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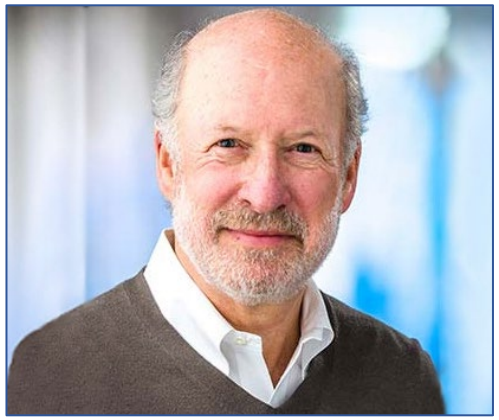
Major Treatment Decisions for Patients with Acute Myeloid Leukemia (AML)

Hosted by

BMT InfoNet

Monday, October 17, 2022



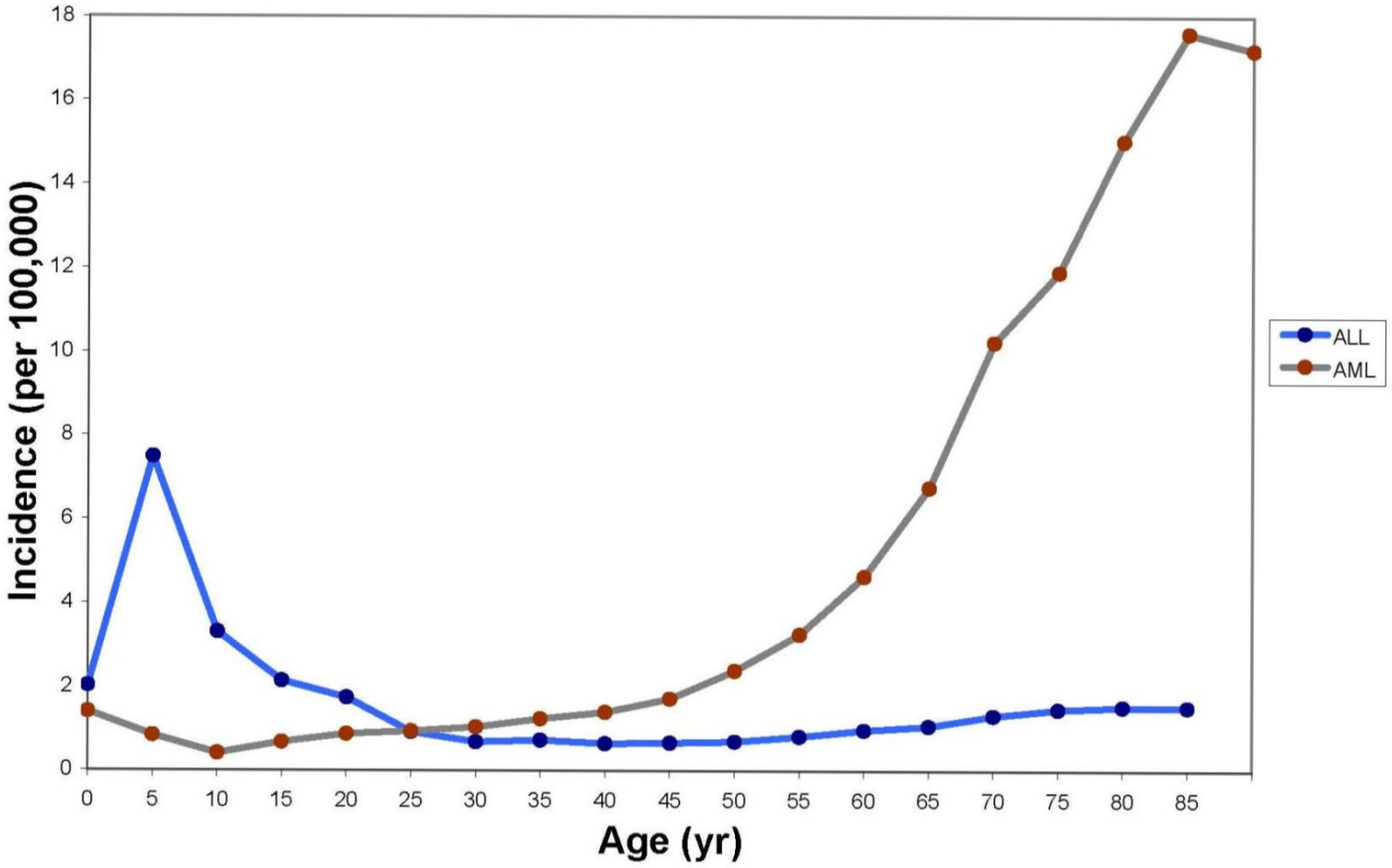
Fred Appelbaum MD,
Executive Vice President and Deputy Director of the Fred Hutchinson Cancer Center

Many thanks to Syndax Pharmaceuticals for its support of this webinar.

Acute Leukemia - 2022

	New Cases	Deaths	5yr Survival
AML	21,380	10,590	26.9%
ALL	5,970	1,440	68.2%

Acute Leukemia Incidence by Age



AML Etiology

Genetic predisposition

Radiation

Smoking

Benzene

Prior chemotherapy

Antecedent hematologic malignancy

AML Clinical and Laboratory Features

Clinical	**Laboratory**
Fatigue	Normochromic, normocytic anemia
Bleeding or bruising	Thrombocytopenia
Fever or infection	Granulocytopenia and peripheral blasts
Soft, non tender mass	Chloroma
	Marrow blasts > 20%

Diagnosis of AML

Peripheral blood (≥20% blasts)

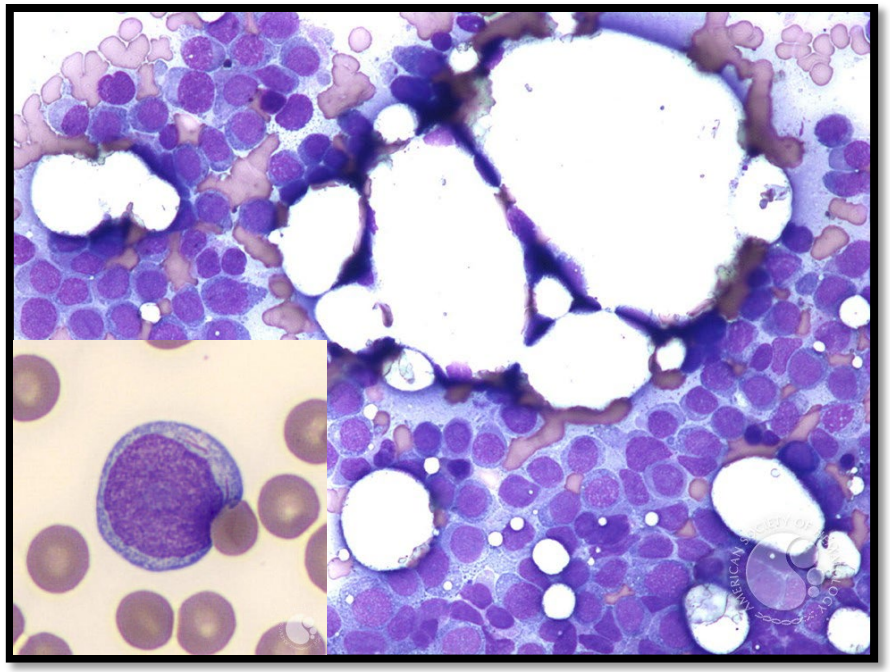
Bone marrow aspirate/biopsy

Mandatory testing on blood and/or marrow at diagnosis

- Morphology
- Immunophenotyping (a.k.a. flow cytometry)
- Cytogenetics/FISH
- Molecular studies

Morphology of AML blast

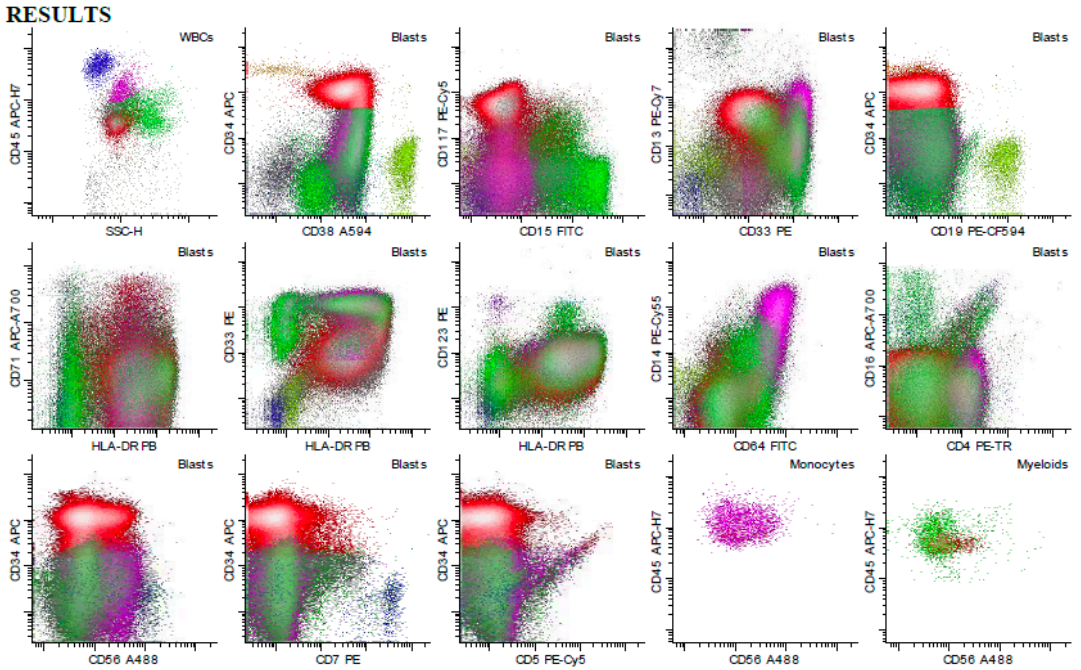
- High N:C ratio
- Large size (diameter ~20 microns)
- Open chromatin
- Multiple nucleoli
- Basophilic cytoplasm +/- azurophilic granules



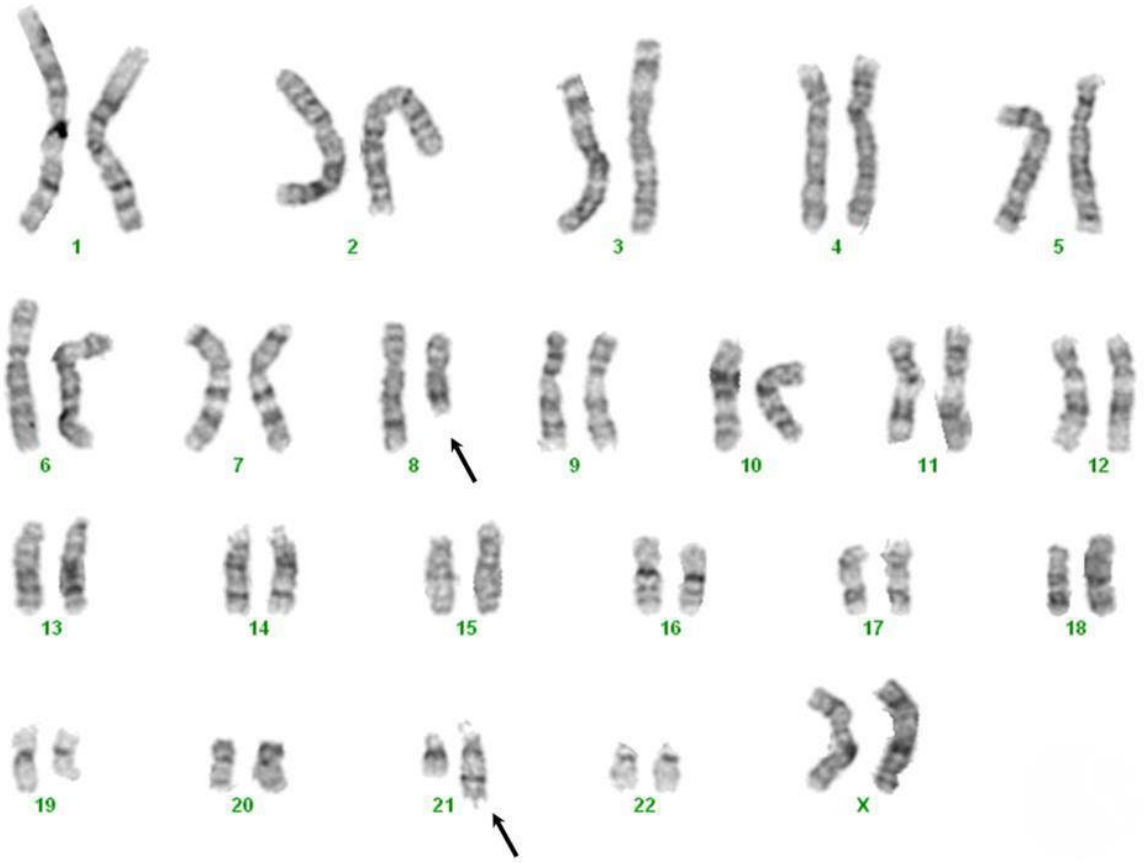
Scordino T. ASH Image Bank 2016; 60924.
Maslak P. ASH Image Bank 2010; 1136.

Flow Cytometry

- a.k.a. immunophenotyping
- Important at diagnosis (AML vs. ALL vs. MPAL)
- Also important at count recovery to help determine measurable residual disease (MRD)

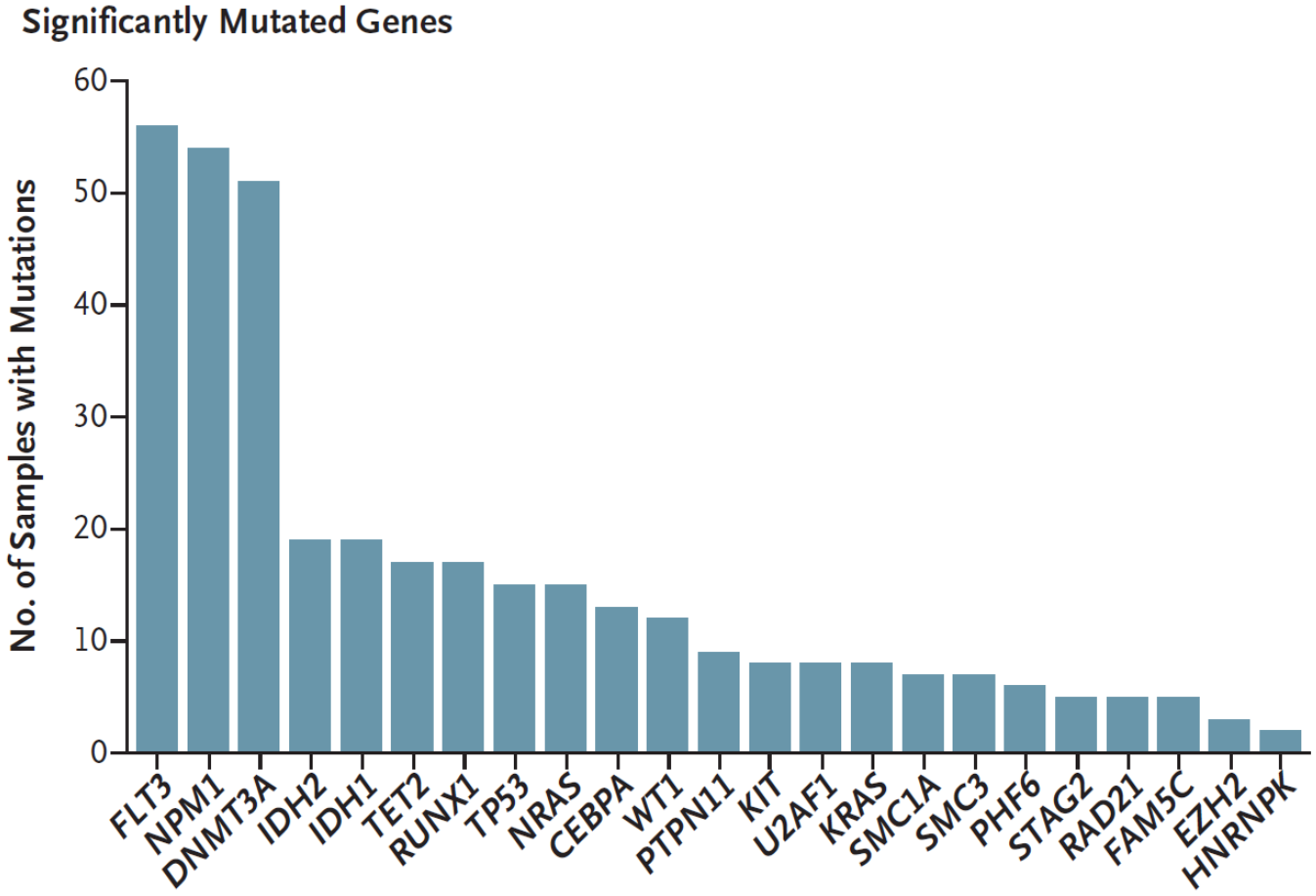


Cytogenetics: Example t(8;21)



Raca G. ASH Image Bank 2015; 60042.

Recurrent Mutations in AML[1]



[1]*NEJM 368:2059, 2013*

AML — 2022

Risk Category	Genetic Abnormality
Favorable	t(8;21)
	inv(16)
	NPM1+ *FLT3*-
	CEBPA+ (biallelic)
Intermediate	*NPM1*+ *FLT3*+
	NPM1- *FLT3*-
	t(9;11)
	Cyto+, not fav or unfav
Adverse	t(6;9), t(v;11q23)
	t(9;22), inv(3)
	-5,-7,-17
	Complex, *NPM1*- *FLT3*+
	RUNX1+, *ASXL1*+, *p53*+

Received: 17 January 2017 | Revised: 8 April 2017 | Accepted: 13 April 2017
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RESEARCH ARTICLE

Early mortality and overall survival of acute myeloid leukemia based on facility type

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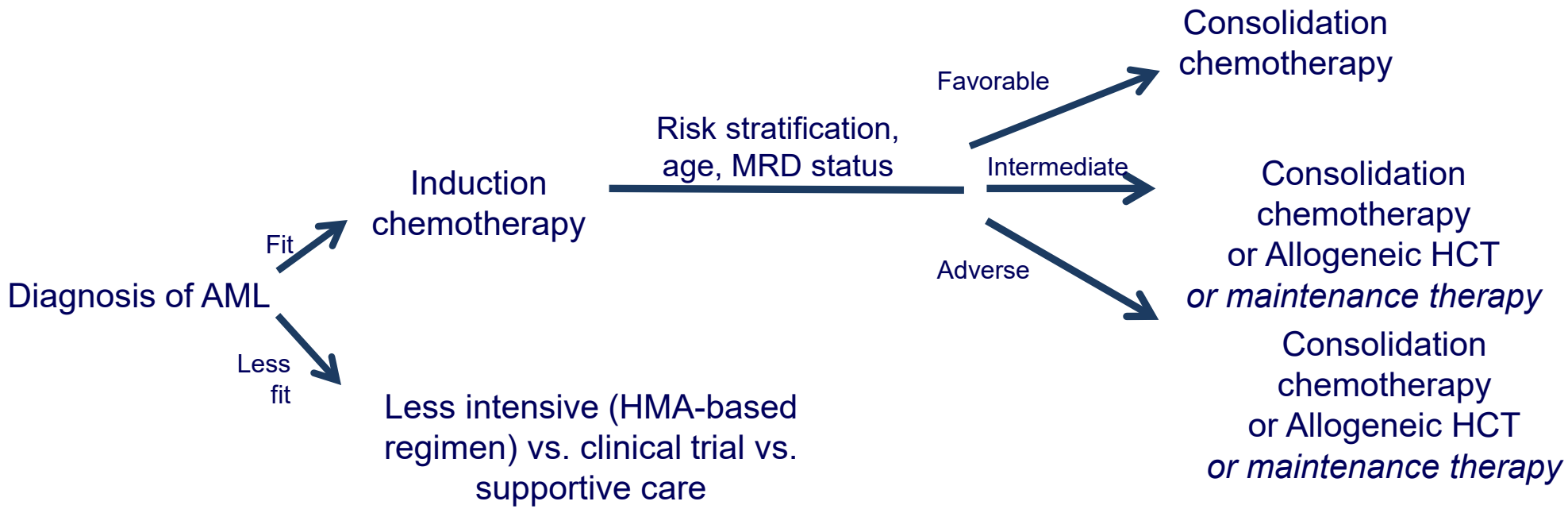
N= 60,738

	Academic Center	Community	p
1 month mortality	16%	29%	<.0001
5 year survival	28%	15%	<.0001

Treatment Schema



Fundamentals of Induction

Most common therapy for 40+ years: “7+3” x 1-2 cycles

- Anthracycline x 3 days
  - Daunorubicin 60-90mg/m^2/day
  - Idarubicin 10-12 mg/m^2/day
  - Mitoxantrone 12-15 mg/m^2/day
- Cytarabine 100-200mg/m^2/day continuous infusion x 7 days

Other options: high-dose cytarabine containing (IA, FLAG-ida or G-CLAM)

NCCN guidelines: “The best management of any cancer patient is in a clinical trial.”

Yates JW et al, Cancer Chemother Rep 1973

Fundamentals of Induction

If favorable or intermediate risk, add gemtuzumab ozogamicin

If FLT3+, add midostaurin

If treatment related or secondary, consider CPX-351 instead of “7+3”

Response Criteria

Response	Definition	Comment
CR without MRD	**CR along with pre-treatment marker by PCR or flow cytometry is negative**	**Sensitivities vary by marker tested and method used**
CR	BM blasts <5%; absence of circulating blasts; absence of extramedullary disease; ANC≥1000/ml; plt≥100K/ml	MRD+ or unknown
CRi	All CR criteria except ANC<1000/ml and/or plt<100K/ml	
MFLS	Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required	Cellularity at least 10% and/or 200 cells counted
PR	Heme criteria of CR; decrease of BM blasts to 5% to 25%; and decrease of pretreatment BM blast percentage by at least 50%	Primarily for clinical trials

Dohner H et al, Blood 2017

Favorable Risk AML

Post-remission therapy

Multiple cycles of HDAC containing chemotherapy

Reserve HCT until 1st relapse

Consider HCT in CR1 if < 3 log reduction in MRD or reappearance

Intermediate Risk AML

Post-remission therapy

Allogeneic HCT in CR1 if appropriate donor available

Consider withholding HCT if MRD negative and HCT CI >2

Advance Risk AML

Post-remission therapy

Allogeneic HCT if possible

Maintenance options

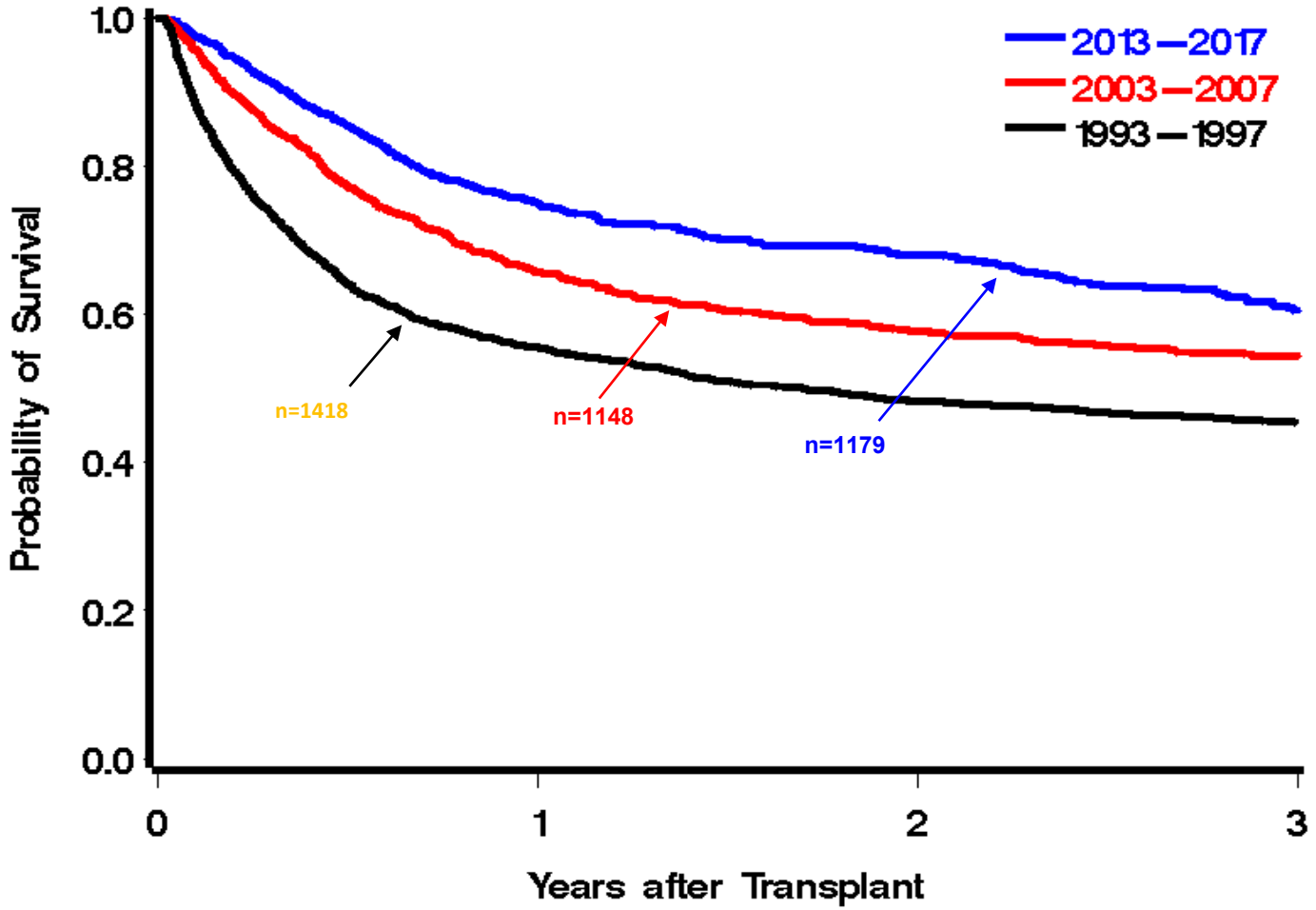
- Midostaurin x 12 months in *FLT3*-mutated patients who do not undergo allogeneic HCT
- 5-day azacitidine 50mg/m^2 in patients >60 after 2 courses of intensive chemo (studied for max 12 cycles)
- Oral azacitidine tablets (Onureg)

Stone RM et al, NEJM 2017; Huls G et al, Blood 2019; Wei et al NEJM 2020

Progress in Allogeneic Transplantation

1. A donor for everyone in need
2. Reduction in transplant-related complications
   - prevention and treatment of infections
   - avoidance of direct organ toxicities
   - reduction in GVHD
3. Better eradication of disease

Survival Following Allogeneic Hematopoietic Cell Transplantation for Hematologic Malignancies



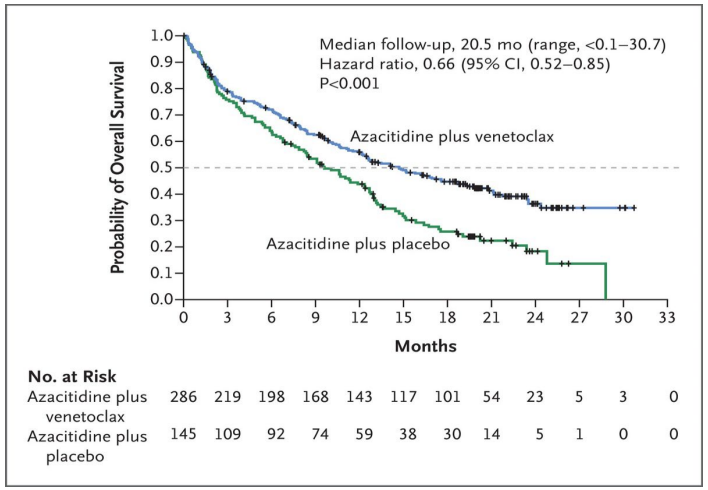
Less Intensive Induction

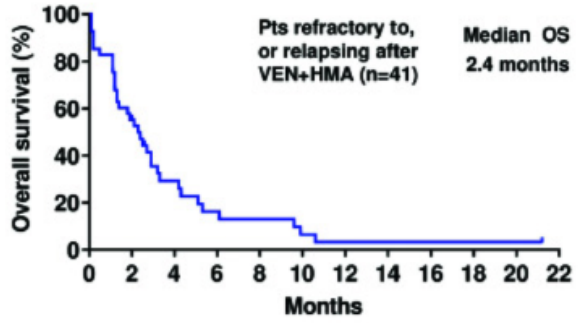
- Generally for “less fit”
- Continue less intensive treatment for as long as patients tolerate and receive clinical benefit
- ?relevance of MRD
- Retrospective analyses: older patients benefit from higher-intensity therapy
- Older age *plus* another factor for non-intense therapy
  - Patient-related factors, such as ECOG PS 3-4 or significant co-morbidities not related to AML
  - Disease-related factor, such as adverse-risk genetics

Juliusson G et al, Blood 2009; Dohner H et al, Blood 2017

FDA Approval 2018: Venetoclax

- Phase 3 VIALE-A trial: azacitidine vs. azacitidine + venetoclax
- Composite CR 66.4% vs. 28.3%
- Median time to response 1.3 months
- Primary endpoint OS 14.7 vs. 9.6 months
- Goal of treatment is not cure (i.e., continue treatment as long as there is clinical benefit and/or patient tolerates it)
- MRD may be less relevant
- Outcomes after ven/HMA failure are very poor





DiNardo C et al, NEJM 2020; Maiti A et al Haematologica 2021

Summary Points

- Diagnosis of AML generally requires 20% or more blasts in blood or marrow
- Cytogenetic and molecular data are used to risk stratify
- Other elements of risk include age, functional status, count recovery, MRD
- Induction chemotherapy is the most common initial treatment for fit patients
- New molecularly targeted drugs have been FDA approved
- Maintenance may be appropriate for some patients
- Allogeneic transplant is a common component of AML treatment
- Venetoclax + azacytidine is effective for less fit patients

Questions?

Fred Appelbaum, MD

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