New Directions in Myeloid Malignancies

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THE ANNUAL APSHO MEETING

Learning Objectives

1. Outline strategies to monitor minimal residual disease (MRD) in myeloid malignancies
2. Evaluate safety and efficacy of novel approaches to treat myeloid malignancies
3. Describe the mechanism of action of agents that target mutations IDH2, TP53, FLT3, BCL2, and cell surface antigen CD33

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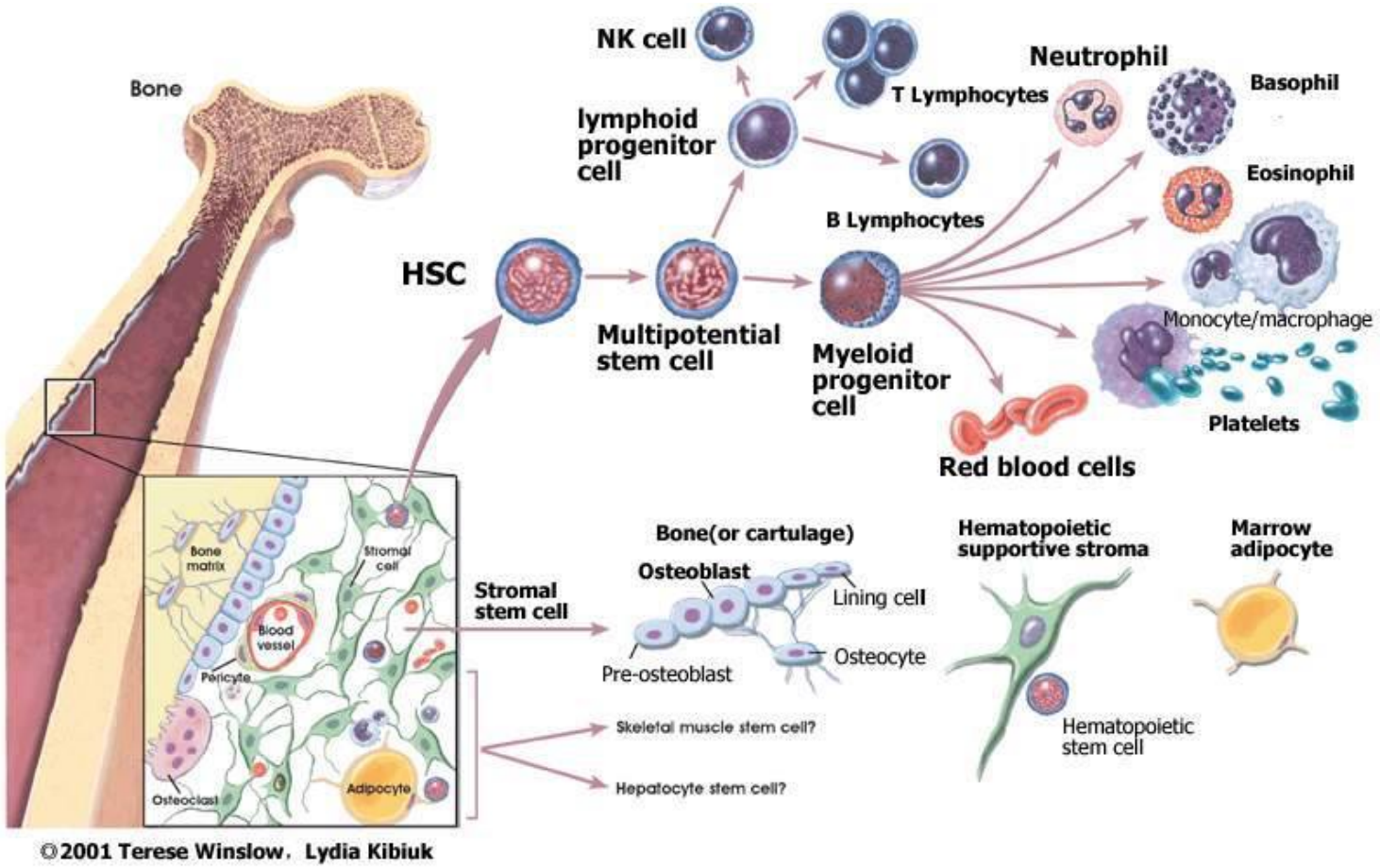
Ms. Gardner and Dr. Tran have nothing to disclose.

Outline

- Epidemiology
- Diagnosis
- Risk classification
- Heme emergencies
- Response criteria
- MRD and relapse
- Therapies/New drugs
- APL

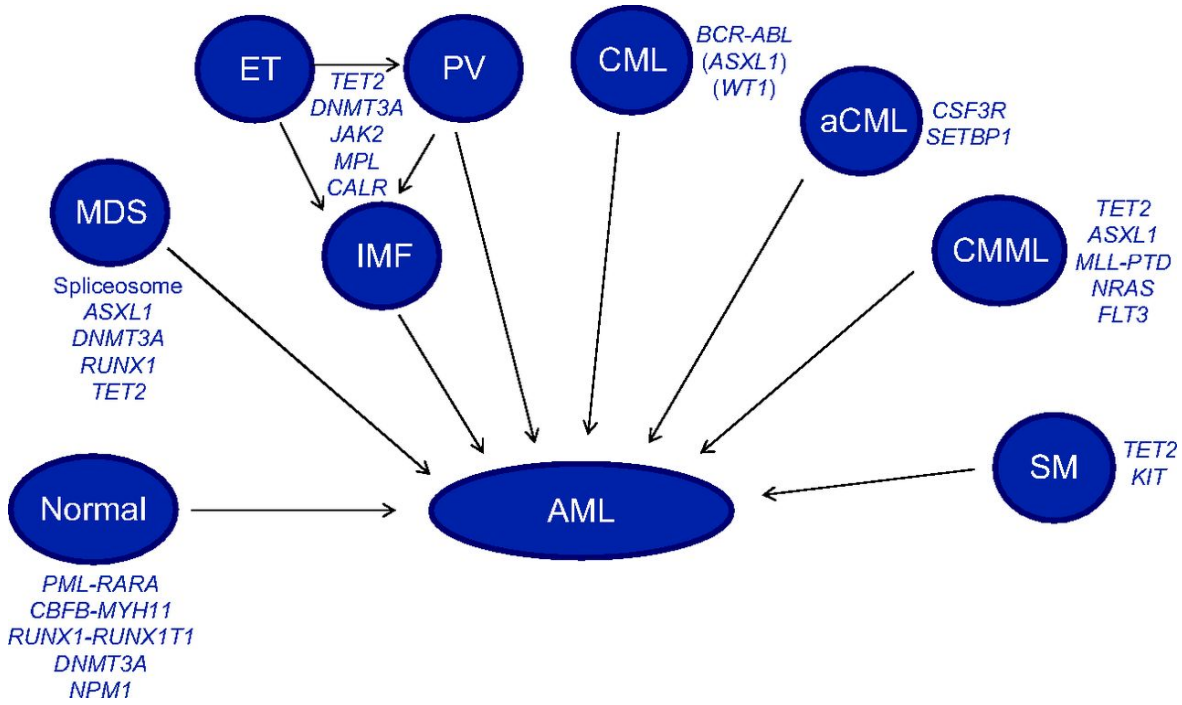
APL = acute promyelocytic leukemia; MRD = minimal residual disease.

Leukemia and Hematopoiesis



HSC = hematopoietic stem cell

Myeloid Phenotypes on Continuum and Recurrent Mutations



Common mutations in *de novo* and secondary AML. A number of clonal blood disorders with a myeloid phenotype are represented. Each of these disorders is characterized by recurrent mutations in specific genes, some of which are shared between several different phenotypes (e.g. *TET2*). All of these disorders can transform to secondary AML upon acquisition of additional somatic mutations. When AML arises in the absence of an antecedent clonal blood disorder, it is known as primary AML.

aCML = atypical CML; CML = chronic myeloid leukemia; ET = essential thrombocythemia; IMF = idiopathic myelofibrosis; PV = polycythemia vera; SM = systemic mastocytosis.

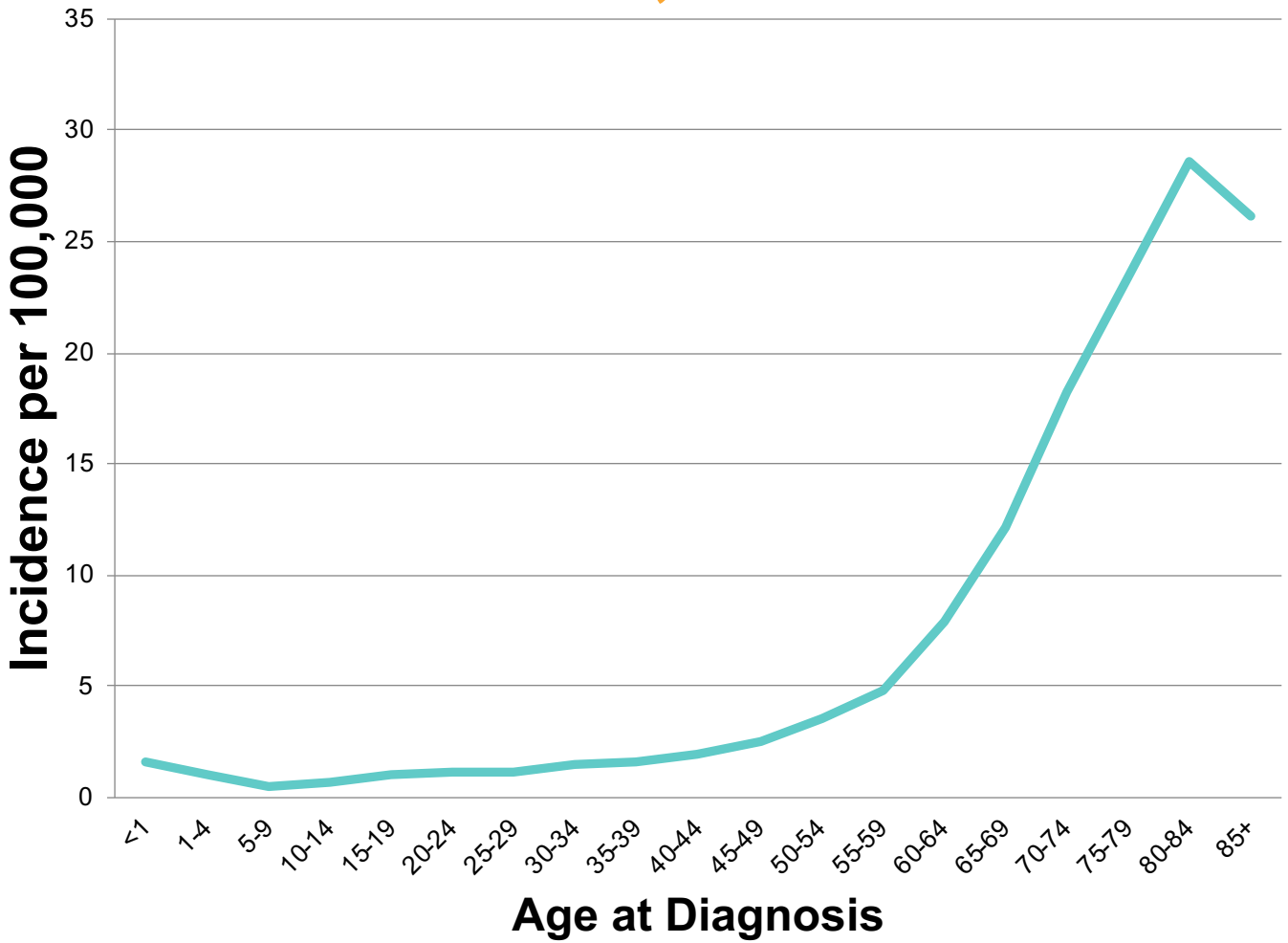
Carolyn S. Grove, George S. Vassiliou, *Disease Models & Mechanisms* 2014;7:941-951

Epidemiology in 2018

- Estimated annual new cases: 19,520
- Estimated annual deaths: 10,670
- 5 year survival rate: 27.4%
  - Improving over time (6.3% survival in 1975)
- M:F predominance of approximately 1.5:1
- Median age at diagnosis: 68

http://seer.cancer.gov/statfacts/html/amyl.html

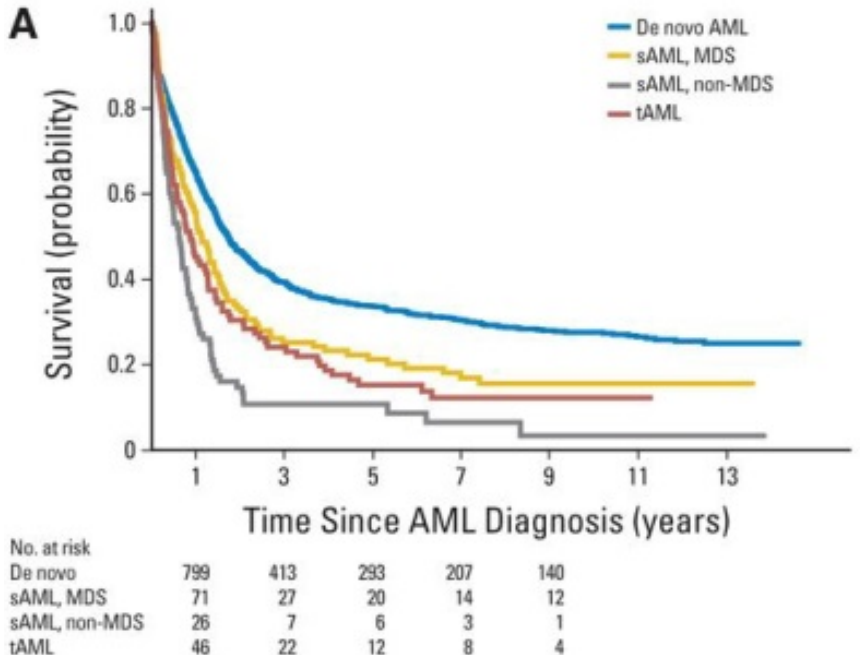
Incidence of AML, 2011-2015

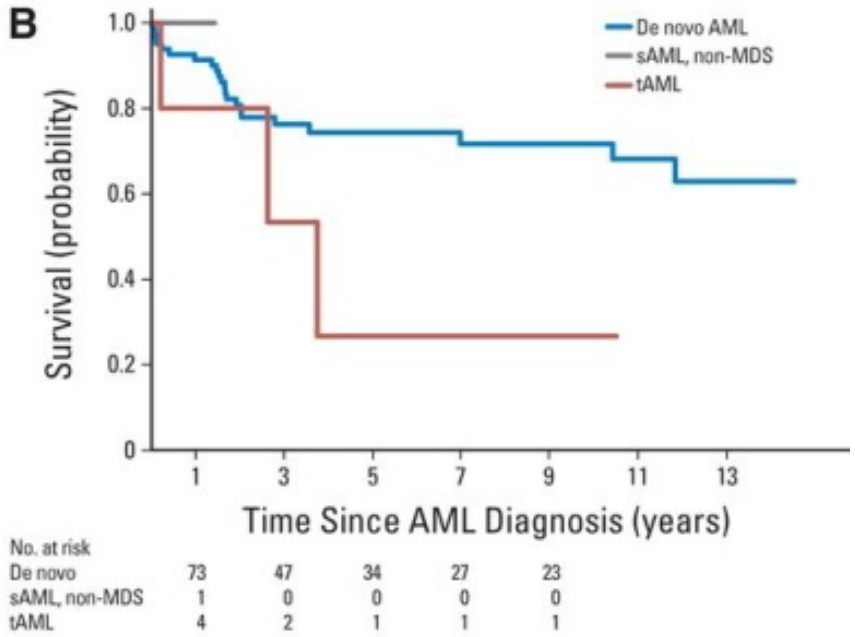


SEER Cancer Statistics Review (https://seer.cancer.gov/csr/1975_2015/)

Etiology

- **Prior chemotherapy/ radiation (therapy-related, or t-AML)**
- **Antecedent hematologic disorder (secondary, or s-AML)**
- Genetic predisposition
- Smoking
- Chemical exposures, such as benzene





Ostgard L *JCO* 2015

Genetic Predisposition

- Many familial AML/MDS syndromes have been described in the past 2 decades
- Most common: *GATA2*, *RUNX1*, *CEBPA*, *TERC/TERT*, Fanconi anemia
- Important to identify!
  - Treatment planning
  - Choice of donors for alloHCT candidates
  - Screening for other associated medical issues
  - Counseling of family members
- Who should be tested for inherited mutations?

AML = acute myeloid leukemia; MDS = myelodysplastic syndrome.

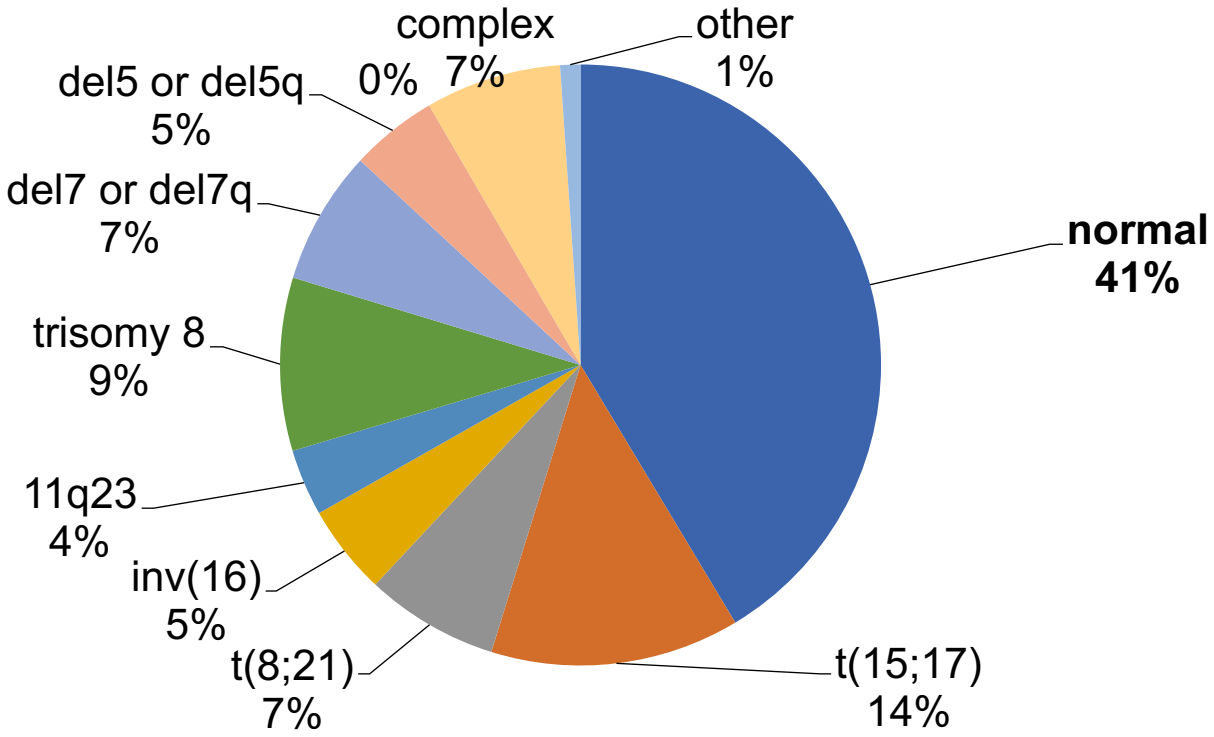
"How I treat inherited AML" *Blood* 2016

Diagnosis of AML

- Peripheral blood (≥20% blasts)
  - If these cytogenetic abnormalities are detected, 20% blasts is not required to make the dx of AML: t(8;21), inv(16) or t(16;16), t(15;17)
- Bone marrow aspirate/biopsy
- **Mandatory testing on blood and/or marrow at diagnosis**
  - Morphology
  - Cytogenetics/FISH
  - Molecular studies
  - Immunophenotyping (a.k.a. flow cytometry)

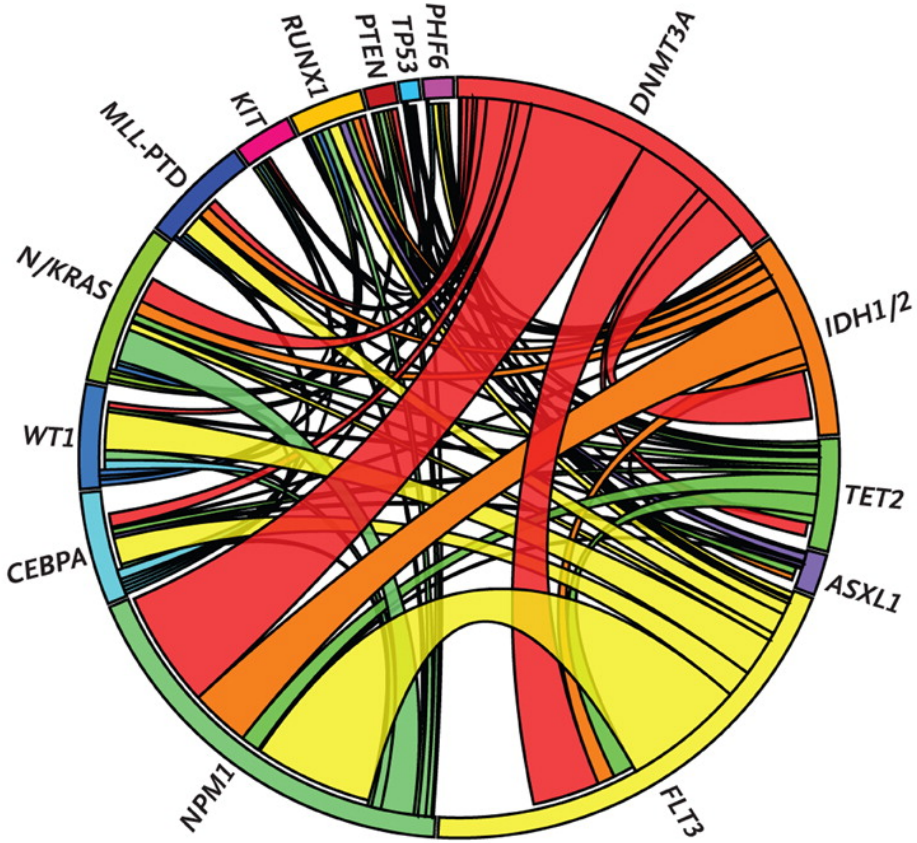
Arber DA, et al. *Blood*. 2016;127:2391-2405; Dohner H, et al, *Blood.* 2017;129:424-447.

Common Cytogenetic Abnormalities



Grimwade D, et al. *Blood.* 2010;116(3):354-365.

Recurrent Molecular Abnormalities



Patel J, *NEJM*. 2012;366(12):1079-1089.

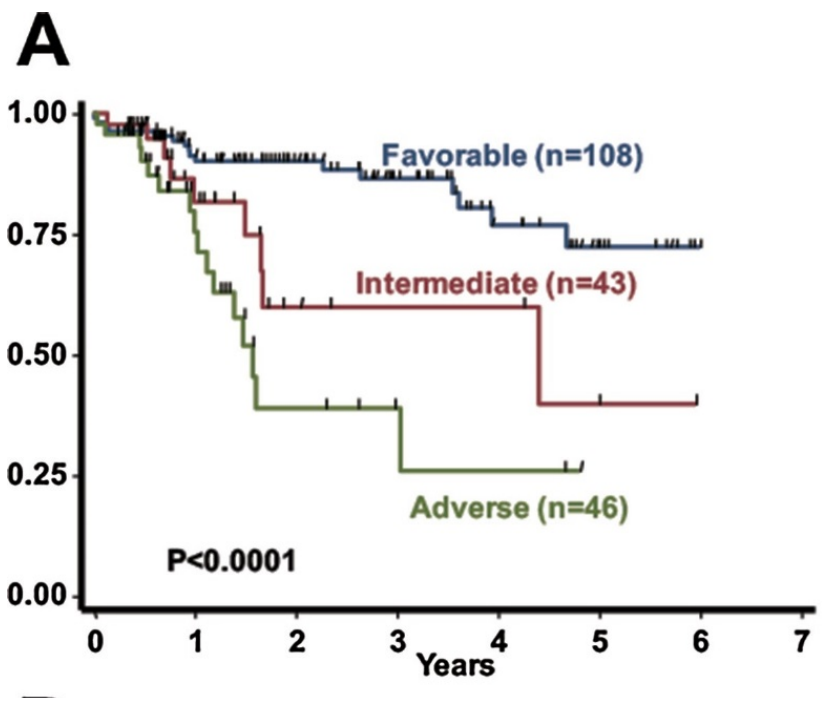
ELN 2017 Risk Classification

Risk status	Subsets
Favorable	t(8;21) inv(16) or t(16;16) Mutated *NPM1* without *FLT3*-ITD ~~(normal karyotype)~~ or with FLT3-ITD^{low} Biallelic mutated *CEBPA* ~~(normal karyotype)~~
Intermediate~~-I~~	Mutated *NPM1* and *FLT3*-ITD^{high} ~~(normal karyotype)~~ ~~Wild-type *NPM1* and *FLT3*-ITD (normal karyotype)~~ Wild-type *NPM1* without *FLT3*-ITD (without adverse-risk genetic lesions)
~~Intermediate-II~~	t(9;11); *MLLT3-MLL* Cytogenetic abnormalities not classified as favorable or adverse
Adverse	inv(3) or t(3;3); t(6;9); t(v;11); -5 or del(5q); -7; -17/abnl(17p); complex karyotype monosomal karyotype; wild-type *NPM1* and *FLT3*-ITD^{high}; mutated *RUNX1*; mutated *ASXL1*; mutated *TP53*

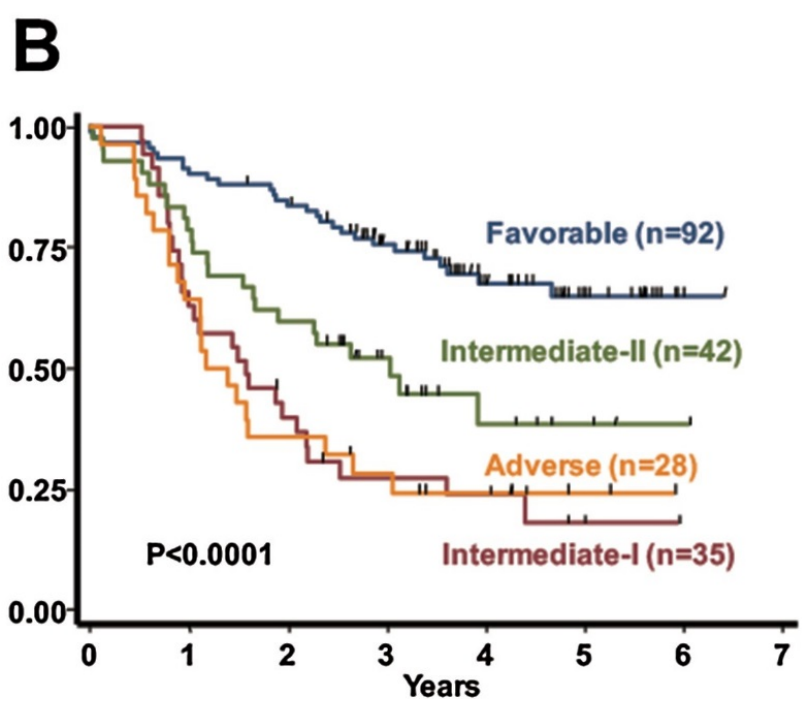
ELN = European LeukemiaNet

Survival Stratified by ELN Risk

ELN 2017



ELN 2010



Harada Y, et al. *Leuk Res.* 2018;66:20-27

Heme Emergencies: Leukostasis

- In AML, hyperleukocytosis defined as WBC >100,000/μL
- Leukostasis most commonly affects CNS and lungs
- Treatment
  - Hydroxyurea 2 g Q6H
  - Leukapheresis
  - +/- cytarabine 500 mg/m^2 x 1-2 doses
  - +/- high-dose dexamethasone for pulmonary symptoms

CNS = central nervous system; WBC = white blood cell.

Heme Emergencies: Tumor Lysis Syndrome

- Spontaneous or chemo-induced
- Hyperkalemia, hyperphosphatemia, hypocalcemia
- Treatment
  - Hydration 4-5 L/day (not necessary or beneficial to alkalinize)
  - “You can’t dialyze the lung”
  - Allopurinol 300-600 mg/day (blocks xanthine oxidase)
  - Rasburicase 0.15 mg/kg (recombinant urate oxidase which metabolizes uric acid to allantoin)
    - G6PD deficiency is a contraindication

Heme Emergencies: Thrombohemorrhagic Syndrome

- Relatively common in APL, due to DIC + fibrinolysis + fibrinogenolysis
- Incidence of fatal hemorrhage in APL is 5-17%
  - Highest rates are outside academic institutions
- Incidence of thrombosis in APL is ~5%
- Supportive care
  - Transfuse platelets to keep >30-50 K/μL
  - Transfuse FFP to keep INR <1.5
  - Transfuse cryo to keep fibrinogen >150 mg/dL

DIC = disseminated intravascular coagulation; FFP = fresh frozen plasma.

Park JH et al, *Blood* 2011

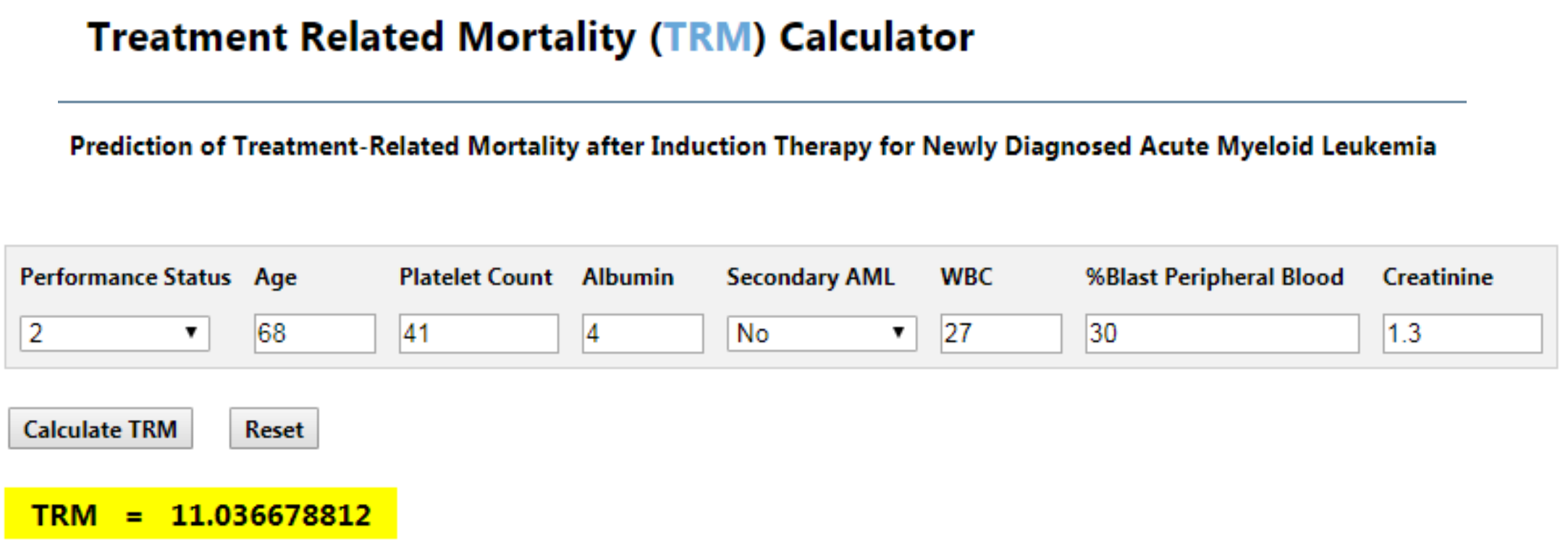
Treatment-Related Mortality (TRM) Calculator

- Treatment-related mortality: Death within 28 days of starting intensive induction chemotherapy (7+3 or more intense) for newly diagnosed AML
- https://cstaging.fhcrc-research.org/TRM/Default.aspx
- To calculate
  - PS, age, platelets, albumin, type of AML (secondary vs. primary), WBC count, % peripheral blasts, and Cr
- TRM value is roughly the likelihood of dying within 28 days

Cr = creatinine; PS = performance status.

Walter RB et al, *JCO* 2011

TRM Calculator



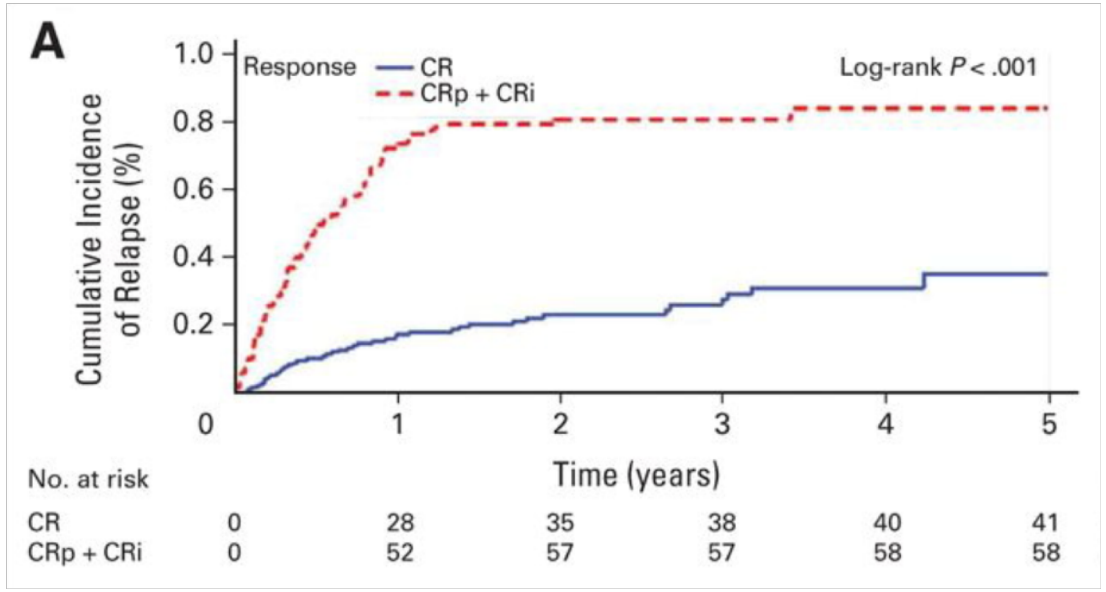
Walter RB et al, *JCO* 2011

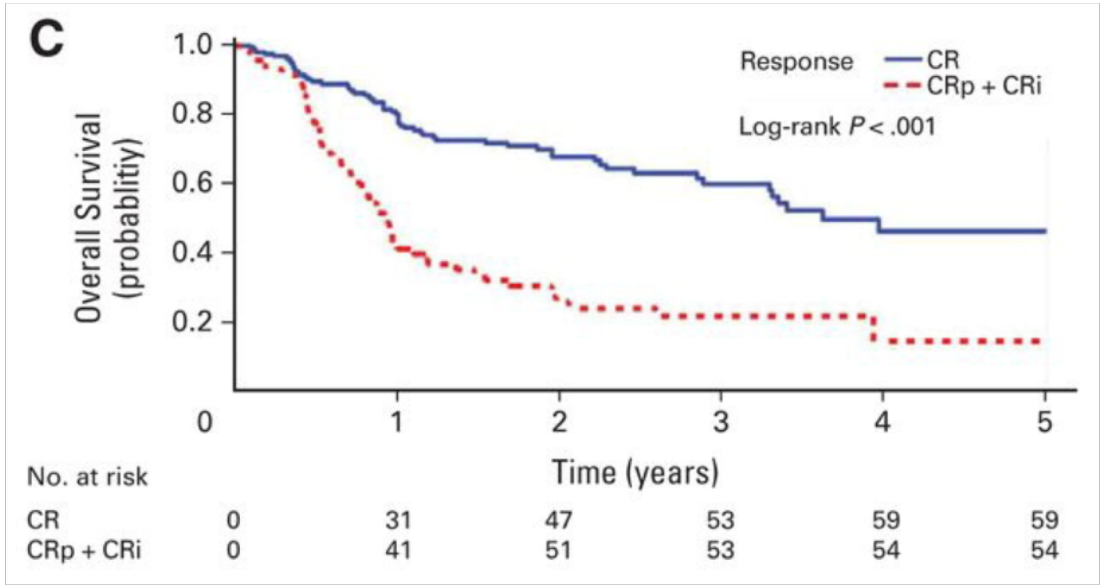
Response Criteria (ELN 2017)

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/μl; plt≥100K/μl	MRD+ or unknown
CRi	All CR criteria except ANC <1000/μl and/or plt <100K/μl	
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

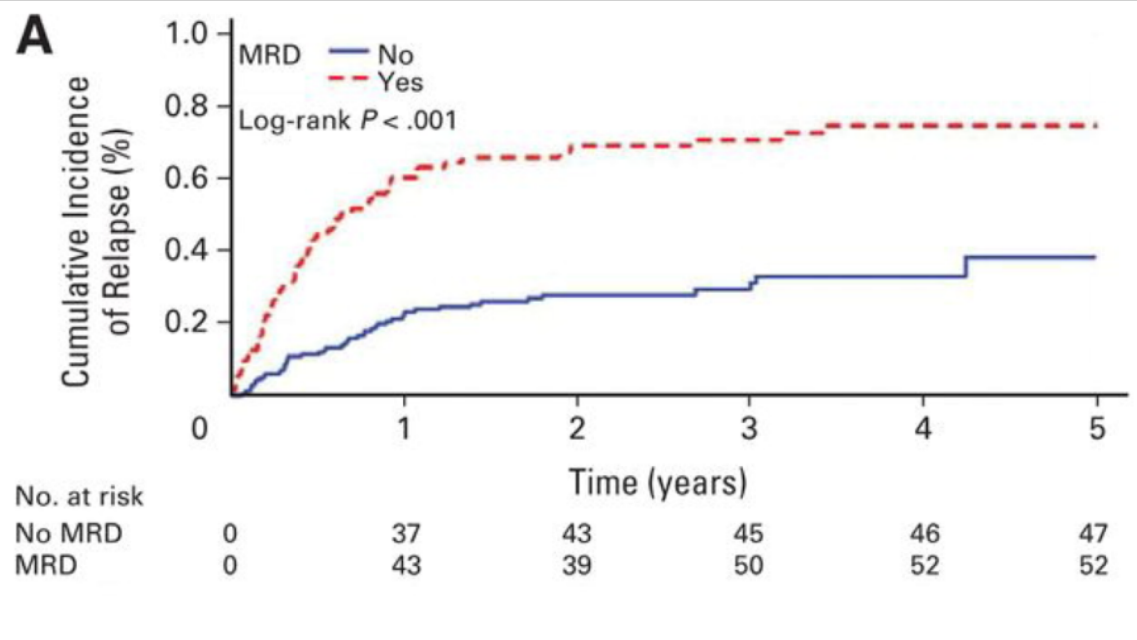
Importance of Depth of Response

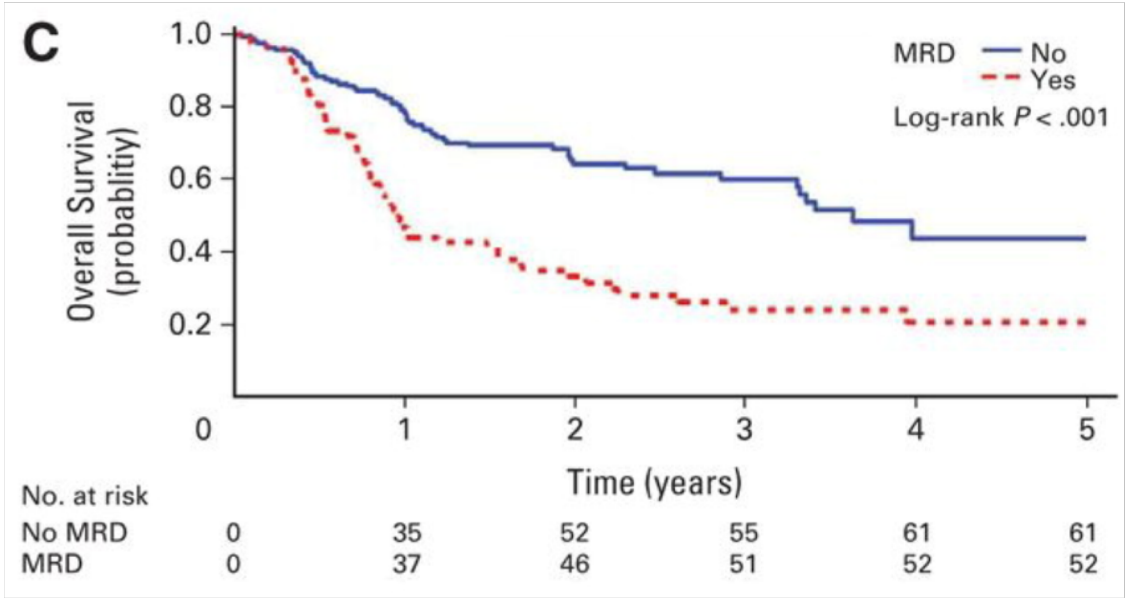




Chen X et al, *JCO* 2015

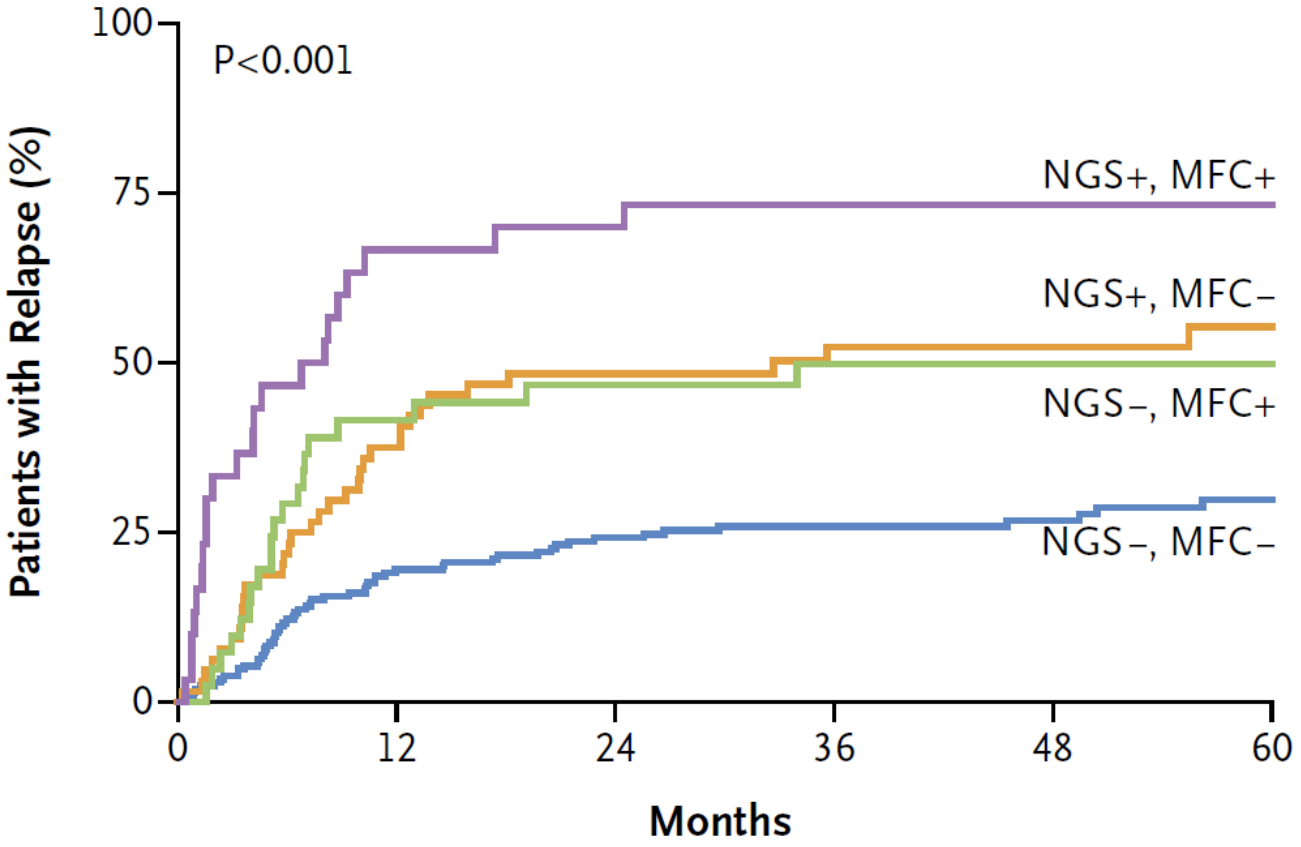
Importance of MRD





Chen X et al, *JCO* 2015

Importance of MRD



No. at Risk						
NGS+, MFC+	30	8	7	5	4	4
NGS–, MFC+	41	22	18	14	11	7
NGS+, MFC–	64	39	30	22	15	11
NGS–, MFC–	205	153	130	101	69	42

Jongen-Lavrencic et al, *NEJM* 2018

What to Do About MRD?

"Minimal residual disease"

- Outcomes are clearly worse (also as a predictor of post-allogeneic HCT outcomes)
- Clinical trials generally ignore patients with <5% blasts
- Novel therapies are needed

Management of Relapsed AML

5-year survival for patients attaining CR2

Risk Group	Treatment	5-year OS
Favorable	Chemo	33%
	Allo HCT	88%
Intermediate	Chemo	31%
	Allo HCT	48%
Poor	Chemo	6%
	Allo HCT	26%

- Many potential salvage regimens exist, but clinical trial is preferred

Breems DA et al, *JCO* 2005; Stein EM et al, *Blood* 2017.

Older AML

- Is age just a number?
  - TRM score can be helpful in stratifying risk of death in induction
- Multiple retrospective analyses (Swedish registry data) indicate that older patients benefit from higher-intensity therapy
- ELN 2017: Patients should have 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

Therapy and New Drugs

Fundamental Principles of Induction

- Most common therapy for 40+ years: “7+3” x 1-2 cycles
  - Anthracycline x 3 days
    - Daunorubicin 60-90 mg/m^2/day
    - Idarubicin 10-12 mg/m^2/day
    - Mitoxantrone 12-15 mg/m^2/day
  - Cytarabine 100-200 mg/m^2/day continuous infusion x 7 days
- Other options include high-dose cytarabine (HiDAC) containing regimens, such as IA, FLAG-idarubicin or G-CLAM
- Moreover, per ELN 2017, age alone should not preclude intensive therapy
- **NCCN Guidelines: “The best management of any cancer patient is in a clinical trial.”**

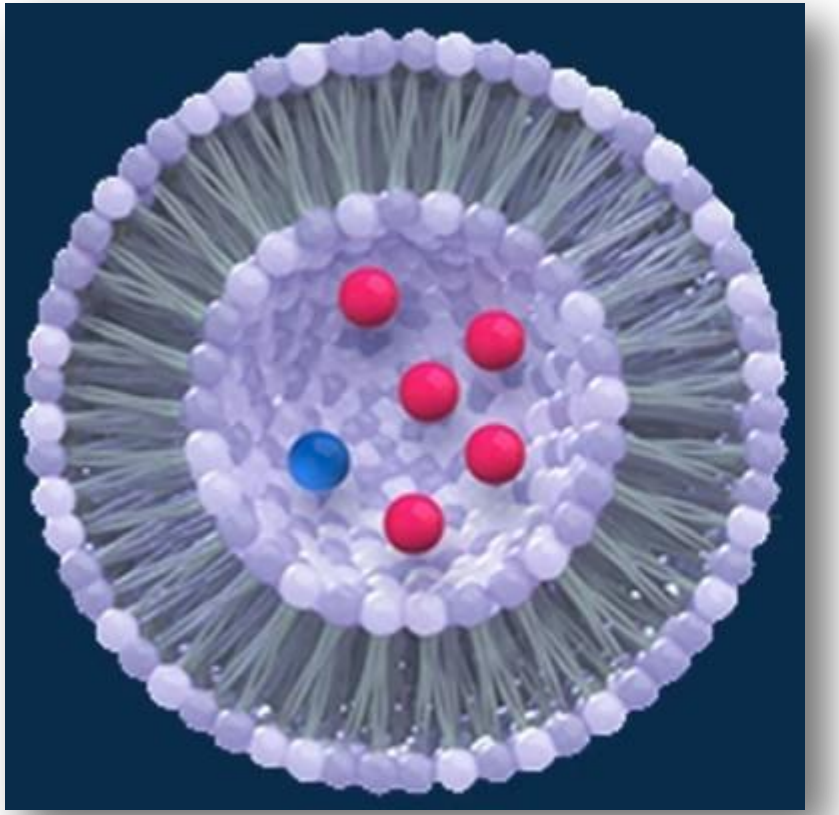
Yates JW et al, Cancer Chemother Rep 1973

Alternatives to Intensive Induction

- Azacitidine
- Decitabine
  - Particularly in *TP53*-mutated AML
- Clofarabine
- Lenalidomide
- **Liposomal daunorubicin + cytarabine**
- **Gemtuzumab ozogamicin**
- **Enasidenib & ivosidenib**
- **Venetoclax**
- **Midostaurin**

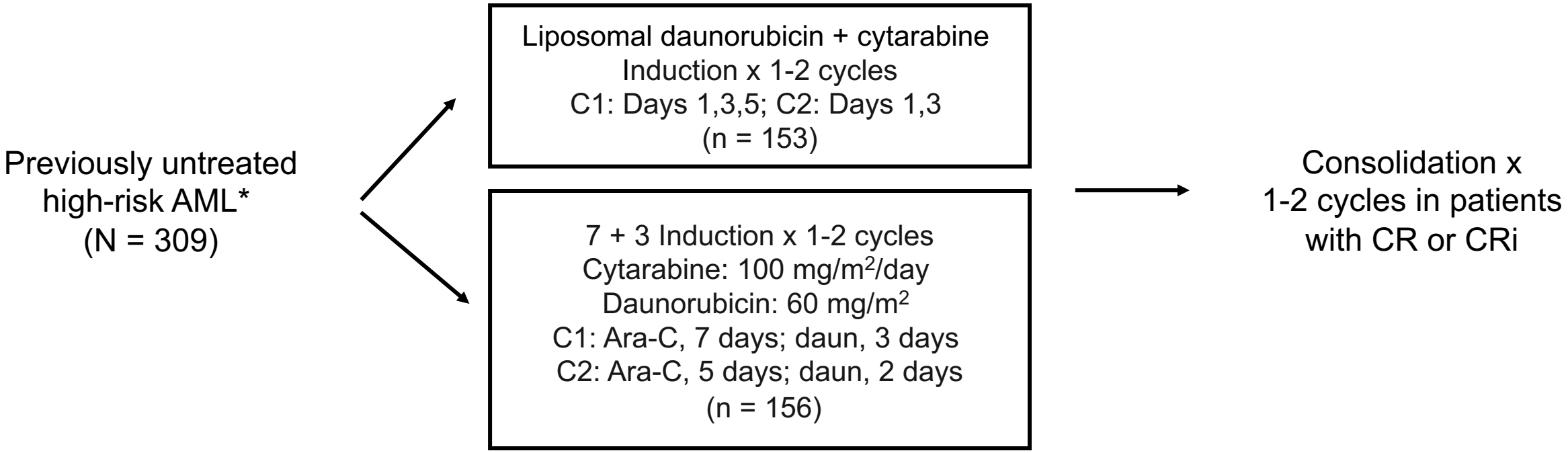
Liposomal Daunorubicin + Cytarabine or *"Purple Rain"*

- 5:1 molar ratio of cytarabine to daunorubicin
- Utilizes nano-scale delivery complex (100-nm bilamellar liposomes)
  - Preferentially taken up by leukemic cells
  - Hypothetically boosts efficacy while maintaining favorable toxicity profile
- Dose: 100 unit/m^2 IV on D1, 3, 5
  - 1 unit = 1 mg cytarabine + 0.44 mg daunorubicin



Vyxeos® Package Insert

Liposomal Daunorubicin + Cytarabine: Phase III Study



* Therapy-related AML; AML with history of MDS ± prior HMA therapy or CMML; de novo AML with MDS karyotype.

Liposomal Daunorubicin + Cytarabine: Phase III Study

Outcome	CPX-351 (n = 153)	7 + 3 (n = 156)	HR	Odds Ratio (95% CI)	P Value
Median OS (mo) (95% CI)	9.56 (6.60-11.86)	5.95 (4.99-7.75)	0.69	NA	.005
Median EFS (mo) (95% CI)	2.53 (2.07-4.99)	1.31 (1.08-1.64)	0.74	NA	.021
Response, % ▪ CR ▪ CR + CRi	 37.3 47.7	 25.6 33.3	 NA NA	 1.69 (1.03-2.78) 1.77 (1.11-2.81)	 .04 .016

- **CPX-351 superior to 7+3 for OS, EFS, CR, CR + Cri**
- Among patients to undergo successful ASCT: Median OS was not reached for CPX-351 treated patients vs. 10.25 months (HR: 0.46, *P* = 0.0046).

Lancet JE, et al. ASCO 2016. Abstract 7000

Liposomal Daunorubicin + Cytarabine: Phase III Study

Grade ≥3 ADEs	CPX-351 (N = 304) (%)	7 + 3 (N = 151) (%)
Febrile neutropenia	108 (69)	107 (71)
Pneumonia	30 (20)	22 (15)
Hypoxia	20 (13)	23 (15)
Sepsis	14 (9)	11 (7)
Hypertension	16 (10)	8 (5)
Respiratory failure	11 (7)	10 (7)
Fatigue	11 (7)	9 (6)
Bacteremia	15 (10)	3 (2)
Reduced ejection fraction	8 (5)	8 (5)

Comparable safety profiles with notable points: CPX-351 causes **more prolonged neutrophil & platelet recovery time** and, higher rate of hemorrhagic and infectious adverse events.

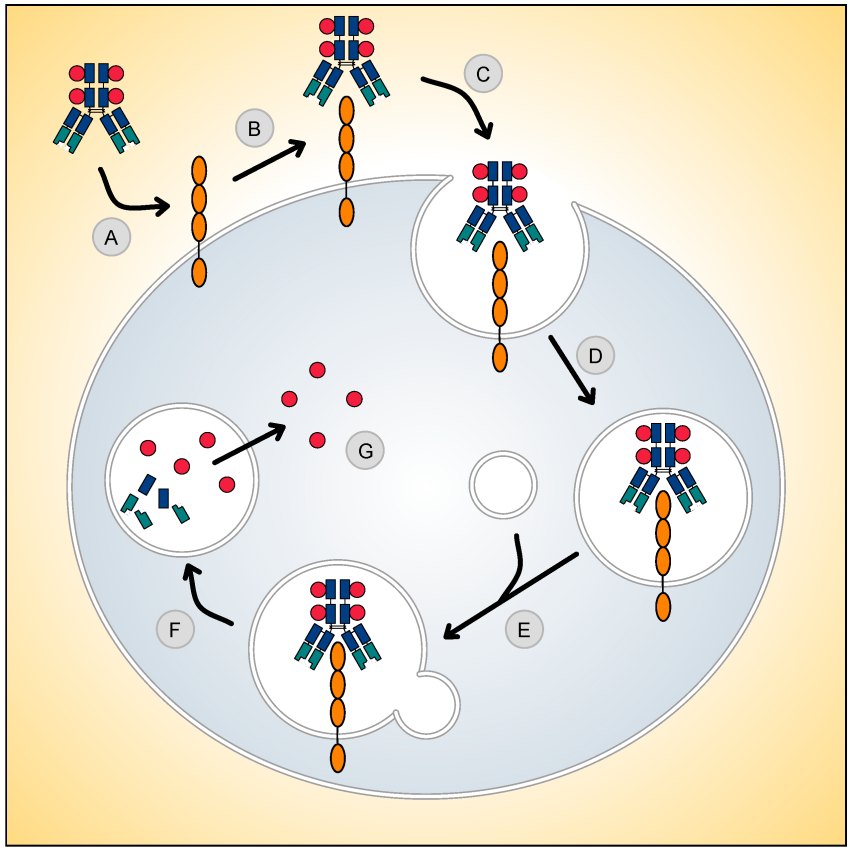
Lancet JE, et al. ASCO 2016. Abstract 7000

Gemtuzumab Ozogamicin

- First antibody-drug complex (ADC) approved (2000); voluntarily removed in 2010; big comeback in 2017
  - Meta-analysis of RCTs suggested benefit, particularly in favorable risk
- Humanized IgG4 monoclonal antibody, conjugated to calicheamicin (toxin)
- Target: CD33 antigen on leukemic blasts and immature normal cells of myelomonocytic lineage
  - Does not affect hematopoietic stem cells
- ADE: Prolong cytopenia and VOD (increased risk at higher doses or in heavily pretreated patients)

Ravandi F, et al. *J Clin Oncol* 2009; 27: 504–510

Gemtuzumab Ozogamicin



Mechanism of Action

- GO binds to CD33 receptors
- Antigen-ADC complex is rapidly internalized into endosomal vesicles
- Complex is processed along the endosomal-lysosomal pathway
- Proteolytic environment results in degradation
- Release of cytotoxic compound

Parslow AC, et al. *Biomedicines* 2016;4(3):14

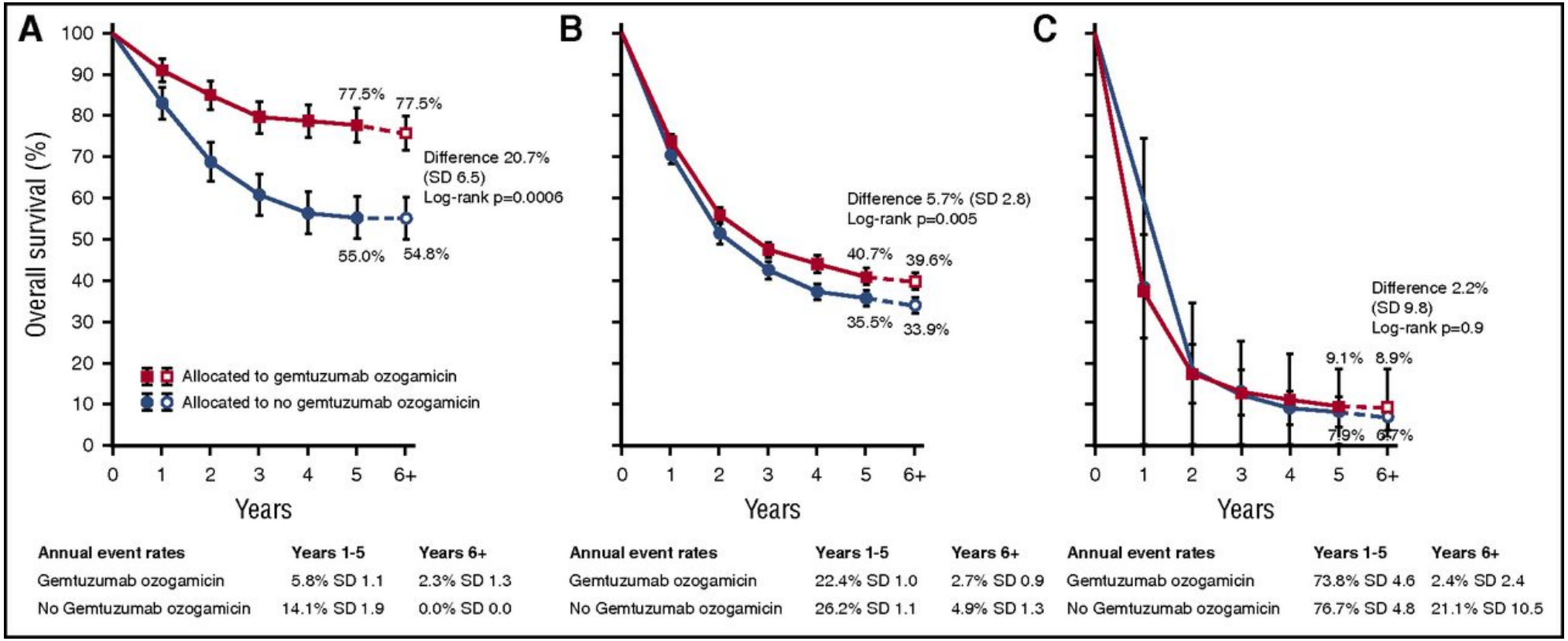
Gemtuzumab Ozogamicin: History

- 2000: Accelerated approval based on interim analysis (n = 142)
  - Dose: 9 mg/m^2 IV on D1 & 14
  - CR = 16.2%, CRp = 13.4%, CR + CRp = 29.6%
- 2010: SWOG S0106 (n = 637), >60 yo with de novo AML
  - Standard daunorubicin*/cytarabine +/- GO 6 mg/m^2 IV on D4
  - No overall improvement in survival & increased treatment-related mortality in experimental arm
- 2017: ALFA-701 & subsequent meta-analyses
  - ALFA-701: Similar CR rates but improved 3-year EFS
  - Meta-analyses (n = 3325): Similar CR rates but reduced RR, improved relapse-free & OS at 5 years

***Daunorubicin dose reduced from 60 mg/m^2 in the control arm to 45 mg/m^2 in the GO arm to balance toxicities.**

Applebaum and Bernstein. Lancet Oncol. 2014;15(9):986-996

Overall Survival According to Cytogenetic Risk Category



Annual event rates	Years 1-5	Years 6+
Gemtuzumab ozogamicin	5.8% SD 1.1	2.3% SD 1.3
No Gemtuzumab ozogamicin	14.1% SD 1.9	0.0% SD 0.0

Annual event rates	Years 1-5	Years 6+
Gemtuzumab ozogamicin	22.4% SD 1.0	2.7% SD 0.9
No Gemtuzumab ozogamicin	26.2% SD 1.1	4.9% SD 1.3

Annual event rates	Years 1-5	Years 6+
Gemtuzumab ozogamicin	73.8% SD 4.6	2.4% SD 2.4
No Gemtuzumab ozogamicin	76.7% SD 4.8	21.1% SD 10.5

Applebaum and Bernstein. *Lancet Oncol*. 2014;15(9):986-996

Isocitrate Dehydrogenase (IDH) Mutations

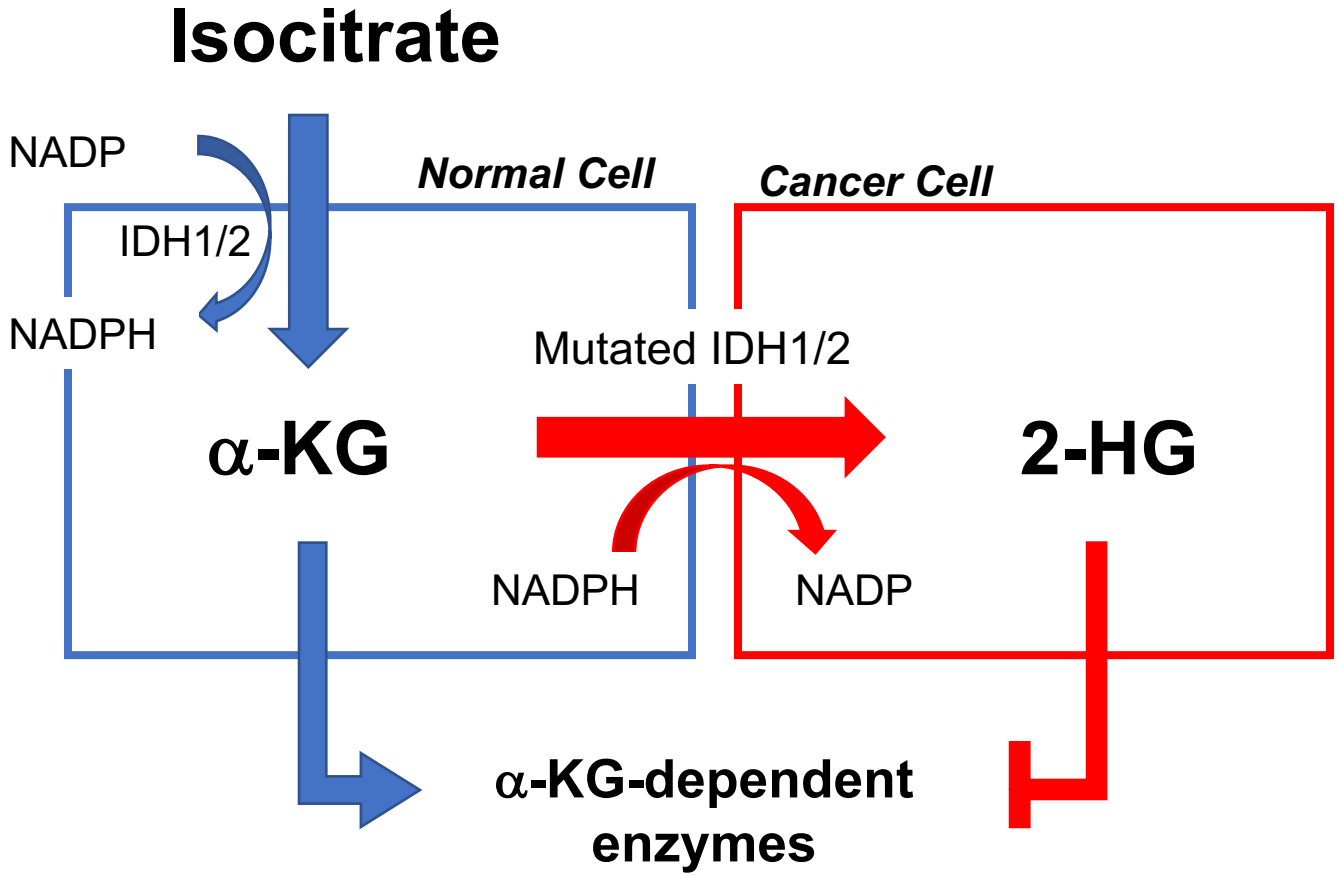
- Found in 15-20% of newly diagnosed AML and increases in frequency with age
  - Associated with poorer overall prognosis in AML patients (prognostic marker in MDS still under debate).

- Isocitrate dehydrogenase (IDH) catalyzes the conversion of isocitrate to alpha-ketoglutarte (α-KG) and NADP+ to NADPH.
  - α-KG and NADPH confer cellular protection against oxidative damage.

- Mutations in IDH1/2 confers neomorphic enzyme activity:
  - Converts α-KG to 2-hydroxyglutarate (oncometabolite)

DiNardo et al. Am J Hematol. 2015;90:732-736; Patel et al. Am J Clin Pathol 2011;135(1);35-45

IDH Mutations



- Mutated IDH1/2 proteins synthesize 2-HG
- 2-HG inhibits normal function of α-KG-dependent enzymes
- Results in epigenetic changes (DNA & histone hypermethylation) and impairs cellular differentiation

Enasidenib

- Approved: 2017
- Mechanism
  - Oral inhibitor of mutated **IDH2** enzyme
  - Induces leukemic cell differentiation
- Dose: 100 mg daily until disease progression or unacceptable toxicity
- Warnings/ADEs
  - **Differentiation syndrome (14%)**
  - Most common (≥20%): hyperbilirubinemia, N/V/D, anorexia, decreased calcium, potassium & phosphorus
- ADME
  - Parent & metabolite are substrates of multiple CYP enzymes & UGTs

ADME = absorption, distribution, metabolism, and excretion; N/V/D = nausea, vomiting, diarrhea; UGT = UDP-glucuronosyltransferase.

Ivosidenib

- Approved: 2018
- Mechanism
  - Oral reversible inhibitor of mutated **IDH1** enzyme
  - Induces leukemic cell differentiation
- Dose
  - 500 mg daily until disease progression or unacceptable toxicity
- Warnings/ADEs
  - **Differentiation syndrome**
  - Most common (≥20%): Fatigue, leukocytosis, mucositis, QT prolongation, rash, cough, N/V/C/D
- ADME
  - Primarily metabolized by CYP3A4

	Enasidenib	Ivosidenib
Number	199	174 (Efficacy) & 179 (Safety)
Median age (range)	68 yr (19 – 100 yr)	67 (18 to 87 yr)
Median prior therapies (range)	2 (1 – 6)	2 (1 - 6)
Rate of CR + CRh (CR, CRh)	23% (19%, 4%) (95% CI, 18 – 30)	32.8% (27%, 8%) (95% CI 25.8 – 40.3)
Median time to first response (range)	1.9 mo (0.5 – 7.5 mo)	1.9 mo (0.8 – 4.7 mo)
Median time to best response of CR or CRh (range)	3.7 mo (0.6 – 11.2 mo)	2.7 mo (0.9 – 5.6 mo)
Median duration of CR + CRh	8.2 mo (4.3 – 19.4 mo)	8.2 mo (5.5 – 12 mo)
Median duration of exposure (range)	4.3 mo (0.3 – 23.6 mo)	3.9 mo (0.1 – 39.5 mo)
Conversion from transfusion-dependent to transfusion-independent	34%	37.3%

DiNardo et al. NEJM 2018; 378:2386-2398

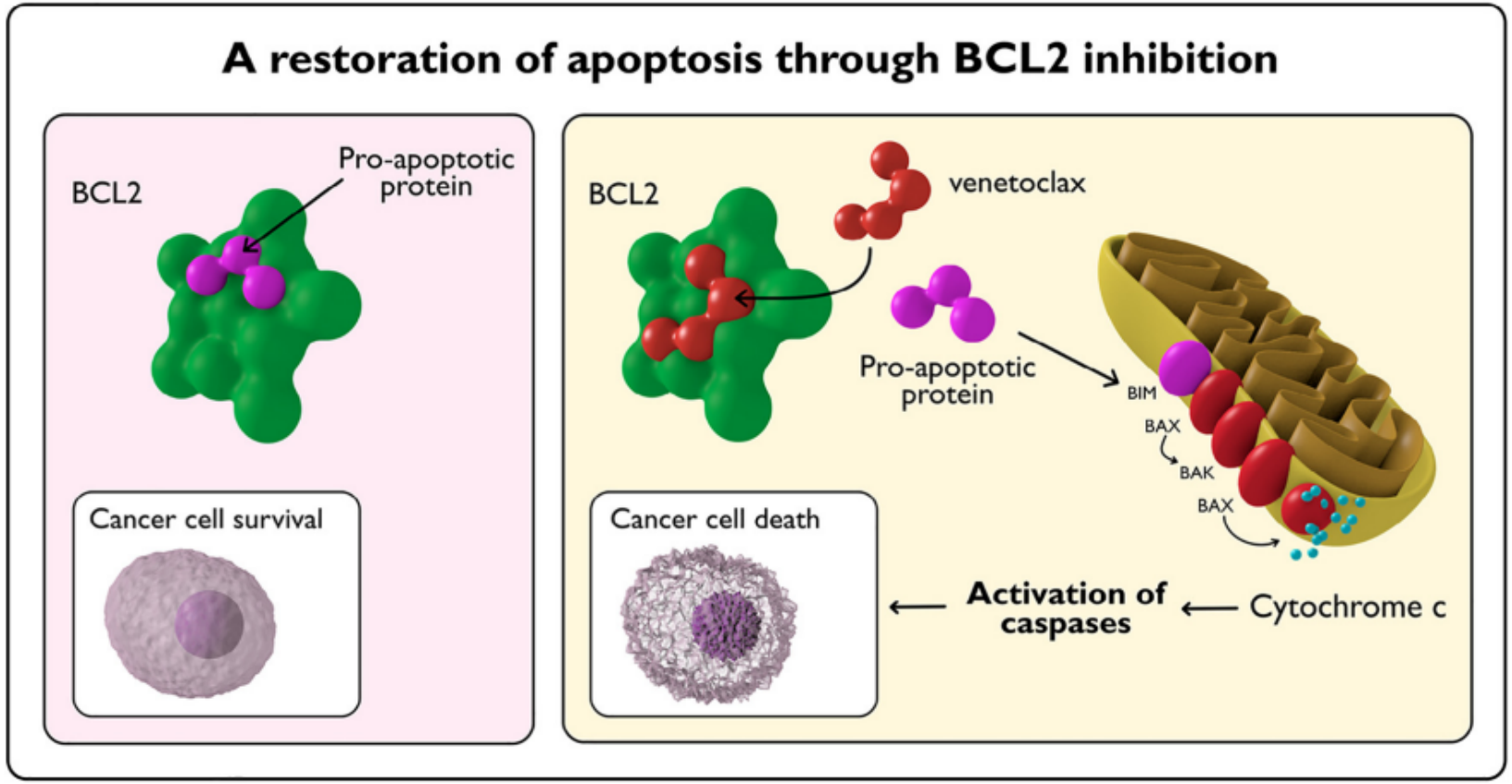
BCL2 Inhibitors

- AML cells are dependent on BCL2 for survival
  - BCL2 is an anti-apoptotic protein expressed at high levels in AML and is associated with poor outcomes and resistance to chemotherapy
- Pre-clinical studies reveal that patients with mutated IDH1/2 are more likely to respond to BCL2 inhibition by venetoclax
- Clinical trials assessing the efficacy of venetoclax in combination for elderly patients with untreated AML
  - Phase I/II: Venetoclax + LD-AraC
  - Phase Ib: Venetoclax + azacitidine or decitabine

Venetoclax

Mechanism of Action

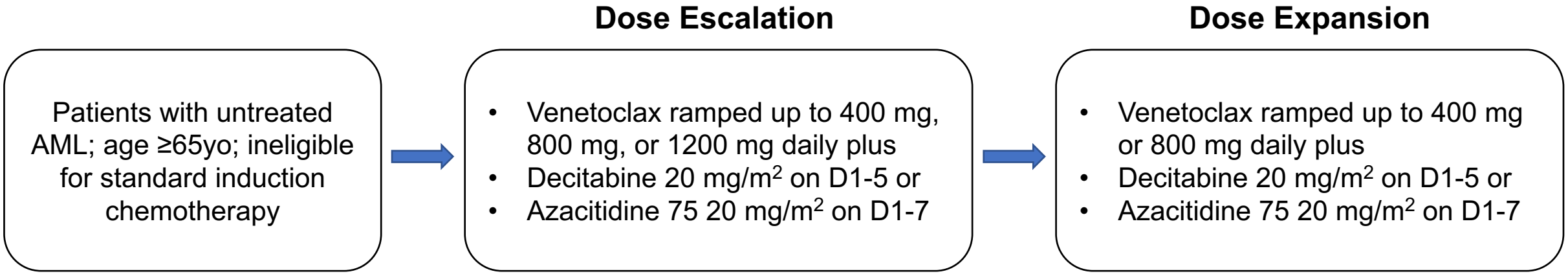
- Venetoclax binds to BH3 domain of BCL2 to displace BH3-only proteins (e.g., BIM) from BCL2
  - Activate apoptotic effectors (BAX & BAK) or inhibit anti-apoptotic members (MCL-1)
- Triggers and restores apoptosis in tumor cells.



Mihalyova et al., *Exp Hematol*. 2018;61:10-25

Venetoclax + Hypomethylating Agent

- Multicenter, open-label, phase Ib dose-escalation and dose-expansion trial
  - Primary: Safety
  - Secondary: CR, CRi, OS, DoR
  - Exploratory: MRD (<10^{-3} leukemic cells as detected by flow cytometry)



Venetoclax + Hypomethylating Agent

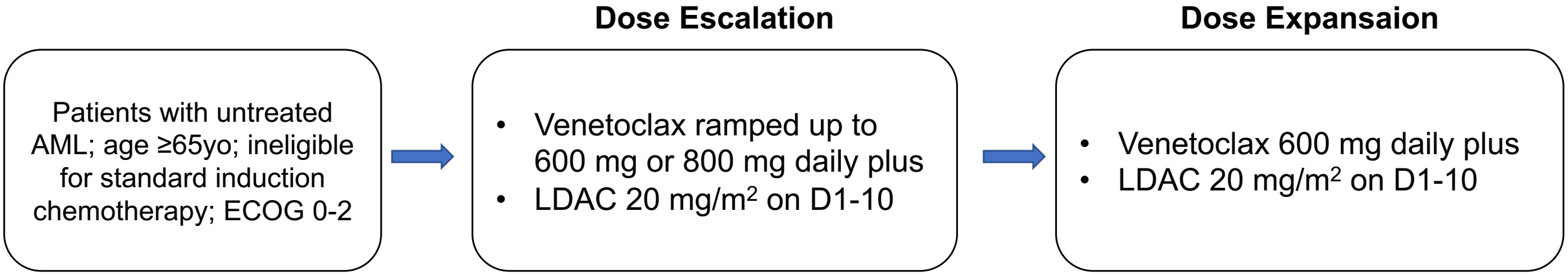
Outcome	Patients (N = 145)	Venetoclax 400 mg		Venetoclax 800 mg	
		Azacitidine (n = 29)	Decitabine (n = 31)	Azacitidine (n = 37)	Decitabine (n = 37)
Rate of CR + CRi (%) ▪ CR ▪ CRi	67 37 30	76 38 38	71 45 26	57 30 27	73 38 35
Median OS, months (95% CI)	17.5 (12.3-NR)	NR (11.0-NR)		17.5 (10.3-NR)	
Median DoR in patients with CR/CRi, months (95% CI)	---	NR (5.6 – NR)	12.5 (5.1 – NR)	11.7 (4.6 – 12.9)	9.2 (5.9 – NR)
MRD negativity in patients with CR/CRi (%)	28/97 (29)	10/22 (45)	7/22 (32)	7/21 (33)	3/27 (11)

Median follow-up: 15.6 months

DiNardo et al. ASCO 2018. Abstract 7010

Venetoclax + Low-Dose Cytarabine (LDAC)

- Multicenter, open-label, phase Ib/II dose-escalation & dose-expansion trial
- Phase I objectives
  - Primary: Safety & PK
  - Secondary: Preliminary efficacy rates, DoR, OS



Venetoclax + Low-Dose Cytarabine (LDAC)

Safety

- Dose-limiting toxicity of thrombocytopenia
- Generally well tolerated with few discontinuations due to AEs

Efficacy

- ORR correlated with OS
  - ORR (CR + CRi + PR) = 75%
  - CR + CRi = 70%
- Median OS
  - Non-responders: 4 months
  - Responders: Not reached
- 12-mo OS: 74.7% (all patients)

Lin TL, et al. ASCO 2016. Abstract 7007

FLT3 Inhibitors

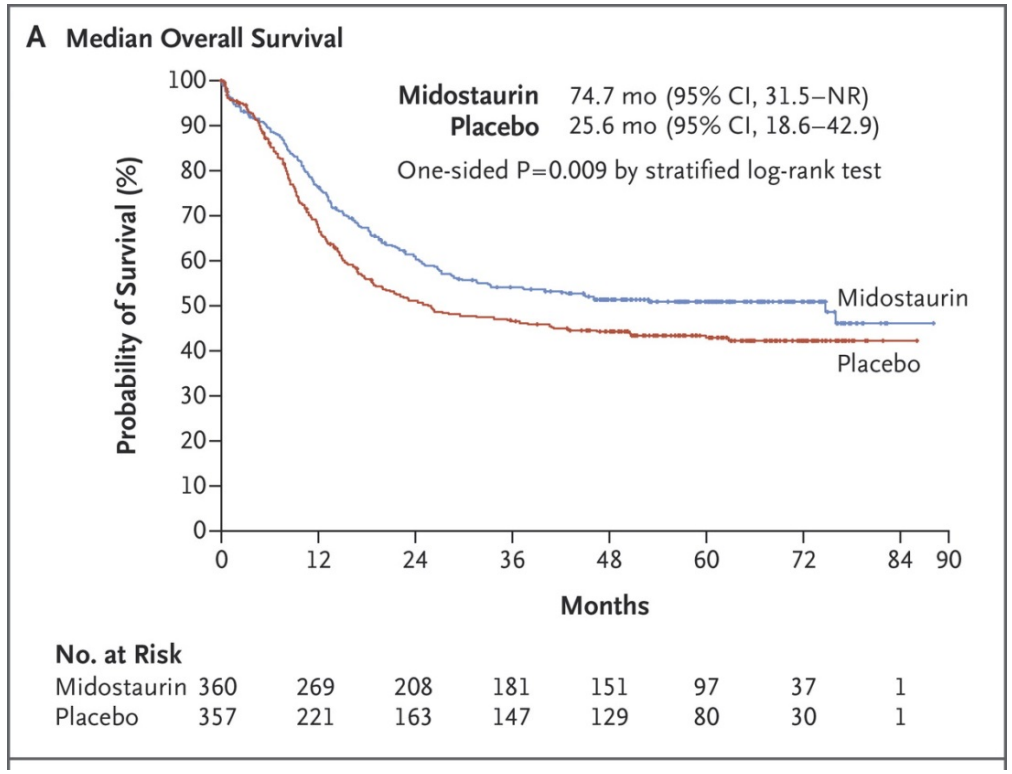
- FLT3 is a receptor tyrosine kinase (RTK), transduces signals promoting proliferation and survival
- FLT3-ITD mutations are found in ~23% of AML cases and results in increased relapse rates and reduced overall survival
- The prognostic impact of the ITD of FLT3 (FLT3-ITD) depends on the allelic ratio.
  - FLT3-ITD allelic ratios (≥0.5) carry a dismal prognosis in the absence of an NPM1 mutation, and these are considered as one of the adverse risk groups in the ELN 2017 risk stratification

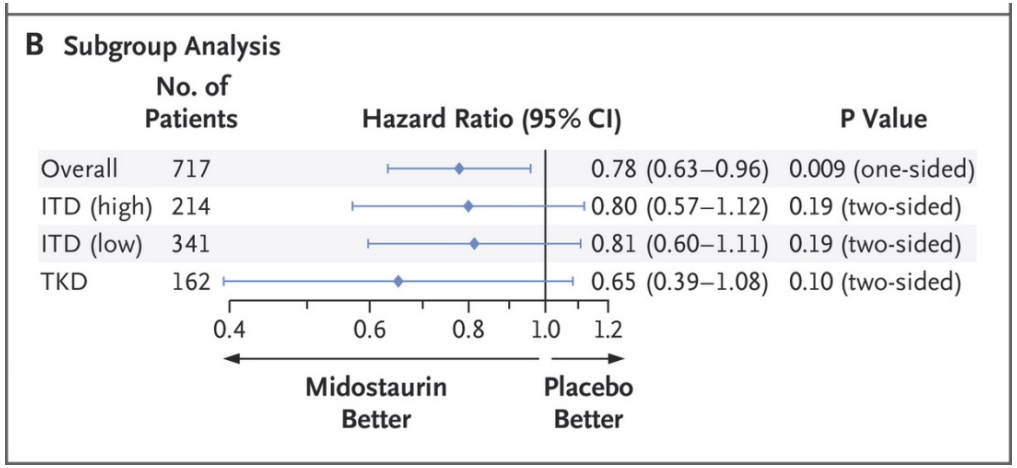
Pratz KW and and Levitz M. Blood 2017; 129:565-571
Fröhling S. Cancer Cell. 2007; 12(6):501-13

Midostaurin

- Approved: 2017
- Mechanism
  - Oral multiple receptor tyrosine kinase inhibitor, which inhibit the activity of FLT3, KIT, PDGF, VEGFR2, protein kinase C family.
  - Midostaurin induces apoptosis in leukemic cells expressing ITD- and TKD-mutant FLT3 receptors or overexpressing wild-type FLT3 and PDGF receptors.
- Dose: 50 mg BID on D8-21 of each induction/consolidation cycle.
- Warnings/ADEs
  - Most common (≥20%): Febrile neutropenia, mucositis, nausea, vomiting, headaches, musculoskeletal pain
- ADME
  - Primarily metabolized by CYP3A4

Addition of Midostaurin in FLT3+ AML





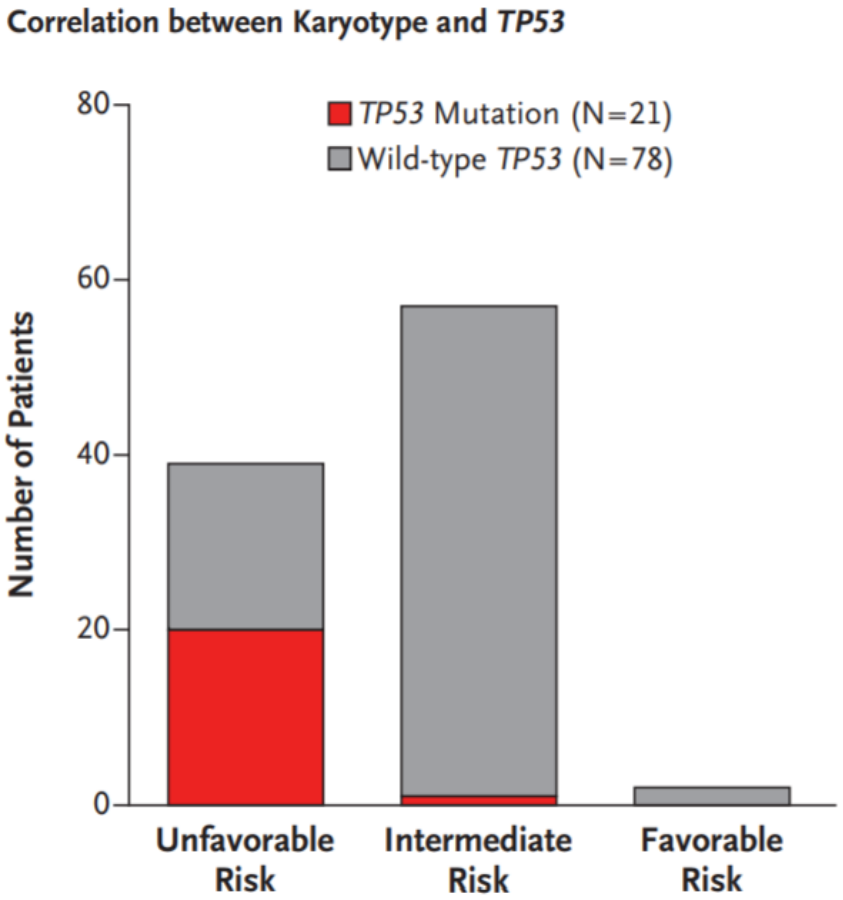
Stone RM et al., N Engl J Med 2017

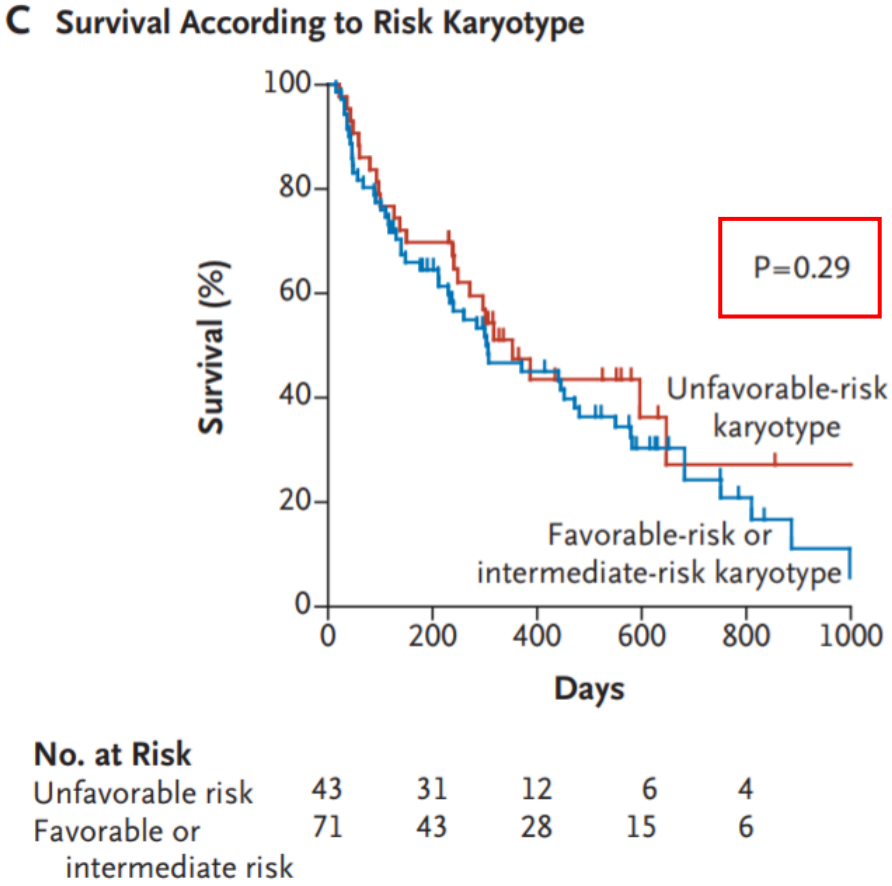
TP53-mutated AML

- TP53 – tumor suppressor gene
  - Critical role in determining whether damaged DNA will undergo repair or apoptosis.
- Patients with AML & TP53 mutation tend to be older and with karyotypes associated with unfavorable risk
  - TP53 mutations in AML (2.1%) vs. AML with complex aberrant karyotype (69-78%)
- Conventional chemotherapy generally results in poor outcomes (median survival 4-6 months)

Hou HA, et al. Blood Cancer J 2015;5(7):e331; Ferrari A, et al. Blood 2014;124:2379

TP53-mutated AML





No. at Risk

Unfavorable risk	43	31	12	6	4
Favorable or intermediate risk	71	43	28	15	6

Welch JS, et al. Blood 2016;375:2023-2036

Future Direction: T-Cell Directed Therapy

- Chimeric antigen receptor (CAR) T cells
  - Genetically engineered cell membrane-bound receptors that combine extracellular antibody binding and intracellular effector cell signaling
  - Enables both MHC-independent antigen binding and highly potent cytotoxic effector cell function

- Difficulty in AML
  - Non-restricted expression of AML-associated antigens can result in unwanted on-target off-leukemia toxicities (i.e., long-term myeloid cell aplasia)
    - Concurrent construct can remain in body for 4 years!
  - Finding a target
  - Optimal timing

Future Direction: T-cell Directed Therapy

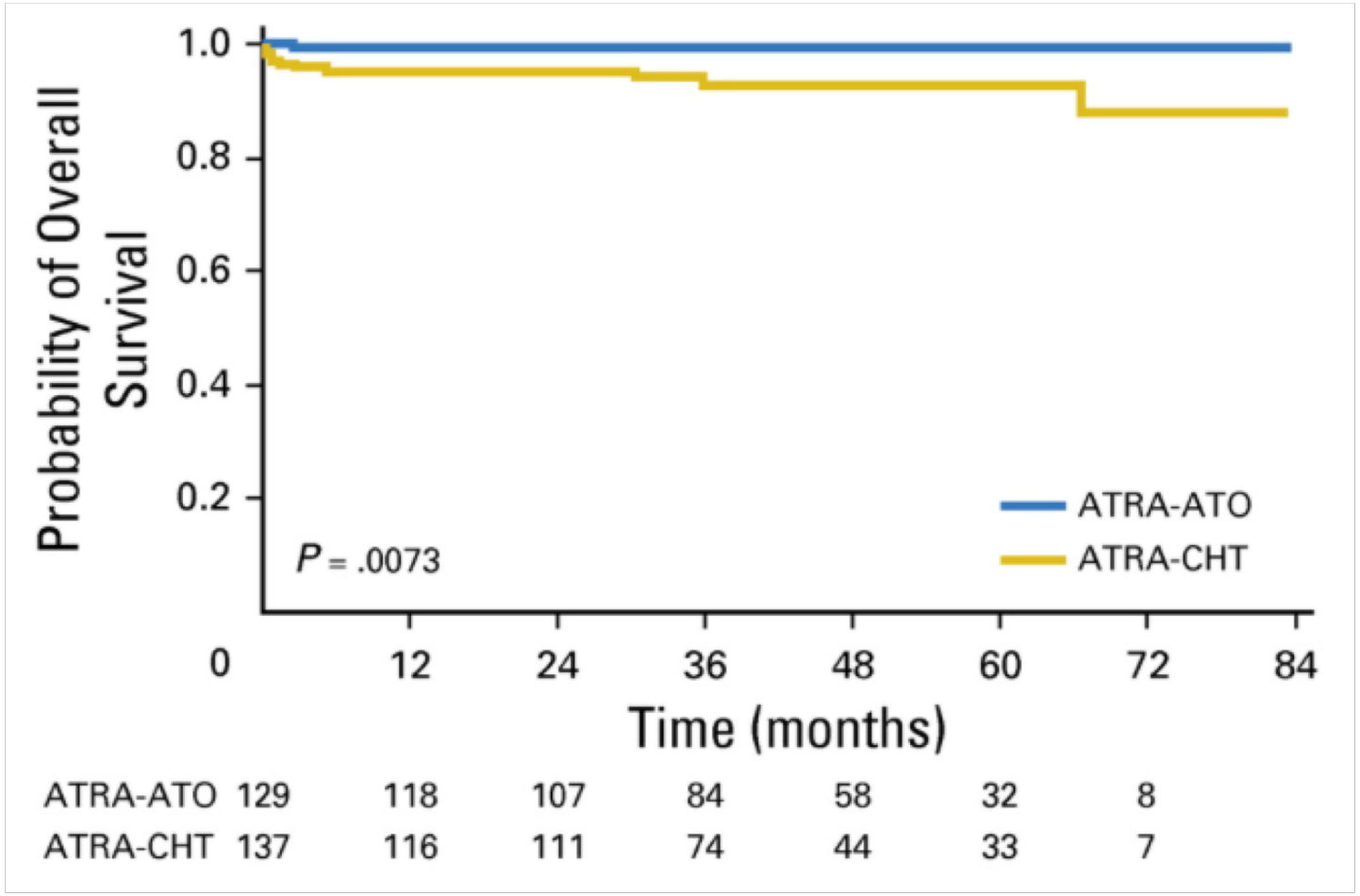
- Bispecific T-cell engager (BiTE)
  - BiTE antibody construct is engineered from two single-chain variable fragments (scFv) of different specificity connected by a short peptide linker.
  - Simultaneously binds a tumor-associated antigen and CD3ε in the T-cell receptor to bring them in close proximity
    - Leads to T-cell activation & expansion resulting in cell lysis

- Difficulty with BiTE (and similar technology) in AML:
  - Limited understanding of optimal target antigen

Acute Promyelocytic Leukemia

- ~10% of new AML (1200 patients/year in US)
- Leukopenia in 85%
  - Divided into low vs. high-risk depending on WBC count at diagnosis (high risk = ≥10,000/μl)
- Coagulopathy at diagnosis
- t(15;17)
- PML-RARα fusion transcript
- Differentiation syndrome with all-*trans* retinoic acid (ATRA) and arsenic trioxide (ATO)

APL 0406 Trial: ATRA + ATO



Platzbecker U et al, *JCO* 2017

THANK YOU!

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