ATOR-1017, a 4-1BB antibody with potential for combination with other immunotherapies

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INTRODUCTION

- 4-1BB is a co-stimulatory receptor highly expressed on tumor reactive CD8+ T cells and NK cells infiltrating the tumor.
- Exhausted tumor specific T cells can be rescued by 4-1BB co-stimulation
- 4-1BB co-stimulation activates cytotoxic T cell and NK cell-mediated anti-tumor responses.

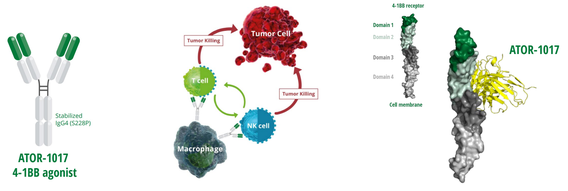

Figure 1. ATOR-1017 4-1BB antibody agonist and mechanism of action

ATOR-1017 is designed for superior efficacy and safety

- ATOR-1017 is a monoclonal antibody (IgG4) dependent on FcγR-mediated crosslinking for its activity.
- ATOR-1017 binds to domain 2 and blocks endogenous 4-1BB ligand which reduces the risk of a potential exaggerated pharmacology .
- No safety concerns identified in GLP non-human primate toxicity studies.

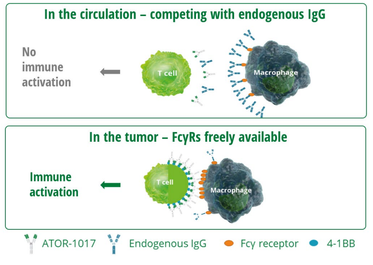

Figure 2. ATOR-1017 was designed to be tumor-directed

ATOR-1017 was designed to be tumor directed

- Co-localized expression of 4-1BB and FcγRs in tumors results in tumor-directed immune activation, hence less risk of systemic toxicity.
- High concentrations of endogenous IgG in the circulation (67 µM) and in highly vascularized tissues (e.g. liver) blocks immune activation with ATOR-1017 by competing for binding to FcγRs
- High expression of 4-1BB on tumor reactive T cells within the tumor and tumor draining lymph nodes enriches ATOR-1017 over endogenous IgG which passively diffuses into the extravascular tissues

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ATOR-1017 induces a potent CD8+ T cell and NK cell activation

- ATOR-1017 induces a potent and cross-linking dependent activation of CD8⁺ T cells and NK cells.
- Activation of cytotoxic CD8⁺ T cells is critical for a long-lasting anti-tumor effect.
- Activation of NK cells further enhances the activity of ATOR-1017.

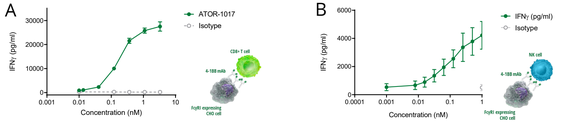

Figure 3. (A) CD8+ T cell activation of ATOR-1017 was demonstrated using primary human CD8+ T cells stimulated with anti-CD3 mAb (to upregulate 4-1BB), and co-stimulated with ATOR-1017 in the presence of FcγR expressing cells (n≥5). (B) NK cells (CD3-CD56+CD16+) were purified from human peripheral blood (n=7), pre-activated with 200 IU (10 ng/ml) IL-2 over night and activated with ATOR-1017 in the presence of FcγR expressing CHO cells. Following incubation, IFN-γ concentrations were determined in supernatants by ELISA and shown as mean ± SEM.

ATOR-1017 induces a potent anti-tumor response

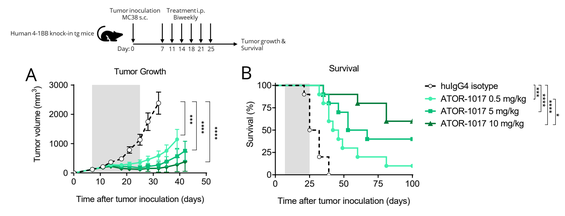

Figure 4. Anti-tumor efficacy demonstrated with ATOR-1017 in human 4-1BB knock-in mice bearing MC38 colon carcinoma (n=10/group). The mice were treated 6 times (0.5, 5 or 10 mg/kg) biweekly starting day 7 after tumor cell inoculation, as indicated by the highlighted area. Anti-tumor efficacy is shown as (A) mean tumor volume +/- SEM and (B) survival. Mann-Whitney, non-parametric 2-tailed t-test and Kaplan Meier, Log-Rank.

ATOR-1017 induces a long-lasting immunological memory

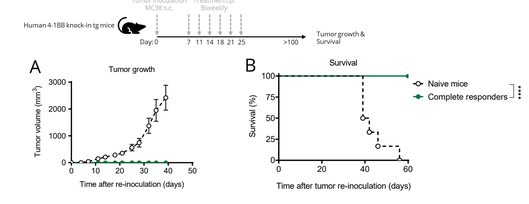

Figure 5. Complete responders (n=11) obtained from all treatment groups (0.5, 5 and 5 mg/kg) from the previously described anti-tumor efficacy study versus a group of naïve mice (n=6) were re-challenged with MC38 colon carcinoma. (A) Tumor volume depicted as mean +/- SEM and (B) survival. Kaplan Meier, Log-Rank.

ATOR-1017 combined with anti-PD-1 improves antitumor responses

- ATOR-1017 combined with anti-PD-1 improves survival and induces a significant reduction in tumor growth compared with each monotherapy.

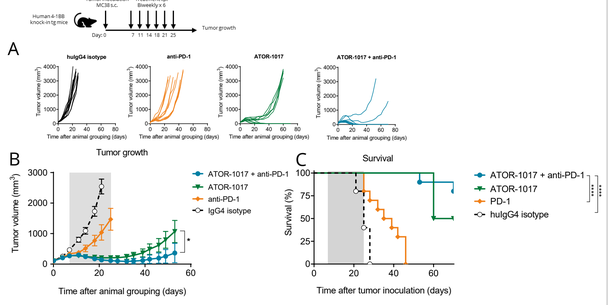

Figure 6. Anti-tumor effect of ATOR-1017 in combination with mouse anti-PD-1 (RMP1-14) given to human 4-1BB knock-in mice bearing MC-38 colon carcinoma (n=10). Seven days post tumor cell inoculation mice were treated IP with huIgG4 (100 µg/dose), mouse anti-PD-1 (100µg/dose) or ATOR-1017 (100 µg/dose) were given on days 0, 4, 7, 11, 14 and 18 as indicated by the highlighted area. (A) Individual tumor growth per treatment, (B) tumor volume depicted as mean +/- SEM. (C) Survival (n=10). Statistical differences were analyzed using Mann-Whitney, non-parametric t-test for tumor growth and Kaplan Meier, Log-Rank for survival.

ATOR-1017 induces a tumor-directed immune activation

- ATOR-1017 expands CD8⁺ T cells and 4-1BB expressing CD8⁺ T cells in the tumor but not in the spleen.

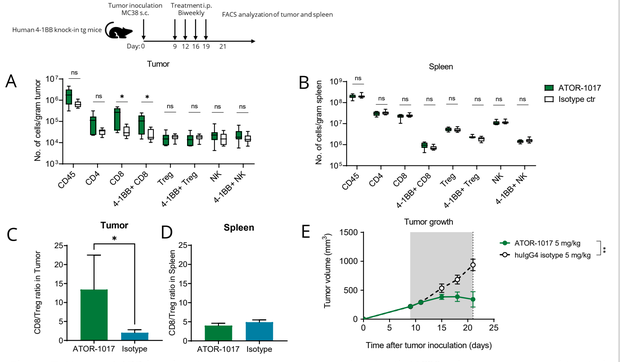

Figure 7. Human 4-1BB knock-in transgenic mice were inoculated with MC38 colon carcinoma and treated with 5 mg/kg ATOR-1017 (n=8) or IgG4 isotype (n=8) 4 times biweekly starting day 9 after tumor inoculation, as indicated by the highlighted area. At day 21, immune cell infiltration in (A) tumors and (B) spleens was analyzed with flow cytometry as absolute counts. CD8/Treg ratio was evaluated in (C) tumor and (D) spleen. (E) Immune cell Infiltration in the tumor correlated with a potent anti tumor efficacy shown as mean tumor volume +/- SEM. Mann-Whitney, non-parametric 2-tailed t-test.

ATOR-1017 combined with anti-PD-1 improves T cell activation and overcomes T cell exhaustion

- ATOR-1017 combined with anti-PD-1 synergistically improves activation of both regular CD4⁺ T cells and exhausted CD4⁺ T cells in a MLR assay.

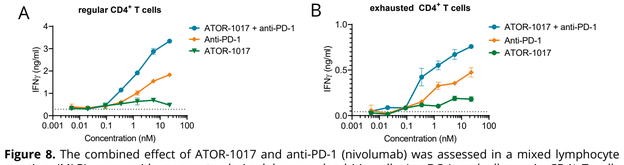

Figure 8. The combined effect of ATOR-1017 and anti-PD-1 (nivolumab) was assessed in a mixed lymphocyte reaction (MLR) assay with monocyte derived human dendritic cells (moDCs) and allogeneic CD4⁺ T cells (unstimulated or exhausted) co-cultures for 7 days (ratio 1:10) in the presence of ATOR-1017, anti-PD-1 and anti-Fc. Exhausted CD4⁺ T cells were generated after repeated anti-CD3/CD28 stimulation and characterized as increased expression of PD-1, LAG-3 and TIM-3 and reduced capacity to respond to allogeneic stimuli. Following incubation, IFN-γ concentrations were determined in supernatants by ELISA. Baseline MLR activation indicated with dotted line. Data from the same DC:T cell donor pair, out of three similar, with (A) regular or (B) exhausted CD4+ T cells is presented.

ATOR-1017 First-in-Human trial, update

- This is a first-in-human, multicenter, open-label, phase 1 dose-escalation trial of ATOR-1017, in patients with advanced and/or metastatic solid malignancies
- ATOR-1017 has been dosed up to 360 mg (data cut-off Oct 19th 2021)
- ATOR-1017 demonstrates an encouraging safety profile (data cut-off Oct 19th 2021).
- No DLTs were observed and most TRAEs were mild to moderate (one transient Grade 4 and no Grade 5 observed).
- The study is still ongoing; no MTD has been reached.

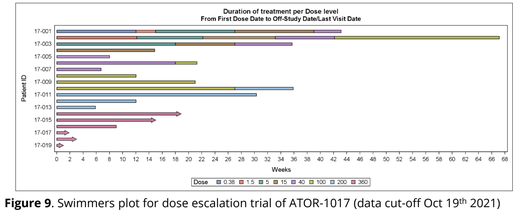

Figure 9. Swimmers plot for dose escalation trial of ATOR-1017 (data cut-off Oct 19th 2021)

CONCLUSIONS

- **The combination of ATOR-1017 and anti-PD-1 was demonstrated to induce a robust antitumor activity, improve immune activation and overcome T cell exhaustion in preclinical models.**
- **ATOR-1017 induces a cytotoxic immune cell response leading to a tumor-directed immune activation in experimental tumor models, a potent anti-tumor response and immunological memory.**
- **ATOR-1017 is FcγR crosslinking dependent and therefore directs the immune response to the tumor tissue and tumor draining lymph nodes where target expression is high, while the risk for immune activation in the circulation is low due to the high concentration of competing endogenous circulating IgG.**
- **The FIH phase I study with ATOR-1017 is ongoing; no MTD reached.**