Two ACTive Immunotherapies (TACTI): Results of a Phase I Trial With Metastatic Melanoma Patients

(TACTI-mel) Treated With a Soluble LAG-3 Receptor (LAG-3Ig Or Eftilagimod Alpha) as an Antigen Presenting Cell

(APC) Activator Combined with Pembrolizumab

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ICI Europe

Berlin, November 28, 2018

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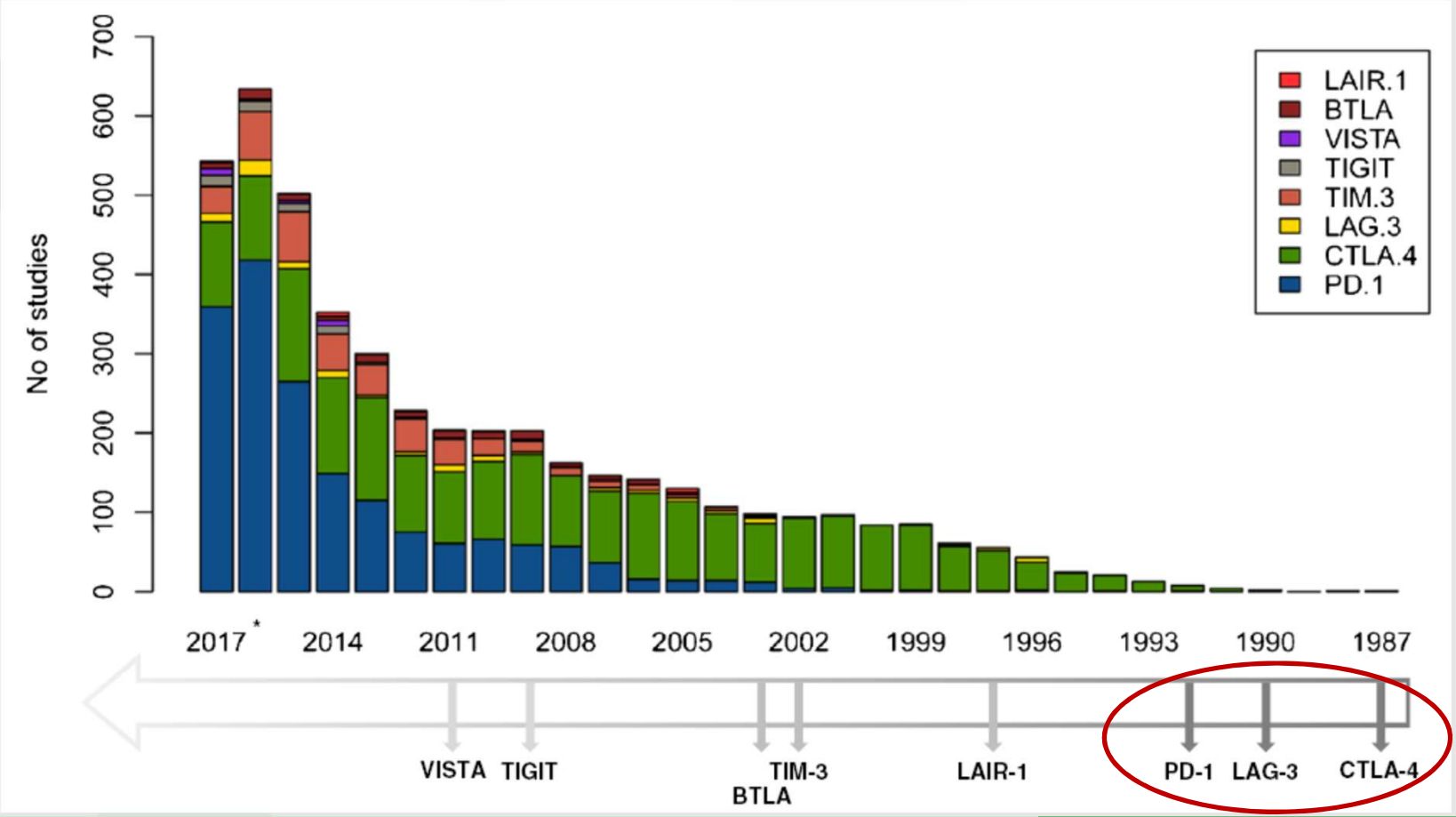
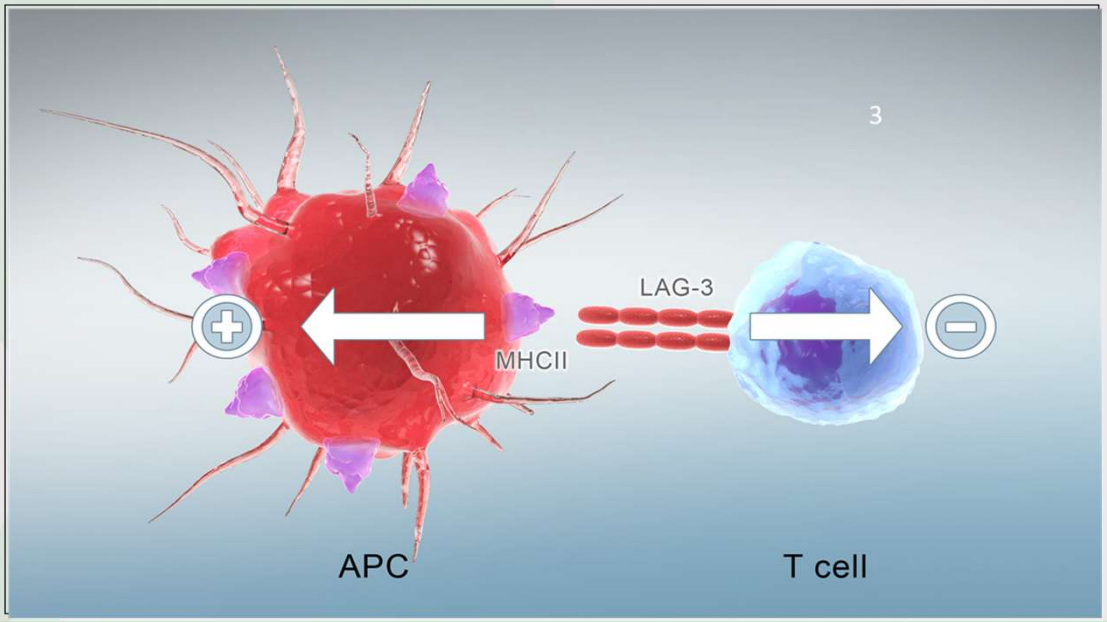
Timeline of immune checkpoint discovery.



LAG-3 as a Therapeutic Target

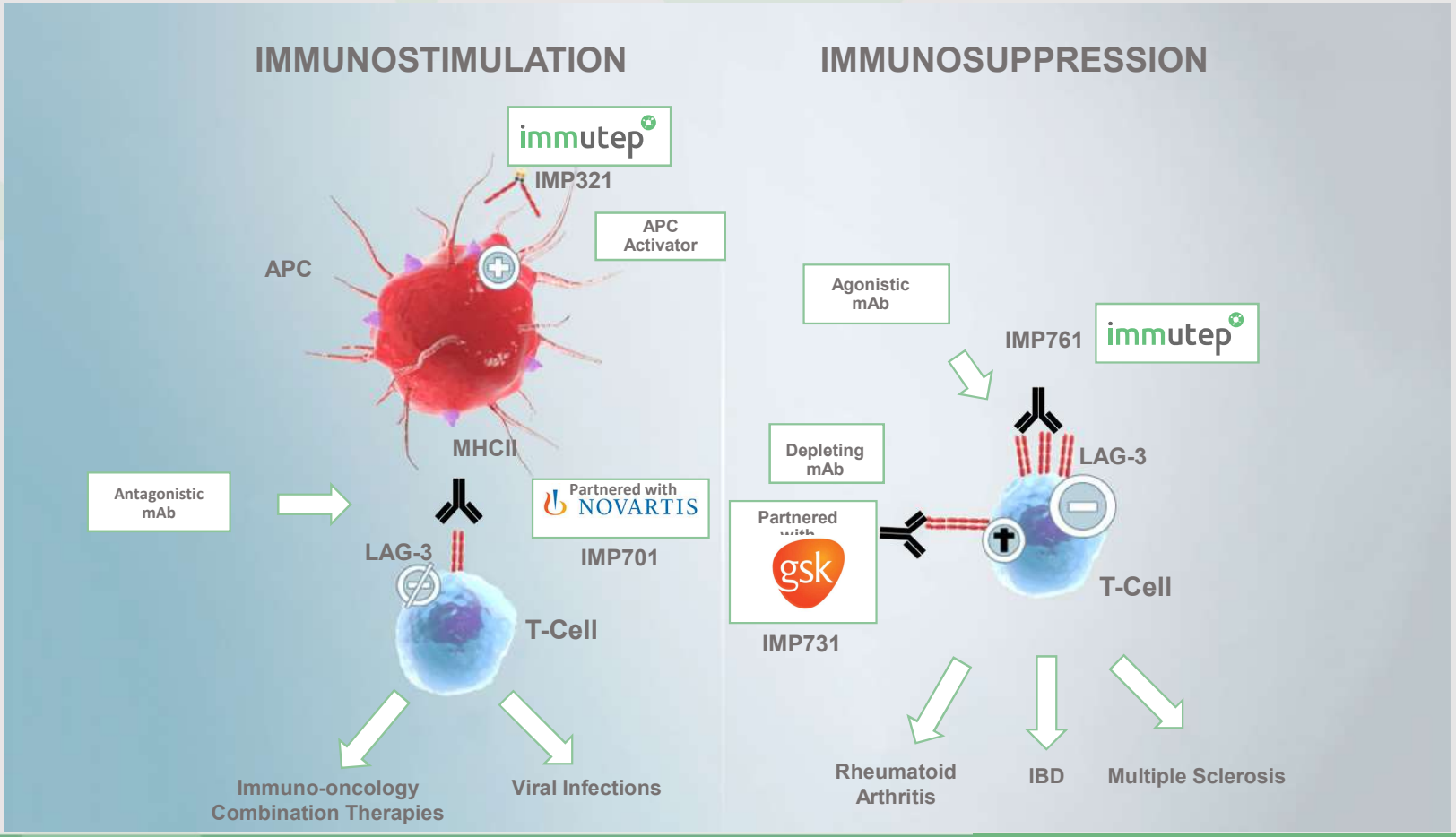
- LAG-3 is widely expressed on tumor infiltrating lymphocytes (TILs) and cytotoxic T cells
  → Prime target for an immune checkpoint blocker
- Functionally similar to PD-1 on T cells (arrow on the right)



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

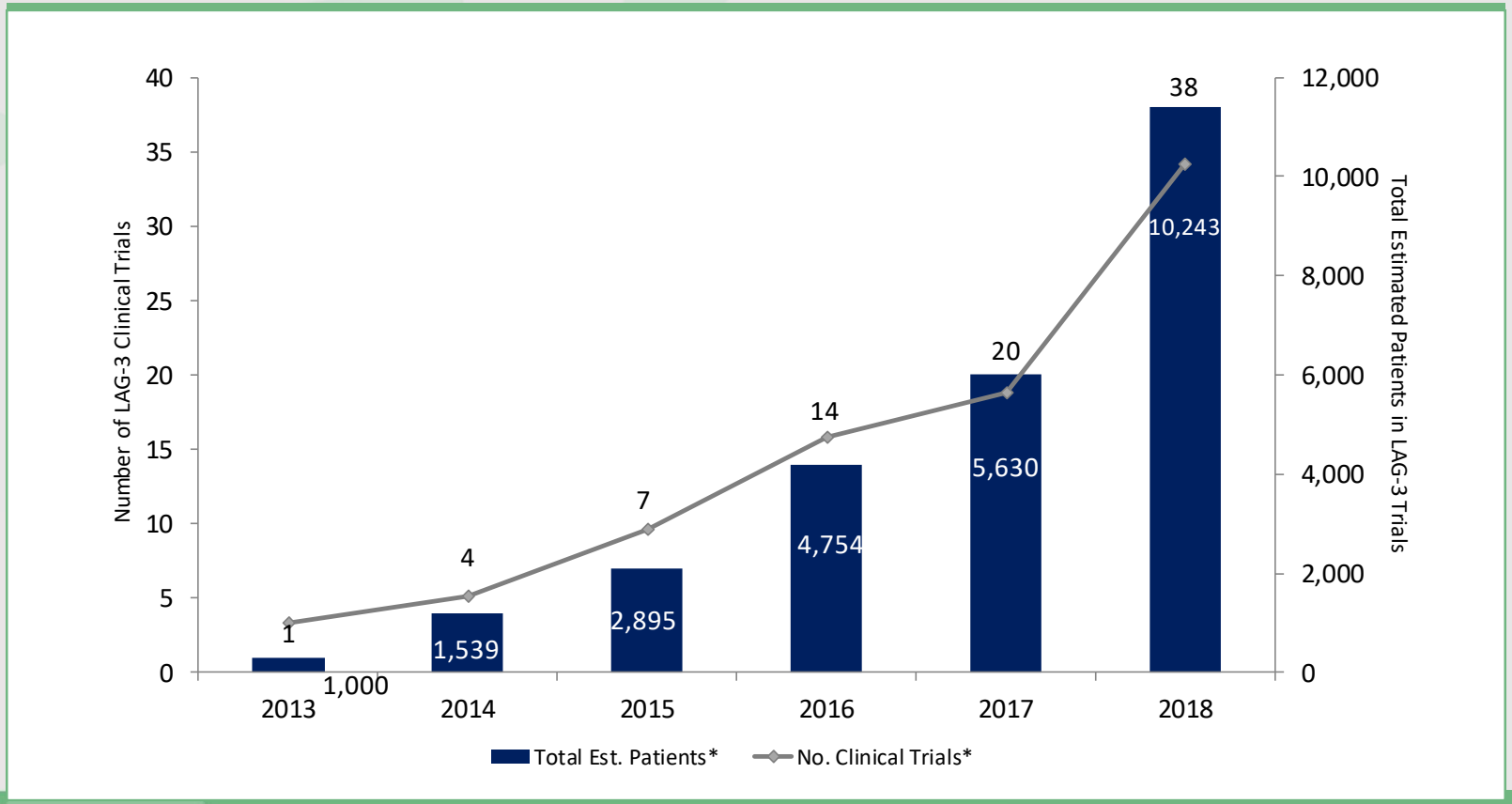
→ **Negative regulation** of $LAG\text{-}3^+$ T cells

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



Increasing Clinical Trials Targeting LAG-3

Industry increasingly deploying resources to development of LAG-3 therapeutics



Sources: GlobalData, company websites, clinical trials.gov, and sec.gov
Information as of August 17, 2018
*2018 includes planned and completed trials, includes trials where the company may not be the sponsor

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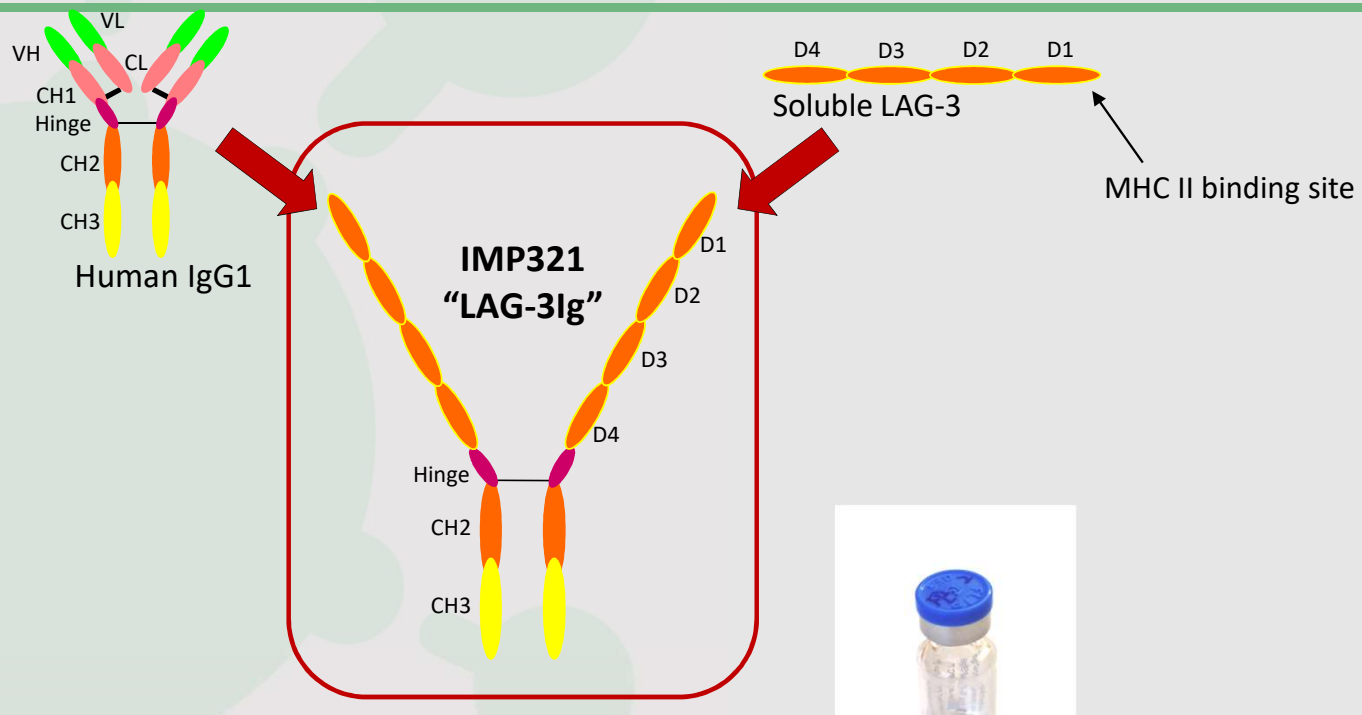
LAG-3 IMMUNOTHERAPY

Lead Program
Eftilagimod Alpha (IMP321)

Eftilagimod alpha (IMP321)
Soluble dimeric recombinant form of LAG-3Ig (fusion protein)



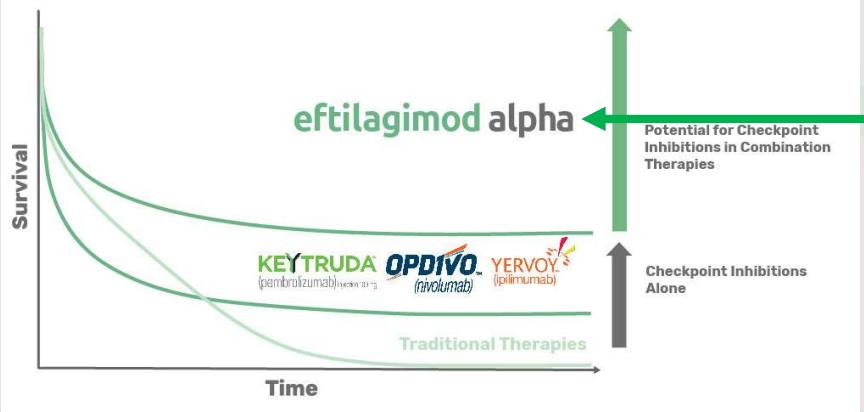
- **Soluble recombinant form of LAG-3**
- Human fusion protein
- Dimeric, very stable, high affinity for DC
- Antigen presenting cell (APC) activator
- **Unique and first-in-class**

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?

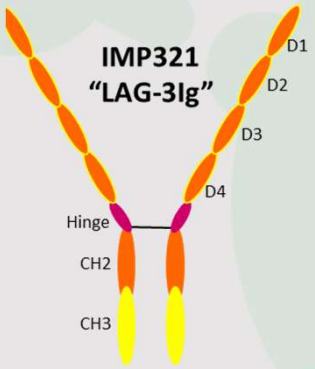
- Immunogenic cell death to liberate/uncover tumor antigens
- Cross-presentation of those antigens
- Recruitment of T cells into the tumor microenvironment
- Reversing the pathways driving a repressive tumor environment

This could be achieved through the right APC activation



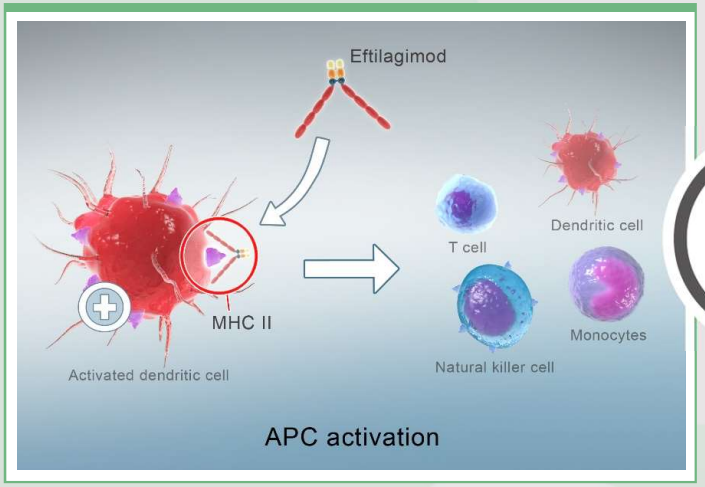
APC activators:
- MHC II agonism
- TLR or STING agonism
- CD40 agonism
- Oncolytic viral therapies

eftilagimod alpha (IMP321): an APC activator (i.e. not an ICI)



eftilagimod alpha:
- MHC II **agonist**
- **LAG-3 fusion protein**

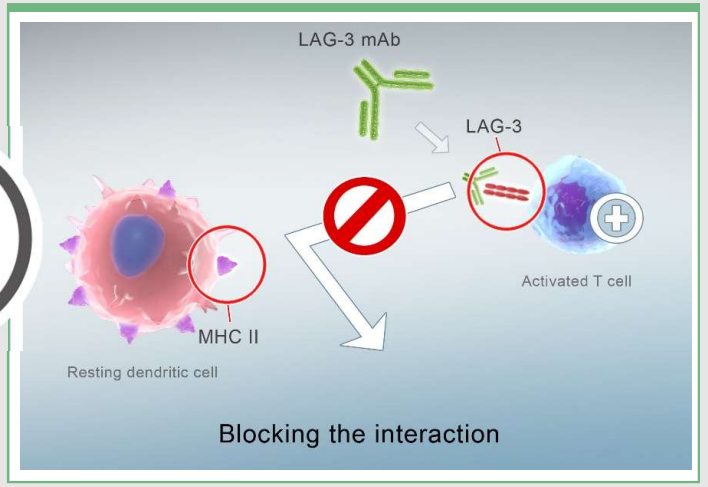
"PUSHING THE ACCELERATOR ON IMMUNE RESPONSES"



eftilagimod alpha (efti, IMP321):

APC activator
- Boost and sustain the $CD8^+$ T cell responses
- Activate multiple immune cell subsets

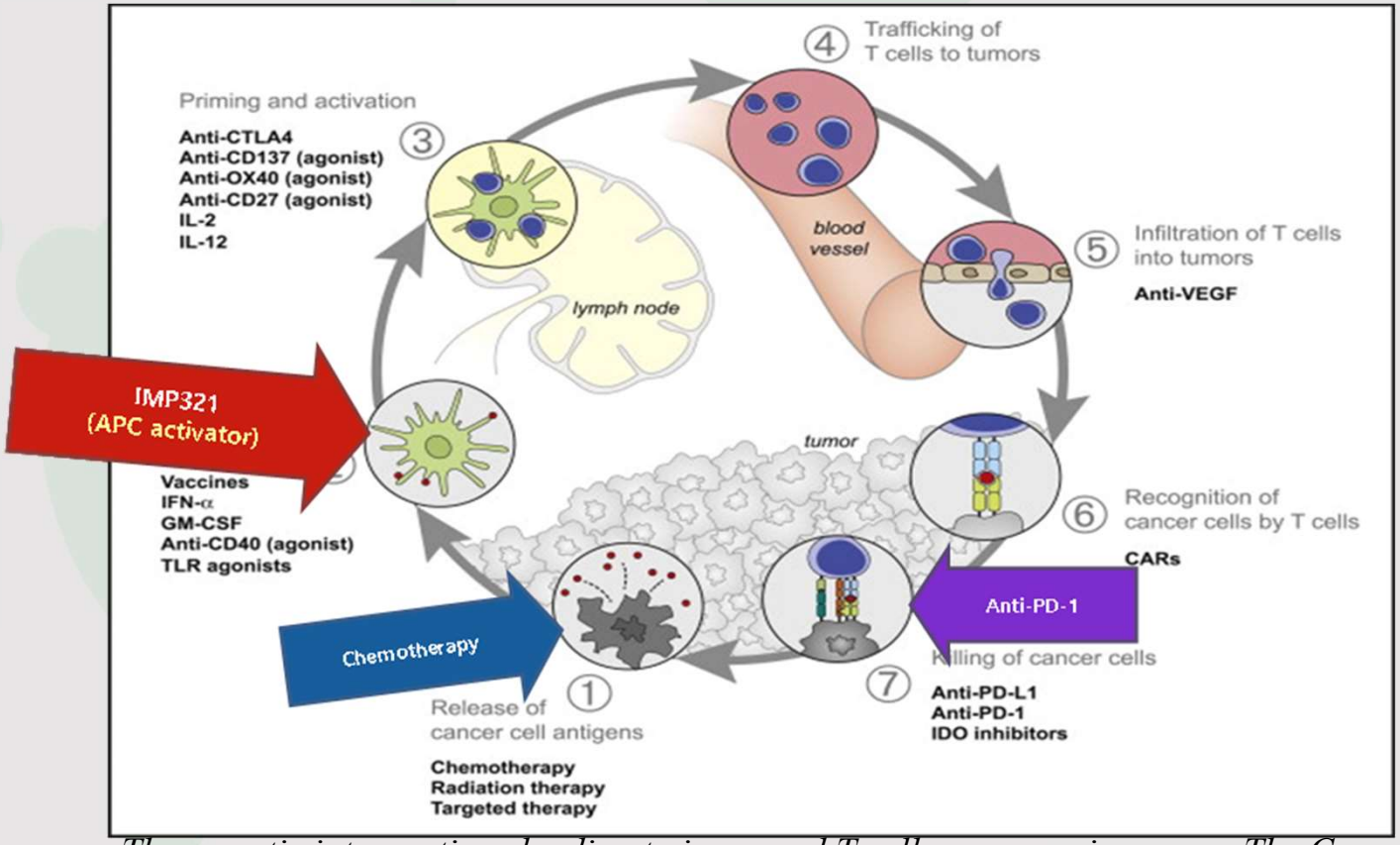
"RELEASING THE BRAKE ON THE T CELL"



LAG-3 antagonist antibodies:

Immune checkpoint inhibitor (ICI)
- increase cytotoxicity of the pre-existing CD8 T cell response

Rationale for Combining efti (IMP321) with Chemotherapy or Anti-PD-1 mAb



Therapeutic interventions leading to increased T cell responses in cancer. The Cancer Immunity Cycle. Adapted from Chen and Mellman (1).

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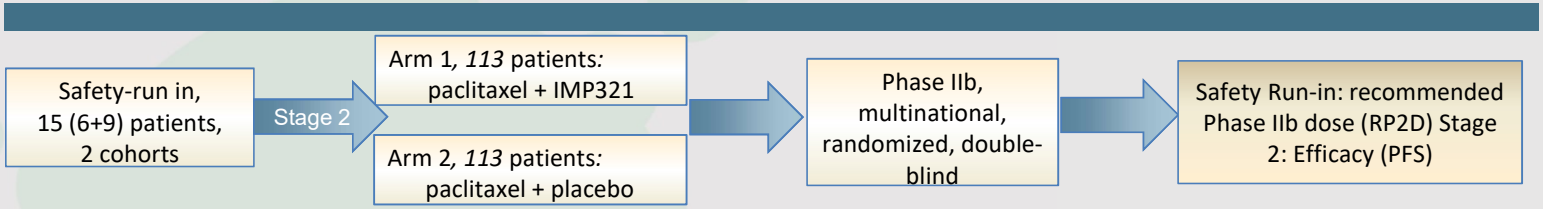
LAG-3 IMMUNOTHERAPY

Combining eftilagimod alpha and first-line single agent chemotherapy

Eftilagimod alpha in MBC
Active Immunotherapy PAClitaxel (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 (Nov 2018)

✓ 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)

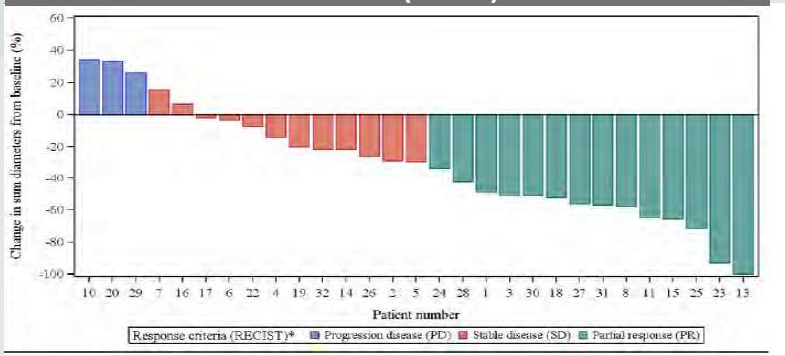
✓ >160 patients recruited in Stage 2

Eftilagimod alpha in MBC

Preliminary Efficacy Results

Observed response rates are substantially better than the 22-33% response rates seen in historical control groups with paclitaxel monotherapy

Phase I (n=30)



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

AIPAC – Safety Run Phase (n=15)

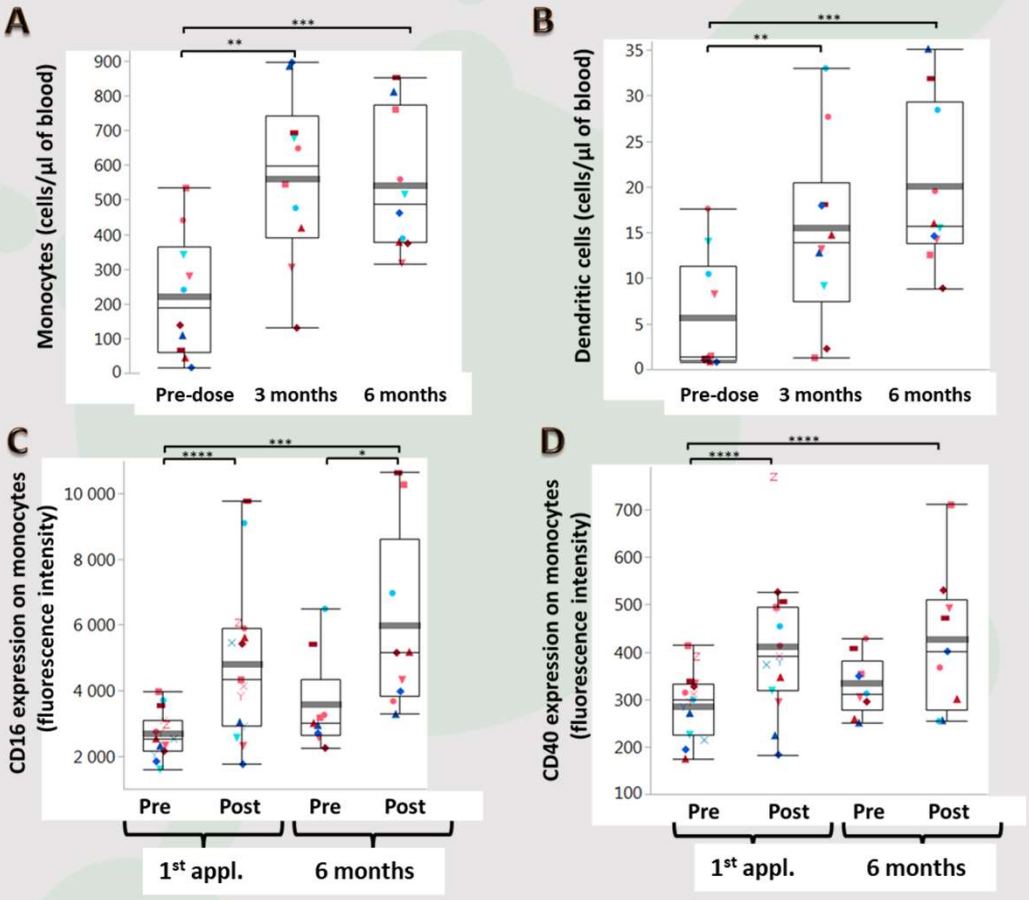
Response Parameter	Paclitaxel + IMP321 (n = 15)
Complete Response (CR)	0/15 (0%)
Partial Response (PR)	7/15 (47%)
Stable Disease (SD)	6/15 (40%)
Progressive Disease (PD)	2/15 (13%)
Overall Response Rate (ORR)	7/15 (47%)
Disease Control Rate (DCR)	13/15 (87%)

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

**Overall Response Rate **Disease Control Rate*

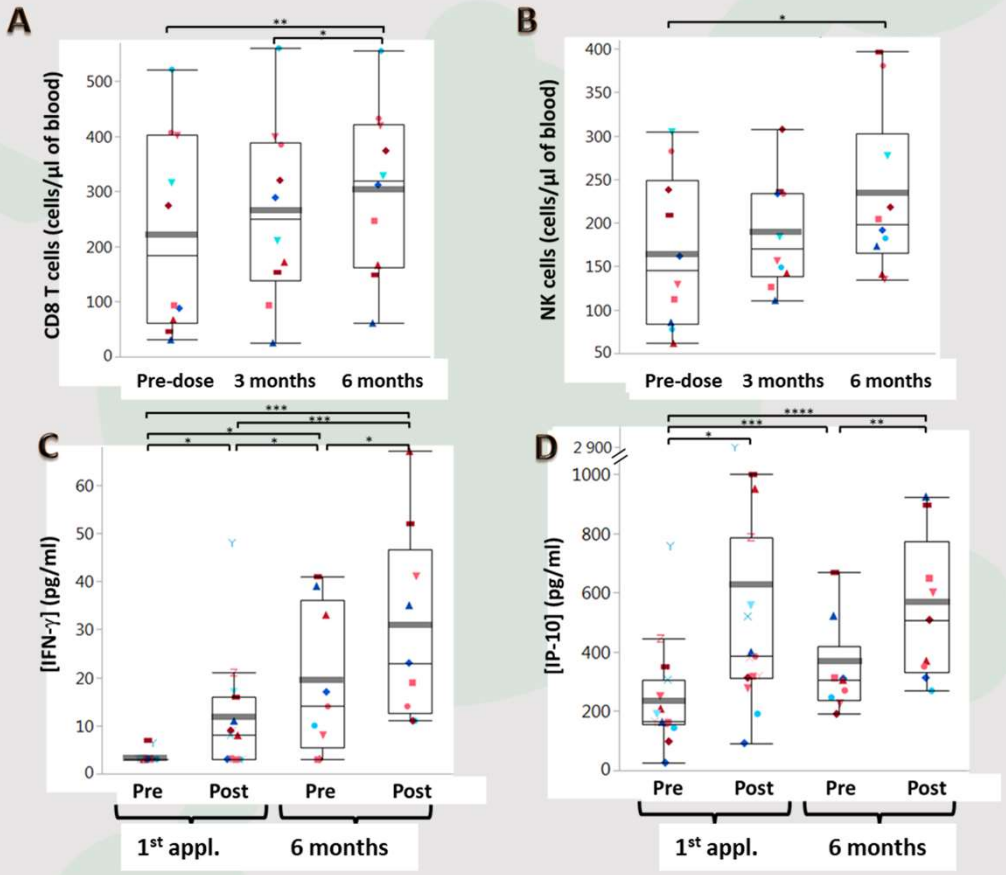
Preliminary data, status Interim CSR April 2018, best response acc. To RECIST 1.1

AIPAC Immunomonitoring
Primary Target Cells



Primary target cells: Sustained increase of circulating Antigen-Presenting Cells (APCs) like monocytes (A) and dendritic cells (B). Rapid activation of monocytes (CD16 (C) and CD40 (D)).

AIPAC Immunomonitoring
Secondary Target Cells



Secondary target cells:
Sustainable increase in absolute numbers of effector cells like i.e. CD8 T cells (A) and Natural Killer cells (B). IMP321 induces early and sustainable increase of Th1 biomarkers like IFN-γ (C) and IP-10 (CXCL10, D).

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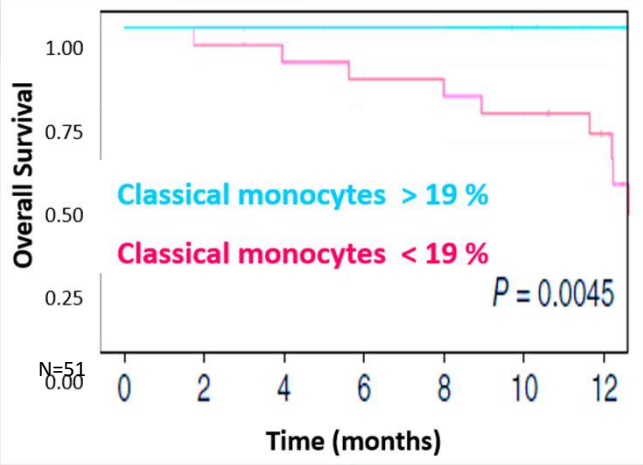
Combining eftilagimod alpha and pembrolizumab

New Rationale for Combining eftilagimod alpha (IMP321) with PD-1 Antagonists (pembrolizumab)



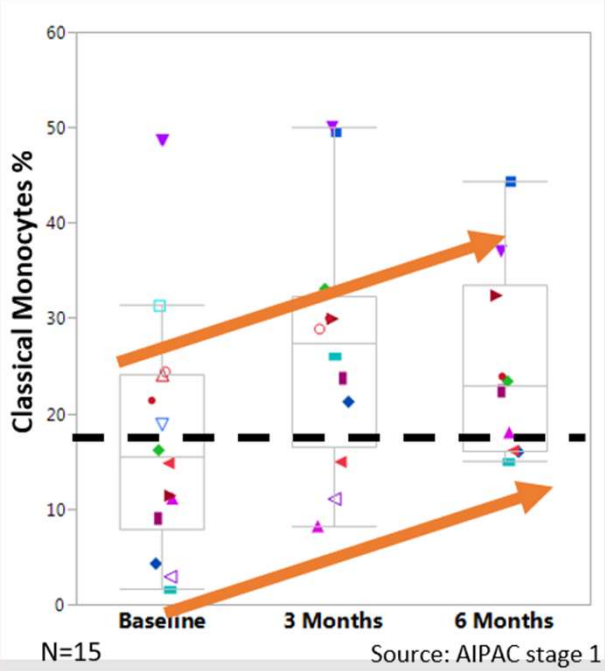
Source: Krieg et al., Nat. Med. 24, 2018.

→ Baseline innate immunity status seems to be important for the response (OS) to pembrolizumab

→ Data suggests that low monocyte numbers at baseline are associated with poor efficacy of anti-PD-1 therapy in melanoma patients

→ Data shows that the APC activator eftilagimod alpha boosts innate immunity

IMP321 increases monocyte number in cancer patients



Source: AIPAC stage 1

TACTI-mel: Two ACTive Immunotherapies (melanoma)

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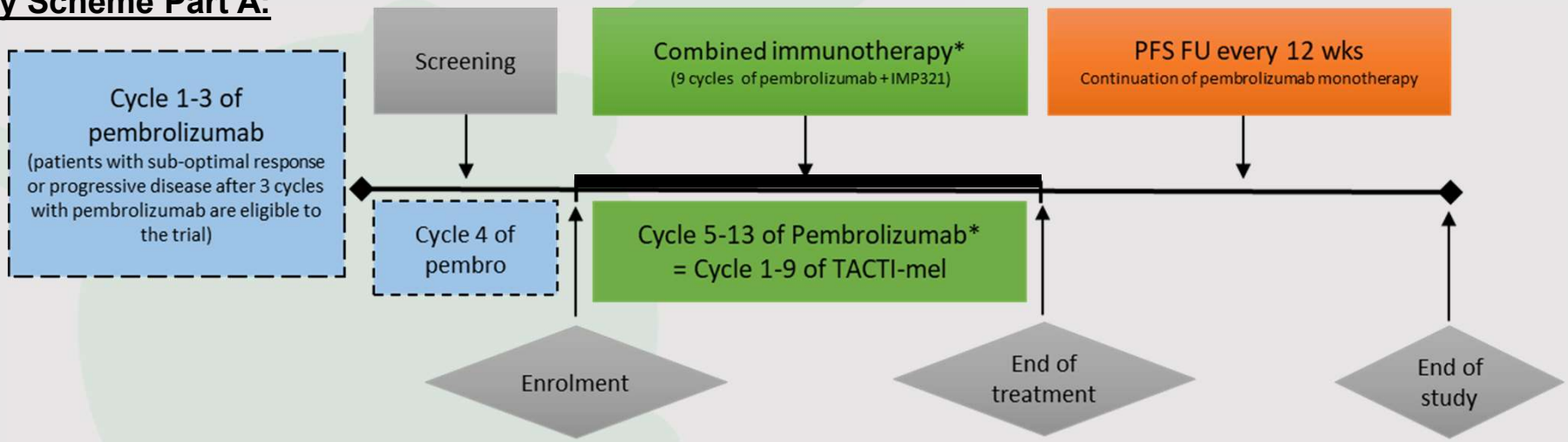
Study Scheme Part A:



- 18 pts in total → 6 pts per efti dose group
- Patients received:
  - *2 mg/kg pembrolizumab i.v. every 3 weeks*
  - *1, 6, 30 mg efti s.c. every 2 weeks for up to 6 months*
- Imaging was done every 12 weeks

* - tumor assessments done acc. to irRC
irRC…Immune-Related Response Criteria, PFS-progression free survival, FU – follow-up

TACTI-mel Part A: Safety Summary

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Overview grade 3 / 4 TEAEs and rel. to study treatment

Preferred term	Grade 3 N (%)	Grade 4 N (%)	Rel to efti / pembro
Maculo-papular rash	1 (6 %)	-	No / Yes
Decreased renal function	1 (6 %)	-	Yes / No
Colitis	1 (6 %)	-	No / Yes
Altered liver functions	1 (6 %)	-	No / Yes

- No Dose limiting toxicities observed
- 6 pts (33 %) with ≥ 1 SAE; none related to any study drug
- 8 pts (44 %) with ≥ 1 AE with ≥ grade 3 (no grade 5)

Overview frequent TEAE (PT selected if ≥ 10 % of the pts)

Adverse Event*,	Any grade N (%)	Grade 3 or 4 N (%)	No of events
Arthralgia	3 (17)	-	3
Diarrhea	5 (28)	-	6
Fatigue	8 (44)	-	10
Hyperglycemia	3 (17)	3 (17)	3
Nausea	5 (28)	-	7
Rash##	7 (39)	1 (6)	7

* - Adverse events occurred in > 10 % of pts
- any kind of rash

- No new safety signals
- 1 pt died due to an AE (grade 4 Intercranial hemorrhage, not rel.)
- 1 pt discontinued due to an AE (not rel.)
- 3 pts experienced treatment delay due to an AE

preliminary data, status Oct 15th 2018

TACTI-mel Part A: Baseline Characteristics + Efficacy Summary

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Baseline Characteristics	N = 18 (%)
Age (median)	67 yrs
Sex (f/m)	1 (6 %) / 17 (94 %)
Elevated LDH	**7 (39%)**
Metastasis stage M1c	**14 (78 %)**
Pre-treated with BRAF/MEK/ipilimumab	5 (28 %)
irPD/irSD to pembro after 3 cycles	11 (61 %)

- Very late stage of disease (M1c, elevated LDH) and majority not responding to pembrolizumab monotherapy

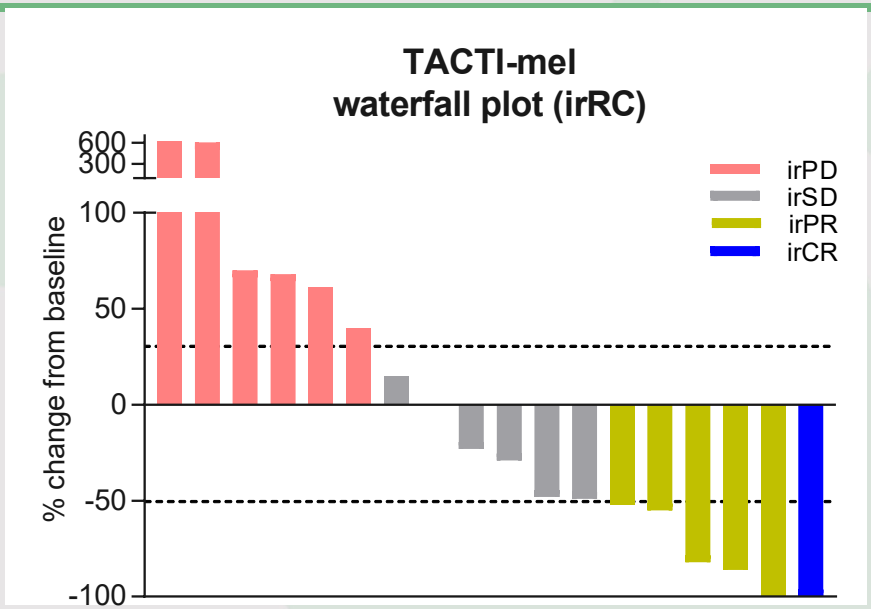
Best Overall Response acc. to irRC	N = 18 (%)
irCR	1 (6 %)
irPR#	5 (28 %)#
irSD	6 (33 %)
irPD	6 (33 %)
Best overall response rate (ORR)	**6 (33 %)**
Patients with tumor shrinkage	**10 (56 %)**
Disease control rate	**12 (66 %)**

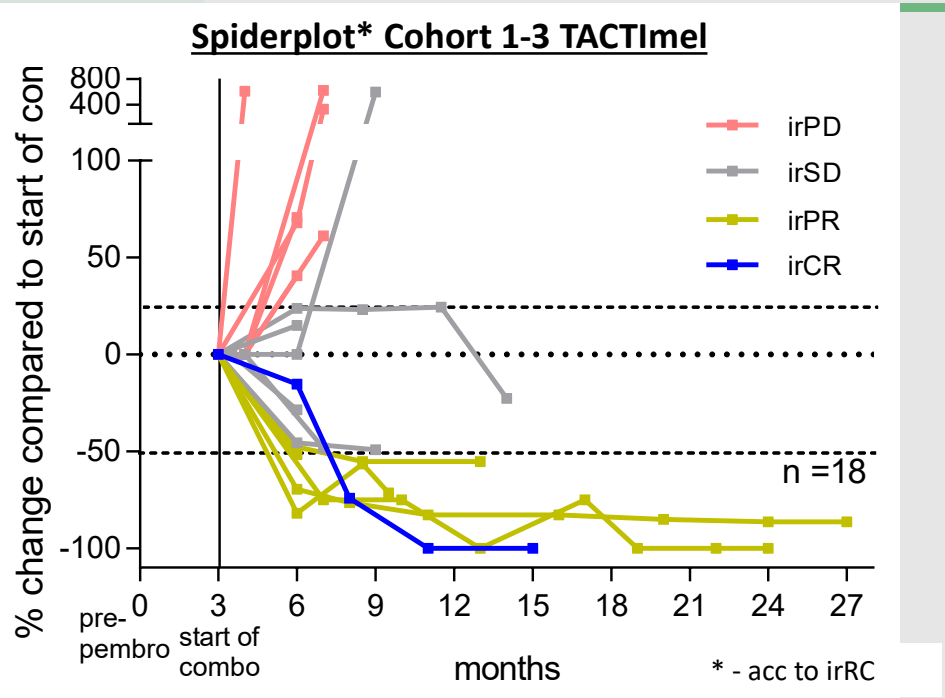
- incl. 1 pt with complete disappearance of all target lesions

- If response is calculated from pre-pembro timepoint → ORR is 61 % acc. to irRC

preliminary data, status Oct 15th 2018

TACTI-mel Part A: Response patterns





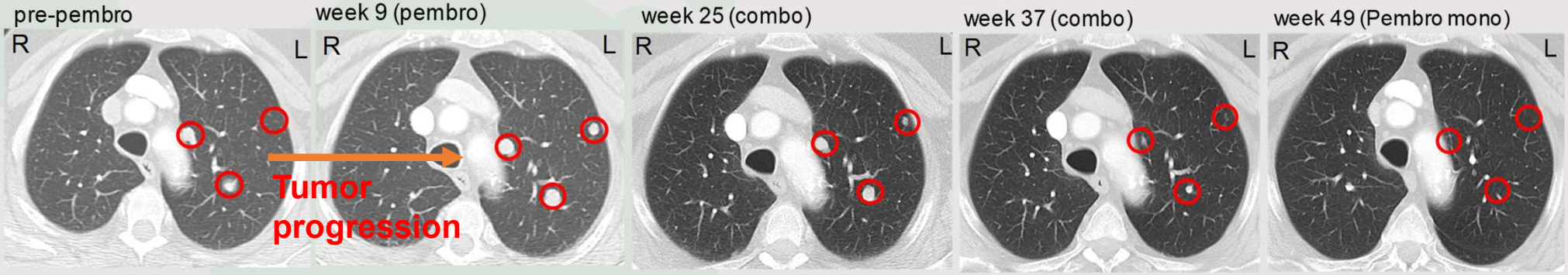
→ Tumor shrinkage in 10 (56 %) of these patients incl. 2 pts with complete disappearance of all target lesions

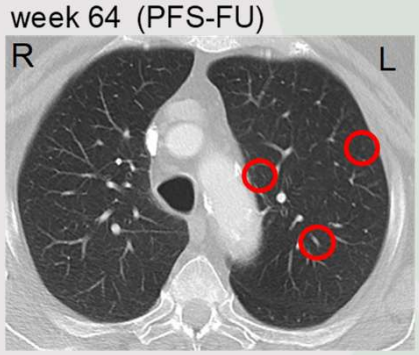
→ 1 pt with confirmed CR + 4 pts still on Tx after 12 months
→ 5 (28 %) pts with long term (>12 mths) treatment/benefit

preliminary data, status Oct 15th 2018

TACTI-mel Part A): Single Case

- 84 year old male with multiple lung metastases from melanoma
- BRAF wild type





- **Patient progressing on pembrolizumab monotherapy**
- **At 1 yr all lesions disappeared → CR (confirmed)**
- **Patient without treatment and disease free → now lost to FU**

preliminary data, status Oct 15th 2018

TACTI-mel Part B: Preliminary results

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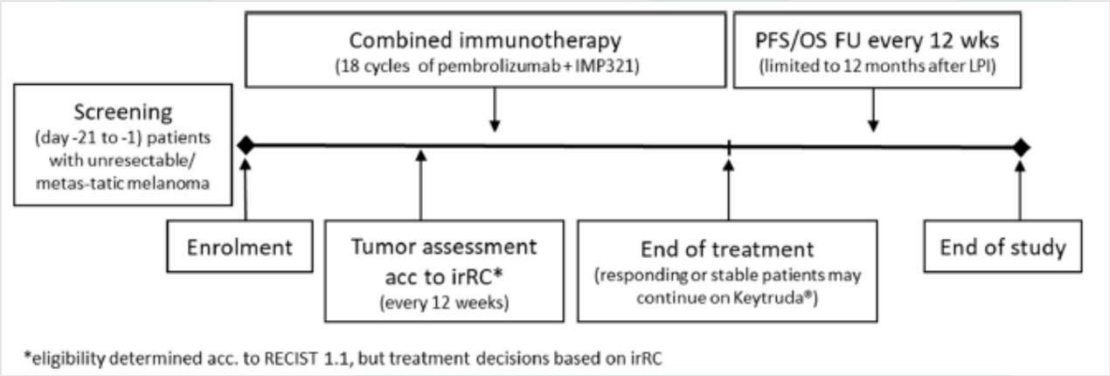
Study Scheme Part B:



Details:
- 6 pts enrolled
- Patients received:
  - *2 mg/kg pembrolizumab i.v. every 3 weeks*
  - *30 mg efti s.c. every 2 weeks for up to 12 months*
- Imaging was done every 12 weeks

Study Status & Results part B:

- Recruitment and safety observation period completed
- 5 pts had at least 1 post baseline CT

Baseline Characteristics	N = 6
Age (median)	65 yrs
Sex (f/m)	1 (13 %) / 5 (83 %)
ECOG (0/1)	**3 (50 %) / 3 (50 %)**
Elevated LDH	**5 (83%)**
Stage M1c	**6 (100 %)**

- No DLTs or new safety signals detected
- 3 / 5 evaluable pts (60 %) had irPR at 3 months
- 4 pts still under treatment (1 pt died due to PD < 3 months, 1 pt left with confirmed irPD)

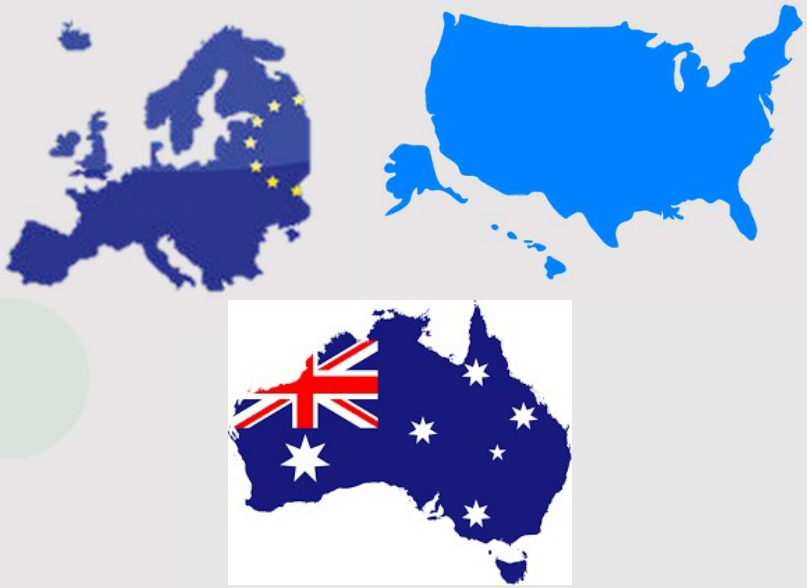
* - tumor assessments done acc. to irRC
irRC…Immune-Related Response Criteria, PFS-progression free survival, FU – follow-up

TACTI-002 Trial Design

An umbrella trial: Two ACTive Immunotherapeutics in different indications

Simon's 2 stage; 3 indications; up to 120 pts → Efti (IMP321) + Pembrolizumab (Keytruda®) for 12 months + max. of 12 months pembrolizumab monotherapy → Phase II, multi-national (EU + US + AUS), open label → Response rate; PFS, OS, PK, Biomarker; Safety and tolerability

Primary Objective	Response rate (iRECIST)
Other Objectives	Safety, PFS+OS, PK, exploratory biomarker analysis
Patient Population	Part A: 1st line NSCLC PD-X naive Part B: 2nd line NSCLC, PD-X refractory Part C: 2nd line HNSCC, PD-X naive
Treatment	30 mg Efti (IMP321) s.c. 200 mg Pembrolizumab i.v.



13 sites in Europe / US / Australia

Notes
NSCLC – non-small-cell lung cancer, HNSCC – head and neck squamous cell cancer, DMC – data monitoring comittee, PFS – progression free survival, OS – overall survival, PK – pharmacokinetics, PD-X – any PD-1 or PDL-1 treatment

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Thank you

Frédéric Triebel MD, PhD

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Berlin, November 28, 2018