

# **Results of a Phase 1b/2 Study of Entospletinib Monotherapy and In Combination With Induction Chemotherapy In Newly Diagnosed Patients With Acute Myeloid Leukemia**

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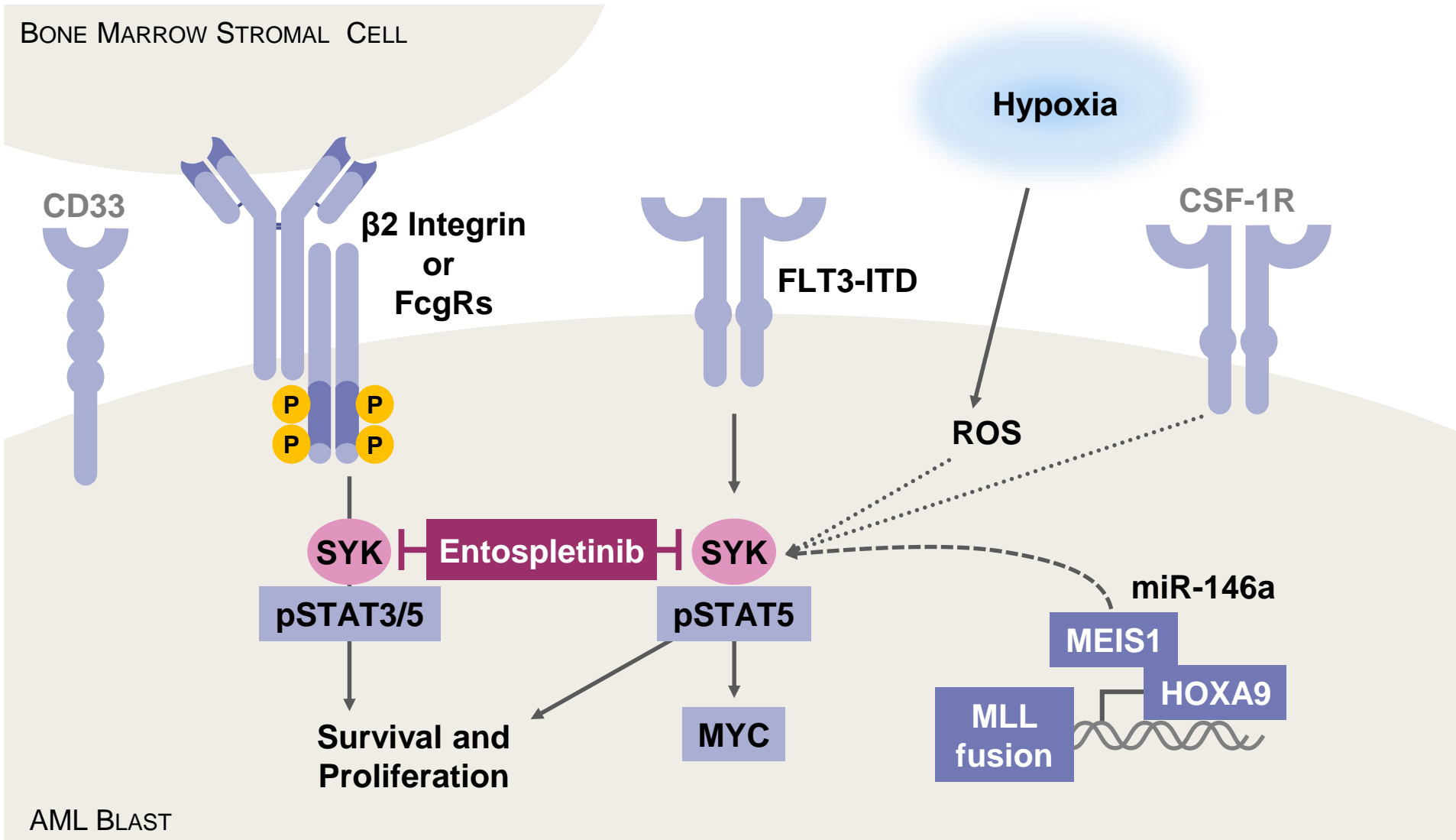
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# Background

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- ◆ Acute myeloid leukemia (AML) is both a biologically and clinically heterogeneous hematologic malignancy
- ◆ The identification of recurrent cytogenetic and molecular mutations has not only led to insights into leukemogenesis, but has identified potential therapeutic targets
- ◆ Current treatment paradigms attempt to individualize therapy rather than a “one fits all” approach

# Investigating SYK as Critical Signaling Node in AML



# Role of SYK in AML

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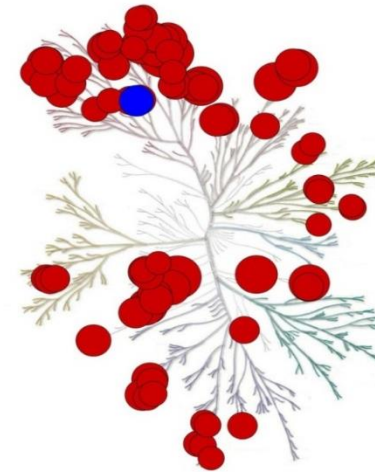
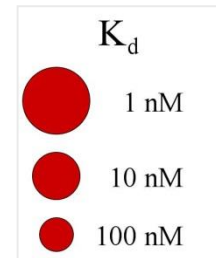
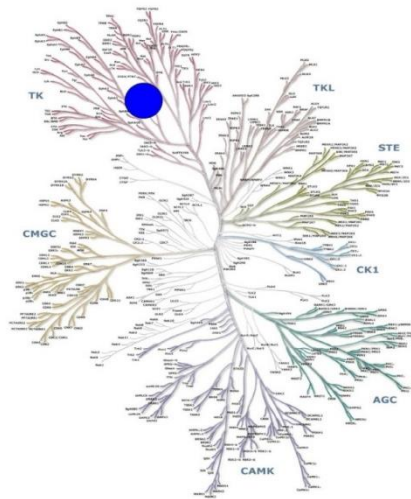
- ◆ Spleen tyrosine kinase (SYK) is a non-receptor tyrosine kinase primarily expressed in hematopoietic cells
- ◆ Constitutive activation of SYK in AML has been reported; targeted inhibition of SYK-induced differentiation in vitro demonstrated anti-leukemia activity in AML mouse models<sup>1</sup>
- ◆ SYK promotes leukemogenesis by directly phosphorylating the *FLT3* receptor, and inducing *MEIS1* in conjunction with *HOXA9* to form a regulatory loop in *KMT2A* (mixed lineage leukemia [MLL]) rearranged leukemia<sup>2,3</sup>

# Entospletinib (ENTO): an Orally Bioavailable, Selective Inhibitor of SYK with Activity in Myeloid and B-lymphoid Malignancies

## ENTO: Syk-selective

Syk  $K_d = 7.6$  nM

No other kinases with  $K_d < 100$  nM



## R406: non-selective

Syk  $K_d = 15$  nM

24 kinases with  $K_d < 15$  nM

54 additional kinases with  $K_d < 100$  nM

- ENTO exposures approach a plateau above 600 mg BID
- Biliary excretion is the major route of elimination
- Absorption is highly pH dependent: drug-drug interaction with PPIs- they decrease the absorption of ENTO by ~60%
- ENTO is an inhibitor of UGT1A1
- Clinical interactions with CYP inhibitors: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A

# Study Objectives

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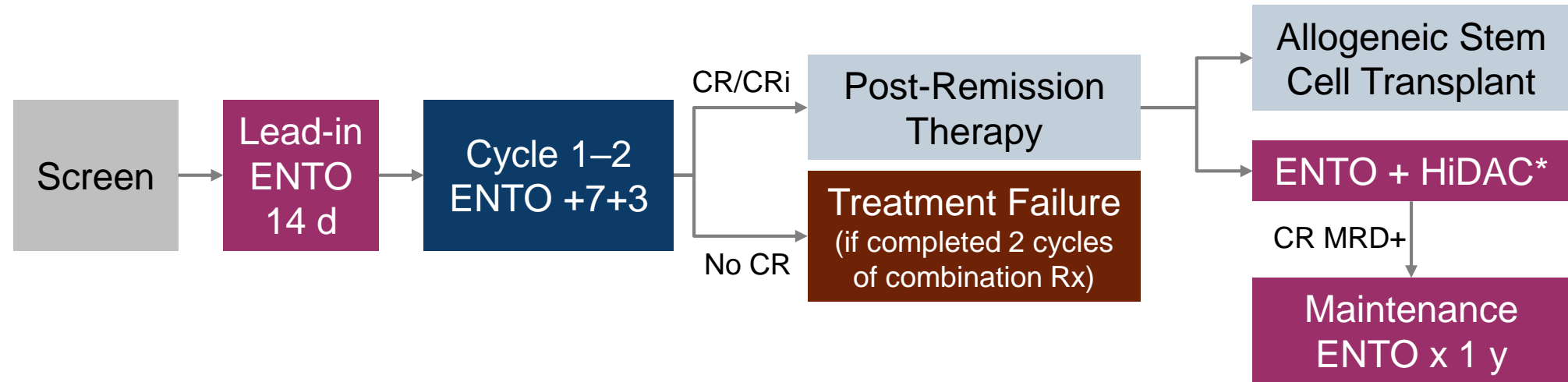
## ◆ Primary

- To demonstrate the overall safety (Phase 1) and efficacy (Phase 2) of entospletinib in combination with standard dose cytarabine and daunorubicin chemotherapy (7+3) in patients with previously untreated AML fit for chemotherapy

## ◆ Secondary

- To assess qualitative and quantitative toxicities of entospletinib as monotherapy and in combination with 7+3
- To document therapeutic response of patients treated with ENTO as monotherapy and in combination with 7+3

# Study Schema



Phase 1b n=12  
No acute promyelocytic (M3) or  
core binding factor leukemias

Phase 2 n=41  
All AML patients except M3

\*HiDAC: 3 gm/m<sup>2</sup> <60 y; 1 gm/m<sup>2</sup> ≥60 y. CR, complete response; MRD, minimal residual disease.

# Results: Demographics and Baseline Characteristics

		Total N=53
Male, n (%)		31 (58)
Median age, y (range)		60 (18, 78)
<60 y, n (%)		26 (49)
≥60 y, n (%)		27 (51)
White/Caucasian, n (%)		47 (89)
ECOG performance status, n (%)	0	24 (45)
	1	27 (51)
	2	2 (4)
Risk-group per ELN criteria, n (%)	Favorable	7 (13)
	Intermediate I	16 (30)
	Intermediate II	12 (23)
	Adverse	18 (34)
Secondary AML, n (%)		14 (26)

ECOG, Eastern Cooperative Oncology Group; ENL, European Leukemia Net.



# Results: CR Rates by ELN Risk Group

<b>ELN Risk-Group</b>	<b>ENTO+7+3 CR% (n=53)</b>	<b>Historical (7+3 regimens) CR%*</b>
Favorable-risk	86	87
Intermediate-I	81	65
Intermediate-II	75	74
Adverse-risk	50	46
<b>Total</b>	<b>70</b>	<b>63</b>

\*Adjusted to patients per age and risk-groups in our Phase 1b/2 study  
Mrozek K. J Clin Oncol 2012;30:4515-23.

# Results: CR Rates in Specific Molecular Subgroups

Molecular Sub-Group	N	CR %
Secondary AML	14	64
De novo AML	39	72
<i>KMT2A/MLL</i>	10	90
<i>NPM1+*</i>	15	87
<i>FLT3-ITD+</i>	6	83

\*4 patients with solitary *NPM1+* without any concomitant mutations

# Results: Disposition After ENTO + 7+3

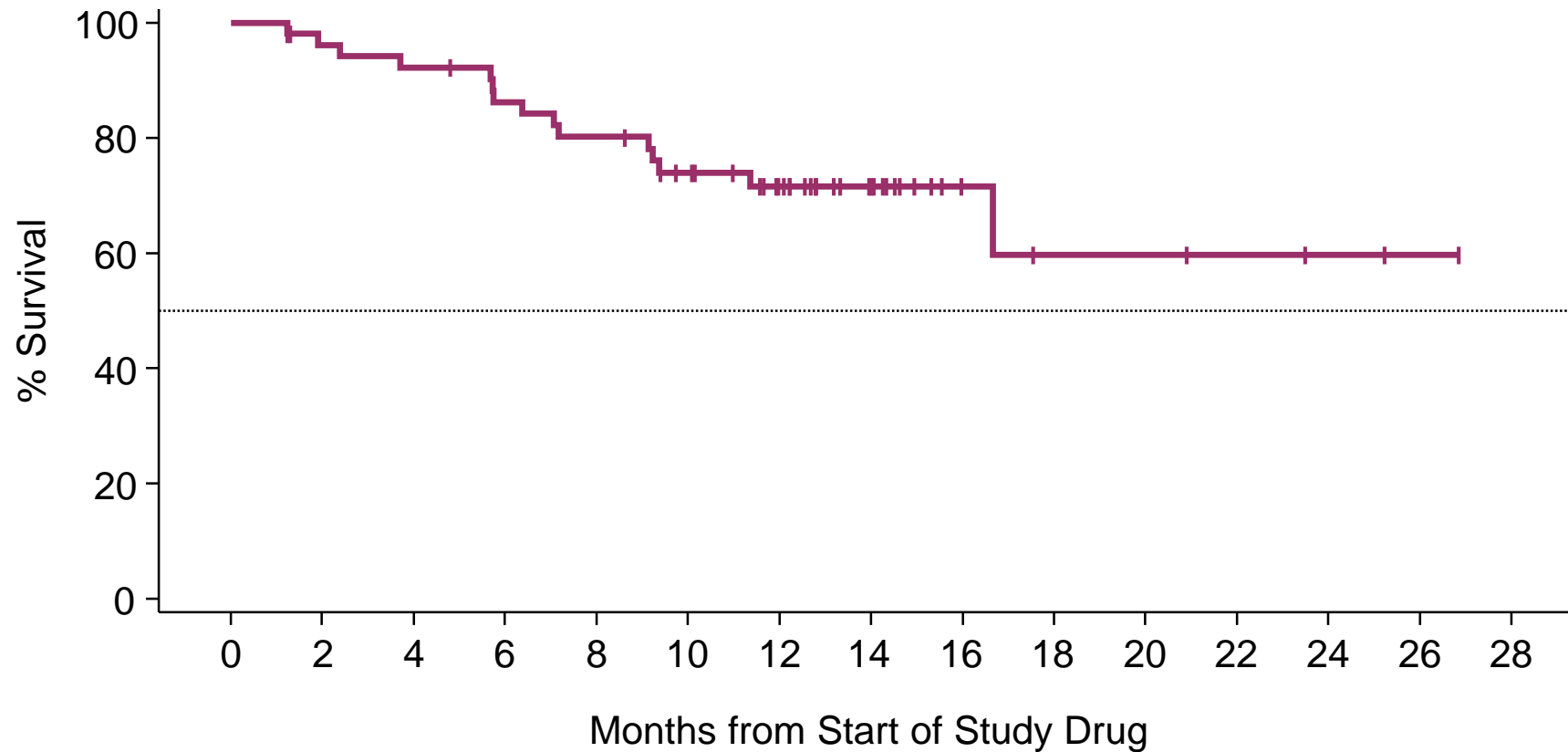
n (%)		Total N=53
No. of induction cycles	1	42 (79)
	2	9 (17)
Received allogeneic SCT		18 (34)
No. of post-remission HiDAC cycles	1	6 (11)
	2	2 (4)
	3	7 (13)
Received ENTO monotherapy maintenance		6 (11)

# ENTO Lead-in: No Effect on Efficacy

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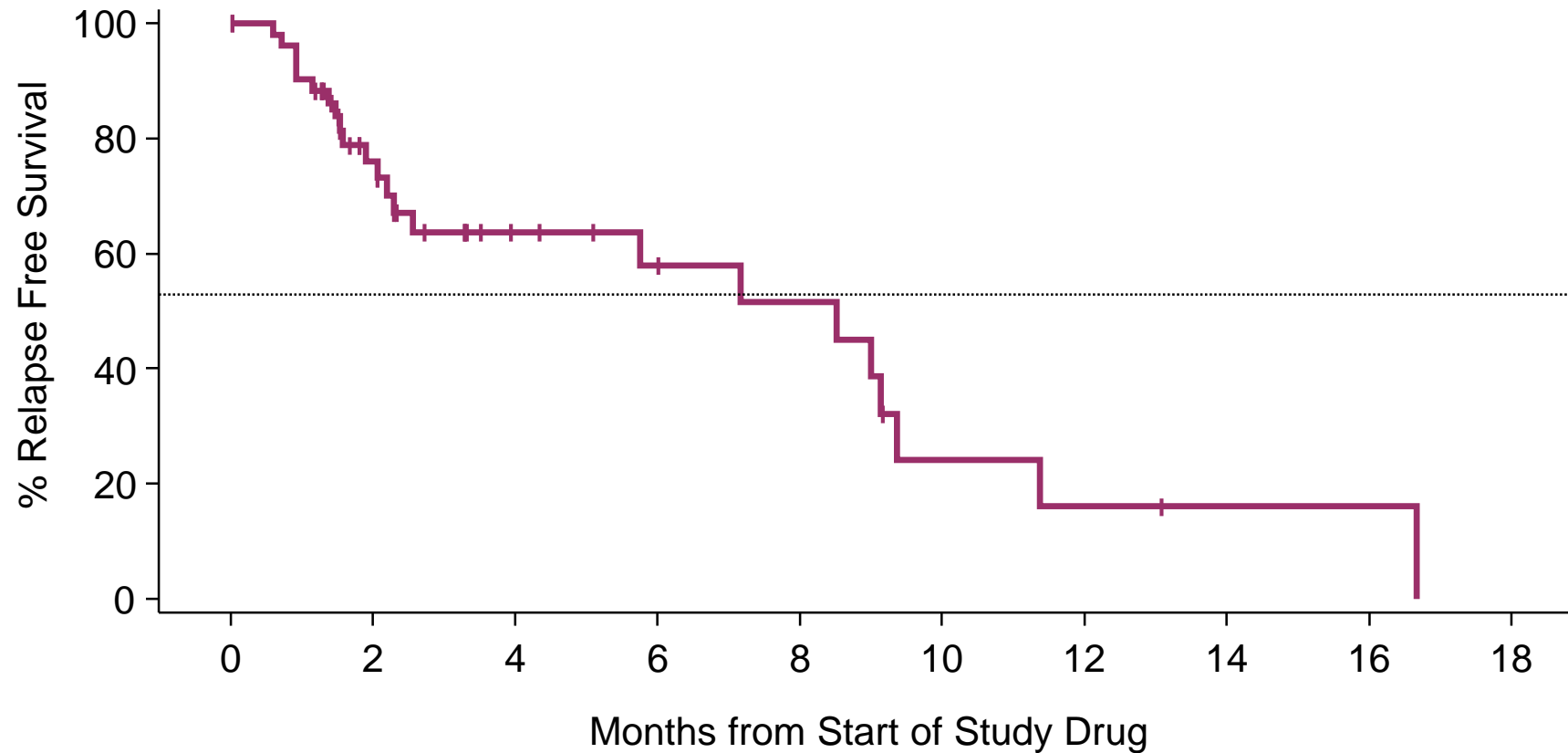
- ◆ No benefit as monotherapy: only 1 out of 53 patients responded to monotherapy
- ◆ 9 patients (17%) required hydroxyurea during lead-in
- ◆ 15 patients (28%) did not get full 14 days of lead-in ENTO either due to physician or patient preference

# Overall Survival: After Median Follow-up of 14.3 Months Median OS Was Not Reached for Phase 1b/2 AML Patients (n=53)



No. of Events	0	2	4	7	10	13	14	14	14	15	15	15	15	15	15
No. at Risk	53	49	47	43	40	34	26	15	6	4	4	3	2	1	0

# Relapse-Free Survival: After Median Follow-Up of 13 Months Median RFS is 7.7 Months for Phase 1b/2 AML Patients (n=53)



No. of Events	0	3	3	4	8	10	10	10	11	11
No. at Risk	37	14	11	9	5	2	1	1	0	0

# Safety: Grade $\geq 3$ Treatment-Emergent Hematologic Toxicity Adverse Events and Lab Abnormalities

Grade $\geq 3$ hematologic toxicity, n (%)	Total N=53 (%)
Febrile neutropenia	44 (83)
Anemia	28 (53)
Thrombocytopenia	41 (77)

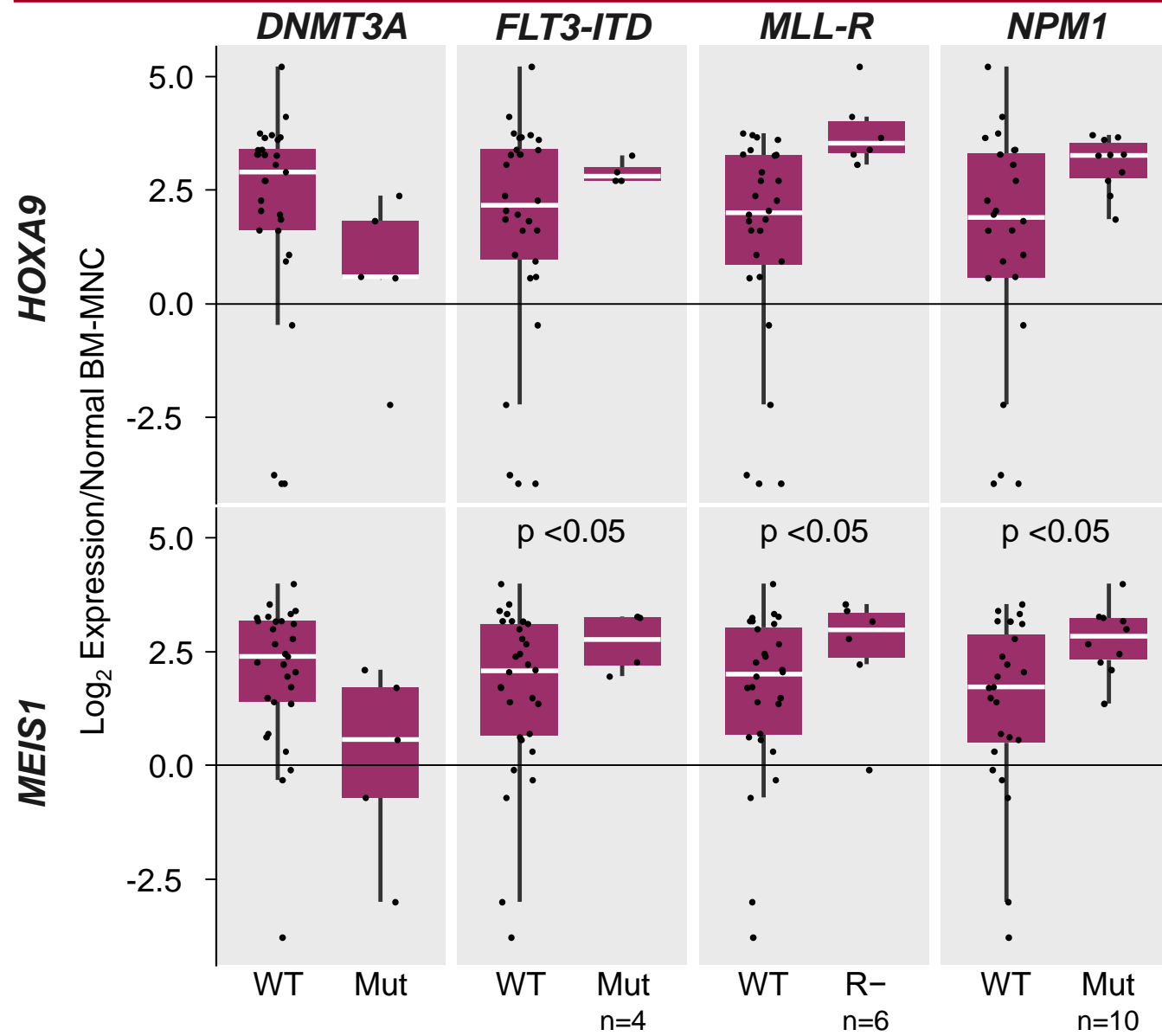
- ◆ Adverse events consistent with expected effects of a myelosuppressive chemotherapy regimen
- ◆ **30-day induction mortality 0 %**

# Safety: Grade $\geq$ 3 Treatment-Emergent Lab Abnormalities and Non-hematologic toxicity

Grade $\geq$ 3 non-hematologic toxicity, n (%)	Total N=53
Hypophosphatemia	8 (15)
Hyperbilirubinemia	6 (11)
ALT increased	3 (6)
AST increased	2 (4)
Rash	7 (13)
Diarrhea	5 (9)
Fatigue	3 (6)
Nausea	1 (2)



# High *H/M* Expression in Phase 1b/2 AML Patients with *MLL-R*, *NPM1*, and *FLT3-ITD* Mutation



Mutation*	CR %	CR/Total
MLL-R	90	9/10
NPM1	87	13/15
FLT3-ITD	83	5/6

\*Some patients have multiple mutations.

# Conclusions

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- ◆ **CR rate 70% in untreated fit AML patients treated with ENTO+7+3**
- ◆ **Overall ENTO is well tolerated and 30-day induction mortality 0%**
- ◆ **Higher response rates with SYK inhibition in AML patients with high *HOXA9/MEIS1* expression**
- ◆ **Potential role in subsets of AML: *KMT2A/MLL* and *NPM1*. Further development ongoing with the Leukemia Lymphoma Society and the BEAT-AML program**

# Acknowledgments

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**We extend our thanks to Steve Abella, MD and A. Mario Marcondes, MD PhD for their help with the design and conduct of this study**

# BACK UP

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# CR rates stratified by age and ELN risk-group

Age Group	ELN Risk-Group	Phase 1 n=12	Phase 2 n=41	Combined CR%
Age < 60 yr	Favorable-risk CR/total	1/1	1/1	100%
	Intermediate-I CR/total	0/0	4/4	100%
	Intermediate-II CR/total	3/3	4/5	87.5%
	Adverse-risk CR/total	2/3	3/9	42%
	<b>Combined CR/total</b>	<b>6/7 (86%)</b>	<b>12/19 (63%)</b>	<b>69%</b>
Age >= 60 yr	Favorable-risk CR/total	2/2	2/3	80%
	Intermediate-I CR/total	0/0	9/12	75%
	Intermediate-II CR/total	1/1	1/3	50%
	Adverse-risk CR/total	1/2	3/4	67%
	<b>Combined CR/total</b>	<b>4/5 (80%)</b>	<b>15/22 (68%)</b>	<b>70%</b>
<b>Total</b>		<b>10/12 (83%)</b>	<b>27/41 (66%)</b>	<b>70%</b>