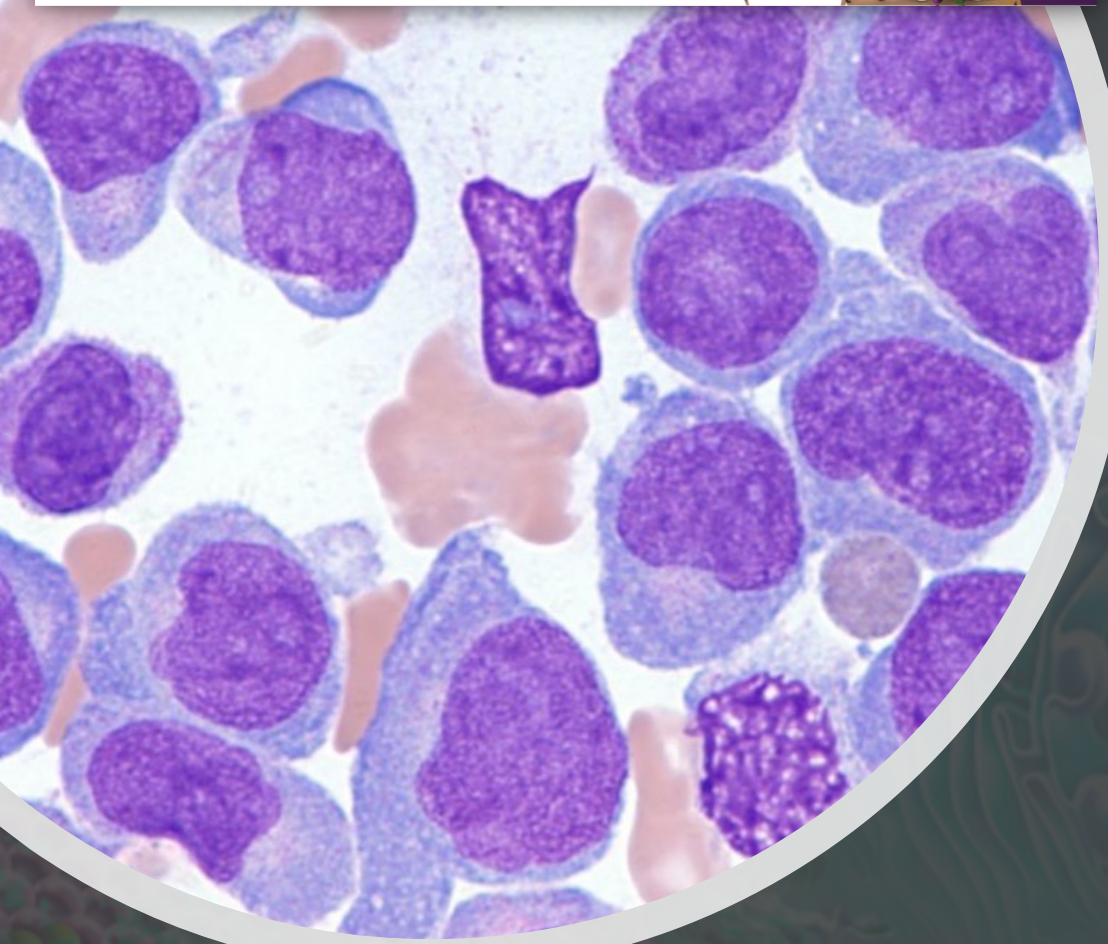


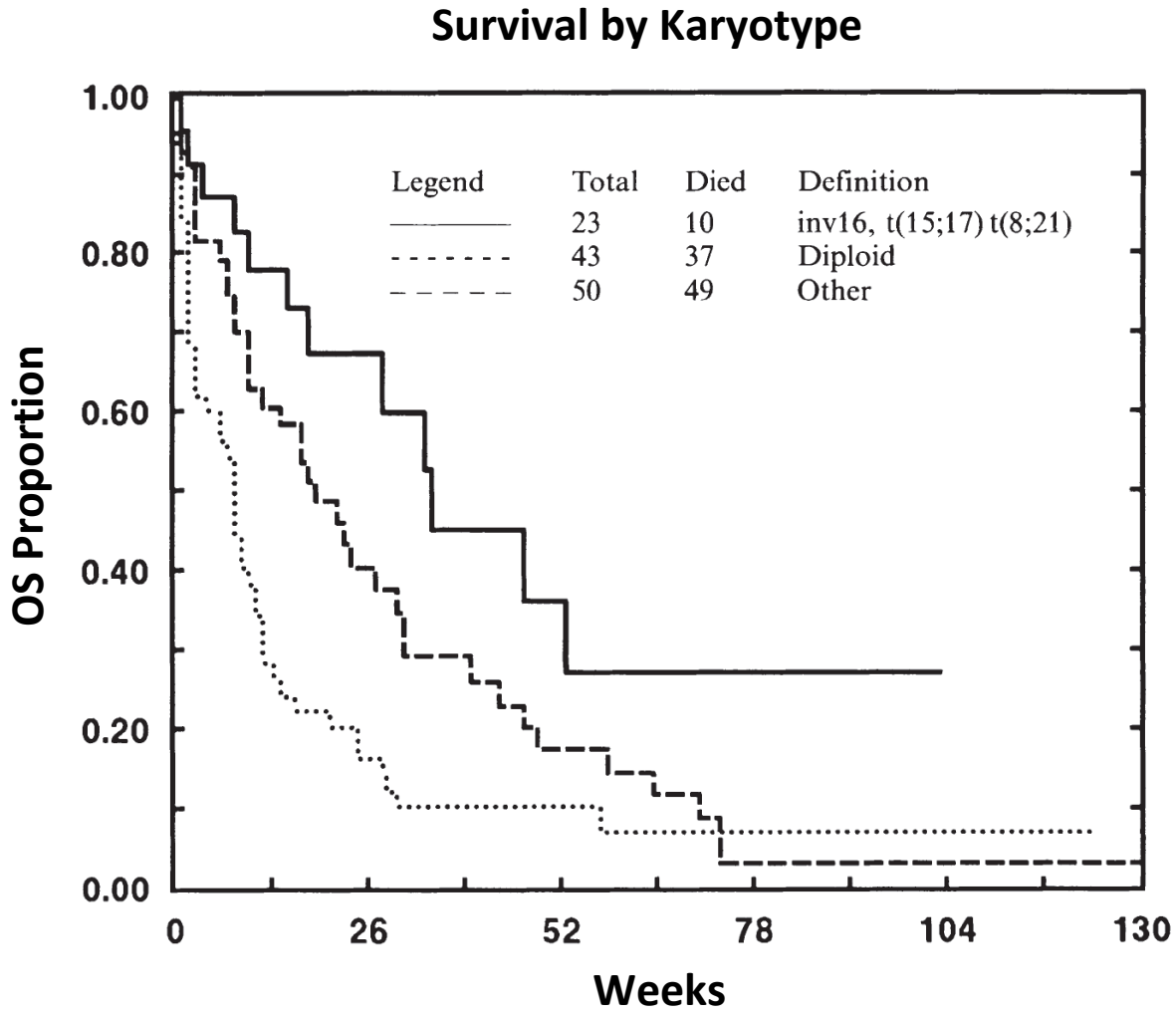
De Novo AML:
An Era of Novel Agents

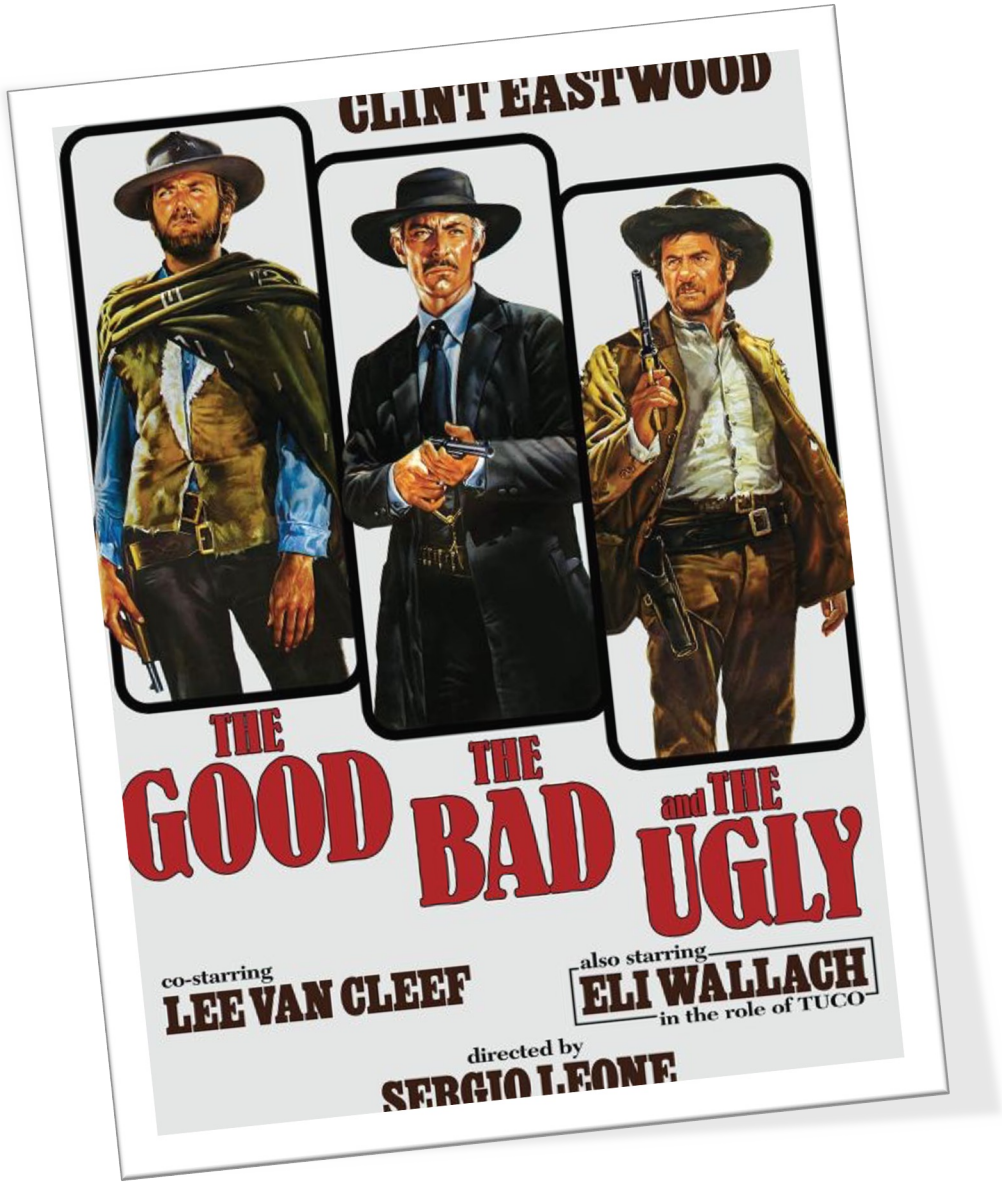
Alexis M. Cruz-Chacon, MD FACP

Hematology and Medical Oncology

Adult Blood and Marrow Transplantation

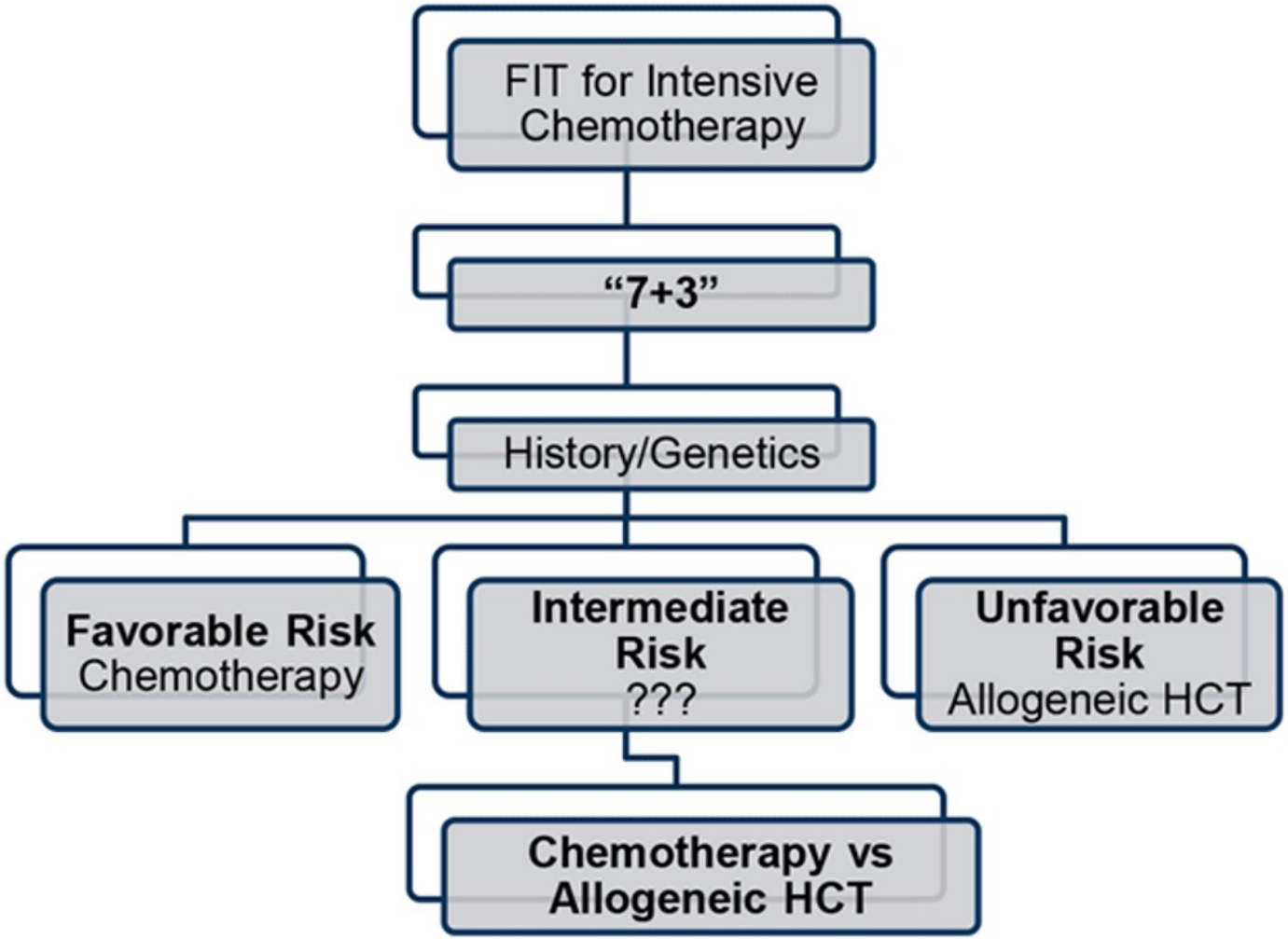
Where It All Began!

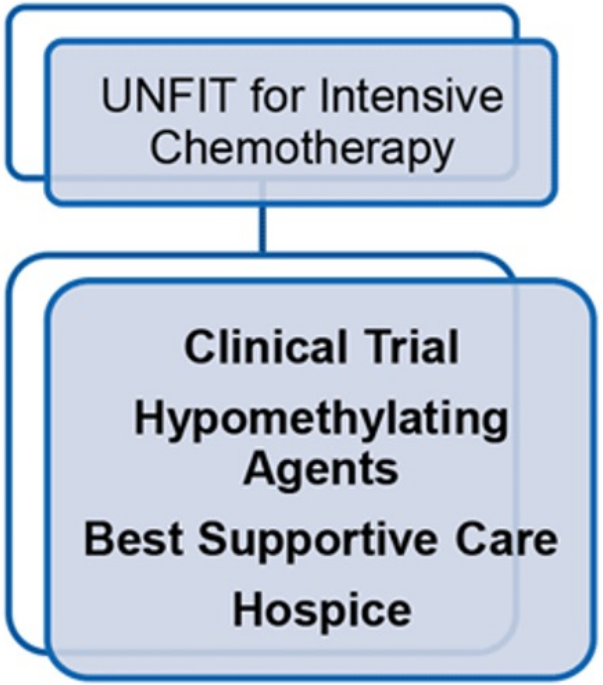




Keating. Haematol Blood Transfus. 1990;33:593.

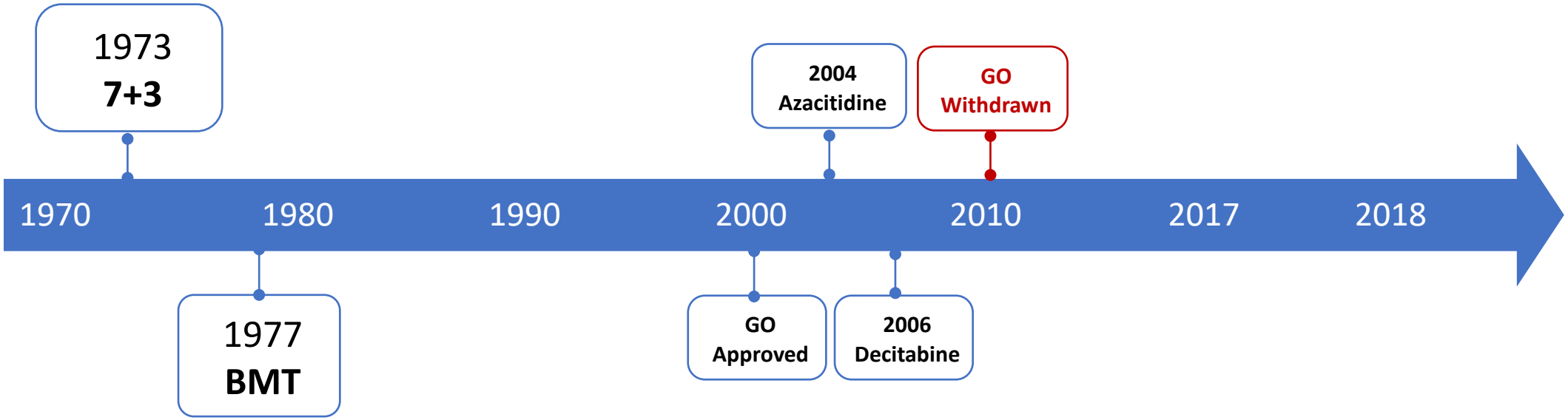
Traditional Approaches to AML therapy





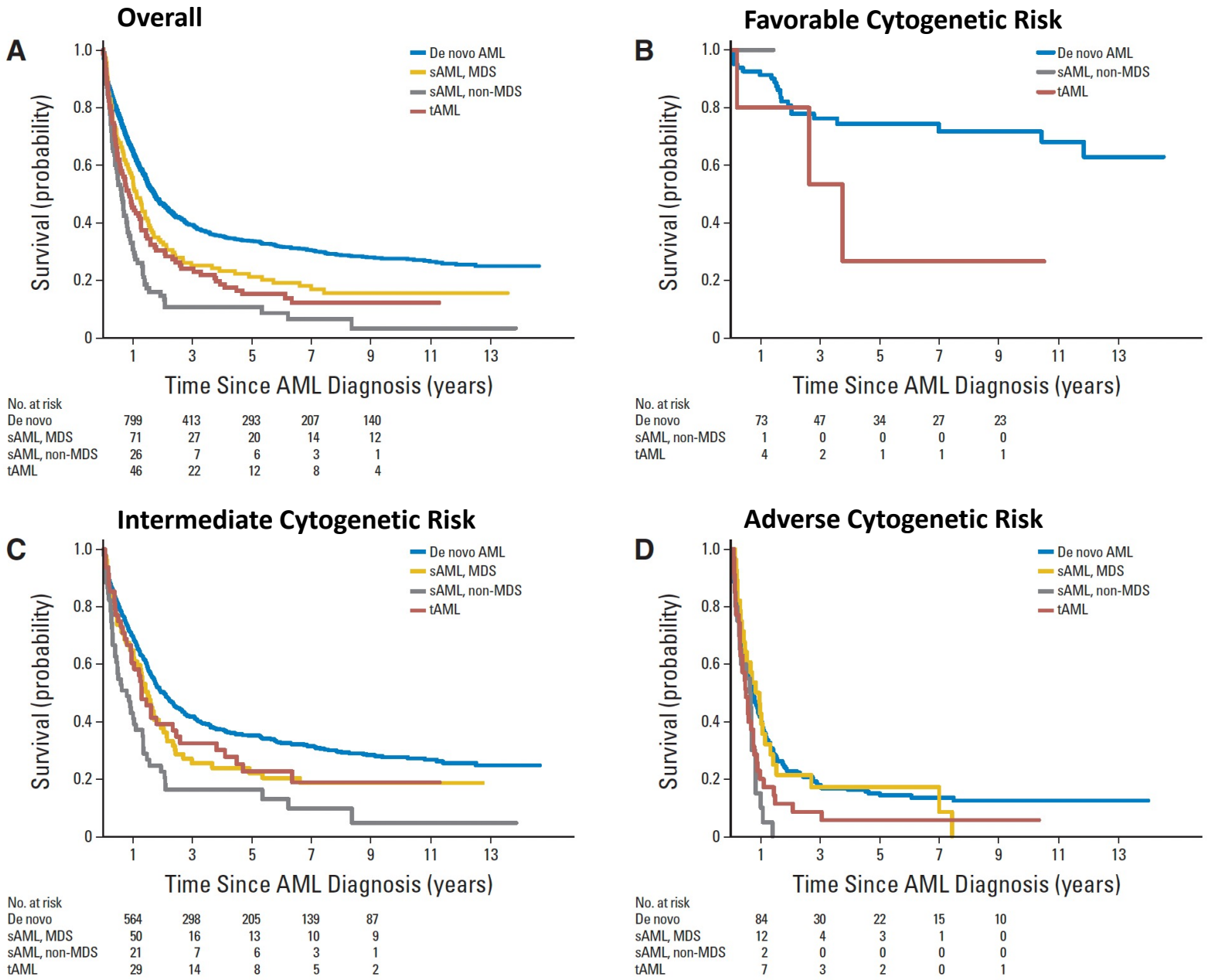
1. Scheinberg DA et al. In: DeVita VT, Jr. et al, eds. *Cancer: Principles and Practice of Oncology*. 5th ed. Philadelphia, PA: Lippincott-Raven; 1997:2293-2321.
2. https://medlineplus.gov/acutemyeloidleukemia.html.

AML Treatment Landscape: PAST



Outcome of Patients With AML after Intensive Therapy

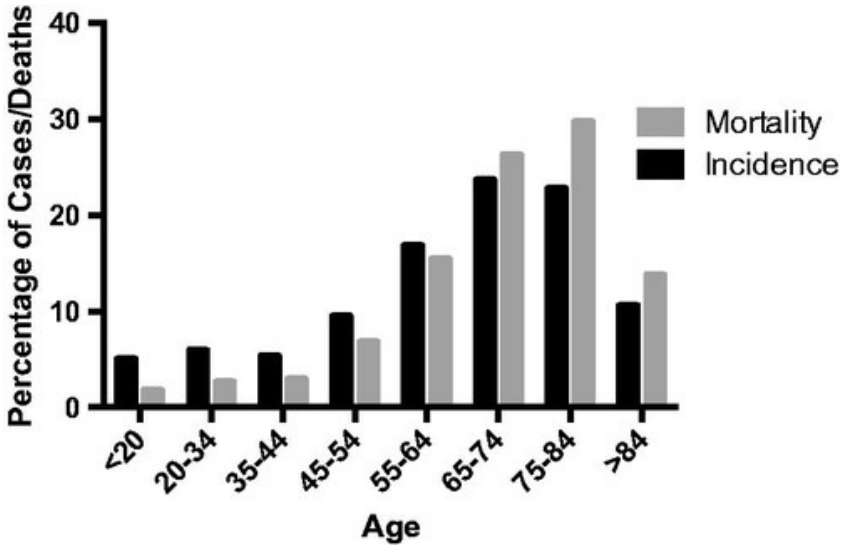
Disease and Risk Group	CR (%)	Crude OR (95% CI)	Adjusted OR* (95% CI)
All patients			
De novo AML	75	1	1
MDS-sAML	59	0.47 (0.32 to 0.67)	0.55 (0.35 to 0.85)
Non-MDS-sAML	54	0.39 (0.25 to 0.60)	0.48 (0.29 to 0.81)
tAML	61	0.51 (0.33 to 0.77)	0.58 (0.34 to 0.99)
Favorable risk†			
De novo AML	91	NA	NA
MDS-sAML	0	NA	NA
Non-MDS-sAML	100	NA	NA
tAML	100	NA	NA
Intermediate risk			
De novo AML	79	1	1
MDS-sAML	62	0.44 (0.27 to 0.71)	0.49 (0.29 to 0.82)
Non-MDS-sAML	57	0.35 (0.20 to 0.62)	0.53 (0.28 to 0.97)
tAML	75	0.81 (0.41 to 1.58)	0.66 (0.30 to 1.42)
Adverse risk			
De novo AML	63	1	1
MDS-sAML	57	0.79 (0.35 to 1.75)	0.73 (0.31 to 1.68)
Non-MDS-sAML	35	0.32 (0.12 to 0.83)	0.33 (0.12 to 0.90)
tAML	43	0.44 (0.21 to 0.91)	0.43 (0.18 to 1.02)

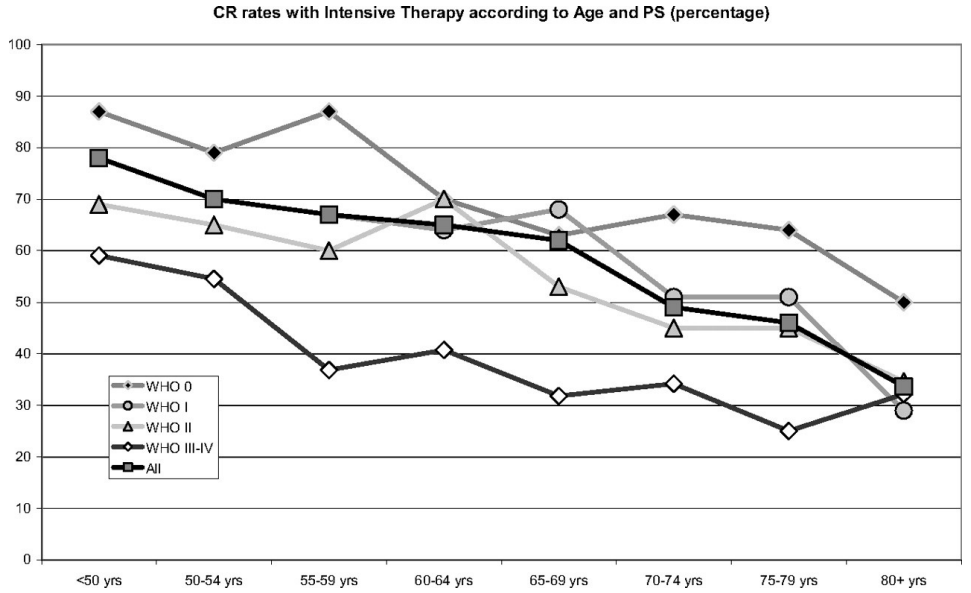


Granfeldt Østgård. JCO. 2015;33:3641.

Older patients do poorly with Intensive Therapy

Age group	Complete remission rate (with "3&7"-like regimens)	Early mortality	Disease-free survival	Long-term overall survival	Median survival
<60 years	70%	10%	45%	30%	24 months
≥60 years	45%	>25%	<20%	10%	10 months





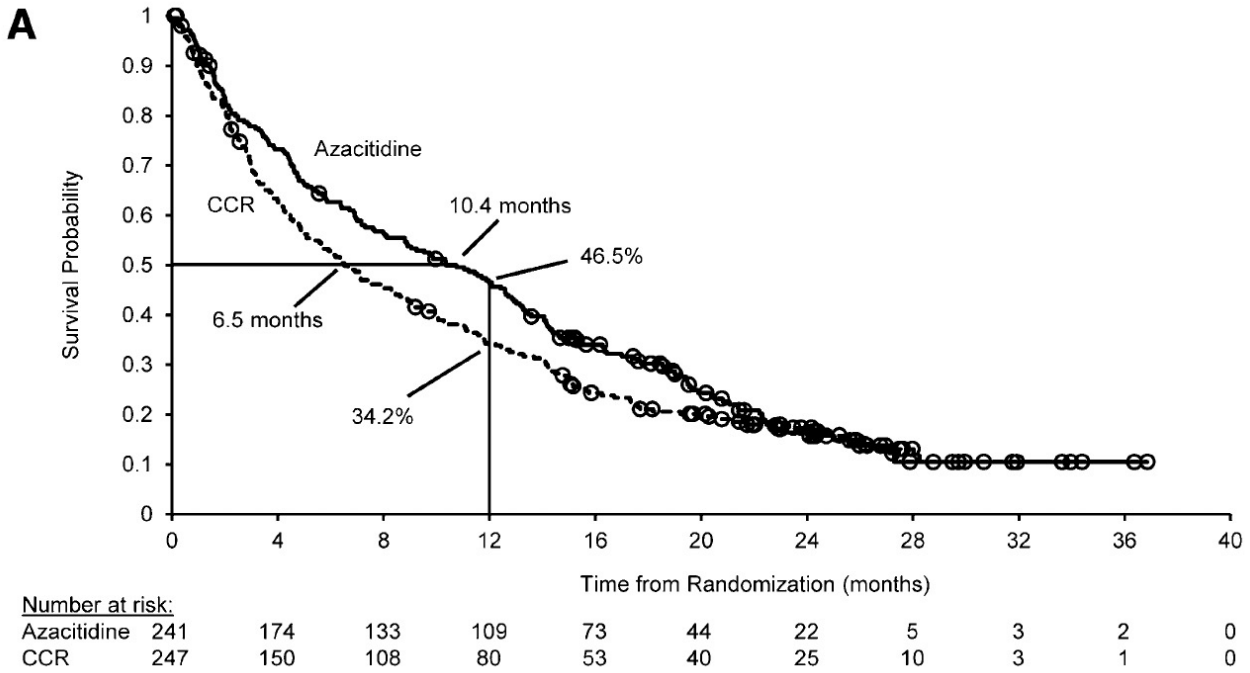
- Poor organ function / comorbidities
- Antecedent hematologic disorders
- Unfavorable risk factors

Gunnar Juliusson et al. Blood 2009;113:4179-4187

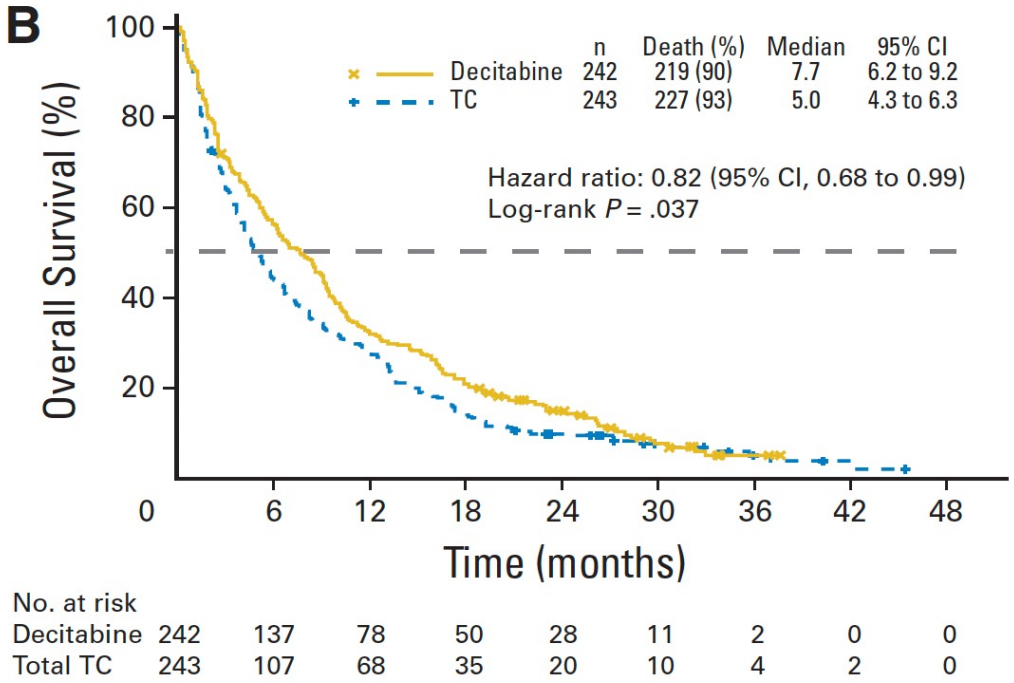
Treatments options for older patients with AML (≥65 years)

Ineligible for Intense Therapy

Azacitidine
75 mg/m^2 IV/SQ x 7 days



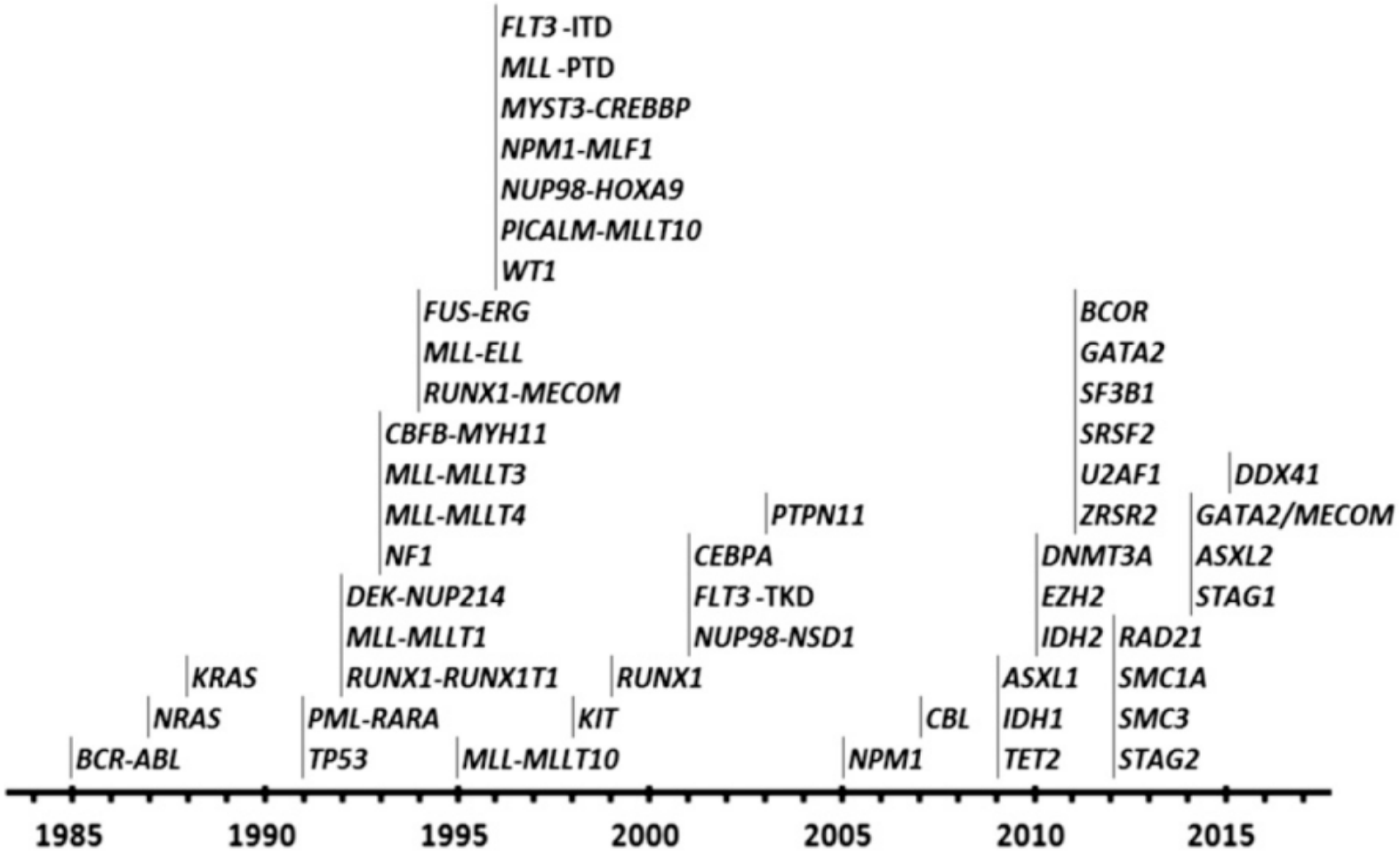
Decitabine
20 mg/m^2 IV x 5 days



Regimen	CR/CRi, %	mOS, Mos	OS Rate, %
Azacitidine[2]	27.8	10.4	At 1 yr: 46.5
Decitabine[3]	17.8	7.7	NR

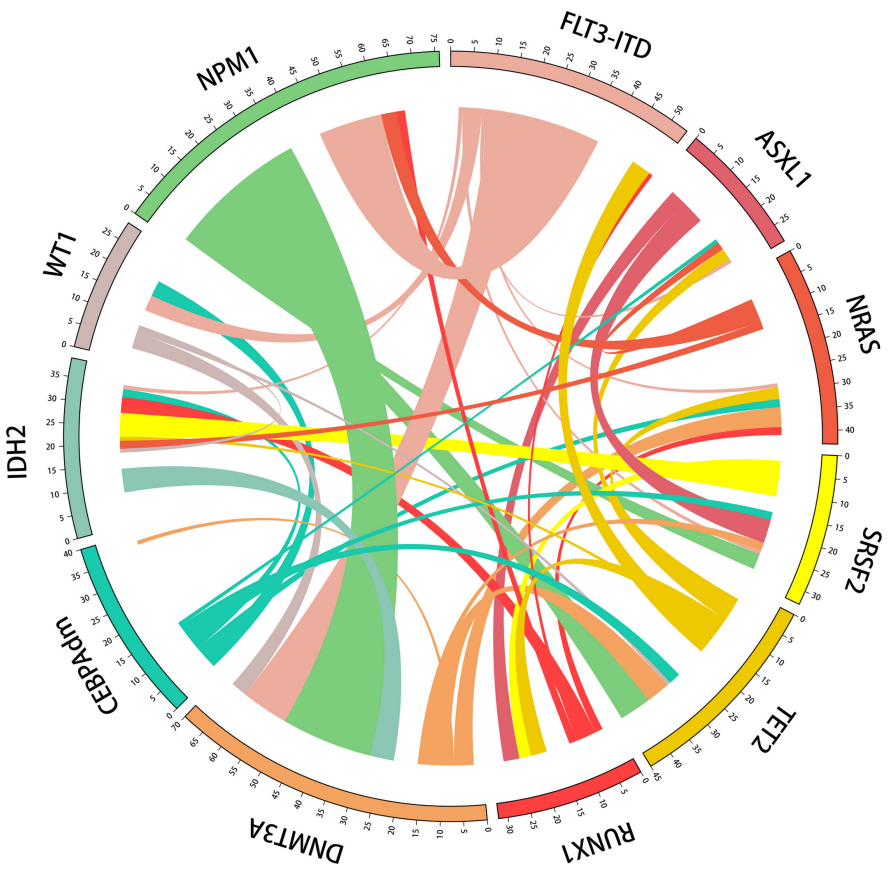
1. Dombret. Blood. 2015;126:291.
2. Kantarjian. JCO. 2012;30:2670.

Timeline of Genetic and Molecular Landscape in AML



Grimwade. Blood. 2016;127:29.

Prognostic relevance of individual mutations in AML



Mutation	Frequency in CN-AML	Mode of action	Prognosis
NPM1	30-45%	Nucleolar component	Favorable
DNMT3A	34%	*De novo* DNA methylation	Inconclusive
FLT3-ITD	28-34%	Receptor tyrosine kinase for FLT3 ligand	Unfavorable
FLT3-TKD	11-14%	Receptor tyrosine kinase for FLT3 ligand	Neutral
IDH1 and *IDH2*	15-30%	Conversion of isocitrate to α-ketoglutarate	Favorable
TET2	10%	Conversion of 5 methylcytosine to 5-hydroxy-methylcytosine, mediating demethylation	Inconclusive
ASXL1	5-16%	Epigenetic regulation by interaction with PRC2	Unfavorable
CEBPA	10-18%	Hemopoietic transcription factor	Favorable
RAS	25% *NRAS*, 15% *KRAS*	G-Protein associated with receptor tyrosine kinases	Neutral
KIT	20-30% of CBF AML	Receptor tyrosine kinase for stem cell factor	Unfavorable
MLL-PTD	5-10%	20-30% of CBF AML	Unfavorable
RUNX1	5-13%	Hemopoietic transcription factor	Unfavorable

CLINICAL RELEVANCE: Prognostic value, Therapeutic targets, Markers for MRD

Medinger *et al*: CANCER GENOMICS & PROTEOMICS *13*: 317-330 (2016).
Grimwade. Blood. 2016;127:29.

Where we are Know!

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2022
Acute Myeloid Leukemia (Age ≥18 years)

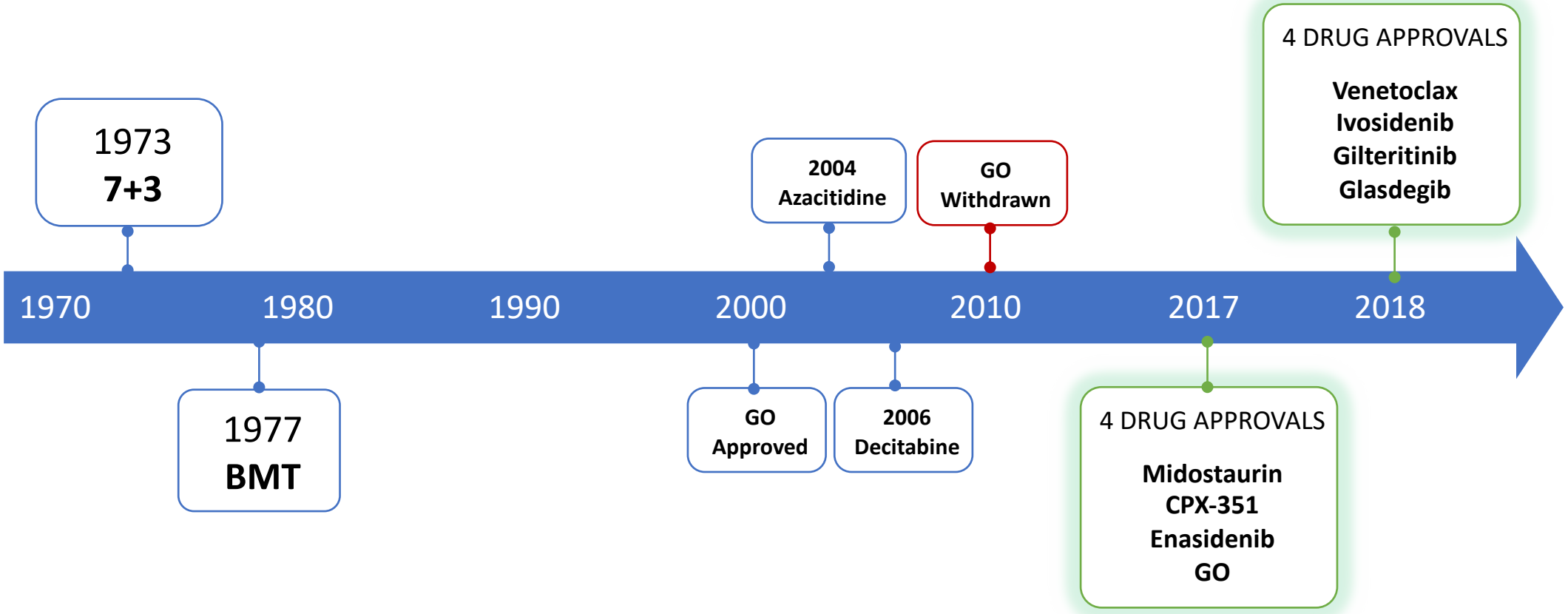
RISK STRATIFICATION BY GENETICS IN NON-APL AML[1,2]

Risk Category*	Genetic Abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Biallelic mutated *CEBPA* Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}†
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}† Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† (without adverse-risk genetic lesions) t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡ Cytogenetic abnormalities not classified as favorable or adverse
Poor/Adverse	t(6;9)(p23;q34.1); *DEK-NUP214* t(v;11q23.3); *KMT2A* rearranged t(9;22)(q34.1;q11.2); *BCR-ABL1* inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)* -5 or del(5q); -7; -17/abn(17p) Complex karyotype,§ monosomal karyotype‖ Wild-type *NPM1* and *FLT3*-ITD^{high}† Mutated *RUNX1*¶ Mutated *ASXL1*¶ Mutated *TP53*#

[1] Dohner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 2017;129:424-447.
[2] Frequencies, response rates, and outcome measures should be reported by risk category, and, if sufficient numbers are available, by specific genetic lesions indicated.

AML Treatment Landscape: PRESENT

SINCE 2017, WE HAVE SEEN THE FDA APPROVAL OF MORE THAN 8 NEW DRUGS FOR AML



FUTURE OF AML CARE	Better approaches to induction in fit patients. Better options for challenging subgroups: Older, tAML, sAML, TP53 Better therapeutic options for R/R disease

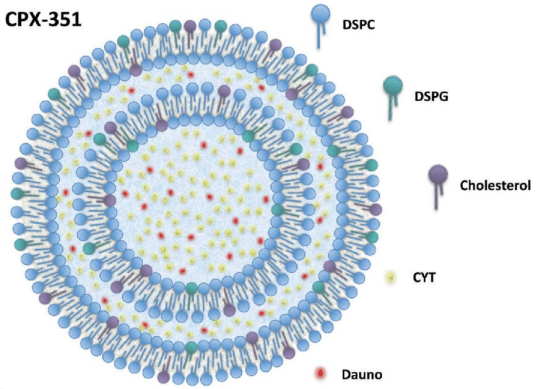
Case 1 and 2: Older Patient with t-AML or AML-MRC

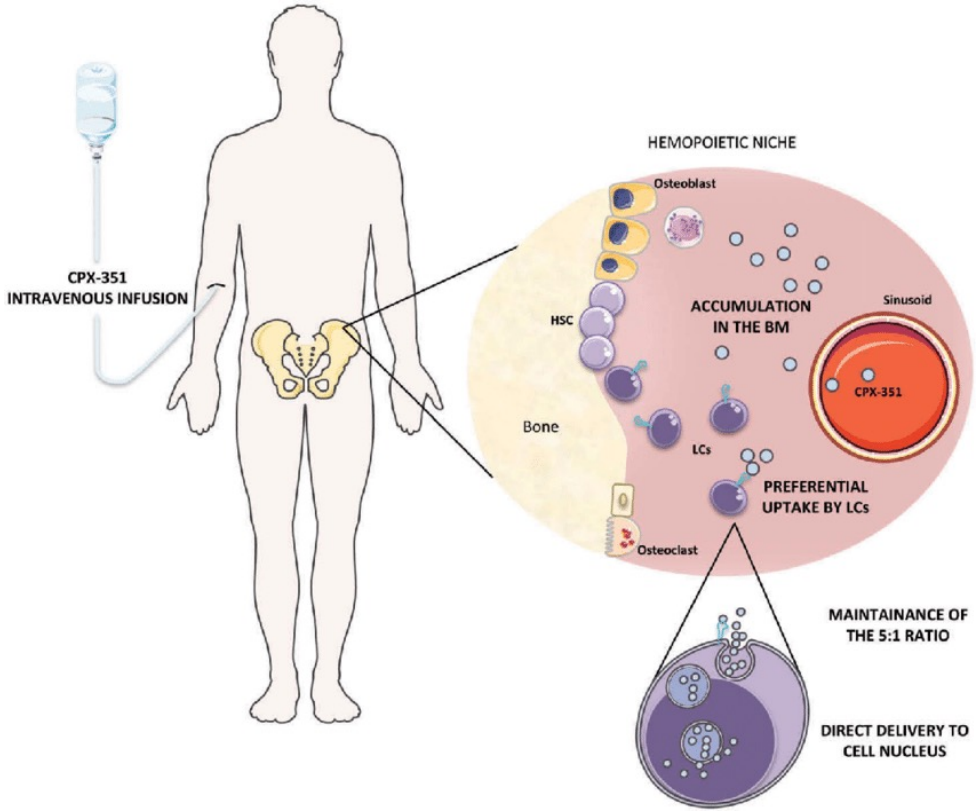
- **65-year-old female presents with pancytopenias**
  - History of breast CA S/P adjuvant chemotherapy 2 years ago
  - CBC: WBC 1.2K, Hb 8.0 gm/dL, PLT 40K, ANC 200
  - BM: AML 60% blasts, Abnormal karyotype with -7, -5
  - No major comorbid illnesses, ECOG PS 0-1

- **69-year-old male presents with monocytosis and thrombocytopenia**
  - History of MDS S/P 12 months of HMA therapy
  - CBC: WBC 30K, 45% atypical monocytes, PLT 30K
  - BM: AML, Complex karyotype
  - NGS panel shows ASXL1, SRSF2, TET2, and RUNX1 mutations
  - No major comorbid illnesses, ECOG PS 0-1

Liposomal Cytarabine and Daunorubicin (CPX-351)

- **STATUS**
  - Approved for first line treatment of older patients with newly diagnosed t-AML and AML-MRC (August 2017)
- **THERAPEUTIC TARGET:** Cytotoxic therapy (liposomal cytarabine + daunorubucin 5:1 molar ratio)
- **DOSING**
  - Induction: daunorubicin 44 mg/m2 and cytarabine 100 mg/m2 liposome IV over 90 min on d 1, 3, and 5
  - Consolidation: daunorubicin 29 mg/m2 and cytarabine 65 mg/m2 liposome IV over 90 min on d 1 and 3
  - **AEs:** Prolonged neutropenia and thrombocytopenia; Less GI sides effects, mucositis and weight loss



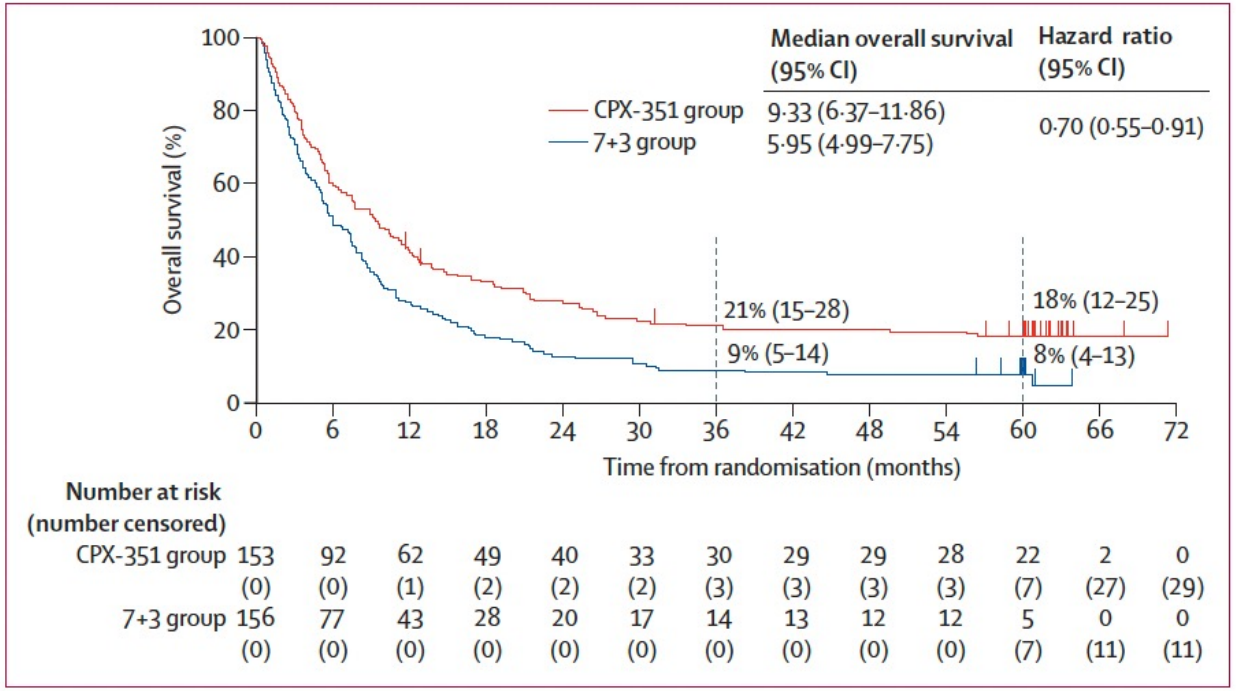


1. Tardi. Leuk Res. 2009;33:129. 2. Feldman. JCO. 2011;29:979. 3. Lim. Leuk Res. 2010;34:1214.

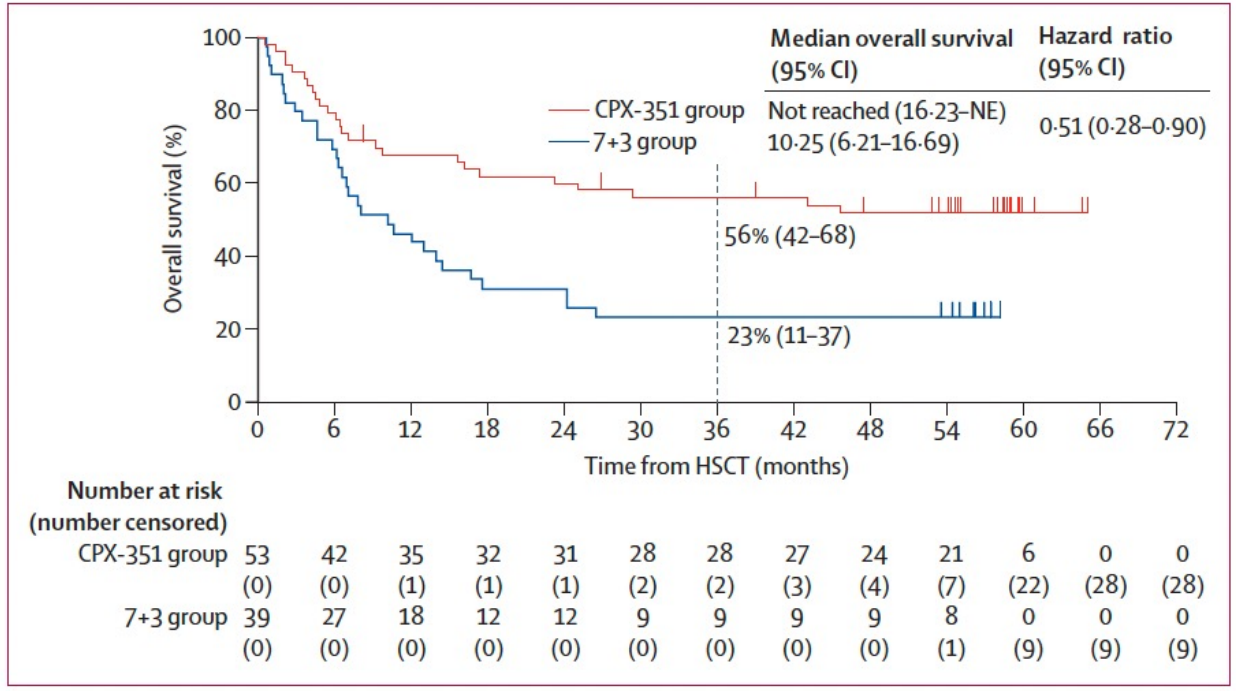
CPX-351 in Older Patients With ND AML

- Phase III trial of CPX-351 vs 7+3 in patients aged 60-75 yr with newly diagnosed high-risk or secondary AML

5-Yr Median OS



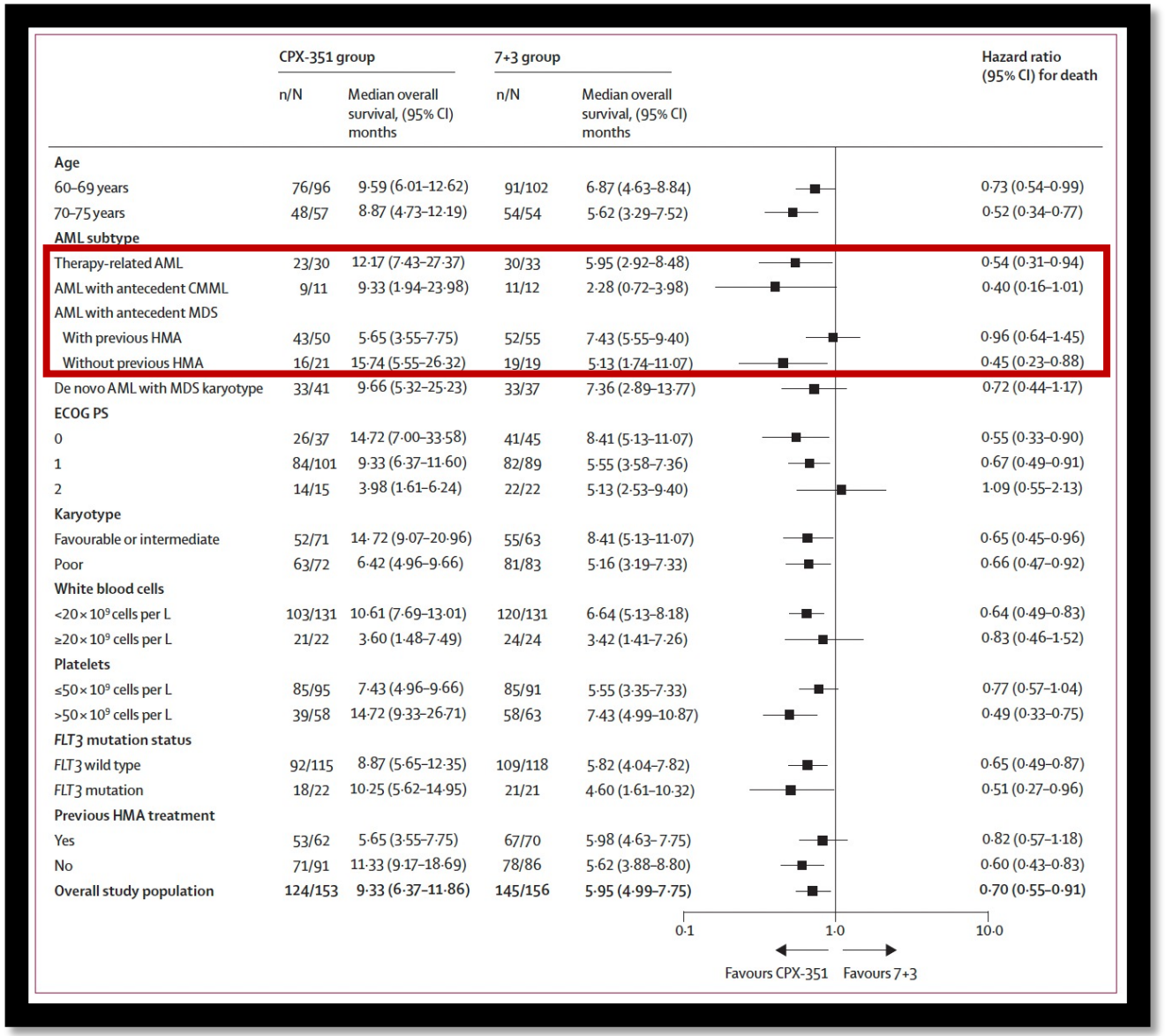
OS by Time Since HST



Lancet. Lancet Haematol. 2021;8:e481.

CPX-351 in Older Patients With Newly Diagnosed AML

OS by Baseline Subgroups



	CPX-351 group		7+3 group		Hazard ratio (95% CI) for death
	n/N	Median overall survival, (95% CI) months	n/N	Median overall survival, (95% CI) months	
Age					
60–69 years	76/96	9·59 (6·01–12·62)	91/102	6·87 (4·63–8·84)	0·73 (0·54–0·99)
70–75 years	48/57	8·87 (4·73–12·19)	54/54	5·62 (3·29–7·52)	0·52 (0·34–0·77)
AML subtype					
Therapy-related AML	23/30	12·17 (7·43–27·37)	30/33	5·95 (2·92–8·48)	0·54 (0·31–0·94)
AML with antecedent CMML	9/11	9·33 (1·94–23·98)	11/12	2·28 (0·72–3·98)	0·40 (0·16–1·01)
AML with antecedent MDS					
With previous HMA	43/50	5·65 (3·55–7·75)	52/55	7·43 (5·55–9·40)	0·96 (0·64–1·45)
Without previous HMA	16/21	15·74 (5·55–26·32)	19/19	5·13 (1·74–11·07)	0·45 (0·23–0·88)
De novo AML with MDS karyotype	33/41	9·66 (5·32–25·23)	33/37	7·36 (2·89–13·77)	0·72 (0·44–1·17)
ECOG PS					
0	26/37	14·72 (7·00–33·58)	41/45	8·41 (5·13–11·07)	0·55 (0·33–0·90)
1	84/101	9·33 (6·37–11·60)	82/89	5·55 (3·58–7·36)	0·67 (0·49–0·91)
2	14/15	3·98 (1·61–6·24)	22/22	5·13 (2·53–9·40)	1·09 (0·55–2·13)
Karyotype					
Favourable or intermediate	52/71	14·72 (9·07–20·96)	55/63	8·41 (5·13–11·07)	0·65 (0·45–0·96)
Poor	63/72	6·42 (4·96–9·66)	81/83	5·16 (3·19–7·33)	0·66 (0·47–0·92)
White blood cells					
<20×10⁹ cells per L	103/131	10·61 (7·69–13·01)	120/131	6·64 (5·13–8·18)	0·64 (0·49–0·83)
≥20×10⁹ cells per L	21/22	3·60 (1·48–7·49)	24/24	3·42 (1·41–7·26)	0·83 (0·46–1·52)
Platelets					
≤50×10⁹ cells per L	85/95	7·43 (4·96–9·66)	85/91	5·55 (3·35–7·33)	0·77 (0·57–1·04)
>50×10⁹ cells per L	39/58	14·72 (9·33–26·71)	58/63	7·43 (4·99–10·87)	0·49 (0·33–0·75)
***FLT3* mutation status**					
FLT3 wild type	92/115	8·87 (5·65–12·35)	109/118	5·82 (4·04–7·82)	0·65 (0·49–0·87)
FLT3 mutation	18/22	10·25 (5·62–14·95)	21/21	4·60 (1·61–10·32)	0·51 (0·27–0·96)
Previous HMA treatment					
Yes	53/62	5·65 (3·55–7·75)	67/70	5·98 (4·63–7·75)	0·82 (0·57–1·18)
No	71/91	11·33 (9·17–18·69)	78/86	5·62 (3·88–8·80)	0·60 (0·43–0·83)
Overall study population	**124/153**	**9·33 (6·37–11·86)**	**145/156**	**5·95 (4·99–7·75)**	**0·70 (0·55–0·91)**

Lancet. Lancet Haematol. 2021;8:e481.

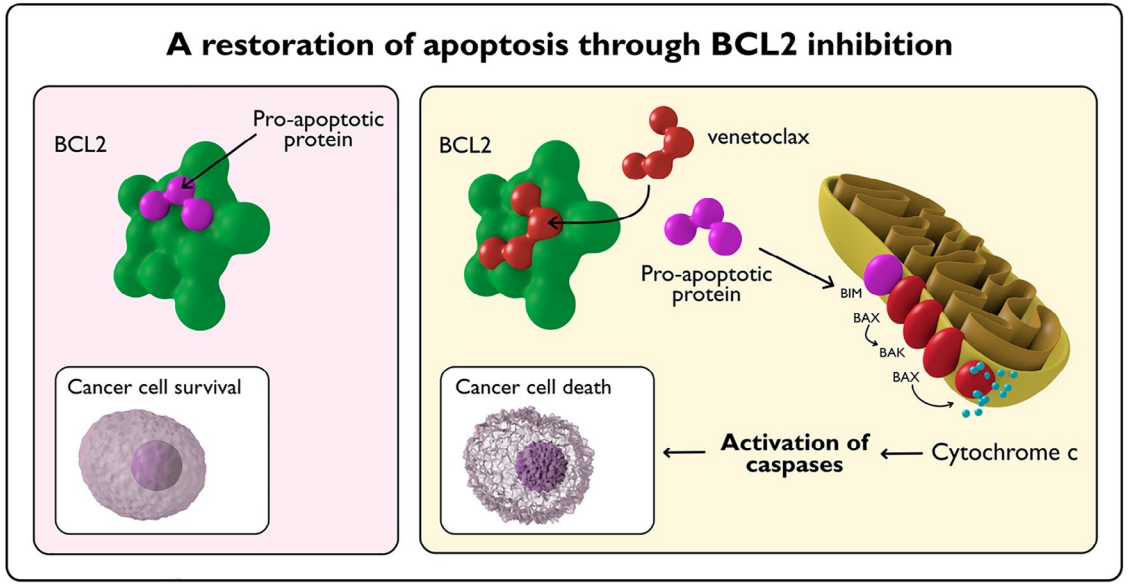
Case 3: Unfit Older Patient with AML

- **70-year-old male presents with fatigue and weight loss**
  - CBC: WBC 22K, Hb 7.2 gm/dL, PLT 30K
  - BM: AML 65% blasts, Complex karyotype
  - NSG panel with RUNX1 and ASXL1
  - History of CAD S/P CABGx2 and uncontrolled DM-II
  - PS of ECOG 2

Venetoclax

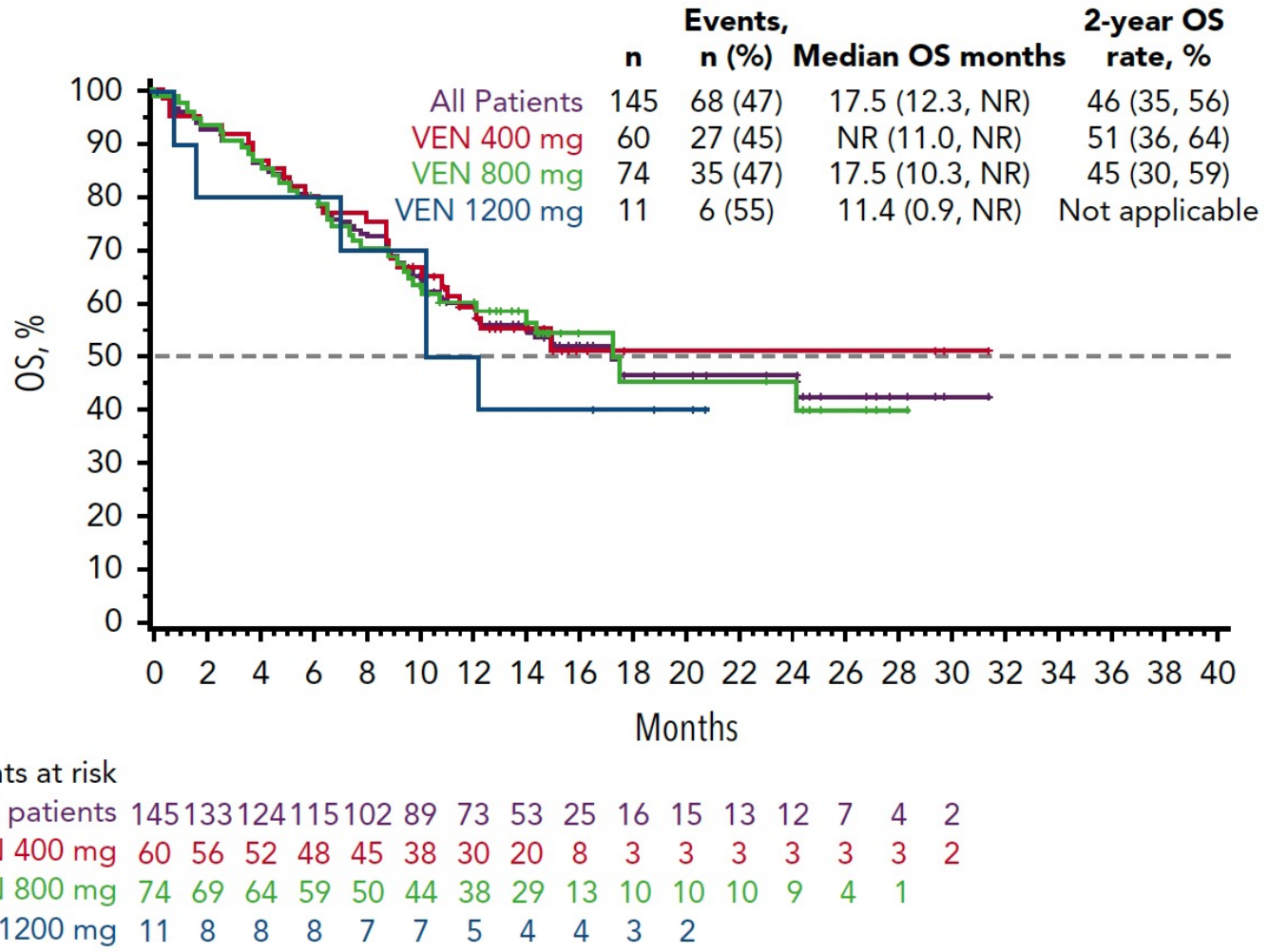
- **STATUS**
  - Approved in combination with azacitidine or decitabine or low-dose cytarabine for newly diagnosed AML in adults ≥75 years or who have comorbidities that preclude use of intensive induction chemotherapy (November 2018)
- **THERAPEUTIC TARGET:** Inhibitor of anti-apoptotic protein BCL-2
- **DOSING**
  - Ramp-up phase: 100 mg orally on d 1, 200 mg on d 2, 400 mg on d 3;
  - 400 mg (with HMA) or 600 mg (with low-dose cytarabine) on d 4 and beyond
  - **AEs:** Prolonged neutropenia

Venetoclax - a BCL2 specific inhibitor



Venetoclax binds directly to BCL-2 protein, displacing pro-apoptotic proteins and restoring the apoptotic process.

Venetoclax + HMA for Unfit Elderly patients with AML

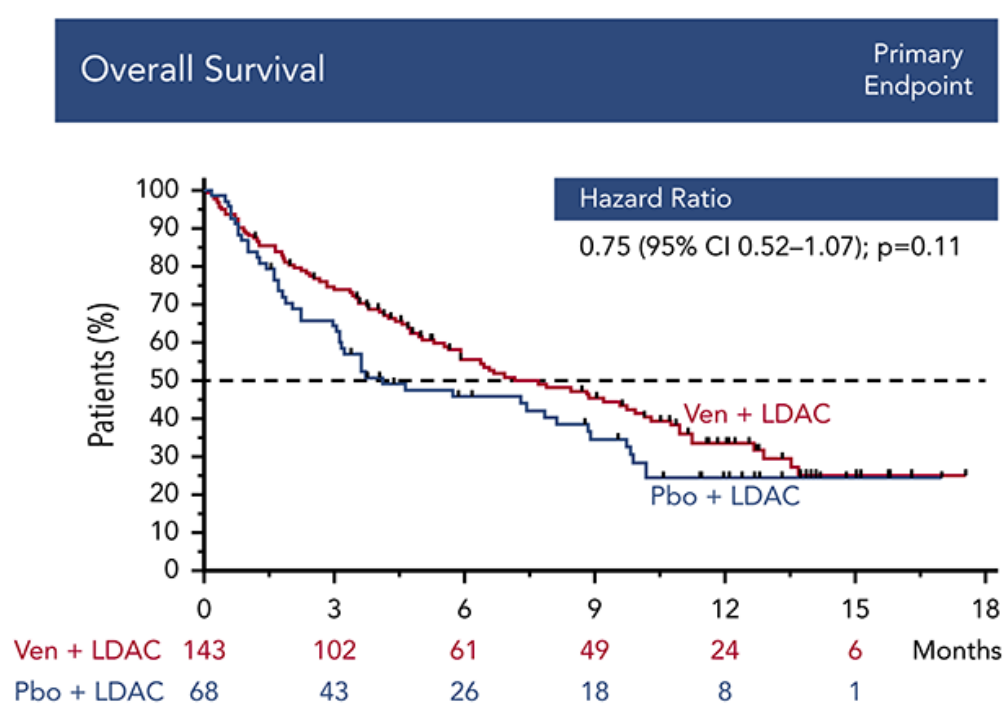


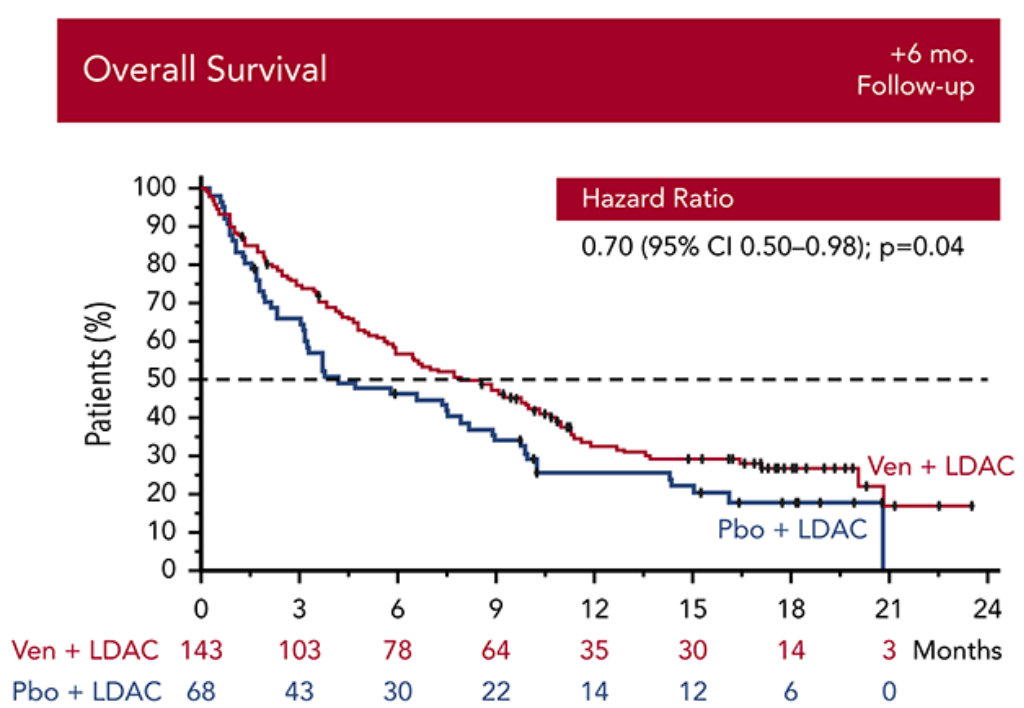
Regimen	CR/CRi, %	mOS, Mos	OS Rate, %
Azacitidine[2]	27.8	10.4	At 1 yr: 46.5
Decitabine[3]	17.8	7.7	NR
Venetoclax + HMA[1]	67	17.5	At 1 yr: 59 At 2 yrs: 46

1. DiNardo. Blood. 2019;133:7. 2. Dombret. Blood. 2015;126:291. 3. Kantarjian. JCO. 2012;30:2670.

Venetoclax + LDAC in Untreated Older AML Patients

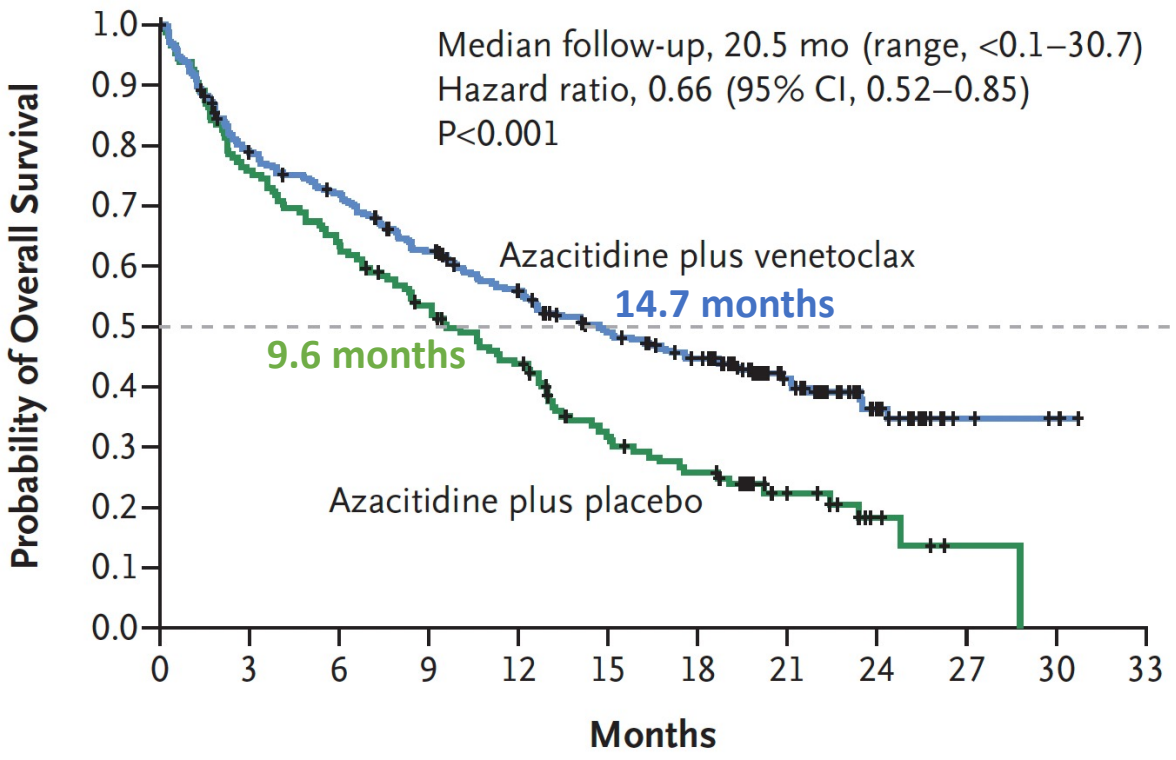
	Response Rate	Median OS Mo. (95% CI)	Transfusion Independence	Quality of Life
Venetoclax + LDAC	48%	8.4 (5.9-10.1)	37%	↑
Placebo + LDAC	13%	4.1 (3.1-8.1)	16%	—





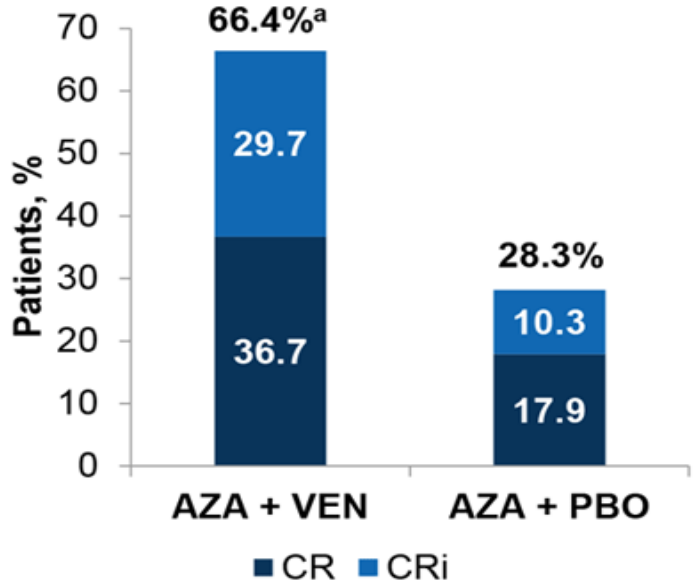
Wei. Blood. 2020;135:24.

VIALE-A: Venetoclax plus Azacitidine



No. at Risk

Azacitidine plus venetoclax	286	219	198	168	143	117	101	54	23	5	3	0
Azacitidine plus placebo	145	109	92	74	59	38	30	14	5	1	0	0



	No. of Treatment Cycles, Median (Range)	Median Time to CR/CRi, mo (Range)	CR + CRi[a] 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)

DiNardo. NEJM. 2020;383:7.

Case 3 with a Twist: Fit Older Patient with AML

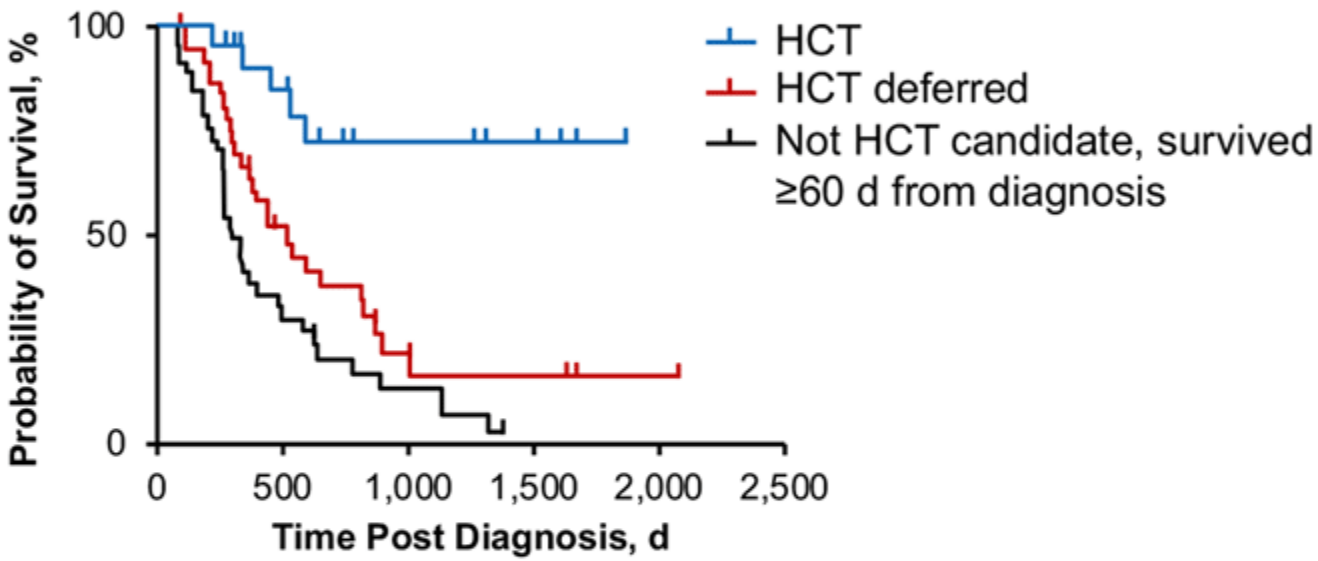
- **67-year-old female presents with fatigue and weight loss**
  - CBC: WBC 22K, Hb 7.2 gm/dL, PLT 30K
  - BM: AML 65% blasts, Complex karyotype
  - NSG panel with RUNX1 and ASXL1
  - History of HTN controlled with meds, PS ECOG 0

- **Received Venetoclax plus AZA– Achieved CR1**
- HLA-identical sibling identified

NEXT STEP?

Outcomes with Allo-HCT vs Maintenance Venetoclax + AZA Following Response to Initial Venetoclax + AZA

- HCT vs HCT deferred
  P = .002
- HCT deferred vs not HCT candidate survived 60 d
  P = .035



	Median Survival, d
HCT	Not reached
HCT deferred	518
Not HCT candidate, survived ≥60 d from diagnosis	291

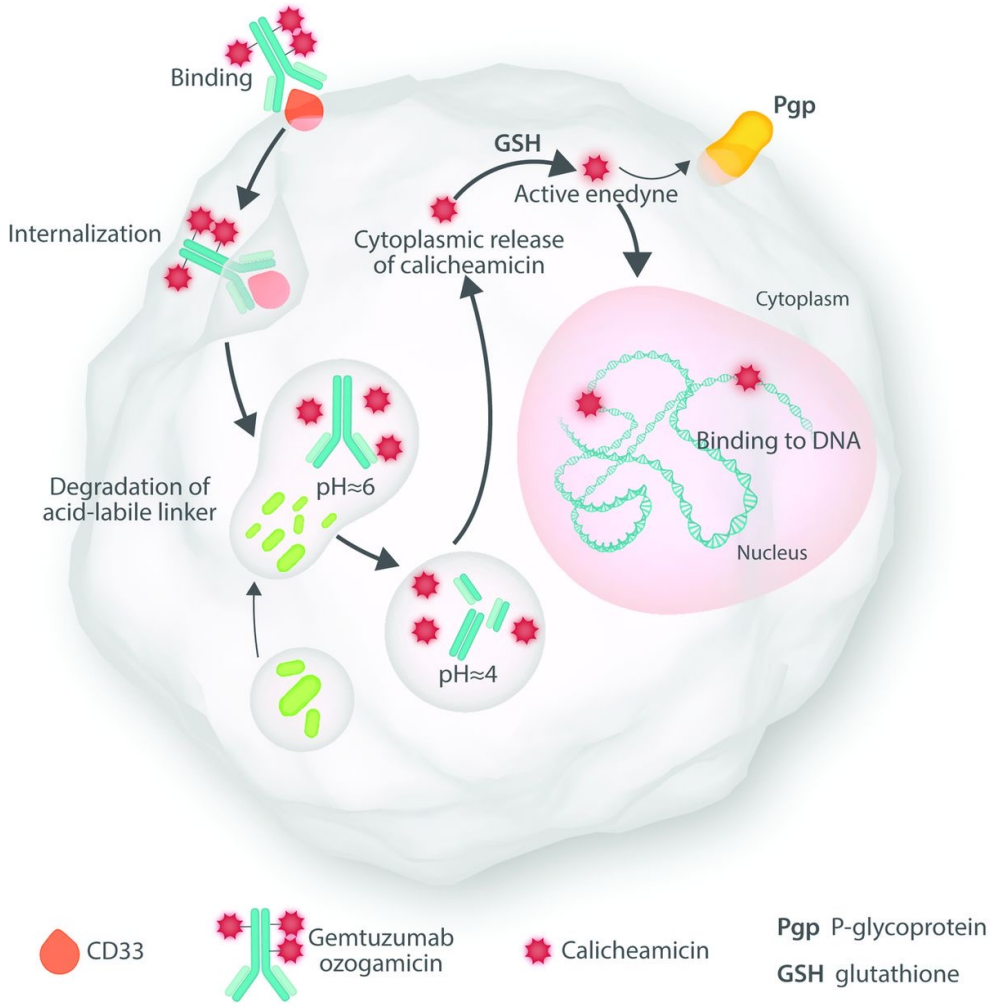
Pollyea. Bone Marrow Transplantation. 2022;57:160

Case 4: Patient with Favorable-Risk AML

- **62-year-old male with fatigue and myalgias**
  - CBC: WBC 1.2K, Hb 8.0 gm/dL, PLT 50K
  - BM: AML 30% blasts
  - Abnormal karyotype: inv(16)(p13.1q22)
  - NGS panel with NPM1 mutation
  - No major comorbid illnesses, ECOG PS 0-1

Gemtuzumab ozogamycin

- **STATUS**
  - Re-approved in Newly diagnosed CD33+ AML in adults, R/R CD33+ AML in adults (September 2017)
- **THERAPEUTIC TARGET:** Monoclonal antibody against CD33 linked to a chemotherapy drug
- **DOSING**
  - Induction: 3 mg/m2 (up to one 4.5-mg vial) on d 1, 4, and 7 in combination with daunorubicin and cytarabine
  - **AEs:** VOD/SOS

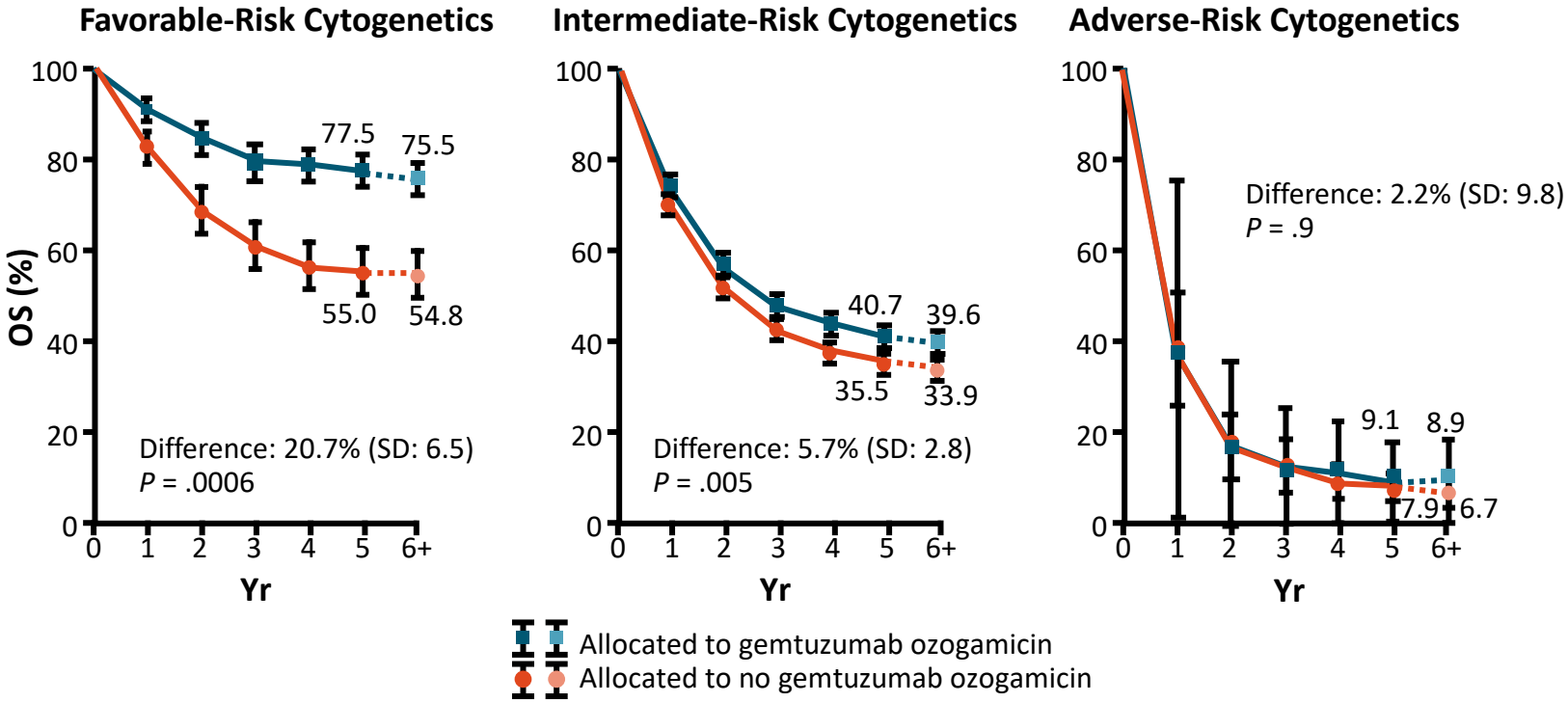


GO acts like a **homing signal**, bringing the chemo drug into the leukemia cells, where it kills them

Gemtuzumab Ozogamicin Reemergence

- **ALFA-0701** (ND, aged 50-70 yr)[1]
  - 7+3 ± GO (3 mg/m^2 d 1, 4, 7)
  - Median OS improved
- **MRC AML16** (untreated, older)[2]
  - LDAC ± GO at 3 mg/m^2
  - OS improved
- **Meta-analysis 5 RCTs** (N = 3325)[3]
  - No improvement in CR rate
  - OS improved
  - Best results in favorable risk

Response to Gemtuzumab Ozogamicin by Cytogenetic Risk[3]



1. Castaigne. Lancet. 2012;379:1508. 2. Burnett. Leukemia. 2013;27:75. 3. Hills. Lancet Oncol. 2014;15:986.

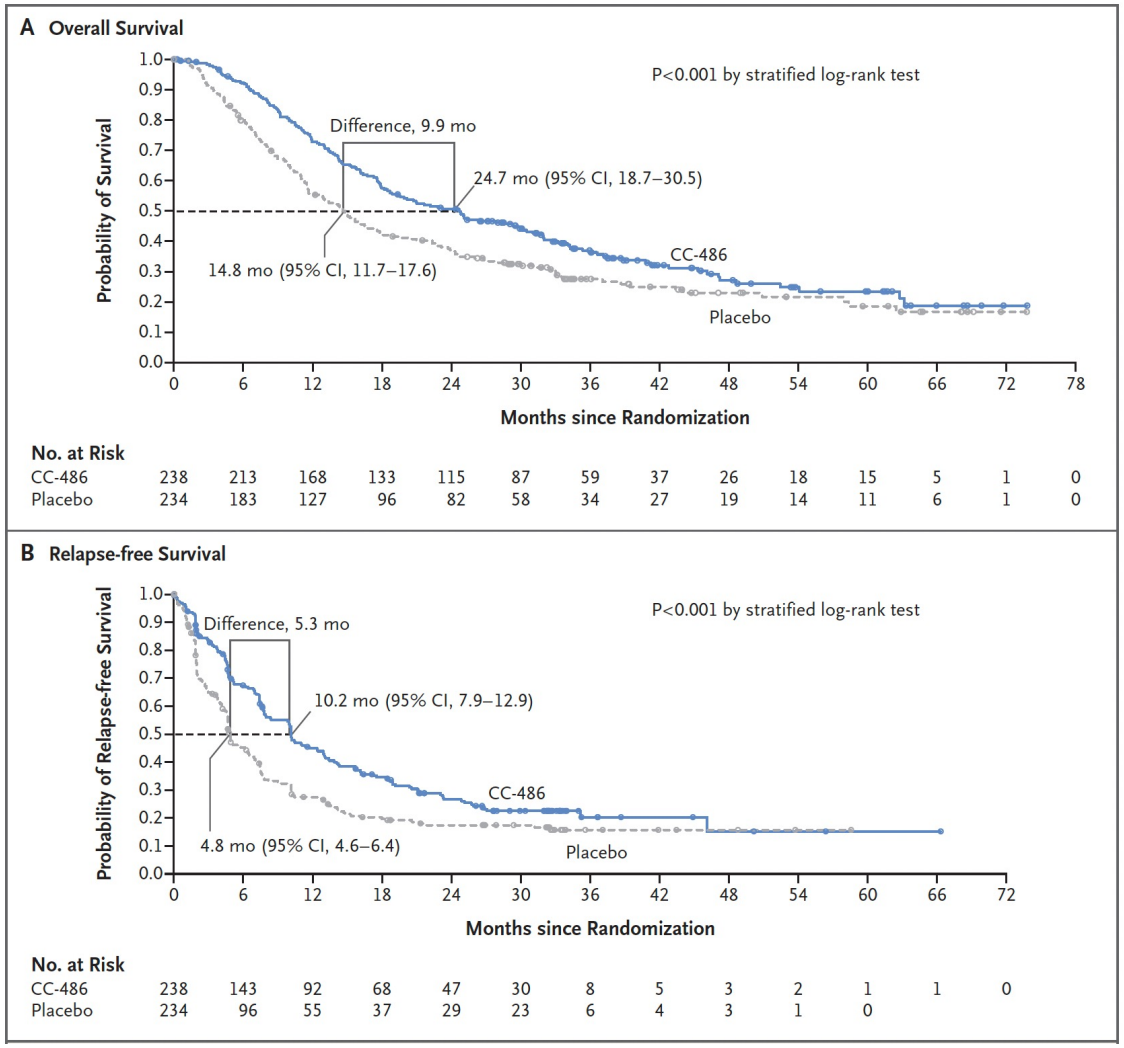
Case 4: Patient with Favorable-Risk AML

- **62-year-old male with fatigue and myalgias**
  - CBC: WBC 1.2K, Hb 8.0 gm/dL, PLT 50K
  - BM: AML 30% blasts
  - Abnormal karyotype: inv(16)(p13.1q22)
  - NGS panel with NPM1 mutation
  - No major comorbid illnesses, ECOG PS 0-1

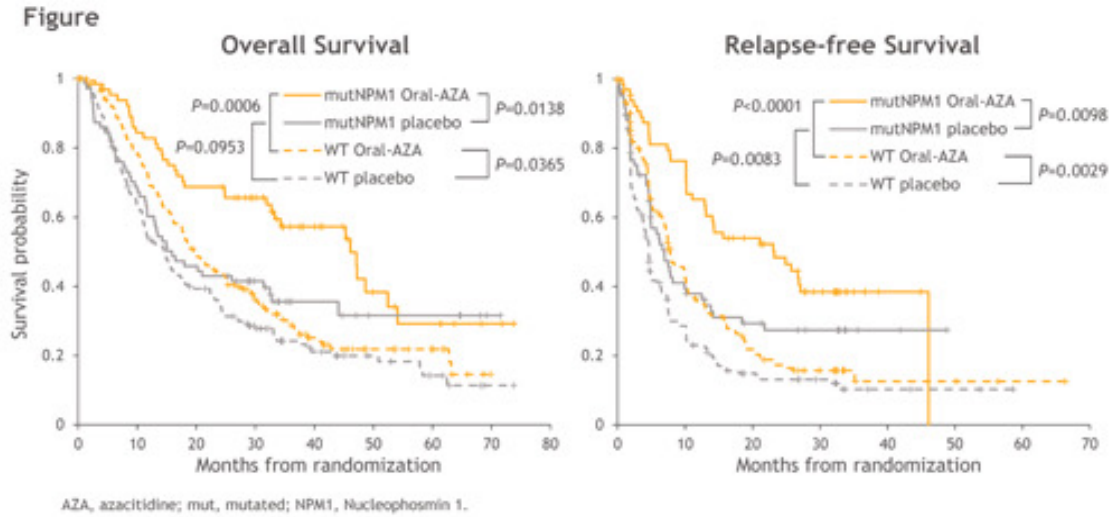
- **Received 7+3 induction plus GO – Achieved CR1**

NEXT STEP?

QUAZAR: Oral AZA Maintenance improves OS and RFS



Extended OS Benefit for patients with NPM1 mutated AML[2]



1. Wei AH. NEJM. 2020;383:2526.
2. Dohner H. EHA 2021. Abstract S131.

What about Post-transplant Maintenance with HMAs?

CC-486 Maintenance after Stem Cell Transplantation in Patients with Acute Myeloid Leukemia or Myelodysplastic Syndromes

Marcos de Lima[1*], Betul Oran[2], Richard E. Champlin[2], Esperanza B. Papadopoulos[3], Sergio A. Giralt[3], Bart L. Scott[4], Basem M. William[5], Joel Hetzer[6], Eric Laille[6], Becky Hubbell[6], Barry S. Skikne[6], Charles Craddock[7]

Oral AZA maintenance post-HCT (N = 30)[1]

- Well tolerated, low rates of relapse, disease progression, and GVHD

REGULAR ARTICLE

blood advances

Check for update

A phase 3 randomized study of 5-azacitidine maintenance vs observation after transplant in high-risk AML and MDS patients

187 patients with high-risk AML/MDS in CR randomized to post-HCT AZA vs observation[2]

- No difference in RFS between the two study arms

original reports

Effect of rhG-CSF Combined With Decitabine Prophylaxis on Relapse of Patients With High-Risk MRD-Negative AML After HSCT: An Open-Label, Multicenter, Randomized Controlled Trial

G-CSF and decitabine vs no intervention in 204 patients with high-risk AML post-HCT[3]

- Lower relapse rate in the decitabine arm (HR = 0.32; $P < .01$)

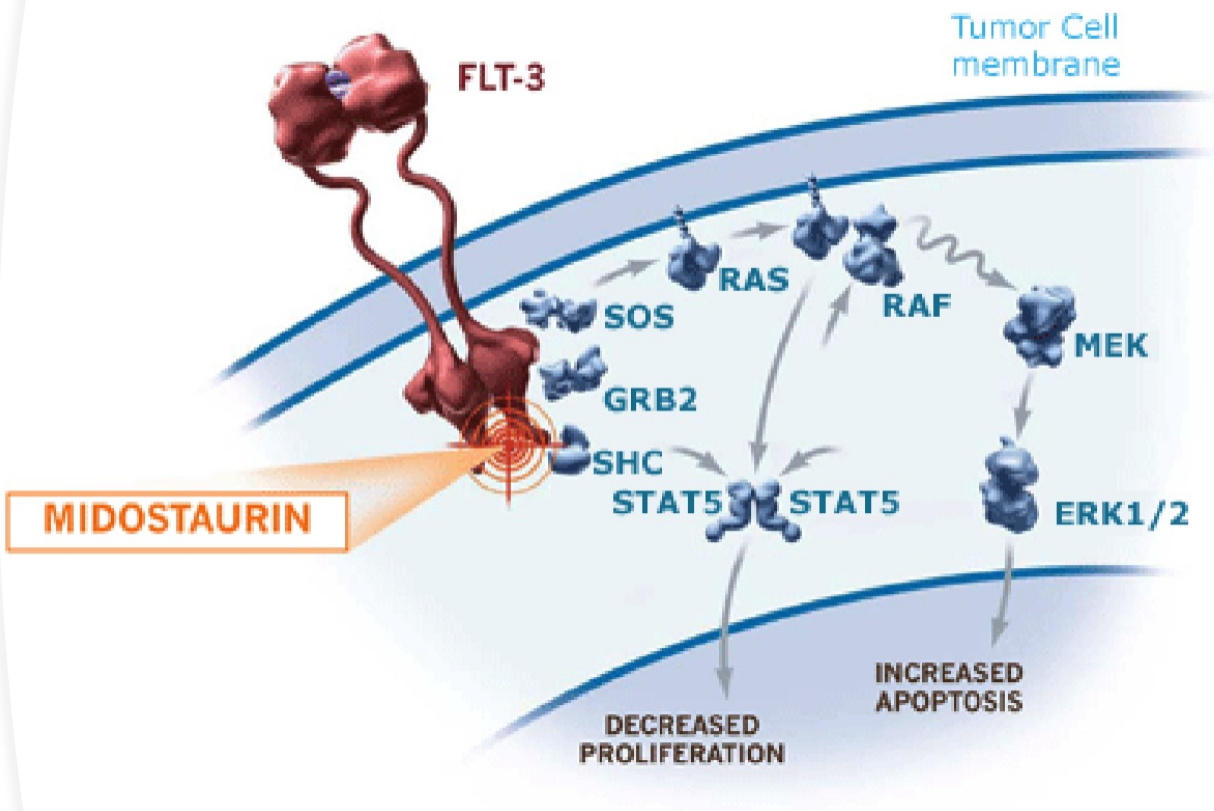
1. de Lima M et al. *Biol Blood Marrow Transplant*. 2018;24:2017-2024. 2.Oran B et al. *Blood Adv*. 2020;4:5580-5588. 3. Gao L et al. *J Clin Oncol*. 2020;38:4249-4259.

Case 5: Patient with AML and FLT3 mutation

- **62-year-old female presents with fatigue and fever**
  - CBC: WBC 80K, Hb 7.5 gm/dL, PLT 21K
  - BM: AML 85% blasts, Normal female karyotype
  - NGS panel shows FLT3-ITD mutation (AR 0.8) and NPM1
  - No major comorbid illnesses, ECOG PS 0-1

Midostaurin

- **STATUS**
  - Approved plus chemotherapy in adults with ND FLT3-mutation–positive AML (April 2017)
- **THERAPEUTIC TARGET:** Inhibitor of FLT3 protein
- **DOSING**
  - 50 mg orally twice daily with food on d 8-21 of each induction cycle with cytarabine and daunorubicin and on d 8-21 of each consolidation cycle with high-dose cytarabine
  - **AEs:** Nausea/Vomiting, Headache, Upper respiratory tract infection

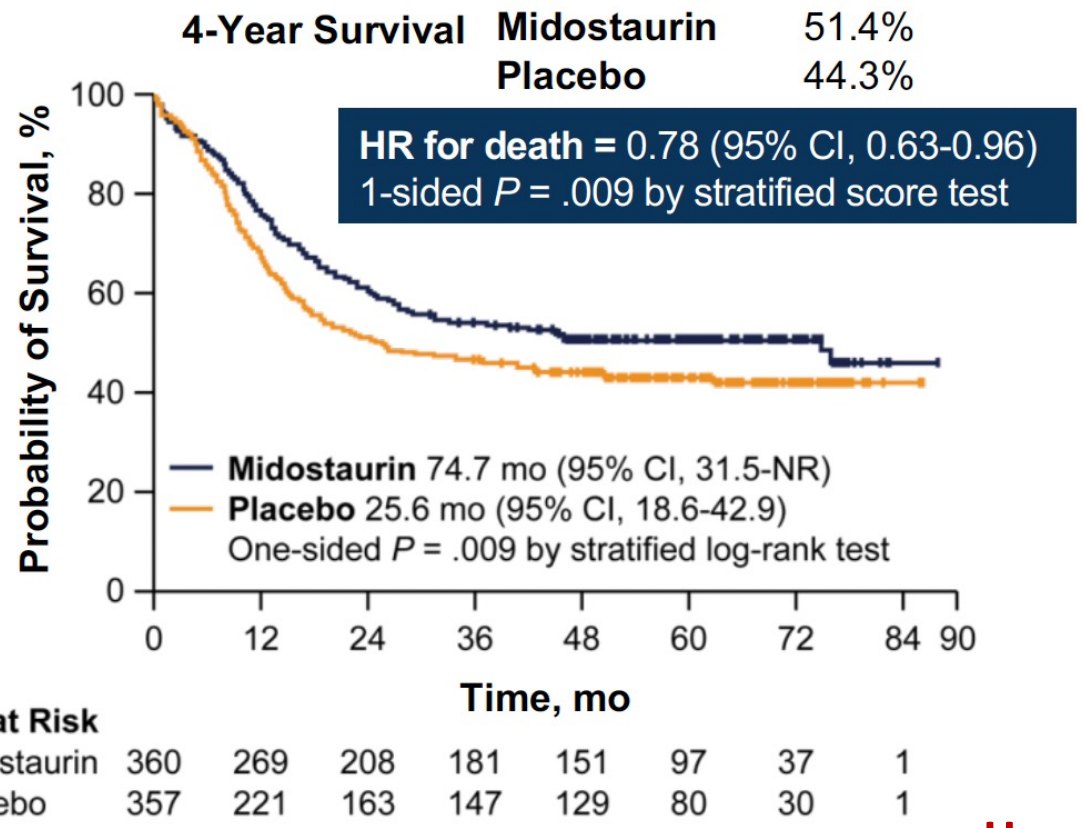


Mutation in FLT3 gene – Produces FLT3 protein

FLT3 protein helps AML cells grow

RATIFY: Midostaurin Plus Chemotherapy for AML With *FLT3* Mutation

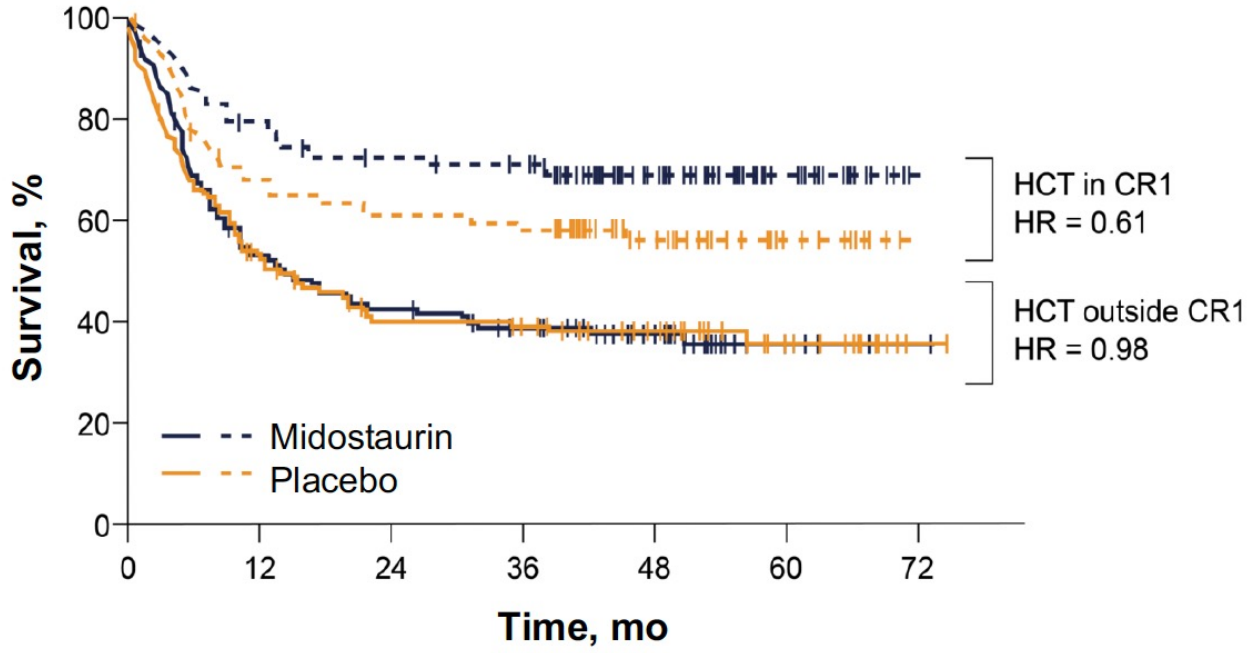
All Patients[1]



No. at Risk

Midostaurin	360	269	208	181	151	97	37	1
Placebo	357	221	163	147	129	80	30	1

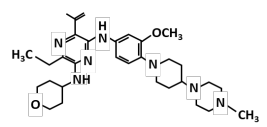
Transplanted Patients[2]



However, efficacy is limited, and patients develop resistance[3]

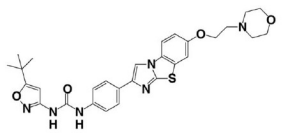
1. Stone RM et al. N Engl J Med. 2017;377:454-464. 2. Stone RM et al. ASH 2015. Abstract 6. 3. Levis. Blood Adv. 2020;4:1178

Other FLT3 Inhibitors Studied for ND *FLT3*-Positive AML



Gilteritinib

- **Approved by the FDA for relapsed/refractory AML**[1]
- Combination with induction/consolidation chemotherapy active and well tolerated[2]
- **PrECOG 0905:** Being compared with midostaurin for frontline *FLT3*-positive AML[3]



Quizartinib

- **Approved in Japan**
- OS benefit in R/R AML[4]
- **QuANTUM-First:** Phase III trial studying quizartinib plus chemotherapy vs chemotherapy plus placebo as induction and consolidation therapy in patients with newly diagnosed AML[5]

1. Perl. NEJM. 2019;381:1728.
2. Pratz. Blood 2020; 136 (Supplement 1): 16
3. NCT03836209
3. Cortes. Lancet Oncol. 2019;20(7):984.
4. NCT02668653

Case 5: Patient with AML and FLT3 mutation

- **62-year-old female presents with fatigue and fever**
  - CBC: WBC 80K, Hb 7.5 gm/dL, PLT 21K
  - BM: AML 85% blasts, Normal female karyotype
  - NGS panel shows FLT3-ITD mutation (AR 0.8) and NPM1
  - No major comorbid illnesses, ECOG PS 0-1

- **7+3 plus midostaurin – Achieved CR1**
- **MUD identified and patient underwent Allo-HCT**

NEXT STEP?

Post-HCT Maintenance options in FLT3 AML

Midostaurin: RATIFY[1]

Figure 1: Landmark analysis of DFS during the 12 cycles of maintenance, censoring pts at the time they completed the planned maintenance or discontinued study drug early.

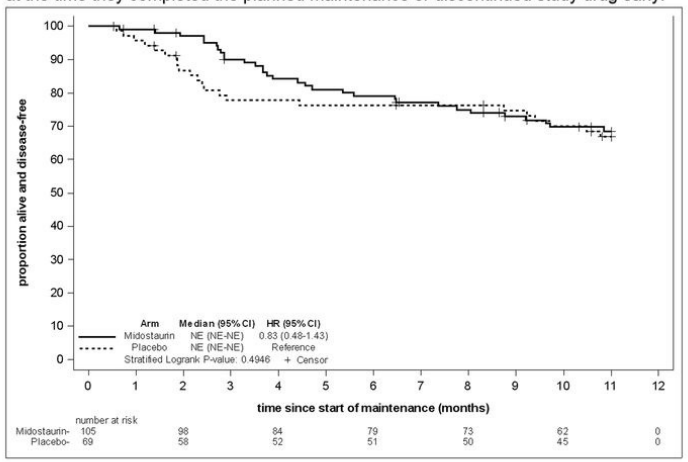
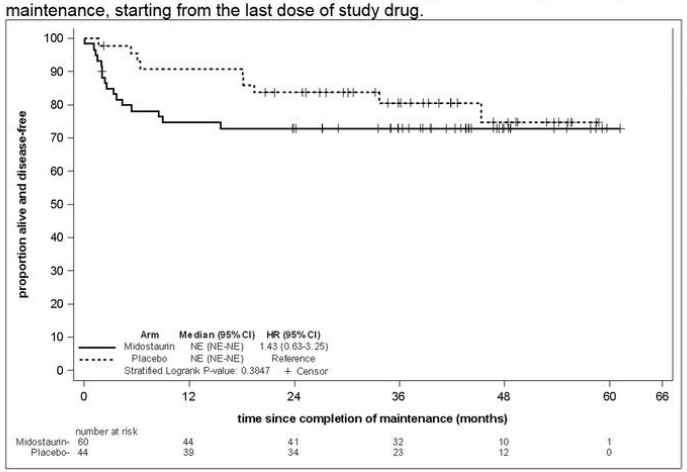
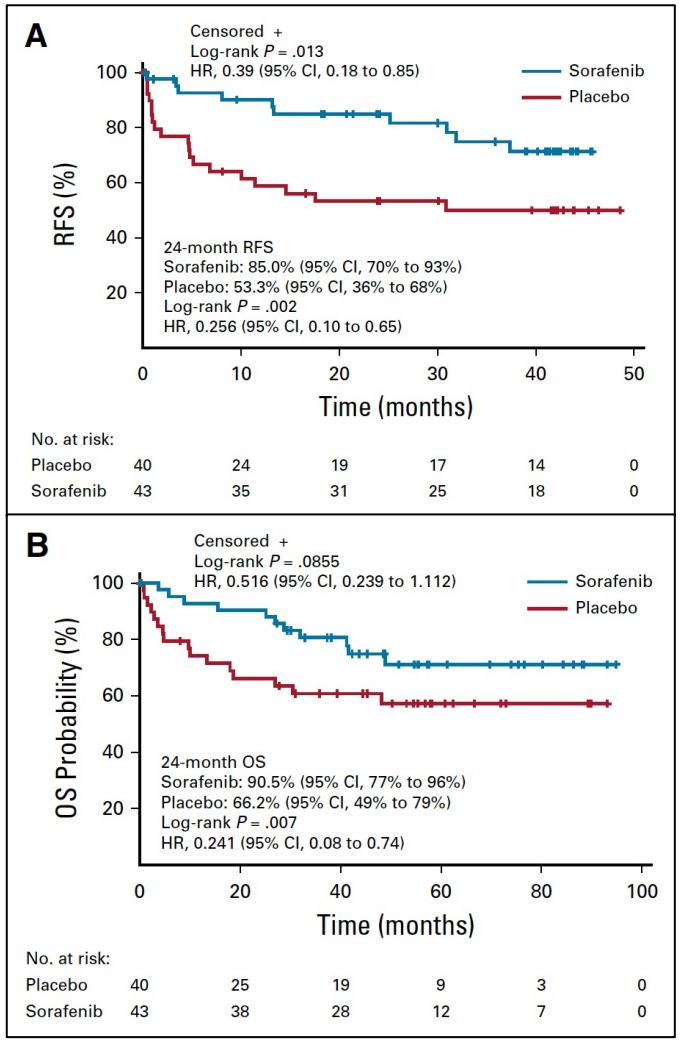


Figure 2: Landmark analysis of DFS for the 104 pts who completed all planned maintenance, starting from the last dose of study drug.



No difference in DFS.
Data not conclusive.

Sorafenib: SORMAIN[2]



Reduction in risk of relapse and death.

BMT-CTN 1506 Morpho Trial[3]

Gilteritinib vs. Placebo

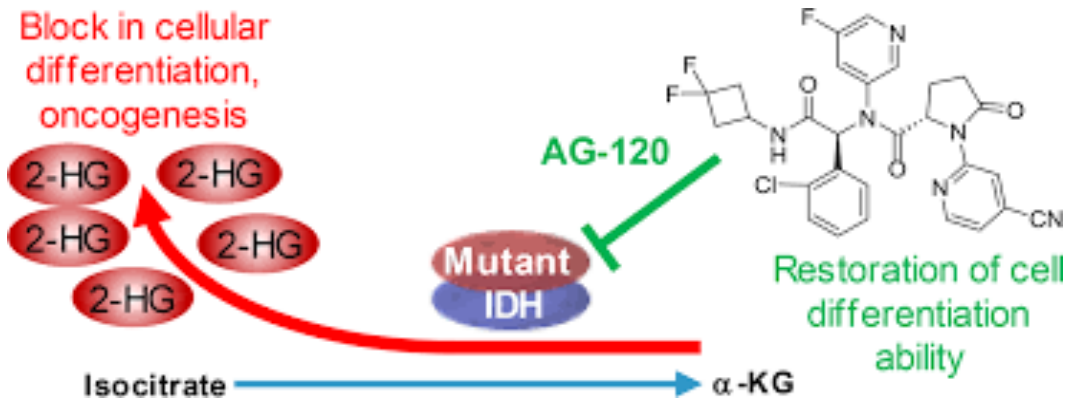
1. Larson. ASH 2017. Abstract 145.
2. Burchert. 2020. J Clin Oncol 38:2993.
3. Levis. ASH 2019. Abstract 732.

Case 6: Patient with AML and IDH1 mutation

- **70-year-old female presents with fatigue and fever**
  - CBC: WBC 2.0K, Hb 7.5 gm/dL, PLT 22K
  - BM: AML 60% blasts with MLD, Normal karyotype
  - NGS panel shows IDH1 and DNMT3A mutations
  - History of HTN and DM-II, ECOG PS 1-2

Ivosidenib

- **STATUS**
  - Approved as single agent for R/R AML with IDH1 mutation (July 2018) or ND AML with IDH1-mutation in adults ≥75 years or who have comorbidities that preclude the use of intensive induction chemotherapy (May 2019)
  - Approved in combination with azacitidine for ND AML with IDH1 mutation in adults ≥75 years or who have comorbidities that preclude use of intensive induction chemotherapy (May 2022).
- **THERAPEUTIC TARGET:** Inhibitor of IDH1 protein
- **DOSING**
  - 500 mg orally daily (May take 3-4 cycles to respond**)**
  - **AEs:** Differentiation Syndrome within first 2 cycles

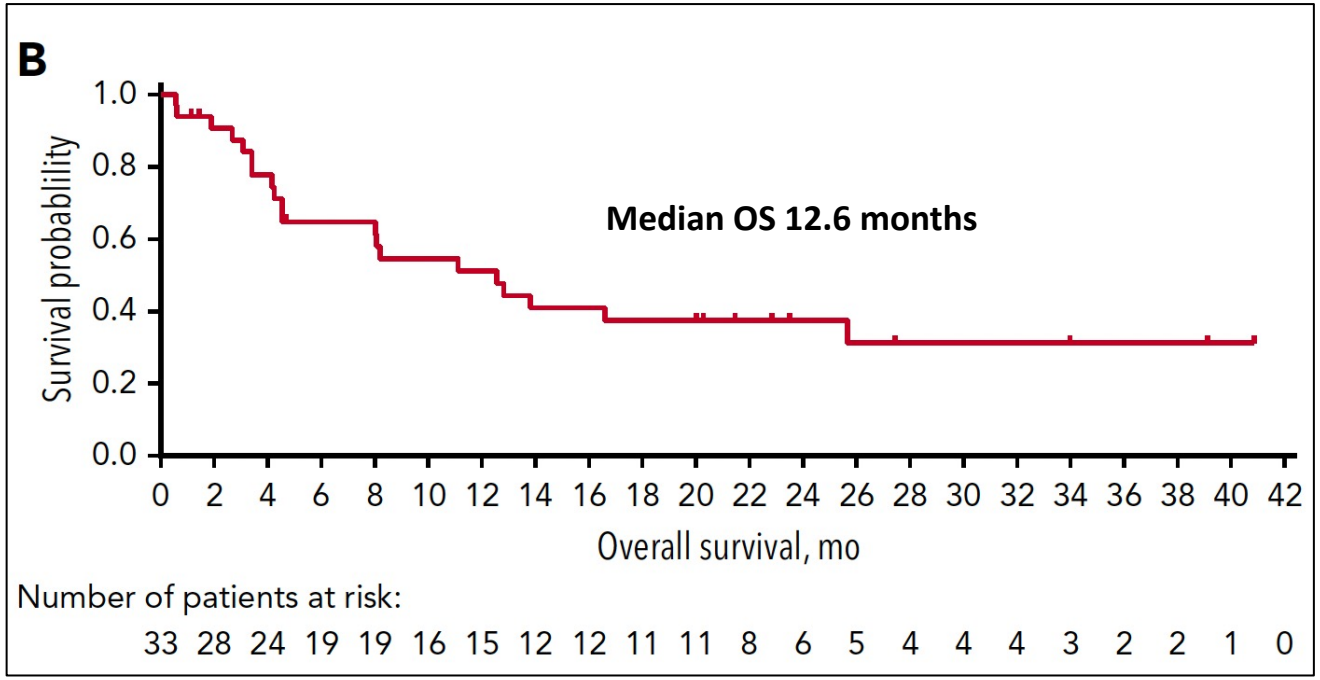


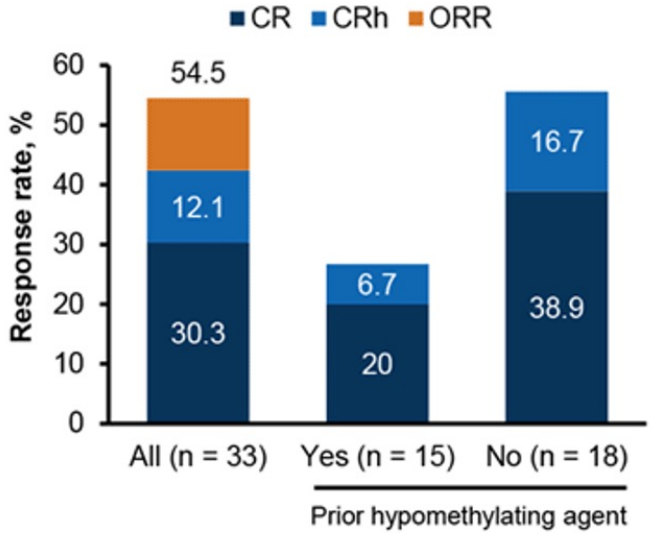
Mutation in IDH1 gene – Produces IDH1 protein
IDH1 protein affect maturation of blood cells

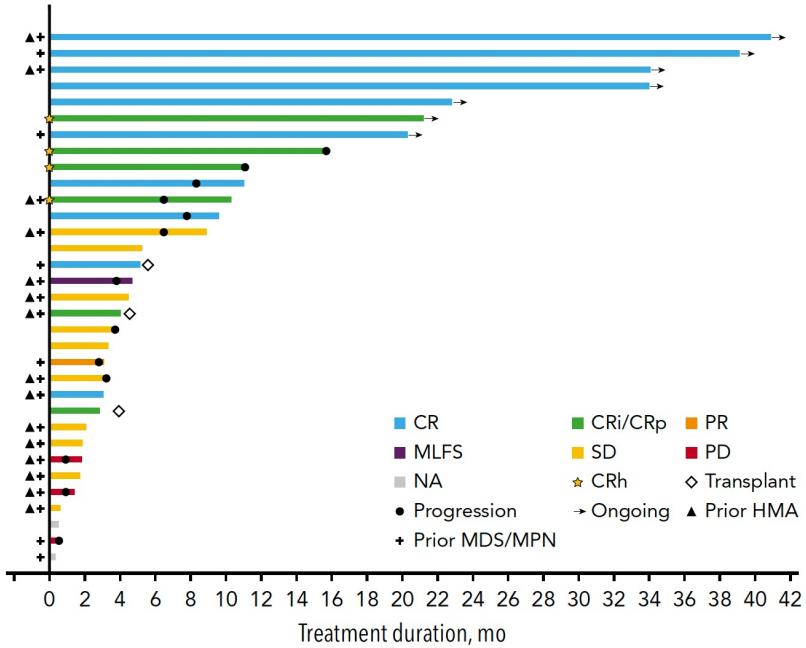
Ivosidenib for ND IDH1-mutant AML

IDH1-mutant ND AML ineligible for Standard Therapy

- 56% aged ≥75 years
- 47% prior exposure to HMA
- 76% secondary AML





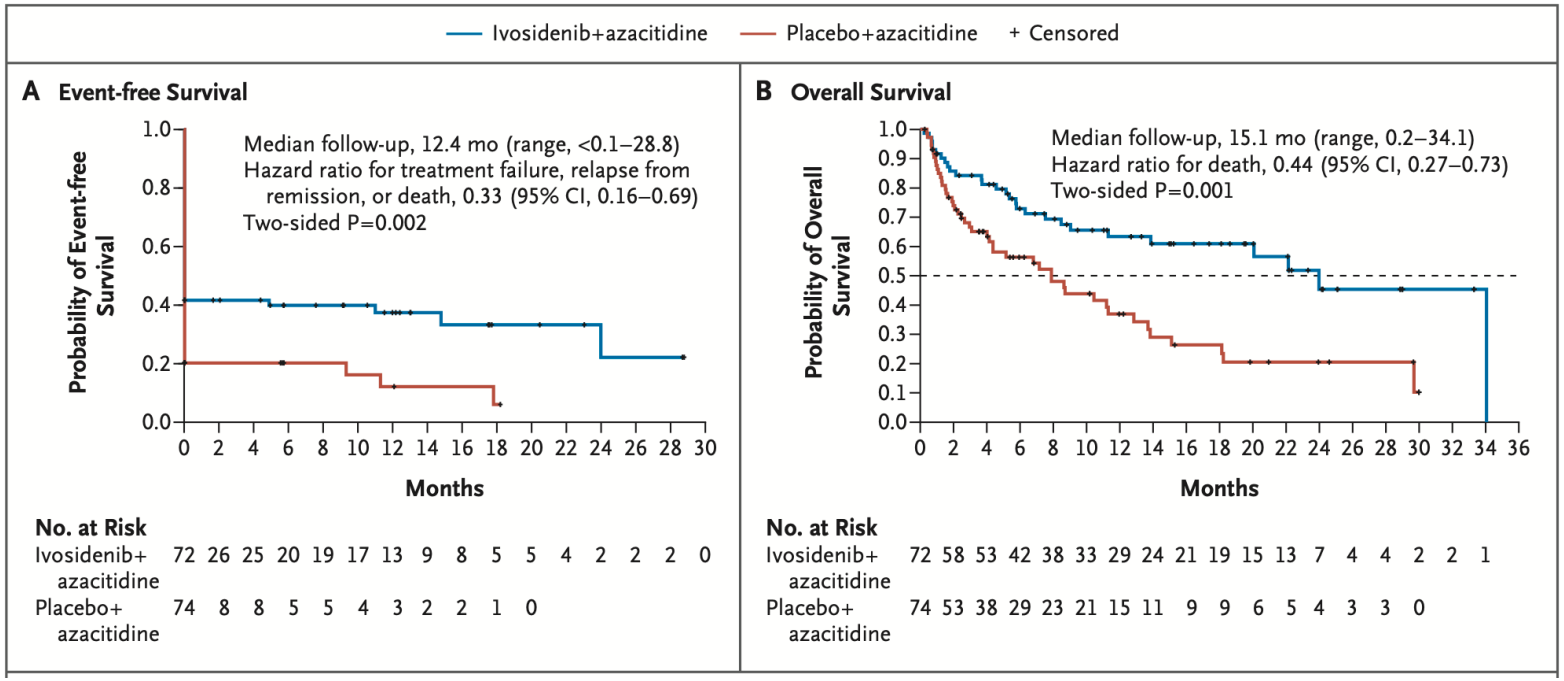


Roboz. Blood. 2020;135(7):463

Ivosidenib plus AZA for ND IDH1-mutant AML

- **AGILE trial**:
  - Ivosidenib/AZA vs AZA/placebo
- OS: 24 months vs 7.9 months
- CR rate: 47% vs 11%
- CR/CRi/CRp: 54% vs 12%

Approved by FDA on May 25, 2022



Montesinos. N Engl J Med 2022;386:1519

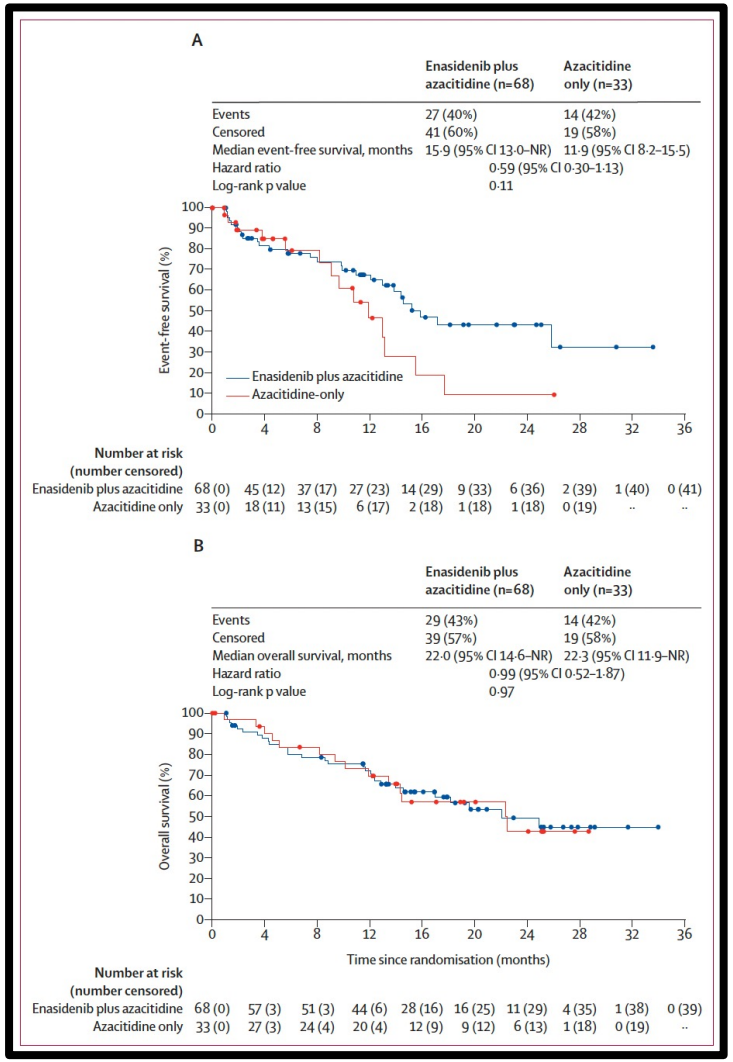
Enasidenib plus AZA for ND IDH2-mutant AML

- Open-label, phase 1b/2 trial
- Enasidenib 100 mg/day plus SC azacitidine 75 mg/m²/day for 7 days

	Enasidenib plus azacitidine (n=68)	Azacitidine only (n=33)	p value
Overall response*	50 (74%; 95% CI 61–84)	12 (36%; 95% CI 20–55)	0·0003
Complete remission	37 (54%; 95% CI 42–67)	4 (12%; 95% CI 3–28)	<0·0001
Complete remission or complete remission with partial haematological recovery	39 (57%)	6 (18%)	0·0002
Complete remission with incomplete blood count or platelet recovery	6 (9%)	6 (18%)	..
Partial remission	4 (6%)	2 (6%)	..
Morphological leukaemia-free state	3 (4%)	0	..
Stable disease	13 (19%)	16 (48%)	..
Disease progression	1 (1%)	1 (3%)	..
Not evaluable or missing data	4 (6%)	4 (12%)	..
Time to first response, months	1·9 (1·1–3·9)	3·6 (1·9–4·4)	..
Time to complete remission, months	5·4 (3·8–7·6)	4·4 (3·8–5·6)	..
Duration of response, months	24·1 (95% CI 10·0–NR)	9·9 (95% CI 5·5–13·6)	..
Duration of complete remission, months	NR (95% CI 7·7–NR)	12·7 (95% CI 11·7–NR)	..

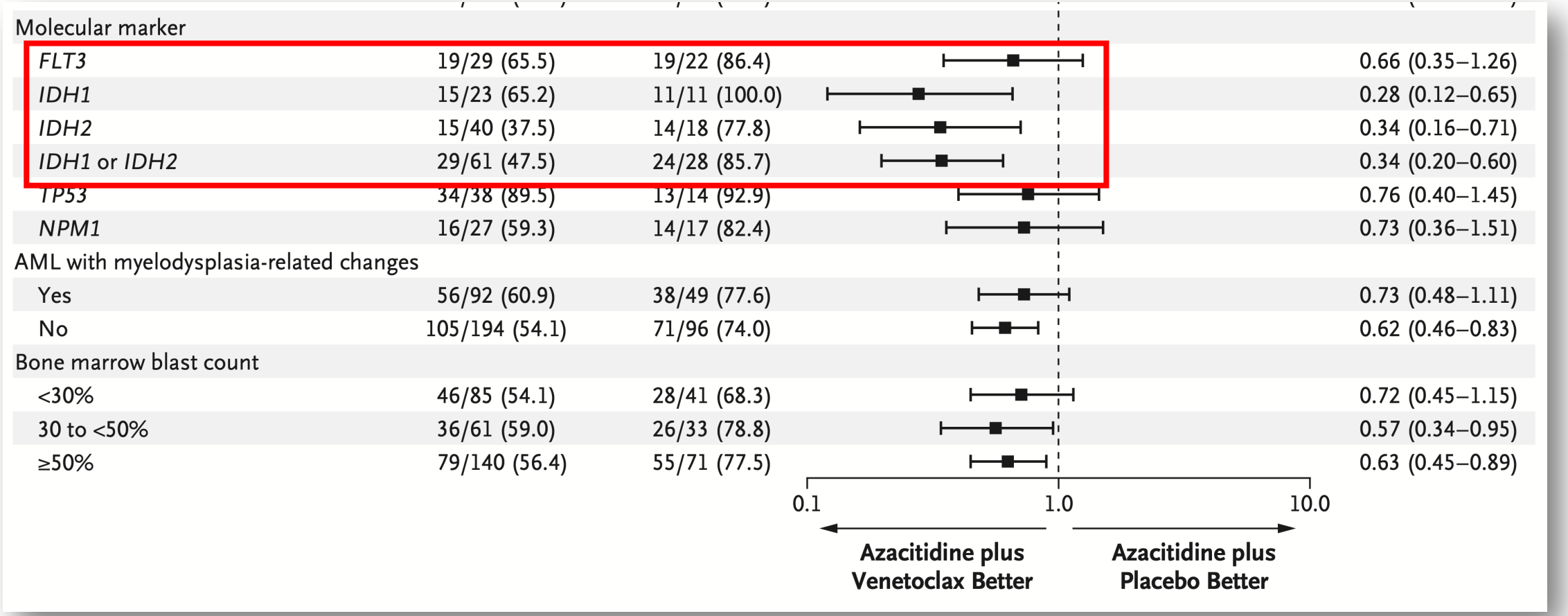
Data are n (%; 95% CI), n (%), median (IQR), or median (95% CI). Data cutoff Aug 20, 2019. NR=not reached. *Overall response defined as proportion of patients with complete remission, complete remission with incomplete blood count or platelet recovery, partial remission, or morphological leukaemia-free state.

Table 2: Haematological responses in the randomised phase 2 study portion



DiNardo. Lancet Oncol. 2021;22:1597

Back to VIALE-A: Venetoclax plus AZA effective in different Molecular Subgroups: FLT3, IDH1, IDH2 Mutated AML



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)

Di Nardo. NEJM. 2020;383:7.

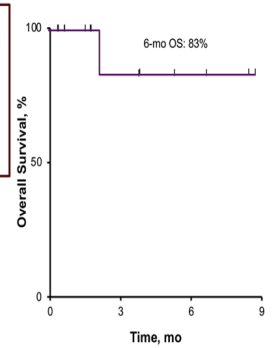
Novel Triplets with Venetoclax/HMA backbone plus targeted agents showing promising activity in Newly Diagnosed AML

ASH 2021: Phase 1/2 study of AZA, venetoclax, and gilteritinib in patients with a *FLT3* mutation (N = 26)[1]

- R/R *FLT3*-mutated AML
- High-risk MDS/CMML
- Patients with ND *FLT3*-mutated AML unsuitable for intensive chemotherapy were eligible

Results: The triplet was effective in this *FLT3*-mutated AML population[1]

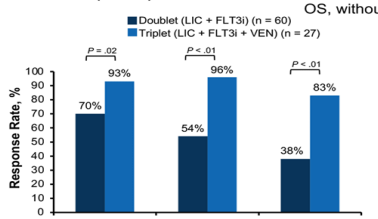
- **mCRc of 100% in the frontline setting (n = 14)**
- Gilteritinib dosing at 80 mg daily was associated with a better safety/efficacy profile (especially myelosuppression) and was selected for future study

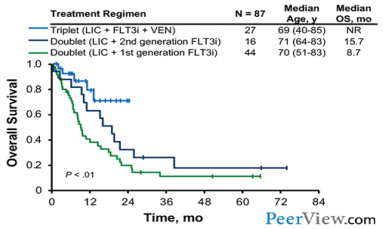


1. Short N et al. ASH 2021. Abstract 696.

Retrospective Assessment Suggests That Triplets May Be Highly Active in *FLT3*-Mutant AML[1]

- **First- and second-generation FLT3i-based doublets, triplets in older/unfit adults with ND *FLT3*-mutated AML (N = 87)**
- **Doublets** (FLT3i + low-intensity chemotherapy): CRc: 70%; survival of 9-16 mo
- **HMA/VEN/FLT3i combination** significantly improved CR/CRi rates, CR rates, FLT3-PCR and MFC MRD rates, as well as OS, without increasing 60-day mortality (7% vs 10%)

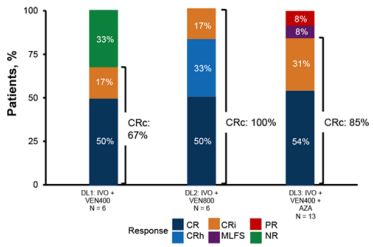


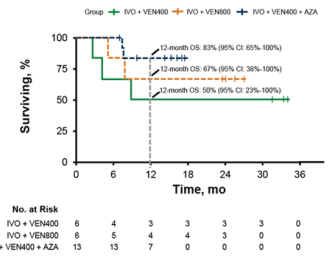


1. Yilmaz M et al. ASH 2021. Abstract 798.

A Role for Doublet and Triplet Therapy in *IDH1*-Mutant AML? Ivosidenib and Venetoclax ± AZA

- N = 25 patients with ND AML, R/R AML, or MDS/MPN[1]
- IVO + VEN ± AZA is active against *IDH1*-mutated myeloid malignancies, with an acceptable and expected toxicity profile and high rates of MRD-negative CRc in AML





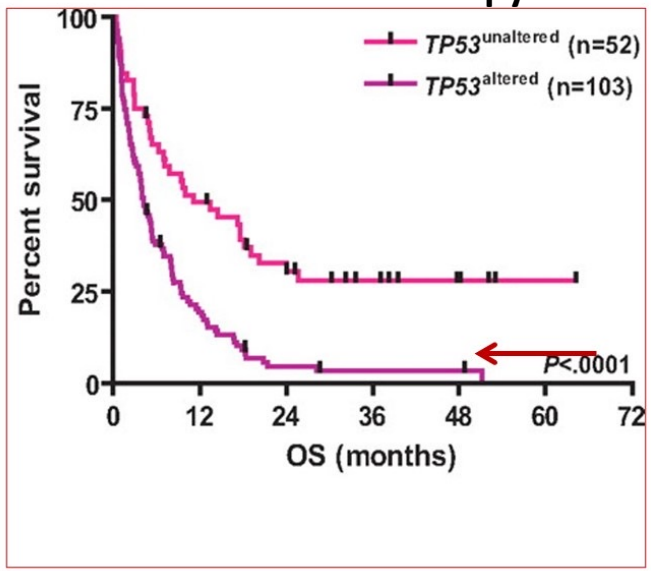
1. Lachowiez C et al. ASCO 2021. Abstract 7012.

Case 7: Patient with AML and TP53 mutation

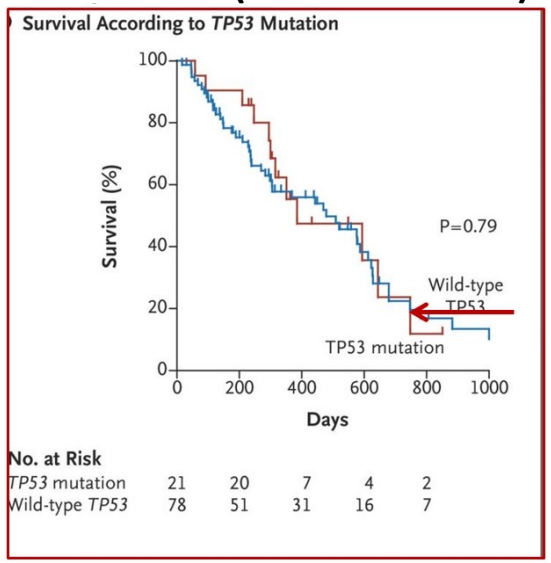
- **60-year-old male with fatigue and SOB in last 3 weeks**
  - CBC: WBC 1.3K, Hb 8.2 g/dL, PLT 54K, ANC 250
  - Normal renal and liver function. LDH 500
  - History of HL 10 years ago and remains on memission
  - BM: AML 32% blasts, MDS panel with complex karyotype
  - NGS panel shows TP53 and ASXL1 mutations
  - ECOG PS 0-1, HTN
  - HLA-identical sibling identified

AML with TP53 mutation is Chemo-resistant

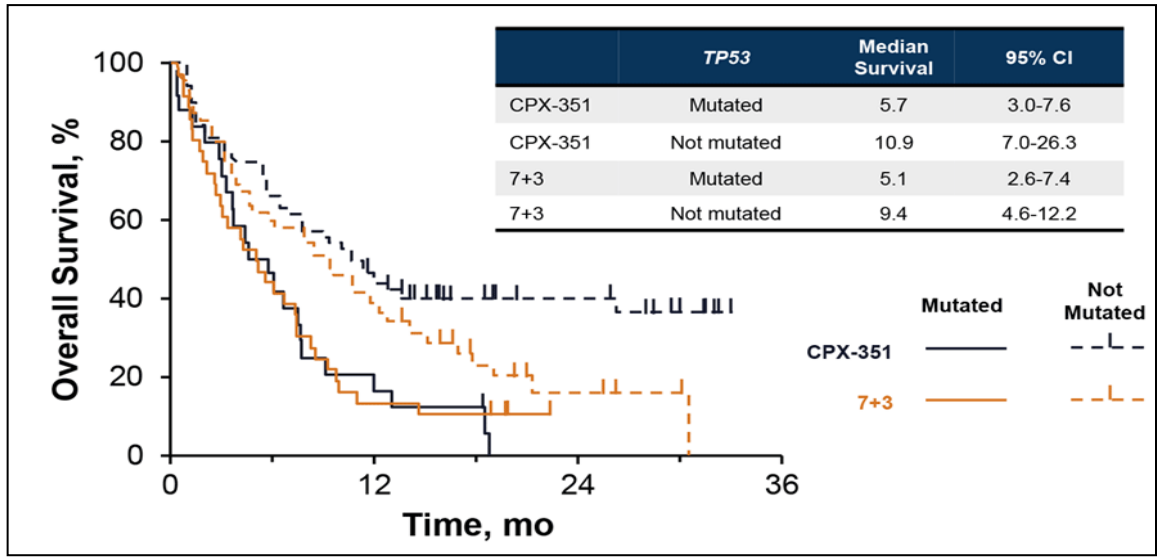
With Intensive Therapy[1]



With HMA (10 d decitabine)[2]



With CPX-351[3]



	TP53	Median Survival	95% CI
CPX-351	Mutated	5.7	3.0-7.6
CPX-351	Not mutated	10.9	7.0-26.3
7+3	Mutated	5.1	2.6-7.4
7+3	Not mutated	9.4	4.6-12.2

- TP53 Mutations occur in 10-20% AML
- More common in: t-AML, MDS/AML, Complex karyotype
- Outcomes poor in multi-hit state = Higher VAF

1. Rucker. Blood 2012. 2. Welch. NEJM 2016. 3. Linsley. ASH 2019. Abstract 15.

AML with TP53 mutation: Outcomes with Ven/HMA

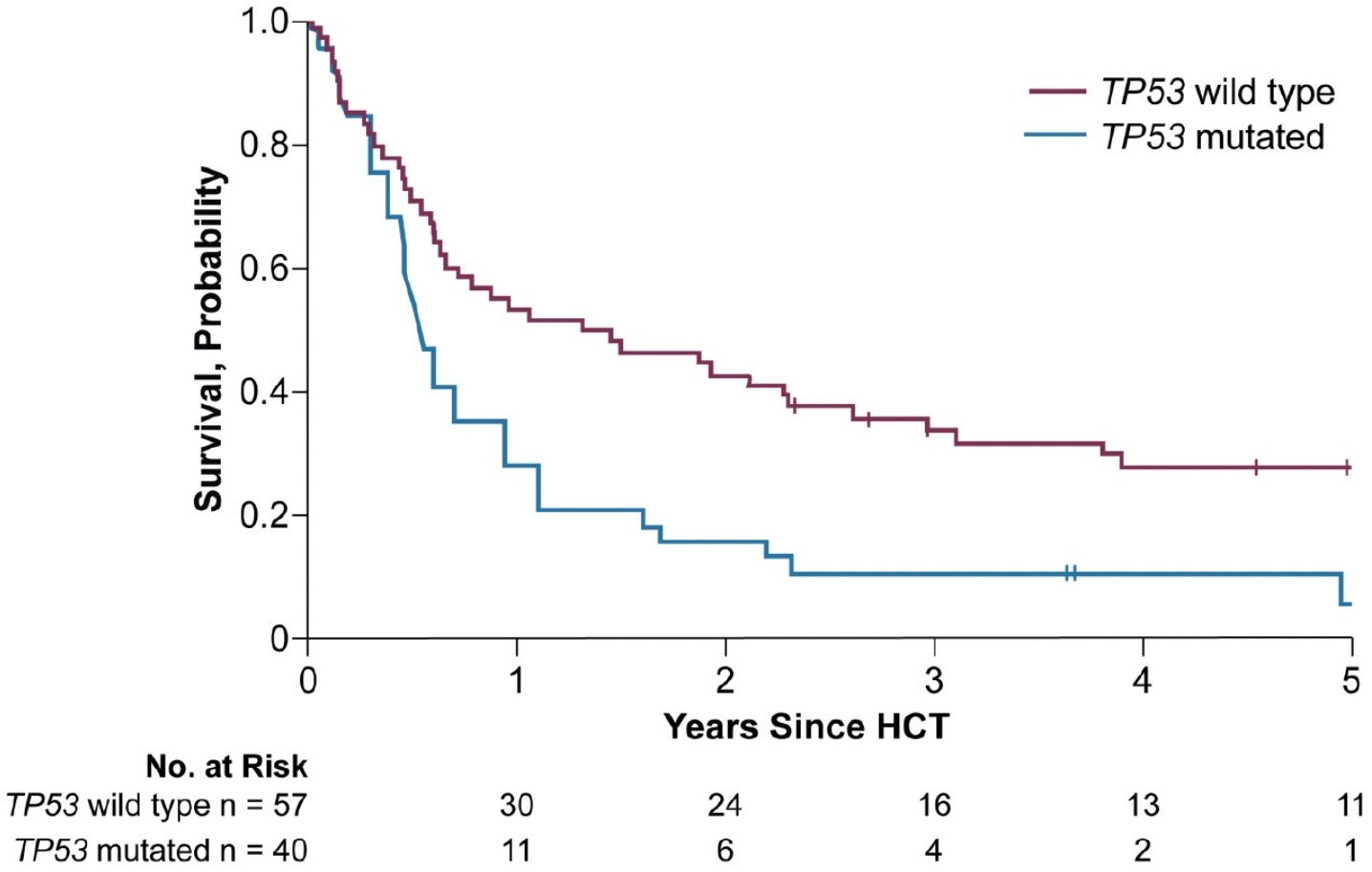
Mutation	No.	Aza +venetoclax (cCR%)	Azacitidine (cCR%)
IDH1/2		75.4	10.7
FLT3		72.4	36.4
NPM1		66.7	23.5
TP53		55.3	0
cCR=composite complete remission includes CR/CRi			

- Phase 1b AZA + Venetoclax: Median DOR 5.6 months, median OS 7.2 months
- 10-day Decitabine/venetoclax: Median OS 5.2 months
- Real world data of CPX-351 vs Venetoclax/AZA: No clear winner

- Venetoclax requires intact TP53 protein function to trigger optimal BAX/BAK mediated apoptosis[5].
- Concurrent targeting of multiple pathways – CCL2/MCL1 overcomes resistance in TP53 deficient cells[5].

1. DiNardo. NEJM. 2012. 2. DiNardo. Blood. 2019. 3. Kim. Cancer. 2021 4. Matthews. Blood Advances. 2022. 5. Thijssen. Blood. 2021

AML with TP53 mutation: Resistant despite use of HCT

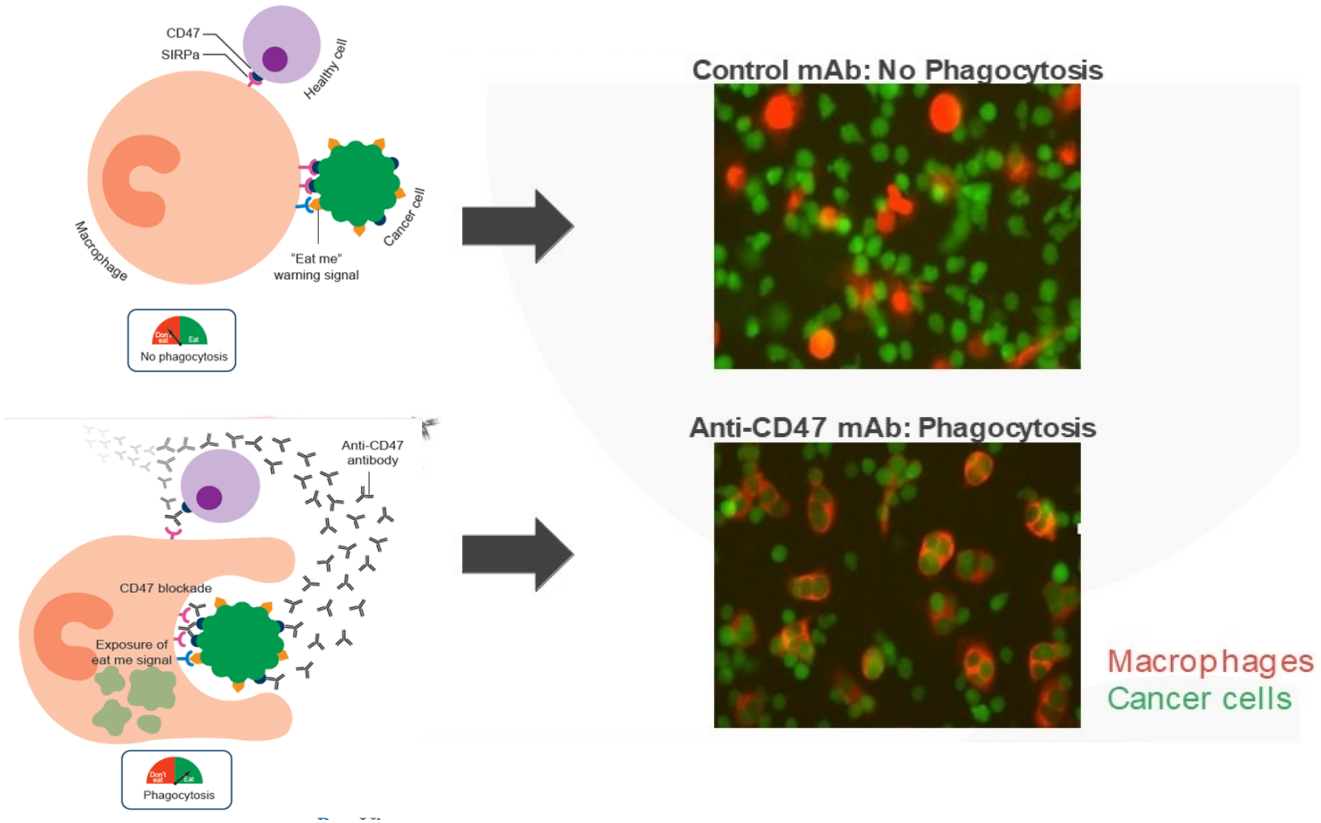


Tandem 2022:[2]

- Systematic review and meta-analysis
- N = 460 *TP53* AML patients from 6 studies were evaluated who underwent HSCT
- Poor outcomes after HCT in *TP53* AML
- **2-year OS of 15.3%**

1. Middeke. Br J Haematol. 2016;172:914 2. Mushtaq. Tandem 2022. Abstract 146.

Magrolimab (5F9) is a novel Macrophage Immune Checkpoint Inhibitor Targeting CD47[1]



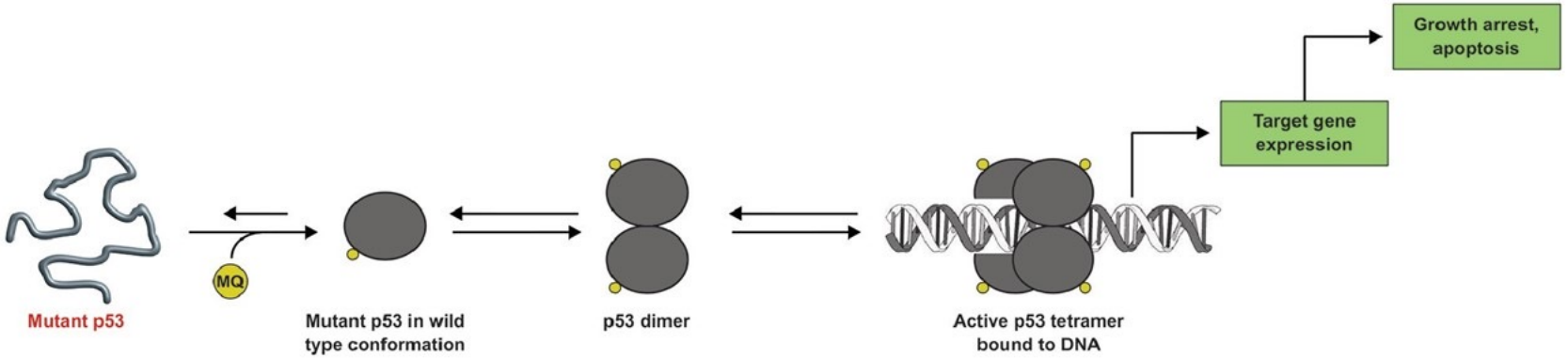
- 5F9 enables macrophages to phagocytose cancer cells by blocking the binding of the "don't eat me" signal CD47 to its receptor SIRPα
- Normal cells are not phagocytosed as they do not express "eat me" signals, except for aged red blood cells
- Additional external "eat me" signals can be provided by cancer-specific antibodies

- Promising early phase results in combination with azacytidine in TP53 mutant AML.

	All AML (N = 43), n (%)	*TP53*-Mutant AML (n = 29), n (%)
ORR	27 (63)	20 (69)
CR	18 (42)	13 (45)
CRi	5 (12)	4 (14)
PR	1 (2)	1 (3)
MLFS	3 (7)	2 (7)
SD	14 (33)	8 (28)
PD	2 (5)	1 (3)

Sallman DA. ASH 2020.

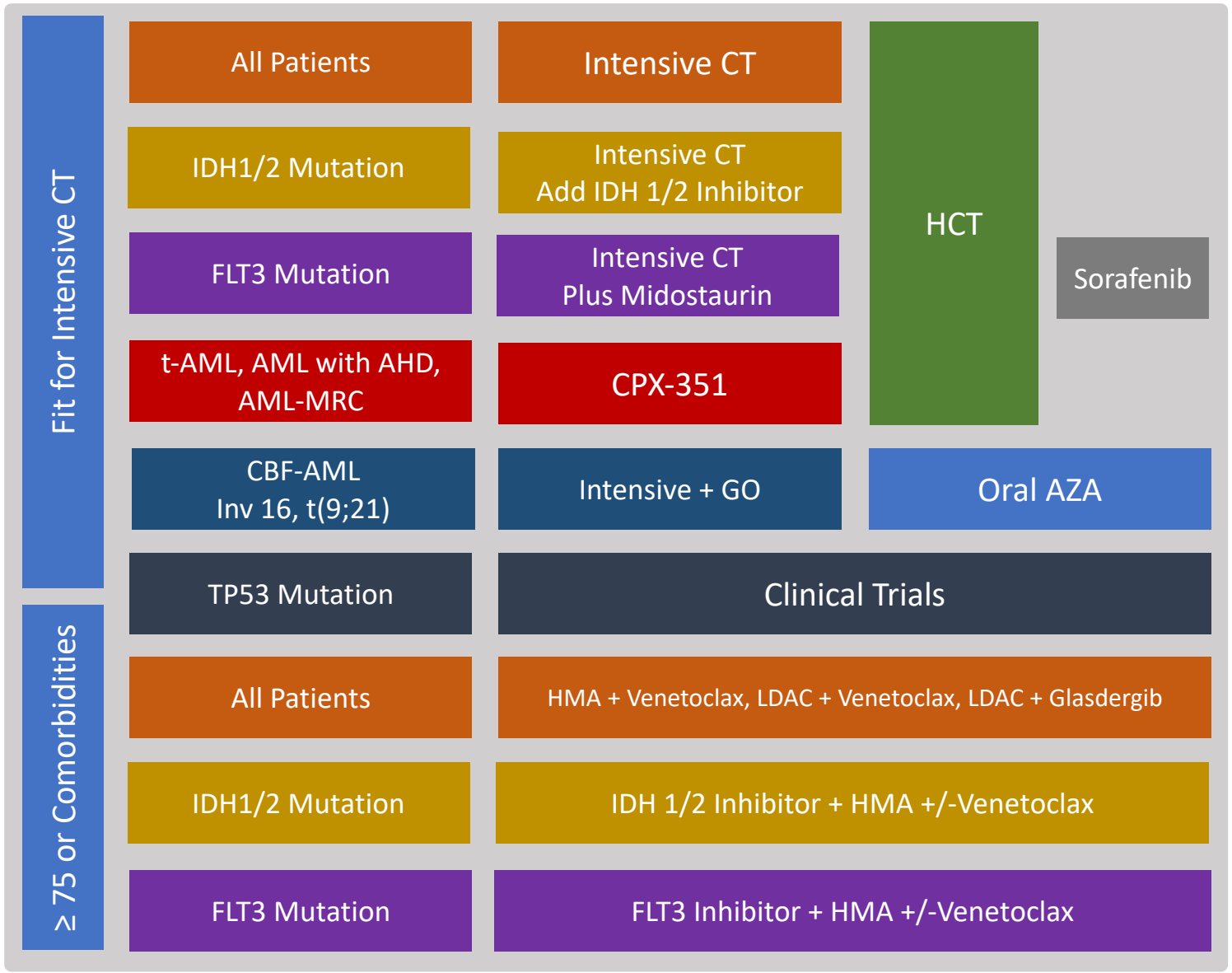
Eprenetapopt (APR-246) in TP53 mutated myeloid malignancies



- APR-246 was developed as a first in class small molecule reactivator of p53 protein function in TP53 mutant cells.
- Recent work has also uncovered TP53 independent activity through triggering of ferroptosis.
- Early phase trials in combination with azacitidine showed promise in AML/MDs.
- A phase III placebo controlled trial conducted in TP53 mutated MDS: APR-246 + AZA vs AZA did not meet the not meet the primary endpoint of CR.
- APR-548, a next generation molecule is in development.

1. Sallman D. JCO. 2021. 2. Cluzeau. 2021. 3. Birsen. Haematologica. 2022

Current Treatment Options for De Novo AML



However, Work Needs to Be Done to Expose Patients to Effective Therapy

ASH 2021: Real-world analysis of 629 newly diagnosed AML patients from a comprehensive health system in the Midwest United States, including metropolitan and rural populations (2011-2018)[1]

- 66% of patients aged ≥75 years did not receive any chemotherapy or alternative treatment
- Only 13% of patients had evidence of a genomic report, although it has been used for prognostication for at least the last decade

ASH 2021: Assessment of EMR data from 2,133 AML patients to determine the effect of COVID-19 on AML care[2]

- Compared with the pre-COVID-19 cohort, post-COVID-19 patients were significantly less likely to receive HCT
- Longer HCT waiting times suggest the pandemic affected access to timely transplantation

1. Byrd. ASH 2021. Abstract 3383 2. Chen. ASH 2021. Abstract 4139

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THANKS