7363: CA-4948 (emavusertib) improves treatment response of preclinical metastatic brain melanoma to anti-PD-1 immune checkpoint blockade

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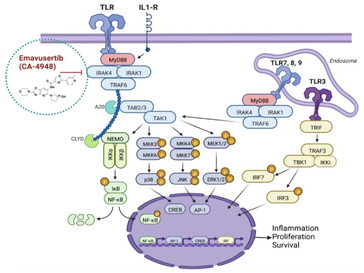
Introduction

Although recent advances in immunotherapy for metastatic melanoma have transformed the treatment paradigm for a disease that once carried a grim prognosis, nearly 50% of patients fail to reach a complete response to immune checkpoint blockade (ICB) due to multiple mechanisms of tumor-induced immune resistance[1]. These challenges are amplified in the CNS tumor microenvironment (TME) where metastatic brain melanoma (MBM) demonstrates diminished clinical benefit to ICB treatment[1]. A deeper understanding of these mechanisms are required to improve therapeutic response to ICB for these patients. Our group has previously identified that activation of the myddosomal cascade through downstream interleukin (IL)-1 receptor-associated kinase (IRAK-4) signaling results in chronic stimulation of MAPK and NF-κB in MBM[2]. Further investigation reveals myddosome signaling emanates in large part from the TME, resulting in reflexive immune suppression. CA-4948 (emavusertib), a small molecule inhibitor of IRAK-4, is capable of reaching therapeutic dose levels in the brain where it demonstrates on-target inhibition of this pathway[2,3]. These data highlight a unique therapeutic opportunity where selective inhibition of immune-suppressive signaling via targeted IRAK-4 blockade may sensitize MBM to anti-PD-1 ICB.



Emavusertib is a blood-brain barrier penetrant small molecule inhibitor of IRAK-4, a rate-limiting step in the myddosome signaling pathway.

Objective

The objective of the present study is to analyze expression of myddosome activation in the melanoma TME, and assess the therapeutic efficacy of emavusertib in combination with ICB.

Methods

RNA sequencing and multispectral imaging of patient melanoma were analyzed for myddosome expression. The effect of targeted myddosome inhibition on MDSC immune suppression was assessed by flow cytometry. Survival response in MBM preclinical models was evaluated in response to emavusertib +/- anti-PD-1 ICB. Immunological responses of tumor to treatment was evaluated in the transgenic reporter model GREAT-IFNγ$^{IRES-EYFP}$ to determine the activation status of infiltrating immune cells.

Results

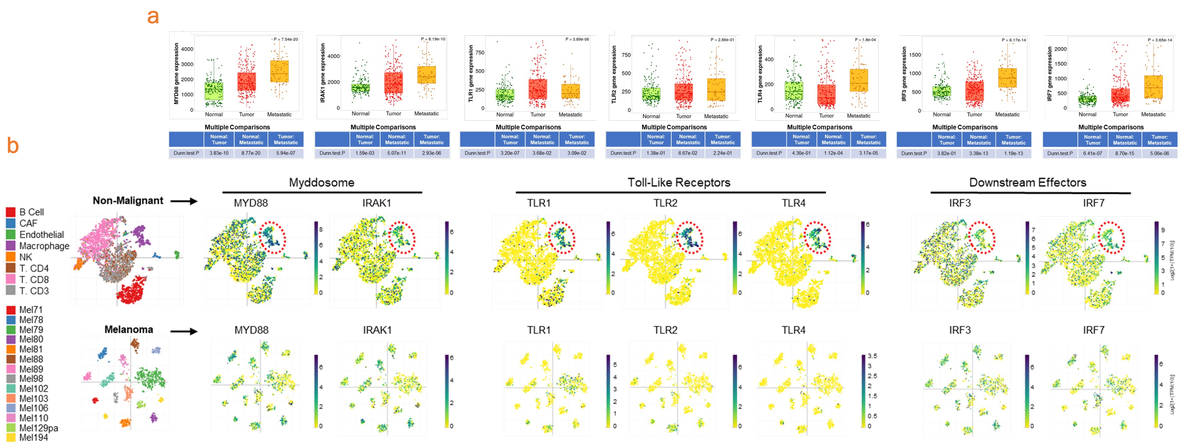


Figure 1. Myddosome signaling is activated in metastatic melanoma. (a) TNMplot[4] of differential gene expression analysis in normal, tumor, and metastatic patient tissue shows increased toll-like receptor (TLR) expression that prompts increased myddosome (MYD88, IRAK1) and downstream effector activity (IRF3, IRF7). (b) Single cell RNA sequencing of individual patient melanomas[5] stratified into tumor and non-malignant cells. Pooled non-malignant cells are stratified into immune, stromal, and endothelial cell clusters, and patient tumor cells are shown as individual clusters. Single cell transcript expression data (log2, TPM) visualized by tSNE plots reveals that macrophages (outlined in red) demonstrate elevated expression of transcripts associated with myddosome activation.

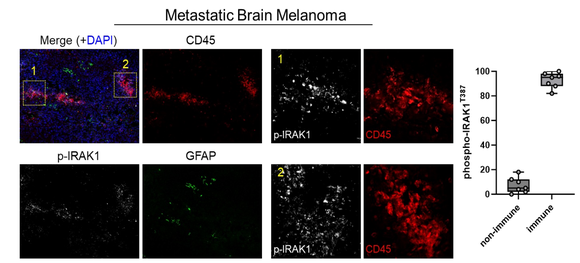


Figure 2. Myddosome signaling in patient MBM is selectively active in CD45+ immune cells. IHC of patient MBM samples for phosphorylated (active) IRAK-1 (white) shows a pattern of expression associated with CD45+ immune cells (red). Representative image of n=7 patient MBM samples. Graphical summary of p-IRAK-1 co-localization with CD45+ immune cells and non-immune cells shown.

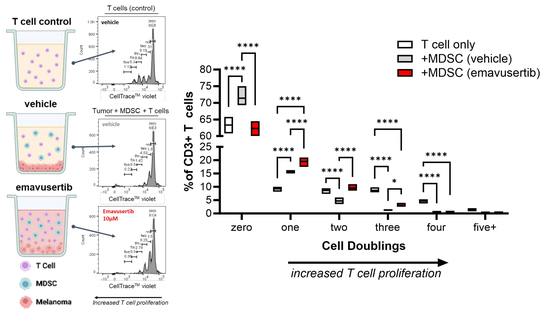


Figure 3. Targeted myddosome inhibition with emavusertib reverses immune suppression. T cell proliferation is inhibited when co-cultured with syngeneic murine melanoma and bone-marrow derived MDSC cells from tumor bearing C57BL/6 mice. Emavusertib treatment is able to reverse this inhibition, restoring T cell proliferation.

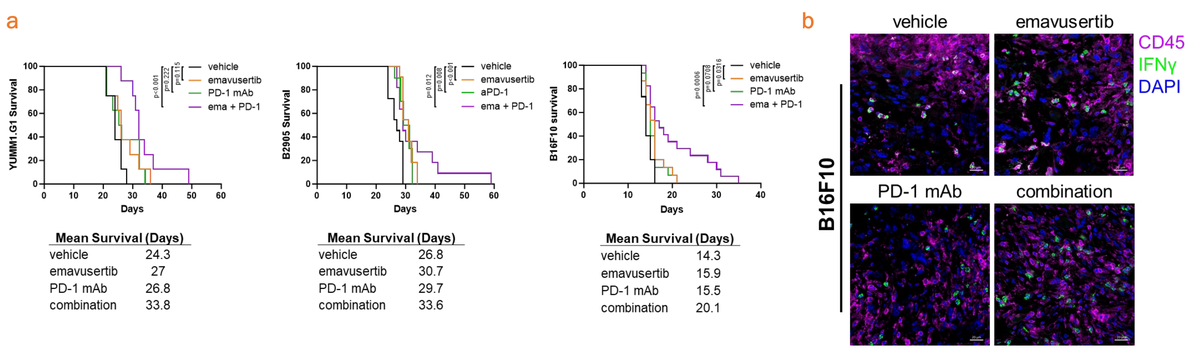


Figure 4. Emavusertib improves anti-tumor response to PD-1 ICB in preclinical MBM. (a) Emavusertib improves survival response to anti-PD-1 ICB in three independent syngeneic murine models of MBM. (b) Combination treated B16F10 tumors resected from GREAT-IFNγ transgenic reporter mice reveal evidence for improved immune activation via increased IFNγ expression (green) by CD45+ immune cells (magenta).

Conclusions

1. Increased myddosome signaling correlates with disease progression in melanoma patients.
2. Myddosome signaling emanates from the TME, in particular tumor-associated immune cells (myeloid/macrophages).
3. Emavusertib (CA-4948) reverses immune suppression mediated by myeloid-derived suppressor cells
4. Combination emavusertib plus PD-1 ICB improves immune activation and survival in aggressive preclinical MBM models.

Significance

Therapeutic inhibition of myddosome signaling in melanoma brain metastases mitigates immune suppression mediated by tumor-associated immune cells, allowing for improved immune surveillance and anti-tumor activity. Early clinical data shows that emavusertib has an acceptable safety and tolerability profile, even with long-term treatment (>6 months), and shows preliminary anti-tumor activity in heavily pretreated patients[6]. Thus, emavusertib may be an effective and safe treatment given alongside PD-1 immune checkpoint blockade for patients with metastatic melanoma in the brain.

References

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