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Alligator Bioscience AB, Lund, Sweden

ATOR-1017, a 4-1BB Antibody Developed for Tumor-Directed Immunotherapy of Cancer

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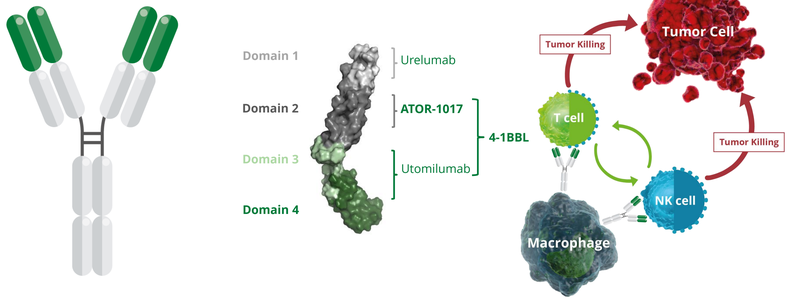
ATOR-1017, background and mode of action

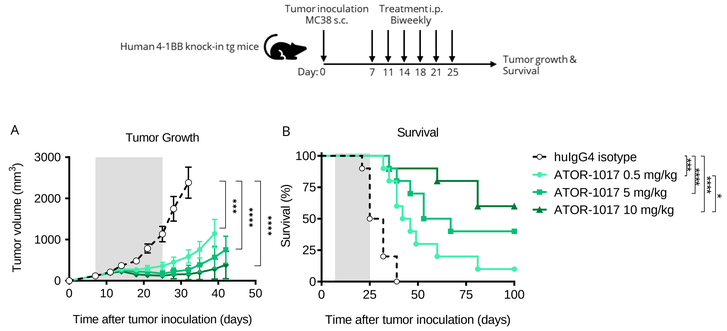


FcγR crosslinking dependent 4-1BB agonist in a stabilized IgG4 format

Binds to a unique domain on the 4-1BB receptor

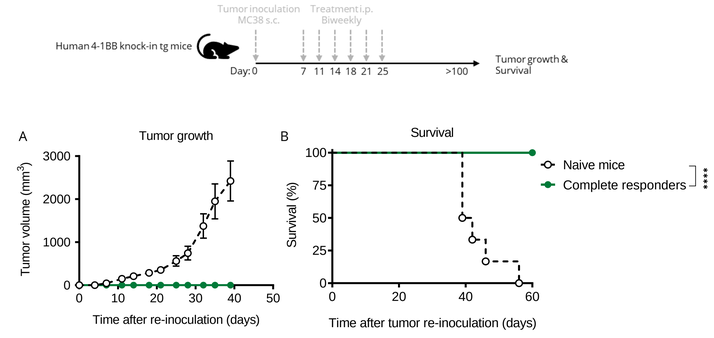
Activates T effector cells and NK cells in the tumor microenvironment

ATOR-1017 induces a potent anti-tumor response



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 an immunological memory

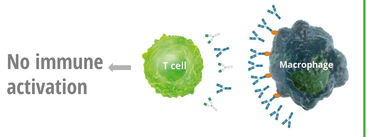


Complete responders (n=11) obtained from all treatment groups (0.5, 5 and 5 mg/kg) from the previously described anti-tumor efficacy study versus a group of naïve mice (n=6) were re-challenged with MC38 colon carcinoma. (A) Tumor volume depicted as mean +/- SEM and (B) survival. Kaplan Meier, Log-Rank.

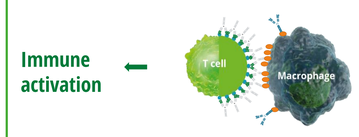
ATOR-1017 is anticipated to be tumor directed

- High concentration 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 within the tumor and tumor draining lymph nodes enriches ATOR-1017 over endogenous IgG which passively diffuses into the extravascular tissues

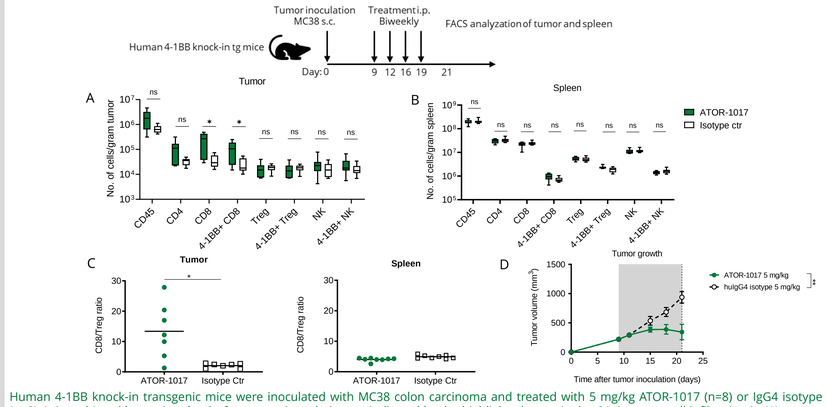
ATOR-1017 in the circulation



ATOR-1017 in the tumor



ATOR-1017 expands effector T cells in the tumor but not in the spleen



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 and (C) CD8/Treg ratio was evaluated. (D) 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.

Summary and conclusions

- ATOR-1017 induced a potent tumor-directed immune response, leading to an efficient tumor eradication and survival
- ATOR-1017 induced a long-lasting immunological memory
- ATOR-1017 increased CD8 T cell infiltration and improved CD8/Treg ratio in the tumor, but no immune effects were detected in the spleen
- ATOR-1017 is FcγR crosslinking dependent and is expected to direct the immune response to the tumor tissue and tumor draining lymph nodes where target expression is high
- The FcγR crosslinking dependency is anticipated to reduce the risk for immune activation in the circulation, due to the high concentration of endogenous circulating IgG
- A first-in-human phase I study of intravenously administered ATOR-1017 is planned for 2019