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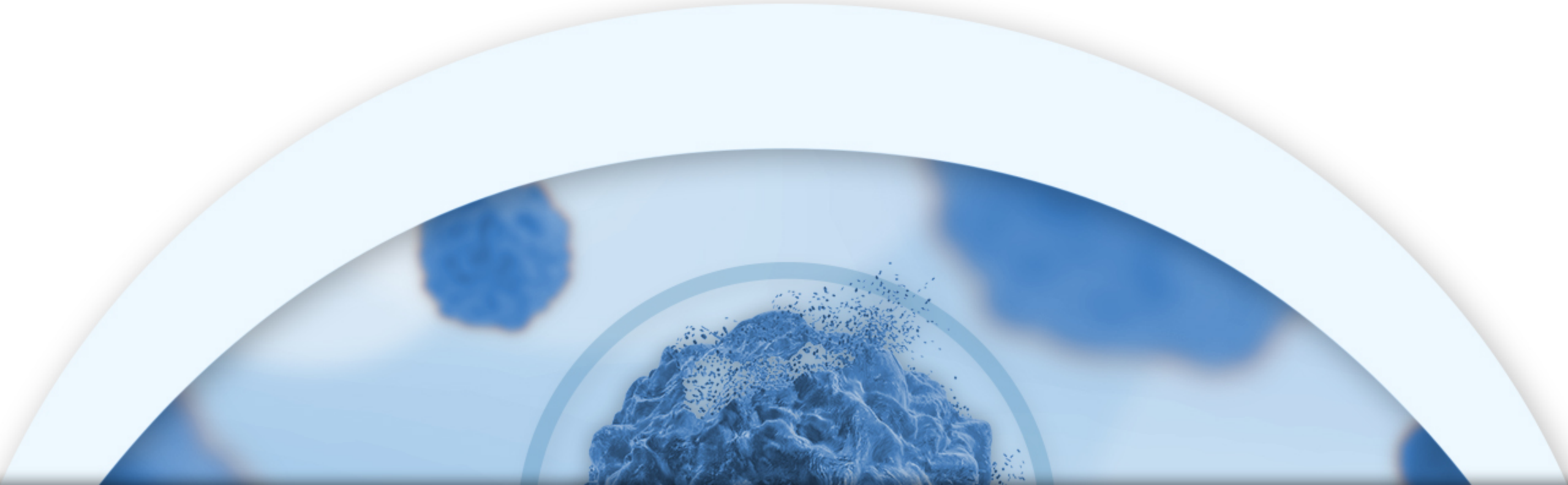
CA-4948 Clinical Study

in Acute Myeloid Leukemia (AML) and high-risk Myelodysplastic Syndrome (hrMDS)



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Cancer Biology and CA-4948

Cancer Biology and CA-4948

Introduction

Curis is developing the leading IRAK4/FLT3 inhibitor,
specifically designed to treat cancer with a new and novel mechanism

IRAK4

A cancer-causing form of the IRAK4 kinase occurs in over 50% of patients with AML/MDS[1]. In its normal form, IRAK4 plays an important role in the immune system. In some patients, however, certain mutations (SF3B1, U2AF1) in the spliceosome lead to IRAK4-L, the cancer-causing long form of IRAK4 that drives leukemic cell production. CA-4948 is designed to block IRAK4-L and slow/stop the leukemia.

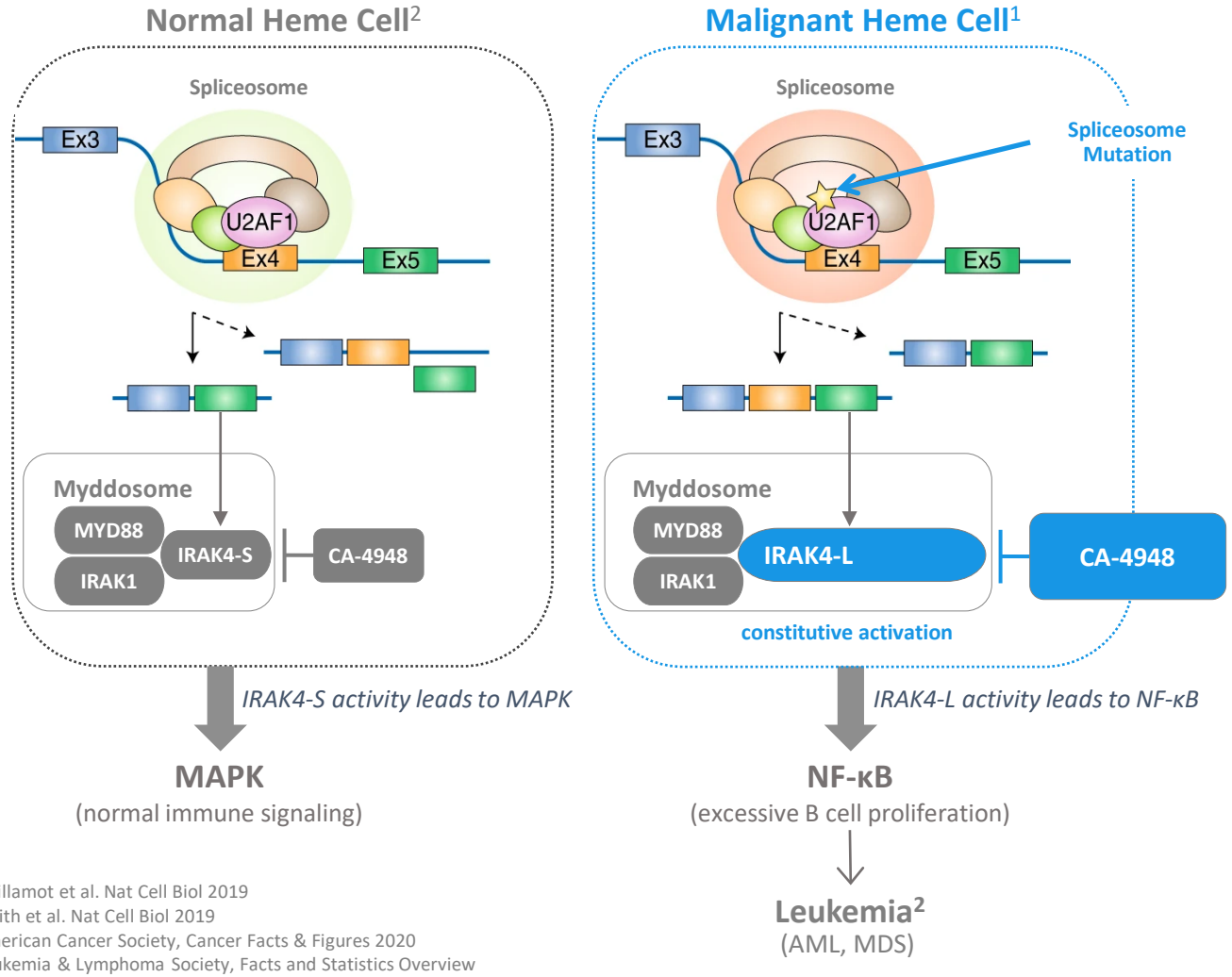
FLT3

The FLT3 gene is one of the most frequently mutated genes in AML. When mutated, FLT3 can cause leukemia or help it grow more quickly. Doctors currently use drugs called FLT3 inhibitors to treat this kind of leukemia. However, many patients see only a brief response followed by the return of the leukemia, and sometimes these FLT3 inhibitors do not work at all. New research published by oncologists at Johns Hopkins University School of Medicine[2] explains why: patients' leukemia develops resistance to the FLT3 inhibitor, and that resistance is facilitated by IRAK4. Their proposed solution to this problem is the inhibition of both FLT3 and IRAK4 at the same time, which is exactly what CA-4948 is designed to do.

1) Smith et al. Nat Cell Biol 2019
2) Rabik et al. Ann Transl Med 2020

Biology and CA-4948

Role of IRAK4 in normal vs. oncogenic activity



Specific genetic mutations (SF3B1, U2AF1) in the spliceosome drive overexpression of IRAK4-L

IRAK4-L then causes constitutive activation of the myddosome, leading to overactivity of NF-κB and excessive proliferation of B cells

1) Guillamot et al. Nat Cell Biol 2019
2) Smith et al. Nat Cell Biol 2019
3) American Cancer Society, Cancer Facts & Figures 2020
4) Leukemia & Lymphoma Society, Facts and Statistics Overview
5) IMBRUVICA Package Insert. Rev 08/2018

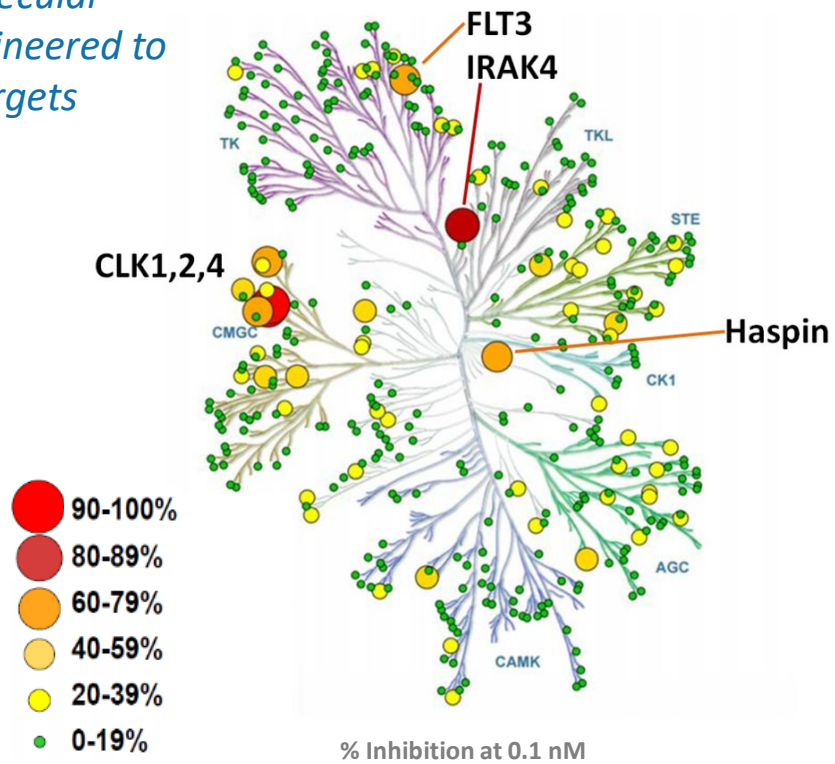
CA-4948 Targeted Design

CA-4948 is the leading IRAK4/FLT3 inhibitor in clinical development for cancer

In Nov 2020, the NCI selected CA-4948, Curis's first-in-class IRAK4 inhibitor, and entered into an agreement ("CRADA") with Curis to conduct both clinical and non-clinical studies of CA-4948 in oncology

CA-4948 "fingerprint" illustrates unique molecular signature specifically engineered to hit key oncogenic targets

CA-4948 Kinase Interaction Map



% Inhibition at 0.1 nM

Illustration reproduced courtesy of Cell Signaling Technology

CA-4948 Binding Affinity

Target	K_d nM
IRAK1	12,000
IRAK2	>20,000
IRAK3	8,500
IRAK4	**23**
DYRK1A	25
FLT3 (D835H)	5
FLT3 (D835V)	44
FLT3 (ITD)	8
FLT3 (K663Q)	47
FLT3 (N841I)	16
Haspin (GSG2)	32
CLK1	10
CLK2	20
CLK3	>20,000
CLK4	14
RET (V804L)	3,000
TrkA	130

DiscoverX Kinase Panel
(378 kinases screened)

CA-4948 binds specifically and with high affinity to both IRAK4 and FLT3

CA-4948 PK/PD

Attractive PK profile supports twice-daily dosing and high target suppression

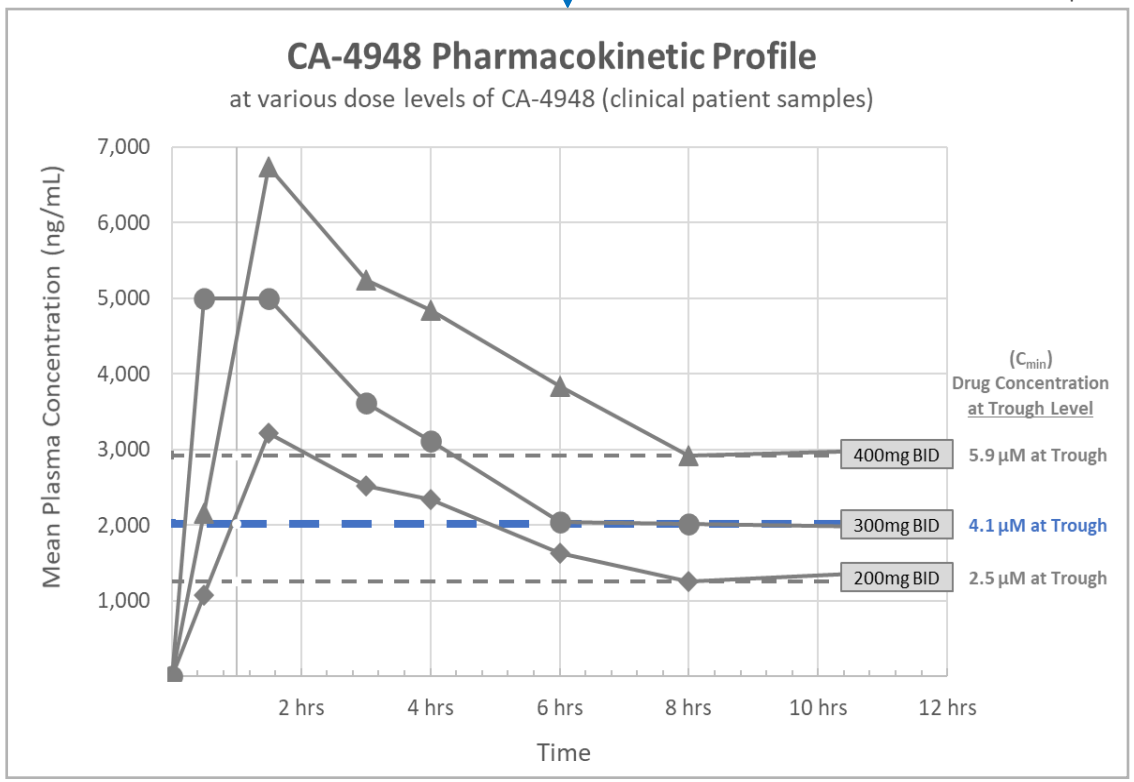
Attractive PK Profile

- Half-life of ~6 hours
- Supports BID dosing regimen

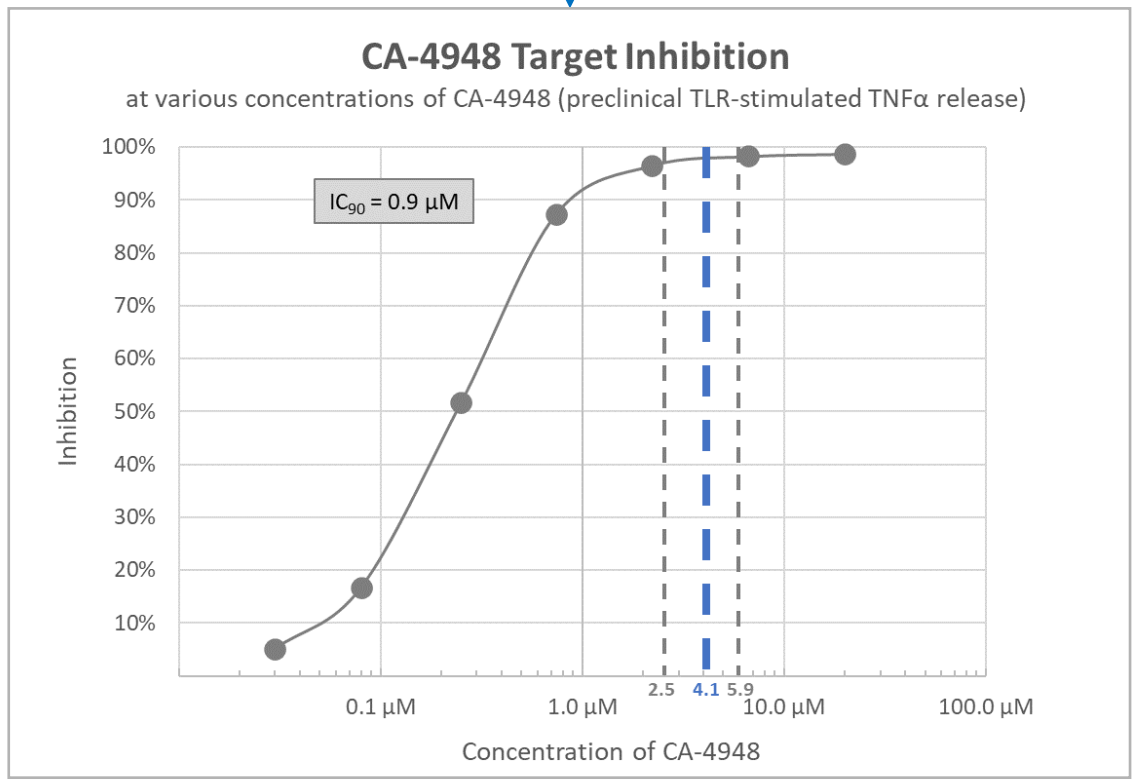
Trough Exposure	Dose	Inhibition
2.5µM	200mg	97%
4.1µM	**300mg**	**98%**
5.9µM	400mg	98%

High Target Suppression

- Exposure at RP2D correlates with 98% inhibition



Data from CA-4948 lymphoma clinical study



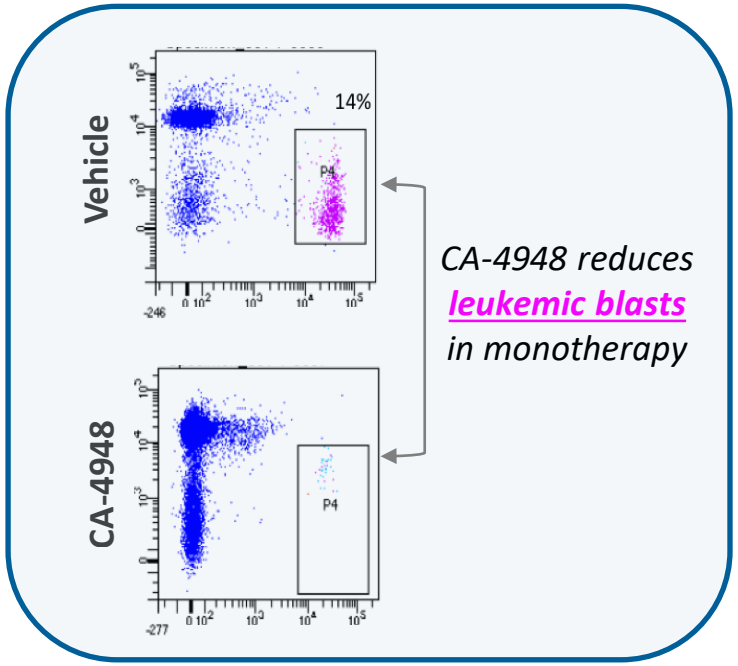
Data from preclinical study of target inhibition

CA-4948 Preclinical Data

Clear anti-cancer activity suggests broad potential across the spectrum of AML/MDS

Monotherapy

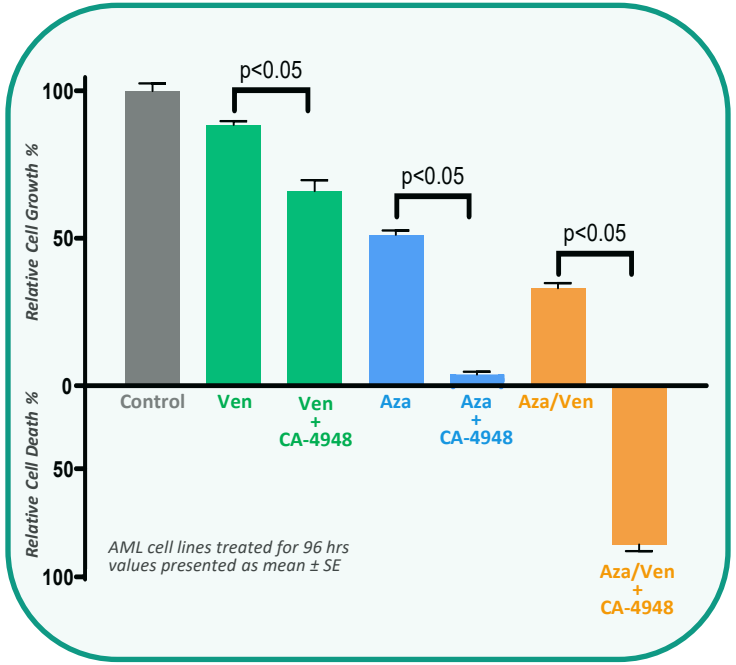
for patients with SF3B1, U2AF1, or FLT3 mutation



CA-4948 demonstrates clear monotherapy activity in patient-derived xenografts[1]

Combination Therapy

with azacitidine and/or venetoclax for the broader population



CA-4948 demonstrates clear synergy with both azacitidine and venetoclax in THP-1 model[2]

1) Choudhary et al. AACR 2017
2) Curis AML MDS poster, EHA 2021
3) Booher et al. Waldenström Roadmap Symposium 2019

CA-4948 Clinical Plan

Targeted clinical studies are enrolling patients with AML/MDS

Monotherapy

for patients with SF3B1, U2AF1, or FLT3 mutation

Specific Subpopulations

1) Patients with SF3B1, U2AF1, or FLT3 mutation
2) Patients with FLT3 mutation

Strong rationale for monotherapy for patients with targeted mutation:

- *Spliceosome mutation (SF3B1, U2AF1) is a leading cause of IRAK4-L overexpression[1]*
- *Signaling through IRAK4 is an adaptive response mechanism for FLT3 patients treated with a FLT3 inhibitor[2]*

Combination Therapy

with azacitidine and/or venetoclax for the broader population

Broader Population

1) Relapsed/Refractory patients, HMA-naïve
2) Relapsed/Refractory patients, venetoclax-naïve

R/R patients who do not have SF3B1, U2AF1, or FLT3 mutation and are ineligible for intensive chemotherapy

Note: Hypomethylating agents (HMA), such as azacitidine, are frequently used to treat MDS

Strong rationale for combination therapy in broader population

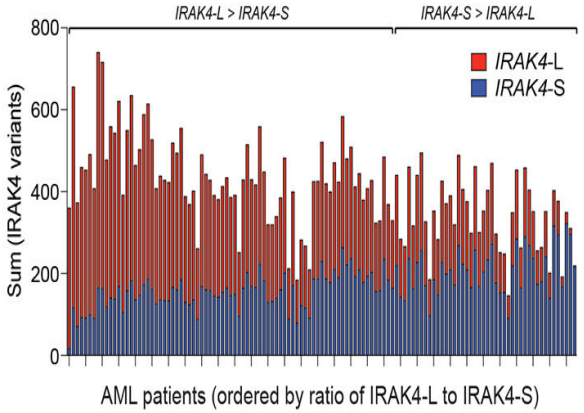
- *Clinical data show CA-4948 reduces tumor burden in the significant majority of evaluable patients*
- *Preclinical data demonstrate synergy with azacitidine and venetoclax*

1) Smith et al. Nat Cell Biol 2019
2) Rabik et al. Ann Transl Med 2020

CA-4948 in AML/MDS

Clinical studies designed to leverage the role of IRAK4 and FLT3 in AML/MDS

Disease Driver	% of Patient Population
IRAK4-L	> 50%[1]
FLT3	25-30%[2]
TET2	10-20%[3]
IDH2	9-13%[4]
IDH1	6-10%[4]
CEBPA	~10%[3]



Rationale for Monotherapy

- IRAK4 / FLT3 is the largest targeted population in AML/MDS[1,2]
- Spliceosome mutation (SF3B1, U2AF1) is a leading cause of IRAK4-L overexpression[1]
- Signaling through IRAK4 is an adaptive response mechanism for FLT3 patients treated with a FLT3 inhibitor[5] (unblocked IRAK4 signaling limits the efficacy of current FLT3 drugs; CA-4948 blocks both FLT3 and IRAK4)

Rationale for Combination

- Nearly all patients express some level of IRAK4-L[1]
- Clinical data show that blocking IRAK4-L with CA-4948 reduces tumor burden in the significant majority of evaluable patients
- Preclinical data demonstrate clear synergy with azacitidine and venetoclax
    - *IRAK4 stimulates NF-κB and ultimately an array of anti-apoptotic factors (beyond BCL2) which prevent the effectiveness of anti-leukemic drugs*
    - *Blocking this effect with CA-4948 synergistically enhances the anti-cancer efficacy of those agents in preclinical models*

1) Smith et al. Nat Cell Biol 2019
2) Saygin, et al. J Hematol Oncol. 2017 Apr 18
3) DiNardo, Cortes. Hematology Am Soc Hematol Educ Program. 2016
4) DiNardo et al. N Engl J Med 2018
5) Rabik et al. Ann Transl Med 2020

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Clinical Data in AML/MDS

CA-4948 in AML/MDS

Study design and patient characteristics

Patients enrolled this study were very sick at baseline; >90% of patients enrolled had intermediate or worse cytogenetic risk

Phase 1/2 Study

- Open-label, single arm
- Dose escalation and expansion

Study Objectives

1°: Determine maximum tolerated dose
Determine recommended Phase 2 dose

2°: Pharmacokinetic (PK) profile
Preliminary anti-cancer activity

Study Population

- Relapsed/Refractory AML or High-Risk MDS
- ECOG performance Status of ≤ 2
- Age ≥ 18 years

Dosing

- Oral, Twice Daily (BID) Dosing
- 28-day cycles
- 3+3 escalation

(200mg → 300mg → 400mg → 500mg)
3 patients 6 patients 10 patients 3 patients

Baseline Patient Characteristics		Patients (n=22)
Female n (%) : Male n (%)		5 (23) : 17 (77)
Median Age		74 yrs
ECOG: n 0/1/2		7 / 11 / 4
Cytogenetic Risk[3] n (%)	AML (favorable, intermediate, adverse)	1 (10) , 2 (20) , 7 (70)
	hrMDS (good, intermediate, poor, very poor)	1 (9) , 4 (36) , 3 (27) , 3 (27)
Diagnosis n (%)	AML	11 (50)
	AML	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)
Relevant Mutations	FLT3	1
	SF3B1	2
	U2AF1	2

Data cut-off: 30Apr2021

CA-4948 in AML/MDS

Preliminary safety data demonstrate safety and tolerability

Predictable and manageable safety profile

- MTD not exceeded until 500mg BID (twice daily)
- No dose-limiting toxicities related to myelosuppression
- No overlap in dose-limiting toxicities with azacitidine and venetoclax, which are planned for combination with CA-4948
- Dose-limiting side effect at higher doses consists of uncomplicated rhabdomyolysis (elevated CPK and muscle soreness), was manageable, quickly and easily detected, readily reversible, and did not limit further treatment at a reduced dose level

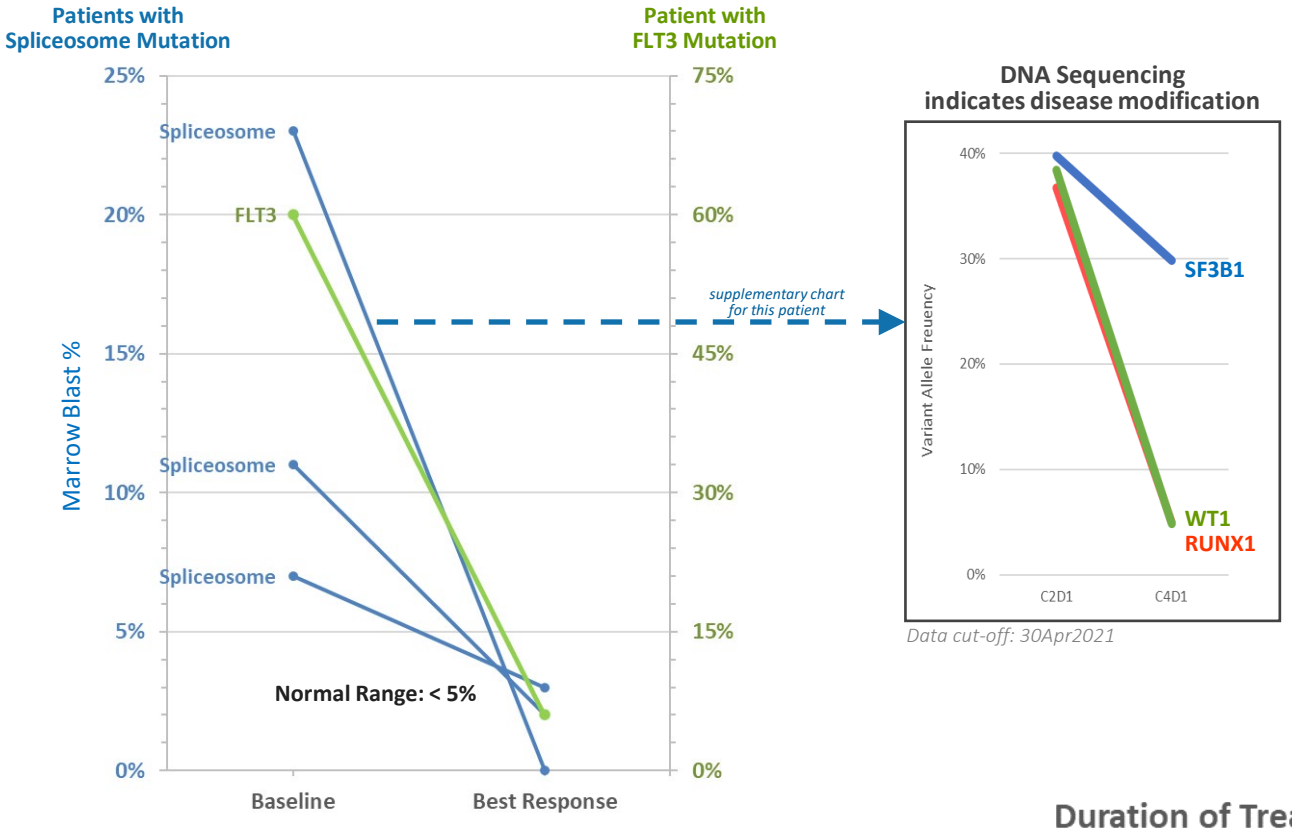
Key Observations

CA-4948 has completed initial Phase 1 testing and a dose has already been determined (300mg twice daily) that is safe and shows clear anti-cancer activity

Especially important, CA-4948 dosing was not limited by damage to the bone marrow, which is a life-threatening problem many other cancer treatments have

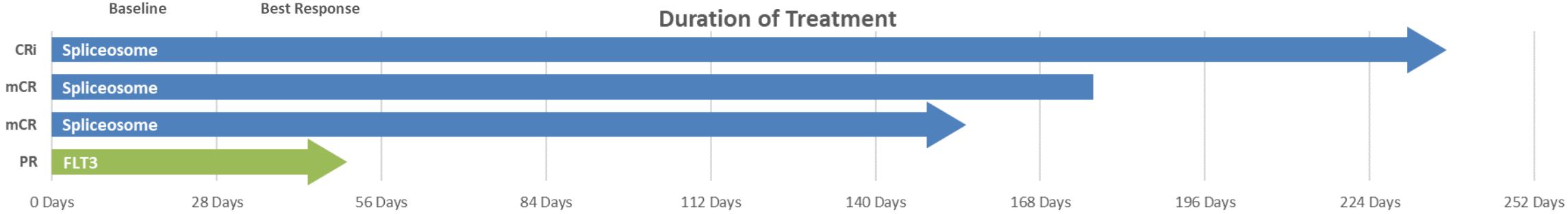
Preliminary Clinical Data: Specific Population in Monotherapy

Clear monotherapy efficacy in patients with spliceosome and FLT3 mutation



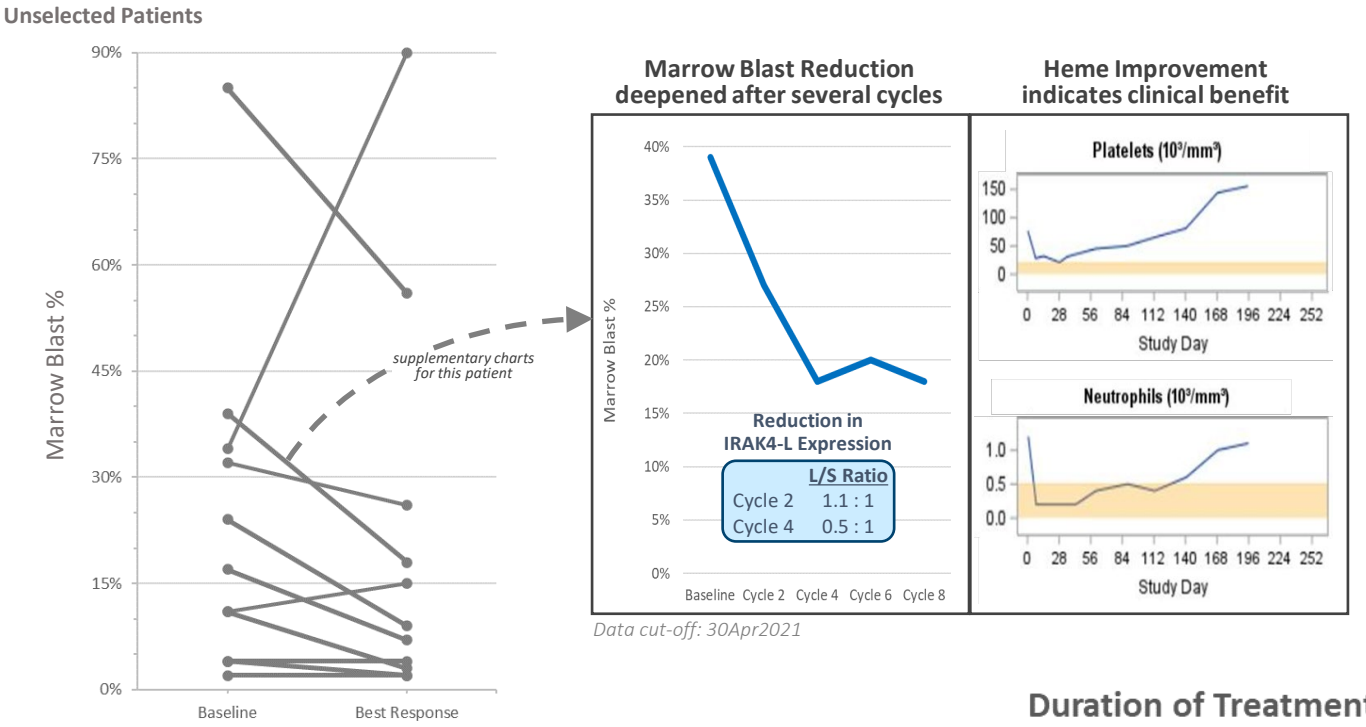
Data cut-off: 30Apr2021

- *4 of 4 evaluable patients w/ targeted mutation achieved objective response*
- *Ablation of cancer confirmed by genetic or morphologic analysis*



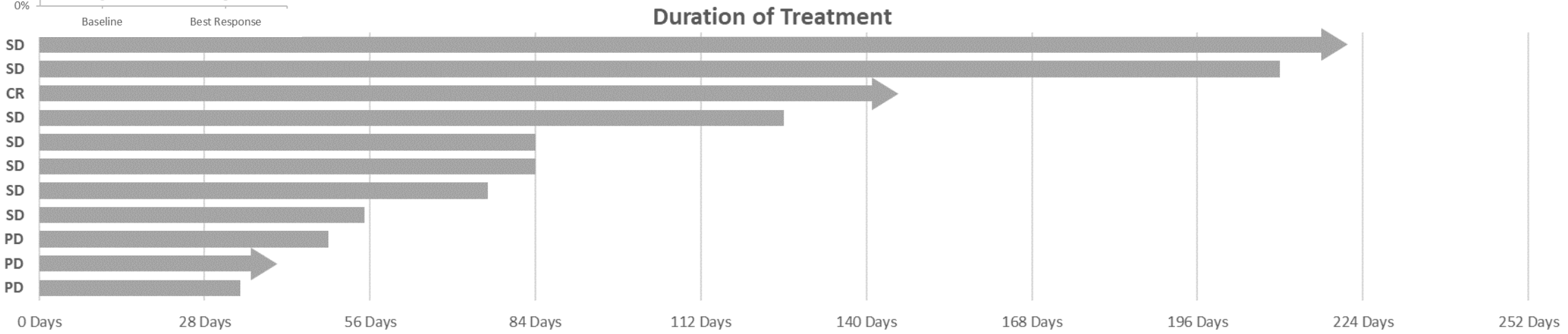
Preliminary Clinical Data: Broader Population in Combination

Efficacy data support use even in patients without spliceosome/FLT3 mutation



Data cut-off: 30Apr2021

- *9 of 11 evaluable patients w/o targeted mutation achieved tumor reduction or maintained counts in normal range*
- *These data support the rationale for adding CA-4948 to a combination therapy regimen for patients without SF3B1, U2AF1, or FLT3 mutation*



CA-4948 in AML/MDS

Clear biologic activity and durable responses

- Clear anti-cancer activity and objective responses in patients with SF3B1, U2AF1, FLT3 mutation support expansion of monotherapy study
  - In population targeted for monotherapy, 4 of 4 patients achieved objective response
  - Ablation of cancer confirmed by genetic or morphologic analysis
- Clear anti-cancer activity in patients without targeted mutation suggests opportunity to combine CA-4948 with azacitidine and/or venetoclax for the broader population

Next Steps in Expansion

For patients with SF3B1, U2AF1, FLT3 mutation:

- *Monotherapy*

For patients without SF3B1, U2AF1, FLT3 mutation:

- *Combination: CA-4948 + azacitidine*
- *Combination: CA-4948 + venetoclax*