A CLOSER LOOK AT NOVEL TREATMENT THERAPIES FOR AML

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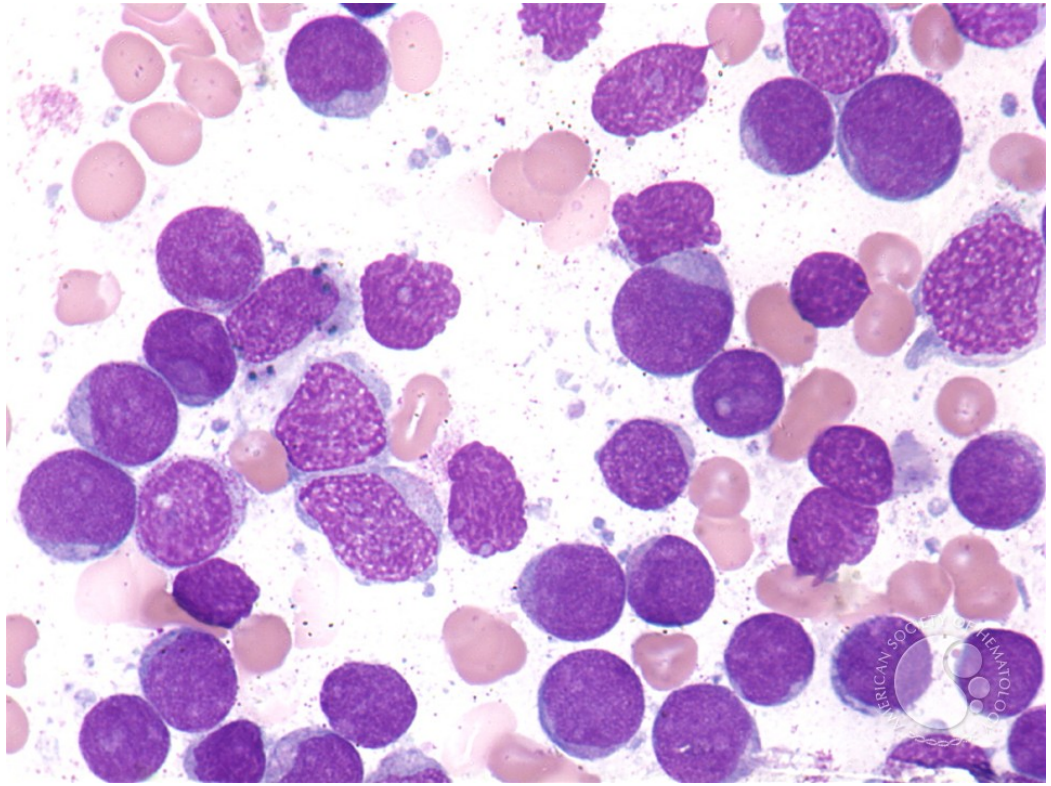
OptumHealth Education's Essential of Oncology
Solid Organ and Blood/Marrow Transplant Management

Learning Objectives

- Discuss the novel AML treatment therapies that have recently become available and review their role in targeting the molecules and pathways involved in AML progression
- Examine indications for the inclusion of novel agents in initial therapy for AML versus in the relapse and salvage setting
- Address which patient populations are likely to benefit from the recently approved and novel investigational agents and combination therapies

Acute Myelogenous Leukemia

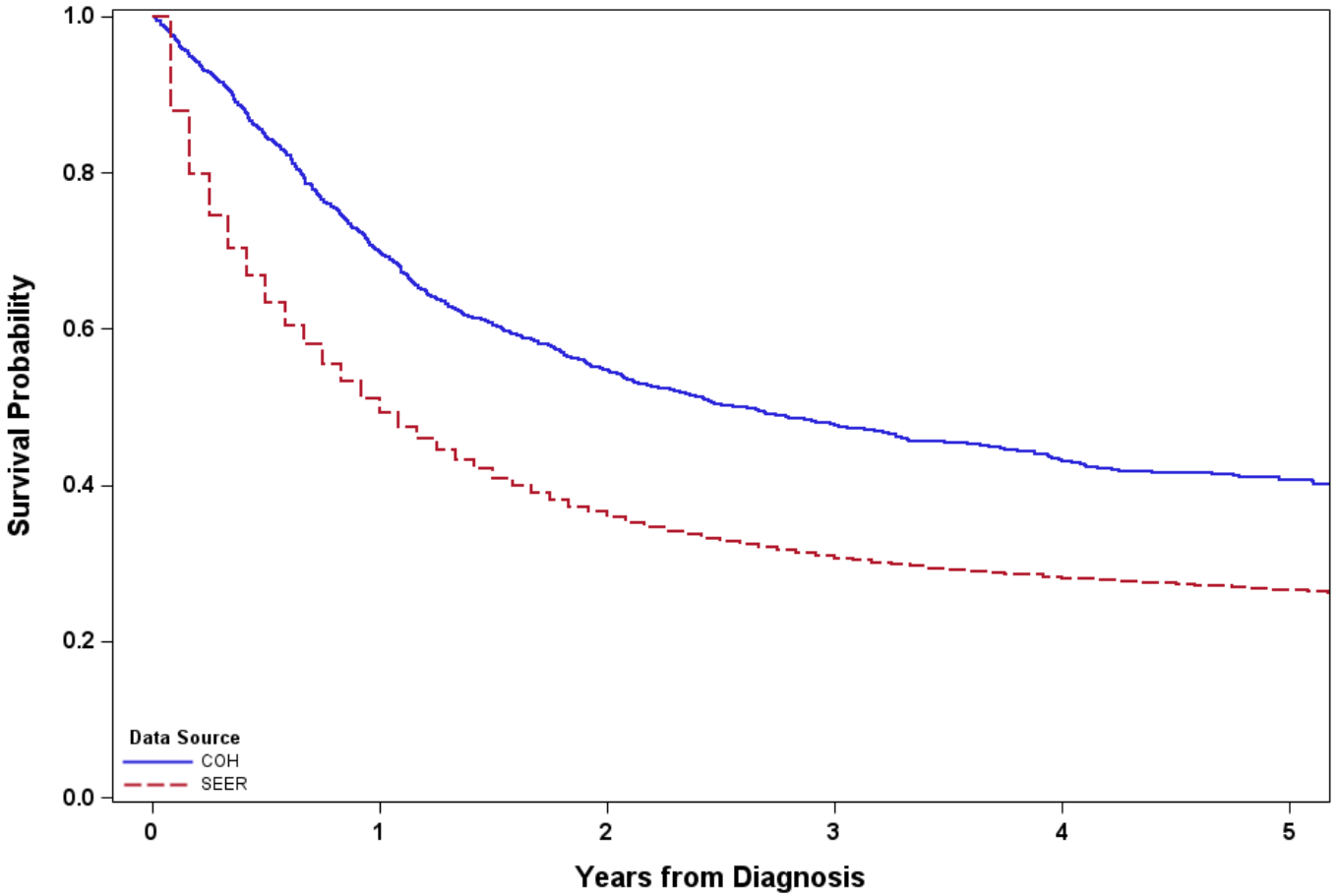


Acute myelogenous leukemia without maturation.

American Society of Hematology

- 20,240 new cases in 2021
- 11,400 estimated deaths in 2021
- 1.1% of all new cancer diagnoses
- Five-year relative survival is 29.5% (2011-2017)
- Slight male predominance (5.2 vs. 3.6/100,000)
- Median age of diagnosis is 68 years
  - 40.4% of cases diagnosed in patients <65
  - Median age at death is 73 years

AML COH vs SEER National, 2004-2017 Unadjusted Overall Survival

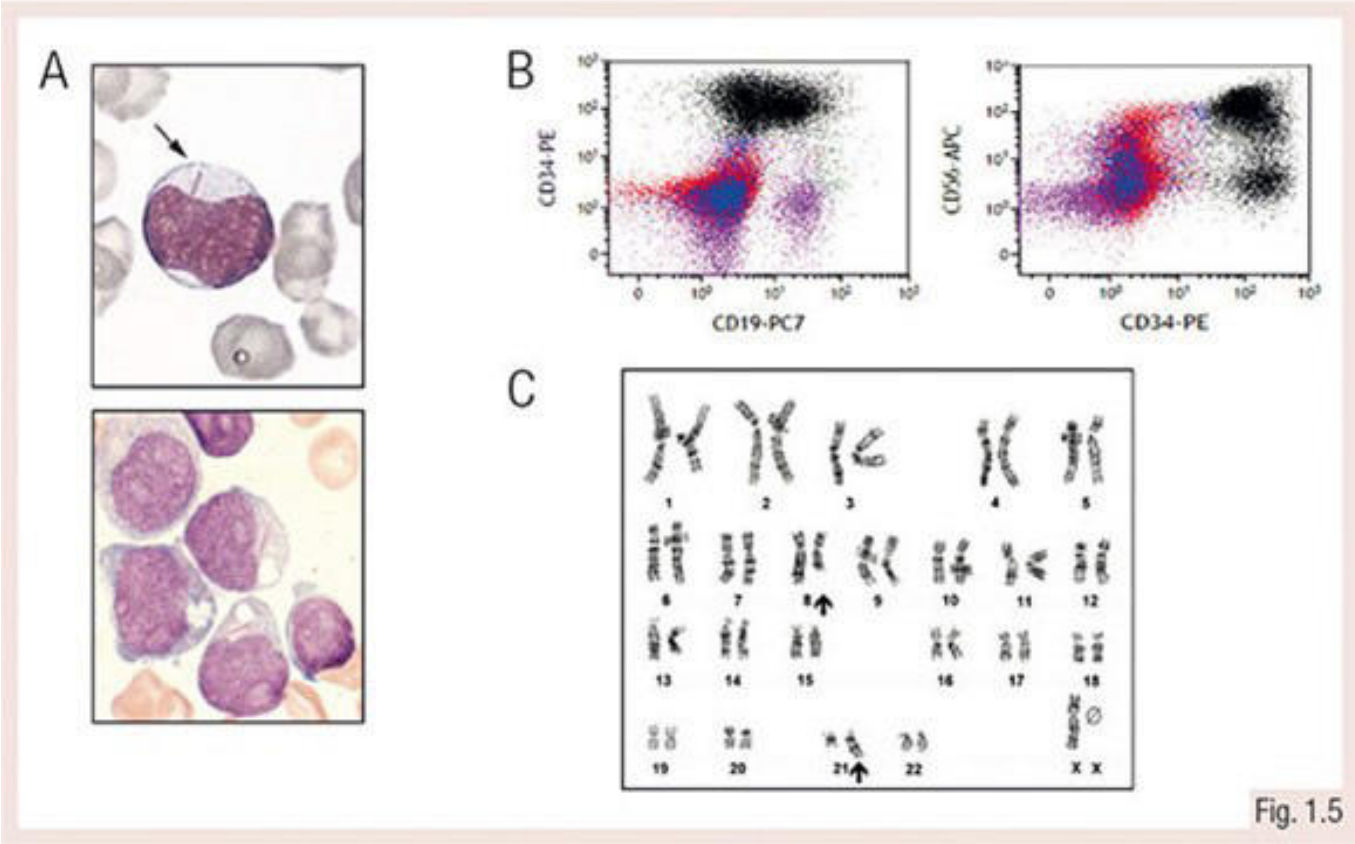


Patients At Risk

COH	1210	844	587	460	368	303
SEER	31051	15643	10116	7705	6242	5171

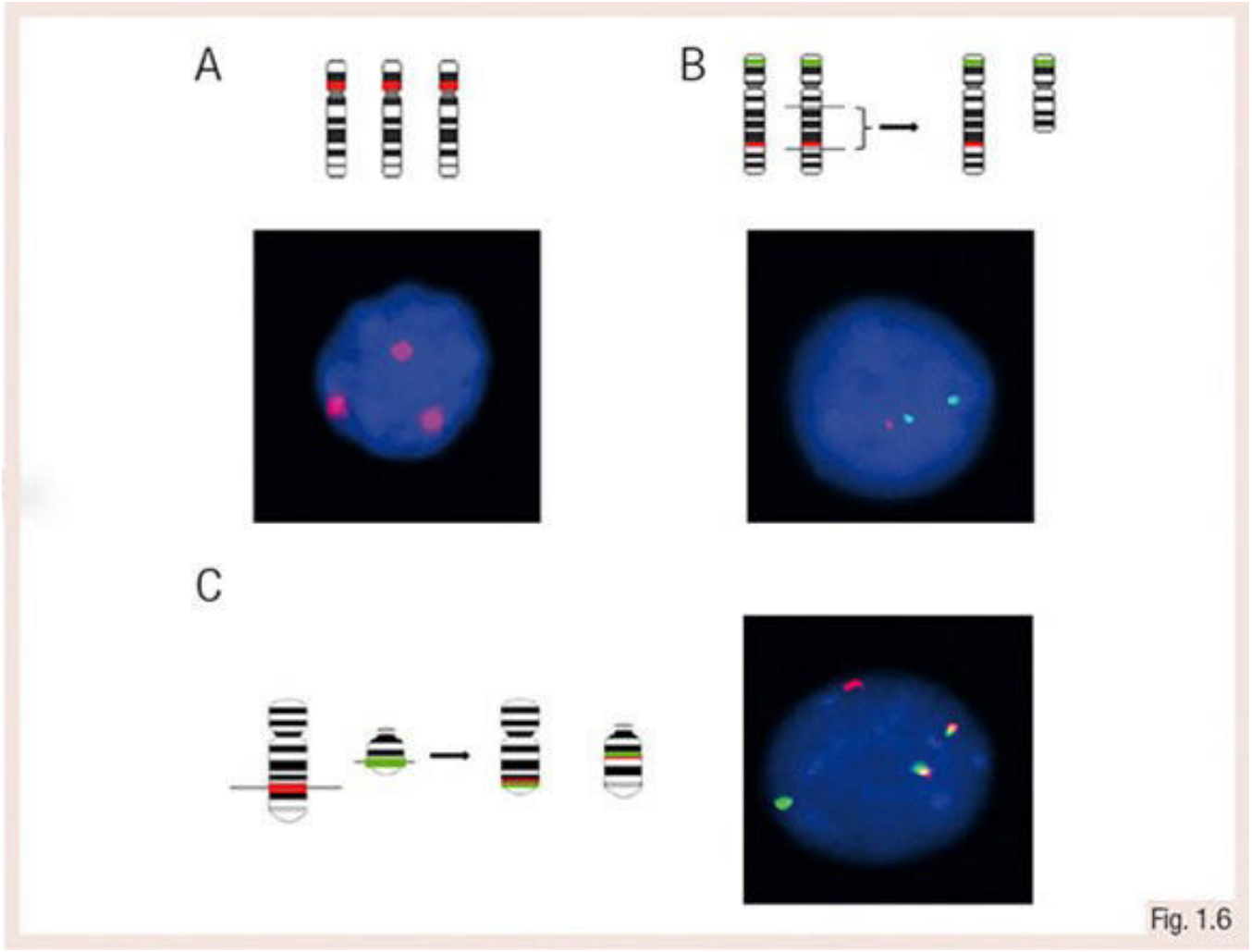
The importance of cytogenetics, molecular diagnostics, and genomics in AML

Workflow for AML diagnosis: A. Cytomorphology showing typical blast cells with Auer rods. B. Immunophenotype with aberrant expression of CD56 and CD19. C. Karyogram showing translocation *t(8;21)*



https://oncologypro.esmo.org/education-library/essentials-for-clinicians/leukaemia-and-myeloma/diagnosis-of-leukaemias-cytogenetic-techniques

Fluorescence in-situ-hybridization



https://oncologypro.esmo.org/education-library/essentials-for-clinicians/leukaemia-and-myeloma/diagnosis-of-leukaemias-cytogenetic-techniques

Genomic testing will play a growing role in the care of AML Patients

Overview of NGS (next generation sequencing) instruments launched since 2005 from Roche(454), Illumina, Ion Torrent and Qiagen; illustrating the development of NGS with increasing sequencing capacities

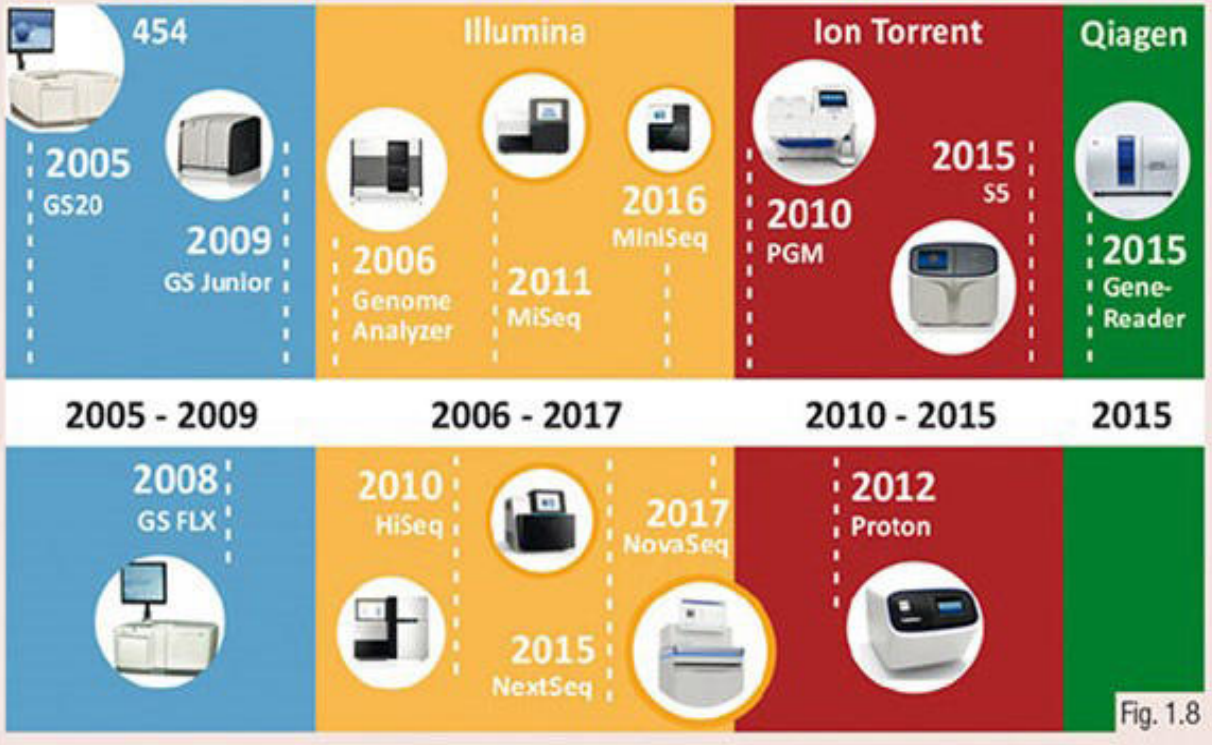
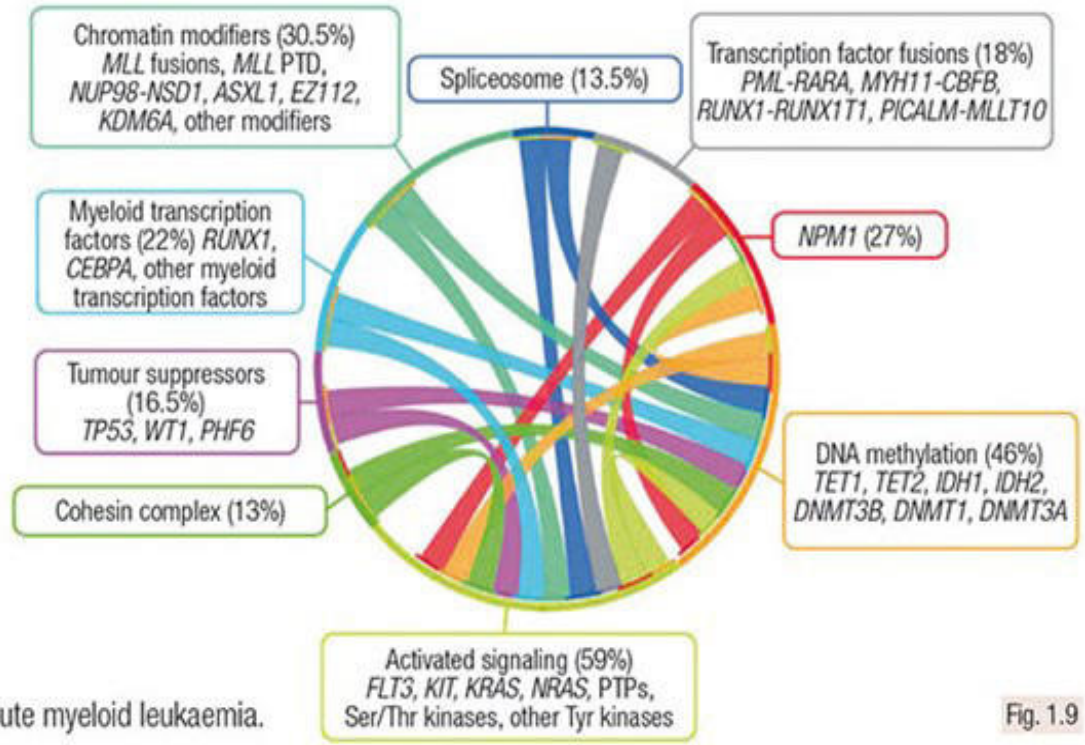


Fig. 1.8

Circos plot showing genetic events leading to AML. Ribbons connecting distinct categories reflect the associations between mutations. Mutual exclusive alterations are not connected



AML, Acute myeloid leukaemia.

Fig. 1.9

https://oncologypro.esmo.org/education-library/essentials-for-clinicians/leukaemia-and-myeloma/diagnosis-of-leukaemias-molecular-techniques

Gene Mutations Found in Patients with AML

FLT3

TP53

IDH1

IDH2

NPM1

ASXL1

RUNX1

DNMT3A

TET2

NRAS

CEBPA

WT1

MLL1

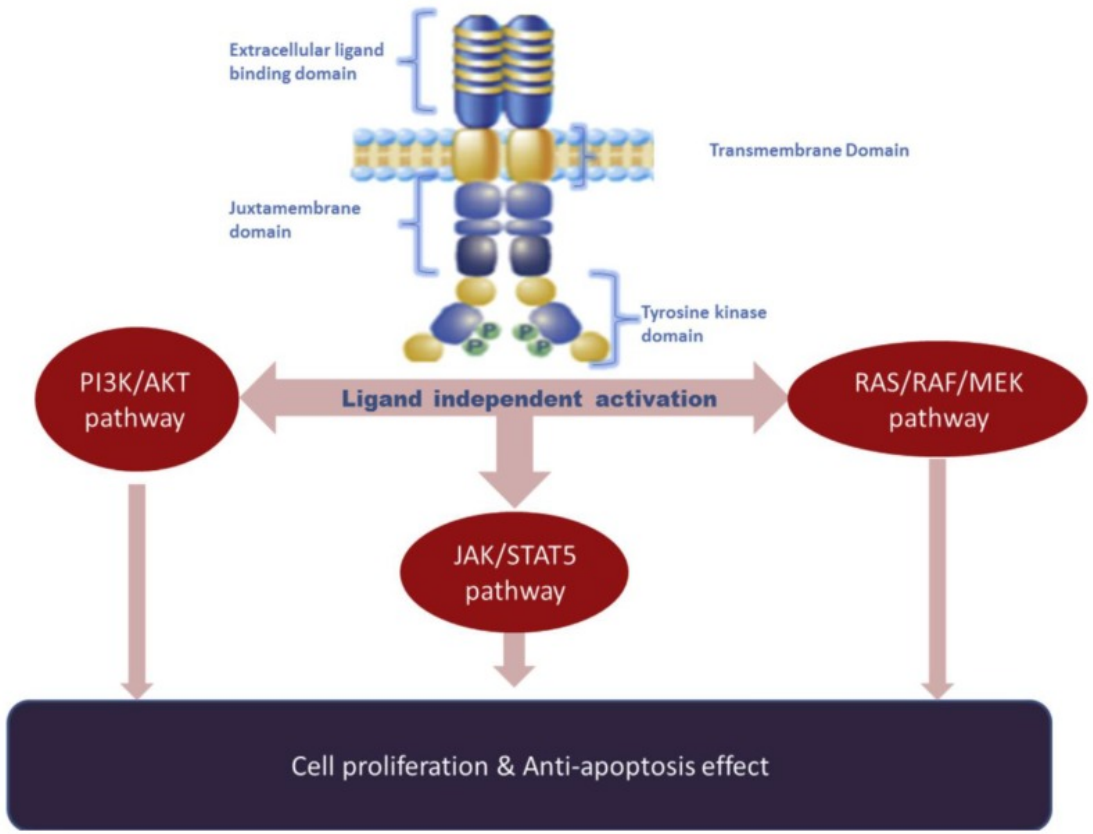
KMT2A

MECOM/EV11

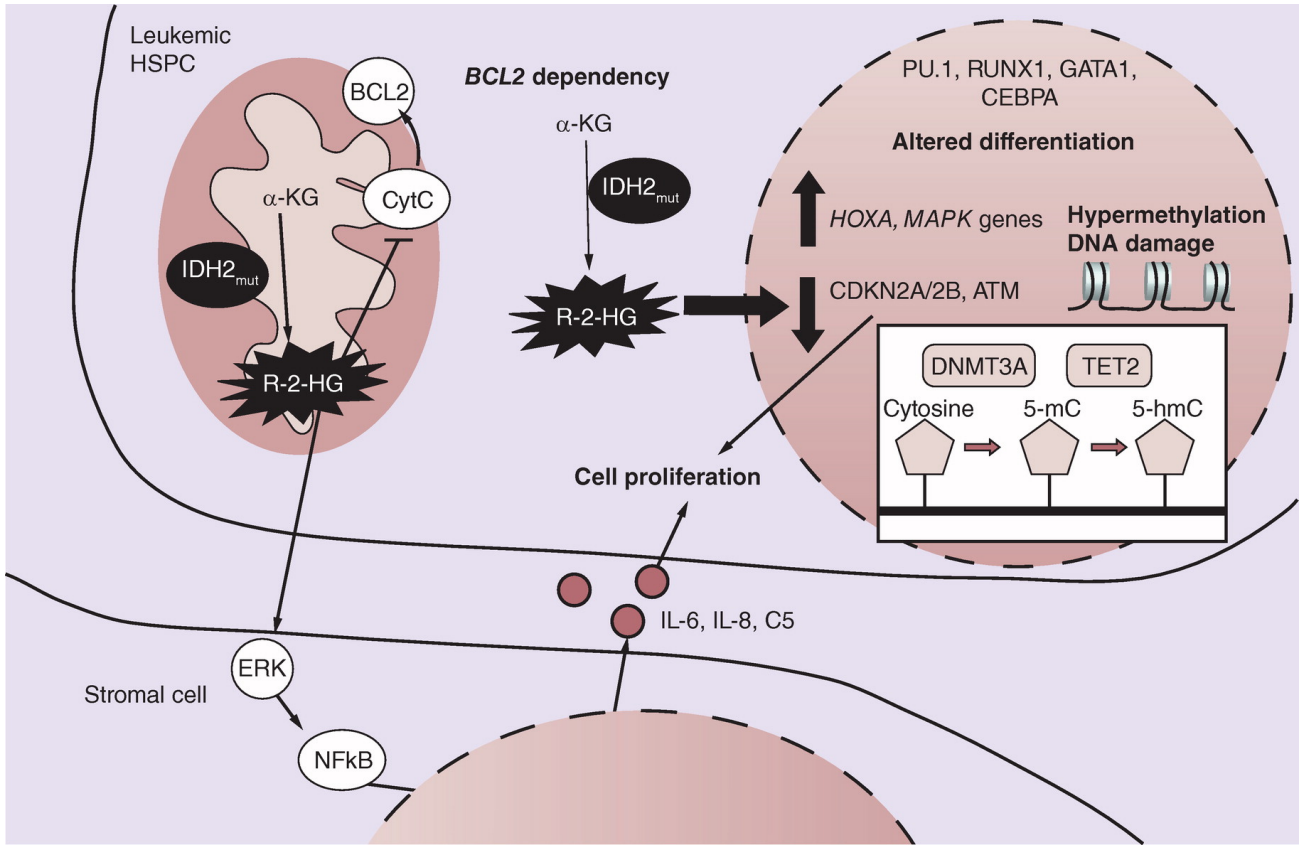
https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf

Functional Impact of FLT3 and IDH1/2 Mutations in AML

FLT3



IDH1/2

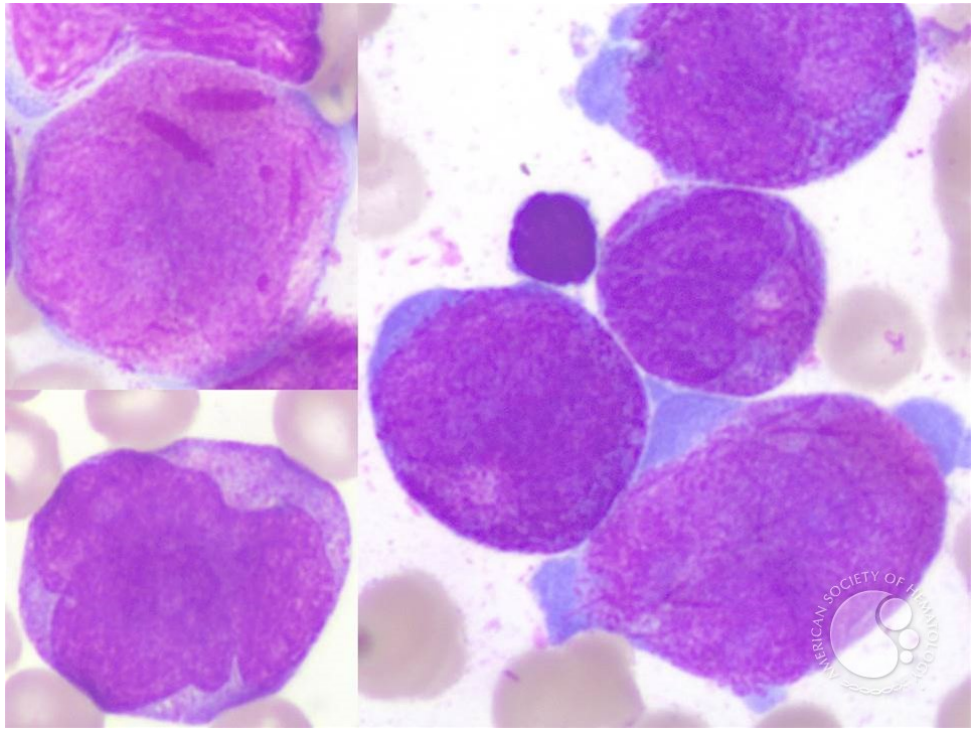


https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5789277/

https://www.futuremedicine.com/doi/10.2217/fon-2017-0523?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

City of Hope

Acute Promyelocytic Leukemia – A Paradigm for Non-chemotherapy-based Treatment of AML



https://imagebank.hematology.org/image/18071/paediatric-acute-promyelocytic-leukemia-with-a-tetraploid-karyotype

- First leukemia type in which biological insights based upon the characterization of a specific genetic/molecular mutation allowed for a novel approach to treatment
- Unique reciprocal translocation t(15;17)(q22;q21) results in the fusion of the promyelocytic leukemia (PML) gene with the retinoic acid receptor (RARα) gene
- Therapy directed at inducing cellular differentiation
- All-Trans Retinoic Acid (ATRA)
- Arsenic Trioxide

https://www.nature.com/articles/2402205

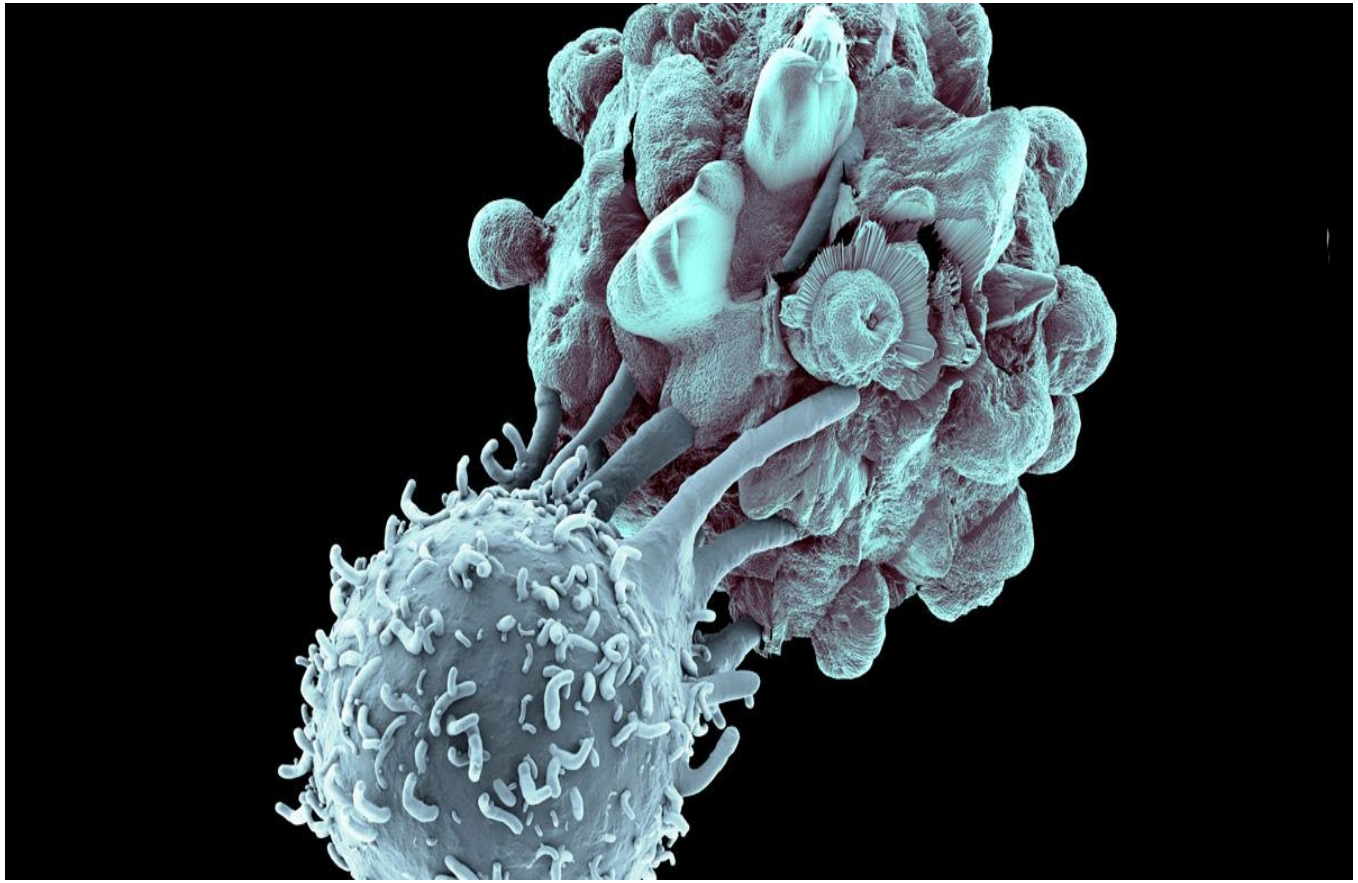
FDA Approved Agents for Treatment of AML

- Arsenic Trioxide
- Azacitidine
- Cerubidine (Daunorubicin Hydrochloride)
- Cyclophosphamide
- Cytarabine
- Daunorubicin Hydrochloride
- Daunorubicin Hydrochloride and Cytarabine Liposome
- Daurismo (Glasdegib Maleate)
- Dexamethasone
- Doxorubicin Hydrochloride
- Enasidenib Mesylate
- Gemtuzumab Ozogamicin
- Gilteritinib Fumarate
- Glasdegib Maleate
- Idamycin PFS (Idarubicin Hydrochloride)
- Idarubicin Hydrochloride
- Idhifa (Enasidenib Mesylate)
- Ivosidenib
- Midostaurin
- Mitoxantrone Hydrochloride
- Mylotarg (Gemtuzumab Ozogamicin)
- Onureg (Azacitidine)
- Prednisone
- Rubidomycin (Daunorubicin Hydrochloride)
- Rydapt (Midostaurin)
- Tabloid (Thioguanine)
- Thioguanine
- Tibsovo (Ivosidenib)
- Trisenox (Arsenic Trioxide)
- Venclexta (Venetoclax)
- Venetoclax
- Vincristine Sulfate
- Vyxeos (Daunorubicin Hydrochloride and Cytarabine Liposome)
- Xospata (Gilteritinib Fumarate)

Emerging Drug Classes in the Treatment of AML

- Enasidenib – targeted treatment for AML with an IDH2 mutation
- Ivosidenib – targeted treatment for AML with an IDH1 mutation
- Gilteritinib – FLT3 inhibitor (novel TKI)
- Midostaurin – FLT3 inhibitor
- Venetoclax – bcl2 inhibitor
- Gemtuzumab ozogomycin – Antibody-drug conjugate (anti-CD33)

AML New Drug Pipeline



- New candidate pharmaceutical pipeline products under study in AML exceed 100
- New therapeutic classes directed at neo-antigens and mutated target genes
- We are also looking at a growing portfolio of cellular therapeutics that include:
  - CAR T-cells
  - Bispecific molecules
  - Bi-/Multi-specific CAR T-cells

Current Risk Stratification in AML Based upon Genetic, Molecular, and Genomic Testing

Favorable Risk

- t(8;21)(q22;q22.1)
- RUNX1-RUNX1T1
  inv(16)(p13.1q22)
  t(16;16)(p13.1;q22)
- CBFB-MYH11 Biallelic mutated CEBPA low†
- Mutated NPM1 without FLT3-ITD or with FLT3-ITD

Intermediate Risk

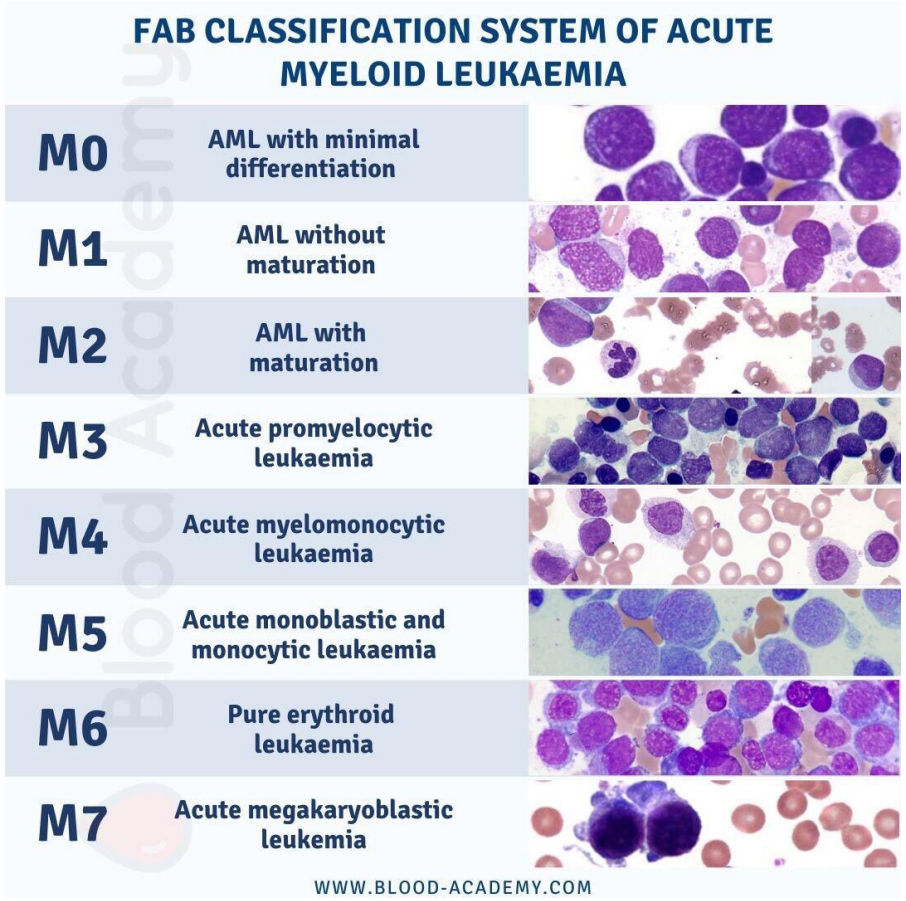
- Mutated NPM1 and FLT3-ITDhigh†
- Wild-type NPM1 without FLT3-ITD or with FLT3-ITDlow† (without adverse-risk genetic lesions)
  t(9;11)(p21.3;q23.3); MLLT3-KMT2A‡
- Cytogenetic abnormalities not classified as favorable or adverse

High-Risk

- 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

https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf

Changes to Induction Therapy in AML



https://twitter.com/blood_academy/status/1281149607238606848

- Patients now receive risk-directed induction therapy which includes therapy directed at targetable molecular mutations
- Low-risk AML in younger patients
  - Gemtuzumab ozogamicin (single dose) combined with “7+3” is now a potential regimen
- FLT3/ITD/TKD
  - Oral midostaurin is now included with standard “7+3”
- Intermediate or poor risk patients
  - ”7+3”
  - HiDAC + idarubicin + etoposide
  - Fludarabine + idarubicin +HiDAC

Induction Therapy for Older Patients with AML

https://www.cancer.gov/news-events/cancer-currents-blog/2018/fda-approval-glasdegib-venetoclax-aml-older

- Induction therapy in older patients must be tailored to suit end-organ function, clinical comorbidities, goals of care and patient preferences
- Regimens for less fit patients:
  - Venetoclax + azacytidine
  - Glasdegib + low-dose ara-C
  - Single agent Gemtuzumab ozogamicin
  - Ivosidenib (IDH1 only)
  - Enasidenib (IDH2 only)
- Regimens for patients who are candidates for intensive induction strategies:
  - “7+3”
  - Venetoclax
  - Venetoclax + azacytidine
  - Venetoclax + low-dose cytarabine
  - Cytarabine + anthracycline + gemtuzumab ozogamicin
  - “7+3” + midostaurin (for FLT3/ITD/TDK)

Post-Induction Treatments in Older and Unfit Patients

- Azacitidine/decitabine maintenance therapy
- Enasidenib maintence or ivosidenib maintenance until progression (IDH2 and IDH1, respectively)
- Venetoclax/decitabine
- Glasdegib
- Azacitidine or decitabine + sorafenib (FLT3/ITD/TKD)
- Gemtuzumab ozogamicin every 4 weeks for 8 doses ($CD33^{+}$)

Maintenance Therapy for Younger Patients who do not Undergo Allogeneic Transplantation

- Oral azacytidine
  - Patients with intermediate or adverse risk disease, in remission

Minimal Residual Disease (MRD)

- Residual detectable leukemia following induction, consolidation treatments portends a much worse prognosis
- Measurable using multiple methodologies
  - Multi-color flow-cytometric measure
  - Polymerase chain reaction-based methods of detecting mutated gene(s)
  - Next Generation sequencing
- Allogeneic transplant for patients in complete remission (CR) who have persisting MRD improves cure rates

Hematopoietic Cell Transplantation

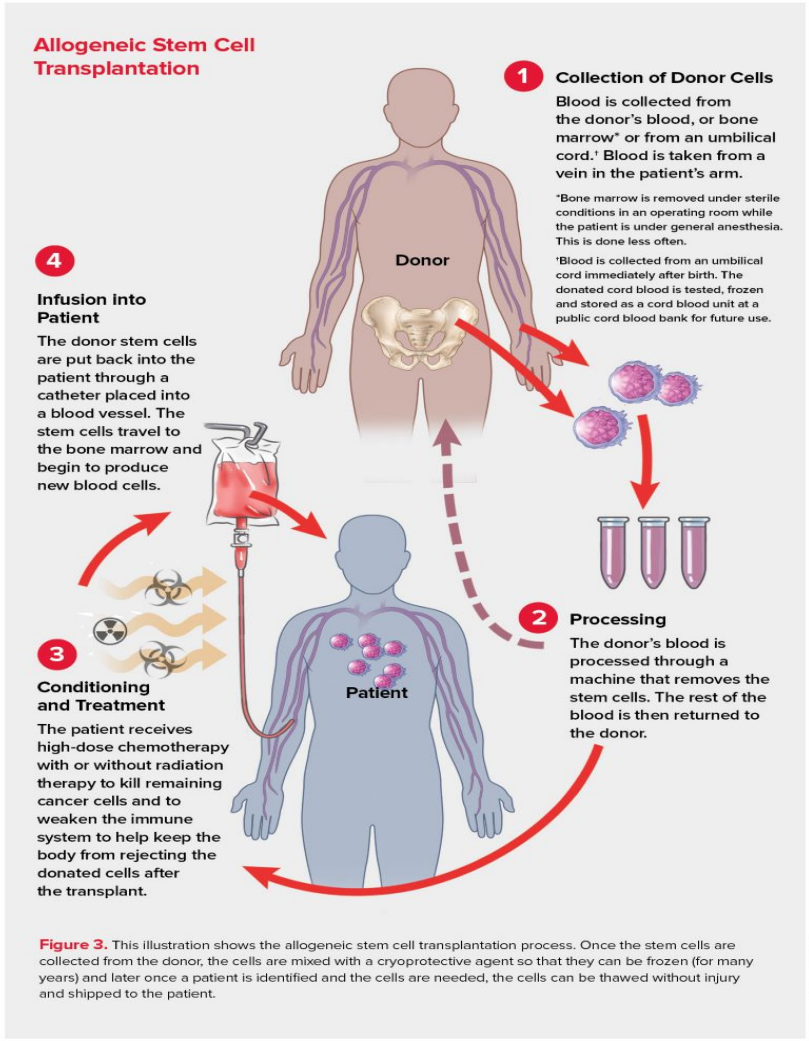
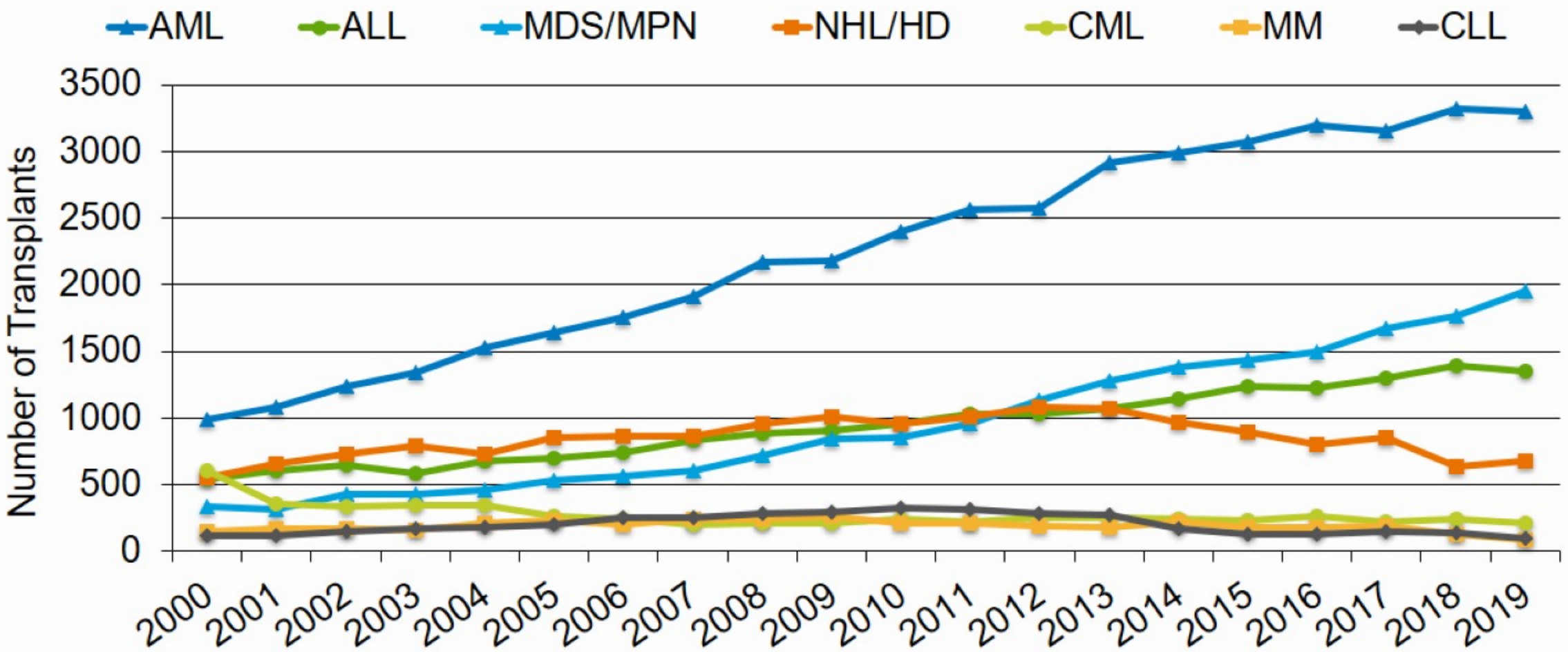


Figure 3. This illustration shows the allogeneic stem cell transplantation process. Once the stem cells are collected from the donor, the cells are mixed with a cryoprotective agent so that they can be frozen (for many years) and later once a patient is identified and the cells are needed, the cells can be thawed without injury and shipped to the patient.

- Allogeneic hematopoietic cell transplantation is a potentially curative set of treatments for patients with AML
- More that 5500 matched related and unrelated donor transplants performed in 2019
- Increasing use of haplo-identical transplantation for patients, exceeding 1250 in 2019
- Growth of Reduced-Intensity Conditioning (RIC), especially for older patients with AML
- Patients over 65 represent the fastest growing group of patients who receive transplants for AML

https://www.lls.org/treatment/types-treatment/stem-cell-transplantation/allogeneic-stem-cell-transplantation

Selected Disease Trends for Allogeneic HCT in the US



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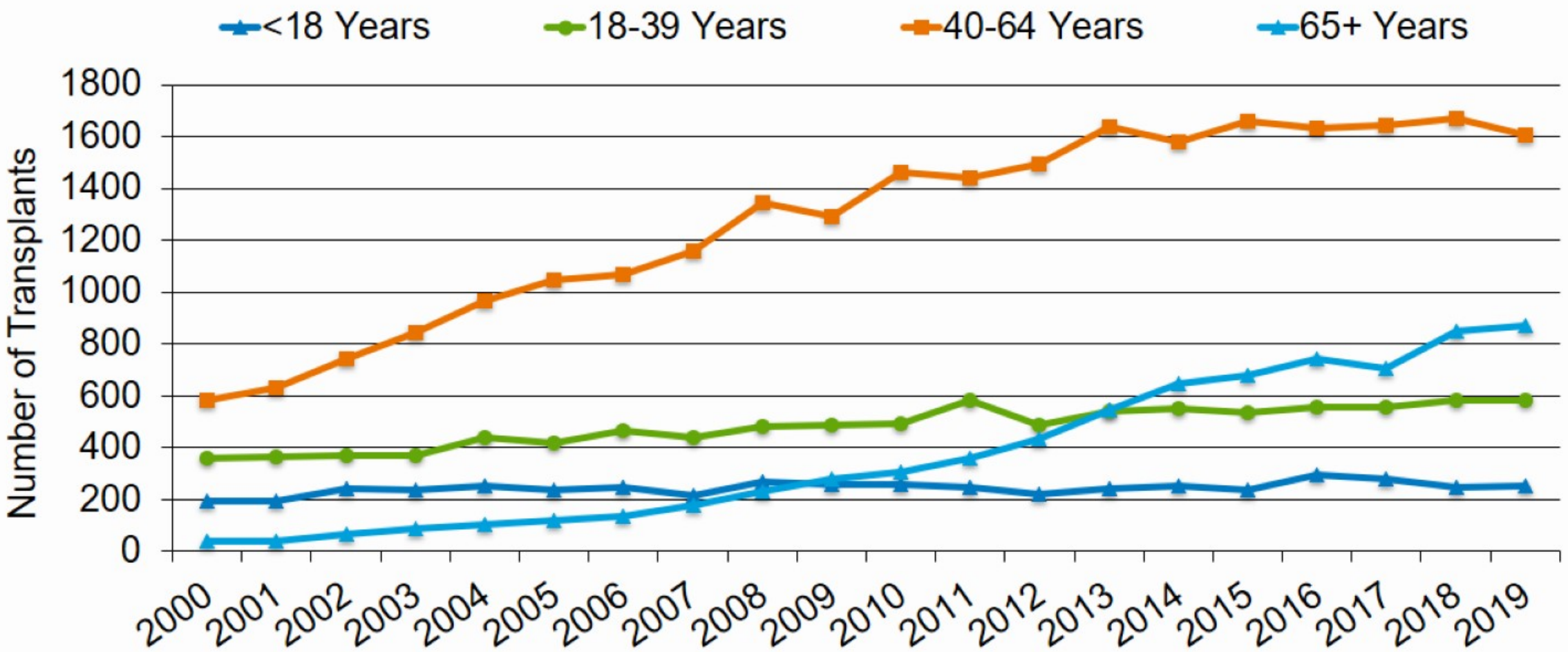
Trends in allogeneic HCT for Acute Myelogenous Leukemia (AML) by Recipient Age in the US



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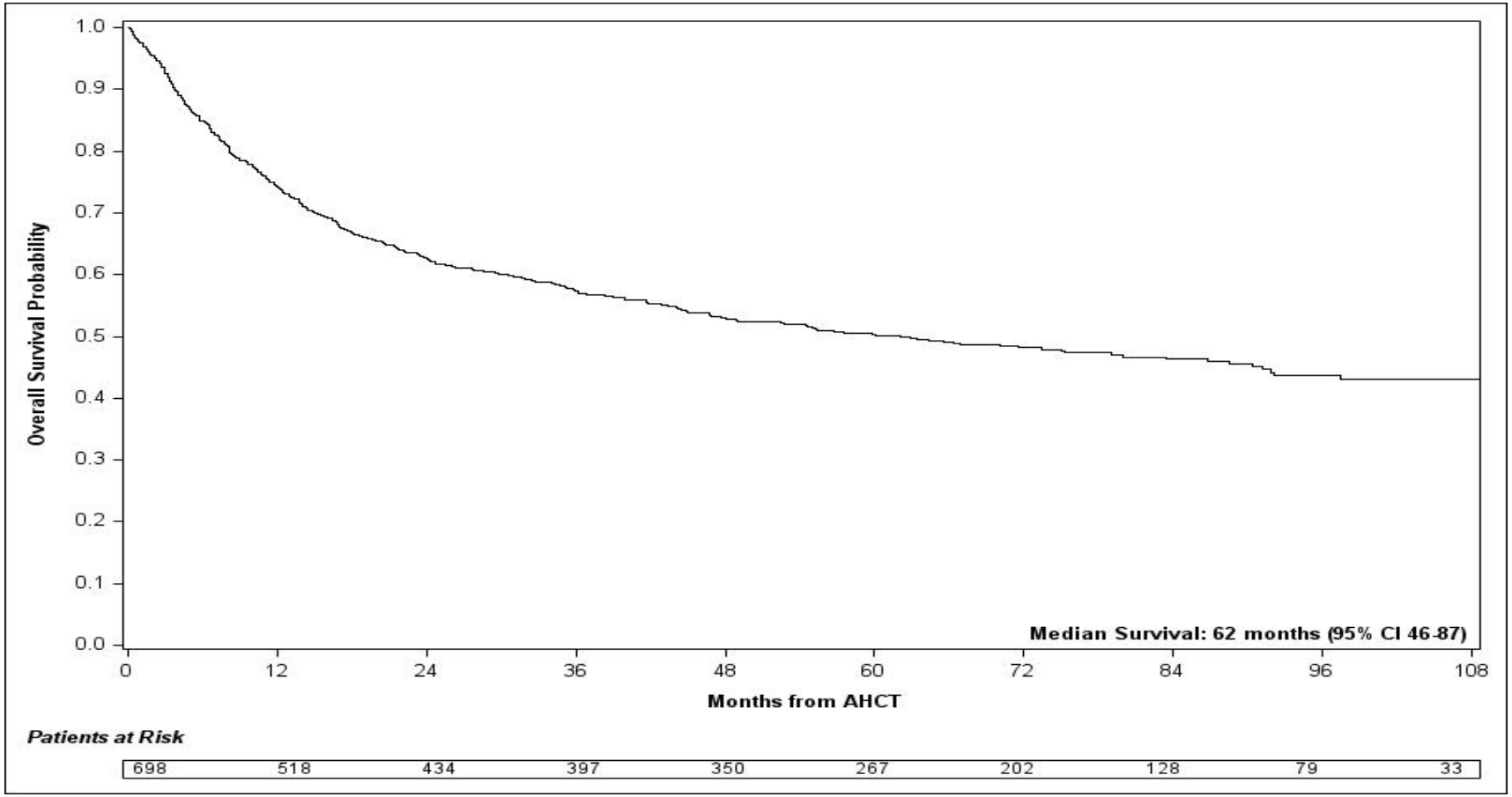
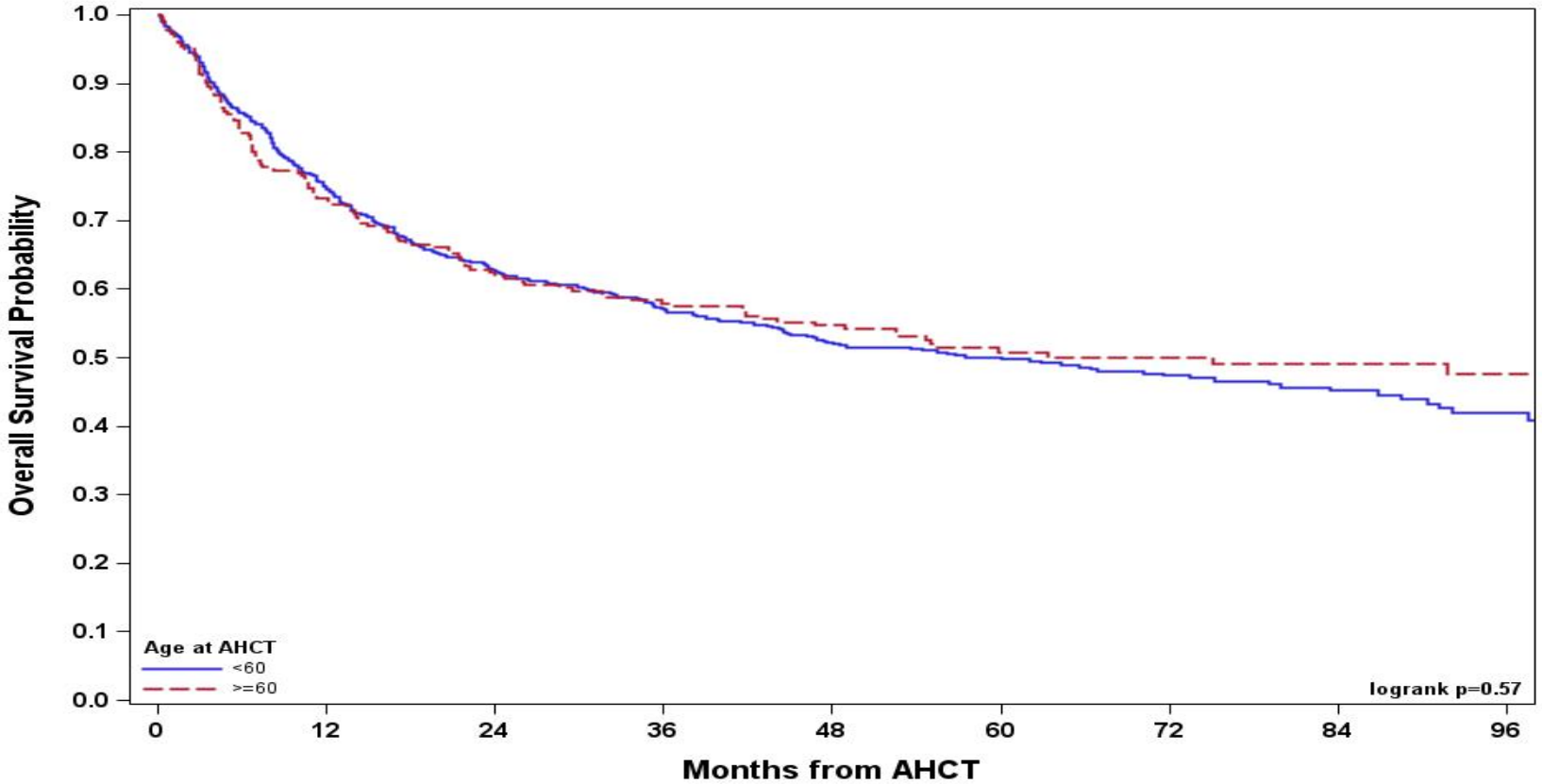
Unadjusted overall survival of acute leukemia patients undergoing allogeneic hematopoietic cell transplant between 1/2011 and 6/2017* (N=698)



*Follow up through December 2021

Unadjusted overall survival by age group of acute leukemia patients undergoing AHCT between 1/2011 and 6/2017* (N=698)

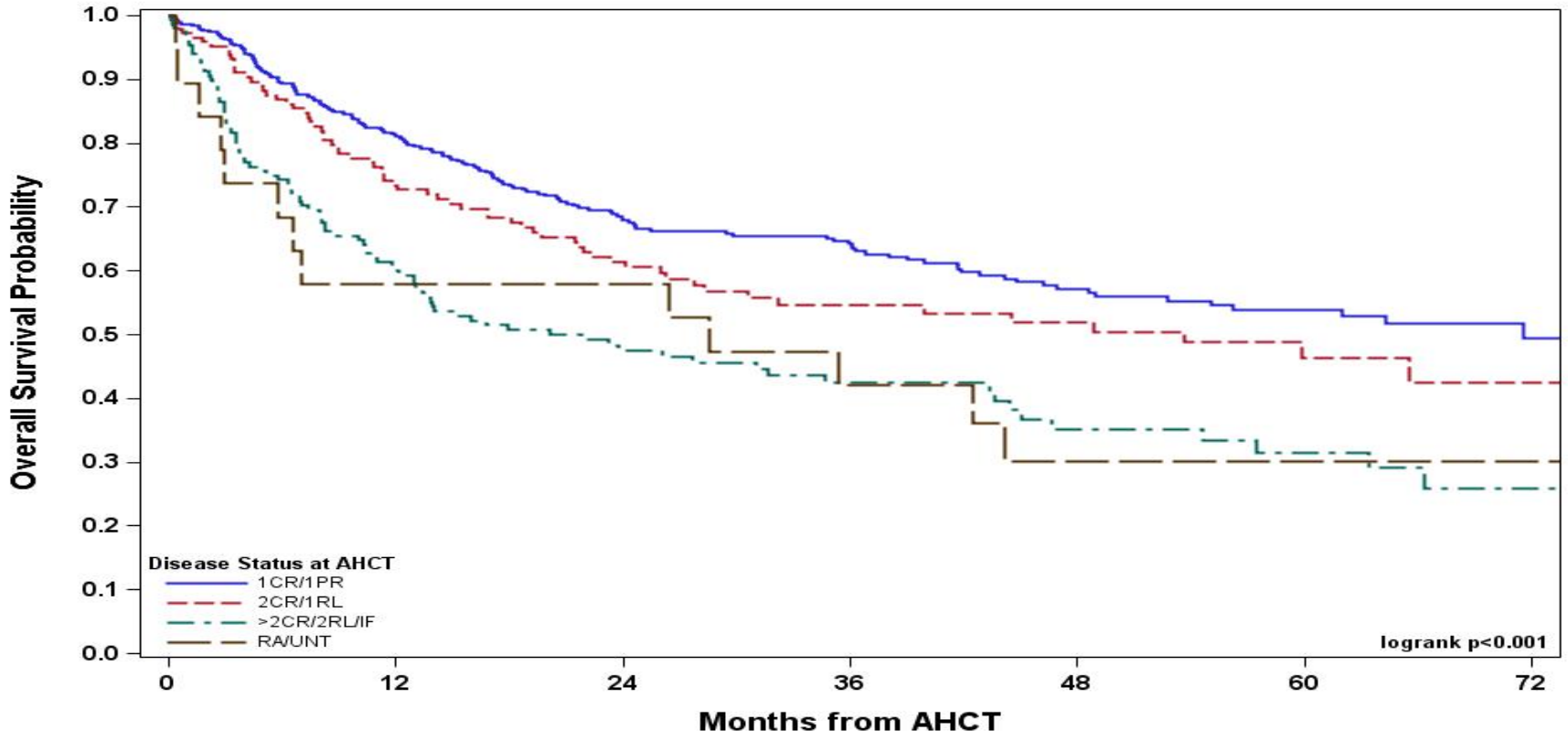


Patients At Risk

<60	477	356	297	270	236	188	143	87	52
>=60	221	162	137	127	114	79	59	41	27

*Follow up through December 2021

Unadjusted overall survival by disease status of acute leukemia patients undergoing AHCT between 1/2011 and 6/2017* (N=698)



Patients At Risk

1CR/1PR	384	301	205	156	99	63	22
2CR/1RL	147	104	77	46	36	19	6
>2CR/2RL/IF	148	87	57	37	23	16	5
RA/UNT	19	11		8	5	4	

*Follow up through May 2019

Post-Transplant Maintenance Therapy in AML

- Sorafenib
  - Patients with FLT3-ITD AML in remission
- Agents under investigation
  - Azacitidine
  - Midostaurine
  - Gilteritinib
  - TKIs (for Ph+ AML)
  - Enasidenib – targeted treatment for AML with an IDH2 mutation
  - Ivosidenib – targeted treatment for AML with an IDH1 mutation
  - Checkpoint inhibitors (Magrolimab)

Key Areas of New Research in AML Treatment

- Polo-like kinase inhibits
- Monoclonal antibody-based treatments
  - Unconjugated
  - MAB-Drug conjugates
  - MAB-radioimmunopharmaceuticals
- Bispecific molecules
- CAR T-cell treatments

CODE ACUTE LEUKEMIA SYSTEM OF CARE

Early Access to High-Expertise Care Saves Lives

Decreased Early Mortality Associated With the Treatment of Acute Myeloid Leukemia at National Cancer Institute-Designated Cancer Centers in California

Gwendolyn Ho, MD, MAS [1,2]; Ted Wun, MD[1]; Lori Muffly, MD[3]; Qian Li, BS[1]; Ann Brunson, MS[1]; Aaron S. Rosenberg, MD, MS [1]; Brian A. Jonas, MD, PhD[1]; and Theresa H.M. Keegan, PhD [1]

"The initial treatment of adult patients with AML at NCI-CCs is associated with a 53% reduction in the odds of early mortality compared with treatment at non-NCI-CCs. Lower early mortality may result from differences in hospital or provider experience and supportive care."

Cancer 2018;124:1938-45.

Code Acute Leukemia Success

- Effective systems of care have a significant impact upon acute leukemia outcomes

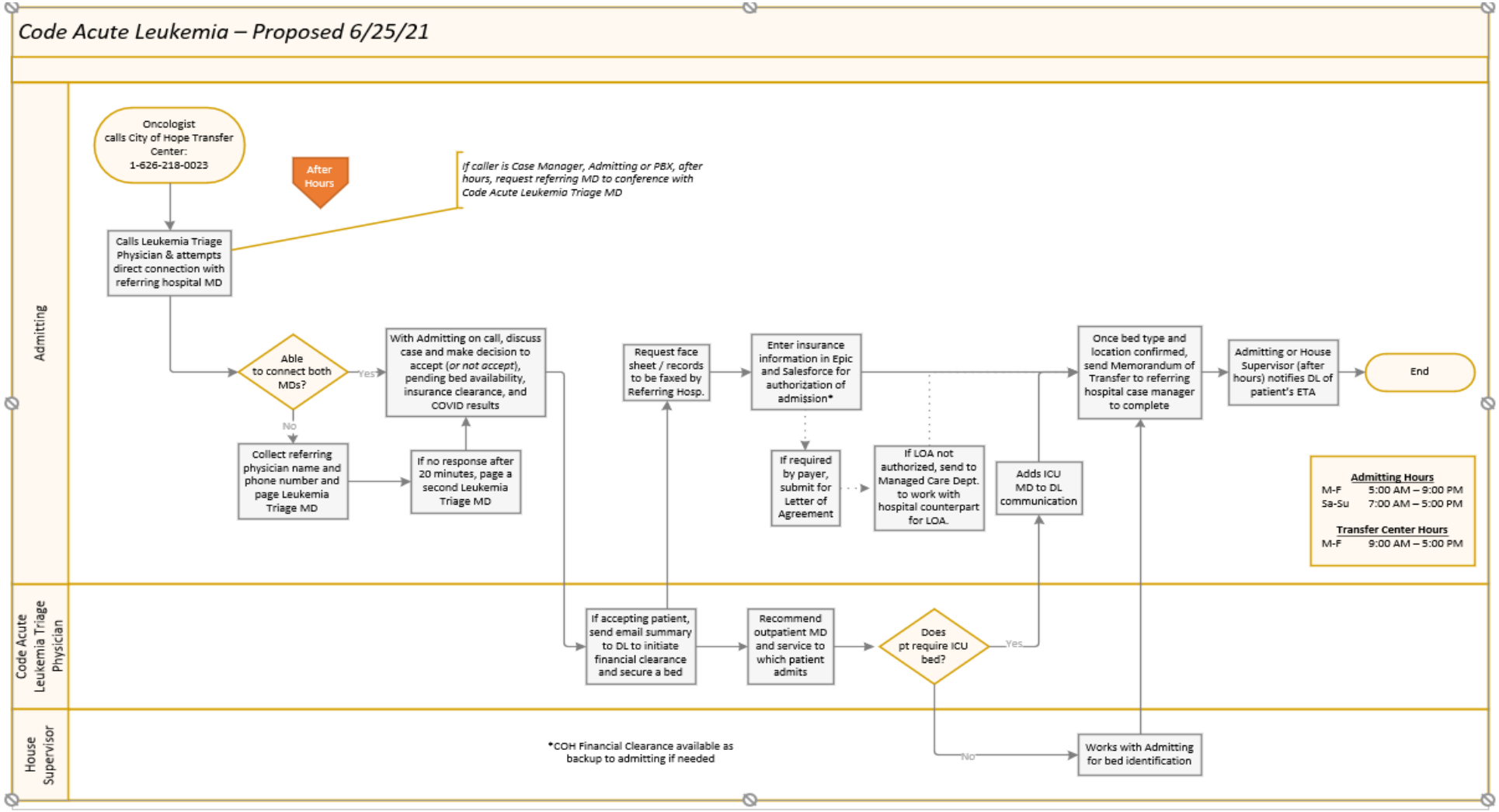
- City of Hope's renowned physicians and researchers utilize the latest technology and innovation coupled with compassionate care to treat acute myeloid leukemia

- From program inception in 2018 City of Hope has successfully transferred and cared for 334 patients.

- The average patient transfer time between the initial email sent to arriving at COH is **21.1 hours**.

- Since 2018, COH has received transfers from over 70 hospitals utilizing Code Acute Leukemia

Current Process




THERE IS NO
PROFIT
IN CURING THE
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SOUL