Two ACTive immunotherapies in melanoma (TACTI-mel): results of a phase I trial combining a soluble LAG-3 receptor (Eftilagimod Alpha) with Pembrolizumab

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World Immunotherapy Congress

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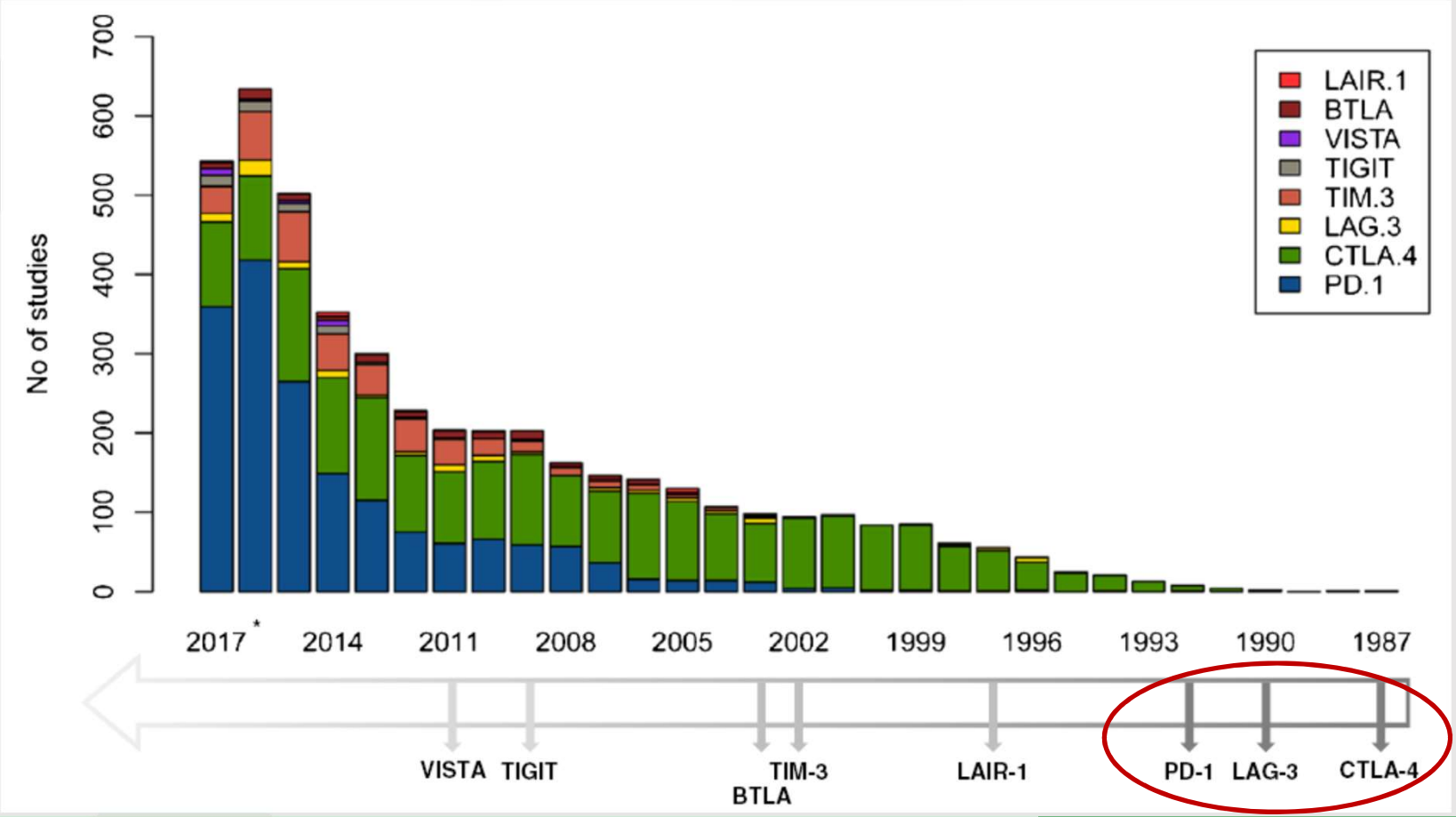
Timeline of immune checkpoint discovery.



LAG-3 as a Therapeutic Target

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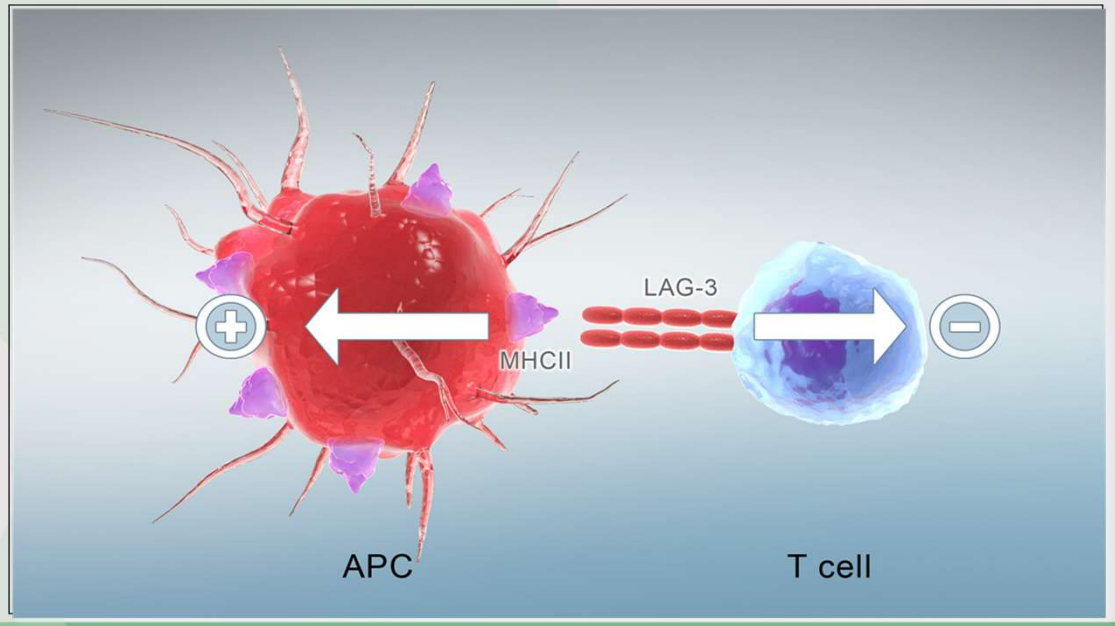
- LAG-3 is widely expressed on tumor infiltrating lymphocytes (TILs) and cytotoxic T cells
  → Prime target for an immune checkpoint blocker
- Functionally similar to PD-1 on T cells (arrow on the right)



→ **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

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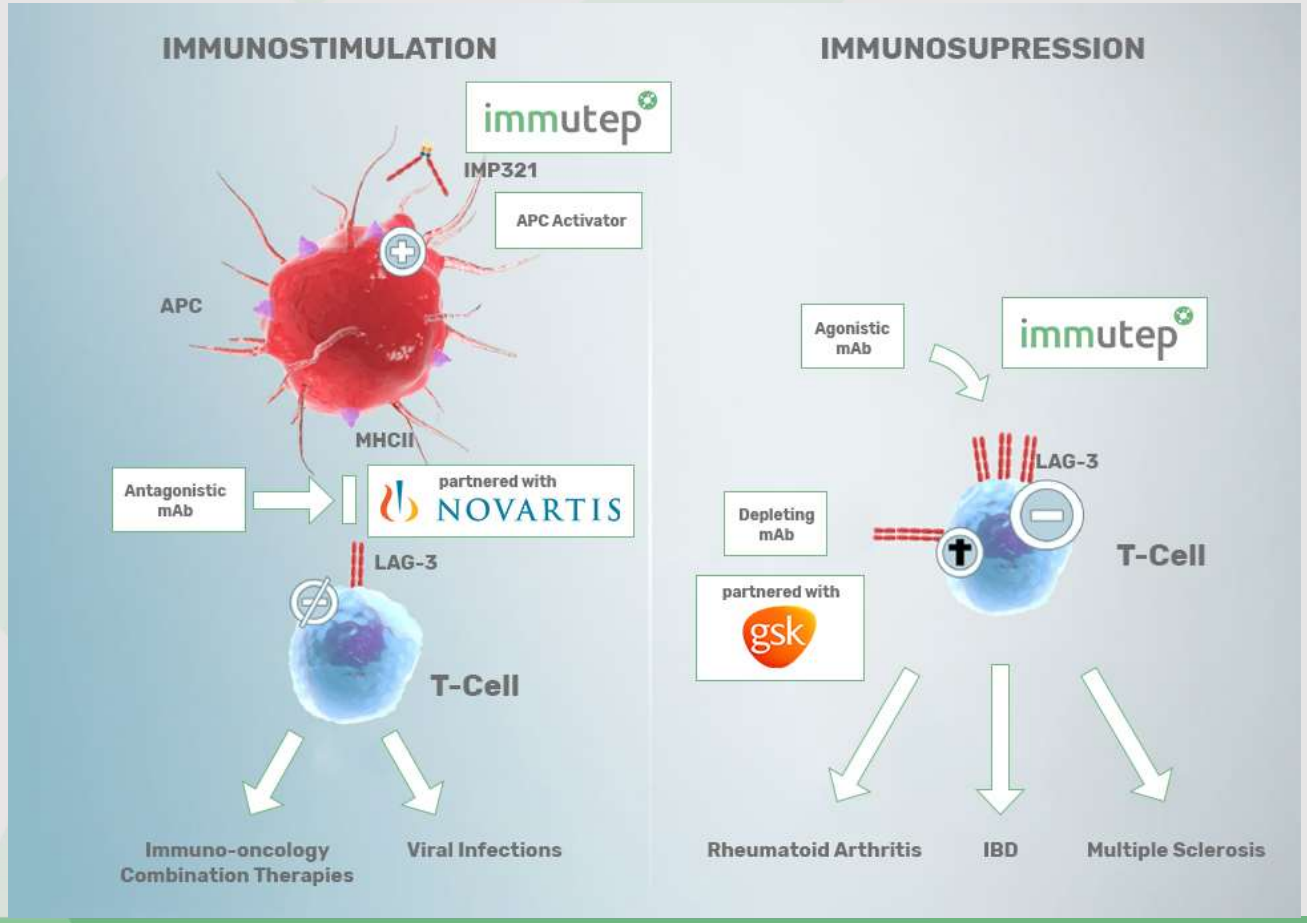

Increasing Clinical Trials Targeting LAG-3

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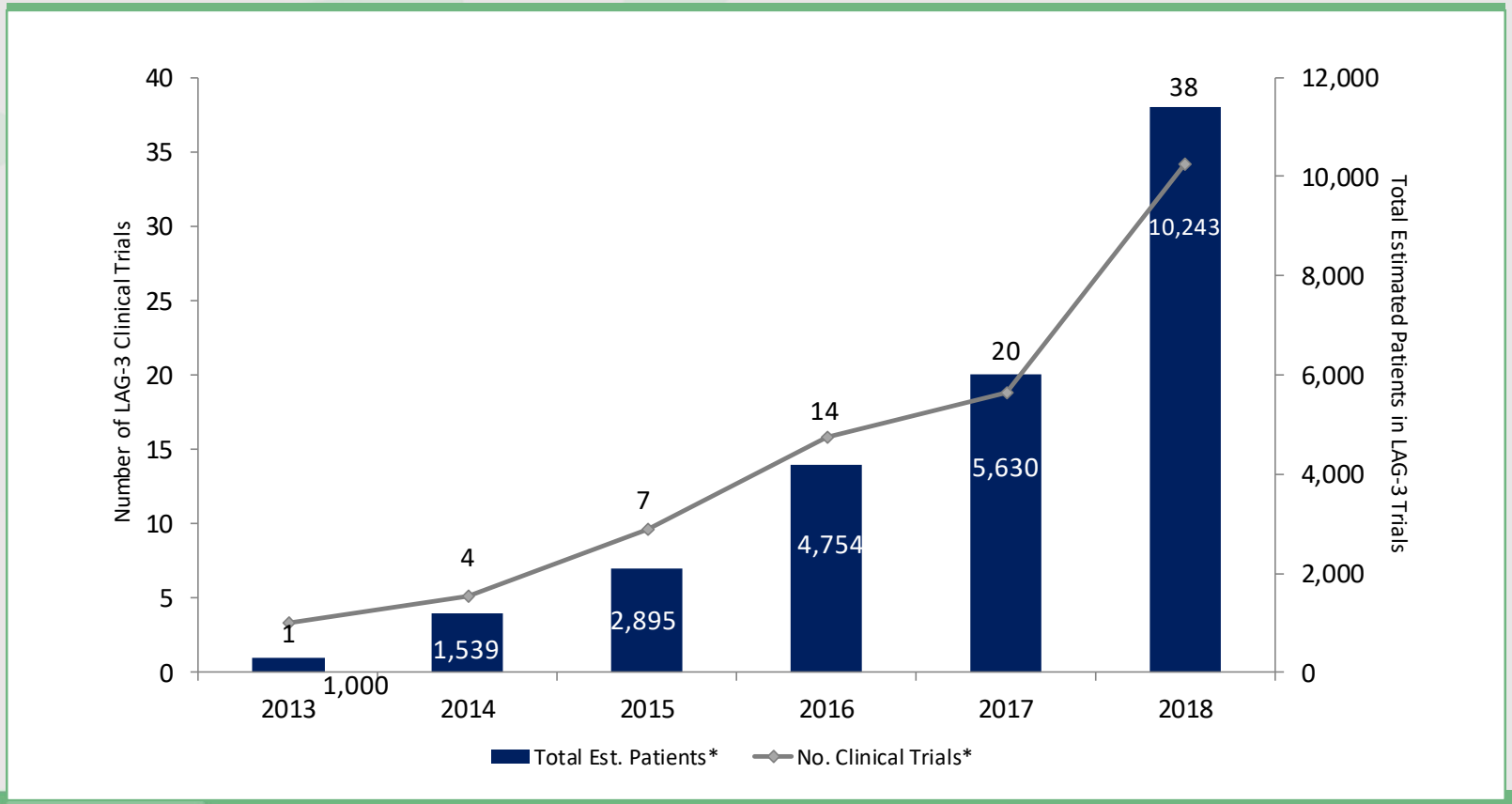
Industry increasingly deploying resources to development of LAG-3 therapeutics



Sources: GlobalData, company websites, clinical trials.gov, and sec.gov
Information as of August 17, 2018
*2018 includes planned and completed trials, includes trials where the company may not be the sponsor

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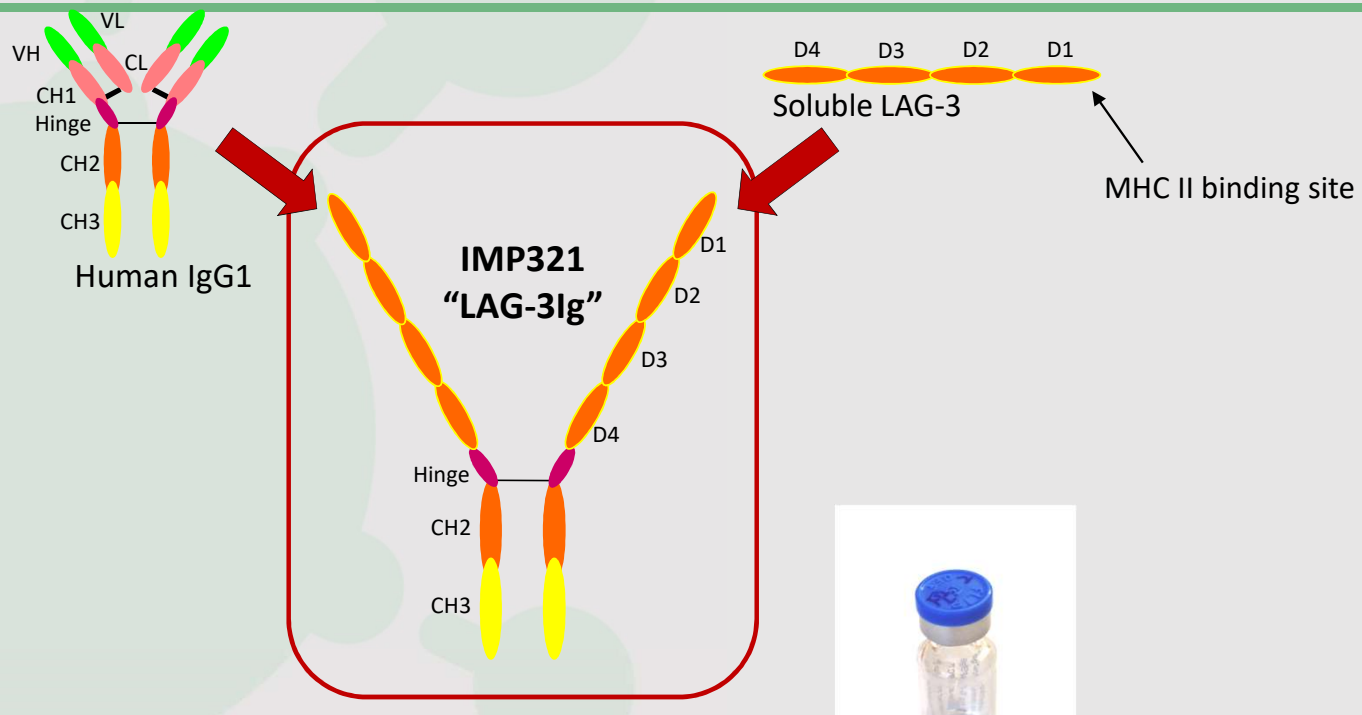
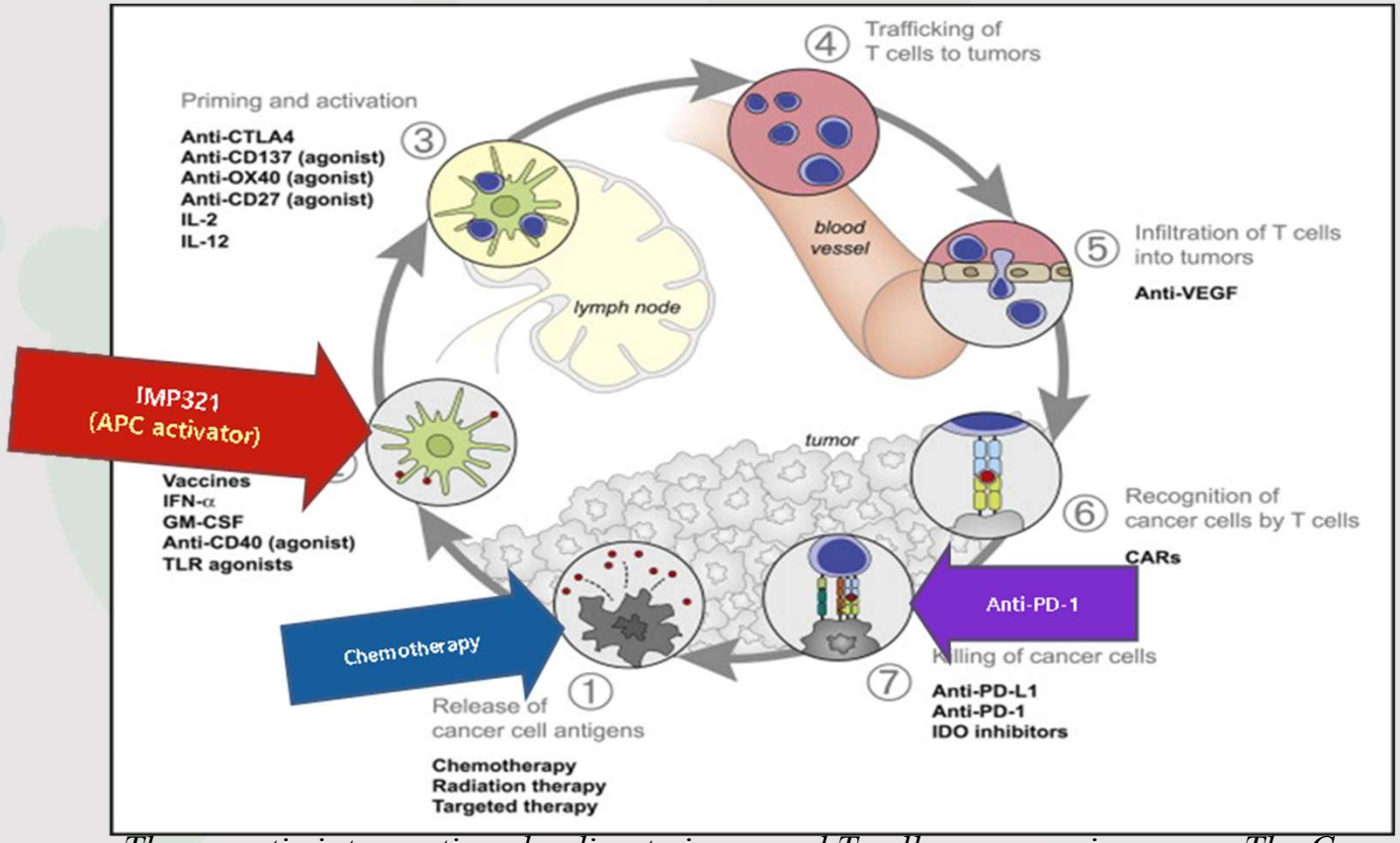
Lead Program
Eftilagimod Alpha (IMP321)

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



- **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**

Rationale for Combining efti (IMP321) with Chemotherapy or Anti-PD-1 mAb



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

IO Therapy Oncology Response Rates

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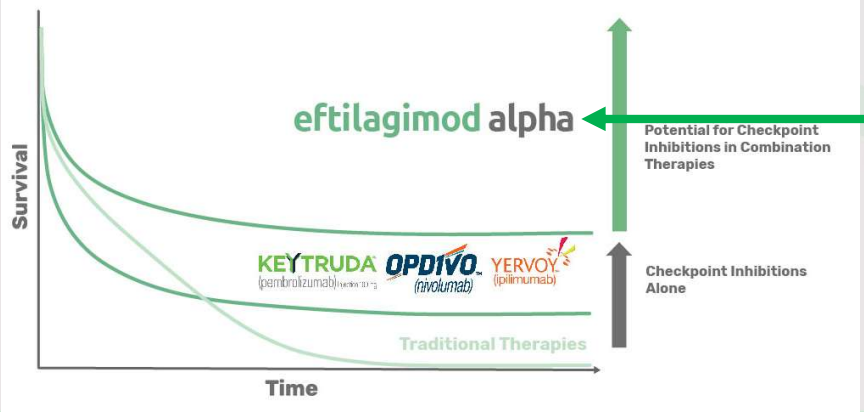
Approximately 70-80% of patients do no respond to anti-PD1 monotherapy.
<u>How can we enable more efficacious T-cell responses?</u>

- 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



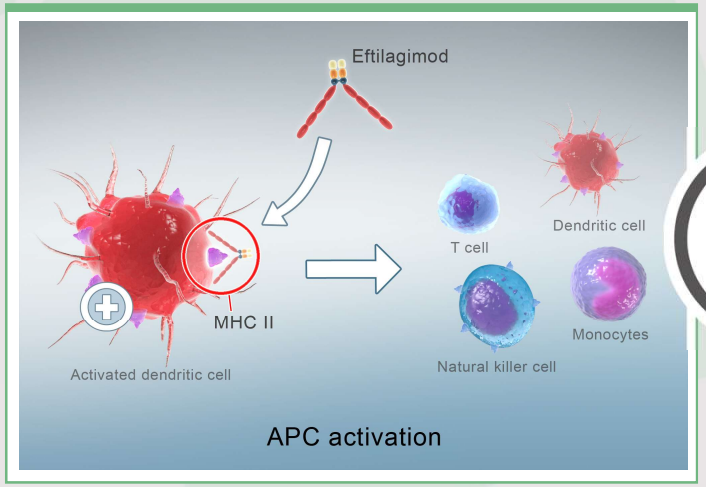
APC activators:

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

Efti - 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”

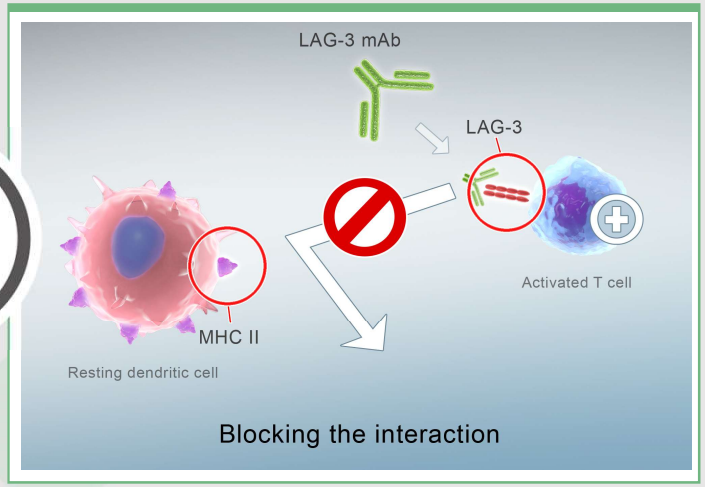


Efti, an MHC II **agonist** (eftilagimod alpha, IMP321) :

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

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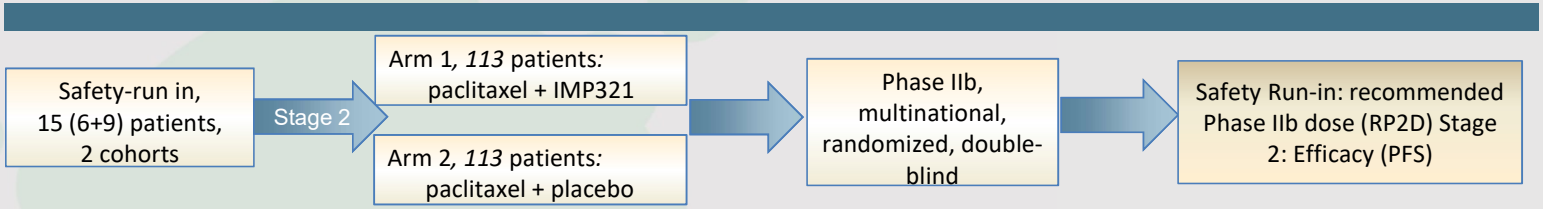
Clinical Development
Eftilagimod Alpha (IMP321)

Eftilagimod alpha in MBC
AIPAC (Pivotal Phase IIb)



Primary Objective	Run-In: Recommended Phase II dose (RP2D) Stage 2: Efficacy (PFS) of paclitaxel + IMP321 vs. paclitaxel + placebo
Other Objectives	Anti-tumor activity, safety and tolerability, pharmacokinetic and immunogenic properties, quality of life of IMP321 plus paclitaxel compared to placebo
Patient Population	Advanced MBC indicated to receive 1st line weekly paclitaxel
Treatment	Run-in: IMP321 (6 or 30 mg) + Paclitaxel Arm 1: Paclitaxel + IMP321 (30 mg) Arm 2: Paclitaxel + Placebo
Countries	NL, BE, PL, DE, HU, UK, FR → overall 30+ sites

Status report (Oct 2017)

✓ Safety run-in completed successfully

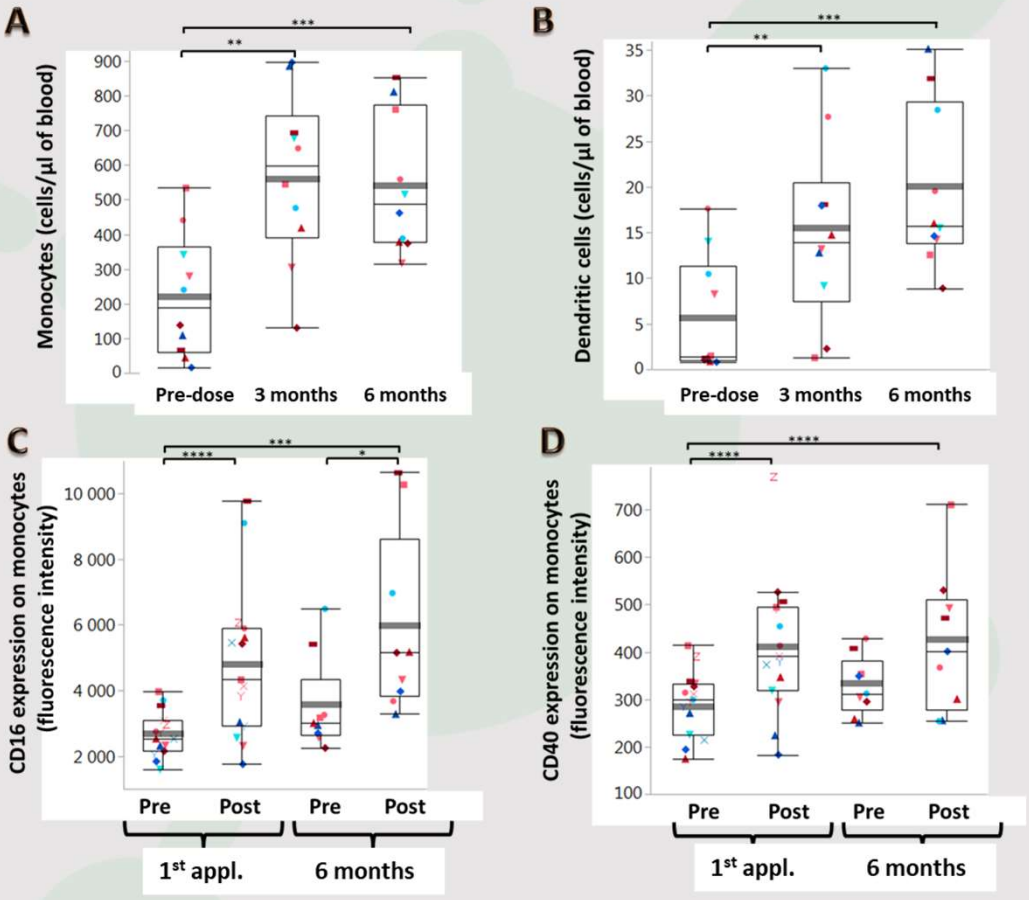
✓ Randomized phase started early 2017 with the RP2D (30 mg)

✓ Interim-data of safety run-in presented at ASCO 2017

✓ To-date, efficacy and safety data in-line with historical control group/ prior clinical trials (Brignone et al Journal Translational Medicine 2010, 8:71)

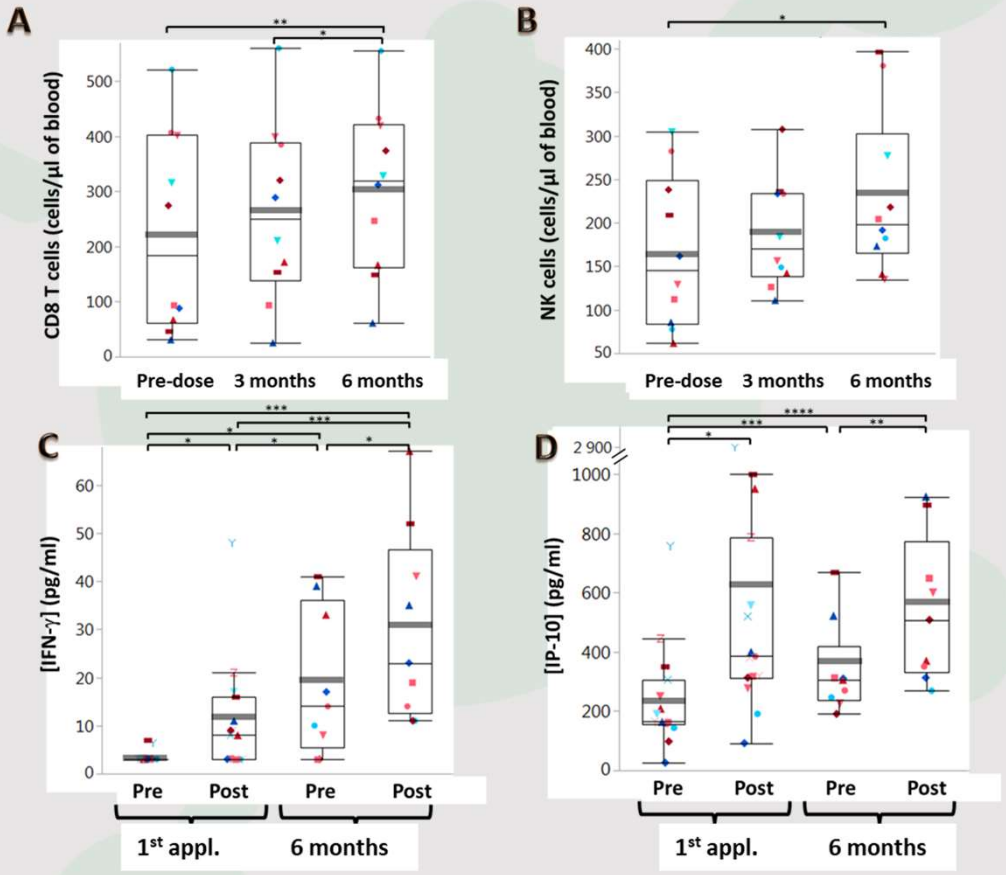
✓ Regulatory approval in 7 EU countries

AIPAC Immunomonitoring
Primary Target Cells



Primary target cells: Sustained increase of circulating Antigen-Presenting Cells (APCs) like monocytes (A) and dendritic cells (B). Rapid activation of monocytes (CD16 (C) and CD40 (D)).

AIPAC Immunomonitoring
Secondary Target Cells



Secondary target cells:
Sustainable increase in absolute numbers of effector cells like i.e. CD8 T cells (A) and Natural Killer cells (B). IMP321 induces early and sustainable increase of Th1 biomarkers like IFN-γ (C) and IP-10 (CXCL10, D).

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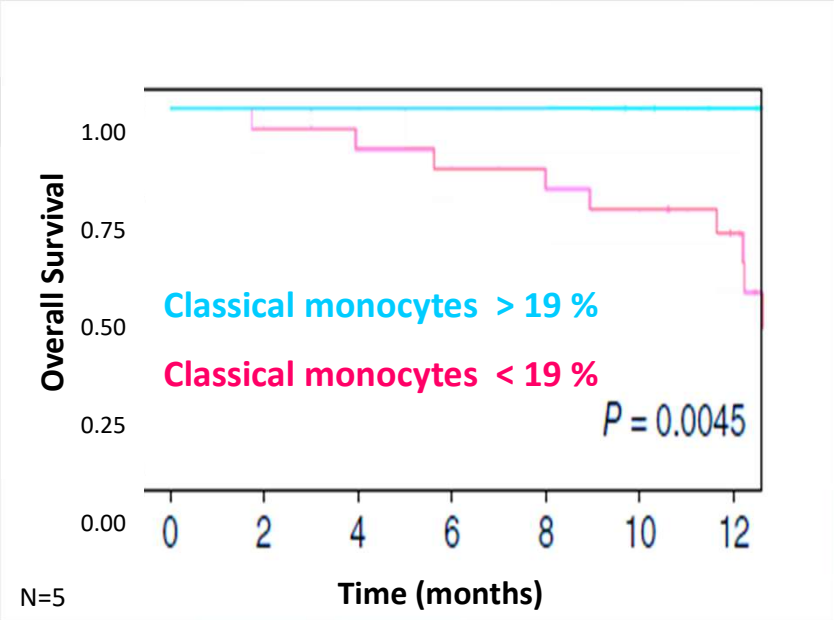
Rationale for combining eftilagimod alpha and pembrolizumab

New Rationale for Combining efti (IMP321) with PD-1 Antagonists (pembrolizumab)

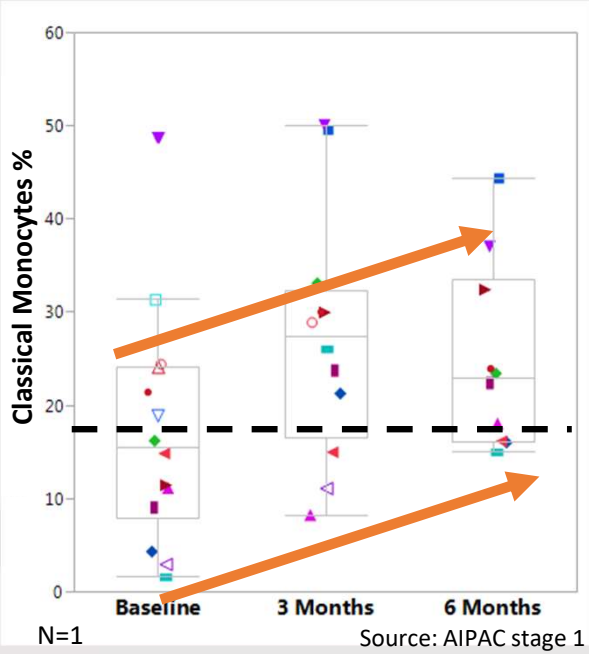
Problem: Low monocyte numbers at baseline leads to poor efficacy of anti-PD-1 therapy



N=51

Source: Krieg et al., Nat. Med. 24, 2018.

Solution: efti (IMP321) increases monocyte numbers in cancer patients



N=15

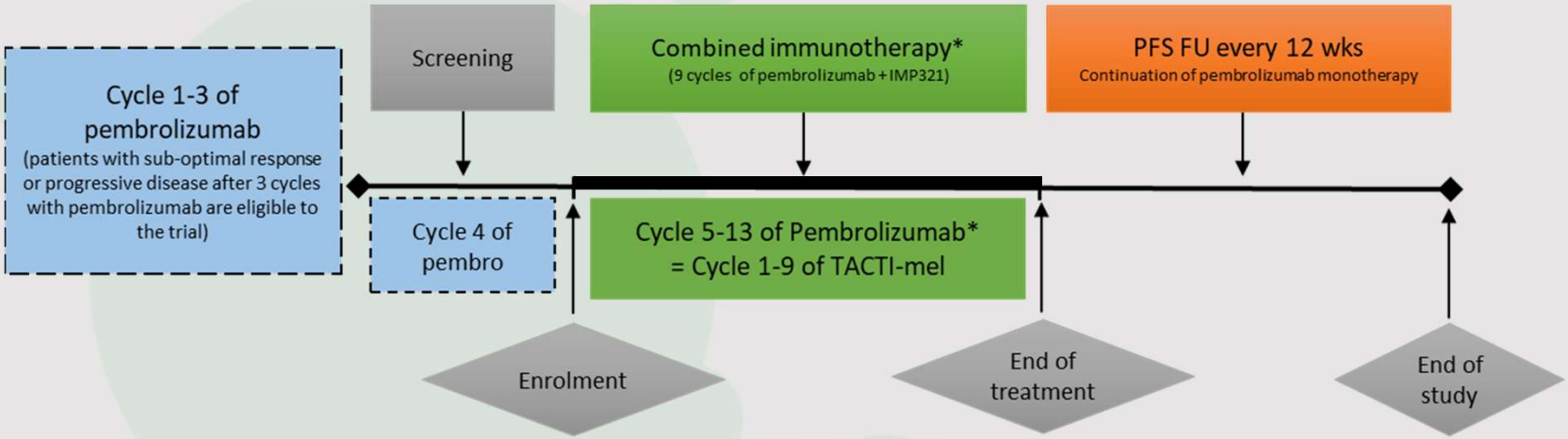
Source: AIPAC stage 1

Monocytes are important for response and survival to pembrolizumab → efti (IMP321) increases monocytes sustainably → response to pembrolizumab more likely

Efti (IMP321) in Melanoma

TACTI-mel (IO combination) – Details Part A

Study Scheme Part A:



*Tumor assessment acc to irRC

irRC…Immune-Related Response Criteria, PFS- progression free survival, FU – follow-up

Patient population Part A:

- Patients with unresectable or metastatic melanoma with **asymptomatic progression or suboptimal response** after 3 cycles of pembrolizumab

Efti (IMP321) in Melanoma

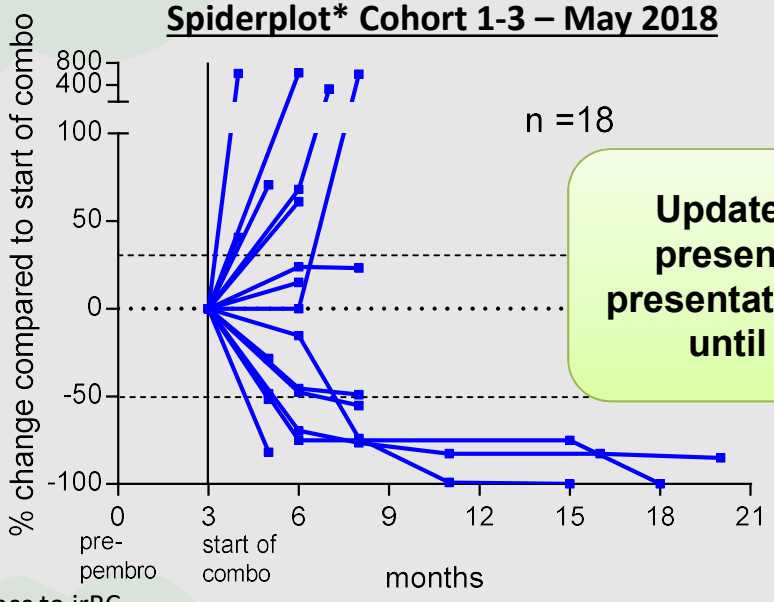
TACTI-mel (IO combination) – Results after Start of Combo

Baseline Characteristics	N = 18 (%)
Elevated LDH	7 (39%)
Metastasis stage M1c	15 (83 %)
Pre-treated with BRAF/MEK/ipilimumab	4 (22 %)
irPD/irSD to pembro after 3 cycles	12 (67 %)

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	**9 (50 %)**
Disease control rate	**12 (66 %)**

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

Spiderplot* Cohort 1-3 – May 2018



* - acc to irRC

Updated results will be presented at SITC (oral presentation under embargo until Nov. 9th, 2018)

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

→ Tumor shrinkage in 50 % of these patients incl. 2 pts with complete disappearance of all target lesions after 11 and 18 months

Efti (IMP321) in Melanoma

TACTI-mel (IO combination) – Single Case at 1 mg efti

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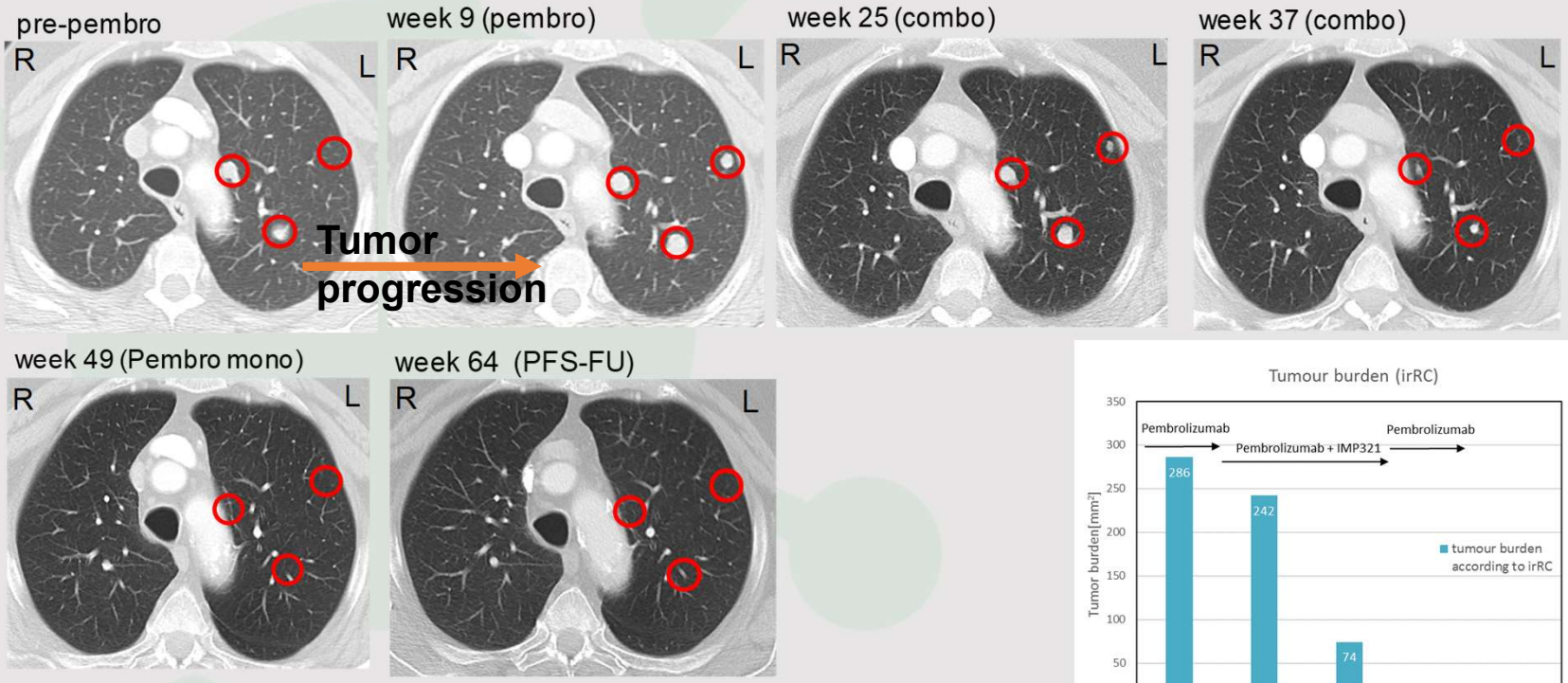
Efficacy: Metastatic Melanoma



All lesions disappeared → CR (confirmed)
patient without treatment and disease free

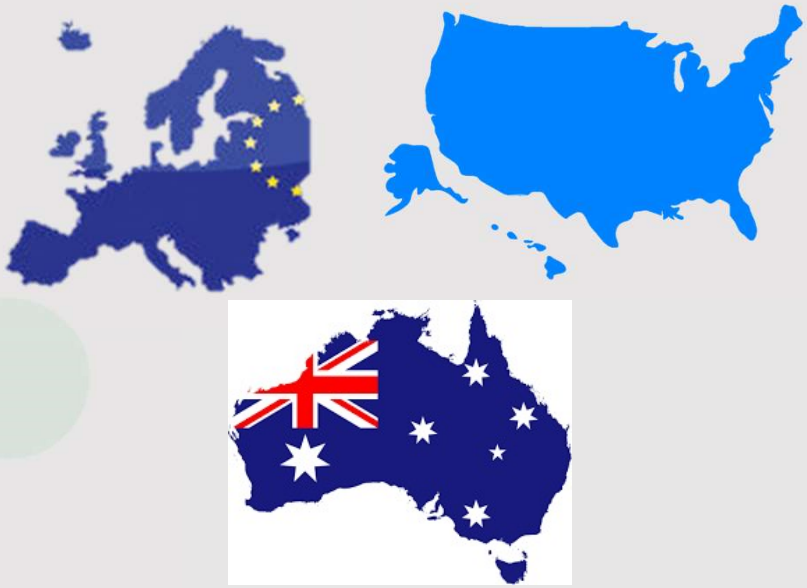
Efti (IMP321) – Clinical Development

TACTI-002 Trial Design

TACTI-002; a basket trial: Two ACTive Immunotherapeutics in different indications

Simons 2 stage; 3 indications; up to 120 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 PDL-1 treatment

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Thank you

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