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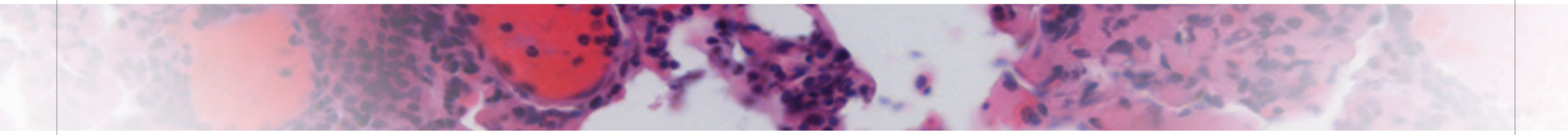

# Safety and Efficacy of Menin Inhibition in Patients with MLL-Rearranged and NPM1 Mutant Acute Leukemia: A Phase 1, First-in-Human Study of SNDX-5613

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# Disclosures

- Advisory services/consulting:
  - Gilead
  - Syndax
  - Abbvie
  - PinotBio
  - Astellas
  - Syros
  - Genentech
  - Novartis
  - Celgene
  - BMS
  - Blueprint
  - Aptose
  - Daiichi Sankyo
  - Ono
  - Janssen
  - Foghorn
  - Agios
  - Servier

# No FDA-approved targeted therapies to treat MLLr or mNPM1 acute leukemias

## MLLr Acute Leukemias

**Global incidence ~7,000**

**4-10%** AML

**10-15%** ALL

**(80 % of infant ALL)**

- **5-year OS for Adult MLLr <25%**

## NPM1 Mutant AML

**Global incidence ~20,000**

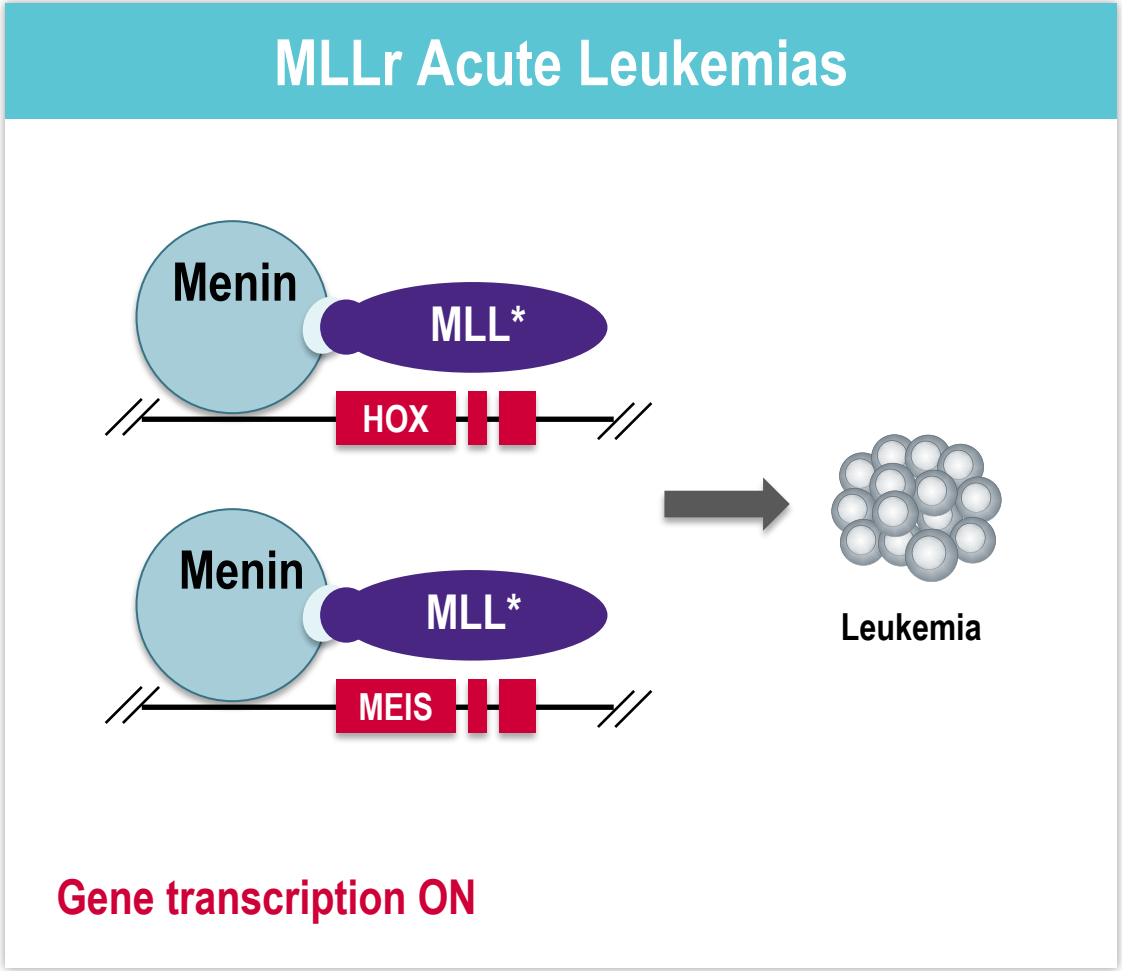
**30%** AML

- **5-year OS for Adult mNPM1 AML 50%**
- **Known NPM1 co-mutations offer rational combination approaches**

**Both MLLr and mNPM1 acute leukemias are readily diagnosed**

Sources: NCCN conference and meetings: NCCN guidelines; Dohner, H. et al. *Blood*, 2017; 129(4):424-447; Falini, B. et al. *Blood,* 2011; 117(4): 1109-1120.

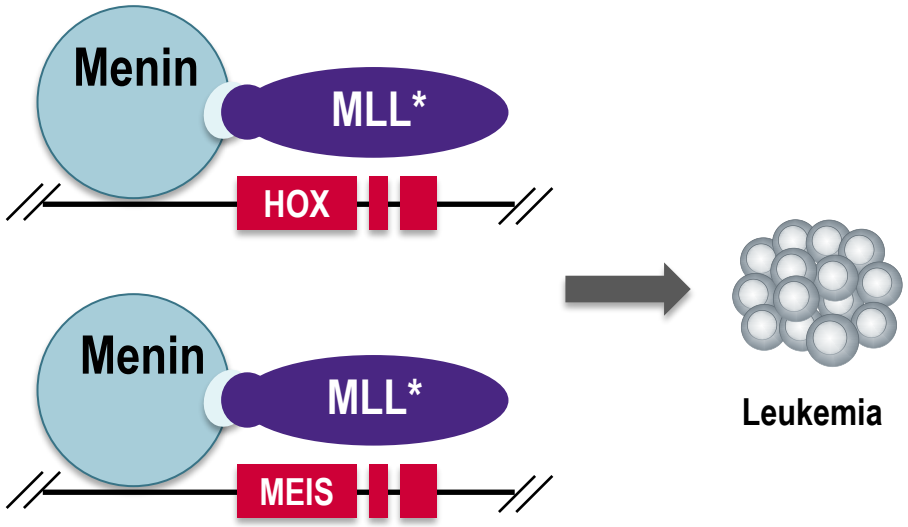
# SNDX-5613 turns off leukemic transcriptional programs by binding to Menin and displacing MLL complexes




MLL* = MLLr or MLL1 wildtype; Adopted from: Uckelmann HJ, et al. Presented at ASH Annual Meeting, 2018

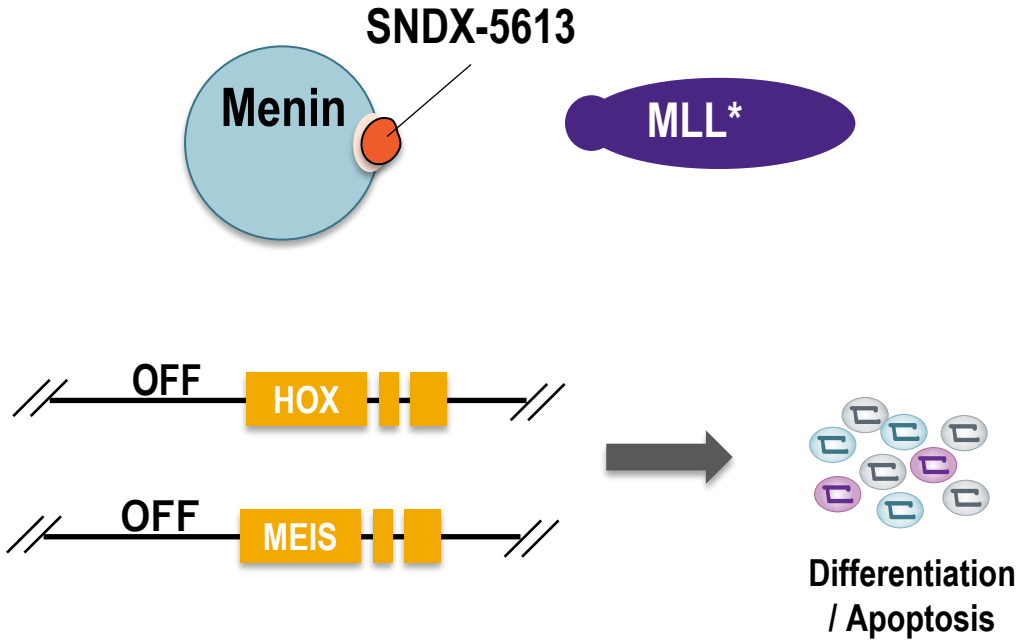
# SNDX-5613 turns off leukemic transcriptional programs by binding to Menin and displacing MLL complexes

## MLLr Acute Leukemias




Gene transcription ON

## SNDX-5613




Gene transcription OFF

MLL* = MLLr or MLL1 wildtype; Adopted from: Uckelmann HJ, et al. Presented at ASH Annual Meeting, 2018

# AUGMENT-101 study design and objectives

## *Trial design at initiation*

- **Primary Objectives**
  - Determine safety, tolerability, RP2D and characterize PK
- **Oral, q12h continuous dosing of SNDX-5613**
- **Accelerated titration into a 3+3**
- **Enrolling "all comers" R/R acute leukemia**

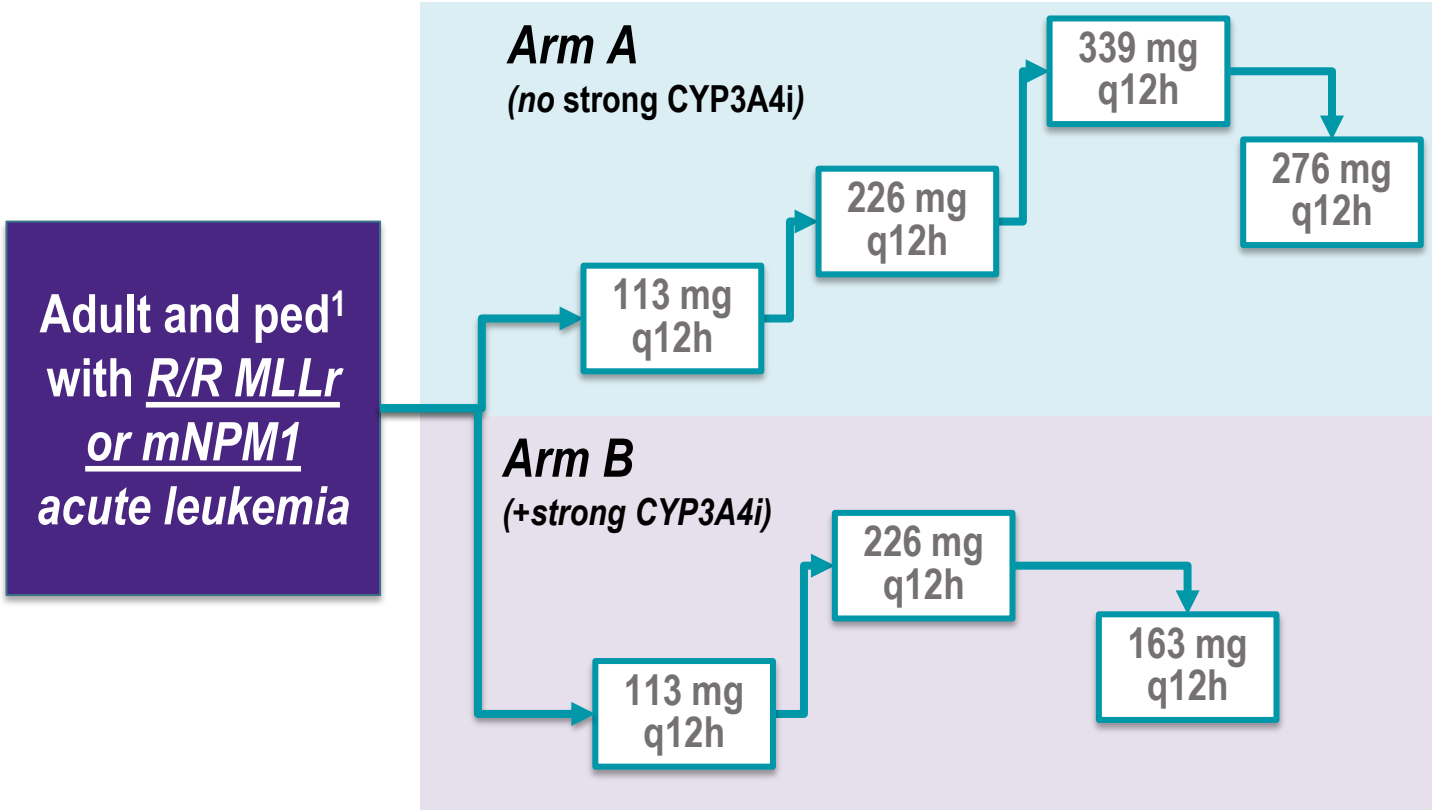
## *Prespecified RP2D selection criteria:*

- **No more than 1 of 6 of evaluable patients experience a DLT**
- **At least 2/3 of patients receive ≥ 80% of their dose in the first two cycles**
- **24-hour AUC ($AUC_{0\text{-}24}$) exceeds 15,000 ng×hr/mL in at least 2/3 of patients**

# Dosing schema in Phase 1

## *Trial Updates*

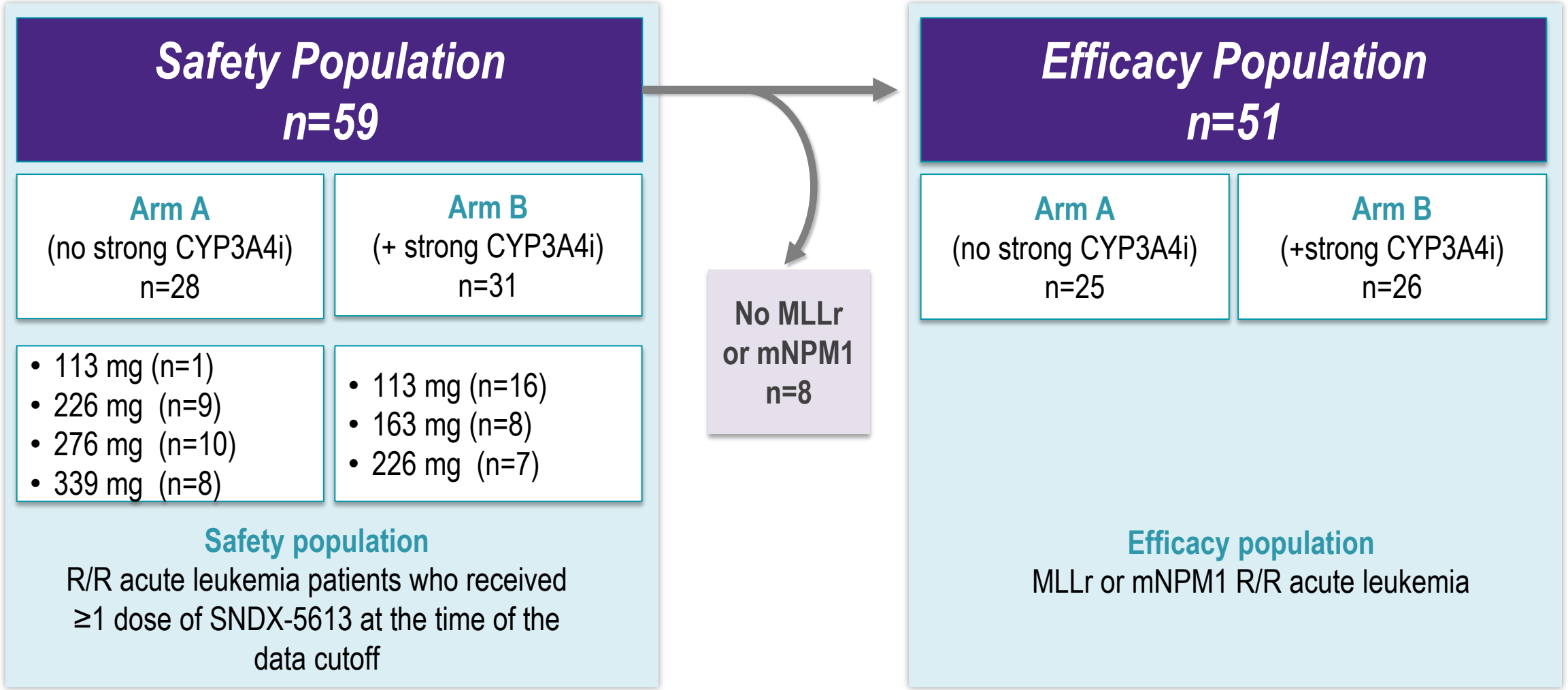
- **Focused to include adult and pediatric* pts with MLLr or mNPM1 acute leukemia**
- **Separated cohorts by CYP3A4i usage:**
  - Arm A (no strong CYP3A4i)
  - Arm B (strong CYP3A4i)
- **Added ability to backfill cohorts if dose level cleared & efficacy observed**




***DLTs observed at Arm A 339mg q12h & Arm B 226mg q12h were Grade 3 QTc prolongation***

[1]Allows patients ≥30 days of age; Abbreviations: MLLr = mixed lineage leukemia rearranged; mNPM1 = mutated nucleophosmin

# Safety and efficacy analysis sets




Abbreviations: MLLr = mixed lineage leukemia rearranged; mNPM1 = mutated nucleophosmin *Data cutoff: 18Oct2021*

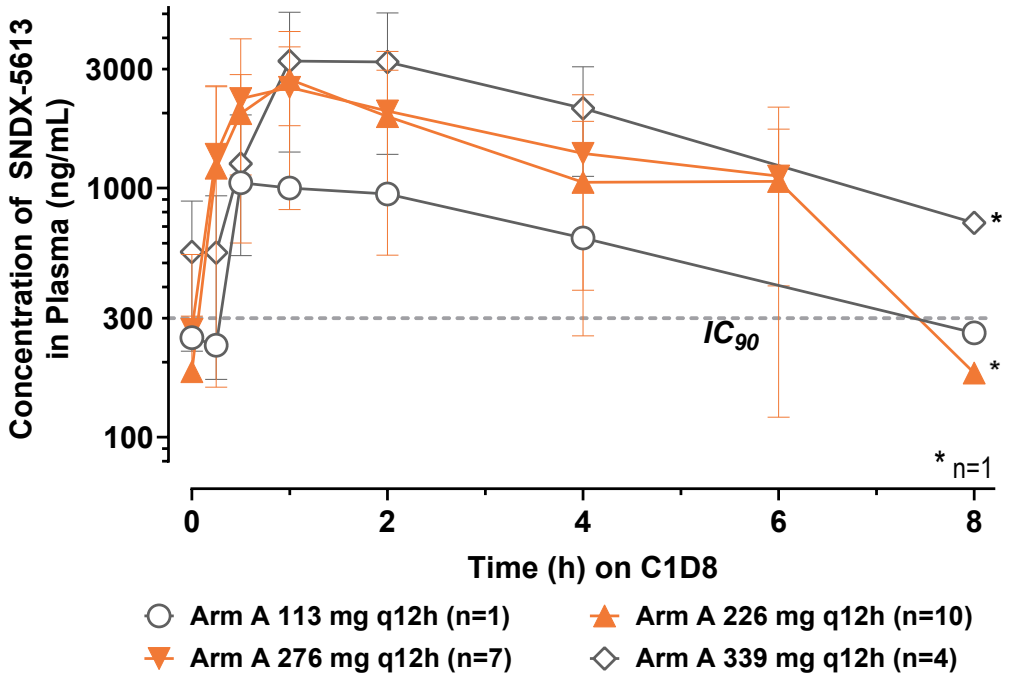
# SNDX-5613 patients are heavily pretreated & have a poor prognosis

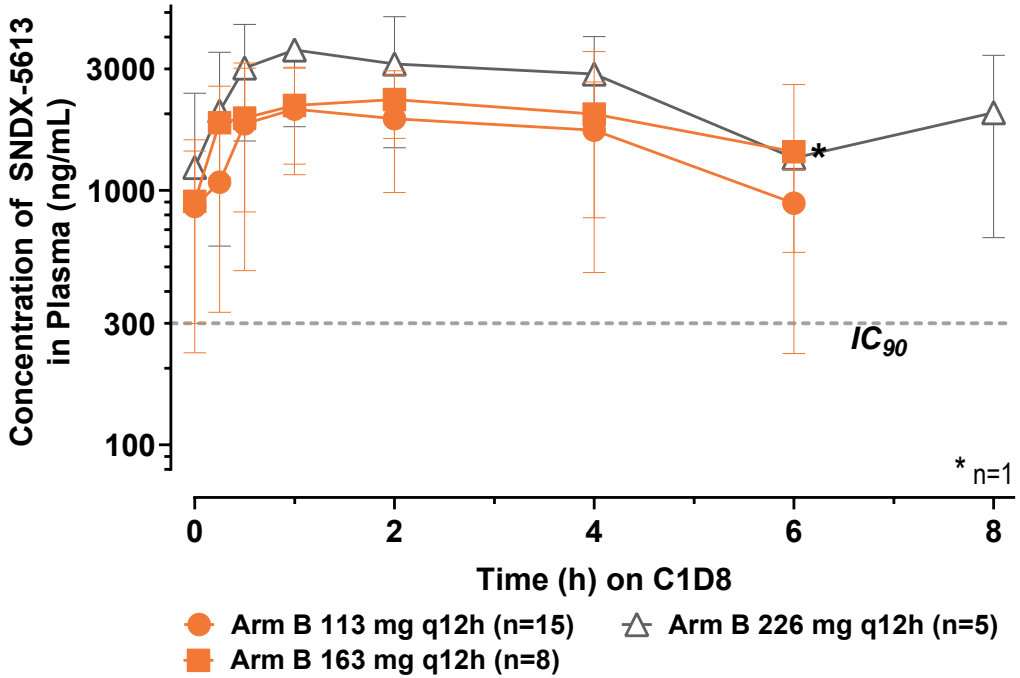
| Baseline Characteristics | Safety Population n=59 |
|---|---|
| **Median age, years (range)** | 47 (1, 78) |
| **Female, n (%)** | 37 (63) |
| **ELN prognosis at study entry (n=36)** | |
| Favorable | 4 (7) |
| Intermediate | 9 (15) |
| Adverse | 23 (39) |
| **Leukemia Type, n (%)** | |
| AML | 49 (83) |
| ALL | 9 (15) |
| MPAL | 1 (2) |

| Baseline Characteristics | Safety Population n=59 |
|---|---|
| **Genetics of enrolled pts, n (%)** | |
| MLLr (translocations in ≥4 pts) | 38 (64) |
| 9;11 | 9 (15) |
| 11;19 | 8 (14) |
| 4;11 | 5 (8) |
| 11;17 | 4 (7) |
| 6;11 | 4 (7) |
| mNPM1 | 13 (22) |
| Non MLLr/Non mNPM1 | 8 (14) |
| **Median prior therapies** (range) | 4 (1,12) |
| Stem cell transplant, n (%) | 25 (42) |
| Venetoclax | 35 (59) |

*Data cutoff: 18Oct2021*

# Dose proportional exposure achieved across both arms




*Steady-state levels achievable in ~2 days, no evidence of drug accumulation*

# No discontinuations for treatment-related AE, and 9 went on to HSCT

| Patient Disposition | Safety Population n=59 |
|---|---|
| **Ongoing Patients, n (%)** | **6 (10)** |
| **Discontinued Treatment** | **53 (90)** |
| Progressive disease/No response | 34 (58) |
| Transplant | 9 (15) |
| Adverse event (AE; all unrelated) | 4 (7) |
| Withdrew consent | 3 (5) |
| Other | 2 (3) |
| Physician decision | 1 (2) |
| Treatment-related adverse event | 0 |

*Data cutoff: 18Oct2021*

# SNDX-5613 was well-tolerated across all doses

| Any-grade treatment-related AE (≥5%) | Safety Population n=59 |
|---|---|
| | All Grade |
| Pts with ≥1 treatment-related AE, n(%) | 46 (78) |
| ECG QTc prolonged | 29 (49) |
| Nausea | 16 (27) |
| Vomiting | 10 (17) |
| Differentiation syndrome | 8 (14) |
| Diarrhea | 7 (12) |
| Dysgeusia | 5 (8) |
| Decreased appetite | 4 (7) |
| Fatigue | 3 (5) |
| Hyperphosphatemia | 3 (5) |
| Neutropenia | 3 (5) |
| Thrombocytopenia | 3 (5) |

| ≥Grade 3 treatment-related AE | Safety Population n=59 |
|---|---|
| Pts with ≥Gr 3 treatment-related AE, n(%) | 11 (19) |
| ECG QTc prolonged | 7 (12) |
| Diarrhea | 2 (3) |
| Anemia | 1 (2) |
| Asthenia | 1 (2) |
| Fatigue | 1 (2) |
| Febrile neutropenia | 1 (2) |
| Hypokalemia | 1 (2) |
| Neutropenia | 1 (2) |
| Thrombocytopenia | 1 (2) |
| Tumor lysis syndrome | 1 (2) |

7% of pts (3/43) reported Gr 3 QTc prolongation at doses meeting criteria for RP2D

*Data cutoff: 18Oct2021*

# SNDX-5613 demonstrates promising antileukemic activity in relapsed/refractory MLLr and mNPM1 leukemias

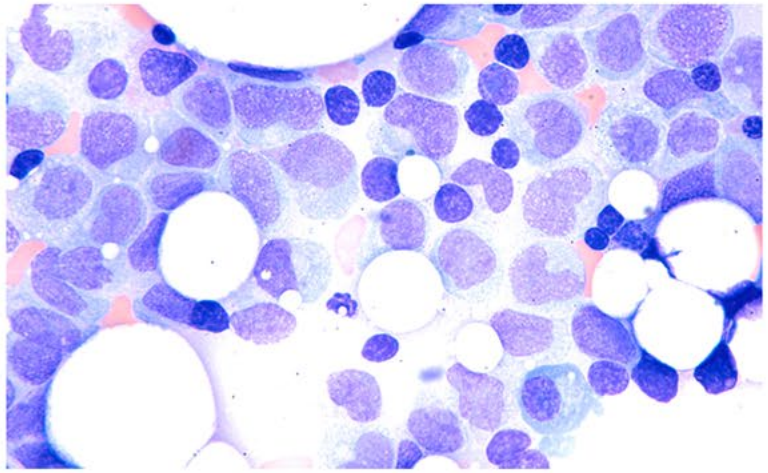
| | Best Response | Efficacy Population n = 51 (%) |
|---|---|---|
| Response | **Overall Response Rate[1]** | **28/51 (55%)** |
| | CR | 8 (16%) |
| | CRh | 4 (8%) |
| | CRp | 7 (14%) |
| | MLFS | 9 (18%) |
| MRD$^{neg}$ | **CRc MRD$^{neg}$ Rate[2]** | **16/51 (31%)** |
| | within CR/CRh MRD$^{neg}$ | 11/12 (92%) |
| | within CR/CRh/CRp MRD$^{neg}$ | 16/19 (84%) |
| MLLr | **Overall Response Rate[1]** | **23/38 (61%)** |
| | CR/CRh | 9/38 (24%) |
| mNPM1 | **Overall Response Rate[1]** | **5/13 (38%)** |
| | CR/CRh | 3/13 (23%) |

**CR/CRh 12 (24%)**

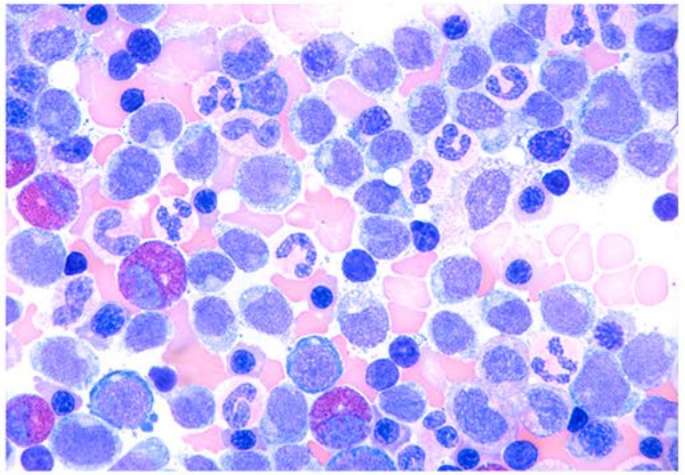
[1]Overall Response Rate = CR + CRh + CRp + MLFS; [2]CR + CRh + CRp ; MRD status assessed locally by PCR or MCF

Data cutoff: 18Oct2021

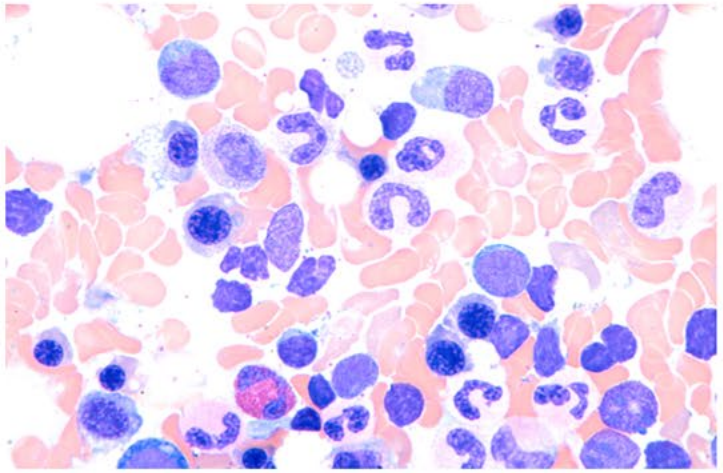
# Morphologic Evidence of Myeloid Differentiation



Screening



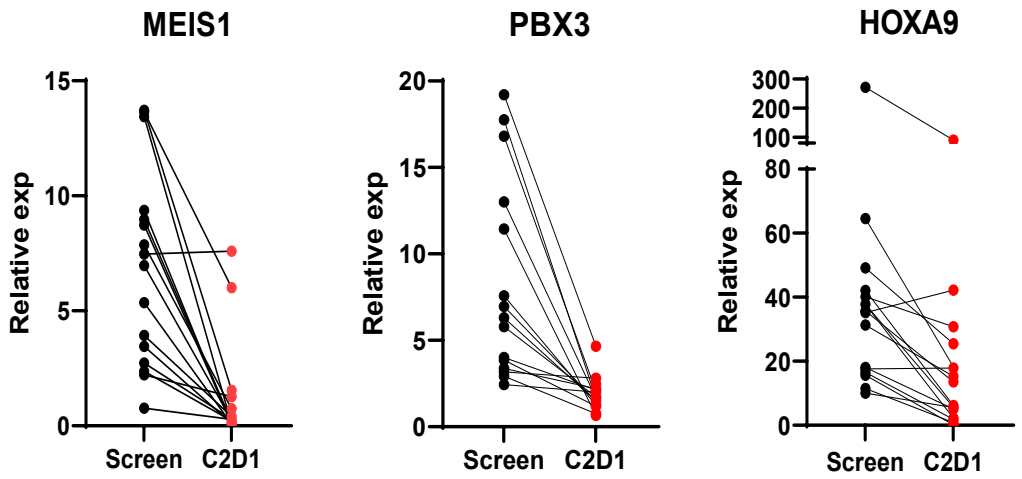
Cycle 2 Day 1



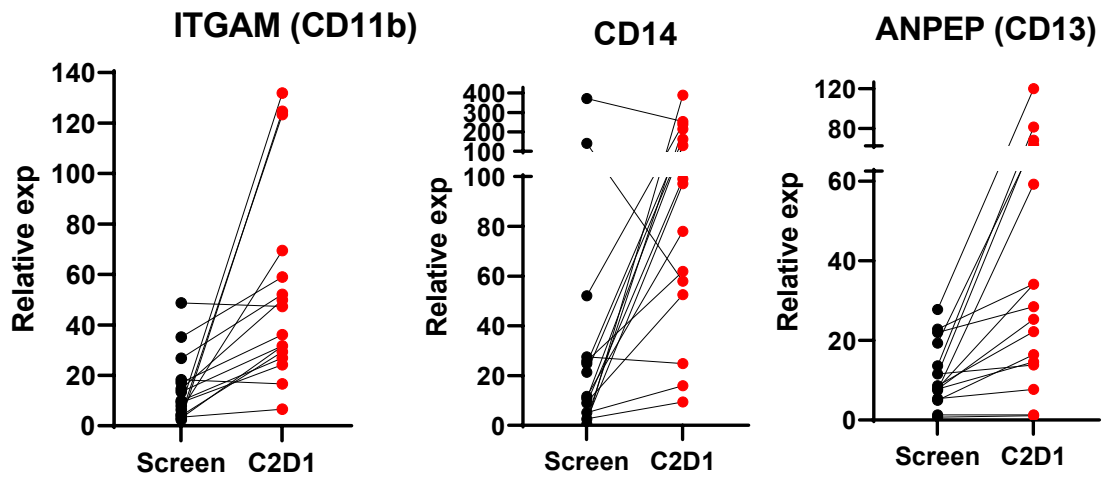
Cycle 3 Day 1

# SNDX-5613 pharmacodynamic activity confirms MOA

## Down-regulated leukemogenic gene expression



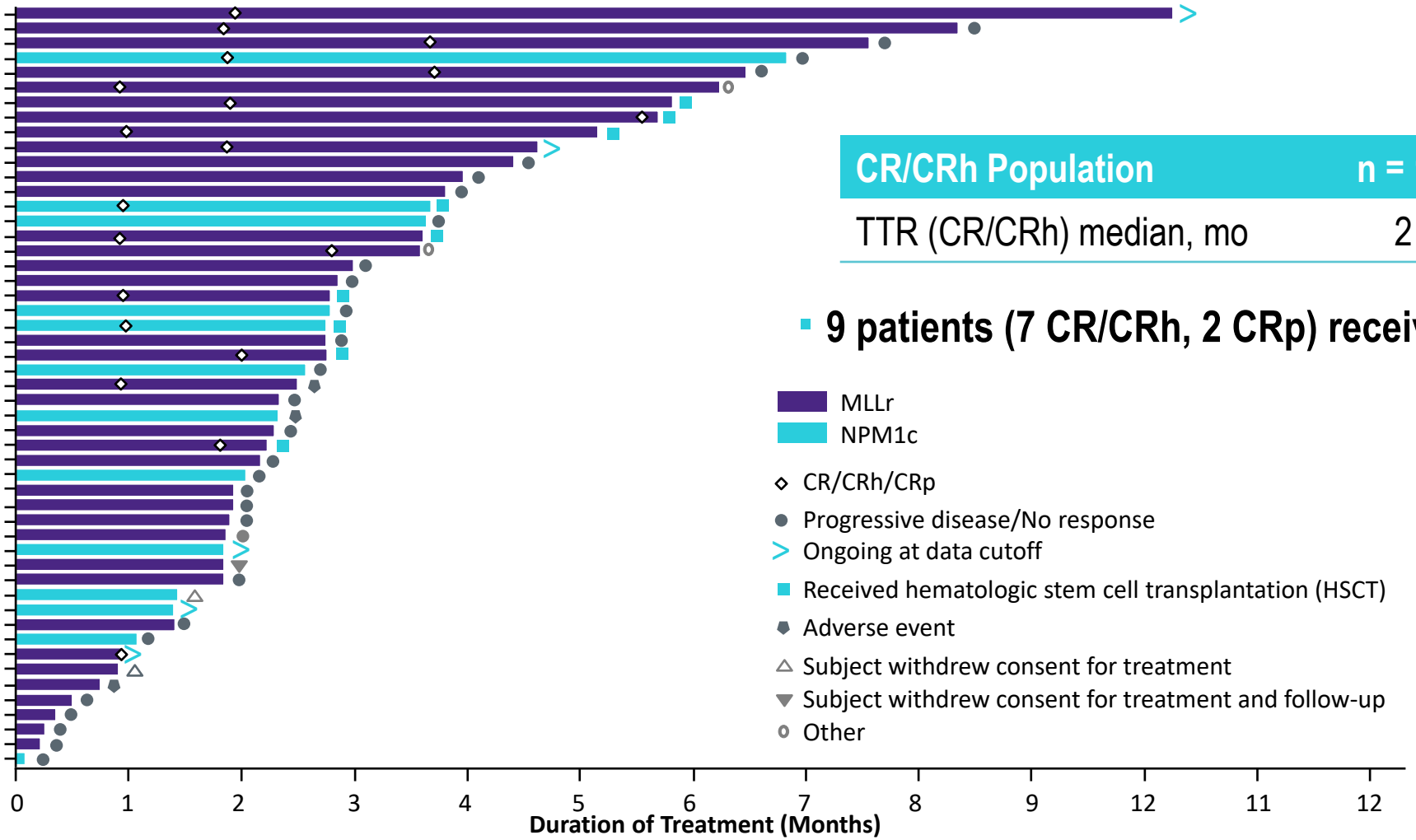

## Up-regulated differentiation markers




Gene expression measured by RNA-seq of bone marrow samples taken at screening and C2D1 (n=16)

***Robust gene expression changes across arms, dose ranges, and in both MLLr and mNPM1***

# SNDX-5613 monotherapy induces rapid response

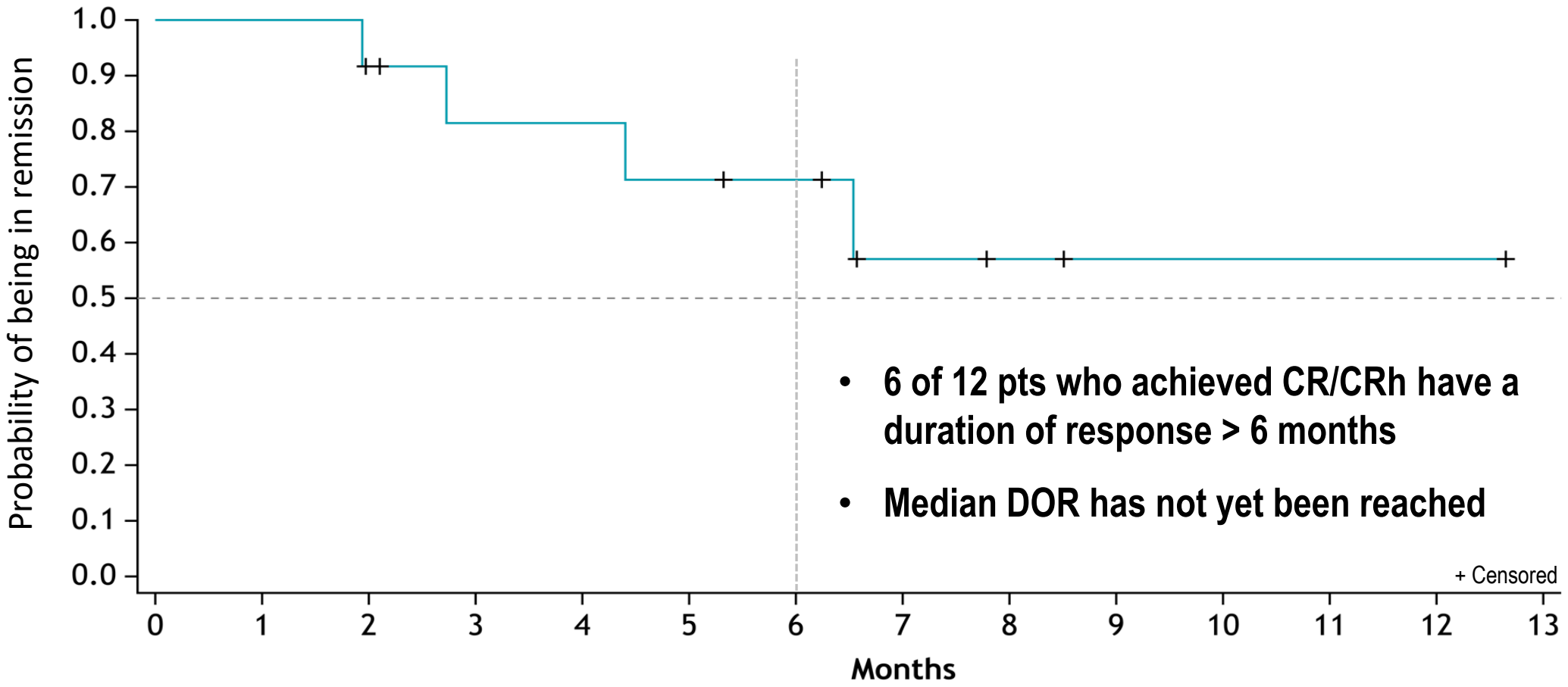



| CR/CRh Population | n = 12 |
|---|---|
| TTR (CR/CRh) median, mo | 2 |

- **9 patients (7 CR/CRh, 2 CRp) received HSCT**

Abbreviations: TTR=time to response; Data cutoff: 18Oct2021

# SNDX-5613 monotherapy CR/CRh responses were durable




[1] Durability measured from time of initial attainment of CR or CRh. Continued remission post-HSCT is included; Abbreviations: DOR=duration of response; Data cutoff: 09Nov2021

# Conclusions

**In this phase 1 FIH study, SNDX-5613 was well-tolerated with a favorable adverse event profile**

- Only DLTs seen were asymptomatic Grade 3 QTc prolongation
  - Of the 4 doses that met pre-defined RP2D criteria, 7% (3/43) experienced Gr 3 QTc prolongation
- Differentiation syndrome seen in 14% patients, all Gr 1/2 and easily managed with standard of care

**High rates of response observed in this heavily pretreated R/R mNPM1 or MLLr acute leukemia population**

- Overall Response Rate of 55%, CRc MRD negative rate was 31% (16/51)
- 92% (11/12) patients achieving a CR/CRh response were MRD negative by local assessment
- CR/CRh rates were similar in patients with R/R mNPM1 (23%) and MLLr (24%) acute leukemia

**CR/CRh responses were durable**

- 6 of 12 pts who achieved CR/CRh have a duration of response > 6 months; Median DOR was not reached

**Nine patients went onto receive HSCT**

**We have identified a RP2D and pivotal Phase 2 cohorts were initiated September 2021**