Preclinical Activity of IRAK4 Kinase Inhibitor CA-4948 Alone or in Combination with Targeted Therapies in Non-Hodgkin Lymphoma

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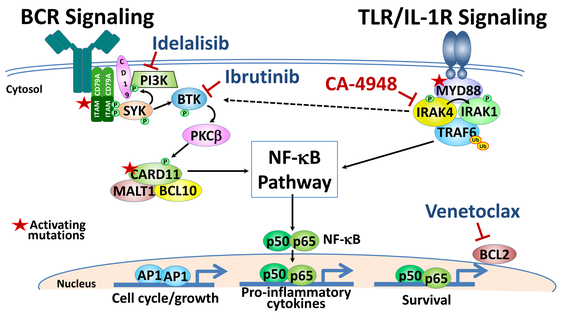
Abstract

The *MYD88*-L265P mutation is one of the most frequent (>95%) genetic abnormalities in WM, leading to constitutive NF-κB activation through IRAK4 and BTK kinases. While BTK inhibitor ibrutinib is highly active in *MYD88* mutant WM patients, the clinical effectiveness of IRAK4 inhibition has not been established. We are developing an IRAK4 kinase inhibitor, CA-4948, as a therapeutic agent for non-Hodgkin lymphoma (NHL), including WM, with dysregulated MYD88/IRAK4 signaling. Here we report nonclinical studies supporting the rationale for evaluating CA-4948 in a Phase 1 trial for R/R non-Hodgkin lymphoma (clinicaltrials.gov NCT03328078).

CA-4948 is a small molecule inhibitor of IRAK4 kinase that modulates the TLR and IL-1R signaling cascades. In preclinical studies, CA-4948 exhibits favorable DMPK properties, oral bioavailability, and is well tolerated at efficacious doses in mice. Importantly, CA-4948 demonstrates pharmacodynamic and antitumor activity in *in vitro* and *in vivo* models with *MYD88* alterations, including dose-dependent efficacy in ABC-subtype diffuse large B-cell lymphoma (DLBCL) *MYD88*-L265P xenograft tumor models OCI-LY3 and OCI-Ly10. *In vivo* drug combination studies of CA-4948 with ibrutinib or venetoclax in the OCI-Ly10 model further demonstrated additive/synergistic anti-tumor activity with these targeted agents. CA-4948 was also tested in a panel of well characterized, patient-derived DLBCL tumor xenograft (PDX) mouse models. CA-4948 exhibited the greatest efficacy in four of the five ABC-DLBCL PDX models tested as compared to the single GBC-DLBCL PDX model. Additionally, CA-4948 was active in ABC-DLBCL PDX tumor models containing activating mutations in both TLR/IL-1R and BCR signaling pathways (MYD88 and CD79B double mutants).

To further guide CA-4948's clinical development in NHL, we have also explored a twice-daily dosing schedule in DLBCL xenograft models and investigated the use of an *ex-vivo* whole-blood TLR-stimulation assay as a surrogate PD response biomarker, the latter of which is currently being implemented in the CA-4948 Phase 1 trial for patients with advanced NHL. In summary, these results underscore the therapeutic potential of IRAK4 kinase inhibition by CA-4948, as a single-agent or in combination with other targeted agents, for the treatment of NHL including WM and DLBCL.

CA-4948 Blocks the TLR/IL-1R Induced Canonical NF-κB Signaling Pathway



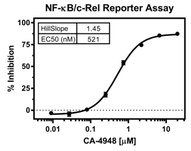
CA-4948:

- **Small molecule inhibitor**
- **ATP-competitive, reversible**
- **Oral bioavailable**

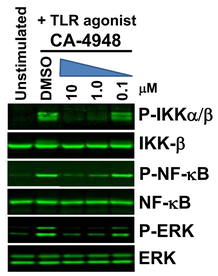
CA-4948 Binding Affinity

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

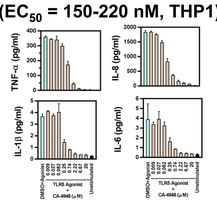
TLR-induced NF-κB reporter assays (EC_{50} = 520 nM, THP1)



In vitro THP1 assay



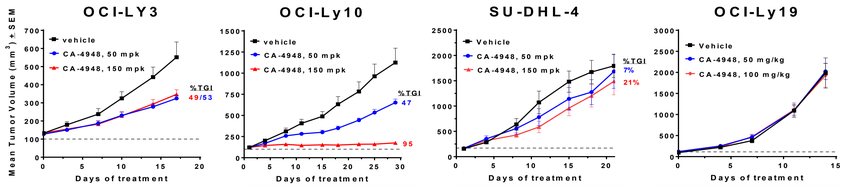
TLR-induced cytokine release (EC_{50} = 150-220 nM, THP1)



CA-4948 inhibition of NF-kB reporter, secreted cytokine levels, and phospho-signals in THP1 monocytic cells

CA-4948 Efficacy in DLBCL Cell Line Xenograft Models: Comparison in ABC vs GCB DLBCL

ABC DLBCL *MYD88*-L265P | **GCB DLBCL *MYD88*-wt**



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

*p<0.05

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

*p <0.02
**p <0.0001

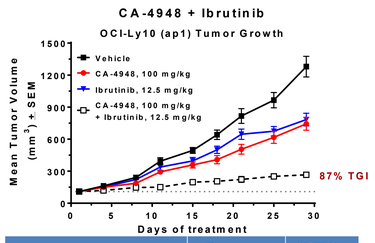
CA-4948	%TGI
50 mg/kg	7*
150 mg/kg	20*

*p = ns

CA-4948	%TGI
50 mg/kg	0
100 mg/kg	0

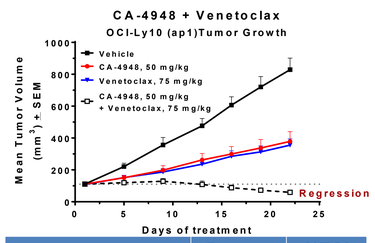
Once-daily CA-4948 dosing shows enhanced *in vivo* activity in MYD88-L265P vs MYD88-wt DLBCL tumors

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



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



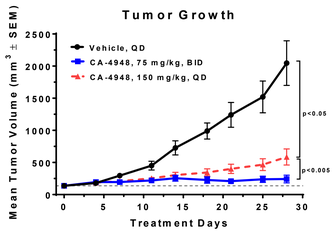
Drug	Dosage (mg/kg)	%TGI (n=9-10)
CA-4948	50	63*
Venetoclax	75	71*
CA-4948 + Venetoclax	50 + 75	regress*

*p<0.0005

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

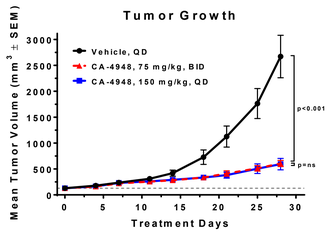
Efficacy of CA-4948 in Two DLBCL PDX Models: QD versus BID Dosing Schedule

LY2345 PDX: ABC DLBCL *MYD88*-wt, *TNFAIP3*-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

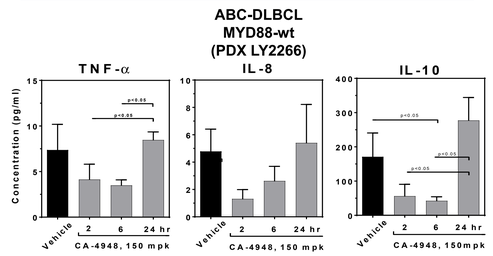


Drug	Dosage (mg/kg)	Schedule	%TGI
CA-4948	75	BID	82
CA-4948	150	QD	81

CA-4948 BID dosing exhibits improved/equivalent efficacy compared to QD dosing

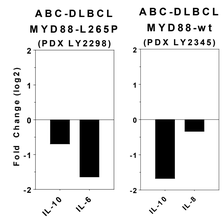
CA-4948 *In Vivo* Pharmacodynamic Effects (Mouse)

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)

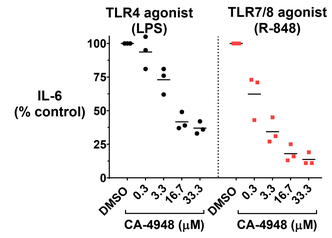
CA-4948 Inhibition of Cytokine RNA Expression in DLBCL PDX Tumors



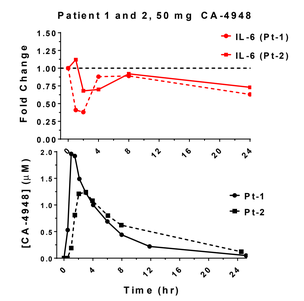
- 150 mg/kg CA-4948, QDx4
- Tumors were harvested 6 hr post final dose
- RNA-Seq analysis (n=3)
- Fold change is relative to vehicle
- p < 0.05 after Benjamini-Hochberg correction

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

IL-6 production in TLR-stimulated whole blood from healthy volunteers (n=3) (CA-4948 spike-in)



IL-6 production in TLR-stimulated whole blood from CA-4948 Ph1 trial patients (TLR7/8 agonist stimulation)



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

Summary

- CA-4948 is a potent, oral inhibitor of IRAK4 Ser/Thr kinase with >500-fold selectivity against IRAK1
- CA-4948 inhibited constitutive or TLR-induced signaling in DLBCL cell lines and xenograft tumors
- 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
- An *ex-vivo* TLR-stimulated whole blood assay was developed for *in vivo* or clinical PK/PD analysis
- 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

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