Immune Modulation of Melanoma Brain Metastases by IRAK-4 Inhibition

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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 [1]. With dual agent immunotherapy or dual BRAF/MEK targeted therapy, the intracranial response rate can reach 50% [2]. 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 [3]. Novel strategies are needed to improve the treatment of MBM patients. We propose IRAK-4 as a novel target in MBM and the use of oral CA-4948 to inhibit IRAK-4 expression in combination with anti-PD1 therapy. We have previously discussed the ability of CA-4948 to rapidly cross the BBB in tumor bearing and naive mice and shown single agent activity of CA-4948 in murine MBM (manuscript in review). In this study, we show that inhibition of IRAK-4 has no detrimental effect on antigen processing, presentation, or T cell activation. We validate the homology between human and mouse CA-4948:IRAK-4 receptor interactions. Additionally, we show that CA-4948 + anti-PD1 therapy has the potential to increase CD8+ TILs in an aggressive murine model of checkpoint resistant MBM. Finally, we show that this interaction occurs in peripheral tumors and combination therapy confers a survival advantage in mice.

BACKGROUND

CA-4 Combination CA

There is direct homology between murine and human machine learning Oncol, 2017. 2(4): p. 572

MBM was then modeled in C57BL6 mice with B16.F10 and tumors Trivedi

CONCLUSIONS

(Emtirex) show that 2019. https://doi.org/10.26434/chemrxiv.9866912.v1

• There is direct homology between murine and human CA-4948:IRAK-4 receptor interactions making murine modeling a tangible corollary for human disease.

• CA-4948 shows no inhibitory effects on antigen processing, presentation, or T cell activation.

• Combination CA-4948 + anti-PD1 therapy significantly increases CD8+ and CD4+ TILs in an aggressive checkpoint resistant MBM mouse model.

• Combination CA-4948 + anti-PD1 therapy additionally shows activity and provides a survival advantage in an aggressive checkpoint resistant cutaneous melanoma model.

METHODS

• IRAK-4 homology modelling and docking study was performed to compare human and mouse interactions between IRAK-4 and CA-4948 using GlideXP [4,5] and DeepAtom [6,7] machine learning based scoring.

• MBM was then modeled in C57BL6 mice with B16.F10 and tumors implanted via stereotaxy. Tumors were allowed to grow for 5 days, and therapy was given for 7 days (excipient, CA-4948 100mg/kg qD, anti-PD1 200ug q72hr, or combination) prior to tumor resection and flow cytometry analysis. Tumors were dissected, enzymatically digested and debris removed prior to CD45+ cell isolation by CD45 MicroBeads (Miltenyi Biotec). Finally, C57BL6 mice had B16.F10 tumors implanted in the flank only and allowed to establish for 5 days prior to starting treatment (as above) for 14 days. Mice were then followed for survival analysis.

REFERENCES


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