The IRAK-4 inhibitor Emavusertib (CA-4948) for the treatment of primary CNS lymphoma

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INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is an aggressive brain tumor accounting for 3% of all CNS malignancies and is usually associated with poor prognosis. 5-year survival is less than 30% with current treatment options. Standard of care treatment includes induction with high-dose methotrexate based chemoimmunotherapy followed by consolidation with autologous stem cell transplant or whole brain radiation. However, more than half of PCNSL patients are not eligible for this type of intensive therapeutic intervention. Novel treatment strategies with better efficacy and toxicity profile are urgently needed. Toll-like receptor signaling pathway via MyD88/IRAK-4 signalosome is constitutively active in PCNSL secondary to MYD88 L265P mutation and represents an excellent therapeutic target. Emavusertib (CA-4948) is an oral first-in-class small molecule inhibitor of IRAK4 that has demonstrated clinical activity in patients with systemic Non-Hodgkin's Lymphoma, however it has not been evaluated in the CNS space.

OBJECTIVES

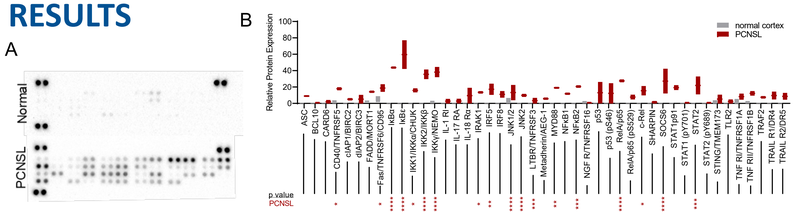
In this study we seek to determine the following:

- Evaluate MyD88 (myddosome) signaling pathway activation in PCNSL patient samples
- Determine if emavusertib can reach therapeutic dose levels in the CNS in preclinical models
- Determine if emavusertib treatment can reduce myddosome signaling in PCNSL tumors
- Assess therapeutic response of preclinical PCNSL to emavusertib *in vitro* and *in vivo*
- Present early clinical evidence for treatment response in a patient with PCNSL to emavusertib

METHODS

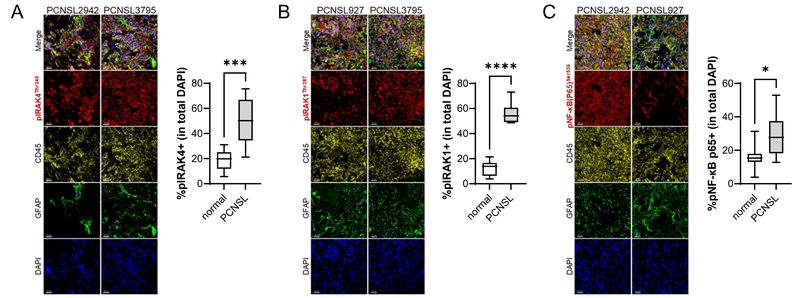
- Multiparameter immunohistochemistry (IHC) and proteomics analysis were used to assess myddosome signalling in patient PCNSL
- UPLC-MS/MS was used to measure emavusertib drug concentration in the plasma, cerebrospinal fluid (CSF), and brain tissue in mice following oral dosing
- Overall survival in preclinical PCNSL was monitored in response to dose-escalation with emavusertib treatment
- Protein expression of biomarker signalling downstream of IRAK-4 was compared between control and emavusertib treated tumors by IHC

RESULTS



Myddosome signaling is active in human PCNSL. (A) Representative NF-κB proteomics immunoblot for each normal cortex (unmatched) and PCNSL. (B) Quantitative comparison of individual protein expression from NF-κB immunoblots. These data confirm increased activation of myddosome signaling in PCNSL including IRAK-1, MyD88, IRF5, and downstream NF-κB: IκB kinase (IKK1, IKK2), NFκB1, NFκB2, RelA/P65, and c-Rel, among others.

RESULTS



IRAK-4 is activated in human PCNSL. IHC for 'active' (A) phospho-IRAK-4, (B) phospho-IRAK-1, and (C) phospho-NF-κB P65 shows elevated protein expression in patient PCNSL tissue (red) as compared to normal cortex (unmatched), confirming myddosome activation is specific to PCNSL. CD45 (pan-leukocyte, yellow), GFAP (astrocyte, green), and DAPI nuclear stain (blue) included to discern tissue landscape.

A

Parameter	Units	Plasma	CSF (Naïve)	Brain (Naïve)	Brain (A20 Tumor)
C_{max}	µg/mL or µg/g	60.3 ± 19.26	1.42±0.52	3.25±1.41	3.22±0.18
T_{max}	h	0.38 ± 0.14	0.25	0.5	0.83±0.29
$T_{1/2}$	h	2.73	1.33	1.39	1.19
$AUC_{0\text{-}8\ h}$	h*µg/mL or h*µg/g	189.51	2.91	8.09	8.68
$AUC_{0-\infty}$	h*µg/mL or h*µg/g	224.46	2.96	8.72	9.39
Brain to plasma ratio	%		1.53	4.26	4.95

B

Emavusertib reaches therapeutic levels in the brain. UPLC/MS/MS was used to determine the concentration of emavusertib in plasma, CSF, and brain tissue of naïve BALB/c mice, and brain tissue in A20 PCNSL tumor bearing mice. (A) Summary pharmacokinetics data. (B) Mean drug concentration measured at 0.25h, 0.5h, 1h, 4h, and 8h following a single oral dose of 150mg/kg. Dashed line represents proliferative IC_{50} dose for A20 model.

Emavusertib has single agent activity in preclinical PCNSL. (A) Emavusertib improves overall survival of A20 PCNSL tumor-bearing mice in a dose-dependent manner. (B) Resected tumors from animals on-study shows decreased Ki67 protein expression, indicating that emavusertib reduces the proliferative capacity of these tumors.

Emavusertib reduces MAPK signaling in preclinical PCNSL tumors. 3D imaging of resected tumors from emavusertib treated mice show reduced protein expression of 'active' (A) phospho-ERK1/2 and (B) phospho-P38 MAPK (red) as compared to control tumors. These data support that emavusertib treatment decreases MAPK signaling downstream of IRAK-4, indicating on-target biological efficacy in the brain. DAPI nuclear stain (blue) and blood vessels (BV, green) included to show tissue architecture.

RESULTS

Emavusertib demonstrates biologic activity in the CNS in a patient with MYD88 L265P PCNSL

Case Report:

November 2021- MR brain scan shows disease progression while on ibrutinib: The residual lesion in the left para trigonal white matter now measures about 5 x 2 mm (AP,TR). The mild fuzzy enhancement of the left superior cerebellar peduncle roughly measures 5 x 2 mm. Patient begins emavusertib plus ibrutinib.

December 2021- MR brain scan shows CR with combination therapy: Previously present patchy foci of enhancement in the left peritrigonal area, along the left temporal lobe, and in the left superior cerebellar peduncle are no longer demonstrated. Subsequent scans continue to show no evidence of disease.

CONCLUSIONS

- Myddosome activation is present in human PCNSL.
- Emavusertib reaches therapeutic dose levels in preclinical brain parenchyma and CSF.
- Emavusertib is effective at reducing proliferation and tumor progression in preclinical PCNSL, resulting in dose-dependent increased survival.
- Emavusertib treatment results in decreased expression of biological pathways downstream of IRAK-4/myddosome signaling, supporting on-target drug activity.
- Early evidence supports clinical activity of emavusertib in the CNS, with a CR observed in one PCNSL patient following combination treatment.

REFERENCES

1. Arvanitis, C.D., G.B. Ferraro, and R.K. Jain, *The blood–brain barrier and blood–tumour barrier in brain tumours and metastases.* Nature Reviews Cancer, 2020. **20**(1): p. 26-41.
2. Mendez, J.S. and C. Grommes, *Treatment of Primary Central Nervous System Lymphoma: From Chemotherapy to Small Molecules.* American Society of Clinical Oncology Educational Book, 2018(38): p. 604-615.
3. De Groen, R.A.L., et al., *MYD88 in the driver's seat of B-cell lymphomagenesis: from molecular mechanisms to clinical implications.* Haematologica, 2019. **104**(12): p. 2337-2348.
4. Saikh, K.U., *MyD88 and beyond: a perspective on MyD88-targeted therapeutic approach for modulation of host immunity.* Immunol Res, 2021. **69**(2): p. 117-128.

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