**Background**

Metabolic control of immune responses can occur through depletion of essential nutrients or accumulation of toxic metabolic products in the tumor microenvironment that impair immune cell function and promote tumor growth. The nucleotide enzyme amine oxidase (A0) is a nutrient-sensor that can promote pro-inflammatory responses and mediate the cytotoxic effects of H2O2 on cells. In this study, we investigated the effects of a small molecule A0 inhibitor, 220307, on immune responses in mouse tumor models and augments the activity of checkpoint blockades.

**Methods**

220307 is a highly selective, orally available compound that inhibits A0 in vitro. The efficacies of 220307 were compared with those of aPD-L1, a single-agent immune checkpoint blocker, in mouse tumor models. To evaluate the therapeutic efficacies of 220307, mice were implanted with mouse tumors on day 0, and treatments with 220307 were initiated starting on day 5 post-implantation. The results were compared with those of aPD-L1, 5 mg/kg. Treatment groups included 220307 (25, 50, 100 mg/kg), aPD-L1 (5 mg/kg), and the combination of 220307 and aPD-L1. The level of A0 in tumor homogenates was measured by LC/MS.

**Results**

We identified 220307, a potent, orally available A0 inhibitor, which inhibits A0 in vitro. Treatment with 220307 increased CD8 TILS by IHC, and decreased tumor burden in several mouse tumor models. In this study, we evaluated the therapeutic efficacy of 220307 in multiple mouse tumor models. Combined treatment with 220307 and aPD-L1 reduced the tumor burden in all tumor models tested, with the largest effect observed in a melanoma model. These data suggest that combined treatment with 220307 and aPD-L1 has the potential to improve outcomes for cancer patients.

**Conclusions**

220307 is a novel small molecule that is highly selective, orally available, and inhibits A0 in vitro. Treatment with 220307 increased CD8 TILS by IHC, and decreased tumor burden in several mouse tumor models. Combined treatment with 220307 and aPD-L1 reduced the tumor burden in all tumor models tested, with the largest effect observed in a melanoma model. These data suggest that combined treatment with 220307 and aPD-L1 has the potential to improve outcomes for cancer patients.

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