## 287 COMBINED COX-2 INHIBITION WITH FISH OIL AND ASPIRIN AS ADJUNCTS TO ANTI-PD-1 IMMUNOTHERAPY IN METASTATIC MELANOMA

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**Background** Only 30–40% of metastatic melanoma patients experience objective responses to first line anti-PD-1 immune checkpoint inhibition (αPD-1 ICI). Cyclooxygenase (COX-1/2) inhibition with aspirin (ASA) and other non-steroidal anti-inflammatory drugs has been associated with prolonged time to recurrence and improved responsiveness to ICI in human melanoma,[1] with inhibition of myeloid-induced immunosuppression in the tumor microenvironment (TME) a purported mechanism.[2] Similarly, dietary omega-3 fatty acids metabolized by COX-2 elicit downstream effects on T-cell differentiation akin to ASA administration, abrogating murine melanoma and human breast cancer progression. Mechanisms of ICI resistance remain unclear, and adjunct therapies look to bridge the gap from current response rates to cure.

**Methods** YUMM 1.7 melanoma cells were injected into flanks of C57-BL6/J mice. Mice were fed control diets or supplemented with omega-3 rich fish oil (FO) chow (10% weight/weight, 30%kcal/kcal), ASA in drinking water (ASA, LO – 300, MED – 600, HI - 1000 ug/mL), or the combination of these agents (COMBO, with ASA-MED) starting at day 7 post tumor implantation. Intraperitoneal αPD1 was administered every 3–4 days starting at day 12. Tumors were assessed for growth, harvested at day 32 (day 26 for ASA LO/HI), and characterized with flow cytometry. All significant results ($p<0.05$) assessed by 2-way ANOVA or t-test as appropriate.

**Results** FO resulted in lesser tumor volume at day 32 in αPD-1 treated mice, while ASA-HI resulted in lesser tumor volume in mice not treated with αPD-1 but did not synergize with αPD-1. ASA-MED and COMBO groups trended towards decreased tumor size ($p = 0.07$ and 0.07 respectively) by day 32 in αPD-1 treated mice. FO and COMBO increased total CD3+ T-cells and monocytes (CD45+, CD19-, CD11b+, Ly6C+, Ly6G -) in the TME. FO increased PD-L1 + CD4+ T-cells, while COMBO increased total CD8+ T-cells and PD1 + CD8+ T-cells. ASA-HI increased monocytes and the proportion of PD-1+, CD8+ T-cells in the TME.

**Conclusions** Myeloid-induced suppression of T-cell function in tumors may contribute to immune checkpoint inhibition resistance. In the present study, both fish oil and aspirin altered melanoma tumor growth, with only fish oil synergizing with anti-PD-1 at the doses assessed. Both fish oil and aspirin augmented monocyte populations in the tumor microenvironment, with differential effects on T-cell populations. The partially synergistic mechanism between substrate-limited (FO) and pharmacologic (ASA) inhibition of cyclooxygenase-2 may provide a cost-effective avenue to combat immune escape in melanoma patients treated with anti-PD-1 immune checkpoint inhibition, requiring further investigation in humans.

### REFERENCES

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