"Real World Evidence"

Nuovi target terapeutici in ematologia

8 - 9 Novembre 2018

Auditorium "Fra Agostino Daniele"
San Giovanni Rotondo

Presidente del Convegno
Nicola Cascavilla

Le nuove frontiere delle leucemie acute

Dalla chemioterapia alla medicina di precisione

Nicola Di Renzo

Lecce

Rete Ematologica Pugliese

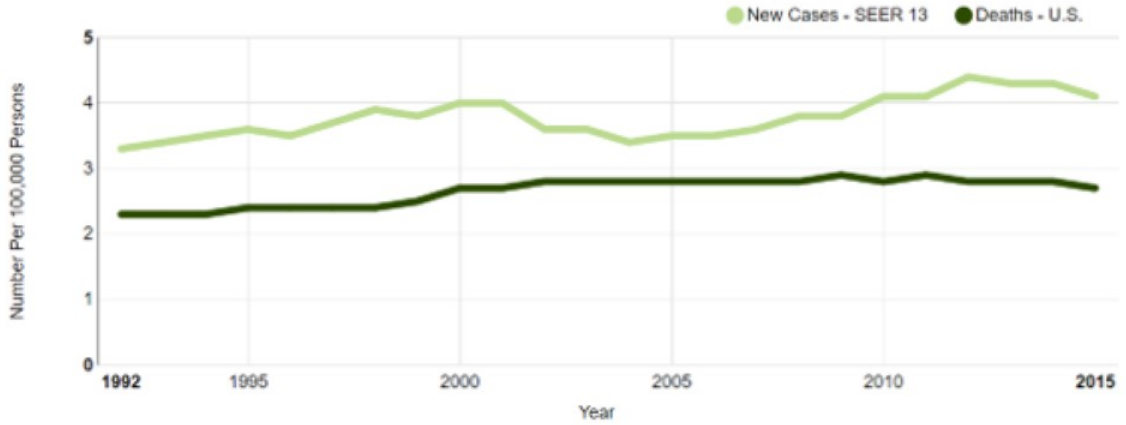
Regione Puglia

ARESS

ASL LECCE
SERVIZIO SANITARIO DELLA PUGLIA

Epidemiology of AML

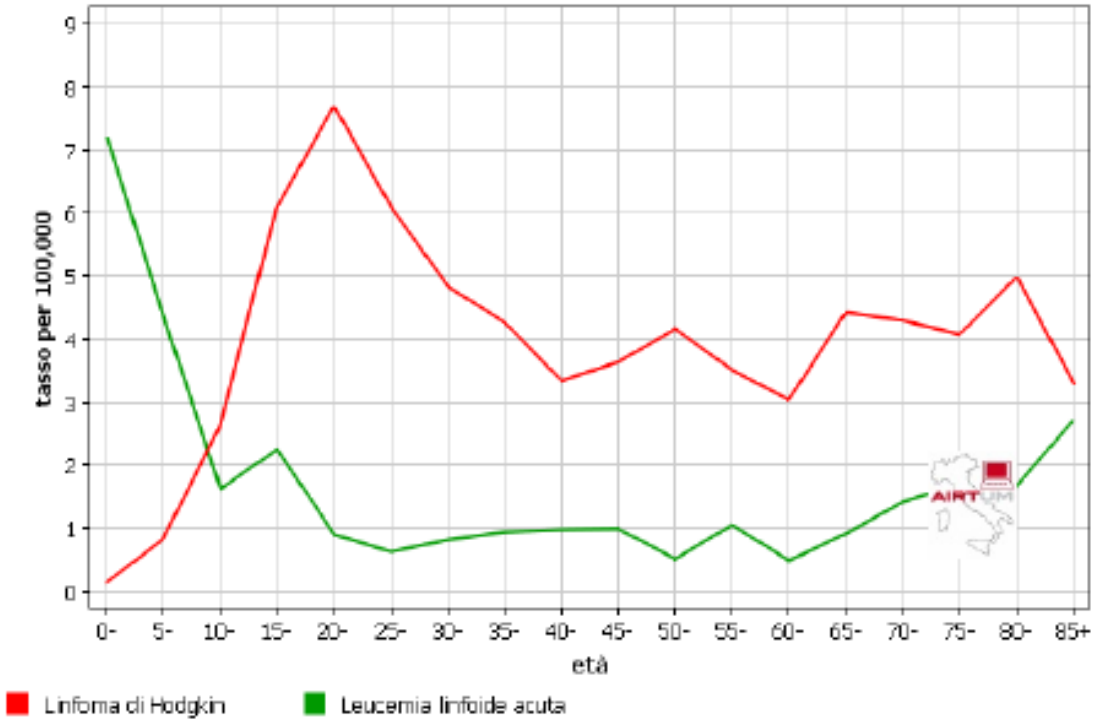
- Most common acute leukemia in adults
- Lifetime risk: ~0.5% of population
- Estimated incidence in 2018: ~19,520 new cases (1.1% of new cancer cases)
- Estimated mortality in 2018: ~10,670 deaths



SEER Cancer Stat Facts: Acute Myeloid Leukemia. National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/statfacts/html/amyl.html

NCI SEER website. Cancer stat facts: AML 2017.

AIRTUM (Pool 38 Registri) 2006-2009-Incidenza
Maschi



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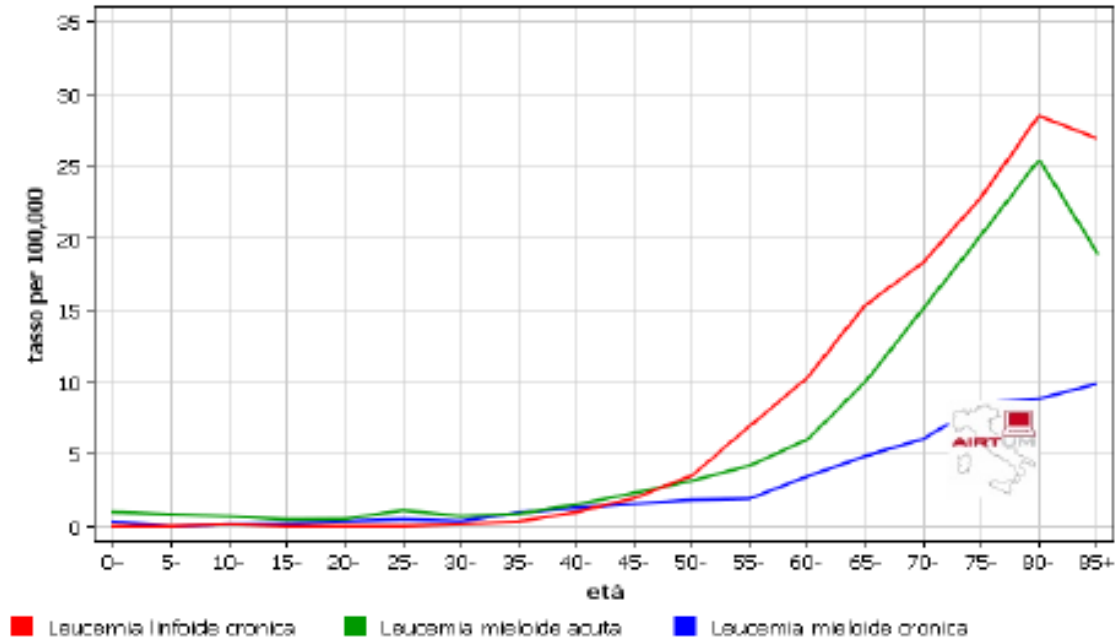
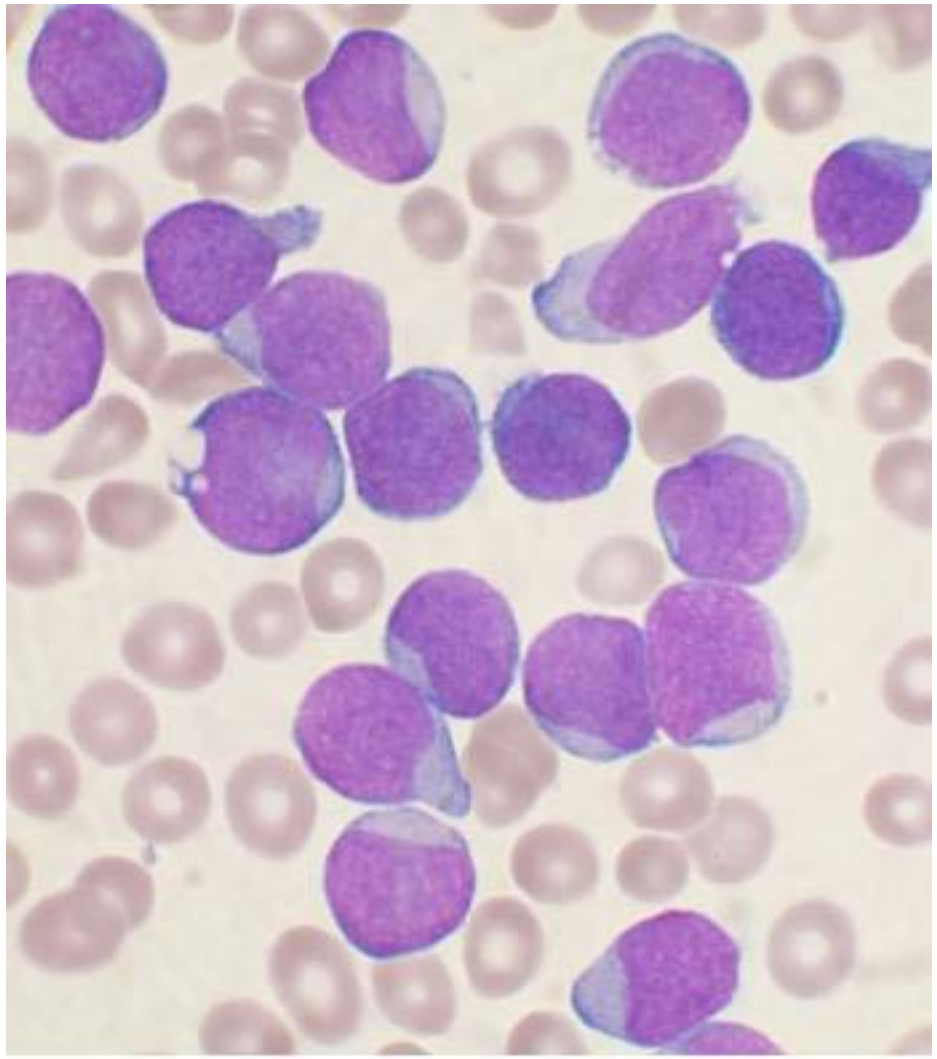


Acute Myeloid Leukemia

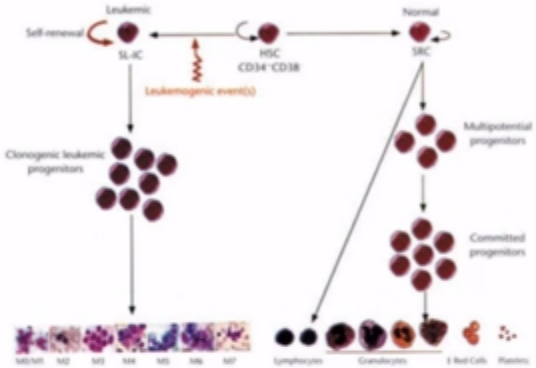


Acute Myeloid Leukemia (AML):
"*A long tradition of being first*"

"Cytogenetics"
(Janet D. Rowley)

t(8;21)

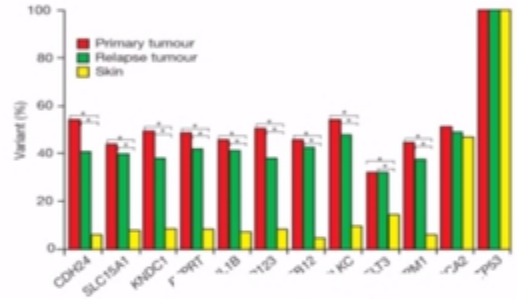
1972



"Cancer stem cells"
(John E. Dick)

1997

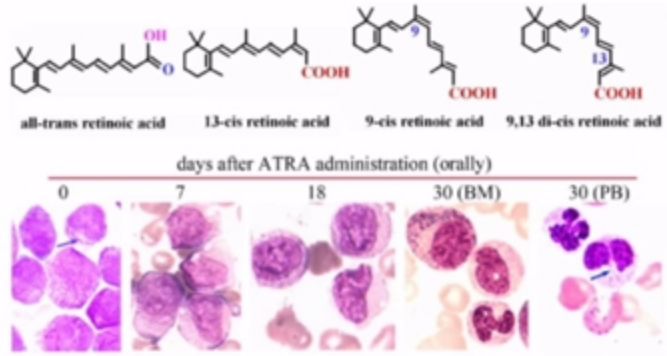
"Next Generation Sequencing (NGS)"
(Timothy Ley)



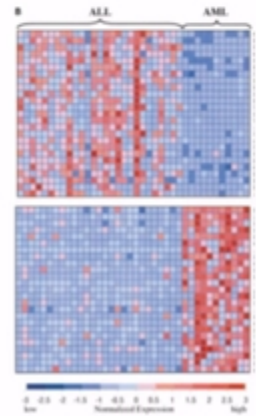
2008

1985

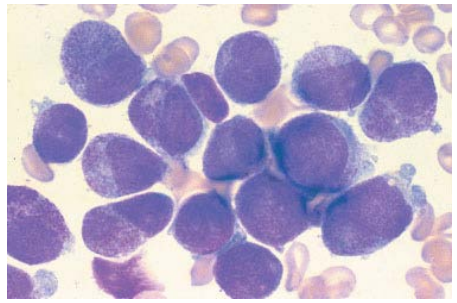
"Targeted therapy":
ATRA in APL
(Zhen-Yi Wang)



1999



"Omics"
(Todd Golub)



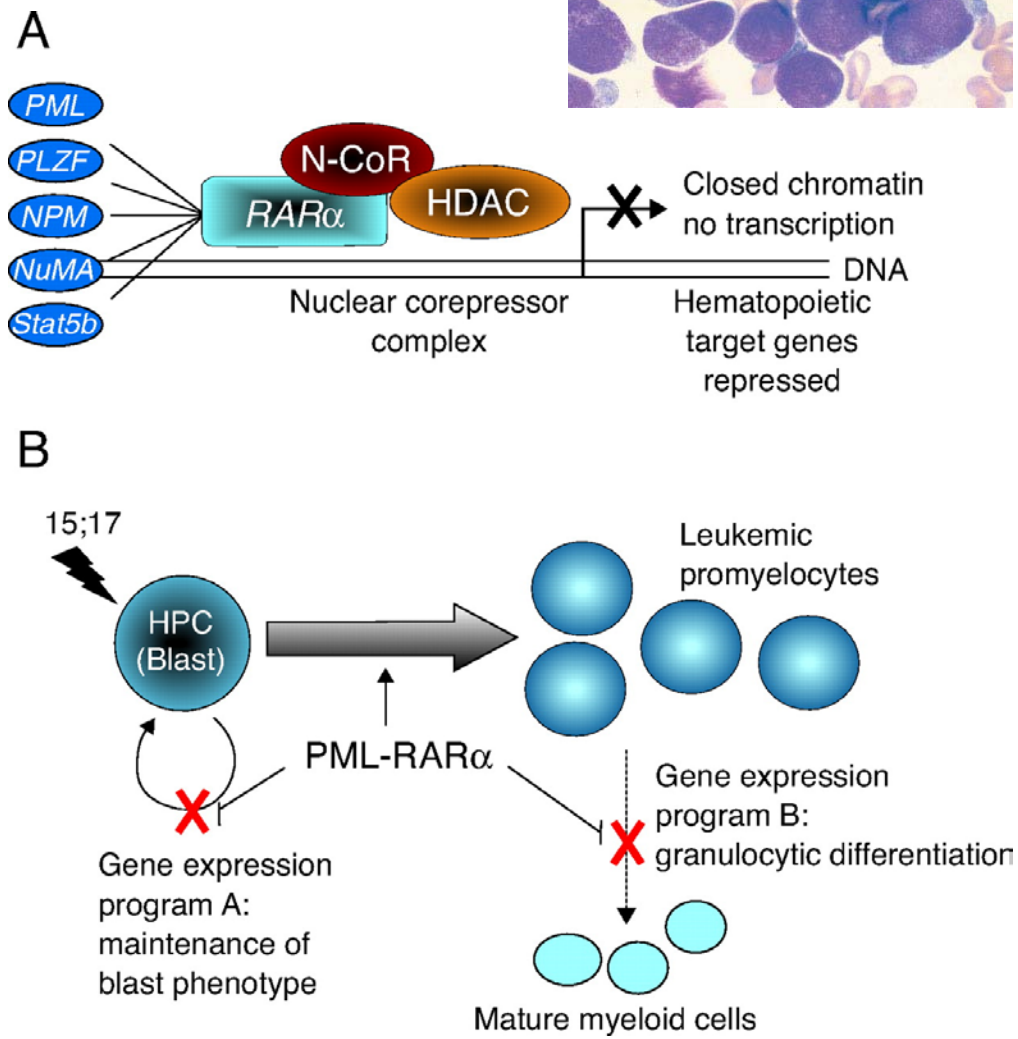
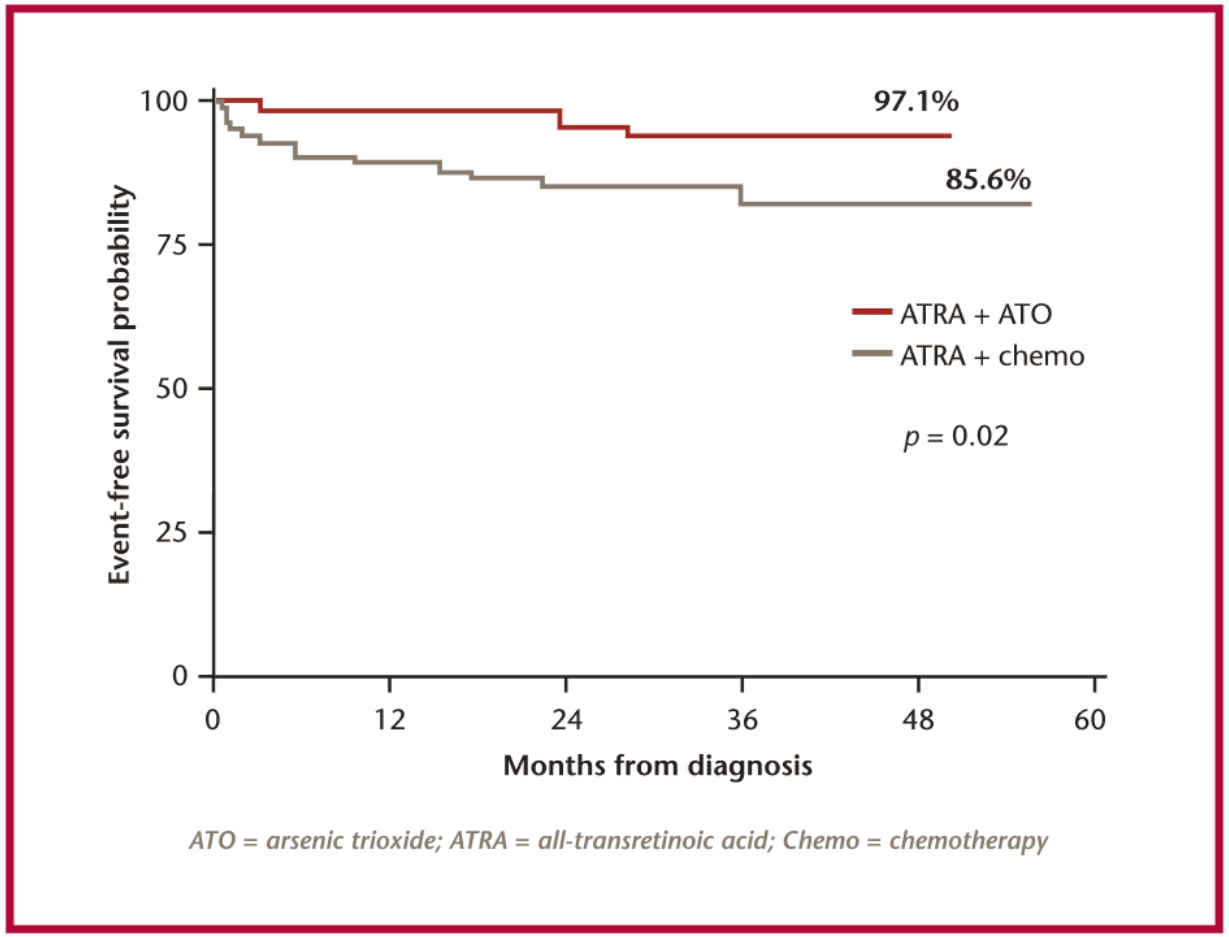
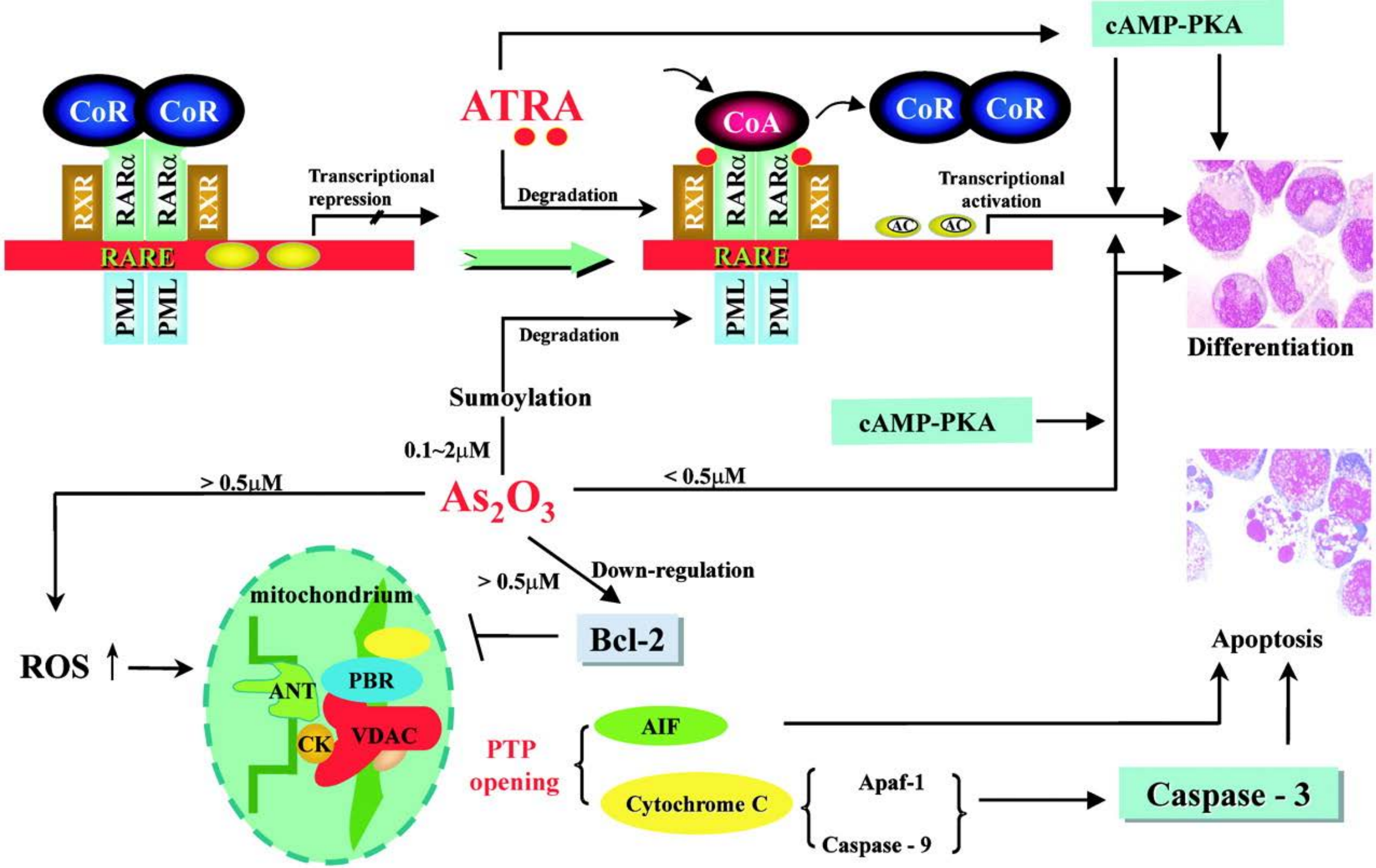


Figure 6. Event-free survival



ATO = arsenic trioxide; ATRA = all-transretinoic acid; Chemo = chemotherapy

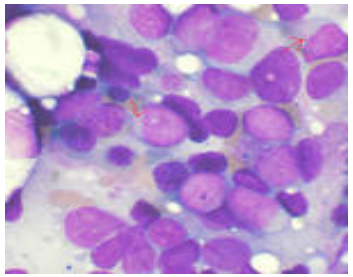
Lococo et al, JCO, 2017


cAMP-PKA
CoR
CoR
RXR
RARα
RARα
RXR
RARE
PML
PML
Transcriptional repression
ATRA
Degradation
CoA
CoR
CoR
RXR
RARα
RARα
RXR
RARE
PML
PML
Transcriptional activation
AC
AC
Differentiation
Degradation
Sumoylation
cAMP-PKA
0.1~2μM
> 0.5μM
< 0.5μM
As2O3
Down-regulation
> 0.5μM
mitochondrium
ROS
ANT
PBR
CK
VDAC
Bcl-2
Apoptosis
PTP opening
AIF
Cytochrome C
Apaf-1
Caspase - 9
Caspase - 3

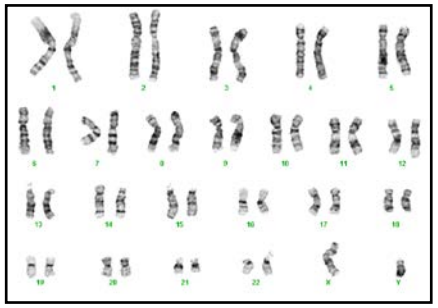
Diagnostic work-up for AML is complex

Molecular characterization

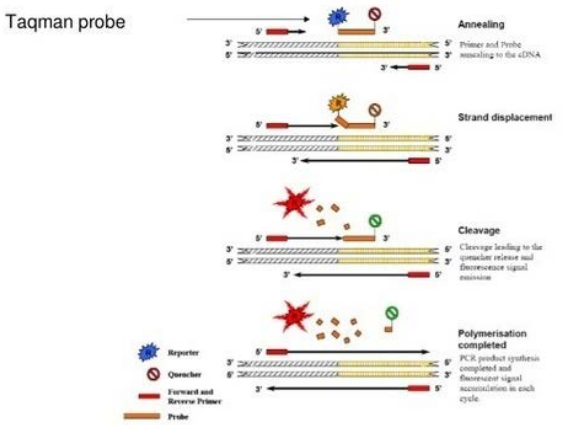
Morphology



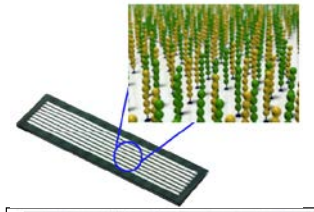
Cytogenetics

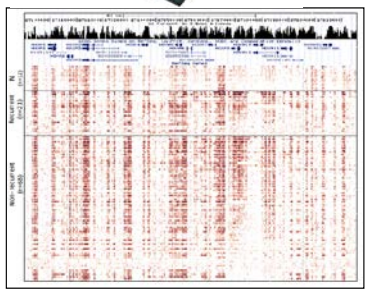


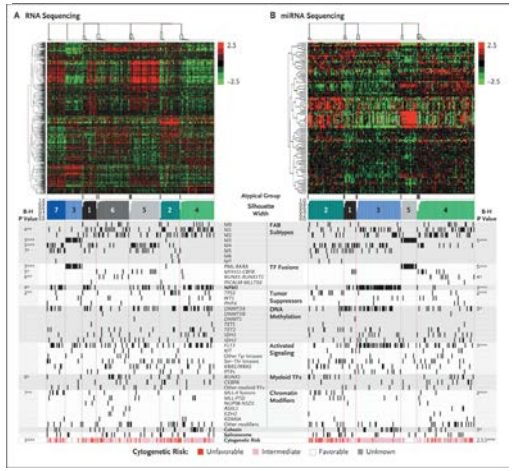
Quantitative real-time-PCR



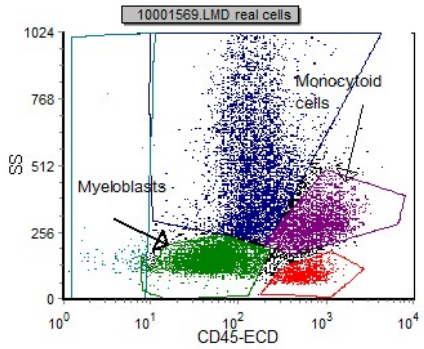
Next Generation Sequencing







Immunophenotype

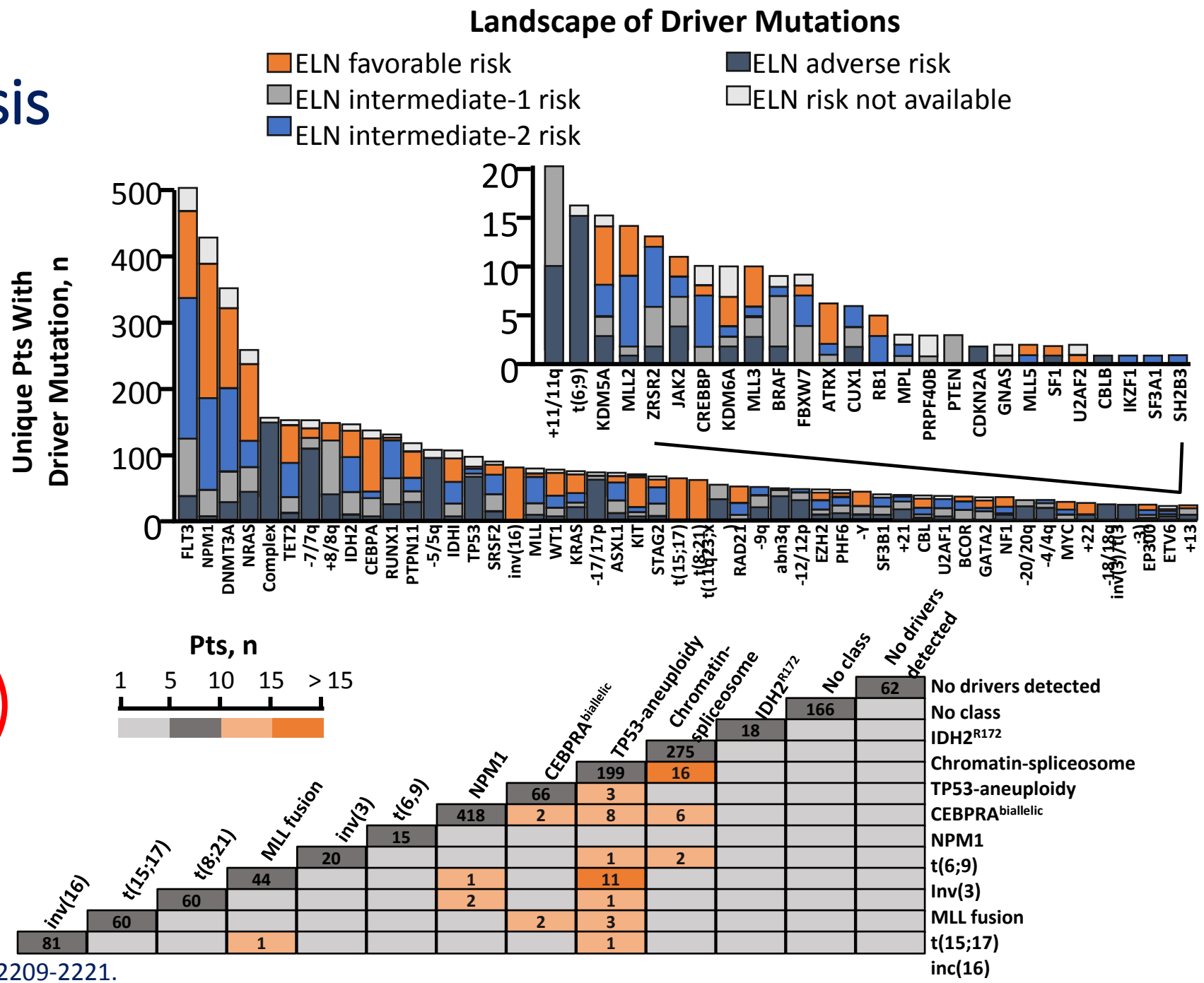


NGS Utility in AML

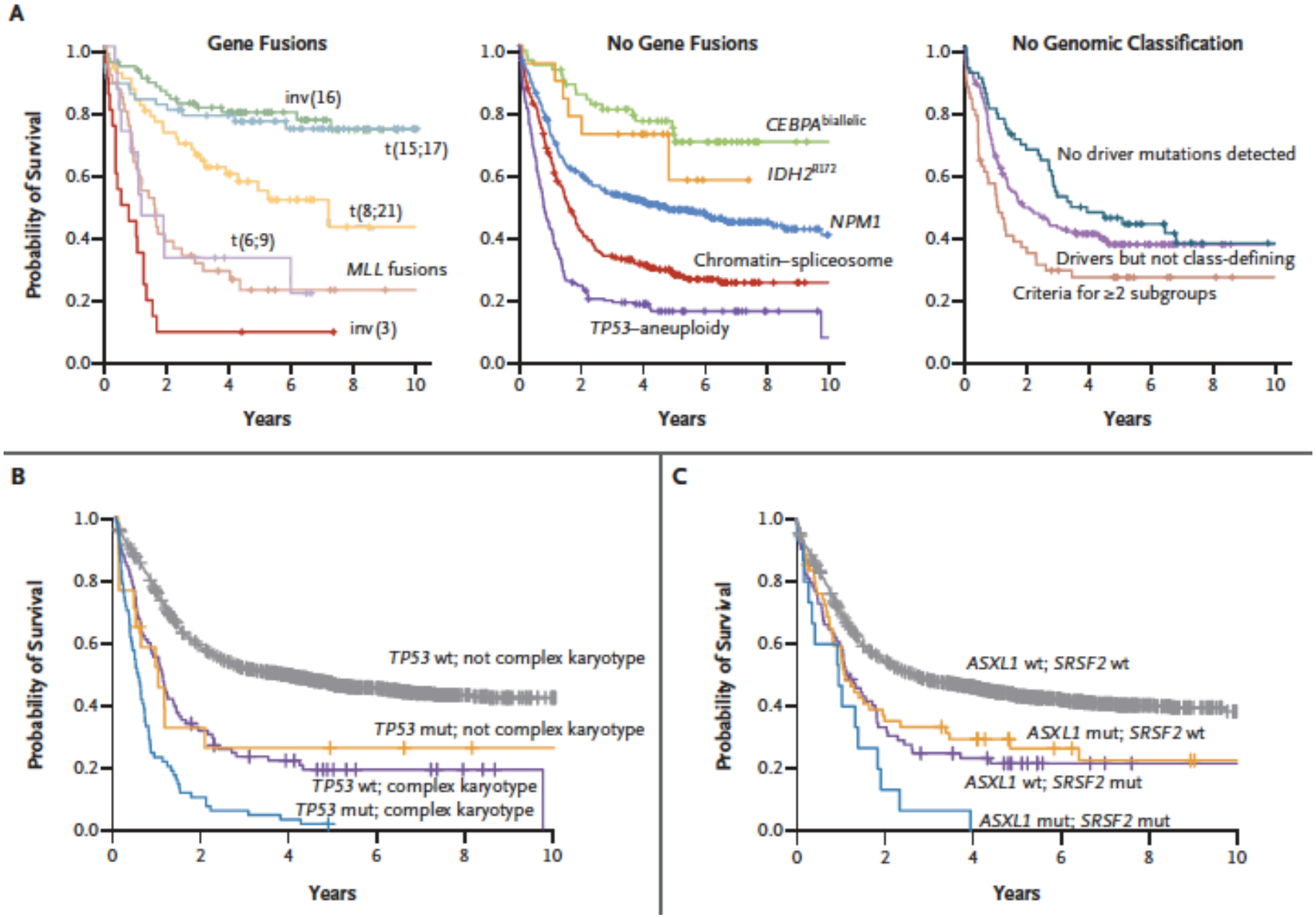
- **Path Classification/Diagnosis:** WHO Classification
- **Prognostication:** ELN classification
- **Risk-adapted Treatment:** chemotherapy vs AlloHCT
- **Molecular Targeting Therapy:** selection of small molecules targeting mutations or aberrantly functioning pathways
- **Treatment Guidance:** MRD vs CHIP
- **Disease evolution:** Changes clonal composition at relapse

AML: Pathogenesis

- Complex, diverse disease
- Genetic abnormalities include ultrastructrual changes to chromosomes, gene mutations (eg, *DNAMT3A, TET2, FLT3, NPM1, IDH1/2, TP53*), epigenetic changes, and changes in RNA splicing factors
- 86% pts have ≥ 2 genetic drivers
- **Conclusion: AML is complicated !**

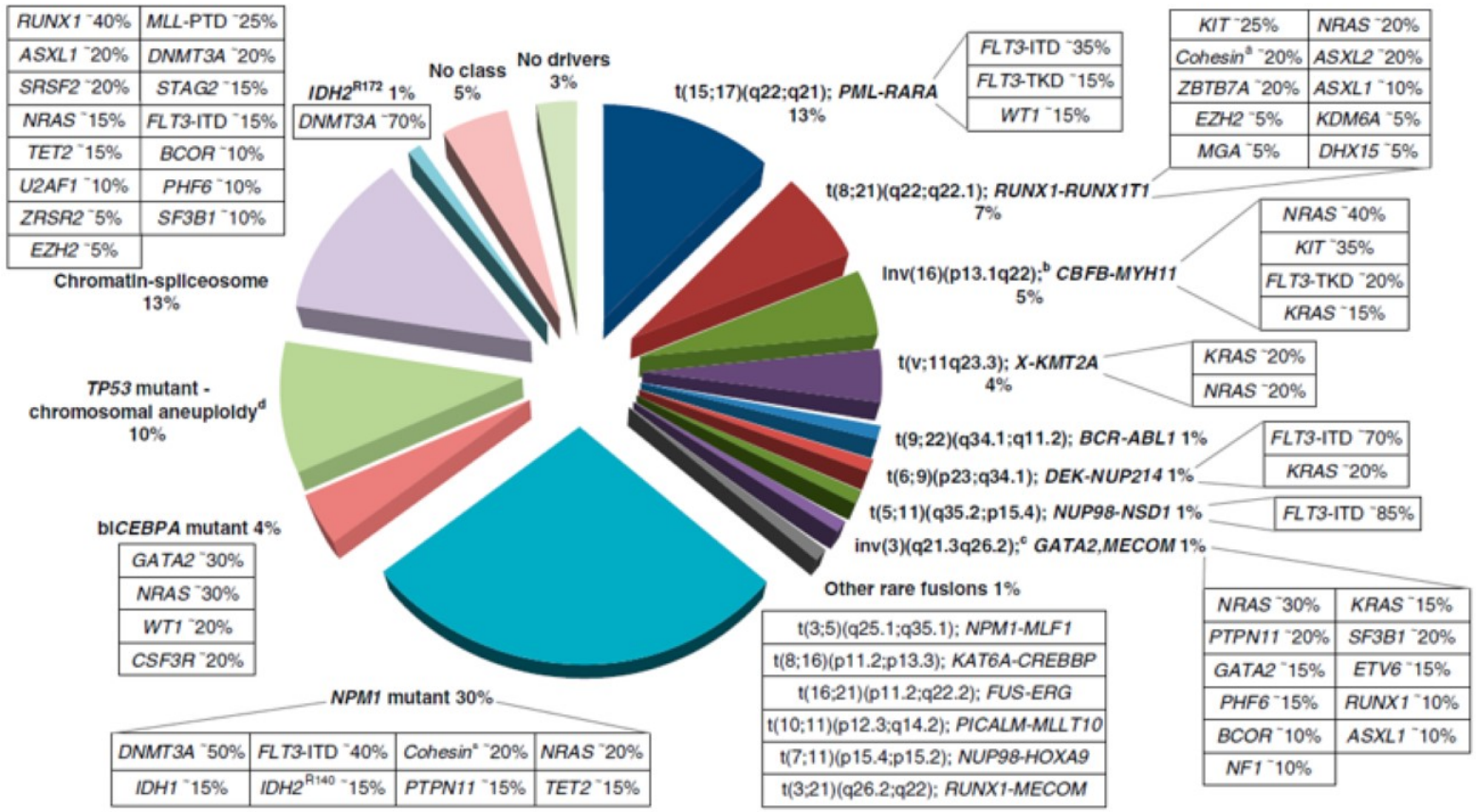


Papaemmanuil E, et al. N Engl J Med. 2016;374:2209-2221.



Papaemmanuil E, et al. N Engl J Med. 2016;374:2209-2221.

Too Many Combinations and Subgroups



Favourable

Cytogenetic

t(8;21)(q22;q22.1) for *RUNX1-RUNX1T1*, and inv(16)(p14.1q22) or t(16;16) (p13.1;q22) for *CBFB-MYH11*

Molecular

Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITDlow, and biallelic mutated *CEBPA*

ELN

Intermediate

Cytogenetic

t(9;11)(p21.3;q23.3) for *MLL3-KMT2A**, and cytogenetic abnormalities not classified as favourable or adverse

Molecular

Mutated *NPM1* and *FLT3*-ITDhigh§, and wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITDlow§ (without adverse-risk genetic lesions)

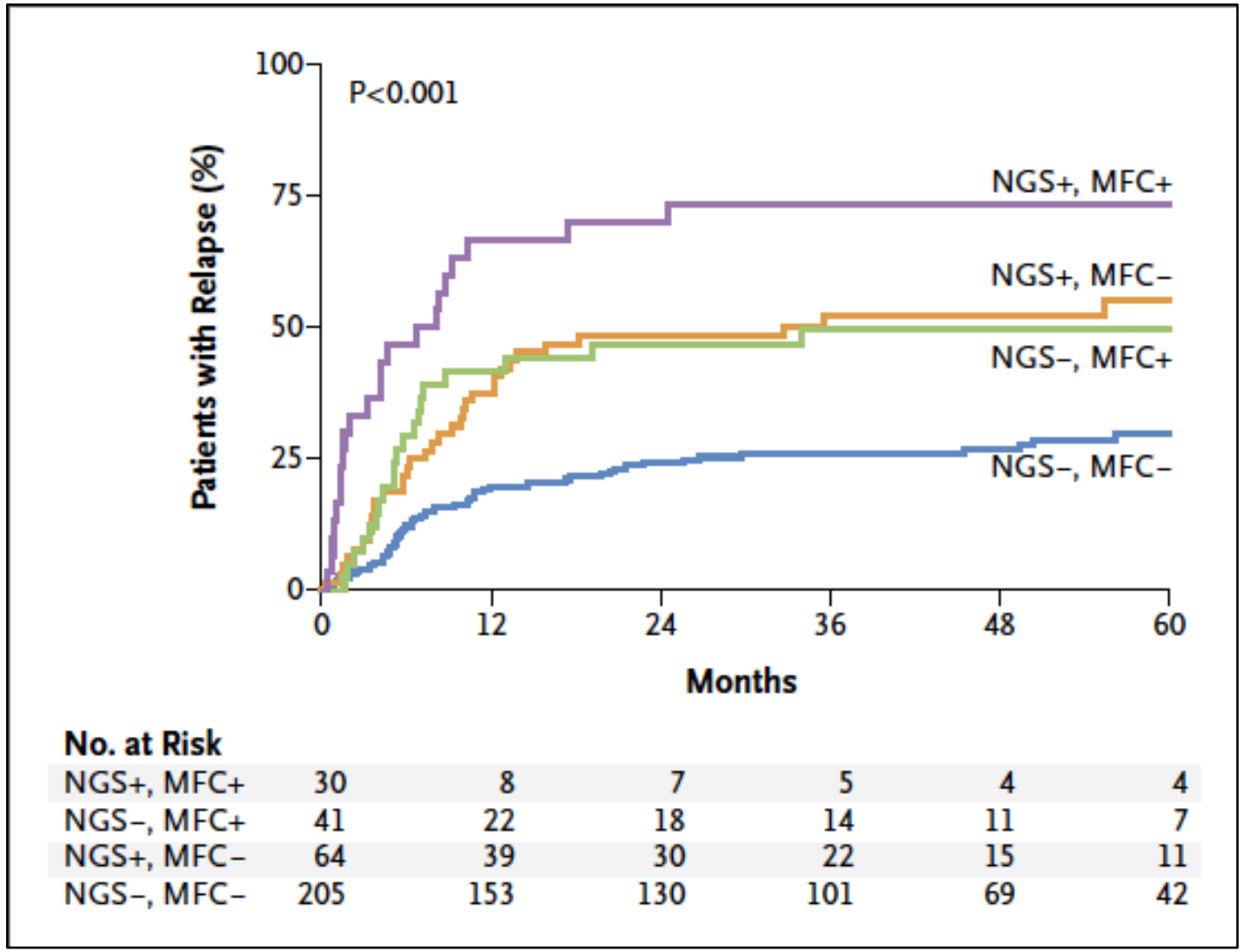
Advverse

Cytogenetic t(6;9)(p23;q34.1) for *DEK-NUP214*; t(v;11q23.3) for *KMT2A* rearranged; t(9;22)(p34.1;q11.2) for *BCR-ABL1*; inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2) for *GATA2* and *MECOM* (*EVI1*); –5 or del(5q), –7, and-17/abn(17p); complex karyotype; and monosomal karyotype

Molecular

Wild-type *NPM1* and *FLT3*-ITDhigh, mutated *RUNX1*, mutated *ASXL1*, and mutated *TP53*

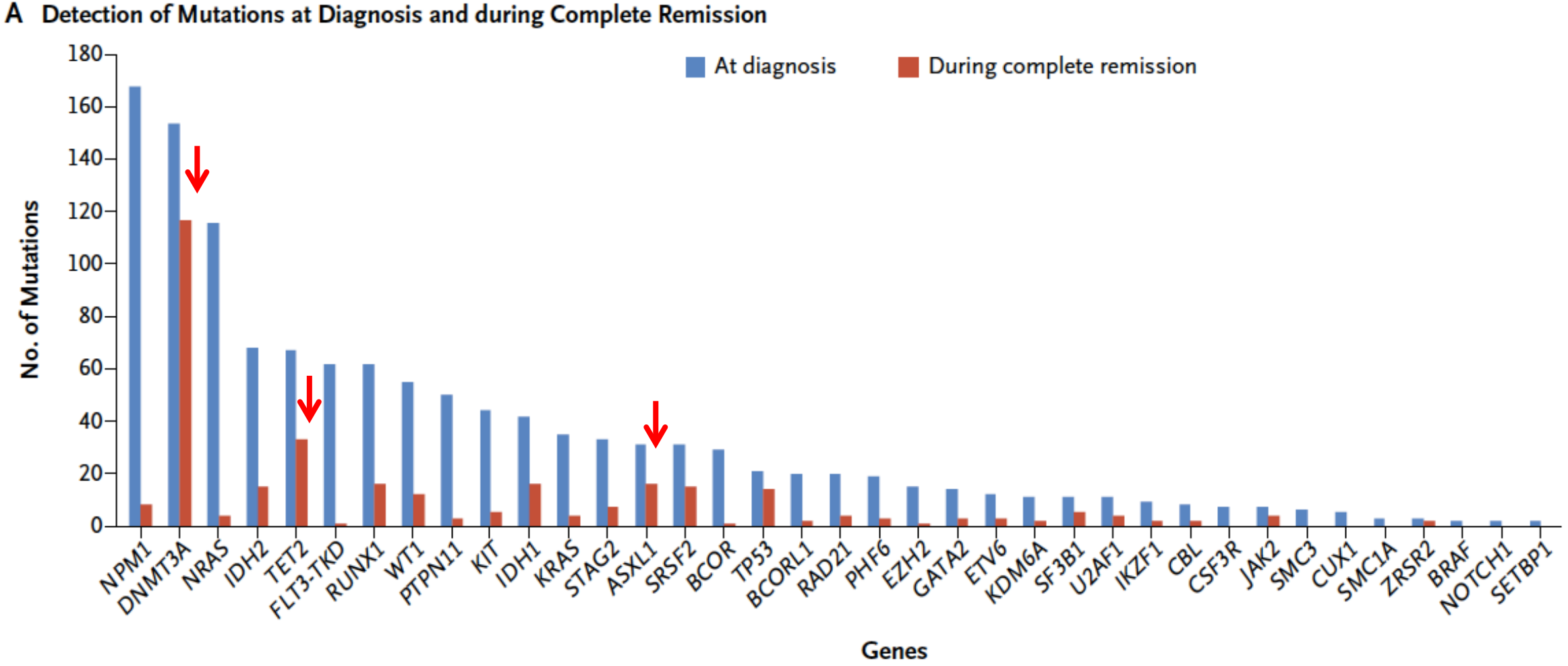
Risk-adapted Treatment: chemotherapy vs AlloHCT



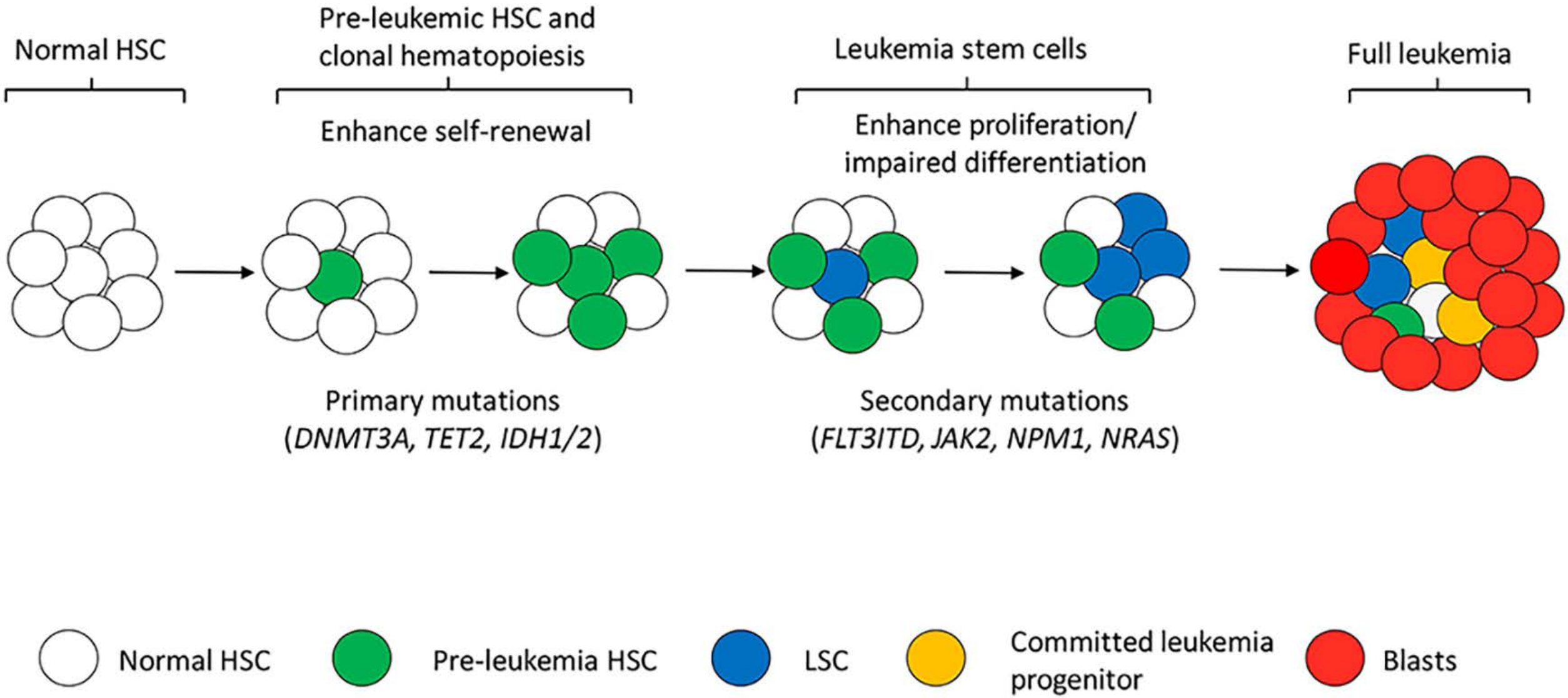
No. at Risk						
NGS+, MFC+	30	8	7	5	4	4
NGS–, MFC+	41	22	18	14	11	7
NGS+, MFC–	64	39	30	22	15	11
NGS–, MFC–	205	153	130	101	69	42

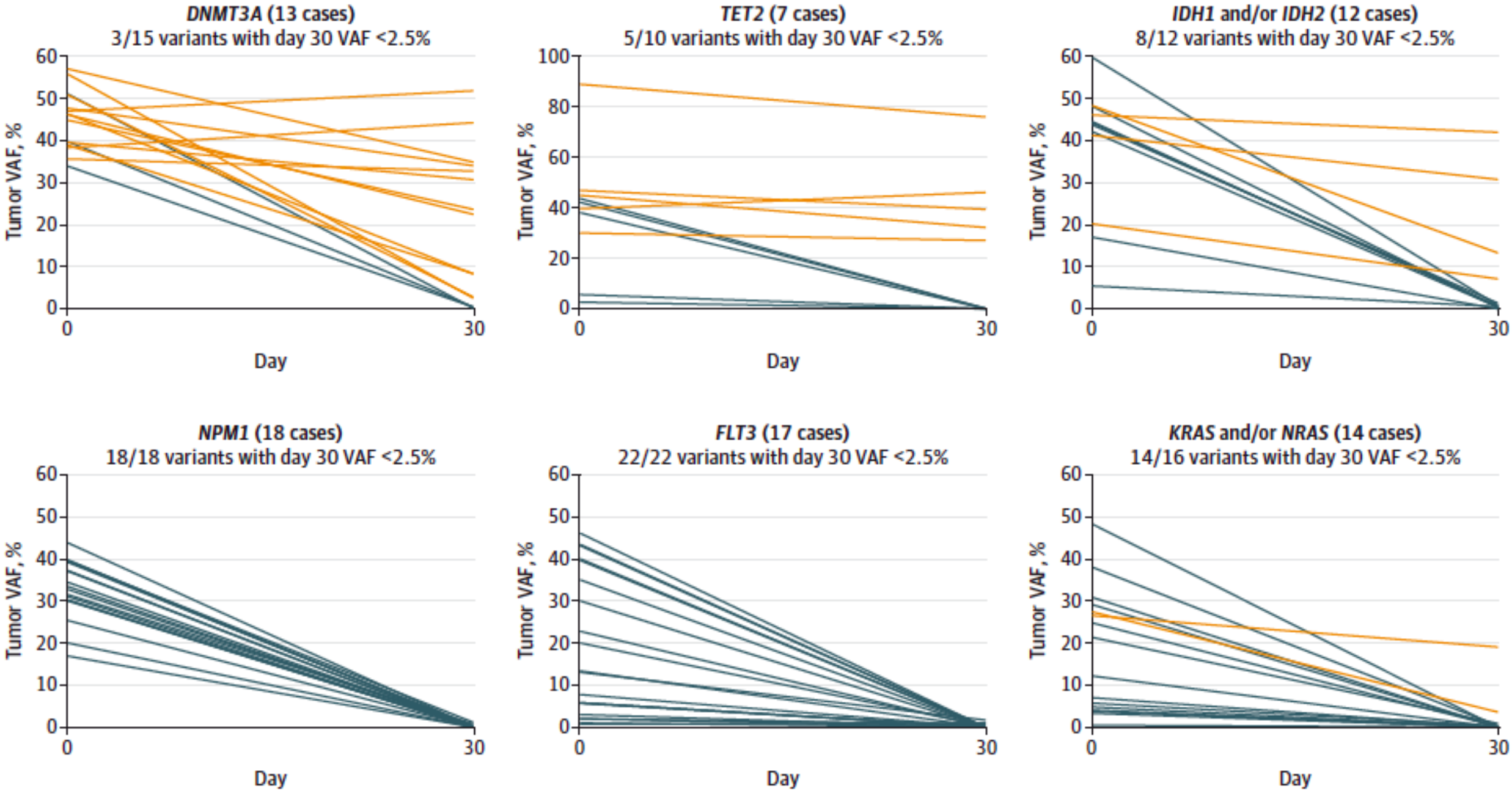
Jongen-Lavrencic M et al, NEJM, 2018

MRD vs CHIP



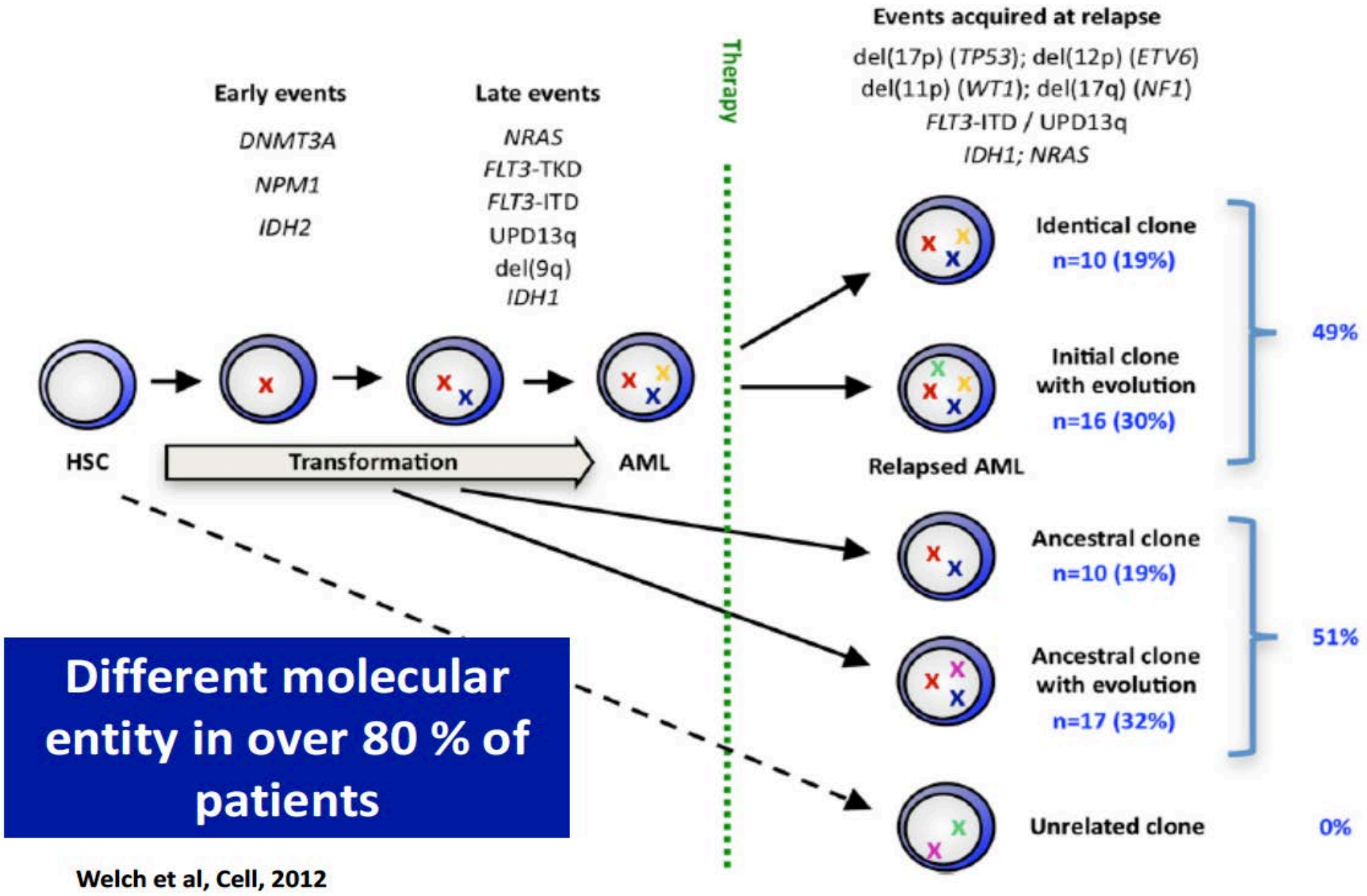
Jongen-Lavrencic M et al, NEJM, 2018


Normal HSC
Pre-leukemic HSC and clonal hematopoiesis
Enhance self-renewal
Leukemia stem cells
Enhance proliferation/ impaired differentiation
Full leukemia
Primary mutations (DNMT3A, TET2, IDH1/2)
Secondary mutations (FLT3ITD, JAK2, NPM1, NRAS)
Normal HSC
Pre-leukemia HSC
LSC
Committed leukemia progenitor
Blasts



Klco et al, JAMA Onc, 2015

Disease evolution: Changes clonal composition at relapse



AML patients' survival has improved

Âge [15;45[	Net 5-yr Survival
1989-1993	38 [30-48]
1994-1998	54 [46-63]
1999-2004	53 [47-61]
2005-2010	59 [52-67]

+21%

Âge [45;55[	
1989-1993	30 [20-46]
1994-1998	28 [20-40]
1999-2004	38 [31-48]
2005-2010	48 [40-57]

+18%

Âge [55;65[	
1989-1993	25 [18-35]
1994-1998	22 [16-30]
1999-2004	35 [28-43]
2005-2010	28 [22-35]
	]

+3%

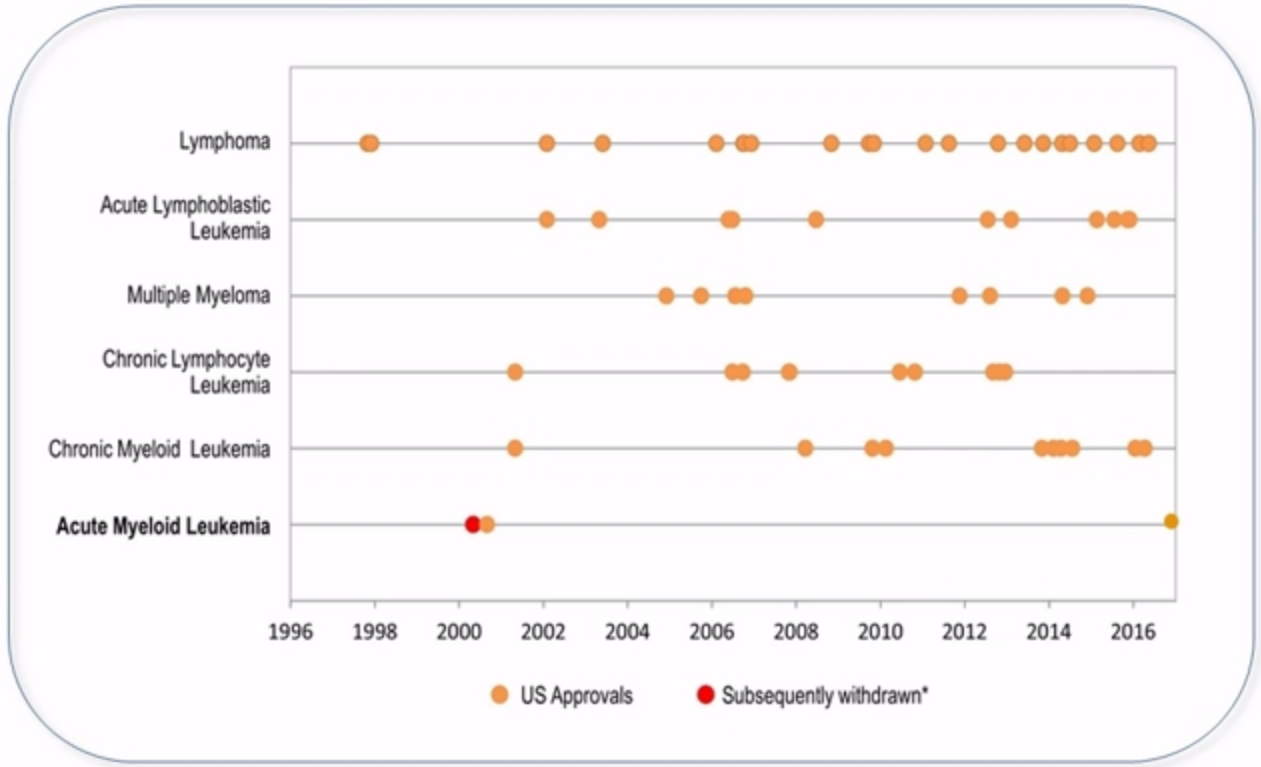
Âge [65;75[	
1989-1993	8 [5-14]
1994-1998	10 [7-15]
1999-2004	14 [10-19]
2005-2010	18 [13-24]
	]

+10%

Âge [75;++[	
1989-1993	5 [2-10]
1994-1998	4 [2-8]
1999-2004	4 [2-7]
2005-2010	3 [2-6]

+0%

… In the absence of registered new agents



http://www.e-cancer.fr/Expertises-et-publications/Catalogue-des-publications/

The Case for Abandoning Induction Chemotherapy

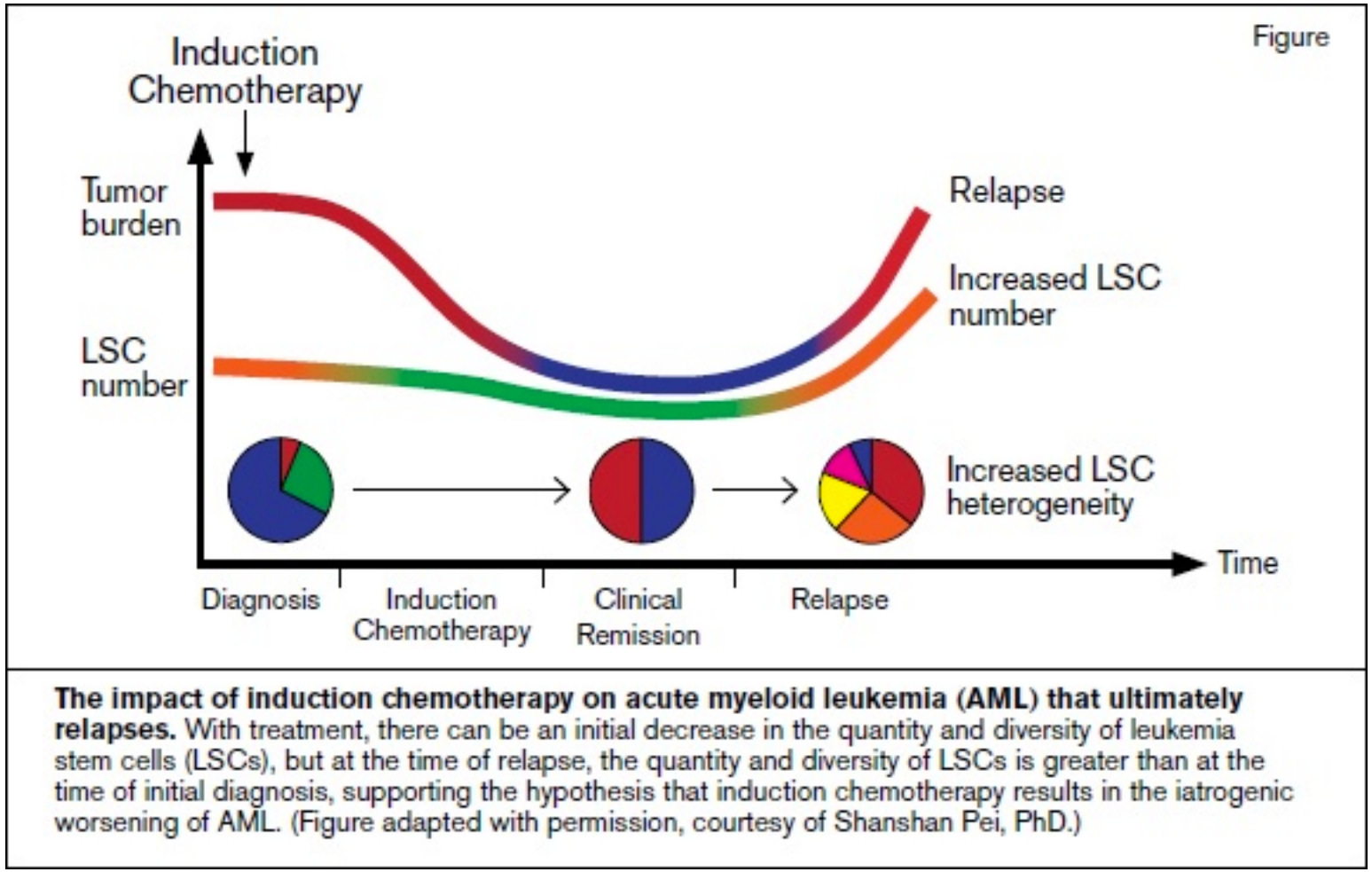
DANIEL A. POLLYEA, MD, MS

Associate Professor of Medicine, Division of Hematology, University of Colorado School of Medicine, Aurora, CO

If the definition of insanity is doing the same thing over and over again and expecting a different result (just as the definition of a bad review article may be one that leads off with a questionable cliché), hematologists treating acute myeloid leukemia (AML) with intensive induction chemotherapy should reconsider the logic of this approach. To be fair, there are subsets of patients, such as those with core binding factor chromosomal rearrangements, or *NPM1* or *CEBPA* mutations, for whom intensive chemotherapy is effective and potentially curative.[1-3] For everyone else, the long-standing argument in favor of induction chemotherapy is that it beats the alternative, which in the absence of any U.S. Food and Drug Administration (FDA) –approved therapies is ... nothing. Generations of hematologists who spent careers banging their heads against the chemotherapy wall would certainly have traded their purine analogs in for a sleek new targeted therapy. Colleagues, the time is now upon us: I am excited to announce that the field has officially entered the postchemotherapy era. Allow me to explain.

First, we must make the case as to why there is a need to abandon intensive induction chemotherapy. For patients younger than 60 years, the complete remission (CR) rate with induction is around 70 percent, but the treatment-related mortality (TRM) rate may be as high as 13 percent; five-year overall survival (OS), the surrogate endpoint for cure, is only around 30 percent.[4] Not surprisingly, given that the basic recipe for induction chemotherapy has not substantially changed in more than 40 years,[5] no meaningful improvements in outcomes have occurred for decades that are not attributable to advancements in supportive care or transplantation.[6]

The Hematologist, 2017



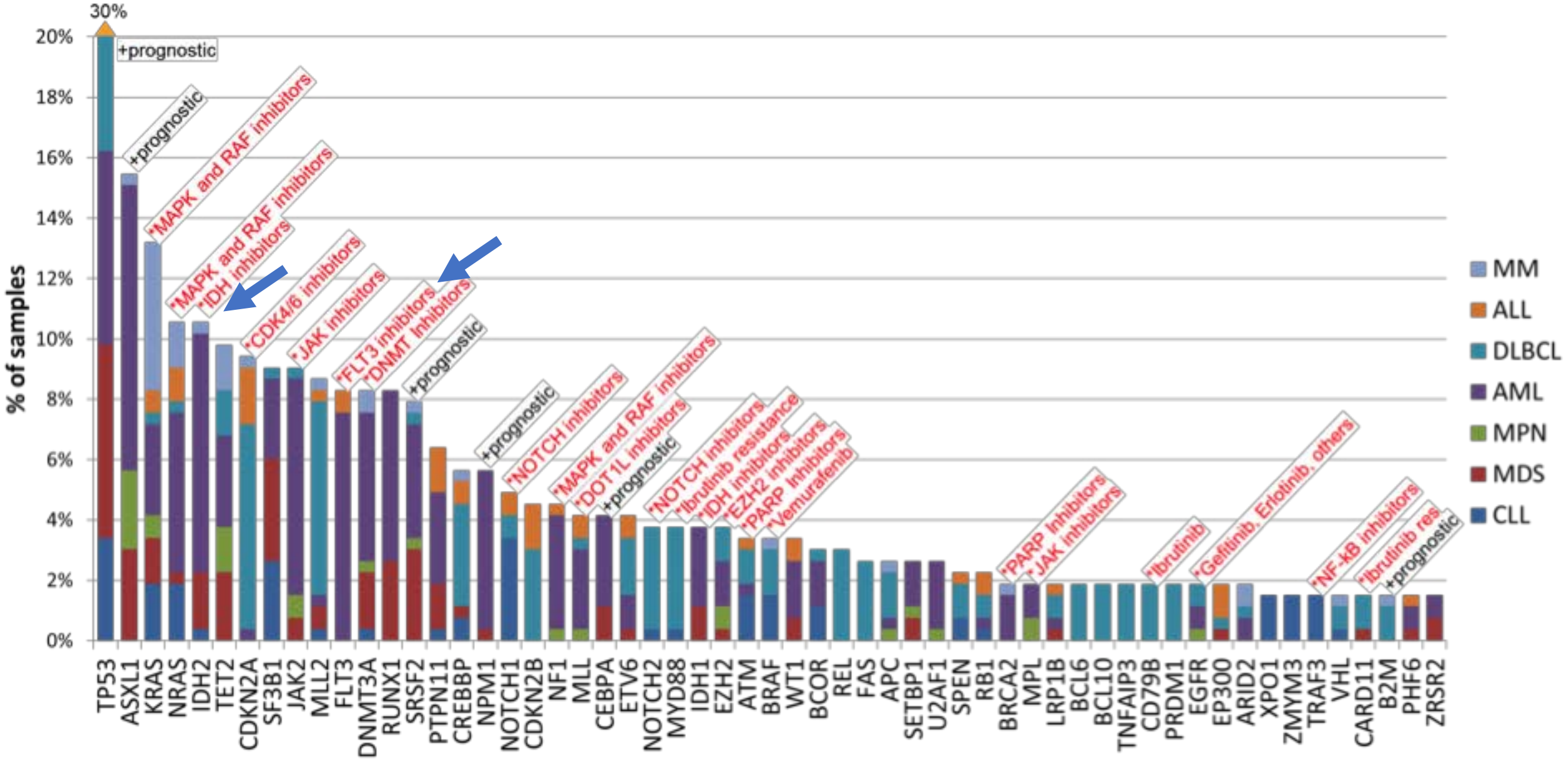
The impact of induction chemotherapy on acute myeloid leukemia (AML) that ultimately relapses. With treatment, there can be an initial decrease in the quantity and diversity of leukemia stem cells (LSCs), but at the time of relapse, the quantity and diversity of LSCs is greater than at the time of initial diagnosis, supporting the hypothesis that induction chemotherapy results in the iatrogenic worsening of AML. (Figure adapted with permission, courtesy of Shanshan Pei, PhD.)

can be slain. In light of these reports, we must consider the reality that very often, when treating AML with intensive chemotherapy, we are not simply passive users of a therapy that doesn't work very well, but instead, *we are responsible for making this disease worse*. Call relapsed AML after induction what it is: iatrogenic AML (Figure).

(Cont. on page 13)

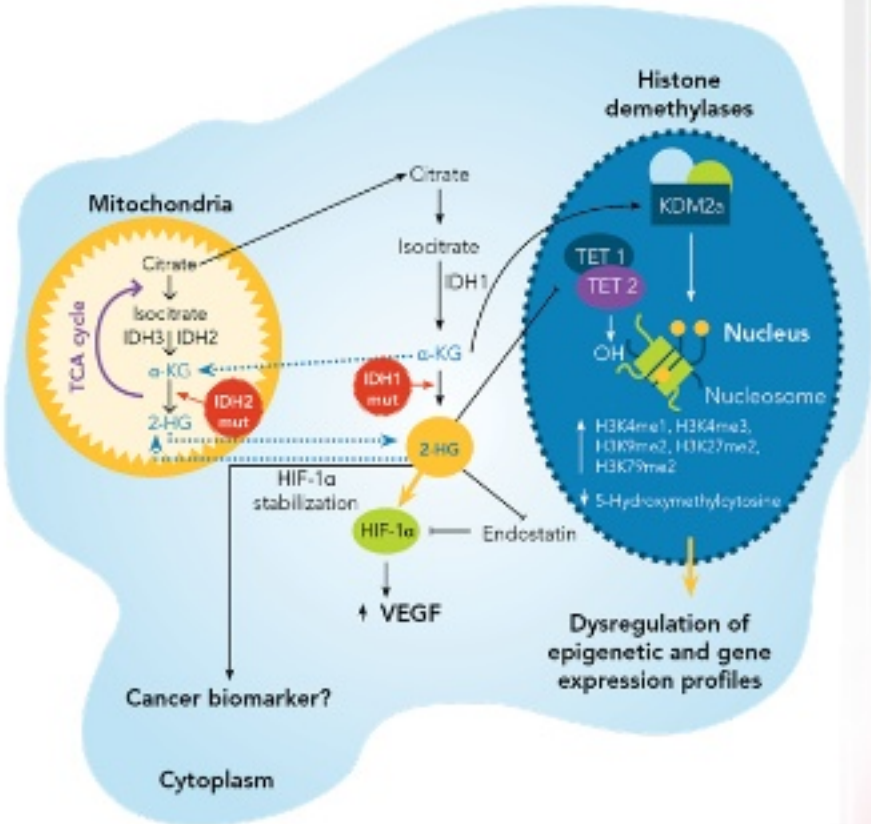
The Hematologist, 2017

ACTIONABLE MUTATIONS IN HEMATOLOGIC MALIGNANCIES

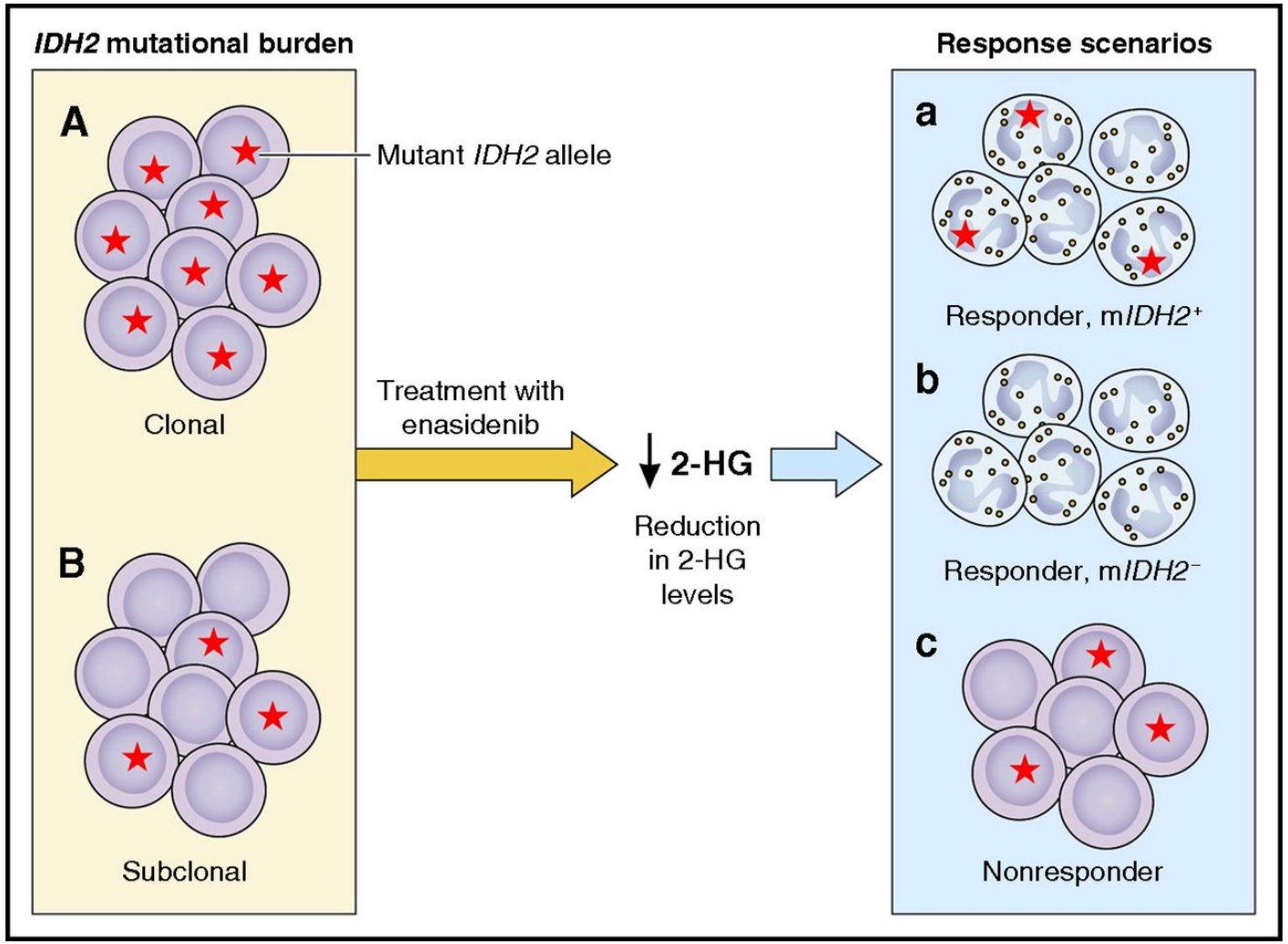


Isocitrate Dehydrogenase (IDH) Mutations as a Target in AML

- **IDH is an enzyme of the citric acid cycle**
- **Mutant *IDH2* produces 2-hydroxyglutarate (2-HG), which alters DNA methylation and leads to a block in cellular differentiation**
- **AG-221 (CC-90007) is a selective, oral, potent inhibitor of the mutant *IDH2* (m*IDH2*) enzyme**

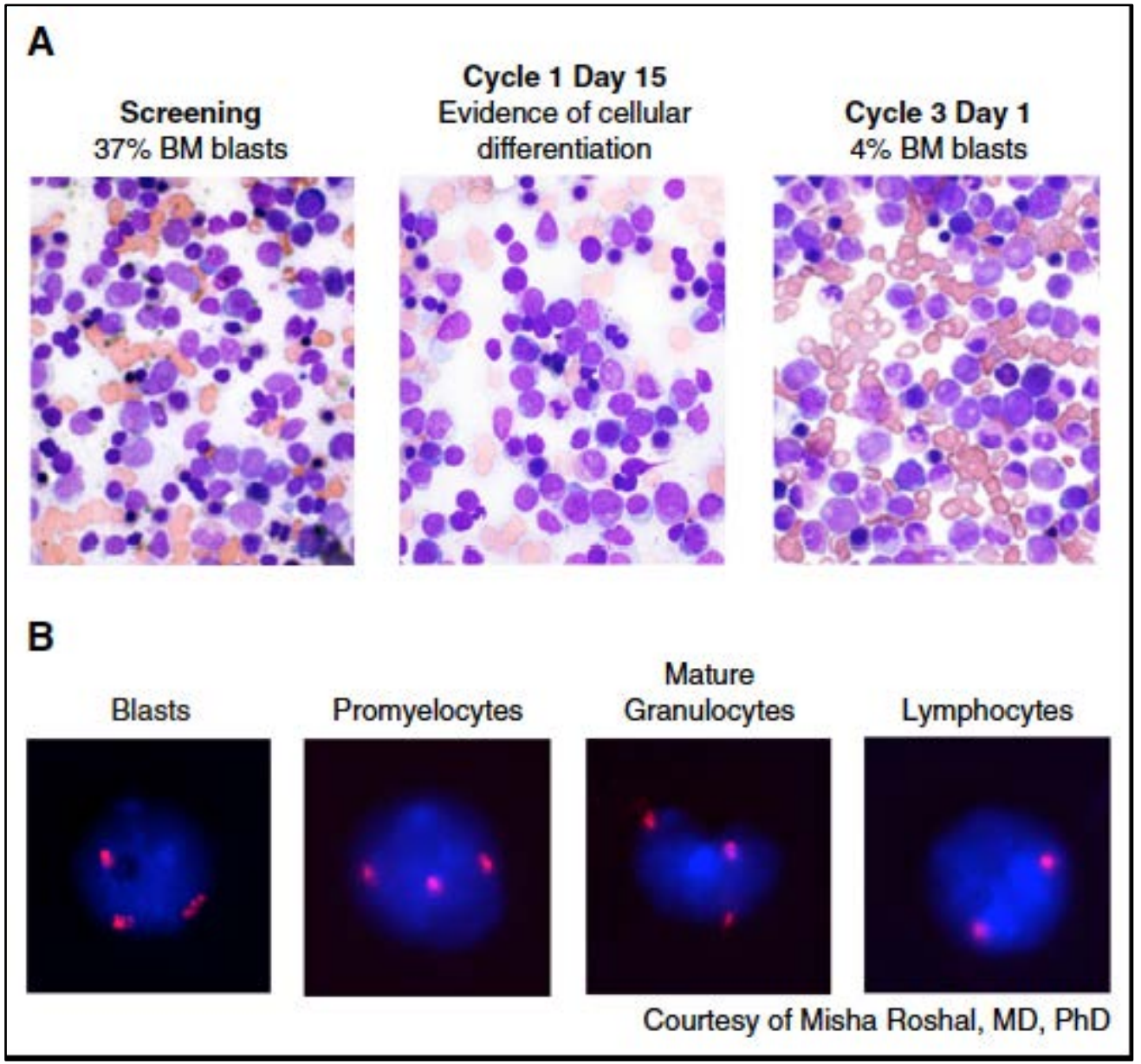


Response dynamics in IDH2 mutant AML patients treated with enasidenib.

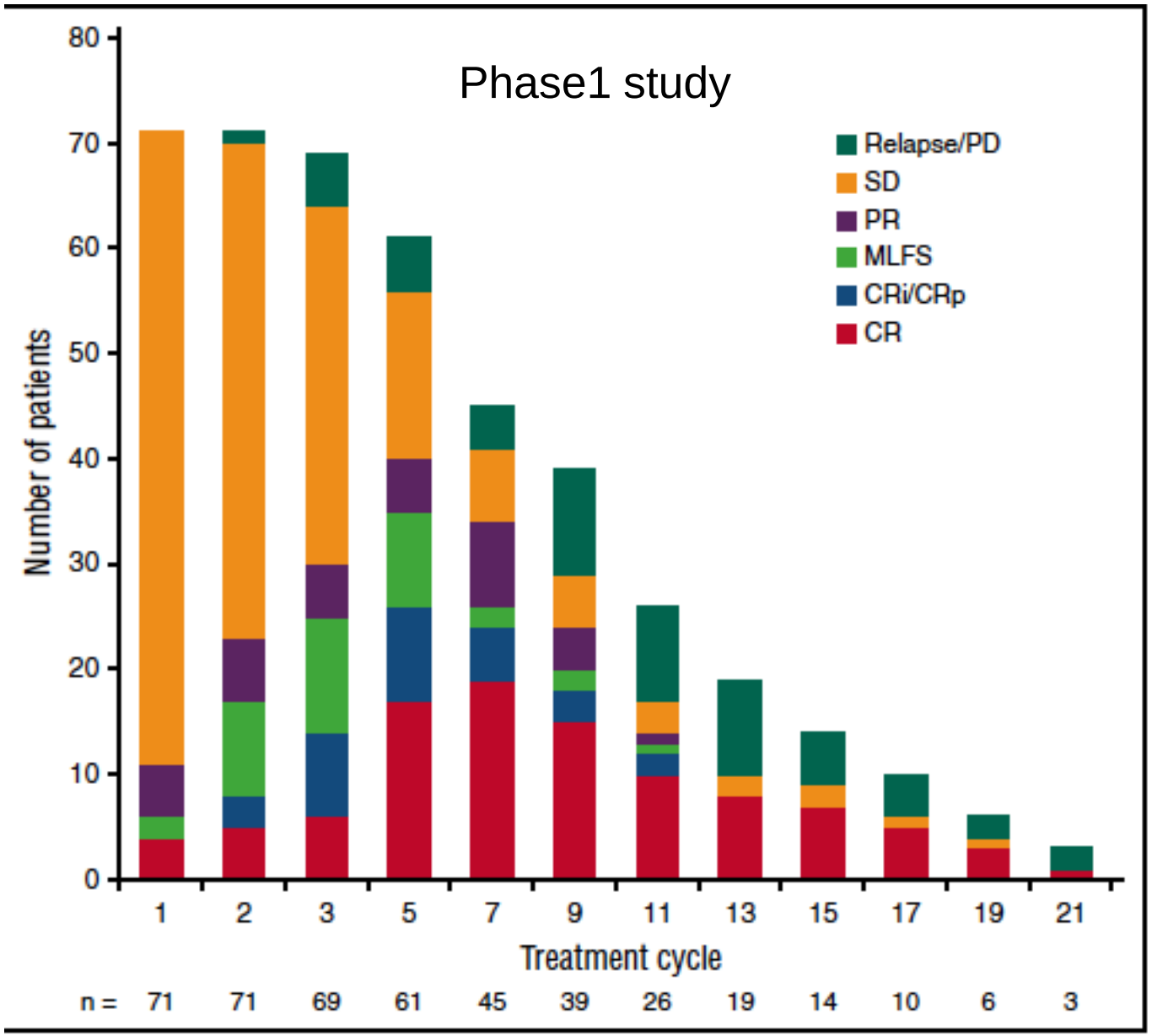


Bas J. Wouters Blood 2017;130:693-694

Enasidenib Induces AML Cell Differentiation to Promote Clinical Response



Amatangelo MD et al. Blood. 2017



Relapsed/refractory AML
Enasidenib 100 mg daily (n=109)

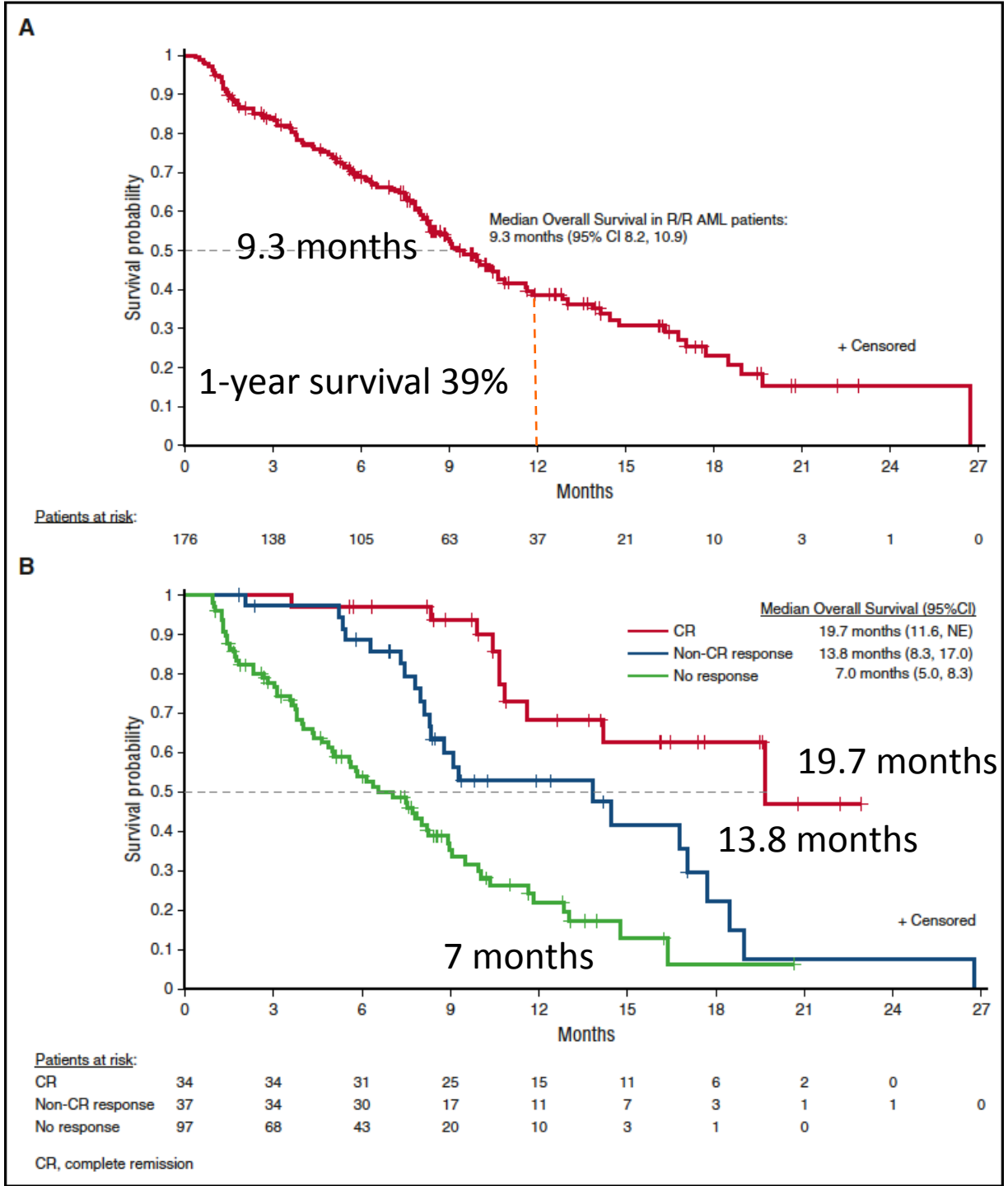
CR=38.5%

Median time to response: 1.9 mo. (range 0.5-9.4)

87.3% of responding patients attained a first response by cycle 5

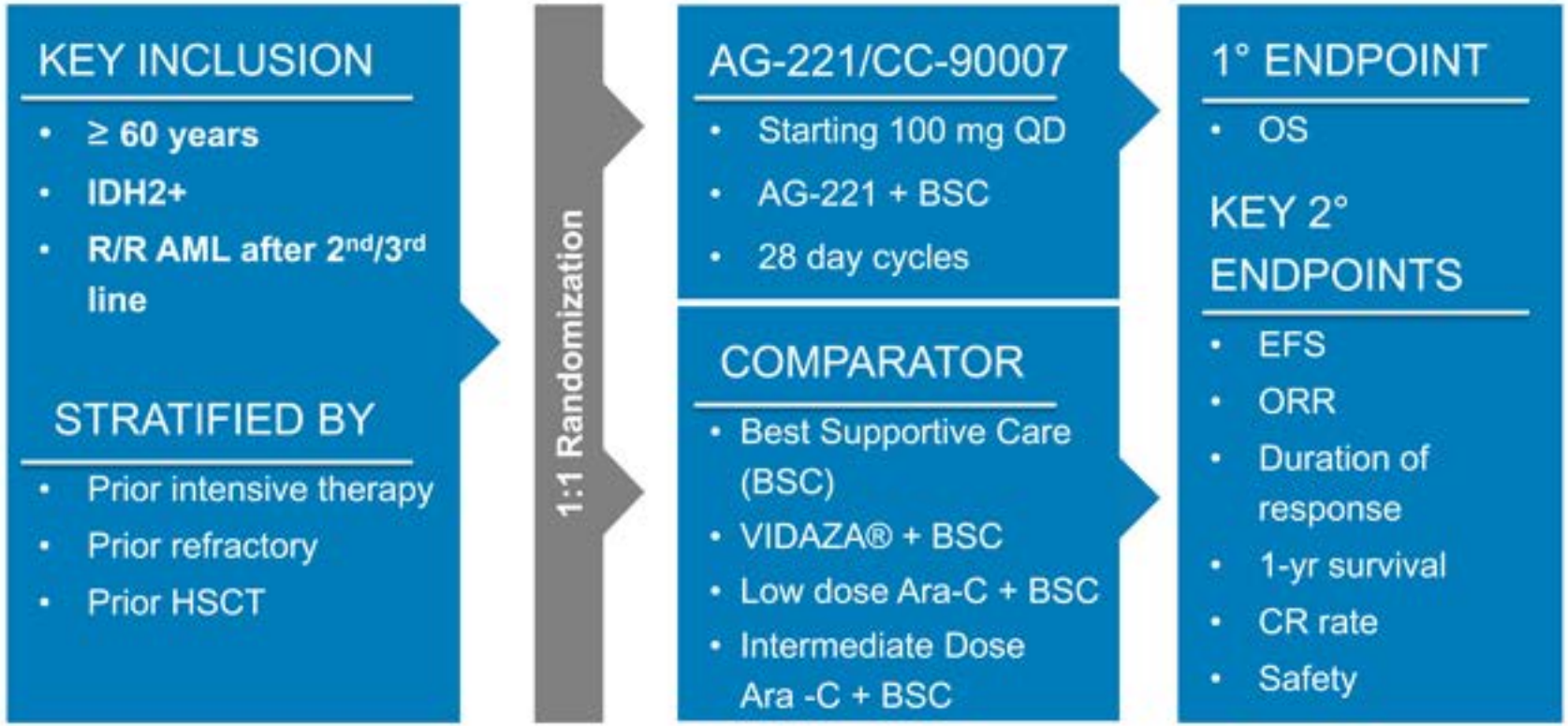
Figure 1. Evolution of response during treatment of responding patients (n = 71). Bars reflect responses at each cycle. CR, complete response; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; MLFS, morphologic leukemia-free state; PD, progressive disease; PR, partial response; SD, stable disease.

Stein et al. Blood. 2017



Stein et al. Blood. 2017

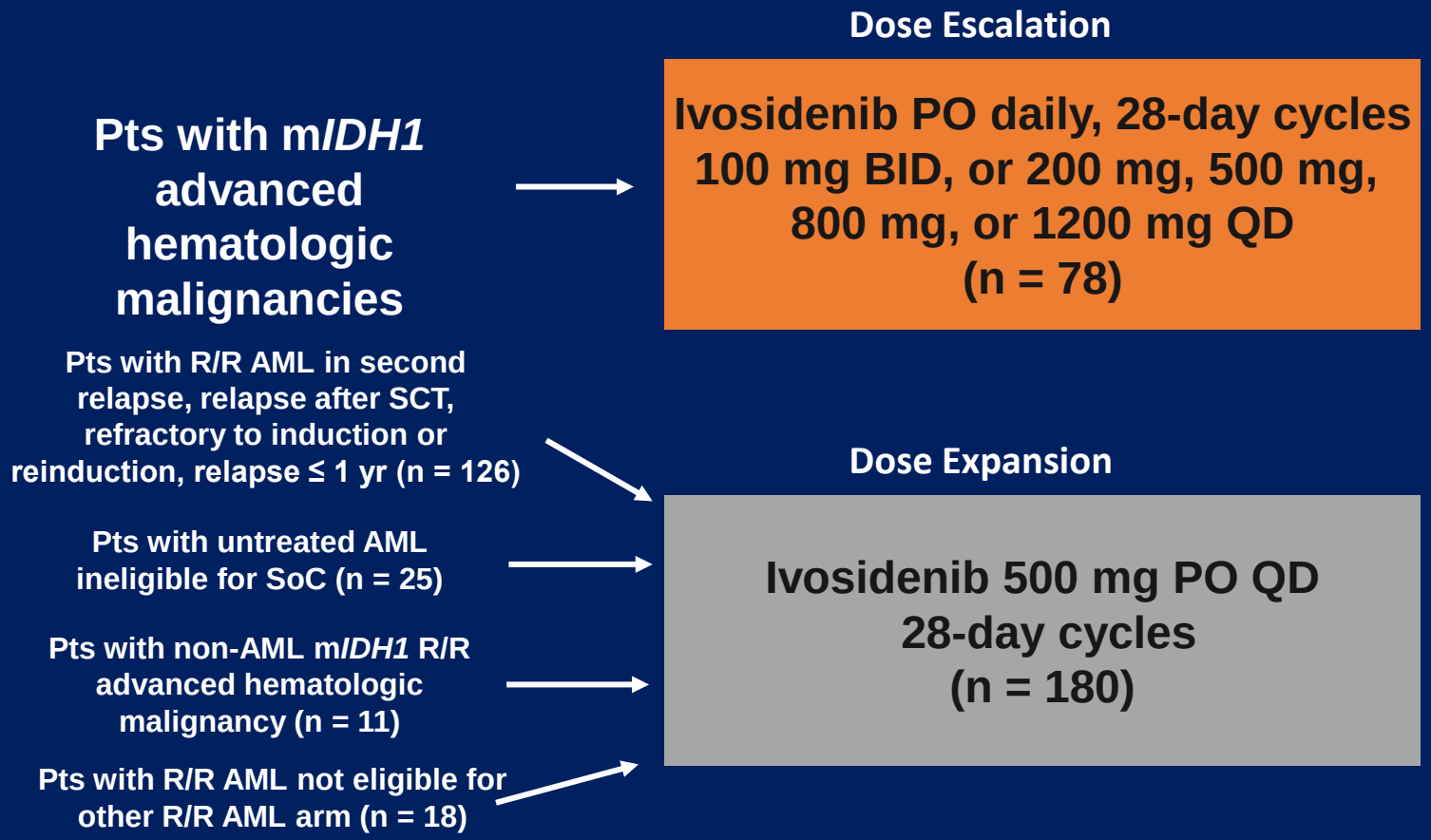
IDHENTIFY: Global Phase 3 Study to Evaluate the Efficacy of AG-221 in R/R AML



- **280 patients**
- **No crossover**

Ivosidenib in Mutant *IDH1* AML: Phase I Study Design

- Multicenter, open-label, dose-escalation/expansion trial



- Primary endpoints: safety and tolerability, MTD and/or RP2D, and clinical activity* in m*IDH1* R/R AML
- Secondary endpoints: DLTs, PD, PK, preliminary clinical activity in advanced hematologic malignancies
- Exploratory endpoints: determination of comutations and m*IDH1* VAF

*CR CRh

DiNardo CD, et al. ASH 2017. Abstract 725.

Ivosidenib in Mutant *IDH1* AML: Response in Primary R/R AML Set

Outcome	Primary R/R AML Set (n = 125)
CR + CRh, % (95% CI)	30.4 (22.5-39.3)
▪ Median time to CR/CRh, mos (range)	2.7 (0.9-5.6)
▪ Median duration of CR/CRh, mos (range)	8.2 (5.5-12.0)
CR, % (95% CI)	21.6 (14.7-29.8)
▪ Median time to CR, mos (range)	2.8 (0.9-8.3)
▪ Median duration of CR, mos (95% CI)	9.3 (5.6-18.3)
CRh, %*	8.8
ORR, % (95% CI)	41.6 (32.9-50.8)
▪ Median time to first response, mos (range)	1.9 (0.8-4.7)
▪ Median duration of response, mos (95% CI)	6.5 (4.6-9.3)
Best response, %	
▪ CR	21.6
▪ CRi or CRp	12.8
▪ MLFS	7.2
▪ SD	35.2
▪ PD	10.4
▪ NA	12.8

- Median treatment duration for primary R/R AML set: 3.9 mos (range: 0.1-25.8)

Duration of Best Overall Response in Responders (n = 52)

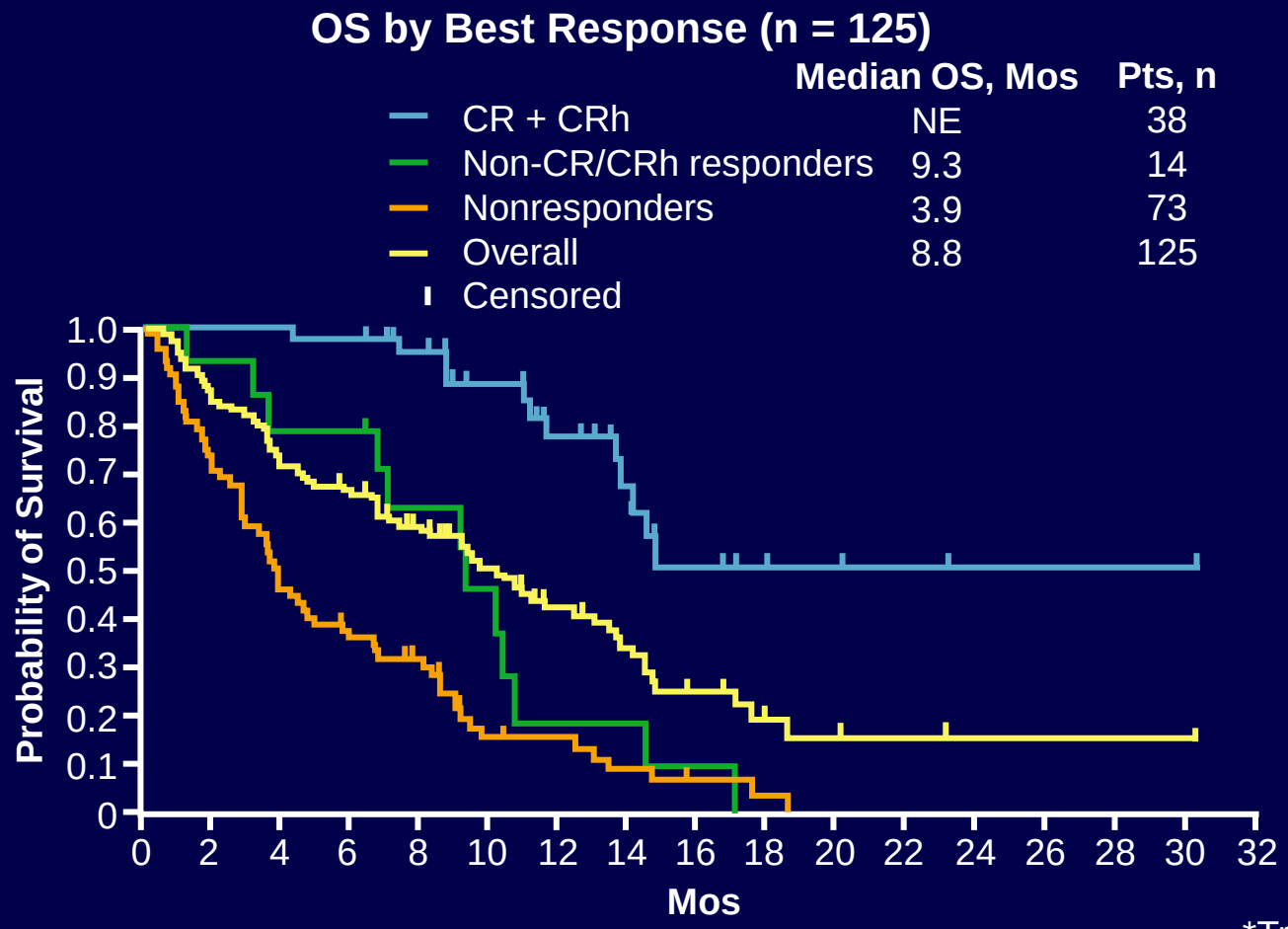
Duration of Response	CR + CRh	CR	All
Median, mos	8.2	9.3	6.5
At 6 mos, %	59.3	67.5	55.0
At 12 mos, %	32.4	41.2	24.6

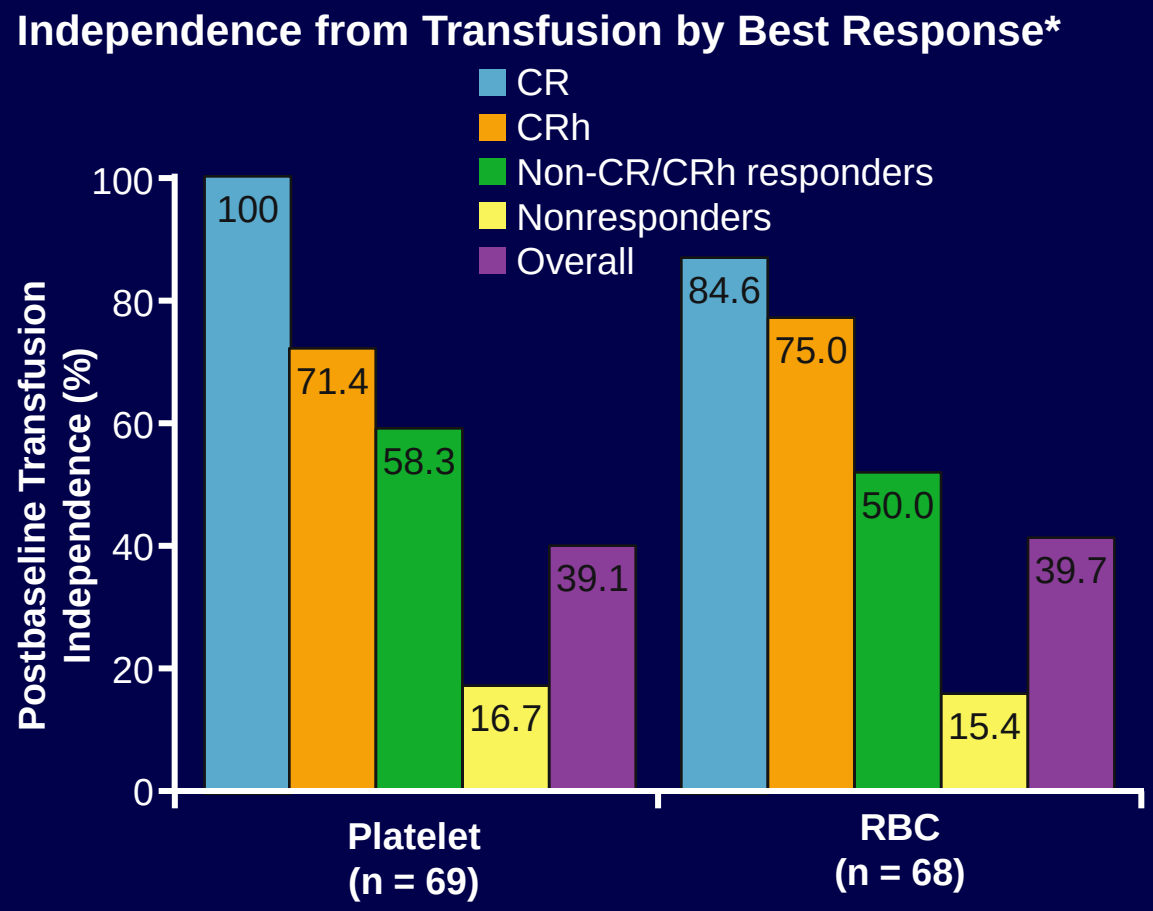
*6 pts w/investigator-assessed CRi/CRp, 5 w/MLFS

MLFS, morphologic leukemia-free status

DiNardo CD, et al. ASH 2017. Abstract 725.

Ivosidenib in Mutant *IDH1* AML: OS and Transfusion Independence in R/R AML





*Transfusion independence: no transfusion for at least 1 56-day period.

DiNardo CD, et al. ASH 2017. Abstract 725.

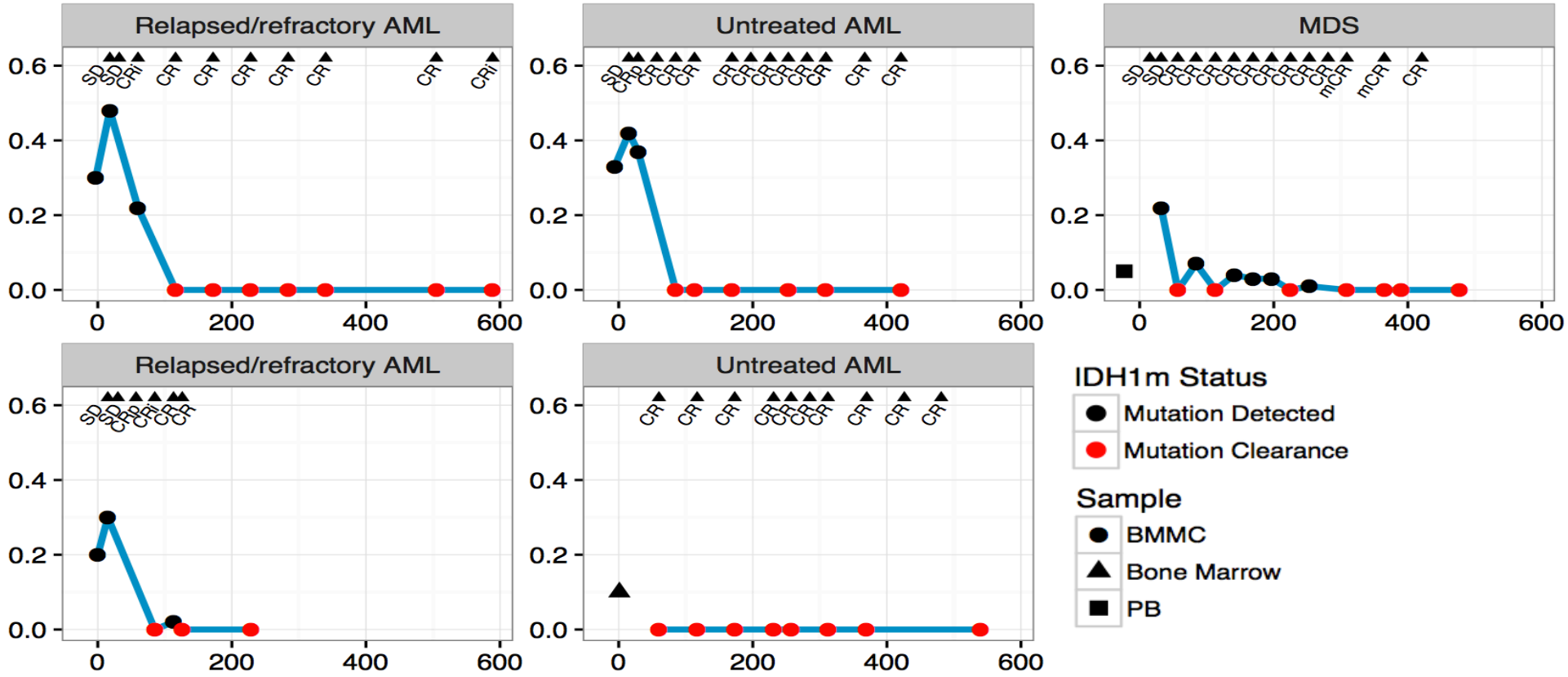
Ivosidenib in Mutant *IDH1* AML: Adverse Events (Any Cause)

Adverse Event, % (N = 258)	Any grade	Grade ≥ 3
Any	98.8	77.5
Diarrhea	33.3	2.3
Leukocytosis	30.2	6.6
Nausea	29.5	1.2
Fatigue	28.7	3.1
Febrile neutropenia	25.2	24.8
Dyspnea	23.6	3.5
Anemia	23.3	19.0
QT segment prolongation	22.5	8.9
Peripheral edema	21.7	0.0

Adverse Event, % (N = 258)	Any grade	Grade ≥ 3
Pyrexia	20.5	1.6
Decreased appetite	19.8	1.6
Constipation	18.6	0.8
Cough	18.6	0.4
Hypokalemia	17.4	2.7
Vomiting	17.4	1.2
Thrombocytopenia	15.9	13.6
Arthralgia	15.9	1.9
Dizziness	15.5	0.4
Epistaxis	15.1	0.8

DiNardo CD, et al. ASH 2017. Abstract 725.

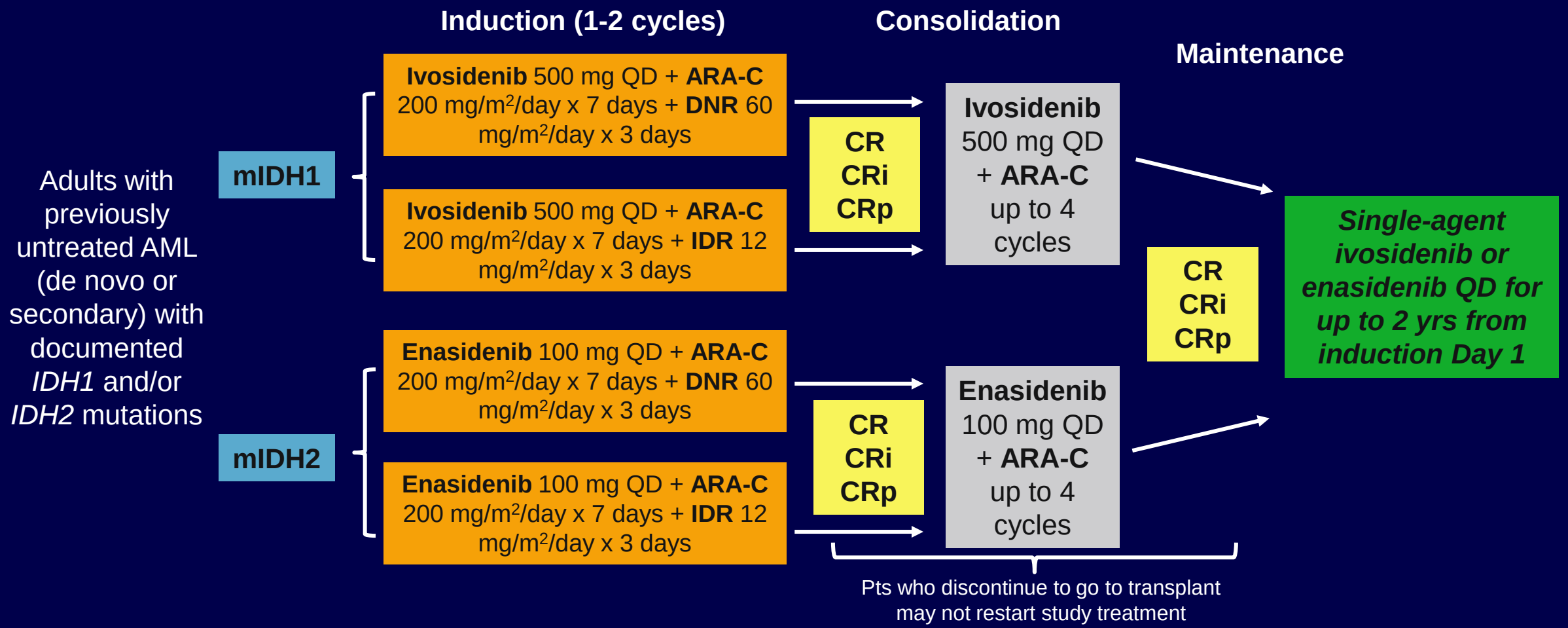
AG-120: IDH1 Mutation Clearance in Patients with CR (5/14 Patients)



Dinardo CD, et al. *Blood.* 2016;128:1070a.

mIDH Inhibition in AML: Study Design

Open-label, phase I dose-escalation and -expansion trial



Primary objectives: safety and tolerability of ivosidenib and enasidenib

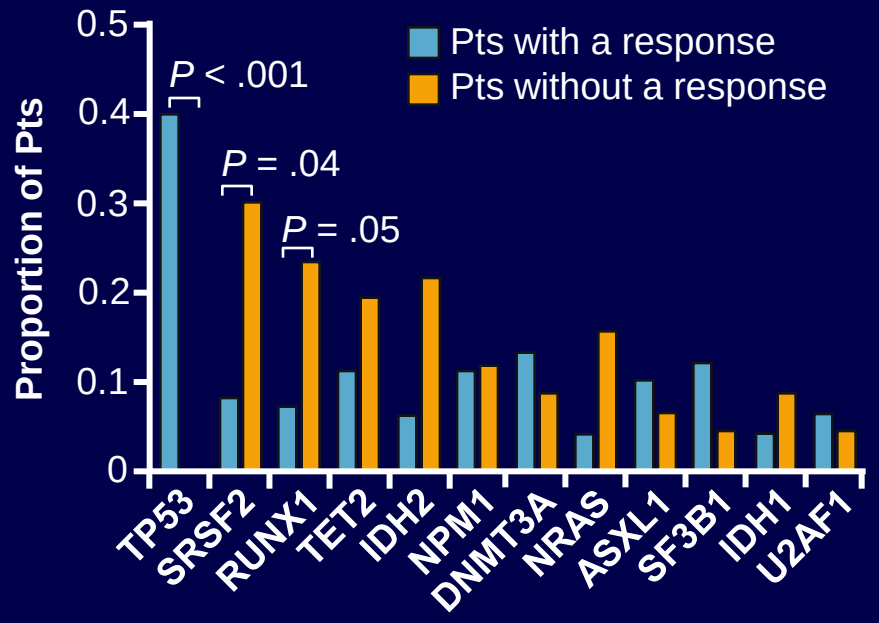
Stein EM, et al. ASH 2017. Abstract 726.

TP53 Mutations: Frequency and Prognosis

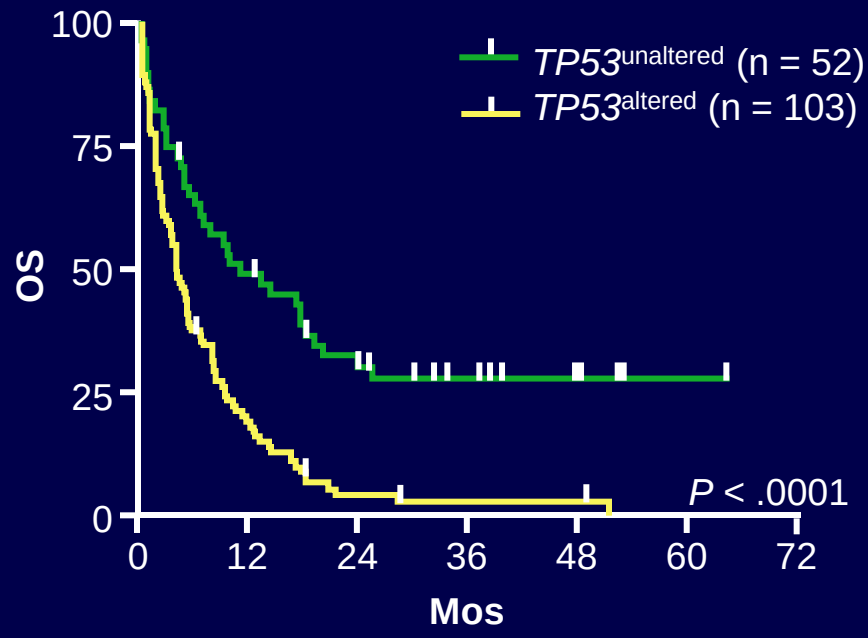
- *TP53* mutations found in ~ 8% of AML pts[1]
  - Incidence increases with age
  - Predominantly in pts with *complex karyotype*
- Confers poor outcome to chemo, including lower CR rates, inferior RFS, OS[2]

All 21 pts w/mutated *TP53* responded

Response to Decitabine by Gene Mutation[3]

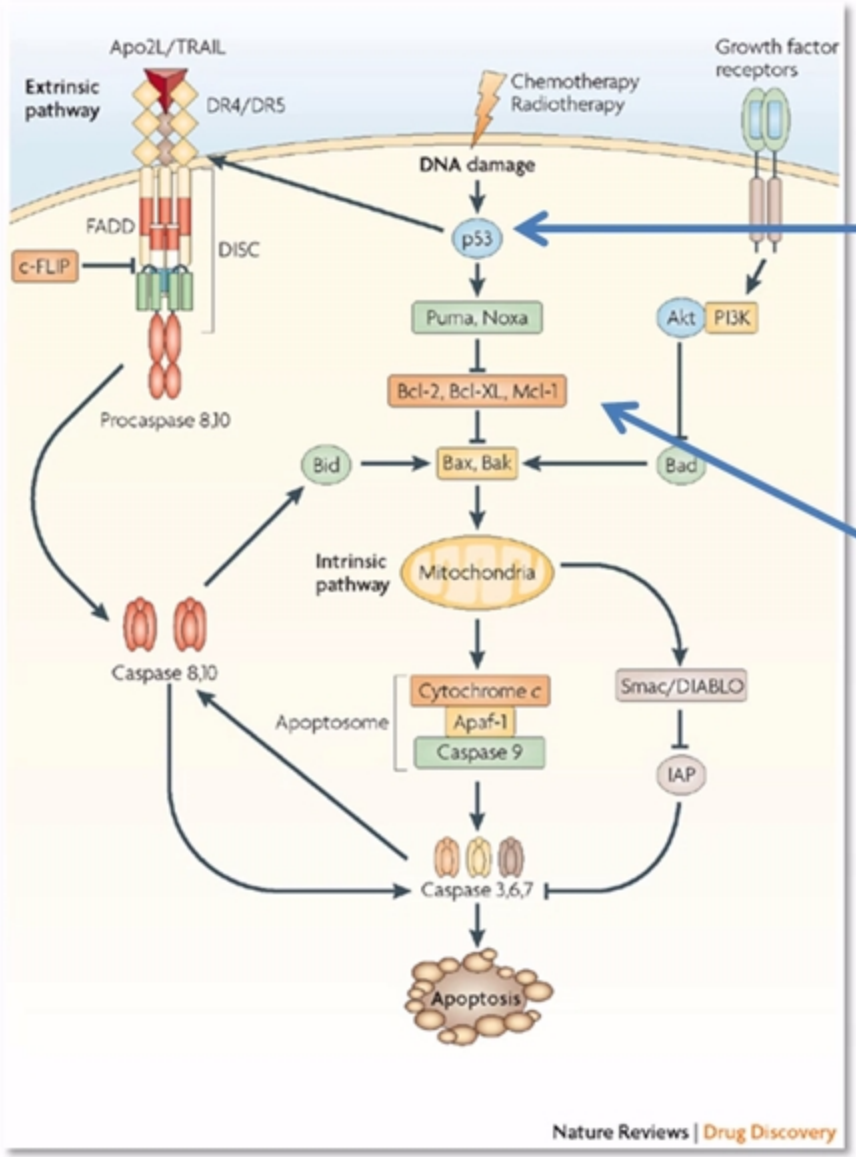


OS by Karyotype Complexity[2]



1. Döhner H, et al. N Engl J Med. 2015;373:1136-1152. 2. Rucker FG, et al. Blood. 2012;119:2114-2121. 3. Welch, et al. N Engl J Med. 2016;375:2023.

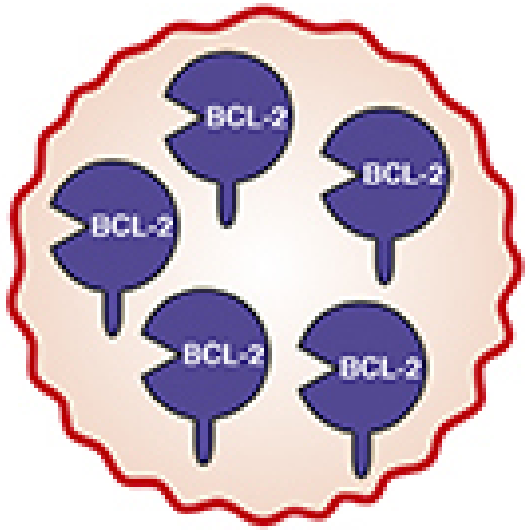
Induction of apoptosis in AML



Activation of wild-type p53

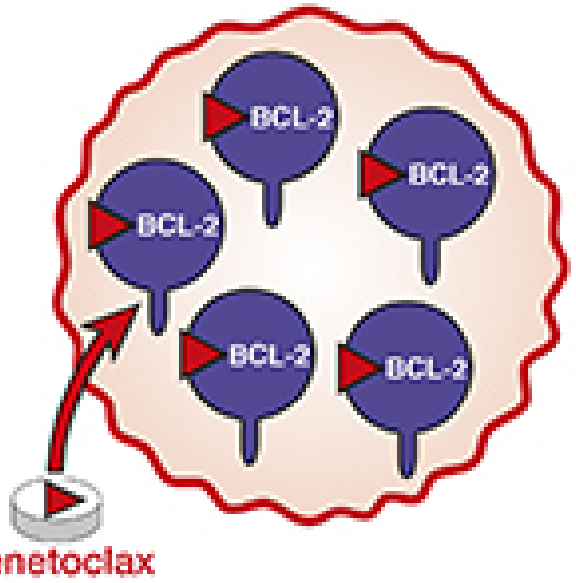
Inhibition of BCL2 and other anti-apoptotic proteins

Cancer cell

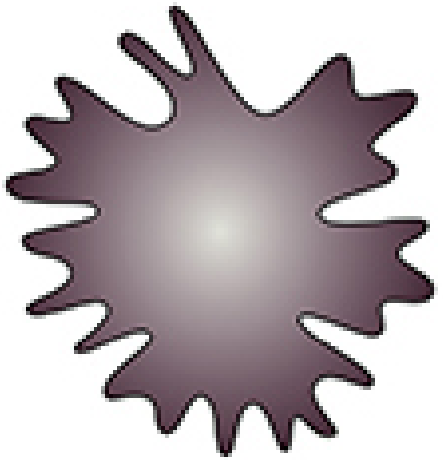


- Addicted to high levels of BCL-2
- Cell becomes long-lived
- Resistant to anti-cancer treatments

Venetoclax treatment



- BCL-2 inhibited
- Cancer cell dies, or responds to other anti-cancer treatments



- Cancer cell dies

Safety and Efficacy of Venetoclax in Combination with Decitabine or Azacitidine in *Treatment-Naive*, Elderly Patients ≥65 Years With Acute Myeloid Leukemia

- Design: Phase 1b, open-label, multicenter study with dose-escalation and expansion stages in elderly newly diagnosed AML (≥65 yo, ineligible for standard induction, prior HMA therapy excluded)

PRIMARY OBJECTIVE

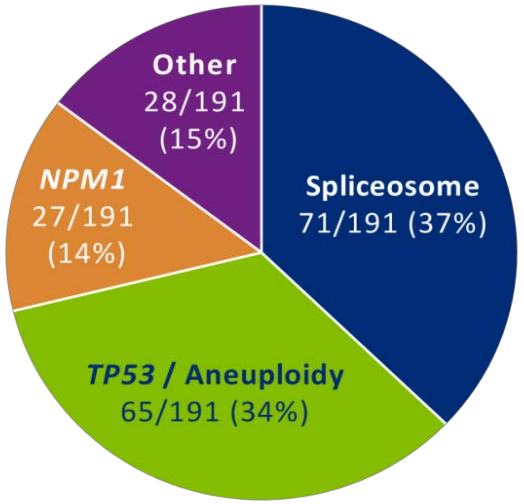
Expansion 1: To assess the efficacy and safety of DEC or AZA + VEN 400 mg or VEN 800 mg in patients ≥65 years of age with newly diagnosed AML who are ineligible for standard induction

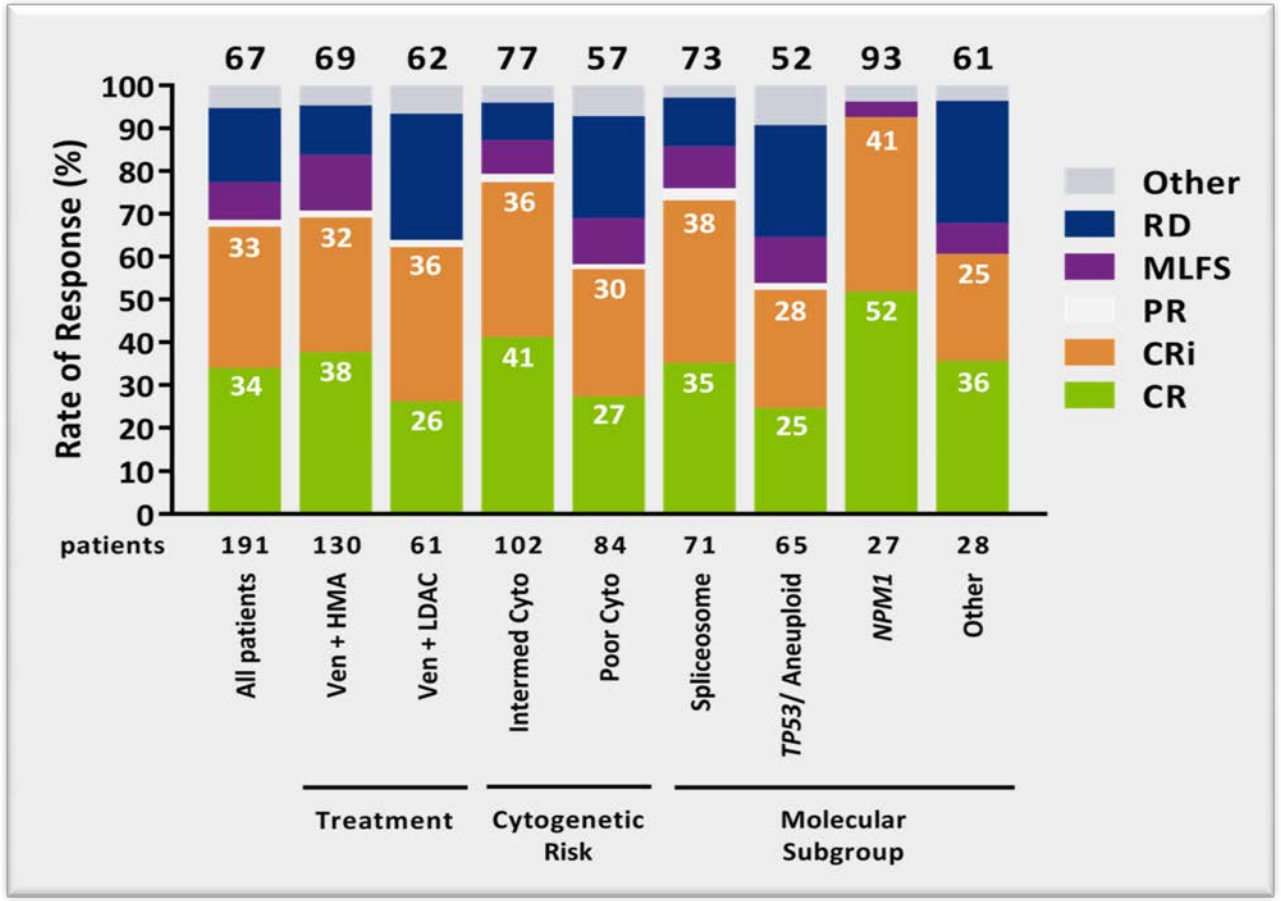
SECONDARY OBJECTIVE

To assess CR, CRi, duration of response (DOR), and overall survival (OS)

- Dose Escalation (n=45) and Dose Expansion (n=100)
  - N=145 overall

Response Rates by Patient Subgroups

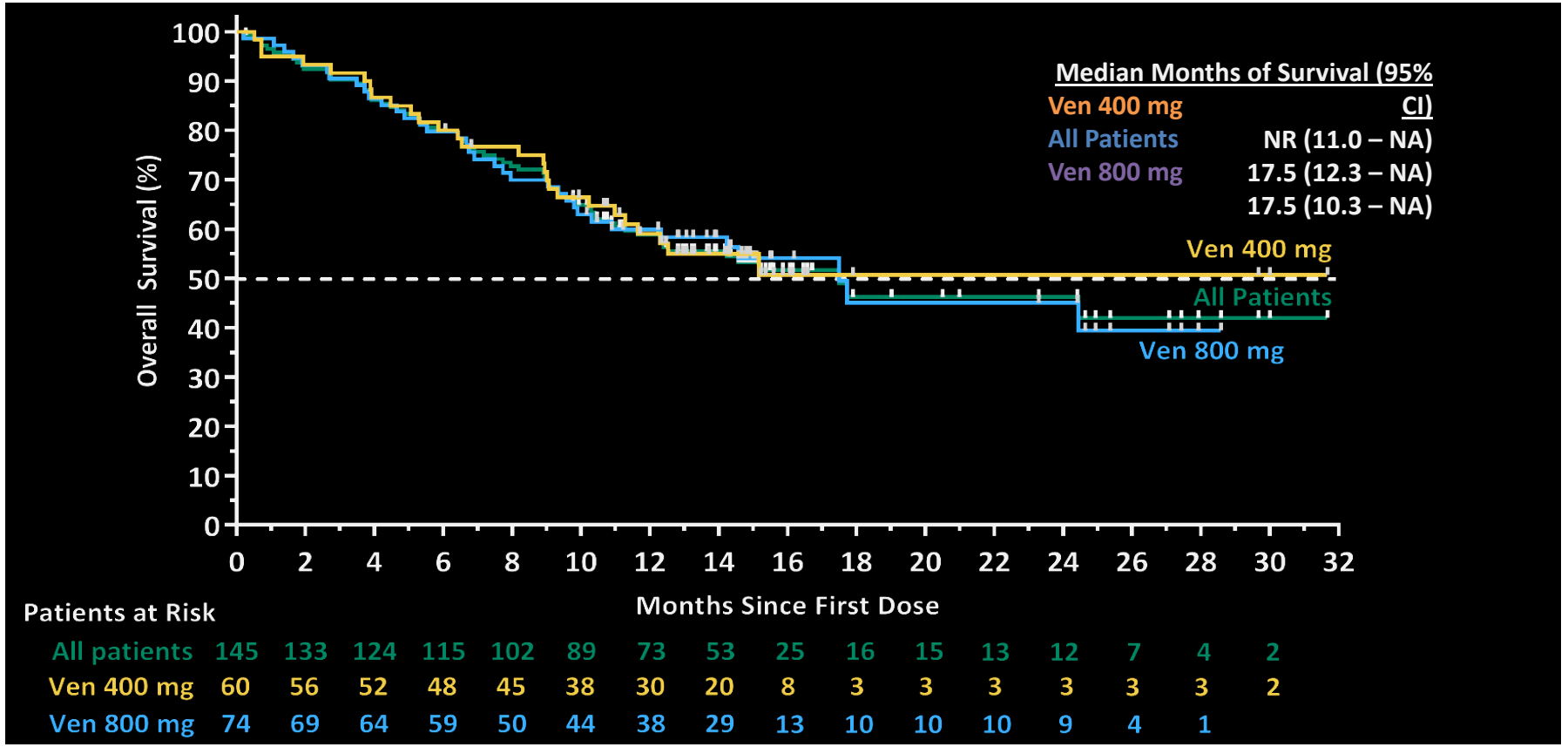




- CR/CRi higher in intermediate cytogenetic risk than in poor risk pts
- Spliceosome or *NPM1* mutations pts higher rates of CR/CRi (>70%)
- *TP53* mutations or aneuploidy pts had a lower rate (52%)

Strickland S, et al. EHA 2018.

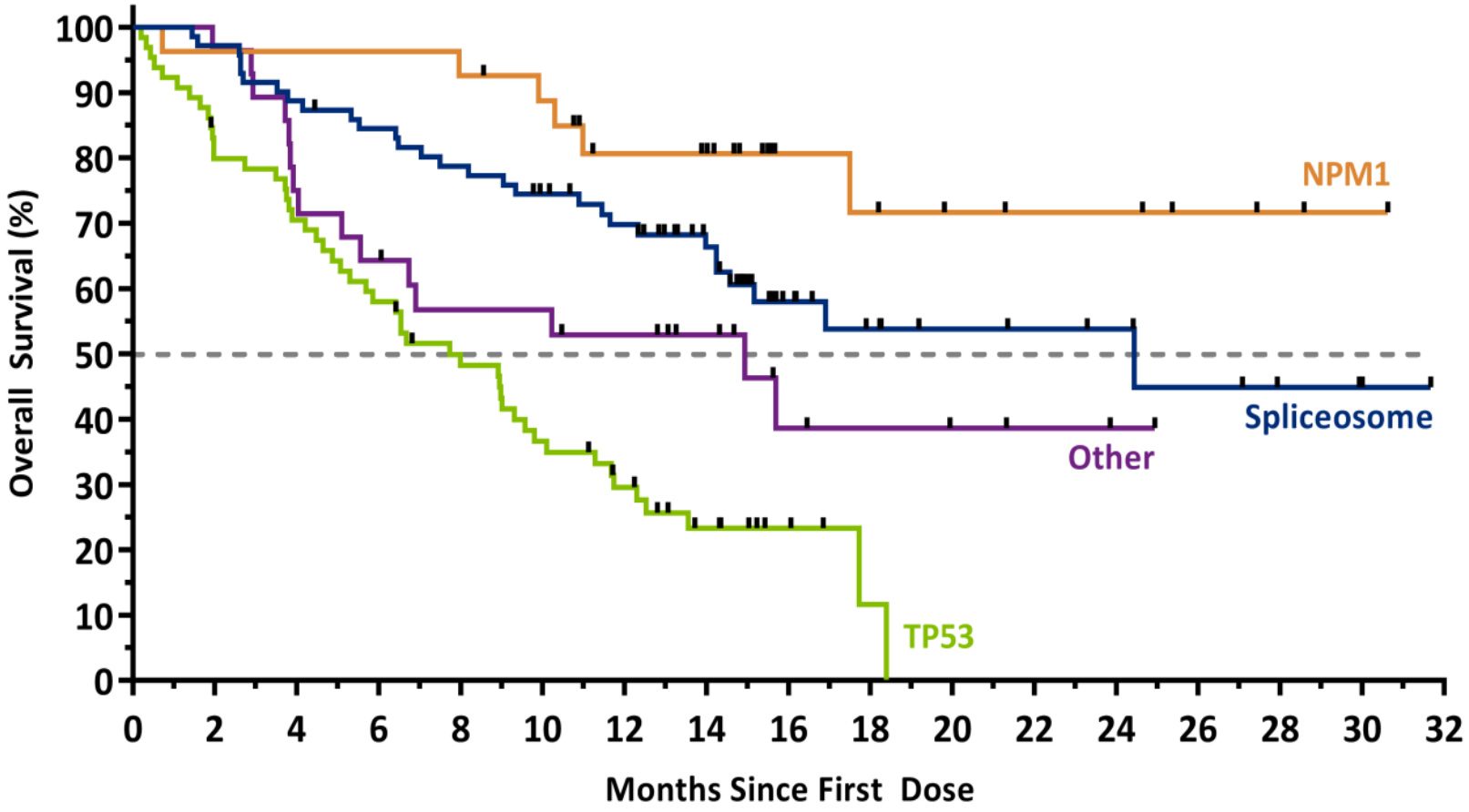
Overall Survival



- At a median time on study of 8.9 months (range, 0.2-31.6), the median overall survival (OS) in all treated patients was 17.5 months (95% CI, 12.3, NR-)
- The estimated 6-month, 1-year, and 2-year OS rates were 80%, 59% and 46%

DiNardo CD, et al. ASCO 2018. Abstract 7042.

Overall Survival by Molecular Subgroup

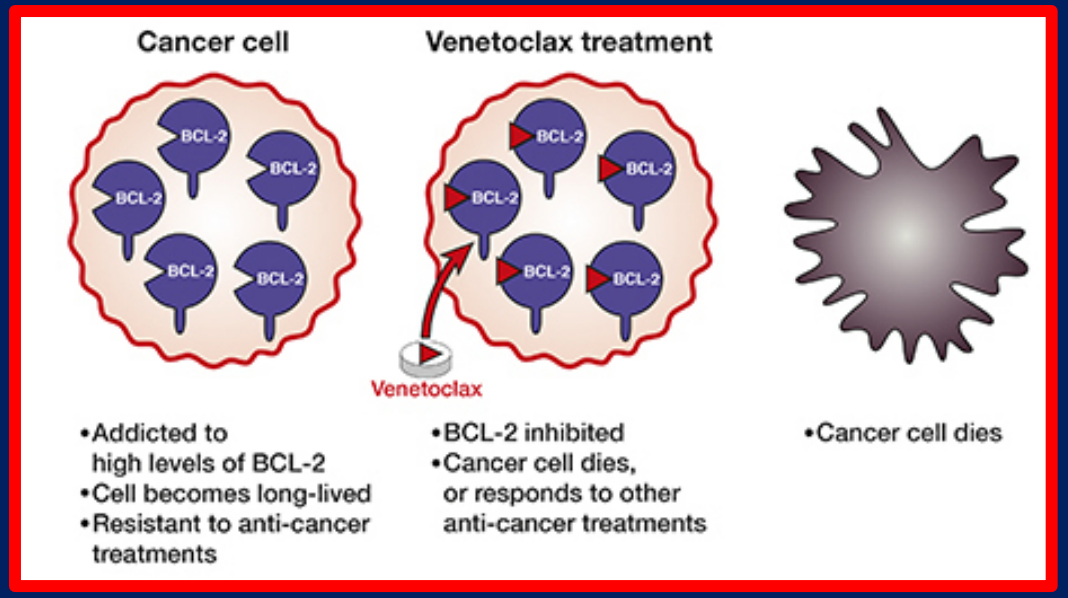


Strickland S, et al. EHA 2018.

Galectin inhibitors

CDK inhibitors

HMA



BH3 mimetics

LD-ARA-C

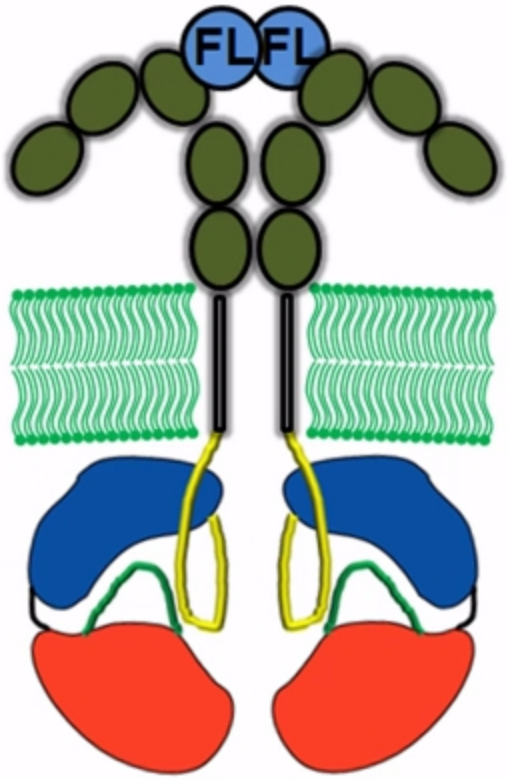
MDM2 antagonists

Alvocidib

Int. CHT

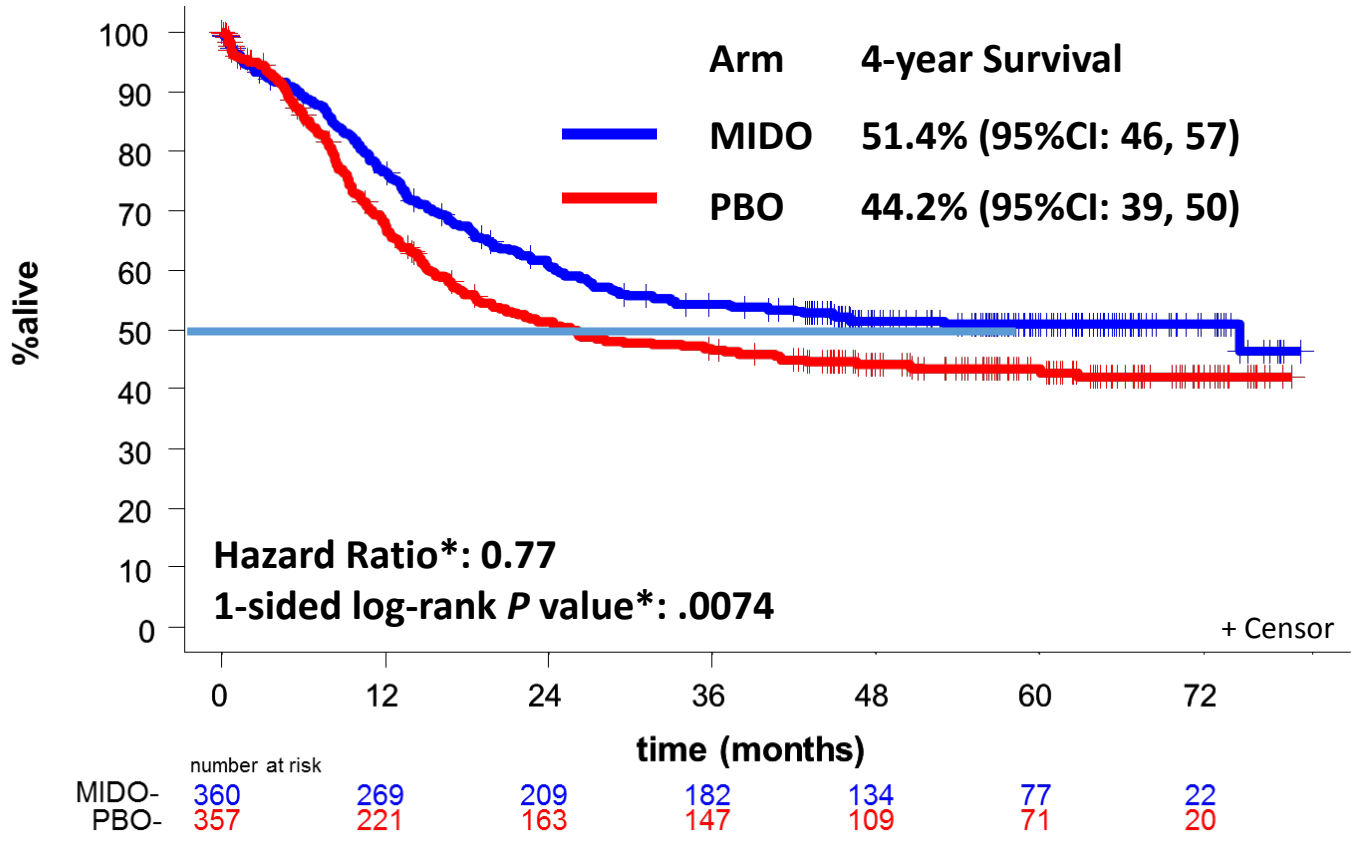
FLT3 and AML

- FLT3 is a receptor tyrosine kinase
  - Expressed on hematopoietic stem/progenitor cells
  - Wild type receptor activated by the cytokine FLT3 ligand (FL)
- FLT3-ITD (internal tandem duplication) mutations are common in AML
  - 20-25%
  - Somewhat younger (median age 58-60)
  - Constitutively activate FLT3 signaling
- FLT3-ITD AML
  - Aggressive, high white count
  - High tendency to relapse- quickly!
  - Negative prognostic impact
- FLT3-TKD (tyrosine kinase domain) mutations-less common (7%)
  - Less impact on prognosis



Rydapt è indicato in combinazione con chemioterapia standard di induzione con daunorubicina e citarabina e di consolidamento con citarabina ad alte dosi seguita, per pazienti in risposta completa, da terapia di mantenimento con Rydapt come agente singolo per pazienti adulti con leucemia mieloide acuta (LMA) di nuova diagnosi con mutazione FLT3 positiva

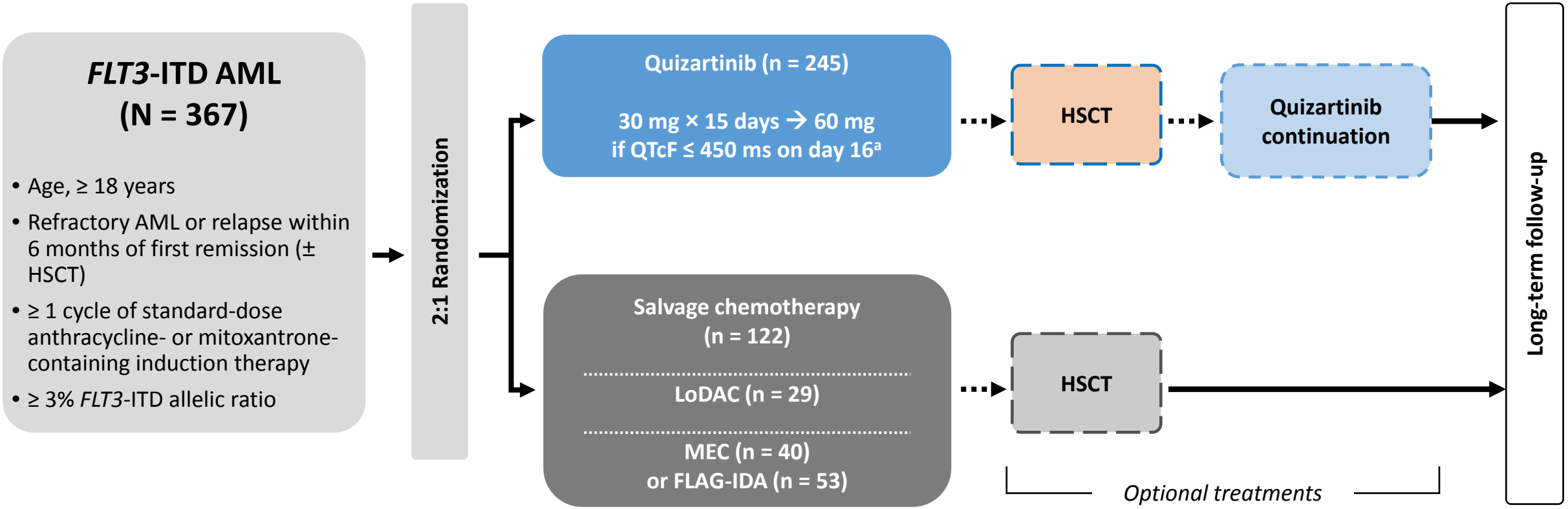
Overall Survival (Primary Endpoint)
23% Reduced Risk of Death in the MIDO Arm



Median OS
MIDO 74.7 (31.7-NE);
PBO 25.6 (18.6-42.9) months

NE, not estimable
***Controlled for *FLT3* subtype (TKD, ITD-Low, ITD-High)**

QuANTUM-R Study Design

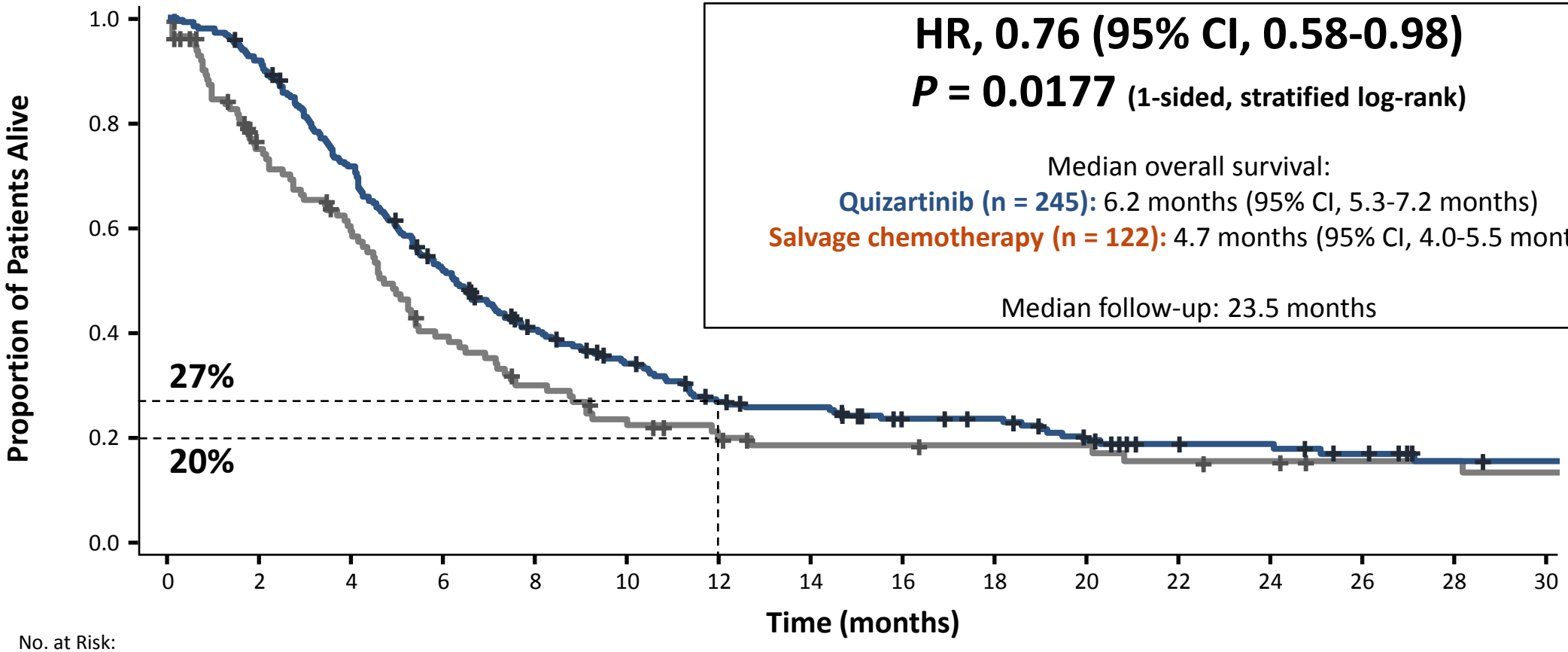


Primary endpoint: overall survival (ITT population)
Secondary endpoint: event-free survival (ITT population)
Select exploratory endpoints: CRc rate, duration of CRc, and transplant rate
Enrollment dates: May 2014 (first patient) to September 2017 (last patient)

[a]20 mg × 15 days → 30 mg if concomitantly taking CYP3A4 inhibitors. Data cutoff: February 2018

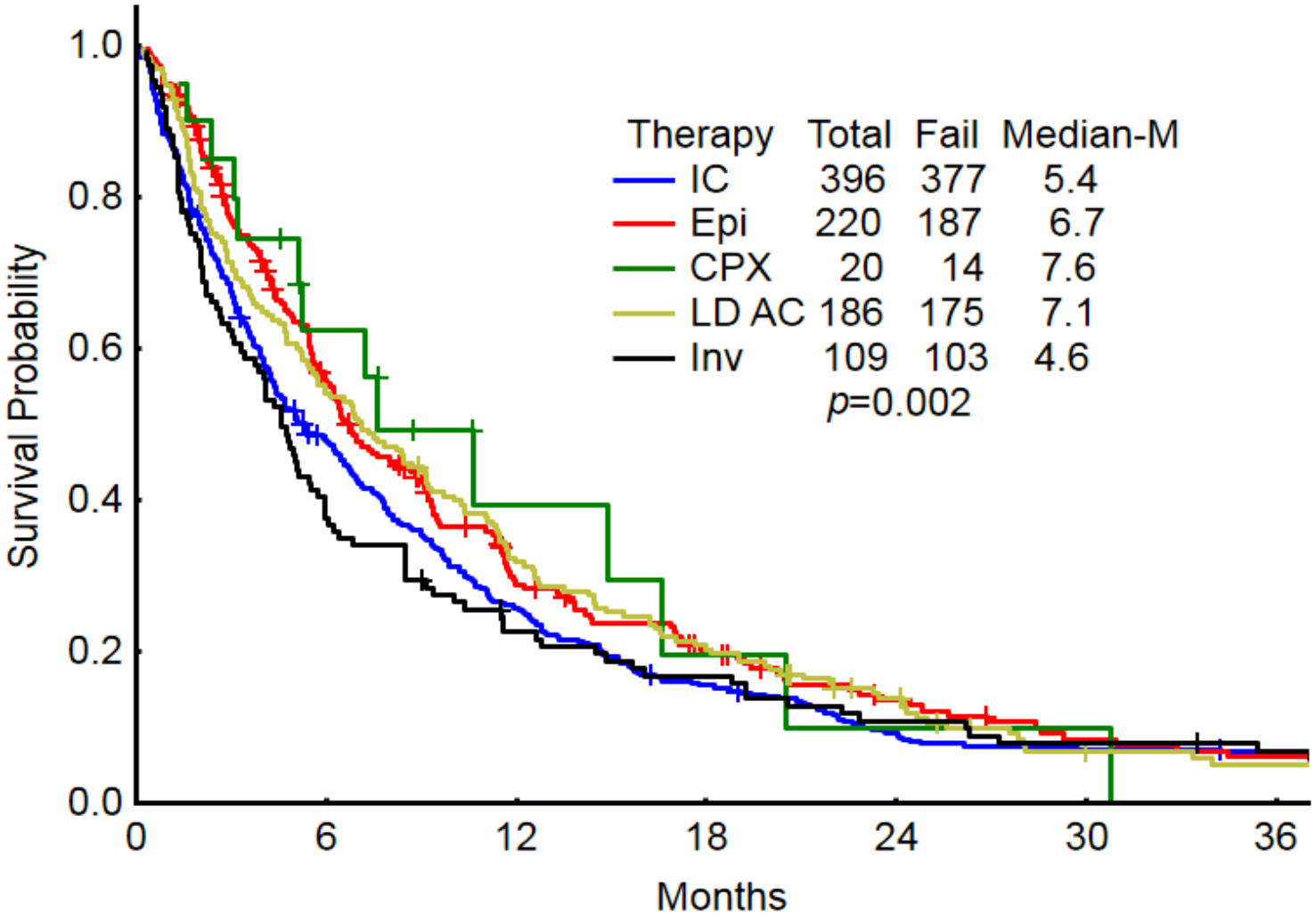
Cortes JE, et al. EHA abstracts 2018.

QuANTUM-R Primary Endpoint: Overall Survival



Cortes JE, et al. EHA abstracts 2018.

OS By Treatment Regimen in poor risk AML (older patients with secondary AML)

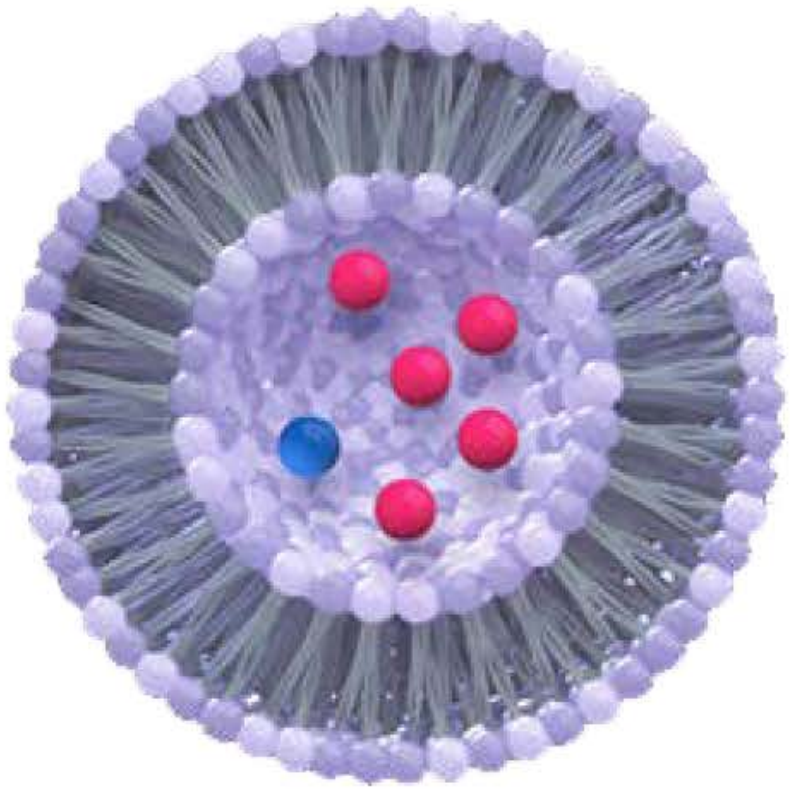


Boddu P, et al. *Cancer.* 2017;123(16):3050-3060.

VYXEOS (CPX-531) 8-3-2017

- Liposome-encapsulated combination of Ara-C and Dauno

- FDA approved for adults with newly-diagnosed therapy-related AML (t-AML), AML with prior history of MDS, or AML with cytogenetic abnormalities diagnostic for MDS

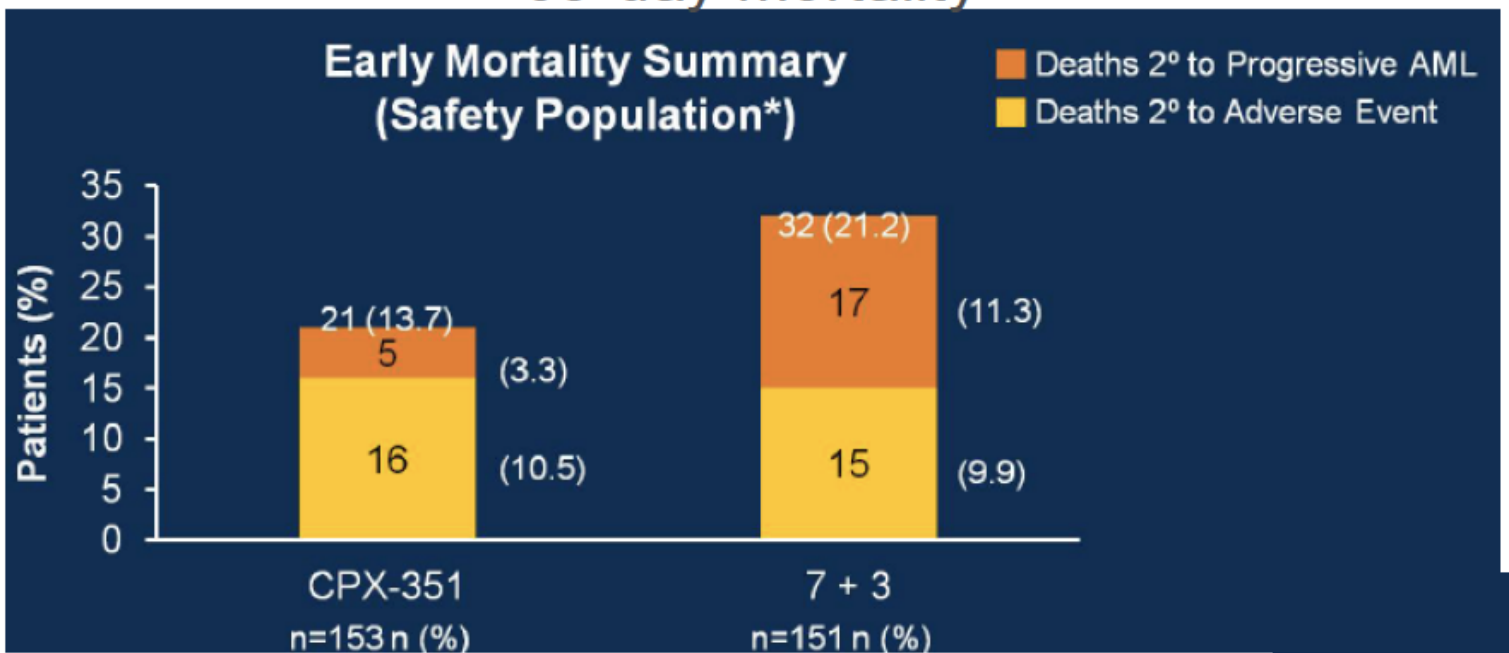


- 100 nm bilamellar liposomes
- 5:1 molar ratio of cytarabine to daunorubicin
- 1 unit = 1.0 mg cytarabine plus 0.44 mg daunorubicin

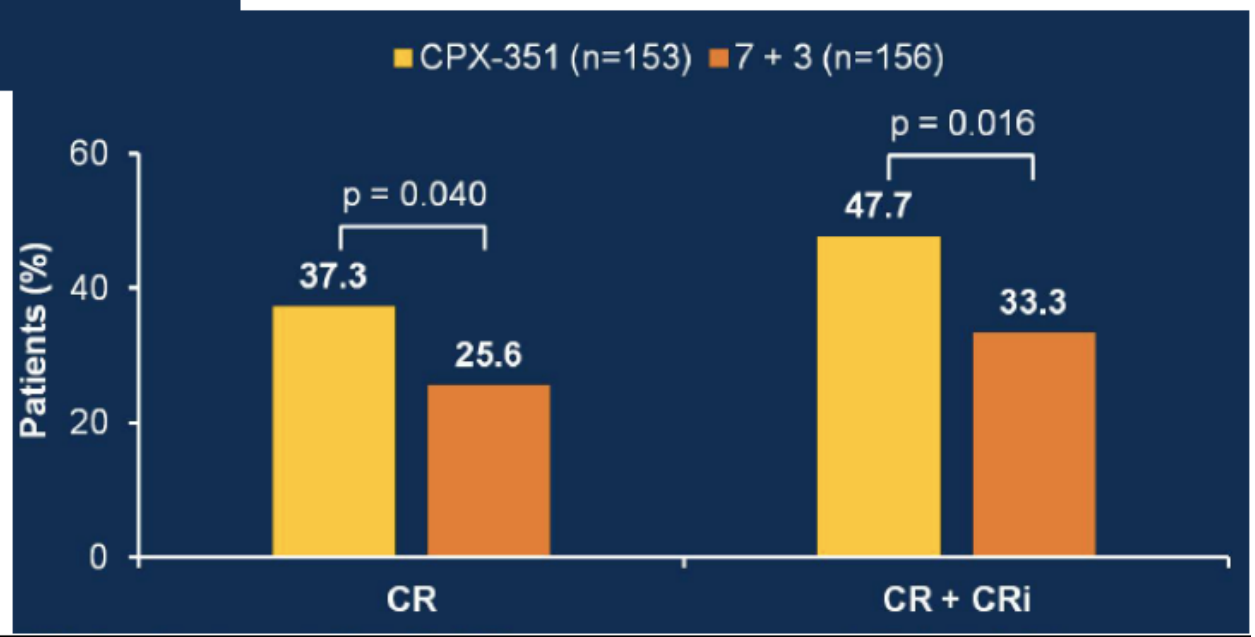
Lancet et al. ASCO Abstract 2016

VYXEOS (CPX-351) IMPROVED 30 AND 60 DAY MORTALITY AND CR RATES

60-day mortality



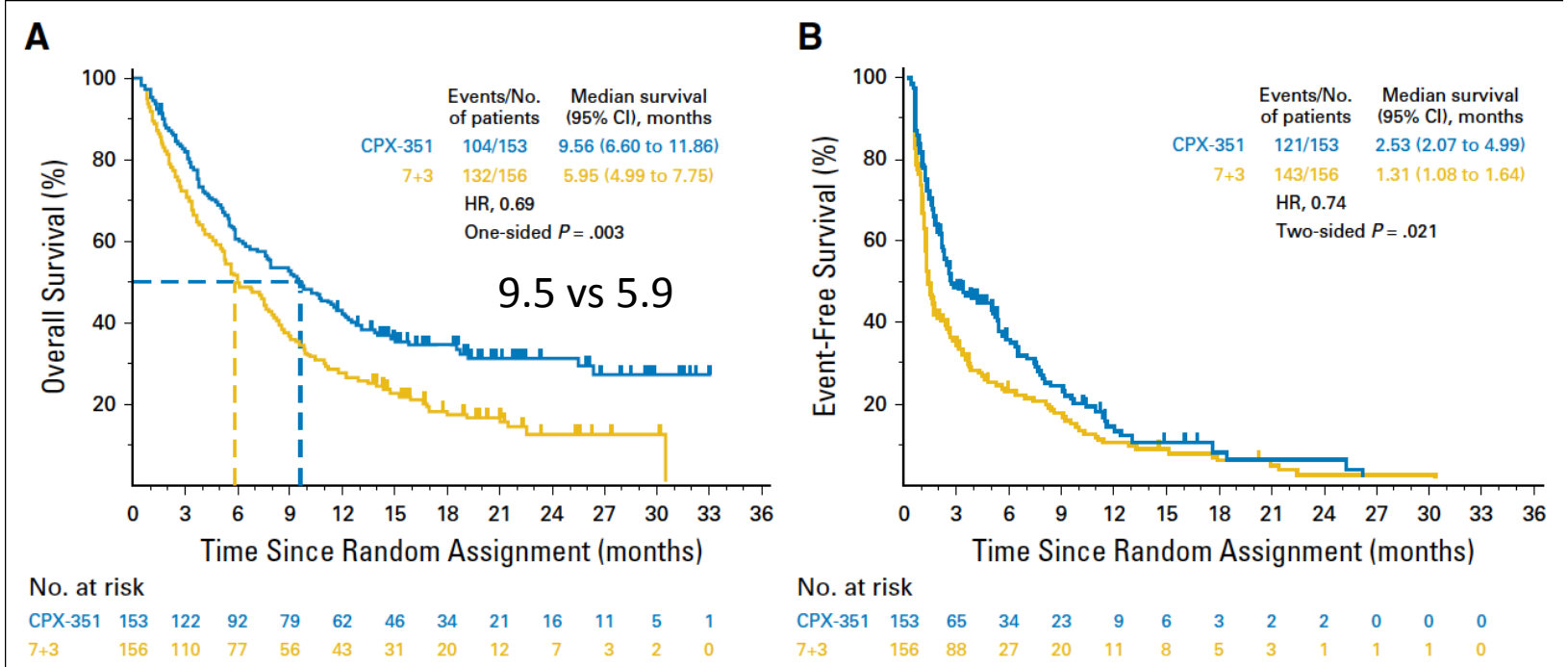
CR rates

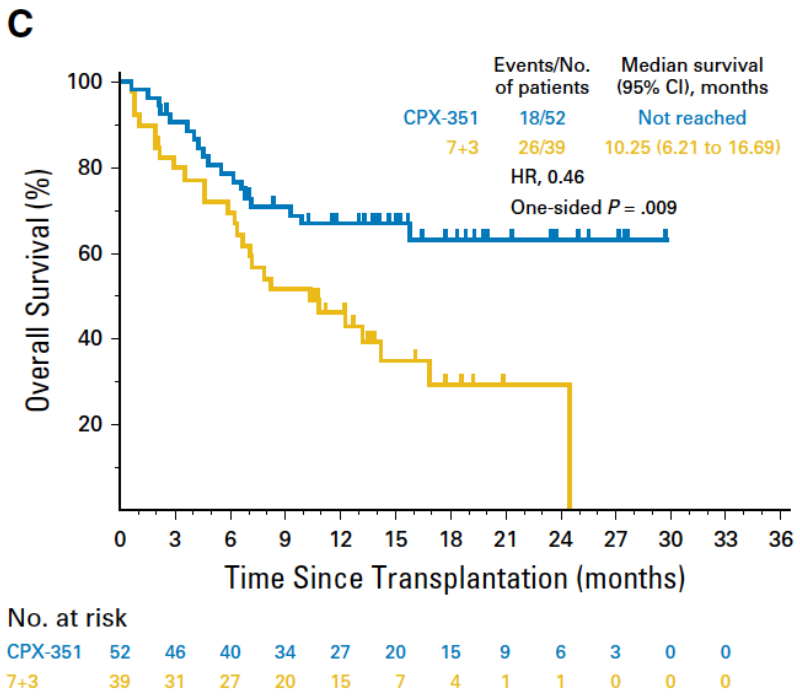


Lancet J, et al. ASCO 2016

ITT

SCT group





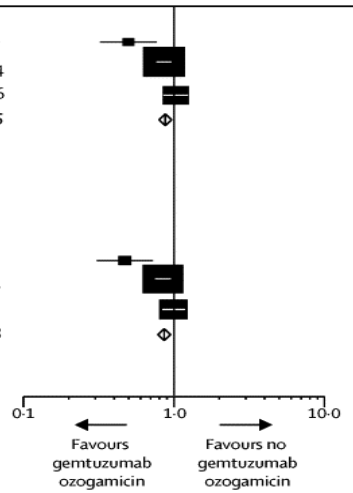
NR vs 10.2

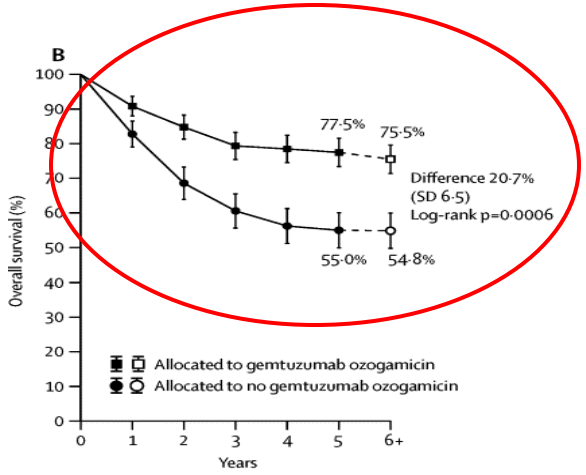
Lancet et al., JCO, 2018

Gemtuzumab Ozogamicin in Induction Therapy
Meta-analysis of 5 Randomized Trials

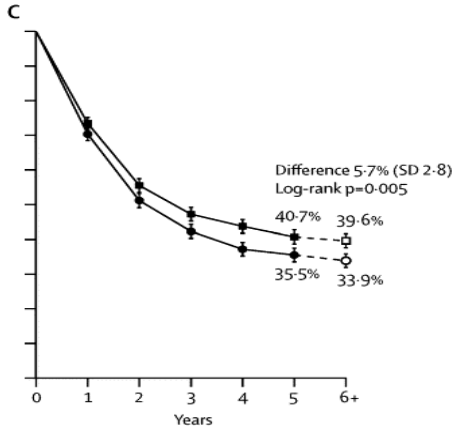
A

	Events/patients		o–e	Variance	OR (95% CI)	p value
	Gemtuzumab ozogamicin group	No gemtuzumab ozogamicin group				
Original coding						
Favourable	32/125	54/126	−14·3	20·5	0·50 (0·32–0·77)	
Intermediate	549/962	596/964	−44·2	284·4	0·86 (0·76–0·96)	
Adverse	223/261	227/256	3·1	110·6	1·03 (0·85–1·24)	
Subtotal	**804/1348**	**877/1346**	**−55·4**	**415·5**	**0·88 (0·79–0·96)**	**0·007**
Test for heterogeneity between subgroups: χ^2=9·6; p=0·008						
Test for trend between subgroups: χ^2=7·8; p=0·005						
Revised MRC coding[12]						
Favourable	30/122	54/124	−15·5	20·6	0·47 (0·31–0·73)	
Intermediate	506/911	559/916	−45·3	264·6	0·84 (0·75–0·95)	
Adverse	260/299	258/284	−1·2	127·6	0·99 (0·83–1·18)	
Subtotal	**796/1332**	**871/1324**	**−61·9**	**412·8**	**0·86 (0·78–0·95)**	**0·002**
Test for heterogeneity between subgroups: χ^2=10·1; p=0·006						
Test for trend between subgroups: χ^2=7·7; p=0·006						

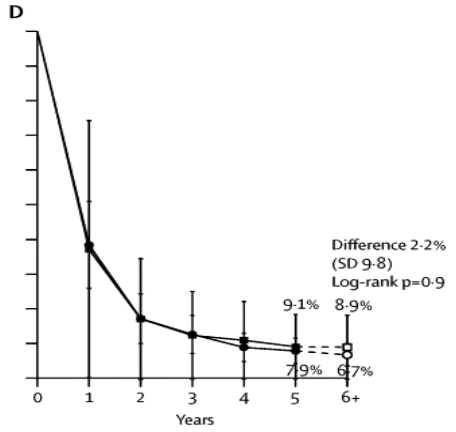




Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	5·8% SD 1·1	2·3% SD 1·3
No gemtuzumab ozogamicin	14·1% SD 1·9	0·0% SD 0·0



Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	22·4% SD 1·0	2·7% SD 0·9
No gemtuzumab ozogamicin	26·2% SD 1·1	4·9% SD 1·3

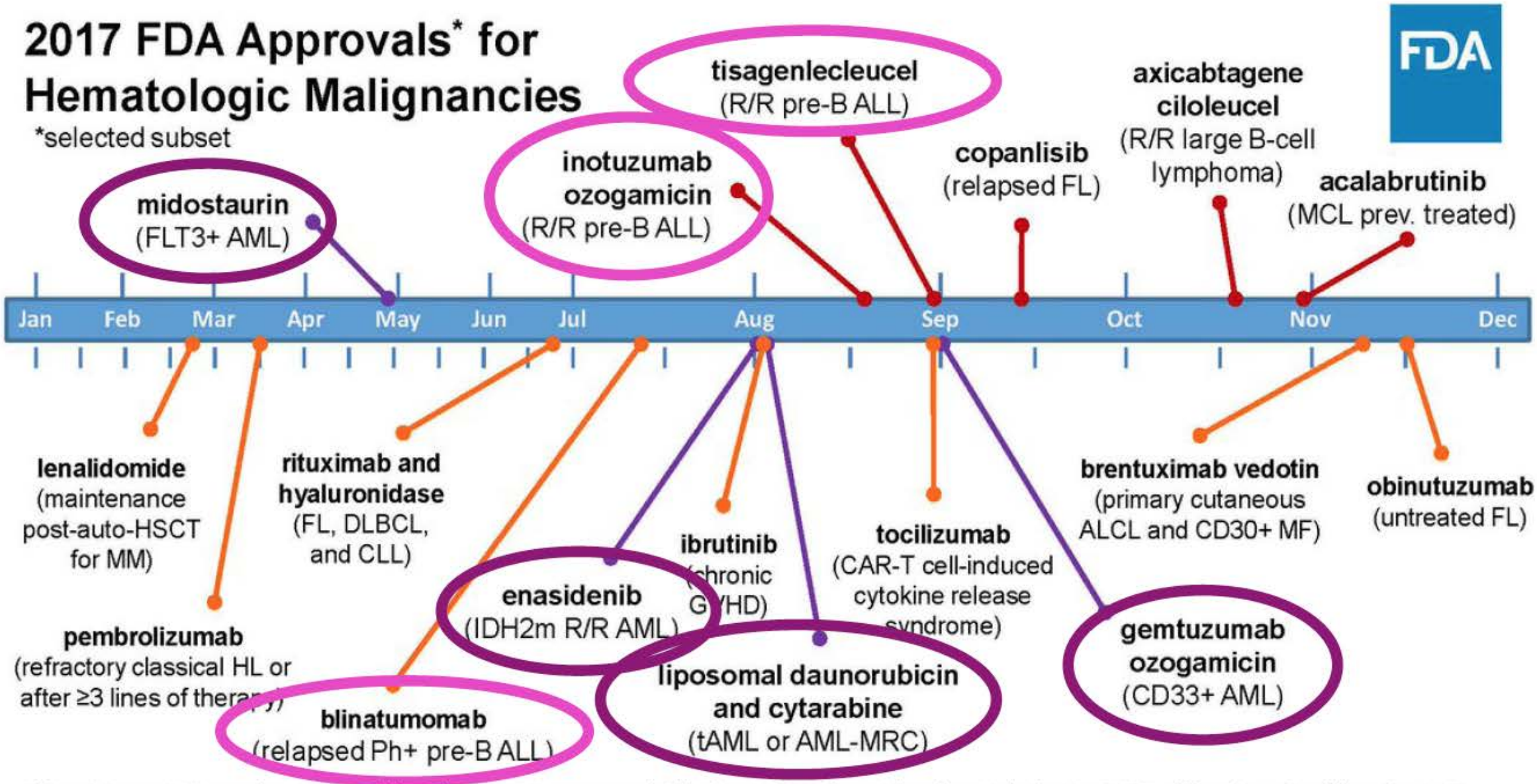


Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	73·8% SD 4·6	2·4% SD 2·4
No gemtuzumab ozogamicin	76·7% SD 4·8	21·1% SD 10·5

Hills RK, et al. *Lancet Oncol.*2014;15(9):986.

2017 FDA Approvals* for Hematologic Malignancies

*selected subset



Abbreviations: ALCL, anaplastic large cell lymphoma; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; GVHD, graft-versus-host disease; HL, Hodgkin lymphoma; IDH2m, isocitrate dehydrogenase 2 mutated; HSCT, hematopoietic stem cell transplantation; MCL, mantle cell lymphoma; MF, mycosis fungoides; MM, multiple myeloma; MRC, myelodysplasia-related changes; pre-B ALL, B-cell precursor acute lymphoblastic leukemia; R/R, relapsed or refractory; tAML, therapy-related AML

AML > 18 years: 2019-2020