Aptose Corporate Presentation

June 27, 2022

APTOSE BIOSCIENCES

PRECISION ONCOLOGY FOR THERAPIES OF TOMORROW

NASDAQ: **APTO**
TSX: **APS**

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Aptose Biosciences (NASDAQ: APTO)

Clinical Stage Oncology Company | Focused on Precision Medicines

Developing highly differentiated oral kinase inhibitors for hematologic malignancies

Experienced leadership with deep expertise in kinase inhibitors & orphan diseases

Planned value-driving clinical updates through 2022 and cash runway through 2023

HM43239 Oral Myeloid Kinome Inhibitor | Clinically Validated for R/R AML Patients

Targets high value kinases operative broadly in AML patients : $FLT3^{WT/MUT}$, SYK, JAK1/2, $cKIT^{MUT}$

CRs in diverse R/R AML patients: $FLT3^{ITD/TKD/WT}$, $NPM1^{MUT}$, $TP53^{MUT}$, $N/K\text{-}RAS^{MUT}$, MLL, RUNX1, IDH^{MUT}

Orphan Drug Designation for AML and Fast Track Designation for R/R AML patients with $FLT3^{MUT}$

→ Now Transitioning to Expansion Trials planned 2H2022 : Doses and patient populations selected

LUXEPTINIB (CG-806) Dual Lymphoid and Myeloid Kinome Inhibitor

High value targets in B-cell cancers, AML, and inflammation : BTK, FLT3, LCK, LYN, Others

Ongoing parallel dose escalations in patients with B-cell lymphomas/CLL and AML/MDS

Clinically active: anti-tumor activity in high-bar clinical setting of R/R patients

→ Encouraging data with G3 formulation to reduce drug substance and increase plasma exposure

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Aptose Leadership Team: Multifaceted Expertise in Therapeutic Development

Rafael Bejar, MD, PhD

Sr. VP & Chief Medical Officer

William G. Rice, PhD

Chairman, President & Chief Executive Officer

Fletcher Payne

Sr. VP & Chief Financial Officer

Philippe Ledru

Sr. VP & Chief Commercial Officer

UC San Diego Moores Cancer Center

mds Myelodysplastic Syndromes (MDS) Foundation

Dana-Farber Cancer Institute

BWH Brigham and Women's Hospital

NIH National Cancer Institute

Emory University School of Medicine

Achillion

Cylene Pharmaceuticals

Catalyst Biosciences

CytomX

Plexxikon

Abgenix

rNAT Neuroscience

Cell Genesys

Syapse

IBM

Sun microsystems

Merck

Novartis

Aptose Biosciences

Aptose SAB: Distinguished Opinion Leaders with Deep Oncology Expertise

Daniel Von Hoff, MD, FACP

Former President of AACR

Board Member of ASCO

Former Presidential Cancer Advisory Board

Physician in Chief, TGen

Medical Director of Research for McKesson Specialty Health

Chief Scientific Officer for US Oncology Research

Professor of Medicine, Mayo Clinic Scottsdale

Brian J. Druker, MD

Pioneer in the field of precision medicine

Key Role in development of Gleevec - the first targeted kinase inhibitor for cancer

Member, National Academy of Medicine, National Academy of Sciences & American Academy of Arts & Sciences

Winner of Karnofsky Award, Lasker Award, Japan Prize in Healthcare and Medical Technology, Tang Prize in Biopharmaceutical Science, Sjöberg Prize

Leader of Inter-institutional Beat AML Initiative

Michael Andreeff, MD, PhD

Renowned hematology specialist

Professor of Medicine
Paul and Mary Haas Chair in Genetics
Chief, Section of Molecular Hematology and Therapy
MD Anderson Cancer Center

Expert in AML and other hematologic malignancies

Expert in drug resistance and drug mechanisms

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Aptose Clinical Stage Pipeline: Oral Kinase Inhibitors that Cover a Broad Spectrum of Hematologic Malignancies

Program	*Target*	*Indication*	*Preclinical*	*Phase 1 Proof-of-Concept*	*Phase 2/3 Registrational*
HM43239	*Myeloid Kinome*	*AML*		**Phase 1/2**	
Luxeptinib	*Myeloid Kinome*	*AML, MDS*		**Phase 1a/b**	
Luxeptinib	*Lymphoid Kinome*	*B-cell Cancers*		**Phase 1a/b**	

- Small molecule kinase inhibitor candidates designed to treat a disease
- Confirmed anti-leukemic activity in dose-escalation studies, with expansion studies planned
- Orphan hematology programs, with broader optionality into solid tumor indications

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HM43239 “239”

Oral Myeloid Kinome Inhibitor

HM43239 Proven Clinical Activity in AML Patients with Significant Unmet Needs

Validated AML Targets

FLT3, SYK, JAK1/2, cKIT^{MUT}

HM43239
Myeloid Kinome Inhibitor

Accelerated paths to approval

Single Agent Activity

3 doses with CRc and no drug-related SAE

Well tolerated

No drug-related SAE, QTc toxicities, or CK increases

CRc in FLT3-mutated R/R AML

FLT3^{MUT} / failed prior FLT3 inhibitors

CRc in FLT3-unmutated R/R AML

FLT3^{WT} / harboring adverse mutations

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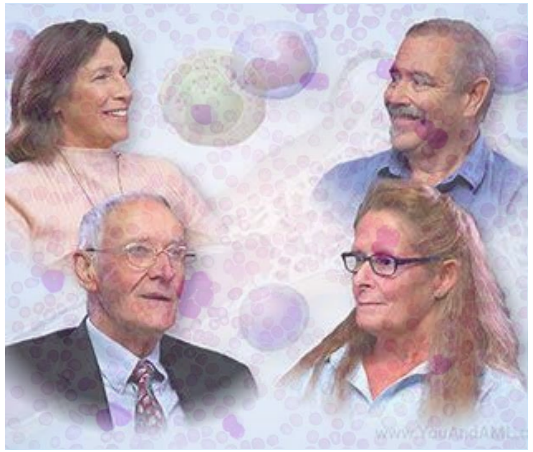
AML in the US: Estimated 20,240 new cases and 11,400 deaths in 2021
Continued Unmet Need for More Effective and Safe Therapies

Epidemiology	US (2021)	EU5 (2020)	Japan (2021)	China (2020)
Leukemia Incidence[3]	61,090[1]	51,820[3]	14,600[7]	85,400
AML Incidence	20,240[2]	16,580[3a]	6,570[7c]	31,430[3b]
5-Year Prevalence (Leukemia) (2020)[3]	187,560	152,230	41,280	241,750
Mortality (Leukemia)	11,400 (AML)[2]	31,690	8,700[7]	61,690



- **Most common acute leukemia in adults**
- **5-year survival rate of approx. 30%**
- **Relapsed AML patients have a median life expectancy of < 6 months* with approved therapies**
- **Need new targeted agents to better treat R/R AML patients and to treat resistance to current agents**
- **Need more effective & better tolerated agents to achieve lasting remissions and extend meaningful life**

Sources: 1. SEER 2021 Leukemia; 2. SEER 2021 AML; 3. The Global Cancer Observatory (GLOBOCAN) - IACR (2020) - Projections; 4. Chihara et al. Br J Haematol. 2014; 5. Chen et al. J Hematol Oncol. 2010: 21; 6. Cancer.net; 7. Ganjoho Cancer Statistics in Japan 2021
*https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7486485/ *https://www.frontiersin.org/articles/10.3389/fonc.2021.649209/full

[a]EU5 incidence calculated by applying 32% (AML) on leukemia to obtain incidence of AML[6]
[b]In China, AML accounted for ~36.8% of all leukemias[5] [c]In Japan, AML accounted for ~45% of all leukemias in 2008[4]

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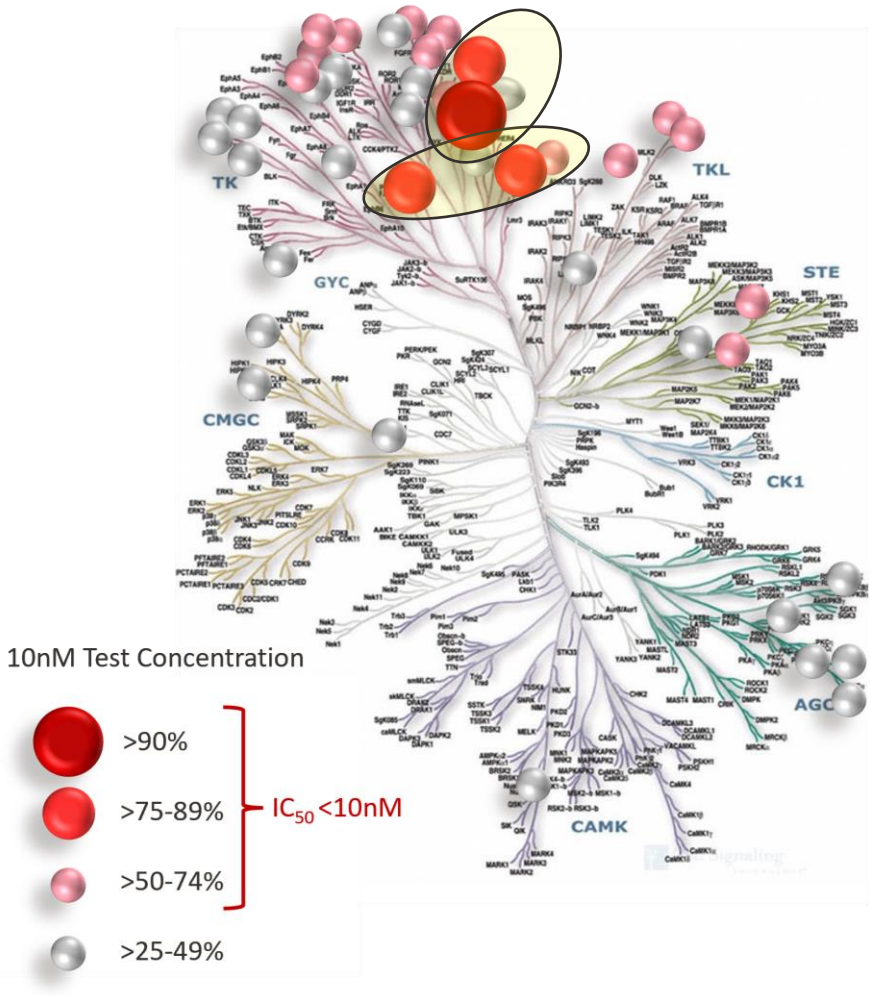
HM43239 Kinase Inhibitory Profile: Predicts Clinical Activity in AML Patients Harboring Mutated FLT3, Unmutated FLT3, and Having a Diverse Collection of Adverse Mutations



Assay Methodology	Kinase	Mutation Type	Activity
Binding Affinity (K_D, nM)	FLT3	WT	0.58
		ITD	0.37
		D835Y	0.29
		D835H	0.4
		ITD/D835V	0.48
		ITD/F691L	1.3
Inhibition of Kinase Enzyme Activity (IC_{50}, nM)	FLT3	WT	1.1
		ITD	1.8
		D835Y	1.0
	SYK	WT	2.9
	JAK	JAK-1	2.8
		JAK-2	6.3
		JAK-2 (V617F)	9.9
	c-KIT	WT	> 500
		D816H	3.6
		D816V	3.5

Potent suppression of driver and compensatory kinases operative in AML

- **All forms of FLT3**: -ITD, -TKD, -GK mutations and FLT3-WT
- **SYK** signal transduction kinase
- **JAK 1/2** signal transduction kinases
- **cKIT^{MUT}** alternative receptor kinases

→ **Serves as a multi drug therapy in a single molecule**

→ **Simultaneously disrupts multiple signal transduction pathways that drive AML proliferation and resistance mechanisms**

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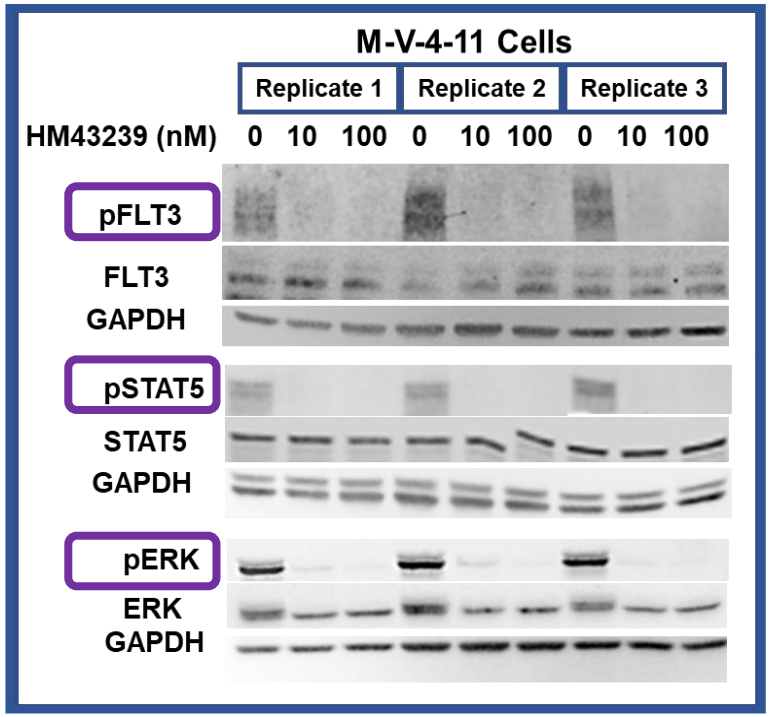
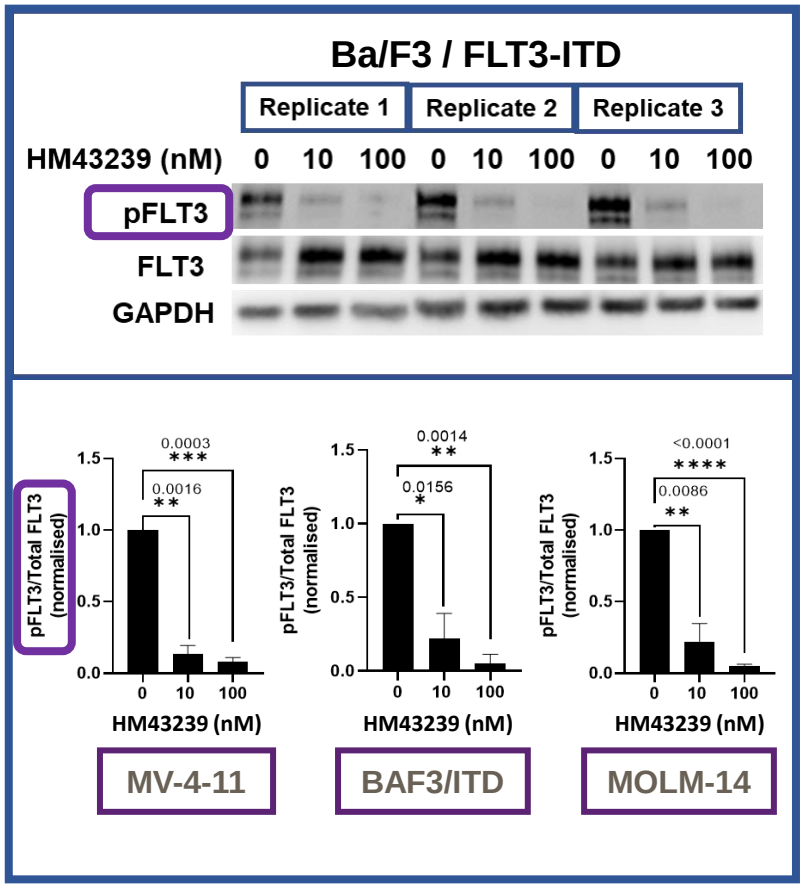
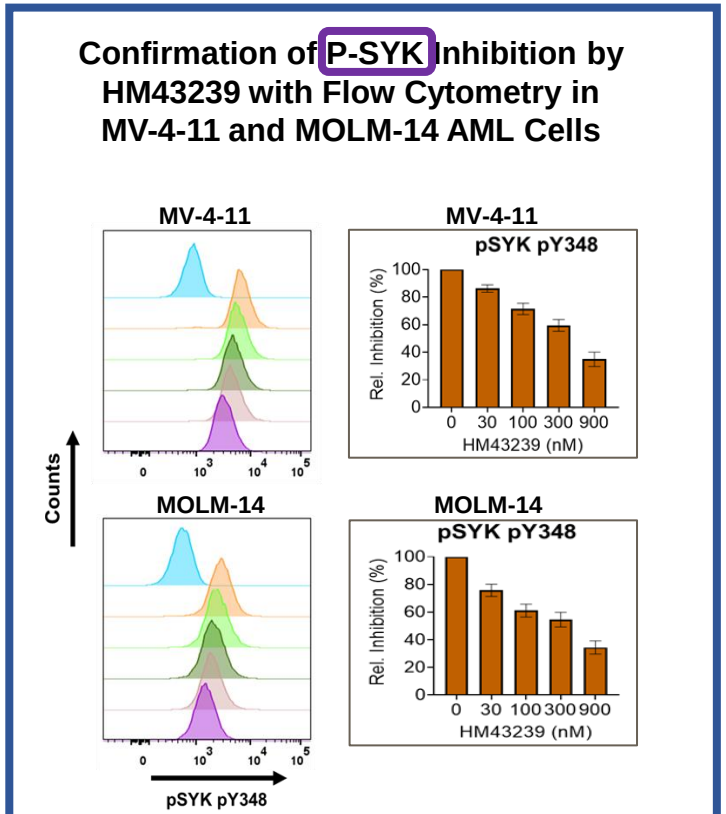
HM43239 Suppresses P-FLT3 / P-SYK and the P-STAT / P-ERK Downstream Pathways in AML Cell Lines



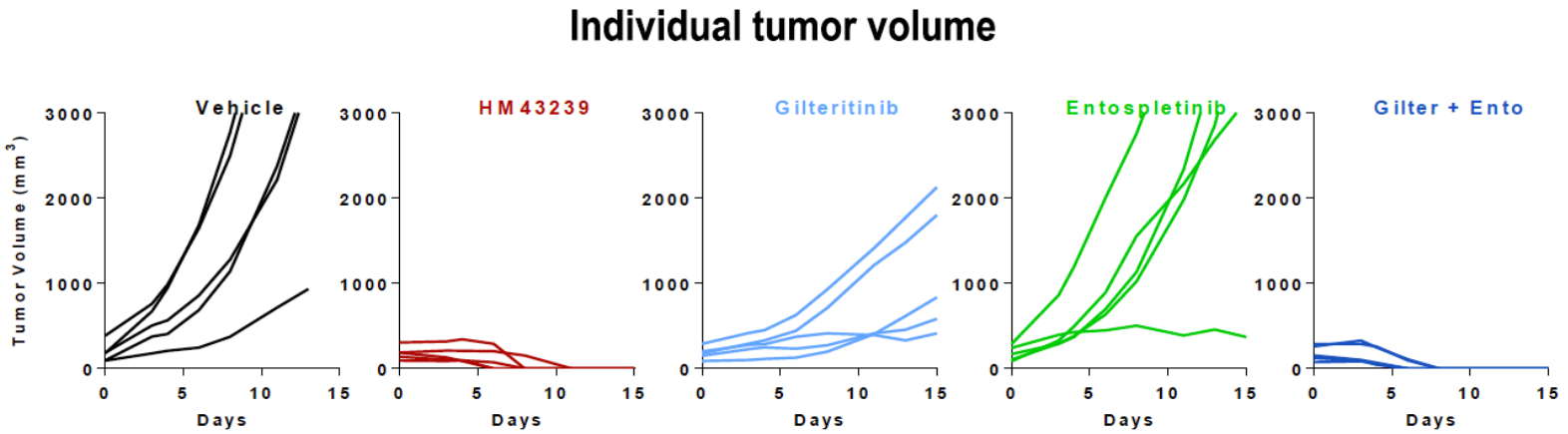


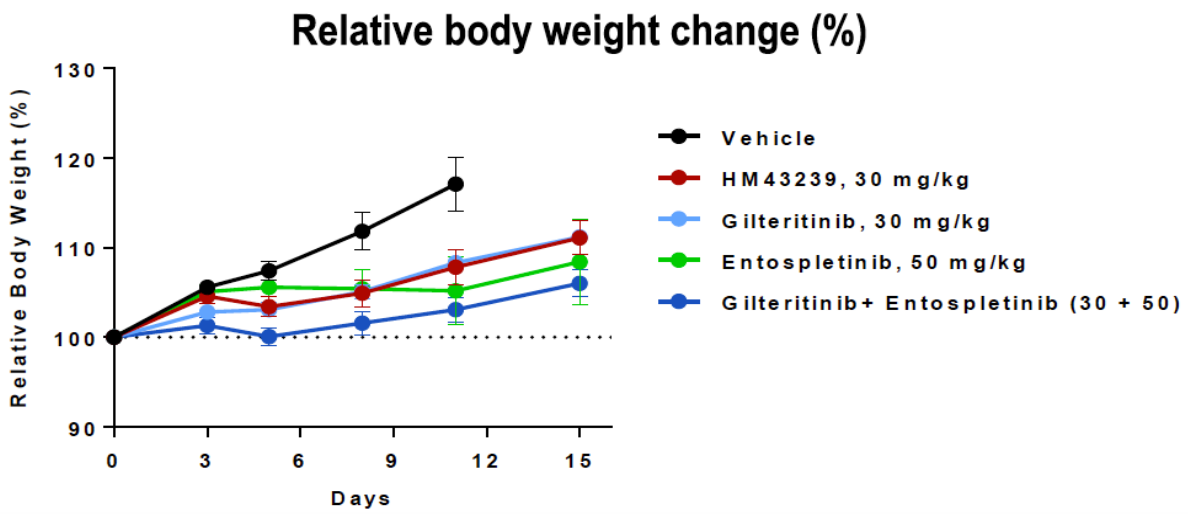


HM43239 *In Vivo* Models Suggest Superior Antitumor Activity and Favorable Tolerability Relative to Established Kinase Inhibitors in AML

MOLM-14$^{ITD/F691L-MUT}$ AML cells used with an *in vivo* murine xenograft model:

- MOLM-14$^{ITD/F691L-MUT}$ is an AML cell harboring the ITD and F691L dual mutant form of FLT3
- Cells resistant to gilteritinib FLT3 inhibitor
- HM43239 inhibits SYK and FLT3 harboring the ITD and F691L
- HM43239 superior antitumor activity to:
  - Gilteritinib FLT3i
  - Entospletinib SYKi
- HM43239 monotherapy shows similar efficacy but better tolerated than combination of Gilteritinib plus Entospletinib





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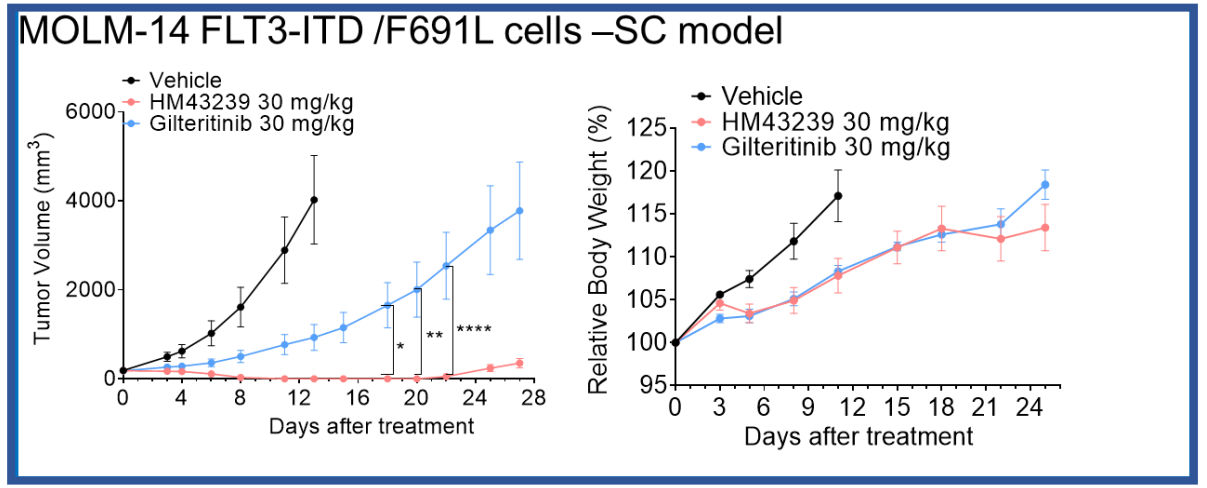
HM43239 Superior to Gilteritinib in AML Models Conducted in Mice: AML with FLT3-ITD/F691L Mutations Resistant to Gilteritinib FLT3 Inhibitor

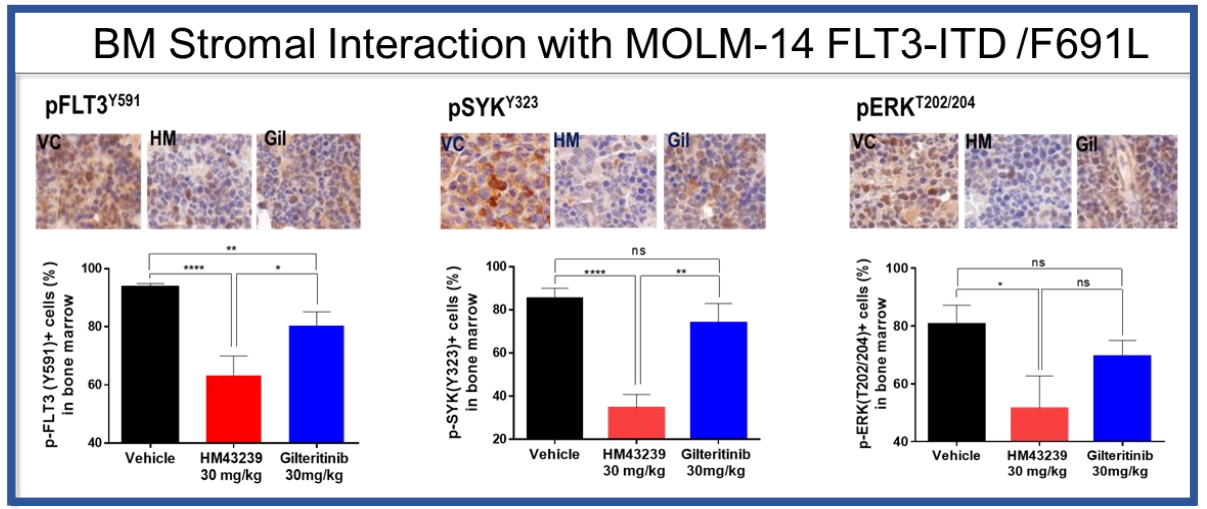
HM43239 more potent than gilteritinib : Subcutaneous AML model resistant to gilteritinib

Three million MOLM-14 FLT3-ITD/F691L cells were implanted SC in nude mice. Fifteen days later they were randomized by their tumor volume into 3 groups of 5 mice each. The mice were then treated orally QD with either placebo, 30mg/kg HM43239 or 30 mg/kg gilteritinib for 28 days. Statistical analysis utilized two-way ANOVA followed by Sidak's test.



HM43239 more potent than gilteritinib : Orthotopic/Systemic AML model resistant to gilteritinib

Mice were administered i.v. MOLM-14 FLT3-ITD/F691L cells and allowed to populate the bone marrow for 7 days, after which drugs were administered orally QD 14 days. Representative images of IHC were collected using a Dako REAL Envision Detection System (400x) and quantified with a Vectra 3 Pathology Imaging Analyzer (200x images). Positive DAB % = DAB positive area pixel / (Hematoxylin pixel + DAB positive area pixel) × 100. ▪ VC, vehicle control; HM, HM43239 30 mg/kg; Gil, Gilteritinib 30mg/kg. ▪ ns, not significant; * p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 (unpaired t test using GraphPad PRISM®, GraphPad Software)



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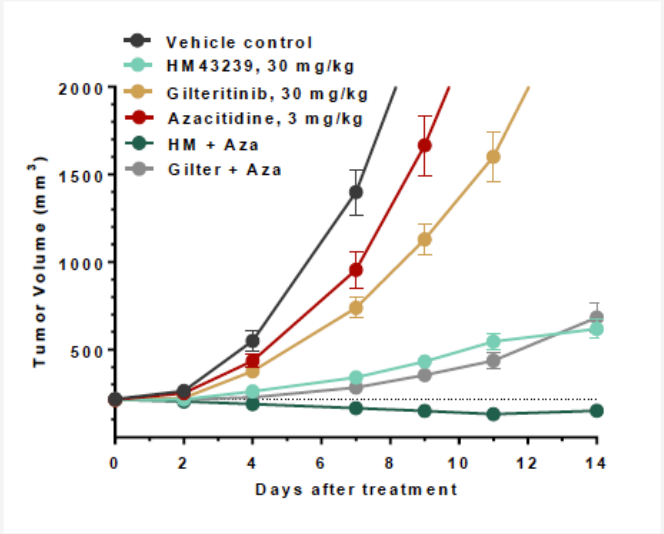
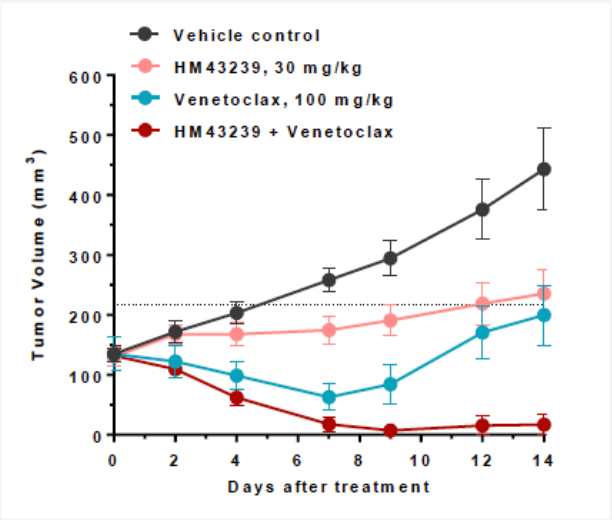
HM43239 *In Vivo* Models Suggest Synergy with Inhibitors of DNMT, BCL-2, or MDM-2, and Combinatorial Optionality in AML

Combo w/ Azacitidine (DNMT)
(MOLM-14-F691L cell model)



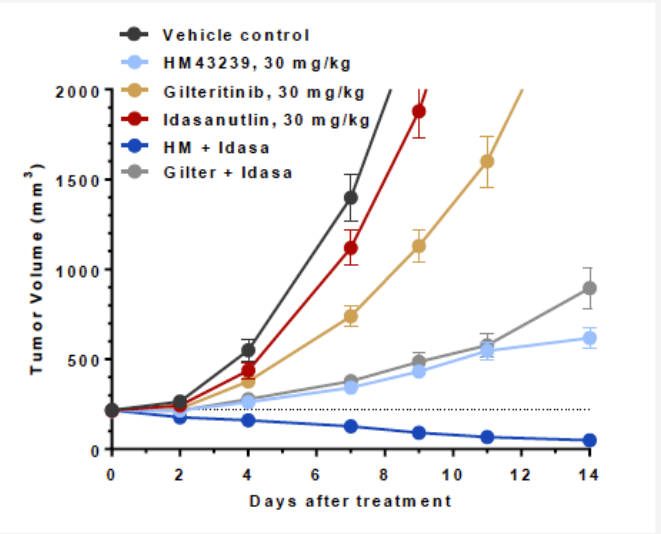
HM43239, in subcutaneous xenograft, superior efficacy to Gilt or Aza alone and combines effectively with each against MOLM-14$^{ITD/F691L\text{-}MUT}$ AML

Combo w/ Venetoclax (BCL-2)
(MV-4-11 cell model)



HM43239, in subcutaneous xenograft, superior efficacy to Venetoclax alone and combines effectively with Ven against MV4-11 AML

Combo w/ Idasanutlin (MDM-2)
(MOLM-14-F691L, NOG mouse n=10)



HM43239, in circulating AML model, superior efficacy to dasanutlin MDM2i alone and combines effectively with Idasanutlin against MOLM-14$^{ITD/F691L\text{-}MUT}$

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HM43239 Preclinical Data Position for Broad Clinical Success in AML Patients

- **Positioned as Superior to Other FLT3 Inhibitors**
  - Inhibits all forms of FLT3
  - Kills AML cells and treats AML disease in animals resistant to other approved FLT3 inhibitors
- **Positioned as a FLT3/SYK/JAK Inhibitor for AML – More than a FLT3 Inhibitor**
  - SYK inhibitor, JAK inhibitor, and c-KIT inhibitor
  - "Combination therapy in one molecule" that suppresses multiple key targets simultaneously
- **Positioned to Achieve Broad Therapeutic Window**
  - Well tolerated with oral activity in animal models
  - Antitumor activity in animal models across multiple safe dose levels
- **Favorable Pharmaceutical and CMC Properties**
  - Stable as drug substance and drug product
  - Orally administered and absorbed efficiently
  - Current tablet presentation appears acceptable for commercialization

HM43239 Phase 1/2 Study in R/R AML: Ongoing Dose Escalation & Dose Exploration

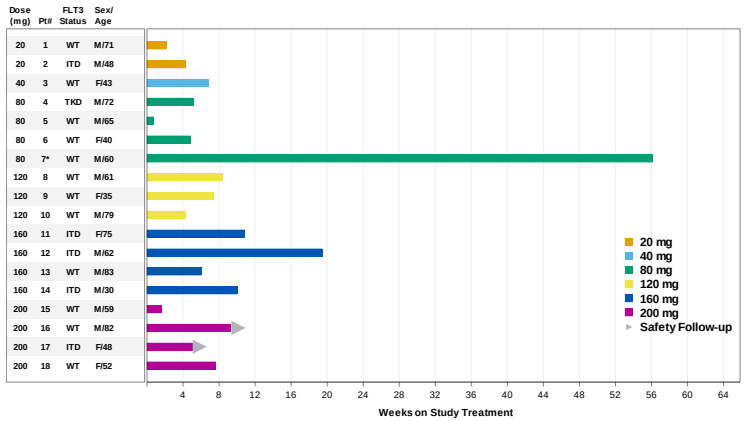
PART A : DOSE ESCALATION			PART B : DOSE EXPLORATION	
Cohort 6	200 mg QD	Ongoing		
Cohort 5	160 mg QD	Completed	160 mg QD	9 Treated → 20 Planned
Cohort 4	120 mg QD	Completed	120 mg QD	12 Treated → 20 Planned
Cohort 3	80 mg QD	Completed	80 mg QD	20 Treated
Cohort 2	40 mg QD	Completed		
Cohort 1	20 mg QD	Completed		

Favorable safety profile: No drug related SAE or death and no observed relation between delta-QTc throughout the trial. And no DLT through 160 mg dose level

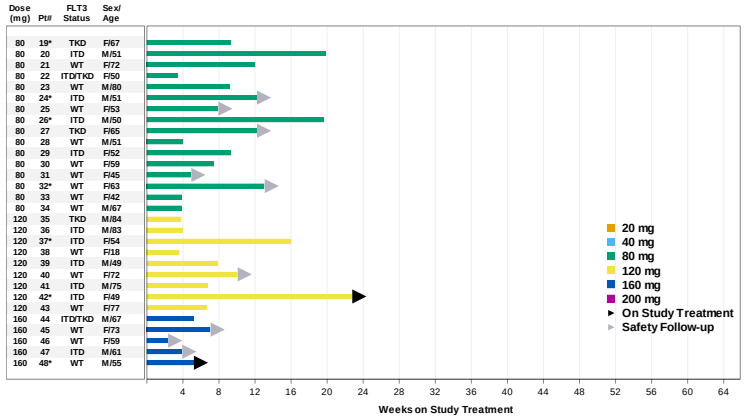
Study ongoing across several cohorts: the dose escalation cohort of 200 mg and the dose exploration cohorts of 120 mg and 160 mg are currently enrolling.

HM32239 Swimmers' Plots of R/R AML Patients Dosed Through Cut-off Date of 31May2022

PART A : DOSE ESCALATION

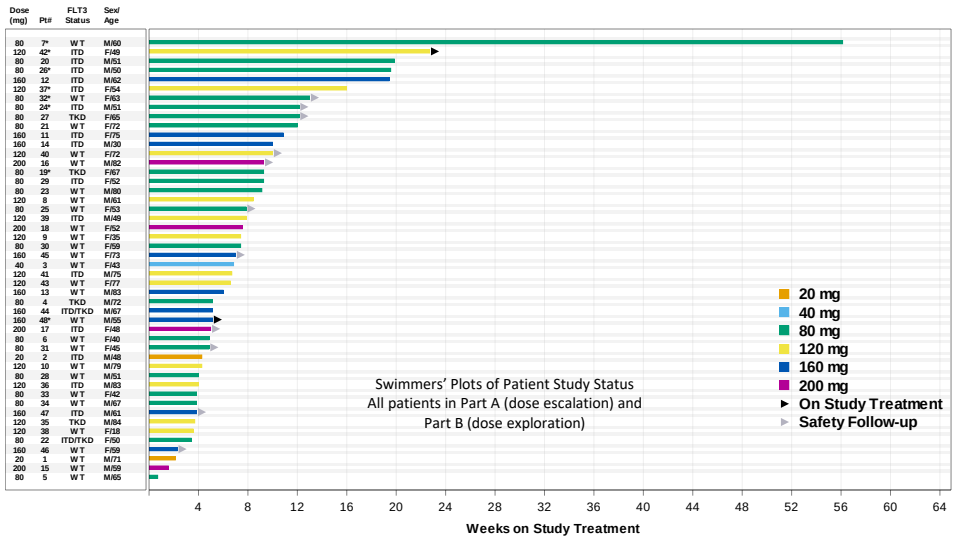


PART B : DOSE EXPLORATION



Composite Swimmers' Plot

All patients dosed through data cut-off date of 31May2022



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HM43239 Demonstrates Dose-Dependent PK and Target Engagement

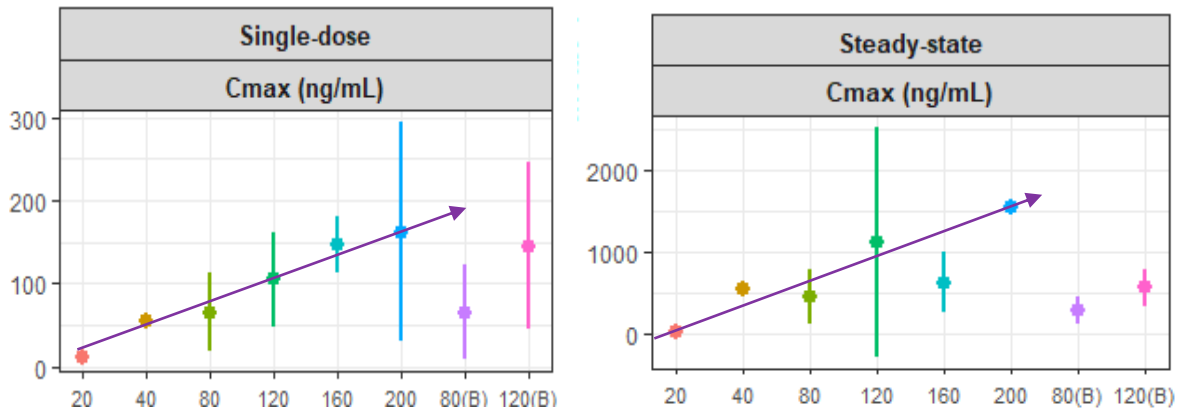
Plasma PK

Daily administered oral doses of 20, 40, 80, 120, 160 and 200mg. Plasma samples not available for all patients to date and all timepoints to date.

FINDINGS:

Generally, dose-related increase in plasma exposures

PK Parameter Mean ± SD

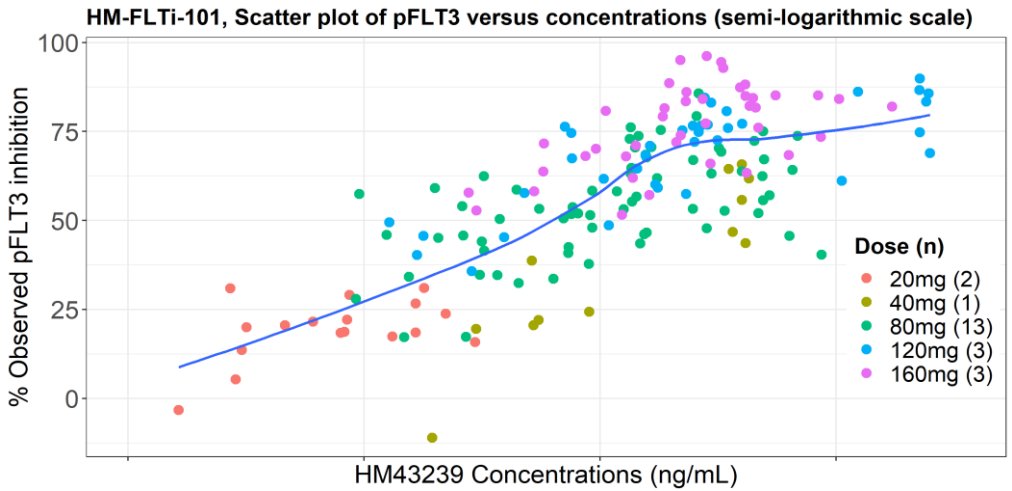


Plasma inhibitory activity (PIA) Assay

Measures the ability of patient plasma to inhibit phospho-FLT3 in MOLM-14 reporter cell line

FINDINGS:

PIA was dose-dependent with up to 90% phospho-FLT3 inhibition at dose levels ≥ 80 mg.



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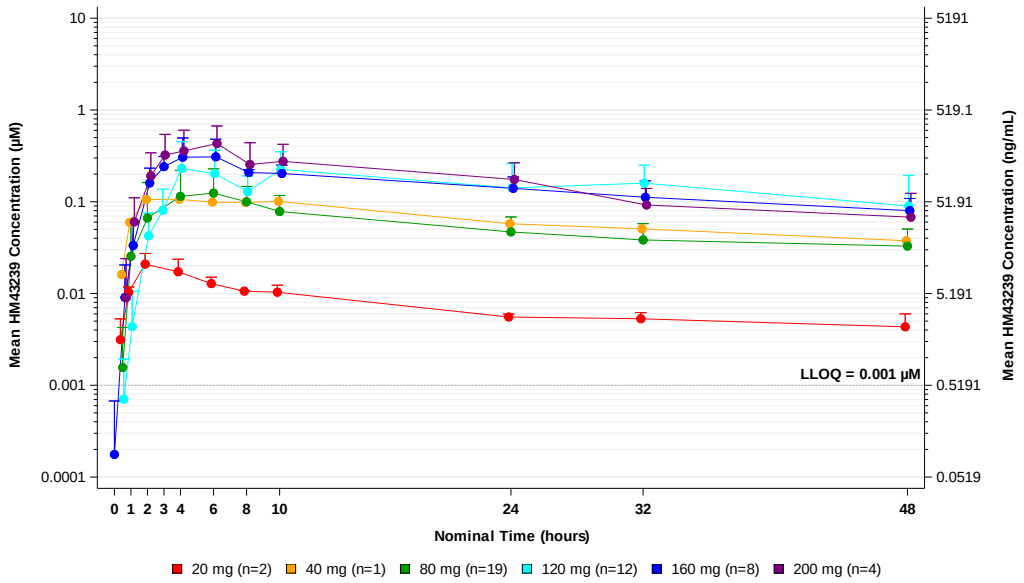
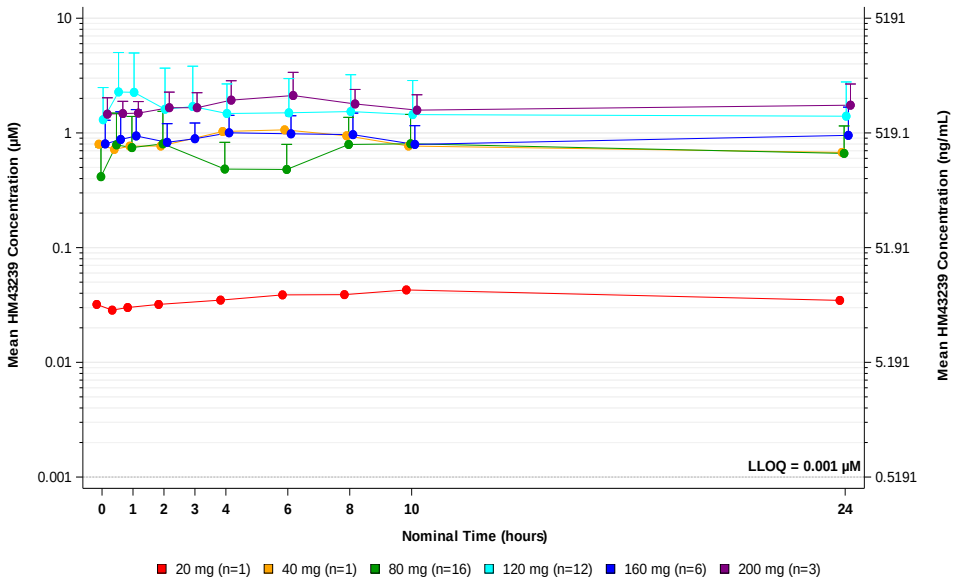
HM43239 Phase 1/2 Study in R/R AML: Pharmacokinetic Properties Following a Single Dose or at Steady State

Mean Plasma PK Concentrations (+SD) by Dose Cohort (Semi-log Scale) Single Dose



Mean Plasma PK Concentrations (+SD) by Dose Cohort (Semi-log Scale) Multiple Doses / Steady State



Data cut-off: 26APR2022

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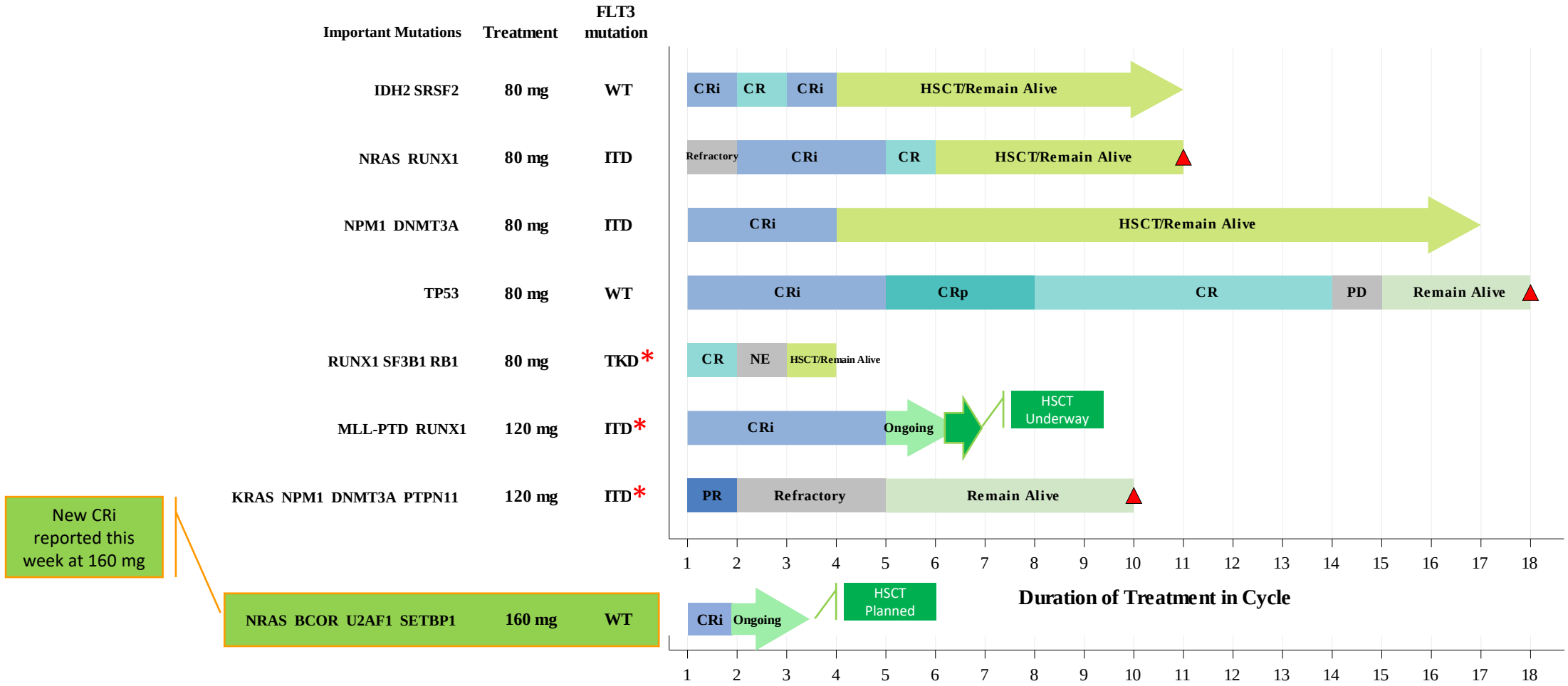
HM43239 Patients Who Achieved a Clinical Response to Date in Phase 1/2 Study of R/R AML Patients



Abbreviation: CR, complete response; CRi, complete response with incomplete hematologic recovery; CRp, complete response with incomplete platelet recovery; HSCT, hematopoietic stem cell transplantation; NE, not evaluable; PD, progressive disease; PR, partial remission.
Note: 'Ongoing' means treatment is still ongoing; 'Remain Alive' indicates patients' status in follow-up after treatment termination; The right arrow at the end of horizontal bar indicates patients are still on study, whereas without the right arrow indicates patients discontinued from study.
Note: Each response assessed at a regular visit is considered to have started 1 cycle before the assessment; however, the start of the response is considered the integer part of (study day/28) if the response occurred at the End of Treatment visit.

*Indicates patients who received prior FLT3 inhibitors, including gilteritinib and/or midostaurin.

▲ Indicates Death

- Data filtered through: 26APR2022 :Includes additional CRi after Cut-off date with $FLT^{WT}/U2AF1^{MUT}$ Patient

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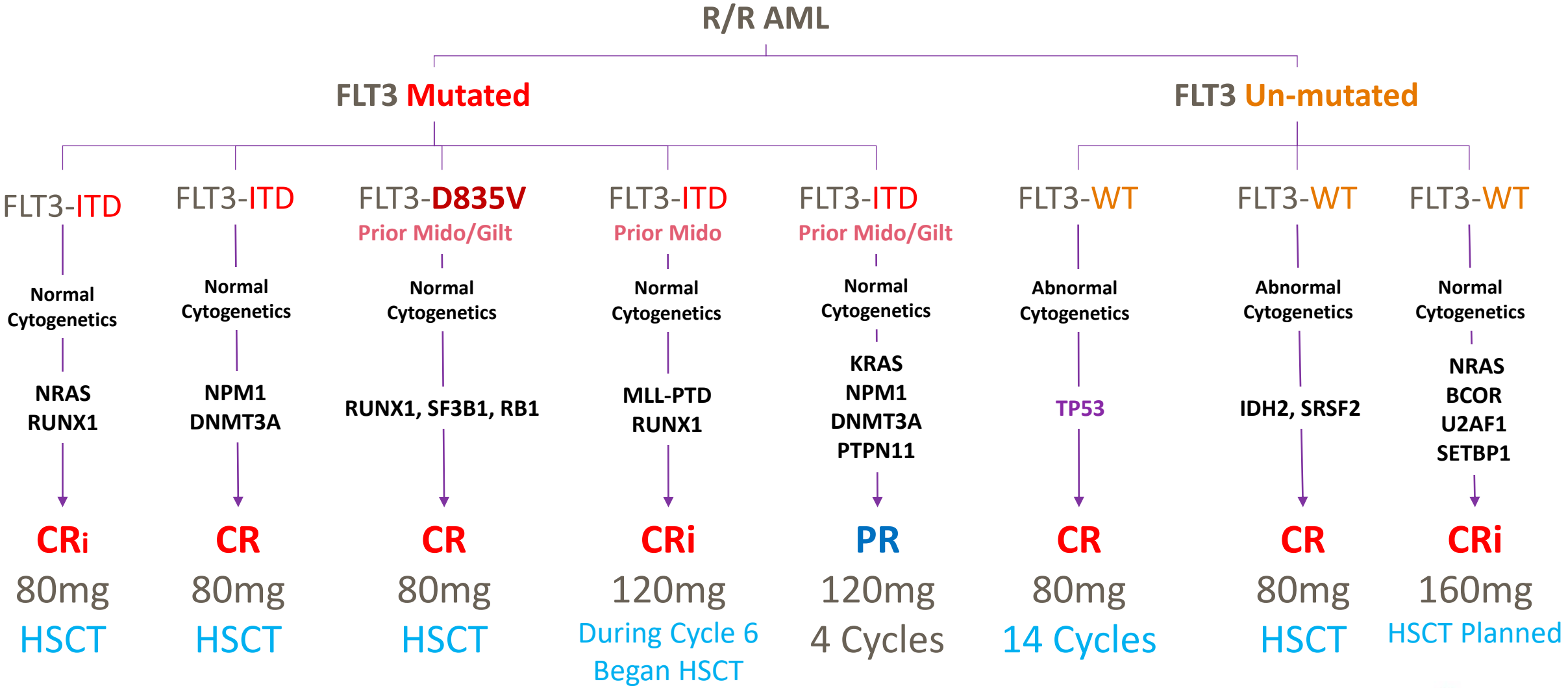
HM43239 AML Patients with Best Clinical Responses to Date
Observed 7 CRc and 1 PR in Diverse and Challenging Patient Populations



- Data as of June 2, 2022 :Includes additional CRi after Cut-off date with FLT^{WT}/$U2AF1^{MUT}$ Patient

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HM43239 Safety and Efficacy Data Revealed a Broad Therapeutic Window

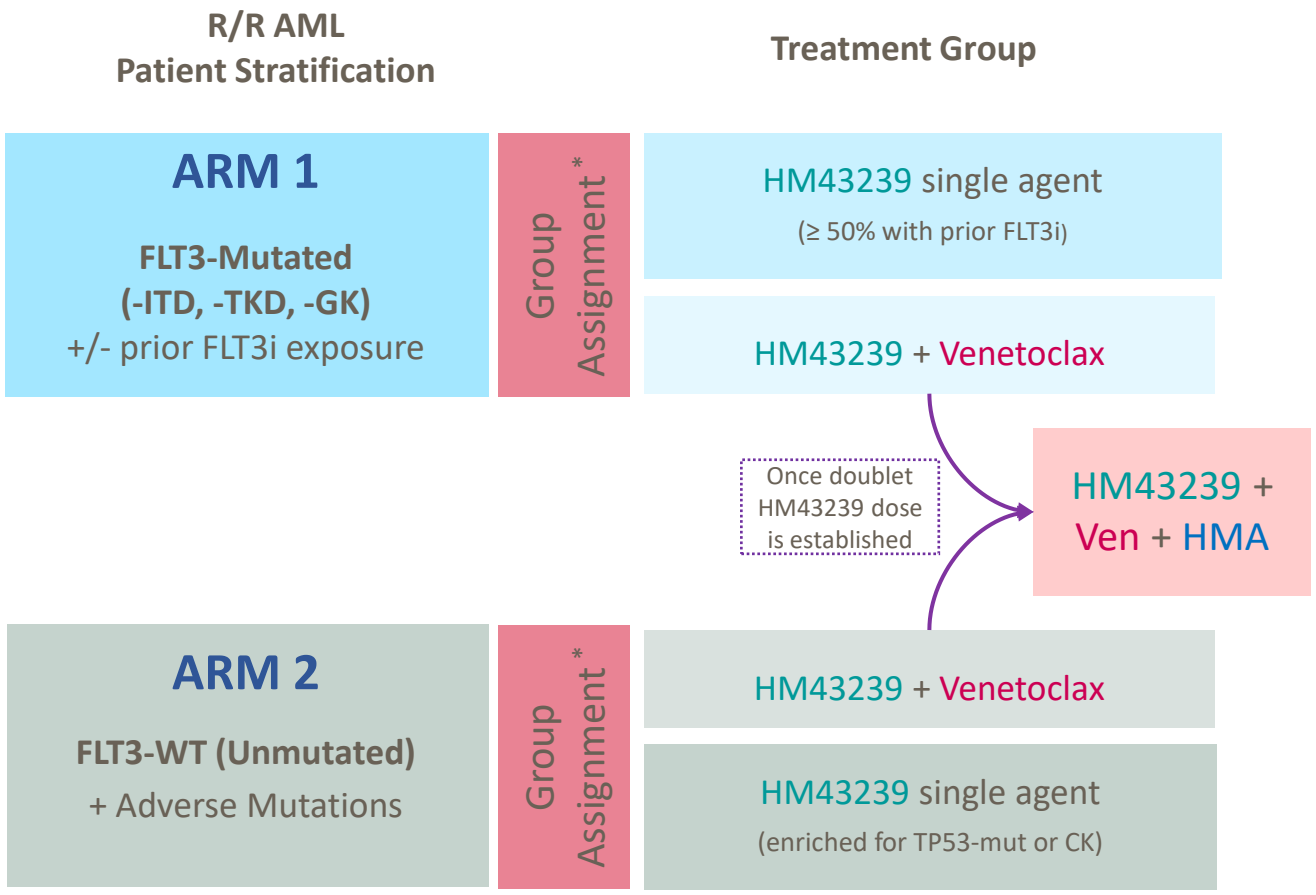
- **Safety Profile Favorable to Date**
  - No drug related SAE
  - No drug related deaths
  - No drug related AE of elevated CK
  - No drug related AE of QT prolongation – No observed relation between ΔQTc and dose
  - No DLT up to 160 mg and one DLT of muscle weakness (not rhabdomyolysis) at 200 mg
- **Identified a Therapeutic Range and Broad Therapeutic Window**
  - Safely achieved efficacy at 3 separate dose levels (80 mg, 120 mg, 160 mg) with no DLT
  - Demonstrated broad therapeutic range across safe dose levels
  - Safety profile supports combination therapy with other agents
- **Study Continuing Across Several Cohorts**
  - Dose exploration cohort of 120 mg currently enrolling and planned for a total of 20 patients
  - Dose exploration cohort of 160 mg currently enrolling and planned for a total of 20 patients
  - Dose escalation at 200 mg dose level planned to continue

Data filtered through: 26APR2022

HM43239 Teachings from Phase 1 Guide the Planned Expansion Clinical Studies

- **Current Dose Escalation/Dose Exploration Phase 1 Trial in R/R AML Patients**
  - Demonstrated **CRc in FLT3-Mutant AML** and received **Fast Track Designation in FLT3-Mutant R/R AML**
  - Selected **3 Expansion Doses** (80 mg, 120 mg, 160 mg) and **Patient Populations** for **Expansion Trials**
  - Continue **Exploration of Molecular Subgroups (Genotypes)** for potential **Fast Track** and **News Flow**
- **Transitioning to Expansion Trials in AML Patients as Prelude to Registrational Trials**
  - Plan **120 mg as Primary Single Agent Expansion Dose** with 80 mg and 160 mg as bracketing doses
  - Plan **FLT3 Mutated** R/R AML (supported by Fast Track Designation)
  - Plan **FLT3-Unmutated** R/R AML (with Adverse Mutations)
  - Plan **Single Agent** in **FLT3-Mutated** and **FLT3-Unmutated** to **begin 2H2022**
  - Plan **Combination (239+Ven)** in **FLT3-Mutated** and **FLT3-Unmutated** to **begin 1H2023**

HM43239 Next Step Planned as Phase 1 Expansion Trials (2H2022) to Provide Data Intended to Support Registrational Studies



*Patients are randomly assigned to single, doublet, or triplet combination groups based on the open slots available in each group.

Key Objectives

Primary:

- Safety and tolerability
- Confirm HM43239 single agent RP2D
- Select HM43239 candidate RP2D in combination with venetoclax
- Select HM43239 candidate R2PD dose in combination with venetoclax and HMA

Secondary:

- CR_c rate (CR + CR_h + CR_p + CR_i)
- Best response rate (CR_c + PR)
- Duration of response (DOR)
- Overall survival (OS)

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Major Objectives and AML Target Populations Sought for HM43239

1. R/R AML FLT3+ post FLT3 inhibitor :
   Limited treatment options for patients

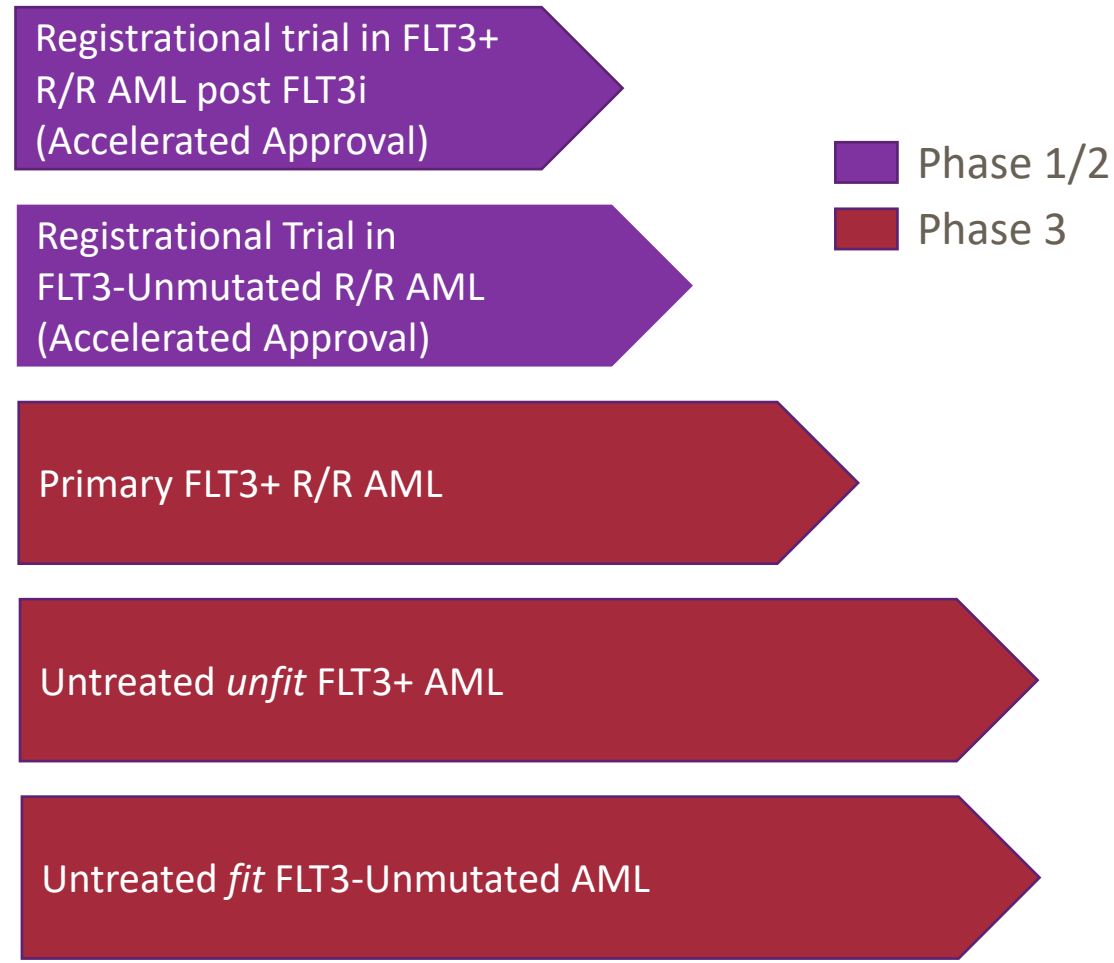
2. R/R AML FLT3-Unmutated with adverse mutations:
   Most patients have limited treatment options, especially if they have received BCL2i and HMAs as frontline treatment

3. R/R AML FLT3+ through combination:
   Build upon standard of care for patients in combination with with BCL2i and/or HMAs

4. 1L *unfit* AML FLT3+ patients:
   Provide superior treatment option for untreated not eligible for high dose chemotherapy

5. 1L *fit* AML FLT3-Unmutated:
   Provide superior non high dose chemotherapy option

6. **High safety & tolerability** suggest potential for use in **maintenance therapy** following HSCT and **preferred partner for oral multi-drug combination therapy**



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HM43239 Overall Response Rate (7 CRc and 1 PR) to Date in Phase 1 as a Single Agent in R/R AML Patients

Mutation Status	All Patients			Evaluable Patients		
	N = 45 Patients	Number Responders	Response Rate	N = 41 Patients	Number Responders	Response Rate
FLT3+	20	5	25%	19	5	26.3%
FLT3+ with prior FLT3i	**7**	**3**	**42.9%**	**7**	**3**	**42.9%**
FLT3-WT	25	3	12%	22	3	13.6%
TP53+	**4**	**1**	**25%**	**3**	**1**	**33.3%**

Overall Response Rate for "All Patients" and "Evaluable Patients" Receiving ≥ 80mg HM43239

- Findings represent a snapshot in time: The reported safety, tolerability, PK, PD and efficacy findings reported herein represent the data available at this time and may change as additional patients are assessed and more data are collected.
- The "Evaluable Patients" removes those non-evaluable patients who did not have a response evaluation and had no other evidence indicating refractory disease in the peripheral blood.
- Most (6 of 7) CRc patients went to HSCT and cannot be evaluated for transfusion independence assessment.
- Analysis Date: 06 June 2022

Abbreviation: CR, complete remission; CRc, composite complete remission; CRp, complete remission with incomplete platelet recovery; CRi, complete remission with incomplete hematological recovery; PR, partial remission.
Note: efficacy evaluable patients include all patients with at least 80% drug compliance during Cycle 1 or who had reported a DLT during Cycle 1, and who reported relevant data for efficacy interpretation such as bone marrow assessment, CBC counts, reason for treatment termination.
[1] Overall response includes CRc and PR.
[2] CRc includes CR, CRh, CRp and CRi.
[3] The reported prior FLT3 inhibitors include gilteritinib, midostaurin and soranfenib.

HM43239 Clinically Validated, Once Daily, Oral Myeloid Kinome Inhibitor

Targets Constellation of Kinases Important in Myeloid Cancers

- Potent inhibitor of kinases associated with malignant transformation and resistance
- Highly active *in vivo* against FLT3 internal tandem duplication (ITD), resistance-conferring tyrosine kinase domain mutations (TKD) , and gatekeeper mutations (F691)
- Highly active on SYK, JAK1/2 and mutant forms of c-KIT

Clinical Validation Supports Path of Rapid Development for AML Patients

- **FLT3-Mutated Patients**
  - CRc in patients with mutated FLT3
  - Including ITD and D835 TKD mutations
  - Including those who failed prior FLT3 inhibitors (midostaurin and gilteritinib)
  - Received FDA Fast Track in $FLT3^{MUT}$ R/R AML
- **FLT3-Unmutated Patients**
  - CRc in patients with unmutated FLT3
  - CRc in patients harboring diverse mutations: NPM1, DNMT3A, N/KRAS, MLL, TP53, IDH2, U2AF1, RUNX1, Others
- **Broad Therapeutic Window**
  - Well tolerated across three active doses supports combination therapy with other agents

Program Goals for 2022 Supporting Rapid Development

- Exploring additional adverse genotypes for sensitivity
- Provide rolling presentation of clinical findings throughout 2022
- Plan to initiate Expansion Trial as single agent 2H2022
- Plan to initiate Expansion Trial as combination 1H2023
- Planning for registrational studies

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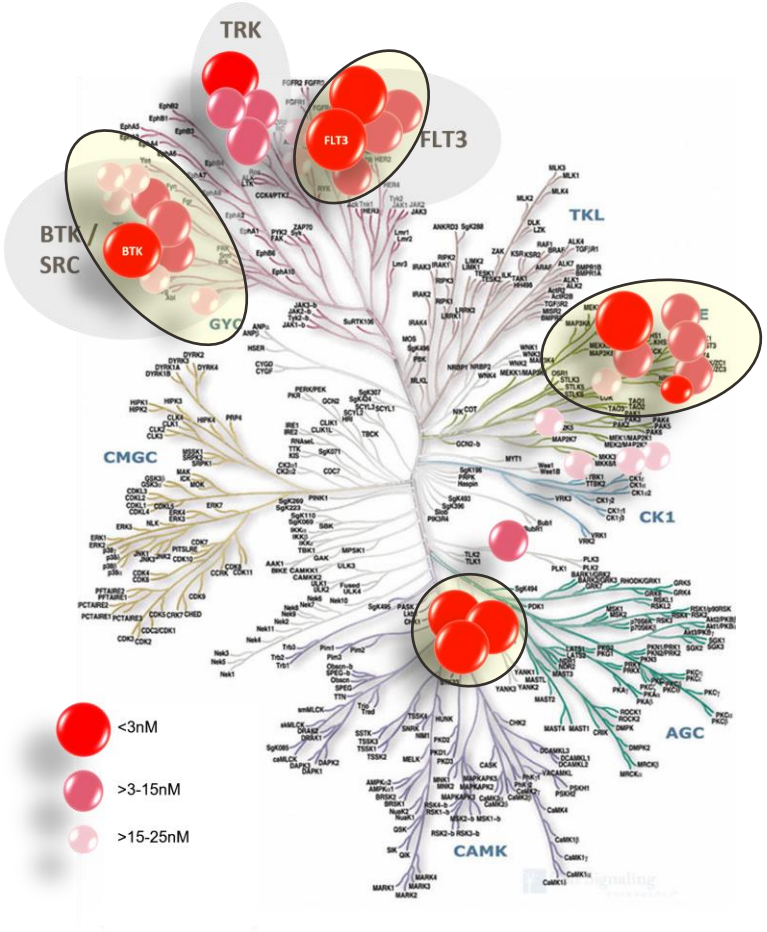
Luxeptinib

Oral Lymphoid & Myeloid Kinome Inhibitor

Luxeptinib: Atypical, Dual Lymphoid and Myeloid Kinome Inhibitor



Unique Kinome Targeting

Inhibits high value targets: BTK, FLT3, CSF1R, PDGFRα, TRK, AURK

Only agent to potently inhibit the validated **BTK** and **FLT3**

In development for the treatment of both lymphoid & myeloid hematologic cancers

Mutation Agnostic

Inhibits **WT and all mutant forms** of BTK

Inhibits **WT and all mutant forms** of FLT3

May avoid rapid emergence of drug resistance

Robust Safety Profile

Simultaneously suppresses multiple oncogenic signaling pathways

Avoids kinases that negatively impact safety

Generally, well tolerated in clinical studies to date

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Published three peer reviewed research articles illustrating the potential of Luxeptinib for application to multiple indications:

AML

Lymphomas

Inflammation

Autoimmunity

May 2, 2022

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Luxeptinib Preclinical Data Extend Potential Applications from Oncology to Inflammation

Three Recent Peer-reviewed Journal Articles Reflect Distinctive Properties of Luxeptinib

SAN DIEGO and TORONTO, May 02, 2022 (GLOBE NEWSWIRE) -- Aptose Biosciences Inc. ("Aptose" or the "Company") (NASDAQ: APTO, TSX: APS), a clinical-stage precision oncology company developing highly differentiated oral kinase inhibitors to treat hematologic malignancies, today highlighted recent publications of preclinical data for luxeptinib (CG-806) in three peer-reviewed scientific journals. Luxeptinib, Aptose's oral, dual lymphoid and myeloid kinome inhibitor, is an investigational drug currently in two Phase 1 a/b trials: one in patients with relapsed or refractory B cell malignancies, and separately in patients with relapsed or refractory acute myeloid leukemias (AML) or high-risk myelodysplastic syndromes (MDS).

Biochemical Pharmacology 195 (2022) 114861

Contents lists available at ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

Luxeptinib disables NLRP3 inflammasome-mediated IL-1β release and pathways required for secretion of inflammatory cytokines IL-6 and TNFα

Himangshu Sonowal [a], Hongying Zhang [b], William Rice [b], Stephen B. Howell [a,*]

[a] Moores Cancer Center, Division of Hematology, Department of Medicine, University of California, San Diego, CA, USA
[b] Aptose Biosciences, Inc., San Diego, CA, USA

ARTICLE INFO

Keywords:
Luxeptinib
CG-806
NLRP3
Caspase-1
Inflammation
IL-1β
IL-6
TNFα

ABSTRACT

Luxeptinib (CG-806) is an orally bioavailable multikinase inhibitor with nanomolar potency against select clusters of kinases including the BTK, FLT3, TRK, STE/MAPK and aurora kinase clusters. It is cytotoxic to primary malignant cells obtained from patients with AML, ALL, and CLL at lower concentrations than other BTK and FLT3 inhibitors, and has activity in AML and lymphoma xenografts at concentrations attainable in patients. Exposure of macrophages and monocytes to endotoxin triggers the release of IL-1β through activation of the NLRP3 inflammasome and IL-6 and TNFα through transcriptional up-regulation. These cytokines are key components of the innate immune signaling network that plays a central role in the pathogenesis of multiple human diseases including cancer. Drugs that concurrently inhibit proliferation and inflammatory signaling pathways may provide better therapeutic efficacy. The aim of this study was to determine the extent to which luxeptinib interferes with the release of IL-1β, IL-6 and TNFα from THP-1 monocytes and bone marrow-derived macrophages following endotoxin exposure and priming of the NLRP3 inflammasome. Luxeptinib inhibited the release of all 3 cytokines from THP-1 monocytes and macrophages at concentrations of 0.1 μM and above. Investigation of the mechanism disclosed that luxeptinib does not inhibit the assembly of the NLRP3 inflammasome but disables its ability to cleave and activate caspase-1 that is required for IL-1β release. It also inhibits the kinases p38MAPK, ERK1/2, SAPK/JNK and activation of transcription factor NF-κBp65 with a concentration profile similar to its inhibition of cytokine release.
Implications: The ability of luxeptinib to inhibit the NLRP3-mediated release of IL-1β and pathways involved in the release of IL-6 and TNFα at concentrations which are well-tolerated in patients makes it a candidate for the treatment of inflammatory diseases and inflammation-associated resistance in cancer.

CDDpress

www.nature.com/cddis

ARTICLE OPEN

Check for updates

Dual BTK/SYK inhibition with CG-806 (luxeptinib) disrupts B-cell receptor and Bcl-2 signaling networks in mantle cell lymphoma

Elana Thieme[1,7], Tingting Liu[1,7], Nur Bruss[2], Carly Roleder[1], Vi Lam[1], Xiaoguang Wang[1], Tamilla Nechiporuk[2,3], Geoffrey Shouse[1], Olga V. Danilova[1], Daniel Bottomly[2,4], Shannon K. McWeeney[2,4,5], Jeffrey W. Tyner[2,3,6], Stephen E. Kurtz[2,3] and Alexey V. Danilov[1,2]

Aberrant B-cell receptor (BCR) signaling is a key driver in lymphoid malignancies. Bruton tyrosine kinase (BTK) inhibitors that disrupt BCR signaling have received regulatory approvals in therapy of mantle cell lymphoma (MCL). However, responses are incomplete and patients who experience BTK inhibitor therapy failure have dire outcomes. CG-806 (luxeptinib) is a dual BTK/SYK inhibitor in clinical development in hematologic malignancies. Here we investigated the pre-clinical activity of CG-806 in MCL. In vitro treatment with CG-806 thwarted survival of MCL cell lines and patient-derived MCL cells in a dose-dependent manner. CG-806 blocked BTK and SYK activation and abrogated BCR signaling. Contrary to ibrutinib, CG-806 downmodulated the anti-apoptotic proteins Mcl-1 and Bcl-xL, abrogated survival of ibrutinib-resistant MCL cell lines, and partially reversed the pro-survival effects of stromal microenvironment-mimicking conditions in primary MCL cells. Dual BTK/SYK inhibition led to mitochondrial membrane depolarization accompanied by mitophagy and metabolic reprogramming toward glycolysis. In vivo studies of CG-806 demonstrated improved survival in one of the two tested aggressive MCL PDX models. While suppression of the anti-apoptotic Bcl-2 family proteins and NFκB signaling correlated with in vivo drug sensitivity, OxPhos and MYC transcriptional programs were upregulated in the resistant model following treatment with CG-806. *BAX* and *NFKBIA* were implicated in susceptibility to CG-806 in a whole-genome CRISPR-Cas9 library screen (in a diffuse large B-cell lymphoma cell line). A high-throughput in vitro functional drug screen demonstrated synergy between CG-806 and Bcl-2 inhibitors. In sum, dual BTK/SYK inhibitor CG-806 disrupts BCR signaling and induces metabolic reprogramming and apoptosis in MCL. The Bcl-2 network is a key mediator of sensitivity to CG-806 and combined targeting of Bcl-2 demonstrates synergy with CG-806 warranting continued exploration in lymphoid malignancies.

Cell Death and Disease (2022)13:246 ; https://doi.org/10.1038/s41419-022-04684-1

Luxeptinib (CG-806) targets FLT3 and clusters of kinases operative in acute myeloid leukemia

William G. Rice[1], Stephen B. Howell[2], Hongying Zhang[1], Nasrin Rastgoo[1], Andrea Local[1*], Stephen E. Kurtz[3,4], Pierrette Lo[3,4], Daniel Bottomly[3,5], Beth Wilmot[3,5], Shannon K. McWeeney[3,5], Brian J. Druker[3,4], Jeffrey W. Tyner[3,4,6]

[1]Aptose Biosciences, Inc, San Diego, CA; [2]Department of Medicine and the Moores Cancer Center, University of California, San Diego, San Diego, CA; [3]Knight Cancer Institute, Oregon Health & Science University, Portland, OR; [4]Division of Hematology and Medical Oncology, Oregon Health & Science University, Portland, OR ; [5]Division of Bioinformatics and Computational Biology; Oregon Health & Science University, Portland, OR; [6]Department of Cell, Developmental & Cancer Biology, Oregon Health & Science University, Portland, OR.

*Current address: Bristol Myers-Squibb, San Diego, CA.

Running Title: Luxeptinib targets kinases in AML

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Luxeptinib: Ongoing Phase 1a/b Study in Heavily Pretreated B-cell Malignancies

Following completion of Cohort 6 with original G1 formulation, patients enrolled to receive single dose of new G3 formulation in addition to G1 at Q12H

Cohort 6	900 mg Q12H	**Completed**
Cohort 5	750 mg Q12H	**Completed**
Cohort 4	600 mg Q12H	**Completed**
Cohort 3	450 mg Q12H	**Completed**
Cohort 2	300 mg Q12H	**Completed**
Cohort 1	150 mg Q12H	**Completed**

Objectives

Ongoing Phase 1 a/b, open-label, single arm, multicenter, 3 + 3 dose-escalation clinical study (NCT03893682).

Primary objectives:

- Assess safety and tolerability of luxeptinib (CG-806)
- Determine recommended Phase 2 dose (RP2D)

Key secondary objectives:

- Assess PK profile and PD activity
- Obtain preliminary evidence of antitumor activity
- Characterize the bioavailability (BA) of G2 vs. the original G1 formulations

Dose Escalation Phase

- Patients administered **oral capsules, twice daily** on a **28-day cycle**
- Plan to perform 7 dose levels
- Planned expansion cohorts
- **Accelerated titration** design
- Additional patients may be enrolled (**back filling**) at dose levels previously declared safe
- **Intra-patient dose escalation** is allowed if higher dose is safe in 3 or more patients

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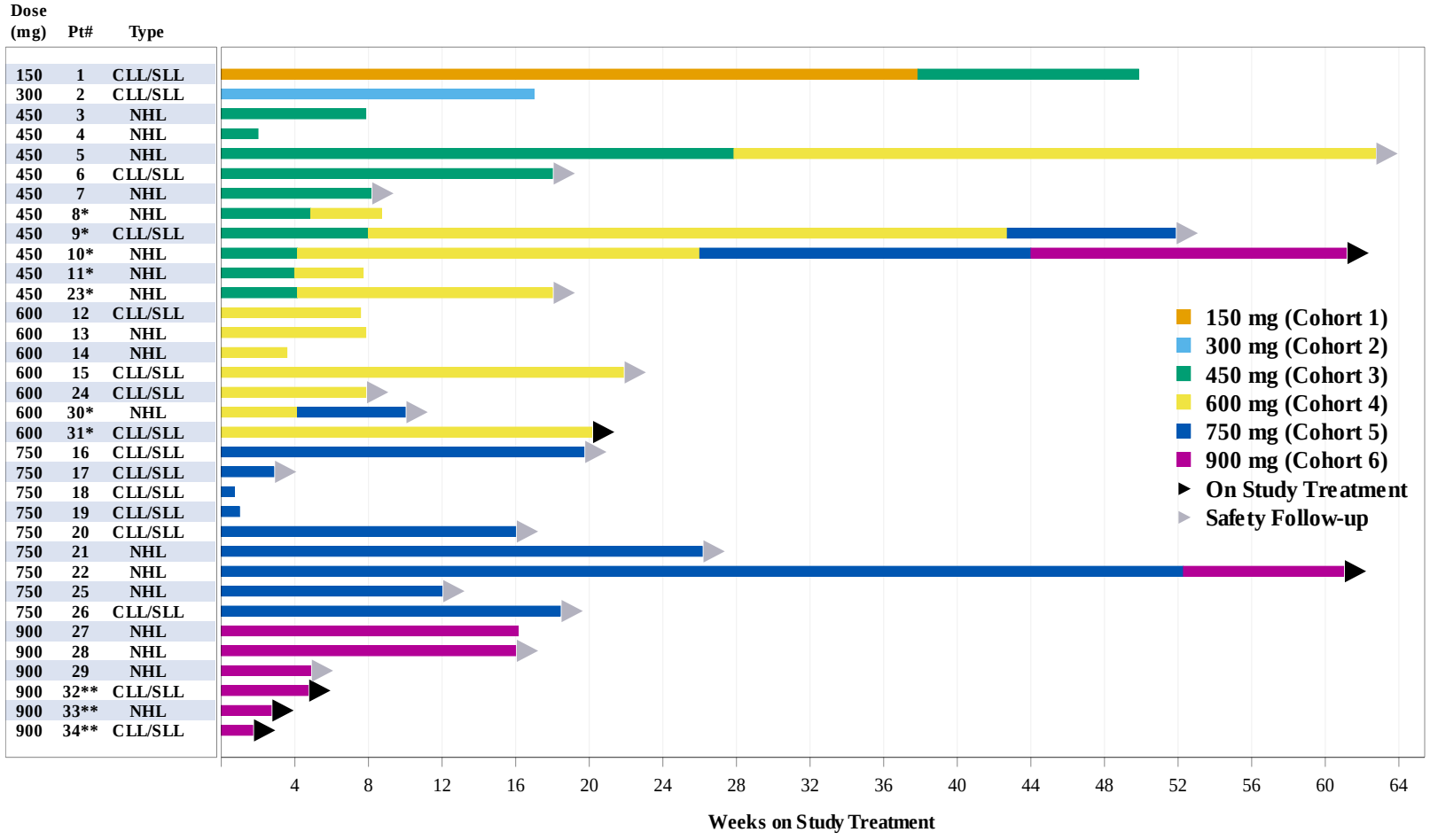
Luxeptinib: Swimmers' Plot of Heavily Pretreated Patients with R/R B-Cell Malignancies Treated with Luxeptinib



Data Cut-off Date of 31 May 2022

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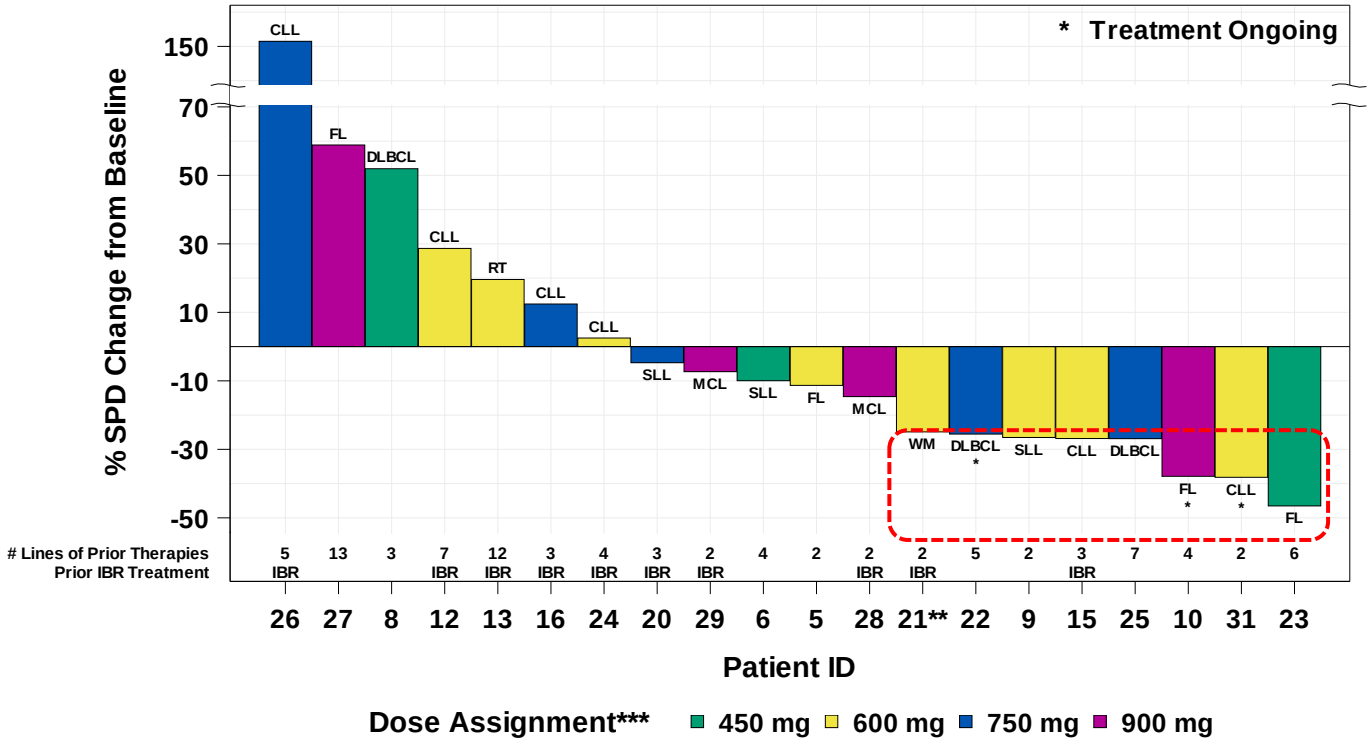
Luxeptinib: Waterfall Plot of Best Response Shows Encouraging Antitumor Activity Trend in Heavily Pretreated Patients with B-Cell Malignancies

Encouraging Trends:

- Observing greater antitumor activity with higher dose levels, higher plasma concentrations, and longer time on study drug
- Observing antitumor activity across diverse B-cell cancers

Best Response in Evaluable Patients

Includes all patients who had at least one imaging for tumor measurements or IgM measurement (WM patient) since starting treatment (n=16)



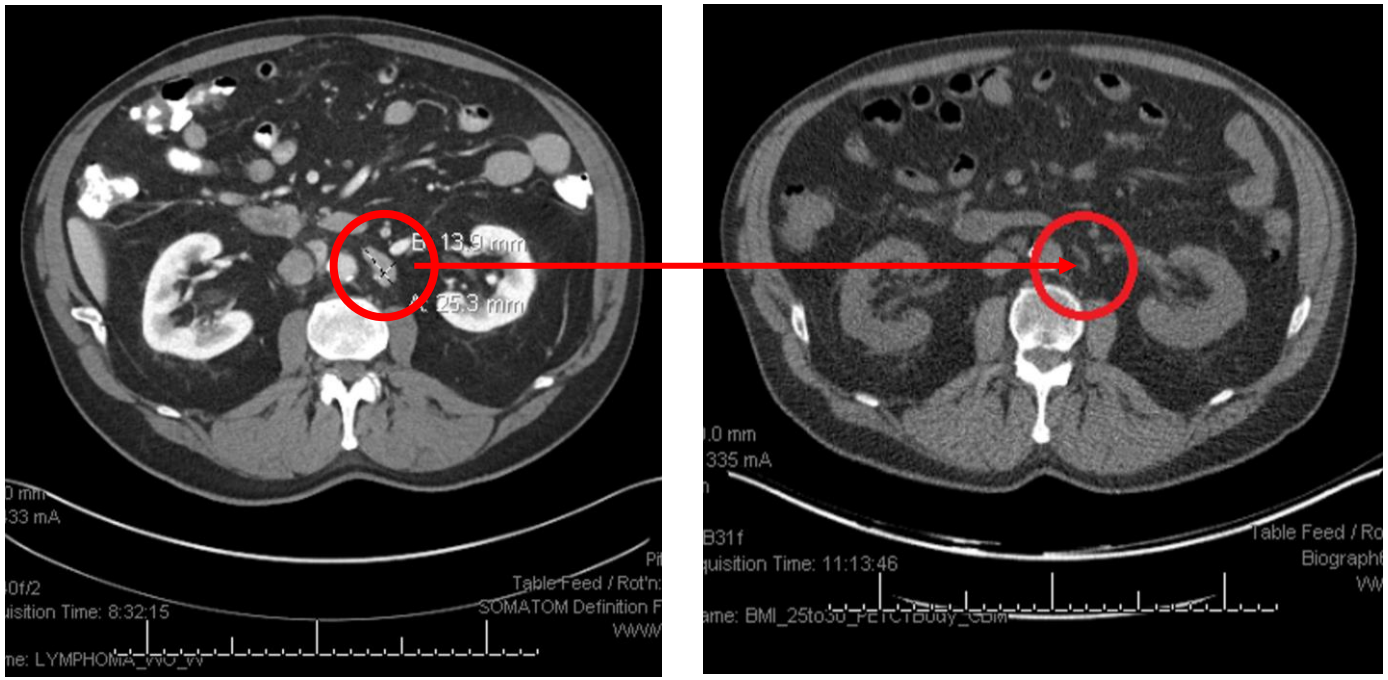
Note: IBR = Ibrutinib
Note: Only patients with post-screening assessments are shown on plot
**WM patient(s) measuring % IgM
***Dose level shown from time of disease assessment, if at least 1 cycle of doses received at this level
Source: Z:\SASShare\CG-806\CG-806-01\Program\Stat\f_waterfall_806_CLL_WM_BTKI.sas 31MAY2022 10:08

Data cut-off: 31May2022

APTOSE BIOSCIENCES

Luxeptinib Case Study: Significant Tumor Reduction (47%) with Accompanying Complete Metabolic Response (CMR) in Patient with Refractory Follicular Lymphoma

Screening



Cycle 5 Day 1

Follicular Lymphoma	Complete Metabolic Response and Tumor Reduction
Patient	72-year-old Male with Follicular Lymphoma : Received 450mg BID Luxeptinib
Prior Therapies Failed	• revlimid+obinutuzumab, obinutuzumab, ublituximab, umbralisib
Response at C5D1	• **47% tumor reduction by SPD (PR requires 50%); 29% Reduction by SLD (PR requires 30%)** • **CMR (Complete Metabolic Response) by Cycle 3**

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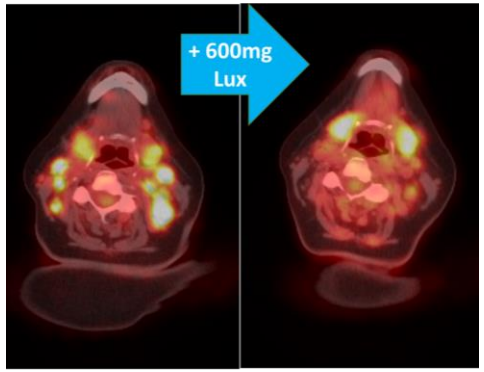
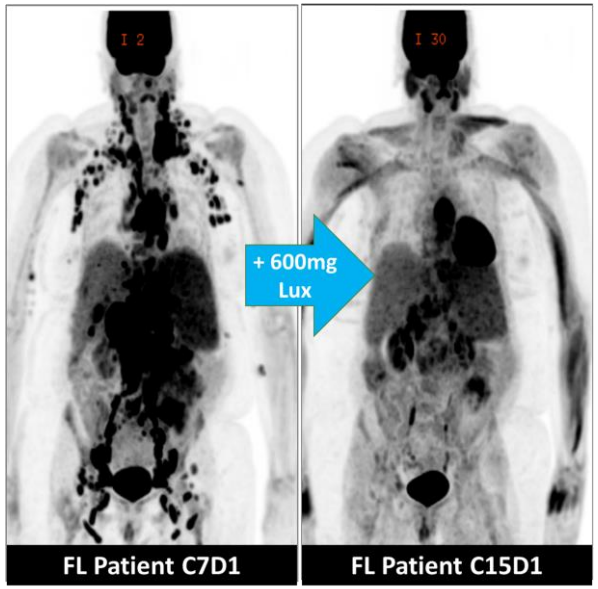
Luxeptinib Case Study: Dose-dependent Anti-tumor Activity in a Patient with Refractory Follicular Lymphoma



FL Patient C7D1 Neck | FL Patient C15D1 Neck



Follicular Lymphoma	Significant Tumor Reduction and Well Tolerated
Demographics	60-year-old female
Diagnosis at Study Entry	Grade 1 FL
Prior Therapies Failed	• bendamustine + obinutuzumab • rituximab
Dose	**450mg** BID 7 cycles, followed by **600mg** BID 8 cycles
Response	**Tumor growth continued, though slowed, while on 450mg BID through 7 cycles:** • SPD increased 28.2%, 10.7% and 8.7% at C3D1, C5D1 and C7D1, respectively, when compared with previous FDG PET-CT scan **43% tumor reduction from peak (12% below baseline) upon dose escalation to 600mg BID:** • Following dose escalation to 600mg in cycle 8, lesion growth arrested, followed by continuous reduction to below baseline • By C15D1, primary lesions shrank by 42.5% and 11.3% when compared with highest measurement (C7D1) and baseline (screening), respectively

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Luxeptinib: Ongoing Phase 1a/b Study in R/R AML and HR MDS

G3 capsules introduced into ongoing cohort 4

Cohort 4	900 mg Q12H	**Ongoing**
Cohort 3	750 mg Q12H	**Completed** ✓
Cohort 2	600 mg Q12H	**Completed** ✓
Cohort 1	450 mg Q12H	**Completed** ✓

PATIENT POPULATION

Relapsed or refractory AML and higher-risk MDS who **failed or are ineligible for / intolerant of** intensive chemotherapy or transplantation

- Patients failed by FLT3i, IDHi, venetoclax, chemotherapy
- Patients unfit for intensive therapy or failed by HSCT

Objectives

Ongoing Phase 1 a/b, open-label, single arm, multicenter, 3+3 dose-escalation clinical study (NCT04477291).

Primary objectives:

- Assess safety and tolerability of luxeptinib (CG-806)
- Determine maximum tolerated dose (MTD) and / or recommended Phase 2 dose (RP2D)

Key secondary objectives:

- Assess PK profile and PD activity
- Obtain preliminary evidence of antitumor activity

Dose Escalation Phase

- **Oral capsules administered twice daily** on a **28-day cycle**
- Planned expansion cohorts after dose escalation
- Additional patients may be enrolled (**back filling**) at dose levels previously declared safe
- **Intra-patient dose escalation** is allowed if higher dose is safe in 3 or more patients

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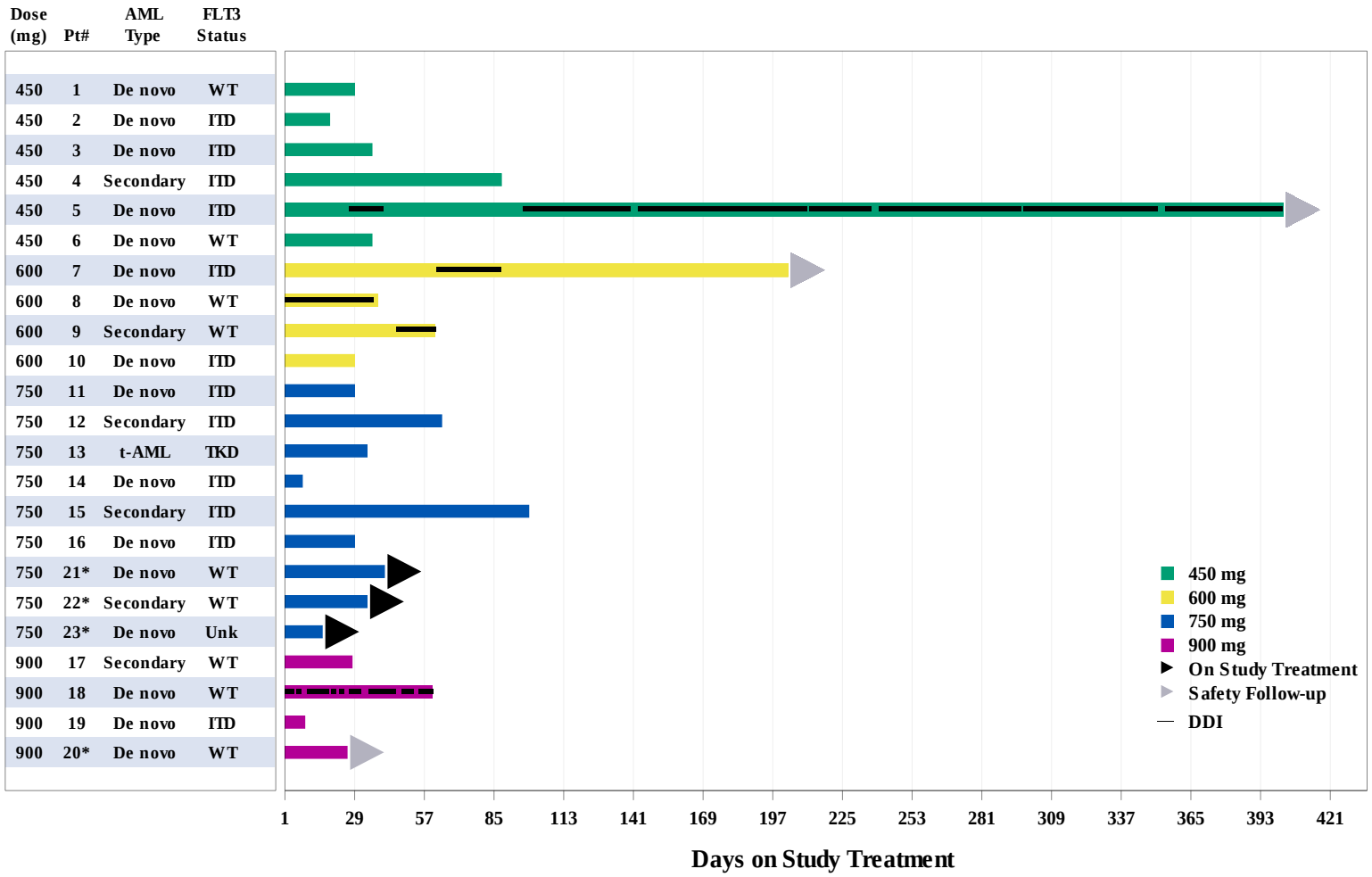
Luxeptinib: Swimmers' Plot of Heavily Pretreated Patients with R/R AML Treated with Luxeptinib



Data Cut-off Date of 31 May 2022

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Luxeptinib Case Study: Durable MRD-negative CR in FLT3+ Patient with high plasma exposure levels

FLT3-ITD+ R/R AML	CR / MRD-
Demographics	46-year-old male
Diagnosis at Study Entry	**FLT3-ITD+, relapsed de novo AML** with myeloid sarcoma (bone marrow & extra medullary disease)
Prior Therapies	• **Heavily pretreated, failed by chemotherapy / prior-FLT3i / 2 allogeneic transplants** • Induction chemotherapy, followed by salvage chemotherapy + **FLT3i** followed by **HSC** Transplant #1 • Following **HSC** relapse, treated with decitabine + venetoclax + **FLT3i** followed by 2nd **HSC** Transplant • Following 2nd **HSC** relapse & increased BM blast received focal radiation to perispinal mass
Dose	450mg BID luxeptinib
Response	• Abnormal bone marrow blast reduced to 0.6% on C2D1 and remained undetectable thereafter • Patient experienced **no myelosuppression** with blood counts sustained at normal levels • Highly sensitive flow cytometry detected **no abnormal blasts in bone marrow** at C4D1 and C5D3

MRD- CR: FLT3+ patient continues on study in Cycle 13

Luxeptinib Ongoing Activities

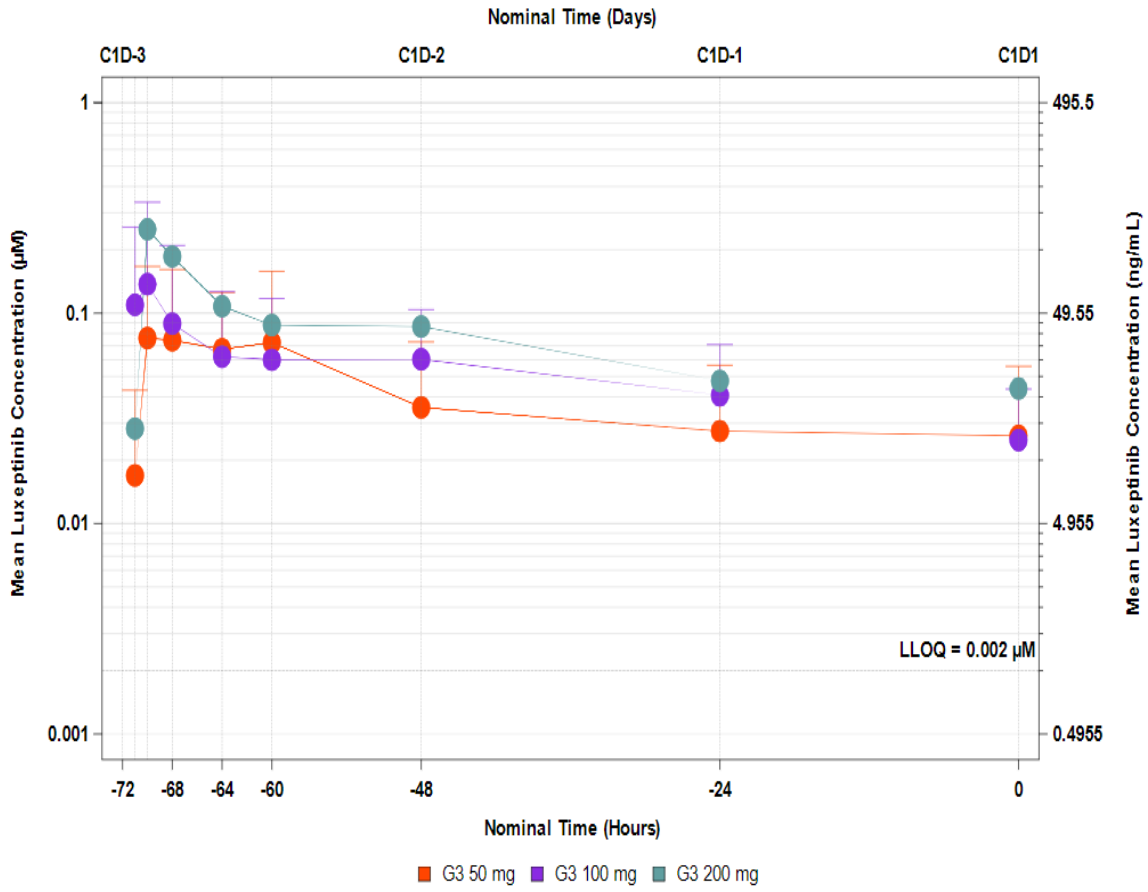
- **Ongoing Clinical Development in Two Separate Trials and Patient Populations**
  - Phase 1 trial in patients with R/R B-cell leukemias|lymphomas
  - Phase 1 trial in patients with R/R AML
- **Critical Step for Lux Program is the Transition to a Novel and Improved Formulation (G3)**
  - Goals to achieve **greater plasma exposures** with administration of **less drug substance and fewer number of pills**
- **Lux G3 Formulation is Being Tested Relative to the Original Formulation in Both Phase 1 trials**
- **Patients Enrolling Well, Allowing us to Test a Single Dose of Lux G3 at Multiple Dose Levels**
  - Already dosed G3 formulation at 50 mg, 100 mg and 200 mg
- **Following a Single Dose of Lux G3, Patients Continue on Study Using the Original Formulation**
  - We plan to provide the antitumor data in a corporate slide deck later and then more rigorously during ASH
- **Presenting PK Data with the Lux G3 Formulation**
  - Four patients dosed with 50 mg, 3 patients dosed with 100 mg, and 3 patients dosed with 200 mg (data from 1 available)

Luxeptinib: Single Dose G3 Formulation with 50 mg, 100mg, or 200 mg Dosages

- **Patients participating in G3 study are derived from:**
  - **Ph 1 R/R B-cell cancers**
  - **Ph 1 R/R AML**
- **72 hr following single dose of G3:**
  - **Some received 750mg G1**
  - **Some received 900mg G1**

G3 Dose	G1 Dose	No. Patients
50 mg	750 mg	1
50 mg	900 mg	3
100 mg	750 mg	2
100 mg	900 mg	1
200 mg	900 mg	3

Encouraging PK data from Single Dose G3 Analysis



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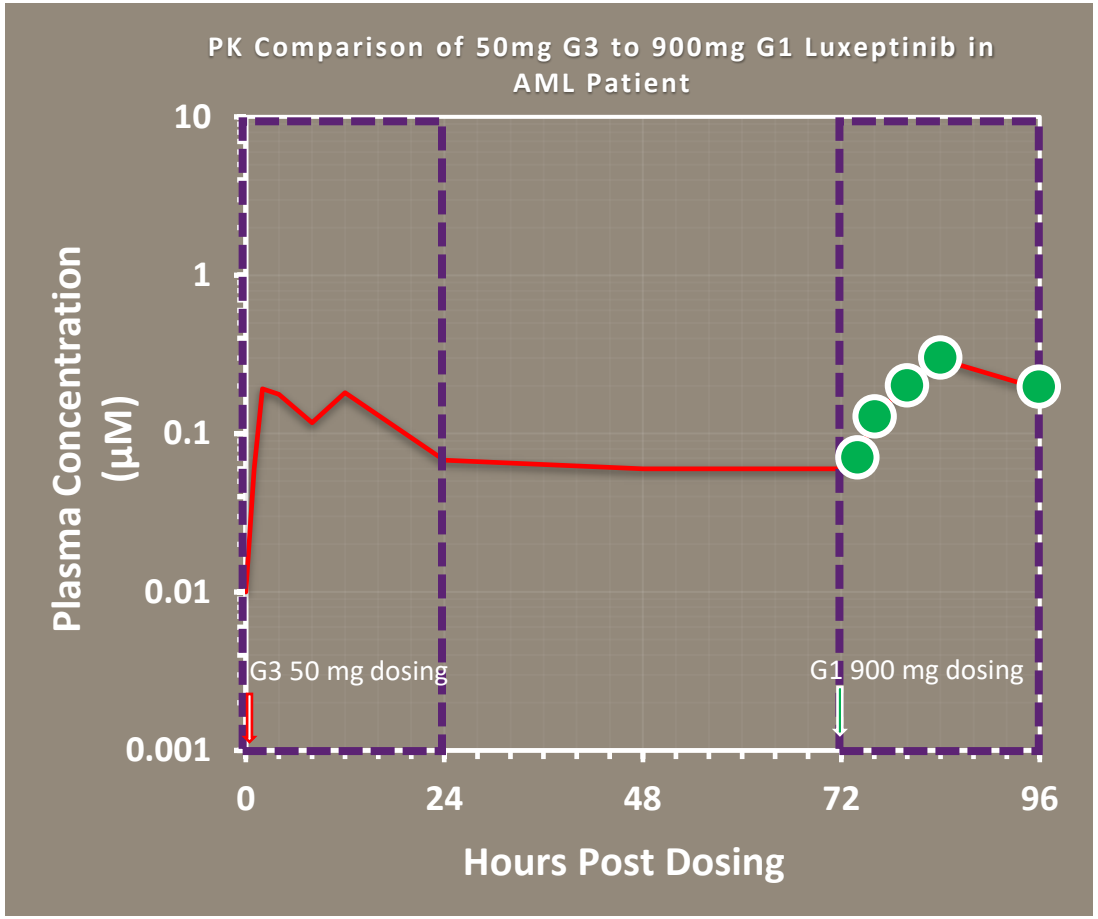
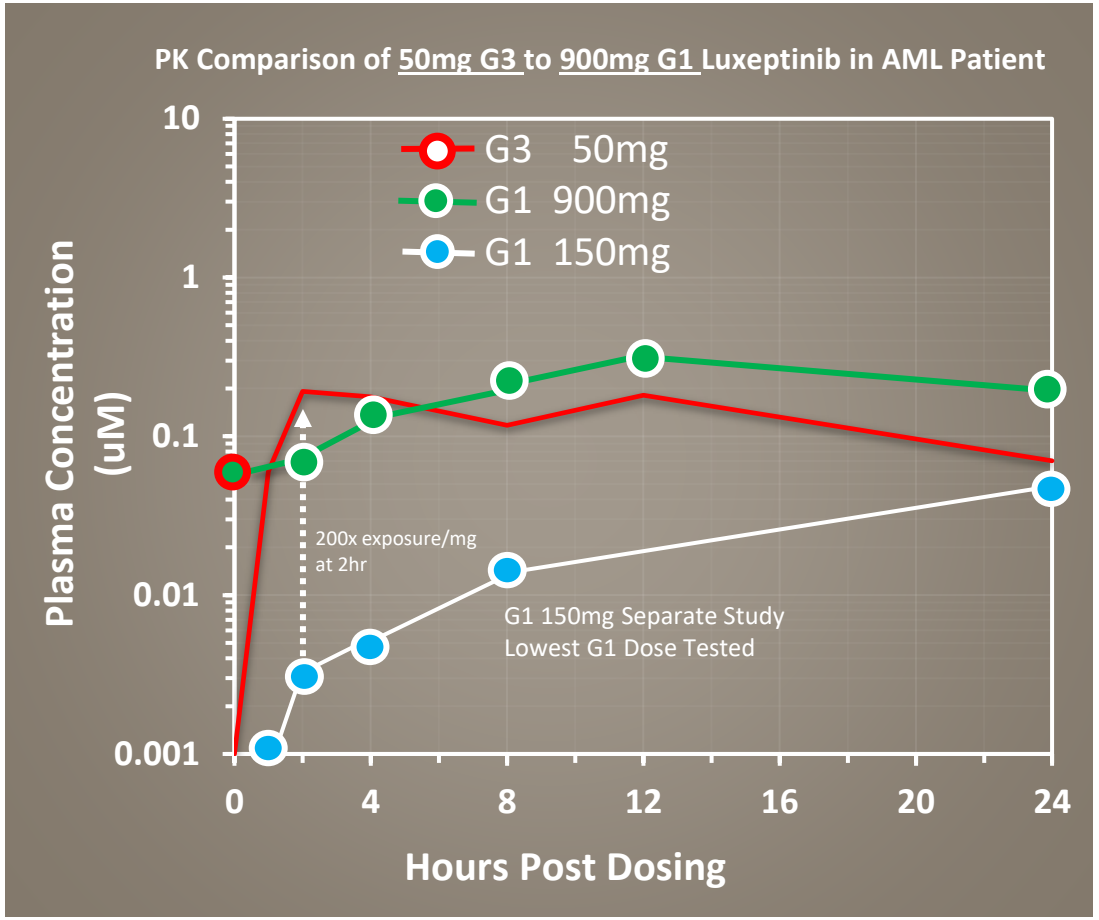
Luxeptinib: First Patient Dosed with G3 Formulation
PK Comparison of **G3 50mg Single Dose** to G1 900mg Single Dose (18X)





G3 50mg Single Dose PK (72hr), followed by G1 900mg Single Dose PK in Same Patient

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Luxeptinib: Oral Lymphoid and Myeloid Kinome Inhibitor

Targets Kinases Important in Lymphoid *and* Myeloid Cancers

- Inhibits BTK, FLT3, CSF1R, PDGFRα, TRK, AURK, others
- Generally well-tolerated – currently dosing at 900mg BID with original formulation
- Delivered antitumor activity in diverse B-cell cancers
- Delivered **MRD- CR in relapsed AML patient** with high exposure

Findings to Date Identify Needs for Future Development

- Clinical activity and tolerability justify further dose exploration
- Doses of 450-750mg with original formulation provided incremental exposure increases
- Identified **need for consistent and higher exposure levels** in AML & B-cell cancer patients

Next Steps for Luxeptinib in 2022

- Continue exploring improved G3 formulation to increasing exposure and to lower pill burden and drug substance manufacture
- **G3 early data are encouraging**
- Higher dosages may be evaluated
- PK modeling of continuous dosing
- Plan continuous dosing with G3 if the data from single dose and modeling are supportive

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Aptose Biosciences (NASDAQ: APTO)

Clinical Stage Oncology Company | Focused on Precision Medicines

Developing highly differentiated oral kinase inhibitors for hematologic malignancies

Experienced leadership with deep expertise in kinase inhibitors & orphan diseases

Planned value-driving clinical updates through 2022 and cash runway through 2023

HM43239 Oral Myeloid Kinome Inhibitor | Clinically Validated for R/R AML Patients

Targets high value kinases operative broadly in AML patients : $FLT3^{WT/MUT}$, SYK, JAK1/2, $cKIT^{MUT}$

CRs in diverse R/R AML patients: $FLT3^{ITD/TKD/WT}$, $NPM1^{MUT}$, $TP53^{MUT}$, $N/K\text{-}RAS^{MUT}$, MLL, RUNX1, IDH^{MUT}

Orphan Drug Designation for AML and Fast Track Designation for R/R AML patients with $FLT3^{MUT}$

→ Now Transitioning to Expansion Trials planned 2H2022 : Doses and patient populations selected

LUXEPTINIB (CG-806) Dual Lymphoid and Myeloid Kinome Inhibitor

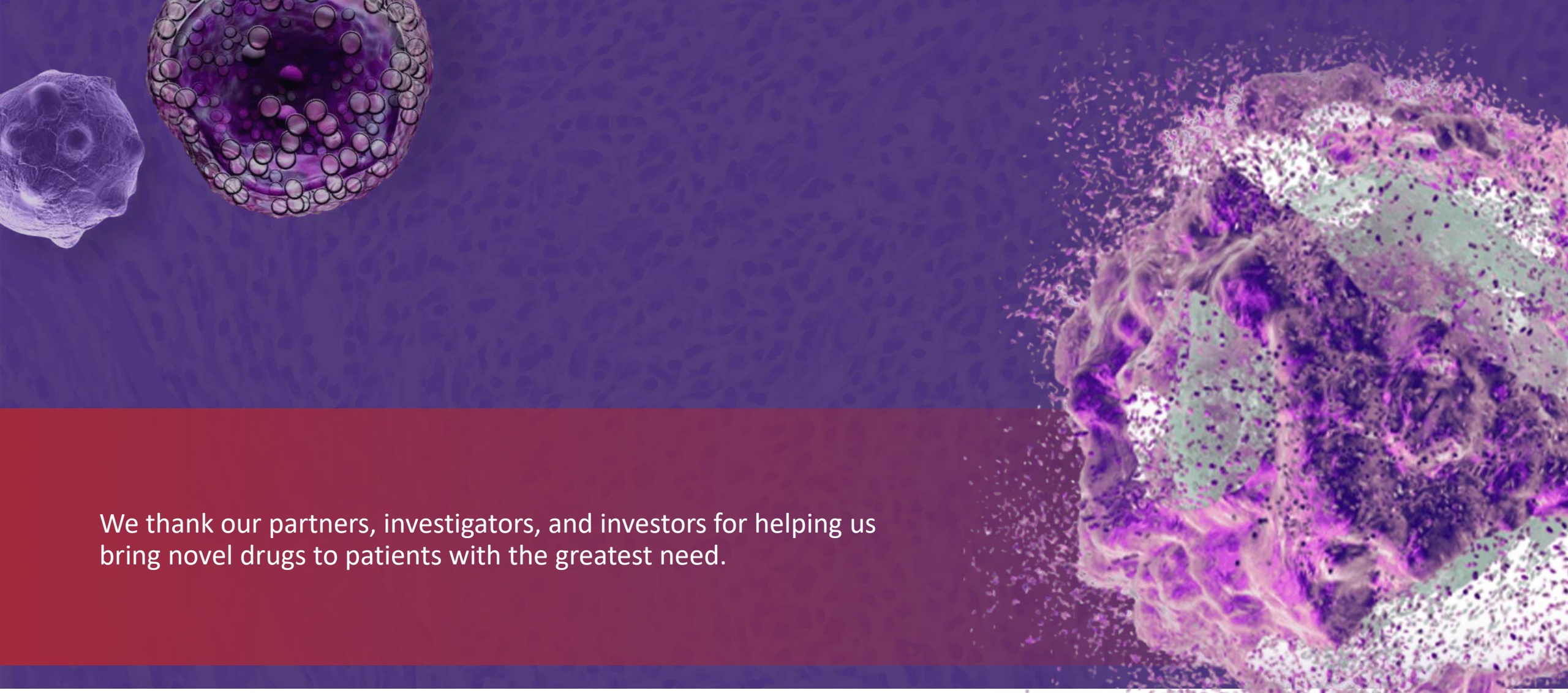
High value targets in B-cell cancers, AML, and inflammation : BTK, FLT3, LCK, LYN, Others

Ongoing parallel dose escalations in patients with B-cell lymphomas/CLL and AML/MDS

Clinically active: anti-tumor activity in high-bar clinical setting of R/R patients

→ Encouraging data with G3 formulation to reduce drug substance and increase plasma exposure

APTOSE BIOSCIENCES



We thank our partners, investigators, and investors for helping us bring novel drugs to patients with the greatest need.

APTOSE BIOSCIENCES

PRECISION ONCOLOGY FOR THERAPIES OF TOMORROW