A first-in-class Menin-MLL1 antagonist for the treatment of MLL-r and NPM1 mutant leukemias

Jerry McGeehan PhD
Syndax Pharmaceuticals

Disclosure

I am an employee and shareholder of Syndax Pharmaceuticals, Inc.

Forward-looking statements disclosure

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Overview of Mixed Lineage Leukemia-rearranged (MLL-r) and Nucleophosmin Mutant AML (NPM1c+ AML)

MLL-r is caused by translocations at the *MLL1* locus that create oncogenic MLL-fusion proteins

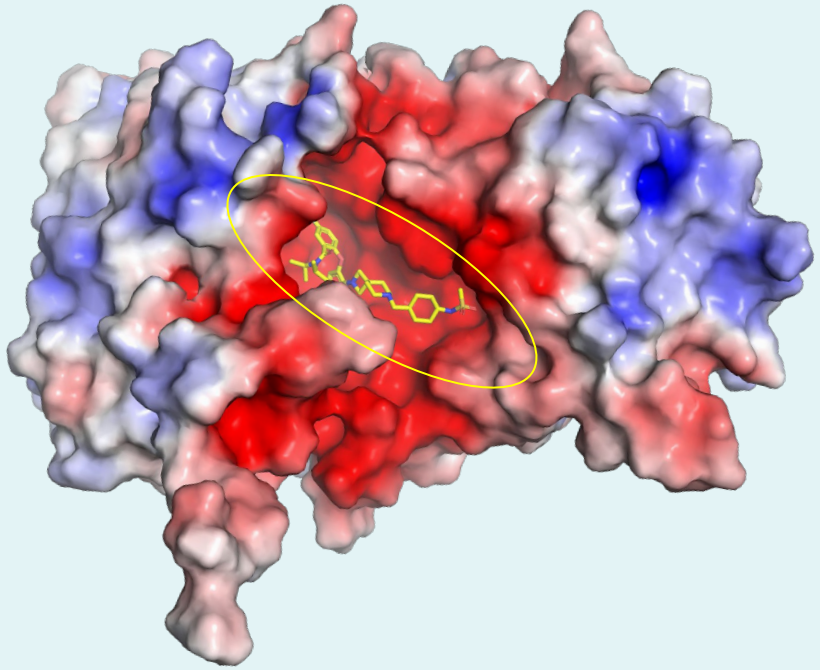
- MLL-r is an acute leukemia that presents as ALL or AML, commonly diagnosed at presentation (FISH)
- *MLL*-rearrangements are found in ~5-10% of AML and ALL cases, for a combined incidence ~7000^{+}/yr
- Targeting of MEN:MLL interaction in *MLL*-r cells blocks cell proliferation

NPM1c^{+} AML is caused by mutations in *NPM1* gene

- NPM1c is one of the most common mutations found in AML, diagnosed with standard NGS panels
- NPM1c represents about 30% of all adult AML and an incidence of ~ 20,000/yr
- Targeting of MEN:MLL1 interaction in *NPM1c*$^{+}$ AML inhibits cell proliferation

Menin-MLL binding inhibition leads to loss of the leukemic transcription program in MLLr/NPM1c, causing terminal differentiation of cells

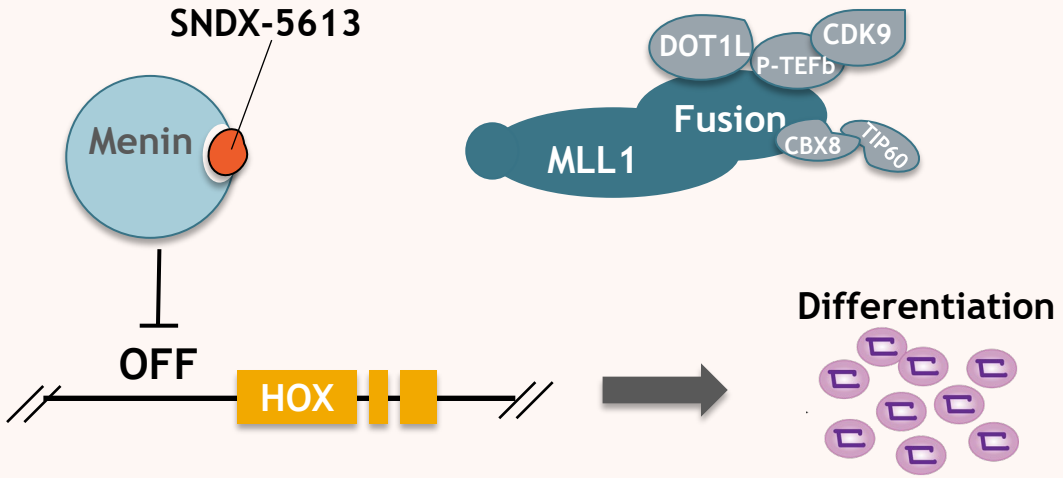
SNDX-5613 occupies the MLL1 binding pocket on Menin



M-A-H-S-C-R-W-R-***F-P-A-R-P***-G-T-T-G-G-G-

9------13

SNDX-5613 inhibits Menin-MLLr interaction



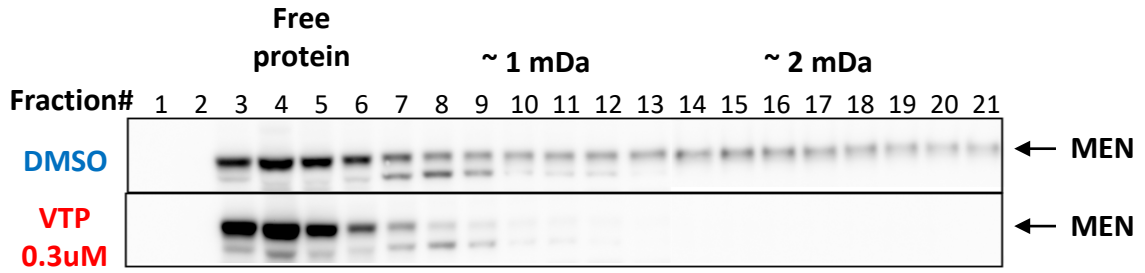
Adopted from: Uckelmann HJ, et al. Presented at ASH Annual Meeting, 2018

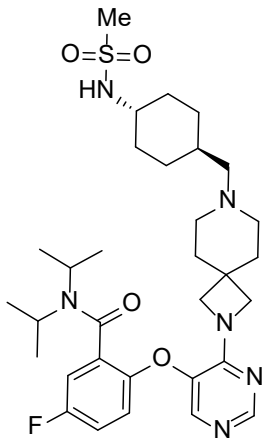
Menin inhibitors cause significant changes in the transcription program by evicting Menin from chromatin

CELL LINE	LINEAGE	GENETIC LESION	IC_{50}, nM
HL-60	AML	PML-RARa	>>2000
MOLM13	AML	MLL-AF9	13 +/-9
THP1	AML	MLL-AF9	37 +/-21
NOMO1	AML	MLL-AF9	30 +/-12
ML2	AML	MLL-AF6	16 +/-9
EOL1	AML	MLL-PTD	20 +/-10

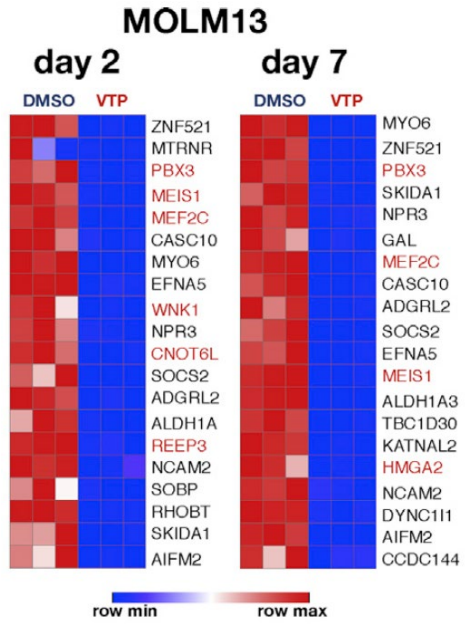
MOLM13 (MLL-AF9)

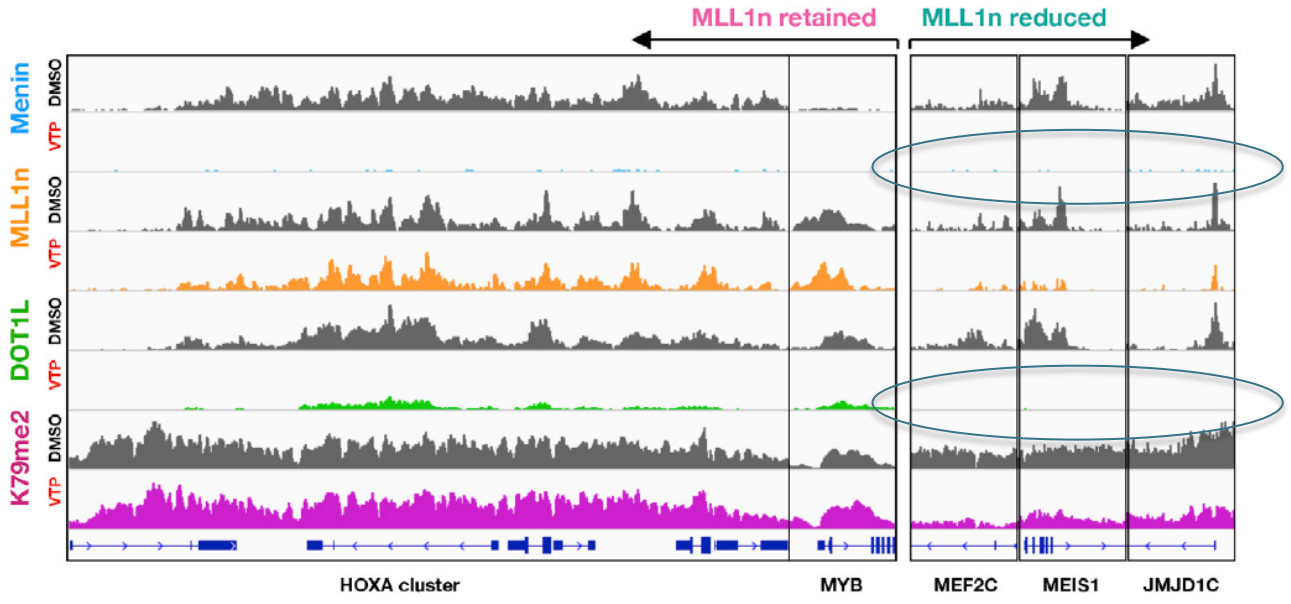
Day 3





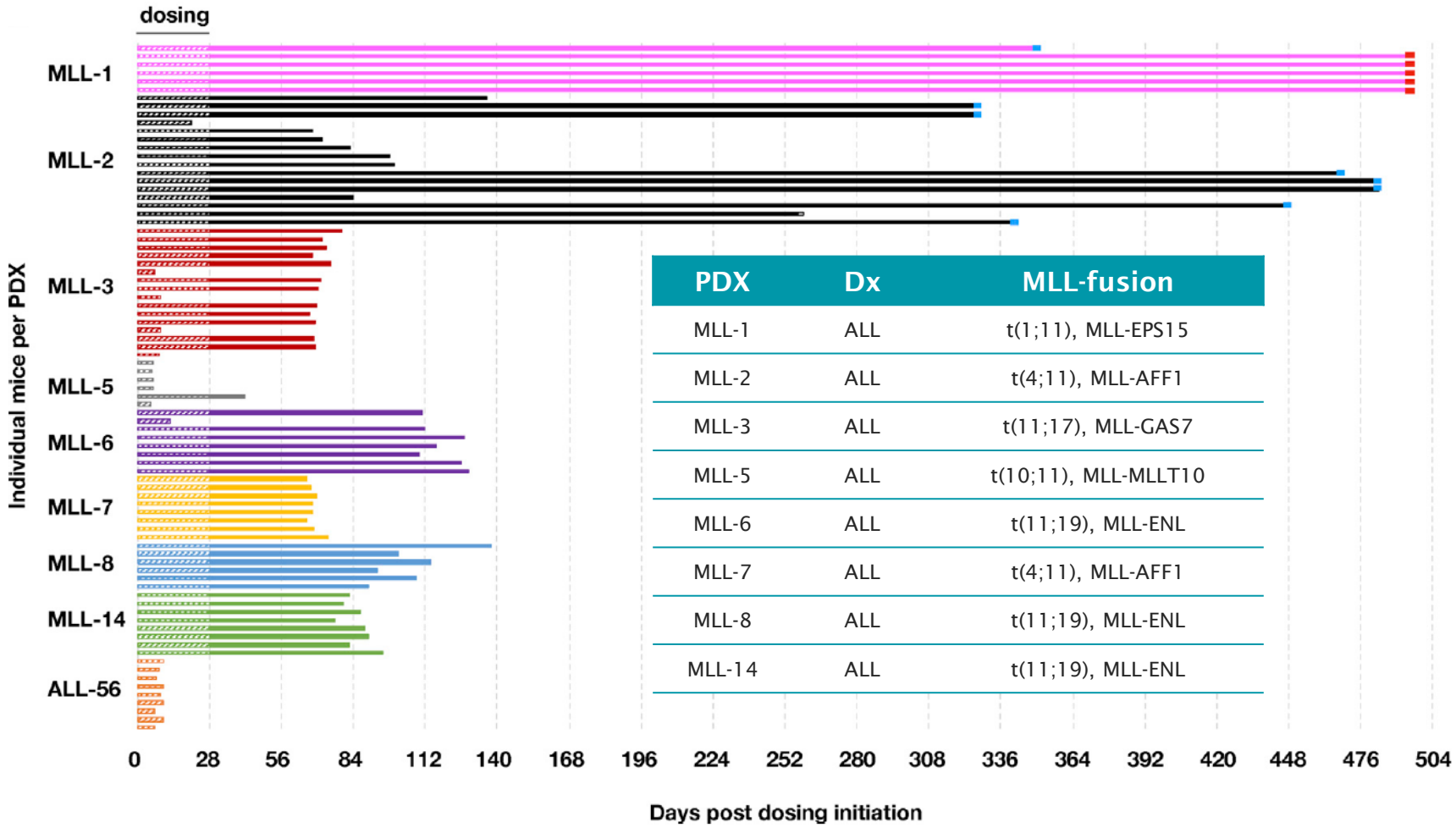
SNDX-50469





Menin inhibitors have profound single-agent activity in MLL-r PDX models, producing deep and durable responses

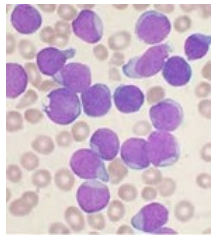
- Significant survival benefit in 7/8 PDXs after single 28d treatment with SNDX-469
- Profound effects on PDX-MLL-1 and PDX-MLL-2 with event free survival >1 yr
- No treatment effect on control non-MLLr leukemia ALL-56 (Ph+)



PDX	Dx	MLL-fusion
MLL-1	ALL	t(1;11), MLL-EPS15
MLL-2	ALL	t(4;11), MLL-AFF1
MLL-3	ALL	t(11;17), MLL-GAS7
MLL-5	ALL	t(10;11), MLL-MLLT10
MLL-6	ALL	t(11;19), MLL-ENL
MLL-7	ALL	t(4;11), MLL-AFF1
MLL-8	ALL	t(11;19), MLL-ENL
MLL-14	ALL	t(11;19), MLL-ENL

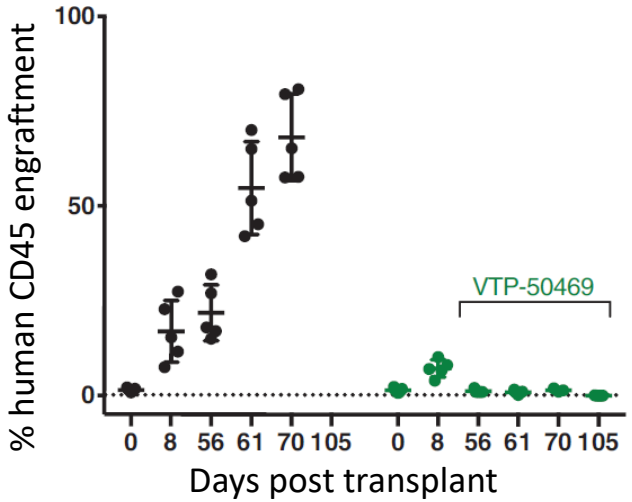
Source: Krivtsov, A. Cancer Cell. 2019 Dec 9;36(6):660-673; Animals treated orally for 28 days with vehicle or VTP-50469 (MTD; 120 mg/kg bid)

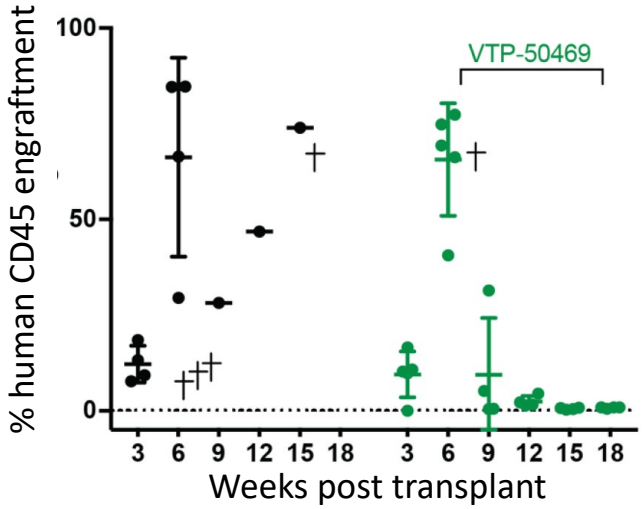
Menin inhibitors also have profound single-agent activity in NPM1c PDX models, producing deep and durable responses

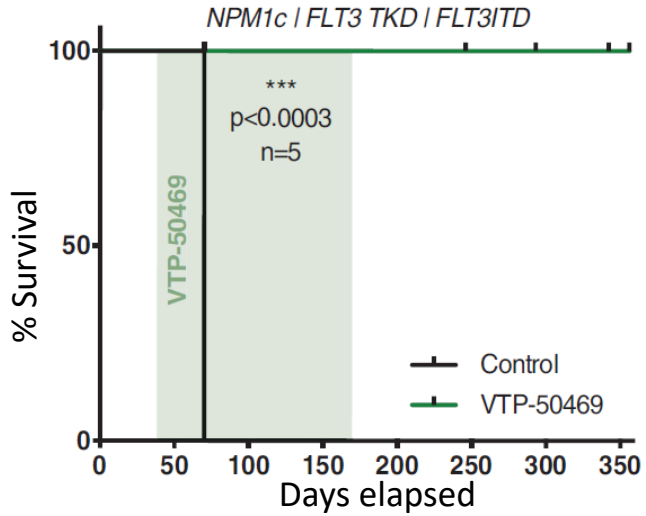


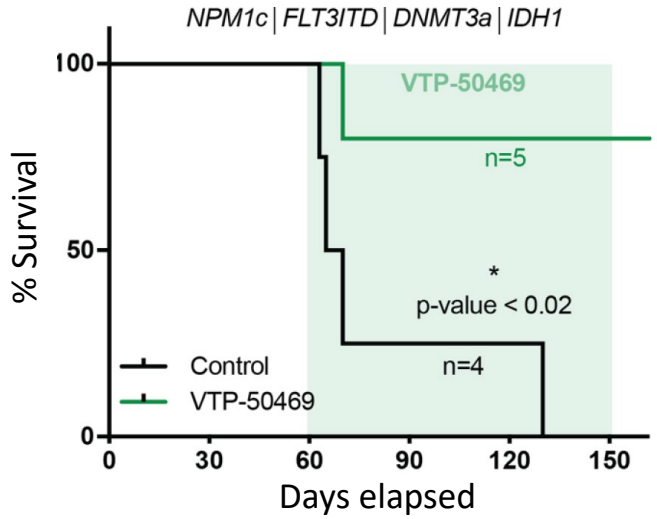
i.v. Engraft
5-75% PB Leukemia

~90 Day Treatment
SNDX-50469
formulated in Chow



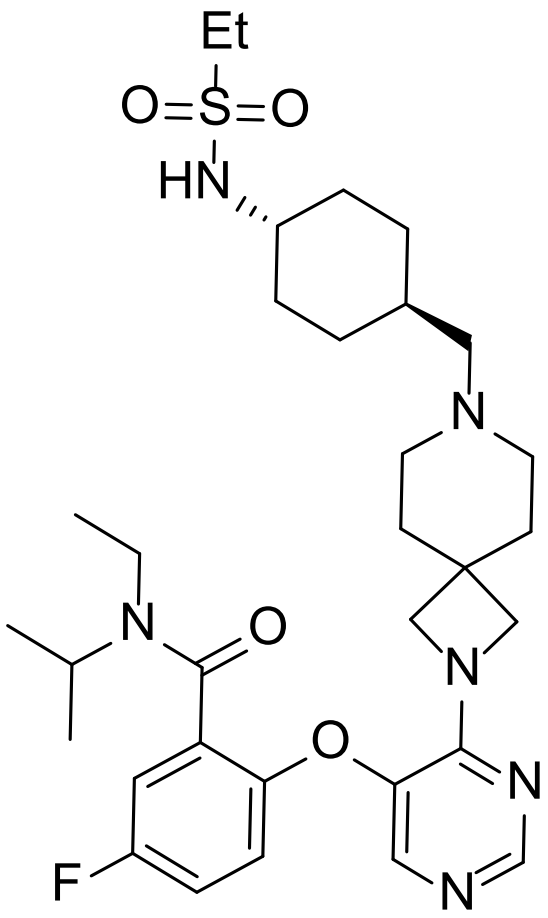






Uckelmann, HJ. *Science*. 2020 Jan 31;367(6477):586-590

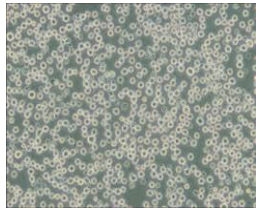
SNDX-5613 pharmacologic profile shows high potency and specificity for Menin - MLL inhibition



SNDX-5613

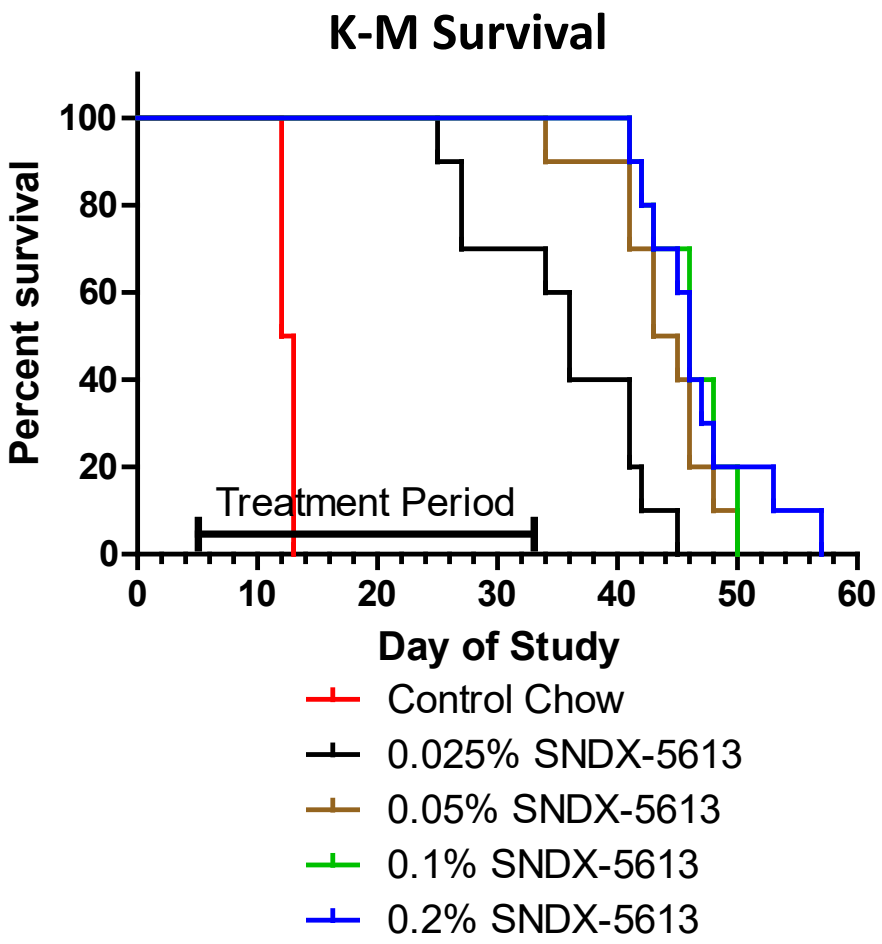
	Parameter	Summary of findings
in vitro / in vivo profile	Binding K_i	0.149 nM
	Cell based IC_{50}	10 – 20 nM
	in vivo (Plasma) IC_{50} (nM)	53 nM
	Specificity (>125 enzyme/receptor)	No off-target binding @10 µM
ADME properties	% F (r, d)	29, 65
	i.v. $t_{1/2}$ (r, d)	2, 3.3
	% unbound at 10 mM (PPB)	32%
	CYP inhibition / induction	> 10 µM
	Metabolism	Primarily via CYP3A4
Safety / toxicology	Safety hERG IC_{50}	5 µM - 15 µM
	GLP toxicity (r, d)	Consistent with primary MOA
	Genotoxicity (Ames, MNT)	Negative

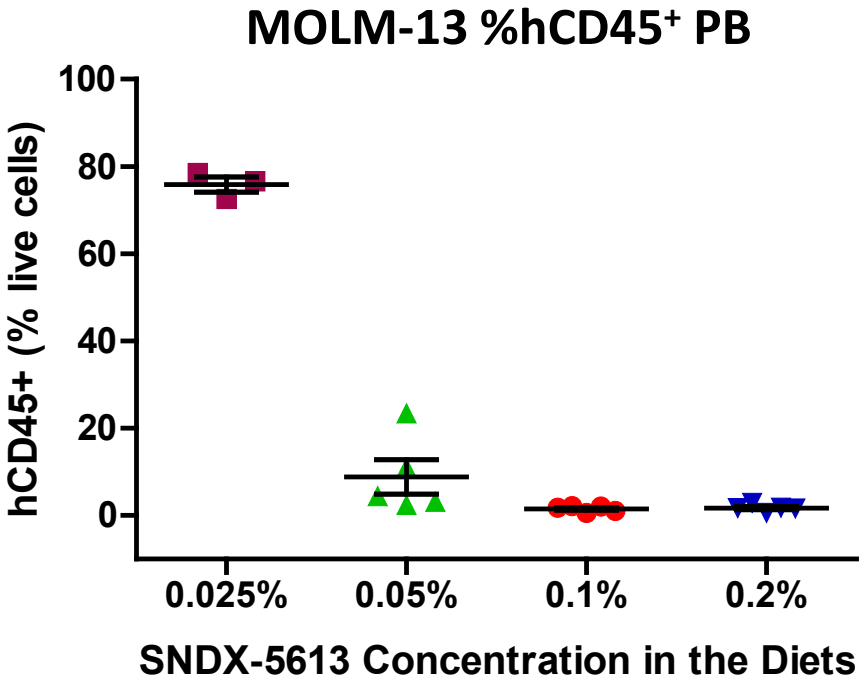
SNDX-5613 treatment provides significant survival benefit and leukemic control in aggressive MOLM-13 disseminated xenografts



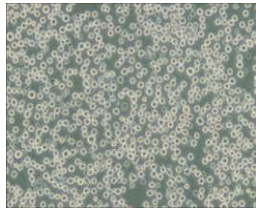
i.v. Engraft 5 days

28 Day Treatment
SNDX-5613
Formulated in Chow



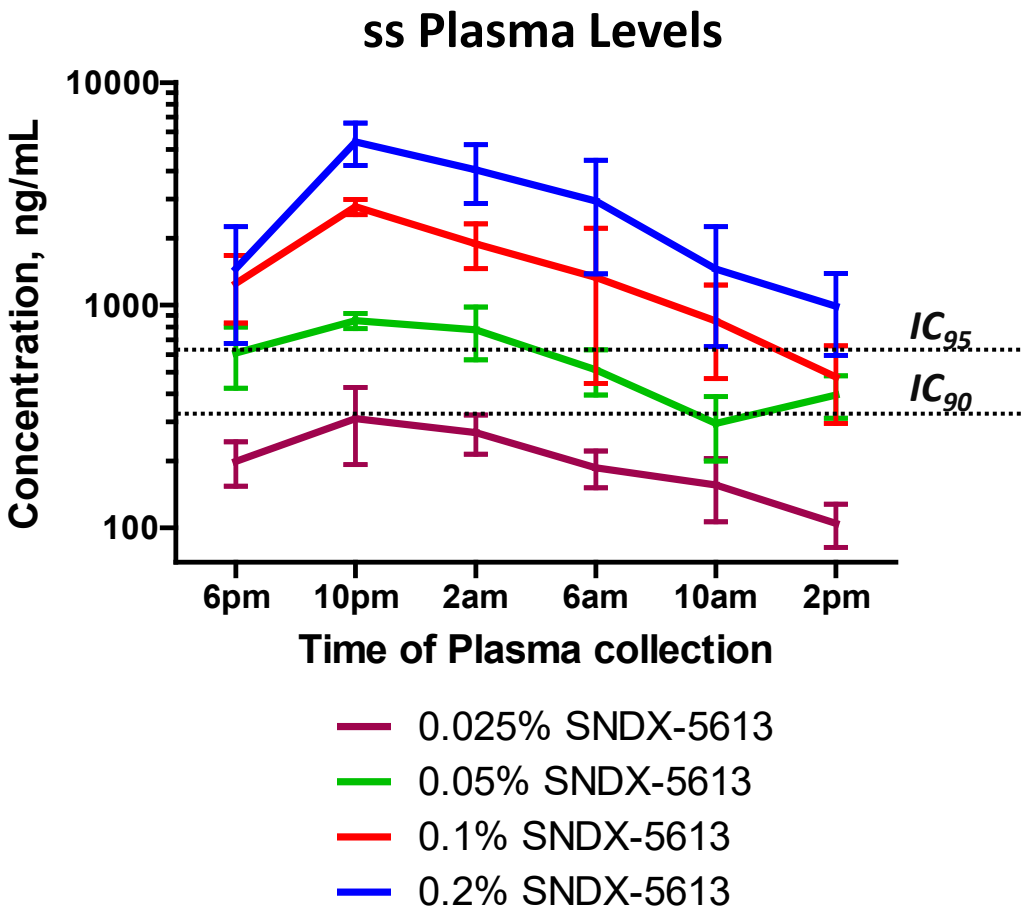


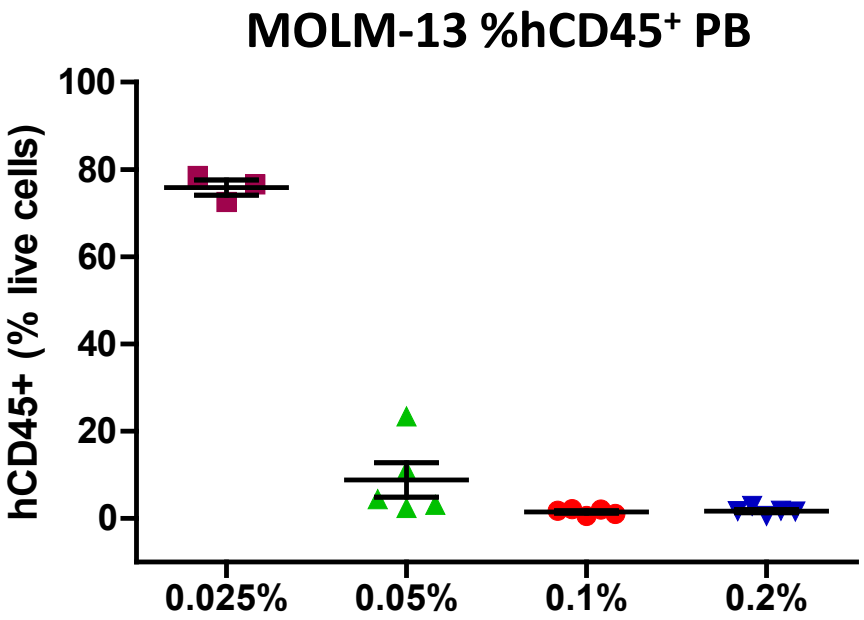
Steady-state plasma PK analysis clarifies the drug exposures required for leukemic control in MOLM-13 xenografts



i.v. Engraft 5 days

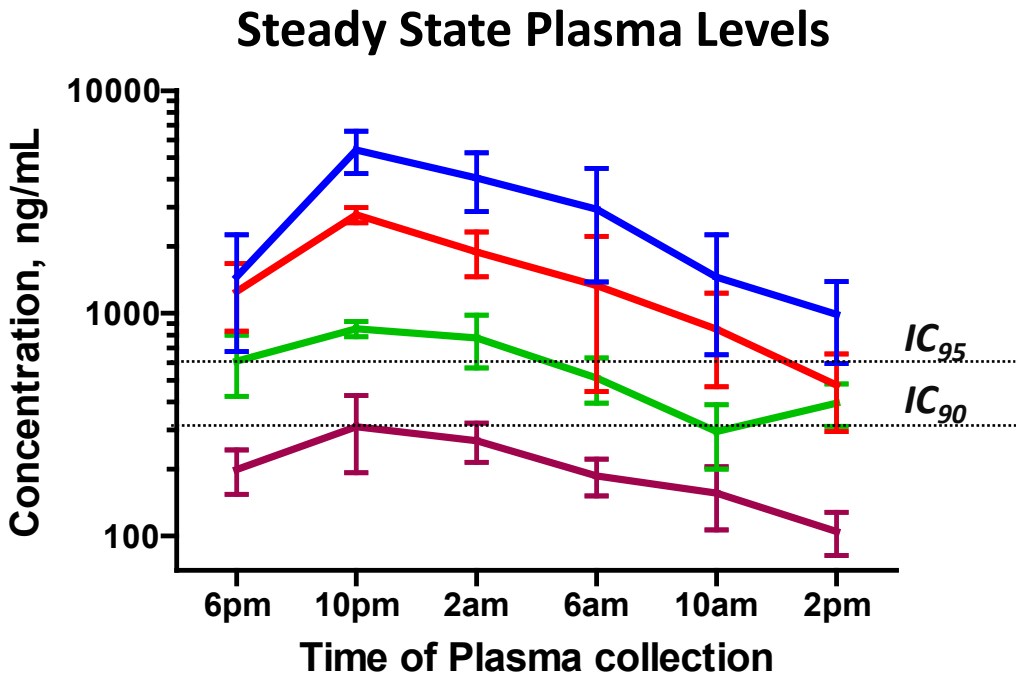
28 Day Treatment
SNDX-5613
Formulated in Chow





DOSE STRENGTH %	AVE CONC ng/ml	AUC_{0-24} ng*hr/ml
0.025	203	4900
0.05	573	13700
0.10	1425	34200
0.20	2713	65100

Projecting pre-clinical PK/PD to target clinical exposure



DOSE STRENGTH %	AVE CONC ng/ml	AUC_{0-24} ng*hr/ml
0.025	203	4900
0.05	573	13700
0.10	1425	34200
0.20	2713	65100

Target PK Profile Requirements

Maintain steady state levels above IC_{95} (~600 ng/mL) for most of dosing interval

AND

Maintain C_{min} level above projected IC_{90} (~300 ng/mL)

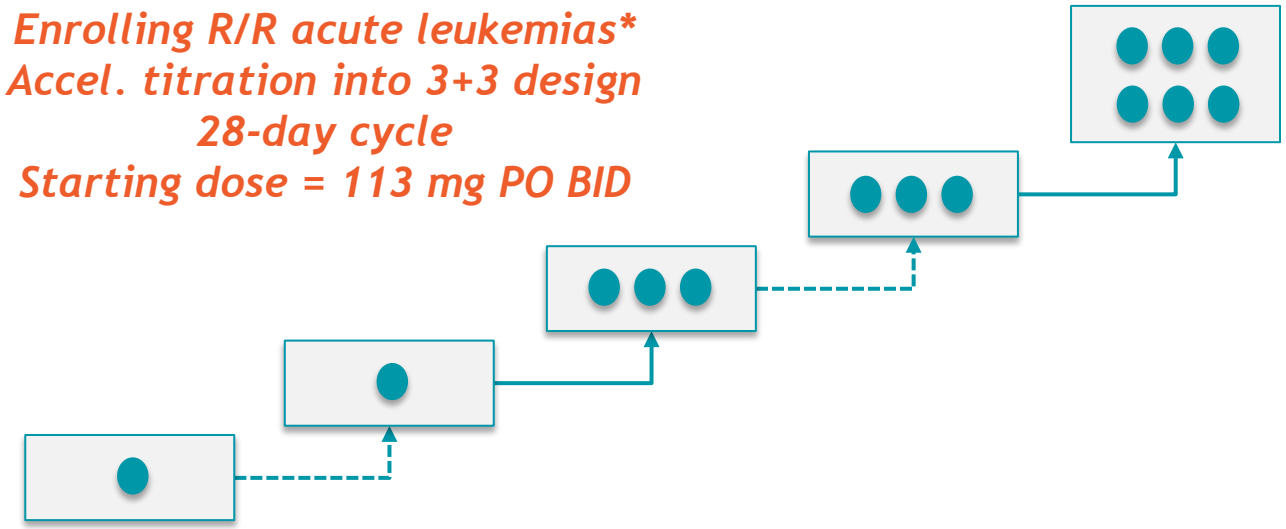
AND

Minimum 24 h AUC of ~30,000 ng*h/mL

AUGMENT-101: Phase 1/2 trial of SNDX-5613, in patients with acute leukemia

Phase 1:
Dose escalation

*Enrolling R/R acute leukemias**
Accel. titration into 3+3 design
28-day cycle
Starting dose = 113 mg PO BID



Endpoints: Safety, PK, RP2D

Phase 2:
Expansion

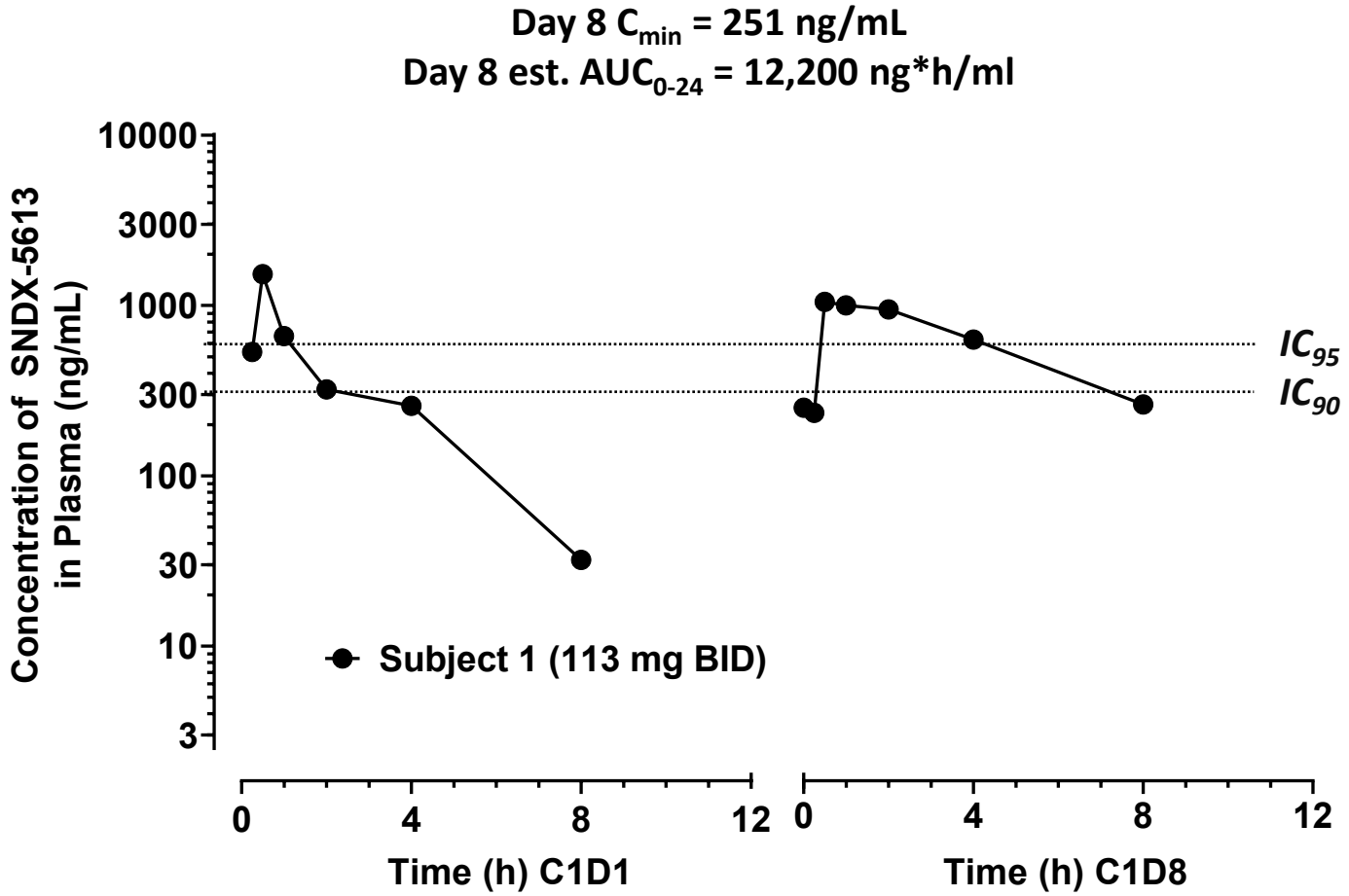
- Adult MLL-r ALL
- Adult MLL-r AML
- Adult NPM1 mut AML

Primary endpoint:
CR Rate (CR + CRh^)

* Unselected population; ^ CR = Complete response, CRh = Complete response with partial hematologic recovery; MLL-r – mixed lineage leukemia rearranged; NPM = nucleophosmin

Patient #1: 113 mg PO q12h

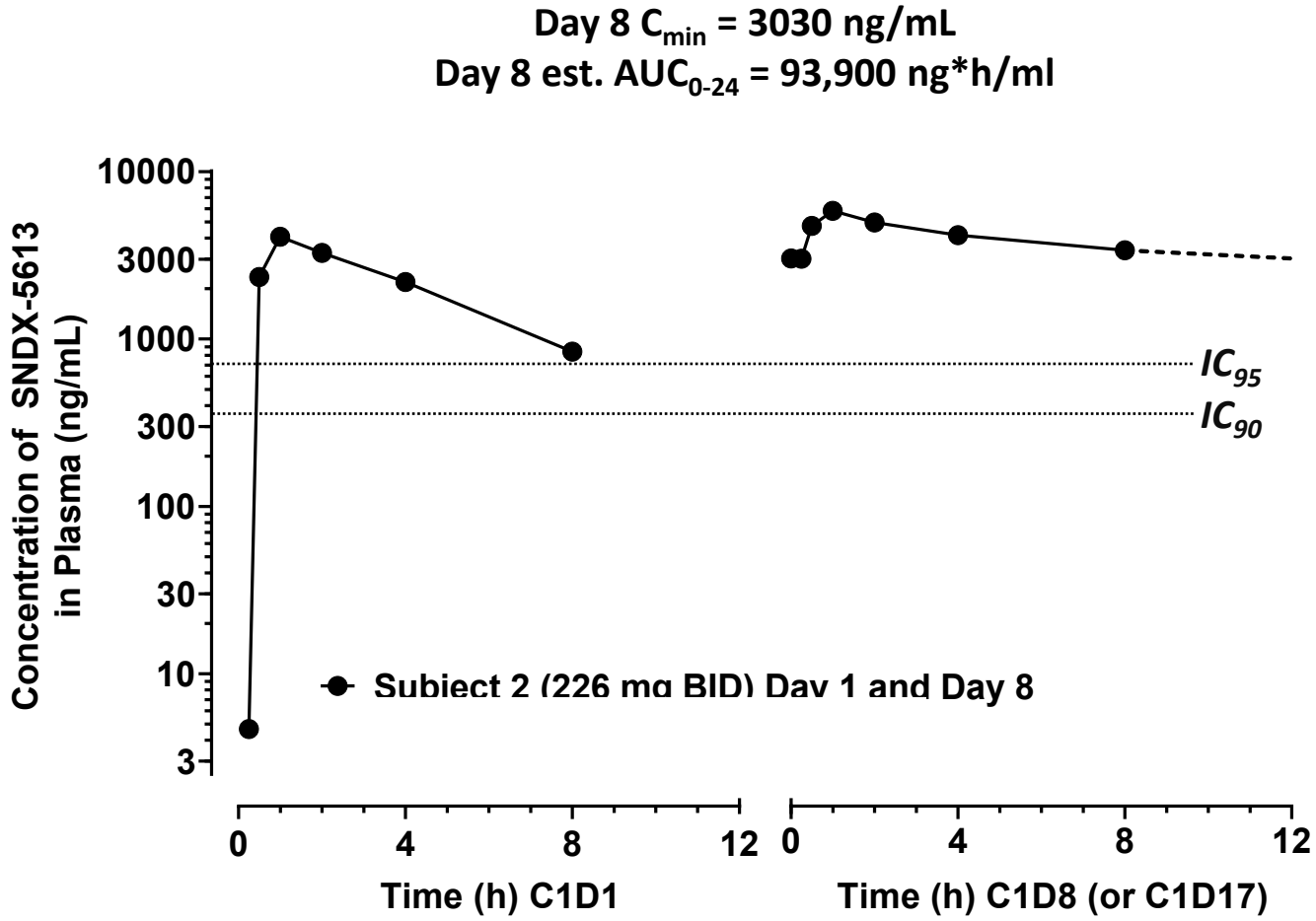
Patient Characteristics	
Gender, Age	Male, 60 yr old
Diagnosis	Refractory AML
Mutational status	No MLLr or NPM1 mutation
Prior lines of therapy	3 (Aza, Dec/Ven, CLAG-M)
SNDX-5613 dose	113 mg PO q12 hr
DLT period	No DLTs
Day 28 response	Progressive disease



CR = Complete response, CRh = Complete response with partial hematologic recovery, CRi = complete remission with incomplete hematologic recovery

Patient #2: 226 mg PO q12h

Patient Characteristics	
Gender, Age	Female, 69 yr old
Diagnosis	Refractory MPAL
Mutational status	MLL-TET1 fusion FLT3 ITD
Prior lines of therapy	2 (chemo, gilteritinb)
SNDX-5613 dose	226 mg PO q12 h
DLT period	No DLTs; Grade 2 QTc → resolved with dose reduced to 113 mg q12h
Day 28 response	CRi; beyond DLT period has improved to CR while on reduced dose



CR = Complete response, CRh = Complete response with partial hematologic recovery, CRi = complete remission with incomplete hematologic recovery

Response summary to date – Patients not on CYP3A4 Inhibitor

Pt #	Age	# Prior Tx	Mutational status	Dose	Meets target PK profile^	DLT period	Response Assessment
1	60	3	None*	113 q12	No	No DLTs	Progressive Disease/ off study
3	32	8	MLL-r t(5;11)	226 q12	No	No DLTs	No Response/ on study

5 pediatric patients (ages 1.5 – 10 years) all with MLL-rearrangements treated on single patient INDs:

- none were on CYP3A4 inhibitors
- none achieved the target PK profile
- and none had a response to date

PK exposures in pediatric patients generally consistent with adult exposures at equivalent dose

**** Patient did not have either MLLr or NPM1 mutant AML; ^ Target PK profile defined as: (1) maintaining steady state levels above IC_{95} (~600 ng/mL) for most of dosing interval, (2) maintaining Cmin level above projected IC_{90} (~300 ng/mL) and (3) achieving a minimum 24 h AUC of ~30,000 ng*h/mL***

Response summary to date – Patients on Strong CYP3A4 Inhibitor

Pt #	Age	# Prior Tx	Mutational status	Dose	Meets target PK profile^	DLT period	Response Assessment
2	69	2	MLL-r t(10;11) FLT3 ITD	226 q12 → 113 q12	Yes	No DLTs Grade 2 QTc, resolved with dose reduction	**Day 28 CRi - improved to CR** FISH neg, Flow neg, on study
4	30	>3	None*	226 q12	PK pending	Inevaluable	**Progressive Disease** off study
5	79	2	MLL PTD	226 q12	PK pending	No DLTs	Day 28: **No Response** on study
6	61	3	MLL-r t(9;11)	113 q12 → 113 QD	PK pending	No DLTs Grade 1 QTc, resolved with dose reduction	**Day 28 PRi** blast count 40%→ 20%; peripheral blood counts improving; FISH positive on study

Patient did not have either MLLr or NPM1 mutant AML; ^Target PK profile defined as: (1) maintaining steady state levels above IC_{95} (~600 ng/mL) for most of dosing interval, (2) maintaining Cmin level above projected IC_{90} (~300 ng/mL) and (3) achieving a minimum 24 h AUC of ~30,000 ng*h/mL

Menin-MLL interaction inhibitors represent a novel, targeted therapy for Mixed Lineage Leukemia-rearranged (MLL-r) and NPM1 mutant AML

SNDX-5613 is a potent, selective, orally available inhibitor of menin-MLL1

- Attractive biopharmaceutical properties
- Monotherapy activity in multiple preclinical xenograft models
- Pharmacokinetics appear affected by concomitant CYP3A4 inhibition
- Clinical responses validate menin-MLL1 inhibition as a target for select patients with acute leukemia

Clinical investigation of SNDX-5613 is ongoing

Acknowledgements

Dana Farber Cancer Institute

Scott A. Armstrong

Andrei V. Krivtsov

Hannah Uckelmann

Children's Cancer Inst. (Sydney)

Richard B. Lock

Kathryn Evans

Tara Pritchard

National Cancer Institute (PPTC)

Malcolm A. Smith

Beverly A. Teicher

Vitae Pharmaceuticals

Deepak Lala

Yi Zhao

Yuri Bukhtiyarov

David Claremon

Shankar Venkatraman

Brian McKeever

Joe Chen

AUGMENT-101 Trialists

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Michael Thirman

Eytan Stein

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