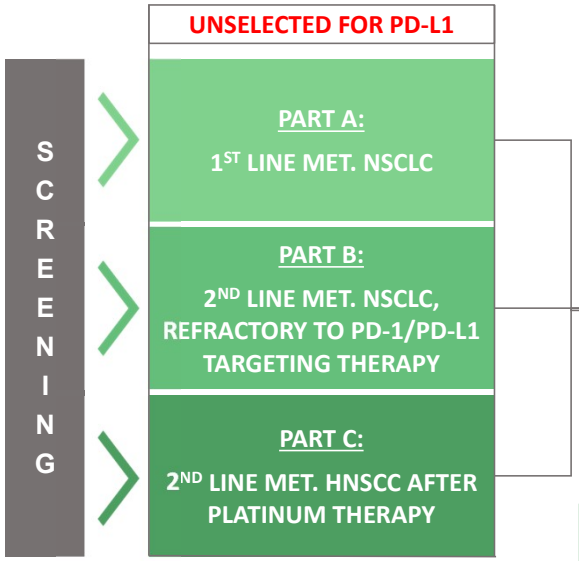
Efti + anti-PD-1 Combination

TACTI-002

“Two ACTive Immunotherapies”

TACTI-002 (Phase II)
Design & Status

TACTI-002: Two ACTive Immunotherapeutics in NSCLC and HNSCC



In collaboration with Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA

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

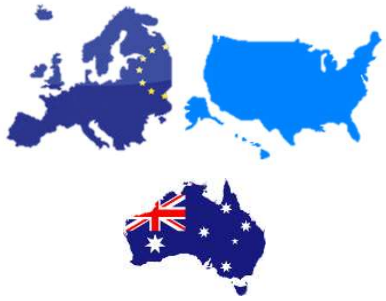
ORR, PFS, OS, PK, biomarker, safety and tolerability

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

Status Report

- ✓ Fully approved in all countries
- ✓ Up to 183 patients in three indications
  - Part A (N=36) completed; extension (N=74 recruiting)
  - ✓ Part C (N=39) completed
  - Part B (N=36); stage 2 recruitment ongoing

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 (Phase II)
Safety

Efti + Pembro combination has a favourable safety profile

Summary TACTI-002
(N=115 in total)

- No (0%) treatment-related death
- 4 (3.5%) subjects with treatment (efti and/or pembro) related adverse events leading to discontinuation
- 57 pts (49.6%) had ≥ 1 adverse events ≥ grade 3
- No new safety signals of this combination identified until cut-off

Selected safety aspects of other treatment regimens

Regimen[2]	Treatment related adverse events leading to discontinuation	Treatment related adverse events leading to death
Double Chemo	8-22%	1-6%
Ipi + Nivo	20%	< 2%
Chemo + Pembro	23-33%	3-8%
Pembro alone	10-15%	< 2%

✓ **Efti + pembrolizumab combination has a very good safety profile**

✓ **Favorable compared to any combination which included chemotherapy**

Notes:
(1) Preliminary data, cut-off 16-Apr 2021
(2) Source: Calculated from corresponding publications e.g.: Checkmate-227; Keynote-40/189/407/48;

TACTI-002 Results(1)

1st line NSCLC (Part A)

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- ***PD-L1 distribution as expected (~70% with < 50% PD-L1 expression) → PD-L1 all comer trial***
- ***Patients are typical NSCLC 1st line pts***

Baseline parameters	N (%)
Age (years), median (range)	68.5 (53-84)
Female Male	11 (30.6) 25 (69.4)
ECOG 0 ECOG 1	15 (41.7) 21 (58.3)
Current / Ex-smokers Non-smokers	34 (94.4) 2 (5.6)
Squamous pathology Non-squamous pathology	15 (41.7) 21 (58.3)
Patients with liver metastasis	14 (38.9)

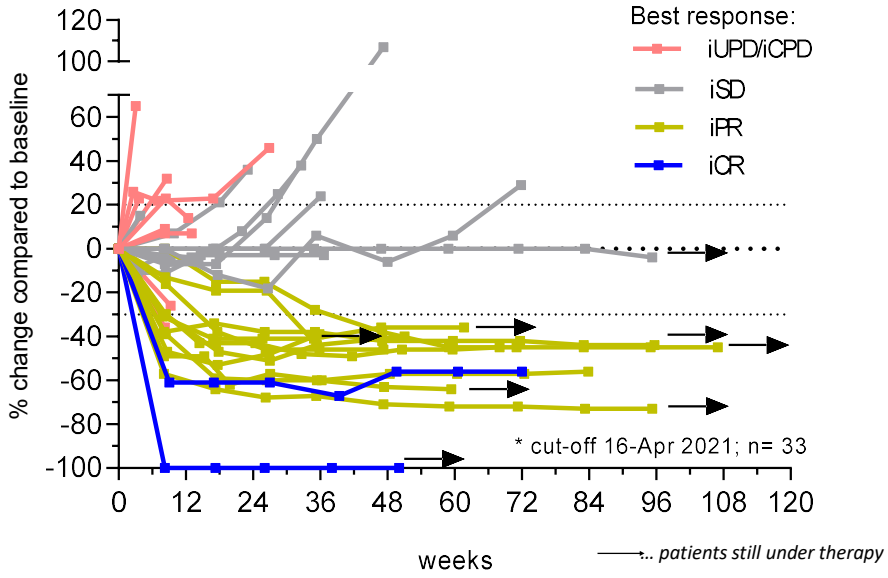
Best overall response, iRECIST, N = 36	Local Read (investigator) N (%)	Blinded Read (BICR) N (%)
Complete Response	**2 (5.6)**	**2 (5.6)**
Partial Response	11 (30.6)	13 (36.1)
Stable Disease	11 (30.6)	10 (27.8)
Progression	8 (22.2)	6 (16.7)
Not Evaluable**	4 (11.1)	5 (13.9)
Disease Control Rate	24 (66.7)	25 (69.4)
Overall Response Rate* [95% CI interval]	**13 (36.1) [20.8-53.8]**	**15 (41.7) [25.5-59.2]**
Overall Response Rate – Evaluable pts* [95% CI interval]**	**13 (40.6) [23.7-59.4]**	**15 (48.4) [30.1-60.9]**

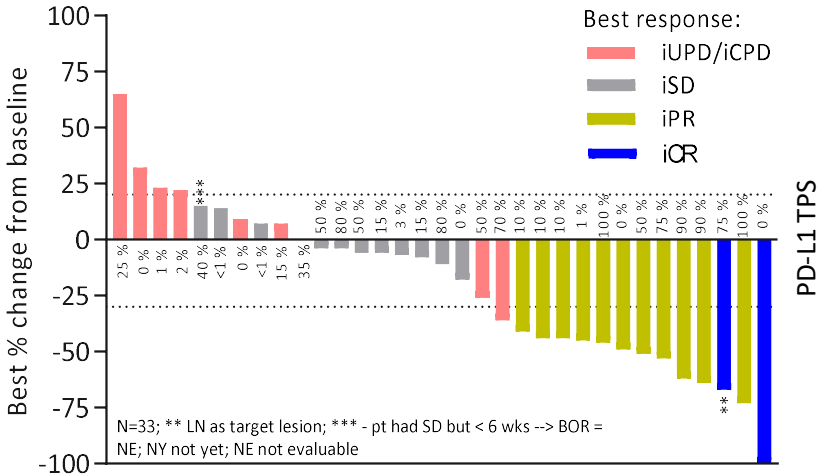
** - All patients stage 1 and 2 (N=36) with* ≥ 1 treatment
*** - dropped off prior to first staging or were not evaluable post-baseline for any reason*
**** - Evaluable for efficacy meaning* ≥ 1 treatment and ≥ 1 post baseline tumor staging

Notes:
(1) Preliminary data, cut-off Apr 16, 2021
ECOG… Eastern Cooperative Oncology Group
iRECIST… Immune Response Evaluation Criteria In Solid Tumors
BICR… Blinded Independent Central Review

TACTI-002 Results(1)

1st line NSCLC (Part A)





Duration of response (DoR)

- 92% responses confirmed
- 58% confirmed responses ongoing with 6+ months
- 42% of confirmed responses progressed after 6.5-13.8 months
- Median DoR estimated 13+ months

- Responses at all PD-L1 levels including 1 Complete Response with TPS of 0%
- At data cut-off, 7 pts still under therapy and 1 patient completed the 2 years of therapy

(1) Preliminary data, cut-off Apr 16, 2021
Graphs represent all patients with at least one post baseline assessment. One patient has no official RECIST assessment as this was done < 6 weeks and this does not qualify according to RECIST. Per local investigator assessment.
iRECIST… Immune Response Evaluation Criteria In Solid Tumors

TACTI-002: Phase II of efti and pembrolizumab in 1st line metastatic NSCLC (Part A)
CONCLUSION

SAFETY

- Treatment with efti plus pembrolizumab is well-tolerated with no new safety signals
- 4 % of patients discontinued treatment due to AEs related to efti/pembrolizumab
- Most frequent AEs include general symptoms frequently occurring in a NSCLC patient population
- Majority of most frequent adverse events are mild to moderate
- Safety profile is similar to KN-042 (pembrolizumab monotherapy)

EFFICACY

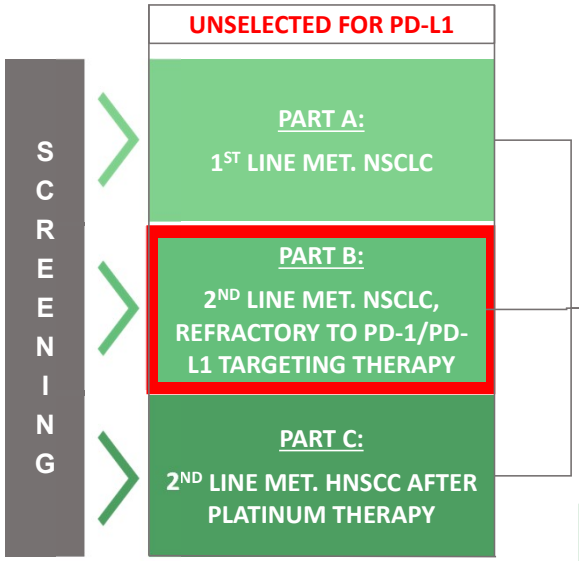
- Encouraging ORR (41.7 % by BICR) in patients unselected for PD-L1
- Median PFS (8.2 months) in patients unselected for PD-L1 is encouraging for a chemo-free 1st line regimen
- Responses observed in all PD-L1 subgroups and responses are durable
- ORR in each PD-L1 subgroup report favorable compared to KN-042 (pembrolizumab monotherapy, PIII randomized trial)

The combination of efti plus pembrolizumab is well-tolerated, showing encouraging signs of activity supporting further clinical investigation. An extension of the study is ongoing.

TACTI-002 (Phase II)

Part B: a difficult to treat population

TACTI-002: Two ACTive Immunotherapeutics in NSCLC and HNSCC



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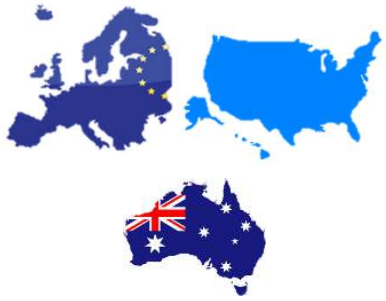

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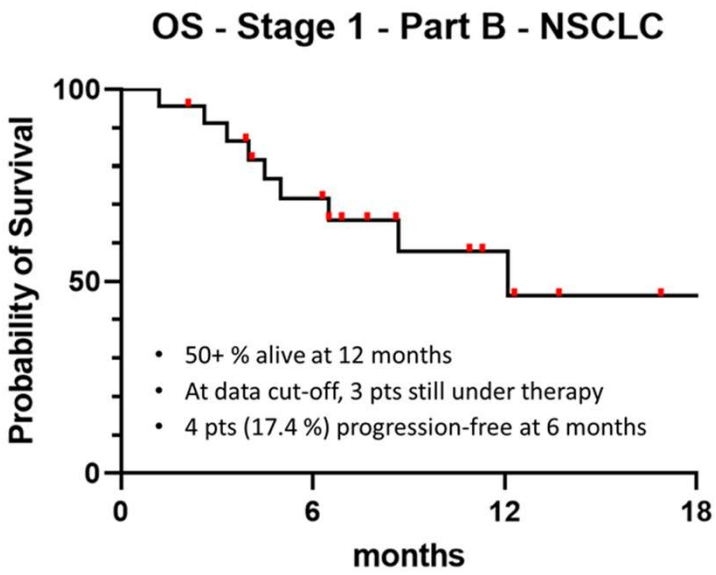
TACTI-002
Results[1] – 2nd line NSCLC PD-X refractory/resistant (Part B)

Enrolment to stage 1 completed Q3 2020

Baseline Characteristics	Stage 1 (N=23) N (%)
Median age, years (range)	67.0 (46-84)
Female Male	10 (43.5) 13 (56.5)
ECOG 0 ECOG 1	7 (30.4) 16 (69.6)
Current or Former smoker	21 (91.3)
Squamous Non-squamous	5 (21.7) 18 (78.3)
Prior PD-1/PD-L1 with chemotherapy	100 % 61 %

Tumor response (RECIST 1.1)	Stage 1 (N=23) N (%)
Partial Response	**1 (4.4)**
Stable Disease	7 (30.4)
Progression	14 (60.9)
Not Evaluable**	1 (4.4)
Overall Response Rate [95 % CI interval]	**1 (4.4) [0.11 – 21.95]**
Disease Control Rate	8 (34.8)



- All pts had confirmed PD on first-line ICI
- 1PR; five pts with target lesion decrease
- Additional 3 pts SD for >6 months → ~17 % disease stability for >6 months
- median OS of 12 months → favorable compared to chemo and better tolerated

Notes:
(1) Preliminary data, cut-off 15 Oct 2020

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Thank You

Frédéric Triebel MD, PhD

Non-Small Cell Cancer Drug Development Summit

Virtual meeting, July 15th, 2021