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LAG-3 IMMUNOTHERAPY

Combining a soluble LAG-3 protein with an anti-PD-1 antibody in phase I-II trials

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Advanced Therapies and Regenerative Medicine

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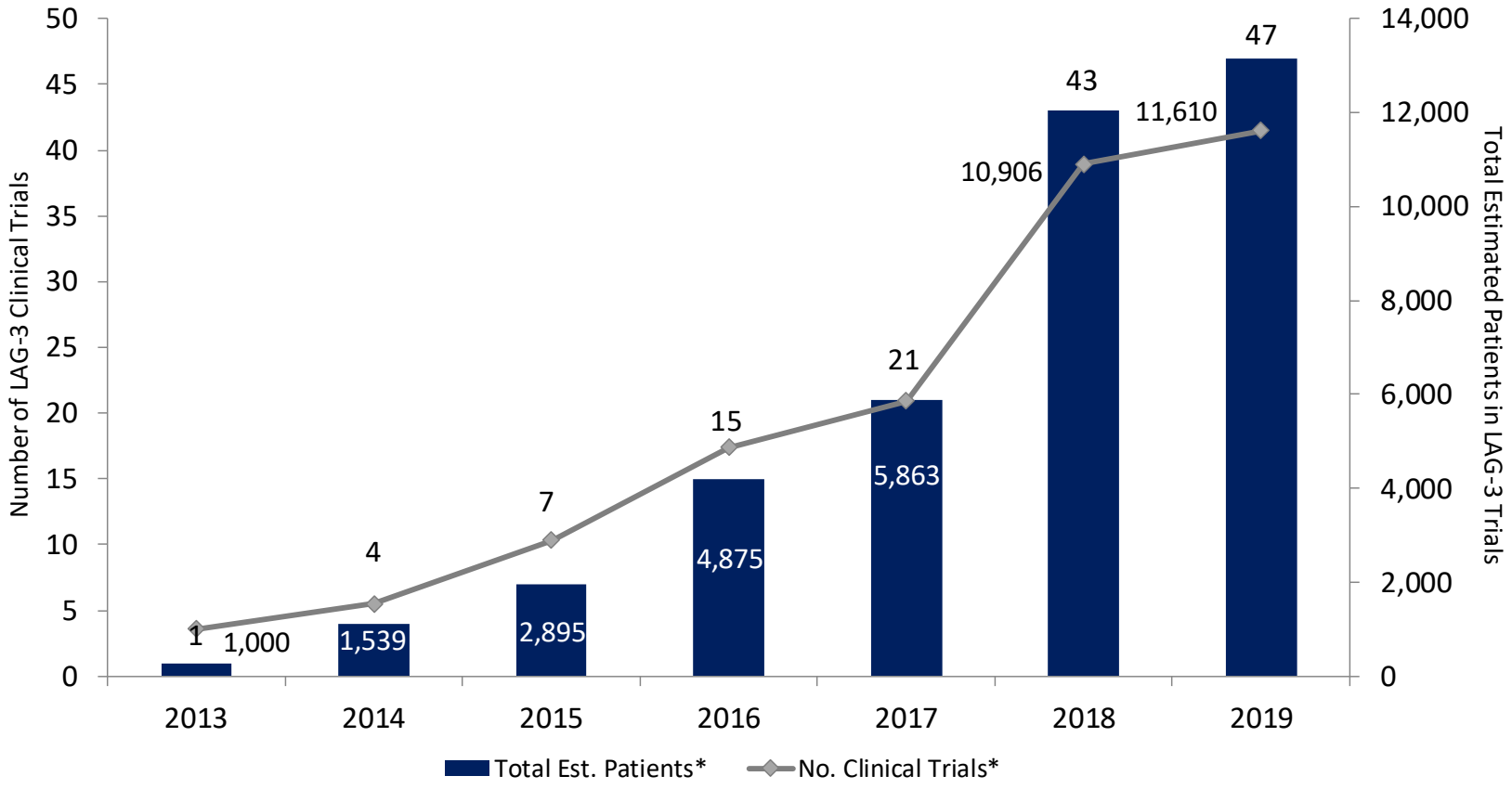
Increasing Clinical Trials Targeting LAG-3

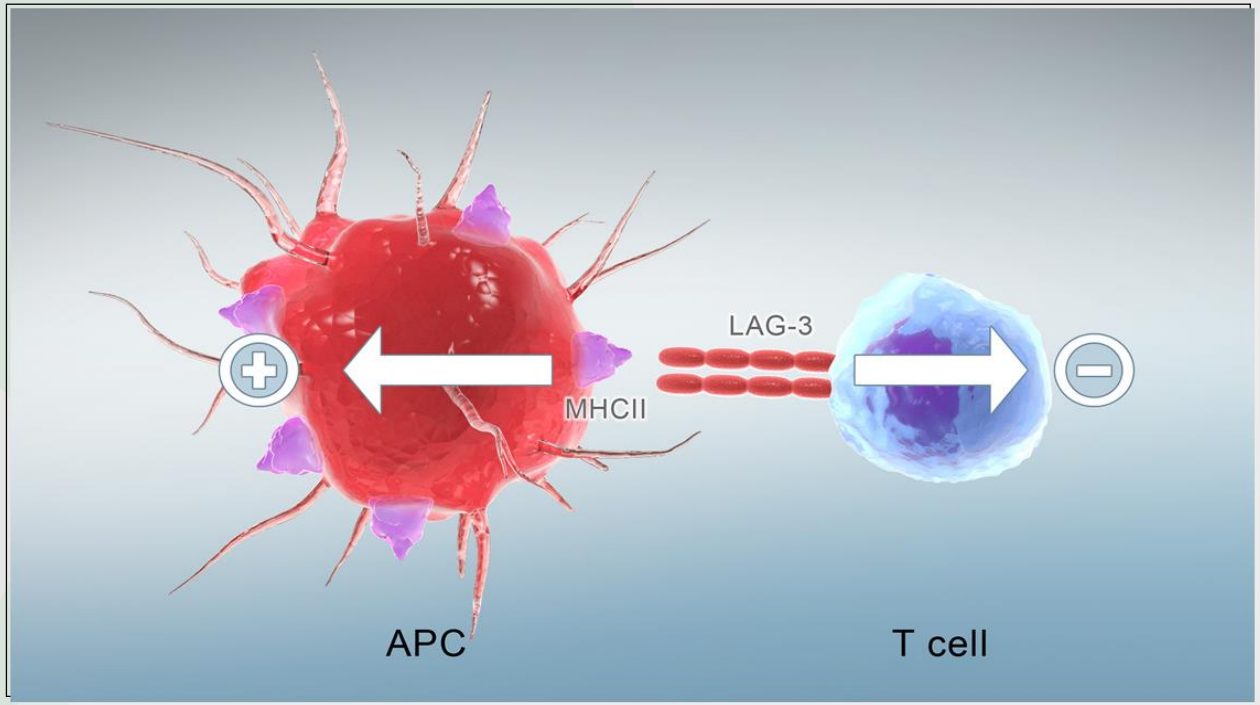
Industry increasingly deploying resources to development of LAG-3 therapeutics



Sources: GlobalData, company websites, clinical trials.gov, and sec.gov
Information as of January 3, 2019
*2019 includes planned and completed trials, includes trials where the company may not be the sponsor

LAG-3 as a Therapeutic Target

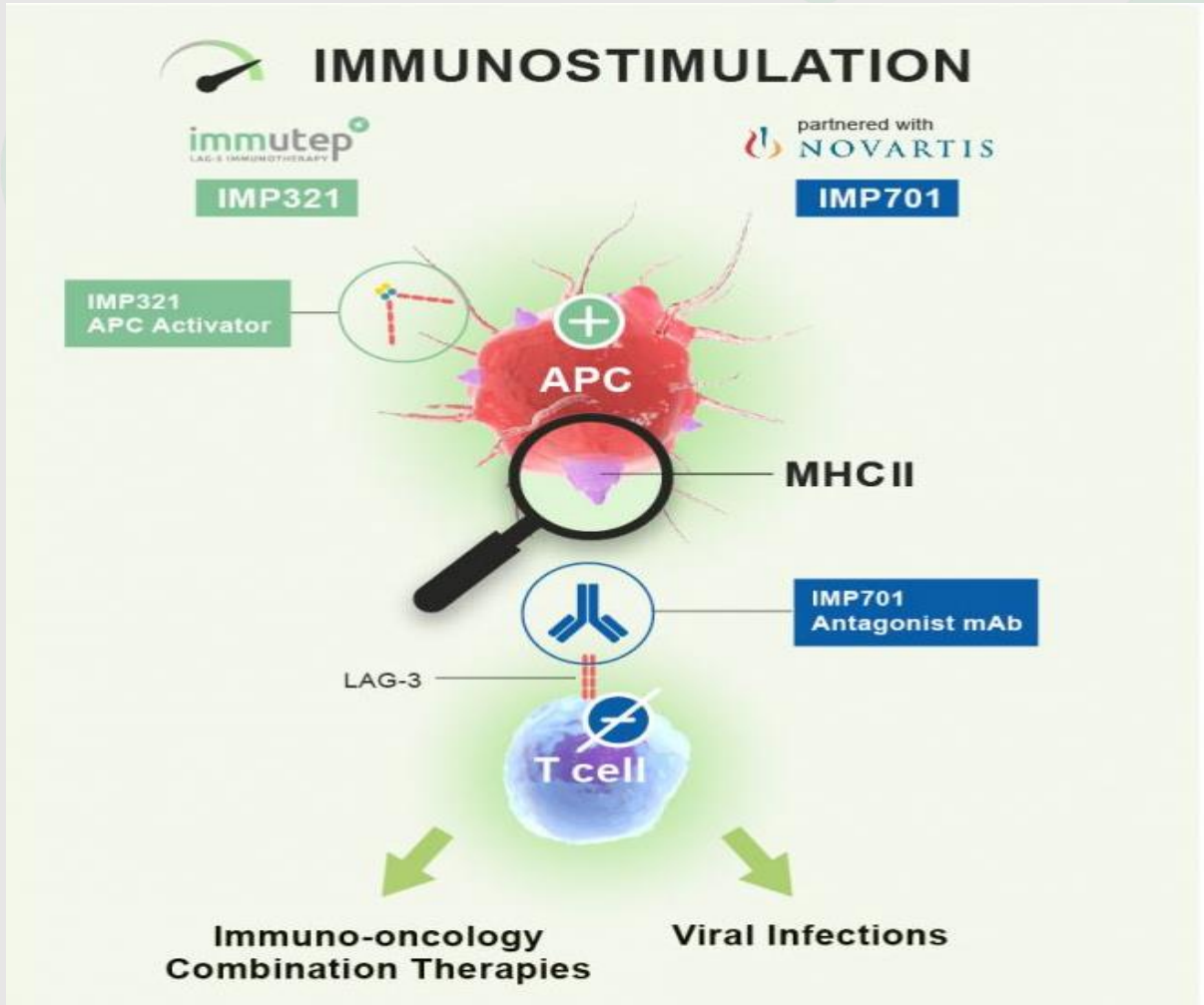
- LAG-3 is widely expressed on tumor infiltrating lymphocytes (TILs) and cytotoxic T cells
  → Prime target for an immune checkpoint blocker
- Functionally similar to PD-1 on T cells (arrow on the right)

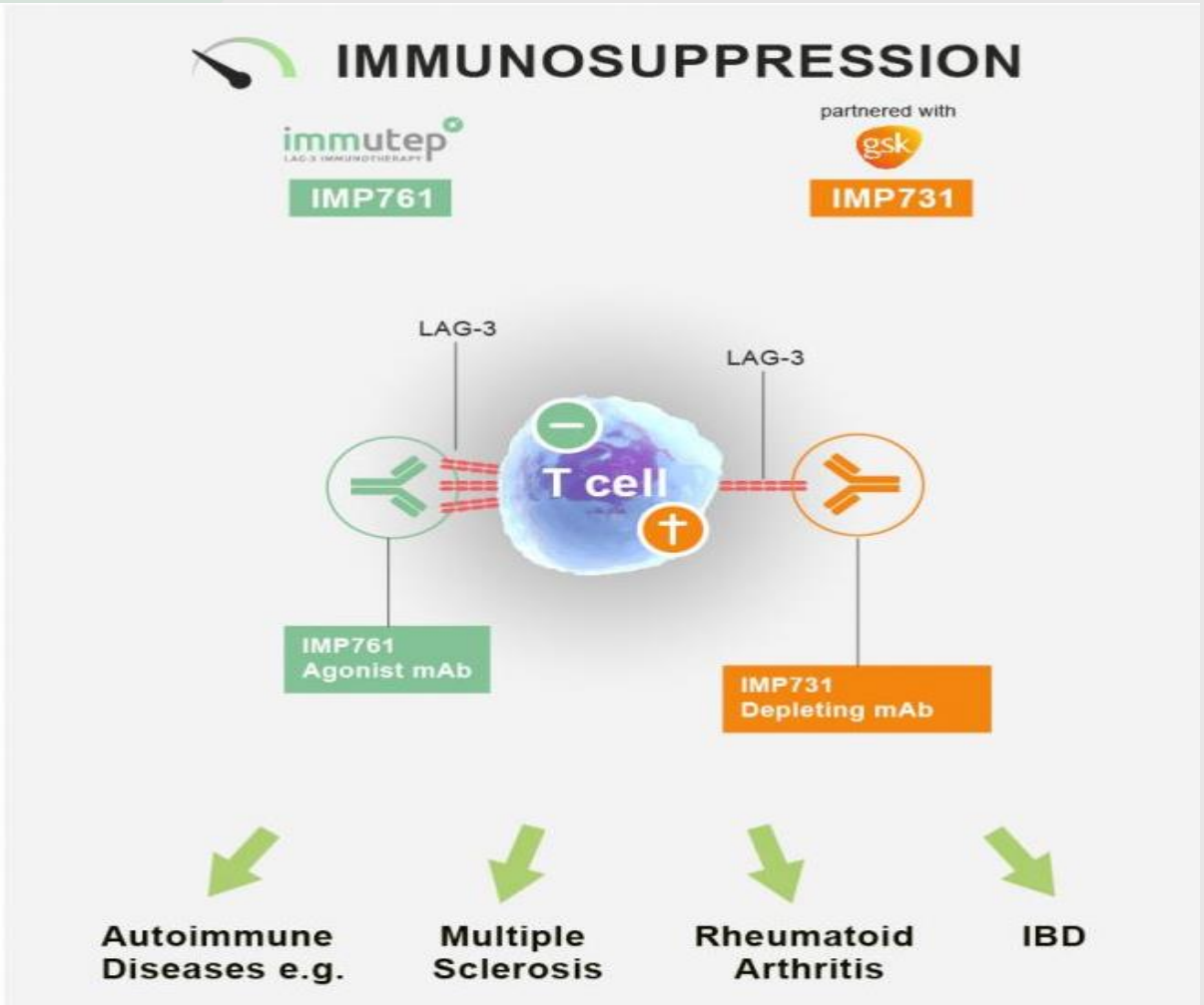


→ **Positive regulation** of antigen presenting cells (APC) → increase in antigen presentation to cytotoxic $CD8^+$ T cells

→ **Negative regulation** of $LAG\text{-}3^+$ T cells

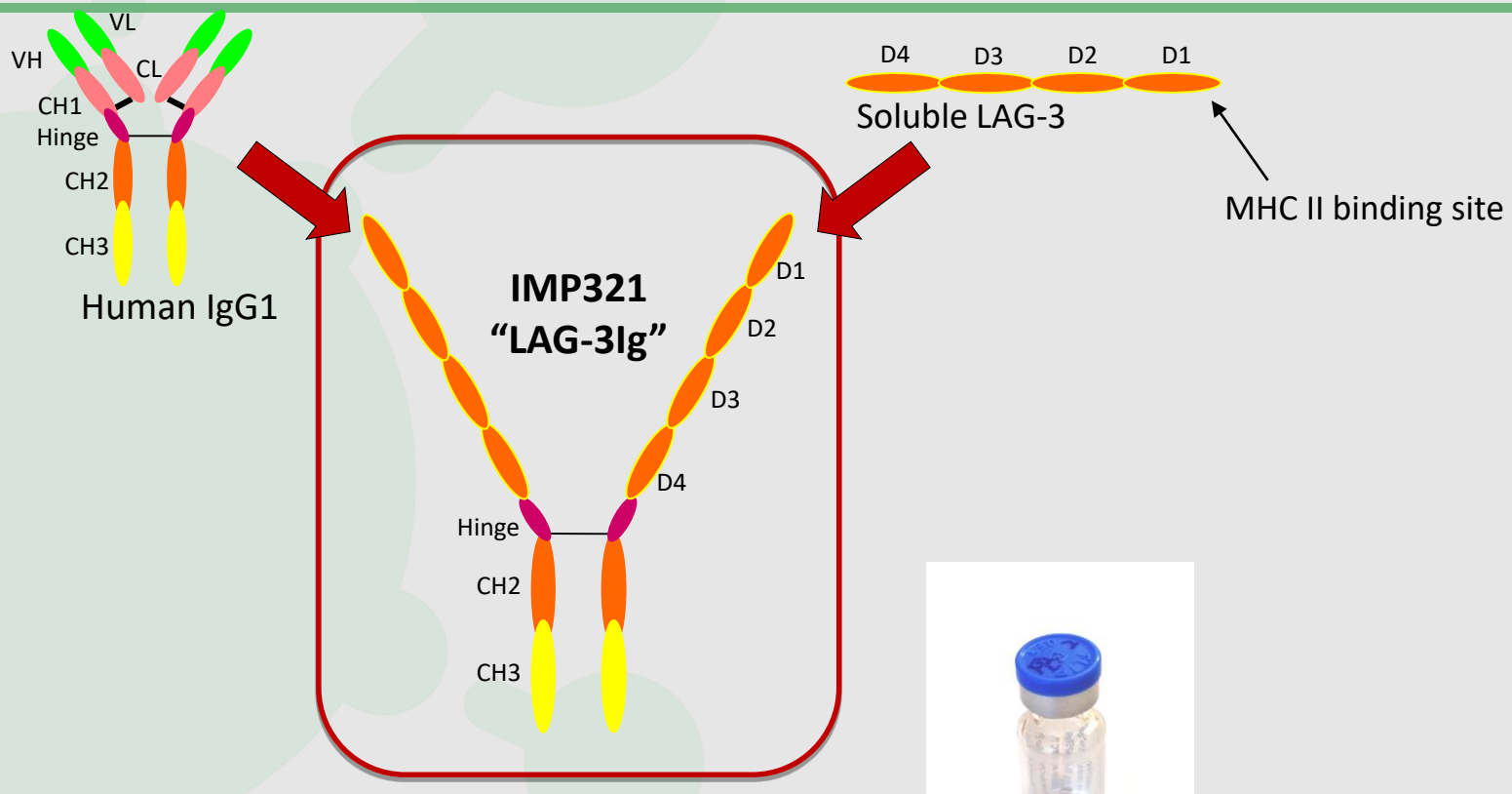
Targeting LAG-3/MHC II May Lead to Multiple Therapeutics in Numerous Indications





Lead Program
Eftilagimod Alpha (IMP321)

Eftilagimod alpha (IMP321)
Soluble dimeric recombinant form of LAG-3

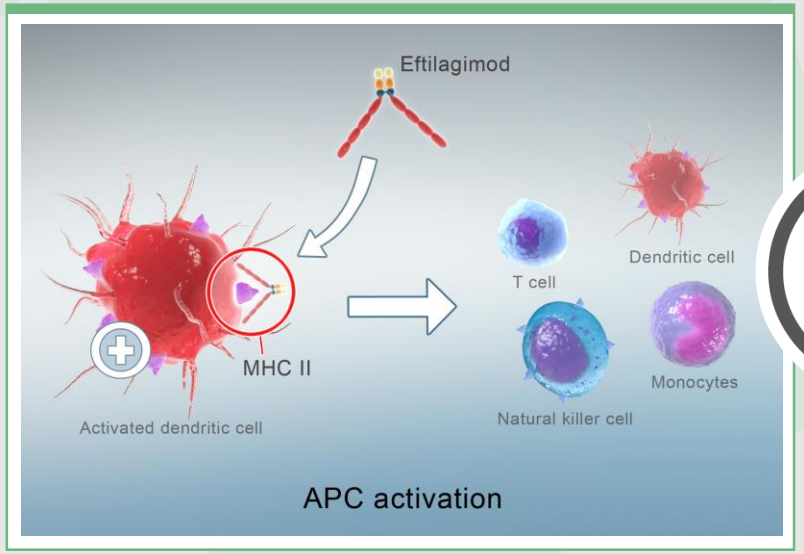


- **Soluble recombinant form of LAG-3**
- Human fusion protein
- Dimeric, very stable, high affinity for DC
- Antigen presenting cell (APC) activator
- **Unique and first-in-class**

Efti - Innovative LAG-3 IO Product Candidate

- The only APC targeting LAG-3 product currently in clinical development
- A unique approach (“turning cold tumors into hot tumors” with an MHC II agonist)
- Synergistic with other IO agents

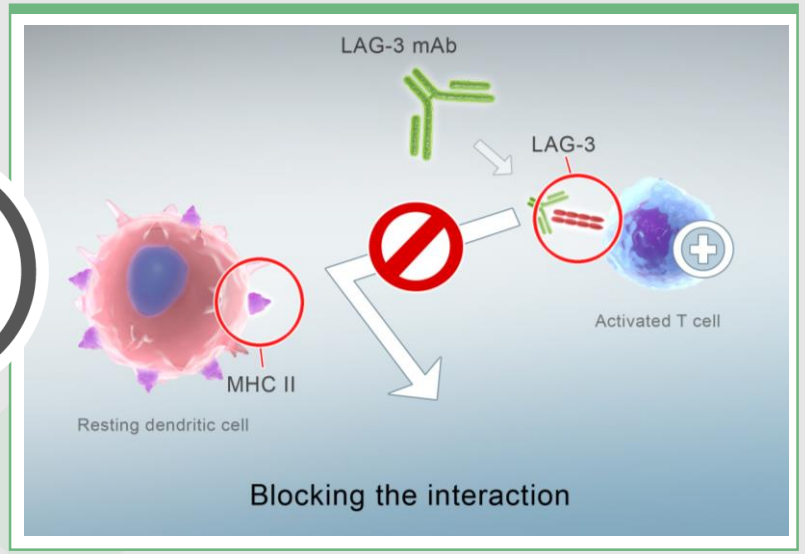
“PUSHING THE ACCELERATOR ON IMMUNE RESPONSES”



Efti, an MHC II **agonist** (eftilagimod alpha, IMP321) :

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 antibodies:

immune checkpoint inhibitor
- increase cytotoxicity of the pre-existing CD8 T cell response

Efti (IMP321) - Areas of development
Multiple strategies

Active clinical trials

- **Chemo-immunotherapy**
  - Exploit the antigen debris from chemotherapy with an APC activator → Combination therapy with active agents such as Taxanes (e.g. Paclitaxel)

AIPAC
MBC study in Chinese pts (EOC)

- **IO-IO combination**
  - Exploit two immuno-oncology agents with complementary mode of action increasing response rate and durability and maybe overcoming resistance → combination with PD-1 or PD-L1 antagonists like pembrolizumab or avelumab

TACTI-mel
TACTI-002
INSIGHT – Stratum D

- **Cancer vaccine or *in situ* immunization**
  - Stimulate the immune system locally → adjuvant to cancer vaccine or intra-tumoral injections

Collaboration with Cytlimic
INSIGHT - Stratum A+B

Efti has multiple shots on goal in different indications (6) and in different combinations (4)

Clinical Development
Eftilagimod Alpha (IMP321)

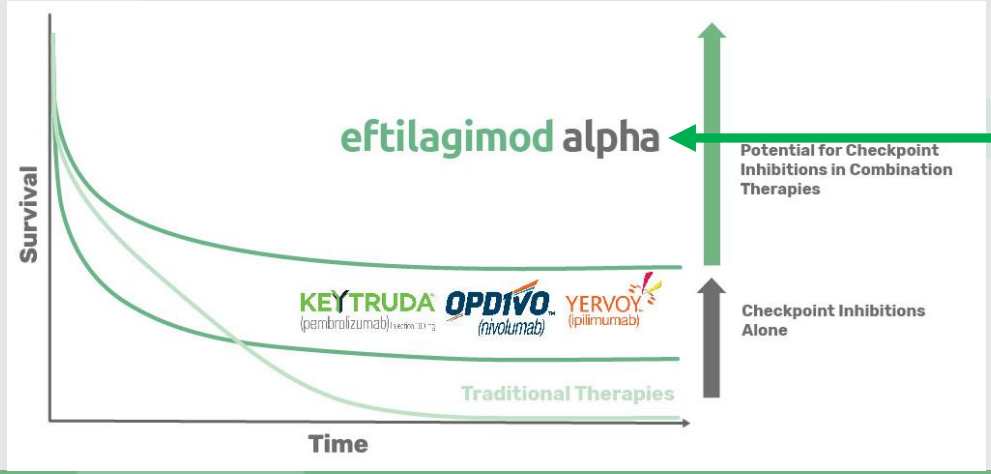
IO Therapy Oncology Response Rates

Approximately 70-80% of patients do no respond to anti-PD1 monotherapy.

How can we enable more efficacious T-cell responses?

- Immunogenic cell death to liberate/uncover tumor antigens
- Cross-presentation of those antigens
- Recruitment of T cells into the tumor microenvironment
- Reversing the pathways driving a repressive tumor environment

This could be achieved through the right APC activation



APC activators:

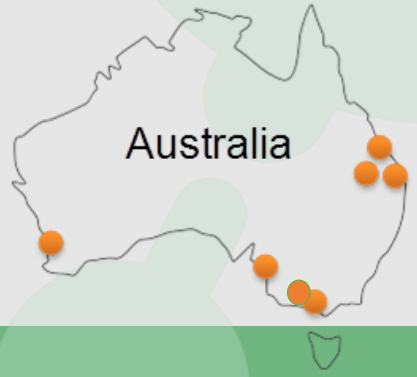
- MHC II agonism
- TLR or STING agonism
- CD40 agonism
- Oncolytic viral therapies

Efti (IMP321) in Melanoma
TACTI-mel (IO combination) – Trial Design

TACTI-mel = Two ACTive Immunotherapeutics in melanoma

24 patients, 4 cohorts of 6 patients → Efti (IMP321) + anti-PD-1 (Keytruda®) → Phase I, multicenter, open label, dose escalation → Recommended Phase II dose, safety and tolerability

Primary Objective	Recommended dose for Phase II with efti (IMP321) + pembrolizumab Safety + tolerability
Other Objectives	PK and PD of IMP321, response rate, time to next treatment, PFS



7 sites in Australia

- Part A: efti (IMP321) at 1, 6 and 30 mg s.c. every 2 weeks starting with cycle 5 of pembrolizumab
- Part B: efti (IMP321) at 30 mg s.c. every 2 weeks starting with cycle 1 of pembrolizumab

→ Status: recruitment completed

- Pembrolizumab (Keytruda®) 2 mg/kg every 3 weeks i.v. part A and B

Efti (IMP321) in Melanoma

TACTI-mel (IO combination) – Results after Start of Combo (part A)

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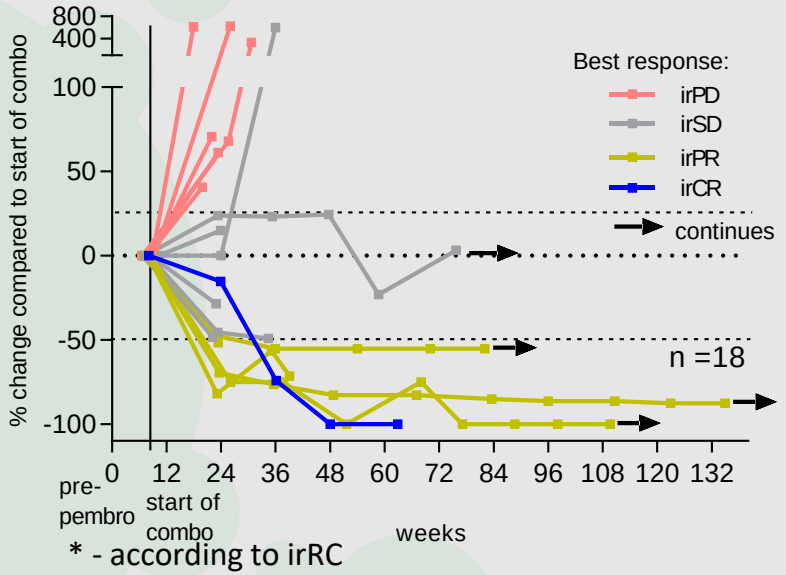
Baseline Characteristics	N = 18 (%)
ECOG 1 / 0	22 % / 78 %
Elevated LDH	7 (39%)
Metastasis stage M1c	14 (78 %)
Pre-treated with BRAF/MEK/ipilimumab	5 (28 %)

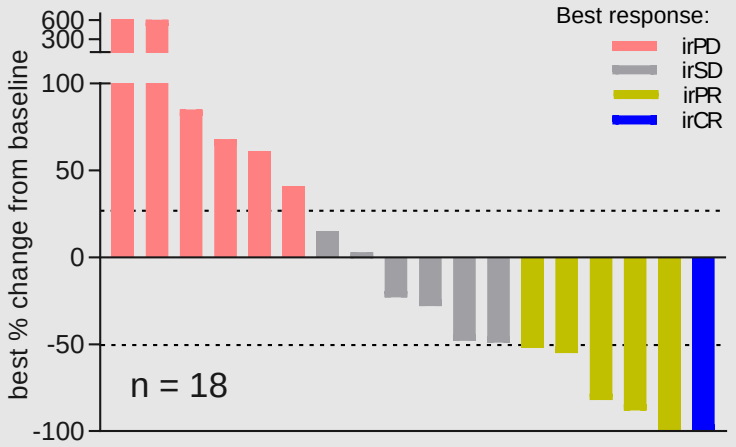
Best Overall Response acc. to irRC	N = 18 (%)
irCR	1 (6 %)
irPR#	5 (28 %)#
irSD	6 (33 %)
irPD	6 (33 %)
Best overall response rate (ORR)	**6 (33 %)**
Patients with tumor shrinkage	**10 (56 %)**
Disease control rate	**12 (66 %)**

Spider plot* (starting with cycle 5 of pembrolizumab)



* - according to irRC

Waterfall plot* (starting with cycle 5 of pembrolizumab)



Exploratory analysis (C1D1 pembrolizumab): **ORR of 61 %**

- Patients with very late stage of disease (M1c, elevated LDH)
- Majority not responding to pembrolizumab

→ Tumor shrinkage in 56 % of these patients incl. 2 pts with complete disappearance of all target lesions

- incl. 1 pt with complete disappearance of all target lesions; CR acc. to RECIST 1.1

Efti (IMP321) in Melanoma
TACTI-mel (IO combination) – Results part B

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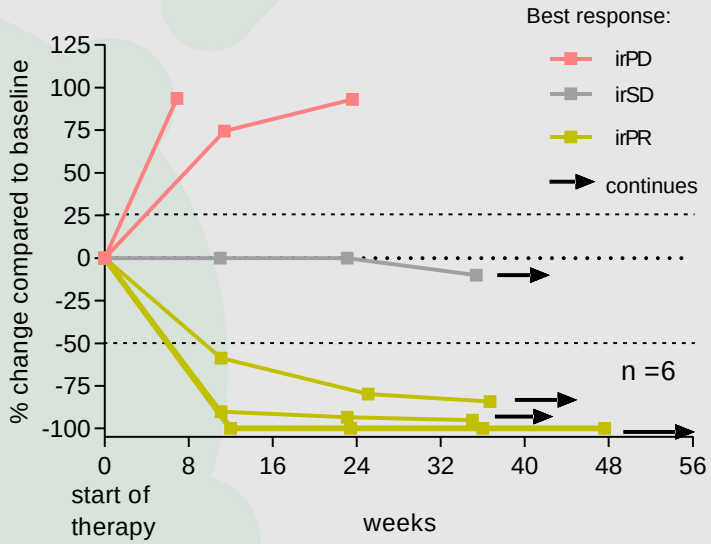
Baseline Characteristics	N = 6 (%)
ECOG (0/1)	3 (50 %) / 3 (50 %)
Sex (f/m)	1 (13 %) / 5 (83 %)
Elevated LDH	5 (83%)
Metastasis stage M1c	6 (100 %)

Best Overall Response acc. to irRC	N = 6 (%)
irCR	0 (0 %)
irPR#	3 (50 %)#
irSD	1 (13 %)
irPD	2 (25 %)
Best overall response rate (ORR)	**3 (50 %)**
Patients with tumor shrinkage	**3 (50 %)**
Disease control rate	**4 (66 %)**

- incl. 1 pt with complete disappearance of all target lesions

Spider plot* (part B)



Waterfall plot* (part B)

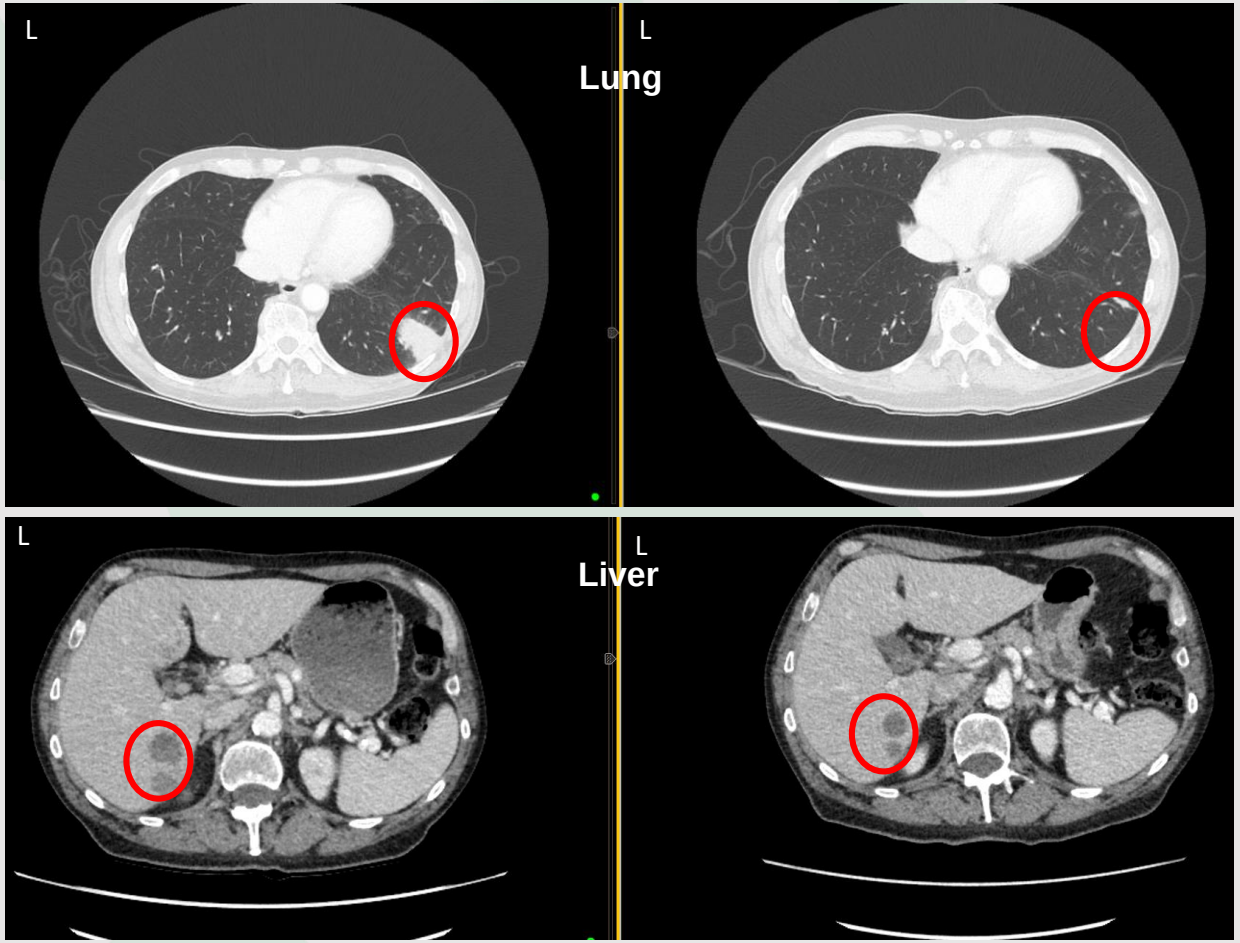
* - acc to irRC

- All patients with very late stage of disease (M1c, elevated LDH)
- No DLTs or new safety signals

→ Confirmed deep partial responses in 3 (50%) of the pts
→ Treatment of 4 pts ongoing (currently 9+ months all)

Efti (IMP321) in Melanoma
TACTI-mel – Results Part B – Single Case

July 2018 (baseline) | January 2019 (6 months)



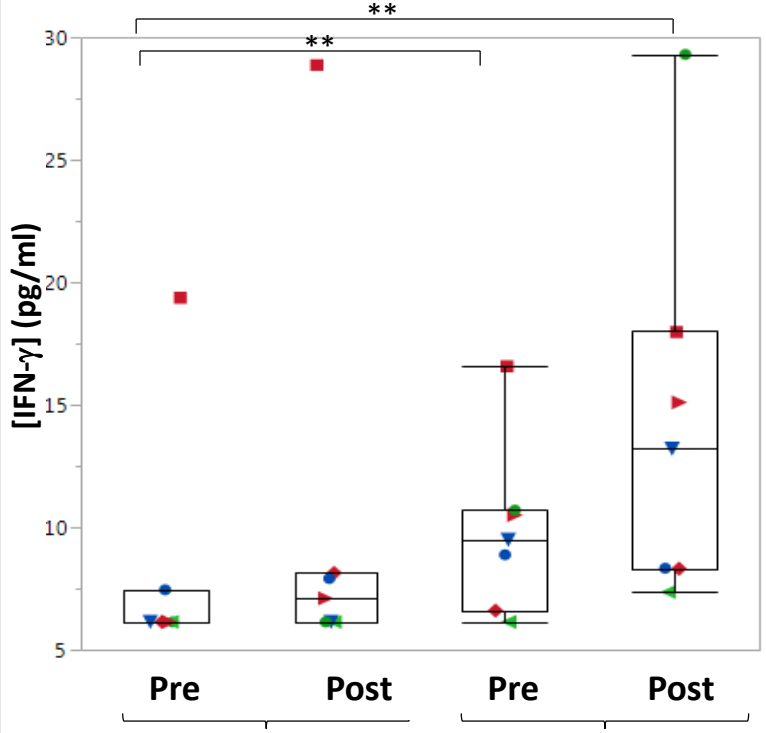
- 69 year old male
- Multiple lung, bone, liver and lymph node metastases from melanoma → **M1C stage**
- BRAF wild type
- ECOG 1

→ clear regression of lung and liver metastases → treatment continues (9+ months)

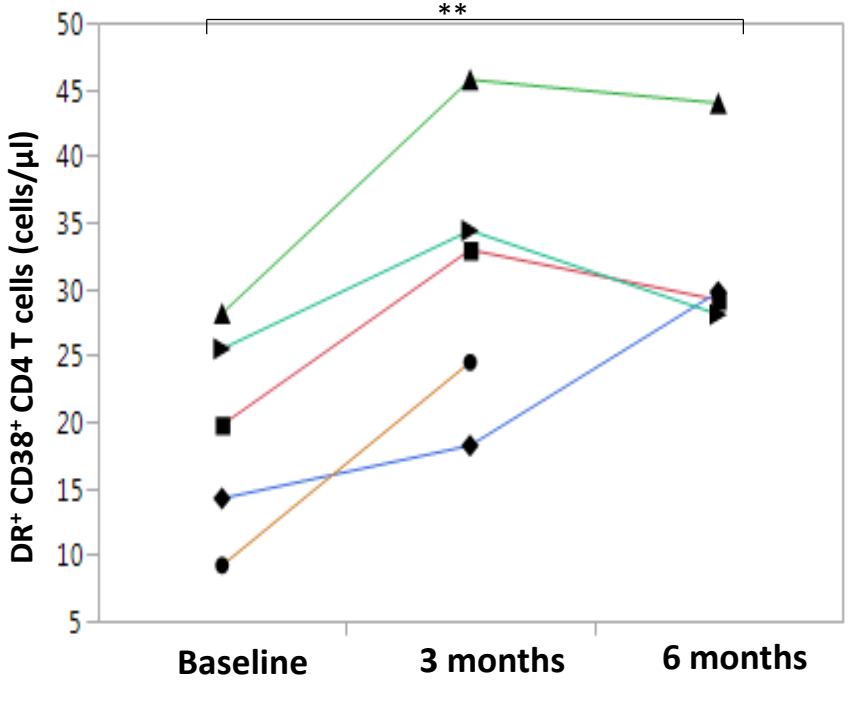
preliminary data, cut-off February 2019

Efti (IMP321) in Melanoma
TACTI-mel (IO combination) – Blood Pharmacodynamics

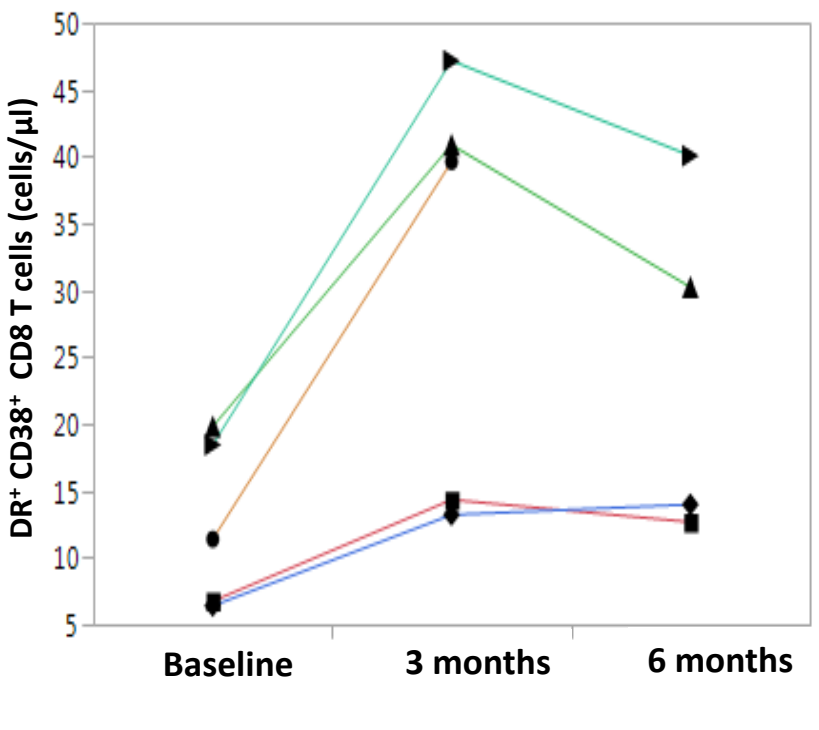
Part A
IFN-γ (not yet available for Part B)



Part B
Activated CD4 T cells



Part B
Activated CD8 T cells



TACTI-002 Trial Design

An umbrella trial: Two ACTive Immunotherapeutics in different indications

Simon's 2 stage; 3 indications; up to 109 pts → Efti (IMP321) + Pembrolizumab (Keytruda®) for 12 months + max. of 12 months pembrolizumab monotherapy → Phase II, multi-national (EU + US + AUS), open label → Response rate; PFS, OS, PK, Biomarker; Safety and tolerability

Primary Objective	Response rate (iRECIST)
Other Objectives	Safety, PFS+OS, PK, exploratory biomarker analysis
Patient Population	Part A: 1st line NSCLC PD-X naive Part B: 2nd line NSCLC, PD-X refractory Part C: 2nd line HNSCC, PD-X naive
Treatment	30 mg Efti (IMP321) s.c. 200 mg Pembrolizumab i.v.

13 sites in Europe / US / Australia

Notes

NSCLC – non-small-cell lung cancer, HNSCC – head and neck squamous cell cancer, DMC –data monitoring comittee, PFS – progression free survival, OS – overall survival, PK – pharmacokinetics, PD-X – any PD-1 or DL-1 treatment

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Thank you

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