Background Melanoma brain metastases (MBM) remain the primary driver of melanoma associated mortality. With improved survival from current therapy, the rate of MBM is expected to rise and it is already estimated that up to 60% of patients with metastatic disease will develop MBM during the course of their disease. With dual agent immunotherapy or dual RAF/MEK targeted therapy, the intracranial response rate can reach 50%. This leaves half of patients in a position of either partial, temporary, or no response to treatment in their area of highest risk disease. Additionally, these sites lose response to both immunotherapy and targeted therapy sooner than areas of peripheral disease. Novel strategies are needed to improve the treatment of MBM patients. We propose the targeting of IRAK-4 as a mechanism of immune modulation in combination with immune checkpoint inhibition in MBM.

Methods We analyzed human MBM samples for expression of IRAK-4 and components of the inflammatory myddosomal pathway of activation through advanced immunohistochemistry (IHC) and protein array. We then modeled MBM in aggressive, PD-1 refractory mouse MBM model system B16.F10. Following implantion of B16.F10 tumor both intracranially and into the flank of C57BL6 mice we treated mice with the oral IRAK-4 inhibitor CA-4948 with or without anti-PD-1 mAb therapy or vehicle control. Mice were treated for 7 days and then the tumor microenvironment of both intracranial and flank tumors was analyzed through IHC and flow cytometry.

Results We show here human MBM samples express high level of IRAK-4 and downstream target proteins in the NF-KB pathway of activation. We additionally show oral CA-4948 is capable of rapid passage across the blood brain barrier and reaches therapeutically significant levels. We further show the addition of the novel oral IRAK-4 inhibitor CA-4948 to immune checkpoint inhibition has a tumor growth restriction capacity through downregulation in MAPK, NF-KB, and pERK and this results in a survival advantage of combination treatment. We also show the combination has a secondary effect of enhanced T cell activation and T cell infiltration in MBM tumors.

Conclusions Though IRAK-4 sits on the pathway of innate inflammation and suppression acts to restrict inflammation, this actually enhances anti-tumor T cell activity unlike traditional anti-inflammatory agents like steroids. We posit IRAK-4 inhibition as a mechanism of restoring the inflammatory balance in MBM to improve immune checkpoint inhibition. We propose the further investigation of IRAK-4 inhibition with combination immunotherapy approaches in MBM patients.

REFERENCES