Acute Myeloid Leukemia

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Disclosures- Richard M. Stone, MD

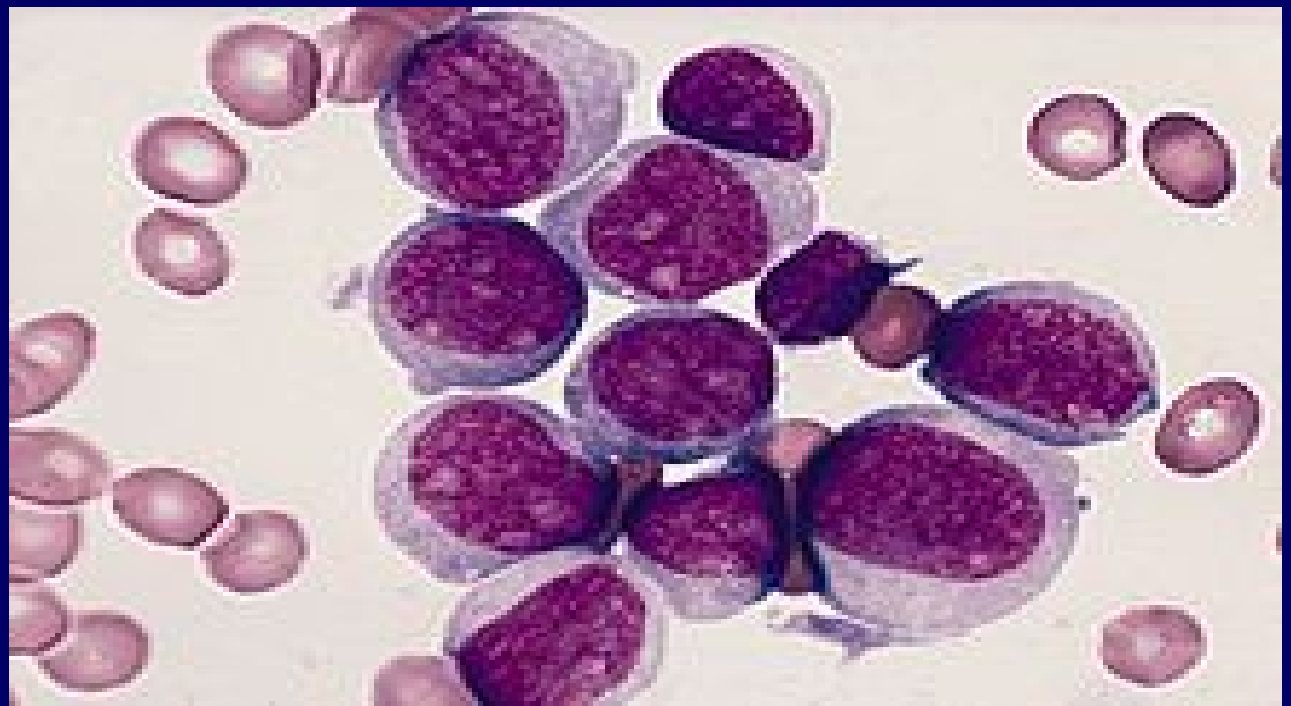
- **Consulting relationships past three years:**
  - **AbbVie*; Actinium, Agios*; Amgen; Argenix (DSMB); Arog*; Astellas; AztraZenaca; Biolinerx, Celgene (includes DSMB and steering committee); Fujifilm, Janssen; Juno; Macrogen-ics; Novartis*; Ono; Orsenix; Pfizer; Roche; Stemline, Sumitomo; Takeda (DSMB), Trovagene**
  - *** denotes support to my institution for clinical trials on which I was local PI**
- **Securities, employment, promotional activities, intellectual property, gifts, grants**
  - **None**

Acute Myeloid Leukemia

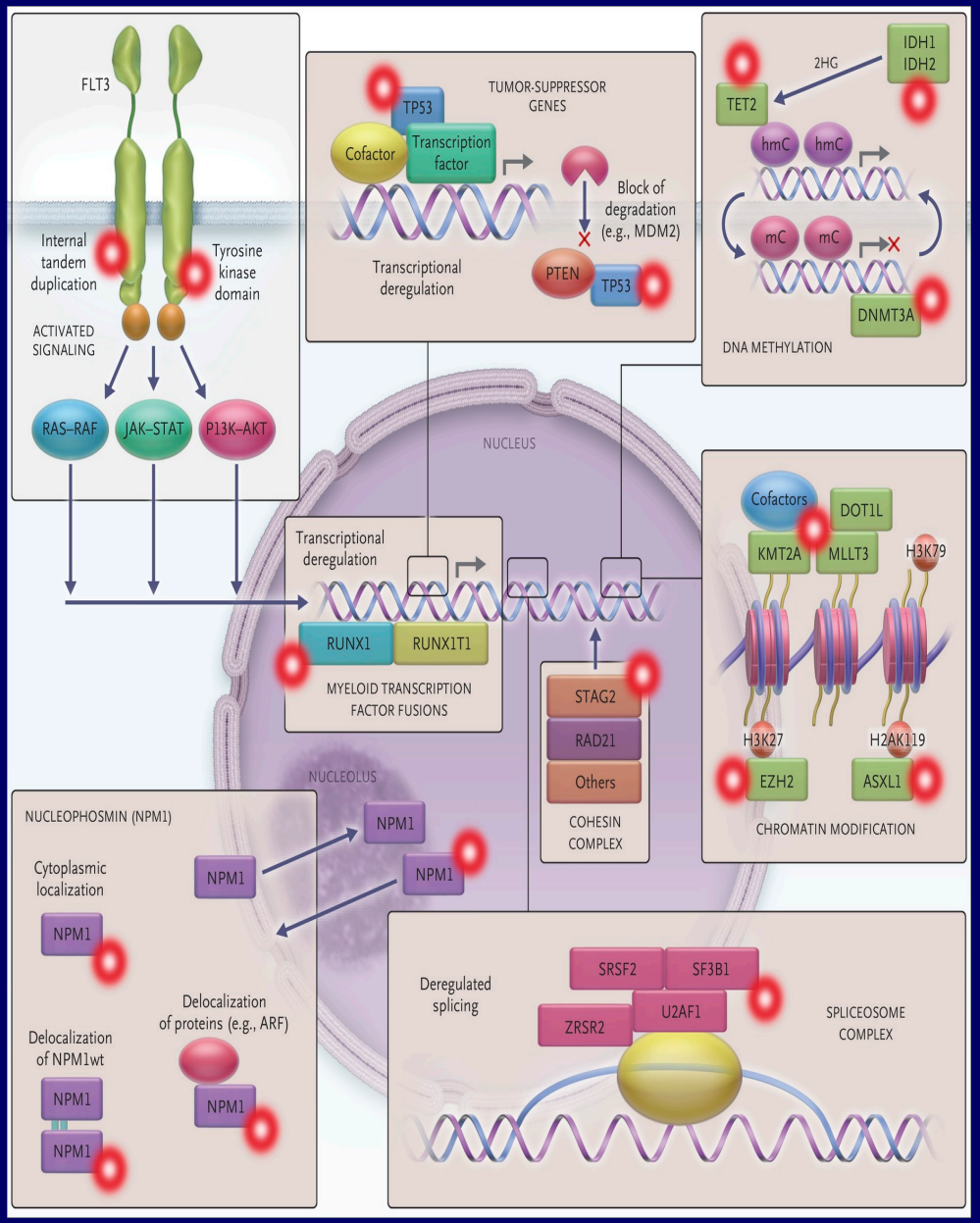
- AML
  - Biology and Epidemiology
  - Endpoints and MRD
  - Integrating New Therapies into Rx Algorithms
    - Acute Promyelocytic Leukemia
    - Younger adults-new dx
      - Midostaurin (+chemo in mutant *FLT3* upfront)
      - Gemtuzumab (+ chemo in CD33+ upfront)
    - Older Adults-new dx
      - CPX-351 (upfront secondary)
      - Venetoclax +low dose chemo (upfront, unfit)
    - Relapsed Disease
      - Gilteritinib (single agent R/R *FLT3* mutant)
      - Enasidenib/(ivosidenib) (R/R *IDH2 (1)* mutant)

AML: What is it and how did it get there?

- Unbridled proliferation of hematopoietic stem cells (myeloid lineage) resulting in marrow failure and patient death unless successfully treated
- Risk factors: AGE, prior chemo for other cancers, ionizing radiation, industrial solvents (last 3 probably <10% of incidence=15K new US cases annually); unusual but kindreds exist w germ-line mutations in >10 genes



Key Points from *de novo* AML Genome Atlas



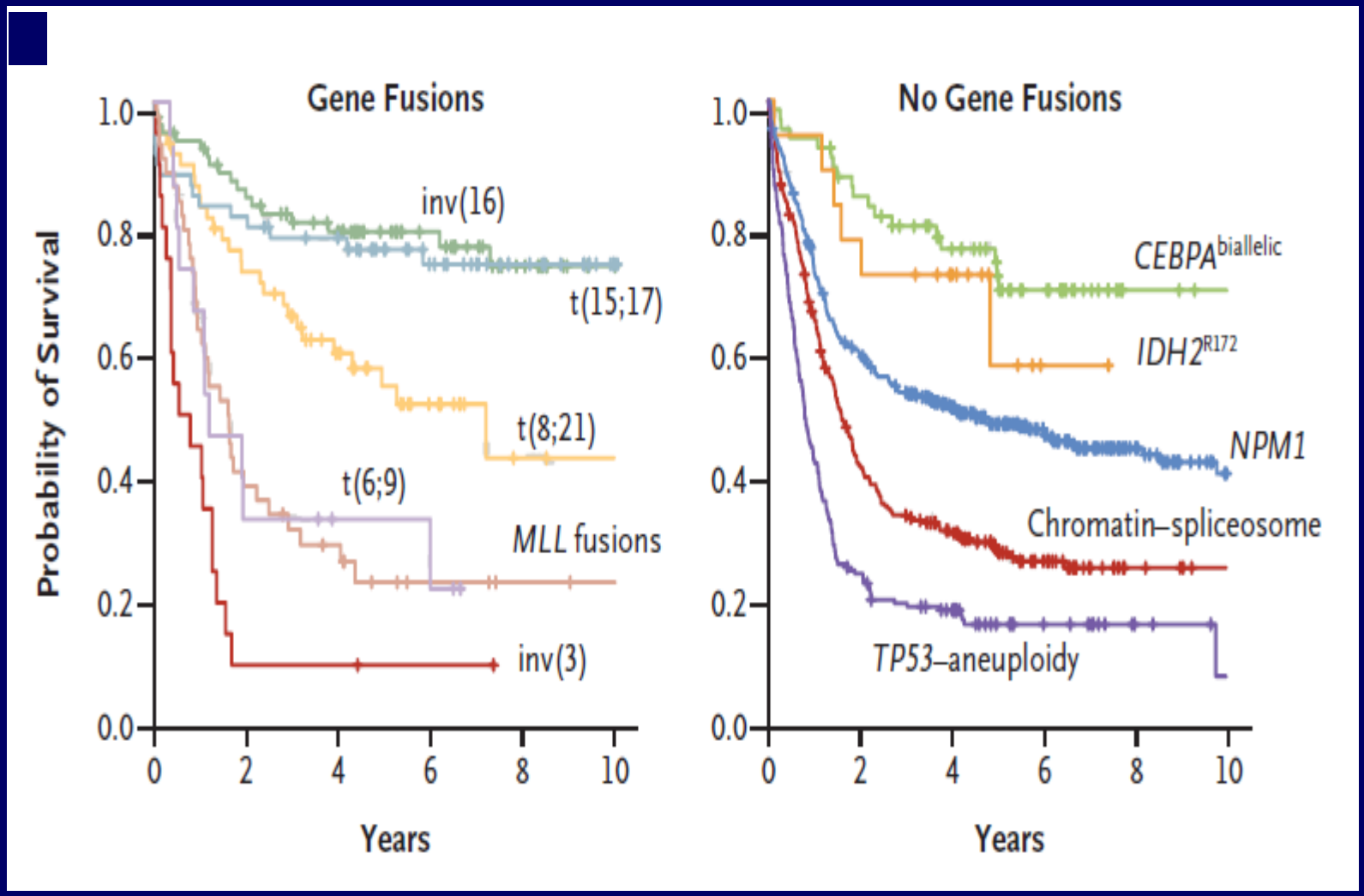
key categories:

transcription-factor fusions (18%)
nucleophosmin (*NPM1*) (27%)
tumor-suppressor genes (16%)
DNA-methylation–related genes (44%)
signaling genes (59%)
chromatin-modifying genes (30%)
myeloid transcription-factor genes (22%)
spliceosome-complex genes (14%)
Cohesin complex (15%)

The Cancer Genome Atlas Research Network *NEJM* 2013; 368:2059-2074.

Döhner H et al, *NEJM* 2015; 373:1136-1152

Genomic Classification and Prognosis in AML



Papaemmanuil E et al. *NEJM.* 2016;374:2209-2221.

Current Risk Assessment in AML

Key Prognostic Data in AML in 2019

Patient **age (** FH, bleeding hx; **?Therapy related; ?Prior MDS**)	
Cytogenetics / fusion mRNA (screen for APL, MLL, Ph+, CBF)	
Multiparameter flow	
Molecular studies:	
• ***FLT3*** **ITD (internal tandem duplication) mutation**	*Unfavorable*
• ***NPM1*** **mutation**	*Favorable*
• ***CEBPA*** **biallelic mutation**	*Favorable*
• *RUNX1, TP53, ASXL1 (? KIT in CBF)*	*Unfavorable*

Of Future Importance: mutation status of ***IDH1/2, DNMT3A, TET2***, etc.

Genetic Risk Group	Frequency	Survival	ELN 2017 Subset
Favorable	**15%**	**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 *FLT3*-ITD ^{low} • Biallelic Mutated *CEBPA*
Intermediate	**55%**	**50%**	• Mutated *NPM1* and *FLT3*-ITD ^{high} • Wild-type *NPM1* without *FLT3*-ITD or *FLT3*-ITD ^{low} (without adverse-risk genetic lesions) • Wild-type *NPM1* and *FLT3*-ITD (normal karyotype) • t(9;11)(p22;q23); *MLLT3-MLL* • Any cytogenetics not classified as favorable or adverse
Adverse	**30%**	**20%**	• t(6;9)(p23;q34); *DEK-NUP214* • t(v;11)(v;q23); *MLL (KMT2A)* rearranged • Inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1 (GATA2, MECOM (EVI1)* • t(9;22)(q34.1;q11.2) *BCR-ABL1* • Monosomy 5 or del(5q); monosomy 7; monosomy 17; abnormal 17p • Complex karyotype(≥ 3 abnormalities) or monosomal karyotype • Wild-type *NPM1* and *FLT3*-ITD ^{high} • Mutated *RUNX1* • Mutated *ASXL1* • Mutated *TP53*

Döhner H et al, *Blood* 2017; 129(4):424-447

AML: General Treatment Principles

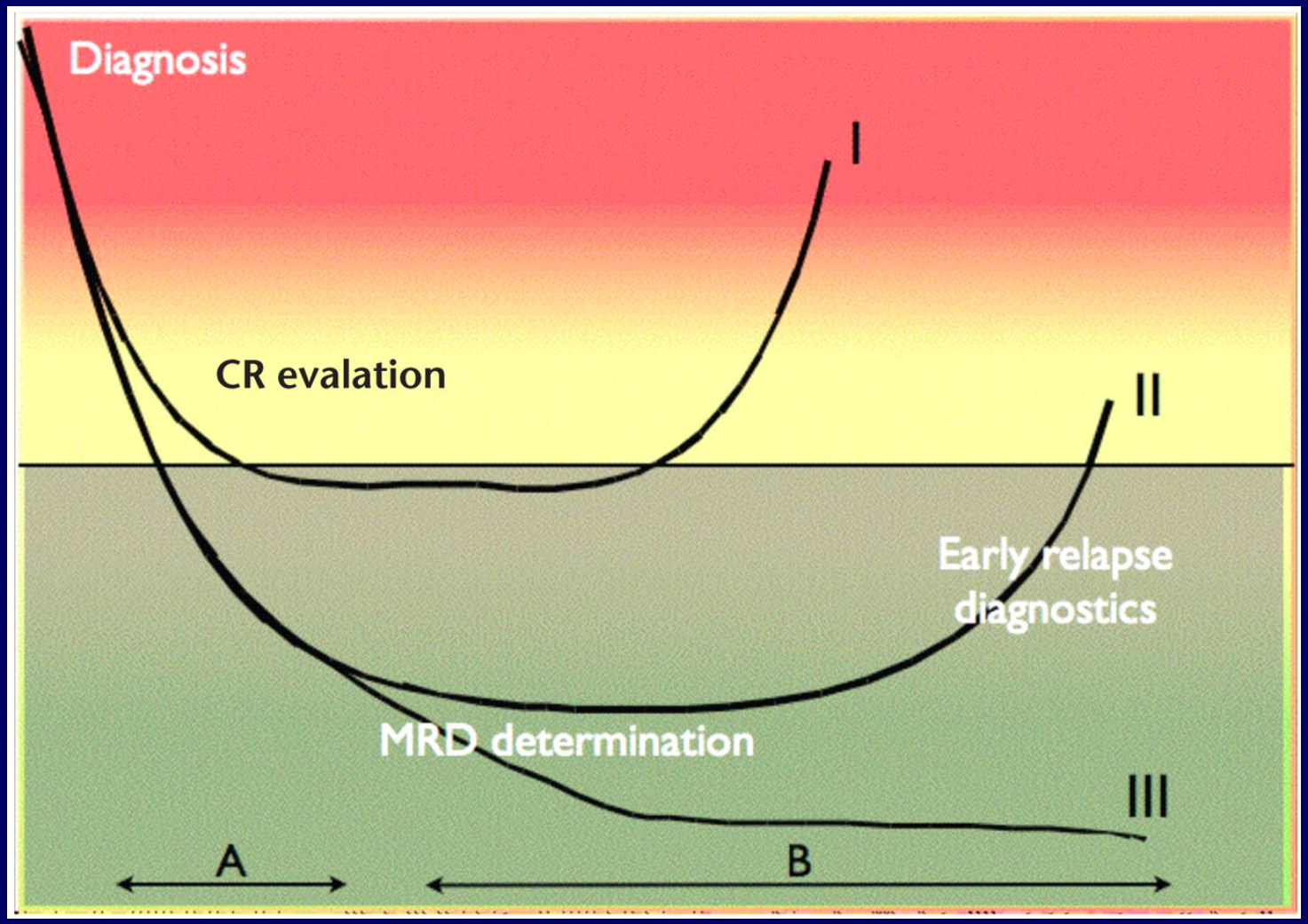
- **Goal 1:** **Induction therapy to reduce gross leukemia to undetectable levels (2-3 log cell kill); to achieve CR (no AML, nl CBC)**

- **Goal 2:** **Reduce 10^9 - 10^{10} cells, undetectable by standard means, present at CR, to a level low enough to achieve prolonged disease-free survival ('cure')**

AML: Key Endpoints

- Overall survival (OS)
- Event-free survival (event= no CR, relapse, death)
  - Somewhat correlated with OS
  - Has intrinsic value to pts: when no event they are in CR with acceptable counts
- Complete remission (CR)
  - CR with incomplete plt (or ANC) recovery has value
  - CR at MRD negative level has most value !

The MRD concept. x-axis represents time; y-axis represents tumor burden.

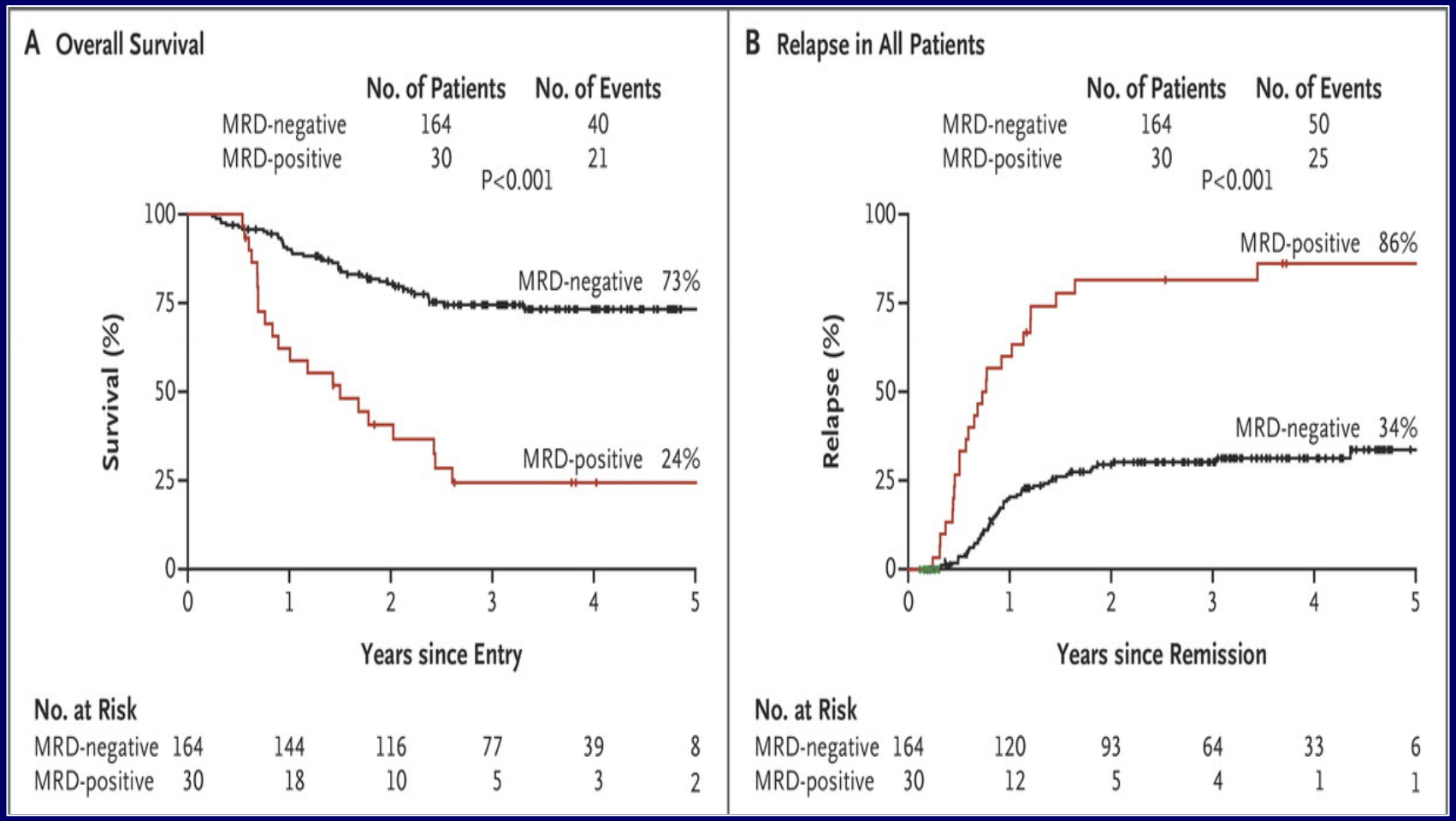


Hokland P , Ommen H B Blood 2011;117:2577-2584

How can we quantitate AML?

- Morphologically: 1 in 20
  - insensitive
- Cytogenetically (metaphase) 1 in 20
- Cytogenetically (interphase) 1 in 100
- Multiparameter flow 1 in 10,000
- PCR based 1 in 10,000

MRD Based on PCR for Mutant NPM1 in Peripheral Blood After the Second Cycle of Chemotherapy Independently Predicts Clinical Outcomes



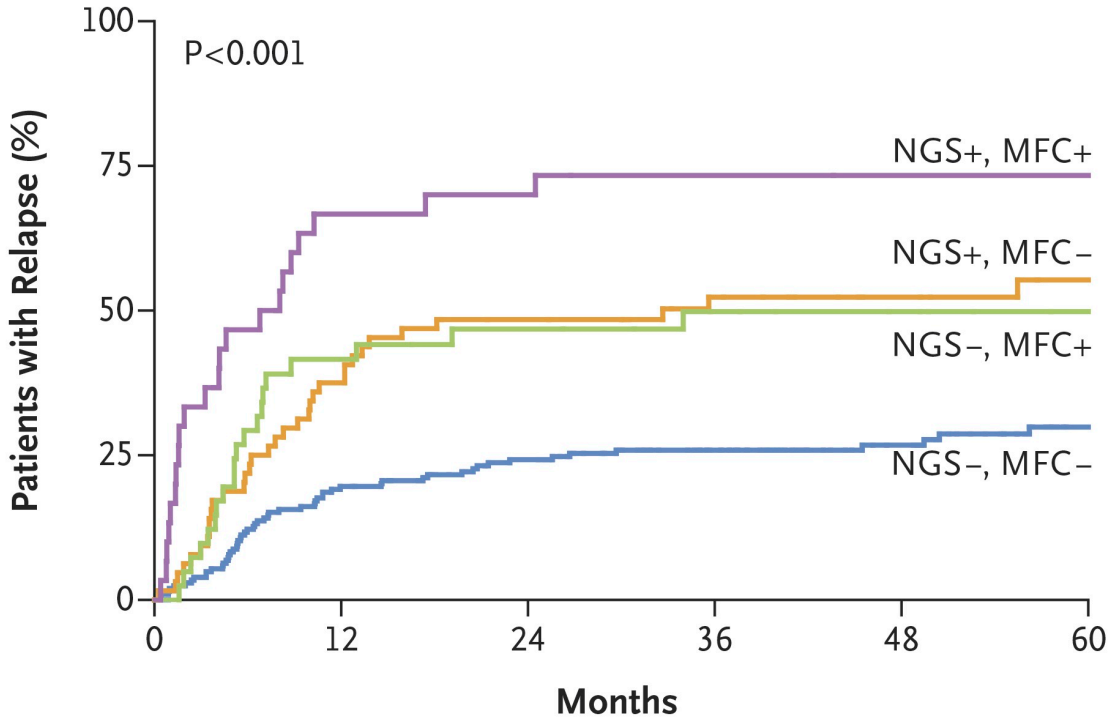
MRD = minimal residual disease; PCR = polymerase chain reaction.

Ivey A et al. *N Engl J Med*. 2016;374:422-433.

NGS-based detection of MRD also useful

- **Jongen-Laurencic, M, et al NEJM 378:1189-1199, 2018 (Hovon-SAKK)**
  - Age 18-65 AML, NGS at dx and relapse (N-482, 430 had at least one mutation at dx)
  - Persistence of DNMT3A, TET2, ASXL1 (DTA [CHIP-like, see Steensma, D et al, Blood , NEJM]) didn't carry risk, others did
    - MRD (non DTA) by NGS: 55 v 32% RR, 43 v 66% OS
    - Flow-based MRD was additive
      - If you were pos by both- worst, but either one pos- worse than neither

Rate of Relapse According to Results of Next-Generation Sequencing and Multiparameter Flow Cytometry.



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. N Engl J Med 2018;378:1189-1199

The NEW ENGLAND JOURNAL of MEDICINE

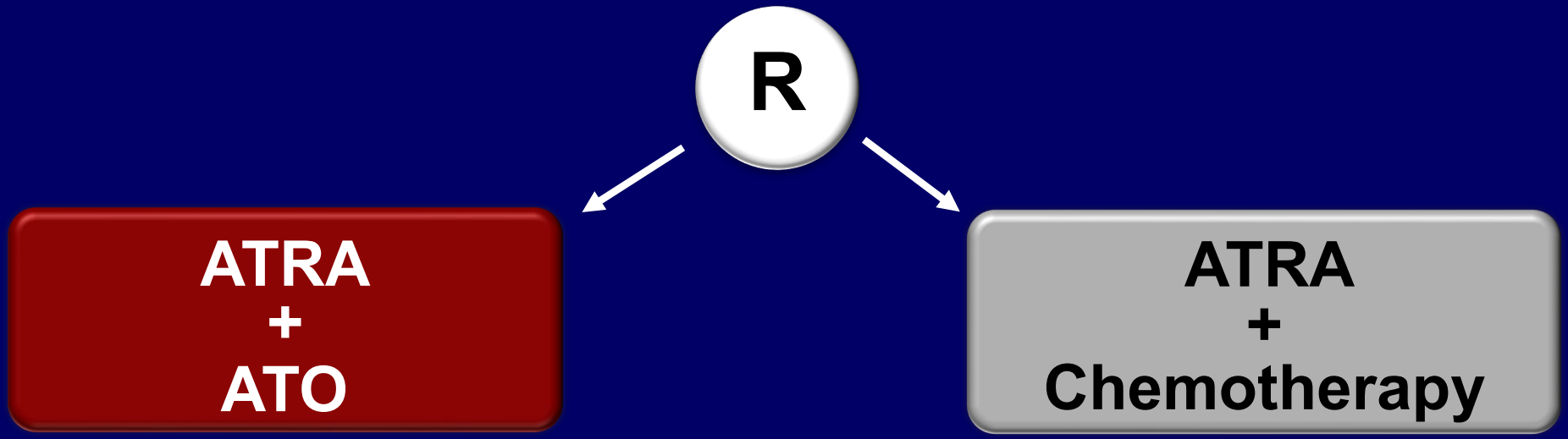
Treatment of Acute Promyelocytic Leukemia

Key Principles of APL Management
Suspect the disease!
• Risk of death is greatest in the first two weeks after diagnosis, especially if ATRA initiation is delayed…
• So, if the clinical setting suggests the possibility of APL (e.g., clefted blasts, strong CD33+, DIC) **do not wait** for molecular confirmation to start ATRA
Document disease
• Use cytogenetics or FISH for t(15;17), or RT-PCR for *PML-RARA* fusion
• Variant translocations are rare, but important to know about, since several do not respond to ATRA
Assess risk
• If WBC >10 x 10^9/L: <u>high risk</u>
• If WBC ≤10 x 10^9/L: <u>standard risk</u> (lowest risk if platelets also >40 x 10^9/L)
Is the patient an anthracycline candidate?

APL 0406 Study

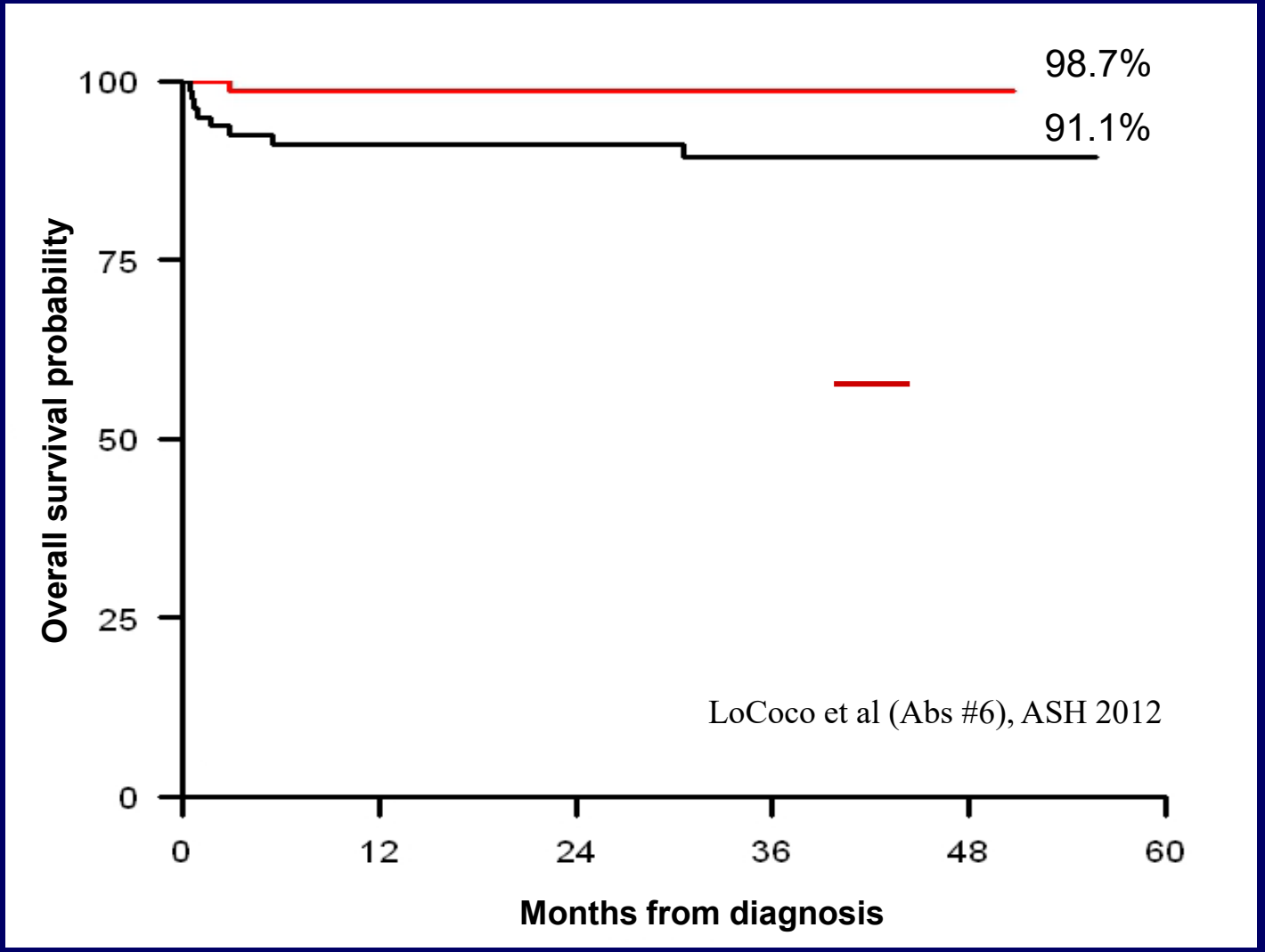
Acute Promyelocytic Leukemia

Low/intermediate risk patients
(WBC ≤10 x 10^9/L, AGE 16-70)



LoCoco et al (NEJM 2013)

Overall Survival



Management of APL

Suspect APL based on:
1. Presence of DIC
2. Atypical promyelocytes
3. Flow Negative for HLA-DR

→ Start ATRA while waiting for cytogenetic and/or molecular confirmation

→ No t(15;17) or No PML-RARa
Stop ATRA
Treat AML

↓ APL confirmed

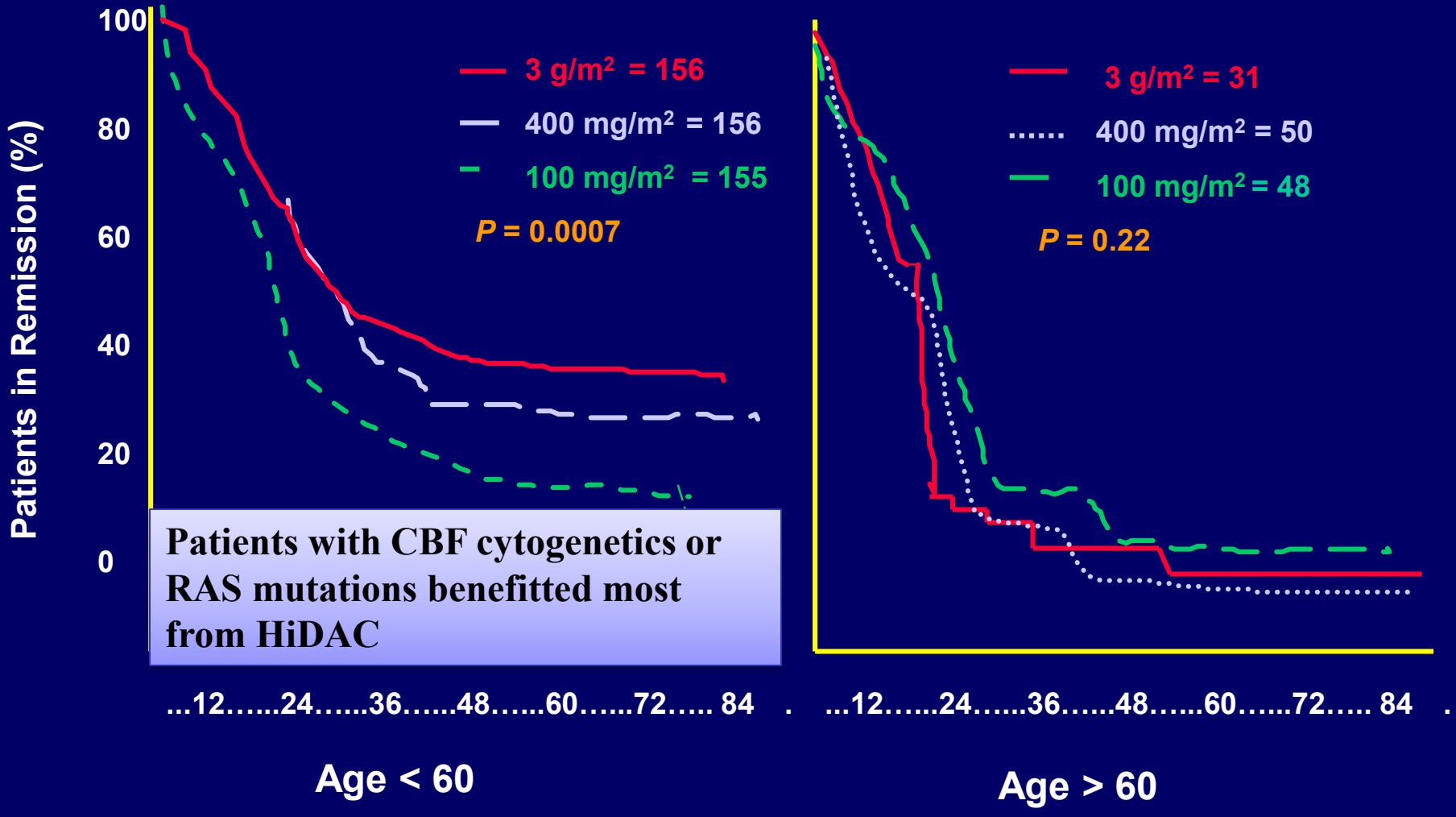
Low/Int Risk APL
No QTc prolongation
ATRA plus ATO
Prednisone for prophylaxis
Hydrea if WBC rises > 10K

High Risk APL (Options)
-ATRA/ATO + GO (if available)
-ATRA/ATO + ida (MRC, Australian)
-Follow CALGB 9710

AML Therapy for Patients Age <60 Years:

- INDUCTION
  - Daunorubicin 60-90 mg/m^2/d x 3 (or ida 12 mg/m2/d x3)
    Cytarabine 100-200 mg/m^2/d x 7 continuous infusion
  - Midostaurin 50 mg bid day 8-21 for mut FLT3
  - ? Add GO 3 mg/m2 d 1, 4, and 7, esp in CBF
  - CPX-351, d 1, 3, and 5 for h/o MDS, MDS-type cytogenetics
  - Decitabine 20 mg/m2 x 10d +venetoclax 400 mg/d: TP53
- POST-REMISSION
  - CBF: High dose ara-C 3 g/m2/3h q12h d1, 3, and 5 x 4 cycles
  - *NPM1* mut/*FLT3* WT: as above, ex ? 1.5 g/m2
  - Adverse risk: Allo SCT w best available donor
  - Intermediate risk: AlloSCT if Sib or MUD, otherwise as per *NPM1* mut/*FLT3* WT

Consolidation: DFS (and OS) Benefit Only in Patients < 60 Years Receiving High-Dose Ara-C



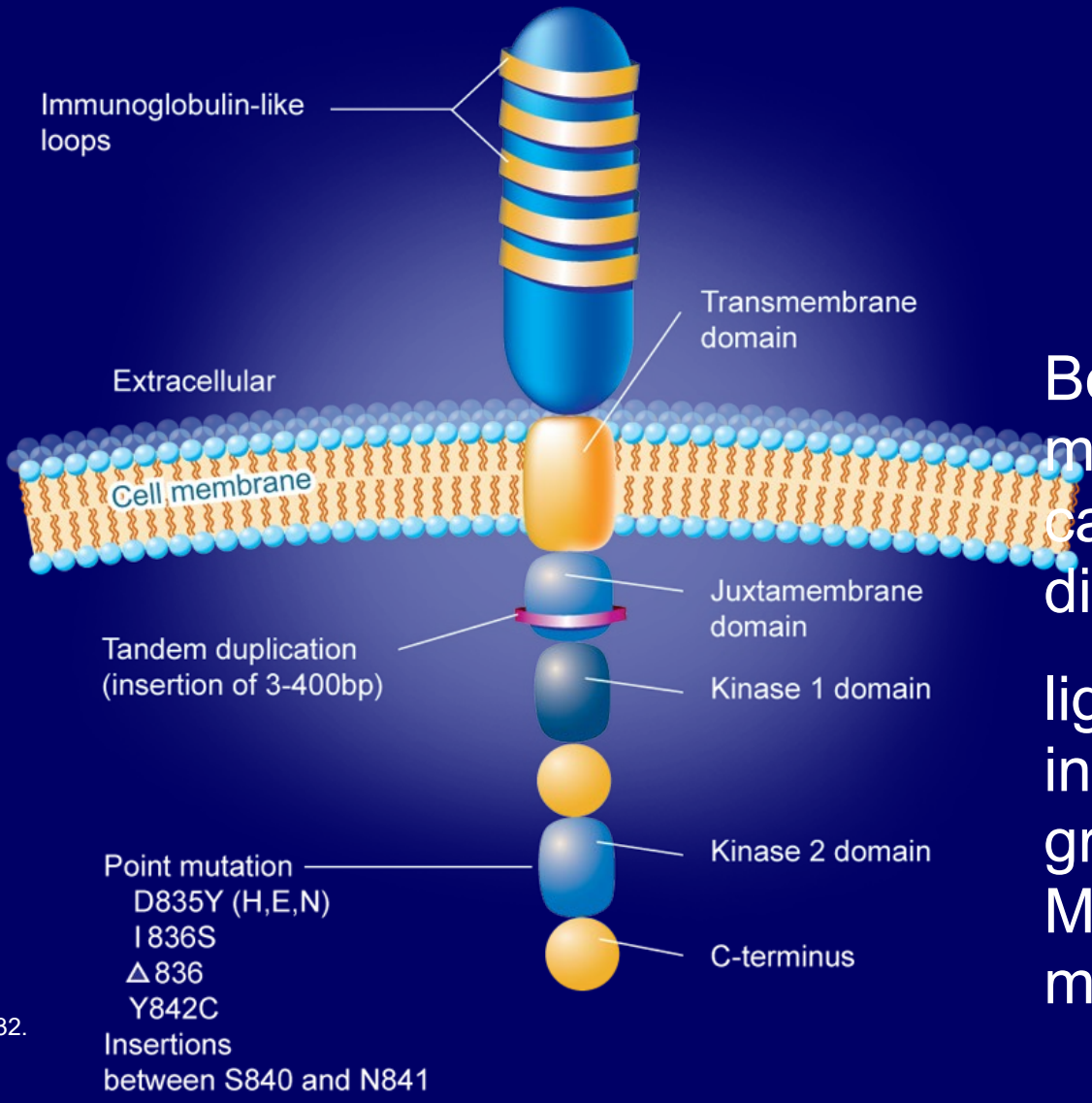
Bloomfield CD, et al. *Cancer Res.*1998;58(18):4173-4179; Neubauer A, et al. *J Clin Oncol.* 2008; 26(28):4603-4609; Mayer RJ, et al. *N Engl J Med*. 1994;33(1):896-903.

FLT3 Structure and Activating Mutations

Over-expression is common

25-30%

5-10%

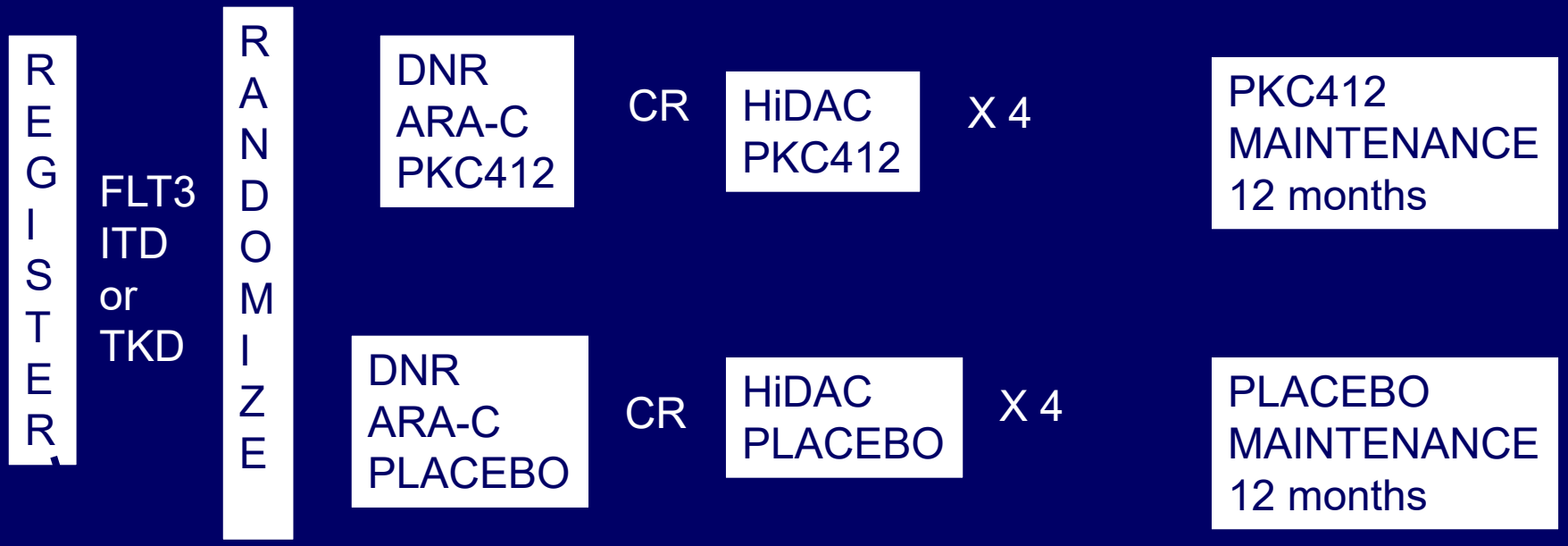


Both mutations cause spont dimerization,

ligand independent growth, and MPD in murine model

Litzow MR. *Blood*. 2005;106:3331-3332.

CALGB 10603: Prospective Phase III, double-blinded randomized study of induction and consolidation +/- Midostaurin (PKC412) in newly diagnosed patients < 60 years old with FLT3 mutated AML



Not on STUDY:
FLT3 WILD TYPE

Study drug is given on Days 8-21 after each course of chemotherapy, and Days 1-28 (note change) of each 28 day Maintenance cycle.

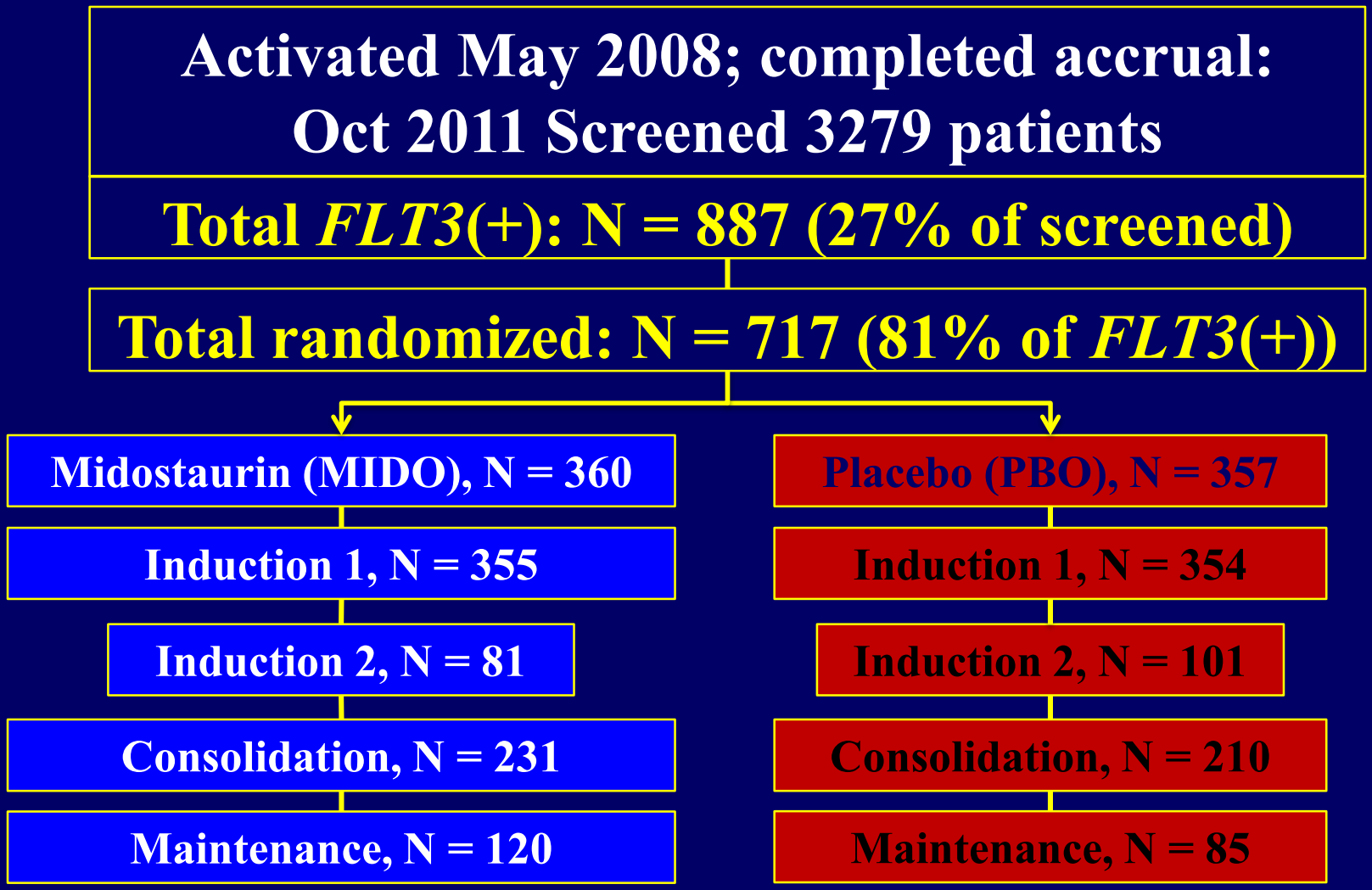
Protocol Therapy

Induction (2nd cycle given based on d21 marrow)	**daunorubicin**	60 mg/m^2 IVP days 1-3
	cytarabine	200 mg/m^2/d d 1-7 via IVCI
	midostaurin or placebo	50 mg po bid days 8-21
Consolidation (up to 4 cycles)	**cytarabine**	3 gm/m^2 over 3h q 12h days 1, 3, and 5
	midostaurin or placebo	50 mg po bid days 8-21
Maintenance	**midostaurin or placebo**	50 mg po bid days 1-28 x 12 cycles

- Transplant not specifically mandated

Stone R, et al. *Blood.* 2015;126: Abstract 6.

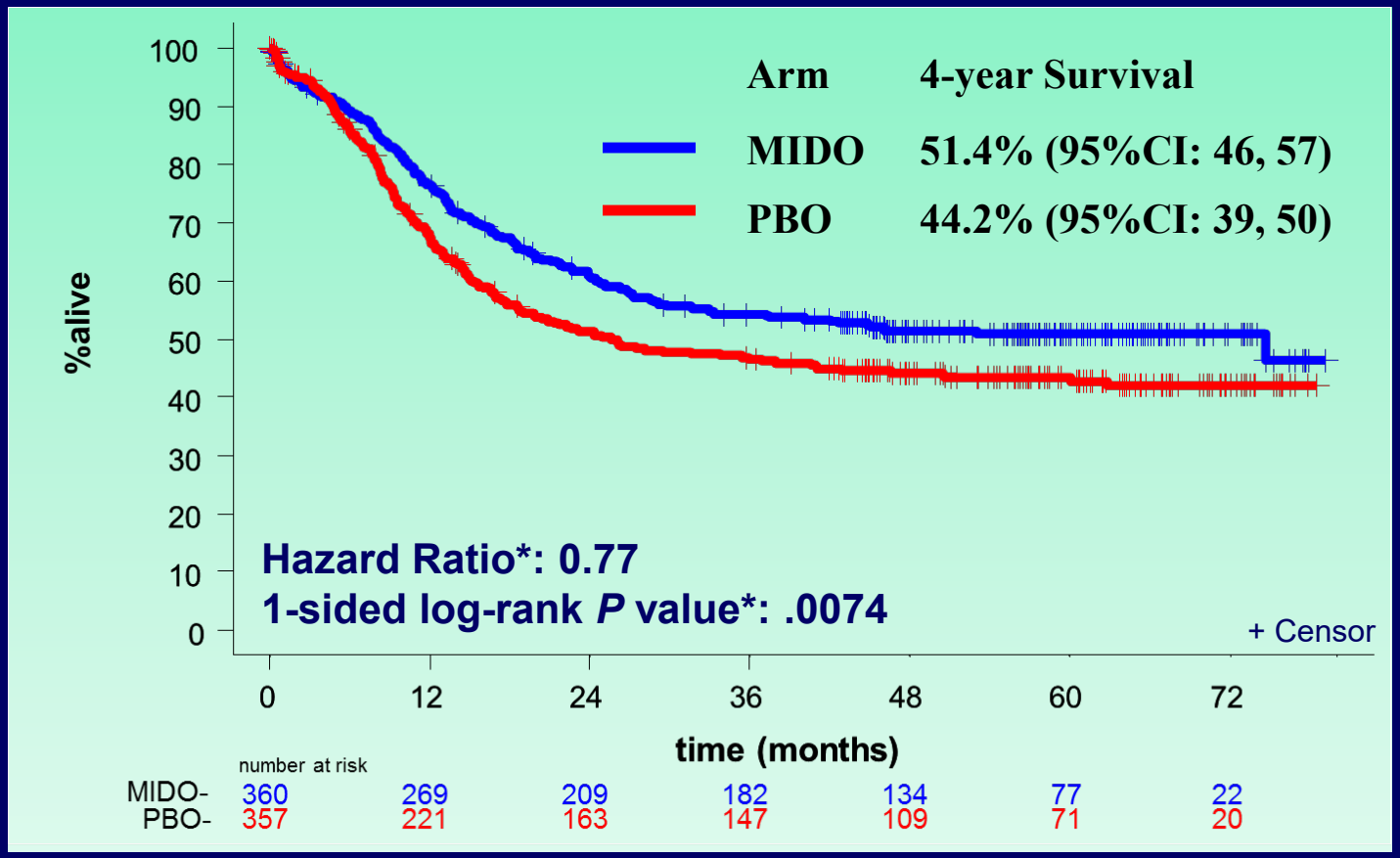
Consort Diagram



Stone RM, et al. *Blood.* 2015;126: Abstract 6.

Overall Survival (Primary Endpoint)

23% Reduced Risk of Death in the MIDO Arm



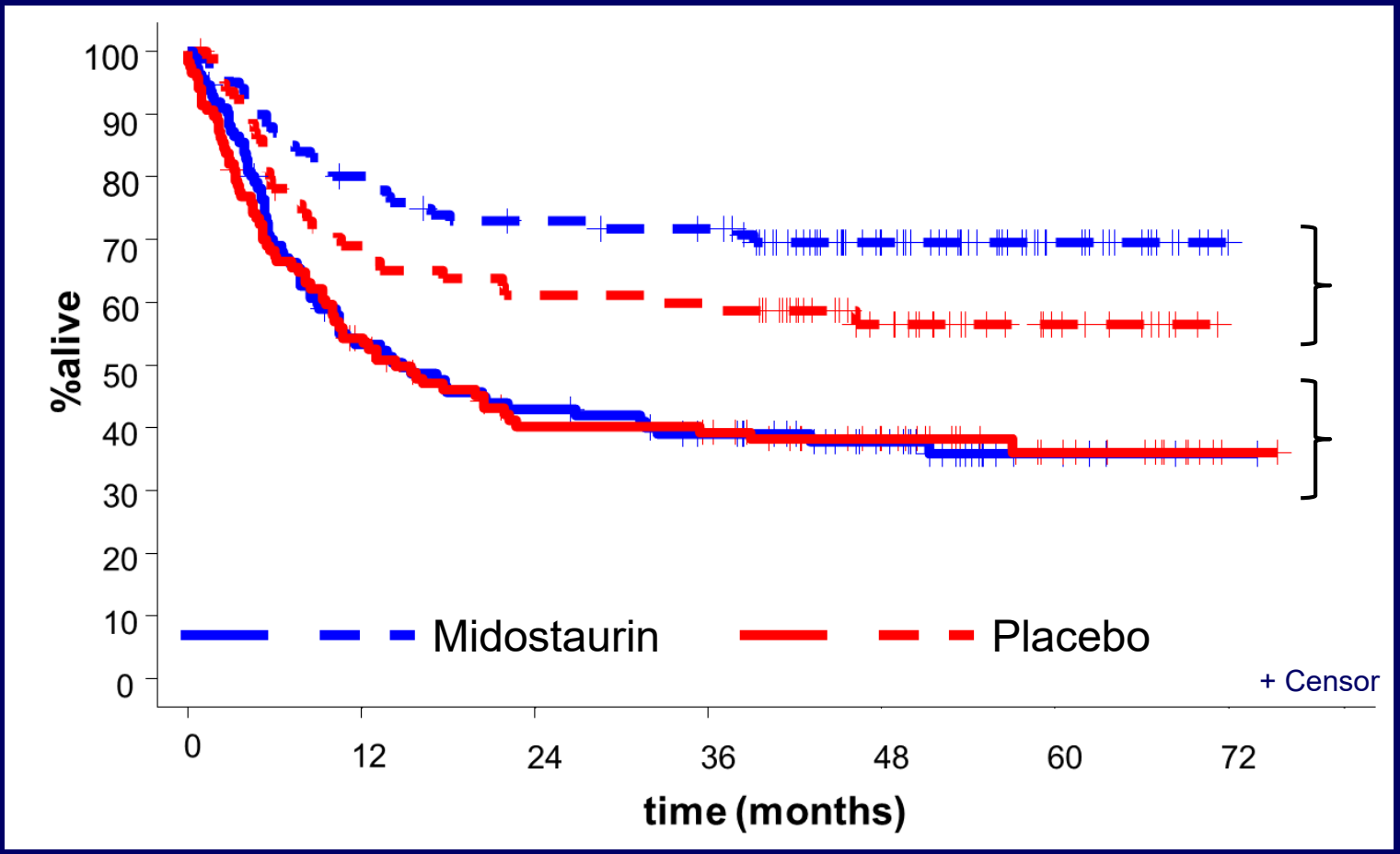
- **Median OS**: MIDO 74.7 (31.7-NE); PBO 25.6 (18.6-42.9) months

Controlled for *FLT3* subtype (TKD, ITD-Low, ITD-High)

Stone RM, et al. *Blood.* 2015;126: Abstract 6.

Overall Survival: Post-Transplant

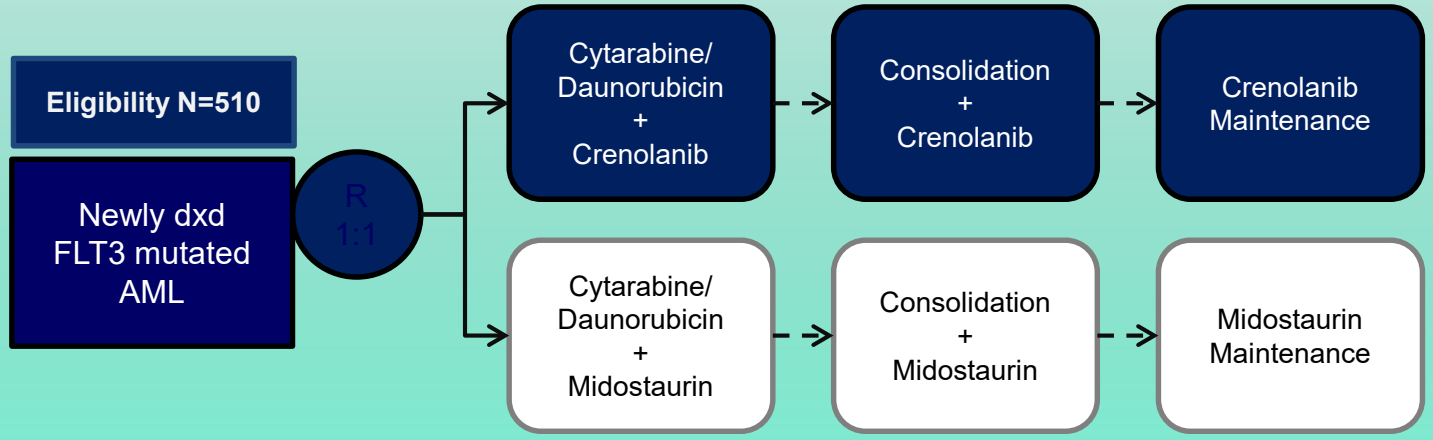
Treatment With MIDO Increases OS After SCT in CR1



SCT in CR1
HR 0.61

SCT outside CR1
HR 0.98

ARO-021: Phase III Comparison of Crenolanib with Midostaurin in Combination with Chemotherapy



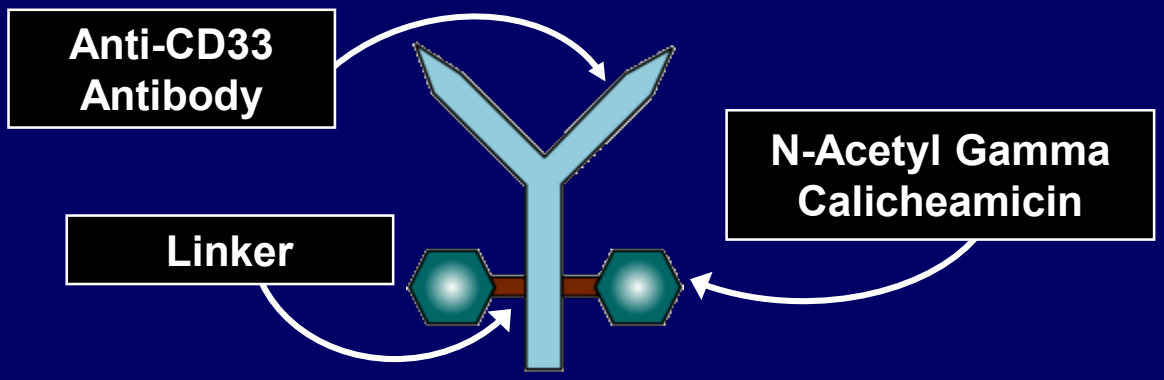
Primary Endpoint

- Event-free survival

Secondary Endpoints

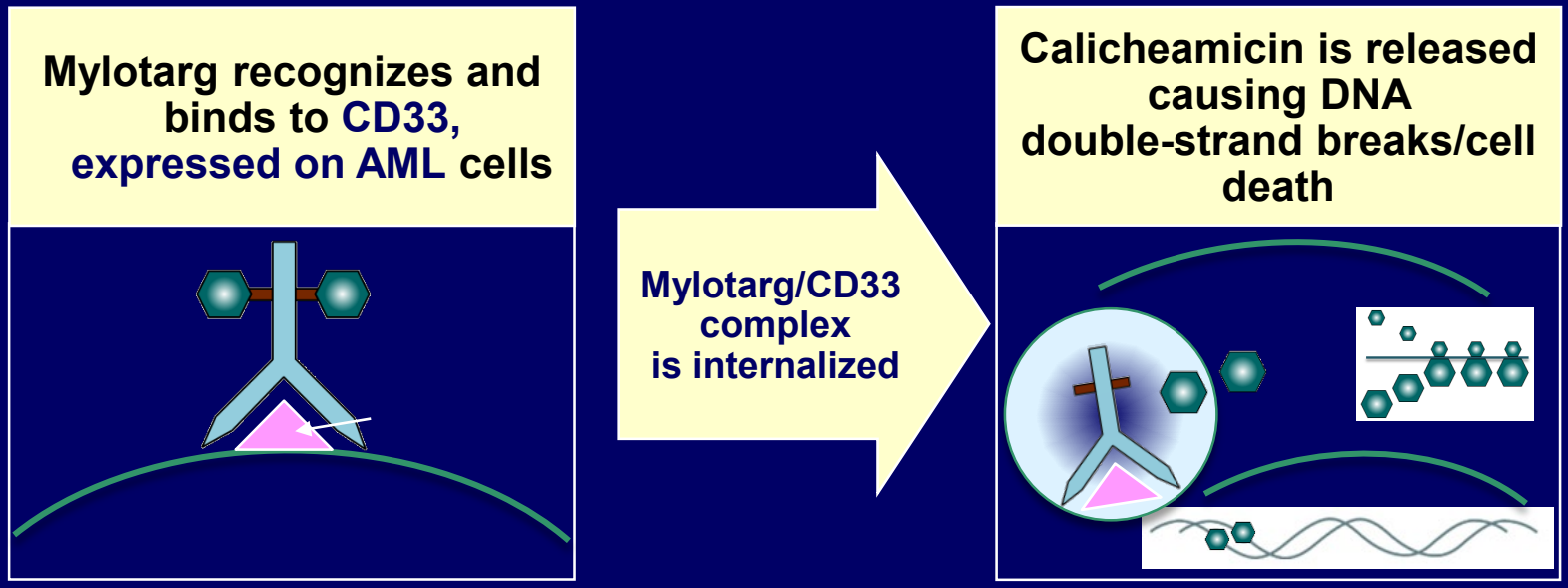
- Overall survival
- Relapse-free survival
- Composite complete remission rate
- Duration of response

Mylotarg (gemtuzumab ozogamicin)

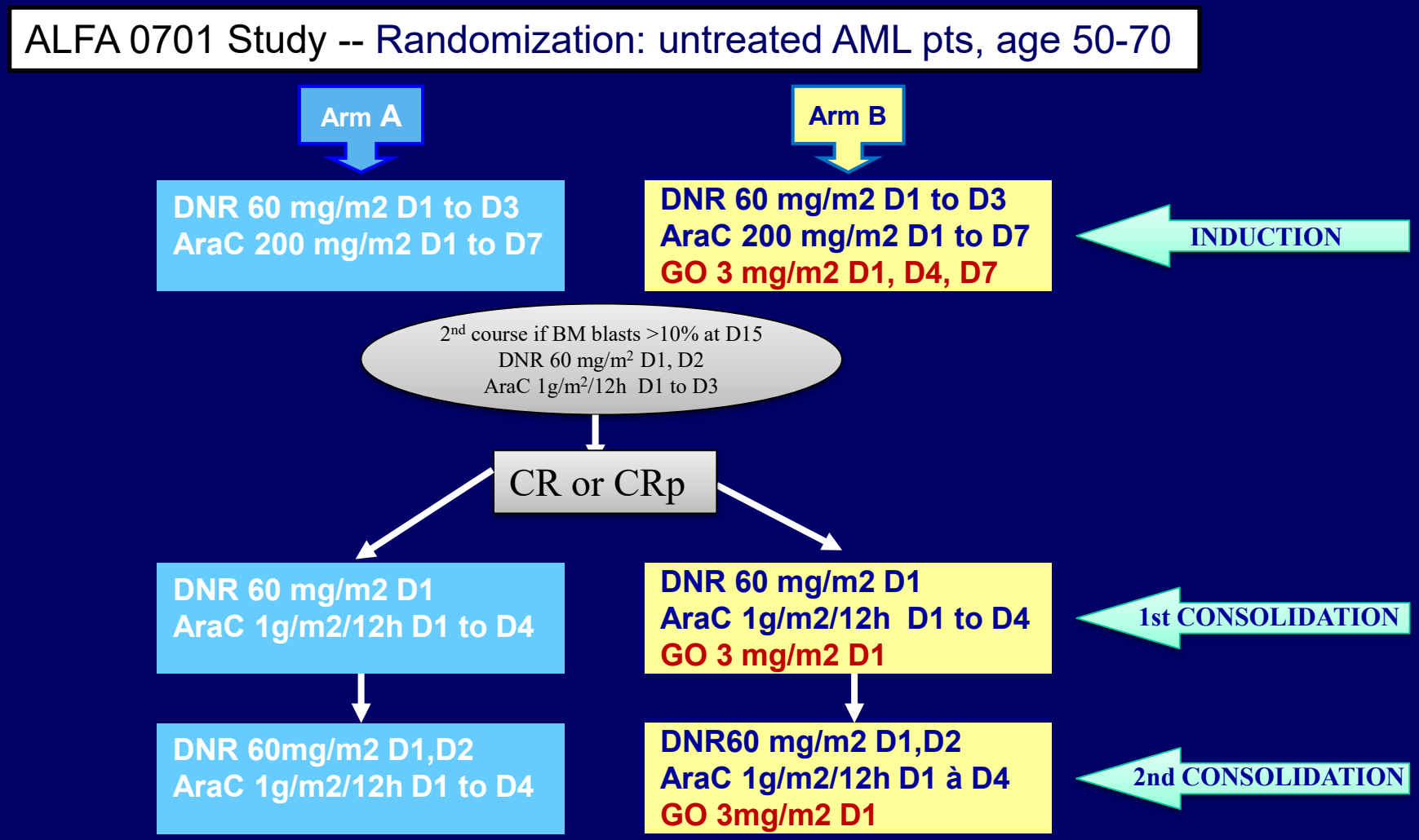


CD33 expressed on blasts in 90% of pts

Mechanism of Action

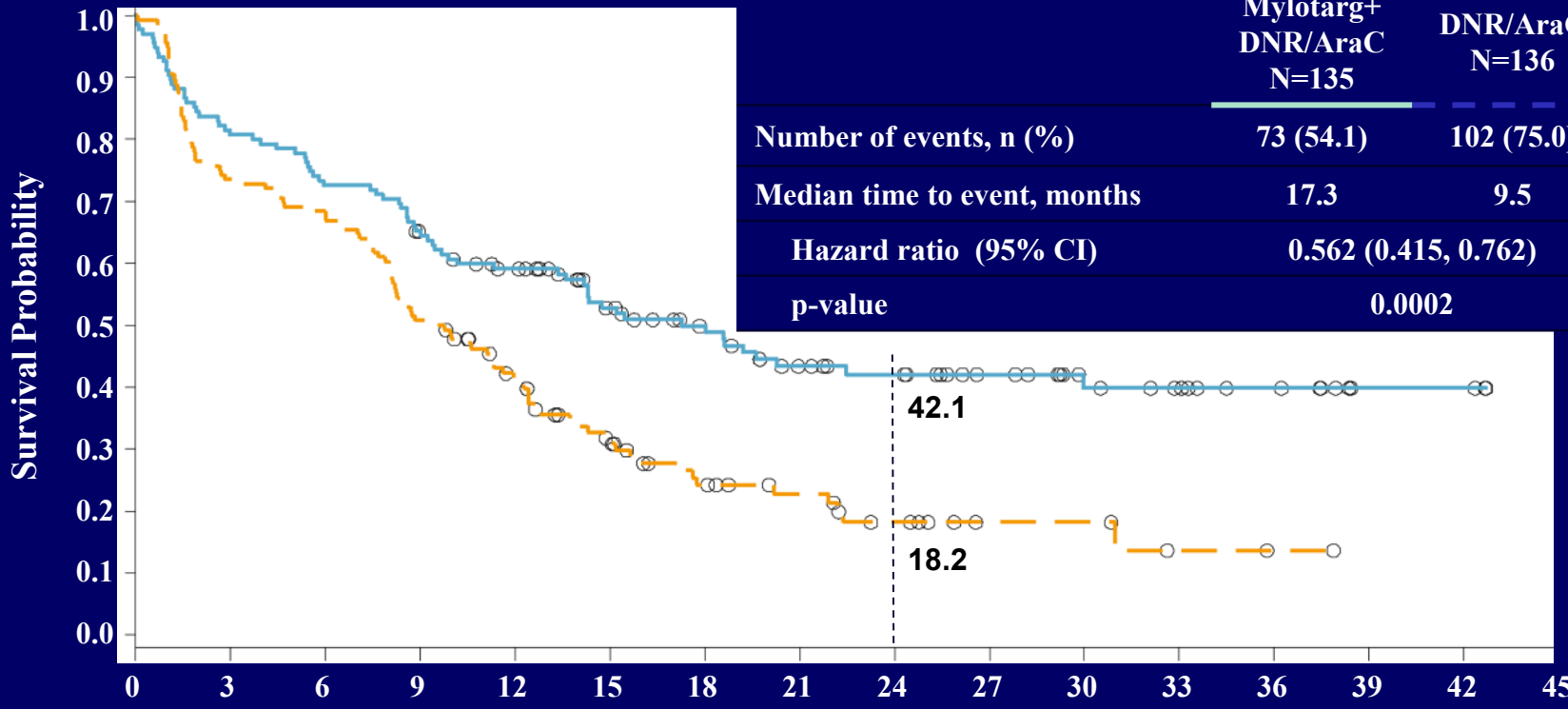


Gemtuzumab Ozogamicin: Recent Re-Approval



Castaigne S et al, Lancet 379:1508-1516, 2012

ALFA-0701:
Event-Free Survival – Primary Analysis



	Mylotarg+ DNR/AraC N=135	DNR/AraC N=136
Number of events, n (%)	73 (54.1)	102 (75.0)
Median time to event, months	17.3	9.5
Hazard ratio (95% CI)	0.562 (0.415, 0.762)	
p-value	0.0002	

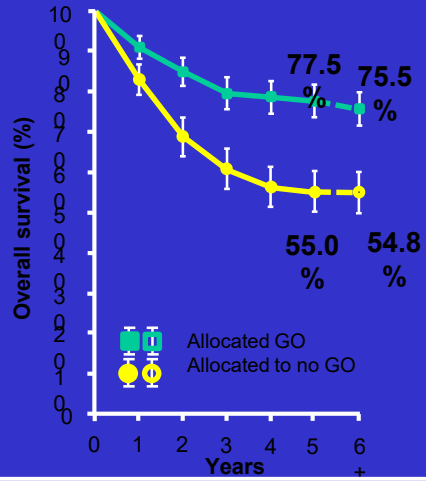
Number at Risk																
Mylotarg+ DNR/AraC	135	109	98	86	74	57	47	36	32	25	18	15	10	3	3	0
DNR/AraC	136	100	93	69	51	32	21	16	10	5	5	2	1	0		

mITT population; Data cutoff date: August 1, 2011
mITT=modified Intention-To-Treat

Hills RK *et al*. *Lancet Onco*l 2014;15:986–996

GO meta-analysis: Cytogenetics

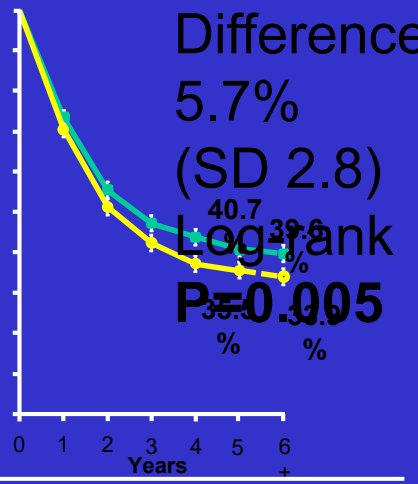
Favourable



Difference 20.7% (SD 6.5)
Log-rank **P=0.0006**

GO	5.8% (SD 1.1)	2.3% SD 1.3
No GO	14.1% (SD 1.9)	0.0% SD 0.0

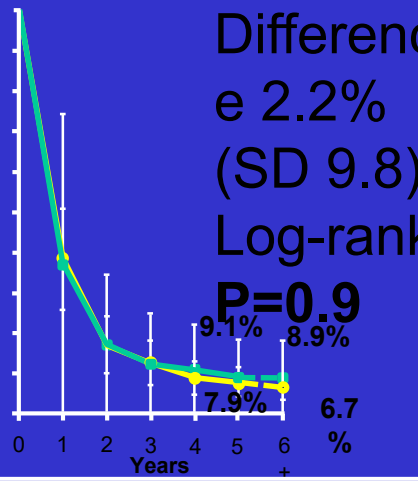
Intermediate



Difference 5.7% (SD 2.8)
Log-rank **P=0.005**

GO	22.4% (SD 1.0)	2.7% SD 0.9
No GO	26.2% (SD 1.1)	4.9% SD 1.3

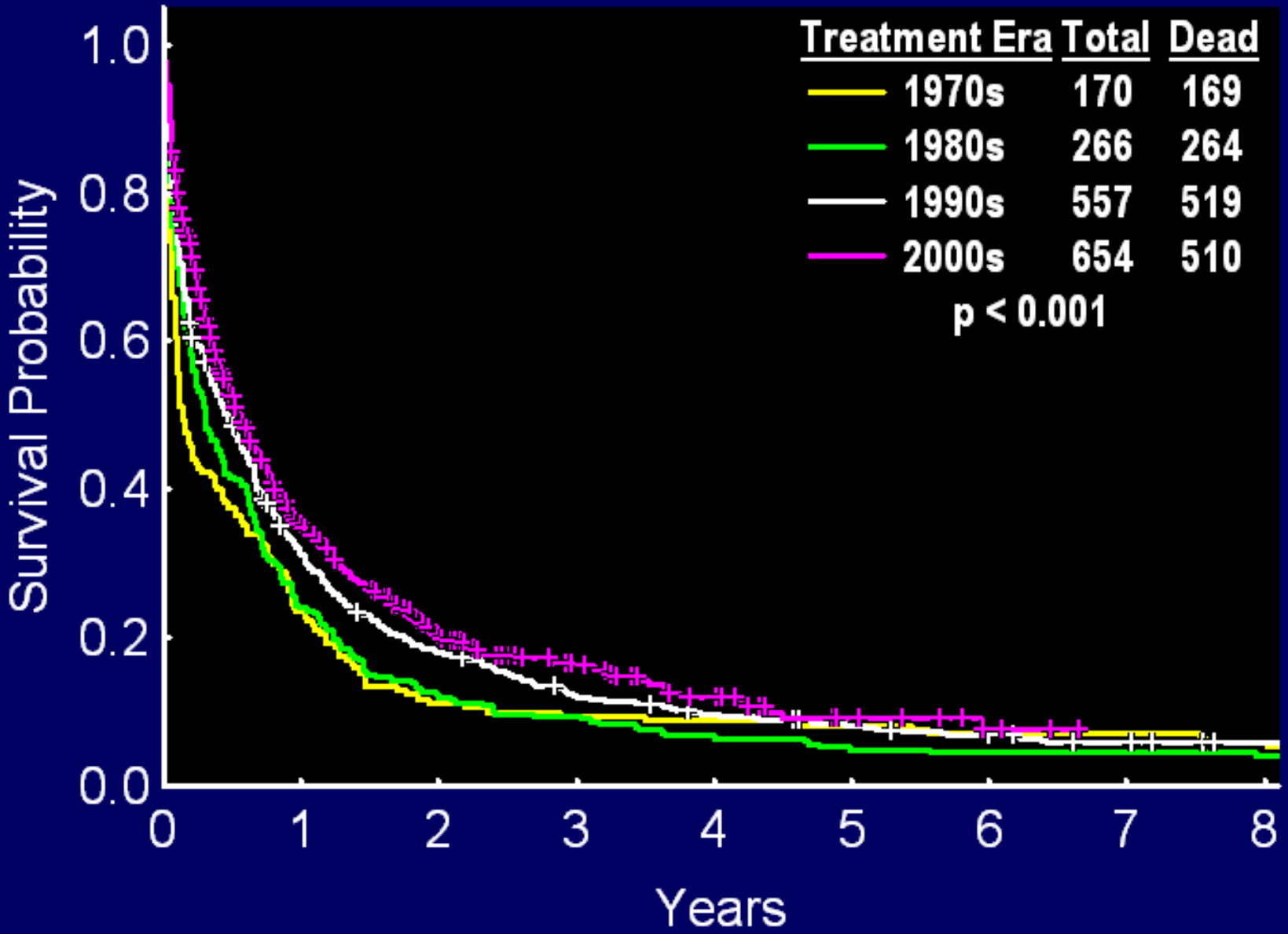
Adverse



Differenc e 2.2% (SD 9.8)
Log-rank **P=0.9**

GO	73.8% (SD 4.6)	2.4% (SD 2.4)
No GO	76.7% (SD 4.8)	21.1% (SD 10.5)

Survival in AML in Age ≥ 60 Years (MDACC, 1973-Present, n=1647)



Why Do Older Patients With AML Experience Inferior Outcomes?

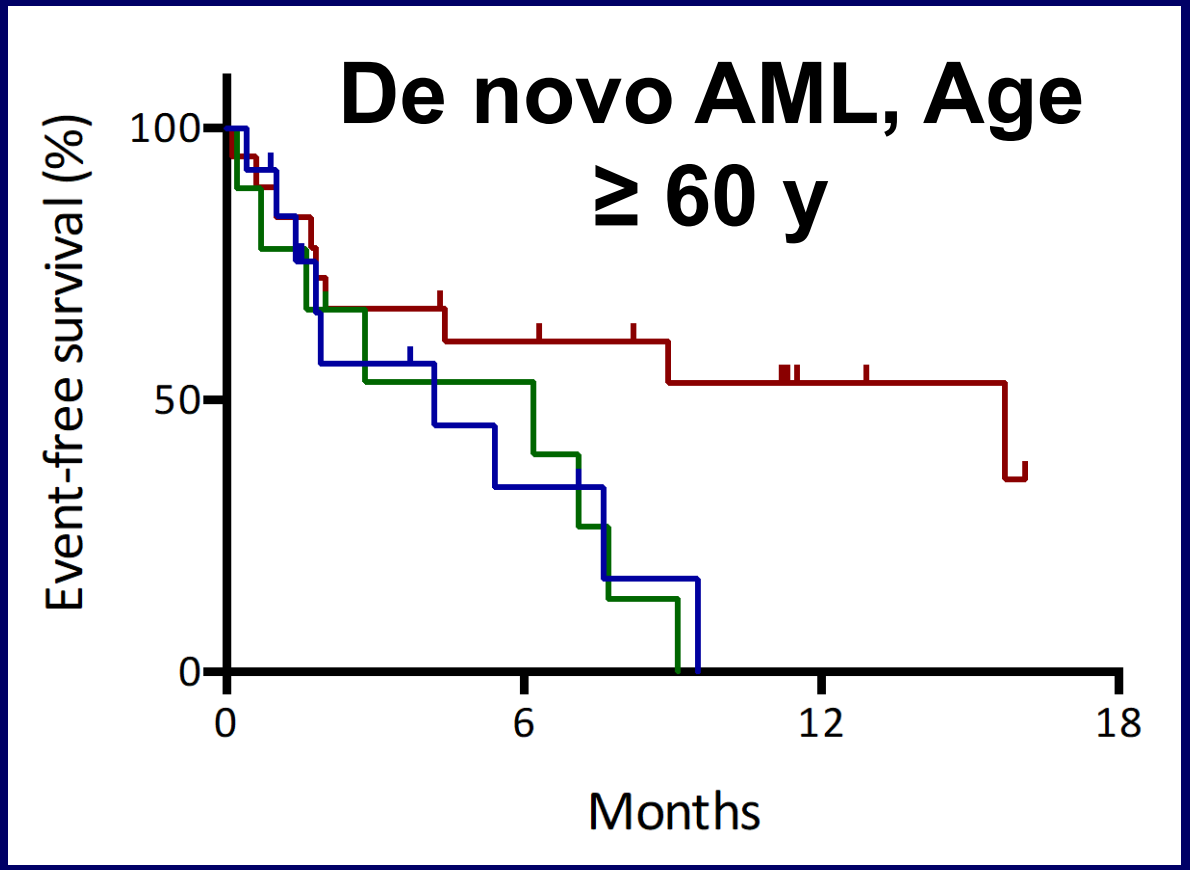
- Decreased host tolerance of intensive therapy
  - Impaired hematopoietic stem cell reserve
  - Presence of comorbid diseases
  - Decreased chemotherapy clearance
- Increased resistance of disease to therapy
  - Ratio of favorable (eg, t[8;21]) to unfavorable (eg, -7) cytogenetics is lower than for younger patients
  - Higher expression of drug resistance proteins (eg, PGP)
  - Higher incidence of antecedent hematologic disorders

PGP = p-glycoprotein.

New RX Algorithm in Older Adults with AML

- FIT, FLT3 mutation (TKD or ITD): 3+7+mido
- FIT, CBF: 3+7+GO
- FIT, MRC-related cytogenetics, h/o MDS, prior rx for CA: CPX-351
- FIT, NOS: 3+7
- UNFIT, or >75 yo: aza (7d) +venetoclax
- UNFIT, IDH1 or IDH2 mut: ivo- or enasidenib
- ANY FITNESS: TP53 mut: 10d decit+ven
- Add lomustine to 3+7 wo unfav cytog (Pigneux A et al, JCO, 2019)
- Post CR
  - alloSCT if poss (Devine et al , JCO 2015)
  - Cont low dose rx (Dinardo et al Blood 2019)
  - Maint aza imp DFS (Huls, et al , Blood 2019)

In Elderly de novo AML, Secondary-Type Mutations Are Associated With Adverse Outcomes



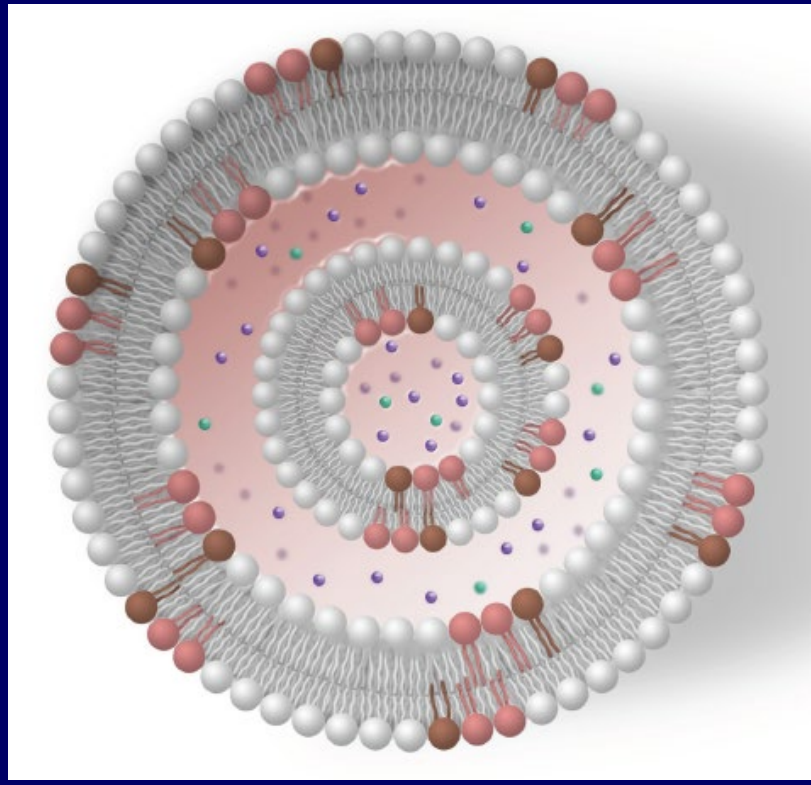
Genetic Subtype

- De novo/pan-AML
- Secondary-type
- *TP53* mutated

Lindsley RC et al. Blood. 2015;125:1367-1376.

CPX-351

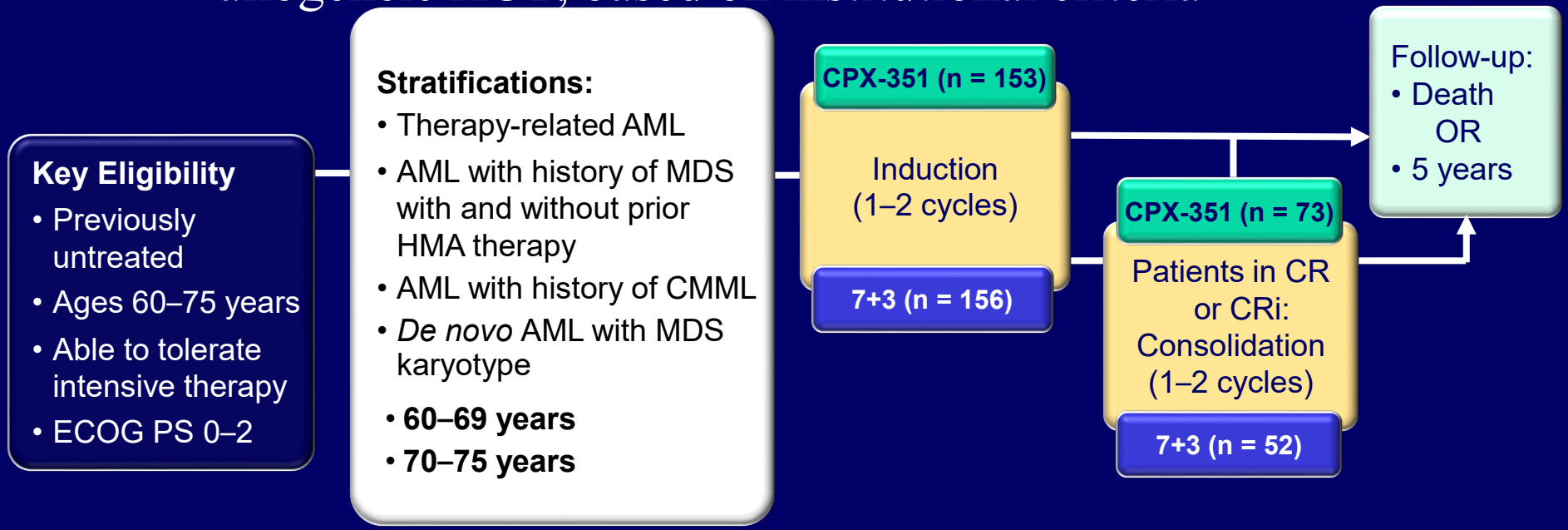
- CPX-351 is a liposomal co-formulation of cytarabine and daunorubicin designed to achieve synergistic antileukemia activity
  - 5:1 molar ratio of cytarabine:daunorubicin provides synergistic leukemia cell killing *in vitro*[1]
  - In patients, CPX-351 preserved delivery of the 5:1 drug ratio for over 24 hours, with drug exposure maintained for 7 days[2]
  - Selective uptake of liposomes by bone marrow leukemia cells in xenograft models[3]



. Tardi P et al. *Leuk Res.* 2009;33(1):129–139.
2. Feldman EJ et al. *J Clin Oncol.* 2011;29(8):979–985;
3. Lim WS et al. *Leuk Res.* 2010;34(9):1245–1223.

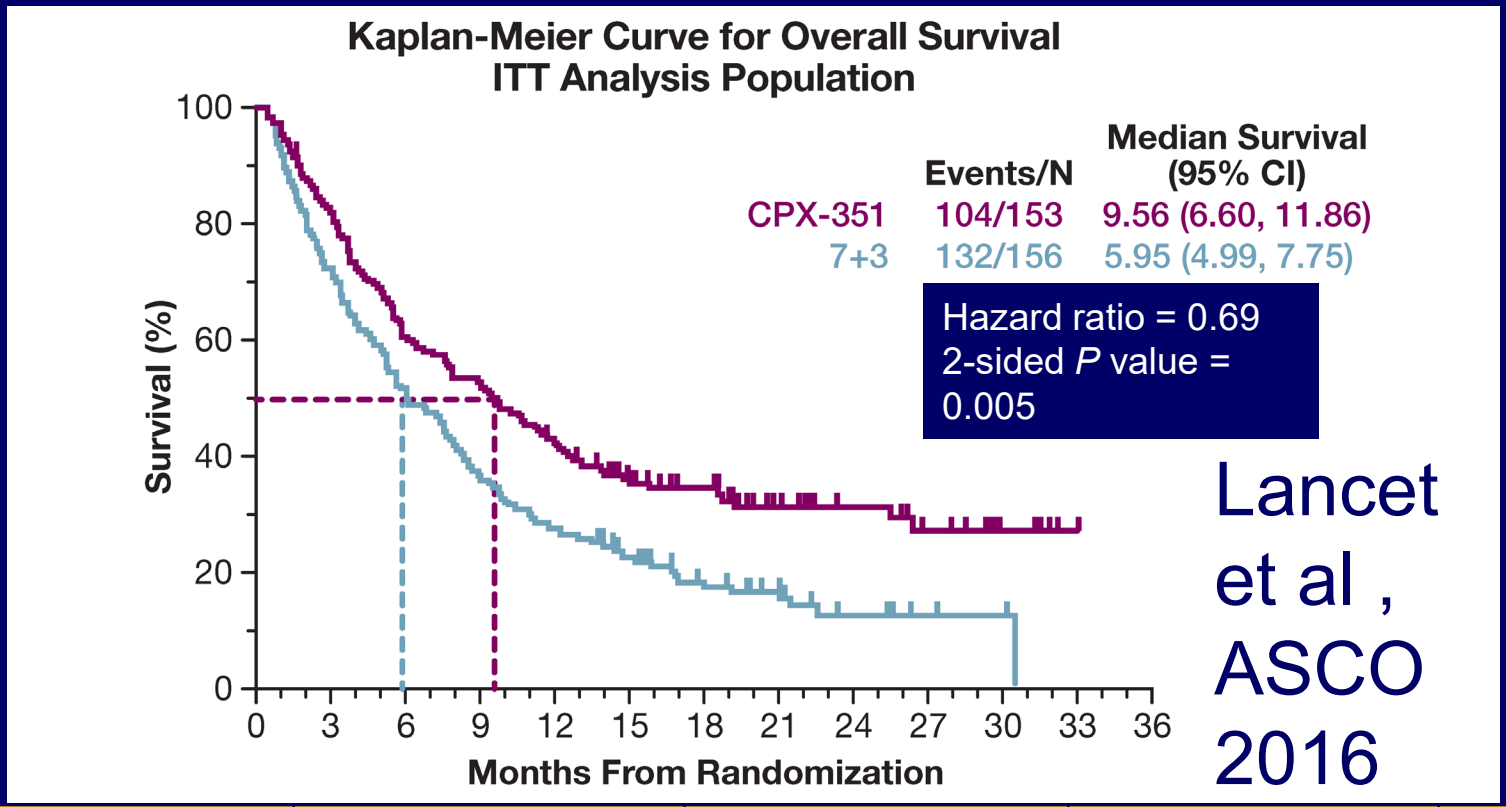
CPX-351 Phase III Study Design

- Randomized, open-label, parallel-arm, standard therapy–controlled
  - 1:1 randomization, enrolled from December 2012 to November 2014
  - Patients with CR or CRi could be considered for allogeneic HCT, based on institutional criteria



recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; HMA, hypomethylating agents; MDS, myelodysplastic syndrome.

1. World Health Organization. *WHO Classification of Tumours of Haematopoitic and Lymphoid Tissues*. Swerdlow S et al (ed). Lyon, IRAC Press, 2008.



Lancet et al , ASCO 2016

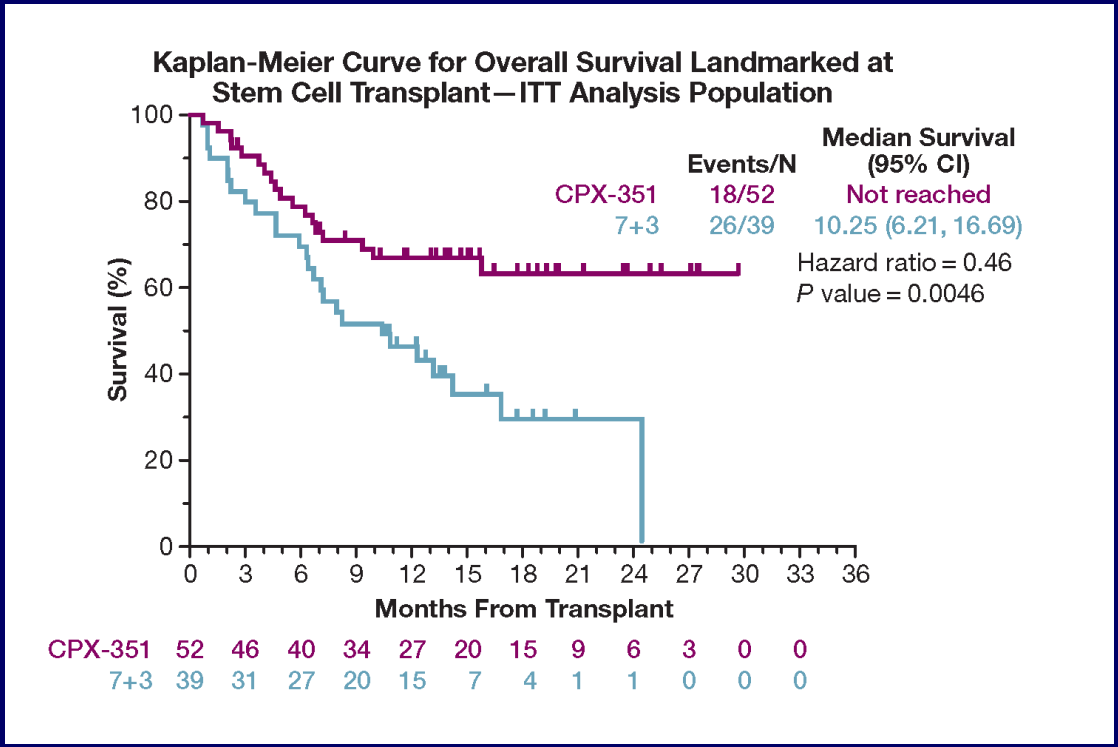
	CPX-351 (n = 153)	7+3 (n = 156)	Odds ratio	*P* value
CR+CRi	47.7%	33.3%	1.77 (1.11, 2.81)	0.016
HSCT rate	34.0%	25.0%	1.54 (0.92, 2.56)	0.098
Deaths ≤30 days*	5.9%	10.3%		
Deaths ≤60 days*	13.7%	21.2%		

were alive: CPX-351 (n = 49): 589 days (range: 44-1007); 7+3 (n = 24): 601 days (range: 417-917).

CI, confidence interval; CR, complete response; CRi, CR with incomplete platelet or neutrophil recovery; HSCT, hematopoietic stem cell transplant.

Survival Landmarked from Time of Transplant

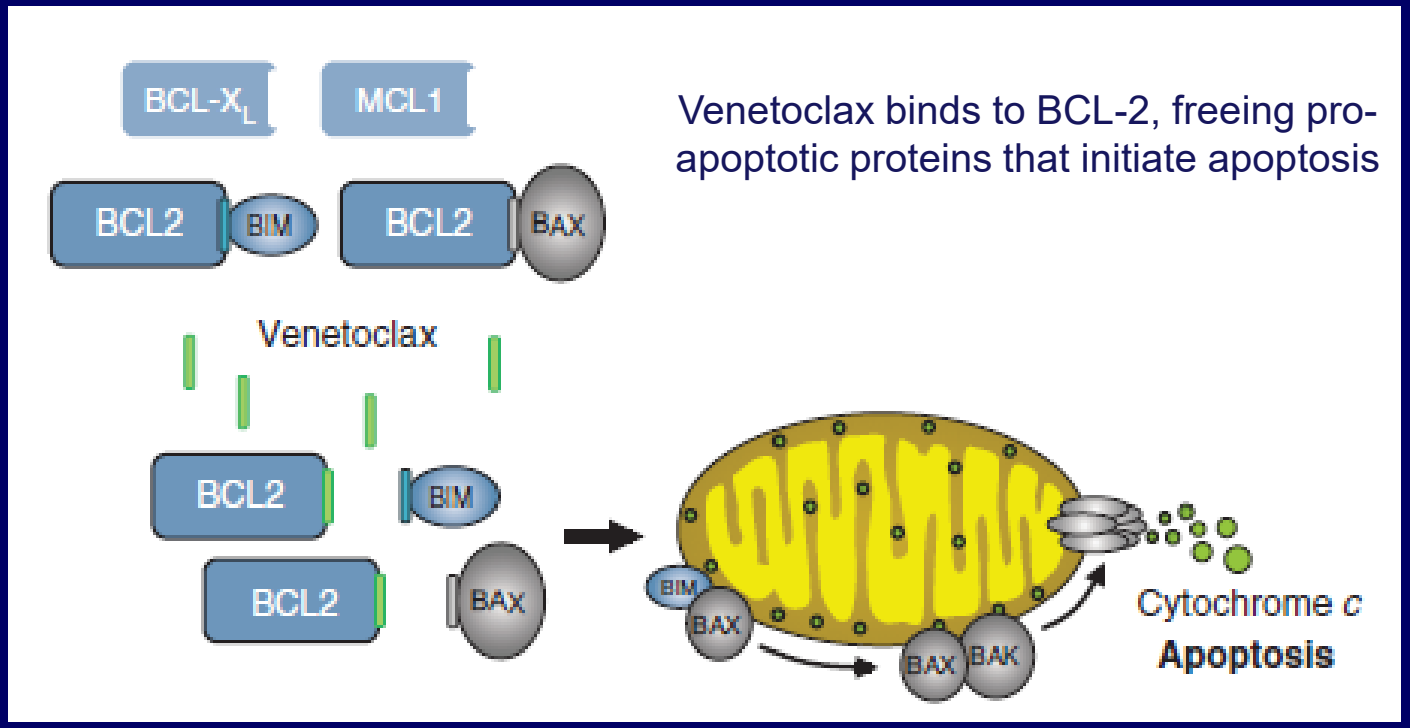
- CPX-351 median OS not reached vs 10.25 months for 7+3
  - HR of 0.46 favoring CPX-351 (*P*=0.0046)
  - Cox proportional hazards HR, including transplant as a time-dependent covariate, was 0.51 (95% CI, 0.35–0.75; *P*=0.0007), favoring CPX-351



Lancet et al, ASH 2016

Venetoclax: BCL-2 Selective Inhibitor

BCL-2 overexpression allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins

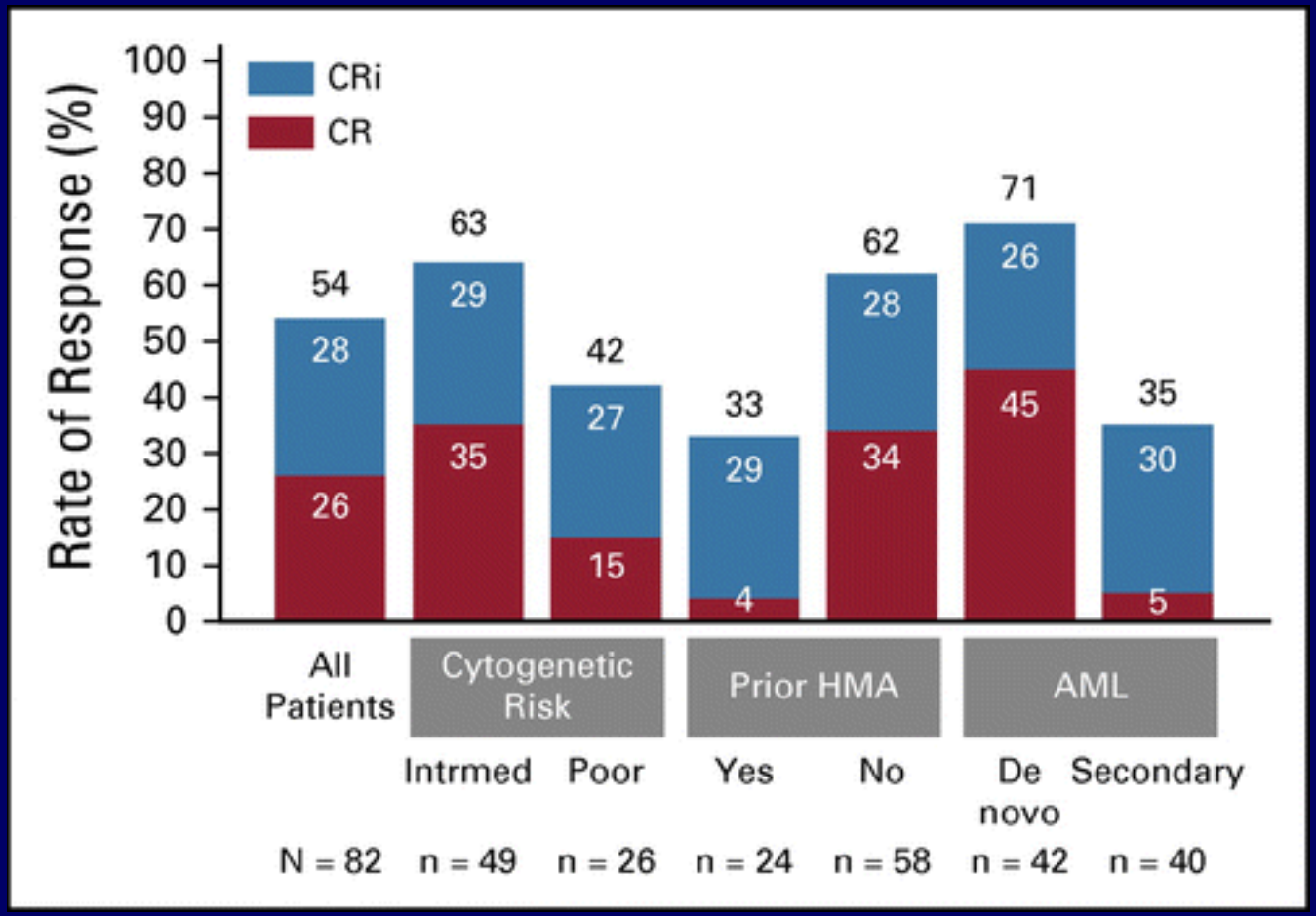


Venetoclax binds to BCL-2, freeing pro-apoptotic proteins that initiate apoptosis

Konopleva M, et al. *Cancer Discov*. 2016. Epub ahead of print. Lin T, et al. ASCO 2016. Abstract 7007.

Venetoclax+low dose ara-C new dx

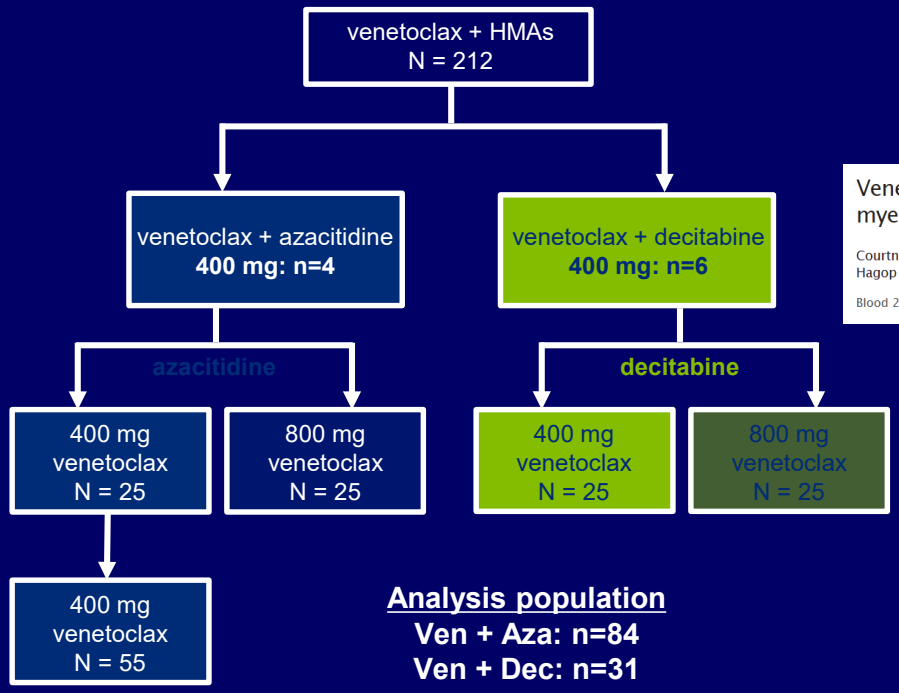
- >60 yo, inelig for intensive chemo (HMA for prior MDS allowed)
- TLS ppx, ramp up ven to target (dose reduced if CYP3Ai used) : 600 mg/d + ara-C 20 mg/m2/d sc x 10d
- N=82



Wei A et al. *Blood*. 2019

Study Overview

NCT02203773



Analysis population
Ven + Aza: n=84
Ven + Dec: n=31

Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia

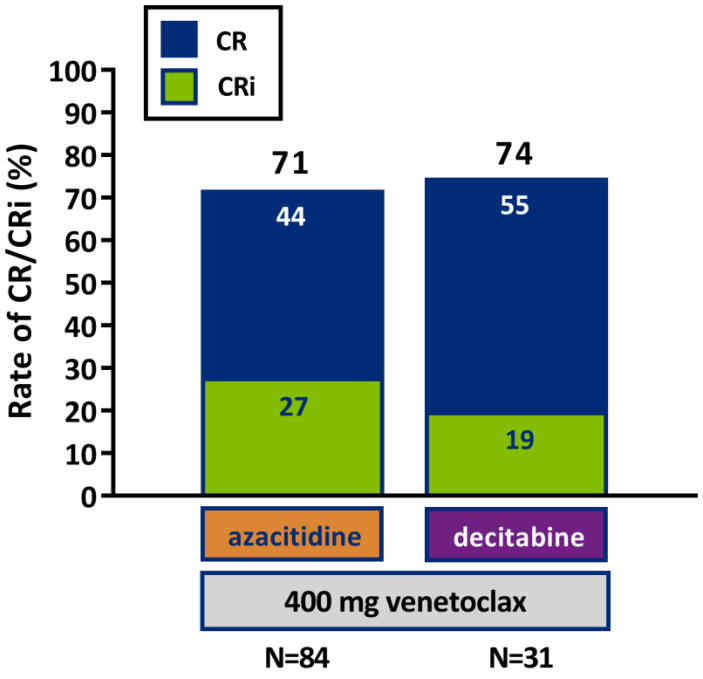
Courtney D. DiNardo, Keith Pratz, Vinod Pullarkat, Brian A. Jonas, Martha Arellano, Pamela S. Becker, Olga Frankfurt, Marina Konopleva, Andrew H. Wei, Hagop M. Kantarjian, Tu Xu, Wan-Jen Hong, Brenda Chyla, Jalaja Potluri, Daniel A. Pollyea, and Anthony Letai

Blood 2018 :blood-2018-08-868752; doi: https://doi.org/10.1182/blood-2018-08-868752

- **CR/CRi** rate of 67% in older AML patients with venetoclax + HMAs
- **Median DOR** was 11.3 months and median OS was 17.5 months
- **400 mg venetoclax** was the recommended phase 2 dose

| Pollyea D, et al , ASH 2018, Dinardo C, Blood, 2019

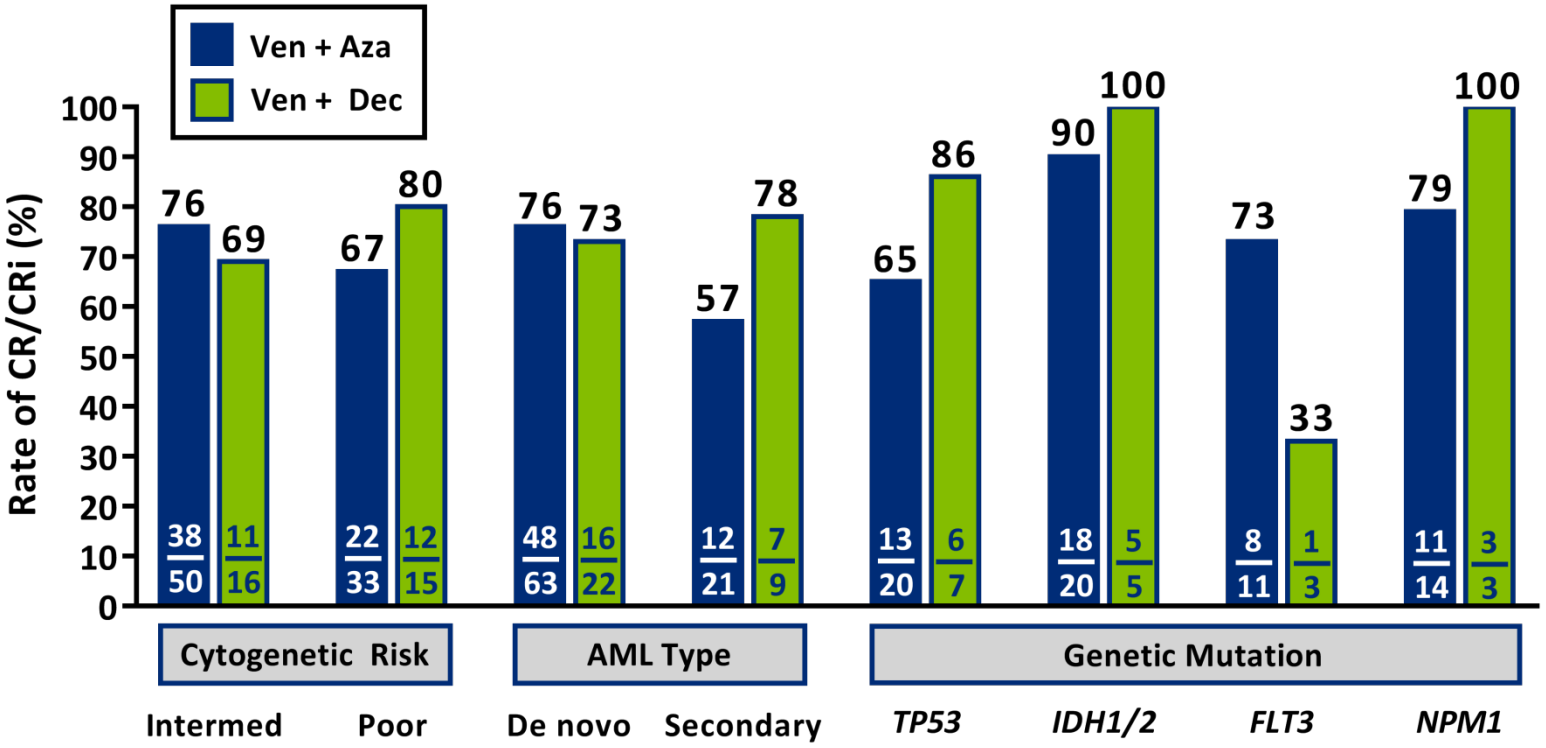
Response Rates of CR/CRi by Combination: VEN+HMA



	Ven + Aza	Ven + Dec
Time to CR median (range)	1.2 (0.7–5.5)	1.9 (0.9–4.6)
No. of treatment cycles for these patients median (range)	6.0 (1–32)	6.0 (1–29)

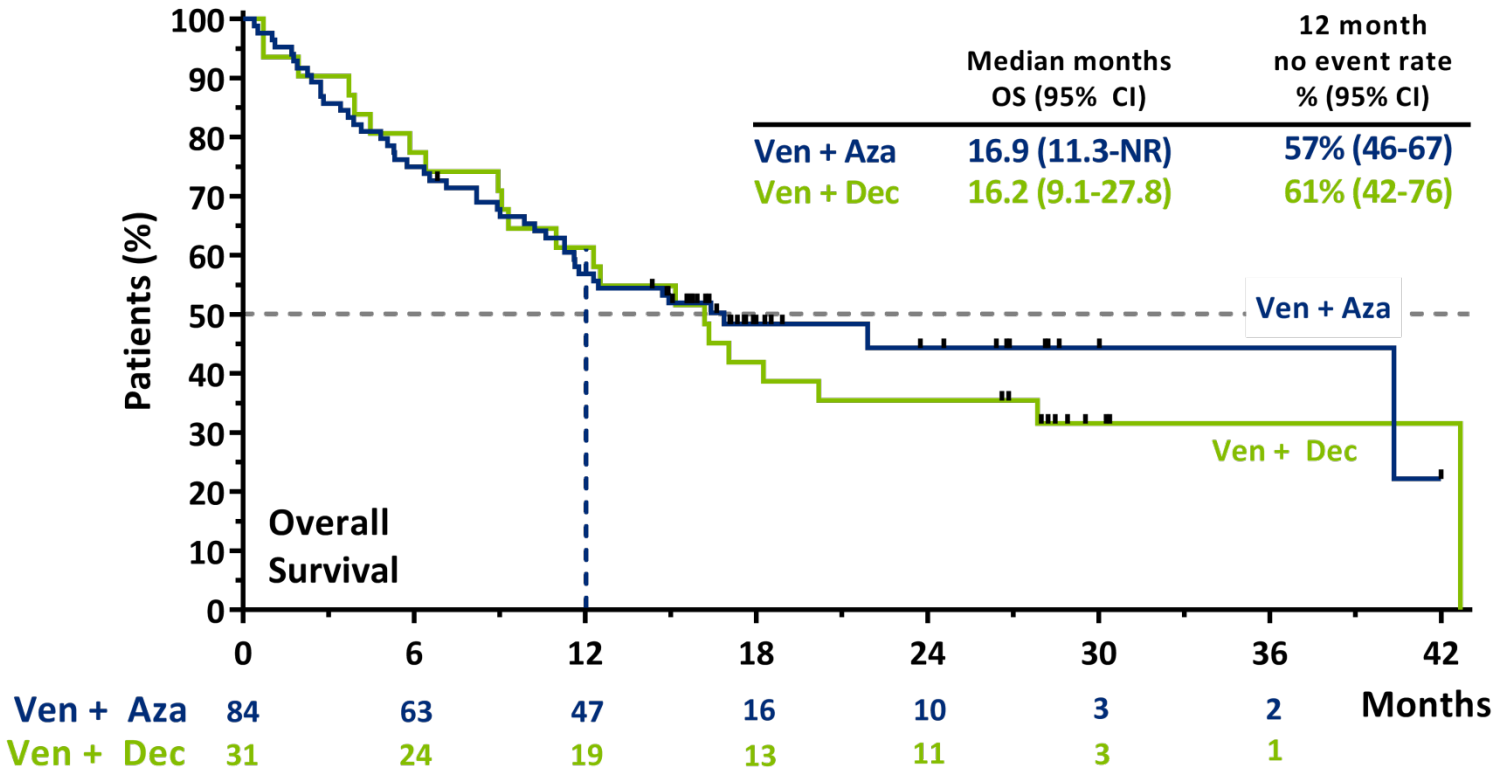
Pollyea D, et al , ASH 2018, Dinardo C, Blood, 2019

Response Rates of CR/CRi by Patient Subgroups

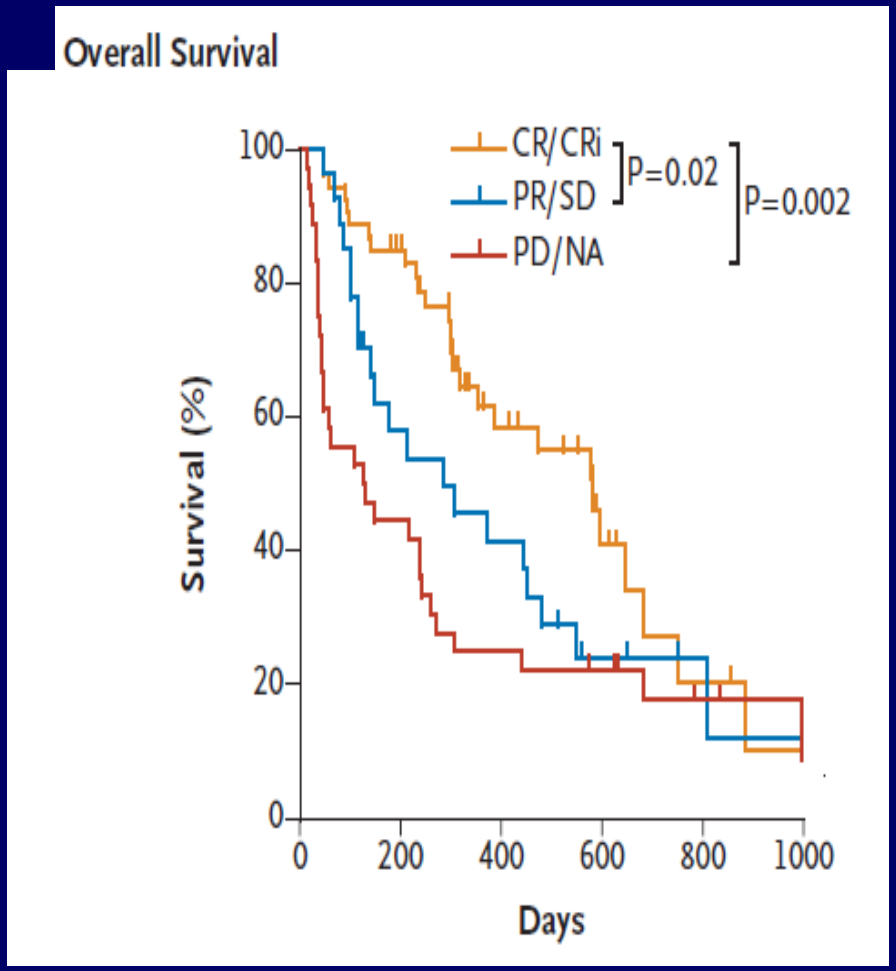


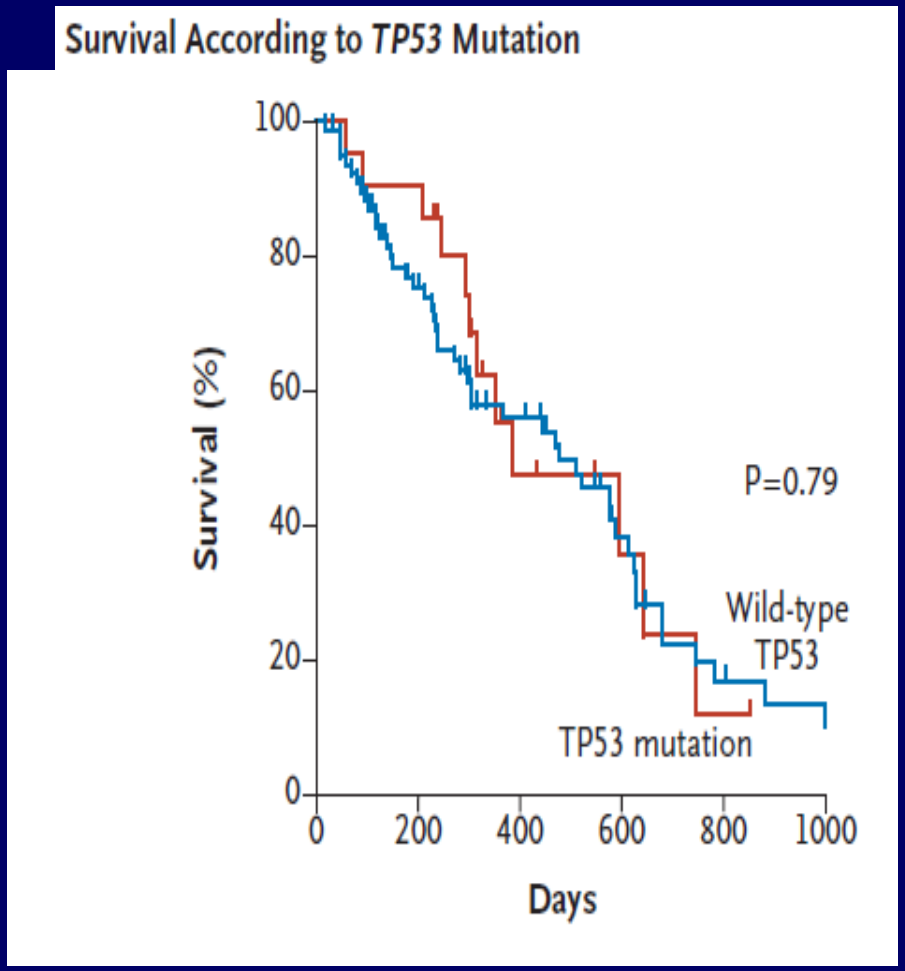
Pollyea D, et al , ASH 2018, Dinardo C, Blood, 2019

Overall Survival



TP53 and Decitabine in AML





NA = not applicable; PD = progressive disease; PR = partial remission; SD = stable disease.

Welch JS et al. *N Engl J Med.* 2016;375:2023-2036.

DEC10-VEN in AML/MDS
CR/CRi Rates in Subgroups

Newly dx AML and untreated sAML	n/N (%)
Mutational subgroups	
NPM1	**8/8 (100)**
IDH1/2	**5/5 (100)**
FLT3	**3/4 (75)**
TP53	**4/4 (100)**
ASXL1	**5/5 (100)**
RUNX1	**5/5 (100)**
RAS	**3/4 (75)**
ELN subgroups	
Favorable	**6/6 (100)**
Intermediate	**10/10 (100)**
Adverse	**10/11 (91)**

30-day mortality – 8%, 60-day mortality – 10%

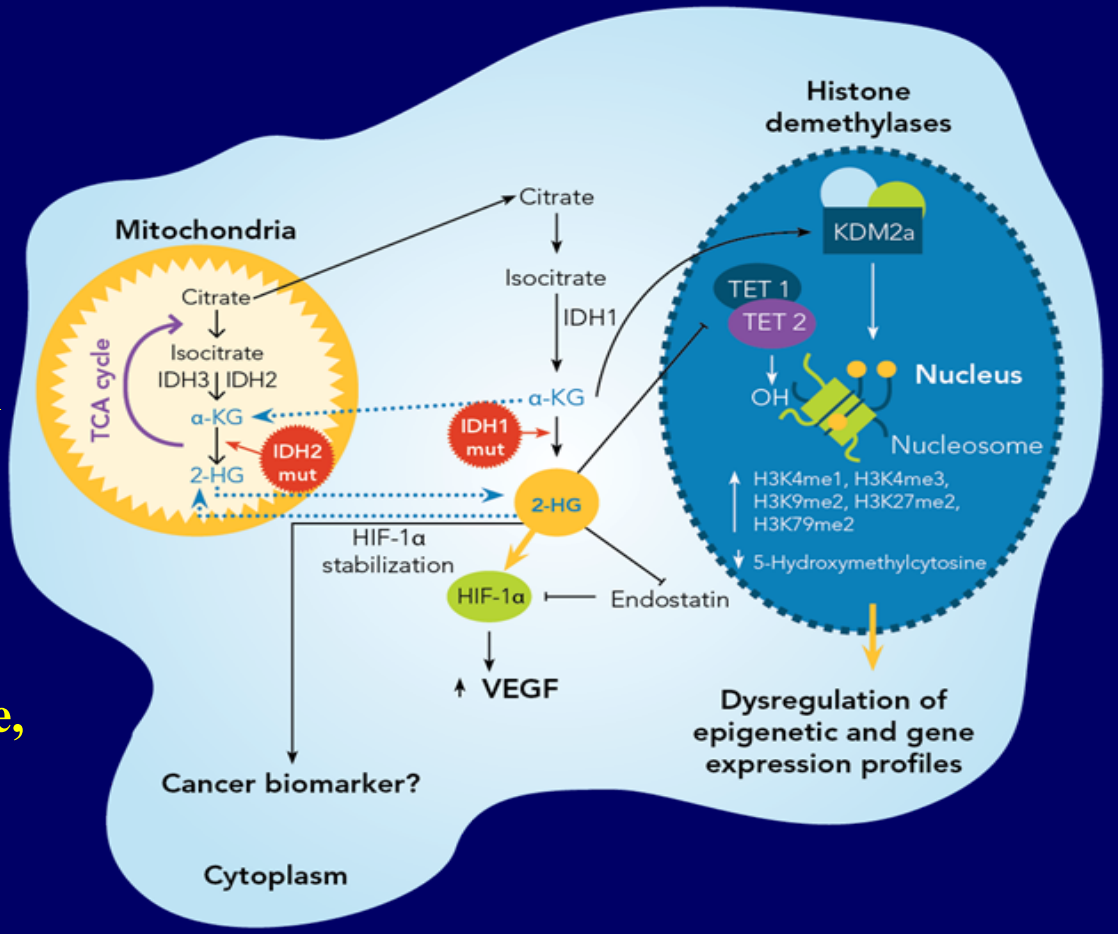
Maiti et al, ASH 2018

Relapsed AML: Induce CR2, then allo SCT

- FLAG-IDA, MEC are typical salvage regimens (can repeat 3+7 if >1 y ds-free interval)
- If IDH2 mutant: consider enasidenib
- IF IDH1 mutant: consider ivosidenib
- IF FLT3 mutant: gilteritinib/quizartinib
- Fractionated gemtuzumab if unfit
- Clinical trial (spliceosome inhib, HH pathway, pro-apoptotic [BCL-2i, MDM2i], chemo + E-selectin inhibitor)

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**



IDH Inhibitor Data

AG120=ivosidenib

- Most common AEs: diarrhea, fatigue, and pyrexia
- **Overall response rate of 35**% and a complete remission rate of 15%
- **In all response evaluable patients, an estimated 55% had treatment duration of at least 33%**
- **Differentiation syndrome**

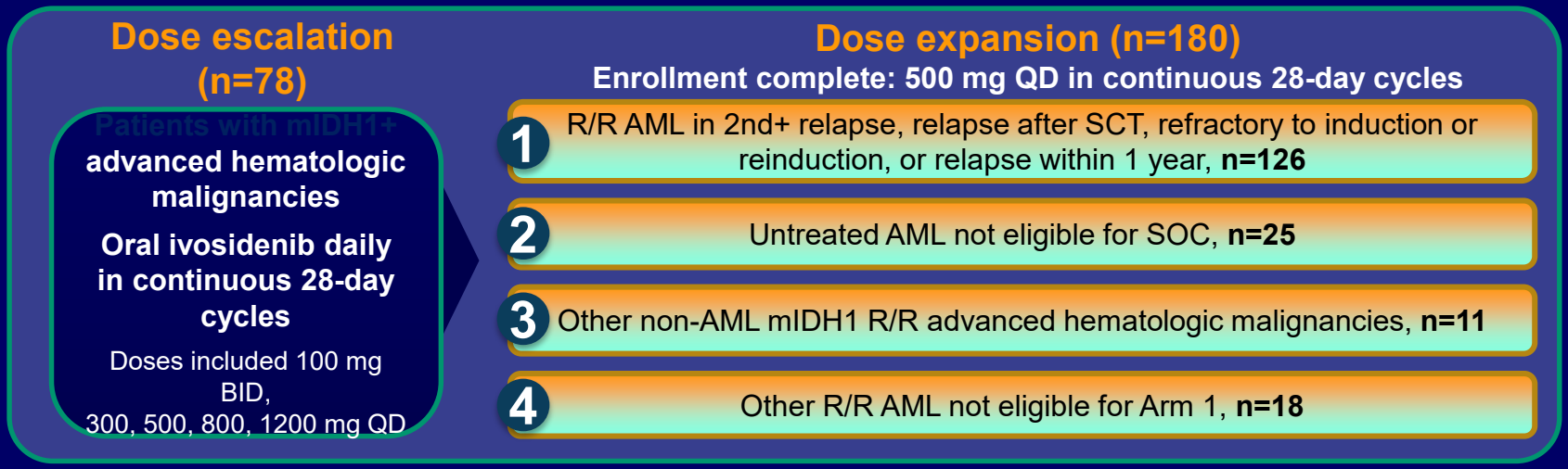
AG221=enasidenib

- Most common AEs: nausea, fatigue, increase in bilirubin, diarrhea
- ORR 37% in 159 adults w R/R AML
  - CR 18%
  - Median duration of response of 6.9 months
- Differentiation syndrome

DiNardo C, et al. NEJM 2018.. Stein E, et al. Blood 2019

Single-arm, open-label, phase 1, multicenter trial study

Study Design and Objectives: Ivosidenib in mutant IDH1 ds



Study objectives

Primary	Safety and tolerability, MTD and/or RP2D, clinical activity mIDH1 R/R AML enrolled in expansion Arm 1
Secondary	DLTs, pharmacokinetics and pharmacodynamics (including 2-HG), preliminary clinical activity in advanced hematologic malignancies
Exploratory	Determination of comutations and mIDH1 variant allele frequency (VAF)

ClinicalTrials.gov NCT02074839. DLTs, dose limiting toxicities; MTD, maximum tolerated dose; RP2D, recommended phase 2 dose

Dinardo et al , NEJM 2018

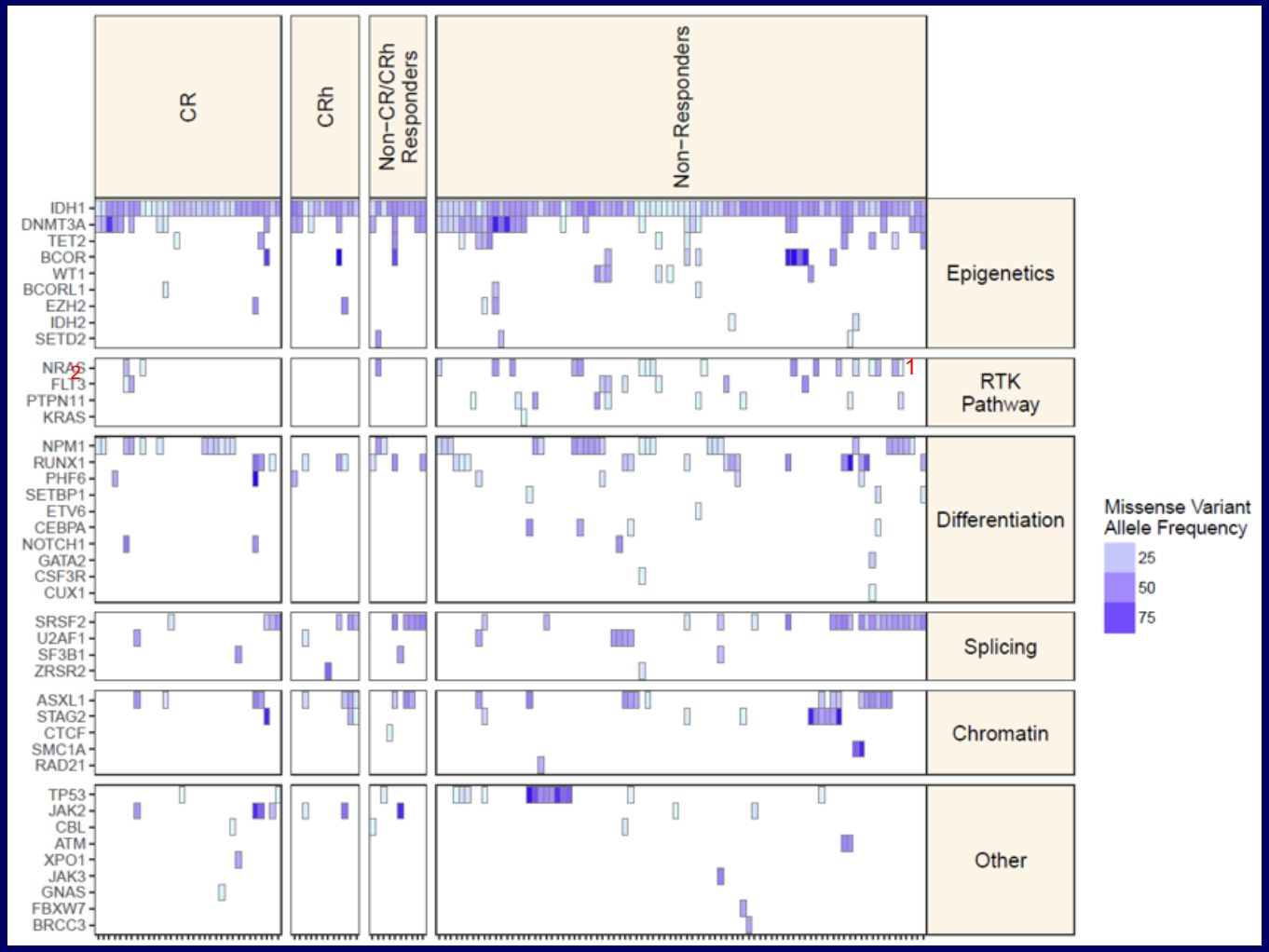
Response in R/R AML

	Primary R/R AML Set (n=125)
CR+CRh rate, n (%) [95% CI]	**38 (30.4%) [22.5, 39.3]**
Time to CR/CRh, median (range) months	2.7 (0.9, 5.6)
Duration of CR/CRh, median [95% CI] months	8.2 [5.5, 12.0]
CR rate, n (%) [95% CI]	27 (21.6%) [14.7, 29.8]
Time to CR, median (range) months	2.8 (0.9, 8.3)
Duration of CR, median [95% CI] months	9.3 [5.6, 18.3]
CRh rate, n (%)	11 (8.8%)
Overall Response Rate, n (%) [95% CI]	**52 (41.6%) [32.9, 50.8]**
Time to first response, median (range) months	1.9 (0.8, 4.7)
Duration of response, median [95% CI] months	6.5 [4.6, 9.3]
Best response	
CR, n (%)	27 (21.6)
CRi or CRp, n (%)	16 (12.8)
MLFS, n (%)	9 (7.2)
SD, n (%)	44 (35.2)
PD, n (%)	13 (10.4)
NA, n (%)	16 (12.8)

Data cutoff: 12May2017. CR, complete remission; CRh, CR with partial hematologic recovery; CRp, CR with incomplete platelet recovery; CRi, CR with incomplete hematologic recovery; MLFS, morphologic leukemia-free state; NA, not assessed; ORR, objective response rate; PD, progressive

Dianrdo et al , NEJM 2018

By-subject VAF of Known/Likely Co-occurring Mutations at Baseline by Response to Ivosidenib Treatment (R/R AML at 500 mg QD (Bone Marrow, N=142, NGS)

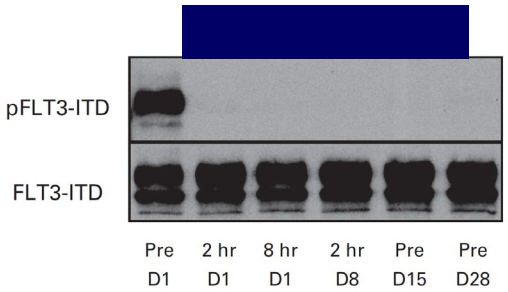


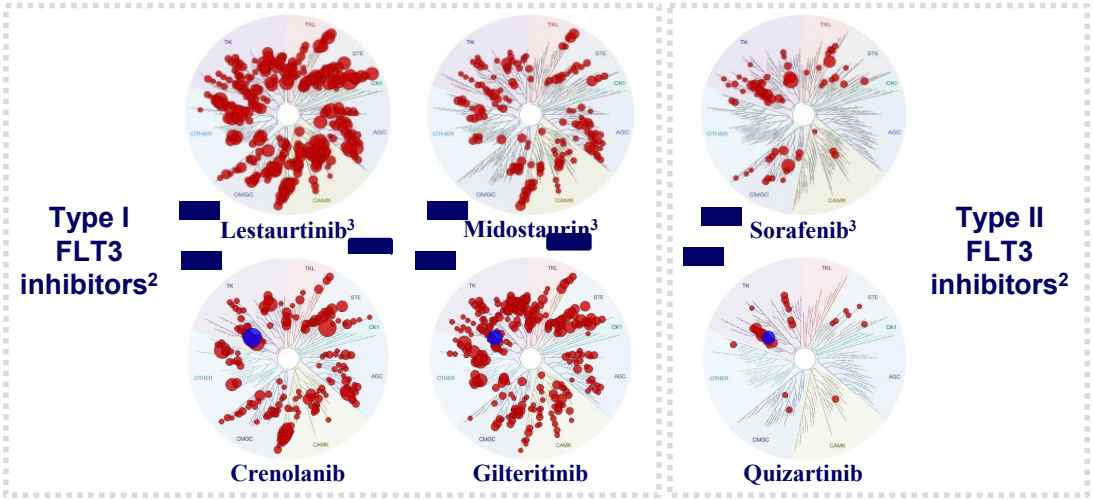
0.001 by Fisher's exact test; ()

[2] All detected FLT3 mutations were FLT3-TKD

Dinardo C, et al, NEJM 2018

Quizartinib and Gilteritib: Second Generation FLT3 Inhibitors

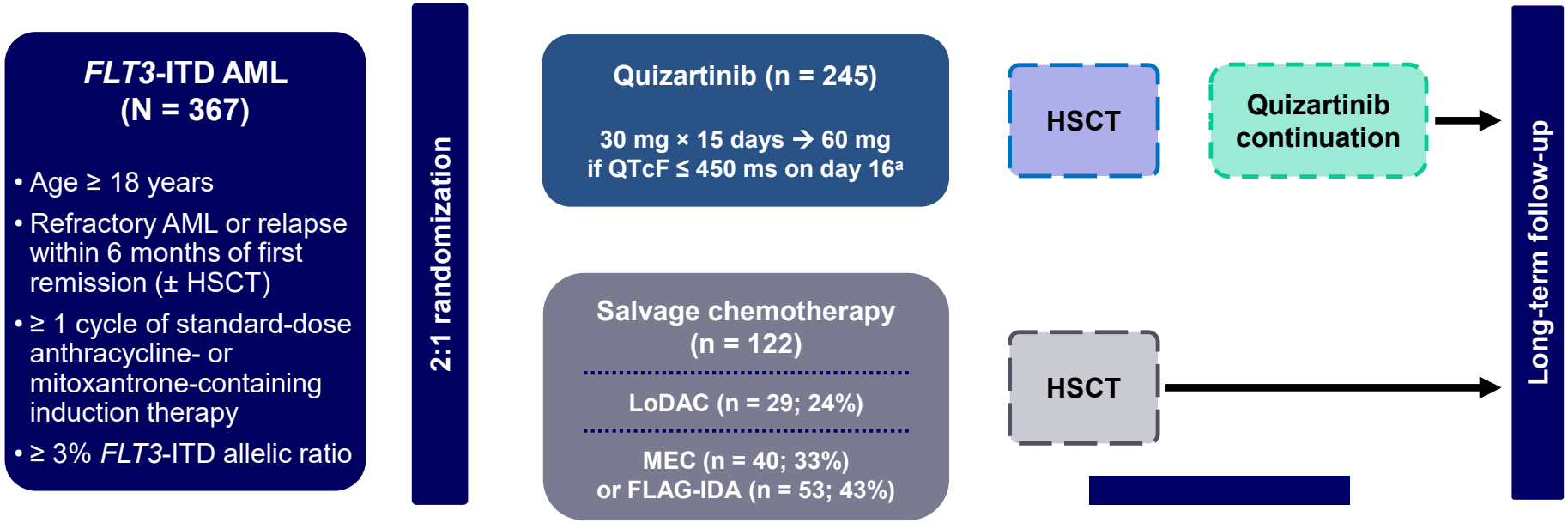




- Quizartinib is potent in vivo than any other FLT3 inhibitor to date[4,5]
- But selection of resistance with FLT3-TKD mutations
- Possible QT prolongation at higher doses

- Gilteritinib 'hits' both ITD and TKD subtypes
- Well tolerated

QuANTUM-R Study Design



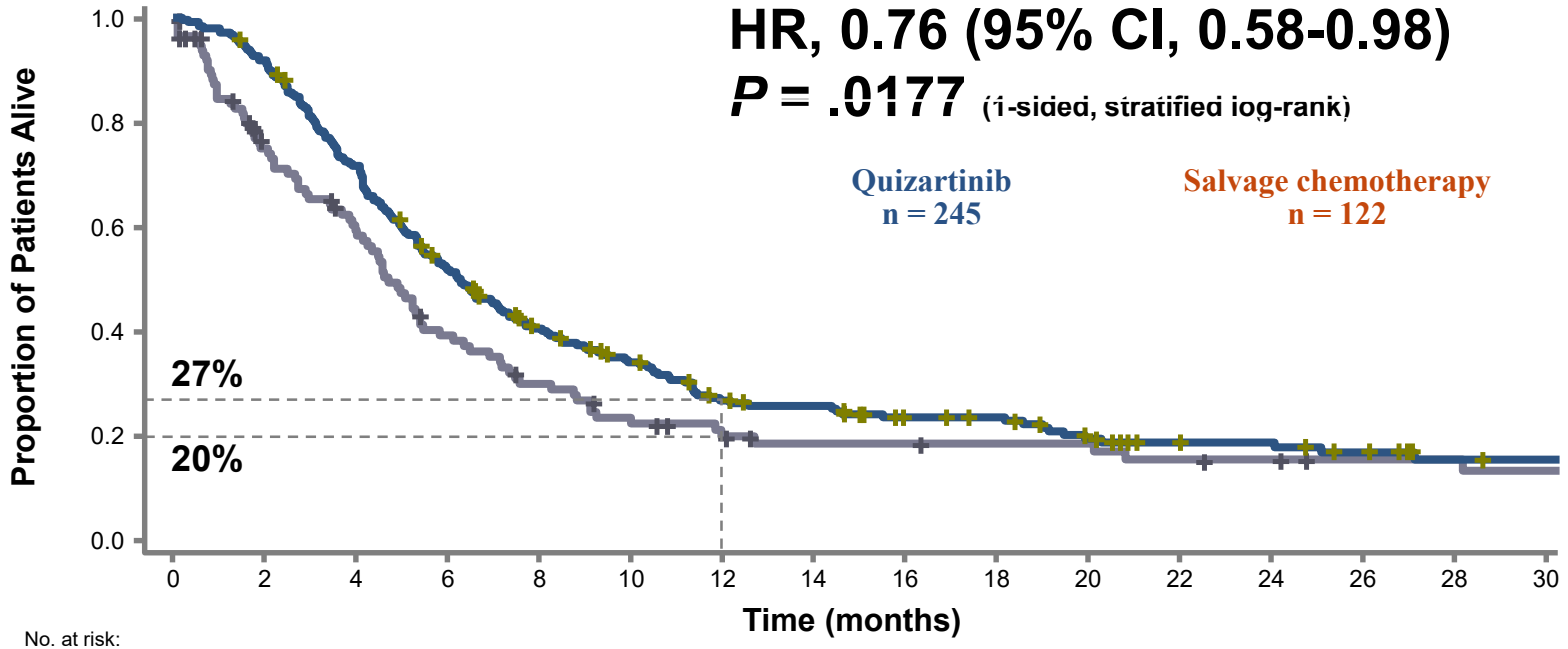
HSCT based on local practice

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)
Data cutoff: February 2018

CRc, composite complete response; QT interval corrected using Fridericia's correction formula.
[a]20 mg × 15 days → 30 mg if concomitantly taking CYP3A4 inhibitors.

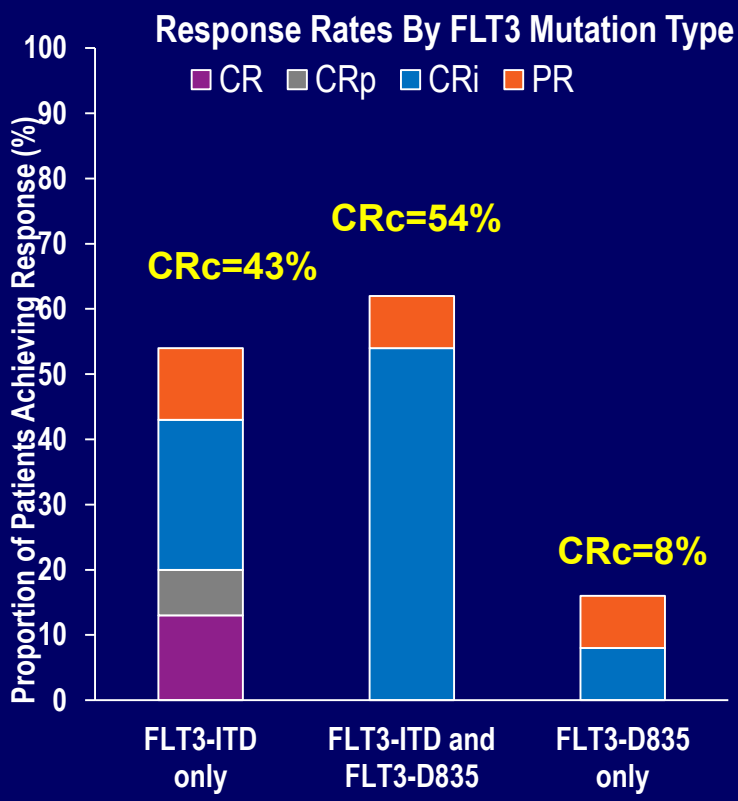
Primary Endpoint: Overall Survival

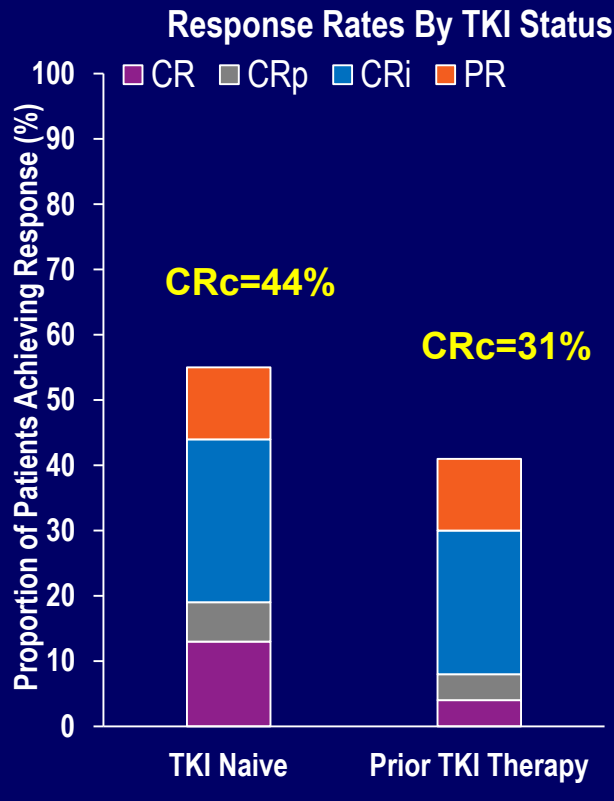
ITT population



- Median follow-up: 23.5 months

Antileukemic Response to ≥80 mg/day Gilteritinib in FLT3^{mut+} Patients by Mutation Type and TKI Status





Perl et al , Lancet Oncology , 2017

Admiral Trial,AACR 2019 (Perl A et al) : Gilteritinib v dealer's choice chemo in R/R mutant *FLT3* AML

- Randomized (2:1) to receive continuous 28-day cycles of 120 mg/day gilteritinib or pre-randomization selected SC: (LoDAC), azacitidine (AZA), (MEC), or (FLAG-IDA).
- N=371 : 247 to gilteritinib and 124 to SC (MEC, 25.7%; FLAG-IDA, 36.7%; LoDAC, 14.7%; AZA, 22.9%).
- Median age = 62 years ; FLT3-ITD, 88.4%; 61% Relapsed, 39% refractory
- OS favored gilt:(9.3 months v 5.6 months; hazard ratio [HR] for death = 0.637; P=0.0007)
- 1-year survival rates were 37.1% and 16.7%, G v chemo.
- CR/CRh 34.0% and 15.3%, respectively (P=0.0001)
- Giltertinib has been approved for R/R mutant FLT3 AML (Quiizartinib has not)

Acute MyeloidLeukemia: Conclusions

- Mutations/Cytogenetics/Host factors
- Still don't know how to use MRD
- New Therapies
  - Midostaurin (+ chemo in *FLT3* mutant upfront)
  - Gilteritinib (single agent R/R *FLT3* mutant)
  - Enasidenib/(ivosidenib) (R/R *IDH2 (1)* mutant)
    - Ivo recently approved for upfront use
  - Gemtuzumab (+chemo in CD33+ upfront)
  - CPX-351 (upfront secondary)
  - Venetoclax +low dose chemo (upfront, unfit)
  - Glasdegib + low dose cytarabie (upfront, unfit)
- Need to wait for rand aza+/- ven and early combo trials (e.g., aza/ven/gilt)

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- Clinical Team at DFCI:
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