Initial Therapy of Acute Myeloid Leukemia: Finally, A Trip Beyond 7+3

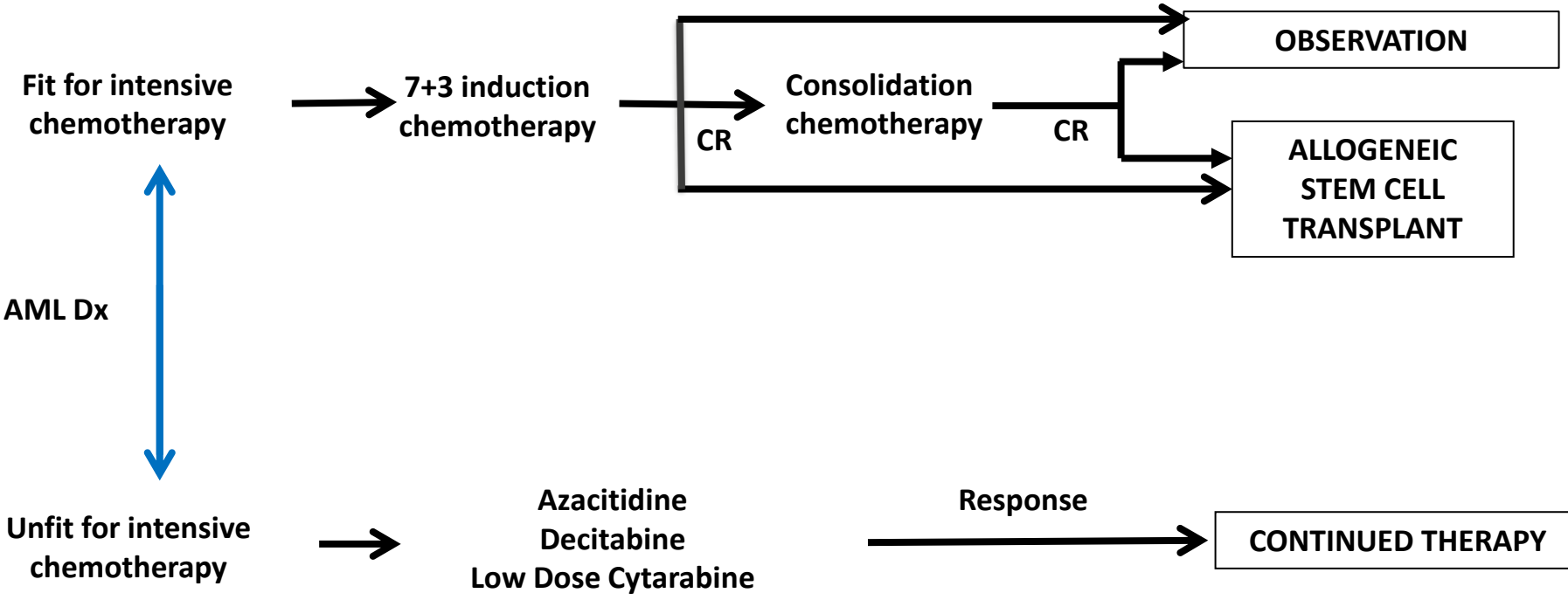
Harry P. Erba, MD, PhD
Professor, Department of Medicine
Director, Leukemia Program
Duke University
Durham, NC

DukeHealth

Disclosures of Potential Conflicts of Interest

- Speaker Bureau: AbbVie, Agios, BMS/Celgene, Incyte, Jazz, Novartis
- Consultant: AbbVie, Agios, Astellas, BMS/Celgene, Daiichi Sankyo, Glycomimetics, Immunogen, Incyte, Jazz, Kura Oncology, MacroGenics, Novartis, Pfizer, Syros, Takeda, Trillium
- Contracted Research: AbbVie, ALX Oncology, Amgen, Daiichi Sankyo, Forma, Forty Seven / Gilead, Glycomimetics, Immunogen, Jazz, MacroGenics, Novartis, PTC
- Other: BMS/Celgene (Chair, AML Registry Steering Committee), AbbVie (Chair, IRC for VIALE A and VIALE C Phase III studies), Glycomimetics (Scientific Steering Committee)

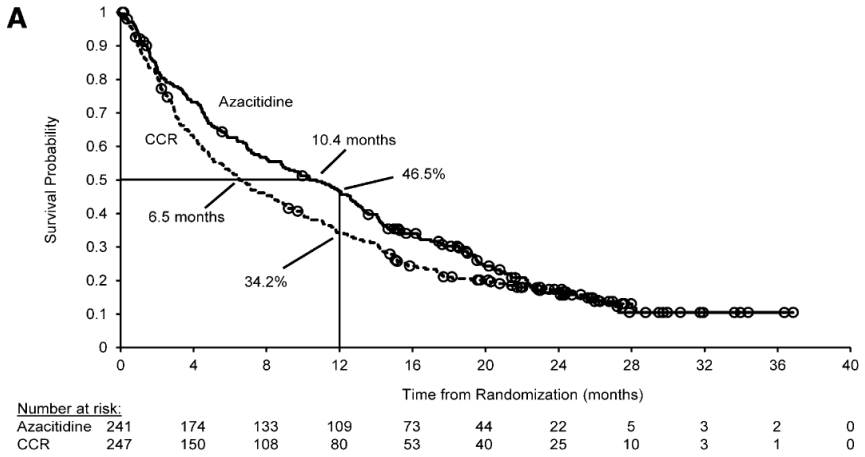
The AML Treatment Algorithm, Pre 2018



AML-001 Study: Aza vs CCR in Older AML Patients

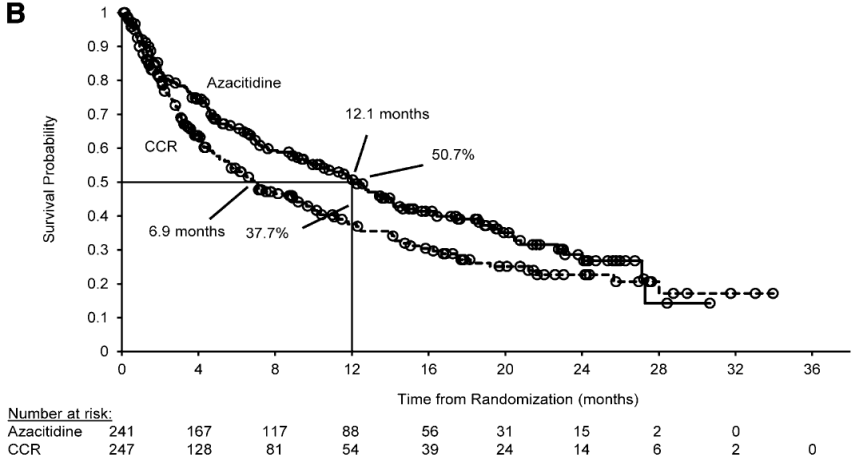
Overall Survival (ITT)

HR = 0.85 (p = 0.1009)



Overall Survival (censor at subsequent AML Tx)

HR = 0.76 (p = 0.0190)



Median follow-up 24.4 months, with 193 deaths in AZA arm (80.1%) and 201 deaths in the CCR arm (81.4%). Stratified by ECOG PS and cytogenetic risk.

	CR/CRi	RBC TI	PLT TI
AZA	**27.8%**	**38.5%**	**40.6%**
CCR	**25.1%**	**27.6%**	**29.3%**

Dombret H et al. *Blood*. 2015; 126: 291-299.

Survival of Older AML Patients: Population Based Study

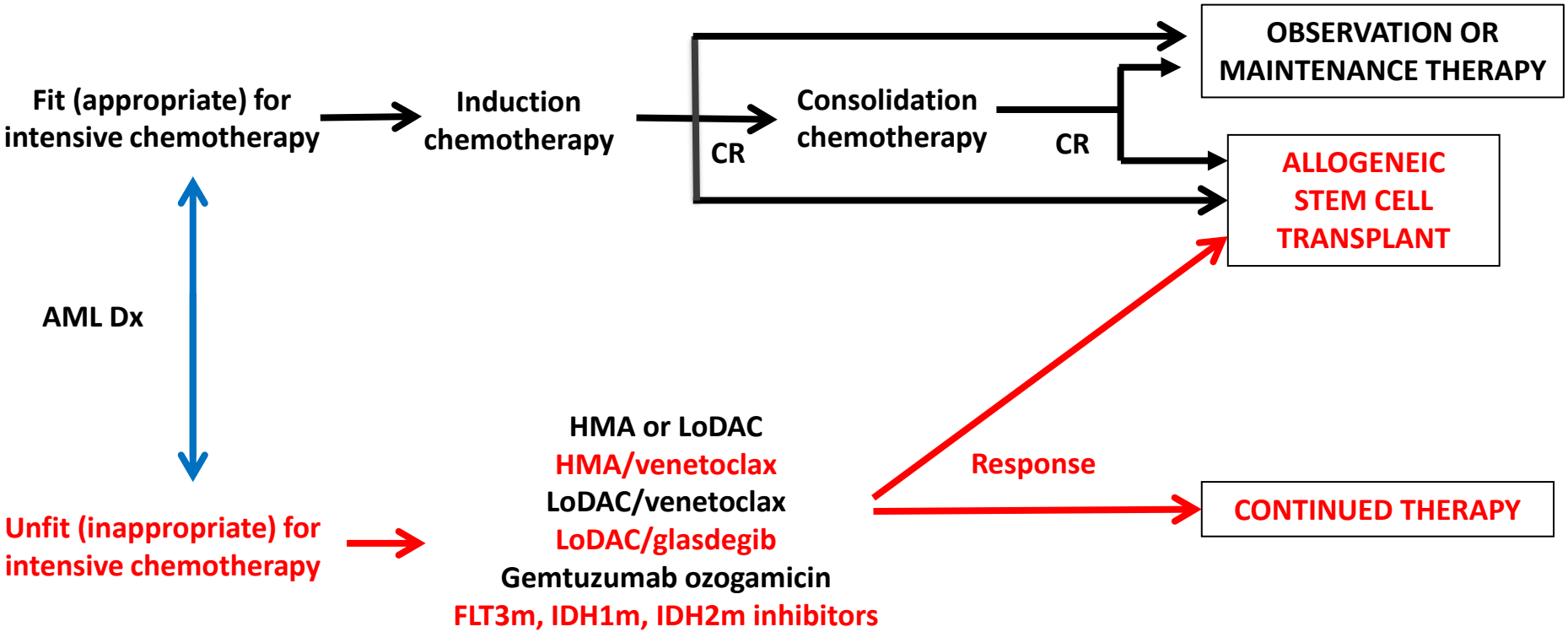
	Study cohort (n=5480) N (%)	Untreated group (n=3367) N (%)	Treated group (n=2113) N (%)	P
Age, years				
65-69	763 (13.9)	251(7.5)	512 (24.2)	
70-74	1139 (20.8)	512 (15.2)	627 (29.7)	
75-79	1293 (23.6)	768 (22.8)	525 (24.8)	
≥80	2285 (41.7)	1836 (54.85	449(21.3)	<0.01
Charlson comorbidity index (CCI) score				
0	3017 (55.0)	1720 (51.1)	1297 (61.4)	
1	1324 (24.2)	835 (24.8)	489 (23.1)	
≥2	1139 (20.8)	812 (24.1)	327 (15.5)	<0.01
Previous myelodysplastic syndrome				
No	4524 (82.5)	2698 (80.1)	1826 (86.4)	
Yes	959 (17.5)	669 (19.9)	287(13.6)	0.01
Use of hypomethylating agents by diagnosis year**				
2005	18 (2.7)	-	18 (7.3)	
2006	41 (6.2)	-	41 (15.9)	
2007	69(10.4)	-	69 (24.3)	

SEER-Medicare
2000-2007
38.6% received therapy
Median age: 78 years

Median OS: 3 mos.
OS treated: 6 mos.
OS untreated: 2 mos.
Allo HSCT: 0.8%

Oran and Weisdorf. *Haematologica* 2012; 97 (12): 1916-1924

The Current AML Treatment Algorithm



VIALE-A Study Design

Eligibility

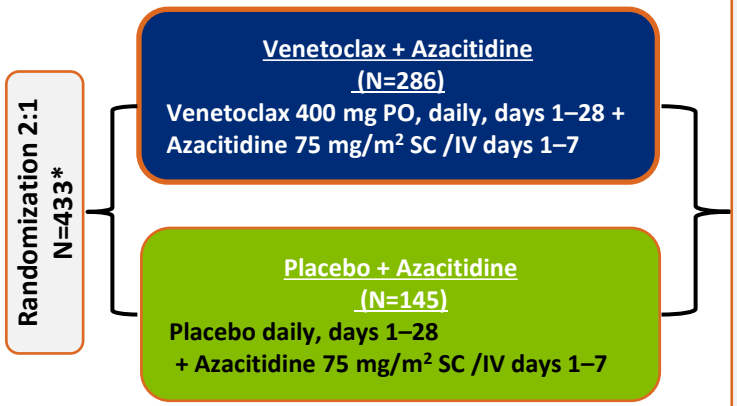
Inclusion

- 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



Endpoints

Primary

- Overall survival

Secondary

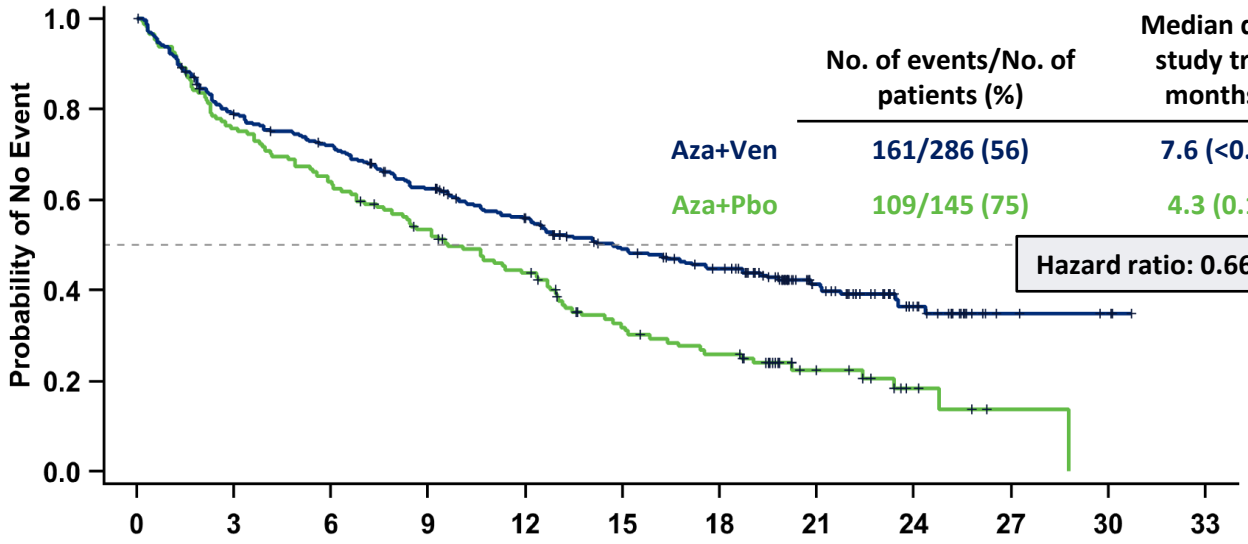
- CR+CRi rate
- CR+CRh rate
- CR+CRi and CR+CRh rates by initiation of cycle 2
- CR rate
- Transfusion independence
- CR+CRi rates and OS in molecular subgroups
- Event-free survival

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

DiNardo C, et al. *N Engl J Med* 2020; 383(7): 617-629.

VIALE A: 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)

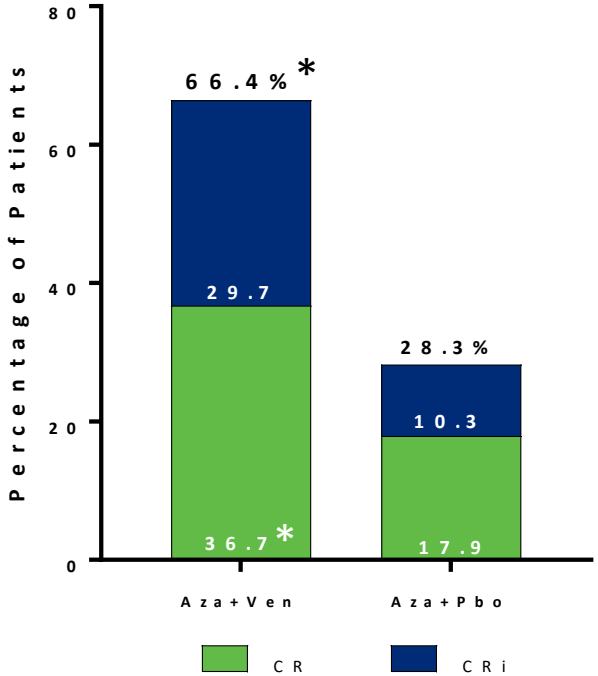
DiNardo C, et al. *N Engl J Med* 2020; 383(7): 617-629.

VIALE A: Overall Survival in Selected Subsets

	Aza+Ven n/N(%)	Aza+Pbo n/N(%)	HR [95% CI] Aza+Ven vs. Aza+Pbo
All Subjects	161/286 (56.3)	109/145 (75.2)	0.64 (0.50, 0.82)
Gender			
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 (Years)			
< 75	66/112 (58.9)	36/ 58 (62.1)	0.89 (0.59, 1.33)
≥ 75	95/174 (54.6)	73/ 87 (83.9)	0.54 (0.39, 0.73)
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)
IDH1/2	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)

DiNardo C, et al. *N Engl J Med* 2020; 383(7): 617-629.

VIALE A: 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).

DiNardo C, et al. *N Engl J Med* 2020; 383(7): 617-629.

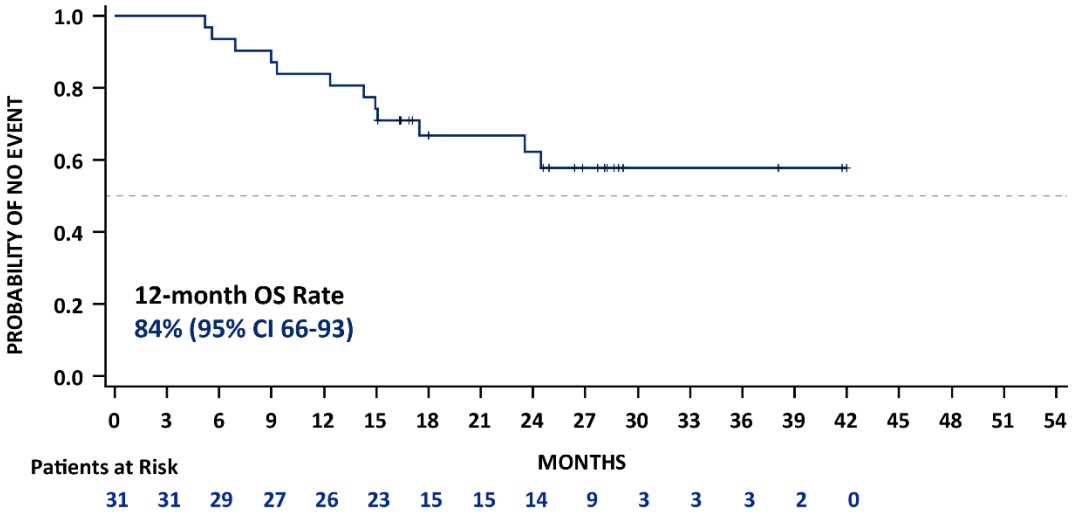
VIALE A: Serious Adverse Events and Dose Modifications

Serious AEs in ≥5% of patients, n (%)	Aza+Ven N = 283	Aza+Pbo N = 144
All serious AEs	**235 (83)**	**105 (73)**
Febrile neutropenia	84 (30)	15 (10)
Anemia	14 (5)	6 (4)
Neutropenia	13 (5)	3 (2)
Atrial fibrillation	13 (5)	2 (1)
Pneumonia	47 (17)	32 (22)
Sepsis	16 (6)	12 (8)
Any AE leading to:		
Dose discontinuation	69 (24)	29 (20)
Dose interruption*	204 (72)	82 (57)
Dose reduction†	7 (3)	6 (4)
Deaths, n (%)		
≤30 days after first dose of study drug	21 (7)	9 (6)
≤60 days after first dose of study drug	43 (15)	24 (17)
Other, n (%)		
Tumor lysis syndrome††	3 (1)	0

*Dose interruptions commonly due to neutropenia (19%/10%), febrile neutropenia (20%/4%), and thrombocytopenia (10%/4%); interruptions include delays between cycles and reduced duration from 28 to 21 days per cycle for count recovery after marrow leukemia clearance; †Dose reduction for AEs or other medications; †† 3 cases of TLS during ramp up.

DiNardo C, et al. *N Engl J Med* 2020; 383(7): 617-629.

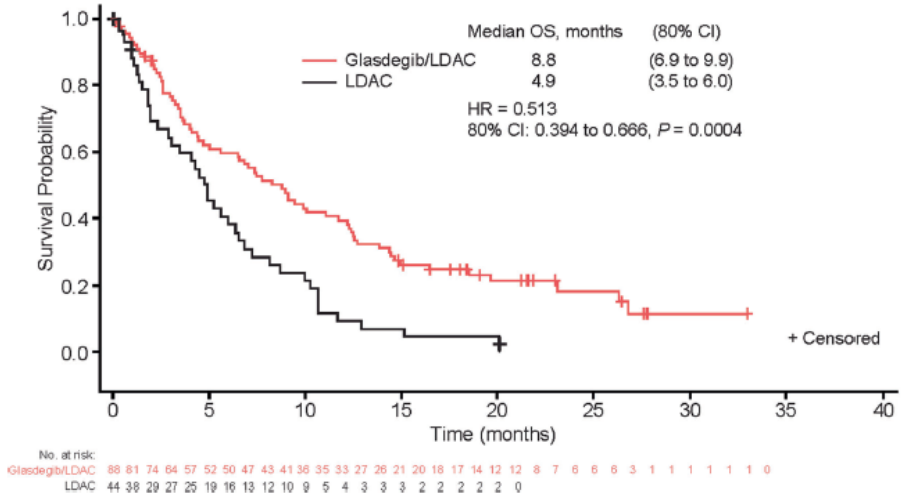
Overall Survival from Venetoclax Initiation with Allo HSCT

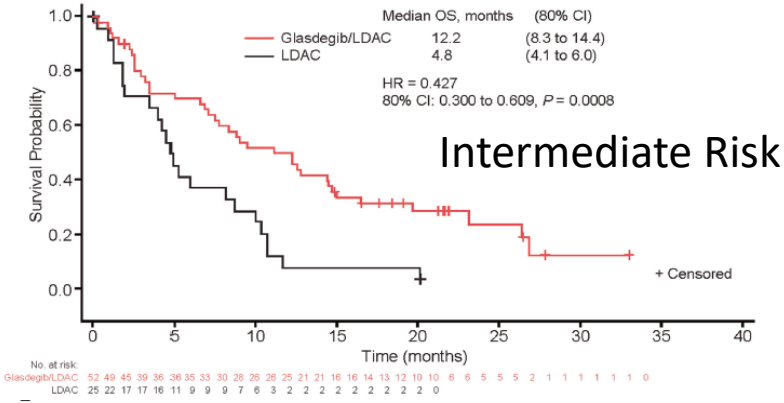


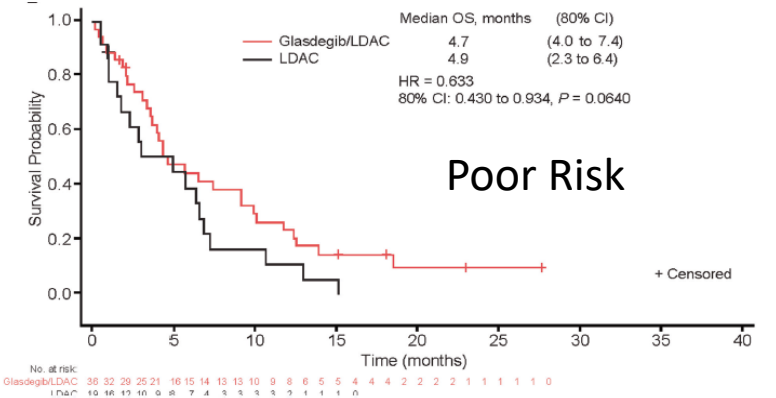
- **68%** (21/31) of patients remained alive at 12 months posttransplant
- **55%** (17/31) of patients that had SCT had posttransplant remission of ≥12 months and **71%** (12/17) of those patients remained in remission for ≥2 years
- **69%** (18/26) and **59%** (13/22) of patients that achieved CR/CRi and CR/CRh, respectively, maintained remission for ≥12 months posttransplant

Pratz K et al. Outcomes after SCT in patients with AML treated with venetoclax-based therapies. ASH 2019

Phase II Study of LoDAC +/- Glasdegib: Overall Survival



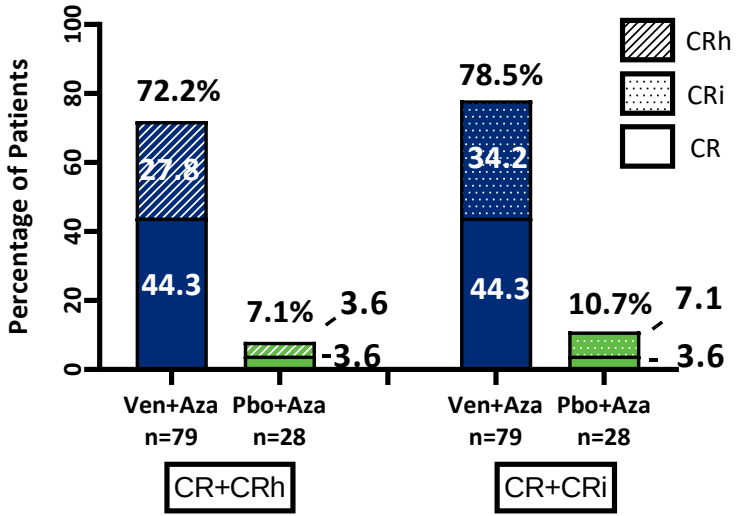


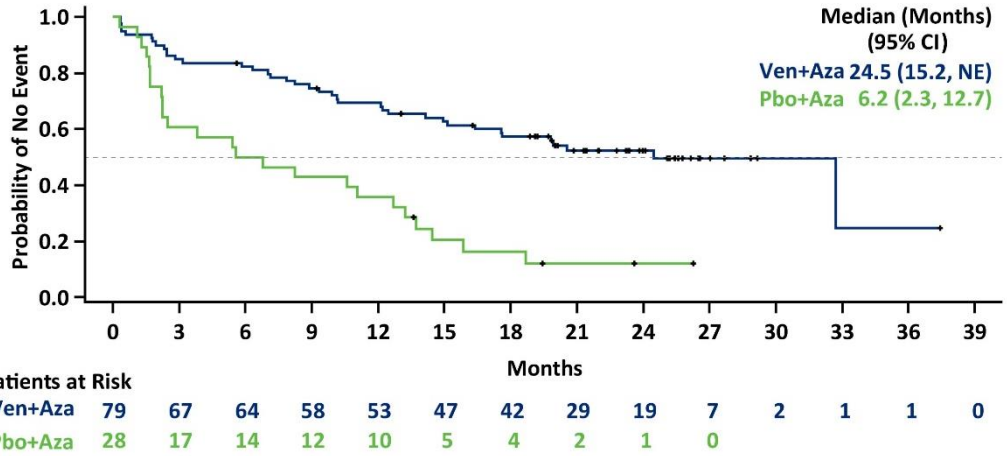


Cortes J et al. *Leukemia* 2019; 33: 379-389.

Should therapy with HMA/venetoclax await mutational analysis in older, UNFIT, treatment-naïve AML patients?

VIALE A: Response and Survival in *IDH1/2*m+ AML





	Ven + Aza n = 79	Pbo + Aza n = 28
CR+CRh: Median time to first response, mo. (min, max)	1.0 (0.7, 9.6)	2.6 (2.1, 3.1)
Median DoR, mo. (95% CI)*	29.6 (16.7, NE)	15.5 (NE)
CR + CRi: Median time to first response, mo. (min, max)	1.1 (0.7, 8.8)	3.4 (2.1, 7.1)
Median DoR, mo. (95% CI)*	29.5 (16.7, NE)	9.5 (3.5, 15.5)
Median treatment cycles (min,max)	8.0 (1, 37)	2.5 (1, 18)

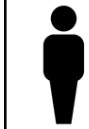
*Results generated using data of responders only

Survival Estimate (%) (95% CI)

	Month 6	Month 12	Month 24
Ven+Aza	82.3 (71.9, 89.1)	69.3 (57.8, 78.3)	52.4 (40.4, 63.1)
Pbo+Aza	50.0 (30.6, 66.6)	35.7 (18.9, 53.0)	12.2 (3.2, 27.8)

Pollyea DA et al. ASH 2020;Abstract 461.

Ivosidenib induces deep durable remissions in patients with newly diagnosed *IDH1*-mutant AML



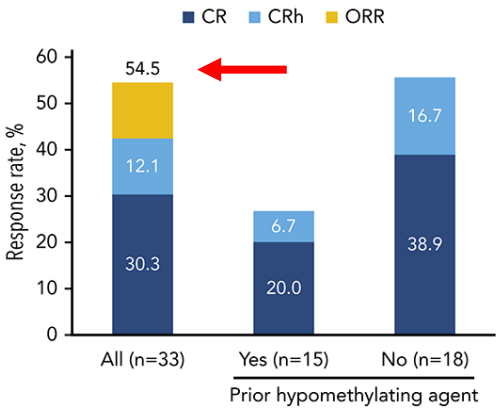
- *IDH1*-mutant newly diagnosed AML
- Ineligible for standard therapy
- N=34

56% aged ≥75 years

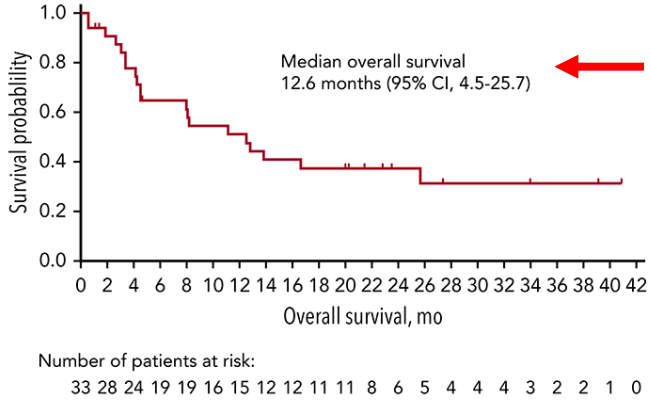
47% prior exposure to HMA

76% secondary AML

Mutant IDH1 inhibitor ivosidenib 500 mg once daily



- Of the patients who were transfusion-dependent at baseline, 43% became transfusion independent



Robox GJ et al. *Blood* 2020; 135(7): 463

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

Response with Ivo/Aza for Treatment Naïve, IC-Unfit AML

Response parameter	All patients N=23
CR, n (%) [95% CI]	13 (56.5) [34.5, 76.8]
Time to CR, median (range), months	3.5 (0.8–6.0)
Duration of CR, median [95% CI], months	NE [7.7, NE]
CR+CRh,[a] n (%) [95% CI]	15 (65.2) [42.7, 83.6]
Time to CR+CRh, median (range), months	2.2 (0.8–6.0)
Duration of CR+CRh, median [95% CI], months	NE [7.7, NE]
CRh, n (%)	2 (8.7)
ORR, n (%) [95% CI]	18 (78.3) [56.3, 92.5]
Time to response, median (range), months	1.8 (0.7–3.8)
Duration of response, median [95% CI], months	NE [9.5, NE]
Best response[b]	
CR, n (%) [95% CI]	13 (56.5) [34.5, 76.8]
CRi/CRp, n (%)	3 (13)
MLFS, n (%)	2 (8.7)
OS, 12-month rate, % [95% CI][c]	82 [59, 93]
Duration of follow-up, median (range), months	9.5 (1.3–24.0)

DiNardo C et al. Acute Leukemias XVII, Munich, Germany, February, 2019

Newly Diagnosed *IDH2*m AML Unfit for Intensive Chemotherapy: Responses in BEAT AML S3 Cohort

Parameter	Phase 2 Enasidenib 100mg/day N=60	Phase 1b Enasidenib + Azacitidine (n=17)
CR/CRi, n/N (%, 95% CI)	28/60 (47%, 34-60)	7/17 (41%, 18-67)
Overall Response Rate [CR/CRi/MLFS], n/N (%, 95% CI)	30/60 (50%, 37-63)	8/17 (47%, 23-72)
Duration of Response (months) Median, 95% CI	NR, 7.1-NR	NR, 2.5 – NR
Overall Survival (months) Median, 95% CI	24.4, 10.6-NE	8.9, 5.2-NE

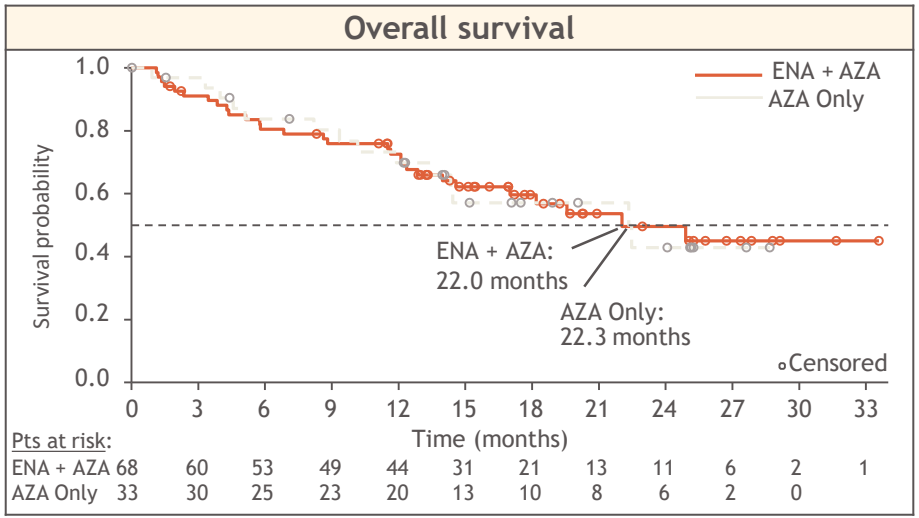
Stein EM et al. ASH 2020; abstract 636.

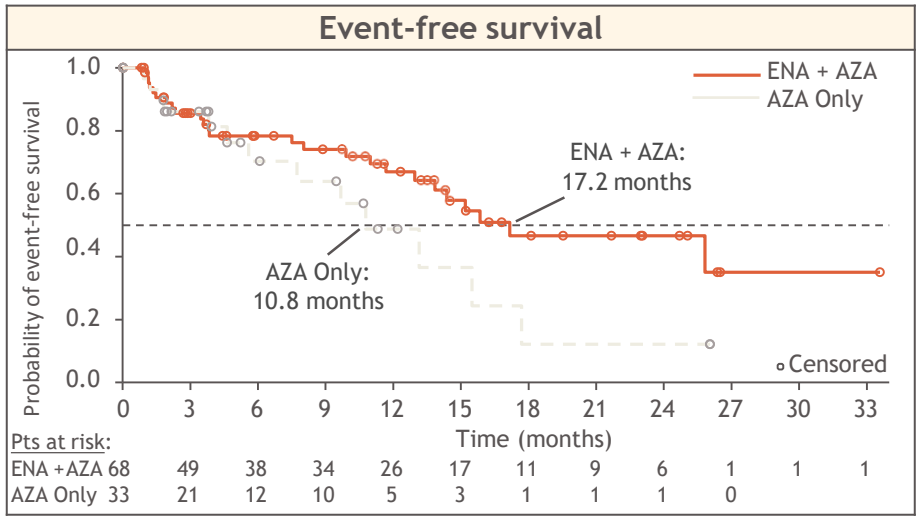
Enasidenib Plus Azacitidine versus AZA Monotherapy in *IDH2*m+ Newly Diagnosed AML

	ENA + AZA (n=68)	AZA Only (n=33)
Overall response (CR, CRi/CRp, PR, MLFS), n (%)	**48 (71)**	**14 (42)**
[ORR 95%CI]	**[58, 81]**	**[26, 61]**
***P* value**	**0.0064**	
CR, n (%)	36 (53)	4 (12)
[CR rate 95%CI]	[41, 65]	[3, 28]
P value	0.0001	
CRi/CRp, n (%)	7 (10)	4 (12)
PR, n (%)	3 (4)	4 (12)
MLFS, n (%)	2 (3)	2 (6)
Stable disease, n (%)	13 (19)	13 (39)
Disease progression, n (%)	2 (3)	1 (3)
Not evaluable / Missing, n (%)	5 (7)	5 (15)
Time to first response, months, median (range)	1.9 (0.7–9.0)	2.0 (0.8–5.8)
Time to CR, months, median (range)	5.5 (0.7–19.5)	3.7 (3.0–4.1)
Duration of response, months, median [95%CI]	24.1 [11.1, NR]	12.1 [2.8, 14.6]

DiNardo C et al. EHA 2019, presentation S139

Enasidenib Plus Azacitidine versus AZA Monotherapy in *IDH2*m+ Newly Diagnosed AML



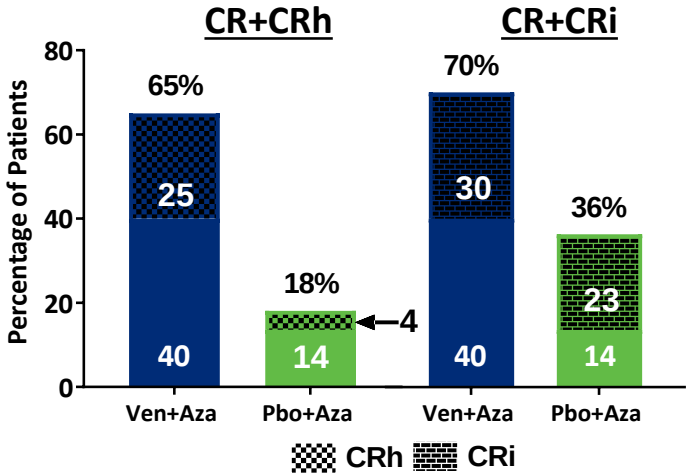


Data cutoff: August 19, 2019
EFS: time from randomization to AML relapse, disease progression (IWG AML 2003 criteria), or death from any cause, whichever occurred first.

DiNardo CD, et al. EHA 2019, presentation S139

VIALE A: Response and Survival in FLT3m+ AML

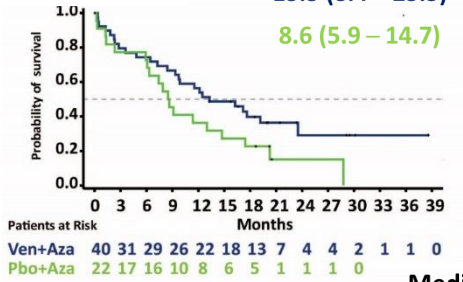
40 FLT3m+ pts (28 ITD) in AZA/VEN, 22 (13 ITD) in AZA/PBO



Median treatment duration of 7 mo
median time to CR/CRh of 1 m (0.8-4.8 mo)
Median DOR of CRh 18.3 mo (17.4 in ITD)
Median OS 13.3 mo/11.5 ITD

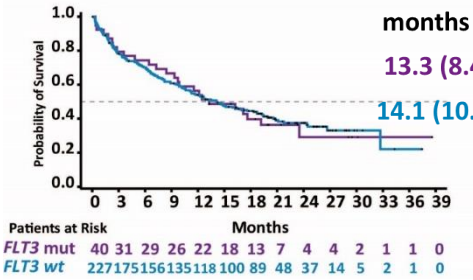
A.
FLT3mut

Median OS, months (95% CI)
13.3 (8.4 – 23.5)
8.6 (5.9 – 14.7)



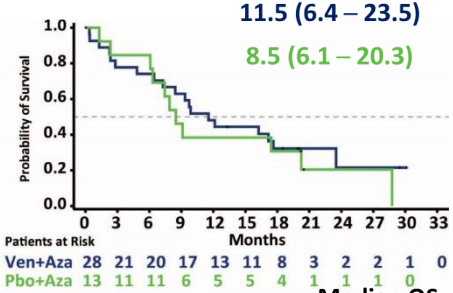
B.
FLT3mut vs. wt in Ven+Aza

Median OS, months (95% CI)
13.3 (8.4 – 23.5)
14.1 (10.6 – 18.7)



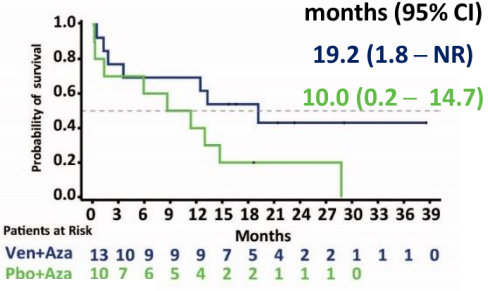
C.
FLT3-ITD

Median OS, months (95% CI)
11.5 (6.4 – 23.5)
8.5 (6.1 – 20.3)



D.
FLT3-TKD

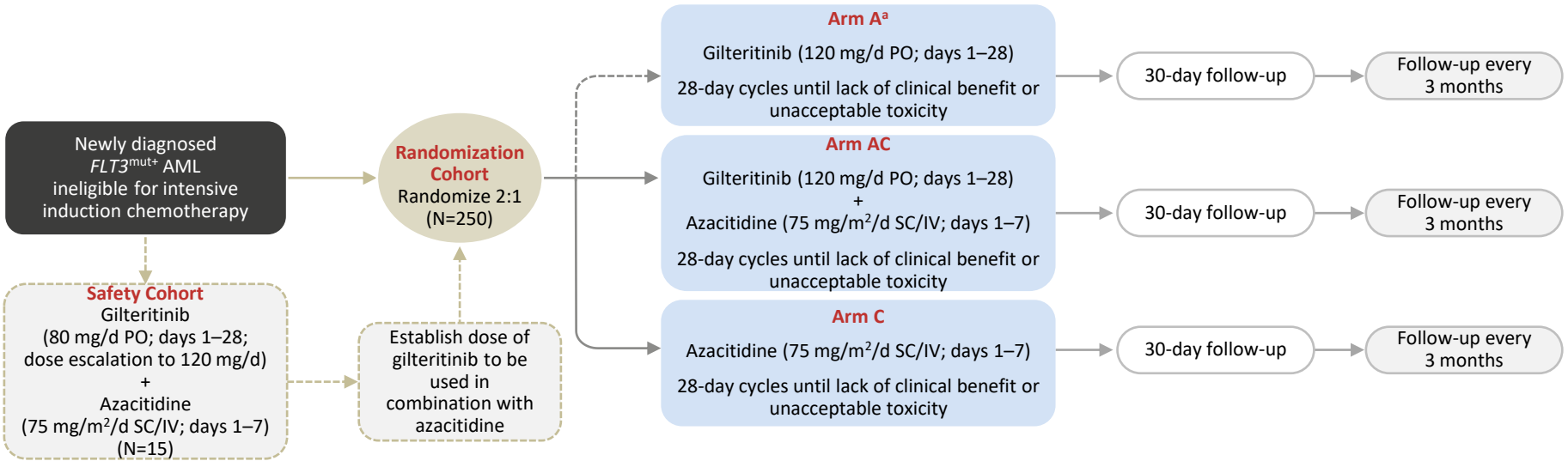
Median OS, months (95% CI)
19.2 (1.8 – NR)
10.0 (0.2 – 14.7)



VIALE-A: In all patients (not just FLT3) with composite complete remission, MRD neg occurred in 23.4% (95% CI, 18.6 to 28.8)
MRD assessed by flow cytometry, with negativity defined according to ELN guidelines

Konopleva M et al. ASH 2020

Treatment-naïve *FLT3*m AML: LACEWING Study



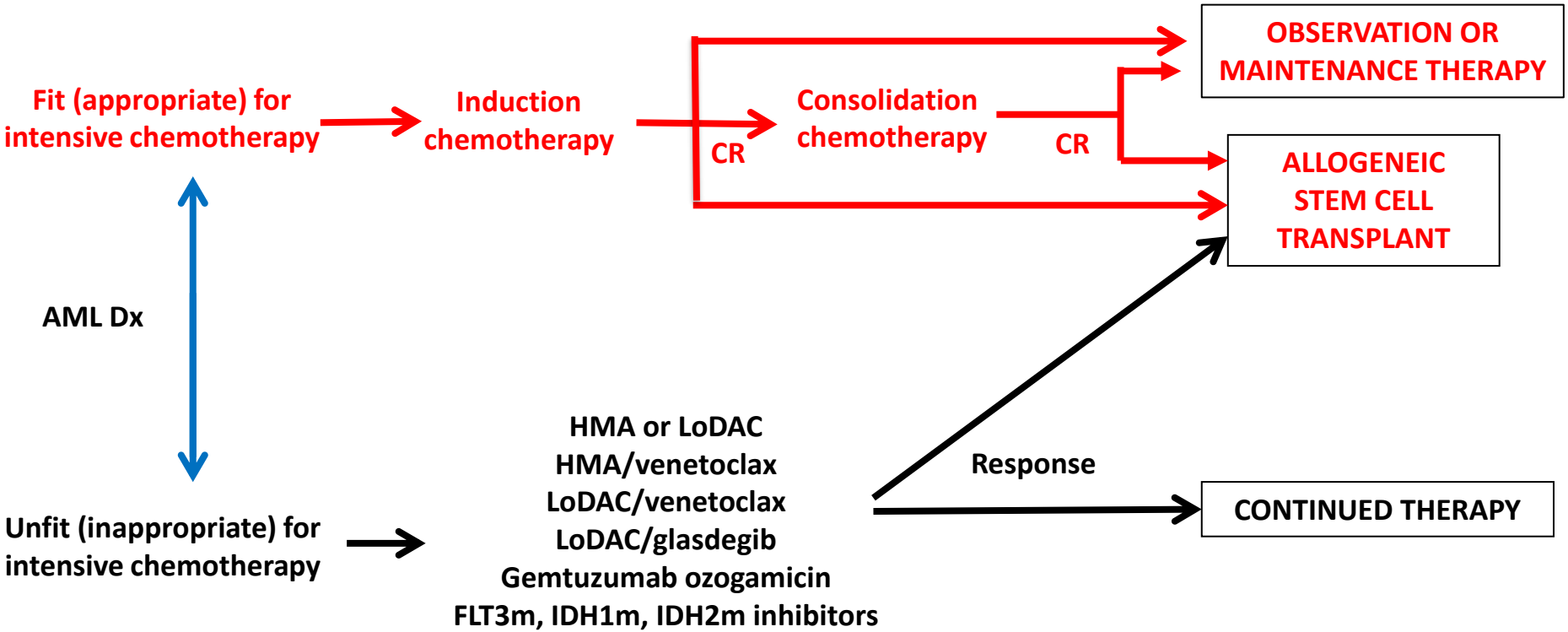
Arm A (Gilt alone) closed by sponsor.

Aza/Gilt CR 33% (5/15), CR/CRi 67% (10/15)

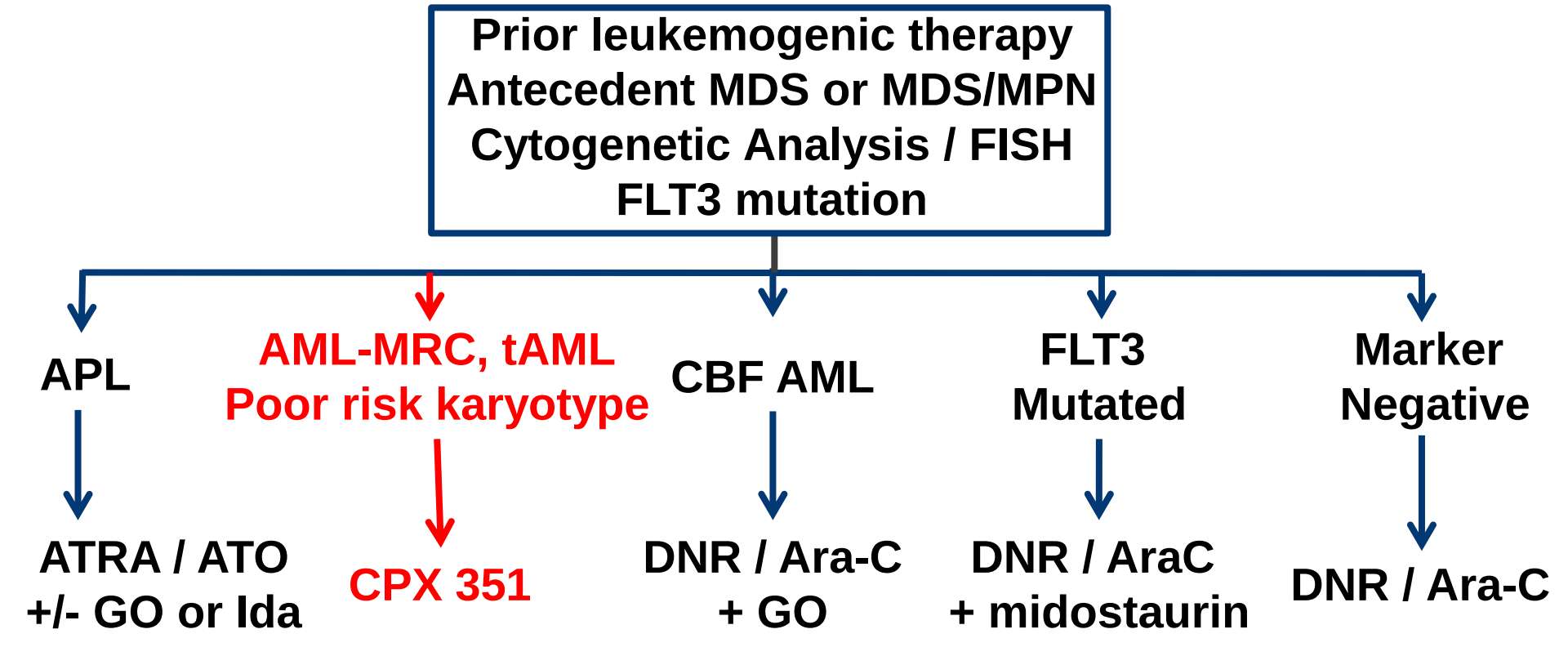
Trial stopped due to no survival difference between Aza/Gilt and Aza alone

Wang ES et al. *ASH Meeting 2020*, abstract 27

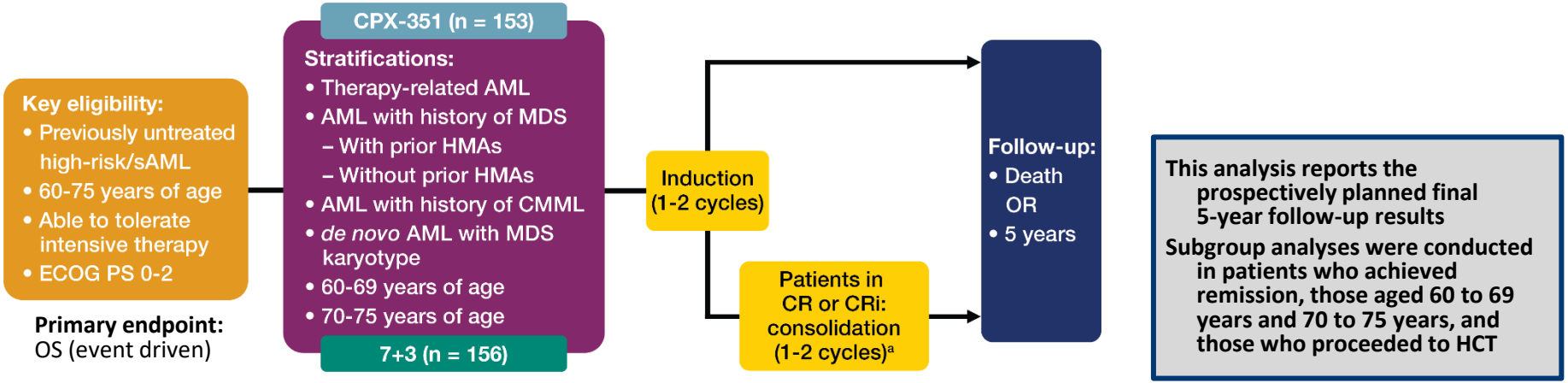
The Current AML Treatment Algorithm



Induction Therapy for IC-Eligible Adult AML



Randomized, Phase 3 Study of CPX-351 vs 7+3: Design



[a]Patients with documented complete remission (CR) or CR with incomplete neutrophil or platelet recovery (CRi) were eligible for consolidation if they had left ventricular ejection fraction of ≥50%, ECOG PS of 0-2, absolute neutrophil count recovered to >500/μL, and platelet count recovered to >50,000/μL. CR was defined as having bone marrow blasts <5%, absence of blasts with Auer rods, absence of extramedullary disease, absolute neutrophil count ≥1.0 × 10^9/L, platelet count ≥100 × 10^9/L, and independence from red cell transfusions; CRi was defined as having all CR criteria except residual neutropenia (<1.0 × 10^9/L) or thrombocytopenia (<100 × 10^9/L).

CPX-351[b]
Administered as a 90-minute infusion

Induction: 100 units/m^2 on Days 1, 3, and 5 (Days 1 and 3 for 2nd induction)
Consolidation: 65 units/m^2 on Days 1 and 3

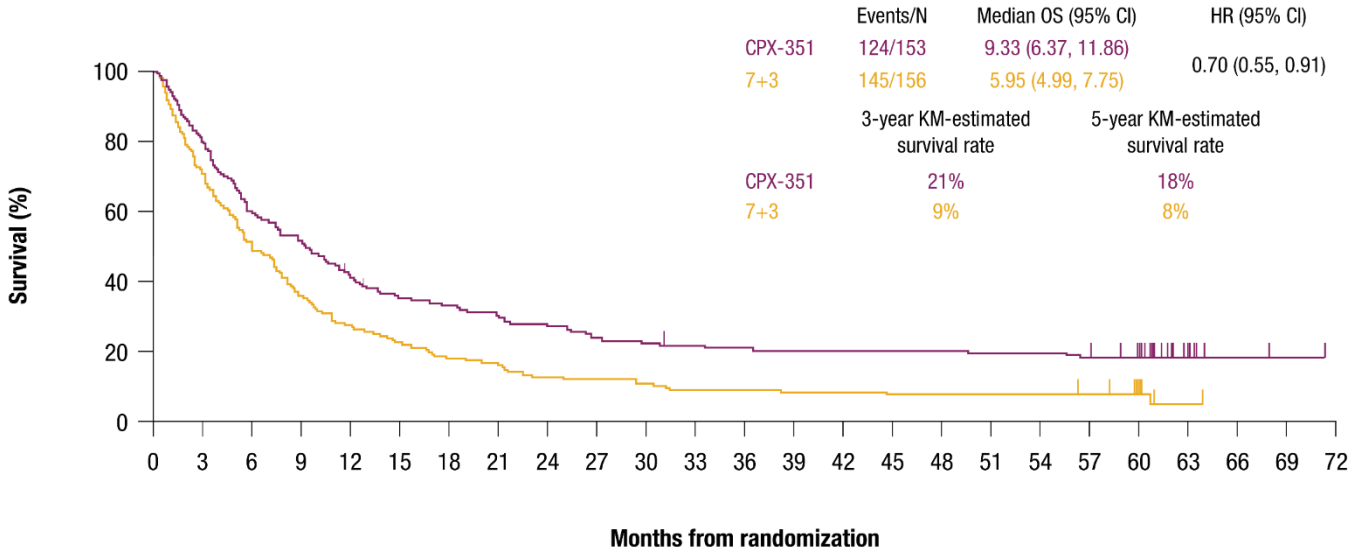
7+3
Cytarabine + daunorubicin

Cytarabine 100 mg/m^2/day continuous infusion + daunorubicin 60 mg/m^2/day
Induction: 7+3 schedule (5+2 for 2nd induction)
Consolidation: 5+2 schedule

[b]1 unit = 0.44 mg daunorubicin + 1 mg cytarabine.

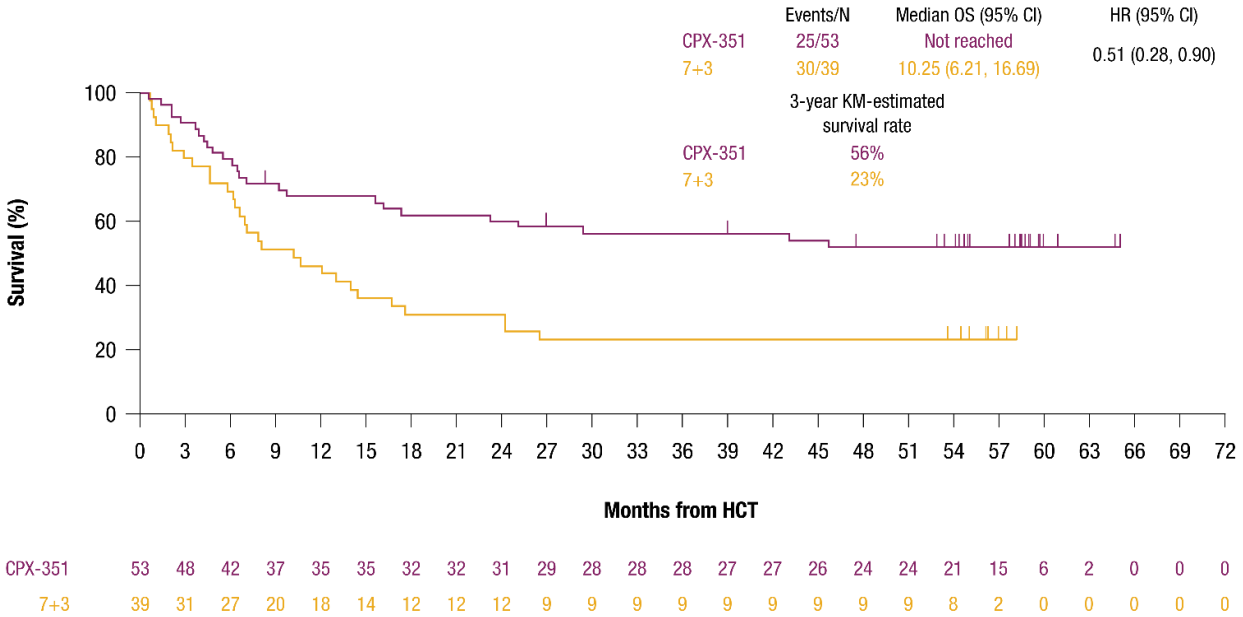
Lancet JE et al. *Lancet Haemat* 2021; 8(7): e481-491

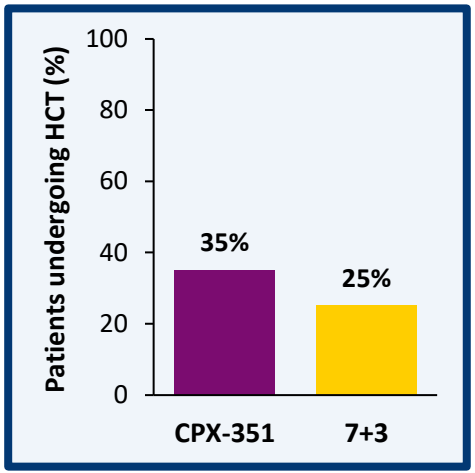
5 Year Update of the Phase 3 Study of CPX-351 vs 7+3: Overall Survival



Lancet JE et al. *Lancet Haemat* 2021; 8(7): e481-491

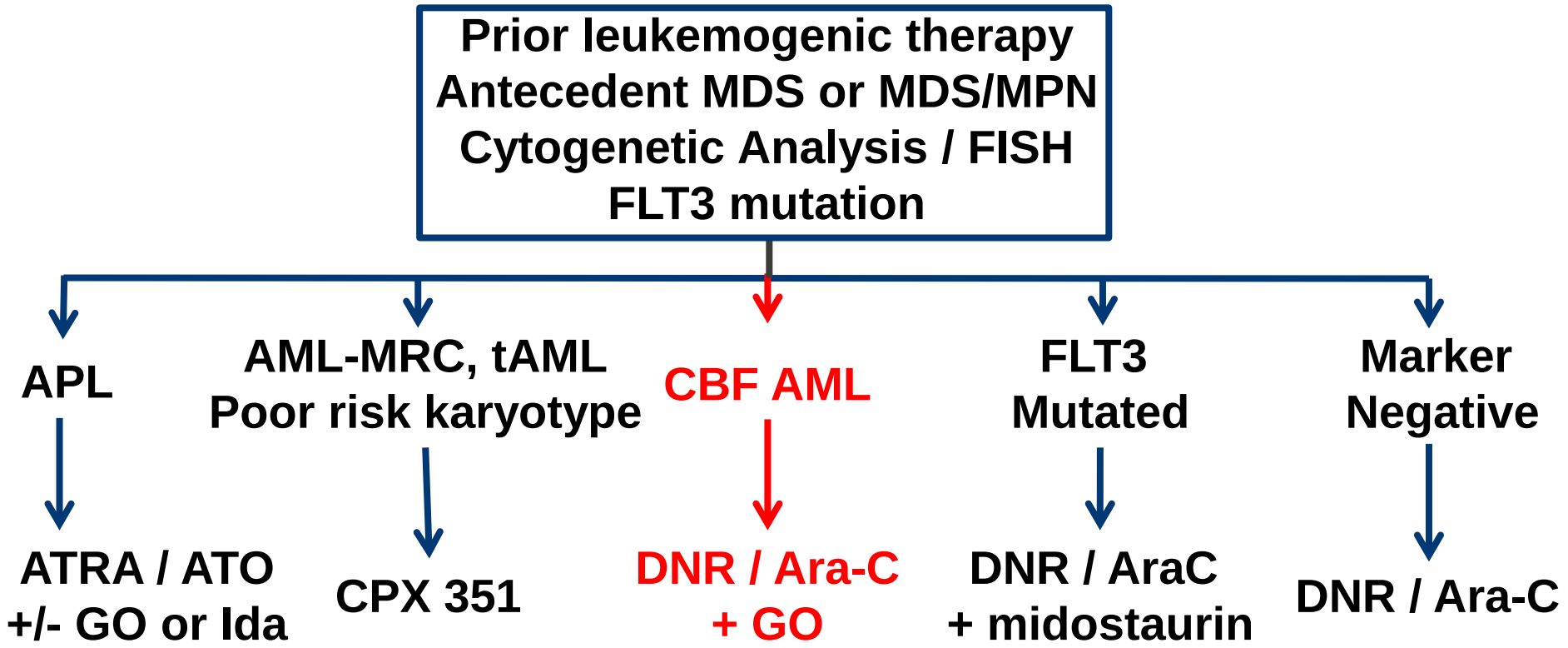
Phase 3 Study of CPX-351 vs 7+3: Overall Survival Landmark from HSCT





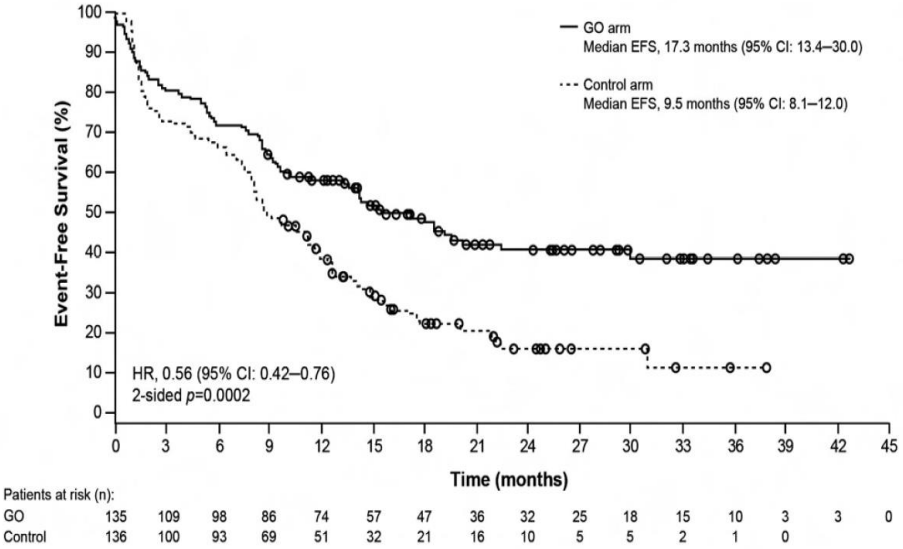
Lancet JE et al. *Lancet Haemat* 2021; 8(7): e481-491

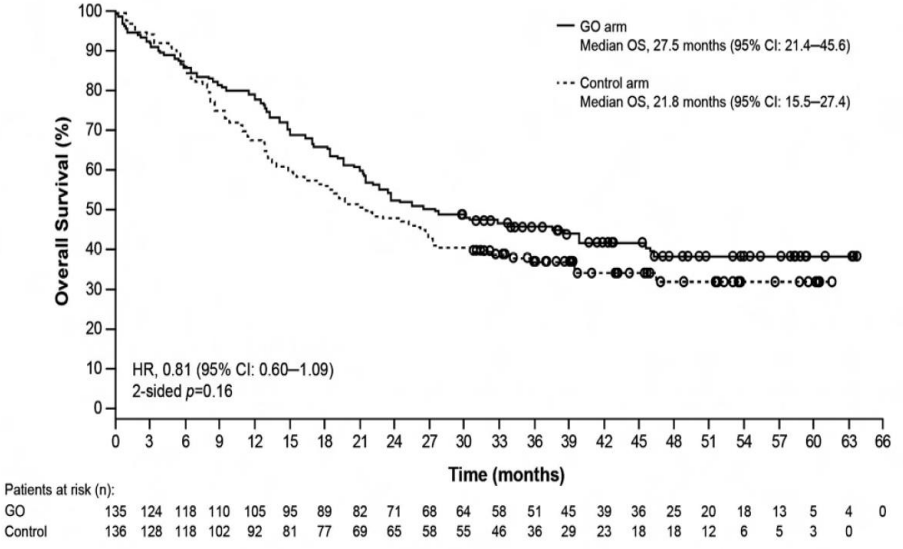
Induction Therapy for IC-Eligible Adult AML



ALFA 0701: Update Event free and Overall Survival

- 280 patients with treatment naïve *de novo* AML, age 50-70
- Induction: DNR 60 mg/m^2/d x 3 and Ara-C 200 mg/m^2/d x 7 +/- GO 3 mg/m^2 d 1, 4, 7
- Consolidation: DNR 60 mg/m^2 d 1 and Ara-C 1 gram/m^2 q12 hr d 1-4 +/- GO 3 mg/m^2 d 1
- Only 11 patients proceeded to allo HSCT in CR1 during consolidation



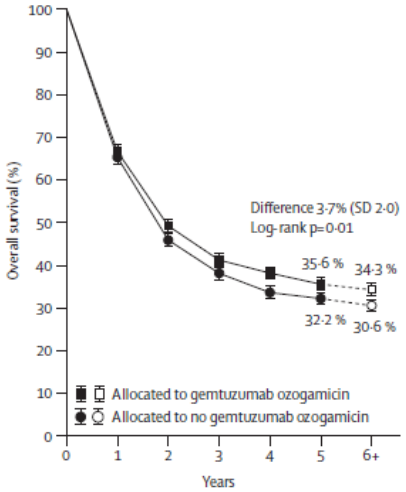


Lambert J, et al. *Haematologica* 2018

Addition of Gemtuzumab Ozogamicin (GO), an anti CD33 ADC, to AML Induction Chemotherapy

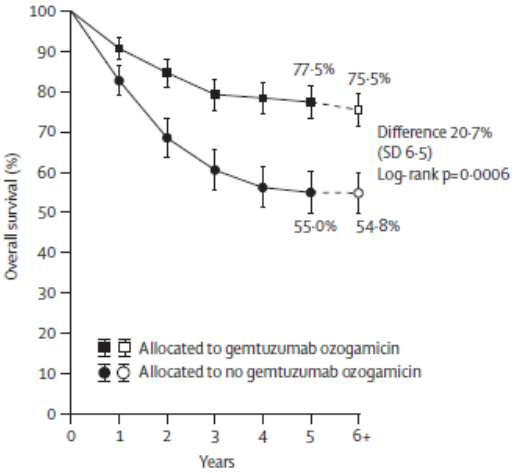
A Meta-Analysis of Data from 3325 Individual Patients in Phase 3 Studies of GO with chemotherapy

All



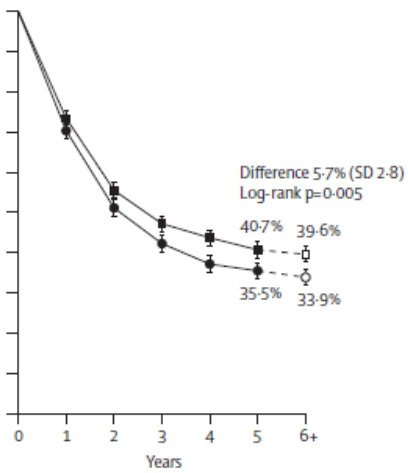
Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	26·7 % SD 0·8	3·5 % SD 0·8
No gemtuzumab ozogamicin	29·5 % SD 0·9	5·2 % SD 1·0

Favorable



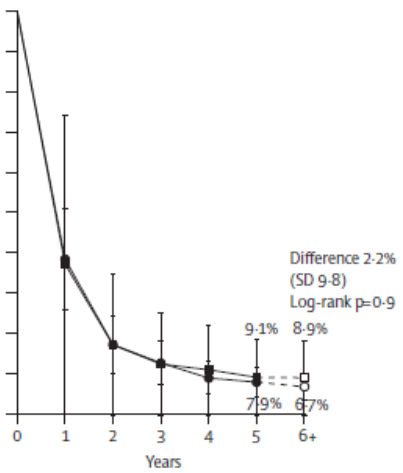
Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	5·8% SD 1·1	2·3% SD 1·3
No gemtuzumab ozogamicin	14·1% SD 1·9	0·0% SD 0·0

Intermediate



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

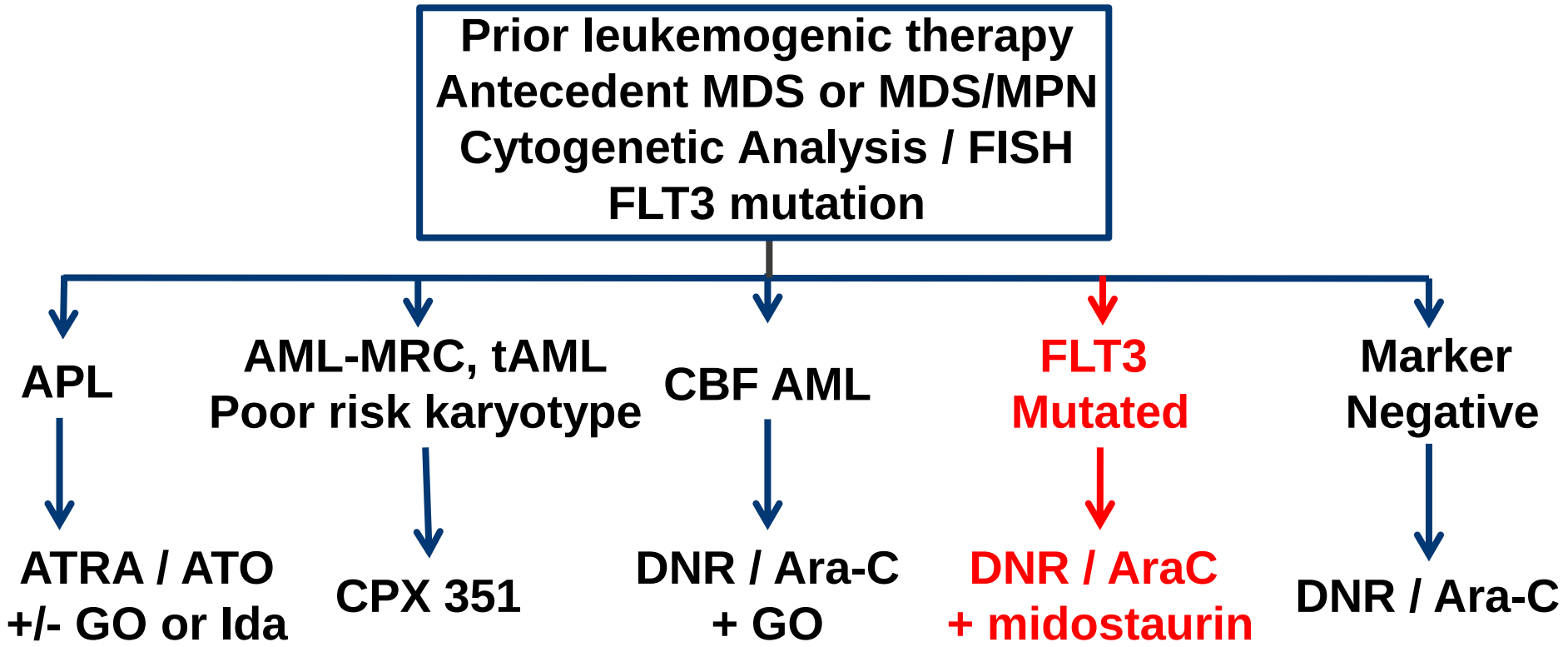
Poor Risk



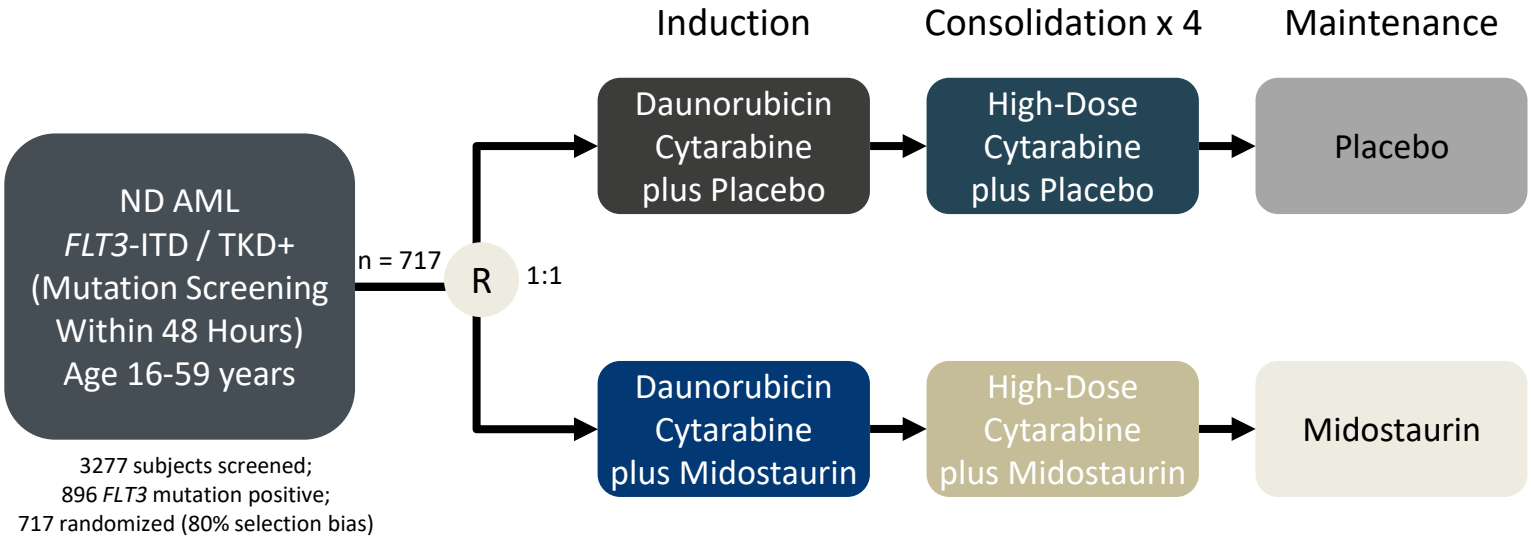
Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	73·8% SD 4·6	2·4% SD 2·4
No gemtuzumab ozogamicin	76·7% SD 4·8	21·1% SD 10·5

Hills RK et al. *Lancet Oncol* 2014; 15: 686-96.

Induction Therapy for IC-Eligible Adult AML



RATIFY (CALGB 10603): Chemotherapy + Midostaurin or Placebo Newly Diagnosed Patients < 60 Years With FLT3-Mutated AML

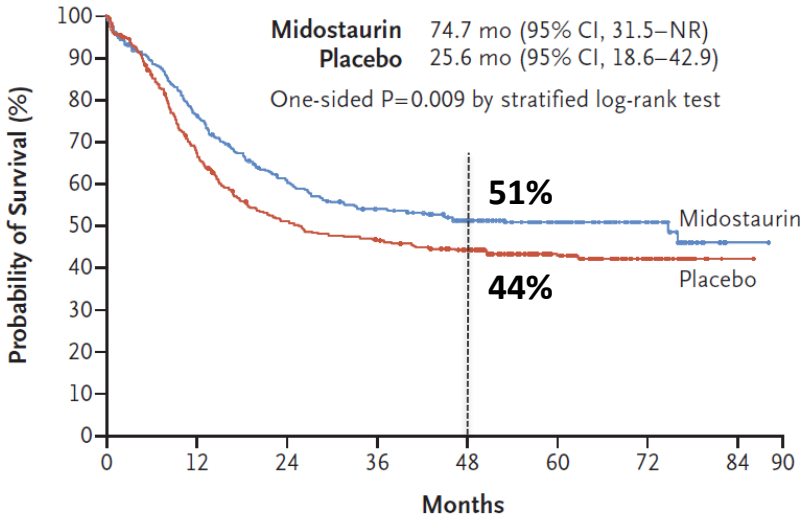


- Collaboration with 13 international cooperative groups; 225 sites from 17 countries
  - Alliance, SWOG, ECOG, NCIC CTG, GIMEMA, EORTC, AMLSG, SAL, OSHO, PETHEMA, CETLAM
  - 9 academic *FLT3* screening laboratories worldwide

Stone RM, et al. *N Engl J Med.* 2017;377:454-464.

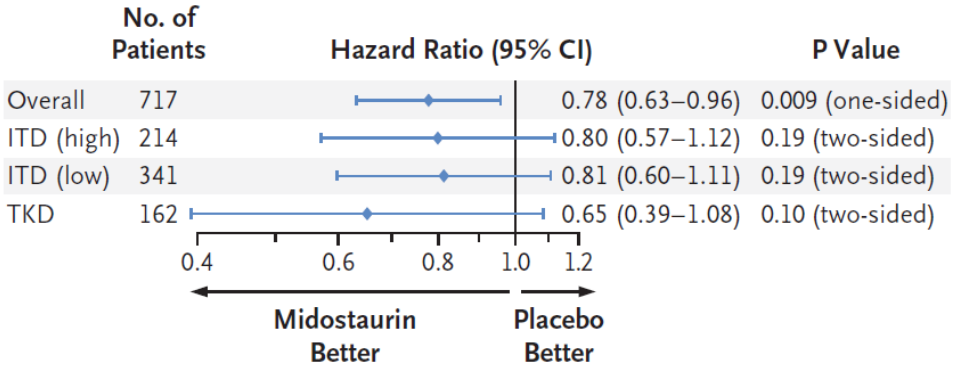
Chemotherapy plus Midostaurin/Placebo for Treatment-Naïve *FLT3*m AML: RATIFY (CALGB 10603)

Median OS



Stone RM, et al. *N Engl J Med.* 2017;377:454-464.

OS Subgroup Analysis



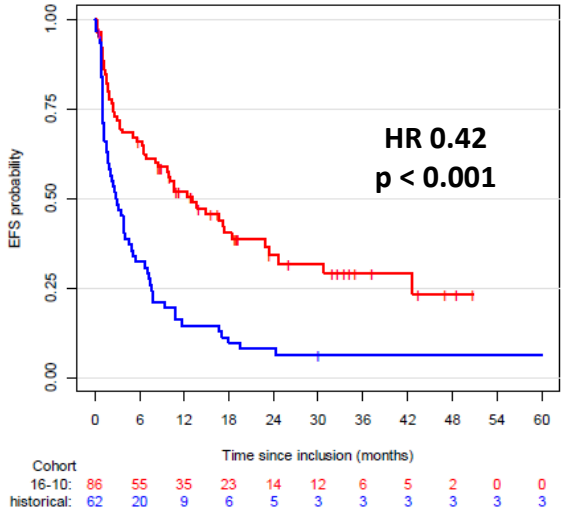
Toxicity

No difference in early mortality

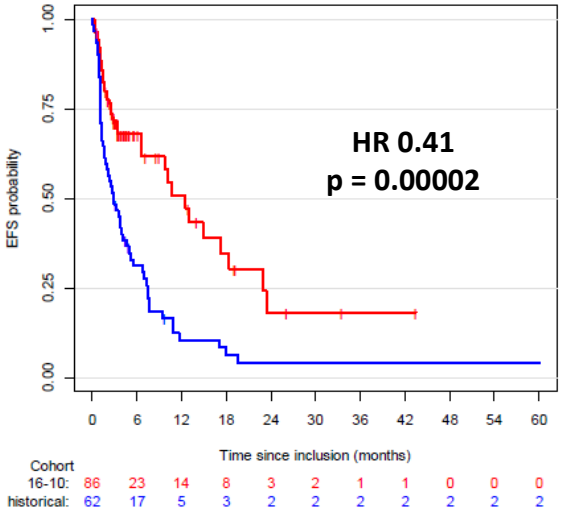
Higher rate of rash and anemia with mido

Chemotherapy/midostaurin for older FLT3 ITD + AML: Event free survival compared with historical controls

Age 61-70



Age 61-70, censor at HSCT

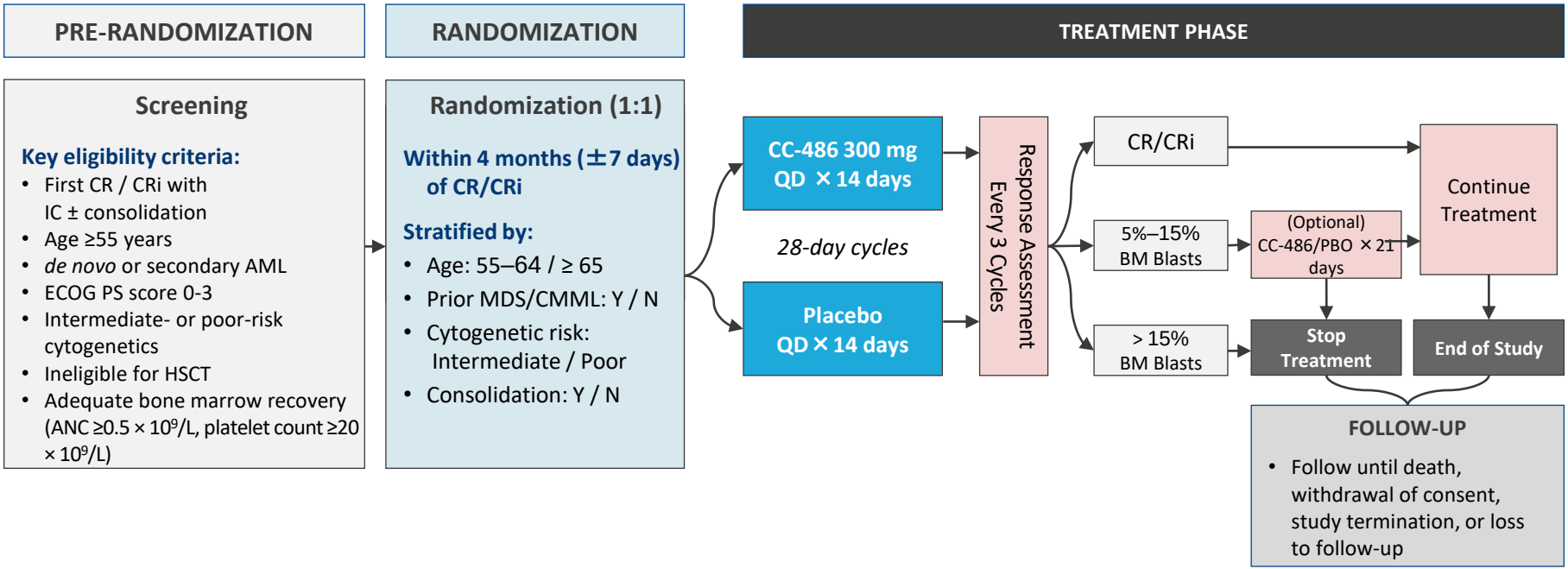


Induction: 7+3, midostaurin 50 mg bid day 8 -
Consolidation: Cytarabine bid days 1, 3, 5 (3 gm/m^2 age 61-65, 1 gram/m^2 age 66-70), midostaurin 50 mg bid day 6 -
Maintenance: Midostaurin 50 mg bid for 365 days (after consolidation or after allo HSCT)

Schlenk R, et al. *Blood* 2019; 133(8): 840-851

QUAZAR AML-001: Study design

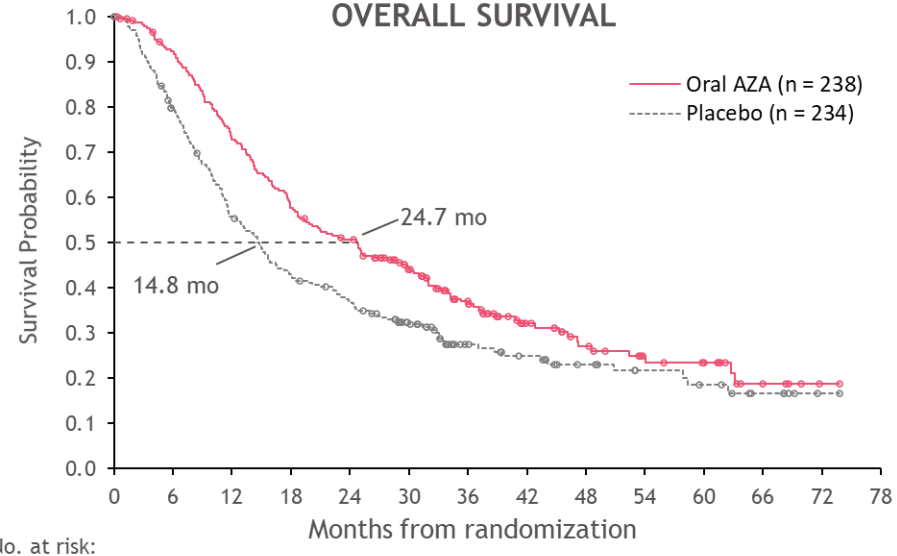
International, multicenter, placebo-controlled, double-blind, randomized, phase III study that enrolled patients from 148 sites in 23 countries (NCT01757535)

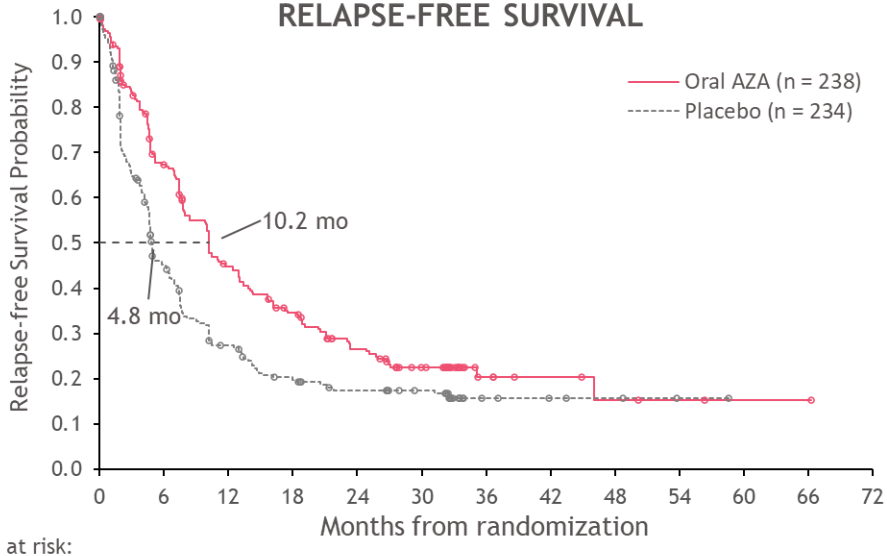


Wei A et al. *N Engl J Med* 2020; 383: 2526-37. Wei A et al. *Blood* 2019;134(Supplement2):LBA-3.

QUAZAR: Overall and Relapse-free Survival

Oral AZA 300 mg QD was associated with significantly improved overall survival (OS) (*P* = 0.0009) and relapse-free survival (RFS) (*P* = 0.0001) vs. PBO

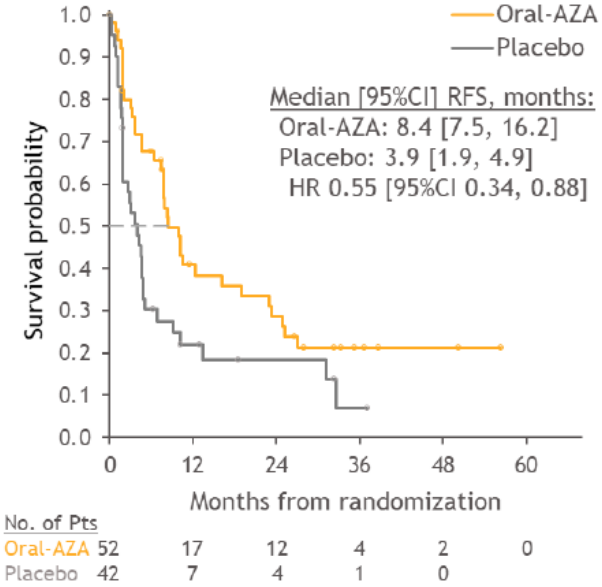




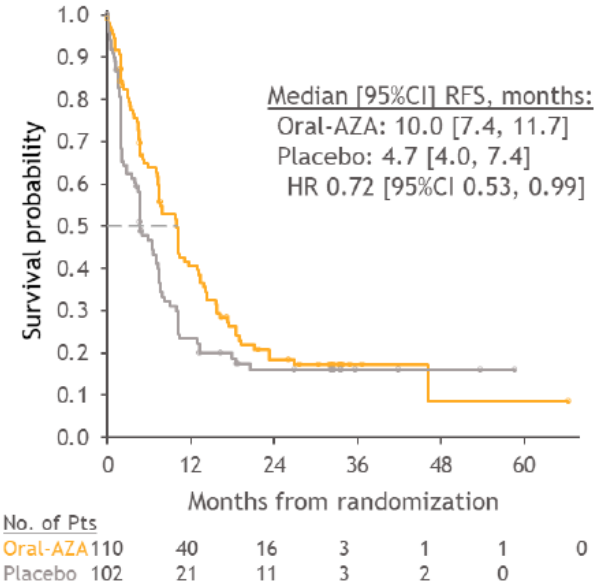
Wei A et al. *N Engl J Med* 2020; 383: 2526-37. Wei A et al. *Blood* 2019;134(Supplement2):LBA-3.

QUAZAR AML-001: RFS by Number of Consolidation Cycles

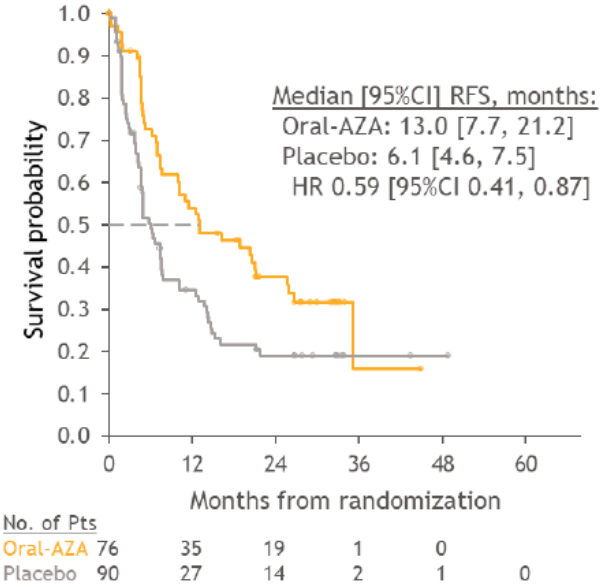
No Consolidation



1 Consolidation



≥2 Consolidations

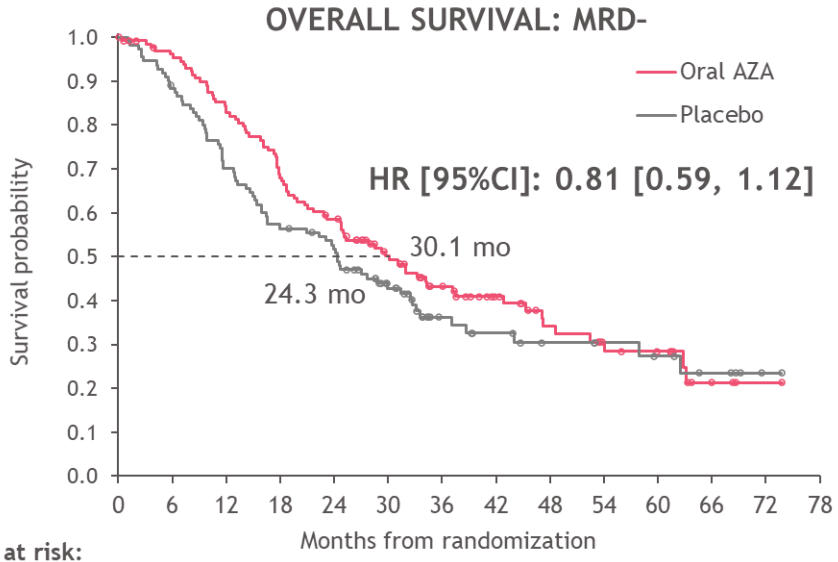


*RFS estimates were derived using Kaplan–Meier methods and compared for Oral-AZA vs. placebo using log-rank test. Hazard ratios (HRs) and 95% CIs were generated using a stratified Cox proportional hazards model.

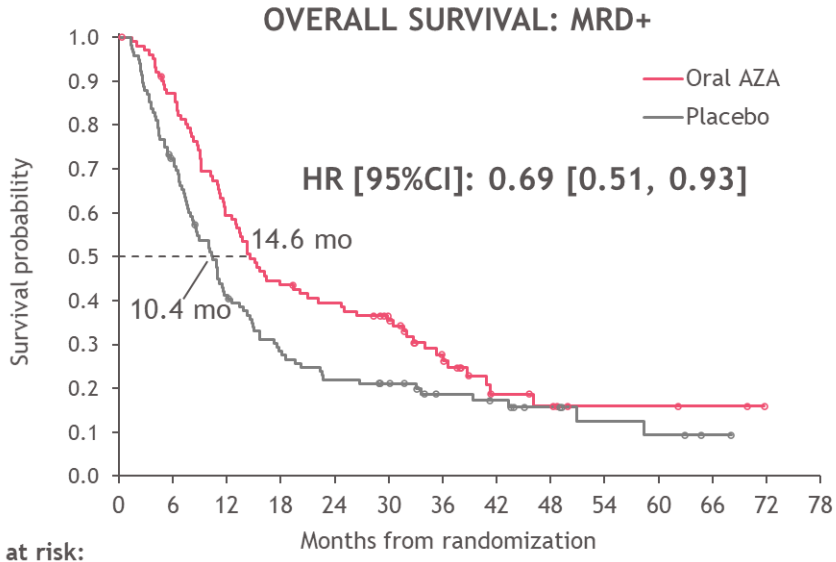
Wei A, et al. ASH 2020. Abstract 1036

QUAZAR: Overall survival by baseline MRD status and treatment arm

Treatement with Oral AZA (CC-486) resulted in improved OS from time of randomization compared with PBO in pts who were MRD+ or MRD– at study entry



No. at risk:														
Oral AZA	133	123	106	87	74	54	39	28	19	14	11	3	1	0
Placebo	111	97	77	62	55	37	20	16	12	10	8	5	1	0

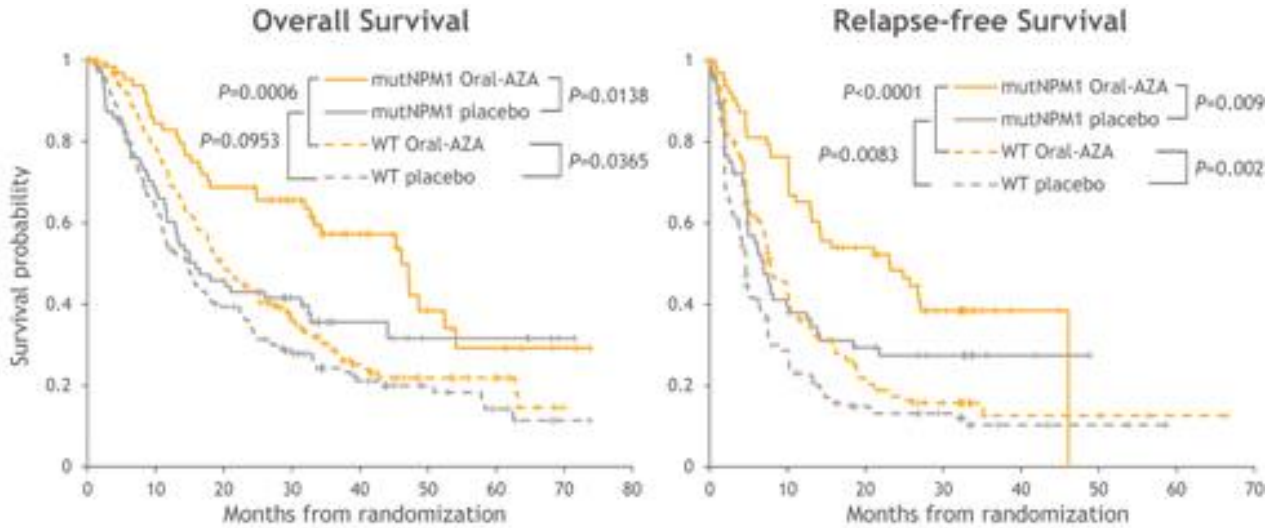


No. at risk:														
Oral AZA	103	88	60	44	39	31	19	8	6	3	3	2	0	
Placebo	116	82	46	31	24	20	13	11	7	4	3	1	0	

Roboz GR et al. ASH 2020; abstract 692

QUAZAR: Effect of AZA/PBO on OS and RFS by NPM1 mutation status

	Median OS (months)			Median RFS (months)		
	AZA	PBO	p	AZA	PBO	p
NPM1 mutated	46.1	15.9	0.0138	23.2	6.9	0.0098
NPM1 wild type	19.6	14.6	0.0365	7.7	4.6	0.0029



Dohner H, et al. EHA 2021, abstract S131

QUAZAR: Safety

- Gastrointestinal adverse events (AEs) in the CC-486 arm were most common during the first 2 treatment cycles
- Serious AEs were reported for 34% and 25% of patients in the CC-486 and placebo arms, respectively
- No treatment-related deaths

Preferred term	CC-486 n = 236		Placebo n = 233	
	All Grades	Grade 3–4	All Grades	Grade 3–4
	n (%)			
Patients with ≥1 AE	**231 (98)**	**169 (72)**	**225 (97)**	**147 (63)**
Gastrointestinal				
Nausea	153 (65)	6 (3)	55 (24)	1 (0.4)
Vomiting	141 (60)	7 (3)	23 (10)	0
Diarrhea	119 (50)	12 (5)	50 (22)	3 (1)
Constipation	91 (39)	3 (1)	56 (24)	0
Hematologic				
Neutropenia	105 (45)	97 (41)	61 (26)	55 (24)
Thrombocytopenia	79 (34)	53 (23)	63 (27)	50 (22)
Anemia	48 (20)	33 (14)	42 (18)	30 (13)
Other				
Fatigue	70 (30)	7 (3)	45 (19)	2 (1)
Asthenia	44 (19)	2 (1)	13 (6)	1 (0.4)
Pyrexia	36 (15)	4 (2)	44 (19)	1 (0.4)
Cough	29 (12)	0	39 (17)	0

Adverse events reported in ≥15% of patients in either arm

Wei A et al. *N Engl J Med* 2020; 383: 2526-37.
Wei A et al. *Blood* 2019;134(Supplement2):LBA-3.

Treatment of AML in Adults

- First, determine the goal of therapy based on patient's clinical status, disease biology, and wishes.
- Some older patients may be cured with time-limited therapy without allo HSCT.
  - Oral azacitidine maintenance therapy delays relapse and can improve survival.
- Older patients may be candidates for allo HSCT after either intensive or less intensive therapies.
- HMA/venetoclax has changed the treatment options for older AML patients.
  - Clinical trials with anti CD47 antibodies, IDHm inhibitors, FLT3m inhibitors, and other targeted therapies may further improve the outcome of these patients