Managing the Continuum of Myeloid Malignancies (CML, MPN, MDS, and AML)

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2017 JADPRO Live at APSHO

Learning Objectives

1. Describe the latest WHO disease definitions for diagnosing myeloid malignancies
2. Discuss the normal physiology of the JAK-STAT biochemical signaling pathway, as well as its dysregulation in myeloproliferative neoplasms
3. Recall the mechanisms of action for novel therapies for AML
4. Summarize the clinical relevance of molecular mutations in AML, including FLT3 and IDH2
5. Identify germline mutations in patients with predisposition for MDS/AML/MPN
6. Describe effective and safe current treatments for patients with myeloid malignancies

Financial Disclosures

- Dr. Artz has nothing to disclose.
- Dr. Ridgeway has served on the advisory board for Celgene Pharmaceuticals.

Outline

- Describe the 2016 WHO disease classification for diagnosing myeloid malignancies
- Identify germline mutations in patients with predisposition for MDS/AML/MPN
- Summarize the clinical relevance of molecular mutations in AML including FLT3 and IDH2
- MPNs and the JAK-STAT pathway
- Novel therapies of myeloid malignancies and MOA
- Allogeneic SCT as a therapy of myeloid malignancies
- The older adult patient and transplant: an interdisciplinary model

Describe the latest WHO disease definitions for diagnosing myeloid malignancies

Entering the Genetic Era

A Primer on Genetics in Malignancy

Category	Diagnostic	Prognostic	Predictive
Genetic change	**Refines diagnosis**	**Informs outcomes**	**Enriches for response +/- targetable**
Examples			
BCR-ABL (9;22 translocation)	CML, Ph+ ALL	Worse outcome in Ph+ ALL	TKIs for disease (e.g. imatinib, dasatinib)
JAK2 mutation	MP neoplasms	Varied	Variable
TP53	Suggests neoplasm, hereditary possible	Often worse and resistant to cytotoxic	Novel agents may be more effective

Familial Myeloid Malignancy Syndromes: 2017

Hematologic malignancies only

1. Familial AML with mutated CEBPA (CEBPA)
2. Familial AML/MPN due to ATG2B and GSKIP duplication (ATG2B, GSKIP)
3. Familial MDS/AL due to DDX41 mutation (DDX41)

Platelet dysfunction

1. Familial platelet disorder with propensity to myeloid malignancies (RUNX1)
2. Thrombocytopenia (ANKRD26)
3. Thrombocytopenia (ETV6)

Additional organ systems affected

1. GATA2 deficiency syndromes (GATA2)
2. Short telomere syndromes (TERT, TERC, RTEL1, PARN)
3. Familial aplastic anemia/MDS due to SRP72 mutation (SRP72)

Others coming soon…SAMD9L, TYK2, etc

AML = acute myeloid leukemia; AL = acute leukemia; MDS = myelodysplastic syndrome; MPN = myeloproliferative neoplasm.

Classification

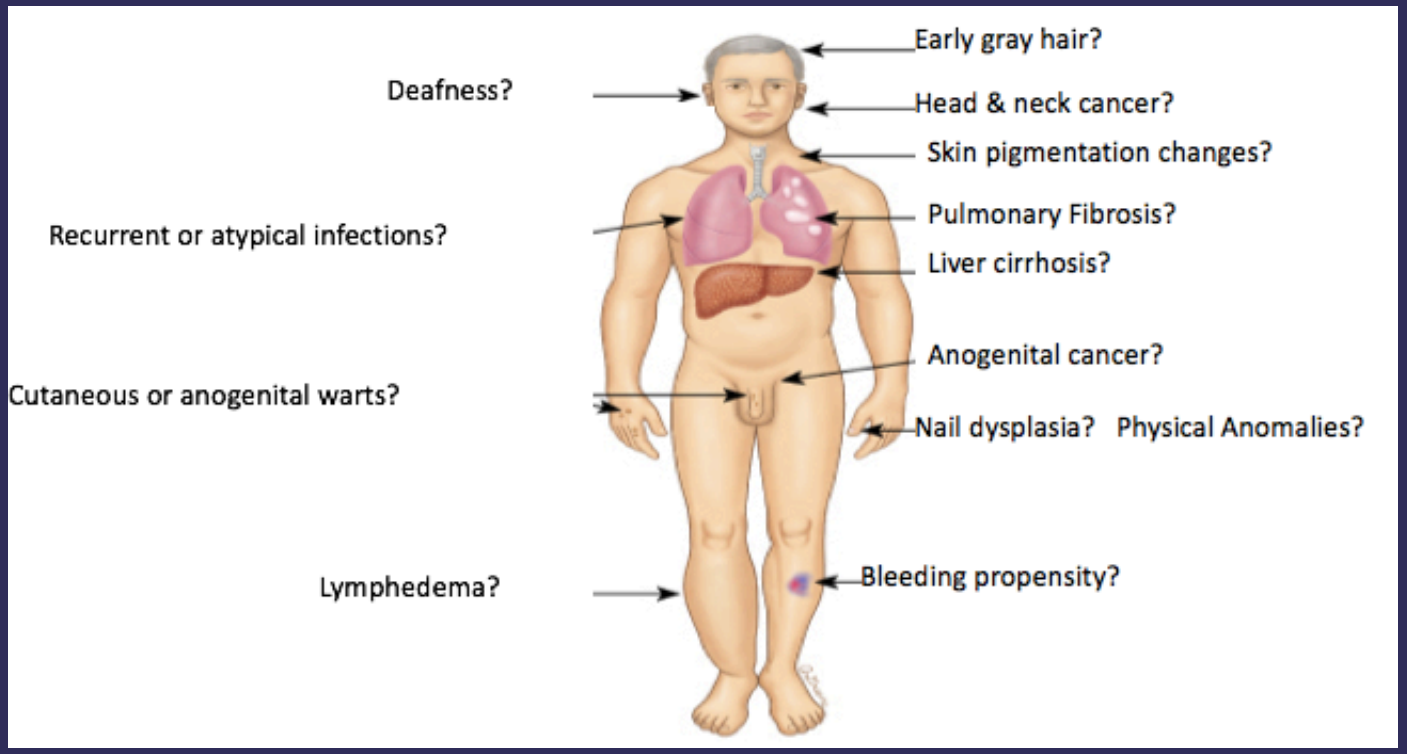
Table 17. Classification of myeloid neoplasms with germ line predisposition

Myeloid neoplasm classification
Myeloid neoplasms with germ line predisposition without a preexisting disorder or organ dysfunction
AML with germ line *CEBPA* mutation
Myeloid neoplasms with germ line *DDX41* mutation*
Myeloid neoplasms with germ line predisposition and preexisting platelet disorders
Myeloid neoplasms with germ line *RUNX1* mutation*
Myeloid neoplasms with germ line *ANKRD26* mutation*
Myeloid neoplasms with germ line *ETV6* mutation*
Myeloid neoplasms with germ line predisposition and other organ dysfunction
Myeloid neoplasms with germ line *GATA2* mutation
Myeloid neoplasms associated with BM failure syndromes
Myeloid neoplasms associated with telomere biology disorders
JMML associated with neurofibromatosis, Noonan syndrome or
Noonan syndrome-like disorders
Myeloid neoplasms associated with Down syndrome*

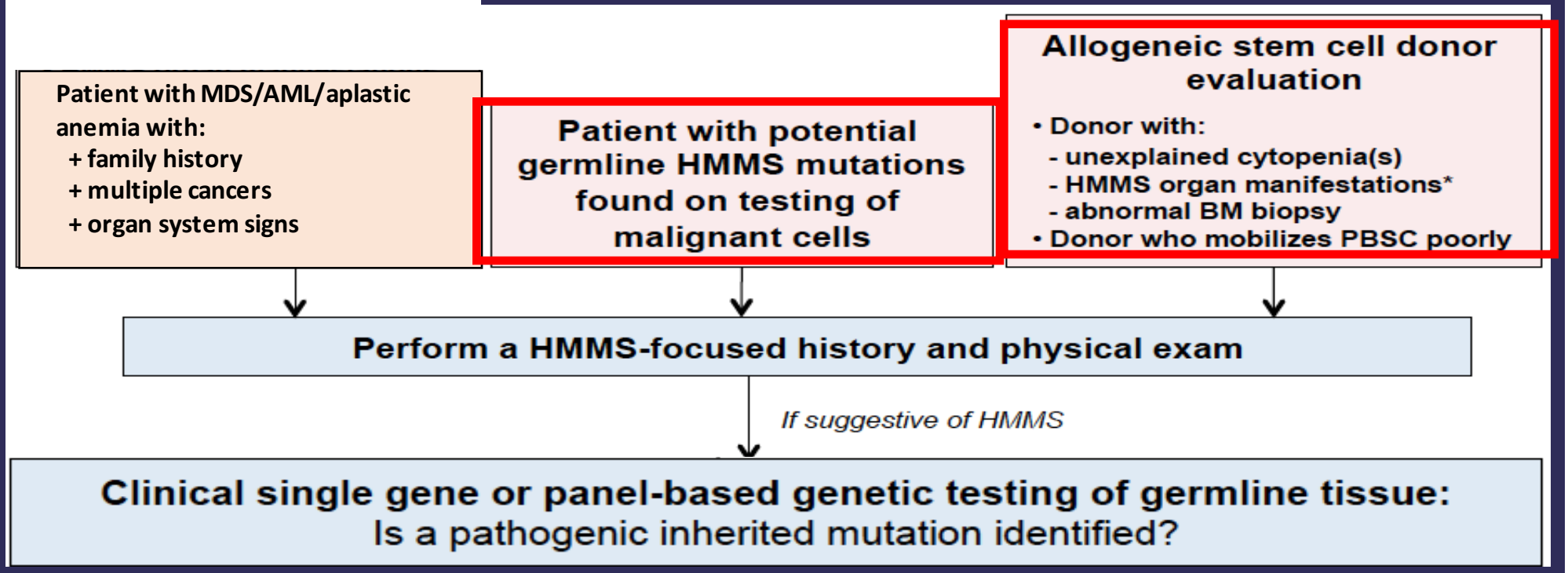
*Lymphoid neoplasms also reported.

Arber et al. *Blood*. 2016;127(20):2391-2405.

Familial MDS/AL Organ System Manifestations



How to Identify, Test, and Manage Adults With HMMS



The U of C Hematopoietic Malignancies Cancer Risk Team. *Blood*. 2016;128(14):1800-13.

2016 WHO Diagnostic Criteria for Overt PMF

Major Criteria (all are required):

1. Presence of megakaryocyte proliferation and atypia, usually accompanied by either reticulin and/or collagen fibrosis
2. Not meeting WHO criteria for PV, CML, MDS, or other myeloid neoplasm
3. Presence of JAK2, CALR. or MPL or other clonal marker; or in absence of clonal marker—no evidence that marrow fibrosis is reactive

Minor Criteria (one of the following):

a. Anemia not due to a comorbid condition
b. Leukocytosis ≥11 x 10^9/L
c. Palpable splenomegaly
d. LDH increased to above upper normal limit
e. Leukoerythroblastosis

CML = chronic myeloid leukemia; LDH = lactate dehydrogenase; PMF = primary myelofibrosis; PV = polycythemia vera; WHO = World Health Organization.

https://www.mpnconnect.com/pdf/who-diagnostic-criteria-mf-pv-et.pdf

Rare Myeloid Neoplasms With Established Targets

Myeloid/lymphoid neoplasms with eosinophilia and PDGFRA/B, FGFR1, or PCM1-JAK2

- PDGFRA or PDGFRA mutant: imatinib
- FGFR1: consider clinical trial with FGFR1 inhibitor
- PCM1-JAK2: ruxolitinib

MDS Requirements for Classification

Feature	Category	Comment	Predictive
Dysplastic lineages	1 vs 2 or 3	Erythroid, myeloid, and mekaryocytic	
Cytopenias	1, 2, or 3	Hb < 10 g/dL, Platelet < 100K/uL, ANC < 1.8 K/uL	MDS may present with mild anemia or thrombocytopena. PB monocytes must be <1 × 10^9/L
Ring sideroblasts	15% or more	5% or more if SF3B1	
Blasts	BM or PB	Also note presence of Auer rods	If 1% PB blasts, must be on at least 2 separate occasions
Karyotype	Del 5q or MDS defining	MDS defining abnormalities when minimal cytopenia	By conventional cytogenetics

BM = bone marrow; PB = peripheral blood.

MDS Classification by WHO 2016

Feature	Comment
Low Blast Categories	<5% BM blasts, <2% blood, no auer rods
MDS with single lineage dysplasia (SLD)	non-5q- and 1 lineage dysplasia
MDS with multi-lineage dysplasia (MLD)	Same with 2-3 lineage dysplasia
MDS with ring sideroblasts (MD RS with SLD or MLD)	15% or more RS or 5% with SF3B1 MDS RS with SLD vs MDS RS with MLD
MDS with isolated deletion 5q-	Can have 1 and cyto abnormality except del 7/7q
with 1% blood blasts, with SLD and pancytopenia, based on defining cytogenetic abnormality and refractory cytopenia of childhood	
High Blasts	
MDS excess blasts-1	BM 5%-9% or PB 2%-4%, no Auer rods
MDS excess blasts-2	BM 10%-19% or PB 5%-19% or Auer rods

Arber DA, et al. *Blood*. 2016;127:2391-405.

Acute Myeloid Leukemia and Related Neoplasms

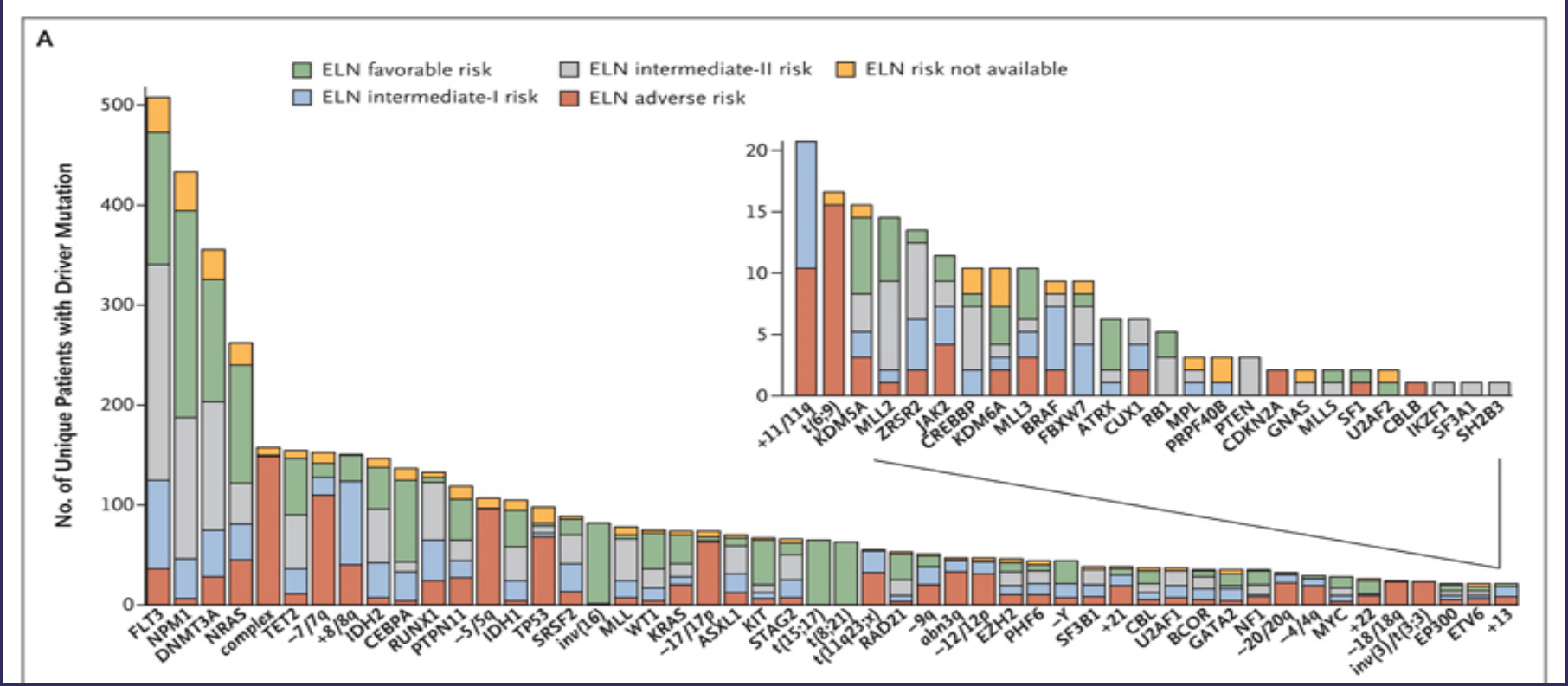
AML with recurrent genetic abnormalities (+ provisional)

Provisional Entities: AML with BCR-ABL1, AML with mutated RUNX1 t(16;16)(p13.1;q22);*CBFB-MYH11; PML-RARA*, t(9;11)(p21.3;q23.3);*MLLT3-KMT2A;* inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2*, *MECOM;* t(6;9)(p23;q34.1);*DEK-NUP214;* t(1;22)(p13.3;q13.3);*RBM15-MKL1*; AML AML minimal differentiation, without maturation, AML with maturation, myelomonocytic leukemia, acute monoblastic/monocytic leukemia, pure erythroid leukemia, acute megakaryoblastic leukemia, acute basophilic leukemia, acute panmyelosis with myelofibrosis

Transient abnormal myelopoiesis (TAM), Myeloid leukemia associated with Down syndrome

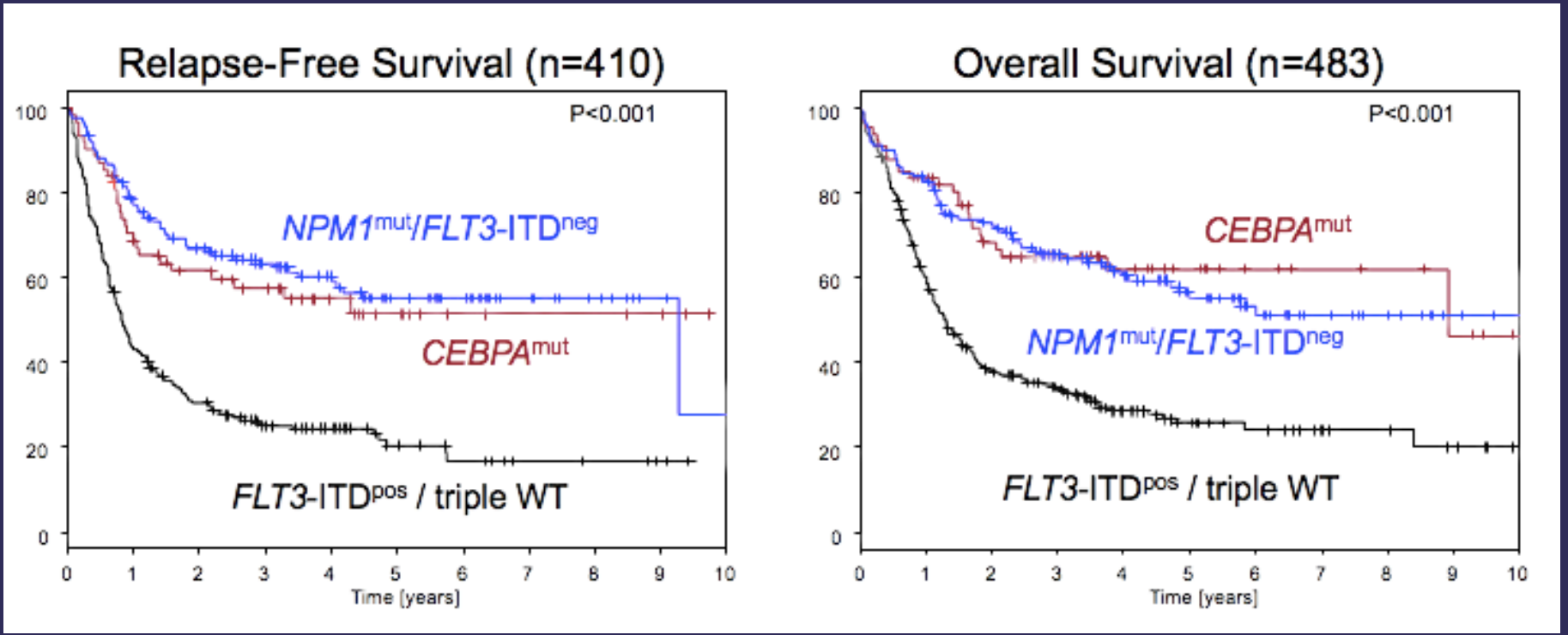
Arber DA, et al. *Blood*. 2016;127:2391-405.

Driver Mutations in 1,540 Patients With AML



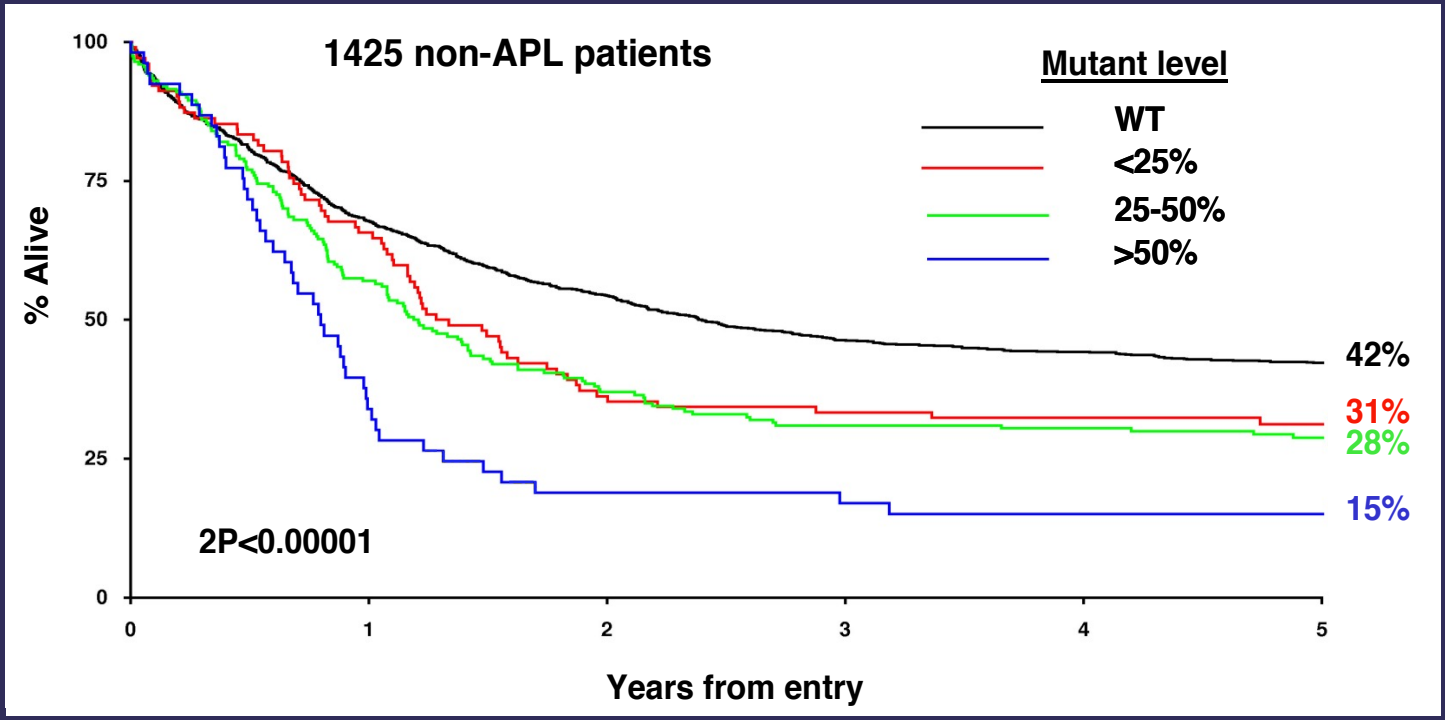
Papaemmanuil E, et al. *N Engl J Med*. 2016;374:2209-21.

Prognostic Impact of Genotypes in Younger Adults With Cytogenetically Normal AML (CN-AML)



Schlenk RF, et al. *N Engl J Med.* 2008;358:1909-18.

Overall Survival According to FLT3-ITD Mutant Level (i.e., “allelic ratio”)



Gale *et al. Blood* 2008; 111: 2776-84. David Grimwade. ASH Education Program 2009; See also Whitman, et al. *Cancer Res.* 2001;61:7233-39; Thiede et al. *Blood.* 2002;99:4326-35.

2017 ELN Risk Stratification by Genetics for AML

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

Döhner et at. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood* 2017.

ELN = European Leukemia Net.

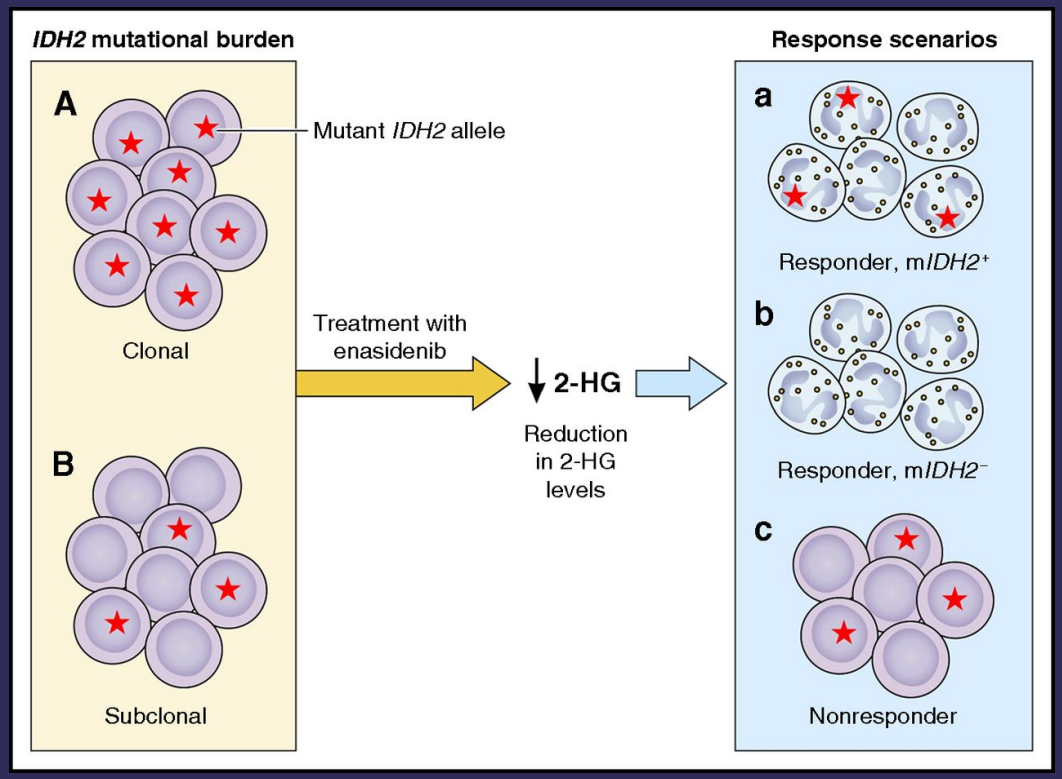
2017 ELN Risk Stratification by Genetics for AML (cont.)

Risk Category	Genetic Abnormality
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/ abnormal (17p)
	Complex karyotype; monosomal karyotype
	Wild type *NPM1* and *FLT3*-ITD^{High}
	Mutated *RUNX1*
	Mutated *ASXL1*
	Mutated *TP53*

Döhner et at. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood* 2017.

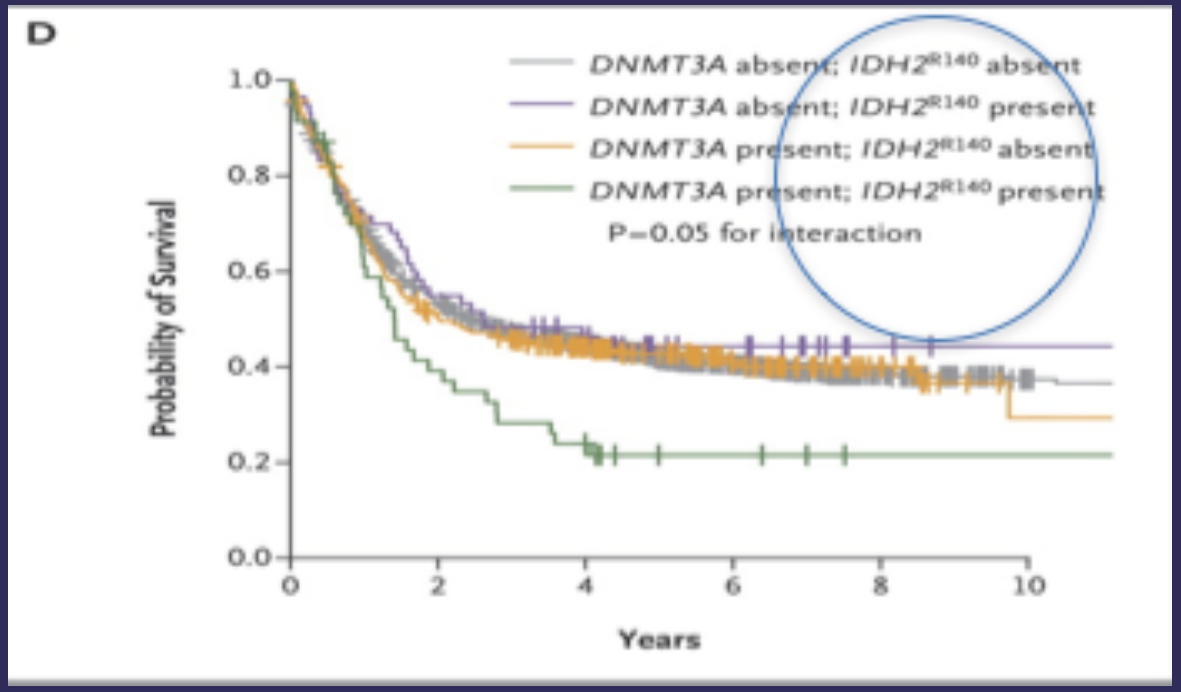
IDH and AML

- 10–12% IDH2 mutations in AML
- 10% IDH1 mutations



Wouters B, *Blood.* 2017;30:693-4.

IDH2 Mutations and AML Outcomes



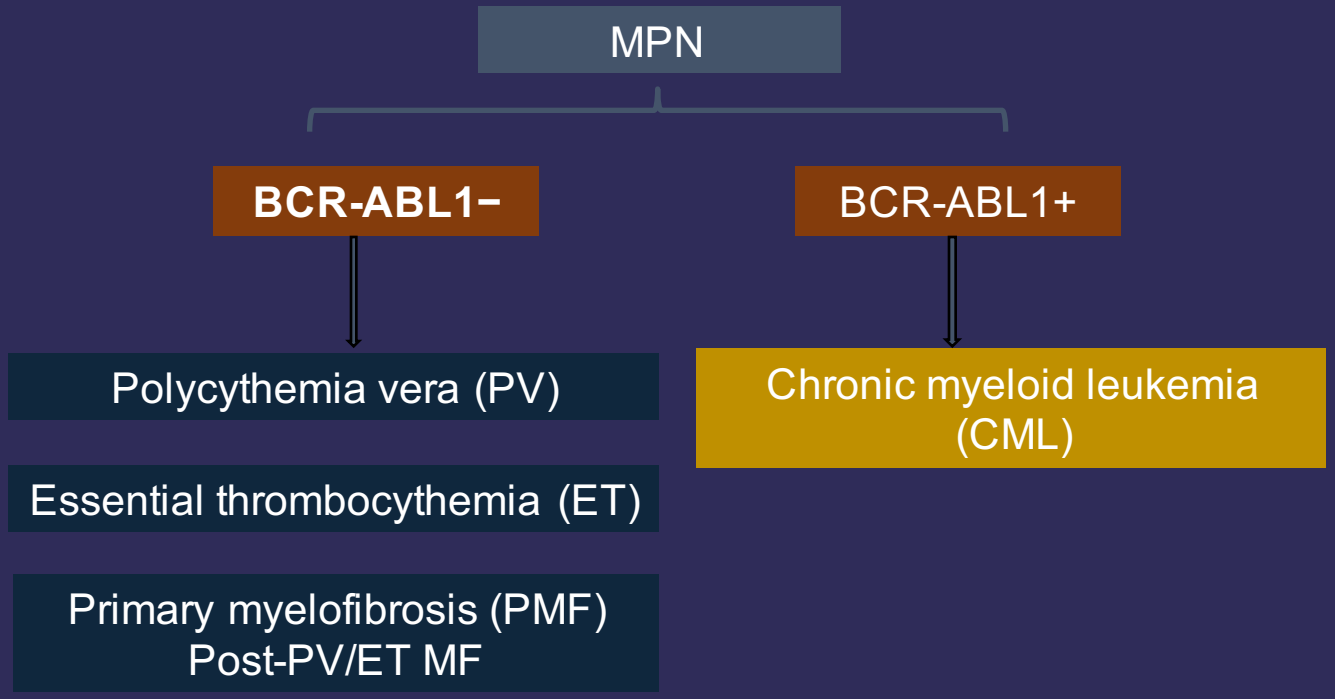
Mutational spectrum: IDH2 R172 likely adverse

Papaemmanuil E, et al. *N Engl J Med*. 2016;374:2209-21.

Key Points for Collaborative Practice in Hematologic Malignancy

- History essential for classification: prior treatment, family history
- Include history in bone marrow requisition (family history, prior therapy, abnormal molecular testing, etc)
- Be aware of molecular testing utilized at your center
- Calibrate patient expectations—complete classification and prognostication may take weeks
- Understand limitations of inadequate sample

“Classic” MPNs[1,2]

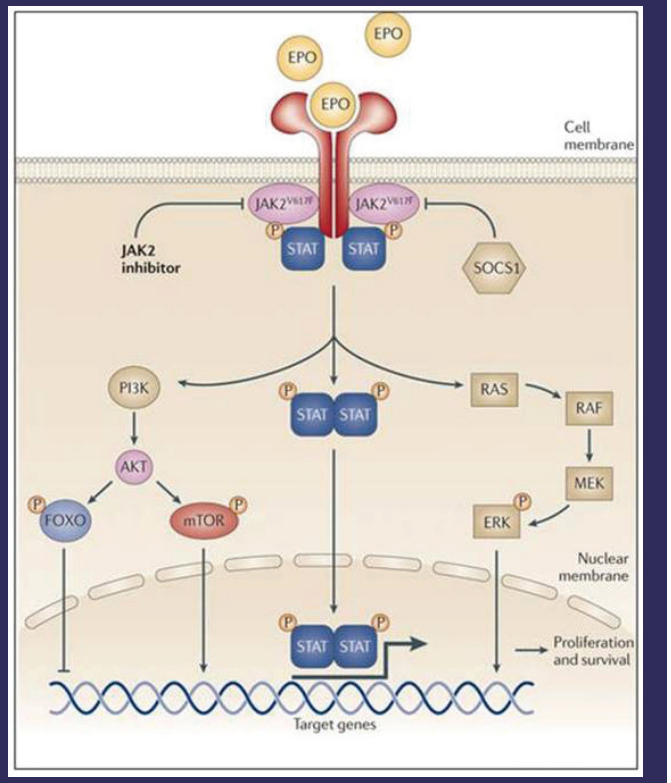


1. Tefferi A et al. *Leukemia*. 2008;22:14-22. 2. Thiele J, Kvasnicka HM. *Curr Hematol Malig Rep*. 2009;4:33-40.

The JAK-STAT Pathway–Normal

- Intracellular signaling pathway
- Transduction of extracellular signals to the nucleus to control gene expression
- Necessary for growth and differentiation:
  - Normal hematopoiesis, fertility, lactation, growth, and embryogenesis
- Involved in inflammatory cytokine signaling and immune regulation
- **Janus kinases (JAKs)**

  A family of 4 cytoplasmic tyrosine kinases: JAK1, JAK2, JAK3, and TYK2

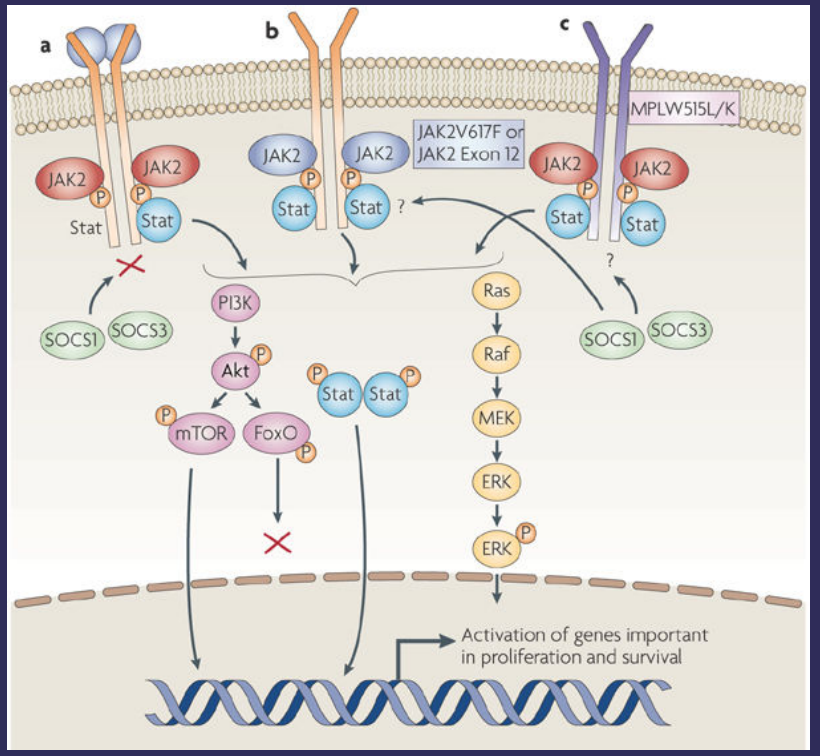


*Janus associated kinase-signal transducer and activator of transcription pathway

Adapted from Macmillan Publishers Ltd: Nature Reviews Drug Discovery 2004;3:555-64, copyright 2004.

JAK-STAT Dysregulation in MPNs

- When disrupted or dysregulated it can result in immune deficiency syndromes and neoplasms
- Results in a constitutively active cytoplasmic activator of transcription STAT
- Mitogen activated protein kinase (MAPK)
- PI3K-phsphotidylinositol 3-kinase
- Promotes transformation and proliferation of hematopoetic progenitors



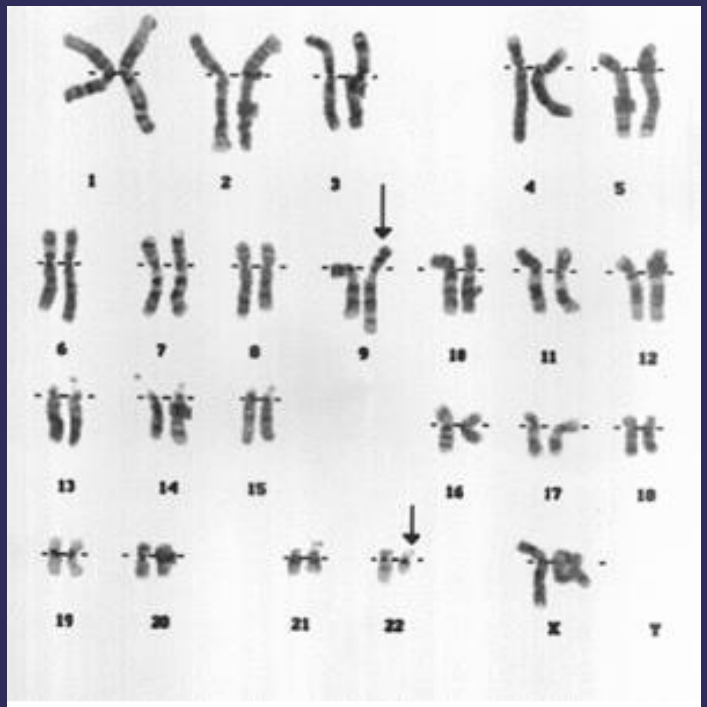
Levine RL, et al. *Nat Rev Cancer*. 2007;7:673-83.

Therapy Significance of JAK2

- 2011 saw the approval of the first JAK2 inhibitor: Ruxolitinib
  - Approved for treatment of intermediate or high-risk MF, including PMF, post-PV MF, and post-ET MF
  - Other therapies in clinical development
- Oral therapy
  - Not selective for mutated JAK2V617F enzyme (ATP-binding inhibitors)
  - Myelosuppression/cytopenias are expected side effects caused by inhibition of normal JAK2
    - Diarrhea most frequent nonhematologic toxicity
    - Individualize dosing based on platelet count to maximize efficacy and minimize toxicities
    - Starting doses are unique depending on disease (PV vs MF)
    - Taper slowly if treatment needs to be discontinued
      - Educate patient on importance of adherence/stopping drug

CML in 2017

- Frontline
  - Imatinib 400 mg daily
  - Nilotinib 300 mg twice daily
  - Dasatinib 100 mg daily
- Second/third line
  - Nilotinib, dasatinib, bosutinib, ponatinib
  - Omacetaxine
  - Allogeneic SCT
- Other
  - Decitabine, interferon
  - Hydroxyurea, cytarabine, combos of TKIs
  - Investigational agents, clinical trials
  - Is there a subset of patients who can stop TKI therapy?



The abnormality seen by Nowell & Hungerford on chromosome 22, Now known as the Philadelphia Chromosome.

SCT = stem cell transplant; TKI = tyrosine kinase inhibitor.

Mechanisms of Action for Novel Therapies for AML

- Midostaurin
- Daunorubicin and cytarabine liposomal
- Gemtuzumab ozogamicin
- Enesidenib
- Investigational agents
  - Vosaroxin, vadastuximab, venetoclax, selinexor, hypomethylators

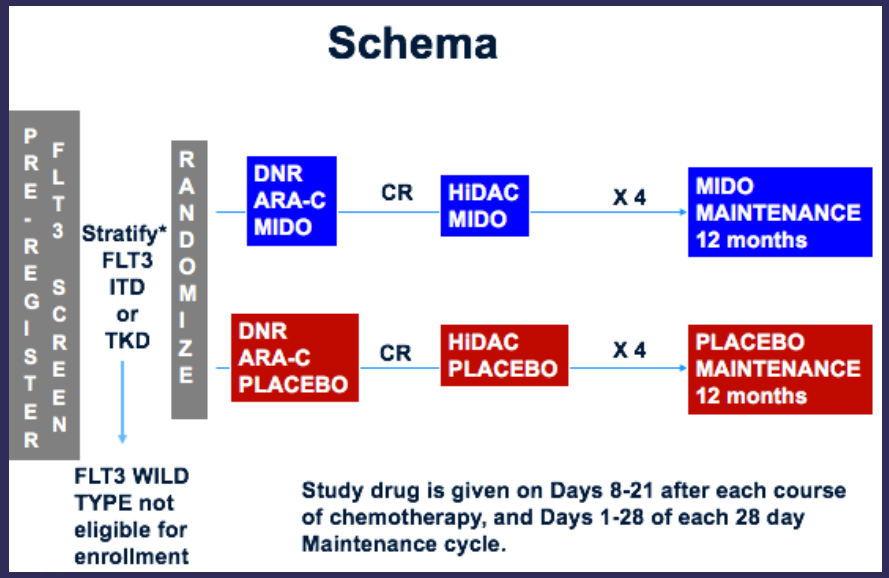
FMS Related Tyrosine Kinase 3 (FLT 3)

- Type III transmembrane receptor tyrosine kinase (RTK)
  - Other subfamily members: c-KIT, c-FMS, and PDGFR-α/β
- Normally expressed by committed myeloid and lymphoid progenitor cells in bone marrow
  - Critical for early progenitor cell development
  - Major role in normal hematopoiesis
- Expressed in the leukemic cells of 80–90% of patients with AML
- 8-10% of AML have TKD mutation
  - Mutations lead to constitutive overexpression of FLT3 and increased blast cell proliferation

Small D, et al. *Proc Natl Acad Sci USA*. 1994;91:459-63; Rosnet O, et al. *Blood*. 1993;82:1110-19; Rosnet O, et al. *Oncogene*. 1991;6:1641-50; Litzow MR. *Blood*. 2005;106:3331-2; Adolfsson J, et al. *Immunity*. 2001;15:659-69; Rosnet O, et al. *Leukemia*. 1996;10:238-48.

Midostaurin

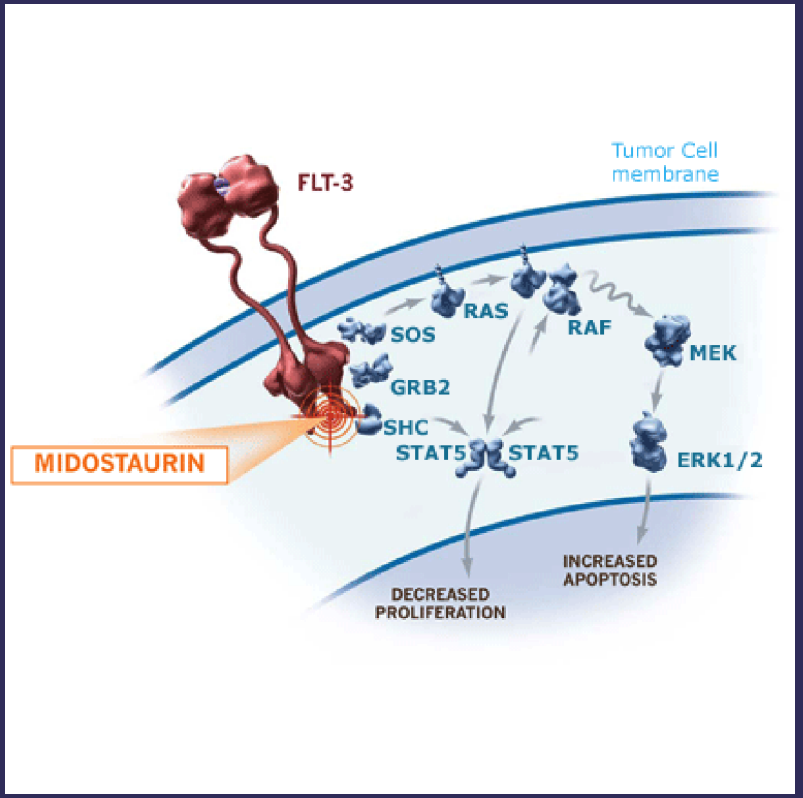
- Approved April 28, 2017
  - First approval since 2000 for AML
  - Oral agent
- Inhibitor of FLT3, c-KIT, PDGFRB, VEGFR-2, and protein kinase C
- RATIFY: Randomized phase III, N = 764
- CR after induction 74% (mido) vs 66% (PBO)
- 5-year survival rate: Mido 51% vs 43%
- Mido effect on OS was similar across FLT3 subtypes



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

Midostaurin

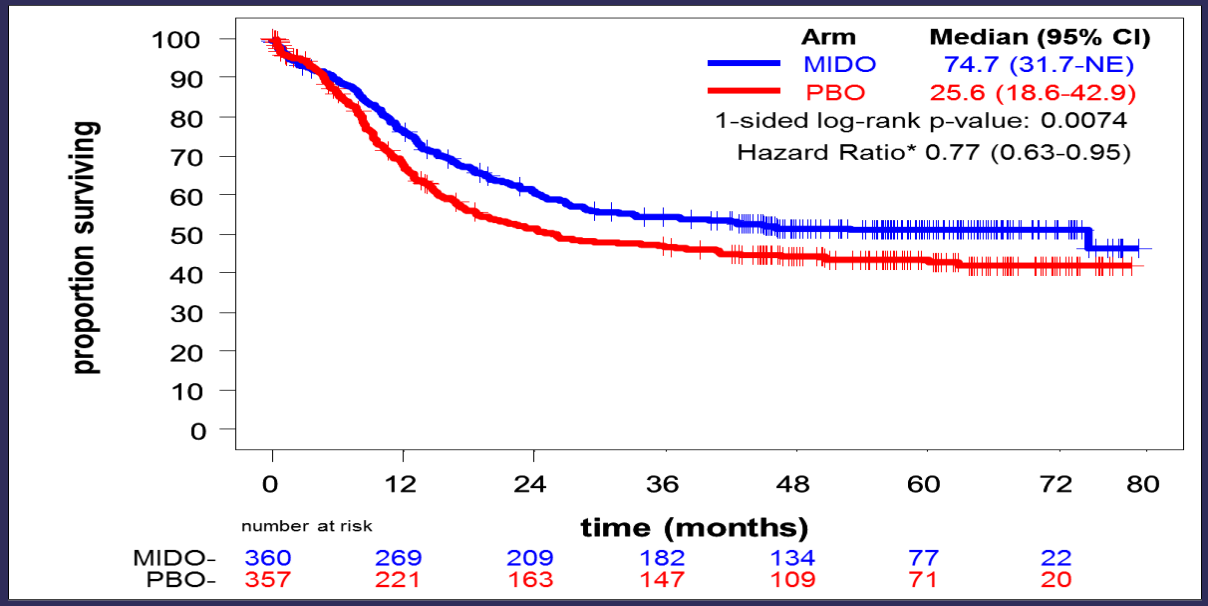
- Approved for the tx of adult patients with newly diagnosed FLT3 mutated AML
- Dose: 50 mg BID on days 8-21 of induction with cytarabine and daunorubicin
- Days 8-21 with of each cycle of consolidation w/high-dose cytarabine
- Not indicated for single-agent treatment of AML
  - Although RATIFY trial used maintenance midostaurin, it is not included in FDA approval



Stone RA et al, NEJM 2017 377(5) 454-464

Kaplan-Meier Curve: Overall Survival (Primary ITT Analysis)

- 5-year survival rate: MIDO 51% vs PBO 43%
- Median follow-up time for survivors 56.7 mo (range: 0.1, 79.2)



ITT = intent to treat; NE = not estimable; PBO = placebo.
*Controlled for FLT3 subtype (TKD, ITD-Low, ITD-High)

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

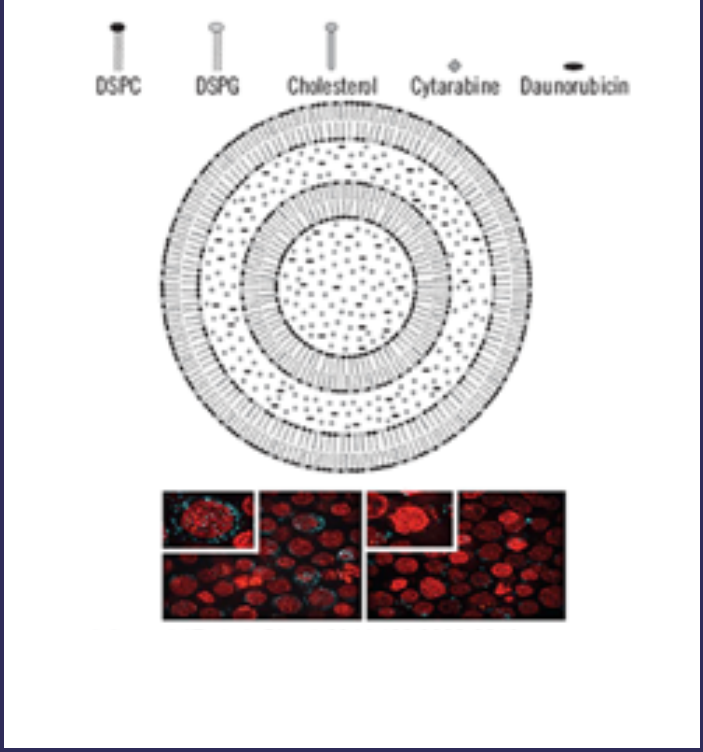
Currently Available FLT3 Inhibitors in Clinical Trials

Inhibitor	Target	IC_{50} Against FLT3-ITD (nM)
First generation		
Sunitinib	FLT3, KIT, KDR, PDGFR	4
Midostaurin*	FLT3, c-KIT, PDGFRB, VEGFR	<10
Lestaurtinib	Jak 2, flt3, TrK A	3
Tandutinib	FLT3, PDGFR, c-KIT	220
Second generation		
Quizartinib	FLT3, c-KIT, PDGFRa	1.1
Sorafenib	FLT3, c-KIT, VEGFR, PDGFR, RAF-1	2
Gilteritinib	FLT3, AXL	0.29
Crenolanib*	FLT3, PDGFR	2
Ponatinib*	BCR/ABL, FLT3, c-KIT, FGFR1, PDGFRa	4

* Also has activity against the FLT3-TKD mutation

Hassanein M, et al. *Clin Lymphoma Myeloma Leuk*. 2016;16(10):543-9.
Courtesy R. Larson, ASH updates 2016.

Liposomal Cytarabine/Daunorubicin (CPX 351)



- 5:1 molar ratio of cytarabine to daunorubicin
- 100-nm bimolar liposomes
- Liposomal cytarabine/daunorubicin accumulates and persists in the bone marrow
- Selective uptake of liposomal cytarabine/daunorubicin by leukemia blasts and intracellular drug release
- IV administration
- 1 unit: 1.0 mg cytarabine plus 0.44 mg daunorubicin

Lancet JE, et al. *Blood*. 2014;123:3239-46.

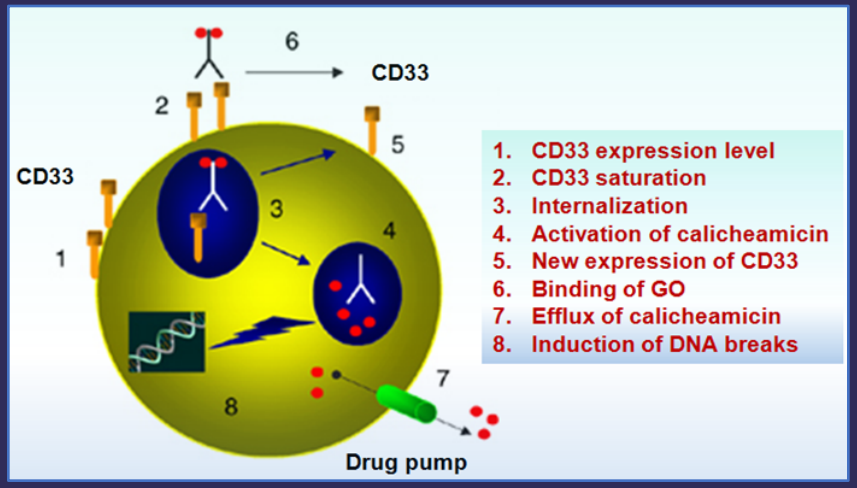
Liposomal Cytarabine/Daunorubicin, 2017 Approval

- FDA approved for the treatment of adults with newly diagnosed t-AML or AML with MDS changes
  - Induction days 1, 3 and 5 (daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2) liposomal over 90 minutes
    - Subsequent induction on days 1 and 3 if needed
  - Consolidation (daunorubicin 20 mg/m^2 and cytarabine 65 mg/m^2) liposomal
- Phase III, 1:1 randomized trial
  - Previously untreated
  - Ages 60-75
  - Able to tolerate intensive therapy
  - PS 0-2
  - Improved survival among older, fit, high risk AML patients'
    - CPX median survival 9.56 vs 5.95 months SOC 7+3
    - CPX demonstrated superior efficacy compared to 7+3: OS, EFS, CR, CR+Cri
    - CPX the new "standard" for older high-risk AML patients candidates for intensive therapy
    - --not on label

Cortes JE, et al. *Cancer*. 2015;121:234-42; Lacet JR, et al. ASCO 2016, Abstract 7000; Liposomal cytarabine/daunorubicin (Vyxeos) package insert.

Gemtuzumab Ozogamicin, 2017 Approval

- Approved: CD33 positive AML
  - Newly diagnosed de novo
    - Induction: 3 mg/m^2 on days 1, 4, 7, in combination with 7 + 3
    - Consolidation: 3 mg/m^2 on day 1, in combination with 7 + 3
  - Newly diagnosed de novo (single-agent regimen)
    - Induction: 6 mg/m^2 on day 1, 3 mg/m^2 on day 8
    - Continuation: Following induction, 2 mg/m^2 on day 1 every 28 days up to 8 courses
  - Relapsed/refractory (single-agent regimen)
    - 3 mg/m^2 on days 1, 4, and 7
- Antibody conjugated to calicheamicin
- Premedicate with corticosteroid, antihistamine, and acetaminophen 1 hour prior
- Hepatotoxicity/VOD issues
- Cytopenias



VOD = veno-occlusive disease.

Pagano L, et al. *Nature*. 2007;26:367-9; Pfizer. Gemtuzumab ozogamicin (Mylotarg) package insert. 2017.

IDH Mutated AML and IDH Directed Therapies

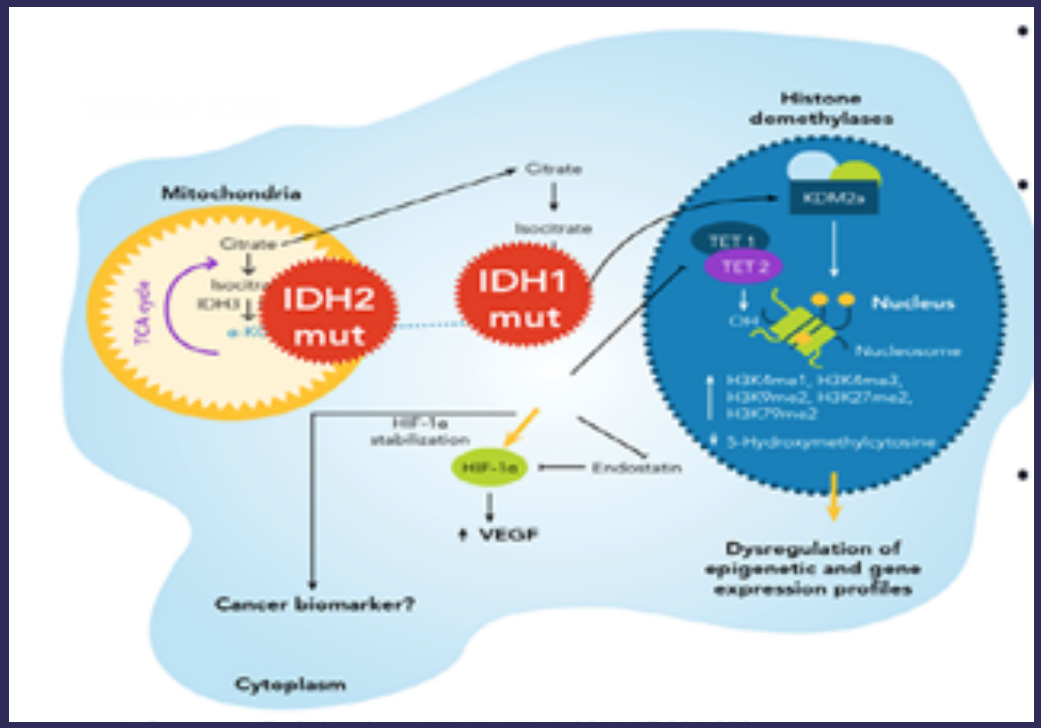
- Isocitrate dehydrogenase (IDH) is an enzyme of the Krebs cycle that converts isocitrate to α-ketoglutarate
- Mutations in either IDH1 or IDH2 are observed in approx. 20% of patients with AML
- Mutations in IDH1 and IDH2 create a neomorphic enzyme activity
- Leads to aberrant production of the oncometabolite 2-hydroxyglutarate (2-HG)…
  - Which leads to inhibition of enzymes involved in epigenetic function and may be sufficient in causing AML
- These mutations lead to the reduction of α-ketoglutarate to 2-hydroglutarate, which accumulates intracellularly and leads to a hypermethylated DNA signature and a block of normal cellular differentiation

Enasidenib for IDH2 for Relapsed/Refractory AML

Category	Result (in 100-mg dose cohort) N=109
Overall response	42 (38.5%)
Best response	
CR	22(20.2%)
CRi (incomplete heme recovery)	7 (6.4%)
PR	3 (2.8%)
Morphologic leukemia-free state	10 (9.2%)
Stable disease	58 (53.2%)
Progressive disease	5 (4.6%)
Not evaluable	2(1.8%)

Stein A, et al. *Blood*. 2017;130:722-31.

Enesidenib IDH2 Inhibitor, 2017 Approval



- Indicated for treatment of adult AML relapsed or refractory patients with IDH2 mutation as detected by an FDA approved test
- Oral tablets: 50 or 100 mg
  - 100 mg daily recommended dose
  - With or without food
  - Until disease progression or unacceptable toxicities
  - Treat for minimum of 6 months to allow time for clinical response
- Most common AEs
  - N/V/D, elevated bilirubin, decreased appetite
- Differentiation Syndrome

Prensner JR, et al. *Nat Med*. 2011;17:291-3.

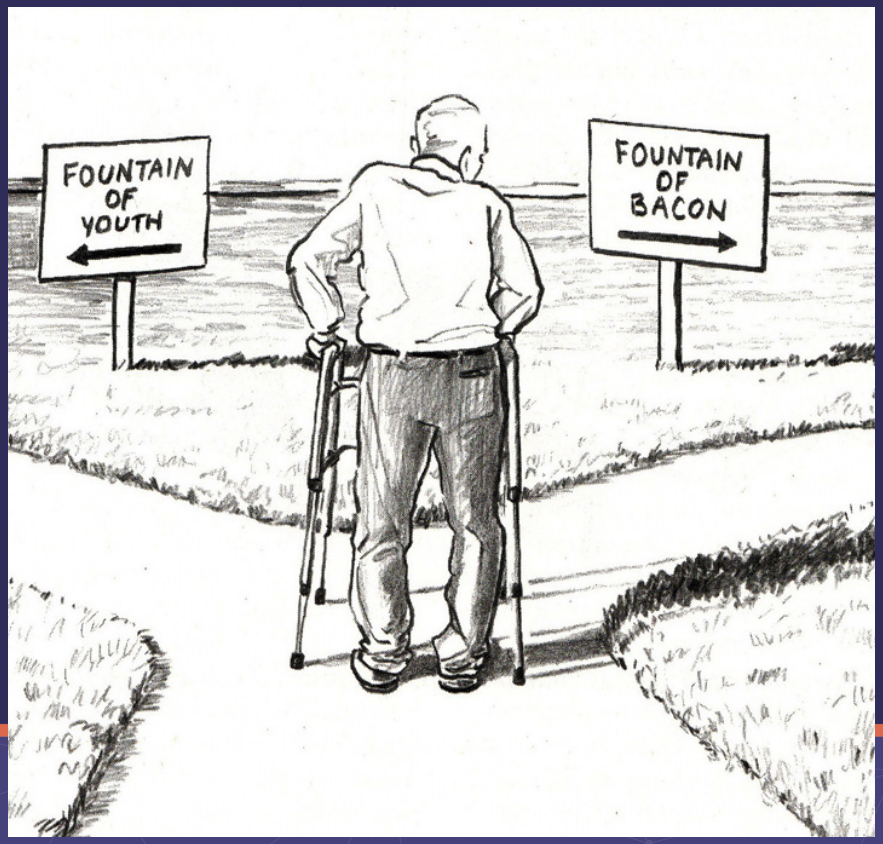
Other New Novel Agents for AML

- Many in clinical trials, various stages of development
- Single agents and combinations
- Targeting unique markers
  - Vosaroxin, vadastuximab, venetoclax, selinexor, hypomethylators
- Looking to shift therapy goals from treatment to cure

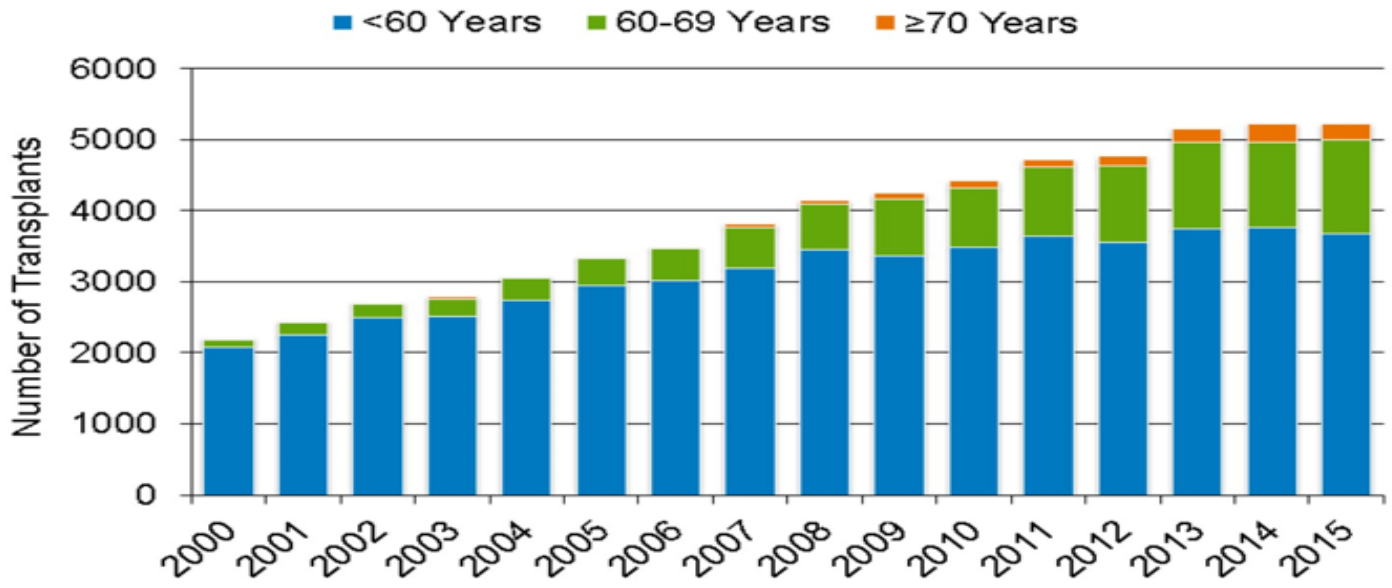
Stem Cell Transplantation as a Therapy for Myeloid Malignancies

- Recommended post-remission therapy for patients < 60 with intermediate-risk cytogenetics and/or molecular abnormalities
- Or treatment-related disease or poor risk cytogenetics and/or molecular abnormalities
- ≥ 60 after induction failure
- Relapsed setting

Allogeneic Transplant in Older Adults: A Model for Hematology Collaborative Practice



Trends in Allogeneic HCT by Recipient Age^



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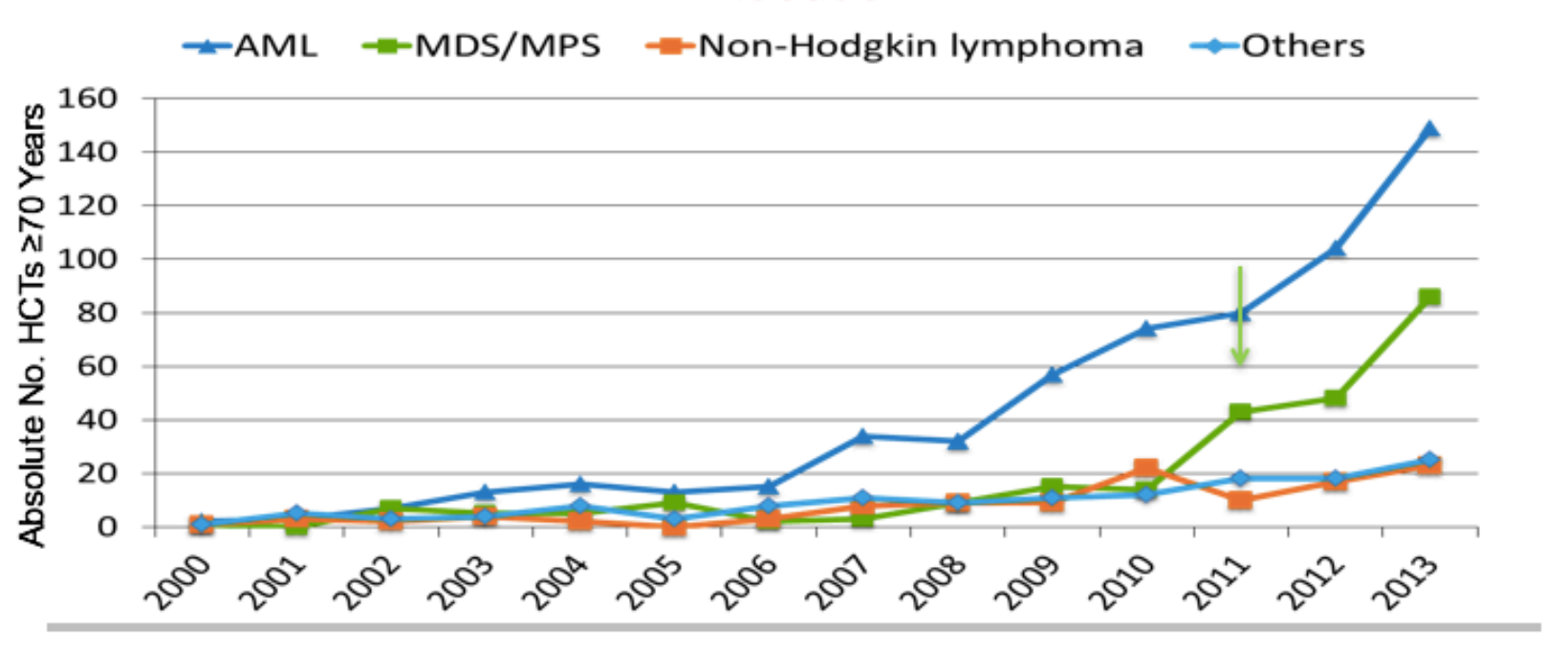
^Transplants for AML, ALL, NHL, Hodgkin Disease, Multiple Myeloma

Allogeneic Transplant Trends for Age 70 and Greater by Disease



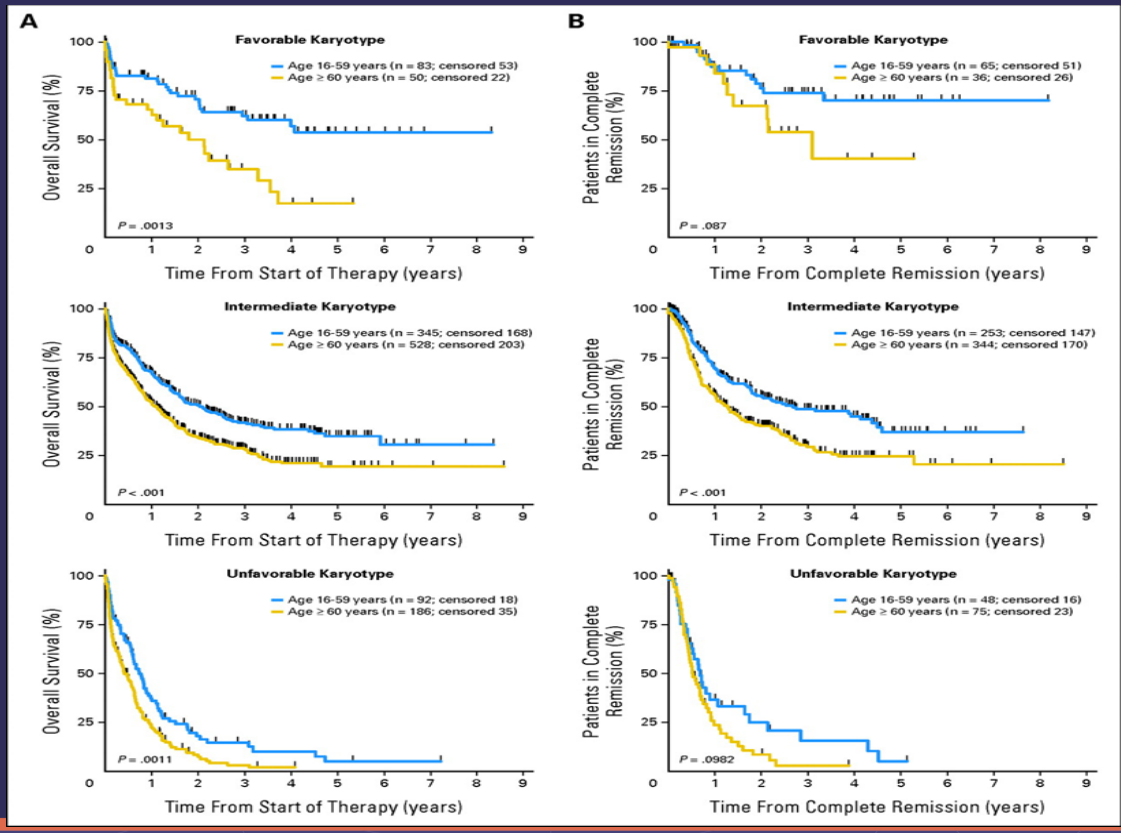
Muffly L, *Blood*. 2017.

AML Outcomes by Cytogenetic Risk: Age 60+ vs Younger

Number of Transplants and Survival After MUD for AML: US data

Age, yrs	US Transplant 2010-14 for AML		Survival after MUD in CR1	
Age	**Auto**	**Allo**	**1 yr**	**3 yr**
21-30	49	1112	73.5	57.7
31-40	62	1428	72.8	56.8
41-50	94	2174	64.4	55.9
51-60	92	3691	61.3	45.1
> 60	82	3998	58.2	40.1

HRSA (bloodcell.transplant.hrsa.gov) extracted Jan 2017



Büchner T, et al. *J Clin Oncol*;2009;27:61-69

Outline

Chronologic Age vs Resiliency in Transplant

- Informing candidacy
- Guiding optimization

Calendar Age vs Physiologic Age

Unfit

Resilient

Chau Smith: 7 marathons, 7 days,
7 continents, age = 70

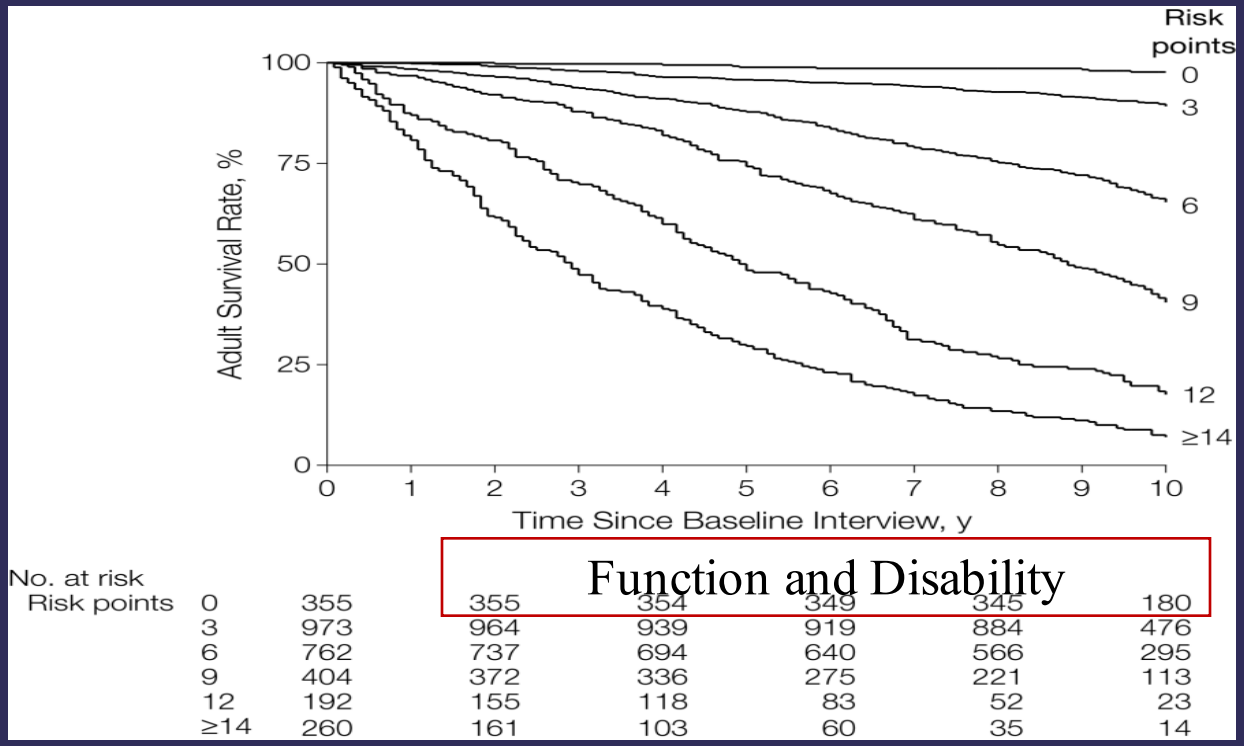
Eligibility by Default: Transplant Exclusions

Factor	Auto (Stamina 0702)	Allo (BMT CTN 0502)
Age	>70	>74
LVEF	</= 40%	N/A
Liver	Bili>1.5x, ALT/AST>2.5X	Bili >2.0 AST >3x
Renal	Cr Clearance <40	Cr Clearance<40
Pulmonary	<50% FEV1, FVC,DLCO	DLCO <40%
Cardiac	MI in 6 months or CHF	EF <30%
Cancer	<5 years	N/A
KPS	<70	<50 (ECOG 3+)

Stadtmauer EA. ASH 2016, LBA-1; Devine S. *J Clin Oncol.* 2015;3(35):4165-75.

TOP: GA to Inform and Optimize Treatment

Domain	Comments	Vulnerability (V) or Asset (A)	Plan
Comorbidity	HCT-CI=2 DM, Depression + OA, Cr clear=50	V	endocrine on admit Non-NSAID OA Tx
Functional	Preserved IADL, Slow 6 minute walk	+/-	Pre-habilitation with PT
Cognition	Normal	A	Detailed education in writing
Emotional	Coping, anxiety	V	Engage family, psych referral
Social support	Initially poor, later strong	A	Family meeting Caregivers in room
Nutrition	No weight loss, partial dentures	A	Educate on supplements
Polypharmacy	3 Rx medication One supplement	A	Safety of other medications, stop supplement



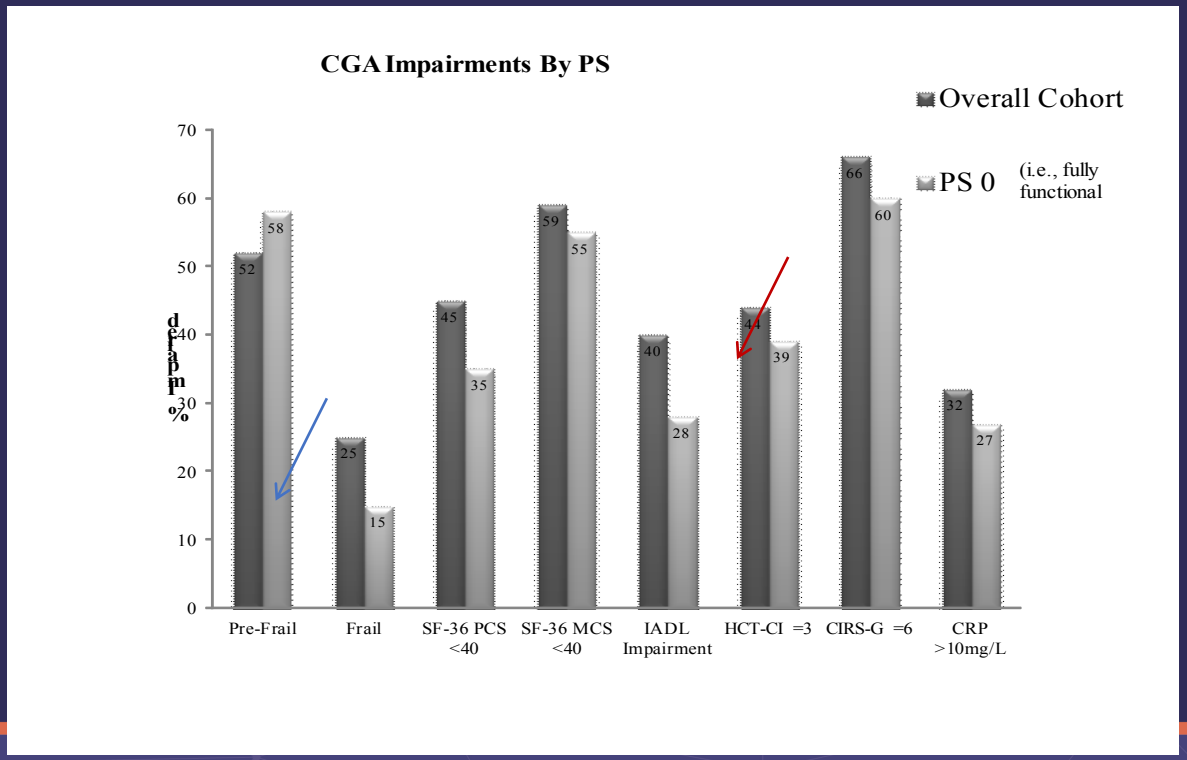
Function and Disability

Item	Pts
Age (<64=0, 85+=7)	1-7 pts
Tobacco use	2
BMI < 25	1
DM	1
Non-skin cancer	2
Chronic lung disease	2
Heart failure	2
Difficulty bathing	2
Difficulty with finances	2
Difficulty walking several blocks	2
Difficulty pushing large objects	1

Cruz M, et al. *JAMA*. 2013;309:874-6.

Geriatric Assessment Prior to Allograft in Pts 50+: Accelerated Aging Phenotype

CGA Toolbox
Frailty: Fried Frailty Index
PCS: SF 36 Physical component score
MCS: SF-36 Mental component score
IADL: Instrumental activities of daily living
HCT-CI: Hematopoietic cell transplantation-comorbidity index
CIRS: Cumulative Illness rating scale-Geriatrics
CRP-C-reactive protein



Muffly L, *Biol Blood Marrow Transplant*, 2013;19(3):429-34;
Also see Holmes HM. *J Geriatr Oncol.* 2014;5(4):422-30.

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Staging the Age: Geriatric Assessment From CARG With Minor Modifications

Domain	Tool
Comorbidity	HCT-CI, OARS scale
Physical Function	IADL, KPS MD and Pt, Falls, timed up and go, 4 meter walk, grip strength
Psychological Health	MHI-17
Cognition	BOMC, neurocognitive testing
Social	MOS Social Activity and Social Limitations
Biomarkers	CRP, ferritin, others
Nutrition	Weight loss, albumin

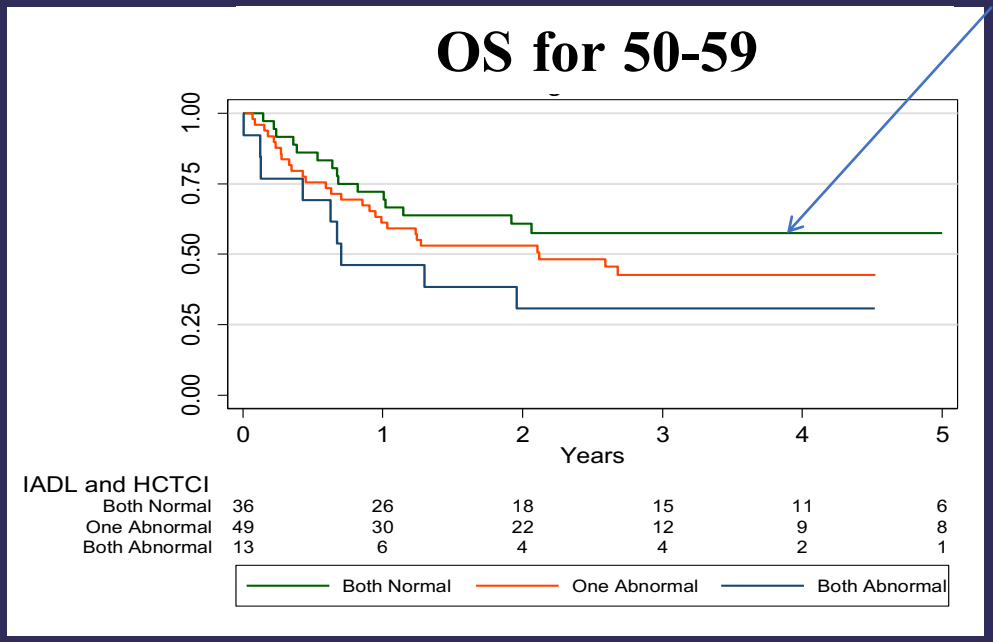
Underline denotes University of Chicago modifications from Hurria, *J Clin Oncol*. 2011;29:1290-6.

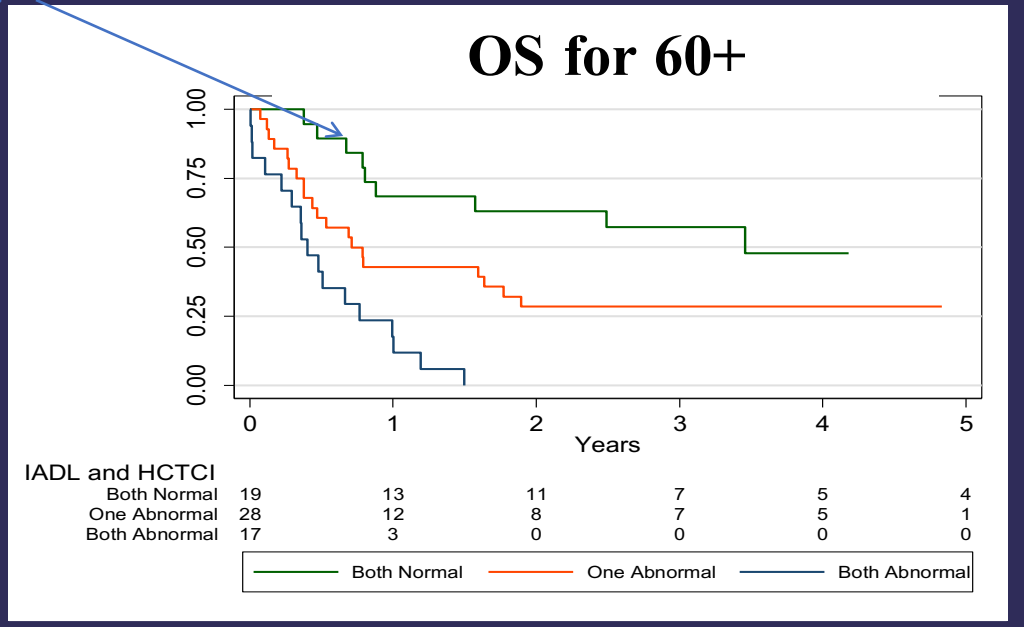
Maximal Support of Vulnerable Hematopoietic Cell Transplant Patients by Domain

Domain Impaired	Intervention*
Comorbid conditions	Severe comorbidity has subspecialty evaluation and follow-up after transplant
Function	All patients given pre-habilitation exercise and request activity monitoring, fall precautions
Social	24/7 caregiver during cytopenia, increase time of caregiver post-transplant, back-up caregiver, live closer to center
Cognitive	Delirium precautions
Emotional Health	Engage social network (family, clergy, friends), require heavy patient motivation
Nutrition	Weight monitoring
Global	TOP reassessment day 30
Transplant	Reduced intensity preparative regimen

High Comorbidity and Functional Limitation Influence Overall Survival

Resilient





Factor	Points
HCT-CI 3+	1 pt
IADL limitation	1 pt

Muffy L. *Haematologica*. 2014;99(8).

What Is the TOP Clinic?

- A multidisciplinary care team dedicated to optimizing blood and stem cell transplants for patients 50 years of age and older
- We offer individualized supportive care plans for each patient that we hope results in more successful transplant outcomes
- Standard Optimization
  - The patient meets the basic requirements based on age and disease status (60+ allo and 70+ auto) and is required to be seen for standard optimization before transplant
- Eligibility Assessment and Optimization
  - The patient may or may not meet the age requirements to be seen in TOP, but has high comorbid burden and their primary treating physician or the transplant team see a need for risk assessment that could potentially hinder a successful HSCT

How Do We Optimize Patients for Transplant?

- Each patient's recommendations are tailored to their needs
  - We do not have a "one size fits all" approach to optimizing patients
- We do see trends in vulnerabilities of older adults seen in TOP Clinic
  - We make recommendations based on those observations
- Overall, our recommendations for patients proceeding to transplant will be one of the following:
  - **Yes:** No issues to preclude a safe transplant
  - **Maybe/Defer:** There are some hindrances to transplant that we feel can be safely addressed or resolved in a reasonable time period to continue safely moving toward transplant
  - **No:** The patient's health and/or disease status do not allow us to safely move forward with transplant and the issues cannot be resolved in a reasonable time frame (usually around 6-8 weeks)

Optimization: A Case Study

- 71-year-old female, AML normal karyotype (no TP53) from MDS after azacitidine. CR1 after induction
- CMV seropositive, donor = potential 10/10 MUD
- KPS = 80%, HCT-CI =2 (DM and depression)
- ROS: Forgetful at times, knee and hip pain, partial dentures
- Social: Widowed, children in area

Interdisciplinary Meeting and Recommendations

- All members of the group attend the meeting to present/discuss patient
  - Identify strengths/vulnerabilities
- Formal written recommendations are provided to primary transplant physician/team
  - Can be viewed by other team members to optimize care throughout the transplant process
- Patient to be contacted by APN, discussion of recommendations and follow-up and treatment plan

From Prognosis to Optimization: Transplant Optimization Program (TOP) for Older Adults

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Transplar
MD and Al

The Integrative Model in Transplant

- Resilient phenotype allows risk stratification among older adults
- Multidisciplinary team approach tailored to vulnerabilities holds promise to improve outcomes and expand transplant eligibility

Conclusions

- Classification of myeloid malignancies requires genetic information and history
- Genetic landscape informs prognosis and therapies
- Oral inhibitors now approved for FLT-3 and IDH2 in AML
- APP plays a central in managing the continuum of myeloid malignancies
- Multi-disciplinary team approach integrating APP can be useful to manage complex patients and/or treatments

Special Thanks

- Slides
  - Jane Churpek: Genetic Risk
  - Toyosi Odenike: Myeloproliferative
  - Richard Larson: AML/MDS and specific mutations
- JADPRO Live and team
- Transplant Optimization Program Team

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