Changing AML Outcomes via Personalized Medicine: Transforming Cancer Management with Genetic Insight

Co-Moderators:

- Rick Winneker, PhD, Senior Vice President, Research, Leukemia & Lymphoma Society
- Mike Rice, Senior Consultant, Defined Health

Panelists:

- Brian J. Druker, MD, Director, OHSU Knight Cancer Institute, JELD-WEN Chair of Leukemia Research, Oregon Health & Science University, Investigator, Howard Hughes Medical Institute
- Eric Hedrick, MD, Chief Medical Officer, Epizyme, Inc.
- Omar Abdel-Wahab, MD, Assistant Member, Memorial Sloan Kettering Cancer Center
- Nicholas J. Sarlis, MD, PhD, Vice President & Head, Medical Affairs, Incyte Corporation
- Scott Biller, PhD, Chief Scientific Officer, Agios Pharmaceuticals

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Recurrent Cytogenentic & Molecular Genetic Events in AML

	CYTOGENETICS	Molecular Genetics
FAVORABLE	t(8;21)(q22;q22)	Mutated *NPM1* without *FLT3*-ITD
	Inv16 or t(16;16)	Mutated *CEBPA*
INTERMEDIATE	t(9;11)	Mutated *FLT3* ITD + *NPM1* mutation
	tri(8)	
	Normal	
ADVERSE	Inv(3)	
	t(6;9)	
	t(v;11)	
	-5 or del(5q); -7; abn(17p); ≥3 abnormalities	

Despite the above a significant proportion of AML patients have none of the above somatic genetic abnormalities PLUS there is significant heterogeneity within each group

Discovery of novel mutations in myeloid malignancy patients

- Whole genome sequencing has identified novel recurrent disease alleles in AML
  - *IDH1* mutations (Mardis *et al. NEJM 2009)*
  - *DNMT3A* mutations (Ley *et al.* NEJM 2010)
- Candidate gene/array based studies have identified novel disease alleles in AML, MDS, MPN
  - *IDH2* (Ward *et al.* Cancer Cell 2010)
  - *TET2* (Delhommeau *et al.* NEJM 2009, Abdel-Wahab *et al*. Blood 2009)
  - *ASXL1* (Birnbaum *et al.* BJM 2009)
  - *PHF6* (Van Vlierberge *et al.* Leukemia 2011)
  - *EZH2* (Ernst *et al.* Nature Genetics 2011)

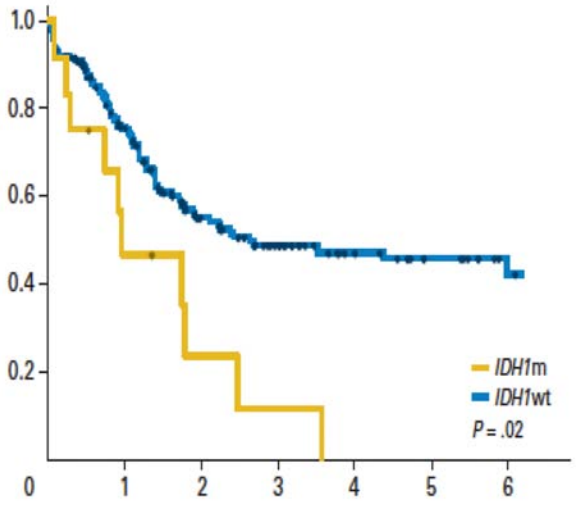
Questions regarding these mutations

1) Clinical Relevance: effect on prognosis, directing therapy (known therapies Or novel).

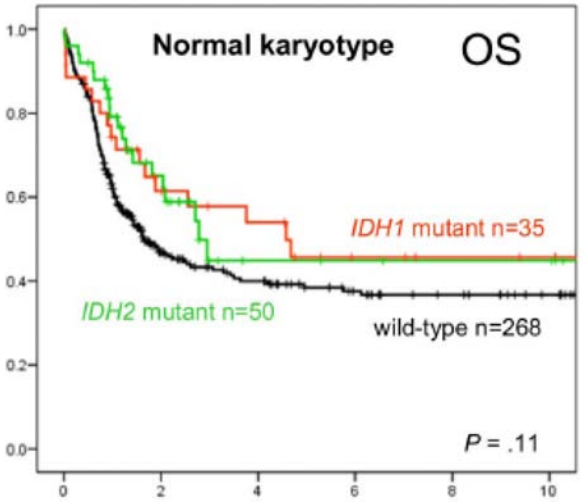
2) Biological Relevance to myeloid malignancy pathogenesis

Discrepant results on prognostic value of novel mutations in AML: *IDH1* mutations

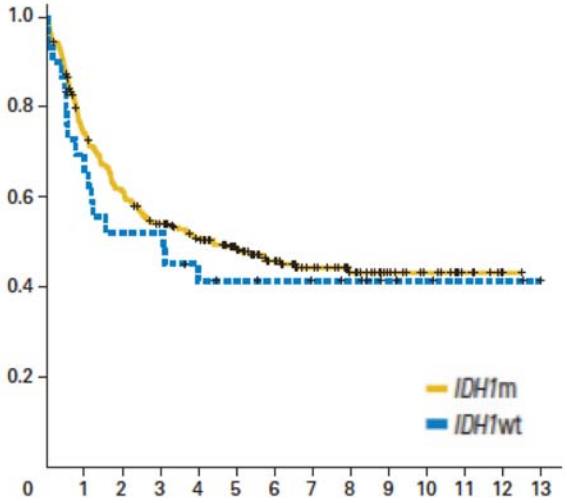
Boissel, et al. *JCO* 2010.



Abbas, et al. *Blood* 2010.



Wagner, et al. *JCO* 2010.



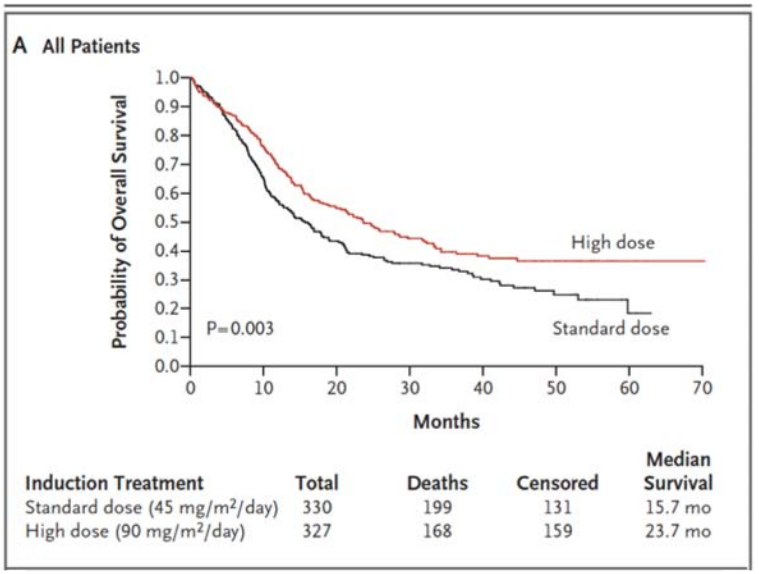
Patient population	Cytogenetically normal	Cytogenetically normal	Cytogenetically normal
# of patients	205	303	217
Effect on OS	Signif. adverse	No significant effect	No significant effect
Treatments rendered	2 different French acute leukemia trials	7 different HOVON AML protocols	2 different AML Suddeutsche Hamablostosse gruppe protocols

Mutational Profiling of ECOG 1900 Cohort

ORIGINAL ARTICLE

Anthracycline Dose Intensification in Acute Myeloid Leukemia

Hugo F. Fernandez, M.D., Zhuoxin Sun, Ph.D., Xiaopan Yao, Ph.D., Mark R. Litzow, M.D., Selina M. Luger, M.D., Elisabeth M. Paietta, Ph.D., Janis Racevskis, Ph.D., Gordon W. Dewald, Ph.D., Rhett P. Ketterling, M.D., John M. Bennett, M.D., Jacob M. Rowe, M.D., Hillard M. Lazarus, M.D., and Martin S. Tallman, M.D.



Induction Treatment	Total	Deaths	Censored	Median Survival
Standard dose (45 mg/m²/day)	330	199	131	15.7 mo
High dose (90 mg/m²/day)	327	168	159	23.7 mo

We performed mutational profiling of the 18 genes known to be mutated in AML in the E1900 phase III trial cohort

1) Identify genes with prognostic relevance
2) Determine if specific genetically defined subsets benefit from high dose induction chemotherapy
3) Identify novel complementation groups to inform us about AML pathogenesis
4) Integrate mutational data with epigenetic analysis of cohort

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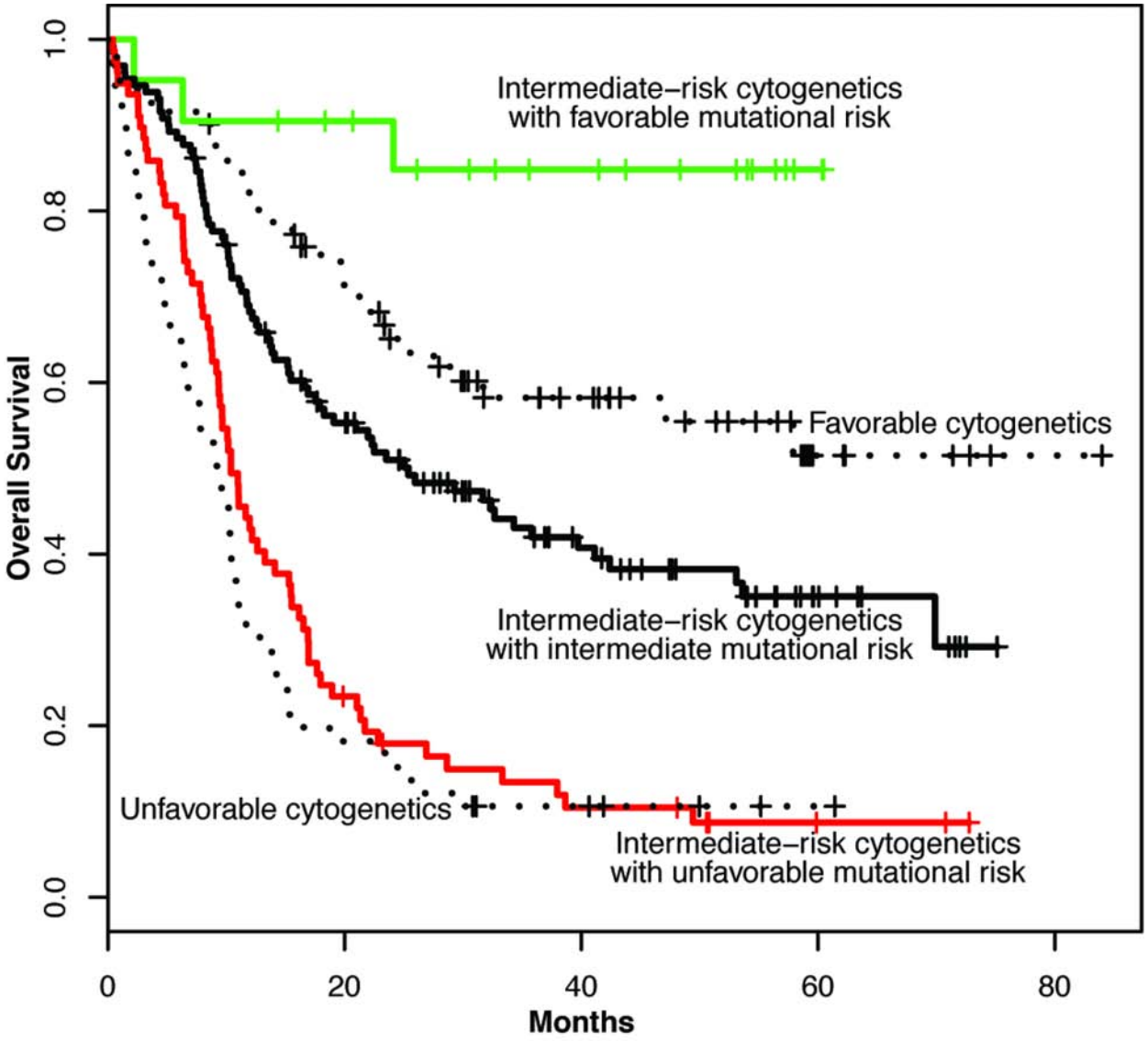
Recurrent somatic mutations in AML patients < 60

Gene	Frequency (%)
FLT3 (ITD, TKD)	37 (30, 7)
DNMT3A	24
NPM1	24
KIT	14
TET2	10
WT1	10
CEBPA	10
NRAS	10
IDH2	8
IDH1	6
ASXL1	4
KRAS	2.5
PHF6	2.5
RUNX1	5
PTEN	1.5
TP53	2
MLL	10

Revised AML Risk Stratification Based on Integrated Mutational Profiling



Green and red curves represent patients whose risk-classification changes using more extensive mutational profiling

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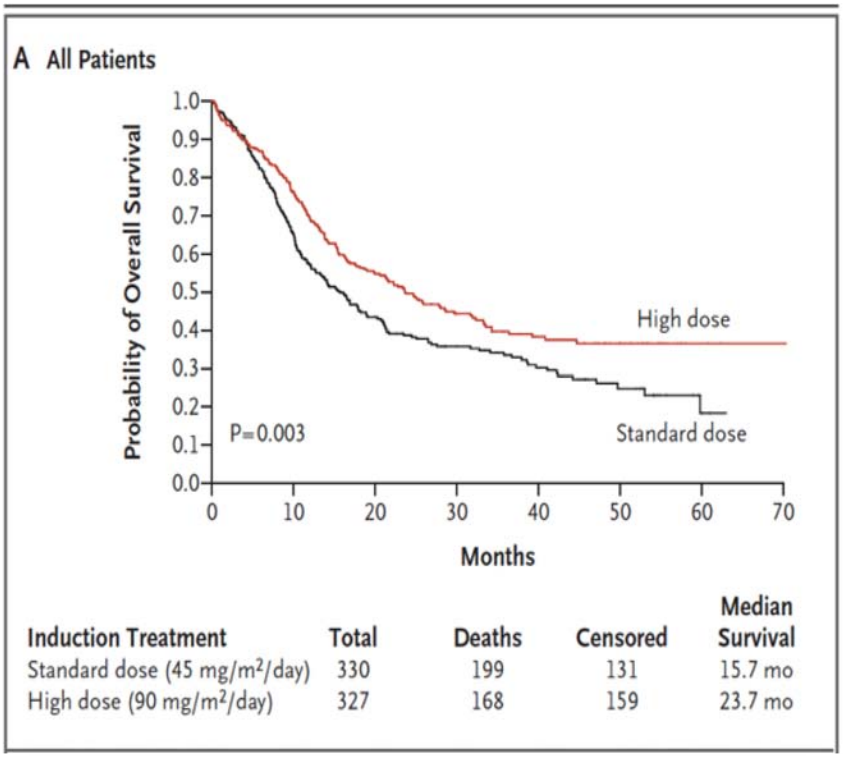
Revised AML Risk Stratification Based on Integrated Mutational Profiling

Cytogenetic Classification	Mutations		Overall Risk
inv(16)/t(16;16) t(8;21)	Any		Favorable
Normal Karyotype or Intermediate-Risk Cytogenetic Lesions	*FLT3*-ITD negative	*NPM1* and *IDH1/2* mutant	Favorable
	FLT3-ITD negative	*ASXL1*, *MLL*-PTD, *PHF6*, and *TET2* widltype	Intermediate
	FLT3-ITD negative or positive	*CEBPA* mutant	Intermediate
	FLT3-ITD positive	*MLL*-PTD, *TET2*, and *DNMT3A* widltype, and trisomy 8 negative	Intermediate
	FLT3-ITD negative	*TET2*, *MLL*-PTD, *ASXL1* or *PHF6* mutant	Unfavorable
	FLT3-ITD positive	*TET2*, *MLL*-PTD, *DNMT3A* mutant or trisomy 8	Unfavorable
Unfavorable			Unfavorable

Genetic predictors of response to high-dose induction chemotherapy?

ECOG E1900 COHORT



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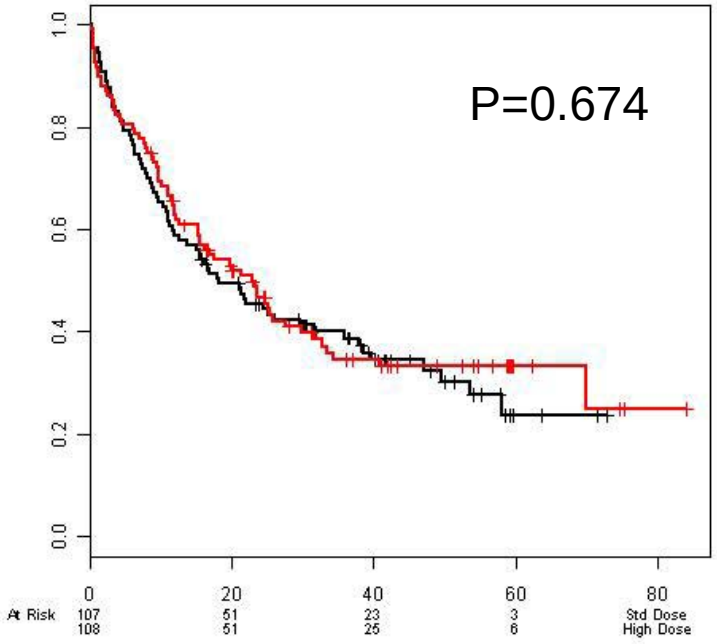
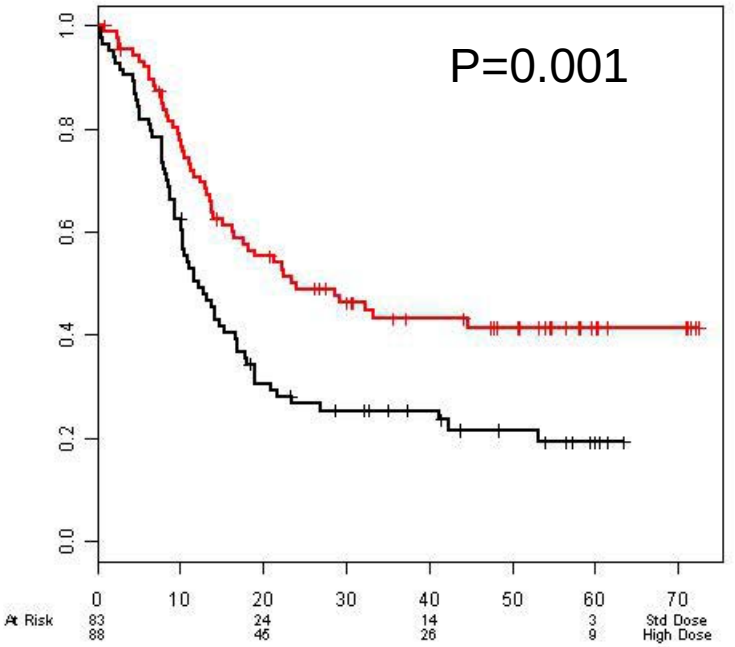
QUESTION: Do any genetic alterations confer Response or resistance to high-dose Induction chemotherapy?

High Dose Daunorubicin Improves Outcome in Patients with *DNMT3A* mutations, *MLL* Fusions, or *NPM1* mutations

***DNMT3A/MLL/NPM1*-WT pts**



***DNMT3A, MLL, NPM1* mutant**



Novel molecular targets in AML:

??mutant selective DNMT3A R882 Inhibition??

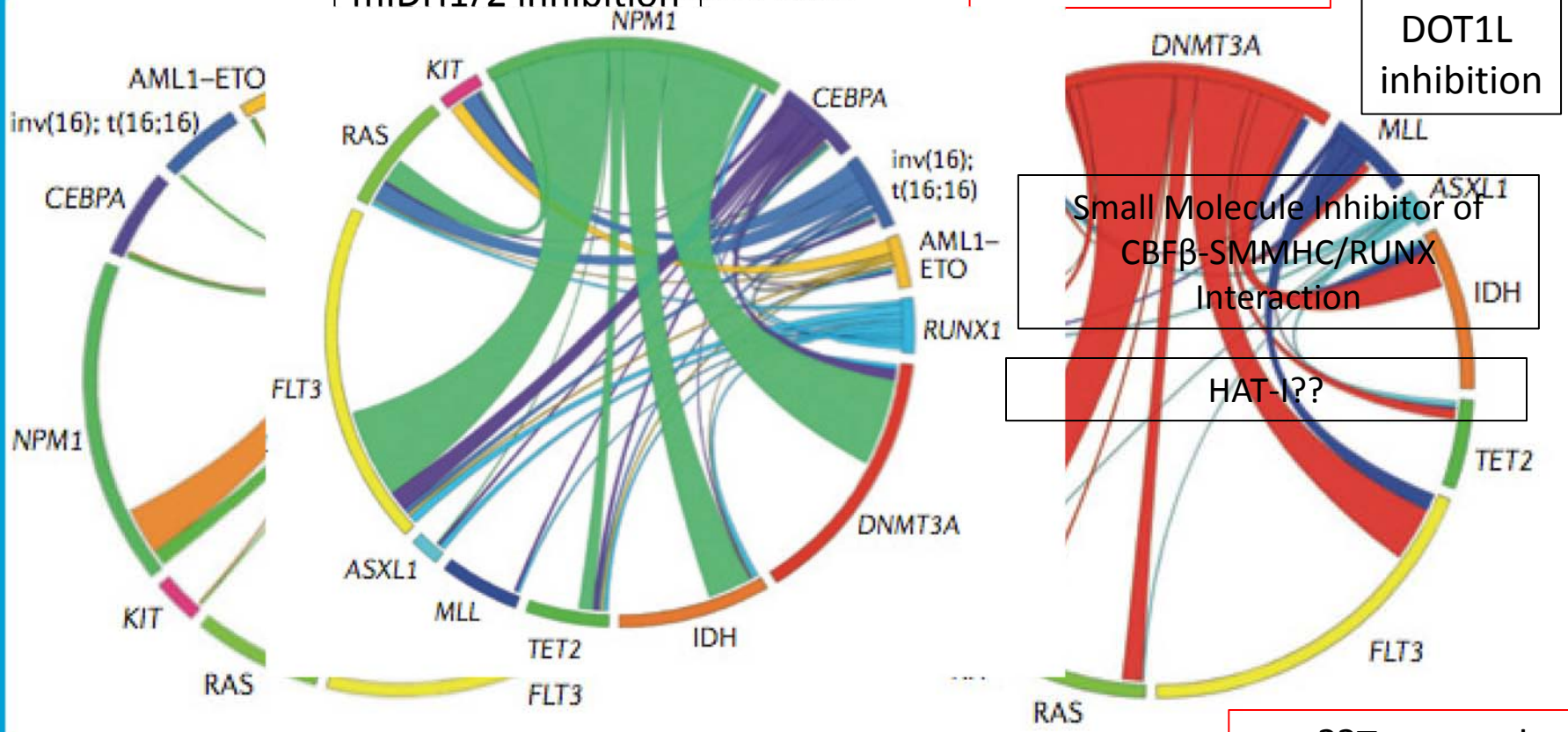
mIDH1/2 inhibition

FLT3 INHIBITORS

DOT1L inhibition

Small Molecule Inhibitor of CBFβ-SMMHC/RUNX Interaction

HAT-I??



??Truncated mASXL1 inhibition??

EZH2-I?
BROMODOMAIN-I?
LSD1-I?

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