Combination Strategies for LAG-3Ig (IMP321) With Either Chemotherapy or Anti-PD-1 Therapy

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ASX:PRR; NASDAQ:PBMD

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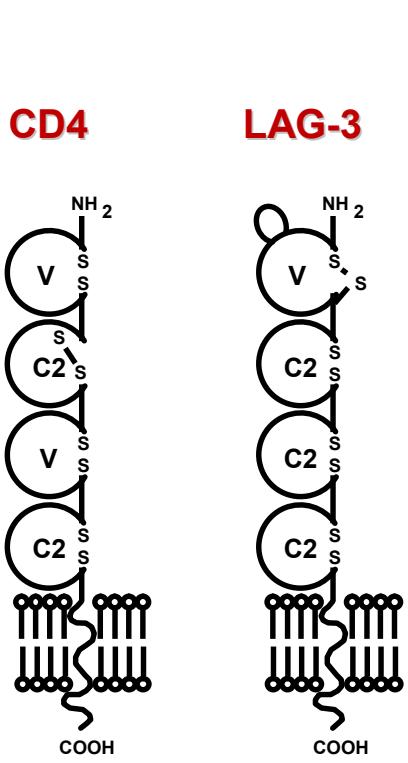
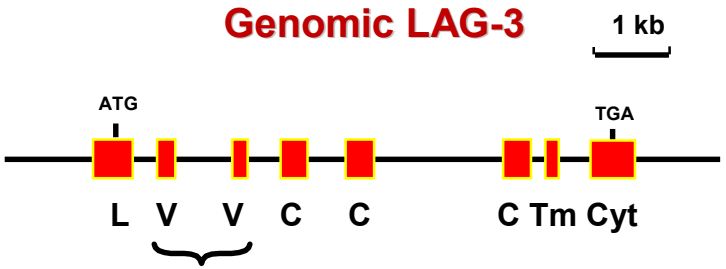
Lymphocyte Activation Gene-3

(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

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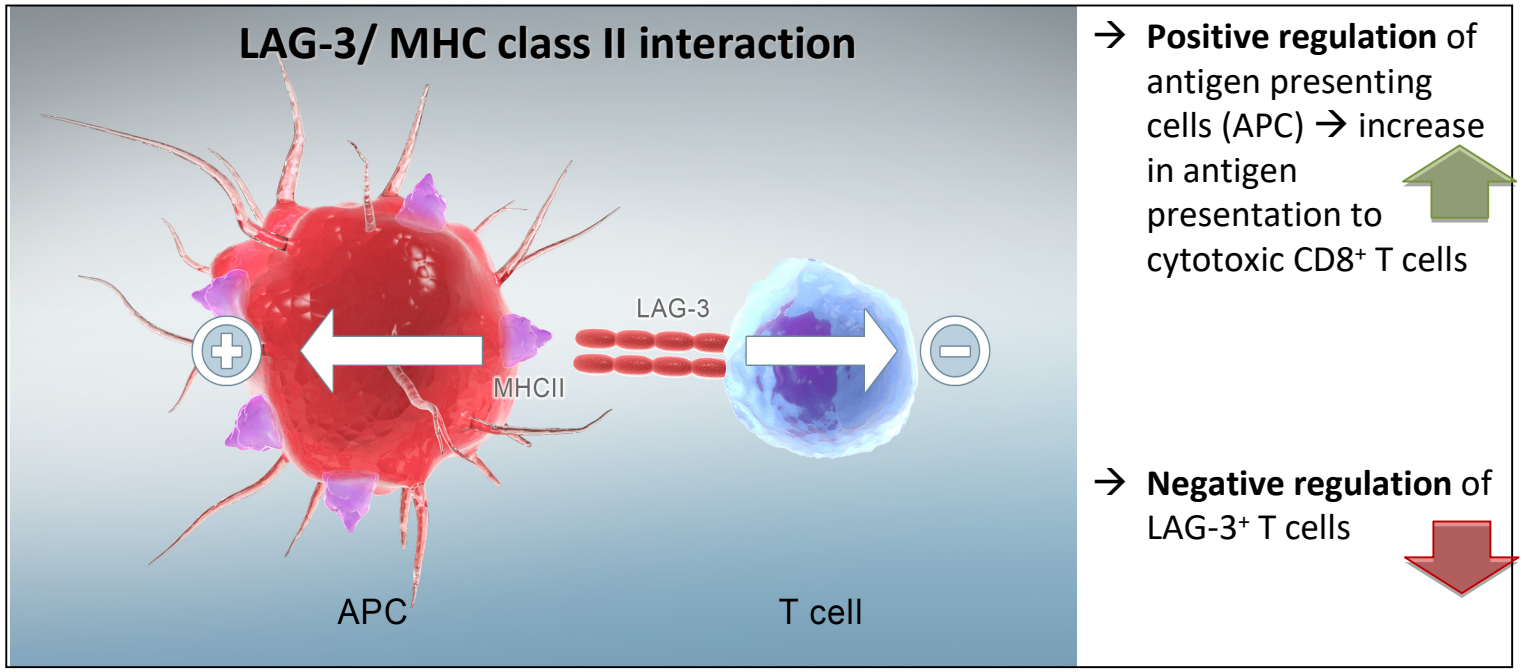
LAG-3 As a Therapeutic Target

- 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®)



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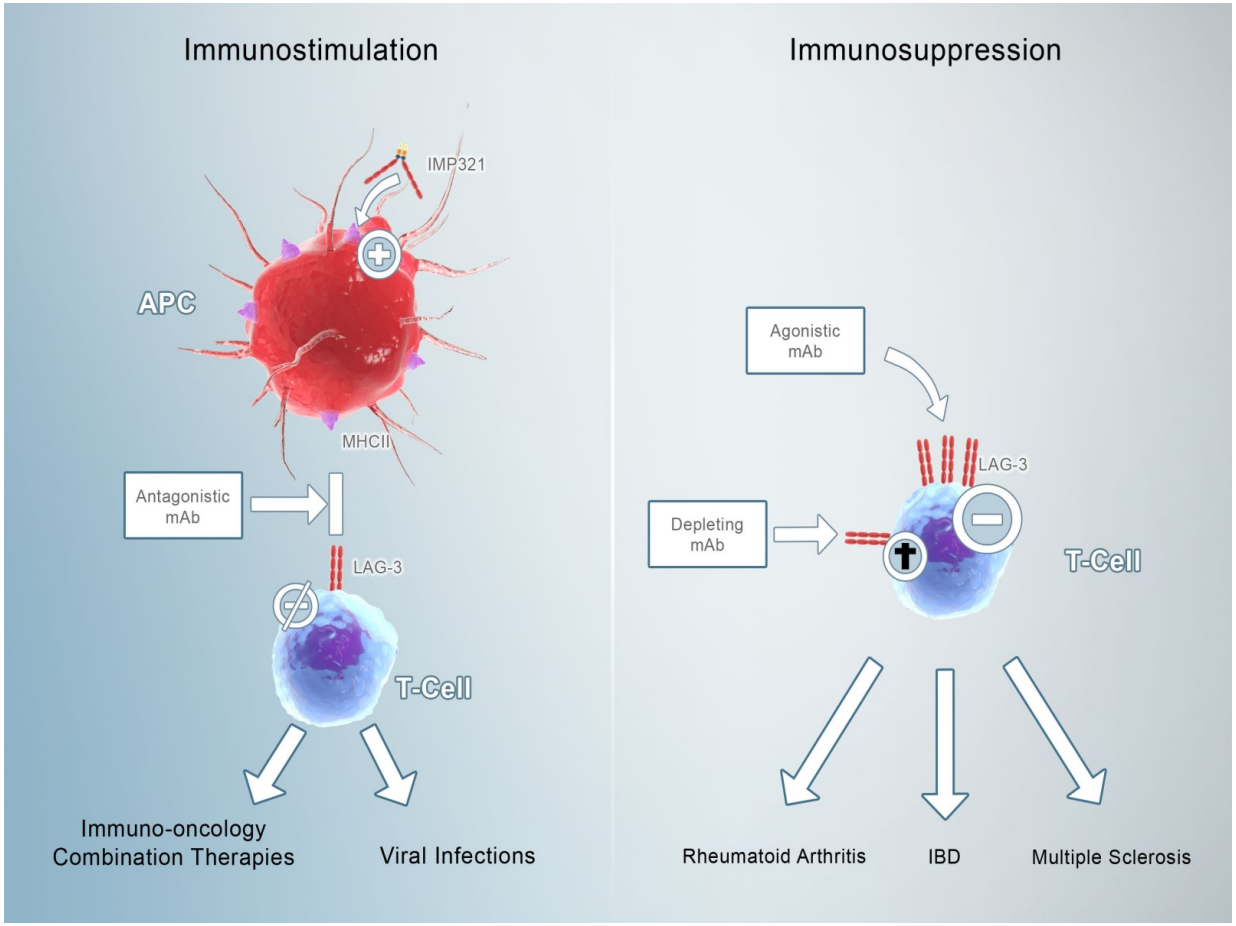
Targeting LAG-3 May Lead to Multiple Therapeutics in Numerous Indications



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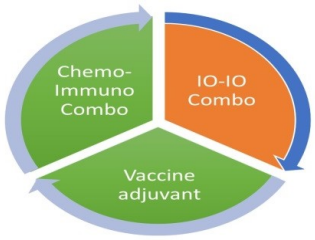
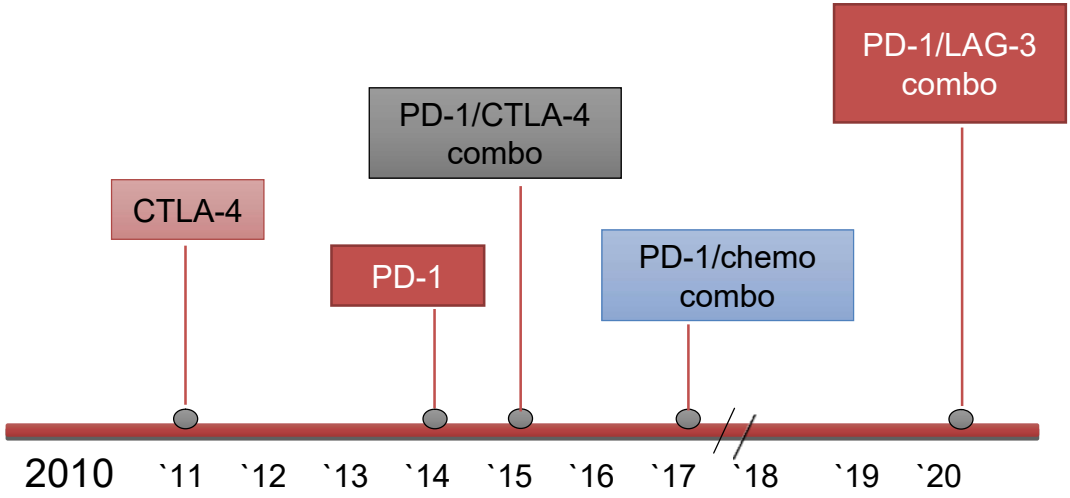


I-O Therapy Landscape and Opportunity

Current Immuno-Oncology Therapies

- CTLA-4, PD-1 and PD-L1 antagonists approved for many indications → only 15 - 40% of solid tumors respond → reasons are absence of TILs and exhausted TILs → rescue strategies necessary
- Combo PD-1 + CTLA-4 relatively toxic
- **<u>Opportunity for IMP321:</u>**
  - ✓ Potential synergistic effect with current I-O therapies → may enhance tumor response to treatment
  - ✓ IMP321 has excellent safety
  - ✓ Unique MoA (i.e. upstream of PD-1)

The Evolution of Immuno-Oncology Therapies



Dose escalation Phase I of IMP321 + Keytruda (TACTI-mel) in melanoma ongoing → extension to other indications possible

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LEAD PRODUCT: eftilagimod alpha (IMP321)

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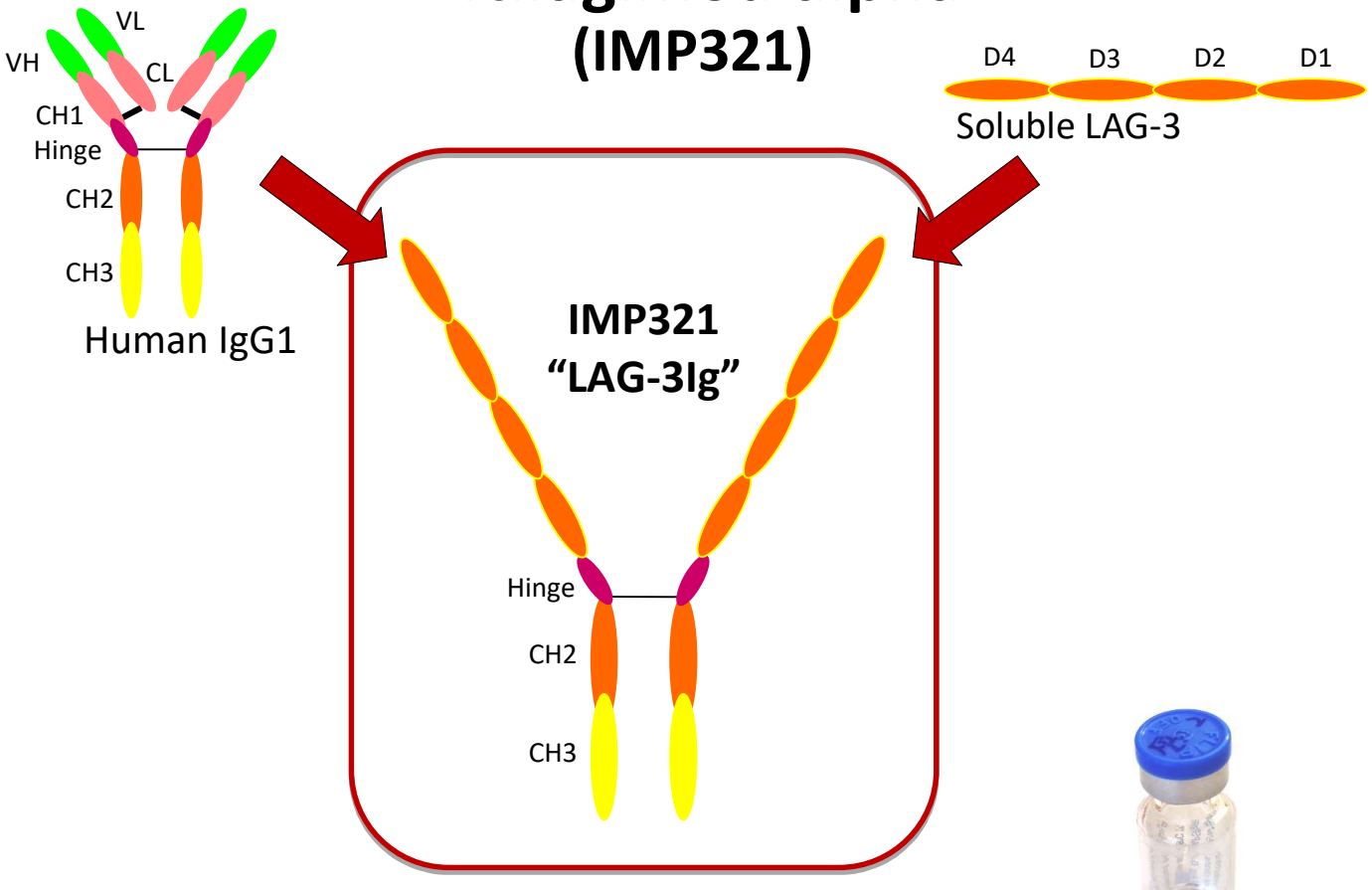
Eftilagimod alpha (IMP321)



- **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**

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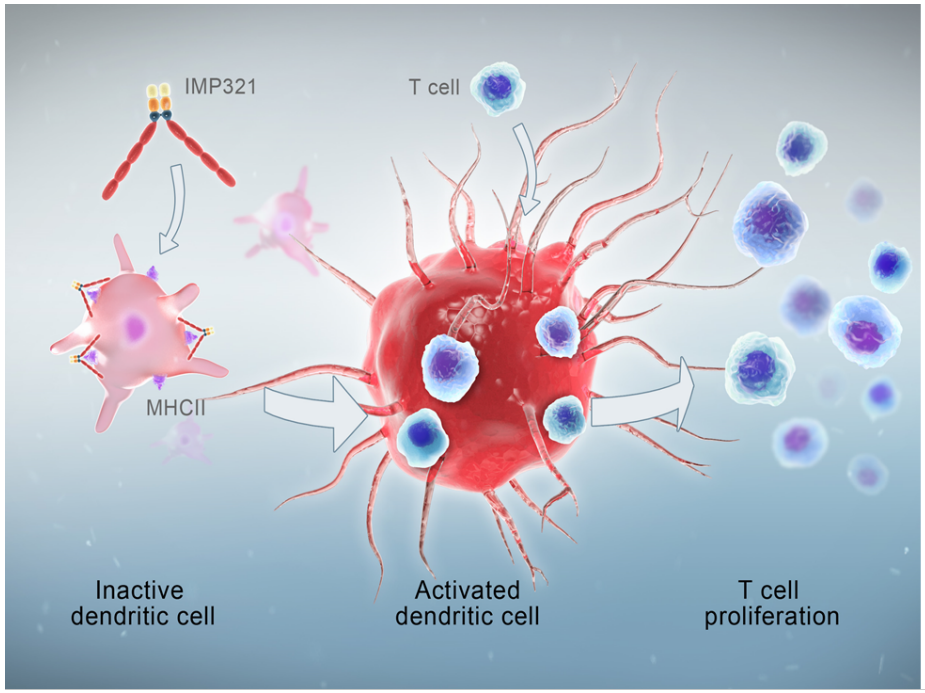
Eftilagimod alpha (IMP321)

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

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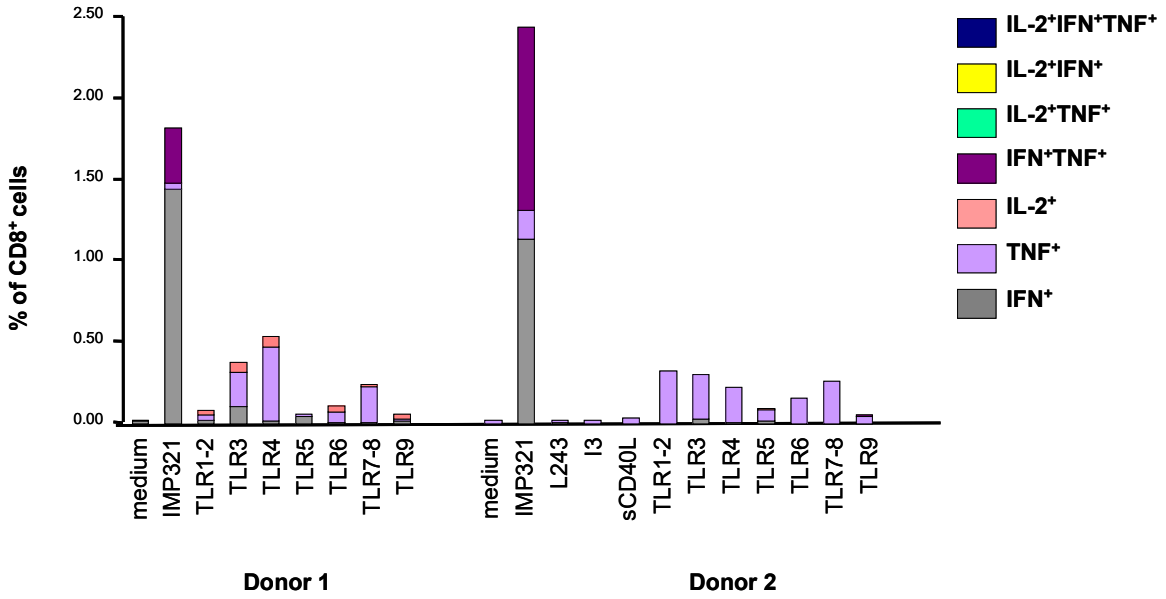
eftilagimod alpha (IMP321)

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

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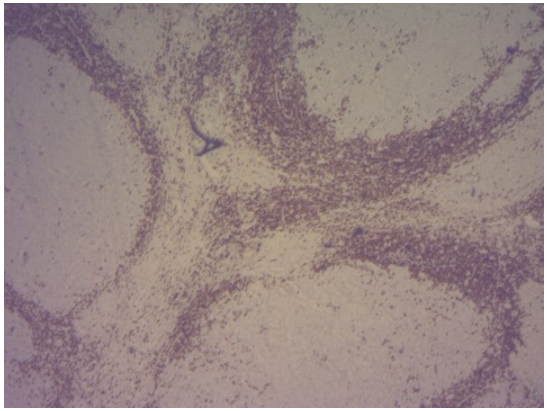
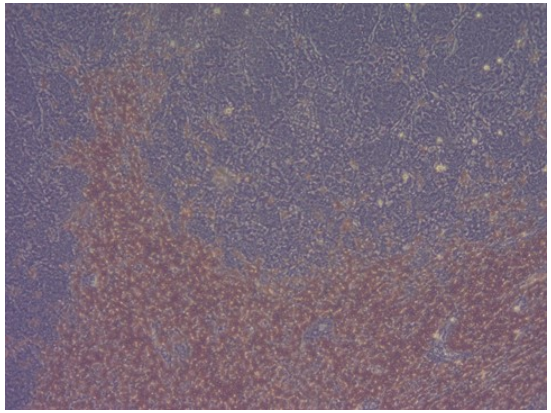
APC Activation Turns on the Heat on a Cold Tumor
(Breast Cancer)

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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eftilagimod alpha (IMP321)
CLINICAL DEVELOPMENT

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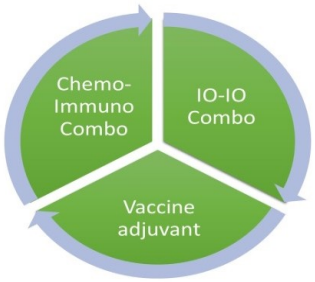

Eftilagimod alpha – Potential Applications

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**
  - To locally stimulate the immune system

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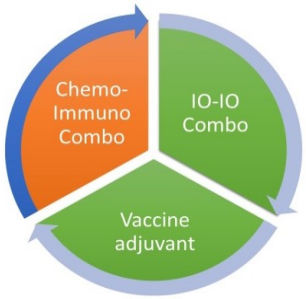
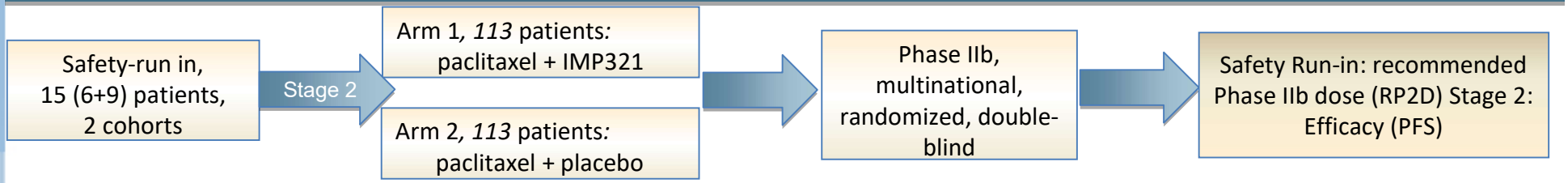


Eftilagimod alpha in MBC

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

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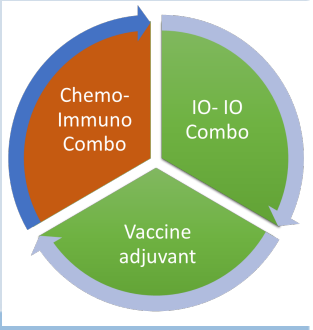
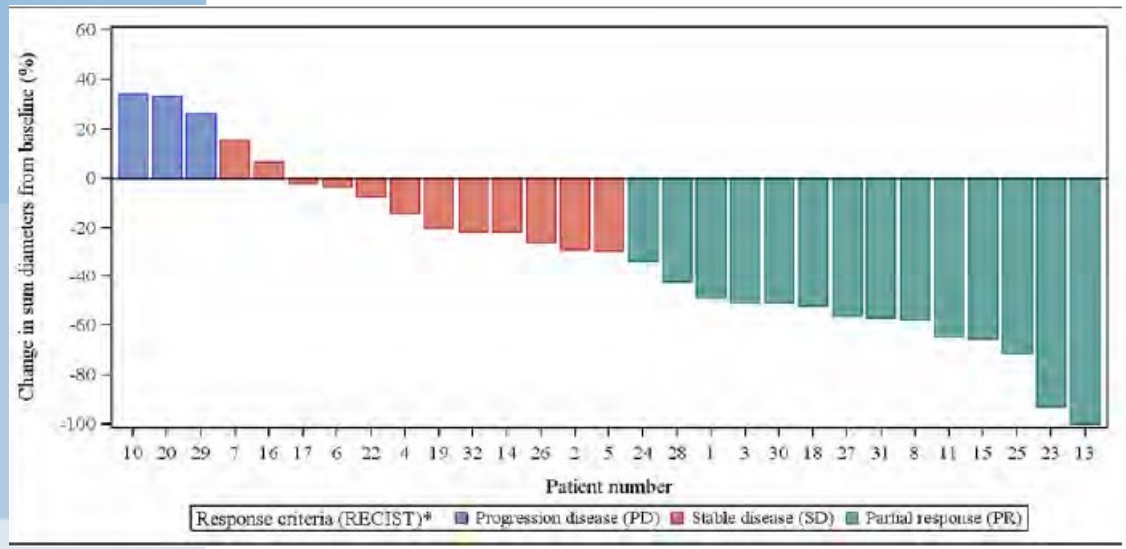


Eftilagimod alpha – Preliminary Efficacy

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

preliminary data, status September 2017, best response acc. To RECIST 1.1

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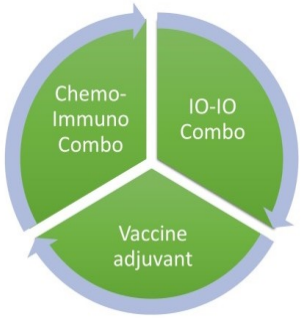
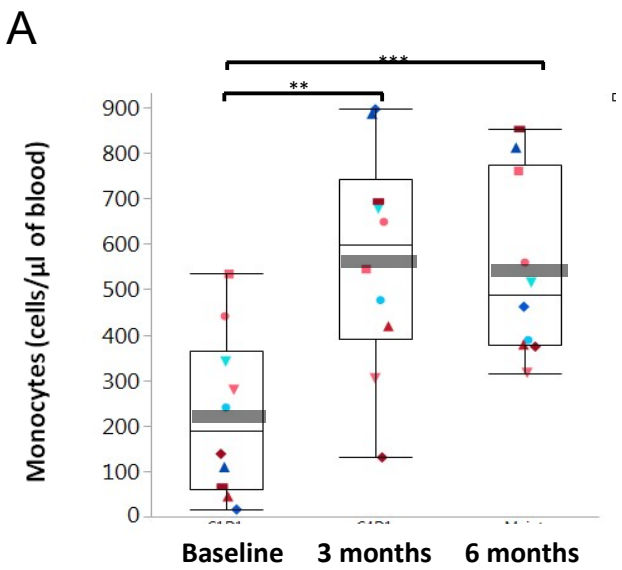
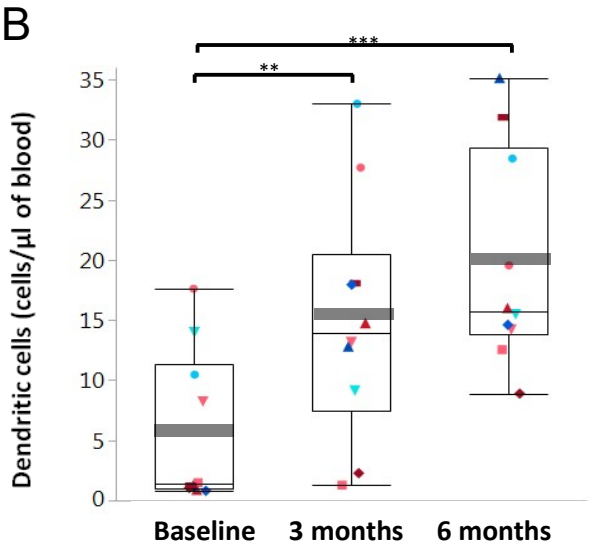


Eftilagimod alpha – Clinical Overview

Pharmacodynamic Results on Primary Target Cells

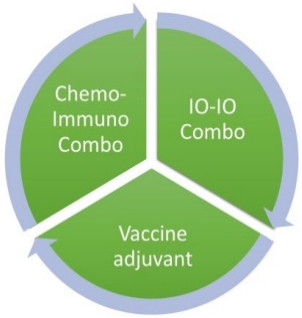




IMP321 leads to sustainable (> 6 months) increase of pre-dose APCs (run-in phase, AIPAC trial).

preliminary data, status September 2017

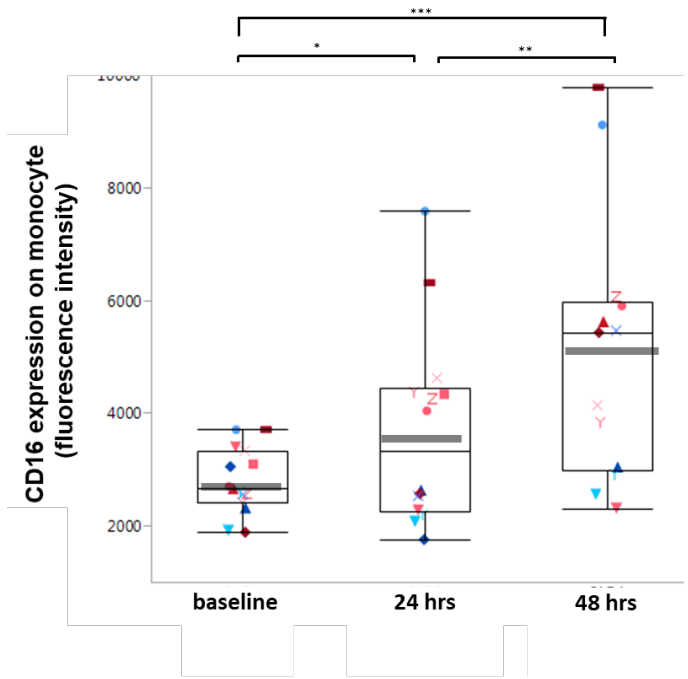
PRIMA BIOMED



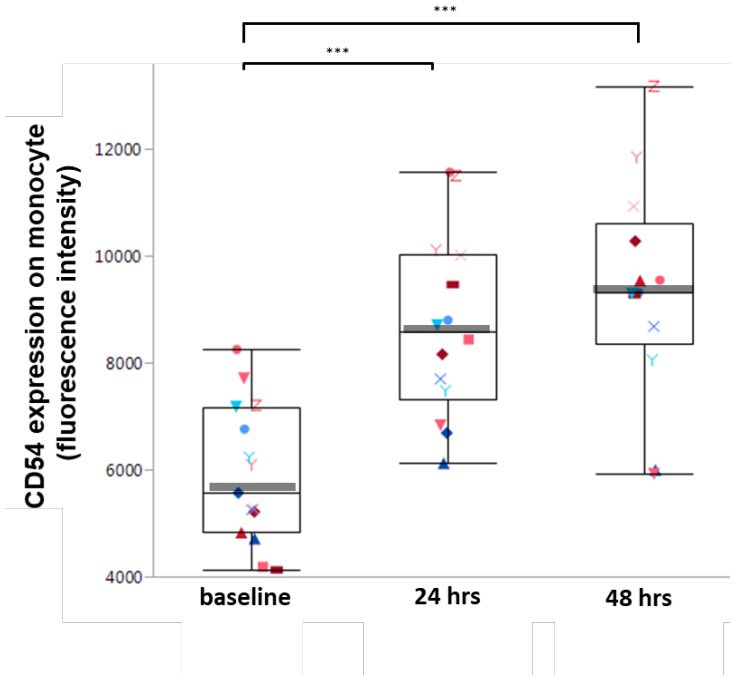
Eftilagimod alpha – Clinical Overview (cont.)

Pharmacodynamic Results on Primary Target Cells

A



B



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

preliminary data, status September 2017

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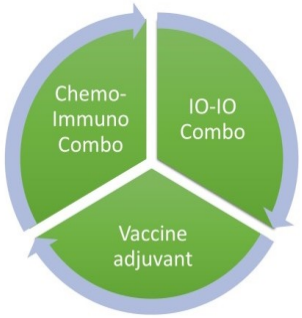
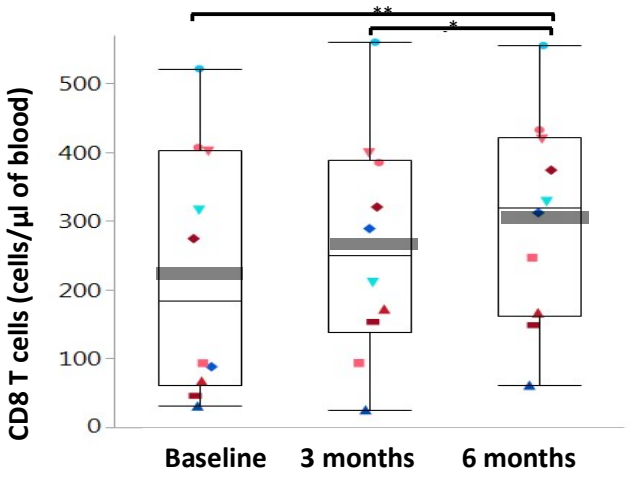


Eftilagimod alpha – Clinical Overview (cont.)

Pharmacodynamic Results on Secondary Target Cells

A



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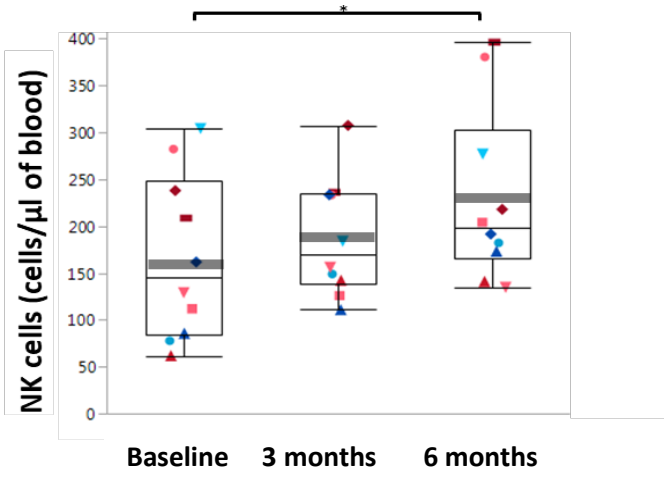

IMP321 leads to sustainable (> 6 months) increase of pre-dose effector CD8 T cells and NK cells (run-in phase, AIPAC trial).

preliminary data, status September 2017

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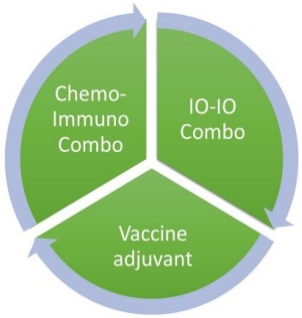
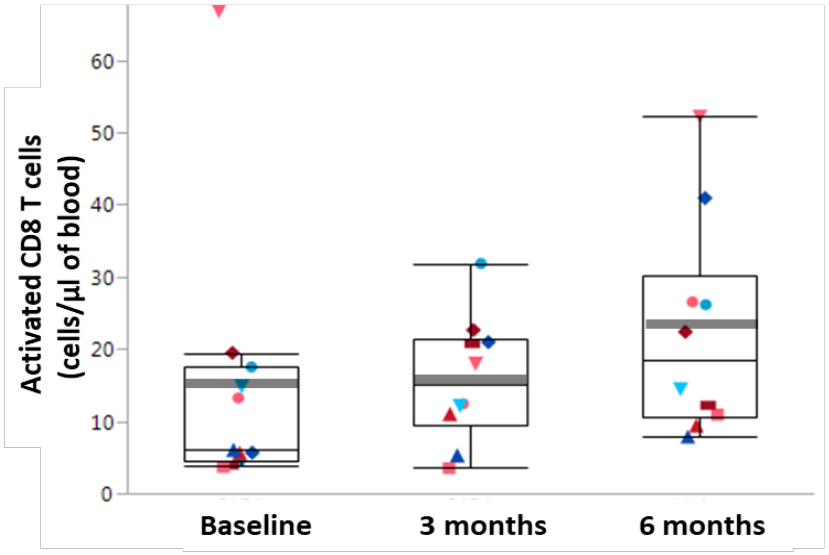
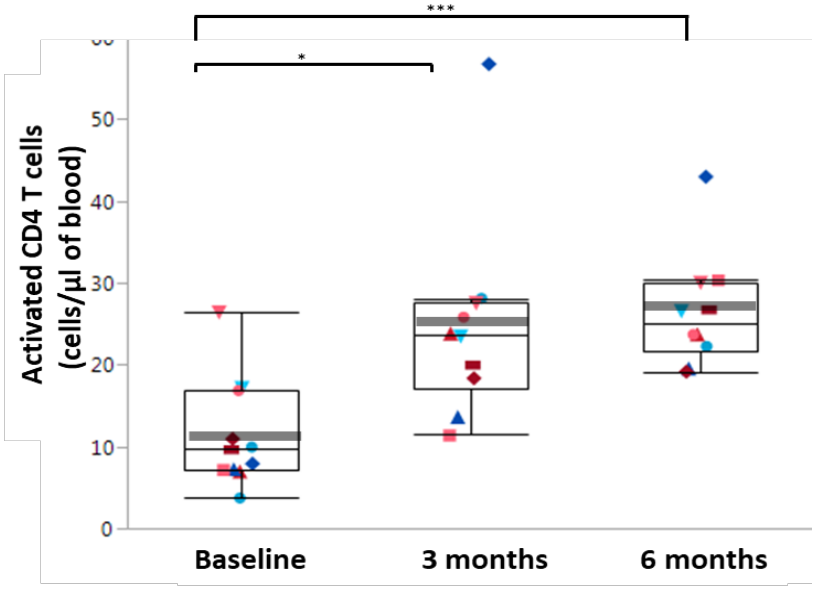


Eftilagimod alpha – Clinical Overview (cont.)

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).

preliminary data, status September 2017

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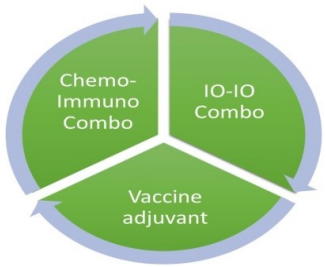
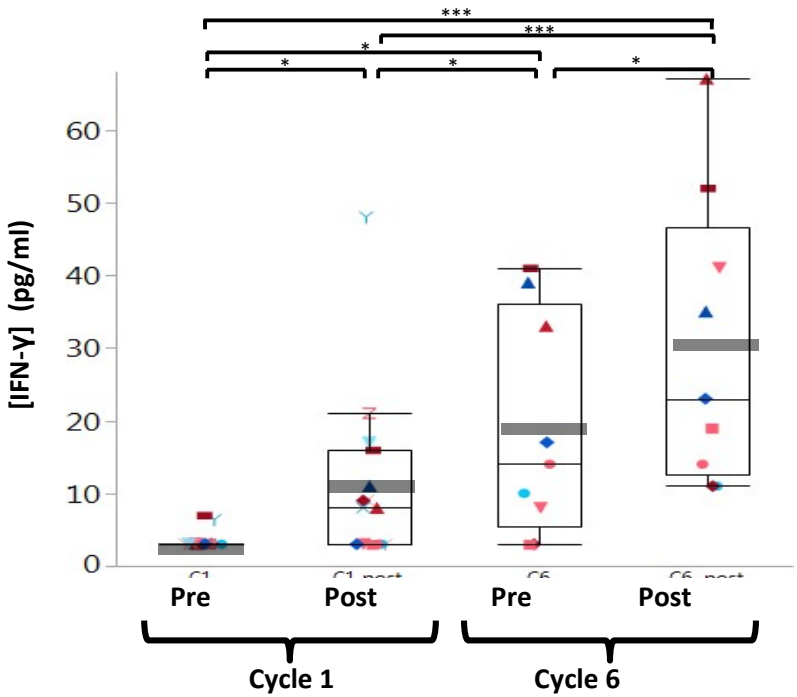


IMP321 – Clinical Overview (cont.)

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.

preliminary data, status September 2017

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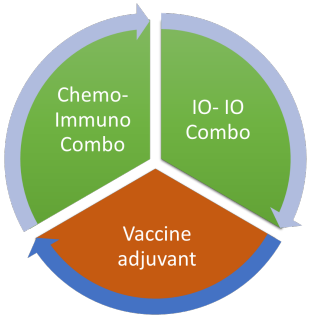
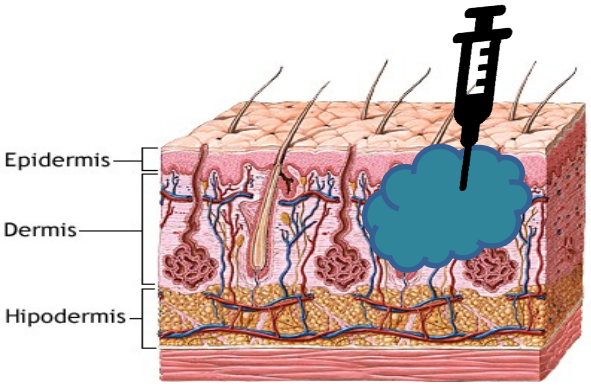


Eftilagimod alpha abscopal effects

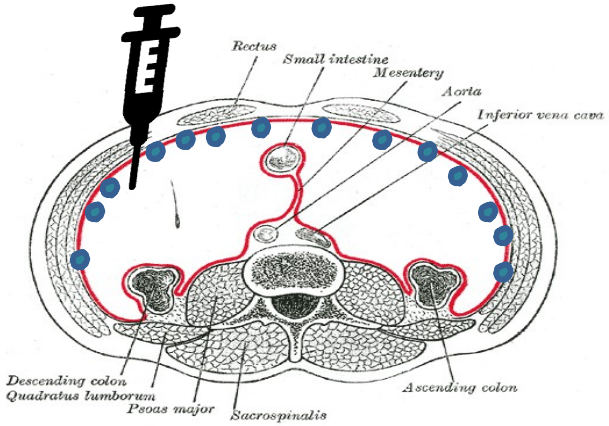
INSIGHT (phase I - IIT)

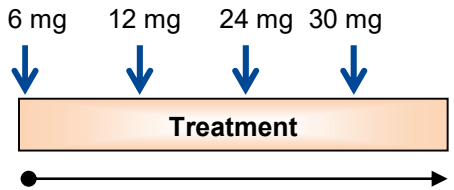
- Population: 18 pts (9 per stratum) with advanced solid tumors w/o standard treatment options
- Objectives: Recommended phase II dose, PD effects of IMP321
- Design: intrapatient escalation

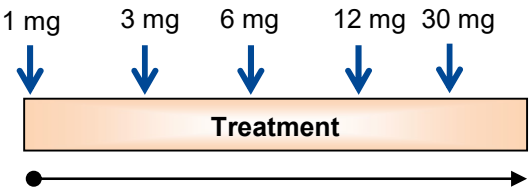
Stratum A: intratumoral (i.t.)



Stratum B: intraperitoneal (i.p.)







Stratum A:

- 1st pt completed escalation w/o DLT,
- 2nd pt ongoing

Stratum B:

- 1st pt ongoing

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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IMP321/PEMBROLIZUMAB COMBINATION

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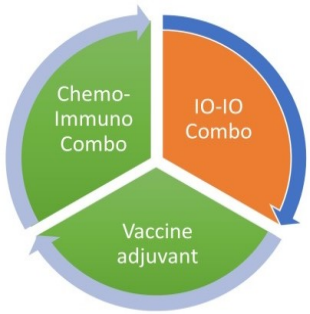

Three Groups of Patients Responding to anti-PD-1

(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

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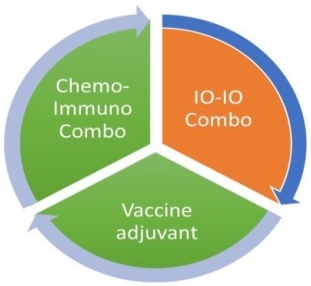


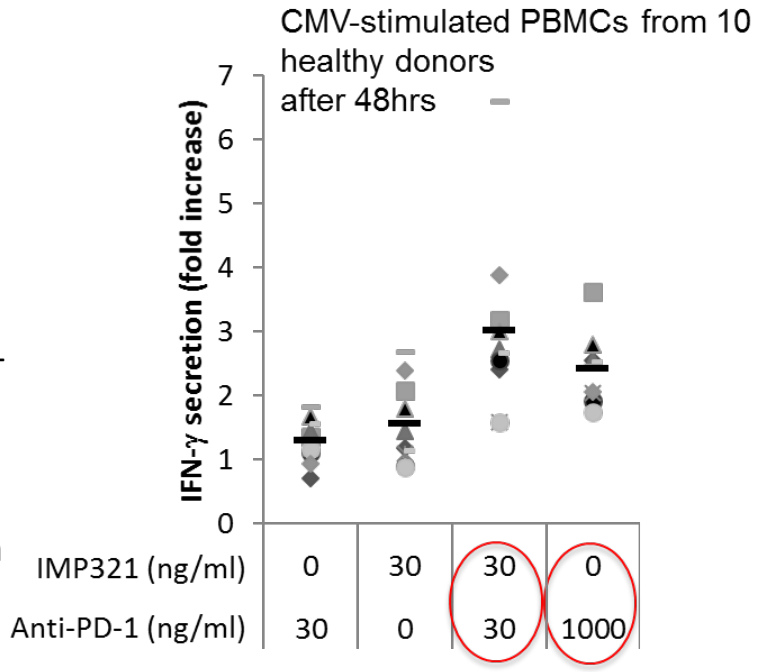
In vitro Human Preclinical Data Support the Combination

- Secretion of IFN-γ by cytomegalovirus (CMV)-specific human T cells in the presence of antigen

- Synergistic effect for the combination at low doses: 30 ng/ml IMP321 + 30 ng/ml anti-PD1 mAb

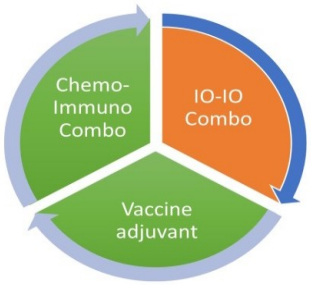
- A better IFN-γ inducing effect than the blocking anti-PD-1 mAb concentration (1,000 ng/ml)

- « Pushing the gas » (IMP321) and « releasing the brake » on CD8 T cell responses: a synergistic combination



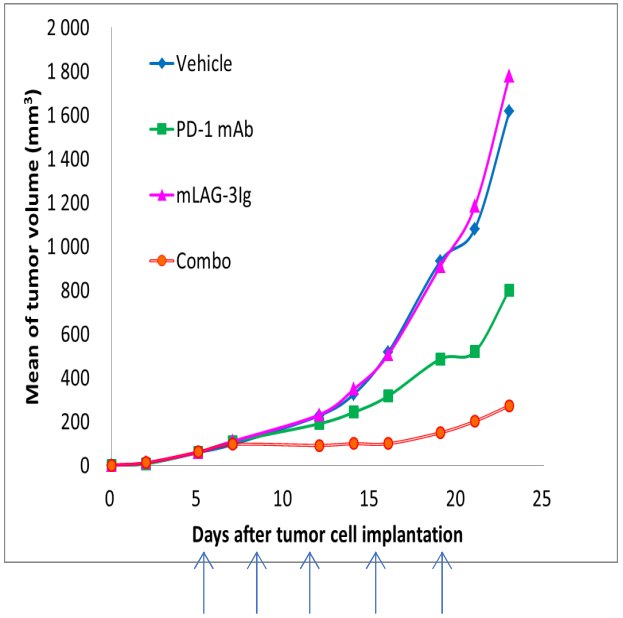
PRIMA BIOMED

24



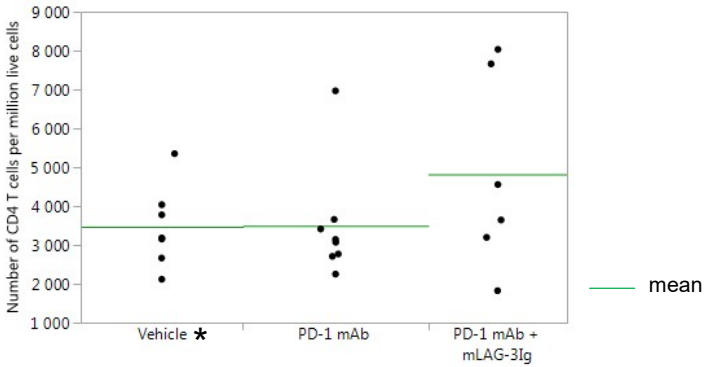
In vivo Mouse Preclinical Data Support the Combination

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

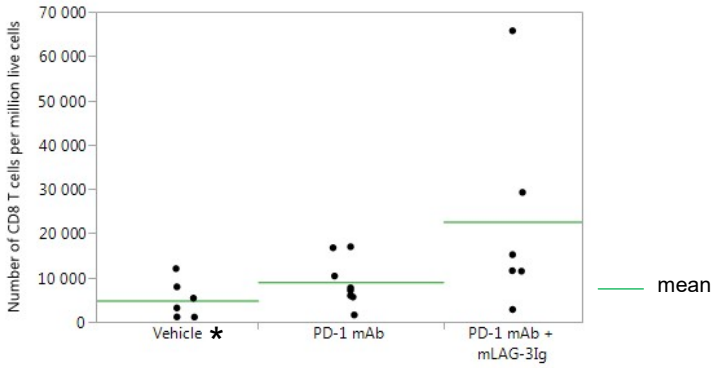


Increase in the number of TILs at day 10
in a subcutaneous CT26wt colon cancer model

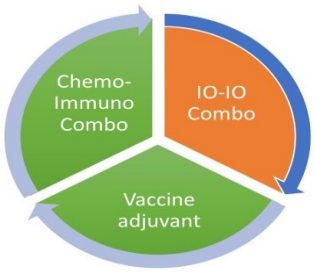
CD4⁺ TIL



CD8⁺ TIL

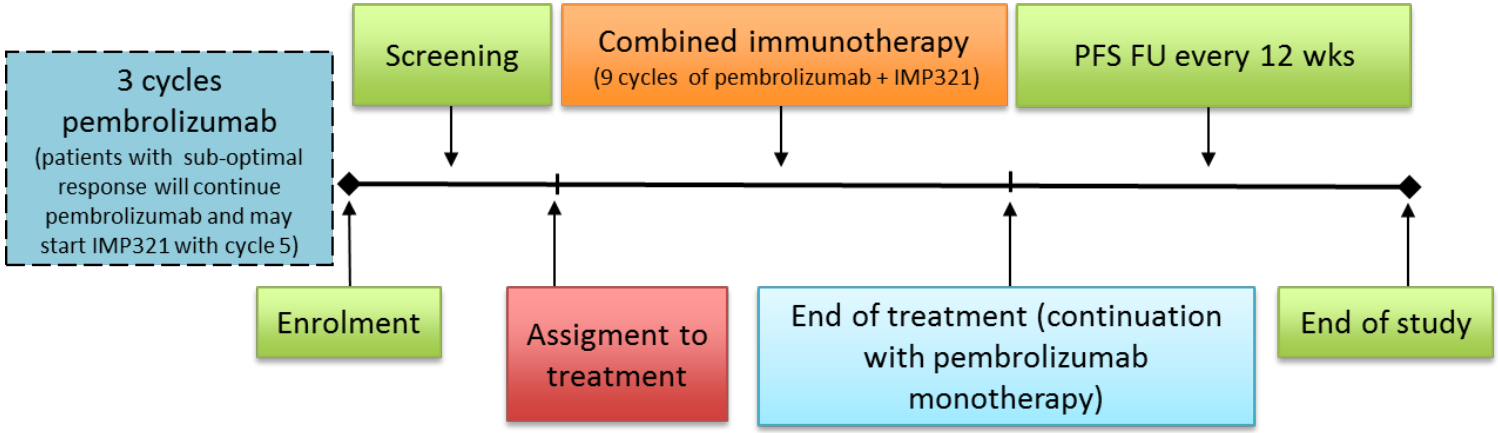


PRIMA BIOMED



Two ACTive Immunotherapies in melanoma
TACTI-mel (phase I)

- Population: 18 pts (6 per cohort) with unresectable or metastatic melanoma and no or suboptimal response to pembrolizumab
- Treatment: IMP321 (1, 6 or 30 mg s.c.) plus pembrolizumab (2 mg/kg, i.v.) for 6 months
- Primary objective: safety, tolerability and recommended phase II dose

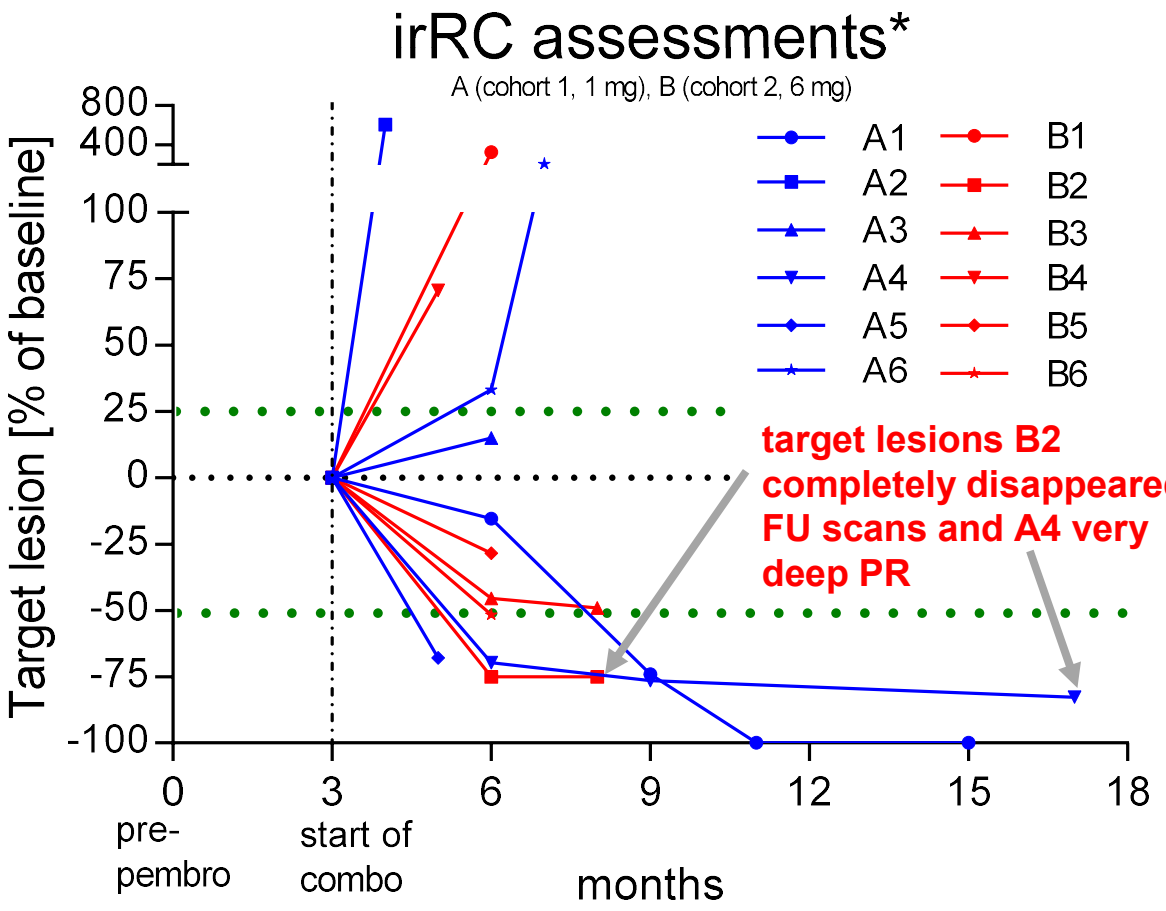


Cohort 1 and 2 finished → results were presented at SITC; Recruitment for cohort 3 is ongoing; 5 pts w/o DLT up to today

PRIMA BIOMED

Eftilagimod alpha - TACTI-mel

Preliminary efficacy data (irRC) - cohort 1 and 2



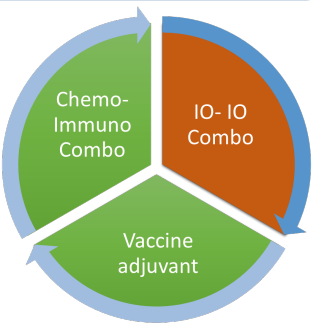
Response parameter (irRC), n (%)	Total (n=12)
irCR	1 (8)
irPR	3 (25)
irSD	3 (25)
irPD	5 (42)
RR	4 (33)
DCR	7 (58)
Patients with tumor reduction	7 (58)

- **Late stage patients with visceral disease (83 %) and elevated LDH (67 %)**
- **7/12 (58 %) patients with suboptimal response or progression on pembrolizumab had a tumor reduction during the study**
- **One confirmed complete response was observed**

* - according to study protocol patients receive pembrolizumab monotherapy for 3 cycles. Patients suboptimally responding to or progressing on pembrolizumab are screened and receive combination treatment beginning with cycle 5 (after 3 months) onwards

preliminary data, status 15th November 2017

PRIMA BIOMED

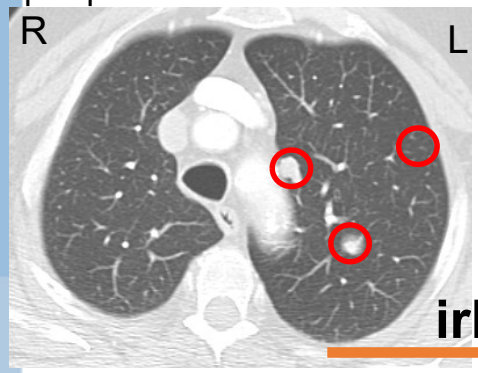


TACTI-mel

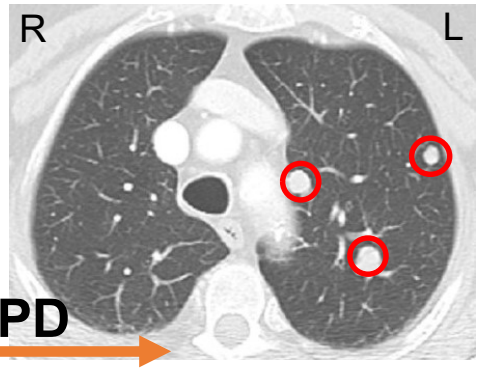
Patient A1 (1 mg): Preliminary results

Efficacy

pre-pembro

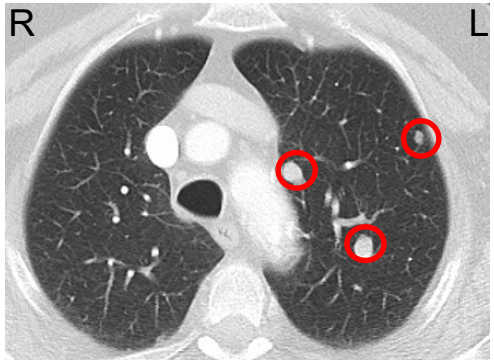


week 9 (pembro)

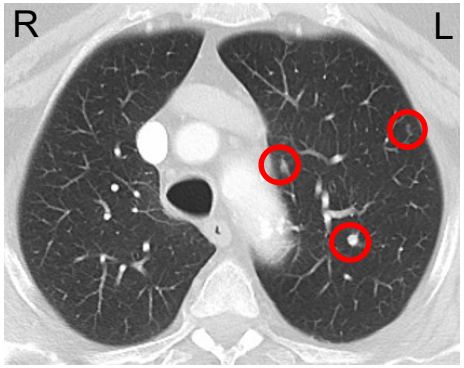


irPD

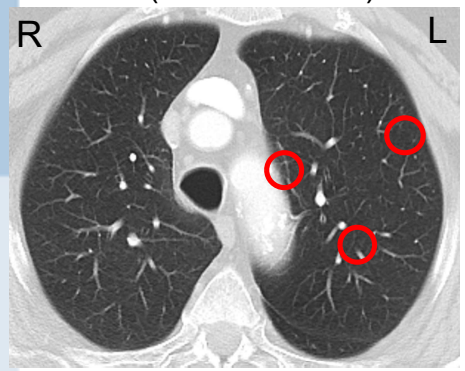
week 25 (combo)



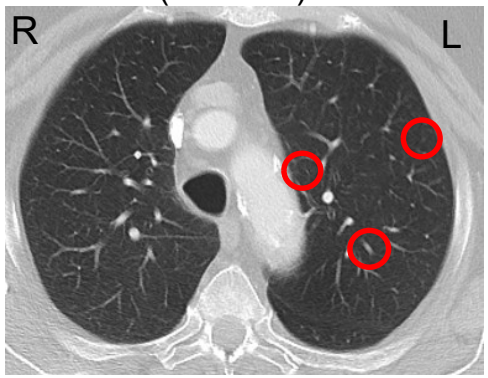
week 37 (combo)

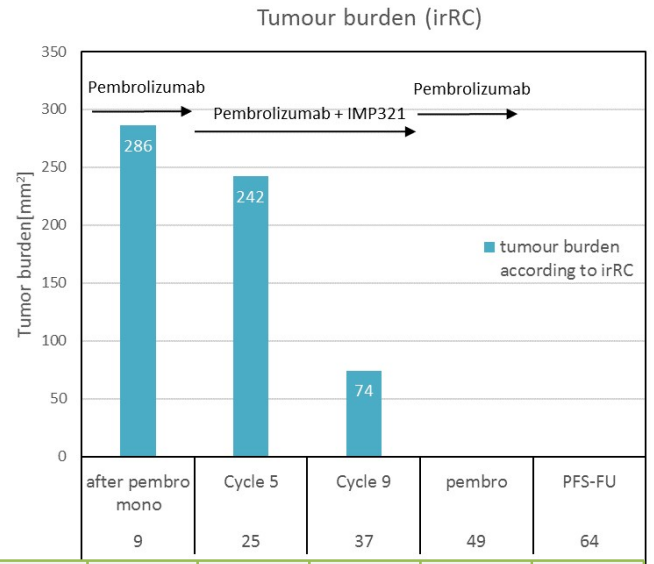


week 49 (Pembro mono)



week 64 (PFS-FU)

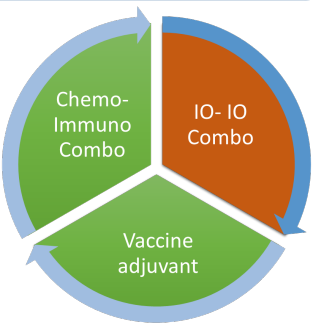




Sum Target Lesions	286 mm²	242 mm²	74 mm²	0 mm²	0 mm²
In %	100%	85%	26%	0%	0%
irRC	N/A	irSD	irPR	irCR	irCR

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

preliminary data, status 06th November, 2017

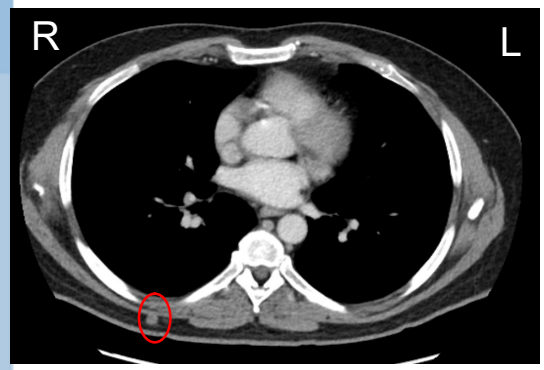


TACTI-mel

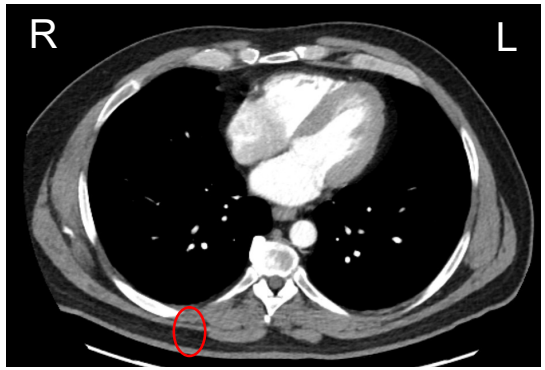
Patient B2 (6 mg): Preliminary results

Efficacy

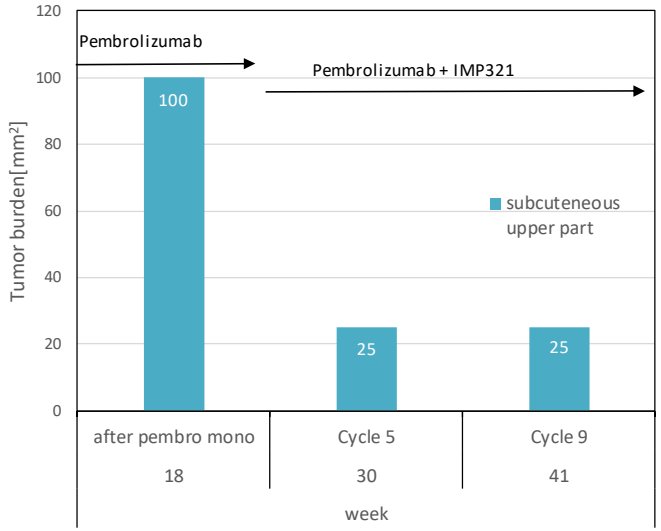
Week 18 (pembro)



Week 41(combo)



Tumour burden (irRC)

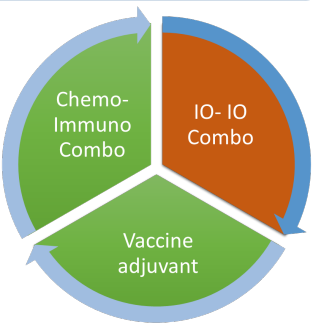


- Patient entered with irSD on Pembro monotherapy
- Confirmed irPR after start of combo → pt completed 6 months Pembro + IMP321
- Target lesion disappears at week 41 (25 mm^3 default value entered due to 5 mm CT section thickness); **disappearance confirmed by FU PET scan but non-target lesions still present**

Sum Target Lesions	100 mm^2	25 mm^2	25 mm^2
In %	100 %	25 %	25 %
irRC	N/A	irPR	irPR

preliminary data, status 15th November, 2017

PRIMA BIOMED

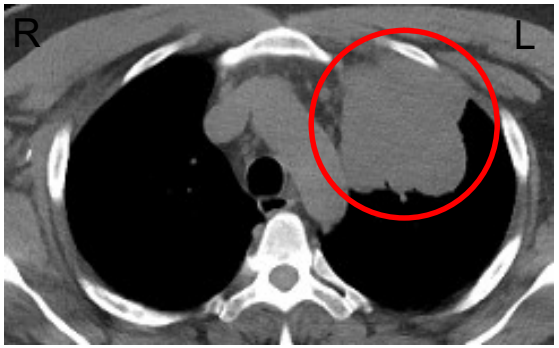


TACTI-mel

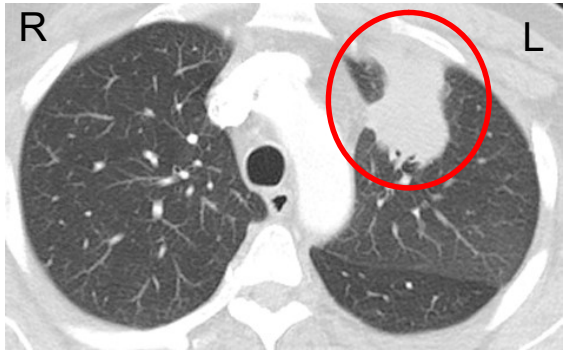
Patient A4 (1 mg): Preliminary results

Efficacy

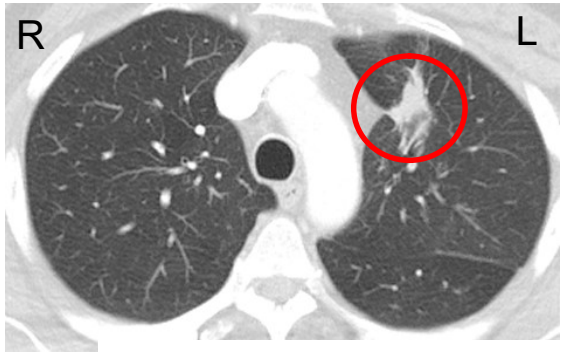
Pre-Pembro



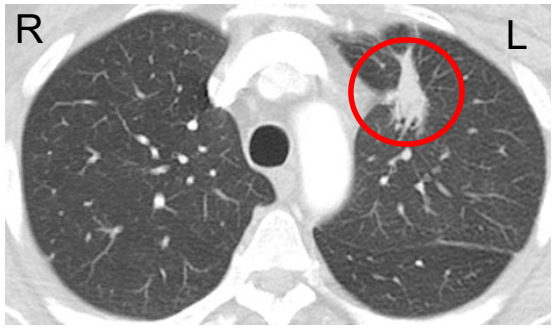
week 13 (pembro)



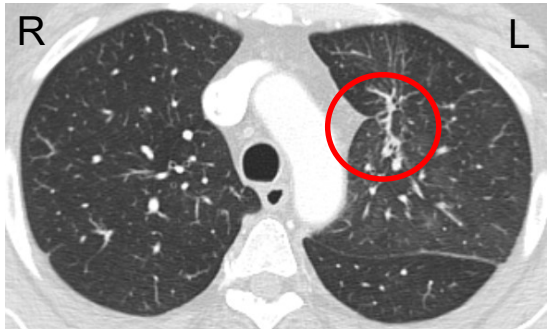
week 29 (combo)

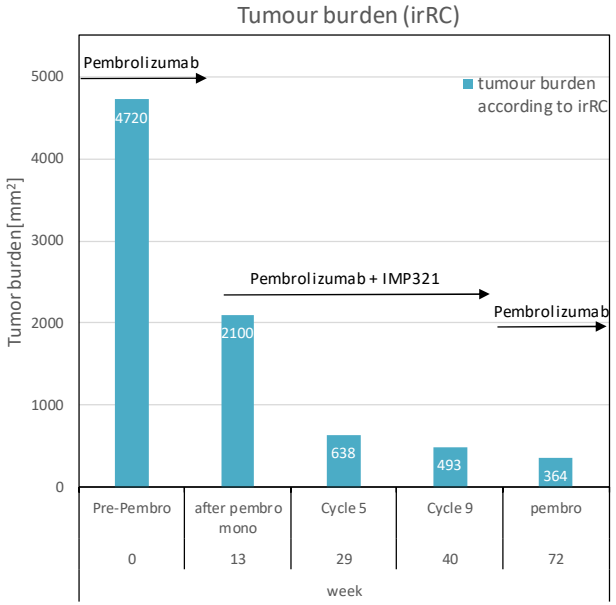


week 40 (combo)



week 72 (pembro)





- Very deep response (confirmed irPR) after start of combo
- pt completed 6 months Pembro + IMP321 → continues on pembro mono
- **Target lesions are highly reduced after combo treatment, complete disappearance of non-target lesions**

preliminary data, status 15th November, 2017

Sum Target Lesions	4720 mm²	2100 mm²	638 mm²	493 mm²	364 mm²
compared to combo start		100 %	30 %	23 %	17%
compared to pre-pembro	100 %	44 %	14 %	10 %	8%
irRC	N/A	irPR	irPR	irPR	irPR

Thank you

Frédéric Triebel, CSO/CMO
ICI Europe Summit
November 16, 2017
Munich, DE.

ASX:PRR; NASDAQ:PBMD

PRIMA BIOMED