Introduction and Background

- Preclinical immuno-oncology (I/O) needs identification and refinement of tumor models that recapitulate relevant biological dynamics.
- We tested several murine models for their response to checkpoint inhibitors like anti-CTLA-4, anti-PD-L1 and anti-PD-1 antibodies and found sensitive, moderately sensitive and insensitive models.
- Since the application of more sophisticated endpoints is critical to confidently assess drug sensitivities we also evaluated the immune profiles of these models following treatment.

Materials and Methods

- Female Balb/C mice (CT26, 4T1-Luc) or C57BL/6 mice (Pan02) were purchased from Envigo and were implanted SC in the high axilla (CT26, Pan02) or in the mammary fat pad (4T1-Luc).
- Mice were treated IP with 10 mg/kg anti-CTLA-4 (9D9) or anti-PD-L1 (clone 6.18.2) antibody twice/week for a total of four or five doses.
- In the 4T1-Luc model, localized radiation of 8 Gy at a rate of 1.50 Gy/min was delivered to the tumor area with an RS2000 Biological X-ray Irradiator (Rad Source Technologies, Alpharetta, GA).
- For flow cytometry the tumors were processed into single-cell suspensions using the gentleMACS™ Dissociators (Miltenyi Biotec). Samples were acquired on an Attune™ Nxt Flow Cytometer (Thermo Fisher Scientific) and data was analyzed using FlowJo software (Tree Star).

Results and Conclusions

- The CT26 model is sensitive to I/O CPIs with 100% of the mice showing anti-tumor response following treatment with anti-CTLA-4 antibody and 40% demonstrating response following treatment with anti-PD-L1 antibody.
- Treatment of CT26 tumor-bearing mice with anti-PD-L1 results in an increase of CD45+ lymphocytes and modifies the composition of the myeloid derived suppressor cell population.
- Treatment of Pan02 results in an increase of CD45+ lymphocytes and anti-PD-L1 antibody triggers both pro- and anti-tumor signaling pathways thus providing a possible explanation for the marginal anti-tumor responses we observed in this model.
- Pan02 is non-immunogenic, similar to human pancreatic cancers. No treatments had anti-tumor effects. The treatments did not alter the immune phenotype of this model. Pan02 may be useful to test CPIs in combination with other I/O agents, targeted agents, chemotherapies or radiation.