Cracking the Code: Exploring Novel Frontline Treatments and Prospects for Maintenance Therapy for AML

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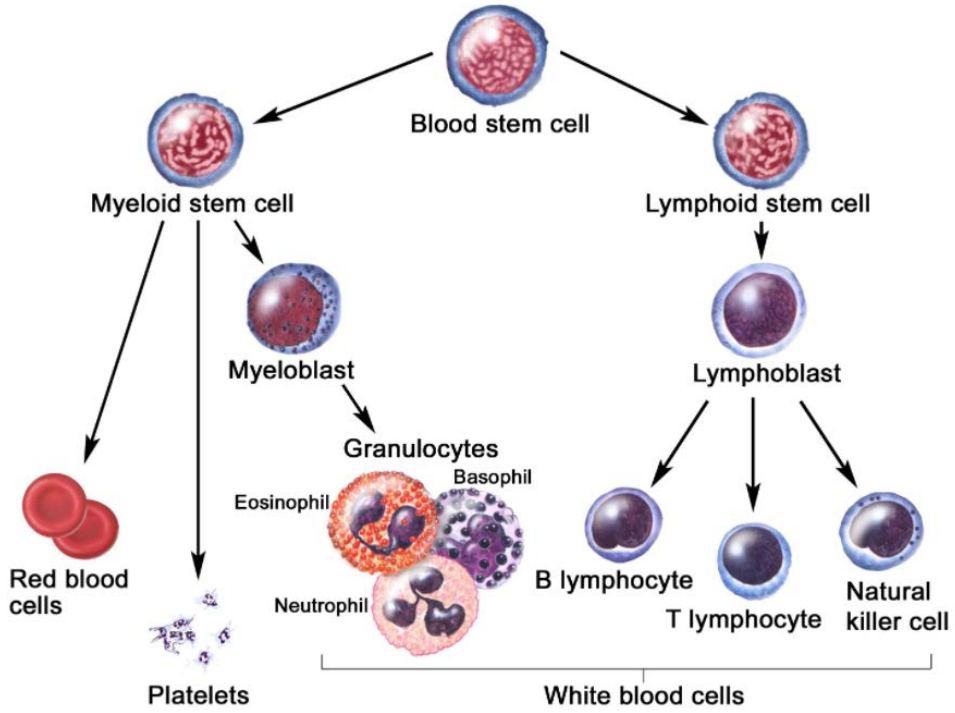
Learning Objectives

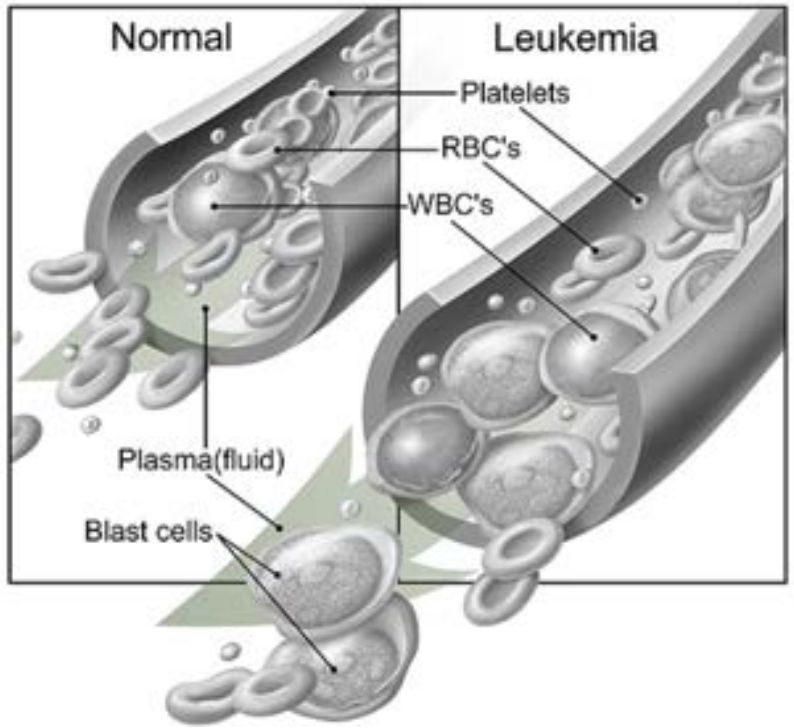
- Correlate disease pathophysiology, cytogenetic, and molecular characteristics with targeted agents to individualize treatment of patients with acute myeloid leukemia (AML)
- Evaluate recent changes to the standard treatment paradigm for newly diagnosed and relapsed/refractory patients with AML
- Analyze data supporting best practice use of maintenance therapy
- Evaluate methods for measuring minimal residual disease (MRD) after complete remission to determine risk of relapse

Overview of AML: Epidemiology, Etiology, and Risk Factors

Blood: Normal vs Abnormal Differentiation



Normal blood cell development: stem cells differentiate through several steps to become a red blood cell, platelet, or white blood cell.[1]



In AML, immature, abnormal blast cells proliferate to crowd out healthy red and white blood cells and other blood components.[2]

1. NCI. Adult Acute Myeloid Leukemia Treatment (PDQ®)—Health Professional Version. https://www.cancer.gov/types/leukemia/hp/adult-aml-treatment-pdq. **2.** NCI. Visuals Online. https://visualsonline.cancer.gov/details.cfm?imageid=4345.

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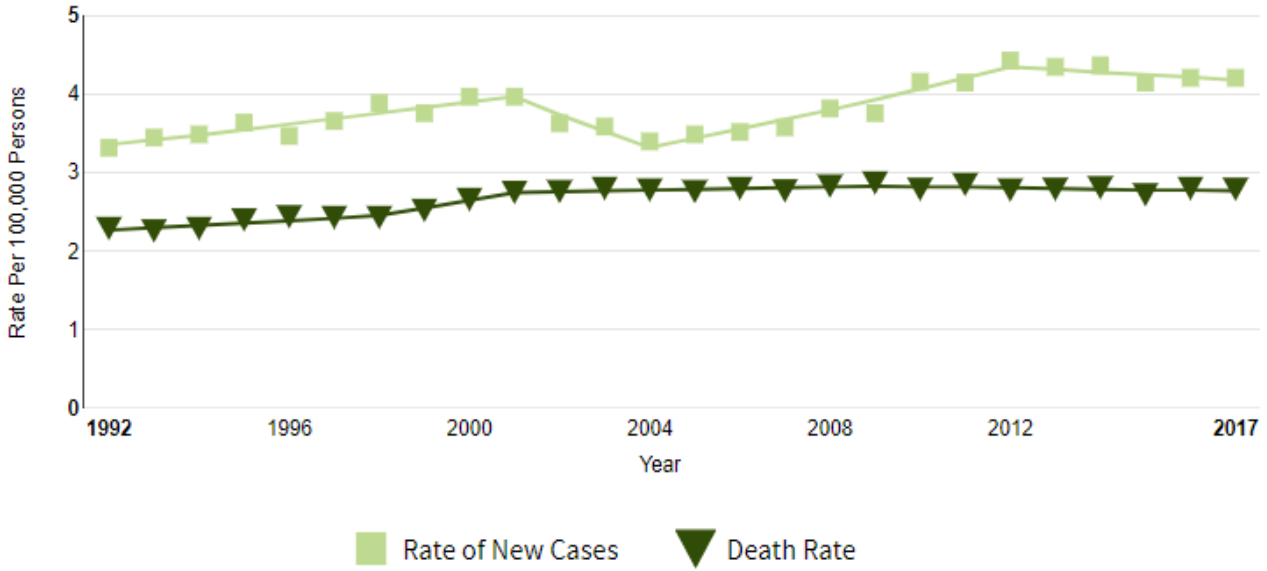
AML By the Numbers: Epidemiology

- Lifetime AML risk: ~0.5%
- AML represents 1.1% of all new cancer cases in the US and 1.8% of cancer deaths
  - Incidence in 2020: ~19,940
  - Mortality in 2020: ~11,180



SEER 2020: https://seer.cancer.gov/statfacts/html/amyl.html

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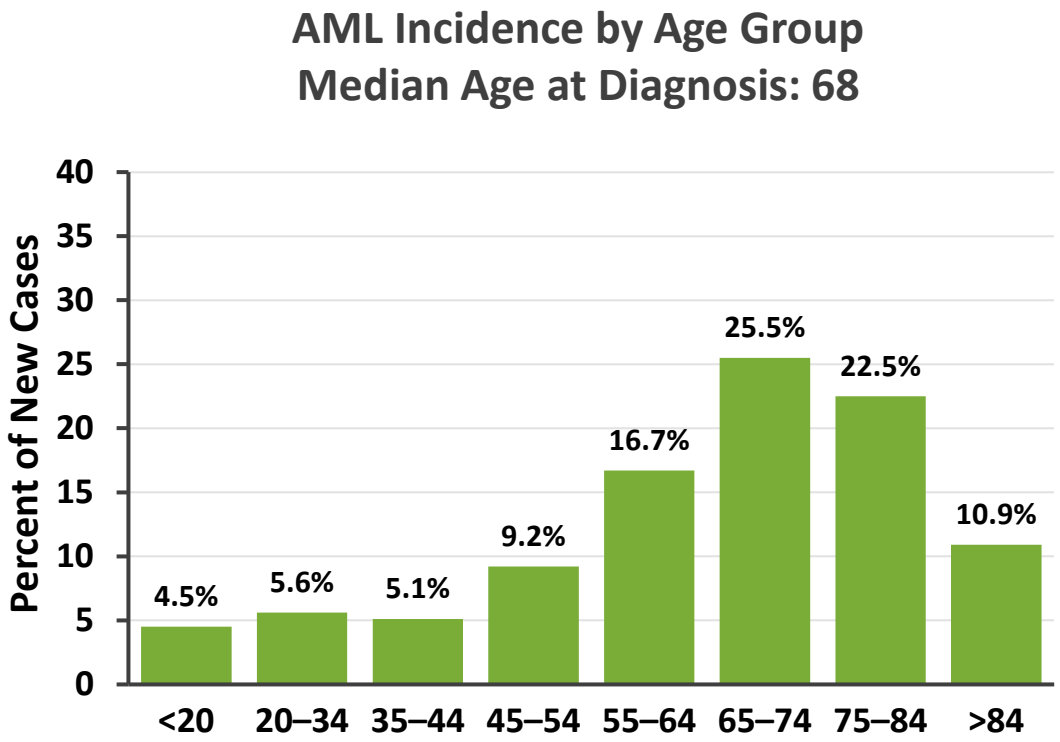
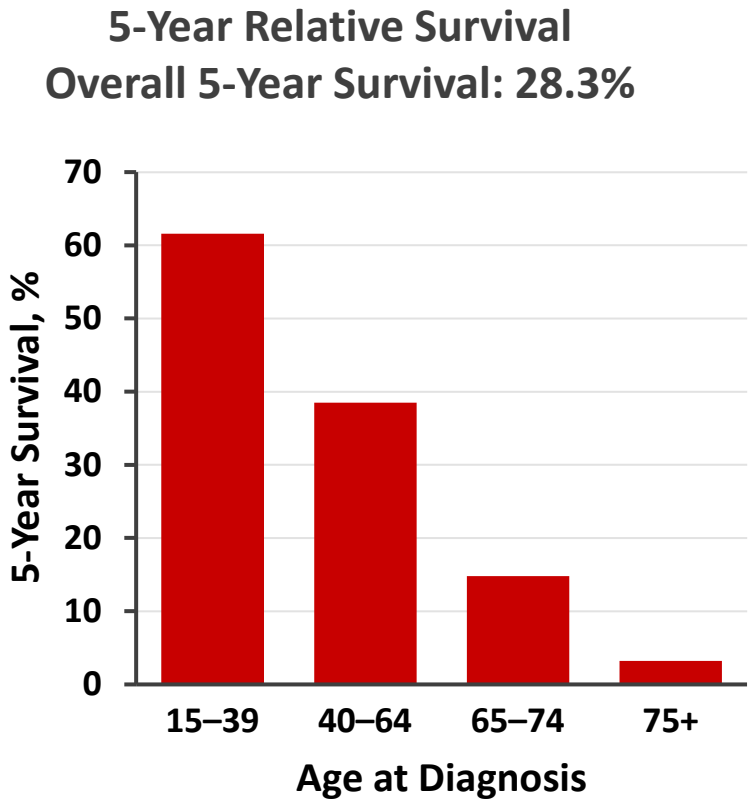
AML Incidence and Survival





SEER 2020: https://seer.cancer.gov/statfacts/html/amyl.html

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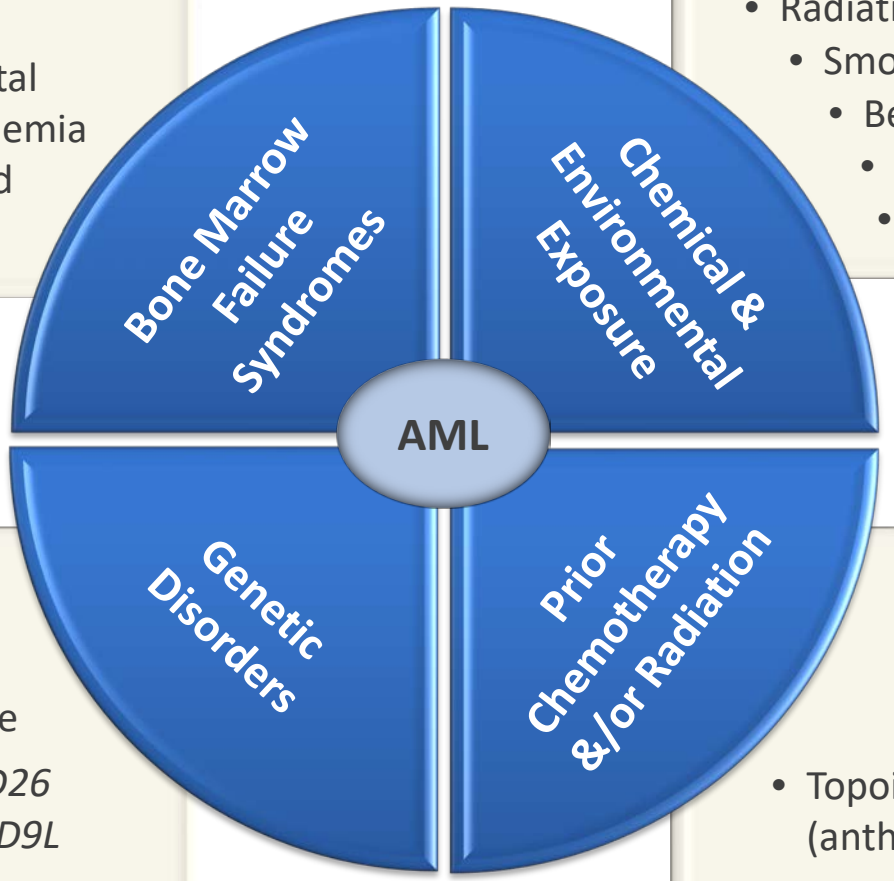
Risk Factors and Etiologies



- Fanconi anemia
- Dyskeratosis congenital
- Diamond-Blackfan anemia
- Shwachman-Diamond syndrome

- Radiation
- Smoking
- Benzene
- Organic solvents
- Pesticides/herbicides

- Down syndrome
- Noonan syndrome
- Neurofibromatosis
- Li-Fraumeni syndrome
- *RUNX1*, *ETV6*, *ANKRD26*
- *GATA2*, *SAMD9*, *SAMD9L*
- *CEBPA*, *DDX41*

- Alkylating agents (platinums, cyclophosphamide)
- Topoisomerase-II inhibitors (anthracyclines, etoposide)

Arber DA, et al. *Blood.* 2016;127:2391-2405. Tamamyan G, et al. *Crit Rev Oncol Hematol.* 2017;110:20-34.

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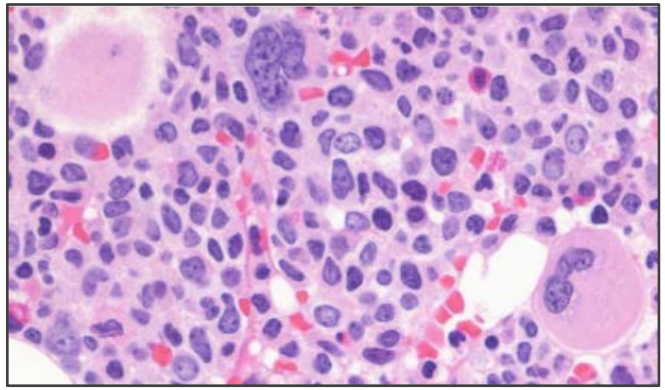
Diagnosis, Assessment, and Prognostic Risk Stratification

Diagnostic Criteria for AML

- ≥20% myeloid blasts of 500 cells (BM and/or PB)
- Evidence of myeloid origin + MPO, NSE, or BE

Stage/Lineage	Marker Expression
Precursors*	CD34, CD117, HLA-DR
Granulocytic	CD13, CD33, MPO
Monocytic	CD11c, CD14, CD36, CD64
Megakaryocytic	CD41 (gp IIb/IIIa), CD61 (gp IIIa)
Erythroid	CD235a (glycophorin A)



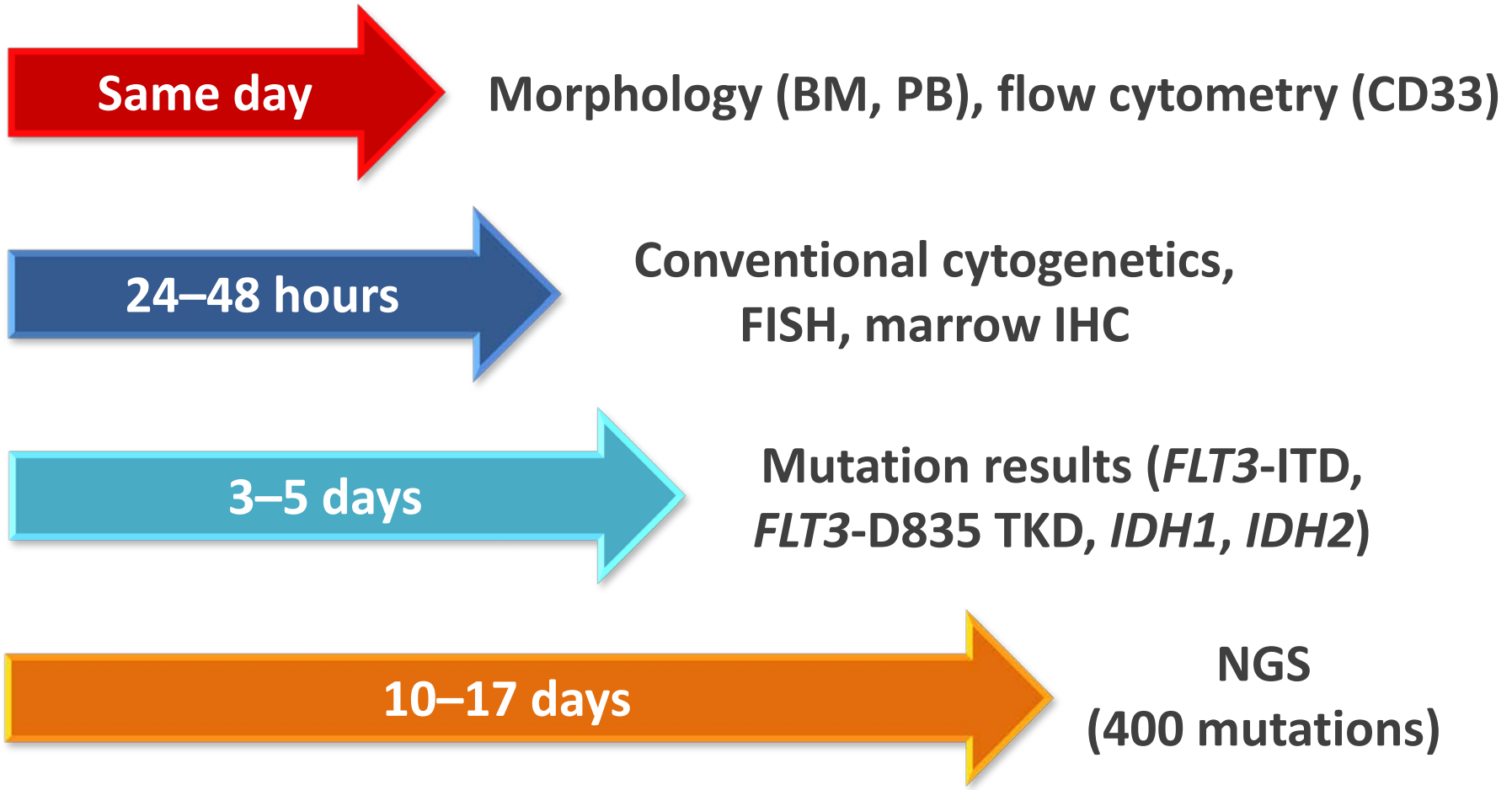
Blasts seen in BM biopsy.
Image courtesy of Reva Channah Goldberg, ASH Image Bank.

*Note that CD34 and HLA-DR are **negative** in APL.

APL, acute promyelocytic leukemia; ASH, American Society of Hematology; BE, butyrate esterase; BM, bone marrow; gp, glycoprotein; MPO, myeloperoxidase; NSE, nonspecific esterase; PB, peripheral blood.

Arber DA, et al. *Blood*. 2016;127:2391-2405. ASH Image Bank. https://imagebank.hematology.org/collection/62449. Döhner H, et al. *Blood*. 2017;129:424-447. Heuser M, et al. *Ann Oncol*. 2020;31:697-712.

Diagnostic Workup for AML



FISH, fluorescence in situ hybridization; FLT3-ITD, fms-related tyrosine kinase 3-internal tandem duplication; IDH, isocitrate dehydrogenase; IHC, immunohistochemistry; NGS, next-generation sequencing; TKD, tyrosine kinase domain.

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Assessing Prognosis in AML

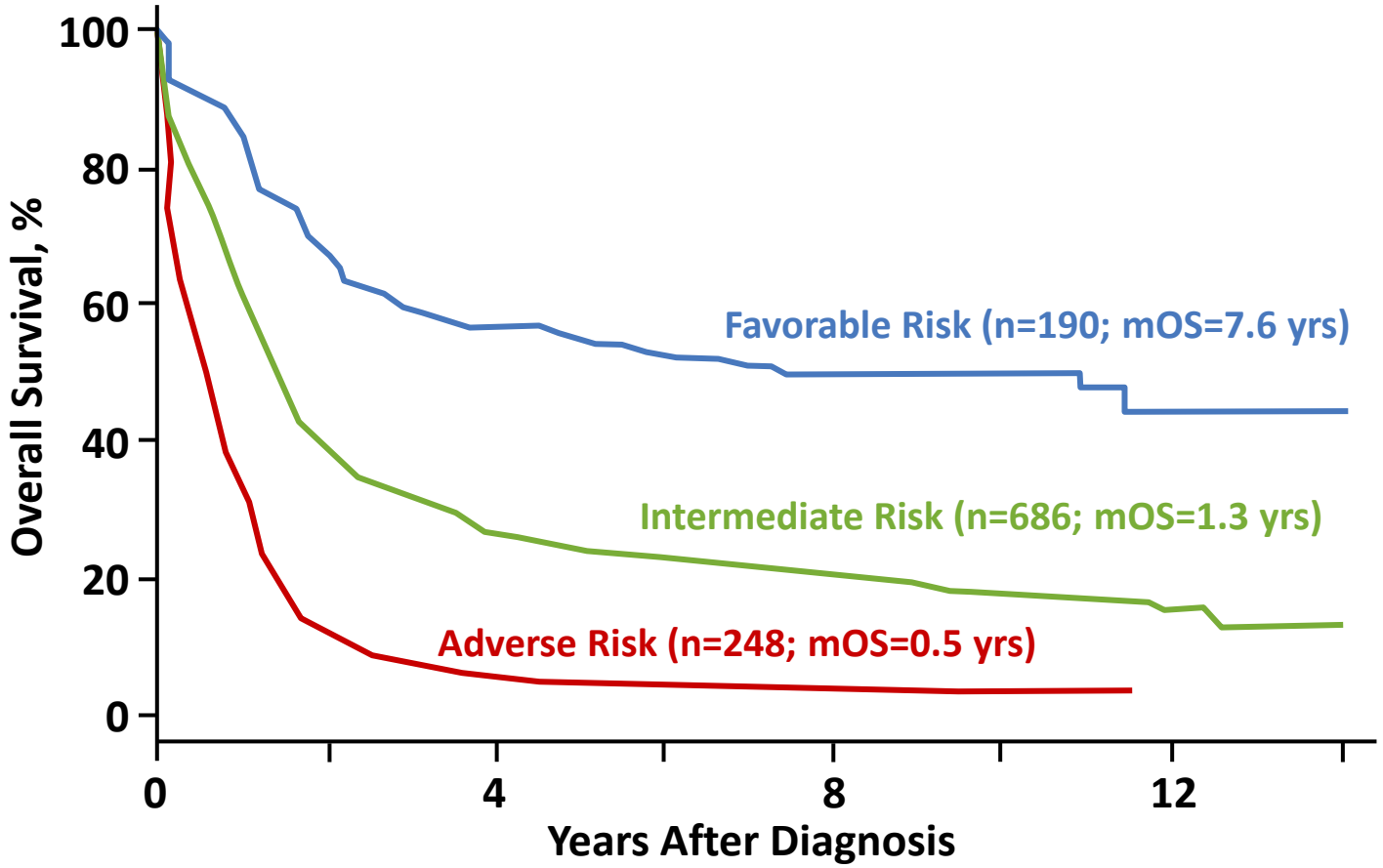
- Historic prognostic factors in AML
  - **Age:** Remission rates inversely related to age
    - ≥65% for younger than 60
    - 5-year survival ≤13% if older than 60[1]
  - **Performance status:** Karnofsky and ECOG most common
    - Performance and age at diagnosis combined to estimate % of patients who will die within first 28 days of treatment[2]
  - **Cytogenetics:** Strongest prognostic information to predict outcome of induction and consolidation/post-remission treatment[3]

ECOG, Eastern Cooperative Oncology Group.

1. Shah A, et al. *Br J Haematol*. 2013;162:509-516. **2.** Estey EH. *Cancer*. 2001;92:1059-1073. **3.** Döhner H, et al. *Blood*. 2017;129:424-447.

Assessing Prognosis in AML

Based on cytogenetic/molecular analysis, patients can be divided into having *favorable*, *intermediate*, or *adverse* risk



mOS, median overall survival.

Adapted from: Byrd JC, et al. *Blood*. 2002;100:4325-4336.

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2017 ELN Risk Stratification by Cytogenetics

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* Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low} Biallelic mutated *CEBPA*
Intermediate (Not classified as favorable or adverse)	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*
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*, *ASXL1*, and/or *TP53*

CBFB-MYH11, core binding-factor subunit beta-myosin heavy chain 11; ELN, European Leukemia-NET; TP53, tumor protein p53.

Döhner H, et al. *Blood.* 2017;129:424-447.

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Essential AML Prognostic Features

Trait	Favorable	Unfavorable
Age		✓ (particularly >65)
***FLT3*-ITD**		✓
TP53		✓
RUNX1* and/or *ASXL1		✓
-5, -7, inv(3), complex cytogenetics		✓
NPM1	✓	
dm*CEBPA* (biallelic, dual mutant)	✓	
t(15;17)	✓	
Inv(16) or t(8;21)	✓	
KIT mutation in inv(16) or t(8;21)		✓ (generally)

Red = unfavorable; Black = favorable. dmCEBPA, double mutated CEBPA.

Courtesy of Gail J. Roboz, MD

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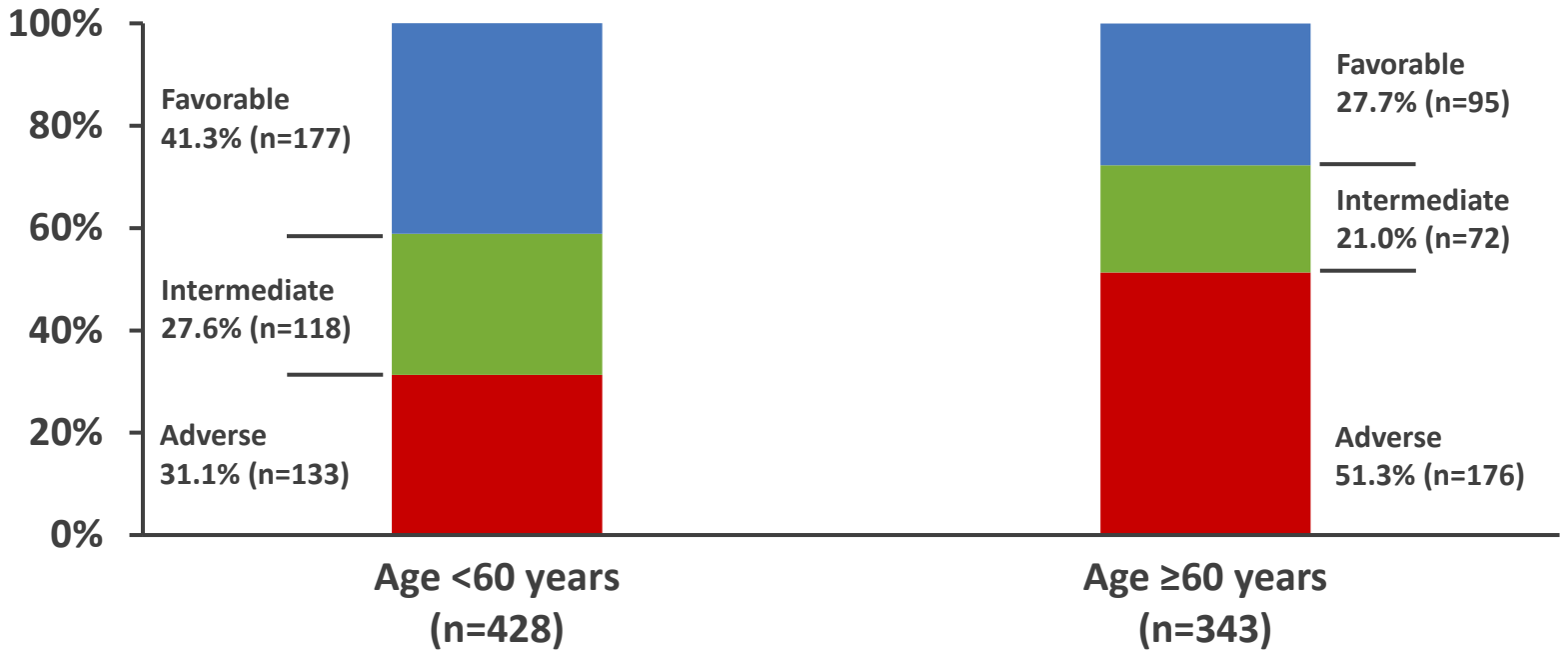
Validation of ELN Risk Categories

Proportion of intensively treated patients in ELN 2017 risk categories* validation study



*Previous separation of intermediate risk into 2 divisions (Intermediate-I and Intermediate-II) was eliminated in the 2017 ELN update.

Adapted from: Herold T, et al. *Leukemia*. Mar 30, 2020. [Online ahead of print]

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Review of Therapeutic Goals and New Treatment Approaches

Principles of AML Therapy

Evaluate eligibility for intensive chemotherapy

Consider age, performance status, comorbidities, cytogenetics/molecular genetics, patient's wishes

	Young, fit patients	Older, less fit patients
Goals of Therapy	Induce remission, treat with curative intent	Control disease progression, improve survival and QOL
Treatment Strategies	Intensive reduction and consolidation treatment alloHSCT in patients with ≥40% risk of relapse	Lower-intensity treatment Clinical trials with investigational drugs Best supportive care
	CR rate: ~75% in young patients 40%–50% in ages ≥60	**CR rate:** ~25% with HMA <10% with LDAC

alloHSCT, allogeneic hematopoietic stem cell transplant; CR, complete remission; HMA, hypomethylating agent; LDAC, low-dose cytarabine; QOL, quality of life.

Döhner H, et al. *Blood*. 2017;129:424-447

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After 40 Years . . . 8 New Targeted Treatments

"Finally, after a prolonged wait [40 years]*, we are witnessing the next wave of AML treatment, characterized by a more precise and personalized understanding of the unique molecular or genetic mapping of individual patients. This trend has been further facilitated with 8 new FDA approvals granted since 2017."*

~Sylvia Park, et al, in *Blood Research*, 2020

Park S, et al. *Blood Res*. 2020;55:S14-S18.

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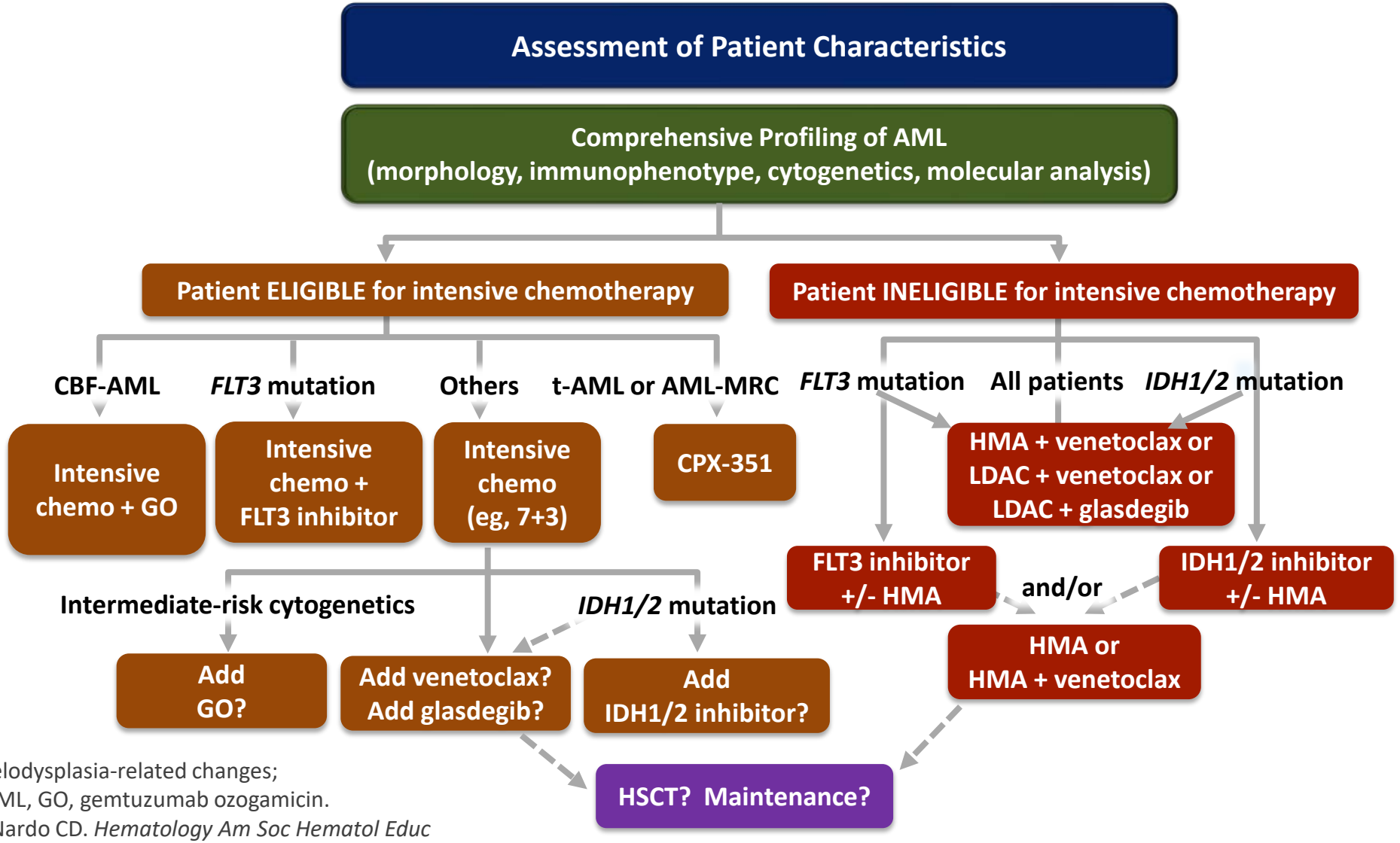
Evolving Treatment Options for Newly Diagnosed AML



AML-MRC, AML with myelodysplasia-related changes;
t-AML, therapy-related AML, GO, gemtuzumab ozogamicin.

Richard-Carpentier G, DiNardo CD. *Hematology Am Soc Hematol Educ Program*. 2019;2019:548-556.

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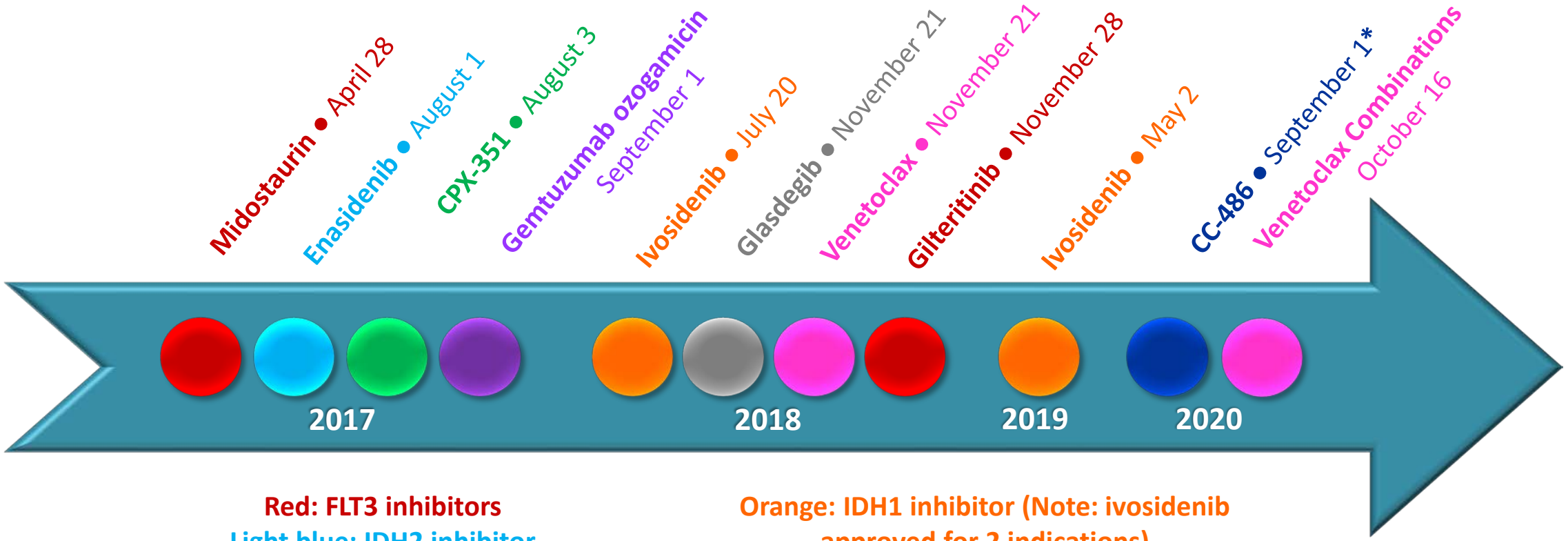
Targeted Treatments Approval Timeline



Red: FLT3 inhibitors
Light blue: IDH2 inhibitor
Green: Liposome-encapsulated cytarabine + daunorubicin
Purple: Anti-CD33 antibody drug conjugate

Orange: IDH1 inhibitor (Note: ivosidenib approved for 2 indications)
Gray: Hedgehog inhibitor
Pink: BCL2 inhibitor
Dark blue: DNA hypomethylator

*CC-486 is an oral formuation of azacytidine, approved as maintenance treatment.

Richard-Carpentier G, DiNardo CD. *Am Soc Hematol Educ Program*. 2019;2019:548-556.

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Novel/Targeted Agents

Class / Target	Agent	Indication	Route	Caution/Monitoring
BCL2	Venetoclax	Newly Dx AML in pts ≥75 yrs or pts w/ comorbidities unfit for intensive induction chemo	Oral	• Common AEs (in combination with azacitdine or decitabine): nausea, diarrhea, constipation, thrombocytopenia, neutropenia, FN, fatigue • Monitor for: TLS
Cytotoxic	CPX-351*	Newly Dx t-AML or AML-MRC	IV	• Monitor for: blood counts for prolongation of blood count suppression • Avoid in pts with decreased cardiac function
Cytotoxic ADC	Gemtuzumab ozogamicin	Newly Dx & R/R CD33+ AML	IV	• Infusion-related reactions • Monitor platelet counts and signs of VOD
Cytotoxic DNMTi	CC-486†	Maintenance Tx in 1st CR or CRi	Oral	• Common AEs: GI effects including nausea, vomiting, diarrhea; thrombocytopenia

*CPX-351 is a liposomal version of cytarabine plus daunorubicin; †CC-486 is an oral formulation of injectable azacitidine with distinctly different pharmacokinetic and pharmacodynamic profile, enabling extended dosing to maximize hypomethylating effects.
ADC, antibody drug conjugate; AEs, adverse events; CRi, complete remission with incomplete hematologic recovery; DNMTi, DNA methyltransferase inhibitor; FN, febrile neutropenia; GI, gastrointestinal; IV, intravenous; pts, patients; R/R, relapsed/refractory; TLS, tumor lysis syndrome; VOD, veno-occlusive disease.

DiNardo CD, Wei AH. *Blood.* 2020;135:85-96. Park S, Cho BS, Kim H-J. *Blood Res.* 2020;55:S14-S18.
Ravandi F, et al. *J Clin Oncol.* 2020;38(Suppl_15):7530.

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Novel/Targeted Agents *(cont)*

Class / Target	Agent	Indication	Route	Caution/Monitoring
FLT3-ITD/TKD	Gilteritinib	R/R *FLT3*^{mut} positive AML	Oral	• Common AEs: myalgias, elevated liver enzymes, dyspnea, edma, rash, pneumonia, nausea, hypotension, dizziness, vomiting
FLT3-ITD/TKD	Midostaurin	Newly Dx *FLT3*^{mut} positive AML	Oral	• Common AEs: GI events • Monitor for: Potential drug-drug reactions
Hhp	Glasdegib	Newly Dx AML in pts ≥75 yrs or pts w/ comorbidities unfit for intensive induction chemo	Oral	• Common AEs: anemia, fatigue, hemorrhage, FN, MSK pain, nausea, edema, dyspnea, thrombocytopenia
IDH1	Ivosidenib	Newly Dx or R/R *IDH*^{mut} positive pts ≥75 yrs or pts w/ comorbidities unfit for intensive induction chemo	Oral	• Monitor for: IDH differentiation syndrome, GI events, nausea, leukocytosis
IDH2	Enasidenib	R/R *IDH2*^{mut} positive AML	Oral	• Monitor for: IDH differentiation syndrome, GI events, elevated bilirubin, leukocytosis

Hhp, hedgehog pathway; MSK, musculoskeletal.

DiNardo CD, Wei AH. *Blood.* 2020;135:85-96. Park S, Cho BS, Kim H-J. *Blood Res.* 2020;55:S14-S18.

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Exploring the Role of Maintenance Therapy

Maintenance therapy: post-remission strategy to clear malignant cells left over after remission induction therapy

Exploration of maintenance therapy in AML ongoing since the 1960s

Goal: extend CR, reduce risk of relapse through lower-intensity treatment

Targeted agents with novel MOAs renews hope for effective maintenance treatment—most notably with oral FLT3 inhibitors

MOAs, methods of action.

Rashidi A, et al. *Blood*. 2016;128:763-773. Tamamyan G, et al. *Crit Rev Oncol Hematol*. 2017;110:20-34.

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Quantifying and Evaluating MRD

Quantifying MRD important after CR to assess:
1) risk of relapse, 2) need for maintenance—but still controversial

Method	Target	Sensitivity	Pros/Cons
Cytogenetics	Chromosomal abnormalities	1 in 20 (5%)	• Inexpensive, readily available • Applicable for ~50% of AML
Flow cytometry	Leukemia-associated aberrant immuno-phenotype	1 in 10,000 (0.01%)	• Applicable to most AML • Relatively cheap • Not easily standardized • Subject to expertise and interpretation
RT-PCR	Fusion transcripts (CBFs), gene mutations (*NPM1*)	Up to 1 in 100,000 (0.001%)	• Highly sensitive • Very standardized • Applicable for ~30%–40% of AML
NGS (mutation analysis)	Gene mutations	Up to 1 in 10,000 (0.01%); typically ~1%	• Genetic heterogeneity and clonal architecture complicate analysis

CBFs, core binding factors; RT-PCR, reverse transcription polymerase chain reaction.

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Frontline Treatment Strategies: Newly Diagnosed Younger, Older, and High-Risk, "Unfit" AML Patients

Initial Therapy for Patients Fit for Intensive, Potentially Curative Chemotherapy

- Patients with AML sensitive to conventional chemo
  - **Younger patients:** <65 years without t-AML recurrent infections
  - **CBF leukemia:** 8;21 and inv(16)
  - **Diploid AML:** with *NPM1* or *dmCEBPA*

Image courtesy of Rhoda Baer. NCI Visuals Online.

dmCEBPA, double mutated; NCI, National Cancer Institute.

NCI Visuals Online. https://visualsonline.cancer.gov/details.cfm?imageid=4453

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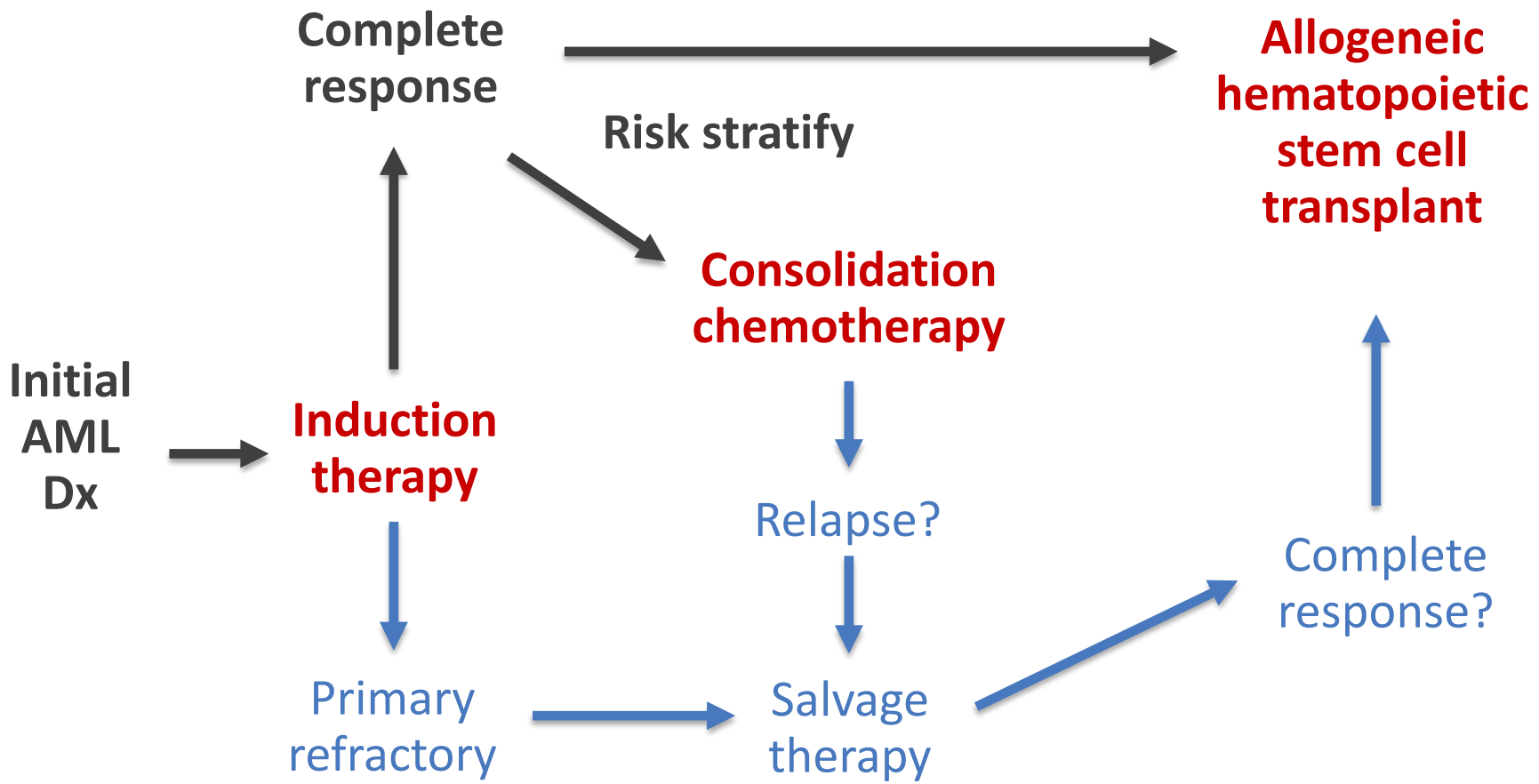
Paradigm for Initial Treatment



Adapted figure courtesy of Harry P. Erba, MD, PhD.

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Chemotherapy Induction and Consolidation

"7+3" Induction

- Cytarabine 100–200 mg/m^2 x 7 days CIV
- Daunorubicin* 60–90 mg/m^2 x 3 days or idarubicin 12 mg/m^2 x 3 days

Consolidation

- HiDAC x 4 cycles
- alloHSCT if patient is high risk (or intermediate risk with appropriate donor)

*Note: daunorubicin **45 mg/m^2 is INFERIOR**

CIV, continuous intravenous infusion; HiDAC, high-dose cytarabine.

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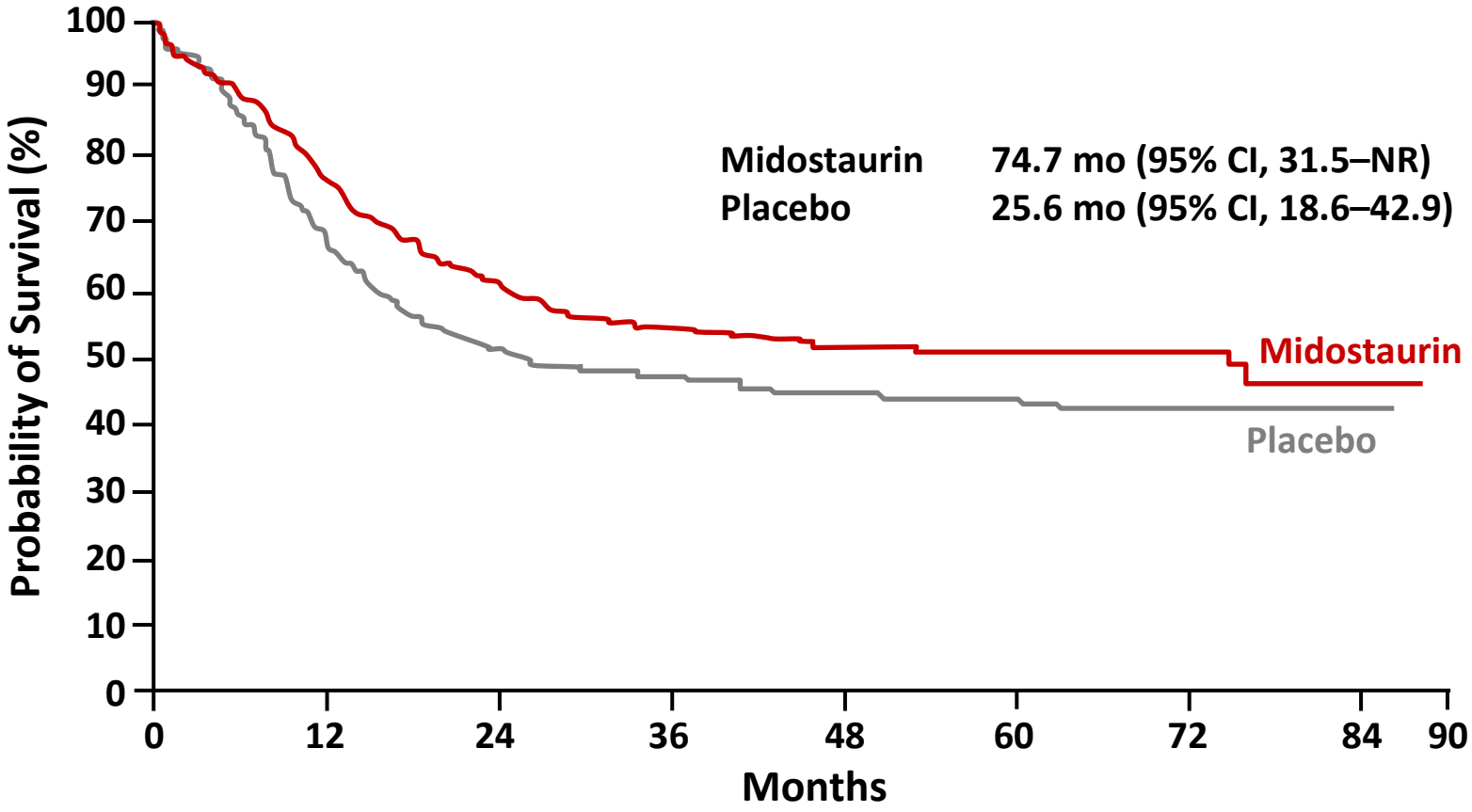
R/R AML Treatment for *FLT3*-Positive Patients: Midostaurin

OS from phase 3 RATIFY trial of midostaurin + standard chemo vs chemo + placebo for *FLT3*-mutated AML (N=717)



OS, overall survival.

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

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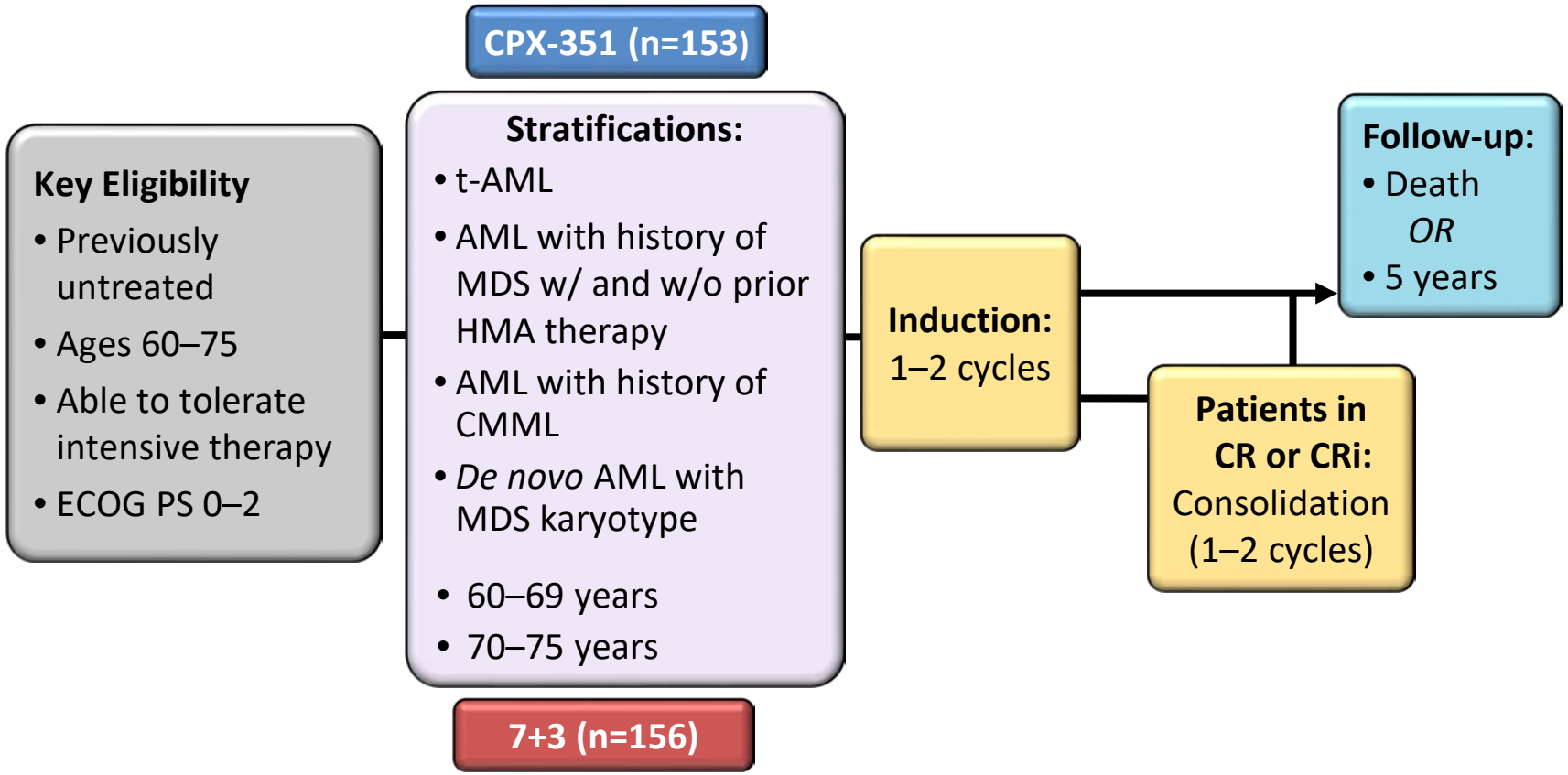
Initial Therapy for Older Patients with Newly Diagnosed Secondary AML



CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndrome.

Lancet JE, et al. *J Clin Oncol*. 2018;36:2684-2692.

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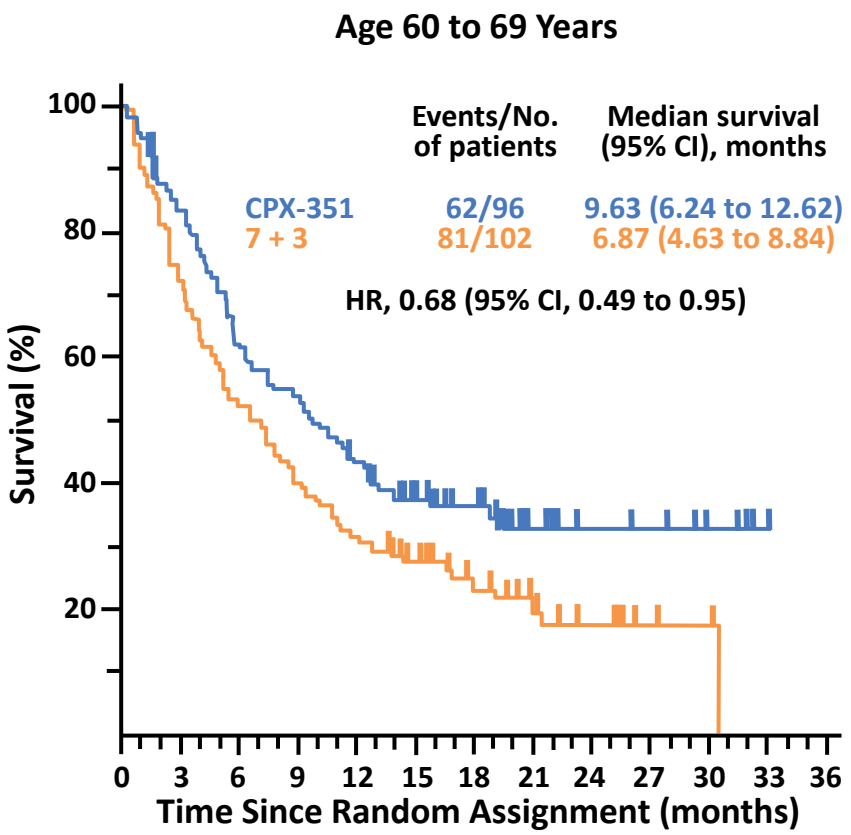
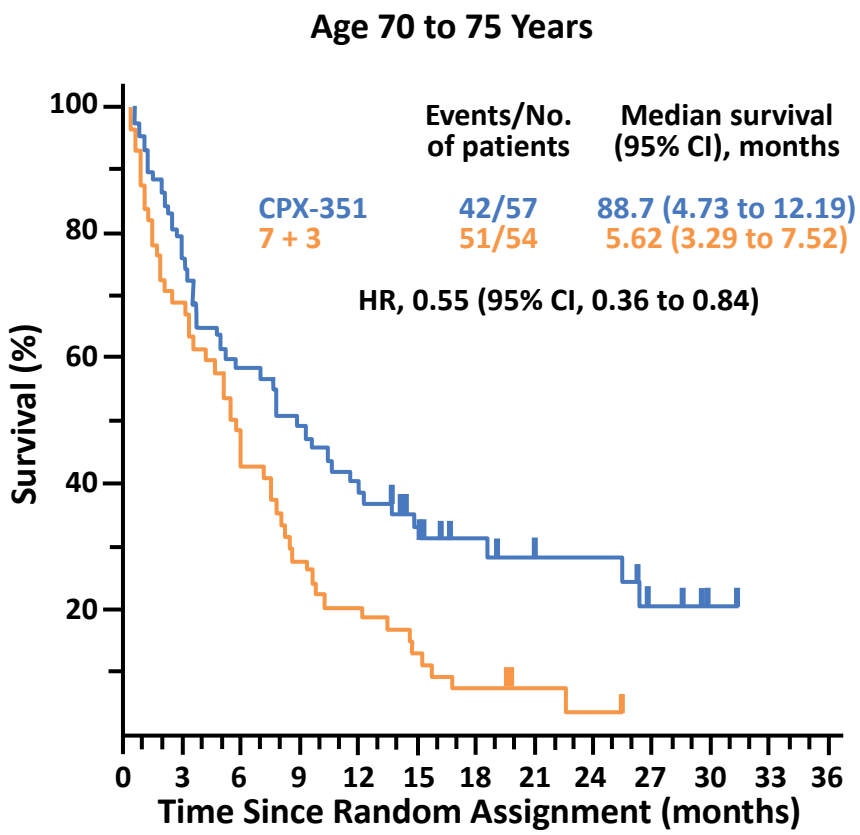
Initial Therapy for Older Patients with Newly Diagnosed Secondary AML

CPX-351 is the new SOC in this population





SOC, standard of care.

Adapted from: Lancet JE, et al. *J Clin Oncol*. 2018;36:2684-2692.

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Initial Treatment: Newly Dx Patients NOT Fit for Intensive Chemotherapy

- Patients unfit for intensive chemo
  - ≥75 years
  - Poor performance status (ECOG PS ≥2)
  - Comorbidities (eg, pulmonary, cardiac, renal, hepatic)
- Best treatment options
  - BSC (hydrea, transfusions)
  - Lower-intensity therapy
  - HMA with azacitidine or decitabine
  - LDAC
  - Lower-intensity combinations (approved in 2018)
    - HMA or LDAC + ventoclax
    - LDAC + glasdegib
  - Molecularly targeted therapy
    - Ivosidenib (patients with *IDH1* mutations)

BSC, best supportive care.

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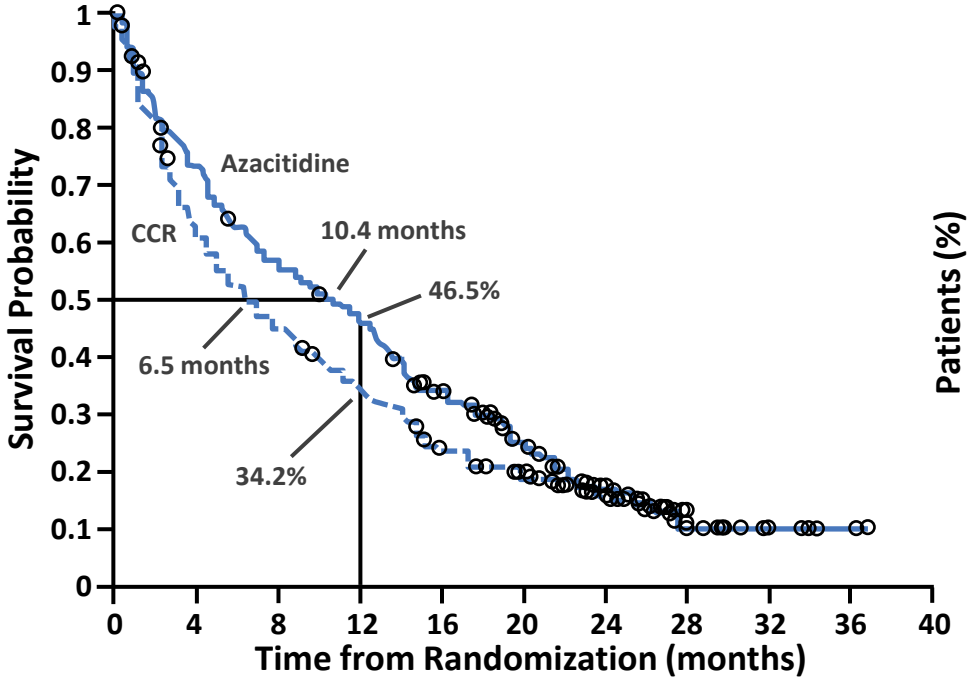
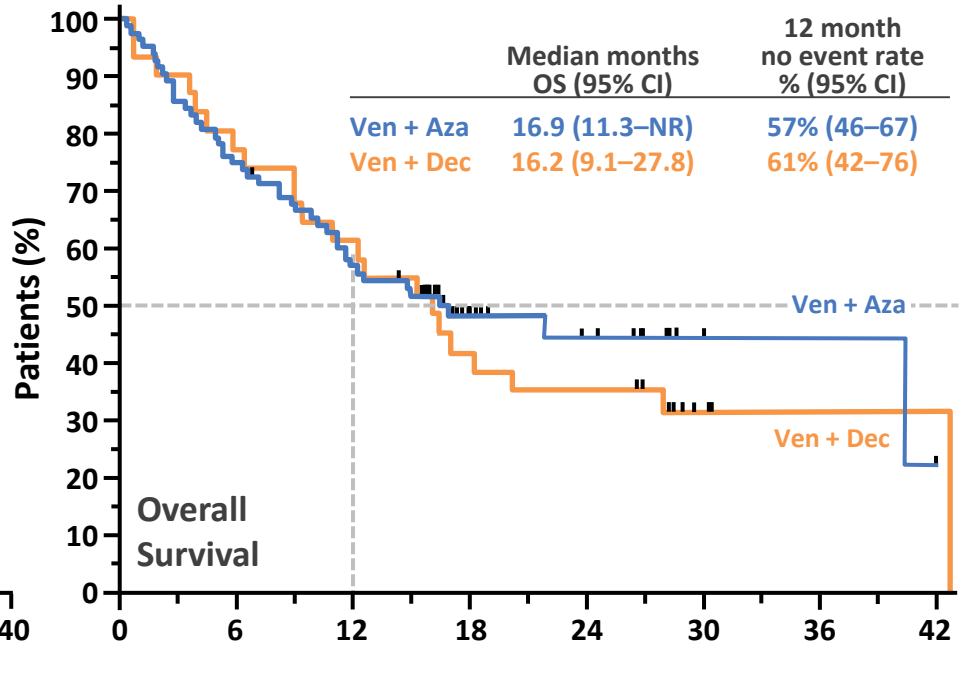
Newly Dx "Unfit" AML: AZA +/- VEN

AZA Alone[1]
CR/CRi 28%
N=241, median age 75
Early death 7.5%



AZA + VEN[2]
CR/CRi 71%
N=84, median age 75
Early death 2%



AZA, azacitidine; VEN, venetoclax.

1. Adapted from: Dombret H, et al. *Blood.* 2015;126:291-299.
2. Adapted from: DiNardo CD, et al. *Lancet Oncol.* 2018;19:216-228.

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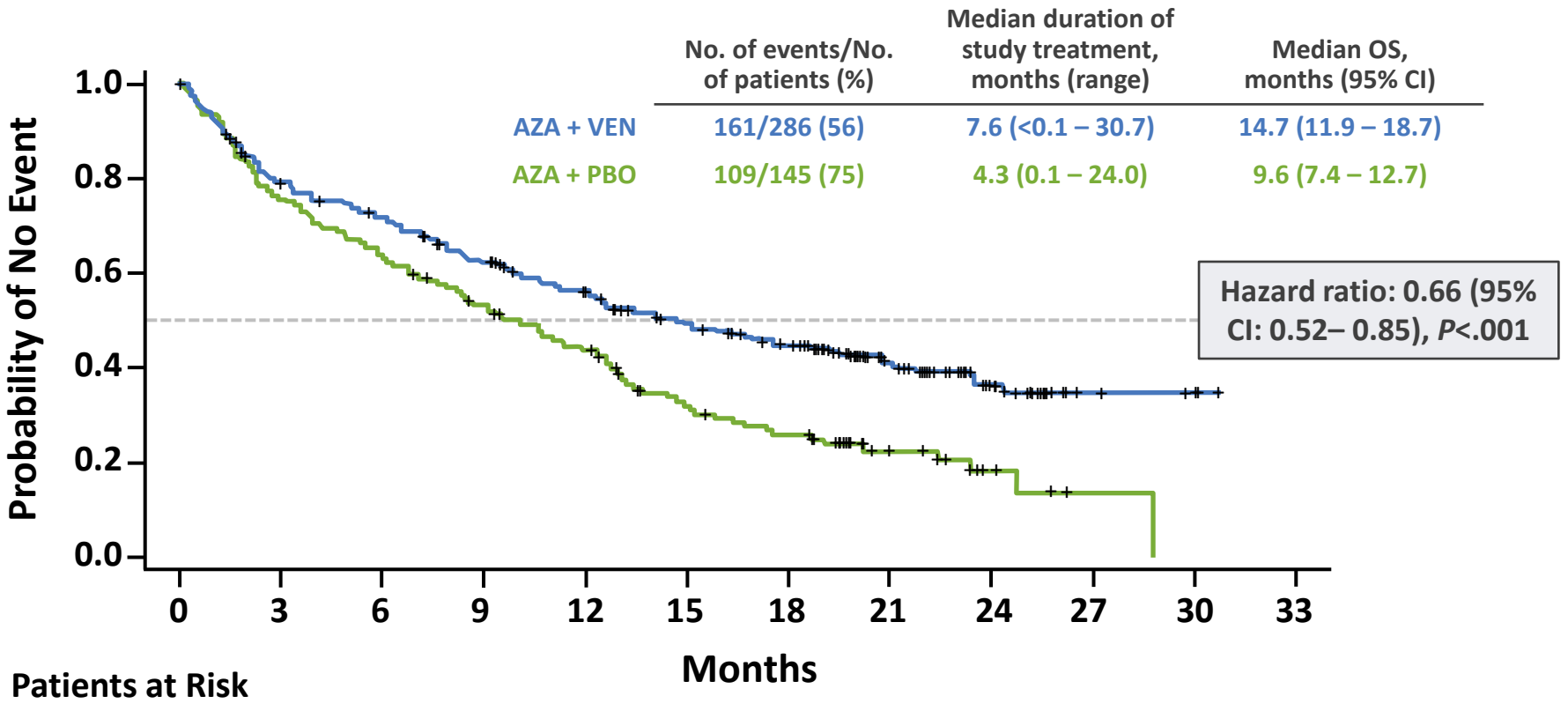
Newly Dx “Unfit” AML: AZA + VEN New SOC

AZA + VEN the new SOC for patients ≥75 not eligible for intensive chemotherapy — phase 3 VIALE-A trial



PBO, placebo.

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

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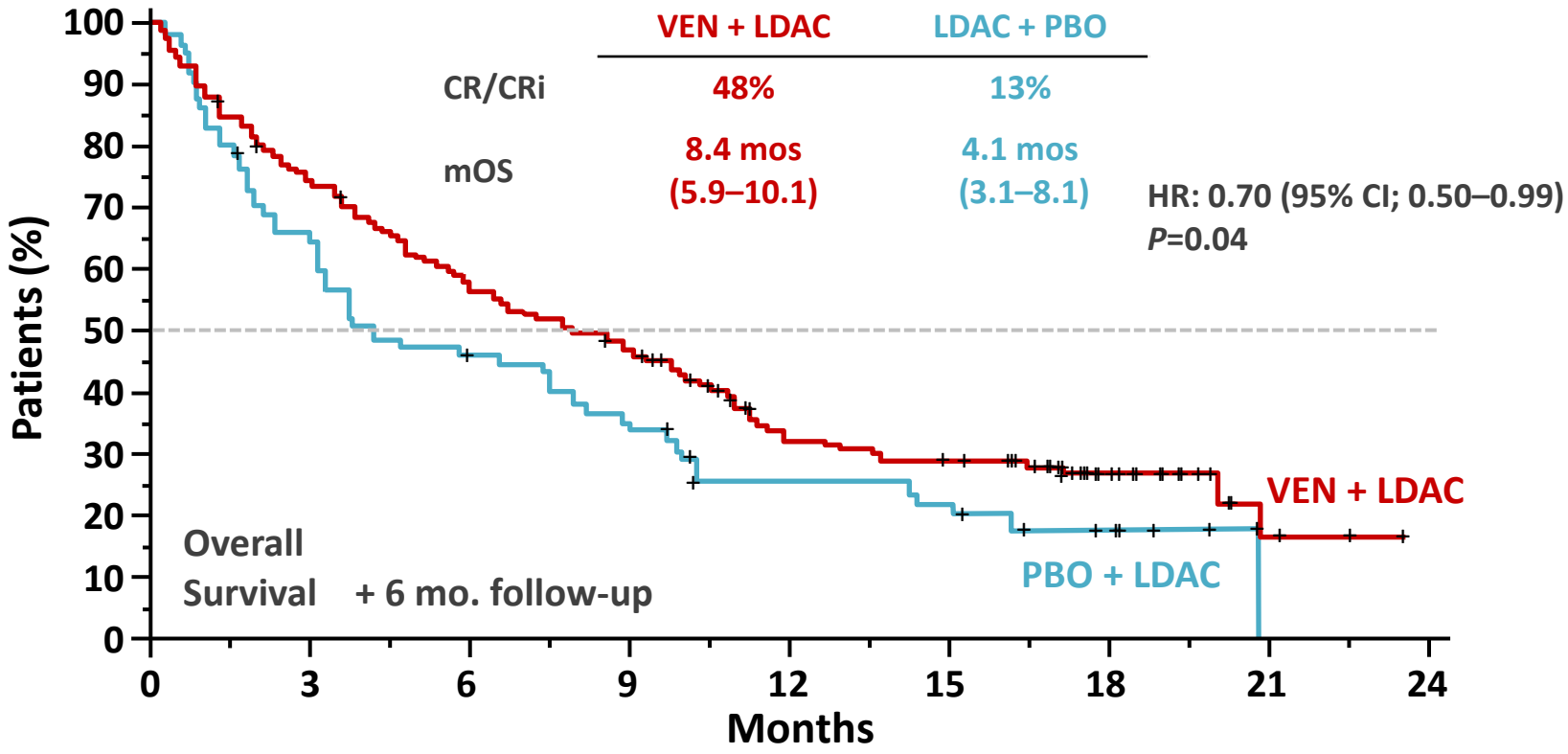
Newly Dx “Unfit” AML: LDAC +/- VEN

LDAC + VEN for patients ≥75 not eligible for intensive chemotherapy—phase 3 VIALE-C trial



Adapted from: Wei AH, et al. *Blood*. 2020;135:2137-2145.

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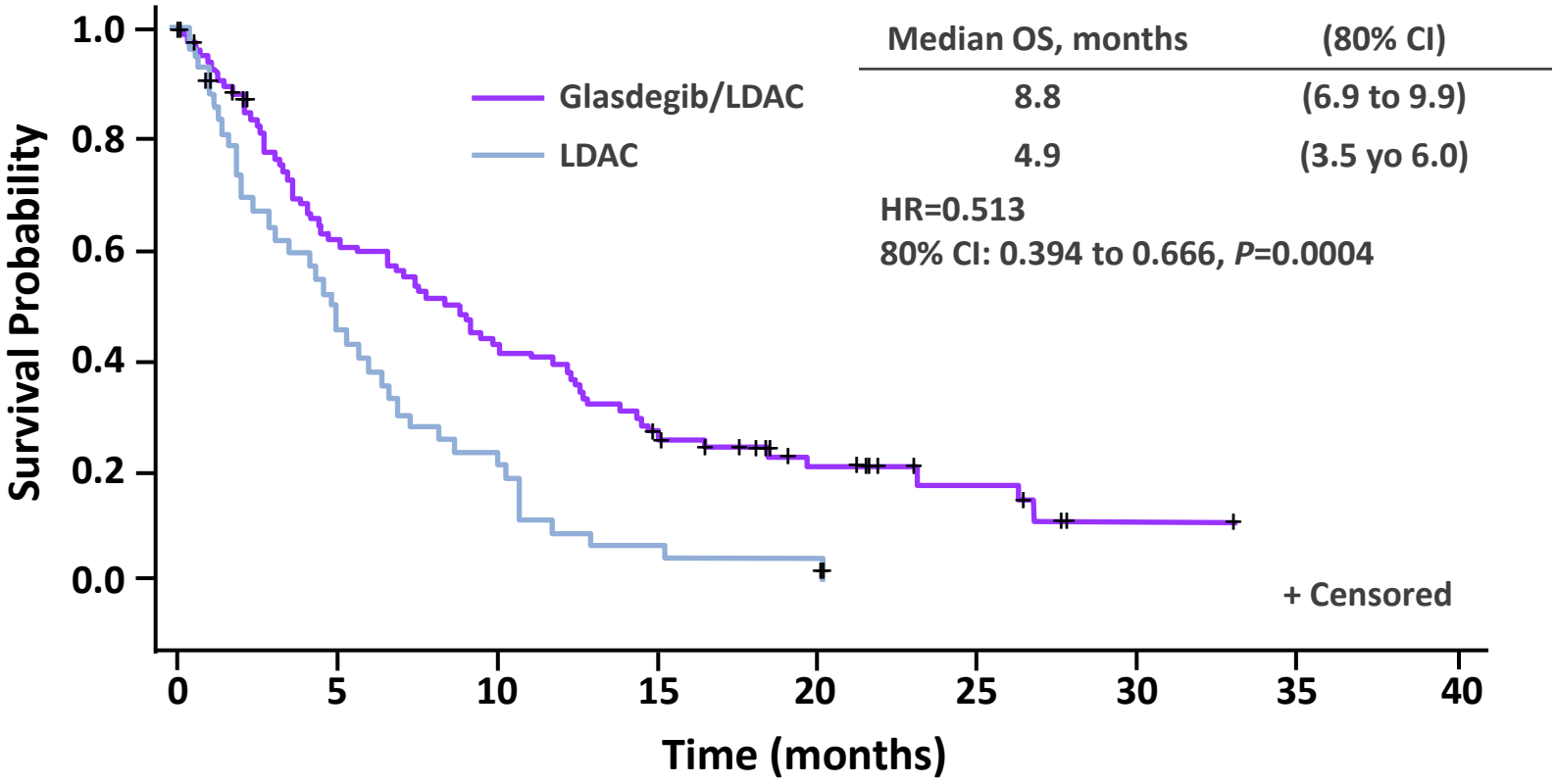
Newly Dx "Unfit" AML: LDAC + Glasdegib

OS from phase 2 randomized trial of LDAC +/- hedgehog inhibitor (N=132)



Median OS, months	(80% CI)
8.8	(6.9 to 9.9)
4.9	(3.5 yo 6.0)

HR=0.513
80% CI: 0.394 to 0.666, *P*=0.0004

Adapted from: Cortes JE, et al. *Leukemia.* 2019;33:379-389.

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Treatment in Patients with "Targetable" Cytogenetic Mutations in Frontline and Relapse Settings

FLT3 and *IDH* Mutations in AML

FLT3[1]

- ***FLT3* mutations common in AML**
  - *FLT3*-ITD in ~25% of AML
  - *FLT3*-TKD in ~10% of AML
- *FLT3* mutations more frequent in younger patients, *de novo* AML, and diploid cytogenetics
- Leads to constitutive activation of *FLT3* receptor
- *FLT3*-ITD an independent predictor of poor prognosis

IDH1/*IDH2*[2]

- ***IDH* mutations in ~20% of AML**
  - *IDH1* in ~8% ; *IDH2* in ~12%
  - ~85% in *de novo* diploid or +8 AML
  - ↑ prevalence with ↑ patient age
- **Hotspot mutations**
  - *IDH1* R132, *IDH2* R140, *IDH2* R172
- ***IDH* mutations can be acquired at disease progression**
  - ~10%–15% of AML from MDS
  - ~20%–25% of AML from MPNs

MPN, myeloproliferative neoplasms.

Daver N, et al. *Leukemia*. 2019;33:299-312. 2. Molenaar RJ, et al. *Leukemia*. 2015;29:2134-2142.

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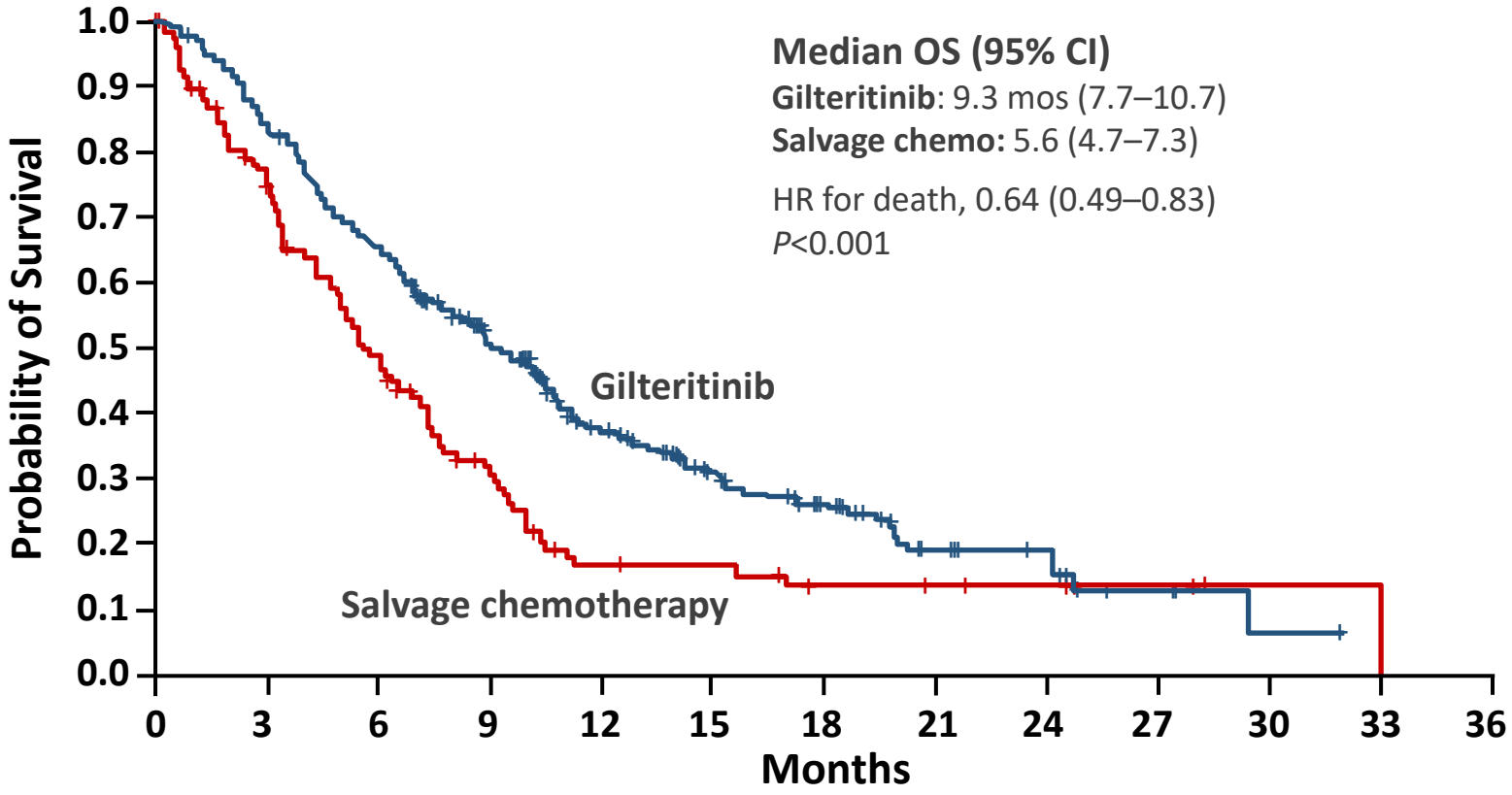
R/R AML Treatment for *FLT3*-Positive Patients: Gilteritinib

OS from phase 3 ADMIRAL trial of gilteritinib vs salvage chemo for *FLT3*-mutated AML (N=371)



Adapted from: Perl AE, Martinelli G, Cortes JE, et al. *N Engl J Med.* 2019;381:1728-1740.

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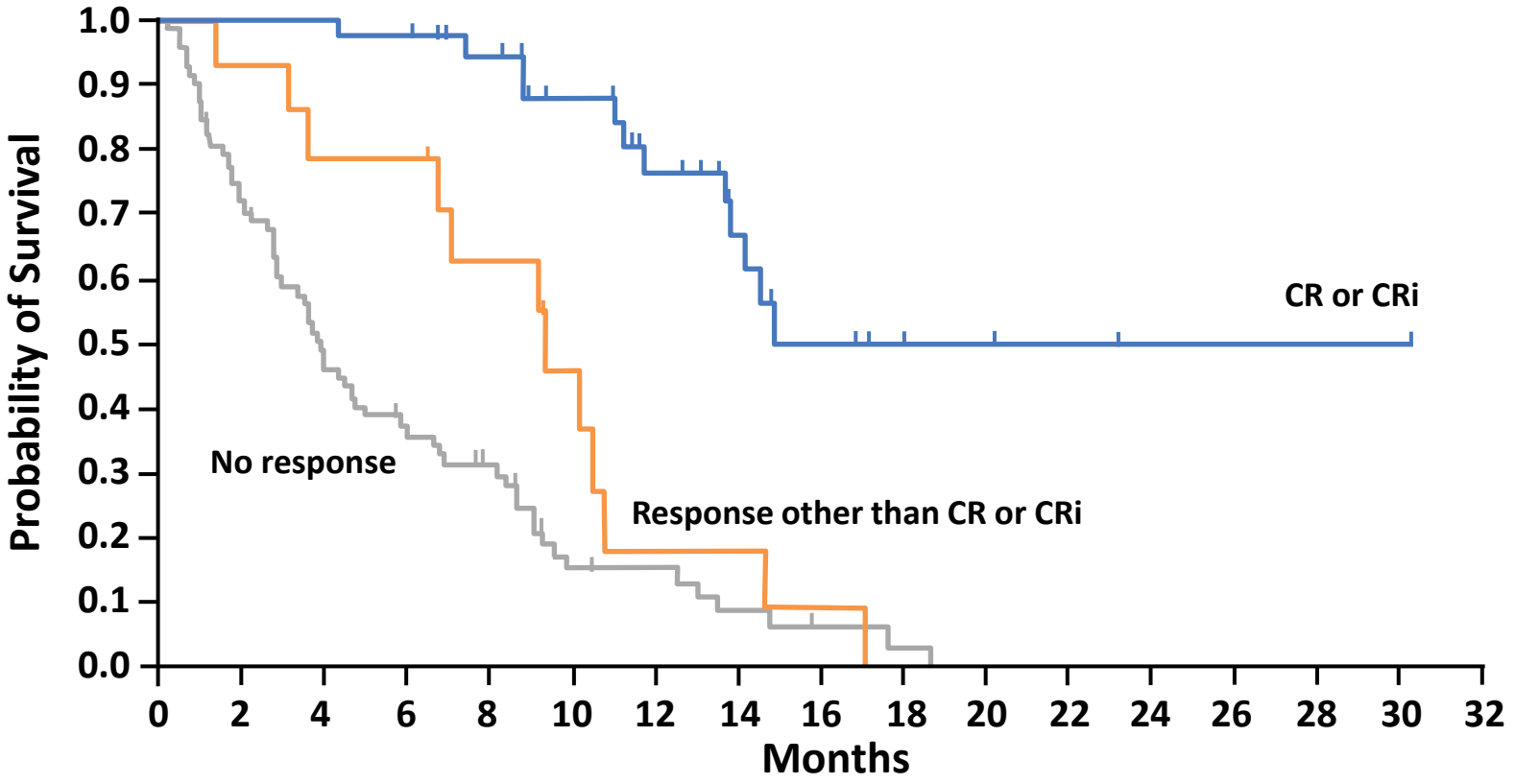
R/R AML Treatment for *IDH1*-Positive Patients: Ivosidenib

OS from phase 1 dose escalation/expansion study of IDH1 inhibitor monotherapy (N=258)

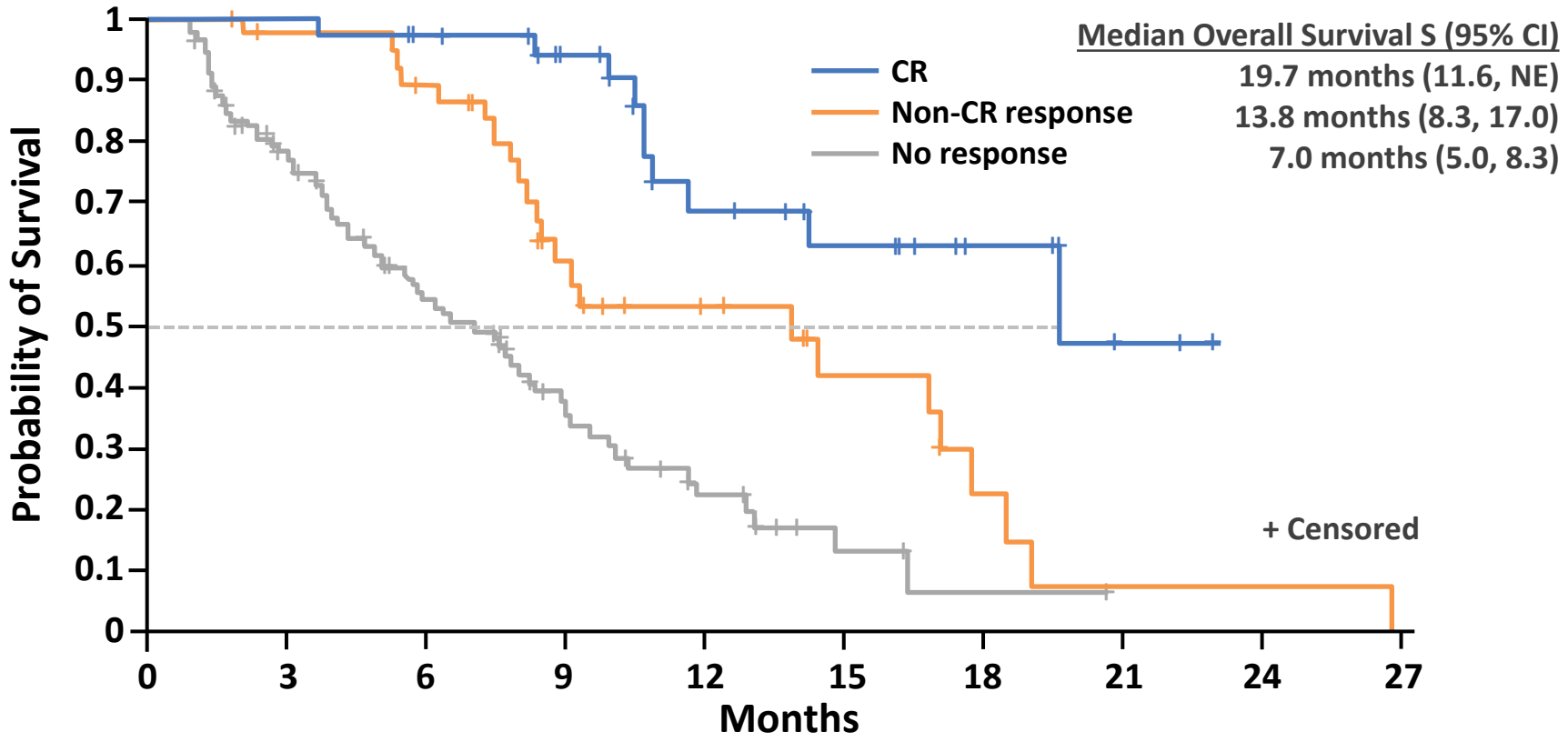


Adapted from: DiNardo CD, et al. *N Engl J Med.* 2018;378:2386-98.

Slide credit: INTEGRITY CONTINUING EDUCATION

R/R AML Treatment for IDH2-Positive Patients: Enasidenib

OS from phase 1/2 AG221-C-001 trial of IDH2 inhibitor monotherapy (N=239)



Adapted from: Stein EM, et al. *Blood.* 2017;130:722-31.

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IDH Inhibitor Studies in R/R AML

Agent	Target	Study	Phase	Efficacy	Safety
Ivosidenib[1]	*IDH1*	NCT0324542	2	ORR 41%; cCr 30%; CR 22%; OS 8.8 mos	Prolonged QTc 7%, GR ≥3; IDH-DS 4.7%, GR ≥3
Enasidenib[2]	*IDH2*	NCT01915498	1/2	ORR 40.3%; cCR 26%; CR 19%; OS 9.3 mos	Hyperbilirubinemia 18%, GR ≥3; IDH-DS 6%, GR ≥3; thrombocytopenia 23%, GR ≥3; anemia 19%, GR ≥3

cCR, complete clinical remission; GR, grade; IDH-DS, IDH differentiation syndrome; ORR, objective response rate.

1. DiNardo CD, et al. *N Engl J Med.* 2018;378:2386–2398.
2. Stein EM, DiNardo CD, Pollyea DA, et al. *Blood.* 2017;130:722–31.

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NCCN Recommendations for Patients with Targetable Cytogenetic Mutations

Young Patients (<60)	Fit, Older Patients (≥60)	Unfit, Older Patients (≥60)
• Favorable-risk & positive for CD33: 7+3 induction & a single dose of GO • Intermediate-risk with *FLT3*^{mut}: 7+3 induction + FLT inhibitor midostaurin • Intermediate or poor risk: 7+3, or 7+3 & single dose of GO	• Favorable-risk & positive for CD33: 7+3 induction & a single dose of GO • *FLT3*^{mut}: 7+3 induction + FLT inhibitor midostaurin • Intermediate or poor risk: 7+3, or 7+3 & single dose of GO	• *IDH1*^{mut}: ivosidenib *or* HMA (ie, azacitidine, decitabine), *or* venetoclax-based Tx • *IDH2*^{mut}: enasidenib *or* HMA, *or* venetoclax-based Tx • *FLT3*^{mut}: HMA & TKI sorafenib, *or* venetoclax-based Tx

GO, gemtuzumab ozogamicin.

Acute Myeloid Leukemia. https://www.nccn.org.

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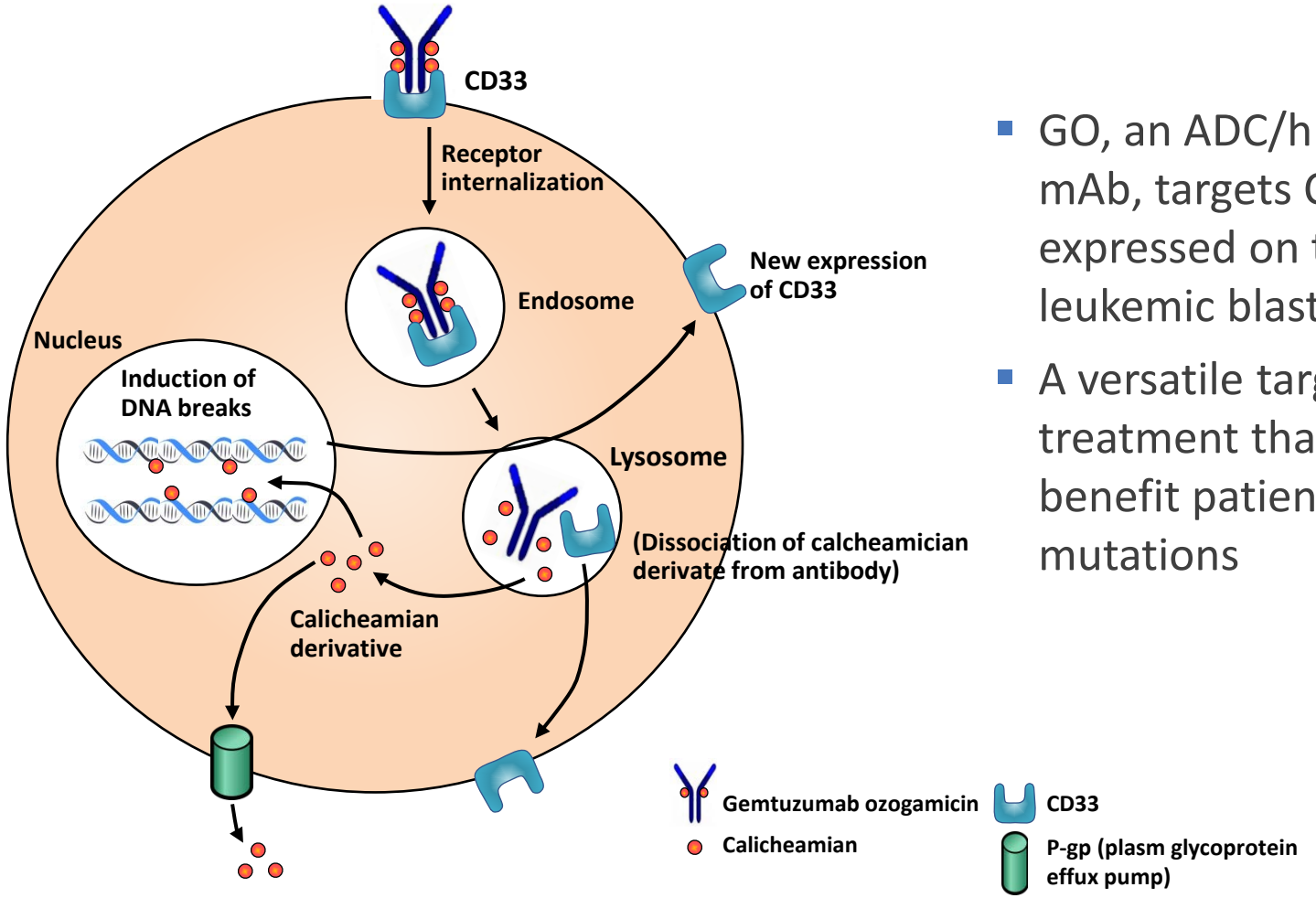
Anti-CD33 Gemtuzumab Ozogamicin, an ADC



- GO, an ADC/humanized mAb, targets CD33 antigens expressed on the surface of leukemic blast cells
- A versatile targeted treatment that can also benefit patients with *FLT3* mutations

Adapted from: Boddu P, Ravandi F. *Adv Cell Gene Ther*. 2018;1:e21.

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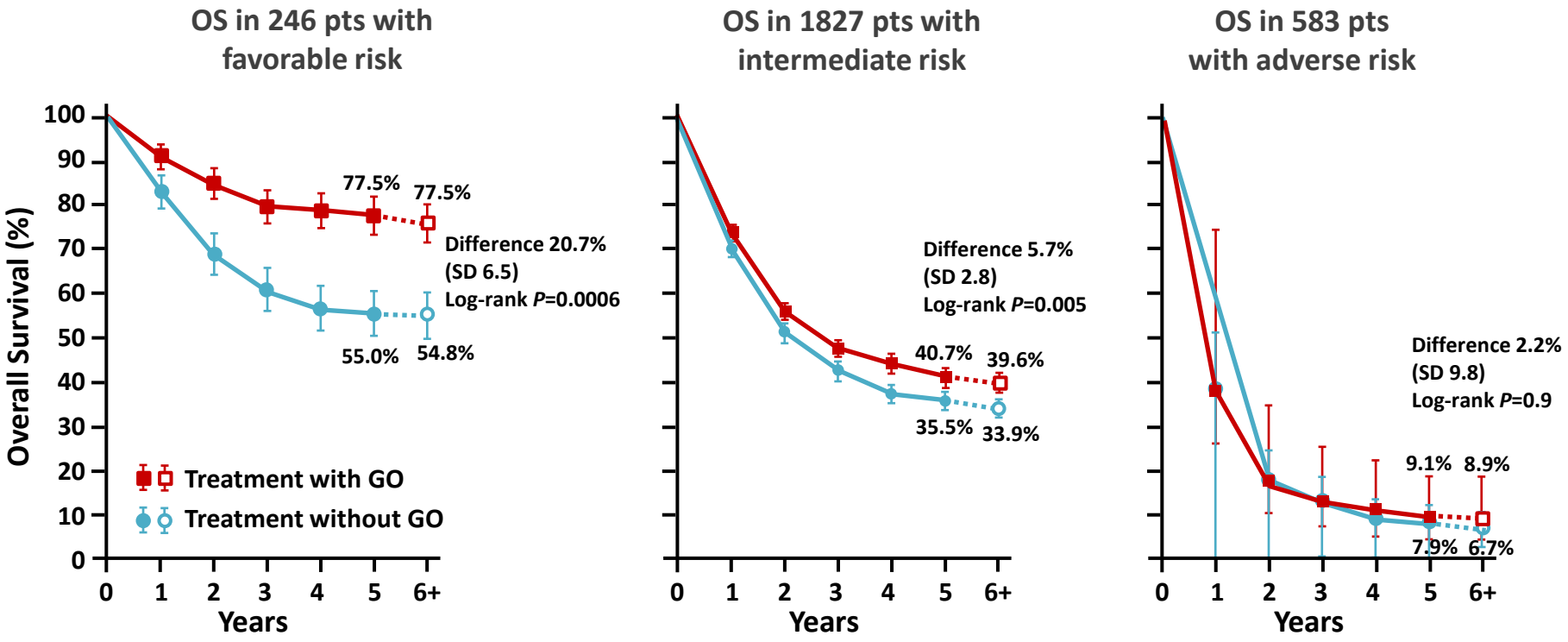
Anti-CD Added to Standard, Intensive Therapy

Meta-analysis of 3325 patients of varying cytogenetic risk levels enrolled in 5 studies of GO + standard therapy



Adapted from: Appelbaum FR, et al. *Blood.* 2017;130:2373-2376.

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Maintenance Treatment

Maintaining Hope for Maintenance Treatments

- Despite advances and new treatments, relapse common
- Effective maintenance to prolong remission, ward off relapse
- Chemo for maintenance doesn't work
- HMA with AZA + FLT3 inhibitors in clinical trials

On September 2, 2020, the FDA approved oral azacitidine as first maintenance treatment of AML

FDA press release. September 1, 2020. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-onureg-azacitidine-tablets-acute-myeloid-leukemia. Accessed September 3, 2020.

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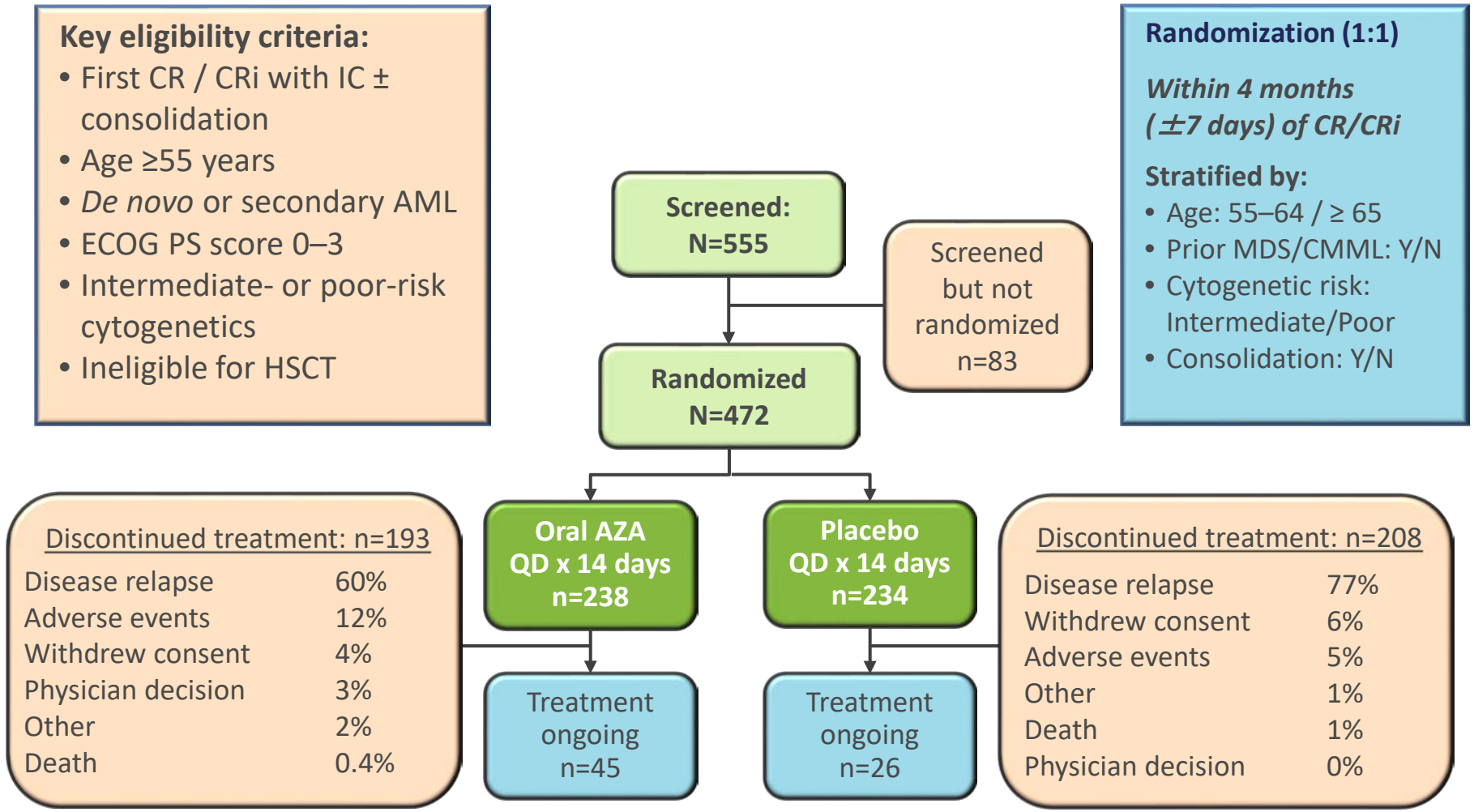
Phase 3 QUAZAR AML-001 Maintenance Trial in Patients ≥55



Adapted from: Wei AH, et al. *Blood.* 2019;134(Suppl_2):LBA-3.

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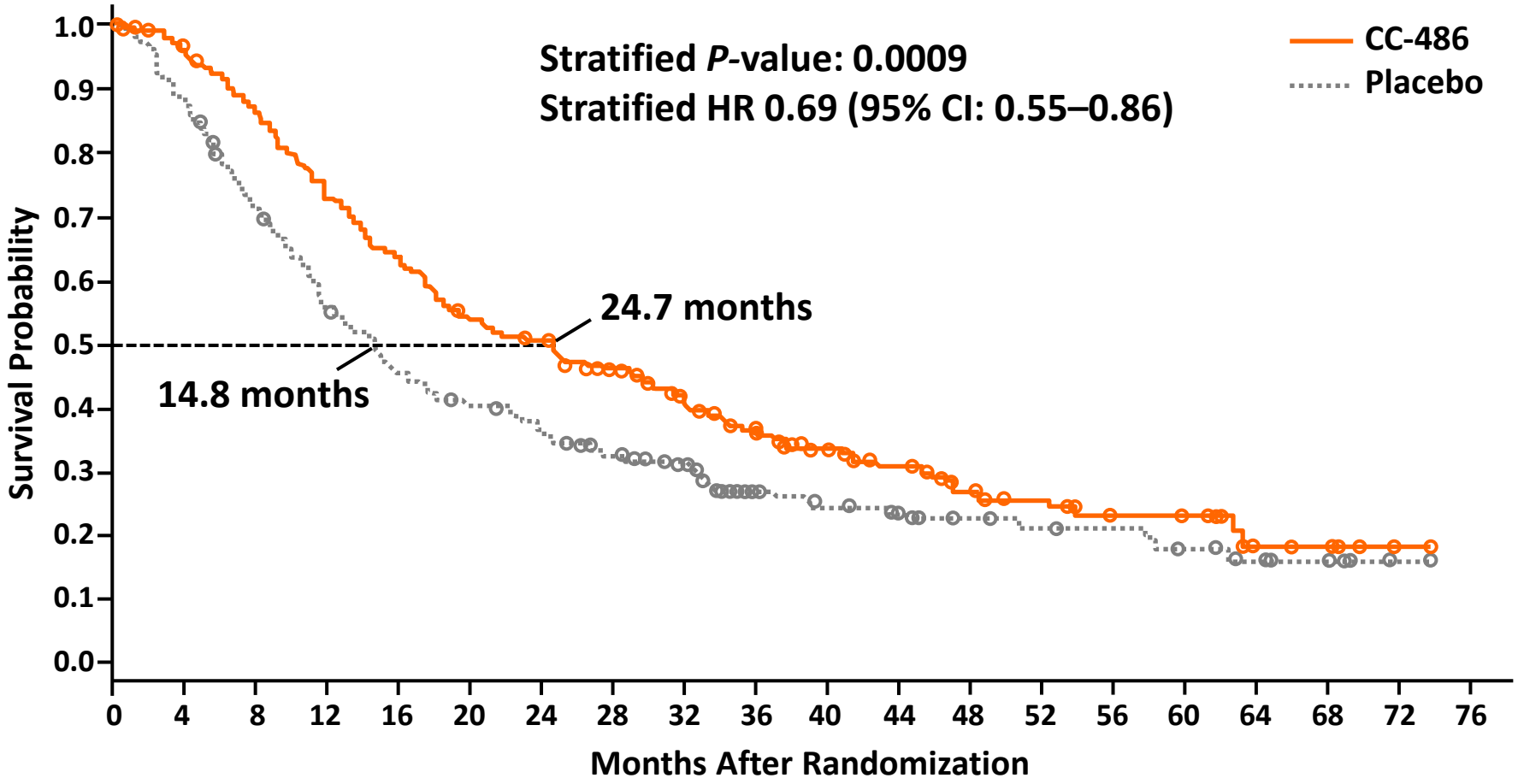
Survival Probability with Oral AZA (CC-486)

OS from phase 3 QUAZAR AML-001 maintenance trial (N=472)



Adapted from: Wei AH, et al. *Blood*. 2019;134(Suppl_2):LBA-3.

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Safety in QUAZAR AML-001

- Median treatment durations
  - Oral AZA: 12 cycles (range 1–80)
  - Placebo: 6 cycles (range 1–73)
- GI AEs in oral AZA most common in the first 2 treatment cycles
- Dose modifications due to AEs
  - Interruptions: Oral AZA 43%, placebo 175
  - Reductions: Oral AZA 16%, placebo 3%

Wei AH, et al. *Blood*. 2019;134(Suppl_2):LBA-3.

Safety in QUAZAR AML-001

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

Adapted from: Wei AH, et al. *Blood*. 2019;134(Suppl_2):LBA-3.

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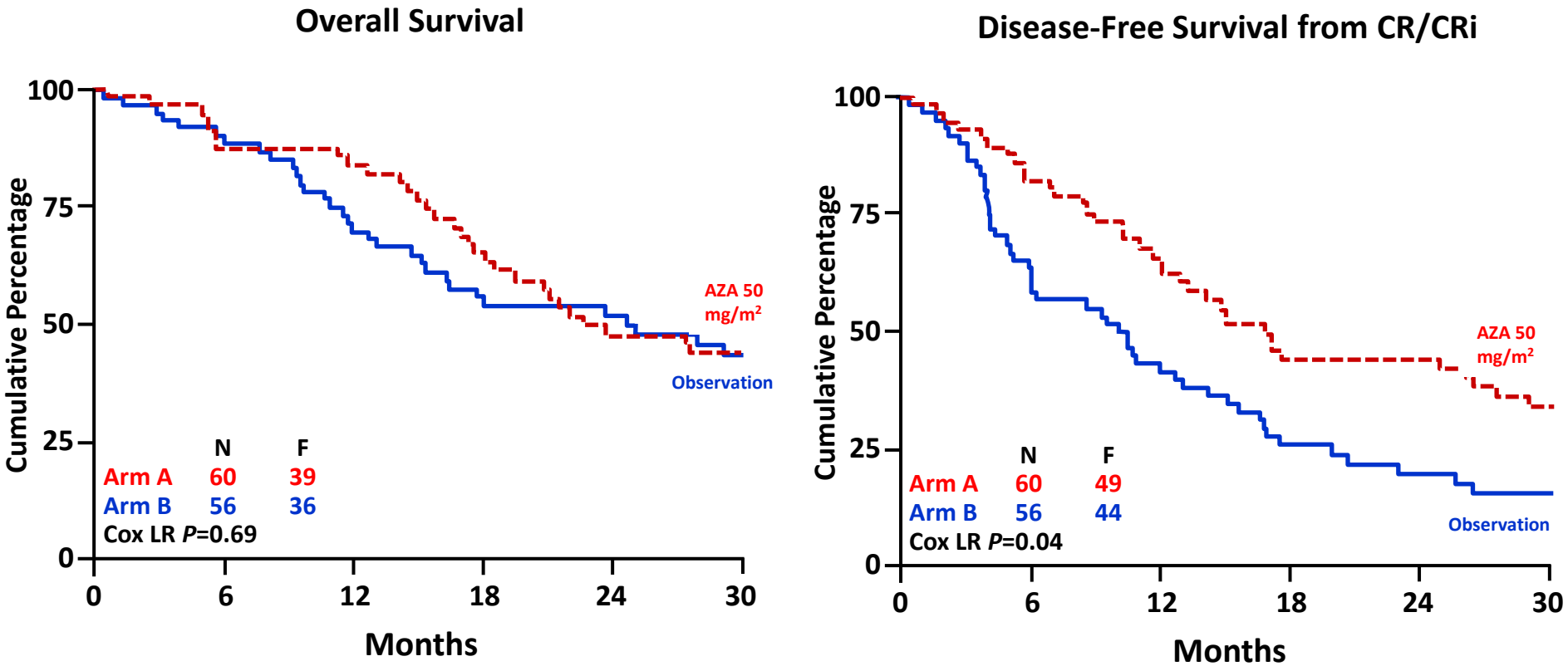
Phase 3 HOVON97 Maintenance Trial in Patients ≥60: Overall Survival

OS and DFS in phase 3 HOVON97 maintenance trial of subcutaneous azacitidine vs observation in patients ≥60 years (N=116)



Huls G, et al. *Blood*. 2019;28:133:1457-1464.

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Summary

- 8 new treatment options with different MOAs and targets available since 2017
- More treatment selections for patients who:
  - Are older and/or unfit for intensive chemo
  - Have *FLT3* or *IDH1/IDH2* mutations
  - Have high numbers of AML cells with high CD33 expression
- Personalized treatment more viable than ever
  - But must select patients appropriately based on cytogenetics
- Maintenance treatment with CC-486 (oral azacytidine) approved in September 2020
  - Could extend remission and event-free survival in patients not eligible for IC or alloHSCT

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