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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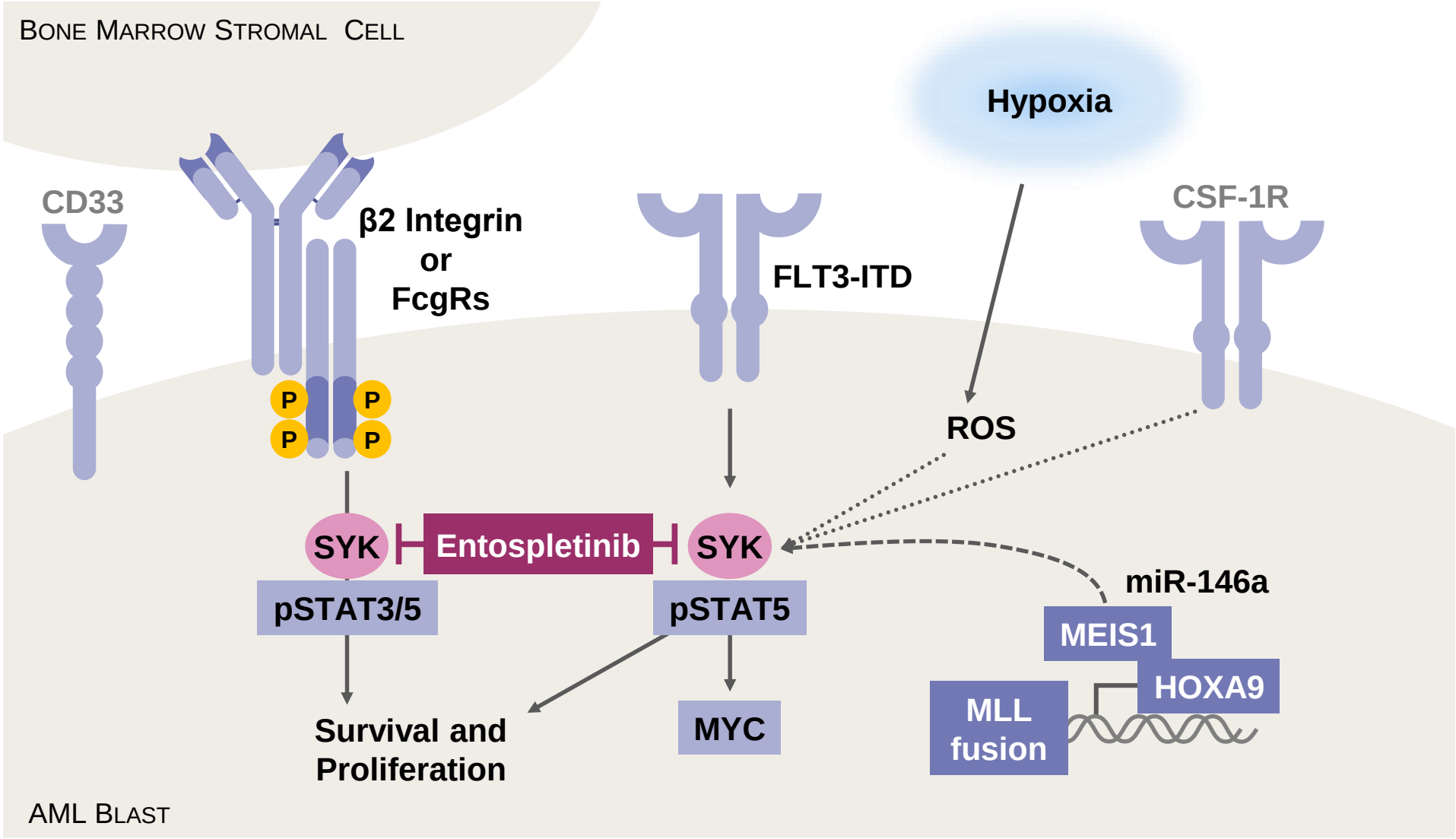
Background

- 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

Dombret H, Gardin C. Blood 2016;127:53-61.

Investigating SYK as Critical Signaling Node in AML



Role of SYK in AML

- 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[1]
- 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[2,3]

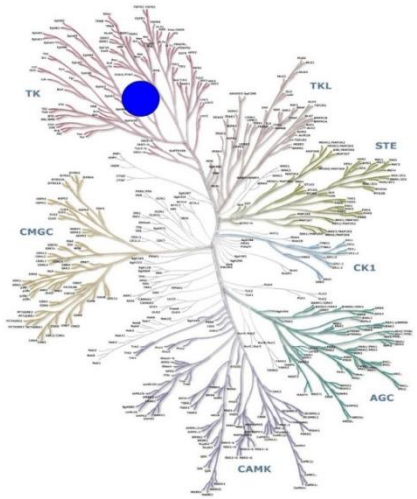
1. Boros et al. Oncotarget 2015;6:25575–87; 2. Puissant A. Cancer Cell 2014;25:226-42; 3. Mohr S. Cancer Cell 2017;31:549-62.e11.

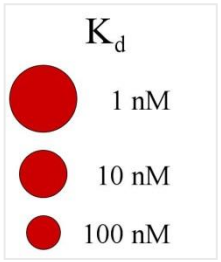
Entospletinib (ENTO): an Orally Bioavailable, Selective Inhibitor of SYK with Activity in Myeloid and B-lymphoid Malignancies

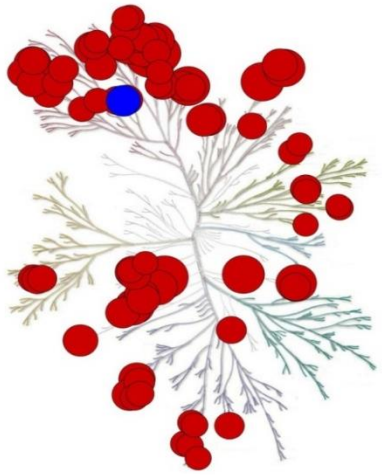
ENTO: Syk-selective

Syk K_d = 7.6 nM

No other kinases with K_d <100nM







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**

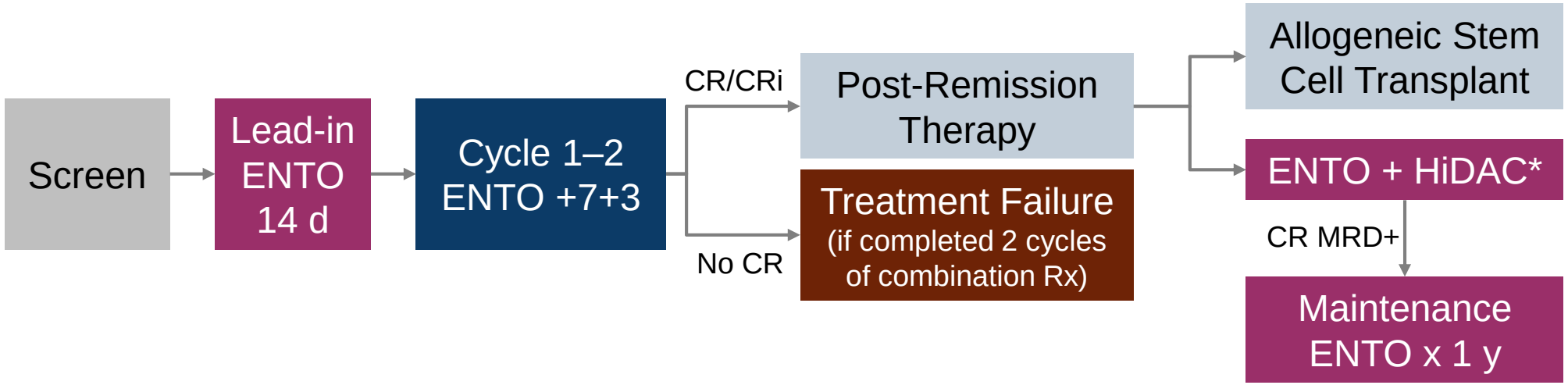
CYP, cytochrome p450; K_d, dissociation constant; PPI, proton pump inhibitor; UGT1A1, uridine diphosphate glucuronosyltransferase 1-1

Study Objectives

- **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^2 <60 y; 1 gm/m^2 ≥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

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

*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
KMT2A/MLL	10	90
NPM1+*	15	87
FLT3-ITD+	6	83

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

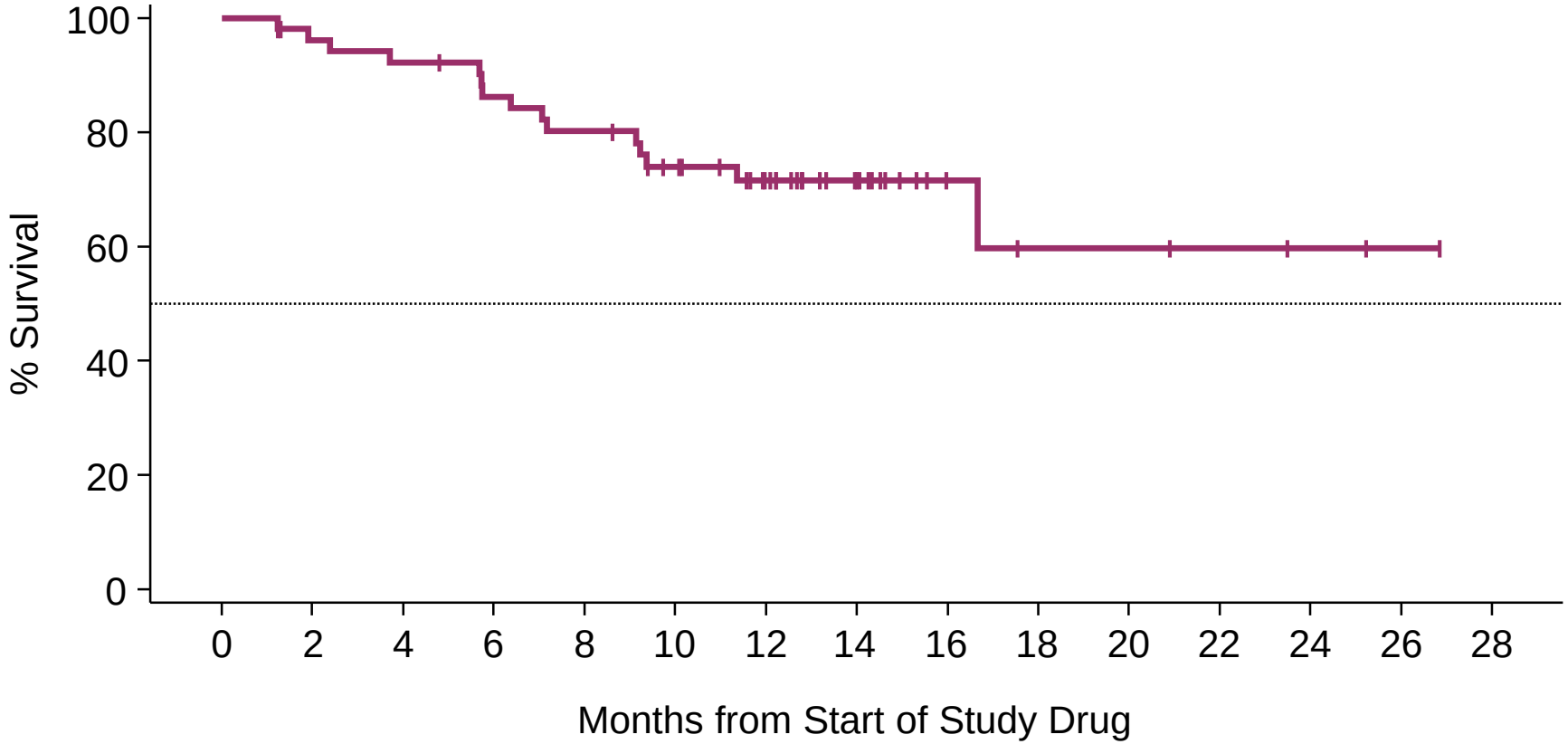
Results: Disposition After ENTO + 7+3

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

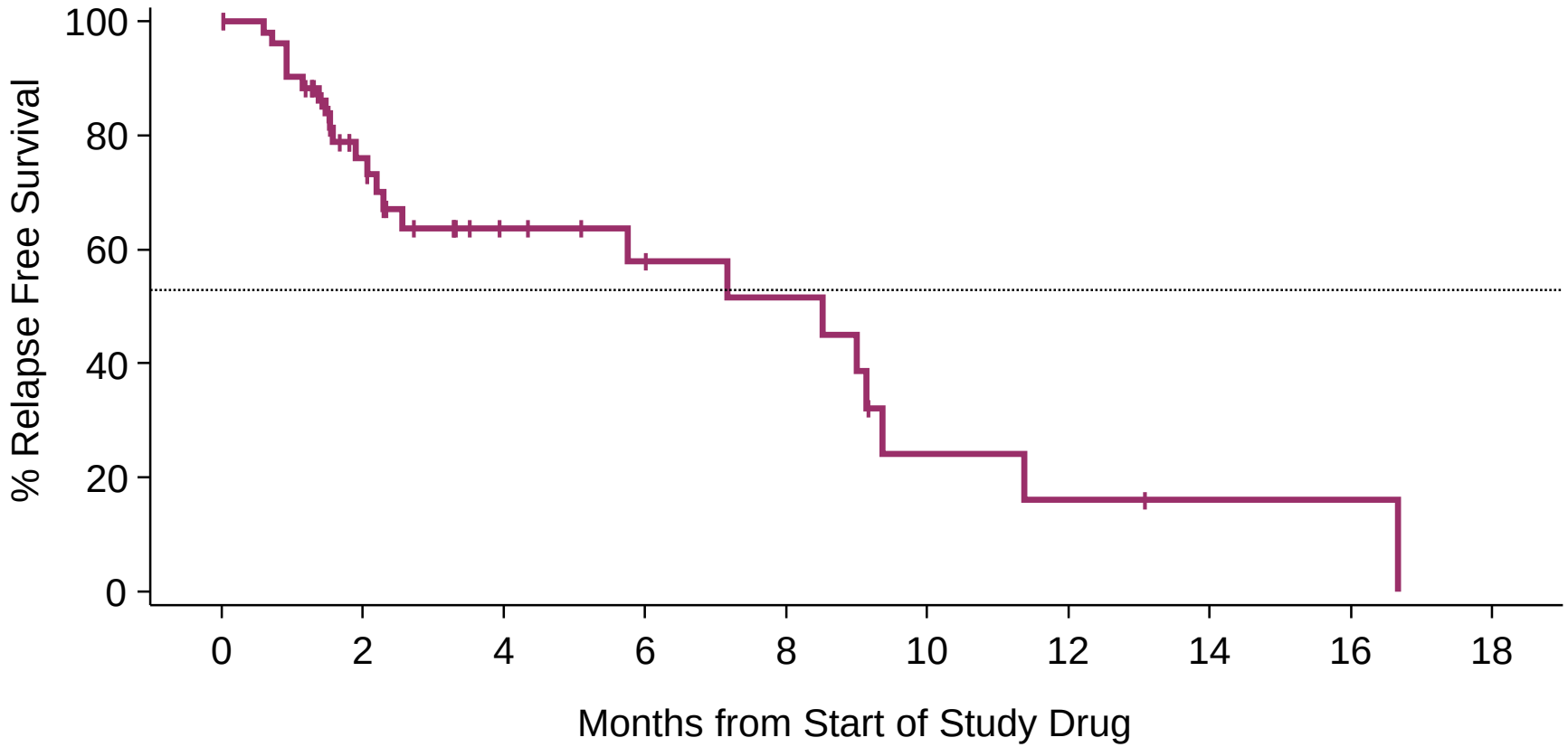
- No benefit as monotherapy: only 1 out of 53 patients responded to monotherapy
- 9 patients (17%) required hydroxyurea during lead-in
- 15 patients (28%) did not get full 14 days of lead-in ENTO either due to physician or patient preference

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 ≥3 Treatment-Emergent Hematologic Toxicity Adverse Events and Lab Abnormalities

Grade ≥ 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

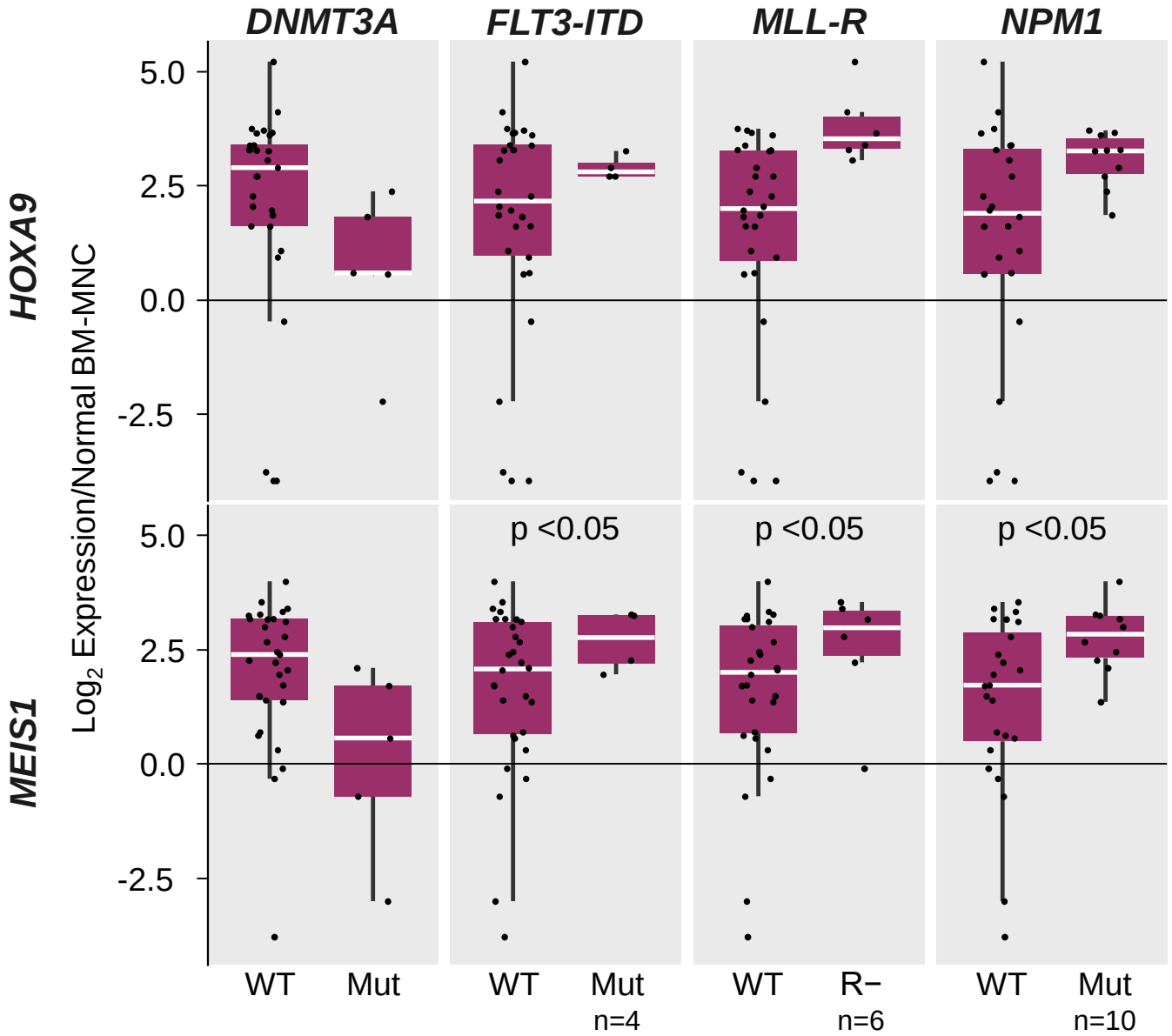
- **30-day induction mortality 0 %**

Safety: Grade ≥ 3 Treatment-Emergent Lab Abnormalities and Non-hematologic toxicity

Grade ≥ 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)

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

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.

Liu J EHA 2018 Poster presentation abstract 2412

Conclusions

- **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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BACK UP

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%
	Combined CR/total	**6/7 (86%)**	**12/19 (63%)**	**69%**
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%
	Combined CR/total	**4/5 (80%)**	**15/22 (68%)**	**70%**
Total		**10/12 (83%)**	**27/41 (66%)**	**70%**