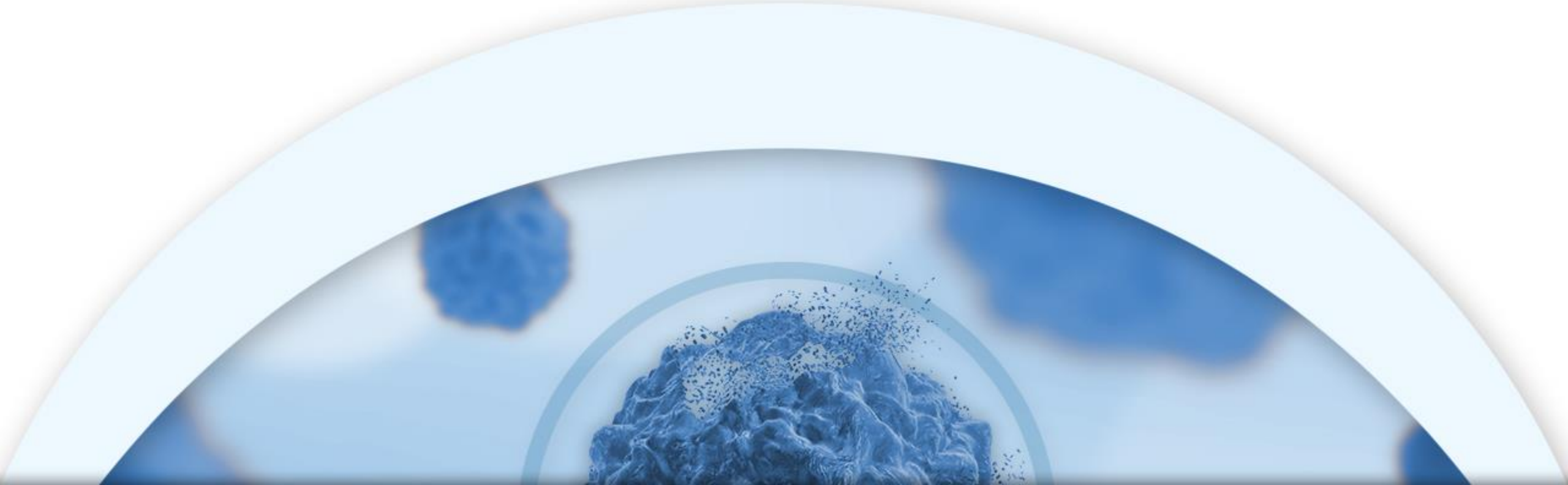
CA-4948 & CI-8993 Clinical Data Update

January 2022



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Today's Participants

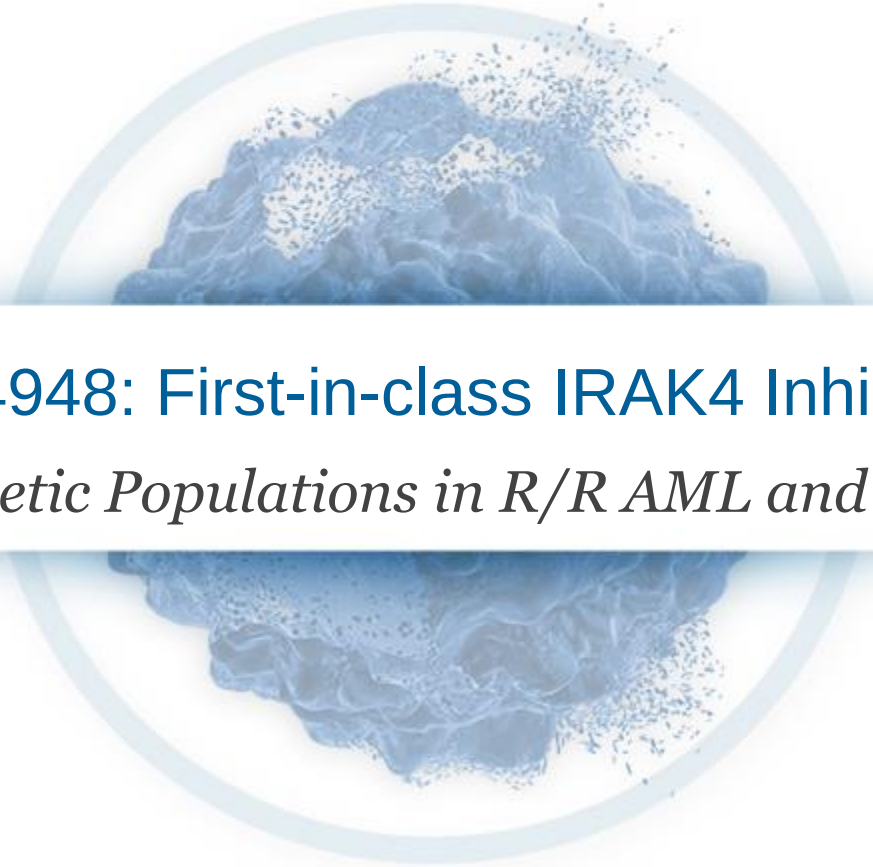
- James Dentzer — President & Chief Executive Officer at Curis
- Robert Martell, MD, PhD — Head of R&D at Curis
- Daniel DeAngelo, MD, PhD — Chief, Division of Leukemia at Dana-Farber Cancer Institute

Introductory Remarks

Clinical update on CA-4948 (IRAK4) and CI-8993 (VISTA)

- CA-4948 addresses a novel target (IRAK4) and:
  - (1) demonstrates clear anti-cancer activity as an oral single agent
  - (2) is active in genetically-defined populations that can be identified and enrolled
  - (3) has the added potential benefit of also hitting FLT3

- CI-8993 addresses a novel target (VISTA) and:
  - (1) has successfully cleared dose level where Janssen observed dose-limiting toxicity (DLT)
  - (2) with pharmacodynamic effects suggesting multiple anti-cancer mechanisms are being activated

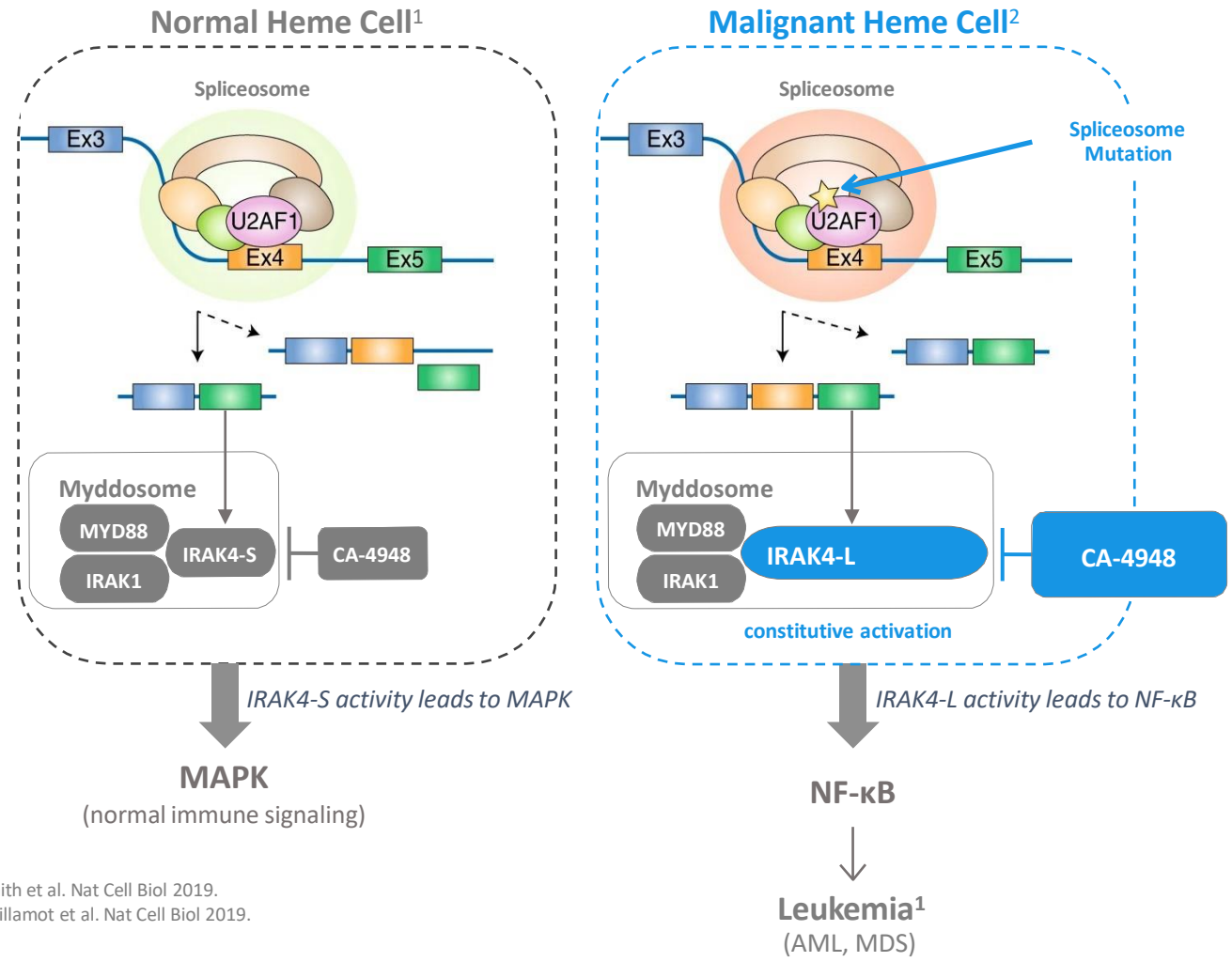


CA-4948: First-in-class IRAK4 Inhibitor

Targeting Specific Genetic Populations in R/R AML and high-risk MDS (MDS)

Biology and CA-4948

Role of IRAK4 in AML/MDS (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

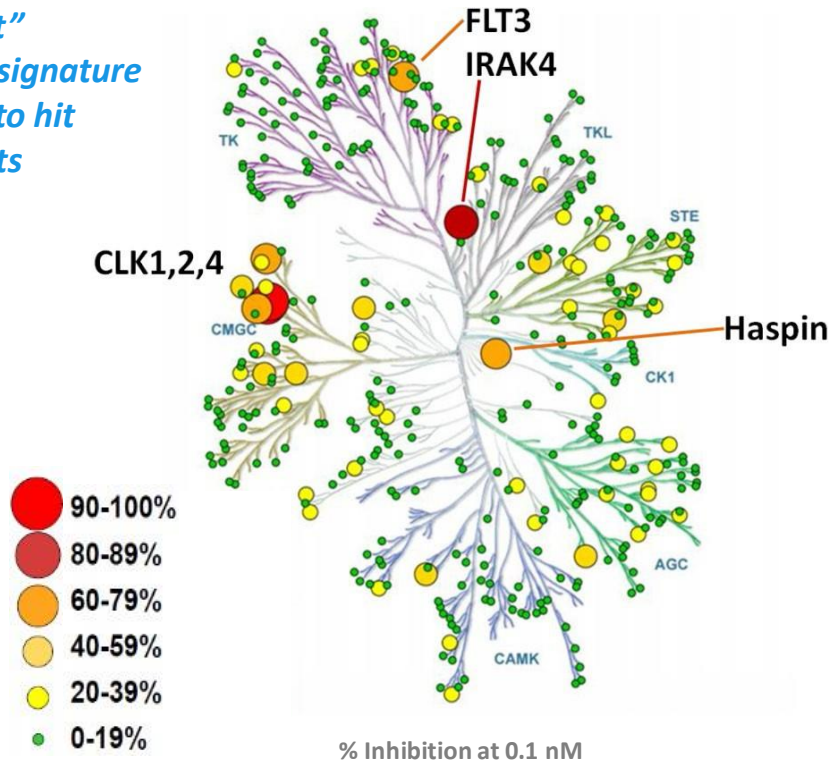
1. Smith et al. Nat Cell Biol 2019.
2. Guillamot et al. Nat Cell Biol 2019.

CA-4948 is the Leading IRAK4 Inhibitor in Development for Cancer

Targeted design offers added potential benefit of also hitting FLT3

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

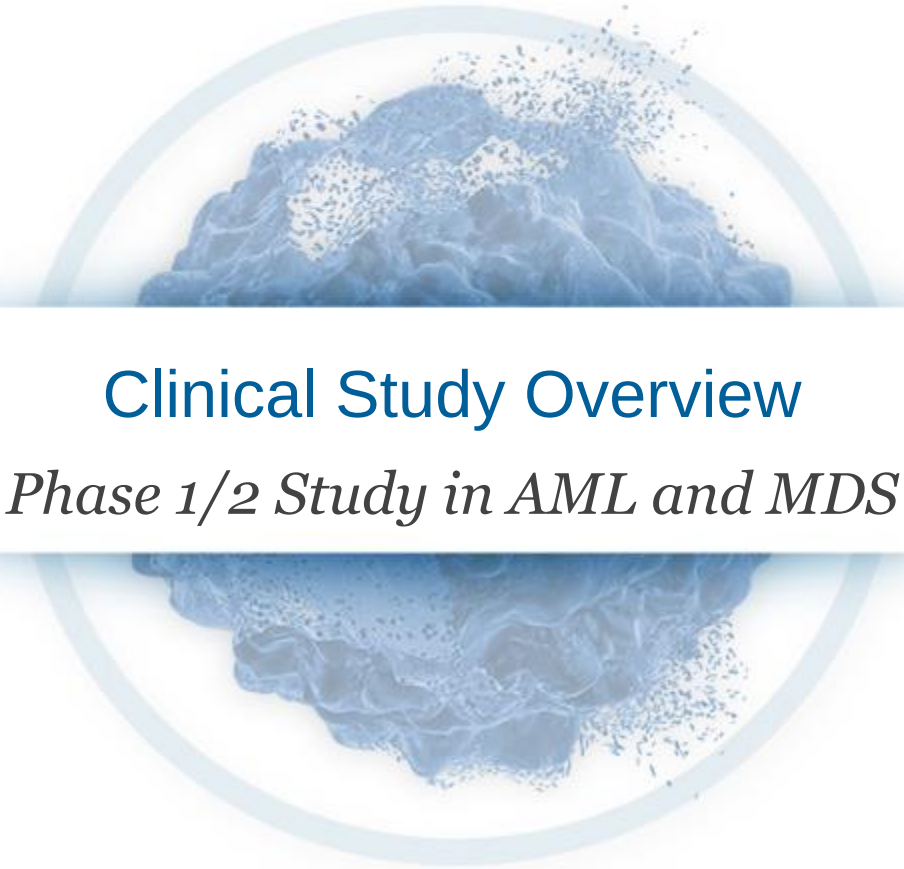
CA-4948 Binding Affinity

Target	K_d nM
IRAK1	12,000
IRAK2	>20,000
IRAK3	8,500
IRAK4	**23**
DYRK1A	25
FLT3 wt	**31**
FLT3 (D835H)	**5**
FLT3 (D835V)	**44**
FLT3 (D835Y)	**3**
FLT3 (ITD)	**8**
FLT3 (K663Q)	**47**
FLT3 (N841I)	**16**
Haspin (GSG2)	32
CLK1	10
CLK2	20
CLK3	>20,000
CLK4	14
TrkA	130

DiscoverX Kinase Panel
(378 kinases screened)

CA-4948 binds specifically and with high affinity to IRAK4

Dual targeting of IRAK4 and FLT3 confers a potential efficacy advantage vs. other IRAK4 inhibitors and expands potential to additional genetic populations

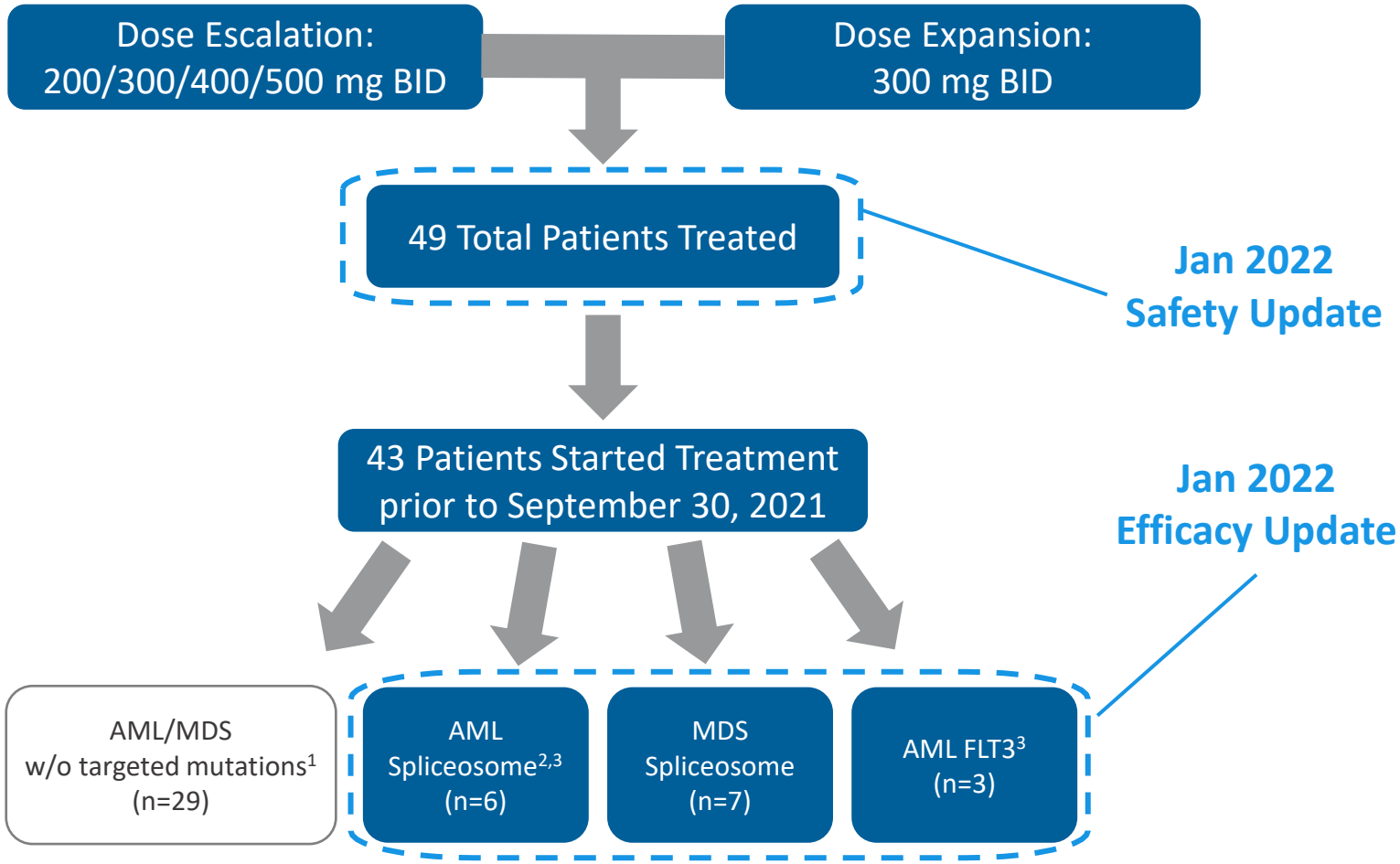


Clinical Study Overview

Phase 1/2 Study in AML and MDS

CA-4948 in AML and MDS

Open-label, single arm, Phase 1/2 dose escalation and expansion study



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

Data extraction date: Dec 16, 2021

1. These are non-targeted patients, due to lack of Spliceosome or FLT3 mutation, this population will be addressed in the combination therapy study; 2. One patient was not response evaluable because of discontinuation due to patient decision;
3. Two AML patients have both a spliceosome and FLT3 mutation and are included in both populations (there are 13 total evaluable patients with Spliceosome or FLT3 mutation)

Well-Tolerated and Manageable AE Profile for CA-4948 in AML/MDS with No Cumulative Toxicities Observed

No Grade 4 or 5 TRAEs reported; all AEs were manageable

Recommended Phase 2 Dose

Grade 3+ Treatment-Related Adverse Event	200 mg BID (N = 3)		300 mg BID (N = 26)		400 mg BID (N = 17)		500 mg BID (N = 3)	
	n (%)		n (%)		n (%)		n (%)	
Number of patients having grade 3+ treatment-related AEs	1	(33.3)	6	(23.1)	6	(35.3)	2	(66.7)
Alanine aminotransferase increased	1	(33.3)	0		0		0	
Blood creatine phosphokinase increased	0		1	(3.8)	0		0	
Dizziness	1	(33.3)	0		0		0	
Dyspnoea	0		0		1	(5.9)	0	
Enterobacter infection	0		0		1	(5.9)	0	
Fatigue	0		0		1	(5.9)	0	
Gastrointestinal haemorrhage	0		1	(3.8)	0		0	
Hypophosphataemia	0		1	(3.8)	0		0	
Hypotension	0		1	(3.8)	0		0	
Lipase increased	0		2	(7.7)	0		0	
Platelet count decreased	0		1	(3.8)	0		0	
Presyncope	0		0		1	(5.9)	0	
Rhabdomyolysis	0		1	(3.8)	2	(11.8)	1	(33.3)
Syncope	0		0		0		1	(33.3)

Data extraction date: Dec 16, 2021.

1. Data for the two patients that have escalated from 300 mg BID to 400 mg BID were included in the 400 mg BID dose group.

Well-tolerated and manageable AE profile with no cumulative toxicities reported

No dose-limiting myelosuppression reported, which is a life-threatening problem characteristic of many cancer treatments, making CA-4948 favorable for combinations

Clinical Data Overview: Three Targeted Patient Populations

(1) AML Spliceosome, (2) MDS Spliceosome, (3) AML FLT3

Heavily Pretreated Patient Population

Baseline Characteristics of AML/MDS Subsets

		AML Spliceosome[1] (n=6)	MDS Spliceosome (n=7)	AML FLT3[1] (n=3)
Female n (%) : Male n (%)		0 (0) : 6 (100)	5 (71) : 2 (29)	0 (0) : 3 (100)
Age (yrs): median (range)		76 (60, 84)	74 (61, 80)	80 (78, 87)
ECOG: n 0/1/2		0/4/2	2/5/0	0/1/2
Median platelets (10^3/mm^3) (range)		28 (21, 80)	16 (7, 146)	21 (9, 23)
Median ANC (10^3/mm^3) (range)		0.23 (0, 3.3)	1.85 (0.15, 11.0)	0.05 (0, 0.11)
Median lines of prior therapy (range)		2.5 (1, 4)	2 (1, 4)	2 (1, 4)
Risk Category (ELN): Favorable / Intermediate / Adverse		0/3/3	NA	0/1/2
IPSS-R: Low / Intermediate / High / Very High		NA	0/0/2/5	NA
Prior therapy, n (%)	HMA[2]	6 (100)	7 (100)	3 (100)
	Chemotherapy[3]	3 (50)	0 (0)	1 (33)
	Venetoclax	4 (67)	1 (14)	3 (100)

Data extraction date: Dec 16, 2021.

1. Two AML patients have both a spliceosome and FLT3 mutation and are included in both populations (there are 13 total evaluable patients with Spliceosome or FLT3 mutation); 2. HMA includes azacitidine, decitabine, and guadecitabine; 3. Chemotherapy includes cytarabine.

Patient demographics indicate older population with poor prognosis; all patients received prior hypomethylating agent (HMA) therapy

Encouraging Clinical Activity in R/R AML/MDS Patient Populations

CA-4948 shows activity as a monotherapy in patients with Spliceosome and FLT3 mutations

Best Response	Efficacy
Population #1: AML Spliceosome Patients[1]	
CR/CRh Rate	**2/5 (40%)**
CR	1/5 (20%)
CRh	1/5 (20%)
Population #2: MDS Spliceosome Patients	
Objective Response Rate (ORR)	**4/7 (57%)**
CR	0/7 (0%)
mCR	4/7 (57%)
Population #3: AML FLT3 Patients[1]	
CR/CRh Rate	**1/3 (33%)**
CR	1/3 (33%)
CRh	0/3 (0%)

Data extraction date: Dec 16, 2021.
1. Two AML patients have both a spliceosome and FLT3 mutation and are included in both populations (there are 13 total evaluable patients with Spliceosome or FLT3 mutation).

Response criteria per 2017 ELN Criteria for AML and Modified IWG Criteria for MDS:
CR = Complete Remission
CRh = CR with partial hematologic recovery
mCR = marrow CR

The CR and CRh patients are both MRD-negative

1 mCR patient went to Stem Cell Transplant (SCT)

FLT3 mutation eradicated in 2 out of 3 patients

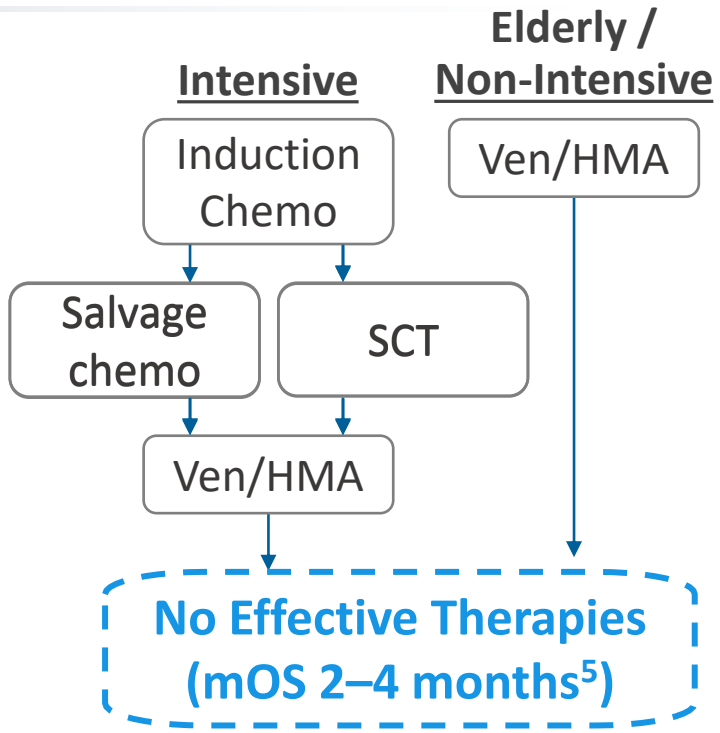
Clinical Data: R/R AML Patients with Spliceosome Mutation

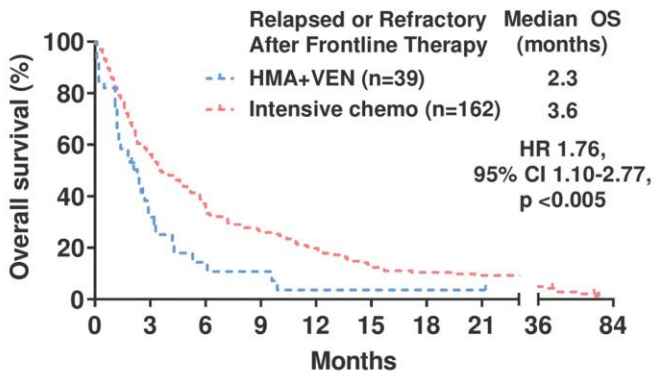
Patient Population #1

Unmet Need for R/R AML Patients with Spliceosome Mutation

No approved targeted therapies and no unified standard of care for these patients

- Spliceosome mutations occur in ~10% of AML patients[1]
  - These mutations create a chronic inflammatory marrow microenvironment[2], which impairs hematologic recovery[3]
  - Ability to achieve CR is impaired in patients with U2AF1/SF3B1 mutation[4]
- There are no effective therapies for patients R/R to Ven/HMA: no unified standard of care





Opportunity to meaningfully improve outcomes in R/R AML patients with spliceosome mutations

1. DiNardo et al, Hematology Am Soc 2016; 2. Smith et al. Nat Cell Biol 2019; 3. Trowbridge JEM 2021. Ochi Cancers 2021. Hou, Oncotarget 2016; 4. Hou, Oncotarget 2016; 5. Maiti et al. Haemtologica 2021

Initial CA-4948 Data Compare Favorably to Existing Therapies

Potential to meaningfully improve outcomes in R/R AML patients with spliceosome mutation

Most Commonly Used in R/R AML with Wild Type FLT3/IDH[1]

CA-4948	Decitabine[2,3]	Azacitidine[2,4]	LoDAC[5]	Gemtuzumab Ozogamicin[2,6]
IRAK4 Inhibitor	*HMA*	*HMA*	*Chemotherapy*	*Monoclonal Anti-CD33 Antibody (ADC)*
• 40% CR/CRh rate (2 of 5 patients)	• ~16% CR rate	• 17% CR/CRi rate	• ~13% ORR	• ~26% CR
• No dose-limiting myelosuppression	• Myelosuppressive	• Myelosuppressive	• Myelosuppressive and Black Box Warning	• Myelosuppressive and Black Box Warning
• Oral Administration	• IV Administration	• IV or SC Administration	• IV Administration	• IV Administration

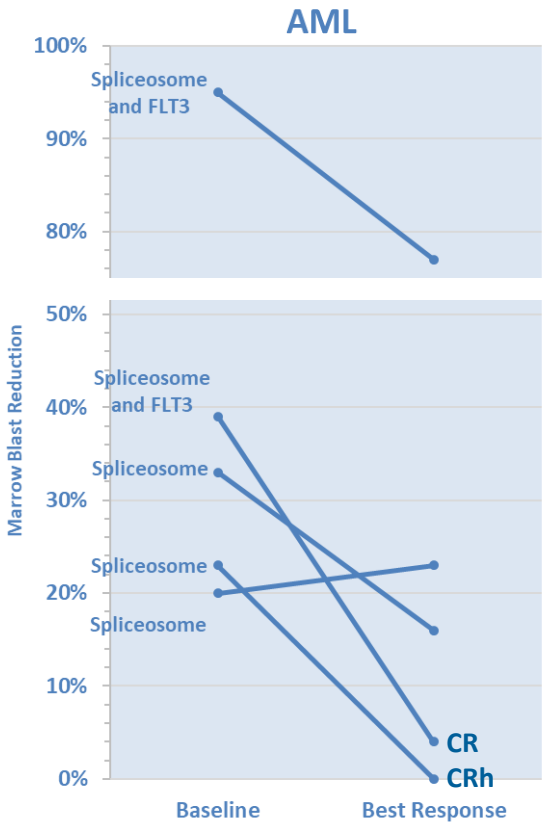
>6 months on CA-4948 for patients with CR/CRh

1. CancerMPact Treatment Architecture U.S. AML, Cerner Enviza, www.cancermpact.com, accessed January 3, 2022. Excludes Investigational Therapies; 2. Product Package Insert; 3. Ritchie et al, Leuk Lymphoma 2013; 4. Itzykson et al, Leuk Res 2014; 5. Frikha et al, Bulletin du Cancer 1996; 6. Gemtuzumab ozogamicin is only approved for patients with newly-diagnosed CD33-positive AML or R/R CD33-positive AML

Initial CA-4948 data compare favorably vs. historical responses with mainstay treatments for R/R AML patients with wild type FLT3/IDH

Encouraging Clinical Activity in R/R AML Patients with Spliceosome Mutation

Achieved 40% CR/CRh rate, with treatment duration >6 months to date in responding patients



Dx	Dose (BID)	Risk Category (ELN)	Baseline Molecular Mutations	Prior Therapies		Duration on CA-4948 (mos)	Blasts Baseline	Blasts Best Response	% Change
				# Lines	Therapy				
sAML	300 mg	Intermediate	RUNX1, WT1, SF3B1	1	decitabine	7	23	0	-100% (CRh)
sAML	300 mg	Intermediate	U2AF1, FLT3, BCOR, WT1	1	decitabine/venetoclax	6+	39	4	-90% (CR)
AML	300 mg	Intermediate	U2AF1, NRAS	4	cytarabine/idarubicin, decitabine/venetoclax, fludarabine/cyclophosphamide /methotrexate, azacitidine	2.5	33	16	-52%
AML	300 mg	Adverse	FLT3, SF3B1, NRAS, PTPN11, RAD21, RUNX1, TET2, GATA, STAT3	4	cytarabine/daunorubicin, decitabine, decitabine/venetoclax, gilteritinib	2.6	95	77	-19%
sAML	400 mg	Adverse	SF3B1, DNMT3A, P53	1	azacitidine/venetoclax	2	20	23	15%

Data extraction date: Dec 16, 2021; "+" in Duration of Treatment indicates the patient remains on treatment as of the date of data extraction.
1. Two AML patients have both a spliceosome and FLT3 mutation and are included in both populations (there are 13 total evaluable patients with Spliceosome or FLT3 mutation).

CA-4948 achieved CR/CRh responses, despite transformed AML being historically highly resistant to treatment

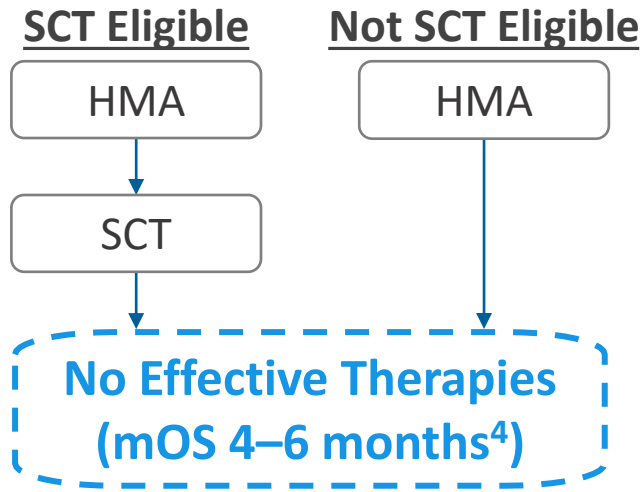
Clinical Data: R/R MDS Patients with Spliceosome Mutation

Patient Population #2

Spliceosome Mutations Common in MDS

Large unmet need for R/R MDS patients with spliceosome mutation

- Spliceosome mutations (U2AF1/SF3B1) are the most prominent mutations in MDS, accounting for ~30% of all MDS patients[1]
  - These mutations create a chronic inflammatory marrow microenvironment[2], which impairs hematologic recovery[3]
- There are no effective therapies for patients R/R to HMA: chemotherapy is standard of care



Current standard of care offers limited therapeutic benefit to patients

1. Ochi Cancers 2021.; 2. Smith et al. Nat Cell Biol 2019.; 3. Trowbridge JEM 2021. Ochi Cancers 2021.; 4. Jabbour et al Cancer 2010; Prebet et al., JCO 2011; Duong et al, Clin Lymphoma Myeloma Leuk, 2013.

Clear Unmet Need in Relapsed/Refractory MDS

Current standard of care offers little therapeutic benefit to patients

Most Commonly Used Therapies in R/R MDS[1]

CA-4948	Chemotherapy[2]	Decitabine[3]	Azacitidine[3]
IRAK4 Inhibitor	*Chemotherapy*	*HMA*	*HMA*
• 57% mCR rate (4 of 7 patients, incl. 1 that went to SCT)	• ~8% ORR	• 2nd line response data unavailable	• 2nd line response data unavailable
• No dose-limiting myelosuppression	• Myelosuppressive and Black Box Warning	• Myelosuppressive	• Myelosuppressive
• Oral Administration	• IV Administration	• IV Administration	• IV or SC Administration

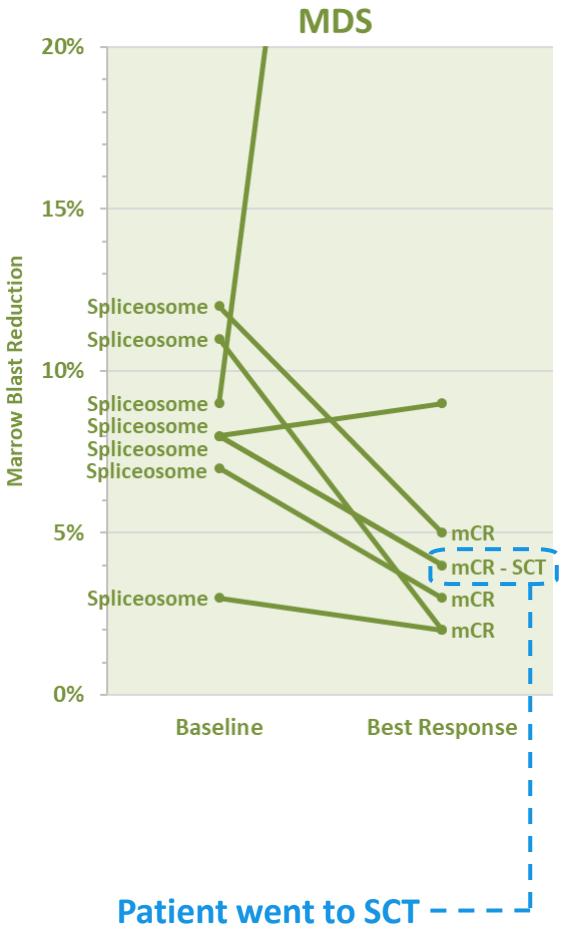
1. CancerMPact Treatment Architecture U.S. AML, Cerner Enviza, www.cancermpact.com, accessed January 3, 2022. Excludes Investigational Therapies; 2. Prébet et al, JCO 2011.; 3. Product Package Insert.; 4. Jabbour et al Cancer 2010; Prébet et al., JCO 2011; Duong et al, Clin Lymphoma Myeloma Leuk, 2013.

In MDS post-HMA mOS is 4–6 months[4]; clear unmet need for these patients

Initial CA-4948 data compared favorably vs. historical responses with the mainstay treatment for R/R MDS patients

Encouraging Clinical Activity in R/R MDS Patients with Spliceosome Mutation

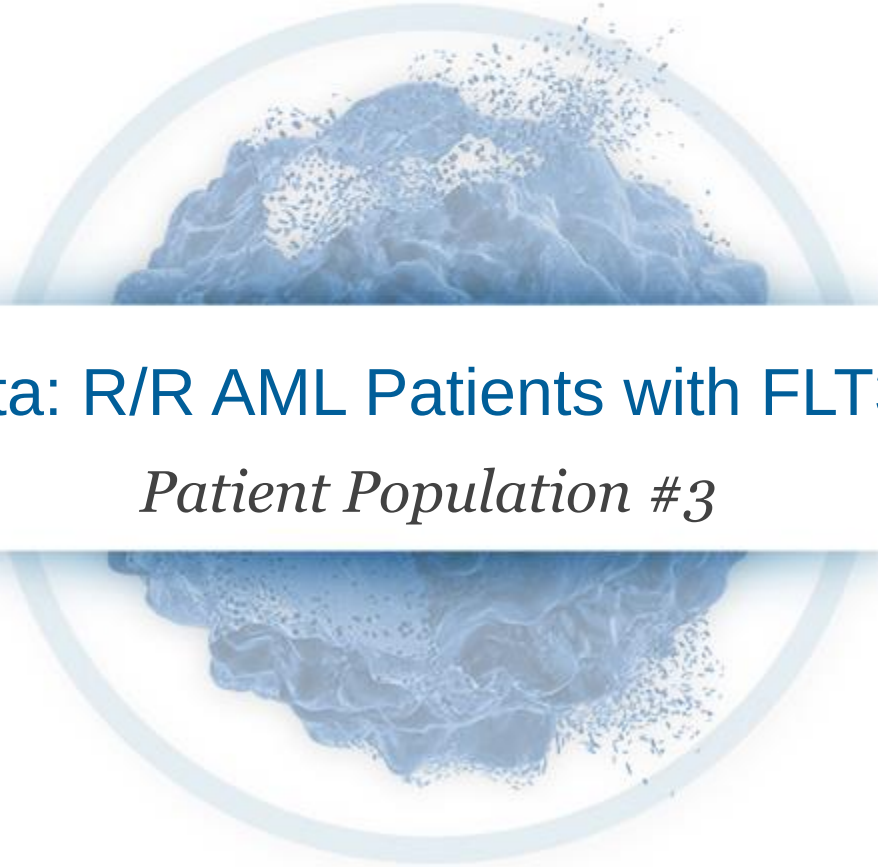
Marrow blast reduction achieved in 5 of 7 patients, including 4 marrow CRs



Dx	Dose (BID)	IPSS-R	Baseline Molecular Mutations	Prior Therapies		Duration on CA-4948 (mos)	Blasts Baseline	Blasts Best Response	% Change
				# Lines	Therapy				
MDS	200 mg	Very High Risk	U2AF1 ,ASXL1, NF1, PHF6, GFI1, KDM6A, TET2	1	azacitidine	5.7	11	2	-82% (mCR)
MDS	300 mg	Very High Risk	U2AF1, DNMT3A, BCOR, STAG2, BCORL1, ETV6, SETBP1	1	magrolimab/azacitidine	3.3+	12	5	-58% (mCR)
MDS	400 mg	Very High Risk	SF3B1, RUNX1, NFE2	2	lenalidomide, guadecitabine	4.3	7	3	-57% (mCR)
MDS	300 mg	High Risk	SF3B1, DNMT3A, ASXL1, TET2, EZH2	2	azacitidine, canakinumab	0.9 *(went to SCT)*	8	4	-50% (mCR)
MDS	300 mg	High Risk	U2AF1, ASXL1	4	lenalidomide, azacitidine, cyclosporine, decitabine	5.3+	3	2	-33%
MDS	300 mg	Very High Risk	SF3B1, ASXL1, NF1, SH2B3, RUNX1, PHF6, CBL, GFI1, EZH2	3	ipilimumab/azacitidine, quizartinib/azacitidine, azacitidine/venetoclax/ pevonedistat	1.6	8	9	13%
MDS	400 mg	Very High Risk	U2AF1, ASXL1, BCOR, DNMTA, GATA2, SETBP1	1	azacitidine	1.2	9	62	>100%

Data extraction date: Dec 16, 2021; "+" in Duration of Treatment indicates the patient remains on treatment as of the date of data extraction.

Consistent tumor burden reduction in targeted population with limited options

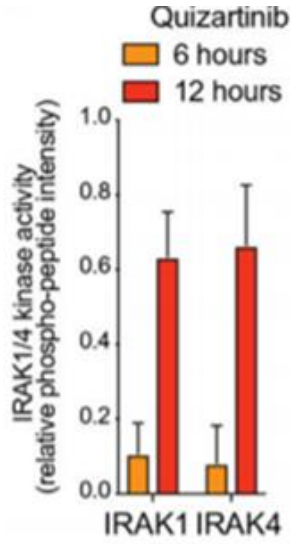


Clinical Data: R/R AML Patients with FLT3 Mutation

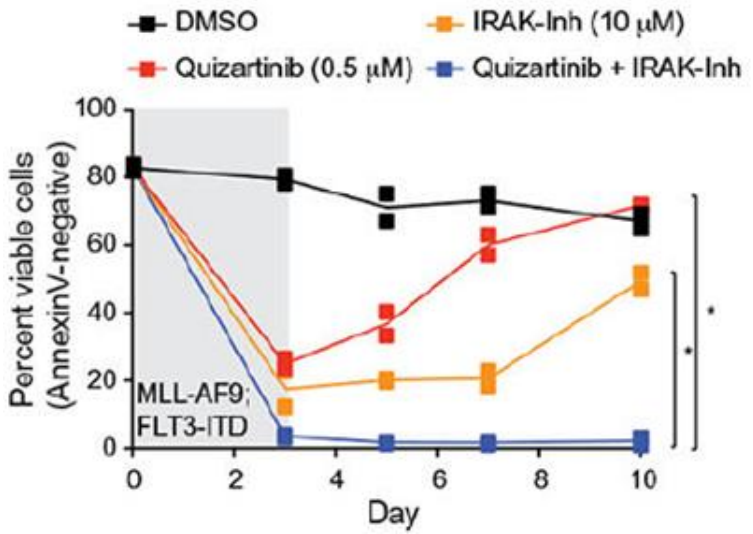
Patient Population #3

IRAK4 Signaling Drives Resistance to FLT3 Inhibitors

IRAK4 inhibition is synergistic with, and prevents adaptive resistance to, FLT3 inhibition

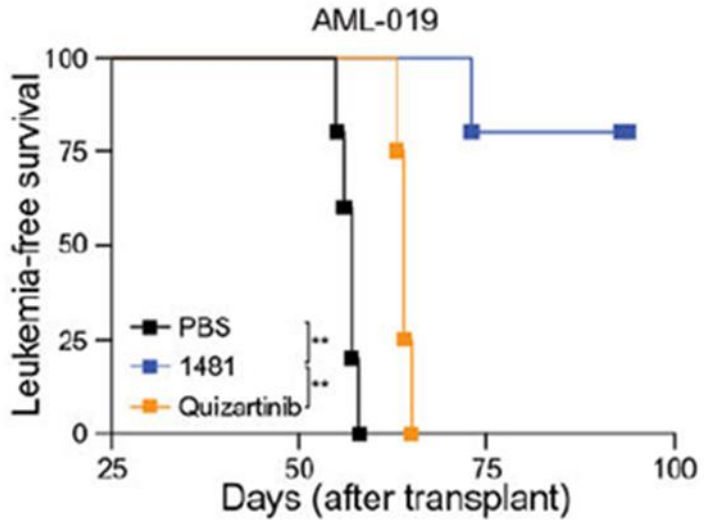


- IRAK4 activity increases after quizartinib treatment of MLL-AF9 FLT3-ITD cells
- IRAK4 activity also shown to increase in patients during gilteritinib treatment



- IRAK and FLT3 inhibition is synergistically cytotoxic

Viability of MLL-AF9;FLT3-ITD cells treated for 3 days with DMSO (vehicle control), quizartinib (0.5 μM), IRAK-Inh (10 μM), or quizartinib and IRAK-Inh



- Mice die if treated with quizartinib, but survive if treated with IRAK/FLT3 inhibitor (1481)

Leukemia-free survival of NRGS mice xenografted with AML-019

Source: Melgar, Sci Transl Med. 2019.

CA-4948 May Address Unmet Need in R/R AML Patients with FLT3 Mutation

No approved therapies for patients R/R to FLT3 inhibitors

Most Commonly Used Therapies in R/R AML Patients with FLT3 Mutation[1]

CA-4948	Gilteritinib[2,3]	Azacitidine[2]	Decitabine[2]	Gemtuzumab Ozogamicin[2,4]
IRAK4 Inhibitor	*FLT3 Inhibitor*	*HMA*	*HMA*	*Monoclonal Anti-CD33 Antibody (ADC)*
• 33% CR (1 of 3 patients) • No dose-limiting myelosuppression • Oral Administration	• ~12% CR • No dose-limiting myelosuppression • Oral Administration	• 2nd line response data unavailable • Myelosuppressive • IV or SC Administration	• 2nd line response data unavailable • Myelosuppressive • IV Administration	• ~26% CR • Myelosuppressive and Black Box Warning • IV Administration

~30% of AML patients have FLT3 mutation[5]

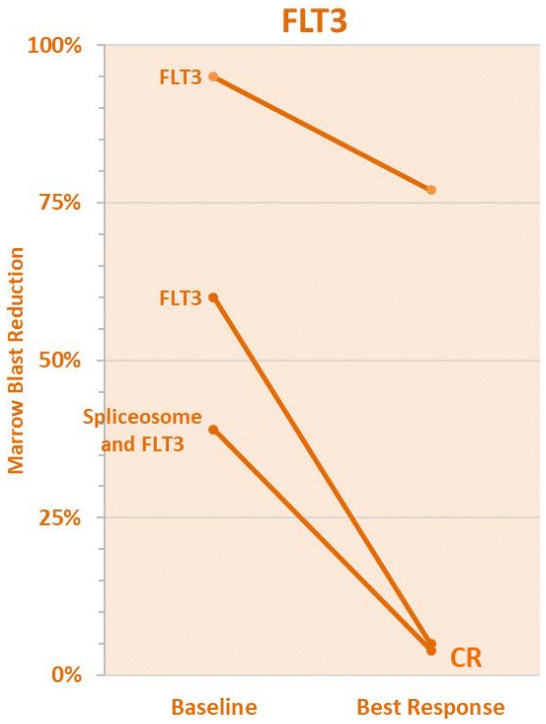
Dual inhibition of IRAK4 and FLT3 may lead to increased efficacy, as signaling through IRAK4 drives resistance to FLT3 inhibitors[6]

1. CancerMPact Treatment Architecture U.S. AML, Cerner Enviza, www.cancermpact.com, accessed January 3, 2022. Excludes Investigational Therapies; 2. Product Package Insert; 3. Perl et al NEJM 2019; 4. Gemtuzumab ozogamicin is only approved for patients with CD33-positive AML; 5. Saygin, et al. J Hematol Oncol. 2017; 6. Melgar, Sci Transl Med. 2019

IRAK4/FLT3 inhibition may improve efficacy in R/R AML patients with FLT3 mutation[5]

Encouraging Clinical Activity in R/R AML Patients with FLT3 Mutation

Achieving disease modification in heavily pretreated patients with CA-4948 monotherapy



Dx	Dose (BID)	Risk Category (ELN)	Baseline Molecular Mutations	Prior Therapies		Duration on CA-4948 (mos)	Blasts Baseline	Blasts Best Response	% Change
				# Lines	Therapy				
AML	400 mg	Adverse	FLT3 ***(eradicated at C3D1)***, ASXL1, BCOR, CEBPA *(eradicated at C3D1)*, CSF3R, EZH2, NRAS, RUNX1 (X3), STAG2, TET2(X2,1) *(eradicated at C3D1)*	2	decitabine/venetoclax, gilteritinib ***(refractory to gilteritinib)***	5.1	60	5	-92%
sAML	300 mg	Intermediate	FLT3 ***(eradicated at C4D1)***, BCOR *(eradicated at C4D1)*, U2AF1 *(decreased to 1.3 VAF at C4D1)*, WT1 *(eradicated at C4D1)*	1	decitabine/venetoclax	6.2+	39	4	-90% (CR)
AML	300 mg	Adverse	FLT3, SF3B1, NRAS, PTPN11, RAD21, RUNX1, TET2, GATA, STAT3	4	cytarabine/daunorubicin, decitabine/PCM-075, decitabine/venetoclax, gilteritinib	2.6	95	77	-19%

Data extraction date: Dec 16, 2021; "+" in Duration of Treatment indicates the patient remains on treatment as of the date of data extraction.
1. Two AML patients have both a spliceosome and FLT3 mutation and are included in both populations (there are 13 total evaluable patients with Spliceosome or FLT3 mutation).

Significant marrow blast reduction and FLT3 mutation eradicated in 2 out of 3 patients

Summary

CA-4948 in Three Targeted Patient Populations

Comments from Clinical Investigator, Daniel DeAngelo, MD, PhD

Chief, Division of Leukemia at Dana-Farber Cancer Institute

- Encouraging clinical activity in patients with R/R disease, all of whom had prior HMA treatment
  - 4 out of 5 patients with spliceosome-mutated AML achieved blast reduction
    - 2 patients achieved CR/CRh with significant hematologic improvement, including 1 full CR
  - 5 out of 7 patients with spliceosome-mutated MDS achieved blast reduction
    - 4 patients achieved marrow CR, 1 of whom proceeded to Stem Cell Transplant
  - All 3 patients with FLT3-mutated AML achieved blast reduction
    - 2 patients achieved eradication of FLT3 mutation, including 1 full CR

- Manageable Toxicity/Safety Profile
  - Oral drug with a well-tolerated and manageable safety profile
  - Supports further development, both as a single agent and in combination therapy

CA-4948 Has Potential to Address Clear Unmet Need in AML and MDS

First-in-class IRAK4 inhibitor targets specific genetic populations in AML and MDS

CA-4948 addresses a novel target (IRAK4) and:

(1) demonstrates clear anti-cancer activity as an oral single agent

(2) is active in genetically-defined populations that can be identified and enrolled

(3) has the added potential benefit of also hitting FLT3

- Well-tolerated and manageable safety profile may provide advantage to existing standard of care therapies as a single agent, and also suggests CA-4948 may be a favorable candidate for addition to combination therapy regimens

- Dual targeting of IRAK4 and FLT3 may prevent adaptive resistance to current FLT3 inhibitors[1]

Next Steps in Expansion

- *Monotherapy: Spliceosome mutation*
- *Monotherapy: FLT3 mutation*
- *Combination: CA-4948 + azacitidine*
- *Combination: CA-4948 + venetoclax*

Plan to discuss potential for a rapid registrational path with FDA in 1H 2022

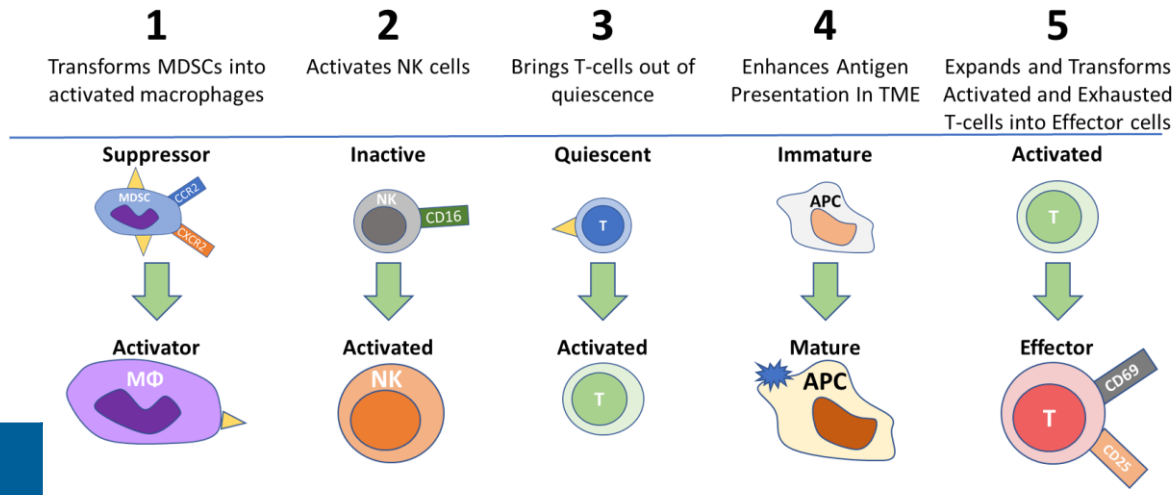
1. Melgar, Sci Transl Med. 2019

CI-8993: First-in-class VISTA Antagonist

Novel Immune Checkpoint Inhibitor for Solid Tumors

Anti-cancer Mechanisms of Checkpoint Inhibitors

Role of VISTA may go beyond other checkpoint inhibitors



Target					
VISTA (CI-8993)	☑	☑	☑	☑	☑
PD-1 (Pembro, Nivo, etc.)	☑	☒	☒	☒	☑
PD-L1 (Atezo, Durva, etc.)	☒	☒	☒	☒	☑
CTLA-4 (Ipi)	☒	☒	☒	☒	☑
TIM3	☑	☒	☒	☒	☑
LAG3	☒	☒	☒	☒	☑
OX40	☒	☒	☒	☒	☑
TIGIT	☒	☒	☒	☒	☑

We believe VISTA inhibition has potential for broad application in many tumor types in monotherapy and in combination with existing checkpoint inhibitors

Checkpoint Inhibitors Approved in Multiple Malignancies:

- Melanoma
- Lung Carcinoma
- Renal Cell Carcinoma
- Head & Neck Squamous Cell Carcinoma
- Lymphoma
- Hepatocellular Carcinoma
- Merkel Cell Carcinoma
- Gastric/Gastroesophageal Adenocarcinoma
- Cervical Carcinoma
- Cutaneous Squamous Cell Carcinoma
- Breast Carcinoma
- Esophageal Carcinoma
- Uterine Carcinoma
- Urothelial Carcinoma
- Genomic Alterations (e.g., MSI-high)

Sources: Curis & ImmuNext internal data, Curis 2021 VISTA Symposium.

Incorporated Learnings from CI-8993 Prior Clinical Study

Pharmacodynamic activity (cytokine release) observed in initial clinical study

CI-8993 is the first anti-VISTA monoclonal antibody (IgG1κ) to be studied in clinical trials

- Janssen initiated a Ph1 study in 2016 and enrolled 12 patients[1]
  - Transient Cytokine Release Syndrome (CRS) observed in several patients at 0.15mg/kg
  - Transient grade 3 CRS-associated encephalopathy observed at 0.3mg/kg, after which Janssen halted the study

CI-8993 Protocol Designed to Manage Expected CRS

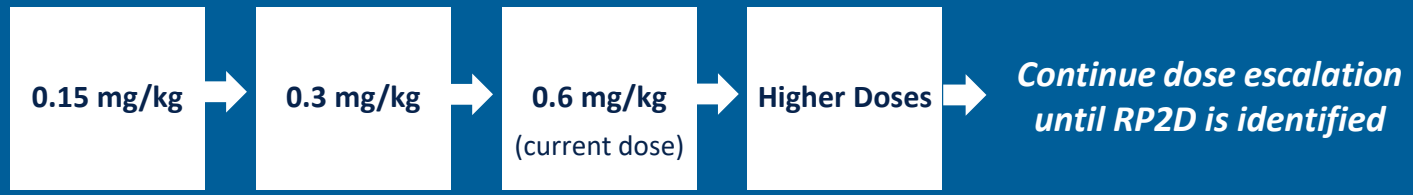
- CRS is likely an on-target effect; indicates drug is hitting the target and inducing immune response
- NCCN guidelines were issued in 2018; oncology community now familiar with managing CRS
- Desensitizing step-dose of CI-8993, and pre/post-infusion medication, administered to mitigate CRS

1. ClinicalTrials.gov, Trial #NCT02671955

CI-8993 Clinical Plan: Phase 1 Dose Escalation Study

On-going clinical study to determine safety

Phase 1 Dose Escalation Study Design



Patient Population

- Patients with advanced refractory solid tumors (includes mesothelioma, melanoma, NSCLC, TNBC)

Treatment

- Bi-weekly dosing
- Plan to mitigate potential toxicities by co-medication and step dosing (desensitization)

Objectives

- Safety, PK/PD, tolerability during dose escalation
- Anti-cancer activity during expansion

NSCLC: Non-Small Cell Lung Cancer; TNBC: Triple Negative Breast Cancer

CI-8993 Has Demonstrated Favorable Safety Profile

Successfully managed expected CRS at all levels dosed to date

All Grades Treatment-Related Adverse Events Occurring in 2+ Patients	0.15 mg/kg (N = 7)		0.3 mg/kg (N = 5)	
	n (%)		n (%)	
Number of patients having any grade treatment-related AEs	4	(57.1)	4	(80.0)
Headache	3	(42.9)	1	(20.0)
Chills	2	(28.6)	1	(20.0)
Alanine aminotransferase increased	1	(14.3)	1	(20.0)
Fatigue	2	(28.6)	0	
Hypotension	0		2	(40.0)

Grade 3+ Treatment-Related Adverse Events	0.15 mg/kg (N = 7)		0.3 mg/kg (N = 5)	
	n (%)		n (%)	
Number of patients having grade 3+ treatment-related AEs	0		1	(20.0)
Leukopenia	0		1	(20.0)

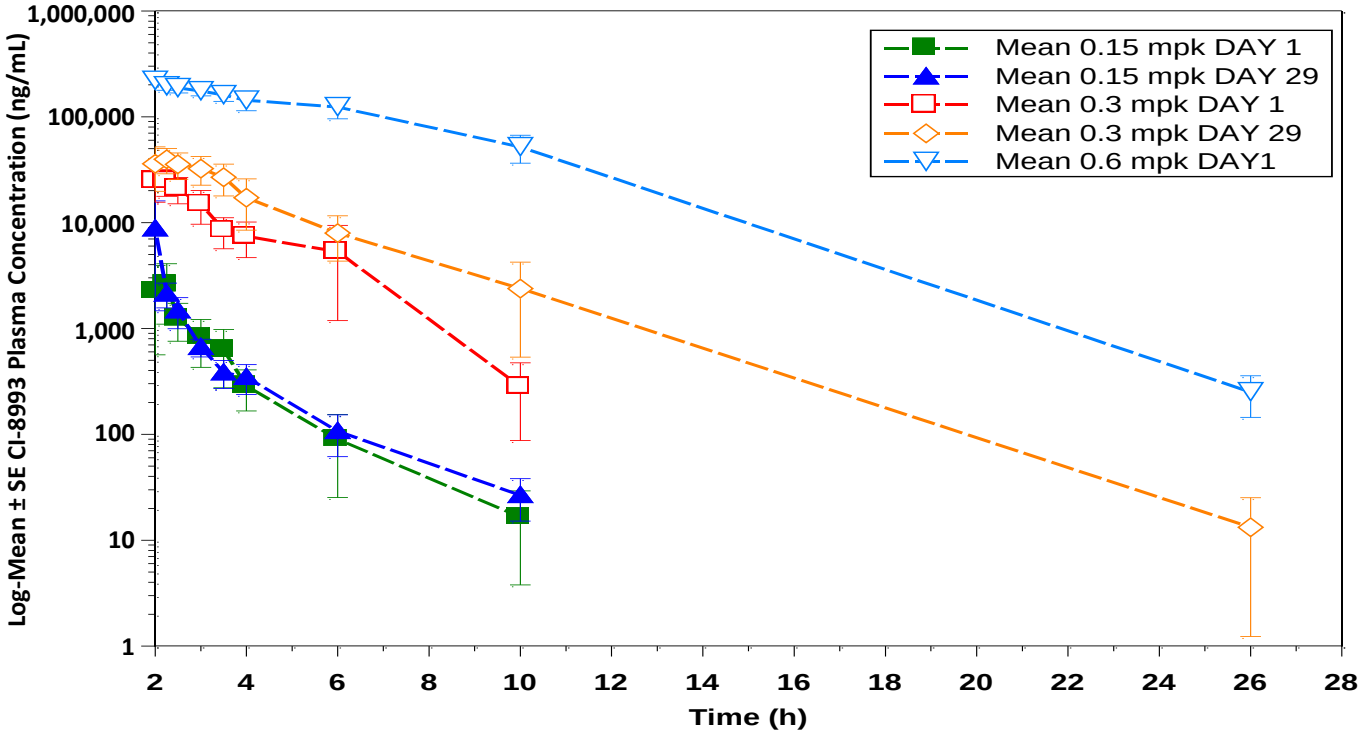
Data extraction date: Dec 11, 2021.
One additional patient experienced grade 2 treatment-related AE after receiving step dose and chose not to proceed to full dose.

CI-8993 has successfully cleared dose level where Janssen observed DLT

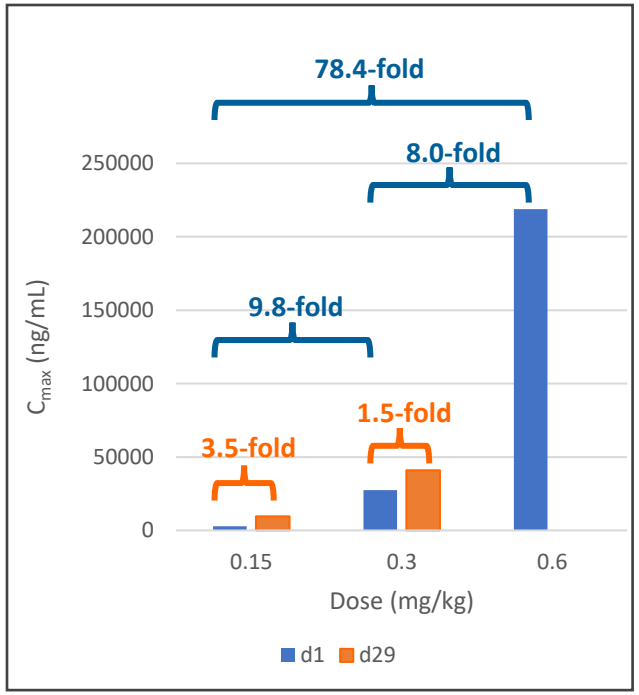
CI-8993 Has Demonstrated Favorable PK Profile

CI-8993 mean plasma concentration vs. time profile following IV administration at full dose

Plasma Concentration



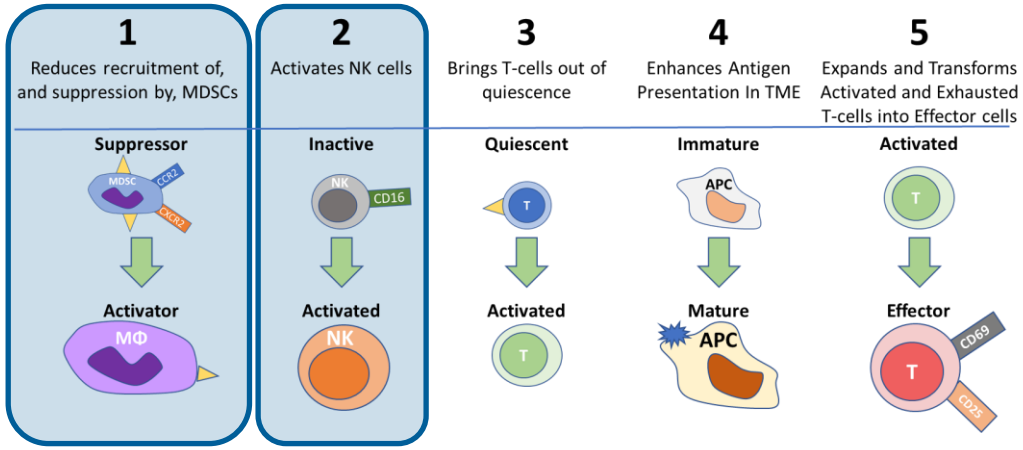
C_{max} Levels



Saturation kinetics in C_{max} data ("sink effect")
suggest potential for broad bioavailability at higher dose levels

Pharmacodynamic Effects of CI-8993 in Patients

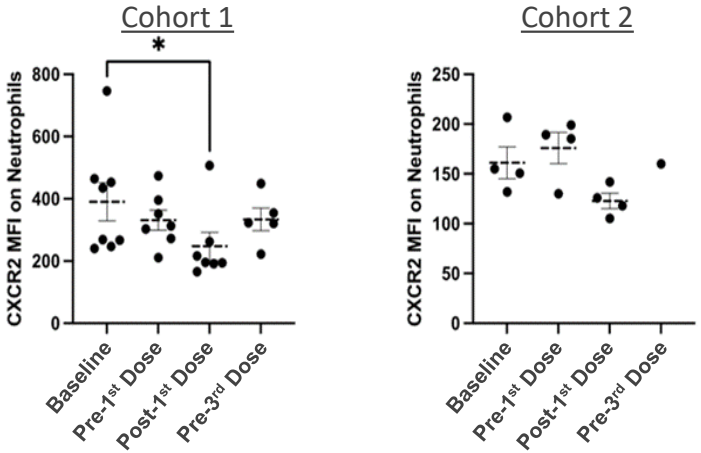
CI-8993 affects multiple anticancer mechanisms supporting VISTA potential



1 Decreased recruitment of MDSCs

Decreased CXCR2 on granulocytes

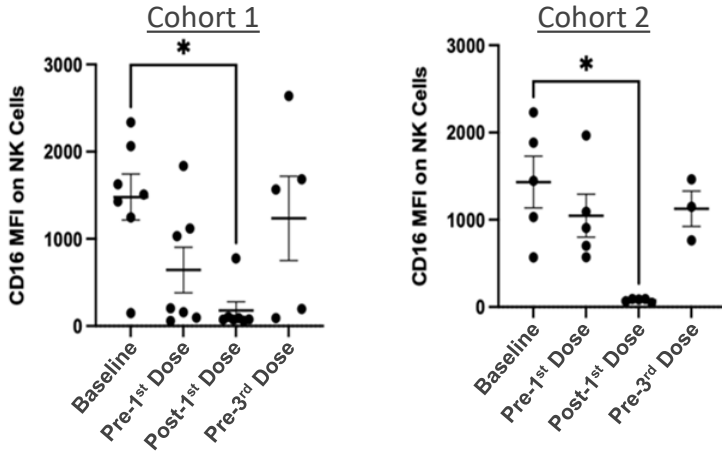
CI-8993 reduces MDSCs (↓CXCR2 and ↓CCR2); MDSCs suppress anti-tumor immunity and impair efficacy of other checkpoint inhibitors



Similar finding for CCR2 on monocytes

2 NK Cell Activation

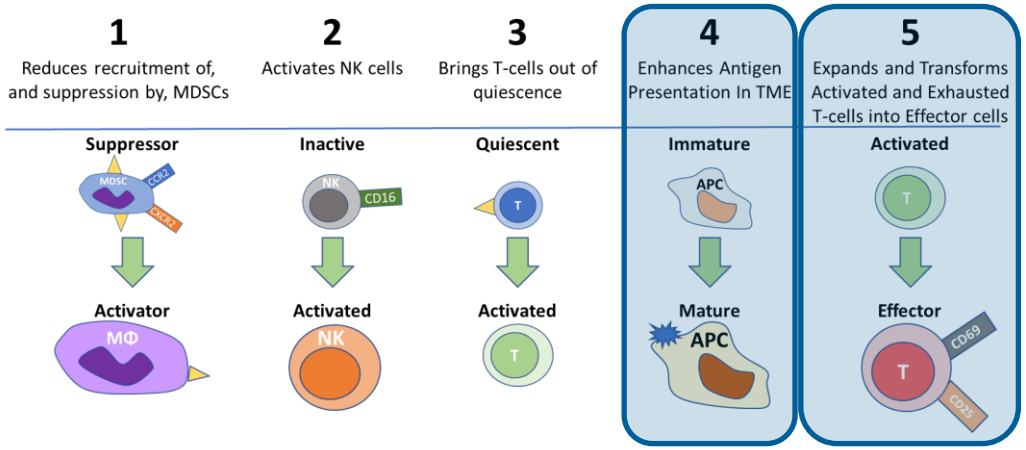
Decreased CD16 on NK cells



CI-8993 activates NK cells (↓CD16 signifies NK activation); activated NK cells exert an important anti-tumor function via the innate immune system

Pharmacodynamic Effects of CI-8993 in Patients

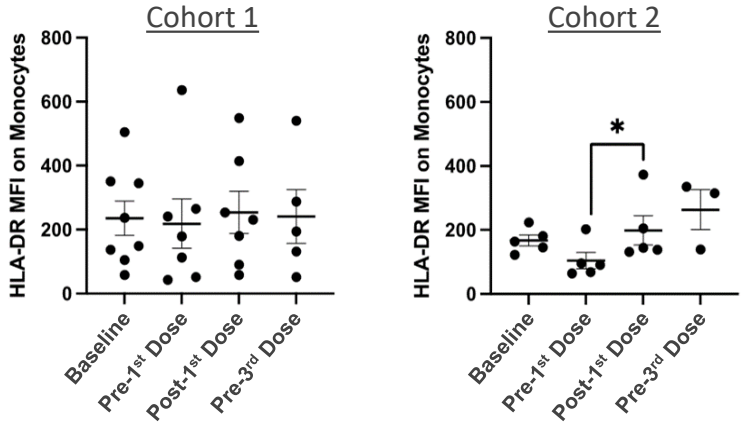
CI-8993 affects multiple anticancer mechanisms supporting VISTA potential



4 Enhanced Antigen Presentation

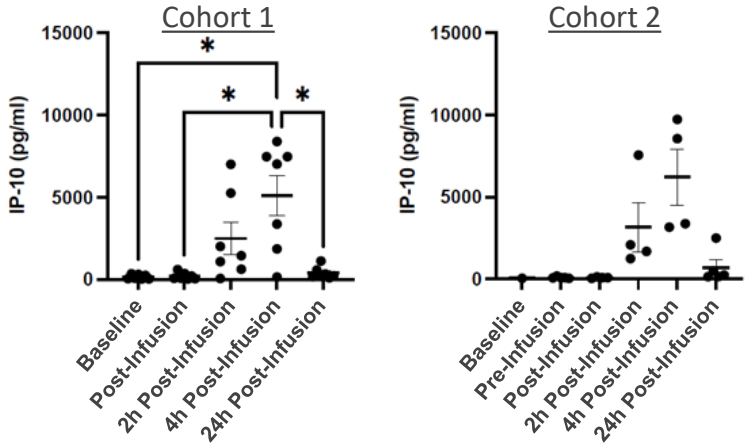
Increased HLA-DR on Monocytes

CI-8993 enhances antigen presentation (↑HLA-DR); antigen presentation allows the immune system to recognize the tumor and attack it



5 Release of T-Cell Activating Factors

Increased Secretion of IP10



CI-8993 increases T-cell factors (↑IP10 and ↑MIP1α); these stimulate T-cell expansion and transformation into effector T-cells

Similar finding for MIP1α

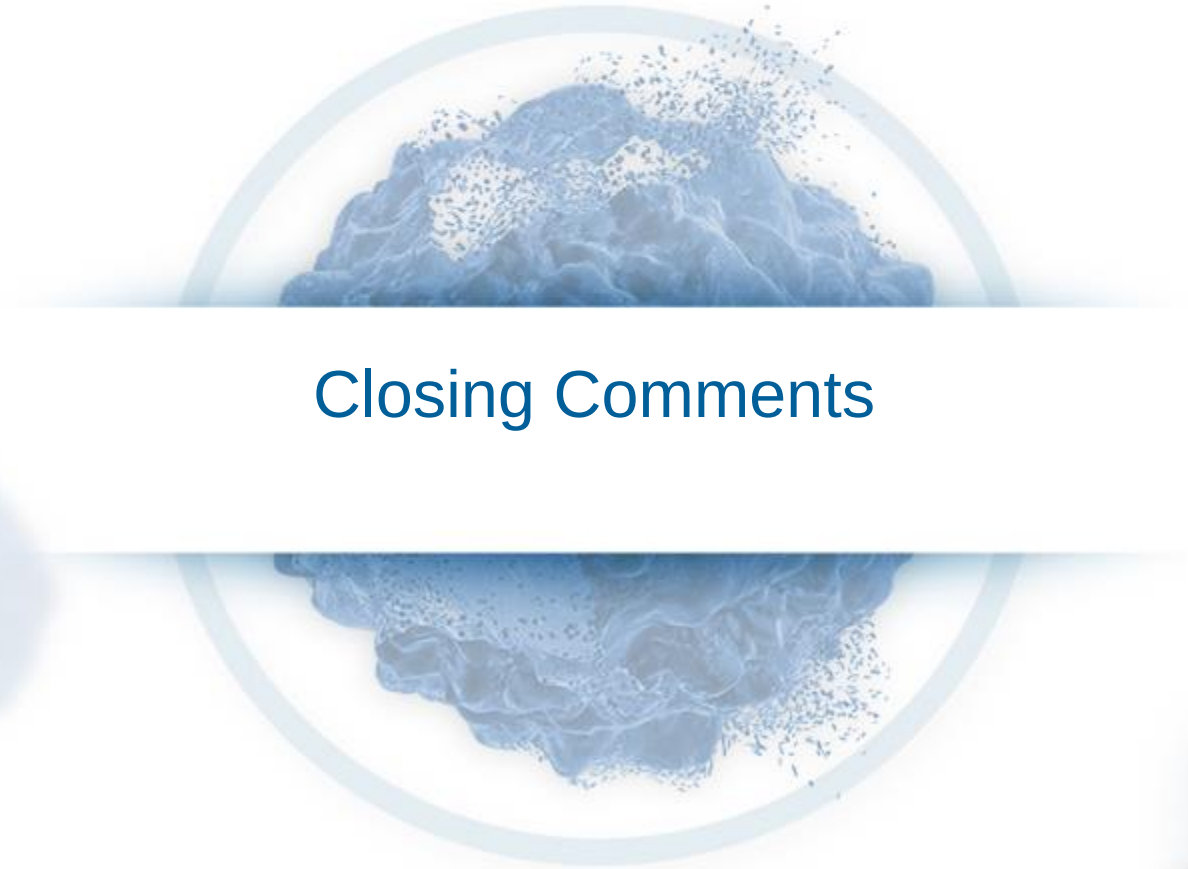
CI-8993 Cleared Initial Safety Hurdle

First-in-class CI-8993 has potential for broad applicability in immune checkpoint therapy

- Encouraging initial safety data appears to demonstrate effectiveness of procedures implemented to manage expected CRS
- Pharmacokinetic profile of CI-8993 exhibits saturation kinetics, suggesting potential to overcome “sink effect”
- Pharmacodynamic effects of CI-8993 in patients suggest multiple anti-cancer mechanisms may be activated

Next Steps in Dose Escalation

- *Continue dose-escalation for signs of anti-cancer activity and determination of RP2D*



Closing Comments

Closing Remarks & Next Steps

Clinical update on CA-4948 (IRAK4) and CI-8993 (VISTA)

CA-4948

- Initial clinical data demonstrate clear anti-cancer activity with a single, oral agent in specific genetic populations of AML/MDS

Next Steps

Plan to discuss potential for a rapid registrational path with FDA in 2022

CI-8993

- Initial safety data appear to demonstrate that expected immune effects (cytokine release) can be managed, and early PK/PD data show that anti-cancer mechanisms are being activated

Next Steps

Continue dose-escalation for signs of anti-cancer activity and determination of RP2D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