

TACTI-mel, Two ACTive Immunotherapies in Melanoma: Combination of IMP321 (LAG-3Ig) with an Anti-PD-1 Antagonist in a Phase I Trial

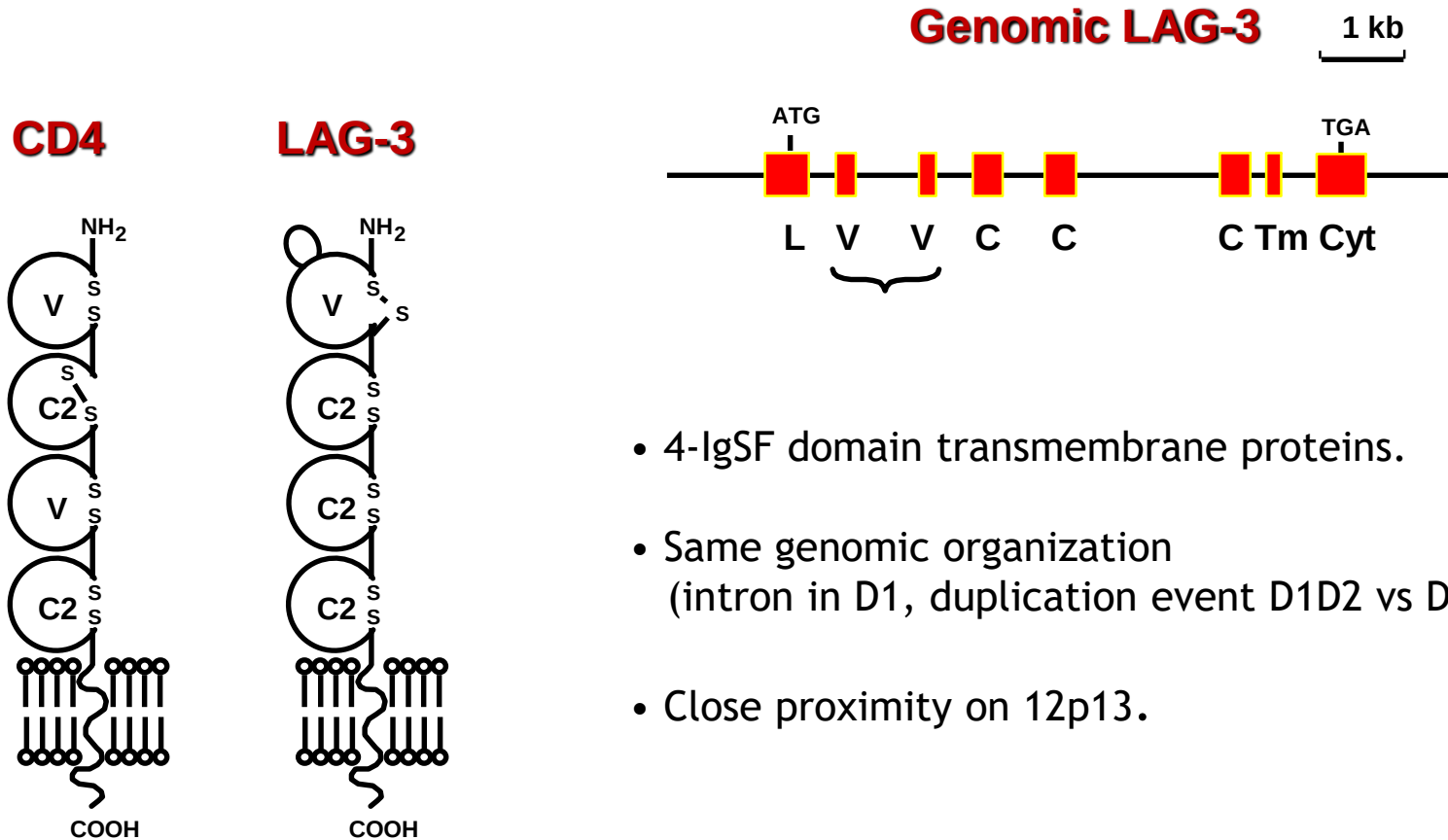


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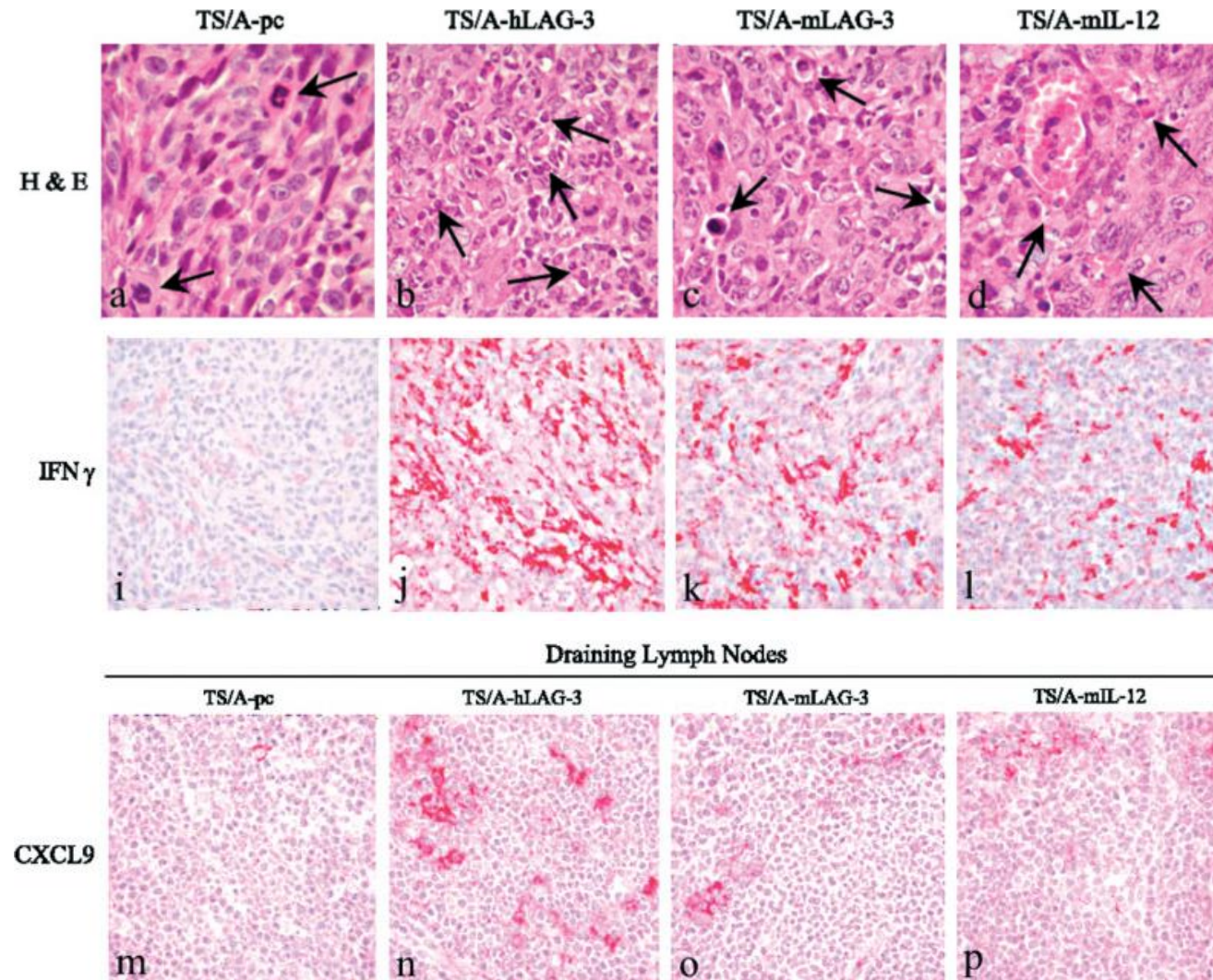
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Lymphocyte Activation Gene-3 (LAG-3 or CD223)

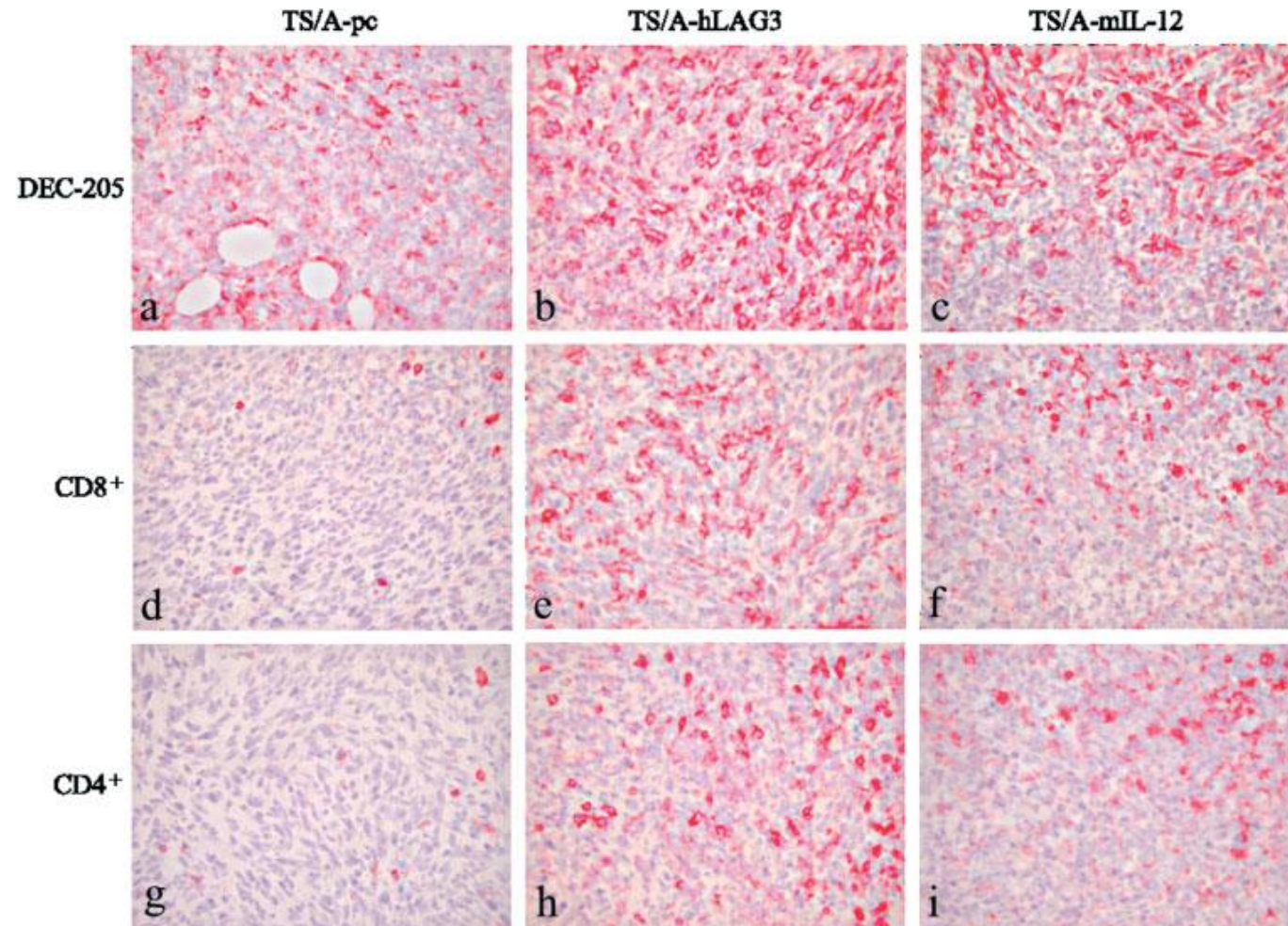


- 4-IgSF domain transmembrane proteins.
- Same genomic organization (intron in D1, duplication event D1D2 vs D3D4)
- Close proximity on 12p13.

Immunological mechanisms elicited at the tumour site
by LAG-3 versus IL-12:
sharing a common Th1 anti-tumour immune pathway

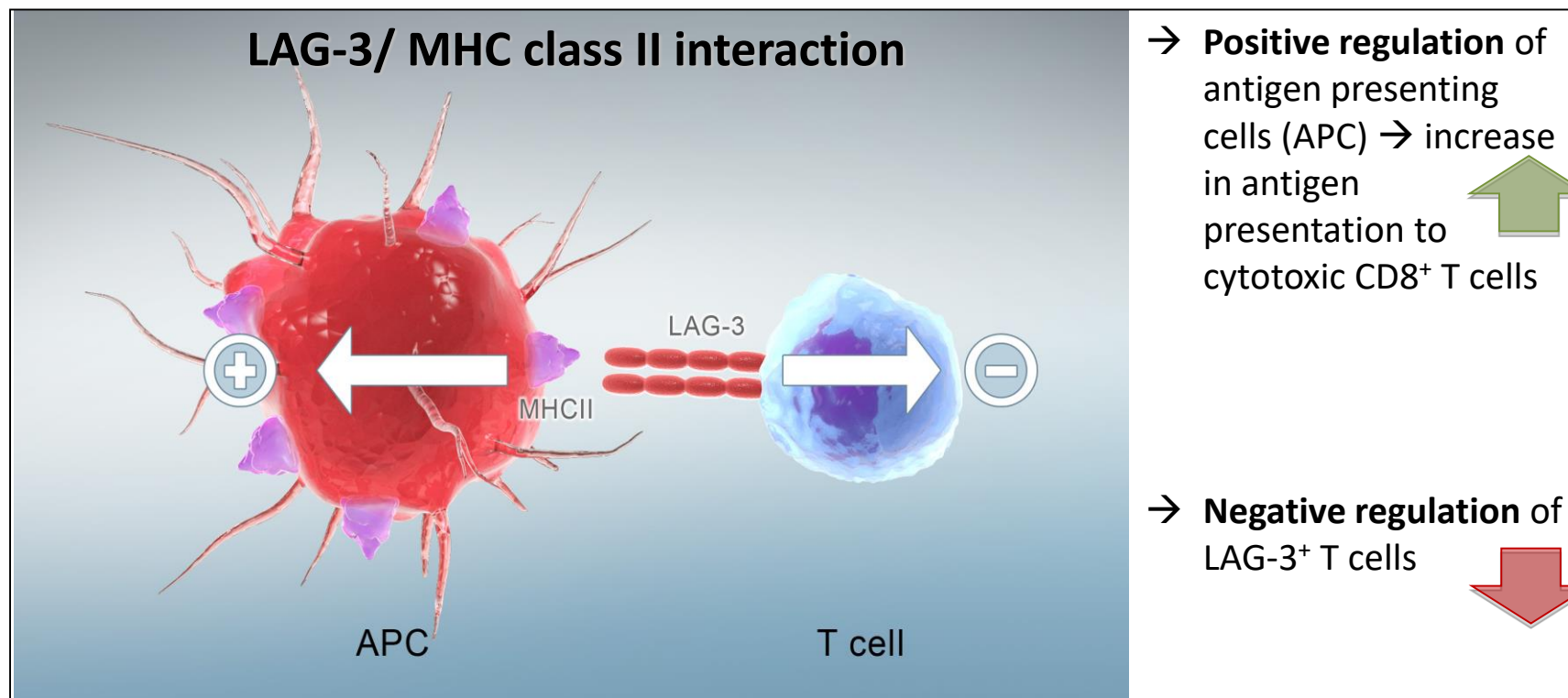


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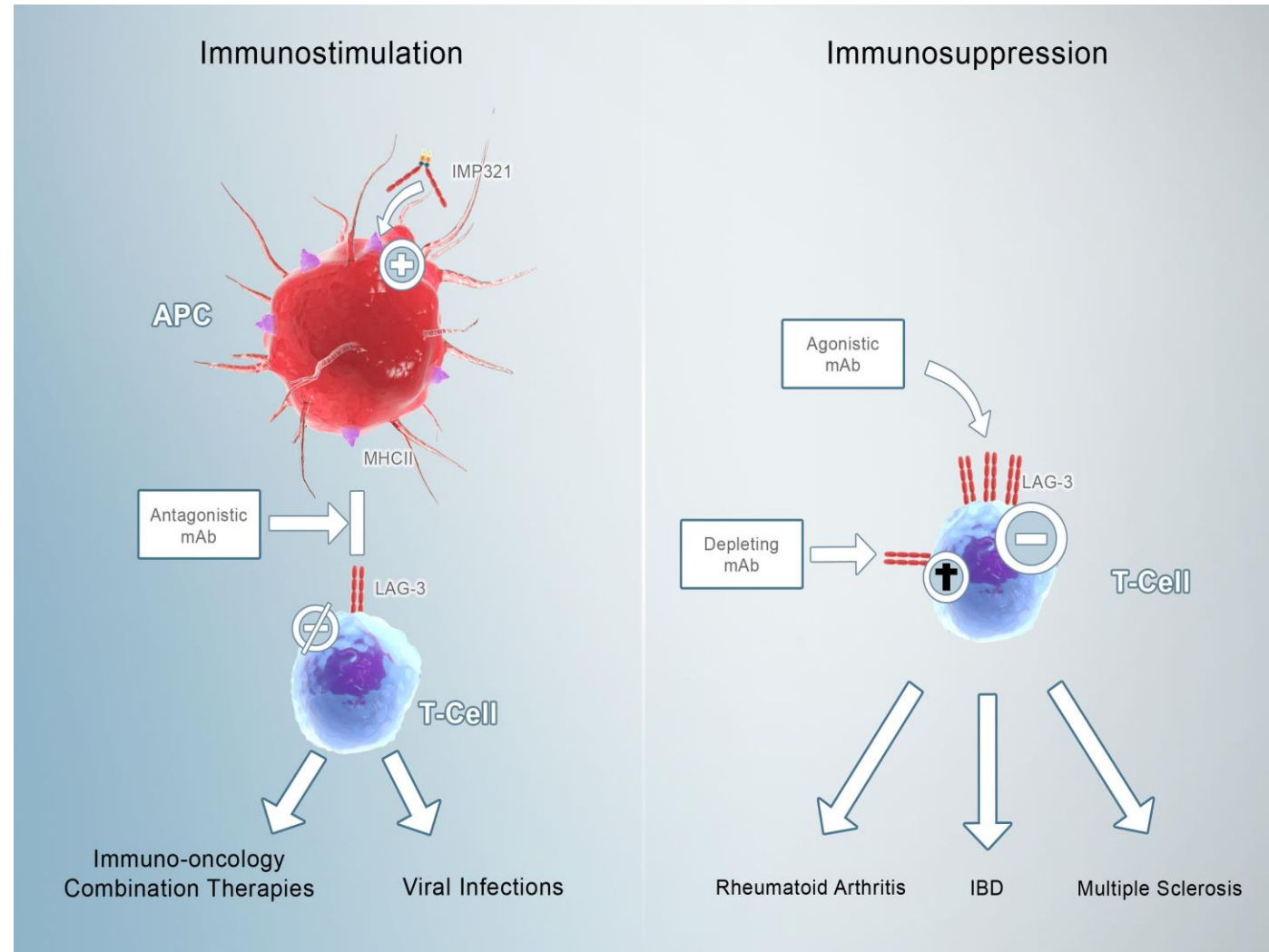


LAG-3 As a Therapeutic Target

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

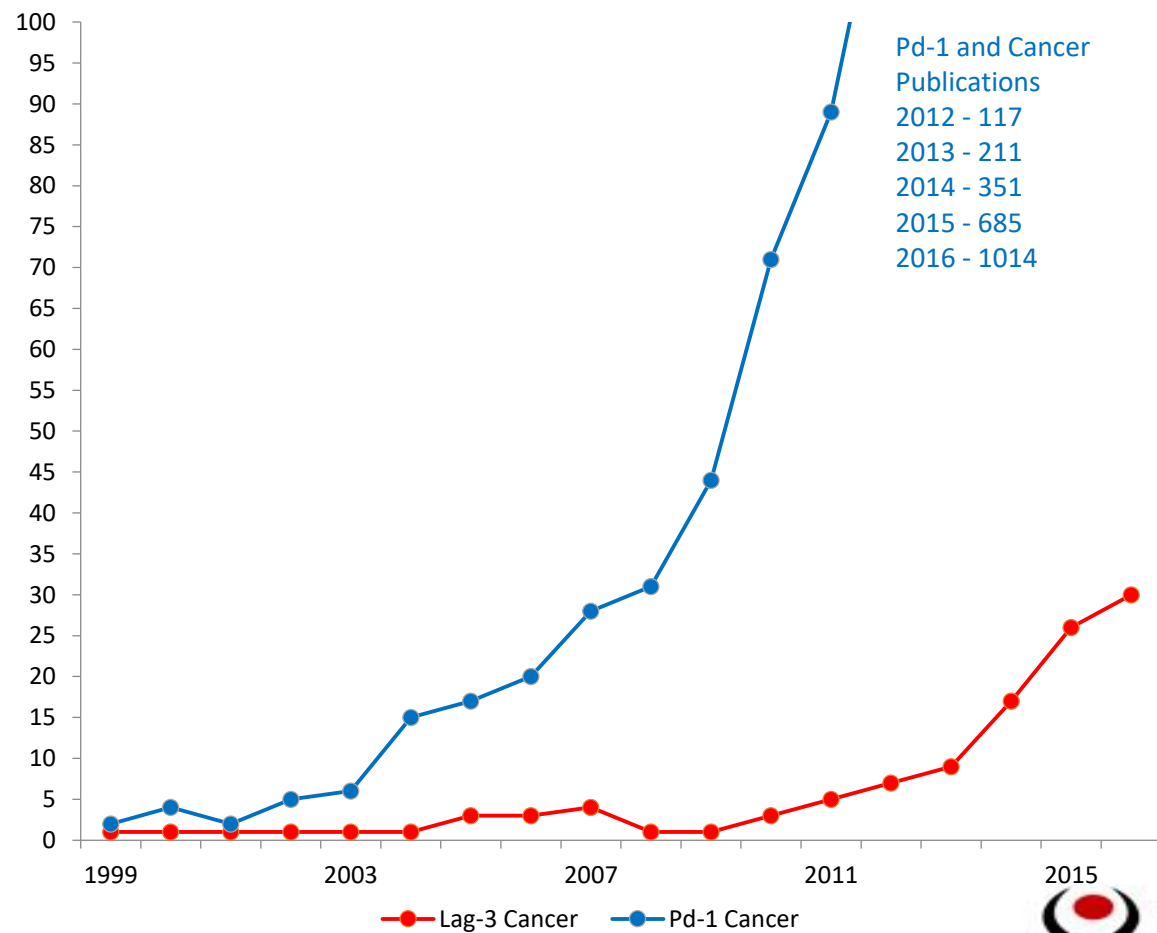


Targeting LAG-3 May Lead to Multiple Therapeutics in Numerous Indications



Growing Interest in LAG-3

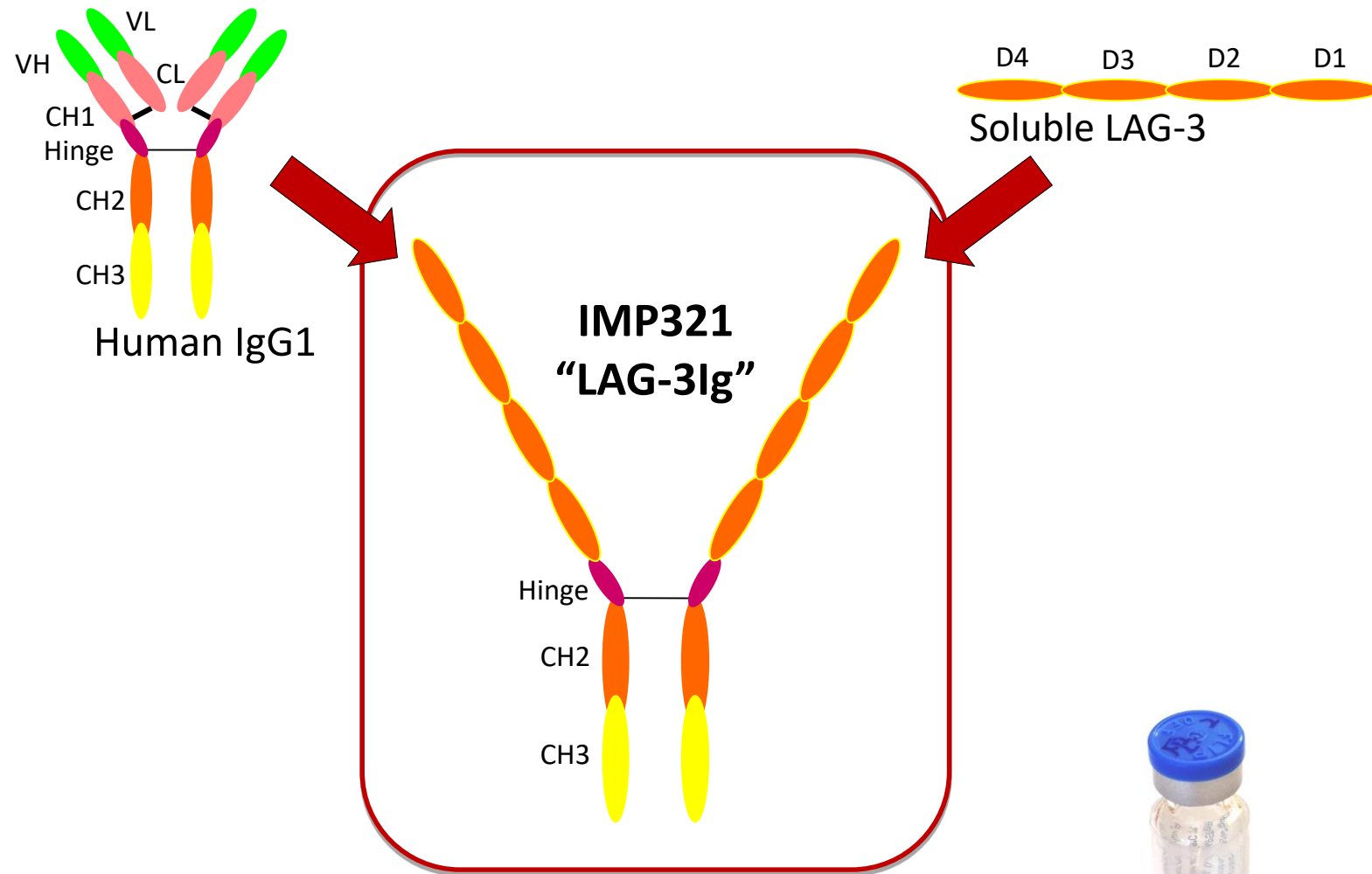
- Overall understanding and appreciation of the importance of LAG-3's role in the immune system continues to grow
- Trajectory of the PubMed articles on „LAG-3 cancer“ is similar to that of „PD-1 cancer“



LEAD PRODUCT IMP321



IMP321

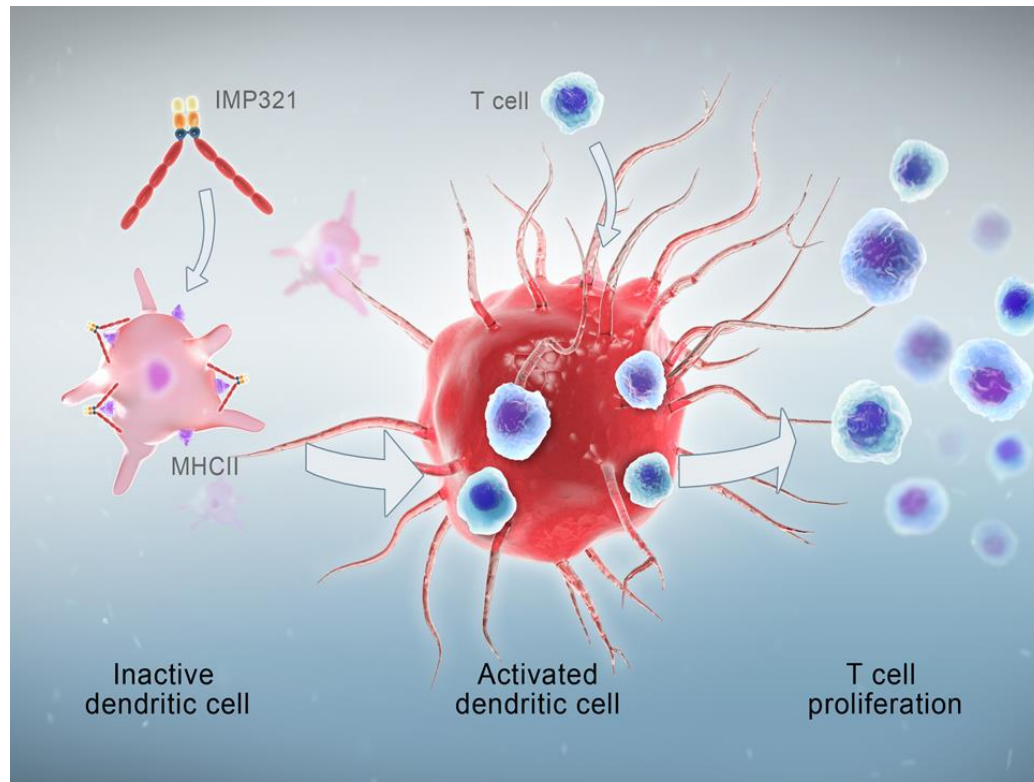


- **Soluble recombinant form of LAG-3**
- Human fusion protein
- Dimeric, very stable, high affinity for DC
- Antigen presenting cell (APC) activator
- **Unique and first-in-class**



IMP321

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



→ IMP321 binds to MHC class II on monocytes

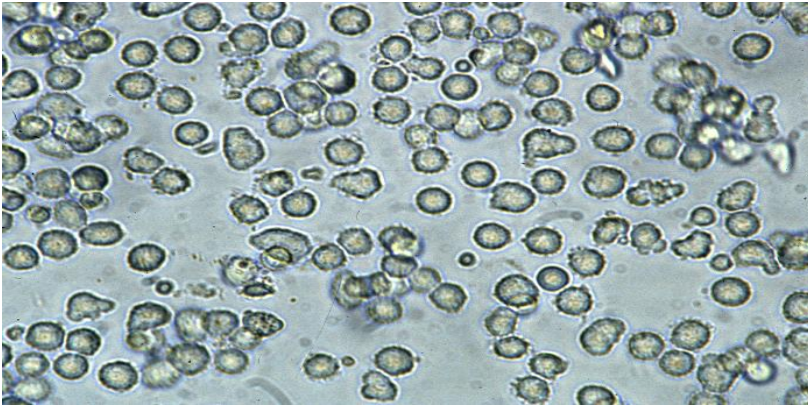
→ DC/monocyte activation induced

→ Leads to T cell expansion and proliferation

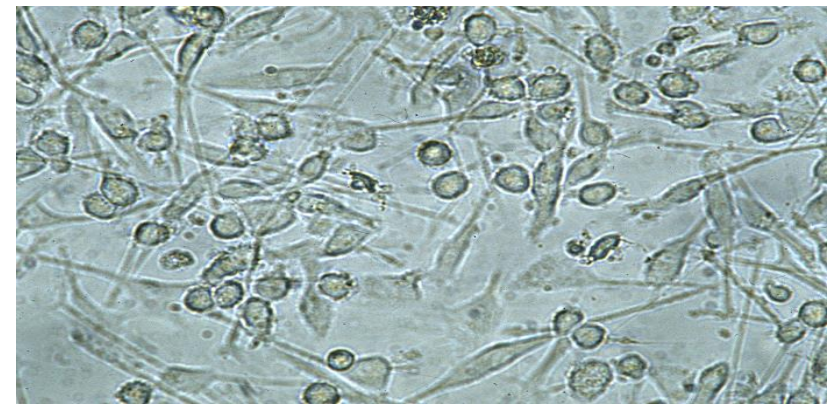
- Highly efficacious in multiple animal models of cancer and infectious disease
- Shown to be safe, non-immunogenic and efficacious in humans

IMP321 as an MHC class II agonist

mDC + hIgG1 (negative control), 4 hrs



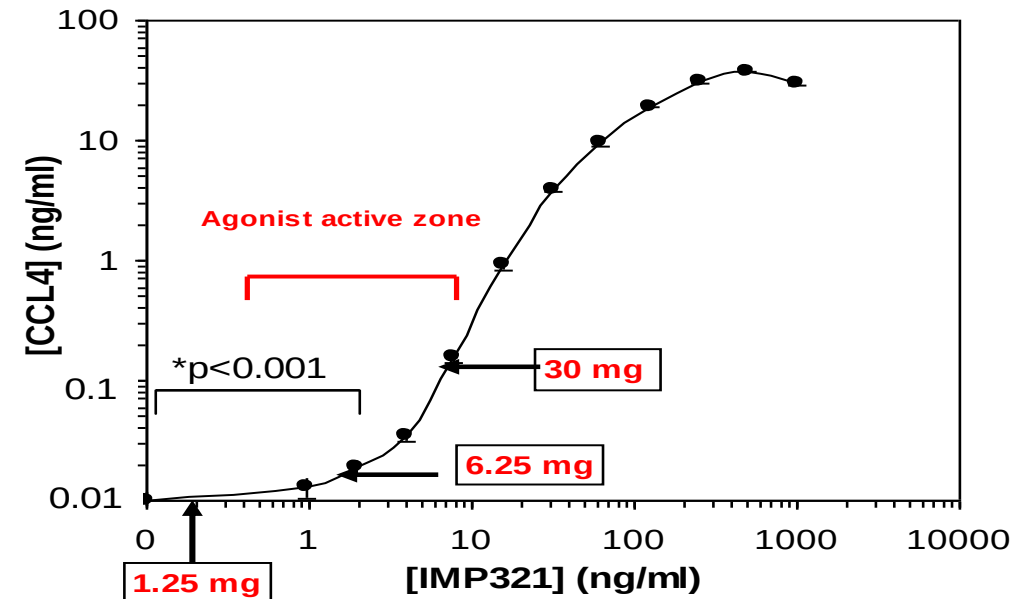
mDC + 1 µg/ml LAG-3Ig, 4 hrs



Monocyte-derived DC (mDC): human blood monocytes are cultured with GM-CSF + IL-4 for 5 days and are differentiated into immature DC

IMP321 as an MHC class II agonist

In vitro bioactivity of IMP321. IMP321 potency to induce CCL4 (MIP-1 β) secretion was tested using the MHC class II⁺ human monocytic THP-1 cells. The results are presented as concentration of CCL4 produced in supernatant after 4 hrs of culture (mean of 5-plicate determinations $\pm$ SD) as a function of IMP321 concentration on a logarithmic scale. The lowest concentration of IMP321 inducing a response statistically different from the baseline is indicated. The concentrations found in the serum 2hr after s.c. injection of 1.25, 6.25 and 30 mg in patients are indicated by arrows.



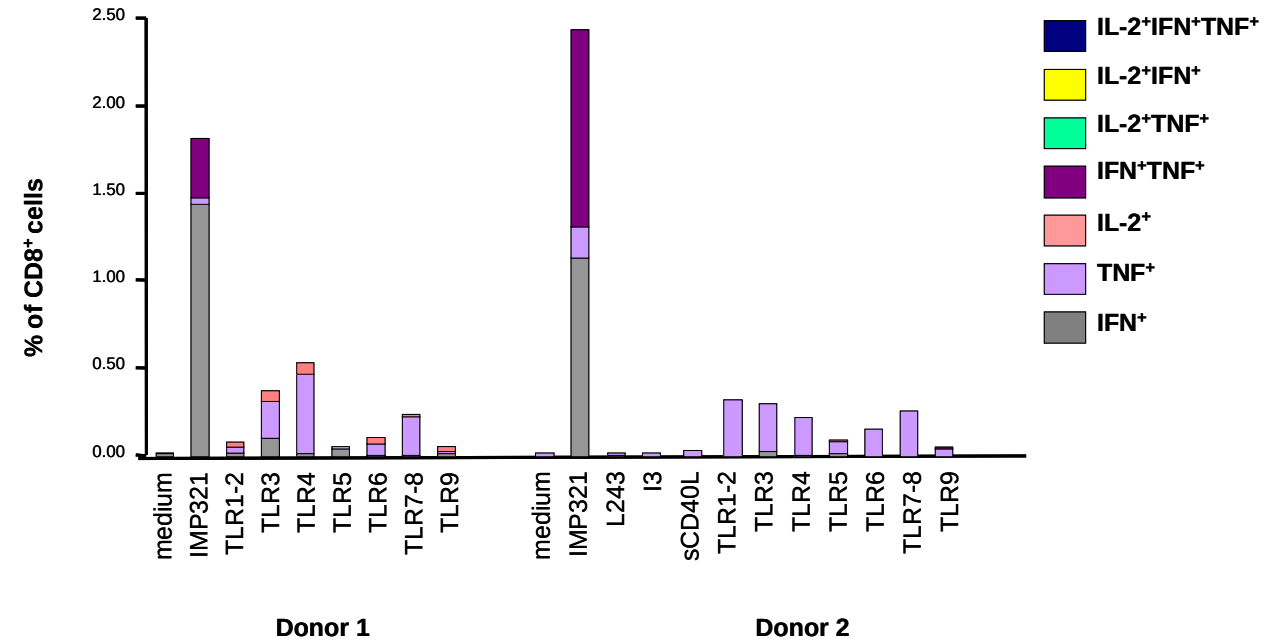
IMP321 induces a better CD8 Tc1 differentiation than sCD40L or TLR agonists

➤ 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



IMP321 Clinical Trials Overview

Protocol	Patient Population	Compound	Status
P001 Phase I	healthy males	IMP321 (adjuvant)	Completed
P002 Phase I	healthy males	IMP321 (adjuvant)	Completed
P003 Phase I	metastatic renal cell carcinoma	IMP321 (monotherapy)	Completed
P005 Phase I	metastatic breast carcinoma	IMP321 (chemo-immunotherapy)	Completed
P006 Phase I/IIa	disease free melanoma	IMP321 (adjuvant)	Completed
P007 Phase I/IIa	metastatic melanoma	IMP321 (adjuvant)	Completed
P008 Phase I/II	advanced pancreatic cancer	IMP321 (chemo-immunotherapy)	Completed
P009 Phase I/IIa	melanoma	IMP321 (adjuvant)	Completed
P010 Phase II	prostate carcinoma	IMP321 (adjuvant)	Completed

 PRIMA BIOMED



IMP321 – Potential Applications

Potential combination therapy strategies:

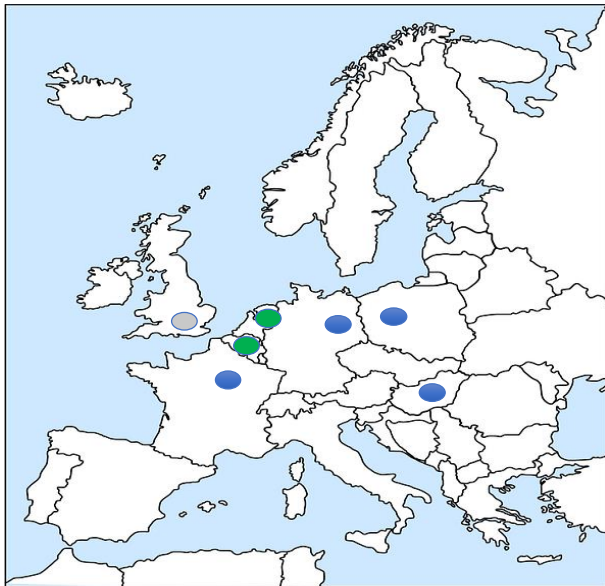
- **Chemo-immunotherapy** in various cancer indications
 - Combination therapy with active agents such as Taxanes (e.g. Paclitaxel), anthracyclines, alkylating agents, anti-metabolites, vincas...
- **I-O combination** in various cancer indications
 - With PD-1, PDL-1 or CTLA-4 antagonists...
- **Cancer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

AIPAC (Active Immunotherapy PAClitaxel)

Multinational, multicenter, placebo-controlled, double blind, 1:1 randomized Phase IIb trial in metastatic breast carcinoma patients treated with first-line weekly paclitaxel.

Two stages:

- **Safety run-in stage:** open-label, determining recommended phase two dose (RPTD) of IMP321 in combination with paclitaxel
- **Randomization stage:** IMP321 + paclitaxel vs. paclitaxel + placebo



Features:

- Proof of concept chemo-immunotherapy
- Potential pivotal character (discussed with EMA)
- > 200 pts
- > 30 sites in BE, NL, UK, PL, HU, FR

IMP321/PEMBROLIZUMAB COMBINATION

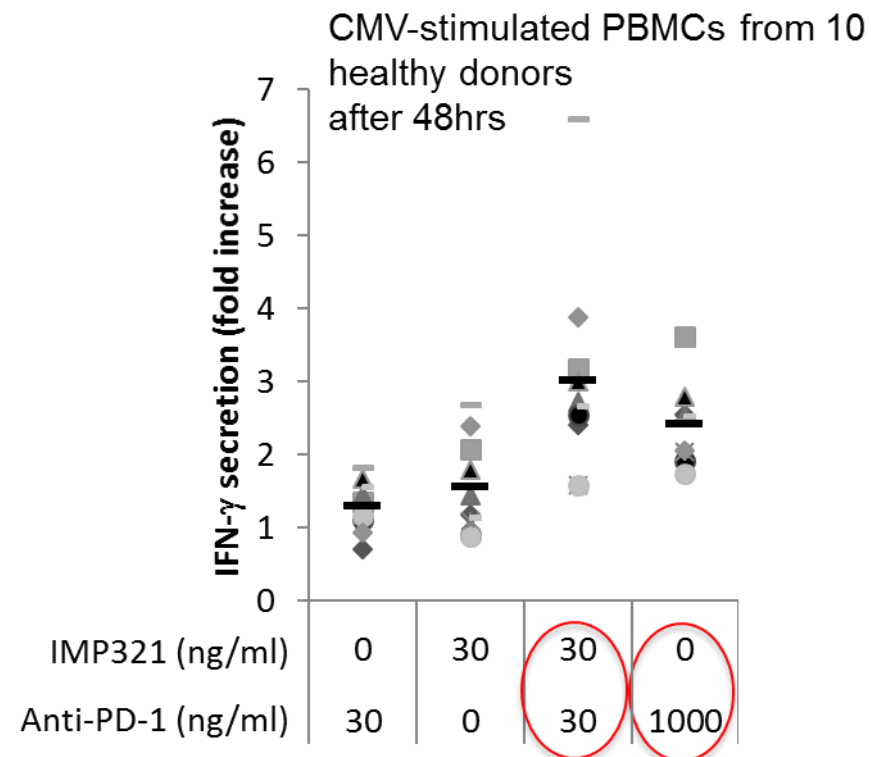


Three groups of patients responding to anti-PD-1 (IFN- γ signature)

- 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

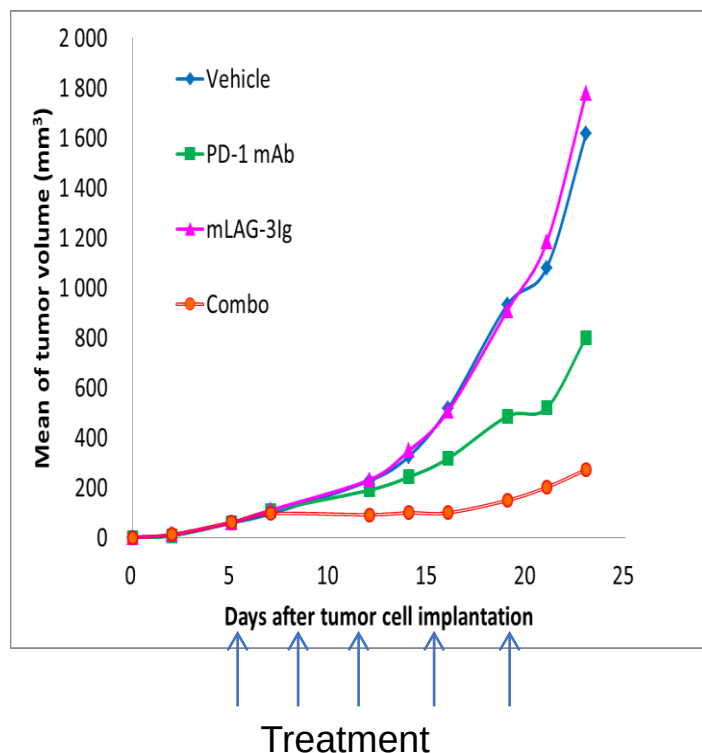
In vitro preclinical data supporting the combination

- Synergistic effect for the combination at low dose: 30 ng/ml IMP321 + 30 ng/ml anti-PD1 mAb
- A better IFN- γ inducing effect than the blocking anti-PD-1 mAb concentration (1,000 ng/ml)
 - « Pushing the gas » (IMP321) and « releasing the brake » on CD8 T cell responses: a synergistic combination



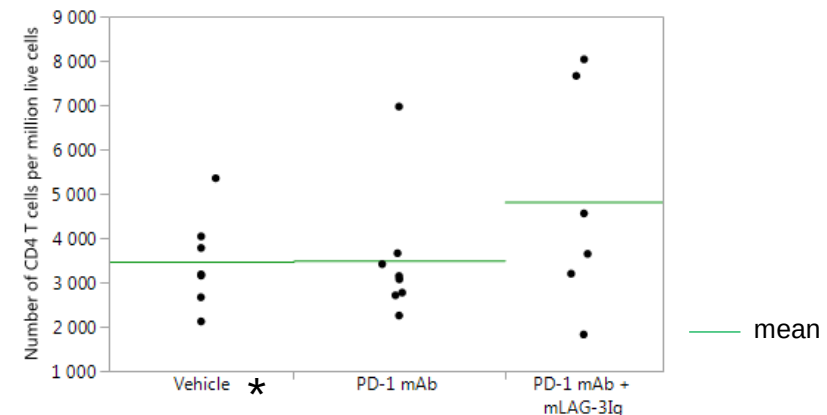
In vivo preclinical data supporting the combination

Anti-PD-1 (10 mg/kg) + mLAG-3Ig (1 mg/kg)
in a subcutaneous CT26wt colon cancer model

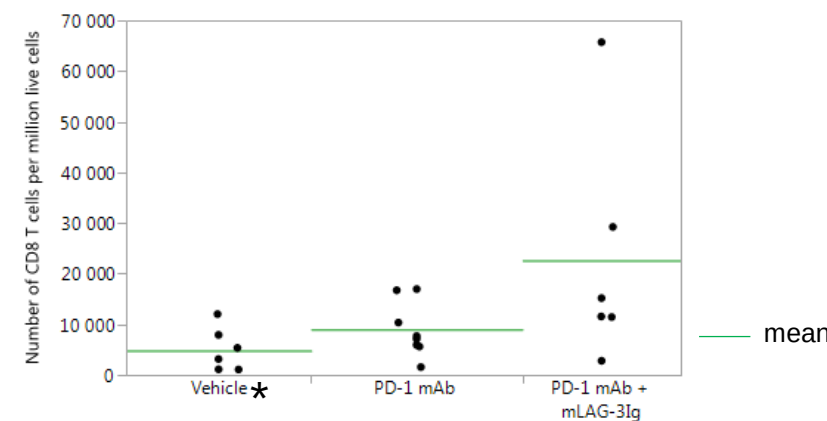


Increase in the number of TILs at day 10
in a subcutaneous CT26wt colon cancer model

CD4⁺ TIL



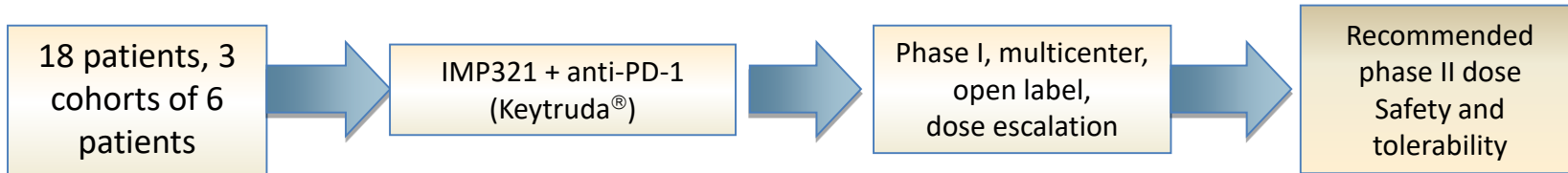
CD8⁺ TIL



IMP321 in Melanoma

TACTI-mel (I-O combination)

TACTI-mel trial: Two ACTive Immunotherapeutics in melanoma



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 5 th cycle of pembrolizumab

Status report

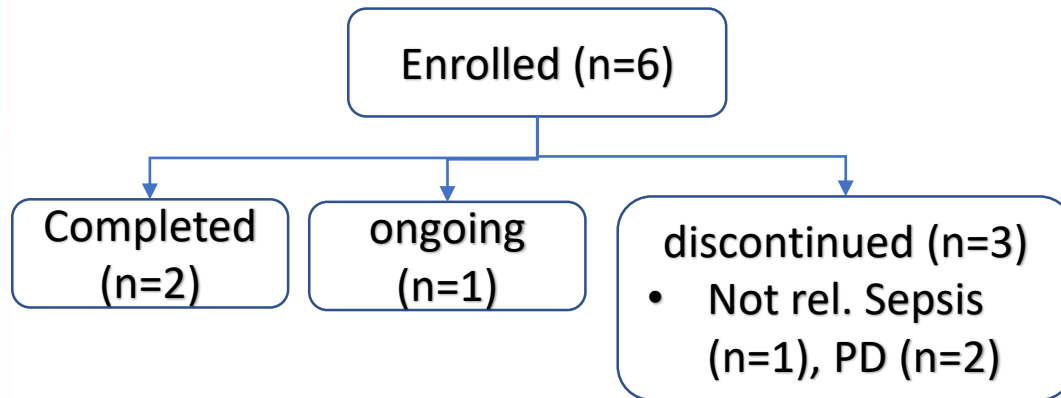
- Enrollment of cohort 2 (6 mg) completed.
- Enrolment completion expected in Q3 2017



6 sites in Australia

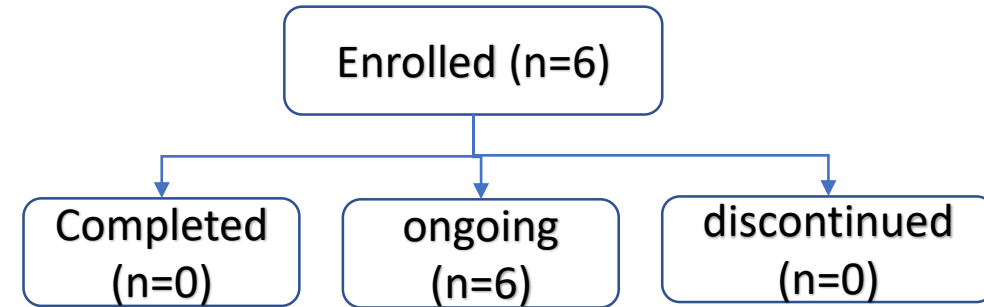
TACTI-mel: status and preliminary results

Cohort 1 (1 mg), start Q2/2016



- pts received 45+ injections IMP321 + pembrolizumab

Cohort 2 (6 mg), start Q1/2017



- pts received 16+ injections IMP321 + pembrolizumab

Both dose levels:

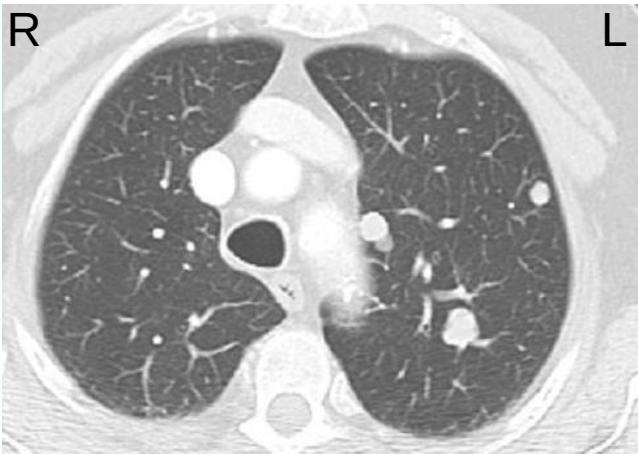
→ No clinically significant AEs related to IMP321 or the combination of IMP321 and pembrolizumab

TACTI-mel first cohort (1 mg IMP321)

Patient 02-01: Preliminary results

Efficacy

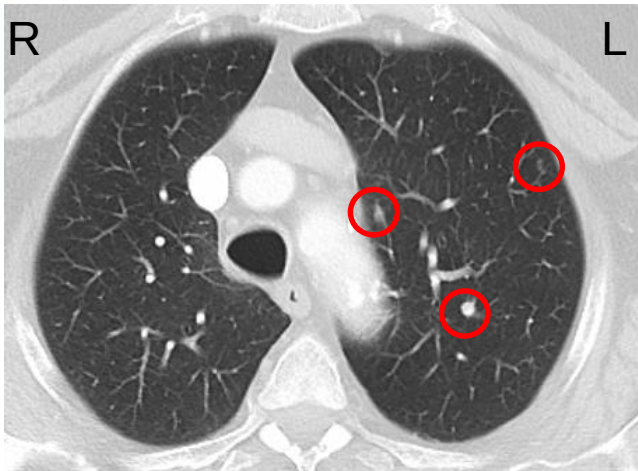
Baseline



week 13 (cycle 5)



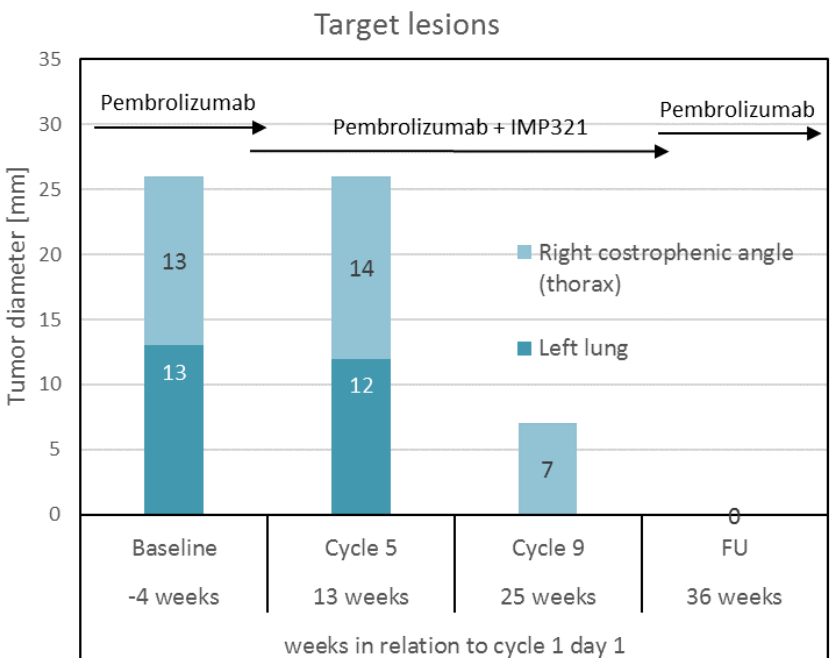
week 25 (cycle 9)



week 36 (FU)



All lesions disappeared → CR



Target	26 mm	26 mm (- 0%) SD	7 mm (-73%) PR	0 mm (-100 %) CR
Non-target	present	Non-CR/ non-PD	CR	CR
Overall	N/A	SD	PR	CR

According to RECIST 1.1

Thank you

A decorative graphic consisting of a grid of colored squares. The top row has six squares: red, red, light gray, light gray, dark gray, and light gray. The second row has three squares: red, light gray, and dark gray. The third row has one square: light gray.

Frédéric Triebel, CSO/CMO
ICI Meeting
March 15-16, 2017
Boston, MA.