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Overcoming genetically-based resistance mechanisms to PD-1 blockade

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Disclosures

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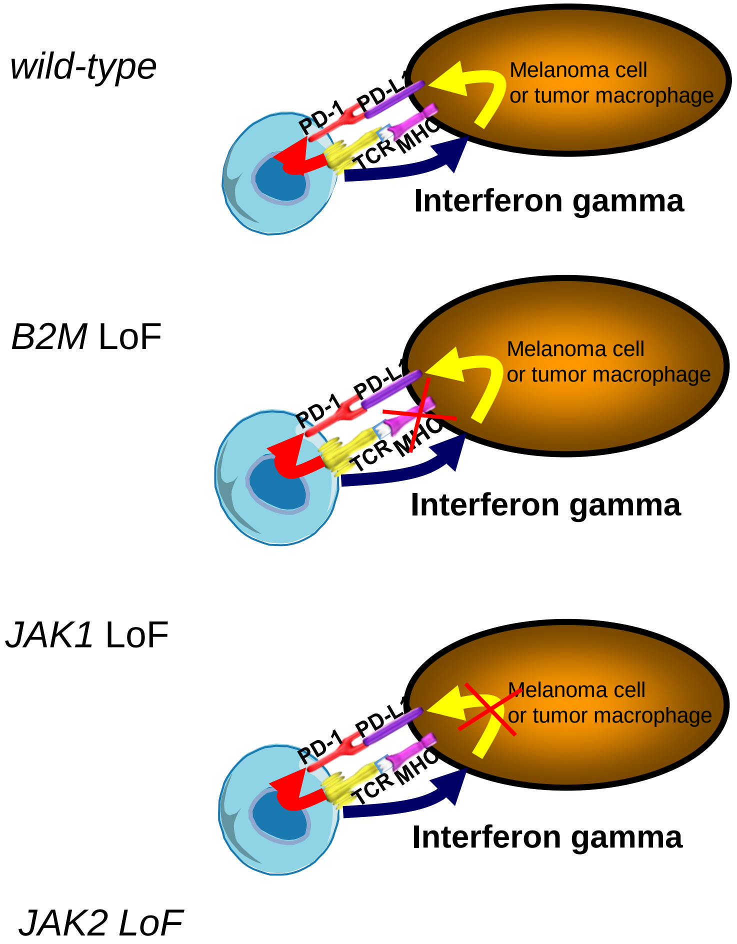
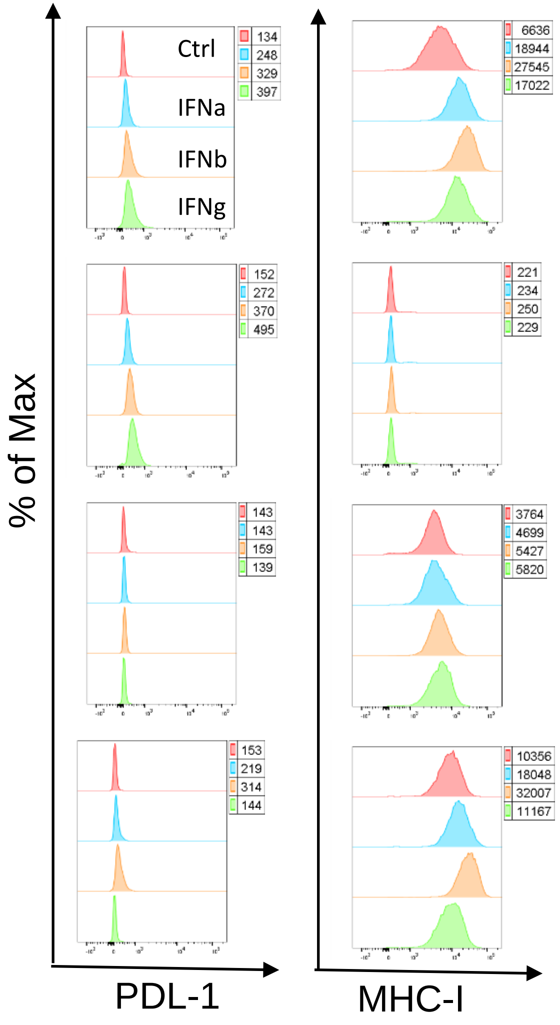
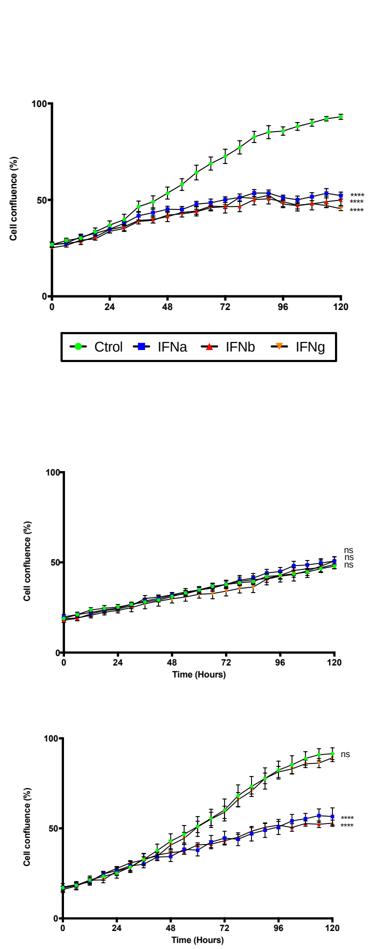
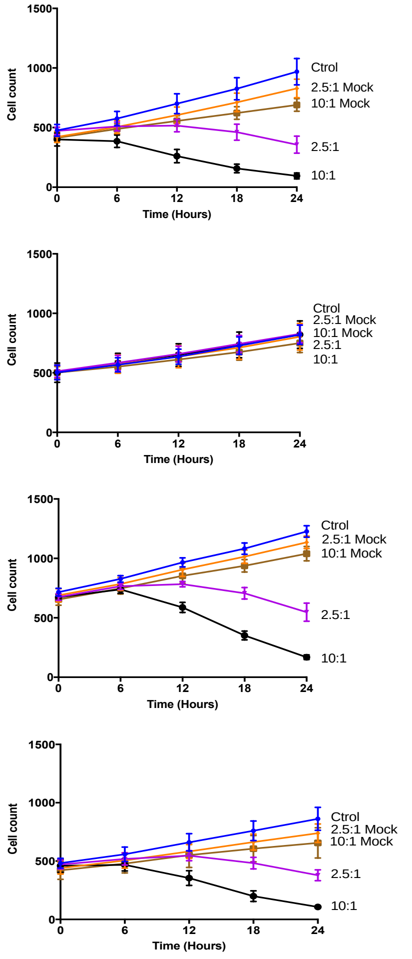
I have no actual or potential conflict of interest in relation to this presentation

B2M LoF mutations results in lack of antigen presentation to T cells, while JAK 1/2 LoF result in insensitivity to IFN, but does not impair T cell recognition and cytotoxicity



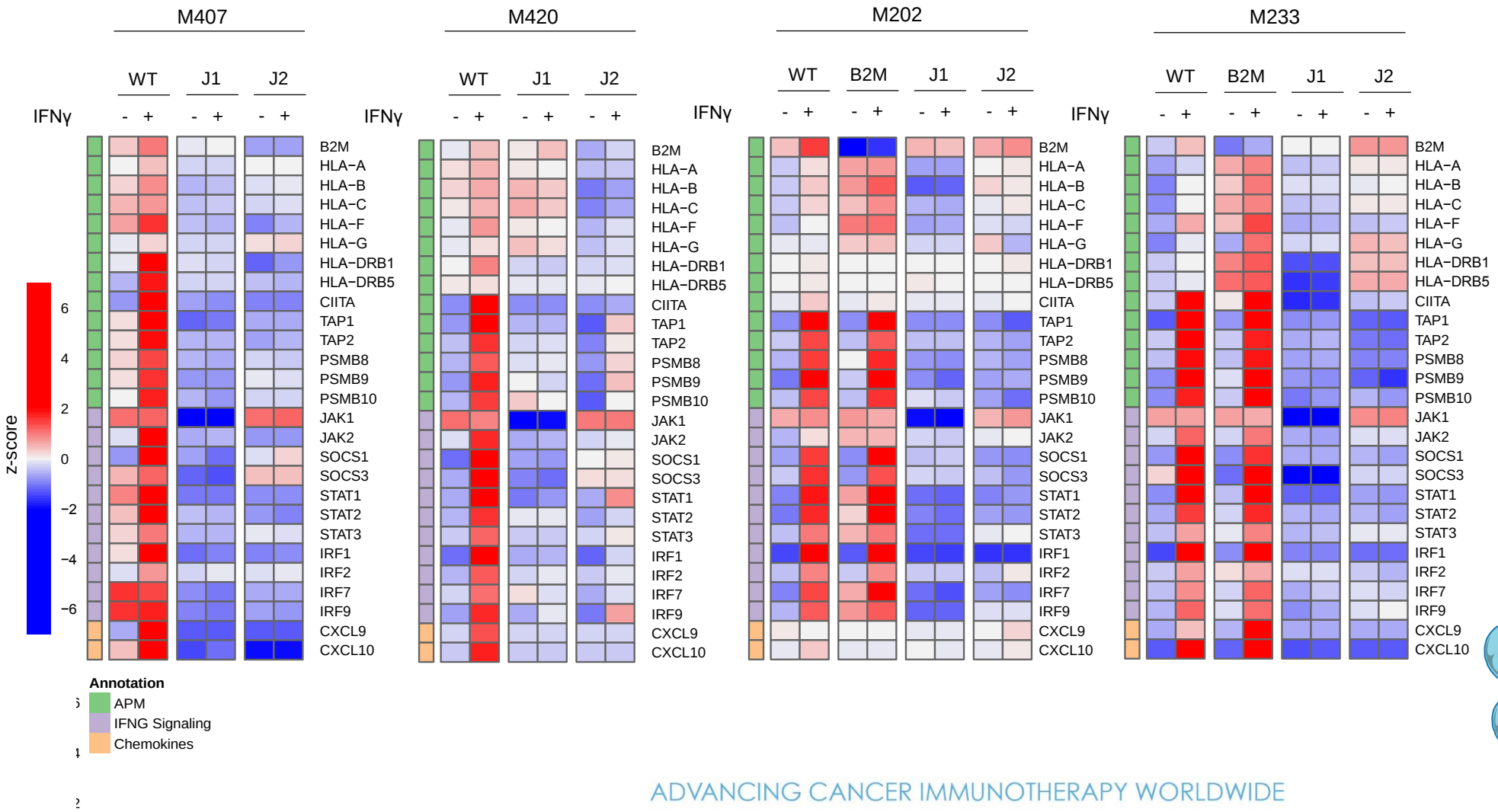


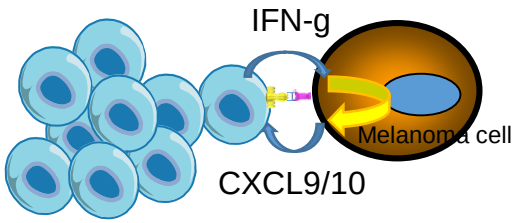


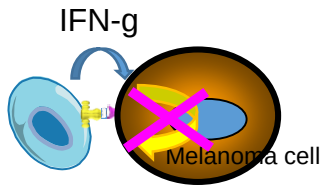


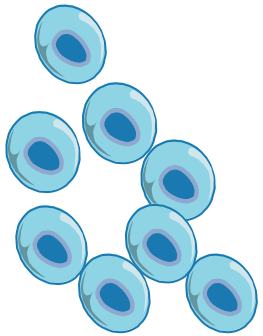
Zaretsky… Ribas, NEJM 2016
Shin… Ribas, Cancer Discovery 2017

The IFN-gamma-induced increased expression of antigen presenting machinery, IFN-gamma signaling and chemokines is lost with *JAK1/2* LoF mutations



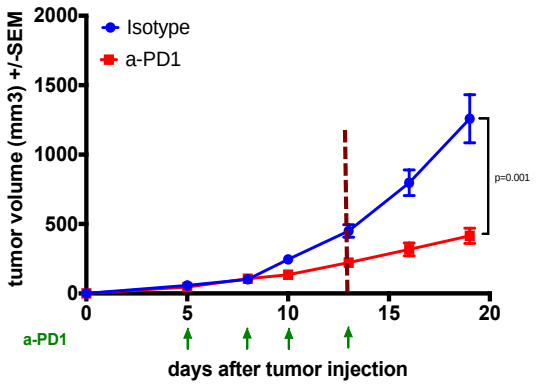




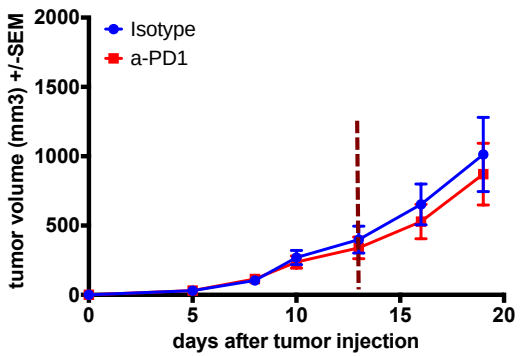


CRISPR/Cas9 knock out of JAK1/2 and B2M results in resistance to a-PD1 in the MC38 model

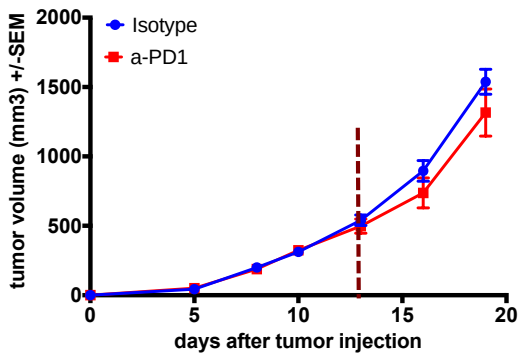
wild-type



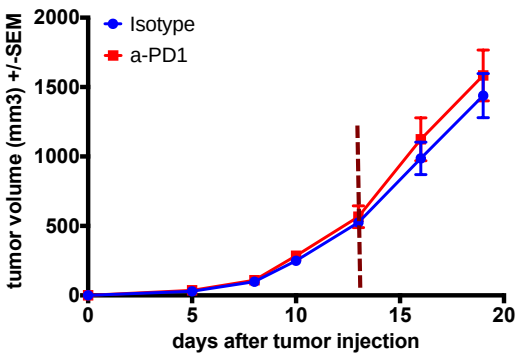
JAK1 KO



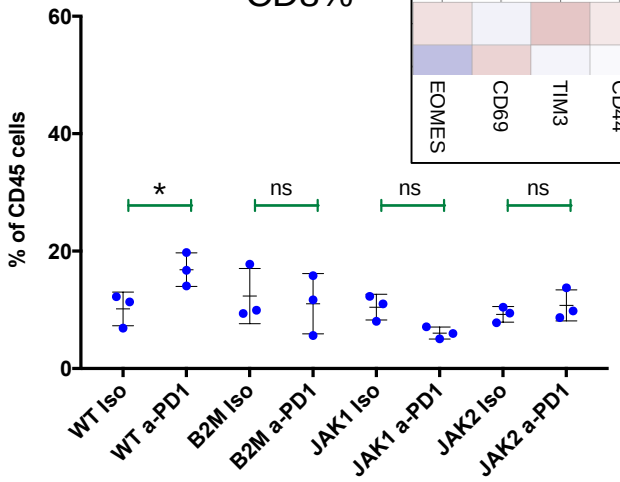
JAK2 KO

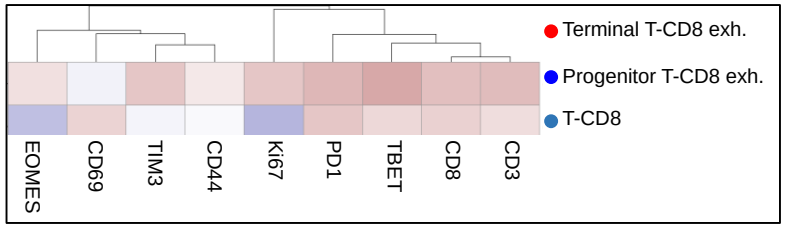


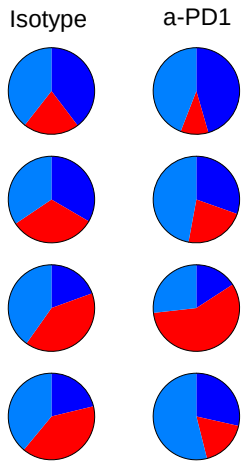
B2M KO

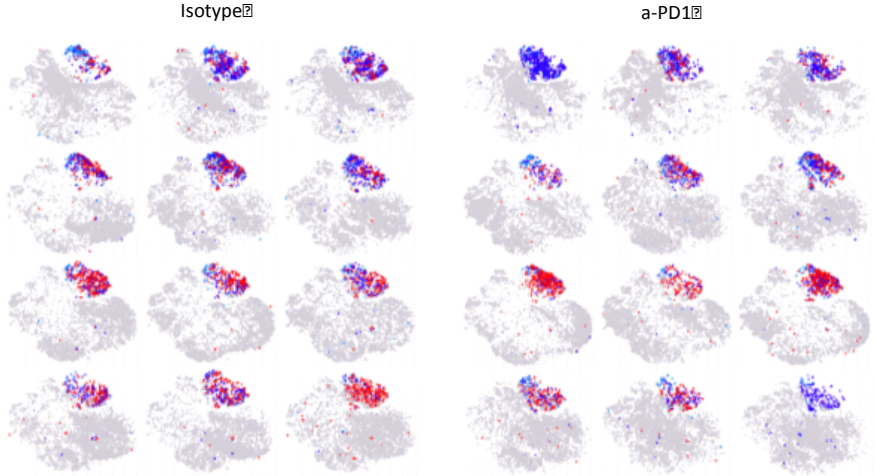


a-PD1 was unable to increase T-CD8 cells in the JAK1/2 and B2M LoF mutant tumors, and predominantly were terminal t-CD8 exhausted



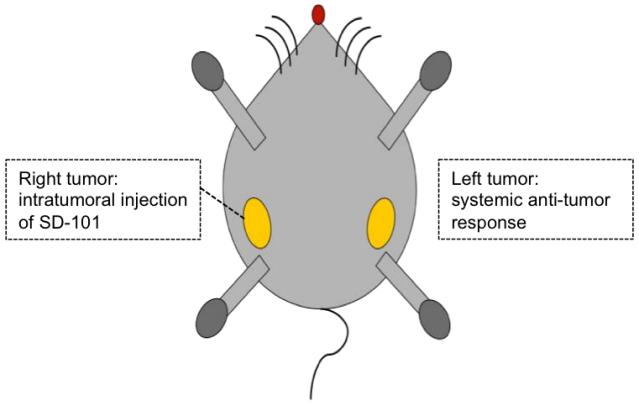




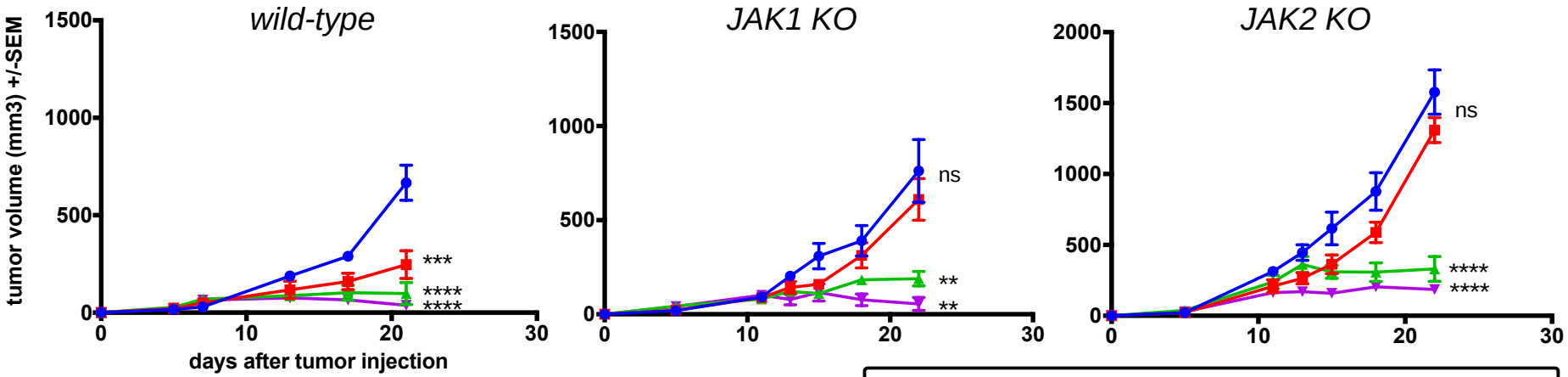


An intratumoral TLR-9 agonist (SD101) to reverse resistance to a-PD1 in JAK 1/2 LoF resistance tumors

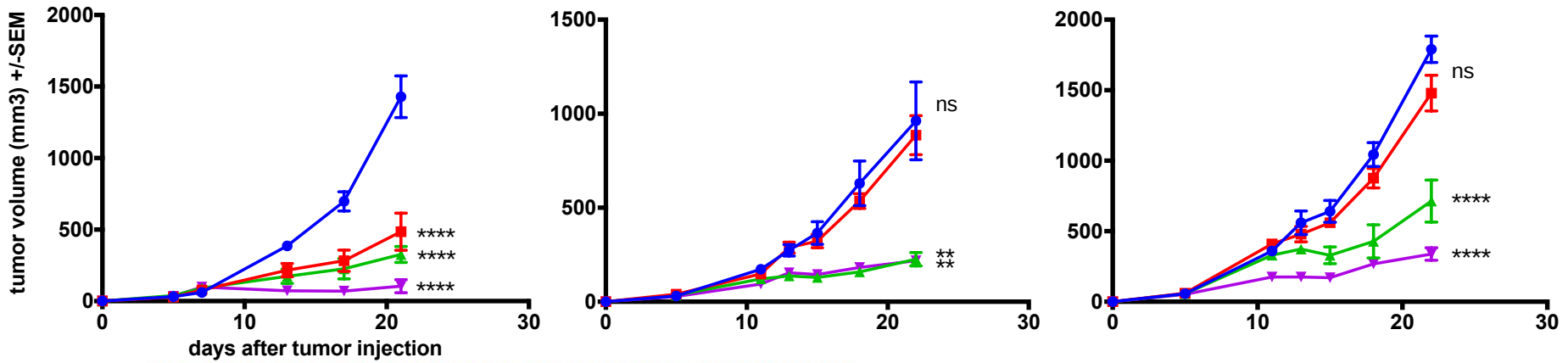
Effects of TLR9 agonist SD101+anti-PD-1 in bilateral MC38 with and without genetic anti-PD-1 resistance mutations



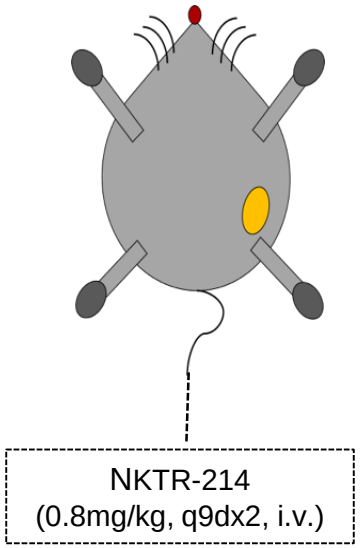
Injected tumors:

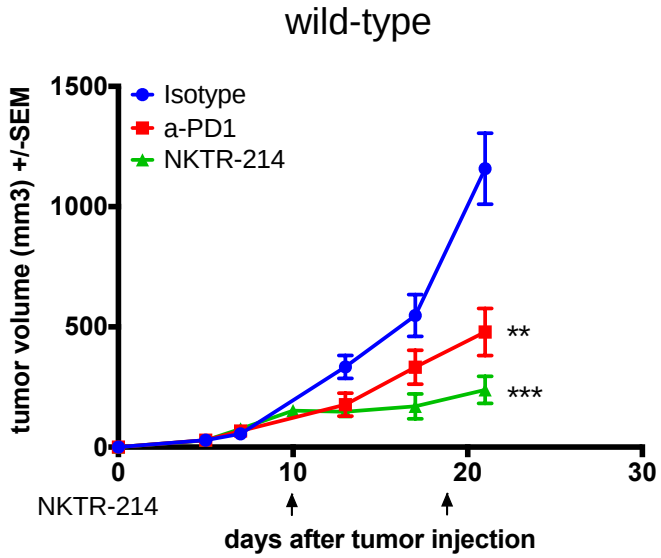


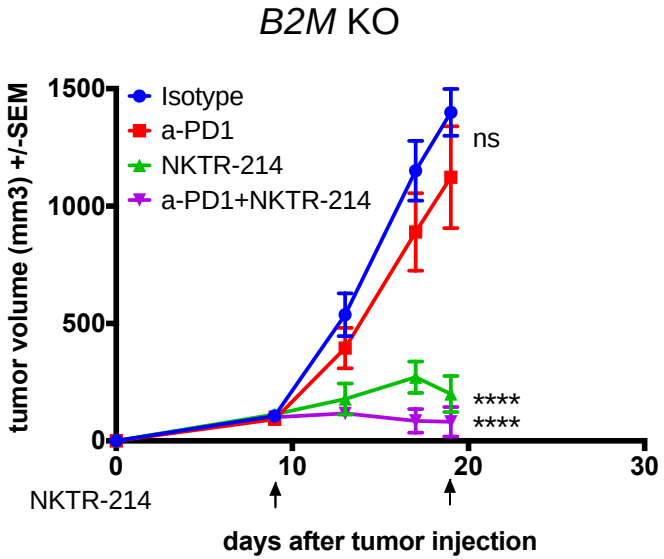
Contralateral:



NKTR-214, a kinetically engineered Il2 receptor agonist that may induce NK responses to B2M- deficient tumors







Take Home Messages

- *JAK1/2* LoF tumors result in loss of sensitivity to IFN induced antitumor effects but does not impair T cell recognition and cytotoxicity.
- *B2M* LoF tumors results in lack of antigen presentation to T cells and loss of antitumor activity.
- JAK1/2 and B2M LoF tumors lead to *in-vivo* resistance to anti-PD-1 therapy.
- *JAK1/2* LoF tumors resistance can be overcome by a TLR9 agonist, and *B2M* LoF tumors resistance can be overcome by a new generation IL-2.

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