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LAG-3 IMMUNOTHERAPY

LAG-3: the next immune checkpoint after CTLA-4 and PD-1/PDL-1?

Frédéric Triebel MD, PhD

Keynote session: immuno-oncology and strategies to improve patient success

WATRMC, London.

May 17, 2018

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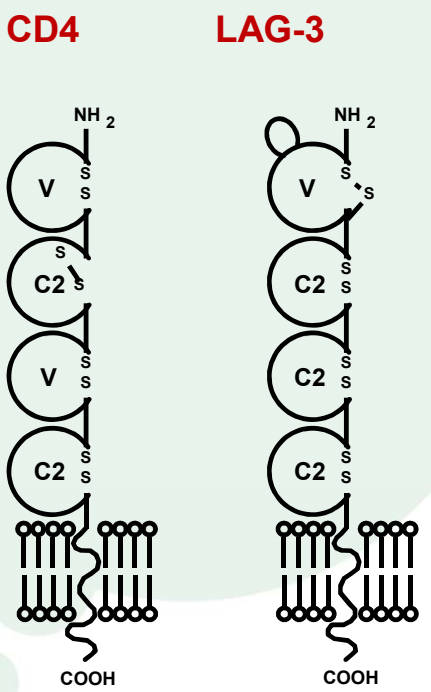
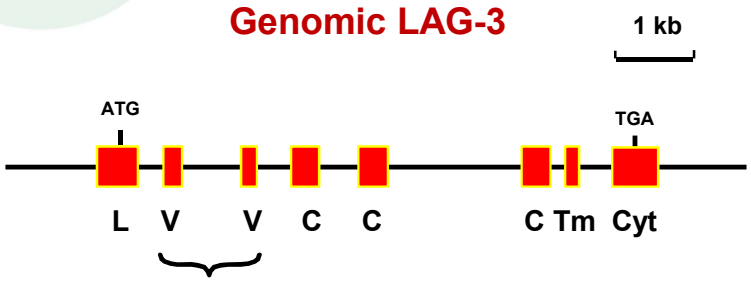
Lymphocyte Activation Gene-3 (LAG-3 or CD223)

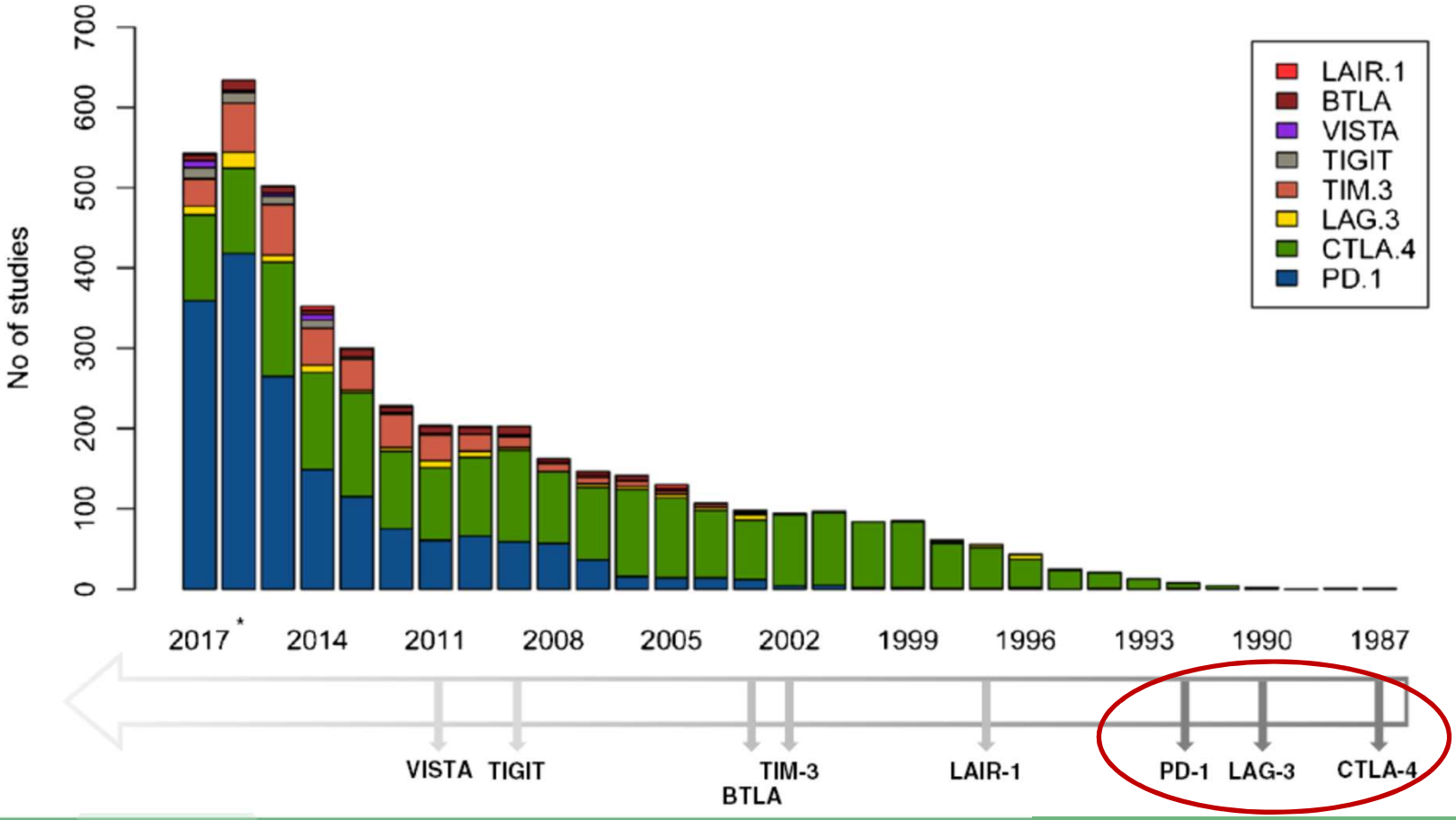




- 4-IgSF domain transmembrane proteins.
- Same genomic organization
  (intron in D1, duplication event D1D2 vs D3D4)
- Close proximity on 12p13.

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

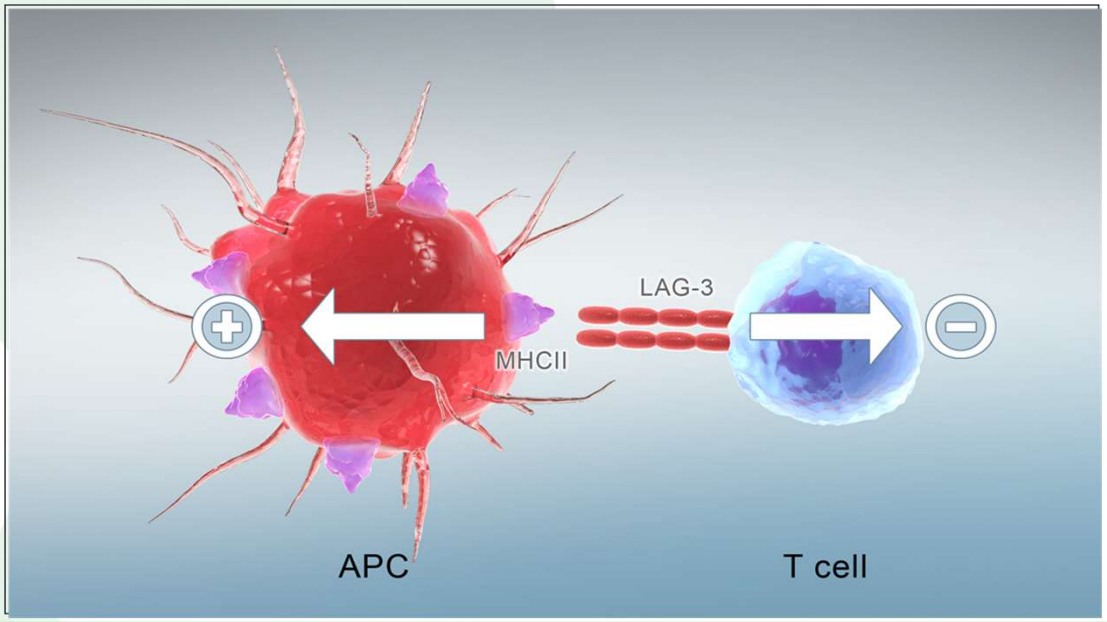
Timeline of immune checkpoint discovery.



LAG-3 as a Therapeutic Target

- LAG-3 is widely expressed on tumor infiltrating lymphocytes (TILs) and cytotoxic T cells

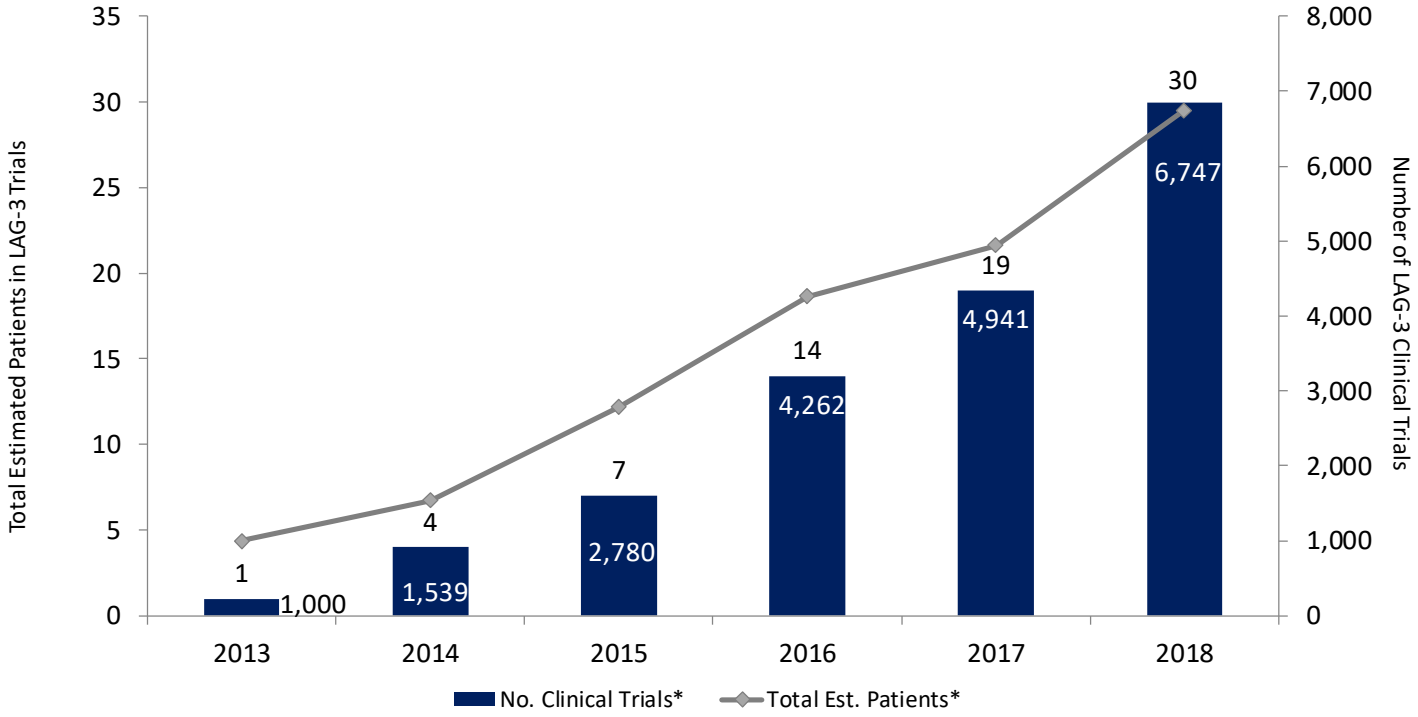
  → Prime target for an immune checkpoint blocker
- Functionally similar to CTLA-4 (targeted by Yervoy®) and PD-1 (targeted by Keytruda®)



→ **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]		●		●	●		370
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	RKF[4]		●					18
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

Notes:

(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

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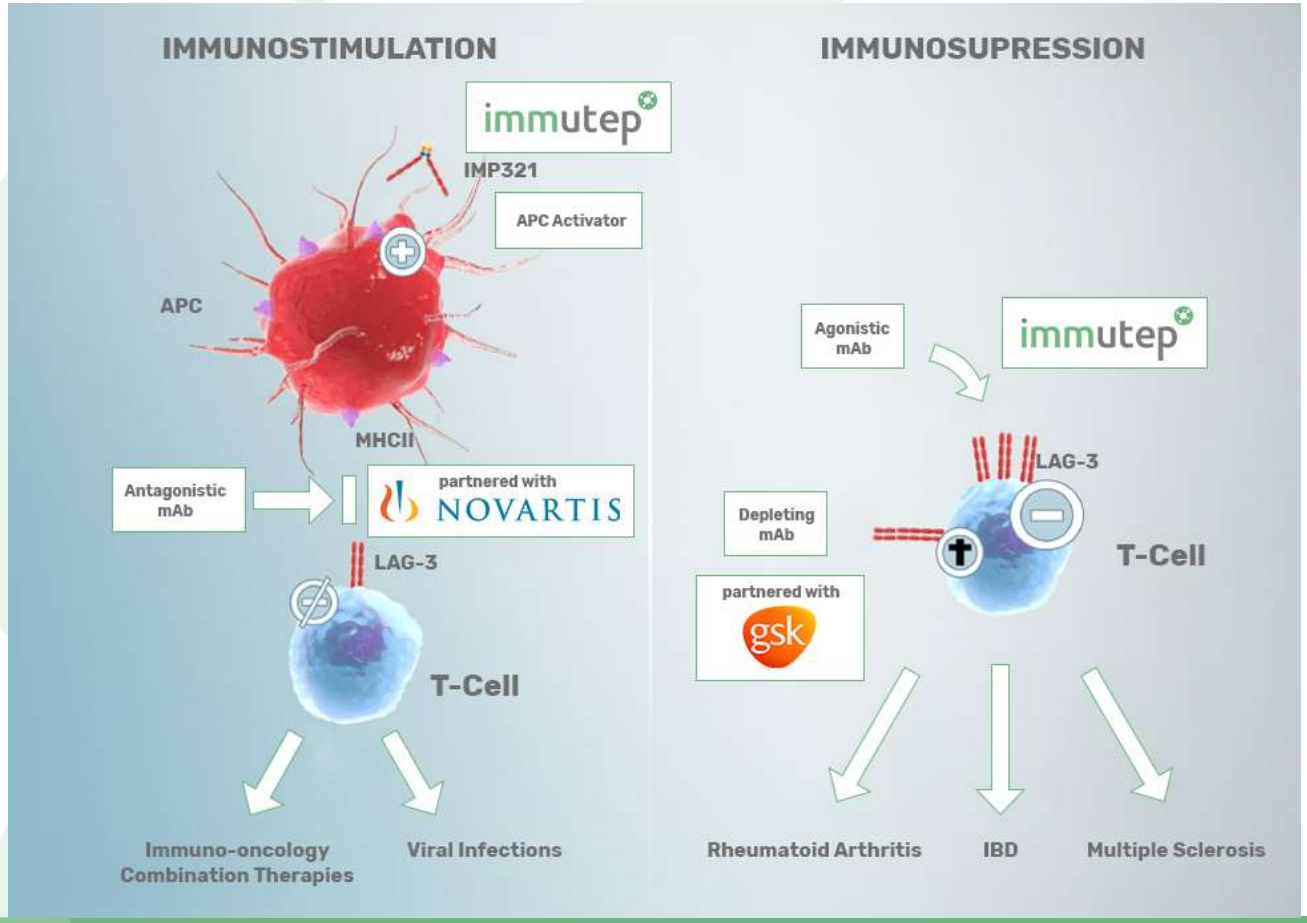
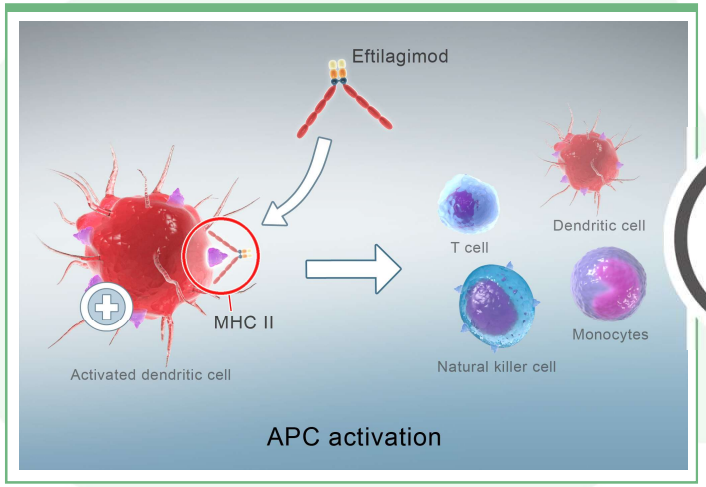


Eftilagimod Alpha: Innovative LAG-3 IO Product Candidate

- 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"

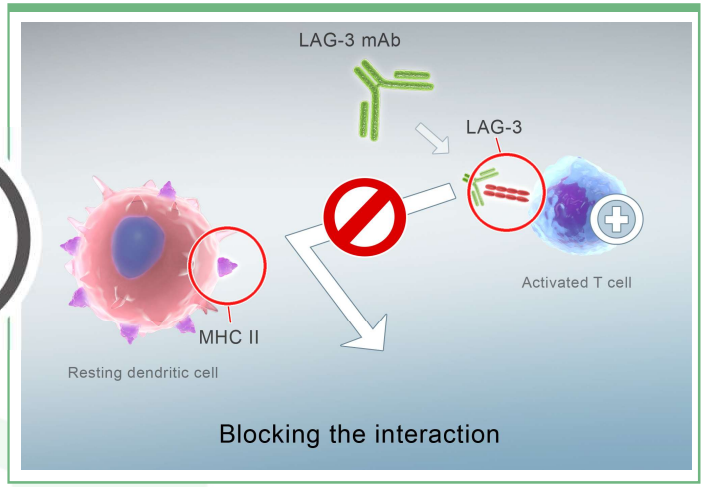


LAG-3Ig, an MHC II **agonist** (eftilagimod alpha) :

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-existing CD8 T cell response

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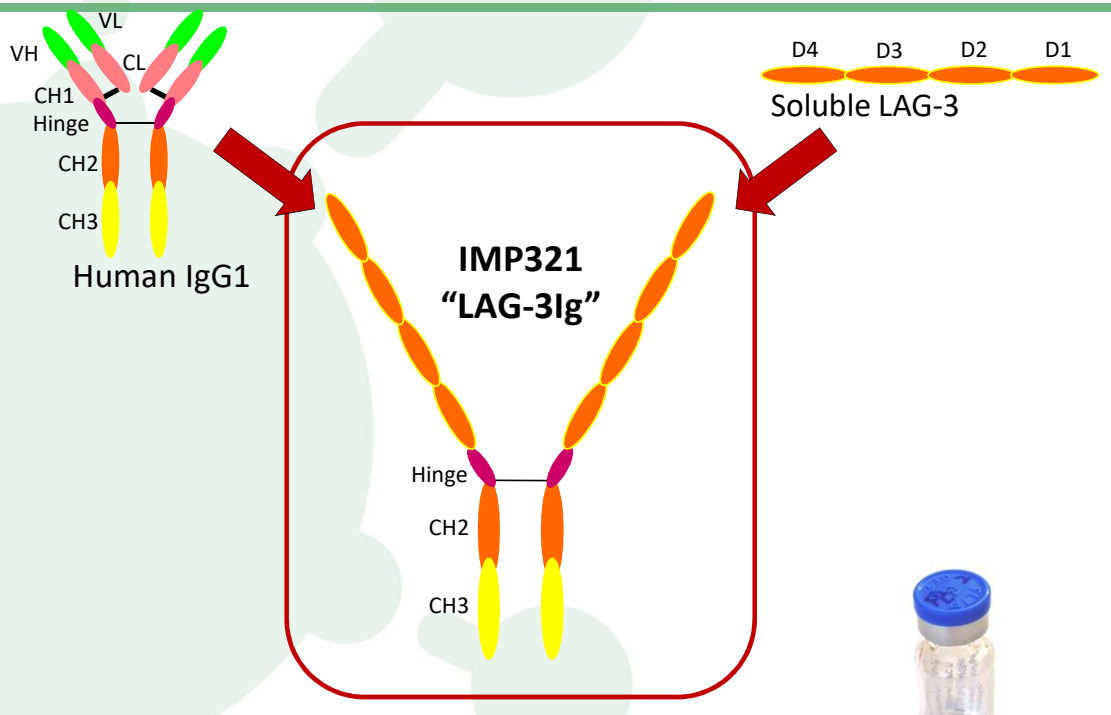
Lead Program
Eftilagimod Alpha (IMP321)

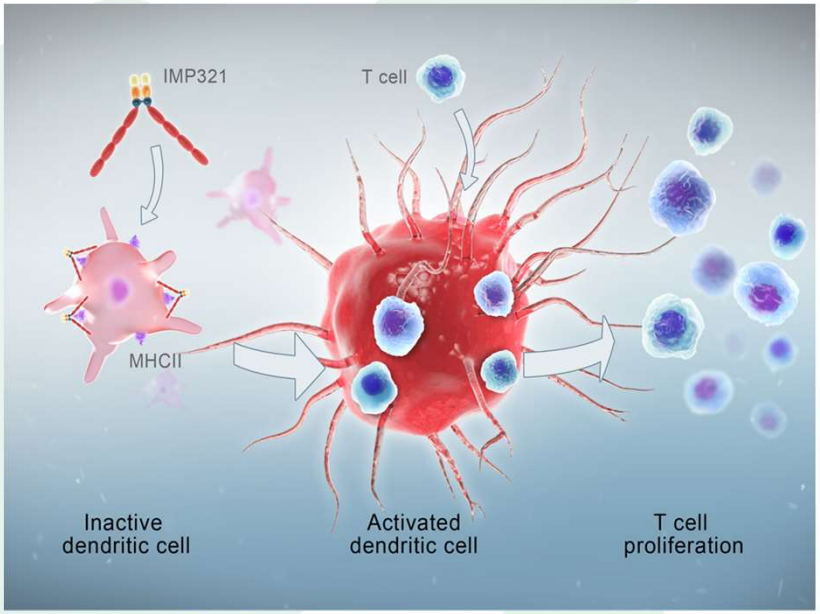
Eftilagimod alpha (IMP321)



- **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)

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



→ IMP321 binds to MHC class II on monocytes

→ DC/ monocyte activation induced

→ Leads to T cell expansion and proliferation

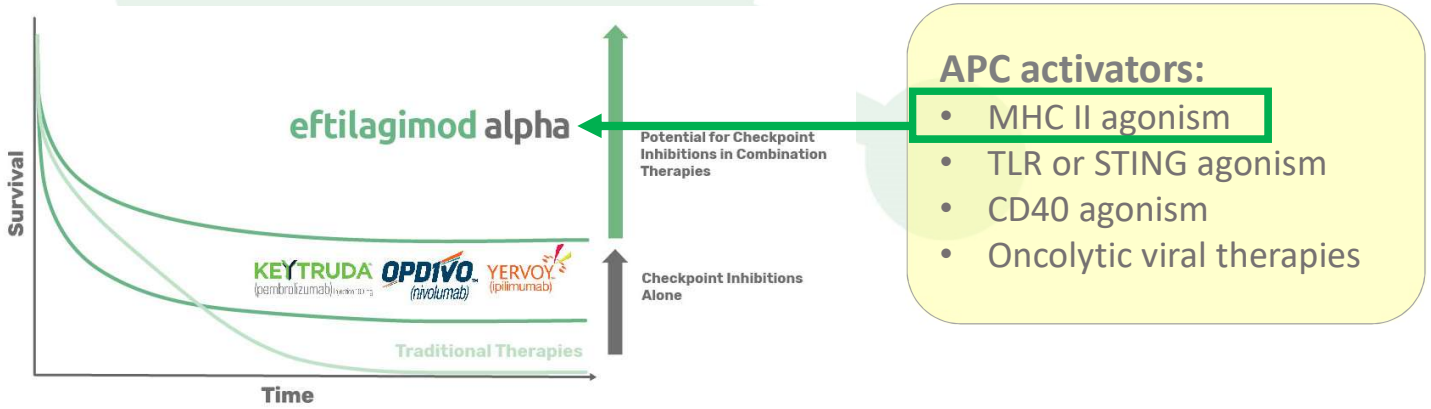
- Highly efficacious in multiple animal models of cancer and infectious disease
- Shown to be safe, non-immunogenic and efficacious in human

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

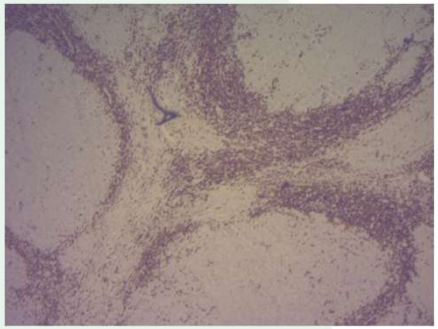
This could be achieved through the right APC activation



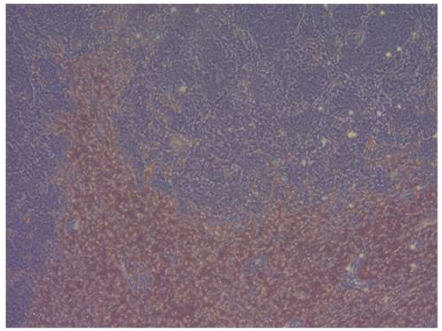
APC activators:
- MHC II agonism
- TLR or STING agonism
- CD40 agonism
- Oncolytic viral therapies

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

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

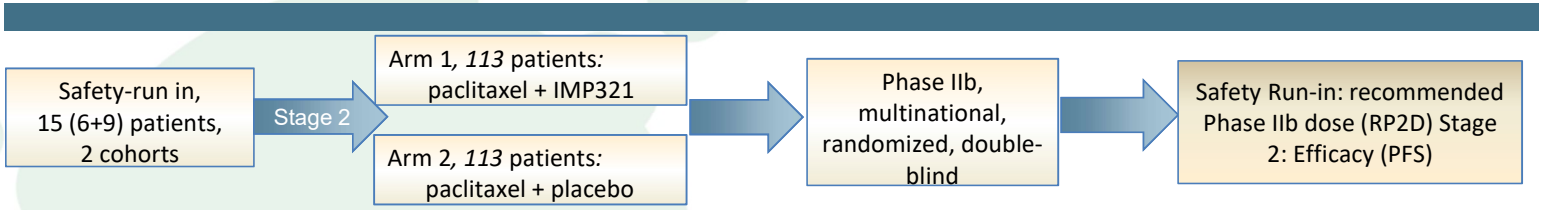
Potential combination therapy strategies:

- **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

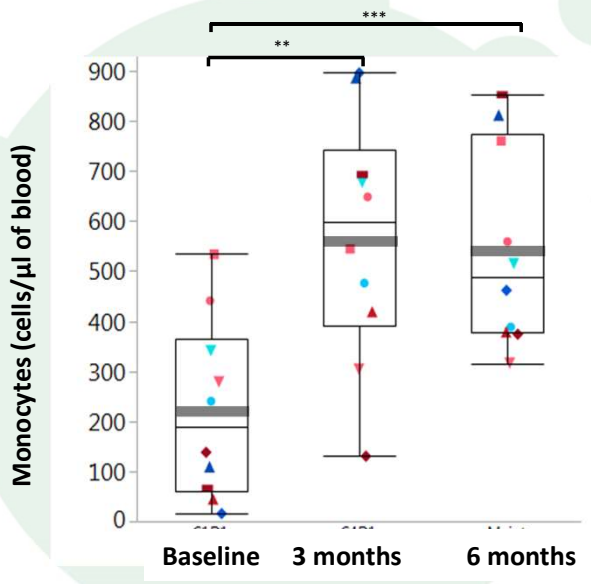
✓ To-date, efficacy and safety data in-line with historical control group/ prior clinical trials (Brignone et al Journal Translational Medicine 2010, 8:71)

✓ Regulatory approval in 7 EU countries

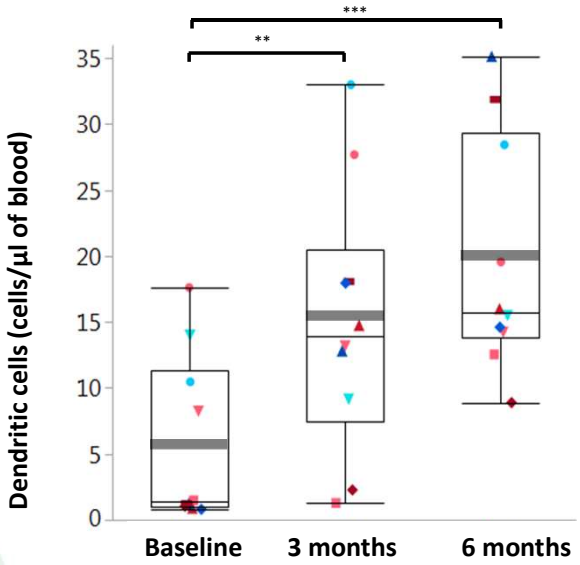
Eftilagimod alpha – Clinical Overview

Pharmacodynamic Results on Primary Target Cells

A



B

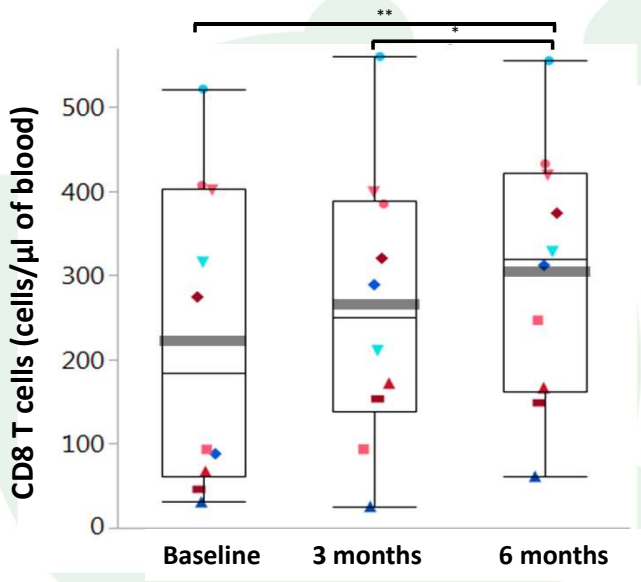


IMP321 leads to sustainable (> 6 months) increase of pre-dose APCs (run-in phase, AIPAC trial).

Eftilagimod alpha – Clinical Overview (cont.)

Pharmacodynamic Results on Secondary Target Cells

A



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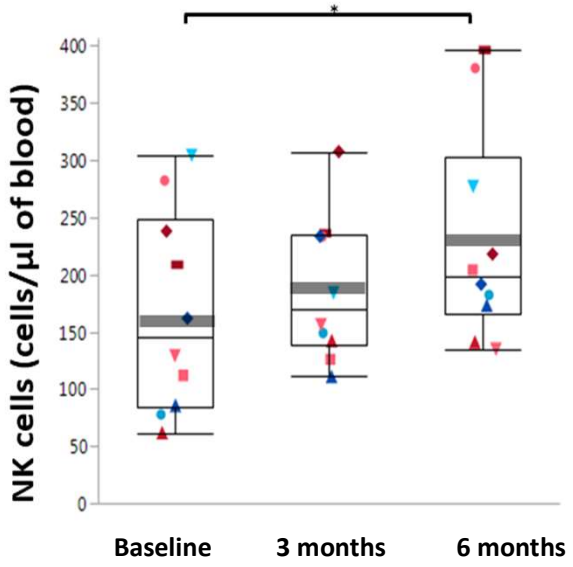
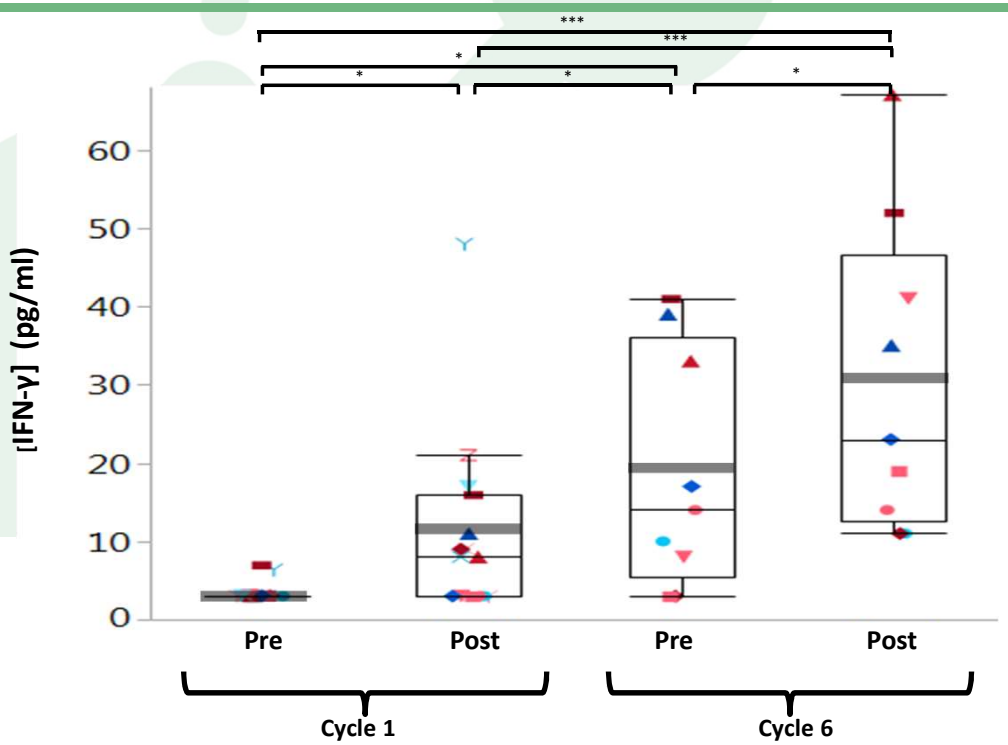


IMP321 leads to sustainable (> 6 months) increase of pre-dose effector CD8 T cells and NK cells (run-in phase, AIPAC trial).

Eftilagimod alpha – Clinical Overview (cont.)

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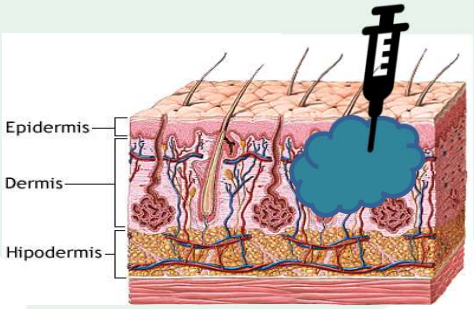
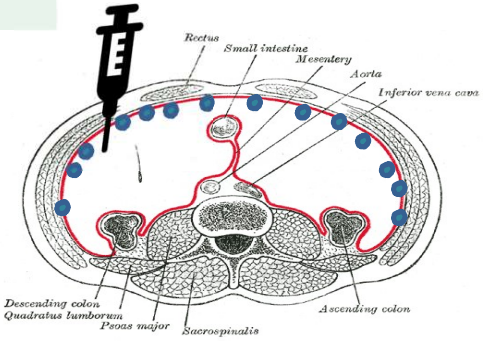
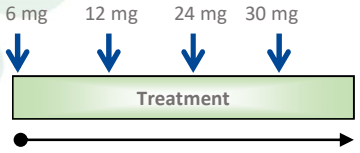
Eftilagimod Alpha in i.t. and i.p. application

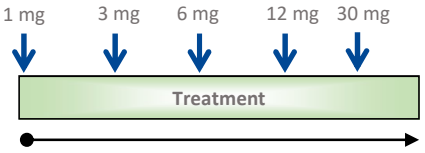
- Prof. Al-Batran, IKF, Frankfurt, Germany
- Population: 18 pts (9 per stratum) with advanced solid tumors w/o standard treatment options
- Objectives: Recommended Phase II dose, PD effects of IMP321
- Design: intrapatient escalation

Group A: intratumoral (i.t.)









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, 3 on treatment → no DLT so far

Group B:
- 2 pts enrolled, 1 on treatment → no DLT so far

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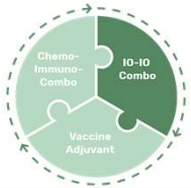
Eftilagimod Alpha/Pembrolizumab Combination



Eftilagimod Alpha in Melanoma
TACTI-mel (IO combination)

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TACTI-mel trial: 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

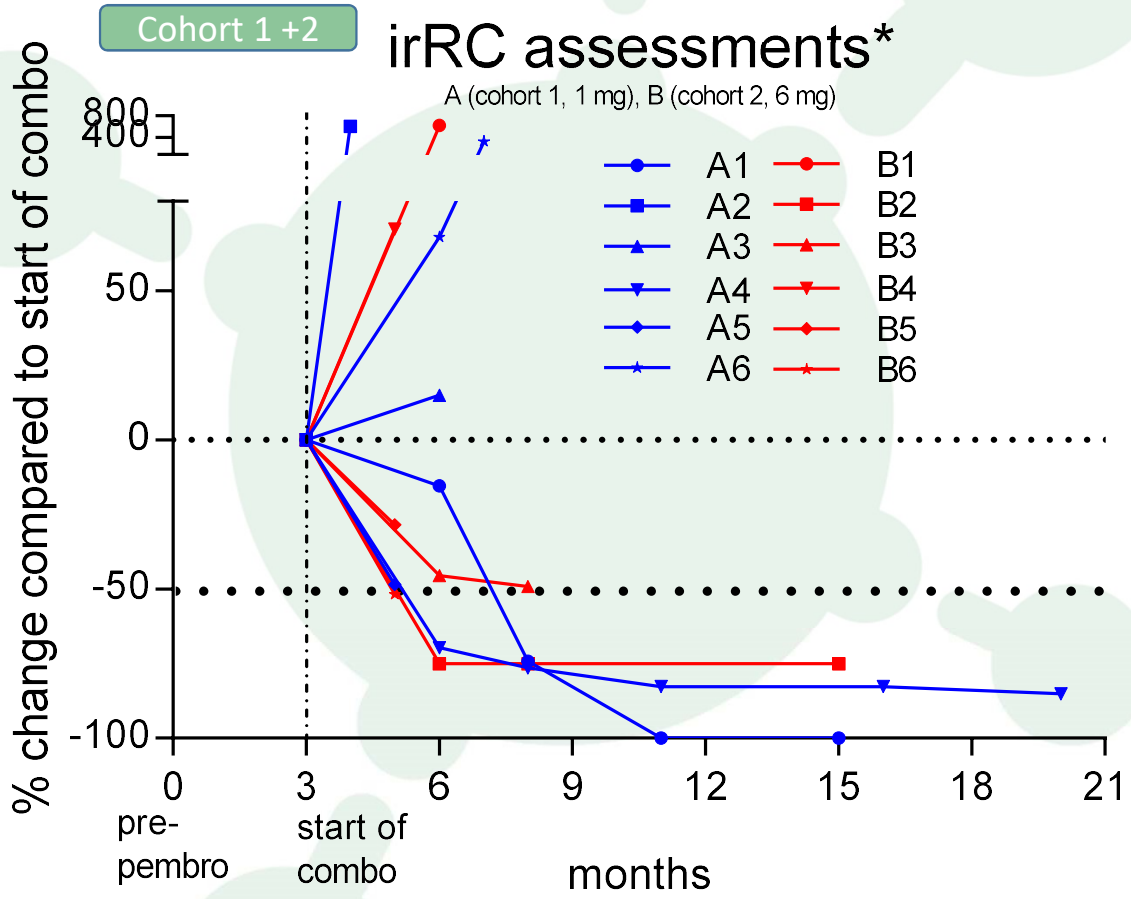
Primary Objective	Recommended dose for phase II (RP2D) with IMP321 + pembrolizumab Safety + tolerability
Other Objectives	PK and PD of IMP321, response rate, time to next treatment, PFS
Patient Population	Unresectable or metastatic melanoma Part A: asymptomatic or suboptimal response after 3 cycles of pembrolizumab Part B: eligible for pembrolizumab
Treatment	Part A: 3 cohorts: 1/6/30 mg IMP321; s.c. q2w Part B: 30 mg s.c. q2w + Both parts: 2mg/kg pembrolizumab IV q3w

Status report

- ✓ Two dose escalations DSMB meetings successfully conducted in 2017
- ✓ Interim data presented at SITC 2017
- ✓ Full recruitment of 3rd cohort December 2017 → extension approved in Feb 2018
- Data from all 3 cohorts expected mid 2018
- Recruitment of 4th cohort (Part B) ongoing

7 sites in Australia

TACTImel – melanoma Phase I study
Efficacy Update



Parameter	Patients	%
Disease Control Rate	8/12	66 %
Overall Response Rate	4/12	33 %
Patients with decrease in tumor burden	7/12	58 %

Eftilagimod Alpha TACTI-mel
Patient 02-01 (1mg): Preliminary Results

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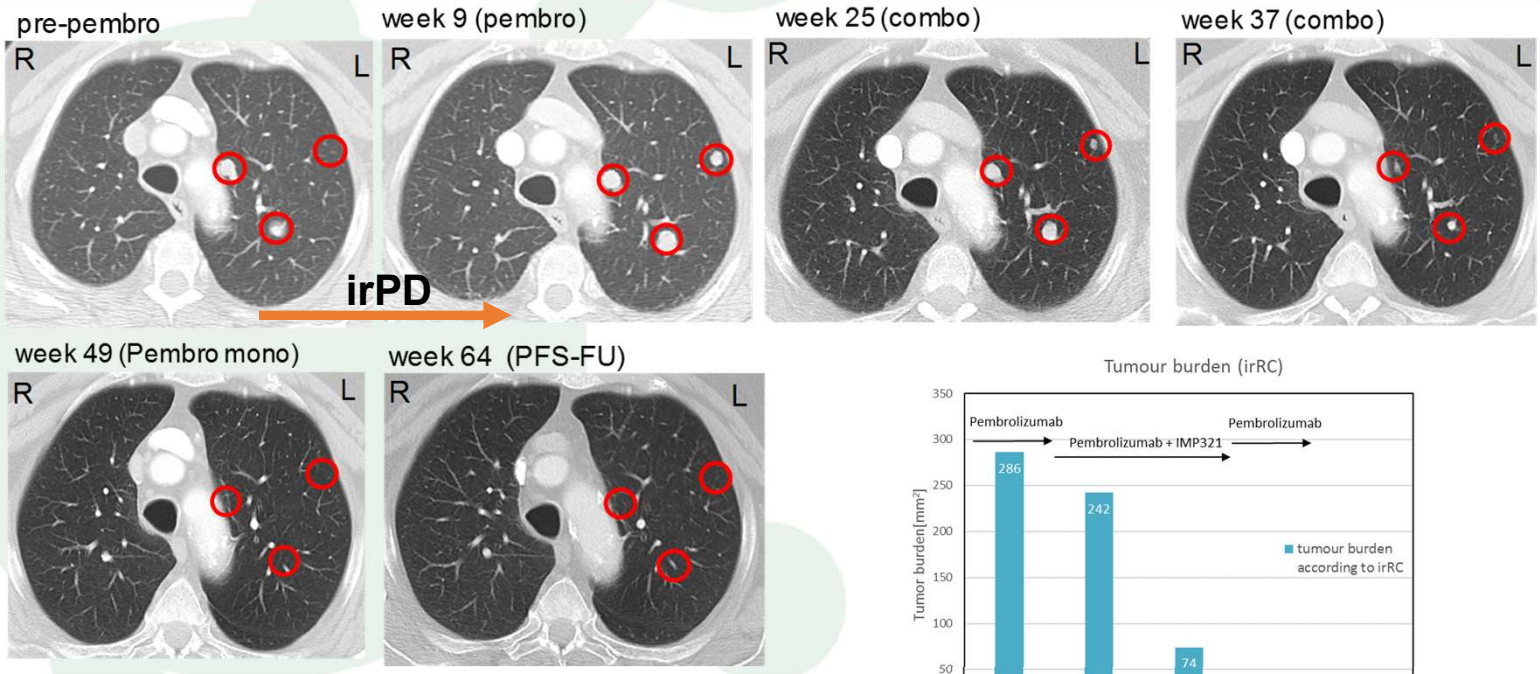
Efficacy: metastatic melanoma



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

Preliminary data, status 06th November, 2017

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Thank you

Frédéric Triebel MD, PhD

Keynote session: immuno-oncology and strategies to improve patient success

WATRMC, London.

May 17, 2018