Global Leukemia Academy

Global Leukemia Academy

Emerging and Practical Concepts and Controversies in Leukemias

24 September 2022

Virtual Breakout: Adult AML

APTITUDE HEALTH

Global Leukemia Academy

Welcome and Meeting Overview

Gail J. Roboz and Naval Daver

APTITUDE HEALTH

FACULTY

Gail J. Roboz, MD
Weill Cornell Medicine and New York-Presbyterian Hospital, USA

CO-CHAIR

Naval Daver, MD
MD Anderson Cancer Center Houston, TX, USA

CO-CHAIR

Agnieszka Wierzbowska, MD, PhD
Medical University of Lodz, Poland

Virtual Breakout – AML Sessions (Day 2)

24 September 2022, 14.30 – 17.15 CEST

Chairs: Dr Gail J. Roboz/Dr Naval Daver

Time (CEST)	Title	Speaker
14.30 – 14.40	**Session Open** • ARS questions	Gail J. Roboz and Naval Daver
14.40 – 15.00	**Personalized Induction and Maintenance Approaches for AML** • Novel therapies and insights about their optimal utilization	Gail J. Roboz
15.00 – 15.25	**Fit and Unfit AML Patients: How Do We Distinguish? How Do We Treat Differently?** • Assessment of patient fitness to maximize therapy	Agnieszka Wierzbowska
15.25 – 16.05	**AML Case-Based Panel Discussion** • Relapsed/Refractory Case 1 • Relapsed/Refractory Case 2	Moderators: Gail J. Roboz and Naval Daver Agnieszka Pluta Anna Torrent All faculty
16.05 – 16.15	***Break***	
16.15 – 16.40	**Optimizing Management of Relapsed/Refractory AML** • Optimal use of treatment choices in relapsed/refractory AML	Naval Daver
16.40 – 17.05	**Interactive Discussion: Treatment Landscape Evolution** • Interactive discussion and Q&A	Moderators: Gail J. Roboz and Naval Daver All faculty
17.05 – 17.15	**Session Close** • ARS questions	Gail J. Roboz and Naval Daver

Question 1

What age group is considered elderly AML patients?

1. ≥50 years
2. ≥55 years
3. ≥60 years
4. ≥65 years
5. ≥70 years

Question 2

Which of the following factors are important in assessing AML patients at diagnosis? Select all that apply.

1. Adverse genetic alterations
2. Age
3. Comorbidities
4. Performance status
5. Prior cytotoxic therapy
6. Prior myelodysplasia

Question 3

Which of the following is not true regarding HMA + venetoclax in AML?

1. The CR/CRi with HMA+VEN in the VIALE-A was >65%
2. HMA+VEN improved median OS compared with HMA alone
3. Lab or clinical TLS is not seen with HMA+VEN in AML
4. The recommended daily dose of venetoclax (without azoles) was 400 mg PO Qday in VIALE-A study
5. Neutropenia is commonly seen with HMA+VEN regimen

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Personalized Induction and Maintenance Approaches for AML

Gail J. Roboz

APTITUDE HEALTH

Weill Cornell Medicine NewYork-Presbyterian

Personalized Induction and Maintenance Approaches for AML

Global Leukemia Academy

Sept 2022

Gail J. Roboz, M.D.

Professor of Medicine

Director, Clinical and Translational Leukemia Programs

DISCLOSURES OF COMMERCIAL SUPPORT

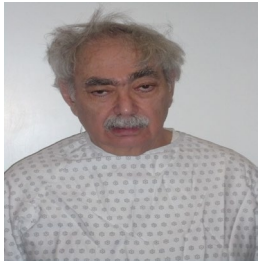
- Consultancy: AbbVie, Actinium, Agios, Amgen, Astellas, AstraZeneca, Bluebird Bio, Blueprint Medicines, Bristol Myers Squibb, Celgene, Glaxo SmithKline, Janssen, Jasper Therapeutics, Jazz, MEI Pharma (IDMC Chair), Mesoblast, Novartis, Pfizer, Syndax, Takeda (IRC Chair)
- Research Support: Janssen

2022 European LeukemiaNet (ELN) risk classification by genetics at initial diagnosis

Risk Category[b]	Genetic Abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*[b,c] • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*[b,c] • Mutated *NPM1*[b,d] without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*[e]
Intermediate	• Mutated *NPM1*[b,d] with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD • t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*[b,f] • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged[g] • t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* • t(8;16)(p11;p13)/*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,[h] monosomal karyotype[i] • Mutated *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, or *ZRSR2*[j] • Mutated *TP53*[k]

Dohner et al. Blood. 2022. Jul7;blood.2022016867.
doi: 10.1182/blood.2022016867.

Evolving diagnostic and treatment paradigm for Newly Diagnosed AML



Assessment of patient characteristics
(age, comorbidities, performance status, prior exposure to chemotherapy or radiotherapy)

Comprehensive profiling of AML
(morphology, immunophenotype, cytogenetics, molecular analysis)

Patient ELIGIBLE for intensive chemotherapy

- CBF-AML → Intensive chemo + gemtuzumab
- *FLT3* mutation → Intensive chemo + FLT3 inhibitor
- Others → Intensive chemo (i.e. 7+3)
  - Intermediate-risk cytogenetics → Add gemtuzumab
  - Intermediate-risk cytogenetics / IDH1/2 mutation → *Add venetoclax? Add glasdegib?*
  - IDH1/2 mutation → *Add IDH1/2 inhibitor?*
- t-AML or AML-MRC → CPX-351

Patient INELIGIBLE for intensive chemotherapy

- *FLT3* mutation → *FLT3 inhibitor +/- HMA*
- All Patients → HMA + venetoclax or LDAC + venetoclax or LDAC + glasdegib
- IDH1/2 mutation → IDH1/2 inhibitor +/- HMA

SCT and/or Maintenance

Italicized = under investigation

CBF = core binding factor
T-AML = therapy-related AML; AML-MRC = AML with MDS related changes

Richard-Carpentier & DiNardo, ASH Education Book 2019.

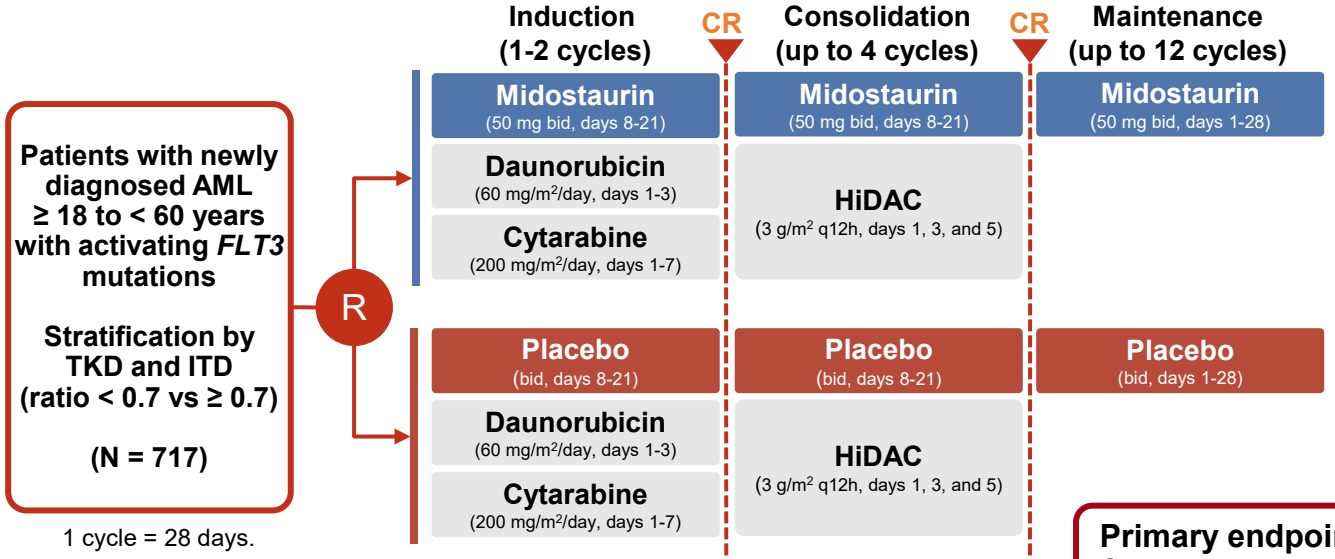
Personalized therapy in AML requires…

- A long, detailed discussion with the patient
- Based on the disease biology, what's the best treatment and can the patient handle it?
- Are there equivalent "best" options?
- How do we get the patient through treatment?
- Location, logistics, caregivers, availability of medications
- Predicted issues with comorbid conditions (e.g. Ferrara criteria) and concomitant medications
- Consideration of how long it will take to achieve remission/response

But, at the end of the day….
In the non-MDACC Real World…

- Can the patient handle anthracycline-based induction, or not?
- If yes, is there a specific reason why you don't want to give it?
  - 5 TP53 mutations
  - daughter's wedding in two weeks
  - another treatment is "just as good, but easier"
  - other

Phase 3 Double-blind Study of Chemotherapy + Midostaurin or Placebo in Patients ≤60 Years of Age With Newly Diagnosed FLT3-Mutated AML (RATIFY)

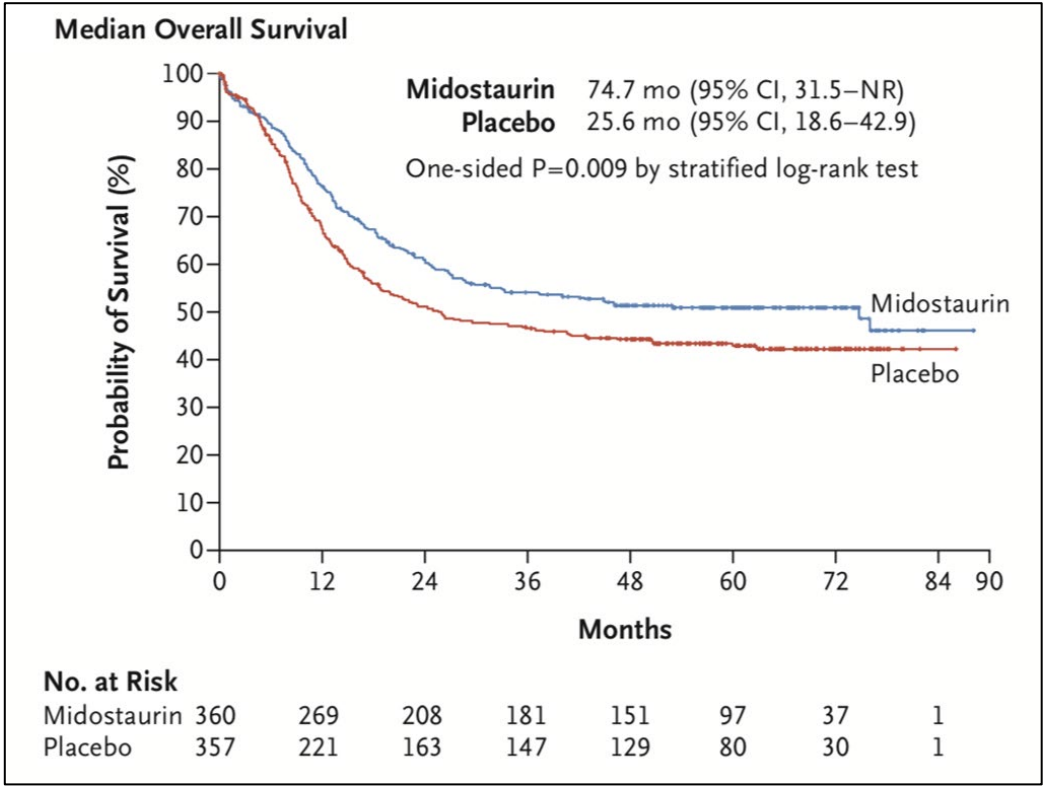


Participating groups: CALGB, AMLSG, CETLAM, ECOG, EORTC, GIMEMA, NCIC, OSHO, PETHEMA, SAL, SWOG

Primary endpoint: OS
Secondary endpoint: EFS

Stone RM, et al. N Engl J Med. 2017;377:454–64.

RATIFY met its primary endpoint: addition of midostaurin to 7+3 improved overall survival

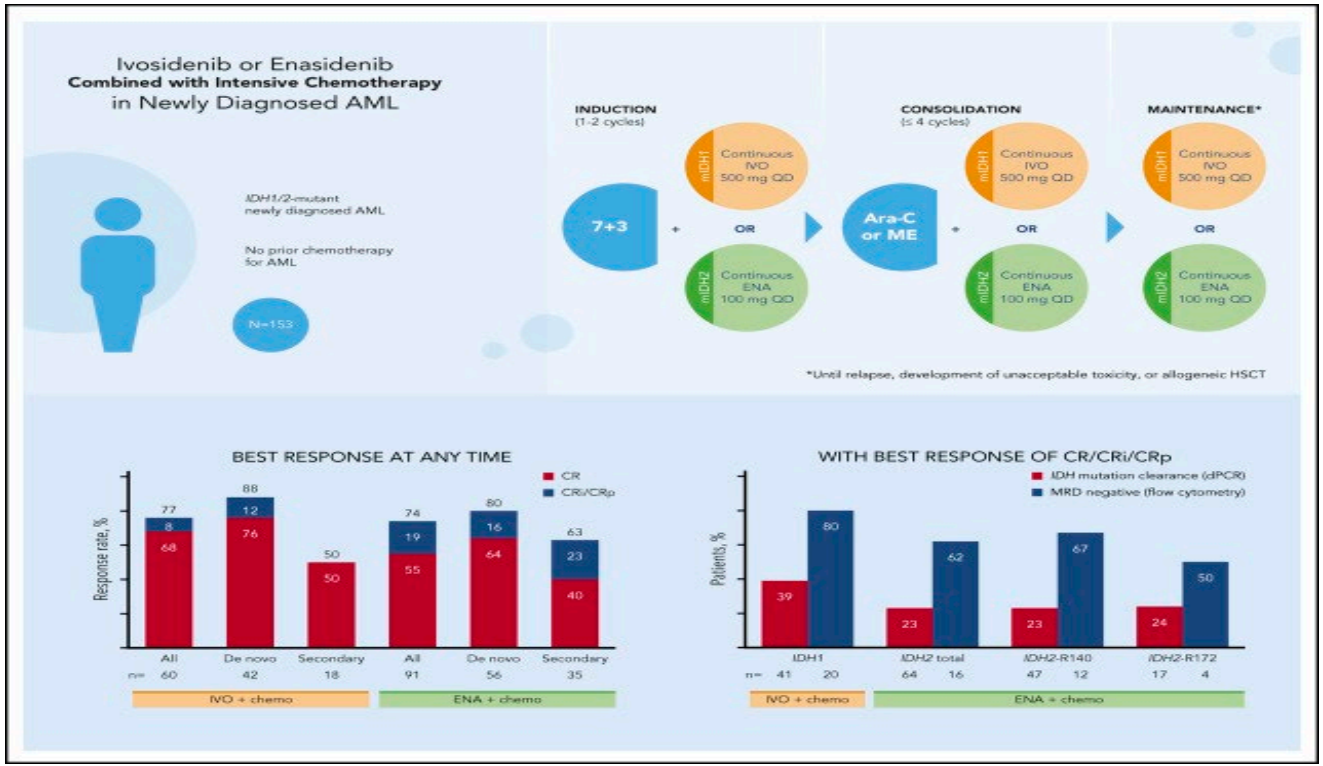


Arm	4-year Survival
MIDO	51.4%
PBO	44.3%

Hazard Ratio*: **0.78**
1-sided p-value*: 0.009
22% reduced risk of death on mido arm

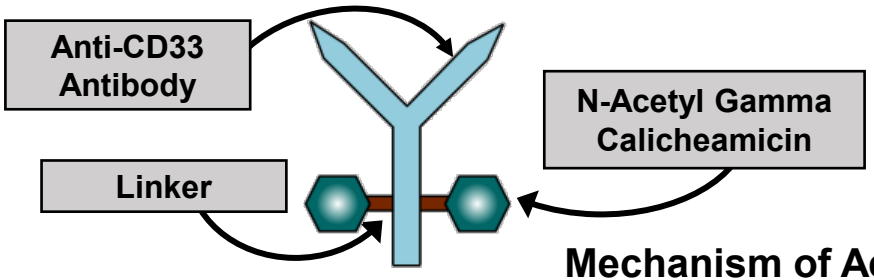
Stone RM, et al. N Engl J Med. 2017;377:454–64.

IDH inhibitors + intensive chemotherpy



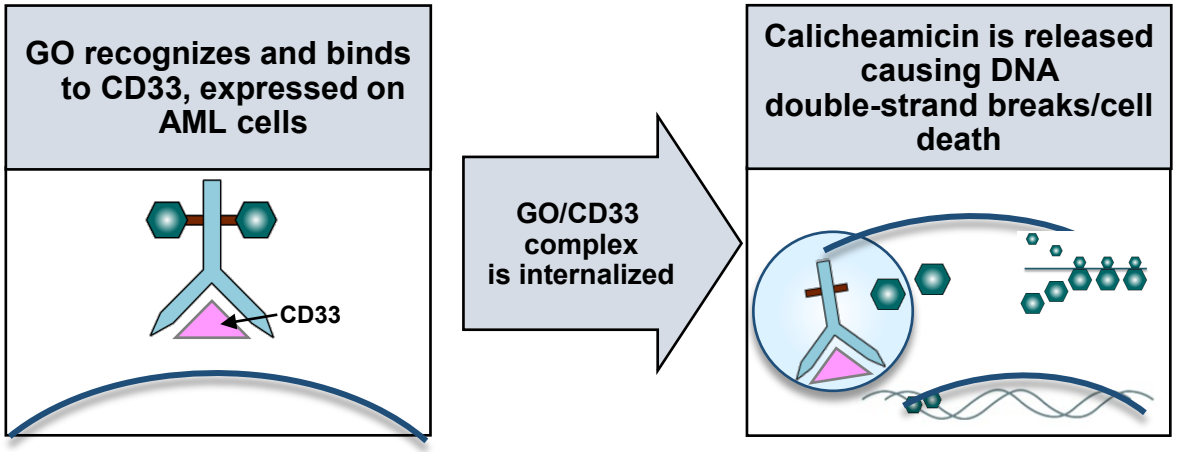
Stein et al. Blood. 2021 Apr 1;137(13):1792-1803. doi: 10.1182/blood.2020007233.

Gemtuzumab Ozogamicin[1]



- In 2000 approved for CD33+ AML in first relapse ≥60 years[1*]
- In 2017 approved for adults with newly diagnosed CD33+ AML, and adults and children 2 years and older with relapsed or refractory CD33+ AML[2*]

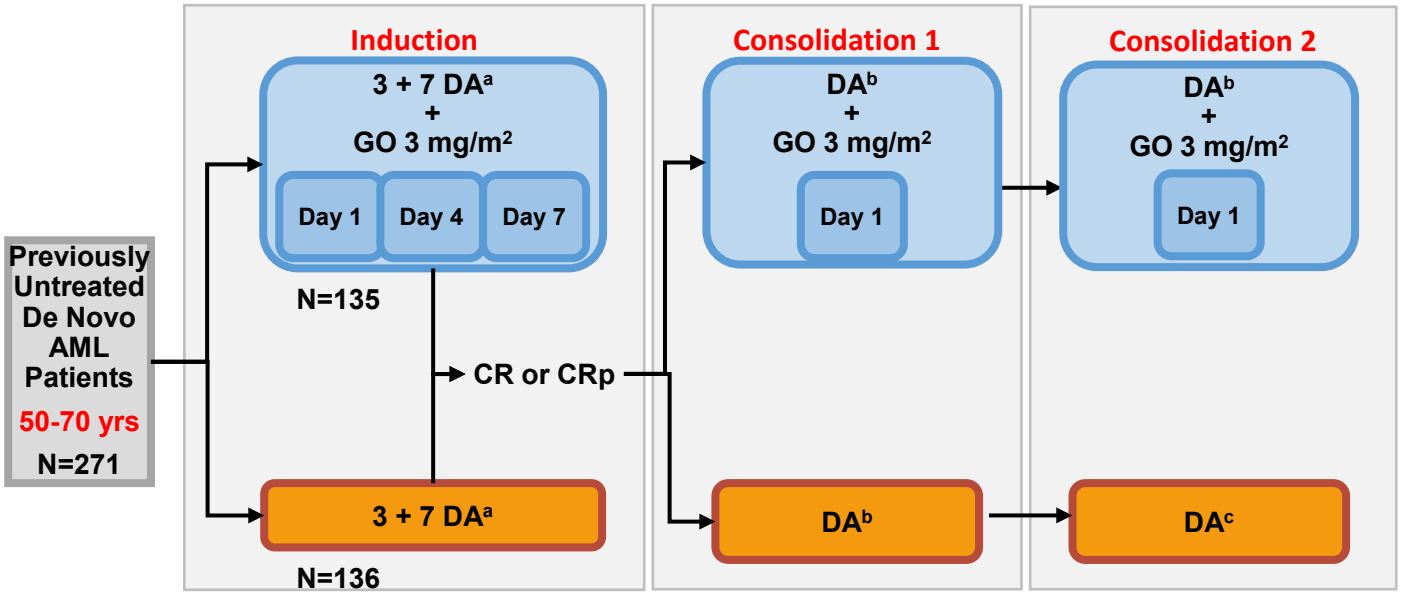
Mechanism of Action



1. FDA. MYLOTARG® (gemtuzumab ozogamicin). Available from: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM567370.pdf Accessed 13 May 2020
2. FDA. FDA Approves Gemtuzumab Ozogamicin for CD33-positive AML. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-gemtuzumab-ozogamicin-cd33-positive-aml Accessed 13 May 2020

*This does not include the full indication or risk profile

ALFA-0701 (MyloFrance3): Phase 3 Study Design

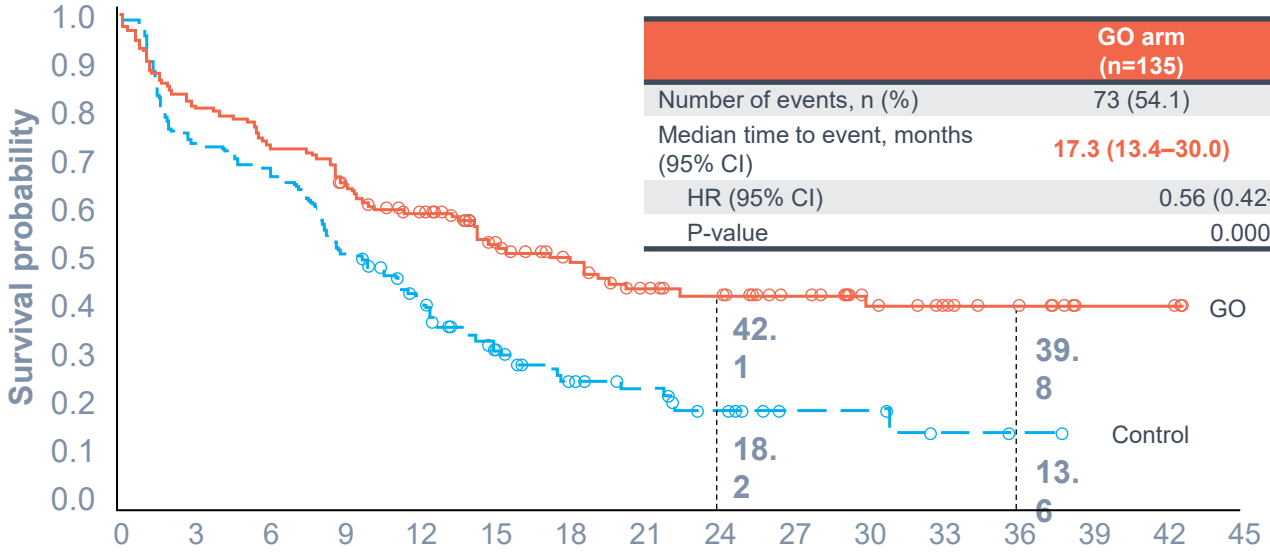


a. 3+7 DA=Daunorubicin 60 mg/m² Days 1 to 3 + Cytarabine 200 mg/m² Days 1 to 7
b. Daunorubicin 60 mg/m² Day 1 + Cytarabine 1 g/m²/12h Days 1 to 4
c. Daunorubicin 60 mg/m² Day 1 and 2 + Cytarabine 1 g/m²/12h Days 1 to 4
DA=Daunorubicin+Cytarabine

Primary endpoint: EFS
Secondary endpoints: RFS, OS, safety

FDA. MYLOTARG® (gemtuzumab ozogamicin). Available from: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM567370.pdf Accessed 13 May 2020
Lambert J, et al. Haematologica 2019;104:113–9

ALFA-0701: Event-free survival (primary endpoint)



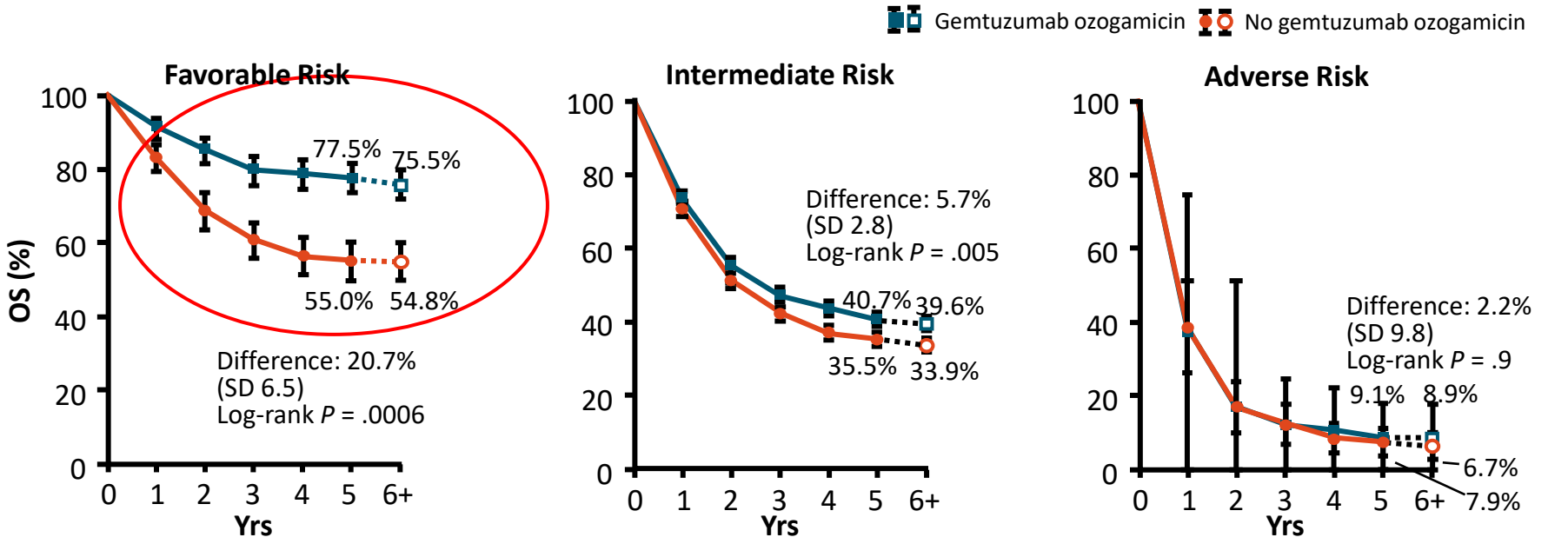
	GO arm (n=135)	Control arm (n=136)
Number of events, n (%)	73 (54.1)	102 (75.0)
Median time to event, months (95% CI)	17.3 (13.4–30.0)	9.5 (8.1–12.0)
HR (95% CI)	0.56 (0.42–0.76)	
P-value	0.0002	

Number at risk

GO	135	109	98	86	74	57	47	36	32	25	18	15	10	3	3	0
Control	136	100	93	69	51	32	21	16	10	5	5	2	1	0		

Adapted from Lambert *et al*. 2019
Modified intention-to-treat population; Data cut-off date: 1 August 2011
CI, confidence interval; GO, gemtuzumab ozogamicin; HR, hazard ratio
Lambert J *et al. Haematologica* 2019;104:113–119

Gemtuzumab Ozogamicin in AML Induction Therapy: Meta-analysis of 5 Randomized Trials



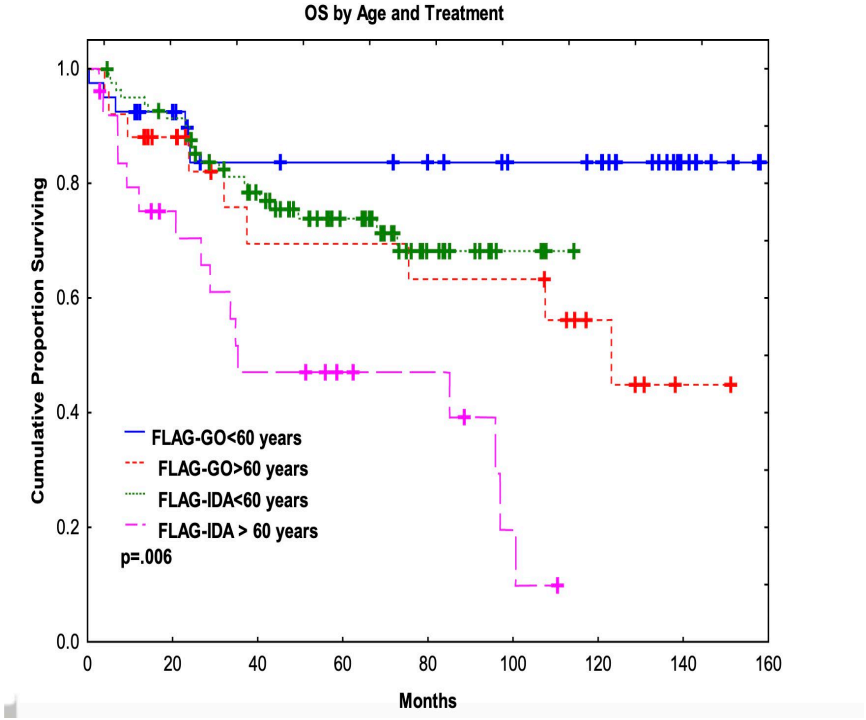
Annual Event Rates	Yrs 1-5	Yrs 6+
Gemtuzumab ozogamicin	5.8% SD 1.1	2.3% SD 1.3
No gemtuzumab ozogamicin	14.1% SD 1.9	0% SD 0

Annual Event Rates	Yrs 1-5	Yrs 6+
Gemtuzumab ozogamicin	22.4% SD 1.0	2.7% SD 0.9
No gemtuzumab ozogamicin	26.2% SD 1.1	4.9% SD 1.3

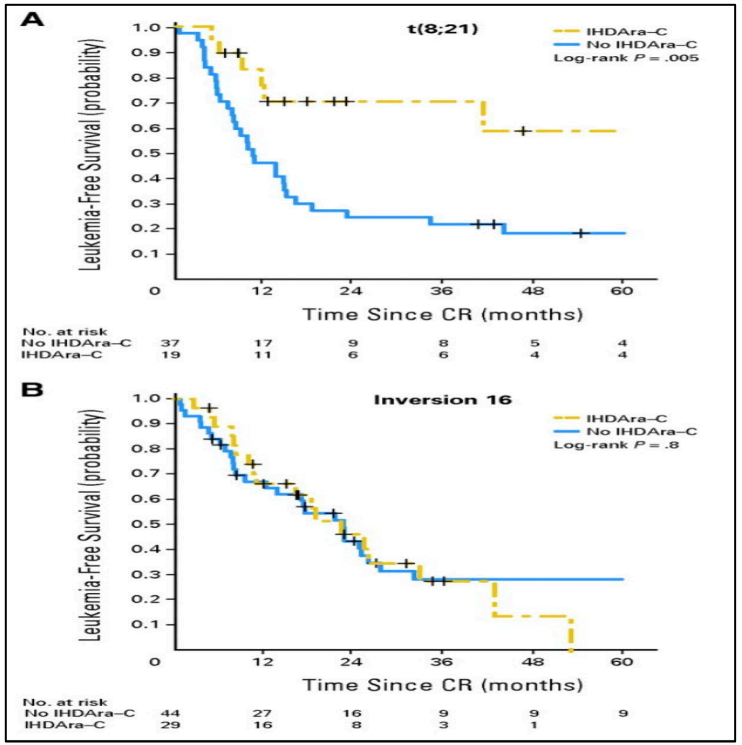
Annual Event Rates	Yrs 1-5	Yrs 6+
Gemtuzumab ozogamicin	73.8% SD 4.6	2.4% SD 2.4
No gemtuzumab ozogamicin	76.7% SD 4.8	21.1% SD 10.5

Hills. Lancet Oncol. 2014;15:986.

CBF AML >60 years



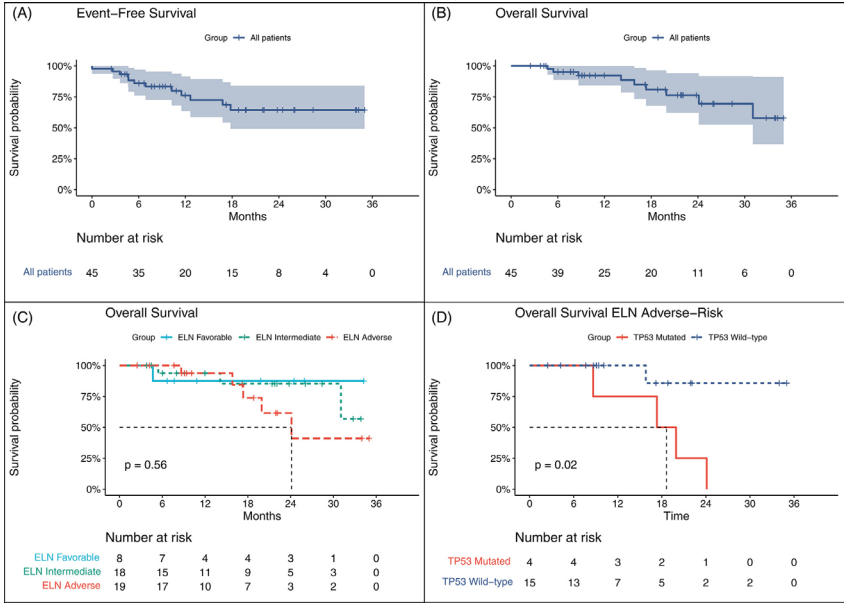
Am J Hematol;2022 Aug 26. doi:10.1002/ajh.26700.



Prebet et al. J Clin Oncol. 2009 Oct1;27(28):4747-53. doi: 10.1200/JCO.2008.21.0674.

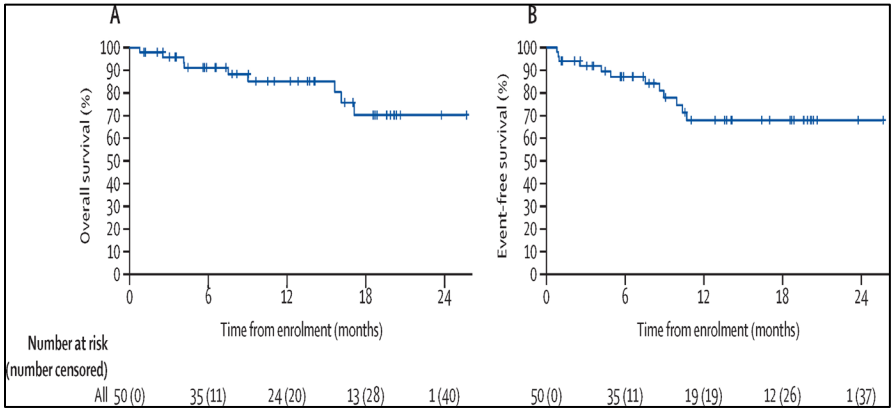
Even more intensive…

FLAG-IDA+Venetoclax



DiNardo et al. Am J Hematol. 2022 Aug;97(8):1035-1043. doi: 10.1002/ajh.26601. Epub 2022 May 30.

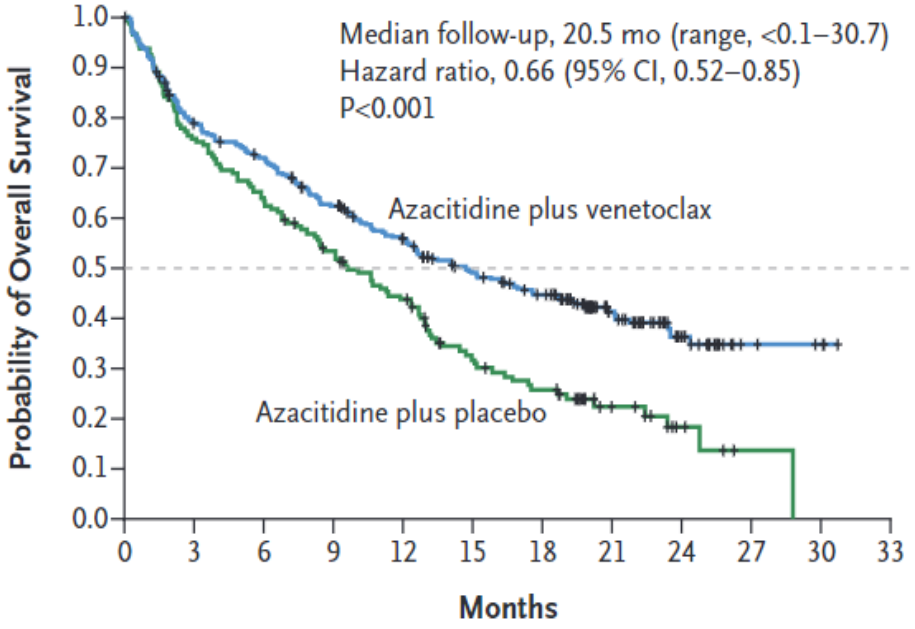
CIIA + Venetoclax



Kadia et al. Lancet Haematol. 2021 Aug;8(8):e552-e561.

Results of VIALE-A : Azacitidine + venetoclax

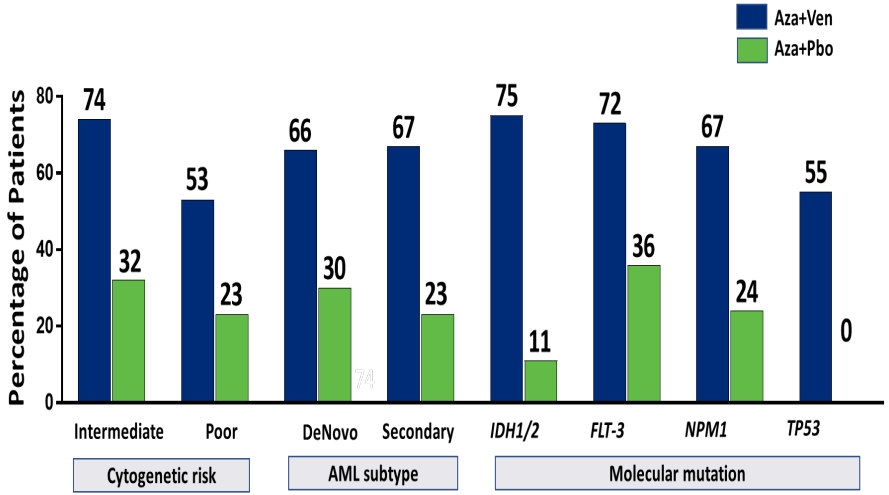
Significant OS improvement with azacitidine + venetoclax (Med OS 14.7 vs 9.6 mos)



CR rate: 36.7% vs 17.9% (*P* < .001)

CR/CRi rate: 66.4% vs 28.3% (*P* < .001)

Improved responses occurred *independent* of high-risk biology



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

American Society *of* Hematology
Helping hematologists conquer blood diseases worldwide

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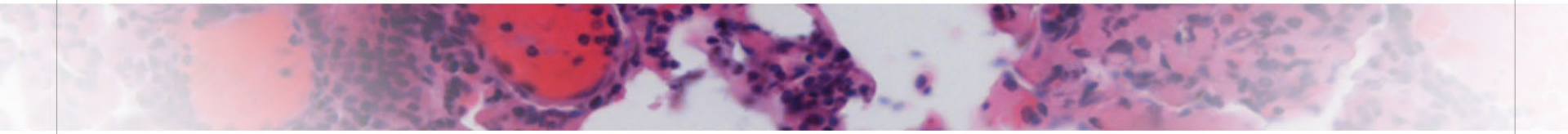

Comparing Outcomes between Liposomal Daunorubicin/Cytarabine (CPX-351) and Hypomethylating agent+Venetoclax (HMA+V) As Frontline Therapy in Acute Myeloid Leukemia

Justin Grenet, MD[1], Akriti G Jain, MD[2], Madelyn Burkart, MD[3*], Julian Waksal, MD[4], Christopher Famulare, MS[5*], Yazan Numan, MD[3], Maximilian Stahl, MD[4], Zoe Mckinnell, MD[4*], Brian Ball, MD[4], Xiaoyue Ma, MS[6*], Paul J Christos, Dr.P.H., M.S.[6*], Ellen Ritchie, MD[7], Michael B. Samuel, MD[8*], Justin D. Kaner, MD[8], Sangmin Lee, MD[9], Aaron D Goldberg, MD, PhD[4], Shira Dinner, MD[3], Kendra Sweet, MD[2], Gail J. Roboz, MD[8] and **Pinkal Desai, MD, MPH**[9]

[1]*New York-Presbyterian/Weill Cornell Medical Center, New York, NY*
[2]*H. Lee Moffitt Cancer Center, Tampa, FL*
[3]*Division of Hematology Oncology, Northwestern University, Chicago, IL*
[4]*Memorial Sloan Kettering Cancer Center, New York, NY*
[5]*Department of Population Health Sciences, Weill Cornell Medical College, New York, NY*
[6]*Division of Hematology and Oncology, Weill Cornell Medical College, New York, NY*

We conducted a large real-world, multicenter retrospective chart review

- Four large academic centers: MSKCC, Northwestern, Moffitt, Cornell
- A real-world analysis of patient characteristics and outcomes in older AML patients receiving either CPX-351 or HMA+V as frontline therapy
- Primary outcomes: response rate (CR+CRi), relapse free survival (RFS), and overall survival (OS)
- Analyses were conducted for overall population (ages 34-93 yrs) and ages 60-75 yrs
- **Most overlap of both treatment groups happened in the age group of 60-75 yrs** with very few <60 getting HMA+V and very few >75 getting CPX-351
- Subgroup analyses: TP53, Adverse ELN Risk, Prior myeloid malignancy, prior HMA therapy

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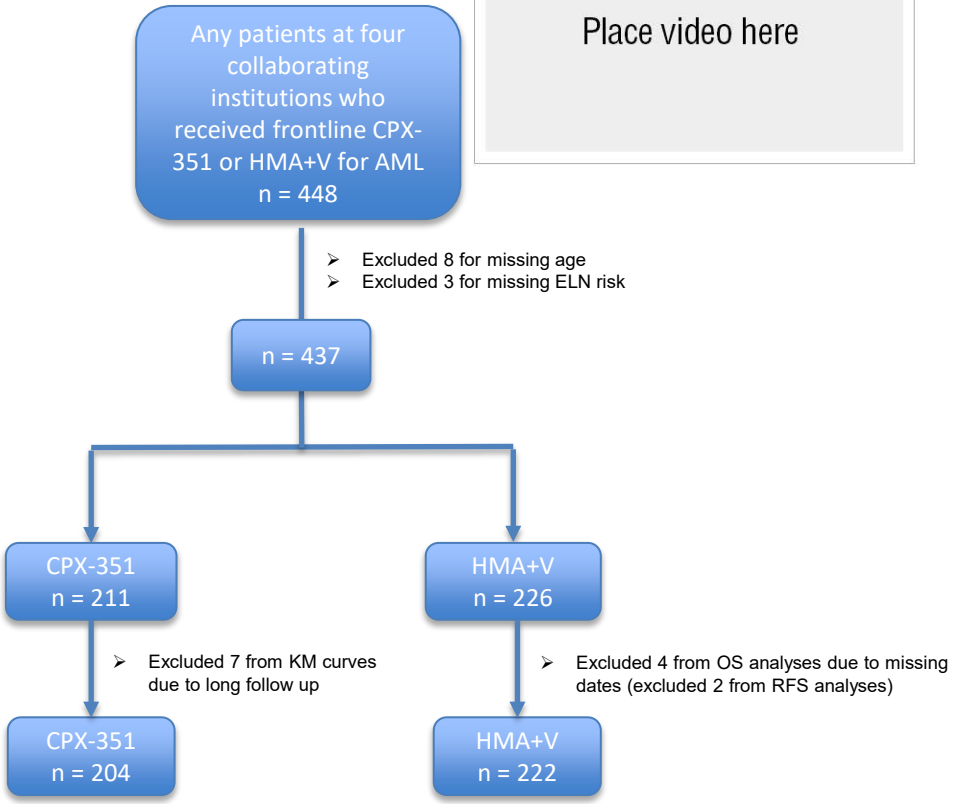
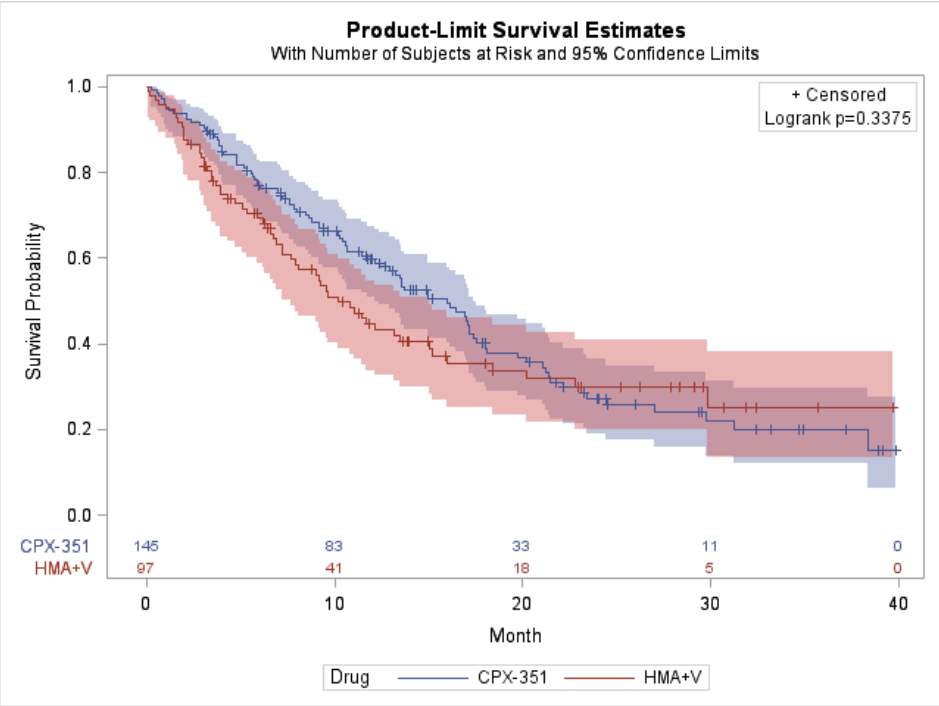


60-75 yrs: No significant difference in OS



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<u>CR+CRi, 60-75yo</u>
CPX-351: 59.2%
HMA+V: 54.0%
***p* = 0.41**

<u>Total "n" and HSCT rates, 60-75yo</u>
CPX-351: n = 152 (47.7% underwent HSCT)
HMA+V: n = 100 (19% underwent HSCT)
p <0.001

- Kaplan Meier curve for OS in 60-75yo (excluded 7 patients from CPX-351 group due to long follow up >40mo; excluded 3 from HMA+V group due to missing dates)

Multivariable analyses, 60-75yo only

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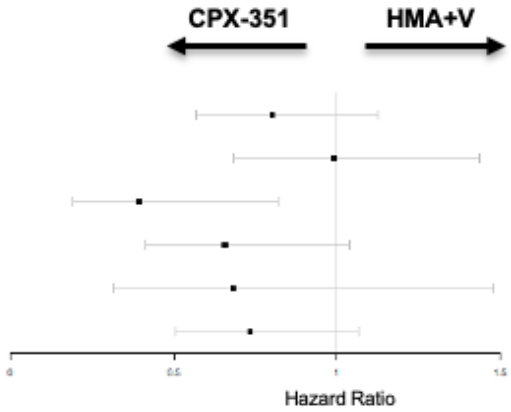
Overall Survival for Age 60-75	Hazard ratio (95% CI)	P value
Overall	0.802 (0.570, 1.127)	0.204
No HSCT	0.991 (0.684, 1.436)	0.96
TP53 status	0.395 (0.191, 0.820)	0.013
Prior Myeloid Malignancy	0.656 (0.414, 1.038)	0.072
Prior HMA use	0.682 (0.314, 1.480)	0.333
ELN adverse	0.735 (0.506, 1.067)	0.105

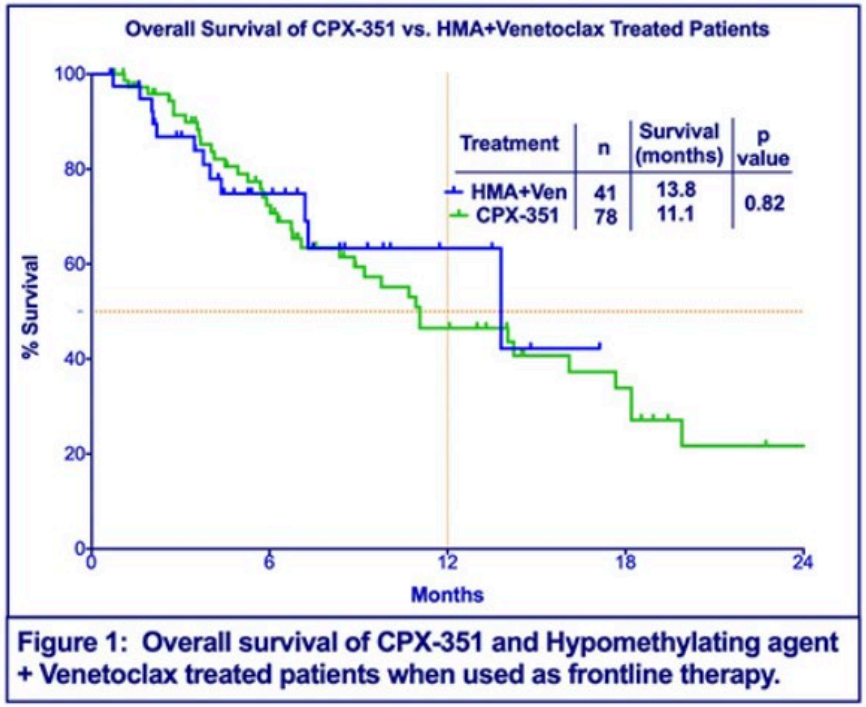


60-75yo only
CPX-351: n = 152 (47.7% underwent HSCT)
HMA+V: n = 100 (19% underwent HSCT)
p <0.001

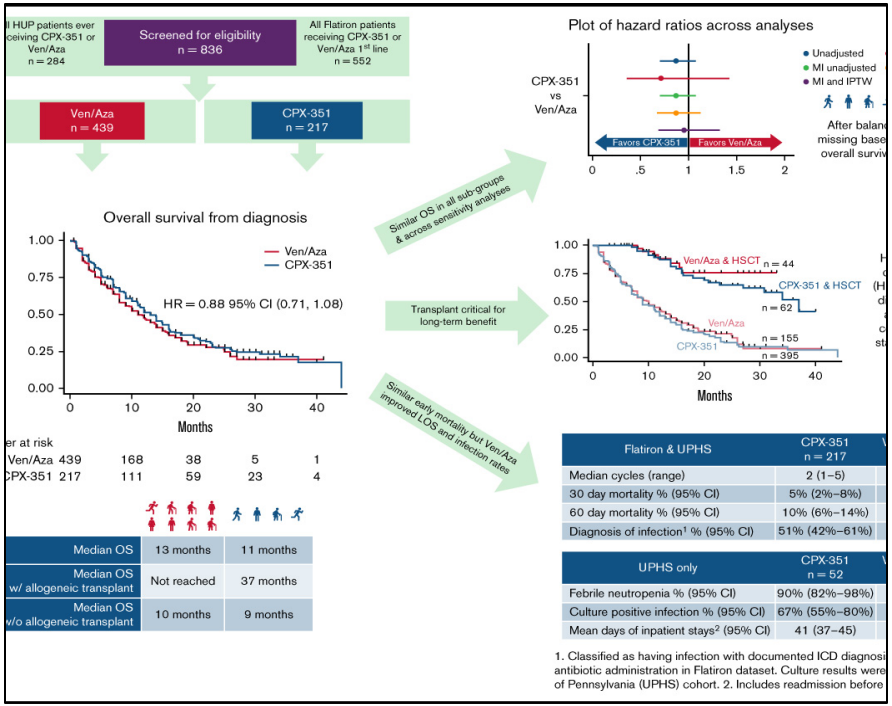
*Multivariable analysis adjusted for age, ELN risk, prior myeloid malignancy, and prior HMA therapy

- **No significant difference in OS in 60-75yo only**, despite more than double the rate of HSCT in CPX-351 cohort
- No significant difference in OS in 60-75yo, censoring for HSCT
- **Higher OS in TP53 positive** patients treated **with CPX-351**
- No significant difference in OS between cohorts for additional three subgroups: prior myeloid malignancy, prior HMA use, adverse ELN risk

Other groups concur…

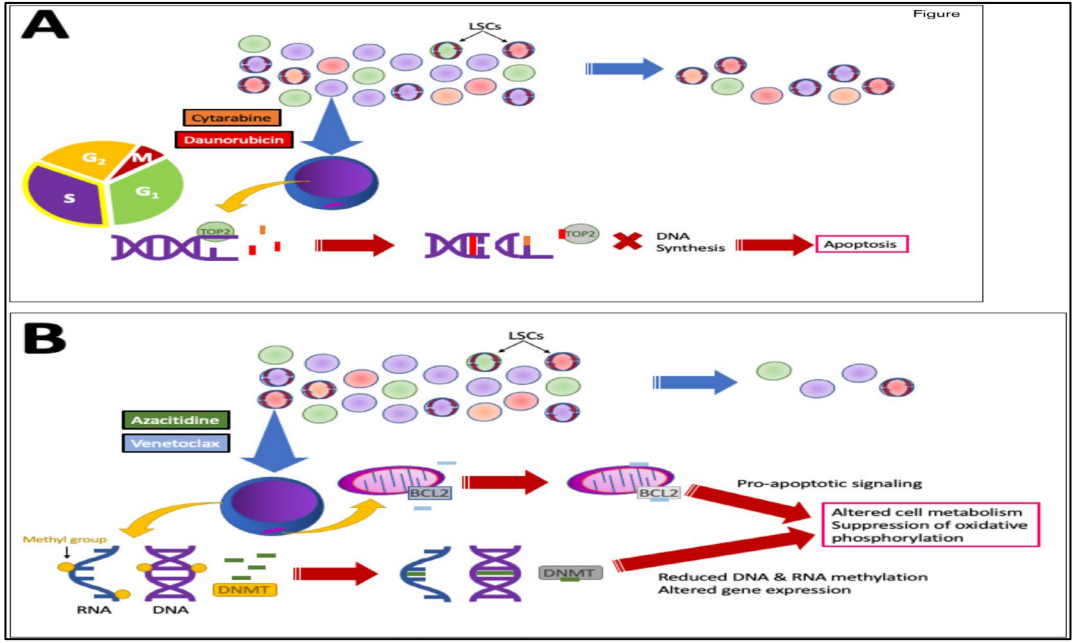


Asghari et al. bloodjournal Blood (2019) 134 (Supplement_1) : 3895.
http://doi.org/10.1182/blood-2019-130379



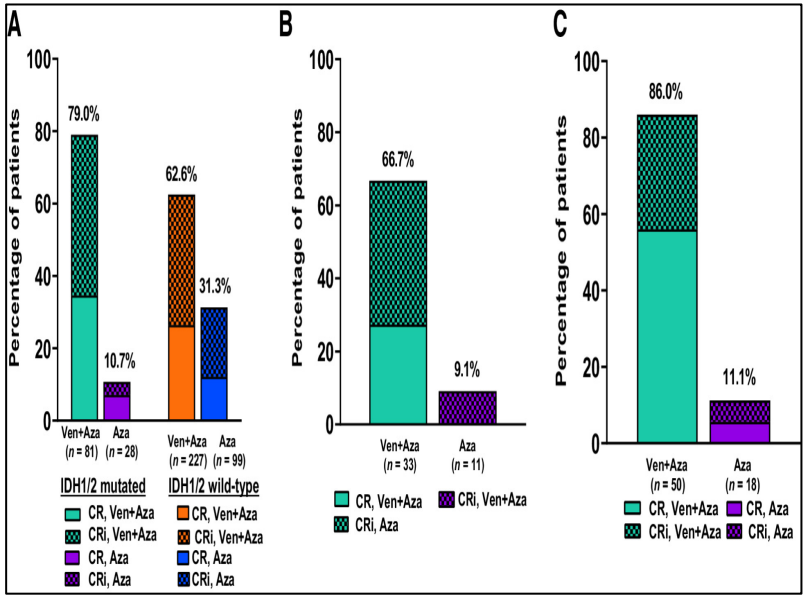
Matthews et al. *Blood Adv* (2022) 6 (13): 3997–4005.

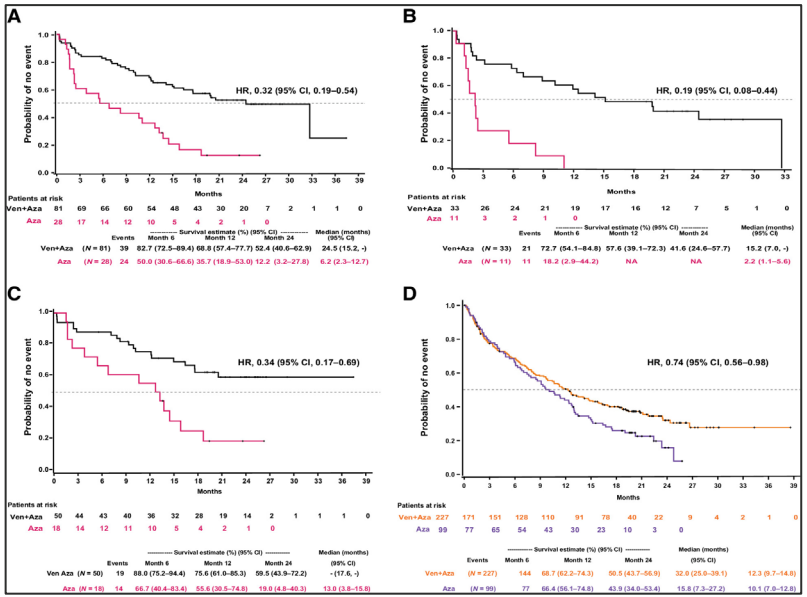
Survival of the Fittest: Hypomethylating Agent/BCL-2 Inhibitor Combination Versus Intensive Chemotherapy As Frontline Treatment for Acute Myeloid Leukemia (NCT04801797)



Hochman and Hasserjian. *The Hematologist* (2022) 19 (2)
https://doi.org/10.1182/hem.V19.2.202228

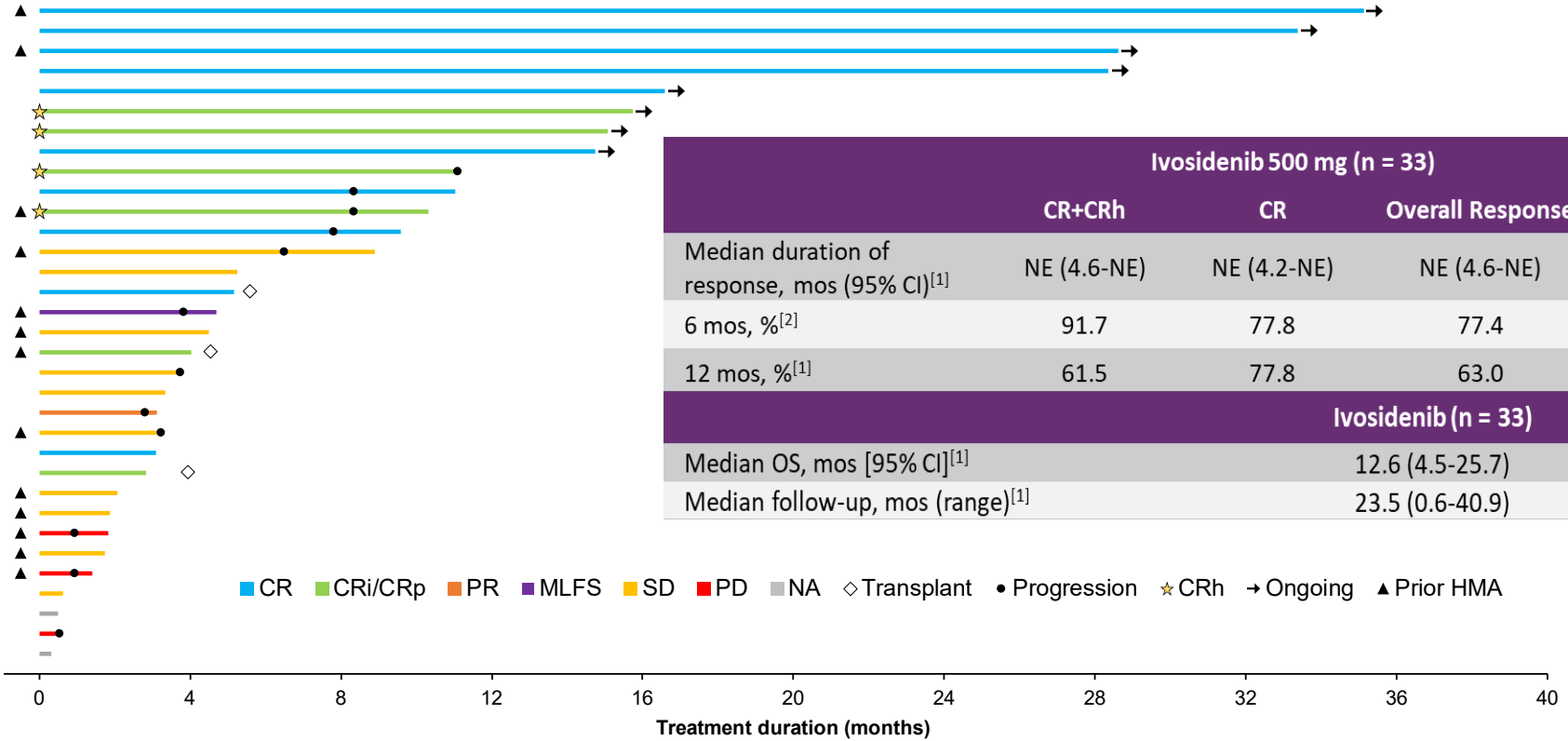
Impact of Venetoclax and Azacitidine in Treatment-Naïve Patients with Acute Myeloid Leukemia and IDH1/2 Mutations





Clin Cancer Res. 2022;28(13):2753-2761. doi:10.1158/1078-0432.CCR-21-3467

Ivosidenib in Untreated *IDH1*-Mutated AML: Duration of Treatment and Best Overall Response

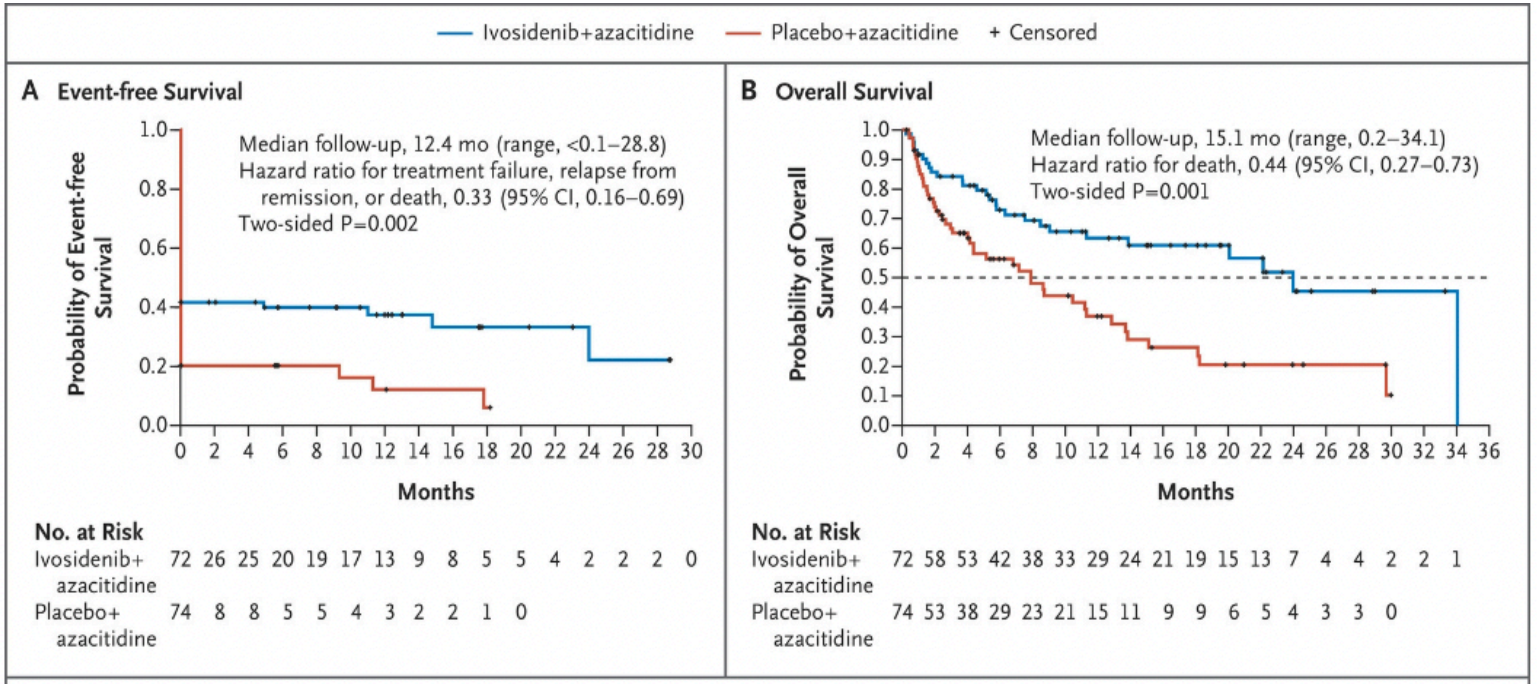


	Ivosidenib 500 mg (n = 33)		
	CR+CRh	CR	Overall Response
Median duration of response, mos (95% CI)[1]	NE (4.6-NE)	NE (4.2-NE)	NE (4.6-NE)
6 mos, %[2]	91.7	77.8	77.4
12 mos, %[1]	61.5	77.8	63.0

	Ivosidenib (n = 33)
Median OS, mos [95% CI][1]	12.6 (4.5-25.7)
Median follow-up, mos (range)[1]	23.5 (0.6-40.9)

1. Roboz GJ. *Blood*. 2020;135:463. 2. Roboz GJ. ASH 2018. Abstr 561. Slide credit: clinicaloptions.com

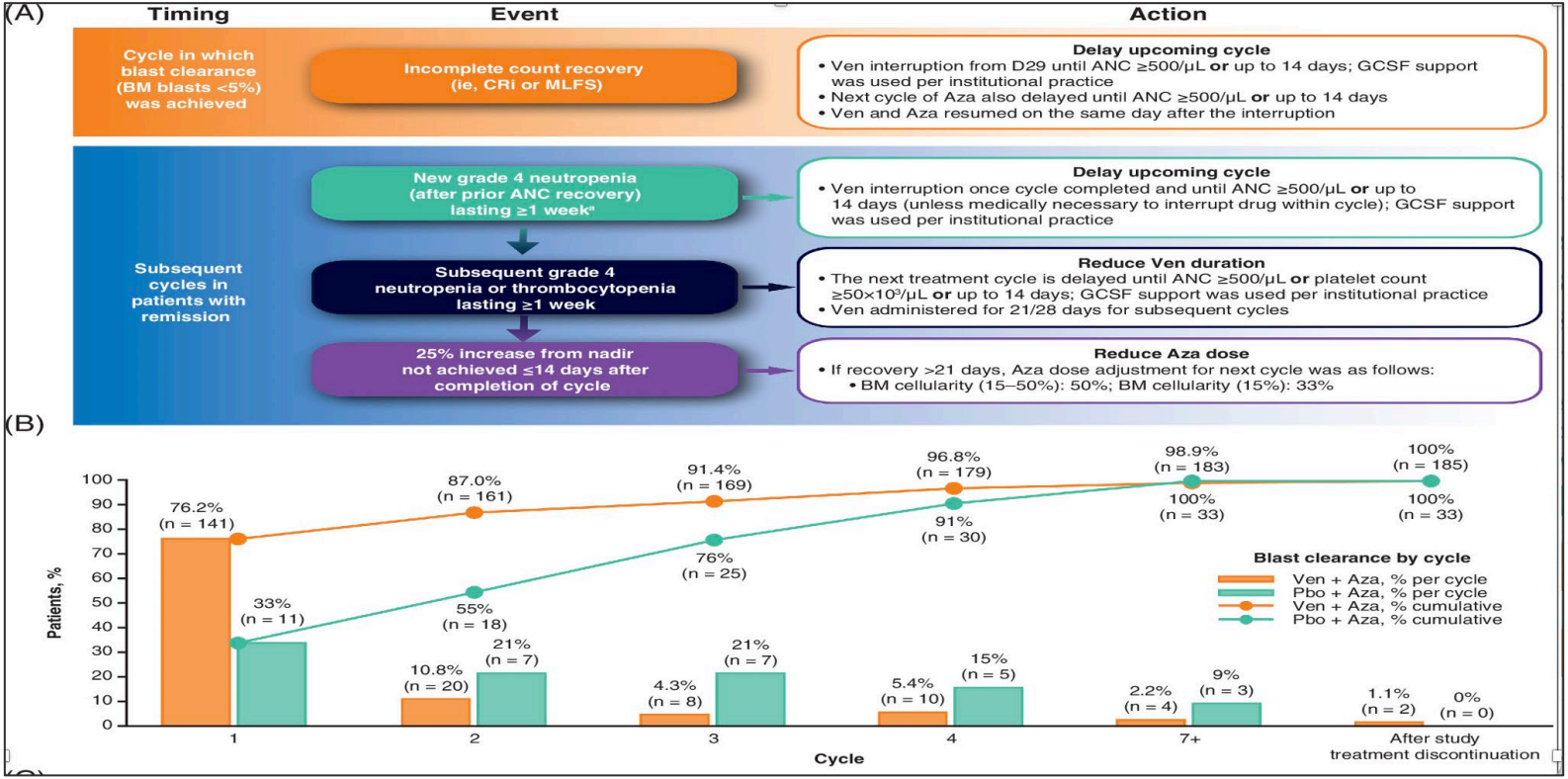
Ivosidenib and Azacitidine in *IDH1*-Mutated AML



Weill Cornell Medicine NewYork-Presbyterian

Montesinos et al. N Engl J Med.2022 Apr 21;386(16):1519-1531.

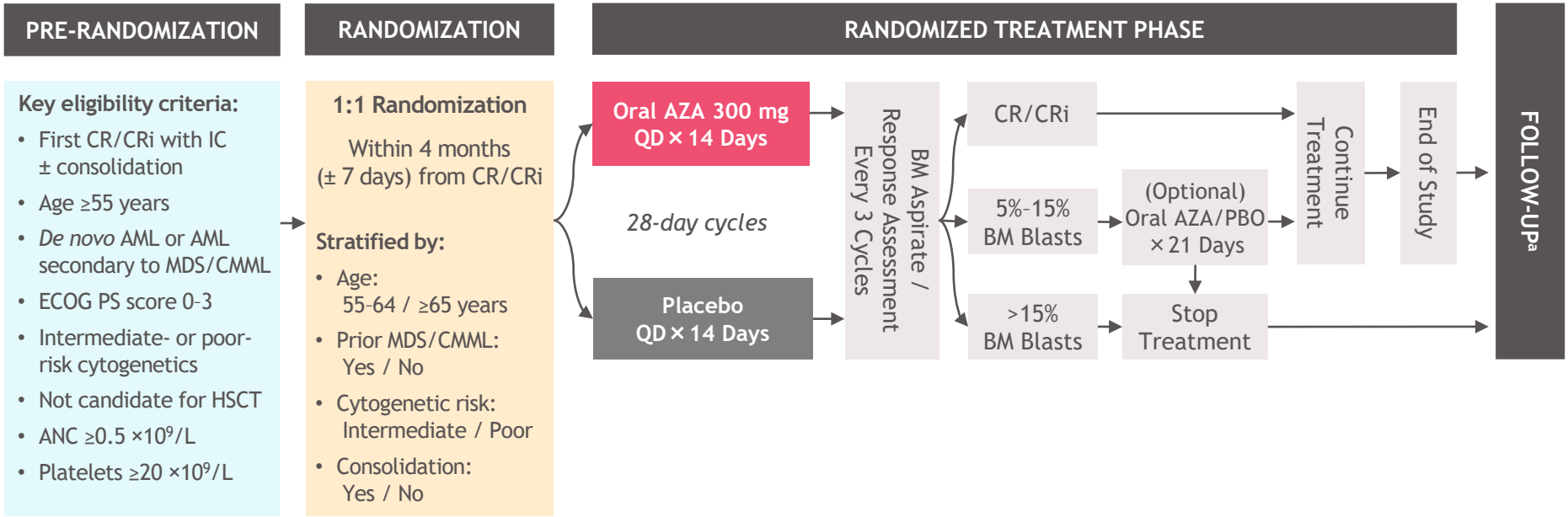
Practical Management of Azacitidine and Venetoclax



Pratz et al. Am J Hematol. 2022 Aug 30. doi:10.1002/ajh.26692

QUAZAR AML-001: Study design and eligibility criteria

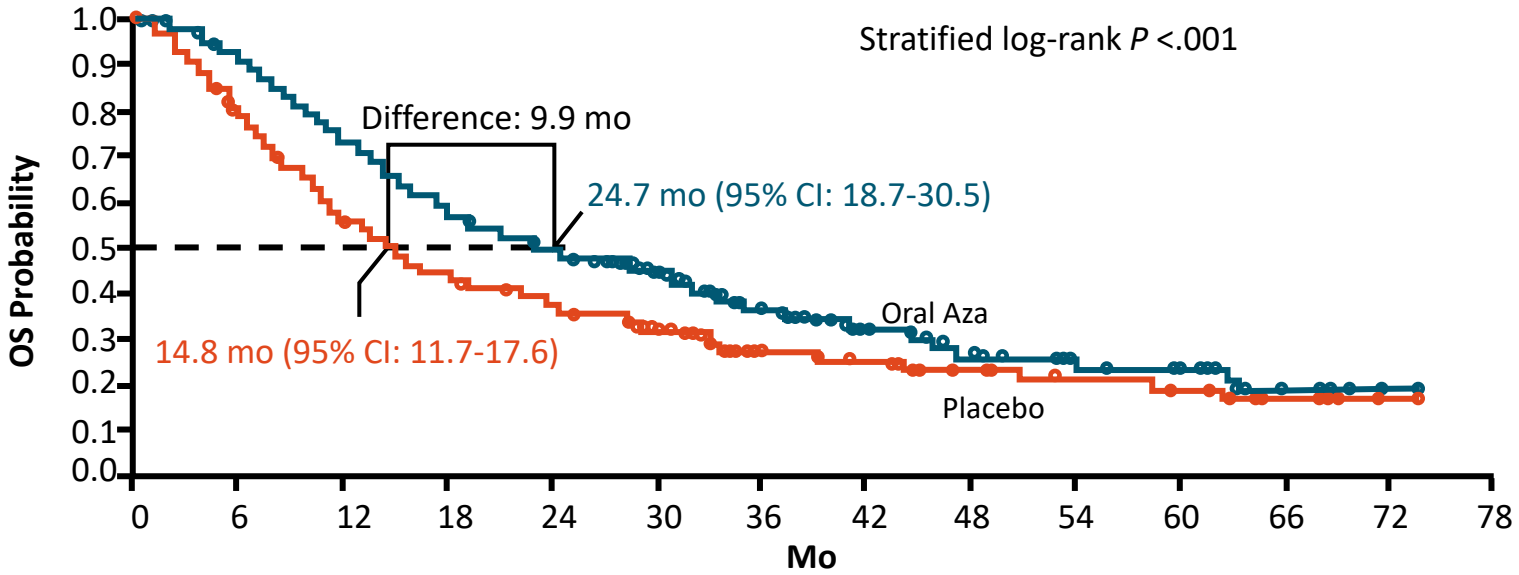
International, multicenter, placebo (PBO)-controlled, double-blind, randomized, phase III trial of Oral AZA as maintenance Tx for patients with AML in first remission (NCT01757535)



[a]Patients were followed until death, withdrawal of consent, study termination, or loss to follow-up.

AML, acute myeloid leukemia; ANC, absolute neutrophil count; AZA, azacitidine; BM, bone marrow; CMML, chronic myelomonocytic leukemia; CR, complete remission; CRi, CR with incomplete blood count recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; HSCT, hematopoietic stem cell transplant; IC, induction chemotherapy; IWG, International Working Group; MDS, myelodysplastic syndromes; PBO, placebo.

QUAZAR AML-001: OS



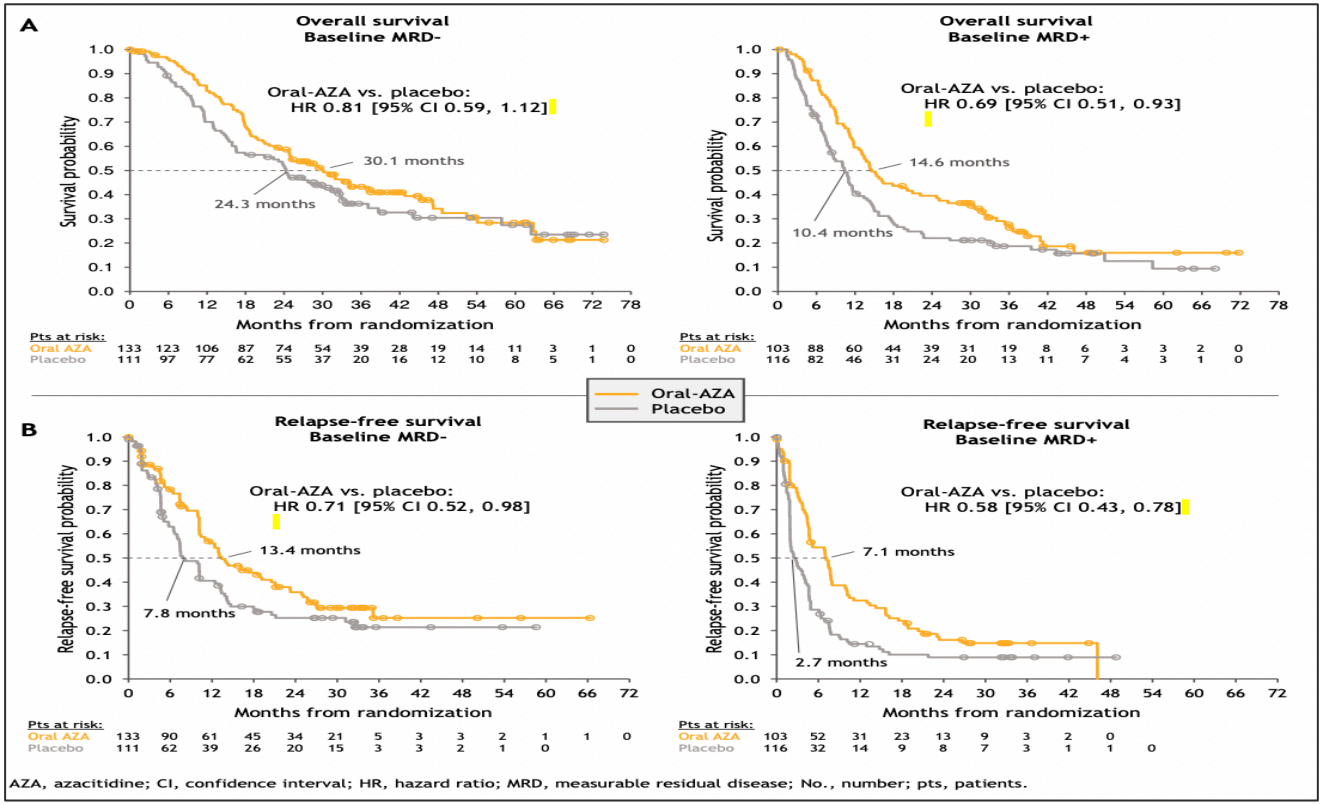
Patients at Risk, n

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.

Slide credit: clinicaloptions.com

Oral azacitidine prolongs survival of patients with AML in remission independent of measurable residual disease status



Roboz et al. Blood. 2022 Jan 7:blood.2021013404. doi: 10.1182/blood.2021013404.

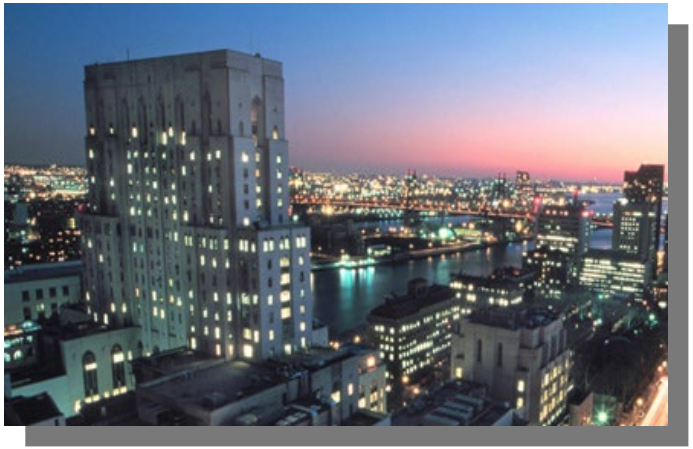
Personalized medicine should not be anecdotal medicine.

We must continue to enroll AML patients onto clinical trials, but large trials in all subgroups are not feasible.

Real-world data are becoming increasingly important and we must all work to facilitate high-quality collaborations.

The Weill Cornell – NY Presbyterian Leukemia Program

- Gail J. Roboz, M.D.
- Ellen K. Ritchie, M.D.
- Pinkal Desai, M.D.
- Michael Samuel, M.D.
- Justin Kaner, M.D.
- David Helfgott, M.D.
- Tania Curcio, N.P.
- Natalie Tafel, P.A.
- Adomah Sakibia Opong, N.P.
- Victoria Mendez, R.N
- Rookmimi Singh, R.N.
- Maureen Thyne, P.A.
- Jill M. Kleczko, MPA, CCRP
- Abeer Elshewehy, BDS, CCRC
- Niamh Savage, BS



WCM Laboratory Collaborators:

- Monica Guzman, Ph.D.
- Olivier Elemento, Ph.D.
- Christopher Mason, Ph.D.
- Ari Melnick, M.D.

Leukemia Fighters

Weill Cornell Medicine

AA&MDSIF • MDS CLINICAL RESEARCH CONSORTIUM

Supported by the Edward P. Evans Foundation

NewYork-Presbyterian

Global Leukemia Academy

Discussion

APTITUDE HEALTH

Global Leukemia Academy

Fit and Unfit AML Patients: How Do We Distinguish? How Do We Treat Differently?

Agnieszka Wierzbowska

APTITUDE HEALTH

UNIWERSYTET MEDYCZNY W ŁODZI

KOPERNIK

Fit and Unfit AML Patients: How Do We Distinguish? How Do We Treat Differently?

Assessment of patient fitness to maximize therapy

Agnieszka Wierzbowska

Patient 1

Would you consider this patient fit for intensive treatment?

A. Yes
B. No
C. I do not know
D. Need more data

- 64, female
- t-AML
- ECOG PS: 1
- brest cancer history 2019 (Tx, sugery)
- ECHO ejection fraction: 52%

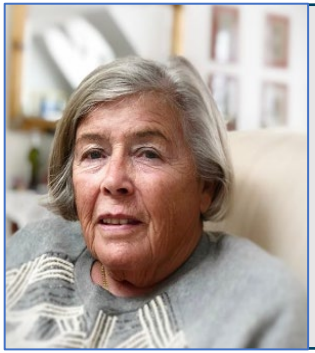
Blood test at diagnosis	
WBC	91.29 × 10^9/L
Hgb, g/L	7.6 g/dL
Platelet count	124 × 10^9/L
Blast, %	88%

Fictitious patient case created by the speaker for educational purposes only.

Patient 2

Would you consider this patient fit for intensive treatment?

A. Yes
B. No
C. I do not know
D. Need more data



- 67, female, retired teacher
- AML, no prior myelodysplasia
- ECOG PS - 1
- CAD, hypertension, diabetes, serum creatinine 1.2 mg/dL, hypercholesterolemia, hyperuricaemia, psoriasis, GERD, hypothyroidism
- ECHO ejection fraction: 55%

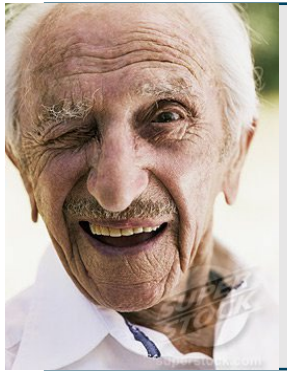
Blood test at diagnosis	
WBC	3.29 × 10^9/L
Hgb, g/L	8.6 g/dL
Platelet count	24 × 10^9/L
Blast, %	34%

Fictitious patient case created by the speaker for educational purposes only.

Patient 3

Would you consider this patient fit for intensive treatment?

A. Yes
B. No
C. I do not know
D. Need more data



- 70, male, smoker
- AML, no prior myelodysplasia
- ECOG PS: 2
- COPD (FEV_1 78%), peptic ulcer requiring treatment
- ECHO ejection fraction: 52%

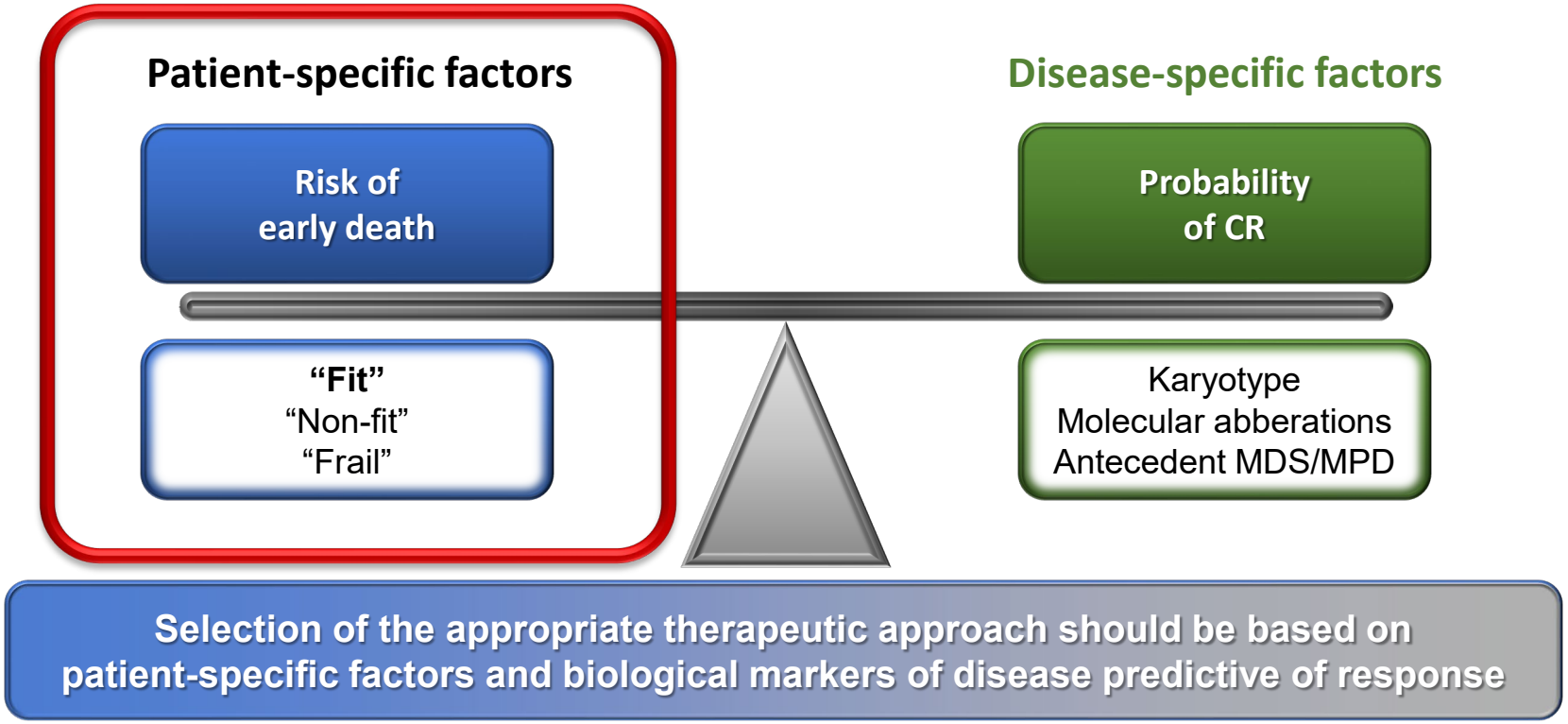
Blood test at diagnosis	
WBC	27.1 × 10^9/L
Hgb, g/L	9.2 g/dL
Platelet count	88 × 10^9/L
Blast, %	61%

Fictitious patient case created by the speaker for educational purposes only.

Fit or unfit?

What factors define „fitness” for intensive Tx?

How to select therapeutic approach AML in elderly patients?



AML, acute myeloid leukaemia; **CR,** complete remission; **MDS,** myelodysplastic syndrome; **MPD**, myeloproliferative neoplasm

Criteria for patients considered not eligible for intensive chemotherapy

Age?

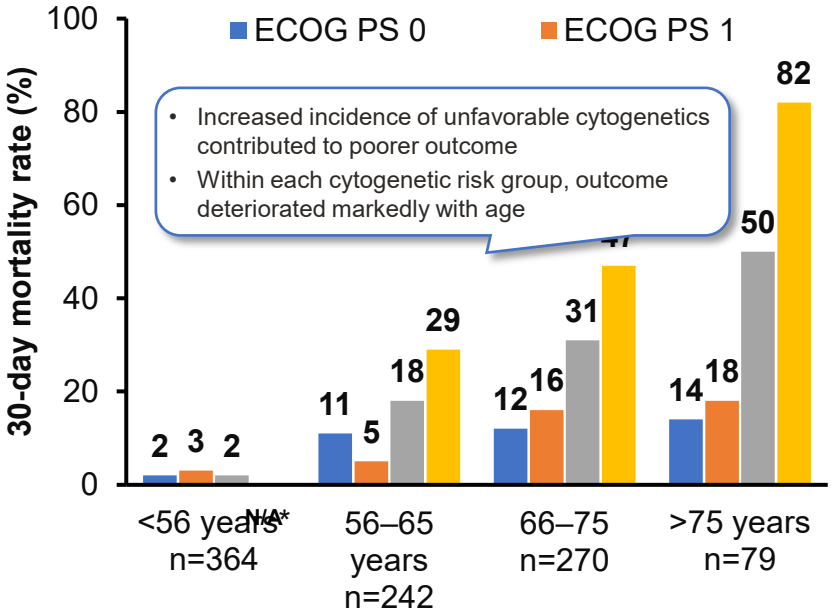
ACCI, Charlson comorbidity index; ELN, European LeukemiaNet; HCT-CI, hematopoietic cell transplantation-comorbidity index; MMSE,Mini-Mental State Examination; Short Physical Performance Battery (SPPB)

Döhner H, et al. *Blood*. 2017;129(4):424-447.

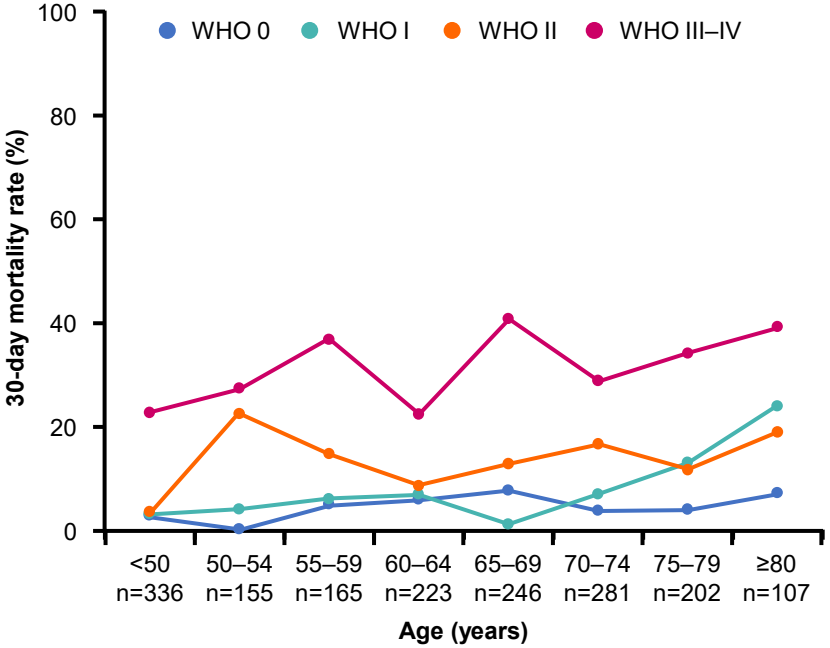
30-day mortality rate after induction therapy

Impact of age and performance status

Retrospective analysis of 968 patients in 5 Southwest Oncology Group trials[1]



Real-world data from 2,767 patients from the Swedish Acute Leukemia Registry[2]



*Note that patients <56 years received more aggressive chemotherapy than older patients, making comparisons between patients younger and older than 56 years difficult.

N/A, not applicable.

1. Appelbaum FR, et al. *Blood* 2006;107:3481-3485; 2. Juliusson G, et al. *Blood.* 2009;113:4179-4187.

Criteria for patients considered not eligible for intensive chemotherapy

Age
(?)

Performance status
(ECOG>2)

Comorbidities?

ACCI, Charlson comorbidity index; ELN, European LeukemiaNet; HCT-CI, hematopoietic cell transplantation-comorbidity index; MMSE,Mini-Mental State Examination; Short Physical Performance Battery (SPPB)

Döhner H, et al. *Blood*. 2017;129(4):424-447.

Comorbid conditions[1,2]

Comorbidity	Definition	Score
Arrhythmia	Atrial fibrillation, sick sinus syndrome, ventricular arrhythmias	1
Cardiac	Coronary artery disease, congestive heart failure, myocardial infarction, or ejection fraction <50%	1
Inflammatory bowel disease	Crohn's disease or ulcerative colitis	1
Diabetes	Requiring treatment with insulin or oral hypoglycemics but not controlled with diet alone	1
Cerebrovascular accident	Transient ischemic attack or cerebrovascular accident	1
Psychiatric disturbance	Depression/anxiety requiring psychiatric consult and/or treatment at the time of HCT	1
Hepatic, mild	Chronic hepatitis, bilirubin > ULN to 1.5× ULN, or AST/ALT > ULN to 2.5× ULN	1
Obesity	Patients with body mass index >35 mg/m^2 for adults or with BMI-for-age percentile of ≥95th percentile for children	1
Infection	Documented infection or fever of unknown etiology requiring antimicrobial treatment before, during, and after the start of conditioning regimen	1
Rheumatologic	Systemic lupus erythematosus, rheumatoid arthritis, polymyositis, mixed connective tissue disease, or polymyalgia rheumatic	2
Peptic ulcer	Requiring treatment	2
Moderate/severe renal	Serum creatinine >2 mg/dL, on dialysis, or prior renal transplantation	2
Moderate pulmonary	DLCO and/or FEV_1 66%–80% or dyspnea on slight activity	2
Prior solid malignancy	Treated at any time point in the patient's past history, excluding nonmelanoma skin cancer	3
Heart valve disease	Except asymptomatic mitral valve prolapse	3
Severe pulmonary	DLCO and/or FEV_1 ≤65%, or dyspnea at rest, or requiring oxygen	3
Moderate/severe hepatic	Liver cirrhosis, bilirubin >1.5× ULN, or AST/ALT >2.5× ULN	3

Risk	HCT-CI score	ED (%)	Me OS (weeks)
Low	0	3	45
Intermediate	1–2	11	31
High	>2	29	19

ffusing capacity of the lungs for carbon
cell transplantation-comorbidity index; Me

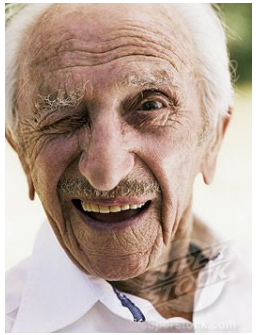
Fit or unfit for intensive chemotherapy?

- 64, female
- t-AML
- ECOG PS: 1
- brest cancer history 2019 (Tx,sugery)
- ECHO ejection fraction: 52%

HCT-CI = 3

- 67, female, retired teacher
- AML, no prior myelodysplasia
- ECOG PS - 1
- CAD, hypertension, diabetes, serum creatinine 1.2 mg/dL, hypercholesterolemia, hyperuricaemia, psoriasis, GERD, hypothyroidism
- ECHO ejection fraction: 55%

HCT-CI = 2



- 70, male, smoker
- AML, no prior myelodysplasia
- ECOG PS: 2
- COPD (FEV_1 78%), peptic ulcer requiring treatment
- ECHO ejection fraction: 52%

HCT-CI = 4

Criteria for unfitness to intensive chemotherapy

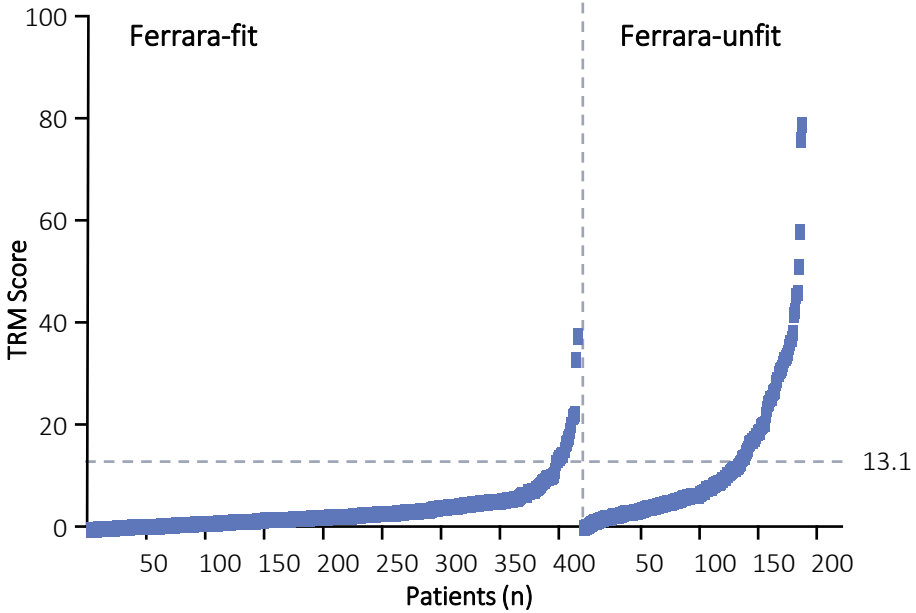
Unfitness defined for at least 1 of 9 criteria

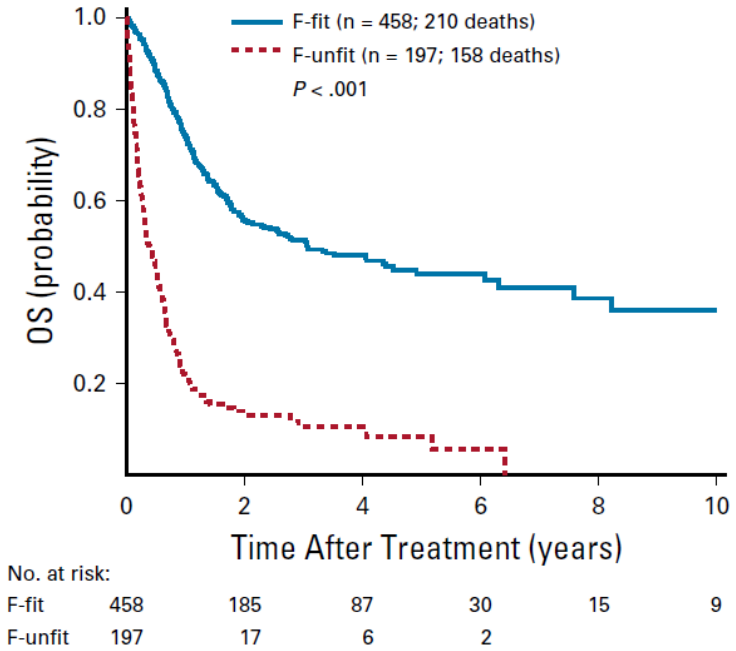
1. Age ≥75 years
2. Congestive heart failure or cardiomyopathy with EF ≤50%
3. Pulmonary disease with DLCO ≤65% or FEV1 ≤65% or dyspnea at rest or requiring oxygen, or any pleural neoplasm or uncontrolled lung neoplasm
4. On dialysis and age ≥60 yr or uncontrolled renal carcinoma
5. Liver cirrhosis Child B or C or documented liver disease with AST/ALT >3 UNL and age >60 years or any biliary tree carcinoma or uncontrolled liver carcinoma or acute viral hepatitis
6. Active infection resistant to anti-infective therapy
7. Current mental illness requiring psychiatric hospitalization, institutionalization, or intensive outpatient management or cognitive dependence status not controlled by the caregiver
8. ECOG ≥3 not related to leukemia
9. Any other comorbidity judged incompatible with conventional intensive chemotherapy

EF, ejection fraction;
Adapted from Ferrara F, et al. *Leukemia.* 2013;27:997-999.

The Ferrara criteria provide a useful tool to predict early mortality after intensive AML chemotherapy

Accuracy of SIE/SIES/GITMO consensus criteria for unfitness to predict early mortality after intensive chemotherapy in adults with AML or other high-grade myeloid neoplasm





Criteria that have been commonly used in the context of clinical trials

Patient not eligible for intensive chemotherapy:

- Age ≥75 years of age or
- ECOG performance status >2; and / or
- age-related comorbidities, such as severe cardiac disorder (eg, congestive heart failure requiring treatment, ejection fraction ≤ 50%, or chronic stable angina); severe pulmonary disorder (eg, DLCO ≤ 65% or FEV1 ≤ 65%); creatinine clearance < 45 mL/min; hepatic disorder with total bilirubin >1.5 time the upper limit of normal;
- any other comorbidity that the physician assesses to be incompatible with intensive chemotherapy.

Criteria for patients considered not eligible for intensive chemotherapy

Age
(≥75y)

Performance status
(ECOG>2)

Comorbidities

(HCT-CI ≥3, augmented HCT-CI, CCI)

Geriatric assessment?

ACCI, Charlson comorbidity index; ELN, European LeukemiaNet; HCT-CI, hematopoietic cell transplantation-comorbidity index; MMSE,Mini-Mental State Examination; Short Physical Performance Battery (SPPB)

Döhner H, et al. *Blood*. 2017;129(4):424-447.

Performance status – SPPB (short physical performance battery)

SPPB

Test	Instructions	Scoring	
Chair stand test	Have patient cross their arms across their chest and stand from a seated position without the use of their arms five times, as quickly as they can. Measure the time this takes the patient	<11.19 s 11.20–13.69 s 13.70–16.69 s >16.7 s Unable to complete	= 4 = 3 = 2 = 1 = 0
Gait speed test	Measure the time required for the patient to walk 4 m at a normal pace (best out of two attempts)	<4.82 s 4.82–6.20 s 6.21–8.70 s >8.70 s Unable to complete	= 4 = 3 = 2 = 1 = 0
Balance tests			
Side-by-side stand	Have patient stand with their feet together for 10 s	Able to complete Unable to complete (and do not proceed to semi-tandem or tandem stands)	= 1 = 0
Semi-tandem stand	Have patient stand with their feet staggered for 10 s	Able to complete Unable to complete (and do not proceed to tandem stand)	= 1 = 0`
Tandem stand	Have patient stand with one foot directly in front of the other for as long as possible (up to 10 s)	10 s 3–9 s <3 s	= 2 = 1 = 0

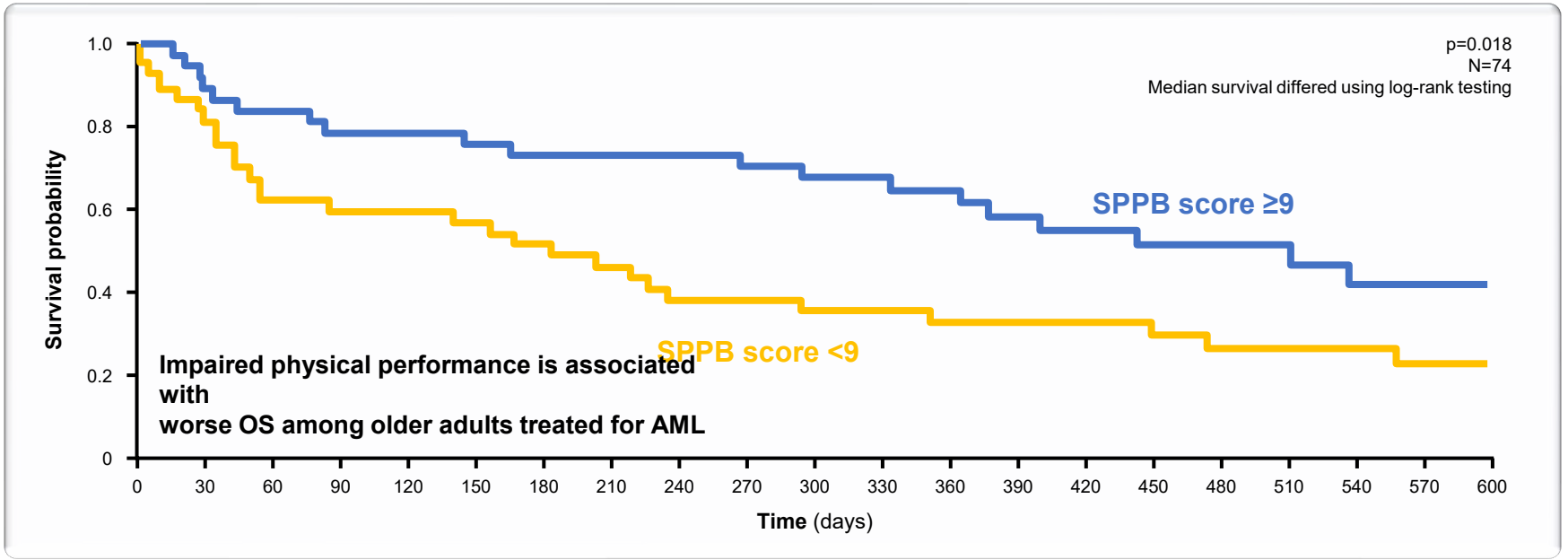
Interpretation

- Objective measure of physical performance
- Predicts future disability, hospitalisations, and mortality
- Scores range 0–12
- Score of 12 represents the most physically fit patient
- An association between lower SPPB score and increased risk of death
  - AML >60 years undergoing intensive induction Tx
  - EGOG PS of 0–1

AML, acute myeloid leukaemia; **ECOG**, Eastern Cooperative Oncology Group performance status.

Klepin H, et al. *J Am Geriatr Soc.* 2011;59(10):1837–46. Klepin H, et al. *Blood* 2013;21:4287–94

Influence of SPPB score on OS in elderly AML



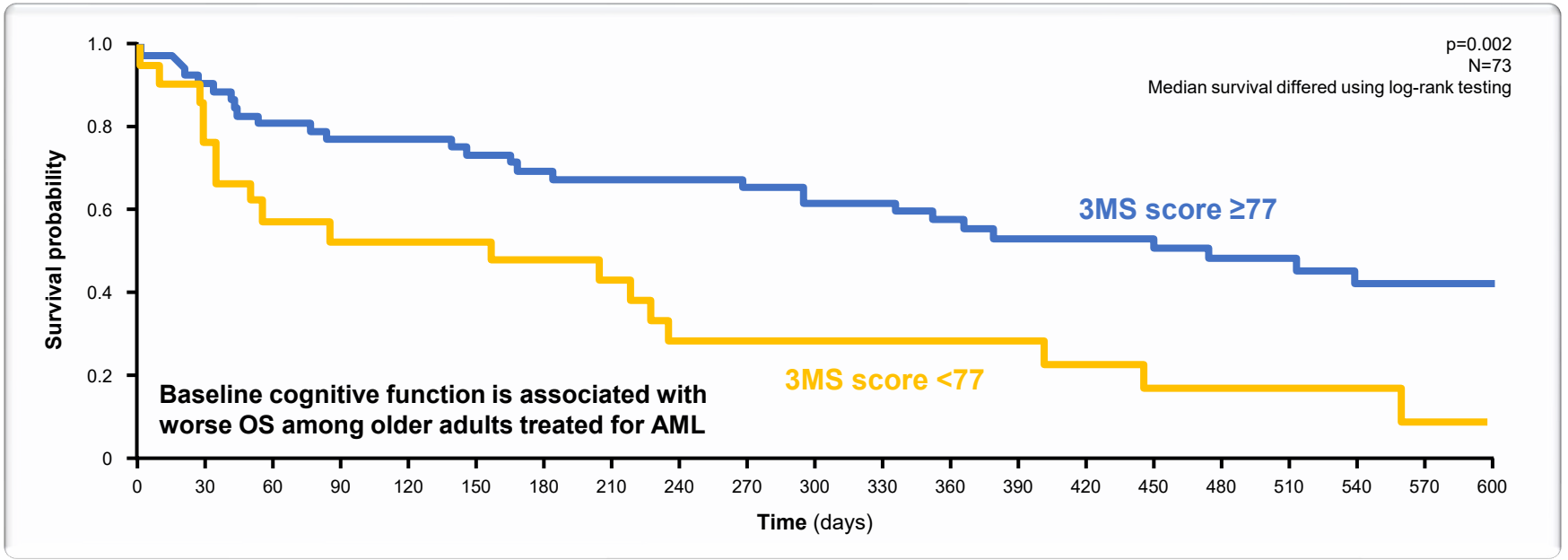
SPPB is a valuable tool to further risk-stratify those patients with good ECOG PS who may have a lower functional reserve

AML, acute myeloid leukaemia; **SPPB**, short physical performance battery; **OS,** overall survival; **PS**, performance status.

Klepin H, et al. *Blood* 2013;21:4287–94

Cognitive function assessmet

100-point modified Mini-Mental State (3MS) exam



Pretreatment cognitive impairment may increase the risk of complications during and after intensive therapy for AML

AML, acute myeloid leukaemia; **OS,** overall survival.

Klepin H, et al. *Blood* 2013;21:4287–94

Prognostic models based on performance status, comorbidity assessment, and cognitive assessment

Evolving criteria for fitness in older adults with AML

Risk category	Patient characteristics
Frail	**ECOG PS ≥3** **Impaired activities of daily living** **Major comorbidity** (CCI or HCT-CI >1)
Vulnerable	**ECOG PS <3 with no major comorbidity** **Impaired objectively measured physical function** (SPPB <9) **Impaired cognition** (modified mini-mental state score <77)
Fit	**Absence of all above risk factors**

GA methods, with a focus on cognitive and physical function, improve risk stratification and may inform interventions to improve outcomes for older AML patients

AML, acute myeloid leukaemia; **CCI,** Charlson comorbidity index; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **GA**, geriatric assessment; **HCT-CI**, hematopoietic cell transplantation-specific comorbidity index; **SPPB**, short physical performance battery.

Klepin HD. *Hematology ASH Educ Program (2014)*. 2014(1):8–13.

Summary 1

- Fitness refers to a comprehensive evaluation of age, performance status, comorbidities, and functional capacity.
- Age alone should not be the decisive determinant to guide therapy.
- For patients older than 75 years, eligibility to intensive chemotherapy should be evaluated very carefully but age ≥ 75 years should not represent an absolute contraindication to intensive chemotherapy
- There are no generally accepted or validated criteria to consider a patient ineligible for intensive chemotherapy

Physician-effect on treatment decisions

Patient-specific factors

Risk of early death

"Fit"
"Non-fit"
"Frail"

Disease-specific factors

Probability of CR

Karyotype
Molecular abberations
Antecedent MDS/MPD

AML, acute myeloid leukaemia; **CR,** complete remission; **MDS,** myelodysplastic syndrome; **MPD**, myeloproliferative neoplasm

Physicians' personalities contribute to treatment-related decision-making for elderly AML patients

Physician uncertainty aversion impacts medical decision making for older patients with acute myeloid leukemia: results of a national survey

Pierre Bories,[1,2] Sébastien Lamy,[3,4] Célestine Simand,[5] Sarah Bertoli,[2] Cyrille Delpierre,[3] Sandra Malak,[6] Luc Fornecker,[5] Stéphane Moreau,[7] Christian Récher[2] and Antoine Nebout[8]

Physicians who recommend significantly more intensive chemotherapy are:

- averse to uncertainty OR=1.15; *P*=0.039
- male physicians who do not conform to the expected utility model (assumed as economically irrational) OR = 3.45 *P*=0.01.
- have higher patient volume per physician OR=0.98 *P*=0.032

Impact of Physicians' Personalities and Behavioral Traits on Treatment-Related Decision-making for Elderly Acute Myeloid Leukemia

Xia Wu, MD[1], Yi-nan Jiang, MD[2], Yue-lun Zhang, PhD[3], Jia Chen, MD[1], Yue-ying Mao, MD[1], Lu Zhang, MD[1], Dao-bin Zhou, MD[1], Xin-xin Cao, MD[1], and Jian Li, MD[1]

Physicians who recommend significantly more intensive chemotherapy are:

- attending physicians with a higher level of extraversion or conscientiousness
- No correlation between physicians' personalities or behavioral traits and medical decisionmaking was observed in chief and associate chief physicians

Fit or unfit?

What factors define selection of the most appropriate therapeutic approach?

US and EU drug approvals for AML 2017–2022

NEW!

	Target	Approval		
Midostaurin (+IC)	FLT3	ND		
CPX-351	t-AML, AML-MRC	ND		
Enasidenib	IDH2	R/R		
Gemtuzumab ozogamicin (±IC)*	CD33	ND and R/R*		
Ivosidenib	IDH1	ND and R/R		
Glasdegib (+LDAC)	Sonic hedgehog pathway	ND		
Gilteritinib	FLT3	R/R		
Venetoclax (+AZA/Dec/LDAC)†	BCL-2	ND		
CC-486 (oral azacitidine)	Hypermethylation	Maintenance		

* EMA: GO+IC in ND; FDA: GO±IC in ND and GO only in R/R; † Ven in combination with LDAC is not EMA approved.
AML-MRC, AML with myelodysplasia-related changes; AZA, azacitidine; BCL-2, B-cell lymphoma 2; Dec, decitabine; FLT3, FMS-like tyrosine kinase 3; GO, gemtuzumab ozogamicin; IC, intensive chemotherapy; IDH, isocitrate dehydrogenase; LDAC, low-dose cytarabine; ND, newly diagnosed; t-AML, therapy-related AML; Ven, venetoclax.

1. EMA. Medicines. Available at: https://www.ema.europa.eu/en/medicines/human (accessed September 2021);
2. FDA. Drugs@FDA: FDA-Approved Drugs. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm (accessed September 2021);
3. Venclyxto® (venetoclax). EMA SmPC (accessed September 2021).

Is it time for a new definition of fitness?

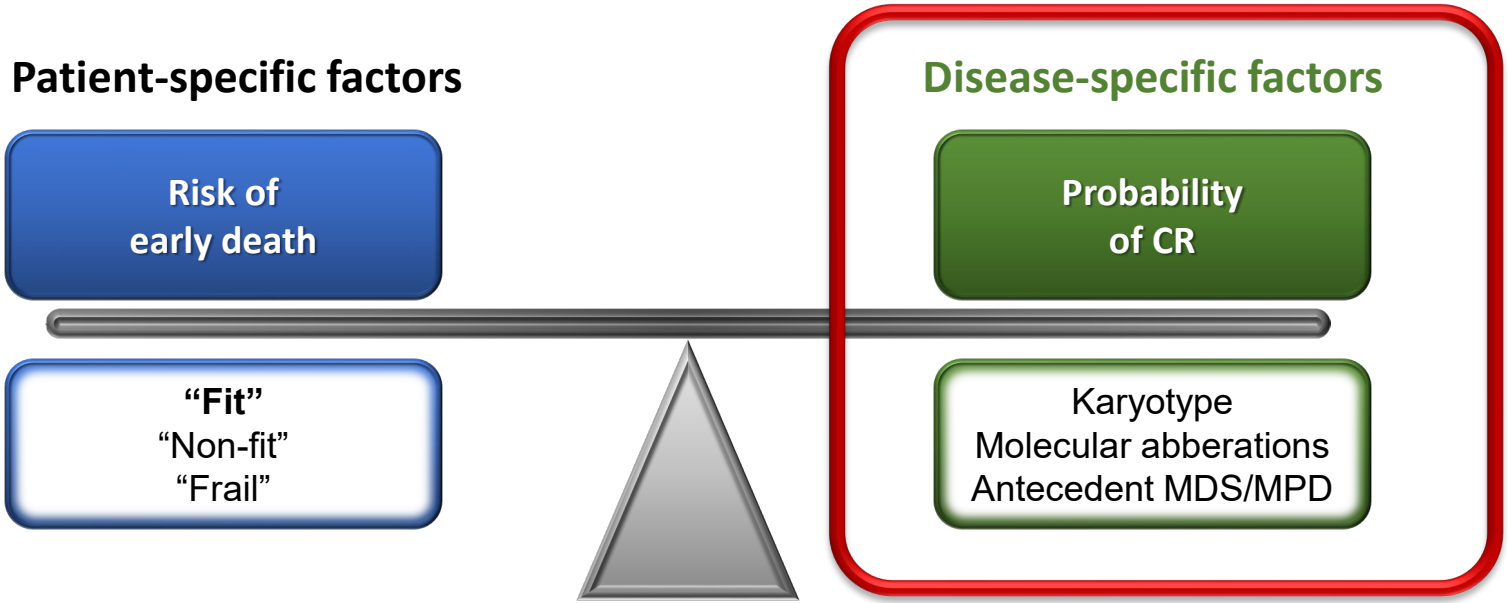
NEW!

Fit vs. unfit → **Fit for….**

Different fitness levels correspond to different treatment intensities. Accordingly, patients should be referred to as “fit for” a given treatment strategy.

- **Fit for 3+7**
- **Fit for CPX-351**
- **Fit for HMA+VEN/IVO**
- **Fit for IVO/ENA**
- **Fit for ….**

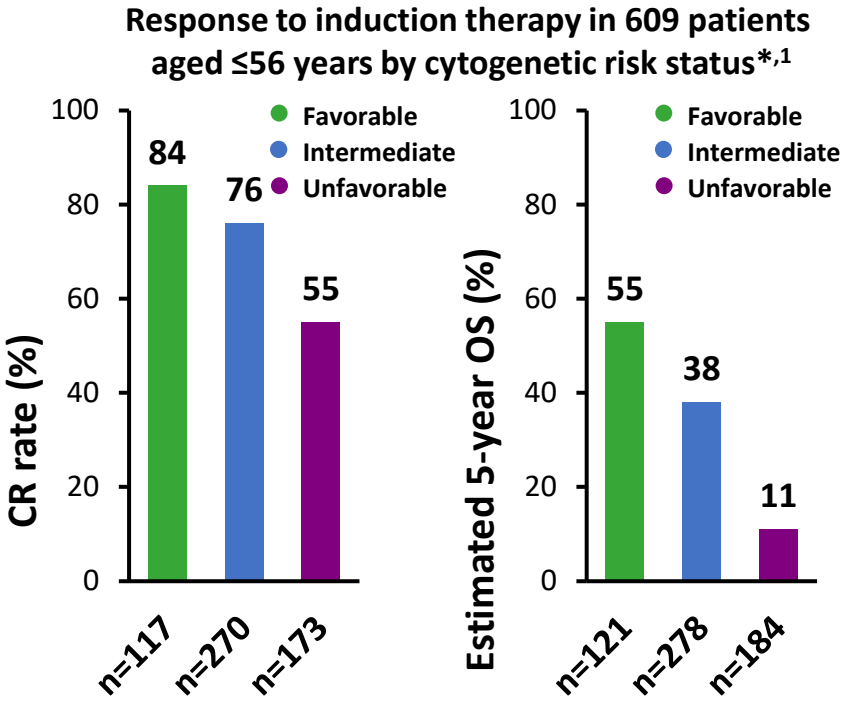
Dieases specific factors – do they matter?



AML, acute myeloid leukaemia; **CR,** complete remission; **MDS,** myelodysplastic syndrome; **MPD**, myeloproliferative neoplasm

CR and OS rates after induction therapy

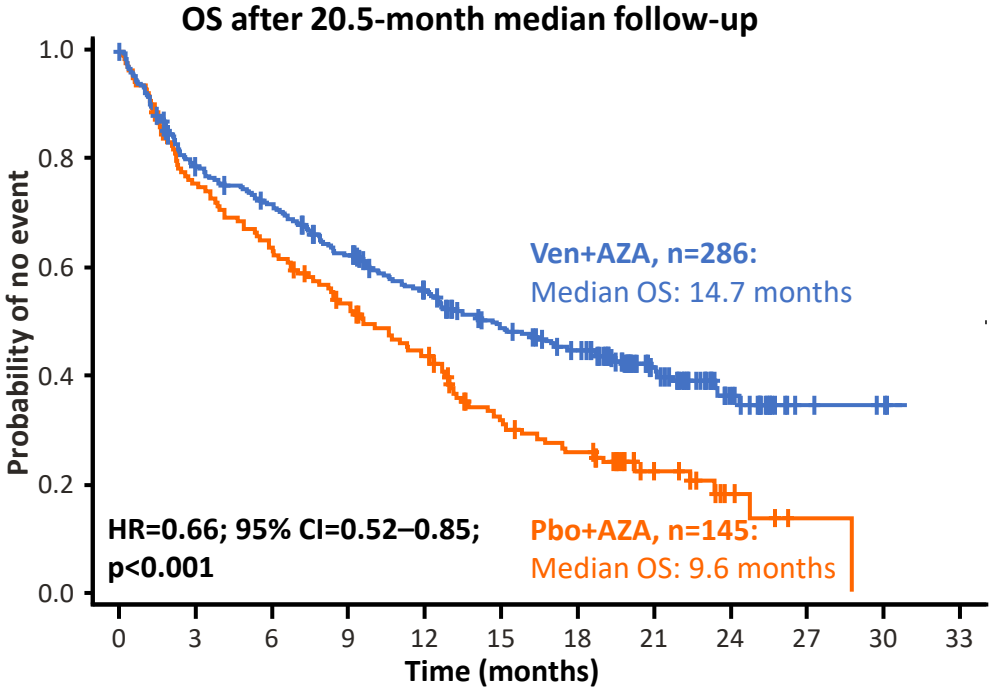
Impact of age, performance status, and karyotype



Adverse cytogenetics and sAML are important predictors of poor response to treatment and OS

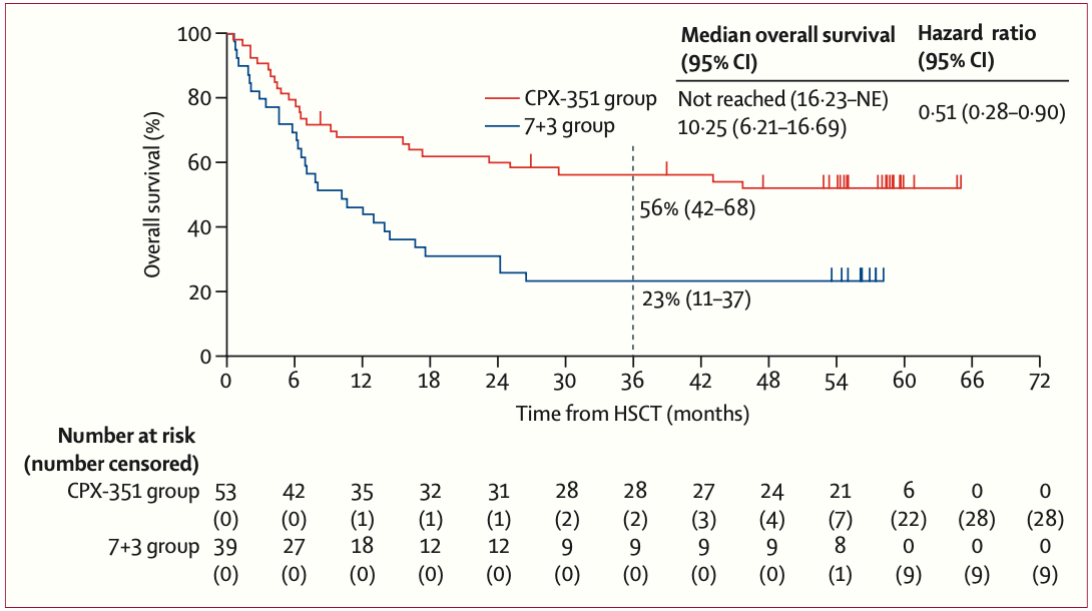
Phase 3 Ven+AZA trial: Efficacy outcomes

VIALE-A: Ven+AZA vs Pbo+AZA in previously untreated patients ineligible for intensive chemotherapy



Endpoint	Ven+AZA n=286	Pbo+AZA n=145
CR+CRi rate	**66.4%**	**28.3%**
CR rate	36.7%	17.9%
CR+CRi by initiation of cycle 2	43.4%	7.6%
CR+CRi rate in molecular subgroups		
IDH1/2	75.4%	10.7%
FLT3	72.4%	36.4%
NPM1	66.7%	23.5%
TP53	55.3%	0
Transfusion independence		
Red blood cells	59.8%	35.2%
Platelets	68.5%	49.7%
Event-free survival	9.8 months	7.0 months

CPX-351 versus 7+3 induction in high-risk or sAML: 5-year results of a randomised, open-label, multicentre, phase 3 trial



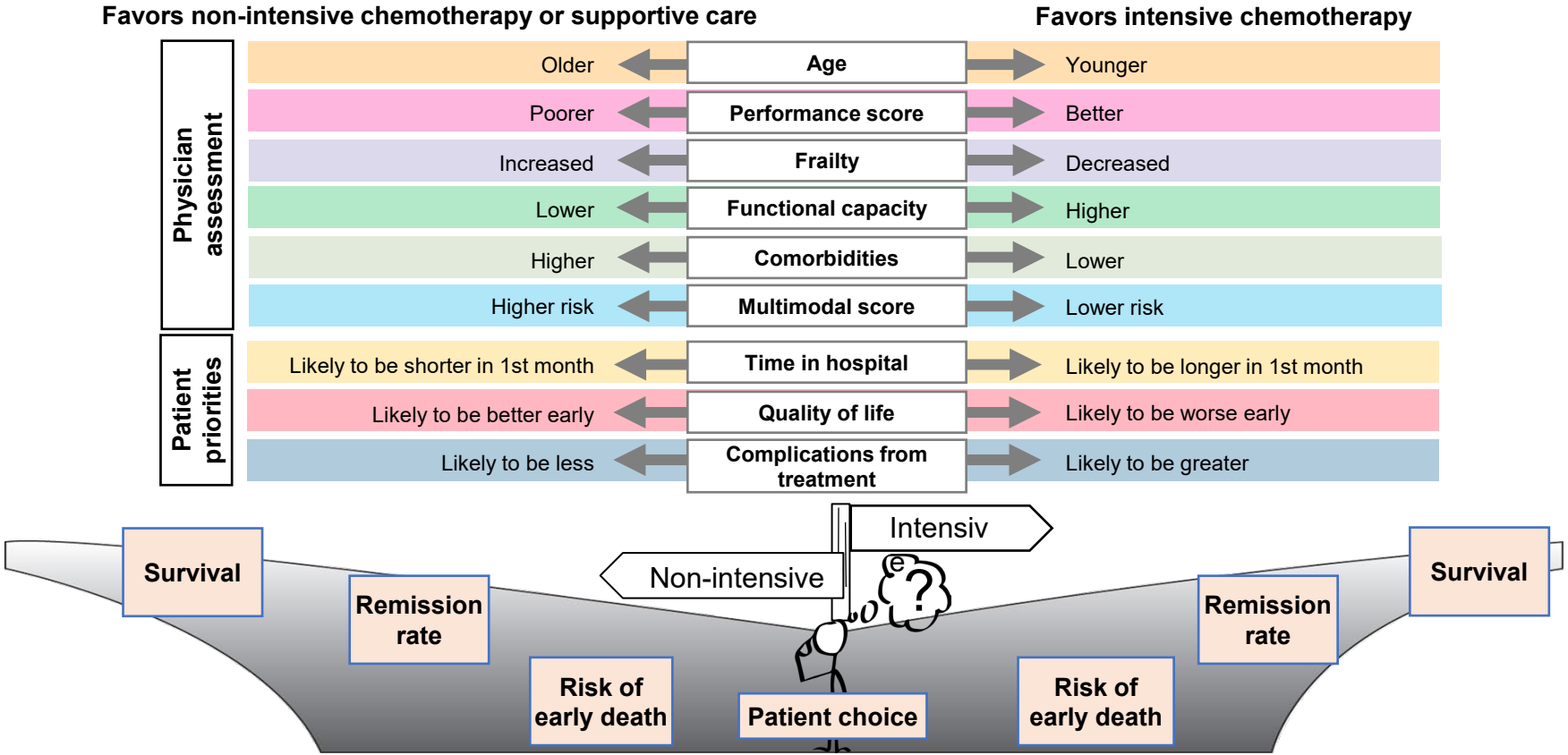
CPX-351 significantly improved OS vs. conventional 7+3 in older adults with newly diagnosed high-risk/sAML

Lancet JE Lancet Haematol. 2021 Jul;8(7):e481-e491.

Summary 2

- Treatment decision should rely on both patient-related (“fitness”) and disease-related (genetic) features
- Adverse genetic/cytogenetic profile is a relative contraindication to intensive chemotherapy, in older, fit patients who are eligible to HSCT
- Patients should be referred to as “fit for” a given treatment strategy

Selection of optimal therapeutic approach



Adapted from Wei AH. *Blood.* 2021;138:356-358.

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Discussion

APTITUDE HEALTH

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Case 1: Adult AML

Agnieszka Pluta

APTITUDE HEALTH

Case Presentation

Agnieszka Pluta

Department of Hematology, Medical University of Lodz

Copernicus Provincial Multidisciplinary Oncology and Traumatology Center

Case

A 27-year-old male patient with dyspnea appeared in the Hematology Department (09.2020)

A medical history

- No chronic disorders
- For 1 month, deterioration of exercise tolerance, loss of weight –10 kg, respiratory tract infection without any improvement after oral antibiotics

At admission

- ECOG: 2, dyspnea, enlargement of tonsils and cervical lymph nodes, gingival infiltrations, HR 120/min, normal bubble murmur, abdomen without abnormalities

Hematology	
WBC	174.84 × 10^3/µL
Hgb	5.4 g/dL
MCV	92 fL
PLT	32 × 10^3/µL
ANC	11.76 × 10^3/µL
Lymph	19.63 × 10^3/µL
Mono	140.32 × 10^3/µL

WB smear	
Blasts	76%
Promyelocytes	1%
Myelocytes	1%
Metamyelocytes	1%
Neutrophils	1%
Eosinophils	2%
Lymphocytes	13%
Monocytes	5%

Biochemistry
CRP 78 mg/dL
LDH 1690 mg/dL
Creatinine 1.1mg/dL
Uric acid 7.8 mg/dL
AST 34 UI/dL
ALT 28 UI/dL
Bilirubin 0.9mg/dL

Case

Bone marrow aspiration: 65% myeloblast

Immunophenotype: AML

Cytogenetic analysis: 46,XY,inv(16)(p13q22)[15]/46,XY[1]

Genetic tests:

NPM1	negative
FLT3-ITD	negative
FLT3-TKD	**positive**
BCR/ABL	negative
AML1-ETO	negative
CBFβ-MYH11	**positive**
MLL-PTD	negative
WT1	**positive**
cKIT	negative

Question

To which risk group should we assign the patient, according to ELN 2022?

1. Low-risk group
2. Intermediate-risk group
3. High-risk group
4. Difficult to say

Diagnosis and Management of AML in Adults: 2022 ELN Recommendations From an International Expert Panel

Risk Category[b]	Genetic Abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1*[b,c] • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11*[b,c] • Mutated *NPM1*[b,d] without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*[e]
Intermediate	• Mutated *NPM1*[b,d] with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD • t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A*[b,f] • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23;q34.1)/*DEK::NUP214* • t(v;11q23.3)/*KMT2A*-rearranged[g] • t(9;22)(q34.1;q11.2)/*BCR::ABL1* • t(8;16)(p11;p13)/*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,[h] monosomal karyotype[i] • Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2*[j] • Mutated *TP53*[k]

Concurrent *KIT* and/or *FLT3* gene mutation does not alter risk categorization!

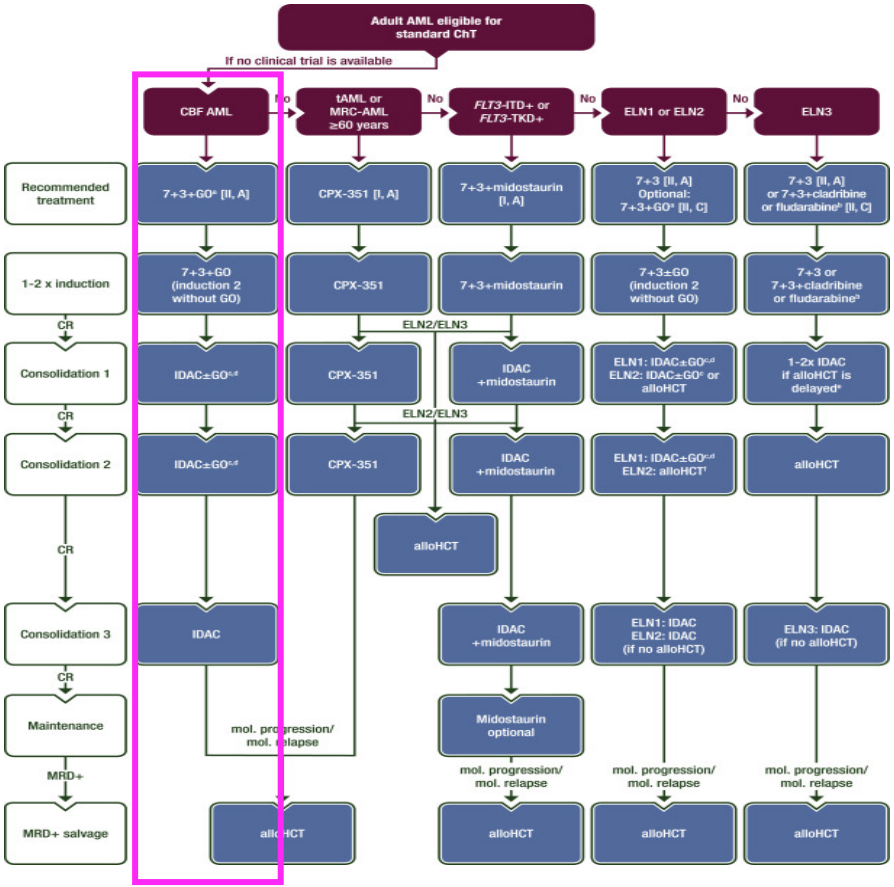
Dohner H, et al. *Blood.* 2022.

Question

What is the best choice for induction treatment?

1. DA (daunorubicin; cytarabine) + midostaurin
2. DA + gemtuzumab ozogamicin
3. DA + cladribine (DAC)
4. DA + venetoclax

Fit AML Patients

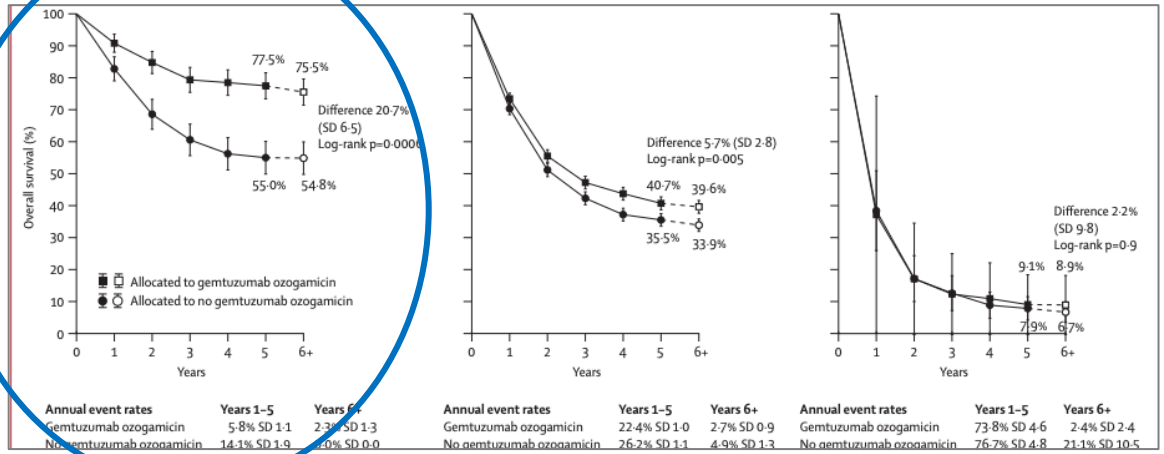


Heuser M, et al. *Ann Oncol.* 2020.

Low-Risk AML Patients: 3+7+ GO

Meta-analysis

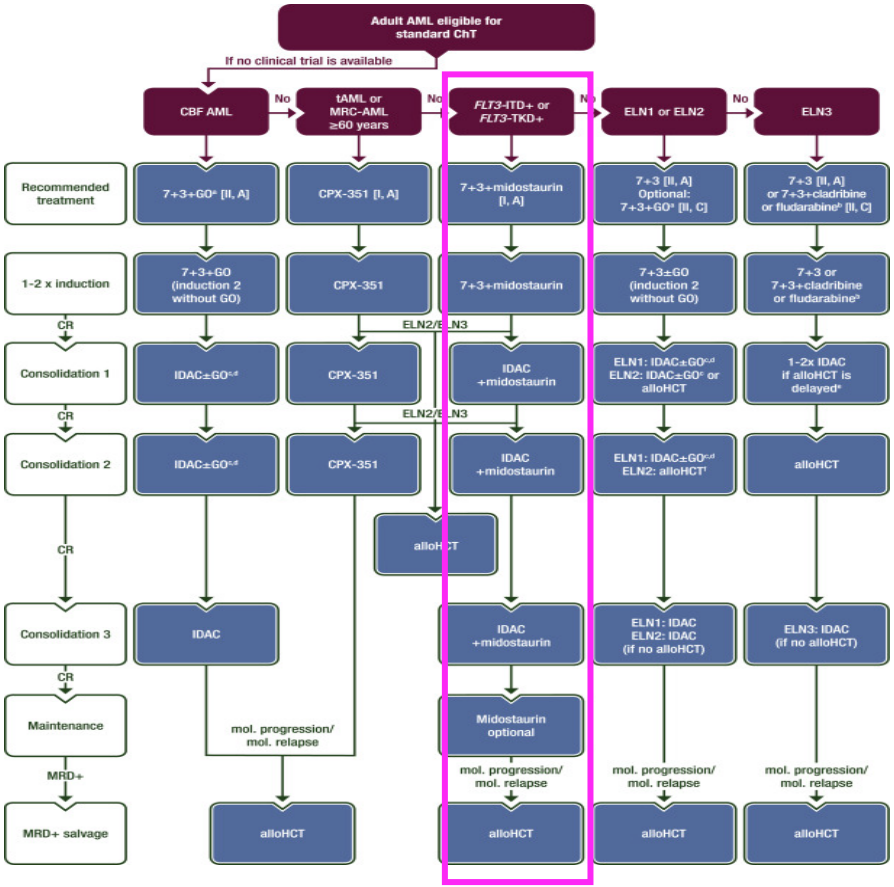
- 5 randomized trials (n = 3325)
- Without impact on CR, CRi
- Prolongation of 5-year OS
- Decreased relapse risk (*P* = .0001)
- Dose 3mg/m^2 equal efficacy as 6 mg/m^2, but with less toxicity



Gemtuzumab ozogamicin improves treatment outcomes in low- and intermediate-risk genetic groups in AML

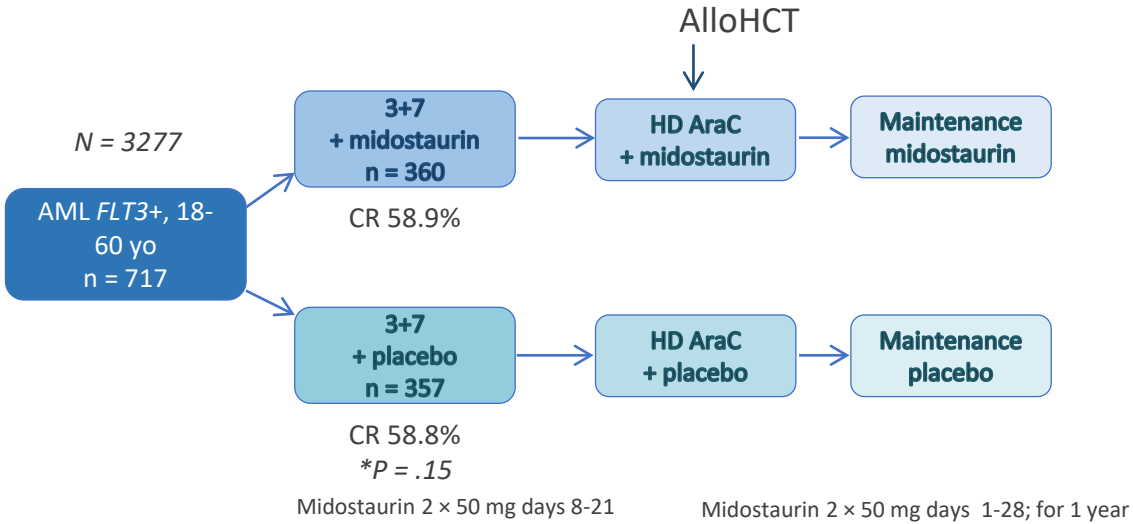
Hills RK, et al. *Lancet Oncol.* 2014.

Fit AML Patients

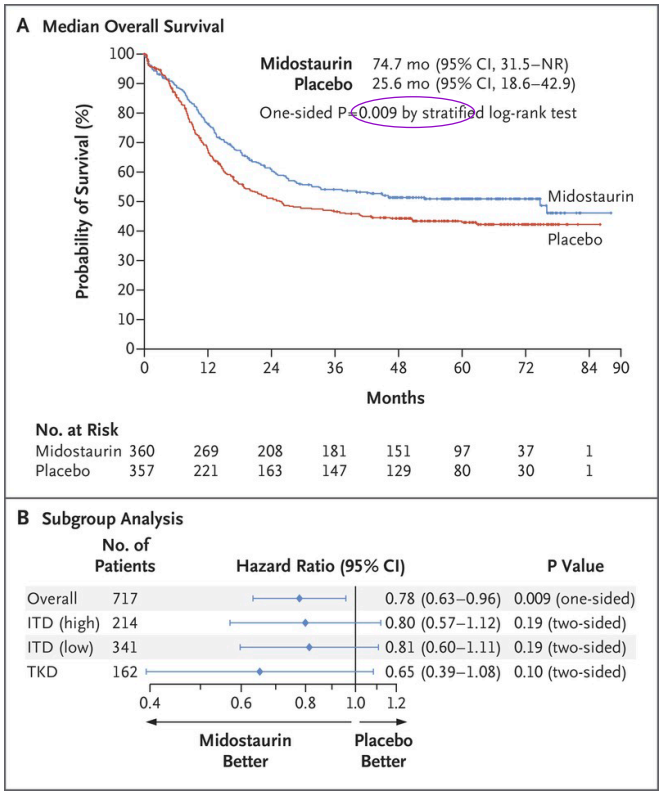


Heuser M, et al. *Ann Oncol.* 2020.

CALGB 10603, RATIFY Trial



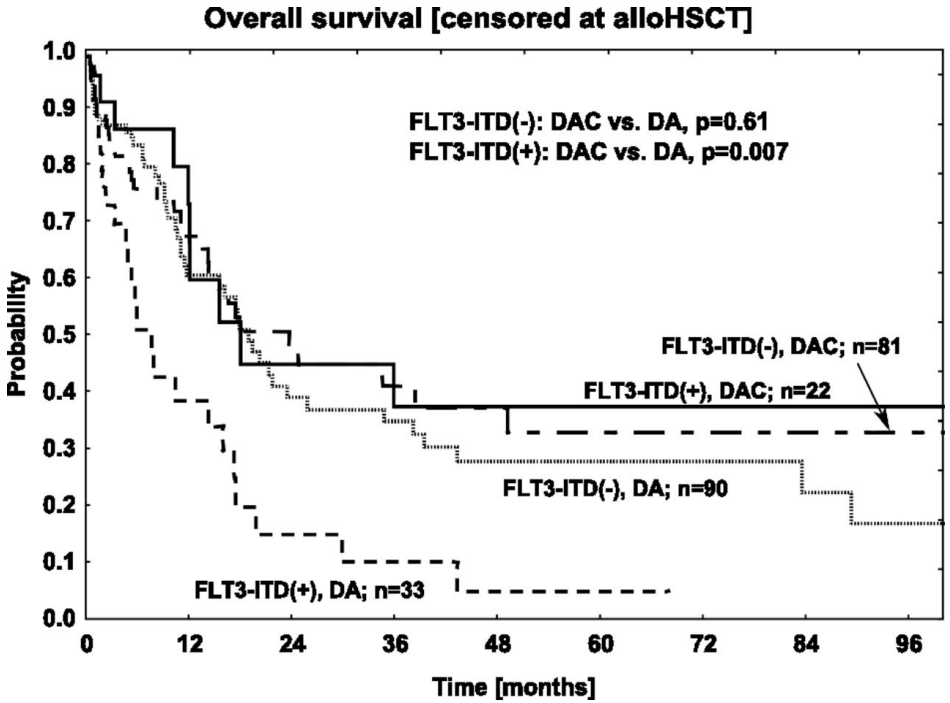
- Median follow-up 59 m-cy
- Median OS 74.7 m-cy
- Median EFS in midostaurin arm 8.2 months and 3.0 months in placebo arm (*P = .002*)



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

PALG Observation: *FLT3*-ITD^{+} NK-AML Patients

- Retrospective analysis
- n = 227 samples from newly diagnosed NK-AML for *FLT3*-ITD and *NPM1* mutations
- Patients treated in 9 PALG centers in the years 1999–2014
- CR rate: DA vs DAC 73.4% (91/124) vs 81.6% (84/103); *P* = .14



Libura M, et al. *Blood*. 2016.

Case

The patient received 09-10.2020 induction treatment DA + midostaurin

- 11.2020 – CR1 MRD: LAIP (-) + CBF-MYH11 (-)
- 11.2020-02.2021 consolidation treatment (3× HD AraC + midostaurin)
  - Taking into consideration that it was a low-risk AML with mutation *FLT3*-TKD, maintenance treatment and alloHSCT were not performed
  - The patient was under observation – CR1 MRD (-)

09.2021 relapse

- Clonal evolution: 47,XY,inv(16)(p13q22)+8[23]/46,XY,inv(16)(p13q22), t(1;17)(p21;q21) [3]; 46XY[4], mutation *FLT3*-ITD (-), *FLT3*-TKD (-), *CBFB-MYH11* (+), *cKIT* (+)
  - **Reinduction cycle:** CLAG-M -> CR2 MRD (-)
  - MUD alloHSCT 12.2021 -> CR2 MRD (-) 08.2022

Summary: Open Questions

- Should MRD monitoring include all subclones of AML?
- Is *cKIT* mutation always associated with an unfavorable prognosis in CBF AML?

Global Leukemia Academy

Discussion

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Case 2: Adult AML

Anna Torrent

APTITUDE HEALTH

Global Leukemia Academy EU Meeting
September 23–24, 2022

AML
Clinical Case

Anna Torrent, MD
Clinical Hematology Department
ICO-Hospital Germans Trias i Pujol
Institut de Recerca contra la Leucemia Josep Carreras
Badalona

Case Presentation

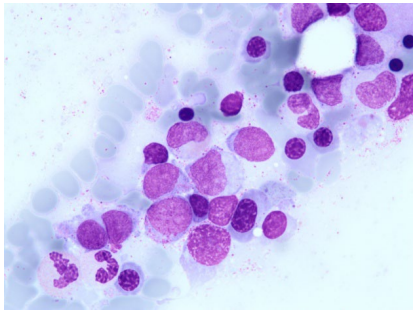
39-yr-old male (Rumania), actor
Gilbert syndrome
06/2020: pancytopenia and asthenia

<u>Peripheral Blood</u>

WBC 2.1x10^9/L (N 1.3 × 10^9/L)
Hb 12.4 g/dL, Volume 99.4 fL
Plat 138 × 10^9/L
Dacrocytes, 25% erythroblast
No blast

<u>Bone Marrow Biopsy</u>

>10% dysplasia in all cell lines
2% blasts (Auer Rods)
Normal karyotype
NGS: WT1 VAF 36.76%
No fibrosis



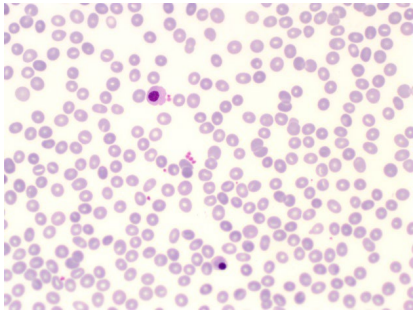
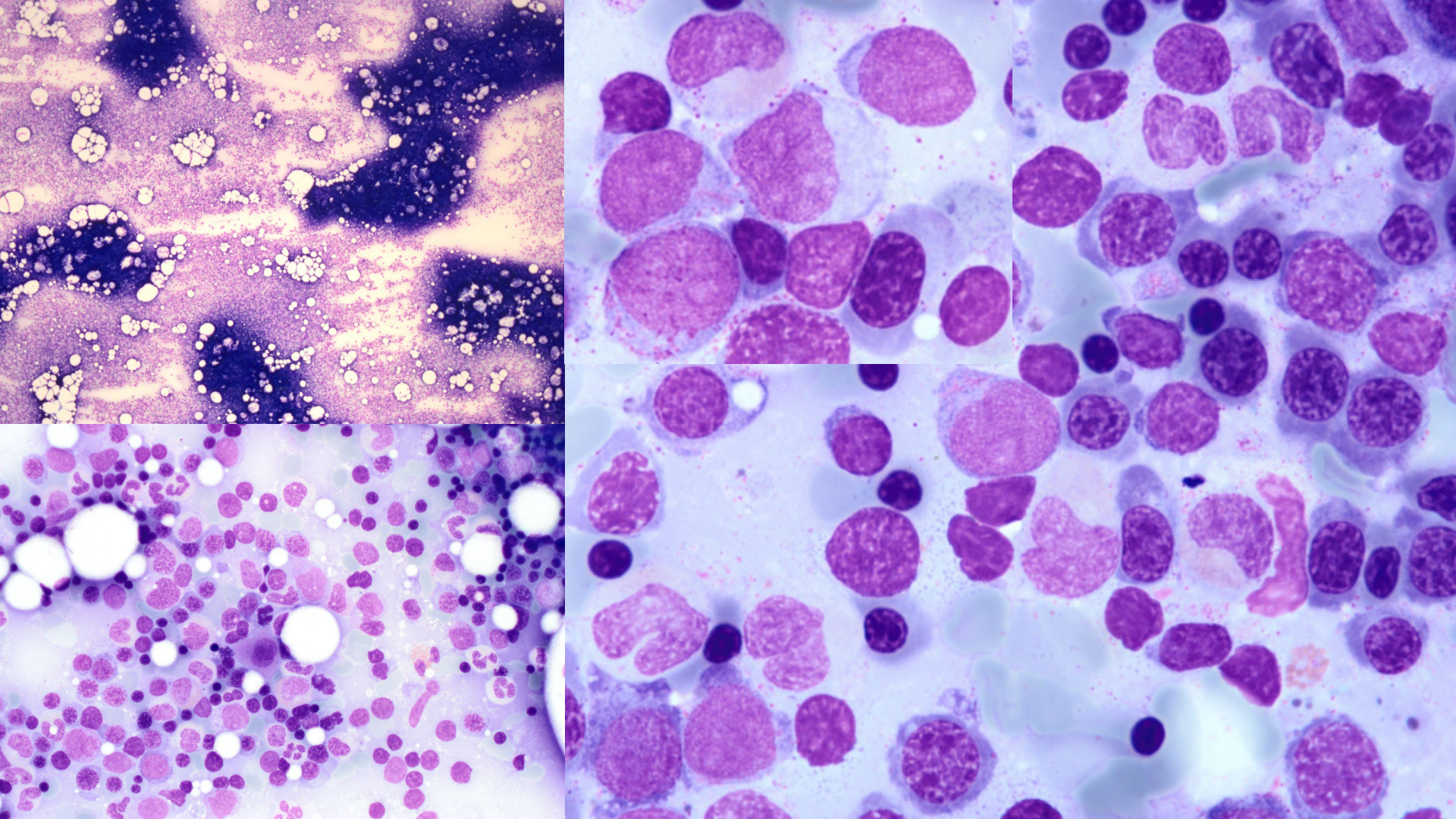


Table 1: 2016 WHO Criteria of classifications of myelodysplastic syndromes

Type	Dysplastic lineages	Cytopenias[1]	Ring sideroblasts in erythroid elements of BM	Blasts	Cytogenetics
MDS-EB					
MDS-EB-1	0-3	1-3	None or any	PB 2~4% or BM 5~9%, no Auer rods	Any
MDS-EB-2	0-3	1-3	None or any	PB 5~19% or BM 10%~19% or Auer	Any
MDS-MLD	2 or 3	1-3	RS<15% (or<5%[2])	PB <1% BM <5% No Auer rods	Any, unless fulfills criteria for isolated del(5q)

MDS-EB-2

IPSS-R 2.5 (low risk), WPSS 3 (high risk)



Question 1

Which is the best treatment option?

1. Azacitidine
2. Clinical trial
3. Allogeneic bone marrow transplantation
4. Azacitidine + SCT
5. Watch and wait

Case Presentation

10/2020 Asthenia

Analytics: WBC 8.01x10e9/L, 59% myeloid blasts, Hb 78 g/L, plat 45 × 10^9/L. Dacrocytes, dysplastic neutrophils, 61% erythroblasts

LDH 678 U/L (N 135-248 U/L).

Bone Marrow

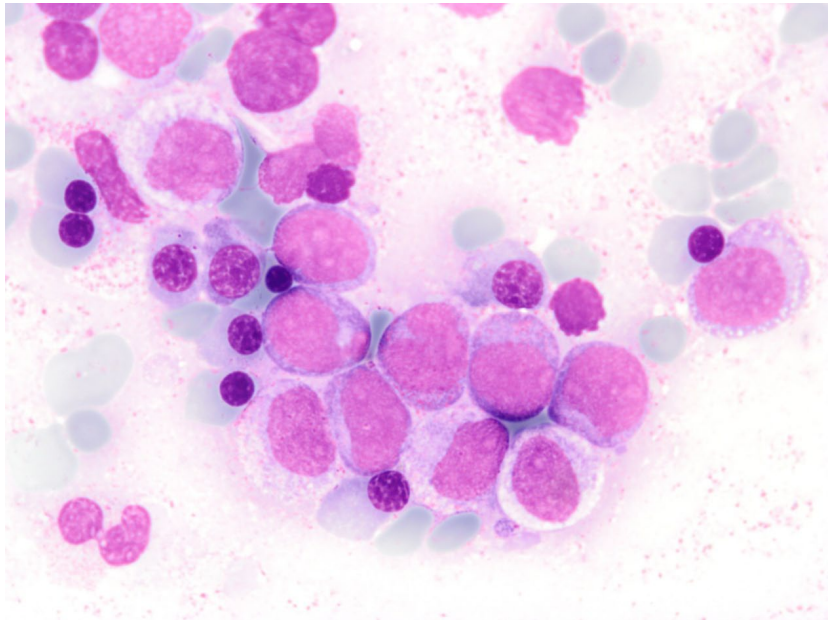
>10% dysplasia in all cell lines

59% blasts (no Auer rods), CD34+

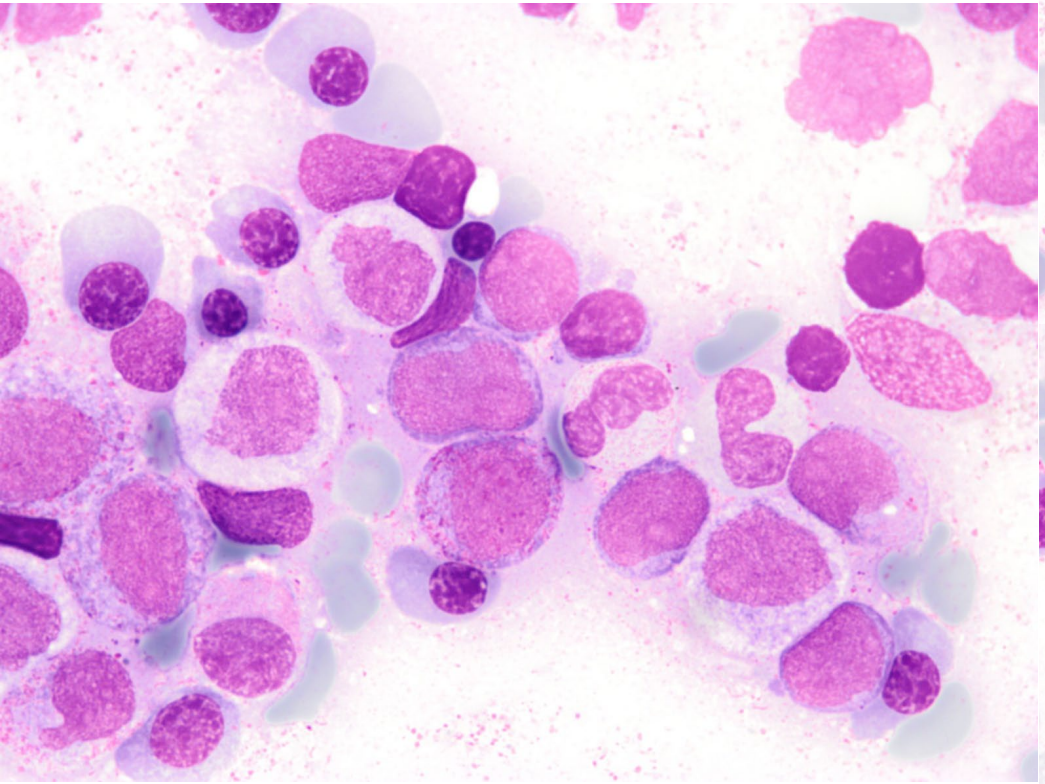
47,XY,+8[11]/46,XY[9]

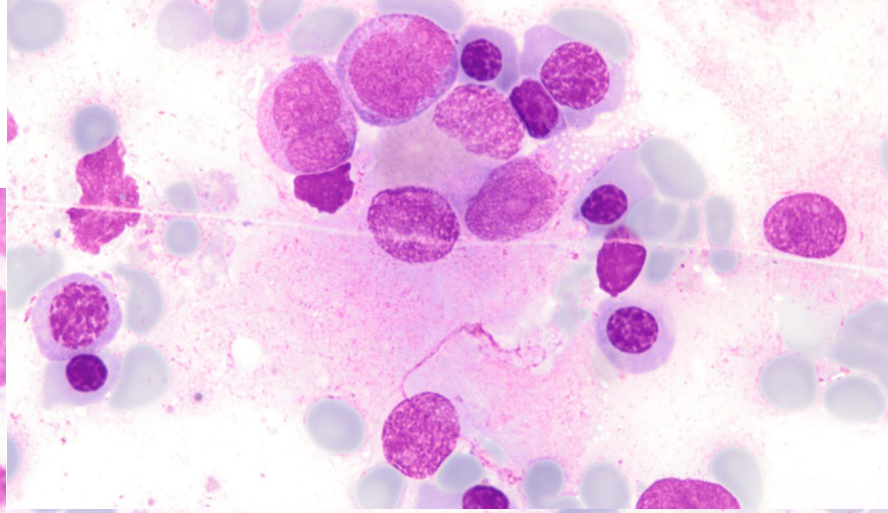
FLT3-ITD ratio >0.5

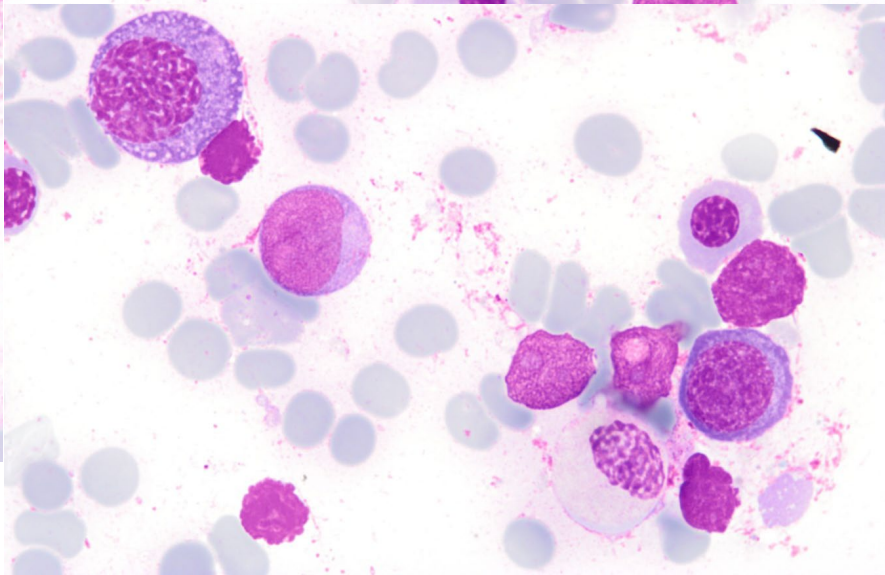
NGS: *FLT3-ITD* (50%), *ZRSR2* (VAF 10%), *WT1* (VAF 53%)



AML with myelodysplasia-related changes







ITD-FLT3 AML

- 30% of newly diagnosed AML carry a genetic modification in the *FLT3* gene:
  - 23% *ITD-FLT3*: kinase autoinhibition by internal tandem duplication → Poor prognosis, higher risk of treatment failure with high relapse risk (Ratio >0.5)
  - 7% *TKD-FLT3*: activation of *FLT3* by tyrosine kinase domain → Prognostic impact debated

Agent	Type	Dose	Target
Sorafenib	First generation, type I	400 mg BID	FLT3-ITD, RAF, VEGFR1/2/3, PDGFRβ, KIT, RET
Midostaurin	First generation, type I	50 mg BID	FLT3-ITD, FLT3-TKD, PKC, SYK, FLK-1, AKT, PKA, KIT, FGR, SRC, PDGFRα/β, VEGFR1/2
Quizartinib	Second generation, type II	60 mg once a day	FLT3-ITD, KIT, PDGFR
Gilteritinib	Second generation, type I	120 mg once a day	FLT3-ITD, FLT3-TKD, LTK, ALK, AXL
Crenolanib	Second generation, type I	100 mg TID	FLT3-ITD, FLT3-TKD, PDGFRβ

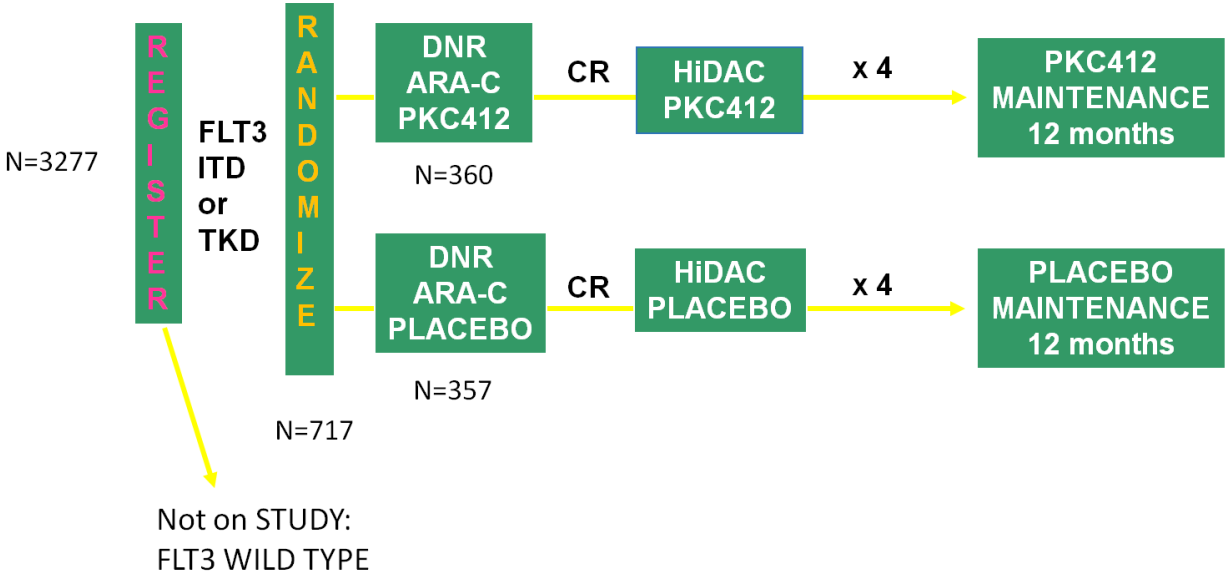
First generation FLT3i:
sorafenib, midostaurin, lestaurtinib
<efficacy, >off-target effects

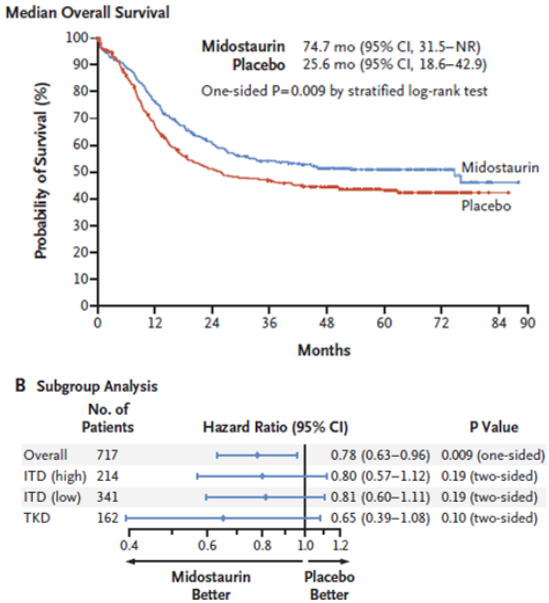
Second generation FLT3i:
gilteritinib, quizartinib, crenolanib
>efficacy, <off-target effects

Loschi M, et al. *Int J Mol Sci.* 2021;22:5873; Daver N, et al. *Leukemia*. 2019;33:299-312.

ITD-FLT3 AML

RATIFY Study: phase III, randomized, double-blind, placebo-controlled trial

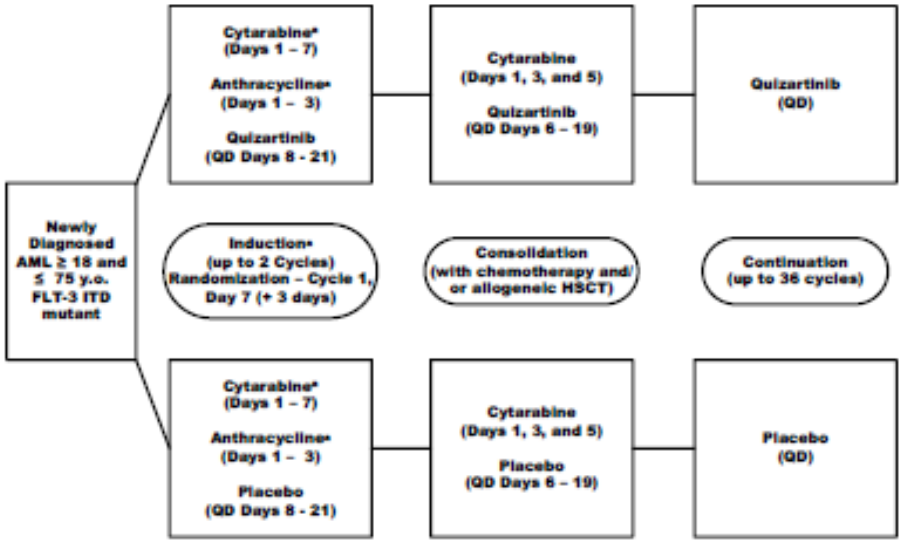


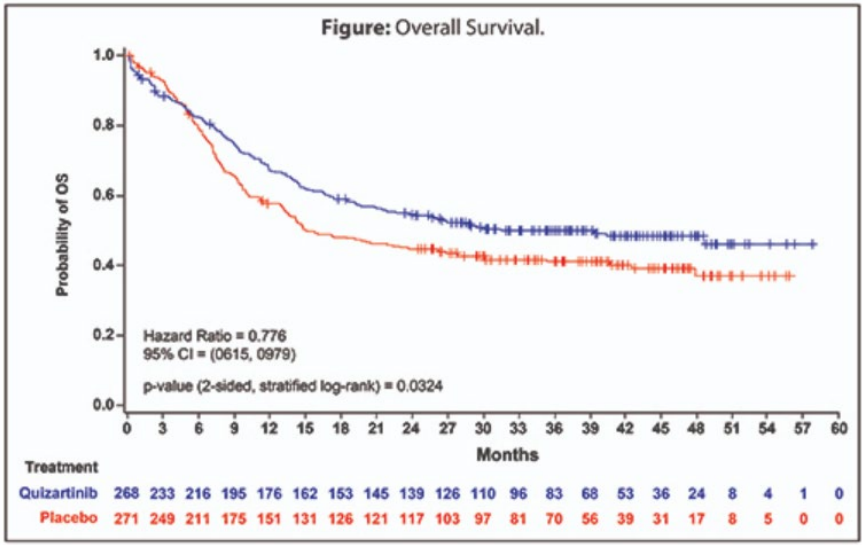


Stone RM, et al. *N Engl J Med*. 2017;377:454-64.

ITD-FLT3 AML

QuANTUM-FIRST Study: phase III, randomized, double-blind, placebo-controlled trial





Erba H, et al. EHA 2022. Abstract S100.

Treatment of *FLT3*-AML

Idarubicin 12 mg/m2/d iv (d 1–3)
Cytarabine 200 mg/m2/d iv (d 1–7)
Midostaurin 50 mg/12h po (d 8–22)

Complications

- Febrile neutropenia with no focus: meropenem, vancomycin and amphotericin.
- Herpetic stomatitis

Partial Response
(22% blasts)

CT FLAG-QUIDA:
Idarubicin 10 mg/m2/d iv (d2–4)
Fludarabine 30 mg/m2/d iv (d2–5)
Cytarabine 2000 mg/m2/d (d2–5)
Quizartinib 60 mg/d (d6–20)

Complications

- Febrile neutropenia due to anal fissure: meropenem
- Herpetic stomatitis

Non-Response
(20% blasts)

Gilteritinib 120 mg/d po (d1–28) × 2 cycles

No complications

Complete Response

Case Continuation

04/03/2021 Haploidentical SCT (5/10)

- Conditioning: Thiotepa, fludarabine, and busulfan
- Prophylaxis GVHD: cyclophosphamide post-SCT and tacrolimus
- 5×10^6 CD34/kg

<u>Complications</u>

- *E.coli* bacteriemia due to anal fissure
- Acute GVHD: skin grade III → glucocorticoids 1 mg/kg/12h po
- Reactivation of CMV: pre-emptive treatment with valganciclovir

CR, negative MRD, Normal NGS and 100% donor chimerism.

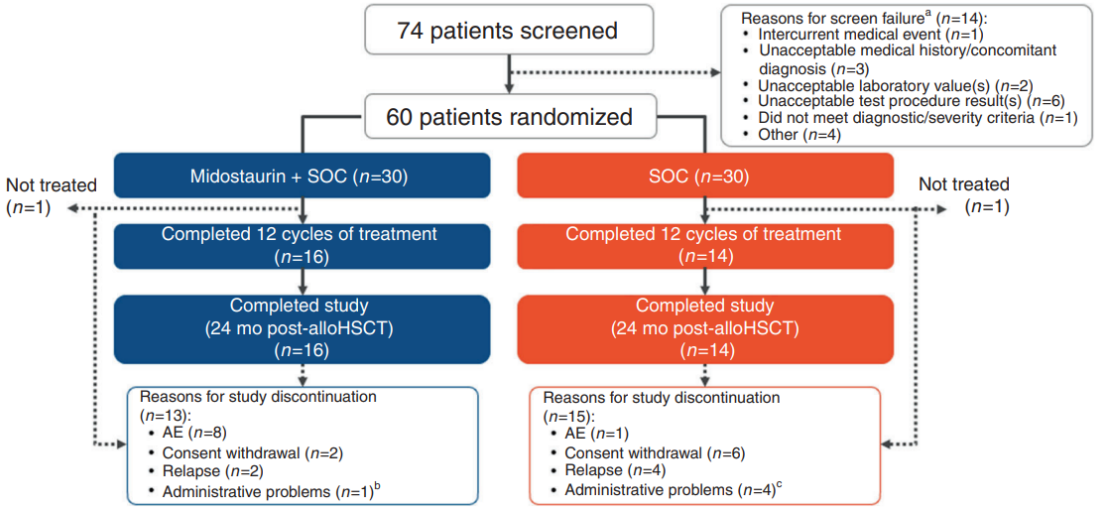
Question 2

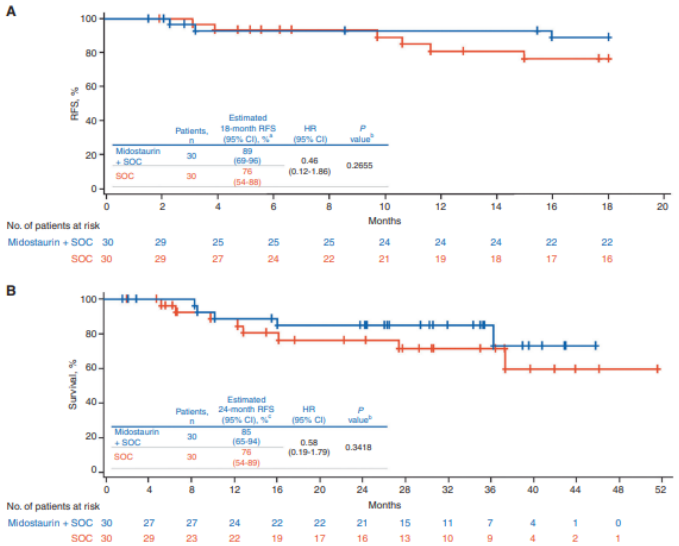
What is next to prevent relapse?

1. Prophylactic DLI
2. Maintenance with midostaurin
3. Watch and wait
4. Prophylactic DLI + FLT3i
5. Maintenance with sorafenib

Maintenance Therapy

RADIUS Study: phase II, randomized, open-label trial SOC vs **midostaurin** *FLT3-ITD* AML

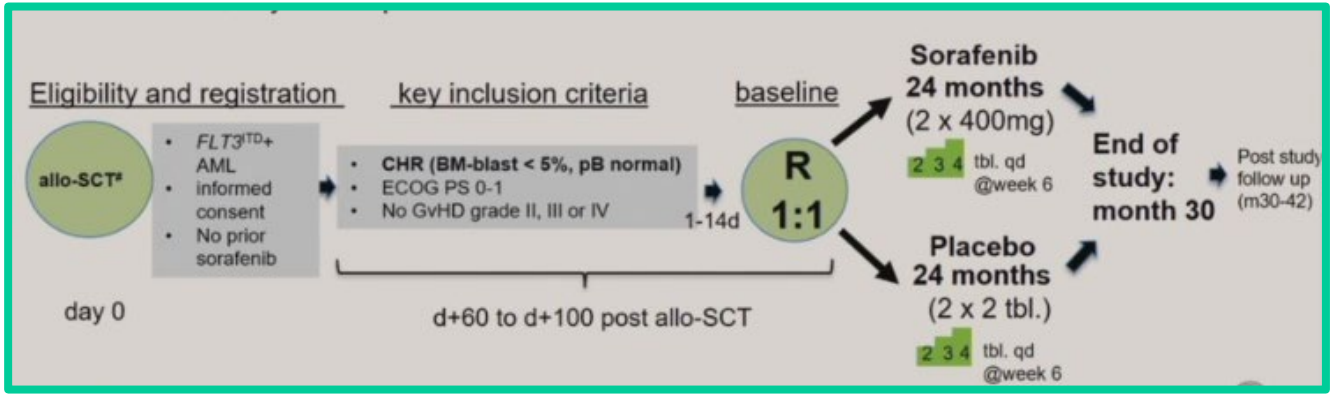


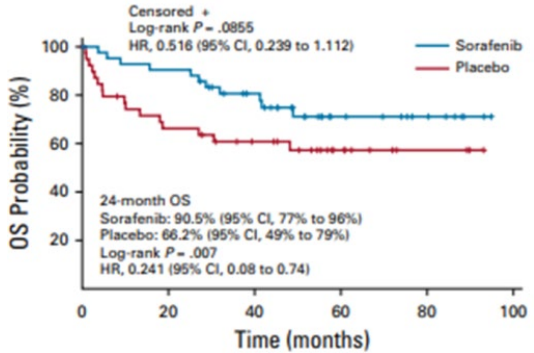


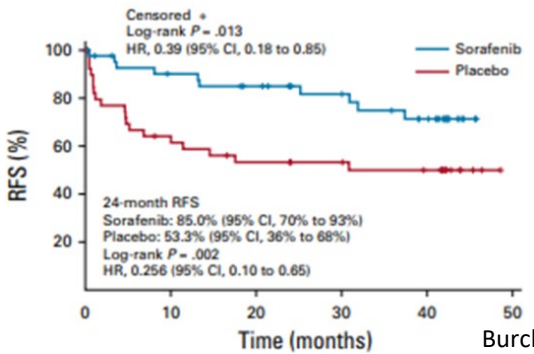
Maziarz RT, et al. *Bone Marrow Transplant.* 2021;56:1180-1189.

Maintenance Therapy

SORMAIN Study: phase II, randomized, double-blind trial **sorafenib** vs placebo



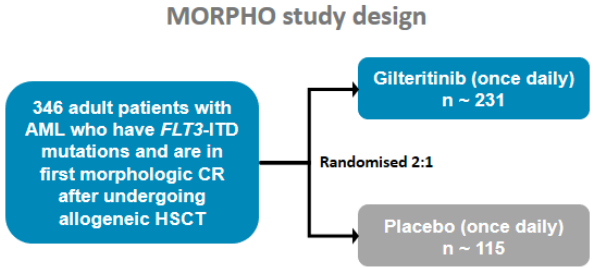




Burchert A, et al. *J Clin Oncol.* 2020;38:2993-3002.

Maintenance Therapy: Ongoing Trials

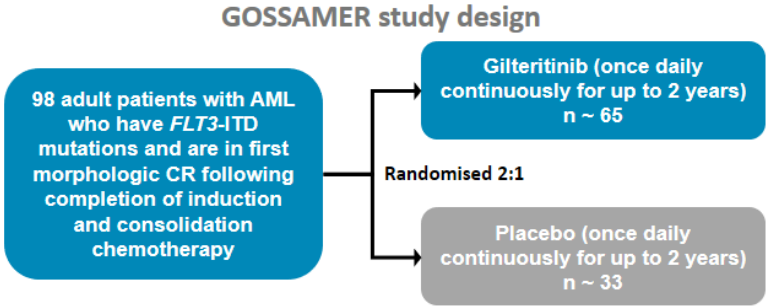
MORPHO Study: phase III, randomized, double-blind trial **gilteritinib** vs placebo in CR1 after SCT.



Primary endpoint:
- Relapse-free survival (RFS)

Secondary endpoints:
- OS
- Safety and tolerability
- Non-relapse mortality
- EFS
- Cumulative incidence of acute graft-versus-host disease (GVHD)
- MRD
- Incidence of severity of infection

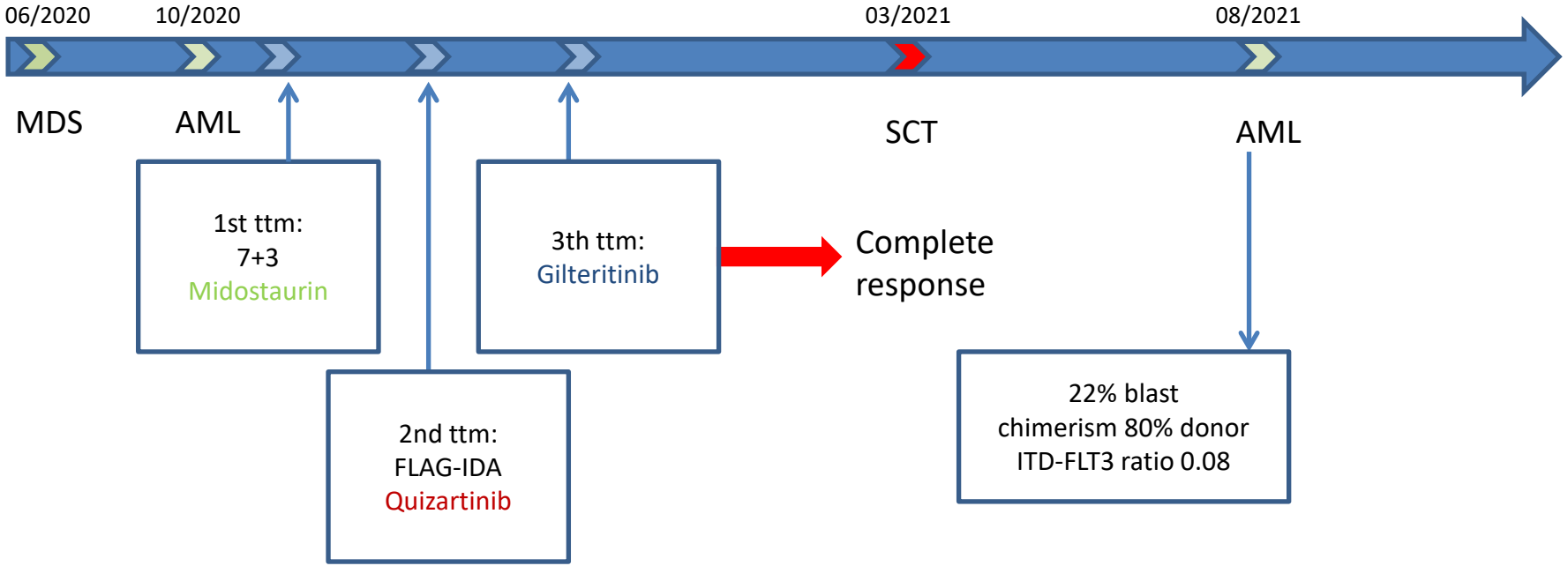
GOSSAMER Study: phase II/III. Maintenance with **gilteritinib** vs placebo (CR1 after HDAC)



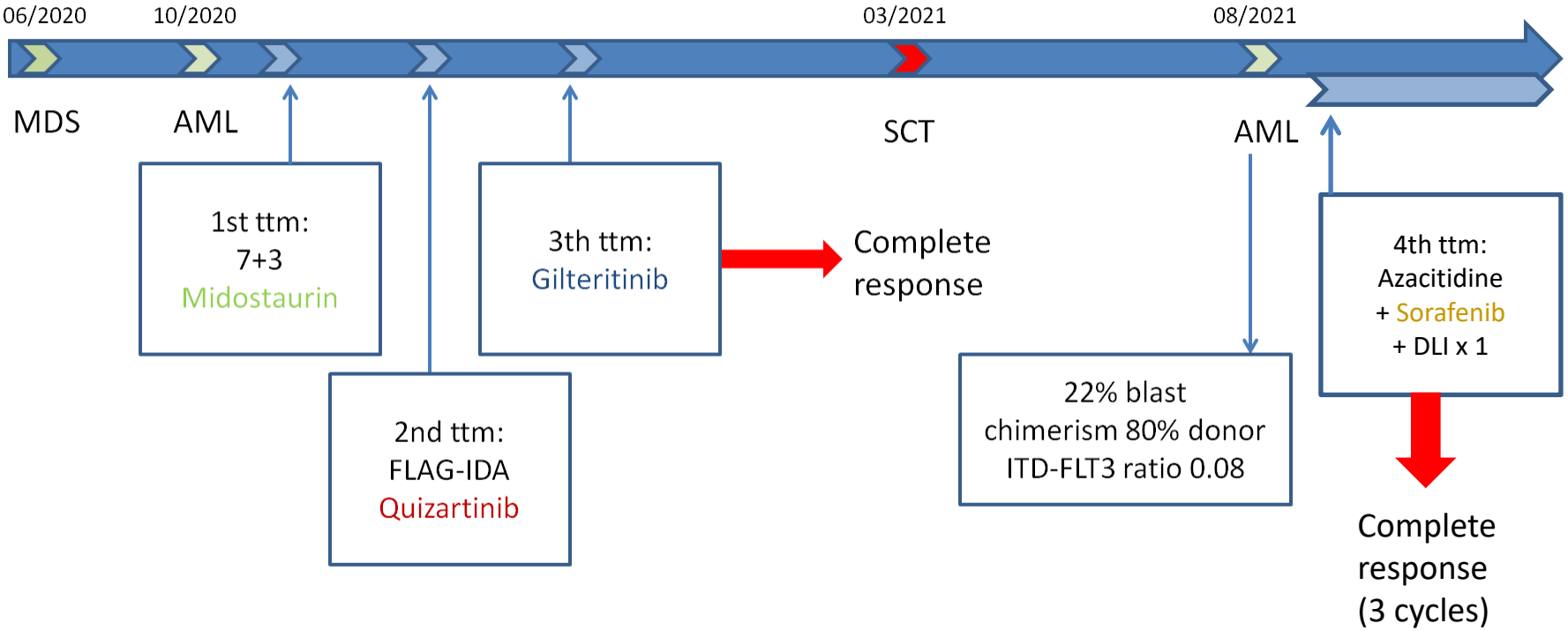
Primary endpoint:
- RFS

Key secondary endpoints:
- OS
- EFS
- MRD
- Safety

Case continuation



Case continuation

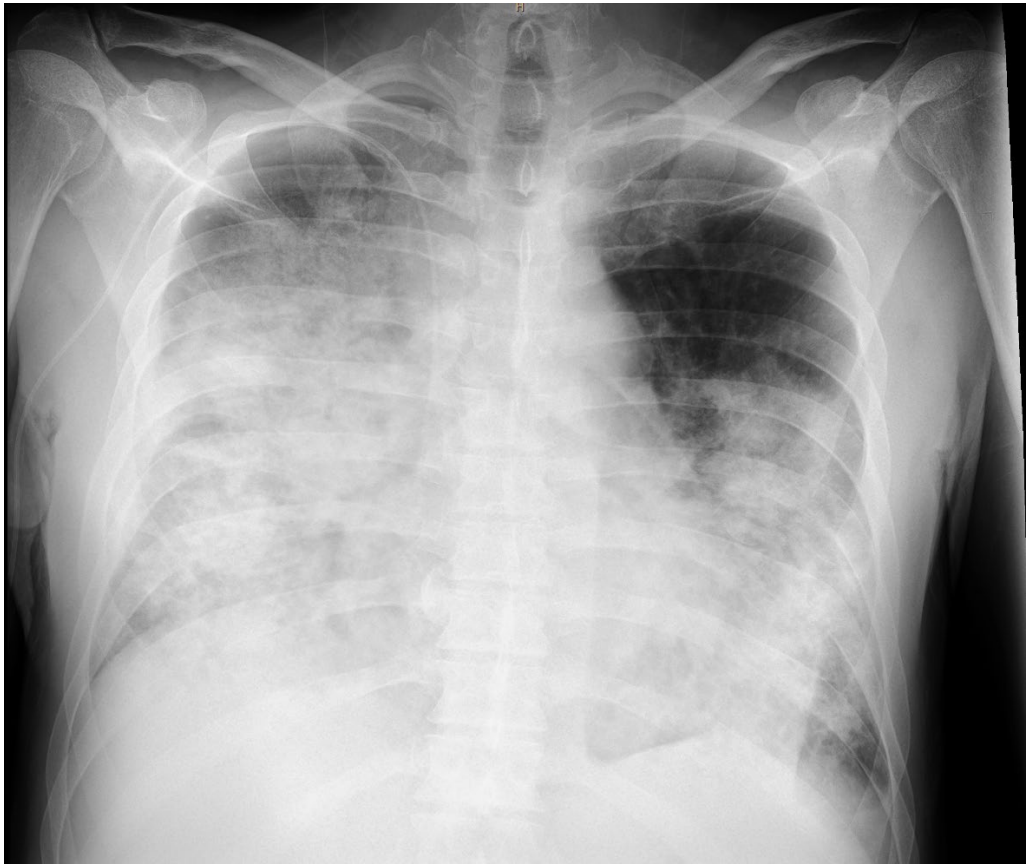


Question 3

Do you think the patient is cured? What's next?

1. Of course
2. Probably no. Watch and wait, second SCT
3. Definitely no. Second SCT after 3–6 cycles of AZA
4. Probably no. AZA × 6 and maintenance with sorafenib
5. No. Palliative care

Case Continuation



Parainfluenza virus type 3

Conclusions

- *FLT3-ITD* AML has poor prognosis, higher risk of treatment failure, with high-relapse risk (ratio >0.5)
- In front-line therapy of *FLT3*-mutated AML, a combination of chemotherapy and midostaurin improves OS
- Other TKI (quizartinib and gilteritinib) improve OS in patients with relapsed or refractory FLT3-mutated AML
- Ongoing post-SCT maintenance therapy studies are using FLT3-specific TKI

Thank you

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Discussion

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BREAK

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Optimizing Management of Relapsed/Refractory AML

Naval Daver

APTITUDE HEALTH

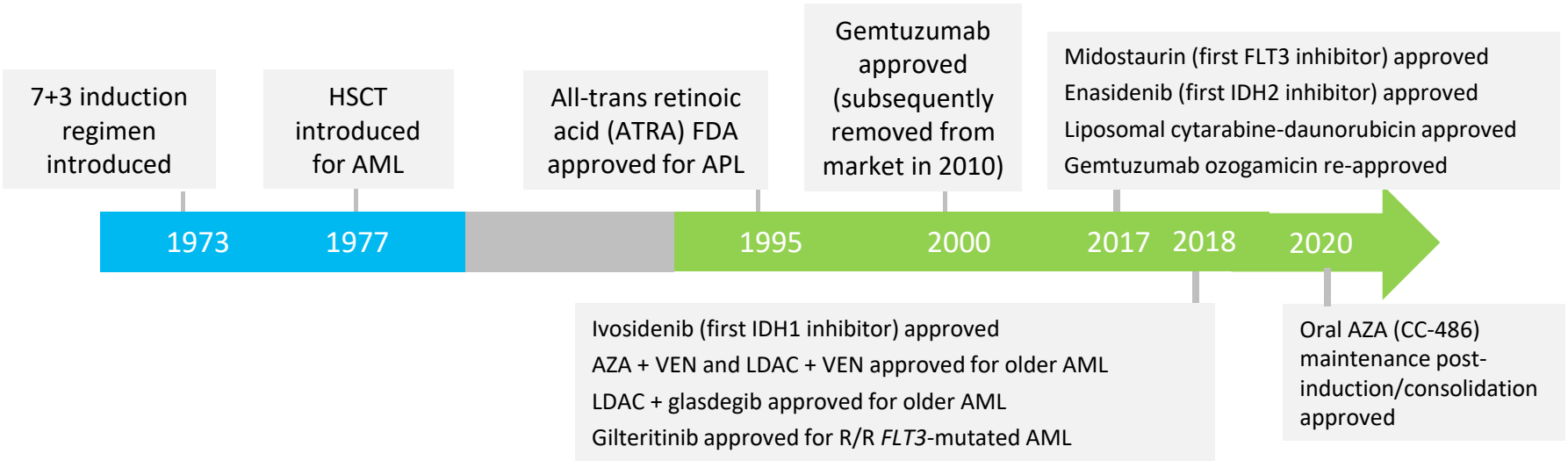
Optimizing Management of Relapsed/Refractory AML

GLA
SEPT 2022

Naval Daver, MD
Director, Leukemia Research Alliance Program,
Associate Professor
Department of Leukemia
MD Anderson Cancer Center

Treatment of AML (Accelerated Progress 2017–2020): History

Since its introduction in the early 1970s, 7+3 therapy (cytarabine for 7 days + anthracycline for 3 days) has been the standard of care for AML



Year	1975	1980	1990	1995	2000	2005	2009	2013	2022
5-year survival	6.3%	6.8%	11.4%	17.3%	16.8%	25.7%	28.1%	27%	??

AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; FDA, United States Food & Drug Administration; HSCT, hematopoietic stem cell transplantation; R/R, relapsed/refractory.

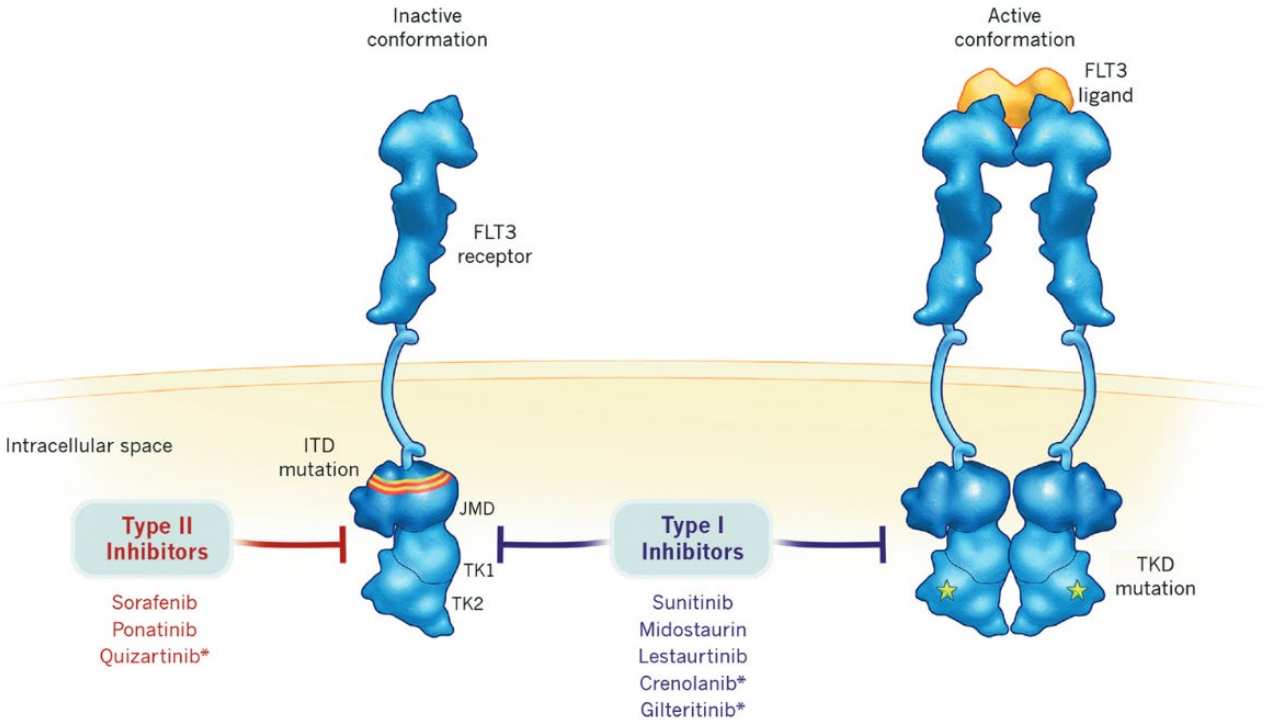
Emerging Molecular Therapies in AML

- *FLT3-ITD* mutations: Add FLT3 inhibitor (gilteritinib, midostaurin, sorafenib), consider allo HSCT and post-HSCT FLT3i
- *IDH1/2* mutations: Add IDH inhibitor – enasidenib (*IDH2)* or ivosidenib (*IDH1*)
- *NPM1* mutation in diploid CG: cytarabine sensitivity
- *TP53* mutation: Consider decitabine 10 days ± others (GO, venetoclax); refer to allo HSCT; role of anti-CD47 (magrolimab)
- MLL-AML; t(11q23;---): Menin inhibitors

FLT3 inhibitors in R/R AML

FLT3-Mutated AML – *Types of FLT3 Inhibitors*

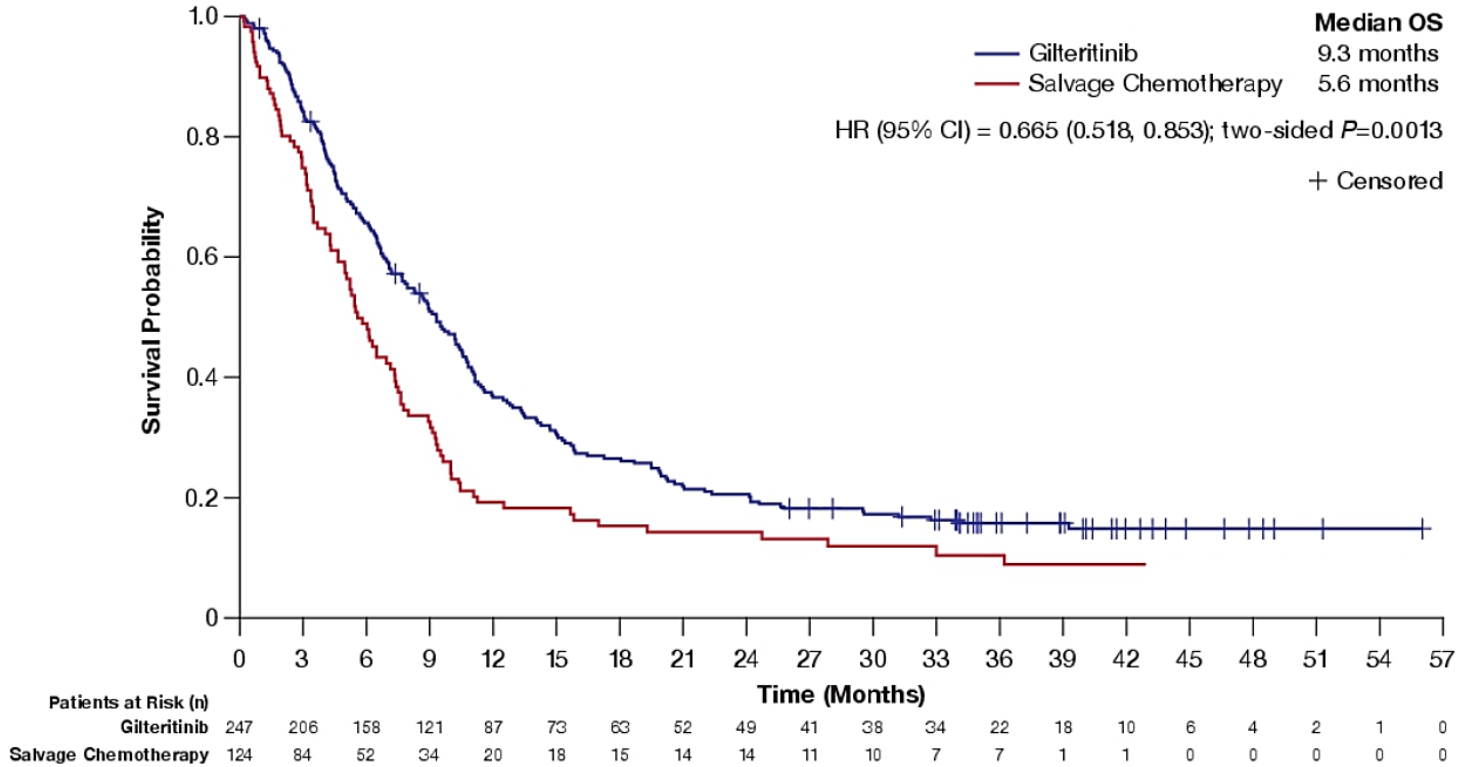
- Type I: Bind receptor "active" conformation near ATP pocket or activation loop; ITD and TKD
- Type II: Bind receptor "inactive" conformation near ATP pocket; ITD only



*Second-generation FLT3 inhibitors.

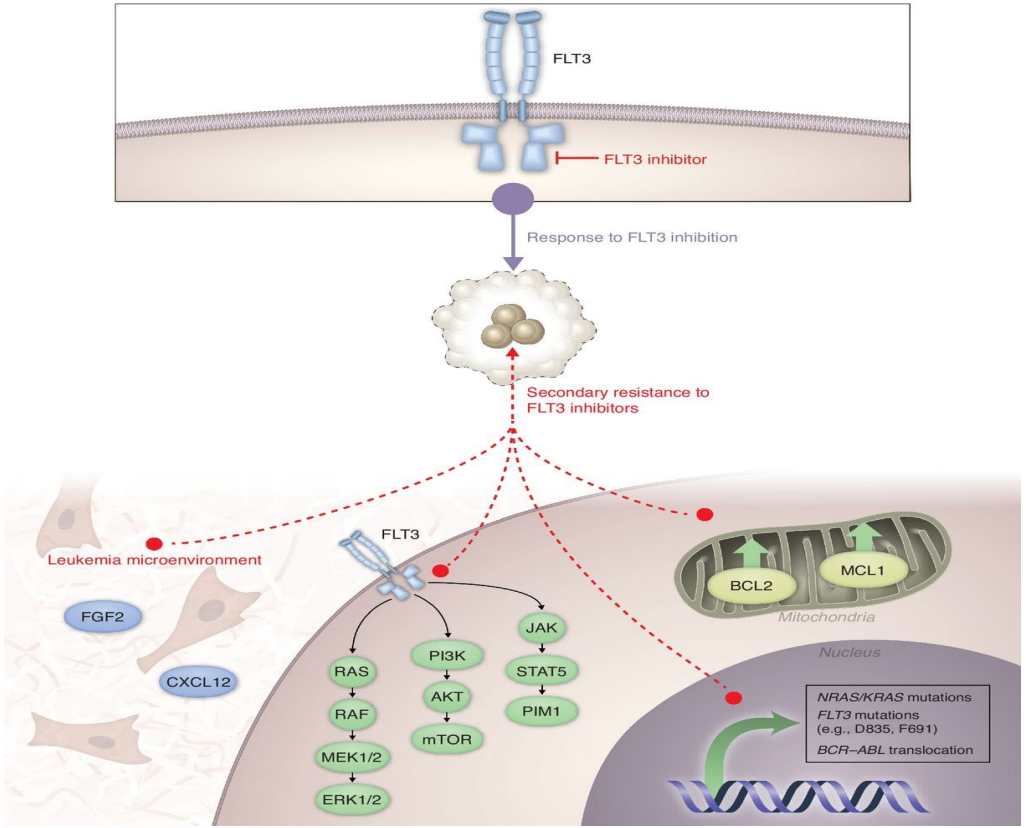
Daver N et al. *Leukemia.* 2019;33:299-312.

ADMIRAL: Longer Follow-Up Confirms OS Benefit With Gilteritinib in R/R *FLT3* Mutant AML



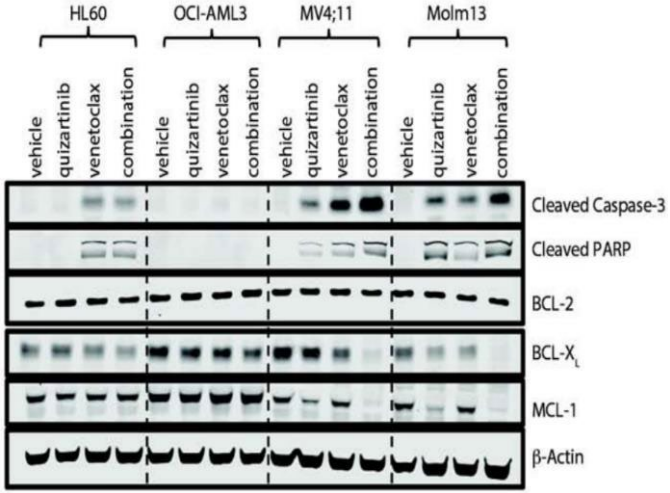
Perl AE, et al. *Blood.* 2022;139:3366-3375.

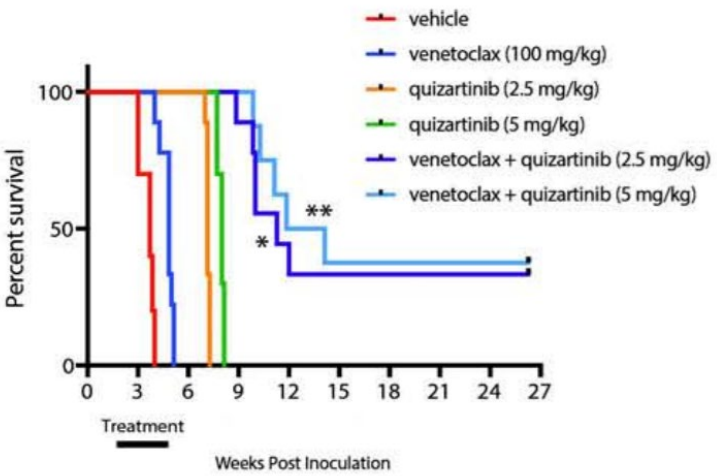
Mechanisms of Resistance to FLT3 Inhibitors

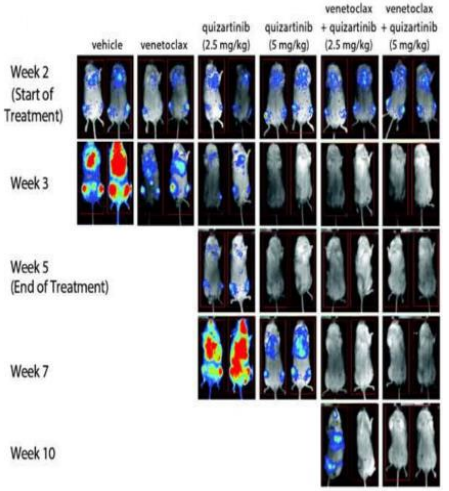


Short N, et al. *Cancer Discov*. 2020;10:506-525.

Venetoclax Combines Synergistically With Quizartinib[1,2]





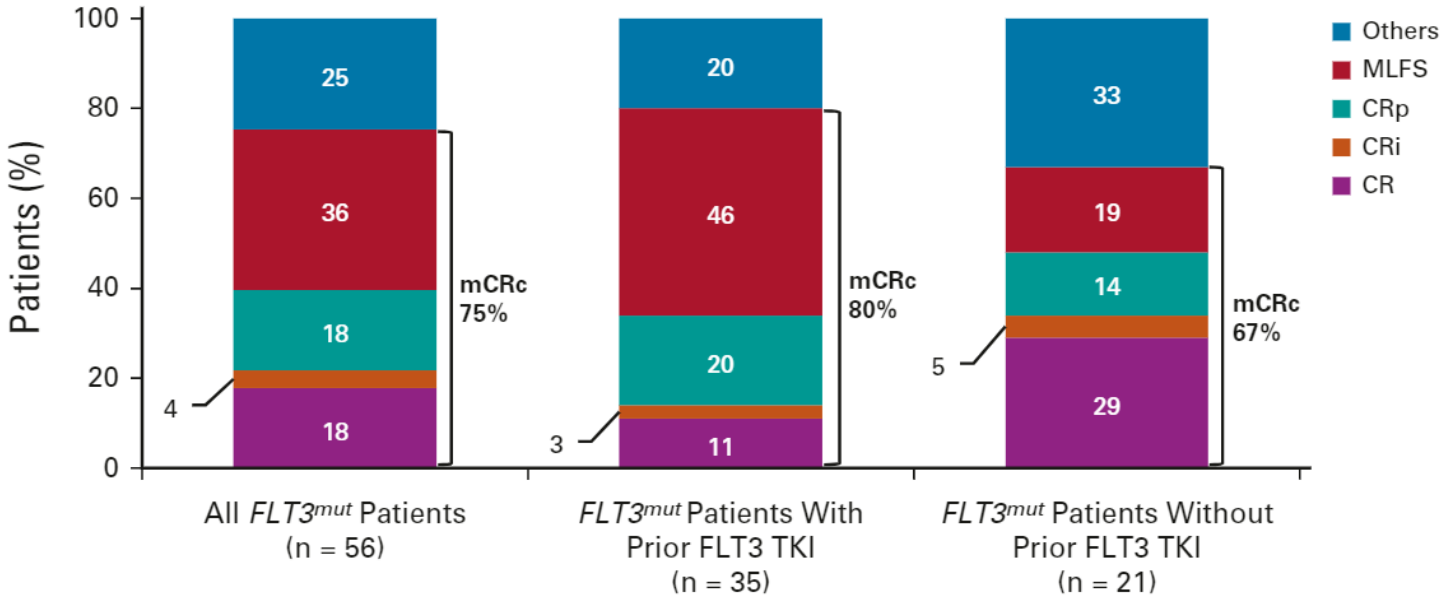


Cell lines were treated with combination – ↓ MCL-1, ↓ BCL-X_L

Venetoclax combined with quizartinib prolonged survival and reduced tumor burden in FLT3-ITD+ xenograft models

1. Yilmaz M, et al. *Blood.* 2021;138: Abstract 370; 2. Singh Mali R, et al. *Haematologica.* 2021;106:1034-1046.

VEN + GILT – *Summary of Best Responses*



The mCRc rate in this study was **75%**,[1] whereas the CRc rate in the ADMIRAL phase III study for single-agent GILT was **54.3%** (using the same response parameters)[2]

mCRc, modified composite complete remission; MLFS, morphologic leukemia-free state.

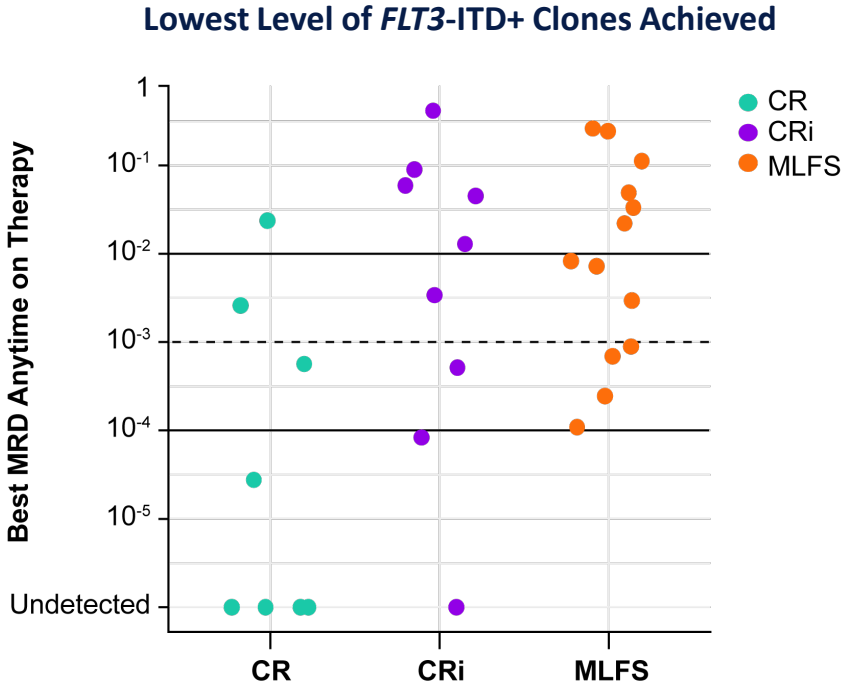
1. Daver N, et al. *J Clin Oncol.* 2022:JCO2200602; 2. Perl AE, et al. *New Engl J Med.* 2019;381:1728-1740.

VEN + GILT Demonstrated Deep Reductions in *FLT3* Allelic Burden in Patients Achieving mCRc

FLT3-ITD burden, n (%)	$<10^{-2}$ (1%)	$<10^{-3}$	$<10^{-4}$
Cycle 1 Day 28	9 (30.0)	3 (10)	0
Any time on therapy	18 (60.0)*	13 (43.3)	7 (23.3)

30/34 *FLT3*-ITD mCRc patients were evaluable for longitudinal reduction in *FLT3*-ITD using an assay with sensitivity of 10^{-6}

The molecular best response ($<10^{-2}$) of VEN + GILT was **60.0%** in *FLT3*-ITD-mutated AML achieving mCRc,[1] whereas the molecular best response ($<10^{-2}$) for GILT alone in a subset analysis from CHRYSALIS was **25%**[2]

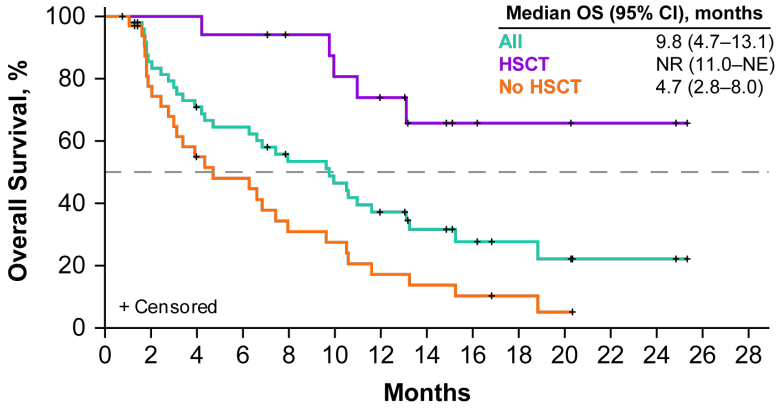


GILT, gilteritinib; mCRc, modified composite complete remission; RP2D, recommended Phase 2 dose; Ven, venetoclax.

1. Daver N, et al. *Blood.* 2021;138: Abstract 691; 2. Levis MJ, et al. *Blood Adv.* 2018;2:825-831.

OS by Transplant or Response Status

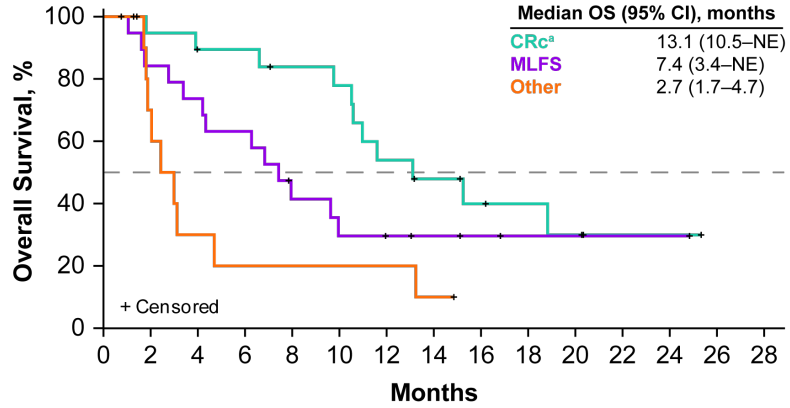
OS by Transplant Status (*FLT3*$^{mut+}$ Patients)



Patients at Risk

All	51	41	33	30	23	20	15	11	7	5	4	2	2	0
HSCT	17	17	17	16	14	12	10	7	4	3	3	2	2	0
No HSCT	34	24	16	14	9	8	5	4	3	2	1	0		

OS by Best Response Status (*FLT3*$^{mut+}$ Patients)



Patients at Risk

CRc	19	18	16	16	14	13	9	7	5	4	3	1	1	0
MLFS	19	16	14	12	7	5	4	3	2	1	1	1	1	0
Other	13	7	3	2	2	2	2	1	0					

- Median duration of follow-up was 15.1 months (range, 0.8 to 25.3)
- Median OS for *FLT3*-ITD patients was 10.0 months (95% CI: 6.6, 13.2)

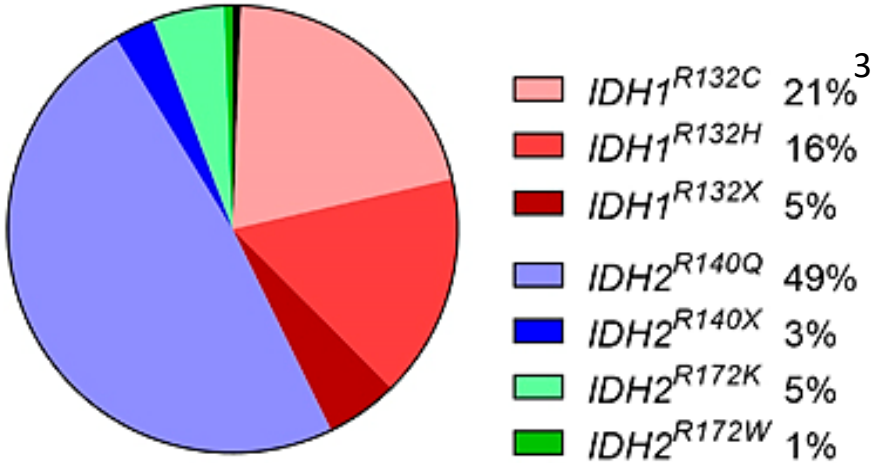
HSCT, hematopoietic stem cell transplantation; ITD, internal tandem duplication; MLFS, morphologic leukemia-free state; NE, not estimable; NR, not reached; OS, overall survival.

Daver N, et al. ASH 2021. Abstract 691.

IDH inhibitors in R/R AML

Characteristics of *IDH*-Mutated AML

- *IDH* mutations occur in ~20% of AML
- *IDH1* in ~8% AML, *IDH2* in ~12% AML
- ↑ prevalence with ↑ patient age
- Hot-spot mutations in enzymatic active site[1]
- ***IDH1*-R132, *IDH2*-R140, or *IDH2*-R172**
- Can be acquired at progression[2]
  - ~10% to 15% of AML from MDS
  - ~20% to 25% of AML from MPN



[3]

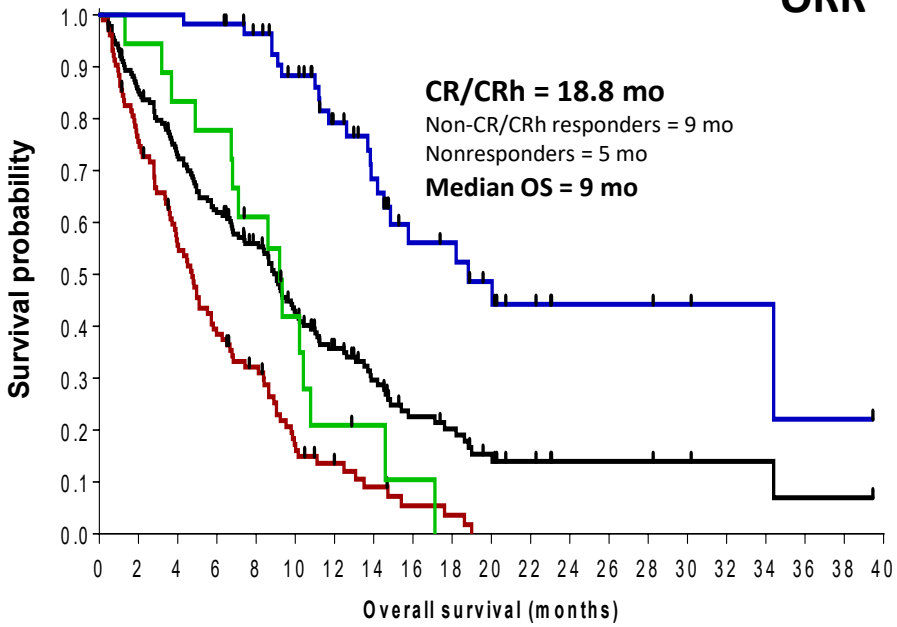
MDS, myelodysplastic syndrome; MPNs, myeloproliferative neoplasms.

1. Dang L, et al. *Trends Mol Med*. 2010;16:387-397; 2. Chou WC, et al. *Leukemia.* 2011;25:246-253; 3. Molenaar RJ, et al. *Leukemia.* 2015;29(11):2134-2142.

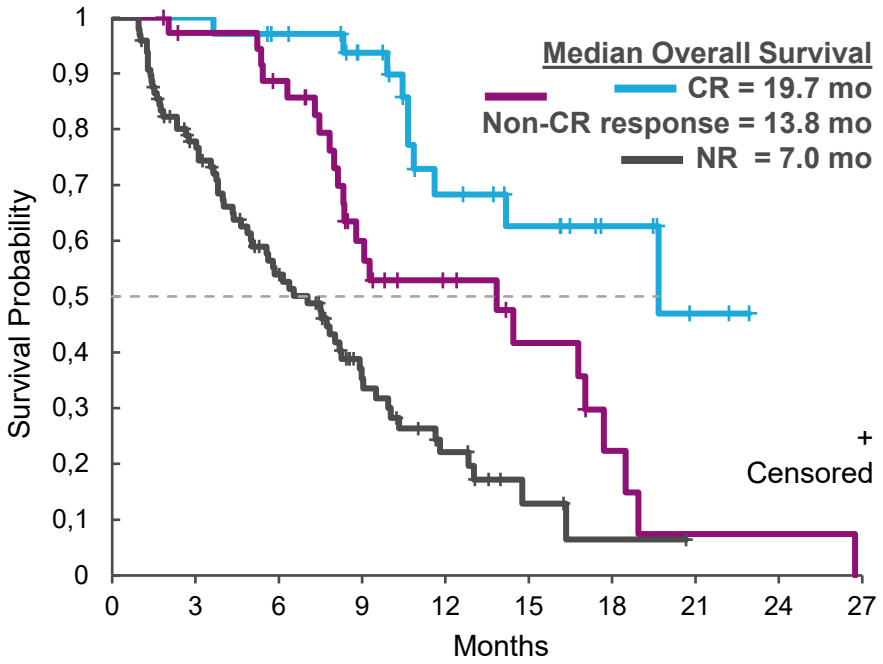
IDH1 or IDH2 Inhibitor Monotherapy[1,2]

CR rate ~20%
CR/CRh rate ~30%
ORR ~40%

Ivosidenib (IDH1 inhibitor)



Enasidenib (IDH2 Inhibitor)



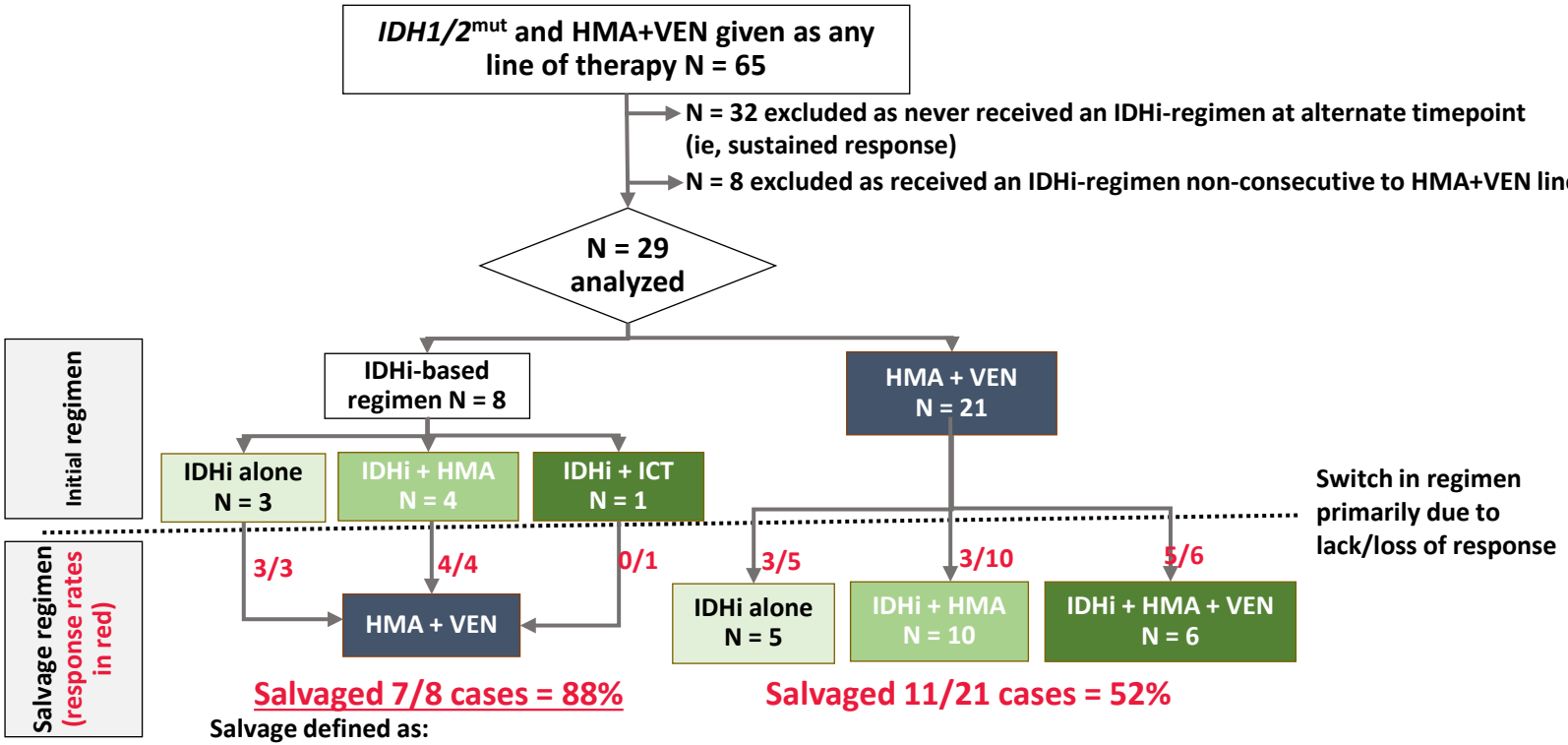
1. DiNardo CD, et al. *N Engl J Med.* 2018;378:2386-2398; 2. Stein EM, et al. *Blood.* 2017;130:722-731.

Practical Considerations With IDH Inhibitors

- Few grade 3 nonhematologic toxicities[1]
  - Those to note include diarrhea, fatigue, and pyrexia[2]
- May take 3 to 4 cycles to respond; late responders noted in studies to date
- Hematologic toxicities are common, particularly during the first cycle of therapy
- Monitor azoles and CYP drug-drug interactions
- Differentiation syndrome: seen during the first 2 cycles[2–4]

1. DiNardo CD, et al. *N Engl J Med.* 2018;378:2386-2398; 2. Roboz G, et al. *J Clin Oncol.* 2019;37(suppl 15):7038; 3. Stein EM, et al. *Blood.* 2017;130:722-731; 4. Fathi AT, et al. *JAMA Oncol.* 2018;4:1106-1110.

Within-Patient Salvage Rates When Switching Between HMA+VEN ←→ IDHi-Based Regimens (MDACC)



Salvage defined as:

a) If given for R/R disease - obtaining (re-obtaining) CR/CRi/MLFS

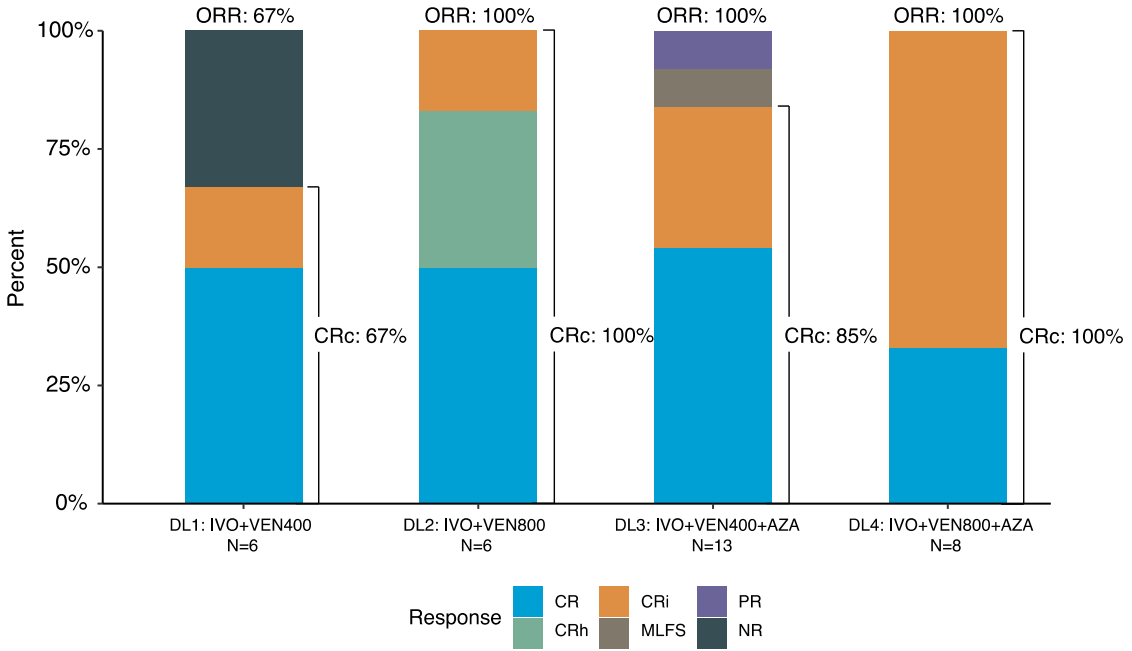
b) If given for new MRD-pos/rising MRD by FC - converting back from MRD-pos to MRD-neg (2 cases)

MRD, minimal residual disease.

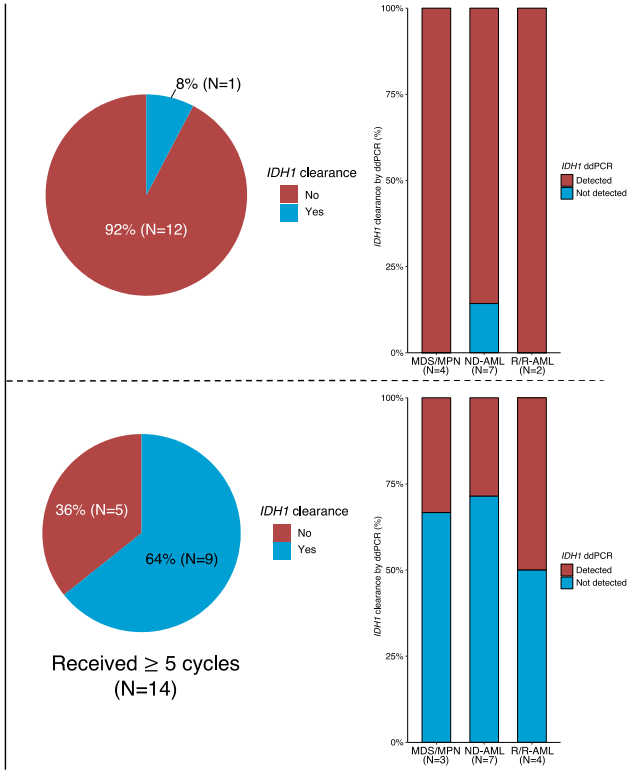
Hammond D, et al. *Blood*. 2020;136:35-36.

IVO + VEN +/- AZA: Response Outcomes

Overall Response by Cohort*



IDH1 Clearance by ddPCR**



*CRc: CR + CRh + CRi
**ddPCR: digital droplet PCR (sensitivity: 0.1% to 0.25%)

Lachowiez CA, et la. *J Clin Oncol.* 2022;40(suppl):7018.

Menin inhibitors in *MLL*r and *NPM1*m R/R AML

Revumenib (SNDX-5613) Is a Potent Selective Protein-Protein Interaction Inhibitor of Menin

Currently being evaluated in the phase I/II AUGMENT-101 study (N = 54)

Median age was 49 years

- 82% (n = 44) of patients had AML
- 65% (n = 35) had *MLL*r leukemia
- 19% (n = 10) had mutated *NPM1* leukemia

Two parallel dose-escalation cohorts

- Arm A: patients not taking strong CYP3A4 inhibitors
- Arm B: patients taking strong CYP3A4 inhibitors
- SYNDX-5613 dosing: orally every 12 hours in continuous 28-day cycles

MTD was 276 mg every 12 hours in arm A and 163 mg every 12 hours in arm B

Best Overall Response	Overall (N = 54), n (%)
CRc (CR + CRh + CRp + CRi/MLFS)	20 (44.4)
CR + CRh	10 (22.2)
CR	7 (15.6)
CRh	3 (6.7)
CRp	3 (6.7)
CRi/MLFS	7 (15.6)

CRh, CR with partial hematologic recovery; MLFS, morphological leukemia-free state; MTD, maximum tolerated dose.
Stein E, et al. *Blood.* 2021;138:699.

Non-molecularly selected approaches to R/R AML

IMGN632 + AZA/VEN Triplet Is Safe and Active in CD123-Positive R/R AML

Phase 1b/2 study designed to determine the safety, tolerability, and activity of IMGN632 combined with AZA and VEN in CD123-positive AML

Results

Efficacy was seen across all cohorts/doses and schedules (N = 29)

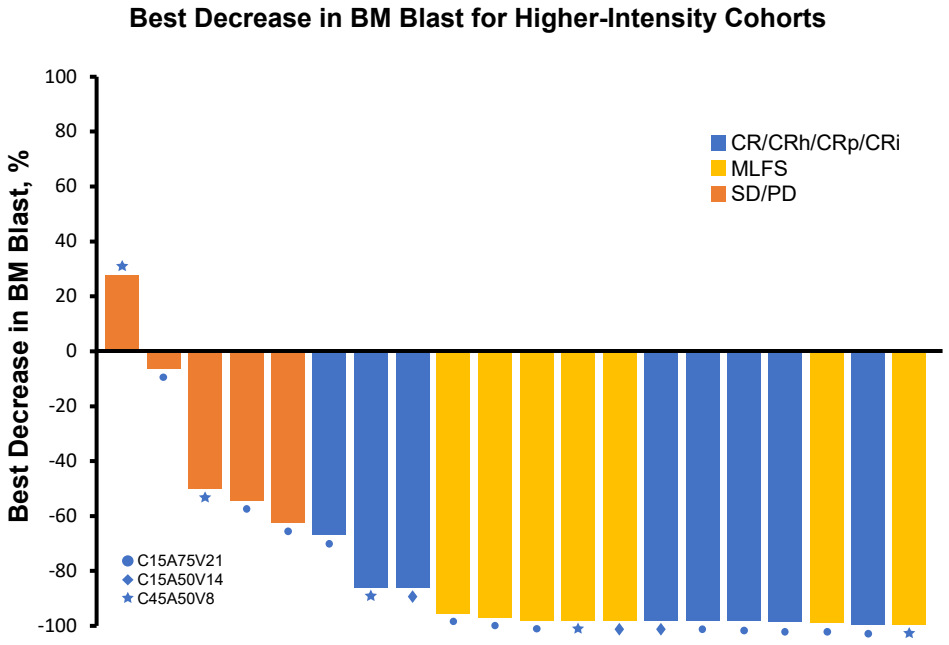
ORR: 55%; cCR rate: 31%

Higher-intensity cohorts (n = 20)

ORR: 75%; cCR rate: 40%

No TLS, VOD, capillary leak, or cytokine release were observed

30-day mortality: 0%

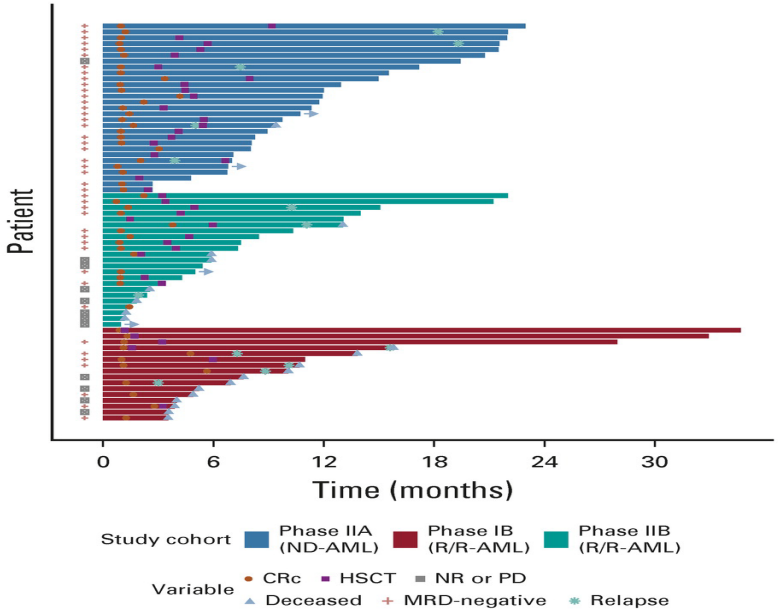


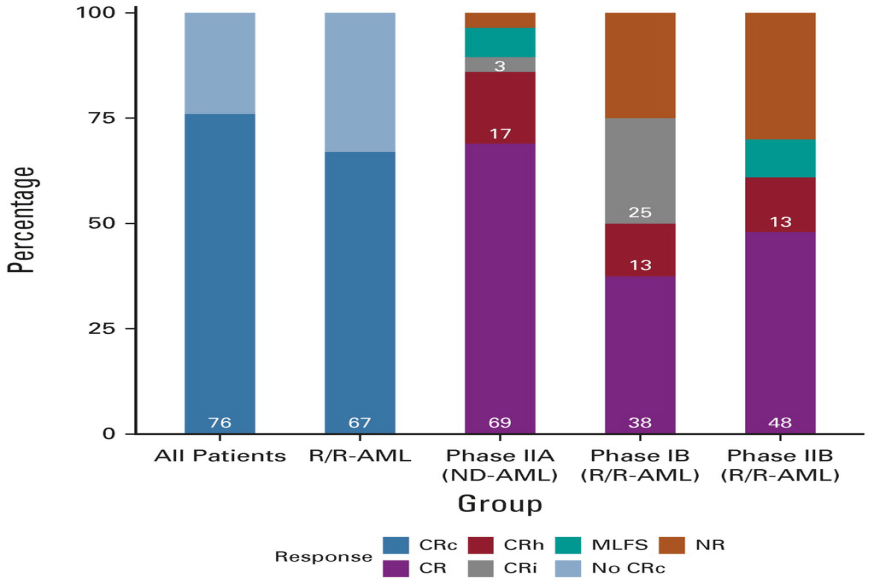
ORR, overall response rate; TLS, tumor lysis syndrome; VOD, veno-occlusive disease.
Daver N, et al. *Blood.* 2021;138:372.

Improving cytotoxic therapy: Back to VEN again?

FLAG-IDA + VEN in AML

- FLAG-IDA + VEN evaluated in R/R AML, then newly diagnosed AML
- 68 patients prescribed: ND AML = 29; R/R AML = 39





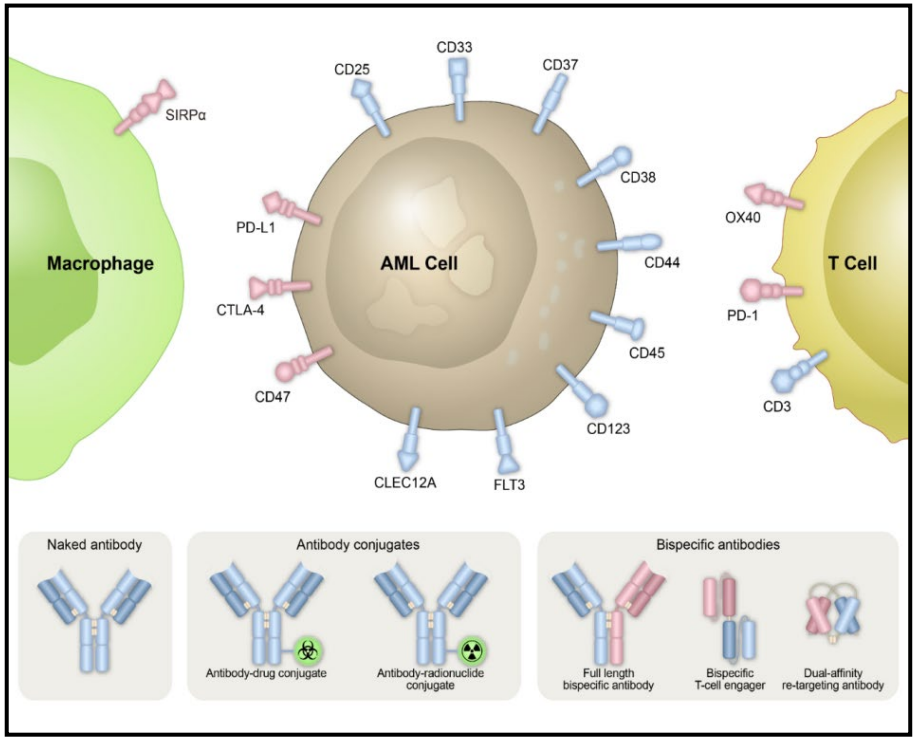
NR, no remission; PD, progressive disease.

DiNardo CD, et al. *J Clin Oncol.* 2021;39:2768-2778.

Immune-based approaches in AML

Immune-Based Approaches in AML May Soon Provide Another Treatment Modality

- **Two major approaches**
  - Antibody–drug conjugates (CD33, CD123, CLL1)
  - Adaptive or innate immune system–harnessing therapies
- **Bispecific antibodies (CD3 × AML antigen, CD47 × CD3, others)**
- **Immune checkpoint-based approaches: T-cell and macrophage checkpoints**
- **CAR T, CAR NK, high-volume hn-NK cells**
- **Vaccines**



CAR, chimeric antigen receptor; NK, natural killer.
Short N, et al. *Cancer Discov*. 2020;10:506-525.

Immune Strategies to Kill AML, Potentially Mutation Agnostic

ADAPTIVE

- Recruiting anti-**CD3** T cells: **BiTEs** linking to CD3 and targeting CD33/123
- **CAR Ts** with modified CD3 killer cells (success in ALL, lymphoma, MM)
- Targets beyond CD33/123 (eg, **CLL1,** IL1RAP, TIM3, CD70)

INNATE (appears to be more resilient and preserved in AML)

- Recruiting **macrophages:** targeting CD47 on AML (magrolimab, lemzoparlimab) or SIRP-alpha on macrophages (Trillium, CC95251, ALX148)
- Recruiting **NK** cells: allo NK-CAR Ts; NK engineered cells (hn, CD38 ko, IL15); repeated infusions

ALL, acute lymphocytic leukemia; BiTE, bispecific T-cell engager; MM, multiple myeloma.
Short N, et al. *Cancer Discov.* 2020;10:506-525.

Anti-CLL1 CARTs in Children With R/R AML

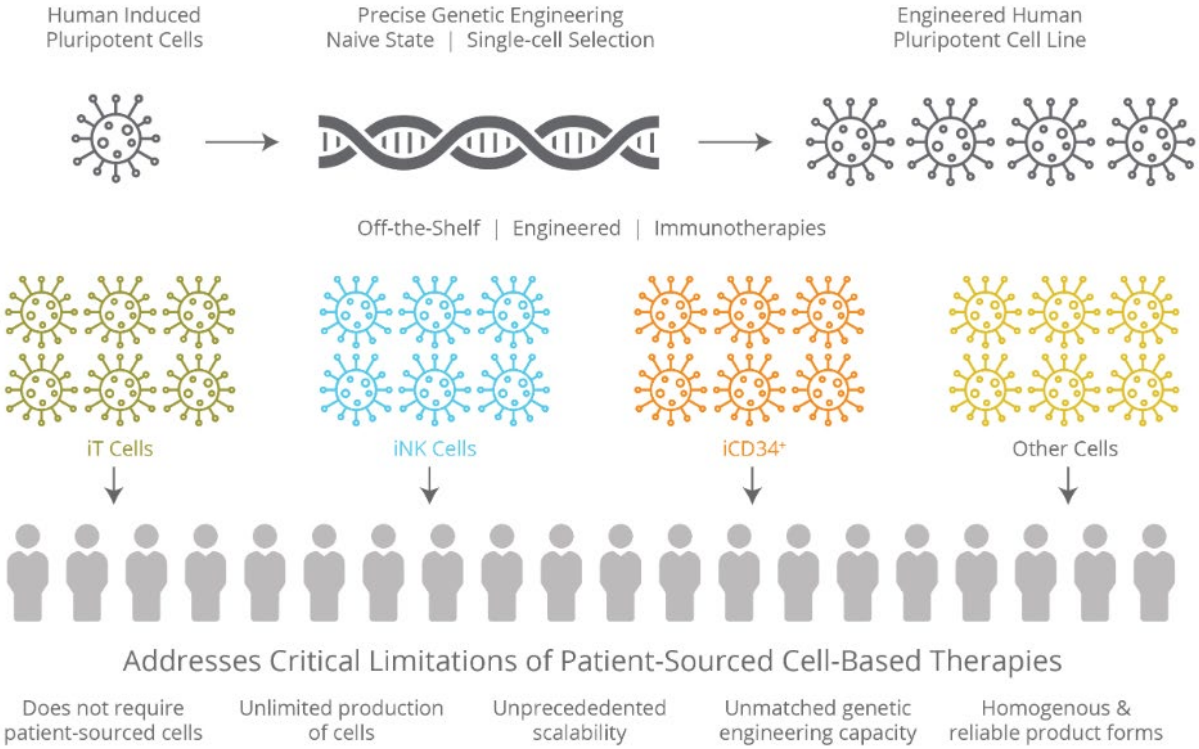
- Second-generation CLL1 CAR T cells 0.3 million/kg to 1 million/kg single dose post lymphodepletion with Flu-CTX
- 11 children with R/R AML treated
- 9 responses = 82%
  - 5 CR MRD-negative
  - 3 CR MRD-positive
  - 1 PR
- 9 of 11 made it to HSCT with durable responses

MRD, minimal residual disease; PR, partial remission.

Zhang H, et al. *J Clin Oncol.* 2021;39(Suppl). Abstract 10000.

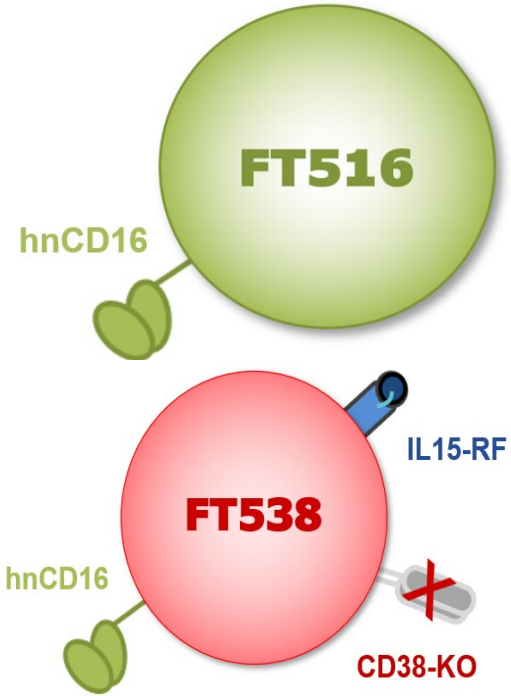
Off-the-Shelf Cell-Based Cancer Immunotherapy

iPSC Product Platform for Mass Production of Universal NK Cell and T-Cell Products



Fate Therapeutics. https://fatetherapeutics.com/about-us/our-cells-of-interest/

FT516/FT538: Monotherapy in Relapsed/Refractory AML



Phase I studies (n = 12 treated)

- 3 doses per cycle (D1, D8, D15) × 2 cycles; each cycle 28 days
- Lympho-conditioning: Cyclophosphamide 500 mg/m2 IV × Fludarabine 30 mg/m^2 IV × 3 days
- FT516 -- IL-2 6MU SC with each dose FT516; FT538 endogenous IL2 (no external IL2 needed)
- Median 3 (1 to 6) prior Rx lines, 9/11 adverse ELN risk
- **5 of 12 (42%) responses (4 CRi + 1 MLFS)**
- FT516 (n = 9): 3 CRi + 1 MLFS (90M and 300M cells); FT538 (n = 3): 1 CRi (100M cells)
- No observed DLTs, No CRS, ICANS, or GVHD of any grade Ongoing remission >6 months in 2 FT516 patients without additional intervention, FT538 CRi ongoing
- Dose escalation continues: FT516 at 900M; and FT538 at 300M, 1B, 1.5B per dose

ClinicalTrials.gov. Accessed September 2, 2022. https://www.clinicaltrials.gov/ct2/show/NCT04023071; ClinicalTrials.gov. Accessed September 2, 2022. https://clinicaltrials.gov/ct2/show/NCT04614636.

Conclusions

- Rational combinations of targeted therapy with venetoclax or with HMA + venetoclax may enhance efficacy (response, molecular clearance, early survival): selection of patients tailored to goal of therapy
- Dose optimization, early bone marrow assessment, and growth factors to safely deliver combination regimens need to be very carefully evaluated and implemented
- Use of molecular clearance may be a useful early surrogate of efficacy in certain combinations such as with FLT3, NPM1 clearance, but maybe not all mutations
- Careful assessment and long-term follow-up of ongoing single-arm studies, with rapidly performed focused, randomized clinical trials needed to confirm benefit

Leukemia Questions: ndaver@mdanderson.org

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Discussion

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Interactive Discussion: Treatment Landscape Evolution

All faculty

APTITUDE HEALTH

Question 1

What method is routinely used at your department for MRD monitoring

1. Multicolor flow cytometry (MFC)
2. PCR
3. FMC and PCR
4. All
5. None

Question 2

What is the average time for conventional cytogenetic analysis

1. 3–5 days
2. 5–7 days
3. 7–10 days
4. 10–14 days
5. >14 days

Question 2

Which novel therapies are available (reimbursed?) in your country?

1. Gemtuzumab ozogamicin
2. Midostaurin
3. Gilteritinib
4. Venetoclax
5. CPX-351
6. Glasdegib

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Session Close

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Question 1

What age group is considered elderly ALL patients?

1. ≥50 years
2. ≥55 years
3. ≥60 years
4. ≥65 years
5. ≥70 years

Question 2

Which of the following factors are important in assessing AML patients at diagnosis? Select all that apply.

1. Adverse genetic alterations
2. Age
3. Comorbidities
4. Performance status
5. Prior cytotoxic therapy
6. Prior myelodysplasia

Question 3

Which of the following is not true regarding HMA + venetoclax in AML?

1. The CR/CRi with HMA+VEN in the VIALE-A was >65%
2. HMA+VEN improved median OS compared with HMA alone
3. Lab or clinical TLS is not seen with HMA+VEN in AML
4. The recommended daily dose of venetoclax (without azoles) was 400 mg PO Qday in VIALE-A study
5. Neutropenia is commonly seen with HMA+VEN regimen

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Closing Remarks

Gail J. Roboz and Naval Daver

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Thank you!

- Thank you to our sponsors, expert presenters, and to you for your participation
- Please complete the **evaluation link** that will be sent to you via chat
- The meeting recording and slides presented today will be shared on the globalleukemiaacademy.com website within a few weeks
- If you have a question for any of our experts that was not answered today, you can submit it through the GLA website in our Ask the Experts section

THANK YOU!

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