SPOTLIGHT ON ACUTE MYELOID LEUKEMIA (AML)

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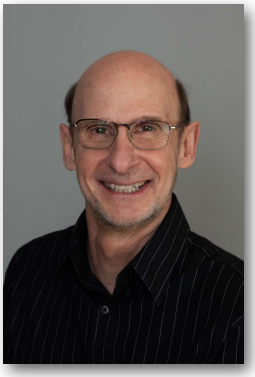
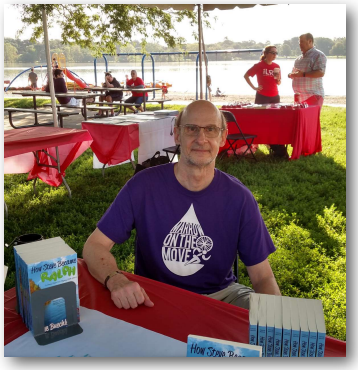
1

WELCOMING REMARKS

SPOTLIGHT ON ACUTE MYELOID LEUKEMIA





Steve Buechler
Acute Myeloid Leukemia (AML Survivor)
Podcast Guest, *The Bloodline with LLS*
Author, *How Steve Became Ralph*
Facilitator, *Pen My Path* Writing Workshops through LLS Community

2

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WELCOMING REMARKS

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3

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Fred Hutch Cancer Center

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UW Medicine

5

Disclosures

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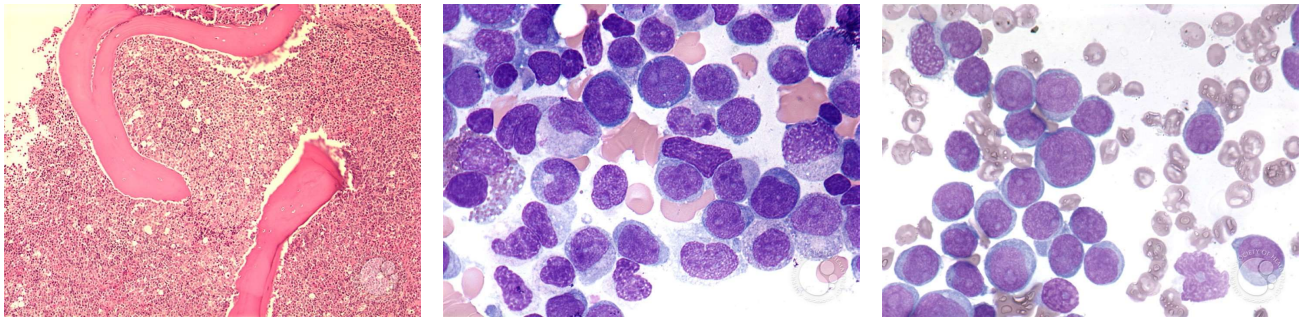
- Clinical trial support: Amgen, Aptevo, ImmunoGen, Janssen, Jazz, Kura, MacroGenics
- Consultancy: Abbvie, Adicet, Amphivena, BerGenBio, Bristol Myers Squibb, GlaxoSmithKline, ImmunoGen, Kura, Orum

6

Acute myeloid leukemia (AML)

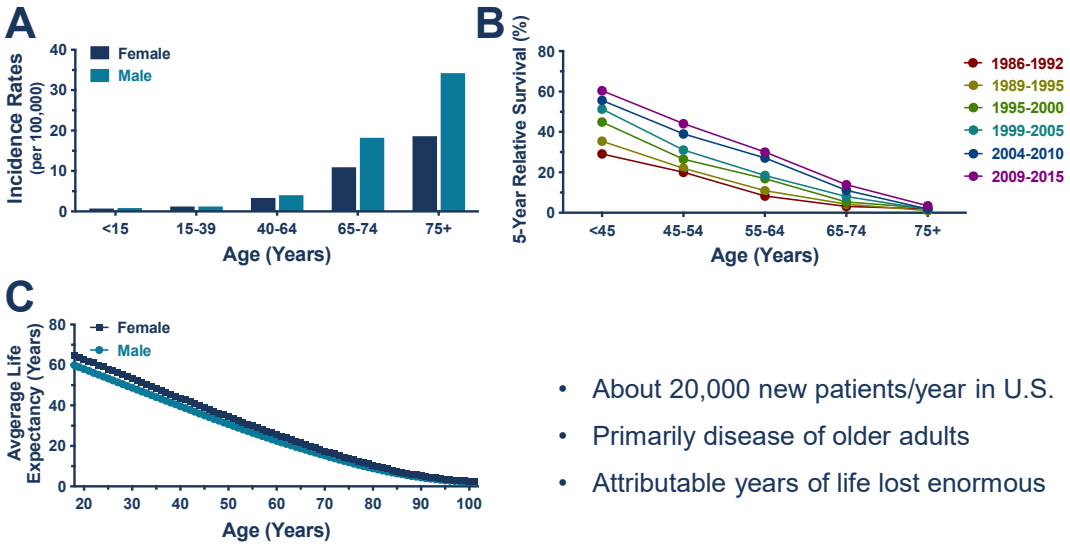
- Diverse group of aggressive blood cancers
- Cells defective in maturation, accumulate at various stages of incomplete maturation/function
- AML cells interfere with production of normal blood cells
  – Weakness/fatigue, infection, bleeding



Images: American Society of Hematology Image Bank

7

AML – disease of older adults with poor outcome



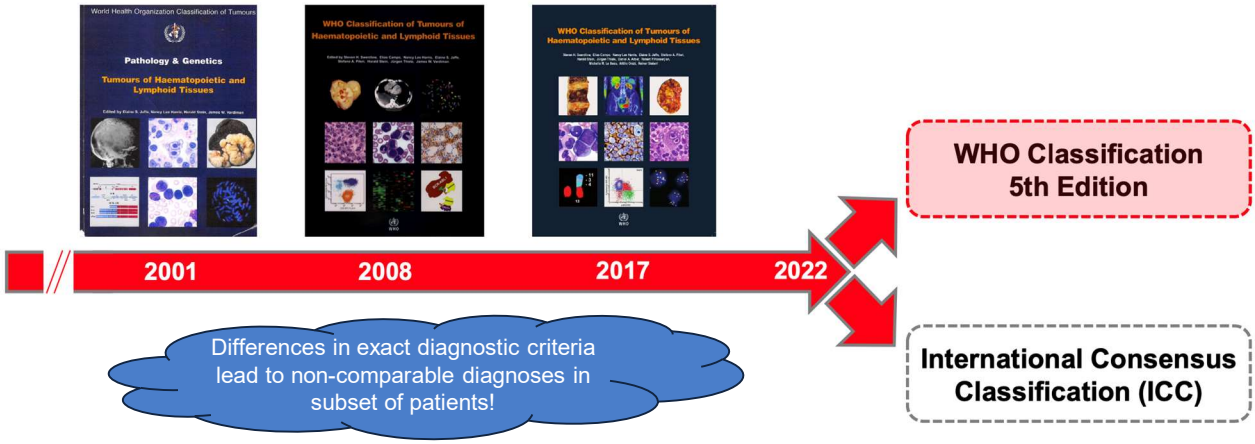
- About 20,000 new patients/year in U.S.
- Primarily disease of older adults
- Attributable years of life lost enormous

Siegel et al. *CA Cancer J Clin* 2022;72(1):7-33; SEER*Explorer, September 2022; Social Security Period Life Table, 2019

8

AML classification

- Increasing priority on genetic profiles to define AML entities
- Arbitrary separation from other diseases, e.g. myelodysplastic syndromes (MDS)



Huber et al. *Blood* 2022;140(Suppl 1):555-556 [abstract #228]

9

European LeukemiaNet (ELN) genetic risk classification

Increasing complexity with refinements from genetic data

ELN 2010[1]

Genetic group	Subsets
Favorable	t(8;21)(q22;q22); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Mutated *NPM1* without *FLT3*-ITD (normal karyotype) Mutated *CEBPA* (normal karyotype)
Intermediate-I*	Mutated *NPM1* and *FLT3*-ITD (normal karyotype) Wild-type *NPM1* and *FLT3*-ITD (normal karyotype) Wild-type *NPM1* without *FLT3*-ITD (normal karyotype)
Intermediate-II	t(9;11)(p22;q23); *MLLT3-MLL* Cytogenetic abnormalities not classified as favorable or adverse†
Adverse	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1* t(6;9)(p23;q34); *DEK-NUP214* t(v;11)(v;q23); *MLL* rearranged −5 or del(5q); −7; abnl(17p); complex karyotype‡

ELN 2017[2]

Risk category*	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}† Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† (without adverse-risk genetic lesions) t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡ Cytogenetic abnormalities not classified as favorable or adverse
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*#

ELN 2022[3]

Risk category†	Genetic abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1*†,‡ • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11*†,‡ • Mutated *NPM1*†,§ without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*‖
Intermediate	• Mutated *NPM1*†,§ with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A*†,¶ • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23.3;q34.1)/*DEK::NUP214* • t(v;11q23.3)/*KMT2A*-rearranged# • t(9;22)(q34.1;q11.2)/*BCR::ABL1* • t(8;16)(p11.2;p13.3)/*KAT6A::CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2, MECOM(EVI1)* • t(3q26.2;v)/*MECOM(EVI1)*-rearranged • −5 or del(5q); −7; −17/abn(17p) • Complex karyotype,** monosomal karyotype†† • Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2*‡‡ • Mutated *TP53*[a]

[1]Döhner et al. *Blood* 2010;115(3):453-474; [2]Döhner et al. *Blood* 2017;129(4):424-447; [3]Döhner et al. *Blood* 2022;140(12):1345-1377

10

Genetic predisposition – increasingly recognized

Important for: choice of donor for transplant, health surveillance strategies, relatives who share causative gene variant, etc.

- Should be considered for all patients regardless of age
- Increasing list of pathogenic and likely pathogenic gene variants
- Certain disorders associated with specific characteristics (*e.g.* platelet defects, organ dysfunction)
- Clinical features prompting consideration of testing for genetic predisposition:

Clinical features
Personal history of ≥2 cancers, 1 of which is a hematopoietic malignancy (order does not matter)
Personal history of a hematopoietic malignancy plus: • Another relative within two generations with another hematopoietic malignancy, or • Another relative within two generations with a solid tumor diagnosed at age 50 or younger, or • Another relative within two generations with other hematopoietic abnormalities
Presence of a deleterious gene variant in tumor profiling that could be a germline allele, especially if that variant is present during remission*
Age of diagnosis of hematopoietic malignancy at an earlier age than average (eg, MDS diagnosed ≤ 40 y)
Germline status of a variant is confirmed by: Its presence in DNA derived from a tissue source not likely to undergo somatic mutation frequently (eg, cultured skin fibroblasts or hair follicles) AND at a variant allele frequency consistent with the germline (generally considered between 30-60%), or Its presence in at least two relatives at a variant allele frequency consistent with the germline

- Testing may require culture, genetic testing of skin cells

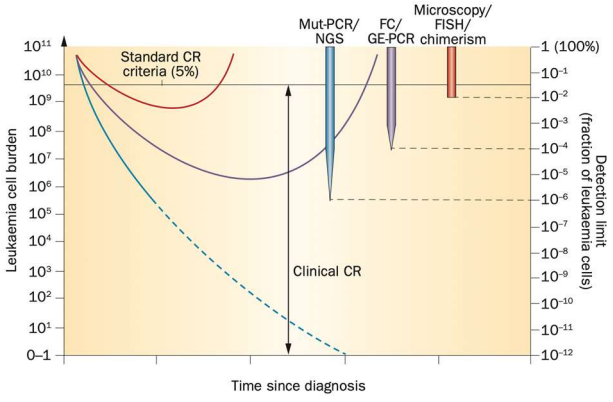
Döhner et al. *Blood* 2022;140(12):1345-1377

11

Treatment response assessment

Provides important prognostic information, guides further treatment decision making

- **Traditional gold standard:** microscopic assessment of blood and bone marrow
  - ➢ Many patients achieving "complete remission (CR)" relapse
- **Increasingly used:** measurable residual disease (MRD) testing
  - – Detects AML cells below microscopy threshold
  - – Improves prognostication, outcome prediction

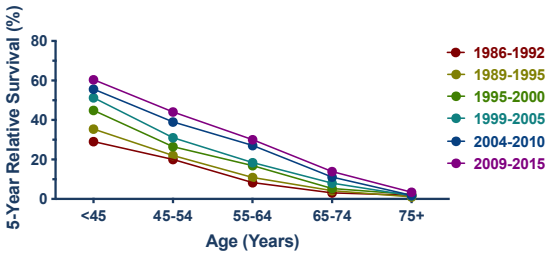


Hourigan & Karp. *Nat Rev Clin Oncol* 2013;10(8):460-471

12

AML therapy over time: until ~5 years ago

- **Begin of modern AML treatment era in 1973** (introduction of "7+3")
- **Relatively simple treatment algorithm**
  - Medically fit ("younger") -> cure possible: induction chemotherapy, choice of post-remission therapy
  - Medically unfit ("older") -> cure not possible: low-intensity chemotherapy or best supportive care
- **Highly variable outcomes**
- **Slow outcome improvements** with advances in supportive care and hematopoietic cell transplantation



Data source: https://seer.cancer.gov/csr/previous.html

13

Induction chemotherapy for fit adults with AML

- **Most common: "7+3" chemotherapy**
  - Cytarabine (intermediate dose) x 7 days, anthracycline (daunorubicin, idarubicin) x 3 days
  - Typically given inpatient (~1 month hospital stay) for monitoring, supportive care
  - Side effects: nausea/vomiting, loss of appetite, mouth sores, diarrhea/constipation, low blood counts (bleeding, fever/infections)
- **Alternative: high-dose cytarabine-based therapies (e.g. FLAG-Ida, CLAG-M)**
  - Slightly more efficacious than 7+3
  - Slightly more toxic than 7+3
  - Fewer relapses but similar overall survival compared to 7+3

❖ Goal: induction of complete remission

Döhner et al. *Blood* 2022;140(12):1345-1377

14

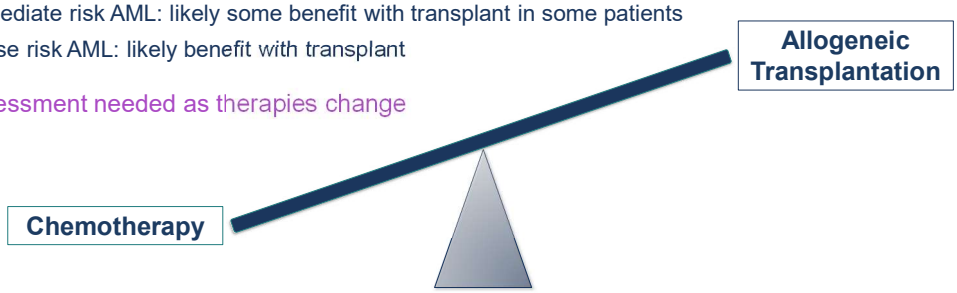
Post-remission ("consolidation") therapy in AML

Additional chemotherapy *vs.* allogeneic hematopoietic cell ("bone marrow") transplantation?

- Balancing risks and benefits for optimal outcome
  - Transplantation: more effective in preventing AML relapse, higher risk of short- and long-term toxicities

➢ Question: are risks with transplantation worth the benefit of better disease control?
  - Favorable risk AML: likely no benefit with transplant if good response to chemotherapy
  - Intermediate risk AML: likely some benefit with transplant in some patients
  - Adverse risk AML: likely benefit with transplant

❖ Re-assessment needed as therapies change



15

Treatment of relapsed/refractory AML

Area of great unmet medical need

- Overall poor outcomes with currently available therapies, especially if
  - Short remission duration, older age, non-favorable cytogenetic risk, prior allogeneic transplant
- Many conventional chemotherapy regimens available, no clear "winner"
- Molecular re-evaluation important to identify actionable mutations
- If treatment successful, strongly consider allogeneic transplant
  - Only cure for primary refractory AML, best chance of cure for relapsed AML

➢ **PLEASE CONSIDER PARTICIPATION IN CLINICAL TRIALS TESTING NEW THERAPIES**

16

AML therapy over time: last ~5 years

- **Approval of 10 new drugs since 2017**

➢ **Substantially increased treatment options**
  – Outcomes may improve incrementally

➢ **Treatment algorithms are changing**
  – Blurrier line between intensive and non-intensive therapy
  – Blurrier line between "curative" and "palliative" therapy

❖ **Treatment decision-making has become more nuanced/complex**

17

Shared decision-making

Information exchange between patient and clinicians to decide on right choice for this individual in that specific situation

- **Unique challenges for patients with AML**
  – Little warning about illness
  – Requirement for urgent treatment initiation, prolonged hospitalizations
  ➢ Difficulty processing information on prognosis, treatment
- **In busy clinical environment, process not used well**
  – Time pressures, conflicting priorities
  – Lack of clinician training in how to operationalize in practice, information "broadcasting"
- **Various frameworks might help shared decision-making, e.g. "COD"**
  – "C": emphasize/discuss that there is choice
  – "O": list/describe the options
  – "D": coming to decision

LeBlanc. *Semin Oncol Nurs* 2019;35(6):150958

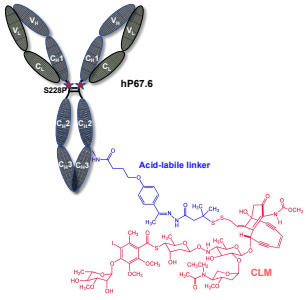
18

Newly approved drugs for AML since 2017

Drug	Drug class	Indication
CC-486	Oral formulation of azacitidine	• Adults with AML who achieved first CR/CRi after intensive chemotherapy and are unable to complete intensive curative therapy
CPX-351	Liposomal formulation of cytarabine/daunorubicin (IV)	• Adults with newly-diagnosed t-AML or AML with myelodysplasia-related changes
Enasidenib	Inhibitor of mutant IDH2 (oral)	• Adults with relapsed/refractory AML with IDH2 mutation
Gemtuzumab ozogamicin	CD33 antibody-drug conjugate (IV)	• Adults with newly-diagnosed CD33+ AML • Adults and children age ≥2 with relapsed/refractory CD33+ AML
Gilteritinib	2nd generation tyrosine kinase inhibitor (oral)	• Adults with relapsed/refractory FLT3-mutated AML
Glasdegib	Inhibitor of hedgehog signaling pathway (oral)	• With low-dose cytarabine for adults ≥75 years or if unfit for intensive chemotherapy
Ivosidenib	Inhibitor of mutant IDH1 (oral)	• Adults with relapsed/refractory AML with IDH1 mutation • Adults with newly diagnosed AML with IDH1 mutation if ≥75 years or unfit for intensive chemotherapy
Midostaurin	1st generation tyrosine kinase inhibitor (oral)	• Adults with newly-diagnosed FLT3-mutated AML, with cytarabine/daunorubicin induction and cytarabine consolidation
Olutasidenib	Inhibitor of mutant IDH1 (oral)	• Adults with relapsed/refractory AML with IDH1 mutation
Venetoclax	Selective BCL-2 inhibitor (oral)	• With azacytidine/decitabine or low-dose cytarabine for adults ≥75 years or if unfit for intensive chemotherapy

19

CD33-targeted immunotherapy

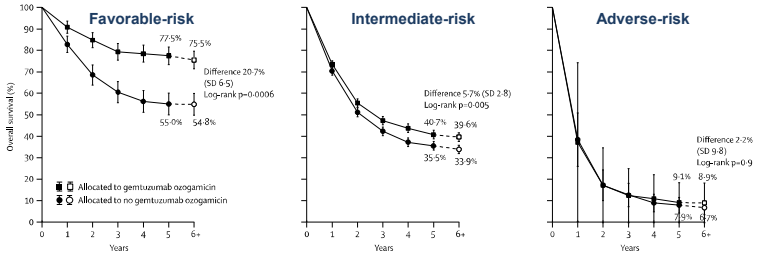


CD33: expressed on some AML blasts in almost all patients, possibly AML stem cells in some[1]

Gemtuzumab ozogamicin

CD33 antibody conjugated to potent toxin (calicheamicin-γ_1 derivative)

- Single agent activity in newly-diagnosed and relapsed/refractory AML[2]
- Reduces relapses, prolongs survival when added to intensive induction chemotherapy[3]

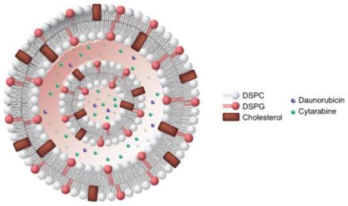


- Side effects: infusion toxicities, severely low blood counts, liver toxicity (veno-occlusive disease/sinusoidal obstruction syndrome)

[1]Walter et al. *Blood* 2012;119(26):6198-6208; [2]Godwin et al. *Leukemia* 2017;31(9):1855-1868; [3]Hills et al. *Lancet Oncol* 2014;15(9):986-996

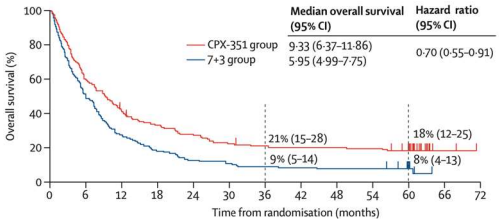
20

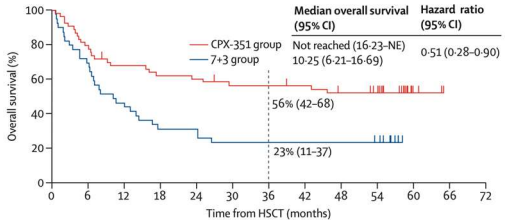
Liposomal 7+3 (CPX-351)



CPX-351: 100 nM bilamellar liposomes, delivers constant ratio of cytarabine and daunorubicin

- Approved for adults with therapy-related AML or AML with myelodysplasia-related changes
- In these patients, better outcomes with CPX-351 than conventional 7+3
  - Higher response rates
  - Slightly lower 30- and 60-day mortality (fewer deaths from progressive AML)
  - Outcomes seem particularly improved in patients who subsequently undergo allogeneic transplant
  - Side effects: similar to 7+3 but less mucositis



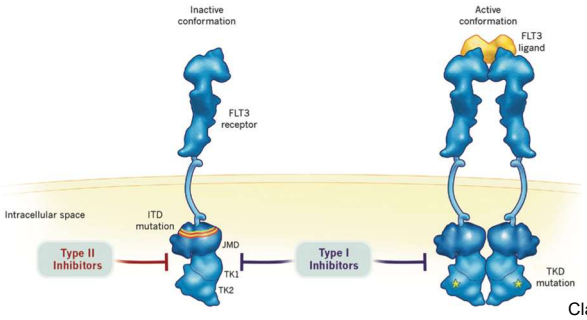


Lancet et al. *J Clin Oncol* 2018;36(26):2684-2692; Lancet et al. *Lancet Haematol* 2021;8(7):e481-e491. Cartoon: Mayer et al. *Int J Nanomedicine* 2019;14:3819-3830

21

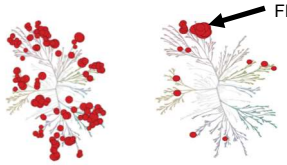
FLT3 inhibitors

- *FLT3* mutations found in ~30% of AML
  - Internal tandem duplication (ITD): ~30%
  - Tyrosine kinase domain mutation (TKD): 7-10%



	Drug	IC_{50} (medium)	IC_{50} (plasma)	Single agent clinical activity	Kinase inhibition
1st Generation	Lestaurtinib	2 nM	700 nM	-	Type I
	Midostaurin	6 nM	~1,000 nM	-	Type I
	Sorafenib	3 nM	~265 nM	+/-	Type II
2nd Generation	Quizartinib	1 nM	18 nM	+	Type II
	Crenolanib	2 nM	48 nM	+	Type I
	Gilteritinib	3 nM	43 nM	+	Type I

Class 3 RTK's: FLT3, KIT, CSF1R, PDGFRA/B



Midostaurin (PKC412)

Quizartinib (AC220)

Side effects: gastrointestinal toxicity, skin rash, low blood counts, differentiation syndrome, drug/drug interactions

Zarrinkar et al. *Blood* 2009;114(14):2984-2992; Pratz et al. *Blood* 2010;115(7):1425-1432; Smith et al. *Nature* 2012;485(7397):260-263; Galanis et al. *Blood* 2014;123(1):94-100; Daver et al. *Leukemia* 2019;33(2):299-312; Tarver et al. *Blood Adv* 2020;4(3):514-524

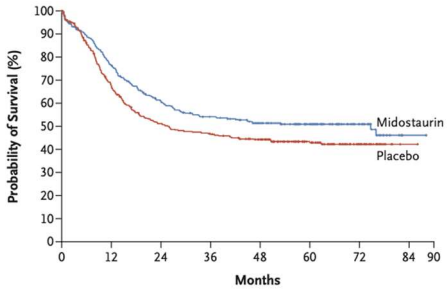
22

*FLT3*i with intensive chemotherapy for newly diagnosed AML

7+3 induction, HiDAC consolidation, maintenance: *FLT3*i *vs*. placebo (1:1 randomization)

Midostaurin (RATIFY[1])

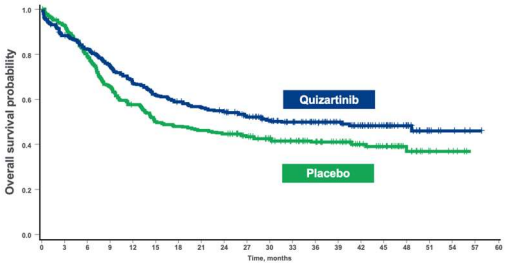
FLT3-ITD/TKD+ AML, age 18-59 years, n=717



	Midostaurin	Placebo	HR	P-value (1-sided)
Median OS	74.7 mo	25.6 mo	0.78	0.009
Median EFS	8.2 mo	3.0 mo	0.78	0.002

Quizartinib (QuANTUM-First[2])

FLT3-ITD+ AML (3% AF), age 18-75 years, n=539



	Quizartinib	Placebo	HR	P-value (2-sided)
Median OS	31.9 mo	15.1 mo	0.78	0.0324
Median EFS			0.92	0.24

[1]Stone et al. *N Engl J Med* 2017;377(5):454-464; [2]Erba et al. *EHA* 2022 (abstract S100)

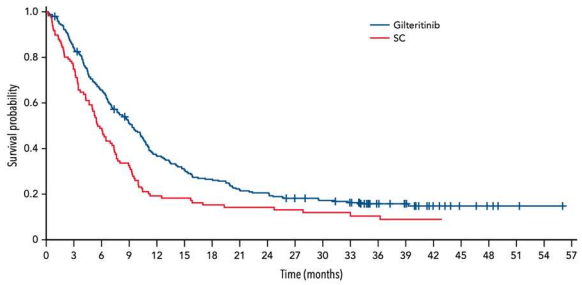
23

*FLT3*i for refractory or 1st relapse AML

*FLT3*i monotherapy *vs*. salvage chemotherapy (2:1 randomization)

Gilteritinib (ADMIRAL[1,2])

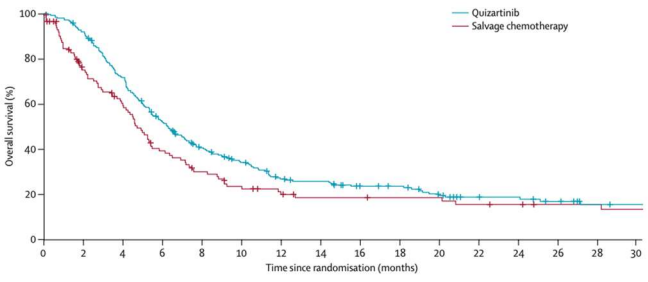
FLT3-ITD/TKD+ AML, age ≥18 years, n=371



	Gilteritinib	Chemo	HR	P-value (2-sided)
CR/CRh	34.0%	15.3%		
Median OS	9.3 mo	5.6 mo	0.67	0.0013

Quizartinib (QuANTUM-R[3])

FLT3-ITD+ AML, age ≥18 years, n=367



	Quizartinib	Chemo	HR	P-value (1-sided)
CR/CRp/CRi	48.2%	27.0%		
Median OS	6.2 mo	4.7 mo	0.76	0.02

[1]Perl et al. *N Engl J Med* 2019;381(18):1728-1740; [2]Perl et al. *Blood* 2022;139(23):3366-3375; [3]Cortes et al. *Lancet Oncol* 2019;20(7):984-997

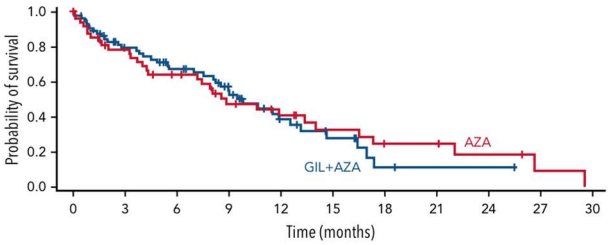
24

*FLT3*i with lower intensity therapy for newly diagnosed AML

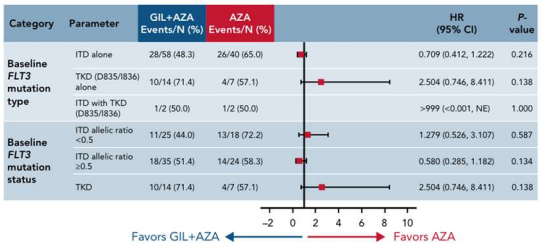
Azacitidine ± *FLT3*i (2:1 randomization)

Gilteritinib (LACEWING[1])

FLT3-ITD/TKD+ AML, age ≥18 years, ineligible for IC; n=123 (stopped early)



	Gilteritinib	Azacitidine	HR	P-value (2-sided)
CR/CRp/CRi	58.1%	26.5%		<0.001
Median OS	9.8 mo	8.9 mo	0.92	0.75

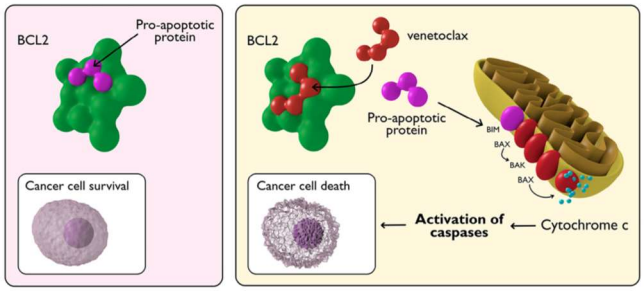


[1]Wang et al. *Blood* 2022;140(17):1845-1857

25

BCL-2 inhibition

BCL-2: allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins



Venetoclax (ABT-199/GDC-0199): oral, selective BCL-2 inhibitor

- Relatively low response rate as single agent in relapsed/refractory AML[1]
- High response rates and broad activity in combination with lower-intensity therapy in newly diagnosed AML[2,3]
- Main side effects: severely low blood counts (myelosuppression), infections

[1]Konopleva et al. *Cancer Discov* 2016;6(10):1106-1117; [2]Wei et al. *J Clin Oncol* 2019;37(15):1277-1284; [3]DiNardo et al. *Blood* 2019;133(1):7-17
cartoon: Mihalyova et al. *Exp Hematol* 2018;61:10-25

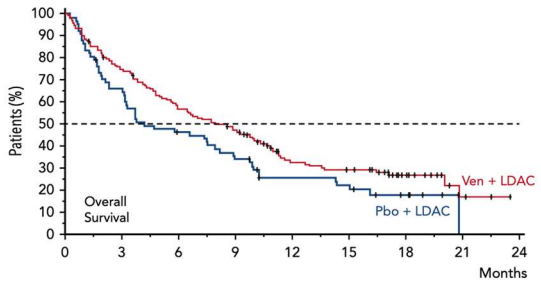
26

Venetoclax with lower intensity therapy for newly diagnosed AML

Low intensity therapy ± venetoclax for adults **unfit** for intensive chemotherapy (2:1 randomization)

VIALE-C[1,2]

Prior HMA therapy permissible, n=211

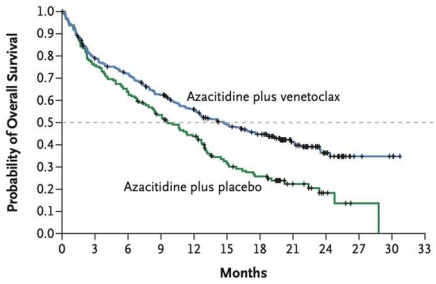


	Ven/LDAC	LDAC	HR	P-value (2-sided)
CR/CRi	48.3%	13.2%		<0.001
Median OS*	8.4 mo	4.1 mo	0.70	0.04

*Unplanned analysis with +6 mo follow-up

VIALE-A[3]

Prior HMA not permissible, n=431

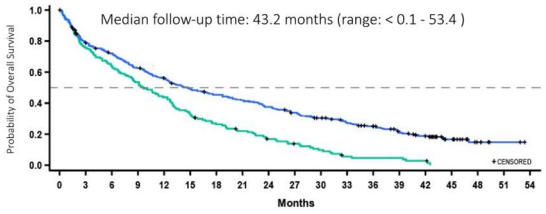


	Ven/Aza	Aza	HR	P-value (2-sided)
CR/CRi	66.4%	28.3%		<0.001
Median OS	14.7 mo	9.6 mo	0.66	<0.001

[1]Wei et al. *Blood* 2020;135(24):2137-2145; [2]Wei et al. *Blood* 2022;140(25):2754-2756; [3]DiNardo et al. *N Engl J Med* 2020;383(7):617-623

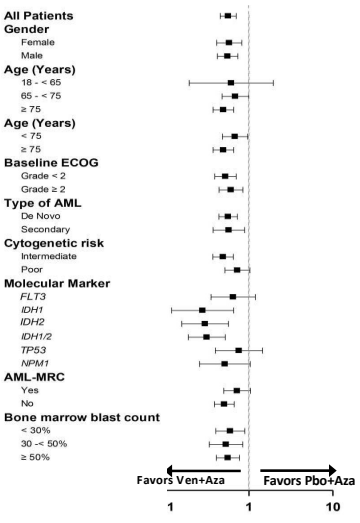
27

VIALE-A: long-term follow-up results



	No. of events/No. of patients (%)	OS (months) median (95% CI)
Ven+Aza	222/286 (77.6)	14.7 (12.1 - 18.7)
Pbo+Aza	138/145 (95.2)	9.6 (7.4 - 12.7)

Hazard ratio: 0.58 (95% CI, 0.465 - 0.723), P < 0.001

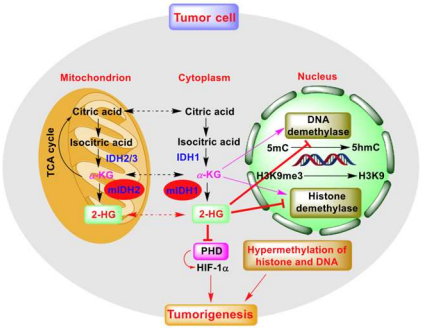


Pratz et al. *Blood* 2022;140(Suppl 1):529-531 [abstract #219]

28

Inhibitors of mutant *IDH*

- Somatic *IDH1* and *IDH2* mutations result in accumulation of oncometabolite (2-HG)
  →Epigenetic changes, impaired cellular differentiation
- Found in 6-10% (m*IDH1*) and 9-13% (m*IDH2*) of AML
- Inhibitors of m*IDH* have single agent activity in AML



Ivosidenib (m*IDH1* inhibitor)[1]
R/R AML, other diseases, n=258

- CR/CRh rate at RP2D: 30.4%
- Duration of CR: 9.3 mo
- Differentiation syndrome: 10.6%

Olutasidenib (m*IDH1* inhibitor)[2]
R/R AML, n=147

- CR/CRh rate at RP2D: 34.7%
- Duration of CR/CRh: 25.9 mo
- Differentiation syndrome: 14%

Enasidenib (m*IDH2* inhibitor)[3]
R/R AML, other diseases, n=239

- CR/CRh rate at RP2D: 26.6%
- Duration of CR: 8.8 mo
- Differentiation syndrome: 7%

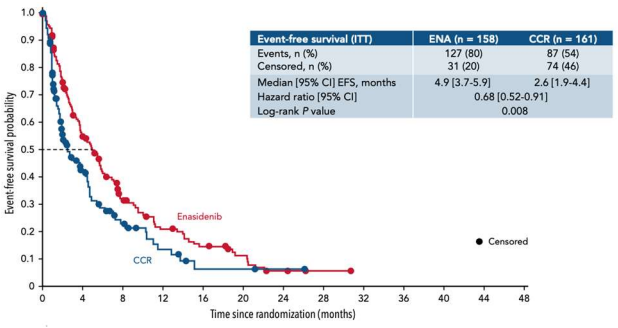
[1]DiNardo et al. *N Engl J Med* 2018:378(25):2386-2398; [2]Cortes et al. *ASH* 2022 [abstract]; [3]Stein et al. *Blood* 2017;130(6):722-731

29

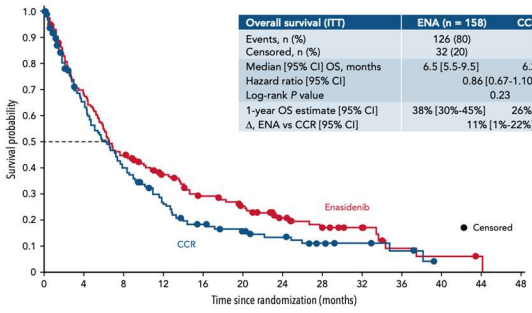
Value as single agent in relapsed/refractory AML?

Randomized phase 3 trial enasidenib vs. conventional care (azacitidine, intermediate-dose cytarabine, low-dose cytarabine, supportive care only), n=319

- Adults ≥60 years with relapsed/refractory AML after 2 or 3 prior AML-directed therapies



Event-free survival (ITT)	ENA (n = 158)	CCR (n = 161)
Events, n (%)	127 (80)	87 (54)
Censored, n (%)	31 (20)	74 (46)
Median [95% CI] EFS, months	4.9 [3.7-5.9]	2.6 [1.9-4.4]
Hazard ratio [95% CI]	0.68 [0.52-0.91]	
Log-rank *P* value	0.008	



Overall survival (ITT)	ENA (n = 158)	CCR (n = 161)
Events, n (%)	126 (80)	125 (78)
Censored, n (%)	32 (20)	36 (22)
Median [95% CI] OS, months	6.5 [5.5-9.5]	6.2 [4.6-7.7]
Hazard ratio [95% CI]	0.86 [0.67-1.10]	
Log-rank *P* value	0.23	
1-year OS estimate [95% CI]	38% [30%-45%]	26% [19%-34%]
Δ, ENA vs CCR [95% CI]	11% [1%-22%]	

de Botton et al. *Blood* 2023;141(2):156-167

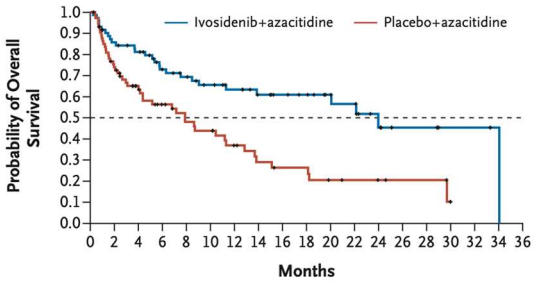
30

*mIDH*i with lower intensity therapy for newly diagnosed AML

Low intensity therapy ± mIDHi for adults unfit for intensive chemotherapy

Ivosidenib (AGILE)[1]

mIDH1 AML, 1:1 randomization, n=146

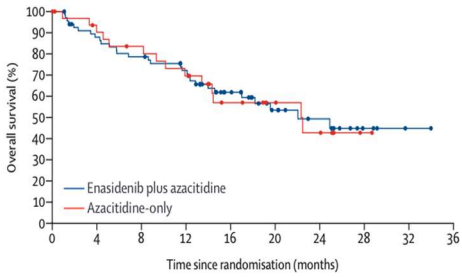


	Ivo/Aza	Aza	HR	P-value (2-sided)
CR/CRh	53%	18%		<0.001
Median OS*	24.0 mo	7.9 mo	0.44	0.001

*Unplanned analysis with +6 mo follow-up

Enasidenib (AG221-AML-005)[2]

mIDH2 AML, 2:1 randomization, n=101

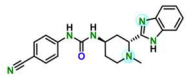


	Ena/Aza	Aza	HR	P-value (2-sided)
CR/CRh	57%	18%		0.0002
Median OS	22.0 mo	22.3 mo	0.99	0.97

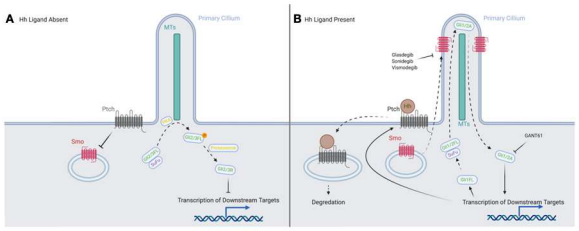
[1]Montesinos et al. *N Engl J Med* 2022;386(16):1519-1531; [2]DiNardo et al. *Lancet Oncol* 2021;22(11):1597-1608

31

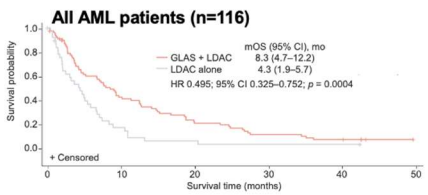
Glasdegib for previously untreated secondary AML

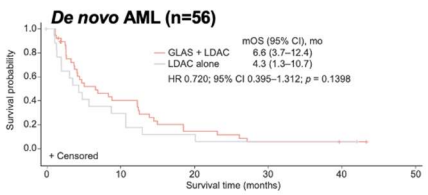


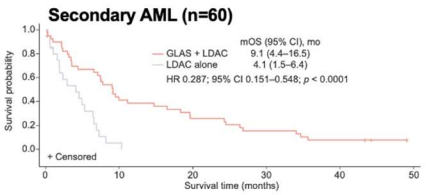
- Hedghog pathway: involved in AML cell survival, resistance to chemotherapy, radiotherapy[1]
- Glasdegib: potent oral inhibitor of Smoothened



- Phase 2 BRIGHT AML 1003: newly-diagnosed AML (n=116)/high-risk MDS (n=16), age ≥55 years, unfit[2,3]
- 2:1 randomization glasdegib (100mg daily)/low-dose cytarabine (LDAC, 10/28 days) *vs*. LDAC







[1]Lemos and Merchant. *Front Oncol* 2022;12:960943; [2]Cortes et al. *Leukemia* 2019;33(2):379-389; Heuser et al. *Ann Hematol* 2021;100(5):1181-1194

32

Maintenance therapy for AML

- Investigated for over 40 years
- Large number of randomized controlled trials
  - Immunotherapies (IL-2, BCG vaccine, interferon-alpha)
  - Conventional cytotoxic chemotherapy
  - Small molecule inhibitors (e.g. tyrosine kinase inhibitors)
- Improved disease-free (but not overall) survival: low-dose IL-2 plus histamine dihydrochloride
  - Approved by EMA in 2008 (hardly used)

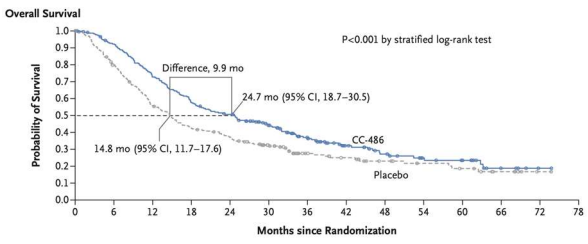
Rashidi et al. *Blood* 2016;128(6):763-773

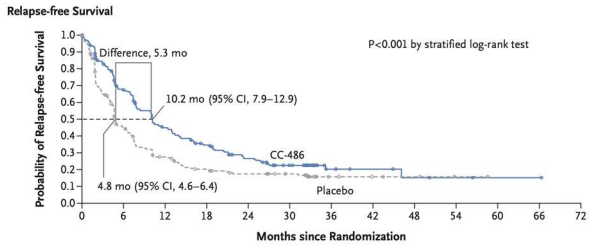
33

Maintenance therapy with CC-486

CC-486: oral formulation of azacitidine

- QUAZAR AML-001: multicenter, international 1:1 randomized phase 3 trial (n=472)
  - Age ≥55 years, intermediate/adverse-risk genetics, in first remission with/without post-remission therapy
  - CC-486 300 mg QD x 14 days *vs.* placebo QD x 14 days (28-day cycles)



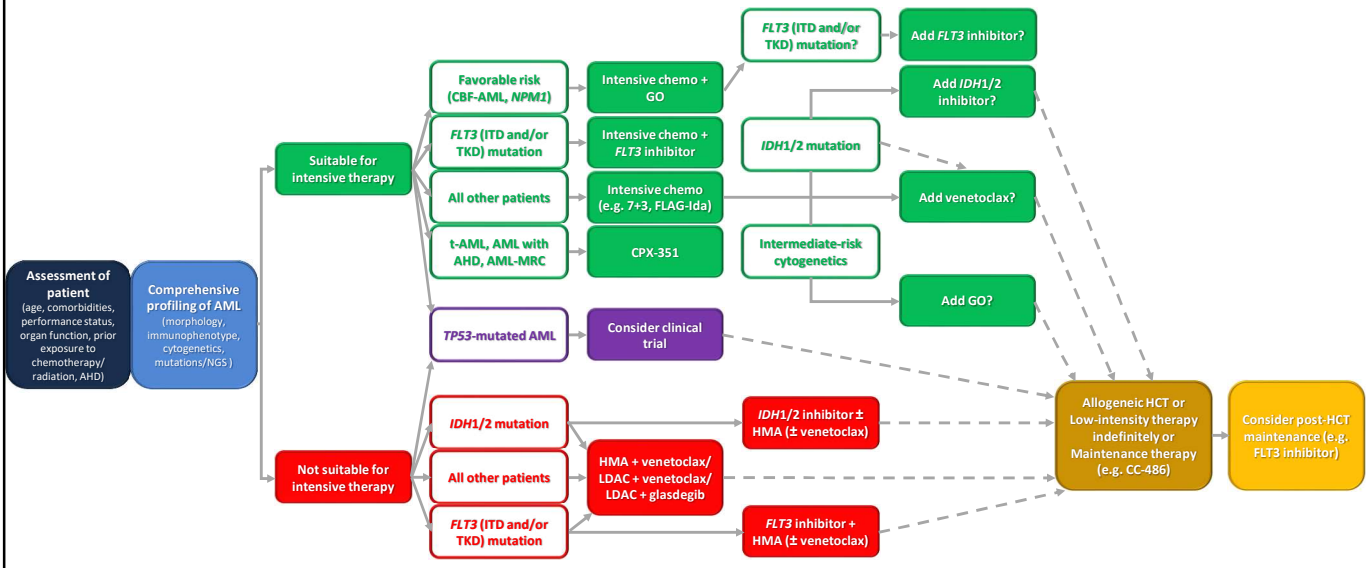


- Most common side effects: nausea, vomiting, diarrhea, low white blood cell counts, infections

Wei et al. *N Engl J Med* 2020;383(26):2526-2537

34

Approach to patient with newly diagnosed AML in 2023



Adapted from: Daver et al. *Blood Cancer J* 2020;10(10):107

35

Conclusions

Some progress made but ongoing need for new therapies

- **Increasing understanding of genetic basis of AML**
  - Changing disease classification, risk stratification
  - Identification of new rational drug targets
- **10 new drugs approved since 2017**
  - Treatment algorithms continue to evolve
  - Blurrier line between "curative" intensive and "palliative" non-intensive therapy
  - ➢ New standard of care for patients "unfit" for intensive chemotherapy
- **No replacement for allogeneic HCT (yet)**

❖ **For many patients, current therapies insufficient – participation in clinical trials important to evaluate new drugs**

36

ASK A QUESTION

SPOTLIGHT ON ACUTE MYELOID LEUKEMIA (AML)

Ask a question by phone:

Press star (*) then the number 1 on your keypad.

Ask a question by web:

Click “Ask a question”
Type your question
Click “Submit”

Due to time constraints, we can only take one question per person. Once you’ve asked your question, the operator will transfer you back into the audience line.

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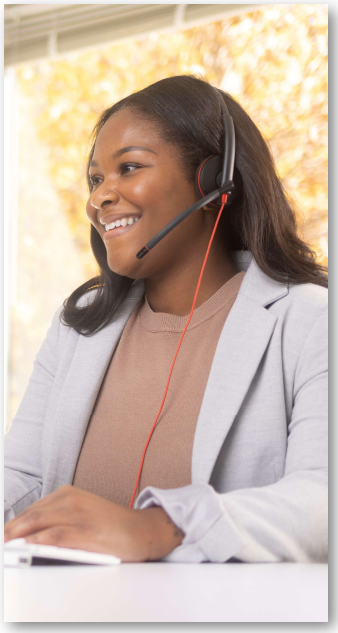
37

LLS EDUCATION & SUPPORT RESOURCES



HOW TO CONTACT US:

To contact an **Information Specialist** about disease, treatment and support information, resources and clinical trials:
www.LLS.org/InformationSpecialists

Call: (800) 955-4572
Monday to Friday, 9 a.m. to 9 p.m. ET
Chat live online: www.LLS.org/InformationSpecialists
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Work one-on-one with an LLS Clinical Trial Nurse Navigator who will help you find clinical trials and personally assist you throughout the entire clinical-trial process.
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38

LLS EDUCATION & SUPPORT RESOURCES

Online Chats

Online Chats are free, live sessions, moderated by oncology social workers. To register for one of the chats below, or for more information, please visit www.LLS.org/Chat

Education Videos

View our free education videos on disease, treatment, and survivorship. To view all patient videos, please visit www.LLS.org/EducationVideos

Patient Podcast

The Bloodline with LLS is here to remind you that after a diagnosis comes hope. To listen to an episode, please visit www.TheBloodline.org

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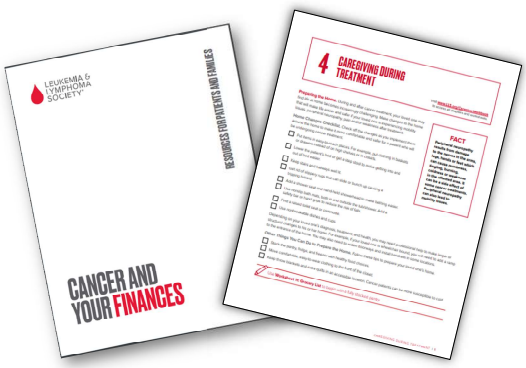
39

LLS EDUCATION & SUPPORT RESOURCES

The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancers: www.LLS.org/Finances



To order free materials: www.LLS.org/Booklets

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40


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We have one goal: A world without cancer.
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