

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



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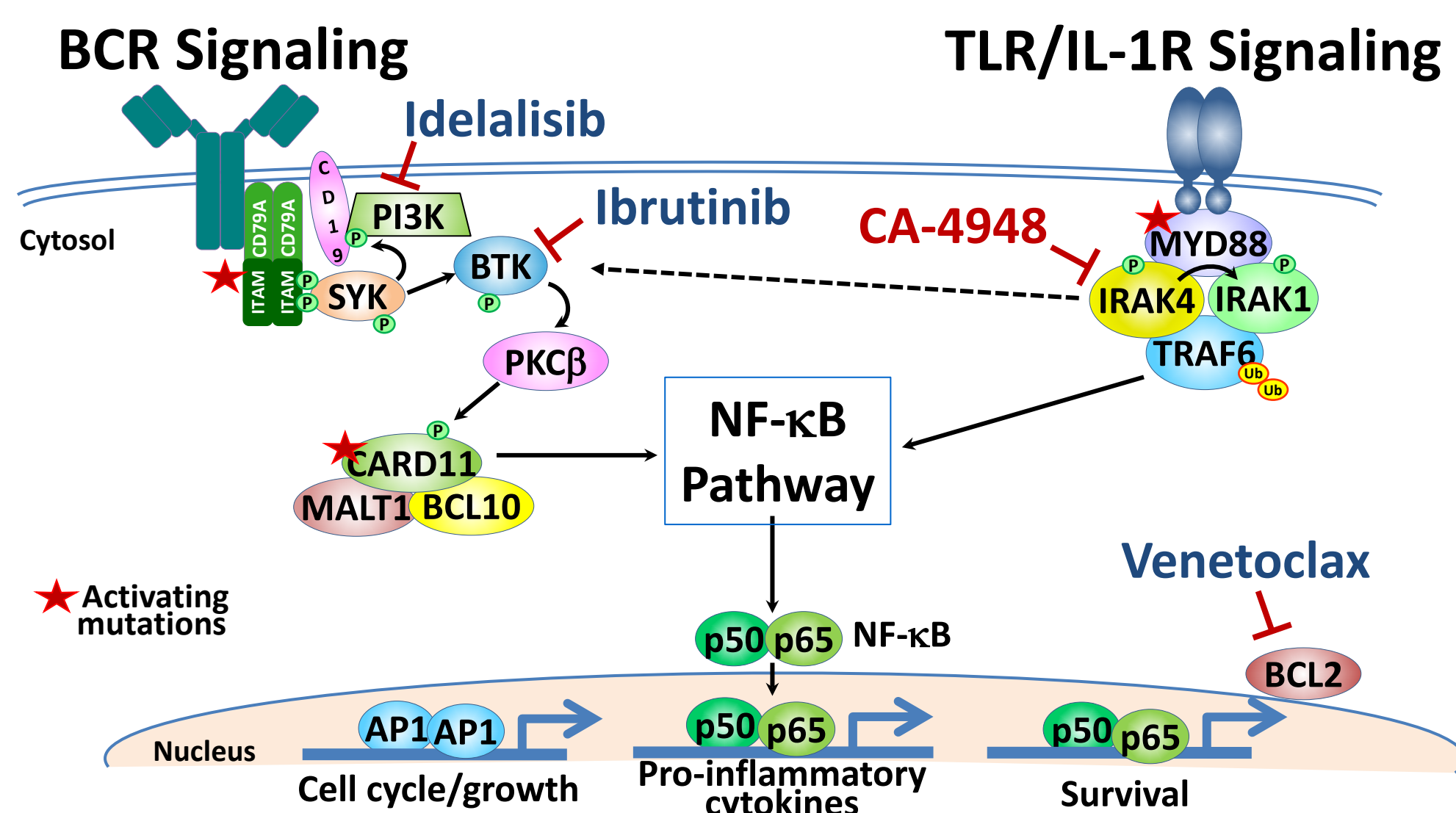
Abstract

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).

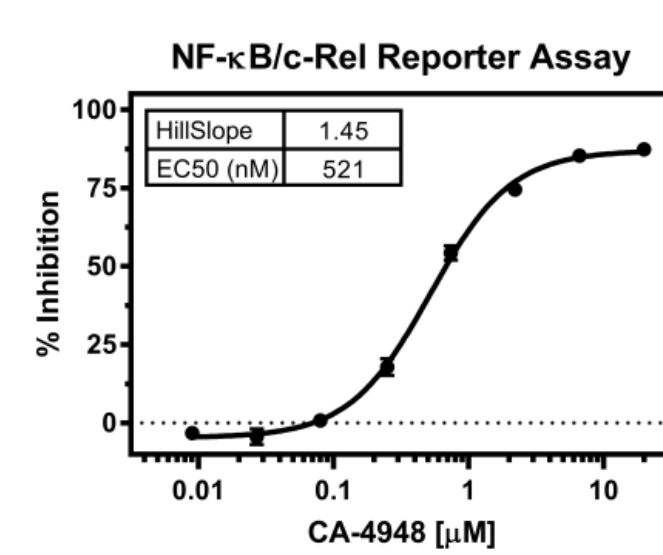
CA-4948 is a small molecule inhibitor of IRAK4 kinase that modulates the TLR and IL-1R signaling cascades. In preclinical studies, CA-4948 exhibits favorable DMPK properties, oral bioavailability, and is well tolerated at efficacious doses in mice. Importantly, CA-4948 demonstrates pharmacodynamic and 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.

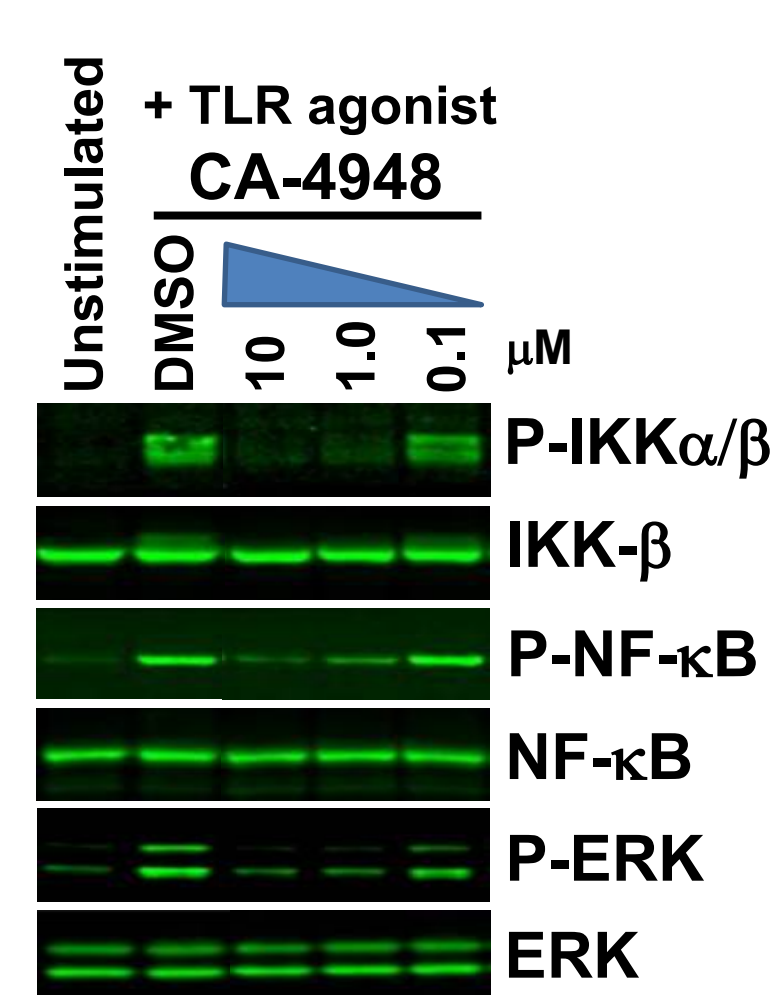
CA-4948 Blocks the TLR/IL-1R Induced Canonical NF-κB Signaling Pathway



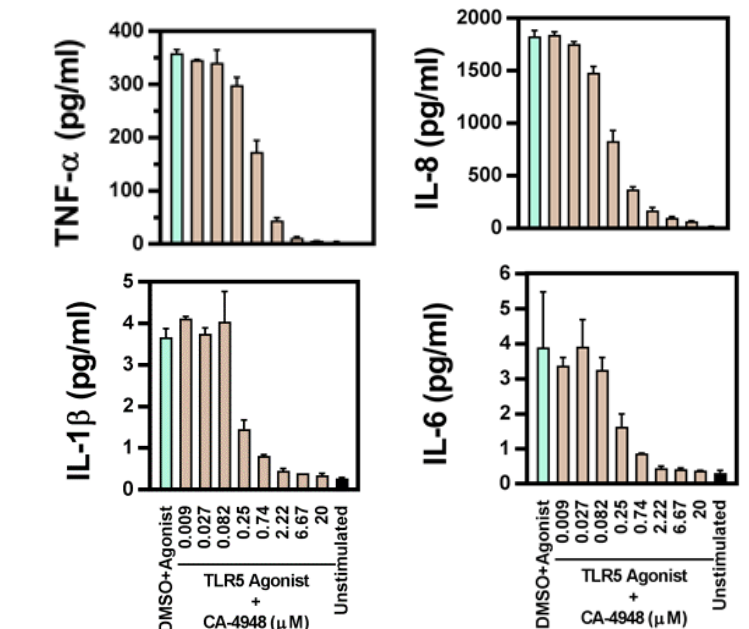
TLR-induced NF-κB reporter assays (EC₅₀ = 520 nM, THP1)



In vitro THP1 assay



TLR-induced cytokine release (EC₅₀ = 150-220 nM, THP1)



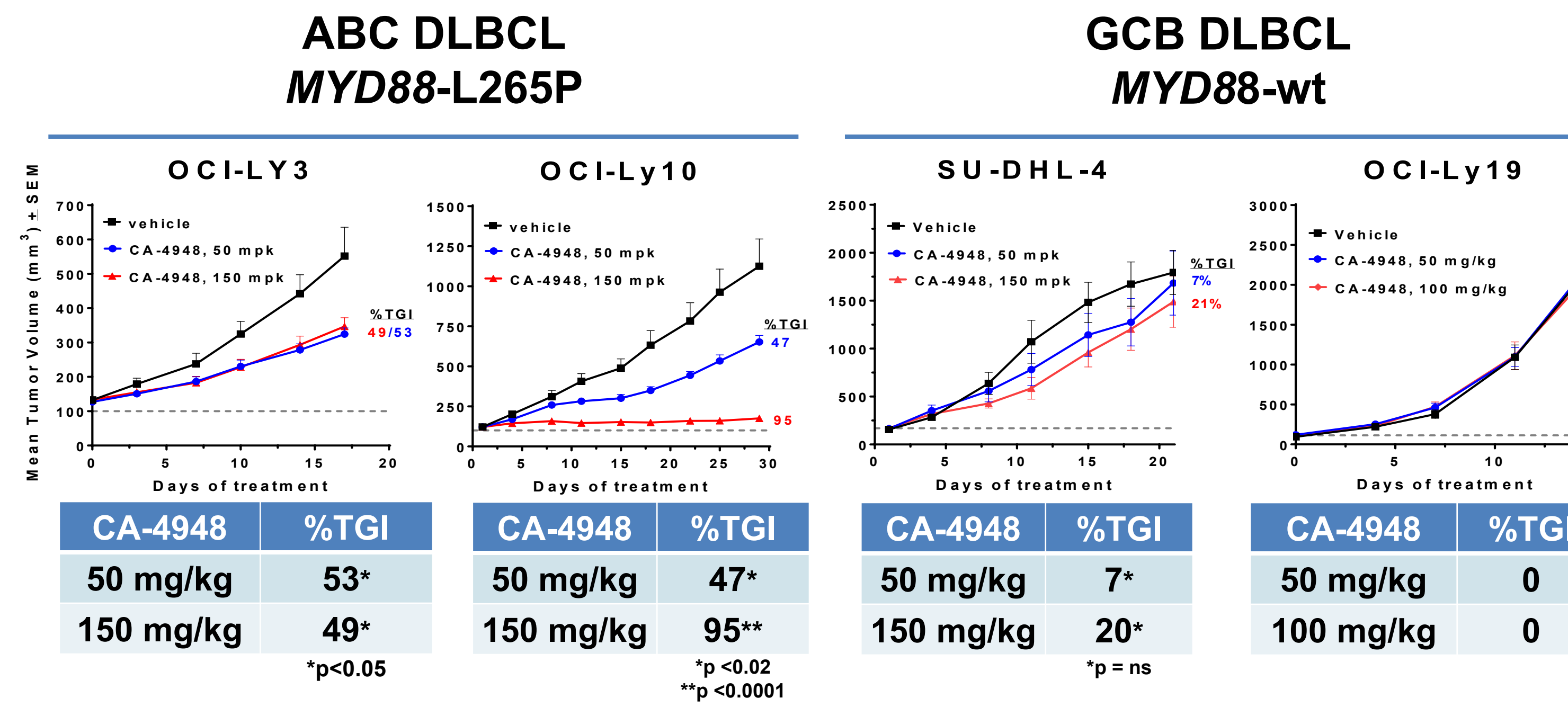
CA-4948 inhibition of NF-κB reporter, secreted cytokine levels, and phospho-signals in THP1 monocytic cells

- CA-4948:**
- Small molecule inhibitor
 - ATP-competitive, reversible
 - Oral bioavailable

CA-4948 Binding Affinity

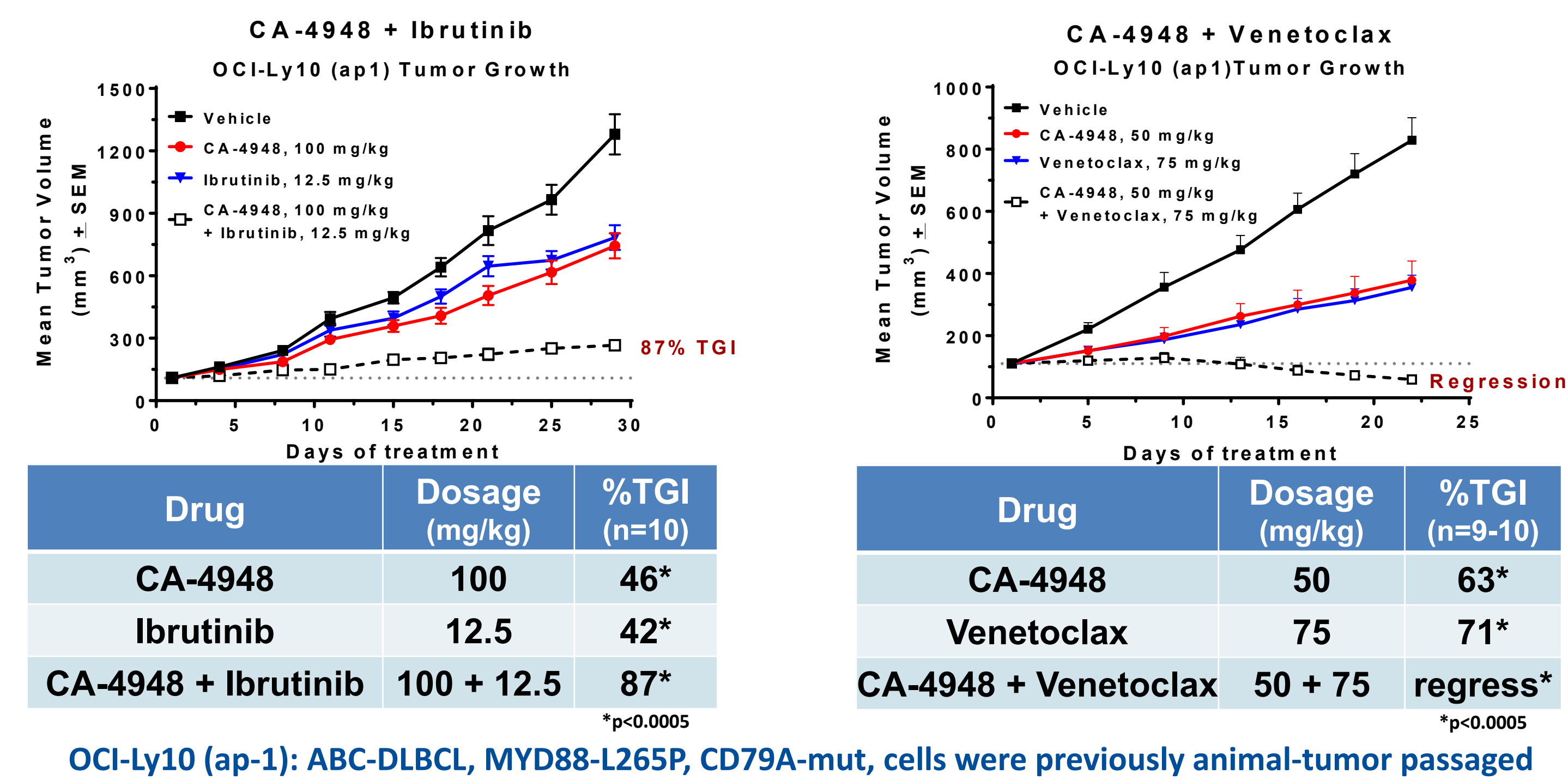
Kinase	DiscoverX Kd (nM)
IRAK4	23
IRAK1	12,000
IRAK2	>20,000
IRAK3	8,500

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



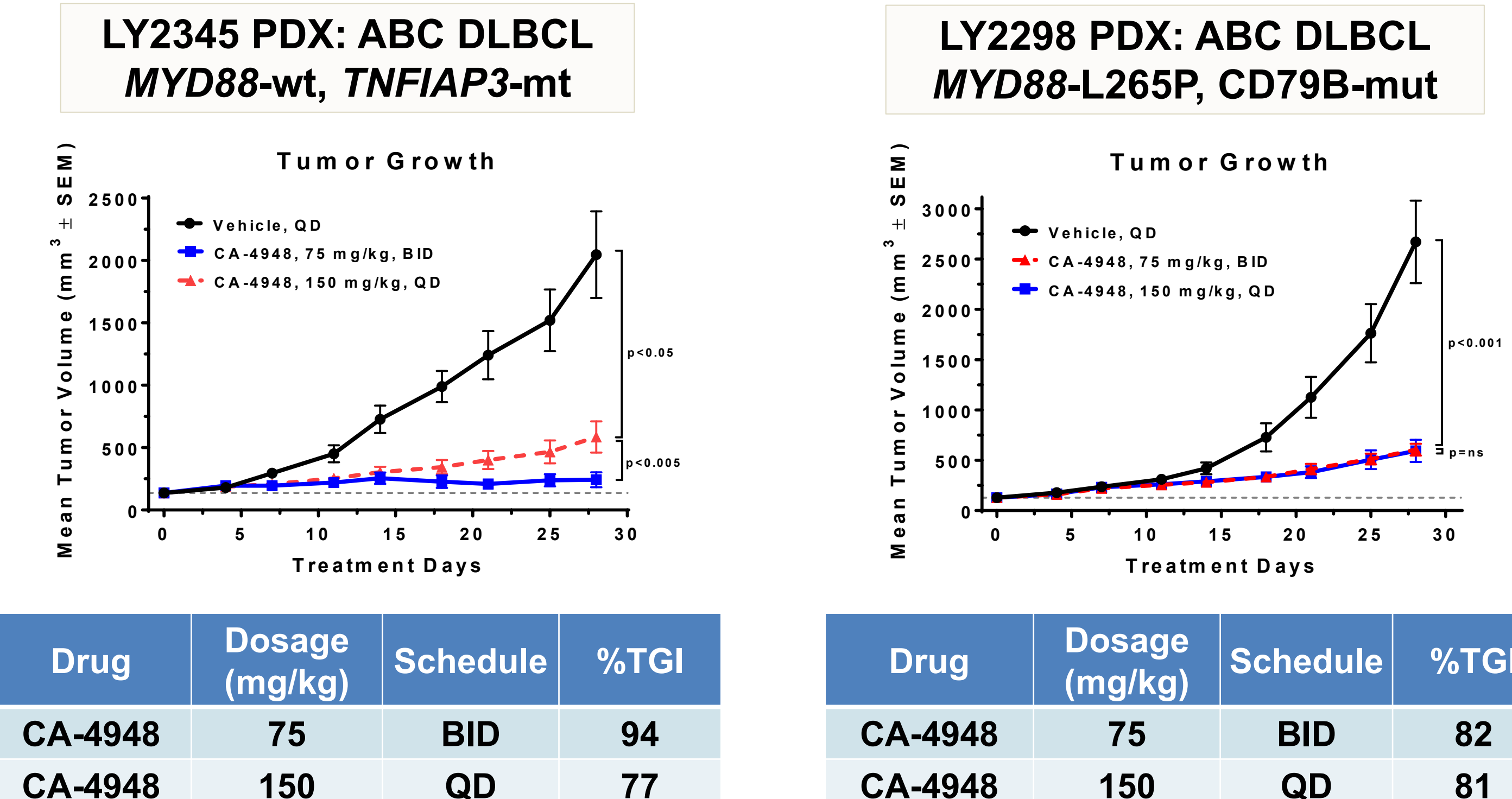
Once-daily CA-4948 dosing shows enhanced *in vivo* activity in MYD88-L265P vs MYD88-wt DLBCL tumors

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



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

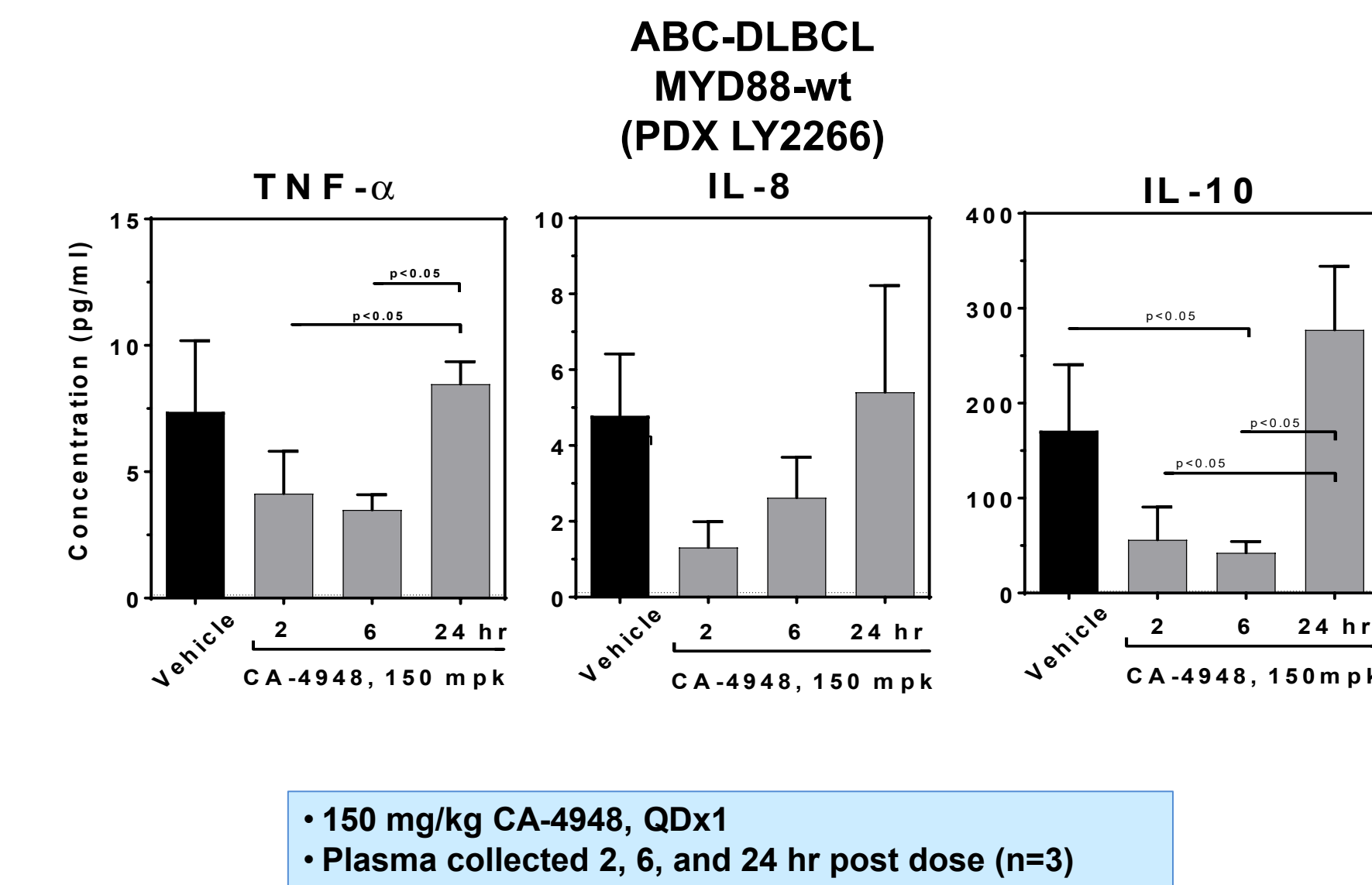
Efficacy of CA-4948 in Two DLBCL PDX Models: QD versus BID Dosing Schedule



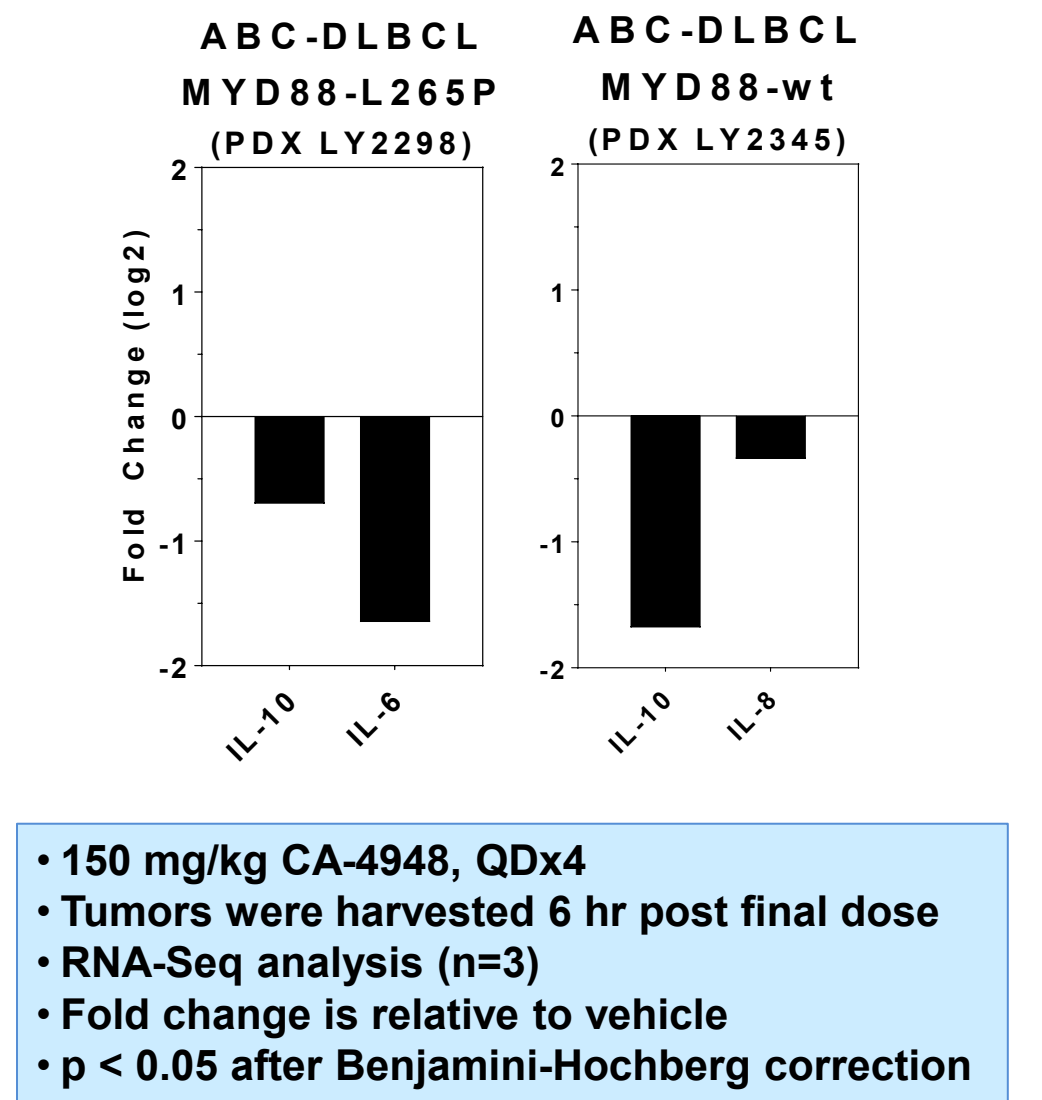
CA-4948 BID dosing exhibits improved/equivalent efficacy compared to QD dosing

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

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

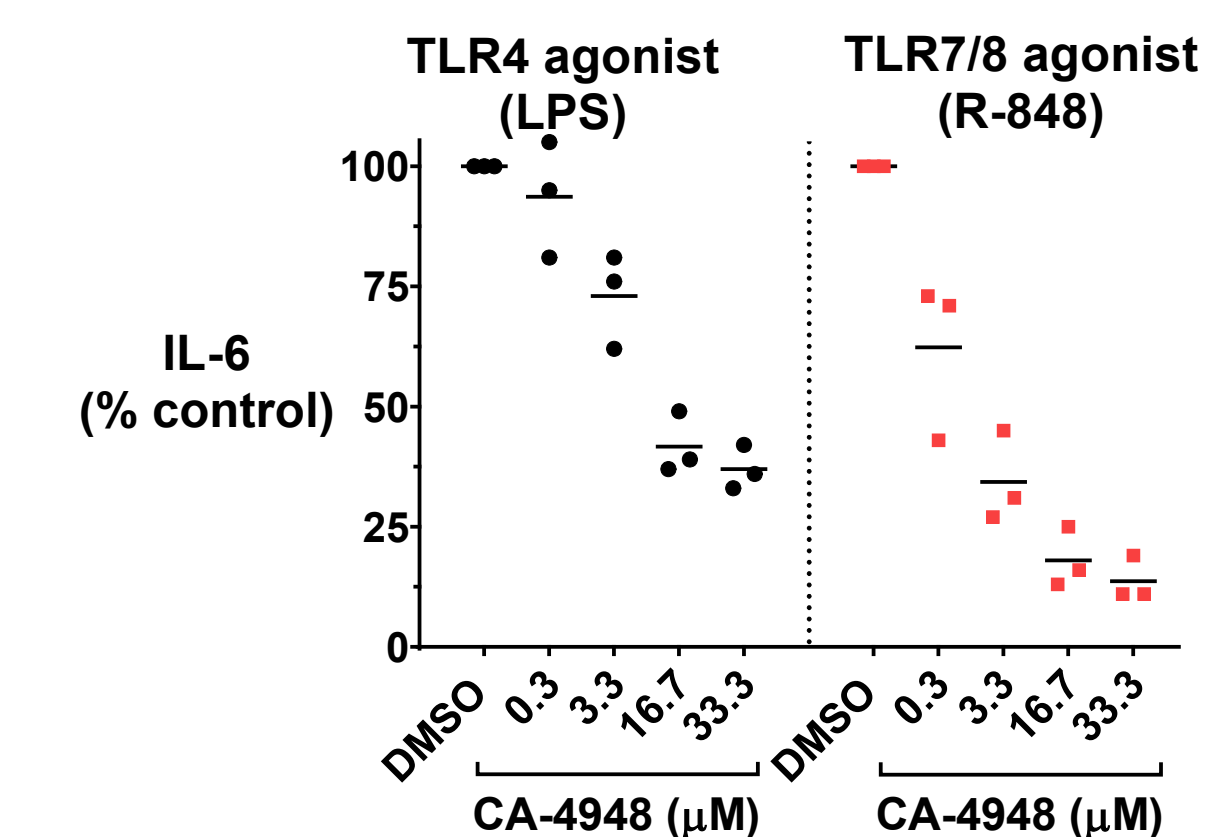


CA-4948 Inhibition of Cytokine RNA Expression in DLBCL PDX Tumors



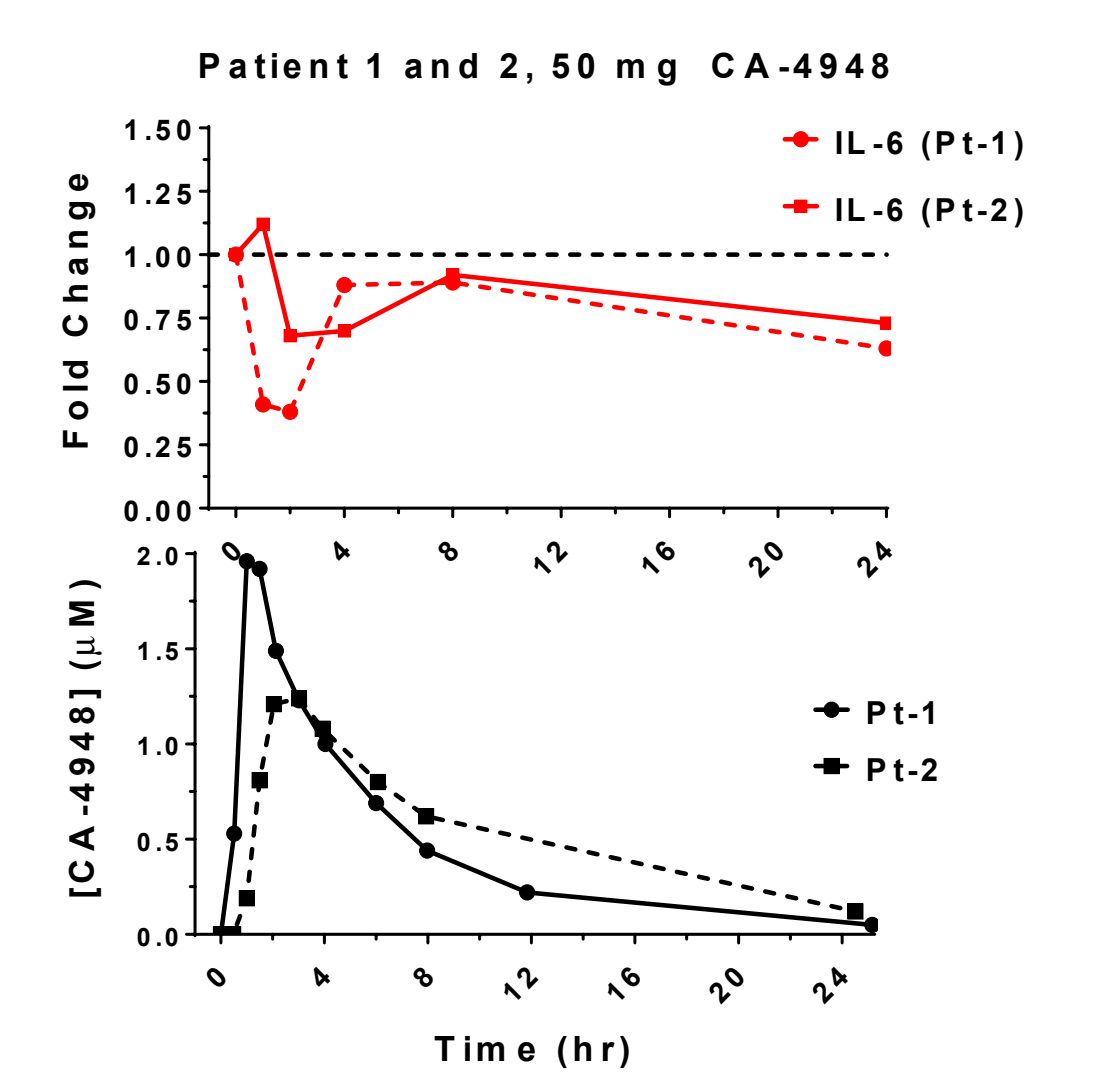
CA-4948 PK/PD Relationship Determined using an *Ex-Vivo* Whole Blood Assay (Human)

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



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

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



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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