Safety and PD-1 Receptor Occupancy following low dose Anti-PD1 in Adults with HIV

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BACKGROUND

Programmed cell death protein (PD-1) is expressed on activated and exhausted T-cells and elevated expression persists on antiretroviral therapy (ART). PD-1 blockade can reverse HIV latency and increase HIV specific T-cell response in people with HIV (PWH) and cancer. We investigated the effects of a single low dose of anti-PD1 (Nivolumab) as a potential strategy to reduce adverse events and still enhance HIV-specific T-cell function.

METHODS

NIVO-LD is a two-part trial in PWH on ART receiving a single low dose of Nivolumab (**Figure 1**). Fine needle aspirates aspirates (FNA) of a groin lymph node were collected before and 2 weeks after Nivolumab with blood sampling up to 24 weeks. The second part (Cohort B) compares Nivolumab to placebo during ART interruption. We assessed safety, PD-1 receptor occupancy in blood and tissue and quantified cell associated total HIV DNA

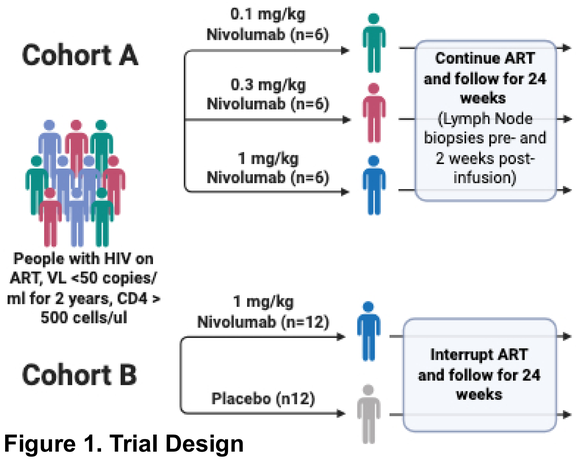


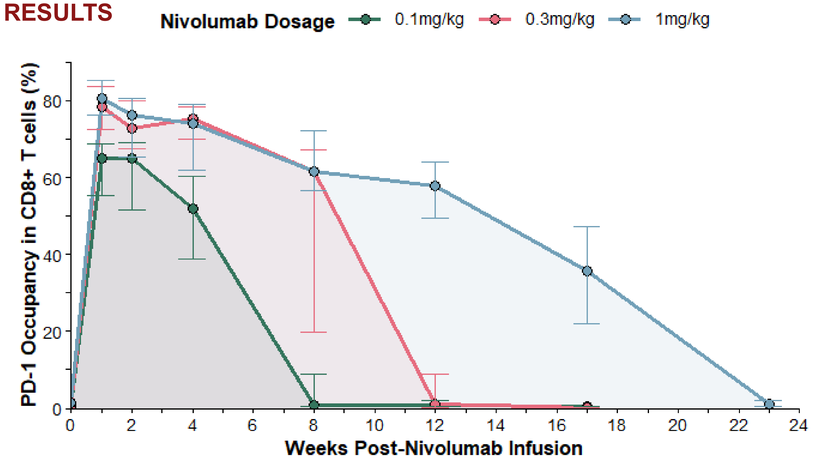
Figure 1. Trial Design

Characteristic	0.1 mg/kg N = 6	0.3 mg/kg N = 6	1 mg/kg N = 6
Age yrs, Median (IQR)	50 (40, 54)	46 (35, 53)	48 (31, 56)
Male (%)	5 (83)	6 (100)	6 (100)
CD4 cells/μL, Median (IQR)	734 (637,956)	797 (762, 946)	581 (538, 656)

Table 1. Study Demographics. 26 PWH enrolled with 18 dosed. 8 screened out (5 +ve anti-nuclear antibodies, 2 +ve Glutamic Acid Decarboxylase, 1 elevated liver function)

Single low-dose Anti-PD1 was safe with prolonged receptor occupancy

RESULTS



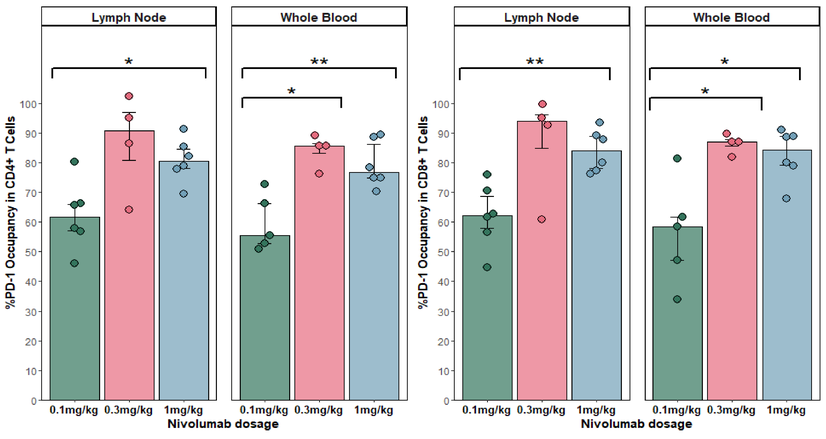


Figure 2. PD1 receptor occupancy in CD8+ T-cells over time (left), and in CD4+ and CD8+ T-cells in lymph node and blood 2 weeks post Nivolumab (below left)

Median PD-1 occupancy in CD4+ / CD8+ T-cells in lymph node 2 weeks after 0.1, 0.3 and 1 mg/kg Nivolumab was 62%/62%, 91%/94%, and 81%/84% respectively. Median PD-1 occupancy in blood was similar to lymph node at 2-weeks with increasing duration of occupancy with increasing dose Median, error bars= IQR. Wilcoxon rank-sum for comparisons. *=p<.05, **=p<.01

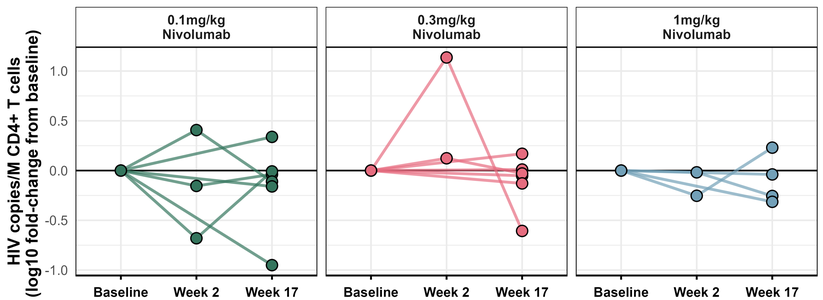


Figure 3. Total HIV DNA. No significant change in HIV DNA after 2- and 17-weeks of Nivolumab for all doses (n=6 [0.1 and 0.3 mg/kg], n=4 [1 mg/kg]; p=0.3)

Drug Related Adverse events	Dose (mg/kg)		
	0.1	0.3	1
Clinical			
Bruising and/or pain in groin biopsy site	7	9	10
Warm Sensation	1		
Anorexia		1	
Nausea		1	
Fatigue		6	3
Visual Aura		1	
Diarrhoea		1	3
Abdominal pain			1
Headache			1
Laboratory			
Increased AST	1	1*	2
Increased ALT		1*	1
Decreased Creatinine Clearance			1

NOTES: Severity Grading Black=1, Green=2, Red=3 *One possible immune related adverse event (hepatitis) at 4 weeks post-Nivolumab (ALT 135 [Grade 2] and AST 181 [Grade 3] units/L) which resolved

Table 2. Adverse events. Table shows drug related events. One unrelated serious adverse event (appendicitis) and two unrelated increases in liver transaminases 12 weeks post Nivolumab after significant alcohol intake which resolved on ceasing alcohol.

CONCLUSIONS A single low dose of Nivolumab was well tolerated. PD-1 receptor occupancy was similar in blood and lymph node and was prolonged following 1mg/kg. The randomised part of the trial will use the 1mg/kg dose.

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PLAIN LANGUAGE SUMMARY

- **Nivolumab is a licensed anti-cancer drug that blocks the PD-1 receptor on T-cells and increases the immune response to cancer and persistent infections like HIV. The penetration of the drug into lymphoid tissue has not previously been studied**
- **To minimise toxicity a single low-dose of Nivolumab was studied**
- **The drug was safe with high levels in tissue (lymph node) and blood and the 1mg/kg dose will be used in the next part of the trial with ART interruption**

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