CA-4948 in combination with BRAF/MEK inhibition in melanoma brain metastases

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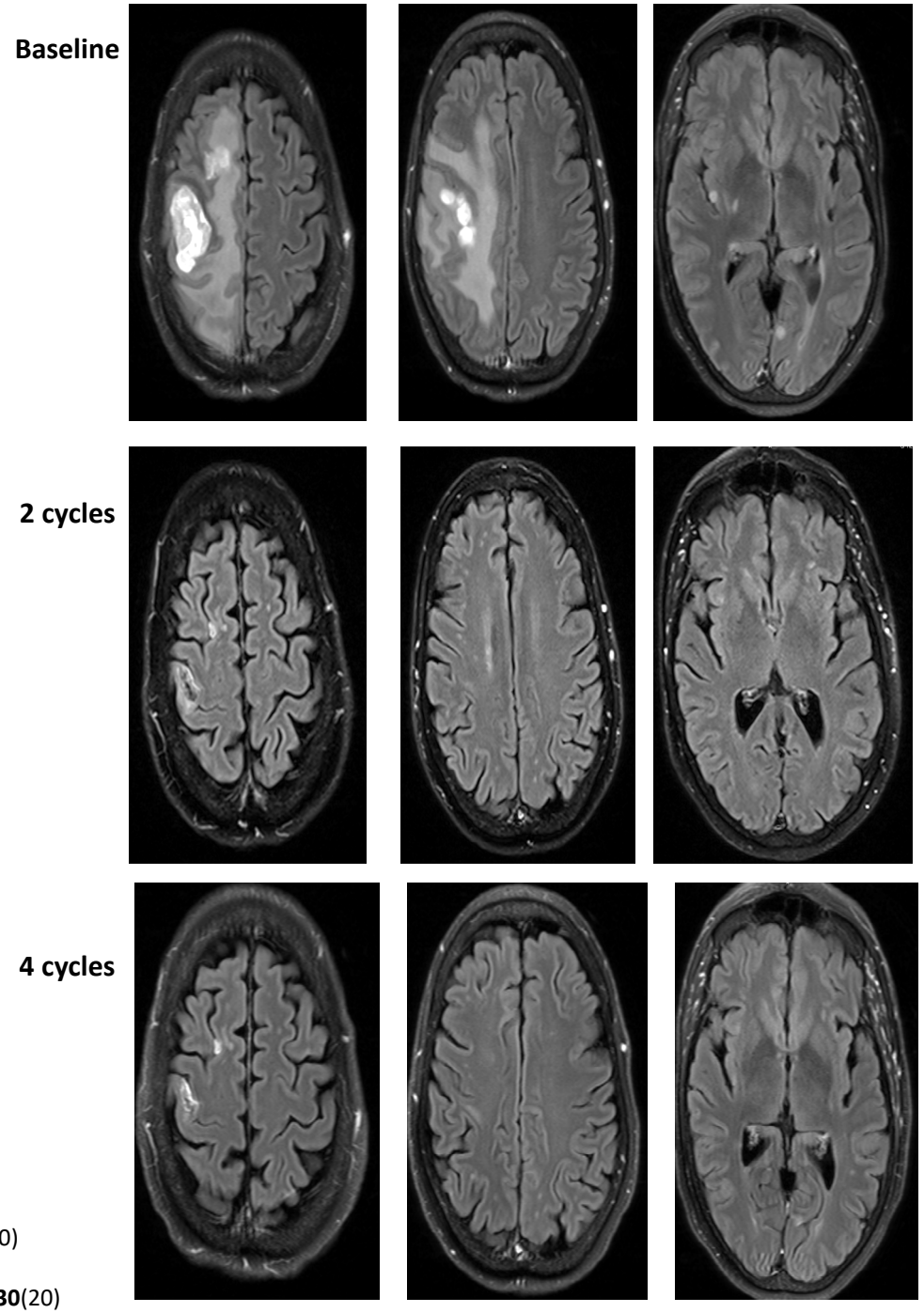
Melanoma Brain Metastases (MBM)

- MBM are detected in 1/3 of newly diagnosed stage IV patients[1]
- 75% of patients will have MBM at time of death[2]
- Roughly 50% of MBM will carry BRAF V600 mutations[3]
- DREAMSEQ and SECOMBIT support use of dual checkpoint inhibitor therapy first, followed by BRAF/MEK inhibition at progression[3]
- This is not possible in all patients
  - Dexamethasone to control edema
  - Autoimmune disease
  - Visceral crisis



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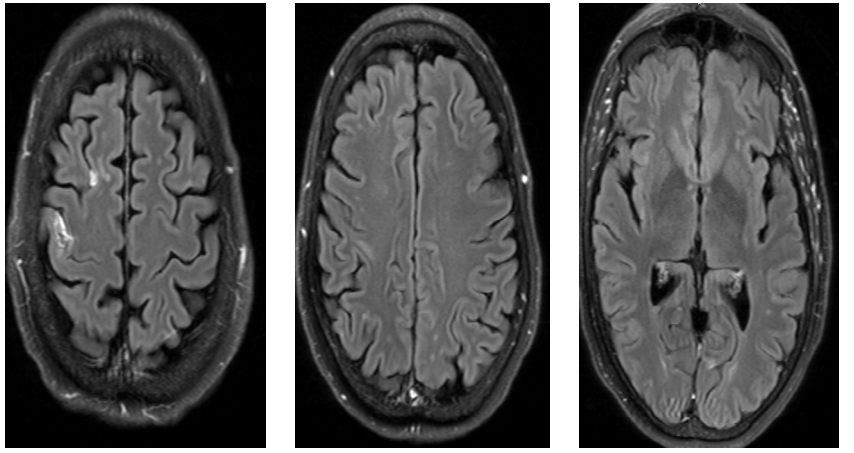
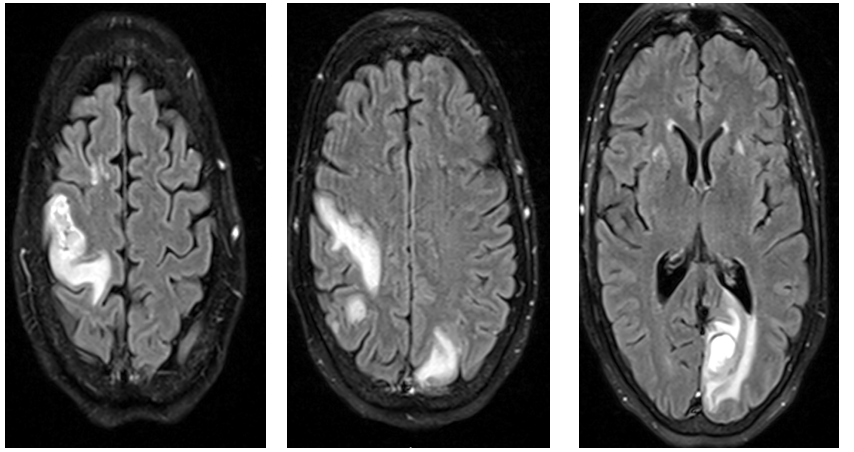
BRAF/MEK therapy

- 3 approved regimens
- Intracranial response rate of 42-50%[1]
- Resistance usually occurs after 6 months[2]
- MBM that progress on BRAF/MEK therapy are resistant to dual checkpoint inhibition through upregulation of IPRES gene signature[2]
- Acquired resistance to BRAF/MEK therapy occurs through multiple mechanisms[3]
  - MAPK-dependent
    - RTKs, NRAS/MEK mut, BRAF amp, COT alteration, etc.
  - MAPK-independent
    - PI3K-AKT, WNT5A/β-catenin pathway

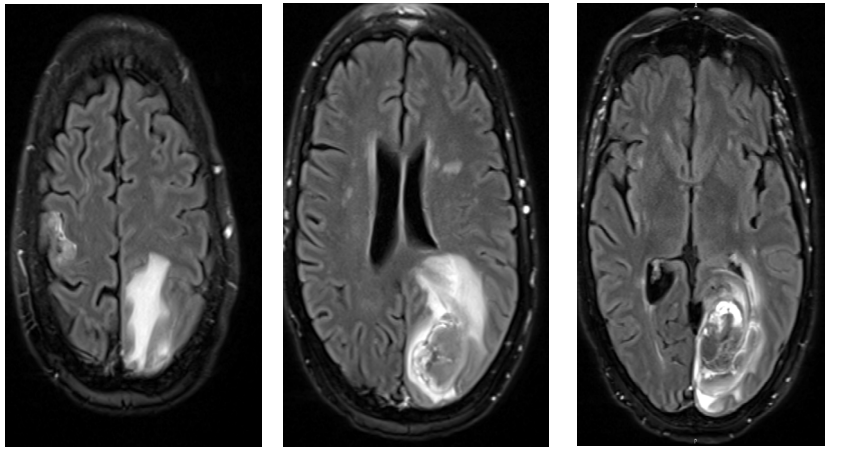
4 cycles



Bridge to Ipi/Nivo



Resume BRAF/MEK Tx for 1.5 cycles



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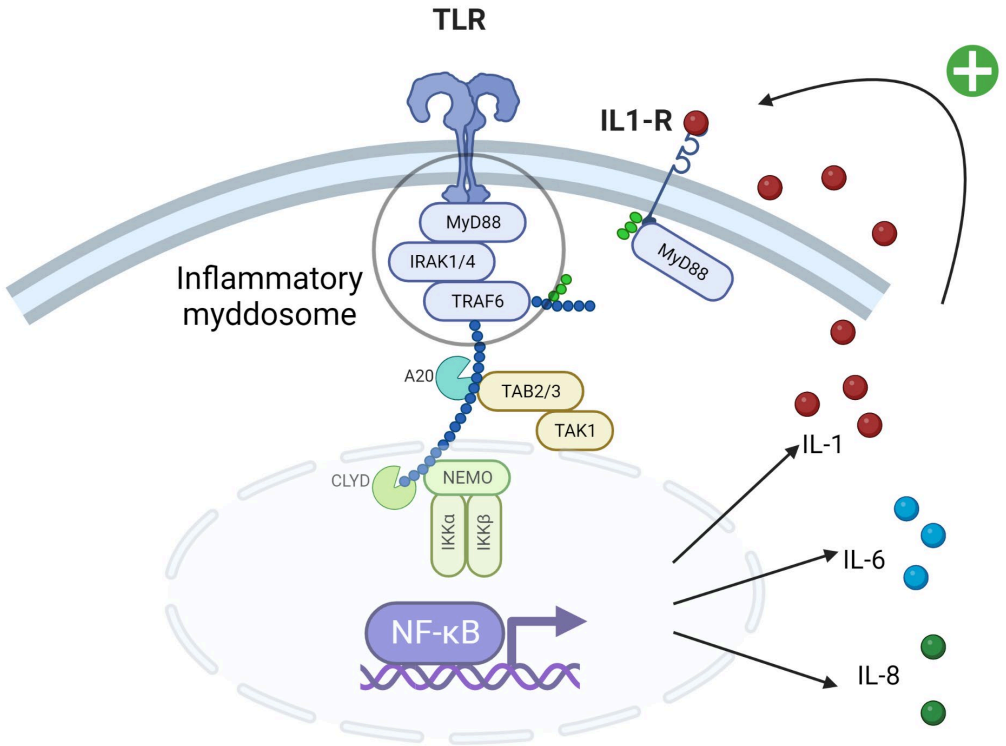
IRAK-4

- Upregulation of IRAK-4 in tumors leads to constitutive activation of NF-κB, JNK, and MAPK[1,2]
- Previous work has shown upregulation of IRAK-4 in cutaneous melanoma, which promotes carcinogenesis regardless of direct mutation or not[3]
- IRAK-4 upregulation is associated with increased phenotypically exhausted TILs, MDSCs, increased CD4+ T regs, and resistance to aPD-1 therapy[4,5]



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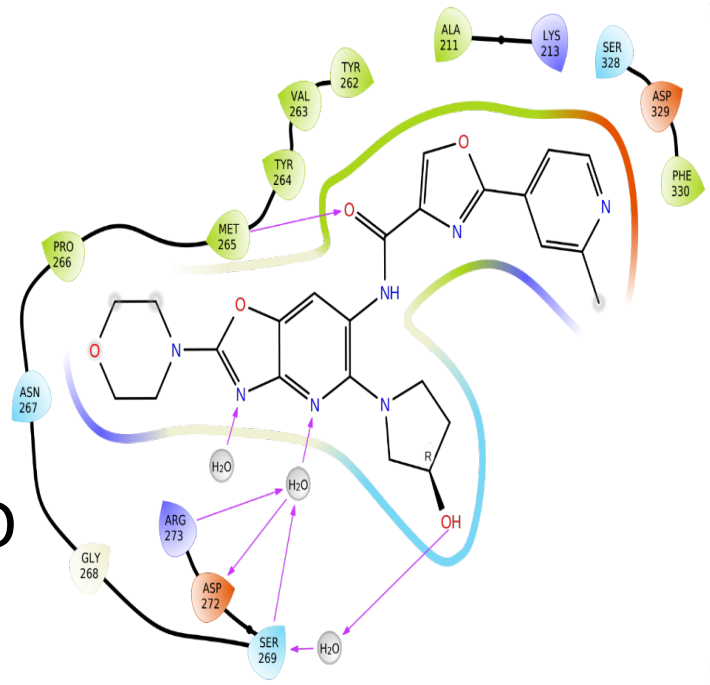
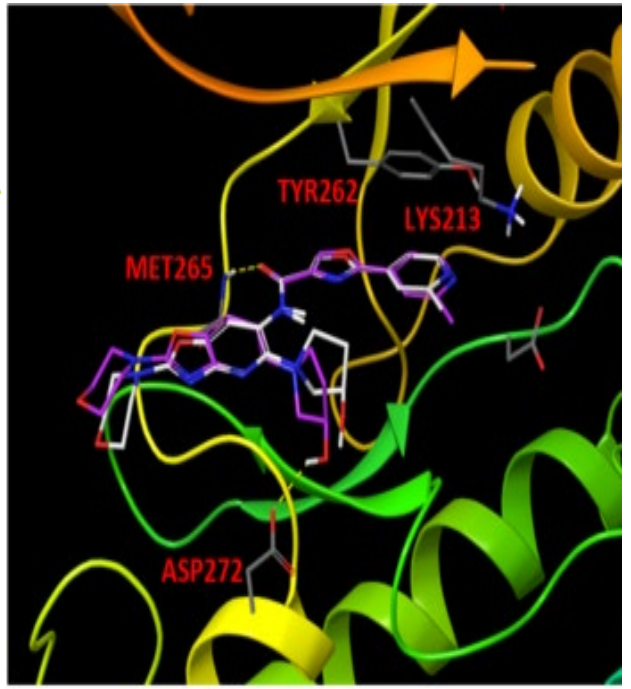
CA-4948 (Emavusertib™)

- First-in-class IRAK-4 inhibitor[1]
- Excellent oral bioavailability
- Rapid absorption and crosses the blood-brain barrier readily
- No inhibition of CYP450s
- $T_{1/2}$ = 6 hrs, no accumulation with qD dosing[1,2]
- Excellent safety profile in Phase I/II trials in NHL (NCT03328078) and AML (NCT04278768)





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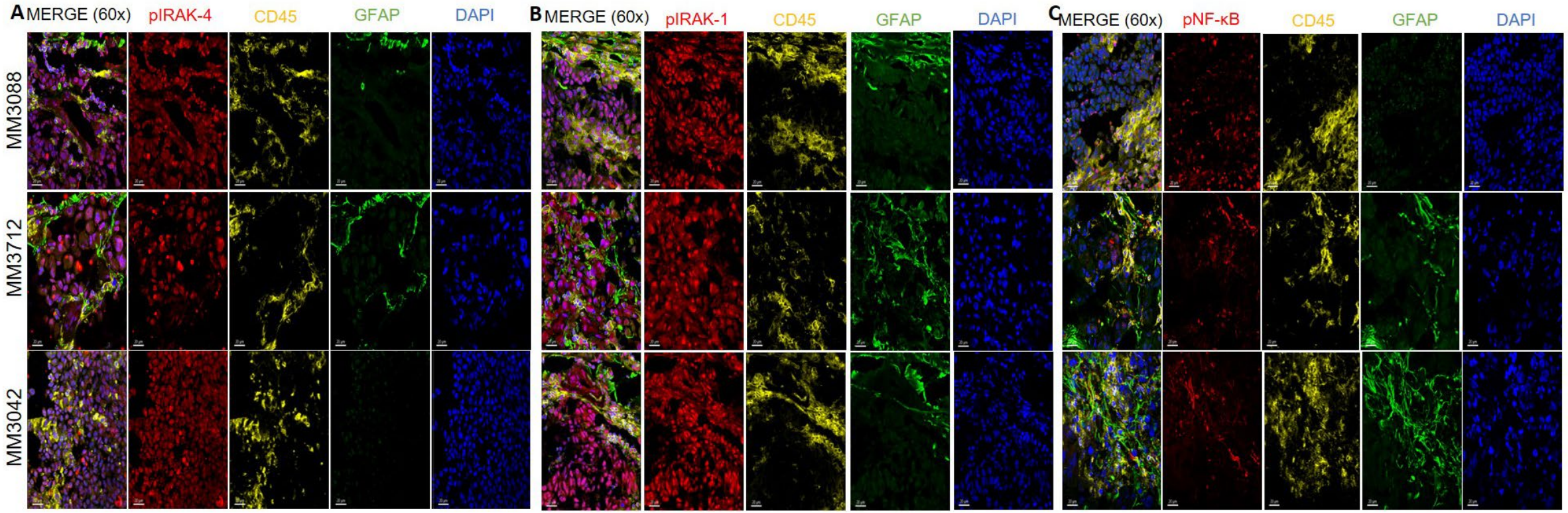
IRAK-4 expression in MBM



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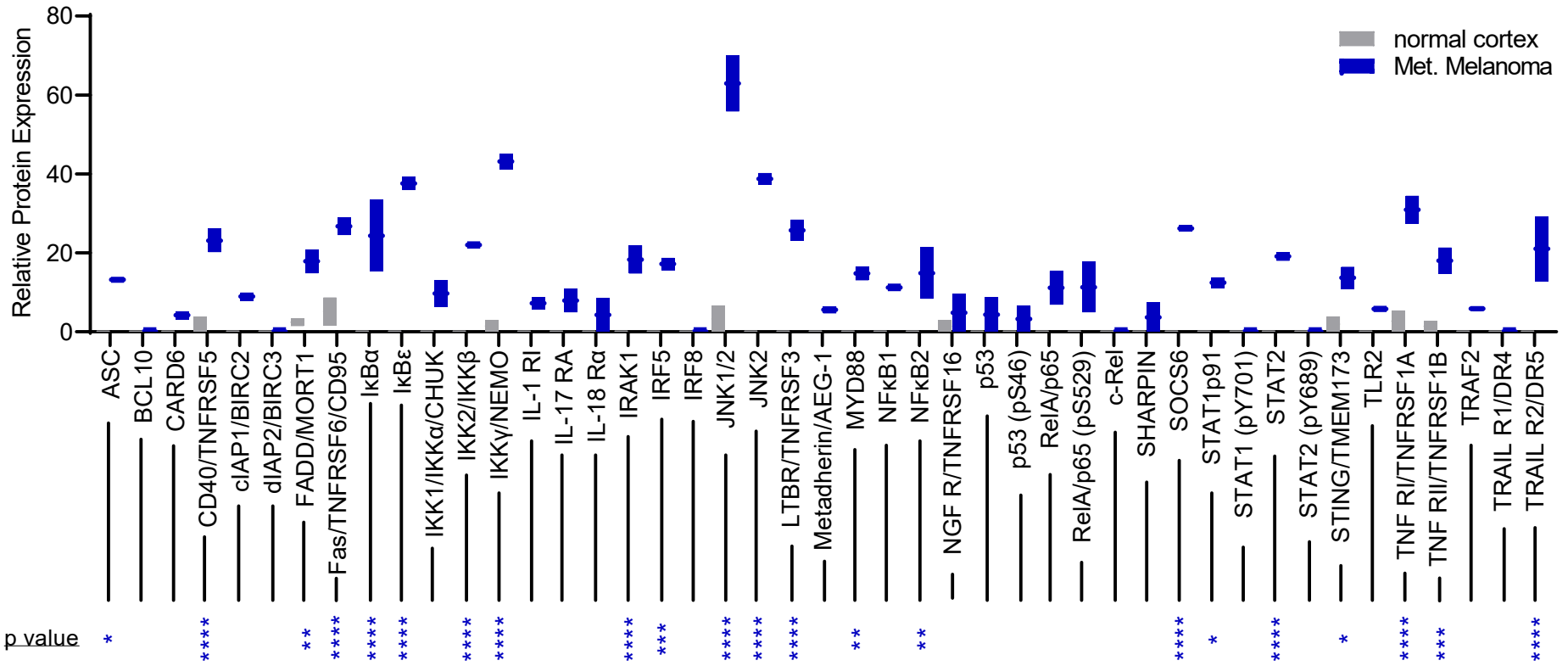
NF-KB pathway protein expression in MBM



Proteomic evaluation of NF-KB pathway in MBM vs normal brain tissue. Human MBM samples (MBM202685, MBM228917) and normal brain tissue were subjected to enzymatic digestion and protein analysis to ensure equal volume loading. Samples were then analyzed for NF-KB pathway proteins using R&D systems Proteome Profiler per protocol. Data representative as aggregate of two samples per type. Significance determined by 2-way Anova, multiple comparisons (column means) *p<0.05.

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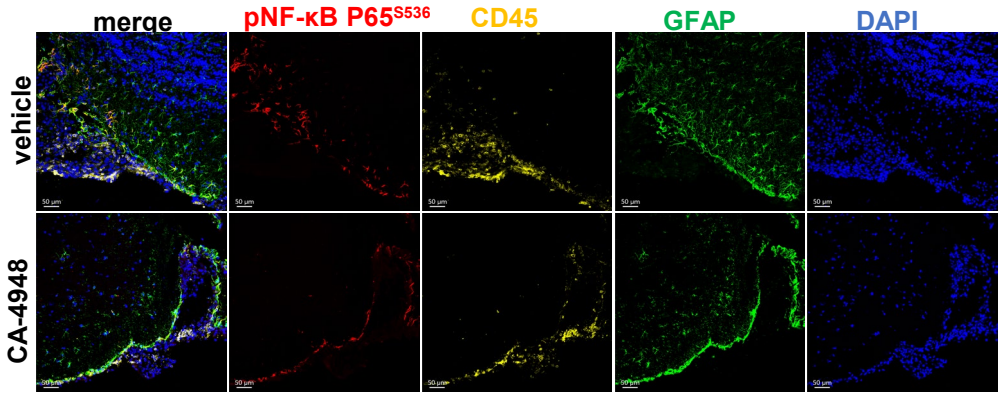
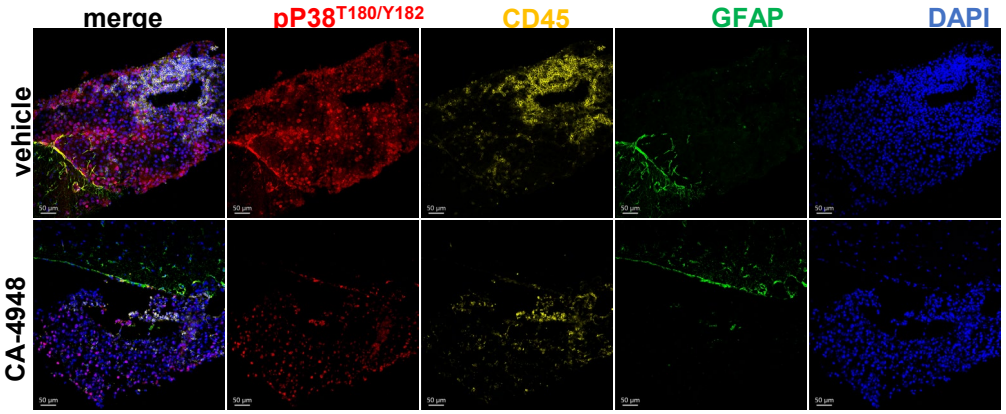
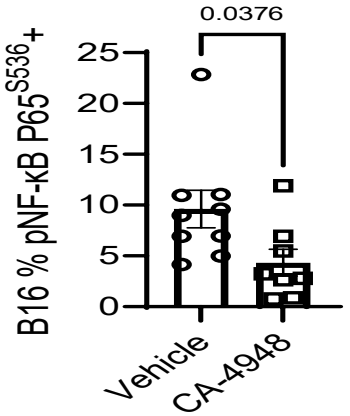
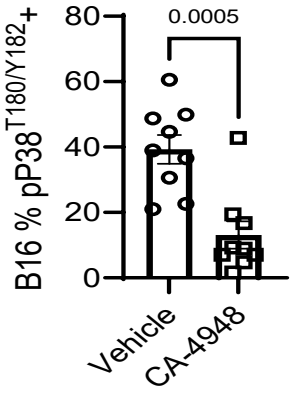
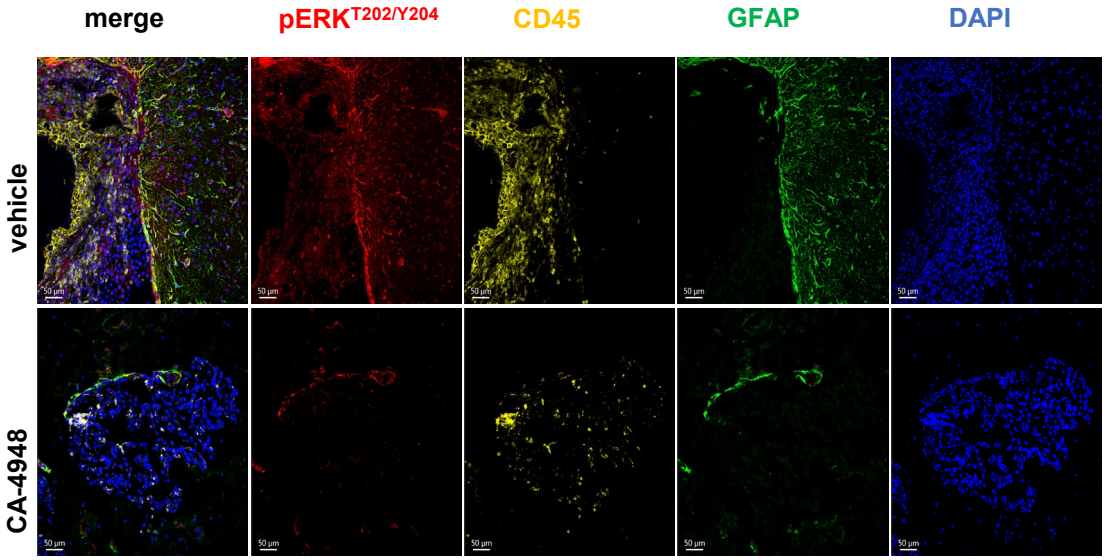
CA-4948 decreases NF-KB, MAPK, and pERK

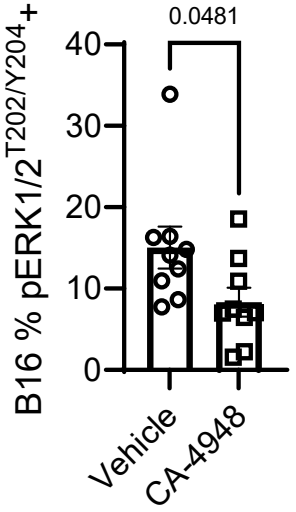






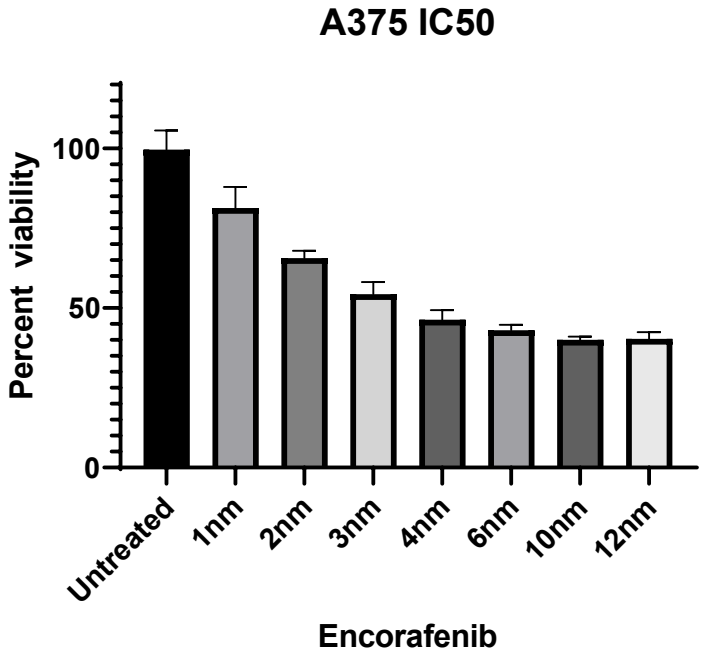


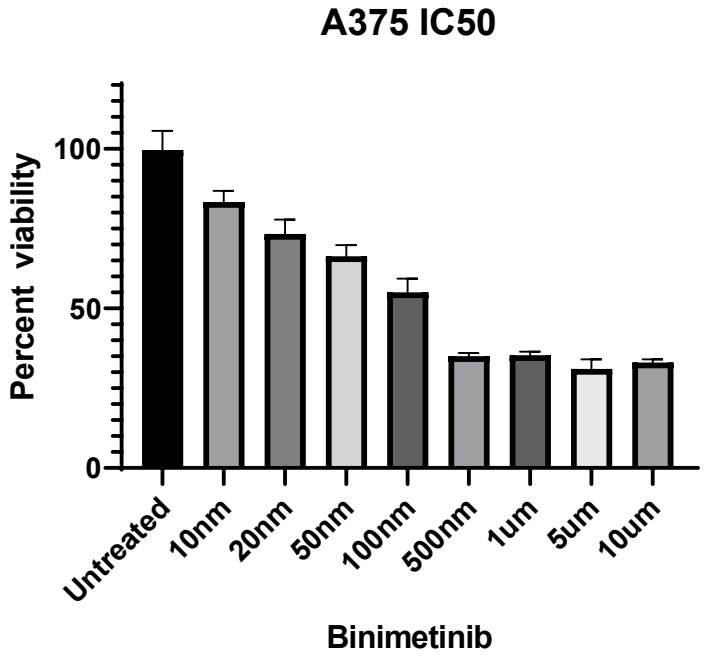


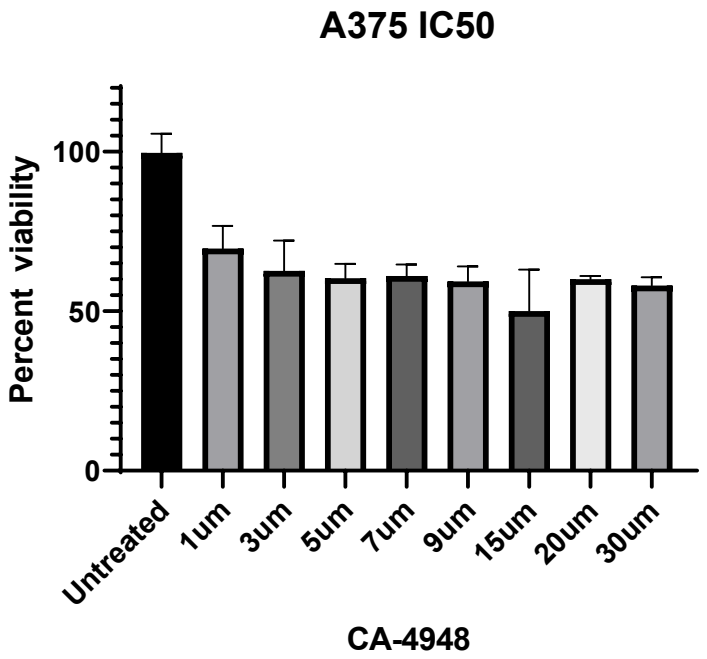


*Manuscript in review

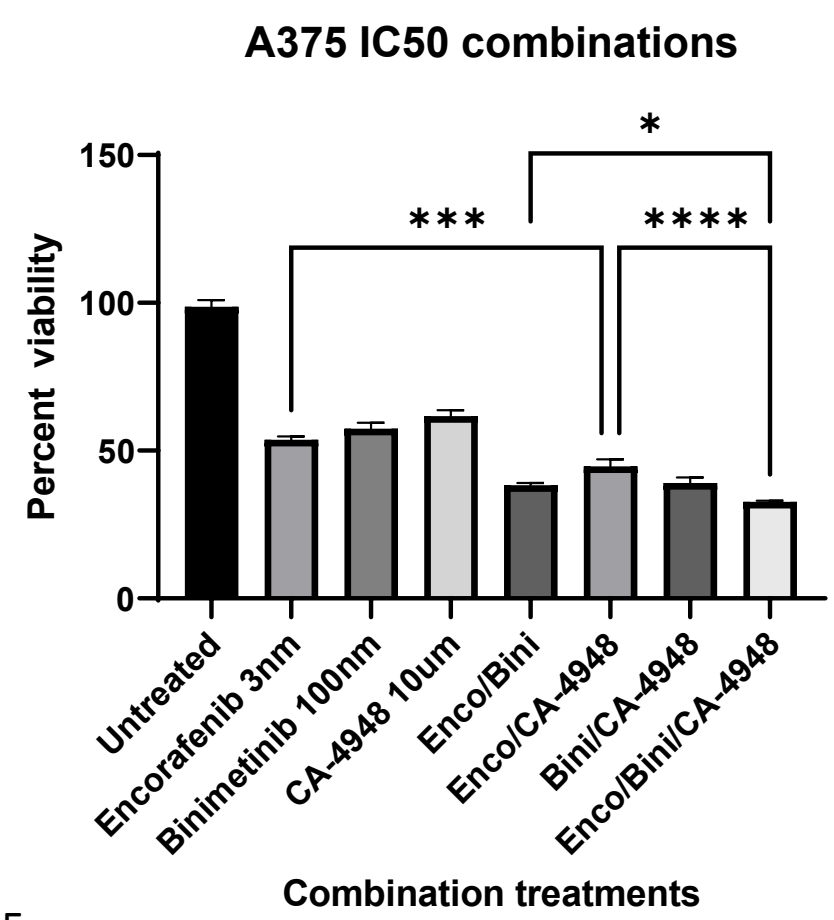
Single-agent effects on human BRAF mutant cells

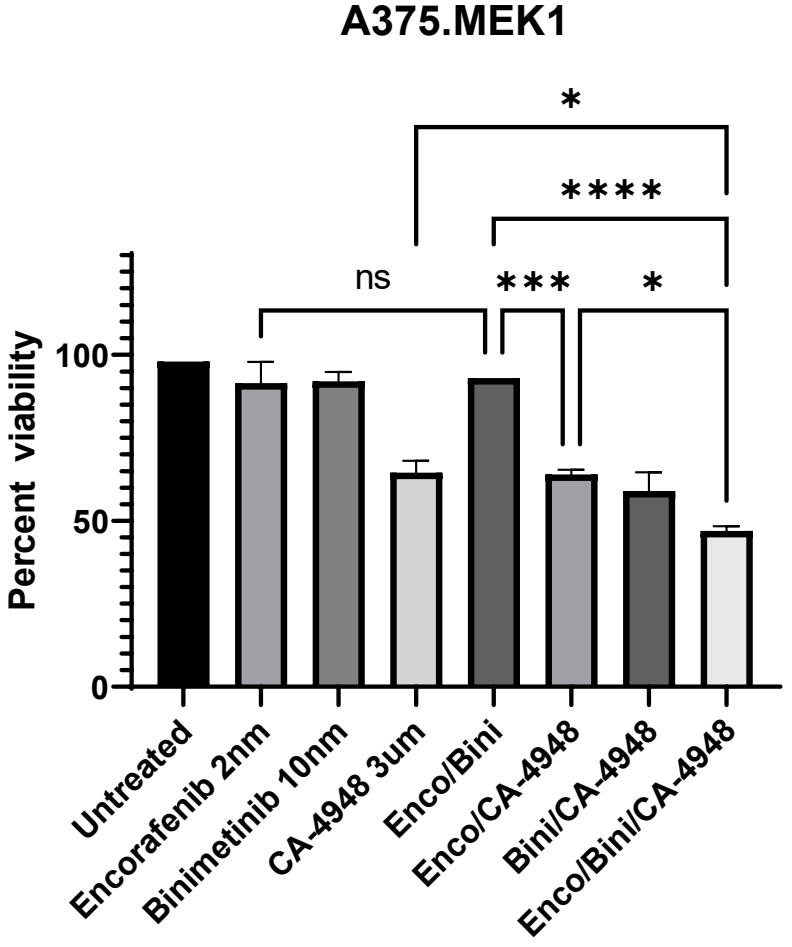






Combination therapy overcomes BRAF therapy resistance





* = p<0.05
**= p<0.01
***= p<0.001
****= p<0.0001, by multiple comparison ANOVA

Conclusions

- IRAK-4 is a novel potential target in MBM with high expression and multiple roles in tumorigenesis
- Inhibition of IRAK-4 in MBM results in downregulation of shared MAPK pathway targets of BRAF/MEK inhibition
- CA-4948 has cytostatic potential in human BRAF-mutant melanoma and could potentiate the effect of BRAF/MEK inhibition
- CA-4948 has a potential role in overcoming BRAF therapy resistance in melanomas, and further exploration into its ability to prevent the development of resistance are underway

UFBTIP collaborators

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