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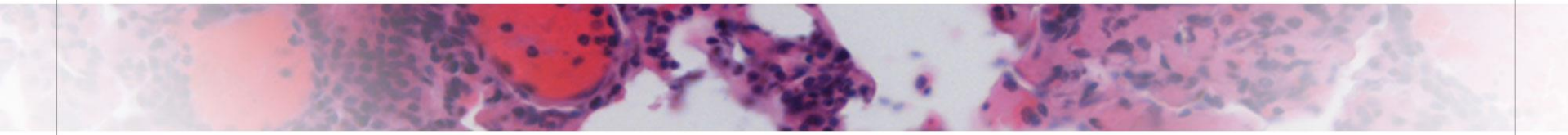

703: Safety, Pharmacokinetics and Activity of CA-4948, an IRAK4 Inhibitor For Treatment of Patients with Relapsed or Refractory Hematologic Malignancies: Results from the Phase 1 Study

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

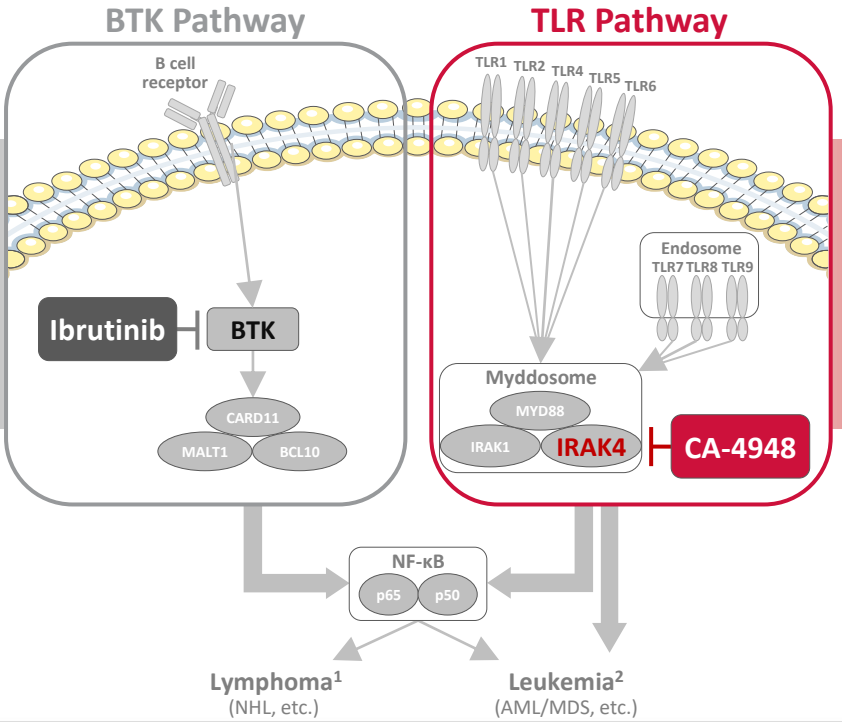
A novel target for addressing cancer through the TLR Pathway

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[1]



TLR Pathway is Oncogenic
- Dysregulation drives excessive B cell proliferation[2,3]

Pathway is dependent upon IRAK4
- Signaling requires myddosome, which requires IRAK4

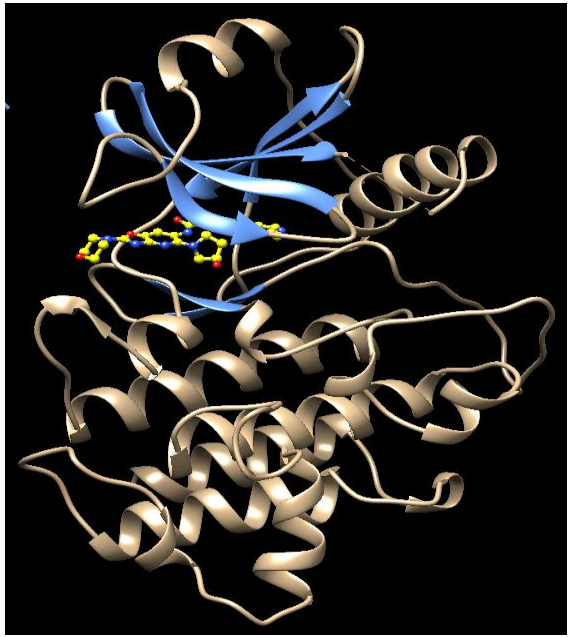
IRAK4 inhibition is effective
- Preliminary clinical data indicate efficacy

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

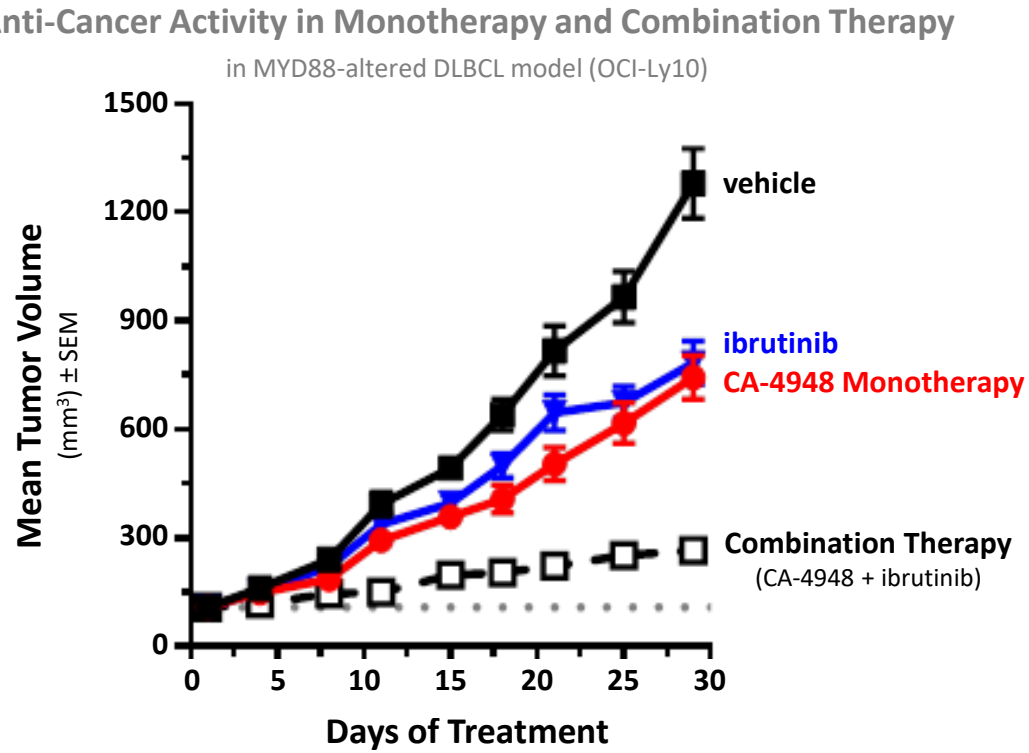
IRAK4/CA-4948 Co-crystal Structure



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



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$_6$ (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 ≥ 18 years
- ECOG performance Status of ≤ 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
	Dyspnoe	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

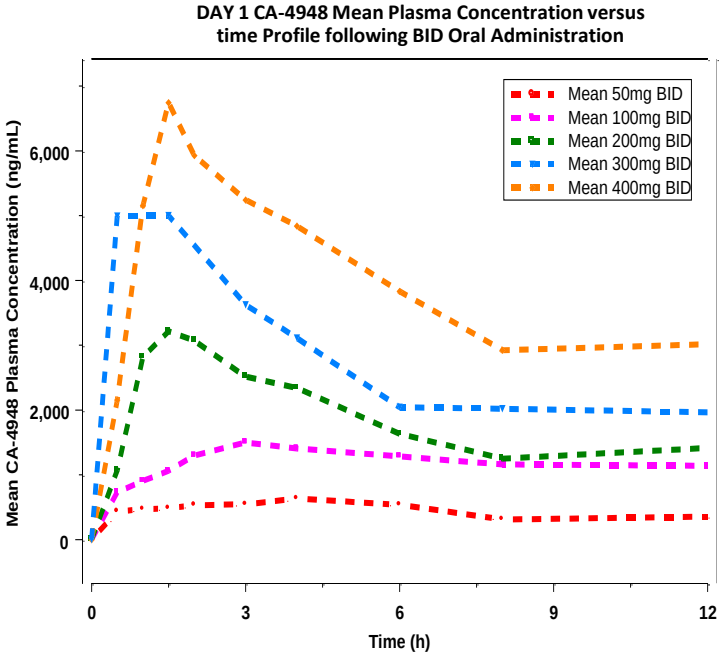
General
- No Grade 5 toxicity
- Only 2 treatment discontinuations due to TEAEs; both at low doses
- (asymptomatic amylase increase; rash)
- Intra-patient dose-reductions: 13%
- Intra-patient dose-escalations: 10%

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

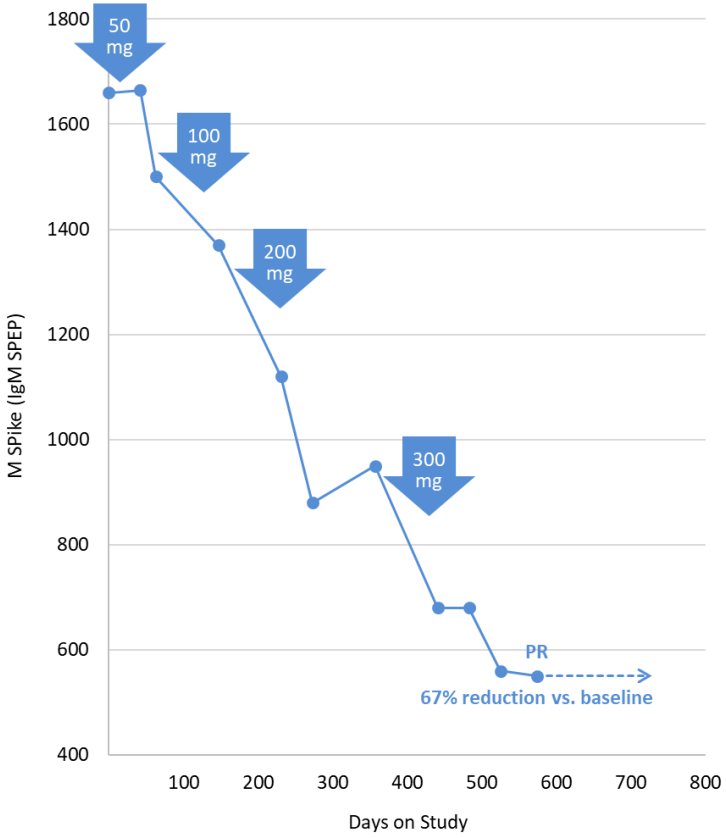
Other
- No TLS
- ECG – no significant changes from baseline; no delayed toxicity

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



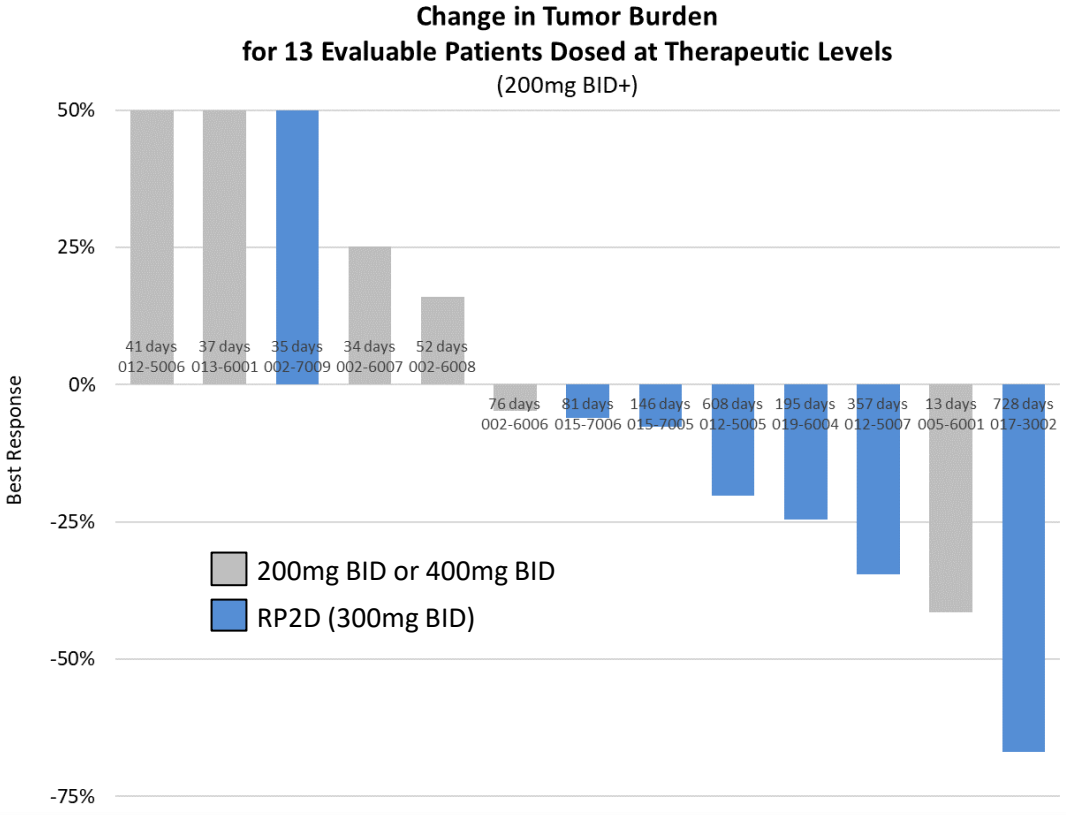
Dose Response in Single Patient at Multiple Dose Levels



Clear dose response observed

Tumor burden reduced with each increase in dose

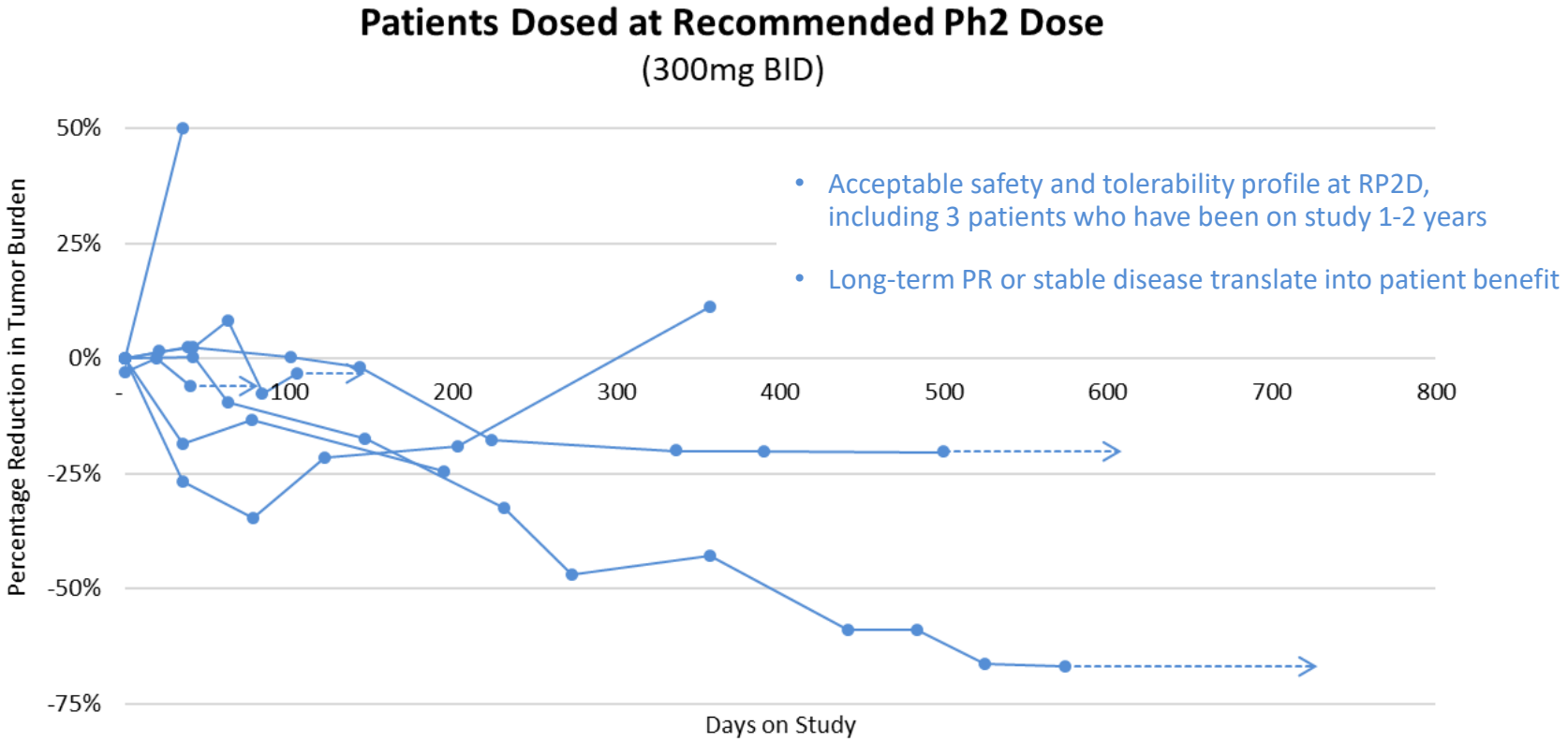
Tumor Response



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%	
WM*	50mg bid	300mg bid	67%	PR
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%	

**MYD88 positive*

Treatment Duration



- Acceptable safety and tolerability profile at RP2D, including 3 patients who have been on study 1-2 years
- Long-term PR or stable disease translate into patient benefit

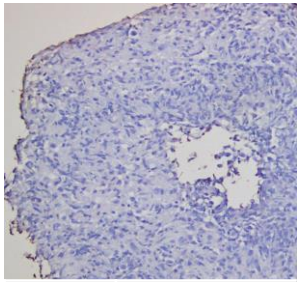
Predictive Biomarkers

Confirmation of 2nd Predictive Biomarker

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

NEGATIVE

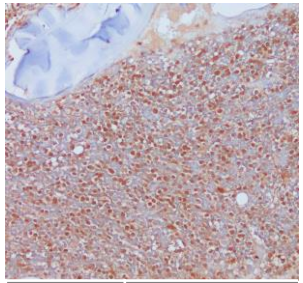
NFκB phospho-p50 expression before treatment with CA-4948



Patient	Best Response
12-1002	+86% PD
018-2004	+156% PD
001-4002	+7% PD
002-4004	+75% PD
012-4004	+125% PD
012-5006	+190% PD
013-6001	+98% PD

POSITIVE

NFκB phospho-p50 expression before treatment with CA-4948



Patient	Best Response
19-1001	-35% SD
02-1001	-23% SD
02-3003	+22% SD
012-5007	-34% SD
002-6007	+25% SD
002-6008	+16% SD
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 expressors were PD

(previously identified)

MYD88

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

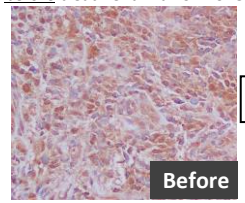
- Only 2 patients in the study have tested positive for MYD88 alteration (one is the patient with the PR)

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

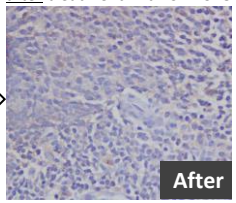
NFκB phospho-p50 expression before treatment with CA-4948



Treatment with CA-4948

NEGATIVE

NFκB phospho-p50 expression after treatment with CA-4948



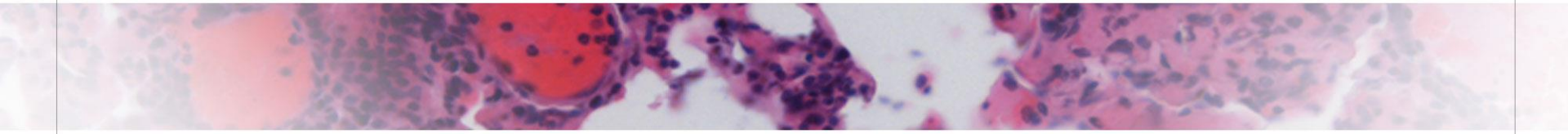
(Day 20)

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



Thank you

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

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