



# Eftilagimod Alpha Clinical Development Update and New Data from Ongoing Melanoma Study

**Date & Time:** Wednesday, April 3, 2019, 7:45am Australian Eastern Standard Time  
Tuesday, April 2, 2019, 4:45pm US Eastern Daylight Time

**Register:** Interested investors can register via the following link to the webcast  
[Register here for webcast](#)

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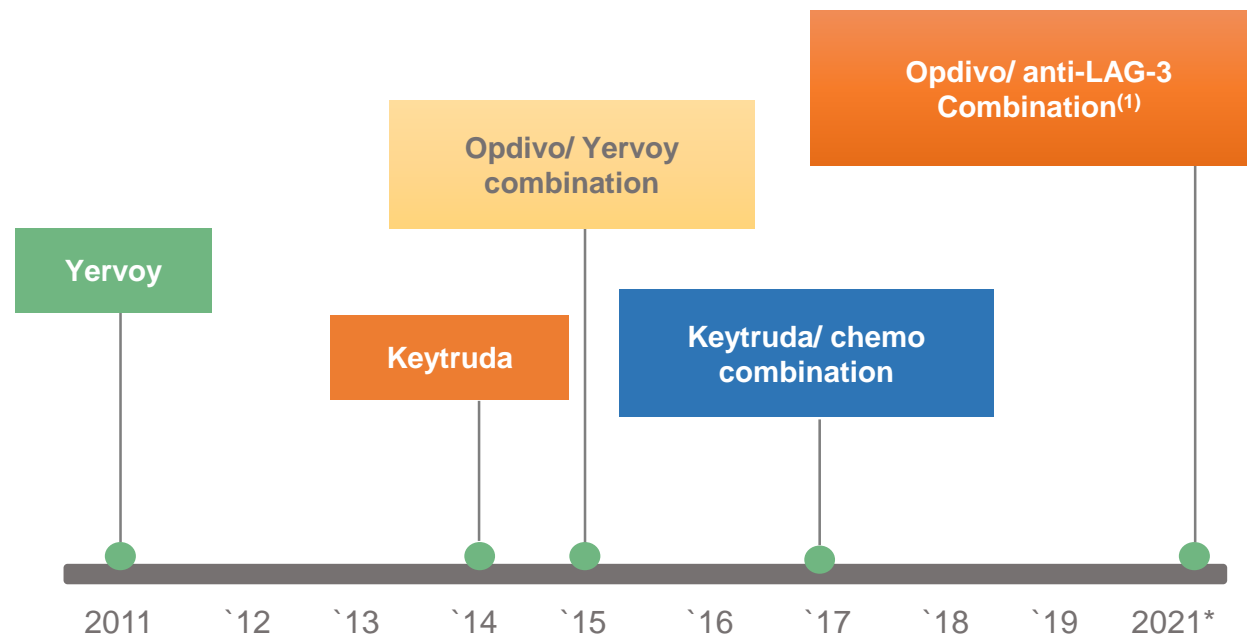
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# LAG-3 Overview

# Evolution of Checkpoint Therapies

*LAG-3 has the potential to be the next meaningful checkpoint target...*

## Evolution of Immuno-Oncology Therapies



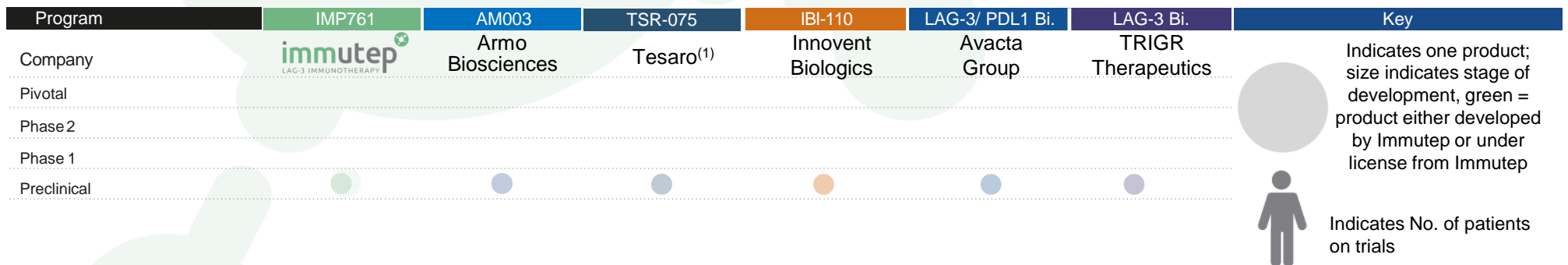
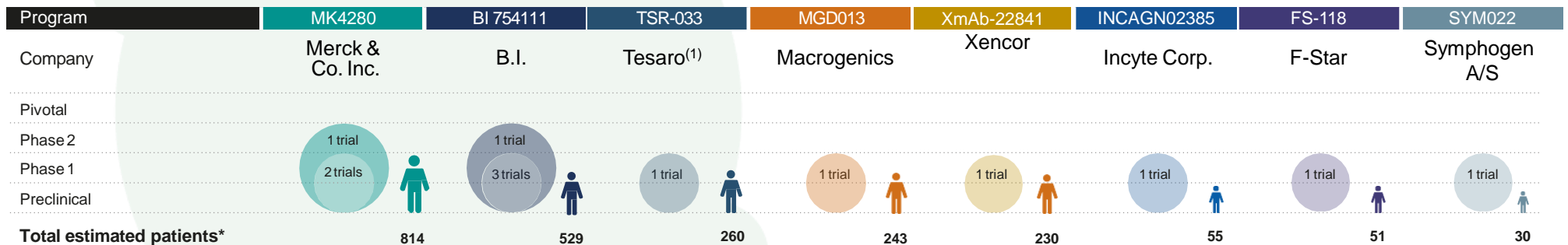
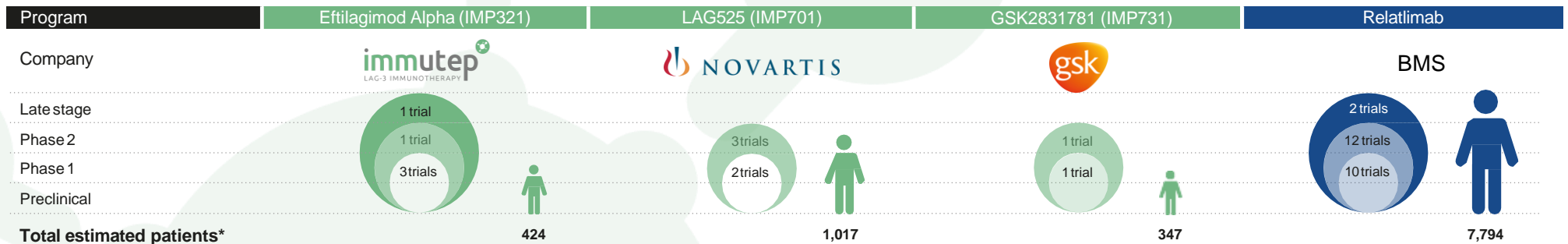
- Existing immuno-oncology therapies are CTLA-4, PD-1 and PD-L1 antagonists and are approved for many disease indications
- However, only 15 - 40% of solid tumors in patients respond to monotherapy
- Immuno-oncology market will be worth approximately US\$14 billion in 2019, rising to US\$34 billion by 2024, with checkpoint therapies accounting for most of the market<sup>(2)</sup>

### Notes

- (1) Expected timing, actual results may differ (BMS ASCO 2017 Investor Presentation)
- (2) Global Data, Immuno-Oncology Strategic Insight: Multi-Indication and Market Size Analysis (May 2016)

# LAG-3 Therapeutic Landscape Overview

*Immutep is the leader in developing LAG-3 modulating therapeutics*



**Notes:**

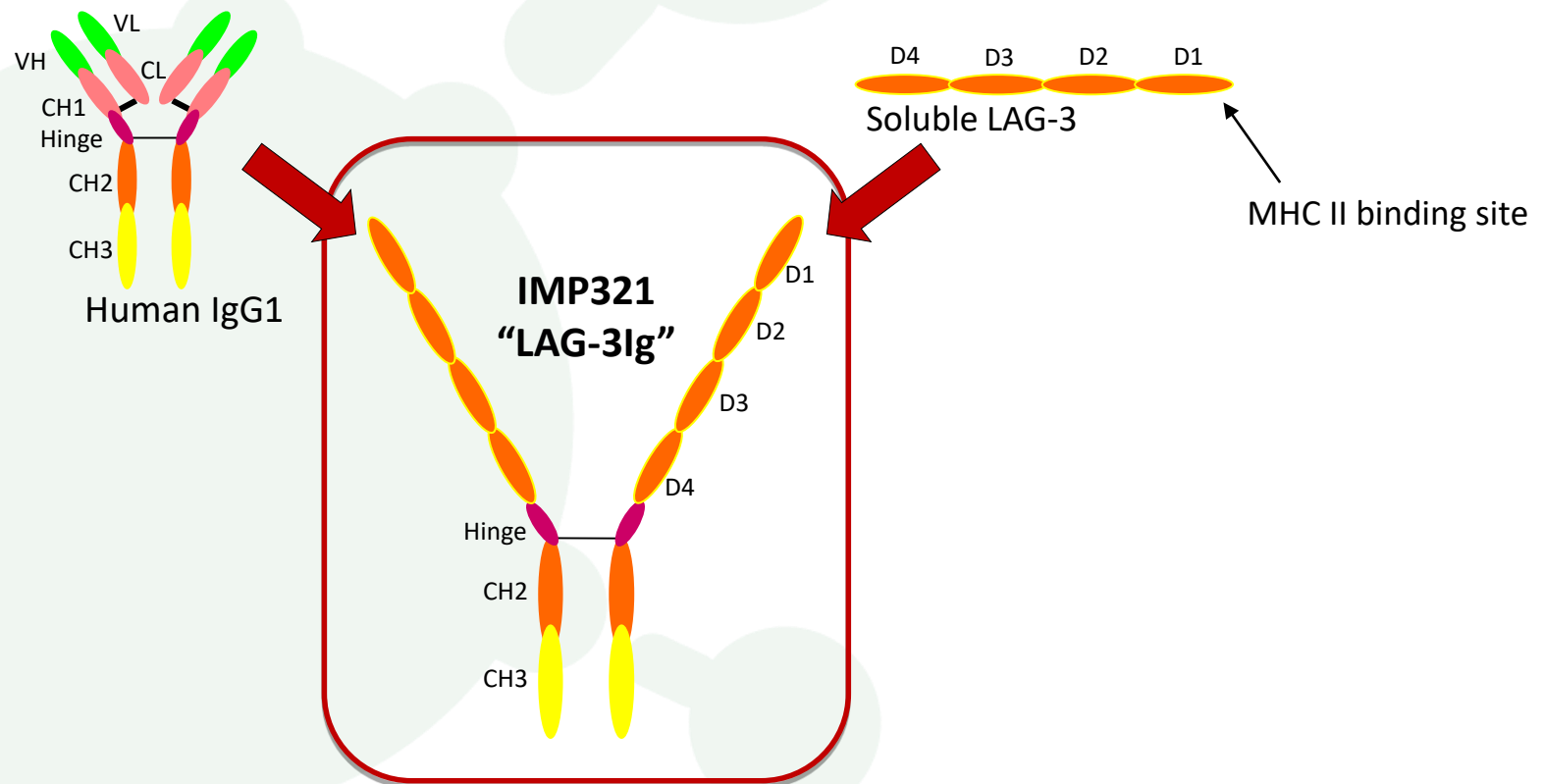
Sources: GlobalData, company websites, clinical trials.gov, and sec.gov  
 Information as of March 28, 2019, includes planned and completed trials, includes trials where the company may not be the sponsor

(1) Tesaro was acquired by and is now part of GSK

# Eftilagimod Alpha (Efti, IMP321)

# Eftilagimod Alpha

*Efti is a soluble recombinant fusion protein consisting of the Fc portion of a human antibody and the four extracellular domains of LAG-3*

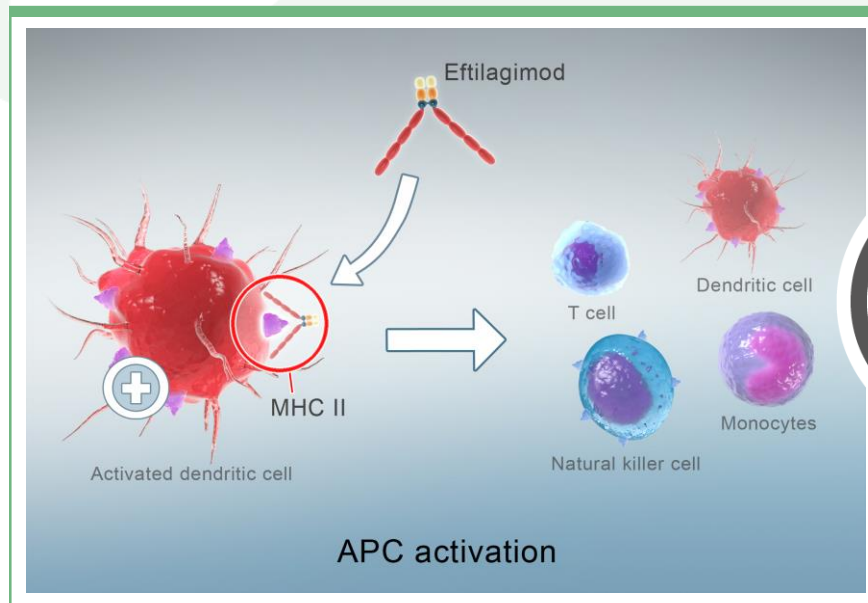


- Dimeric, very stable, high affinity for DC
- Antigen presenting cell (APC) activator
- Unique mechanism of action and potentially first-in-class

# Efti - Innovative LAG-3 IO Product Candidate **immunetep** LAG-3 IMMUNOTHERAPY

- Only APC targeting LAG-3 product candidate currently in clinical development
- A unique approach (“turning cold tumors into hot tumors” with LAG-3)
- Synergistic with other therapeutic agents and modalities e.g. IO agents, chemotherapy

“PUSHING THE ACCELERATOR ON IMMUNE RESPONSES”

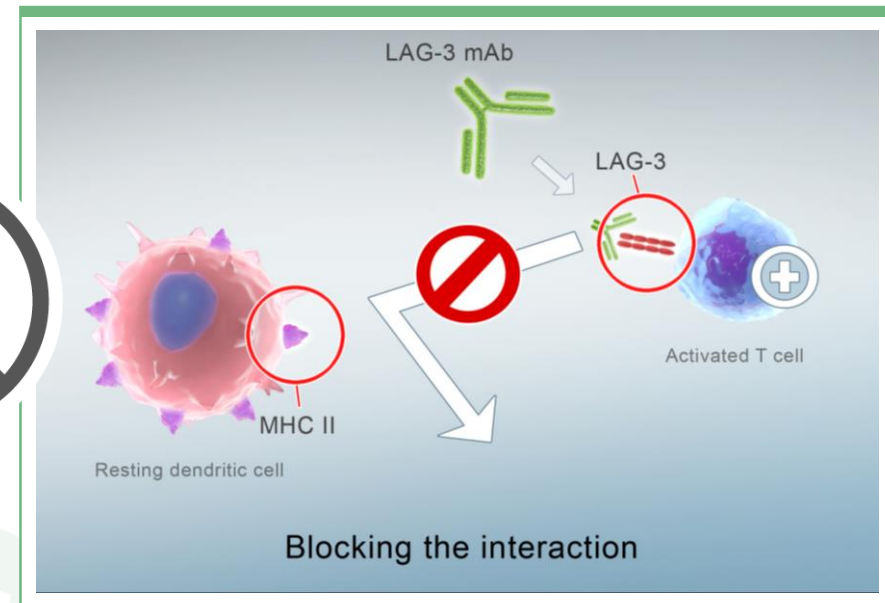


Efti is a MHC II **agonist**

### APC activator

- Boost and sustain the CD8<sup>+</sup> T cell responses
- Activate multiple immune cell subsets

“RELEASING THE BRAKE ON THE T CELL”



LAG-3 antagonist, or blocking, antibodies:

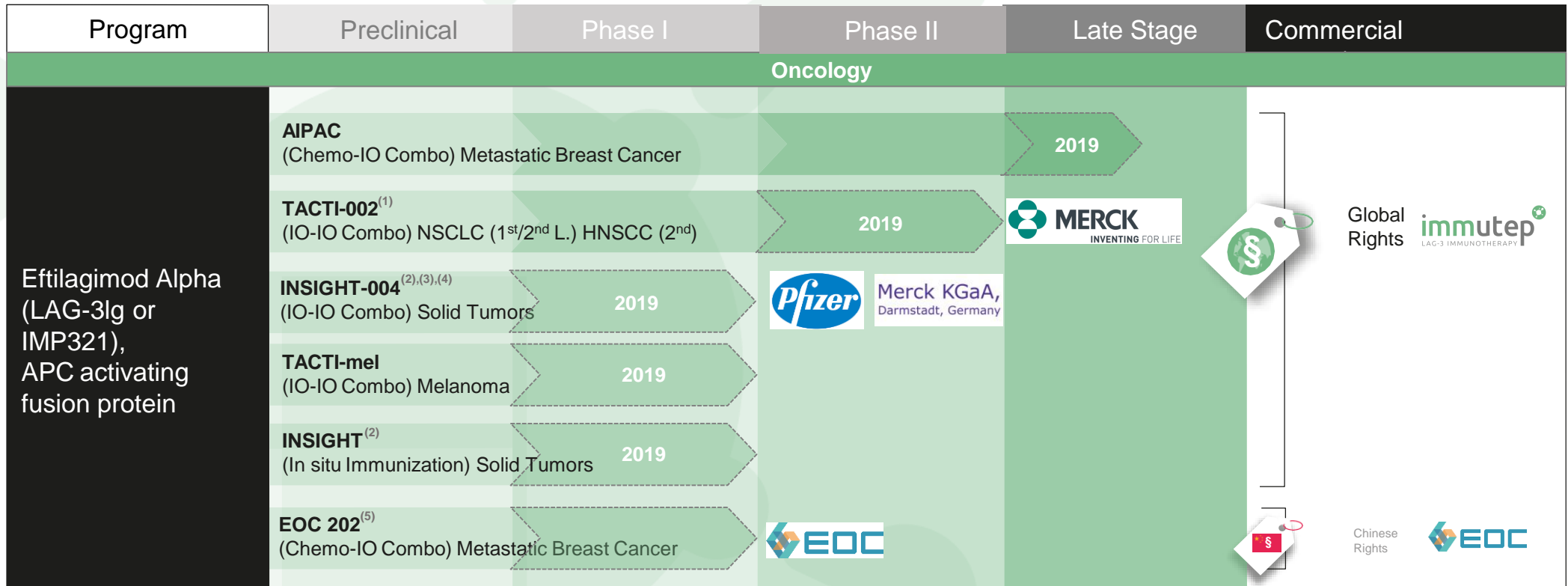
### Immune checkpoint inhibitor

- Increase cytotoxicity of the pre-existing CD8 T cell response



# Eftilagimod Alpha Clinical Trials\*

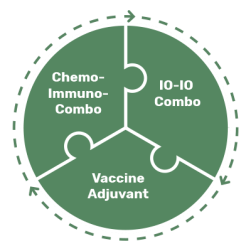
*Expecting multiple data readouts throughout H2 2019\**



**Notes**

- \* Actual timing of data readouts may differ from expected timing shown above. Information in pipeline chart current as at 12 February 2019.
- (1) In combination with KEYTRUDA® (pembrolizumab) in non-small cell lung carcinoma ("NSCLC") or head and neck carcinoma ("HNSCC"); clinical trial is currently planned and not active
- (2) INSIGHT Investigator Initiated Trial ("IIT") is controlled by lead investigator and therefore ImmuteP has no control over this clinical trial
- (3) In combination with BAVENCIO® (avelumab)
- (4) Clinical trial is currently planned and not active
- (5) EOC Pharma is the sponsor of the EOC 202 clinical trial which is being conducted in the People's Republic of China

# Efti Clinical Development Overview



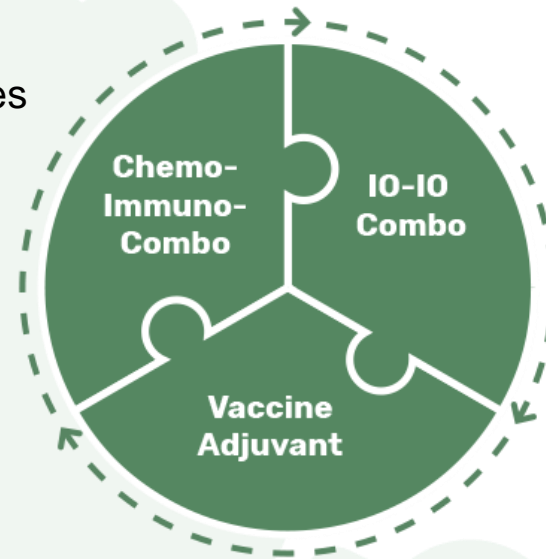
# Efti - Areas of Development Multiple Strategies

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

## Chemo-immunotherapy

- Exploit the antigen debris from chemotherapy with an APC activator → combination with agents such as taxanes (e.g. paclitaxel)

- *European Phase IIb AIPAC (Immutep)*
- *Chinese Phase I Chemo Combo in MBC pts (EOC)*



## IO-IO combination

- Increase response rates and durability, overcoming resistance in combination with IO agents with complementary mechanisms (e.g. pembrolizumab, avelumab)

- *Phase I TACTI-mel (Immutep)*
- *Phase II TACTI-002 (Immutep<sup>1</sup>)*
- *Phase I INSIGHT – Stratum D (Immutep<sup>2</sup>)*

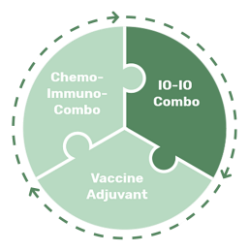
## Cancer vaccine or in situ vaccination

- Stimulate the immune system locally → intratumoral or in vaccination studies

- *Phase I Solid Tumors (Cytlimic)*
- *Phase I INSIGHT - Stratum A+B (IKF<sup>3</sup>)*

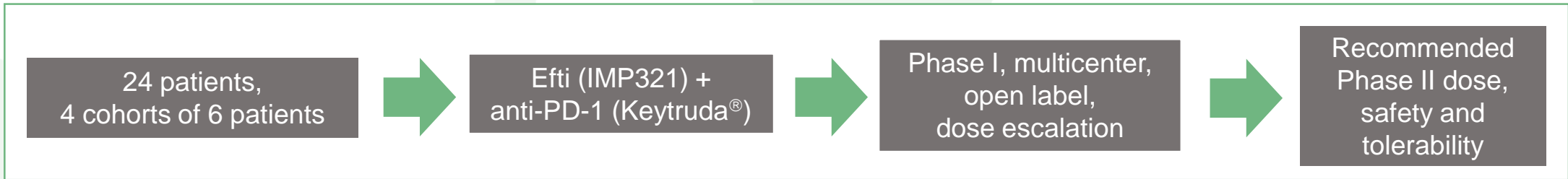
Notes  
 (1) In collaboration with Merck & Co., Inc., Kenilworth, NJ, USA (known as MSD outside the United States and Canada) and in combination with KEYTRUDA® (pembrolizumab)  
 (2) In collaboration with Merck KGaA, Darmstadt, Germany and Pfizer Inc. and in combination with BAVENCIO® (avelumab)  
 (3)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

# Efti TACTI-mel results



# Efti in Melanoma TACTI-mel – Trial Design

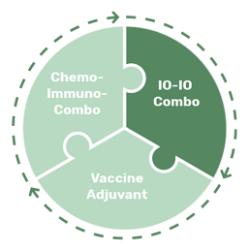
## TACTI-mel: Two ACTive Immunotherapeutics in Melanoma



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 ≥ 15 % of pts)

Adverse Event*	Any grade N (%)	≥ 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)

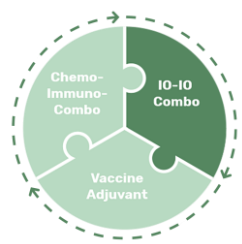
\* - Adverse events occurred in > 15 % of pts  
## - any kind of rash

- 10 SAEs in 9 pts; one related to pembrolizumab, none to efti
- 6 pts (25 %) with ≥ 1 AE ≥ 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

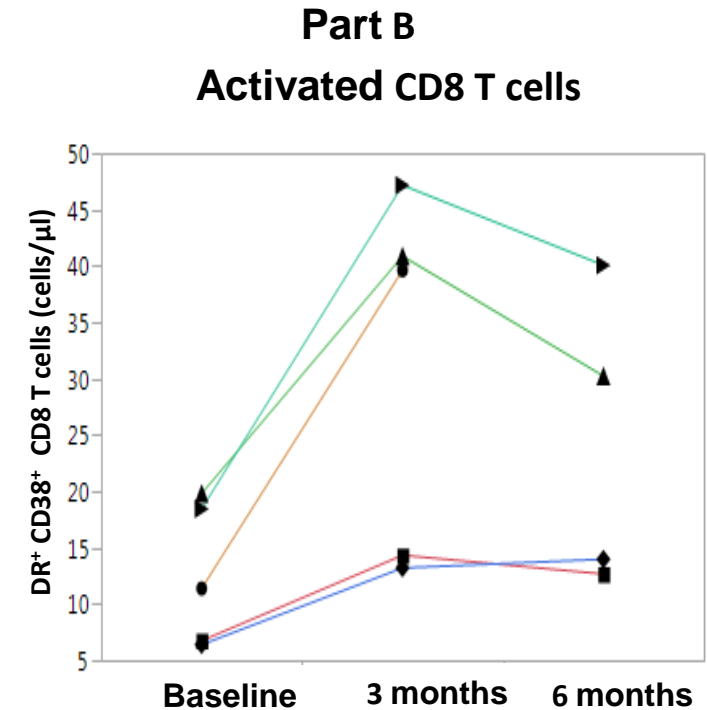
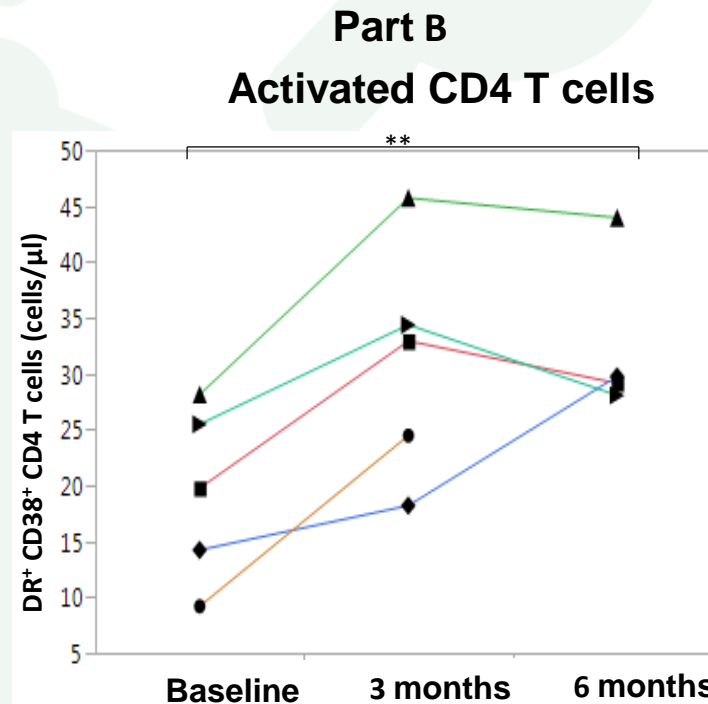
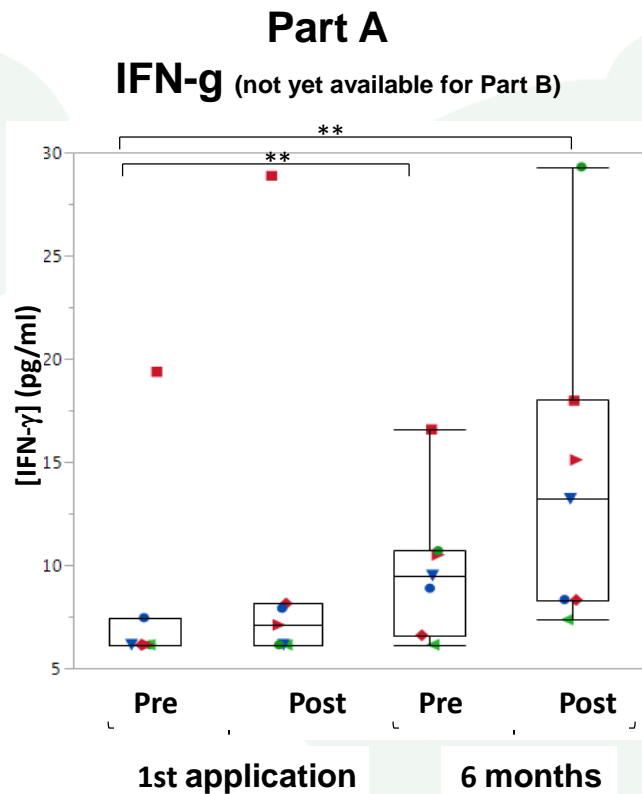
- 2 pts died due to AE (grade 4 intracranial hemorrhage, not related to treatment; grade 4 Sepsis, not related to treatment)
- 1 pt disc. due to an AE (anaemia; not related to treatment)
- 6 pts experienced treatment delays due to AEs



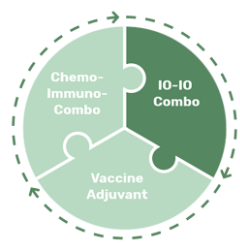
# Efti in Melanoma TACTI-mel – Blood Pharmacodynamics



*Sustained markers of immune response observed*



- ✓ At 6 months, pre-dose (i.e. 14 days after last injection) serum IFN- $\gamma$  is elevated: sustained increase of systemic Th1 status (i.e. not at the tumor site only, but in the whole organism)
- ✓ Also increased absolute numbers of activated CD4 and CD8 cells for all patients in part B
- ✓ Improved Th1 status and increased activated T cells numbers have also been reported for efti + chemo (AIPAC)



# Efti in Melanoma

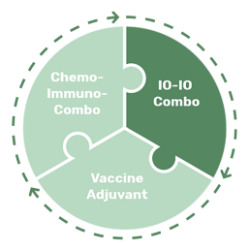
## TACTI-mel – Baseline Characteristics



*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 %)
<b>Poor prognostic marker at study entry</b>			
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 %)	6 (100 %)	20 (83 %)





# Efti in Melanoma TACTI-mel – Results Part A

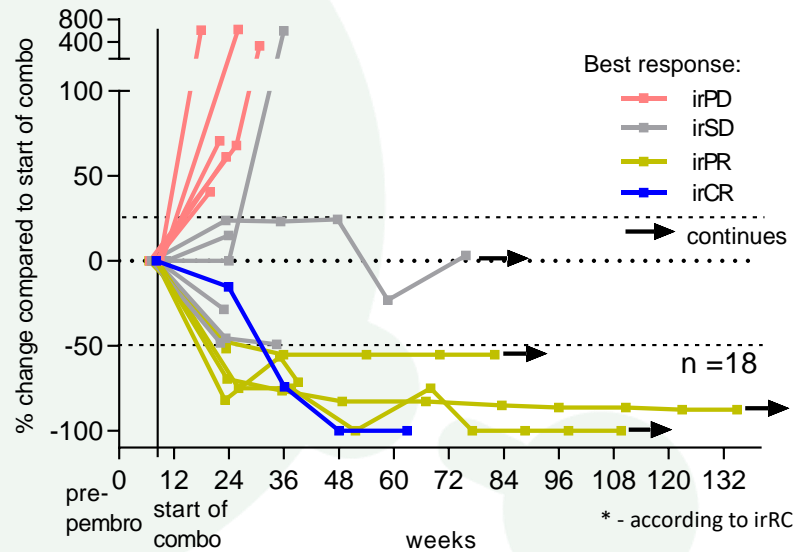


**Majority not responding to pembrolizumab monotherapy**  
**→ Tumor shrinkage in 56 % incl. 2 pts with disappearance of all target lesions**

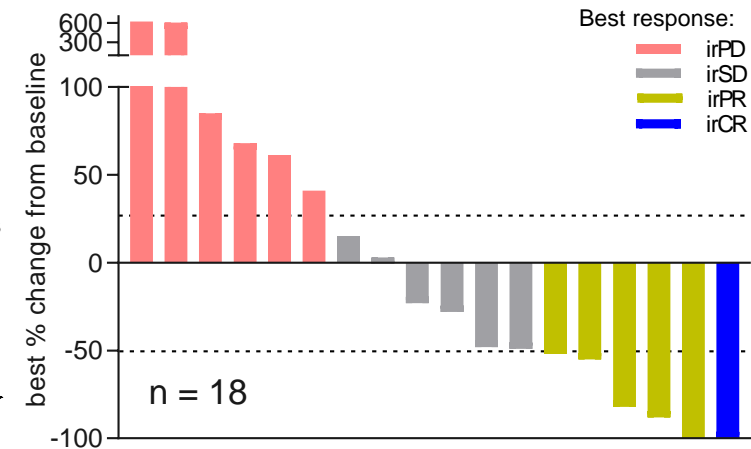
Best Overall Response acc. to irRC	N = 18 (%)
irCR	1 (6 %)
irPR#	5 (28 %) #
irSD	6 (33 %)
irPD	6 (33 %)
<b>Best overall response rate (ORR)</b>	<b>6 (33 %)</b>
<b>Patients with tumor shrinkage</b>	<b>10 (56 %)</b>
<b>Disease control rate</b>	<b>12 (66 %)</b>

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

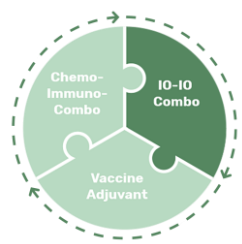
**Spider plot\* (part A)**  
**(starting with cycle 5 of pembrolizumab)**



**Waterfall plot\* (part A)**  
**(starting with cycle 5 of pembrolizumab)**



Exploratory analysis  
 (C1D1 pembrolizumab):  
**ORR of 61 %**



# Efti in Melanoma TACTI-mel – Results Part B

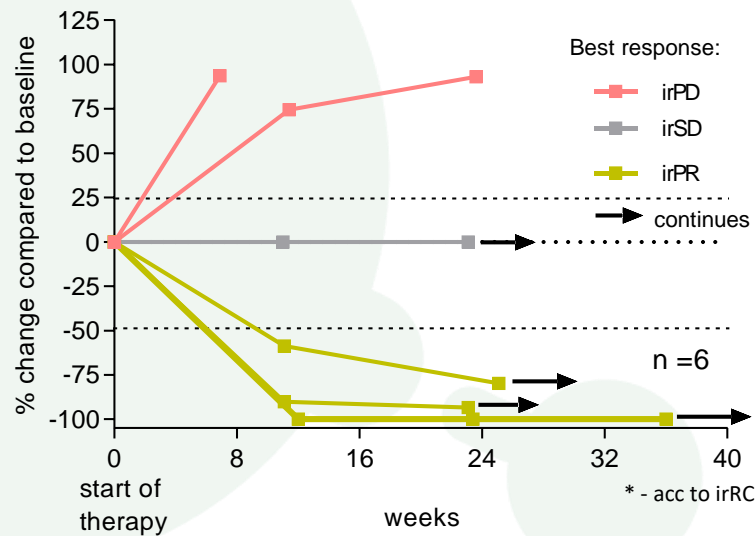


**Confirmed deep partial responses in 3 (50%) of the pts  
Treatment of 4 pts ongoing, all over 6 months**

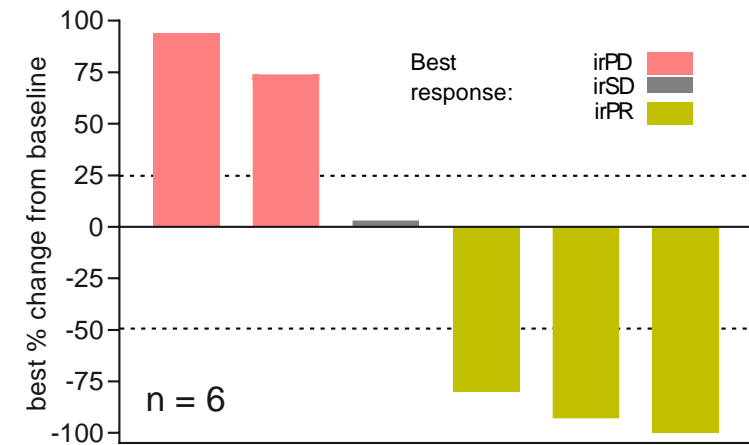
Best Overall Response acc. to irRC	N = 6 (%)
irCR	0 (0 %)
irPR#	3 (50 %)#
irSD	1 (13 %)
irPD	2 (25 %)
<b>Best overall response rate (ORR)</b>	<b>3 (50 %)</b>
<b>Patients with tumor shrinkage</b>	<b>3 (50 %)</b>
<b>Disease control rate</b>	<b>4 (66 %)</b>

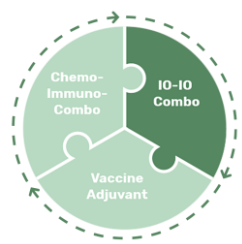
# - incl. 1 pt with complete disappearance of all target lesions

**Spider plot\* (part B)**



**Waterfall plot\* (part B)**

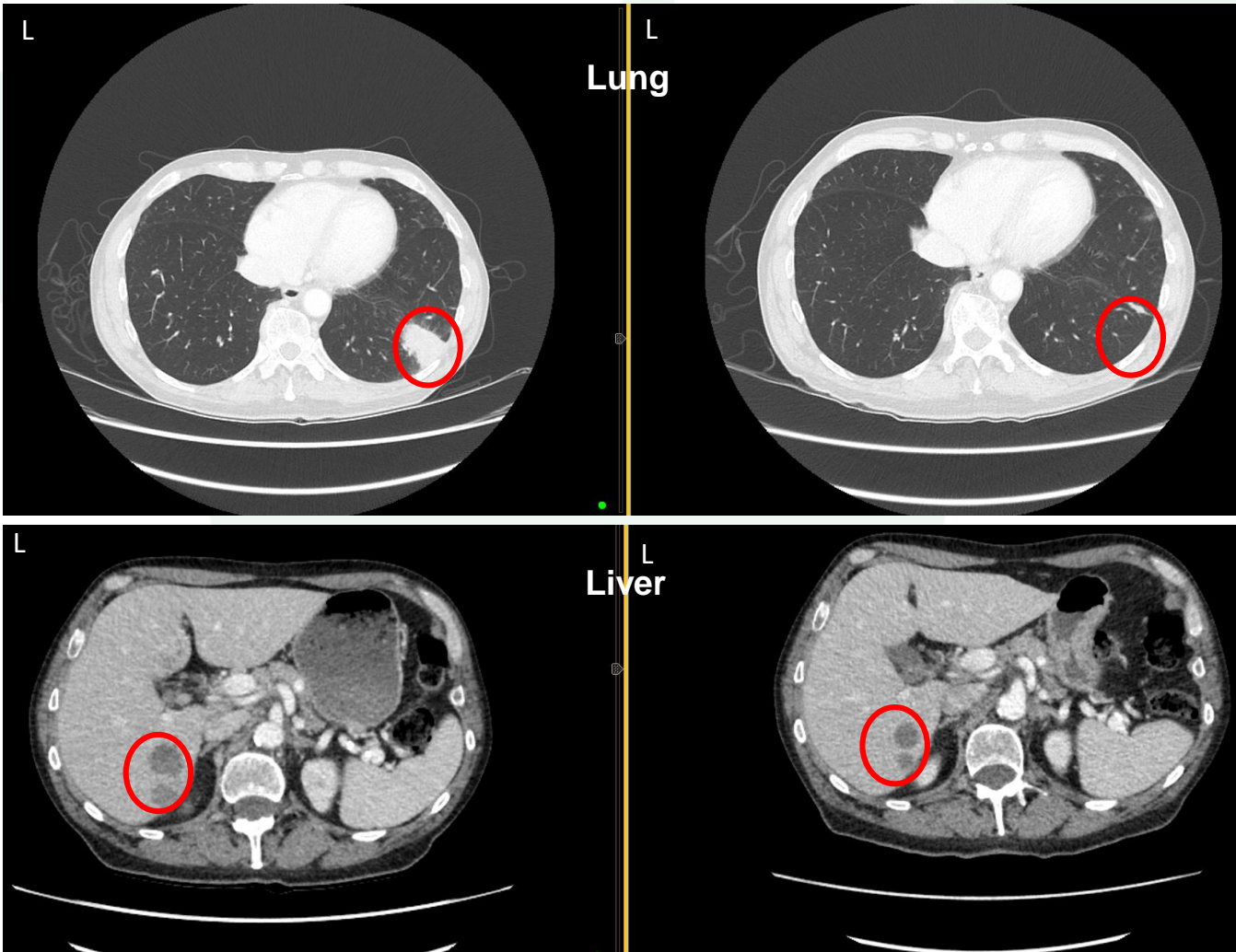




# Efti (IMP321) in Melanoma TACTI-mel – Results Part B – Single Case

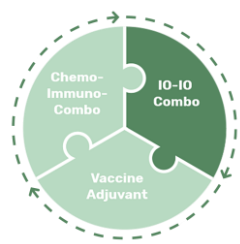
July 2018 (baseline)

January 2019 (6 months)



- 69 year old male
- Multiple lung, bone, liver and lymph node metastases from melanoma → **M1C stage**
- BRAF wild type
- ECOG 1

→ clear regression of lung and liver metastases → treatment continues (6+ months)

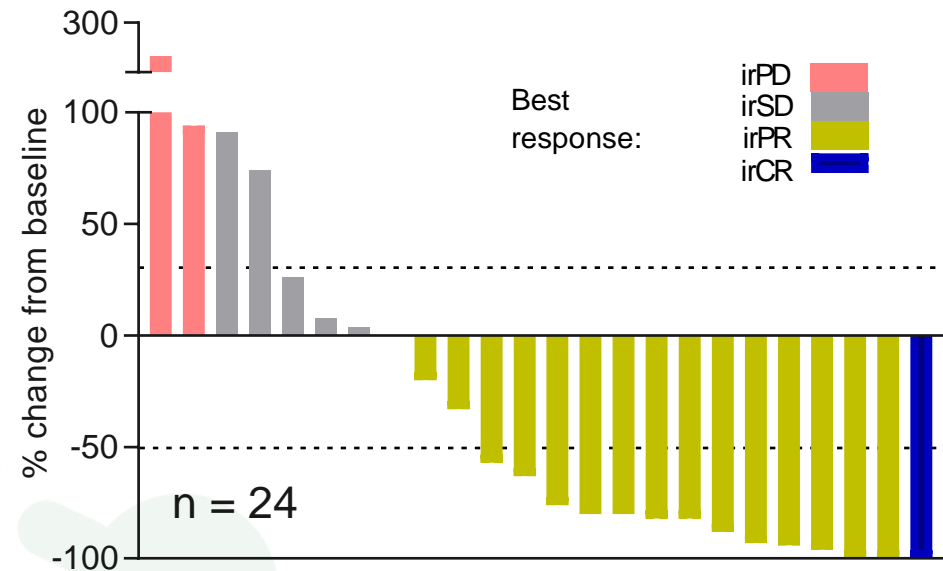


# Efti in Melanoma TACTI-mel – Analysis Parts A+B (1)

**Overall response rate is 58% and 58% of patients are progression-free 6 months after start of pembrolizumab (1)**

ORR acc. to irRC (C1/D1 analysis) <sup>(1)</sup>	N = 24 (%)
irCR	1 (4%) <sup>(1)</sup>
irPR#	13 (54%) <sup>(1),(2)</sup>
irSD	6 (25%) <sup>(1)</sup>
irPD	4 (17%) <sup>(1)</sup>
<b>Overall response rate (ORR)</b>	<b>14 (58%)<sup>(1)</sup></b>
<b>Progression-free at 6 months</b>	<b>14 (58%)<sup>(1)</sup></b>

**Waterfall Plot\* (part A+B)  
(starting cycle 1 day 1 pembrolizumab)**

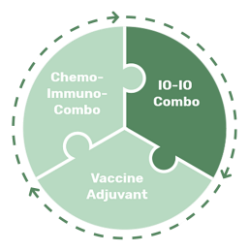


Note Trial Design TACTI-mel part A: Combination treatment of efti and pembrolizumab starts at cycle 5 in patients not responding well or progressing on pembrolizumab → difficult to compare to any historical control

How does the efficacy look from the start of pembrolizumab?

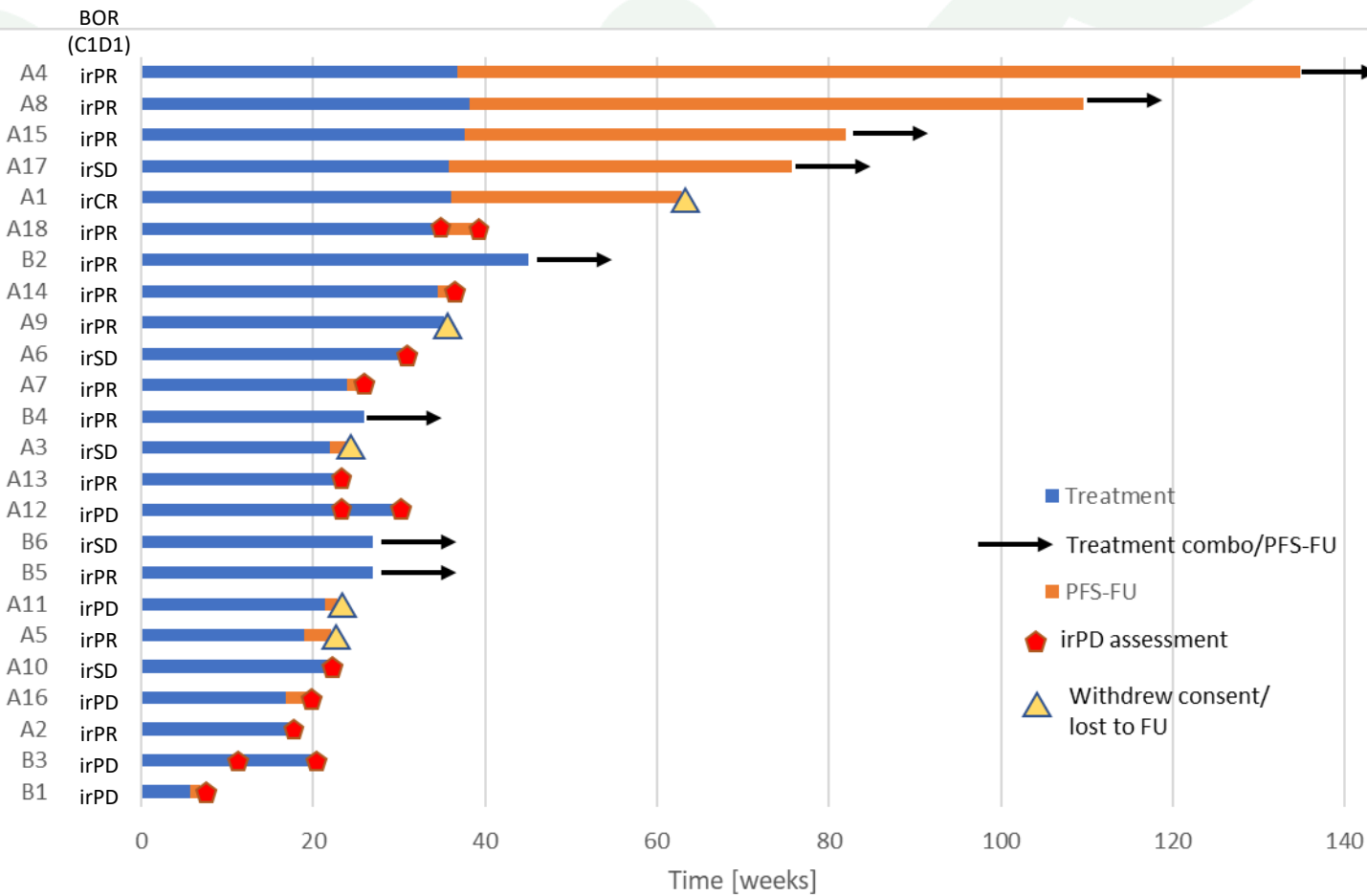
→ Performed exploratory analysis starting from cycle 1 day 1 of pembrolizumab, including the 4 cycles pembrolizumab monotherapy (“C1/D1 Analysis”) and include pts from part B

(1) Response rates determined by C1/D1 Analysis for part A  
 (2) Includes 2 patients with complete disappearance of all target lesions, but with remaining non-target lesions or lymph nodes



# Efti in Melanoma TACTI-mel – Analysis Parts A+B (2)

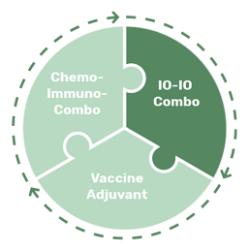
**Swimmerplot parts A + B  
(starting cycle 1 day 1 pembrolizumab)**



**Conclusion**

- No treatment termination due to safety issues of the combination
- 5+ pts on treatment for > 12 months → durable responses
- 8 (4 part A) and (4 part B) patients still progression free and under treatment

Note: BOR – best overall response per patient with start of pembrolizumab as baseline



# Efti in Melanoma Comparison to historical controls

How does the data fit in the treatment landscape and in comparison to pembro monotherapy?

TACTI-Mel enrolled ipilimumab (ipi) naive and ipi pre-treated patients → Keynote-002 (pre-treated) and Keynote-006 (naive) used for comparison

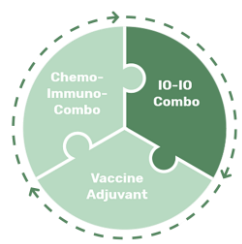
Baseline Characteristics	Tacti-Mel (C1/D1 response analysis) Pembro 2 mg/kg N=24 in %	KN-006 (ipi naive) Pembro 10 mg/kg n=277 in %	KN-002 (ipi pre-treated) Pembro 2 mg/kg n=180 in %
Metastatic stage M1c	83%	68%	82%
ECOG 1 / 0	29% / 71%	32% / 68%	45% / 55%
irCR	4% <sup>(1)</sup>	6% <sup>(2)</sup>	2% <sup>(2)</sup>
<b>ORR</b>	<b>58%<sup>(1)</sup></b>	<b>33%<sup>(2)</sup></b>	<b>21%<sup>(2)</sup></b>
<b>Progression-free at 6 months</b>	<b>58%<sup>(1)</sup></b>	<b>46%<sup>(2)</sup></b>	<b>34%<sup>(2)</sup></b>

**58 % response rate<sup>(1, 2)</sup> and 58 % progression free at 6 months<sup>(1, 2)</sup> with the PD-1 antagonist pembrolizumab and APC activator eftilagimod alpha in very late stage partly pre-treated metastatic melanoma patients**

Notes

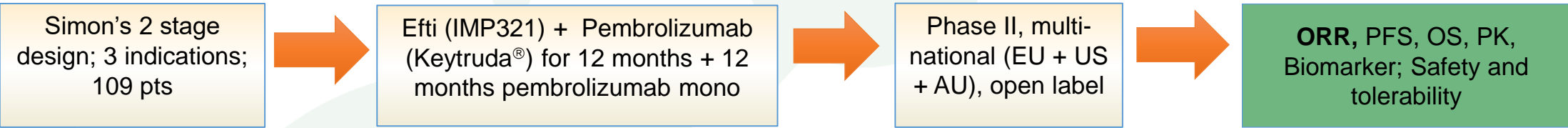
- (1) Response rates determined by C1/D1 Analysis
- (2) TACTImel used irRC and KN-002 and KN-006 ECIS1.1
- (3) Source of the figure: 7th edition (2010) of the AJCC cancer staging manual

**Efti**  
**Clinical Development Updates**  
**TACTI-002 / INSIGHT-004**  
**/AIPAC**



# Efti - Clinical Development TACTI-002 (Phase II)

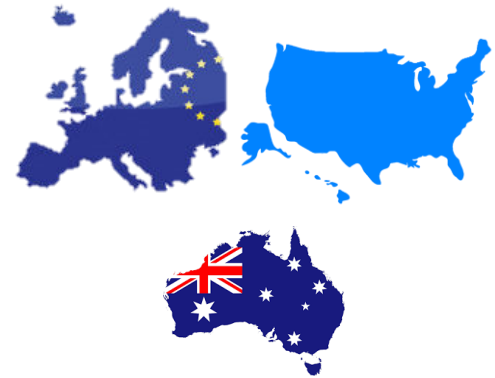
## TACTI-002: Two ACTive Immunotherapeutics in different indications



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

### Status Report (Apr 2019)

- ✓ Fully approved in all countries (ES, GB, US, AU)
- ✓ >10 patients enrolled
- First data expected mid 2019



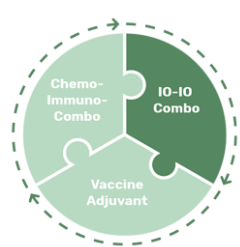
13 sites in Europe / US / Australia

In collaboration with



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

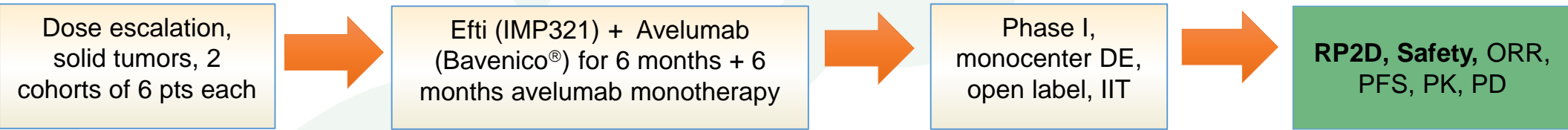




# Efti - Clinical Development INSIGHT-004 (Phase I)



## INSIGHT-004 – Dose escalation of efti in combination with avelumab



<b>Patient Population</b>	Solid tumors after failure of standard therapy
<b>Treatment</b>	6/30 mg Efti (IMP321) s.c. 800 mg avelumab i.v.; Both every 2 weeks

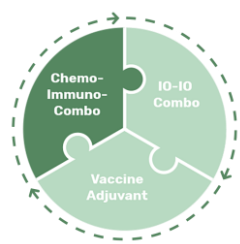
### Status Report (Apr 2019)

- ✓ 1 site in Germany
- ✓ Protocol approved by CA/ ED
- First patient expected in Q2 2019

### In collaboration with

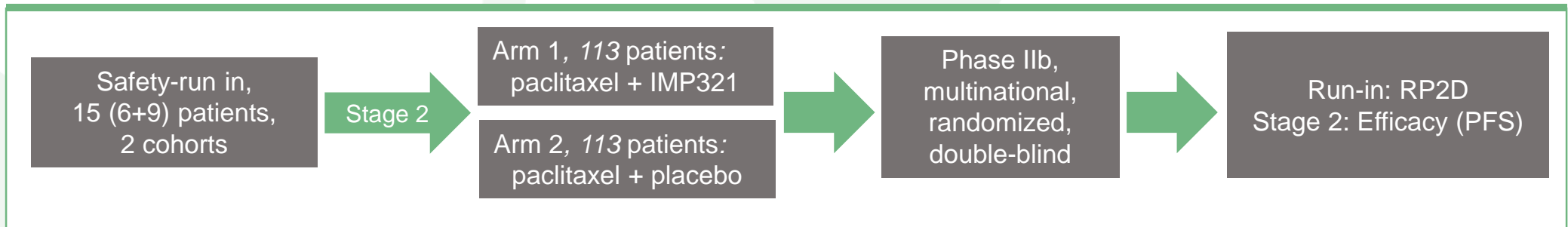


**Key features: safety with a PD-L1 antagonist avelumab**



# Efti - Clinical Development AIPAC

## AIPAC: Active Immunotherapy PAClitaxel in MBC

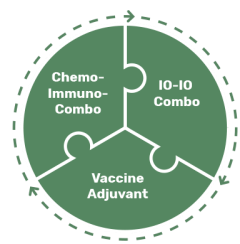


<b>Other Objectives</b>	Anti-tumor activity, safety and tolerability, PK, immunogenicity, quality of life
<b>Patient Population</b>	Advanced MBC indicated to receive 1 <sup>st</sup> line weekly paclitaxel
<b>Treatment</b>	Run-in: Paclitaxel + IMP321 (6 or 30 mg) Arm 1: Paclitaxel + IMP321 (30 mg) Arm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

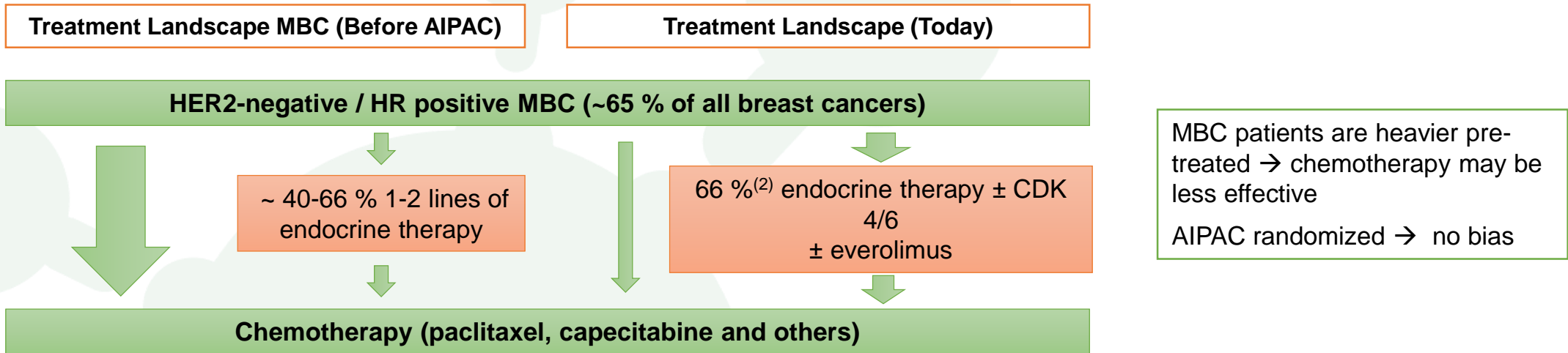
### Status Report (Apr 2019)

- ✓ 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
- ✓ >200 patients recruited in Stage 2 → LPI expected May/June 2019
- Primary read out expected within 12 months dependent on the number of events, but not before Q.4 2019

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



# Efti - Areas of Development Potential Target Markets



## MBC

- ~**800,000 new cases** p.a. worldwide with **HER+HR + BC**
- Despite all changes → no improvement for patients receiving chemotherapy
- Paclitaxel one of the most widely used chemotherapies

## Other indications/combinations

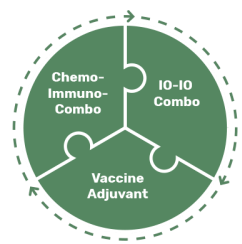
- Efti is investigated in **melanoma** with **pembrolizumab** (2019 estimated global sales of US\$9.8 billion<sup>(1)</sup>)
- Efti is investigated in **head and neck** and two different treatment lines of **NSCLC with pembrolizumab**
- Efti is investigated with **avelumab** (2019 estimated sales of US\$242 million<sup>(1)</sup>)

**Multiple shots on goal in large indications → efti not limited by indication/combination**

### Notes

(1) Source: GlobalData 2019  
(2) Caldeira et al Oncology and therapy 2016; 4:189-197

MBC – metastatic breast cancer BC – breast Cancer  
NSCLC – non-small cell lung cancer



# Efti Summary

- ✓ Favorable safety profile
- ✓ Sustained systemic immune response
- ✓ Encouraging efficacy data in different settings
- ✓ Clinical trials with industry leading collaborators
- ✓ Potentially low cost of goods
- ✓ Potential pipeline in a product
- ✓ Late stage clinical development with multiple “shots on goal”

**Thank you!**