Uncoupling Toxicity from Therapeutic Efficacy: A Case Study on ATOR-1015

13/04/2021

As previously discussed in our related commentary[a], several studies have shown that CTLA-4 blockade, especially when combined with PD-1 targeting, improves overall survival of cancer patients.[1–3] However, existing anti-CTLA-4 treatments, both in mono and combination therapies, are associated with severe immune adverse effects that strongly limit their use, thus calling for the development of new treatments against this negative T-cell regulator.

A promising approach to uncouple toxicity from efficacy is the use of bispecific antibodies (BsAb) targeting two markers of interest, aiming at favoring their localization to the tumor. To this end, scientists at Alligator Bioscience developed a novel BsAb—ATOR-1015—that simultaneously targets CTLA-4 and OX40.[4] This compound was shown to be able, *in vitro*, to crosslink cells expressing CTLA-4 and cells expressing OX40, and to induce T-cell activation and depletion of Tregs.

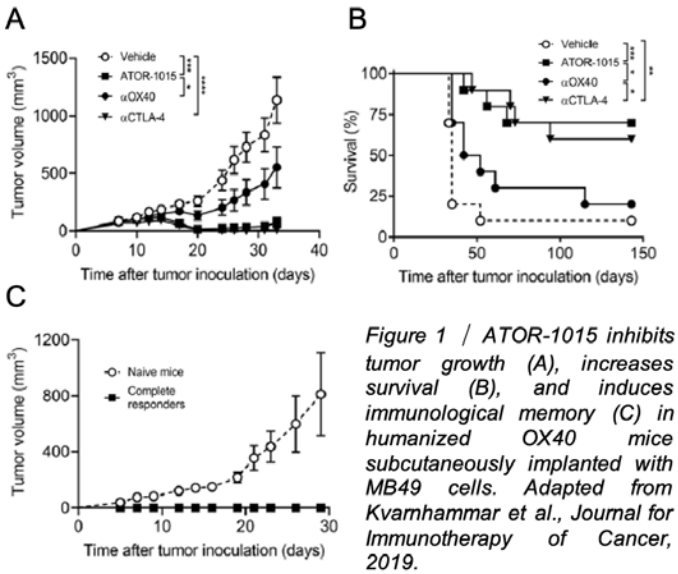

Figure 1 / ATOR-1015 inhibits tumor growth (A), increases survival (B), and induces immunological memory (C) in humanized OX40 mice subcutaneously implanted with MB49 cells. Adapted from Kvarnhammar et al., Journal for Immunotherapy of Cancer, 2019.

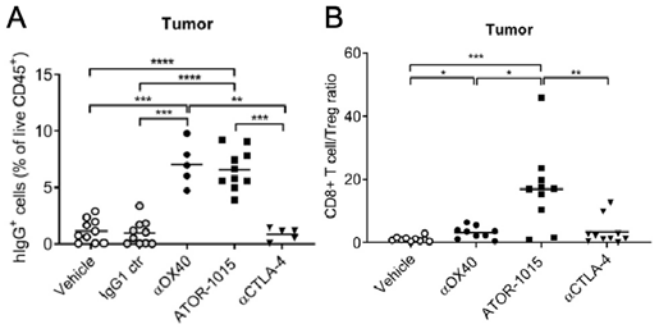

Figure 2 / ATOR-1015 preferentially binds tumor-infiltrating cells (A), and increases CD8⁺ T-cell/Treg ratio in humanized OX40 mice subcutaneously implanted with MC38 cells. Adapted from Kvarnhammar et al., Journal for Immunotherapy of Cancer, 2019.

To assess their compound *in vivo*, the authors tested ATOR-1015 efficacy in syngeneic models using humanized OX40 (hOX40) mice. They showed that this novel BsAb reduced tumor volume (Fig.1A) and improved survival (Fig.1B) compared to last-generation CTLA-4 monotherapies. Interestingly, this treatment also induced immunological memory, as mice cleared of tumor after ATOR-1015 treatment (complete responders) did not develop tumor in a re-challenge assay (Fig. 1C).

These syngeneic models were also used to more specifically study ATOR-1015 targeting of immune cells in the tumor, and its potential to activate said immune cells. Indeed, ATOR-1015 was shown to be directed to the tumor, where it selectively bound to tumor-infiltrating cells (Fig. 2A) and increased CD8⁺ T-cell/Treg ratio (Fig. 2B). Interestingly, the novel BsAb performed better than both anti-CTLA-4 and anti-OX40 antibodies alone in these assays, demonstrating its superiority to conventional treatments.

These encouraging preclinical results prompted the initiation of a first-in-human trial to treat patients with advanced and/or refractory solid malignancies with ATOR-1015. Preliminary results are already available and suggest a positive effect on clinical outcomes and reduced irAEs.[5,6]

Of note, the humanized mouse preclinical model used in this study was generated by genOway, designer and provider of multiple preclinical models[(b)] in immuno-oncology. The hOX40 mouse[(c)] enables the *in vivo* efficacy assessment and profiling of immuno-oncology agents targeting the human immune checkpoint OX40 in fully immunocompetent mice.

See also:

Uncoupling Toxicity from Therapeutic Efficacy: A Case Study on MEDI5752
https://www.genoway.com/case-studies/medi5752.htm

References:

1. Rotte A. Combination of CTLA-4 and PD-1 blockers for treatment of cancer. *J Exp Clin Cancer Res.* 2019;38(1):255. doi:10.1186/s13046-019-1259-z
2. Antonia SJ, López-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. *The Lancet Oncology.* 2016;17(7):883-895. doi:10.1016/S1470-2045(16)30098-5
3. Robert C. A decade of immune-checkpoint inhibitors in cancer therapy. Nat Commun. 2020;11(1):3801. doi:10.1038/s41467-020-17670-y
4. Kvarnhammar AM, Veitonmäki N, Hägerbrand K, et al. The CTLA-4 x OX40 bispecific antibody ATOR-1015 induces anti-tumor effects through tumor-directed immune activation. *J Immunother Cancer.* 2019;7(1):103. doi:10.1186/s40425-019-0570-8
5. Yachnin J, Ullenhag GJ, Carneiro A, et al. A first-in-human phase I study in patients with advanced and/or refractory solid malignancies to evaluate the safety of ATOR-1015, a CTLA-4 x OX40 bispecific antibody. *JCO.* 2020;38(15_suppl):3061-3061. doi:10.1200/JCO.2020.38.15_suppl.3061
6. Alligator Bioscience AB. *ATOR-1015 First-in-Human Study.* https://clinicaltrials.gov/ct2/show/study/NCT03782467

(a) genOway. https://www.genoway.com/commentaries/uncoupling-toxicity-from-therapeutic-efficacy.htm
(b) genOway. https://www.genoway.com/catalog/overview.htm
(c) genOway. https://www.genoway.com/catalog/humanized-immune-checkpoints/st/hox40.htm