Open-Label, Dose Escalation and Expansion Trial Evaluating the Safety, PK, PD and Clinical Activity of CA-4948 in Patients with Relapsed or Refractory NHL

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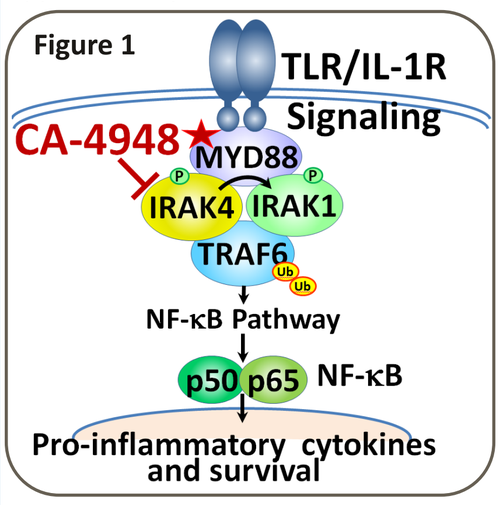
SOHO 2019
ABCL-350

Introduction

Toll-like receptors (TLRs) and interleukin receptors signal through the myddosome, a complex of proteins which includes the adaptor protein MYD88, IRAK4, and others. Ligand binding at the receptor results in activation of IRAK4, initiating a downstream signaling cascade that induces cytokine and survival factor expression mediated by the transcription factor NF-κB (*see Figure 1*).

IRAK4 is a serine/threonine protein kinase, and mice and patients with deleted IRAK4 genes have defective immune responses (1). Components of the myddosome are recognized to be genetically altered in pathologic states and have important roles in cancer and other diseases. MYD88-L265P, a protein mutation resulting in constitutive activation, is shown to occur in approximately 30% of Activated B-Cell (ABC) subtype of diffuse large B-cell lymphomas (DLBCL)(2) and in over 90% of patients with the B-cell malignancy Waldenstrom's macroglobulinemia (3).

Figure 1



Due to IRAK4's central role in these signaling pathways, it represents a clinically meaningful target for the treatment of patients with B-cell malignancies as well as certain inflammatory diseases. CA-4948, a potent and selective IRAK4 kinase inhibitor (4), is currently being tested in a Phase 1 clinical study in patients with non-Hodgkin's lymphoma.

This is the first presentation of human clinical trial data from oncology patients treated with an IRAK4 kinase inhibitor. This presentation summarizes baseline disease characteristics, safety, PK and PD from treated patients in the on-going Phase 1 trial CA-4948-101 (*Clinical trial:* NCT03328078).

Methods

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

Phase 1a Dose Escalation – This dose-escalation study is enrolling advanced non-Hodgkin lymphoma (NHL) patients, including WM, with or with MYD88 mutation or TLR pathway alterations

Objectives:

Primary

- To determine the safety and tolerability, dose-limiting toxicities (DLTs), maximum tolerated dose (MTD), and recommended Phase 2 dose (RP2D) of oral CA-4948 in patients with relapsed/refractory (RR) NHL

Secondary

- To assess the PK profile of CA-4948 in patients with R/R NHL
- To assess the preliminary anti-cancer activity of CA-4948 in patients with R/R NHL

Exploratory

- To assess PD effects of CA-4948 on selected biomarkers in tissues

Patient Population and sites

→Patients with advanced relapsed/refractory non-Hodgkin lymphoma for which standard therapy, does not exist, is not available, or is no longer effective.

→Study sites in USA

Study Design

Relapsed/Refractory NHL with or without MYD88 mutation or TLR pathway alterations

↓

Screening

ClinicalTrials.gov: NCT03328078

FIH dose-escalation trial: CA-4948 monotherapy

- Treatment in 21-day cycles until disease progression, death or protocol-defined criteria
- Dose/Schedule: QD or BID, continuous daily dosing
- 3+3 design; cohorts up to 6 patients each

Dose escalation: 50 mg QD → 100 mg QD → 50 mg BID → 100 mg BID → 200 mg BID → *400 mg BID*

Starting dose level → 50 mg QD

Current dose level

Dose-expansion: CA-4948 monotherapy
➢ NHL/WM +/- MYD88 mutation/TLR pathway alteration

Baseline Characteristics

Characteristics	n (%)
Male	18 (81.8)
Female	4 (18.2)
Age, median (range)	71.3 (58-87)
Weight [kg], median (range)	87.8 (62.7-131.6)
ECOG PS 0	11 (50)
ECOG PS 1	11 (50)

Dose Level	Total daily dose	*n*
50mg QD	50mg	6
100mg QD	100mg	3
50mg BID	100mg	4
100mg BID	200mg	4
200mg BID	400mg	3
400mg BID	800mg	2
Total # of pts treated		22

References and thank you

1. Suzuki N, *et al.,* (2002). Severe impairment of interleukin-1 and Toll-like receptor signalling in mice lacking IRAK-4. N*ature*. 416 (6882): 750–6.

2. Siegel, R.L., K.D. Miller, *et al.,* (2017). Cancer Statistics. *CA Cancer J Clin.* 67(1): p. 7-30.

3. Rhyasen GW and Starczynowski DT. (2015). IRAK signalling in cancer. *Br J of Cancer*. 112;232.

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Curis would like to thank the patients, their families, caregivers and site staff for their invaluable contribution and participation in this study.

Baseline Disease Characteristics

Tumor type	Total N=22 n (%)
Diffuse Large B-Cell Lymphoma (DLBCL)	13 (59)
Follicular Lymphoma (FL)	5 (23)
High Grade B-Cell Lymphoma (HGBL)	1 (4.5)
Mantle Cell Lymphoma (MCL)	1 (4.5)
Waldenstrom Macroglobulinemia (WM)	1 (4.5)
Lymphoplasmacytic Lymphoma (LPL)	1 (4.5)

Stage at Study Entry	Total N=22 n (%)
Stage I	1 (4.5)
Stage II	4 (18.2)
Stage III	6 (27.3)
Stage IV	8 (36.4)
Unknown	3 (13.6)

Safety Summary

The most common TEAEs without relationship to CA-4948, were: fatigue (36%), nausea (27%), neutrophil count decreased (23%), dizziness (18%), hypercalcemia (18%), hypophosphatemia (18%), vomiting (18%)

- ❑ Grade 3/4 TEAEs have occurred in 11 patients (50%) with most occurring within the Investigations Systems-Organ-Class (SOC)
  - 6 patients had Grade 3/4 AEs which were considered *related* to CA-4948
- ❑ 18 patients (81%) experienced any-grade related TEAEs (*see Table below*)
- ❑ 4 patients have experienced SAEs
  - One SAE was considered related to CA-4948: Grade 3 rhabdomyolysis
- ❑ No Grade 5 TEAEs occurred unrelated to disease progression

Related TEAEs by Preferred Term (Highest Severity) Occurring in >1 Patient:

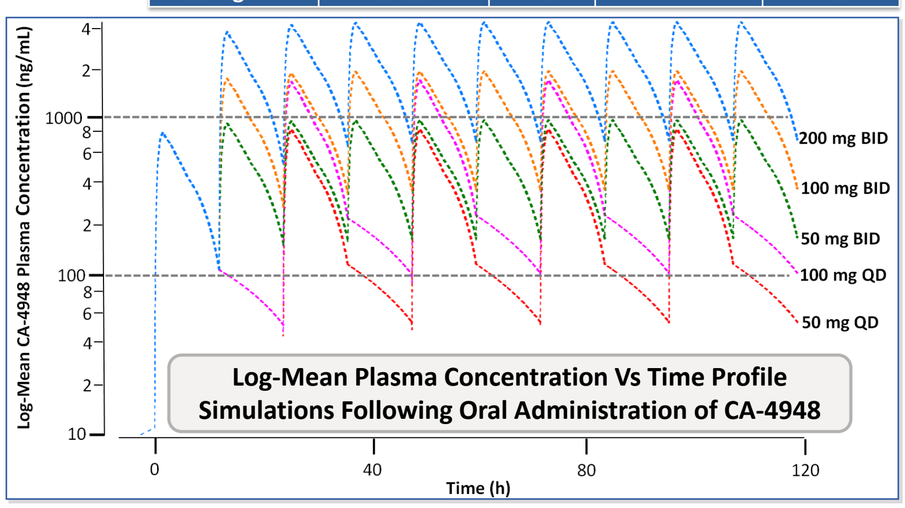
Related TEAEs by Preferred Term	Grade 1/2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total, N=22 n (%)
Diarrhoea	2 (9)	1 (4.5)	0	3 (13.6)
Fatigue	3 (13.6)	0	0	3 (13.6)
Nausea	3 (13.6)	0	0	3 (13.6)
Neutrophil count decreased	1 (4.5)	2 (9)	0	3 (13.6)
Anaemia	2 (9)	0	0	2 (9)
Blood creatine phosphokinase increased	1 (4.5)	0	1 (4.5)	2 (9)
Hypomagnesaemia	2 (9)	0	0	2 (9)
Lipase increased	1 (4.5)	0	1 (4.5)	2 (9)
Myalgia	2 (9)	0	0	2 (9)

Pharmacokinetics

Summary of human oral pharmacokinetics of CA-4948:

- ❑ After oral administration, CA-4948 is rapidly absorbed with maximum plasma concentrations observed at 0.5-8 hours post dose
- ❑ Exhibits dose-proportional increase in exposure
- ❑ CA-4948 has a short half-life of ~6 hours
- ❑ Minimal to no accumulation is observed following multiple daily single dose administration
- ❑ Accumulation is observed following multiple daily twice dose administration
- ❑ Collectively, the oral pharmacokinetics of CA-4948 are desirable and predictable

Dose	Cmax (ng/mL) Mean (CV%)	Tmax (h) Mean	AUC_{0-t} (ng·h/mL) Mean (CV%)	Half-Life (h) Mean (CV%)
50 mg QD	946 (45)	1.5	4213 (35)	5.1 (26)
100 mg QD	1995 (91)	3.8	8315 (68)	4.3 (30)
50 mg BID	927 (31)	2.7	3654 (30)	6.4 (41)
100 mg BID	2065 (35)	4.0	10394 (24)	5.8 (47)
200 mg BID*	5438	4.5	24711	4.5



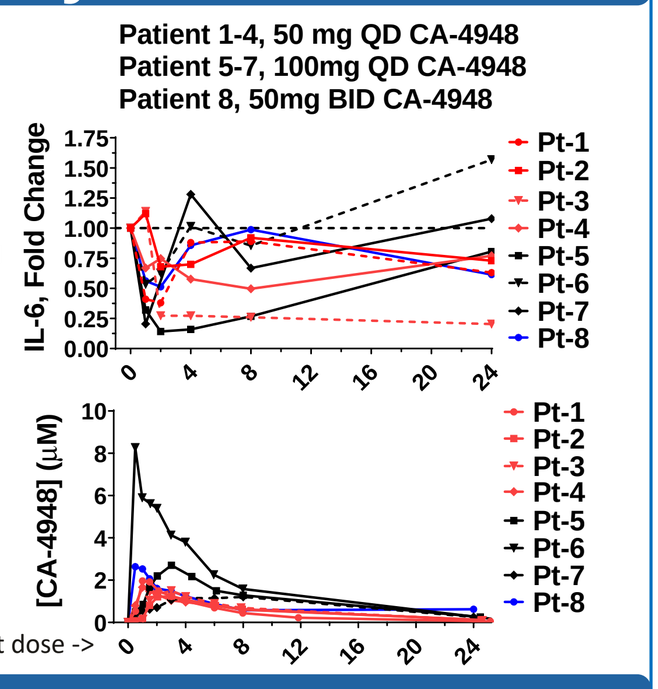
Pharmacodynamics

Human *ex vivo* whole blood assay:

- ❑ Collect 1 mL blood in TruCulture tube containing 1 mL media with TLR agonist
- ❑ Incubate, measure plasma cytokine levels

Cytokine production in TLR-stimulated whole blood from CA-4948 –treated patients (TLR7/8 agonist stimulation)

- ❑ An *ex-vivo* TLR-stimulated whole blood assay was developed for *in vivo* or clinical PK/PD analysis to assess for on-target IRAK4 inhibitory
- ❑ Preliminary PK/PD relationship is observed with patients treated with 50 and 100 mg QD and 50 mg BID CA-4948



Conclusions

- ❑ CA-4948 is a potent, oral inhibitor of IRAK4 Ser/Thr kinase with high selectivity against IRAK1
- ❑ The Phase 1 FIH trial of CA-4948 is on-going; the most recent cleared dose level is 200 mg BID; a 400 mg BID cohort is open to enrollment – The MTD/RP2D has not been reached
- ❑ Dose levels completed through the 200 mg BID dose level were well-tolerated and toxicities have primarily been mild to moderate in severity and self-limiting or resolved with concomitant medications
- ❑ QD and BID doses have been tested for pharmacokinetic and pharmacodynamic effects:
  - ❑ CA-4948 demonstrates dose-proportional increase in exposure with a half-life of approx. 6 hrs
  - ❑ BID dosing is supported by PD ex vivo whole-blood cytokine production assay
- ❑ CA-4948 has been tested in small cohorts and at low initial dose levels, however patients have already experienced anti-tumor activity at multiple dose levels, including 2 patients at 200mg BID
- ❑ Dose expansion at the RP2D will occur in NHL patients with MYD88 mutations and without, or patients with TLR pathway alteration