Acute Myeloid Leukemia

2022 Management Landscape for newly diagnosed patients

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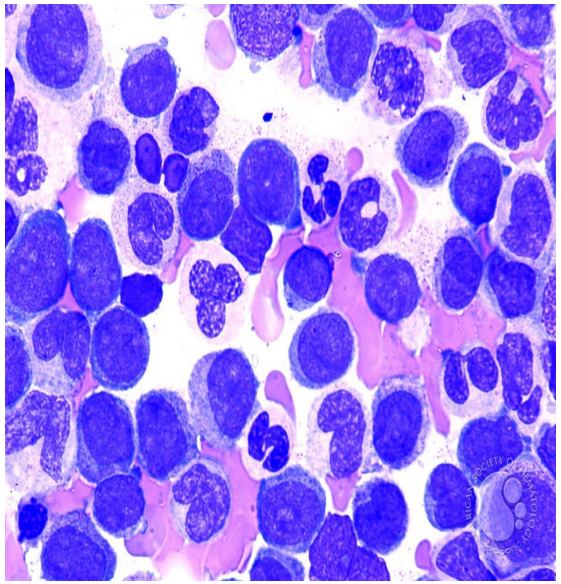
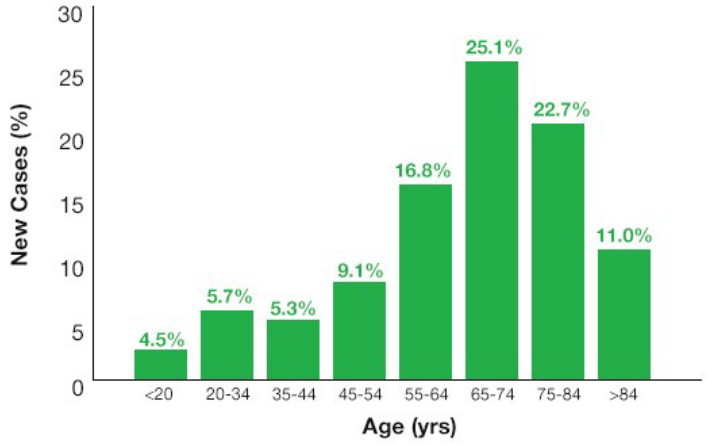
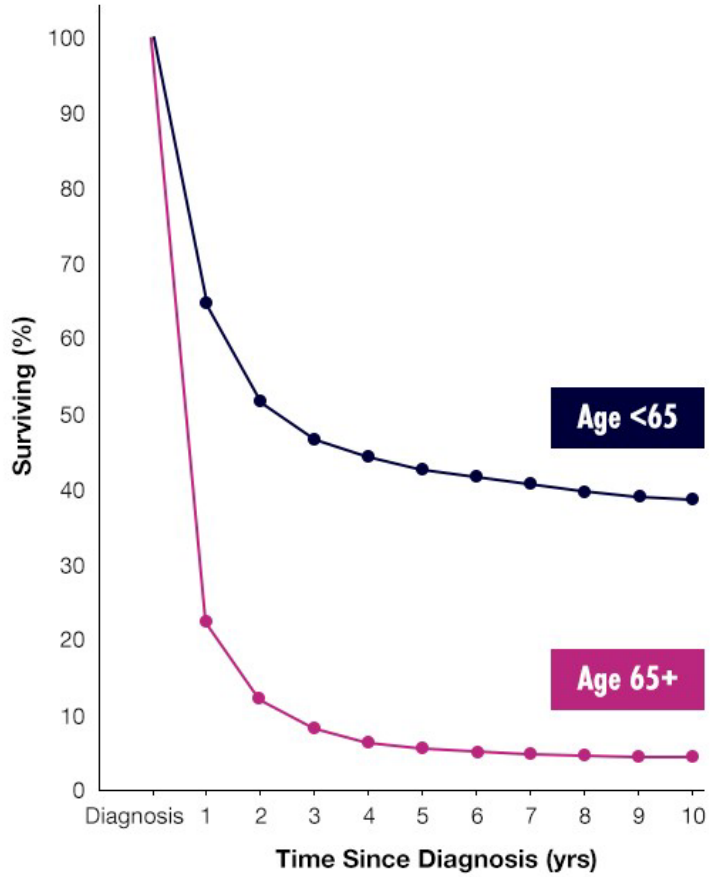
Acute Myeloid Leukemia



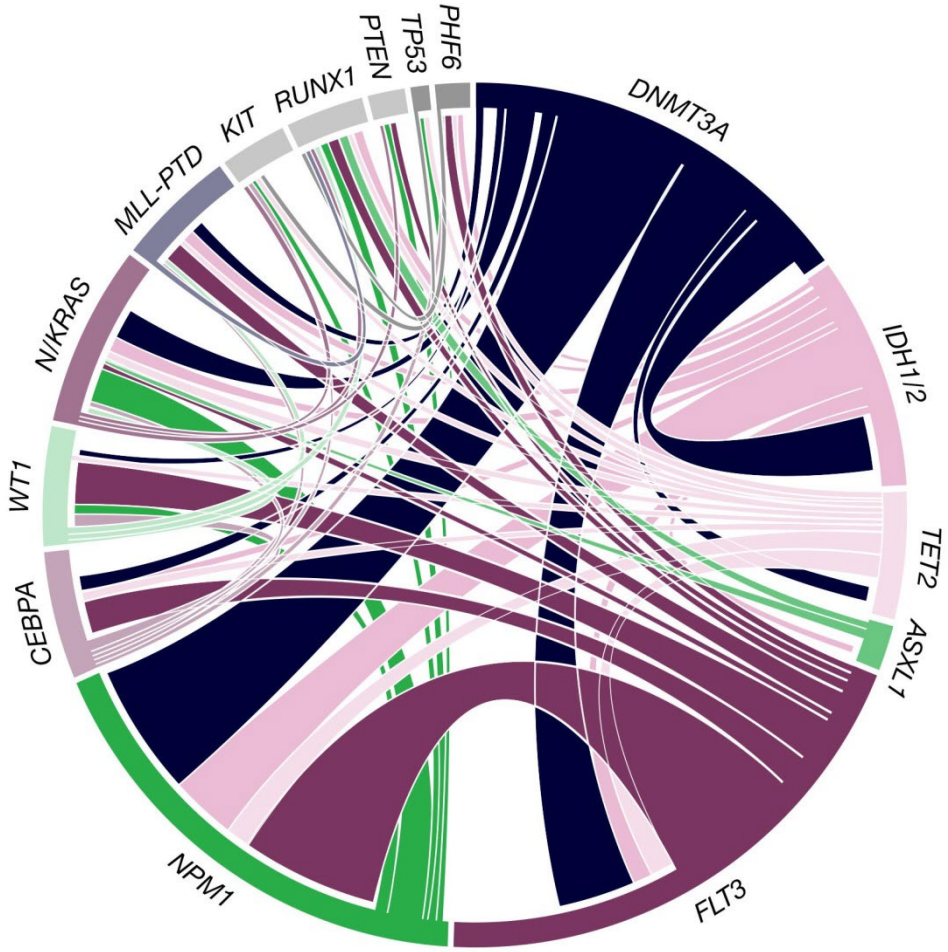




. American Society of Clinical Oncology. http://www.cancer.net/cancer-types/leukemia-acute-myeloid-aml/statistics. Accessed July 23, 2019

AML is characterized by genetic heterogeneity

- **The complexity of each case is illustrated by the presence of multiple leukemic blast clones harboring varying genetic and epigenetic aberrations[1-3]**
- **A study of 1540 patients found[2]:**
  - 5234 driver mutations across 76 genes or genomic regions
  - 86% of patients have ***at least*** 2 mutations
- **Clonal evolution involves the acquisition and loss of specific mutations over the course of disease[4,5]**



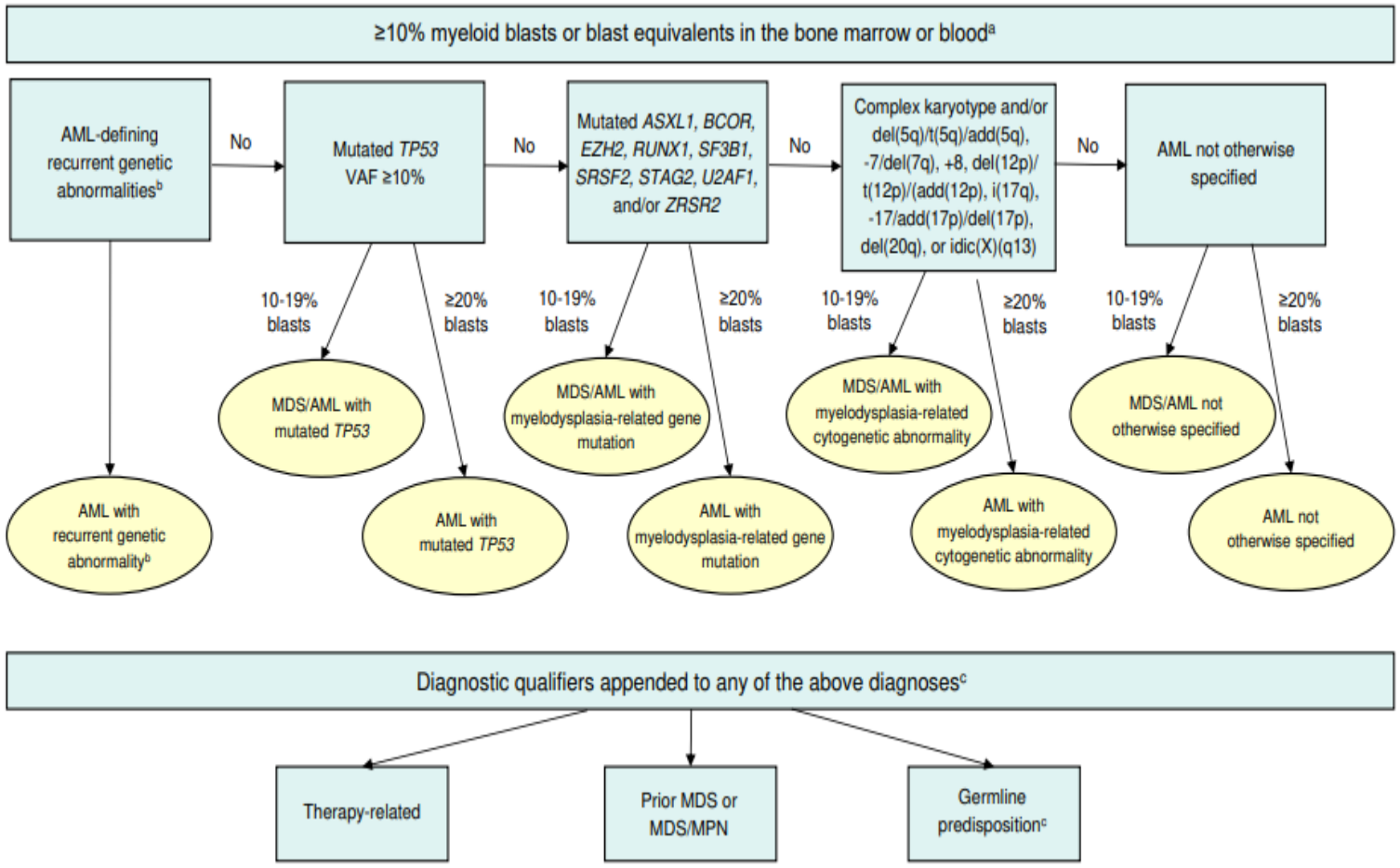
Adapted from Patel et al, 2012.

References: 1. Riether C, et al. *Cell Death Differ*. 2015;22:187-198. **2.** Papaemmanuil E, et al. *N Engl J Med*. 2016;374(23):2209-2221. **3.** Watts J, et al. *F1000Research*. 2018;7:(F1000 Faculty Rev):1196. **4.** Ding L, et al. *Nature*. 2012;481(7382):506-510. **5.** Paguirigan AL, et al. *Sci Transl Med*. 2015;7(281):1-18. **6.** Patel JP, et al. *N Engl J Med*. 2012;366(12):1079-1089.

AML new ELN classfication

Table 1. AML and related neoplasms and acute leukemias of ambiguous lineage

AML and related neoplasms
AML with recurrent genetic abnormalities (requiring ≥10% blasts in BM or PB)[a]
• APL with t(15;17)(q24.1;q21.2)/*PML*::*RARA*[b]
• AML with t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*
• AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*
• AML with t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*[c]
• AML with t(6;9)(p22.3;q34.1)/*DEK*::*NUP214*
• AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2, MECOM(EVI1)*[d]
• AML with other rare recurring translocations[e]
• AML with mutated *NPM1*
• AML with in-frame bZIP mutated *CEBPA*[f]
• AML with t(9;22)(q34.1;q11.2)/*BCR*::*ABL1*[a]
Categories designated AML (if ≥20% blasts in BM or PB) or MDS/AML (if 10-19% blasts in BM or PB)
• AML with mutated *TP53*[g]
• AML with myelodysplasia-related gene mutations Defined by mutations in *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, or *ZRSR2*
• AML with myelodysplasia-related cytogenetic abnormalities[h]
• AML not otherwise specified (NOS)
Myeloid sarcoma
Myeloid proliferations related to Down Syndrome
• Transient abnormal myelopoiesis associated with Down syndrome
• Myeloid leukemia associated with Down syndrome
Blastic plasmacytoid dendritic cell neoplasm
Acute leukemias of ambiguous lineage
• Acute undifferentiated leukemia
• MPAL with t(9;22)(q34.1;q11.2)/*BCR::ABL1*
• MPAL with t(v;11q23.3)/*KMT2A* rearranged
• MPAL, B/myeloid, not otherwise specified
• MPAL, T/myeloid, not otherwise specified



Hartmut Döhner et al; Diagnosis and Management of AML in Adults: 2022 ELN Recommendations from an International Expert Panel. *Blood* 2022; blood.2022016867

Diagnosis and work up for AML

Tests to establish the diagnosis	
Complete blood count and differential count[a]	
Bone marrow aspirate[b]	
Bone marrow trephine biopsy[c]	
Immunophenotyping by flow cytometry (see Table 5)	
Genetic analyses	Results preferably available within
Cytogenetics[d]	• 5-7 days
Screening for gene mutations required for establishing the diagnosis and to identify actionable therapeutic targets[e]	
• *FLT3*,[f] *IDH1*, *IDH2*	• 3-5 days
• *NPM1*	• 3-5 days
• *CEBPA*,[g] *DDX41*, *TP53*; *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, *ZRSR2*	• 1st cycle
Screening for gene rearrangements[h] • *PML*::*RARA*, *CBFB*::*MYH11*, *RUNX1*::*RUNX1T1*, *KMT2A* rearrangements, *BCR*::*ABL1*, other fusion genes (if available)	• 3-5 days
Additional genes recommended to test at diagnosis[i] • *ANKRD26*, *BCORL1*, *BRAF*, *CBL*, *CSF3R*, *DNMT3A*, *ETV6*, *GATA2*, *JAK2*, *KIT*, *KRAS*, *NRAS*, *NF1*, *PHF6*, *PPM1D*, *PTPN11*, *RAD21*, *SETBP1*, *TET2*, *WT1*	
Medical history	
Demographics and medical history[j]	
Detailed family history[k]	
Patient bleeding history[l]	
Analysis of comorbidities	
Additional tests and procedures	
Complete physical examination[m]	
Performance status (ECOG/WHO score)	
Geriatric assessment[n] (optional)	
Biochemistry, coagulation tests[o]	
Hepatitis A, B, C; HIV-1 testing; CMV, EBV, HSV, VZV	
Serum pregnancy test[p]	
Eligibility assessment for allogeneic HCT (incl. HLA-typing)[q]	
Chest x-ray, 12-lead electrocardiogram, echocardiography or MUGA (on indication)	
Computed tomography of the chest (on indication)[r]	
Lumbar puncture (on indication)[s]	
Information on oocyte and sperm cryopreservation[t]	
Biobanking[u]	

- Assure diagnosis.
- Obtain all information for risk stratification.
- Tailor treatment and baseline testing prior to treatment.
- **AML treatment is not Emergency in most of cases.**

Hartmut Döhner et al; Diagnosis and Management of AML in Adults: 2022 ELN Recommendations from an International Expert Panel. *Blood* 2022; blood.2022016867

AML Risk Stratification by Cytogenetics and Molecular Abnormalities (ELN 2022 Recommendations)

Risk Category[b]	Genetic Abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*[b,c] • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*[b,c] • Mutated *NPM1*[b,d] without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*[e]
Intermediate	• Mutated *NPM1*[b,d] with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD • t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*[b,f] • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged[g] • t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* • t(8;16)(p11;p13)/*KAT6A*::*CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2*, *MECOM(EVI1)* • t(3q26.2;v)/*MECOM(EVI1)*-rearranged • -5 or del(5q); -7; -17/abn(17p) • Complex karyotype,[h] monosomal karyotype[i] • Mutated *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, or *ZRSR2*[j] • Mutated *TP53*[k]

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Therapeutic Decision Making 2022

Induction Chemotherapy

Non induction treatment

Upfront Treatment of De Novo AML in patients eligible for Intensive chemotherapy

Who is eligible?

1. Non P53 MT AML
2. Absence of comorbidities
3. Not frail

Good risk AML

Induction: 3+7+GO

Consolidation: HiDAC/IDAC+/-GO

FLt-3 MT AML

Induction: 3+7 + Midostaurin

Consolidation : Allo-SCT

Maintenance post allo SCT: Sorafenib

Intermediate/poor risk

Induction: 3+7

Consolidation: allo SCT

Maintenance: oral azacitidine if no transplant

MT: mutation
GO: Gemtuzumab Ozogamicin
Allo-SCT: allogeneic stem cell transplant
HiDAC: high dose cytarabine
IDAC: intermediate dose cytarabine

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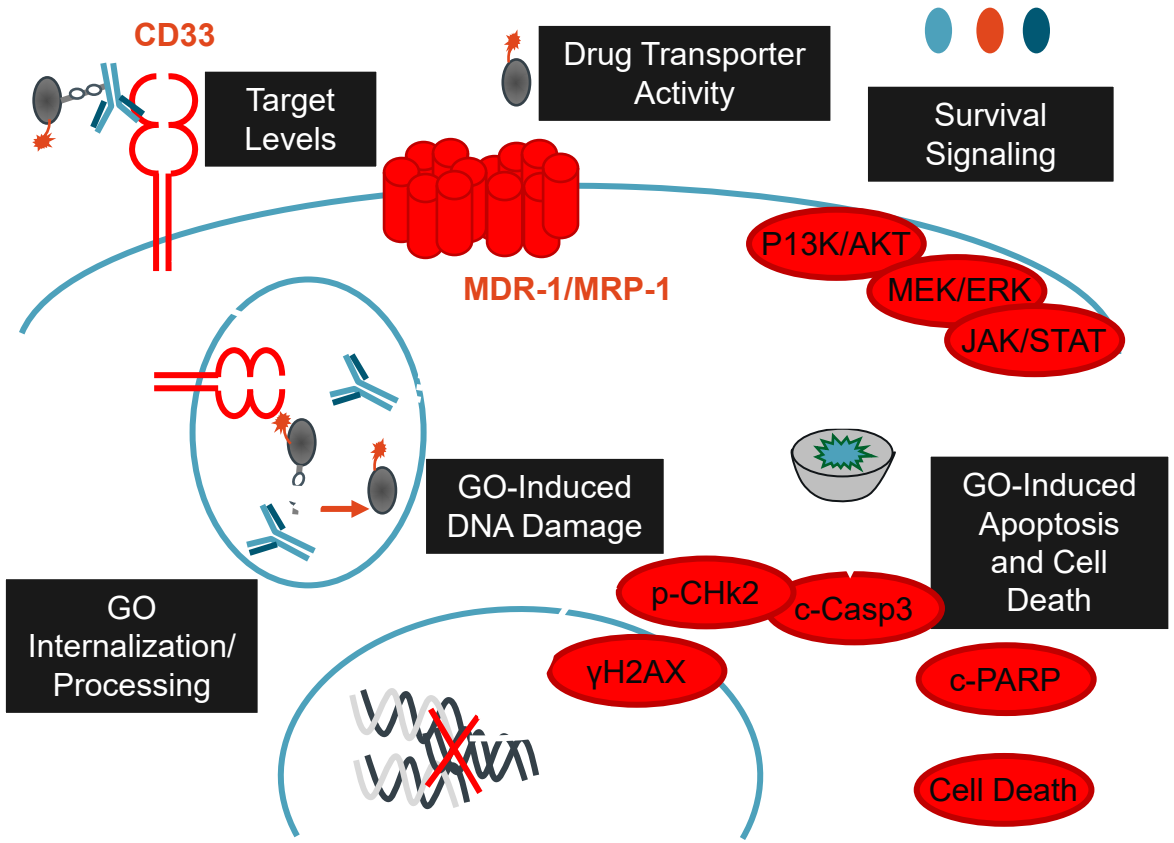
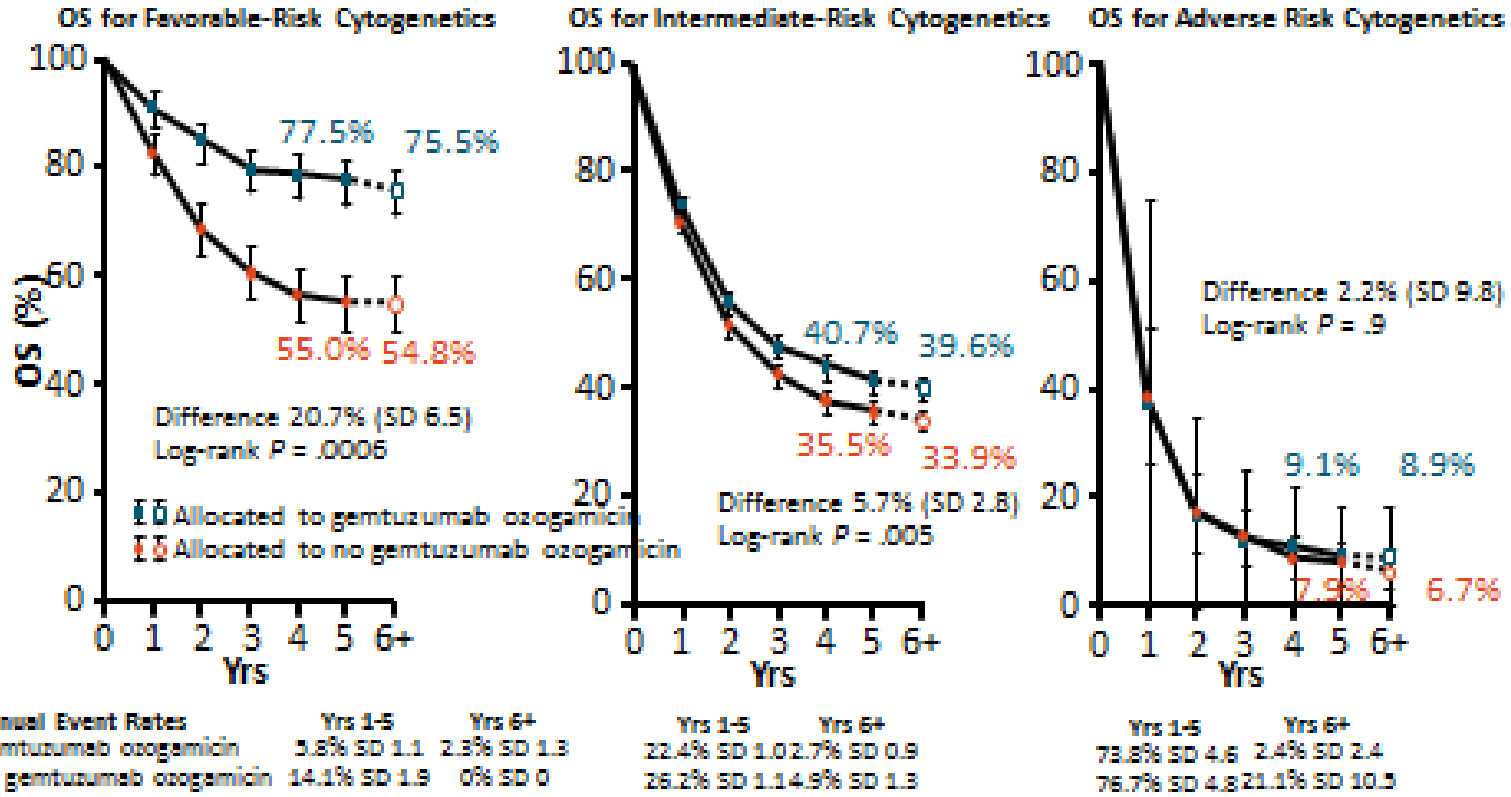
Gemtuzumab Ozogamicin: MOA

- Monoclonal anti-CD33 antibody linked to calicheamicin-γ1[1]
- Internalized and cleaved in lysosomes to release free calicheamicin moiety[2]
- Calicheamicin moiety enters nucleus and interacts with DNA causing double-strand breaks initiating apoptosis[1-3]



1. Zein N, et al. *Science.* 1988;240:1198-1201; 2. Naito K, et al. *Leukemia.* 2000; 14:1436-1443;
3. Elmroth K, et al. *DNA Repair (Amst).* 2003;2:363-374.

Addition of Gemtuzumab Ozogamicin to Induction Therapy: Meta-analysis of 5 Randomized Trials



Annual Event Rates	Yrs 1-5	Yrs 6+
Gemtuzumab ozogamicin	5.8% SD 1.1	2.3% SD 1.3
No gemtuzumab ozogamicin	14.1% SD 1.9	0% SD 0

	Yrs 1-5	Yrs 6+
	22.4% SD 1.0	2.7% SD 0.9
	26.2% SD 1.1	4.9% SD 1.3

	Yrs 1-5	Yrs 6+
	73.8% SD 4.6	2.4% SD 2.4
	76.7% SD 4.8	21.1% SD 10.5

Hills RK, et al. Lancet Oncol. 2014;15:986-996.

Fludarabine, Cytarabine, G-CSF and Gemtuzumab Ozogamicin (FLAG-GO) Regimen Results in Better Molecular Response and Relapse-Free Survival in Core Binding Factor Acute Myeloid Leukemia Than FLAG and Idarubicin (FLAG-Ida)

Figure 1 Relapse free survival (RFS) by treatment regimen

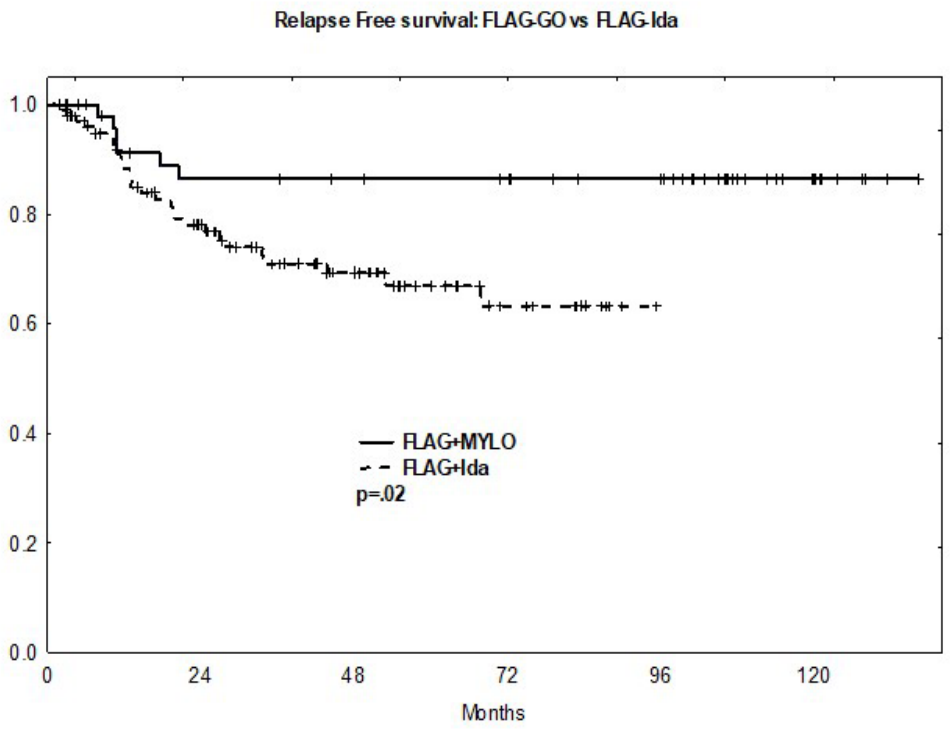
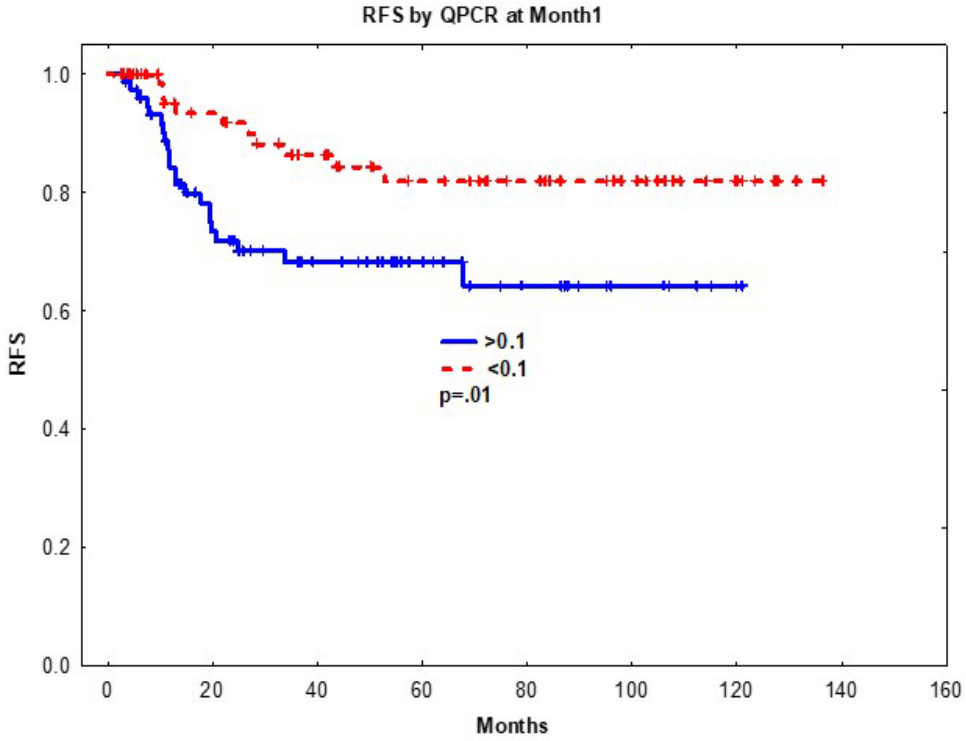


Figure 2 RFS by QPCR response at end of induction



Gautam M. Borthakur, Blood, 2019, 134 (Supplement_1): 290.

Clinical pearls, monitoring and adverse events

- Two regimens commonly used, day 1 or day 1,3,5.

Gemtuzumab ozogamicin	Transaminase elevation (24.5%)[a] Bilirubin elevation (13%)[a]	Dose interruption/reduction
	VOD/SOS (2.9-4.6%)	Dose interruption, supportive care, fluid management, possibly defibrotide

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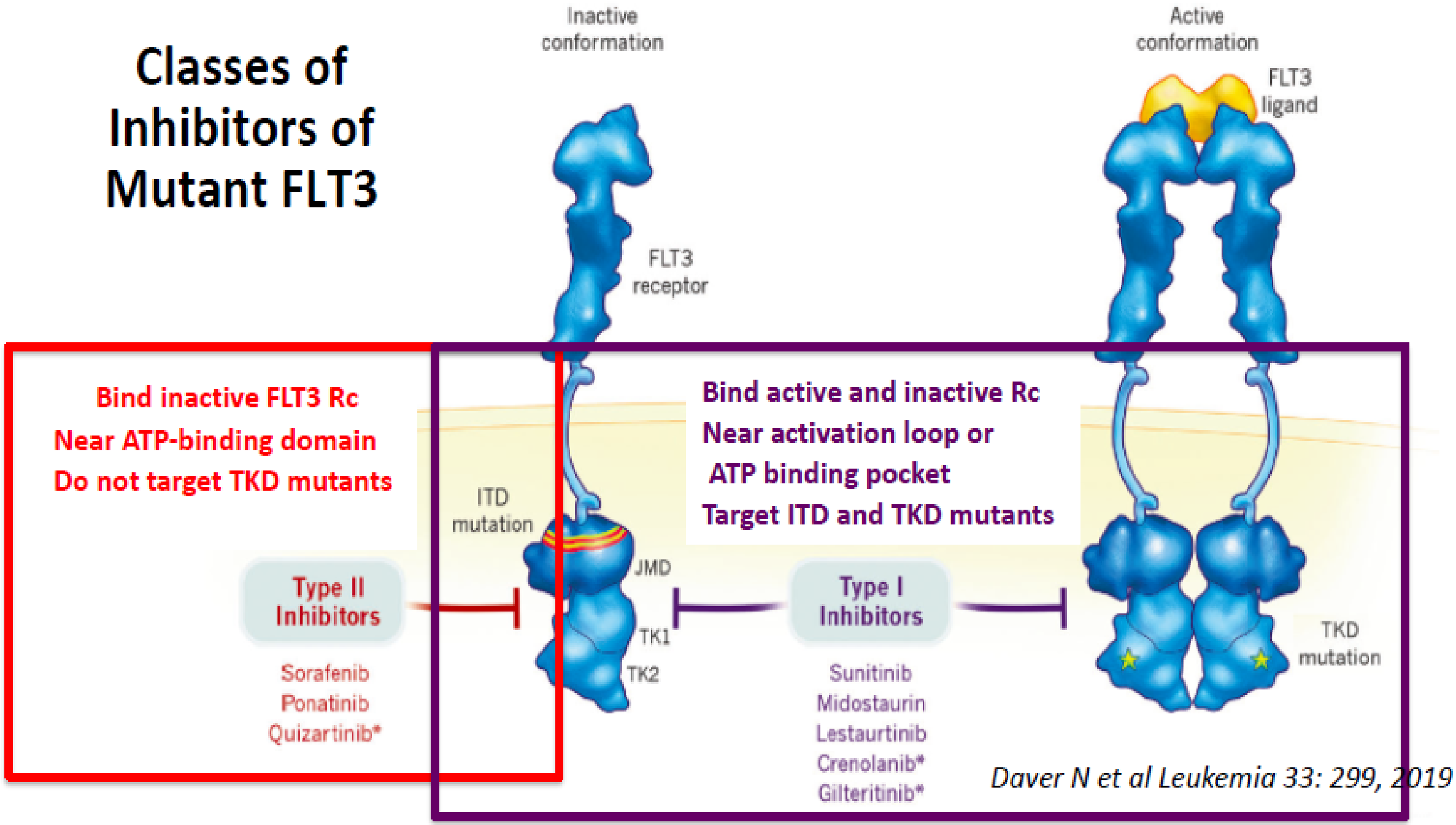
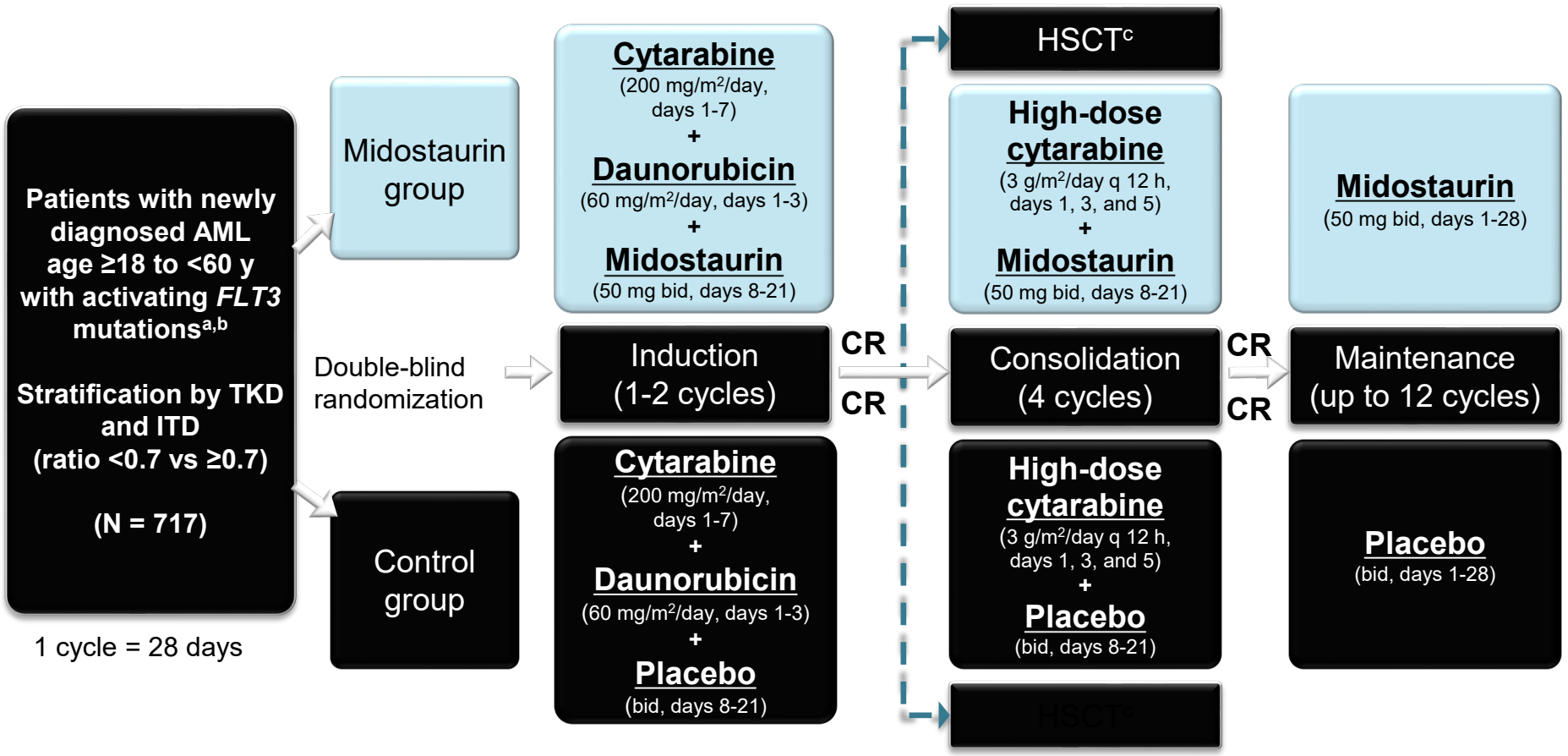
Classes of Inhibitors of Mutant FLT3



Daver N et al Leukemia 33: 299, 2019

The RATIFY Trial



Primary Endpoint: Overall Survival
not censored for transplantation

[a] Documented AML (no APL).

[b] Hydroxyurea therapy allowed ≤5 days prior to start of study treatment.

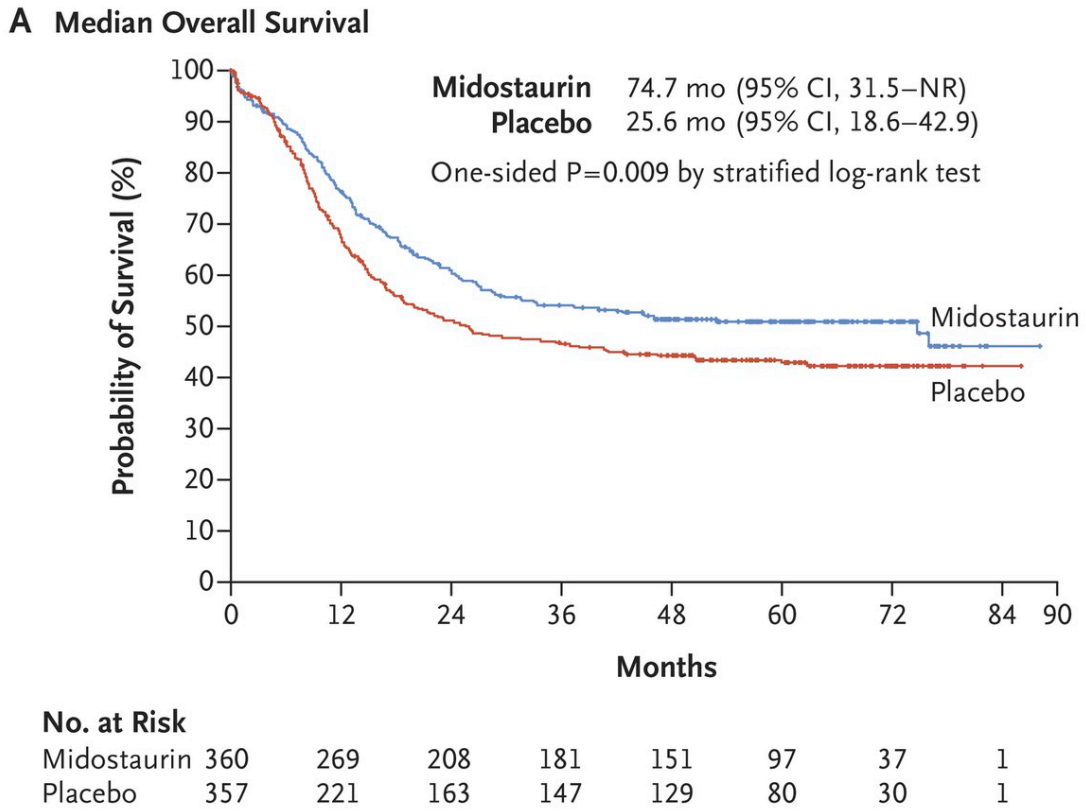
[c] Patients eligible for HSCT therapy no longer receive the study drug following the HSCT.

Stone R. N Engl J Med. 2017 Aug 3;377(5):454-464.

RATIFY: Overall Survival

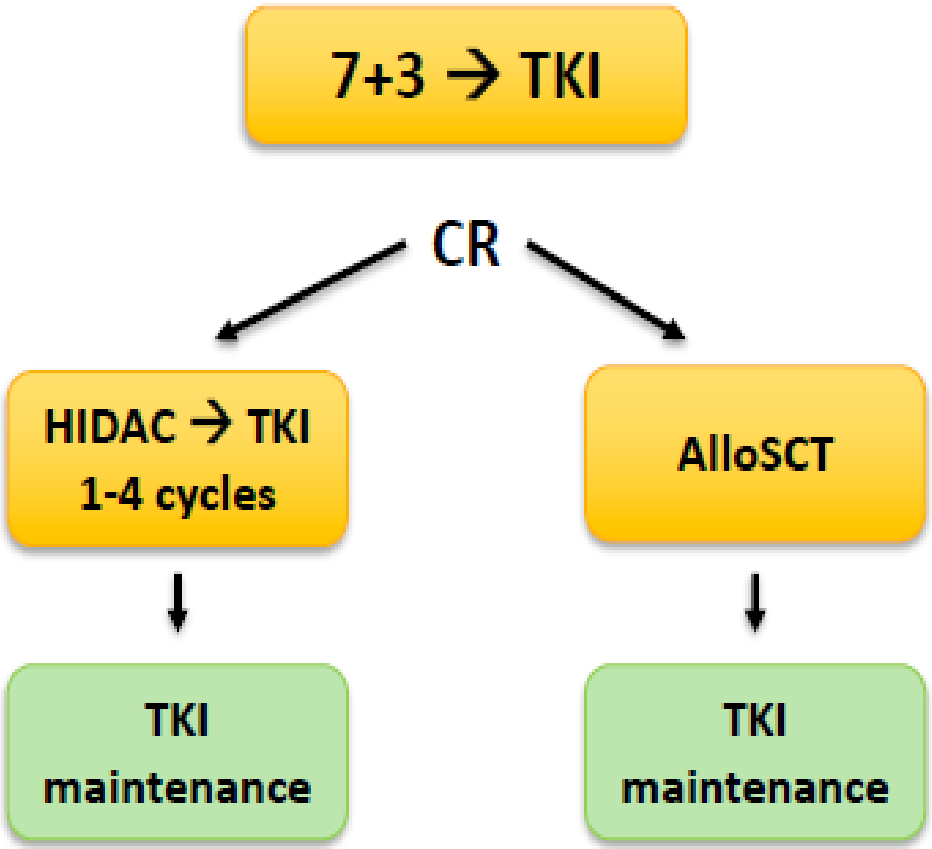
23% reduced risk of death in the midostaurin arm

Arm	4-Year Survival
MIDO	51.4% (95% CI, 46, 57)
PBO	44.2% (95% CI, 39, 50)



Stone R. N Engl J Med. 2017 Aug 3;377(5):454-464.

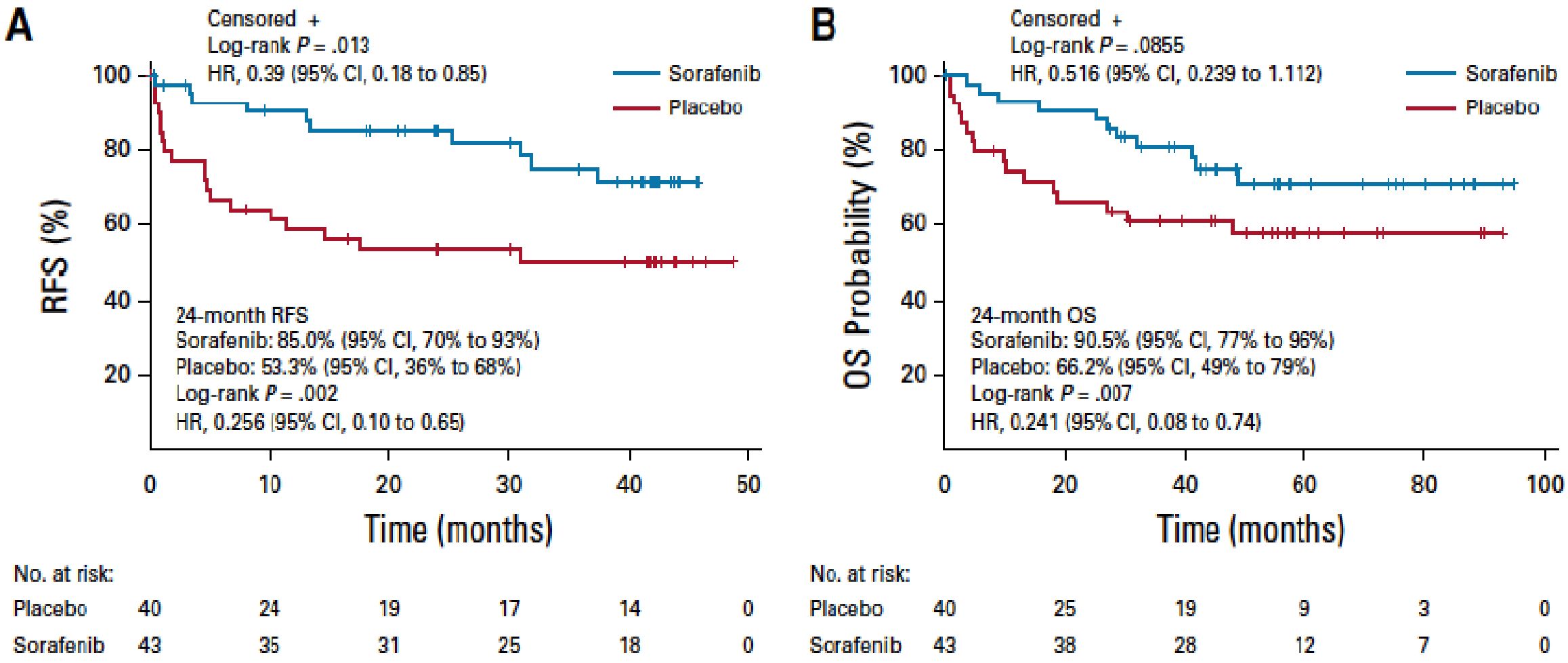
Upfront intensive therapy + TKI for newly diagnosed AML



FLT3 TKI	No. pts	CRCR/CRi/CRh
Midostaurin plus 7+3	N=717 (ph 3)	**59%**
Quizartinib plus 7+3	N=16 (ph 1)	**84%**
Crenolanib plus 7+3	N=38 (ph 2)	**88%**
Gilteritinib plus 7+3	N=33 (ph 1)	**94%**

Stone R et al NEJM 377(5): 454, 2017; Wang E et al ASH 2017;
Altman J et al AJH 93(2): 213, 2018;
Pratz K et al ASH 2018

SORMAIN: TKI maintenance following alloSCT



Burchert A et al J Clin Oncol 38(26): 2993, 2020

Clinical pearls, monitoring and adverse events

- GI toxicity common feature of FLT-3 inhibitors

Midostaurin	QT prolongation (10%)	Dose interruption/reduction, substitution of QT prolonging co-medication if possible, otherwise additional ECG controls
Gilteritinib	Transaminase elevation (81%)	Dose interruption/reduction (if grade ≥3)
	QT prolongation (9%)	Dose interruption/reduction, substitution of QT prolonging co-medication if possible
	PRES (1%)	Discontinuation

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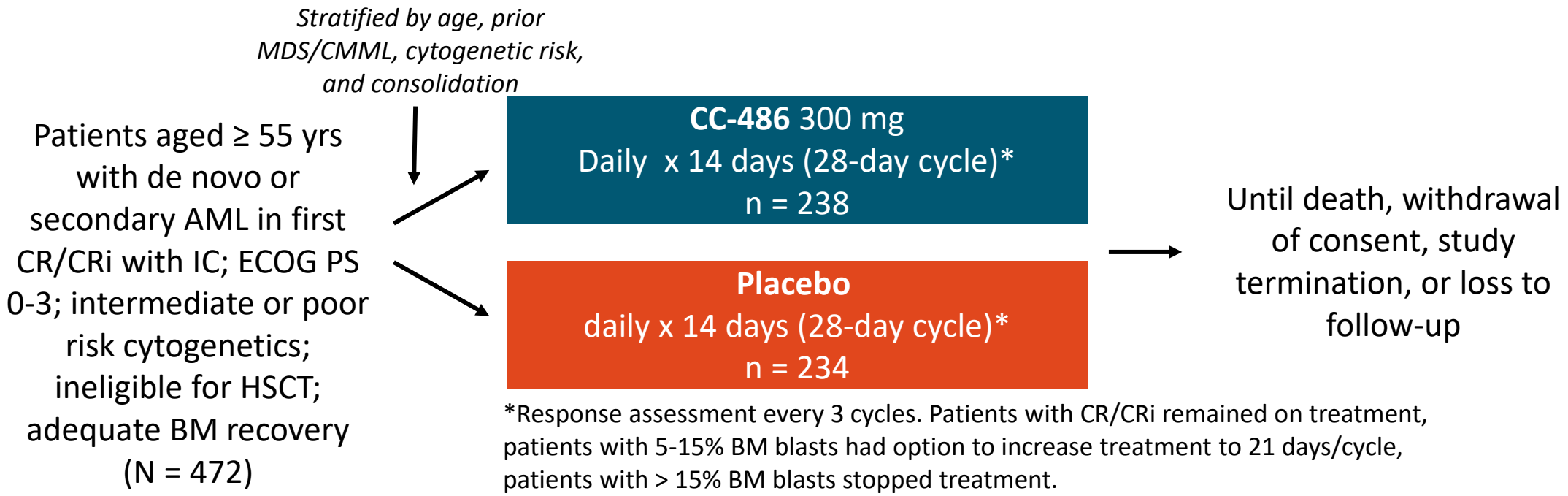
Phase III QUAZAR AML-001: CC-486 as Maintenance Therapy in First-Remission AML—Study Design

- Multicenter, randomized, placebo-controlled, double-blind, phase III study



- Primary endpoint: overall survival
- Key secondary endpoints: relapse-free survival, health-related QoL, and safety

Wei. ASH 2019. Abstr LBA_3.

QUAZAR AML-001: Baseline Characteristics

Characteristic	CC-486 n = 238	Placebo n = 234
Median age, yrs (range)	68 (55-86)	68 (55-82)
▪ ≥ 65 yrs, n (%)	172 (72)	166 (71)
Male, n (%)	118 (50)	127 (54)
ECOG PS score, n (%)		
▪ 0	116 (49)	111 (47)
▪ 1	101 (42)	106 (45)
▪ 2	21 (9)	15 (6)
▪ 3	0	2 (1)
De novo AML, n (%)	213 (89)	216 (92)
WHO classification, n (%)		
▪ Not otherwise specified	148 (62)	145 (62)
▪ Myelodysplasia-related changes	49 (21)	42 (18)
▪ Recurrent genetic abnormalities	39 (16)	46 (20)

Characteristic, n (%)	CC-486 n = 238	Placebo n = 234
NCCN cytogenetic risk		
▪ Intermediate	203 (85)	203 (87)
▪ Poor	35 (15)	31 (13)
Response after induction		
▪ CR	187 (79)	197 (84)
▪ CRi	51 (21)	37 (16)
Received consolidation therapy	186 (78)	192 (82)
▪ 1 cycle	110 (46)	102 (44)
▪ 2 cycles	70 (29)	77 (33)
▪ 3 cycles	6 (3)	13 (6)
MRD status at randomization*		
▪ Positive	103 (43)	116 (50)
▪ Negative	133 (56)	111 (47)

*Central assessment by flow cytometry with a positive threshold of ≥ 0.1% using “different-from-normal” method.

QUAZAR AML-001: Survival

Outcome	CC-486 n = 238	Placebo n = 234
Median OS, mos (95% CI)	24.7 (18.7-30.5)	14.8 (11.7-17.6)
▪ Stratified *P* value	.0009	
▪ Stratified HR (95% CI)	0.69 (0.55-0.86)	
1-yr survival rate, % (95% CI)	73 (67-78)	56 (49-62)
2-yr survival rate, % (95% CI)	51 (44-57)	37 (31-43)
Relapse-free survival, mos (95% CI)	10.2 (7.9-12.9)	4.8 (4.6-6.4)
▪ Stratified *P* value	.0001	
▪ Stratified HR (95% CI)	0.65 (0.52-0.81)	

- Median follow up: 41.2 months
- 1-yr relapse rate was 53% (95% CI: 46-59) in CC-486 arm vs 71% (95% CI: 65-77) in placebo arm

Wei. ASH 2019. Abstr LBA_3.

Clinical pearls, monitoring and adverse events

- Not interchangeable with IV or SC azacitidine

CC-486/oral azacitidine	Neutropenia (44%) Thrombocytopenia (33%) Nausea (65%), vomiting (60%),	Dose interruption/reduction, myeloid growth factors Prophylactic anti-emetics

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Upfront Treatment of De Novo AML in patients not eligible for Intensive chemotherapy

Who is ineligible?

1. P53 MT AML
2. Age > 75
3. Major comorbidities
4. frail

Intermediate/poor risk

Azacitidine + Venetoclax

FLt-3 MT AML

Azacitidine + Venetoclax

Or

Azactidine+Flt-3 inhibitor

P53 MT AML
Clinical trials
APR-246
Magrolimab

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Clinical trials
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Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia

VIALE-A Study Design (NCT02993523)

Eligibility

Inclusion

- Patients with newly diagnosed confirmed AML
- Ineligible for induction therapy defined as **either**
  - ≥75 years of age
  - 18 to 74 years of age with at least one of the co-morbidities:
    - CHF requiring treatment or Ejection Fraction ≤50%
    - Chronic stable angina
    - DLCO ≤ 65% or FEV1 ≤ 65%
    - ECOG 2 or 3

Exclusion

- Prior receipt of any HMA, venetoclax, or chemotherapy for myelodysplastic syndrome
- Favorable risk cytogenetics per NCCN
- Active CNS involvement

Treatment

Randomization 2:1
N=433*

Venetoclax + Azacitidine (N=286)
Venetoclax 400 mg PO, daily, days 1–28 +
Azacitidine 75 mg/m² SC /IV days 1–7

Placebo + Azacitidine (N=145)
Placebo daily, days 1–28
+ Azacitidine 75 mg/m² SC /IV days 1–7

Endpoints

Primary

- Overall survival

Secondary

- CR+CRi rate
- CR+CRh rate
- CR+CRi and CR+CRh rates by initiation of cycle 2
- CR rate
- Transfusion independence
- CR+CRi rates and OS in molecular subgroups
- Event-free survival

Randomization Stratification Factors: Age (<75 vs. ≥75 years); Cytogenetic Risk (intermediate, Poor); Region

Venetoclax dosing ramp-up: Cycle 1 ramp-up Day 1: 100 mg, Day 2: 200 mg, Day 3 - 28: 400 mg
Cycle 2 → Day 1-28: 400 mg

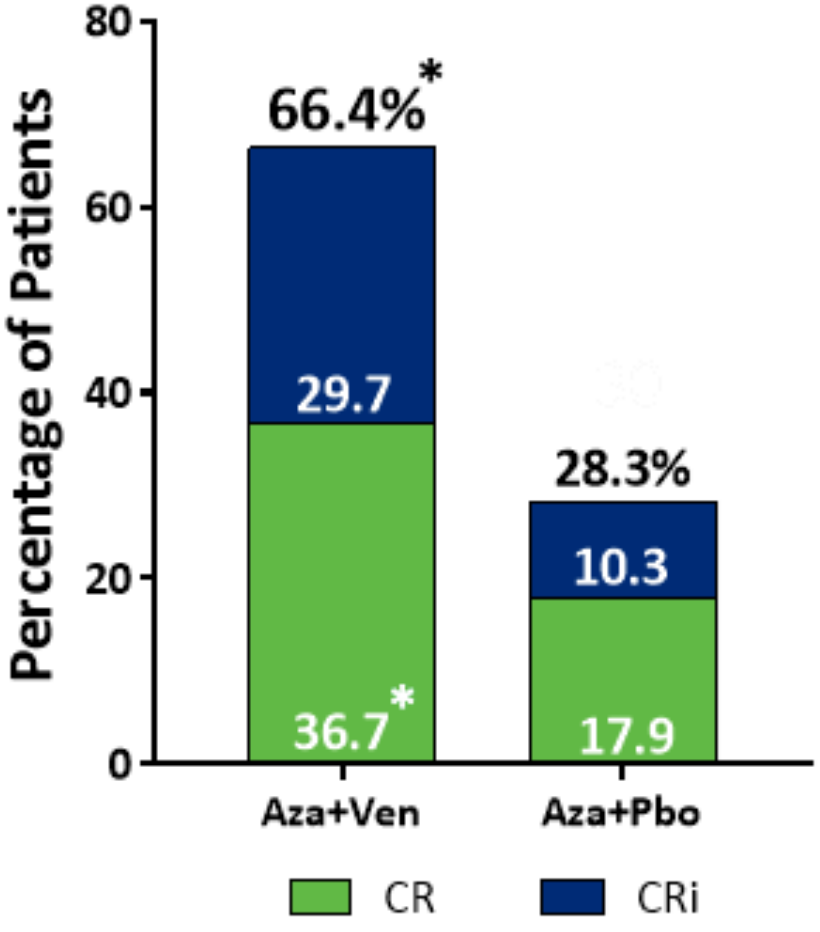
* 2 patients were not stratified by cytogenetic risk. They were excluded from efficacy analysis but included in the safety analysis. 6 patients who did not receive treatment were excluded from the safety analysis set.

AML: Acute myeloid leukemia; CHF: Congestive heart failure; CNS: Central nervous system; CR: Complete remission; CRi: CR+ incomplete marrow remission; CRh: CR+ incomplete hematologic recovery; DCLO: diffusion lung capacity for carbon monoxide; ECOG: Eastern Cooperative Oncology Group; FEV1 : Forced expiratory volume; HMA: Hypomethylating agent; NCCN: National Comprehensive Cancer Network

4

CD DiNardo et al. N Engl J Med 2020;383:617-629.

Composite Response Rate (CR+CRi)



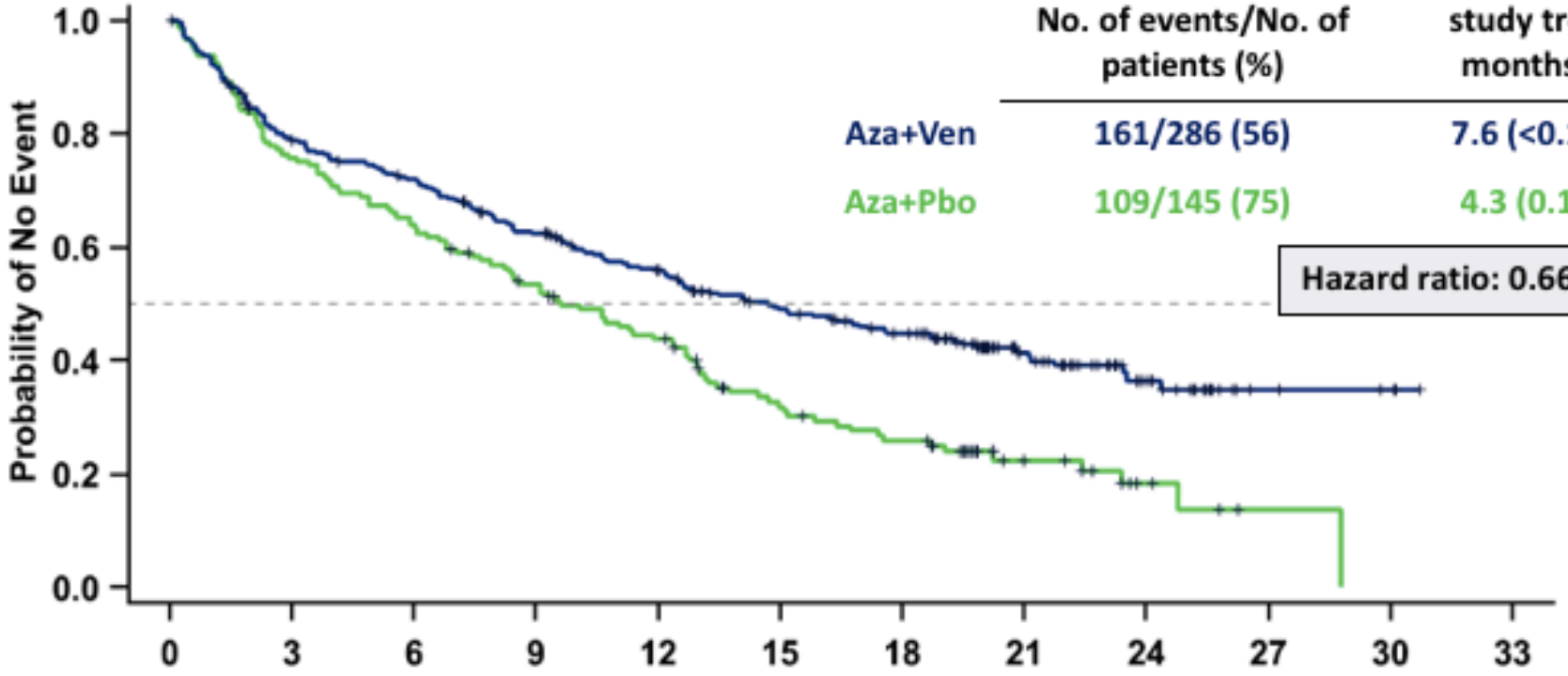
	No. of treatment cycles, median (range)	Median time to CR/CRi, Months (range)	*CR+CRi by initiation of Cycle 2, n (%)
Aza+Ven (n=286)	7.0 (1.0 – 30.0)	1.3 (0.6 – 9.9)	124 (43.4)
Aza+Pbo (n=145)	4.5 (1.0 –26.0)	2.8 (0.8 – 13.2)	11 (7.6)

*CR+CRi rate, CR rate, and CR+CRi by initiation of cycle 2 are statistically significant with p<0.001 by CMH test

Aza: Azacitidine; Pbo: Placebo; Ven: Venetoclax; CR: Complete remission; CRi: CR with incomplete-count recovery; CR was defined as absolute neutrophil count >10^3/µL, platelets >10^5/µL, red cell transfusion independence (TI), and bone marrow with <5% blasts; CRi was defined as all criteria for CR, except for neutropenia ≤10^3/µL or thrombocytopenia ≤10^5/µL.
CR + CRi rate was compared using Cochran-Mantel-Haenszel (CMH) test stratified by age (18 – < 75, ≥ 75) and cytogenetic risk (intermediate, poor).

CD DiNardo et al. N Engl J Med 2020;383:617-629.

Overall Survival



	No. of events/No. of patients (%)	Median duration of study treatment, months (range)	Median overall survival, months (95% CI)
Aza+Ven	161/286 (56)	7.6 (<0.1 – 30.7)	14.7 (11.9 – 18.7)
Aza+Pbo	109/145 (75)	4.3 (0.1 – 24.0)	9.6 (7.4 – 12.7)

Hazard ratio: 0.66 (95% CI: 0.52 – 0.85), p<0.001

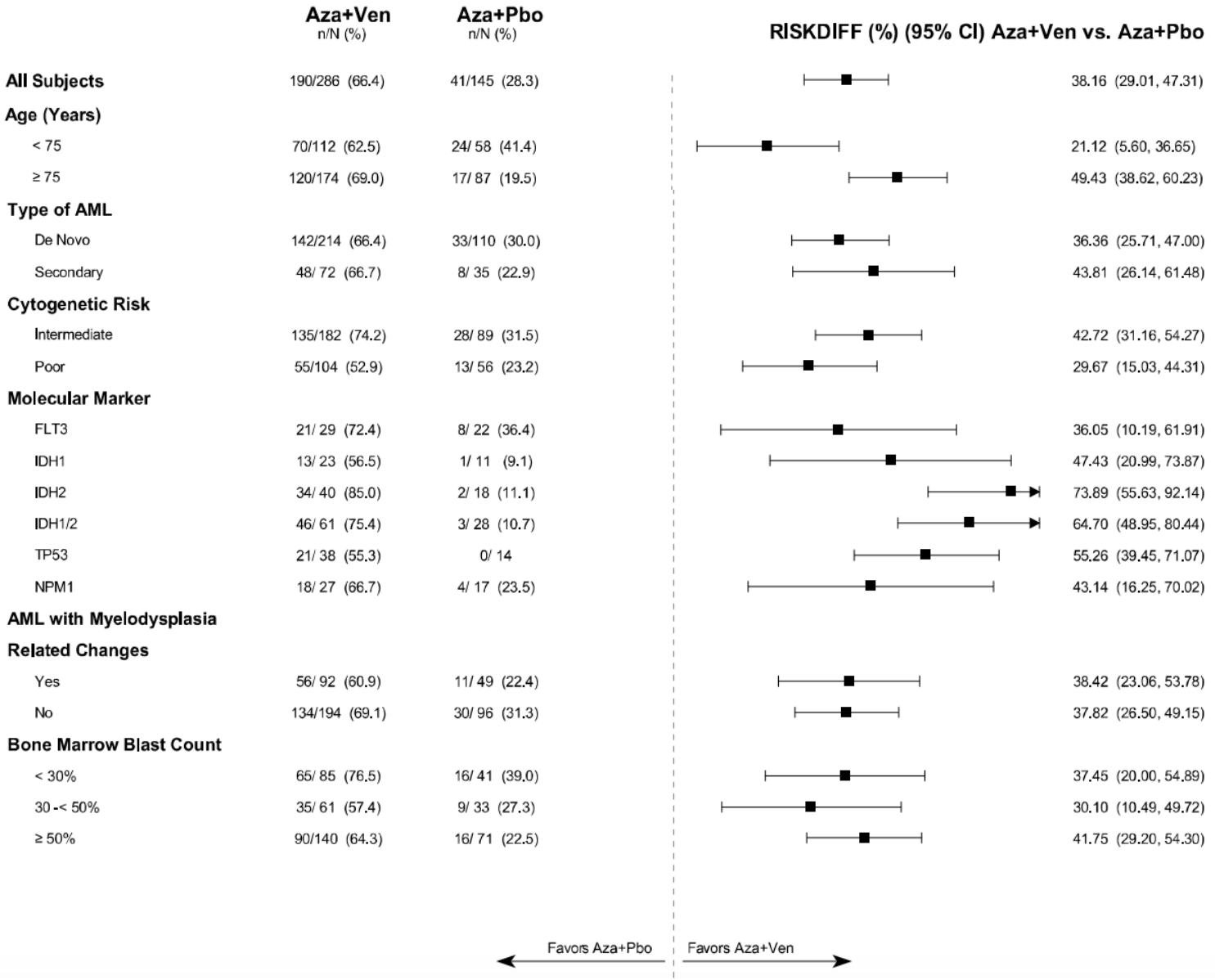
Patients at Risk

Aza+Ven	286	219	198	168	143	117	101	54	23	5	3	0
Aza+Pbo	145	109	92	74	59	38	30	14	5	1	0	0

Median follow-up time: 20.5 months (range: <0.1 – 30.7)

Aza: Azacitidine; Pbo: Placebo; Ven: Venetoclax; The distributions were estimated for each treatment arm using Kaplan-Meier methodology and compared using the log-rank test stratified by age (18-<75, ≥75 years) and cytogenetic risk (intermediate risk, poor risk). The hazard ratio between treatment arms were estimated using the Cox proportional hazards model with the same stratification factors used in the log-rank test.

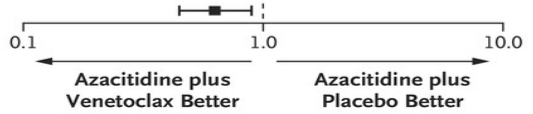
Response to Azacitidine + Venetoclax



DiNardo et al, NEJM 2020

Subgroup Analysis of Overall Survival.

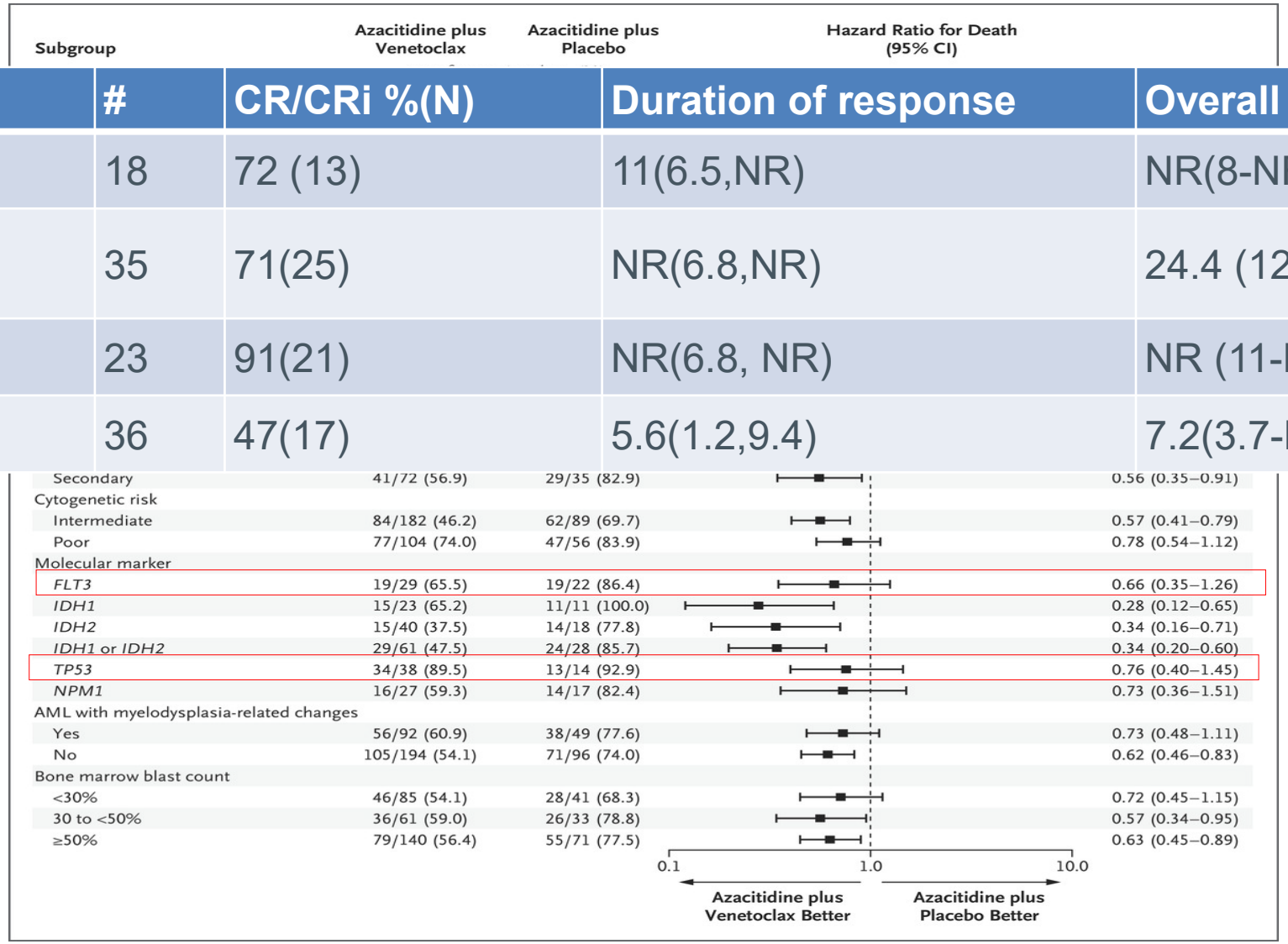
Subgroup	Azacitidine plus Venetoclax	Azacitidine plus Placebo	Hazard Ratio for Death (95% CI)
	no. of events/total no. (%)		
All patients	161/286 (56.3)	109/145 (75.2)	0.64 (0.50–0.82)
Sex			
Female	61/114 (53.5)	41/58 (70.7)	0.68 (0.46–1.02)
Male	100/172 (58.1)	68/87 (78.2)	0.62 (0.46–0.85)
Age			
<75 yr	66/112 (58.9)	36/58 (62.1)	0.89 (0.59–1.33)
≥75 yr	95/174 (54.6)	73/87 (83.9)	0.54 (0.39–0.73)
Geographic region			
United States	27/50 (54.0)	21/24 (87.5)	0.47 (0.26–0.83)
Europe	70/116 (60.3)	46/59 (78.0)	0.67 (0.46–0.97)
China	9/24 (37.5)	5/13 (38.5)	1.05 (0.35–3.13)
Japan	10/24 (41.7)	9/13 (69.2)	0.52 (0.20–1.33)
Rest of world	45/72 (62.5)	28/36 (77.8)	0.73 (0.45–1.17)
Baseline ECOG score			
Grade <2	89/157 (56.7)	65/81 (80.2)	0.61 (0.44–0.84)
Grade ≥2	72/129 (55.8)	44/64 (68.8)	0.70 (0.48–1.03)
Type of AML			
De novo	120/214 (56.1)	80/110 (72.7)	0.67 (0.51–0.90)
Secondary	41/72 (56.9)	29/35 (82.9)	0.56 (0.35–0.91)
Cytogenetic risk			
Intermediate	84/182 (46.2)	62/89 (69.7)	0.57 (0.41–0.79)
Poor	77/104 (74.0)	47/56 (83.9)	0.78 (0.54–1.12)
Molecular marker			
FLT3	19/29 (65.5)	19/22 (86.4)	0.66 (0.35–1.26)
IDH1	15/23 (65.2)	11/11 (100.0)	0.28 (0.12–0.65)
IDH2	15/40 (37.5)	14/18 (77.8)	0.34 (0.16–0.71)
IDH1 or *IDH2*	29/61 (47.5)	24/28 (85.7)	0.34 (0.20–0.60)
TP53	34/38 (89.5)	13/14 (92.9)	0.76 (0.40–1.45)
NPM1	16/27 (59.3)	14/17 (82.4)	0.73 (0.36–1.51)
AML with myelodysplasia-related changes			
Yes	56/92 (60.9)	38/49 (77.6)	0.73 (0.48–1.11)
No	105/194 (54.1)	71/96 (74.0)	0.62 (0.46–0.83)
Bone marrow blast count			
<30%	46/85 (54.1)	28/41 (68.3)	0.72 (0.45–1.15)
30 to <50%	36/61 (59.0)	26/33 (78.8)	0.57 (0.34–0.95)
≥50%	79/140 (56.4)	55/71 (77.5)	0.63 (0.45–0.89)



CD DiNardo et al. N Engl J Med 2020;383:617-629.

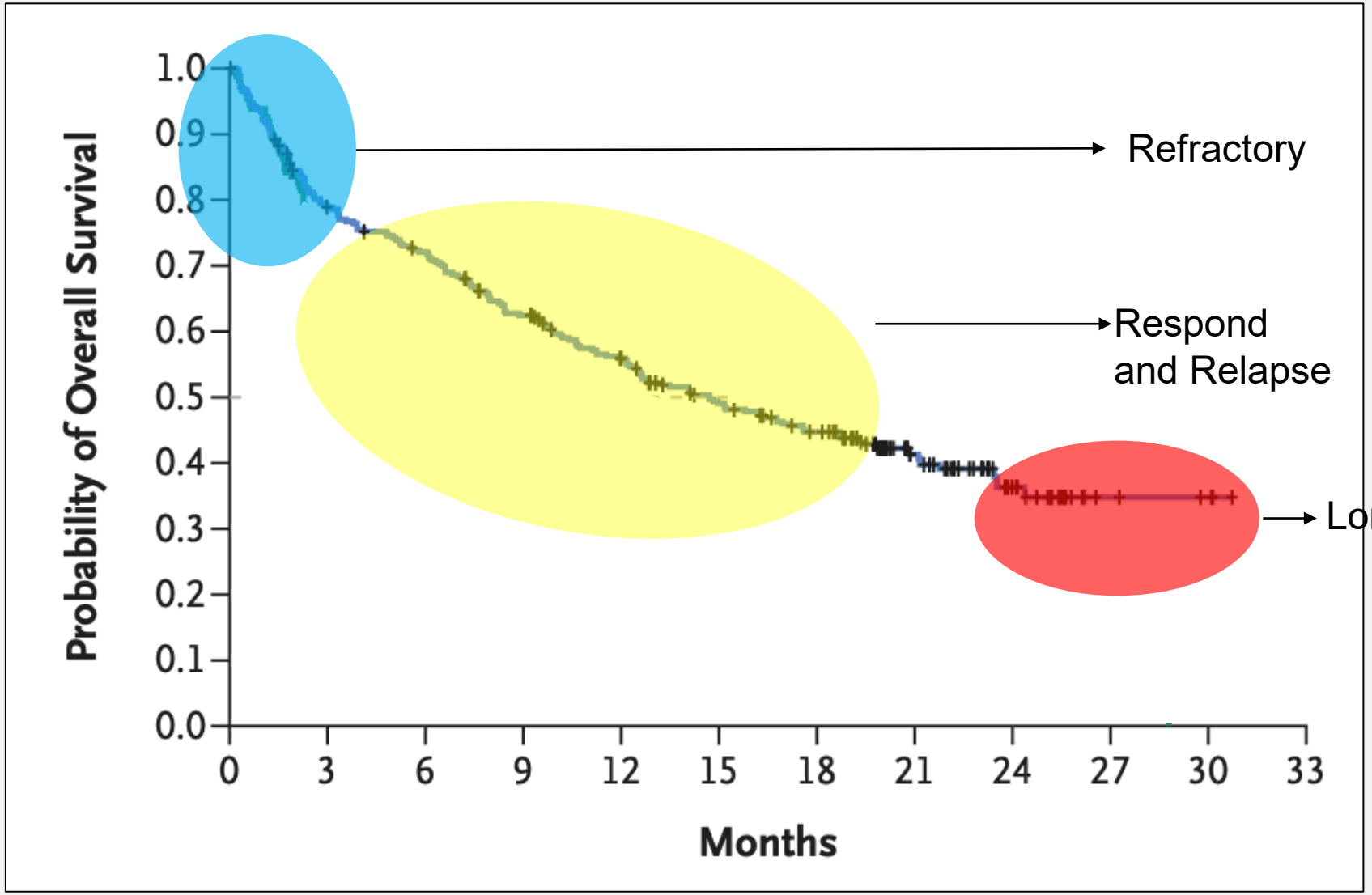
Subgroup Analysis of Overall Survival.

Mutation	#	CR/CRi %(N)	Duration of response	Overall Survival (mo)
FLT3	18	72 (13)	11(6.5,NR)	NR(8-NR)
IDH ½	35	71(25)	NR(6.8,NR)	24.4 (12.3-NR)
NPM1	23	91(21)	NR(6.8, NR)	NR (11-NR)
TP53	36	47(17)	5.6(1.2,9.4)	7.2(3.7-NR)



CD DiNardo et al. N Engl J Med 2020;383:617-629.

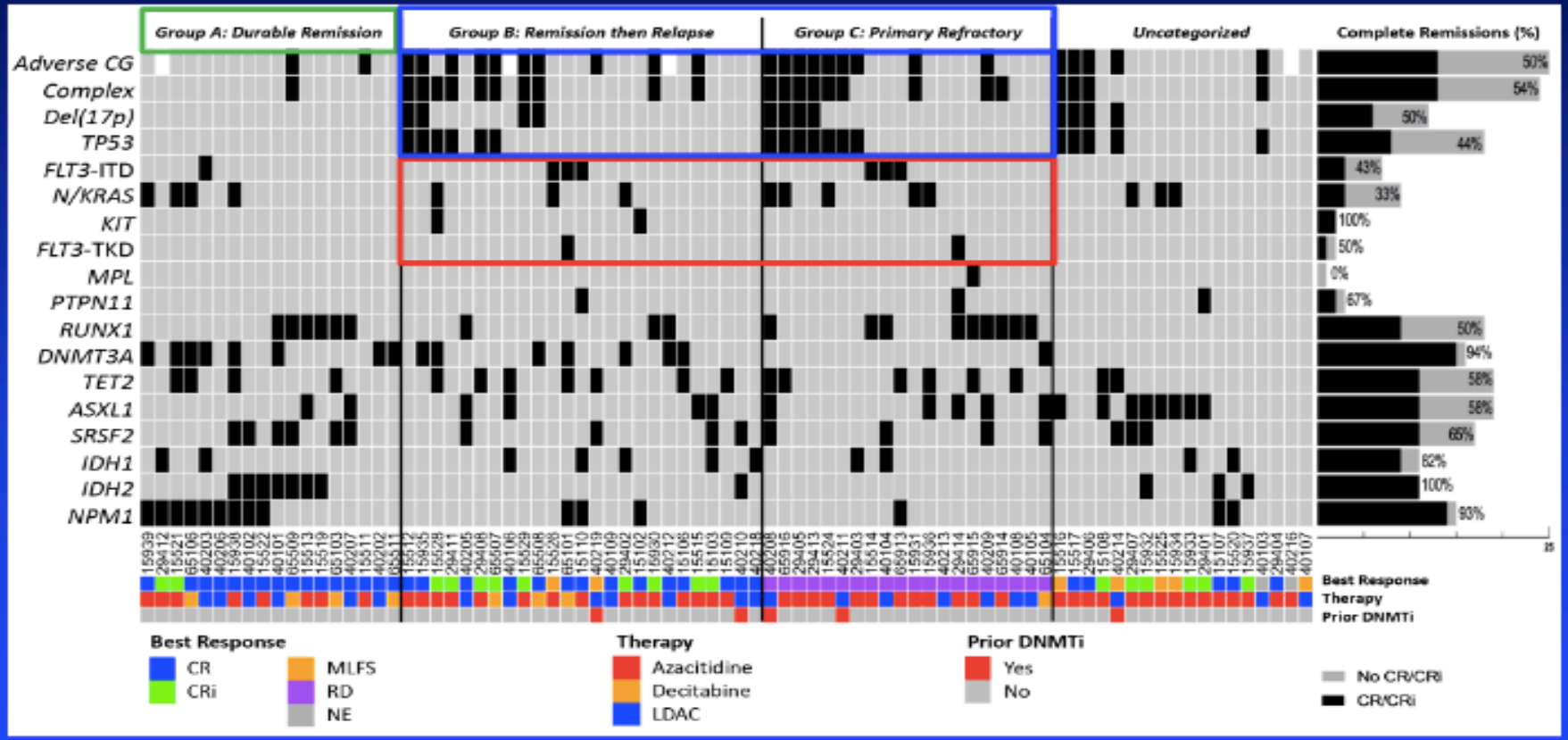
Breaking Down the Azacitidine + Venetoclax Outcomes



DiNardo et al, NEJM 2020

Mechanisms of Treatment Failure After Ven + HMA/LDAC: Mutant p53

Durable remission *Remission/Relapse* *Primary refractory*



C. DiNardo, M. Konopleva, A. Wei
BLOOD 2020

Clinical pearls, monitoring and adverse events

Venetoclax	Neutropenia Thrombocytopenia	Early response assessment, eg, on day 14-21 of cycle 1, if bone marrow blasts <5%, cease venetoclax for up to 14 days to allow count recovery to ≥ CRh. If neutropenia does not recover with 7 days of ceasing venetoclax, addition of G-CSF may augment recovery. Subsequent cycles: azacitidine 75 mg/m^2 SC/IV d1-7 (or d1-5 + d8-9) or decitabine 20 mg/m^2 IV d1-5 plus venetoclax 400 mg QD, or LDC 20 mg/m^2 SC d1-10 plus venetoclax 600 mg QD q4 weeks until progression. Delayed count recovery or recurrent treatment-emergent grade 4 neutropenia/thrombocytopenia lasting ≥7 days require reductions in the duration of administered venetoclax (from 28 to 21 or 14 days, or even less) and/or reductions in the dose of azacitidine, decitabine, or LDC if severe bone marrow hypoplasia.
	Tumor lysis syndrome	Dose ramp up in cycle 1; hydration, the prophylactic use of uric acid lowering drugs, close electrolyte monitoring and reduction of WBC to <25 x 10^9/L (<25,000/µL) is recommended.
	Interaction with CYP3A inhibitors	• Moderate CYP3A inhibitors (eg, ciprofloxacin): reduce the venetoclax dose by at least 50%; ramp-up phase: 50 mg on d1, 100 mg on d2, 200 mg PO QD from d3 • Strong CYP3A inhibitors (eg, posaconazole): ramp-up phase: 10 mg on d1, 20 mg on d2, 50 mg on d3, 100 mg (or less[6])[208] QD PO from d4.

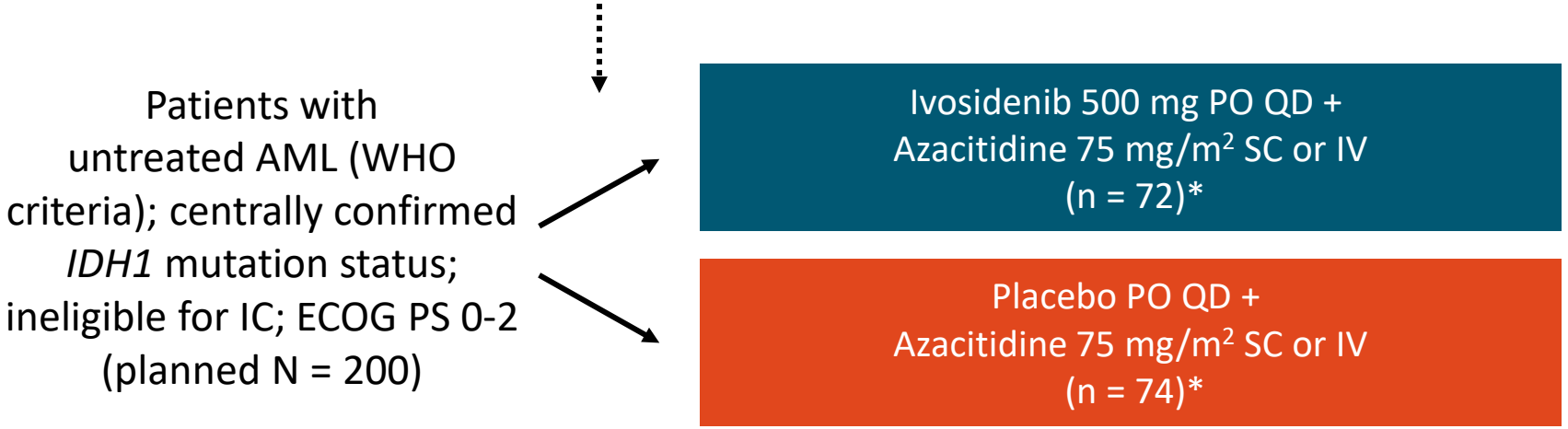
- Start when WBC < 25 K
- Tumor lysis prophylaxis C1
- Antibiotics prophylaxis when ANC < 500.
- Adjust dose of venetoclax based on antibiotics prophylaxis.
- No dose ramping needed.
- Repeat bone marrow after C1, hold next cycle if responding until count recovery and adjust venetoclax dosing for next cycles.

Hartmut Döhner et al; Diagnosis and Management of AML in Adults: 2022 ELN Recommendations from an International Expert Panel. *Blood* 2022; blood.2022016867

AGILE: Study Design

- Multicenter, double-blind, randomized phase III trial

Stratified by region (US/Canada vs Western Europe, Israel, and Australia vs Japan vs rest of world) and disease history (de novo vs secondary AML)



*Enrollment at time of data cutoff (May 18, 2021).

- Enrollment halted based on efficacy as of May 12, 2021 (N = 148)
- **Primary endpoint:** EFS with ~173 events (52 mo)
- **Secondary endpoints:** CRR, OS, CR + CRh rate, ORR

AGILE: Baseline Characteristics

Characteristic	IVO + AZA (n = 72)	PBO + AZA (n = 74)
Median age, yr (range)	76.0 (58-84)	75.5 (45-94)
Sex, n (%)		
▪ Male	42 (58.3)	38 (51.4)
▪ Female	30 (41.7)	36 (48.6)
ECOG PS, n (%)		
▪ 0	14 (19.4)	10 (13.5)
▪ 1	32 (44.4)	40 (54.1)
▪ 2	26 (36.1)	24 (32.4)
Disease history, n (%)		
▪ De novo AML	54 (75.0)	53 (71.6)
▪ Secondary AML	18 (25.0)	21 (28.4)

Characteristic	IVO + AZA (n = 72)	PBO + AZA (n = 74)
Median m*IDH1* VAF in BMA, % (range)	36.7 (3.1-50.5)	35.5 (3.0-48.6)
Cytogenetic risk, n (%)		
▪ Favorable	3 (4.2)	7 (9.5)
▪ Intermediate	48 (66.7)	44 (59.5)
▪ Poor	16 (22.2)	20 (27.0)
Median bone marrow blasts, % (range)	54.0 (20-95)	48.0 (17-100)

Montesinos. ASH 2021. Abstr 697.

AGILE: EFS and Other Efficacy Outcomes

Survival Outcome	IVO + AZA	PBO + AZA	HR (95% CI)	*P* Value
Median EFS in ITT population	NR	NR	0.33 (0.16-0.69)	.0011
Median EFS in patients achieving CR by Wk 24, mo (95% CI)	NE (14.8-NE)	17.8 (9.3-NE)	NR	NR
Median OS, mo	24.0	7.9	0.44 (0.27-0.73)	.0005

- EFS benefit associated with IVO consistent across subgroups: de novo status, region, age, ECOG PS at BL, sex, race, BL cytogenetic risk, WHO AML classification, WBC at BL, percentage of BM blasts at BL
- OS benefit associated with IVO consistent against same subgroups
- Change in markers of health-related QoL favored IVO + AZA over PBO + AZA

Montesinos. ASH 2021. Abstr 697.

AGILE: TEAEs

TEAEs, n (%)	IVO + AZA (n = 71)		PBO + AZA (n = 73)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any TEAE	70 (98.6)	66 (93.0)	73 (100)	69 (94.5)
Any hematologic TEAE	55 (77.5)	50 (70.4)	48 (65.8)	47 (64.4)
Most common hematologic TEAEs*				
▪ Anemia	22 (31.0)	18 (25.4)	21 (28.8)	19 (26.0)
▪ Febrile neutropenia	20 (28.2)	20 (28.2)	25 (34.2)	25 (34.2)
▪ Neutropenia	20 (28.2)	19 (26.8)	12 (16.4)	12 (16.4)
▪ Thrombocytopenia	20 (28.2)	17 (23.9)	15 (20.5)	15 (20.5)
Most common TEAEs*				
▪ Nausea	30 (42.3)	2 (3.8)	28 (38.4)	3 (4.1)
▪ Vomiting	29 (40.8)	0	19 (36.0)	1 (1.4)
▪ Diarrhea	25 (35.2)	1 (1.4)	26 (35.6)	5 (6.8)
▪ Pyrexia	24 (33.8)	1 (1.4)	29 (39.7)	2 (2.7)
▪ Constipation	19 (26.8)	0	38 (52.1)	1 (1.4)
▪ Pneumonia	17 (23.9)	16 (22.5)	23 (31.5)	21 (28.8)
Bleeding	29 (40.8)	4 (5.6)	21 (28.8)	5 (6.8)
Infections	20 (28.2)	15 (21.1)	36 (49.3)	22 (30.1)

*Occurring in >20% of patients.

- AEs of special interest (IVO + AZA vs PBO + AZA):
  - Grade ≥2 differentiation syndrome: 14.1% vs 8.2%
  - Grade ≥3 QT prolongation: 9.9% vs 4.1%
- Fewer infections with IVO + AZA vs PBO + AZA (28.2% vs 49.3%)
- No treatment-related deaths

Montesinos. ASH 2021. Abstr 697.

Upfront Treatment of De Novo AML in patients not eligible for Intensive chemotherapy

Who is ineligible?

1. P53 MT AML
2. Age > 75
3. Major comorbidities
4. frail

Intermediate/poor risk

Azacitidine + Venetoclax

FLt-3 MT AML

Azacitidine + Venetoclax

Or

Azactidine+Flt-3 inhibitor

P53 MT AML
Clinical trials
APR-246
Magrolimab

Upfront therapy of older/unfit patient with FLT3 mutant AML

FLT3 TKI	No pts	ORR	Duration of response
Midostaurin + Aza	27	33%	31 wks (no prior TKI) vs. 16 wks (prior TKI)
Sorafenib + Aza	27	78%	14.5 mos (1.1 to 28.7 mos)
Sorafenib + Dec	6	83% (CR16%, CRi 66%)	Not determined
Gilteritinib + Aza	15	60% (2CR, 8CRi)	Not determined

Wang ES. Blood. 2022 Aug 2:2021014586.

Upfront Treatment of De Novo AML in patients not eligible for Intensive chemotherapy

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FLt-3 MT AML

Azacitidine + Venetoclax

Or

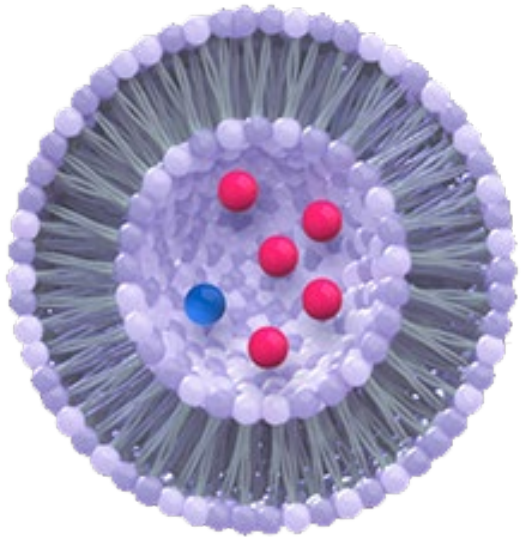
Azactidine+Flt-3 inhibitor

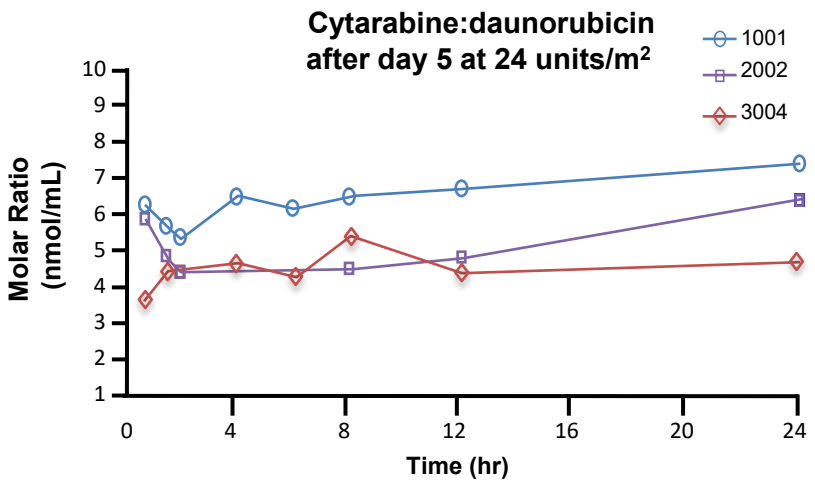
P53 MT AML
Clinical trials

Upfront management of secondary AML

- Candidates for IC
  - No prior HMA therapy
    - CPX-351 FDA approved
  - Prior HMA therapy
    - CLAG-M
- Not candidate for IC
  - No prior HMA
    - Similar algorithm to de novo AML
  - Prior HMA therapy
    - IDH-1/IDH-2 mutant- IDH inhibitors
    - FLt-3 mutant- Giltertinib + venetoclax +/-HMA
    - Gemtuzumab in selected cases with no poor risk cytogenetics

CPX-351 Uses a Nano-Scale Delivery Complex



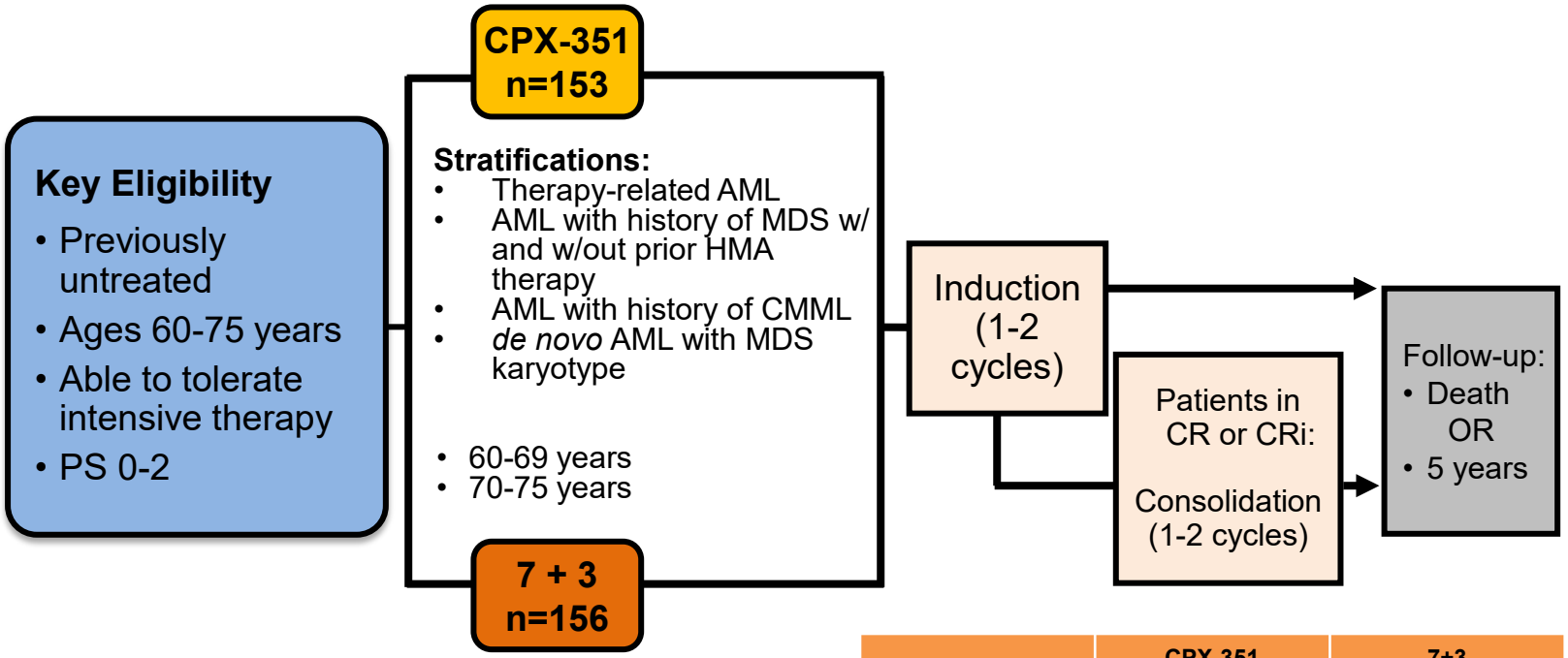


- 100 nm bilamellar liposomes
- 5:1 molar ratio of cytarabine to daunorubicin
- 1 unit = 1.0 mg cytarabine plus 0.44 mg daunorubicin

- **Phase 1 Data**
- Fixed molar ratio maintained for 24 hours after final dose
- Drug exposure was maintained for 7 days
- CPX-351 had potent anti-leukemic efficacy
- CPX-351 was well-tolerated

Feldman EJ, et al. *J Clin Oncol.* 2011;29(8):979-985.

Phase 3 Study of CPX-351 vs Standard Induction in Older Patients with Newly Diagnosed High-Risk (Secondary) AML

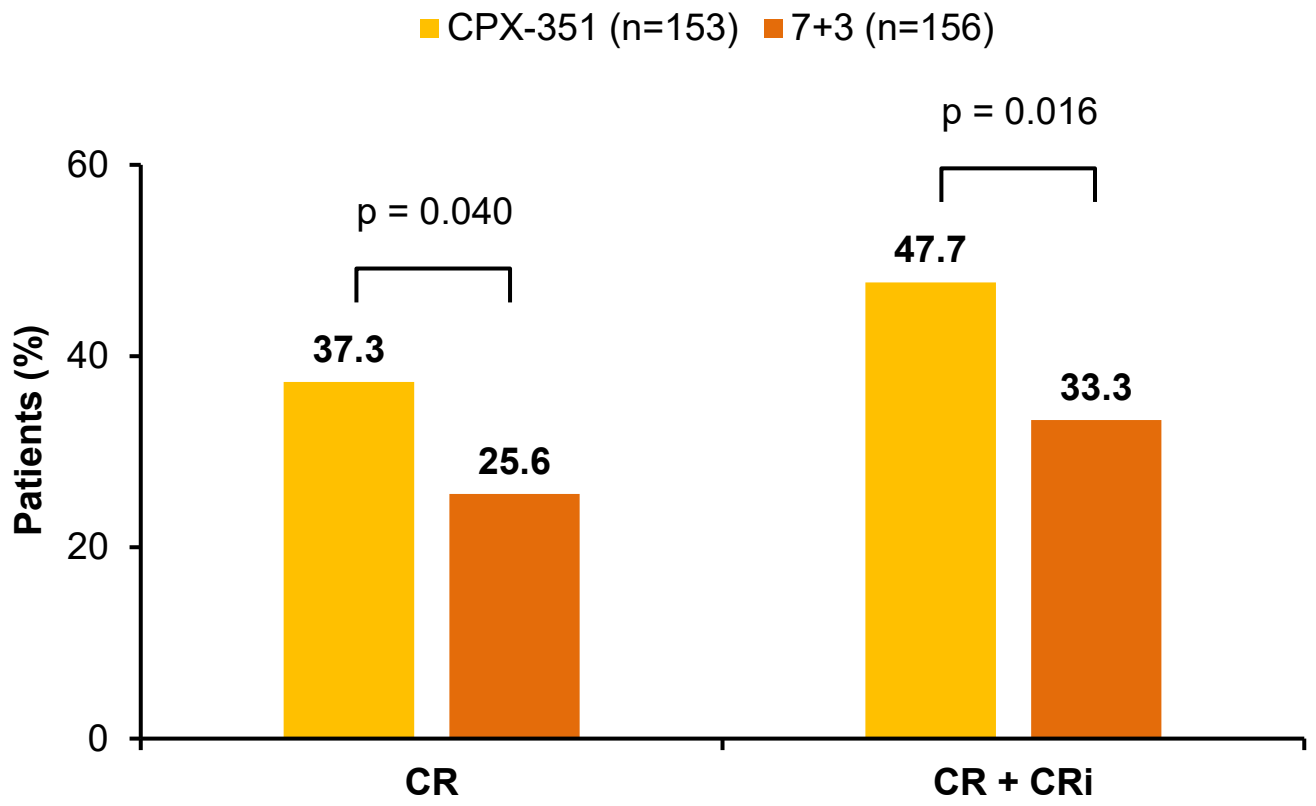


- **Primary Endpoint:** Overall survival

	CPX-351	7+3
First Induction	• 100 units/m^2 • Days 1, 3 and 5	• Cytarabine 100mg/m^2 x 7 d • Daunorubicin 60mg/m^2 x 3 d
Re-induction	• 100 units/m^2 • Days 1 and 3	• Cytarabine 100mg/m^2 x 5 d • Daunorubicin 60mg/m^2 x 2 d
Consolidation	• 65 units/m^2 • Days 1 and 3	• Cytarabine 100mg/m^2 x 5 d • Daunorubicin 60mg/m^2 x 2 d

Lancet J. J Clin Oncol. 2018 Sep 10;36(26):2684-2692.

Response Rates

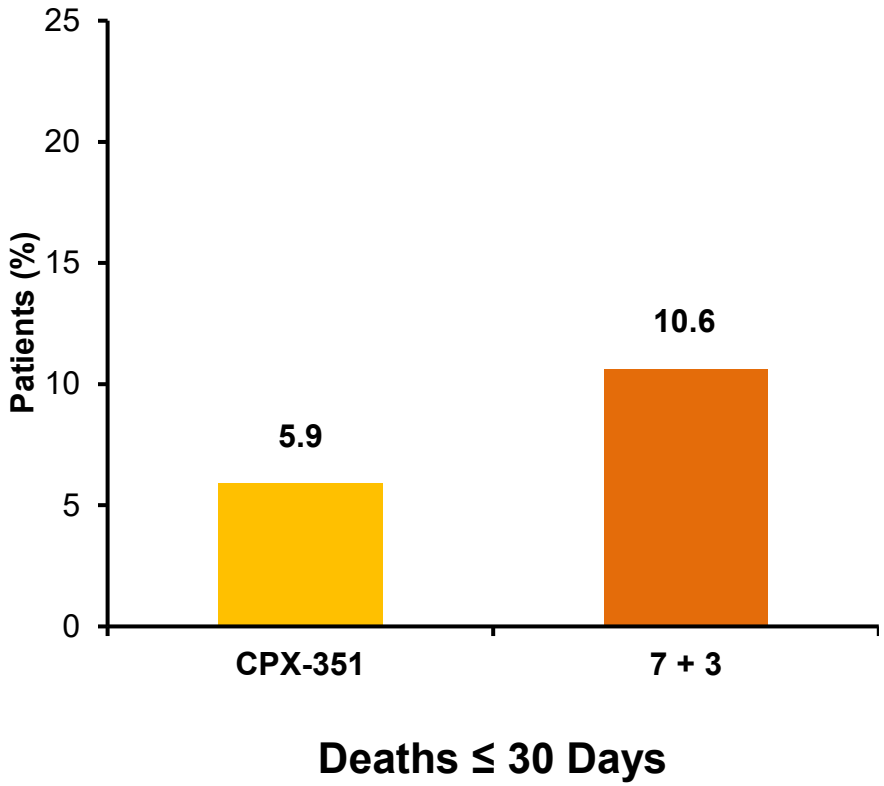


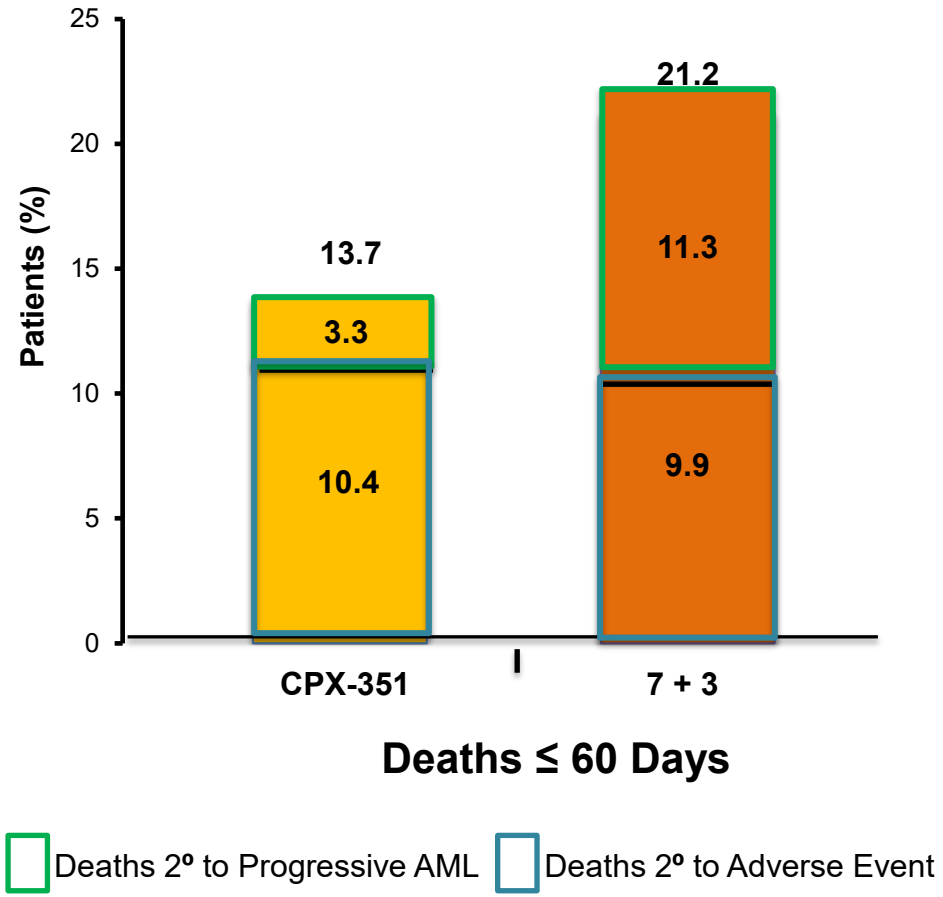
Odds Ratio (95% Conf. Int.)	1.69 (1.03, 2.78)	1.77 (1.11, 2.81)

Note: Percentages reflect number with endpoint out of column total. Odds ratios are calculated with the 7+3 arm as the reference group.
P-value is from a comparison of rates between treatment arms and is based on the Mantel-Haenszel test stratifying by age and AML type.

Lancet J. J Clin Oncol. 2018 Sep 10;36(26):2684-2692.

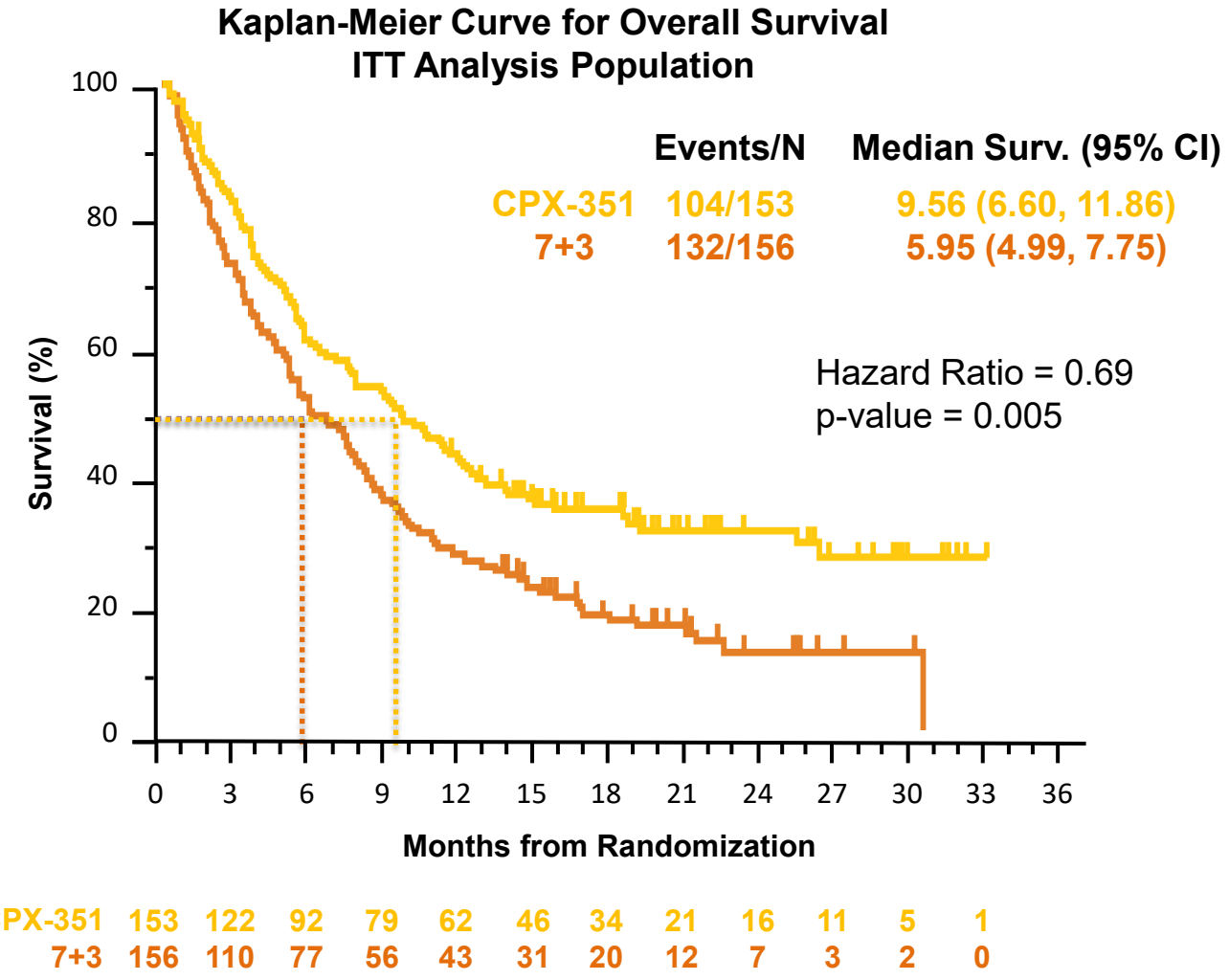
30 and 60-Day Mortality Rates





Lancet J. J Clin Oncol. 2018 Sep 10;36(26):2684-2692.

CPX-351 Improves Overall Survival



Lancet J. J Clin Oncol. 2018 Sep 10;36(26):2684-2692.

WHY? Not all CRs are the same--MRD

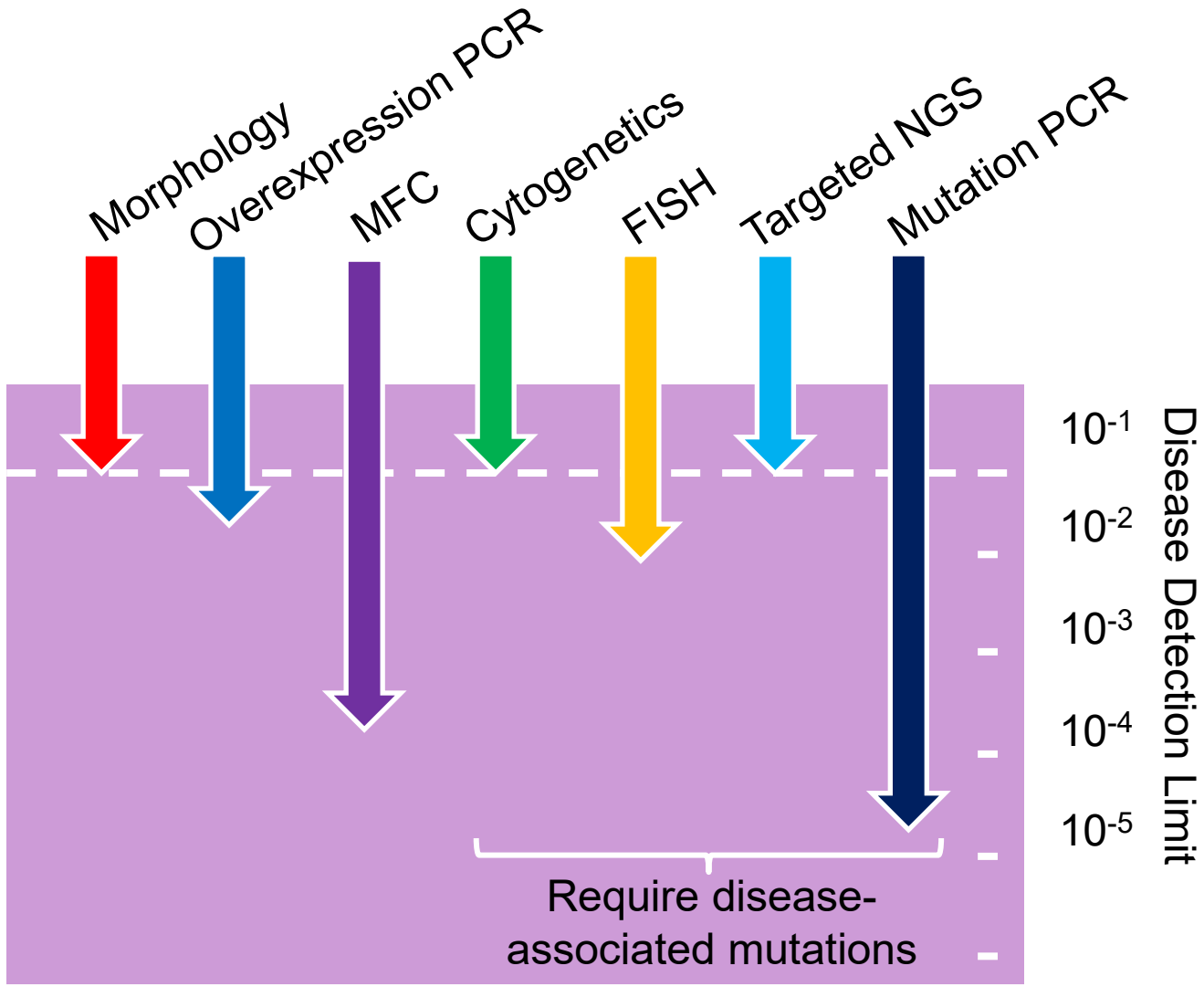
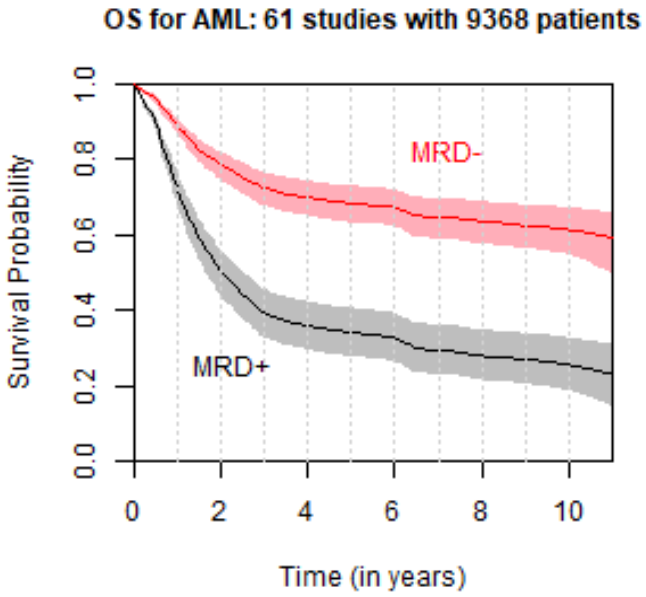


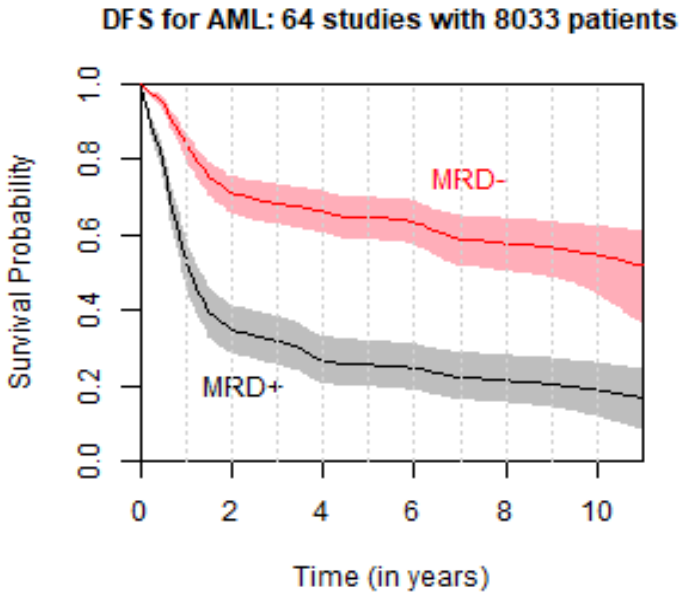
Figure 1. Comparison of detection limits for methods of MRD assessment. Standard morphological assessment defines CR as <5% blasts. Cytogenetics and targeted NGS have similar detection limits to morphology though can detect if the residual blasts harbor clonal abnormalities. Overexpression PCR (*e.g.*WT1) requires at least a 2-log difference in expression to discriminate from healthy BM. FISH has the sensitivity to detect 0.5% residual disease. MFC and mutation PCR have vastly improved the sensitivity of detection of MRD with detection limits ranging from 0.01% to 0.001%.

Sung et al. Current Treatment Options in Oncology. 18. 10.1007/s11864-017-0447-3.

MRD and survival

- Meta-analysis of 81 Publications





Short N, et al JAMA Oncol. 2020 Dec 1;6(12):1890-1899

Conclusions

- Landscape of AML management is changing and improved
- Molecular diagnostic and risk stratification should be standard approach.
- GO addition to intensive chemotherapy (IC) improves overall survival in Good risk AML and future directions to eliminate anthracycline use.
- Flt-3 inhibitors combinations with IC is standard of care for FLT-3 MT AML.
- Maintenance therapy in AML is standard care now in FLT-3 AML after allo-SCT and for intermediate and poor risk AML after IC if no allo-SCT.
- Azacitidine and venetoclax combination is the new standard of upfront treatment in AML patients not eligible for IC.
  - Exceptions?: TP53, M5, FLT-3?
- Azacitidine and IDH inhibitors are option for patients with IDH mutations
- Patients with TP53 MT AML should be enrolled on clinical trials.
- CPX-351 is approved by FDA for induction therapy for secondary AML
- MRD assessment and disease status will guide our future tailoring of treatment.

Thank You

Rami.Komrokji@moffitt.org

Moffitt leukemia team: Only perfect counts !!!

Acknowledgements:

- Our patients and their caregivers
- Moffitt MDS team