The agonistic CD40 antibody ADC-1013 improves T cell responses and delays growth of a syngeneic tumor in an ovalbumin vaccination model

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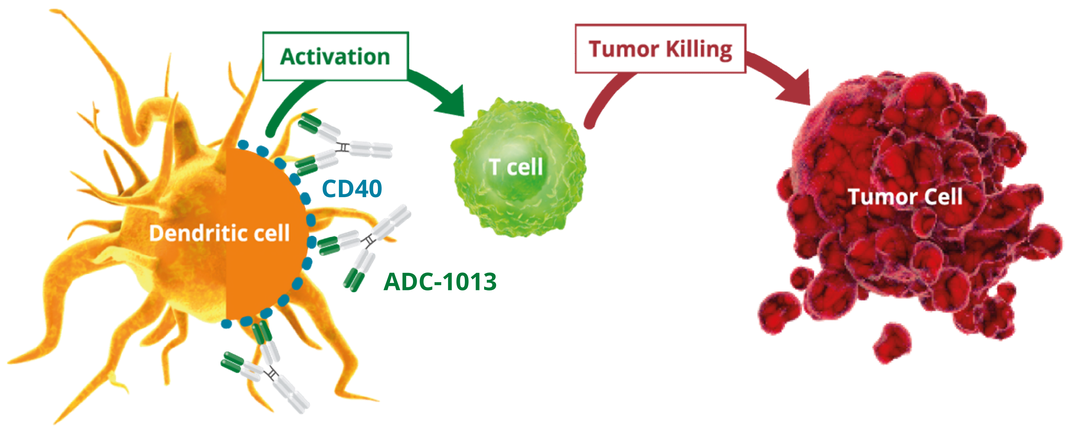
Mechanism of action of ADC-1013



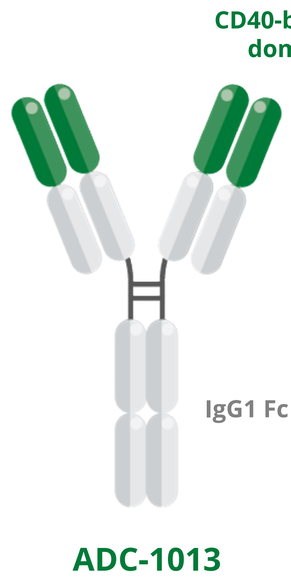
- ADC-1013 (JNJ-64457107) is a human CD40 agonistic IgG1 antibody.
- It activates antigen-presenting cells (APC) by stimulating CD40 on the surface of e.g. dendritic cells.
- Mediated by its effect on APC, ADC-1013 treatment results in activation of tumor-directed cytotoxic T cells with capacity to eradicate tumors.

Summary

Aim:
To demonstrate the in vivo effect of systemically administered ADC-1013 on APC and antigen-specific T cells.

Methods:
Mice transgenic for human CD40 (hCD40tg) were immunized with ovalbumin (OVA) and treated systemically with ADC-1013 and APC and T cell activation analyzed by flow cytometry. Mice were also inoculated with an OVA-expressing tumor and anti-tumor efficacy of this treatment evaluated.

Conclusions:
- ADC-1013 activates splenic dendritic cells as shown by an increase of the co-stimulatory molecules CD80 and CD86.
- ADC-1013 improves T cell activation as shown by an increase of ICOS and CD44^{hi} CD62L^{-} effector memory cells.
- In an OVA vaccination model, ADC-1013 expands OVA-specific T cells and delays growth of an OVA-expressing tumor, demonstrating potential for combination with tumor vaccines.



ADC-1013 eradicates the syngeneic MB49 bladder tumor in hCD40tg mice

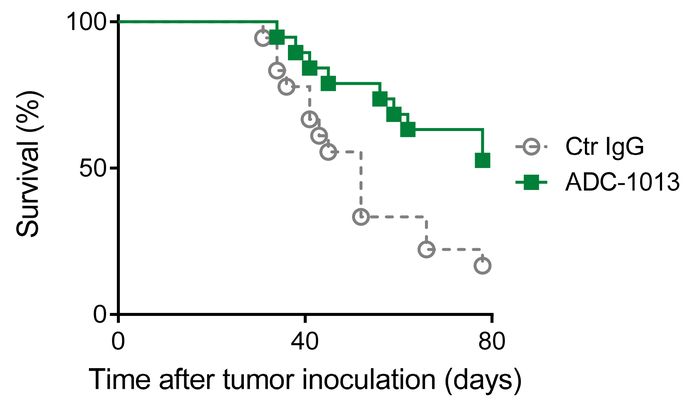
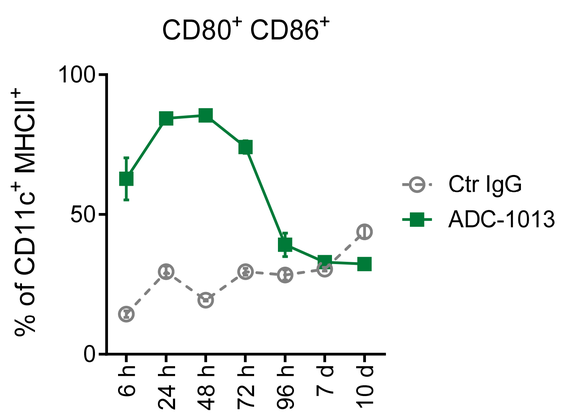


Figure 1 – Effect of systemically administered ADC-1013 on MB49 tumor growth. Mice (hCD40tg) were inoculated with 2.5x10^5 MB49 cells s.c. and administered 100 µg ADC-1013 or Ctr IgG i.p. on days 7, 10 and 13 post-inoculation. Graph shows percent survival from two pooled experiments.

A single systemic dose of ADC-1013 induces activation of splenic dendritic cells



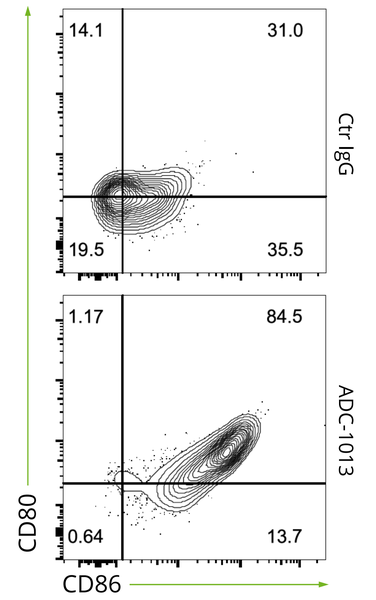


Figure 2 – Effect of ADC-1013 on splenic dendritic cell activation. Mice (hCD40tg) were administered one dose of 100 µg ADC-1013 i.p. and spleens collected for FACS analysis at the indicated time points following treatment. Graph shows percent CD80$^+$ CD86$^+$ cells ± SEM within the CD11c$^+$ MHCII$^+$ population. Representative FACS plots are shown for the 24 h time point.

OVA vaccination model for evaluation of ADC-1013 effect on antigen-specific T cells

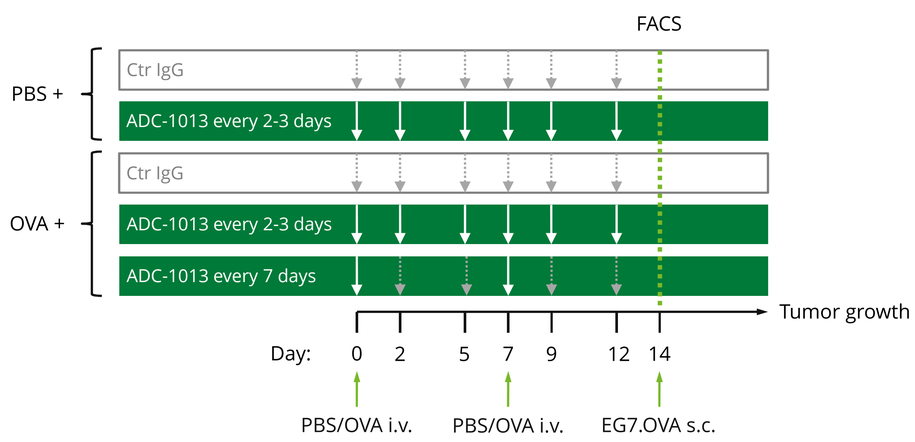
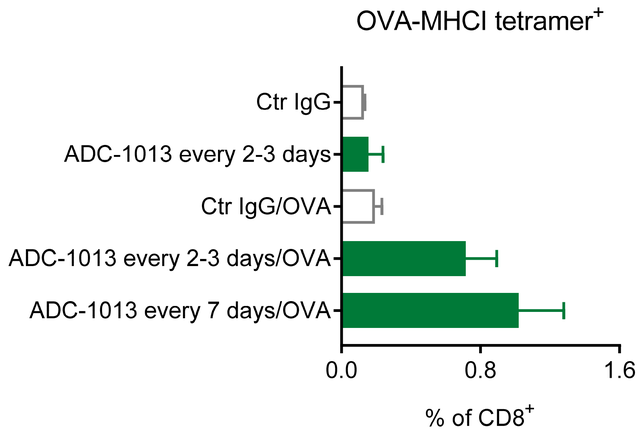


Figure 3 – Experimental strategy for the OVA vaccination model. Mice (hCD40tg) were divided in five groups. Three groups were administered 200 µg OVA i.v. and the remaining two received PBS i.v. on days 0 and 7. Mice were additionally treated with 100 µg ADC-1013 (white arrows) every 2-3 days or every 7 days as outlined. Ctr IgG (100 µg, grey stippled arrows) was administered to two of the groups as control. On day 14, a cohort of mice from each group was sacrificed for FACS analysis of spleens. The remaining mice were inoculated with 1x10^6 EG7.OVA cells s.c. and tumor growth evaluated.

ADC-1013 treatment expands antigen-specific T cells in an OVA vaccination model



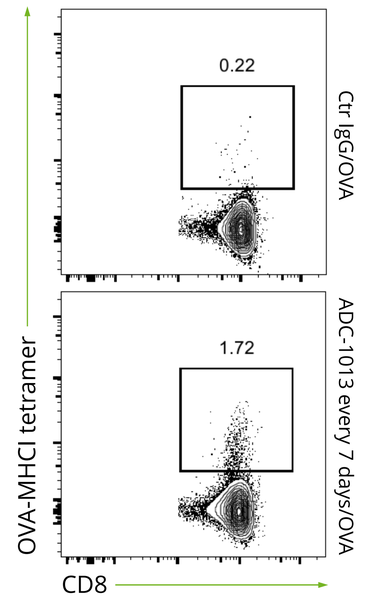
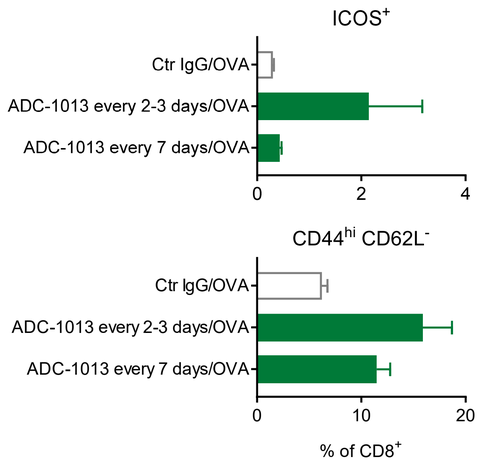


Figure 4 – Effect of ADC-1013 on expansion of OVA-specific T cells. Mice (hCD40tg) were administered 200 µg OVA i.v. and 100 µg ADC-1013 i.p. as shown in Figure 3. Spleens were collected for FACS analysis on day 14. Graph shows percent OVA peptide (SIINFEKL)-MHCI tetramer$^+$ cells ± SEM within the CD8$^+$ population. Representative FACS plots from two groups are shown.

ADC-1013 treatment results in improved T cell activation



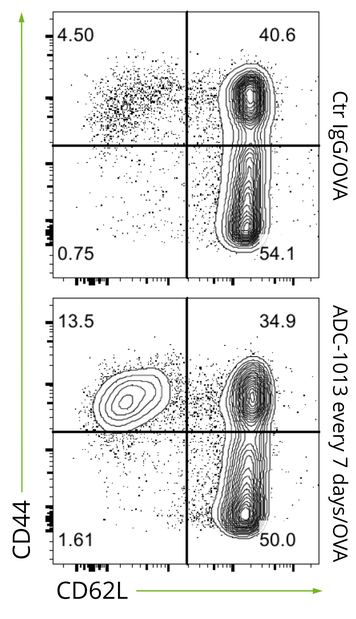


Figure 5 – Effect of ADC-1013 on splenic T cell activation. Mice (hCD40tg) were administered 200 µg OVA i.v. and 100 µg ADC-1013 i.p. as shown in Figure 3. Spleens were collected for FACS analysis on day 14. Graphs show percent ICOS$^+$ (top) and CD44^{hi} CD62L$^-$ (bottom) cells ± SEM within the CD8$^+$ population. Representative FACS plots from two groups are shown for CD44^{hi} CD62L$^-$ cells.

OVA vaccination combined with ADC-1013 treatment delays EG7.OVA tumor growth

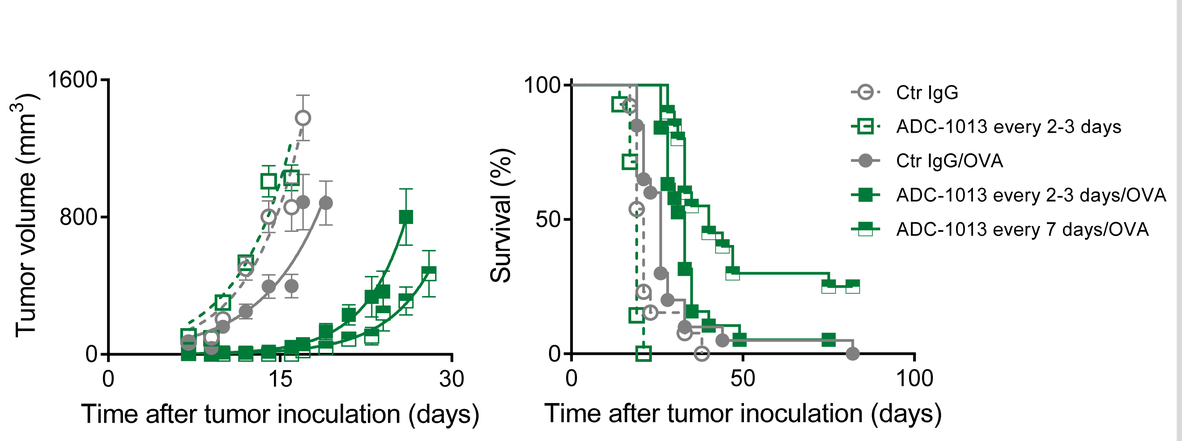


Figure 6 – Effect of OVA vaccination combined with prophylactic ADC-1013 treatment on EG7.OVA tumor growth. Mice (hCD40tg) were administered 200 µg OVA i.v. and 100 µg ADC-1013 i.p. as shown in Figure 3 and were inoculated with 1x10^6 EG7.OVA cells s.c. No additional treatments were administered following tumor inoculation. Graphs show tumor volume ± SEM (left) and percent survival (right) from two pooled experiments.

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