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Inhibition of toll-like receptor 7 (TLR7) with the potent and selective inhibitor of human TLR7 and TLR8, BMS-986256, provides robust efficacy in murine lupus models, reversing established disease

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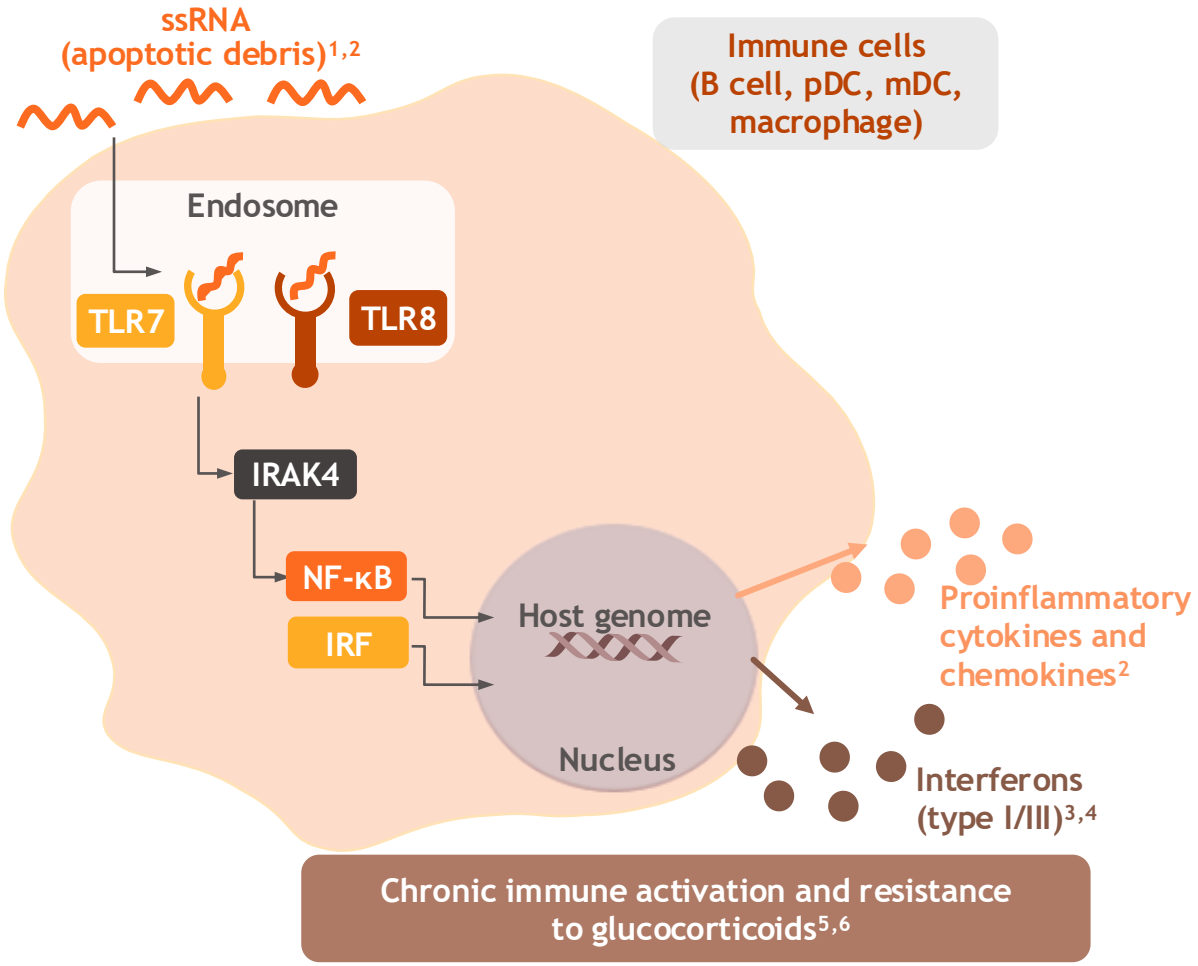
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[a]Gary Schieven was affiliated with Bristol Myers Squibb when the analysis was conducted

Disclosures

- All authors involved in this presentation were employees of Bristol Myers Squibb or Biocon Bristol Myers Squibb Research Center at the time the research was completed
- Gary Schieven is currently employed by the Genesis Biotechnology Group, Hamilton, NJ

Endosomal TLR7 and TLR8 play key roles in the pathology of lupus



- TLR7 and TLR8 detect ssRNA from pathogens or self-apoptotic sources[1,2]
- Activation of TLR7 and TLR8 within multiple immune cell types leads to
  - Elevated pro-inflammatory cytokines[2,3]
  - Production of type I/III interferons[4,5]
  - Steroid resistance[6]
- TLR7 and TLR8 may play an important role in the initiation and progression of disease in cutaneous and renal lupus[7-9]
  - Lupus is associated with defects in clearance of apoptotic debris, which can activate TLR7 and TLR8[1,2,9]
  - Genetic evidence supports a role for TLR7 and TLR8 in lupus[10,11]

IRAK4, interleukin-1 receptor-associated kinase 4; IRF, interferon regulatory factor; NF-κB, nuclear factor kappa B; mDC, myeloid dendritic cell; pDC, plasmacytoid dendritic cell; ssRNA, single-strand ribonucleic acid; TLR, toll-like receptor.

1. Diebold S, et al. *Science* 2004;303:1529–1531. 2. Guiducci C, et al. *J Exp Med* 2013;210:2903–2919. 3. Kawai T, et al. *Trends Mol Med* 2007;13:460–469. 4. Saitoh SI, et al. *Nat Commun* 2017;8:1592. 5. Ioannidis I, et al. *J Virol* 2013;87:3261–3270. 6. Guiducci C, et al. *Nature* 2010;465:937–941. 7. Celhar T, et al. *Proc Natl Acad Sci* 2015 10;112:6195-6204. 8. Leeb T, et al. *Genes (Basel)* 2020;11:159. 9. Demaria O, et al. *J Clin Invest* 2010;120:3651-3662. 10. Wang CM, et al. *Sci Rep* 2014;4:3792. 11. Shen N, et al. *Proc Natl Acad Sci* 2010;107:15838-15843.

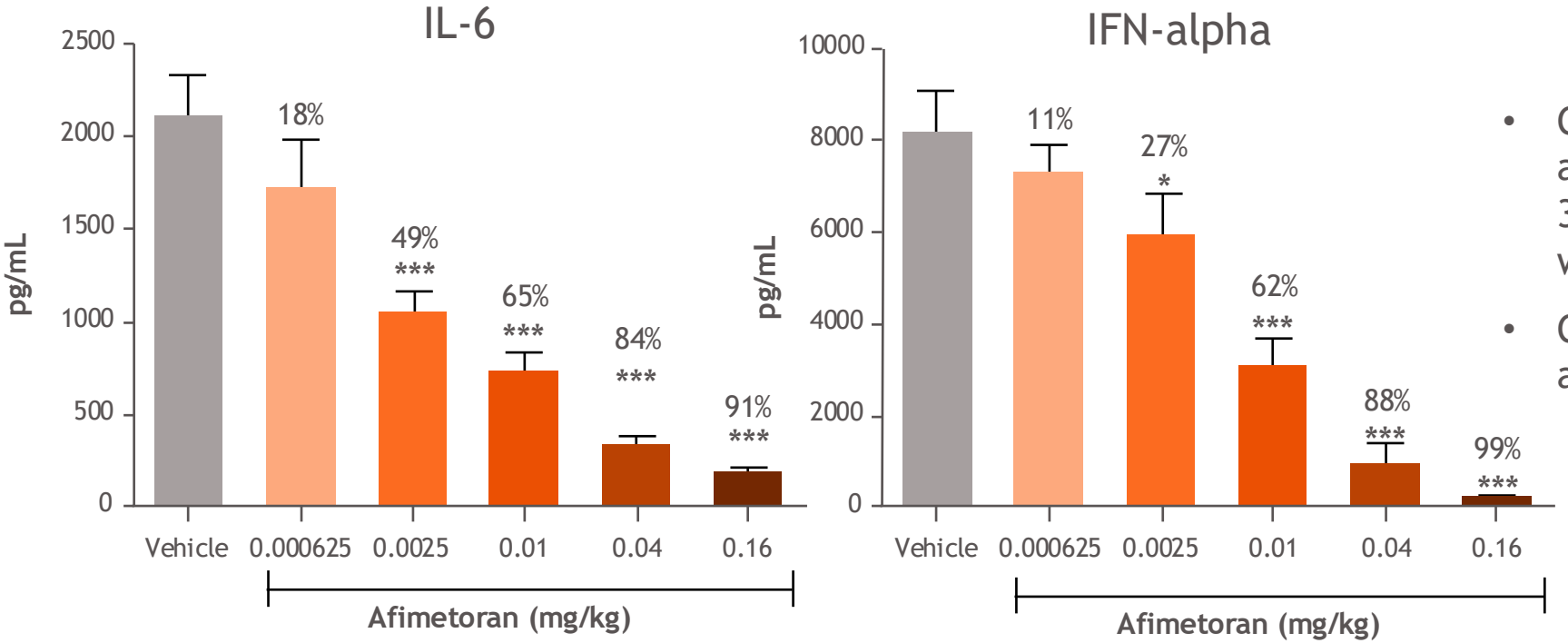
BMS-986256 (afimetoran) is a highly potent and selective inhibitor of TLR7 and TLR8 in vitro and in vivo

In HEK293 cells, the IC50 of afimetoran was:
- < 1 nM for TLR7 and TLR8
- > 5000 nM for TLR3, TLR4, and TLR9

Afimetoran had potent and balanced TLR7 and TLR8 activity. In human whole blood, the IC50 of afimetoran was:
- 4.5 nM for TLR7
- 1.5 nM for TLR8

The mouse pharmacodynamic IC50 of 1.4 nM[a] closely matched the IC50 of 2.4 nM obtained in mouse whole blood

Inhibition of TLR7 agonist-induced cytokines in mice



- Challenge with gardiquimod, a TLR7 agonist in mice, took place 30 minutes after oral dosing with **afimetoran**
- Cytokines were measured 2 hours after the challenge with gardiquimod

[a]This value is the in vivo IC50 calculated from the IL-6 secretion inhibition. *$P < 0.05$. ***$P < 0.001$.
HEK, human embryonic kidney; IC50, half-maximal inhibitory concentration; IFN-alpha, interferon-alpha; IL-6, interleukin 6; TLR, toll-like receptor.
Dyckman AJ, et al. Poster presentation at the LUPUS & CORA 2021 congress; October 6–9, 2021. Abstract 257.

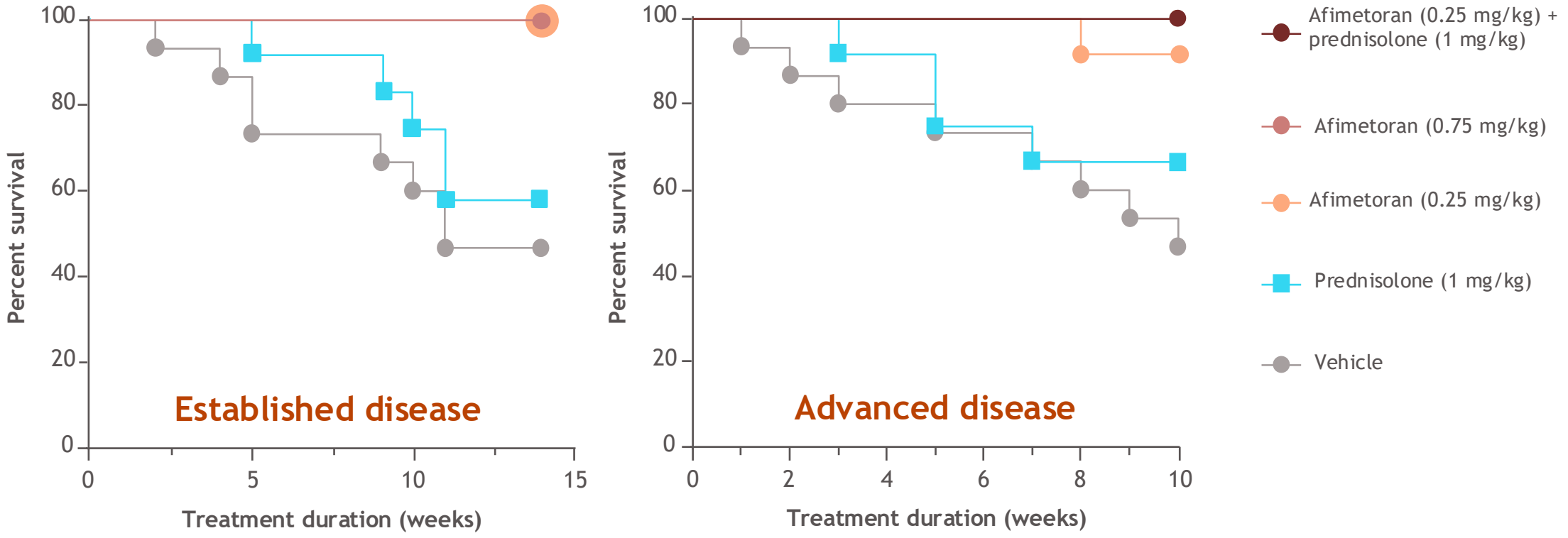
Efficacy of afimetoran in murine models of lupus

- A prophylactic regimen of afimetoran administered in MRL/lpr (IFN-I–independent model) and NZB/W models (IFN-I–dependent model) was associated with decreased proteinuria, autoantibody titer, and cytokines[1,2]
- The objective of this study was to examine the therapeutic efficacy of afimetoran in the NZB/W model
  - Established disease corresponds to moderate form of disease at the time of treatment initiation with proteinuria 60–100 mg/dL[a]
  - Advanced disease corresponds to severe form of disease at the time of treatment initiation with proteinuria > 100 mg/dL[a]

[a]The proteinuria in normal NZB/W mice without any disease is < 30 mg/dL. IFN-I, interferon I; MRL/lpr, mice homozygous for the lymphoproliferation spontaneous mutation (*Fas*^{lpr}); NZB/W, New Zealand black mouse crossed with a New Zealand white mouse.

1. Dudhgaonkar S, et al. Poster presentation at the LUPUS & CORA 2021 congress; October 6–9, 2021. Abstract 238. 2. Dyckman AJ, et al. Poster presentation at the LUPUS & CORA 2021 congress; October 6–9, 2021. Abstract 257.

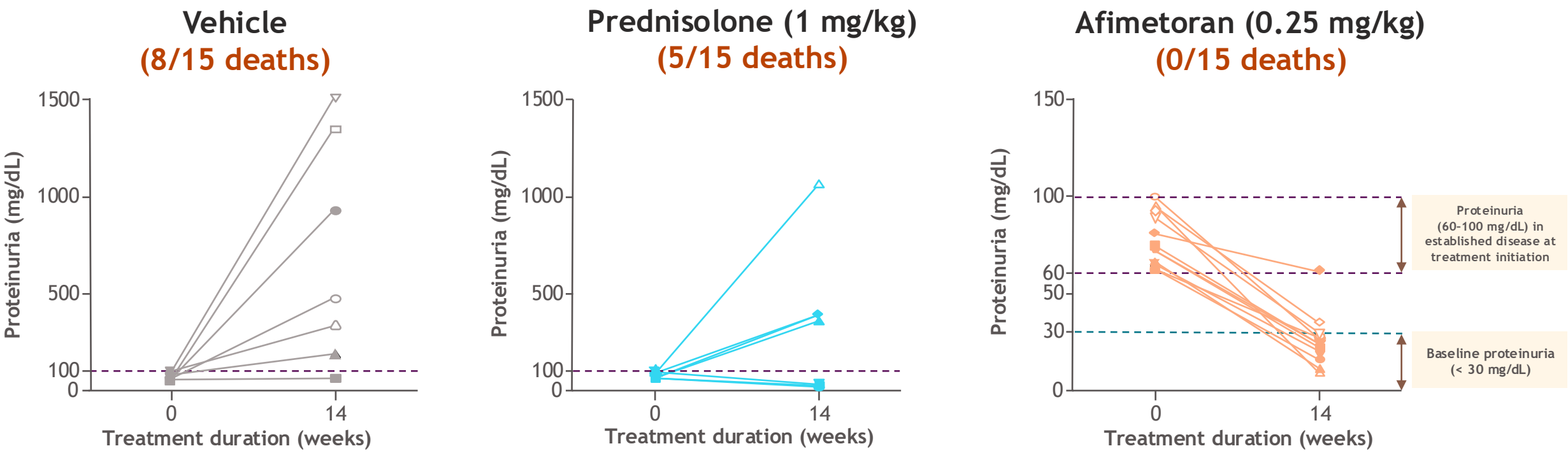
Afimetoran improved survival of the NZB/W murine model of established and advanced lupus nephritis



- In the established disease setting, afimetoran resulted in 100% survival
- In the advanced disease setting, afimetoran alone resulted in near-complete survival, reaching 100% in combination with low-dose steroid

NZB/W, New Zealand black mouse crossed with a New Zealand white mouse.

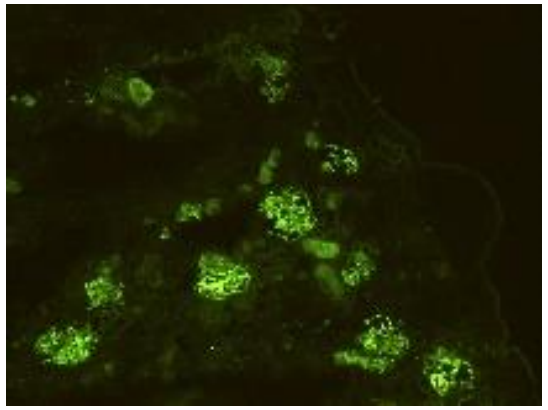
Afimetoran reversed proteinuria in the NZB/W murine model of established lupus nephritis



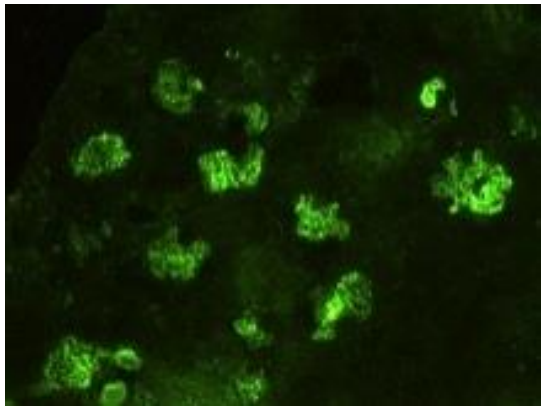
- Proteinuria decreased to baseline levels in almost all animals treated with afimetoran
- Proteinuria was blunted, but not reversed, in the group treated with low-dose prednisolone
- Kidney histology also demonstrated reversal of disease with afimetoran
- A similar observation was also reported in NZB/W mice with advanced disease

NZB/W, New Zealand black mouse crossed with a New Zealand white mouse.

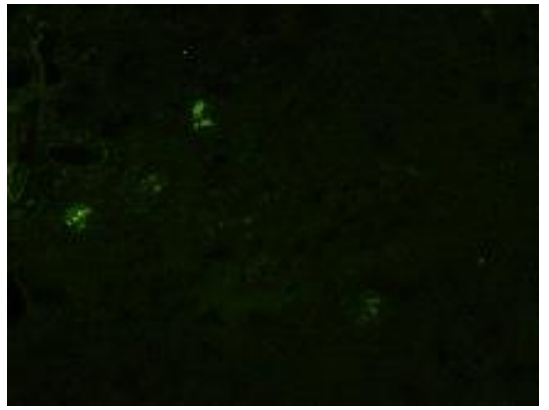
Afimetoran reversed IgG deposition in kidneys in the NZB/W murine model of established lupus nephritis



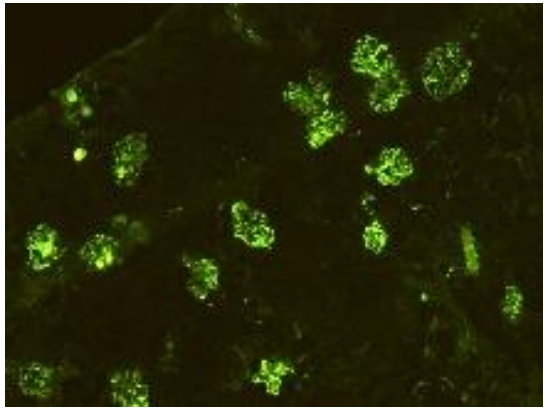
Satellite
(at treatment initiation)



Vehicle
(end of study)



Afimetoran
(0.25 mg/kg)

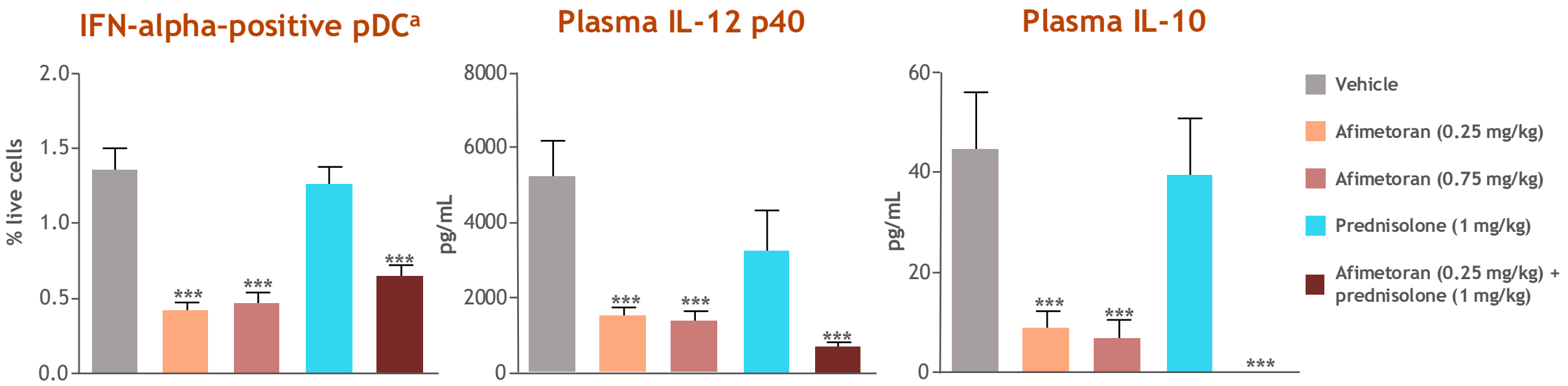


Prednisolone
(1 mg/kg)

- Satellite mice showed IgG deposition in kidney before the initiation of treatment
- Afimetoran reversed both the number of positive glomeruli and the amount of IgG deposition, as detected by immunofluorescence
- The combination of afimetoran with prednisolone also reversed both the number of IgG-positive glomeruli and the amount of IgG deposition in glomeruli
- A similar observation was also reported in NZB/W mice with advanced disease

IgG, immunoglobulin G; NZB/W, New Zealand black mouse crossed with a New Zealand white mouse.

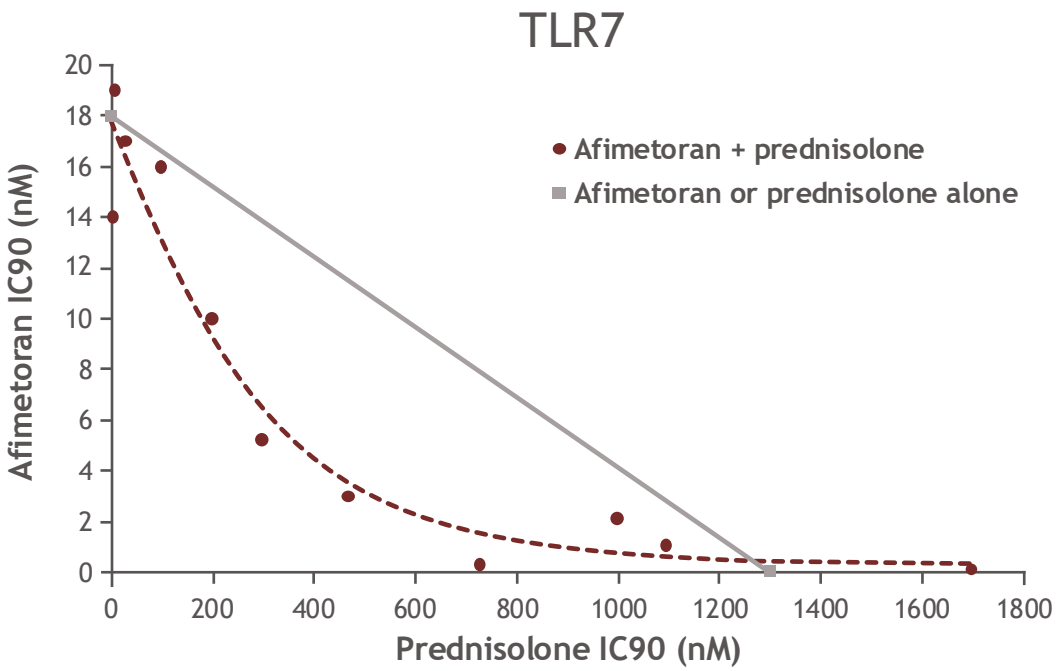
Afimetoran reduced cytokine-secreting cells and circulating cytokines in the NZB/W murine model of established lupus nephritis

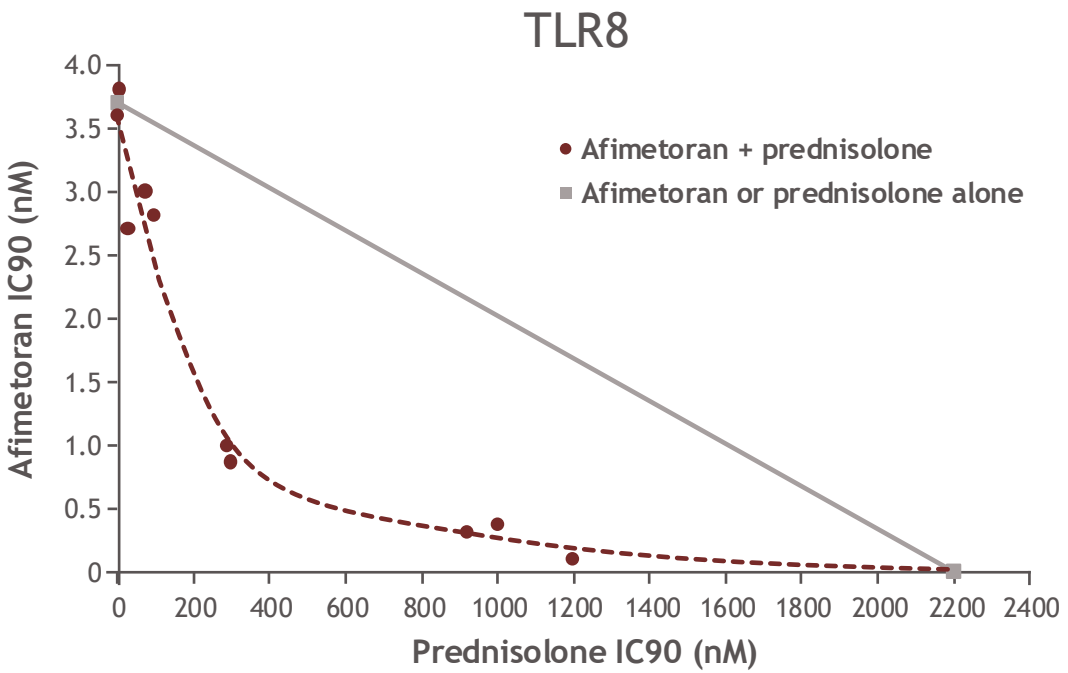


- Afimetoran led to the reduction of cytokine-secreting cells such as pDCs and secreted cytokines
- The combination of afimetoran + prednisolone also reduced cytokine-secreting cells and cytokines
- A similar observation was also reported in NZB/W mice with advanced disease

[a]Cells were considered to be pDC if they were positive for CD317. ***$P < 0.001$. IFN-alpha, interferon-alpha; IL, interleukin; pDC, plasmacytoid dendritic cell; NZB/W, New Zealand black mouse crossed with a New Zealand white mouse.

Afimetoran acted synergistically with prednisolone to inhibit pro-inflammatory cytokine secretion in human whole blood





- The IC90 values for the combination afimetoran + prednisolone are lower than the line of additivity
- Afimetoran acted synergistically with prednisolone to inhibit IL-6 secretion induced by either a TLR7 agonist (gardiquimod) or a TLR8 agonist (TL8-506) in human whole blood

IC90, concentration producing 90% inhibition; IL, interleukin; TLR, toll-like receptor.

Summary

- Afimetoran, a highly potent and selective TLR7 and TLR8 antagonist, showed efficacy in murine models of established or advanced lupus nephritis and led to
  - Improved survival
  - Reversal of IgG deposition in kidney and proteinuria
  - Suppression of kidney injury markers
  - Reduced proportion of cytokine-secreting cells and levels of circulating cytokines
- Afimetoran acted synergistically with prednisolone in vitro to reduce TLR7- and TLR8-induced IL-6 in human whole blood
- Afimetoran may offer a novel therapeutic approach for the treatment of lupus and is currently being investigated in a phase 2 clinical trial (NCT04895696)

IgG, immunoglobulin G; IL, interleukin; TLR, toll-like receptor.

Acknowledgments

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