

A soluble LAG-3 protein (eftilagimod alpha) with an anti-PD-1 antibody (pembrolizumab): a new combination in immuno-oncology.

Frédéric Triebel MD, PhD
World Immunotherapy Congress
Basel, October 15, 2019

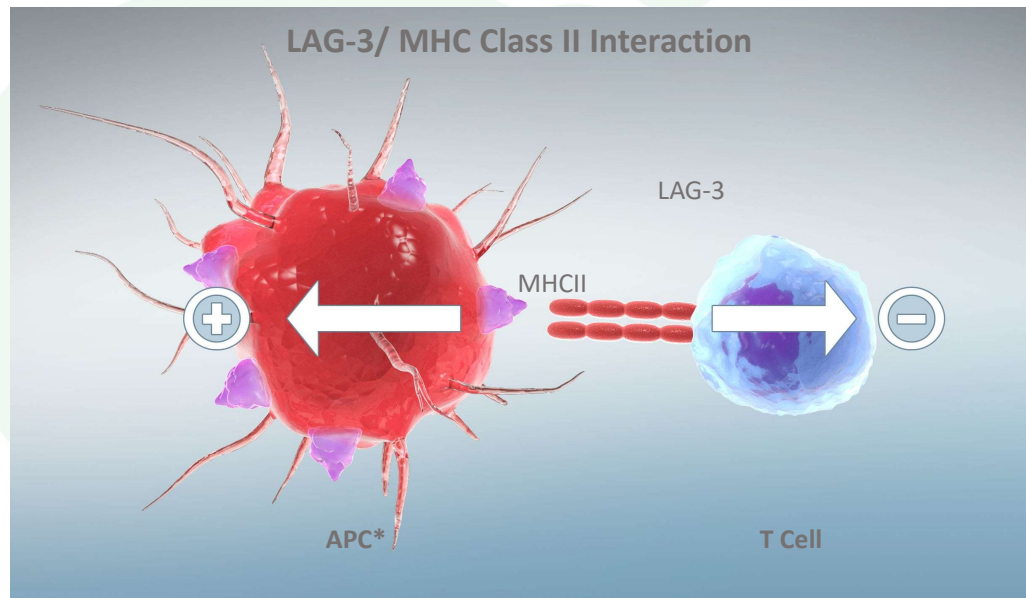
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LAG-3 as a Therapeutic Target

LAG-3 is widely expressed on tumor infiltrating lymphocytes (TILs) and cytotoxic T cells →
Prime target for an immune checkpoint blocker



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



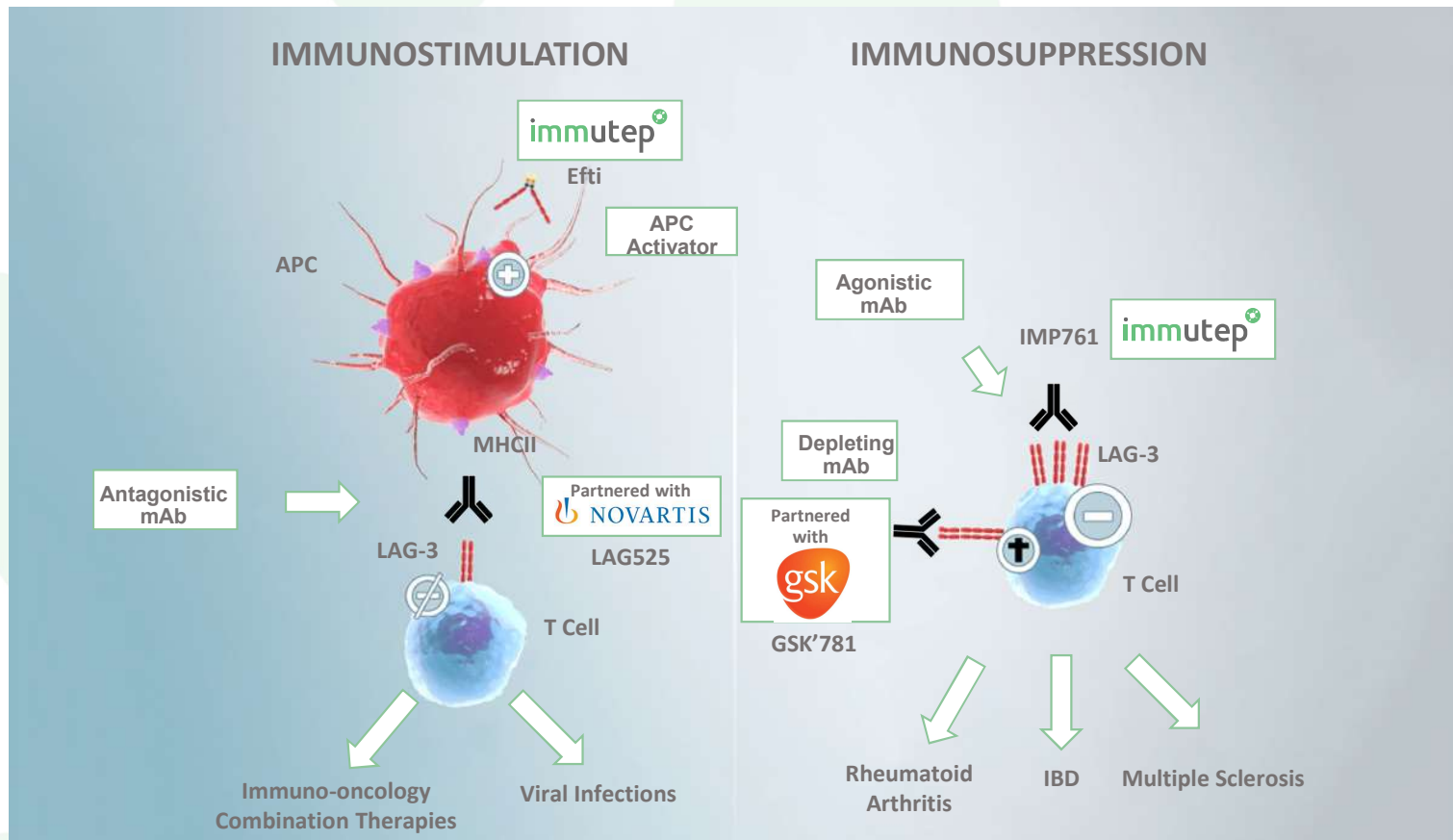
→ **Negative regulation** of LAG-3⁺ T Cells



Notes:

* APC: antigen presenting cell

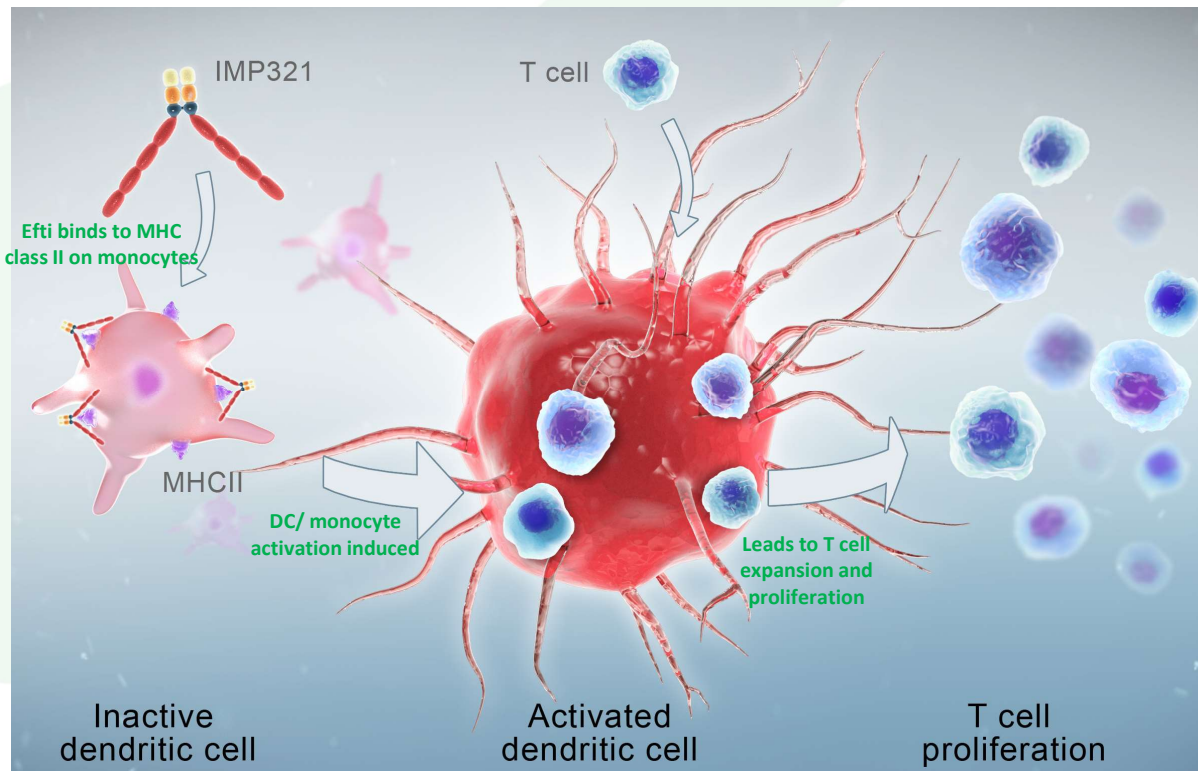
Targeting LAG-3/MHC II May Lead to Multiple Therapeutics in Numerous Indications

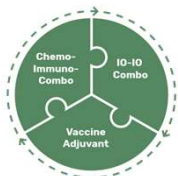


Lead Program Eftilagimod Alpha (IMP321)

Efti Mechanism of Action (MOA)

Efti's unique agonistic MOA leads to T cell expansion and proliferation => pushing the gas on the immune response



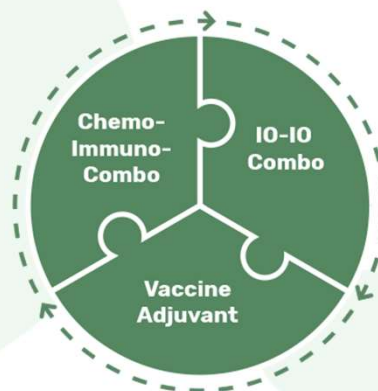


Opportunity for Eftilagimod Alpha

Efti has multiple shots on goal in different indications and in different combinations

- **Best-and-First-In-Class** MHCII agonist
- Good safety profile and encouraging efficacy data thus far
- Estimated favorable (low) cost of goods, current flat dosing and manufacturing process
- Potential for use in various combination settings – **potential pipeline in a product**

• *Late Stage European Phase IIb AIPAC (Immutep)*

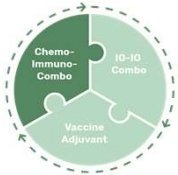


• *Phase I TACTI-mel (Immutep)*
• *Phase II TACTI-002 (Immutep⁽¹⁾)*
• *Phase I INSIGHT – Stratum D (Immutep⁽²⁾)*

• *Phase I Solid Tumors (Cytlimic)*
• *Phase I INSIGHT - Stratum A+B (IKF⁽³⁾)*

Notes

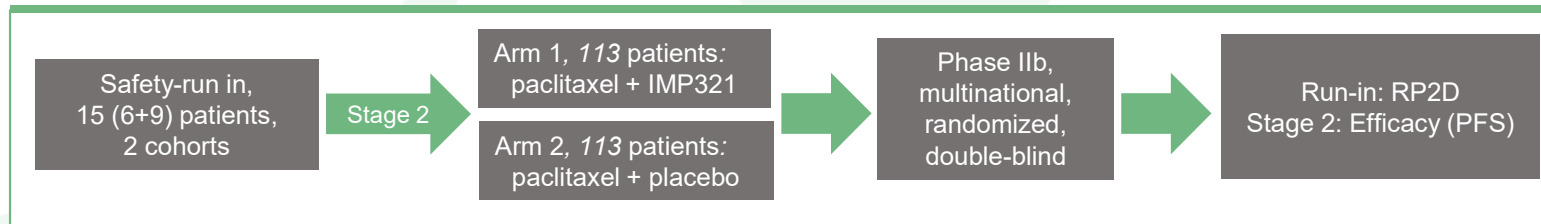
- (1) In collaboration with Merck & Co., Inc., Kenilworth, NJ, USA (known as MSD outside the United States and Canada) and in combination with KEYTRUDA® (pembrolizumab)
(2) In collaboration with Merck KGaA, Darmstadt, Germany and Pfizer Inc. and in combination with BAVENCIO® (avelumab). This extension of INSIGHT is also referred to as INSIGHT-004
(3) INSIGHT Investigator Initiated Trial ("IIT") is controlled by lead investigator and therefore Immutep has no control over this clinical trial



Efti - Clinical Development AIPAC



AIPAC: Active Immunotherapy PAClitaxel in HER2-/ HR+ MBC

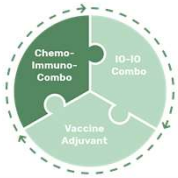


Other Objectives	Anti-tumor activity, safety and tolerability, PK, immunogenicity, quality of life
Patient Population	Advanced MBC indicated to receive 1 st line weekly paclitaxel
Treatment	Run-in: Paclitaxel + IMP321 (6 or 30 mg) Arm 1: Paclitaxel + IMP321 (30 mg) Arm 2: Paclitaxel + Placebo
Location	>30 sites in 7 (GB, DE, PL, HU, FR, BE, NL) EU countries

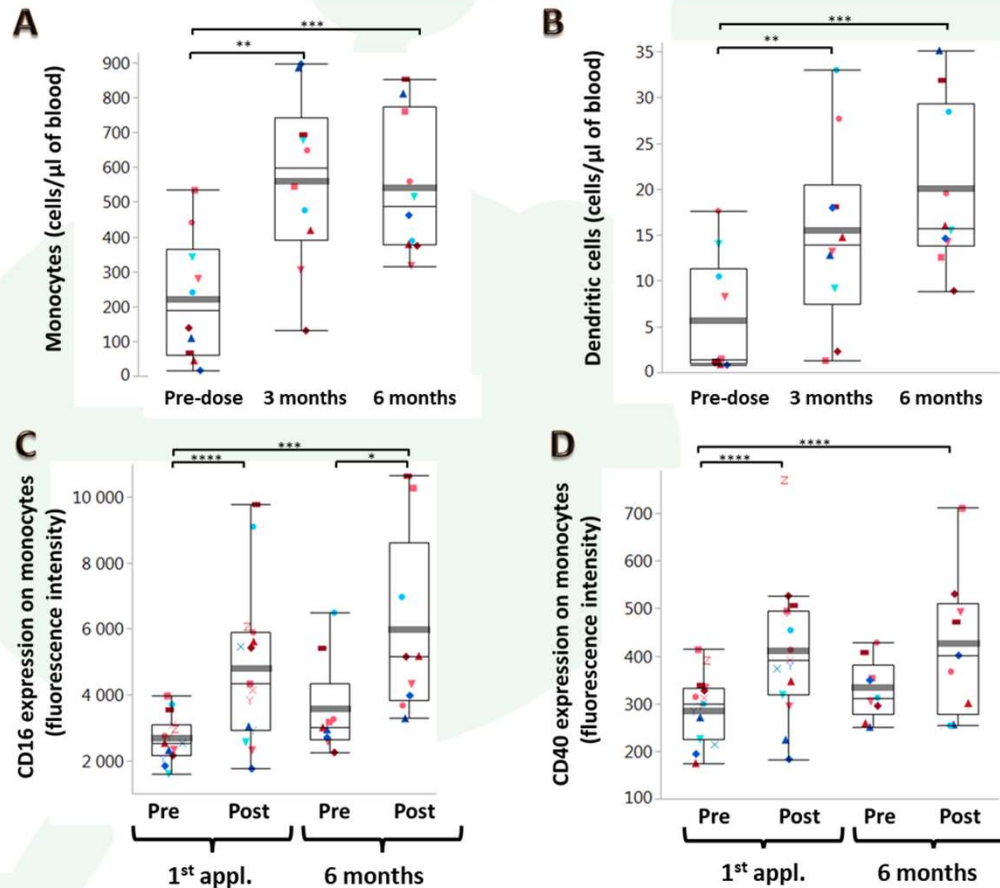
Status Report (Sep 2019)

- ✓ To-date, efficacy and safety data (ASCO 2018) in-line with historical control group / prior clinical trials (Brignone et al J Trans Med 2010, 8:71)
- ✓ Regulatory approval in 7 EU countries
- ✓ 227 patients recruited in Stage 2 → LPI Jun 2019
- PFS data expected calendar Q1 2020

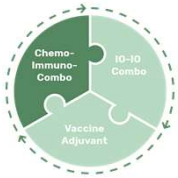
Key features: double blinded, potentially pivotal trial in metastatic breast cancer patients



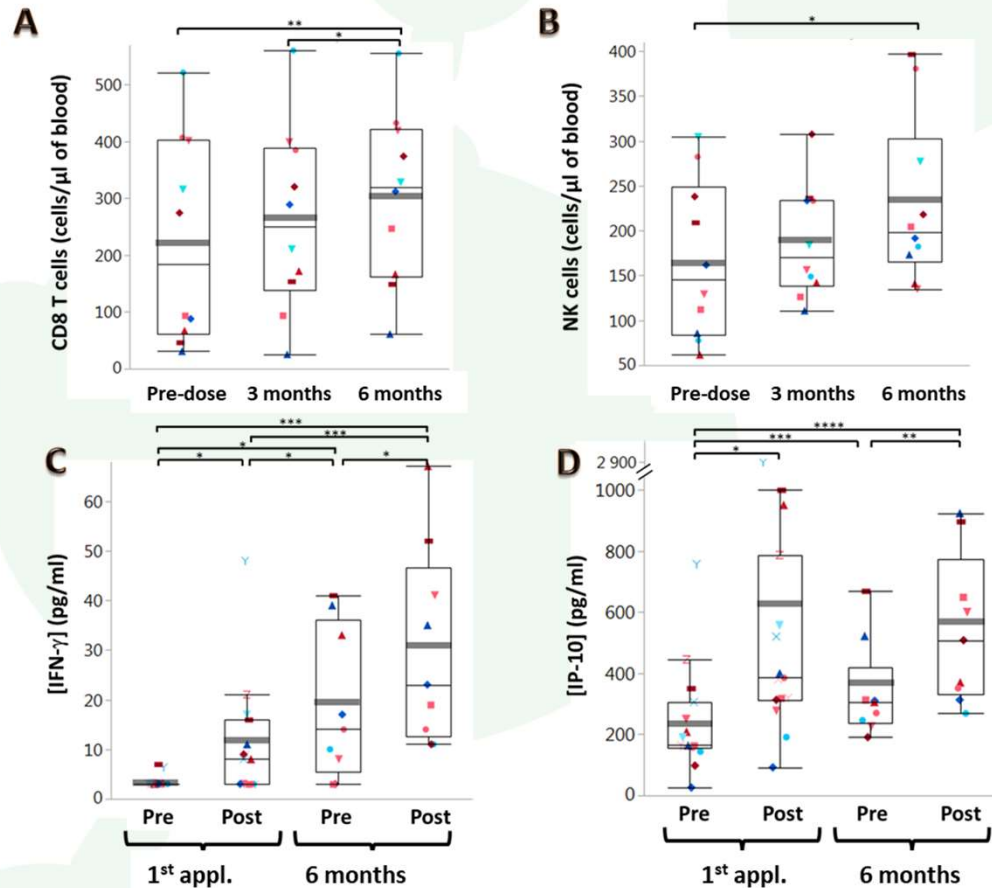
Efti Pharmacodynamic Effect AIPAC Immunomonitoring: Primary Target Cells



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)).



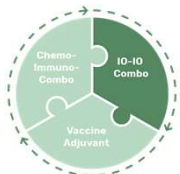
Efti Pharmacodynamic Effect AIPAC Immunomonitoring: Secondary Target Cells



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).

TACTI trials: Two ACTive Immunotherapies

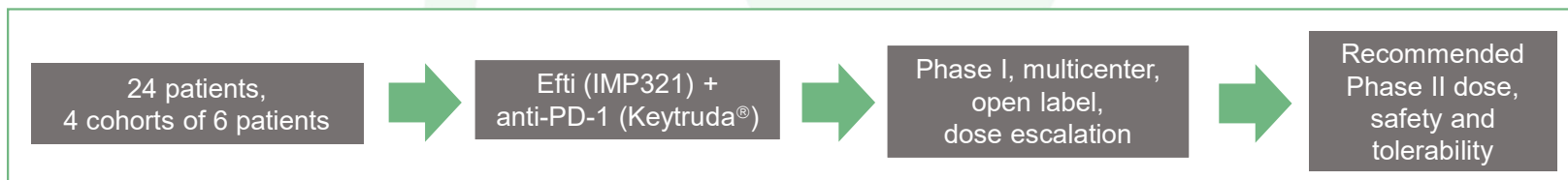
“Pushing the gas on the APC
while releasing the brake on the T cell”



Efti in Melanoma TACTI-mel – Trial Design



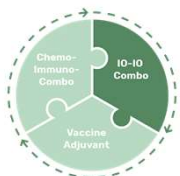
TACTI-mel: Two ACTive Immunotherapeutics in Melanoma



Other objectives	PK and PD of efti, response rate, PFS
Patient Population	Metastatic melanoma



- Part A: 1, 6 and 30 mg efti s.c. every 2 weeks **starting with cycle 5** of pembrolizumab
 - Part B: efti at 30 mg s.c. every 2 weeks **starting with cycle 1** of pembrolizumab
- Status: recruitment completed; interim results on following slides
- Pembrolizumab (Keytruda®) 2 mg/kg every 3 weeks i.v. part A and B



Efti in Melanoma TACTI-mel – Safety Part A + B



*Efti has a favorable safety profile in combination with pembrolizumab -
No DLTs or MTDs and no new safety signals observed*

Frequent TEAE (selected if $\geq 15\%$ of pts)

Adverse Event*	Any grade N (%)	\geq Grade 3 N (%)
Abdominal pain (various terms)	5 (21)	-
Arthralgia	5 (21)	1 (4)
Cough	4 (17)	-
Diarrhea / Colitis	6 (25)	1 (4)
Fatigue	12 (50)	-
Headache	4 (17)	-
Injection site reaction	6 (25)	-
Nausea	7 (29)	-
Rash##	12 (50)	1 (4)

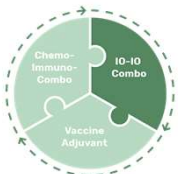
* - Adverse events occurred in $> 15\%$ of pts
- any kind of rash

- 10 SAEs in 9 pts; one related to pembrolizumab, none to efti
- 6 pts (25 %) with ≥ 1 AE \geq grade 3 (no grade 5)

Grade 3 / 4 TEAEs and rel. to study treatment

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

- 2 pts died due to AE (grade 4 intracranial hemorrhage, not related to treatment; grade 4 Sepsis, not related to treatment)
- 1 pt disc. due to an AE (anaemia; not related to treatment)
- 6 pts experienced treatment delays due to AEs



Efti in Melanoma TACTI-mel – Baseline Characteristics



Patients in very late stage of disease (M1c, elevated LDH, liver metastasis)

Baseline Characteristics	Part A N = 18 (%)	Part B N = 6 (%)	Overall N =24 (%)
Median Age	67 yrs	61 yrs	62 yrs
Sex (f/m)	6 % / 94 %	17 % / 83 %	8 % / 92 %
ECOG 1 / 0	22 % / 78 %	50 % / 50 %	29 % / 71 %
Pre-treated with BRAF/MEK/ipilimumab	5 (28 %)	0 (0 %)	5 (21 %)
Poor prognostic marker at study entry			
Elevated LDH (>ULN)	7 (39%)	5 (83%)	12 (50 %)
Liver metastasis	10 (56 %)	2 (33 %)	12 (50 %)
Lung metastasis	11 (61 %)	5 (83 %)	16 (67 %)
Metastatic, stage M1c	14 (78 %)	4 (66 %)	18 (75%)



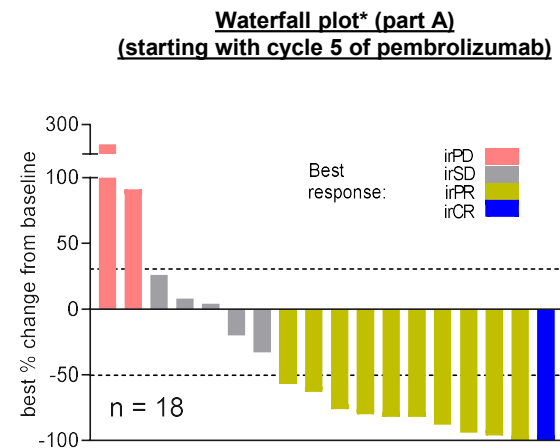
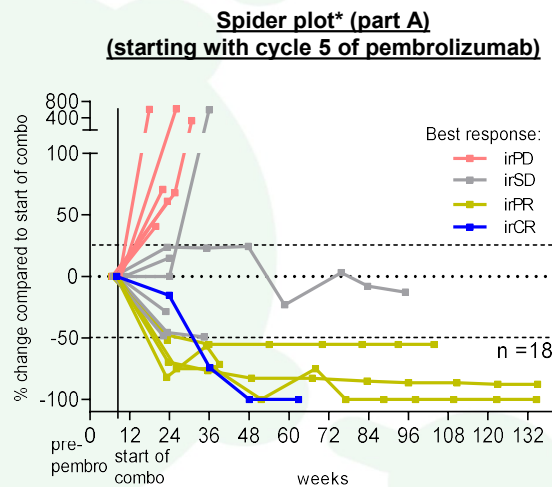
Efti in Melanoma TACTI-mel – Results Part A

Majority not responding to pembrolizumab monotherapy
→ Tumor shrinkage in 56 % incl. 2 pts with disappearance of all baseline index lesions

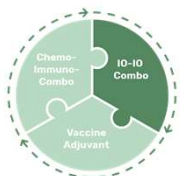
Best Overall Response acc. to irRC	N = 18 (%)
irCR	1 (6 %)
irPR#	5 (28 %) #
irSD	6 (33 %)
irPD	6 (33 %)
Best overall response rate (ORR)	6 (33 %)
Patients with tumor shrinkage	10 (56 %)
Disease control rate	12 (66 %)

- incl. 1 pt with complete disappearance of all target lesions; CR acc. to RECIST 1.1

Exploratory analysis
(C1D1 pembrolizumab):
ORR of 61 %



* - according to irRC



Efti in Melanoma TACTI-mel – Results Part B

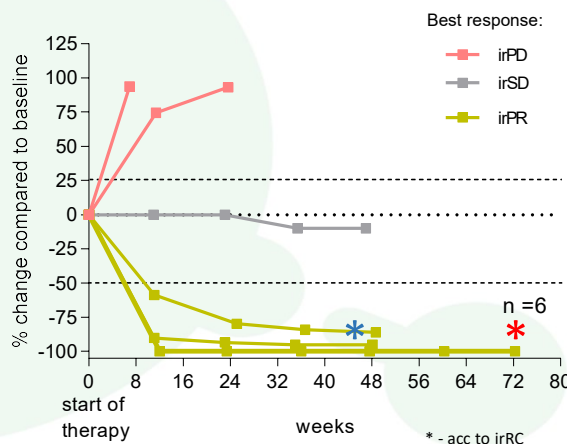


Confirmed deep partial responses in 3 (50%) of the pts

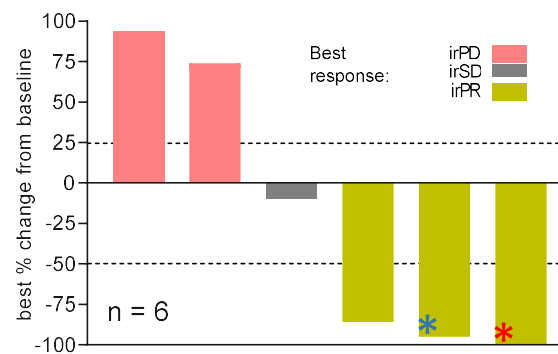
Best Overall Response acc. to irRC	N = 6 (%)
irCR	0 (0 %)
irPR#	3 (50 %)#
irSD	1 (17 %)
irPD	2 (33 %)
Best overall response rate (ORR)	3 (50 %)
Patients with tumor shrinkage	4 (66 %)
Disease control rate	4 (66 %)

- incl. 1 pt with complete disappearance of all target lesions (**red asterix, case 1**) and incl 1 add. pt with no metabolic active disease as per PET-CT (**blue asterix, case 2**)

Spider plot* (part B)



Waterfall plot* (part B)

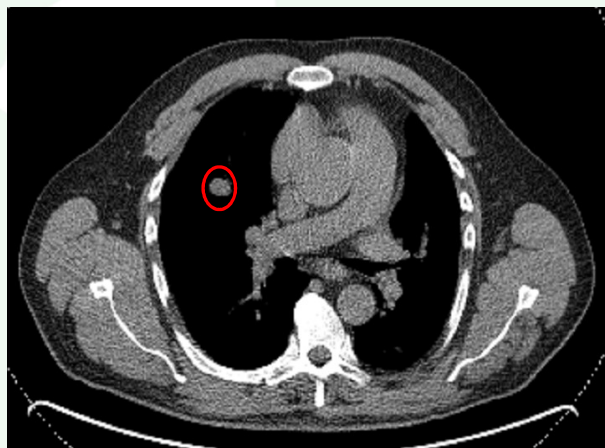


- 4 patients (all non-PD) continue on pembrolizumab monotherapy after completion of the trial

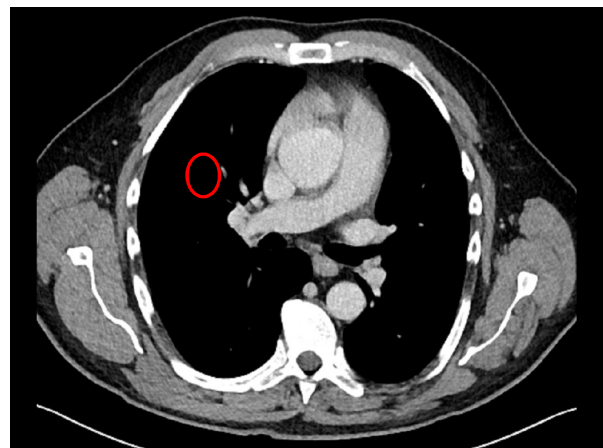


Efti in Melanoma TACTI-mel – Results Part B Single Case study (1)

- 61-year old male patient
- TxNxM1b at study entry in March 2018
- irPR reached by week 12 and maintained until end of study (week 72)



Baseline; lesion 17 mm



Week 72; lesion 0 mm

Single index (or target) lesion completely disappeared by week 12
Non-index lesions remained present



Efti in Melanoma TACTI-mel – Results Part B Single Case study (2)



- 46-year old female patient
- TxNxM1c at study entry in August 2018
- irPR reached by week 12 and maintained until end of study
- PET-scans negative on two occasions – at the time of end of treatment and after end of study

Deep irPR, residual tumor mass not metabolically active
(complete metabolic response, CMR)

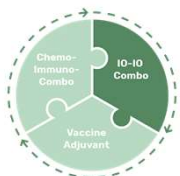


PET-scans

June 2018

May 2019

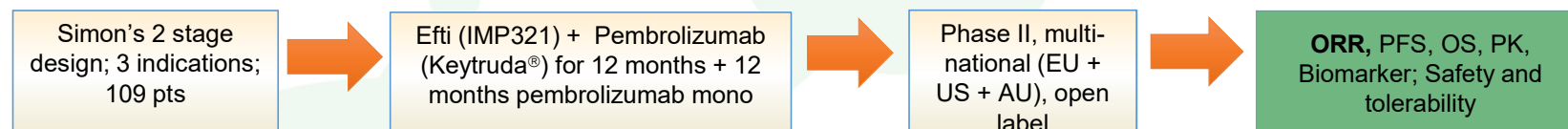
August 2019



Efti - Clinical Development TACTI-002 (Phase II)



TACTI-002: Two ACTive Immunotherapeutics in different indications



Patient Population	A: 1 st line NSCLC PD-X naïve B: 2 nd line NSCLC, PD-X refractory C: 2 nd line HNSCC, PD-X naïve
Treatment	30 mg Efti (IMP321) s.c. 200 mg Pembrolizumab i.v.

In collaboration with



Status Report (Sep 2019)

- ✓ Fully approved in all countries (ES, GB, US, AU)
- ✓ Part A (PD-L1 all comers, 1st line NSCLC): 41 % ORR in stage 1 → 2nd cohort will be opened Q4 2019
- ✓ 32 pts recruited in total



13 sites in Europe / US / Australia

Updated results will be presented at SITC (under embargo until Nov. 9th, 2019)

Key features: PD-X refractory patients (part B), chemo-free option for NSCLC, first FDA IND

NSCLC – non-small-cell lung cancer, HNSCC – head and neck squamous cell cancer, ORR – overall response rate, PFS – progression free survival, OS – overall survival, PK –

pharmacokinetics, PD-X – any PD-1 or PD-L1 treatment

Preliminary data, cut-off September 2019

Thank you

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