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

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Abstract

Background: BMS-936559, a fully human antibody against huPD-L1, was tested in antiretroviral-suppressed SIVmac251-infected rhesus macaques. The primary endpoints for this study were to assess safety during repeated i.v. administration of BMS-936559, to determine any improvement in the function of SIV-specific T cells and to monitor for effects on viral recrudescence after cessation of ARV therapy.

Methods: 13 MHC-defined rhesus macaques were confirmed to be SIVmac251 positive and ARV treatment was initiated, using a 3-4 drug ARV regimen, for an average of 6 months prior to the administration of BMS-936559. Animals received either BMS-936559 (N=8) or iso-type control antibody (N=5). Multiple immunologic and virologic analyses were used to evaluate ARV regimen efficacy, safety and occupancy of PD-L1 by BMS-936559.

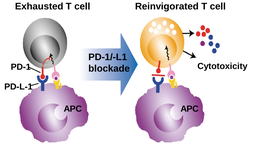
Results: Durable virologic suppression of SIVmac251 at ≤50 RNA copies/ml was achieved in all animals with the administration of a well-tolerated ARV regimen. Significant reductions in inflammatory markers were observed during ARV treatment. Repeat dosing of BMS-936559 was well tolerated in all animals with no noted untoward effects based on physical examination and laboratory assessments. Occupancy of PD-L1 by BMS-936559 was observed throughout the dosing period and pharmacokinetic analyses verified exposure of antibody. Perturbations in SIV viral RNA levels were observed after ARV treatment interruption, such that 4 of 8 animals in the BMS-936559 treatment group had a delay in viral load rebound and a significantly lower viral load set point, with 2 animal having undetectable VL for 3-4 weeks after an initial rebound. Changes in proviral DNA levels and T cell functional assays have been assessed.

Conclusions: These data provide proof of concept for the safety of repeated high-level dosing of BMS-936559 in vivo. The effects on viral suppression observed in this study may reflect a restoration of immune function by anti-PD-L1 in SIV-infected rhesus monkeyse have developed a dual approach to discover agents with complementary mechanisms of action and whose combination may eradicate latent HIV-1 infection. Future studies will be directed at a combination of these approaches.

Key Hypothesis: *PD-1/PD-L1 blockade restores function to exhausted T cells*

Fig. 1

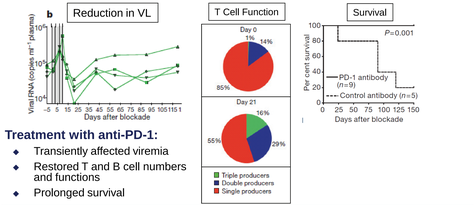
- **Persistent antigenemia leads to T-cell exhaustion in chronic viral diseases and cancer**
- **PD-1 is a key inhibitory receptor affecting T-cell responses**
  - Increased on virus-specific T cells in chronic HIV
  - CD4+ and CD8+ cells
- **Inhibition of PD-1/PD-L1**
  - Alters the course of cancers
  - Affects chronic viral diseases
  - Restores virus-specific T cell function *in vitro, ex vivo* and *in vivo*



APC, antigen presenting cell.
Adapted from Freeman G, et.al. J Exp Med 2006
Trautmann L. et al Nat.Med. 2006; Day CL. et.al. Nature. 2006; Petrovas C. et al., JEM 2006; Velu V. et al. Nature. 2009; Palmer B et al. J Immunol 2013

PD-1 blockade in unsuppressed SIV-infected macaques

Fig. 2



Treatment with anti-PD-1:

- Transiently affected viremia
- Restored T and B cell numbers and functions
- Prolonged survival

What would be the outcome of PD-1 pathway blockade if the SIV-infected macaques were on suppressive ARV?

Velu et al, Nature 2009

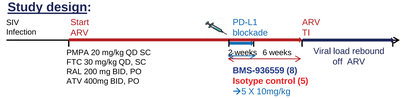
PD-L1 blockade in ARV suppressed SIVmac251-infected Rhesus Macaques

Fig. 3

Hypothesis:

– **Treatment of ARV-suppressed SIV infected macaques with anti-PD-L1 should:**
  – restore SIV-specific T cell function. Subsequently, this may:
    – reduce the latent SIV reservoir
    – lead to host control of virus following interruption of ARV

Study design:



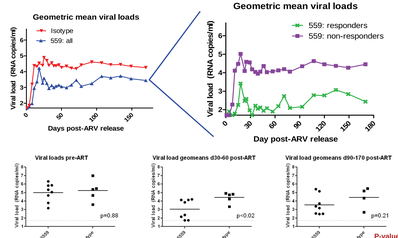
Objectives:

– **Determine whether multiple doses of BMS-936559 (anti-PD-L1) affect:**

1. Virus-specific T cell functionality,
2. Cell-associated viral DNA (latent reservoir) in tissues and periphery,
3. Virus recrudescence after cessation of ARV treatment.

Kinetics of viral load rebound post-treatment interruption

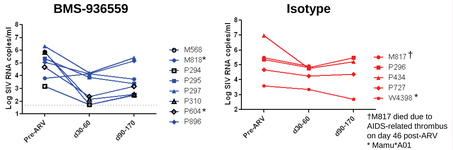
Fig. 4



- **Significant difference in rebound VL observed between treatment groups early after treatment interruption (TI)**
- **"BMS-936559-treatment responders" defined as having slower rebound and viral load <1000 RNA cp/mL for ≥3 weeks**

Comparison of pre-ART and post-TI VL

Fig. 5

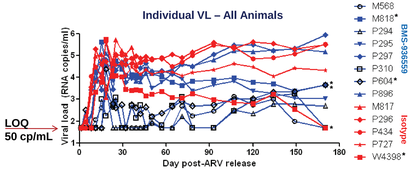


- **Most animals in the BMS-936559-treatment group had a much lower VL post-TI compared to pre-ART set point VL**

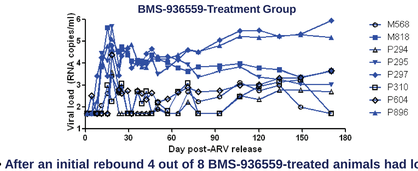
†M817 died due to AIDS-related thrombus on day 46 post-ARV
* Mamu*A01

Individual VL rebound kinetics post-TI: *Evidence of treatment response*

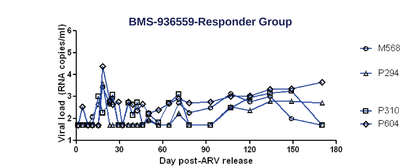
Fig. 6



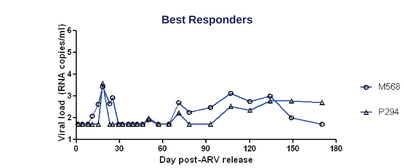
- **Viral loads for most animals stabilized except:**
  - The group of BMS-936559-treatment responders whose VL fluctuated
  - One animal in the Isotype treatment group dropped to undetectable by the end of the study → Mamu*A01 controller (*)



- **After an initial rebound 4 out of 8 BMS-936559-treated animals had lower VL than the remaining animals in this group**



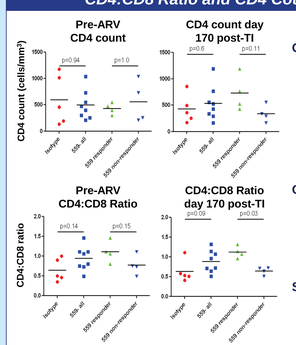
- **Treatment responders fluctuated between LOQ and ~1000 RNA cp/mL for first 90 day post-TI**
  - Some had intermittent periods of undetectable VL
- **But responses were not sustained**



- **2 of 4 treatment responders had undetectable VL for 3-4 weeks and remained <1000 RNA cp/mL through day 170 post-TI**

Trends for Treatment Response: *CD4:CD8 Ratio and CD4 Counts*

Fig. 7a



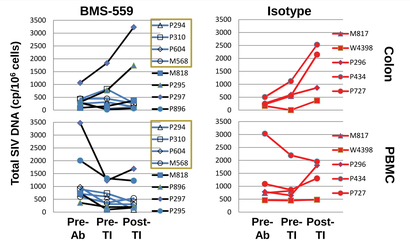
Good randomization for pre-ARV CD4 counts
→ Non-statistically significant difference between responders and non-responders for post-TI CD4 count (p=0.11)

CD4:CD8 ratio was not randomized pre-ARV
→ Non-statistically significant difference between responders and non-responders for pre-ARV CD4:CD8 ratio (p=0.15)

Significant association between response and post-TI CD4:CD8 ratio (p<0.05)

Total SIV DNA

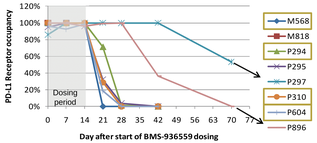
Fig. 7b



- **SIV DNA was stable post-treatment interruption in BMS-936559 treatment responders but tended to increase in Isotype group**

Anti-PD-L1/PD-L1 Occupancy

Fig. 8



- **Receptor occupancy (RO) maintained at 100% throughout dosing period**
- **2 animals with sustained RO were not treatment responders**
- **Preliminary PK:**
  - Rapid clearance of BMS-936559 after last dose (except P297, P896)
  - Clearance likely related to immunogenicity of antibody (data pending)

Summary

Fig. 9

Efficacy:

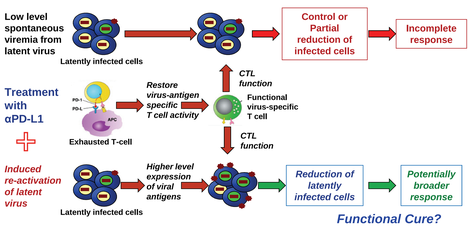
- **Treatment with BMS-936559 (anti-PD-L1) resulted in lower post-TI rebound VL**
  - Effect was not sustained beyond 90 days post-TI
    - Suggests blockade of PD-L1 may induce a period of immune control but multiple cycles of treatments or combinations with other interventions may be necessary for sustained response
- **Trends in CD4:CD8 ratio and total SIV DNA were observed**

Safety:

- **Multiple doses of BMS-936559 in ARV -suppressed SIV-infected Rhesus macaques appeared to be well tolerated**

Model for Effect of Anti-PD-L1 in SIV study *Strategy for Functional Cure*

Fig. 10



Future Directions

Fig. 11

Complete analysis of:

- PK and immunogenicity
- SIV-specific immune responses
- Gene expression profiling and exome analysis
- Viral sequence analysis

Determine if a predictive biomarker of response can be identified

Investigate whether initial VL rebound post-TI plays a role in response to BMS-936559

Understand how to induce a more sustained response

- Additional studies with combinations
  - Latency reactivation agent, other co-inhibitory receptors
- Additional studies to investigate parameters with associations

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BMS

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