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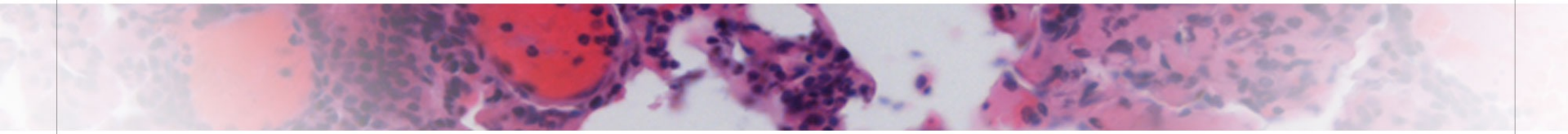

Abst #702

First in Human (FIH) FLT3 and SYK Inhibitor HM43239 Shows Single Agent Activity in Patients (pts) with Relapsed or Refractory (R/R) FLT3 Mutated and Wild-Type Acute Myeloid Leukemia (AML)

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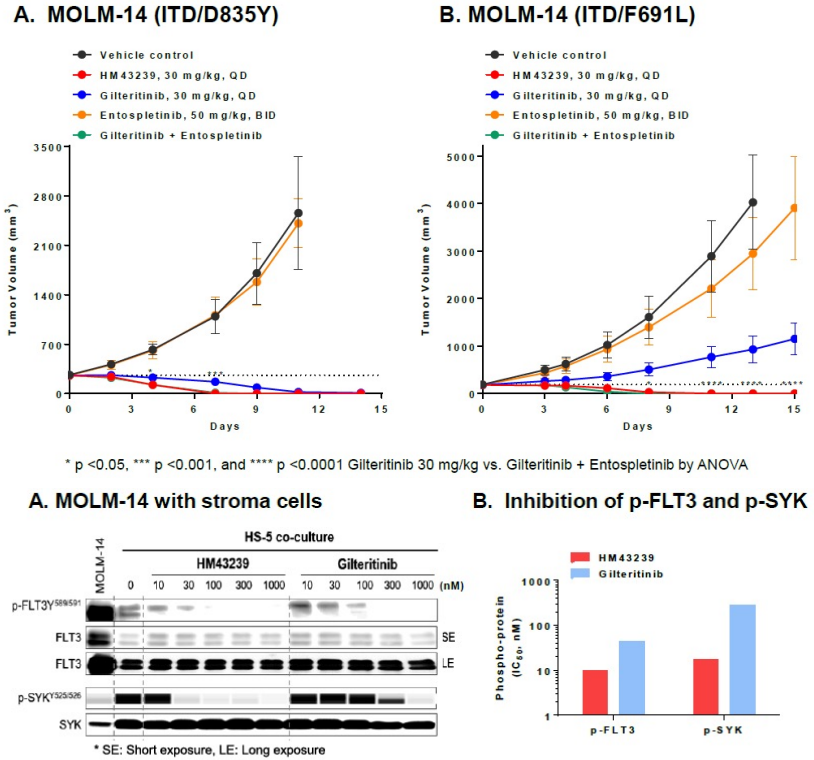
HM43239

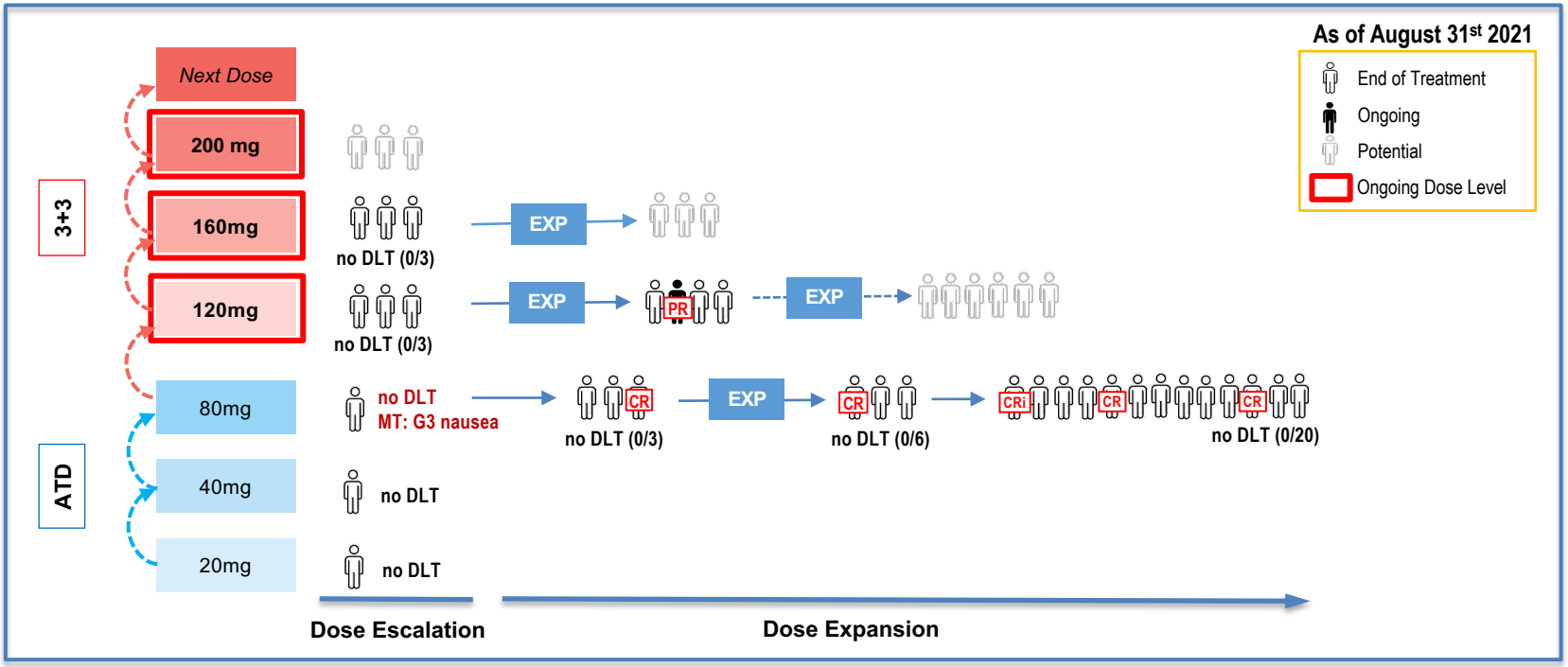


- Oral, highly potent clinical-stage myeloid kinome inhibitor designed to target a distinct kinases operative in myeloid malignancies including FLT3 and SYK
- Highly active against FLT3 ITD mutated as well as resistance-conferring D835 and gatekeeper (F691) TKD mutated AML cell lines and xenograft models
- Additionally, inhibits phosphorylation of SYK known to be highly activated in AML and associated with resistance to FLT3 targeted therapy

AACR 2021 Abst#1257

Study Design and Status

First in Human, Open-label, Multicenter, Phase I/II Study



Note, non-evaluable pt is not included.
ATD: Accelerated Titration Design, EXP: Dose expansion, MT: Moderate toxicity (non hematologic toxicities, IP related ≥G2 AEs), CR: complete remission, CRp: complete remission with incomplete platelet recovery, CRi: complete remission with incomplete hematologic recovery, PR: partial remission, CRc: Composite complete remission

Demographics and Disease Characteristics

Data cutoff: August 31 2021

	Total (n=34)
Age (years)	
Median (range)	59.5 (18, 84)
Sex, n (%)	
Female	16 (47.1)
Race, n (%)	
American Indian or Alaska Native	1 (2.9)
Asian	21 (61.8)
Black or African American	1 (2.9)
White	9 (26.5)
Not specified	1 (2.9)
Unknown	1 (2.9)
Bone marrow baseline (%)	
Median (range)	27.5 (0-96)
FLT3 mutation status, n (%)	
Negative	18 (52.9)
Positive	14 (41.2) ITD 9 (26.5), TKD 4 (11.8), ITD/TKD 1 (2.9)
Invalid/Unknown	2 (5.9)
FLT3 mutation to wild-type signal ratio (AR)	
Median (range)	1.38 (0.11-23.82)
Prior AML therapy, n (%)	
Chemotherapy	34 (100.0)
HSCT	10 (29.4)
Radiotherapy	2 (5.9)
No. of prior AML lines of therapy	
Median (range)	2 (1-7)
No. of prior FLT inhibitors*, n (%)	
0	29 (85.3)
1	2 (5.9)
≥2	3 (8.8)

*FLT inhibitors include sorafenib, midostaurin and gilteritinib.

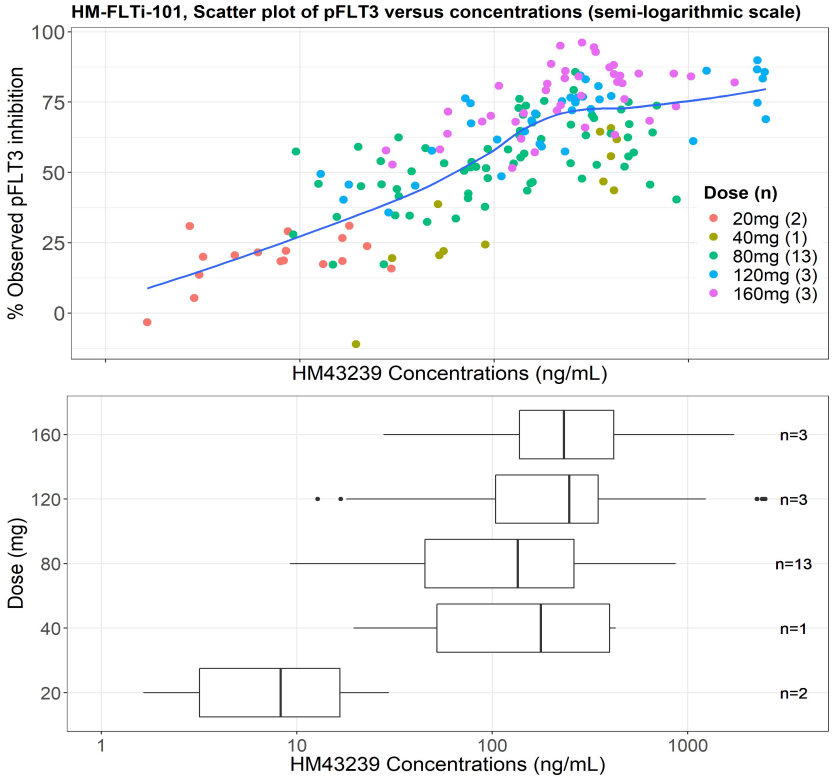
Safety and Tolerability

Data cutoff: August 31 2021

	All Grades, n (%)	≥ Grade 3, n (%)
Any TEAEs, n (%)	**32 (94.1)**	**20 (58.8)**
Any related TEAEs, n (%)	**11 (32.4)**	**3 (8.8)**
Drug-related AEs % (n=34)		
Gastrointestinal disorders	**8 (23.5)**	**1 (2.9)**
Diarrhoea	4 (11.8)	0 (0.0)
Nausea	4 (11.8)	1 (2.9)
Vomiting	2 (5.9)	0 (0.0)
Gastrooesophageal reflux disease	1 (2.9)	0 (0.0)
Investigations	**4 (11.8)**	**1 (2.9)**
Alanine aminotransferase increased	2 (5.9)	0 (0.0)
Aspartate aminotransferase increased	1 (2.9)	0 (0.0)
Blood alkaline phosphatase increased	1 (2.9)	0 (0.0)
Blood bicarbonate decreased	1 (2.9)	0 (0.0)
Blood urea decreased	1 (2.9)	0 (0.0)
Neutrophil count decreased	1 (2.9)	1 (2.9)
Platelet count decreased	1 (2.9)	0 (0.0)
General disorders and administration site conditions	**2 (5.9)**	**0 (0.0)**
Fatigue	1 (2.9)	0 (0.0)
Mucosal inflammation	1 (2.9)	0 (0.0)
Blood and lymphatic system disorders	**1 (2.9)**	**1 (2.9)**
Leukopenia	1 (2.9)	1 (2.9)
Cardiac disorders	**1 (2.9)**	**0 (0.0)**
Pericarditis	1 (2.9)	0 (0.0)
Eye disorders	**1 (2.9)**	**0 (0.0)**
Blepharitis	1 (2.9)	0 (0.0)
Immune system disorders	**1 (2.9)**	**0 (0.0)**
Graft versus host disease	1 (2.9)	0 (0.0)
Infections and infestations	**1 (2.9)**	**0 (0.0)**
Herpes zoster	1 (2.9)	0 (0.0)
Metabolism and nutrition disorders	**1 (2.9)**	**0 (0.0)**
Decreased appetite	1 (2.9)	0 (0.0)
Hypocalcaemia	1 (2.9)	0 (0.0)
Musculoskeletal and connective tissue disorders	**1 (2.9)**	**0 (0.0)**
Back pain	1 (2.9)	0 (0.0)
Nervous system disorders	**1 (2.9)**	**0 (0.0)**
Headache	1 (2.9)	0 (0.0)

FLT3 Plasma Inhibitory Activity

%pFLT3 inhibition vs. plasma concentration



Clinical Response by Mutation Status

Data cutoff: August 31 2021

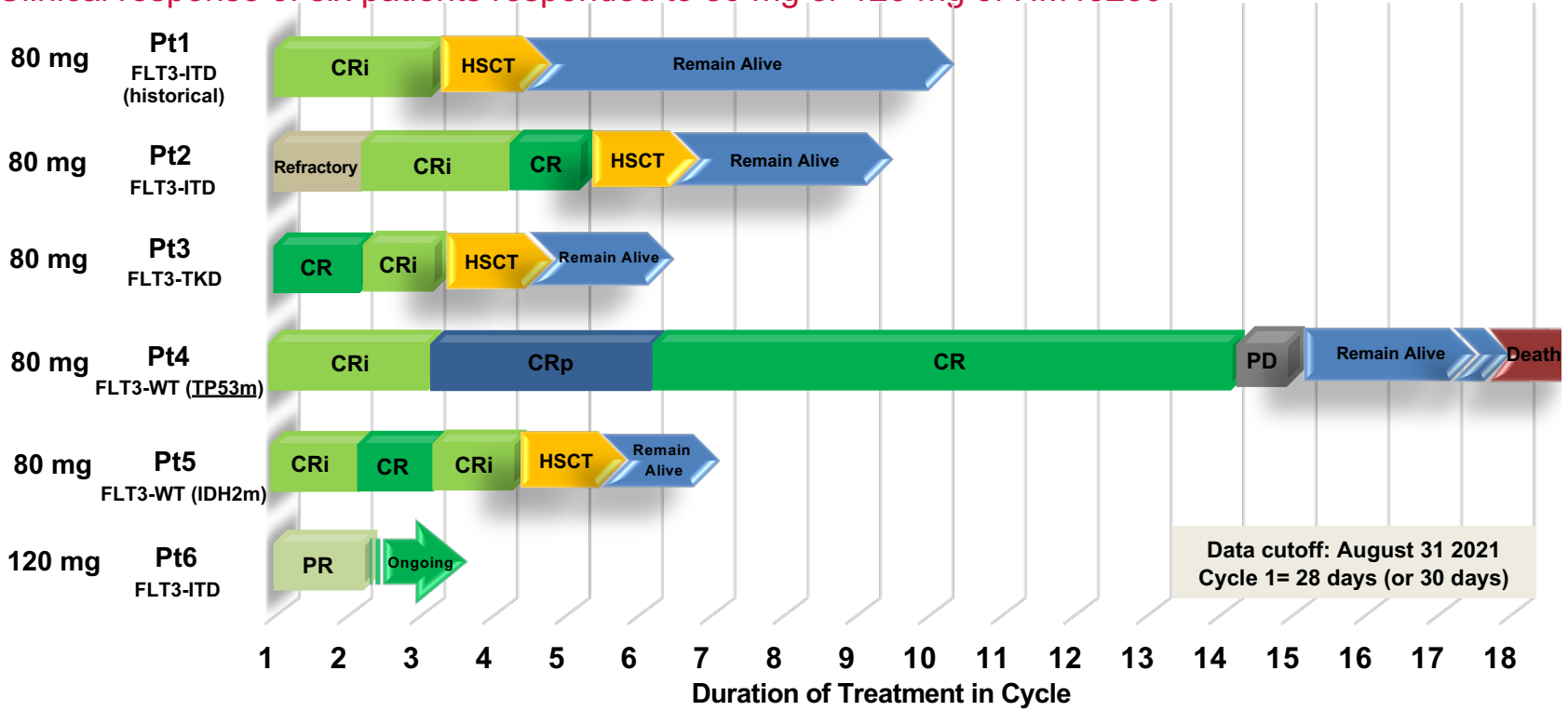
Response	80 mg (n=20)		120 mg (n=7)		20-160 mg (n=34)	
	FLT3 Mutated	FLT3 Wild Type	FLT3 Mutated	FLT3 Wild Type	FLT3 Mutated	FLT3 Wild Type
	n (%) n= 8†	n (%) n= 12†	n (%) n= 3	n (%) n= 4	n (%) n= 15†	n (%) n= 19†
CR	2 (25)	2 (16.7))	-	-	2 (13.3)	2 (10.5)
CRi	1 (12.5)	-	-	-	1 (6.7)	-
PR	-	-	1 (33.3)	-	1 (6.7)	-
CRc	**3 (37.5)**	**2 (16.7)**	**-**	**-**	**3 (20)**	**2 (10.5)**
ORR	**3 (37.5)**	**2 (16.7)**	**1 (33.3)**		**4 (26.7)**	**2 (10.5)**

Note, patients who receive at least one dose and have at least one post-treatment data point are included in the data set for response analysis.
†Two pts were based on initial diagnosis – historically one pt was FLT3-ITD mutated and the other pt was FLT wild type.
CR: complete remission; CRp: complete remission with incomplete platelet recovery; CRi: complete remission with incomplete hematologic recovery; PR: partial remission
CRc: composite complete remission rate (CR +CRp + CRi); ORR: overall response rate (CR + CRp + CRi + PR)

- **30-day mortality = 11.4% (n=4), 60-day mortality = 17.6% (n=6)**
- **Median time to first response = 29 days (1 Cycle)**
- **Median duration on study = 51 days (range, 6-394 days)**

Response to Treatment

Clinical response of six patients responded to 80 mg or 120 mg of HM43239



Note, Pt1, 2, 5 remain alive at the time of long term follow up; Pt 2 remain alive at the time of 30 days follow up; Pt3 is dead at the time of long term follow up.
CR: complete remission, CRp: complete remission with incomplete platelet recovery, CRi: complete remission with incomplete hematologic recovery, PR: partial remission
HSCT: hematopoietic stem cell transplantation, PD: progression of disease

Characteristics of Responding Patients

Data cutoff: August 31 2021

Patients	Age/ Sex	Dose Level (QD)	AML status	FLT3 mutation* (mt to WT signal ratio)	Other mutation	No. prior therapies	No. prior FLT3i's	Cytogenetics	Best response	Cycles** to first response	Cycles** to best response	Duration on study (weeks)	Reason of discontinuation
Pt1	51/M	80mg	AML NOS	FLT3-ITD† (0.7)	NRAS, RUNX1	3	0	Normal	CRi	1	1	12	HSCT (remains in remission)
Pt2	50/M	80mg	AML NOS	FLT3-ITD (13.5)	NPM1, DNMT3A	1	0	Normal	CR	2	5	20	HSCT (remains in remission)
Pt3	67/F	80mg	AML NOS	FLT3-D835V† (0.11)	RUNX1	2	2# (midostaurin, gilteritinib)	Normal	CR	1	1	7	HSCT (remains in remission)
Pt4	60/M	80mg	AML-MRC	FLT3-WT (0)	TP53	3	0	Abnormal‡	CR	1	8	56	PD → death (remains in remission)
Pt5	63/F	80mg	AML NOS	FLT3-WT† (0)	IDH2	1	0	Abnormal‡	CR	1	2	13	HSCT (remains in remission)
Pt6	54/F	120mg	AML NOS	FLT3-ITD† (23.82)	NPM1, DNMT3A, KRAS, PTPN11	2	2# (midostaurin, gilteritinib)	Normal	PR	1	1	-	Ongoing in PR in C#2

*FLT3 mutation status is based on the results from invivoscribe using the Leukostrat® CDx FLT3 Mutation Assay approved by FDA. **1 Cycle is 28 or 30 days.
†Pt1 mutation status is based on initial diagnosis; Pt3 mutation result was obtained after dosing; Pt5 mutation status at initial diagnosis was FLT3-ITD; Pt6 mutation at initial diagnosis was FLT3-ITD/TKD.
‡Karyotypes for Pt4: Abnormal, Complex, 50~52,XY,del(5)(13q31),-7, dup(8)(q22), dup(9)(q13), +dup(11)(p11.2), -13,-15,+5~7mar[cp14]/46,XY[6]; Karyotypes for Pt5: Abnormal, +8, +13, t(X;9)(q28;p21)
AML NOS: AML not otherwise specified, AML-MRC: AML with myelodysplasia-related changes, HSCT: hematopoietic stem cell transplantation, PD: progression of disease
#Pt3 previously received midostaurin and gilteritinib with no responses; Pt6 previously received midostuarin with CR and gilteritinib with no response.

Conclusions

- HM43239 showed a favorable safety profile with only mild AEs and no DLTs up to 160 mg per day. No drug discontinuations from drug related toxicity.
- HM43239 PIA activity was dose-dependent with up to 90% pFLT3 inhibition at the dose levels ≥ 80 mg.
- At 80 mg dose, composite CR rate of 25% was observed in both FLT3m (including a prior gilteritinib failure pt) and FLT3wt AML (including >1 year CR without HSCT in a relapsed TP53m AML).
- Among FLT3m patients treated at the 80mg dose, 3 of 8 (37.5%) achieved durable CR/CRi.
- Recently, another prior gilteritinib failure patient achieved PR after C1 at 120 mg dose.
- The study is ongoing in the cohorts – the dose escalation cohort of 200 mg and the dose expansion cohorts of 120 mg and 160 mg are currently enrolling (NCT03850574).

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  - Martha L. Arellano (Winship Cancer Institute of Emory University, Atlanta, GA)
  - Kyoo Hyung Lee (Asan Medical Center, University of Ulsan, Seoul, Korea)
  - Chul Won Jung (Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea)
  - Sung Soo Yoon (Seoul National University, Seoul, Korea)

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