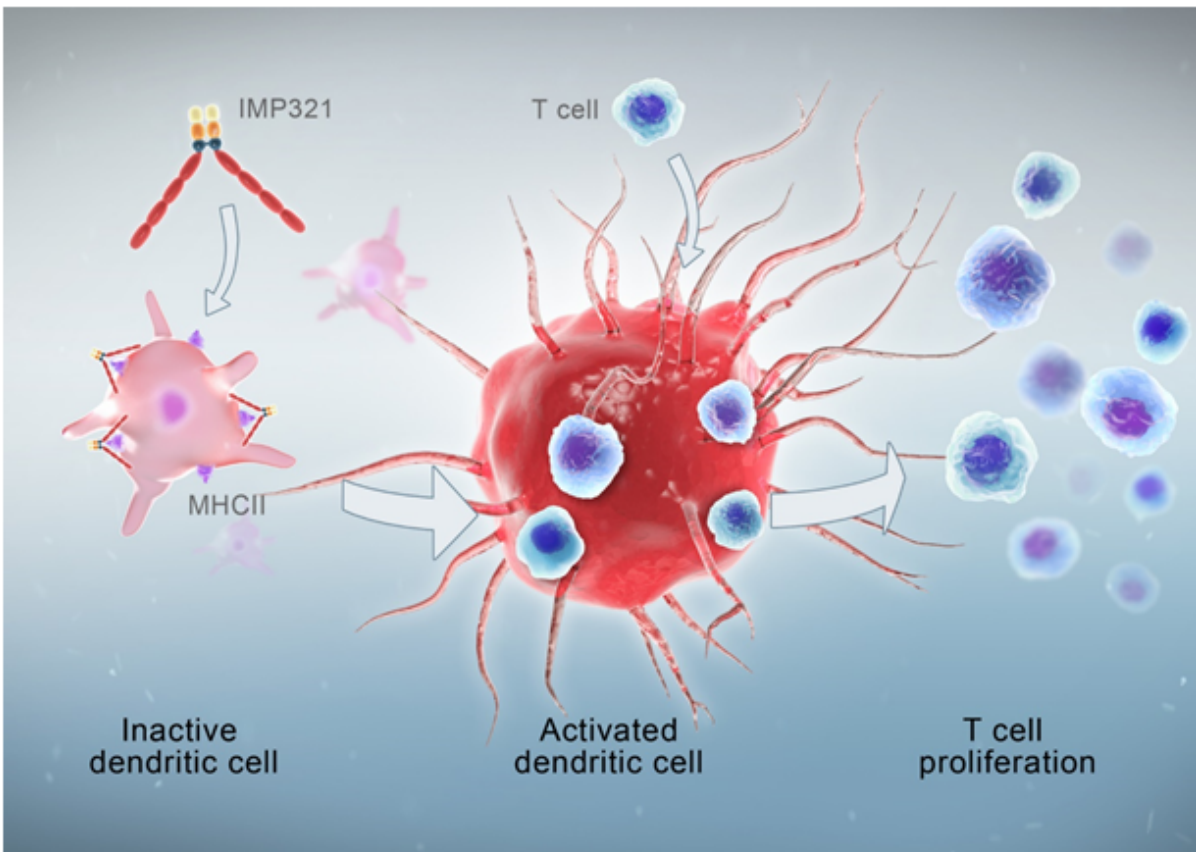


Pushing the accelerator and releasing the brake: testing the soluble LAG-3 protein (IMP321), an antigen presenting cell activator, together with pembrolizumab in unresectable or metastatic melanoma

Victoria Atkinson^{1,2}, Andrew Haydon³, Melissa Eastgate⁴, Amitesh Roy⁵, Adnan Khattak⁶, Christian Mueller⁷, Tina Dunkelman⁷, Chrystelle Brignone⁸, Frederic Triebel⁸:

- 1- Division of Cancer Services, Princess Alexandra Hospital, Woolloongabba and Gallipoli
 2- Medical Research Foundation Greenslopes Private Hospital, Greenslopes, Australia
 3- Alfred Hospital, Melbourne, Australia
 4- Medical Oncology Clinical Trials Unit, Royal Brisbane Womens Hospital, Herston, Australia
 5- Oncology Research, Flinders Centre for Innovation in Cancer, Bedford Park, Australia
 6- Cancer Centre Clinical Trials Unit, Fiona Stanley Hospital, Murdoch, Australia
 7- Clinical Development, Prima Biomed GmbH, Berlin, Germany
 8- Research & Development, ImmuteP S.A.S., Paris, France

Background



IMP321 (eftilagimod alpha), a LAG-3Ig fusion protein, is a MHC class II agonist that activates antigen-presenting cell (APC) such as dendritic cells and monocytes (primary target cells) and then CD8 T-cells (secondary target cells). The activation of the dendritic cell network and the subsequent T cell recruitment at the tumor site with IMP321 may lead to stronger anti-tumor CD8 T cell responses than observed with pembrolizumab monotherapy. We hypothesize that the combination of an APC activator with an immune checkpoint inhibitor (ICI) will increase efficacy without additional toxicity.

We report here initial results of the first 2 cohorts of a dose escalation Phase 1 clinical trial investigating the use of pembrolizumab in combination with IMP321 at different dose levels (1 and 6 mg) in patients with unresectable or metastatic melanoma (TACTI-mel clinical trial).

For more information, please visit: <http://primabiomed.com.au/products/LAG-3.php>

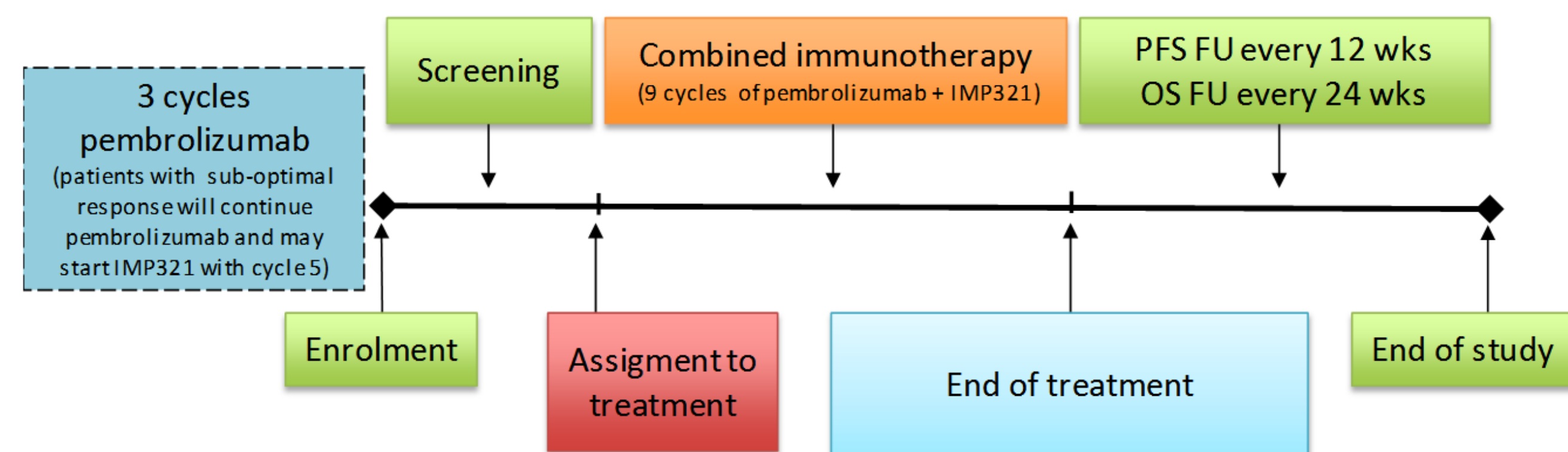


The trial identifiers are IMP321-P012 (sponsor code) and NCT02676869 (ClinicalTrials.gov). Corresponding author: Victoria Atkinson, Victoria.Atkinson@health.qld.gov.au



Trial Design

- Phase I, multi-center, open-label, dose escalation
- Recruitment of 18 patients at 6 sites in Australia
- Patients are on pembrolizumab monotherapy. After 3 cycles patients response to pembrolizumab is investigated. In the case of suboptimal response (irPR, irSD, irPD) and measurable disease patients are eligible for the study
- Beginning with cycle 5 of pembrolizumab, IMP321 injections are administered every 2 weeks for a duration of 6 months (maximum of 13 injections)
- In each cohort (1, 6, or 30 mg IMP321), the first 3 patients will start treatment one week apart. After these 3 patients complete the safety observation period (24 hours after the 3rd injection), the remaining 3 patients can be enrolled in parallel
- Decision for dose escalation is done by the Data Safety Monitoring Board (DSMB). If more than 2 patients per cohort experience a dose-limiting toxicity (DLT), this dose will be considered at maximum tolerated dose



Objectives

Primary:

- To evaluate the safety, tolerability, and recommended Phase 2 dose of IMP321 when combined with anti-PD-1 treatment in patients with unresectable or metastatic melanoma

Secondary:

- To assess pharmacokinetics and pharmacodynamics of different doses of IMP321 when combined with anti-PD-1 treatment in patients with unresectable or metastatic melanoma
- To assess response to treatment by immune related response criteria (irRC) and response evaluation criteria in solid tumors (RECIST 1.1)
- To assess objective response rate, time to and duration of response, time to next treatment, and progression-free survival

Preliminary Safety Results

- Patients received median 8.5 (range 3-13) IMP321 injections and median of 5 (range 2-9) pembrolizumab infusions within the treatment period
- No dose reductions were applied

Safety Parameter	N (%)
Pts with any AE	11 (92)
Pts with any SAE	3 (25)
No of SAEs	3 (25)
Pts with any grade 3/4 AE	4 (33)
thereof rel. to IMP321	1 (8)
thereof rel. to Pembrolizumab	1 (8)

Adverse Event*, n(%)	Any grade	Grade 3 or 4
Arthralgia	2 (17)	-
Diarrhea	2 (17)	-
Fatigue	5 (42)	-
Nausea	3 (25)	-
Rash	5 (42)	1 (8)

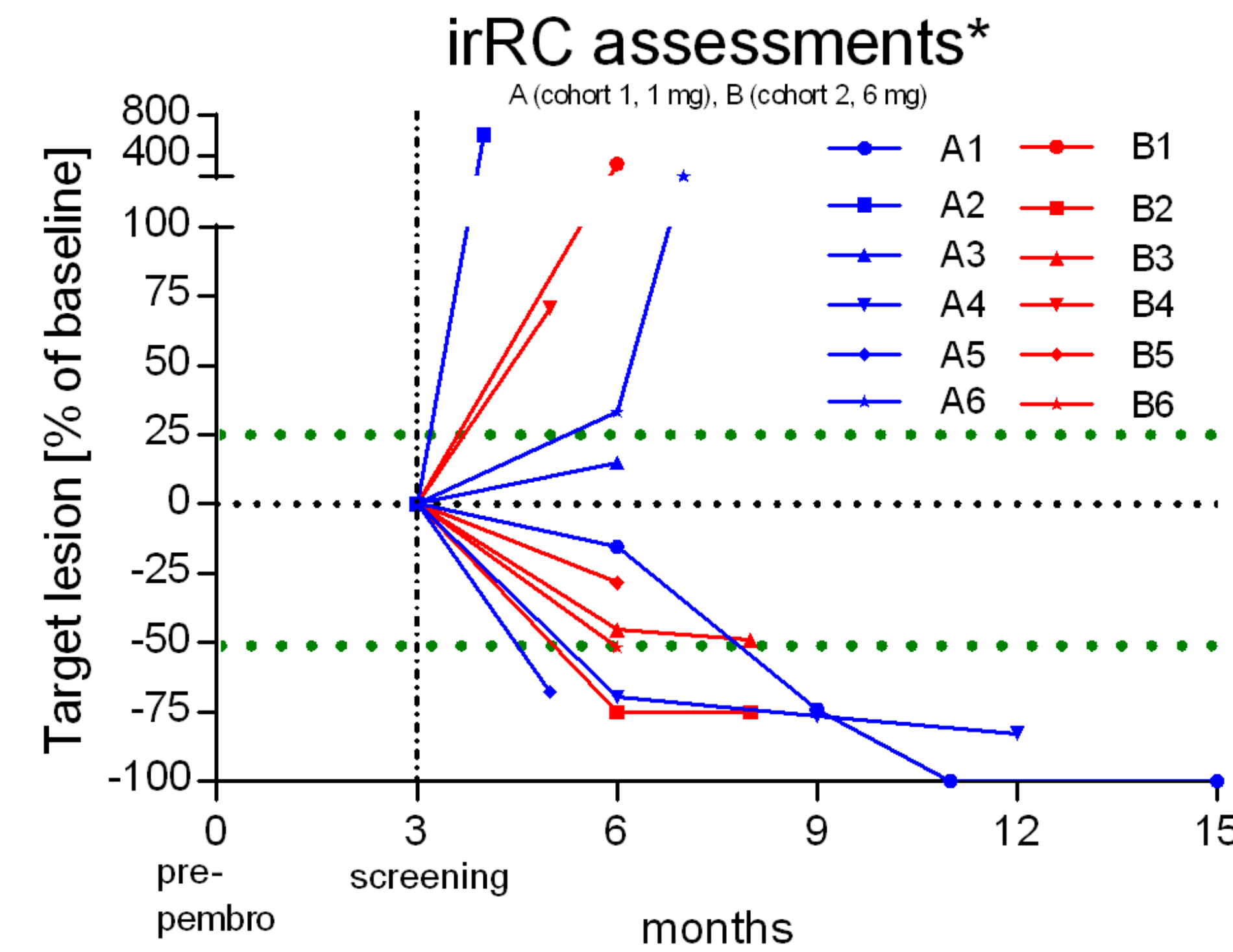
* - Adverse events occurred in > 10 % of pts

- 1 death (intracranial hemorrhage), not related to IMP321 or pembrolizumab
- 3 SAEs in 3 pts; no treatment related SAE
- 6 AEs grade 3 or 4 in 4 patients; thereof 2 treatment related AEs grade 3 or 4 in 1 patient:
 - decreased renal function grade 3 and maculo papular rash grade 3 (→ only pt with treatment delay)
- No treatment discontinuations due to AE
- No dose limiting toxicities in both cohorts
- No noteworthy differences between the two dose groups (1 and 6 mg IMP321)

AE...adverse event
 APC...Antigen-presenting cell
 DCR...Disease Control Rate
 DLT...dose-limiting toxicity
 DSMB...Data Safety Monitoring Board
 FU...follow up
 ICI...immune checkpoint inhibitor
 irPD...progressive disease

irPR...immune-related partial response
 irRC...immune related Response Criteria
 irSD...immune-related stable disease
 PFS...progression-free survival
 Pt...patient
 RECIST...Response Evaluation Criteria In Solid Tumors
 RR...Response Rate
 SAE...Serious adverse event

Baseline Demographics and Efficacy Results



* - 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

Baseline Variable	Total (n=12)
Median (range) age, year	61 (48-88)
Men, n (%)	11 (92)
Caucasian, n (%)	12 (100)
ECOG 0, n (%)	11 (92)
Visceral disease, n (%)	10 (83)
Elevated LDH, n (%)	8 (67)
BRAF mutation n (%)	2 (17)
Prior BRAF/MEK/IPI treatment	4 (33)

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)

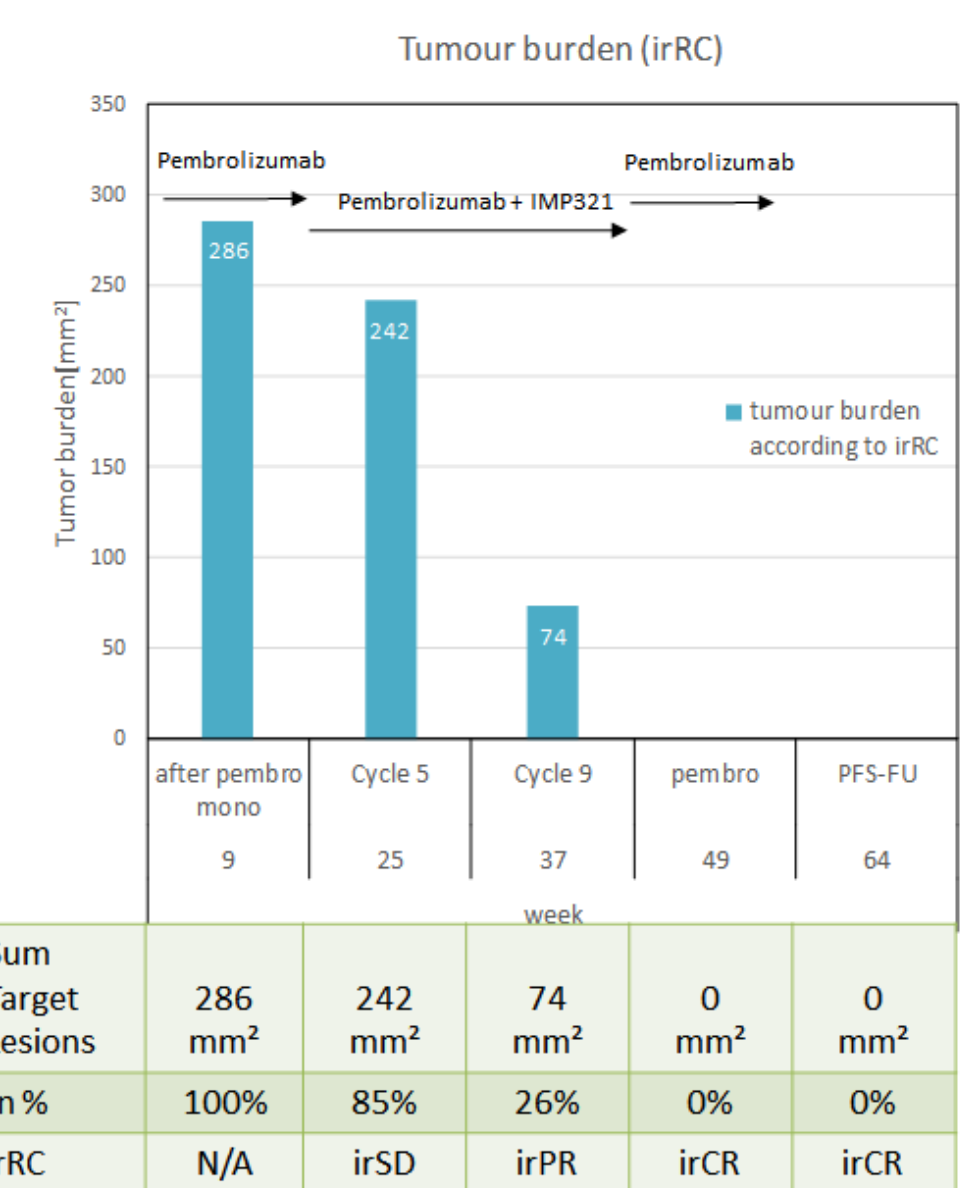
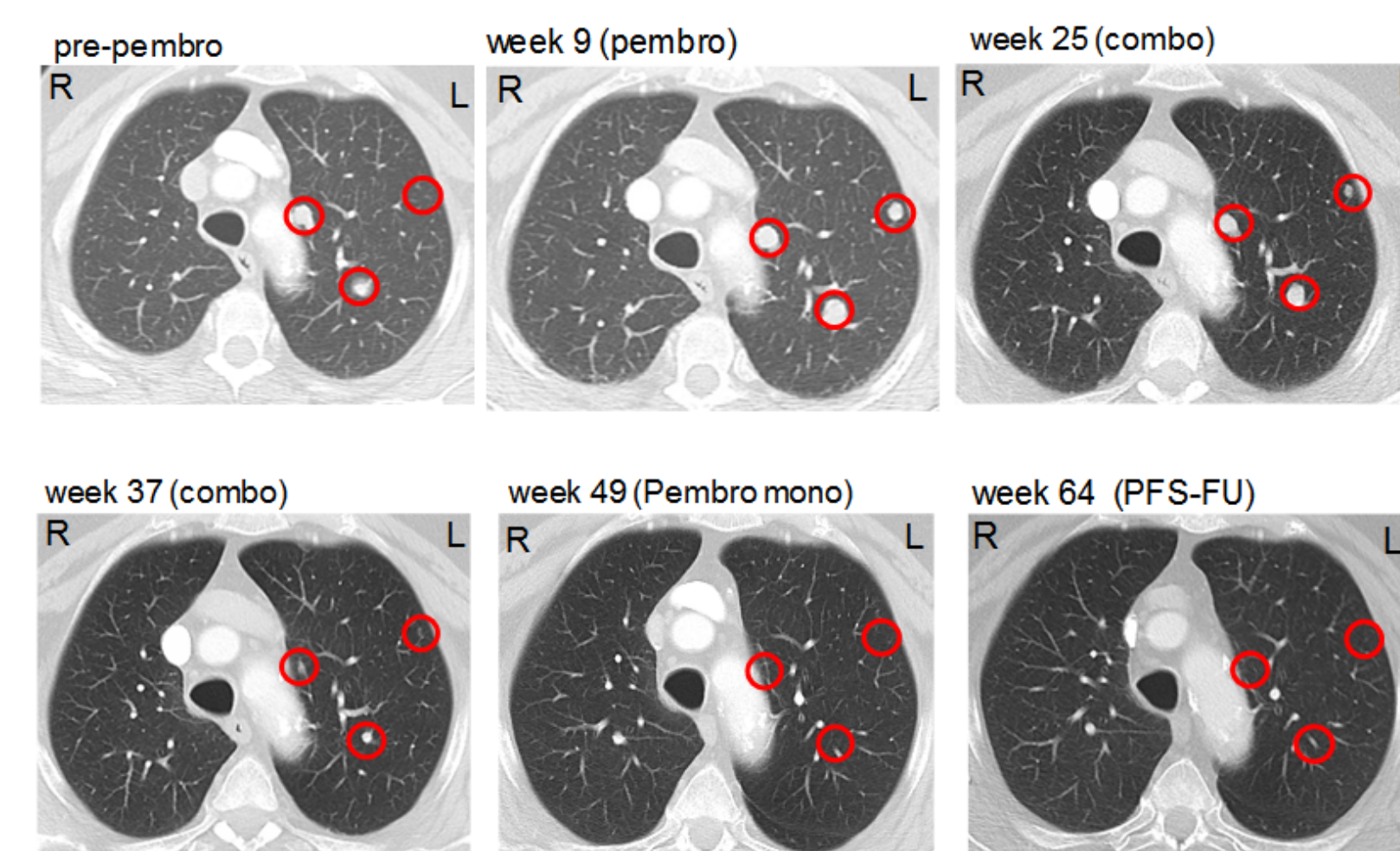
- Vast majority visceral disease and elevated LDH at study entry
- 5/12 (42 %) had PD as best response on pembrolizumab monotherapy

- 7/12 (58 %) patients with suboptimal response or progression on pembrolizumab had a tumor reduction during the study**
- One confirmed complete response was observed**

Patient Case A1 (Pembrolizumab + 1 mg IMP321)

Patient characteristics

- Male, Caucasian, 84 years
- Diagnosis at screening: stage IV visceral disease (lung and thorax metastases) → best response pembrolizumab monotherapy was irPD
- Patient has completed the study treatment, progression-free survival follow up (incl. Pembrolizumab monotherapy) was stopped due to patient wishes after week 64
- Best Response: confirmed complete response**



Conclusion:

- Combination of IMP321 (1 and 6 mg) and pembrolizumab in advanced metastatic melanoma patients is safe and well tolerated**
- Anti-tumor activity (tumor reduction) was observed in 7/12 patients (58 %) in this study; prior to study all of these patients either had a suboptimal response to or had disease progression when treated with pembrolizumab monotherapy**
- Data presented support the hypothesis that combining an APC activator (IMP321) with a checkpoint inhibitor (pembrolizumab) results in a therapeutic synergy and a potential clinical benefit over checkpoint inhibitor monotherapy**
- The third cohort (30 mg) of this clinical trial is ongoing**
- Data presented support further investigation of IMP321 in combination with PD-1/ PD-L1 checkpoint inhibitors in different tumor types**