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LAG-3 IMMUNOTHERAPY

LAG-3: Identification & Validation Of Next Generation Checkpoint Pathway

Frédéric Triebel

Checkpoint blockade: Measures to Enhance Efficacy

Immuno-Oncology Summit, London.

March 22, 2018

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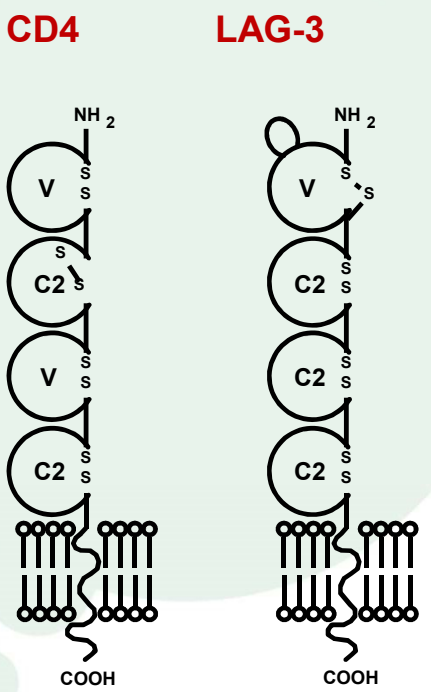
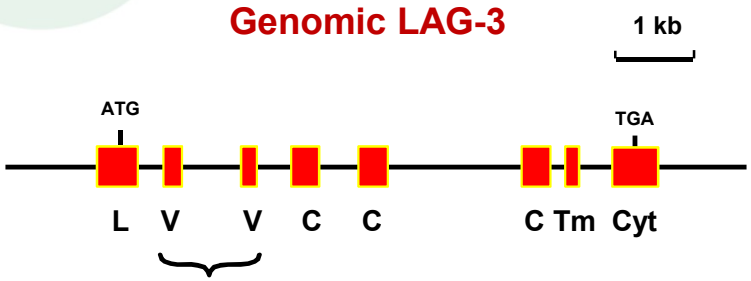
Lymphocyte Activation Gene-3 (LAG-3 or CD223)

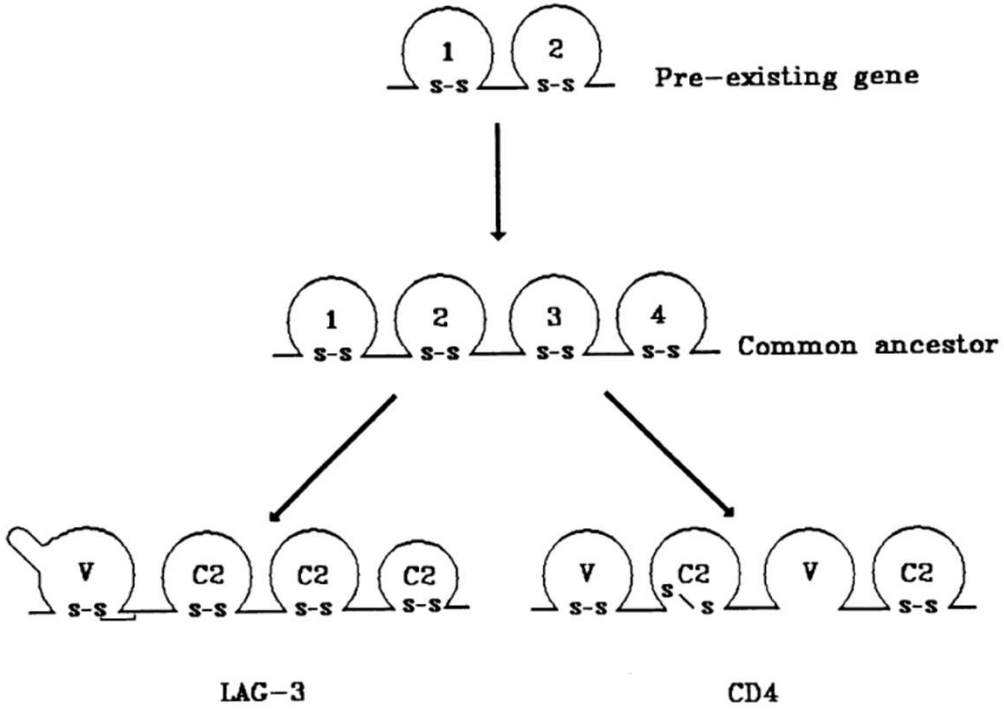




- 4-IgSF domain transmembrane proteins.
- Same genomic organization
  (intron in D1, duplication event D1D2 vs D3D4)
- Close proximity on 12p13.

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

Proposed Evolutionary Pattern for LAG-3/CD4



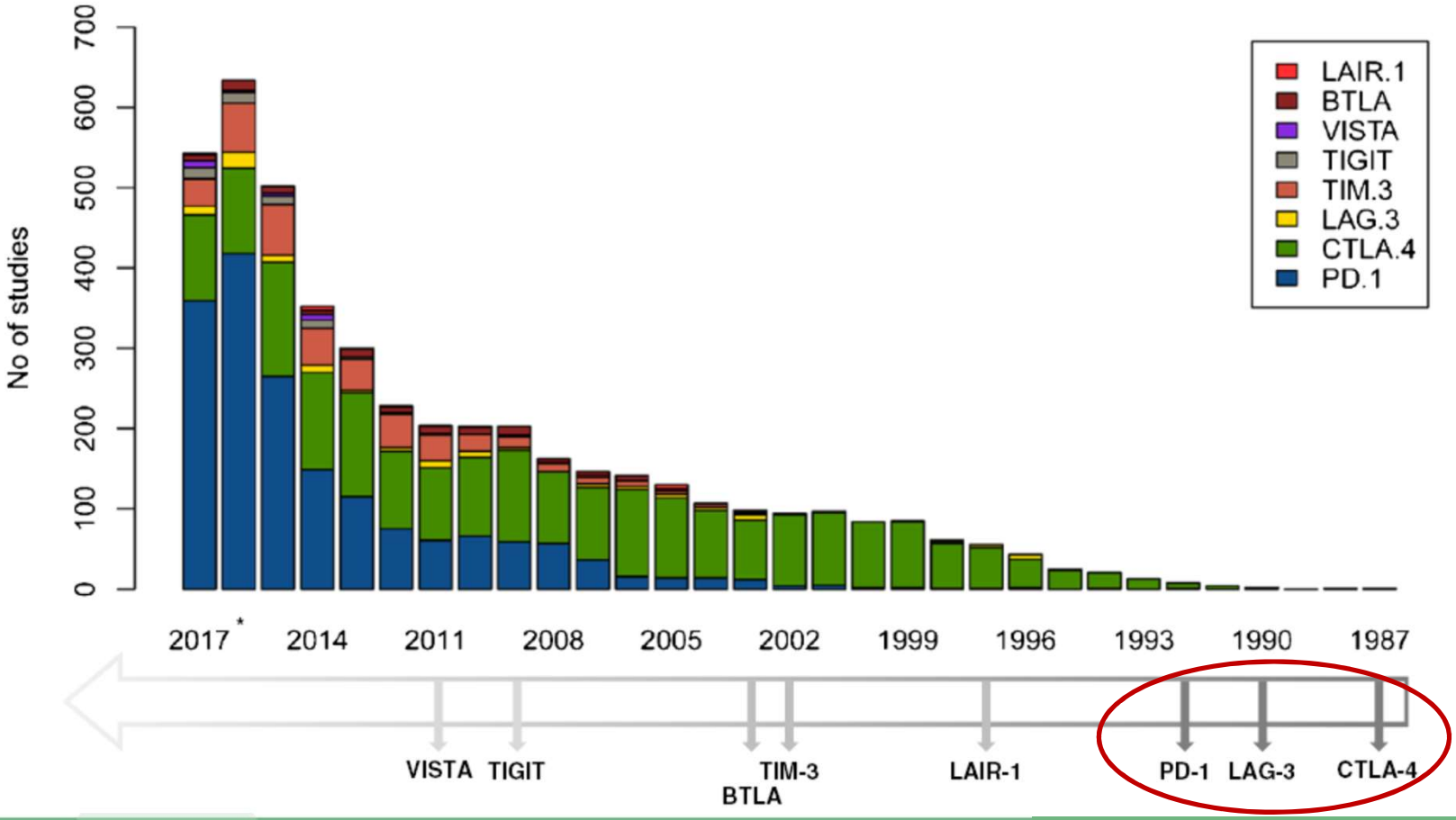
Co-inhibitory

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

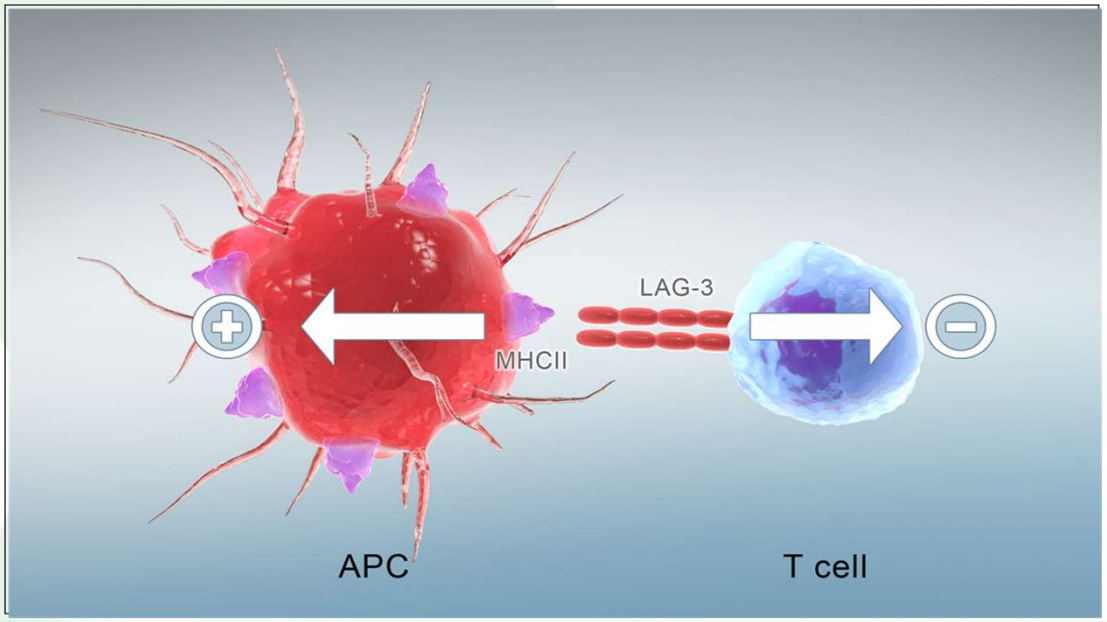
Timeline of immune checkpoint discovery.



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

Increasing Clinical Trials Targeting LAG-3

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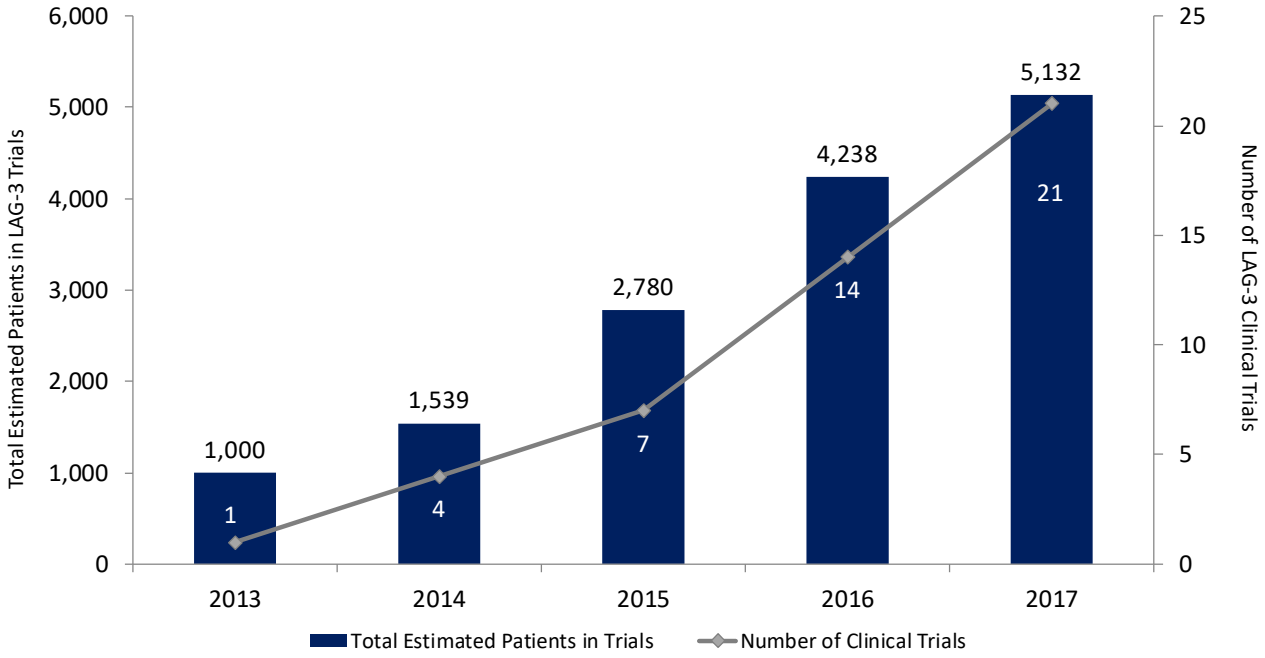
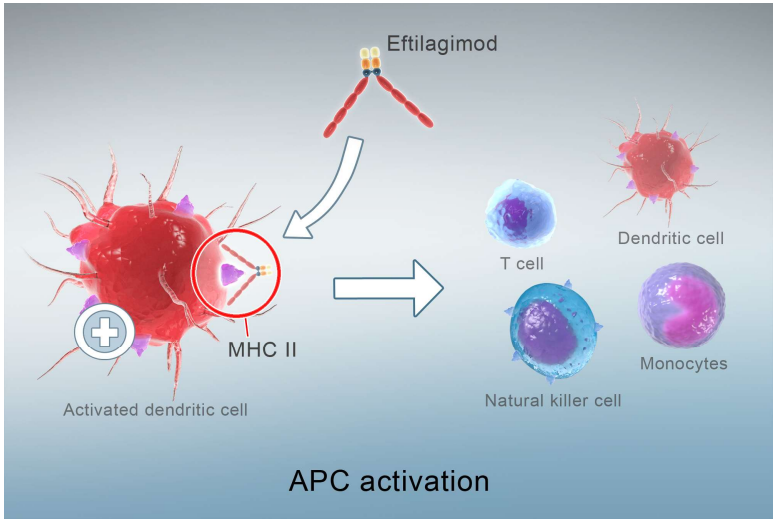
Industry increasingly deploying resources to development of LAG-3 technologies…

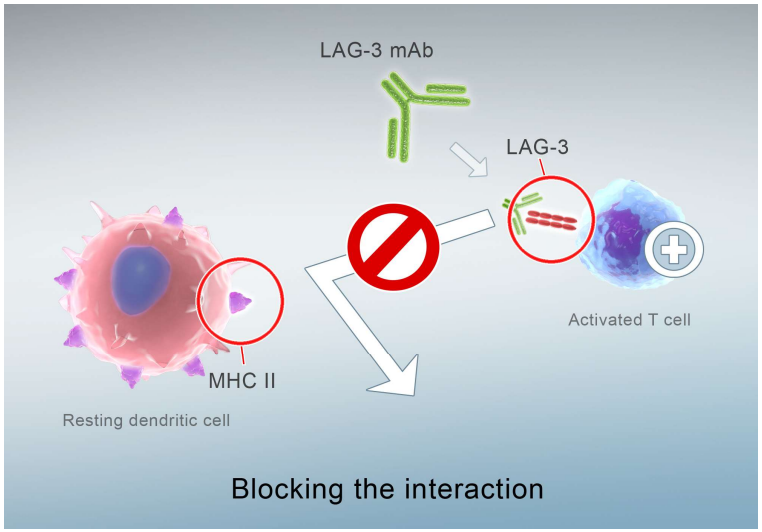


Sources: GlobalData, company websites, clinical trials.gov, and sec.gov
As of January 2, 2018

Eftilagimod Alpha: an innovative LAG-3 I-O agent

- 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





- LAG-3Ig, an MHC II **agonist** (eftilagimod alpha) : <u>APC activator</u>
  - Boost and sustain the $CD8^+$ T cell responses
  - Activate multiple immune cell subsets

"pushing the accelerator on immune responses"

- LAG-3 **antagonist** antibodies: <u>immune checkpoint inhibitor</u>
  - Increase cytotoxicity of the pre-existing CD8 T cell response

"releasing the brake on the T cell"

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

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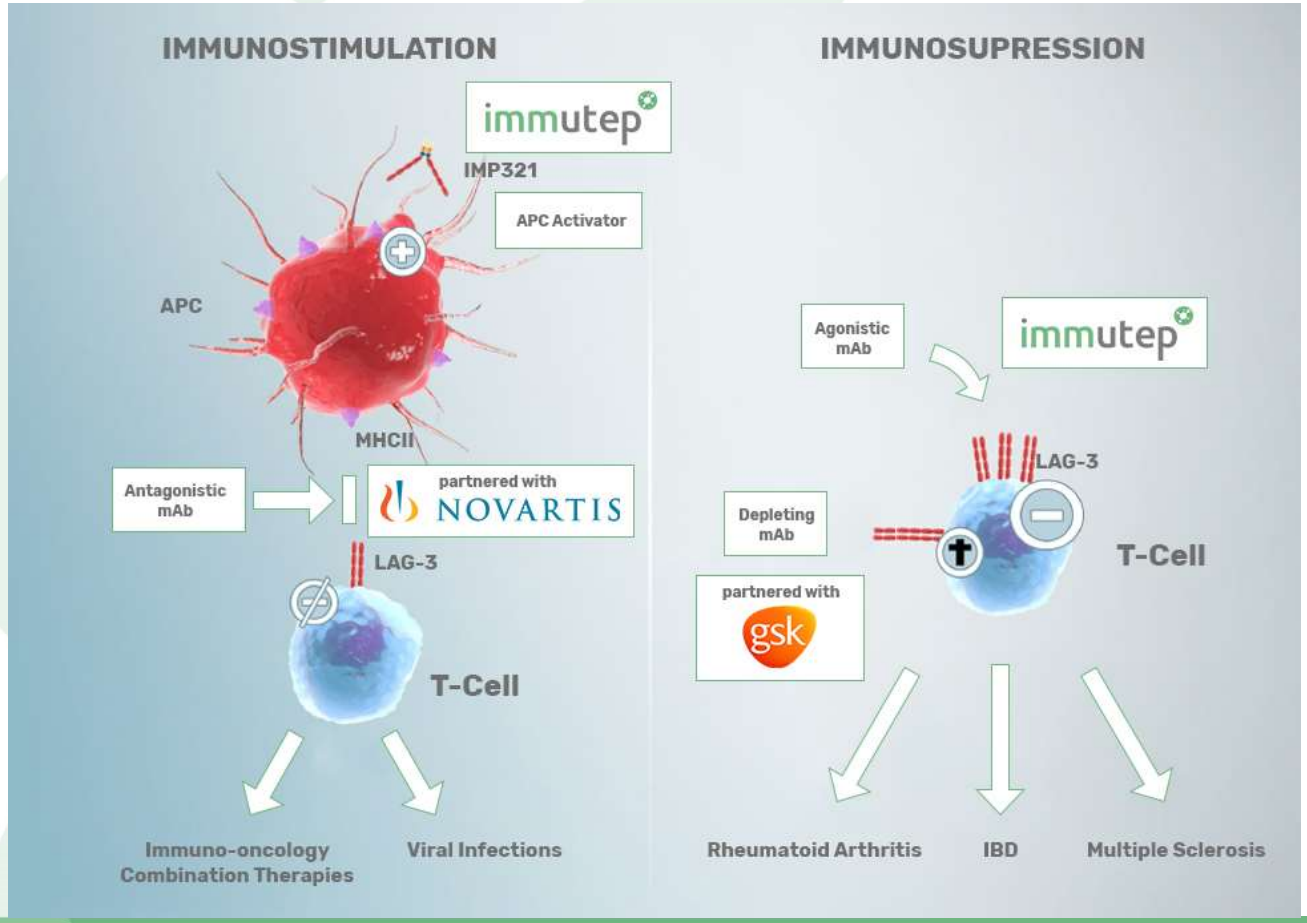

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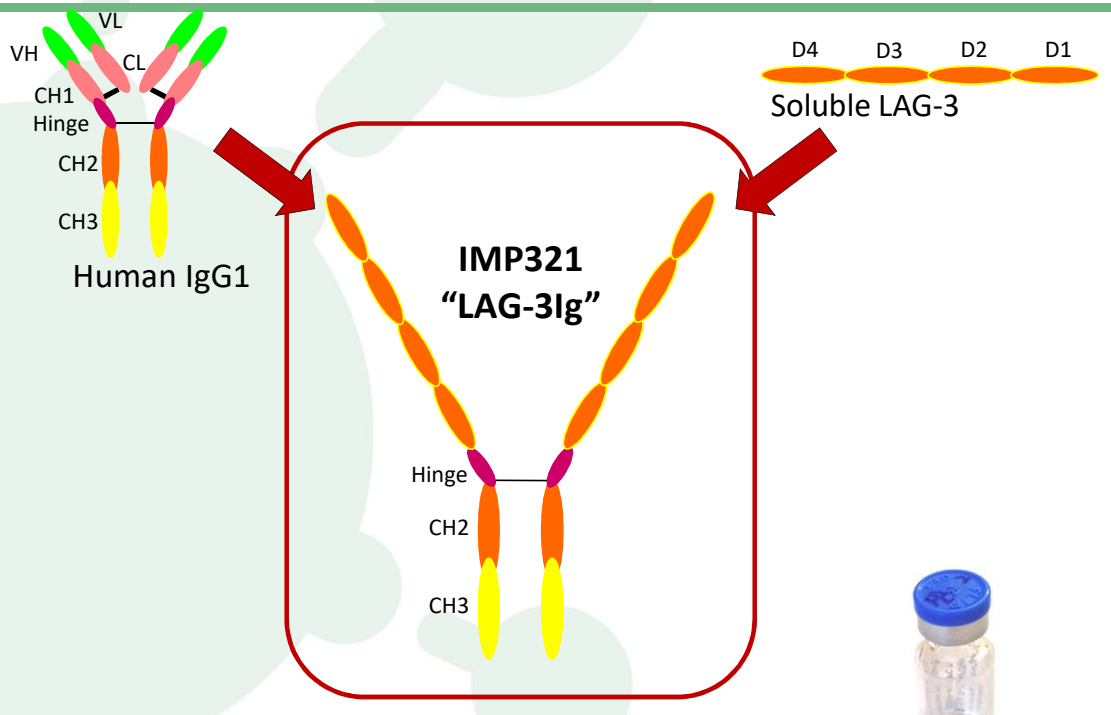
Lead Program
Eftilagimod Alpha (IMP321)

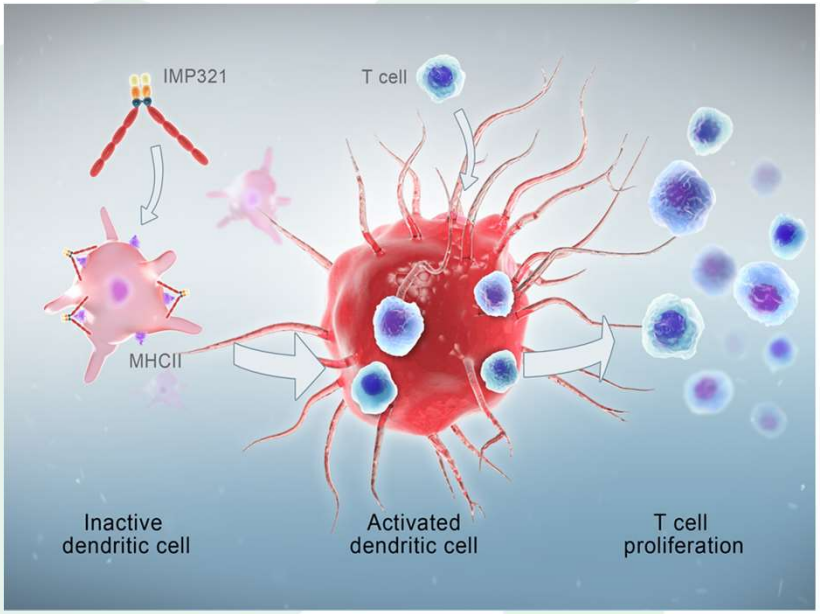
Eftilagimod alpha (IMP321)



- **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

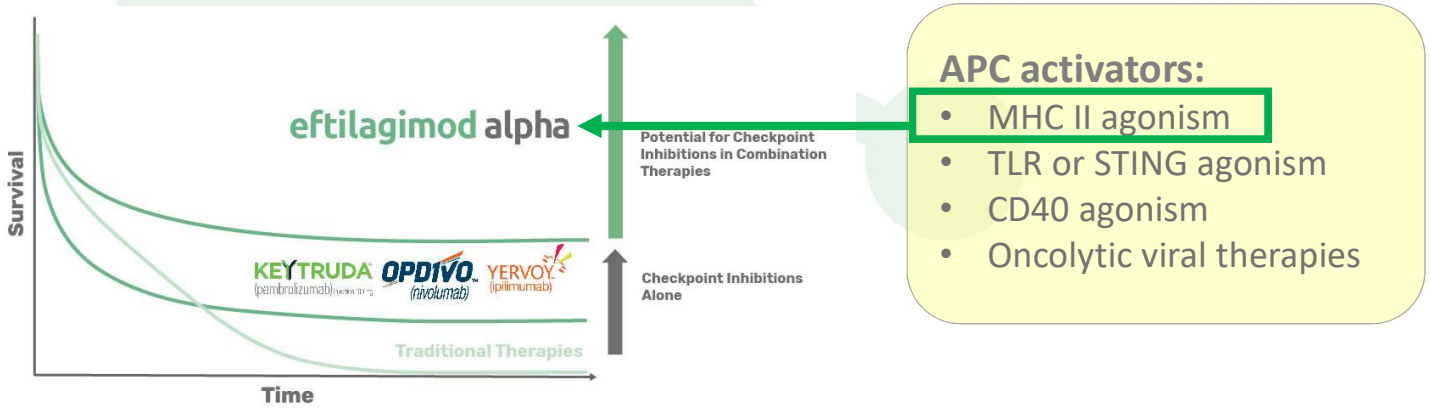
- Highly efficacious in multiple animal models of cancer and infectious disease
- Shown to be safe, non-immunogenic and efficacious in human

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

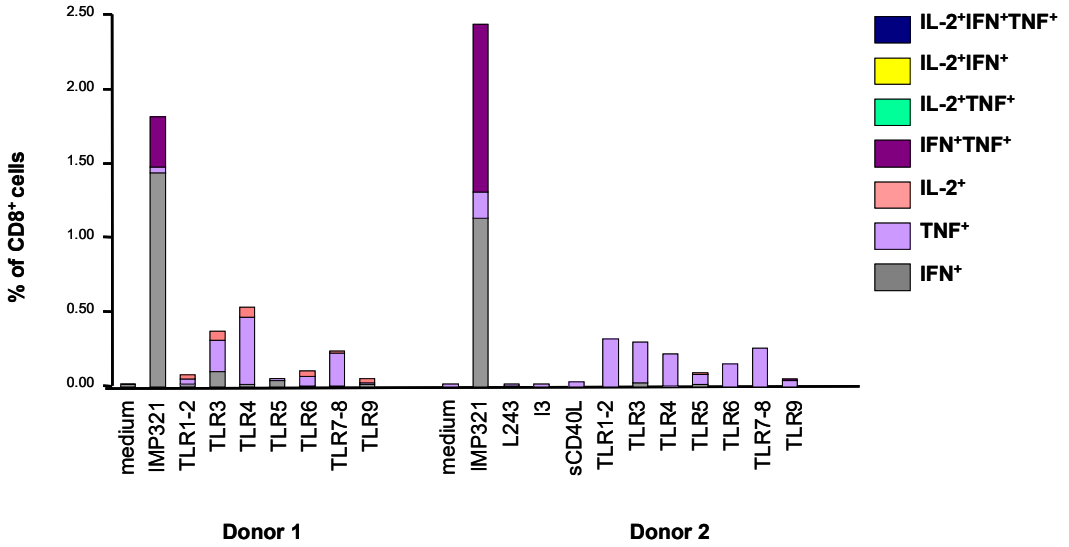


APC activators:
- MHC II agonism
- TLR or STING agonism
- CD40 agonism
- Oncolytic viral therapies

Eftilagimod alpha (IMP321)

Induces Better CD8 Tc1 Differentiation Than sCD40L or TLR Agonists

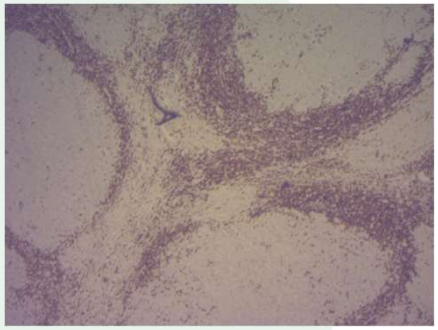
- Human blood lymphocytes are analyzed in a 16 hr *ex vivo* assay
- Intracellular staining of CD8 T cells
  - Only IMP321 induces strong IFN^+ or IFN^+/TNF^+ CD8 T cell responses
  - explanation: TLR agonists but not IMP321 induce IL-10 production which suppresses Tc1 differentiation



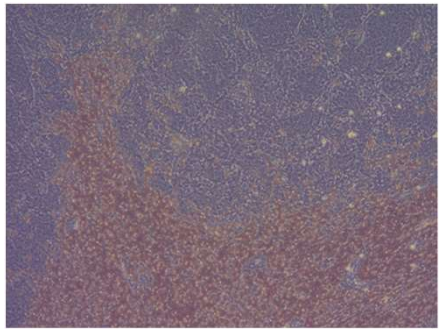
J. Immunol. 179: 4202–4211, 2007

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

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

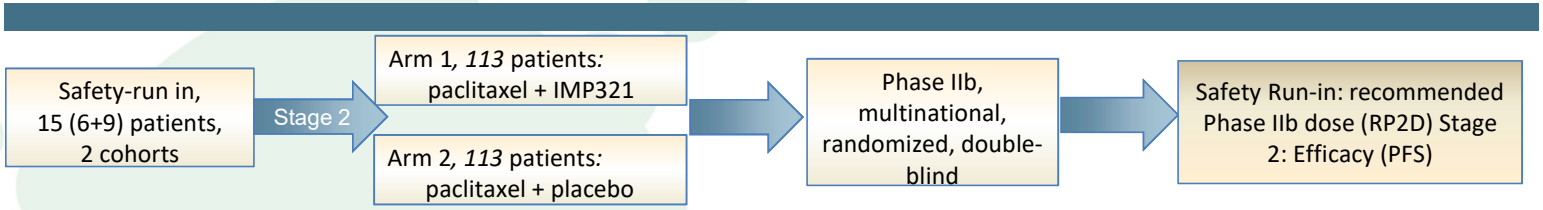
Potential combination therapy strategies:

- **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)

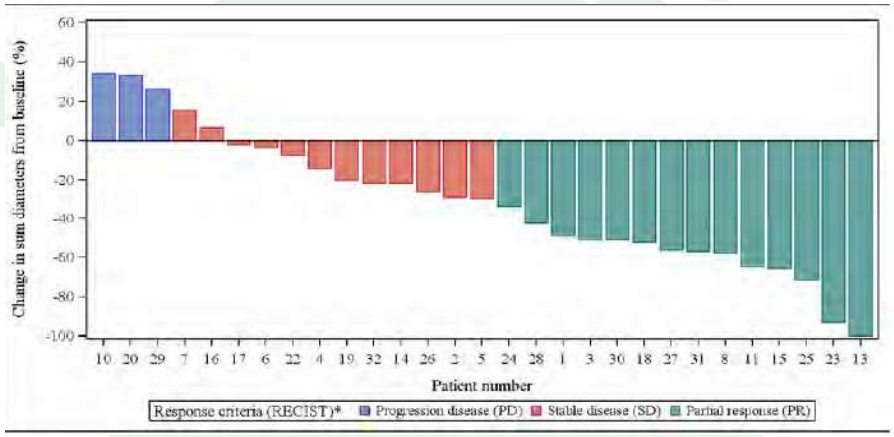
✓ Interim-data of safety run-in presented at ASCO 2017

✓ 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 %)

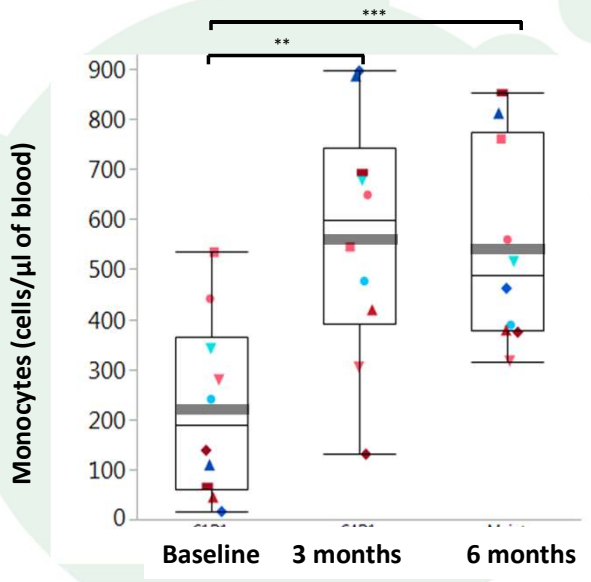
- **ORR of 47 % and DCR of 87 %**
- Two of the responses occurred relatively late (after ~6 months)

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

Eftilagimod alpha – Clinical Overview

Pharmacodynamic Results on Primary Target Cells

A



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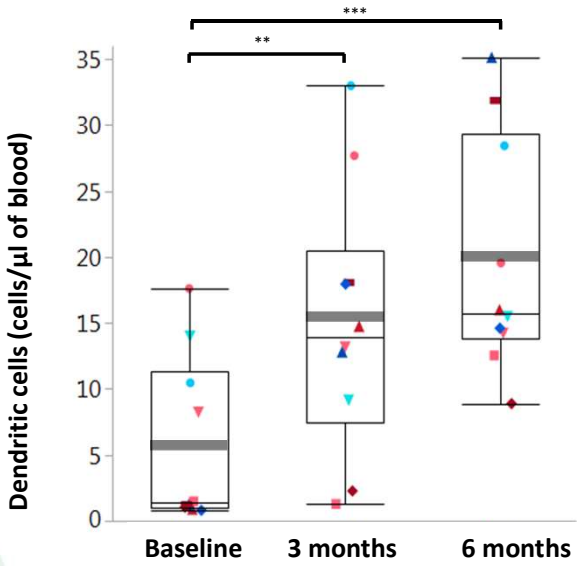
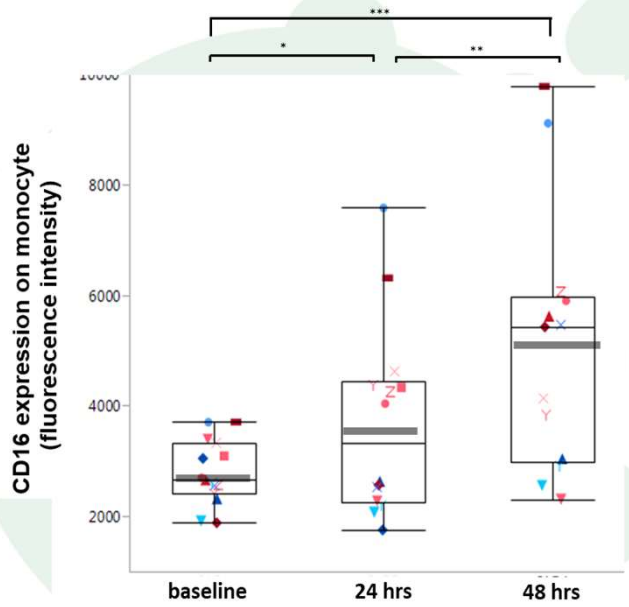


IMP321 leads to sustainable (> 6 months) increase of pre-dose APCs (run-in phase, AIPAC trial).

Eftilagimod alpha – Clinical Overview (cont.)

Pharmacodynamic Results on Primary Target Cells

A



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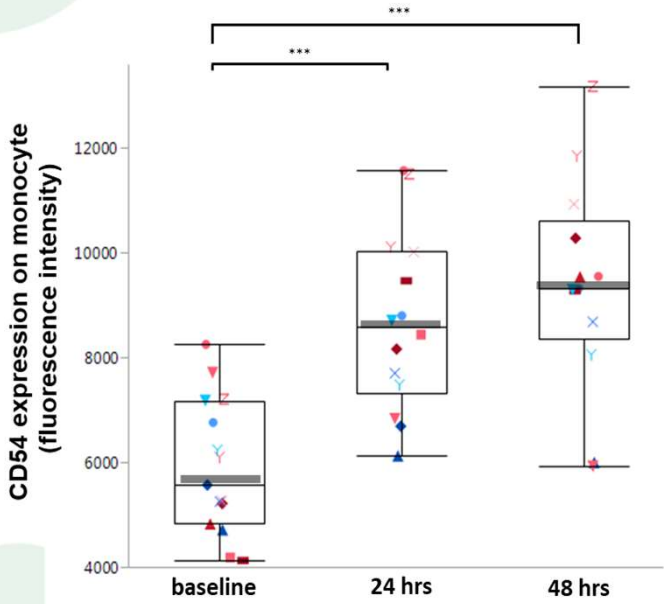
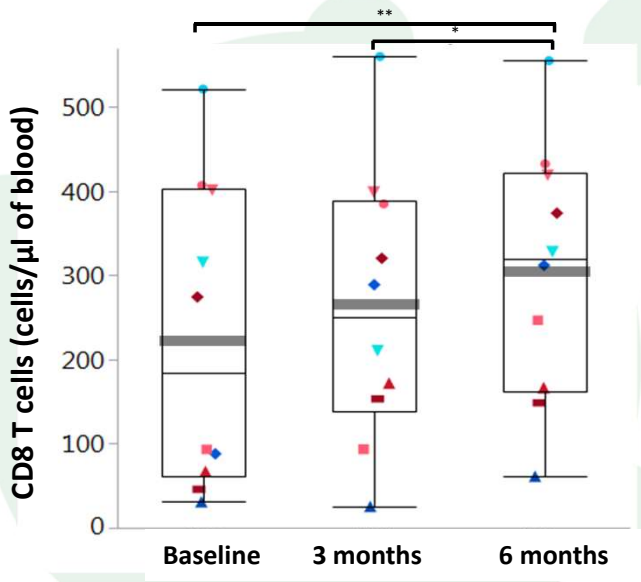


IMP321 activates APCs (run-in phase, AIPAC trial).

Eftilagimod alpha – Clinical Overview (cont.)

Pharmacodynamic Results on Secondary Target Cells

A



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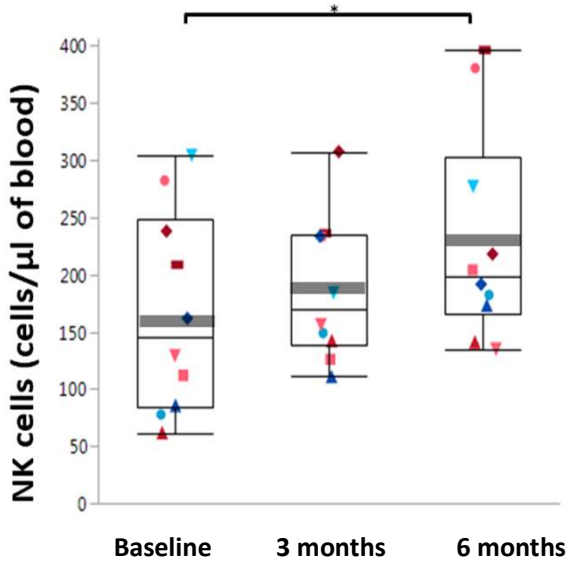
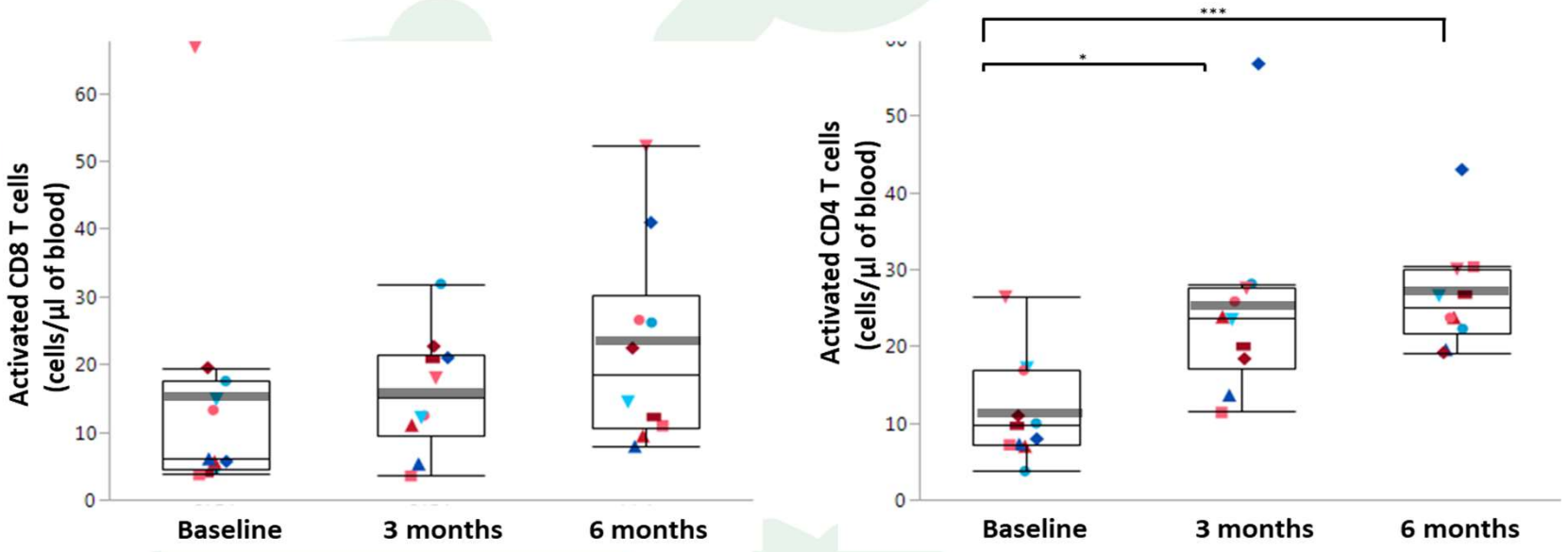


IMP321 leads to sustainable (> 6 months) increase of pre-dose effector CD8 T cells and NK cells (run-in phase, AIPAC trial).

Eftilagimod alpha – Clinical Overview (cont.)

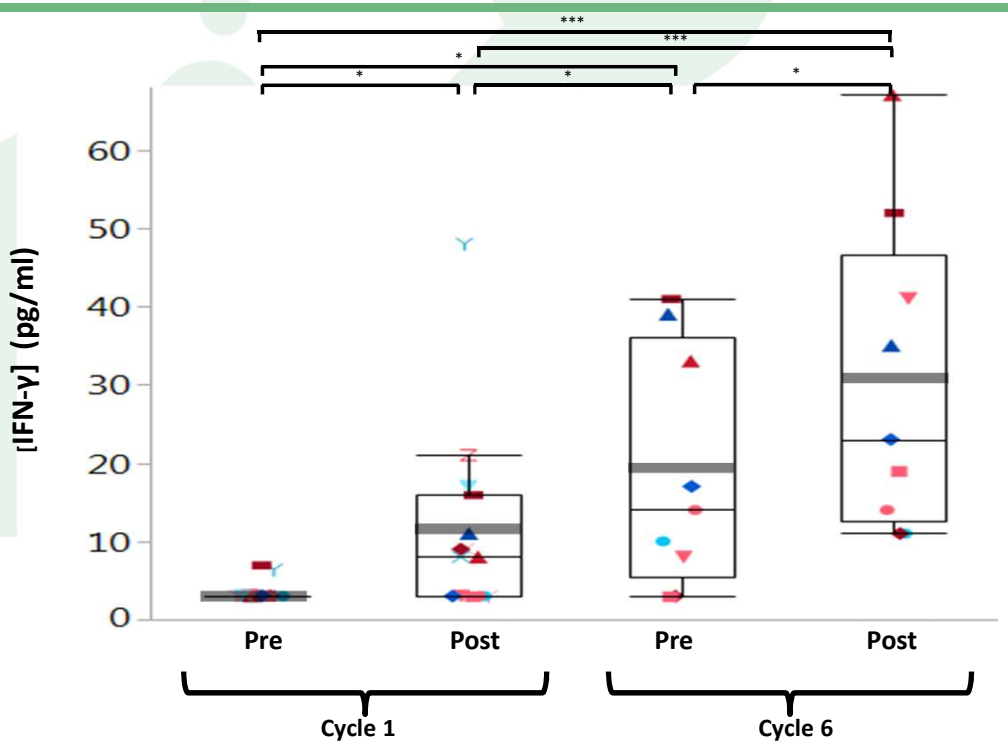
Pharmacodynamic Results on Secondary Target Cells



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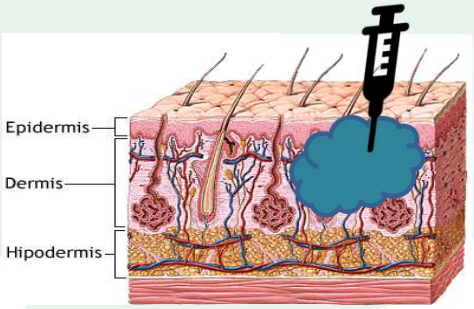
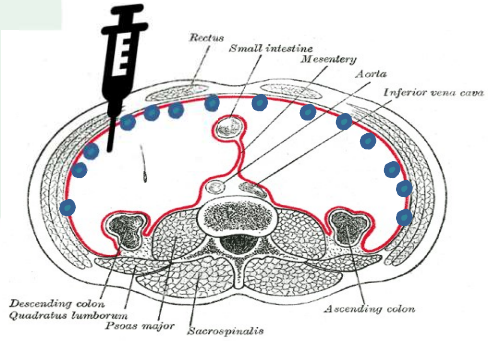
Eftilagimod Alpha in i.t. and i.p. application

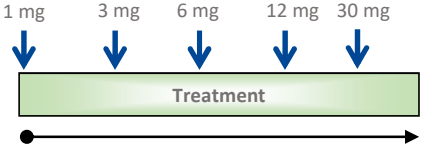
- Prof. Al-Batran, IKF, Frankfurt, Germany
- Population: 18 pts (9 per stratum) with advanced solid tumors w/o standard treatment options
- Objectives: Recommended Phase II dose, PD effects of IMP321
- Design: intrapatient escalation

Group A: intratumoral (i.t.)



Group B: intraperitoneal (i.p.)





Group A:
- First 3 patients completed escalation w/o DLT,

Group B:
- 1st patient completed escalation w/o DLT

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

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Eftilagimod Alpha/Pembrolizumab Combination

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

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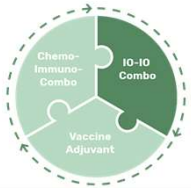
- A- Inflamed responders – respond to anti-PD-1
- B- Inflamed non-responders (some infiltrates in the tumor margins but no response)
- C- Non inflamed. “Cold tumor” with no response

- 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



Eftilagimod Alpha in Melanoma
TACTI-mel (IO combination)

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TACTI-mel trial: Two ACTive Immunotherapeutics in melanoma

18 patients, 3 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 with asymptomatic or suboptimal response after 3 cycles of pembrolizumab
Treatment	3 cohorts: 1/6/30 mg IMP321; s.c. q2w + pembrolizumab; starting with the 5th cycle of pembrolizumab

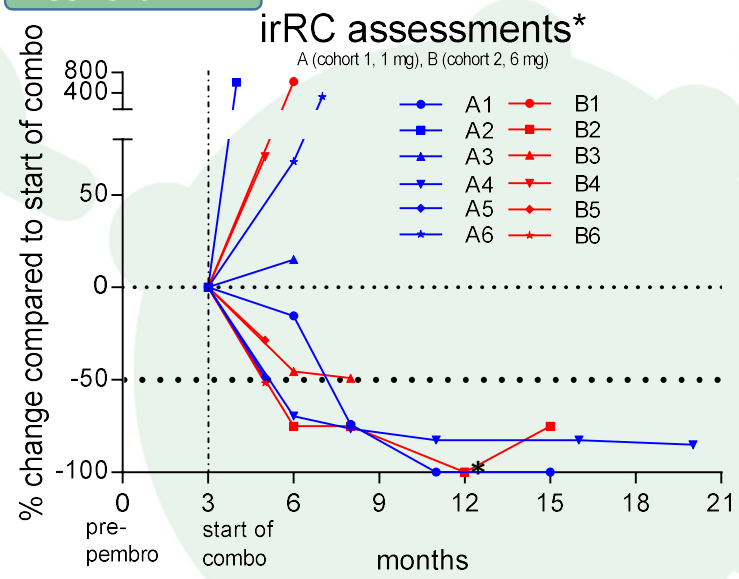
Status report

- ✓ First dose escalation (1mg → 6mg) successfully confirmed by DSMB in Dec 2016
- ✓ Enrolment of cohort 2 (6 mg) completed in Mar 2017
- ✓ Interim data presented at SITC 2017
- ✓ Full recruitment of 3rd cohort completed in December 2017
- Data from all 3 cohorts expected mid 2018

6 sites in Australia

TACTImel – melanoma Phase I study
Safety and Efficacy Update

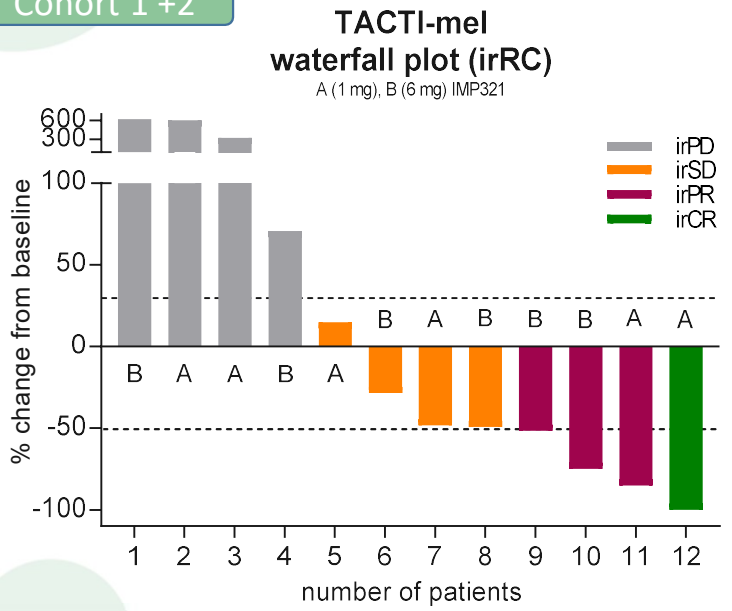
Cohort 1 +2



*irPR due to non-target lesions

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

Cohort 1 +2



Safety cohort 1-3:

- In total 114 AEs in 18 patients; thereof 14 AEs >= G3 in 7 pts
- In total 7 SAEs in 6 pts; none related to IMP321 or pembrolizumab
- Related to IMP321: 12 AEs in 9 pts; 1 G3 decreased renal function; 1 G2 rash; rest G1
- Related to Pembro: 35 AEs in 13 pts;3 G3 in 3 pts (diarrhea, altered liver functions, maculopapular rash)
- No noteworthy abnormalities in lab parameters not coded as AE

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

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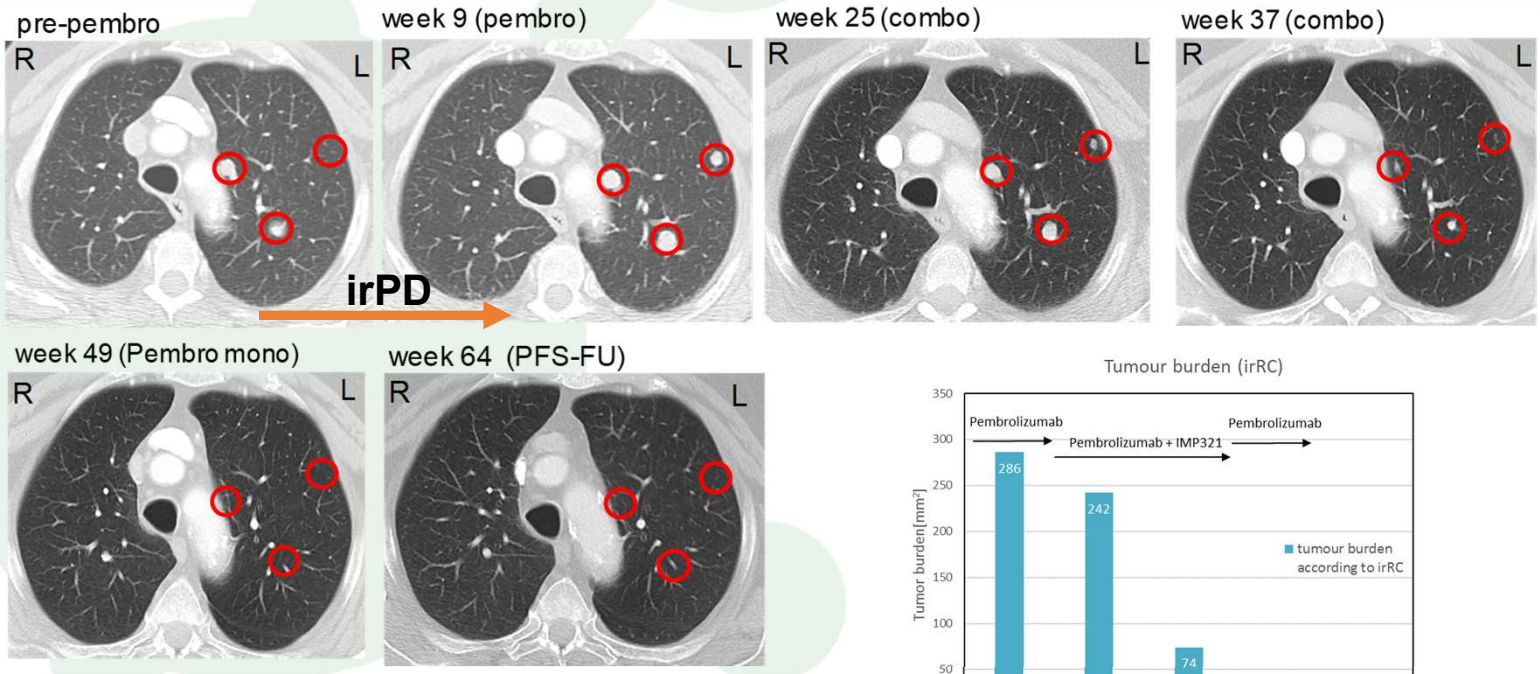
Efficacy: metastatic melanoma



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

Checkpoint blockade: Measures to Enhance Efficacy

Immuno-Oncology Summit, London.

March 22, 2018