SITC 2018

NOVEMBER 7-11
WASHINGTON, D.C.
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Society for Immunotherapy of Cancer

Results from a Phase I dose escalation trial (TACTI-mel) with the soluble LAG-3 protein (IMP321, eftilagimod alpha) together with pembrolizumab in unresectable or metastatic melanoma

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[5] Flinders Centre for Innovation in Cancer, Adelaide
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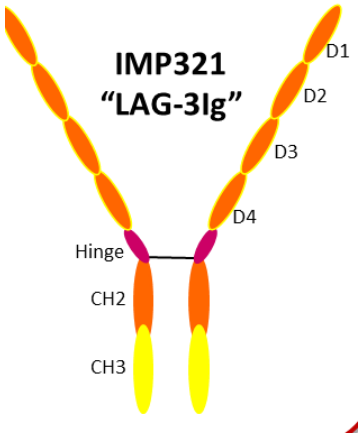
Presenter Disclosure Information

The following relationships exist related to this presentation:

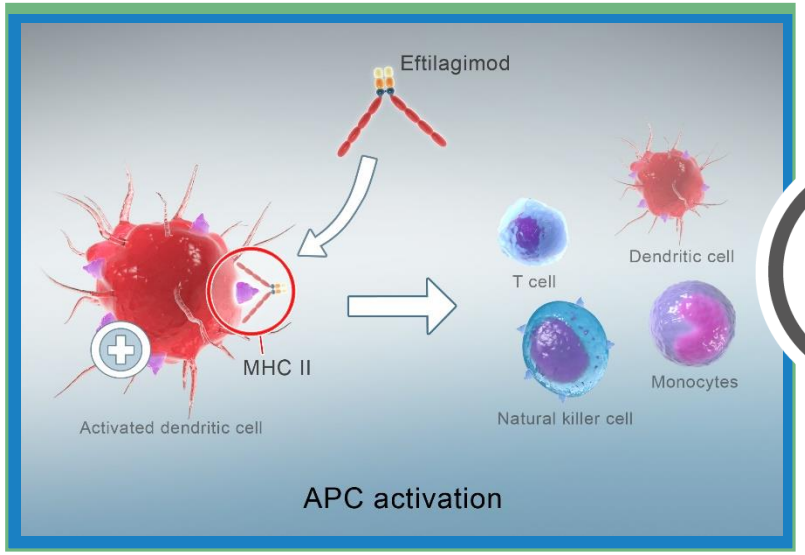
Travel Sponsorship & Speaker Honorarium: Immutep

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



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

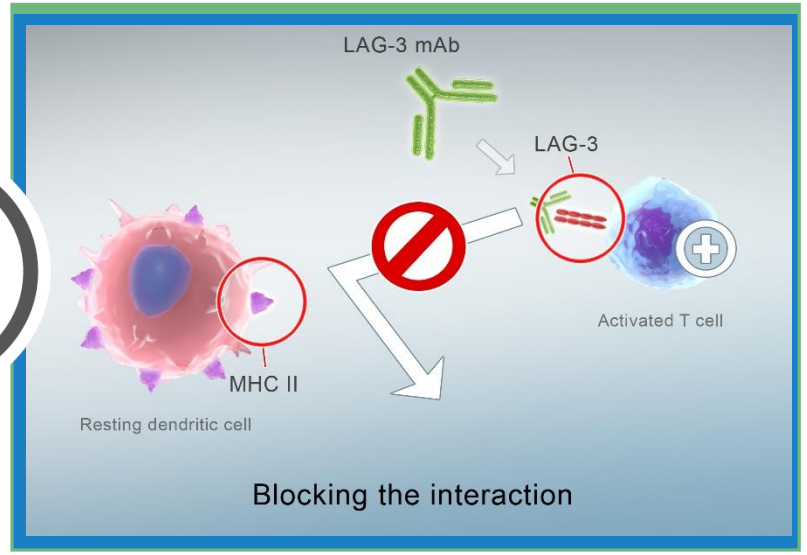
"PUSHING THE ACCELERATOR ON IMMUNE RESPONSES"



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"

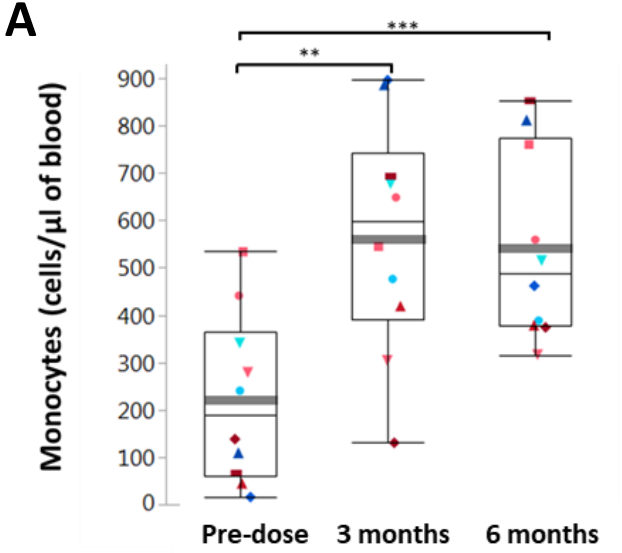


LAG-3 antagonist antibodies:

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

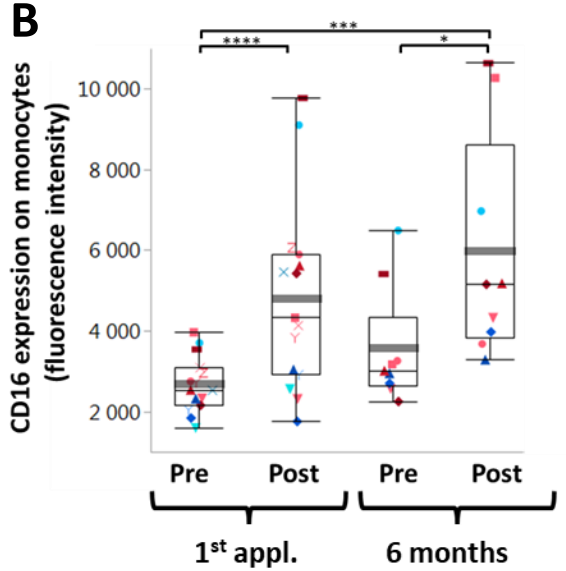
Pharmacodynamics eftilagimod alpha (IMP321)

A

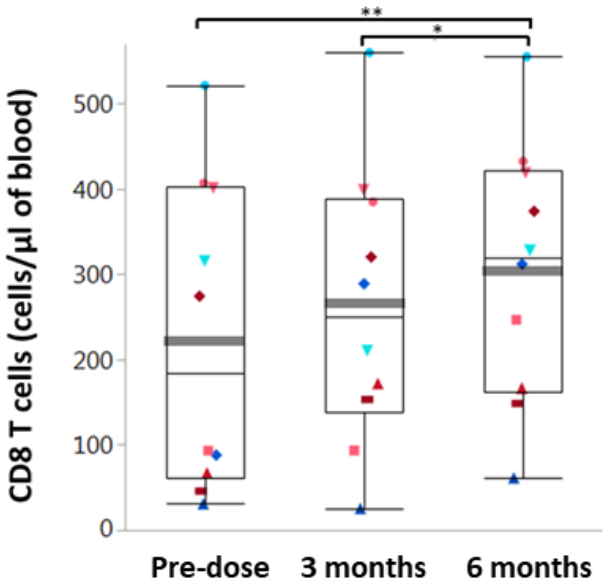


Primary target cells: Sustained increase of circulating Antigen-Presenting Cells (APCs) such as monocytes (A) and dendritic cells (not shown). Rapid activation of monocytes (CD16 (B) and CD40 (not shown).

B

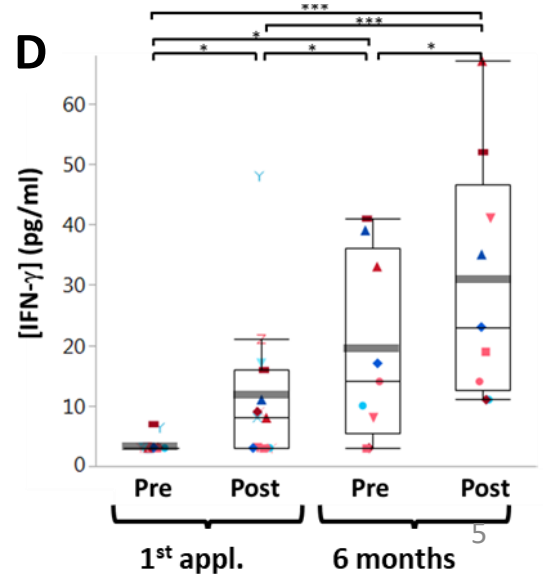


C



Secondary target cells: Sustainable increase in absolute numbers of effector cells such as i.e. CD8 T cells (C) and Natural Killer cells (not shown). IMP321 induces early and sustainable increase of Th1 biomarkers like IFN-γ (D) and IP-10 (not shown).

D



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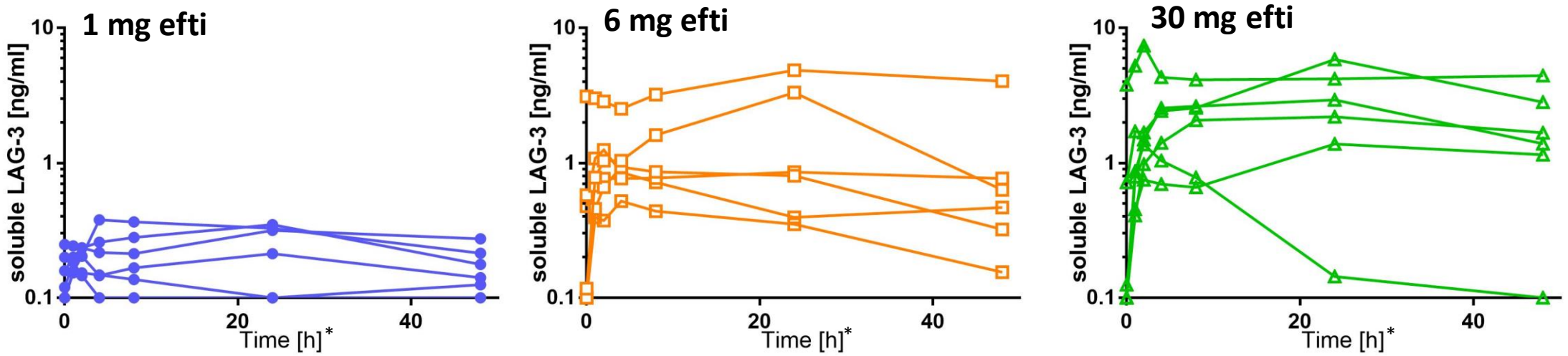
Pharmacokinetics eftilagimod alpha (IMP321)

Soluble LAG-3 (efti) blood concentration after 1st dose



- Dose proportional increase in PK parameters
- Variability between patients receiving the same dose
- Efti is an MHC II agonist: a few ng/ml in the blood is enough to see sustained APC activation

* Theoretical time points, actual measurement might differ

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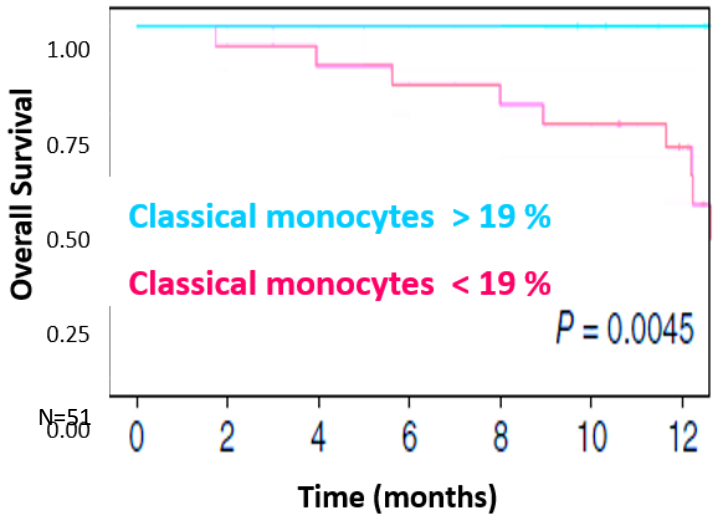
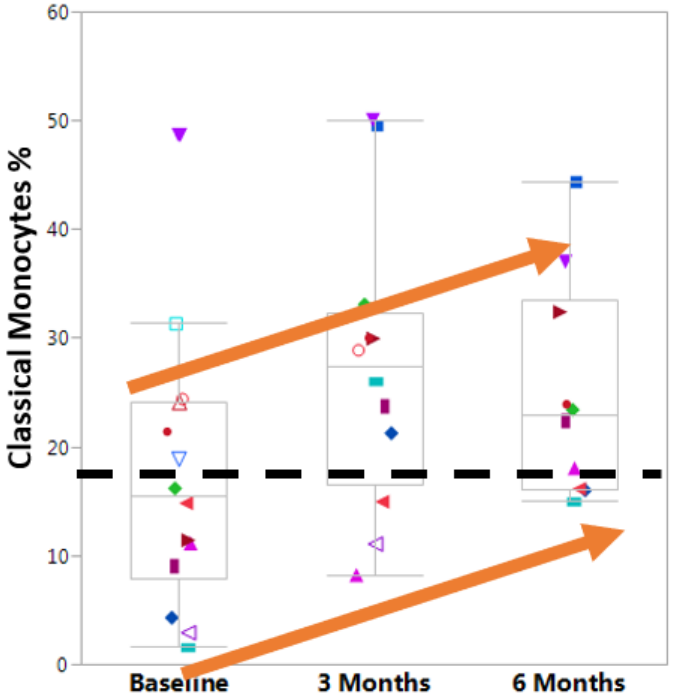
New Rationale for Combining eftilagimod alpha (IMP321) with PD-1 Antagonists (pembrolizumab)



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

- → Baseline innate immunity status seems to be important for the response and survival 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



N=15

Source: AIPAC stage 1

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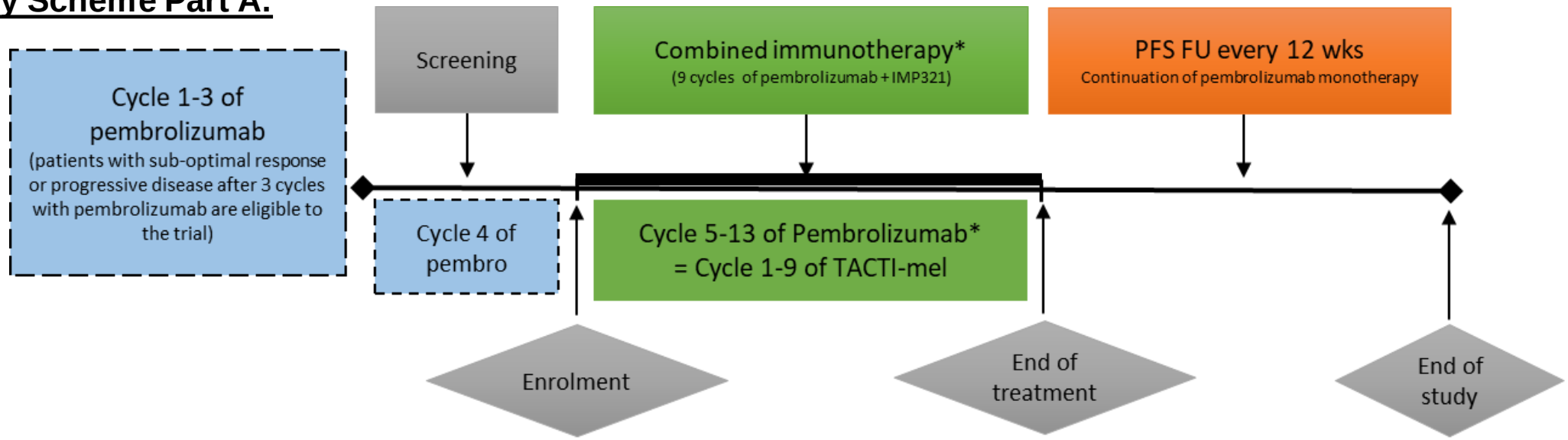
TACTI-mel: Trial Design

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: Safety Summary

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: Baseline Characteristics + Efficacy Summary

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 %)

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

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

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

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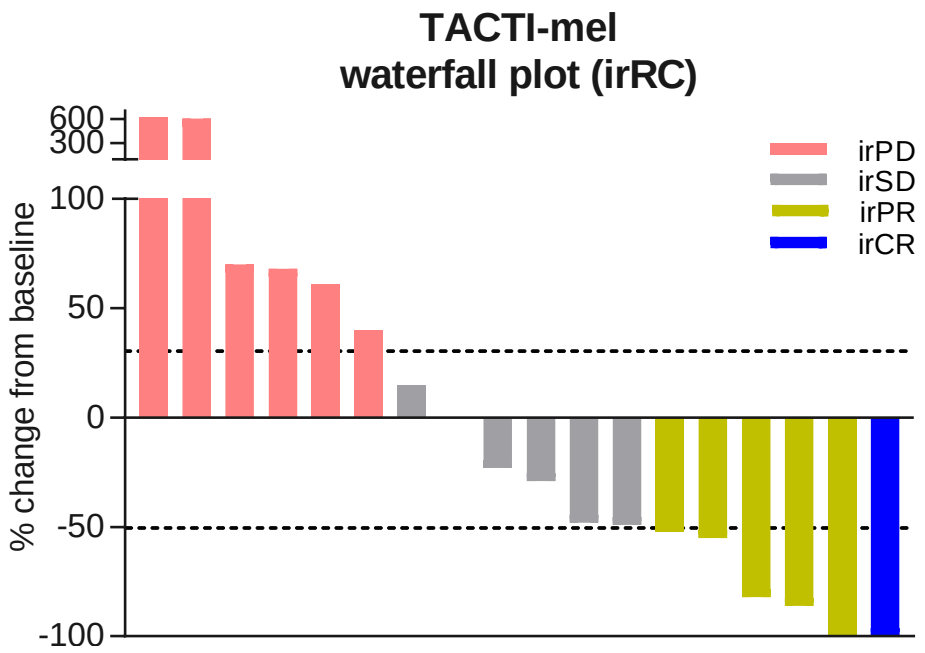
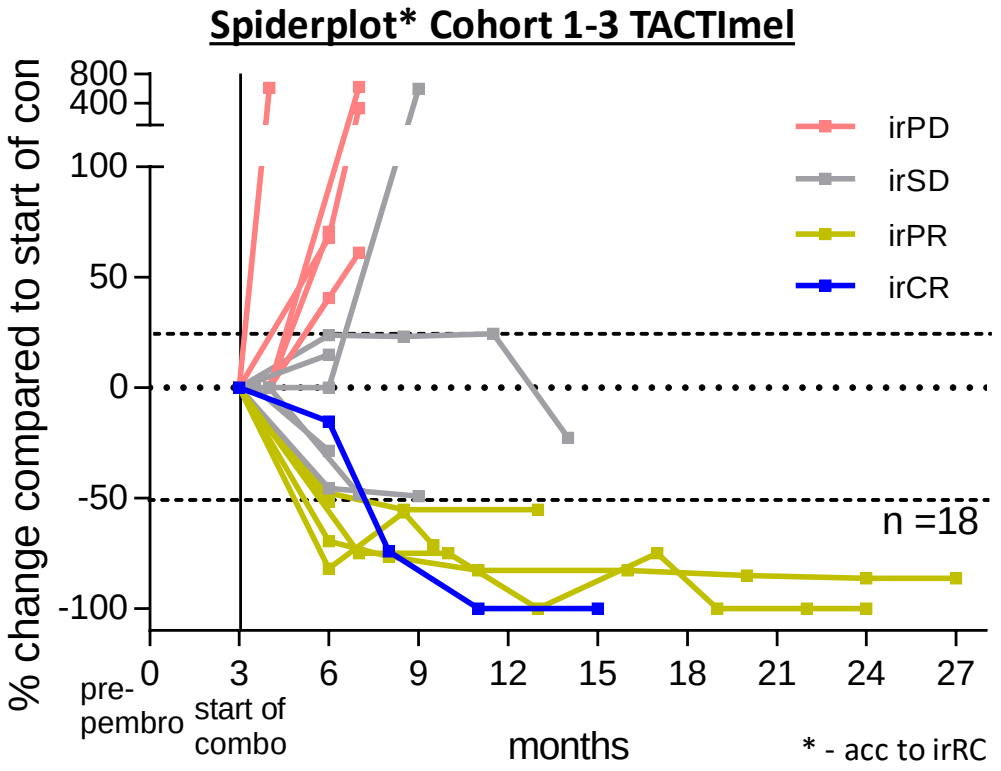
TACTI-mel: Response patterns





→ 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

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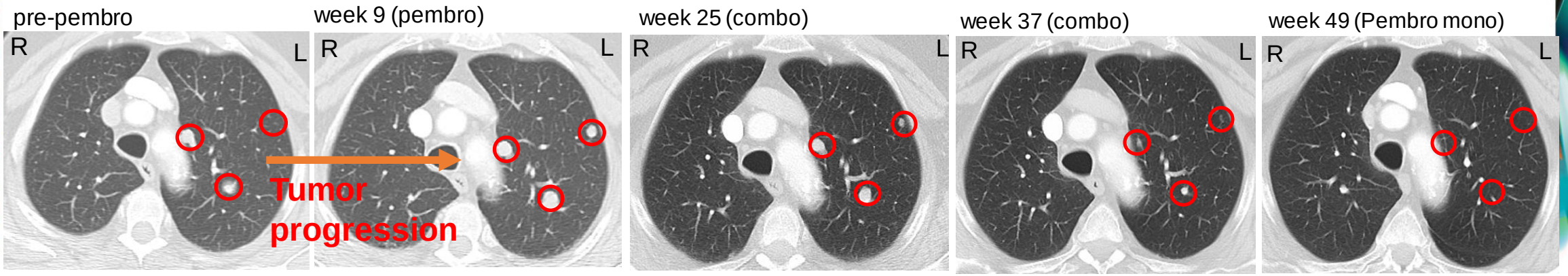
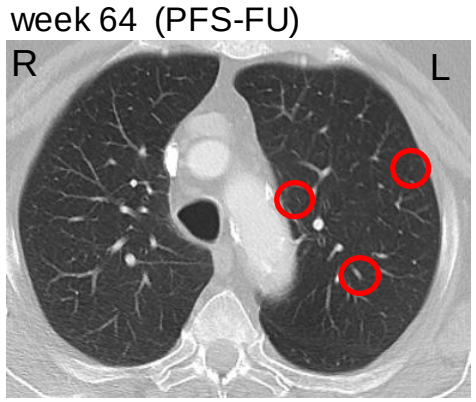
TACTI-mel: Single Case

- 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**

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Lessons and Take Home Messages

- Efti in combination with Pembrolizumab was well tolerated and no new safety concerns were observed
- The combination showed encouraging clinical activity in patients with sub-optimal response to pembrolizumab monotherapy
- TACTI-mel Part B is ongoing in Australia with no DLTs observed so far
- Results warrant further investigation of efti + pembrolizumab, potentially also in other indications (NSCLC and HNSCC) → TACTI-002 trial being initiated (NCT03625323; Poster for Abstract ID: 10328)

Acknowledgement and Thank You

We would like to thank to all patients and their families for participation

The sites and the study teams at:

- Royal Brisbane Womens Hospital, Brisbane, Queensland, Australia, 4029
- Princess Alexandra Hospital, Brisbane, Queensland, Australia, 4102
- Greenslopes Private Hospital, Brisbane, Queensland, Australia, 4120
- Fiona Stanley Hospital, Perth, Western Australia, Australia, 6150
- Ballarat Hospital, Ballarat, Victoria, Australia, 3353
- Alfred Hospital, Melbourne, Victoria, Australia, 3181
- Flinders Medical Centre, Adelaide, South Australia, Australia, 5042

The study was sponsored by **Immutep Australia PTY Ltd**