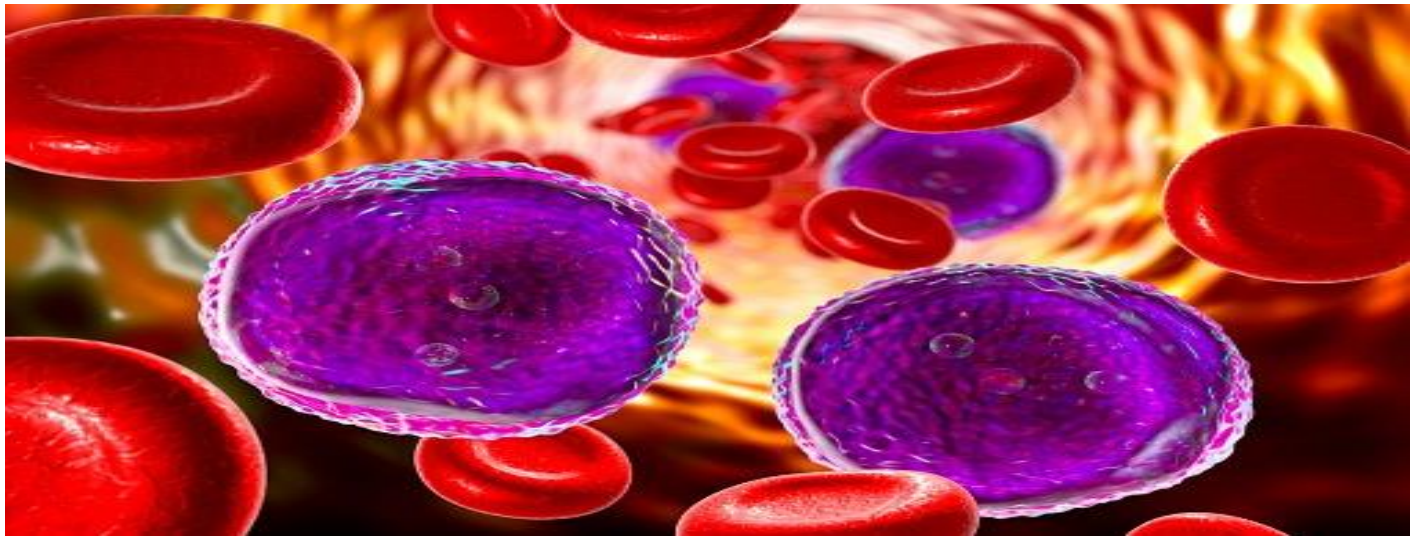
20th Congress of Iranian Society of Medical Oncology & Hematology

بیستمین کنگره سراسری انجمن پزشکان انکولوژی و هماتولوژی ایران (سال ۱۴۰۰)

Treatment Advances in Acute Myeloid Leukemia



Presented by: Dr. Abolfazl Khalafi-Nezhad

Hematologist and medical oncologist

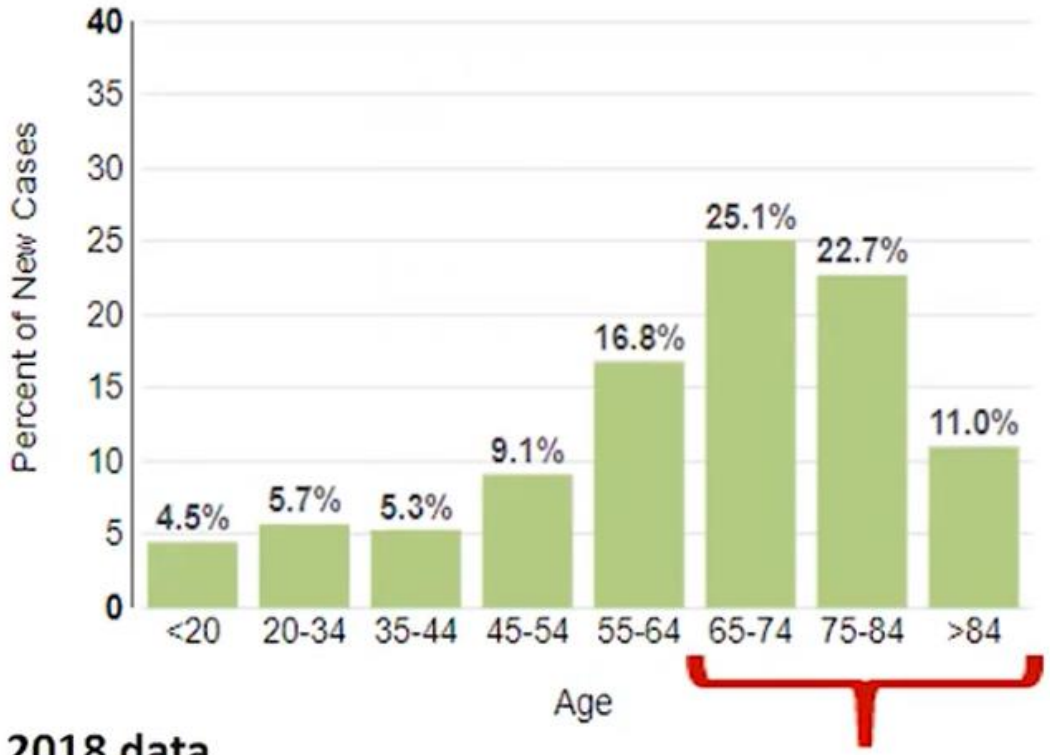
(Assistant Professor at Shiraz University of Medical Sciences)

January 2022

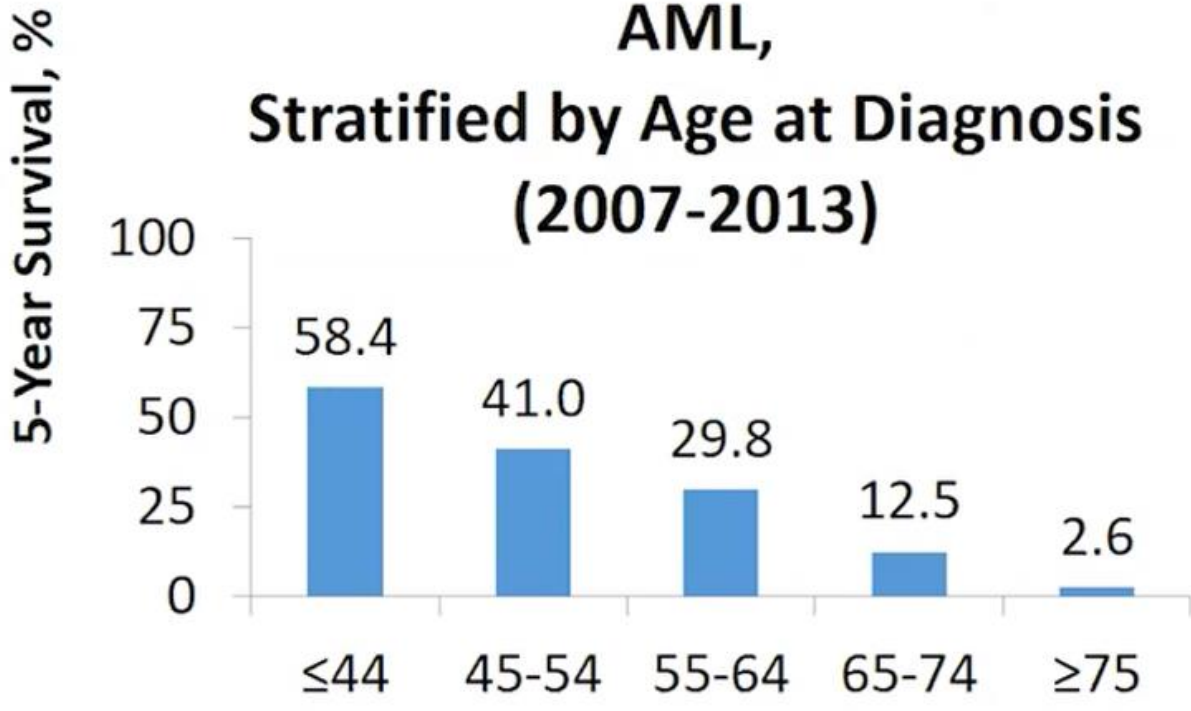
Median age at diagnosis:
68-70+ years

5-yr survival is 28.3%

Incidence of AML by Age Group



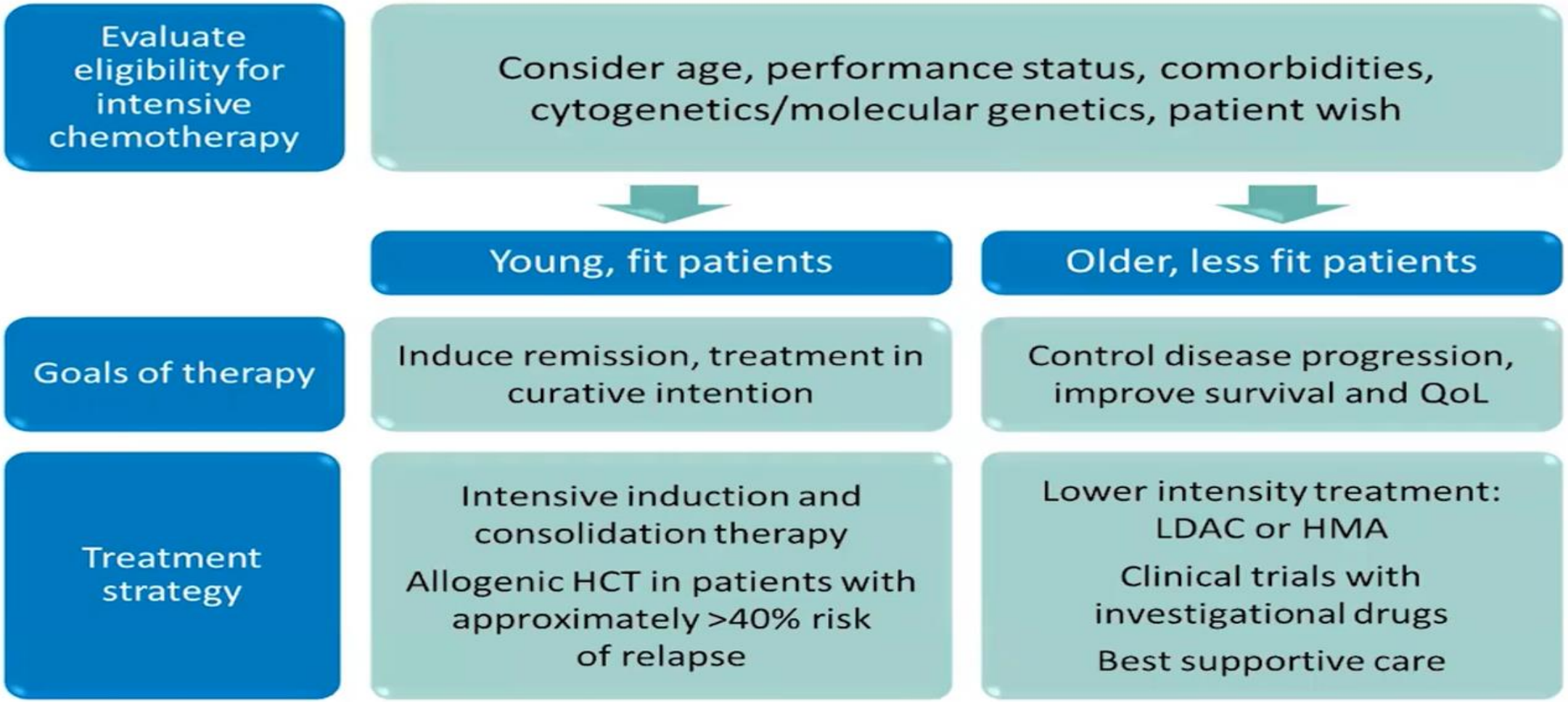
5-Year Survival of Newly Dx AML, Stratified by Age at Diagnosis (2007-2013)



SEER 2018 data

https://seer.cancer.gov/statfacts/html

Principles of AML therapy



Döhner H, *et al. Blood* 2017; **129(4)**

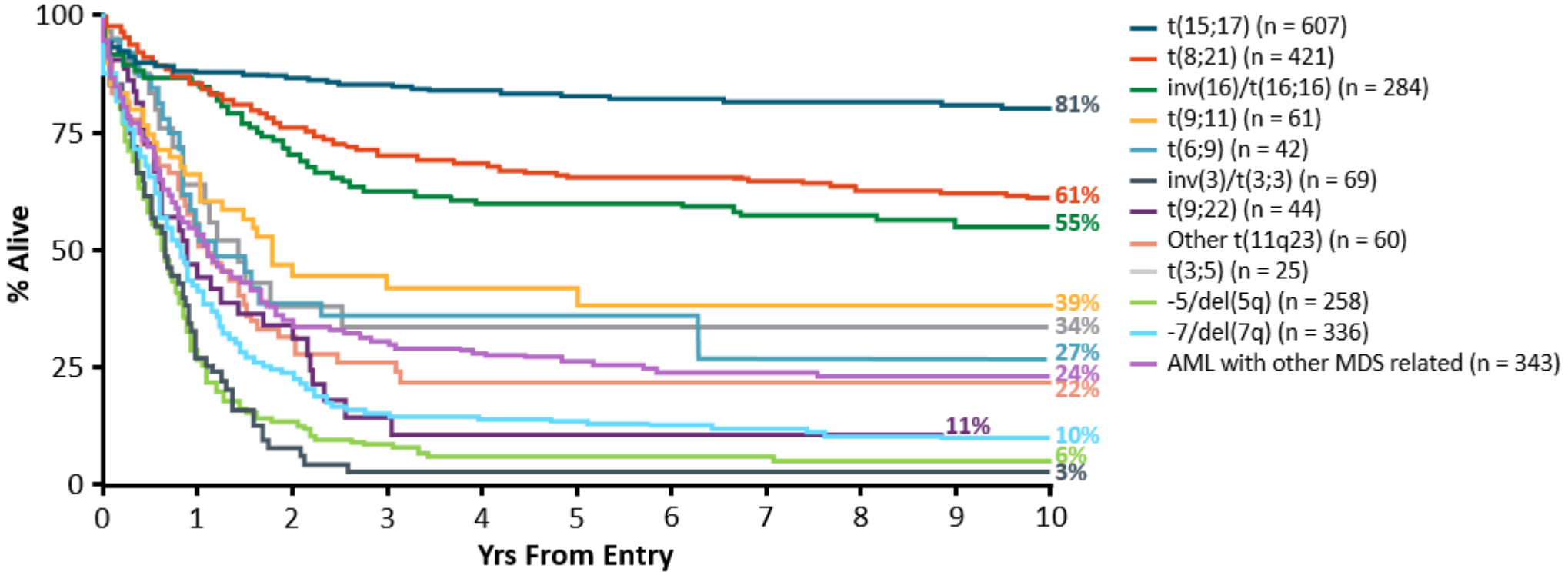
AML Risk Stratification by Cytogenetics and Molecular Abnormalities (ELN Recommendations)

Risk Status	Cytogenetics	Molecular 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 or with *FLT3*-ITD^{low} or Biallelic mutated *CEBPA*
Intermediate	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A* Cytogenetic abnormalities 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)
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*

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

Cytogenetic Entities and Survival in AML (2008 WHO Classification)

- OS in MRC/NCRI AML trials (N = 5876 patients, 16-59 yrs of age)

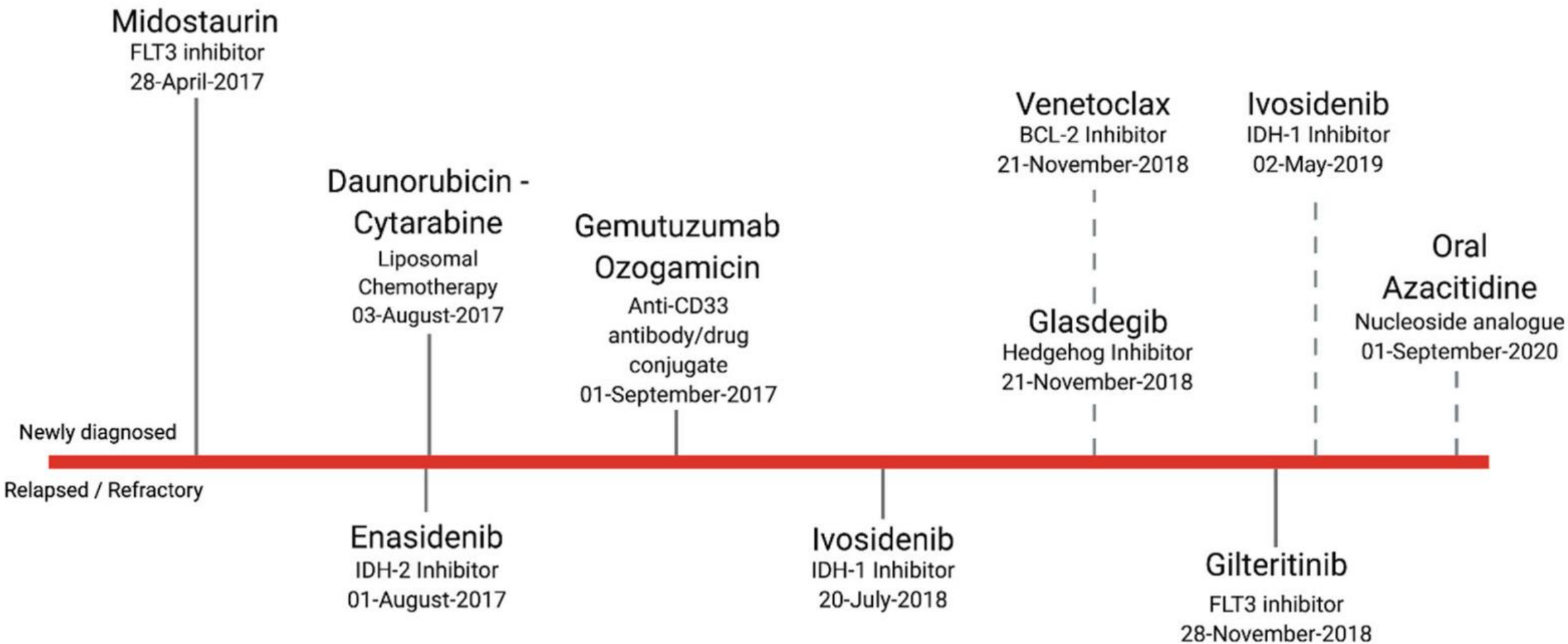


Grimwade D, et al. Blood. 2010;116:354-365.

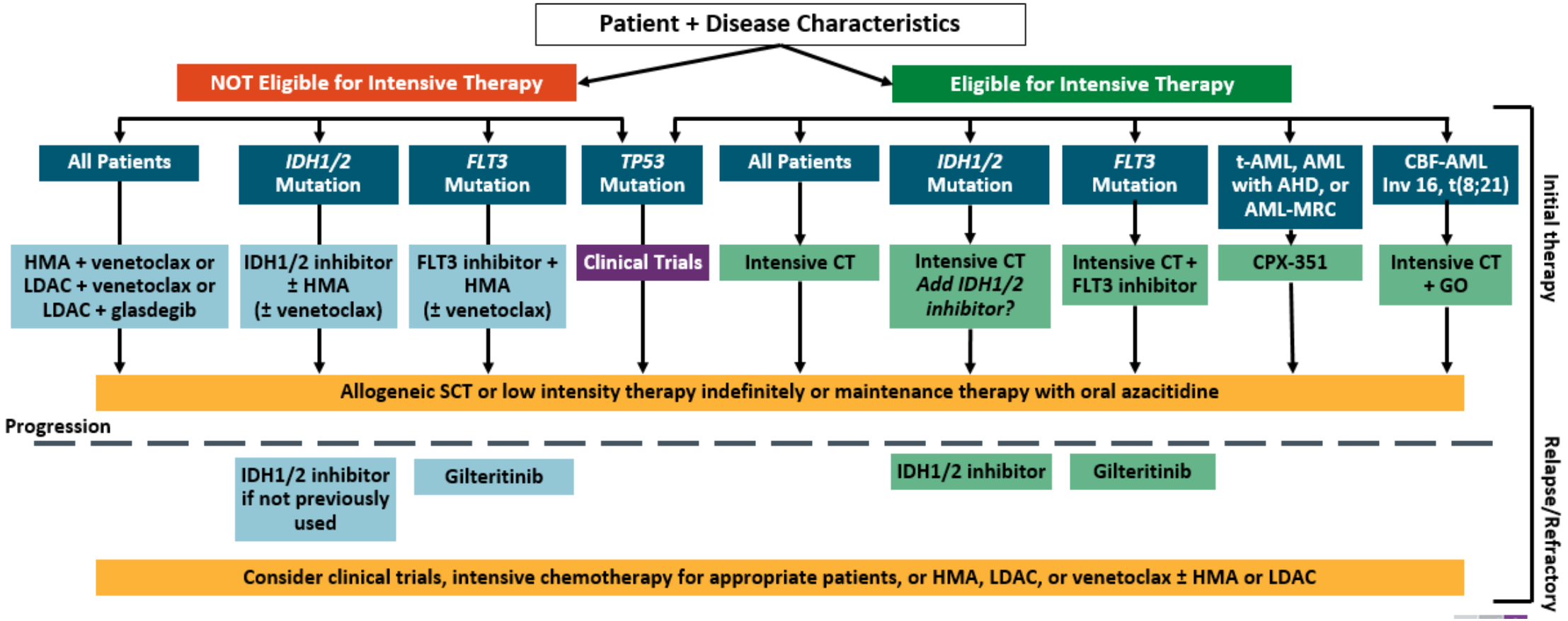
Selected Targets for AML Treatment

- Targets that can be distinctly identified
  - Cell surface epitopes: CD33, CD123, NGK2D
  - Activated kinases: FLT3, KIT
  - Other gain-of-function mutations: mutant *RAS, IDH1/2*
  - Spliceosome inhibition: U2AF1, SF3B1

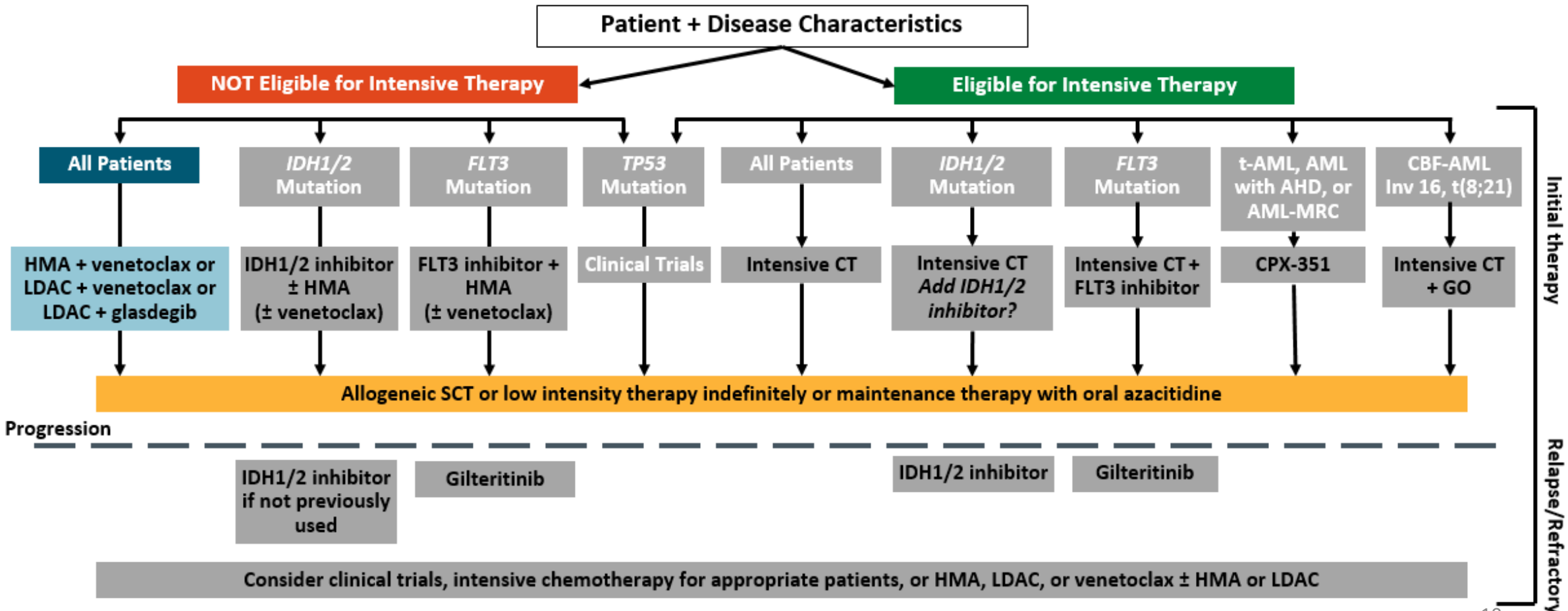
- Targets that are less distinct
  - Internal antigens: WT1, unknown antigen (vaccines, CPI)
  - Activated transcription (bromodomain)
  - (Anti)-apoptotic machinery (BCL-2, MDM2)
  - Histone methylation (DOT1L in MLL rearranged)
  - Transcriptional repression (HDAC, DNAMT)
  - Mitotic machinery (PLK)
  - Other altered cellular biology (nuclear export protein, altered PS on cell surface, Hedgehog)
  - Cytotoxics (vosaroxin, sapacitabine)


Midostaurin
FLT3 inhibitor
28-April-2017
Daunorubicin - Cytarabine
Liposomal Chemotherapy
03-August-2017
Gemutuzumab Ozogamicin
Anti-CD33 antibody/drug conjugate
01-September-2017
Venetoclax
BCL-2 Inhibitor
21-November-2018
Ivosidenib
IDH-1 Inhibitor
02-May-2019
Oral Azacitidine
Nucleoside analogue
01-September-2020
Glasdegib
Hedgehog Inhibitor
21-November-2018
Newly diagnosed
Relapsed / Refractory
Enasidenib
IDH-2 Inhibitor
01-August-2017
Ivosidenib
IDH-1 Inhibitor
20-July-2018
Gilteritinib
FLT3 inhibitor
28-November-2018

AML Treatment Overview



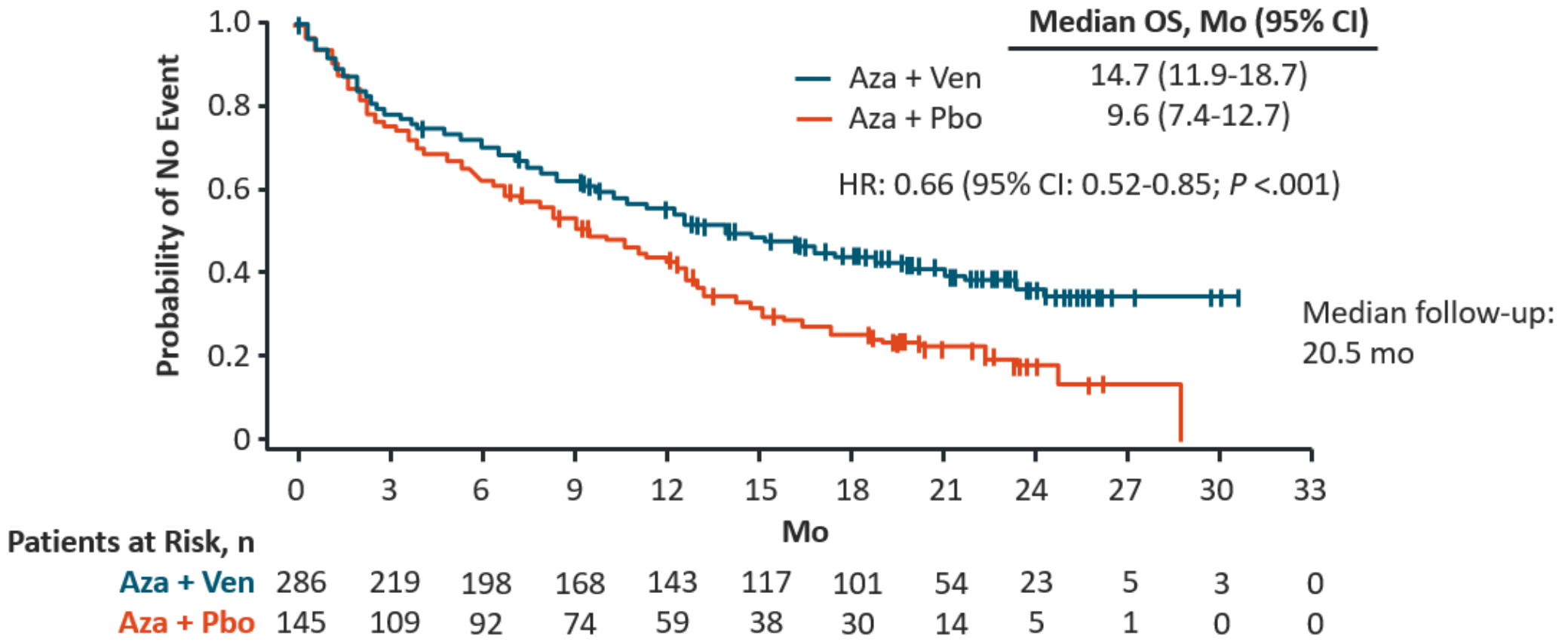
Daver. Blood Cancer J. 2020;10:107. NCCN Guidelines: AML. V3.2021.


Patient + Disease Characteristics
NOT Eligible for Intensive Therapy
Eligible for Intensive Therapy
All Patients
IDH1/2 Mutation
FLT3 Mutation
TP53 Mutation
All Patients
IDH1/2 Mutation
FLT3 Mutation
t-AML, AML with AHD, or AML-MRC
CBF-AML Inv 16, t(8;21)
HMA + venetoclax or LDAC + venetoclax or LDAC + glasdegib
IDH1/2 inhibitor ± HMA (± venetoclax)
FLT3 inhibitor + HMA (± venetoclax)
Clinical Trials
Intensive CT
Intensive CT Add IDH1/2 inhibitor?
Intensive CT + FLT3 inhibitor
CPX-351
Intensive CT + GO
Allogeneic SCT or low intensity therapy indefinitely or maintenance therapy with oral azacitidine
Progression
IDH1/2 inhibitor if not previously used
Gilteritinib
IDH1/2 inhibitor
Gilteritinib
Consider clinical trials, intensive chemotherapy for appropriate patients, or HMA, LDAC, or venetoclax ± HMA or LDAC
Initial therapy
Relapse/Refractory

Low-Dose (Nonintensive) Therapy for Older Patients With AML

- Chemotherapy
  - Cure rate ≤15% in patients >60 yr of age
  - Median survival: 6-10 mo
  - LDAC
  - HMA
    - Azacitidine, decitabine (SC or IV)
- Targeted agents
  - Venetoclax plus HMA (superior to venetoclax + LDAC)

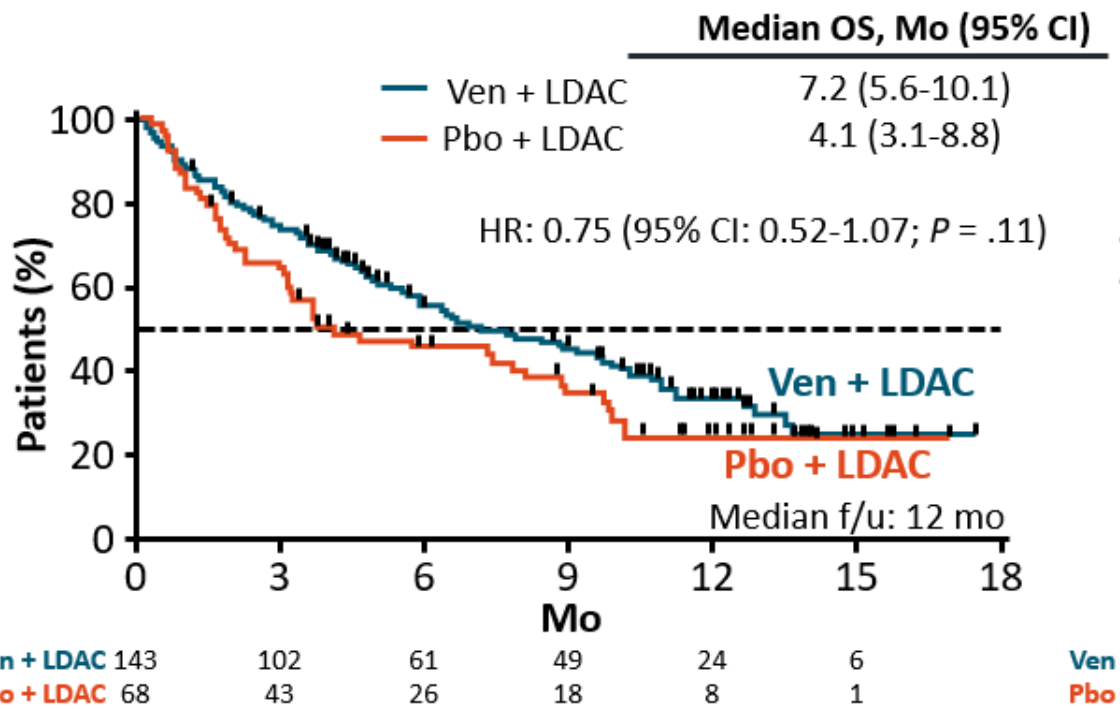
VIALE-A: Azacitidine ± Venetoclax in Treatment-Naive AML Ineligible for Standard Induction Therapy



DiNardo. NEJM. 2020;383:617.

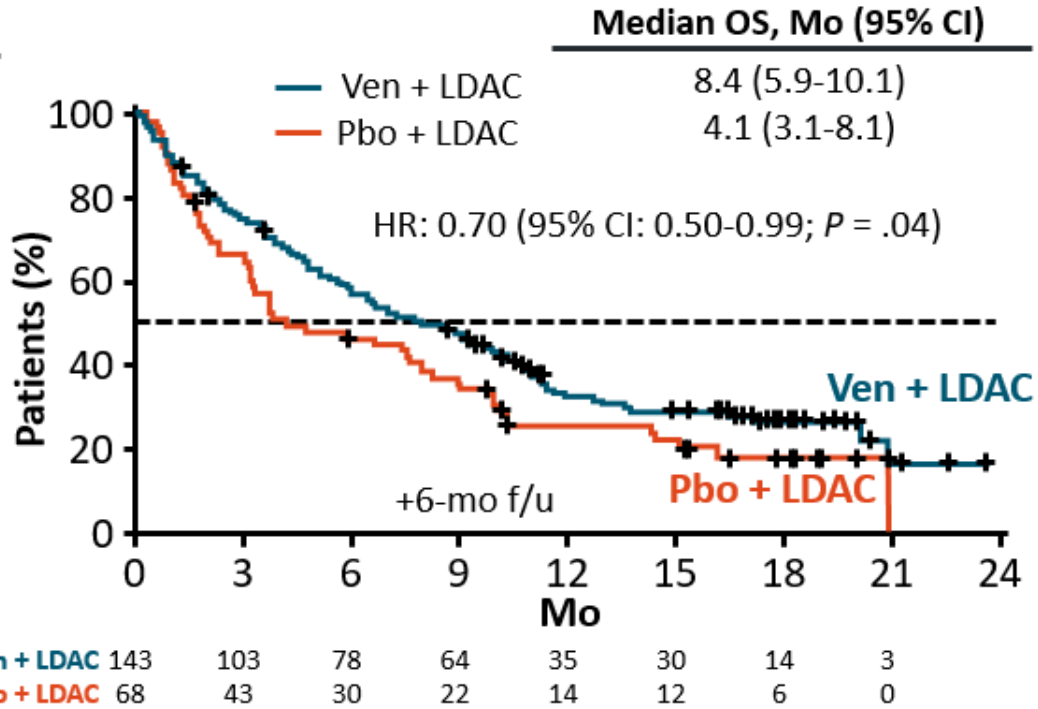
VIALE-C: LDAC ± Venetoclax in Treatment-Naive AML Ineligible for Standard Induction Therapy

Preplanned OS Analysis (Median F/u: 12.0 mo)



Ven + LDAC	143	102	61	49	24	6	
Pbo + LDAC	68	43	26	18	8	1	

OS Analysis With 6 Additional Mo of F/u



Ven + LDAC	143	103	78	64	35	30	14	3
Pbo + LDAC	68	43	30	22	14	12	6	0

	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;135:2137.

Venetoclax Dosing in AML

Dosing	Venetoclax + HMA		Venetoclax + LDAC	
	Venetoclax	HMA	Venetoclax	LDAC
Day 1	100 mg	Aza 75 mg/m^2 IV or SC, D1-7 or Dec 20 mg/m^2 IV, D1-5	100 mg	20 mg/m^2 SC, D1-10
Day 2	200 mg		200 mg	
Day 3	400 mg		400 mg	
Day 4			600 mg	

Treat until disease progression or unacceptable toxicity

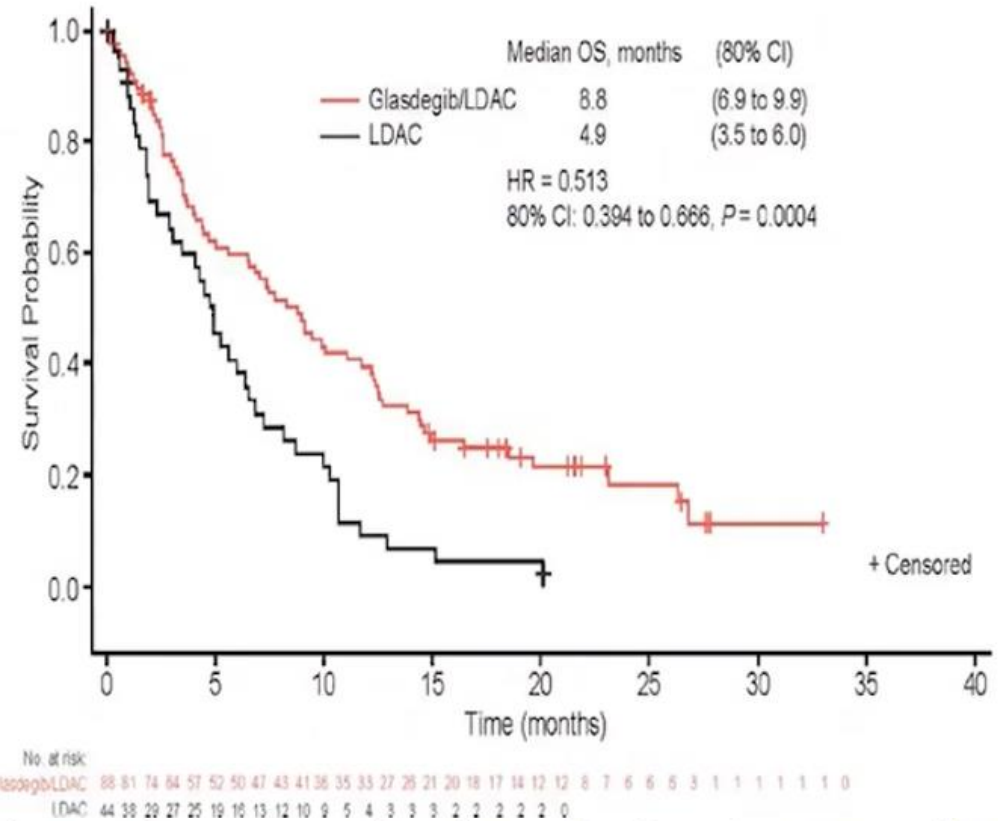
For all patients prescribed venetoclax

- WBC <25 x 10^9/L required
- Take venetoclax tablets with food and water at approximately the same time each day; swallow whole,
  do not crush or break first
- No biomarker or cytogenetic testing required prior to initiation
- Assess individual patient risk of TLS

Glasdegib in AML and MDS

- Phase II study in pts with AML and high-risk myelodysplastic syndrome (N = 132)

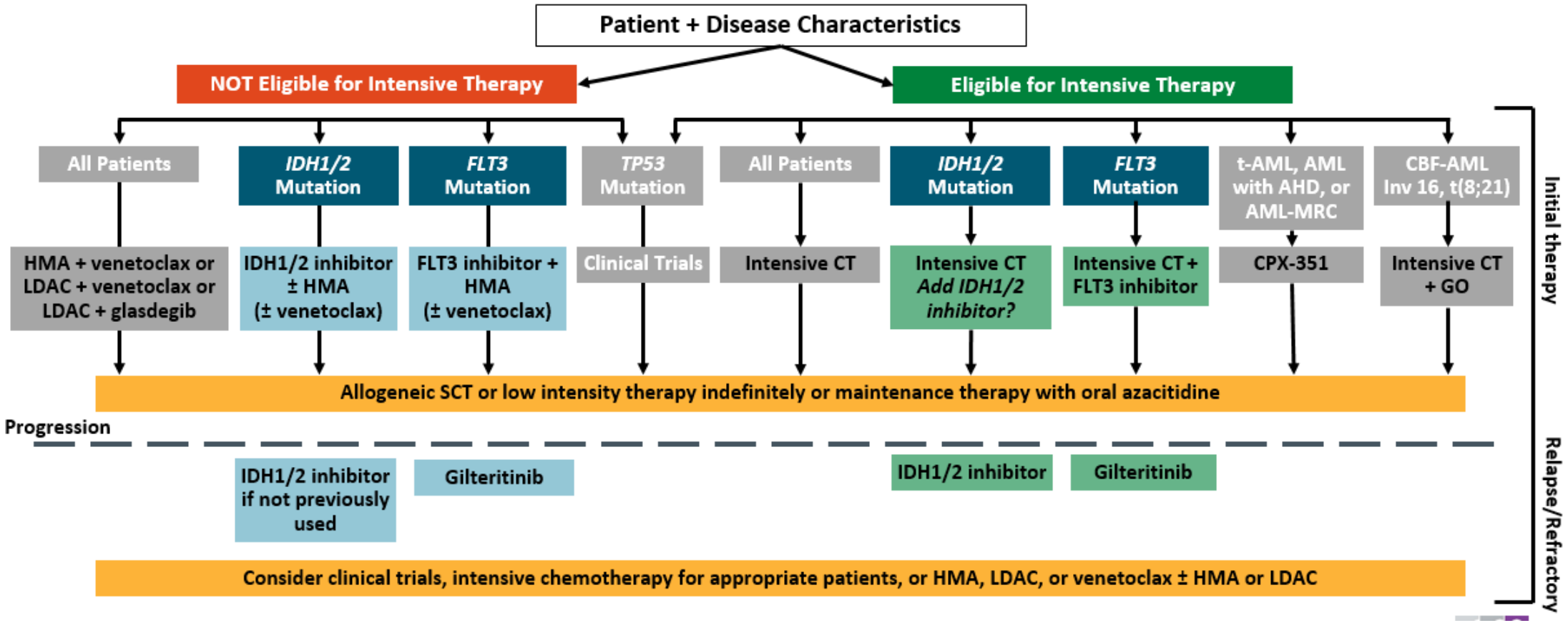
	LDAC + Glasdegib (n = 88)	LDAC Alone (n = 44)
Median age, yrs (range)	77 (63-92)	75 (58-83)
Good/Int CG, n (%)	52 (60)	25 (57)
CR/CRi (n, %)	**20 (23)**	**2 (4.5)**
Median OS (mos)	**8.8 mos**	**4.9 mos**



- Inhibition of Hh signaling pathway increases sensitivity to chemotherapy and reduces leukemic stem cell growth
- Gladegib is currently in Phase 3 development for AML in combination with AZA or 7+3

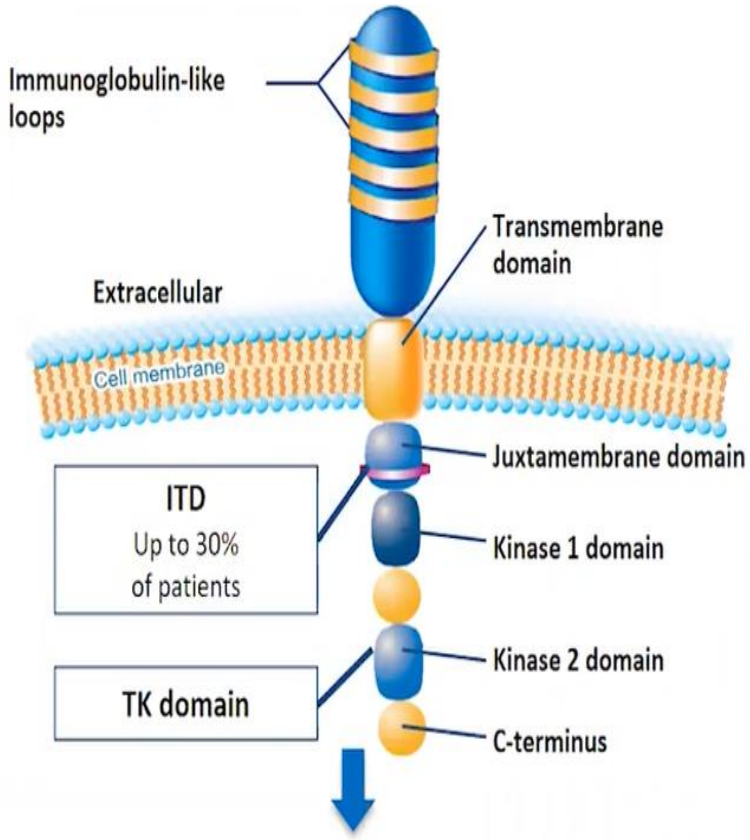
Cortes J, et al. *Leukemia*. 2019
Fukushima N et al, Cancer Sci 2016

Targeted Treatment Options for Patients With *FLT3* or *IDH1/2* Mutations



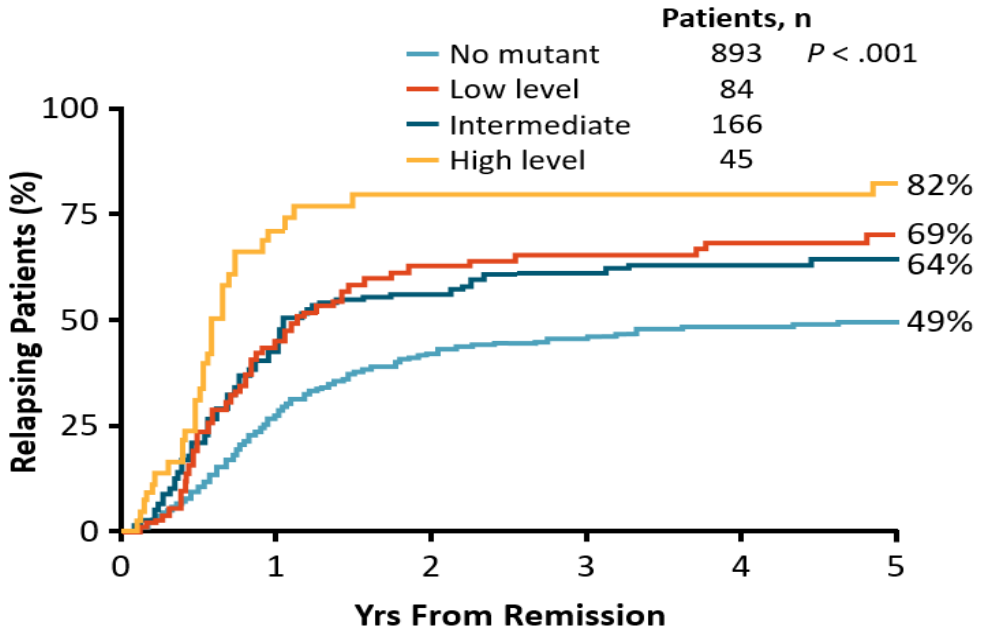
Targeted Treatment Options for Patients With AML and *FLT3* Mutations

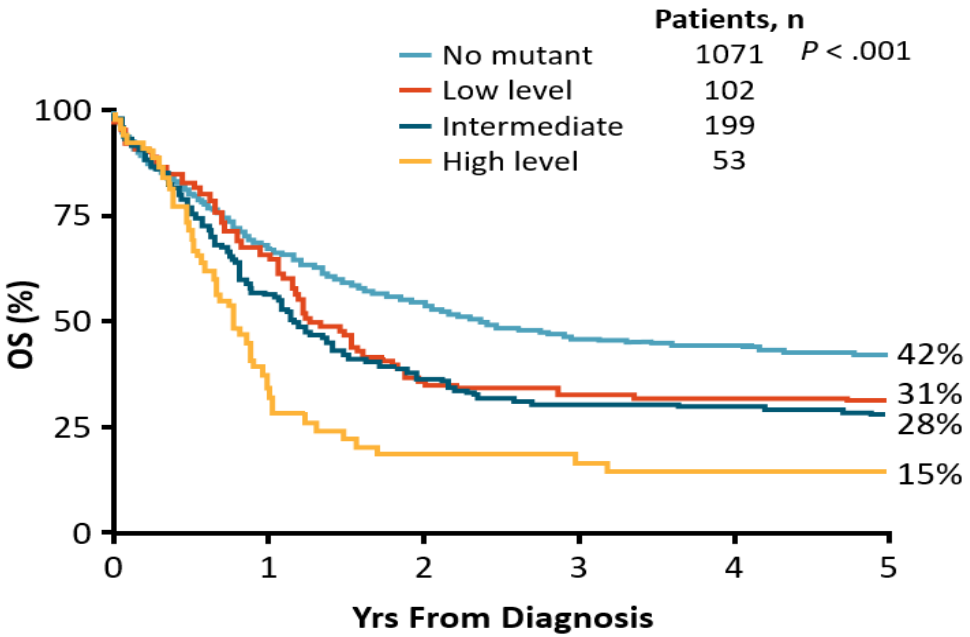
- Overexpression of *FLT3* common in AML
- *FLT3* mutations present in ~ 30% patients with AML
  - 23%: internal tandem duplication
  - 7%: point mutation in tyrosine kinase domain
- Mutations constitutively activate *FLT3*
  - Ligand-independent cell growth
- *FLT3*-ITD associated with increased frequency of relapse, short survival
  - Allelic ratio, ITD insertion site



Leick MB, et al. Curr Hematol Malig Rep. 2017;12:153-167.

Outcomes in Young Adults With AML by *FLT3*-ITD Level



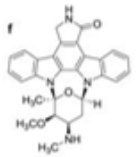


Mutation Level

- Low: < 25%
- Intermediate: 25% to 50%
- High: > 50%

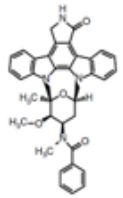
Gale RE, et al. Blood. 2008;111:2776-2784.

FLT3 Inhibitors



Staurosporine[1,2]

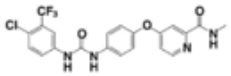
Reference compound



Midostaurin[1,3]

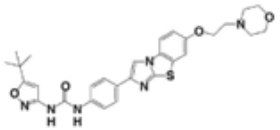
No activity in relapse[4]

FDA approved in front line when combined with chemotherapy[5]



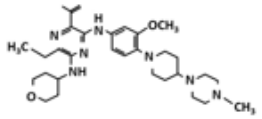
Sorafenib[1,3]

Some activity at relapse, but not well tolerated[6]



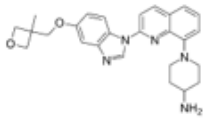
Quizartinib[1,3]

OS benefit in R/R AML[7]



Gilteritinib[1,3]

FDA approved in R/R AML as detected by FDA-approved test[8]

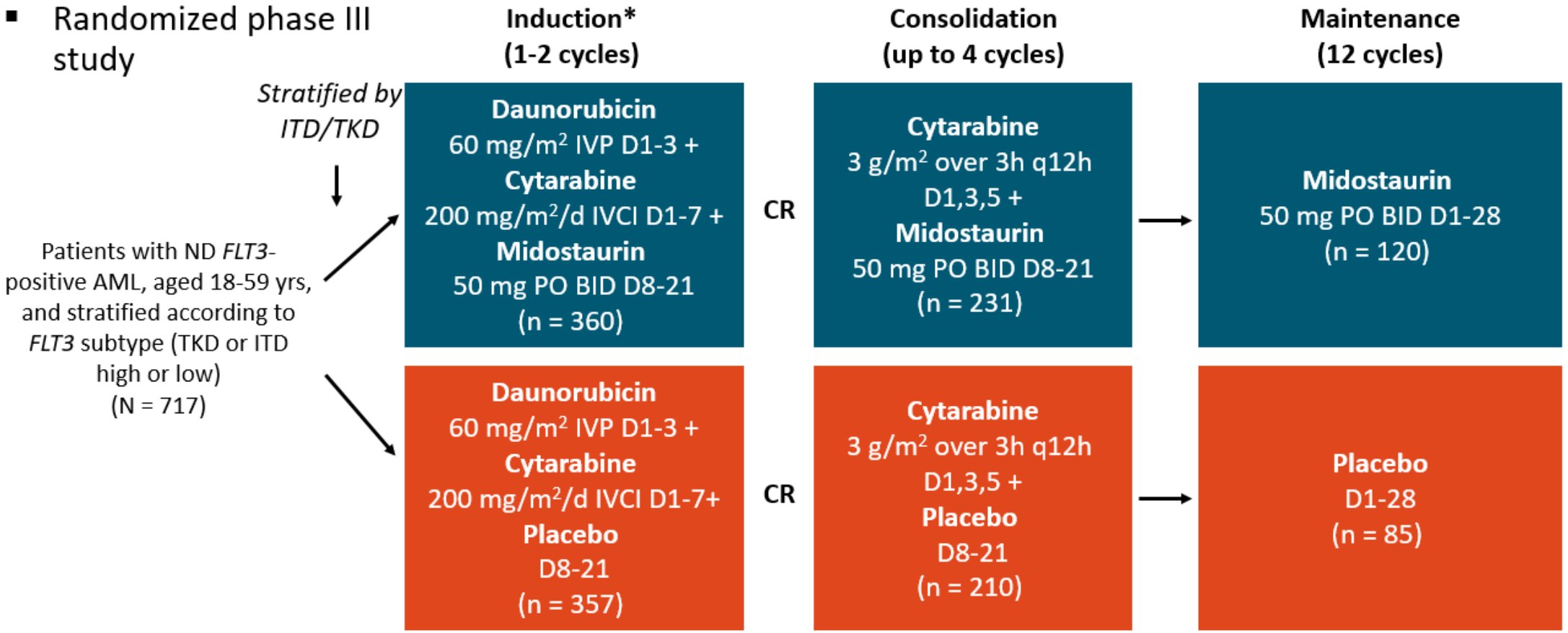


Crenolanib[1,3]

Some activity at relapse[9]

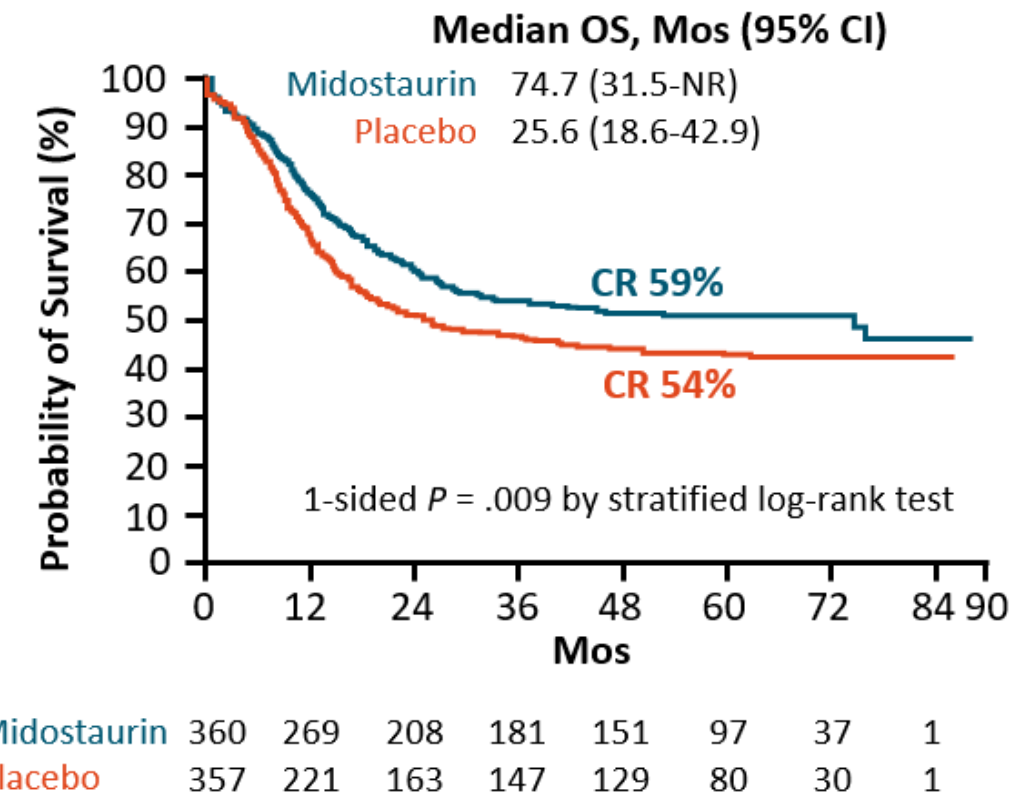
RATIFY: First-line Chemo ± Midostaurin in *FLT3*-Mutated AML

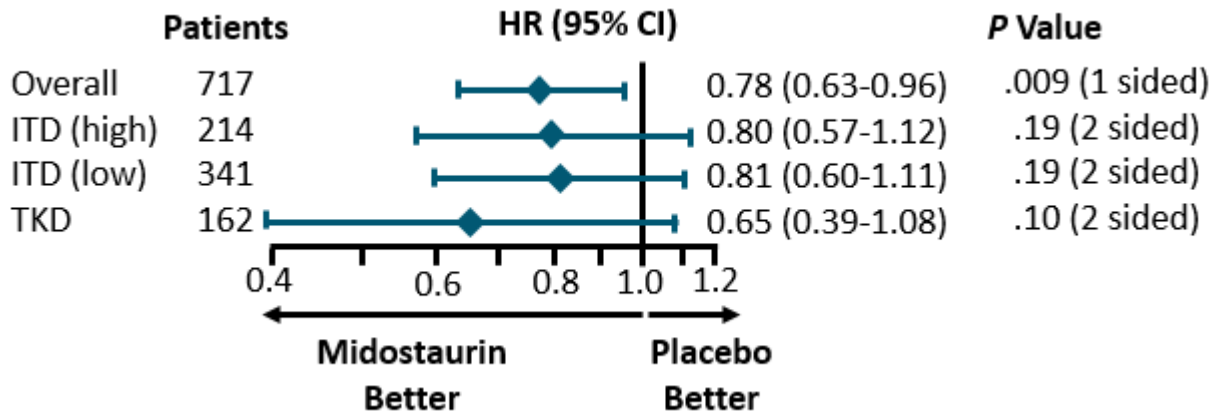
- Randomized phase III study



*Hydroxyurea allowed for ≤ 5 days prior to induction therapy.

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

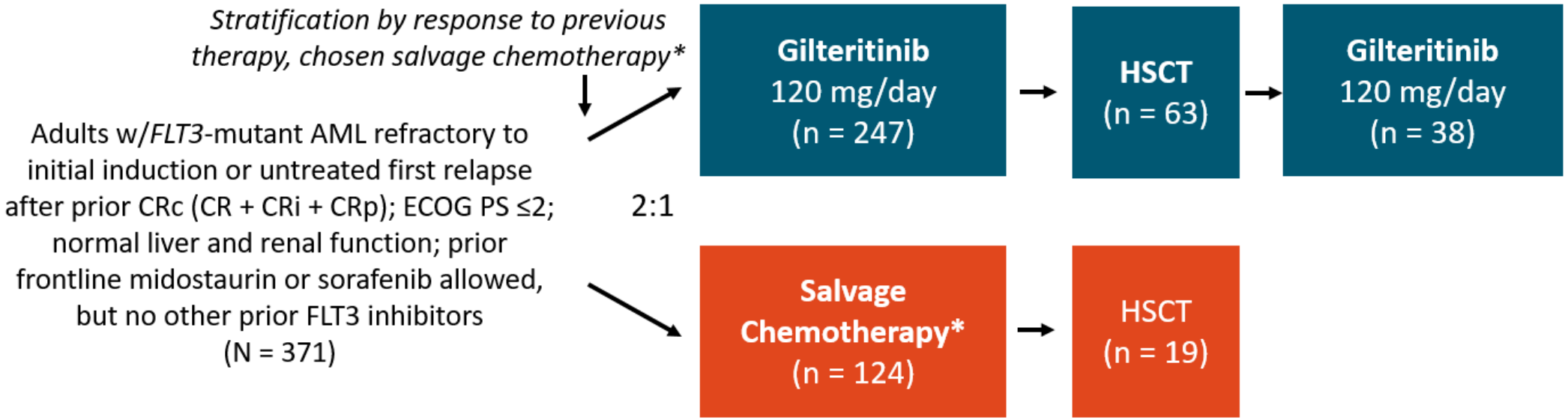




Stone RM, et al. N Engl J Med. 2017;377:454-464.

ADMIRAL: Gilteritinib in *FLT3*-Mutant R/R AML

- International, randomized, controlled phase III trial



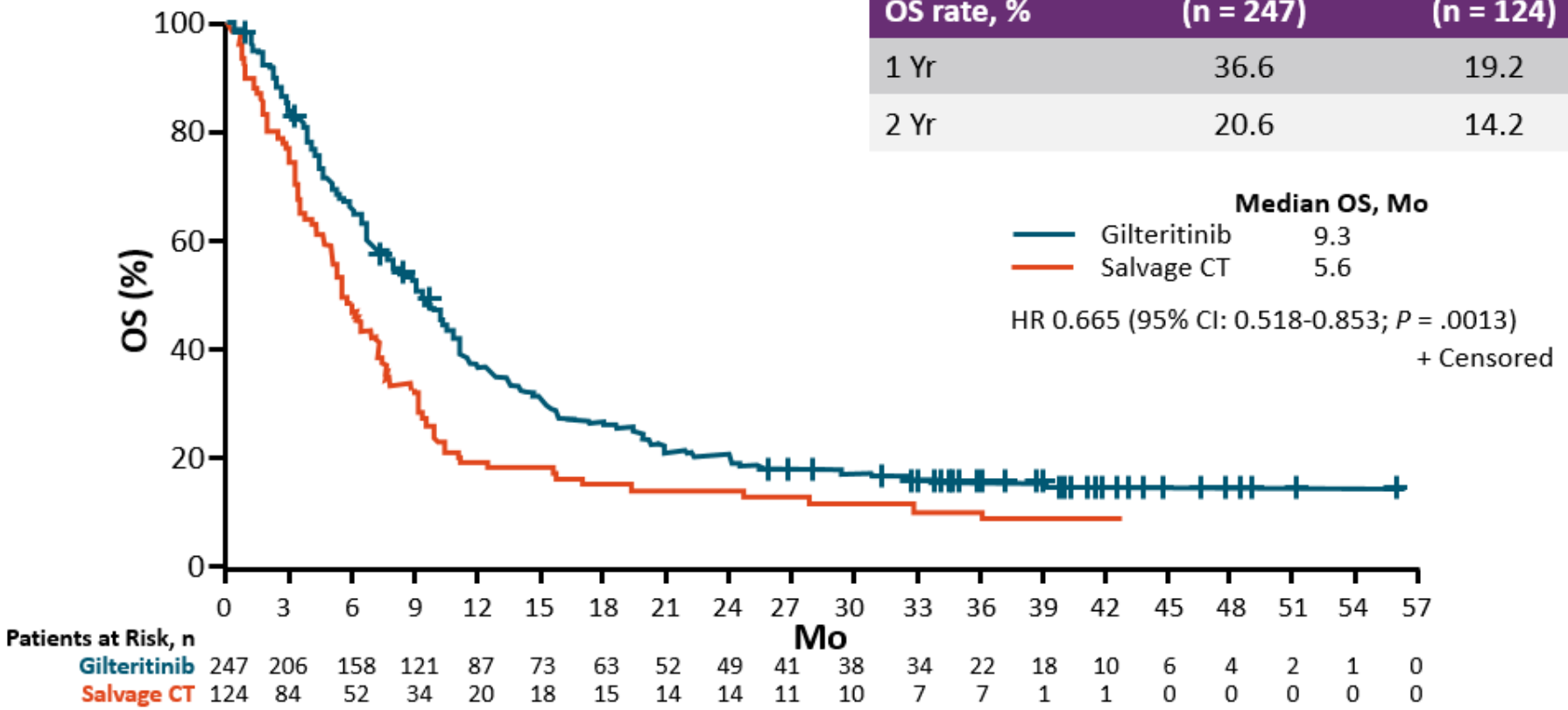
*Salvage chemotherapy selected prior to randomization: MEC + FLAG-IDA (high intensity) for 1-2 cycles; low-dose cytarabine + azacytidine (low intensity) administered until disease progression or intolerance.

- Primary endpoints: OS, CR/CRh rate
- Secondary endpoints: EFS, CR rate

Perl. NEJM. 2019;381;1728.

Gilteritinib Prolongs OS vs Chemo in *FLT3*-Mutant R/R AML: Phase III ADMIRAL Study

OS rate, %	Gilteritinib (n = 247)	Salvage CT (n = 124)
1 Yr	36.6	19.2
2 Yr	20.6	14.2



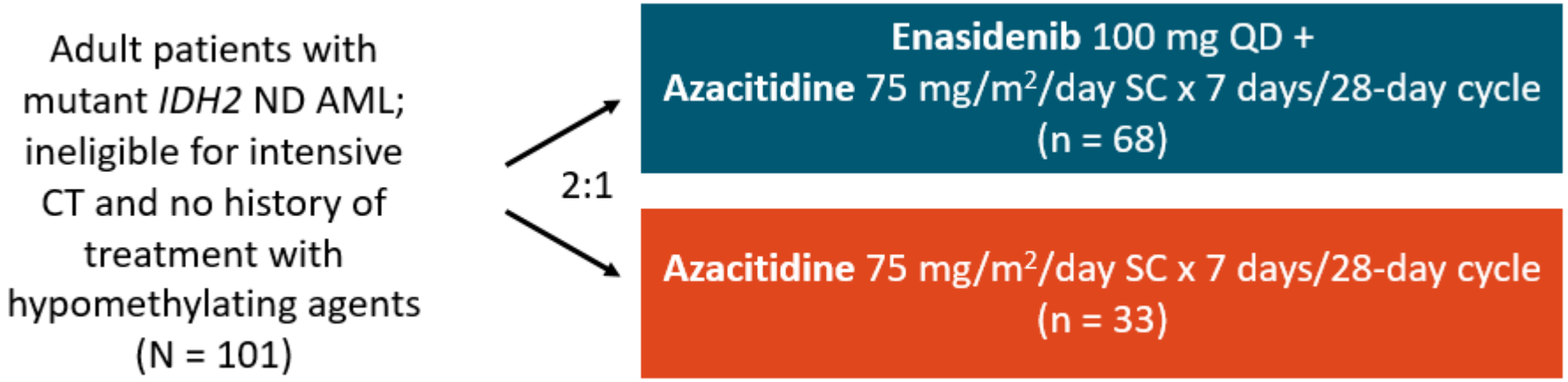
Perl. ASCO 2021. Abstr 7013.

IDH1/2-Mutant AML

- *IDH1/2* mutations present in 8% to 15% of patients with AML; associated with normal cytogenetic status (cn-AML)
- IDH proteins are essential to the Krebs cycle and catalyze decarboxylation of isocitrate to α-KG in cytoplasm (IDH1) and mitochondria (IDH2)
- Mutant IDH enzymes catalyze an NADPH-dependent reduction of α-KG to 2-HG
- This leads to accumulation of 2-HG oncometabolite in *IDH1/2*-mutant tumors
- Management of AML with *IDH* mutation
  - Selective inhibitors of mutant IDH2
    - Enasidenib
  - Selective inhibitors of mutant IDH1
    - Ivosidenib

AG221-AML-005: Addition of Enasidenib to Azacitidine in Newly Diagnosed AML With Mutated *IDH2*

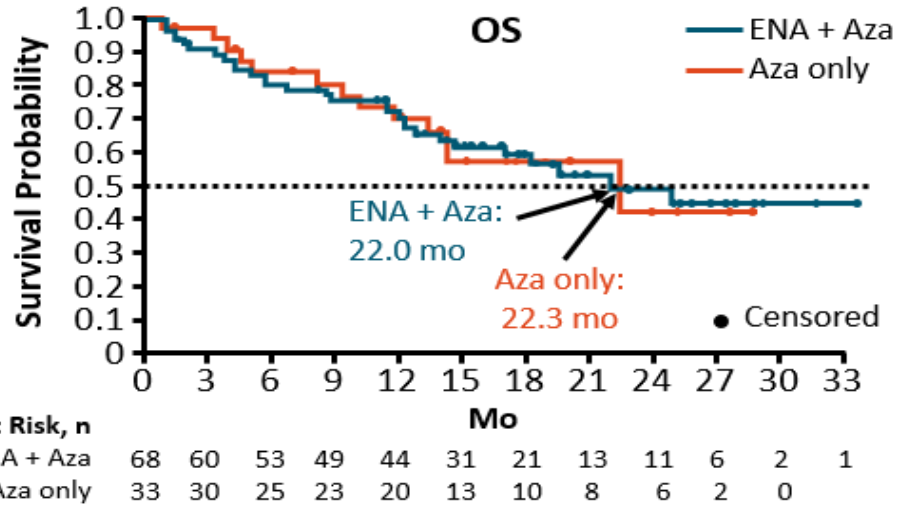
- Dose-finding (3 + 3) phase Ib study followed by randomized phase II study

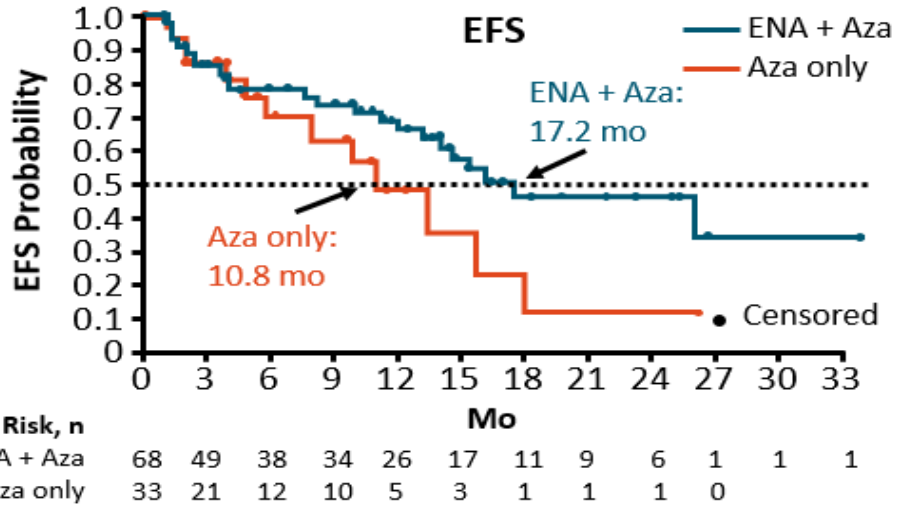


- Primary endpoint: ORR
- Key secondary endpoints: CR rate, DoR, safety, OS, EFS

AG221-AML-005: OS and EFS

- Median OS in enasidenib arm in patients with CR: not reached, with 1-yr OS >90%
- In azacitidine-only arm, 8 patients (24%) crossed over to enasidenib



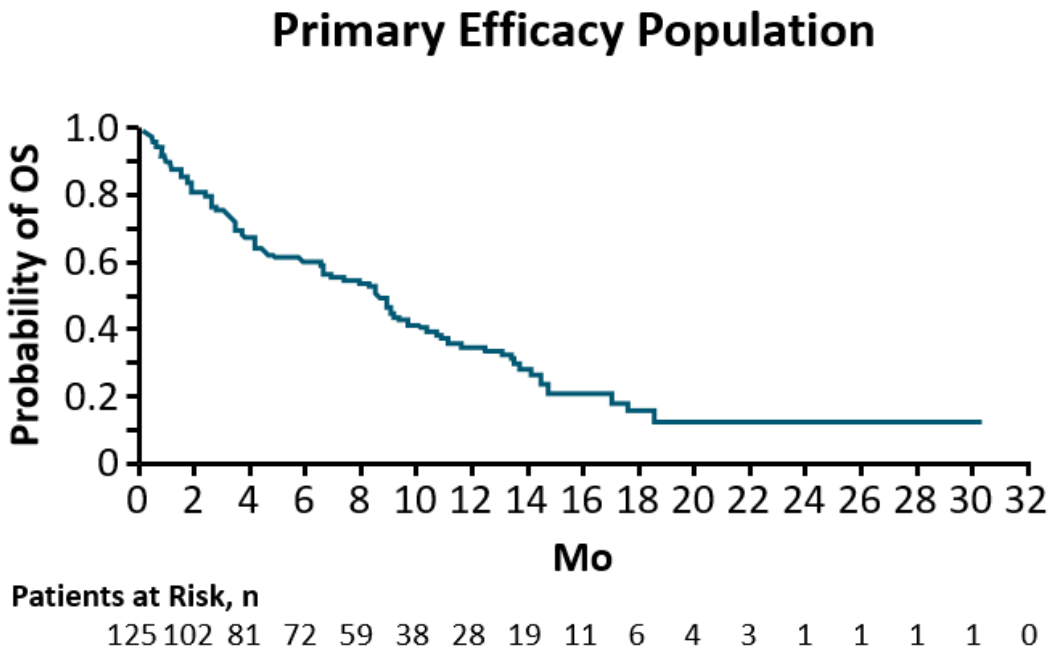


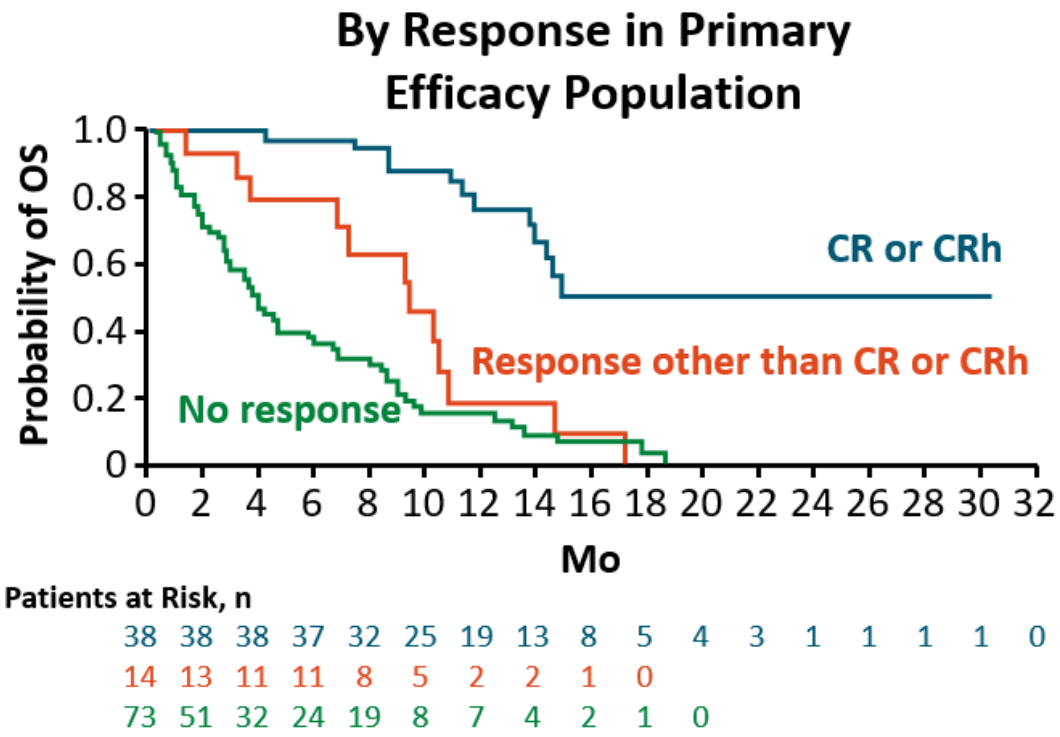
Endpoint, Mo	ENA + Aza (n = 68)	Aza Monotherapy (n = 33)	HR (95% CI)	*P* Value
Median OS	22.0	22.3	0.99 (0.52-1.87)	.9686
Median EFS	17.2	10.8	0.59 (0.30-1.17)	.1278

Median follow-up in both arms: 14 mo

DiNardo. ASCO 2020. Abstr 7501.

Ivosidenib in *IDH1*-Mutated R/R AML: OS





median overall survival in the primary efficacy population was 8.8 months

ivosidenib at a dose of 500 mg daily

DiNardo. NEJM. 2018;378:2386.

Ivosidenib in *IDH1*-Mutated Newly Diagnosed AML: OS

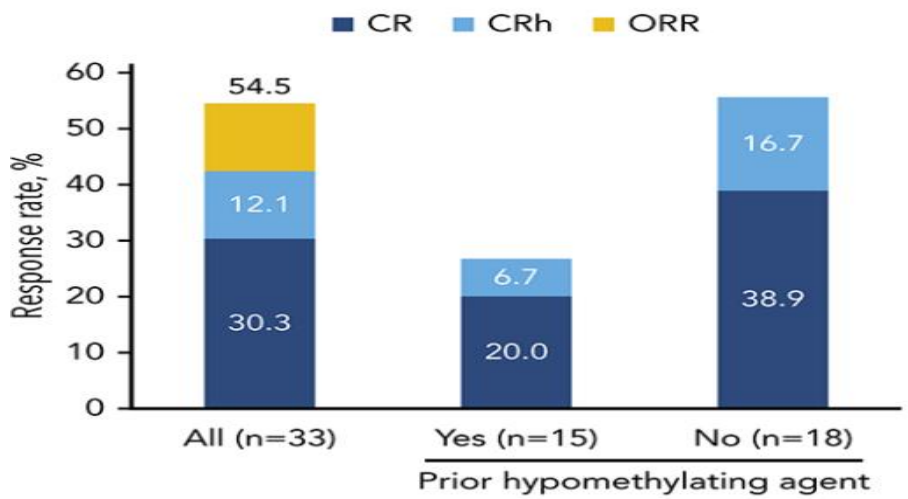
- *IDH1*-mutant newly diagnosed AML
- Ineligible for standard therapy
- N=34

56% aged ≥75 years

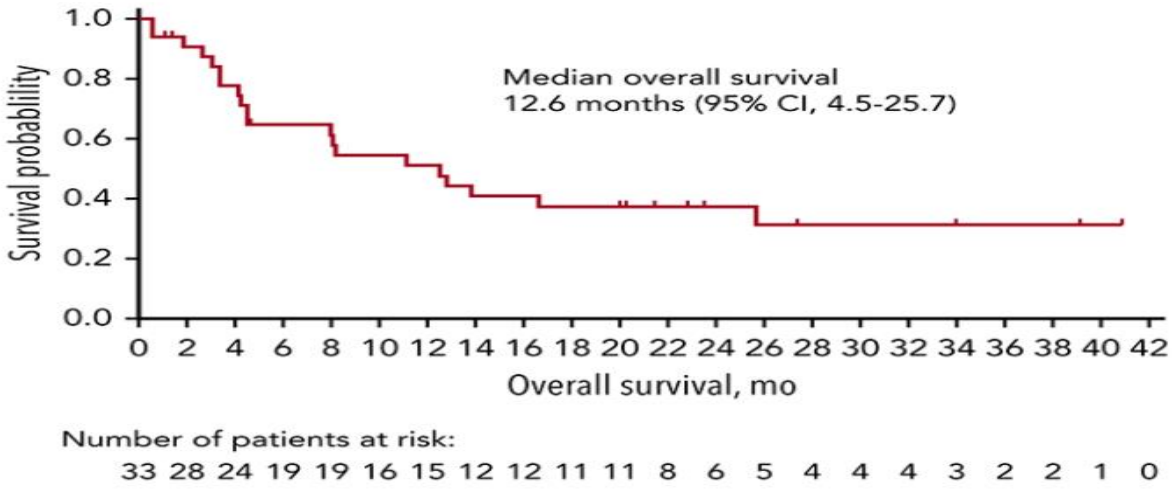
47% prior exposure to HMA

76% secondary AML

Mutant IDH1 inhibitor ivosidenib 500 mg once daily



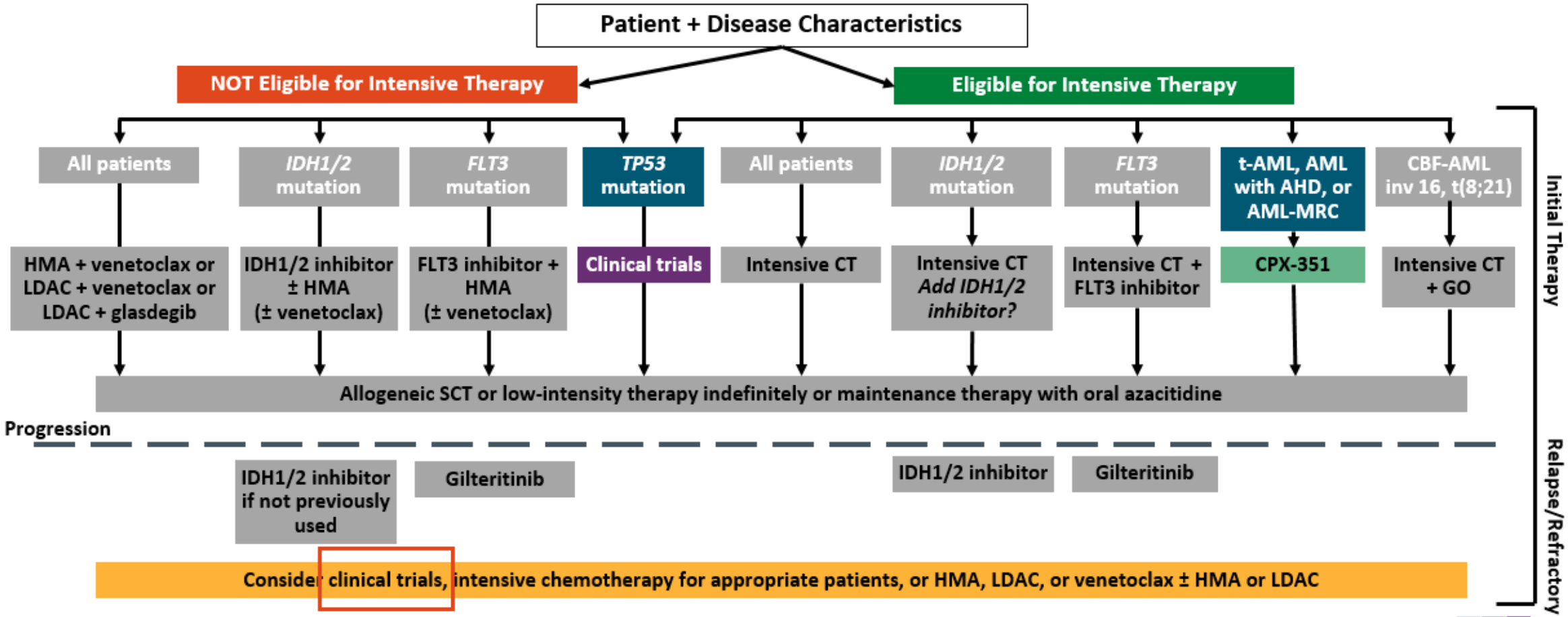
- Of the patients who were transfusion-dependent at baseline, 43% became transfusion independent



Blood. 2020 Feb 13;135(7):463-471. doi: 10.1182/blood.2019002140.

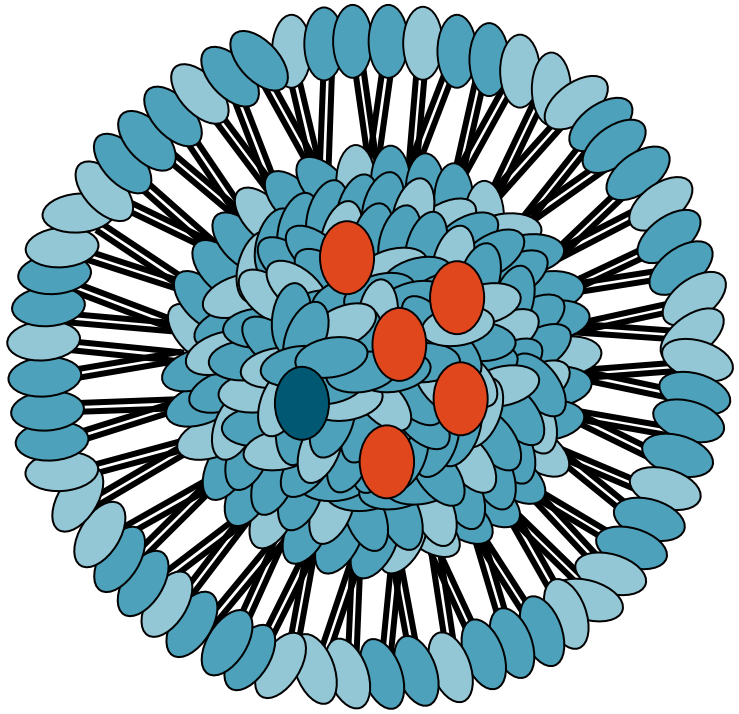
FLT3 or *IDH* Inhibitor Approvals for AML

Drug Name	Approval	Indications
Midostaurin + 7 + 3*	4/17	Adult patients with newly diagnosed AML who have an *FLT3* mutation
Enasidenib†	8/17	Adult patients with relapsed/refractory AML who have an *IDH2* mutation
Ivosidenib‡	7/18	Adult patients with relapsed/refractory AML who have an *IDH1* mutation
	5/19	Newly diagnosed patients with *IDH1*-mutated AML aged 75 yr or older or with comorbidity precluding intensive therapy
Gilteritinib*	11/18	Adult patients with relapsed/refractory AML who have an *FLT3* mutation


Patient + Disease Characteristics
NOT Eligible for Intensive Therapy
Eligible for Intensive Therapy
All patients
IDH1/2 mutation
FLT3 mutation
TP53 mutation
All patients
IDH1/2 mutation
FLT3 mutation
t-AML, AML with AHD, or AML-MRC
CBF-AML inv 16, t(8;21)
HMA + venetoclax or LDAC + venetoclax or LDAC + glasdegib
IDH1/2 inhibitor ± HMA (± venetoclax)
FLT3 inhibitor + HMA (± venetoclax)
Clinical trials
Intensive CT
Intensive CT Add IDH1/2 inhibitor?
Intensive CT + FLT3 inhibitor
CPX-351
Intensive CT + GO
Allogeneic SCT or low-intensity therapy indefinitely or maintenance therapy with oral azacitidine
Progression
IDH1/2 inhibitor if not previously used
Gilteritinib
IDH1/2 inhibitor
Gilteritinib
Consider clinical trials, intensive chemotherapy for appropriate patients, or HMA, LDAC, or venetoclax ± HMA or LDAC
Initial Therapy
Relapse/Refractory

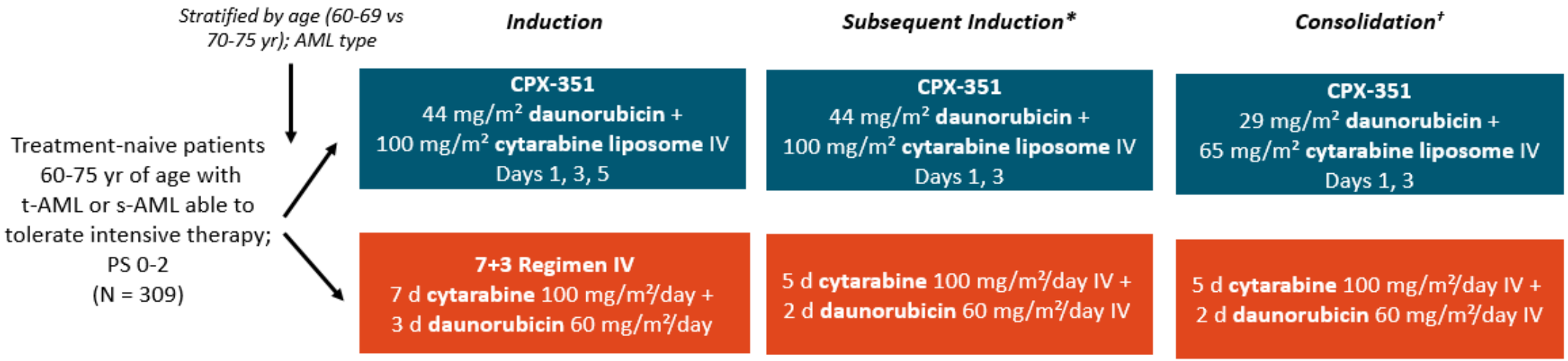
Secondary AML: A Difficult Subtype of AML

- **Liposomal Cytarabine and Daunorubicin (CPX-351)**



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

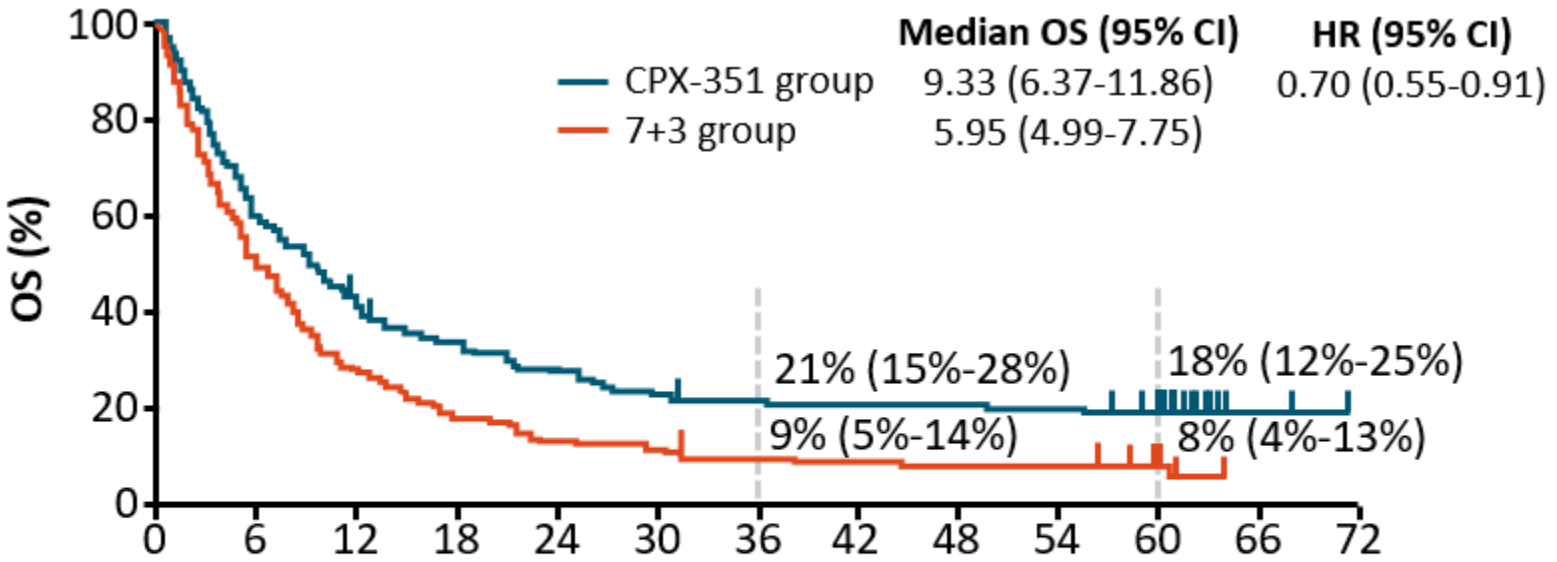
CPX-351 vs Conventional Chemotherapy in Older Patients With Newly Diagnosed t-AML or s-AML



*Subsequent induction was recommended for patients who did not achieve a CR or CRi and was mandatory for patients achieving >50% reduction in percent blasts.

†Postremission therapy with allogeneic HCT permitted either in place of or after consolidation.

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



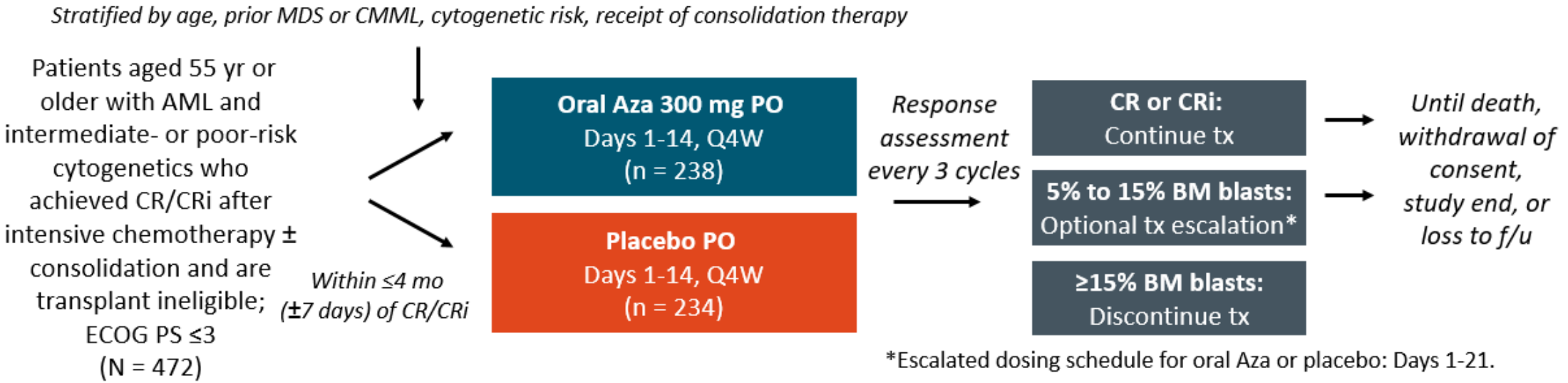
Patients at Risk, n

CPX-351 group	153	92	62	49	40	33	30	29	29	28	22	2	0
7+3 group	156	77	43	28	20	17	14	13	12	12	5	0	0

FDA approval of CPX-351 as frontline therapy of secondary AML

Lancet. Lancet Haematol. 2021;8:e481.

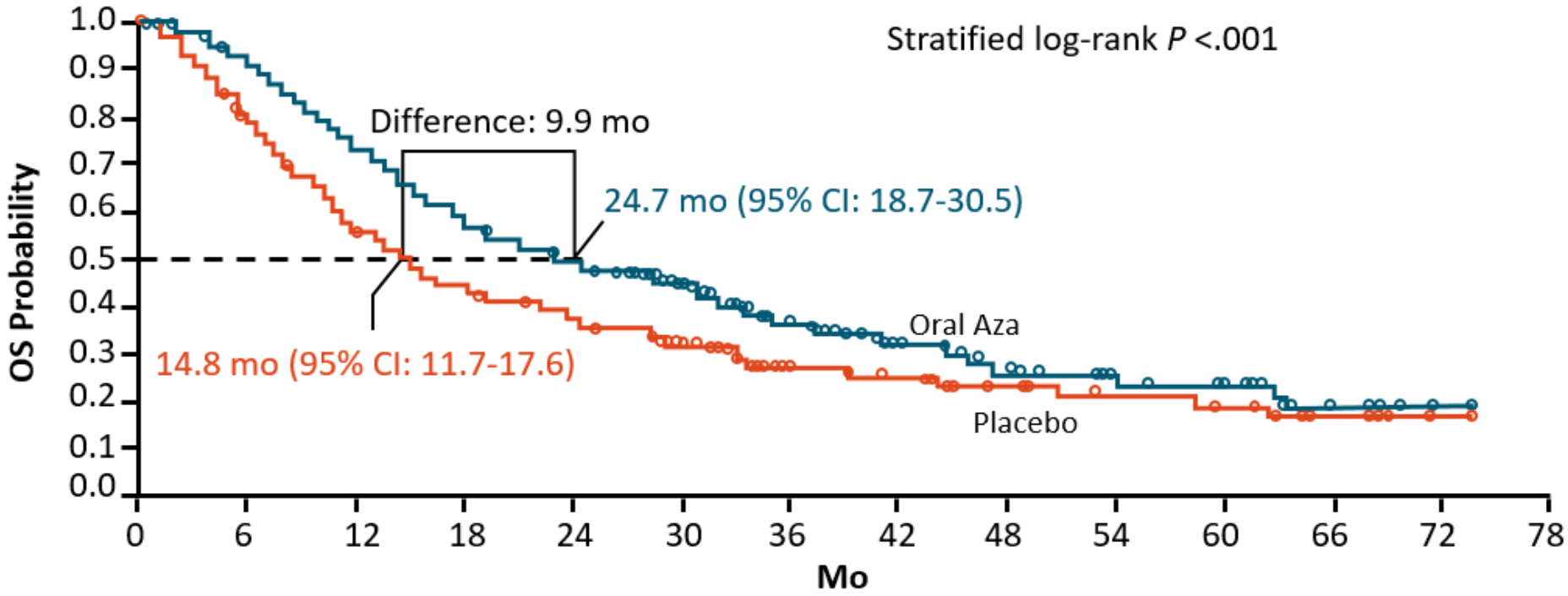
QUAZAR AML-001 Oral Aza in AML: Study Design



- Primary endpoint: OS

Wei. NEJM. 2020;383:2526.

QUAZAR AML-001: OS



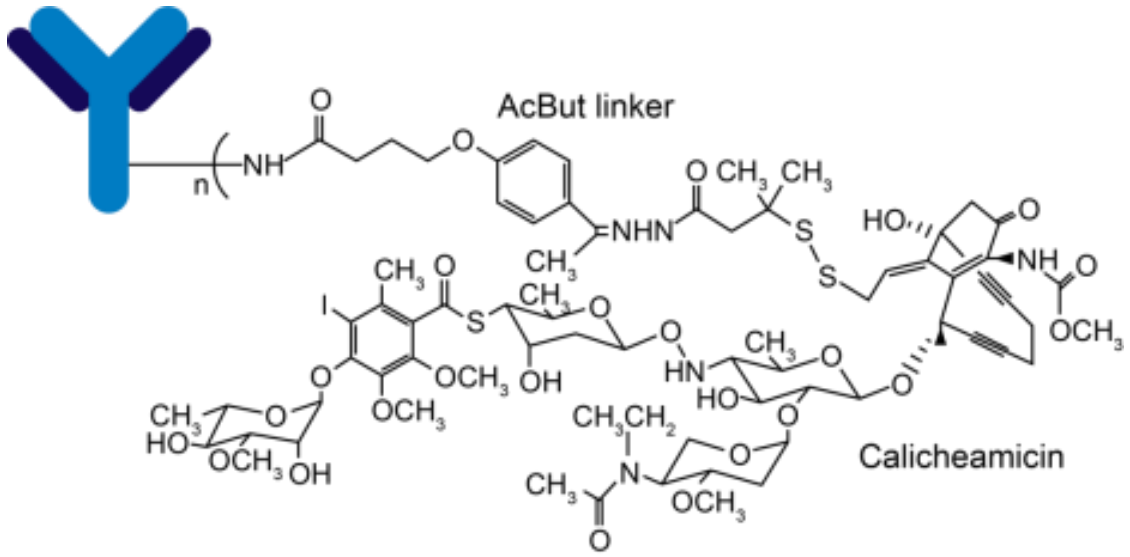
Patients at Risk, n

Oral Aza	238	213	168	133	115	87	59	37	26	18	15	5	1	0
Placebo	234	183	127	96	82	58	34	27	19	14	11	6	1	0

Wei. NEJM. 2020;383:2526.

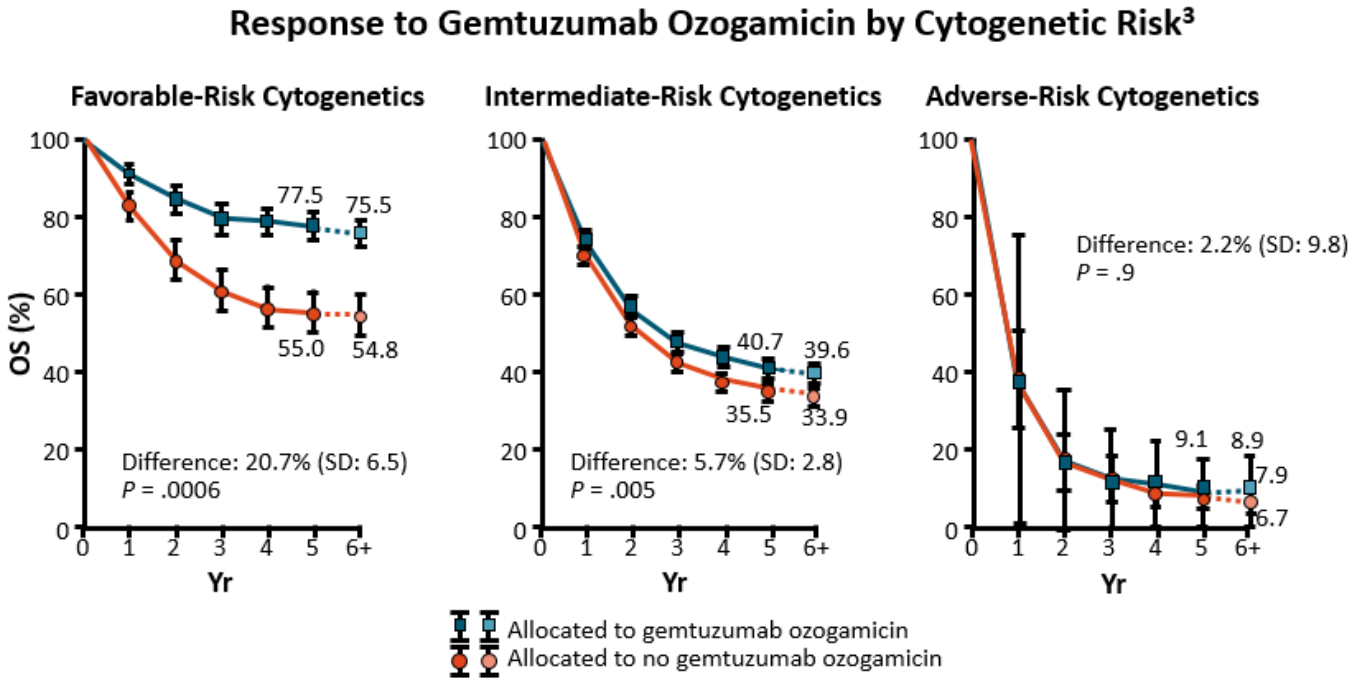
Gemtuzumab Ozogamicin

- Anti-CD33 antibody conjugated to calicheamicin
- Accelerated approval granted May 17, 2000, by FDA based on phase II trials
  - ORR 30% (42/142 CR + CRp) in relapsed AML
- Hepatotoxicity/hVOD
- Led to subsequent withdrawal



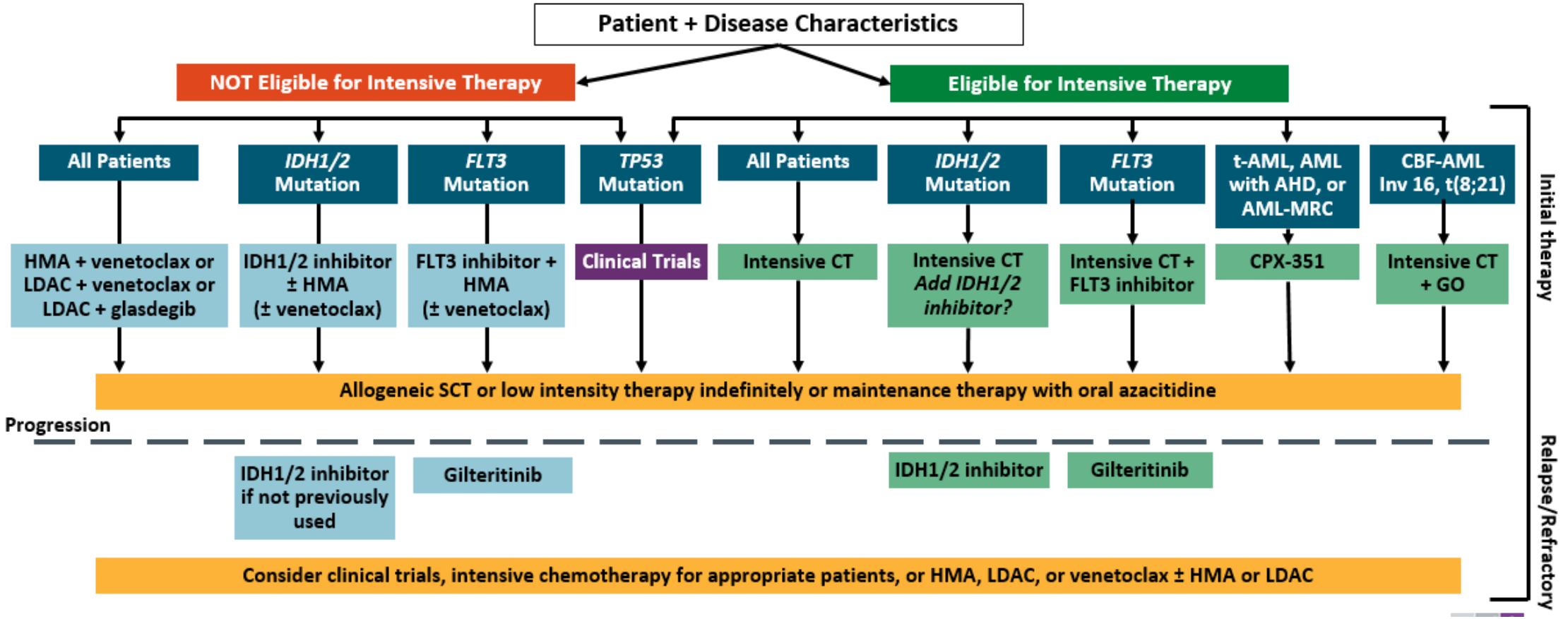
Gemtuzumab Ozogamicin Reemergence

- ALFA-0701: ND, aged 50-70 yr[1]
  - 7 + 3 ± gemtuzumab ozogamicin (3 mg/m^2)
  - Median OS improved
- MRC AML16: untreated, older[2]
  - LDAC ± gemtuzumab ozogamicin at 5 mg/m^2
  - Improved CR rate; no improvement in OS
- Meta-analysis of 5 RCTs (N = 3325)[3]
  - No improvement in CR rate; improved OS rate in favorable-risk and intermediate-risk cytogenetics, with best response in patients with favorable risk



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

AML Treatment Overview



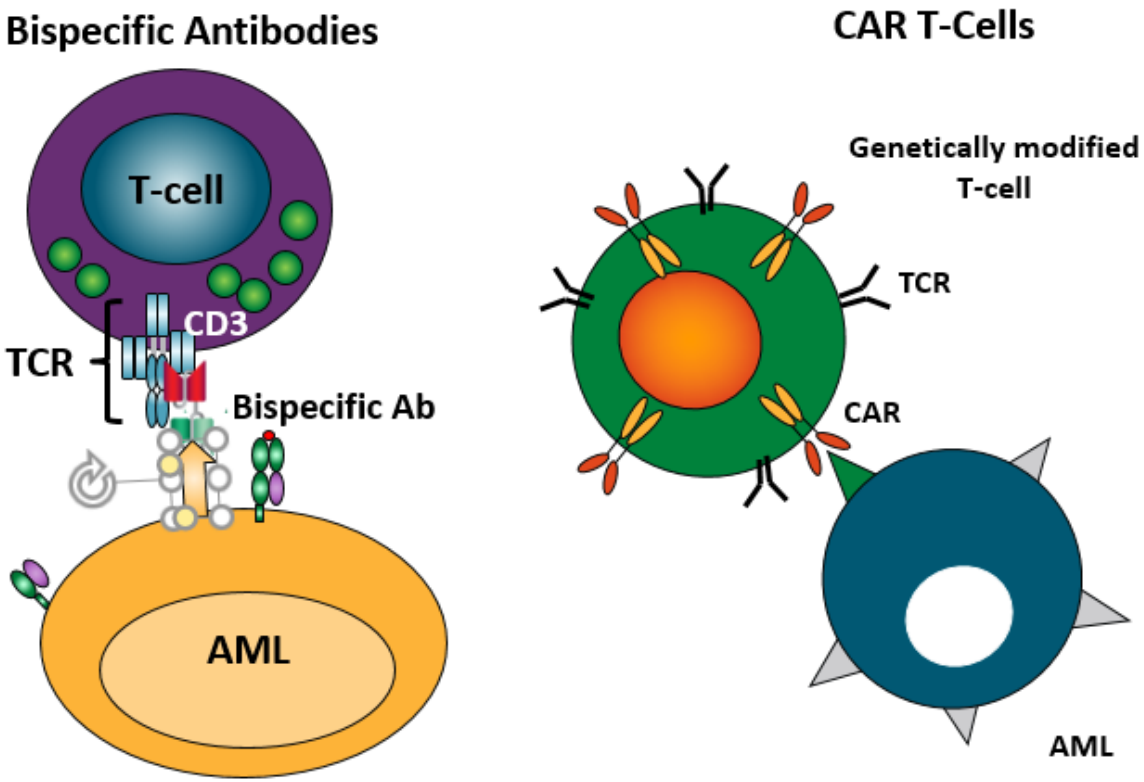
Daver. Blood Cancer J. 2020;10:107. NCCN Guidelines: AML. V3.2021.

Immunotherapeutic Principles and a Potential Paradigm Shift in the Management of AML

T-Cell–Directed Therapy for AML: Bispecific Antibodies vs CAR T-Cells

AML antigens:

- CD123
- CD33
- NKG2D



Bispecific antibodies and CAR T-cell therapies engage the immune system

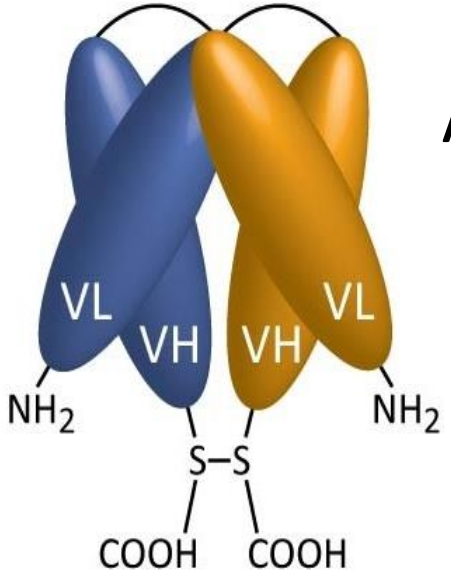
Maino. Exp Rev Hema. 2016;9:563.

Flotetuzumab: CD123 x CD3 Bispecific Molecule

- Bivalent, bispecific (CD3 x CD123) construct coengaging T-cells with a tumor-associated antigen
- CD123: low-affinity receptor for IL-3
  - Usually present on basophils, monocytes, hematopoietic progenitor cells, plasmacytoid dendritic cells
  - Overexpressed on leukemic stem cells in hematologic malignancies, including AML
- Flotetuzumab engineered to redirect T-cells to kill tumor cells and recognize tumors regardless of TCR, MHC

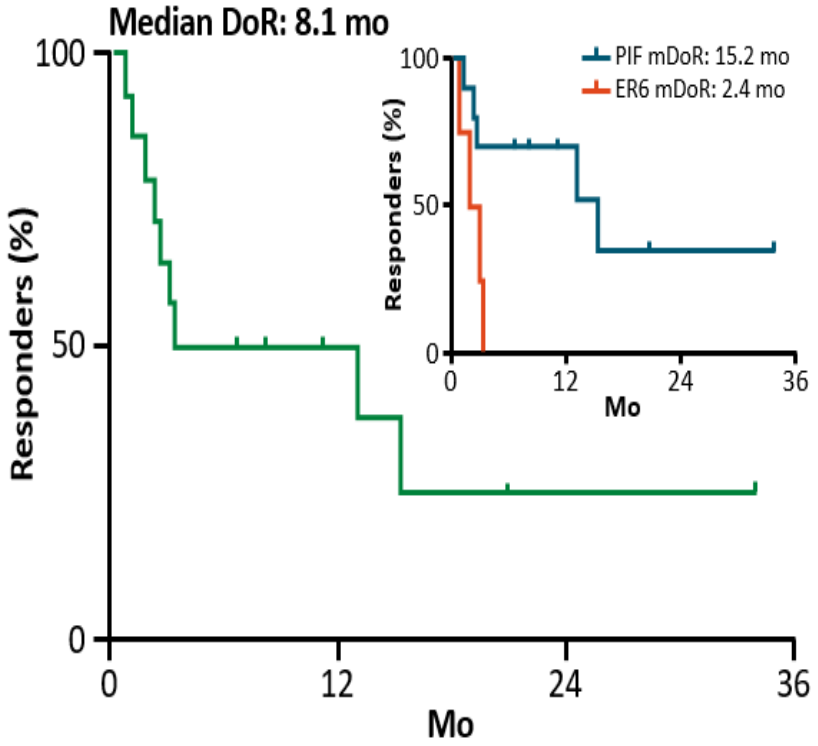
Flotetuzumab

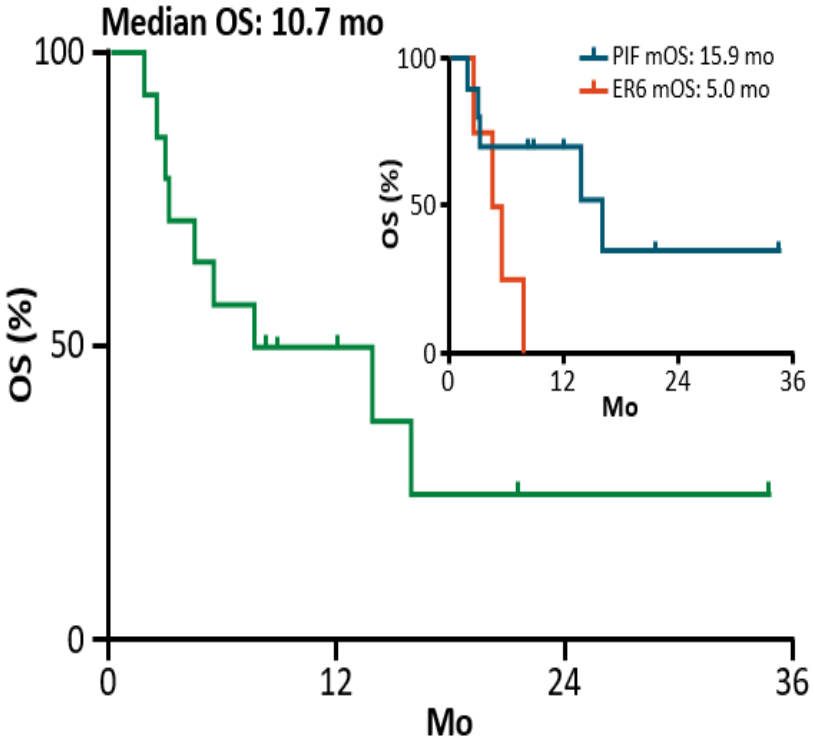
Anti-CD3



Anti-CD123

Flotetuzumab in PIF/ER AML: DoR and OS in Responders



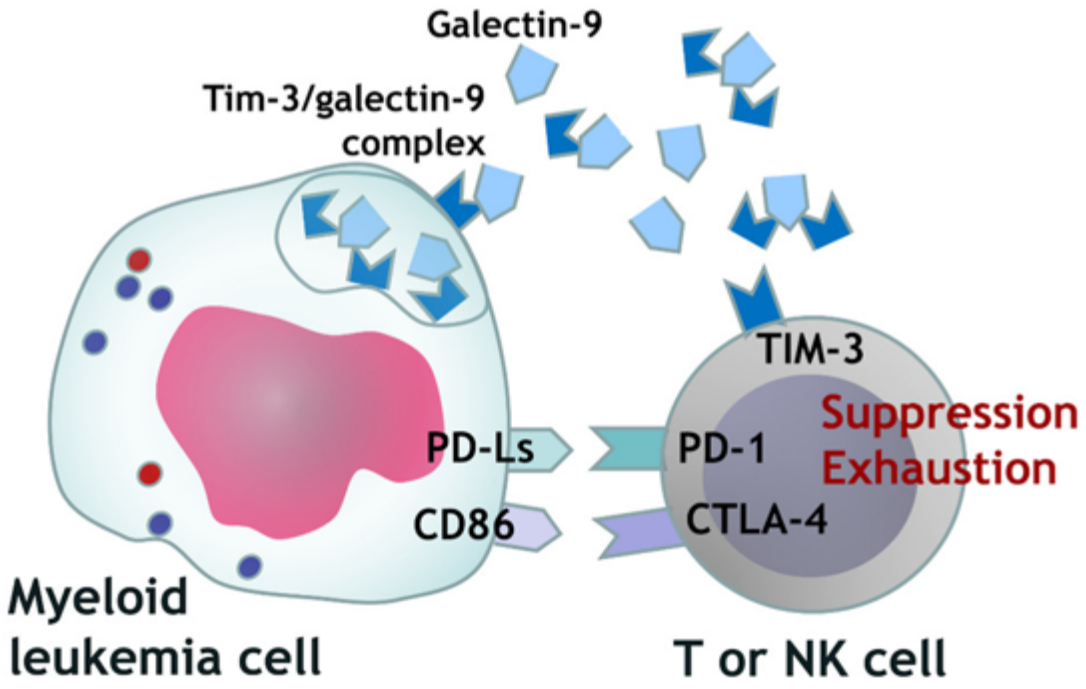


The investigators concluded that flotetuzumab demonstrated encouraging activity in patients with PIF/ER6 AML with a CR/CRh/CRi rate of 31.8%,

Aldoss. ASH 2020. Abstr 331.

Targeting Immune Checkpoints in AML

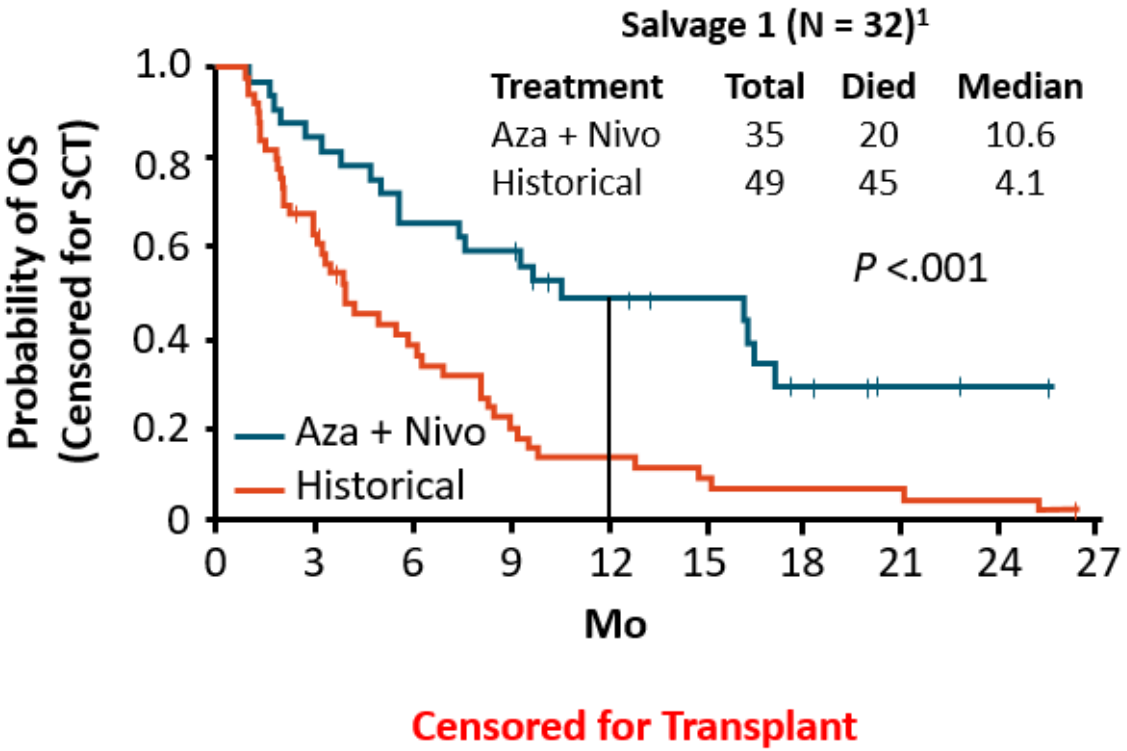
Inhibition of T/NK Cells by Immune Checkpoints[1]



Antibodies under clinical investigation

- Nivolumab (anti–PD-1)[2]
- Ipilimumab (anti–CTLA-4)[2]
- Magrolimab (anti-CD47)[3]
- Sabatolimab (anti–Tim-3)[4]

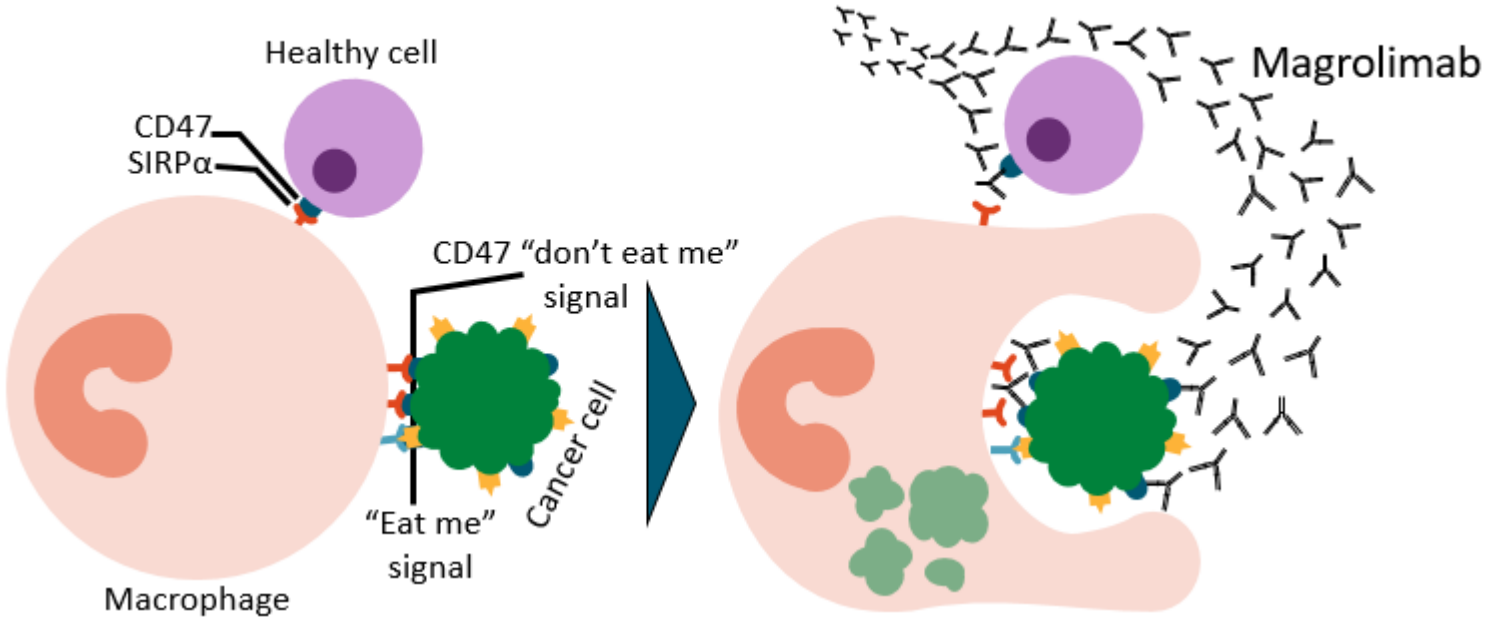
OS of Nivolumab + Azacitidine vs Historical HMA Regimens



- Salvage 1[1]
  - Median age: 72 yr
  - Secondary AML: 42%
  - Adverse cytogenetics: 35%
- Expected survival in salvage 1/2: 5-7 mo, 12-mo OS (N = 655): 16%[2]
- Survival with HMA + venetoclax in salvage (off protocol): 3-4 mo[3]

1. Daver. EHA. 2017. Abstr S474. 2. Stahl. Blood Adv. 2018;2:293.
3. DiNardo. Am J Hematol. 2018;93:401.

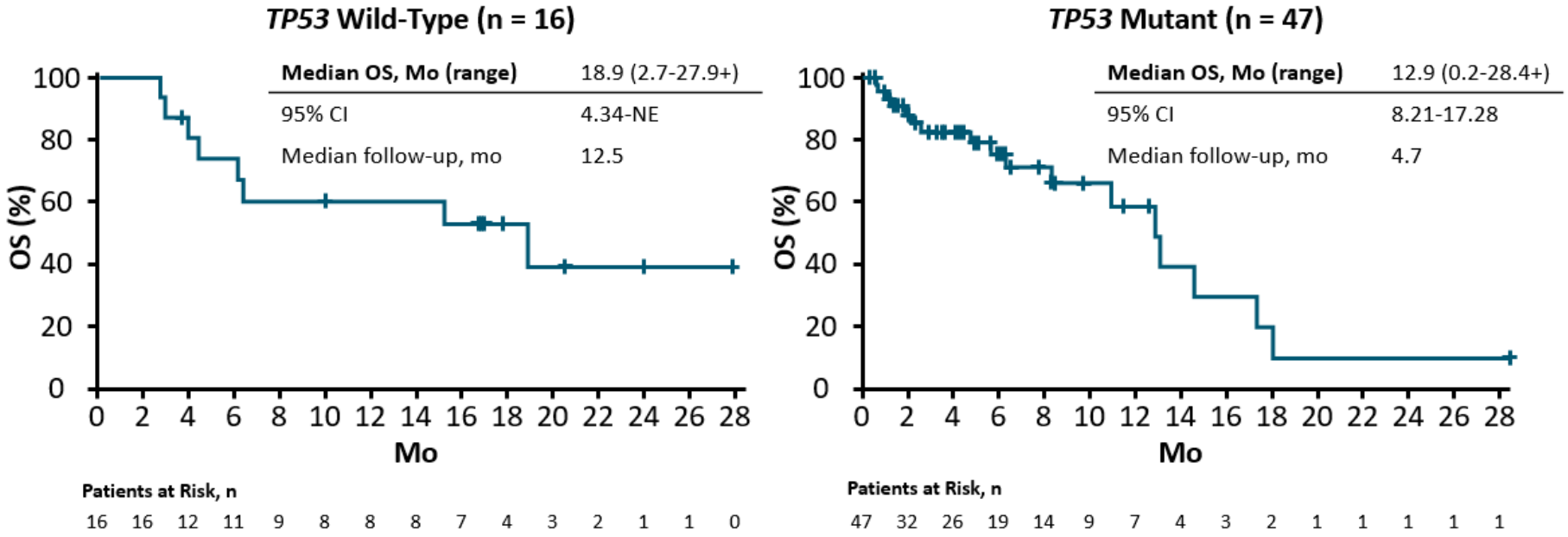
Magrolimab Induces Macrophage Phagocytosis



- Magrolimab: lgG4 anti-CD47 mAb that eliminates tumor cells via macrophage phagocytosis
- Magrolimab is being studied in various cancers with >500 patients dosed

Chao. Front Oncol. 2020;9:1380. Sallman. ASCO 2020. Abstr 7507.

Magrolimab + Azacitidine in Untreated AML: Preliminary OS



- ENHANCE-2: phase III trial of magrolimab + azacitidine vs venetoclax/azacitidine or intensive CT in newly diagnosed *TP53*-mutant AML

Efficacy was particularly encouraging in *TP53*-mutant AML, with a 71% response rate (15 of 21), including a complete response rate of 48%, and a median overall survival of 12.9 months

Sallman. ASH 2020. Abstr 330.

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