PD-1 Occupancy Following Low Dose Nivolumab Treatment in Adults Living with HIV on Antiretroviral therapy: The NIVO-LD Trial

Wallace L[2], Lau JSY[1,2,3], Kaiser K[1], Chang J[2], Solomon A[2], King H[2], Scher B[2], Beech P[3], Moore M[4], Tang M[1], Le Couteur J[1], Price DJ[2], Meagher N[2], Rasmussen TA[2.5], McMahon JH[1] & Lewin SR[1,2,3]

1 Department of Infectious Diseases, Alfred Health and School of Translational Medicine, Monash University, Melbourne, Victoria, Australia
2 Department of Infectious Diseases, University of Melbourne at the Peter Doherty Institute for Infection and Immunity, Melbourne, Victoria, Australia
3 Victorian Infectious Disease Service, Royal Melbourne Hospital at the Peter Doherty Institute for Infection and Immunity, Melbourne, Victoria, Australia
3 Department of Radiology, Alfred Health, Melbourne, Victoria, Australia
4 Department of Medical Oncology, Alfred Health, Melbourne, Victoria, Australia
5 Aarhus University Hospital, Aarhus, Denmark

Background:
Programmed death-1 (PD-1) is an immune checkpoint molecule upregulated in people living with HIV (PLWH) on antiretroviral therapy (ART). PD-1 blockade can reverse HIV latency and enhance HIV-specific T-cell responses. Low-dose Nivolumab, an anti-PD-1 antibody, reduces immune-related adverse events while maintaining PD-1 inhibition, potentially providing a preferred approach to HIV cure interventions.

Methods:
In NIVO-LD, PLWH on ART received a single low-dose Nivolumab infusion (0.1, 0.3 or 1mg/kg, n=6 for each dose). PD-1 occupancy was measured in CD4+ and CD8+ T-cells collected from lymph node fine needle aspirates at baseline and week 2, and from blood at frequent intervals until week 17. Occupancy was quantified by flow cytometry, as the proportion of free PD-1 post-infusion, relative to total PD-1 after ex vivo treatment with saturating concentrations of Nivolumab.

Results:
Two weeks post-infusion, median PD-1 occupancy in lymph nodes was 62% in both CD4+ and CD8+ T-cells following 0.1mg/kg Nivolumab (n=6), significantly lower than occupancy following 0.3mg/kg (91% in CD4+ and CD8+ T-cells, n=4, $P<0.01$) and 1mg/kg dosing (84% in CD4+ and 89% in CD8+ T-cells, n=4, $P<0.01$). No significant difference between PD-1 occupancy was observed between 0.3mg/kg and 1mg/kg at week 2. Occupancy in blood was comparable to lymph node. At week 8, median occupancy in blood CD4+ T cells following 0.1mg/kg dosing was <1% (n=6), 0.3mg/kg was 57% (n=6) and 1mg/kg was 61% (n=2). By week 17, the median PD-1 occupancy was <1% for both 0.1mg/kg and 0.3mg/kg dosing (n=6 for both), whilst occupancy in 1mg/kg group was 34% in CD4+ and 37% in CD8+ T-cells (n=2).

Conclusion:
Single low dose Nivolumab at 0.1, 0.3 or 1mg/kg achieves high PD-1 occupancy in lymph node and blood; and is prolonged with 0.3 and 1mg/kg. Similar occupancy between blood and lymph nodes indicates low-dose Nivolumab can reach a key anatomical reservoir of HIV latency.

DISCLOSURE OF INTEREST STATEMENT:

This research is funded by grants from the Melbourne HIV Cure Consortium.
SRL receives honoraria for participation in scientific advisory boards for Gilead Sciences, Merck and Abbvie. She has received funding for an investigator initiated clinical trial from Gilead Sciences. JSYL receives honoraria for participation in Advisory Boards and Consultancy roles for ViiV Healthcare and Gilead Sciences, and an investigator-initiated research grant from Merck, Sharp and Dohme which is unrelated to this project