A precision medicine approach to MDS?

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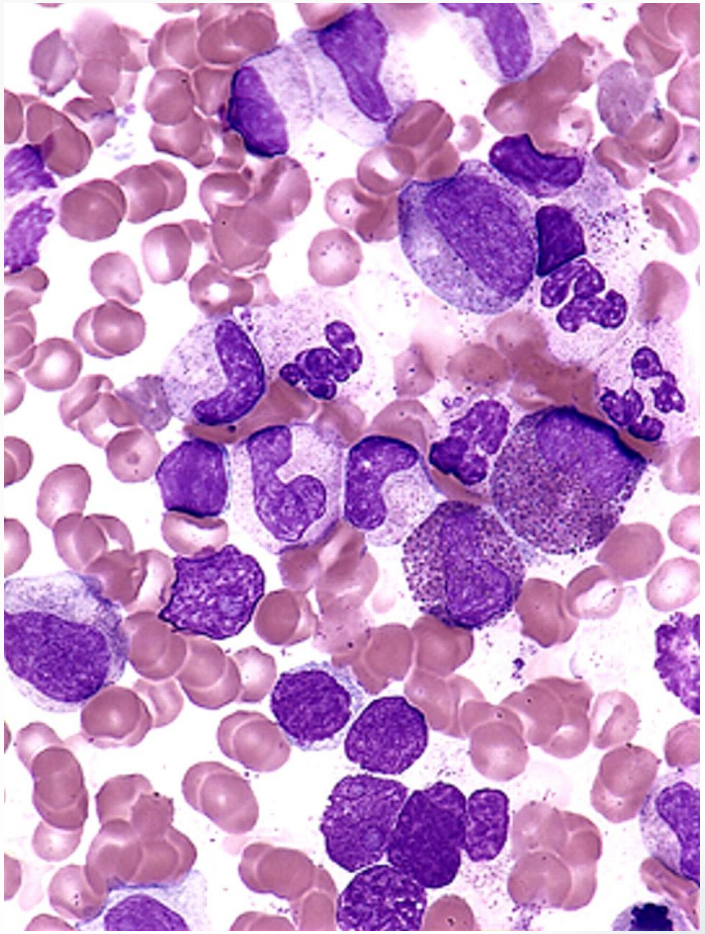
DISCLOSURE

I have no relevant financial relationships to disclose.

Myelodysplastic syndromes: what does precision medicine look like?

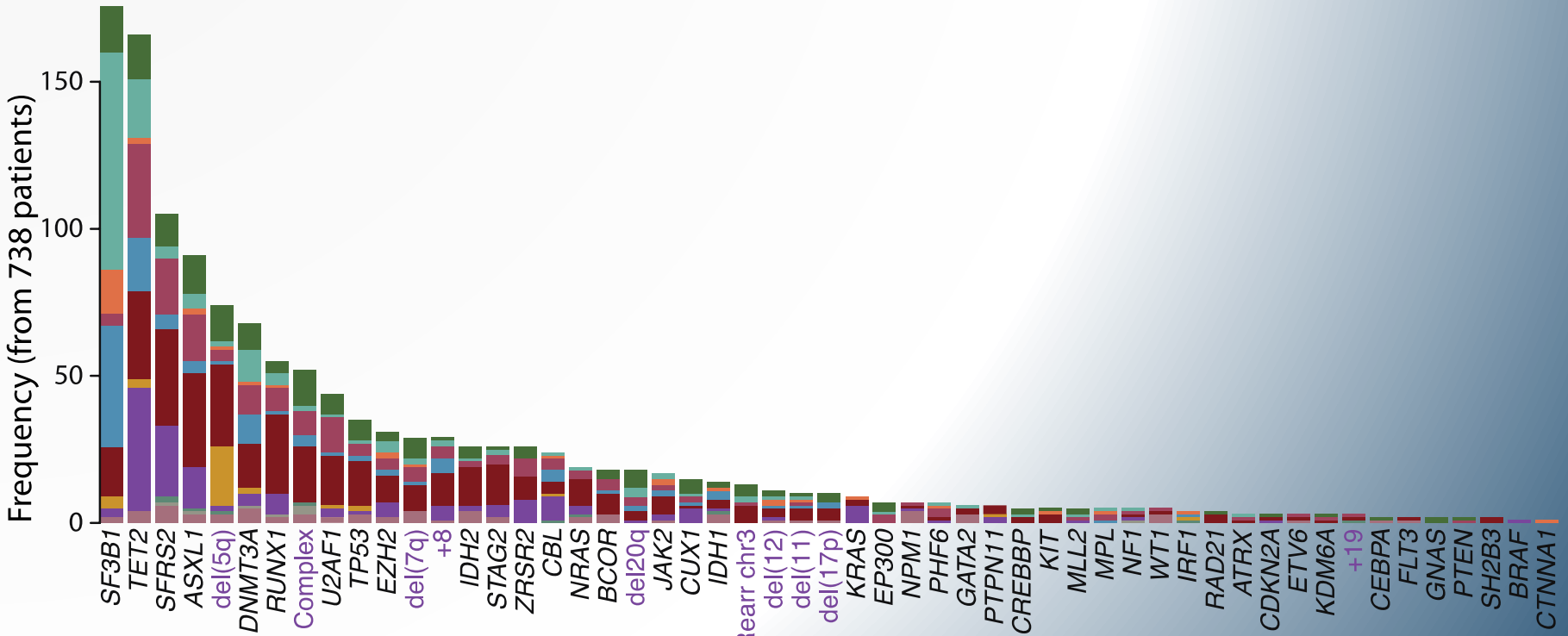
- Assess diagnosis
- (Define pathogenesis of the disease)
- Define the natural history of disease
- Define response to therapy (and mechanism of response for specific therapies?)
- Determine duration or intensity of therapy
- Determine choice of therapy
- Be a target for therapy

Diagnosis of MDS: morphology + cytogenetic abnormalities



- Numerical chromosomal losses or gains
- Large interstitial deletions (5q-, 7q-, 20q-, 17p)
- Translocations [t(5;12), t(5;11), t(3;21)]
- Unbalanced translocations
  - Flow cytometry
  - Molecular studies (gene expression, genetics, epigenetics)

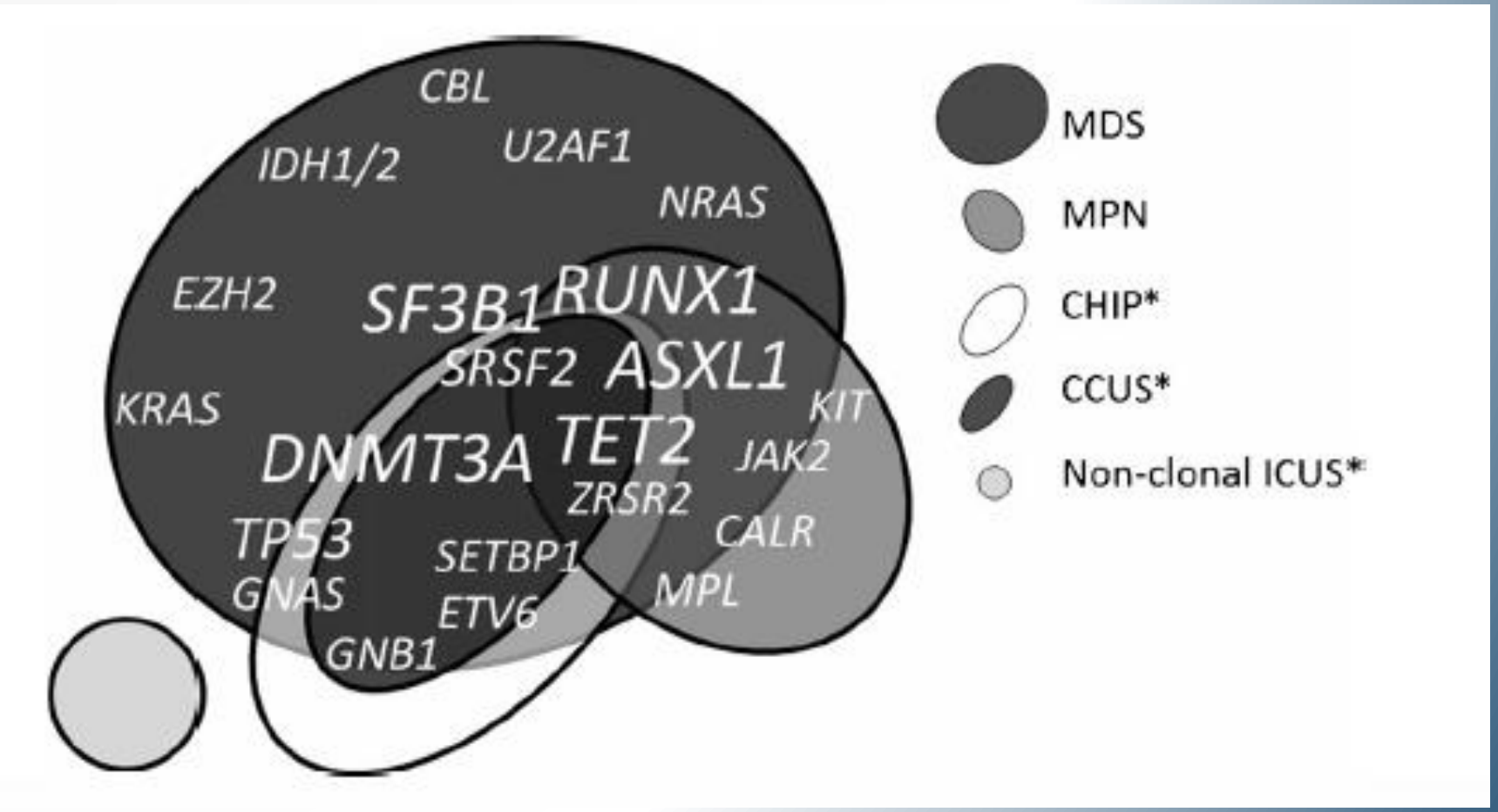
Somatic gene mutations in patients with MDS



Papaemmanuil et al. Blood. 2013 122(22):3616-27

Haferlach et al. Leukemia. 2014 28(2):241-7

What is my diagnosis?



Peripheral cytopenias
Bone marrow morphology incl. percent blasts
Cytogenetics
VAF

T Moyo & M Savona; Cur Hem Malign Rep 2016

Clinical Effect of Point Mutations in Myelodysplastic Syndromes

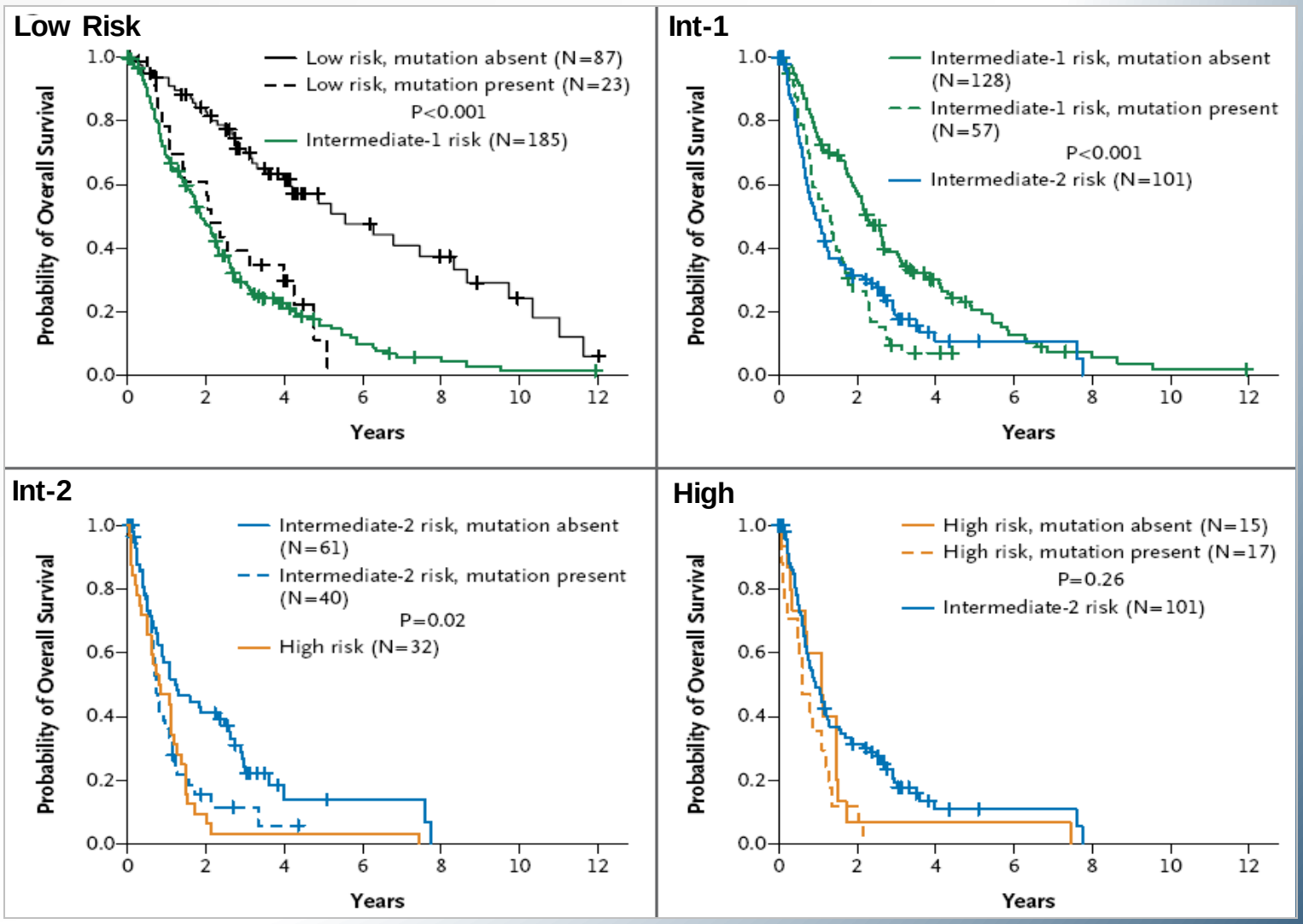
Table 2. Hazard Ratios for Death in a Multivariable Model.*

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

O.S. based on IPSS Risk Category & Mutation Status



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

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]

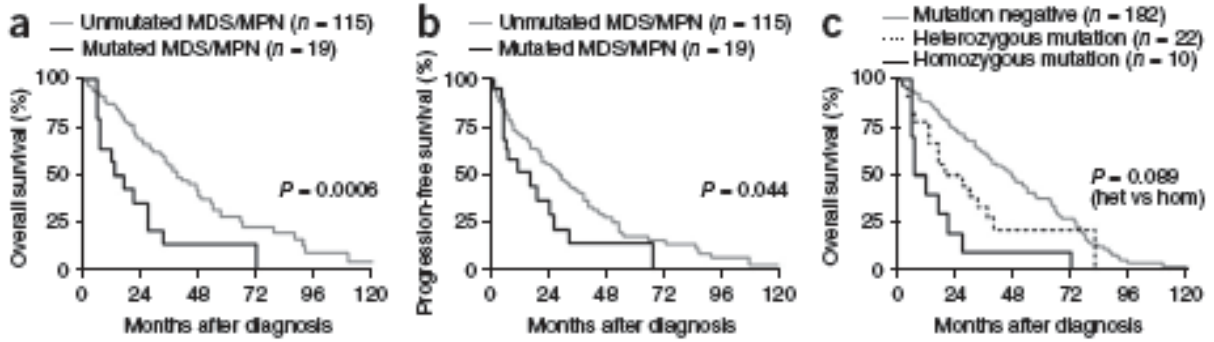


Figure 2 Survival and expression analysis. (a,b) Kaplan-Meier analysis showing overall survival (a) and progression-free survival (b) of the 134 individuals with MDS/MPN for whom follow-up data was available (CMML, $n = 77$; aCML, $n = 44$; MDS/MPN-U, $n = 13$). None of the individuals with *EZH2* mutations 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

Felicitas Thol, Inna Friesen, Frederik Damm, Haiyang Yun, Eva M. Weissinger, Jürgen Krauter, Katharina Wagner, Anuhar Chaturvedi, Amit Sharma, Martin Wichmann, Gudrun Göhring, Christiane Schumann, Gesine Bug, Oliver Ottmann, Wolf-Karsten Hofmann, Brigitte Schlegelberger, Michael Heuser, and Arnold Ganser

› Hannover Medical School, r; University Hospital Mann- annheim; and University of , Frankfurt, Germany.

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. and A.G. contributed equally ork.

disclosures of potential con- nterest and author contribu- found at the end of this

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0X/11/2918-2499/$20.00

A B S T R A C T

Purpose
To study the incidence and prognostic impact of mutations in Additional sex comb-like 1 (*ASXL1*) in a large cohort of patients with myelodysplastic syndrome (MDS).

Patients, Materials, and Methods
Overall, 193 patients with MDS and 65 healthy volunteers were examined for *ASXL1* mutations by direct sequencing and for expression levels of *ASXL1*. The prognostic impact of *ASXL1* mutation and expression levels was evaluated in the context of other clinical and molecular prognostic markers.

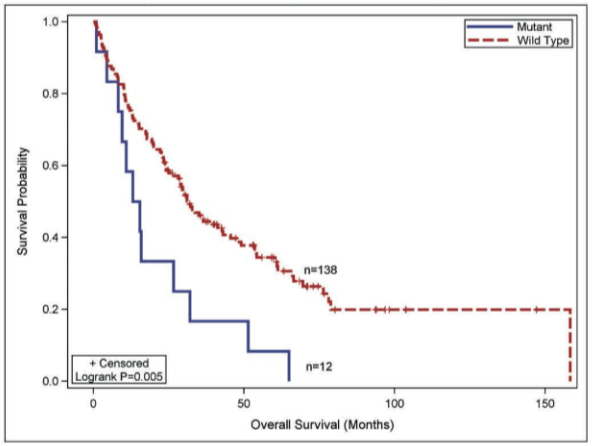
Results
Mutations in *ASXL1* occurred with a frequency of 20.7% in MDS (n = 40 of 193) with 70% (n = 28) of mutations being frameshift mutations and 30% (n = 12) being heterozygous point mutations leading to translational changes. *ASXL1* mutations were correlated with an intermediate-risk karyotype ($P = .002$) but not with other clinical parameters. The presence of *ASXL1* mutations was associated with a shorter overall survival for frameshift and point mutations combined (hazard ratio [HR], 1.744; 95% CI, 1.08 to 2.82; $P = .024$) and for frameshift mutations only (HR, 2.06; 95% CI, 1.21 to 3.50; $P = .008$). *ASXL1* frameshift mutations were associated with a reduced time to progression of acute myeloid leukemia (AML; HR 2.35; 95% CI, 1.17 to 4.74; $P = .017$). In multivariate analysis, when considering karyotype, transfusion dependence, and *IDH1* mutation status, *ASXL1* frameshift mutations remained an independent prognostic marker in MDS (overall survival: HR, 1.85; 95% CI, 1.03 to 3.34; $P = .040$; time to AML progression: HR, 2.39; 95% CI, 1.12 to 5.09; $P = .024$).

Conclusion
These results suggest that *ASXL1* mutations are frequent molecular aberrations in MDS that predict an adverse prognostic outcome. Screening of patients for *ASXL1* mutations might be useful for clinical risk stratification and treatment decisions in the future.

J Clin Oncol 29:2499-2506. © 2011 by American Society of Clinical Oncology

Effect of DNMT3A mutations on MDS outcome

A.



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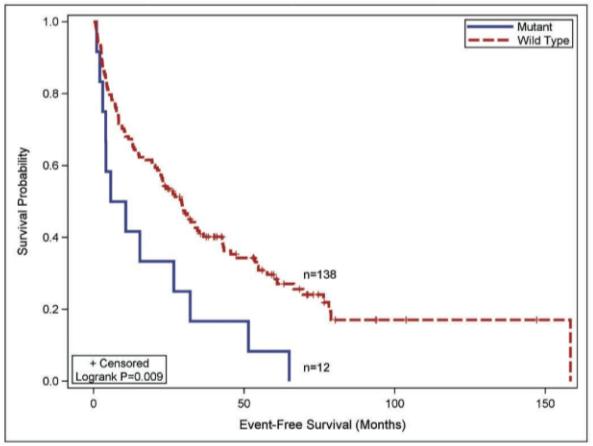
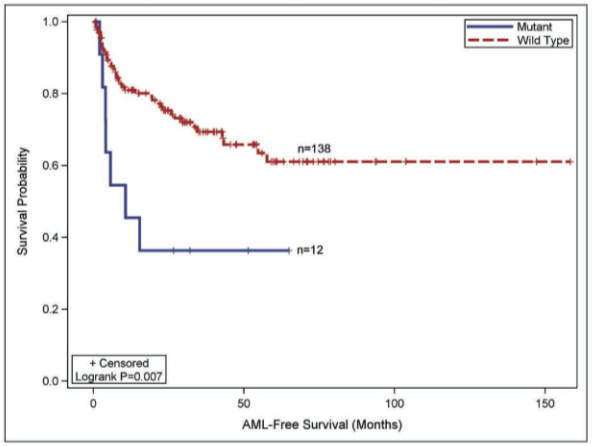
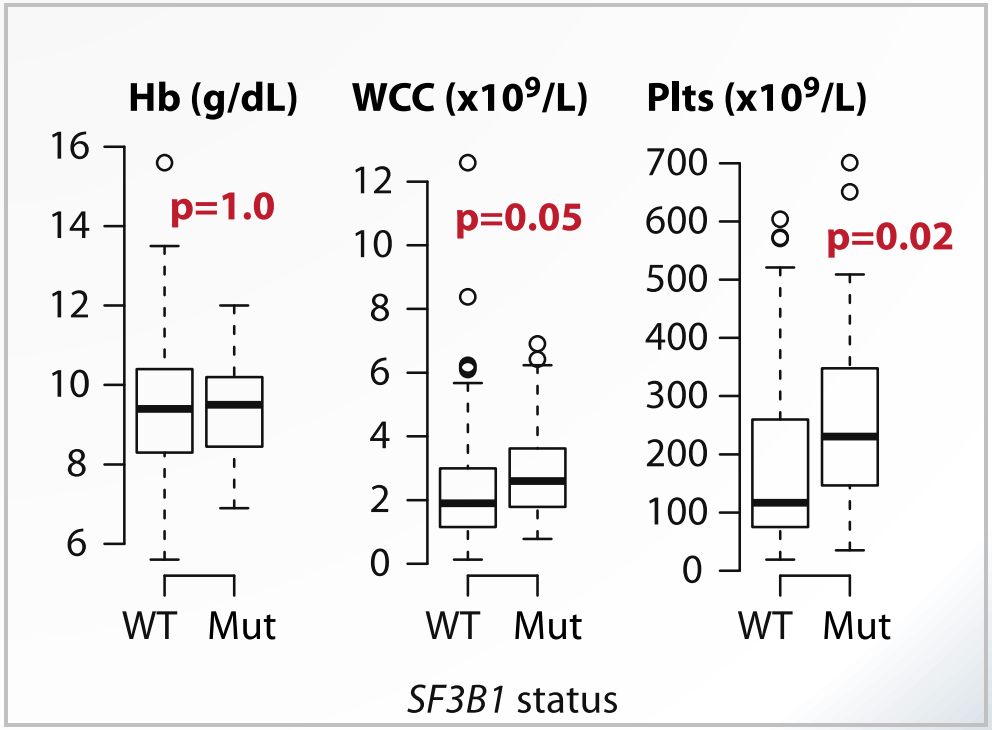


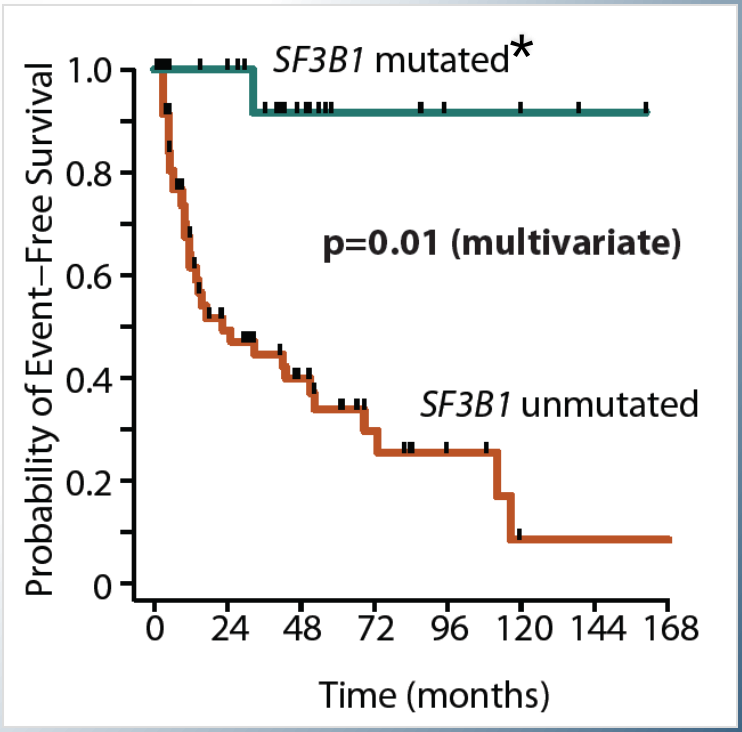
C.



M. Walter et al Leukemia 25: 1153; 2011

Clinical Significance of SF3B1 Mutations



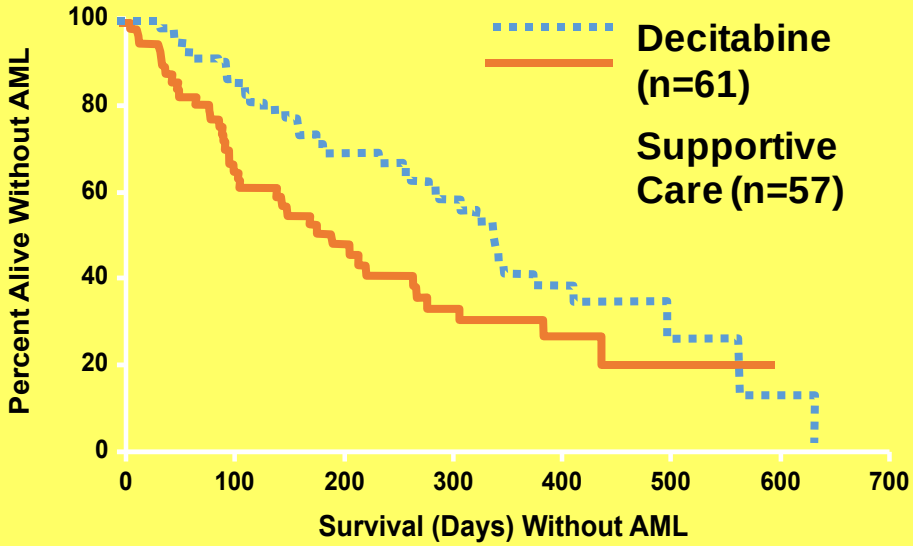


*Prolonged EFS independent of age, gender and karyotype.

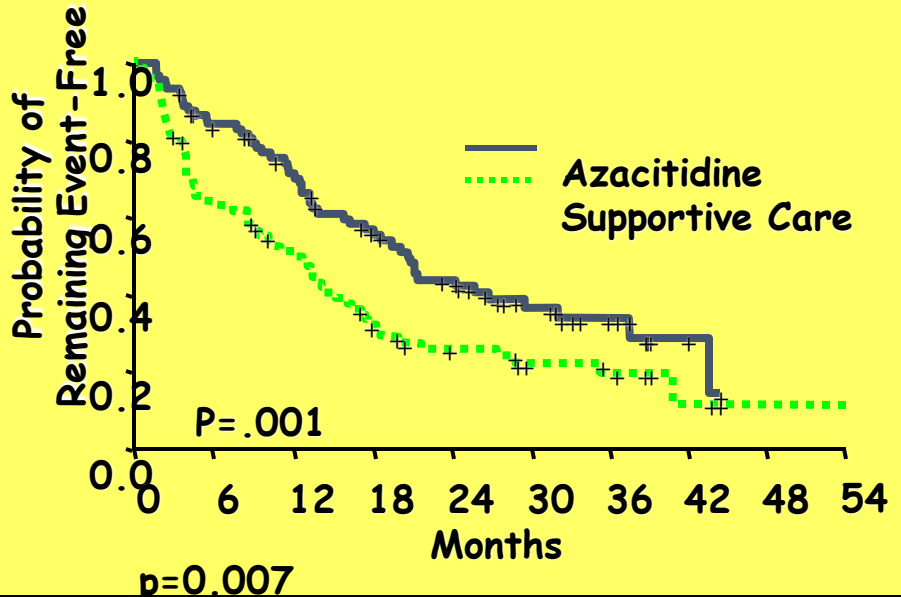
Papaemmanuil E, et al. NEJM 2011; 365: 1384

Two hypomethylating agents FDA-approved for MDS pts

Can we enrich for responding patients?



L. Silverman et al Cancer 2002



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

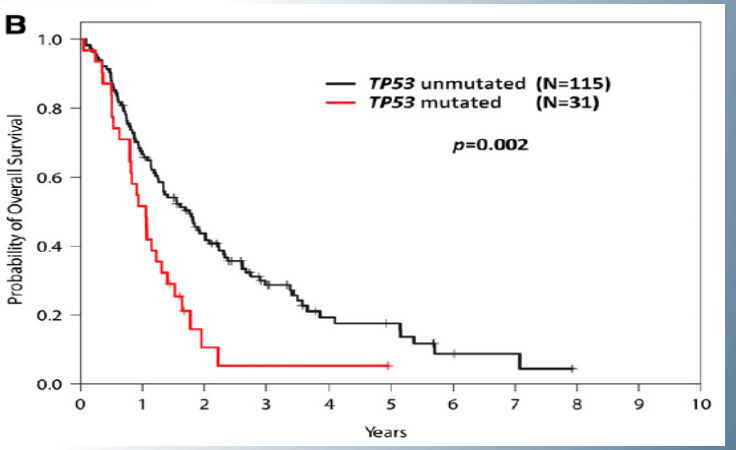
- Higher abundance *TET2* mutations are associated with increased response to hypomethylating agents, particularly when *ASXL1* is not mutated.
- *TP53* and *PTPN11* mutations are associated with shorter overall survival after hypomethylating agent treatment, but do not predict response.

BLOOD, 23 OCTOBER 2014 • VOLUME 124, NUMBER 17

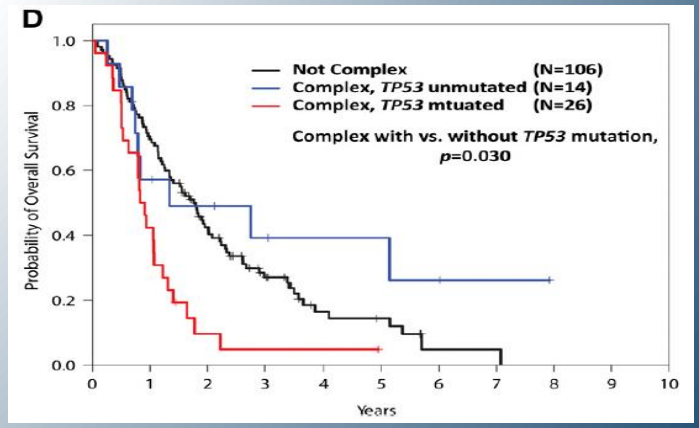
TET2 Mutations Sensitize MDS Clones to Azanucleosides

- 213 pts rcving azanucleosides (100 LR-MDS)
- NGS analysis of 40 myeloid genes to assess relation to response & OS
- Clonal *TET2* mutations predicted response (OR 1.99, *P*=.036) when subclones unlikely to be detected by Sanger sequencing (VAF<10%) were treated as wild-type (WT).
- Response rate highest in ***TET2*** mutant patients without ***ASXL1*** mutations (OR 3.65, *P*=.009).
- Mutant *TP53* (HR 2.01, *P*=.002) associated with shorter OS but not drug response

OS by *TP53* Mutation Status



OS in Complex Karyotype vs *TP53*



Bejar R, et. al. BLOOD 2014; 124:2706.

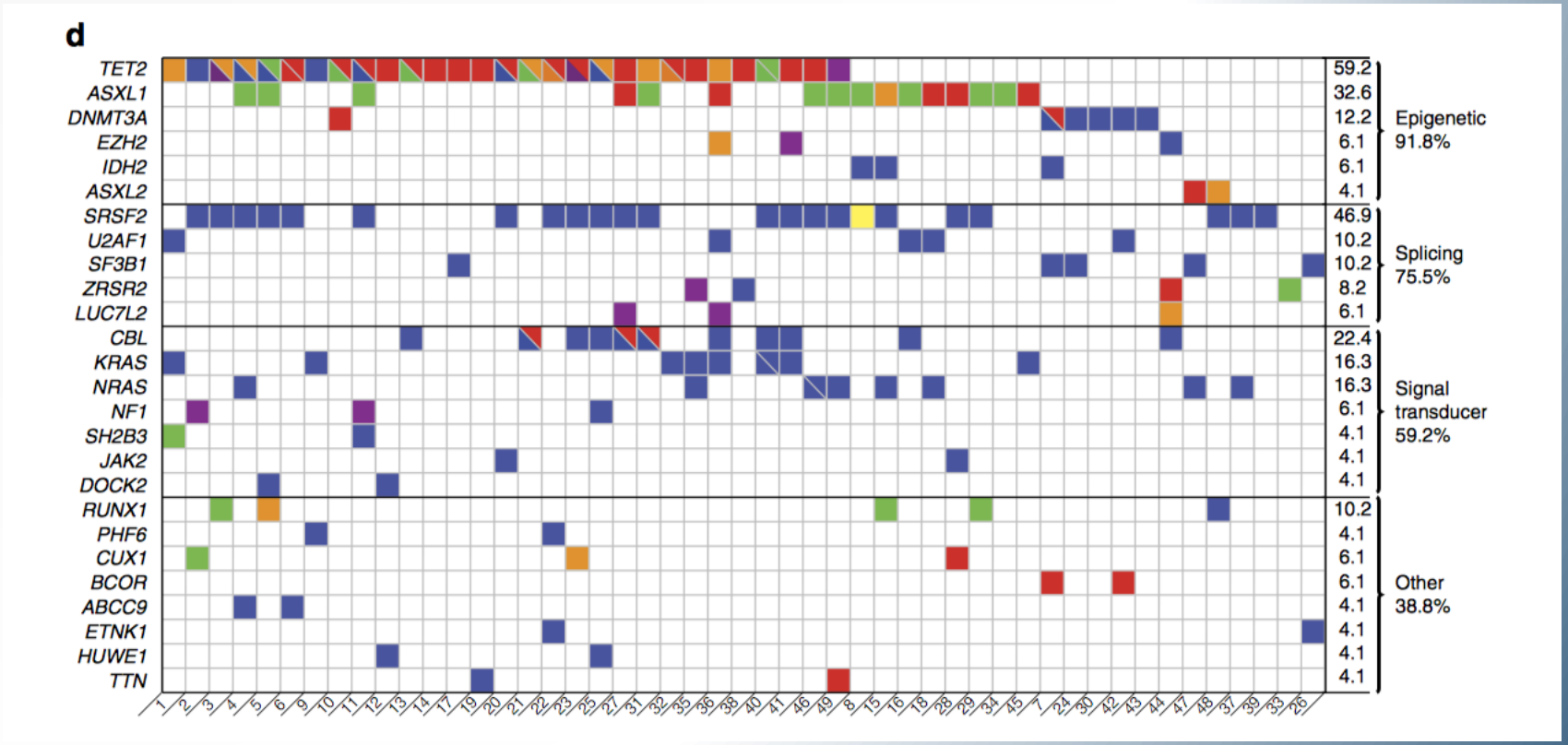
Response to HMA Treatment by Mutational Status

Institution	# Pts.	Gene(s)	Overall Response *Mutant*	*WT (%)*	P value
GFM	86	*TET2*	11/13 (85)*	34/73 (47)	0.01
Taussig (#3461a)	88	*DNMT3A,TET2 , IDH1/2*	12/28 (64)	21/60 (35)	0.01
		DNMT3A	6/7 (86)	33/81 (41)	0.02
		TET2	12/18 (67)	27/70 (39)	0.03
		ASXL1	11/13 (85)	14/37 (38)	0.003
OSU^ (#944a)	46	*DNMT3A*	6/8 (75)	13/38 (34)	0.05

*includes mCR in ORR.

^AML pts treated with decitabine.

Itzykson R, et. al. Leukemia 2011; 25: 1147.



Merlevede et al Nat Comm 2016

nature COMMUNICATIONS

ARTICLE

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Mutation allele burden remains unchanged in chronic myelomonocytic leukaemia responding to hypomethylating agents

Jane Merlevede[1,2,*], Nathalie Droin[1,2,3,*], Tingting Qin[4], Kristen Meldi[4], Kenichi Yoshida[5], Margot Morabito[1,2], Emilie Chautard[6], Didier Auboeuf[7], Pierre Fenaux[8], Thorsten Braun[9], Raphael Itzykson[8], Stéphane de Botton[1,2], Bruno Quesnel[10], Thérèse Commes[11], Eric Jourdan[12], William Vainchenker[1,2], Olivier Bernard[1,2], Noemie Pata-Merci[3], Stéphanie Solier[1,2], Velimir Gayevskiy[13], Marcel E. Dinger[13], Mark J. Cowley[13], Dorothée Selimoglu-Buet[1,2], Vincent Meyer[14], François Artiguenave[14], Jean-François Deleuze[14], Claude Preudhomme[10], Michael R. Stratton[15], Ludmil B. Alexandrov[15,16,17], Eric Padron[18], Seishi Ogawa[5], Serge Koscielny[19], Maria Figueroa[4] & Eric Solary[1,2,20]

Myelodysplastic syndromes: what does precision medicine look like?

- Assess diagnosis
- (Define pathogenesis of the disease)
- Define the natural history of disease
- **Define response to therapy**
- Determine duration or intensity of therapy
- Determine choice of therapy
- Be a target for therapy

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Article

Integrative Genomics Identifies the Molecular Basis of Resistance to Azacitidine Therapy in Myelodysplastic Syndromes

Ashwin Unnikrishnan,[1,2,29,*] Elli Papaemmanuil,[3,4,28] Dominik Beck,[1,2,5,28] Nandan P. Deshpande,[6,7] Arjun Verma,[1,2,8] Ashu Kumari,[9] Petter S. Woll,[10,11] Laura A. Richards,[9] Kathy Knezevic,[1,2] Vashe Chandrakanthan,[1,2] Julie A.I. Thoms,[1,2] Melinda L. Tursky,[1,2,9,12] Yizhou Huang,[1,2,5] Zara Ali,[9] Jake Olivier,[13] Sally Galbraith,[13] Austin G. Kulasekararaj,[14] Magnus Tobiasson,[10] Mohsen Karimi,[10] Andrea Pellagatti,[15] Susan R. Wilson,[13,16] Robert Lindeman,[17] Boris Young,[17] Raj Ramakrishna,[18] Christopher Arthur,[19] Richard Stark,[20] Philip Crispin,[21] Jennifer Curnow,[22,27] Pauline Warburton,[23] Fernando Roncolato,[24] Jacqueline Boultwood,[15] Kevin Lynch,[25] Sten Eirik W. Jacobsen,[10,11] Ghulam J. Mufti,[14] Eva Hellstrom-Lindberg,[10] Marc R. Wilkins,[6,7,26] Karen L. MacKenzie,[9] Jason W.H. Wong,[1,2] Peter J. Campbell,[3,29,*] and John E. Pimanda[1,2,17,29,30,*]

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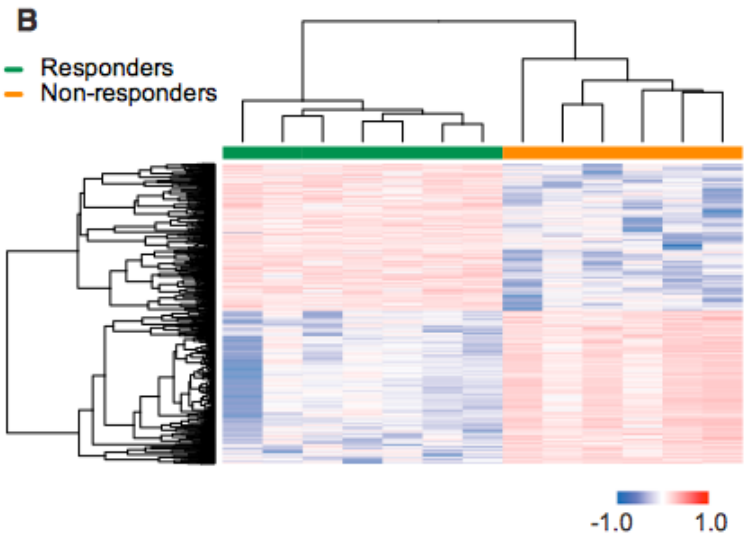
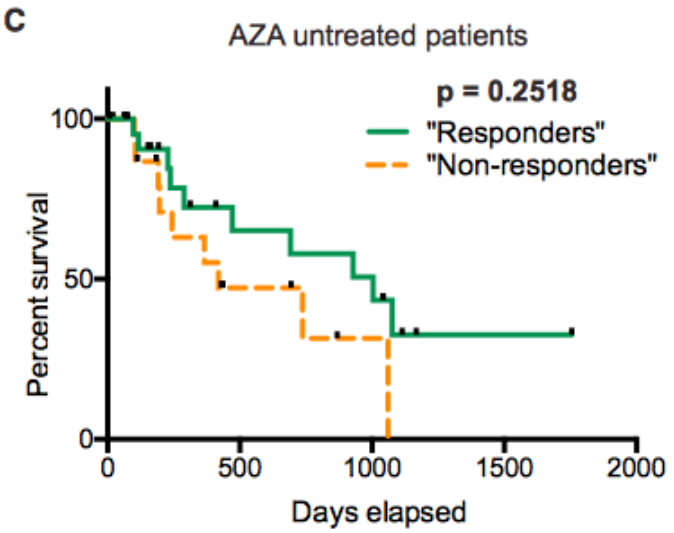
Unnikrishnan et al Cell Reports 2017

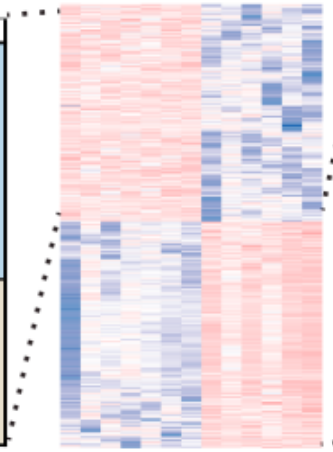




D

Upregulated in Responders

Pathways	p value
Mitotic Roles of Polo-Like Kinase	5.01E-15
Cell Cycle Control of Chromosomal Replication	6.31E-12
Cell Cycle: G2/M DNA Damage Checkpoint Regulation	1.26E-11
Estrogen-mediated S-phase Entry	6.31E-11
Cyclins and Cell Cycle Regulation	4.37E-08
Pyrimidine Deoxyribonucleotides De Novo Biosynthesis I	7.08E-07
Cell Cycle: G1/S Checkpoint Regulation	7.76E-07
Role of BRCA1 in DNA Damage Response	2.51E-20
Role of CHK Proteins in Cell Cycle Checkpoint Control	5.01E-15
Hereditary Breast Cancer Signaling	2.00E-14
ATM Signaling	3.98E-13
Mismatch Repair in Eukaryotes	5.01E-11



Upregulated in Non-Responders

Pathways	p value
Integrin Signaling	1.00E-06
Phospholipase C Signaling	5.37E-06
Signaling by Rho Family GTPases	2.04E-05
ERK/MAPK Signaling	4.07E-05
p70S6K Signaling	1.07E-04
Tec Kinase Signaling	1.86E-04
FAK Signaling	4.27E-04
Paxillin Signaling	1.05E-03
PI3K/AKT Signaling	3.24E-03
Gαi Signaling	2.95E-06
G Beta Gamma Signaling	9.77E-06
cAMP-mediated signaling	2.45E-03

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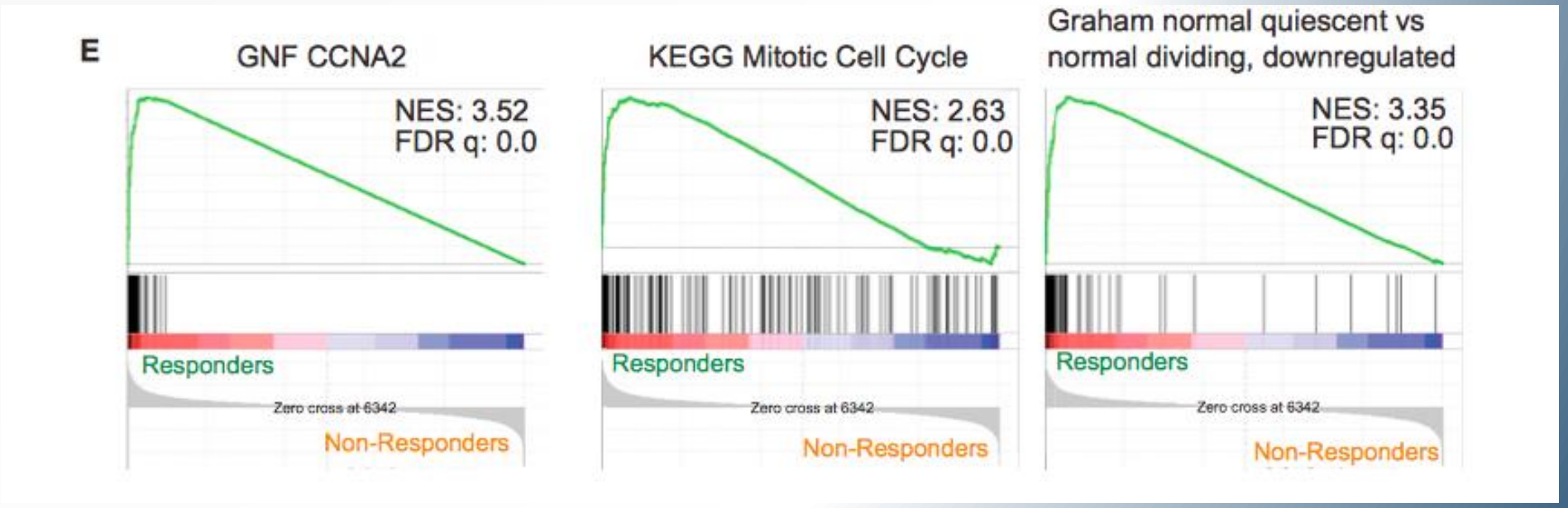

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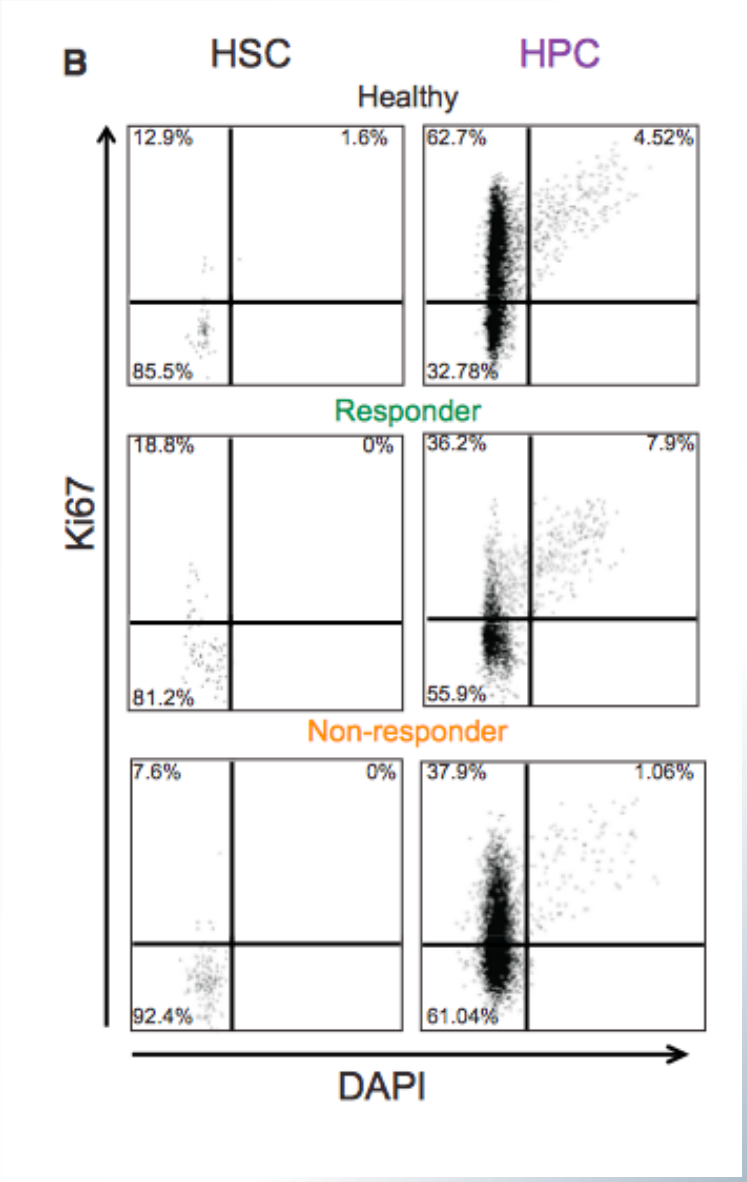

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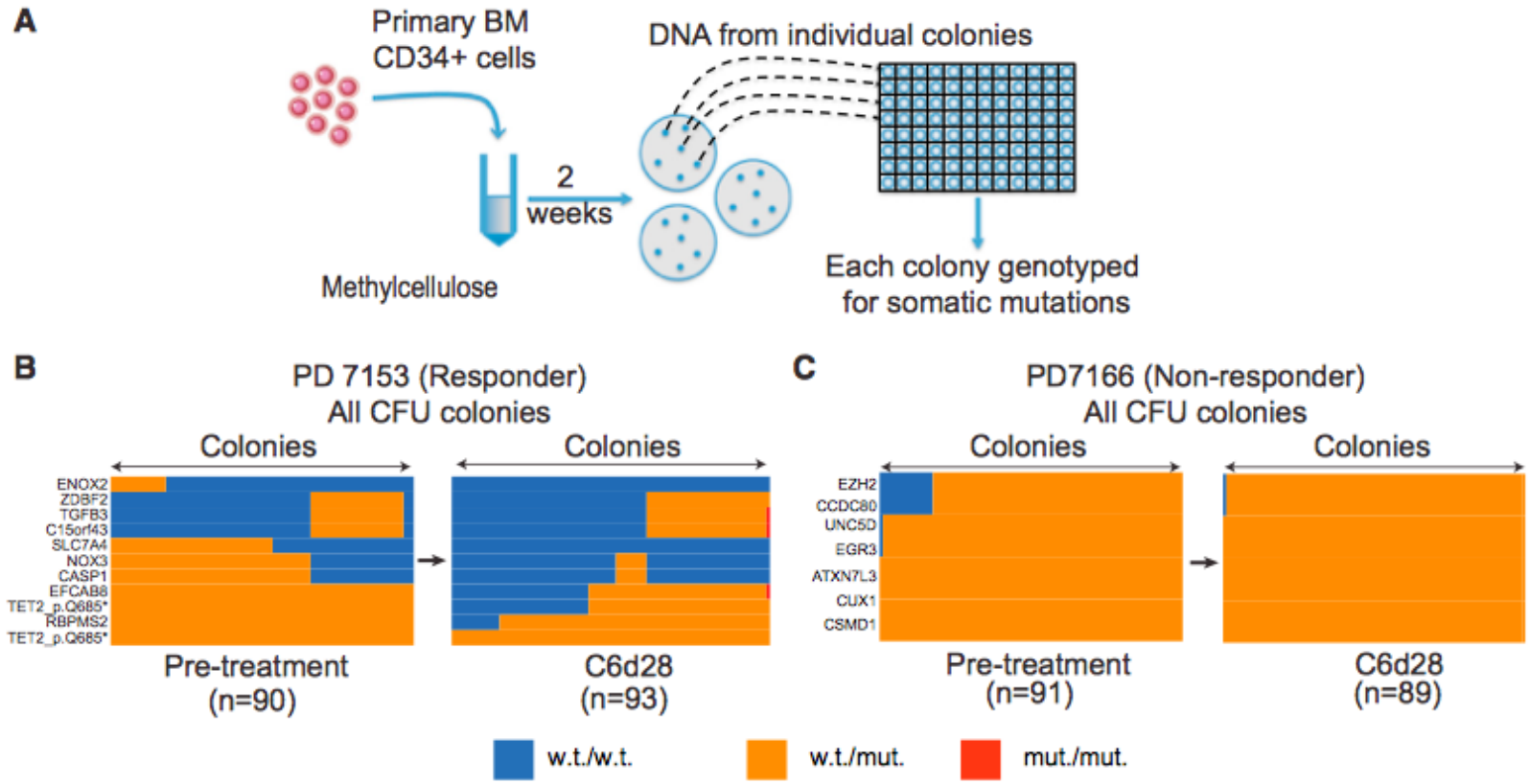

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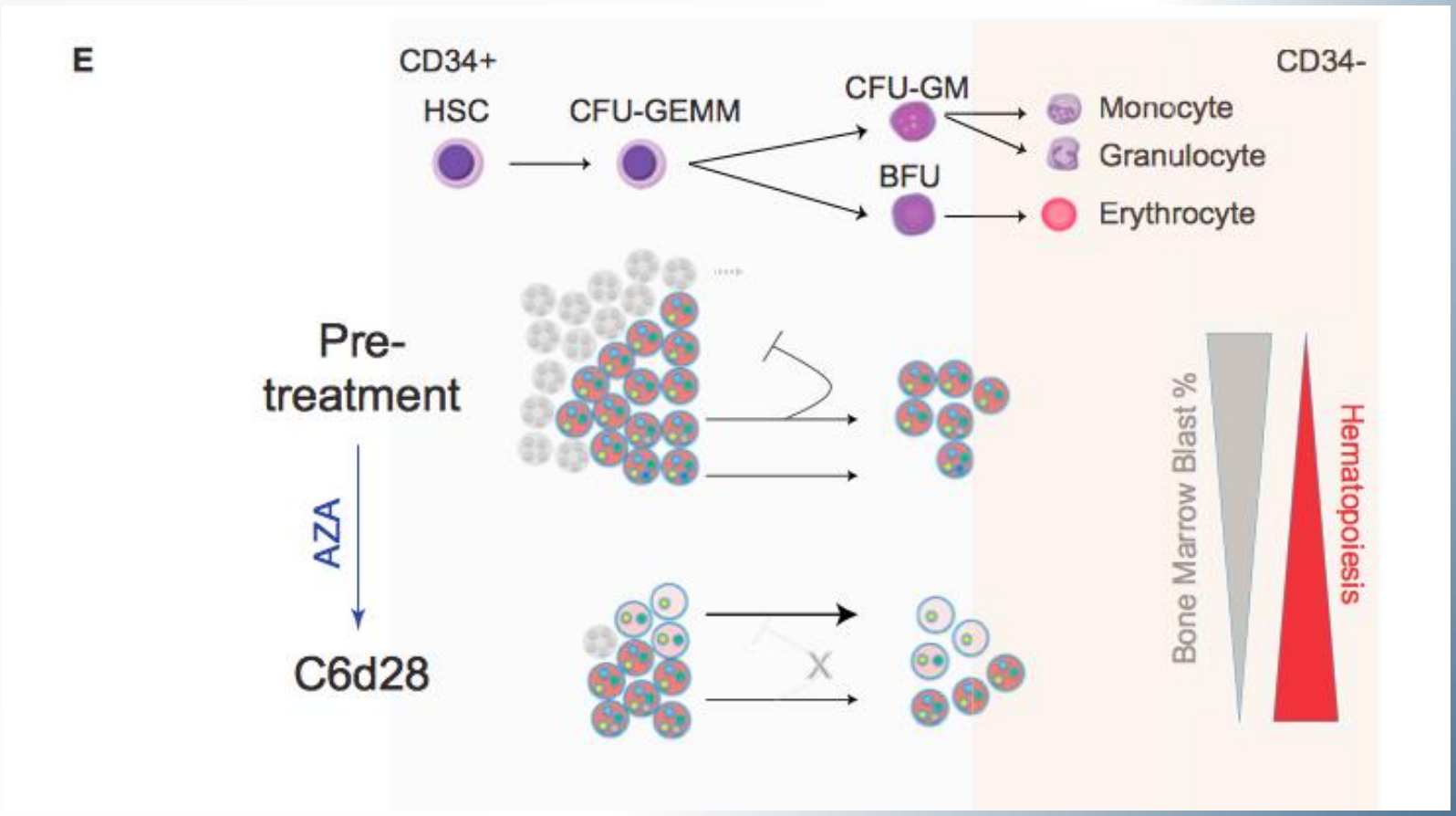

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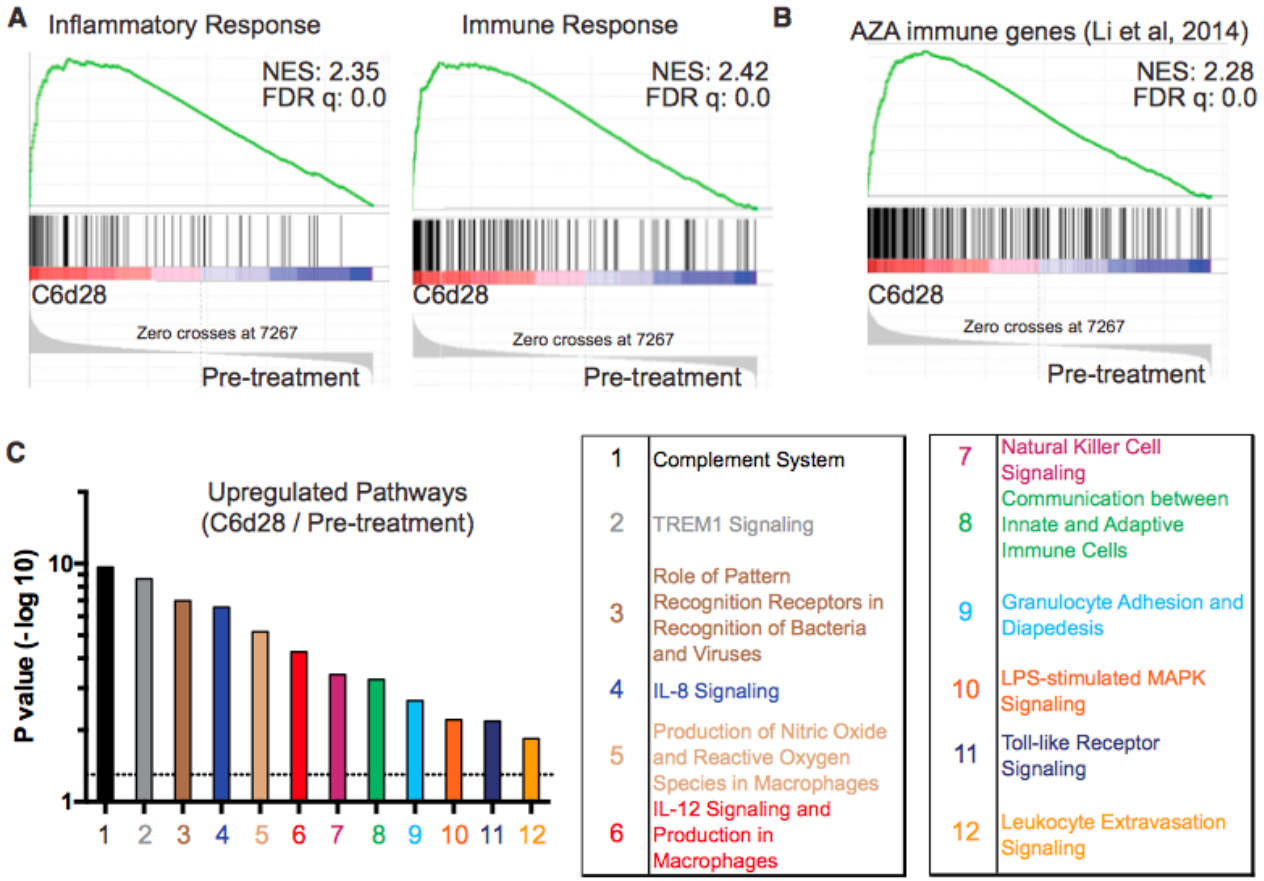

Figure 4. AZA Therapy Induces Pro-inflammatory Pathways In Vivo in Responders

(A) GSEA plots illustrating strong enrichment for inflammatory and immune response pathways in vivo at C6d28 compared with pre-treatment in AZA responders. NES and FDR for the gene sets are indicated.

(B) GSEA plot showing enrichment for a previously identified set of immune genes whose expression is induced by AZA treatment (Li et al., 2014).

(C) Significant enrichment for a number of immune- and inflammation-related pathways upregulated in vivo at C6d28 in AZA responders, as identified by IPA.

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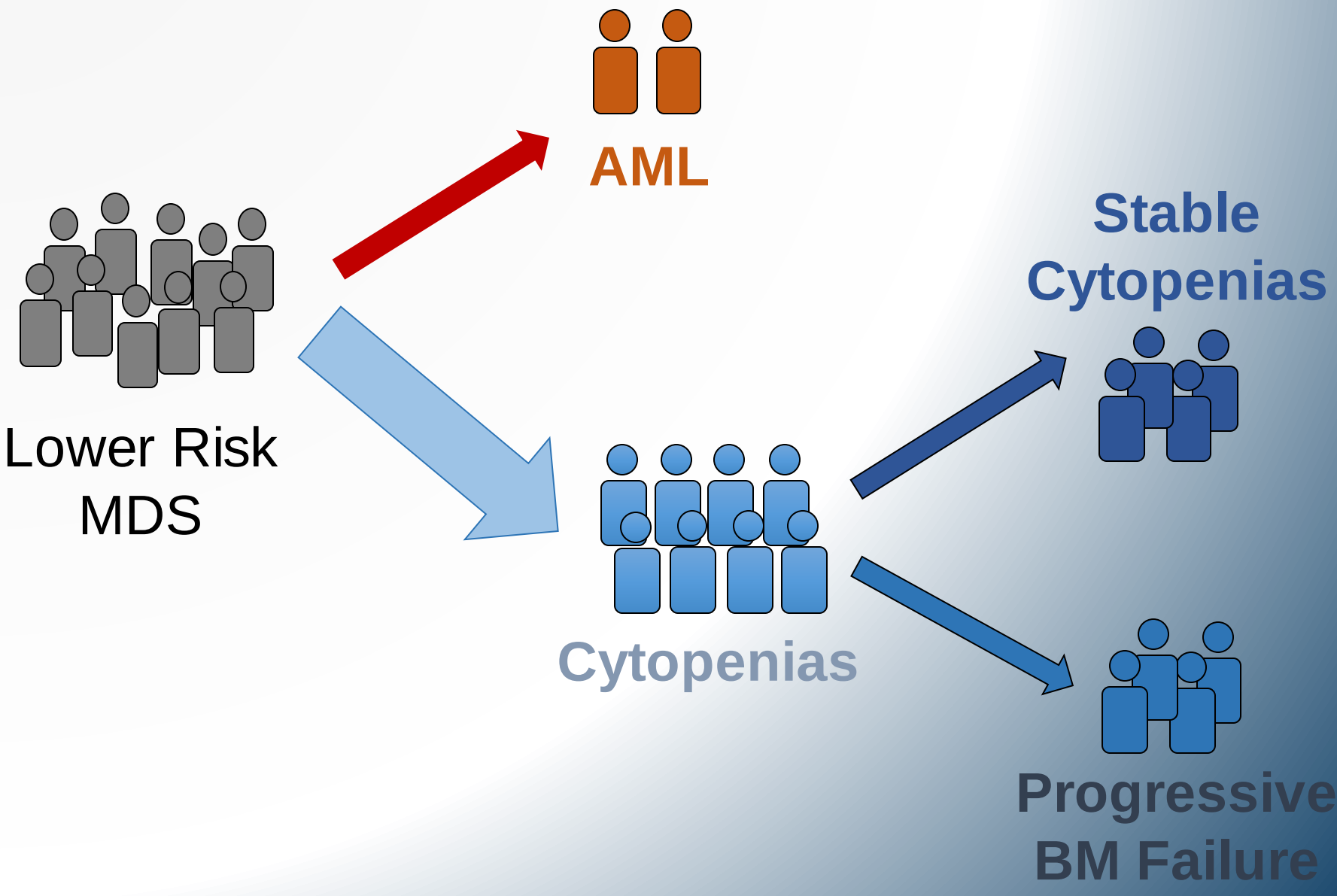
Clinical Evolution and Bone Marrow Failure in Lower Risk MDS



OPEN

Targeted resequencing analysis of 31 genes commonly mutated in myeloid disorders in serial samples from myelodysplastic syndrome patients showing disease progression

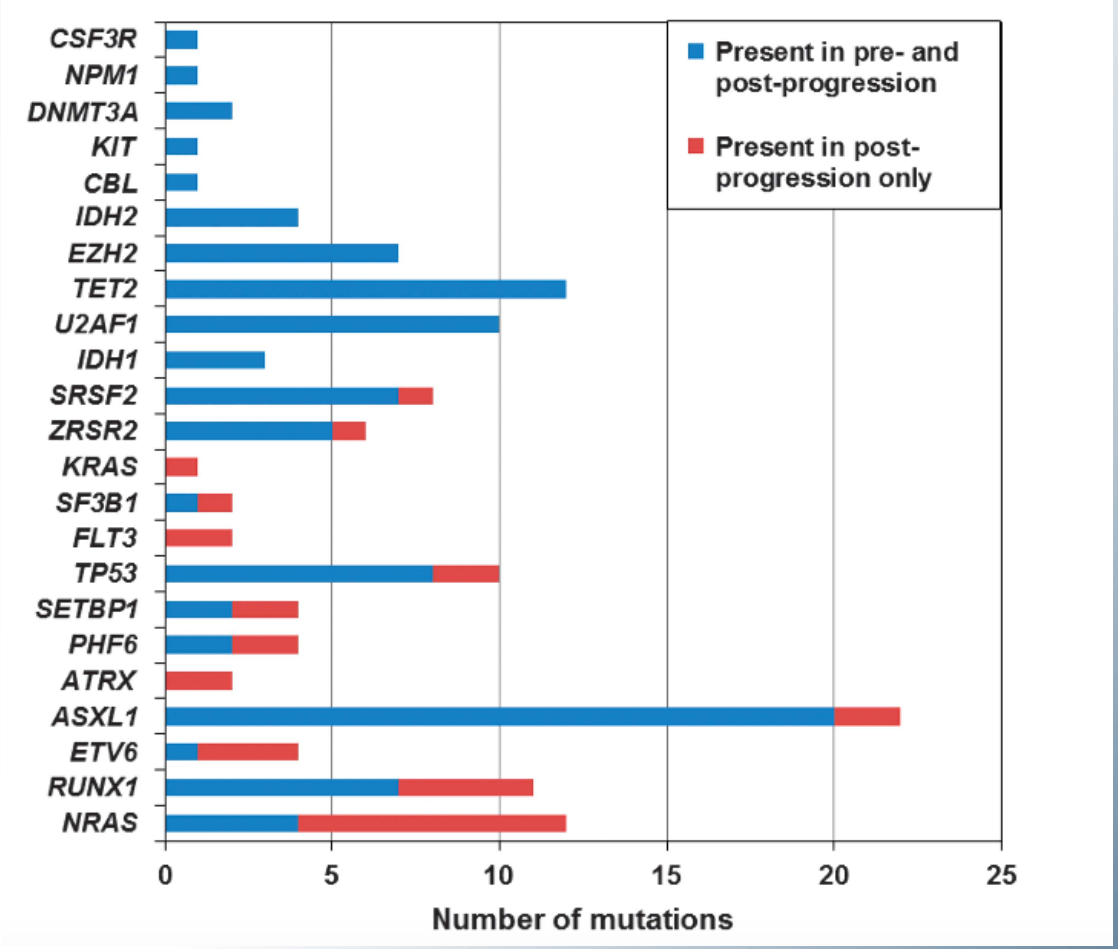
A Pellagatti[1], S Roy[1], C Di Genua[1], A Burns[2], K McGraw[3], S Valletta[1], MJ Larrayoz[4], M Fernandez-Mercado[1], J Mason[2], S Killick[5], C Mecucci[6], MJ Calasanz[4], A List[3], A Schuh[2] and J Boultwood[1]

[1]*LLR Molecular Haematology Unit, Nuffield Division of Clinical Laboratory Sciences, Radcliffe Department of Medicine, University of Oxford, Oxford, UK;*

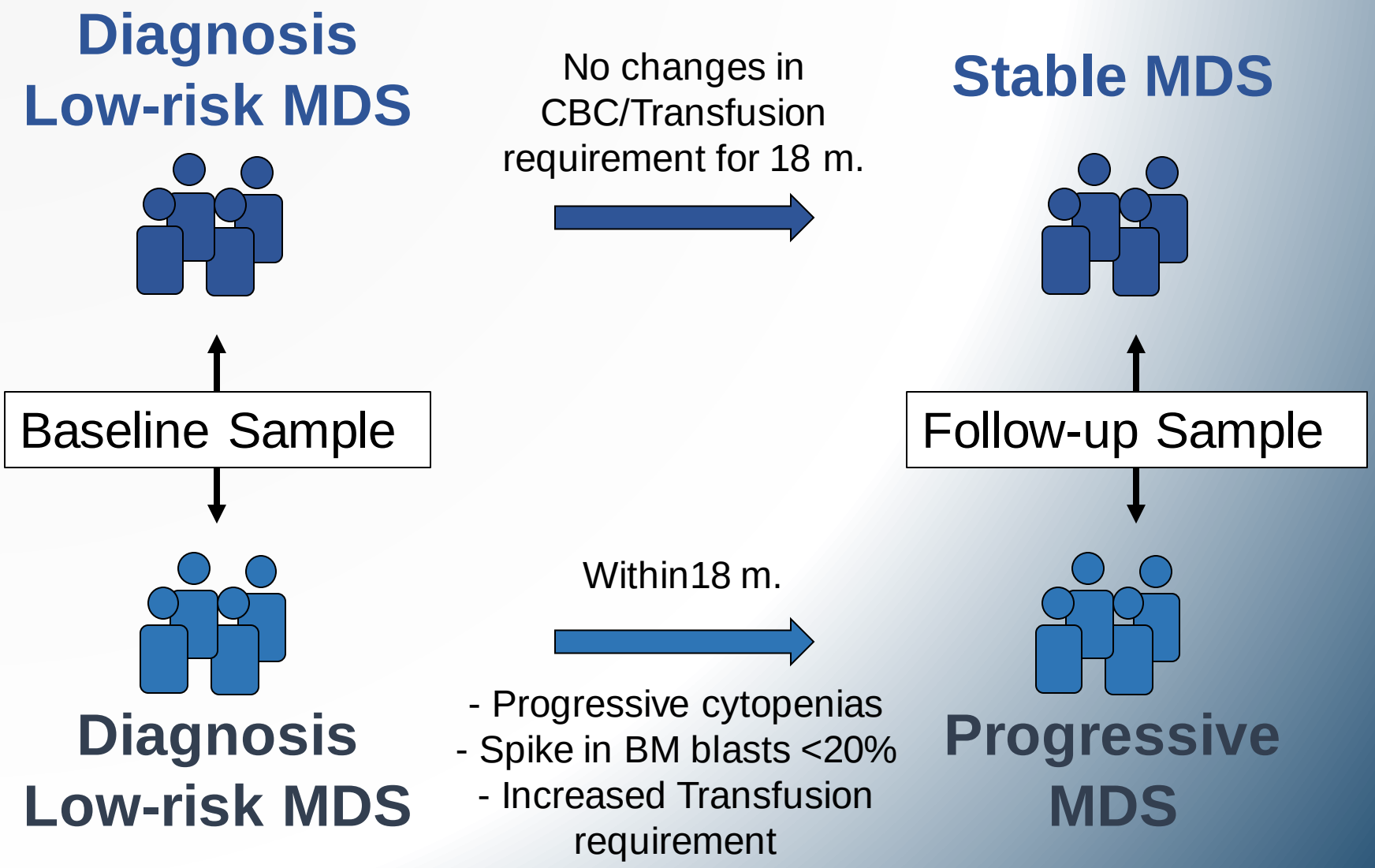
Leukemia (2016) **30,** 247–250; doi:10.1038/leu.2015.129

The myelodysplastic syndromes (MDS) are clonal disorders of the

(>1%) mutated genes in myeloid malignancies (Supplementary Table 2). Dual-barcoded TSCA libraries were sequenced on an Illumina MiSeq platform, and variants were annotated and filtered using Illumina VariantStudio (Supplementary Methods). The

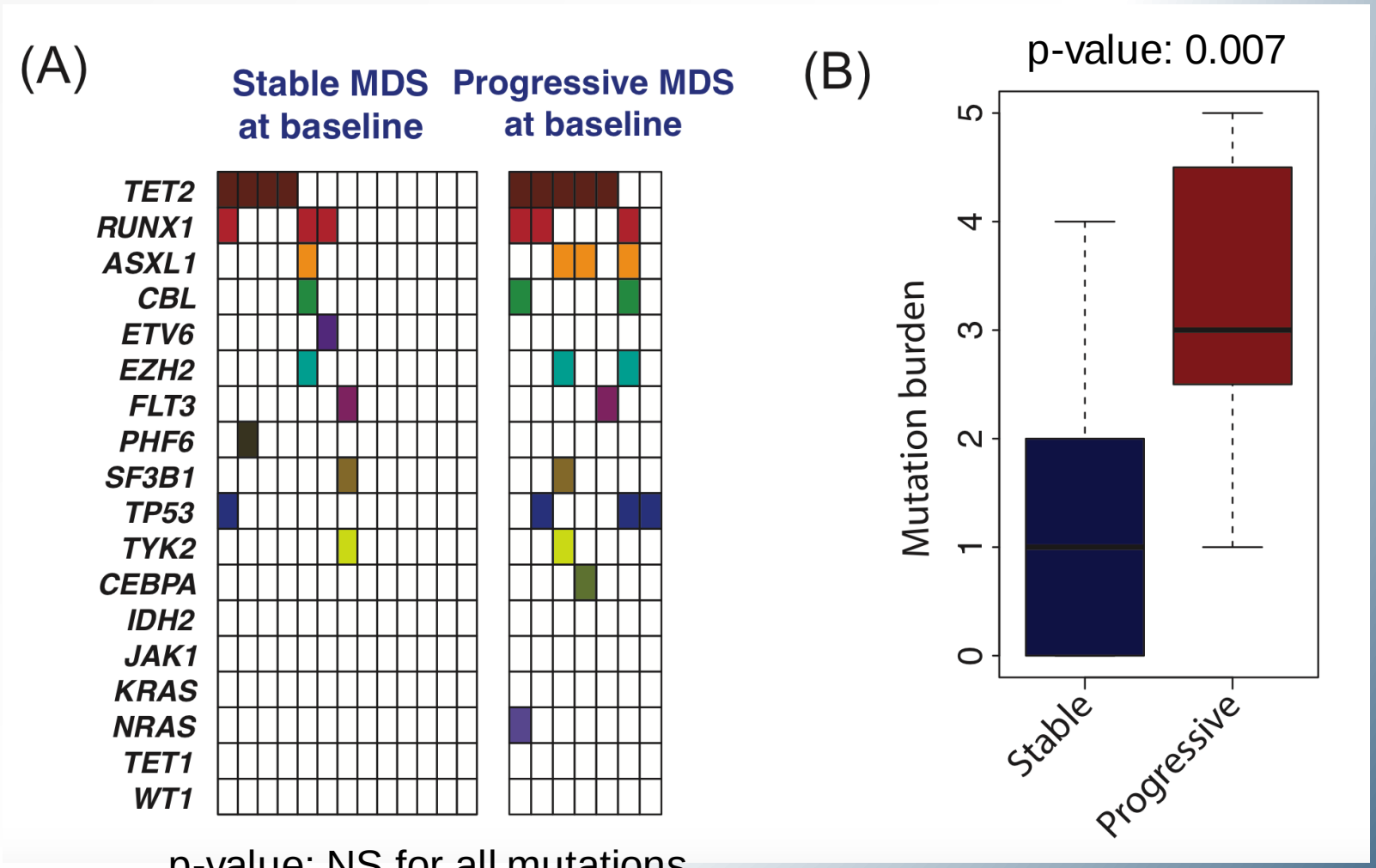


Can epigenetic profiles help explain biology and predict clinical outcome in low-risk MDS?



SYLVESTER COMPREHENSIVE CANCER CENTER

Progressive MDS presents with a higher mutational burden at diagnosis

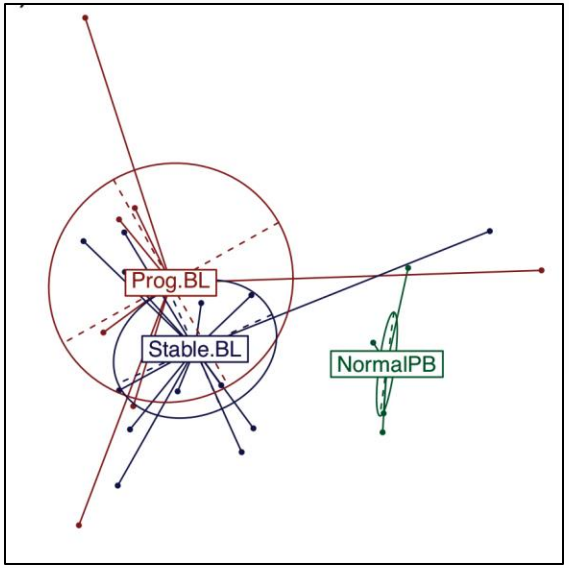


SYLVESTER COMPREHENSIVE CANCER CENTER

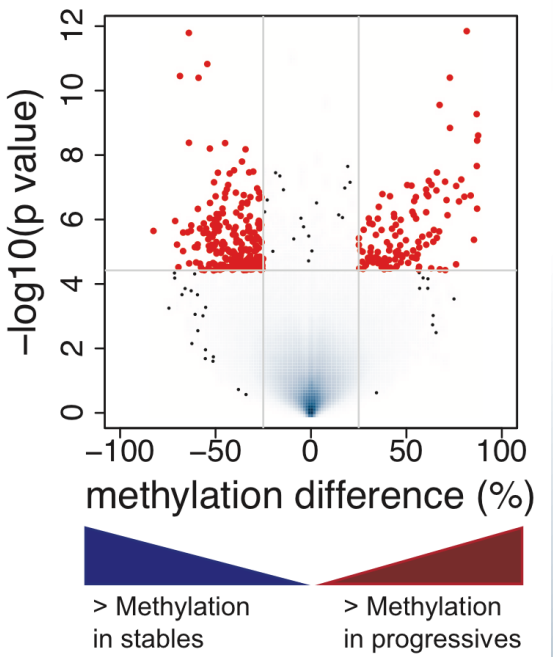
T. Qin et al. Leukemia 2019

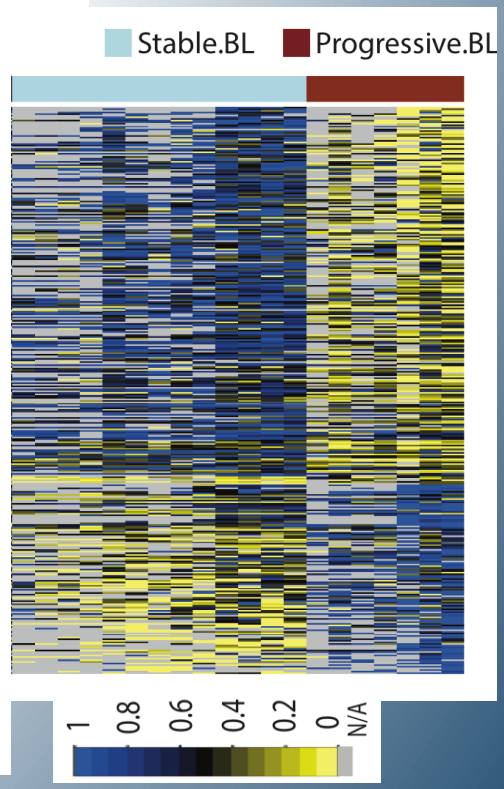
Epigenetic differences at diagnosis correlate with disease progression in low risk MDS

Unsupervised analysis



Supervised analysis



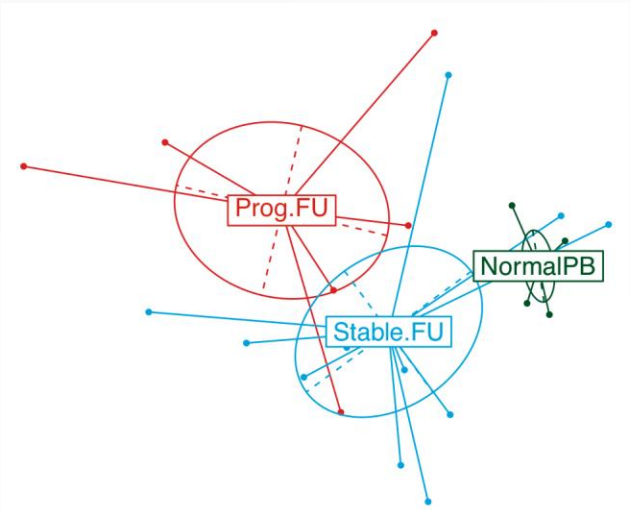


SYLVESTER COMPREHENSIVE CANCER CENTER

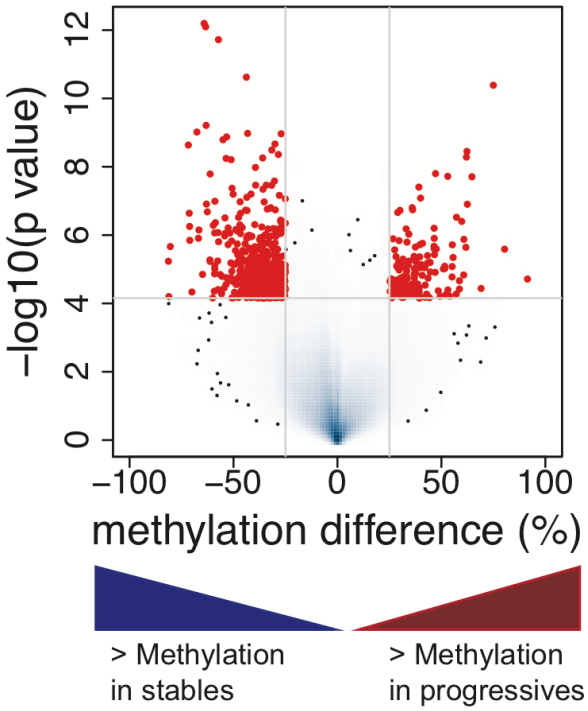
T. Qin et al. Leukemia 2019

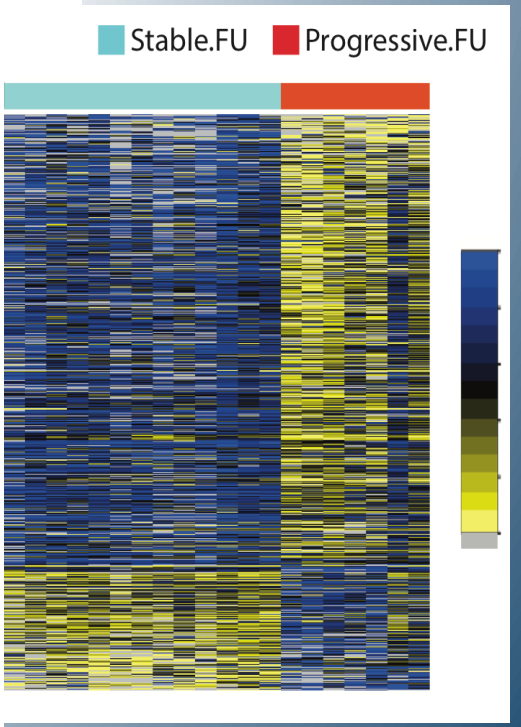
Epigenetic distances increase with disease progression

Unsupervised analysis



Supervised analysis

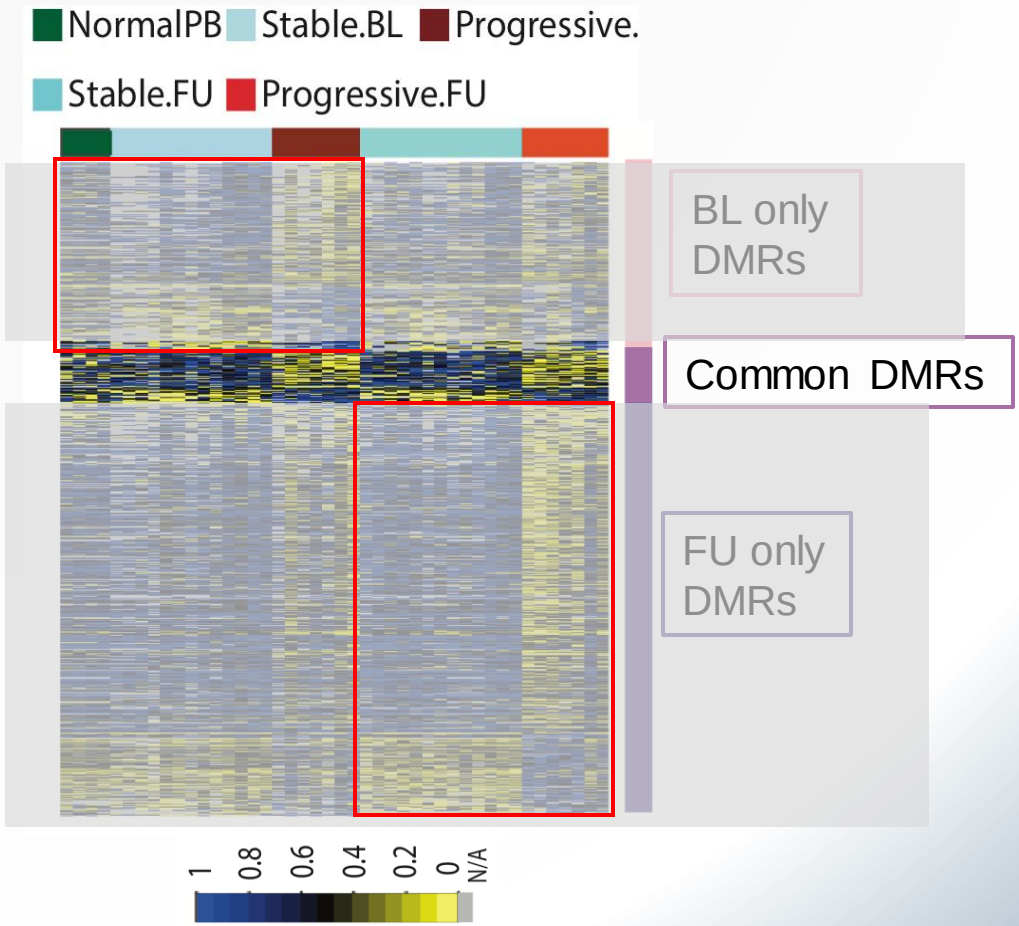


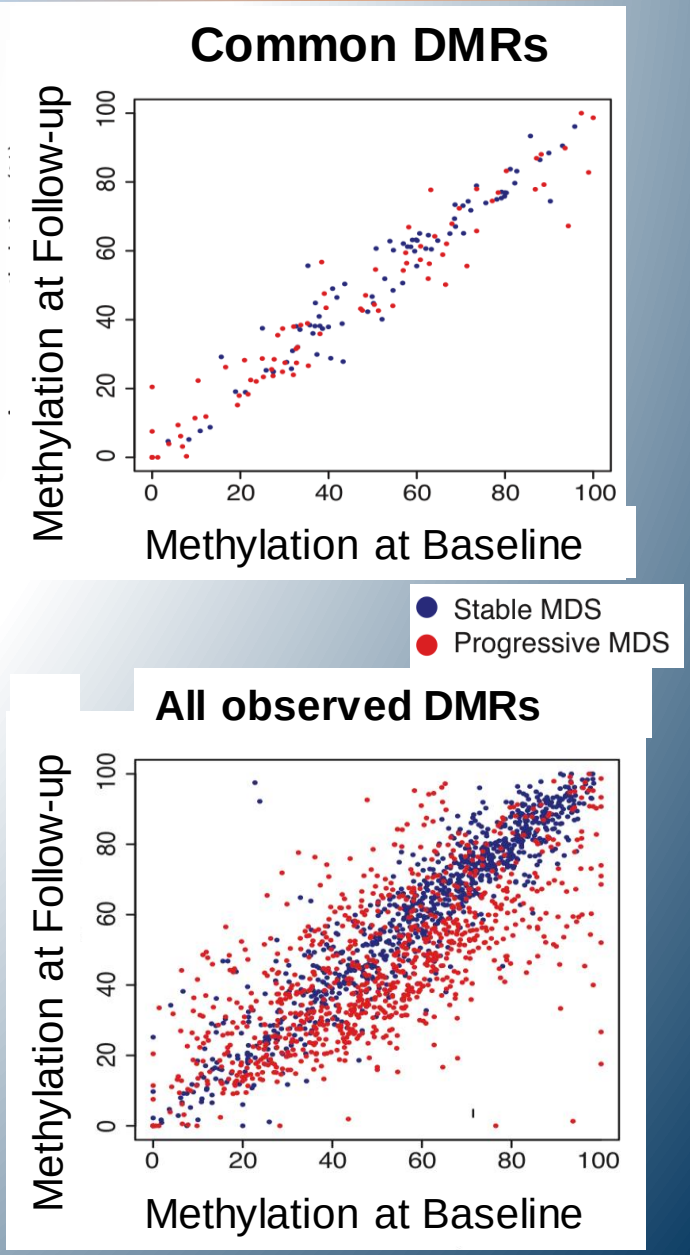


SYLVESTER COMPREHENSIVE CANCER CENTER

T. Qin et al. Leukemia 2019

Progressive MDS shows greater epigenetic variability





T. Qin et al. Leukemia 2019

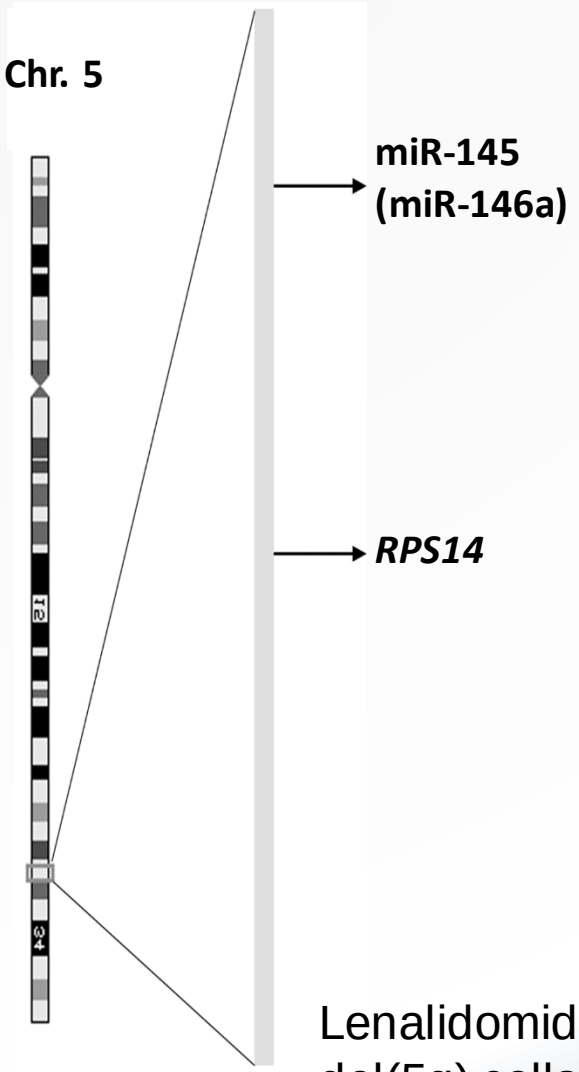
SUMMARY I

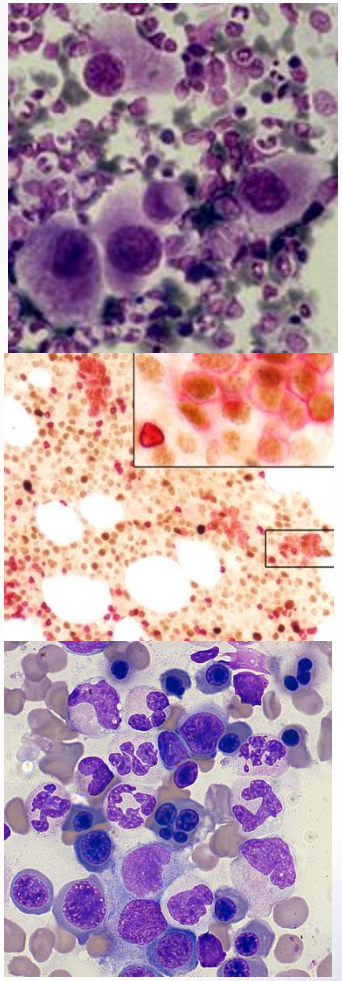
- ✓ Low-risk MDS is epigenetically heterogeneous
- ✓ DNA methylation profiles and mutational burden at diagnosis correlate with clinical evolution
- ✓ These differences have the potential to be harnessed as clinical biomarkers predictive of outcome
- ✓ Progression of low-risk MDS to greater marrow failure correlates with increased epigenetic variability; this may reflect the appearance of competing clones rather than the emergence of a single dominant clone

Myelodysplastic syndromes: what does precision medicine look like?

- Assess diagnosis
- (Define pathogenesis of the disease)
- Define the natural history of disease
- Define response to therapy
- Determine duration or intensity of therapy
- **Determine choice of therapy**
- Be a target for therapy

del(5q) MDS: caused by gene haploinsufficiency





Loss of a micro RNA and thrombocytosis
Starczynowski et al. Nat Med. 2010 Jan;16(1):49-58.

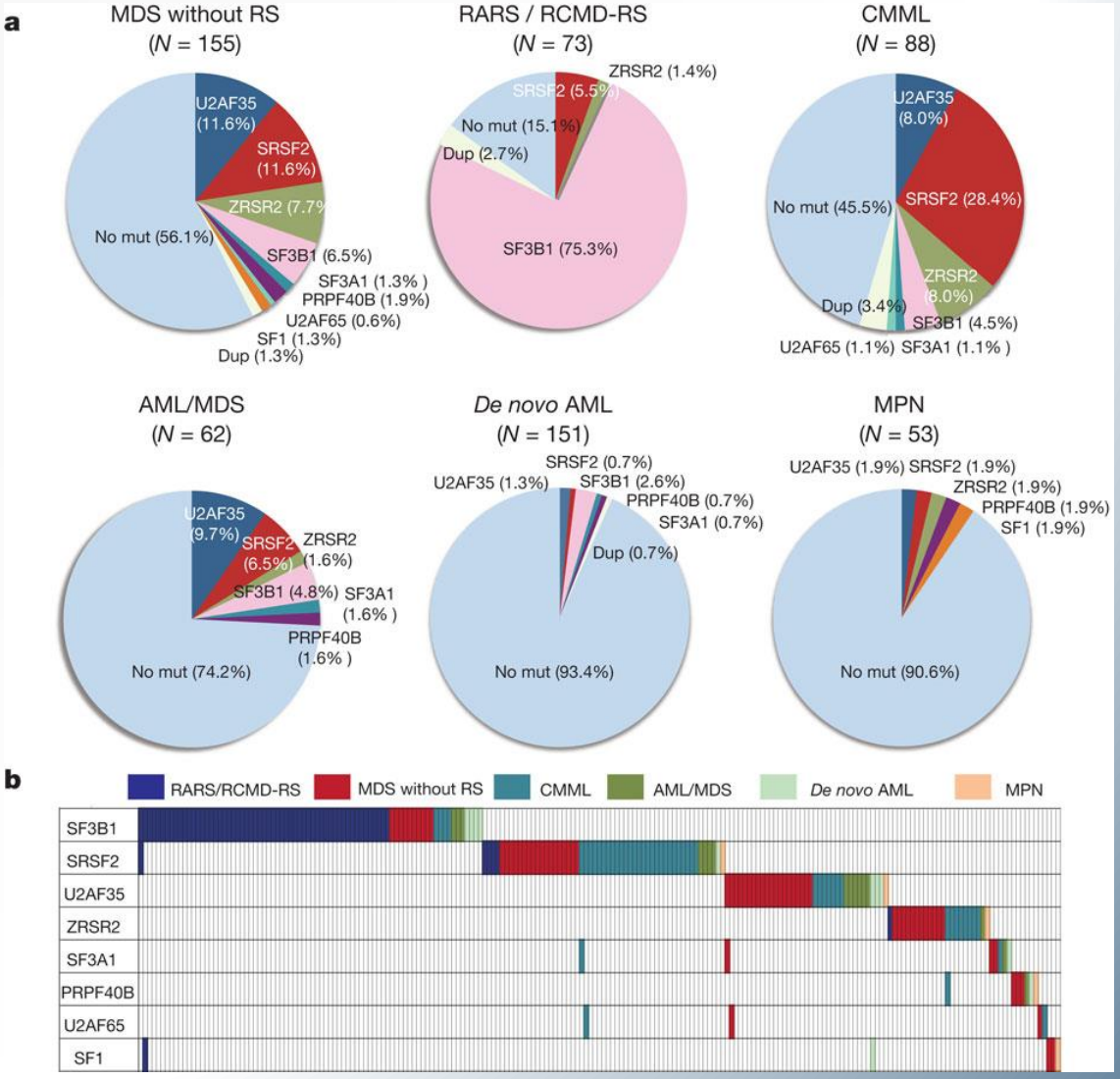
Coordinate loss of a microRNA and protein-coding gene cooperate in the pathogenesis of 5q- syndrome
Kumar et al. Blood. 2011 Oct 27;118(17):4666-73

Activation of p53 and apoptosis of immature red cells
Barlow et al. Nat Med. 2010 Jan;16(1):59-66
Pellagatti et al. Blood. 2010 Apr 1;115(13):2721-3
Dutt et al. Blood. 2011 Mar 3;117(9):2567-76

Haploinsufficiency of *RPS14* phenocopies the disease in normal hematopoietic progenitor cells
Ebert et al. Nature. 2008;451(7176):335-9

Lenalidomide triggers ubiquitination and degradation of CSNK1A1 ; del(5q) cells have one copy of *CSNK1A1;* they are selectively depleted

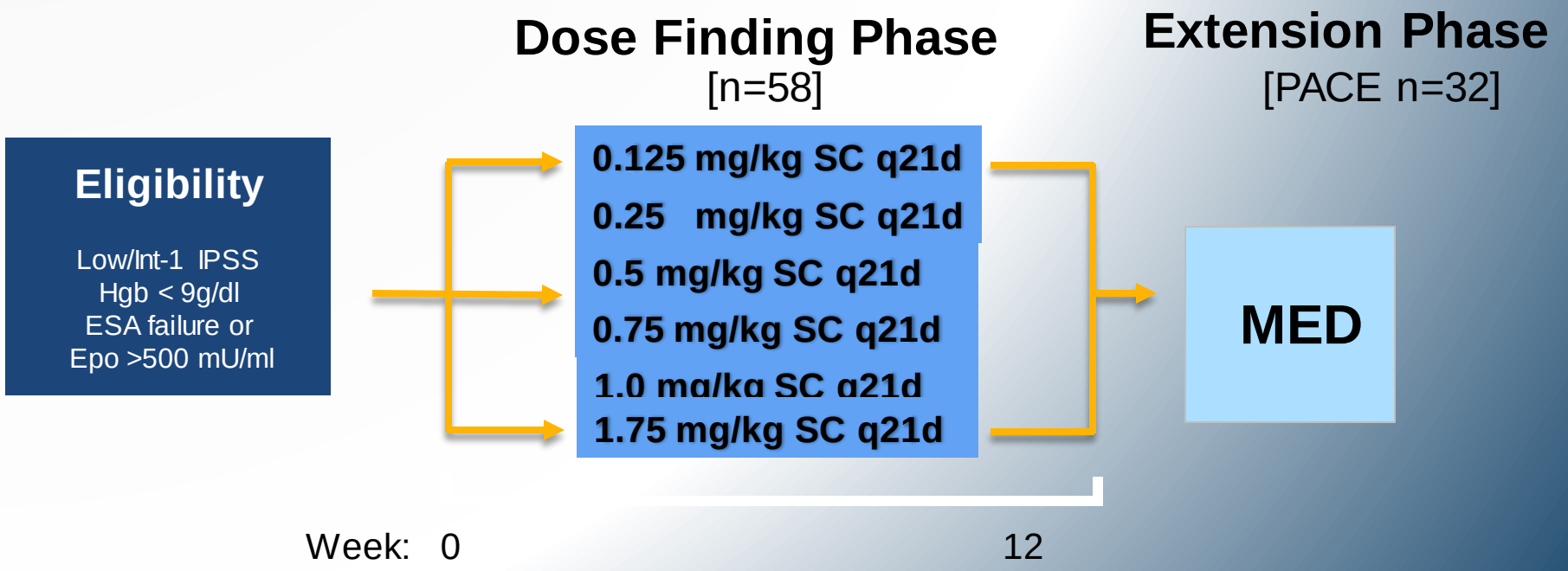
Spliceosome gene mutations in myeloid neoplasms



Yoshida et al. Nature. 2011 478:64-9

Luspatercept for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes (PACE-MDS): a multicentre, open-label phase 2 dose-finding study with long-term extension study

Uwe Platzbecker*, Ulrich Germing*, Katharina S Götze*, Philipp Kiewe*, Karin Mayer*, Jörg Chromik*, Markus Radsak*, Thomas Wolff*, Xiaosha Zhang, Abderrahmane Laadem, Matthew L Sherman, Kenneth M Attie, Aristoteles Giagounidis*



Principal Objective: LTB: Low transfusion burden (<4U/8wk, Hb<10): Hb increase ≥ 1.5 g/dL; HTB: High transfusion burden (≥4U/8wk): 4U or 50% decrease U/8wk

MEDALIST: Phase 3 Randomized Double-blind Study of Luspatercept vs Placebo in Transfusion-Dependent LR-MDS With Ring Sideroblasts [ACE-536-MDS-001]

ACCELERON

Previous Release | Next Release

Jun 1, 2017

Celgene and Acceleron Complete Target Enrollment in the MEDALIST and BELIEVE Phase 3 Studies of Luspatercept in Myelodysplastic Syndromes and Beta-Thalassemia

- Companies expect to report top-line results from the Phase 3 studies in mid-2018 -

SUMMIT, N.J. & CAMBRIDGE, Ma.--(BUSINESS WIRE)-- Celgene Corporation (NASDAQ: CELG) and Acceleron Pharma Inc. (NASDAQ: XLRN) today announced that they have completed target enrollment in the MEDALIST and BELIEVE Phase 3 studies of luspatercept in patients with myelodysplastic syndromes (MDS) and beta-thalassemia. The Companies expect to report top-line results from the clinical trials in the middle of 2018. Luspatercept is being developed to treat a range of hematologic diseases including MDS, beta-thalassemia, and myelofibrosis as part of a global collaboration between Acceleron and Celgene.

Eligibility: Non-del(5q) MDS with ≥15% RS, VL-Int. IPSS-R, □ 2 U PRBC/8 wks, prior ESA
Key Exclusions: Prior treatment with IMiDs, azanucleosides or IST; ANC < 500, plat<50K
Stratification: RBC transfusion burden (< 6 vs ≥6 U/8wk), IPSS-R VL/Low vs. Int.
Primary end-point: Transfusion Independence x ≥ 8 weeks

Myelodysplastic syndromes: what does precision medicine look like? How has it evolved?

- Assess diagnosis
- (Define pathogenesis of the disease)
- Define the natural history of disease
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- Be a target for therapy

Cancer Cell
Article

Leukemic IDH1 and IDH2 Mutations Result in a Hypermethylation Phenotype, Disrupt TET2 Function, and Impair Hematopoietic Differentiation

Maria E. Figueroa,[1,12] Omar Abdel-Wahab,[2,3,12] Chao Lu,[4,12] Patrick S. Ward,[4] Jay Patel,[2] Alan Shih,[2,3] Yushan Li,[1] Neha Bhagwat,[2] Aparna Vasanthakumar,[5] Hugo F. Fernandez,[6] Martin S. Tallman,[3] Zhuoxin Sun,[7] Kristy Wolniak,[8] Justine K. Peeters,[9] Wei Liu,[10] Sung E. Choe,[10] Valeria R. Fantin,[10] Elisabeth Paietta,[11] Bob Löwenberg,[9] Jonathan D. Licht,[8] Lucy A. Godley,[5] Ruud Delwel,[9] Peter J.M. Valk,[9] Craig B. Thompson,[4,*] Ross L. Levine,[2,3,*] and Ari Melnick[1,*]

[1]Division of Hematology/Oncology, Weill Cornell Medical College, New York, NY 10065, USA

[2]Human Oncology and Pathogenesis Program

Significance

Aberrant epigenetic programming is a hallmark of cancer and yet very little is known concerning the mechanisms through which this occurs. Here we demonstrate that leukemic neomorphic mutations of the citrate metabolism genes *IDH1* and *IDH2* that generate the aberrant metabolite 2HG induce DNA hypermethylation and impair differentiation in hematopoietic cells. These effects are caused in part through inhibition of TET2, a DNA demethylase enzyme also mutated in leukemia. IDH1/2- and TET2-mutant primary AML cells displayed a similar defect in epigenetic programming consisting of global hypermethylation and a gene-specific methylation signature. This work identifies IDH1/2- and TET2-mutant leukemias as a biologically distinct disease subtype, and links cancer metabolism with epigenetic control of gene expression.

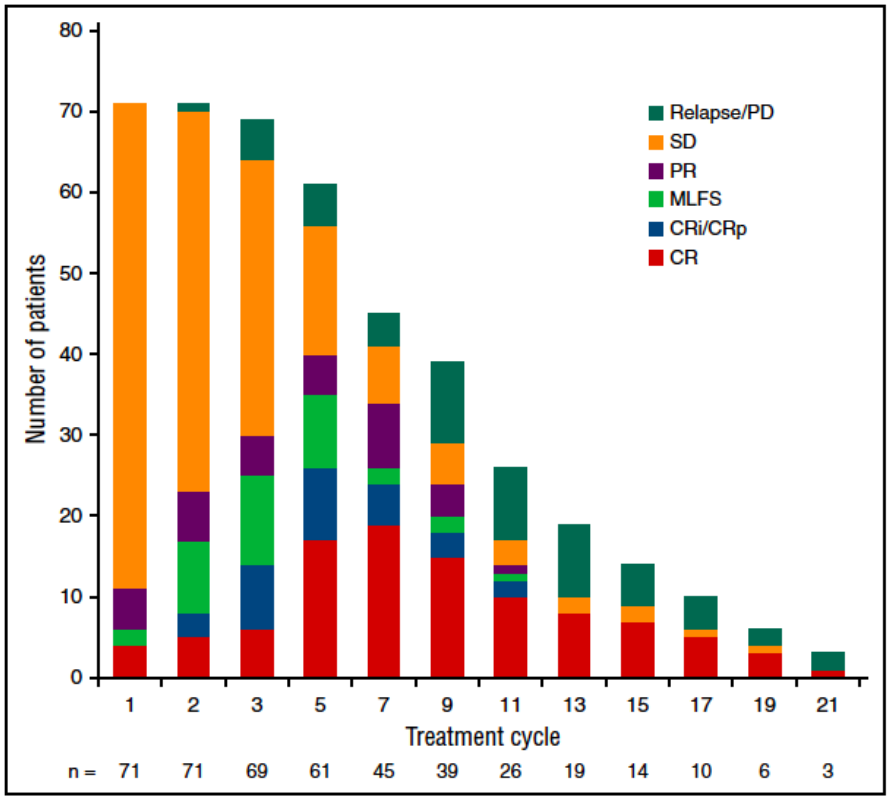
Regular Article

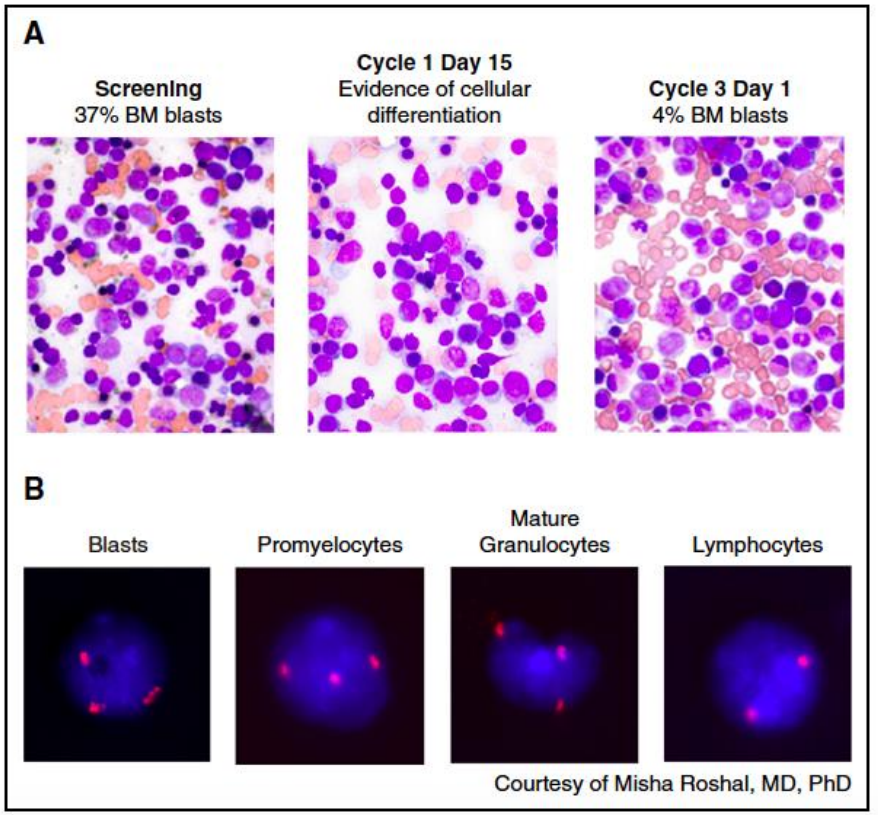
blood

CLINICAL TRIALS AND OBSERVATIONS

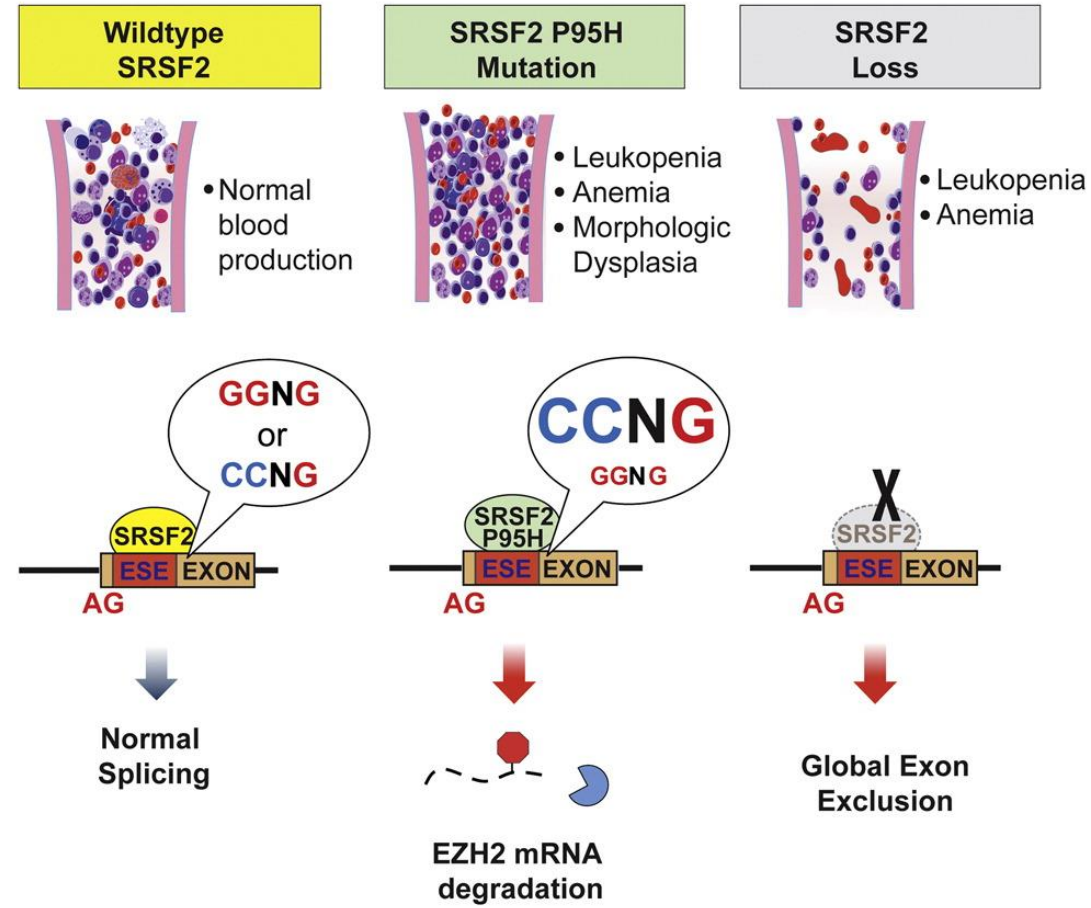
Enasidenib in mutant *IDH2* relapsed or refractory acute myeloid leukemia

Eytan M. Stein,[1,2,*] Courtney D. DiNardo,[3,*] Daniel A. Pollyea,[4] Amir T. Fathi,[5,6] Gail J. Roboz,[2,7] Jessica K. Altman,[8] Richard M. Stone,[9] Daniel J. DeAngelo,[9] Ross L. Levine,[1] Ian W. Flinn,[10] Hagop M. Kantarjian,[3] Robert Collins,[11] Manish R. Patel,[12] Arthur E. Frankel,[11] Anthony Stein,[13] Mikkael A. Sekeres,[14] Ronan T. Swords,[15] Bruno C. Medeiros,[16] Christophe Willekens,[17,18] Paresh Vyas,[19,20] Alessandra Tosolini,[21] Qiang Xu,[21] Robert D. Knight,[21] Katharine E. Yen,[22] Sam Agresta,[22] Stephane de Botton,[17,18,†] and Martin S. Tallman[1,2,†]



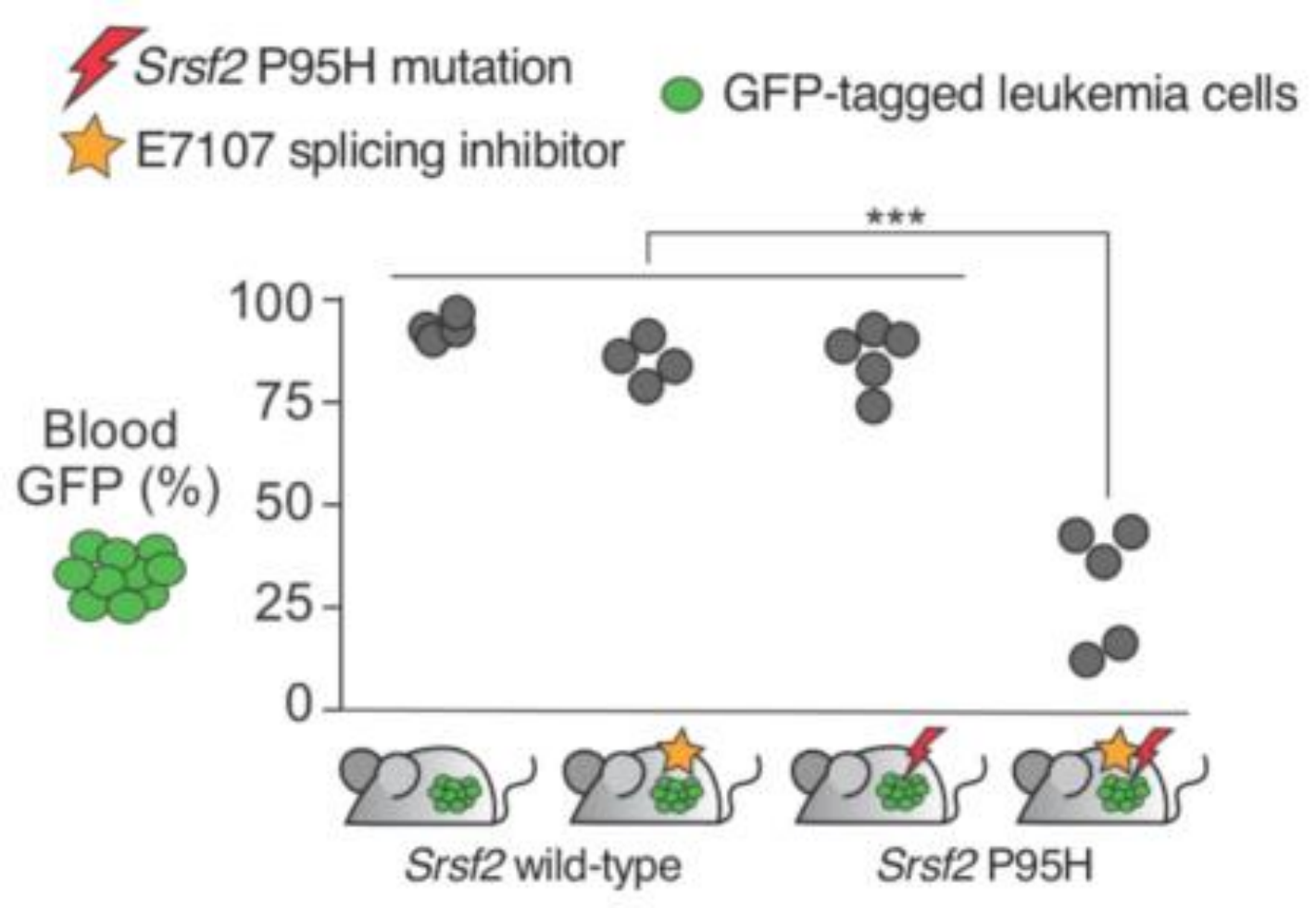


SRSF2 Mutations Contribute to Myelodysplasia by Mutant-Specific Effects on Exon Recognition

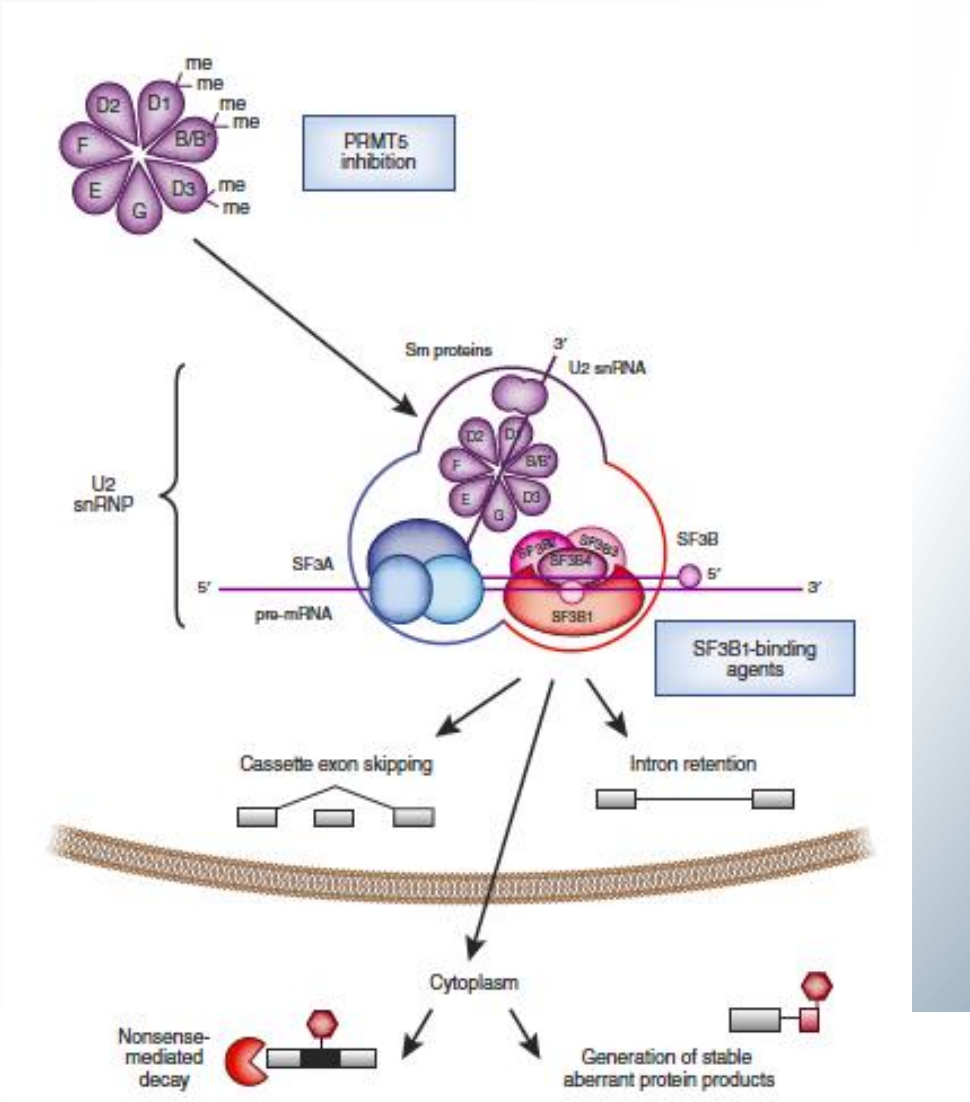


E Kim et al, Cancer Cell 2015 27, 617-630

E7107 splicing inhibitor



Interfering with RNA splicing



nature medicine

Therapeutic targeting of splicing in cancer

Stanley Chun-Wei Lee[1] & Omar Abdel-Wahab[1,2]

Myelodysplastic syndromes: what does precision medicine look like? How has it evolved?

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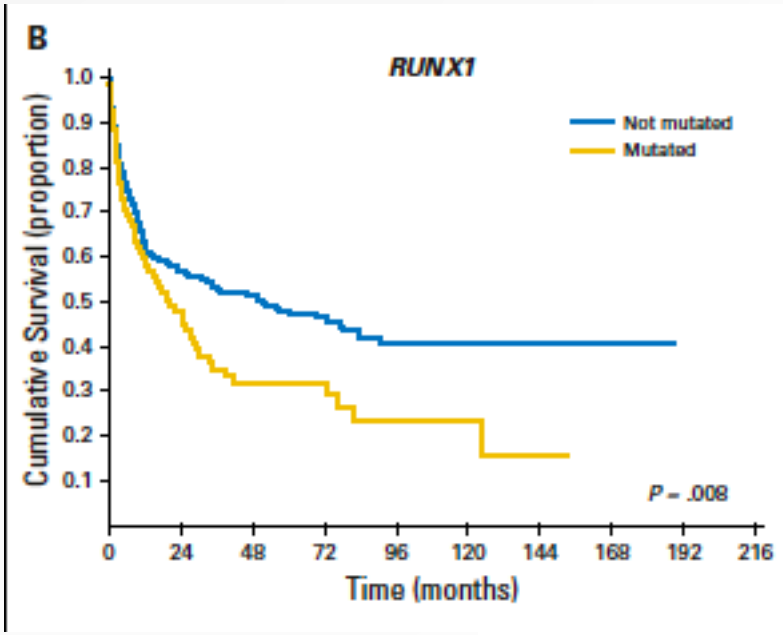
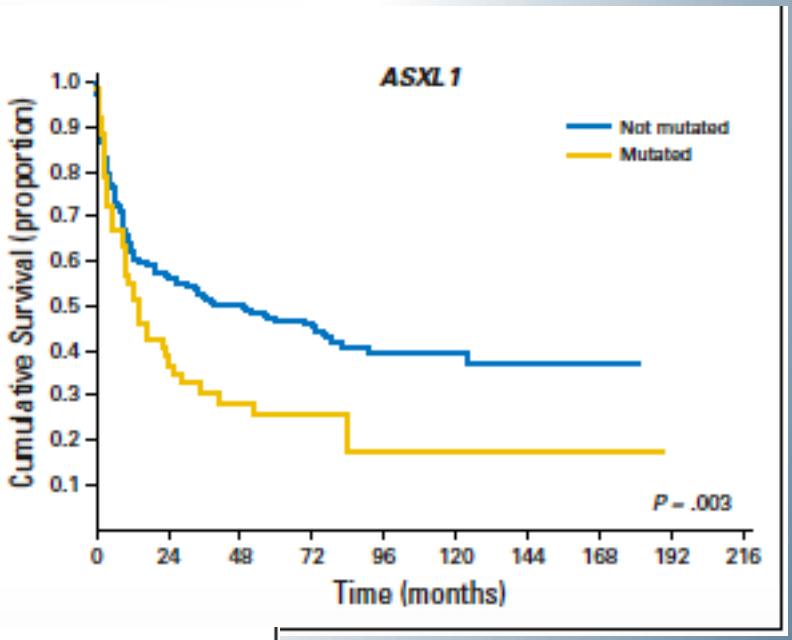
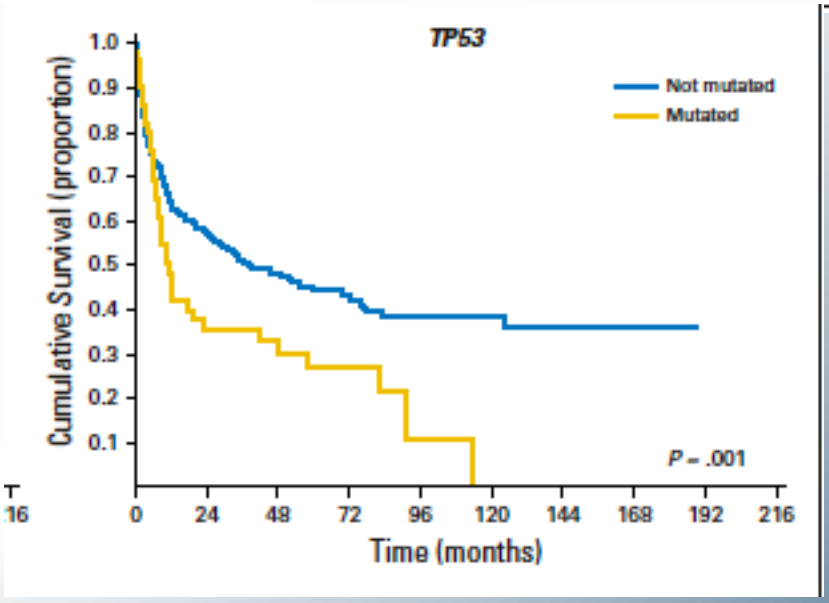
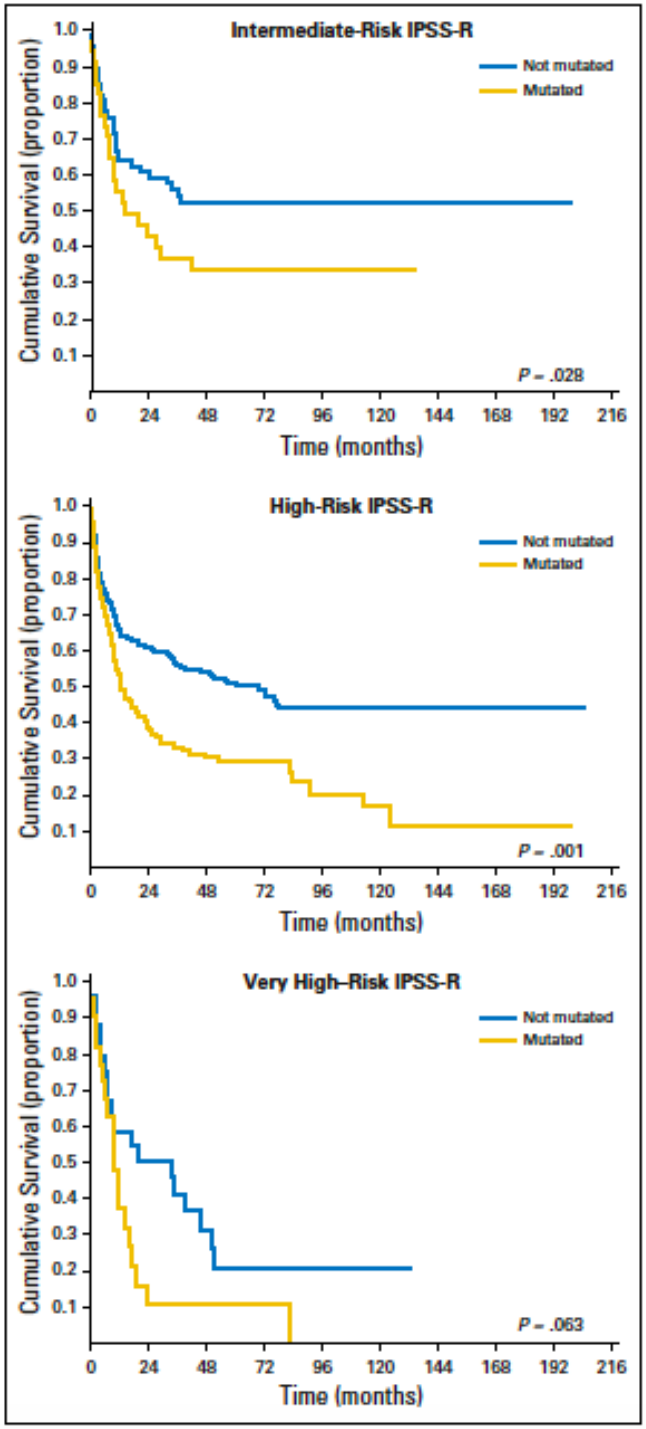
Allotransplantation outcomes based on mutational status







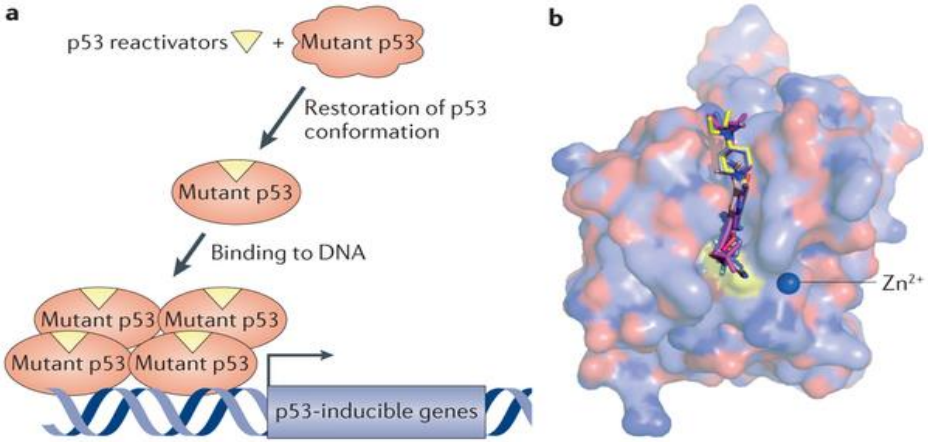
MG Della Porta
et al JCO 2016



Allotransplant outcomes based on mutational status

MG Della Porta et al JCO 2016

APR-246 (PRIMA^{MET}) Restores WTp53 Function



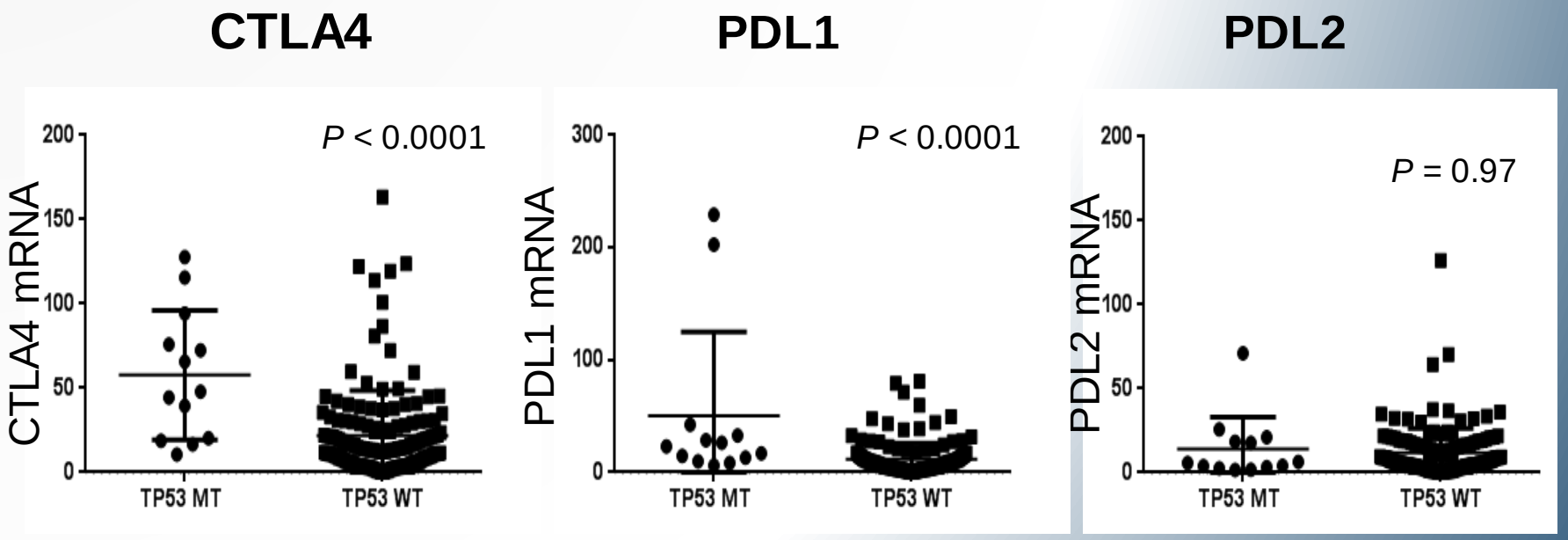
Khoo et al., Nature Reviews Drug Discovery; 2014

Phase I/II study of APR-246 with Aza in *TP53* mutant MDS or AML

TP53 mutant MDS/AML → **APR d1-4 iv AZA d4-10** → **Response** Continue APR + AZA

Week: 0 — Cycle q 28d x 6 — 24

TP53 mutations assoc. w CTLA4 & PDL1 expression



The Cancer Genome Atlas (TCGA) data set for AML.

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TP5
ukemia

J.S. Welch, A.A. Pett
B. Tandon, Y.-S. L
K.E. Stockerl-Gol
K. Luber, M.R. Jan
J.D. Baty, E.J. Duncavage,
. Romee, T.A. Fehniger,
I.A. Jacoby, S.E. Heath,
. Graubert, M.J. Walter,

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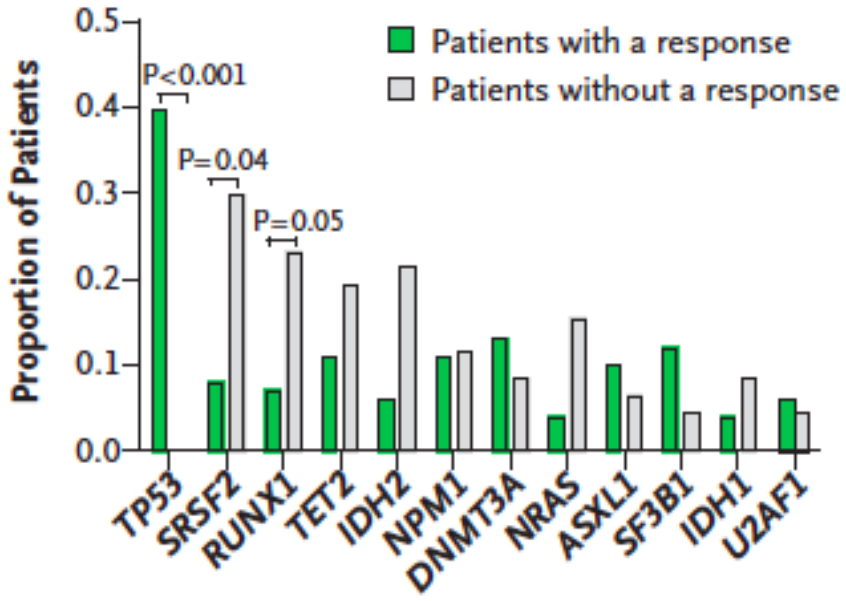


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mutation Clearance after Transplantation for Myelodysplastic Syndrome

E.J. Duncavage, M.A. Jacoby, G.S. Chang, C.A. Miller, N. Edwin, J. Shao, K. Elliott, J. Robinson, H. Abel, R.S. Fulton, C.C. Fronick, M. O'Laughlin, S.E. Heath, K. Brendel, R. Saba, L.D. Wartman, M.J. Christopher, I. Pusic, J.S. Welch, G.L. Uy, D.C. Link, J.F. DiPersio, P. Westervelt, T.J. Ley, K. Trinkaus, T.A. Graubert, and M.J. Walter

ABSTRACT

BACKGROUND

Allogeneic hematopoietic stem-cell transplantation is the only curative treatment for patients with myelodysplastic syndrome (MDS). The molecular predictors of disease progression after transplantation are unclear.

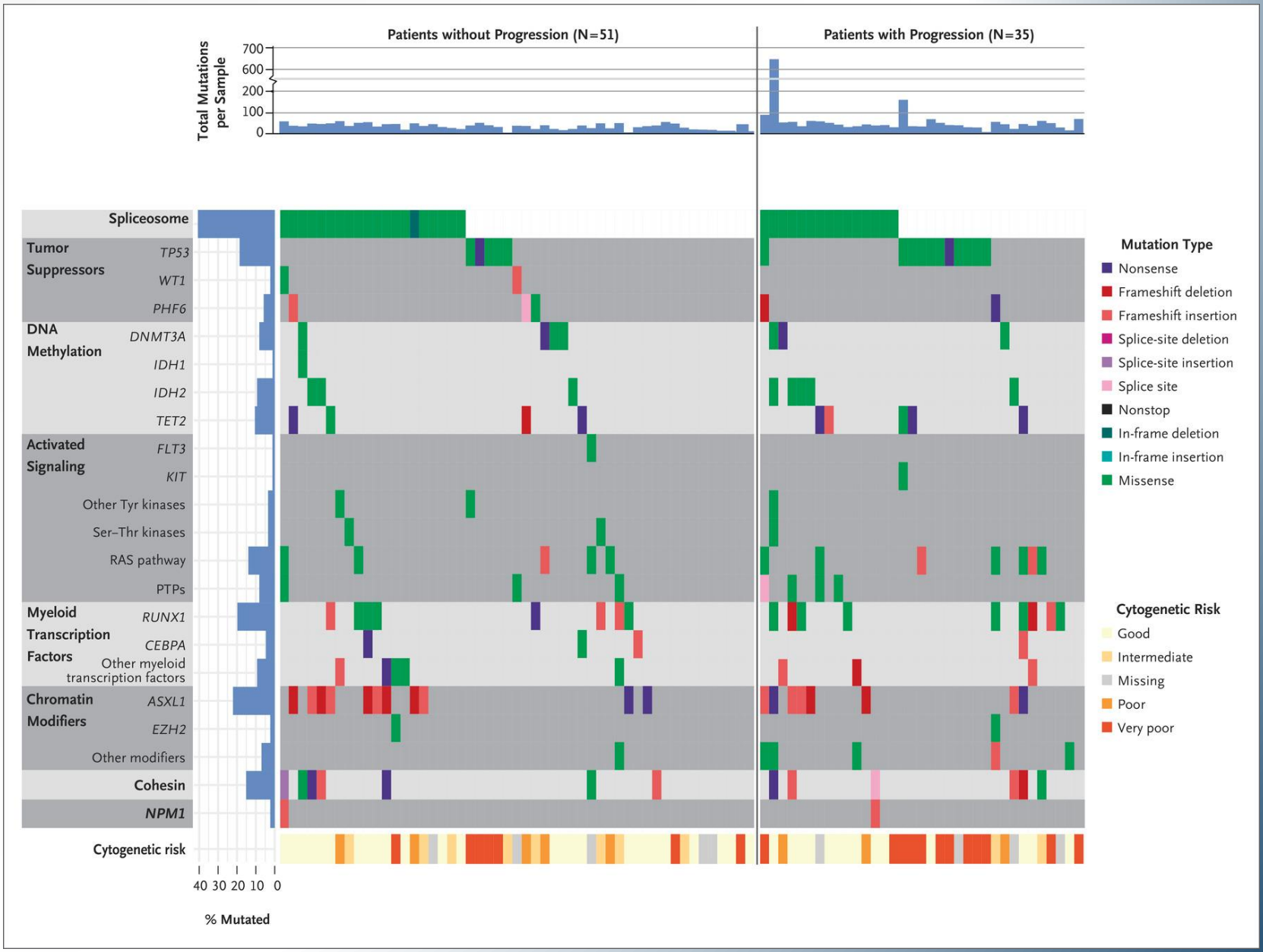
METHODS

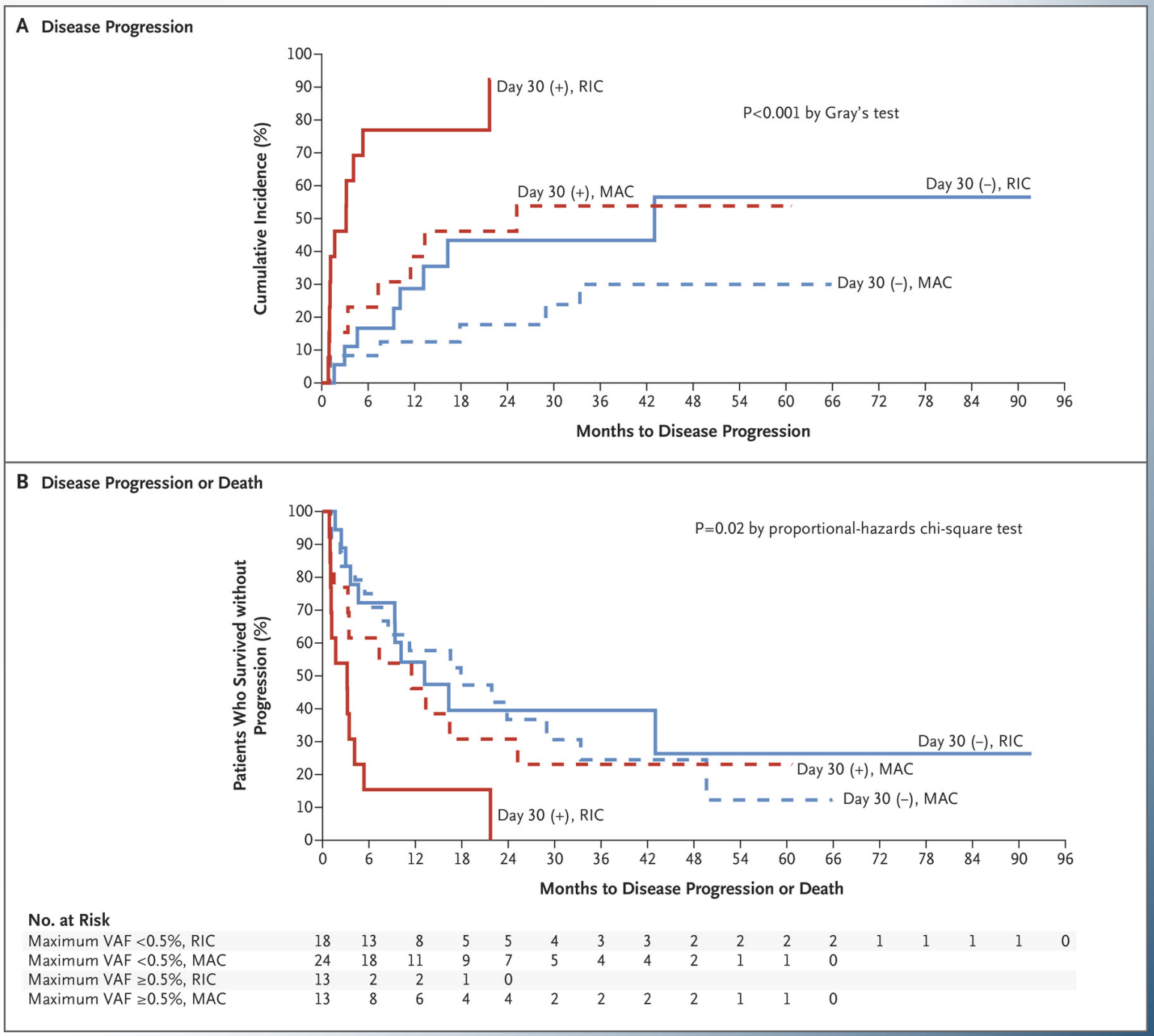
We sequenced bone marrow and skin samples from 90 adults with MDS who underwent allogeneic hematopoietic stem-cell transplantation after a myeloablative or reduced-intensity conditioning regimen. We detected mutations before transplantation using enhanced exome sequencing, and we evaluated mutation clearance by using error-corrected sequencing to genotype mutations in bone marrow samples obtained 30 days after transplantation. In this exploratory study, we evaluated the association of a mutation detected after transplantation with disease progression and survival.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Walter at the Washington University School of Medicine in St. Louis, 660 S. Euclid Ave., Campus Box 8007, St. Louis, MO 63110, or at mjwalter@wustl.edu.

Drs. Duncavage, Jacoby, and Chang contributed equally to this article.

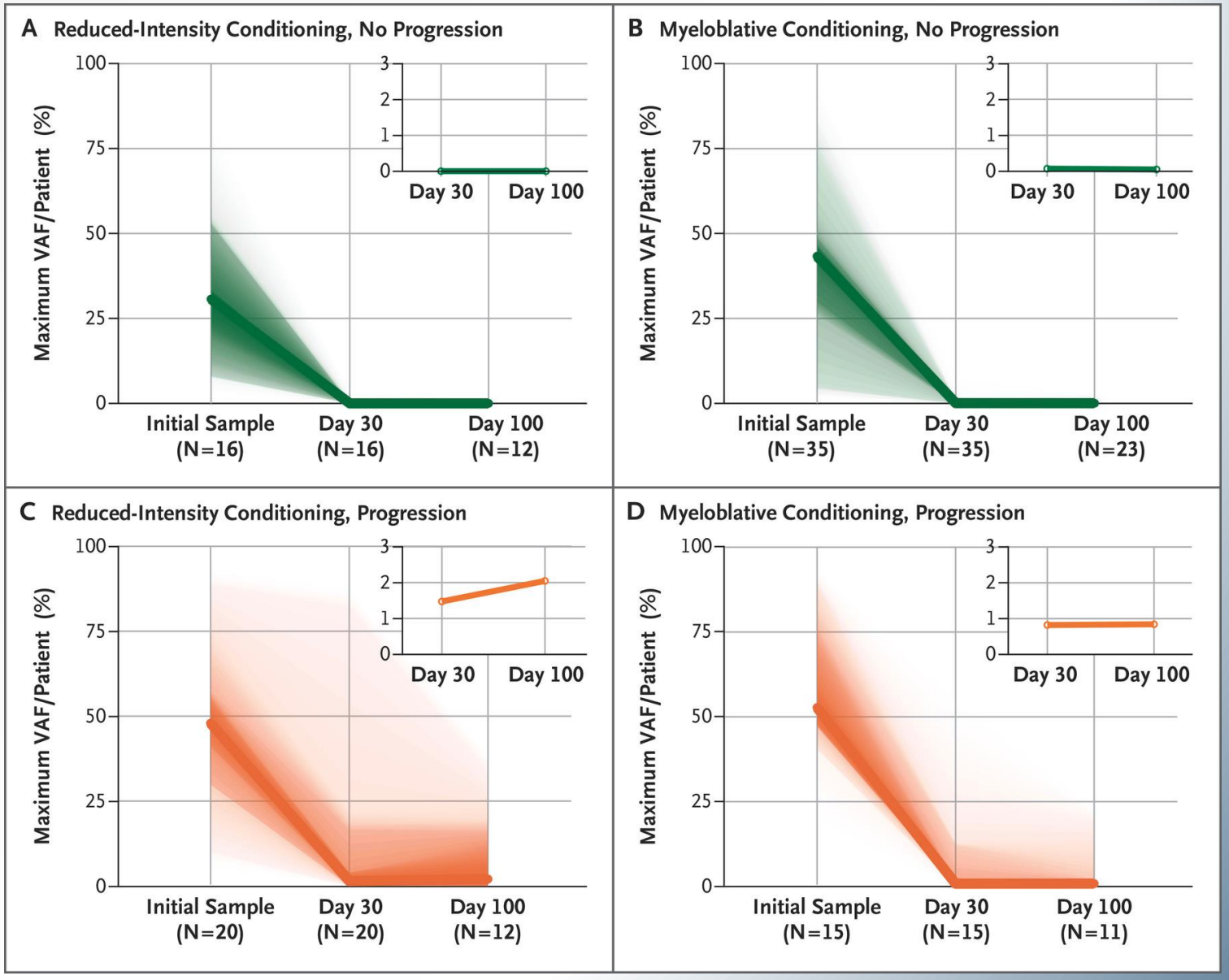
N Engl J Med 2018;379:1028-41.
DOI: 10.1056/NEJMoa1804714


Patients without Progression (N=51)
Patients with Progression (N=35)
Total Mutations per Sample
700
600
200
100
0
Spliceosome
Tumor Suppressors
TP53
WT1
PHF6
DNA Methylation
DNMT3A
IDH1
IDH2
TET2
Activated Signaling
FLT3
KIT
Other Tyr kinases
Ser–Thr kinases
RAS pathway
PTPs
Myeloid Transcription Factors
RUNX1
CEBPA
Other myeloid transcription factors
Chromatin Modifiers
ASXL1
EZH2
Other modifiers
Cohesin
NPM1
Cytogenetic risk
40 30 20 10 0
% Mutated
Mutation Type
Nonsense
Frameshift deletion
Frameshift insertion
Splice-site deletion
Splice-site insertion
Splice site
Nonstop
In-frame deletion
In-frame insertion
Missense
Cytogenetic Risk
Good
Intermediate
Missing
Poor
Very poor



No. at Risk

Maximum VAF <0.5%, RIC	18	13	8	5	5	4	3	3	2	2	2	2	1	1	1	1	0
Maximum VAF <0.5%, MAC	24	18	11	9	7	5	4	4	2	1	1	0					
Maximum VAF ≥0.5%, RIC	13	2	2	1	0												
Maximum VAF ≥0.5%, MAC	13	8	6	4	4	2	2	2	2	1	1	0					



Post-transplant HMA therapy?

Myelodysplastic syndromes
-key questions to address-

- **What is the basis for the impaired differentiation seen in MDS patients?**
- **What accounts for the increased cell death in MDS bone marrow?**
- **What is the basis for the clonal dominance of MDS stem cells over the normal HSCs?**
- **What accounts for the progressive cytopenias in MDS?**
- **Why is lenalidomide so effective in RBC transfusion dependent 5q- MDS?**
- **How do 5-azacytidine and decitabine work in MDS?**
- **How much of the disease relates to aberrant immunity and an abnormal microenvironment?**

Are there good targets for alloreactive immune cells?

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