EXPLORING NEW APPROACHES IN AML TREATMENT

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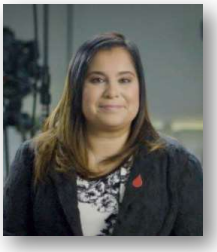
LEUKEMIA & LYMPHOMA SOCIETY®

INTRODUCTION

Treating Slow-Growing Non-Hodgkin Lymphomas (NHL)



Lizette Figueroa-Rivera
Sr. Director, Education & Support
The Leukemia & Lymphoma Society

Disclosures

Research Funding
- AbbVie
- Arog Pharmaceuticals
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- Celgene
- Daiichi-Sankyo
- Forma Therapeutics
- Genentech
- Kura Oncology
- PTC Therapeutics
- Syros Pharmaceuticals

Clinical Advisory Board
- Actinium Pharmaceuticals

***Ad Hoc* Advisor**
- AbbVie
- Celgene
- Daiichi-Sankyo

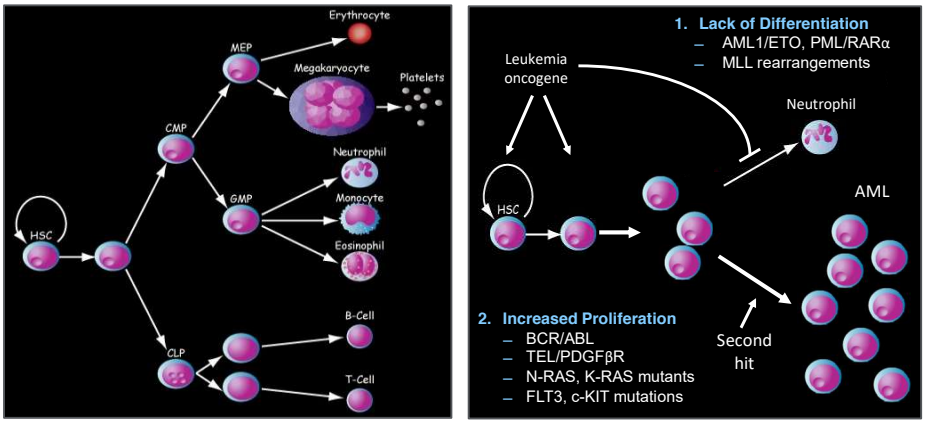
Consultancy
- Novartis

Outline

- Diagnosing and classifying acute myeloid leukemia (AML)
- Recently approved therapies for AML
- Role of clinical trials
- Communication with healthcare team

Development of Acute Myeloid Leukemia

Normal Blood Production ***Development of AML***

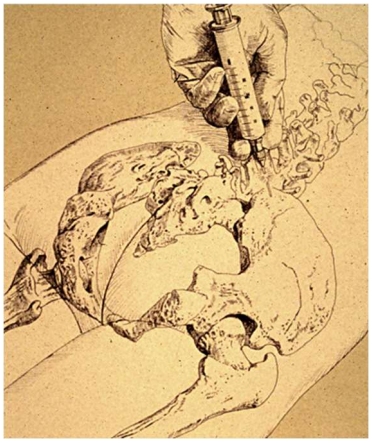


Abbreviations: HSC, hematopoietic stem cell; CMP, common myeloid progenitor; MEP, megakaryocyte-erythroid progenitor; GMP, granulocyte-macrophage progenitor; CLP, common lymphoid progenitor.

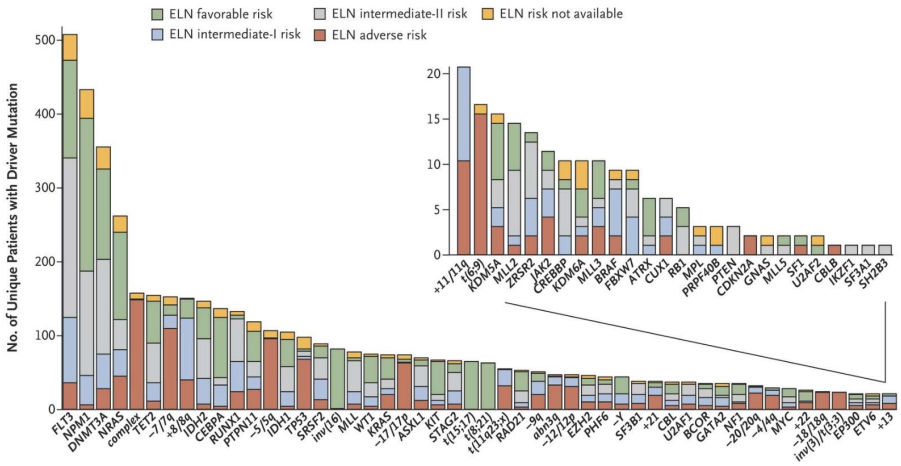
Gilliland DG. *Curr Opin Hematol* 2001; 8:189-191.

Key Diagnostic Questions in Leukemia

- What is the lineage?
- What is the maturational stage?
- What is the genotype?



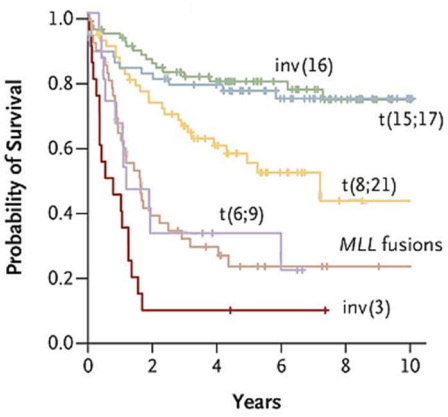
Driver Mutations in AML



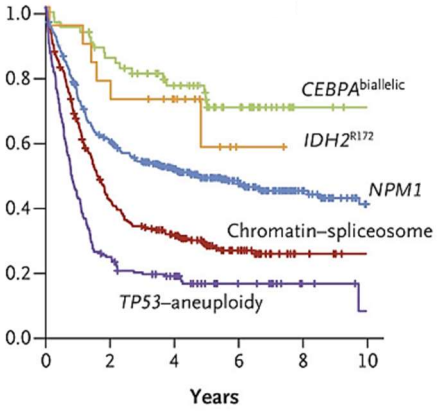
Papaemmanuil E *et al. N Engl J Med* 2016; 2209-2221.

Cytogenetic and Molecular Abnormalities Determine Survival

Cytogenetic Abnormalities



Molecular Abnormalities



Papaemmanuil E *et al. N Engl J Med* 2016; 2209-2221.

Classification of AML

FAB Classification

- **M0** Minimally differentiated
- **M1** Myeloblastic leukemia without differentiation
- **M2** Myeloblastic leukemia with differentiation
- **M3** Acute promyelocytic leukemia
- **M4** Myelomonocytic leukemia
- **M5** Monocytic leukemia
- **M6** Erythroleukemia
- **M7** Megakaryoblastic leukemia

2016 WHO Classification

AML with recurrent genetic abnormalities

- AML with t(8;21); *RUNX1-RUNX1T1*
- AML with inv(16); *CBFB-MYH11*
- APL with t(15;17); *PML-RARA*
- AML with t(9;11); *MLLT3-KMT2A*
- AML with t(6;9); *DEK-NUP214*
- AML with inv(3) or t(3;3); *GATA2, MECOM*
- AML (megakaryoblastic) with t(1;22); *RBM15-MKL1*
- AML with mutated *NPM1*
- AML with biallelic mutations of *CEBPA*
- *Provisional entity: AML with BCR-ABL1*
- *Provisional entity: AML with mutated RUNX1*

AML with MDS-related changes

Therapy-related myeloid neoplasms

Arber DA *et al.* Blood 2016; 127:2391-2405.

Risk Status Based on Genetic Abnormalities

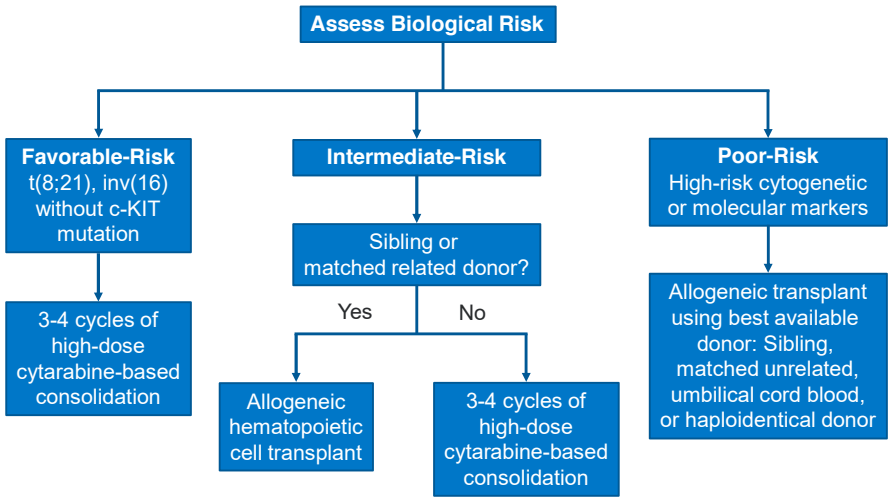
Risk Category	Genetic Abnormality
Favorable	t(8;21)(q22;q22.1); RUNX1-RUNX1T1 inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11 Mutated NPM1 without FLT3-ITD or with FLT3-ITD^{low} Bilallelic mutated CEBPA
Intermediate	Mutated NPM1 and FLT3-ITD^{high} Wild-type NPM1 without FLT3-ITD or with FLT3-ITD^{low} (without adverse-risk genetic lesions t(9;11)(p21.3;q23.3); MLLT3-KMT2A Cytogenetics 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/abnl(17p) Complex karyotype, monosomal karyotype Wild-type NPM1 and FLT3-ITD^{high} Mutated RUNX1 without favorable-risk genetic lesions Mutated ASXL1 without favorable-risk genetic lesions Mutated TP53

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

Phases of AML Therapy

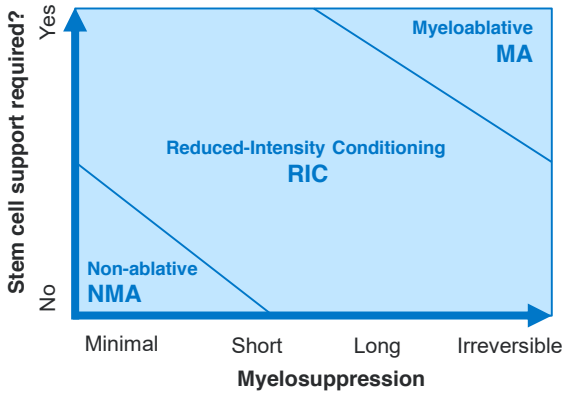
- **Induction:** restore normal blood production
  - Cytarabine + daunorubicin or idarubicin
- **Postremission:** prevent relapse
  - Consolidation: high-dose cytarabine
  - Allogeneic stem cell transplant
  - Maintenance: lower doses of chemotherapy or targeted agents over a longer period

Algorithm for Allogeneic Hematopoietic Cell Transplant



Adapted from Stone RM. *J Clin Oncol* 2013; 31:1262-1266.

Conditioning Regimens and Stem Cell Sources for Allogeneic HCT



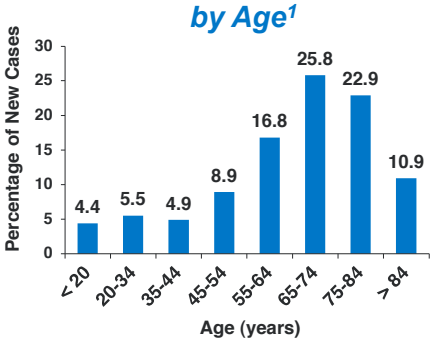
Stem Cell Sources

- Sibling donor (HLA-matched)
- Matched unrelated donor
- Haploidentical donor
- Umbilical cord donor

Bacigalupo A *et al. BBMT* 2009;15:1628-33.

Treatment for Older AML Patients

Incidence of AML by Age[1]



Treatment Options for Older Patients

Regimen	Overall Response Rate	Median Survival (months)
LDAC[2]	18%	~ 5
Decitabine[3]	18%	7.7
Azacitidine[4]	28.3%	9.6

Abbreviations: LDAC, low-dose cytarabine; HMA, hypomethylating agent; CR, complete remission; CRi, CR with incomplete count recovery; OS, overall survival.

[1]SEER Cancer Statistics Factsheets: AML. NCI. Bethesda, MD; [2]Burnett AK *et al. Cancer* 2007; 109:1114-1124; [3]Kantarjian KM *et al. J Clin Oncol* 2012; 30:2670-2677; [4]DiNardo CD *et al. New Engl J Med* 2020; 383:617-629.

New Agents for AML

Drug	Target	Indication	Year Approved
Oral azacitidine[1]	HMA	Maintenance therapy	2020
Gilteritinib[2]	FLT3	Relapsed FLT3-mutated AML	2018
Ivosidenib[3]	IDH1	IDH1-mutated AML	2018
Venetoclax[4]	BCL2	Untreated older AML patients unfit for intensive therapy with HMA or LDAC	2018
Glasdegib[5]	Hedgehog	Untreated older AML patients unfit for intensive therapy with LDAC	2018
Enasidenib[6]	IDH2	Relapsed IDH2-mutated AML	2017
Gemtuzumab ozogamicin[7,8]	CD33	Untreated AML with chemotherapy, relapsed AML	2017
CPX-351[9]	NA	Untreated poor-risk or secondary AML	2017
Midostaurin[10]	Pan-kinase	Untreated FLT3-mutated AML with chemotherapy	2017

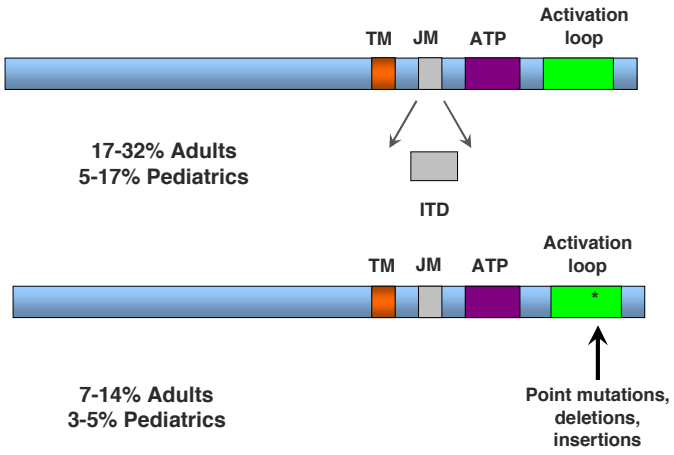
Abbreviations: HMA, hypomethylating agent; FLT3, fms-like tyrosine kinase-3; IDH1, isocitrate dehydrogenase-1; BCL2, B-cell lymphoma 2; IDH2, isocitrate dehydrogenase-2; HMA, hypomethylating agent; LDAC, low-dose cytarabine.

[1]Wei AH *et al. New Engl J Med* 2020; 383:2526-2537. [2]Perl AE *et al. Lancet Oncol* 2017; 18:1061-1075; [3]DiNardo CD *et al. New Engl J Med* 2018; 378:2386-2398; [4]DiNardo CD *et al. N Engl J Med 2020;* 383:617-629; [5]Cortes JE *et al. Leukemia* 2019; 33:379-389; [6]Stein EM *et al. Blood* 2017; 130:722-731;; [7]Castaigne S *et al. Lancet* 2012; 379:1508-1516; [8]Amadori S *et al. J Clin Oncol* 2016; 34:972-979; [9]Lancet *JE et al. J Clin Oncol* 2018; 36:2684-2692; [10]Stone RM *et al. N Engl J Med* 2017; 377:454-464.

Small Molecule Inhibitors for AML

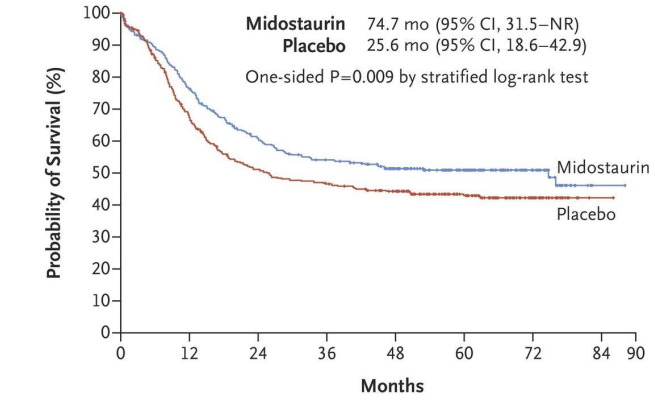
- FLT3 inhibitors
- IDH inhibitors
- BCL-2 inhibitor

FLT3 Mutations in AML



Kottaridis PD *et al. Blood* 2001; 98:1752-1759.

Midostaurin + Chemotherapy for Newly Diagnosed FLT3-Mutated AML



No. at Risk

Midostaurin	360	269	208	181	151	97	37	1
Placebo	357	221	163	147	129	80	30	1

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

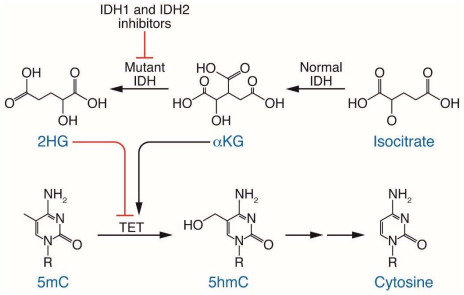
Gilteritinib for Relapsed FLT3-Mutated AML

	Gilteritinib (N = 247)	Chemotherapy (N = 124)
Overall response rate	34.0%	15.3%
Median overall survival	9.3 months	5.6 months

Perl AE *et al. N Engl J Med* 2019; 381:1728-1740.

Inhibiting IDH in AML

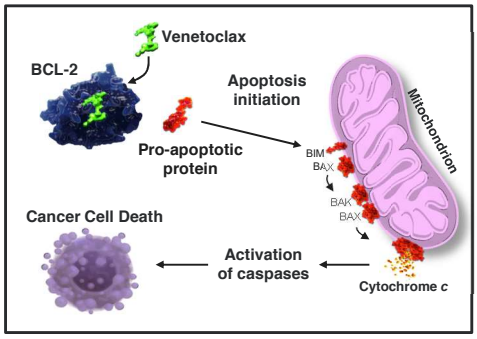
- IDH1 and 2 are enzymes generate energy for cells.
- Mutated IDH alters genetic programming of cells.
  - Causes cells to remain immature and grow quickly.[1]

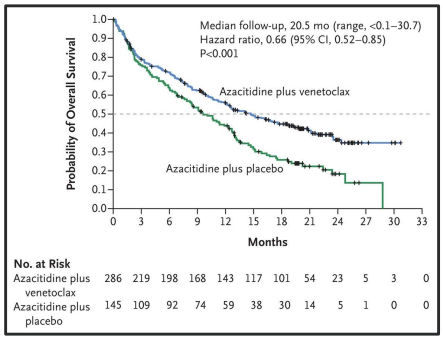


- Ivosidenib is approved for newly diagnosed[2] and relapsed/ refractory IDH1-mutated AML.[3]
- Enasidenib is approved for relapsed/refractory AML.

[1]McKenney AS *et al. JCI* 2013; 123:3672-3677; [2]Roboz GJ *et al. Blood* 2020; 135:463-471; [3]DiNardo CD *et al. N Engl J Med* 2018; 378:2386-2398; [4]Stein EM *et al. Blood* 2017; 130:722-731.

BCL-2 Inhibition in AML





- BCL-2 overexpression allows cancer cells to evade apoptosis.
- Venetoclax binds to BCL-2, freeing pro-apoptotic proteins.
- Azacitidine-venetoclax compared to azacitidine produced superior response rates (66% vs. 28%) and survival (median, 14.7 vs. 9.6 months).

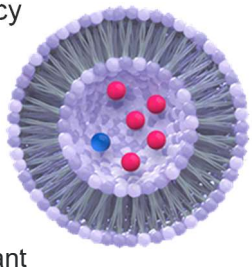
DiNardo CD et al. *New Engl J Med* 2020; 383:617-629.

Side Effects of Targeted Agents

- Elevated white blood count
- Differentiation syndrome
- ECG changes
- Tumor lysis syndrome

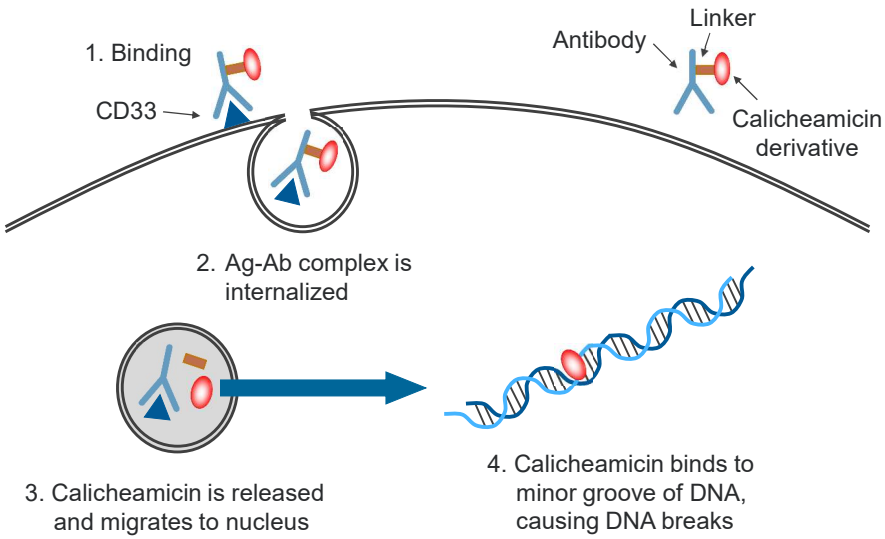
CPX-351

- Consists of cytarabine and daunorubicin encapsulated in a liposome
- Ratio of drug concentrations maximizes efficacy
- Randomized trial of CPX-351 versus 7+3 was superior in terms of:
  - Overall survival
  - Event-free survival
  - Remission rates
  - Outcomes following allogeneic stem cell transplant
- Early mortality rates were lower in the CPX-351 arm and safety was comparable to 7+3



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

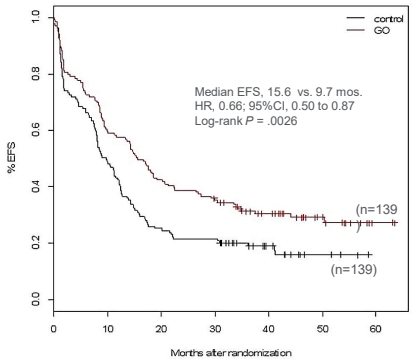
Gemtuzumab Ozogamicin



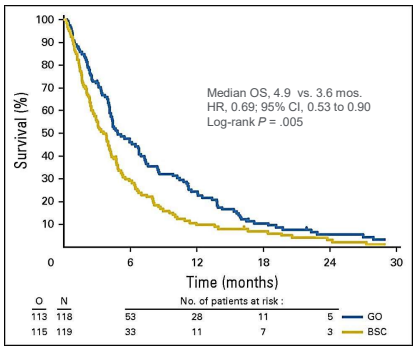
Hinman LM et al. *Cancer Res* 1993; 53:3336-42.

Gemtuzumab Ozogamicin (GO) With and Without Chemotherapy

ALFA-0701: Chemo ± GO in Patients Age 50-70 Years[1,2]



AML-19: GO vs. Supportive Care in Patients Age > 60 Years[3]



[1]Castaigne S *et al. Lancet* 2012; 379:1508-16.
[2]Castaigne S *et al. Blood* 2014; 124:abstr 376.
[3]Amadori S *et al. J Clin Oncol* 2016; 34:972-9.

Oral Azacitidine (CC-486) Maintenance for AML in First Remission

	CC-486 (N = 238)	Placebo (N = 234)
Median relapse-free survival	10.2 months	4.8 months
Median overall survival	24.7 months	14.8 months

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

Upfront Treatment Strategies for AML

Less than 60 years old:

- Favorable-Risk → 7+3 (+ GO for CBF AML) → HiDAC ± GO
- Intermediate-Risk → 7+3 ± GO → Allogeneic SCT or HiDAC
- Adverse-Risk → 7+3 (+ midostaurin if FLT3+) → Allogeneic SCT

60 years or older:

- Fit → As above; CPX-351 in adverse-risk and secondary AML
- Not able to receive intensive chemotherapy
  - No targetable mutations → HMA/venetoclax
  - IDH1 → Ivosidenib or HMA/venetoclax
  - IDH2 → HMA/venetoclax
  - FLT3 → HMA/venetoclax

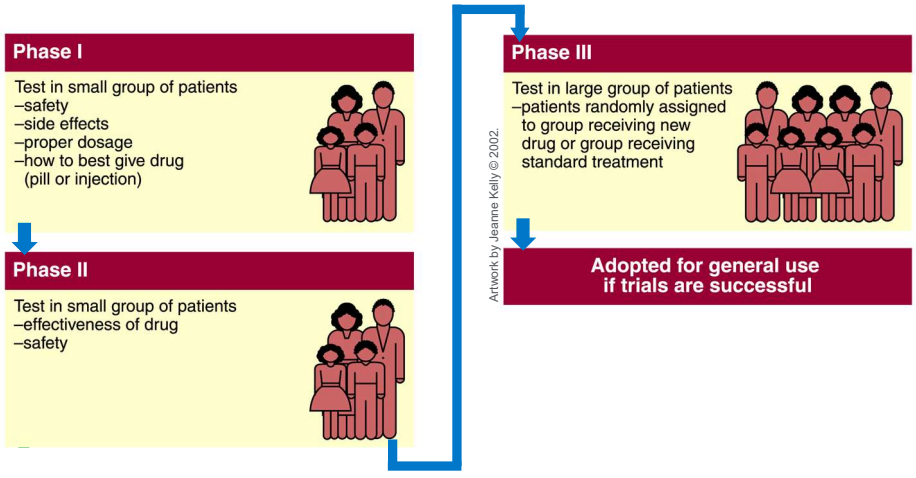
Abbreviations: GO, gemtuzumab ozogamicin; CBF, core-binding factor; HiDAC, high-dose cytarabine; SCT, stem cell transplant; HMA; hypomethylating agent.

Role of Clinical Trials in AML

- Clinical trials are the only way more progress can be made.
- Clinical trials allow us to determine if new treatments:
  - Are safe.
  - Are effective.
  - Work better than current treatments.
- They can also help us find new ways to prevent and detect cancer.
- They help us improve the quality of life for people during and after treatment.
- By taking part in a clinical trial, you add to our knowledge about leukemia and help improve care for future patients.

Drug Development

Phases of Clinical Trials



Risks and Benefits of Clinical Trials

Possible Benefits

- You will have access to a new treatment not available otherwise.
- The research team will watch you closely.
- If the new treatment is more effective than the standard treatment, you may be among the first to benefit.
- The trial may help us learn more about cancer and benefit people in the future.

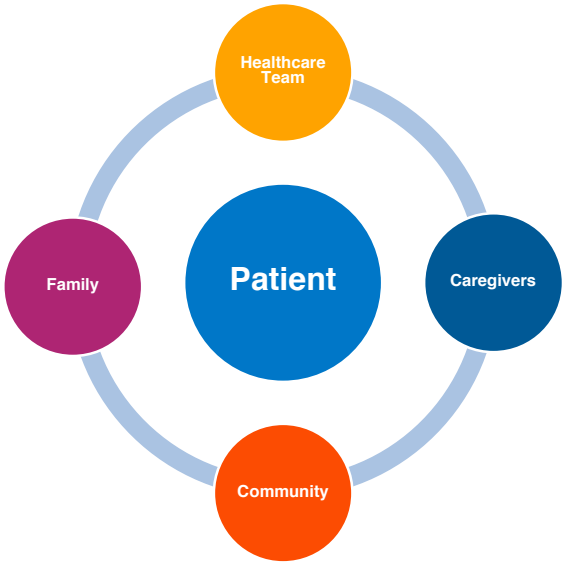
Possible Risks

- The new treatment may not be better than the standard treatment.
- New treatments may have unexpected side effects that could be worse than the standard treatment.
- You may be required to make more doctors visits than if you were receiving standard treatment.
- You may need extra tests.
- Even if a new treatment benefits some patients, it may not work for you.
- Health insurance may not cover all costs in a trial.

It Takes a Village to Treat AML

- Treating Physicians
  - Leukemia Physician
  - BMT Physician
- Consulting Physicians
  - Infectious Disease
  - Radiation Oncology
  - Others
- Diagnostic Services
  - Hematopathology
  - Cytogenetics
  - Molecular Diagnostics
  - Radiology
- Blood Bank
- Nursing
  - Inpatient
  - Outpatient
- Social Work
- Physical & Occupational Therapy
- Nutrition Service
- Pharmacy

Working Together Towards One Goal



Conclusions

- AML is characterized by increased growth and impaired maturation of early blood cells.
- Chromosome and molecular abnormalities can determine prognosis and direct therapy:
  - Favorable-risk AML: Intensive chemotherapy, gemtuzumab ozogamcin
  - Adverse-risk AML: Allogeneic stem cell transplant
  - Older patients: Lower-intensity chemotherapy, targeted therapies
- Molecular abnormalities can serve as targets for therapy.
- Clinical trials allow more progress to be made.
- Partnership among patients, caregivers, and healthcare team members is critical.

Q&A SESSION

Exploring New Approaches in AML Treatment

- **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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To contact an **Information Specialist** about disease, treatment and support information, resources and clinical trials:

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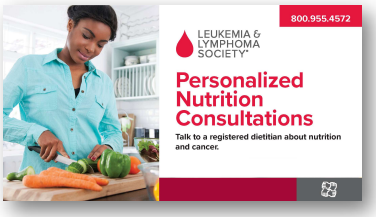
Monday to Friday, 9 a.m. to 9 p.m. ET

Chat live online:
www.LLS.org/InformationSpecialists
Monday to Friday, 10 a.m. to 7 p.m. ET

Email: infocenter@LLS.org
All email messages are answered within one business day.

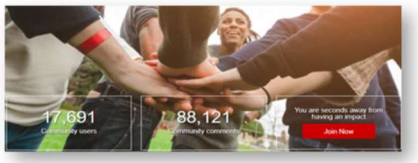


NUTRITION CONSULTATIONS
Our registered dietitian has expertise in oncology nutrition and provides free one-on-one consultations by phone or email.
www.LLS.org/Consult

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**



LLS Online Community

Community of blood cancer patients, survivors and caregivers supporting each other and giving trusted information and resources, please visit **www.LLS.org/Community**

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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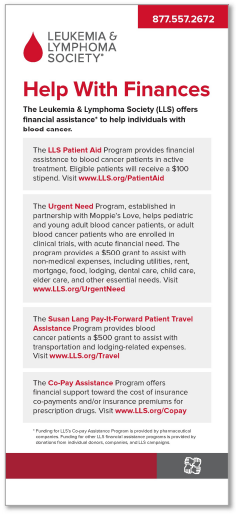

The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancer:
www.LLS.org/Finances

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

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THANK YOU
We have one goal: A world without blood cancers
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39