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## # 703: Safety, Pharmacokinetics and Activity of CA-4948, an IRAK4 Inhibitor For Treatment of Patients with Relapsed or Refractory Hematologic Malignancies: Results from the Phase 1 Study

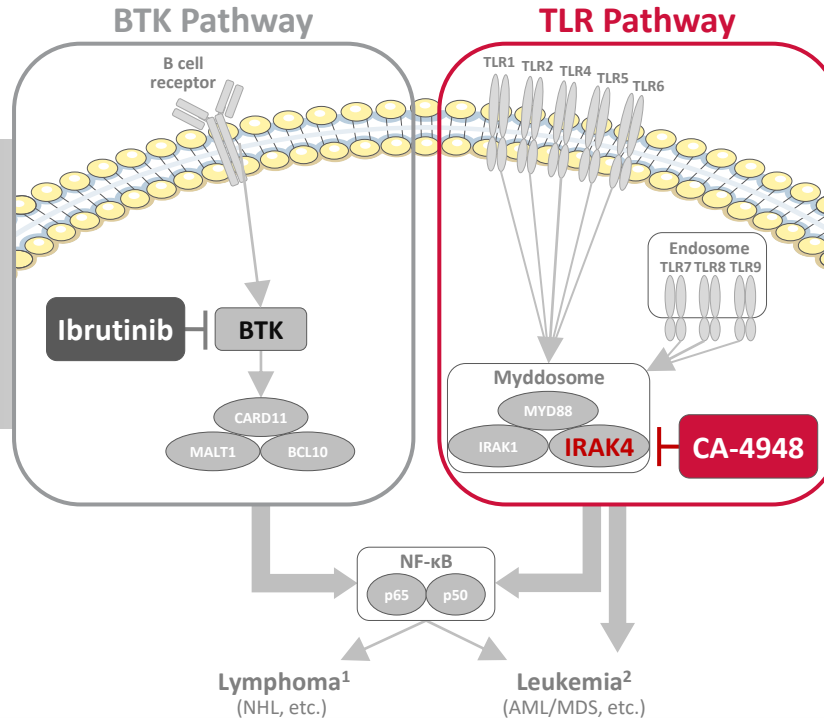
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# Interleukin-1 Receptor-Associated Kinase-4 (IRAK4)

## A novel target for addressing cancer through the TLR Pathway

*BTK and TLR are parallel pathways that drive oncogenic activity as primary independent activators of NF-κB*



### BTK Pathway is Oncogenic

– Dysregulation drives excessive B Cell proliferation

### Pathway is dependent upon BTK

– Signaling requires BTK

### BTK inhibition is effective

– Ibrutinib is FDA approved<sup>1</sup>

### TLR Pathway is Oncogenic

– Dysregulation drives excessive B cell proliferation<sup>2,3</sup>

### Pathway is dependent upon IRAK4

– Signaling requires myddosome, which requires IRAK4

### IRAK4 inhibition is effective

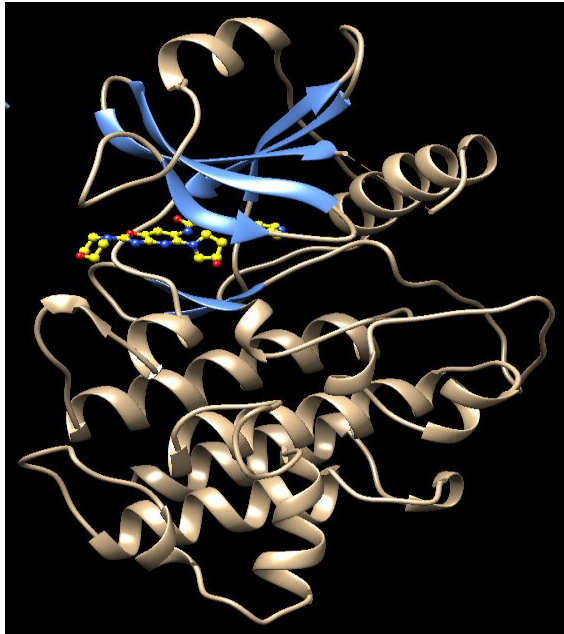
– Preliminary clinical data indicate efficacy

*In November 2020, the NCI initiated a CRADA to conduct clinical and non-clinical studies of CA-4948 in its role as an anti-cancer agent that works via suppression of the TLR Pathway*

1) IMBRUVICA Package Insert. Rev 08/2018  
2) Ngo et al. Nature. 2011 Feb 3;470(7332):115-9  
3) Küppers et al. J Exp Med. 2015. 212(13): 2184  
4) Smith et al. Nat Cell Biol 2019

# CA-4948: A Novel Small Molecule IRAK4 Kinase Inhibitor

IRAK4/CA-4948 Co-crystal Structure



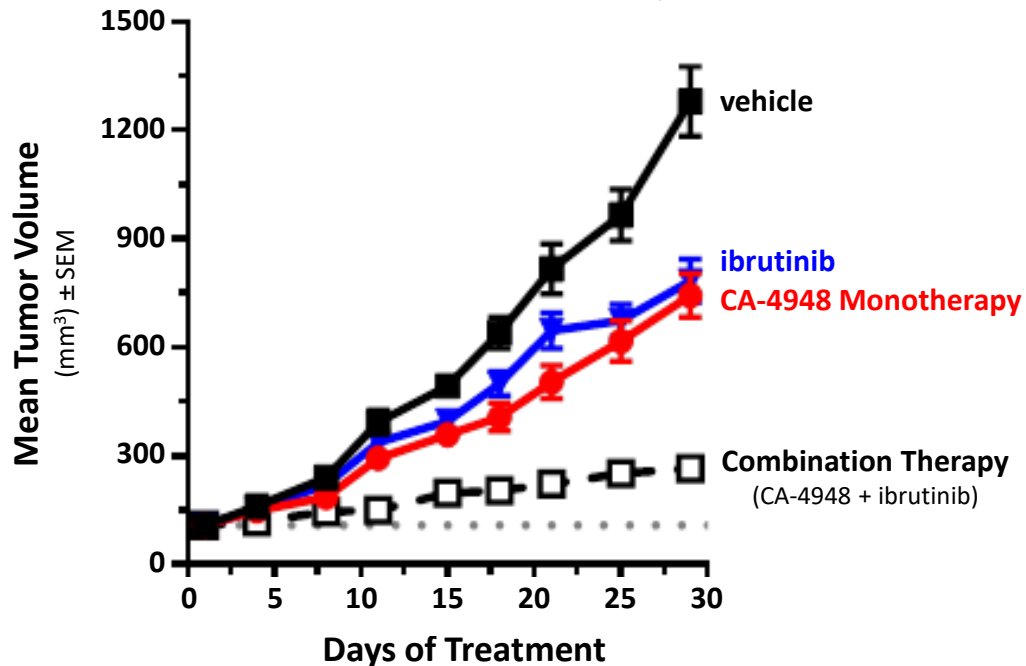
2.4Å resolution

- First-in-class IRAK4 inhibitor in oncology
- Very good oral bioavailability
- ATP-competitive, type 1 reversible inhibitor
- High binding affinity to IRAK4 (23 nM) and FLT3
- Inhibits hematological malignancies that are driven by over-activity of the TLR/IL-1R pathway

# In-Vivo Activity

## Anti-Cancer Activity in Monotherapy and Combination Therapy

in MYD88-altered DLBCL model (OCI-Ly10)



ibrutinib dosing 12.5mg/kg;  
CA-4948 dosing 100mg/kg



# Trial Design

Phase 1 dose escalation study  
in patients with relapsed/refractory (R/R) NHL

Characteristics & Study Disposition	Overall (N=31)
Male, n (%)	26 (80)
Female, n (%)	5 (16)
Age, median years (range)	69 (40-75)
Histology, n (%)	
Diffuse large B-cell lymphoma (DLBCL)	14 (45)
Transformed follicular lymphoma (t-FL/DLBCL)	6 (19)
Waldenström's Macroglobulinemia (WM)	4 (13)
Other Lymphoma*	7 (23)
Prior Therapies	
No. prior regimens [Median (range)]	4 (1-8)
BTK inhibitor, n (%)	6 (19)
CAR-T, n (%)	5 (16)
ASCT, n (%)	7(23)
MYD88 Status	
Positive, n (%)	2 (10)
Negative, n (%)	18 (58)
Unknown, n (%)	10 (32)

\*Includes Lymphoplasmacytic (n=2), mantle cell (n=2),  
marginal zone (n=2), high grade MYC-BCL<sub>6</sub> (n=1)

## Study Objectives

Primary: Safety and tolerability, DLTs, MTD and RP2D

Secondary: Pharmacokinetic (PK) profile

Preliminary anti-cancer activity

## Study Population

- Relapsed or refractory disease
- Histopathologically confirmed B-cell NHL, including WM/LPL
- Age  $\geq$  18 years
- ECOG performance Status of  $\leq$  1

## Dosing

- Oral, QD or BID continuous dosing, 21-day cycles

## Dose Levels, 3+3 Design

QD: 50, 100mg

BID: 50, 100, 200, 300 or 400mg

# Treatment Emerging Adverse Events

*As of the cut-off date, most AEs have been Grade 1-2, manageable, and reversible*

	Adverse Reaction	200 mg BID (n=5); (%)		300 mg BID (n=6); (%)		400 mg BID (n=8); (%)		All (n=30); (%)
		All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades
Gastrointestinal disorders	Diarrhea	20	0	33	0	25	0	20
	Nausea	20	0	17	0	38	0	27
	Vomiting	20	0	17	17	25	0	20
	Constipation	20	0	0	0	13	0	20
Respiratory	Upper respiratory infection	40	20	0	0	13	0	7
	Dyspnoea	20	0	0	0	13	13	7
	Upper-airway cough	40	0	0	0	0	0	7
General & Other	Fatigue	40	0	0	0	50	0	37
	Oedema	20	0	0	0	0	0	10
	Dehydration	20	0	0	0	13	13	10
Nervous system disorders	Headache	20	0	0	0	13	0	10
	Dizziness	0	0	0	0	25	0	20
	Insomnia	20	0	0	0	13	0	7
	Peripheral sensory neuropathy	0	0	0	0	25	0	7
Musculoskeletal disorders	Back pain	20	0	0	0	13	0	10
	Myalgia	40	0	0	0	38	0	17
	Rhabdomyolysis	0	0	0	0	25	25	7
	Muscle weakness	20	20	0	0	13	0	7
Hematological	Neutropenia	40	40	17	17	25	0	7
	Anemia	20	0	33	0	13	13	20
	Thrombocytopenia	0	0	0	0	13	13	7

Data cut-off: 11Oct2020

## General

- No Grade 5 toxicity
- Only 2 treatment discontinuations due to TEAEs; both at low doses
- (asymptomatic amylase increase; rash)
- Intra-patient dose-reductions: 13%
- Intra-patient dose-escalations: 10%

## Rhabdomyolysis

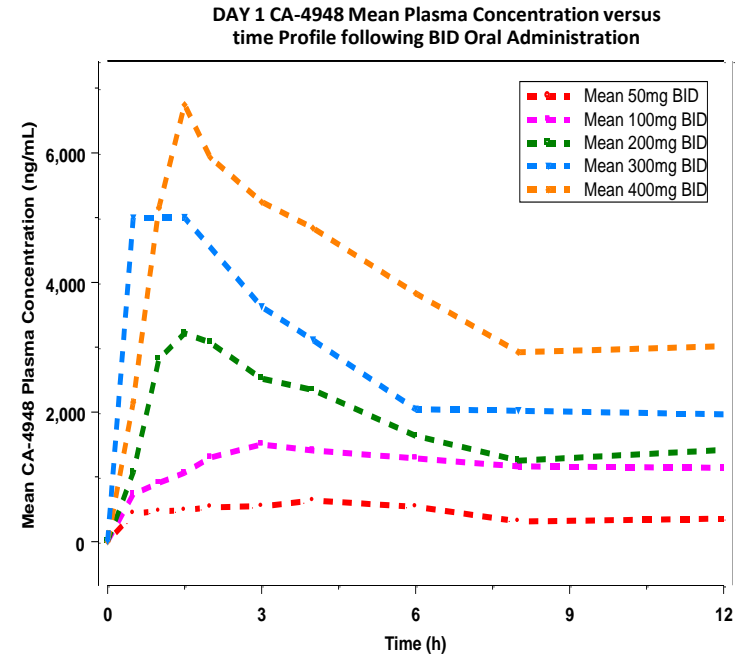
- Observed in 2 patients, based on muscle soreness and CPK elevation
- No renal dysfunction was observed
- Both cases observed in Cycle 1 of dosing, early monitoring of CPK required
- Additional risk factors may be present (vigorous exercise, dehydration, co-medications such as lipid-lowering statins)
- Requires dose interruption; treatment according to clinical presentation; in our uncomplicated cases, hydration, symptom control
- Both cases were reversible; treatment can be resumed at lower dose level

## Other

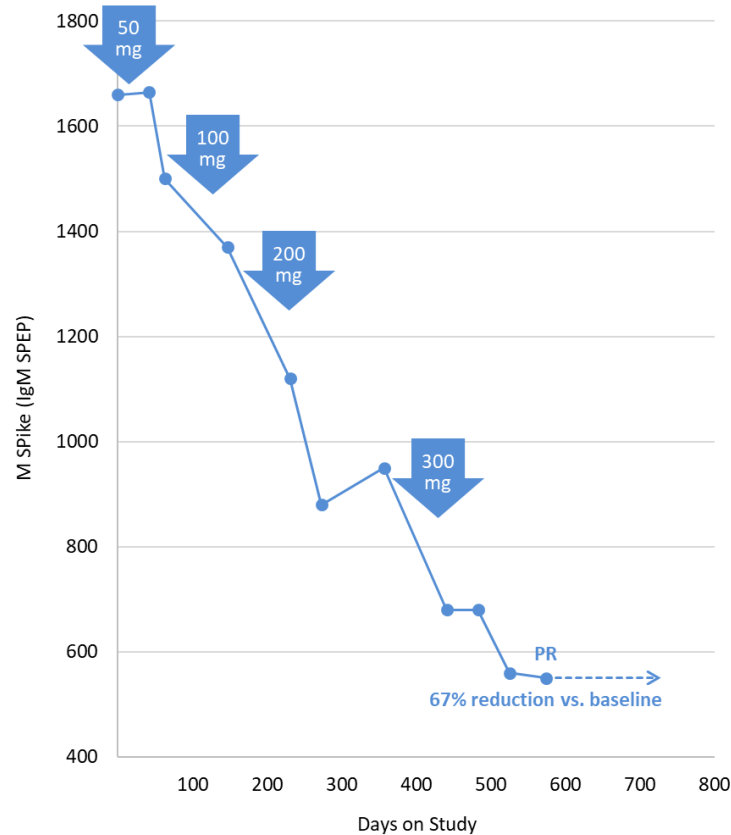
- No TLS
- ECG – no significant changes from baseline; no delayed toxicity

# Clinical PK

- CA-4948 is rapidly absorbed, with maximum plasma concentrations observed 0.5 - 8.0 hours after dosing
- Half-life is ~6 hours
- Dose-proportional increase in exposure
- Minimal accumulation observed following QD dose administration
- Moderate accumulation observed at steady state following BID dose administration
- Trough concentrations at 200mg twice daily (and higher) are above biologically active levels, allowing continuous exposure at biologically relevant concentrations



# Dose Response in Single Patient at Multiple Dose Levels



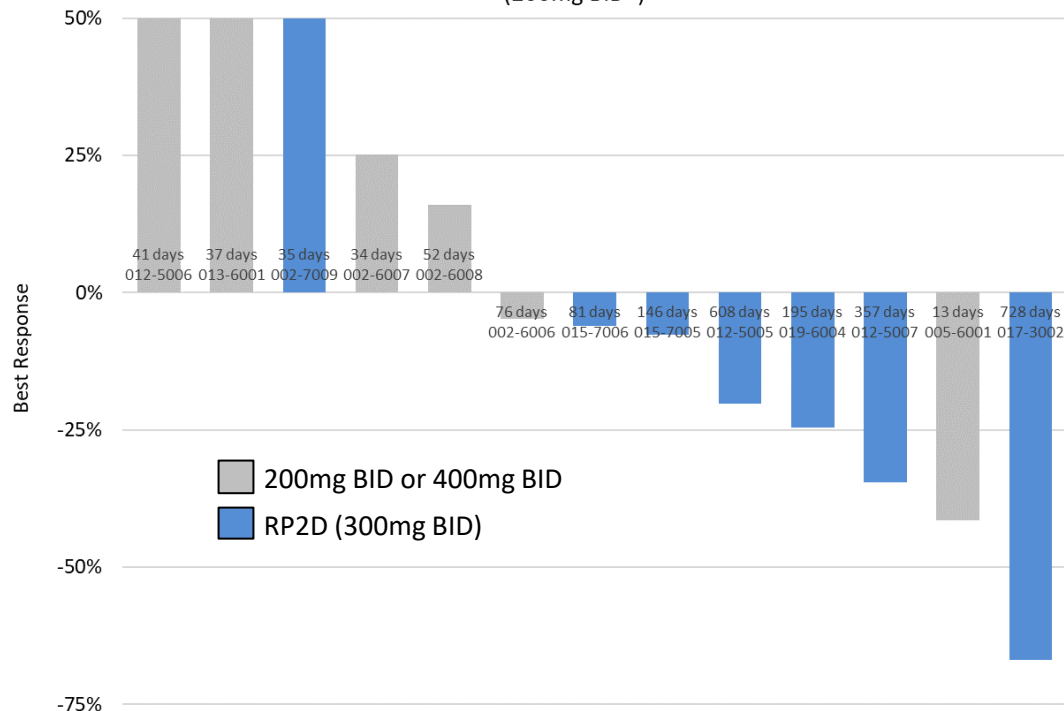
*Clear dose response observed*

*Tumor burden reduced with each increase in dose*



# Tumor Response

**Change in Tumor Burden  
for 13 Evaluable Patients Dosed at Therapeutic Levels  
(200mg BID+)**



NHL Subtype	Initial Dose Level	Final Dose Level	Tumor Reduction
DLBCL	50mg bid	50mg bid	11%
DLBCL (t-MZL)	50mg qd	50mg qd	24%
FL	50mg qd	50mg qd	35%
FL	100mg qd	50mg qd	49%
<b>WM*</b>	<b>50mg bid</b>	<b>300mg bid</b>	<b>67%</b>
LPL*	200mg bid	300mg bid	20%
DLBCL	200mg bid	300mg bid	35%
WM	300mg bid	300mg bid	6%
WM	300mg bid	300mg bid	8%
MALT/MZL	400mg bid	300mg bid	25%
DLBCL-ABC	400mg bid	400mg bid	41%
MZL	400mg bid	400mg bid	5%

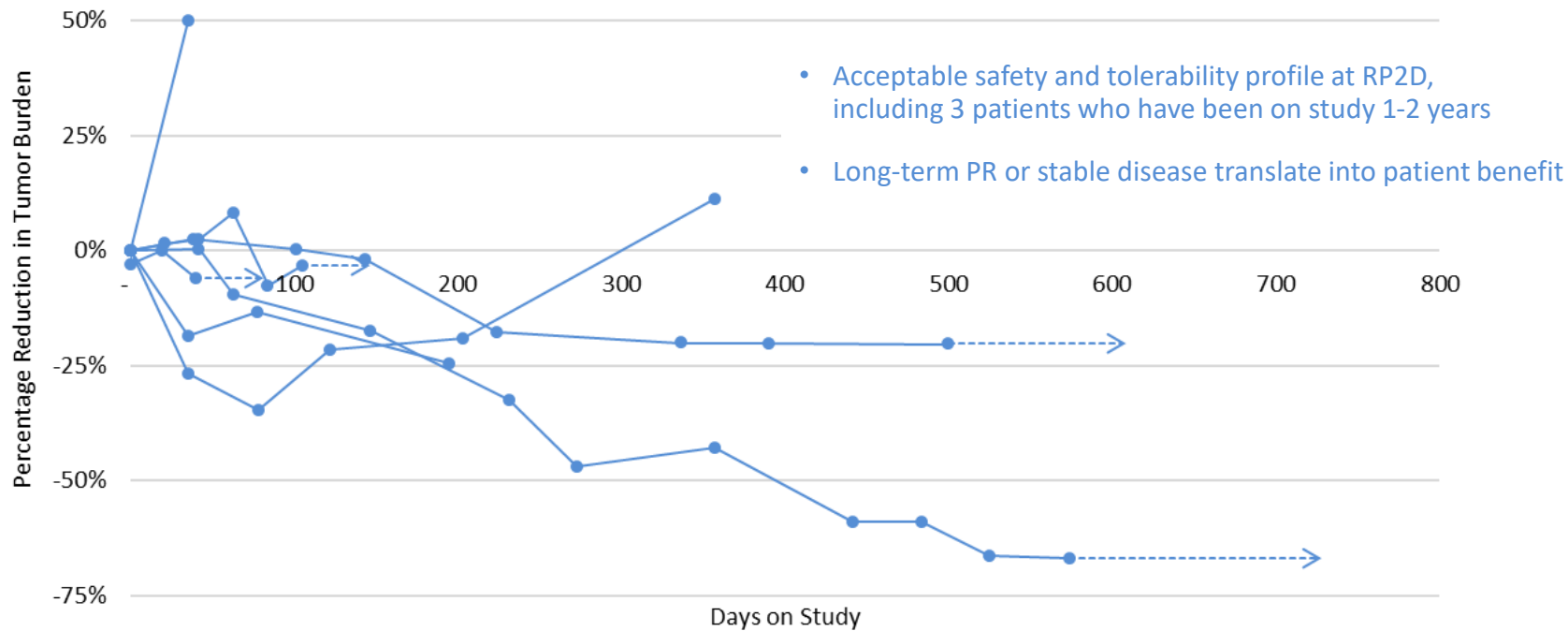
PR

\*MYD88 positive



# Treatment Duration

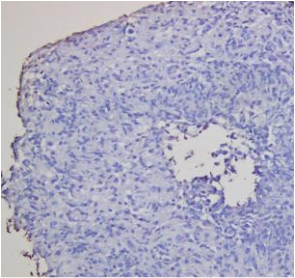
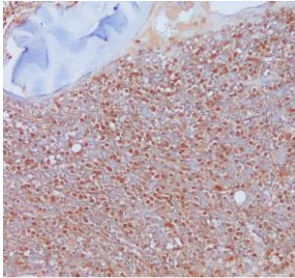
## Patients Dosed at Recommended Ph2 Dose (300mg BID)



# Predictive Biomarkers

## Confirmation of 2<sup>nd</sup> Predictive Biomarker

Positive NFκB phospho-p50 protein expression correlates with Lymphoma Shrinkage or Stable Disease

NEGATIVE		POSITIVE	
NFκB phospho-p50 expression before treatment with CA-4948		NFκB phospho-p50 expression before treatment with CA-4948	
			
Patient	Best Response	Patient	Best Response
12-1002	+86% PD	19-1001	-35% SD
018-2004	+156% PD	02-1001	-23% SD
001-4002	+7% PD	02-3003	+22% SD
002-4004	+75% PD	012-5007	-34% SD
012-4004	+125% PD	002-6007	+25% SD
012-5006	+190% PD	002-6008	+16% SD
013-6001	+98% PD	15-1001	+66% PD

Note: data included for all patients for whom pre/post samples were available at cut off date

## Two Potential Predictive Biomarkers for CA-4948:

### NFκB phospho-p50

Positive expression indicates a patient is more likely to benefit from downregulation of NFκB

- 6 of 7 positive expressers were SD
- 7 of 7 negative expressers were PD

(previously identified)

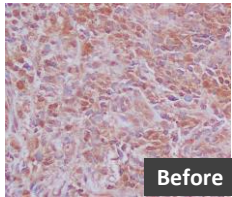
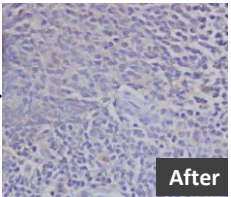
### MYD88

Genetic alteration indicates a patient is more likely to benefit from inhibition of TLR/myddosome

- Only 2 patients in the study have tested positive for MYD88 alteration (one is the patient with the PR)

## Confirmation of Thesis that CA-4948 downregulates NFκB

Treatment with CA-4948 inhibits tumor progression through NFκB inactivation and corresponding reduction of cytokine release (IL6, IL8, TNFα, IFNγ data not shown here)

POSITIVE	NEGATIVE
NFκB phospho-p50 expression before treatment with CA-4948	NFκB phospho-p50 expression after treatment with CA-4948
	
Before	After

Treatment with CA-4948

(Day 20)

# Conclusions

## CA-4948 is a novel oral IRAK4 inhibitor of the TLR/myddosome Pathway

- Well absorbed; pharmacokinetics are predictable and support BID dosing
- Well tolerated; safety profile allows long-term treatment and combination with other active drugs against NHL
- Pharmacodynamic analyses demonstrate NFκB inhibition and reduction of cytokine release
- Dose-dependent tumor shrinkage observed in heavily pretreated, resistant/refractory NHL patients
- Durable monotherapy activity observed at RP2D (300mg BID)

**Next step:** Evaluation in combination with ibrutinib

*This combination trial is being presented in poster #2945*



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## Thank you

Thanks to the participating trial investigators, clinical staff, the patients and their families.

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