Viral Suppression Induced by Anti-PD-L1 Following ARV-Interruption in SIV-Infected Monkeys

Stephen W. Mason1, Srismowmy Sanisetty2, Christa Osnar3, So-Yon Lim4, Susan Chaniewski5, Shalyn Campbell2, Daniel Tennyson2, Scott Balsitis2, and James B. Whitney2

1Center for Virology and Vaccine Research, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts 02115, 2Bristol-Myers Squibb, 3Research Parkway, Washington, CT 06892

Background: BMS-936559, a fully human antibody against huPD-L1, was tested in a non-human primate model to determine if it could be used to achieve viral suppression. The primary endpoints of the study were to evaluate the effect of treatment on viral load, immune function, and safety. The results of this study were used to inform the design of future clinical trials.

Methods: 133B6F10-infected macaques were randomized pre-ARV (8) or post-ARV (12) to one of three groups: 1) saline; 2) BMS-936559, 5 μg/kg; or 3) BMS-936559, 50 μg/kg. Viral load, immune function, and safety were assessed during the 60-day treatment period, followed by 24 weeks of post-TI observation.

Results: Viral suppression of SIVmac251 at 400 RNA copies/mL was achieved in 14/16 animals. Significant differences in viral load were observed between 1) saline and 2) BMS-936559 (5 μg/kg) and 3) saline and 2) BMS-936559 (50 μg/kg). Additionally, significant differences were noted in the distribution of CD4+ and CD8+ T cells, virus-specific T cell responses, and safety.

Conclusion: The results of this study demonstrate the potential of BMS-936559 to achieve viral suppression in SIV-infected macaques. Future studies will be directed at a combination of these approaches.

Key Hypotheses: PD-1/PD-L1 blockades restore function to exhausted T cells

1. Persistent antigenicity leads to T cell exhaustion in chronic viral diseases and cancer
2. PD-1/PD-L1 is a key inhibitory receptor affecting T cell responses
3. Blockade of PD-1/PD-L1 restores T cell function

PD-1 blockade in uninfected SIV-infected macaques

- Significant difference in rebound VL observed between treatment groups early after treatment interruption (TI)
- Viral response was defined as having slower rebound and viral load <1000 RNA copies/mL for 24 weeks.

Comparison of pre-ART and post-TI VL

- Most animals in the BMS-936559-TI group had a much lower VL post-TI compared to pre-ART set point VL.

Future Directions

- Complete analysis of: PD-L1 expression and PD-1/PD-L1 occupancy
- Clinical trial with human subjects
- Additional studies to evaluate clinical applicability of the discovery

Acknowledgements

- We thank the study team at the AIDS Research Center for their contributions.

References


Figures

- Figure 1: Kinetics of viral load rebound during TI.
- Figure 2: Comparison of pre-ART and post-TI VL.
- Figure 3: Trends for Treatment Response: CD4-CD8 Ratio and CD Counts.