Therapeutic and Prognostic Role of Epigenetic Abnormalities in MDS

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Sylvester Comprehensive Cancer Center
December 5, 2014

DISCLOSURE

I have no relevant financial relationships to disclose.

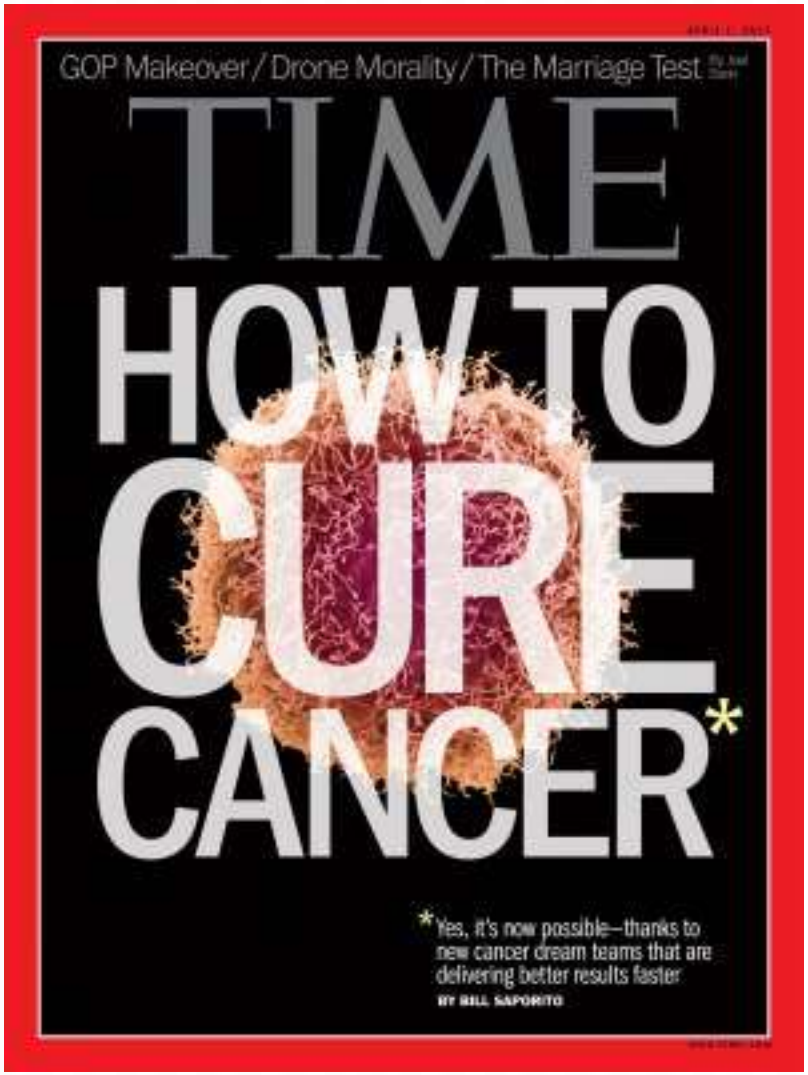
Outline

- **Epigenetics: study of heritable traits independent of underlying DNA sequence**; maintenance of cell identity, cellular response to the environment

- Epigenetic abnormalities in MDS: what is their role in disease initiation? Phenotype? Disease evolution? Response to therapy?

- Epigenetic therapies: What epigenetic-based therapies exist? Do they work? How do they work? Why do they stop working? Can they be rationally combined (and with what)?

- What is on the horizon? How will we make progress (mouse models, biomarkers, randomized clinical trials)?



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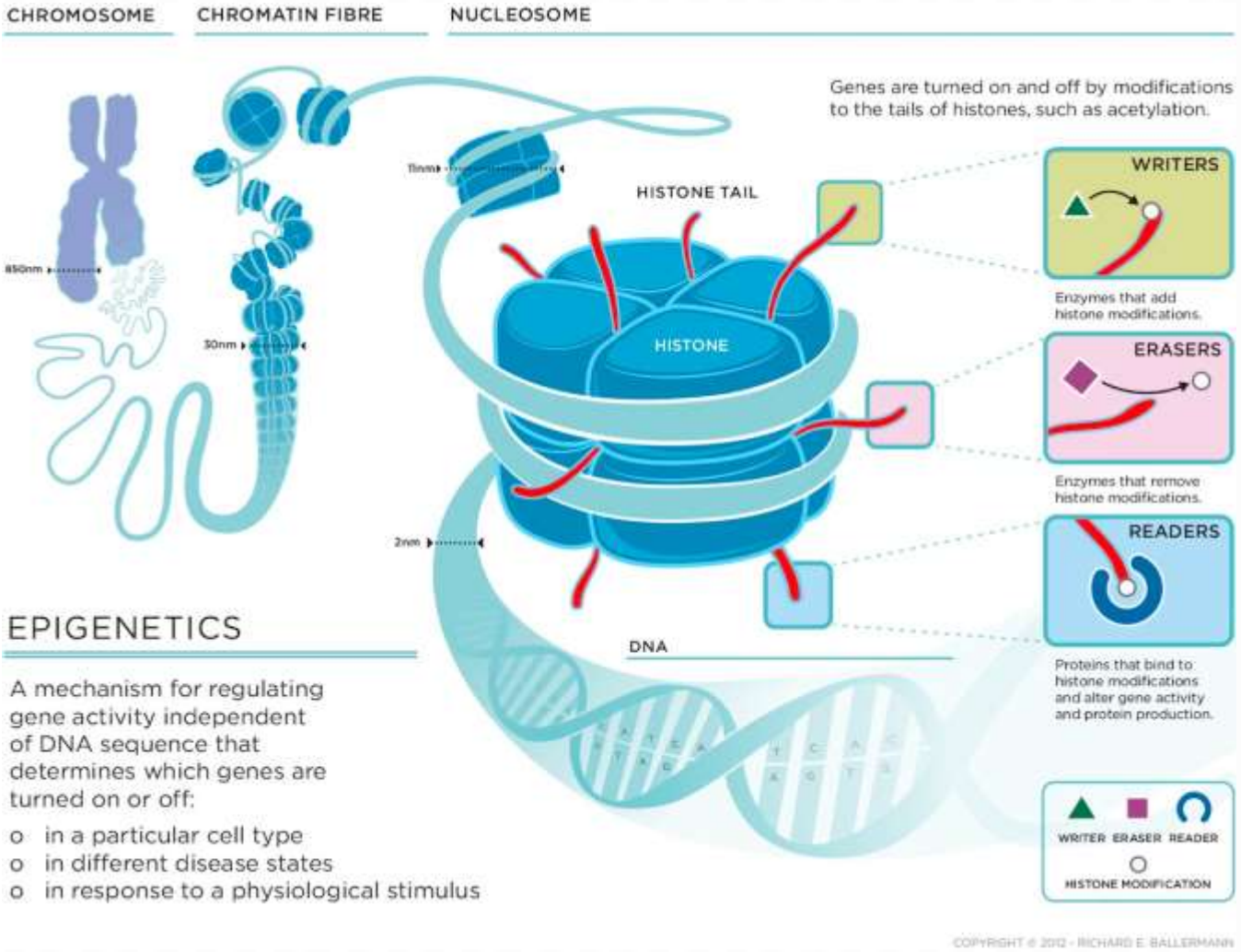
EPIGENETICS



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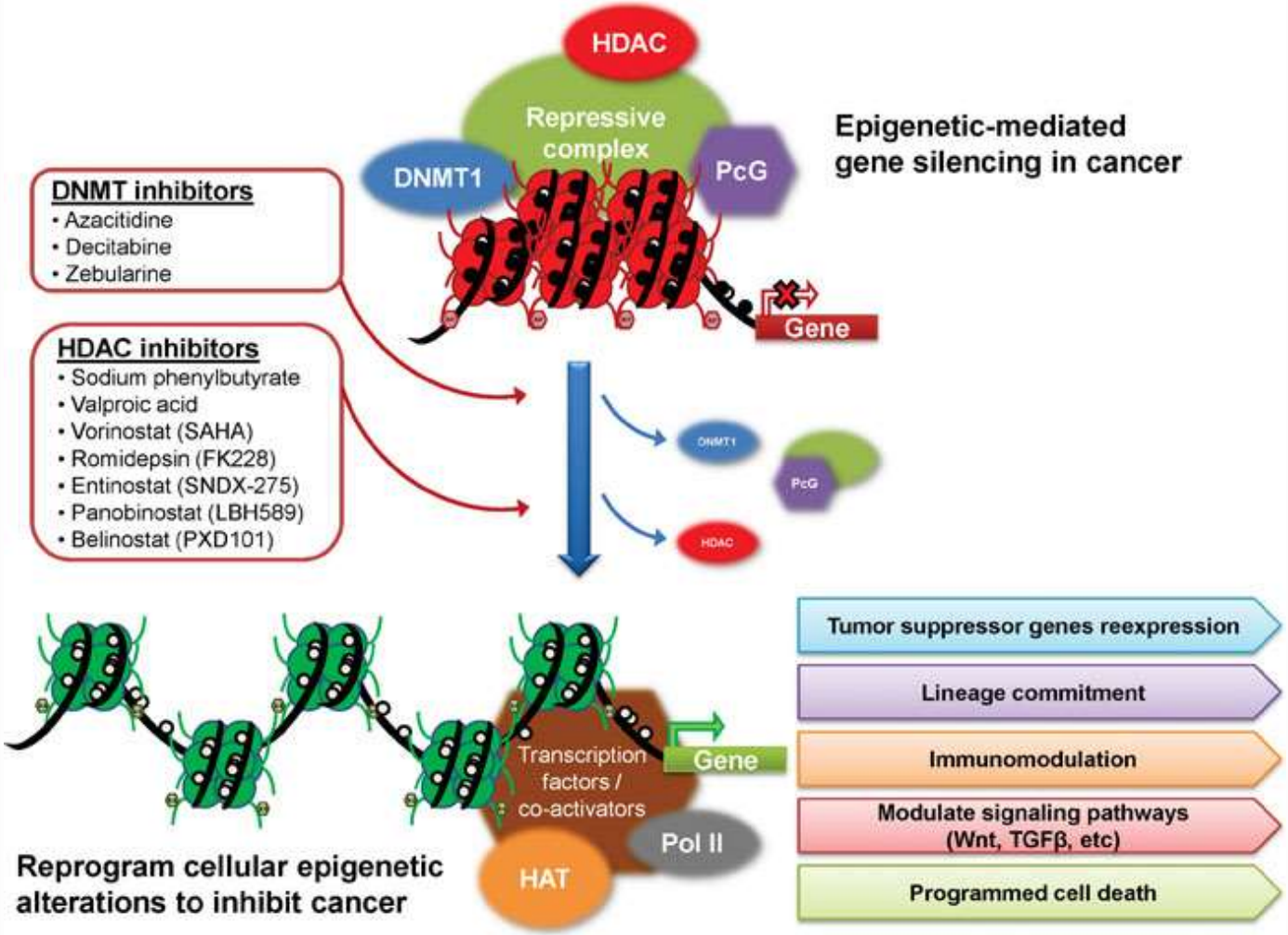
Taken from Resverlogix Corp.website



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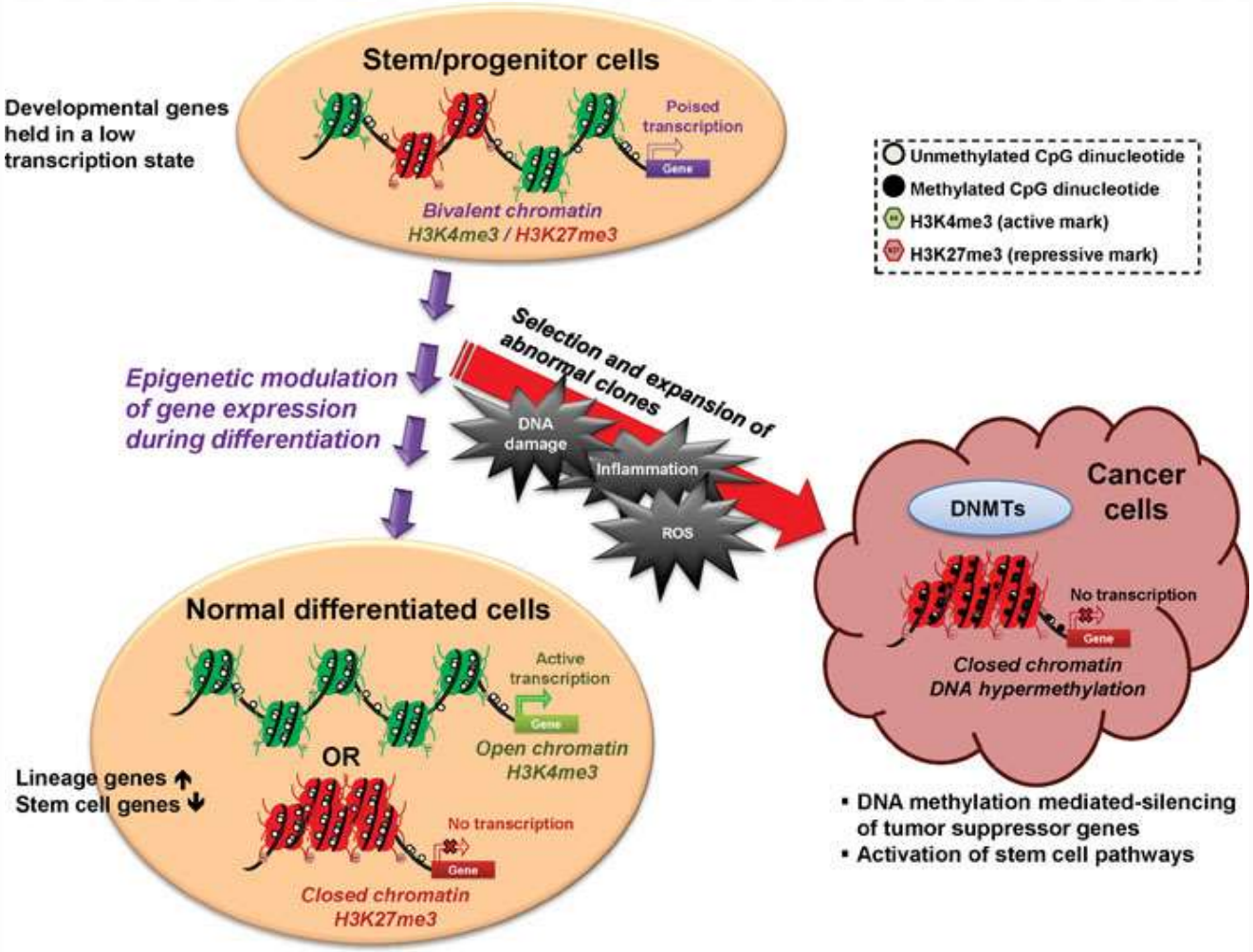
H-C Tsai and S. Baylin; Cell Res 2011



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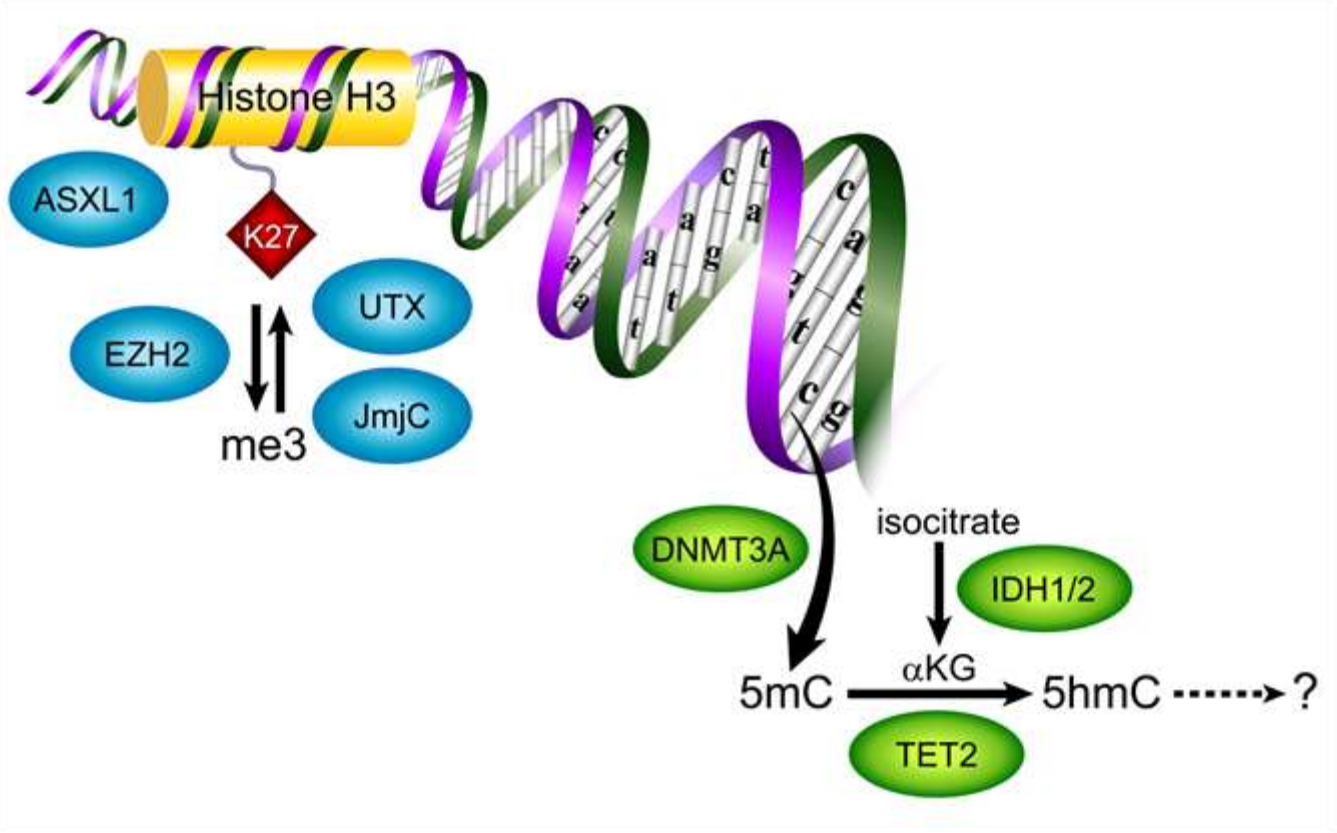
H-C Tsai and S. Baylin; Cell Res 2011

Epigenetic abnormalities in MDS

- Aberrant DNA methylation, DNA hydroxymethylation, histone modifications (gene promoters, enhancers, super-enhancers, gene bodies, intergenic regions)
- Are they distinct from other cancers? Distinct from AML?
- Mutations in epigenetic modifiers (e.g. DNMT3A, IDH1/2, TET2, ASXL1, EZH2,…)

Epigenetic abnormalities in MDS



Graubert & Walter, *ASH Ed. Program*, 2011

Acquisition of mutations in epigenetic regulators with age

ANALYSIS

nature medicine

Age-related mutations associated with clonal hematopoietic expansion and malignancies

Mingchao Xie[1,2,7], Charles Lu[1,7], Jiayin Wang[1,2,7], Michael D McLellan[1], Kimberly J Johnson[3], Michael C Wendl[1,4,5], Joshua F McMichael[1], Heather K Schmidt[1], Venkata Yellapantula[1,2], Christopher A Miller[1], Bradley A Ozenberger[1,2], John S Welch[2,6], Daniel C Link[2,6], Matthew J Walter[2,6], Elaine R Mardis[1,2,4,6], John F Dipersio[2,6], Feng Chen[2,6], Richard K Wilson[1,2,4,6], Timothy J Ley[1,2,4,6] & Li Ding[1,2,4,6]

M. Xie et al Nature Medicine 2014

Acquisition of mutations in epigenetic regulators with age

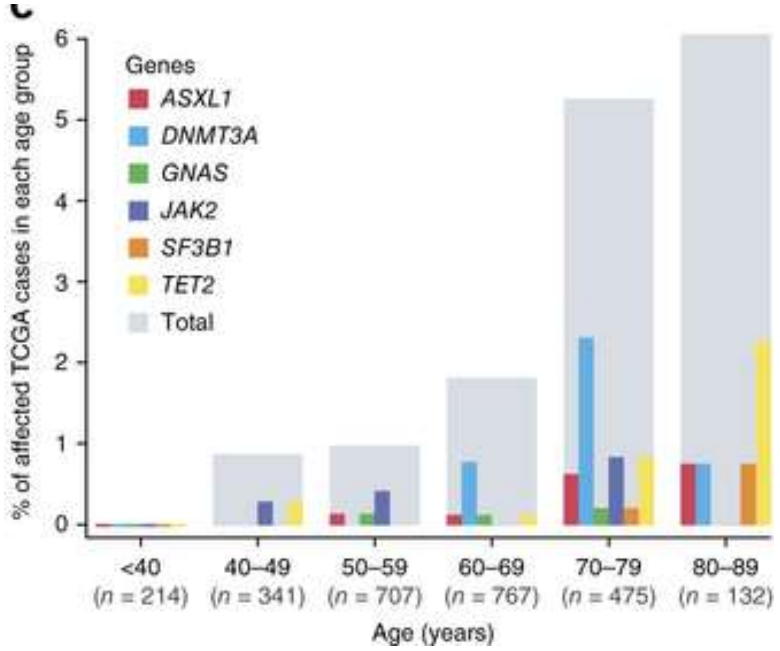
Table 1 Blood-specific mutations in nine recurrently mutated genes identified in TCGA cases

		Case					Case		
Gene	Mutation	Type	Age	VAF (%)	Gene	Mutation	Type	Age	VAF (%)
DNMT3A	p.R882C	GBM	81	15.79	*JAK2*	p.V617F	GBM	57	21.52
		STAD	60	18.29			GBM	72	73.39
		STAD	69	12.17			KIRC	59	28.57
	p.R882H	BRCA	62	21.43			LGG	45	15.87
		GBM	64	35.56			LUAD	72	27.62
		LUSC	76	31.91			LUAD	76	41.62
	e13+1	KIRC	79	15.94			UCEC	59	35.90
		LUAD	76	11.11			UCEC	74	42.92
	p.E469*	GBM	72	20.60	*ASXL1*	p.Q575*	LUAD	75	20
	p.F851fs	BRCA	64	34.88		p.Q733*	LUAD	72	14.29
	p.K577fs	HNSC	72	24.14		p.Q733fs	UCEC	81	27.27
	p.N516fs	LUSC	71	33.33		p.R548fs	LUAD	76	35.03
	p.S770*	STAD	75	16.03		p.Y591*	STAD	65	17.88
	p.W314*	UCEC	74	22.06		p.Y591fs	LUSC	56	29.70
	p.Y584fs	GBM	75	38	*TP53*	p.C275Y	OV	52	14.29
	e12-1	PRAD	60	35.79		p.Q136*	LUAD	Null	18
	e21-2	GBM	76	11.81		p.Q144*	STAD	62	15.96
	e22-1	UCEC	77	33.85		p.R273L	LUAD	70	34.62
TET2	p.F381fs	GBM	83	50	*GNAS*	p.R202H	GBM	76	14.44
	p.H863fs	GBM	64	11.67			HNSC	59	11.54
	p.K889*	OV	85	15.09			LUAD	69	21.43
	p.Q531*	KIRC	48	11.90	*PPM1D*	p.Q520*	BRCA	79	35.42
	p.Q644*	UCEC	89	16.78		p.S468*	UCEC	49	21.23
	p.Q764fs	GBM	75	33.01	*BCORL1*	p.G883E	LUAD	Null	16.67
	p.Q831fs	LUAD	75	26.42		p.S264*	PRAD	56	22.45
	p.Q888*	GBM	83	20.39	*SF3B1*	p.K700E	GBM	89	13.86
	p.R550*	LUAD	76	16.25			KIRC	77	43.04
	p.T229fs	GBM	72	19.05					

'e' signifies exon (for example, e12-1 represents a splice-site mutation 1 nt upstream of exon 12); asterisk indicates nonsense mutation and 'fs' stands for frameshift. VAF is defined as the proportion of reads supporting the variant allele. Eleven cancer types were investigated in this study: BRCA, GBM, HNSC, KIRC, LGG, LUAD, LUSC, OV, PRAD, STAD and UCEC.

M. Xie et al Nature Medicine 2014

Age-related mutations associated with clonal hematopoietic expansion and malignanices



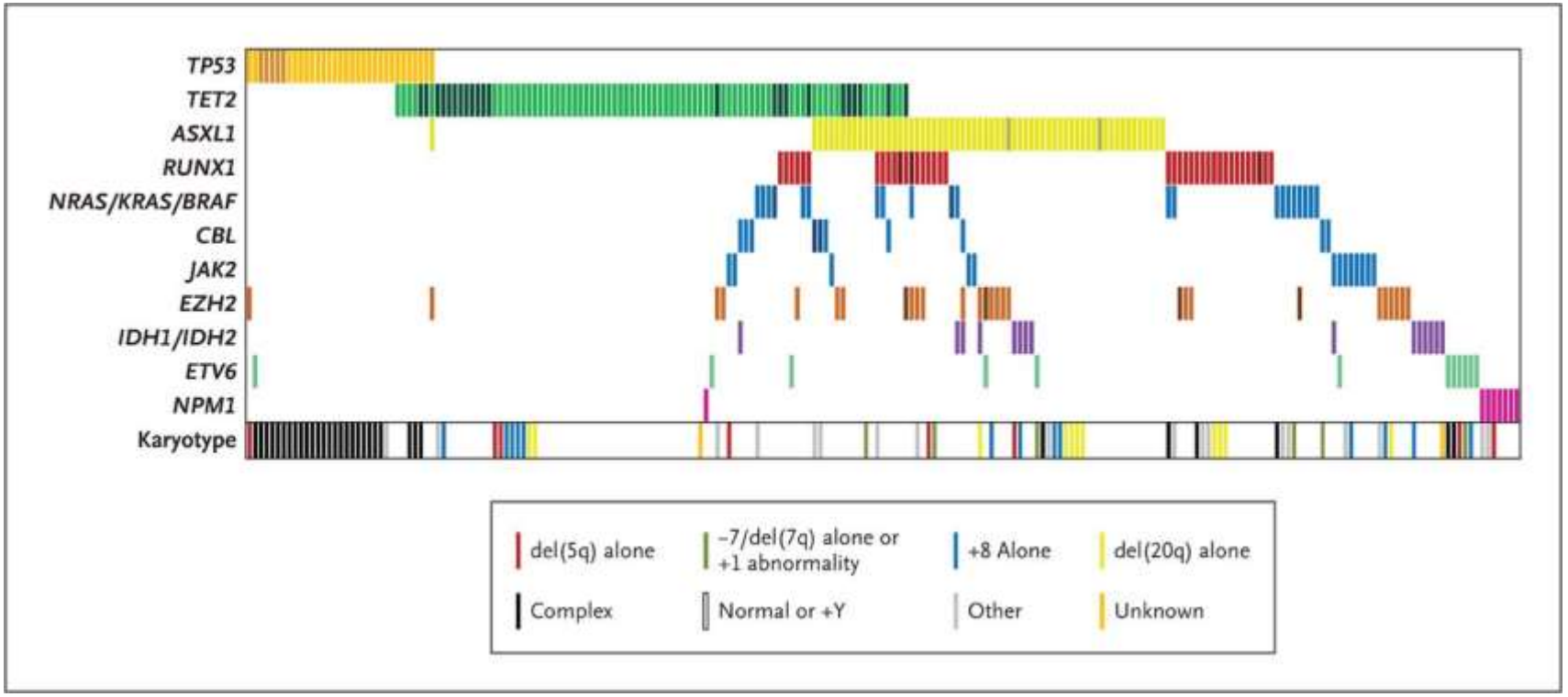
M. Xie et al Nature Medicine 2014

Impact of mutations on prognosis: independent of clinical variables? response to therapies?

Epigenetic mutations
Patterns of epigenetic modifications (aren't they linked?)

Clinical Effect of Point Mutations in Myelodysplastic Syndromes

Rafael Bejar, M.D., Ph.D., Kristen Stevenson, M.S., Omar Abdel-Wahab, M.D., Naomi Galili, Ph.D., Björn Nilsson, M.D., Ph.D., Guillermo Garcia-Manero, M.D., Hagop Kantarjian, M.D., Azra Raza, M.D., Ross L. Levine, M.D., Donna Neuberg, Sc.D., and Benjamin L. Ebert, M.D., Ph.D.



Bejar R et al. N Engl J Med 2011;364:2496-2506

Hazard Ratios for Death in a Multivariable Model

Table 2. Hazard Ratios for Death in a Multivariable Model.*

Risk Factor	Hazard Ratio (95% CI)	P Value
Age ≥55 yr vs. <55 yr	1.81 (1.20–2.73)	0.004
IPSS risk group		
Intermediate-1 vs. low	2.29 (1.69–3.11)	<0.001
Intermediate-2 vs. low	3.45 (2.42–4.91)	<0.001
High vs. low	5.85 (3.63–9.40)	<0.001
Mutational status		
TP53 mutation present vs. absent	2.48 (1.60–3.84)	<0.001
EZH2 mutation present vs. absent	2.13 (1.36–3.33)	<0.001
ETV6 mutation present vs. absent	2.04 (1.08–3.86)	0.03
RUNX1 mutation present vs. absent	1.47 (1.01–2.15)	0.047
ASXL1 mutation present vs. absent	1.38 (1.00–1.89)	0.049

* The model was generated from a stepwise Cox regression model that included the International Prognostic Scoring System (IPSS) risk category (based on the percentage of blasts in bone marrow, the karyotype, and the number of cytopenias [see Table 2 in the Supplementary Appendix]), age, sex, and mutation status for genes that were mutated in 1% or more of the 428 samples for which the IPSS classification was recalculated. Age was included in the analysis as a categorical variable on the basis of a best-split algorithm showing a significant difference in overall survival between patients less than 55 years of age and those 55 years of age or older (see Table 8 in the Supplementary Appendix).

Bejar R et al. N Engl J Med 2011;364:2496-2506

EZH2: POOR PROGNOSIS IN LR-PSS MDS PATIENTS

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Validation of a Prognostic Model and the Impact of Mutations in Patients With Lower-Risk Myelodysplastic Syndromes

Rafael Bejar, Kristen E. Stevenson, Bennett A. Caughey, Omar Abdel-Wahab, David P. Steensma, Naomi Galili, Azra Raza, Hagop Kantarjian, Ross L. Levine, Donna Neuberg, Guillermo Garcia-Manero, and Benjamin L. Ebert

Rafael Bejar, Bennett A. Caughey, and Benjamin L. Ebert, Brigham and Women's Hospital, Harvard Medical School; Rafael Bejar, Kristen E. Stevenson, David P. Steensma, Donna Neuberg, and Benjamin L. Ebert, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Omar Abdel-Wahab and Ross L. Levine, Memorial Sloan-Kettering Cancer Center; Naomi Galili and Azra Raza, New York Presbyterian Hospital-Columbia University Medical Center, New York, NY; and Hagop Kantarjian and Guillermo Garcia-Manero, MD Anderson Cancer Center, University of Texas, Houston, TX.

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Benjamin L. Ebert, MD, PhD, Brigham and

A B S T R A C T

Purpose
A subset of patients with myelodysplastic syndromes (MDS) who are predicted to have lower-risk disease as defined by the International Prognostic Scoring System (IPSS) demonstrate more aggressive disease and shorter overall survival than expected. The identification of patients with greater-than-predicted prognostic risk could influence the selection of therapy and improve the care of patients with lower-risk MDS.

Patients and Methods
We performed an independent validation of the MD Anderson Lower-Risk Prognostic Scoring System (LR-PSS) in a cohort of 288 patients with low- or intermediate-1 IPSS risk MDS and examined bone marrow samples from these patients for mutations in 22 genes, including *SF3B1*, *SRSF2*, *U2AF1*, and *DNMT3A*.

Results
The LR-PSS successfully stratified patients with lower-risk MDS into three risk categories with significant differences in overall survival (20% in category 1 with median of 5.19 years [95% CI, 3.01 to 10.34 years], 56% in category 2 with median of 2.65 years [95% CI, 2.18 to 3.30 years], and 25% in category 3 with median of 1.11 years [95% CI, 0.82 to 1.51 years]), thus validating this prognostic model. Mutations were identified in 71% of all samples, and mutations associated with a poor prognosis were enriched in the highest-risk LR-PSS category. Mutations of *EZH2*, *RUNX1*, *TP53*, and *ASXL1* were associated with shorter overall survival independent of the LR-PSS. Only *EZH2* mutations retained prognostic significance in a multivariable model that included LR-PSS and other mutations (hazard ratio, 2.90; 95% CI, 1.85 to 4.52).

Conclusion
Combining the LR-PSS and *EZH2* mutation status identifies 29% of patients with lower-risk MDS with a worse-than-expected prognosis. These patients may benefit from earlier initiation of disease-modifying therapy.

J Clin Oncol 30. © 2012 by American Society of Clinical Oncology

EZH2, TP53, RUNX1, ASXL1

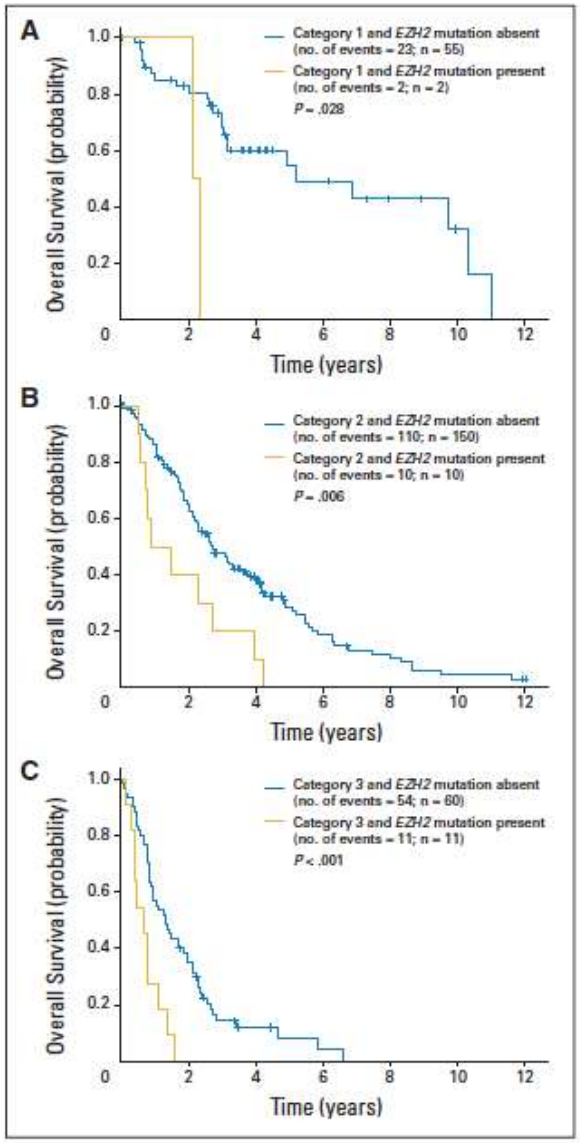

Fig 3. Kaplan-Meier overall survival curves for patients with myelodysplastic syndromes in each Lower-Risk Prognostic Scoring System (LR-PSS) risk category stratified by *EZH2* mutation status. (A) Category 1 patients; (B) category 2 patients; (C) category 3 patients.

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Effect of EZH2 mutations on survival in MDS

LETTERS

nature genetics

Inactivating mutations of the histone methyltransferase gene *EZH2* in myeloid disorders

Thomas Ernst[1–3,11], Andrew J Chase[1,2,11], Joannah Score[1,2], Claire E Hidalgo-Curtis[1,2], Catherine Bryant[1,2], Amy V Jones[1,2], Katherine Waghorn[1,2], Katerina Zoi[4], Fiona M Ross[1,2], Andreas Reiter[5], Andreas Hochhaus[3], Hans G Drexler[6], Andrew Duncombe[7], Francisco Cervantes[8], David Oscier[9], Jacqueline Boultwood[10], Francis H Grand[1,2] & Nicholas C P Cross[1,2]

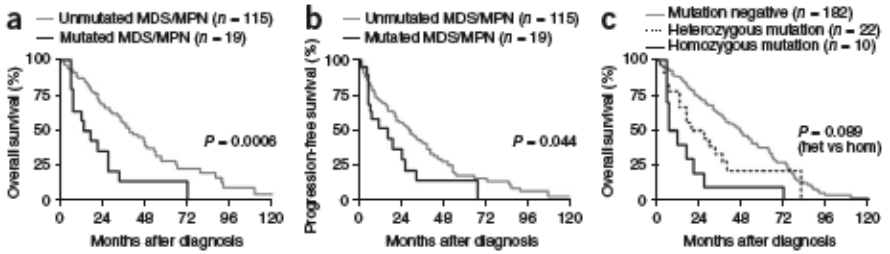


Figure 2 Survival and expression analysis. (a,b) Kaplan-Meier analysis showing overall survival (a) and progression-free survival (b) of the 134 individuals with MDS/MPN for whom follow-up data was available (CMML, $n = 77$; aCML, $n = 44$; MDS/MPN-U, $n = 13$). None of the individuals with *EZH2* mutations in this analysis had cytogenetically visible abnormalities of chromosome 7. (c) The survival of individuals with homozygous mutations was shorter than those with heterozygous *EZH2* mutations, although the difference was not significant ($P = 0.089$).

ASXL1 PROGNOSTIC IMPORTANCE

VOLUME 29 · NUMBER 18 · JUNE 20 2011

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Prognostic Significance of *ASXL1* Mutations in Patients With Myelodysplastic Syndromes

Table 3. Univariate and Multivariate Analyses for OS in Patients With MDS and With Mutated or Unmutated *ASXL1*

	OS					
	Univariate Analysis			Multivariate Analysis		
Variable	HR	95% CI	*P*	HR	95% CI	*P*
ASXL1 mutation status: mutated *v* unmutated	2.06	1.21 to 3.50	.008	1.85	1.03 to 3.34	.04
IPSS-based karyotype: high *v* intermediate *v* favorable risk	1.84	1.40 to 2.43	< .001	1.83	1.36 to 2.46	< .001
Transfusion dependence: dependent *v* independent	3.72	1.70 to 8.14	.001	3.19	1.45 to 7.06	.004
IDH1 mutation status: mutated *v* unmutated	3.76	1.71 to 8.24	.001	3.64	1.62 to 8.16	.002

NOTE. Number of patients with mutated gene = 24; with unmutated gene, 130; only frameshift mutations considered. Hazard ratios greater than 1 indicate an increased risk of an event for the first category listed.
Abbreviations: OS, overall survival; MDS, myelodysplastic syndrome; HR, hazard ratio; IPSS, International Prognostic Scoring System.

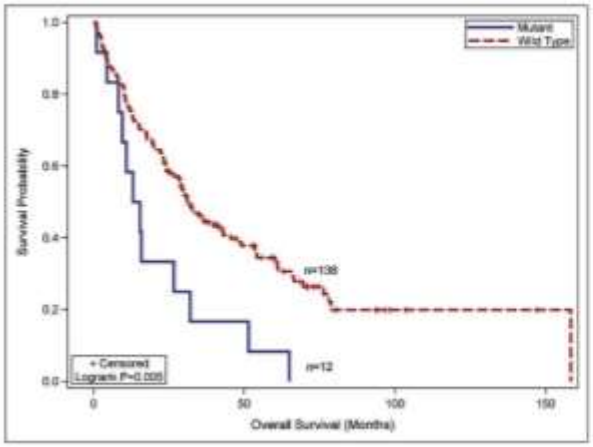
Table 4. Univariate and Multivariate Analyses for Time to AML Transformation in Patients With MDS and With Mutated or Unmutated *ASXL1*

	Time to AML Transformation					
	Univariate Analysis			Multivariate Analysis		
Variable	HR	95% CI	*P*	HR	95% CI	*P*
ASXL1 mutation status: mutated *v* unmutated	2.35	1.17 to 4.74	.017	2.39	1.12 to 5.09	.024
IPSS-based karyotype: high *v* intermediate *v* favorable risk	1.60	1.08 to 2.36	.018	1.50	0.98 to 2.28	.063
Transfusion dependence: dependent *v* independent	6.63	1.60 to 27.54	.009	6.12	1.46 to 25.64	.013
IDH1 mutation status: mutated *v* unmutated	3.40	1.21 to 9.61	.021	2.94	1.03 to 8.41	.044

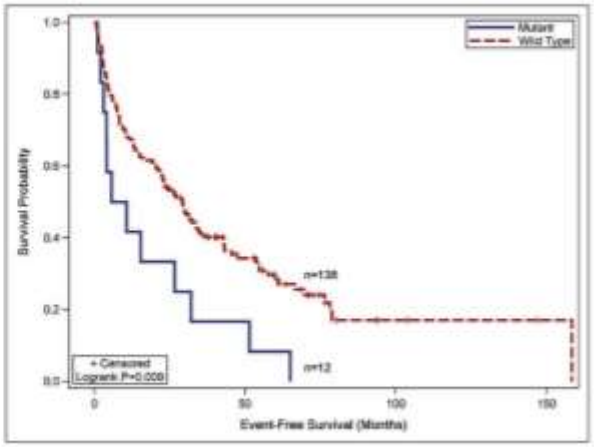
NOTE. Number of patients with mutated gene = 24; with unmutated gene, 124; only frameshift mutations considered. Hazard ratios greater than 1 indicate an increased risk of an event for the first category listed.
Abbreviations: AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; HR, hazard ratio; IPSS, International Prognostic Scoring System.

Effect of DNMT3A mutations on outcome in MDS (N=150 patients)

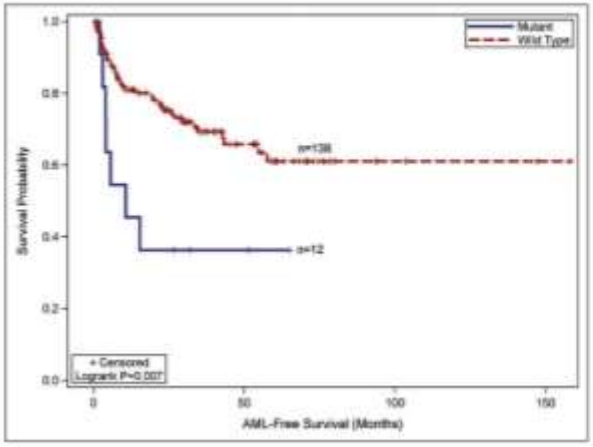
A.



B.



C.



M. Walter et al Leukemia 25: 1153; 2011

TET2 mutations predict response to hypomethylating agents in myelodysplastic syndrome patients

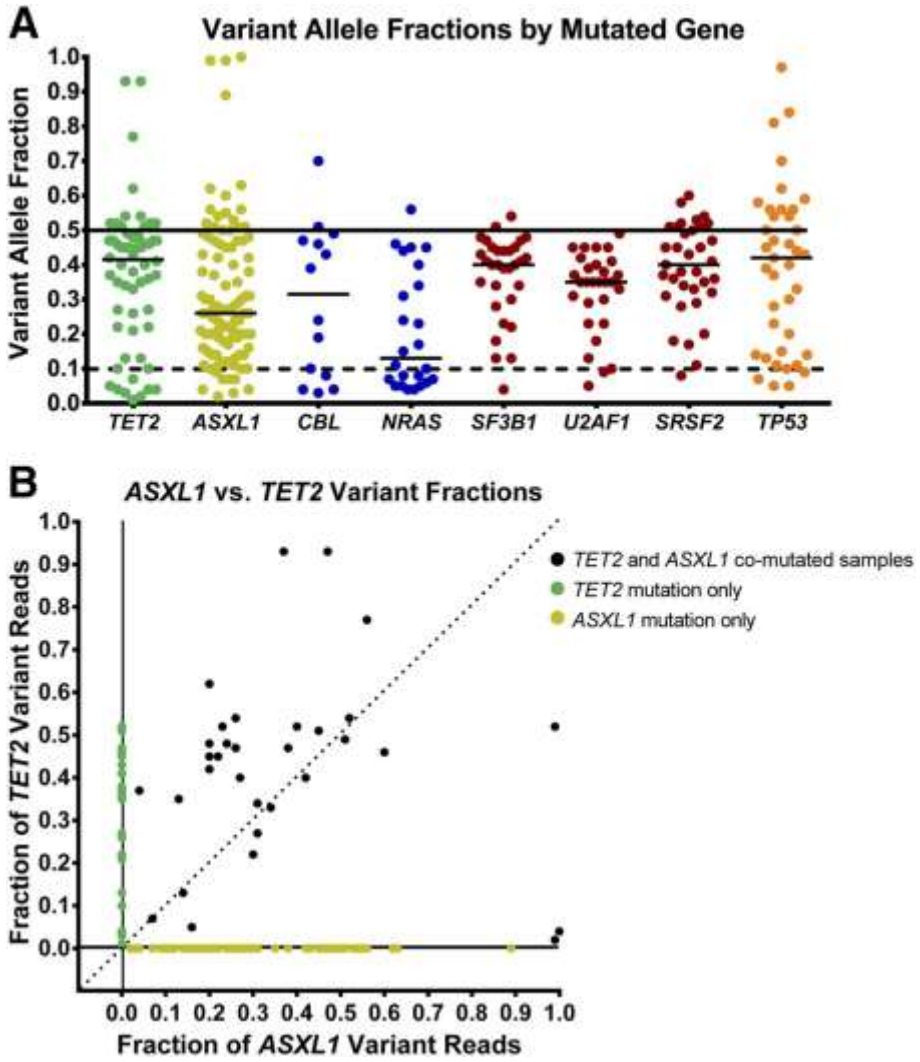
Rafael Bejar,[1] Allegra Lord,[2] Kristen Stevenson,[3] Michal Bar-Natan,[4] Albert Pérez-Ladaga,[1] Jacques Zaneveld,[5] Hui Wang,[5] Bennett Caughey,[1] Petar Stojanov,[6] Gad Getz,[6] Guillermo Garcia-Manero,[7] Hagop Kantarjian,[7] Rui Chen,[5] Richard M. Stone,[4] Donna Neuberg,[3] David P. Steensma,[4] and Benjamin L. Ebert[2,6]

[1]Division of Hematology and Oncology, University of California San Diego Moores Cancer Center, La Jolla, CA; [2]Division of Hematology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [3]Department of Biostatistics and Computational Biology and [4]Department of Medical Oncology, Division of Hematological Malignancies, Dana-Farber Cancer Institute, Boston, MA; [5]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX; [6]Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge, MA; and [7]Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX

Key Points

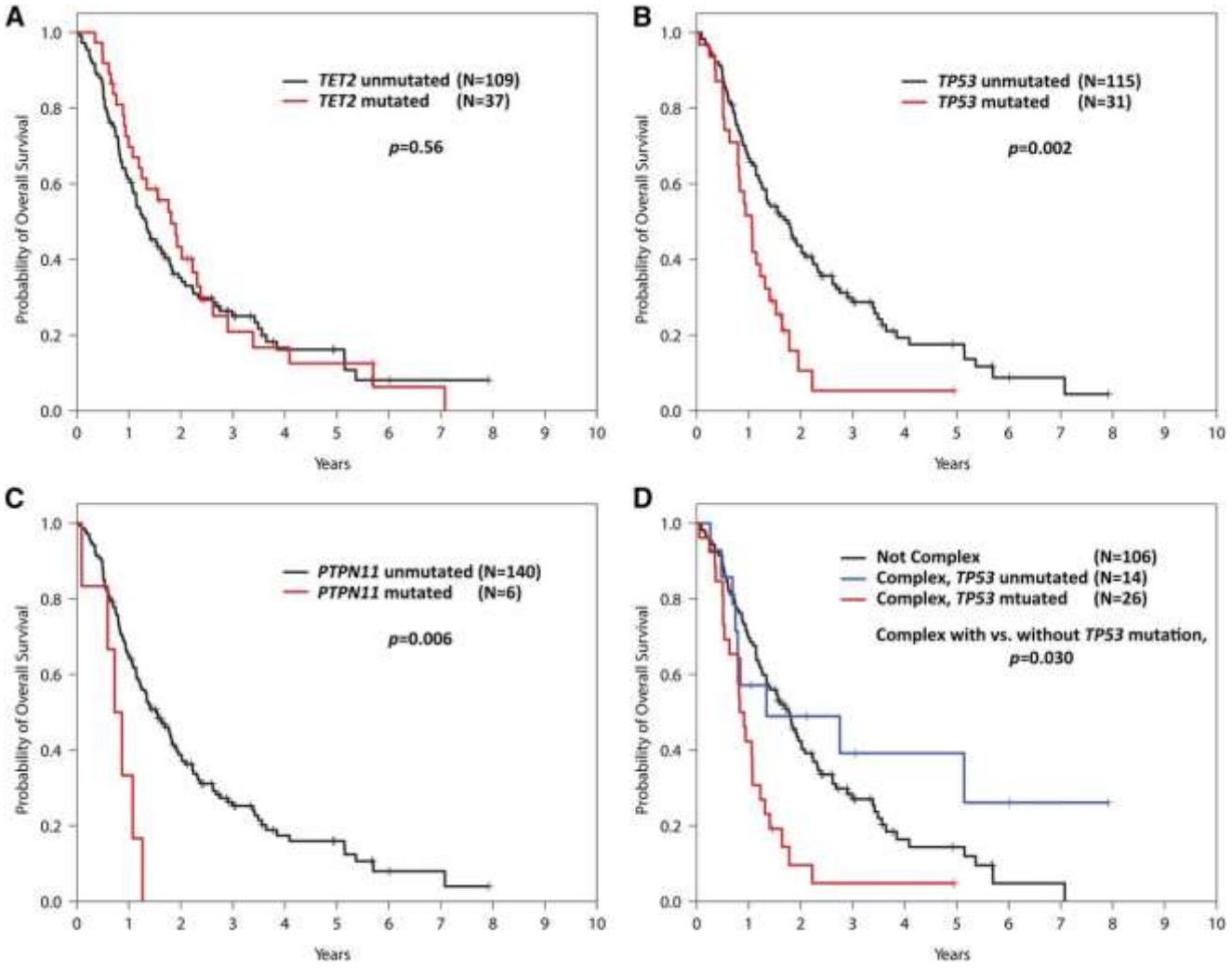
- Higher abundance *TET2* mutations are associated with increased response to hypomethylating agents, particularly when *ASXL1* is not mutated.
- *TP53* and *PTPN11* mutations are associated with shorter overall survival after hypomethylating agent treatment, but do not predict response.

Variant allele frequencies help order the sequence of mutations



Bejar R et al. Blood 2014;124:2705-2712

Overall survival data (146/213 patients)



Bejar R et al. Blood 2014;124:2705-2712

TET2 PROGNOSTIC IMPORTANCE IN HIGH RISK MDS

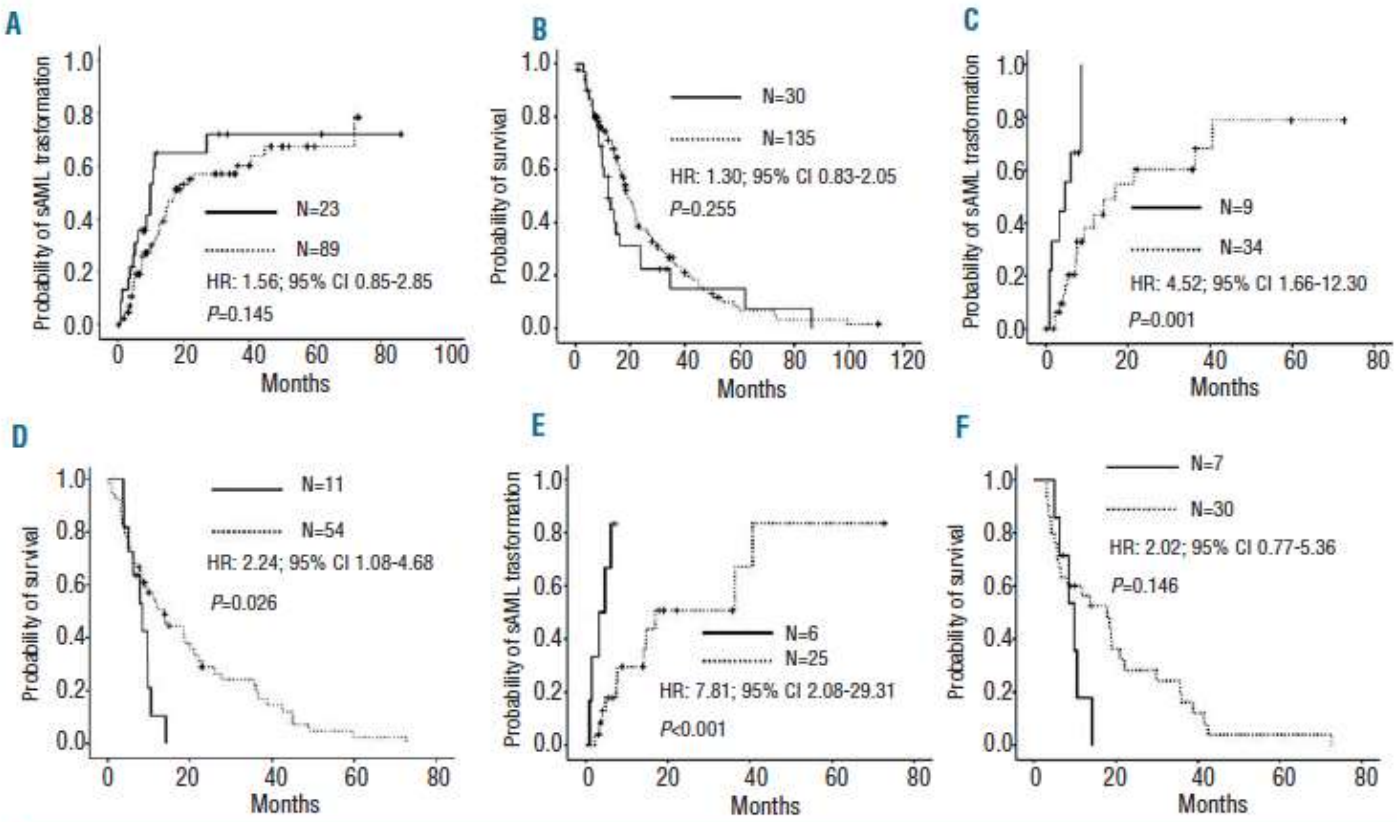


Figure 2. Kaplan-Meier survival curves in patients with MDS according to the *TET2* mutation status (solid line indicating mutation-positive and dotted line indicating mutation-negative). Time to sAML transformation (A) and overall survival (B) in the whole cohort of patients according to *TET2* mutation status; time to sAML transformation (C) and overall survival (D) in patients in RAEB-2 subgroup according to *TET2* mutation status; time to sAML transformation (E) and overall survival (F) in MDS in IPSS-R very high-risk group according to *TET2* mutation status.

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T-L. Lin et al Haematologica 2013

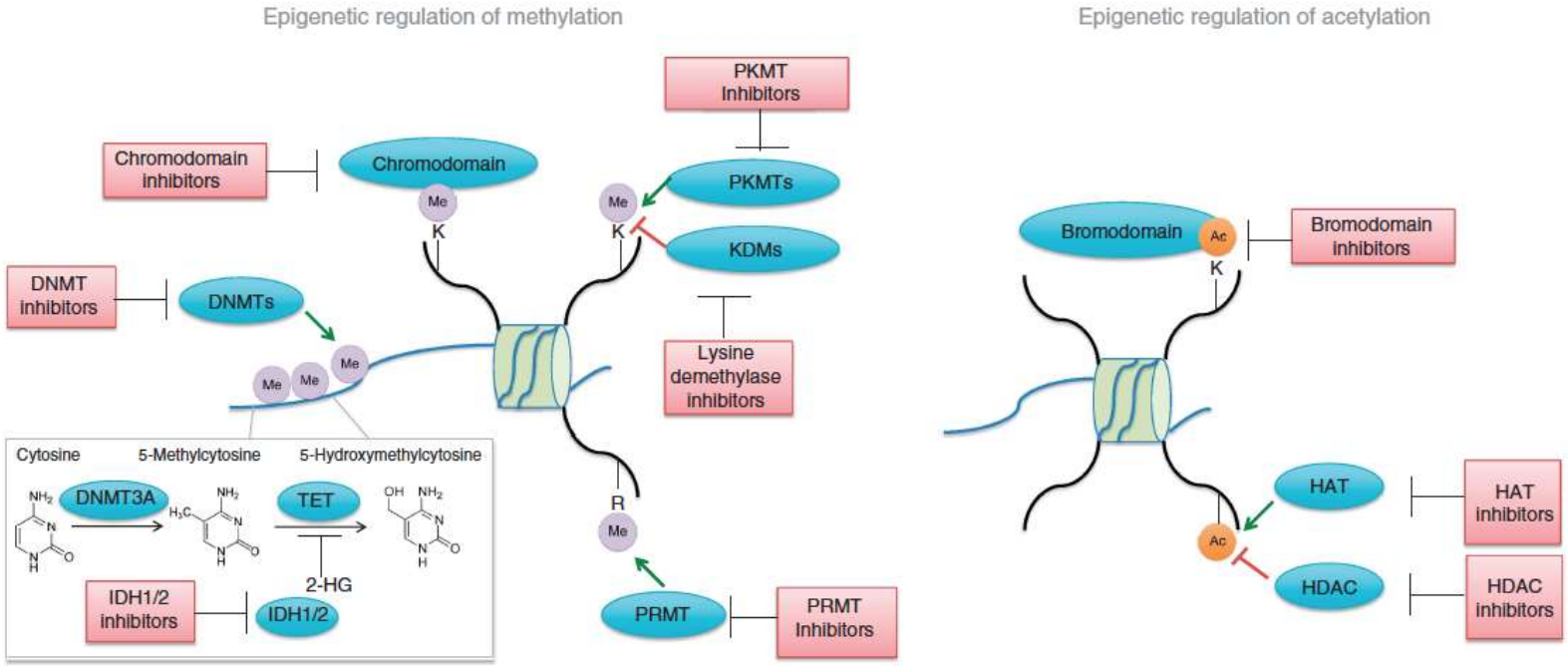

Figure 1. Regulation of methylation and acetylation in leukemia and their therapeutic potential. The figure shows a selection of proteins that add, remove and recognize chromatin modifications, as well as the the proteins that regulate DNA methylation. The genes encoding these proteins can be altered through mutation, deletion or altered expression in leukemia. Ac, acetylation; DNMT, DNA methyltransferase; HAT, histone acetyltransferase; HDAC, histone deacetylase; KDM, lysine demethylase; Me, methylation; PKMT, lysine methyltransferase; PRMT, arginine methyltransferase.

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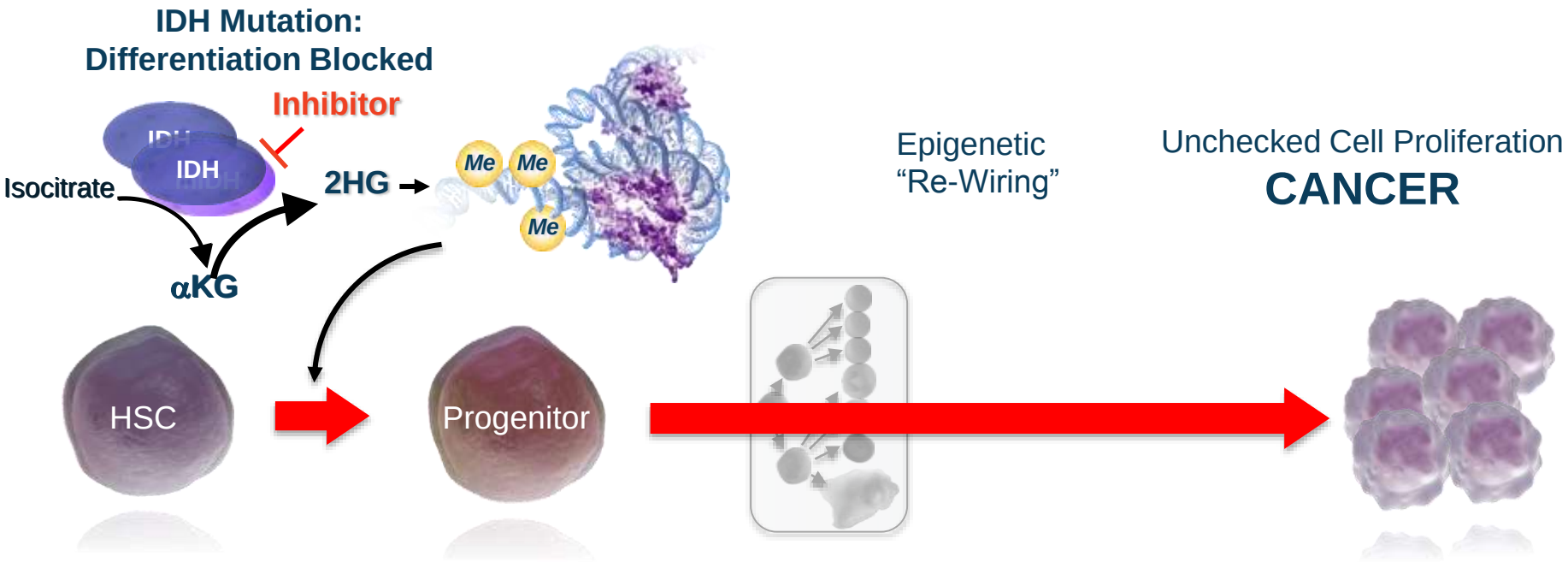
S. Greenblatt and S. Nimer Leukemia 2014

IDH MUTATIONS LEAD TO CELL DIFFERENTIATION BLOCK



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Dang L et al. *Nature*. 2009;462(7274):739-744. Figueroa ME et al. *Cancer Cell*. 2010; 18:553-567. Yen KE, Schenkein DP. *The Oncologist*. 2012;17:5-8.

HISTONE METHYLTRANSFERASE INHIBITORS

- **EPZ-5676** A highly potent and selective inhibitor of DOT1L in clinical development.
- **EPZ-6438** A potent and selective small molecule inhibitor of EZH2 in clinical development.
- **GSK126, GSK343** Small molecule inhibitors of EZH2.
- **PFI-2** A potent and selective SETD7 inhibitor.
- **SGC0946** A potent and selective inhibitor of DOT1L.
- **UNC0638, UNC0642, UNC0646** Selective and cell permeable inhibitors of G9a and GLP

HISTONE DEMETHYLASE INHIBITORS

- **Daminozide** A small molecule inhibitor of the KDM2/7 family of JmjC demethylases.
- **GSK-J1 / GSK-J4** Selective inhibitors of the UTX and JMJD3 H3K27 demethylases
- **GSK-LSD1** A specific and irreversible inhibitor of LSD1.
- **LSD1-C12, LSD1-C76** Specific, and reversible LSD1 inhibitors, with in vivo efficacy
- **JIB-04 (NSC693627)** A cell permeable Jumonji demethylase inhibitor,
- **ML324** A potent and cell permeable inhibitor of the JMJD2 histone demethylase.
- **PBIT** A reversible and cell-permeable inhibitor of JARID1 histone demethylases.

Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Phase 2 study of azacytidine plus sorafenib in patients with acute myeloid leukemia and *FLT*-3 internal tandem duplication mutation

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Key Points

- Azacytidine and sorafenib are effective in patients with relapsed and refractory *FLT3*-mutated AML.

Patients received 5-azacytidine (AZA) 75 mg/m^2 intravenously daily for 7 days and sorafenib 400 mg orally twice daily continuously; cycles were repeated at ~1-month intervals. Forty-three acute myeloid leukemia (AML) patients with a median age of 64 years (range, 24-87 years) were enrolled; 37 were evaluable for response. FMS-like tyrosine kinase-3 (FLT3)-internal tandem duplication (ITD) mutation was detected in 40 (93%) patients, with a median allelic ratio of 0.32 (range, 0.009-0.93). They had received a median of 2 prior treatment regimens (range, 0-7); 9 had failed prior therapy with a FLT3 kinase inhibitor. The response rate was 46%, including 10 (27%) complete response with incomplete count recovery (CRi), 6 (16%) complete responses (CR), and 1 (3%) partial response. The median time to achieve CR/CRi was 2 cycles (range, 1-4), and the median duration of CR/CRi was 2.3 months (range, 1-14.3 months). Sixty-four percent of patients achieved adequate (defined as >85%) FLT3 inhibition during their first cycle of therapy. The degree of FLT3 inhibition correlated with plasma sorafenib concentrations. FLT3 ligand levels did not rise to levels seen in prior studies of patients receiving cytotoxic chemotherapy. The combination of AZA and sorafenib is effective for patients with relapsed AML and *FLT-3*-ITD. This trial was registered at clinicaltrials.gov as #NCT01254890. (*Blood*. 2013;121(23): 4655-4662)

CONCLUSIONS

- **Epigenetic abnormalities can predict prognosis in untreated and treated MDS pts** (DNMT3A bad, EZH2 bad, ASXL1 bad, TET2 neutral)
- **Certain abnormalities may predict for a response to specific therapies (e.g. TET2)**
- **HDACi plus HMAs not a home run….**
- **New epigenetic focused therapies are in the pipeline**

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