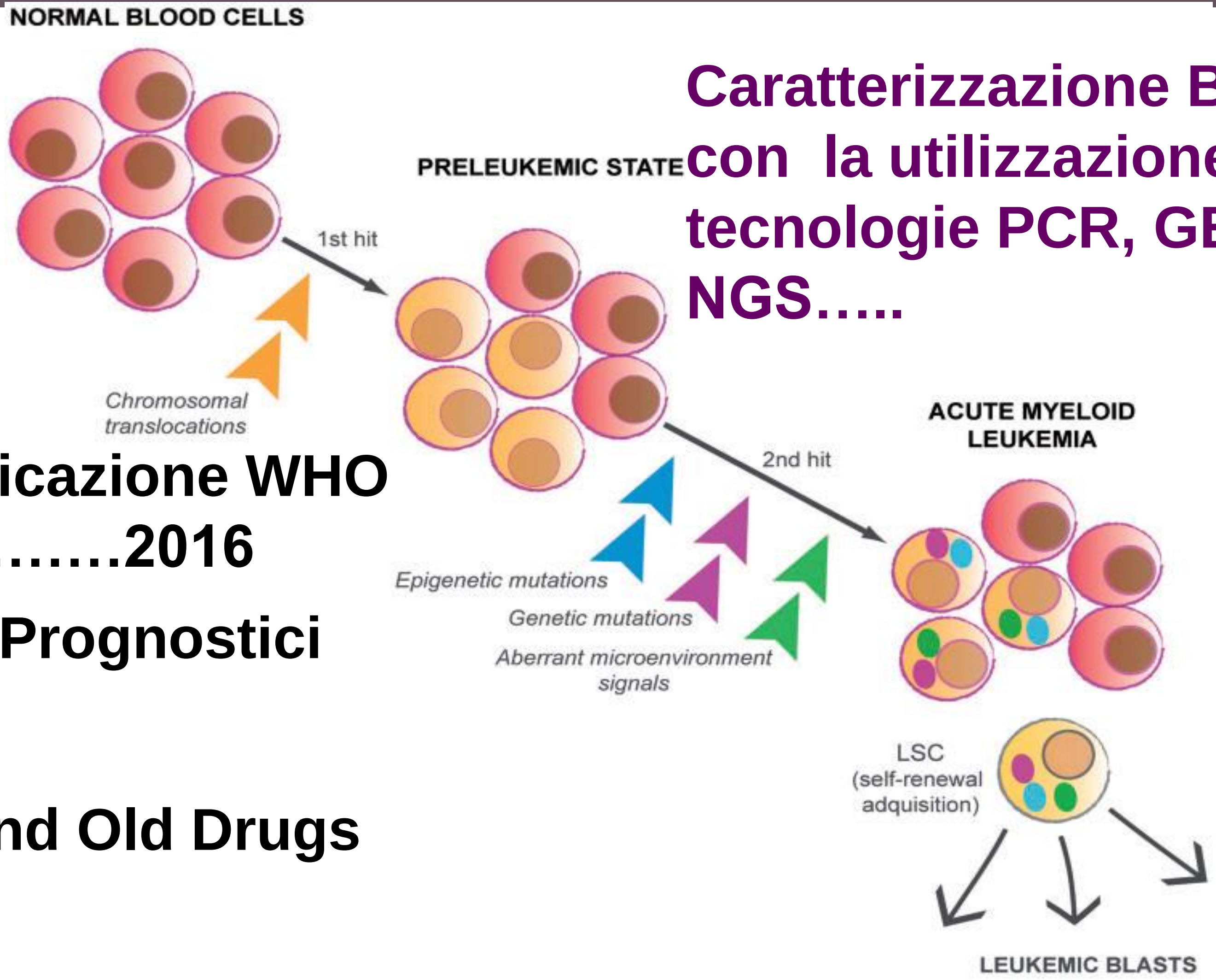
Dal 2008 al…



Caratterizzazione Biologica con la utilizzazione delle tecnologie PCR, GEP, NGS…..

- ✓**Classificazione WHO 2008…………2016**
- ✓**Score Prognostici ELN…**
- ✓**New and Old Drugs**

WILMS' TUMOR GENE MUTATIONS IN CHILDHOOD AML: CHARACTERISTICS, PROGNOSTIC VALUE AND CONSEQUENCES FOR MRD DETECTION (Hollink et al, #457)

AMONAFIDE: A TOPO II INHIBITOR WITH NOVEL PHARMACOLOGICAL PROPERTIES AND UNIQUE ACTIVITY FOR THE TREATMENT OF SEC. AML (Capizzi et al, #890)

PHASE II STUDY OF SINGLE AGENT CLOFARABINE IN UNTREATED ELDERLY PATIENTS WITH AML UNLIKELY TO BENEFIT FROM STANDARD INDUCTION CHEMOTHERAPY (Erba et al, #892)

The molecular basis of AML

K.L. Rice

Genetic markers in relations to the therapeutic management

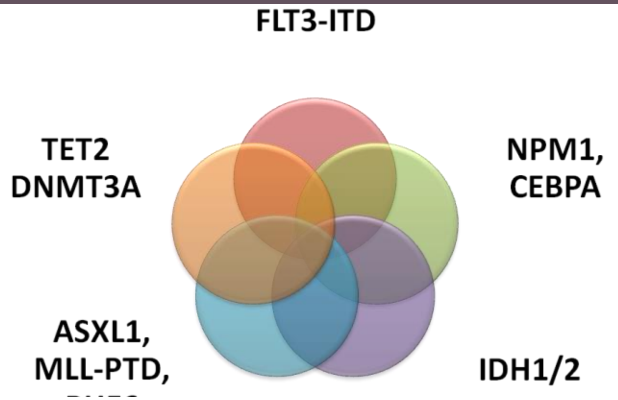
B. Lowenberg,

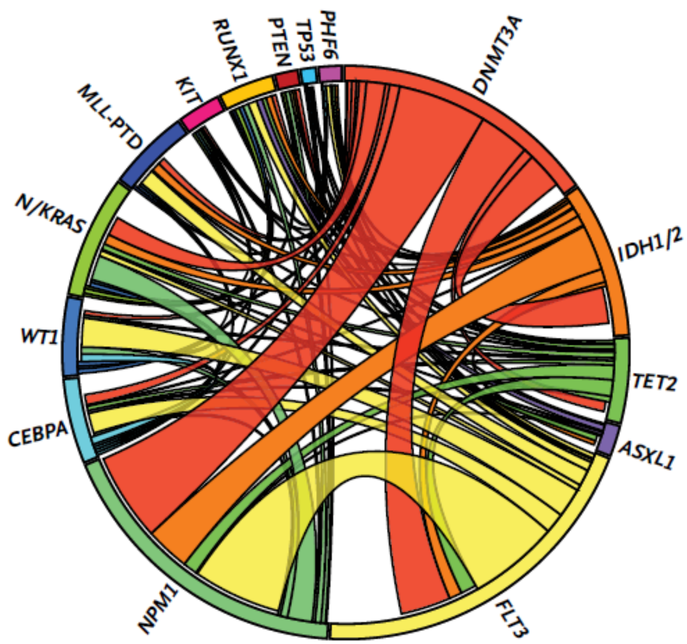
The NEW ENGLAND JOURNAL of MEDICINE

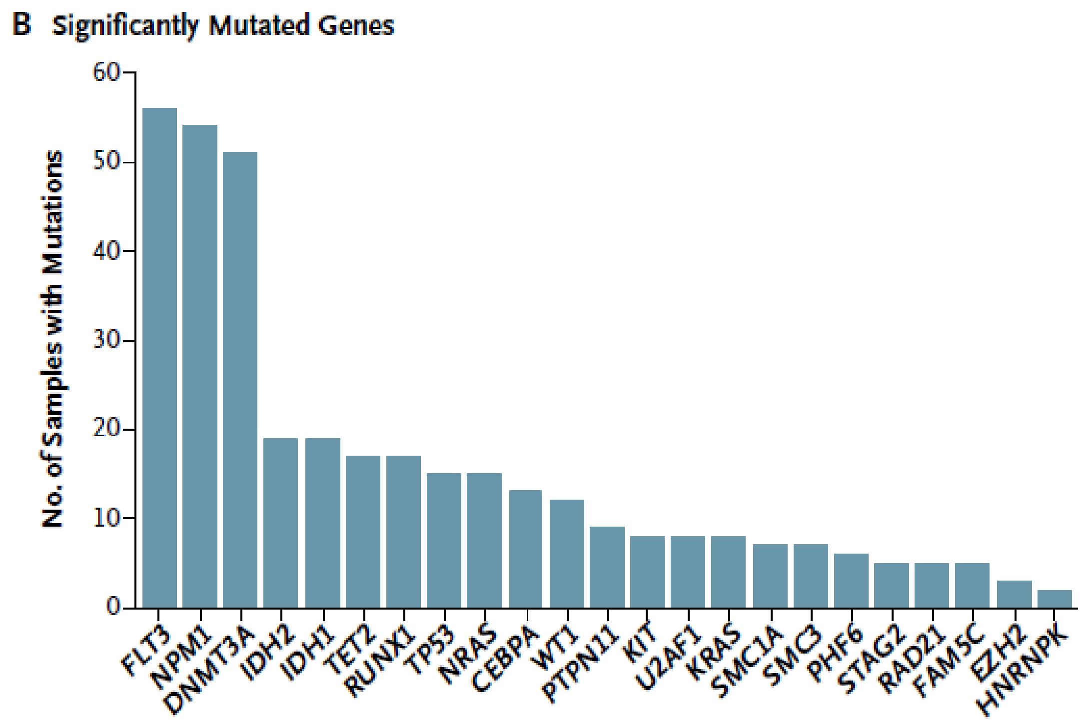
ESTABLISHED IN 1812 MARCH 22, 2012 VOL. 366 NO. 12

Prognostic Relevance of Integrated Genetic Profiling in Acute Myeloid Leukemia

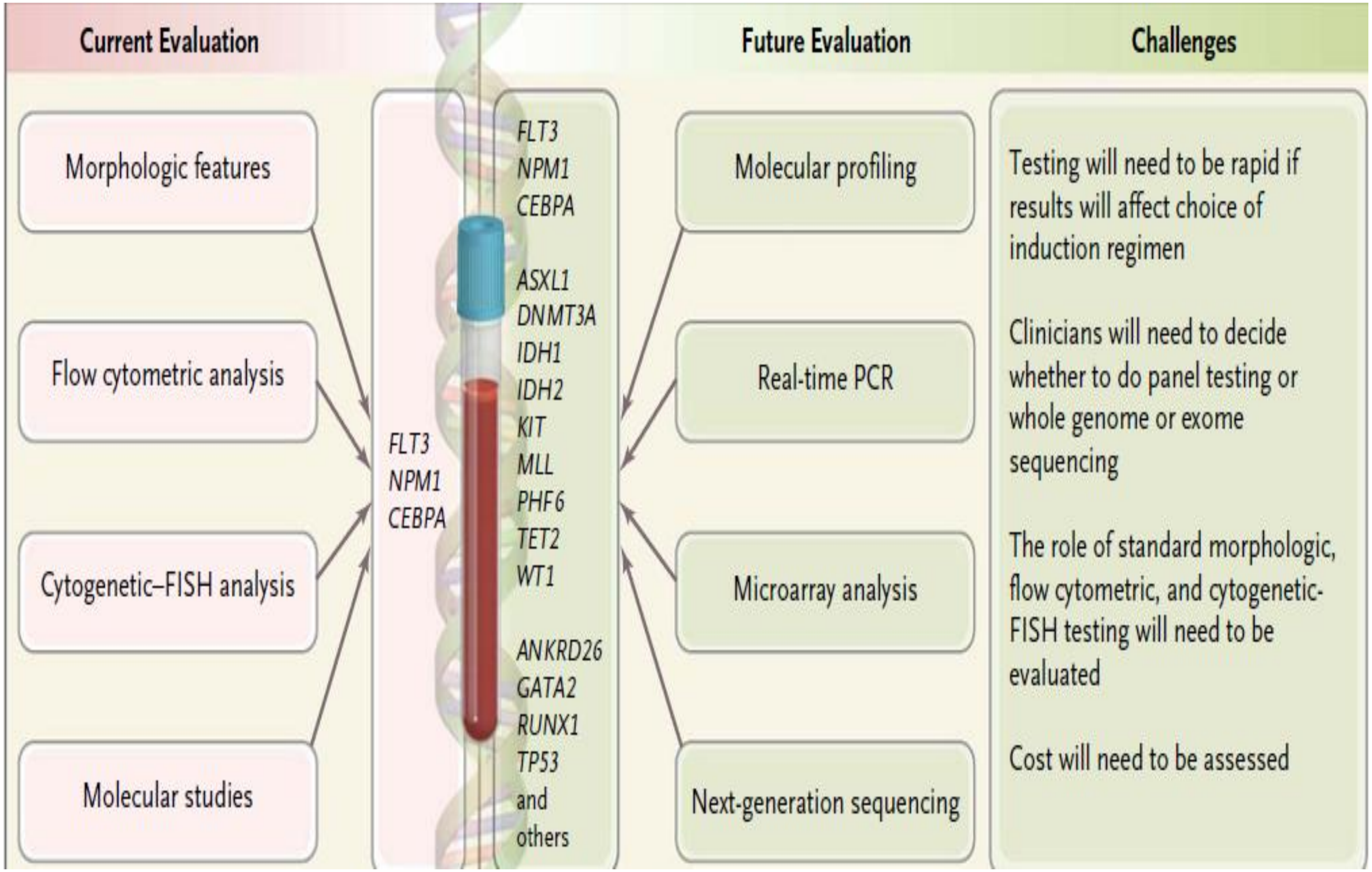
Jay P. Patel, Mithat Gönen, Ph.D., Maria E. Figueroa, M.D., Hugo Fernandez, M.D., Zhuoxin Sun, Ph.D., Janis Racevskis, Ph.D., Pieter Van Vlierberghe, Ph.D., Igor Dolgalev, B.S., Sabrena Thomas, B.S., Olga Aminova, B.S., Kety Huberman, B.S., Janice Cheng, B.S., Agnes Viale, Ph.D., Nicholas D. Socci, Ph.D., Adriana Heguy, Ph.D., Athena Cherry, Ph.D., Gail Vance, M.D., Rodney R. Higgins, Ph.D., Rhett P. Ketterling, M.D., Robert E. Gallagher, M.D., Mark Litzow, M.D., Marcel R.M. van den Brink, M.D., Ph.D., Hillard M. Lazarus, M.D., Jacob M. Rowe, M.D., Selina Luger, M.D., Adolfo Ferrando, M.D., Ph.D., Elisabeth Paietta, Ph.D., Martin S. Tallman, M.D., Ari Melnick, M.D., Omar Abdel-Wahab, M.D., and Ross L. Levine, M.D.


FLT3-ITD
TET2
DNMT3A
NPM1,
CEBPA
ASXL1,
MLL-PTD,
IDH1/2


DNMT3A
IDH1/2
TET2
ASXL1
FLT3
NPM1
CEBPA
WT1
N/KRAS
MLL-PTD
KIT
RUNX1
PTEN
TP53
PHF6


B Significantly Mutated Genes
No. of Samples with Mutations
0
10
20
30
40
50
60
FLT3
NPM1
DNMT3A
IDH2
IDH1
TET2
RUNX1
TP53
NRAS
CEBPA
WT1
PTPN11
KIT
U2AF1
KRAS
SMC1A
SMC3
PHF6
STAG2
RAD21
FAM5C
EZH2
HNRNPK

AML Diagnosis



Do they have prognostic value?

Poor Survival:

FLT3^{+} or MLL and in those with point mutations of ASXL1 or PHF6.

Favorable Survival:

CEBPA or IDH2 mutations; NPM1 mutations with concurrent IDH1 or IDH2 mutations.

Lestaurtinib / Sorafenib

Inhibition of constitutively activated FLT3, lestaurtinib in relapsed AML and sorafenib in newly diagnosed older AML, have failed to demonstrated significant benefit when combined to intensive chemotherapy.

Midostaurin /Quizartinib

- Phase III randomized study of midostaurin restricted to FLT3 mutated pts younger than 60 yrs is ongoing.
- Phase II study of quizartinib or AC220, the most selective FLT3 inhibitor available, in relapsed AML have confirmed that clonal responses could be observed with monotherapy.

Best of EHA in acute myeloid leukemia (AML)

Biological studies:

Murine models of NPM1-mutated AML

Mutations in AML secondary to congenital neutropenia (Plenary Session)

Mutations in AML secondary to Down syndrome (Plenary ession)

Clinical Studies:

Value of MRD monitoring in NPM1-mutated AML

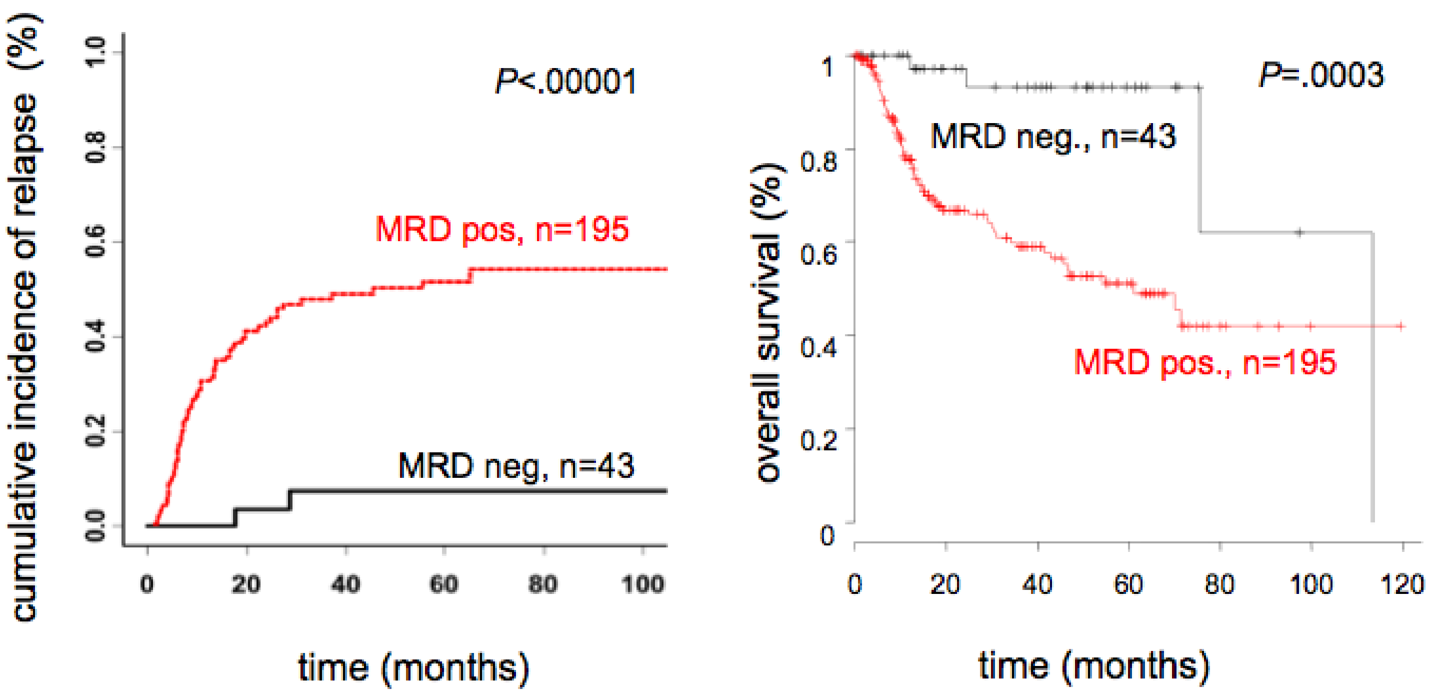
First trial with Plk1 inhibitor Volasertib in relapsed/refractory AML

Development of bispecific CLL-1 x CD3 antibody for therapy of AML

MRD Monitoring in *NPM1* mutated AML:

A Study of the German-Austrian AML Study Group (AMLSG)

After double induction in patients in CR (n=238)



2014

- Conventional & novel hypomethylating agents
- Novel targeted therapies
- AML founding mutations and HSC

RESULTS OF A PHASE III, MULTICENTER, RANDOMIZED, OPEN-LABEL STUDY OF AZACITIDINE (AZA) VS CONVENTIONAL CARE REGIMENS (CCR) IN OLDER PATIENTS WITH NEWLY DIAGNOSED AML

PHASE I/II STUDY OF VOLASERTIB, A POLO-LIKE KINASE INHIBITOR (PLK), IN PATIENTS WITH RELAPSED/REFRACTORY AML: UPDATED PHASE I RESULTS FOR VOLASERTIB MONOTHERAPY

A PHASE I STUDY OF AG-221, A FIRST IN CLASS, POTENT INHIBITOR OF THE IDH2-MUTANT PROTEIN, IN PATIENTS WITH IDH2 MUTANT POSITIVE ADVANCED HEMATOLOGIC MALIGNANCIES

Dnmt3a R882 Mutations Promote Chemoresistance and Therapeutic Relapse Through Impaired DNA Damage Sensing

***DNMT3A**^{mut}* AML patients are less sensitive to anthracyclines and benefit from dose-intensification

What's new in the WHO cassification ?

Clara Bloomfield
Wthe Ohio State University, Columbus, Ohio, USA)

WHO 2016: proposed changes in the category of "AML with recurrent genetic abnormalities"

- Switching from provisional to distinct entities:

AML with mutated NPM1 (distinct entity)

*AML with double mutated CEBPA (distinct entity)**

2016

Clinical trials

- Benefit of HD-DAU in FLT3-ITD^{mut} AML (NCRI-AML17)
- Benefit of CPX-351 in FLT3^{mut} AML (update on phase 3/HR-AML)
- Volasertib+LDAC (phase 3/elderly AML)
- Vosaroxin+Decitabine (phase 1-2/elderly AML+HR-MDS)

Novel targeted agents to watch....

- SGN-CD33A in combination with HMA (phase 1/CD33+ AML)

New approaches starting to bear fruit…

MRD: nuovo endpoint surrogato (OS, EFS) nella AML?

Quali tecnologie?; quali time-points?

L'era della chemio intensiva di prima linea ("AML Dogma") è ormai prossima alla fine?

Eccellenti risultati (CR/CRi, tossicità) con nuovi farmaci mirati (Venetoclax in primis) in combinazione con HMAs o chemio a bassa intensità (LDAC) in pazienti anziani poor-risk (età/fitness, biologia)

Tutti gli anziani?

Anche nei giovani?

Chi dovrebbe continuare ad essere trattato con chemio intensiva?

Acute myeloid leukemia

Gert Ossenkoppele (Coordinating Author)

Molecular diagnostics in acute myeloid leukemia

Lars Bullinger

Department of Internal Medicine III, Ulm University, Germany

Targeting mutated FLT3 in acute myeloid leukemia

Mark Levis

Johns Hopkins University, Baltimore, USA

3+7 and beyond

Norbert Vey

Institut Paoli Calmettes and Aix-Marseille Université, Marseille, France

Risk Stratification and Cytogenetic and Molecular Abnormalities in AML

Favorable Genetic Risk

Frequency: 15%

Survival: 65%

- t(8;21)(q22;q22); *RUNX1-RUNX1T1*
- inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
- Mutated *NPM1* without *FLT3* ITD or with *FLT3*-ITD^{low}
- Biallelic mutated *CEBPA* (normal karyotype)

Intermediate Genetic Risk

Frequency: 55%

Survival: 50%

- Mutated *NPM1* and *FLT3*-ITD^{high} (normal karyotype)
- Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}
- t (9;11) (p21.3;q23.3); *MLLT3-KMT2A*

Adverse Genetic Risk Group

Frequency: 30%

Survival: 20%

- t(6;9)(p23;q34.1); *DEK-NUP214*
- t(v;11;q23.3); *KMT2A* rearranged
- t(9;22)(q34.1; q11.2) *BCR-ABL1*
- inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2 MECOM (EVI1)*
- -5 or del(5q)-7; -17/abn(17p)
- Complex and/or monosomal karyotype
- Wild-type *NPM1 and FLT3*-ITD^{high}
- Mutations in *RUNX1, ASXL1, TP53*

Dohner H, et al. *Blood.* 2017;129:424-447.

- ✓ **Genomic knowledge** does now also facilitate monitoring of **MRD** (DPCR, NGS, qRT-PCR, MFC).
- ✓ Comprensive and individualized **MRD assessment** is useful to identify pts at high relapse risk at early time points.
- ✓ **Genomic knowledge** will allow us to better guide the use of novel drugs

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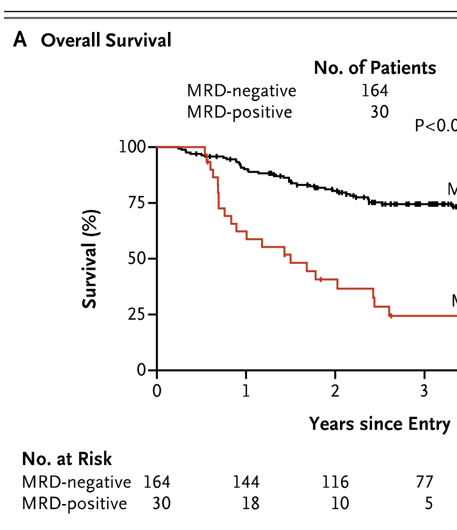
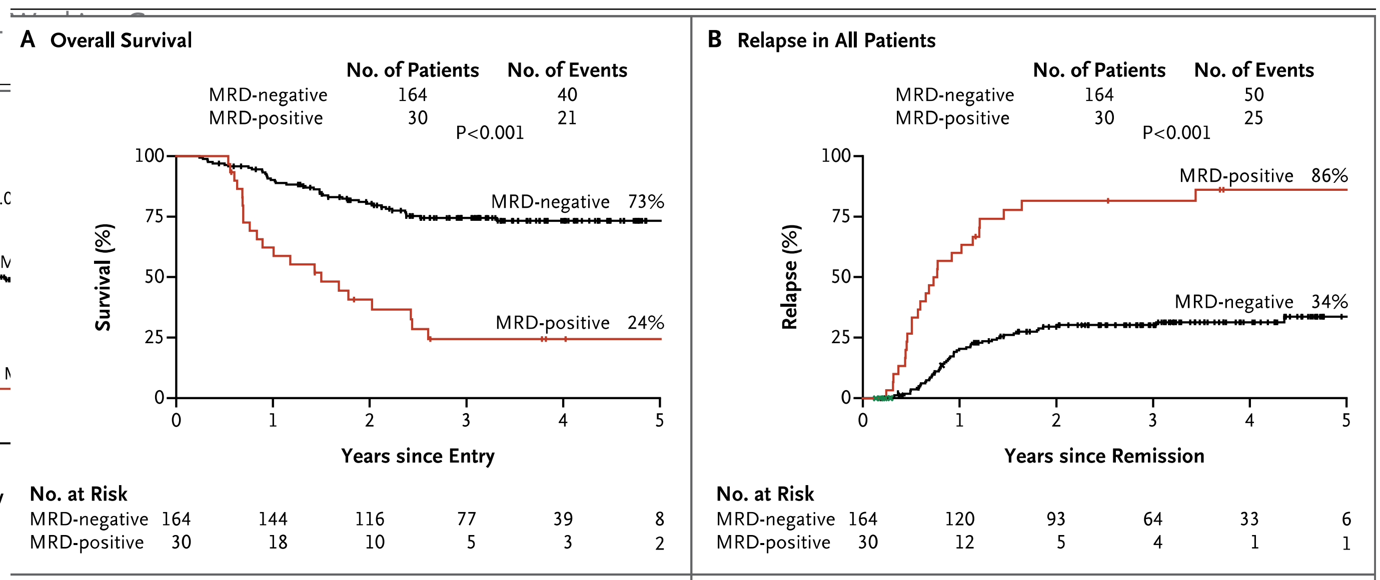
Assessment of Minimal Residual Disease in Standard-Risk AML

A. Ivey, R.K. Hills, M.A. Simpson, J.V. Jovanovic, A. Gilkes, A. Grech, Y. Patel, N. Bhudia, H. Farah, J. Mason, K. Wall, S. Akiki, M. Griffiths, E. Solomon, F. McCaughan, D.C. Linch, R.E. Gale, P. Vyas, S.D. Freeman, N. Russell, A.K. Burnett, and D. Grimwade, for the UK National Cancer Research Institute AML





Problematiche nella real life per la valutazione della MRD

Quali BioMarkers PML/RARα, NPM1,

MFC ma in tutti i Laboratori è standardizzata ? no

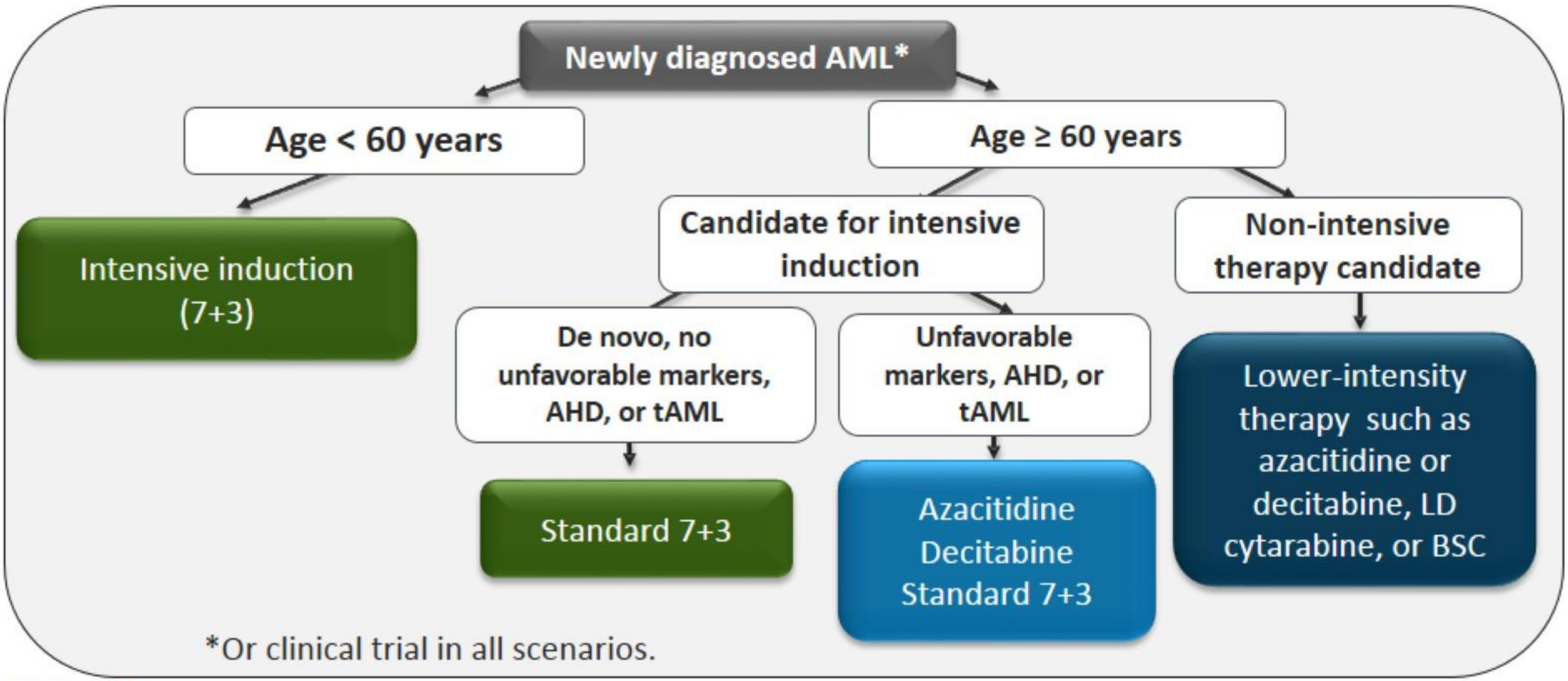
Sono necessari altri trials?

Potremmo utilizzare la piattaforma LabNet AML anche per standardizzare ?

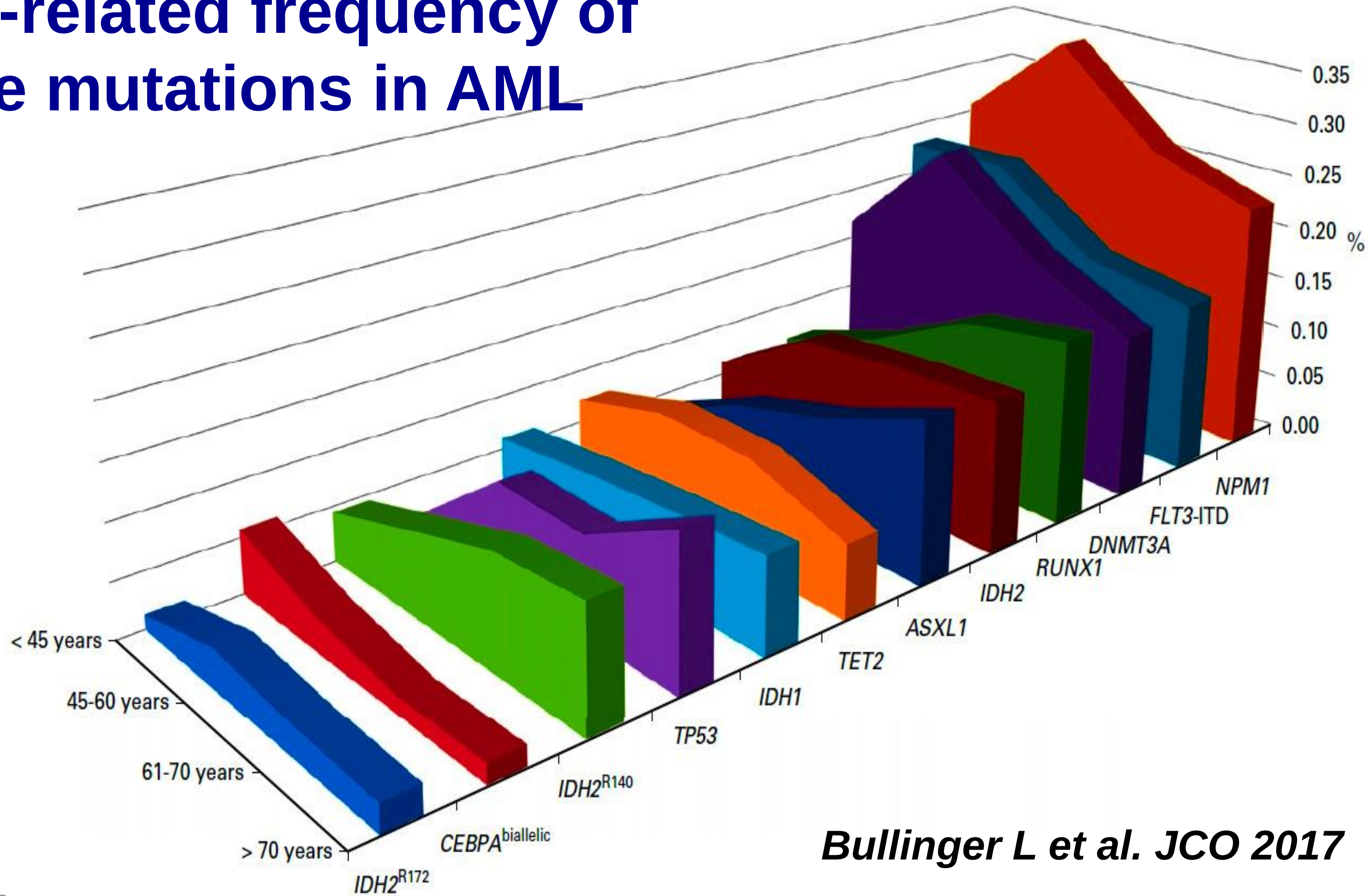
L’era della chemio intensiva di prima linea (“AML Dogma”) è ormai prossima alla fine?

Chi dovrebbe continuare ad essere trattato con CHT Intensiva?
Tutti i pazienti elegibili per la CHT standard/intensiva !!
DNR/IDA (> 60mg/m, 12 mg/m) ; ARA-C 100-200-1000mg)
FLAG-Ida ?

Treating Newly Diagnosed AML
Current Paradigms



Age-related frequency of gene mutations in AML



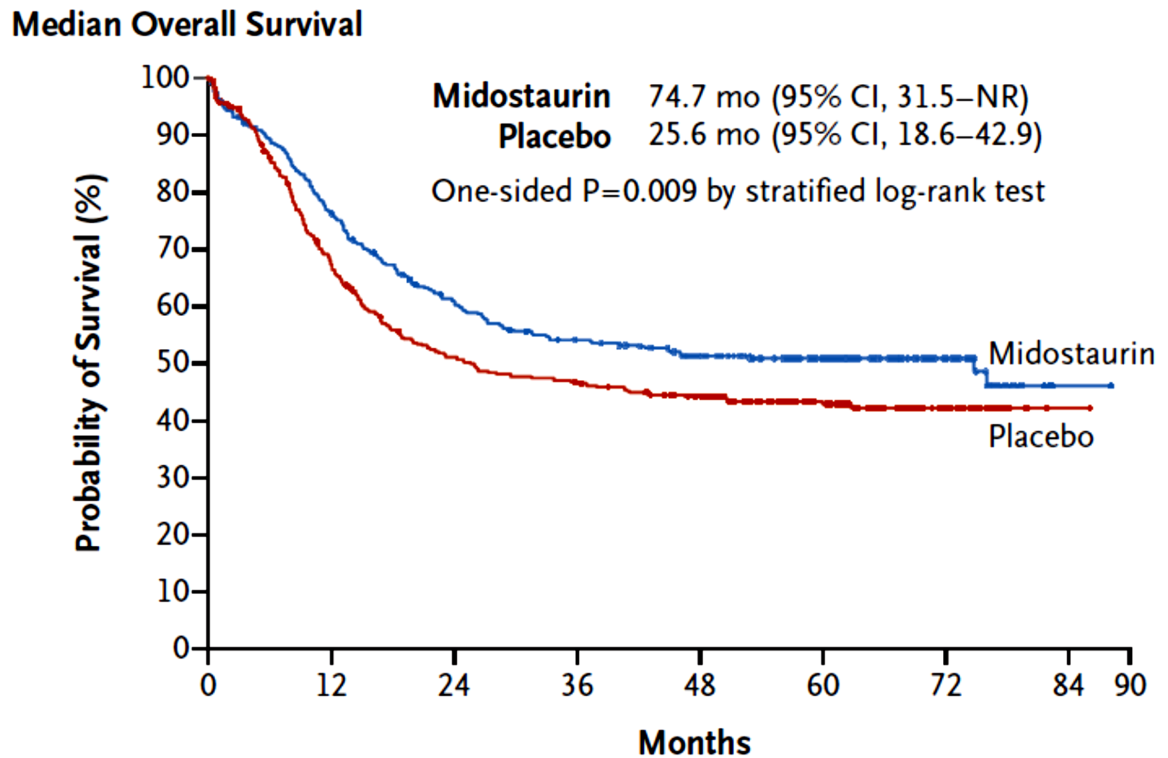
Bullinger L et al. JCO 2017

Examples of Novel Targeted Therapies in AML

- FLT3 inhibitors
- IDH inhibitors
- Venetoclax
- Monoclonal antibody-drug conjugates, such as gemtuzumab-ozogamicin and SGN-CD33A
- BiTE antibodies
- Immune checkpoint inhibitors
- Novel formulations of cytotoxic agents
- CPX-351 (combination of daunorubicin and cytarabine)
- Vosaroxin, a TP53-independent drug that may be particularly useful in patients with relapsed disease and those older than 60 years
- Hedgehog pathway/MEK pathway inhibitors
- MDM2 inhibitors

a. Stein EM. *Hematology.* 2015;2015:579-583; b. Stein EM, et al. *Blood.* 2016;127:71-78; c. D'Angelo DJ, et al. *Am Soc Clin Oncol Educ Book.* 2016;35:e302-e312.

Midostaurin plus Chemotherapy for AML with a FLT3 Mutation

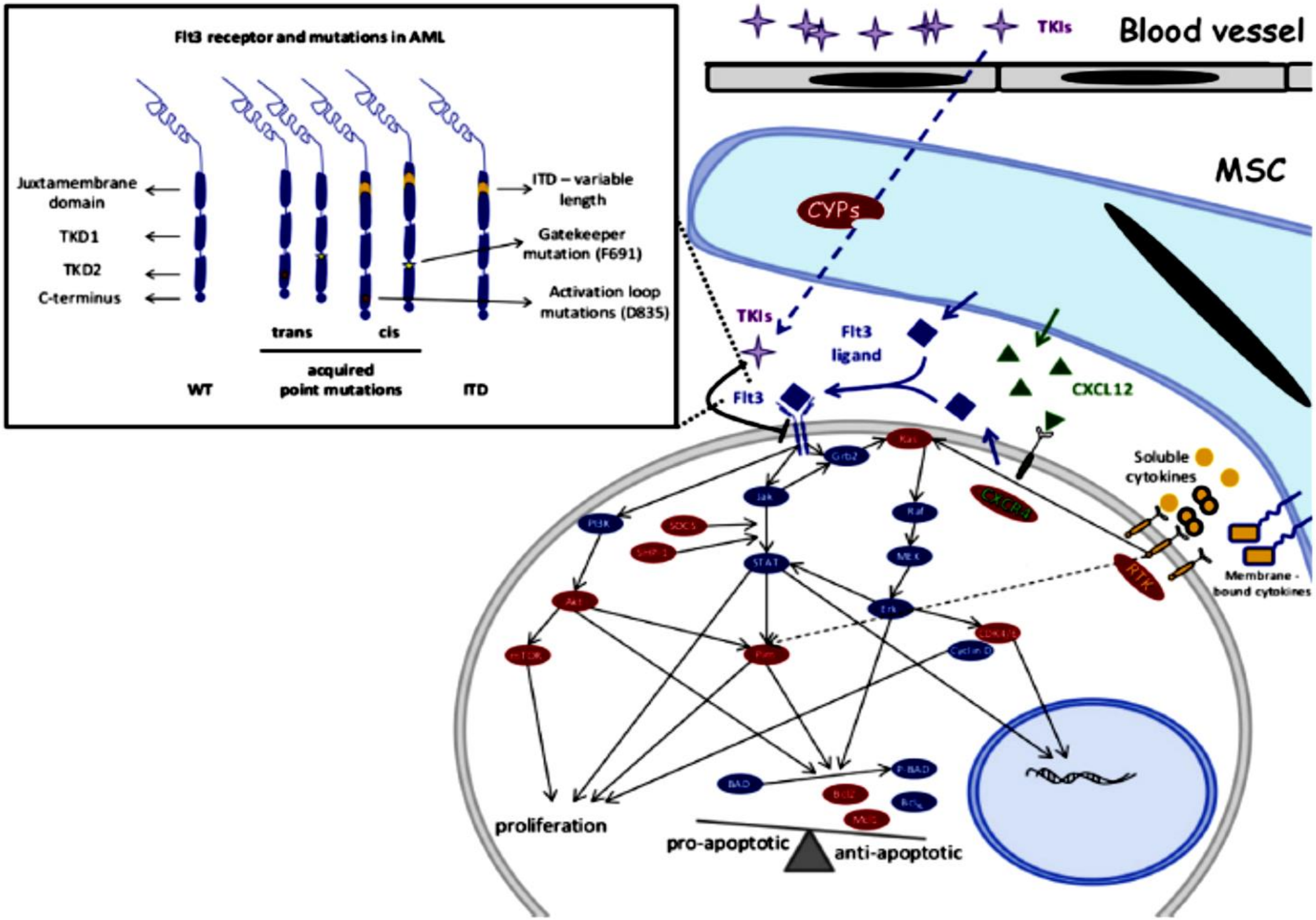


No. at Risk								
Midostaurin	360	269	208	181	151	97	37	1
Placebo	357	221	163	147	129	80	30	1

The addition of the multitargeted kinase inhibitor midostaurin to standard chemotherapy significantly prolonged overall and event-free survival among patients with AML and a FLT3 mutation

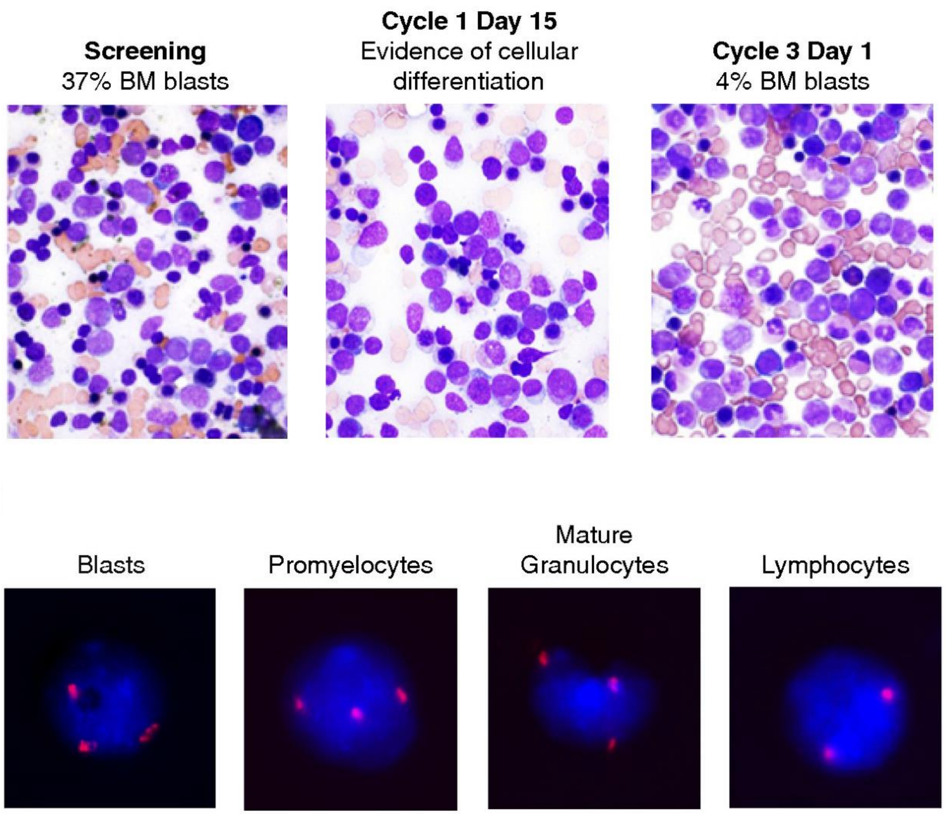
Stone MR et al. NEJM 377:454-464, 2017

Resistance to FLT3 Inhibitors



Ghiaur G et al. Hematol Oncol Clin North Am 2017

Enasidenib induces AML cell differentiation to promote clinical response



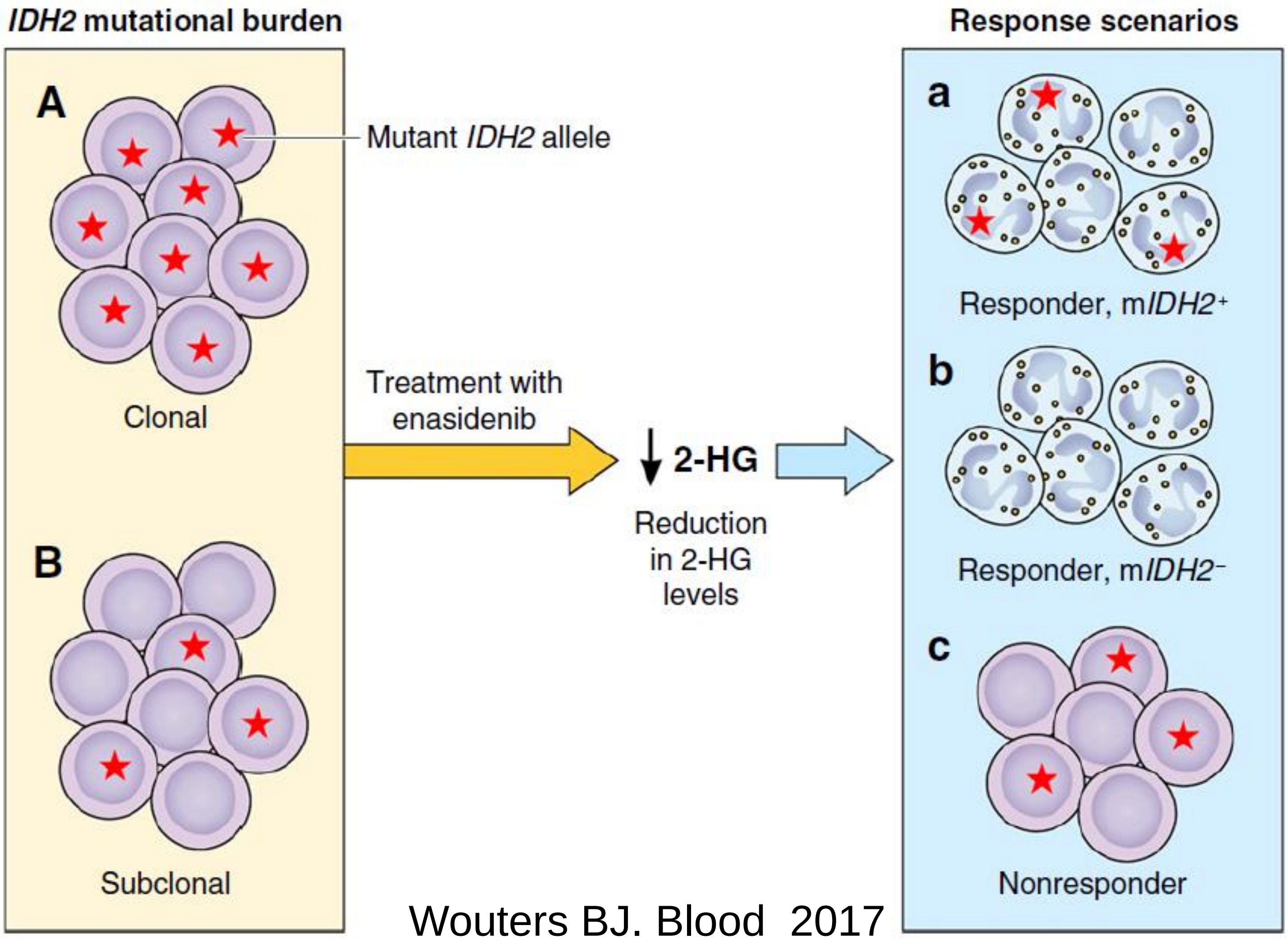
CR with persistence of mIDH2 and normalization of hematopoietic stem and progenitor compartments with emergence of functional mIDH2 neutrophils were observed. In a subset of CR patients, mIDH2 allele burden was reduced and remained undetectable with response.

Co-occurring mutations in NRAS and other MAPK pathway effectors were enriched in nonresponding patients, consistent with RAS signaling contributing to primary therapeutic resistance.

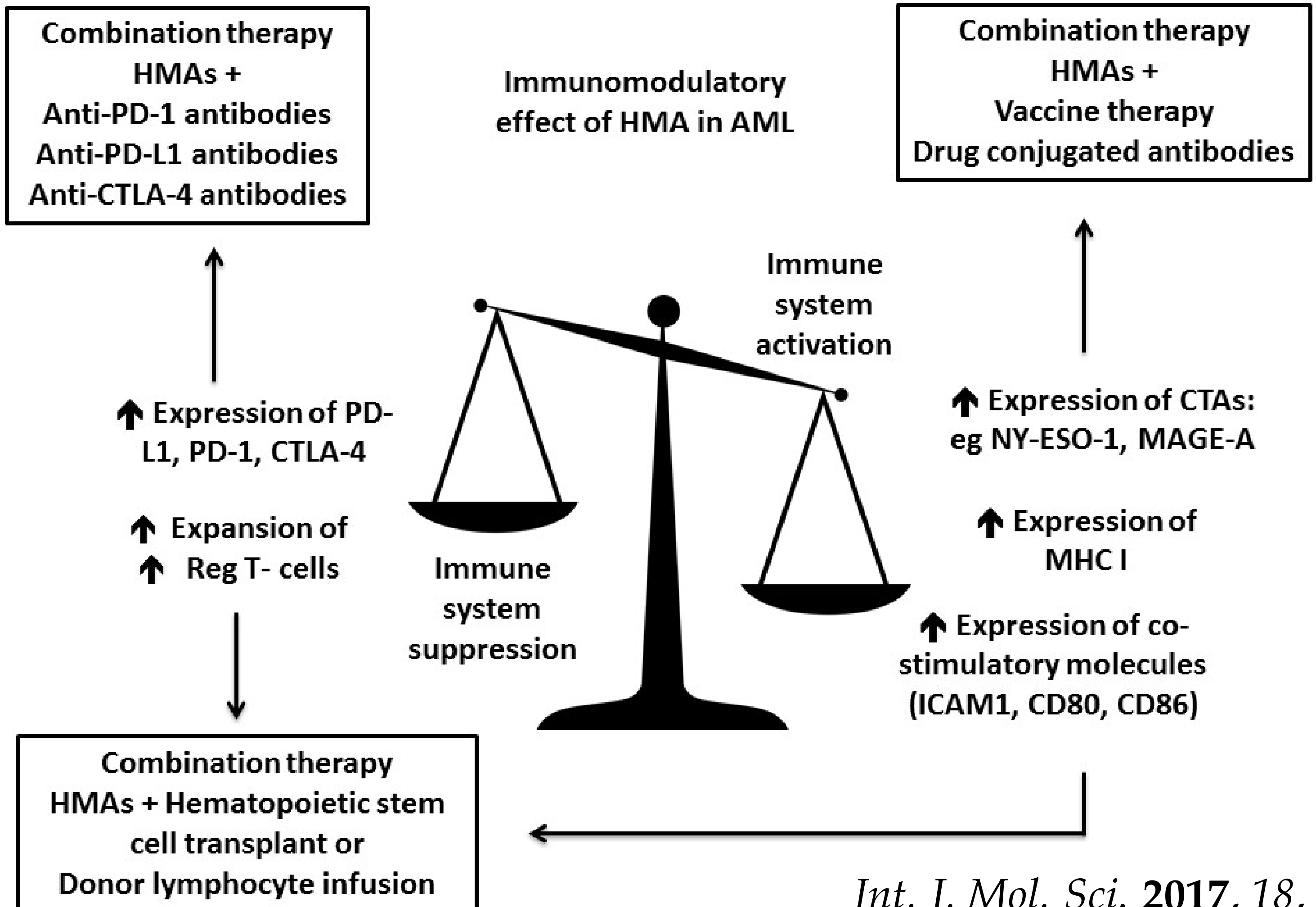
Together, these data support differentiation as the main mechanism of enasidenib efficacy in relapsed/refractory AML patients and provide insight into resistance mechanisms to inform future mechanism-based combination treatment studies

Stein EM et al. Blood 2017
Amatangelo MD et al. Blood. 2017

Enasidenib induces AML cell differentiation to promote clinical response



Wouters BJ. Blood 2017



Int. J. Mol. Sci. **2017**, *18*, 1660

New approaches starting to bear fruit…

Cytotoxic agents			
Liposomal D+A	CPX 351	HR elderly AML frontline	Rando Phase 2
Topo-II inhibitor	Vosaroxin	R/R AML	Phase 3 R/R
Monoclonal antibodies			
AntiCD33 mAb	lintuzumab	Misc.	Phase 3
AntiCD33 ADC	GO	frontline	Phase 3
	SGN-33A	R/R AML +frontline	Phase 3 combo
AntiCD33/CD3	AMG330	R/R AML	Phase 1 single agent
Anti-CD123 mAb	Talacotuzumab	R/R AML	Phase 2 combo
Anti-CD123 ADC	SGN-CD123A	R/R AML	Phase 1 single agent
Anti-CD3/CD123	MGD006	R/R AML	Phase 1 single agent
	JNJ-63709178	R/R AML	Phase 1 single agent
Apoptosis targeting agents			
BCL2-i	Venetoclax	R/R AML	Phase 2 combos
	S55746	R/R AML	Phase 1
MCL1-i	S64315	R/R AML	Phase 1
MDM2-i	Idasanutlin	R/R AML	Phase 3 combo
Kinase/Cell cycle-i			
PIM kinase-i	CLGH447	R/R AML	Phase 1 combo
MEK-i	Cobimetinib	R/R AML	Phase 1 combo
PI3K/RAS-i	Rigosertib	R/R AML	Phase 1
CDK-i	Palbociclib	R/R AML	Phase 1
Epigenetic drugs			
Oral azacitidine	CC486	Frontline	Phase 3 combo
Decitabine prodrug	SGI-110	Frontline elderly	Phase 3
Bromodomaine-i	OTX015	R/R AML	Phase 1
DOTL1-i	EPZ-5676	R/R MLL AML	Phase 1

Immunotherapy			
ICB			
Anti-CTLA4	Ipilimumab	R/R AML	Phase 1-2
Anti-PD1	Nivolumab	R/R + frontline AML	Phase 1-2 combo
Anti-KIR	IPH2101	R/R AML	Phase 1
	Lirilumab	frontline elderly AML	Phase 2-3
Anti-NKG2A	Monalizumab	Maintenance post allo	Phase 1
CAR-T cells			
Anti-CD33	CART33	R/R AML	Phase 1
Anti-CD123	CART123	R/R AML	Phase 1
Anti-CD133	CART133	R/R AML	Phase 1

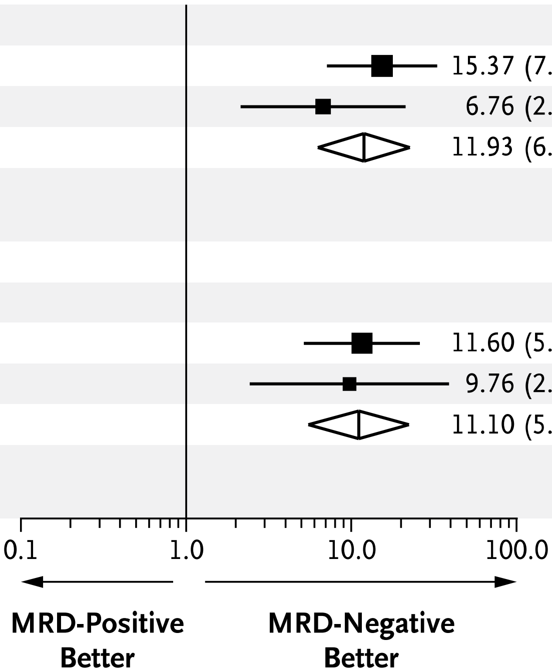
Table 2
Selected upfront acute myeloid leukemia clinical studies with FLT3 inhibitors

Drug, Reference	Patients	FLT3 Status	Phase and Treatment Regimen	Treatment Response
Sorafenib[49]	18 yo+	+/− *FLT3* mutation	II: Sor 400 mg po bid plus AraC + Ida for induction, Sor plus cytarabine for consolidation, and Sor alone as maintenance × 1 y	• CR in 79% (n = 49 of 61) and CRp in 8% (n = 5 of 61), including CR/CRp 95% (n = 18 of 19) and 84% (n = 36 of 43) with and without *FLT3*-ITD, respectively • Median OS: 29 mo • Median DFS: 13.8 mo
Sorafenib[50]	60 yo+	+/− *FLT3* mutation	II: randomized to Sor 400 mg PO BID vs placebo after DNR + AraC, after cytarabine for consolidation and as maintenance × 1 y	Placebo vs sorafenib: • ORR (CR + CRi) 64 of 95 vs 57 of 102 (*P* = .34), respectively • EFS 7 m vs 5 m (HR 1.26; 95% CI, 0.94–1.70) • OS 15 m vs 13 m (HR 1.03; 95% CI, 0.73–1.44) • Sorafenib arm had higher 60-d mortality (*P* = .035) attributable to infections (*P* = .015)
Sorafenib[51]	60 yo+	+ *FLT3*-ITD or + *FLT3* TKD	II: sorafenib 400 mg po bid days 1–7 plus 7 + 3, followed by Sor plus intermediate dose AraC for consolidation and Sor alone as maintenance × 1 y	• CR or CRi in 69% (n = 37 of 54) • 1 y observed OS: 62% for *FLT3*-ITD and 71% for *FLT3*-TKD • Favorable outcome (1-y OS) compared with historical controls for *FLT3*-ITD (62% vs 30%; *P*<.0001)
Sorafenib[52]	18–60 yo	+/− *FLT3* mutation	II: randomized to Sor 400 mg po bid vs placebo after 7 + 3 for induction, after cytarabine for consolidation and as maintenance × 1 y	Placebo (n = 133) vs sorafenib (n = 134): • CR: 59 vs 60% • 3-y EFS 22% (95% CI, 13–32) vs 40% (HR 0.64; 95% CI, 0.45–0.91; *P* = .013) • No OS difference

Midostaurin[55]	18–60 yo	+/− *FLT3* mutation	Ib: M 50–100 mg, po bid, either concomitantly or sequentially with 7 + 3, M with HiDAC consolidation and M alone as maintenance	• 100-mg cohort: CR 45% (n = 13 of 29, including 8 of 23 with *FLT3* WT and 5 of 6 with *FLT3*-mutant) • 50-mg cohort: CR 80% (n = 32 of 40, including 20 of 27 with *FLT3 WT* and 12 of 13 with *FLT3*-mutant) • *FLT3*-mutant cohort: 1-y OS of 0.85 (95% CI, 0.65–1.0); 2-y OS of 0.62 (95% CI, 0.35–0.88); 1-y DFS of 0.50 (95% CI, 0.22–0.78) • *FLT3* WT cohort: 1-y OS of 0.78 (95% CI, 0.62–0.93); 2-y OS of 0.52 (95% CI, 0.33–0.71) in *FLT3* WT; 1-y DFS of 0.60 (95% CI, 0.39–0.81)
Midostaurin[56]	18–60 yo	+ any activating *FLT3* mutation	III: M 50 mg po bid vs placebo after 7 + 3 for induction, after HiDAC for consolidation, and as maintenance	M vs placebo: • CR: 59% vs 54%; *P* = .18 • 5-y OS: median 74.7 mo vs 26.0 mo, HR 0.77 (1-sided; *P* = .007) • 5-y EFS: median 8.0 mo vs 3.0 mo, HR 0.80 (1-sided; *P* = .004)
Midostaurin[57]	18–70 yo	+ *FLT3*-ITD mutation	II: M 50 mg po bid after 7 + 3 for induction, after HiDAC for consolidation, and as maintenance after chemo or allo-HCT	• Overall CR 75% after induction

Midostaurin[55]	18–60 yo	+/− *FLT3* mutation	Ib: M 50–100 mg, po bid, either concomitantly or sequentially with 7 + 3, M with HiDAC consolidation and M alone as maintenance	• 100-mg cohort: CR 45% (n = 13 of 29, including 8 of 23 with *FLT3* WT and 5 of 6 with *FLT3*-mutant) • 50-mg cohort: CR 80% (n = 32 of 40, including 20 of 27 with *FLT3 WT* and 12 of 13 with *FLT3*-mutant) • *FLT3*-mutant cohort: 1-y OS of 0.85 (95% CI, 0.65–1.0); 2-y OS of 0.62 (95% CI, 0.35–0.88); 1-y DFS of 0.50 (95% CI, 0.22–0.78) • *FLT3* WT cohort: 1-y OS of 0.78 (95% CI, 0.62–0.93); 2-y OS of 0.52 (95% CI, 0.33–0.71) in *FLT3* WT; 1-y DFS of 0.60 (95% CI, 0.39–0.81)
Midostaurin[56]	18–60 yo	+ any activating *FLT3* mutation	III: M 50 mg po bid vs placebo after 7 + 3 for induction, after HiDAC for consolidation, and as maintenance	M vs placebo: • CR: 59% vs 54%; *P* = .18 • 5-y OS: median 74.7 mo vs 26.0 mo, HR 0.77 (1-sided; *P* = .007) • 5-y EFS: median 8.0 mo vs 3.0 mo, HR 0.80 (1-sided; *P* = .004)
Midostaurin[57]	18–70 yo	+ *FLT3*-ITD mutation	II: M 50 mg po bid after 7 + 3 for induction, after HiDAC for consolidation, and as maintenance after chemo or allo-HCT	• Overall CR 75% after induction

Subgroup	MRD-Positive	MRD-Negative	Statistics		Hazard Ratio (95% CI)	P Value
	no. of events/ no. of patients		*O−E*	*Variance*		
Relapse						
Development	25/30	50/164	17.7	6.5	15.37 (7.12–33.18)	
Validation	9/16	13/75	5.5	2.9	6.76 (2.14–21.38)	
Subtotal	34/46	63/239	23.3	9.4	11.93 (6.29–22.62)	<0.001
Test of heterogeneity between subgroups: χ^2=1.4; P=0.25						
Death						
Development	21/30	40/164	14.4	5.9	11.60 (5.16–26.06)	
Validation	7/16	6/75	4.5	2.0	9.76 (2.43–39.17)	
Subtotal	28/46	46/239	18.9	7.9	11.10 (5.52–22.35)	<0.001
Test of heterogeneity between subgroups: χ^2=0.0; P=0.83						



Pts 346 (2569 samples)

Age[nn,oo] <60 y ►

- Clinical trial (preferred)
- or
- Standard-dose cytarabine 100–200 mg/m² continuous infusion x 7 days with idarubicin 12 mg/m² or daunorubicin 60–90 mg/m² x 3 days[rr,ss] (category 1)
- or
- Standard-dose cytarabine 200 mg/m² continuous infusion x 7 days with daunorubicin 60 mg/m² x 3 days and cladribine 5 mg/m² x 5 days (category 2A)[tt]
- or
- High-dose cytarabine (HiDAC)[ss,uu] 2 g/m² every 12 hours x 6 days[vv] or 3 g/m² every 12 h x 4 days[ww] with idarubicin 12 mg/m² or daunorubicin 60 mg/m² x 3 days (1 cycle) (category 1 for patients ≤45 y, category 2B for other age groups)
- or
- Standard dose cytarabine 200 mg/m² continuous infusion x 7 days with daunorubicin 60 mg/m² x 3 days and oral midostaurin 50 mg every 12 hours, days 8-21[xx] (FLT3-mutated AML)
- or
- Fludarabine 30 mg/m² IV days 2–6, HiDAC 2 g/m² over 4 hours starting 4 hours after fludarabine on days 2–6, idarubicin 8 mg/m² IV days 4–6, and G-CSF SC daily days 1–7 (category 2B)[yy]

AML ≥60 y
See AML-11

Risk Stratification and Treatment Selection

- Genetic risk informs likelihood of responding to intensive chemotherapy
- Performance status and comorbidities (and possibly age) inform likelihood of treatment benefit outweighing risk

Induction

All risk groups (patients considered eligible for intensive chemotherapy)

Treatment: 7+3 chemotherapy

Consolidation

Favorable risk: IDAC chemotherapy (regimen adjusted for patient age)

Intermediate risk, age 18-60/65: IDAC or allo-HSCT

Intermediate risk, age >60/65: Allo-HSCT

Adverse risk: Allo-HSCT

Döhner H, et al. *Blood*. 2017;129:424-447.

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CPX-351 vs 7+3
Older ND High-Risk (Secondary) AML, Phase 3

CPX-351: liposome-encapsulated 5:1 fixed molar ratio of cytarabine:daunorubicin

Key Eligibility
- Secondary AML
- Newly diagnosed secondary AML*
- Ages 60-75 years
- Able to tolerate intensive therapy
- PS 0-2

CPX-351
n =153

7+3
n =156

Induction
(1-2 cycles)

Patients in CR or CRi:
Consolidation
(1-2 cycles)

Follow-up:
Death
OR
5 years

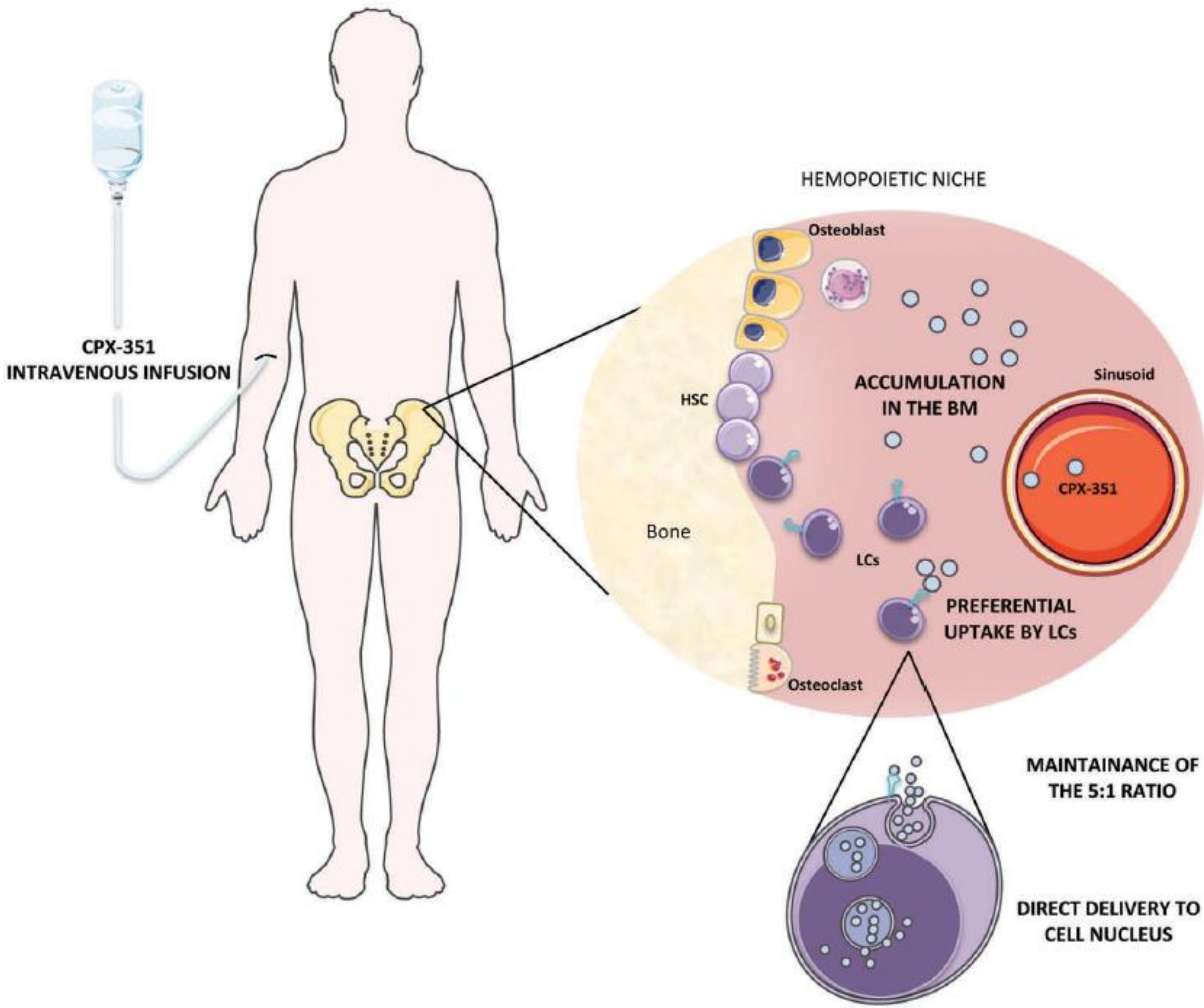
*Secondary AML defined as having a history of prior cytotoxic treatment, antecedent MDS +/- a prior history of HMA, or AML with WHO-defined MDS-

Primary Endpoint: OS

	CPX-351 n = 153	7+3 n = 156	HR; *P* Value
Median OS, mo	9.56	5.95	.69; .005
Median EFS, mo	2.53	1.31	.74; .021
CR, %	37.3	25.6	.040
CR + CRi, %	47.7	33.3	.016

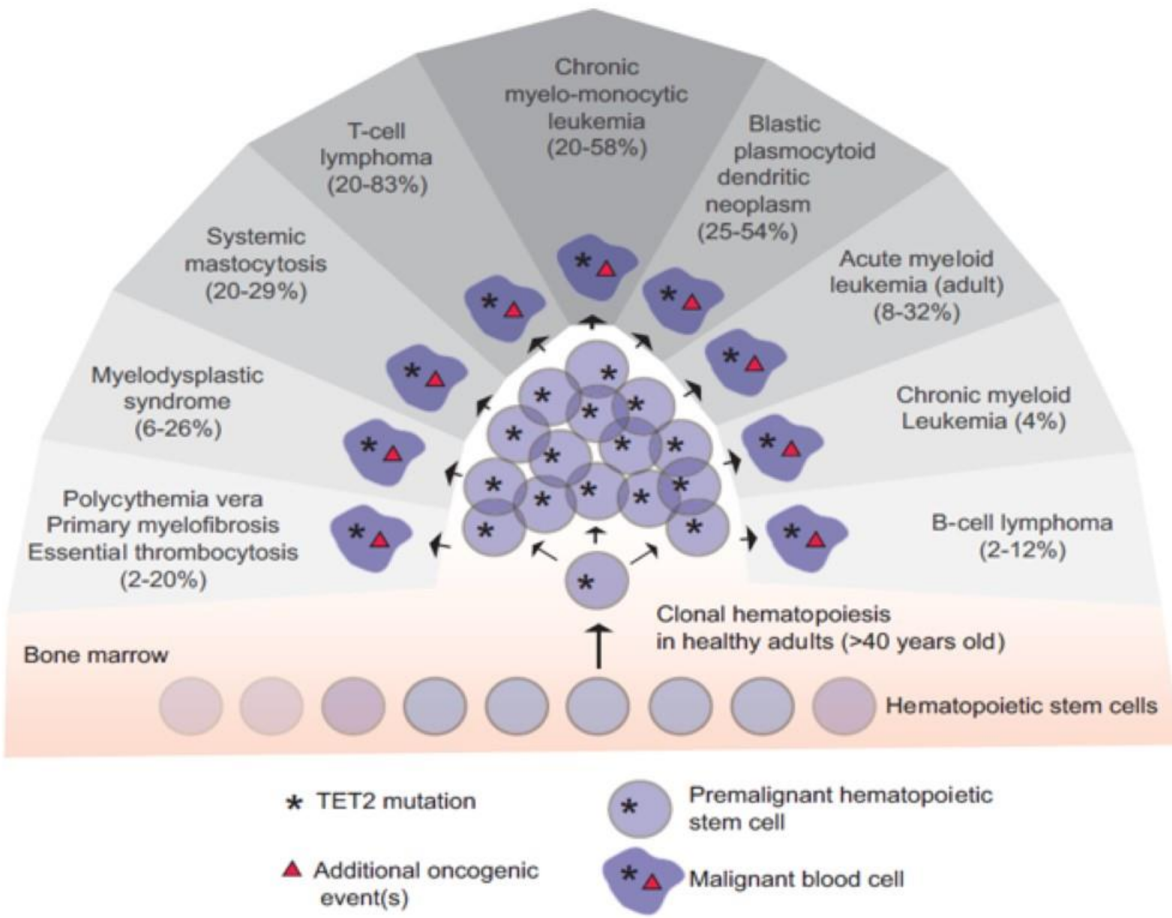
Lancet JE, et al. *J Clin Oncol.* 2016;34. Abstract 7000.

CPX-351 in AML



Brunetti C et al. Expert Rev Hematol. 2017 Aug 24:1-10. [Epub ahead of

TET2 Mutation in Hematologic Malignancies



- A somatic mutation in *TET2* results in premalignant hematopoiesis and clonal expansion
- Additional oncogenic events cooperate with the initial *TET2* mutation to drive the onset of a wide variety of hematopoietic malignancies

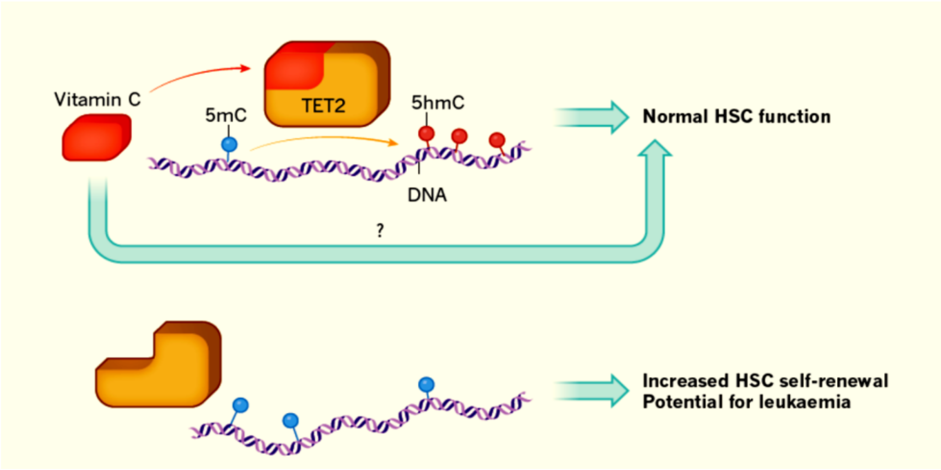
Rasmussen KD. *Genes and Development*. 2016;30:733-750.

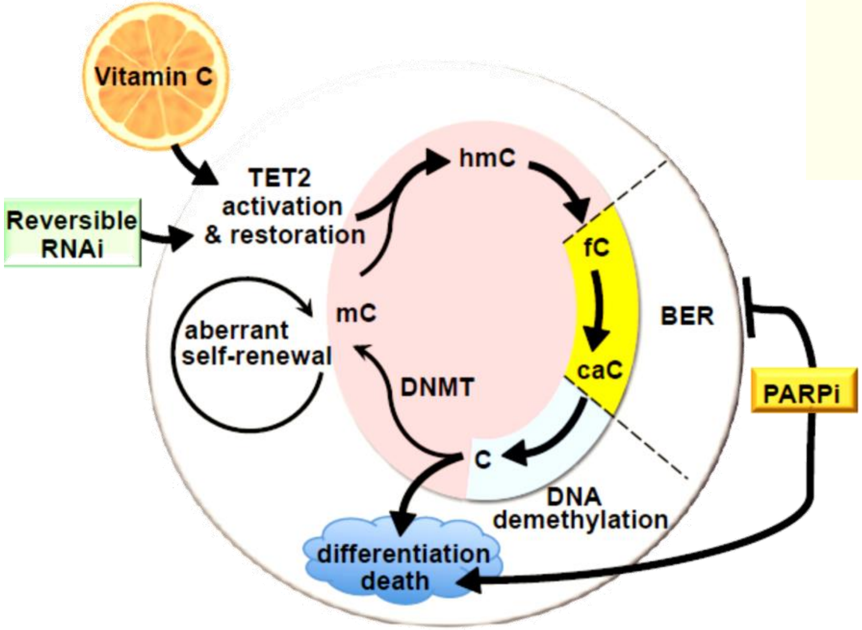
Role of TET2 in DNA Methylation

- TET2 is one of a family of TET proteins that catalyzes the hydroxylation of 5-methyl cytosine, promoting hypomethylation of DNA
- Precise regulation of DNA methylation patterns is important for normal development
  - Methylated DNA provides protection against cellular transformation
- *TET2* mutation and altered gene expression is common in myeloid neoplasms
- *TET2* mutation is common in MDS and AML
  - Often "first hit" founder mutations in cancer development

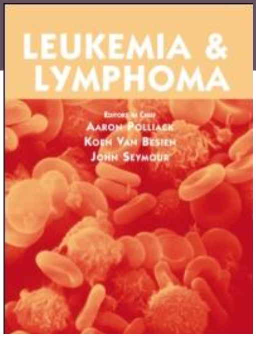
Rasmussen KD. *Genes and Development*. 2016;30:733-750.

Restoration of TET2 Function Blocks Aberrant Self-Renewal and Leukemia Progression





Cimmino L et al. Cell 170:1079-1095.e20, 2017
Agathocleous M et al. Nature 21 August 2017



REVIEW

Check for updates

The emerging role of immune checkpoint based approaches in AML and MDS

Prajwal Boddu[a], Hagop Kantarjian[a], Guillermo Garcia-Manero[a], James Allison[a], Padmanee Sharma[b] and Naval Daver[a]