Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Acute Myeloid Leukemia in 2021

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Disclosures (Percival)

- **Clinical trial support:** Pfizer, Trillium, Nohla, Oscotec, Cardiff Oncology, Glycomimetics, Biosight, Celgene/BMS
- **Pending clinical trial support:** Abbvie

Outline

Epidemiology

Diagnosis

Treatment

- Heme emergencies
- New drugs
- Regimens at UW/FHCRC/SCCA

Relapse

Indications for transplant

Older AML

APL

Epidemiology in 2021

Estimated annual new cases: 20,240

- 1.1% of all new cancer cases in the US

Estimated annual deaths: 11,400

5 year survival rate: 29.5%

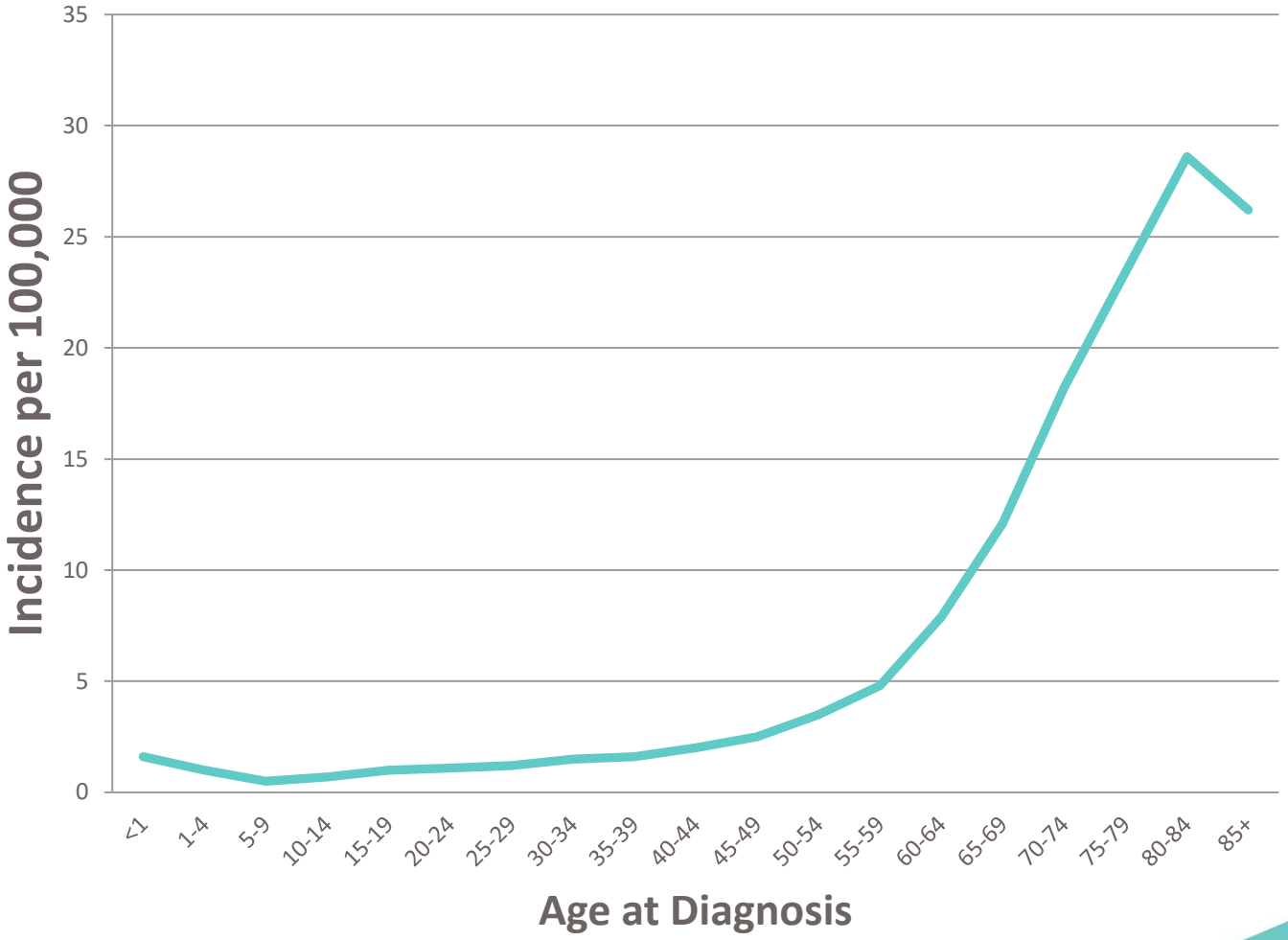
- Improving over time (6.3% survival in 1975)

M:F predominance of approximately 1.5:1

Median age at diagnosis: 68

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

Incidence by age, 2011-2015



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

Etiology

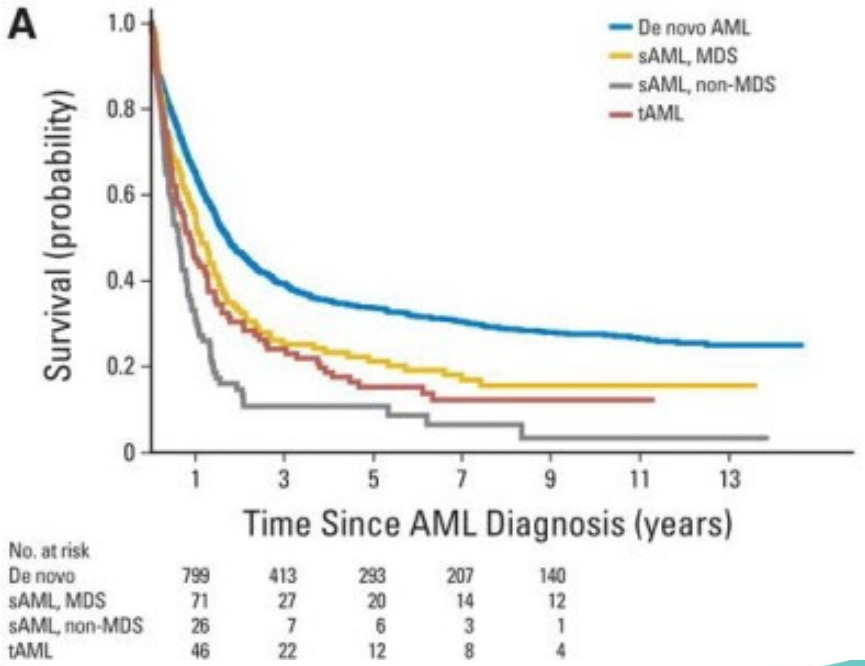
Prior chemotherapy/radiation (therapy-related, or t-AML)

Antecedent hematologic disorder (secondary, or s-AML)

Genetic predisposition

Smoking

Chemical exposures, such as benzene



Ostgard L et al *JCO* 2015

Genetic Predisposition

Many familial AML/MDS syndromes described in the past 2 decades

Most common: *GATA2*, *RUNX1*, *CEBPA*, *TERC/TERT*, Fanconi anemia, Li Fraumeni

Important to identify!

- Treatment planning
- Choice of donors for allogeneic HCT candidates
- Screening for other associated medical issues
- Counseling of family members

Consider referral to genetics clinic specializing in heme malignancy

Ongoing question: who should undergo germline testing?

"How I treat inherited AML" *Blood* 2016

Diagnosis of AML

Peripheral blood (≥20% blasts)

- <20% blasts also diagnostic in the setting of recurrent genetic abnormalities: t(8;21), inv(16) or t(16;16), t(15;17)

Bone marrow aspirate/biopsy

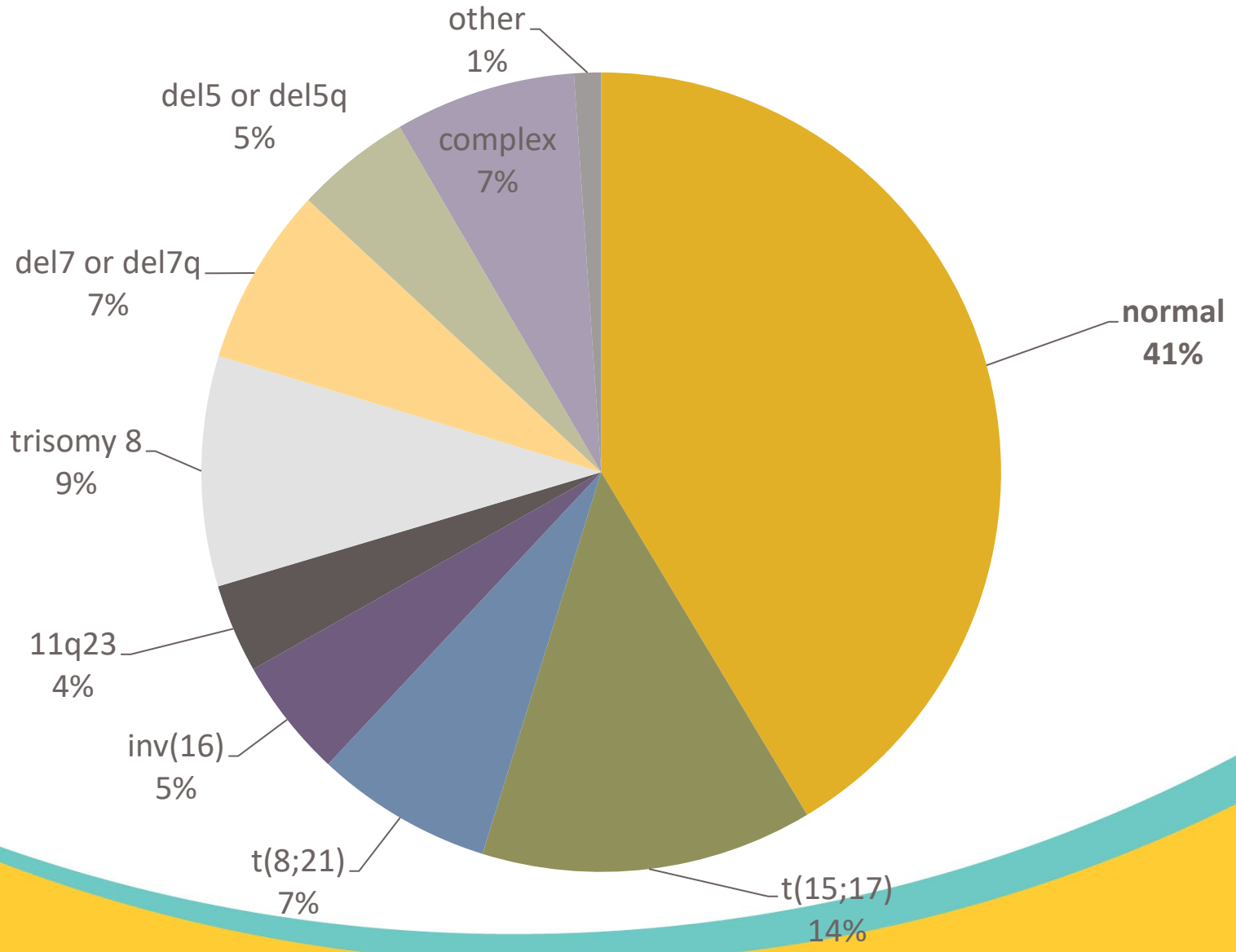
- Generally not necessary if >2K blasts in peripheral blood

Mandatory testing on blood and/or marrow at diagnosis

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

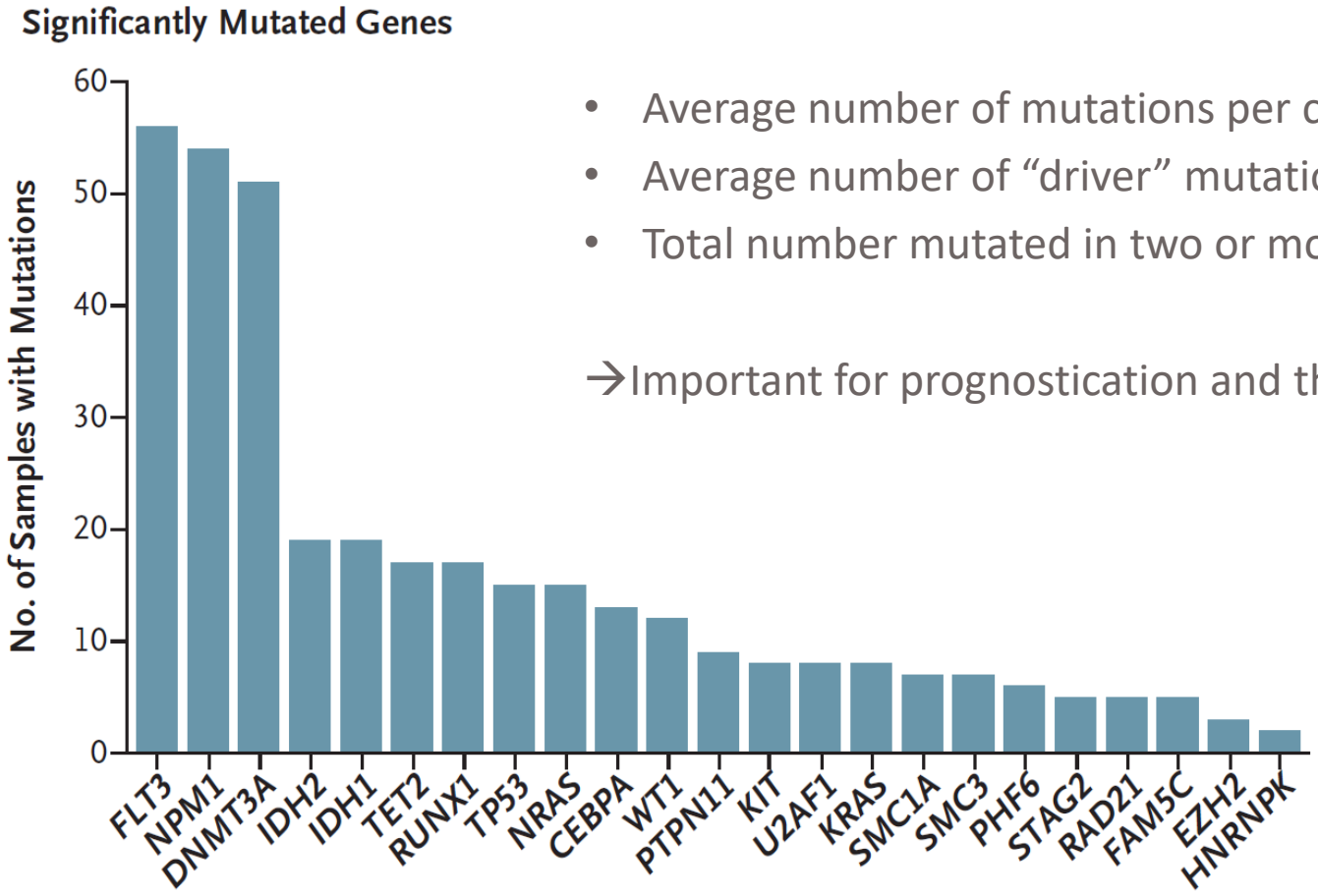
Arber DA et al, *Blood* 2016; Dohner H et al, *Blood* 2017

Common cytogenetic abnormalities



Grimwade D et al, *Blood* 2010

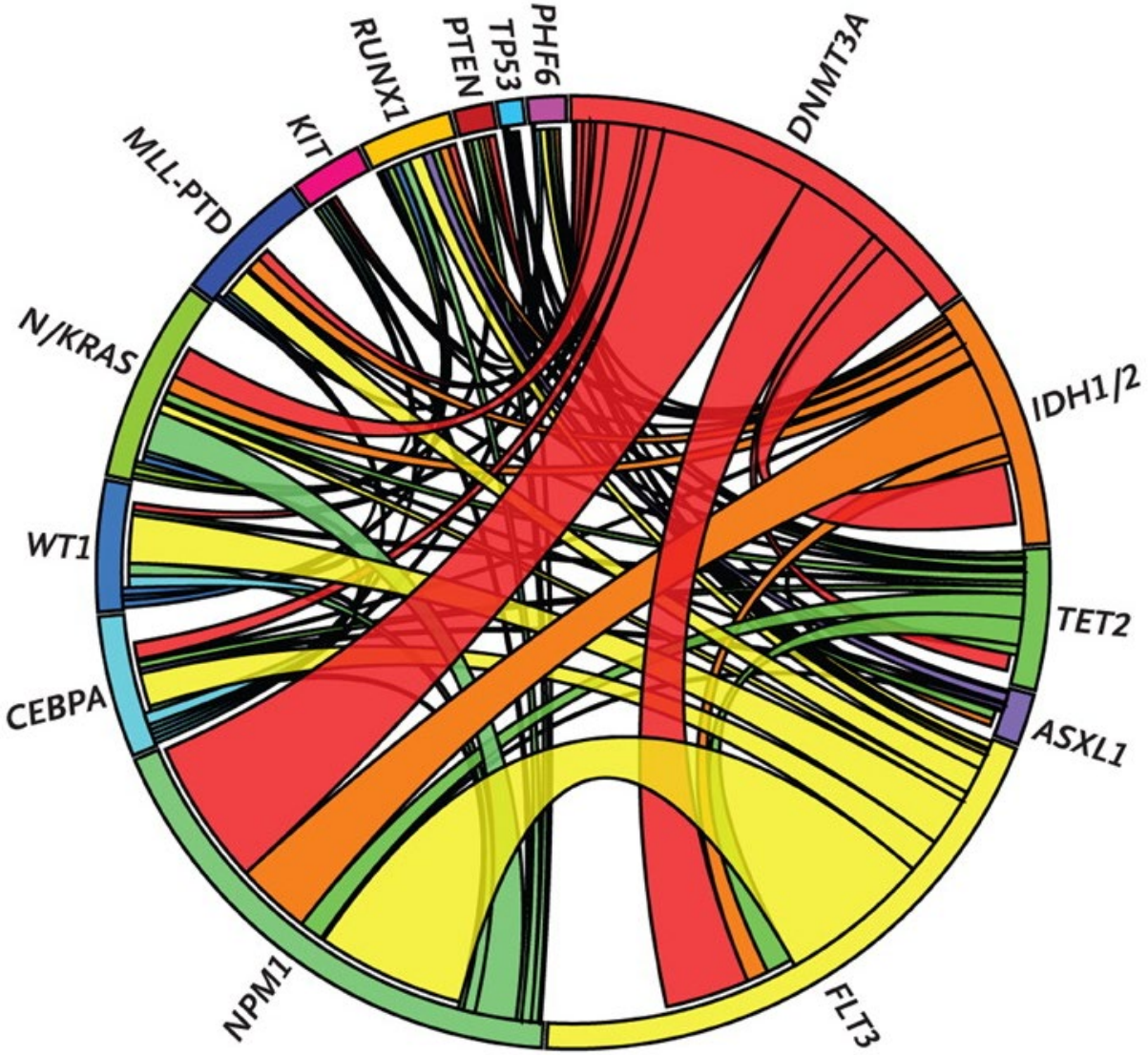
Recurrent mutations in 200 AML samples



- Average number of mutations per case: 13
- Average number of "driver" mutations per case: 5
- Total number mutated in two or more samples: 237

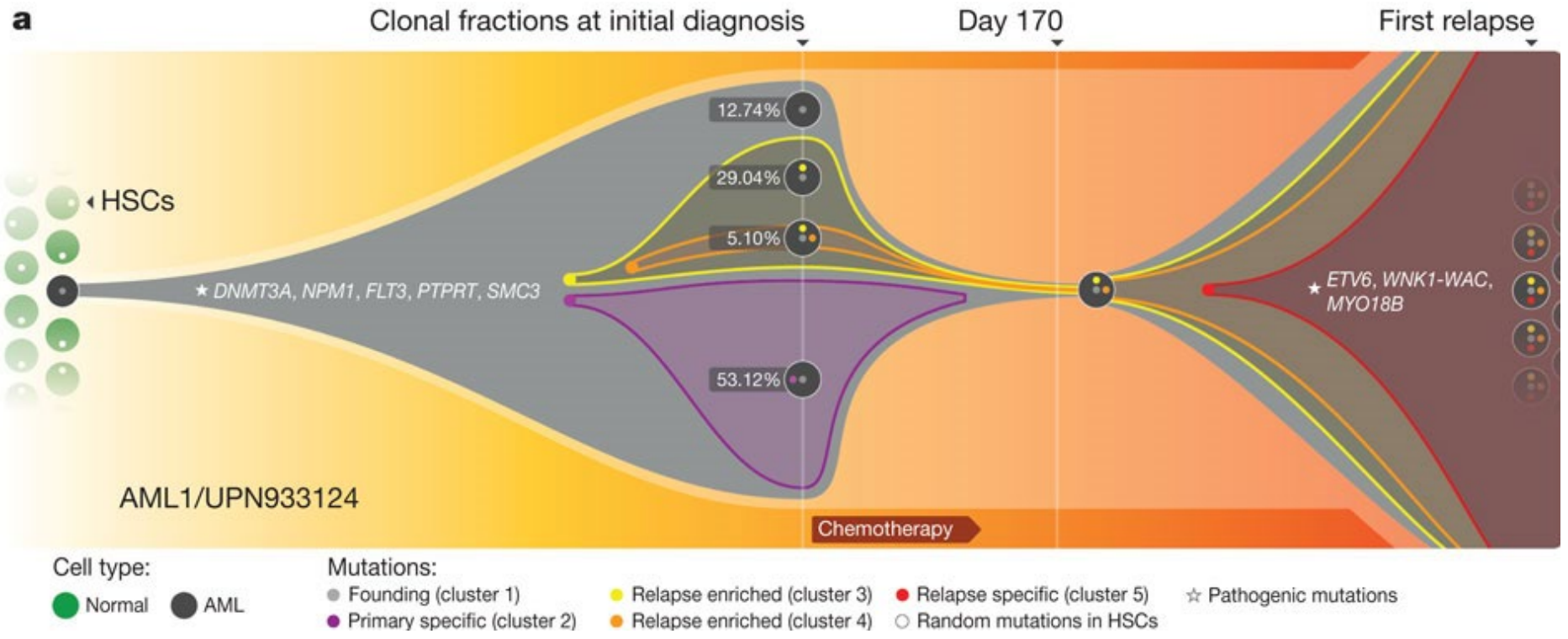
→Important for prognostication and therapeutic targets!

TCGA, *NEJM* 2013



Patel J, *NEJM* 2012

Clonal evolution



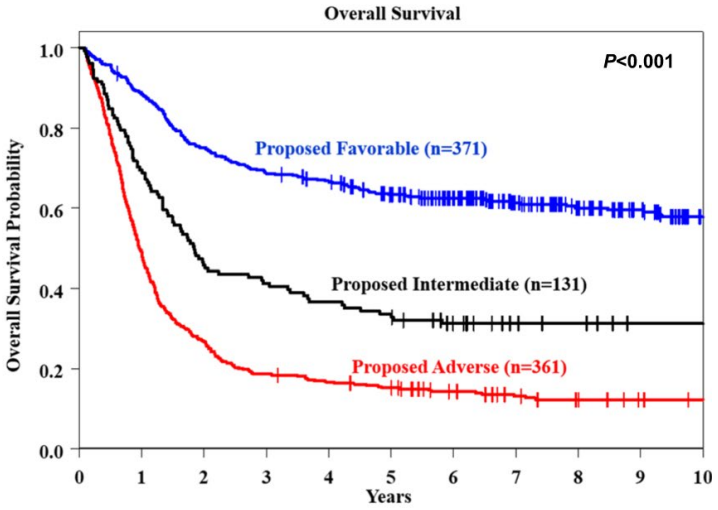
Ding *et al*. *Nature* 2012

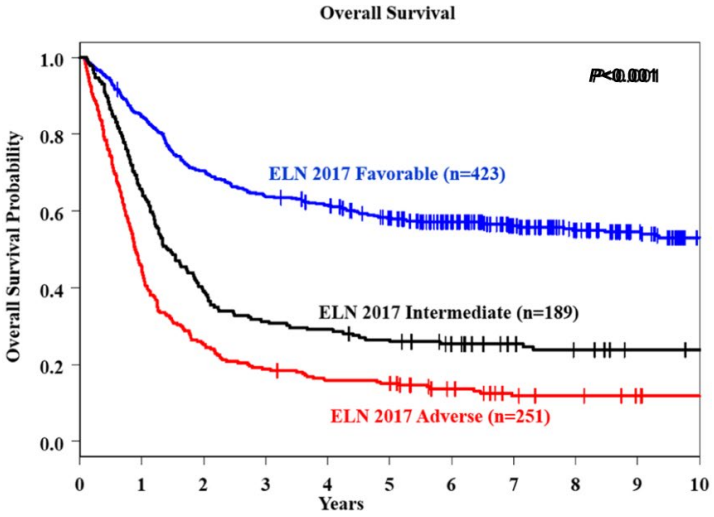
European LeukemiaNet criteria 2017

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*

Dohner H et al, *Blood* 2017

Proposed modification for <60 years





Eisfeld AK et al, *Leukemia* 2020

Heme emergencies: leukostasis

In AML, hyperleukocytosis defined as WBC>100,000/μl

Hyperleukocytosis ≠ leukostasis

Leukostasis most commonly affects CNS and lungs

Treatment:

- Starting definitive induction chemotherapy
- Hydroxyurea 2g q6hr
- (Leukapheresis)
- +/- cytarabine 500mg/m^2 x 1-2 doses
- +/- high-dose dexamethasone for pulmonary symptoms

Stahl M et al *Leukemia* 2020; Bewersdorf J et al *Transfusion* 2020

Heme emergencies: tumor lysis

Spontaneous or chemo-induced

Hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia

Treatment:

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

Cortes J et al, *JCO* 2010

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%

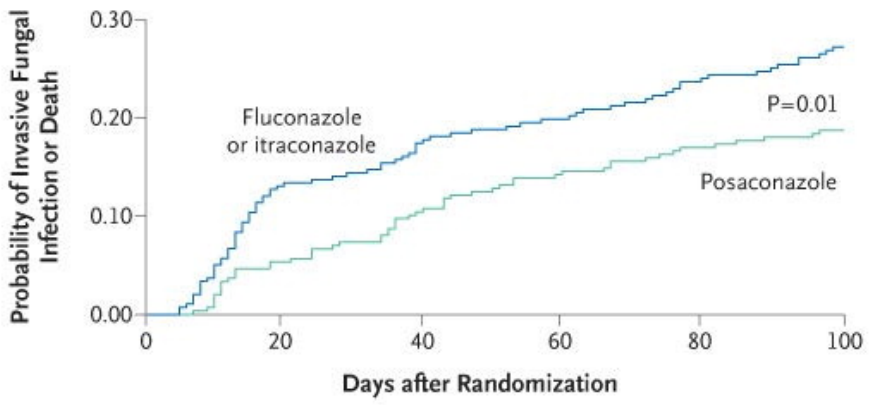
Supportive care

- Transfuse platelets to keep >30-50K/μl
- Transfuse FFP to keep INR<1.5
- Transfuse cryo to keep fibrinogen >150mg/dl

Park JH et al, *Blood* 2011

Neutropenic fever

- All patients with prolonged neutropenia (>1 week) receive prophylaxis
  - Levofloxacin (oral Pseudomonal coverage), acyclovir, posaconazole

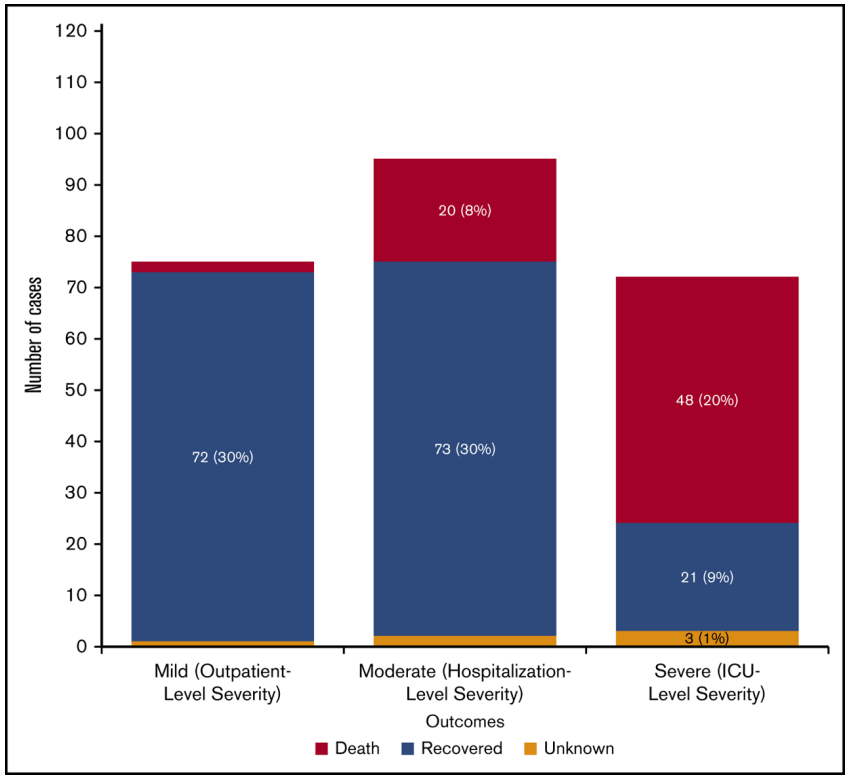


- Treatment of FN with cefepime +/- vanc

Cornely et al, *NEJM* 2007

COVID-19 in patients with heme malignancies

- ASH Research Collaborative COVID-19 Registry
- Overall mortality 28% in first 250 patients analyzed



Wood WA et al *Blood Adv* 2020

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

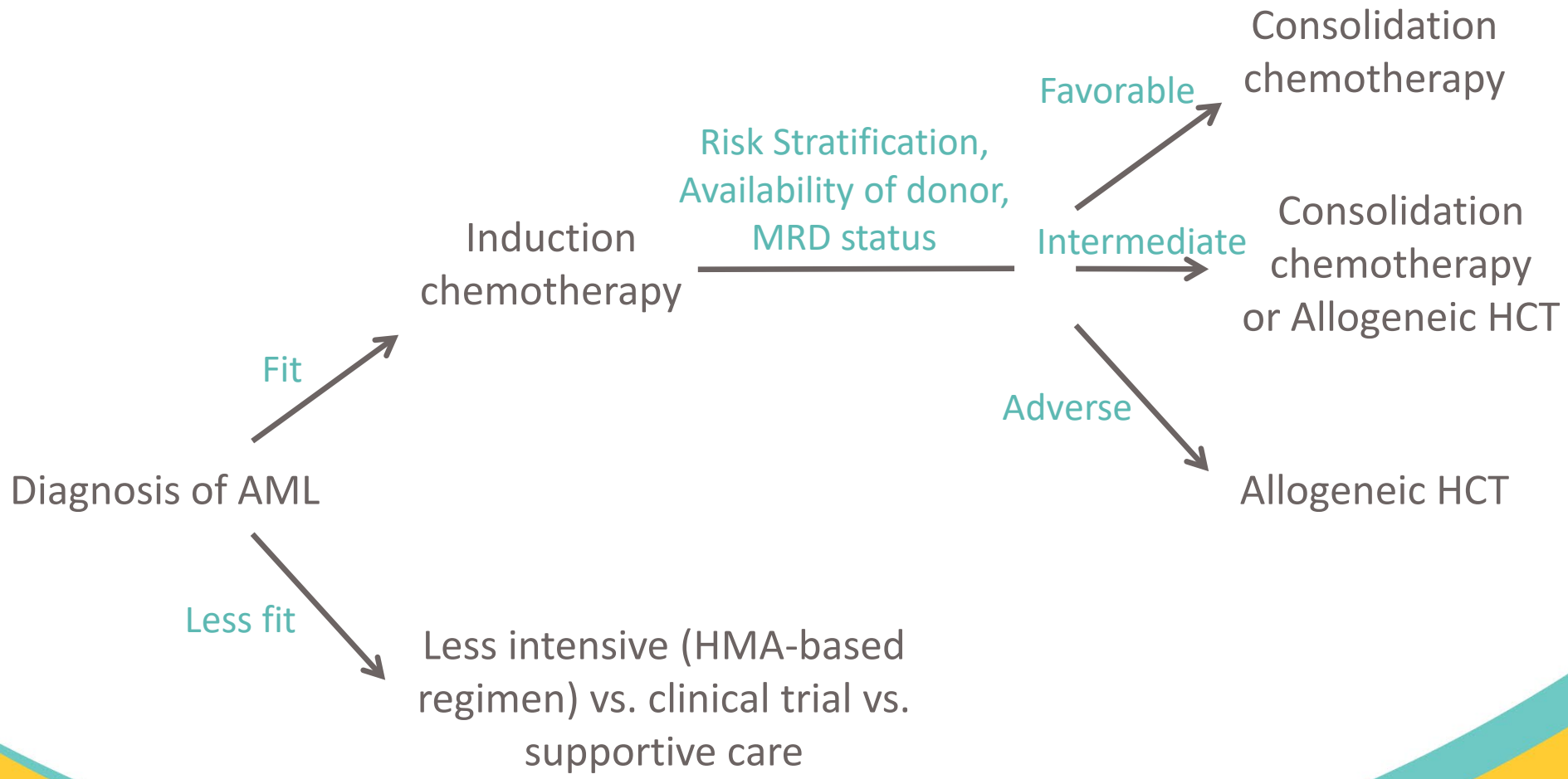
  Mitoxantrone 12-15 mg/m^2/day
- Cytarabine 100-200mg/m^2/day continuous infusion x 7 days

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

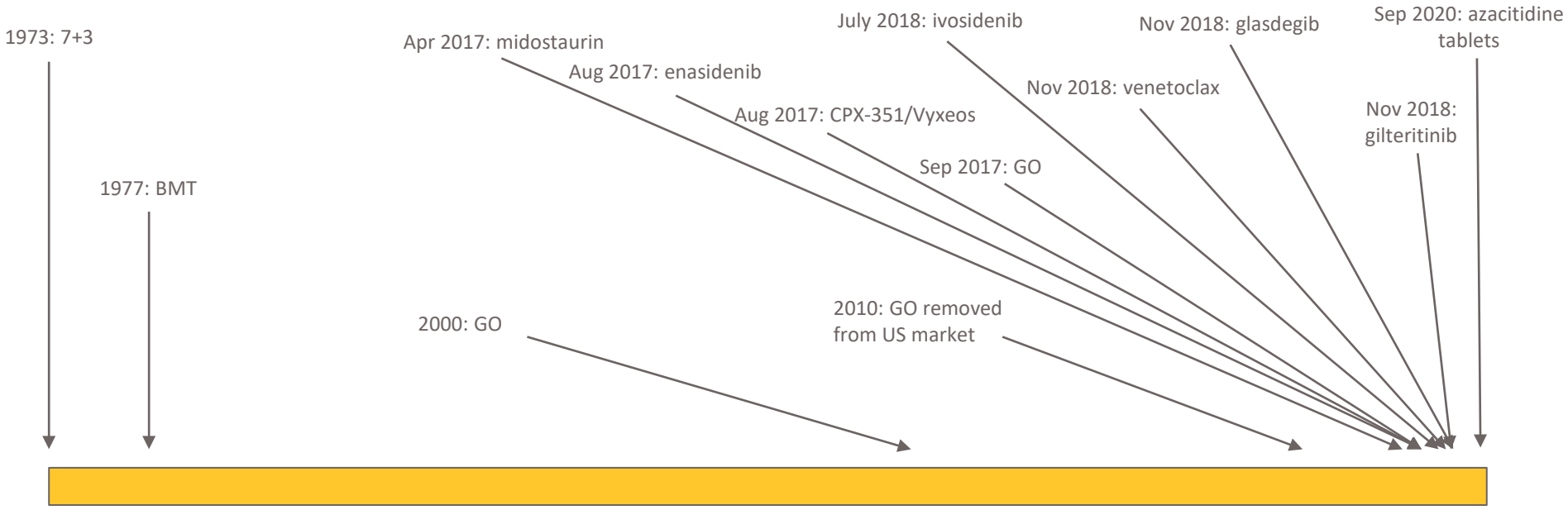
NCCN guidelines: “The best management of any cancer patient is in a clinical trial.”

Yates JW et al, *Cancer Chemother Rep* 1973

Treatment schema



New AML drug approvals



Issues with recent drug approvals

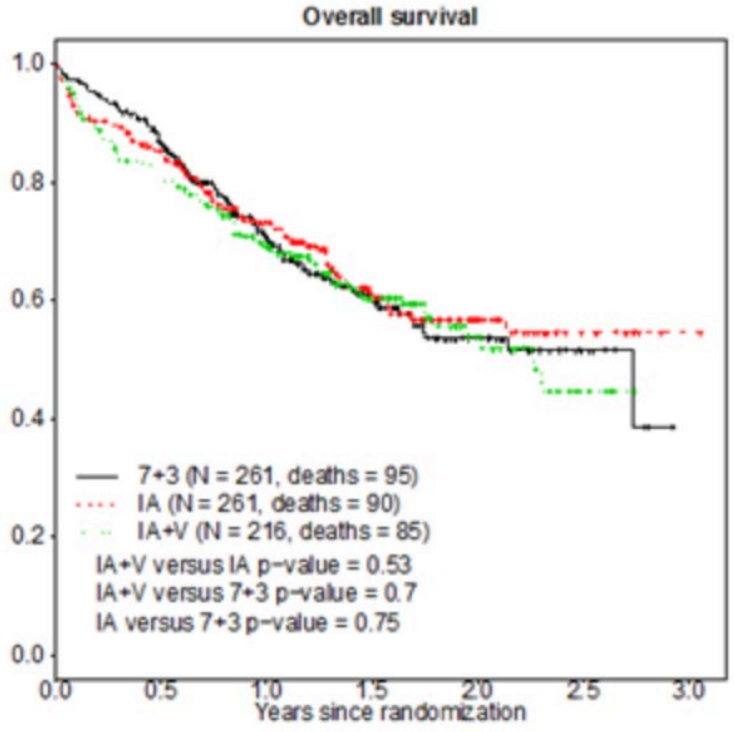
- Many single-arm phase 1/2 studies
- FDA label not always consistent with population studied
- Few drug combinations examined
- Drug hierarchy unknown (which mutation to prioritize, how to sequence treatments, etc.)
- What is the definition of “unfit”?

7+3 vs. high-dose Ara-C in induction

SWOG 1203: 738 patients randomized to 7+3 vs. IA vs. IA+vorinostat

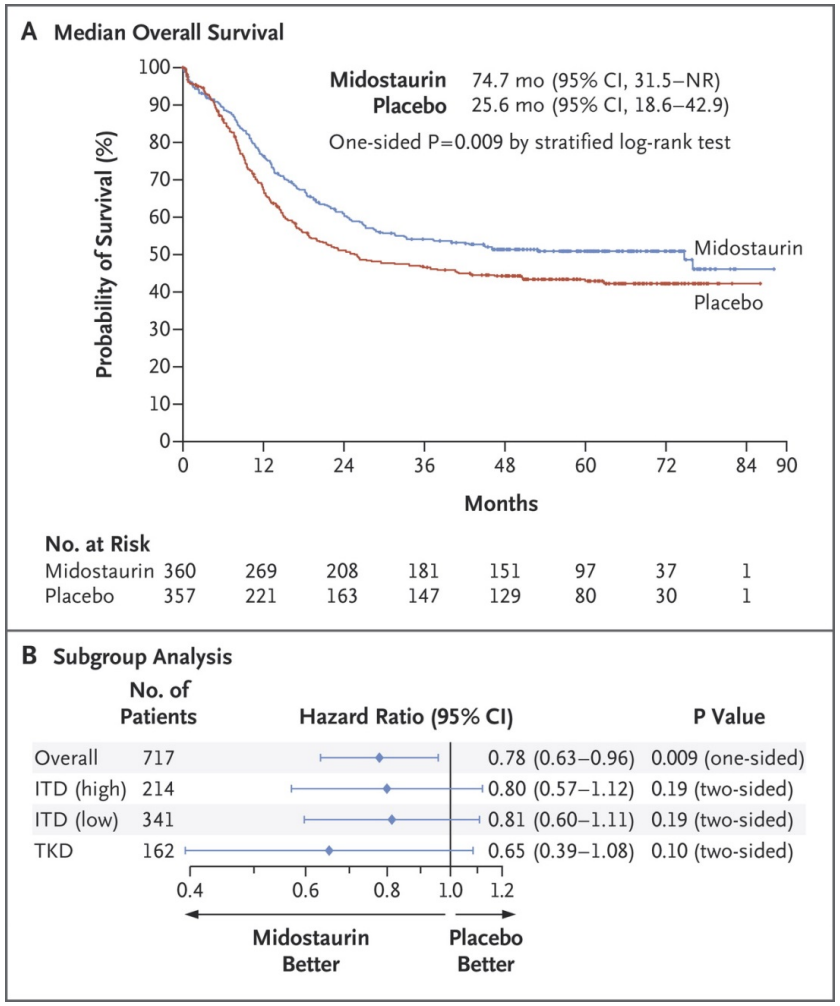
No differences in EFS, RFS, or OS

Favorable cytogenetics: outcomes were inferior with IA or IA+V (?Ara-C dose)



Garcia-Manero et al, *ASH annual meeting* 2016

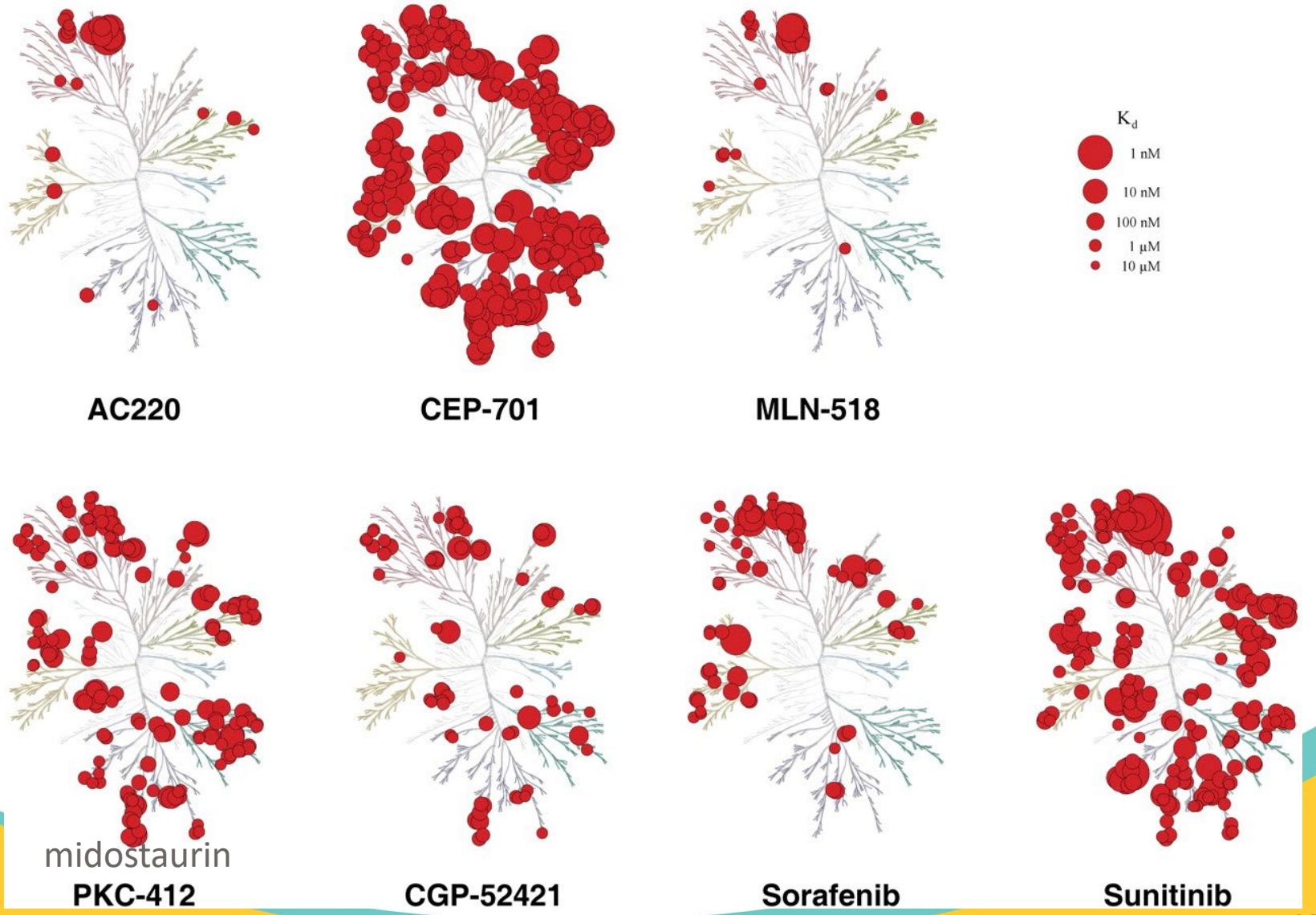
FDA approval 2017: midostaurin



- Multikinase inhibitor added to 7+3 induction, consolidation, maintenance
- Approved for *FLT3*+ AML (both ITD and TKD mutation)
- Main toxicities: cytopenias, GI, rash

Stone RM et al. *N Engl J Med* 2017

Selectivity of FLT3 inhibitors



Zarrinkar PP et al, *Blood* 2009

FDA approval 2017: GO

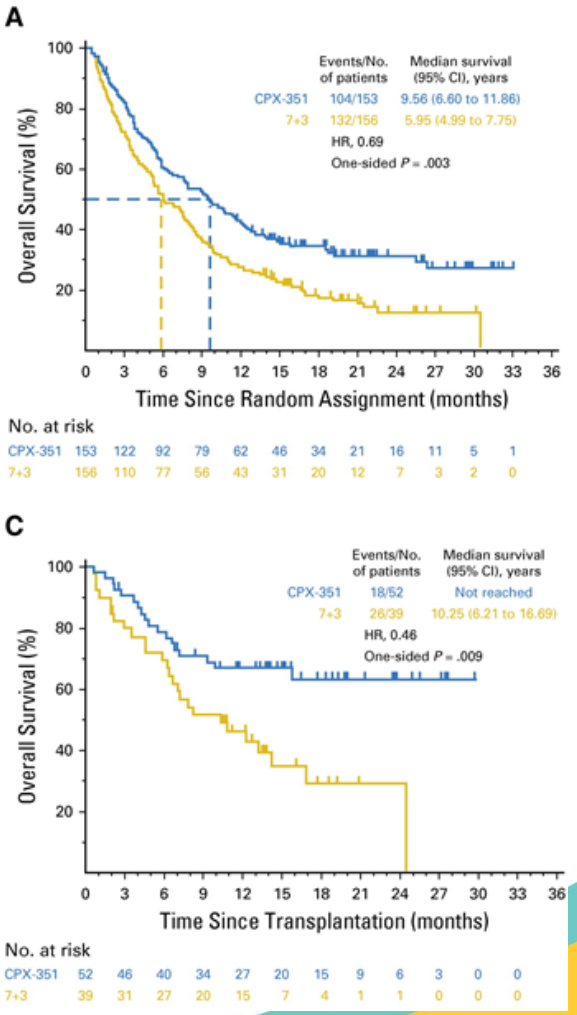
- Gemtuzumab ozogamicin, first antibody-drug conjugate ever developed
- Targets CD33 (splice variants may be important for response)
- Approved in 2000, but voluntarily removed from market in 2010
- Meta-analysis of RCTs showed benefit, particularly in favorable risk
- Induction regimens:
  - ALFA-0701: 7+3+GO 3mg/m^2 on days 1, 4, 7
  - MRC AML15: FLAG-ida + GO (single dose)
- Side effects: prolonged cytopenias (particularly thrombocytopenia) and increase rate of SOS

- APL is highly sensitive to GO
- Also approved for R/R disease as a single agent

Hills RK et al, *Lancet Oncol* 2014; Lamba JK et al, *JCO* 2017; Lambert J, *Haematologica* 2018; Burnett AK et al *JCO* 2013

FDA approval 2017: CPX-351 (Vyxeos)

- Liposomal formulation with fixed 5:1 molar ratio of cytarabine:daunorubicin
- Phase 3 randomized trial vs. 7+3
- Eligible: 60-75 years of age with untreated high-risk or sAML
- Superior overall survival (HR=0.69)
  - Median 9.56 vs. 5.95 months
  - Improved EFS and 60-day mortality
  - HIGH rate of grade 3-5 AEs (92% vs. 91%)
  - More patients underwent alloHCT, and survival better after alloHCT



Lancet JE et al, *JCO* 2018

Induction at UW/FHCRC/SCCA

Intensive (for TRM<13.1)

- GCLAM + sorafenib (age ≤60)

Less fit (for TRM ≥13.1)

- GCLAM vs. CPX-351

→Induction choices are frequently based on TRM score, allowing for risk-adapted therapy (https://cstaging.fhcrc-research.org/TRM/Default.aspx)

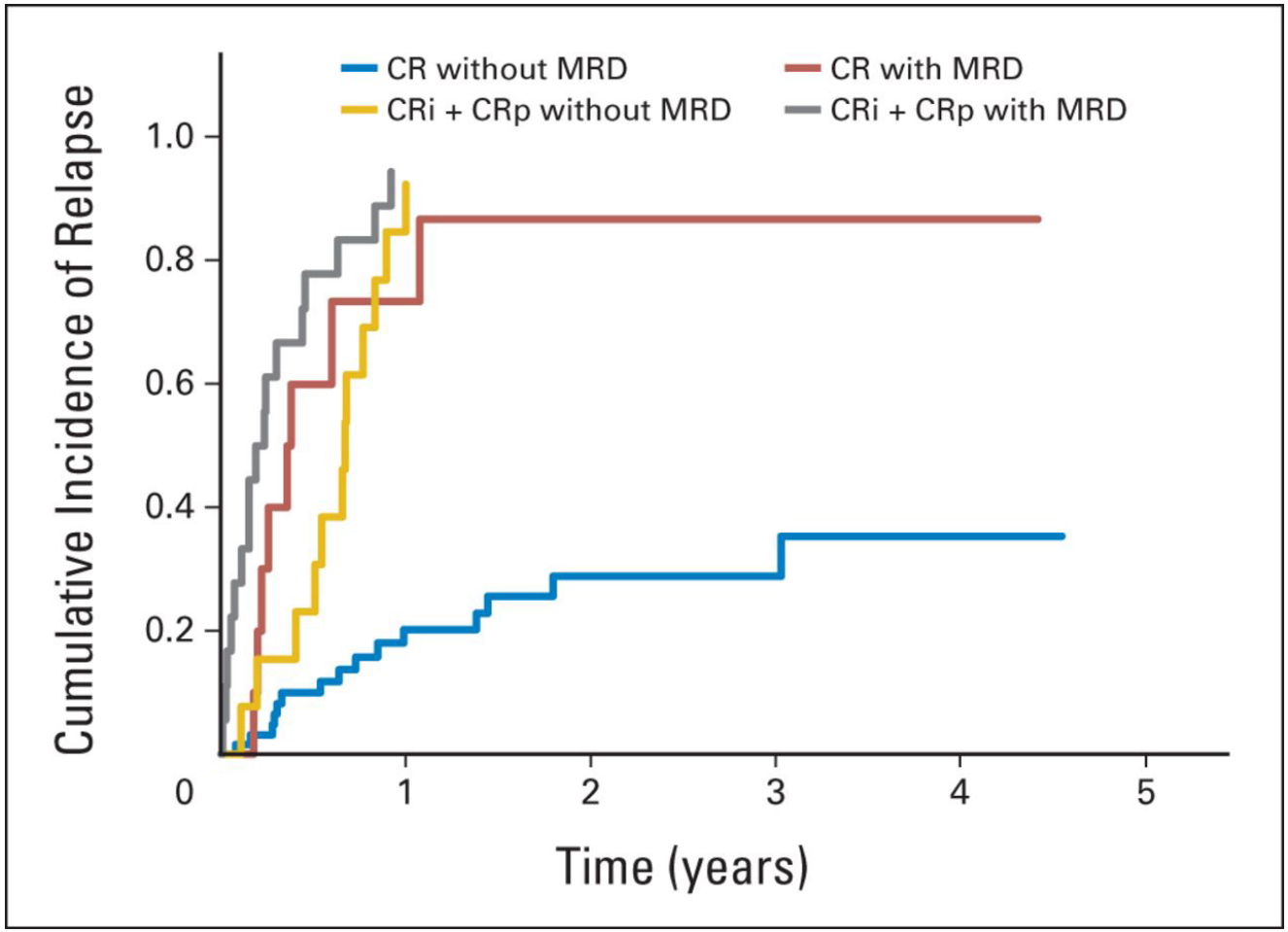
→Clinical trial options change frequently!

Response criteria (ELN 2017)

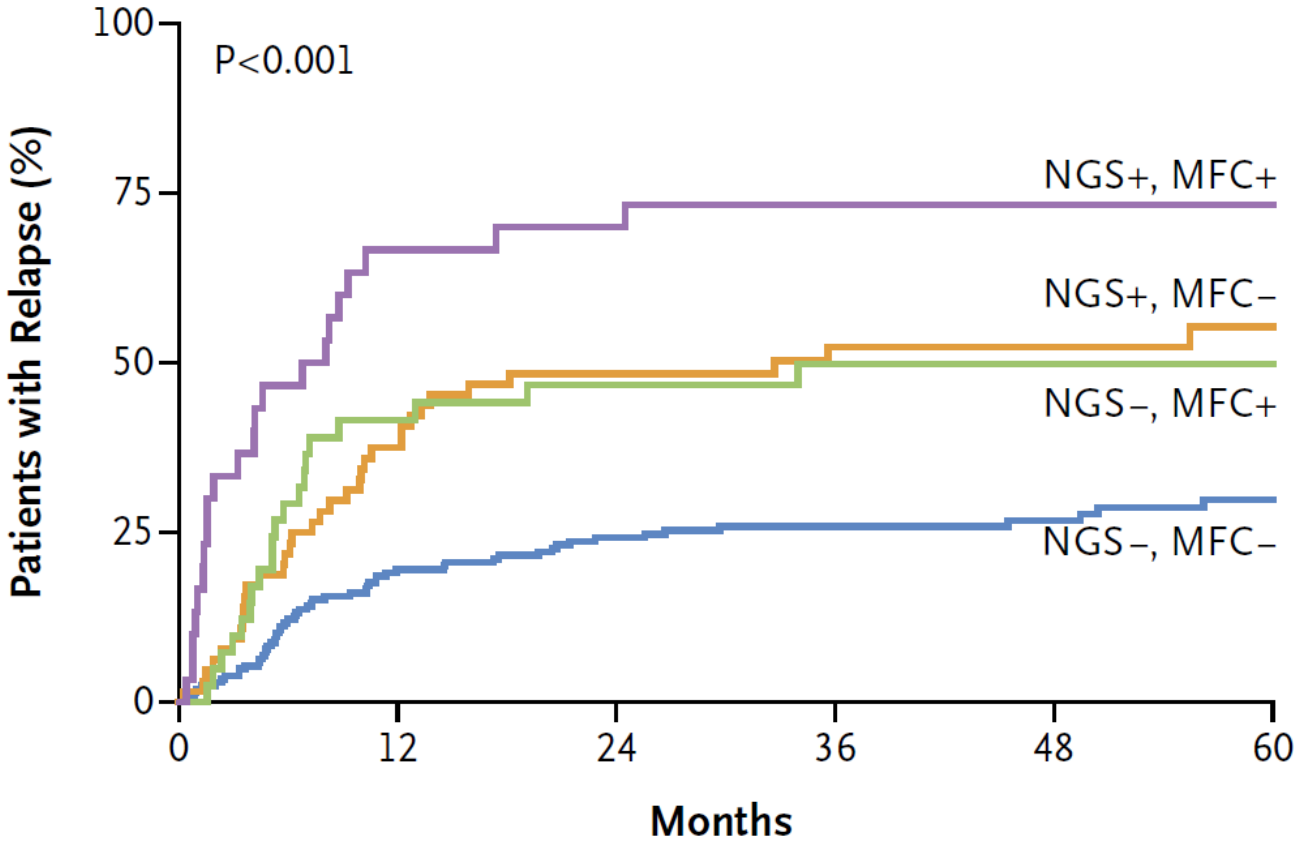
Response	Definition	Comment
CR without MRD	**CR along with pre-treatment marker by PCR or flow cytometry is negative**	**Sensitivities vary by marker tested and method used**
CR	BM blasts <5%; absence of circulating blasts; absence of extramedullary disease; ANC≥1000/μl; plt≥100K/μl	MRD+ or unknown
CRi	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 count recovery/MRD



Chen X et al, *JCO* 2015



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?

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

Post-remission therapy

Induction x 1-2 cycles

Post-remission therapy:

- Consolidation x 3-4 cycles
  - HiDAC (3g/m^2 q12hr on days 1, 3, 5; or 1g/m^2 q12hr x 12 doses)
- Allogeneic transplant (for intermediate or high-risk AML)

Maintenance:

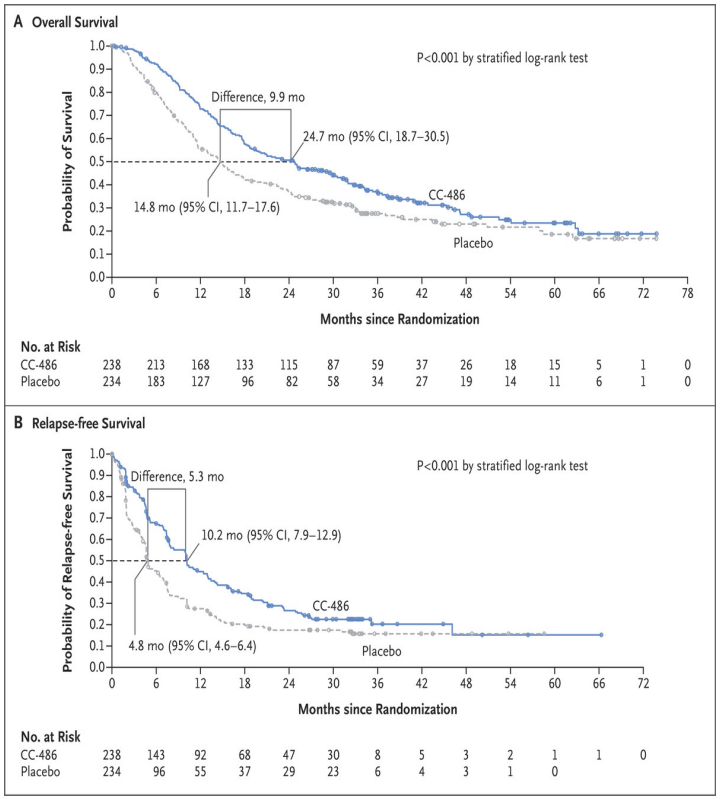
- midostaurin x 1 year in *FLT3*-mutated patients who do not undergo alloHCT
- 5-day azacitidine in patients >60 after 2 courses of intensive chemo
- Oral azacitidine tablets

Huls G et al, *Blood* 2019

FDA approval 2020: azacitidine tablets

- Inclusion: AML in CR1 (CR or CRi), age≥55, not an HCT candidate, at least one cycle of induction, intermediate or adverse risk cytogenetics
- Median OS 24.7 vs. 14.8 months
- PRO studies similar
- Main toxicity: GI and hematologic

Azacitidine tablets ≠ subQ/IV azacitidine



Management of relapsed AML

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

FDA approval 2017/18: IDH inhibitors

Found in 10-20% of newly diagnosed AML, and increase in frequency with age

Ivosidenib (AG-120): selective IDH1 inhibitor

- Approved for newly diagnosed and R/R AML

Enasidenib (AG-221): selective IDH2 inhibitor

- Approved for R/R AML

NB: phase 3 IDHENTIFY study of enasidenib for R/R AML vs. BSC, aza, cytarabine did not meet primary endpoint in Aug 2020

Pros	Cons
CR rate 19.3%; ORR 40.3%	Comparative efficacy unknown
Oral	Combination with chemo?
Well-tolerated	Differentiation syndrome (~10%)

Stein EM et al, *Blood* 2017; DiNardo et al, NEJM 2018; Paschka P et al, *EHA annual meeting abstracts* 2016

FDA approval 2018: gilteritinib

- ADMIRAL trial: phase 3 RCT of gilteritinib vs. salvage in R/R *FLT3*-mutated AML
- 371 patients randomized 2:1
  - Gilteritinib: n=247
  - Salvage: n=124 (MEC 25.7%, FLAG-ida 36.7%, LoDAC 14.7%, aza 22.9%)
- OS favored gilteritinib (HR 0.637, p = 0.0007)
  - Median OS 9.3 months vs. 5.6 months

Many ongoing trials (though NB: LACEWING with aza +/- gilteritinib for upfront AML failed to meet primary endpoint in Dec 2020)

Perl A et al, *NEJM* 2019

Salvage regimens at UW/FHCRC/SCCA

Straight to alloHCT (radiolabeled antibody)

Bispecific antibodies

→Clinical trial options change frequently!

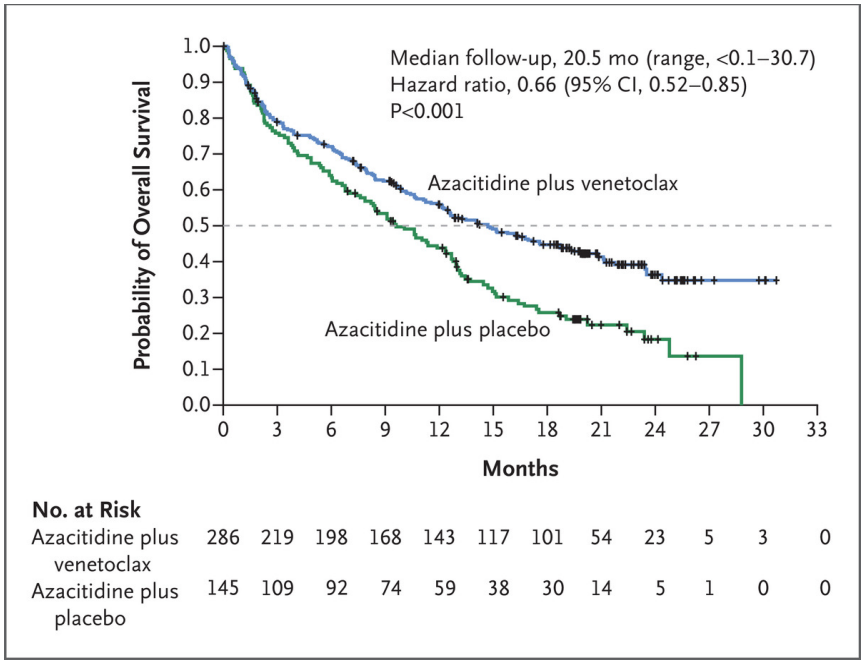
Less intensive induction

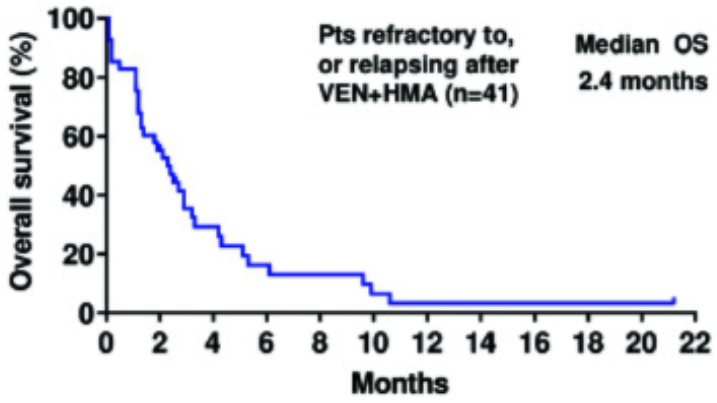
- Generally for “less fit”
- Continue less intensive treatment for as long as patients tolerate and receive clinical benefit
- ?relevance of MRD
- Retrospective analyses: older patients benefit from higher-intensity therapy
- ELN 2017: older age *plus* another factor for non-intense therapy
  - Patient-related 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

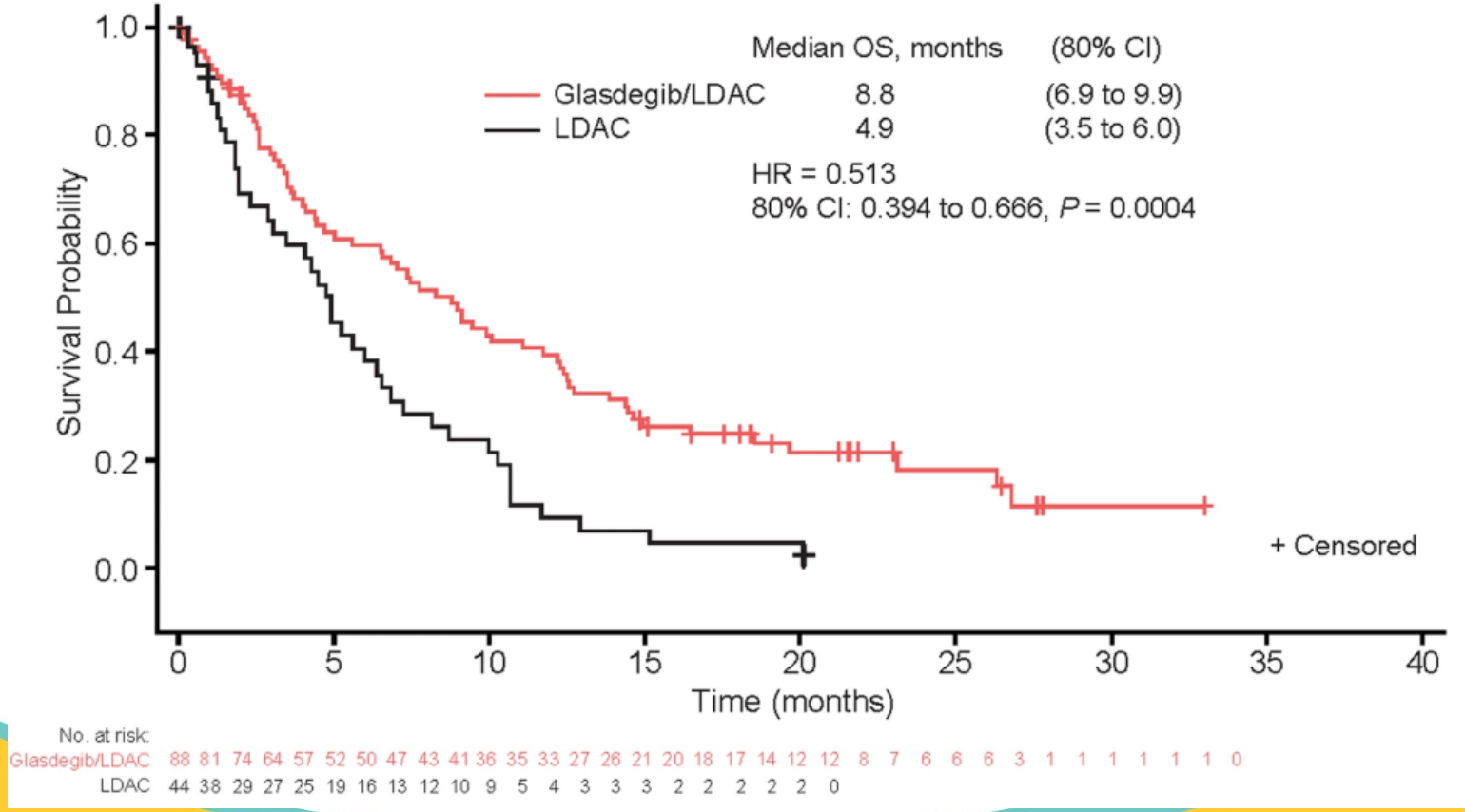




DiNardo C et al, *NEJM* 2020; Maiti A et al *Haematologica* 2021

FDA approval 2018: glasdegib

- Hedgehog pathway inhibitor
- Approved +/- low dose cytarabine



Cortes JE et al, *Leukemia* 2019

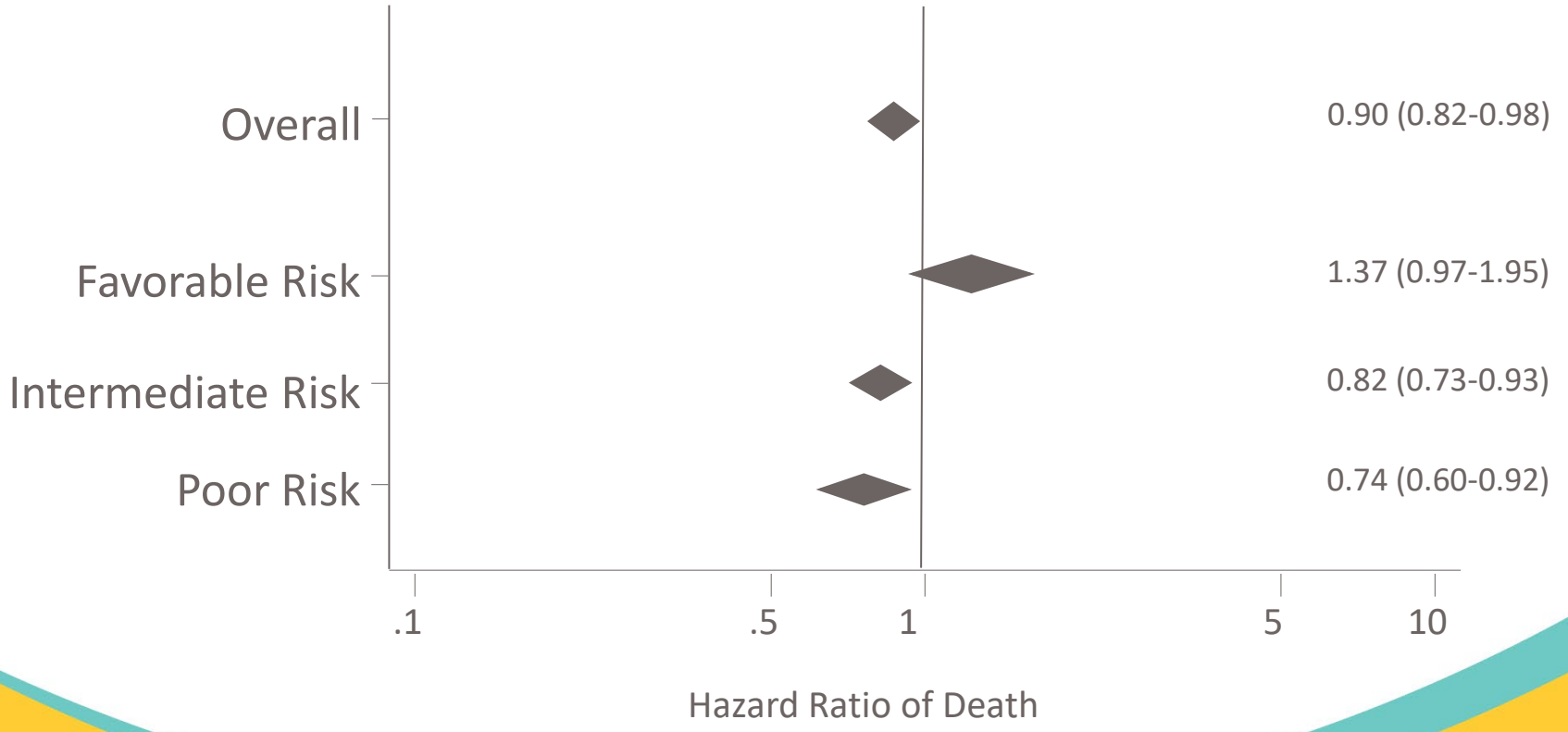
Indications for transplant referral

- Intermediate or adverse risk AML in CR1
- AML in CR2
- Primary refractory AML

- ?CR with incomplete count recovery
- ?CR or CRi with MRD

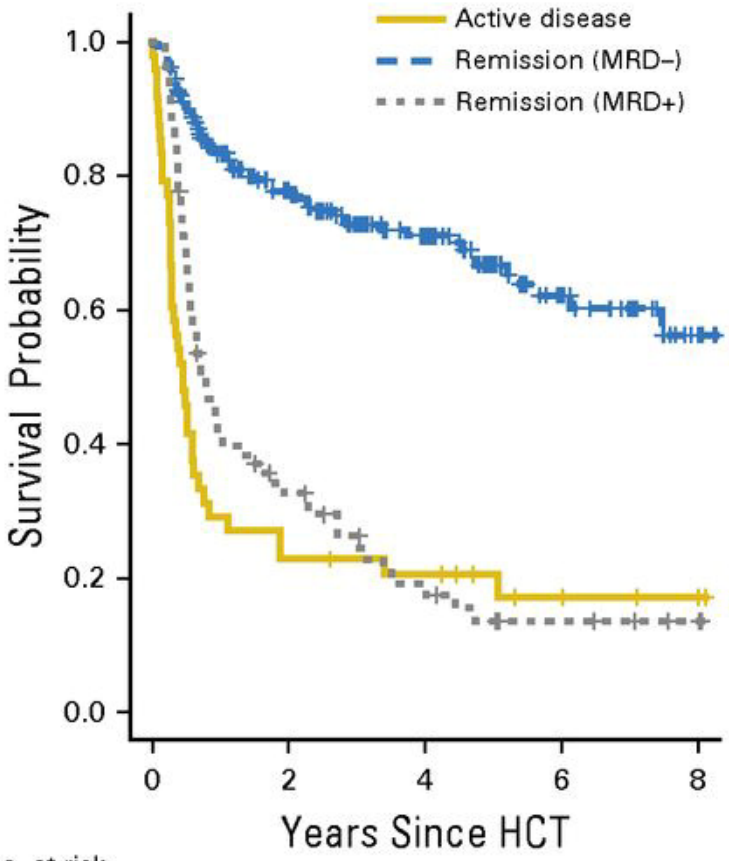
Meta-analysis of survival using allo HCT in CR1

- **Randomized trials = 23**
- **Patients = 5,839**



Koreth, et al JAMA 301:2349, 2009

Post-transplant survival with MRD



No. at risk					
Active disease	48	11	9	4	2
Remission (MRD–)	235	136	80	34	8
Remission (MRD+)	76	22	11	5	2

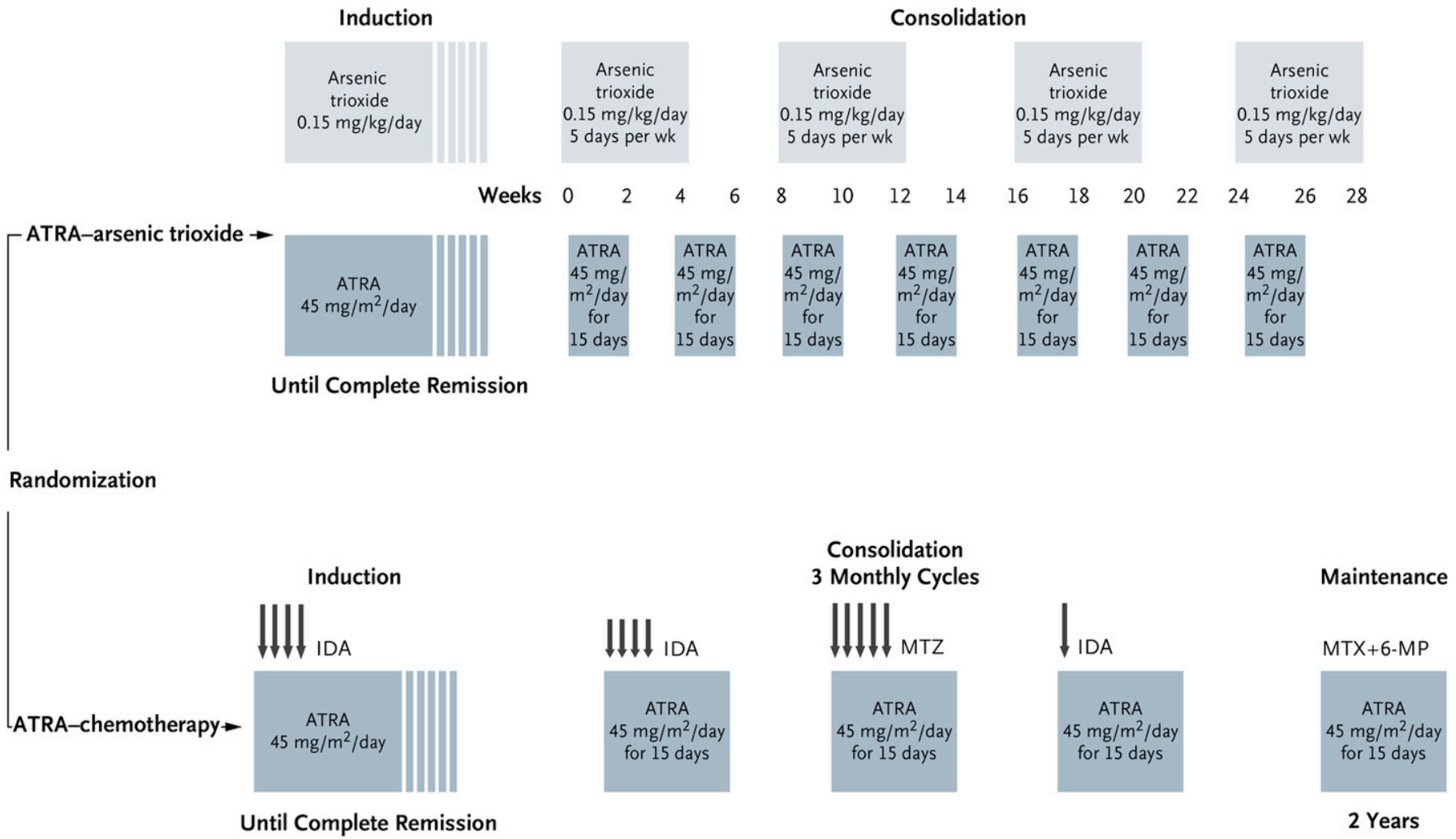
Araki D et al, *JCO* 2016

Acute promyelocytic leukemia

- ~10% of new AML (1200 pts/year in US)
- Leukopenia in 85%
- Divided into low vs. high-risk depending on WBC count at diagnosis

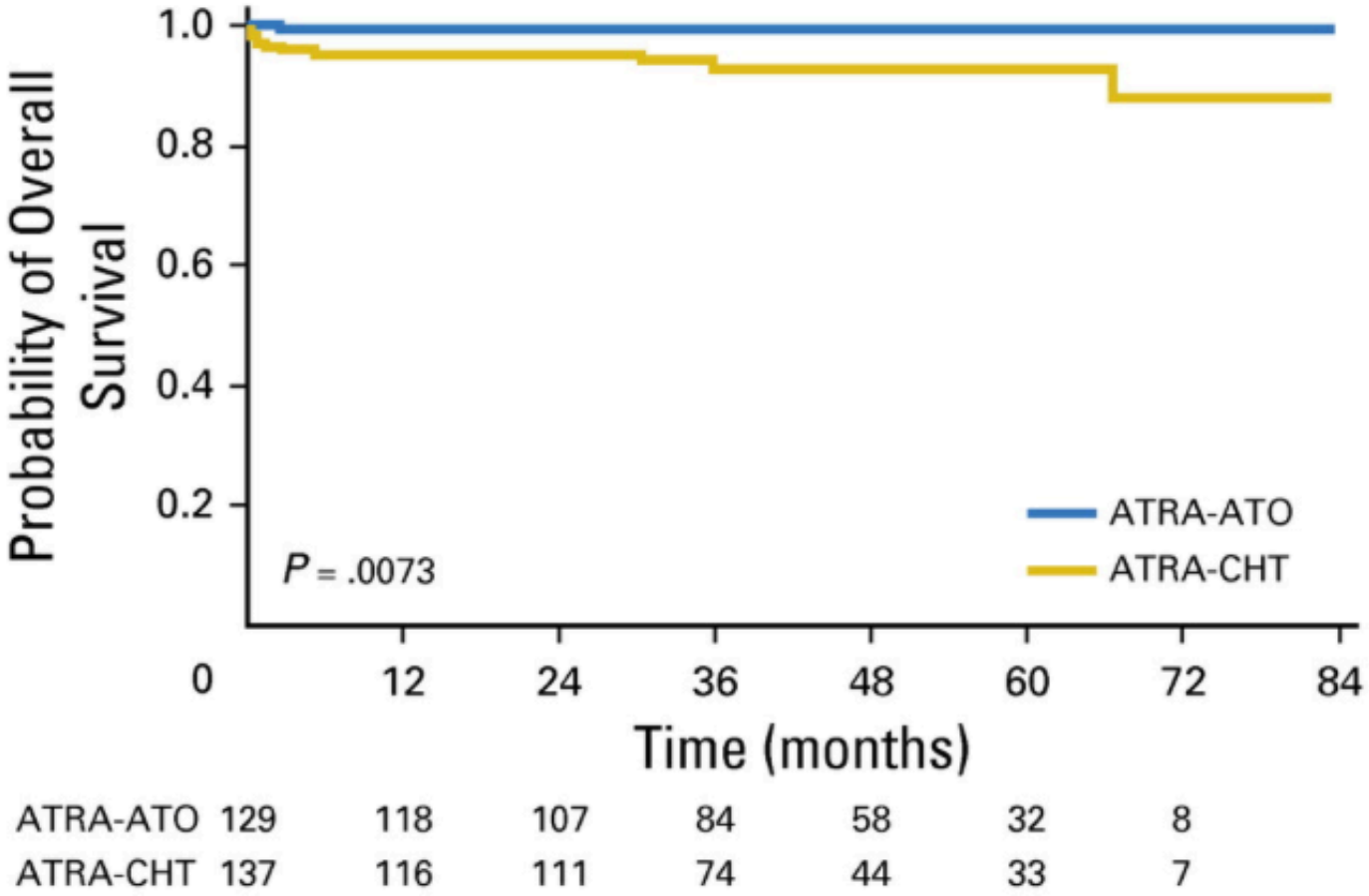
  →high risk = ≥10,000/μl
- Common to have coagulopathy at diagnosis
- t(15;17)→PML-RARα fusion transcript
- Differentiation syndrome can happen with ATRA or ATO (treat promptly with dexamethasone)

“Lo-Coco regimen”



Lo-Coco F et al, *NEJM* 2013

APL 0406 trial: ATRA + ATO



Platzbecker U et al, *JCO* 2017

Contact with questions

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