A MAGYAR TUDOMÁNY ÜNNEPE

Terápiás célpontok, új utak az akut leukaemia kezelésében

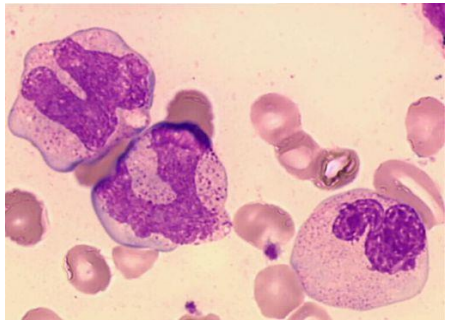
DR. BORBÉNYI ZITA

SZTE, HEMATOLÓGIA CENTRUM

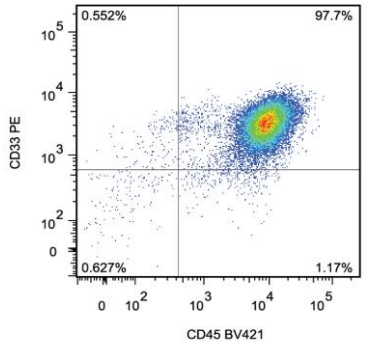
MTA MAGYAR TUDOMÁNYOS AKADÉMIA

Current Testing Used in AML Diagnostics

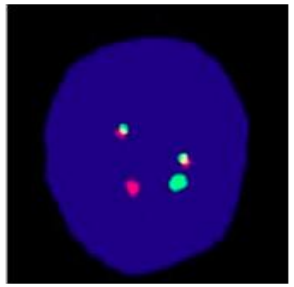
Morphology



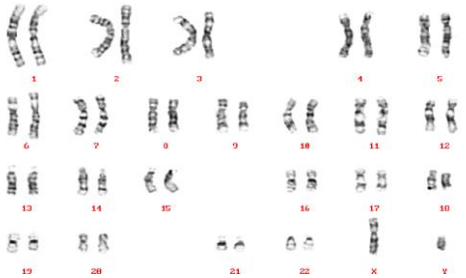
Flow Cytometry



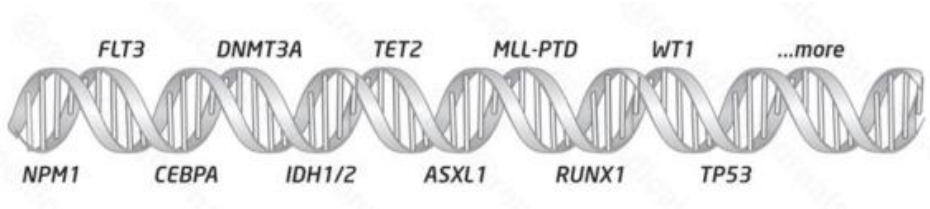
FISH



Cytogenetics



Mutation Profiling



- Risk stratification
- Guide treatment
- MRD monitoring?

Döhner. Blood. 2022;140:1345.

2022 ELN Risk Categorization for AML

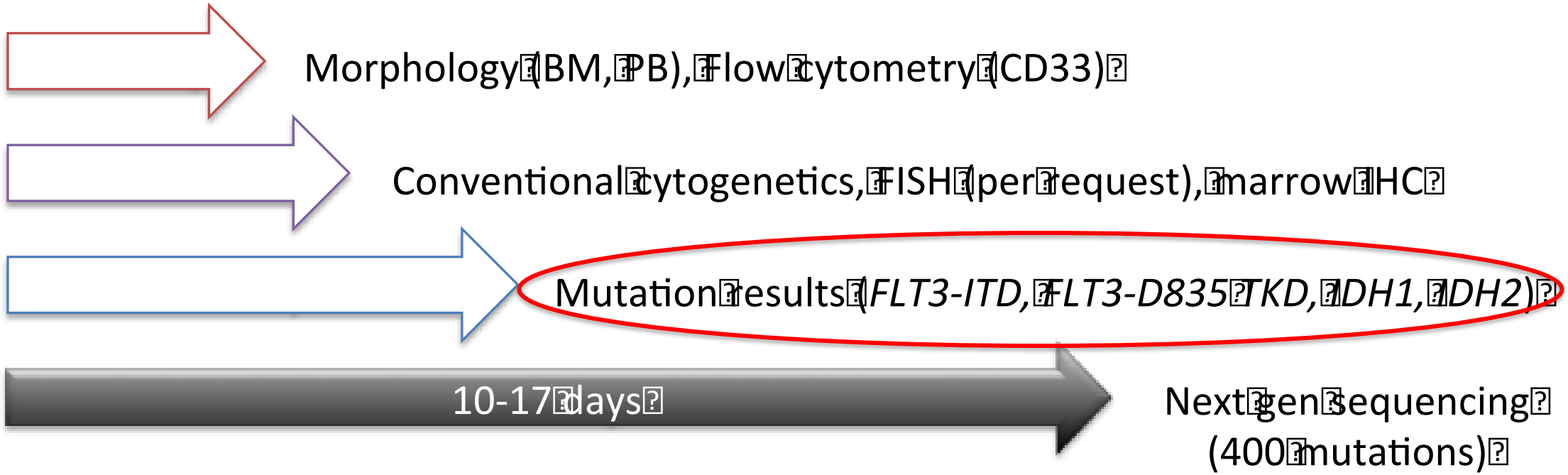
- The ELN AML risk classification is based on data from intensively treated patients and may need modifications for less-intensive therapies
- Preliminary risk assignment may change during treatment based on MRD analyses

Risk Category	Genetic Abnormalities
Favorable	▪ t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1* ▪ inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11* ▪ Mutated *NPM1* without *FLT3*-ITD ▪ bZIP in-frame mutated *CEBPA*
Intermediate	▪ Mutated *NPM1* with *FLT3*-ITD ▪ Wild-type *NPM1* with *FLT3*-ITD ▪ t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A* ▪ Cytogenetic and/or molecular abnormalities not classified as favorable or adverse

Risk Category	Genetic Abnormalities
Adverse	▪ t(6;9)(p23;q34.1)/*DEK*::*NUP214* ▪ t(v;11q23.3)/*KMT2A* rearranged ▪ t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* ▪ t(8;16)(p11.2;p13.3)/*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, monosomal karyotype ▪ Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2* ▪ Mutated *TP53*

Döhner. Blood. 2022;140:1345.

“IDEAL” Diagnostic Workup for AML



Typically we wait for reports from the top 3 test results to initiate treatment

Slide credit: clinicaloptions.com

2022 WHO Classification of Hematolymphoid Tumors

- Separation of AML into 2 families
  - AML with defining genetic abnormalities
    - Most may be diagnosed with <20% blasts (exception: *CEBPA* and *BCR::ABL1*)
  - AML defined by differentiation
- AML NOS is no longer applicable
- AML with myelodysplasia-related changes now called AML-MR
  - Mutation-based definition
  - 8 genes present in >95% of AML-MR cases: *SRSF2, SF3B1, U2AF1, ZRSR2, ASXL1, EZH2, BCOR, STAG2*

Acute myeloid leukaemia with defining genetic abnormalities
Acute promyelocytic leukaemia with *PML::RARA* fusion
Acute myeloid leukaemia with *RUNX1::RUNX1T1* fusion
Acute myeloid leukaemia with *CBFB::MYH11* fusion
Acute myeloid leukaemia with *DEK::NUP214* fusion
Acute myeloid leukaemia with *RBM15::MRTFA* fusion
Acute myeloid leukaemia with *BCR::ABL1* fusion
Acute myeloid leukaemia with *KMT2A* rearrangement
Acute myeloid leukaemia with *MECOM* rearrangement
Acute myeloid leukaemia with *NUP98* rearrangement
Acute myeloid leukaemia with *NPM1* mutation
Acute myeloid leukaemia with *CEBPA* mutation
Acute myeloid leukaemia, myelodysplasia-related
Acute myeloid leukaemia with other defined genetic alterations
Acute myeloid leukaemia, defined by differentiation
Acute myeloid leukaemia with minimal differentiation
Acute myeloid leukaemia without maturation
Acute myeloid leukaemia with maturation
Acute basophilic leukaemia
Acute myelomonocytic leukaemia
Acute monocytic leukaemia
Acute erythroid leukaemia
Acute megakaryoblastic leukaemia

Khoury. Leukemia. 2022;36:1703.

Selecting Therapy for AML Without Predictive Biomarkers

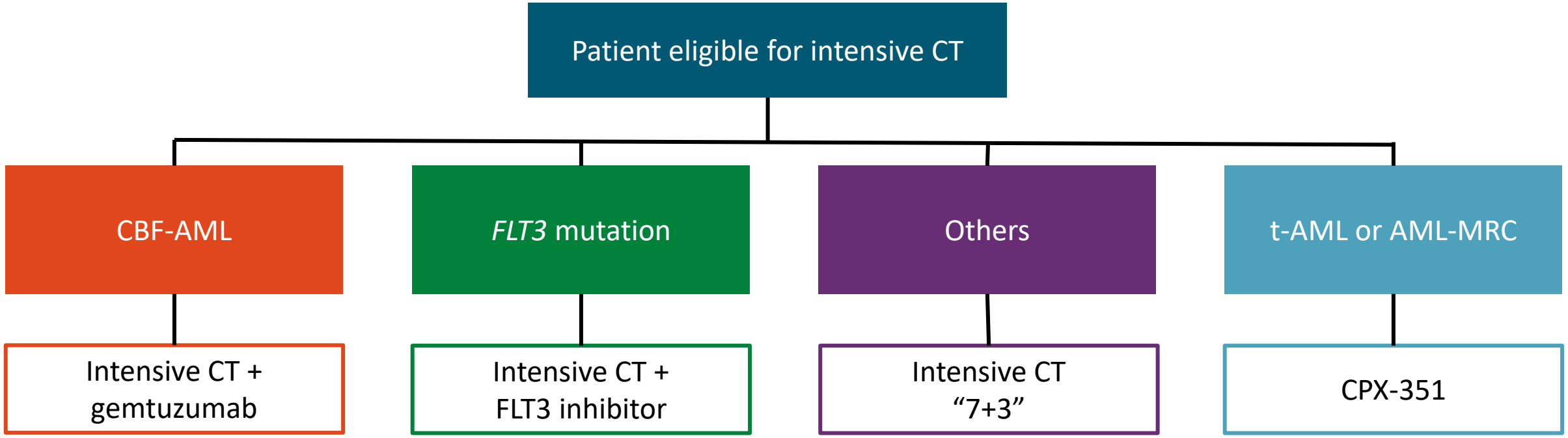
Fit for Intensive, Potentially Curative CT

Ineligible for Standard Induction Therapy

Selecting Therapy for AML With Predictive Biomarkers

AML Maintenance Strategies

Updated Paradigm of Newly Diagnosed AML Eligible for Intensive Therapy



- SCT (especially if adverse risk, please *consider* in intermediate risk)
- CC-486 (oral AZA) maintenance for patients NOT proceeding to SCT in CR1

Richard-Carpentier. Clin Lymphoma Myeloma Leuk. 2020;20:212.

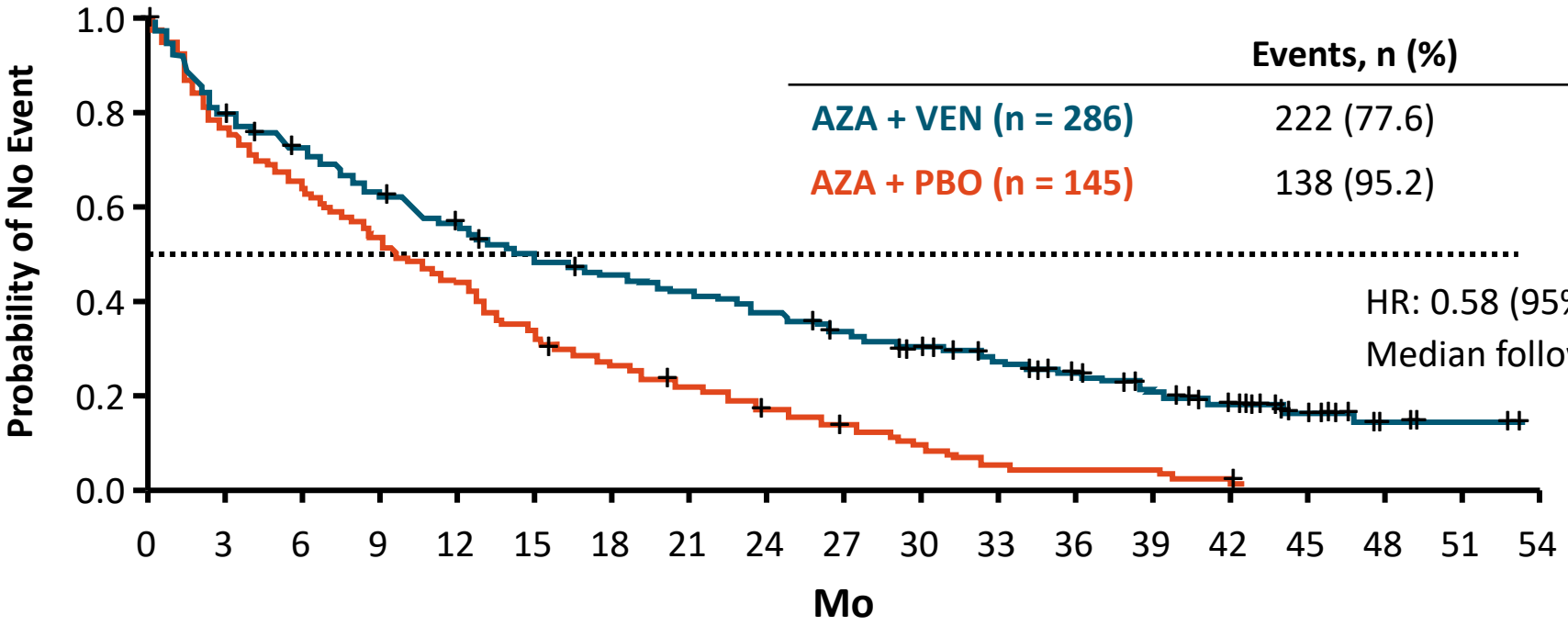
Initial Therapy for Adult Patients With AML
Fit for Intensive, Potentially Curative CT

Patients with AML particularly sensitive to conventional CT:

- Younger patients (<65 yr) without therapy-related AML
- Core binding factor leukemia = t(8;21) or inv(16)
- Diploid (normal karyotype) AML with *NPM1* mutation

Selecting Therapy for AML Without Predictive Biomarkers/Actionable Alterations

Azacitidine ± Venetoclax in Treatment-Naive AML Ineligible for Standard Induction Therapy Overall Survival



	Events, n (%)	Median OS, Mo (95% CI)
AZA + VEN (n = 286)	222 (77.6)	14.7 (12.1–18.7)
AZA + PBO (n = 145)	138 (95.2)	9.6 (7.4-12.7)

HR: 0.58 (95% CI: 0.47-0.72; *P* <.001)
Median follow-up: 43.2 mo

\+ Censored

Patients at Risk, n

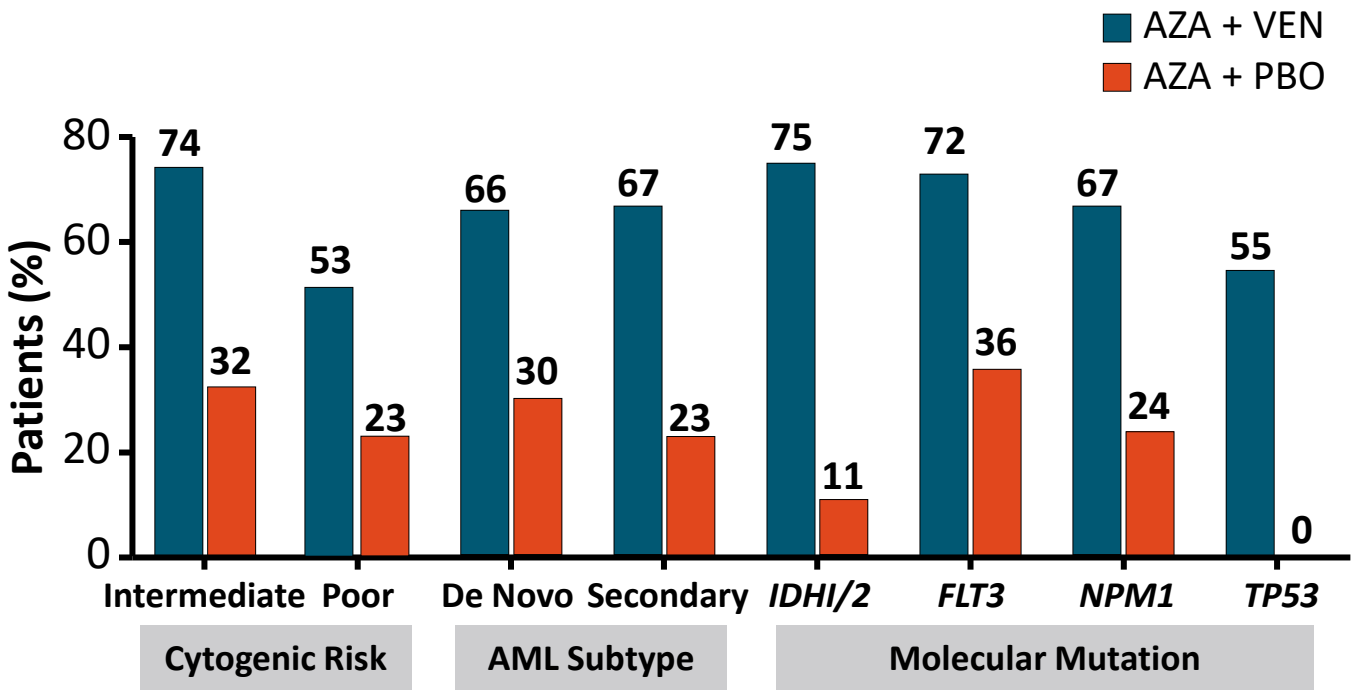
AZA + VEN	286	220	199	173	153	133	122	113	101	89	78	67	57	45	34	18	6	2	0
AZA + PBO	145	109	92	77	63	47	37	30	22	17	12	6	5	5	3	0	0	0	0

Pratz. ASH 2022. Abstr 219.

VIALE-A: Responses by Baseline Genomics

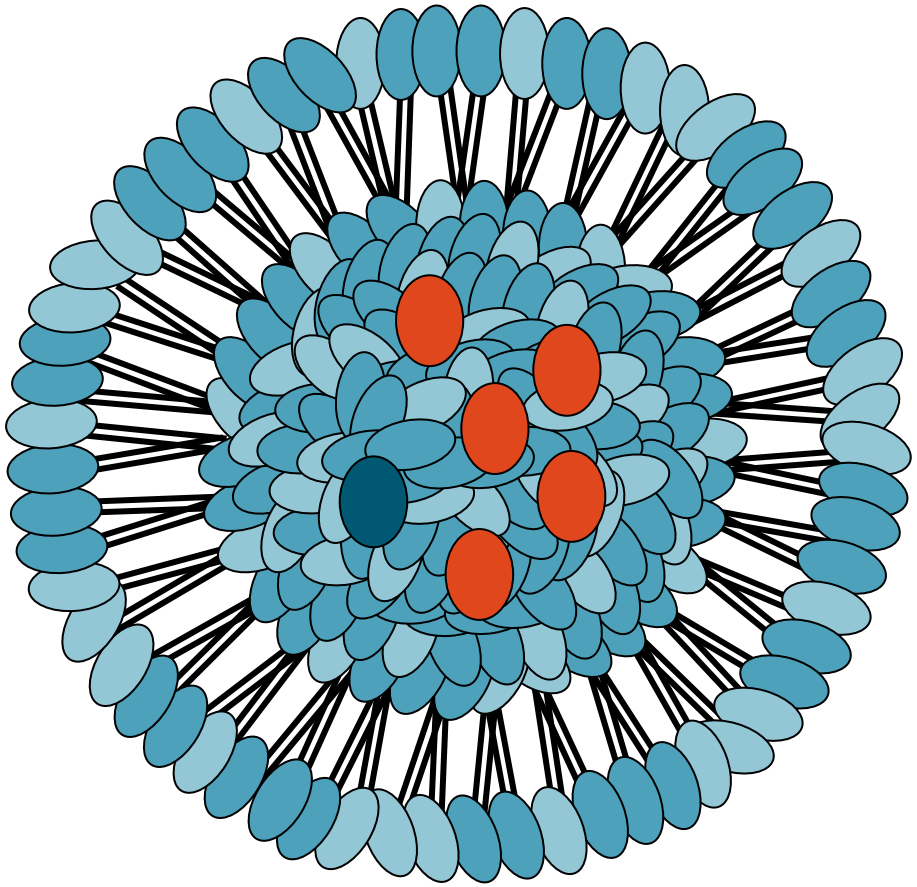
CR rate: 36.7% vs 17.9% (*P* <.001)
CR/CRi rate: 66.4% vs 28.3% (*P* <.001)
Median time to response: 1 vs 3 cycles (*P* <.001)

Improved Responses Occurred *Independently* of High-Risk Genomics



DiNardo. EHA 2020. Abstr LB2601.

Liposomal Cytarabine and Daunorubicin (CPX-351)

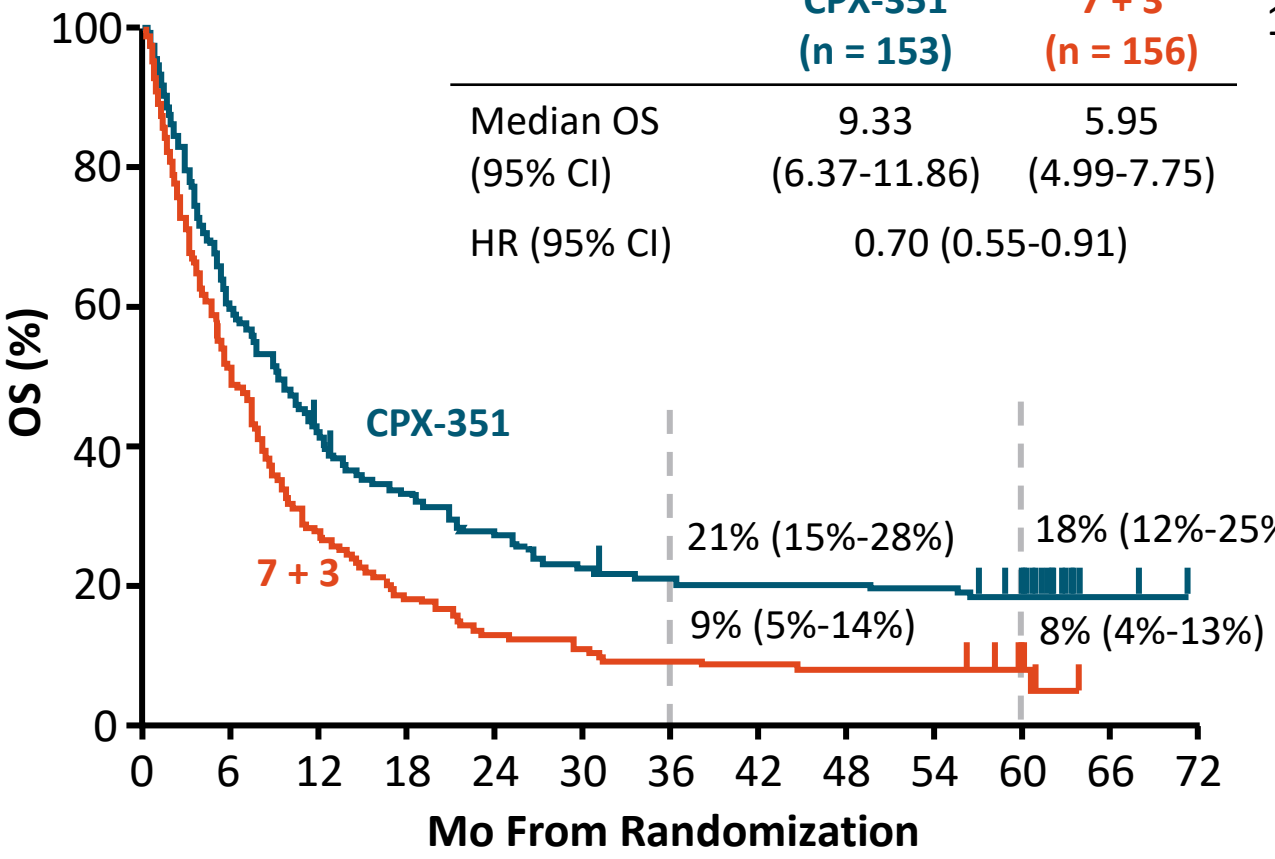


- CPX-351 maintains 5:1 molar ratio of cytarabine:daunorubicin
- Formulation provides synergistic leukemia cell killing in vitro[1]
- In humans
  - CPX-351 preserved delivery of 5:1 drug ratio for >24 hr
  - Drug exposure maintained for >7 days[2]
- Selective uptake of liposomes by bone marrow leukemia cells in xenograft models[3]

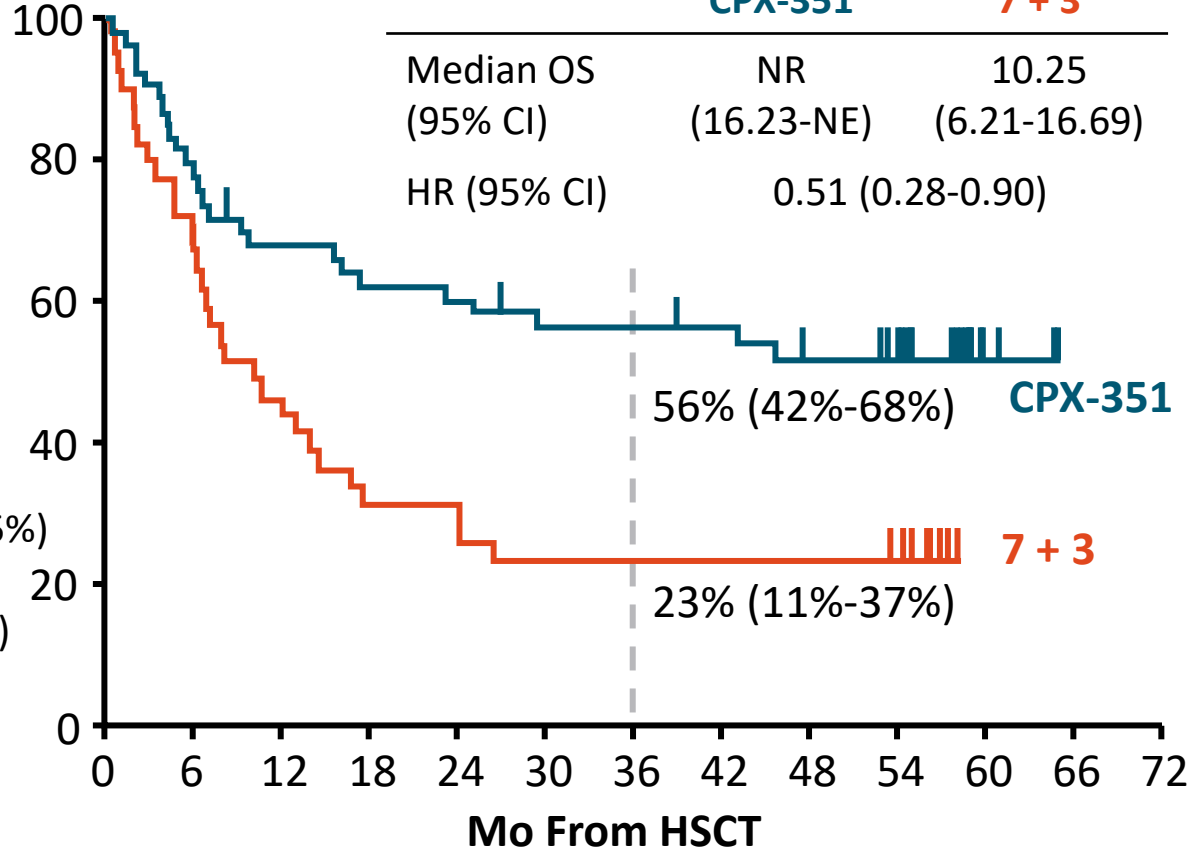
1. Tardi. Leuk Res. 2009;33:129. 2. Feldman. JCO. 2011;29:979. 3. Lim. Leuk Res. 2010;34:1214.

CPX-351 in Older Patients With Newly Diagnosed s-AML

Overall Survival



OS by Time Since HSCT

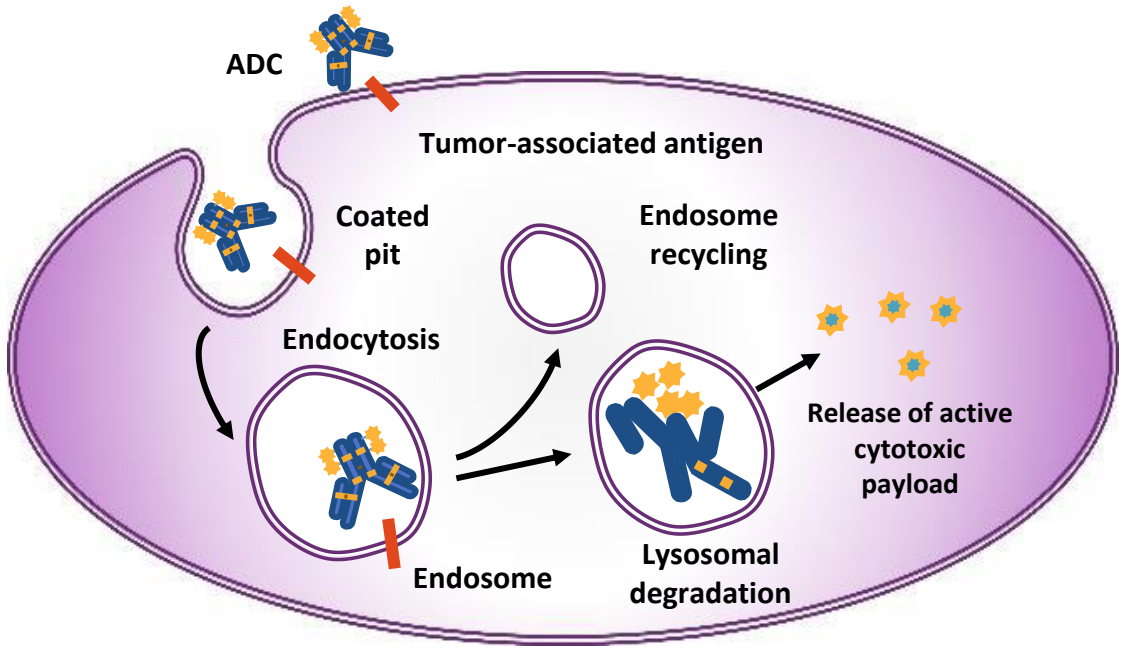


Lancet. Lancet Haematol. 2021;8:e481.

Selecting Therapy for AML With Predictive Biomarkers/Actionable Alterations

Gemtuzumab Ozogamicin (CD33-Targeted ADC)

- CD33 is present on >90% of AML blasts

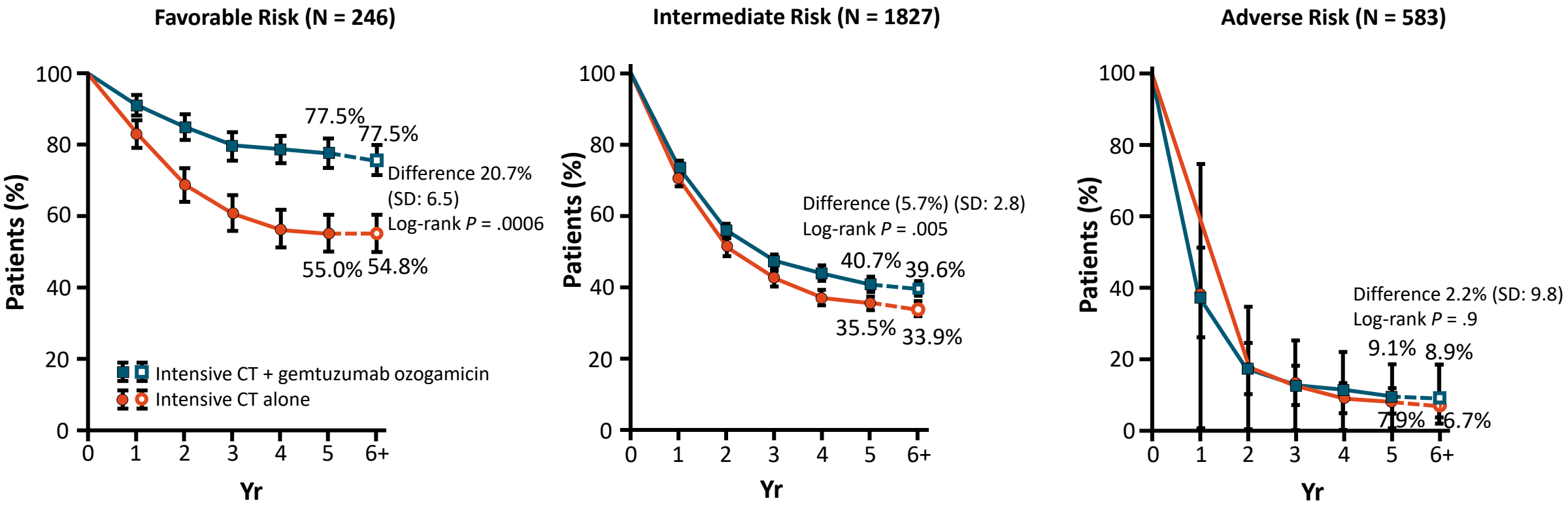


- Approved in 2000: CT-ineligible patients with R/R CD33-positive AML aged ≥60 yr (9 mg/m^2)
  - Confirmatory phase III trial suggested higher toxicity and induction mortality, concerns about hepatotoxicity and veno-occlusive disease → withdrawn from market in 2010
- Reapproved in 2017: patients with ND CD33-positive AML (≥1 mo) or R/R CD33-positive AML (≥2 yr)
  - 3 mg/m^2 (with 7+3) *or* 6 mg/m^2 followed by 3 mg/m^2 (single agent)

Schrama. Nat Rev Drug Discov. 2006;5:147. Bross. Clin Cancer Res. 2001;7:1490. Gemtuzumab ozogamicin PI.

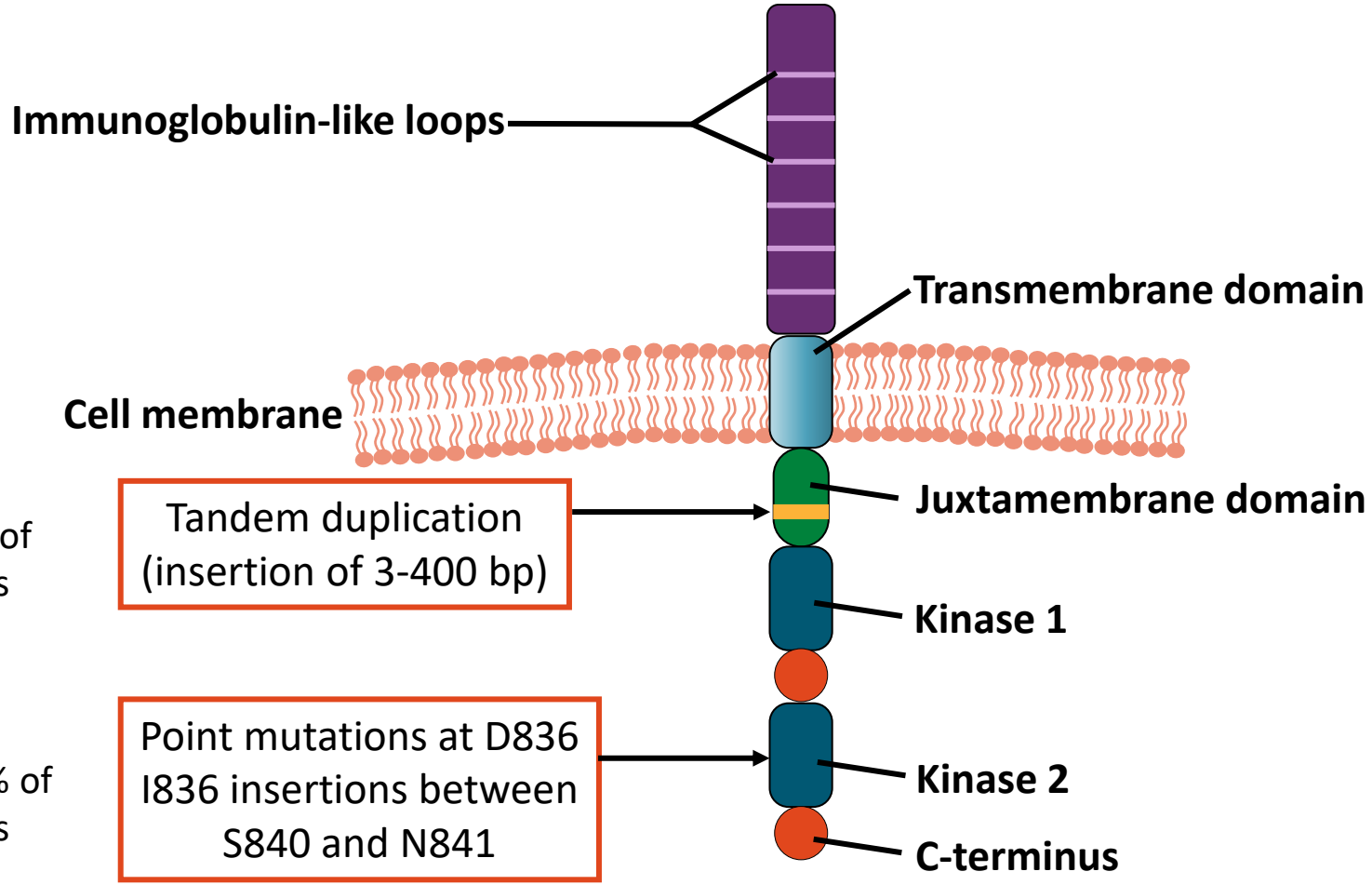
Addition of Gemtuzumab Ozogamicin to Standard Intensive Therapy Most Benefits Favorable-Risk Cytogenetics

Meta-analysis of Overall Survival in 5 Trials (N = 3325)



Hills. Lancet Oncol. 2014;15:986.

Activating *FLT3* Mutations



ITD Mutations ~25% of cases

Tandem duplication (insertion of 3-400 bp)

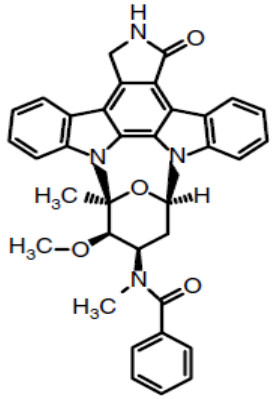
TKD Mutations 5%-10% of cases

Point mutations at D836
I836 insertions between S840 and N841

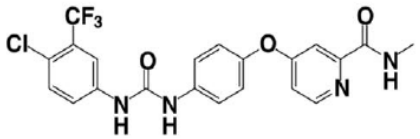
Litzow. Blood. 2005;106:3331. Almatani. Pharmacol Ther. 2021;225:107844.

FLT3 Inhibitors

First Generation

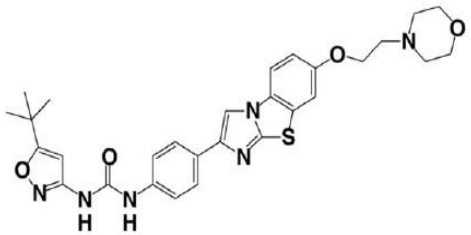


Midostaurin

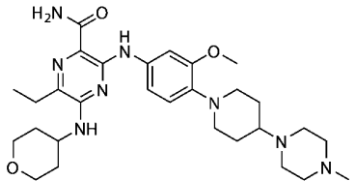


Sorafenib

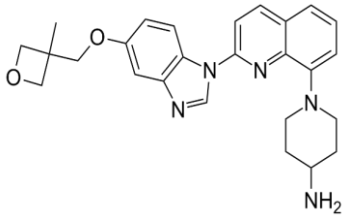
Second Generation



Quizartinib



Gilteritinib

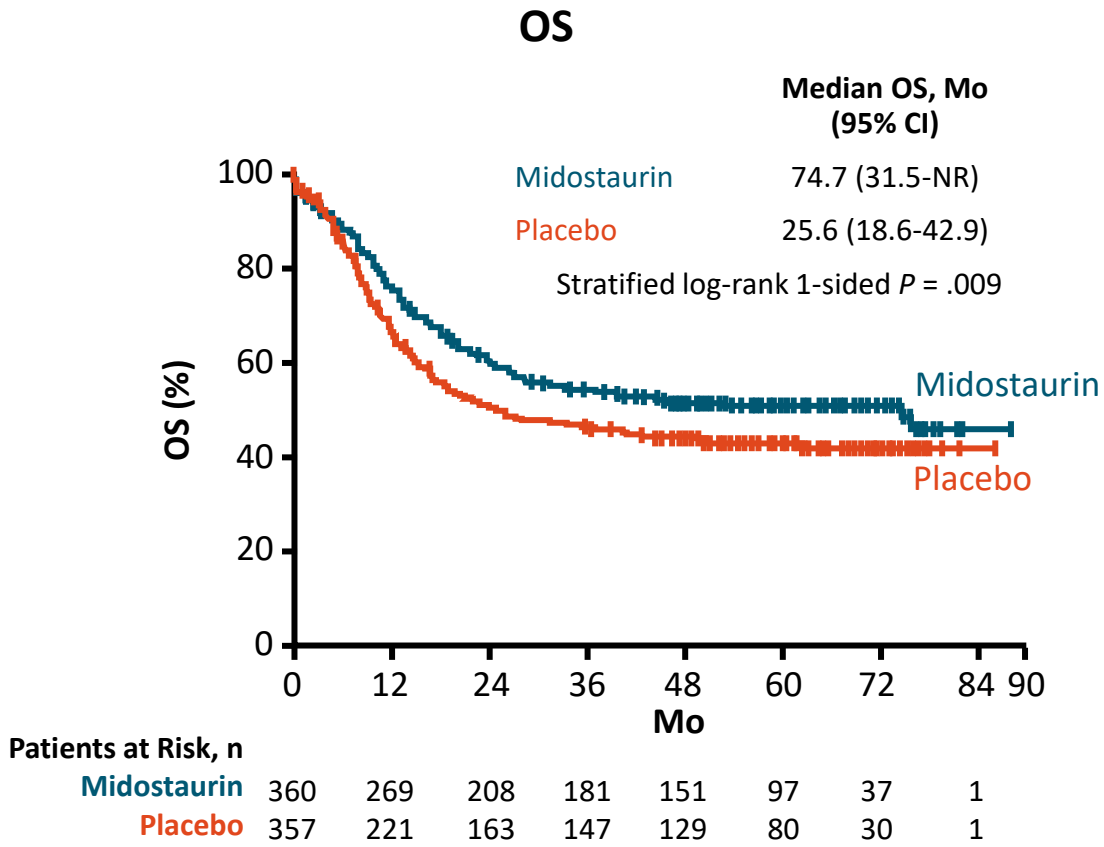


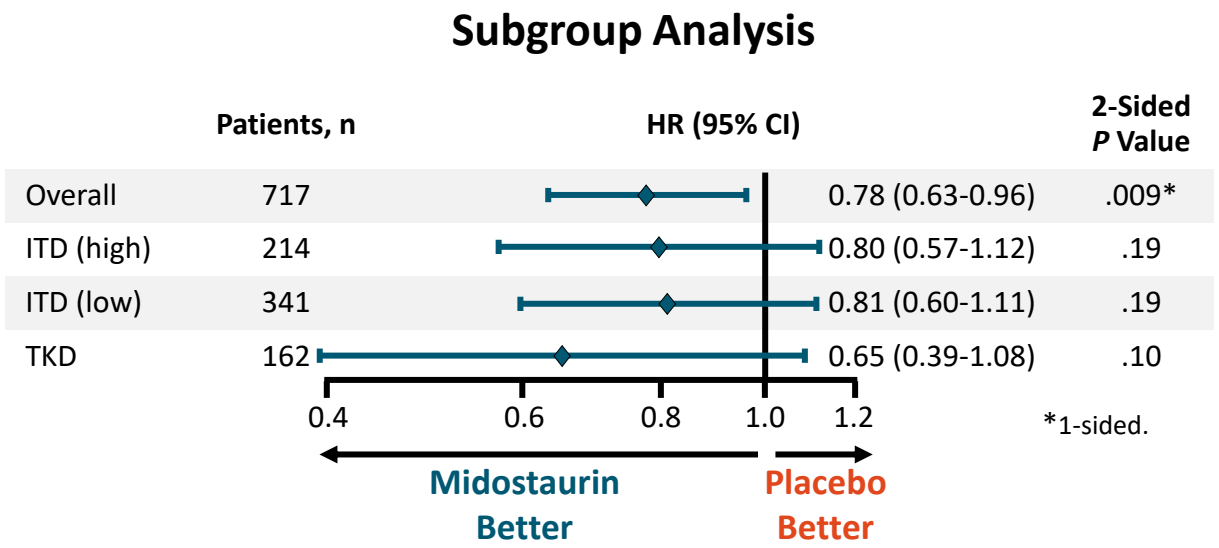
Crenolanib

- **Type I FLT3 inhibitor:** inhibits *FLT3*-ITD and TKD mutations
- **Type II FLT3 inhibitor:** inhibits only *FLT3*-ITD mutations

Zhi. Int J Mol Sci. 2019;20:5739. Novatcheva. Clin Lymphoma Myeloma Leuk. 2022;22:e161.

RATIFY: Overall Survival

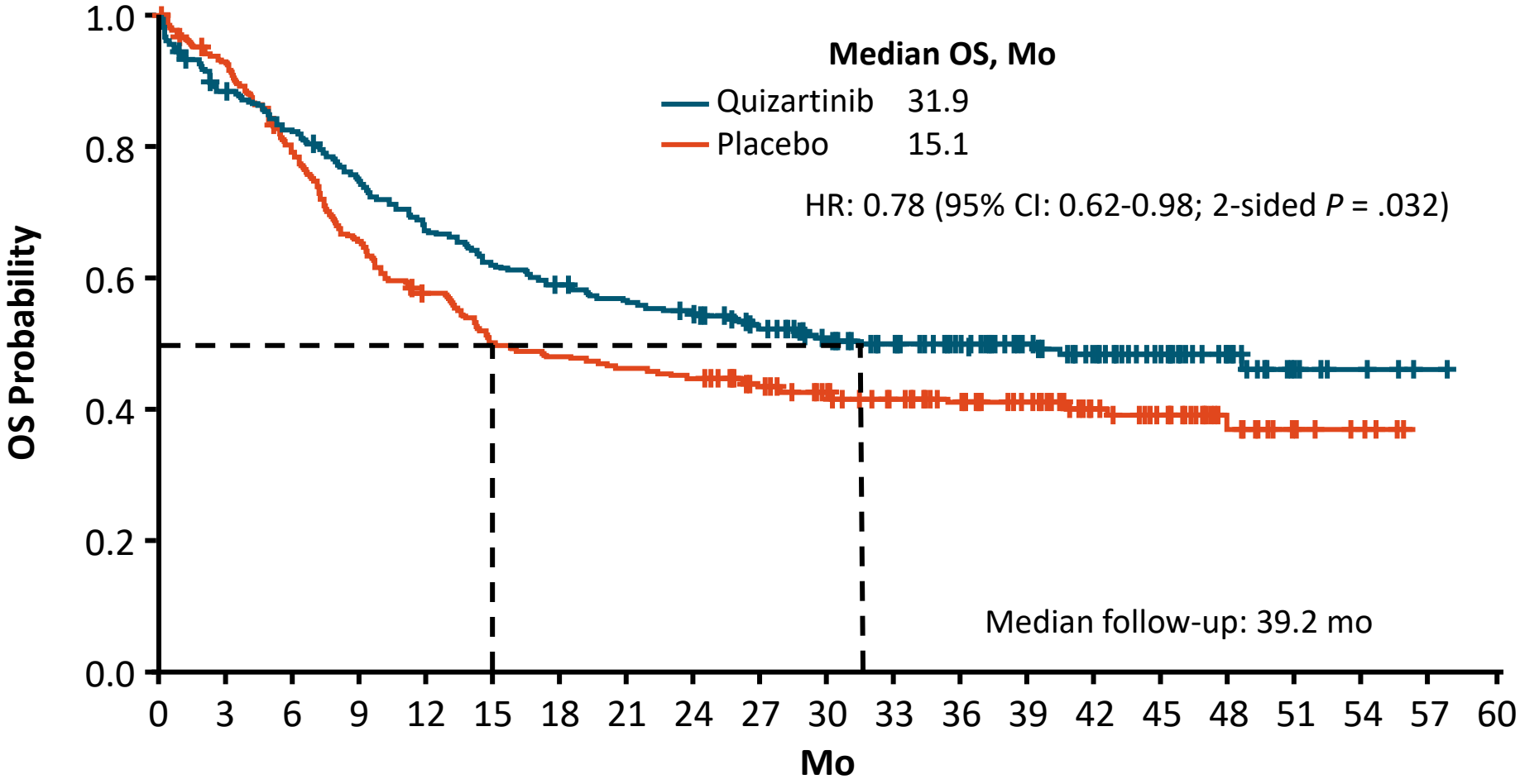




- **OS was significantly longer with midostaurin vs placebo group (HR: 0.78; *P* = .009)**
- 24.3% reduced risk of death in midostaurin arm
- At 4 yr, 63.7% were alive in midostaurin arm vs 55.7% in placebo arm

Stone. NEJM. 2017;377:454.

QuANTUM-First: OS (Primary Endpoint)

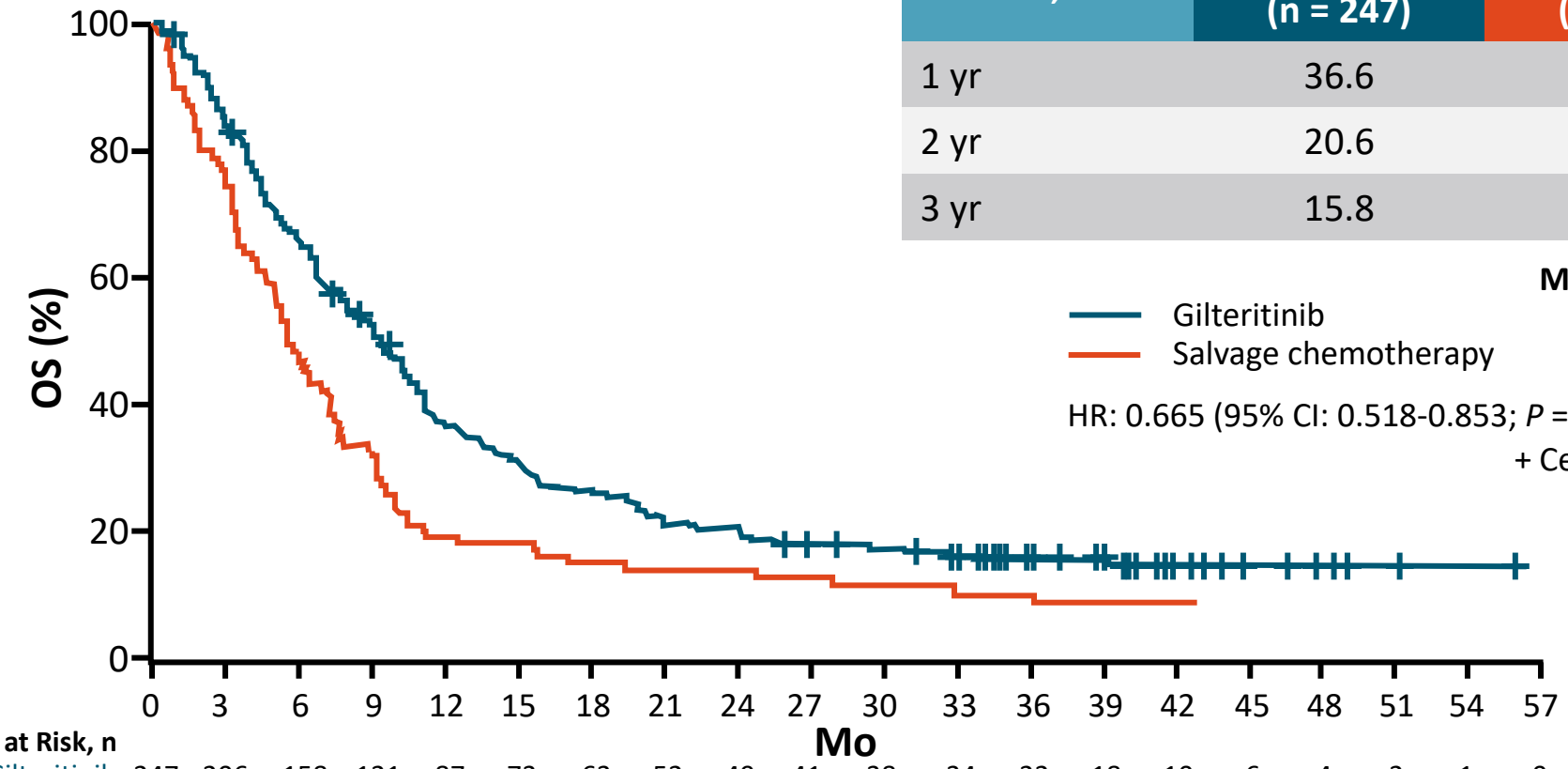


On July 20, 2023, the FDA approved quizartinib + cytarabine and anthracycline induction and cytarabine consolidation, and quizartinib maintenance monotherapy after consolidation CT for adults with newly diagnosed *FLT3-ITD+* AML

Erba. Lancet. 2023;401:1571. Erba. EHA 2022. Abstr S100. Quizartinib PI.

ADMIRAL: Gilteritinib Prolongs OS in m*FLT3* R/R AML

OS Rate, %	Gilteritinib (n = 247)	Salvage CT (n = 124)
1 yr	36.6	19.2
2 yr	20.6	14.2
3 yr	15.8	10.4



Perl. Blood. 2022;139:3366.

IDH1/2-Mutant AML

- *IDH1/2* mutations present in 8% to 15% of patients with AML, respectively; associated with normal cytogenetic status
- IDH proteins are essential to Krebs cycle; catalyze decarboxylation of isocitrate to α-ketoglutarate in cytoplasm (IDH1) and mitochondria (IDH2)
- Mutant IDH enzymes catalyze NADPH-dependent reduction of α-ketoglutarate to 2-hydroxyglutarate
- This leads to accumulation of 2-hydroxyglutarate oncometabolite in *IDH1/2*-mutant tumors

Issa. Blood Cancer J. 2021;11:107. Mardis. NEJM. 2009;361:1058. Ward. Cancer Cell. 2010;17:225.
Gross. J Exp Med. 2010;207:339. Dang. Nature. 2009;462:739.

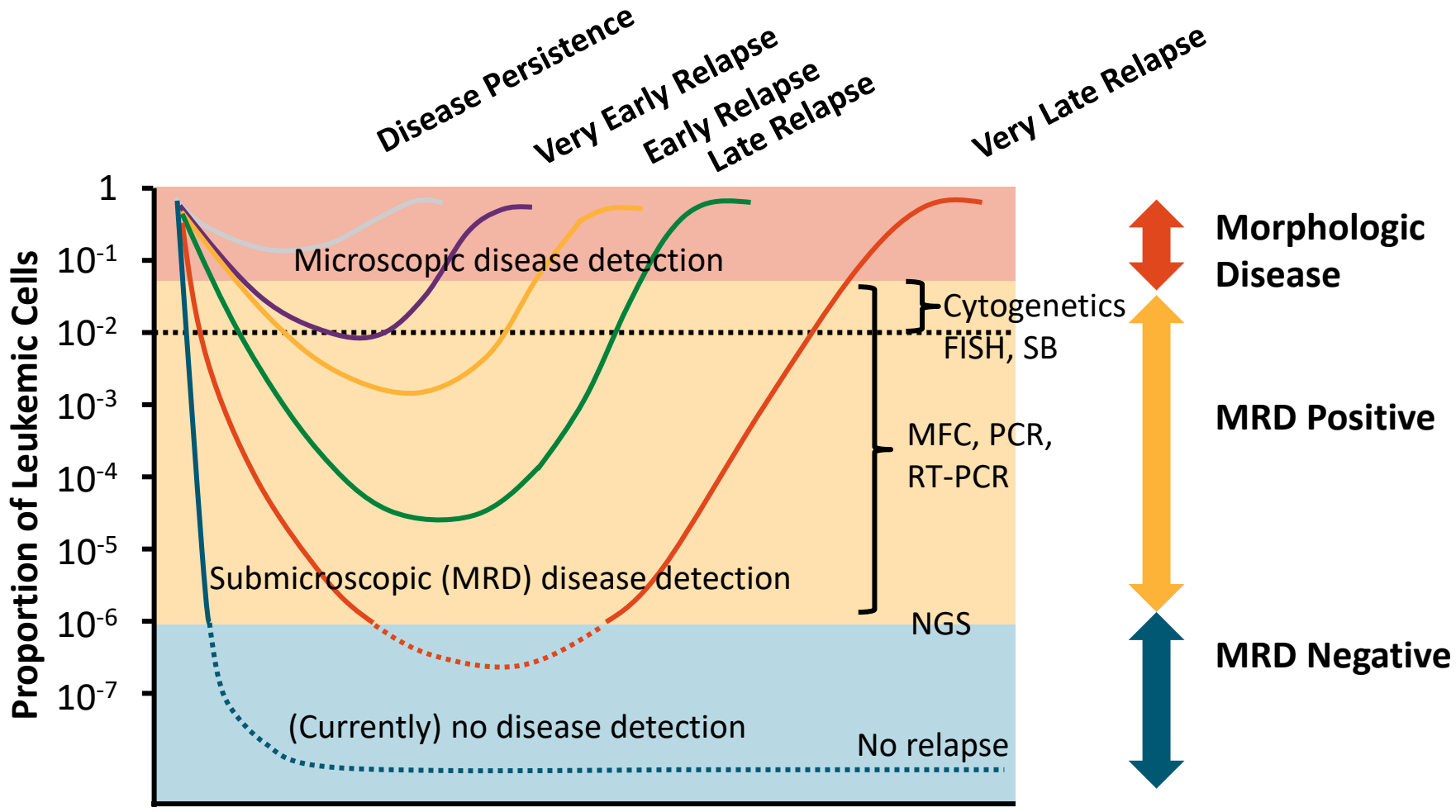
FDA-Approved IDH Inhibitors for AML

IDH Inhibitor	Indications	Key Trials
Enasidenib	▪ Adults with relapsed/refractory AML who have *IDH2* mutation	AG221-C-001 (NCT01915498)
Ivosidenib	▪ Adults with relapsed/refractory AML who have susceptible *IDH1* mutation	AG120-C-001 (NCT02074839)
	▪ Adults aged 75 yr or older or who have comorbidities that preclude use of induction chemotherapy, in combination with azacitidine or as monotherapy, for newly diagnosed AML with a susceptible *IDH1* mutation	AG120-C-009/AGILE (NCT03173248)
Olutasidenib	▪ Adults with relapsed/refractory AML with susceptible *IDH1* mutation	Study 2102-HEM-101 (NCT02719574)

Enasidenib PI. NCT01915498. Ivosidenib PI. NCT02074839. NCT03173248. Olutasidenib PI. NCT02719574.

Measurable Residual Disease

MRD Definition:
Residual leukemia not detected by morphology (<5% blasts)



Adapted from: Buckley. Bone Marrow Transplant. 2013;48:630.

Measuring MRD in AML

Method	Target	Sensitivity	Strengths	Weaknesses
Cytogenetics	Chromosomal aberrations	1/20 (5%)	Widely available	Insensitive
FISH	Chromosomal aberrations	1/500 (0.2%)	Widely available; detects numeric cytogenetic abnormalities	Insensitive
Flow cytometry	Leukemia-associated aberrant immunophenotype	1/10,000 to 1/100,000 (0.01% to 0.001%)	Wide applicability (>90%), results in ≤1 day, leukemia stem cell phenotype	Requires experienced pathologist; sensitivity depends on antibody panel; phenotype not always stable
RT-qPCR	Fusion transcripts, gene mutations, overexpressed genes	1/100,000 to 1/1,000,000 (0.001% to 0.0001%)	Wide applicability; high sensitivity; well standardized	Multiple days; expensive; applicable to only ~50% of AML
NGS	Gene mutations	1/100,000 to 1/1,000,000 (0.001% to 0.0001%)	Relatively easy to perform; sensitive	Limited standardization; CHIP-mutated genes; persistent mutants in CR

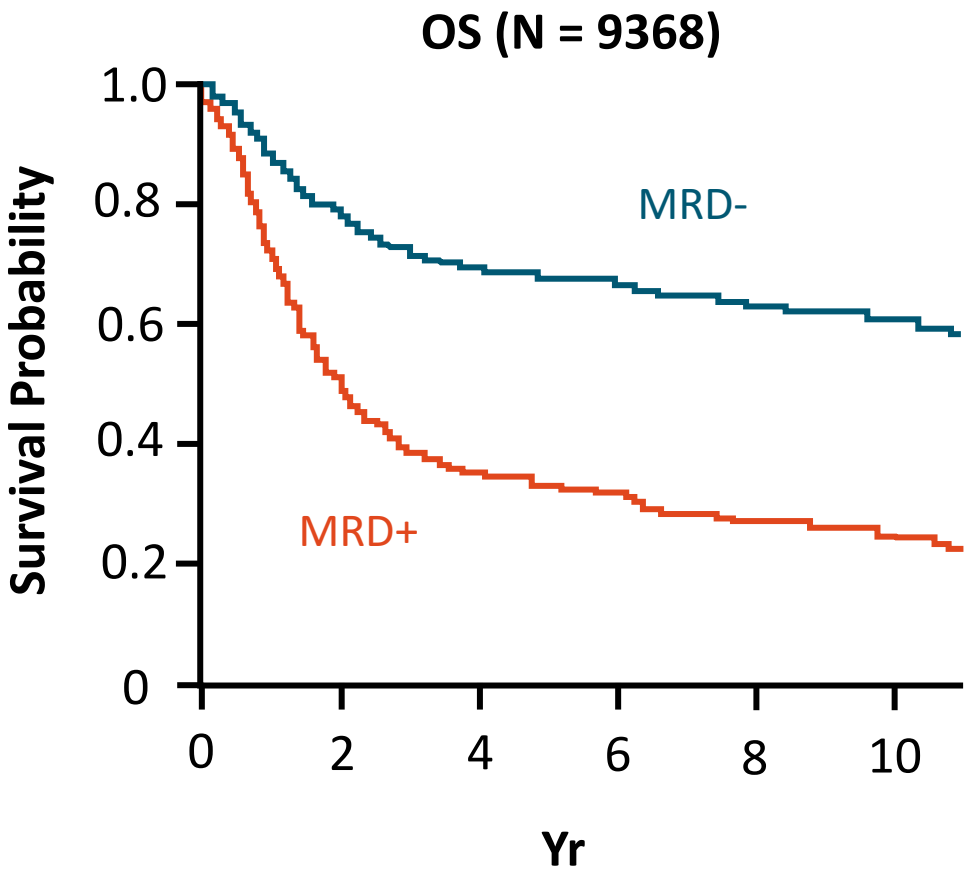
Schuurhuis. Blood. 2018;131:1275. Ravandi. Blood Adv. 2018;2:1356.

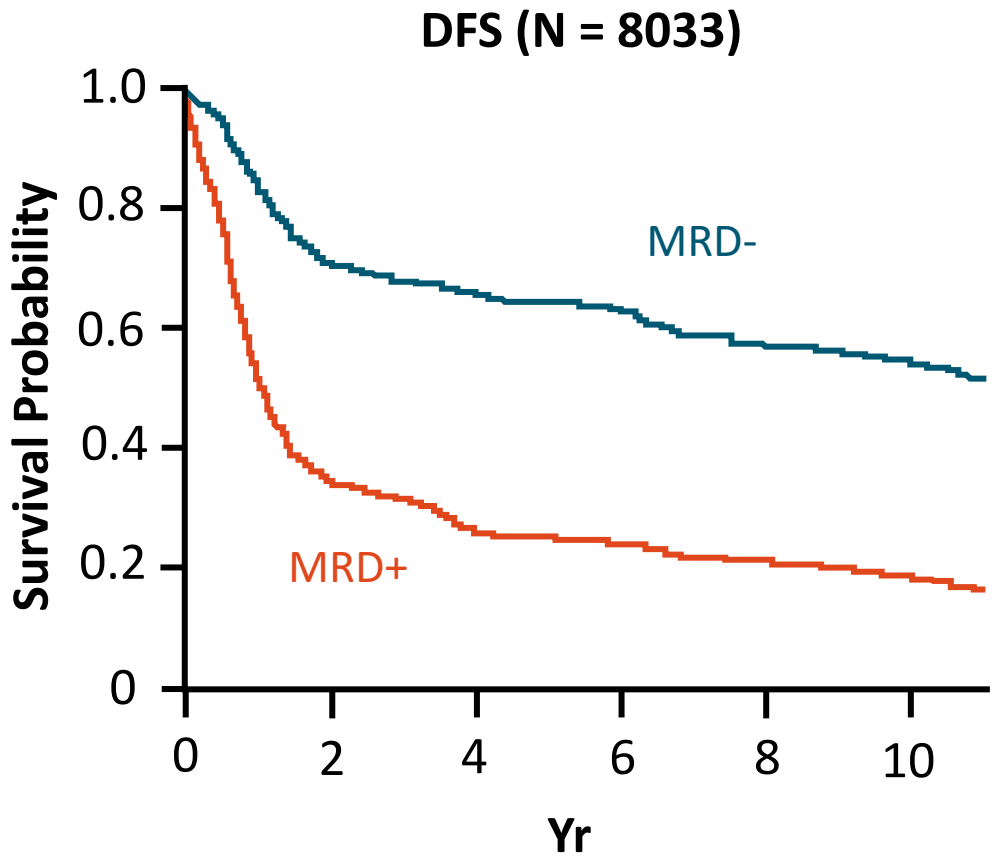
Implementing MRD Testing Into Treatment Decision Making

- **Recommended timing of MRD assessment:**
  - At the completion of initial induction
  - Prior to transplantation
  - Additional testing should be guided by the regimen being used
- MRD positivity is correlated with an increased risk of relapse and poor posttransplant outcomes
- MRD testing is limited by the sensitivity, specificity, and reproducibility of different assays
  - MRD positivity is not proof of relapse, and relapse may occur in patients who are MRD negative

Döhner. Blood. 2022;140:1345. Walter. Leukemia. 2021;35:1529. Short. JAMA Oncol. 2020;6:1890.
NCCN. Clinical practice guidelines in oncology: acute myeloid leukemia. v3.2023.

MRD and Survival in AML: Meta-analysis of 81 Publications





Short. JAMA Oncol. 2020;6:1890.

AML Maintenance Strategies

Recommended Postchemotherapy Maintenance

Patient with intermediate or adverse risk disease who meets the following criteria:

- Received intensive CT and AML is in remission
- Completed no consolidation, a recommended consolidation treatment course, or some consolidation
- No alloHCT planned

→

Recommended maintenance therapy until PD or unacceptable toxicity:

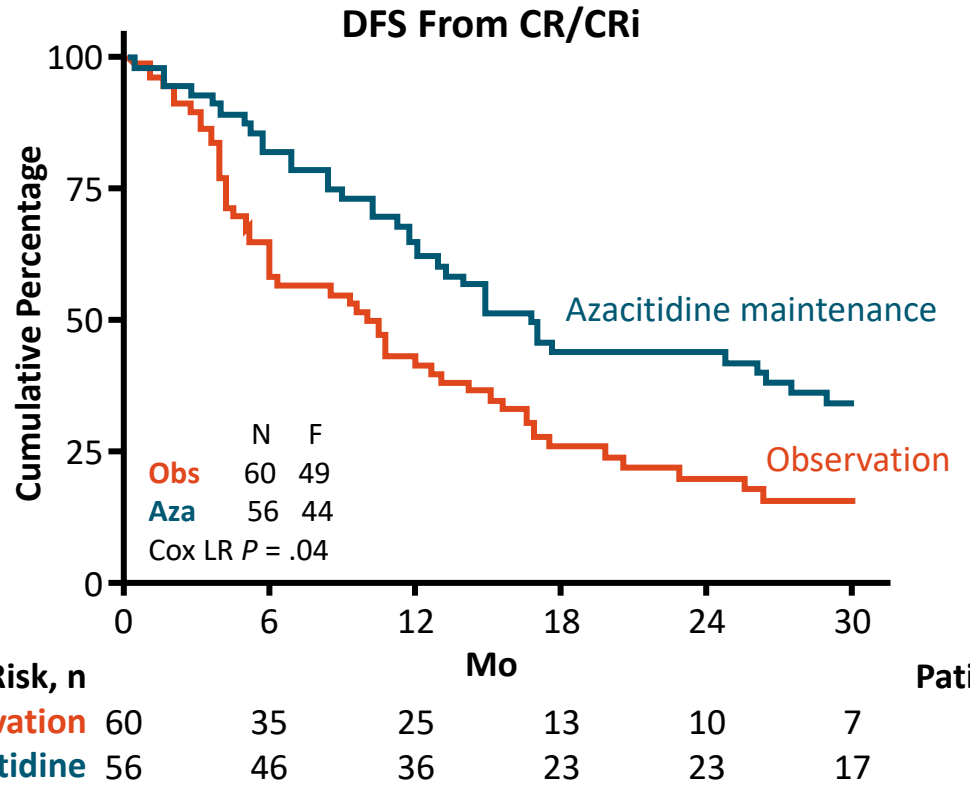
- Oral azacitidine (category 1, preferred for age ≥55 yr)*
- Azacitidine (category 2A)
- Decitabine (category 2B)

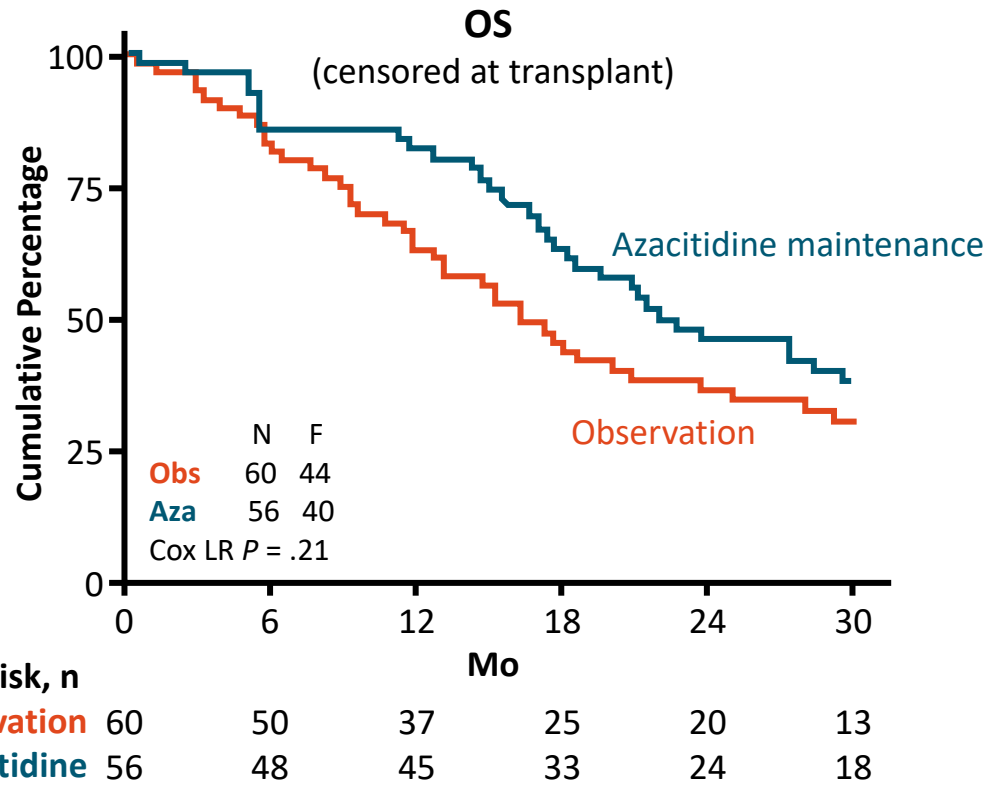
*Oral azacitidine is not intended to replace consolidation CT. Fit patients with AML and intermediate and/or adverse-risk cytogenetics in first CR may benefit from transplantation. There are currently no data supporting the replacement of HCT with oral azacitidine maintenance therapy.

NCCN. Clinical practice guidelines in oncology: acute myeloid leukemia. v3.2023.

HOVON97: Azacitidine Maintenance After Intensive Chemotherapy

- Randomized phase III study of azacitidine maintenance vs observation after intensive CT (N = 116)





Median DFS: 15.9 vs 10.3 mo

12-mo OS: 82% vs 63%

Huls. Blood. 2019;133:1457.

Guideline Recommended Posttransplant Maintenance

Patient who underwent alloHCT and meets the following criteria:

- In remission
- History of *FLT3*-ITD

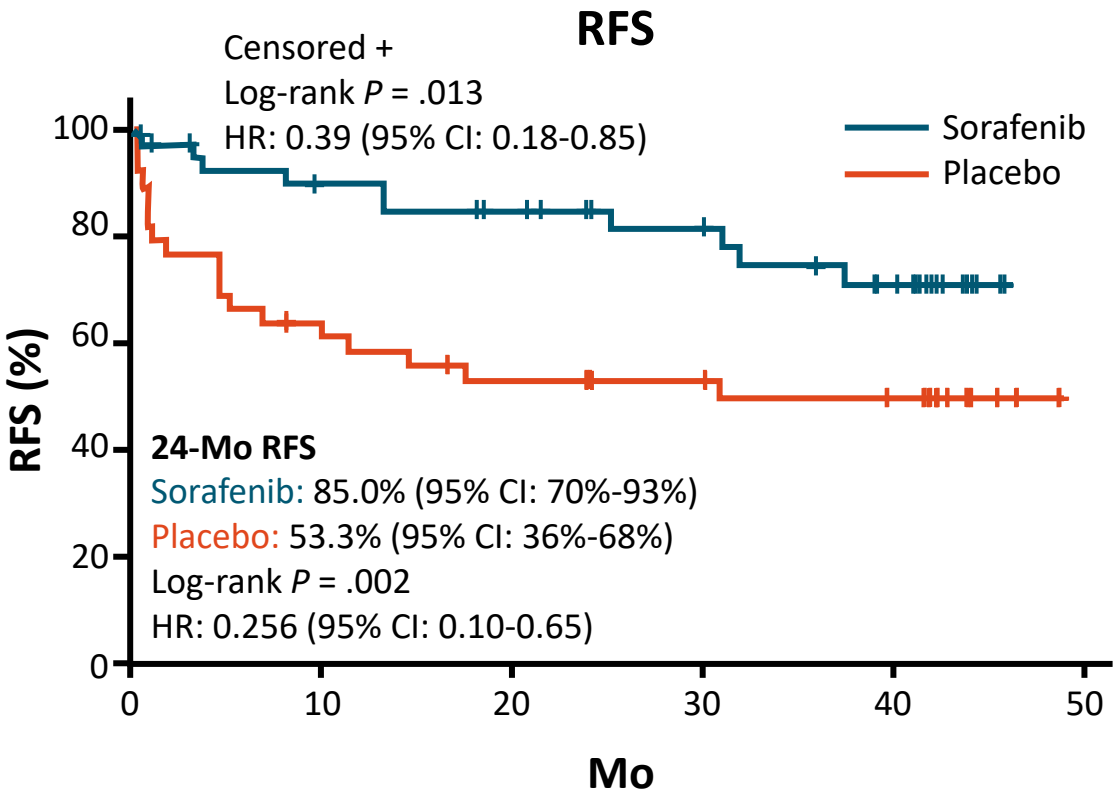
→

FLT3 inhibitor maintenance:

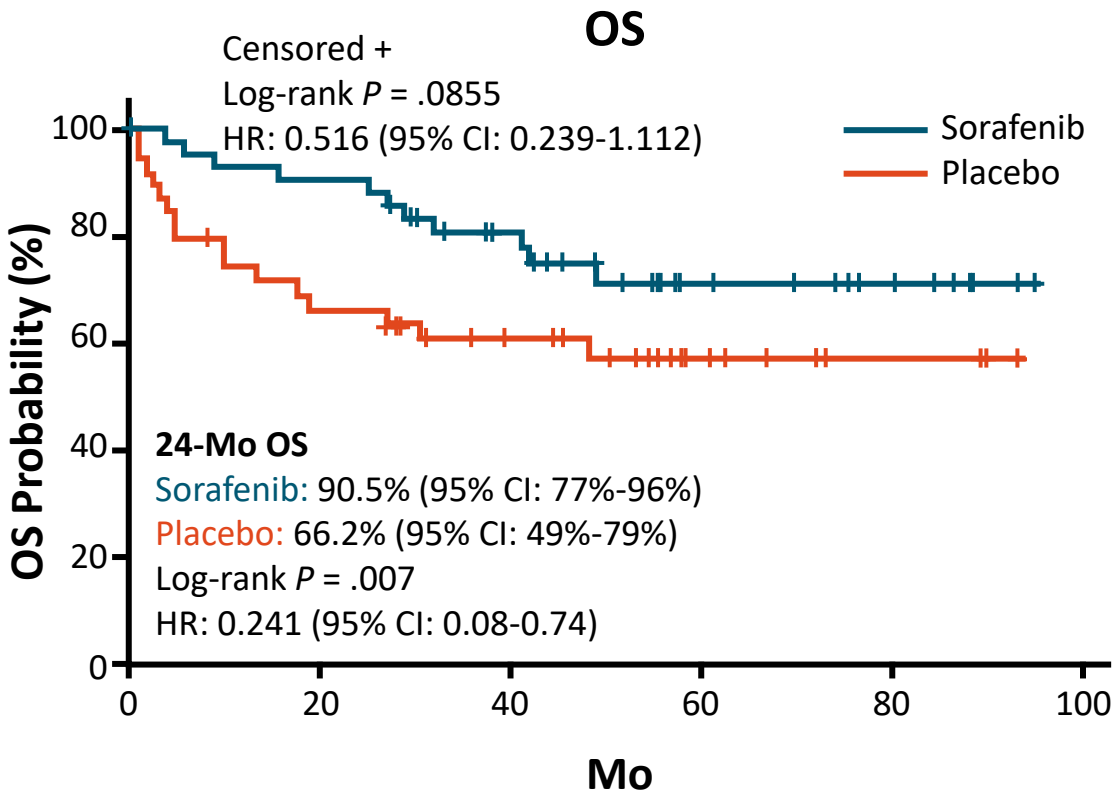
- Sorafenib (category 2A)
- Midostaurin (category 2B)
- Gilteritinib (category 2B)

NCCN. Clinical practice guidelines in oncology: acute myeloid leukemia. v3.2023.

Sorafenib Maintenance After AlloHSCT in *FLT3*-ITD AML: Relapse-Free and Overall Survival



- Median f/u: 41.8 mo
- mRFS (sorafenib vs placebo): NR vs 30.9



- Median f/u: 55.1 mo
- mOS NR in either treatment arm

Burchert. JCO. 2020;38:2993.

Ongoing Challenges in Managing AML

- Patients with R/R AML have potential for aggressive disease and historically have experienced rapid disease progression and poor survival
- Certain molecular alterations, such as *KMT2A* rearrangements and *TP53*-mutations, are associated with poor outcomes
- Frail patients with AML are more likely to experience treatment-related toxicities
- Despite recent advances in AML, there is ongoing need for novel, less toxic therapies

Döhner. Blood. 2022;140:1345. Wang. Hematology Am Soc Hematol Educ Program. 2020(1):57-66.
Wang. Front Oncol. 2022;12:972606.

Importance of an Individualized Treatment Plan for AML

Fit or Unfit

Patient Choice/QoL

Transplant Eligible?

Community vs Academic

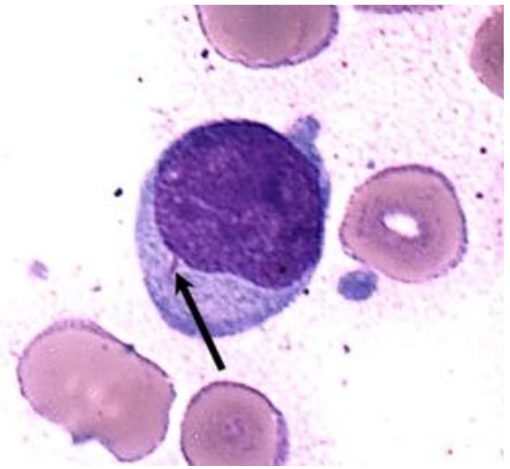
Clinical Trial Eligible?

Secondary? Therapy Related?

Mutations *FLT3*, *IDH1/2*

Cytogenetics

CD33?



KÖSZÖNÖM A FIGYELMET!

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MTA MAGYAR TUDOMÁNYOS AKADÉMIA