Two ACTive Immunotherapies In Melanoma (TACTI-mel): Results Of A Phase I Trial With Metastatic Melanoma Patients Treated With A Soluble LAG-3 Receptor (LAG-3Ig Or Eftilagimod Alpha) As An Antigen Presenting (APC) Activator Combined With Pembrolizumab

Frédéric Triebel MD, PhD

Third Annual Advances in Immuno-oncology Congress

London, May 25, 2018

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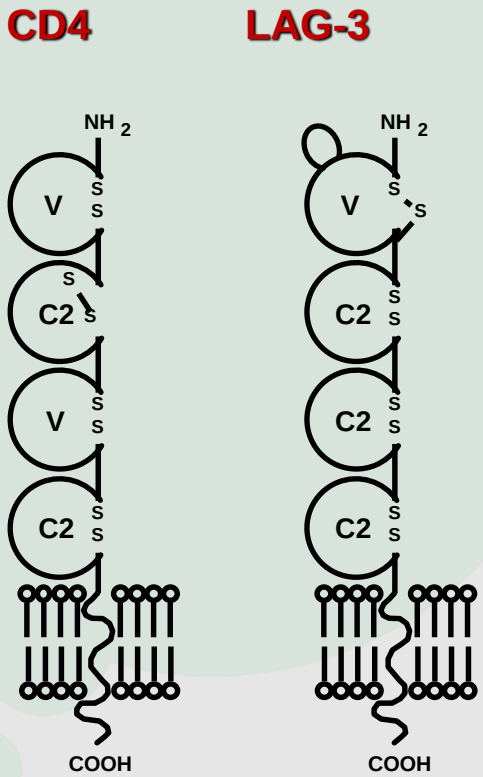
EXPLANATORY NOTE FOR READERS

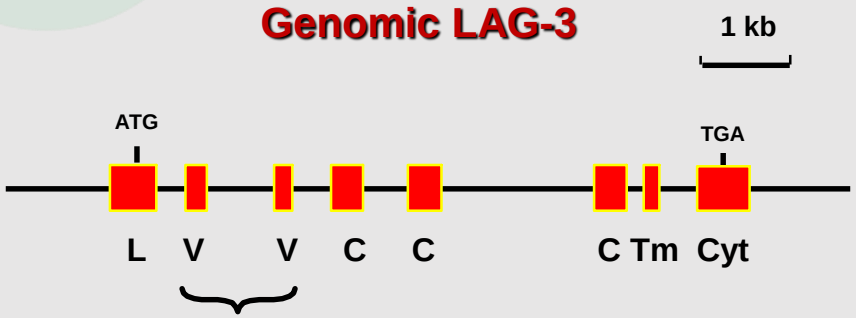
This presentation contains the following information (excerpt):

- Very favorable safety profile no MTD (maximum tolerated dose) reached; efti based combination therapies are feasible and safe
- Encouraging activity in metastatic breast cancer when combined with paclitaxel
- Able to induce a IFN-γ type response in patients
- Encouraging activity in later stage metastatic melanoma patients when combined with pembrolizumab (important note: full data including updated Overall Response Rate will be presented during a webcast at 29th/30th of May)
- Eftilagimod alpha will be investigated in combination with pembrolizumab in 3 new indications starting 2018

3

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

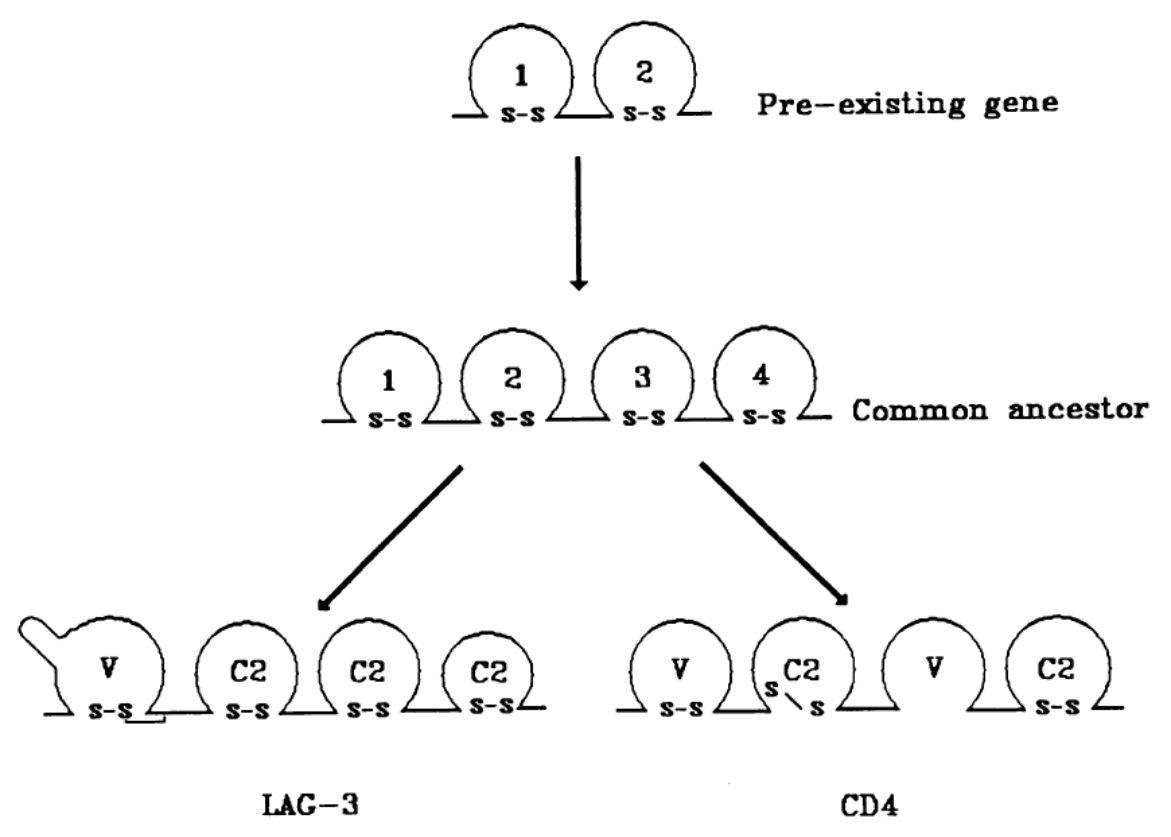




- 4-IgSF domain transmembrane proteins.
- Same genomic organization
  (intron in D1, duplication event D1D2 vs D3D4)
- Close proximity on 12p13.

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

Proposed Evolutionary Pattern for LAG-3/CD4



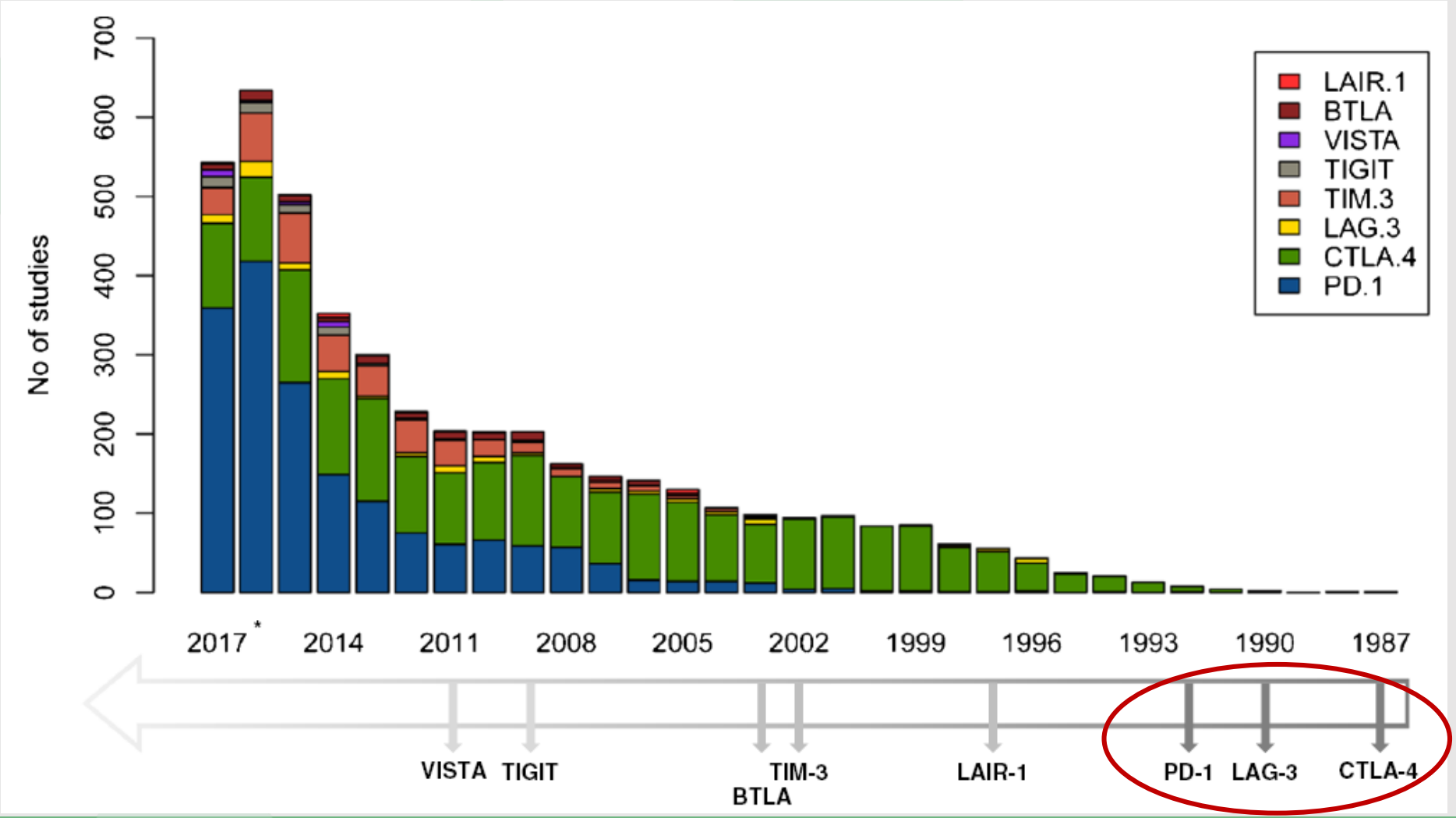
Co-inhibitory

Co-stimulatory

Immunogenetics 39: 213–217, 1994

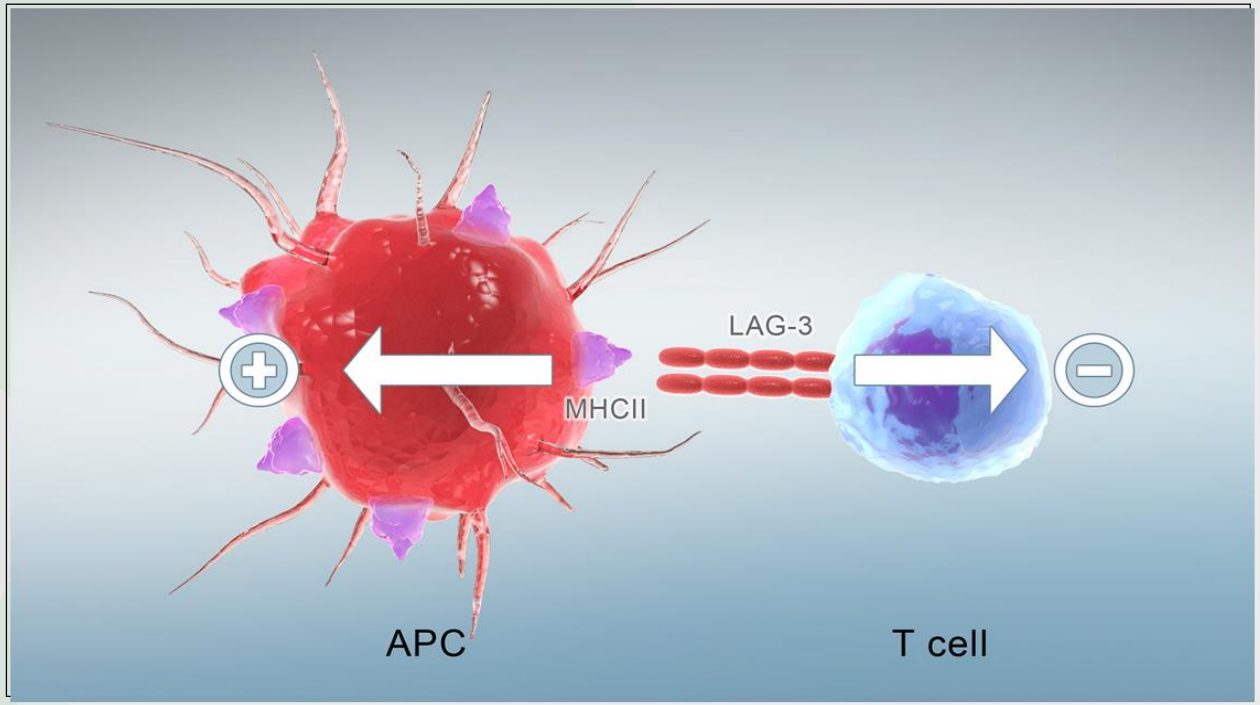
- Duplication of a two Ig domain ancestor
- The LAG-3/CD4 subfamily has evolved like the CTLA-4/CD28 subfamily: one inhibitory and one stimulatory receptor modulating TCR signaling

Timeline of immune checkpoint discovery.



LAG-3 as a Therapeutic Target

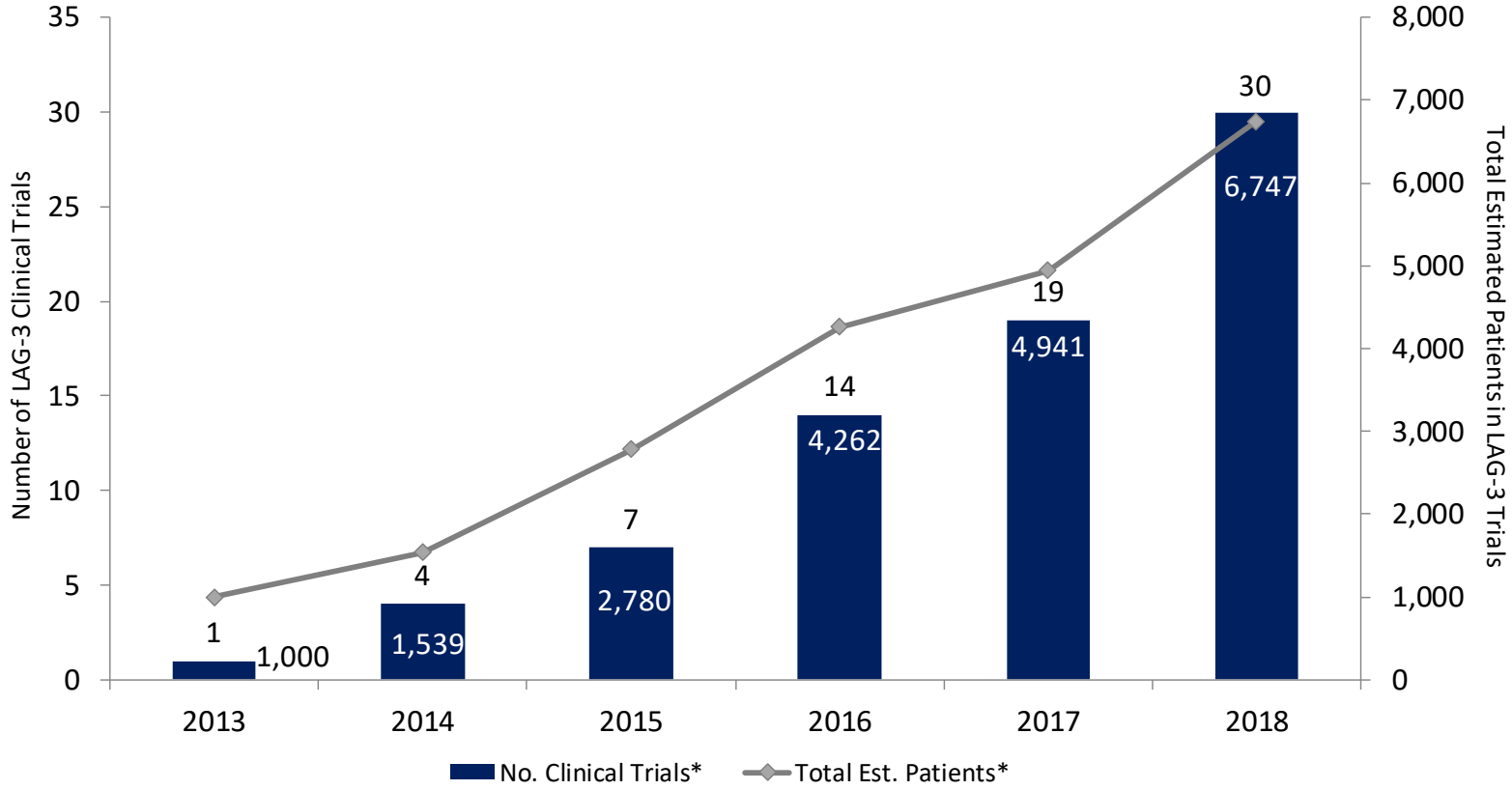
- LAG-3 is widely expressed on tumor infiltrating lymphocytes (TILs) and cytotoxic T cells
  → Prime target for an immune checkpoint blocker
- Functionally similar to CTLA-4 (targeted by Yervoy®) and PD-1 (targeted by Keytruda®)



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

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

LAG-3 Competitive Landscape



Sources: GlobalData, company websites, clinical trials.gov, and sec.gov

* 2018 includes planned clinical trials that are currently not recruiting patients

As of April 23, 2018

LAG-3 Therapeutic Landscape Overview

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Immutep is the leader in developing LAG-3 modulating therapeutics

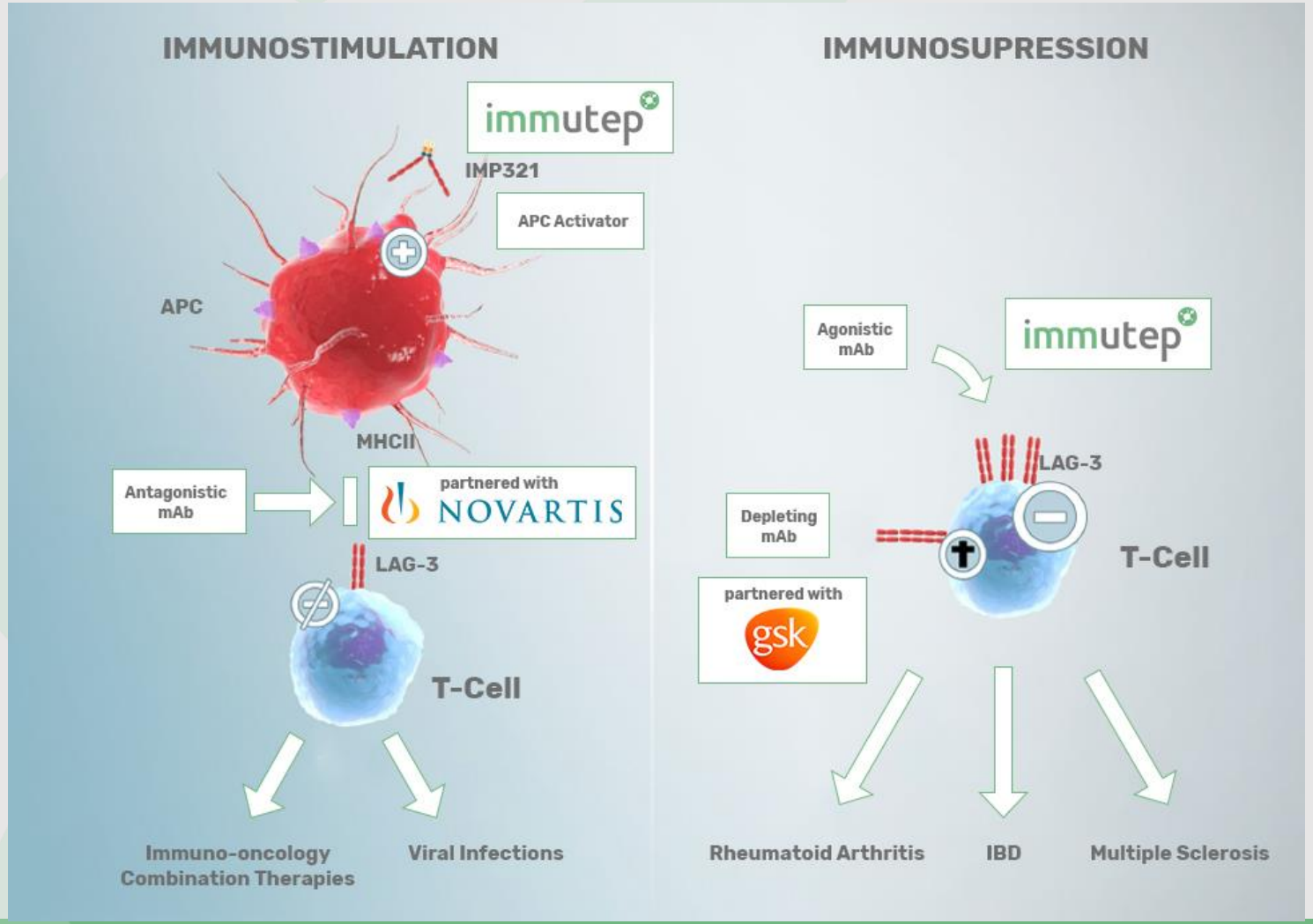
Program	Company	Preclinical	Phase I	Phase I/ II	Phase II	Phase IIb	Phase II/III	Total Estimated Patients
Eftilagimod Alpha	Immutep[1], [2]		●		●	●		385
LAG525	Novartis[3], [4]			●	● ● ●			961
Relatlimab	BMS[4], [5]		● ● ● ●	● ● ● ●	● ● ● ●		●	4,084
GSK2831781	GSK(3)			●				67
BI 754111	B.I.		● ●					234
MGD013	Macrogenics		●					131
MK4280	Merck & Co. Inc.		●					240
REGN3767	Regeneron/ Sanofi		●					301
TSR-033	Tesaro		●					260
Eftilagimod Alpha	IKF[6]		●					38
FS-118	F-Star		●					51
SYM022	Symphogen A/S		●					30
IMP761	Immutep	●						N/A
N/A	Agenus/ Incyte	●						N/A
AM003	Armo Biosciences	●						N/A

(1) Includes AIPAC, TACTI-mel, and planned Phase 2 clinical trial in collaboration with Merck & Co., Inc. (MSD)
(2) As of April 23, 2018, one clinical trial has not opened for recruitment
(3) Immutep partnered program
(4) As of April 23, 2018, two clinical trials have not opened for recruitment
(5) Includes one clinical trial involving relatlimab where BMS is not the sponsor
(6) INSIGHT investigator sponsored clinical trial

● Indicates product candidate developed by Immutep research & development

Sources: GlobalData, company websites, clinical trials.gov, and sec.gov
Information as of April 23, 2018

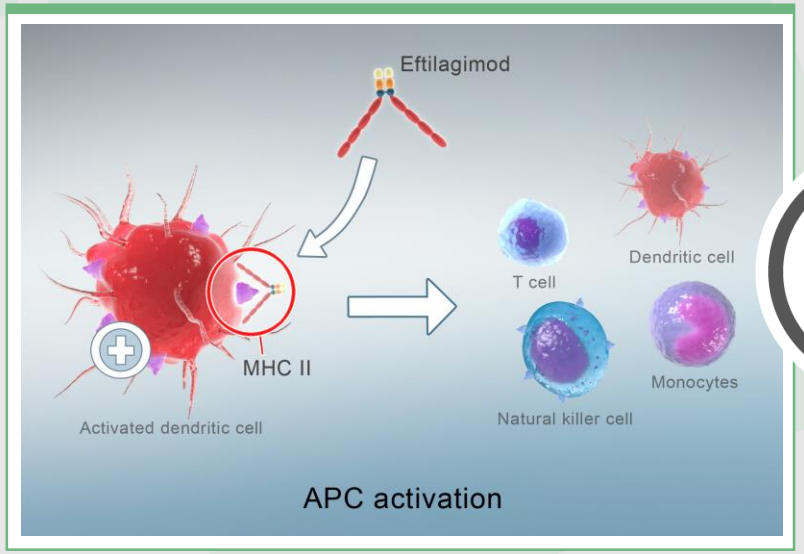
Targeting LAG-3 May Lead to Multiple Therapeutics in Numerous Indications



Eftilagimod Alpha: 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 LAG-3)
- Synergistic with other I-O agents

“PUSHING THE ACCELERATOR ON IMMUNE RESPONSES”

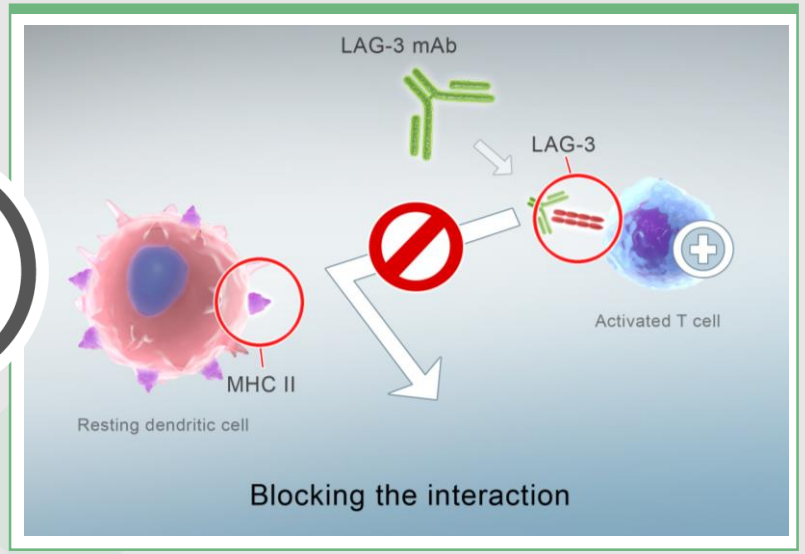


LAG-3Ig, an MHC II **agonist** (eftilagimod alpha) :

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-existingCD8 T cell response

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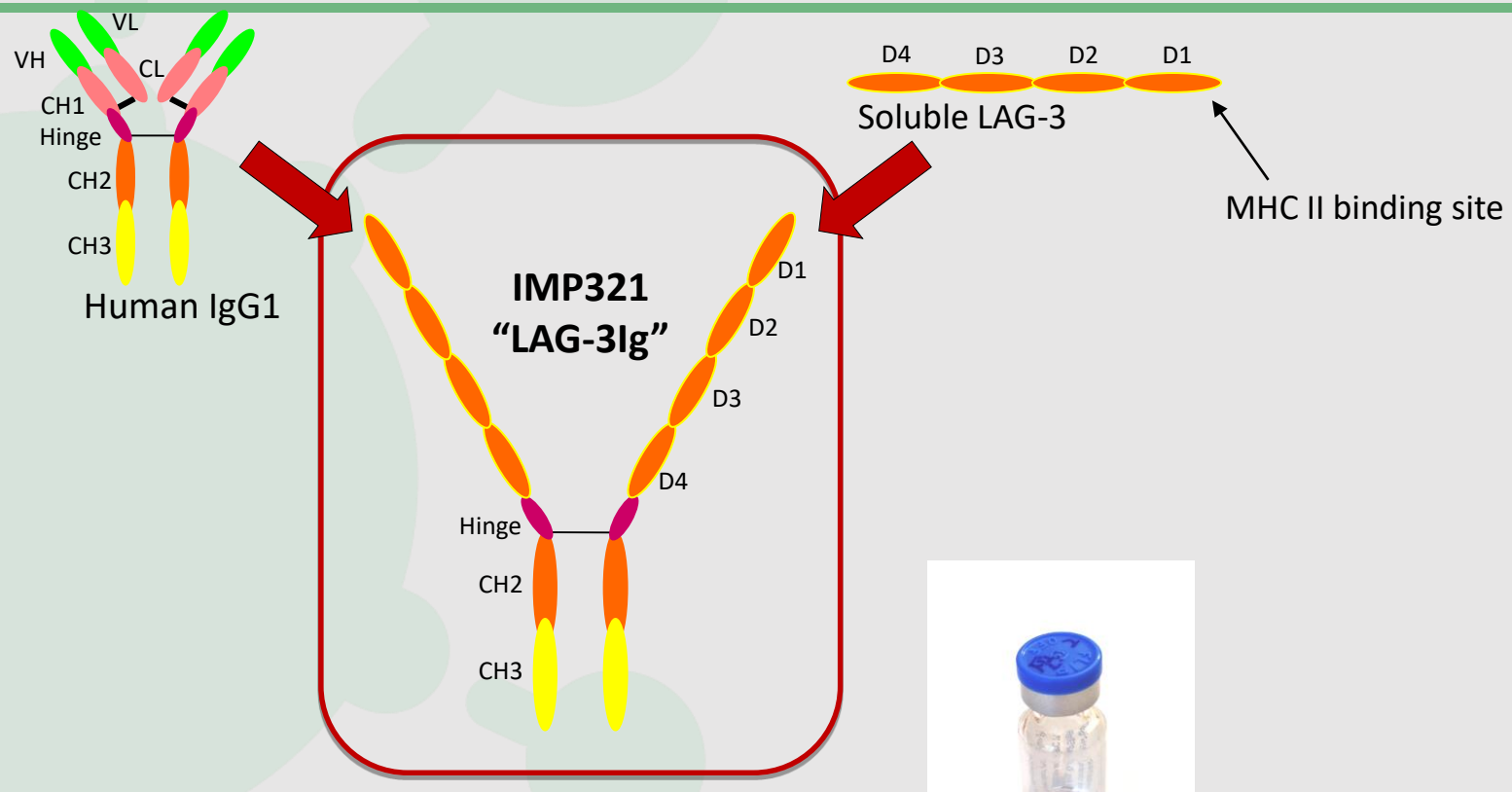
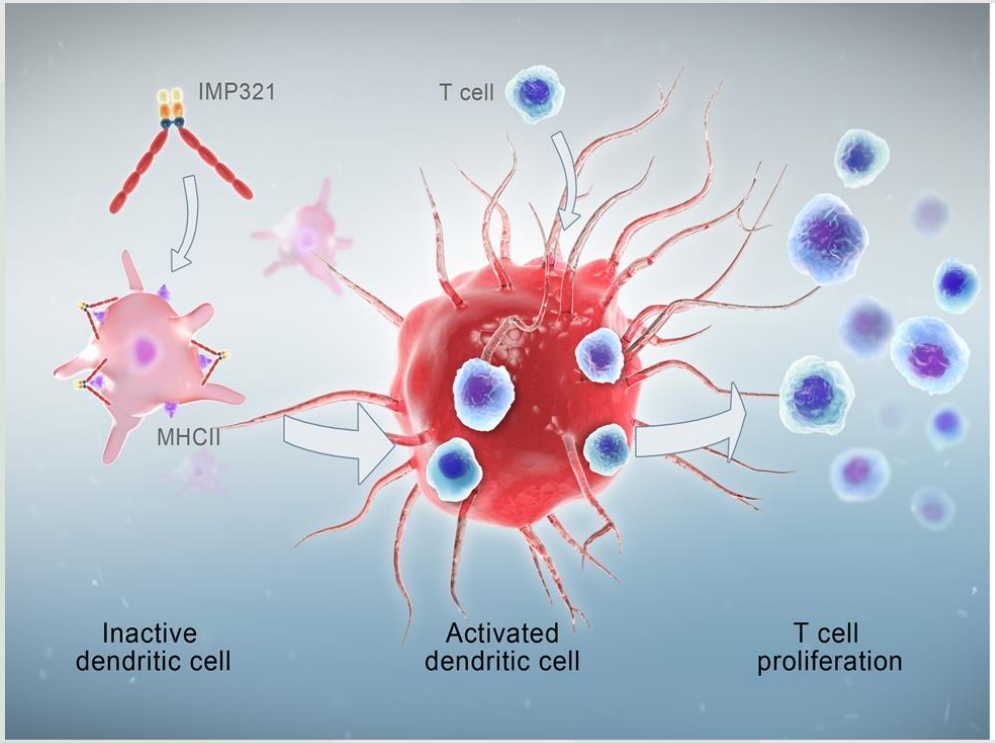
Lead Program
Eftilagimod Alpha (IMP321)

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**

Eftilagimod alpha (IMP321) MoA



→ IMP321 binds to MHC class II on monocytes

→ DC/ monocyte activation induced

→ Leads to T cell expansion and proliferation

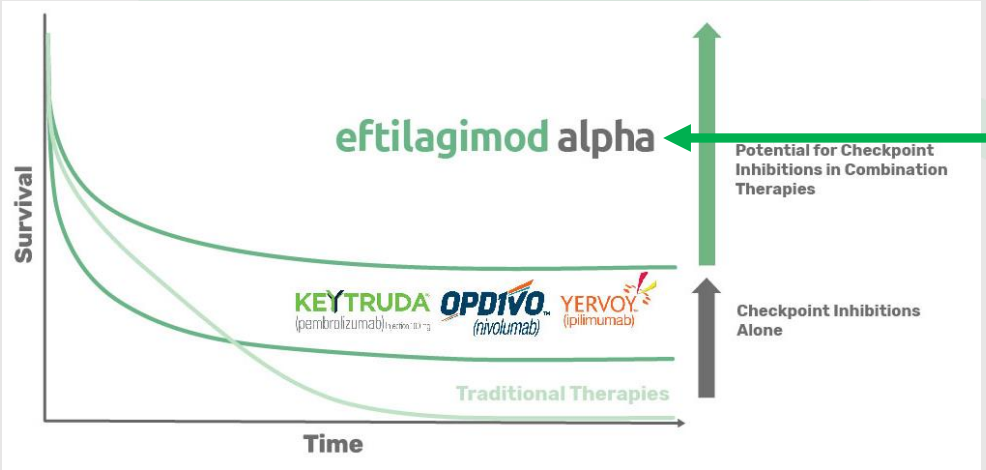
- Highly efficacious in multiple animal models of cancer and infectious disease
- Shown to be safe, non-immunogenic and efficacious in human

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



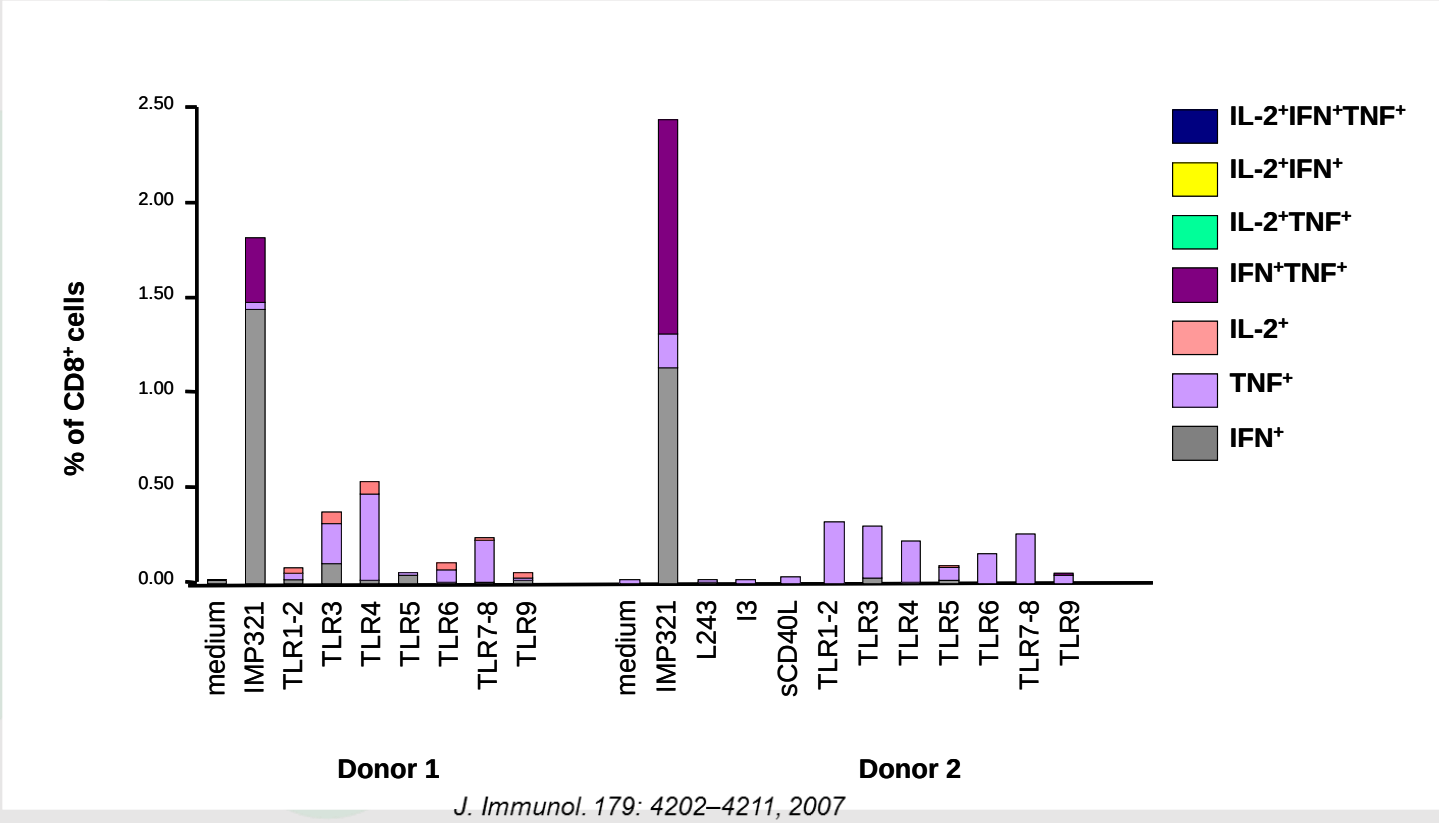
APC activators:

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

Eftilagimod alpha (IMP321)

Induces Better CD8 Tc1 Differentiation Than sCD40L or TLR Agonists

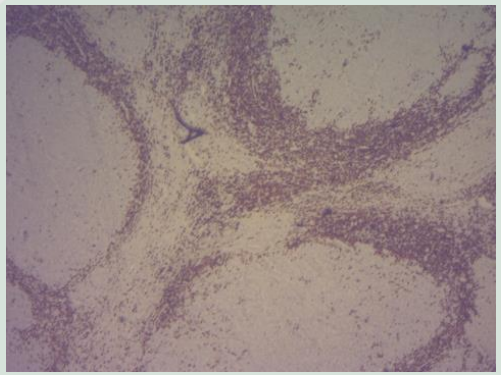
- Human blood lymphocytes are analyzed in a 16 hr *ex vivo* assay
- Intracellular staining of CD8 T cells
  - Only IMP321 induces strong IFN^+ or IFN^+/TNF^+ CD8 T cell responses
  - explanation: TLR agonists but not IMP321 induce IL-10 production which suppresses Tc1 differentiation



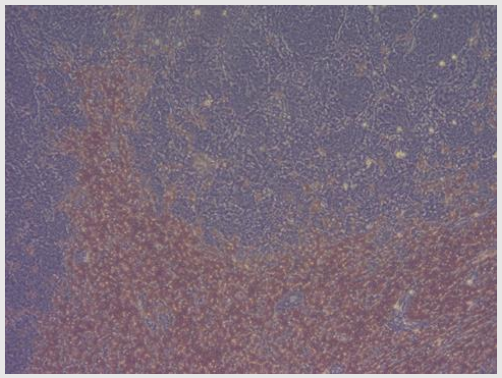
J. Immunol. 179: 4202–4211, 2007

APC Activation Turns on the Heat on a Cold Tumor
(Breast Cancer Liver Metastasis)

CD3 (x5)



CD3 (x10)



Massive infiltration of T cells (IHC) around the tumor nodules. Some CD3 T cells infiltrating the tumor nodules.

Hemihepatectomy for single residual tumor mass after 13 IMP321 s.c. injections in a MBC patient treated with weekly paclitaxel (AIPAC run-in phase)

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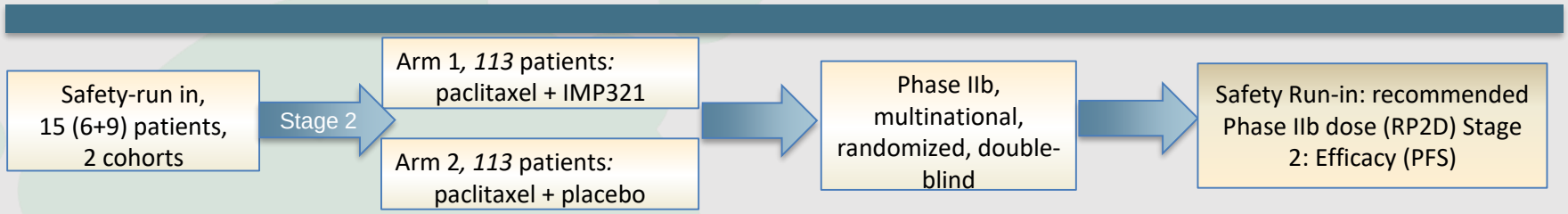
Clinical Development
Eftilagimod Alpha (IMP321)

Eftilagimod alpha – Potential Applications

Potential combination therapy strategies:

- **Chemo-immunotherapy** in various cancer indications
  - Combination therapy with active agents such as Taxanes (e.g. Paclitaxel), anthracyclines, alkylating agents, anti-metabolites, vincas…
- **I-O combination** in various cancer indications
  - With PD-1, PDL-1 or CTLA-4 antagonists…
- **Cancer vaccine or intra-tumoral injections (in situ immunization)**
  - To locally stimulate the immune system

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)

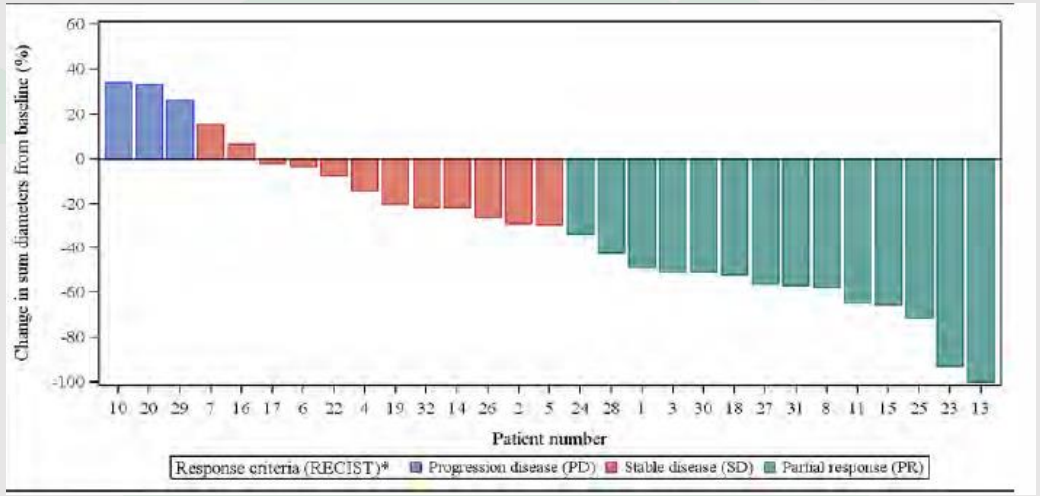
✓ Interim-data of safety run-in presented at ASCO 2017

✓ 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

Eftilagimod alpha – Preliminary Efficacy
MBC – 1st line chemotherapy + IMP321

P005 – phase I



- **ORR of 47 % and DCR of 83 % after 6 months**
- Responders had further tumor shrinkage between months 3 and 6

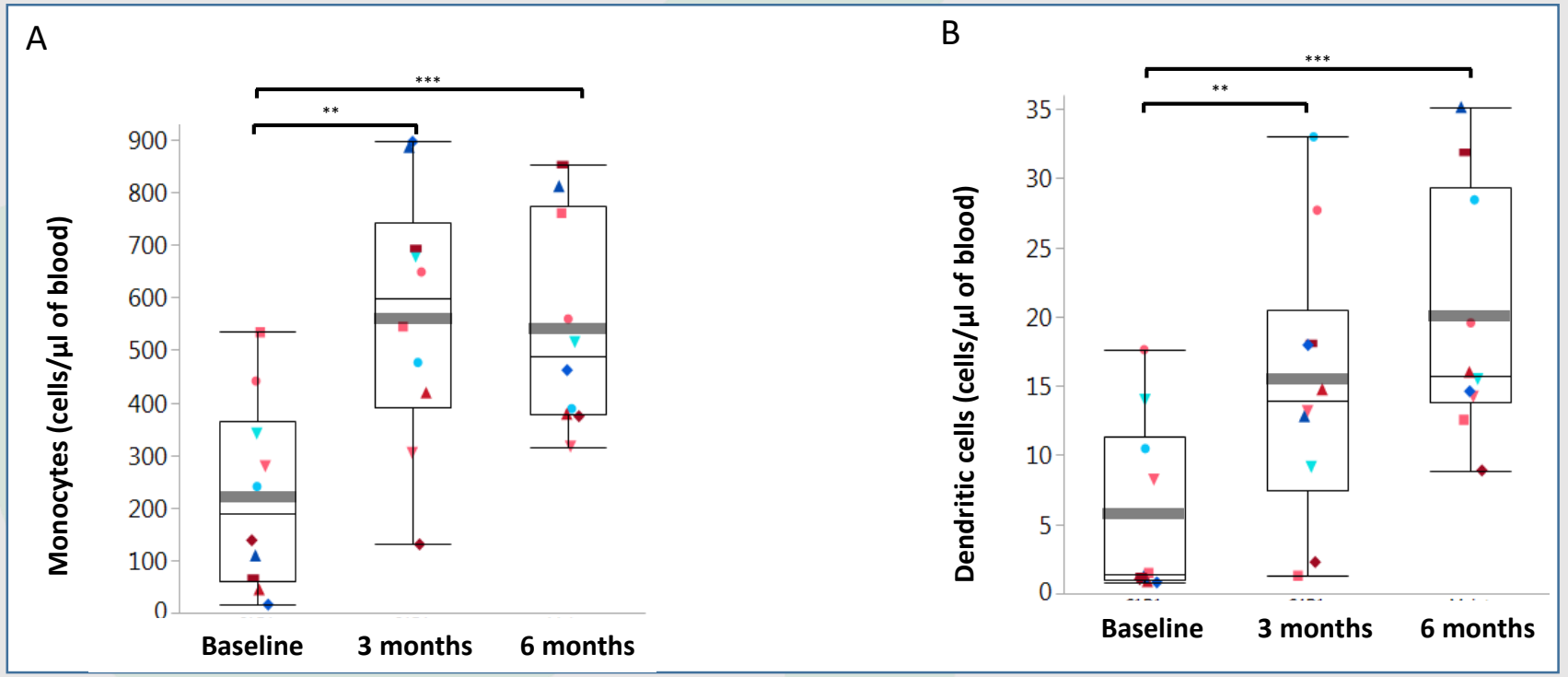
AIPAC (P011) – phase I trial

Response parameter	Paclitaxel + IMP321 (n = 15)
Complete Response (CR)	0/15 (0 %)
Partial Response (PR)	7/15 (47 %)
Stable Disease (SD)	6/15 (40 %)
Progressive Disease (PD)	2/15 (13 %)
Overall Response Rate (ORR)	7/15 (47 %)
Disease Control Rate (DCR)	13/15 (87 %)

- **ORR of 47 % and DCR of 87 %**
- Two of the responses occurred relatively late (after ~6 months)

Compared to historical control groups with 22-33 %, response rates are encouraging

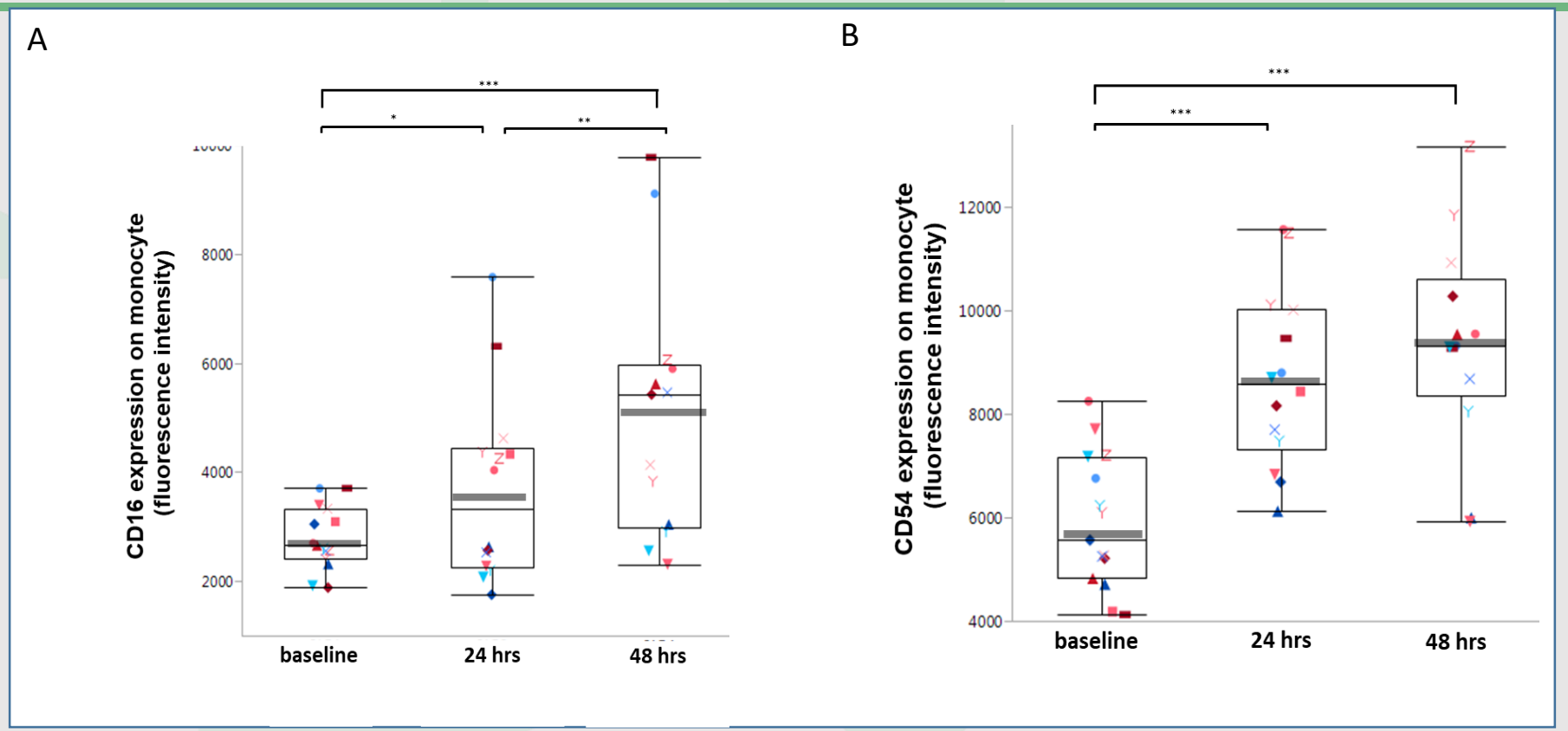
Eftilagimod alpha – Clinical Overview
Pharmacodynamic Results on Primary Target Cells



IMP321 leads to sustainable (> 6 months) increase of pre-dose APCs (run-in phase, AIPAC trial).

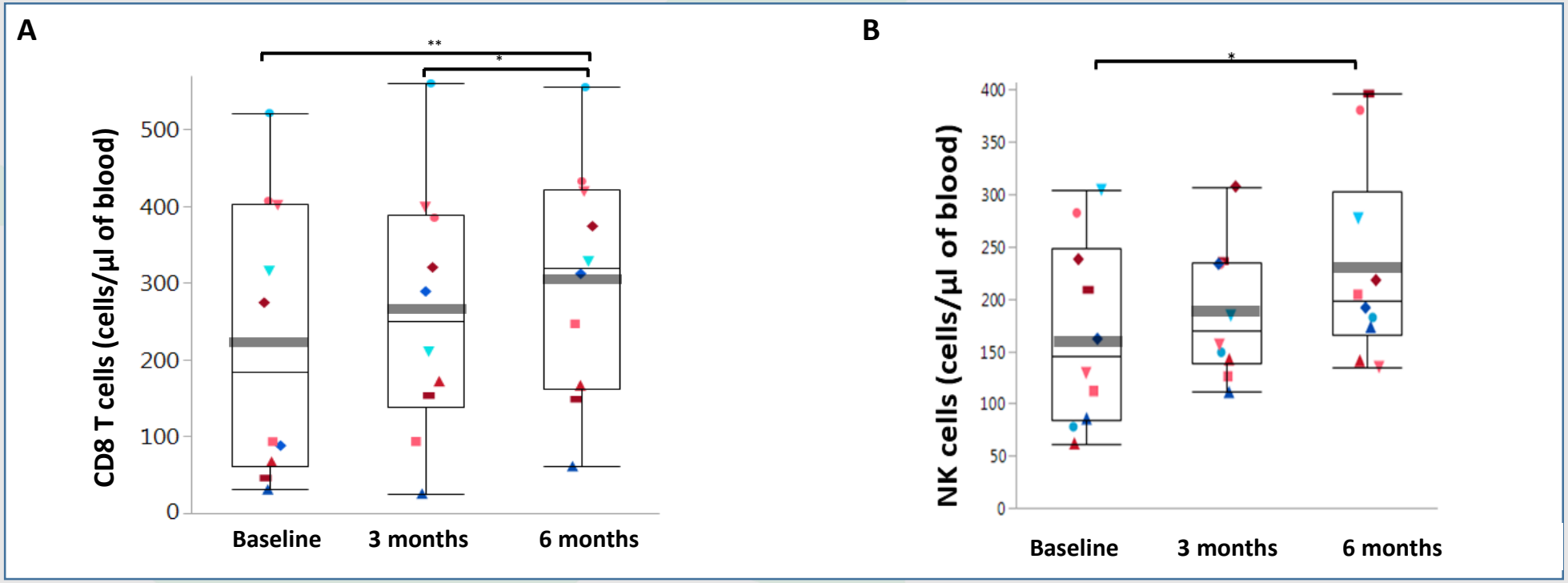
Eftilagimod alpha – Clinical Overview (cont.)

Pharmacodynamic Results on Primary Target Cells



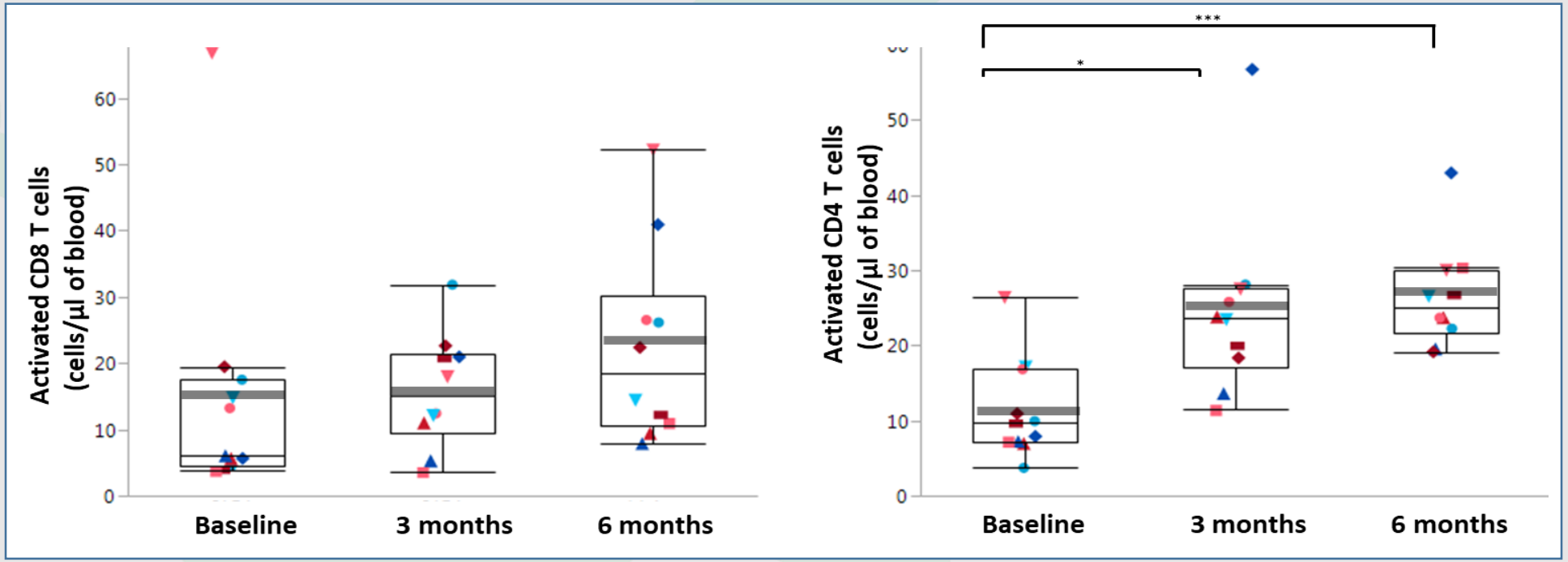
IMP321 activates APCs (run-in phase, AIPAC trial).

Eftilagimod alpha – Clinical Overview (cont.)
Pharmacodynamic Results on Secondary Target Cells



IMP321 leads to sustainable (> 6 months) increase of pre-dose effector CD8 T cells and NK cells (run-in phase, AIPAC trial).

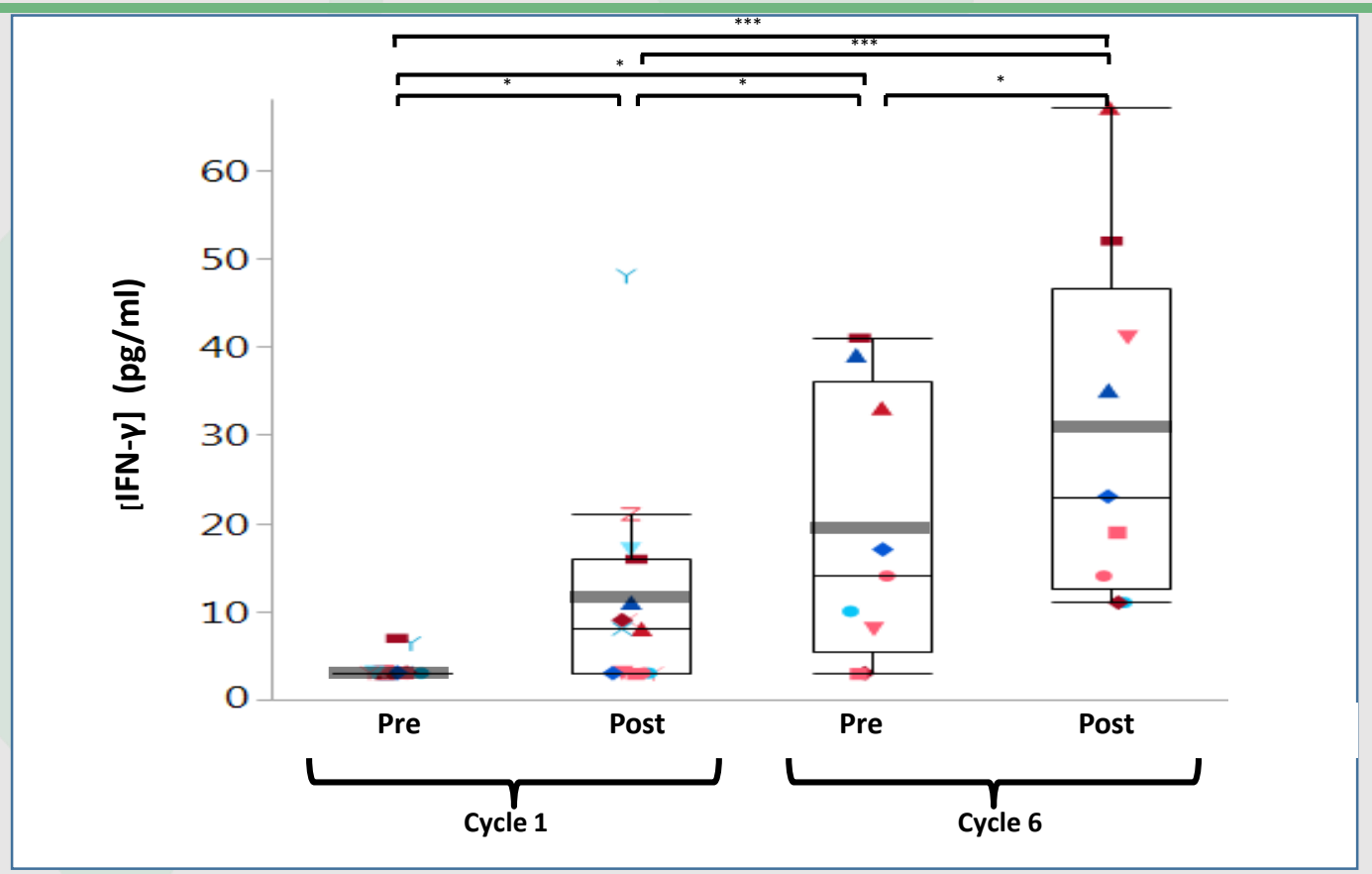
Eftilagimod alpha – Clinical Overview (cont.)
Pharmacodynamic Results on Secondary Target Cells



IMP321 leads to sustainable (> 6 months) increase of pre-dose activated (HLA-DR $^{+}$ CD38+) CD4 and CD8 T cells (run-in phase, AIPAC trial).

Eftilagimod alpha – Clinical Overview (cont.)

Improved Th1 status



IMP321 leads to an improved pre-dose Th1 status (IFNγ, IP-10 not shown) (run-in phase, AIPAC trial), a phenomenon not seen with therapeutic anti-PD-1 mAbs.

Eftilagimod Alpha INSIGHT Clinical Trial
Investigator Initiated Trial

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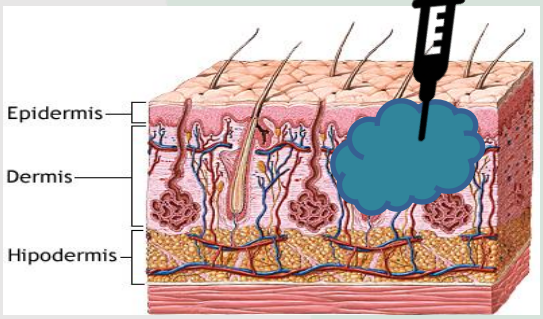
Eftilagimod Alpha in i.t. and i.p. application

- Prof. Al-Batran, IKF, Frankfurt, Germany
- Population: 38 pts (9 pts per stratum A and B, 20 pts in stratum C) with advanced solid tumors w/o standard treatment options
- Objectives: Recommended Phase II dose, PD effects of IMP321
- Design: intrapatient escalation

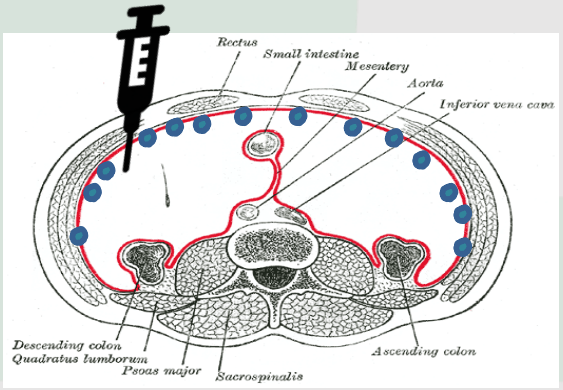
Group A: intratumoral (i.t.)



6 mg 12 mg 24 mg 30 mg

Treatment

Group B: intraperitoneal (i.p.)



1 mg 3 mg 6 mg 12 mg 30 mg

Treatment

https://upload.wikimedia.org/wikipedia/commons/thumb/1/19/Gray1038.png/250px-Gray1038.png
https://cdn.thinglink.me/api/image/578616053681094658/1240/10/scaletowidth

Group A:

- 6 pts enrolled, 6 on treatment → no DLT so far

Group B:

- 2 pts enrolled, 2 on treatment → no DLT so far

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Eftilagimod Alpha/Pembrolizumab Combination

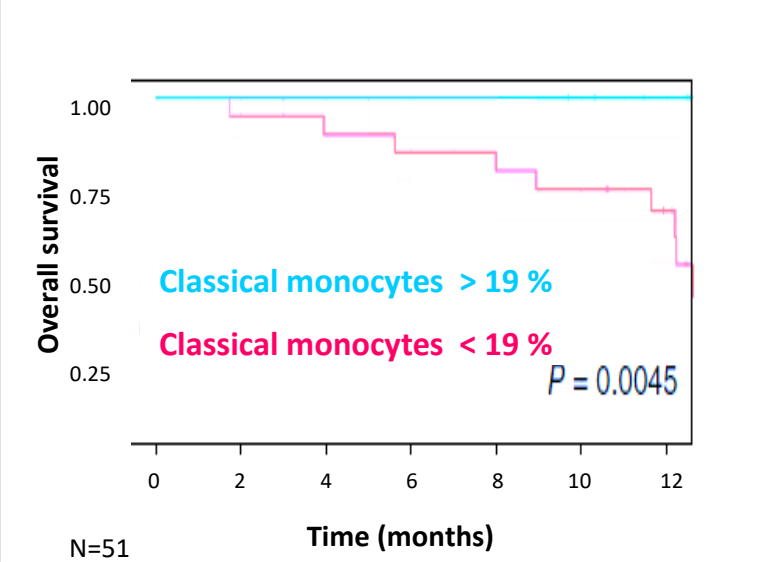
Three Groups of Patients Responding to anti-PD-1 (IFN-γ signature)

- A- Inflamed responders – respond to anti-PD-1
- B- Inflamed non-responders (some infiltrates in the tumor margins but no response)
- C- Non inflamed. “Cold tumor” with no response

- Optimal checkpoint combos will target groups B and C and help them:
  - Promote cross presentation of tumor antigens
  - Induce T cell recruitment into tumor microenvironment

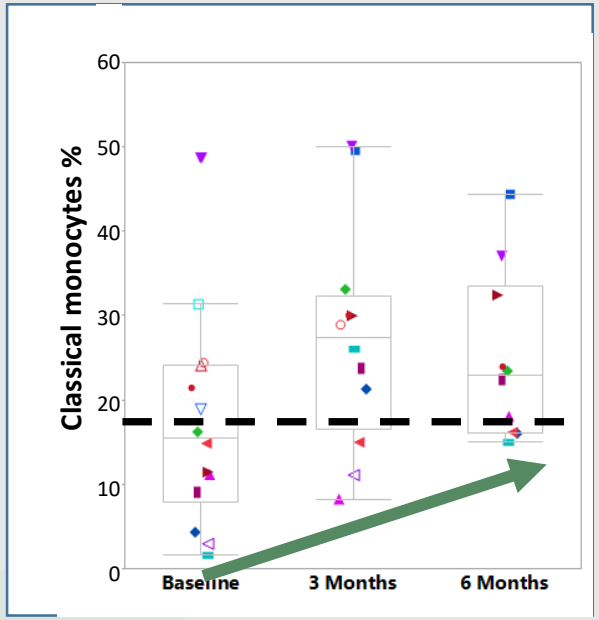
New rationale for combining eftilagimod alpha to pembrolizumab

Problem: melanoma patients with low monocyte numbers at base line are not responding well to anti-PD-1 therapy.



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

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



Source: AIPAC stage 1

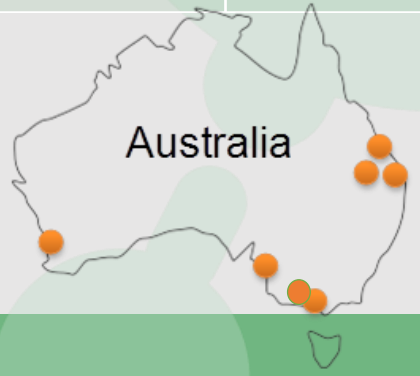
Monocytes are important for response to pembrolizumab → IMP321 (eftilagimod) increases monocytes sustainably above the threshold of 19 % →it increases the chance to respond to pembrolizumab

Efti (IMP321) in Melanoma
TACTI-mel (IO combination) – trial design

TACTI-mel = Two ACTive Immunotherapeutics in melanoma

24 patients, 4 cohorts of 6 patients → 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 (RP2D) 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

→ Status: recruitment completed; interim results on next slides

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

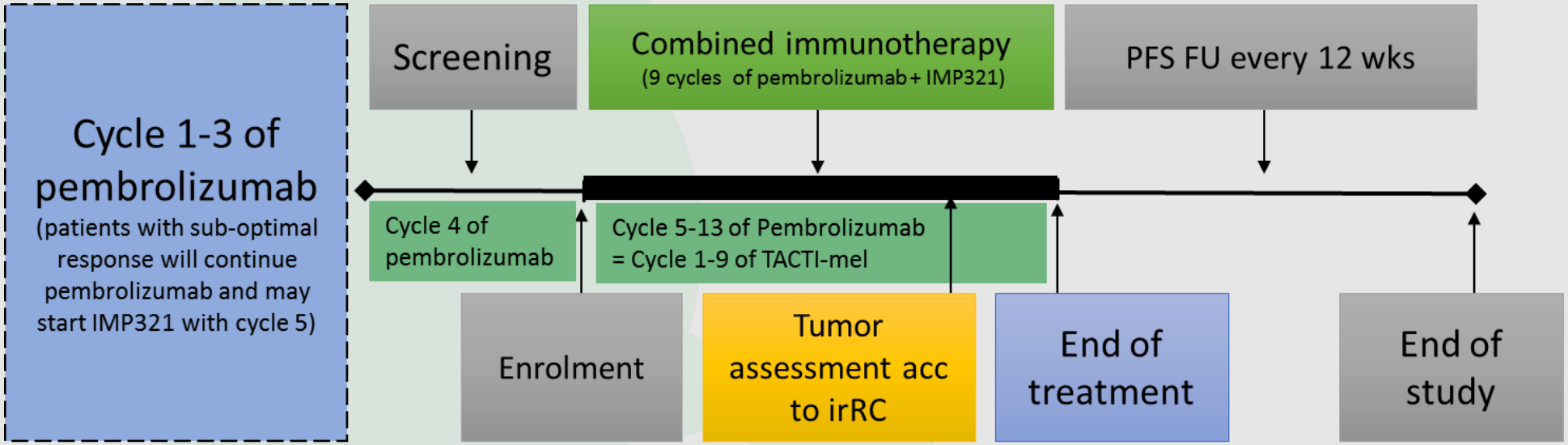
→ Status: 3 pts enrolled w/o DLTs

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

preliminary data, status 9th May 2018

Efti (IMP321) in Melanoma
TACTI-mel (IO combination) – details part A

Study Scheme Part A:



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

preliminary data, status 9th May 2018

Efti (IMP321) in Melanoma
TACTI-mel (IO combination) – results after start of combo (1)

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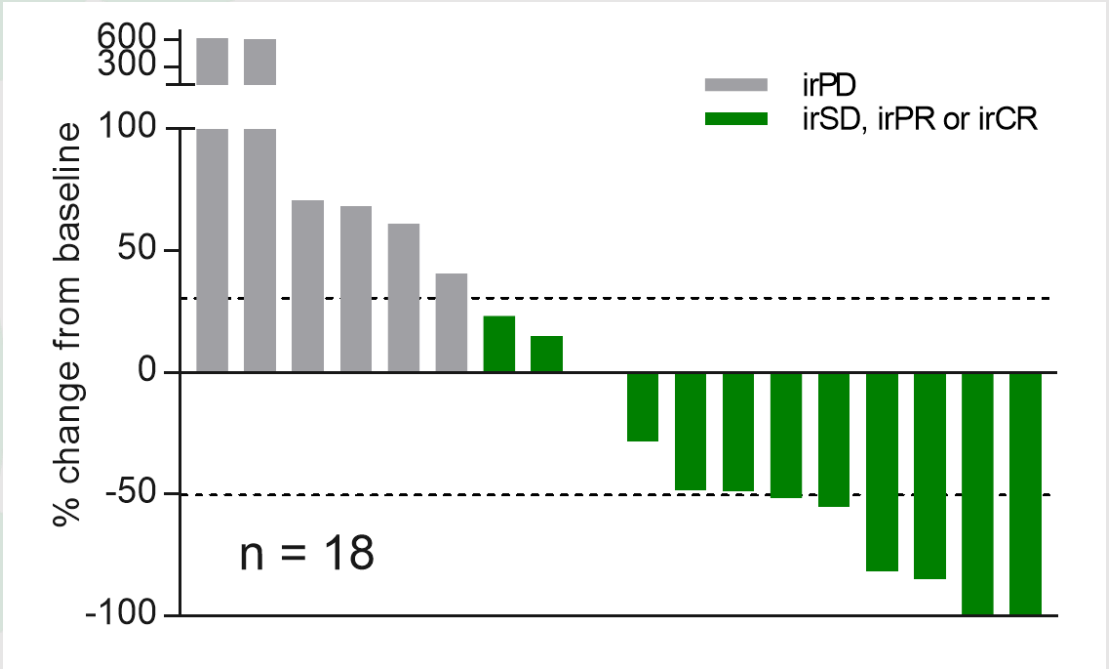
Baseline Characteristics	N = 18 (%)
Visceral Disease	15 (83 %)
Pre-treated with BRAF/MEK/ipilimumab	4 (22 %)
irPD/irSD to pembrolizumab after 3 cycles	12 (67 %)

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

Waterfall plot starting from cycle 5 of pembrolizumab



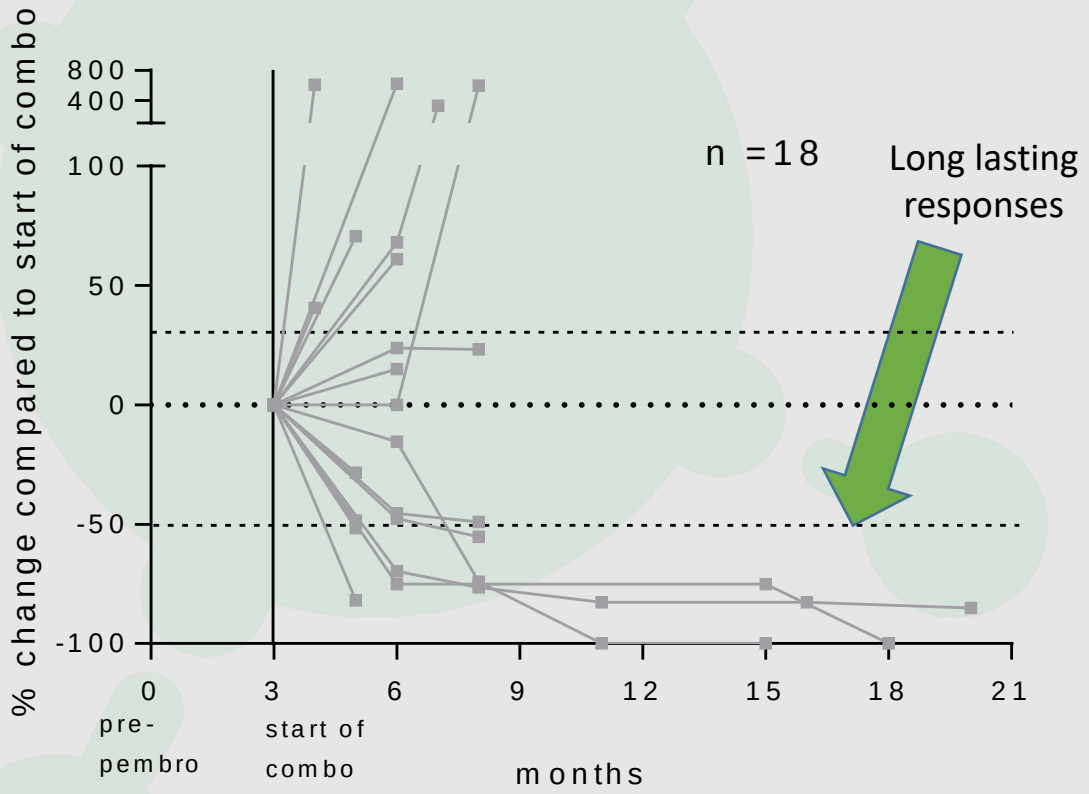
- Patients very late stage of disease (M1C)
- Majority not responding to pembrolizumab

→ Tumor shrinkage in 50 % of these patients incl. 2 pts with complete disappearance of all target lesions

preliminary data, status 9th May 2018

Efti (IMP321) in Melanoma
TACTI-mel (IO combination) – results after start of combo (2)

Spiderplot - cohort 1-3 (n=18) – May 2018



Conclusion

- Complete responses of target lesions occurred after 11 and 18 months --> **combination takes time to act**
- 3 (out of 12 = 25 %) durable responses in first 2 dose levels → treatment and FU ongoing
- **Treatment and follow-up of 3 patients in 3rd cohort (30 mg) ongoing**

preliminary data, status 9th May 2018

Efti (IMP321) in Melanoma
TACTI-mel (IO combination) – single case at 1 mg efti

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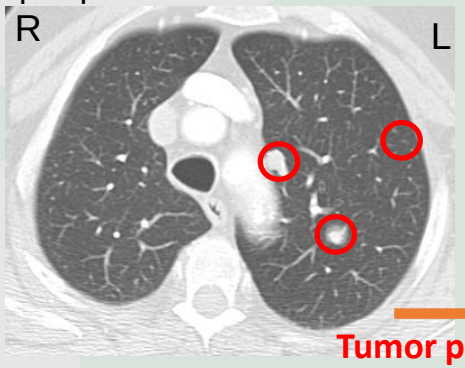
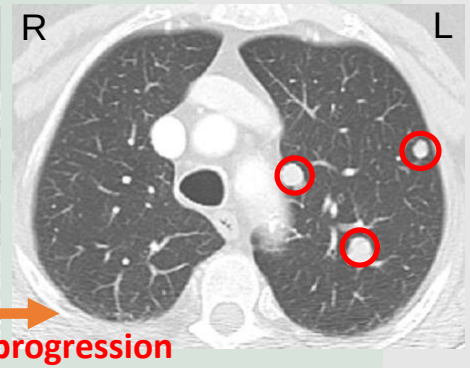
Efficacy: metastatic melanoma

pre-pembro

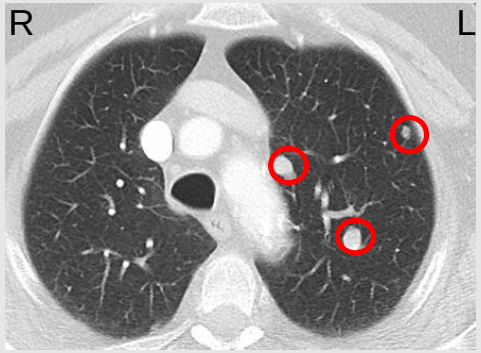


week 9 (pembro)

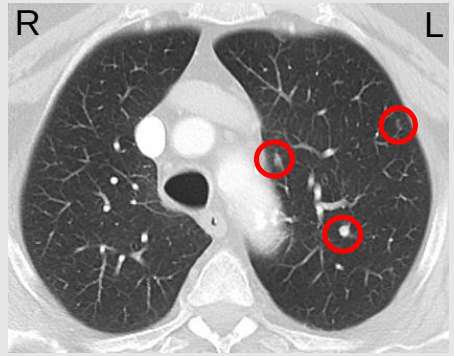


Tumor progression

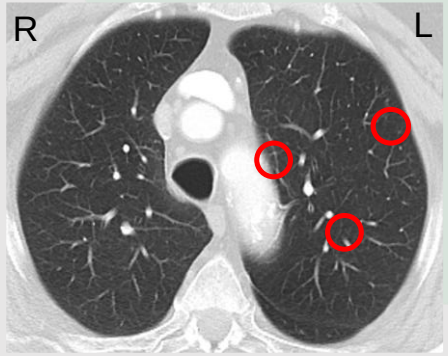
week 25 (combo)



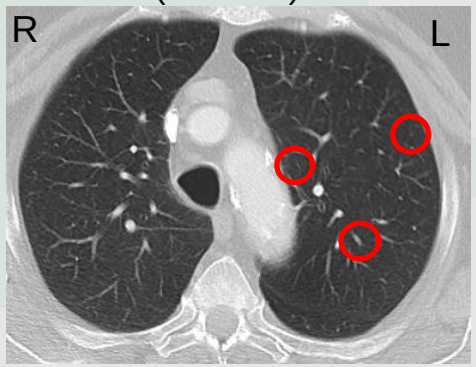
week 37 (combo)



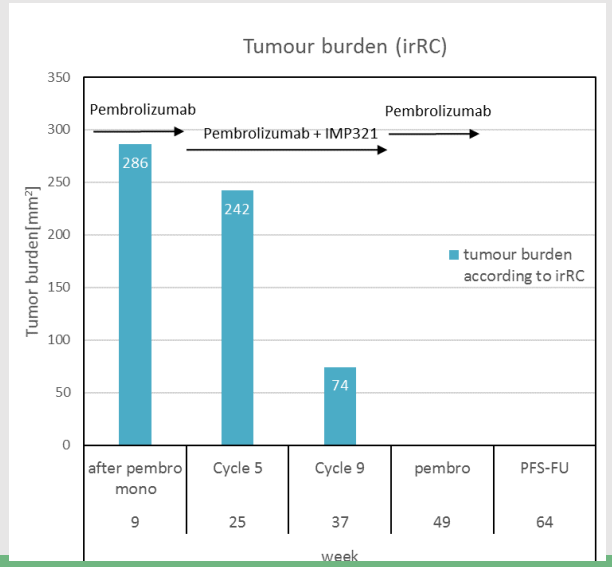
week 49 (Pembro mono)



week 64 (PFS-FU)



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



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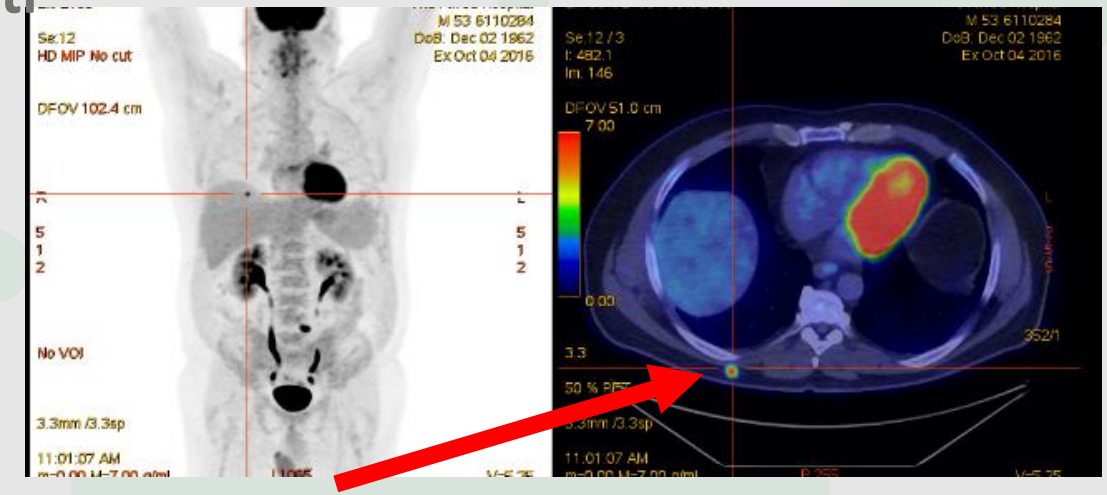
confidential

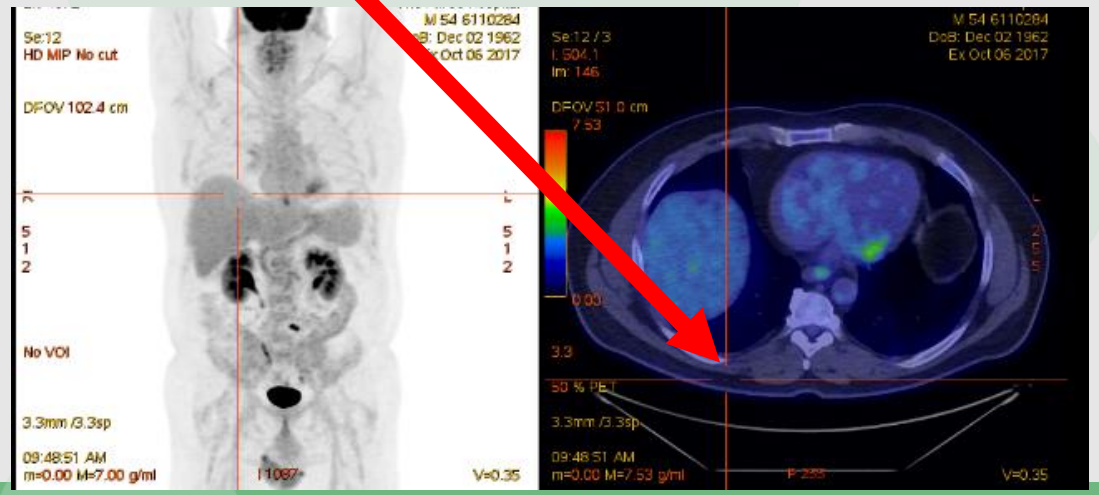
Efti (IMP321) in Melanoma
TACTI-mel (IO combination) – single case at 6 mg efti

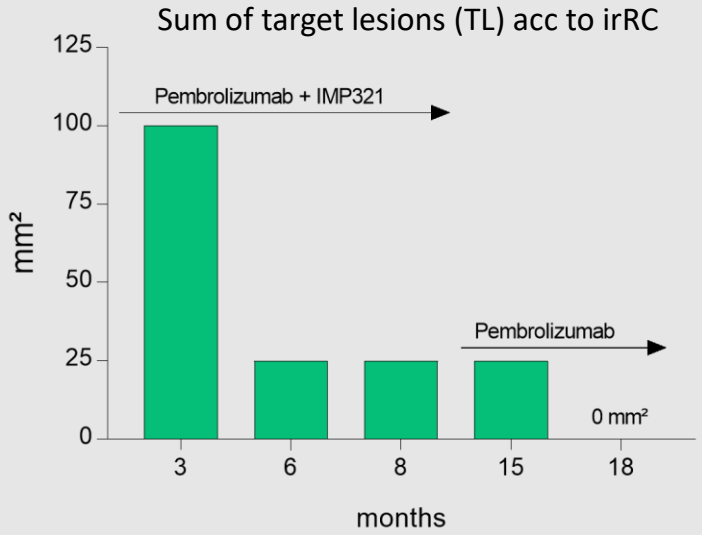
Pre pembro



Target lesion: chest wall

9 months after start of combo





Σ TL (irRC)	100 mm²	25 mm²	25 mm²	25 mm²	0 mm²
In %	0 %	-75 %	-75 %	-75 %	-100 %
Response	NA	irPR	irPR	irPR	irPR

- **Complete disappearance of target lesions → CR acc. to RECIST 1.1**
- **Patient still on pembrolizumab**

preliminary data, status 9th May 2018

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Thank you

Frédéric Triebel MD, PhD

Third Annual Advances in Immuno-oncology Congress

London, May 25, 2018