A Phase 1/2 Open-label, Multicenter, Dose Escalation and Expansion Study of the Myeloid Kinase Inhibitor HM43239 (Tuspetinib) in Patients with Relapsed or Refractory Acute Myeloid Leukemia

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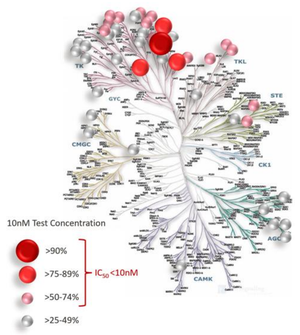
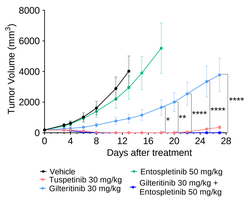
BACKGROUND

Tuspetinib (HM43239) is an oral kinase inhibitor that potently inhibits myeloid kinases including FLT3, SYK, JAK1/2, and mutant KIT kinases at low nanomolar concentrations. These kinases and their mutant forms drive aberrant activation of downstream proliferation pathways and are associated with a high risk of relapse and drug resistance in acute myeloid leukemia (AML) at nanomolar concentrations. In preclinical xenograft and orthoptic models of AML, tuspetinib exhibited greater *in vitro* potency than gilteritinib, entospletinib, venetoclax, and azacitidine when given as single agents. Tuspetinib is being evaluated in an international Phase 1/2 trial in patients with relapsed or refractory (R/R) AML. (NCT03850574)

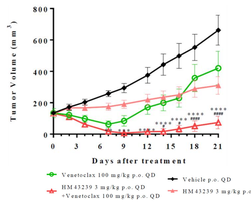


Assay Methodology	Kinase	Mutation Status	Activity
Binding Affinity (K_D, nM)	FLT3	WT	0.58
		ITD	0.37
		D835Y	0.29
		D835H	0.4
		ITD/D835V	0.48
		ITD/F691L	1.3
Inhibition of Kinase Enzyme Activity (IC_{50}, nM)	FLT3	WT	1.1
		ITD	1.8
		D835Y	1.0
	SYK	WT	2.9
	JAK	JAK-1	2.8
		JAK-2	6.3
		JAK-2 (V617F)	9.9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

Antitumor Activity in Mice Bearing MOLM-14 FLT3-ITD/F691L Cells



Antitumor Activity in Mice Bearing MV-4-11 cells



STUDY DESIGN & OBJECTIVES

Phase 1/2, open-label, international, dose escalation and exploration clinical study of tuspetinib for treatment of relapsed or refractory AML in patients for whom there are no other standard-of-care options.

- Accelerated titration design, switched to 3+3 design following MT at 80 mg dose
- Dose Expansion includes single agent and venetoclax combination treatment groups
- Tuspetinib tablets administered once daily
- Safety Review Meeting outcomes determine dose level for subsequent cohort
- Safety/tolerability, PK, PD, and efficacy outcomes assessed

Primary objectives:

- Assess the safety, tolerability, and PK parameters of tuspetinib (as a single agent and in combination with venetoclax) when administered to patients with R/R AML
- Establish the recommended phase 2 dose of tuspetinib based on safety, efficacy, PK, and PD data

Secondary objectives:

- Investigate anti-leukemic activity of tuspetinib as a single agent and in combination with venetoclax in patients with relapsed or treatment-refractory AML

We thank our principal investigators, clinical site staff, and most importantly, our patients and their families for their participation in this clinical trial.
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STUDY STATUS

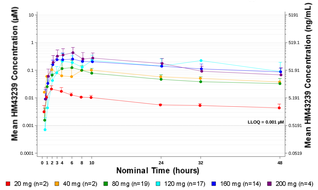
As of October 6, 2022, 60 patients have been treated across 6 dose levels (20, 40, 80, 120, 160, and 200 mg QD) in Dose Escalation (Part A) and Dose Exploration (Part B) at 8 sites in the US and Korea Republic of (South). The majority of patients are male (58.3%), Asian (53.3%) or White (36.7%), with a median age of 61 years (range 18-84). Enrolled patients have been heavily pre-treated, with 100% having received prior chemotherapy, 28.3% prior HSCT, and 23.3% prior FLT3 inhibitor. Approximately 43% of study patients have a FLT3 mutation (FLT3+).

Patient Disease Characteristics	
FLT3 Mutation Status	**N (%)**
FLT3+	26 (43.3%)
FLT3-	33 (55.0%)
Unknown	1 (1.7%)
Prior AML Therapy	
Lines of prior therapy - Mean (Range)	2.7 (1,8)
Type	**N (%)**
Cytotoxic chemotherapy	43 (71.7%)
HSCT	17 (28.3%)
FLT3 Inhibitor	14 (23.3%)

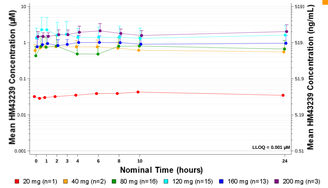
PHARMACOKINETICS

Plasma PK Findings: Generally, dose-related increase in tuspetinib plasma exposures after first dose and at steady state. Approximately 17-28 days to approach steady state and terminal $t_{1/2}$ approximately 5.5 days.

Mean PK Concentrations After Single Dose



Day 15 Mean PK Concentrations



SAFETY

Tuspetinib has been well tolerated with no DLTs through 160 mg QD. Related events occurred in only 28.3% of patients. Across all dose levels, the most frequent related TEAEs are diarrhea (11.7%) and nausea (8.3%). Related events of ≥ Grade 3 in more than 1 patient include decreased neutrophil count and muscle weakness.

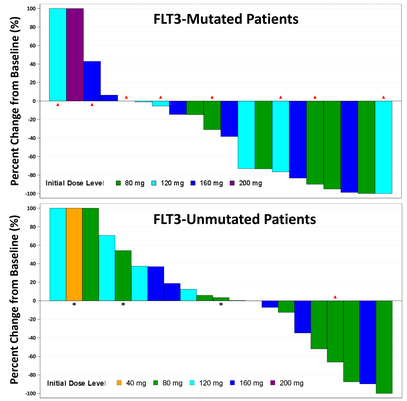
- No drug-related SAEs, deaths, or discontinuations reported
- No drug-related AE, differentiation syndrome, or QT prolongation

Treatment-emergent AEs (TEAEs), Safety Analysis Set, Parts A and B (N=60)	
Patients Experiencing TEAEs	**N (%)**
Any	56 (93.3%)
Most Frequent TEAEs (>15% of patients)	
Pneumonia	18 (30.0%)
Pyrexia	12 (20.0%)
Nausea	11 (18.3%)
Diarrhea	9 (15.0%)
≥ Grade 3	41 (68.3%)
SAEs	31 (51.7%)
Leading to treatment discontinuation	6 (10.0%)
Leading to death	11 (18.3%)
Patients Experiencing TEAEs Related to HM43239	**N (%)**
Any	17 (28.3%)
Most Frequent Related TEAEs (>5% of patients)	
Diarrhea	7 (11.7%)
Nausea	5 (8.3%)
≥ Grade 3	6 (10.0%)
Decreased neutrophil count	2 (3.3%)
Muscle weakness	2 (3.3%)
Decreased white blood cell count	1 (1.7%)
Nausea	1 (1.7%)
Leukopenia	1 (1.7%)
SAEs	0 (0%)
Leading to death	0 (0%)
Dose Limiting Toxicity (DLT)*	1 (1.7%)

* A DLT of G3 muscle weakness was experienced by a patient at the 200 mg QD dose level.

BLAST REDUCTION IN FLT3+/WT PATIENTS

Waterfall plot of Bone Marrow Blast Percent Change from Baseline for heavily pre-treated patients assigned to 80 mg, 120 mg and 160 mg dose levels. Significant blast count reductions were seen in both FLT3 mutated and unmutated patients.

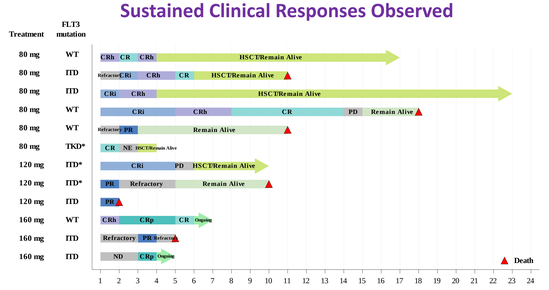


Note: Patients with blast percent change ≥100% are shown as 100%.
* Patients who were administered hydroxyurea within 7 days prior to the lowest marrow blast value.
▲ Patients who received prior FLT3 inhibitors before starting HM43239, including gilteritinib, midostaurin, and/or sorafenib.

CLINICAL RESPONSES

- Clinical responses have been achieved across 80 mg, 120 mg, and 160 mg QD dose levels in patients with diverse mutation profiles (**figure below**).
  - Responses achieved during 2022 after Aptose assumed control of the tuspetinib clinical program shown in the lower **table to the right**.
- ORR and CRc response rates among specific mutationally defined patient populations and at particular dose levels are illustrated in the **table below**.

Sustained Clinical Responses Observed



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

HM43239 Best Response in Efficacy Evaluable R/R AML Population		
Population	**Dose Level(s)**	**Overall Response Rate[1]**
FLT3+	80 mg	42.9% (3/7)
FLT3+	120 mg	42.9% (3/7)
FLT3+ | NPM1+	80 mg, 120 mg, 160 mg	66.7% (4/6)
FLT3+ | Prior FLT3i	80 mg	33.3% (1/3)
FLT3+ | Prior FLT3i	120 mg	40.0% (2/5)

Population	Dose Level(s)	CRc Response Rate[2]
FLT3+	80 mg, 120 mg, 160 mg	23.8% (5/21)
FLT3+ | NPM1+	80 mg, 120 mg, 160 mg	33.3% (2/6)
FLT3-WT | TP53+	80 mg, 120 mg, 160 mg	33.3% (1/3)

Analysis is based on efficacy evaluable patients including those who received at least 2 cycles of treatment or discontinued due to progressive disease, unless a response has already been achieved.
[1] Overall Response Rate (ORR) = CR + CRh + CRi + CRp + PR
[2] CRc Response Rate = CR + CRh + CRi + CRp

RESPONSES IN DIFFICULT-TO-TREAT PATIENTS

Case Study 1: 55-year-old male with refractory AML-MRC and 42% bone marrow blasts*
- **FLT3-WT, NRAS mutation** with BCOR, SETBP1, and U2AF1 mutations treated at 160 mg
- **Achieved CR after 5 Cycles demonstrating response in FLT3-WT, NRAS mutant AML**

Case Study 2: 60-year-old male with refractory AML-MRC and 71% bone marrow blasts*
- **FLT3-WT, TP53 mutation** and complex karyotype, prior HSCT, treated at 80 mg
- **Achieved CR by Cycle 9 demonstrating duration of response without myelosuppression**

Case Study 3: 67-year-old female with refractory AML and 40% bone marrow blasts*
- **FLT3-TKD, prior Mido- and Gilt-failure,** with SF3B1, RUNX1, & RB1 mutations at 80 mg
- **Achieved CR at Cycle 1, bridged to HSCT demonstrating response in TKD with prior FLT3i**

Case Study 4: 49-year-old female with relapsed AML and 66% bone marrow blasts*
- **FLT3-ITD, MLL-PTD mutation, prior Mido-failure**, with RUNX1 mutation treated at 120 mg
- **Achieved CRi at Cycle 1, bridged to HSCT demonstrating response in ITD with prior FLT3i**

***Blast count provided at time of diagnosis.**

Important Mutations	FLT3 Status	Dose Level	Best Response	Bridged to HSCT
IDH2 SRSF2	WT	80mg	CR	Yes
TP53	WT	80mg	CR	No
NPM1 DNMT3A	ITD	80mg	CR	Yes
NRAS RUNX1	ITD	80mg	CRh	Yes
RUNX1 SF3B1 RB1	TKD – Prior FLT3i	80mg	CR	Yes
KRAS NPM1 DNMT3A PTPN11	ITD – Prior FLT3i	120mg	PR	No
MLL-PTD RUNX1*	ITD – Prior FLT3i	120mg	CRi	Yes
Not Reported*	ITD	120mg	PR	No
NRAS BCOR U2AF1 SETBP1*	WT	160mg	CR	Tx Ongoing
NPM1*	ITD	160mg	CRp	Tx Ongoing
NPM1 IDH1 DNMT3A*	ITD	160mg	PR	No
ASXL1 CBL*	WT	80mg	PR	No
Not Reported*	ITD	160mg	SD	Tx Ongoing

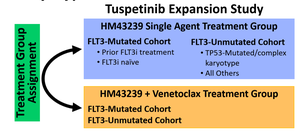
*** New Responses Observed Since Aptose Assumed Responsibility for Clinical Trial 1 January 2022**

EXPANSION AND COMBINATION STUDY

The **single agent** expansion cohort will be treated at 120 mg daily with an opportunity to dose escalate to 160 mg if no clinical benefit observed after the first cycle.
This cohort will enrich for ***FLT3 mutated patients previously treated with FLT3 inhibitors*** and ***FLT3 unmutated patients with TP53 mutation/complex karyotype.***

The **combination cohort** will be treated at 80 mg daily in combination with venetoclax.

Patients are randomly assigned to a treatment group based on their FLT3 mutation status and the number of available slots in each cohort.



CONCLUSIONS

- **Tuspetinib achieved multiple complete remissions as a single agent across three dose levels (80 mg, 120 mg, 160 mg) in heavily pretreated patients**
- **Tuspetinib exhibits broad activity across difficult-to-treat FLT3 mutated and FLT3-unmutated patients, and among patients with adverse mutations (RAS, TP53, NPM1, DNMT3A, RUNX1, IDH2, and others)**
- **Tuspetinib delivered responses in patients who failed prior FLT3 inhibitors**
- **Tuspetinib is well tolerated with no DLTs through 160 mg dose level and no drug related SAEs, differentiation syndrome, QTc events, or deaths**
- **Tuspetinib is now entering dose expansion in R/R AML as a single agent and in combination with venetoclax**

Disclosures: Current clinical study is sponsored by Aptose Biosciences. The following authors are employees of Aptose Biosciences: R Sinha, DN Haney, A Capell, J Hu, N Khan, W Rice, and R Bejar