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

Abstract EXTH-93

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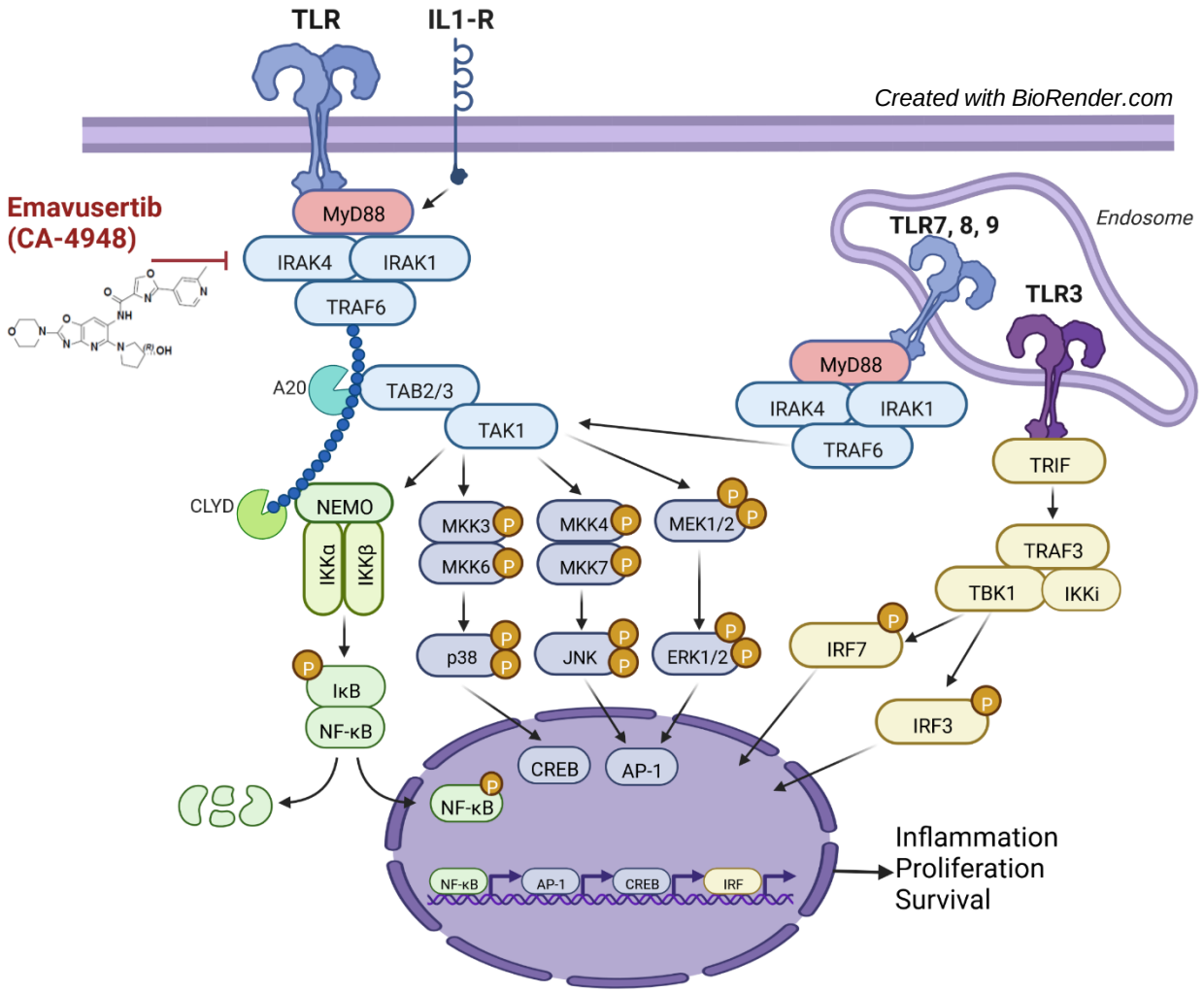
Project Overview

- Demonstrate MyD88 activation in PCNSL
- Determine CNS concentrations of Emavusertib (CA-4948) & determine if within therapeutic range
- Assess Emavusertib (CA-4948) anti-tumor efficacy in PCNSL preclinical models

MYD88 is a driver of lymphomagenesis

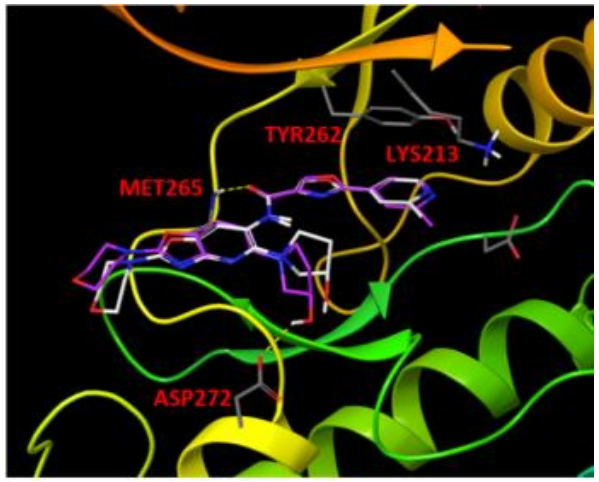
Mature B-cell neoplasms	*MYD88*(L265P) prevalence	*MYD88*(L265P) incidence	Total sequenced	Range	Number of studies	References
Chronic lymphocytic leukemia/small lymphocytic lymphoma	2.5%	221	8773	0 – 25%	41	18, 22-24, 28, 38-53
Monoclonal B-cell lymphocytosis	0%	0	75	N.A.	2	53, 54
B-cell prolymphocytic leukemia	Unknown*					
Splenic marginal zone lymphoma	7.0%	59	840	0 – 50%	19	18, 23, 29, 55, 56
Hairy cell leukemia	1.1%	1	89	0 – 8%	5	22, 30, 57-59
Splenic B-cell lymphoma/leukemia, unclassifiable	16.7%	1	6	N.A.	1	60
Lymphoplasmacytic lymphoma	85.5%	337	394	0 – 100%	16	18, 22-30
Non-IgM lymphoplasmacytic lymphoma	55.0%	33	60	42 – 100%	7	18, 23, 31, 33, 61
Waldenström macroglobulinemia	85.3%	1888	2213	57 – 100%	34	18, 22, 23, 31-37
Monoclonal gammopathy of undetermined significance, IgM	52.7%	301	571	0 – 100%	13	18, 22, 23, 62
Monoclonal gammopathy of undetermined significance, IgG/A	0%	0	41	N.A.	3	18, 22, 23, 34
Plasma cell myeloma	1.5%	3	205	0 – 30%	14	18, 22, 23, 30, 43, 63, 106, 107
Solitary plasmacytoma of bone	Unknown*					
Extraosseous plasmacytoma	Unknown*					
Monoclonal immunoglobulin deposition diseases	Unknown*					
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)	3.9%	15	383	0 – 13%	9	18, 22, 23, 64, 65
Nodal marginal zone lymphoma	10.3%	16	156	0 – 71%	9	18, 22, 23, 66
Follicular lymphoma	1.9%	5	264	0 – 50%	10	18, 22, 23, 67, 68
Pediatric-type follicular lymphoma	0%	0	27	N.A.	2	69, 70
Large B-cell lymphoma with *IRF4* rearrangement	Unknown*					
Primary cutaneous follicle center lymphoma	0%	0	60	N.A.	3	71-73
Mantle cell lymphoma	6.7%	2	30	0 – 50%	6	30, 43, 74
Diffuse large B-cell lymphoma (DLBCL), NOS Germinal center B-cell type Activated B-cell type	15.6% 5.3% 22.9%	853 81 492	5457 1520 2151	0 – 71% 0 – 57% 8 – 61%	43 21 21	3, 18, 22, 23, 67, 75-84, 113 3, 22, 23, 79-81, 85 3, 22, 23, 79-81, 85
T-cell/histiocyte-rich large B-cell lymphoma	Unknown*					
Primary DLBCL of the central nervous system	60.8%	382	628	33 – 100%	21	18, 22, 23, 86-88,96
Primary cutaneous DLBCL, leg type	62.2%	138	222	40 – 73%	9	22, 71, 89-91
EBV+ DLBCL, NOS	4.4%	4	90	0 – 22%	4	22, 83, 92
EBV+ mucocutaneous ulcer	0%	0	14	N.A.	1	93
DLBCL associated with chronic inflammation	Unknown*					
Lymphomatoid granulomatosis	Unknown*					
Primary mediastinal (thymic) large B-cell lymphoma	0%	0	68	N.A.	3	2, 3, 94
Intravascular large B-cell lymphoma	44.0%	11	25	N.A.	1	95
ALK+ Large B-cell lymphoma	Unknown*					
Plasmablastic lymphoma	Unknown*					
Primary effusion lymphoma HHV8+ DLBCL, NOS	Unknown* Unknown*					
Burkitt lymphoma	1.5%	1	67	0 – 2%	2	2, 74
Burkitt-like lymphoma with 11q aberration	Unknown*					
High-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements	11.1%	1	9	N.A.	1	83
High-grade B-cell lymphoma, NOS	Unknown*					
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma	Unknown*					

Haematologica (2019) 104, 12: 2337-2348

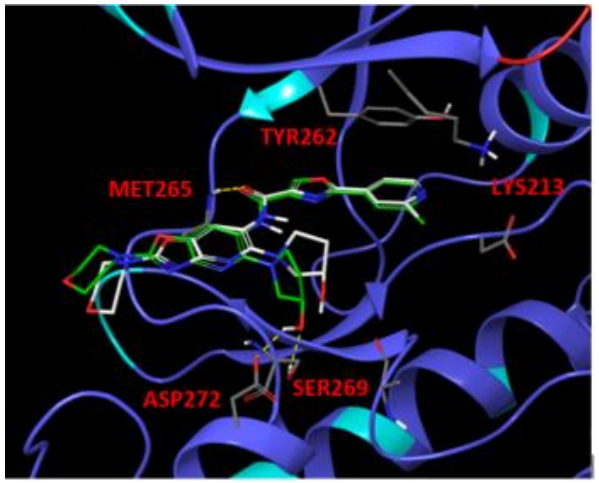


Emavusertib (CA-4948): A novel small molecule IRAK4 Kinase Inhibitor

Human



Murine



Receptor	GlideXP Docking Score (kcal/mol)	RMSD to Crystal Structure Ligand Pose (Å)	DeepAtom Score (kcal/mol)
Human IRAK4	-6.5	0.743	-11.1
Mouse Homolog	-8.9	0.870	-11.1

- First-in-class inhibitor
- Good oral bioavailability
- 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
- Anti-tumor activity in hematological malignancies that are driven by activation of TLR/IL-1R pathways

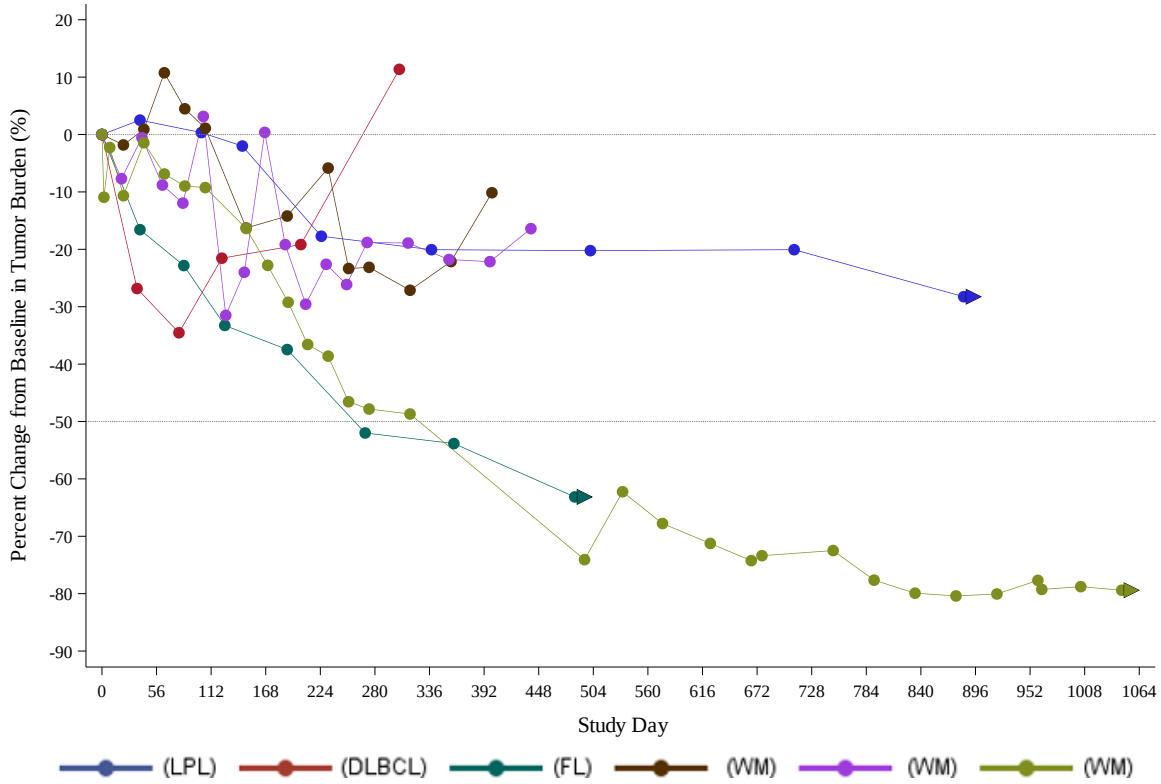
Emavusertib in B Cell Cancers

Monotherapy

6 patients were treated with emavusertib for ~1 year or longer

- 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)

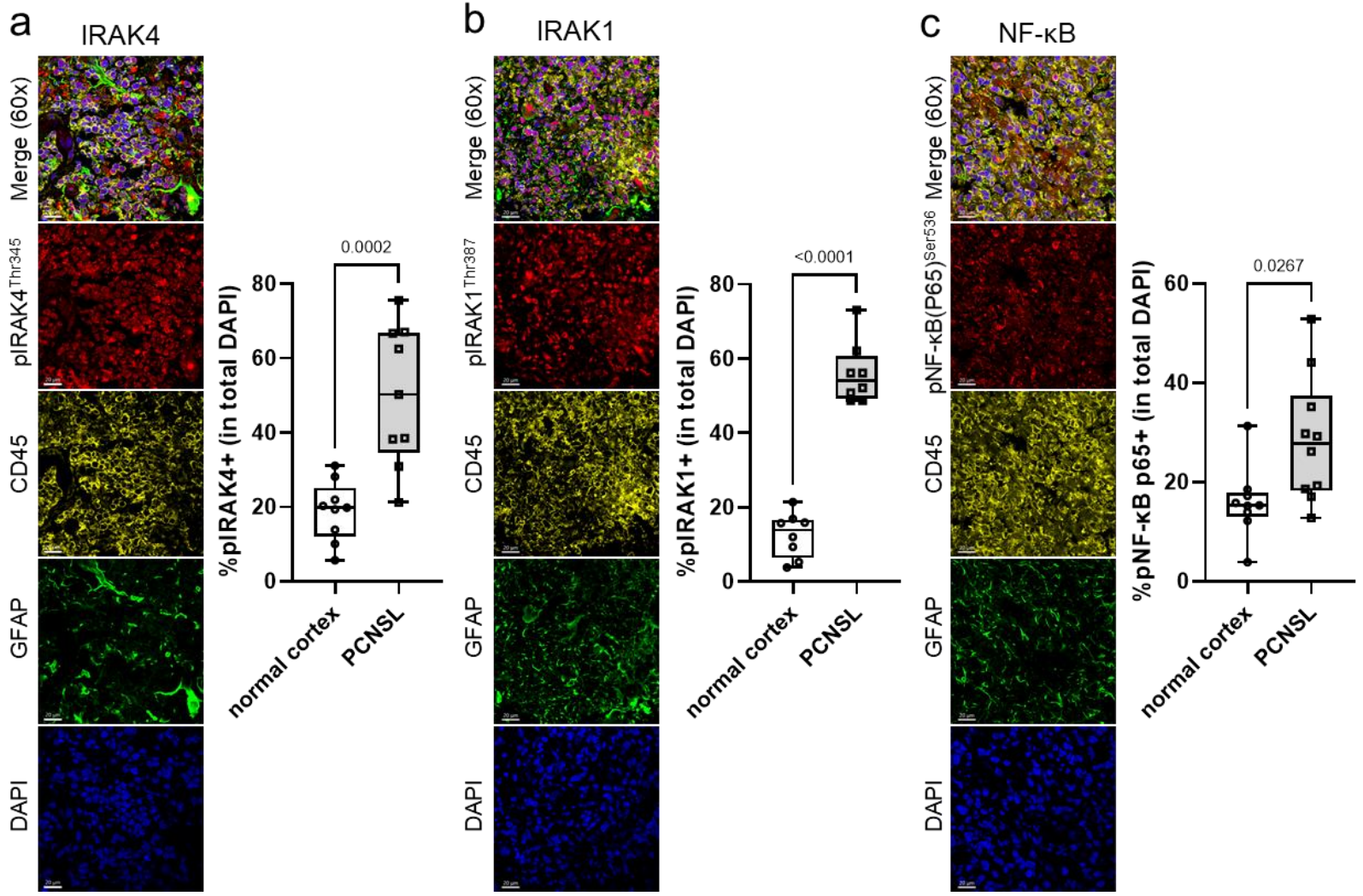
Percent Change in Tumor Burden from Baseline
(6 patients treated for ~ 1 year or longer)



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.

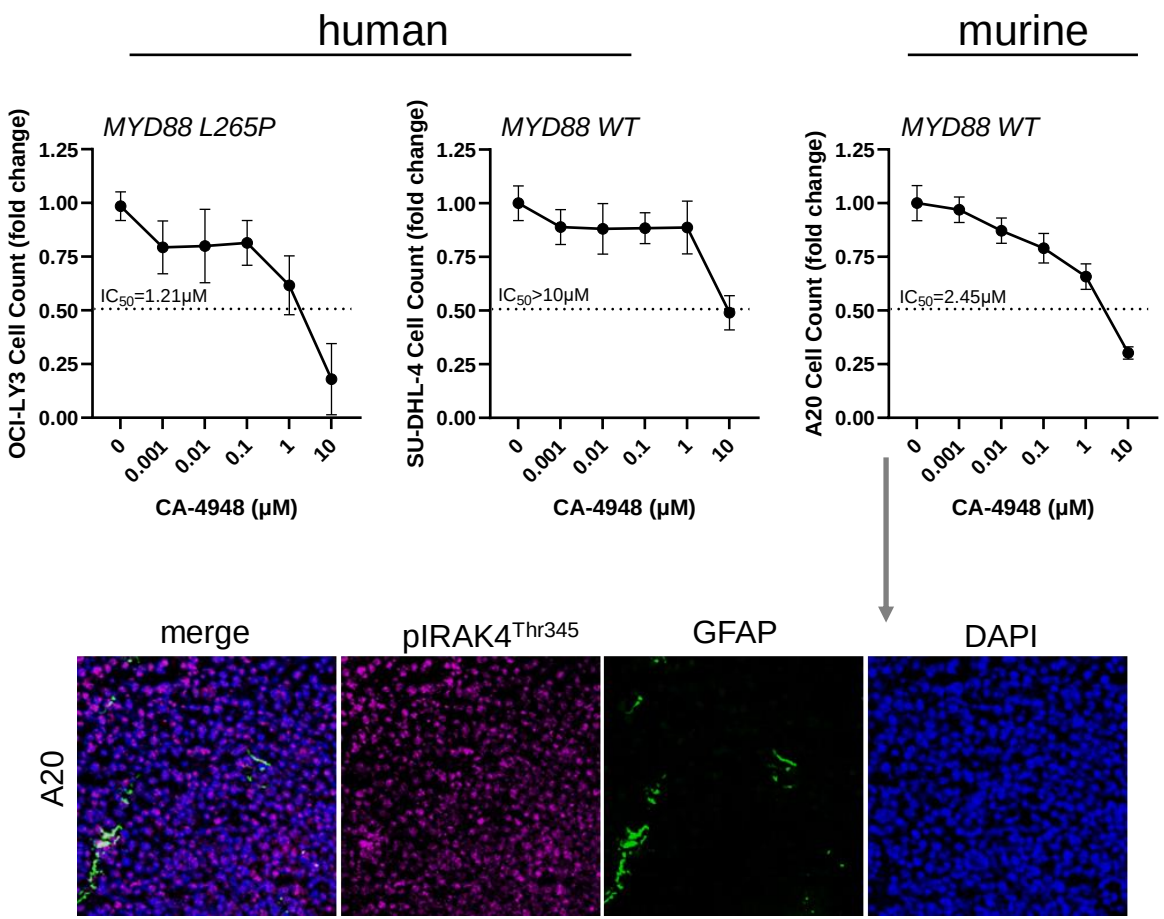
Previously presented at IWWM 2022
Data extracted on May 6th, 2022

MYD88 activation in patient PCNSL

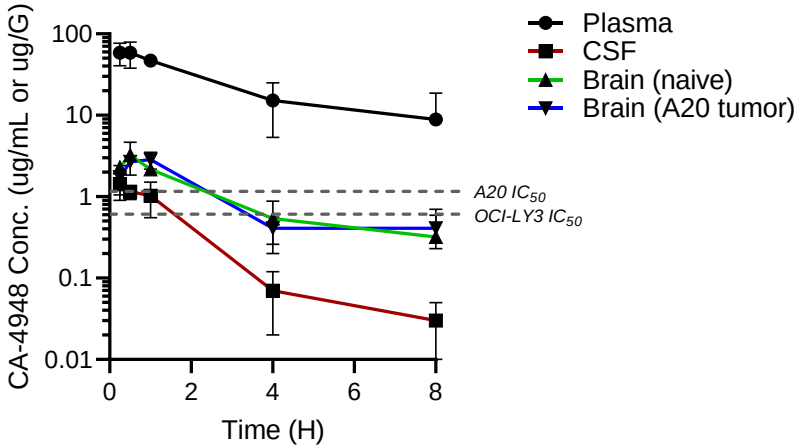


Emavusertib reaches therapeutic doses in CNS

Preclinical model sensitivity to CA-4948



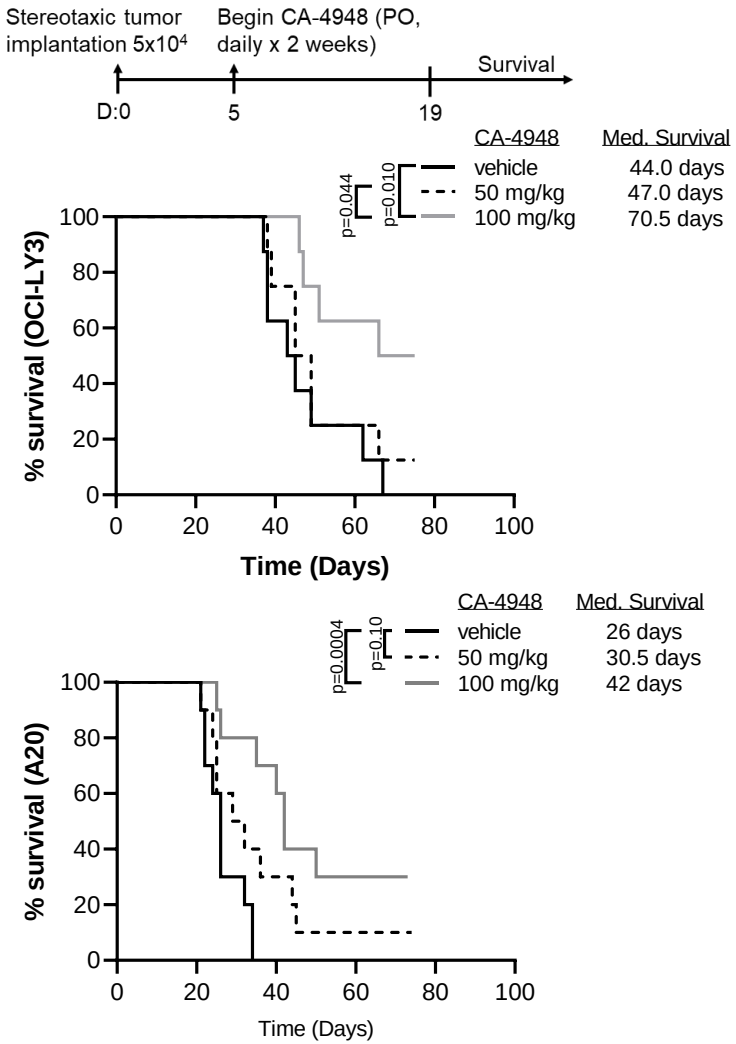
LC-MS/MS detection of CA-4948 in murine CNS



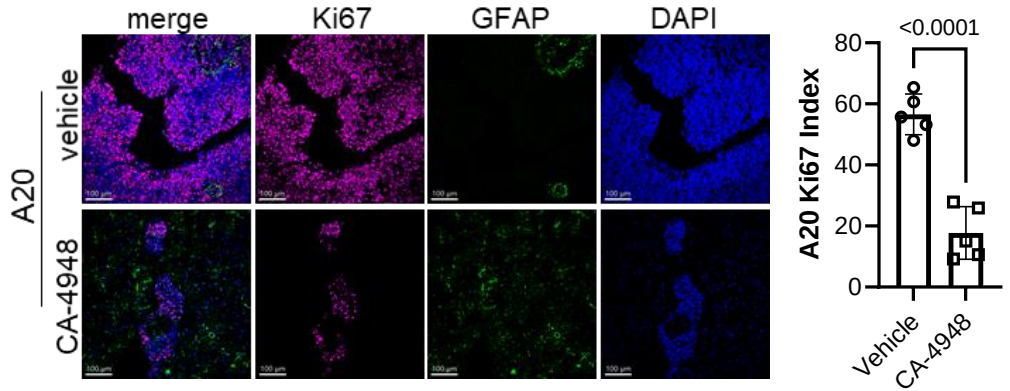
Parameter	Units	Plasma	CSF (Naïve)	Brain (Naïve)	Brain (Tumor)
C_{max}	μg/mL or μg/g	60.3 ± 19.26	1.42±0.52	3.25±1.41	3.22±0.18
T_{max}	h	0.38 ± 0.14	0.25	0.5	0.83±0.29
$T_{1/2}$	h	2.73	1.33	1.39	1.19
$AUC_{0\text{-}8\ h}$	h*μg/mL or h*μg/g	189.51	2.91	8.09	8.68
$AUC_{0\text{-}\infty}$	h*μg/mL or h*μg/g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

Emavusertib: preclinical anti-tumor activity in CNS

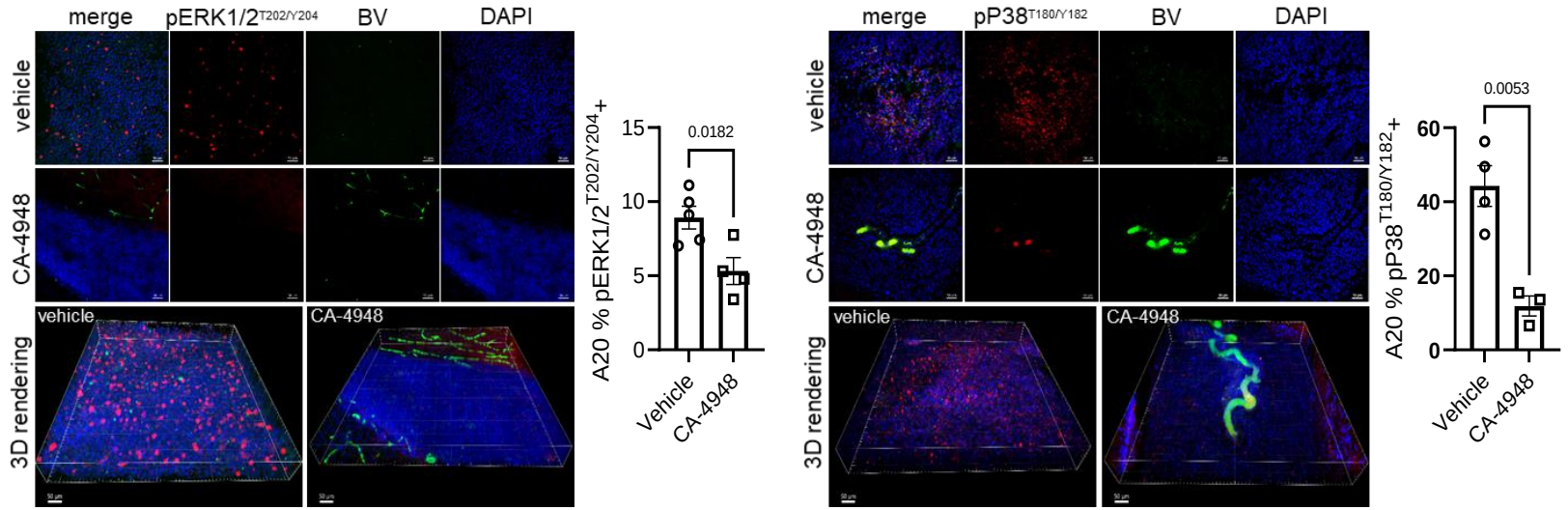
Improved survival in preclinical PCNSL



CA-4948 reduces *in vivo* tumor proliferation



CA-4948 inhibits tumor MAPK signaling



Thank you

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