

IOA-237 – A potent anti-CD73 mAb demonstrates monotherapeutic and combination efficacy in solid tumor models

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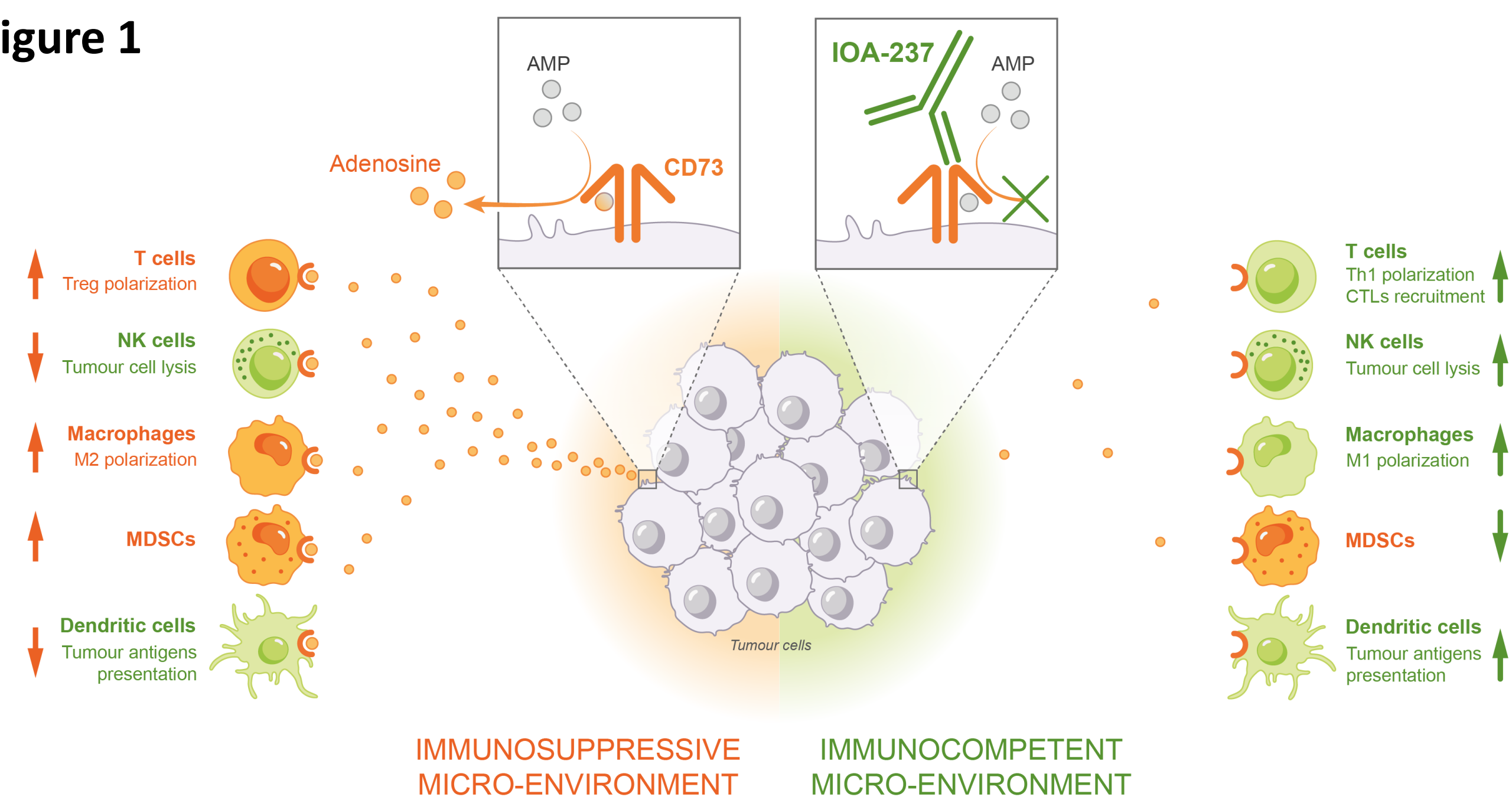


Background

CD73, an ecto-5'-nucleotidase, is frequently overexpressed in the tumor microenvironment and can be found on tumor, stromal cells and immune cells. Its function is to catalyse the conversion of adenosine monophosphate (AMP) to adenosine and phosphate, both at the cell membrane and as a soluble factor. CD73 has gained interest as a therapeutic target in cancer due to the immunosuppressive role of adenosine in the tumor microenvironment. High levels of adenosine cause an immunosuppressive microenvironment in the tumor by signalling via adenosine receptors on a multitude of immune cells.

IOA-237 is a fully human, phage derived monoclonal antibody with high potency against CD73. Inhibition of CD73 by IOA-237 results in reduced levels of adenosine thereby limiting tumor immune suppression. This novel antibody demonstrates in vitro and in vivo characteristics that suggest best-in-class potential (Figure 1).

Figure 1



Methods

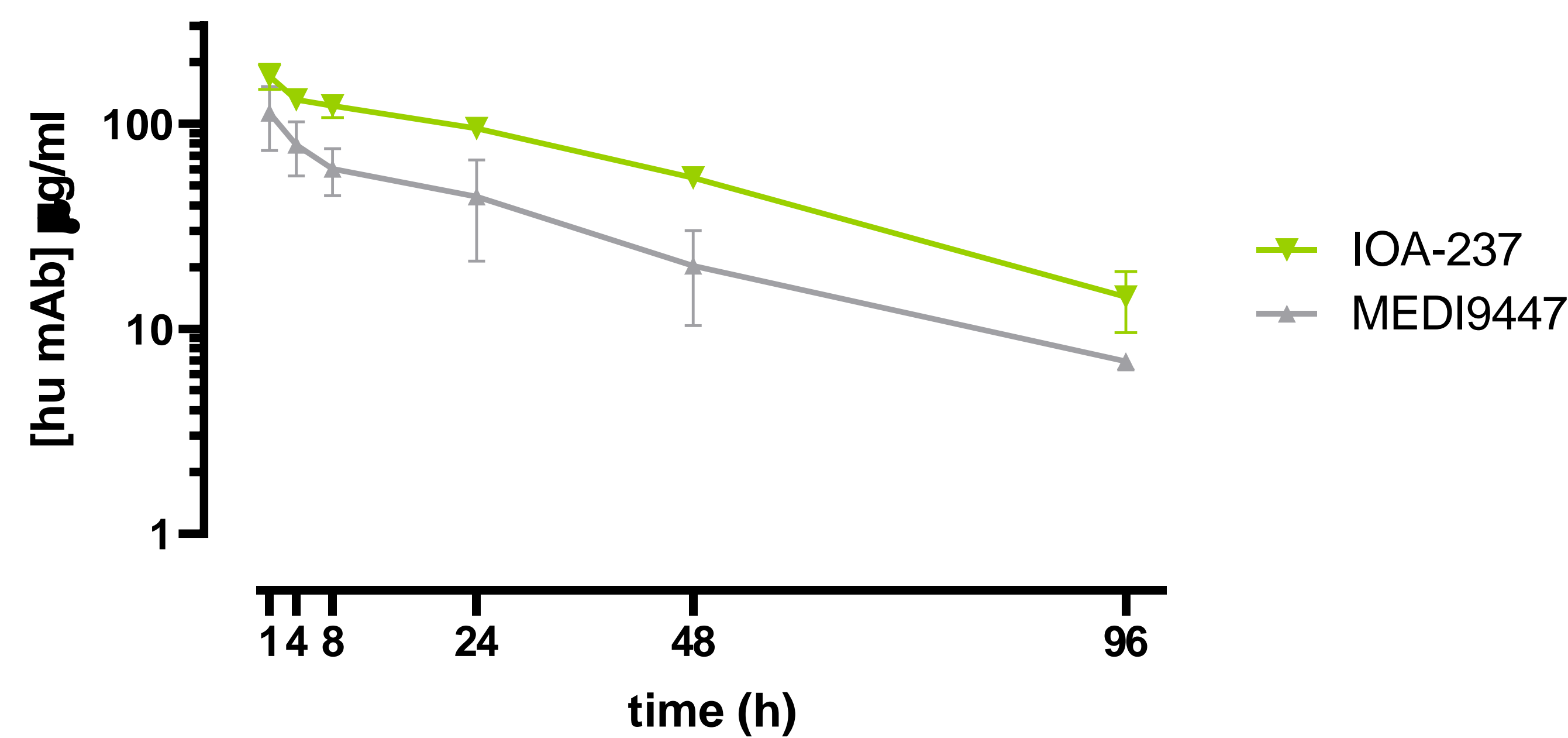
To evaluate the pharmacokinetics of IOA-237, the antibody was injected intravenously in female Balb/c mice at a concentration of 10mg/kg. MEDI9447 was administered intravenously at 10mg/kg. The concentration of antibodies present in serum was measured by ELISA using anti-Human IgG, Fcγ fragment specific goat pAb as capture antibodies and anti-human λ chain-HRP mouse mAb for detection.

For hypersensitivity and efficacy studies, Balb/c (n=5/group) were subcutaneously implanted with CT26 cells and treatment with IOA-237 (10mg/kg) was started at day 3 over 4 twice weekly administrations. In the follow-up study, CT26 tumor-bearing mice (n=12/group) were treated with isotype, IOA-237 or MEDI9447 (10mg/kg). Female C57BL/6 mice (n=10/group) were orthotopically injected in the mammary fatpad with E0771 cells and twice weekly treatment with isotype or IOA-237 (10mg/kg) started on day 3 and continued throughout the experiment. Isotype control groups received human isotype antibody. AUC was calculated with an unpaired t-test.

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IOA-237 has a favorable PK profile

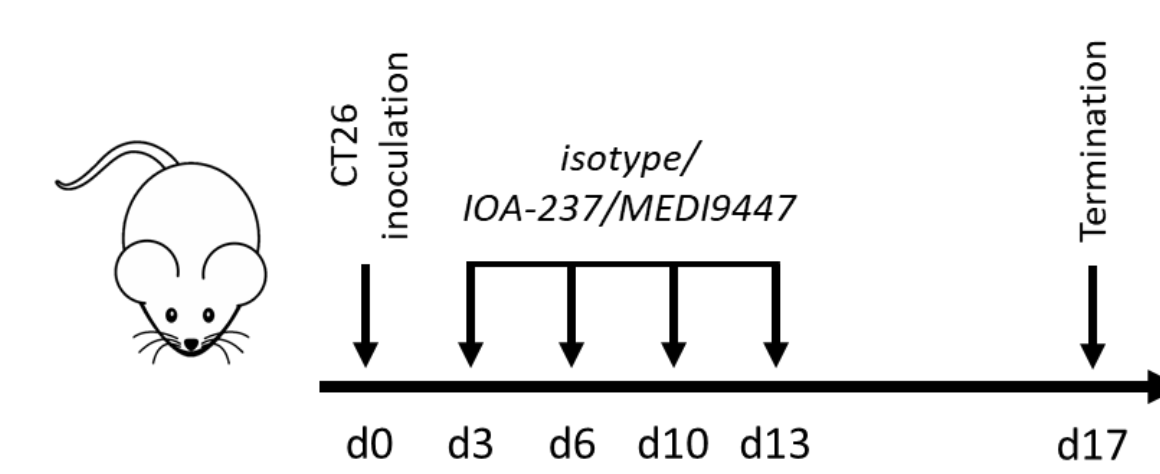
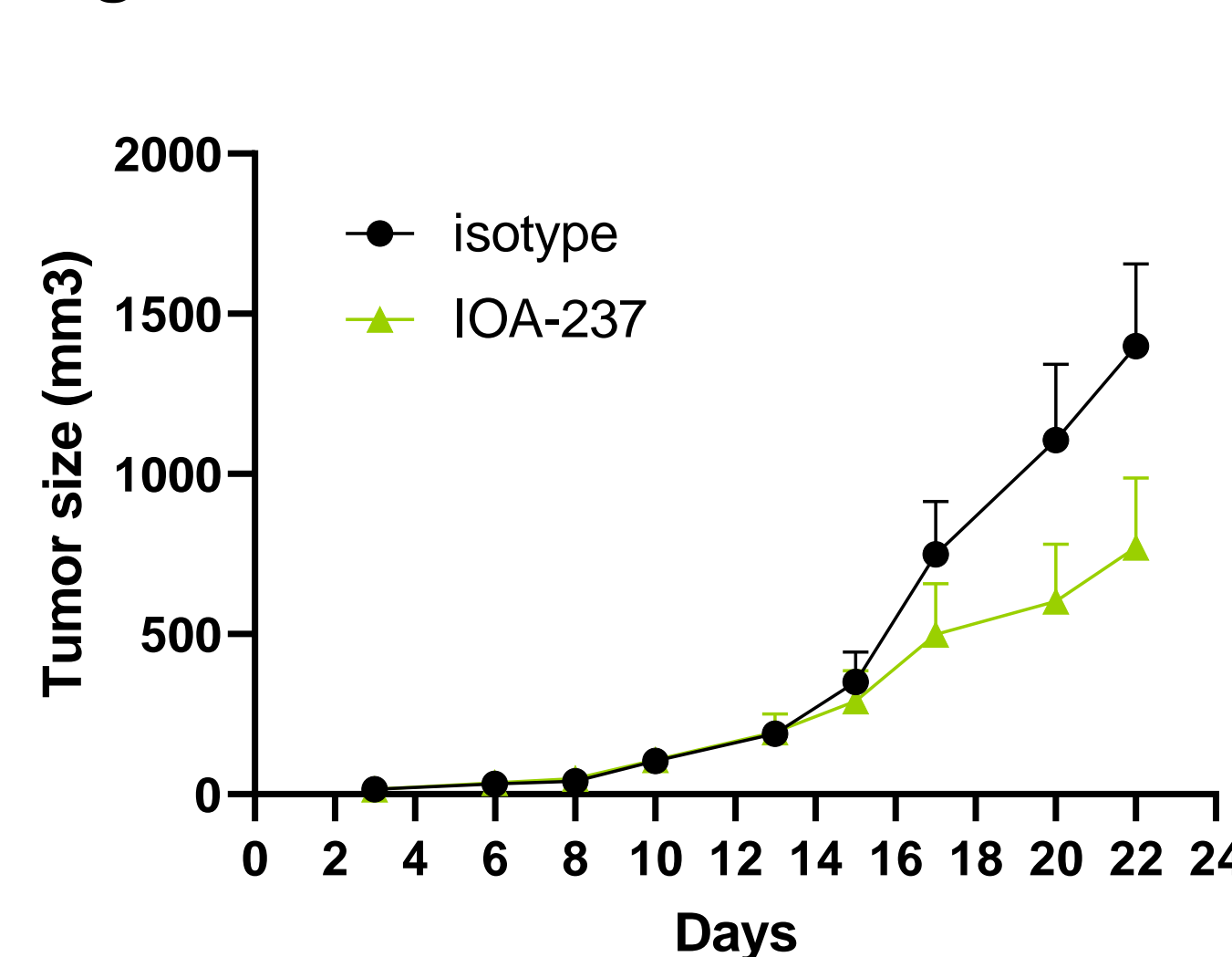
Figure 2



The pharmacokinetic profile of IOA-237 showed to be favorable over the clinical stage competitor MEDI9447 when administered intravenously to Balb/c mice. (Figure 2).

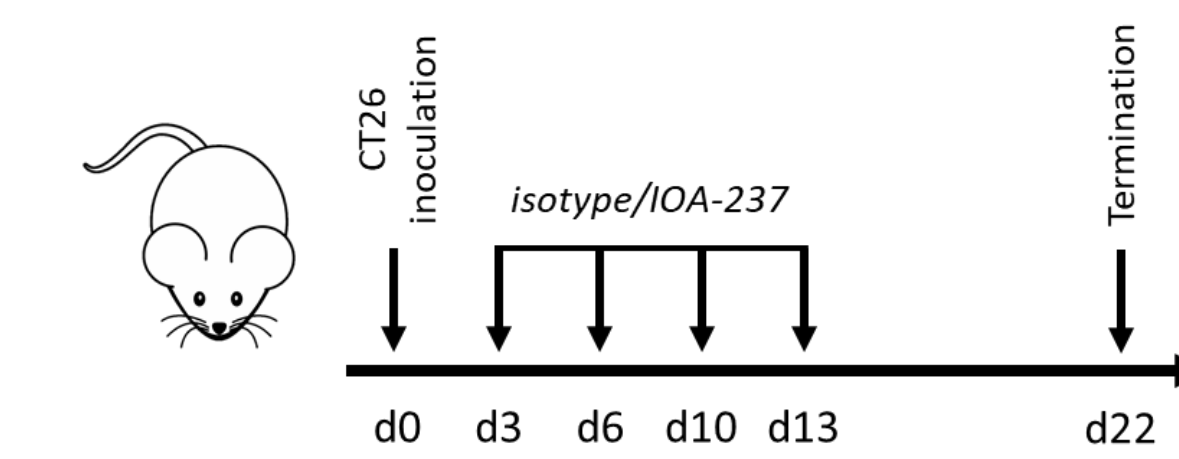
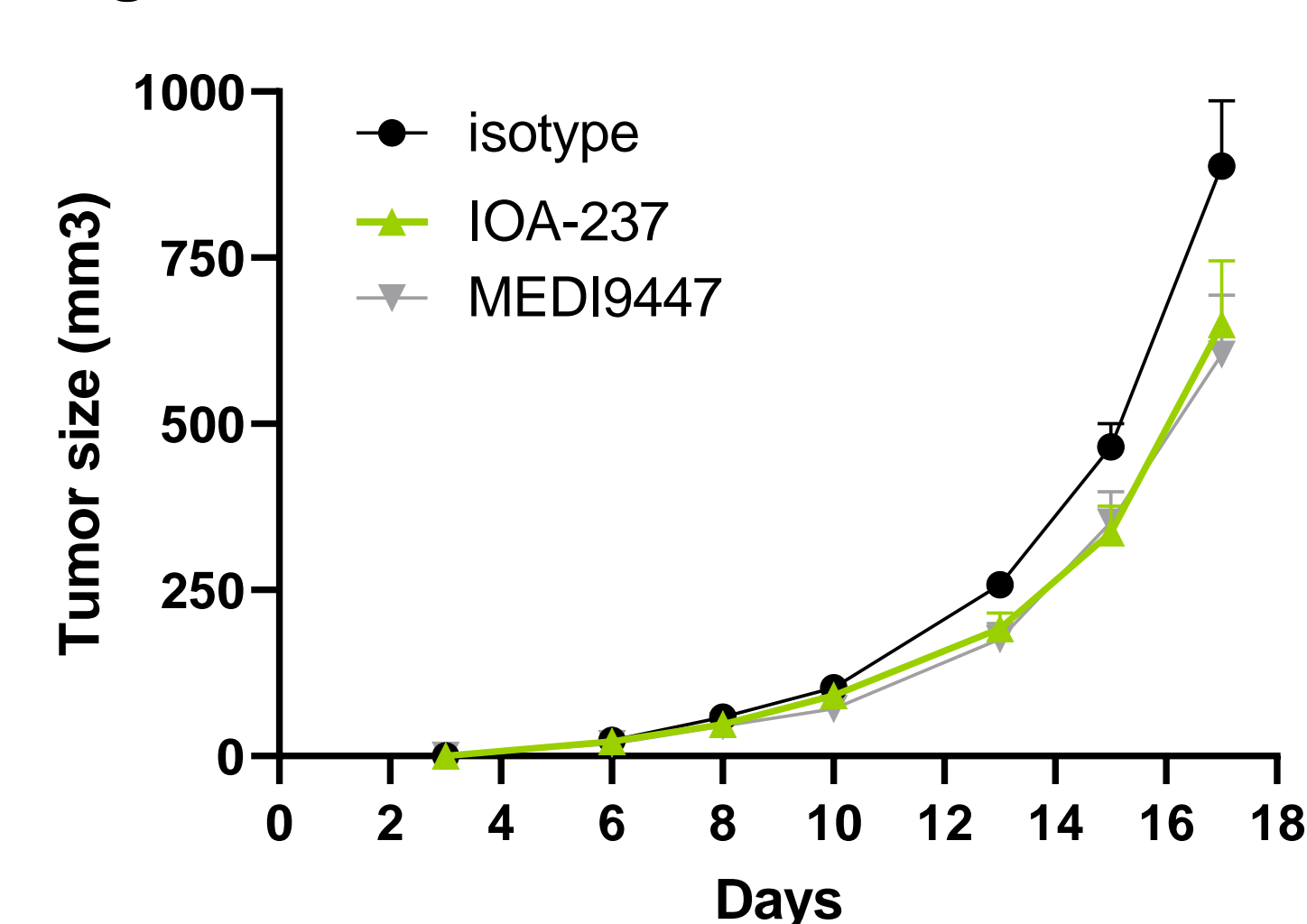
IOA-237 does not induce hypersensitivity and shows efficacy in mouse model of colon cancer

Figure 3



To directly compare IOA-237 efficacy to MEDI9447, CT26 tumor-bearing Balb/c mice were administered with isotype or the respective antibodies. IOA-237 and MEDI9447 showed a comparable trend towards reduction in tumor outgrowth (Figure 4).

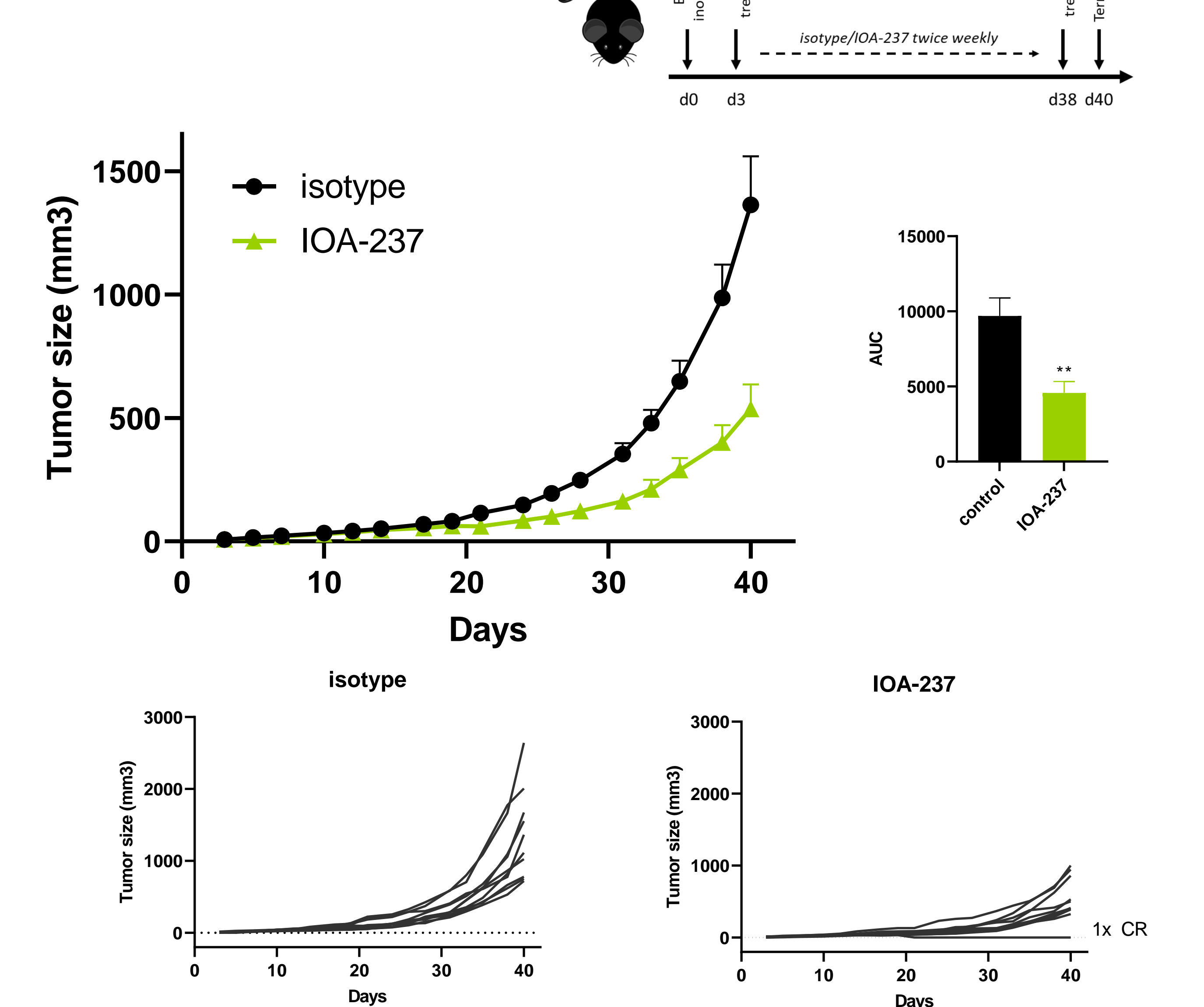
Figure 4



To test potential induction of hypersensitivity, IOA-237 was administered to CT26 tumor-bearing Balb/c mice. IOA-237 did not induce hypersensitivity at the treatment schedule used in and showed a trend towards reduced tumor outgrowth (Figure 3).

Single agent activity of IOA-237 in the E0771 orthotopic mouse model of breast cancer

Figure 5



In the orthotopic E0771 mouse model of triple negative breast cancer, IOA-237 twice weekly and continuously administered at 10mg/kg showed statistically significant inhibition of tumor outgrowth as measured by area under the curve (AUC). In the IOA-237 treated group one animal showed initial outgrowth of the tumor but regressed upon prolonged treatment and resulted into a complete responder (Figure 5).

Conclusion

- IOA-237 is a novel and potent anti-CD73 mAb that can be used to block adenosine generation in the tumor microenvironment.
- IOA-237 has a favorable PK profile when comparing intravenous administration to MEDI9447.
- No hypersensitivity was induced by the fully human antibody when used in twice weekly administration to tumor-bearing Balb/c mice and continuous twice weekly administration to tumor-bearing C57BL/6 mice.
- IOA-237 showed a trend towards reduced tumor outgrowth in the subcutaneous CT26 mouse model of colon carcinoma and showed comparable efficacy as MEDI9447.
- IOA-237 showed statistically significant inhibition of tumor outgrowth in the orthotopic E0771 mouse model of triple negative breast cancer.
- Efficacy studies to test combinations with checkpoint inhibitors and other agents are ongoing.

Conflict of Interest Statement:

MD, KNS, ML and ZJ are employees and shareholders of iOnctura.