

The CTLA-4 x OX40 bispecific antibody ATOR-1015 induces anti-tumor effects through tumor-directed immune activation

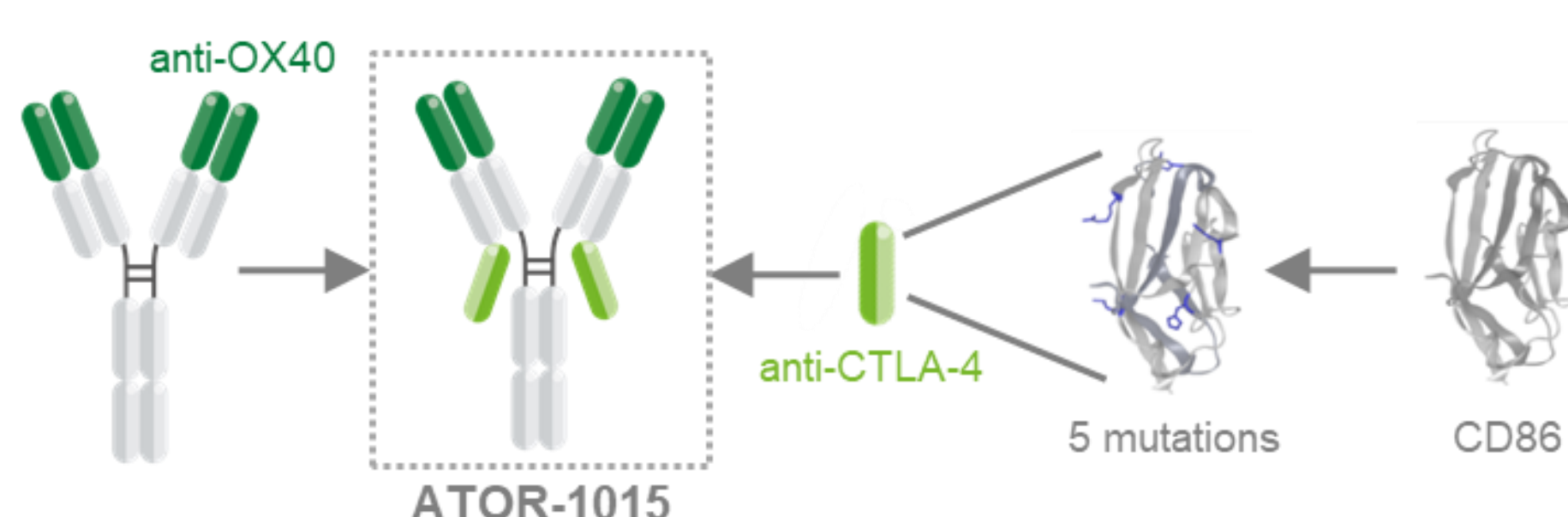
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ATOR-1015 – a human CTLA-4 x OX40 IgG1 bsAb

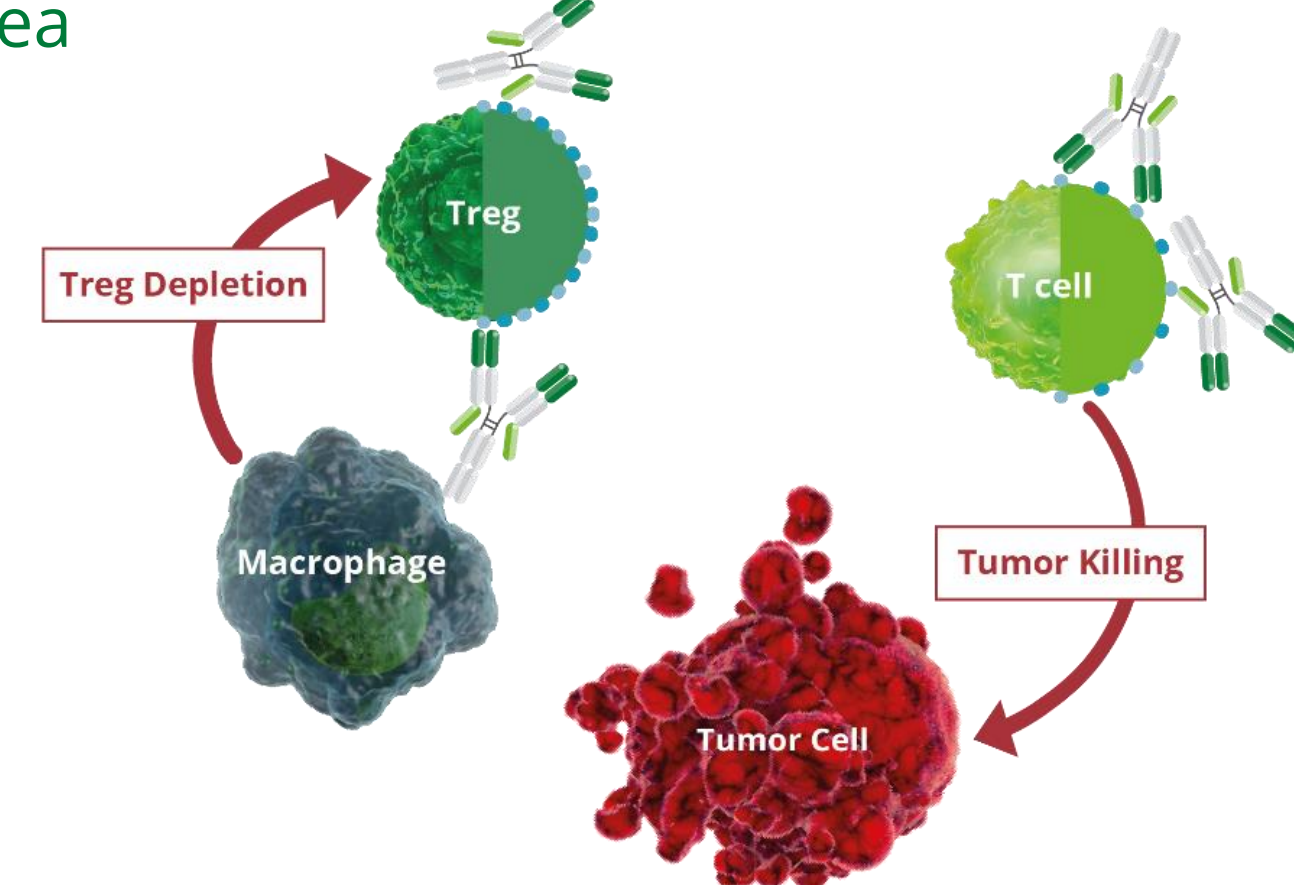
Molecular design

- The Fab domains consist of an OX40 binder generated using ALLIGATOR-GOLD®
- The CTLA-4 binder was generated by FIND® optimization of the VH domain of CD86
- The CTLA-4 binder was fused to the κ light chain via a linker



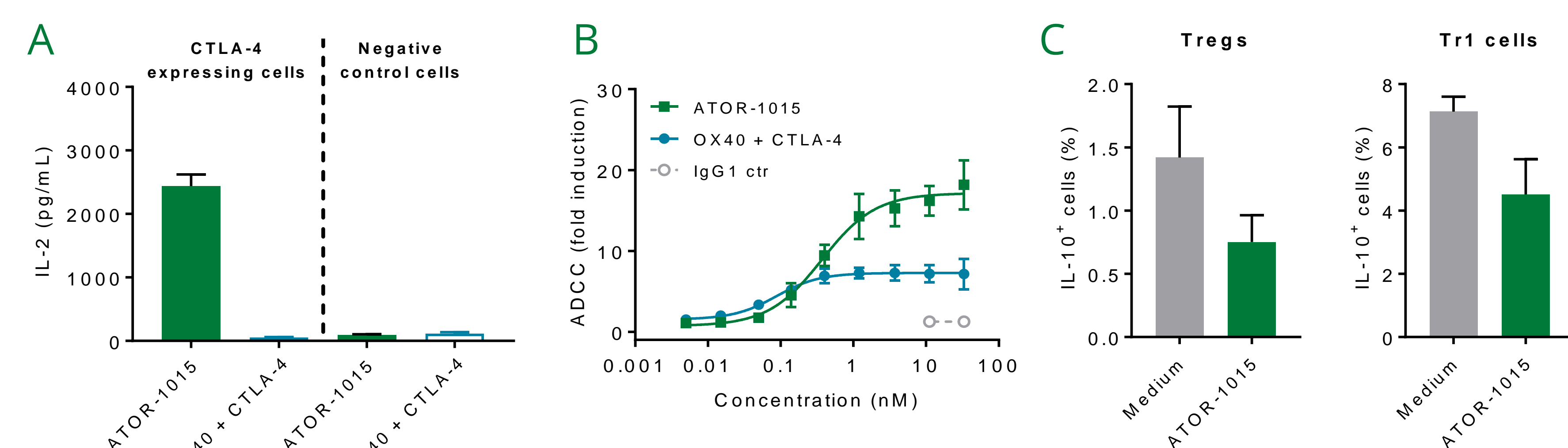
Mode of action

- CTLA-4 and OX40 are highly expressed on Tregs in the tumor area
- ATOR-1015 activates T cells and depletes Tregs
- Dual targeting directs the effect to the tumor area



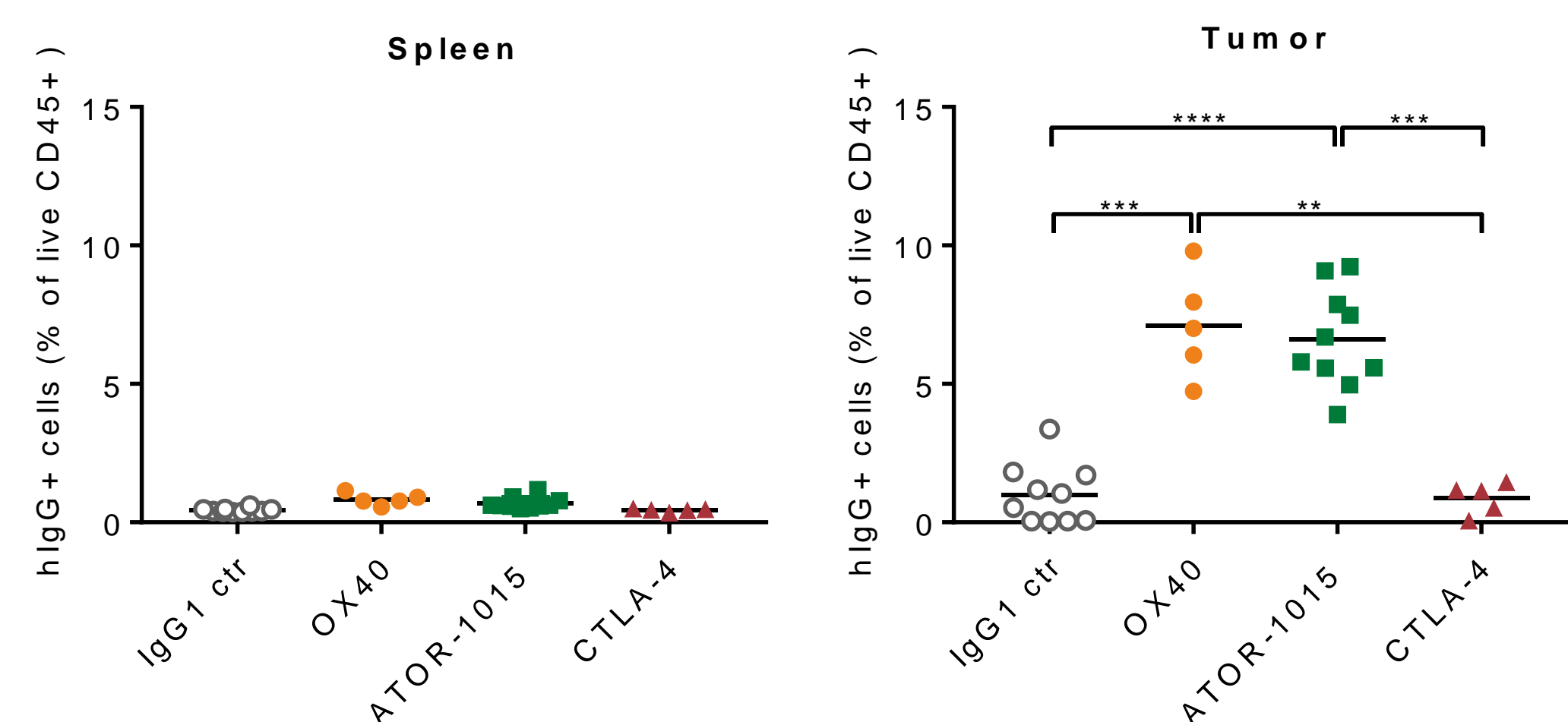
ATOR-1015 activates human T cells and depletes/suppresses Tregs

Superior effect of ATOR-1015 compared to the combination of OX40 and CTLA-4



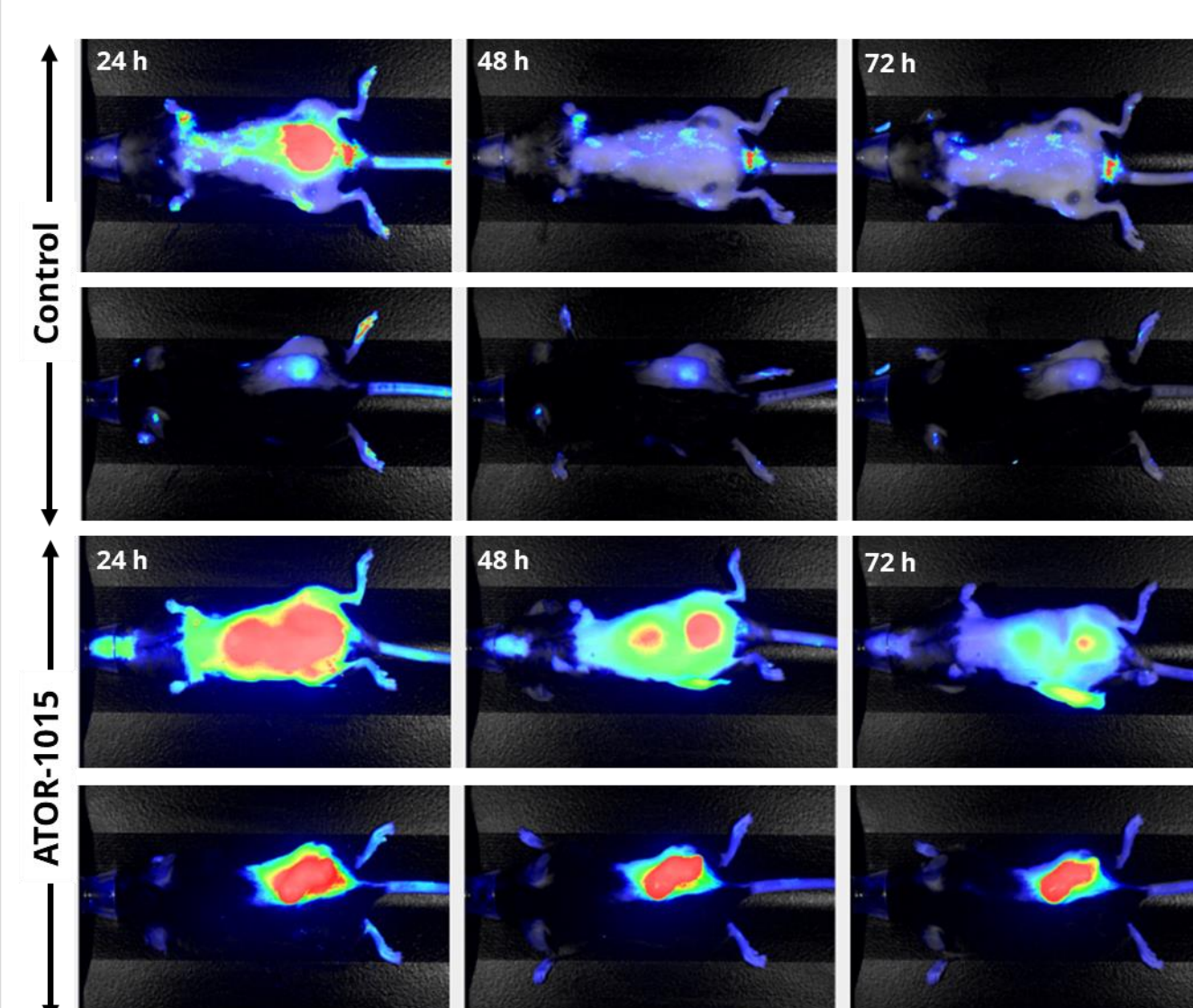
ATOR-1015 targets the tumor

ATOR-1015 selectively binds to target-expressing cells in the tumor

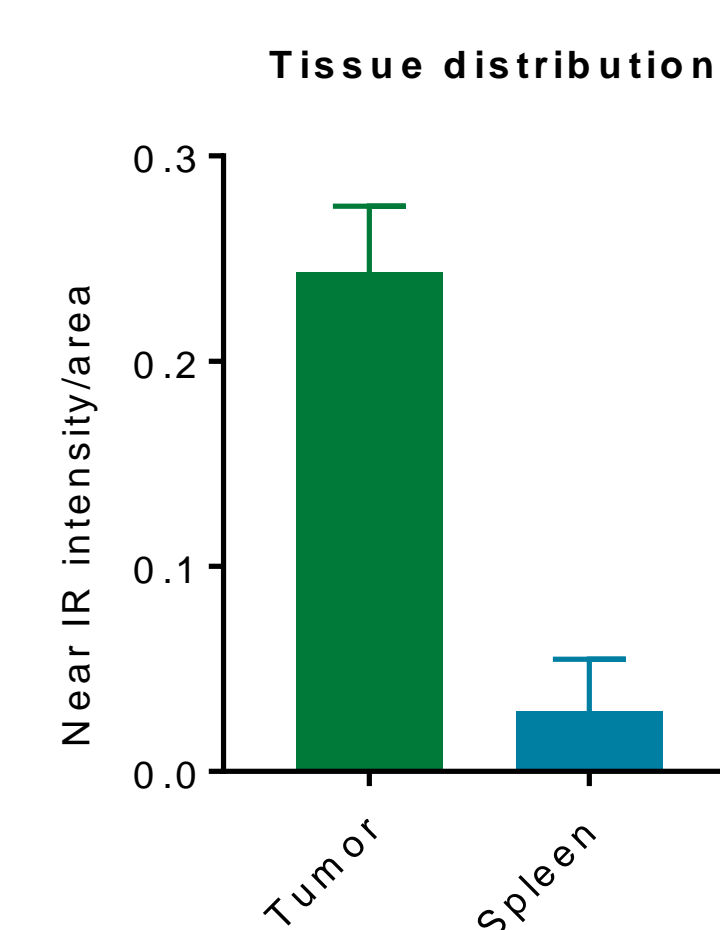


hOX40tg mice with MC38 tumors were treated with antibodies (10 mg/kg) on day 17. Tumors and spleens were collected 24 h later, stained with an anti-human IgG antibody and analyzed by flow cytometry. Data show the percentage of hlgG⁺ cells out of total live CD45⁺ cells. Statistics, Mann-Whitney, two-tailed.

ATOR-1015 localizes to the tumor

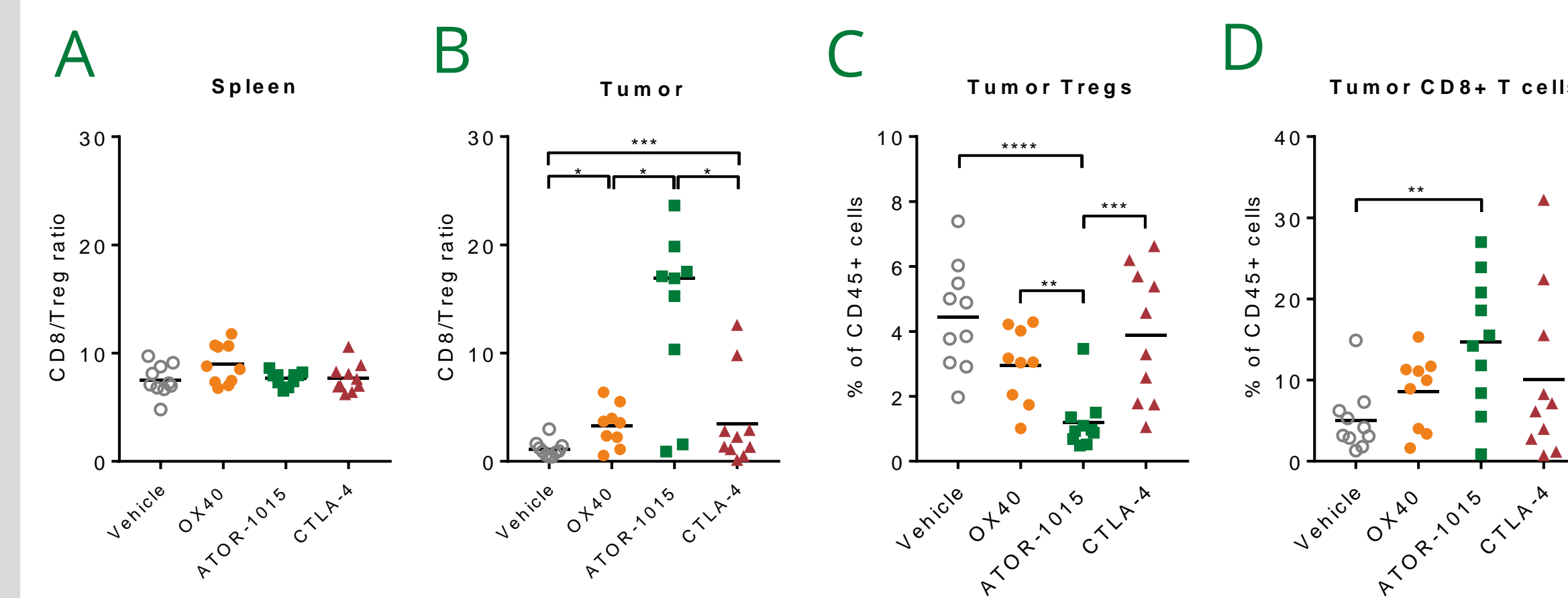


hOX40tg mice with MC38 tumors were treated i.v. with IRDye800CW-labelled ATOR-1015 or labelled probe on day 17. Tumor targeting was investigated prior to and 24, 48 and 72 h post administration using *in vivo* imaging. Distribution of ATOR-1015 in tumor and spleen was measured at study termination (n=3).



ATOR-1015 has tumor-directed activity

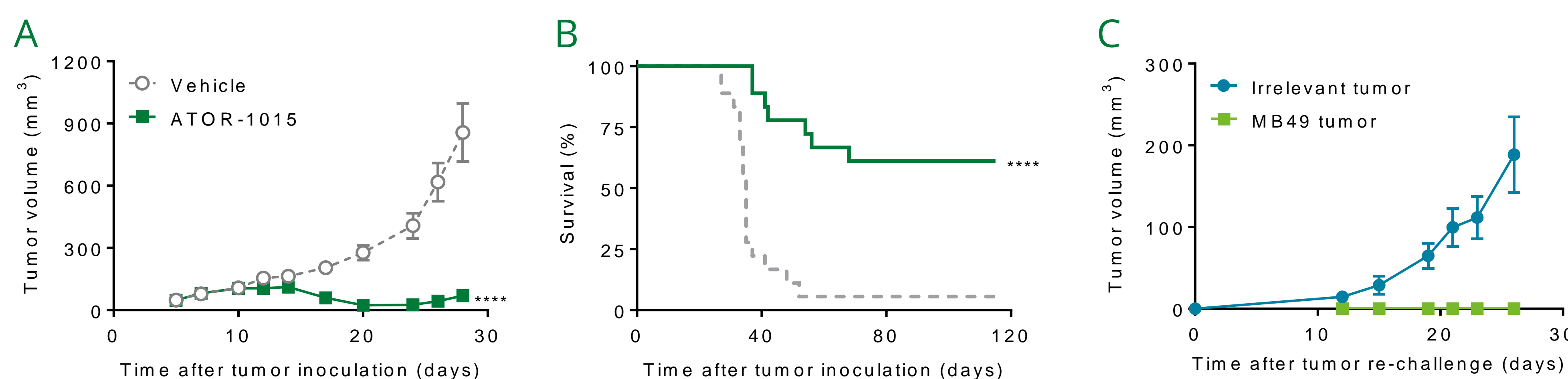
ATOR-1015 depletes Tregs and activates Teffs in the tumor



hOX40tg mice with MC38 tumors were treated with Abs (10 mg/kg) on days 10, 14, and 18. Flow cytometry analysis of the tumors and spleens were done 24 h after last the treatment. **(A-B)** CD8⁺ Teff/Treg ratio systemically (spleen) and in the tumor, **(C-D)** Intratumoral Treg content and CD8⁺ Teff content. Statistics, Mann-Whitney, two-tailed.

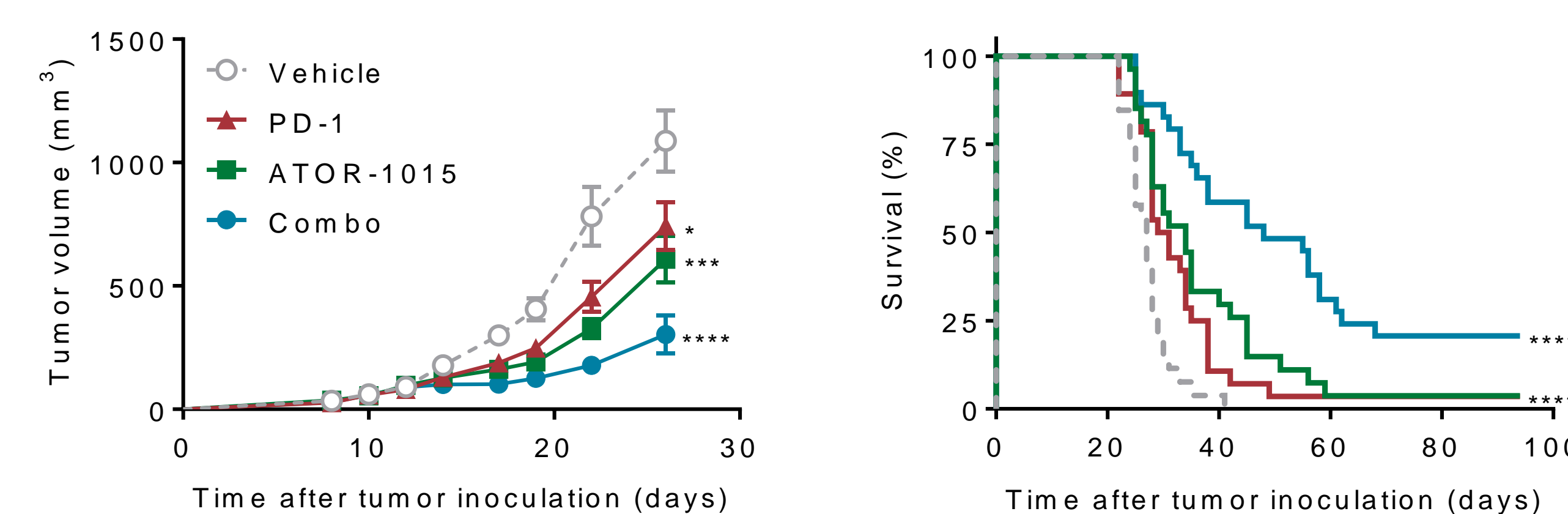
ATOR-1015 treatment induces potent anti-tumor effects in hOX40tg mice with syngeneic tumors

ATOR-1015 cures mice from MB49 bladder cancer and induces long-term tumor-specific immunological memory



The effect of ATOR-1015 in MB49 bladder carcinoma in terms of **(A)** tumor growth, and **(B)** survival (n=18). hOX40tg mice were inoculated s.c. with MB49 tumor cells. ATOR-1015 (10 mg/kg) or vehicle was administered i.p. on days 7, 10, and 13. Statistics versus vehicle, Mann-Whitney, two-tailed. **(C)** Re-challenge of cured mice from (B) in a twin tumor model with a specific (MB49) or an irrelevant tumor (PANC02) demonstrating tumor-specific immunological memory. The graphs show mean \pm SEM.

ATOR-1015 enhances the effect of PD-1 treatment in mice with MC38 colon cancer



Anti-tumor effects of ATOR-1015 with an α PD-1 antibody (RPM1-14) in MC38 colon carcinoma (n=10). Tumor cells were implanted s.c. in hOX40tg mice. ATOR-1015 (10 mg/kg) with or without α PD-1 antibody (10 mg/kg) was administered i.p. on days 7, 10, and 13. The graphs show mean \pm SEM. Statistics versus vehicle, Mann-Whitney, two-tailed.

ATOR-1015 is a next generation CTLA-4 antibody with enhanced Treg depletion and tumor-directed activity for improved efficacy and reduced toxicity