UF Evelyn F. & William L. McKnight Brain Institute
UNIVERSITY of FLORIDA

IRAK-4 as a therapeutic target in primary CNS lymphoma

Christina von Roemeling, PhD

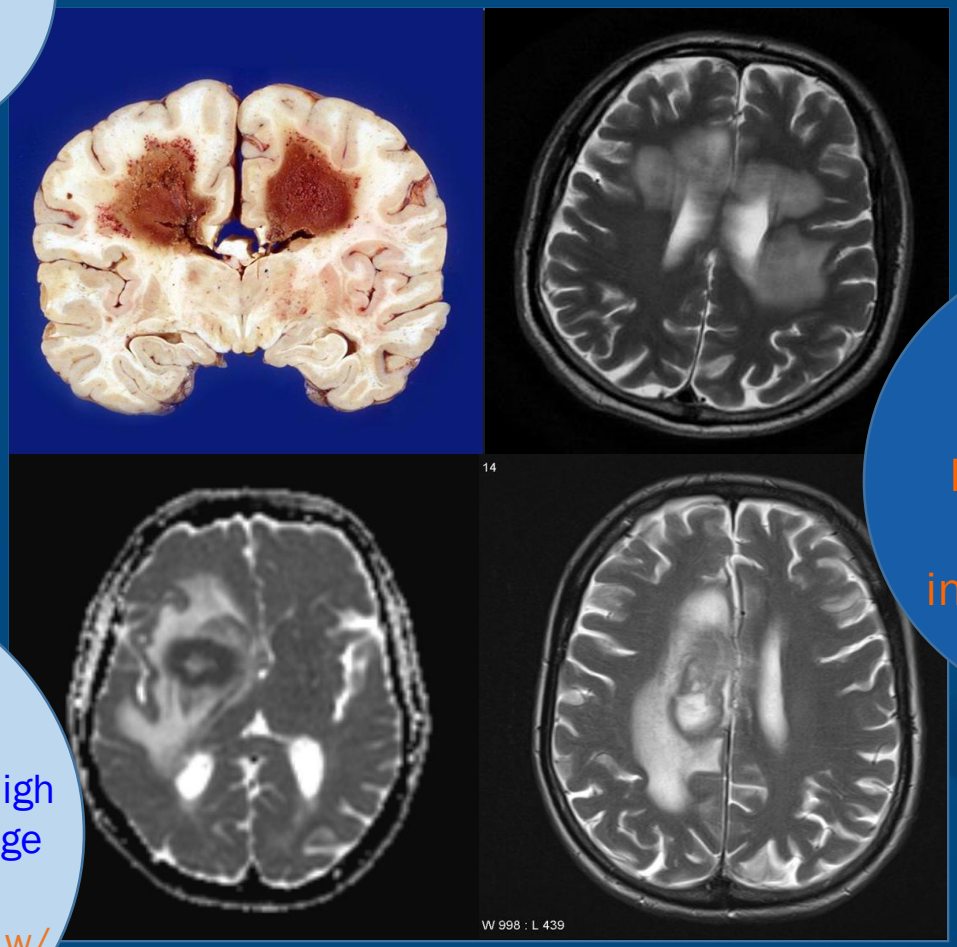
CURIS®

UF Clinical and Translational Science Institute
UNIVERSITY of FLORIDA

CNS Lymphoma

Primary CNSL: represents ~4% of all brain tumors

Secondary CNSL: 2-10% of pts with systemic disease develop SCNSL



Cell origin: >90% diffuse large B cell lymphoma

Location: Parenchyma, dura, leptomeninges, cranial nerves, intraocular, spinal cord

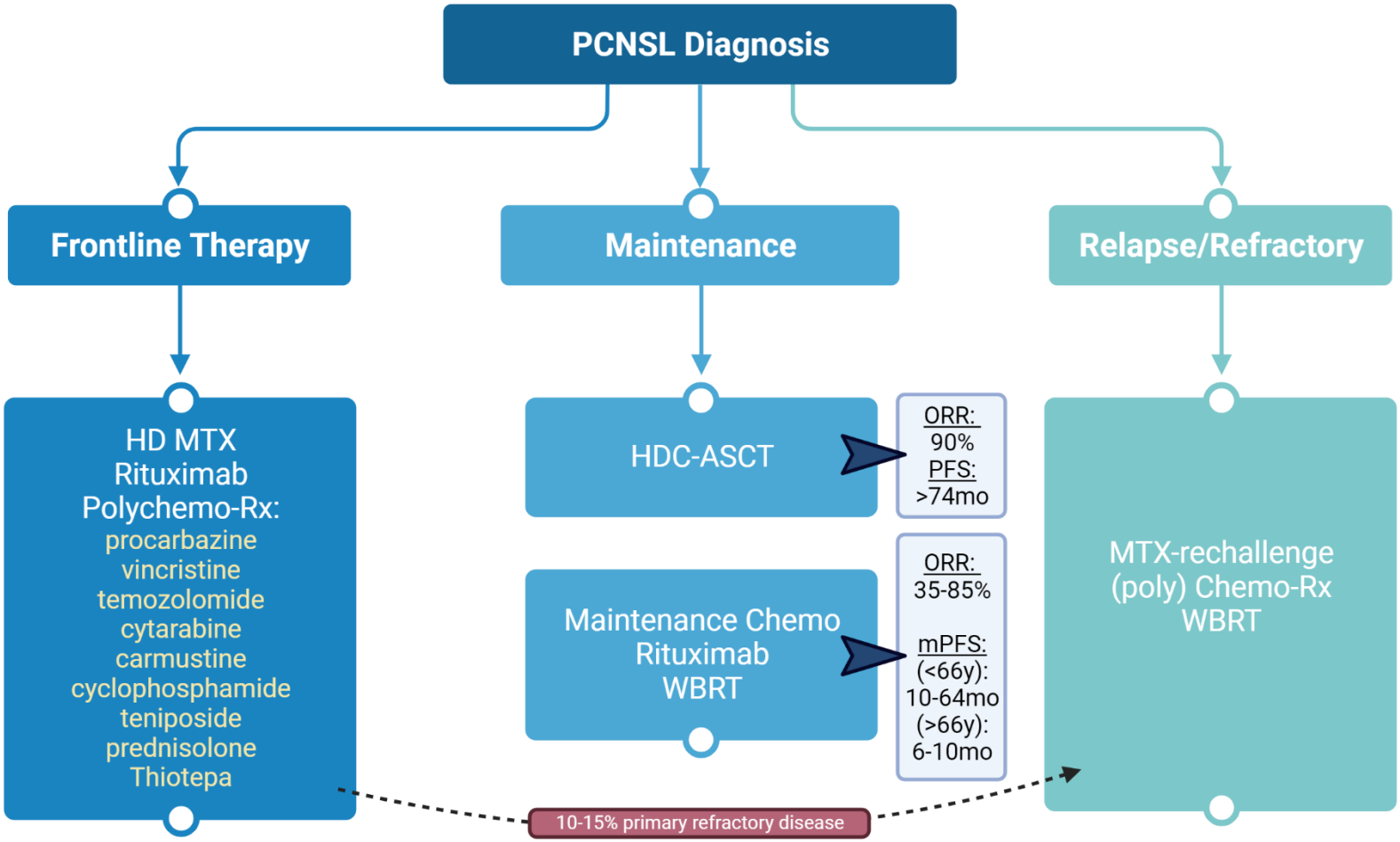
Epidemiology

- Males>Females
- Immunodeficiency: High Risk (HIV: 35Y med age @ diagnosis)
- Increasing incidence w/ higher age

Predilection for periventricular (and perivascular) niche

Dtsch Arztebl Int. 2018; 115: 419-26.
Cancers. 2021; 13, 5372.
.BJH. 2022; 196, 473-487.
J Hematol Oncol. 2022; 15:136.

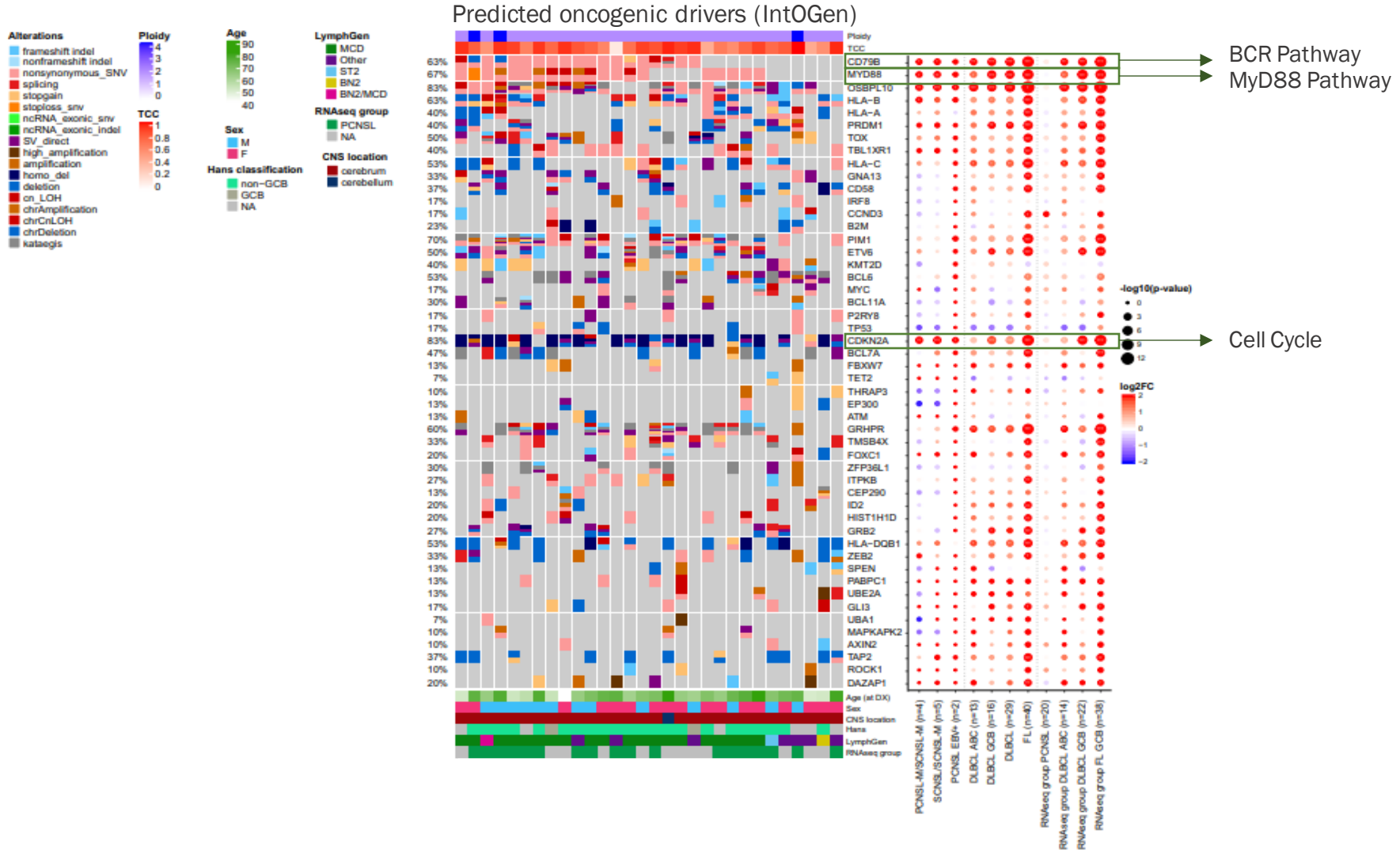
PCNSL Treatment



BioRender.com

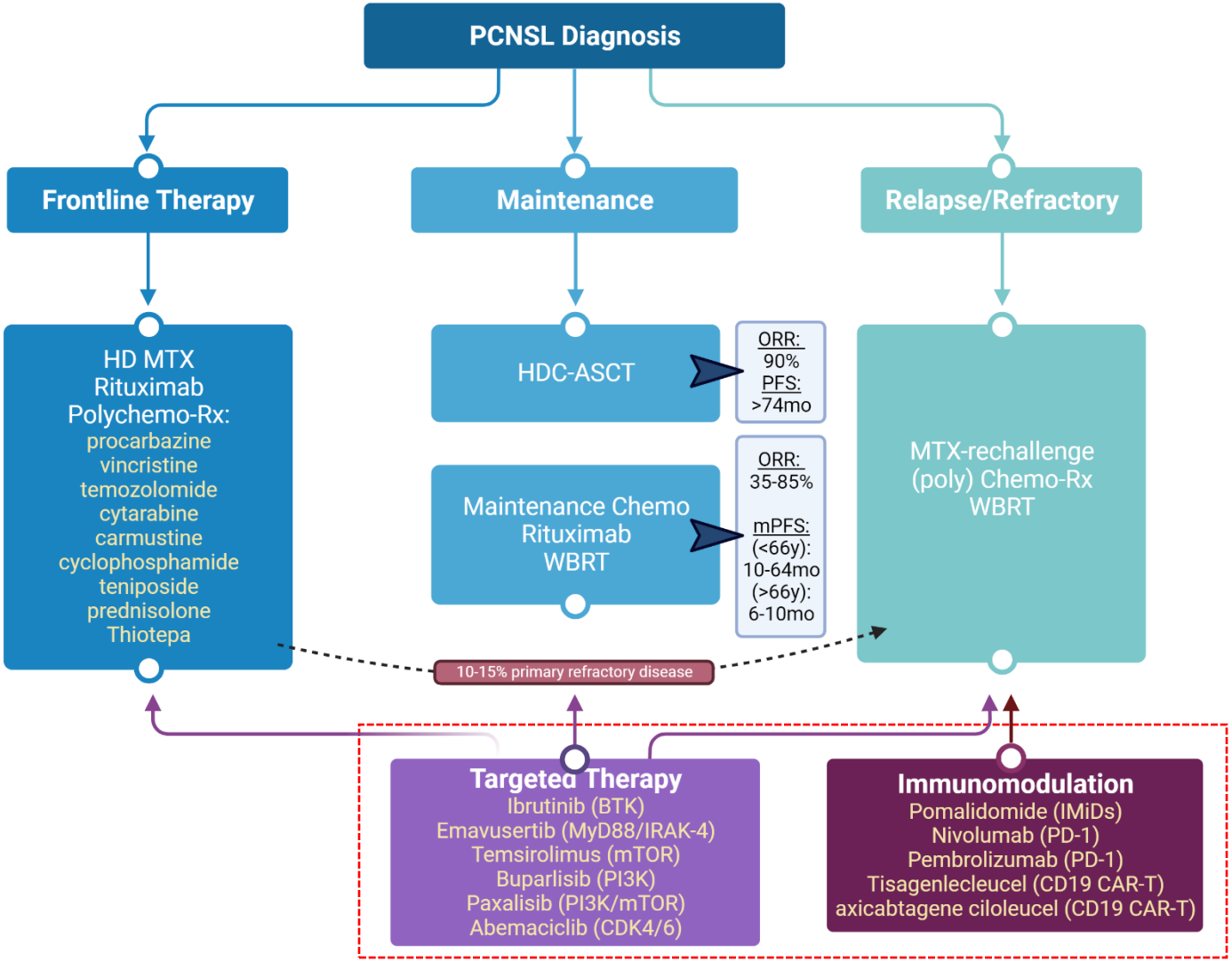
Dtsch Arztebl Int. 2018; 115: 419-26.
Cancers. 2021; 13, 5372.
.BJH. 2022; 196, 473-487.
J Hematol Oncol. 2022; 15:136.

The oncogenic landscape of PCNSL



Nat Comms. 2022; 13:2558.

PCNSL Treatment

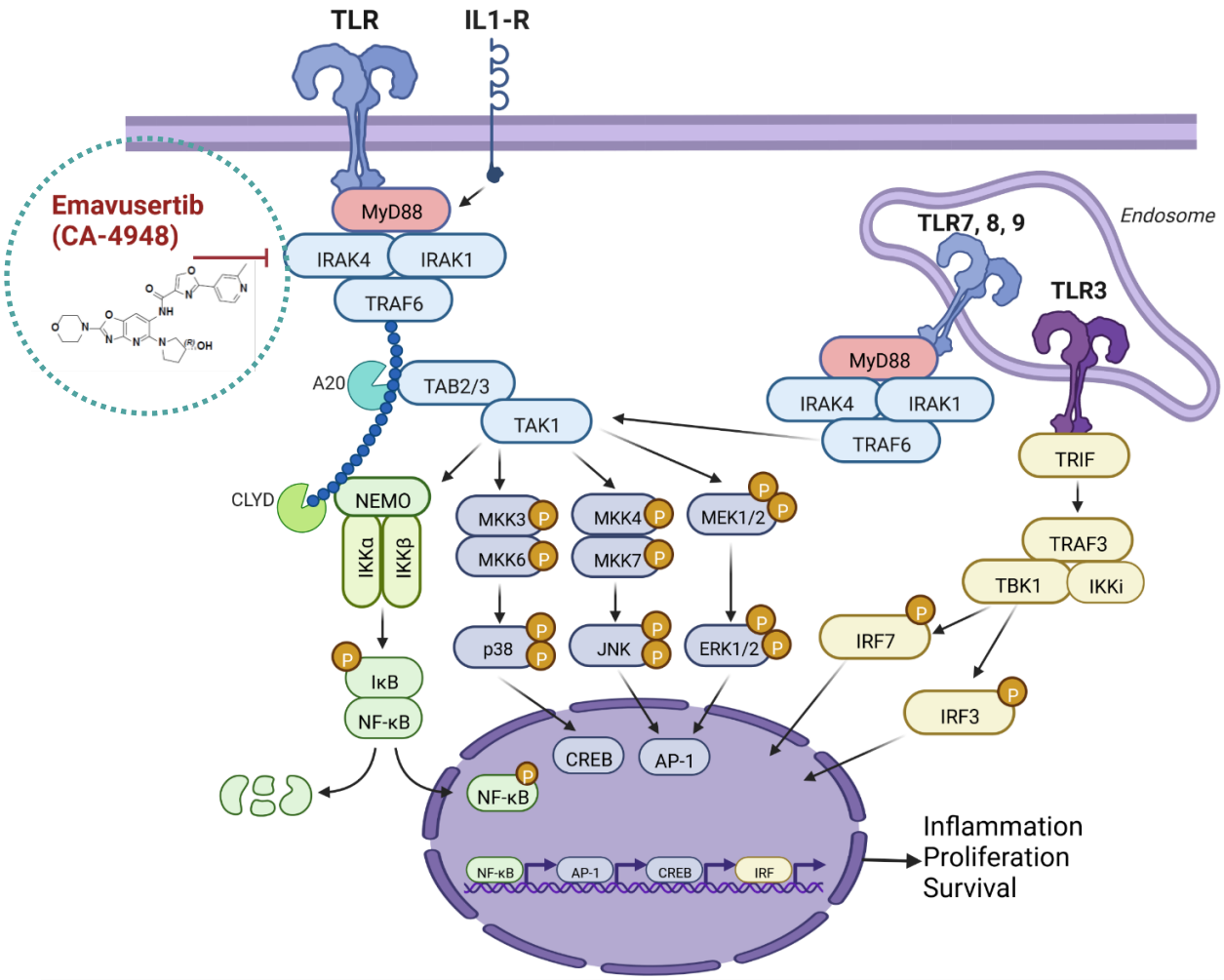


BioRender.com

Dtsch Arztebl Int. 2018; 115: 419-26.
Cancers. 2021; 13, 5372.
.BJH. 2022; 196, 473-487.
J Hematol Oncol. 2022; 15:136.

MyD88: In the driver's seat of lymphomagenesis

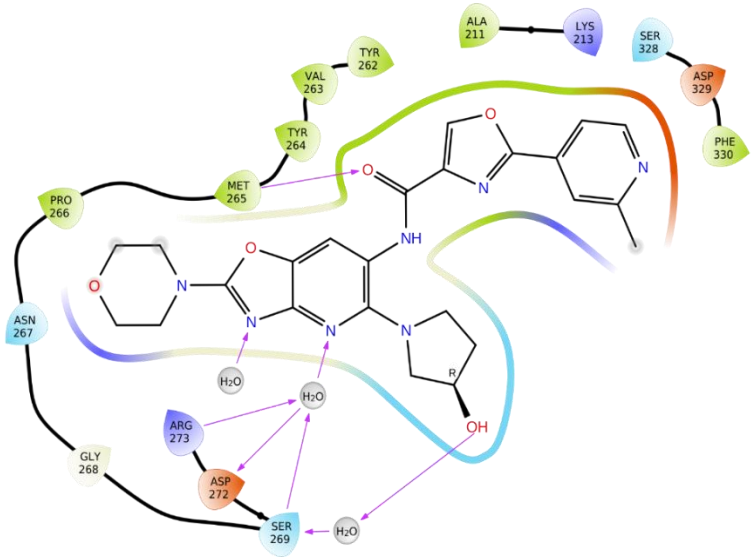
- High frequency of 'hotspot' L265P gain-of-function mutation
- Constitutive activation of NF-κB and MAPK
- Supports proliferation and survival
- Causes immune suppression through IL-6 & IL-10 production → STAT3 activation



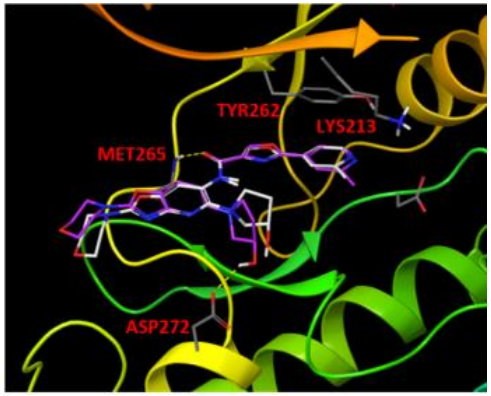
BioRender.com

Emavusertib (CA-4948)

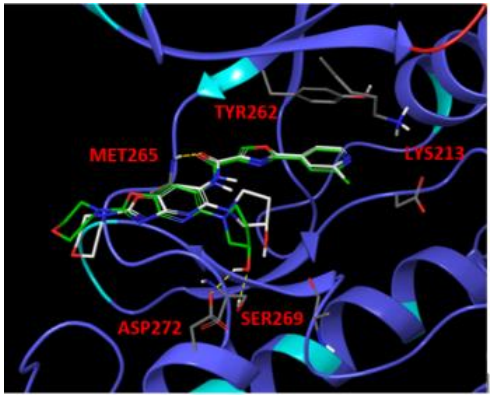
- First-in-class inhibitor
- High binding affinity to human IRAK4 (**23 nM**), high predicted binding affinity to murine IRAK4
- Well tolerated; safety profile allows long-term treatment and combination with other therapies



Human



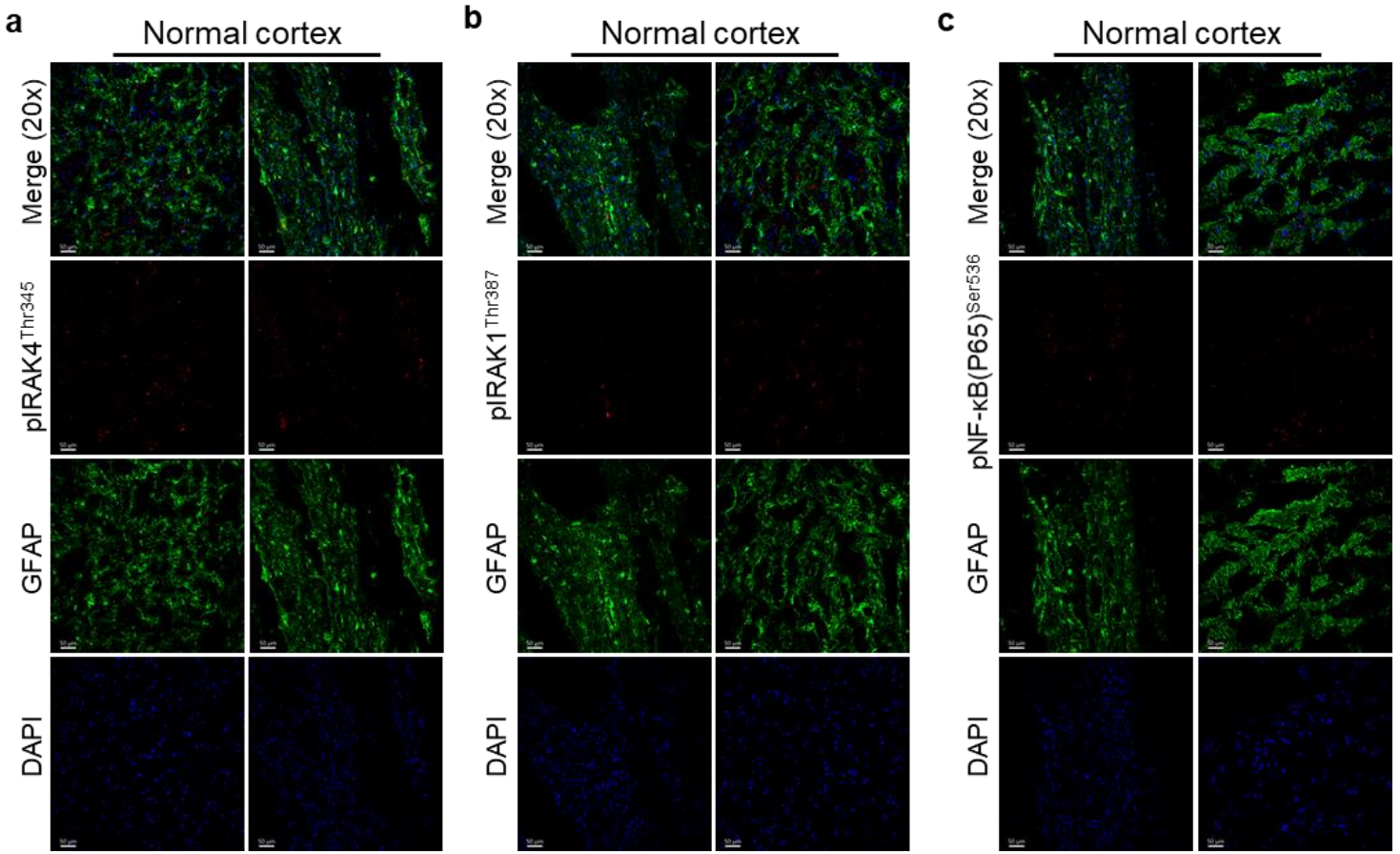
Murine



Project Overview

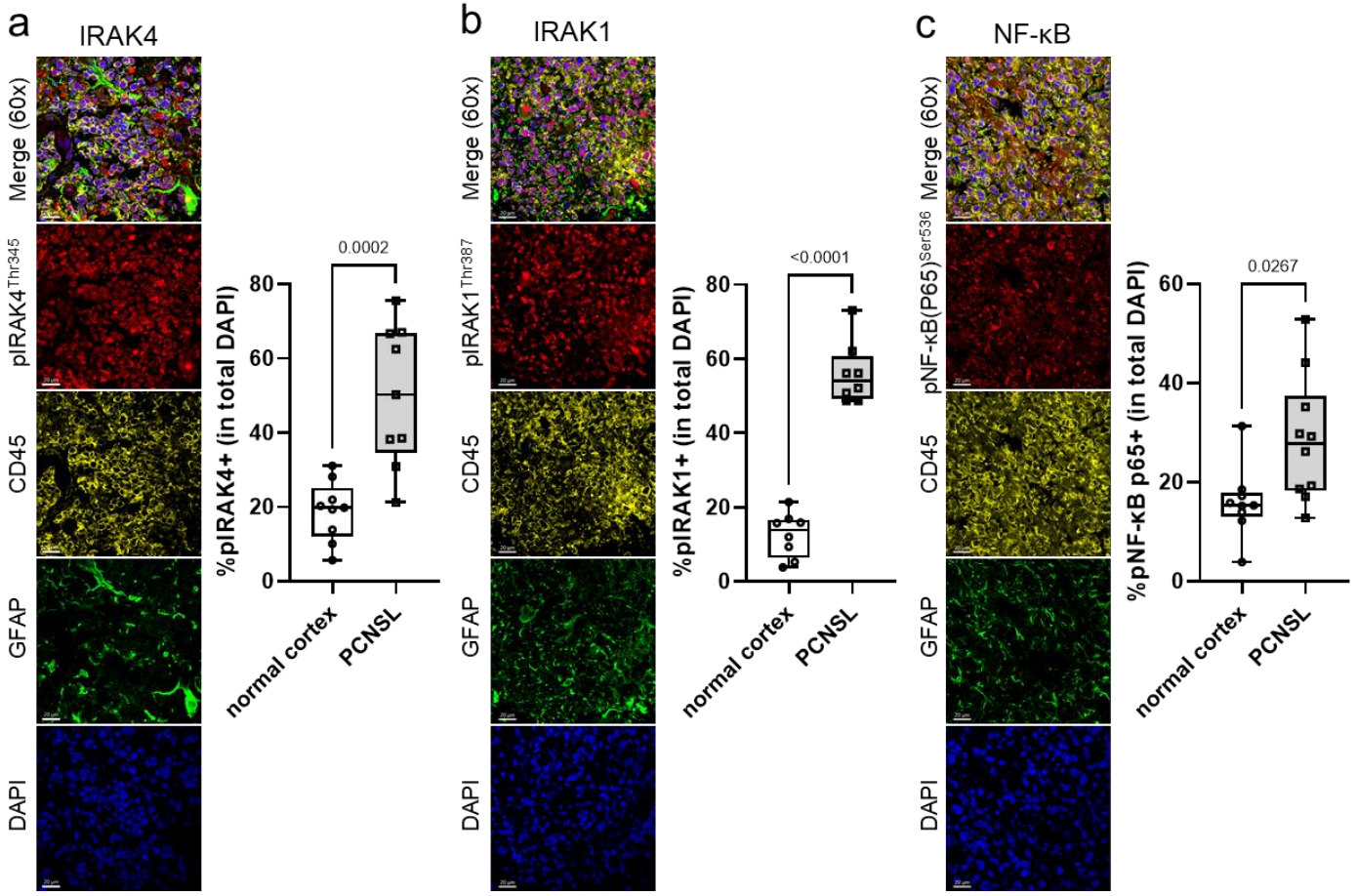
- Demonstrate myddosome activation in PCNSL
- Determine CNS penetration of emavusertib (CA-4948)
- Assess if CNS concentration reach therapeutic levels
- Evaluate anti-tumor efficacy of emavusertib in preclinical models of PCNSL

Myddosome expression in normal human brain



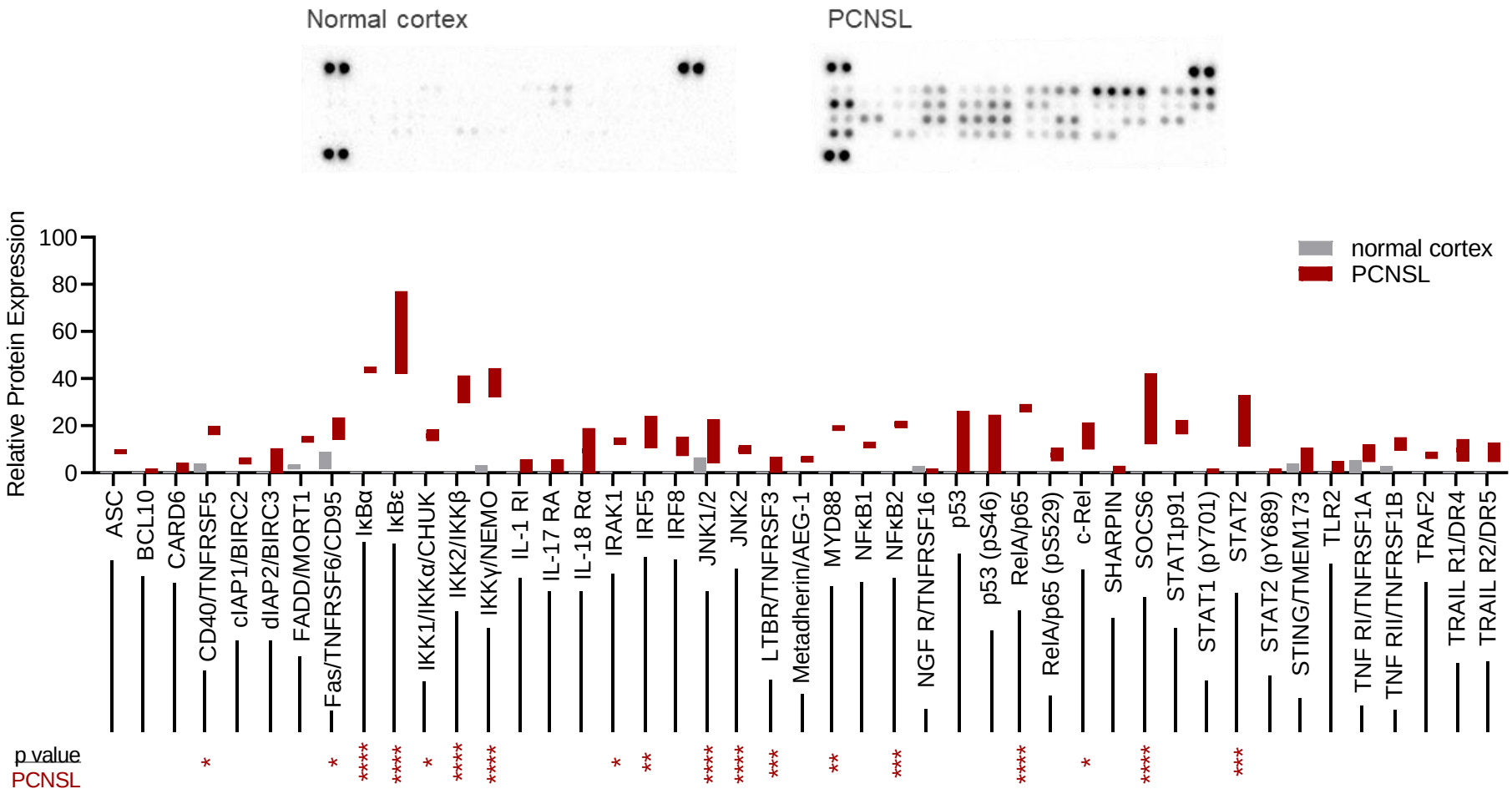
- Little to no expression of MyD88 downstream constituents
  - No CD45 infiltration

Myddosome expression in human PCNSL



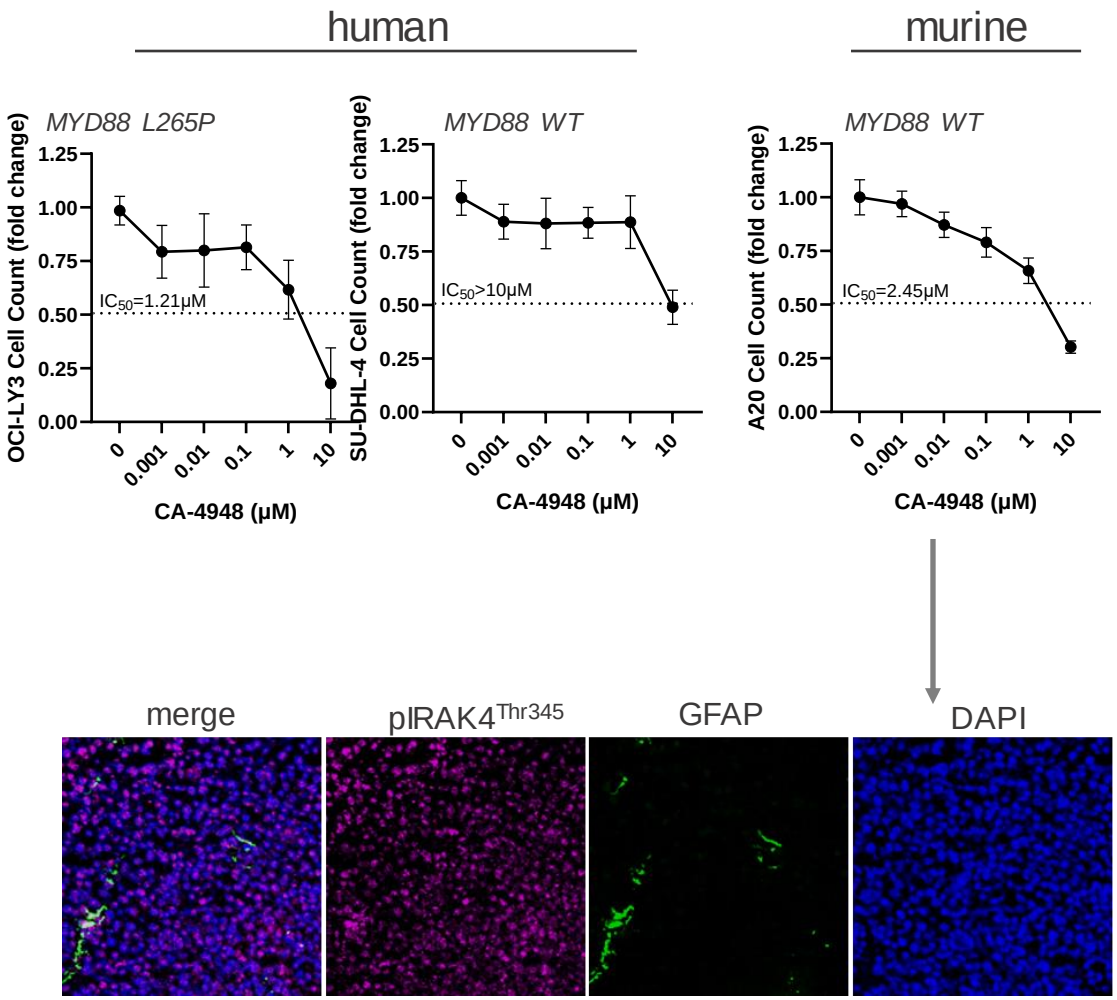
- High levels of p-IRAK4, p-IRAK1, and p-NF-κB
- High CD45 infiltration

Myddosome expression in human PCNSL



Emavusertib anti-lymphoma activity

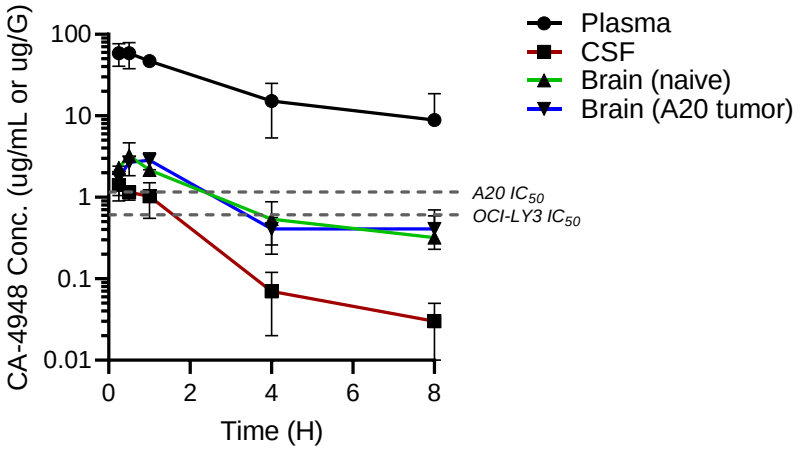
- Dose-dependent decrease in lymphoma proliferation
- MYD88 L265P sensitivity
- Anti-tumor activity in immune-competent *MYD88* WT lymphoma



CNS penetration (preclinical)

- Emavusertib can cross the BBB
- Relevant therapeutic dose levels detected in naïve parenchyma and CSF
- No notable changes in permeability in tumor-bearing mice

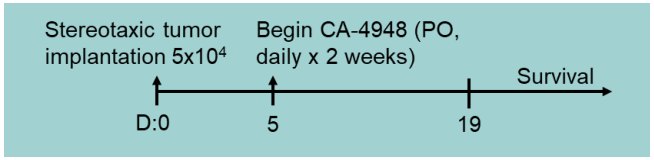
LC-MS/MS detection of CA-4948 in murine CNS



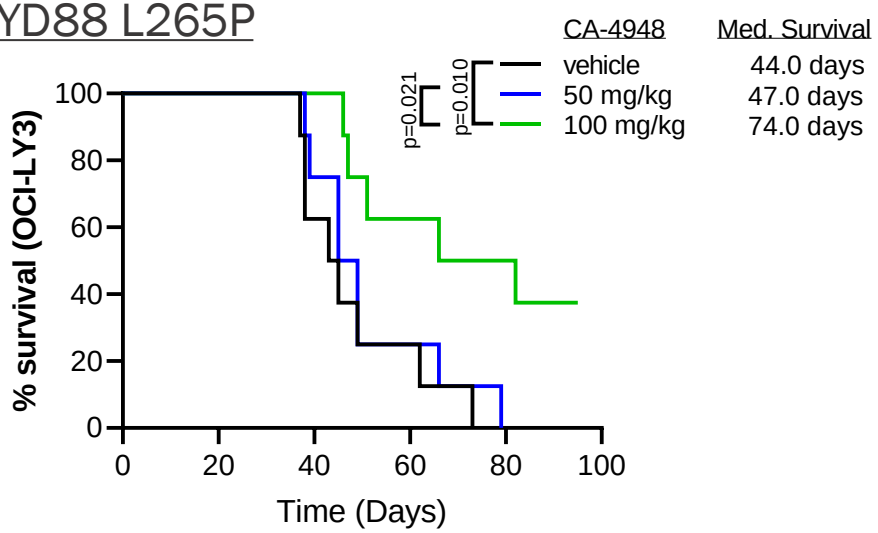
Parameter	Units	Plasma	CSF (Naïve)	Brain (Naïve)	Brain (Tumor)
C_{max}	µg/mL or µg/g	60.3 ± 19.26	1.42±0.52	3.25±1.41	3.22±0.18
T_{max}	h	0.38 ± 0.14	0.25	0.5	0.83±0.29
$T_{1/2}$	h	2.73	1.33	1.39	1.19
$AUC_{0\text{-}8\ h}$	h*µg/mL or h*µg/g	189.51	2.91	8.09	8.68
$AUC_{0\text{-}\infty}$	h*µg/mL or h*µg/g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

Emavusertib

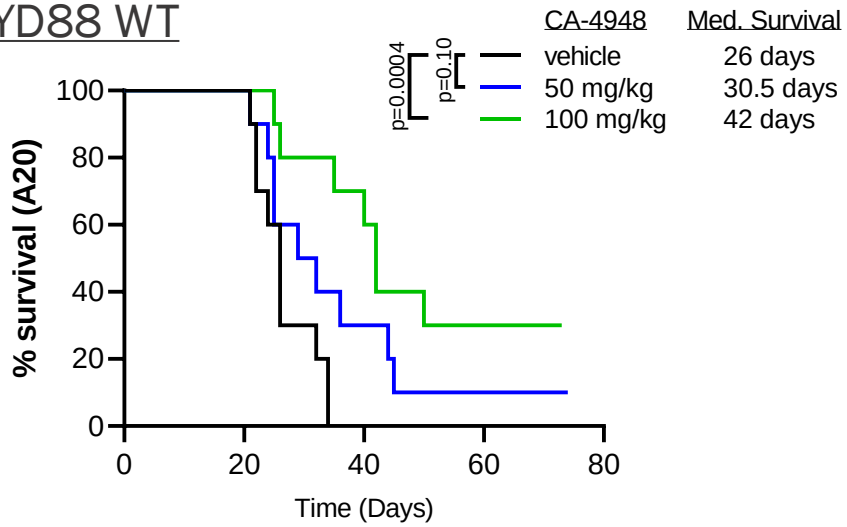
Preclinical PCNSL anti-tumor activity



Human MYD88 L265P

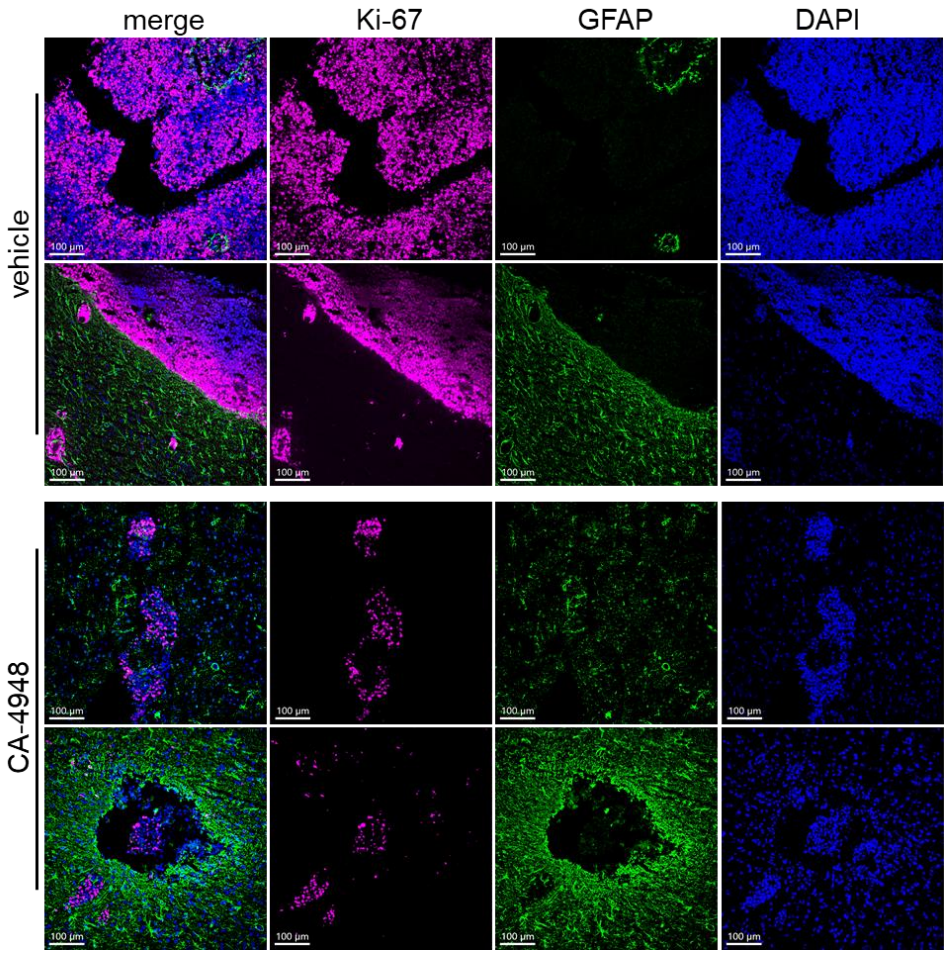


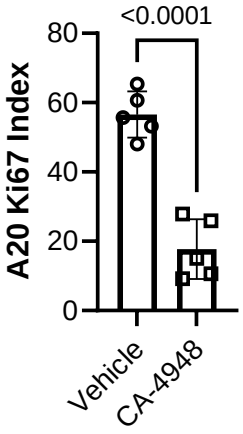
Murine MYD88 WT



Emavusertib

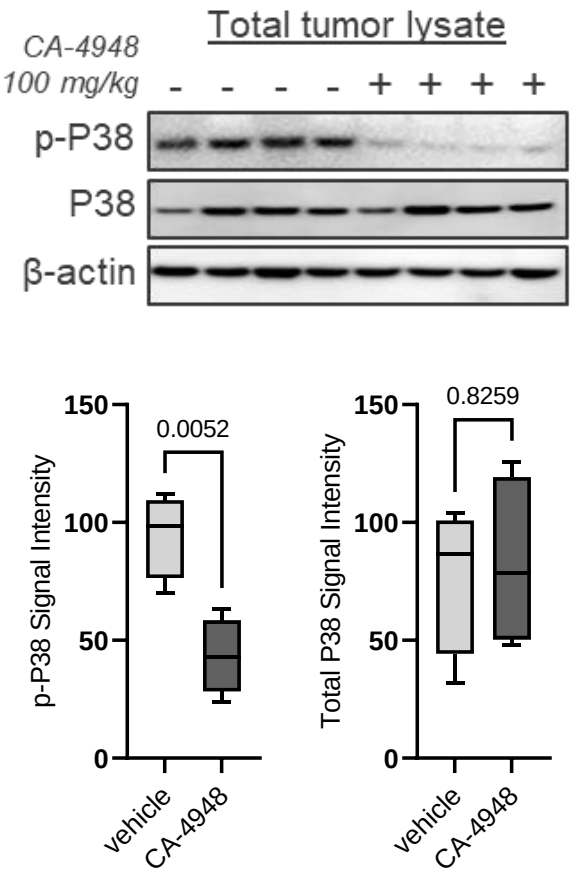
Preclinical PCNSL anti-tumor activity

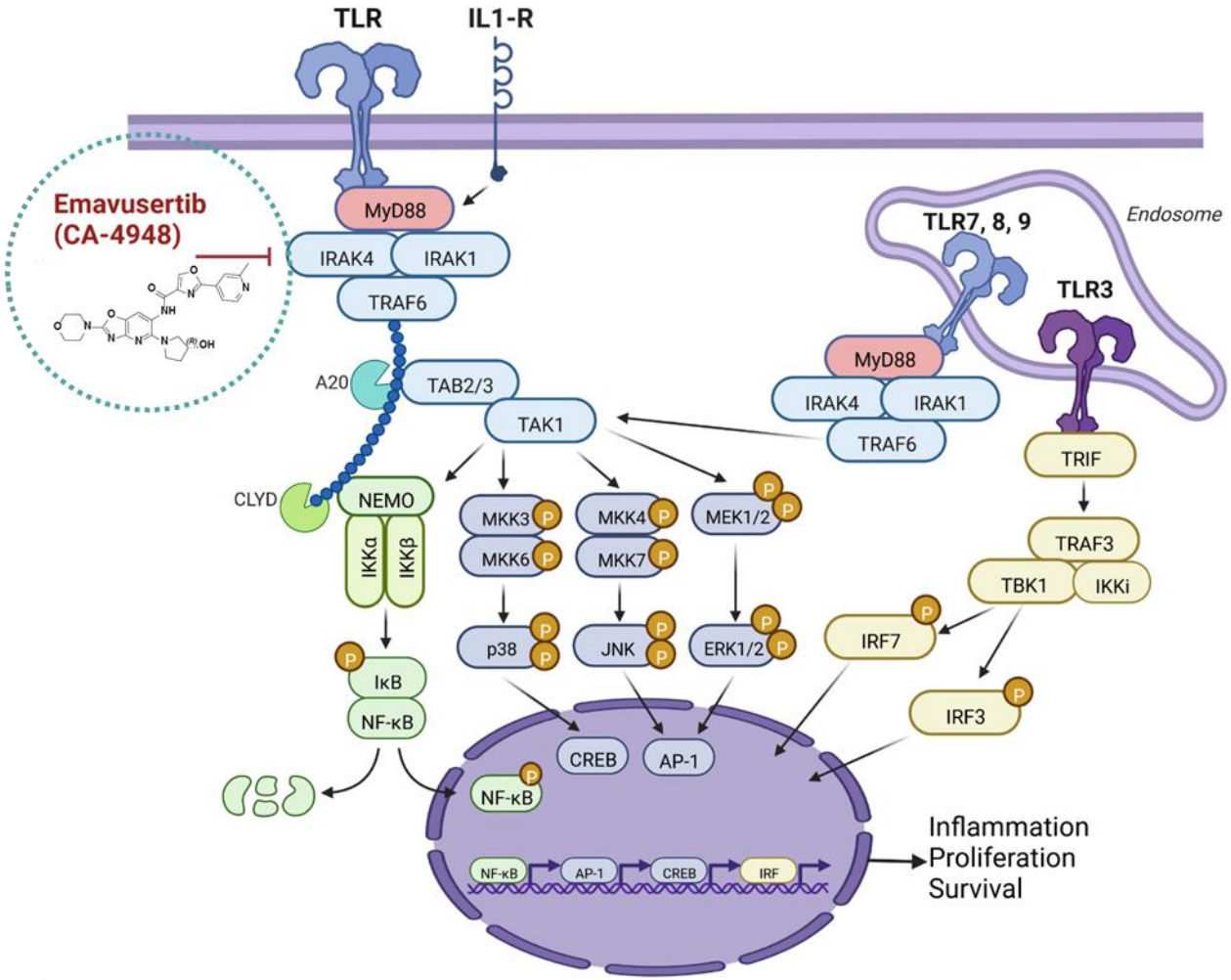




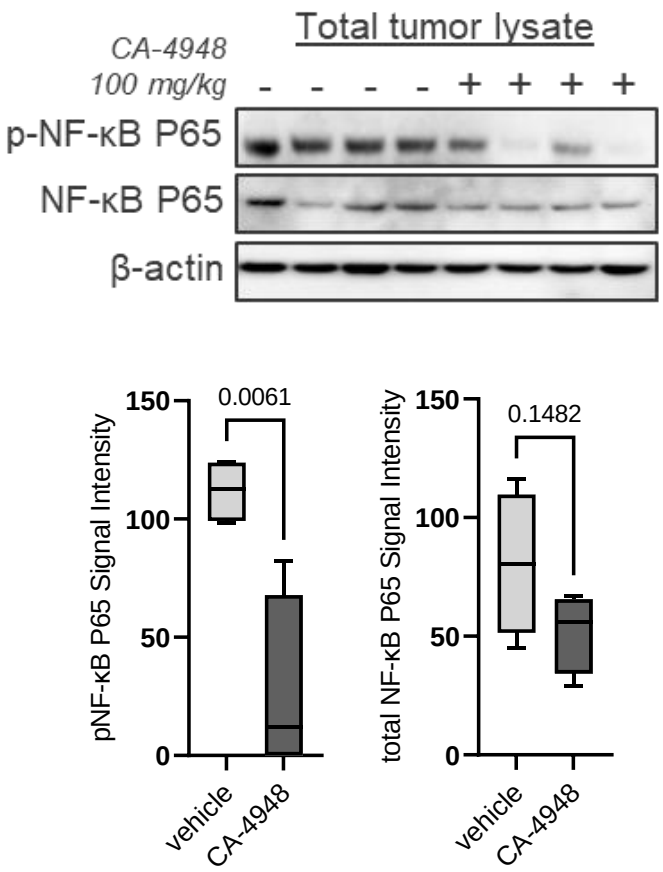
- Emavusertib reduces proliferative capacity of A20 tumors

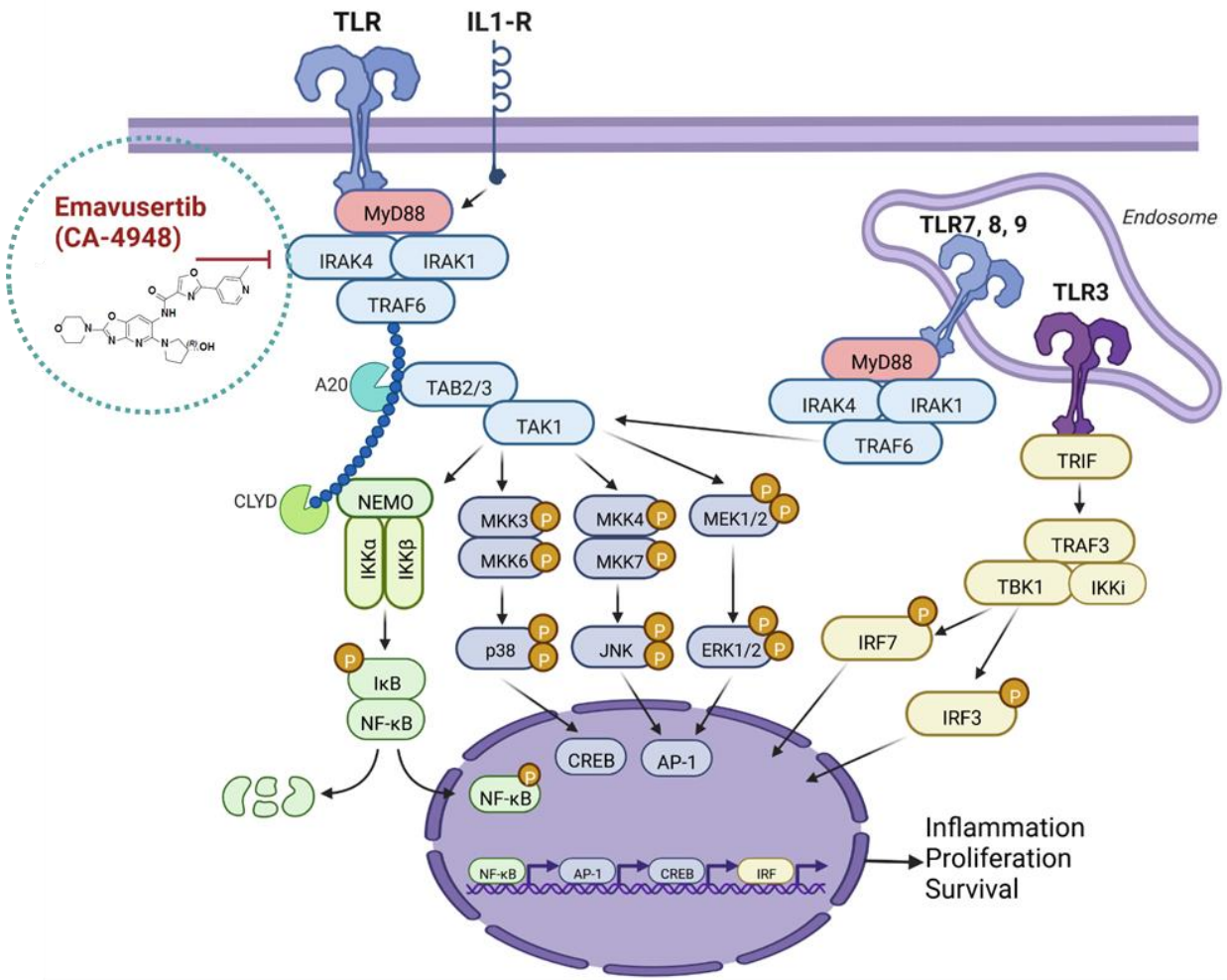
MAPK biomarker downregulation



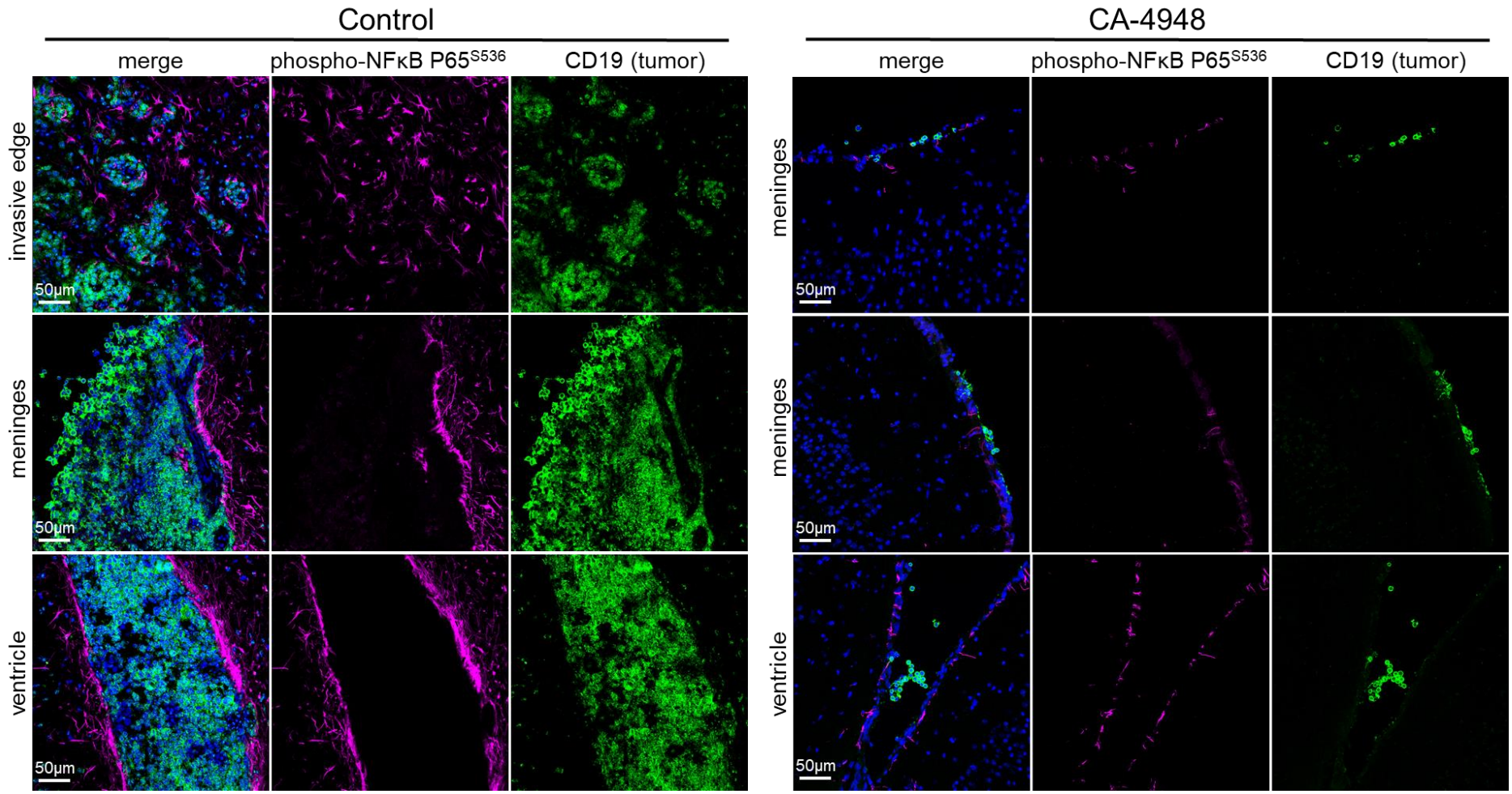


NF-κB biomarker downregulation

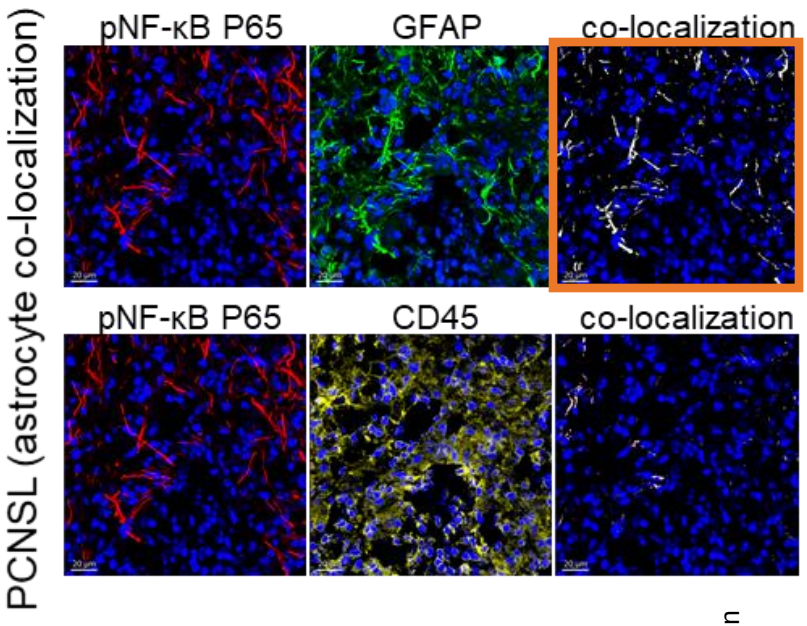


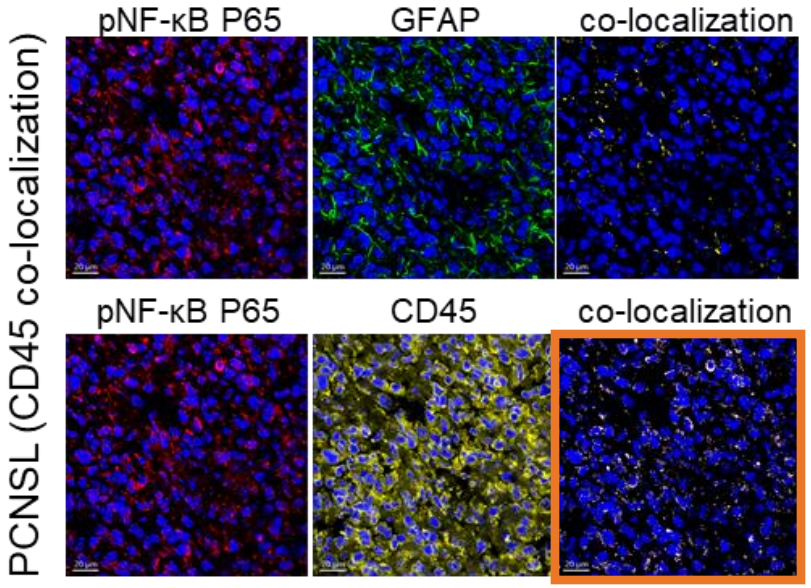


NF-κB biomarker downregulation

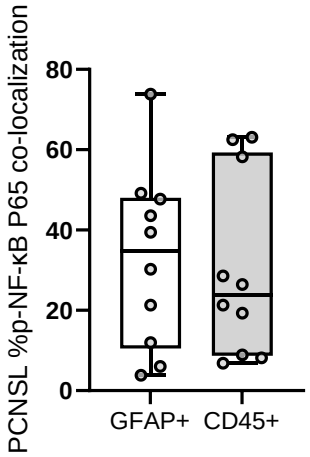


Therapeutic modulation of PCNSL TME?





- NF-κB+ astrocytes
- Implicates emavusertib therapeutic modulation in TME
- *MyD88-independent activity*



- NF-κB+ immune cells (tumor)
- Implicates emavusertib therapeutic modulation in cancer cells
- *MyD88-dependent activity*

TakeAim

Lymphoma Study (NCT03328078)

Study Overview

1.Part A1 (completed): dose escalation of emavusertib as **monotherapy** in relapsed or refractory HNL (n=34): 50 mg QD to 400 mg BID

- Monotherapy RP2D: 300 mg BID

2.Part A2: dose escalation of emavusertib **in combination with ibrutinib**

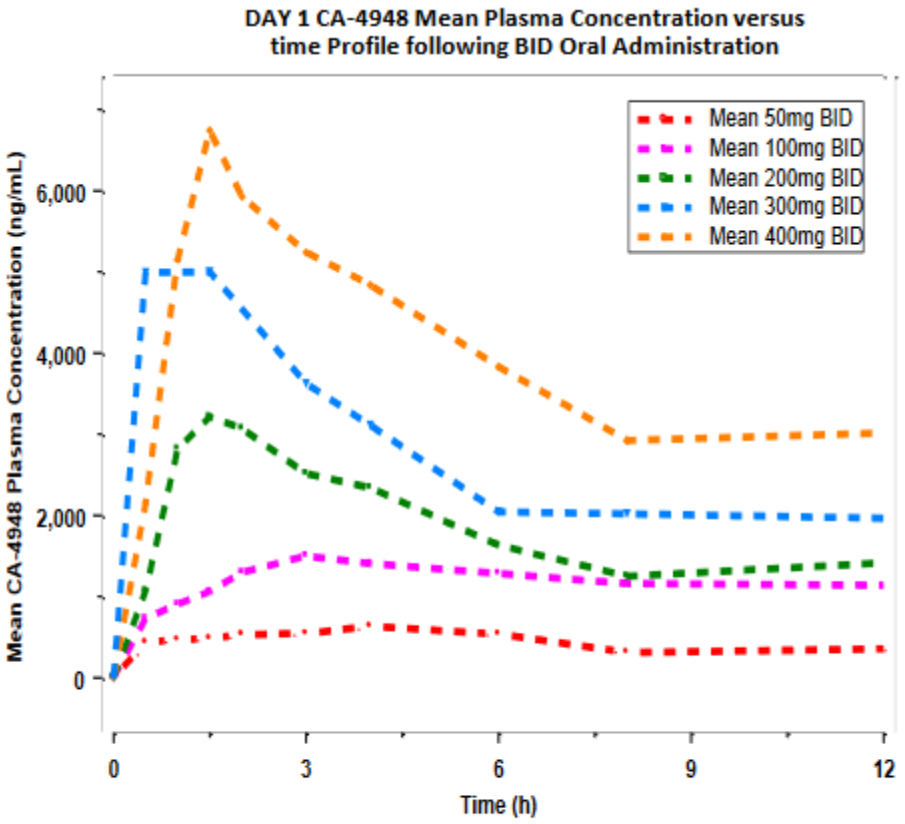
- Dose levels of 200-300 mg BID combined with full ibrutinib as per approved label (n=13)
- 200 mg BID of emavusertib is well tolerated in combination
- In transition to Part B

3.Part B: expansion cohort of emavusertib in combination with ibrutinib:

- **Focus on pCNSL**

Pharmacokinetics (human)

- Excellent oral bioavailability
- Rapidly absorbed, maximum plasma concentrations 0.5-8 hours after dosing
- Half-life ~ 6 hours
- Dose-proportional increase in exposure
- Minimal accumulation following single daily dose

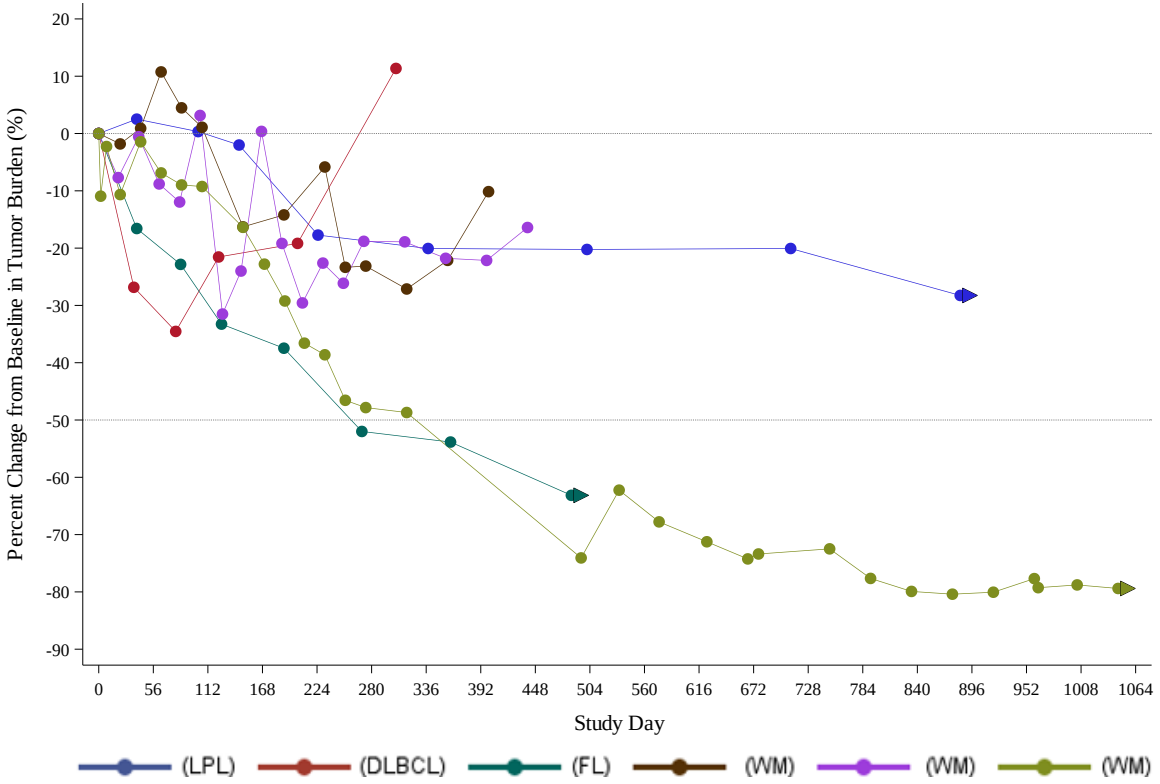


NHL Patient Responses

6 patients were treated with emavusertib (CA-4948) monotherapy for 1 to 3 years

- 3 patients ongoing with treatment with duration ranging 19-41 months
- 1 FL patient achieved PR after 13+ cycles of treatment
- 1 WM patient achieved PR after 21 cycles of treatment, and IgM values continued to decrease (~80% reduction)

Good long-term monotherapy tolerance of emavusertib CA-4948 at 200-300 mg BID



IgM values were used as the measure for tumor burden for WM/LPL patients; sum of product of diameters of target lesions were used as the measure for other lymphoma types.

Previously presented at IWWM 2022
Data extracted on May 6th, 2022

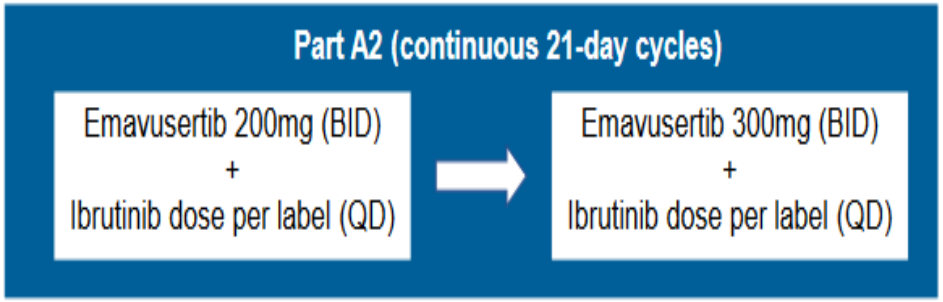
TakeAim

Lymphoma Study (NCT03328078)

Study Design

TakeAim-Lymphoma (NCT03328078)

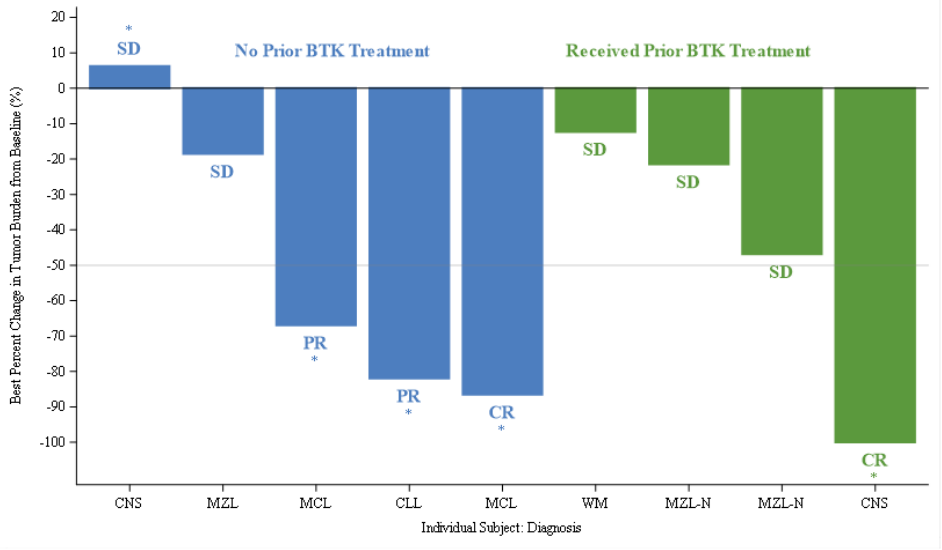
Part A2: dose escalation of emavusertib in combination with ibrutinib



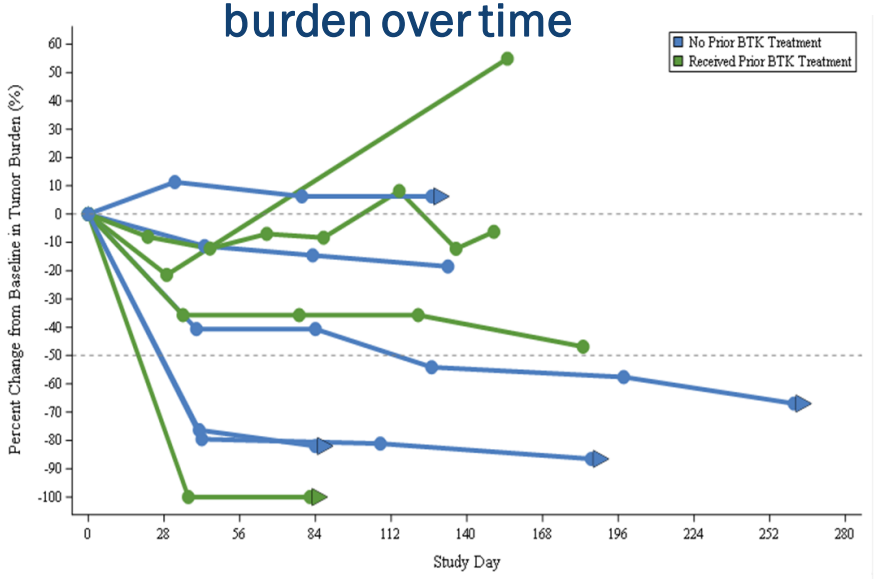
- Endpoints include safety, tolerability, and RP2D
- As of October 12th, 2022, two patients with relapsed/refractory CNS lymphoma (CNSL) have been treated with emavusertib + ibrutinib combination therapy.

Preliminary Efficacy Data From Patients with Combination Therapy

Best Response



Change in tumor burden over time



- Majority of patients had decreases in tumor burden or stable disease
- 4 patients that received prior BTK treatment show promising anti-cancer activity (SD/CR)
- 4/13 patients were not evaluable for tumor burden

TakeAim

PCNSL

Baseline Characteristics

	Case 1	Case 2
Gender	Female	Male
Age (yrs)	66	65
Diagnosis	Primary CNSL	Secondary CNSL
MYD88 mutation	Yes (L265P)	NA
Prior BTK inhibitor / Best Response	Yes / PR	No / NA
# of measurable disease at baseline	2	1
Prior lines of anti-cancer therapy	2	4
Prior bone marrow transplant	No	Yes (autologous)

Safety Profile

Grade 3+ Treatment-Related Adverse Event	emavusertib (300 mg BID) + ibrutinib (560 mg QD)	
	Case 1	Case 2
Thrombocytopenia	Gr 3	-
Pain	Gr 3	-
Muscular weakness	Gr 3	-
Blood Bilirubin increased	-	Gr 3
Alanine aminotransferase increase	-	Gr 3
Aspartate aminotransferase increase	-	Gr 3

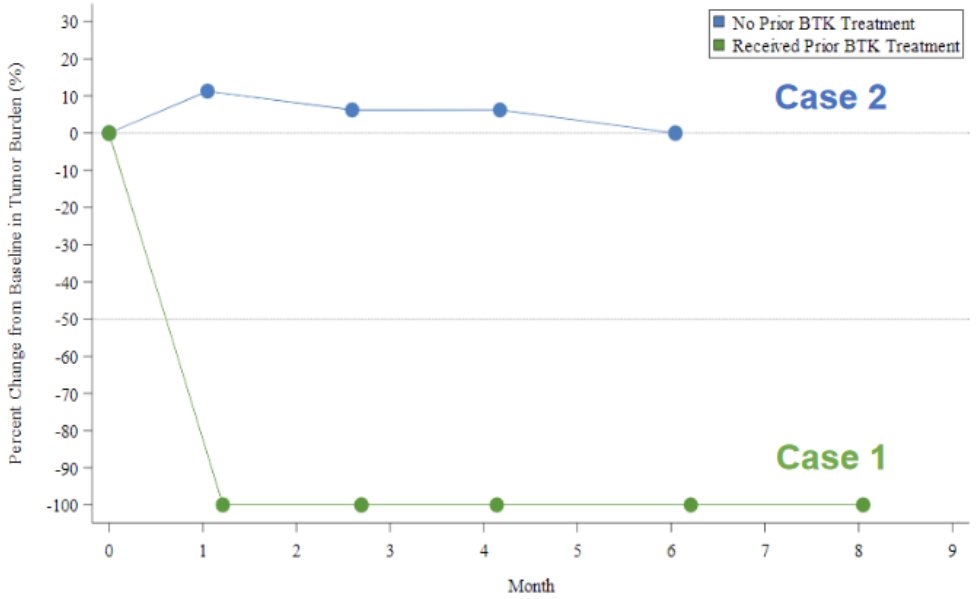
Data extracted October 12th, 2022

- No DLT and no treatment-related SAE was reported
- Majority of Gr 3 TRAEs were recovered or resolved

TakeAim

PCNSL

Change in tumor burden over time



- Preliminary efficacy data: 1 CR and 1 SD
- Case 1 was originally intolerant to high-dose methotrexate-based chemoimmunotherapy & achieved PR after switching to ibrutinib. Patient then achieved CR with combination ibrutinib+emavusertib
- Case 2 achieved and maintained radiographic SD for ~5 mo, with clinical resolution of associated symptoms

Date extracted 10.12.2022

Summary

- Confirmation of IRAK4 activation in human PCNSL
- Emavusertib crosses BBB & reaches therapeutic dose levels in CNS
- Evidence of targeted IRAK4 inhibition: Reduced Ki67, MAPK biomarker downregulation
- Anti-tumor activity (preclinical): dose-dependent survival outcomes
- Anti-tumor activity (clinical): 2 cases of tumor response (CNSL)
- Preliminary data suggests combination treatment may overcome ibrutinib resistance in hematological malignancies
- pCNSL cohort will be expanded (open at UNCC)

Thank you

UF Preston A. Wells, Jr. Center for Brain Tumor Therapy
UNIVERSITY of FLORIDA

Duane A. Mitchell, M.D., Ph.D.
Bently Doonan, M.D.
Kelena Klippel, M.S.
Rylynn Russell
Daniel Schulz, Ph.D.
Lan Hoang-Minh, Ph.D.
Vrunda Trivedi, M.S.
Chenglong Li, Ph.D.
Paul Castillo, M.D.
Elizabeth Ogando-Rivas, M.D.
The Florida Center for Brain Tumor Research
UF Drug Development Core

MAYO CLINIC

Grzegorz Nowakowski, M.D.
Han W. Tun, M.D.
Madiha Iqbal, M.D.

CURIS®

Jamison Hoffman, Pharm. D.

OUR BRAINS HELPING YOURS