Development of IRAK4 Kinase Inhibitor CA-4948 for NHL

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Disclosures

Robert Booher, Ph.D.
Receives direct remuneration from Curis

Dena Grayson, M.D., Ph.D.
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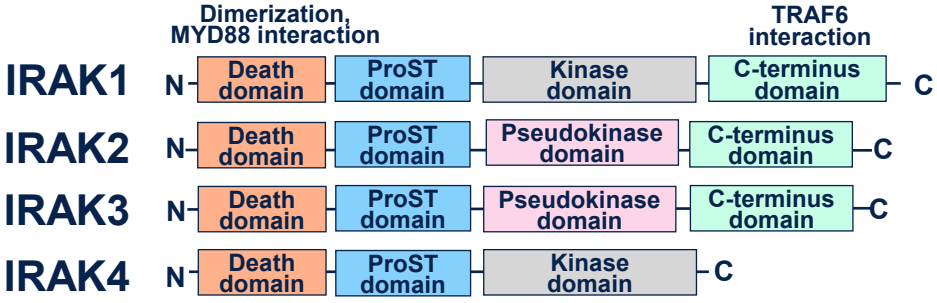
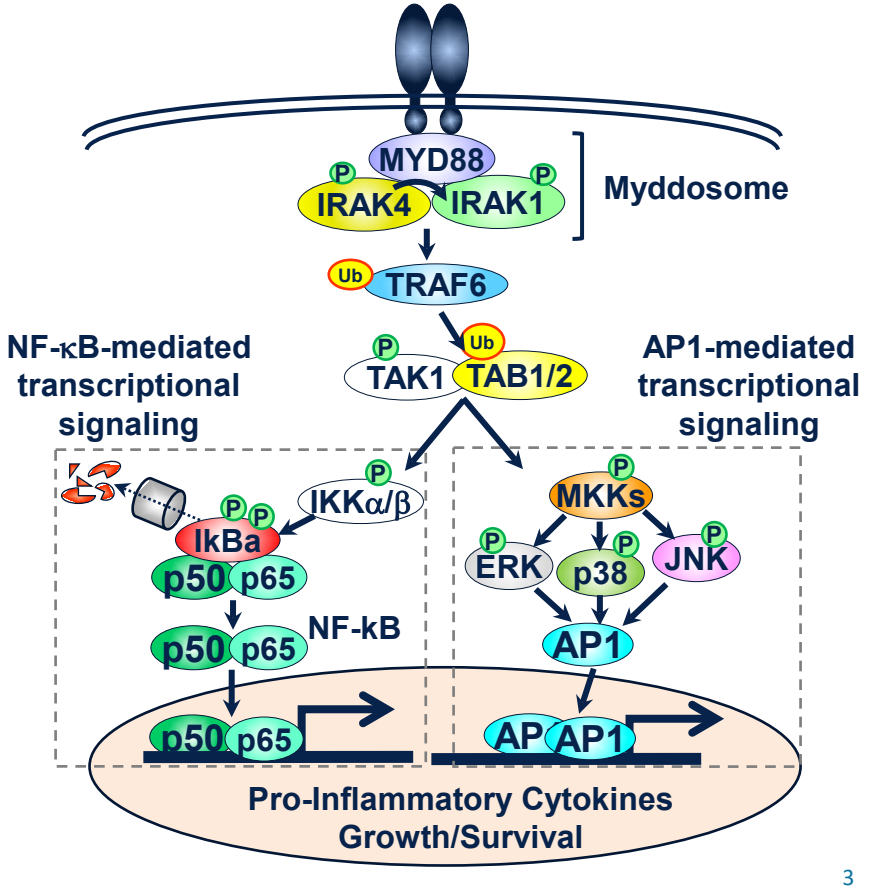
Interleukin-1 Receptor-Associated Kinase-4 (IRAK4)

IRAK Kinase Family

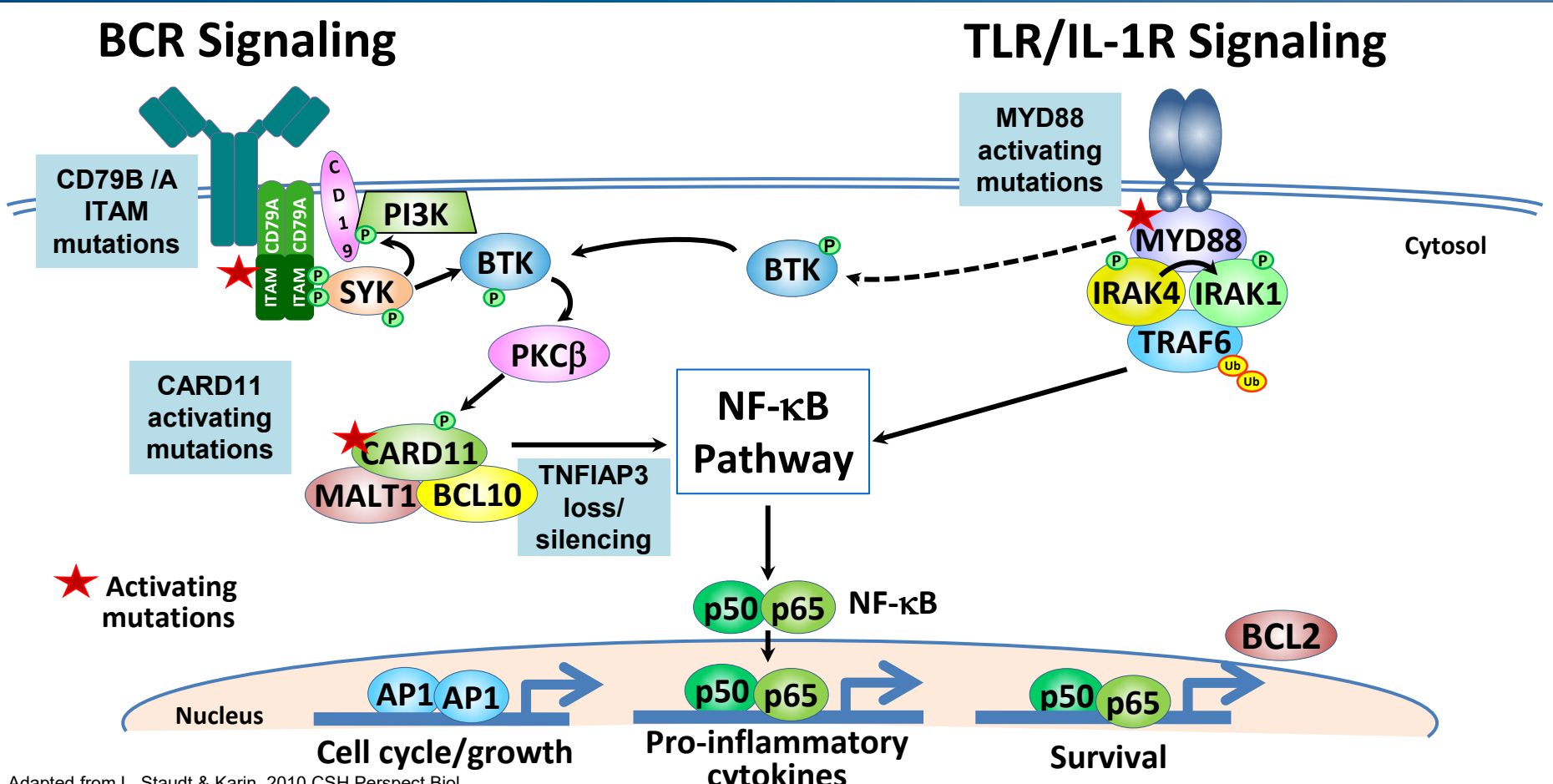


- IRAK4 is a serine/threonine kinase that is a key component in the signal transduction pathways mediated by Toll-like receptors (TLRs) and interleukin-1 receptor (IL-1R)
- Ligand-bound TLR/IL1R recruits the MYD88 adaptor protein, followed by IRAK4 and IRAK1, forming the Myddosome with activated IRAK4, leading to phosphorylation and activation of IRAK1

TLR and IL-1R Signaling



Activating Mutations in TLR/IL-1R and BCR Signaling Pathways Resulting in NF-kB Induction



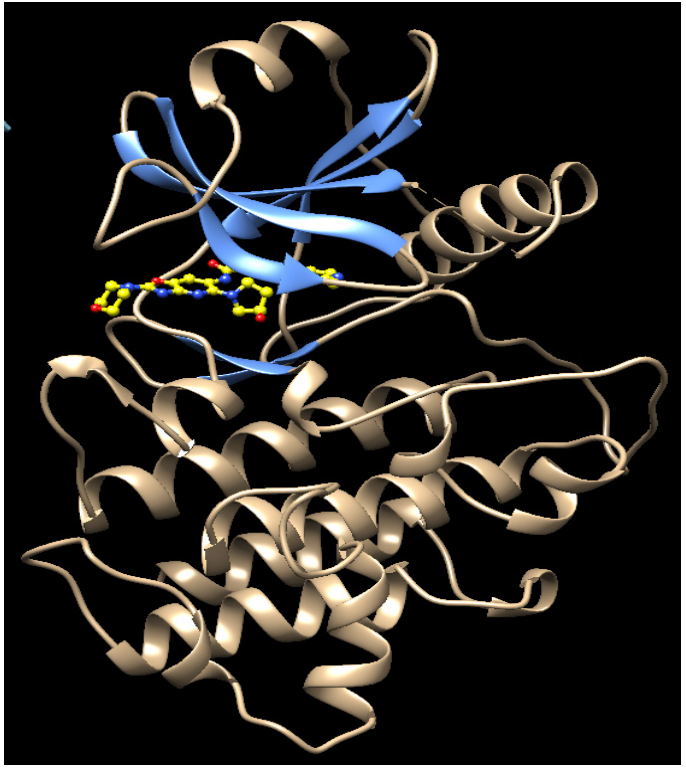
Adapted from L. Staudt & Karin, 2010 CSH Perspect Biol.
Mutation frequencies from Ngo et al. 2011 Nature 470:115

CA-4948, A Selective Oral Inhibitor of IRAK4 for the Treatment of NHL

CA-4948:

- Selective, small molecule inhibitor of IRAK4
- ATP-competitive, type 1 inhibitor, reversible
- Excellent drug-like properties:
  - Orally bioavailable (>100% dog/mouse)
  - Moderate plasma binding (77% human)
  - Stable in plasma, liver microsomes, hepatocytes
  - No inhibition of 7 major CYP450s
  - No significant metabolism *in vitro*
  - Humans: rapid absorption/clearance, $T_{1/2}$ 6 hr, no accumulation with QD dosing

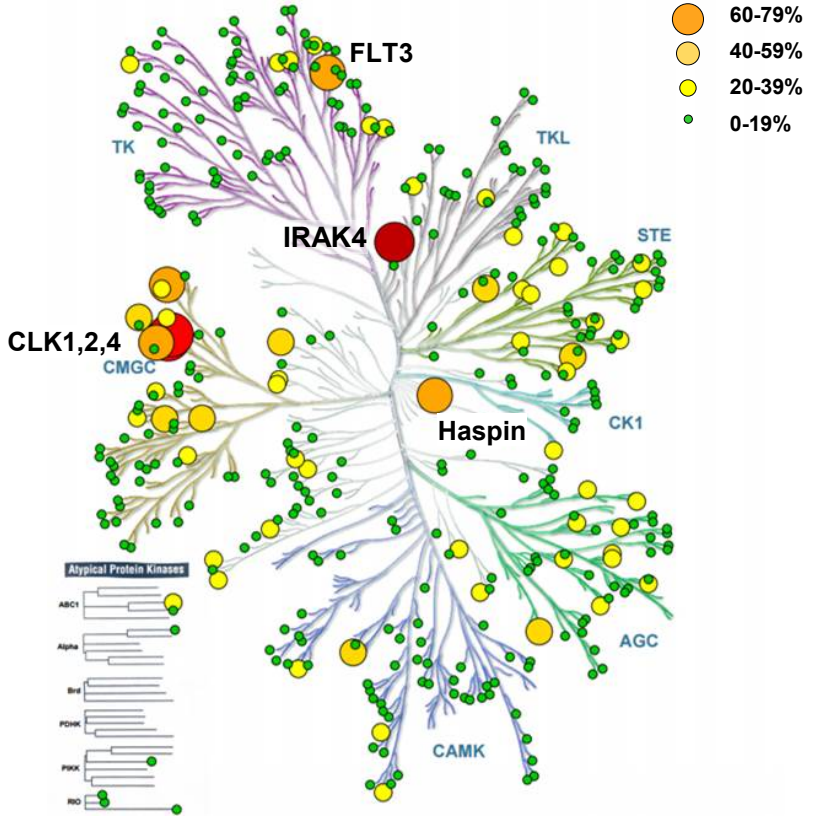
IRAK4/CA-4948 Co-crystal Structure



2.4Å resolution

CA-4948 Kinase Selectivity Profile

Active-site binding
(DiscoverX, 378 kinases)
% Inhibition at 0.1 μM



Kinome illustration reproduced courtesy of Cell Signaling Technology.

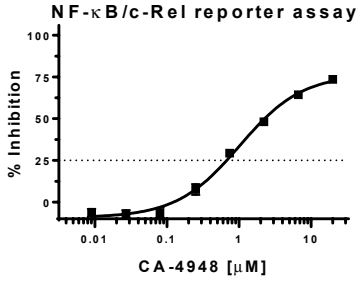
CA-4948 Binding Affinity Activity

	DiscoverX
Kinase	K_d (nM)
IRAK4	23
IRAK1	12,000
IRAK2	>20,000
IRAK3	8,500

Other top hits:

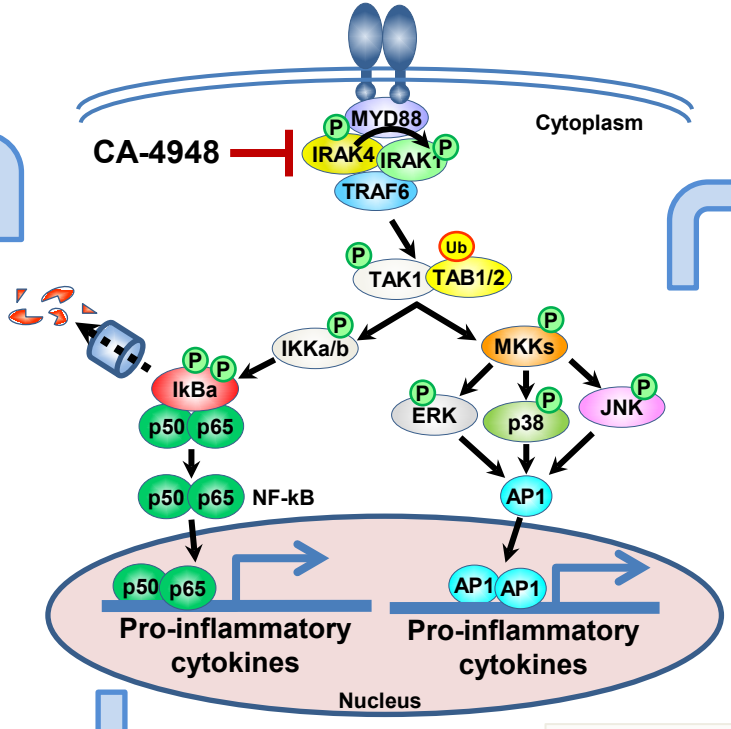
CLK1	10
CLK4	14
CLK2	20
FLT3	31
DYRK1A	25
Haspin (GSG2)	32
TrkA	130

CA-4948 IRAK4 Kinase Inhibitor Blocks the TLR/ IL-1R Induced Canonical NF-kB Signaling Pathway

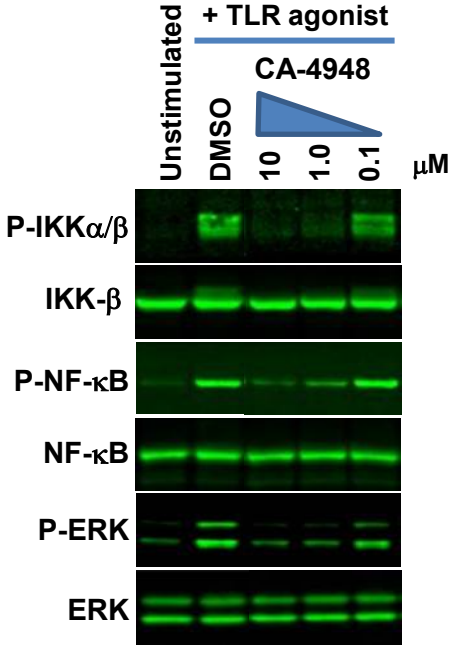


TLR and IL-1R-induced NF-κB reporter assays (IC_{50} = 502-520 nM, THP1)

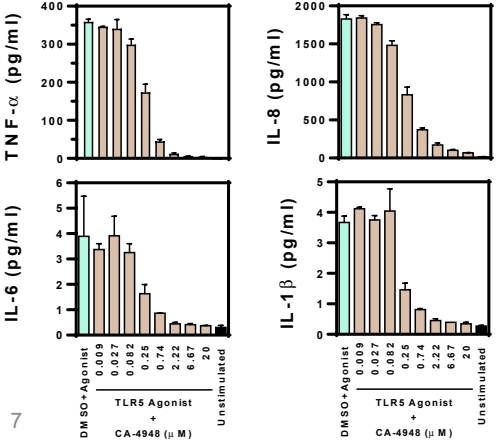
TLR/IL-1R Signaling



In vitro THP1 monocytic cell assays



Meso Scale Discovery: 4-Plex

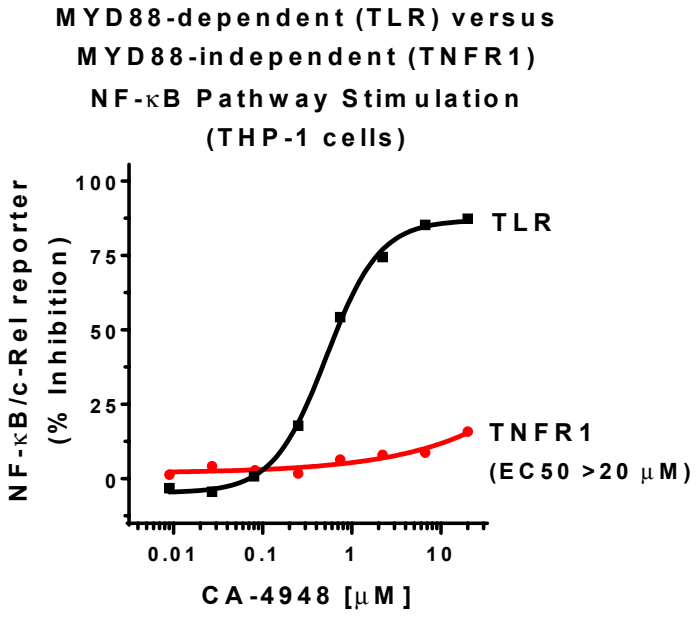


TLR-induced cytokine release assays (IC_{50} = 201-242 nM, THP1)

- **Good correlation between inhibition of phospho-signals, TLR/IL-1R signaling pathway, NF-kB reporter and secreted cytokine levels**

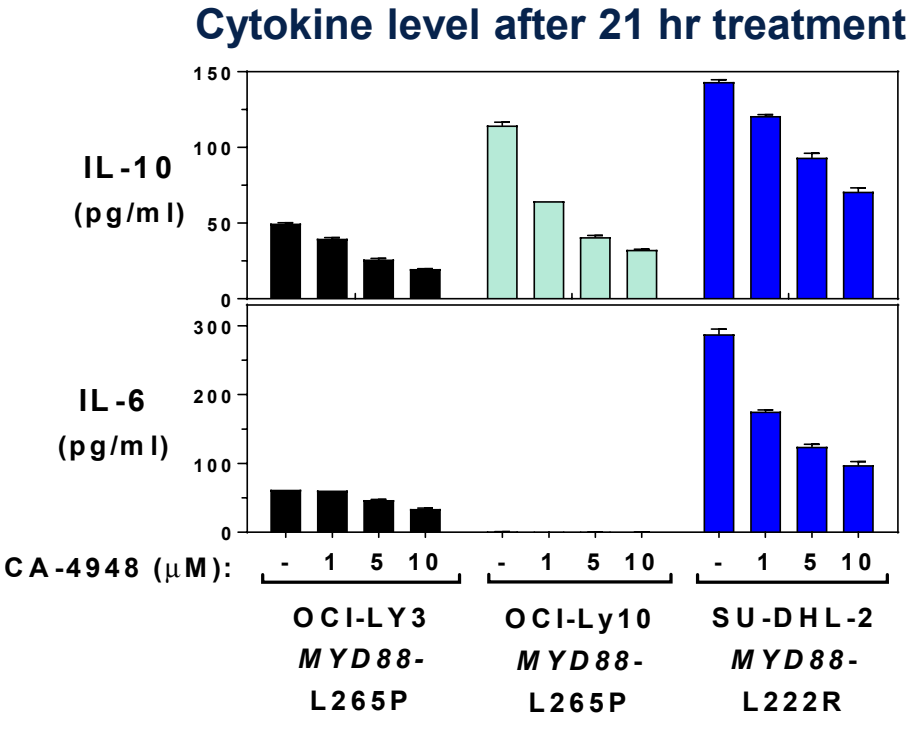
7

CA-4948 Selectively Inhibits NF-κB Signaling Pathways that are MYD88-Dependent



CA-4948 exhibits minimal inhibition of MYD88-independent NF-kB signaling pathway

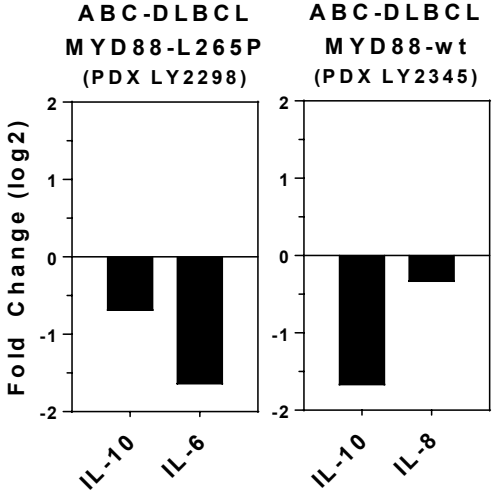
CA-4948 Inhibits Constitutive Cytokine Production in MYD88mut ABC-DLBCL Cell Lines



In vitro cytokine production

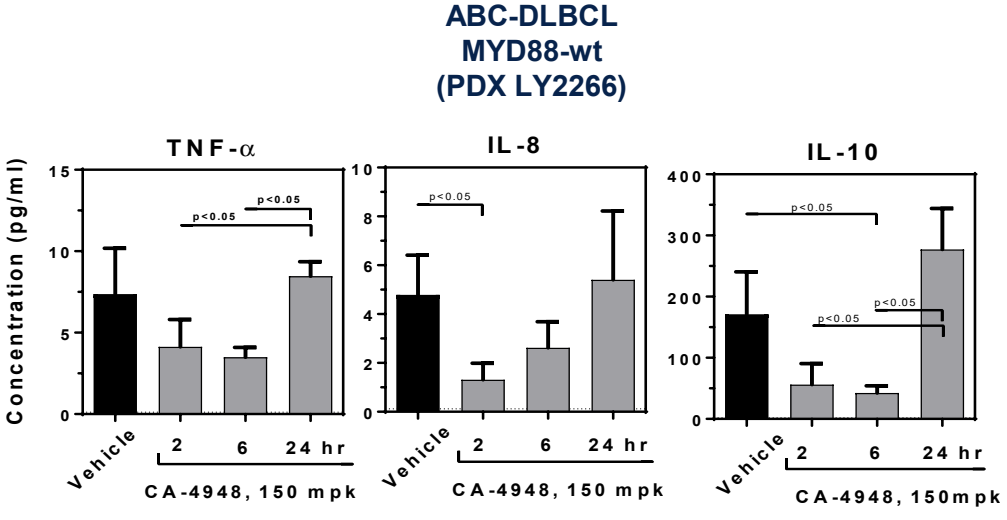
CA-4948 Inhibits Cytokine RNA and Protein Production in DLBCL PDX Tumors

CA-4948 Inhibition of Cytokine RNA Expression in DLBCL PDX Tumors



- 150 mg/kg CA-4948, QDx4
- Tumors were harvested 6 hr post final dose
- RNA-Seq analysis (n=3)
- Fold change is relative to vehicle
- $p < 0.05$ after Benjamini-Hochberg correction

CA-4948 Inhibition of Tumor-Derived Cytokines in Plasma From DLBCL PDX-Tumor Bearing Mouse

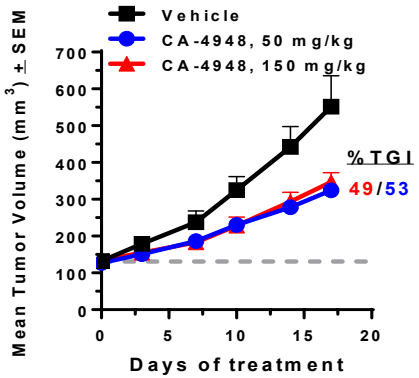


- 150 mg/kg CA-4948, QDx1
- Plasma collected 2, 6, and 24 hr post dose (n=3)

CA-4948 Shows Enhanced Efficacy in ABC vs. GCB DLBCL Tumors

ABC DLBCL

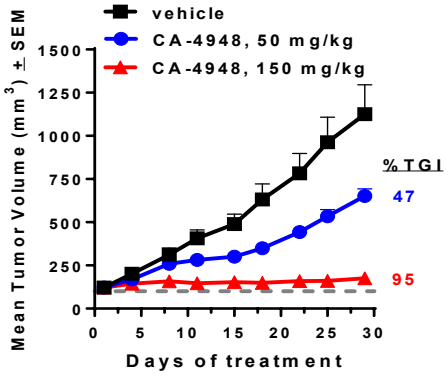
OCI-LY3
(*MYD88*-L265P)



CA-4948	%TGI	n
50 mg/kg	53*	8/8
150 mg/kg	49*	7/8

*p<0.05

OCI-Ly10
(*MYD88*-L265P)

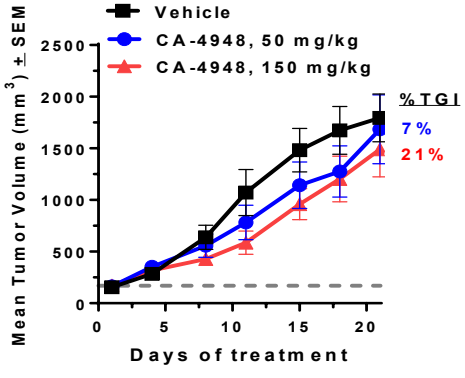


CA-4948	%TGI	n
50 mg/kg	47*	9/9
150 mg/kg	95**	9/9

*p <0.02
**p <0.0001

GCB DLBCL

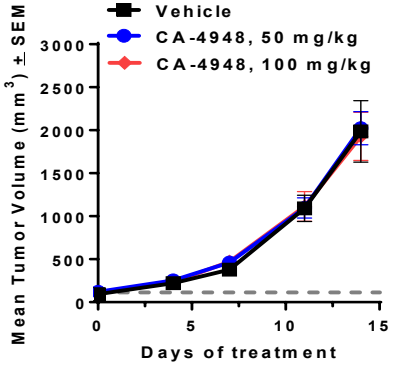
SU-DHL-4



CA-4948	%TGI	n
50 mg/kg	7*	7/8
150 mg/kg	20*	8/8

*p = ns

OCI-Ly19



CA-4948	%TGI	n
50 mg/kg	0	8/8
100 mg/kg	0	7/7

Once-daily, oral CA-4948 dosing

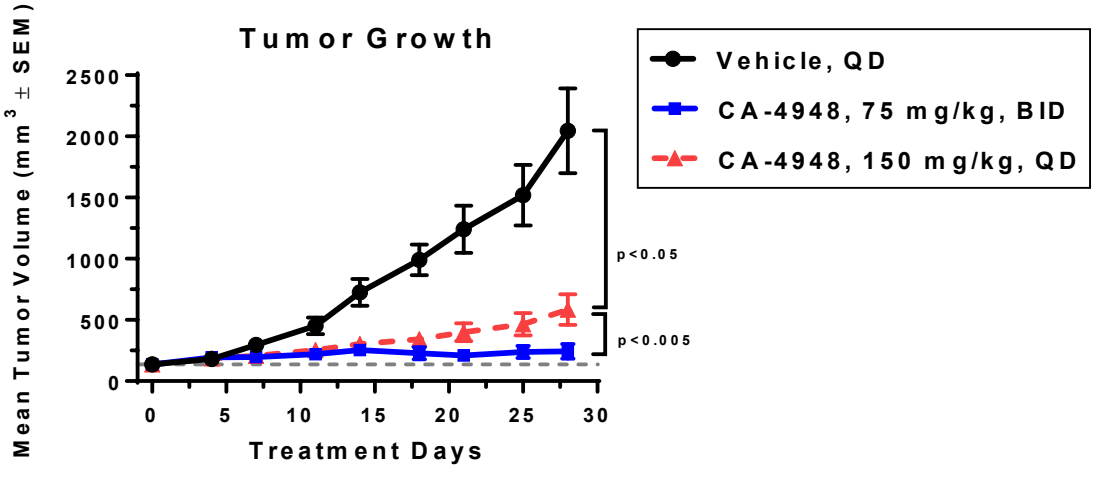
CA-4948 Efficacy in 6 DLBCL PDX Models

		Mutations/Expression			CA-4948 Efficacy
DLBCL PDX Model	Cell of Origin	MYD88 Mutation	B-Cell Receptor Mutation	BCL6 Expression (IHC)	100 mg/kg, QD %TGI
LY2345	ABC	WT	CARD11, TNFAIP3	2%	71**
LY2264	ABC	L265P	CD79B	60%	70**
LY2298	ABC	L265P	CD79B	20%	54*
LY2214	GCB	WT	WT	95%	38
LY2266	ABC	WT	WT	0%	30*
LY0257	ABC	L265P	WT	95%	0

*$p<0.05$
**$p\leq0.001$

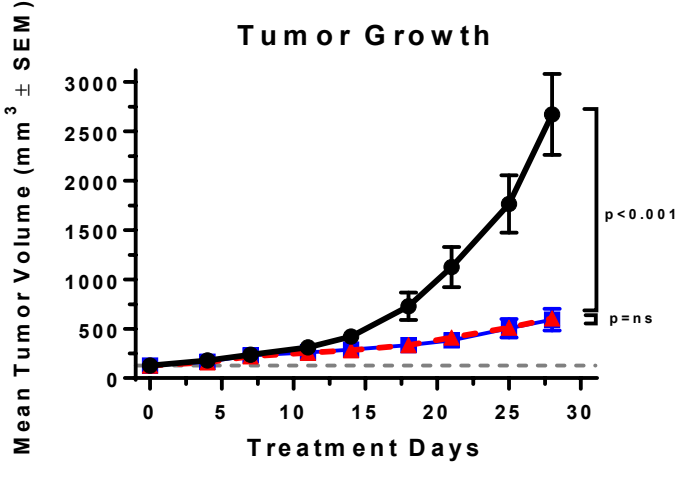
CA-4948 BID Dosing Exhibits Improved/ Equivalent Efficacy Compared to QD Dosing

LY2345 PDX: ABC DLBCL
***MYD88*-wt, *TNFIAP3*-mt**



Drug	Dosage (mg/kg)	Schedule	%TGI
CA-4948	75	BID	94
CA-4948	150	QD	77

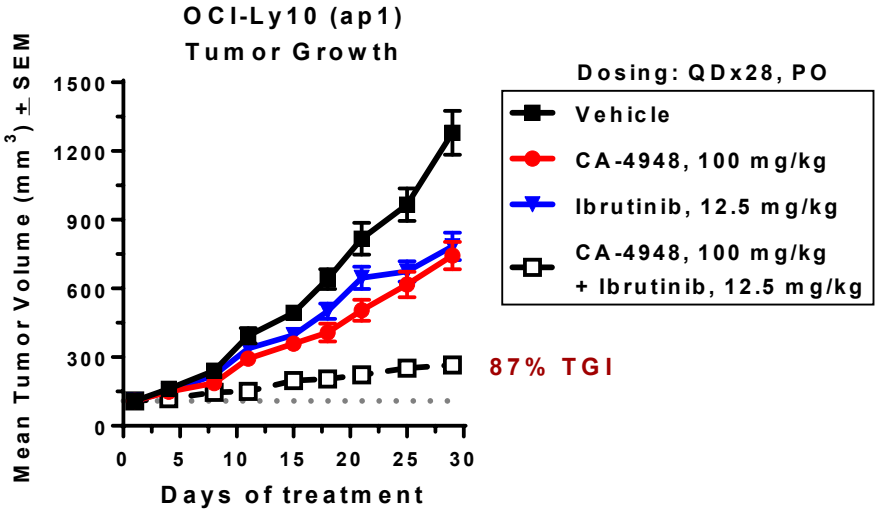
LY2298 PDX: ABC DLBCL
***MYD88*-L265P, CD79B-mut**



Drug	Dosage (mg/kg)	Schedule	%TGI
CA-4948	75	BID	82
CA-4948	150	QD	81

CA-4948 Exhibits Combination Effects with Ibrutinib or Venetoclax in an ABC-DLBCL Xenograft Model

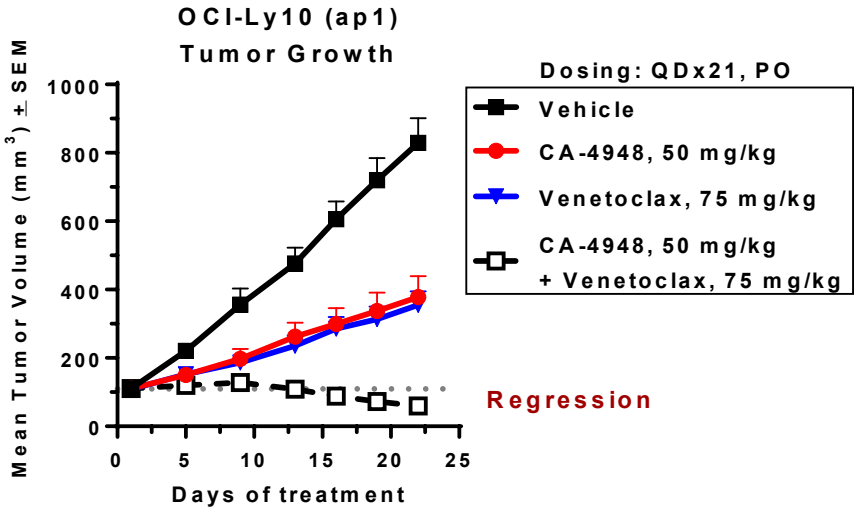
CA-4948 + Ibrutinib



Drug	Dosage (mg/kg)	%TGI (n=10)
CA-4948	100	46*
Ibrutinib	12.5	42*
CA-4948 + Ibrutinib	100 + 12.5	87*

*p<0.0005

CA-4948 + Venetoclax



Drug	Dosage (mg/kg)	%TGI (n=9-10)
CA-4948	50	63*
Venetoclax	75	71*
CA-4948 + Venetoclax	50 + 75	regress*

*p<0.0005

OCI-Ly10 (ap-1): ABC-DLBCL, MYD88-L265P, CD79A-mut, cells were previously animal-tumor passaged

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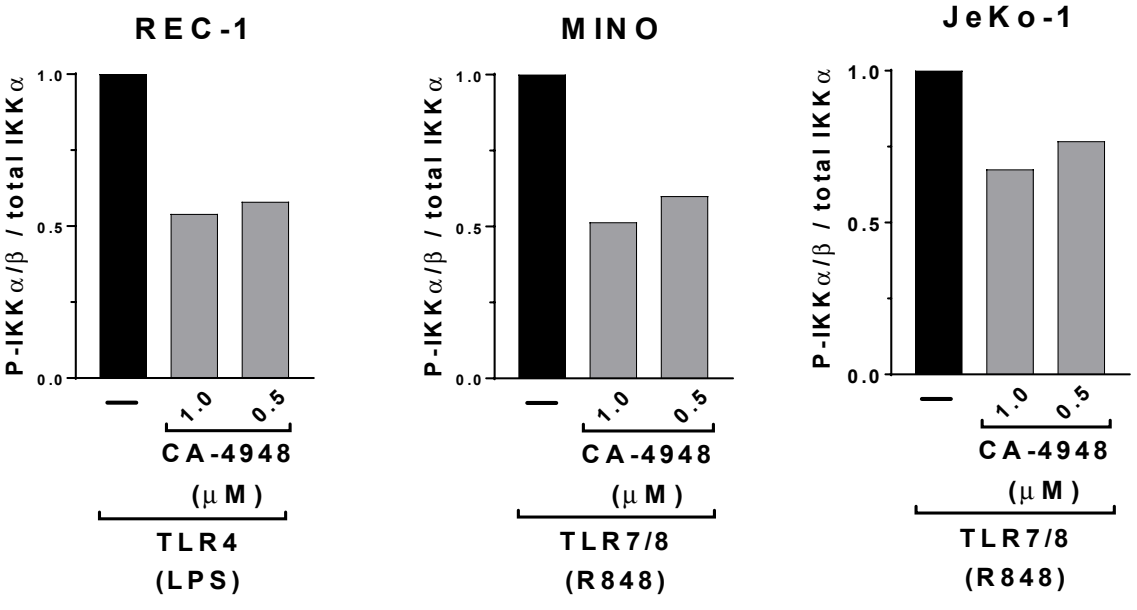
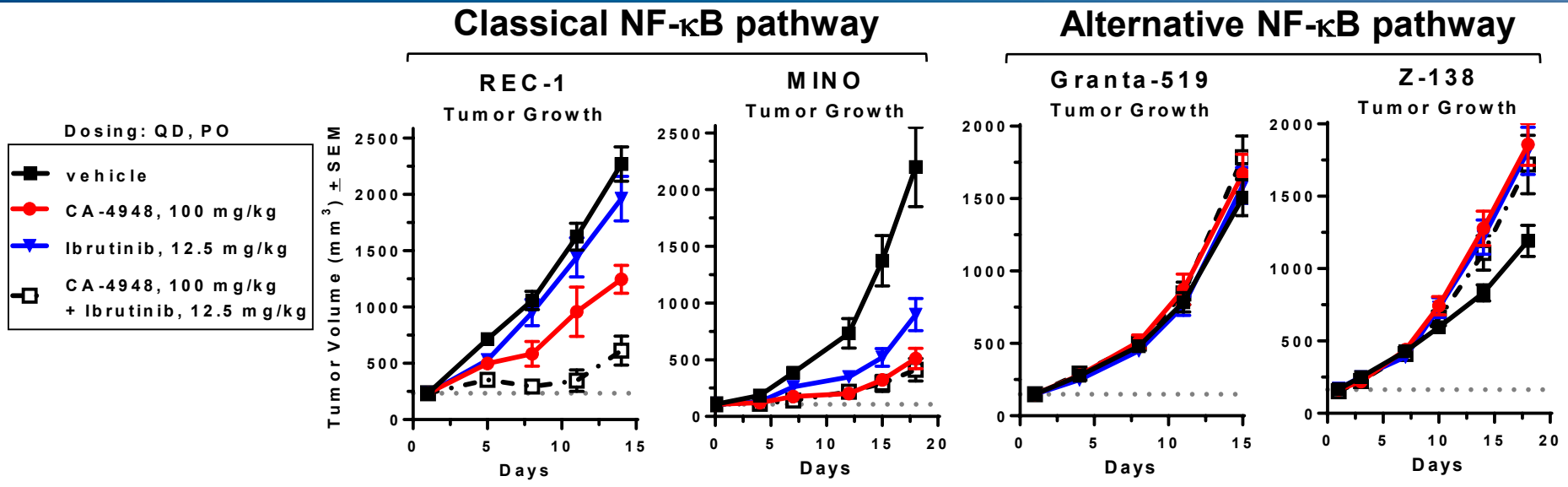
CA-4948 *In Vitro* Effect on TLR Signaling Pathway in Mantle Cell Lymphoma Lines

Classical NF-κB pathway



CA-4948 downregulates TLR-stimulated signaling pathway components (P-IKKα/β) in MCL cell lines with classical NF-κB signaling

CA-4948 ± Ibrutinib Exhibits Efficacy in MCL Xenograft Models with Canonical NF-κB Signaling



Drug	Dose (mg/kg)	%TGI* (n=9-10)	%TGI* (n=11-12)	%TGI (n=10)	%TGI (n=10)
CA-4948	100	50*	81	0	0
Ibrutinib	12.5	15**	62	0	0
CA-4948 + Ibrutinib	100 + 12.5	81*	85	0	0

*p<0001
**p=ns

*p<002

CA-4948 exhibits *in vivo* activity in MCL cell lines with chronic activated NF-κB pathway

CA-4948-101 Phase 1 First-in-Human Trial *(NCT03328078)*

IRAK4 Pathway Alterations in Hematologic Malignancies

Targeting IRAK4 in NHL: Rationale

Prevalence of Oncogenic *MYD88*-L265P Mutations

Diffuse Large B-cell Lymphoma (ABC-DLBCL)	29%
Waldenstrom's Macroglobulinemia (WM)	95-97%
Lymphoplasmacytic Lymphoma (LPL)	79-96%
Orbital and ocular adnexal DLBCL	71%
Immune-privileged DLBCL (IP-DLBCL)	50-80%
Splenic Marginal Zone Lymphoma (SMZL)	6-10%
Mucosa-Associated Lymphoid Tissue (MALT)	9%
Chronic Lymphocytic Leukemia (CLL)	2.9%

Targeting IRAK4 in AML/MDS: Rationale

Prevalence of TLR/IL-R1/MYD88 Alterations

- TLR or IL1R alterations
  - TLR1, 2 and 4 overexpression in MDS and AML
  - IL1R alterations in AML
  - 67% of primary AML pt samples exhibited profound IL-1 induced myeloid progenitor cell expansion
  - 40% of MDS pts had increased MYD88 expression in bone marrow CD34+ cells
  - 11% of MDS pts harbored the TLR2-F217S mutation, which induces enhanced NF-kB signaling
- MYD88 alterations
  - Overexpression in AML
- IRAK4 alterations
  - Overexpression in MDS

CA-4948-101 Phase 1 First-in-Human Trial
(NCT03328078)

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Phase 1a: Single Agent Dose Escalation

- 3 + 3 Design
- Dose escalation guided by safety
- Starting dose = 50 mg QD
- N = ~ 30
- R/R NHL, including WM

MTD or RP2D

Phase 1b: Dose Expansion

- N = 45 ~ 50
- WM
- ABC DLBCL MYD88mut
- ABC DLBCL MYD88wt

Objectives

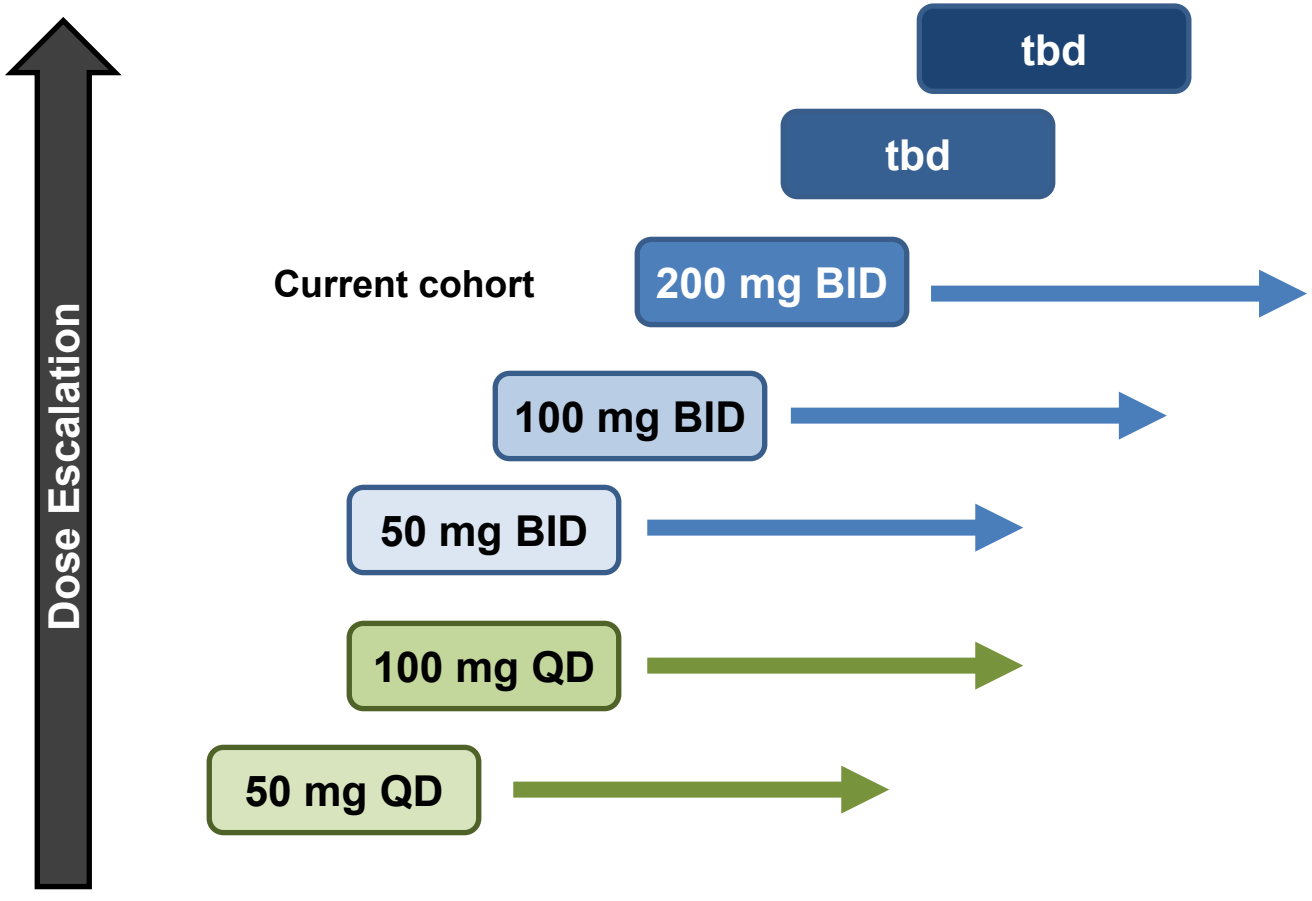
- Primary: MTD or RP2D, Safety
- Secondary: pharmacodynamics, anti-cancer activity
- Exploratory: pharmacodynamics and correlative research

Treatment

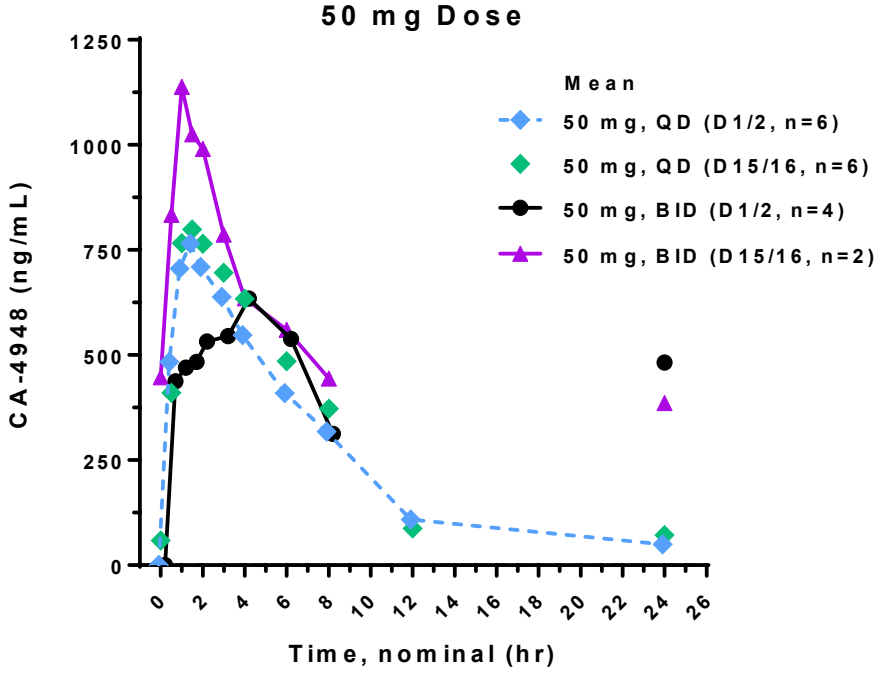
- Oral, once or twice daily, dosing in continuous 21-day cycles until unacceptable toxicity or progression

Participating country: US

CA-4948-101 Study Design and Cohort Accrual



CA-4948 Plasma Concentration (ng/mL) vs. Time Profile (Cycle 1)



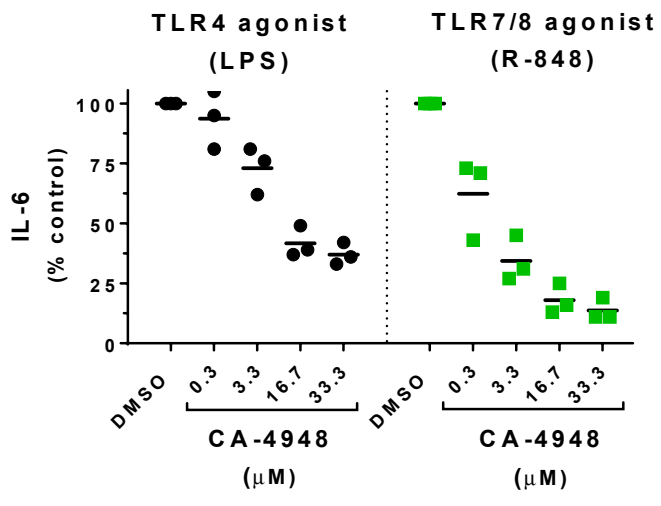
At current sample analysis, CA-4948 exhibits:

- **Rapid absorption and clearance ($t_{1/2}$ ~ 6 hr)**
- **Dose proportional increase in exposure**
- **Increased trough levels with BID dosing**

CA-4948 PK/PD Relationship Determined Using an *Ex-Vivo* Whole Blood Assay (Human)

In whole blood from healthy volunteers, cytokine production dropped when incubated with CA-4948

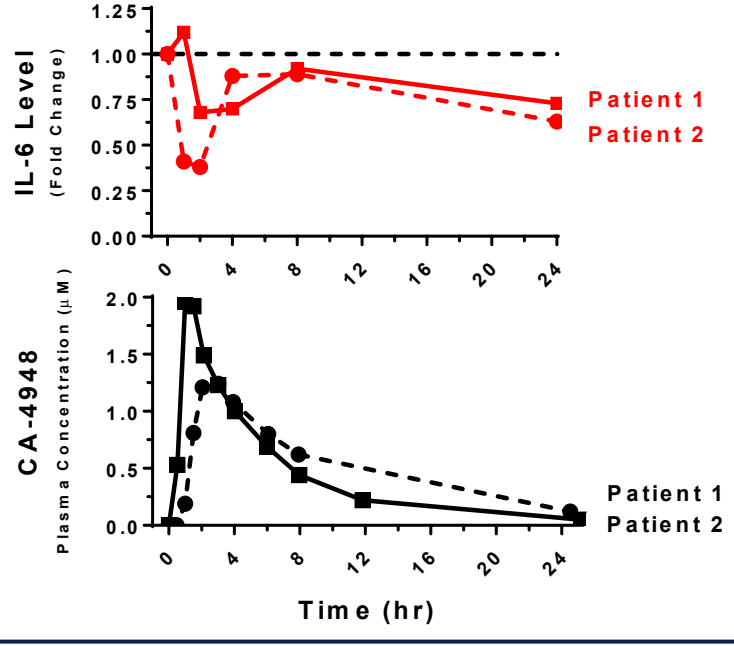
IL-6 Production in TLR-stimulated Whole Blood
(healthy volunteers)



Whole Blood Assay Development

In whole blood from patients treated with CA-4948 cytokine production dropped, mirroring drug exposure

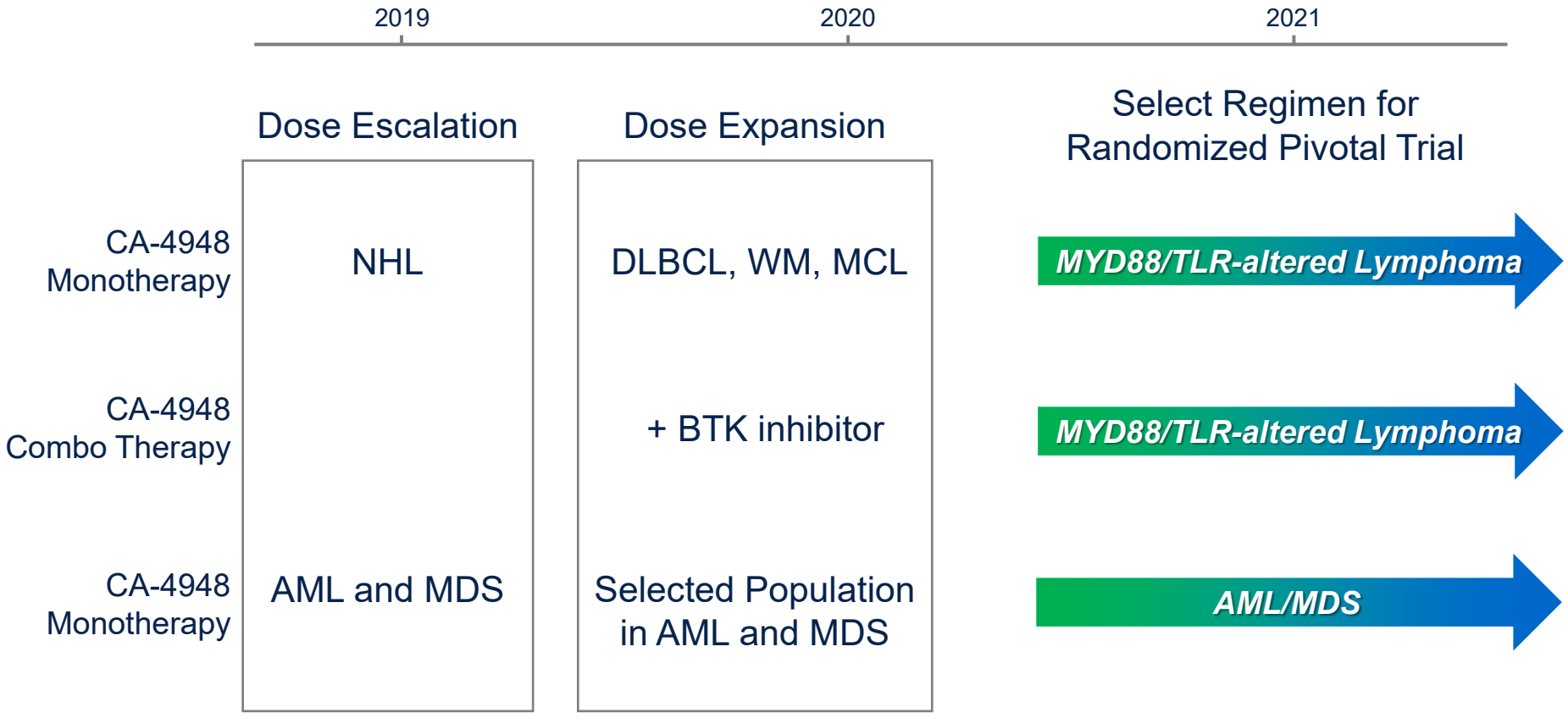
IL-6 Production in TLR-7/8 stimulated Whole Blood
(CA-4948, 50 mg, Ph1 patients)



CA-4948 PK/PD (whole-blood TLR inhibitory assays) supports BID dosing

CA-4948 Development Plan

Expansion in patients with MYD88 or TLR/IL-1R pathway altered lymphomas



Conclusions

- CA-4948 is a potent, oral inhibitor of IRAK4 Ser/Thr kinase with >500-fold selectivity vs. IRAK1
- CA-4948 inhibited constitutive or TLR-induced signaling in ABC-DLBCL and MCL cell lines and xenograft tumor models
- CA-4948 exhibited *in vivo* anti-tumor activity in NHL models with intact canonical NF-κB signaling, which was enhanced in combination with ibrutinib or venetoclax treatment
- Samples from patients treated with CA-4948 showed decreased TLR pathway activity when stimulated *ex vivo*
- Phase 1 PK analysis showed CA-4948 dose-dependent C_{max} and AUC increases, and higher trough levels with BID dosing
- Phase 1 has initiated the fifth dose cohort with 200 mg BID
- These results underscore the therapeutic potential of targeting IRAK4 kinase with CA-4948 alone and in combination with targeted agents for the treatment of NHL with MYD88 or TLR/IL-1R pathway alterations

Acknowledgments

- Participating patients and their families
- Investigators, research coordinators, and site personnel
  - Iris Isufi, Yale School of Medicine, New Haven, CT
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  - Matthew A. Lunning, University of Nebraska Medical Center, Omaha, NE
  - Grzegorz Nowakowski, Mayo Clinic, Rochester, MN
  - Krish Patel, Swedish Cancer Institute, Seattle, WA
  - Allison Rosenthal, Mayo Clinic, Scottsdale, AZ
  - Han Tun, Mayo Clinic, Jacksonville, FL
  - Anas Younes, Memorial Sloan Kettering Cancer Center, New York, NY
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