Safety and PD-1 receptor occupancy with low dose Nivolumab in adults living with HIV on antiretroviral therapy: NIVO-LD

Prof. James H McMahon PhD FRACP

Department of Infectious Diseases, Alfred Health and School of Translational Medicine, Monash University, Melbourne, Victoria, Australia

theAlfred
Part of AlfredHealth

MONASH University

Doherty Institute

THE UNIVERSITY OF MELBOURNE

The Royal Melbourne Hospital

A joint venture between The University of Melbourne and The Royal Melbourne Hospital

Rationale for anti-PD1 for HIV cure

- Latent virus is enriched in cells that express PD-1 and other immune checkpoints (CTLA-4, TIGIT) and immune checkpoint blockade can reverse latency in vitro, ex vivo and in vivo
- Exhausted T-cells that express PD-1 and other immune checkpoints can persist in people with HIV on ART
- In SIV-infected non human primates on ART, anti PD-1 given alone or in combination with anti-IL-10 at the time of ART interruption resulted in lower viral set point
- Therefore, given anti PD-1 can both reverse latency AND enhance HIV-specific T-cell function, it may play a role in cure strategies

Chomont, Nat Med 2009; Fromentin, Plos Path 2016; McGarry, Immunity 2017; Evans AIDS 2018; Fromentin Nature Comms 2019; Uldrick Sci Transl Med 2022; Rasmussen Cell Rep Med 2022; Okoye, CROI, 2020; Pereira Ribeiro, Nat Immunol 2024

Low dose anti-PD1 has potentially lower adverse events and can achieve high receptor occupancy

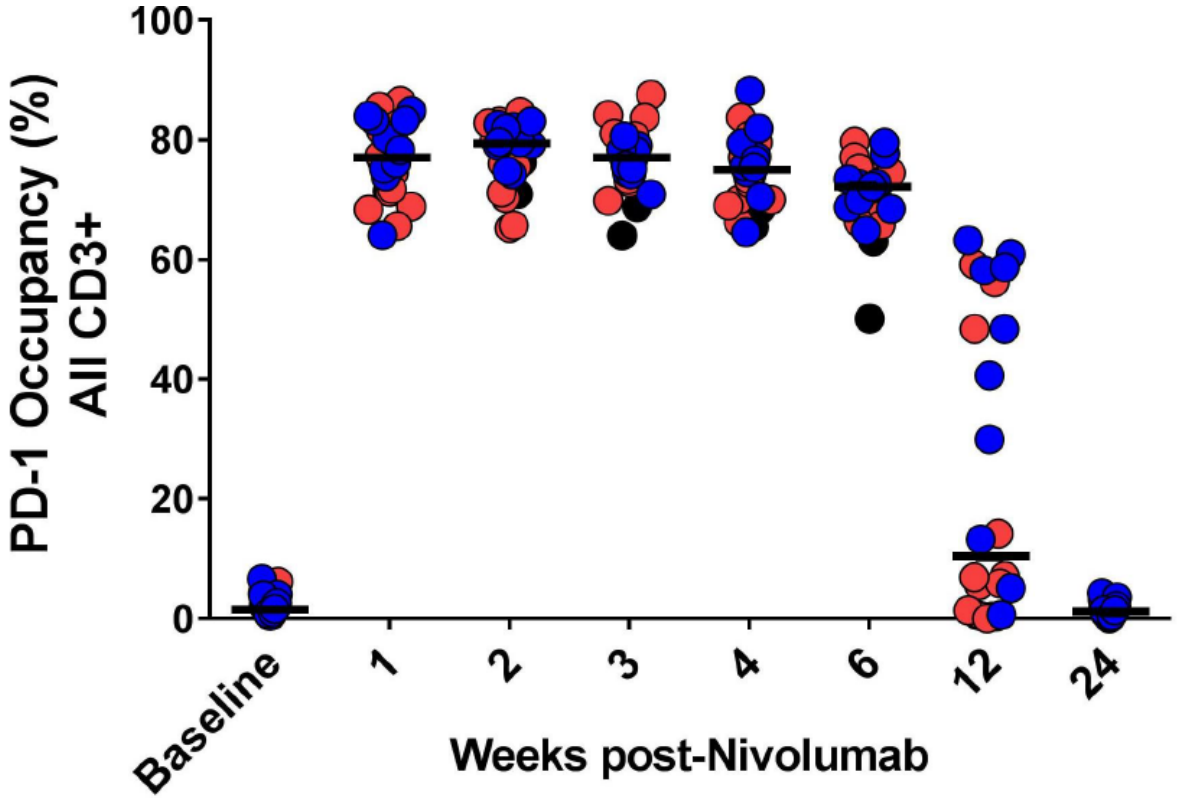
Initial dose finding studies in oncology and HCV for anti-PD1 included

- Single low dose (n=147; 3 separate studies)
- Multiple low dose (n=797; 4 separate studies)

Immune related AEs after low dose anti-PD1 were rare

- Single low dose 0.3 mg/kg (n=27) - no Grade 3-4 irAEs
- Multi dose 0.3 mg/kg (n=50) - two Grade 3-4 irAEs

Low dose anti-PD1 in chronic hepatitis B infection resulted in high and prolonged receptor occupancy



Red/blue = 0.3 mg/kg n=22; black = 0.1 mg/kg n=2

1 Topalian NEJM 2012, 2 Brahmer JCO 2010, 3 Choueiri Clin Cancer Res 2016, 4 George JAMA Oncol 2016, 5 Gardiner PLoS One 2013, 6 El-Khoueiry Lancet 2017, 7 Gane J Hepatol 2019

Hypothesis and objectives

Hypothesis

We hypothesize that single low dose nivolumab will be safe and induce high levels of receptor occupancy in blood and lymph node

Primary objective

To determine the safety and duration of PD-1 blockade in blood and lymph node following single low-dose nivolumab

Secondary objectives

To determine the effect of single low-dose nivolumab and a time-limited ART interruption on HIV-specific T-cell function and the transcriptional activity and frequency of latently infected cells

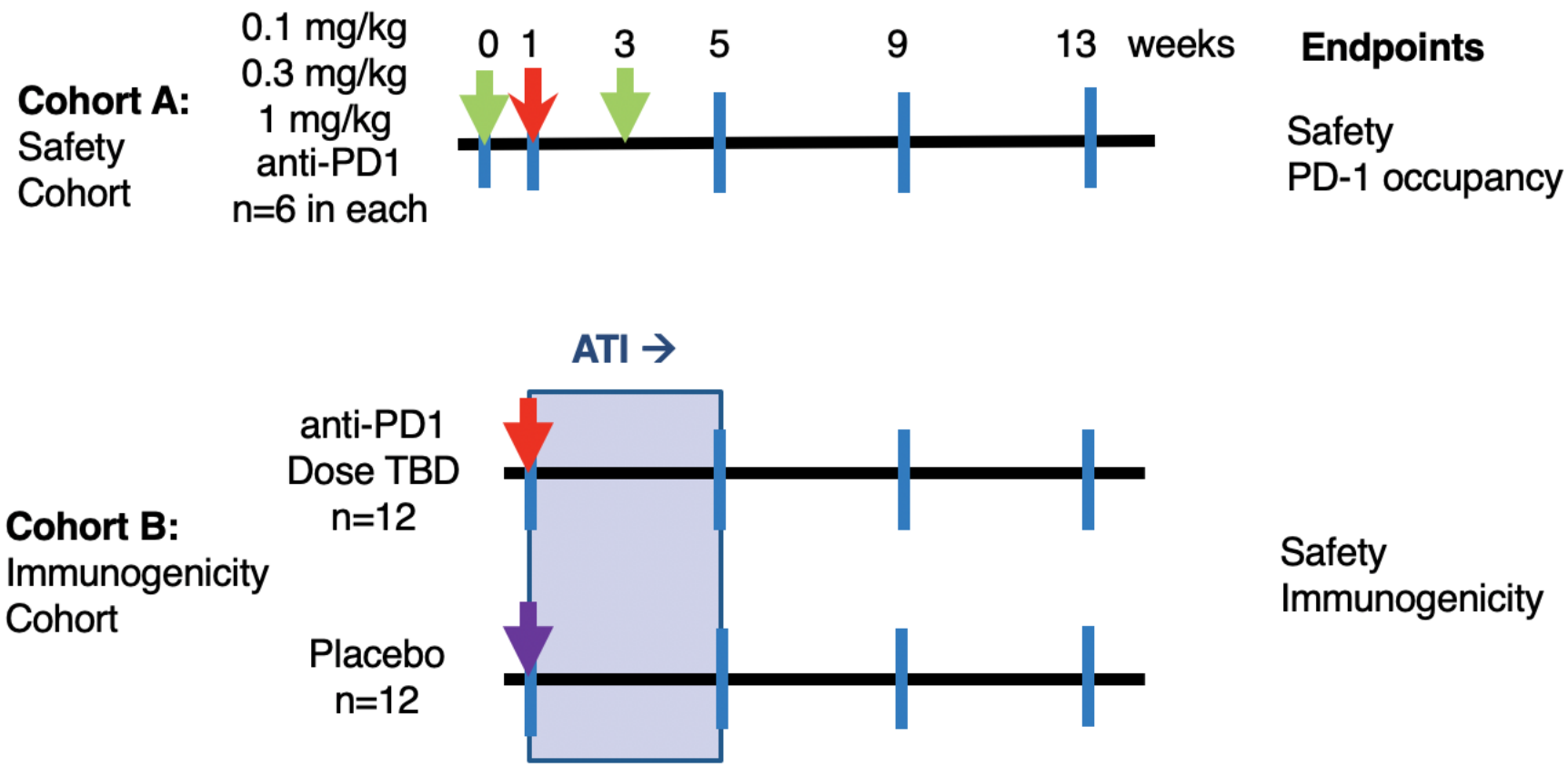
Study design

Low dose nivolumab

FNA

Placebo

HIV-infected, on ART; VL <50 copies/ml for 2 years; CD4 > 500 cells/ul



Selected inclusion and exclusion criteria

Inclusion

- Viral load > 400 copies/mL prior to initiation of ART;
- Age 18 – 65 years;
- HIV-1 plasma RNA <50 copies/mL for >2 years
- CD4+ T cell counts >500 cells/

Exclusion

- Autoimmune disease, interstitial lung disease, COPD, Type 1 diabetes
- History of TB or IRIS
- Presence of autoantibodies: ANA, GAD, TPO
- Positive Quantiferon Gold
- AST or ALT > 1.25 x ULN

Primary and secondary endpoints

Primary

Safety defined as AEs of grade 3 or higher definitely, probably or possibly related to study treatment

Secondary

Cohort A (safety cohort):

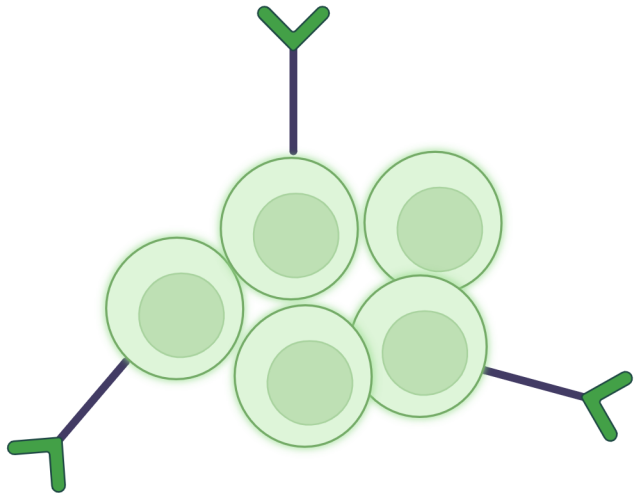
- Percentage PD-1 receptor occupancy in blood and lymph node
- Safety - all AEs related to study treatment
- Viral reservoir assessments
- HIV-specific T-cell responses (Number of CD4 and/or CD8 T-cell responses to Gag and Pol/Env/Nef peptides by intracellular cytokine staining in blood and lymph node)

Cohort B (immunogenicity cohort):

- Safety - all AEs related to study treatment
- Proportion of participants with a viral load > 50 and > 1000 c/ml post ATI
- Time to viral rebound defined as first VL > 50 c/mL
- Viral reservoir assessments
- Percentage PD-1 receptor occupancy in blood
- HIV-specific T-cell responses

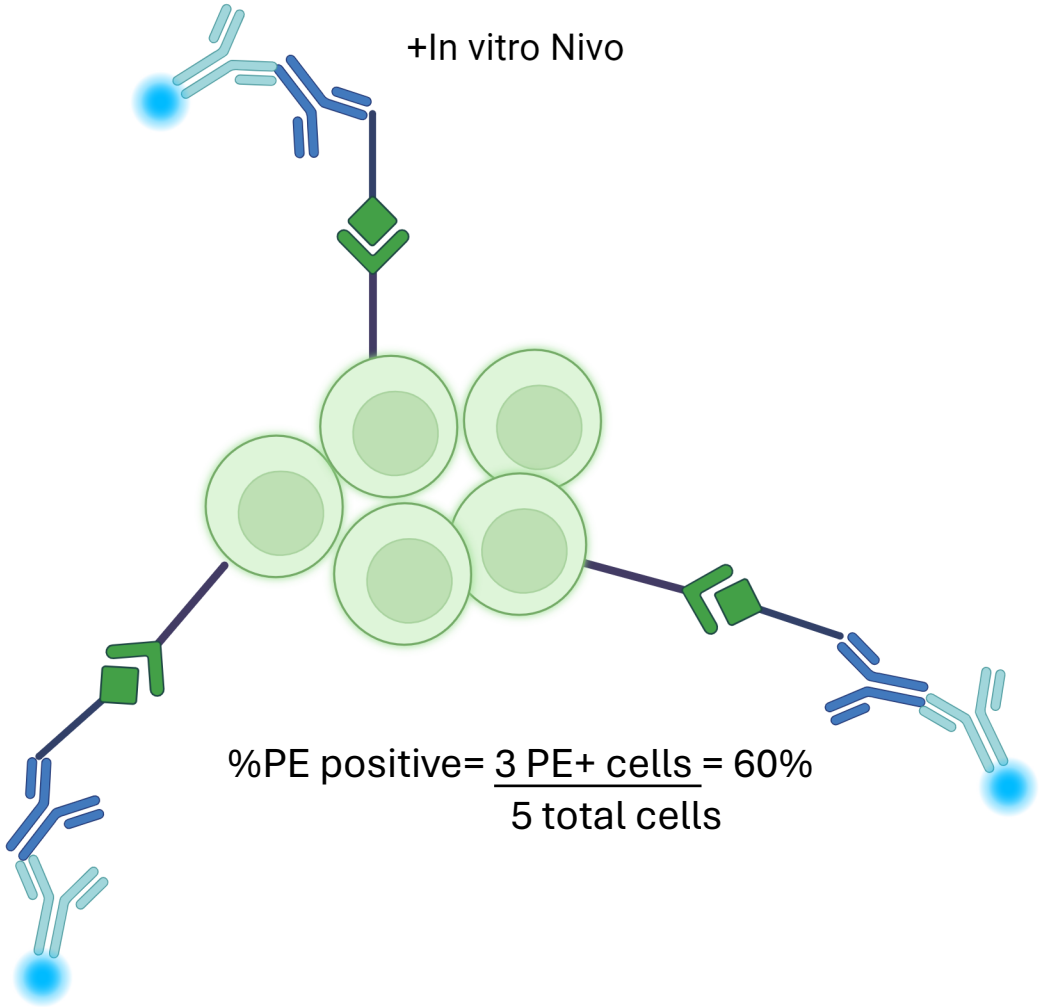
PD-1 occupancy: baseline measurements (pre nivolumab)

+IgG4 isotype control

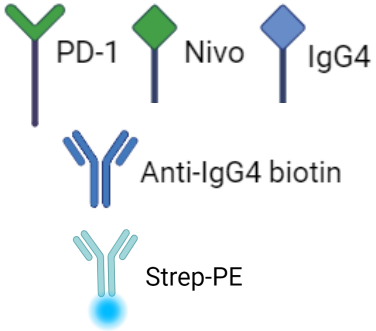


%PE positive= background only (<1%)

+In vitro Nivo



%PE positive= 3 PE+ cells / 5 total cells = 60%



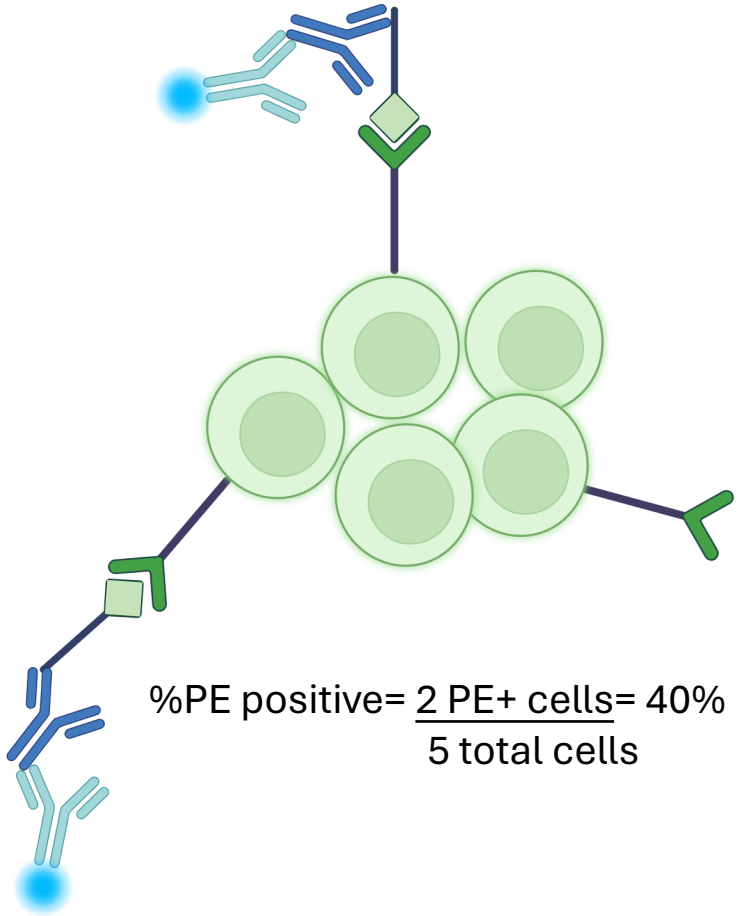
$$\%\text{PD-1 Occupancy} = \frac{\%\text{PE+ cells incubated with IgG4}}{\%\text{PE+ cells incubated with Nivolumab}}$$

$$\text{Baseline occupancy} = \frac{1}{60}\% = < 1$$

Based on protocol by Daniel Verdon, WEHI

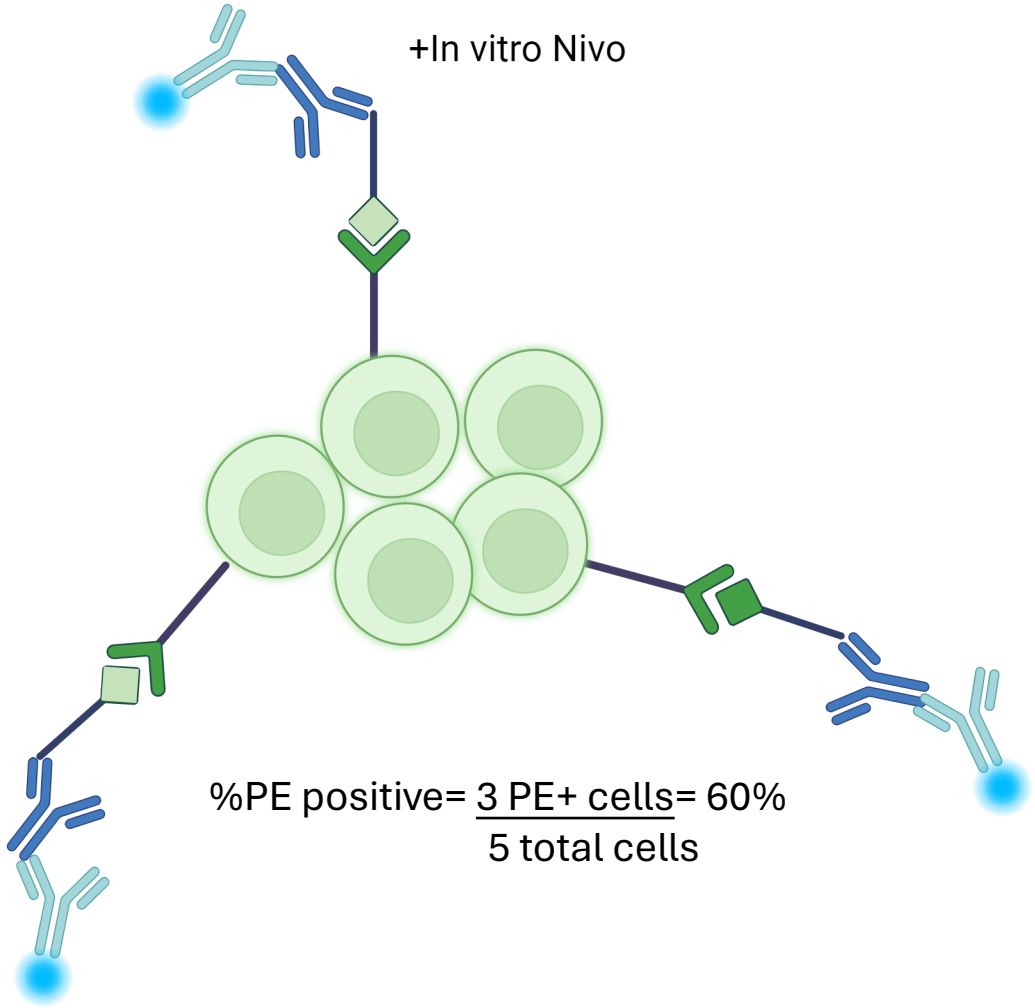
PD-1 occupancy: post nivolumab infusion

+IgG4 isotype control

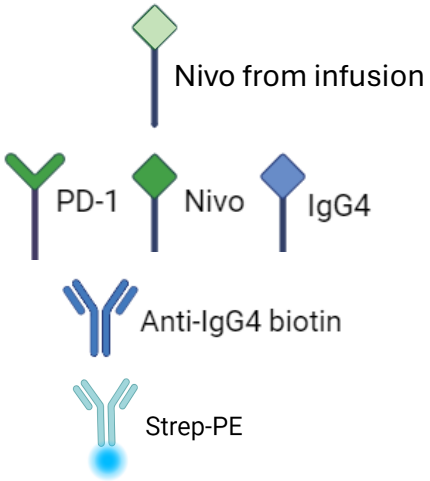


%PE positive= 2 PE+ cells= 40%
5 total cells

+In vitro Nivo



%PE positive= 3 PE+ cells= 60%
5 total cells



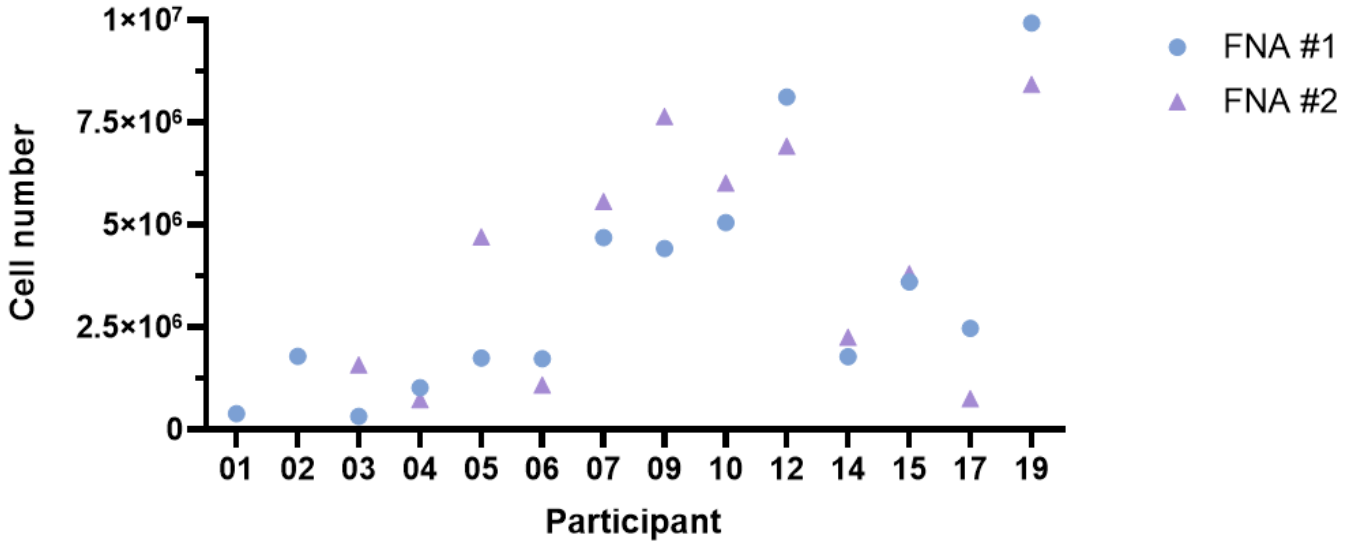
%PD-1 Occupancy = $\dfrac{\textbf{\%PE+ cells incubated with IgG4}}{\textbf{\%PE+ cells incubated with Nivolumab}}$

Occupancy following infusion= $\dfrac{40}{60} = 67$ **%**

Based on protocol by Daniel Verdon, WEHI

Cell recovery from fine needle aspirates

	Participant	FNA #1 - Baseline	FNA #2 – Week 3
Healthy donors (to set up assay)	01	385,000	*Only 1 FNA
	02	1,785,000	*Only 1 FNA
Arm 1: 0.1mg/kg Nivolumab	03	324,000	1,575,000
	04	1,020,000	729,000
	05	1,749,000	4,700,000
	06	1,730,000	1,090,000
	07	4,690,000	5,570,000
	09	4,420,000	7,650,000
Arm 2: 0.3mg/kg Nivolumab	010	5,055,000	6,020,000
	012	8,120,000	6,920,000
	014	1,779,000	2,250,000
	015	3,605,000	3,805,000
	017	2,470,000	750,000
	019	9,930,000	8,430,000



Participant number and demographics

Month	HIV Neg	Cohort A 0.1 mg/kg	Cohort A 0.3 mg/kg	Cohort A 1 mg/kg	Cumulative
10-2022	2	-	xx	xx	2
08-2023	-	7	xx	xx	9
11-2023	-	-	3	xx	12
02-2024	-	-	2	xx	14
05-2024	-	-	3	xx	17
08-2024	-	-	2	xx	19
11-2024	-	-	-	4	23
Total	2	7[a]	10[b]	4[c]	23

[a] One screen failure (positive ANA)
[b] Four screen failures (2 positive ANA, 2 positive GAD antibodies)
[c] Two screen failure (2 positive ANA)

Characteristic	HIV negative, N = 2	Cohort A 0.1 mg/kg N = 7	Cohort A 0.3 mg/kg N = 10	Cohort A 1 mg/kg N = 4
Age	47, 35	50 (44, 52)	46 (35, 53)	48 (43, 52)
Gender				
Male	1	6 (86)	9 (90)	4 (100)
Female	1	1 (14)	1 (10)	-
Other	-	-	-	-

Adverse events: nivolumab 0.1 mg/kg

Related adverse events	Severity			Day of Onset (Median and Range)	Duration of symptoms (Median and Range)	Total
	Mild	Moderate	Severe			
Clinical (n=6)						
Bruising groin biopsy site	6	-	-			6
Pain groin biopsy site	1	-	-			1
Warm Sensation	1	-	-	7	1	1
Laboratory (n=1)						
Increased Aspartate aminotransferase	1	-	-	35	34	1

No immune related events

One serious adverse event: appendicitis (Day 42. presented with 3 days abdominal pain, unrelated)

Adverse events: nivolumab 0.3 mg/kg

Related adverse events	Severity			Day of Onset (Values)	Duration of symptoms (Values)	Total
	Mild	Moderate	Severe			
Clinical (n=6)						
Anorexia*	1	-	-	8	2	
Nausea*	1	-	-	8	2	
Fatigue*, #	6	-	-	8,7,7,7,7,7	2,2,1,1,1,2	
Visual Aura #	1	-	-	7	1	
Diarrhoea #	1	-	-	9	1	
Bruising groin biopsy site	5	-	-	3,0,0,0,0	4,16,10,3,3	5
Pain groin biopsy site	4	-	-	0,0,0,0	3,10,3,3	4
Laboratory (n=1)						
Increased Aspartate aminotransferase	-	-	1	35	6	1
Increased Alanine aminotransferase	-	1	-	35	6	1

One possible immune related event – elevated liver function tests (PID 019)
One unrelated event - elevated liver function tests (PID 015)
*, # Same participant

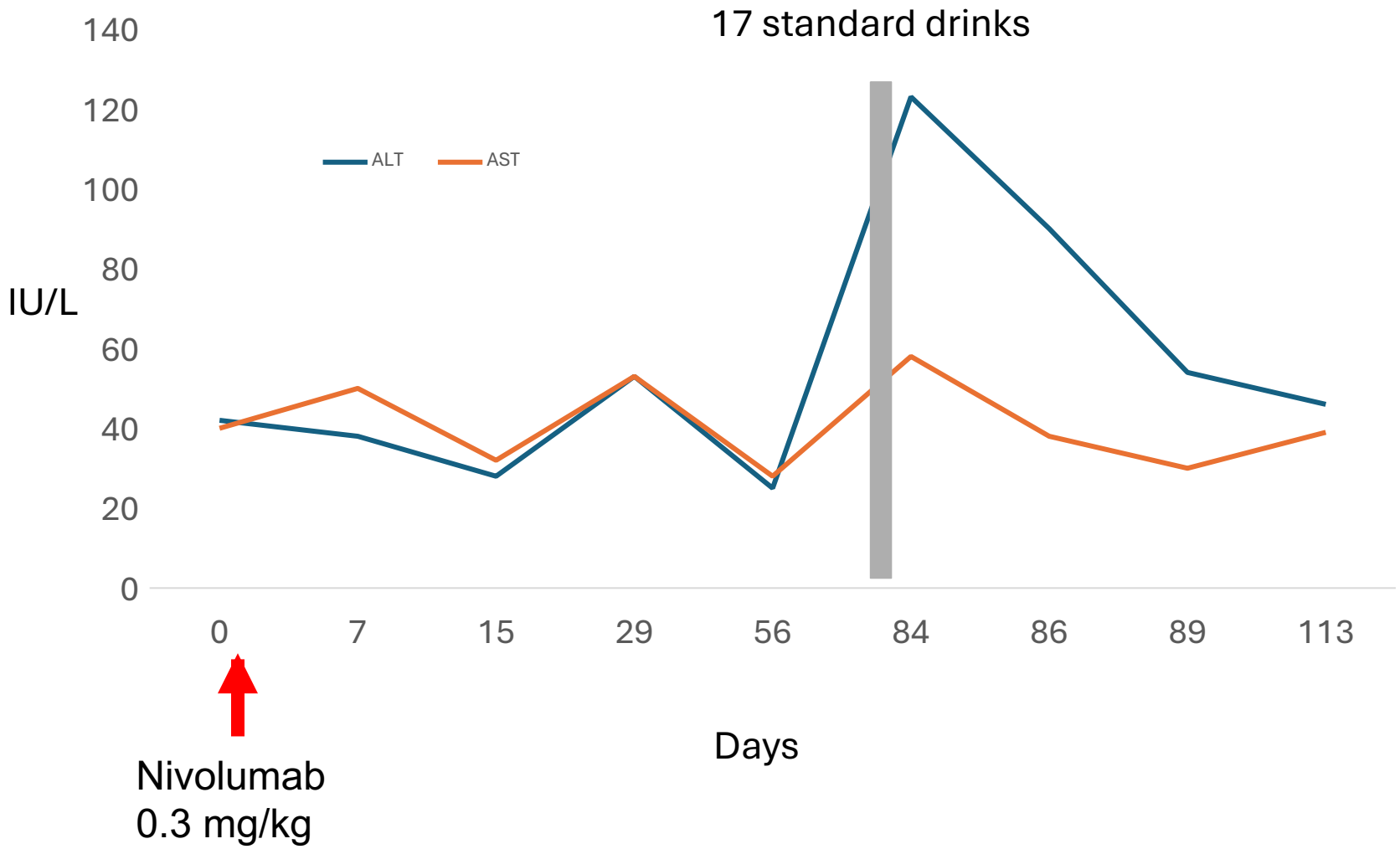
Liver function abnormalities (PID 015, 0.3 mg/kg)

Clinically well throughout.

17 standard drinks on Days 82-83

Rapid LFT reduction over week following 17 standard drinks and abstaining

Increased LFTs considered related to EtOH and ***not related to Nivolumab***



Liver function abnormalities (PID 019, 0.3 mg/kg)

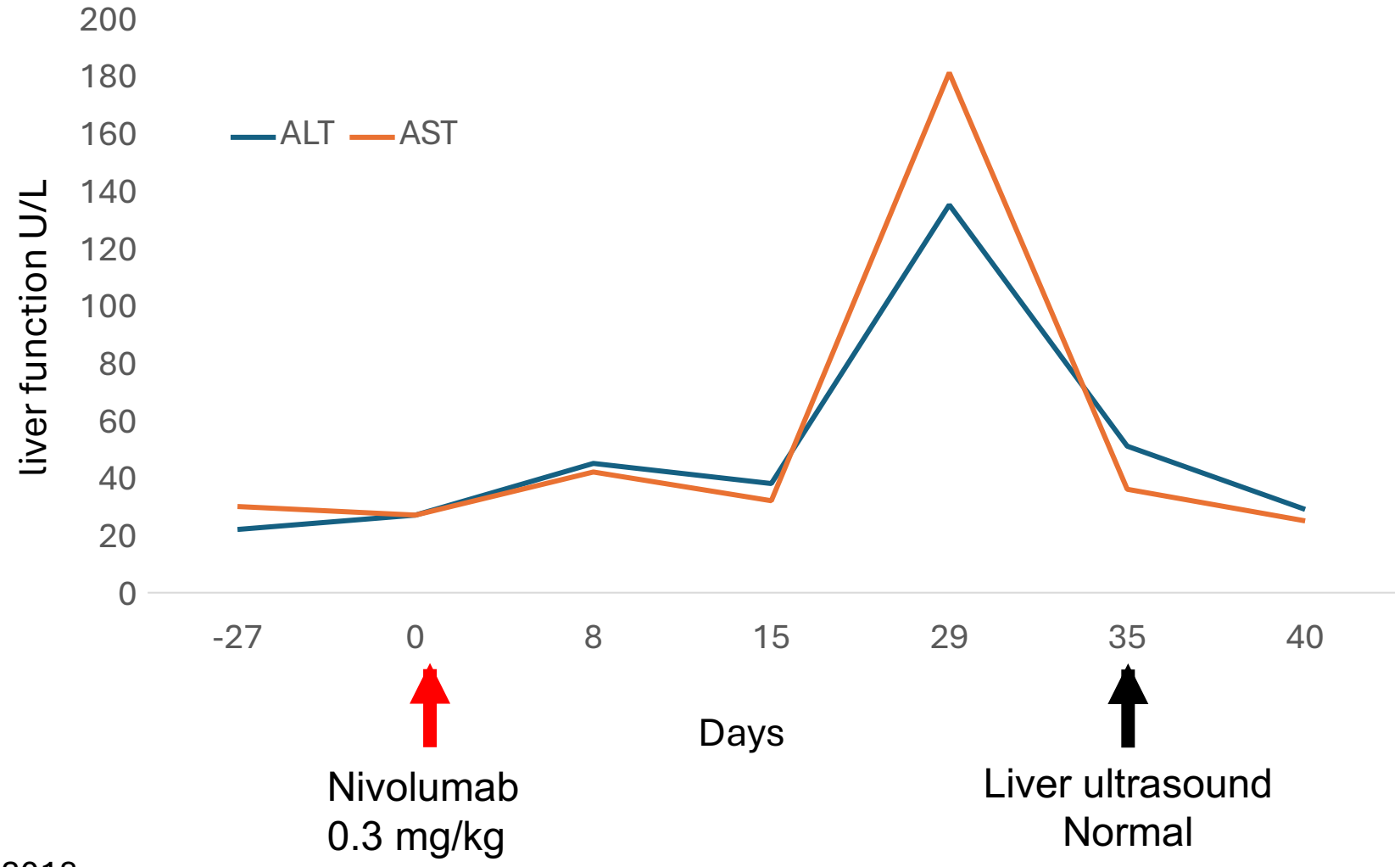
Participant well throughout and LFTs quickly normalized

2 glasses wine day 28

Normal liver ultrasound, Hep B SAg, HCV Ab and syphilis Ab negative

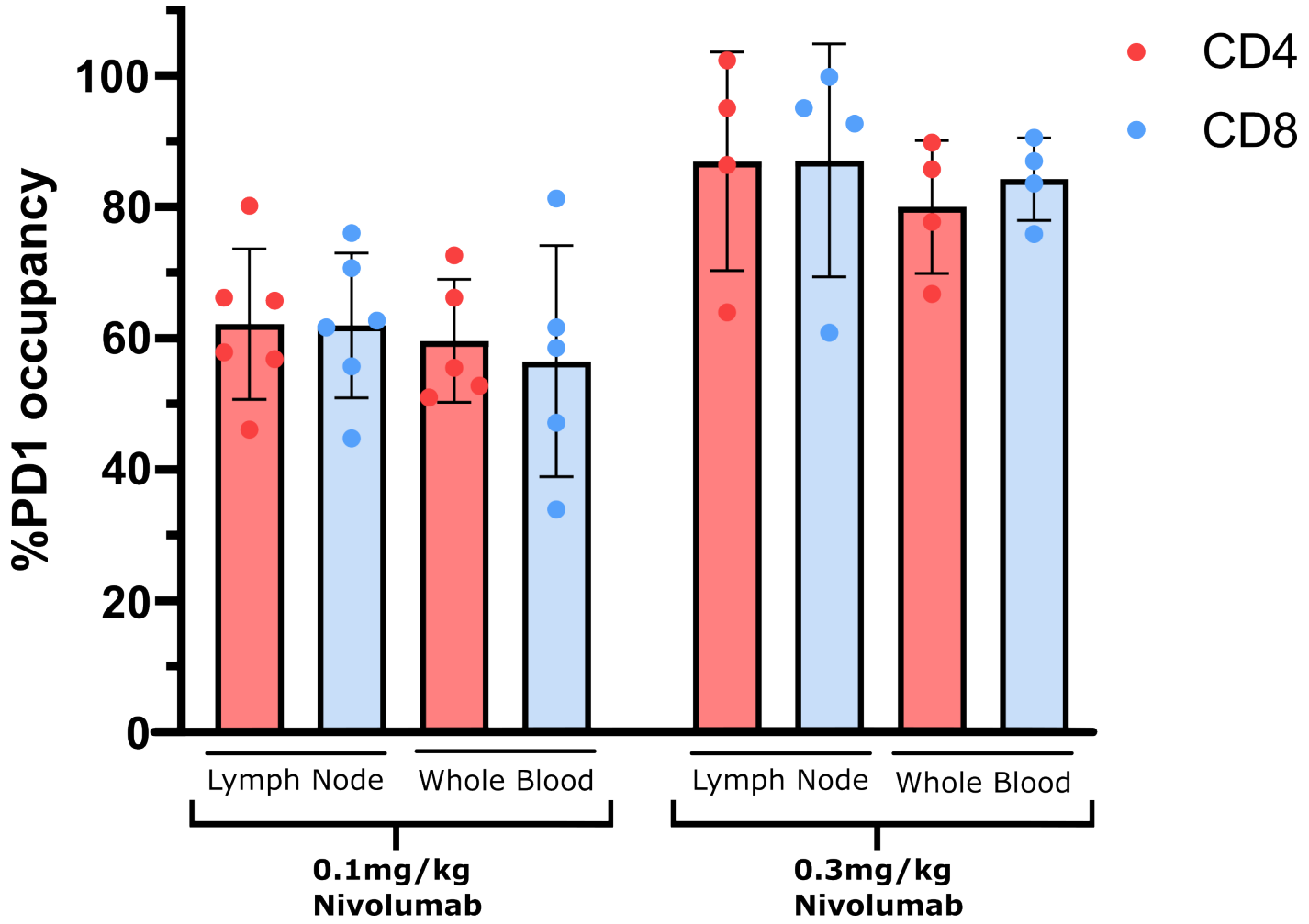
Rapid rise and reduction in LFTs is atypical for immune related hepatitis post anti-PD1[1] .

No alternate cause was found so ***considered a possibly immune related event.***

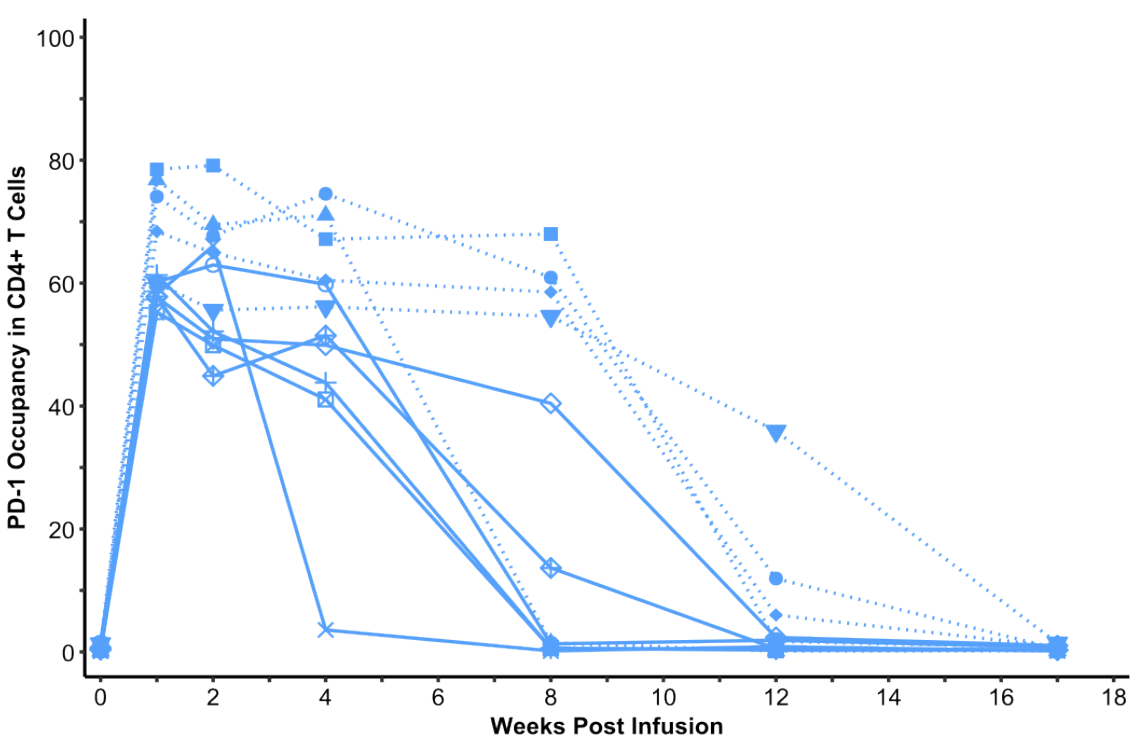


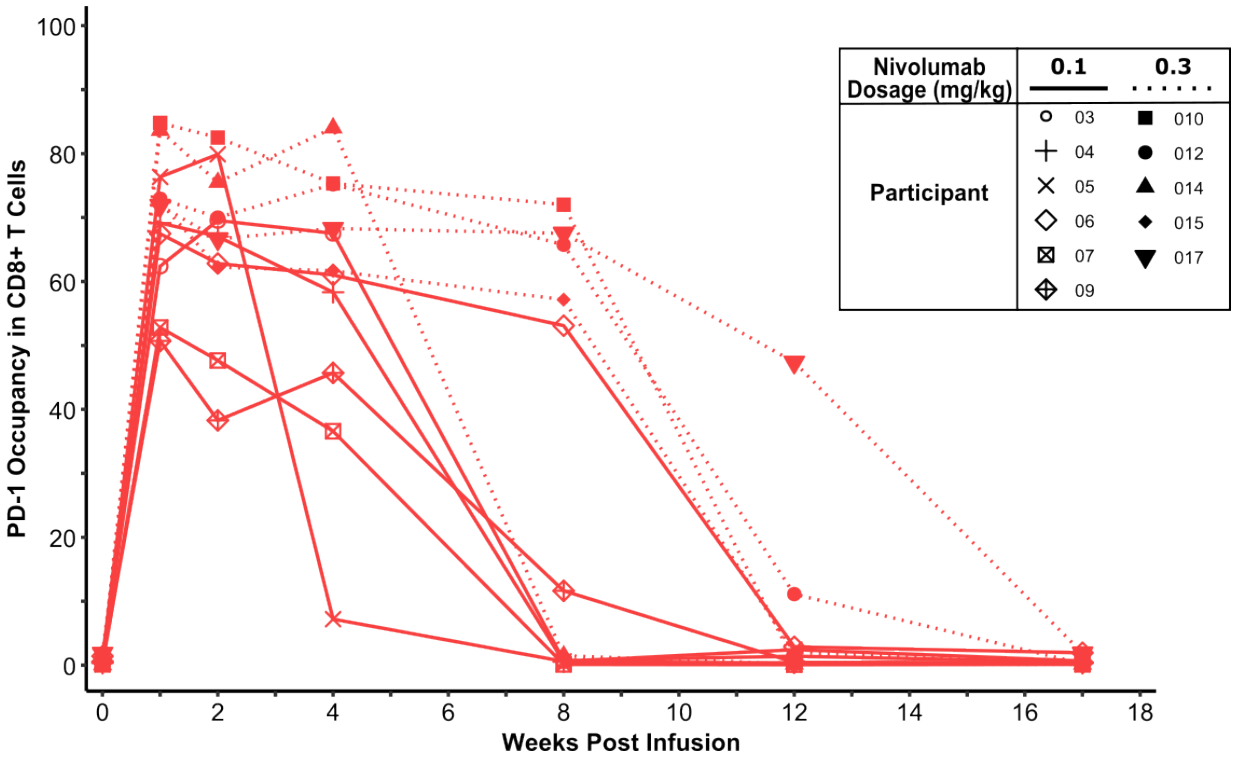
1 De Martin J Hepatol 2018; Gauci J Hepatol 2018

PD-1 receptor occupancy in blood and lymph node



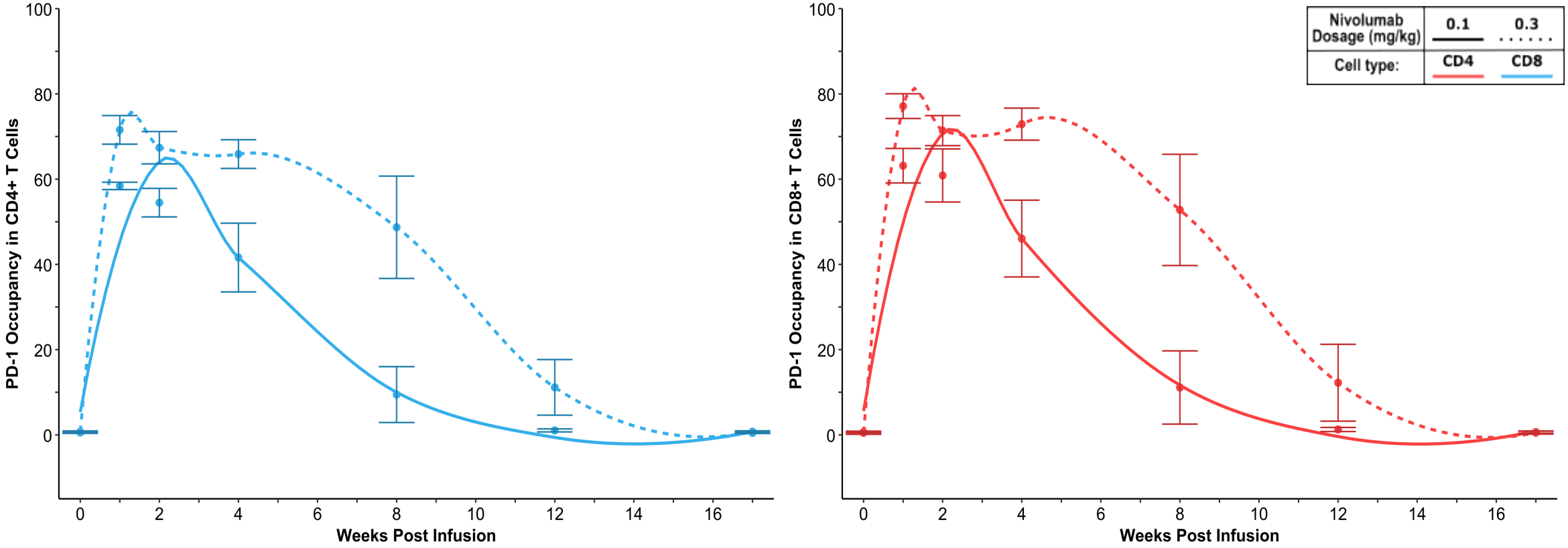
PD-1 receptor occupancy over time in blood





n=6 for the 0.1mg/kg dosage group, n=5 for the 0.3mg/kg for the dosage group.

Mean PD-1 receptor occupancy over time in blood



Locally estimated scatterplot smoothing (LOESS) regression curve plotted for each dosage group. Error bars represent the mean ± standard error for occupancy at each timepoint.
n=6 for the 0.1mg/kg dosage group, n=5 for the 0.3mg/kg for the dosage group.

Summary

- Completed single low dose Nivolumab at 0.1 and 0.3 mg/kg with pre- and post-dosing lymph node fine needle aspirates
- Study progressing safely
- PD-1 receptor occupancy on fresh lymph node was high and equivalent to levels found in blood
- PD-1 receptor occupancy higher and for longer duration following 0.3 mg/kg compared with 0.1 mg/kg nivolumab
- 1 mg/kg dosing cohort initiated

Acknowledgements

The Alfred Hospital, Melbourne, Australia
Department of Infectious Disease
James McMahon
Jill Lau
Marti Kaiser
Mei Tang
Janine Roney
ID Department research co-ordinators
Department of Radiology
Paul Beech
Department of Oncology
Maggie Moore

Aarhus University, Aarhus, Denmark
Thomas Rasmussen

Doherty Institute, Uni Melb and Royal Melbourne Hospital
Department of Infectious Disease
Lewin lab
Sharon Lewin
Judy Chang
Lauren Wallace
Ajantha Solomon
Hannah King
Barbara Scher
Abraham Freijah
Michael Roche
Statistics core
David Price
Niamh Meagher

National Centre for Infectious Disease, Singapore
Chen Seong Wong
Chiaw Yee Choy
Barnaby Young

Australian Government
National Health and Medical Research Council

NHMRC

MELBOURNE HIV CURE CONSORTIUM

ACH2 Australian Centre for HIV and Hepatitis Virology Research