EUROPEAN HEMATOLOGY ASSOCIATION

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A PHASE 1, DOSE ESCALATION TRIAL WITH NOVEL ORAL IRAK4 INHIBITOR CA-4948 IN PATIENTS WITH ACUTE MYELOGENOUS LEUKEMIA OR MYELODYSPLASTIC SYNDROME – INTERIM REPORT

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DISCLOSURES

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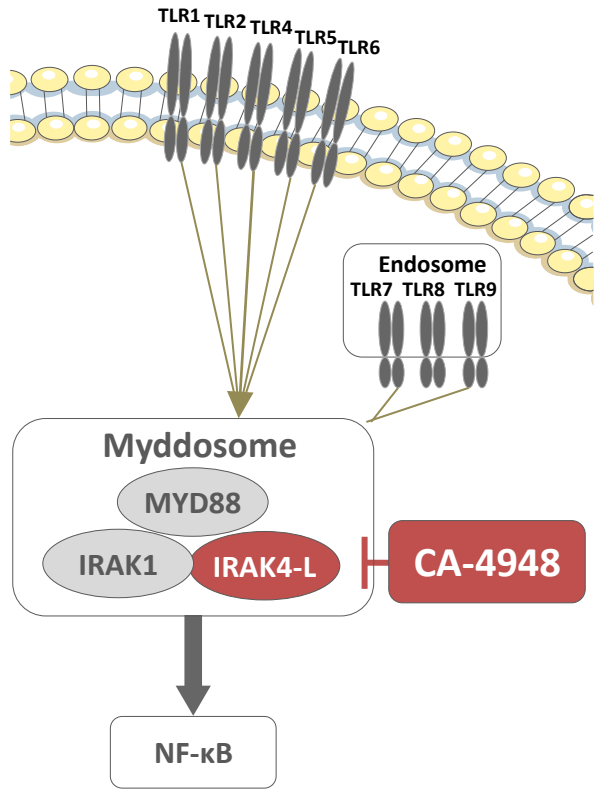
Introduction

- Interleukin-1 receptor associated kinase 4 (IRAK4) plays an essential role in toll-like receptor (TLR) and interleukin 1 receptor (IL-1R) signaling pathways
- These pathways are frequently dysregulated in Non-Hodgkin Lymphomas (NHL) and AML/MDS[1]
- Oncogenic IRAK4-L, frequently driven by spliceosome mutations, is preferentially expressed in > 50% of AML/MDS patients[2,3]
- Activated IRAK4 has been identified as a driver of adaptive resistance in AML[4]

TLR Pathway



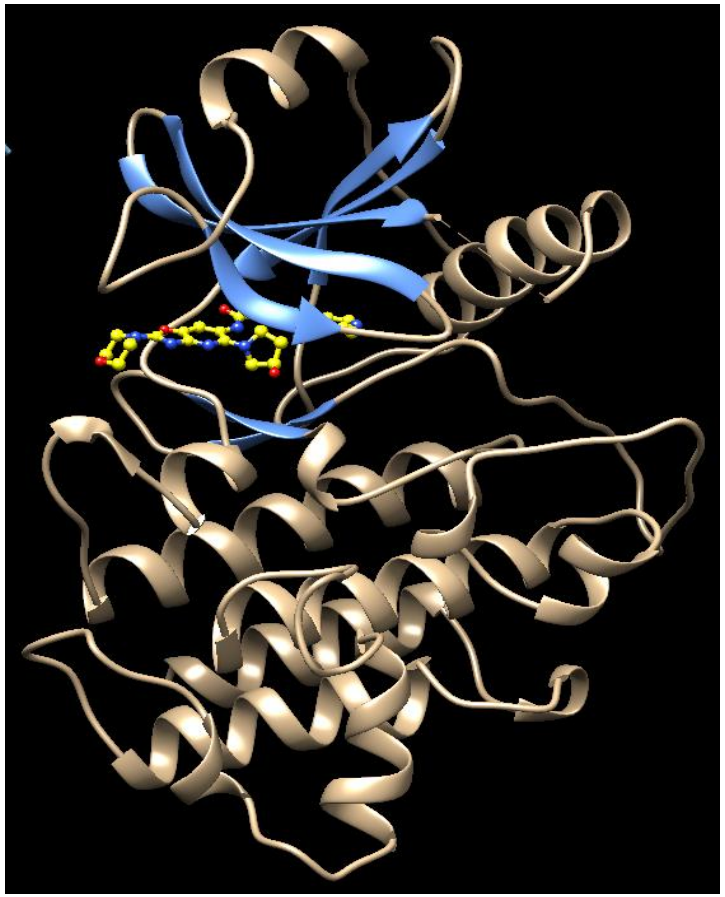
Over-activity of NF-κB drives
- Inflammation
- Cancer cell survival
- Malignant proliferation
- Suppression of apoptosis

1) Rhyasen GW and Starczynowski DT. Br J Cancer 2015
2) Choudhary G *et al.* Blood 2019
3) Smith MA *et al*. Nat Cell Biol 2019
4) Melgar K *et al.* Sci Transl Med 2019

CA-4948: A novel small molecule IRAK4 inhibitor

- First-in-class IRAK4 inhibitor in oncology
- Inhibits hematological malignancies that are driven by over-activity of the TLR/IL-1R pathway, which is dependent on IRAK4
- CA-4948 also inhibits FLT3-mutated AML *in vitro* and *in vivo*
- High binding affinity to IRAK4 (23 nM) and FLT3 (31 nM)
- No myelosuppressive DLTs
- Excellent oral bioavailability
- Dose-dependent PK with clear PD correlates
- Safe (RP2D 300 mg BID) and active in relapsed or refractory (R/R) NHL

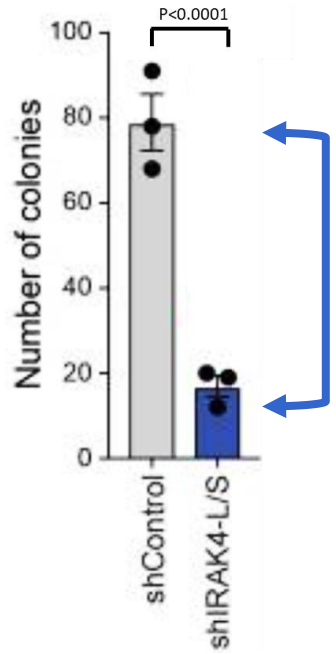
IRAK4/CA-4948 Co-crystal Structure



ATP-competitive, type 1 reversible inhibitor

CA-4948 targets IRAK4-L, a key driver of leukemia

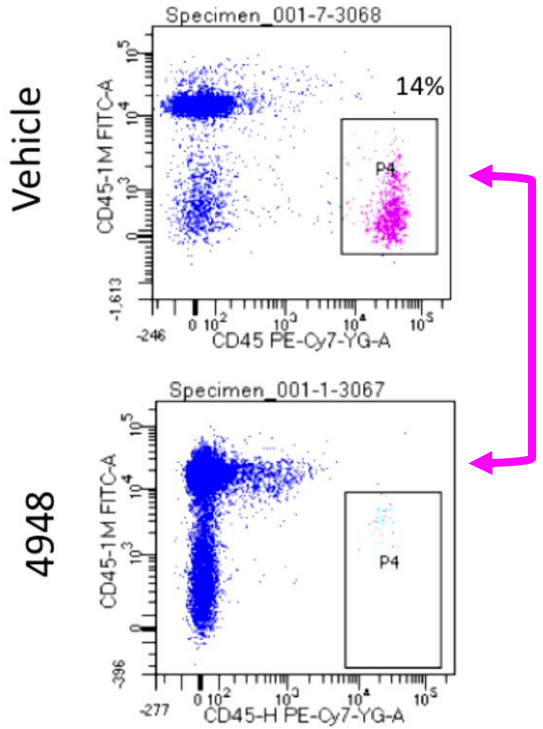
IRAK4-L is oncogenic



Blocking IRAK4-L reduces formation of leukemia colonies in preclinical studies[1]

IRAK4-L knockdown models demonstrate genetic link to oncogenic immune signaling in AML/MDS[1]

CA-4948 targets IRAK4-L



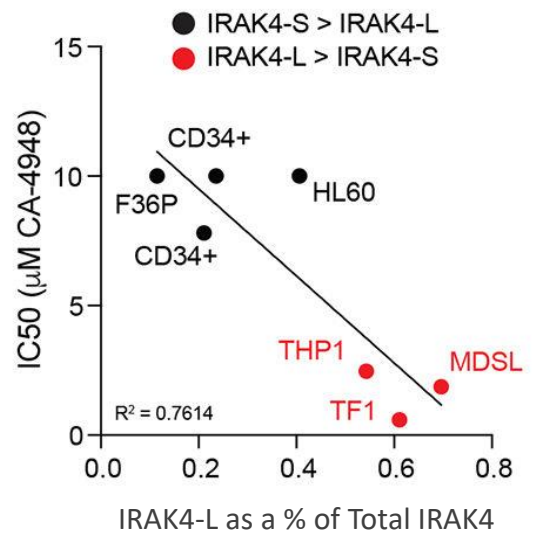
CA-4948 treatment reduces leukemic blasts in patient-derived xenografts[2]

In preclinical model, IRAK4-L inhibition with CA-4948 demonstrates anti-cancer activity consistent with knockdown models[2]

1) Smith et al. Nat Cell Biol 2019
2) Choudhary et al. AACR 2017

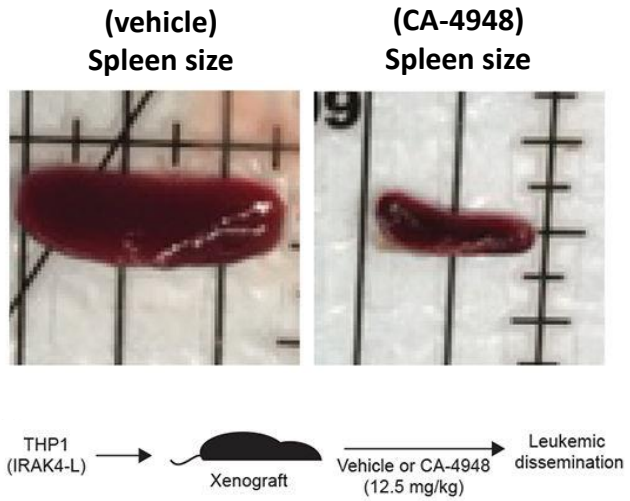
CA-4948 reduces tumor burden in preclinical models

CA-4948 is more active in cell lines overexpressing IRAK4-L



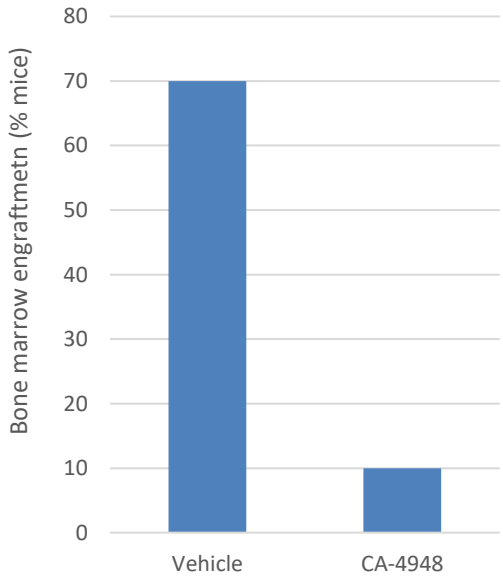
Smith et al. 2019

Xenografts treated with CA-4948 maintained normal spleen size (surrogate for leukemic burden)

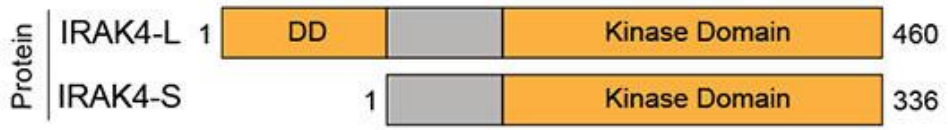


Smith et al. 2019

Treatment with CA-4948 prevented leukemic engraftment in almost all xenografts

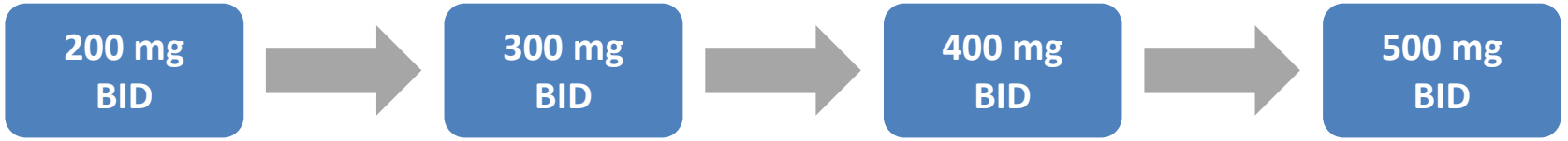


Smith et al. 2019



IRAK4-L is a negative prognosticator of survival

Study design: multicenter single arm Phase 1 dose escalation study of CA-4948 monotherapy in adult patients with AML or high risk MDS



3+3 design; continuous 28-day cycles in the absence of unacceptable toxicity or disease progression (NCT04278768)

Primary Objective

Safety and RP2D

Secondary Objectives

Pharmacokinetics

Initial efficacy, including ORR for evaluable patients with baseline and at least 1 follow-up assessment

Exploratory Objectives

Pharmacodynamics

Biomarkers related to mechanism of action

Patient eligibility

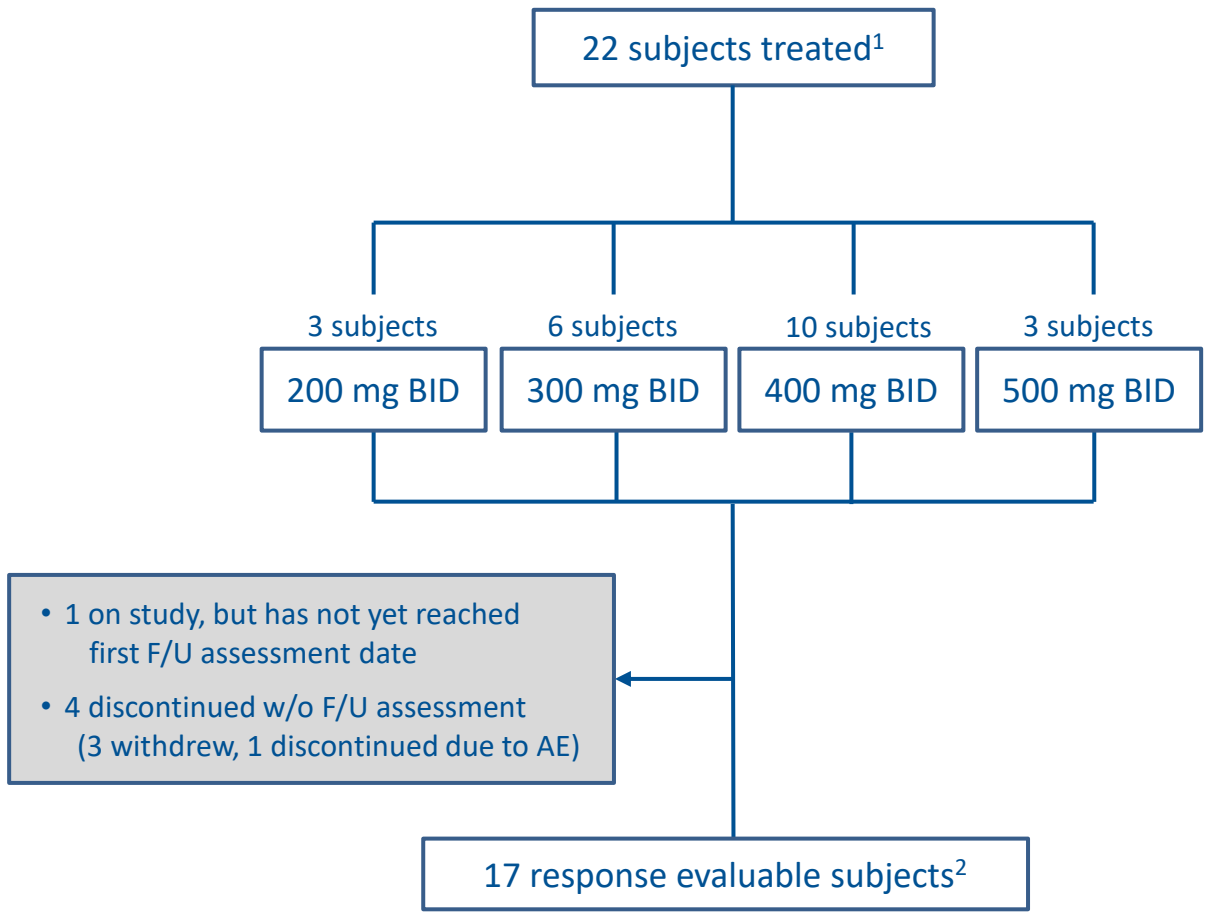
Inclusion:

- ≥ 18 years of age
- ECOG ≤ 2
- hrMDS or AML (WHO 2016 classification):
  - R/R after failing at least 1 standard treatment

Exclusion:

- Acute promyelocytic leukemia (APL, M3)
- Active central nervous system leukemia
- Blast stage of chronic myelogenous leukemia
- Allo-HSCT within 60 days of the first dose of CA-4948 or clinically significant GvHD

Baseline characteristics of patients who received CA-4948



Characteristics		Patients (n=22)
Female n (%) : Male n (%)		5 (23):17 (77)
Age (yrs): median (range)		74 (32 - 87)
Race, n (%)	White	18 (82)
	African American	1 (4)
	Not reported	3 (14)
ECOG: n 0/1/2		7/11/4
Diagnosis	AML, n (%)	11 (50)
	hrMDS, n (%)	11 (50)
Median platelets ($10^3/mm^3$) (range)		33 (7, 275)
Median ANC ($10^3/mm^3$) (range)		1.2 (0.1, 14.8)
Median lines of prior therapy (range)		2 (1-4)
Prior therapy, n (%)	Azacitidine	14 (64)
	Decitabine	7 (32)
	Cytarabine	3 (14)
	Venetoclax	10 (45)
Cytogenetic risk, n (%)[3]	AML (favorable/intermediate/ adverse)	1 (10) / 2 (20) / 7 (70)
	hrMDS (good/intermediate/poor/ very poor)	1 (9) / 4 (36) / 3 (27) / 3 (27)
Relavant mutations[4]	FLT3	1
	SF3B1	2
	U2AF1	2

1) Data extraction date: Apr 30th, 2021
2) Response evaluable: baseline and post-baseline disease evaluation or progressive disease
3) Analysis for cytogenetic risks includes 10 AML patients (ELN) and 11 hrMDS patients (IPSS-R)
4) Mutational analysis is ongoing

Treatment-related adverse events occurring in ≥ 2 patients

Per patient, highest grade

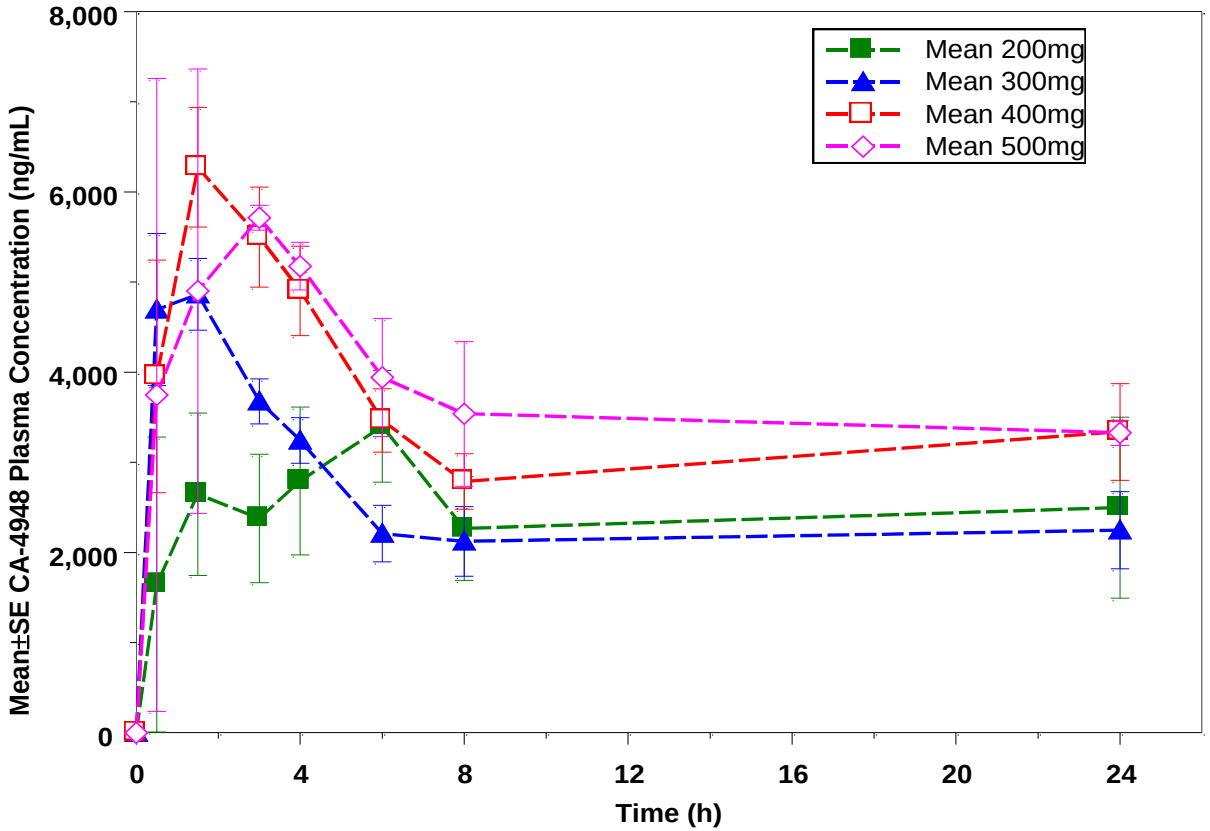
Preferred Terms	200 mg BID (n=3) Grade All	200 mg BID (n=3) Grade 3 or 4	300 mg BID (n=6) Grade All	300 mg BID (n=6) Grade 3 or 4	400 mg BID (n=10) Grade All	400 mg BID (n=10) Grade 3 or 4	500 mg BID (n=3) Grade All	500 mg BID (n=3) Grade 3 or 4	All (n=22) All Grades n (%)	All (n=22) Grade 3 or 4 n (%)
Dizziness	2	1	0	0	1	0	2	0	5 (22.7)	1 (4.5)
Nausea	1	0	1	0	0	0	2	0	4 (18.2)	0
Alanine aminotransferase increased	1	1	1	0	0	0	1	0	3 (13.6)	1 (4.5)
Fatigue	0	0	1	0	0	0	2	0	3 (13.6)	0
Muscular weakness	0	0	1	0	2	0	0	0	3 (13.6)	0
Myalgia	0	0	0	0	2	0	1	0	3 (13.6)	0
Chromaturia	0	0	0	0	2	0	0	0	2 (9.1)	0
Diarrhoea	0	0	1	0	1	0	0	0	2 (9.1)	0
Dyspnoea	0	0	1	0	1	0	0	0	2 (9.1)	0
Presyncope	0	0	1	0	1	1	0	0	2 (9.1)	1 (4.5)
Rhabdomyolysis	0	0	0	0	0	0	2	1	2 (9.1)	1 (4.5)

- During the dose-escalation phase, no DLT was observed for 200-400 mg BID cohorts
- DLTs observed in 2 patients at 500 mg BID (1 patient with Gr 3 rhabdomyolysis and 1 patient with Gr 3 syncope), both AEs resolved after dosing interruption; rhabdomyolysis AE was quickly detected by elevated CPK, did not involve renal dysfunction, and was quickly resolved after dosing interruption

Predictable clinical PK of CA-4948

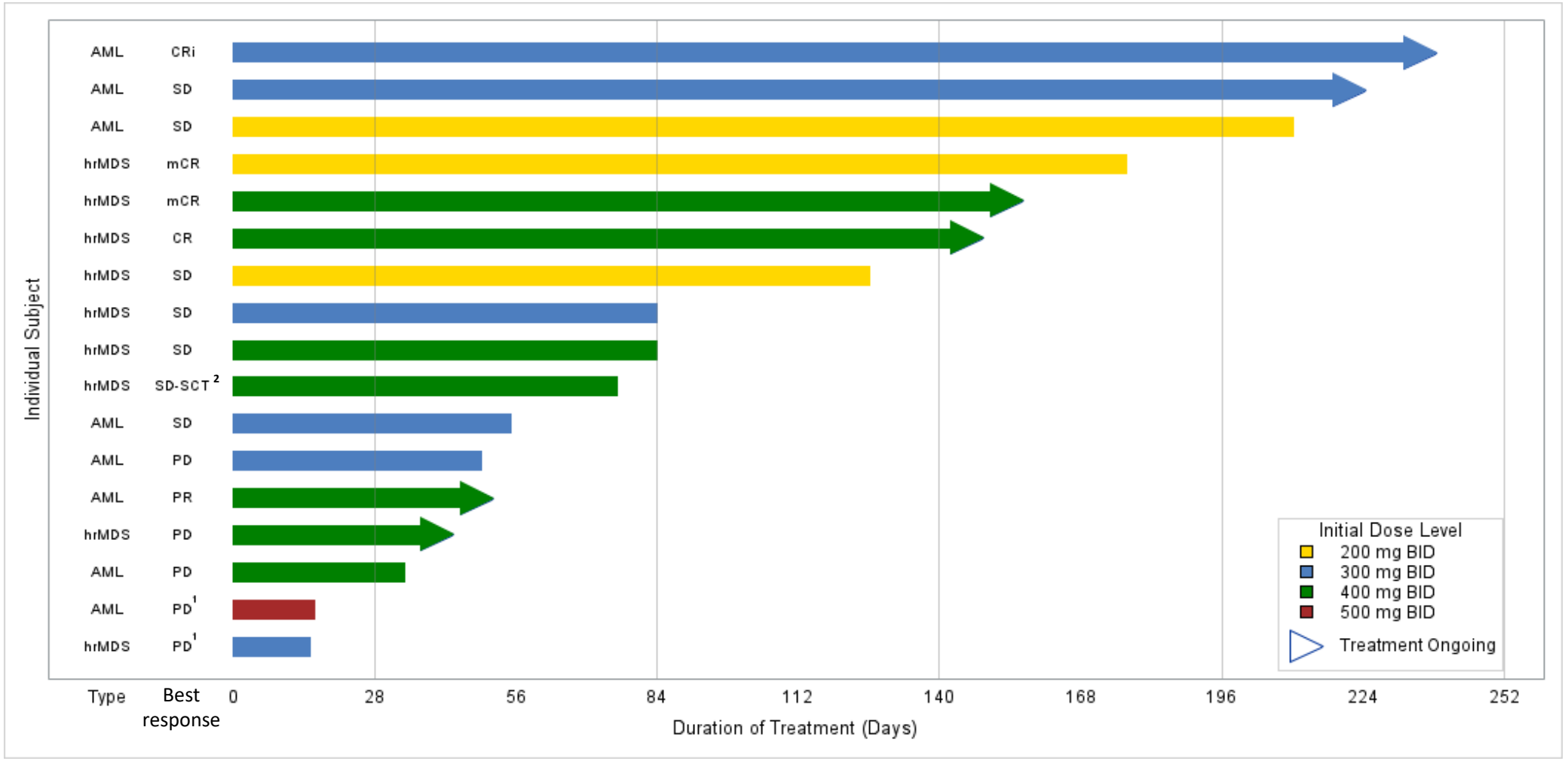
- Half-life ~6 hours
- Rapidly absorbed with maximum plasma concentrations observed at 0.5-3 hours post dose
- CA-4948 exposure levels not altered in the presence of strong CYP450 inhibitors (*e.g.*, anti-fungal azoles)
- Dose proportional exposure with minimal or no accumulation with continuous BID administration

CA-4948 mean ± SE plasma concentration versus time profile following BID oral administration



Treatment duration and patient response to CA-4948

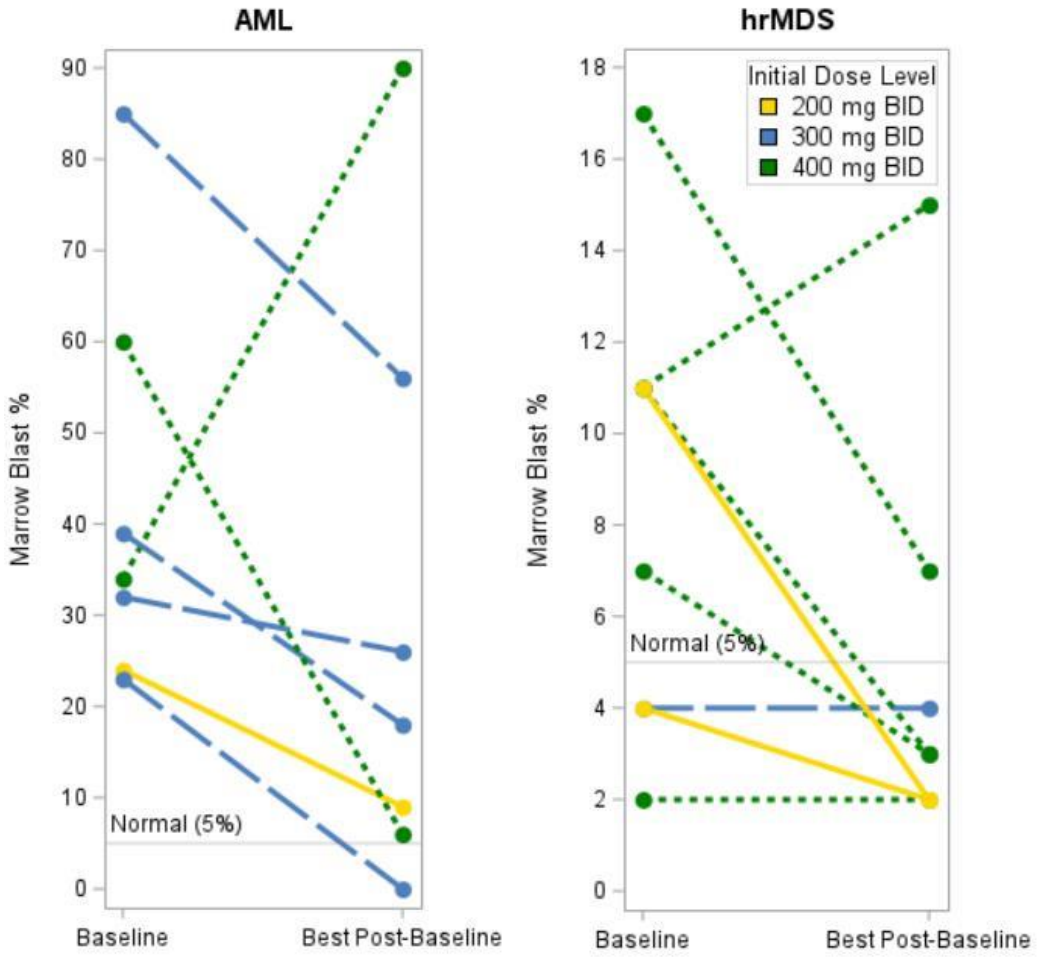
17 evaluable patients, including 5 with responses, and 1 patient who proceeded to SCT



Best Response	
hrMDS (n=9)	
CR	1
mCR	2
SD	4
PD[1]	2
AML (n=8)	
CRi	1
PR	1
SD	3
PD[1]	3

1) Includes two patients who discontinued treatment due to PD prior to first follow-up disease assessment
2) One patient who achieved SD was able to proceed to stem cell transplant (SCT)

CA-4948 reduces marrow blasts in 10 of 12 patients with elevated blast counts at baseline



Dose level	Diagnosis	Baseline blast (%)	Post-tx blast (%)	Change
200 mg BID	hrMDS	11	2	-82%
	AML	24	9	-63%
	hrMDS	4	2	-50%
300 mg BID	hrMDS	4	4	0%
	AML	23	0	-100%
	AML	39	18	-54%
	AML	32	26	-19%
	AML	85	56	-34%
	hrMDS	11	n/a	n/a
400 mg BID	AML	60	6	-90%
	hrMDS	17	7	-59%
	hrMDS	7	3	-57%
	hrMDS	2	2	0%
	hrMDS	11	15	36%
	hrMDS	11	3	-73%
	AML	34	90	165%
500 mg BID	AML	28	n/a	n/a

17 evaluable patients, including 2 discontinued treatment due to PD prior to disease assessment

Durable responses achieved in a high-risk population

- Responses achieved in heavily pre-treated, late line patient population
- Responses achieved in spliceosome and FLT3 mutated patients supports CA-4948 dual mechanism of action
- FLT3 patient had 90% blast reduction at C2D1 (from 60% to 6%)

Dx	Cytogenetics ELN or IPSS-R[3]	Molecular Mutations	Prior Lines Tx (#)	Prior Tx	CA-4948 Duration (months)	Best Response to CA-4948
t-hrMDS[1]	Intermediate	ASXL1, NF1, PHF6, **U2AF1**	1	azacitidine	6	Marrow CR
sAML[2]	Favorable	RUNX1, WT1, **SF3B1**	1	decitabine	8	CRi MRD-
AML	Intermediate	CBLC, DNMT3A, SMC1A, IDH2, STAG2, ETV6	4	daunorubicin/cytarabine idarubicin/cytarabine cytarabine/mitoxantrone high dose cytarabine	7	SD
hrMDS	Intermediate	CEP8	1	decitabine	5	CR
hrMDS	Poor	RUNX1, NFE2, **SF3B1**	2	guadecitabine lenalidomide	5	Marrow CR
sAML[2]	Adverse	ASXL1, CSF3R	3	azacitadine, lenalidomide cytarabine/daunorubicin	7	SD
AML	Adverse	**FLT3**, ASXL1, BCOR, CEBPA, CSF3R, EZH2, NRAS, RUNX1, STAG2, TET2	2	decitabine/venetoclax gilteritinib	2	PR

1) t-hrMDS: therapy related hrMDS
2) sAML: secondary AML
3) ELN scoring for AML; IPSS-R scoring for hrMDS

Signs of hematologic improvement observed in patients achieving significant marrow blast reduction

- Following reduction in marrow blasts, patients saw signs of hematologic recovery
- Full hematologic recovery may be delayed or prevented by damage to the marrow from both disease and prior lines of cytotoxic therapy
- Patients who have not seen marrow blast reduction return to normal range have experienced limited or no hematologic recovery

mCR
82% blast reduction (11 to 2)
1 prior lines of therapy

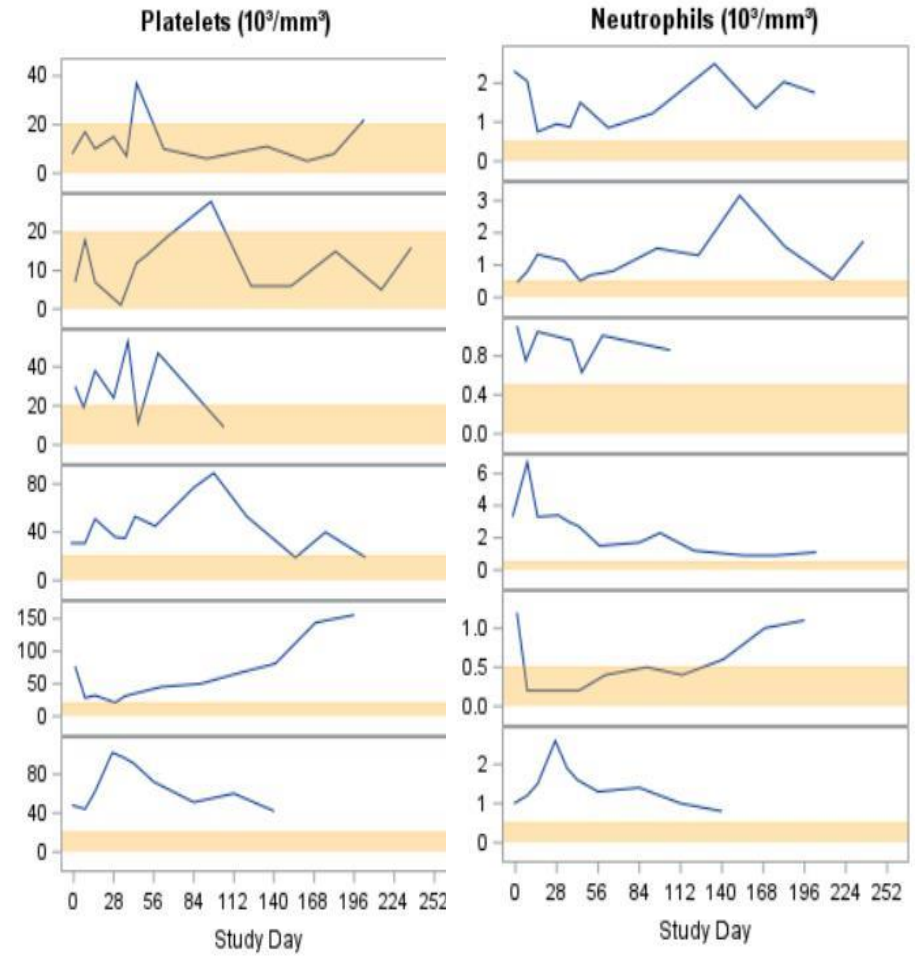
SD
63% blast reduction (24 to 9)
3 prior lines of therapy

mCR
57% blast reduction (7 to 3)
2 prior lines of therapy

CRi, MRD-
100% blast reduction (23 to 0)
1 prior lines of therapy

SD
54% blast reduction (39 to 18)
4 prior lines of therapy

CR
73% blast reduction (11 to 3)
1 prior lines of therapy

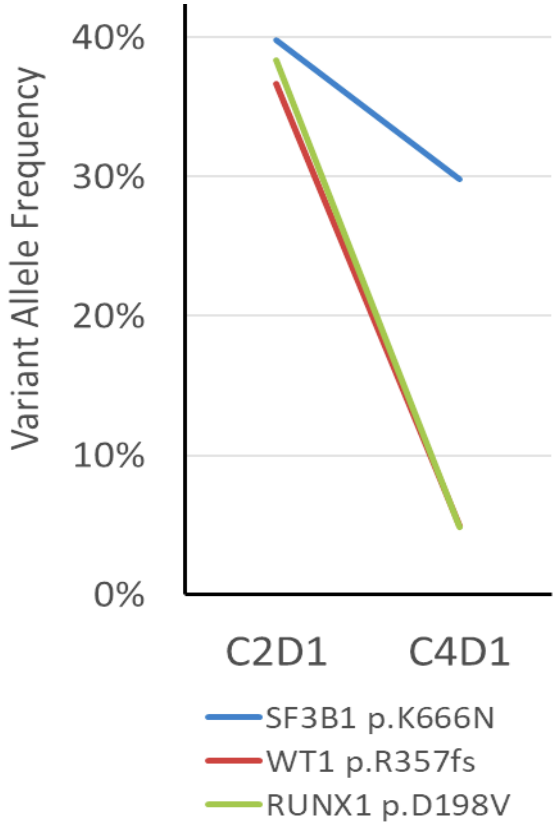


Orange bands denote increased bleeding or infection risk : < $20x10^3/mm^3$ for platelets and < $0.5x10^3/mm^3$ for neutrophils.

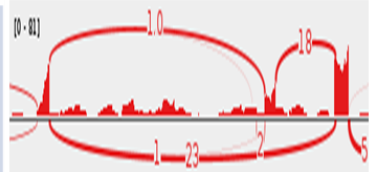
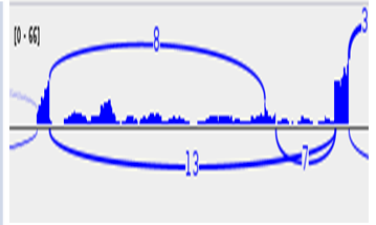
Genomic analyses suggest disease-modifying activity of CA-4948

- Genomic analyses depicted are from samples of two patients
- DNA sequencing demonstrates the reduction of variant allele frequency after CA-4948 treatment
- RNA sequencing demonstrates the reduction of long/short ratio of IRAK4 after CA-4948 treatment

NGS
Patient DNA Sequencing



RNA-seq
Patient RNA Sequencing

CA-4948 Tx Cycle	Long/Short Ratio	3 EXON 4 5
Control: Healthy CD34	18/23 (0.78)	
C2D1	8/7 (1.14)	
C4D1	7/13 (0.53)	

Summary

- Oral CA-4948 monotherapy is safe and well tolerated at 200 mg, 300 mg, and 400 mg BID
- Dose proportional exposure with minimal or no accumulation with continuous BID administration
- Clear anti-cancer activity in R/R AML and hrMDS patients
  - Three of 3 evaluable patients with IRAK4-related spliceosome mutations achieved a marrow CR or better
  - Patients with objective response also showed signs of hematologic recovery
- The study is ongoing
- The future direction
  - Expansion of monotherapy into molecularly defined subgroups (*e.g.*, spliceosome and FLT3 patient populations)
  - Expansion into combination therapy, including azacitidine and venetoclax

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