Fred Hutch
Cancer Center

Acute Myeloid Leukemia in 2024

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UW Medicine

Land Acknowledgment

Fred Hutchinson Cancer Center acknowledges the Coast Salish peoples of this land, the land which touches the shared waters of all tribes and bands within the Duwamish, Puyallup, Suquamish, Tulalip and Muckleshoot nations.

Disclosures

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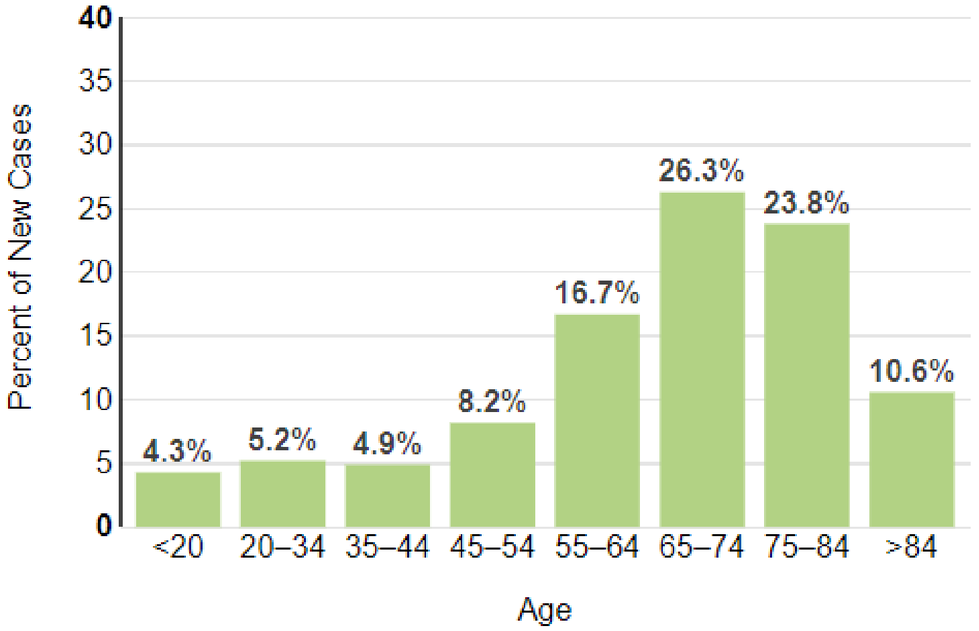
Outline

- Epidemiology
- Diagnosis and risk stratification
- Leukemia emergencies
- Treatment
- Transplant indications
- APL

AML epidemiology in 2024

- Estimated annual new cases: 20,800
  → 1% of all new cancer cases in the US
  → Incidence: 4.1 per 100,000 people
- Estimated annual deaths: 11,220
- 5 year survival rate: 31.9%
  → Improving over time (6.3% survival in 1975)
- M:F predominance of approximately 1.5:1
- Median age at diagnosis: 69

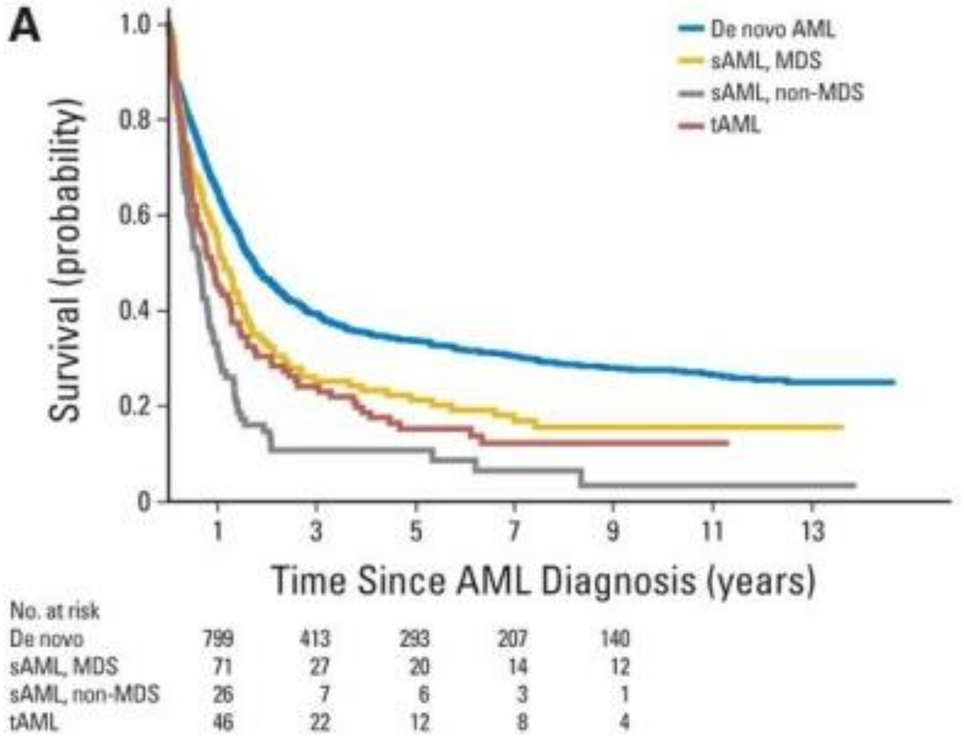


https://seer.cancer.gov/statfacts/html/amyl.html

Etiology

- **Prior chemotherapy/radiation (therapy-related, or tAML)**
- **Antecedent hematologic disorder (secondary, or sAML)**

- Genetic predisposition
- Smoking
- Chemical exposures, such as benzene



Ostgard L et al *JCO* 2015

Etiology: genetic predisposition

- Many familial AML/MDS syndromes described in the past 2 decades
- Most common: *GATA2*, *RUNX1*, *CEBPA*, *TERC/TERT*, *DDX41*, 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
- Anyone under 50 with new MDS/AML should consider germline testing

"How I treat inherited AML" *Blood* 2016

Clinical signs and symptoms of AML

- **Neutropenia** (actual or functional) → fever, chills, localized infectious symptoms
- **Anemia** → pallor, weakness, fatigue, dyspnea on exertion
- **Thrombocytopenia** → bleeding, bruising, petechiae
- **Expansion of medullary cavity** → bone pain
- **Constitutional symptoms** → night sweats, weight loss, poor appetite
- **Extramedullary disease** including infiltration of skin (leukemia cutis), soft tissue (a.k.a. myeloid sarcoma, chloroma, granulocytic sarcoma), CNS

Mandatory testing on blood/marrow at diagnosis

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

Khoury JD et al *Leukemia* 2022; Dohner H et al, *Blood* 2022

Diagnosis of AML

WHO 5th edition (2022): "The boundary between MDS and AML is softened, but the 20% blast cutoff to define AML is retained"

ICC 2022: "Patients with MDS/AML should be eligible for both MDS and AML trials"

- Peripheral blood (≥20% blasts); <20% blasts also diagnostic in the setting of defining genetic abnormalities:
  - *PML::RARA* fusion
  - *RUNX1::RUNX1T1* fusion
  - *CBFB::MYH11* fusion
  - *DEK:NUP214* fusion
  - *RBM15:MRTFA* fusion
  - *KMT2A* rearrangement
  - *MECOM* rearrangement
  - *NUP98* rearrangement
  - *NPM1* mutation

- Bone marrow aspirate/biopsy → generally not necessary if >2K blasts in peripheral blood

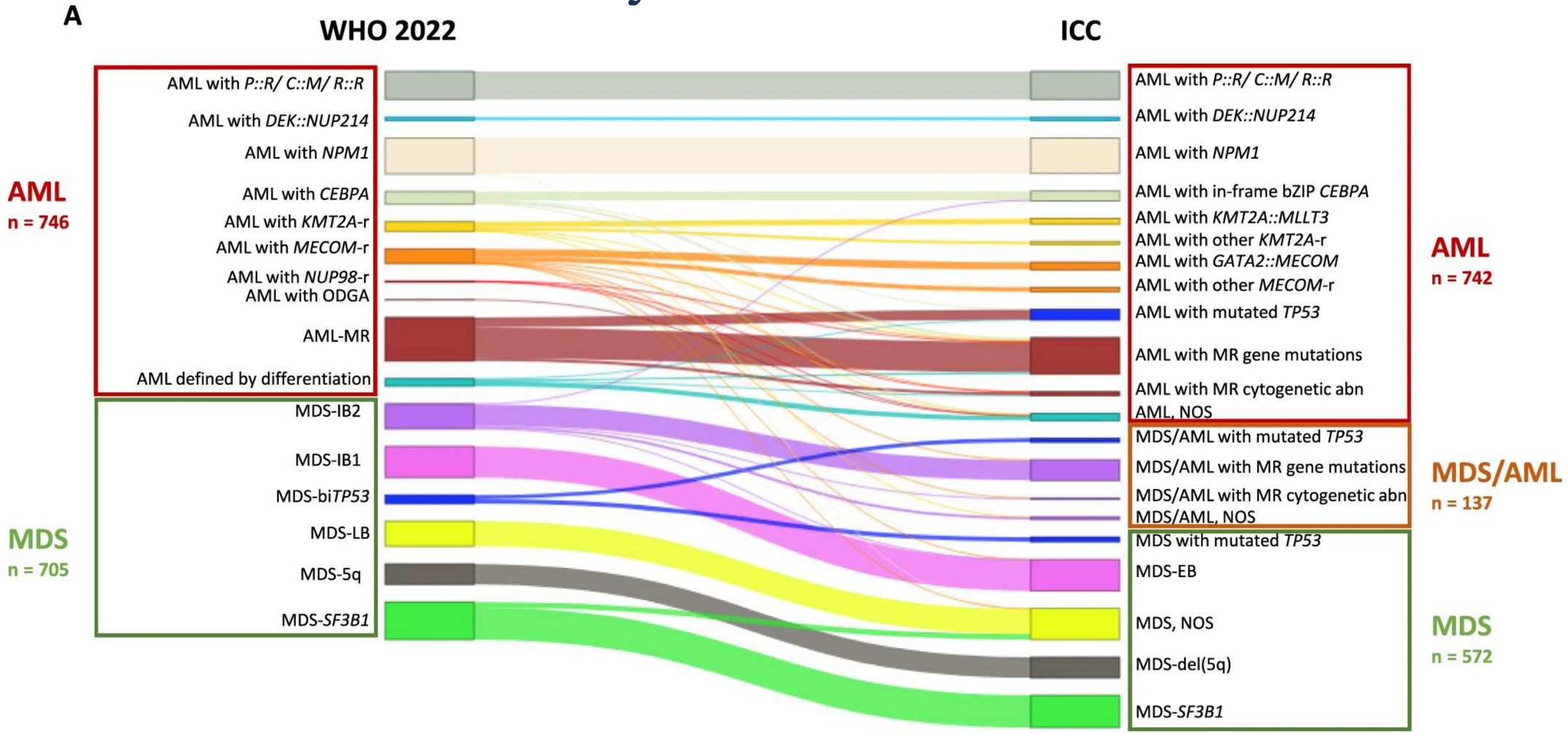
Khoury JD et al *Leukemia* 2022; Dohner H et al, *Blood* 2022; Arber DA et al, *Blood* 2022

WHO 5th edition (2022) classification of AML

AML with defining genetic abnormalities	AML, defined by differentiation
APL with *PML::RARA* fusion AML with *RUNX1::RUNX1T1* fusion AML with *CBFB::MYH11* fusion AML with *DEK::NUP214* fusion AML with *RBM15::MRTFA* fusion AML with *BCR::ABL1* fusion AML with *KMT2A* rearrangement AML with *MECOM* rearrangement AML with *NUP98* rearrangement AML with *NPM1* mutation AML with *CEBPA* mutation AML, myelodysplasia-related AML with other defined genetic alterations	AML with minimal differentiation AML without maturation AML with maturation Acute basophilic leukaemia Acute myelomonocytic leukaemia Acute monocytic leukaemia Acute erythroid leukaemia Acute megakaryoblastic leukaemia

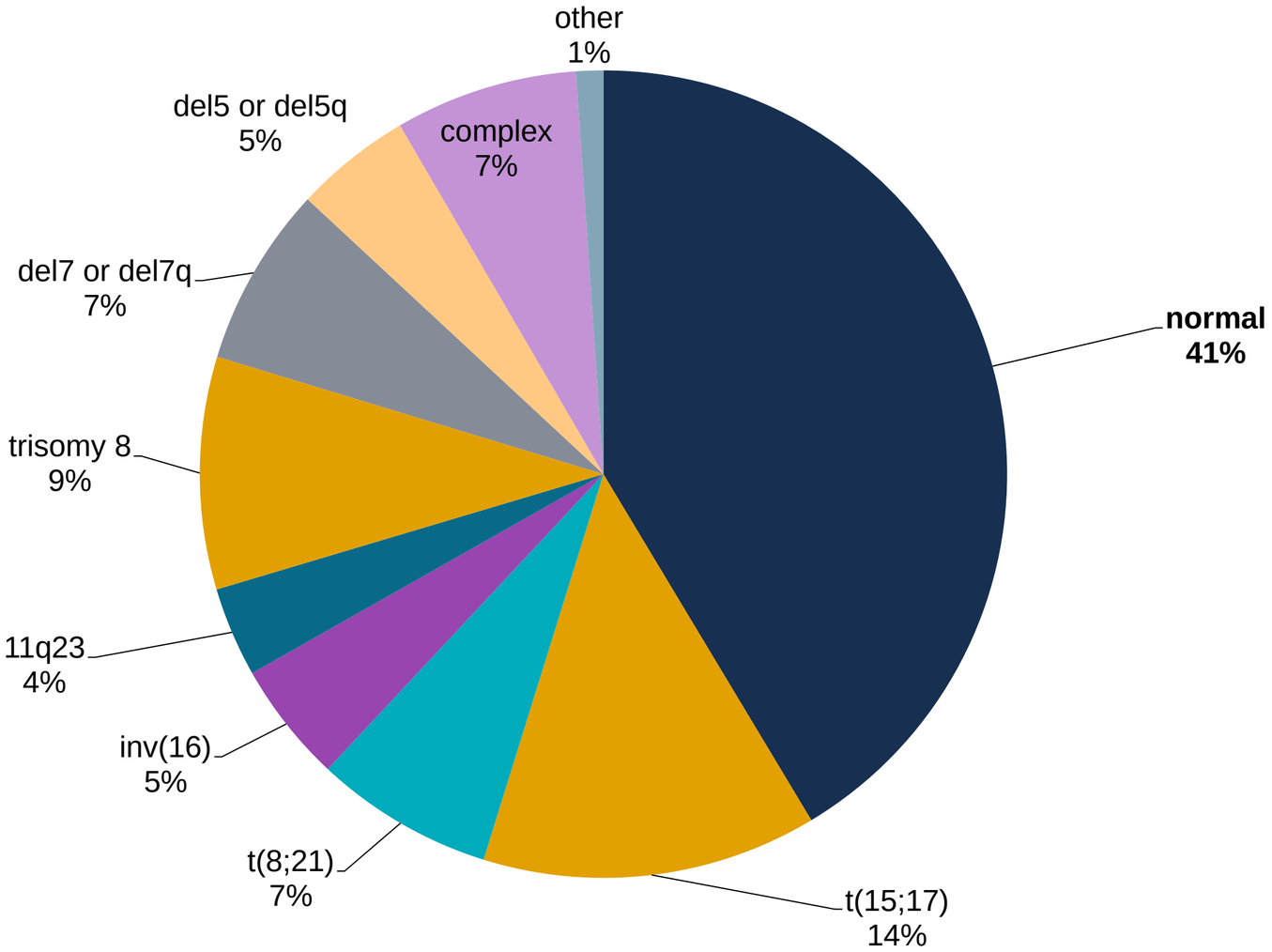
Khoury JD et al *Leukemia* 2022

AML classification in the year 2023



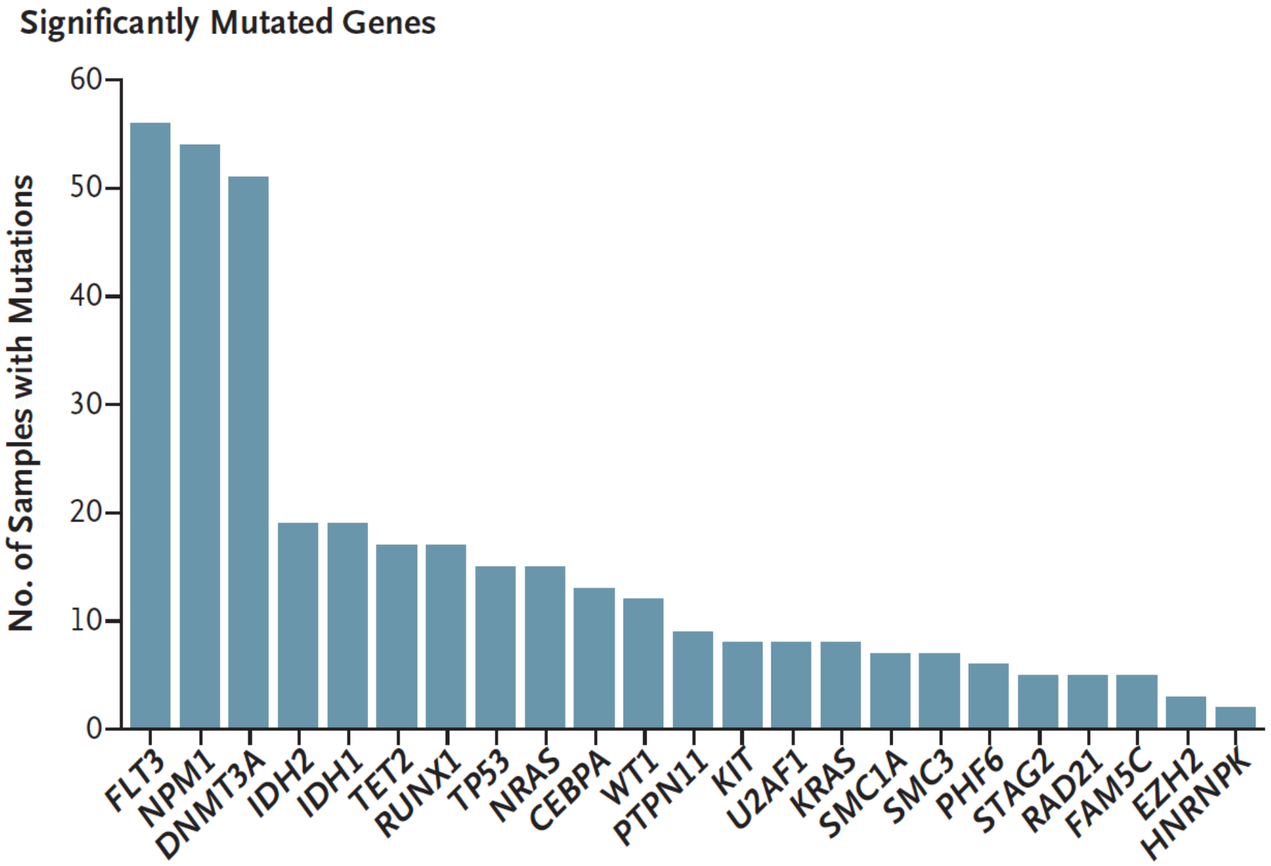
Huber S et al *Leukemia* 2023

Common cytogenetic abnormalities



Grimwade D et al, *Blood* 2010

Molecular testing: mutations in 200 samples

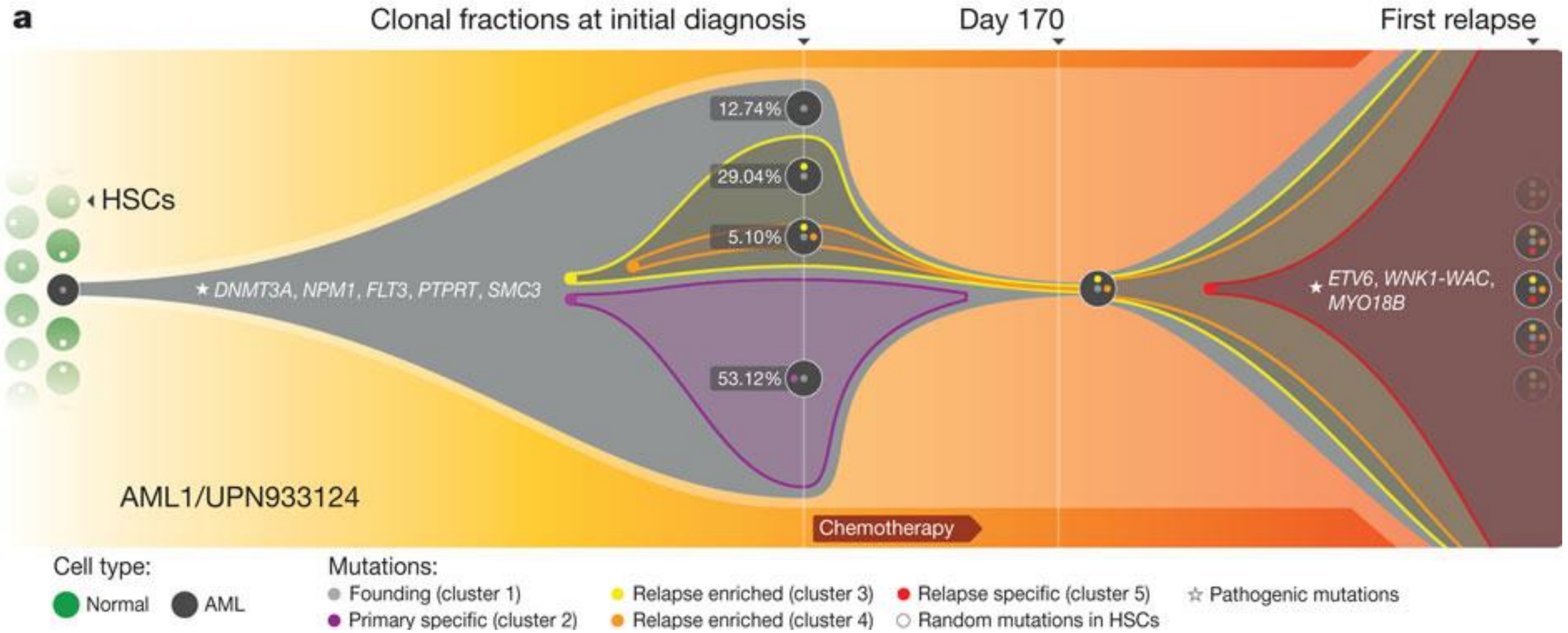


- Average number of mutations per case: 13
- Average number of “driver” mutations per case: 5
- Total number mutated in two or more samples: 237

→Important for prognostication and therapeutic targets!

TCGA, *NEJM* 2013

Molecular testing: clonal evolution



Ding *et al*. *Nature* 2012

Risk stratification: ELN criteria 2022

Risk status	Subsets
Favorable	t(8;21)/*RUNX1::RUNX1T1* inv(16) or t(16;16)/*CBFB::MYH11* Mutated *NPM1* without *FLT3*-ITD bZIP in-frame mutated *CEBPA*
Intermediate	Mutated *NPM1* with *FLT3*-ITD Wild-type *NPM1* with *FLT3*-ITD t(9;11); *MLLT3-MLL* Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	inv(3) or t(3;3); t(6;9); t(v;11); t(9;22); t(8;16); -5 or del(5q); -7; -17/abn(17p) complex karyotype monosomal karyotype mutated *RUNX1, ASXL1, EZH2, SF3B1, SRSF2, STAG2, U2AF1,* or *ZRSR2* mutated *TP53* (at least 10%)

Dohner H et al, *Blood* 2022

Leukemia emergencies: leukostasis

- In AML, hyperleukocytosis defined as WBC>100,000/μl
- Hyperleukocytosis ≠ leukostasis
- Leukostasis most commonly affects CNS and lungs
- Very high mortality
- Treatment options:
  - ➢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; Connelly-Smith L and Linenberger ML, *Transfusion* 2020

Leukemia emergencies: tumor lysis

- Spontaneous or chemo-induced
- Hyperkalemia, hyperphosphatemia (→hypocalcemia), hyperuricemia
- Treatment:
  - ➢Hydration (not necessary or beneficial to alkalinize)
    - ○But remember that “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

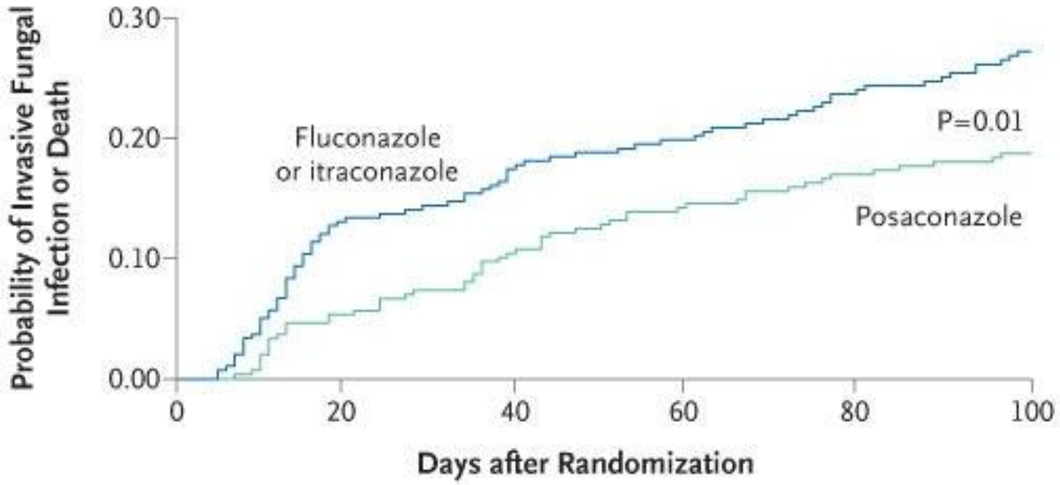
Leukemia emergencies: thrombohemorrhagic syndrome

- 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% (e.g., migratory thrombophlebitis or DVT/PE)
- 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

Leukemia emergencies: neutropenic fever

- All patients with prolonged neutropenia (>1 week) receive prophylaxis
  - Levofloxacin (oral Pseudomonal coverage)
  - Acyclovir
  - Posaconazole
- Treat febrile neutropenia with cefepime +/- vancomycin



Cornely et al, *NEJM* 2007

Leukemia complications: CNS involvement

- Relatively uncommon (especially compared to ALL), ~5% of patients
- Perform LP with IT chemotherapy (usually cytarabine 100mg) in patients with CNS symptoms
- Consider screening LP:
  - Monocytic differentiation
  - High WBC at diagnosis (>50K)
  - Extramedullary disease, mixed phenotype, high risk APL

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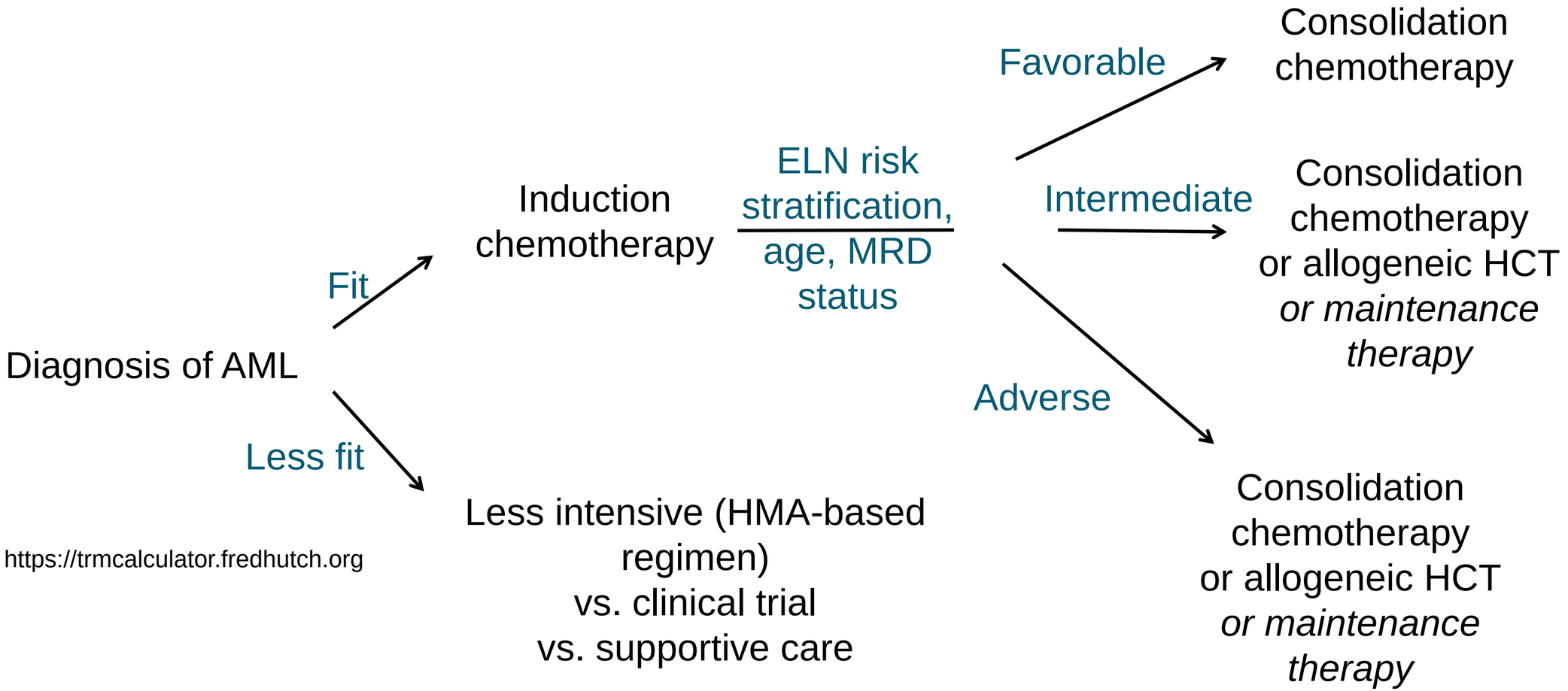
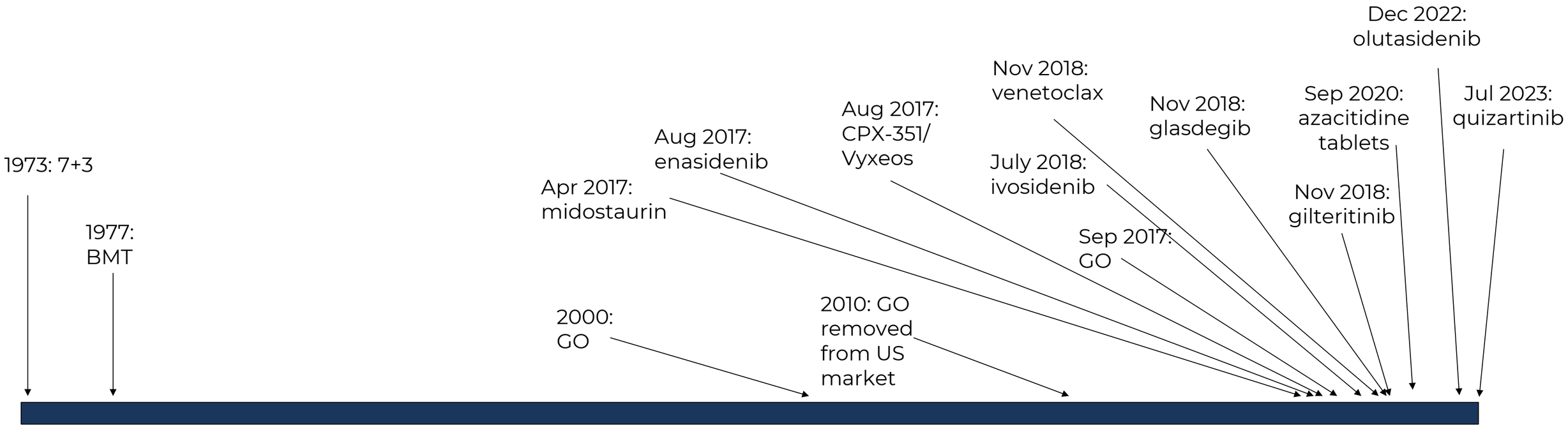
Treatment schema



https://trmcalculator.fredhutch.org

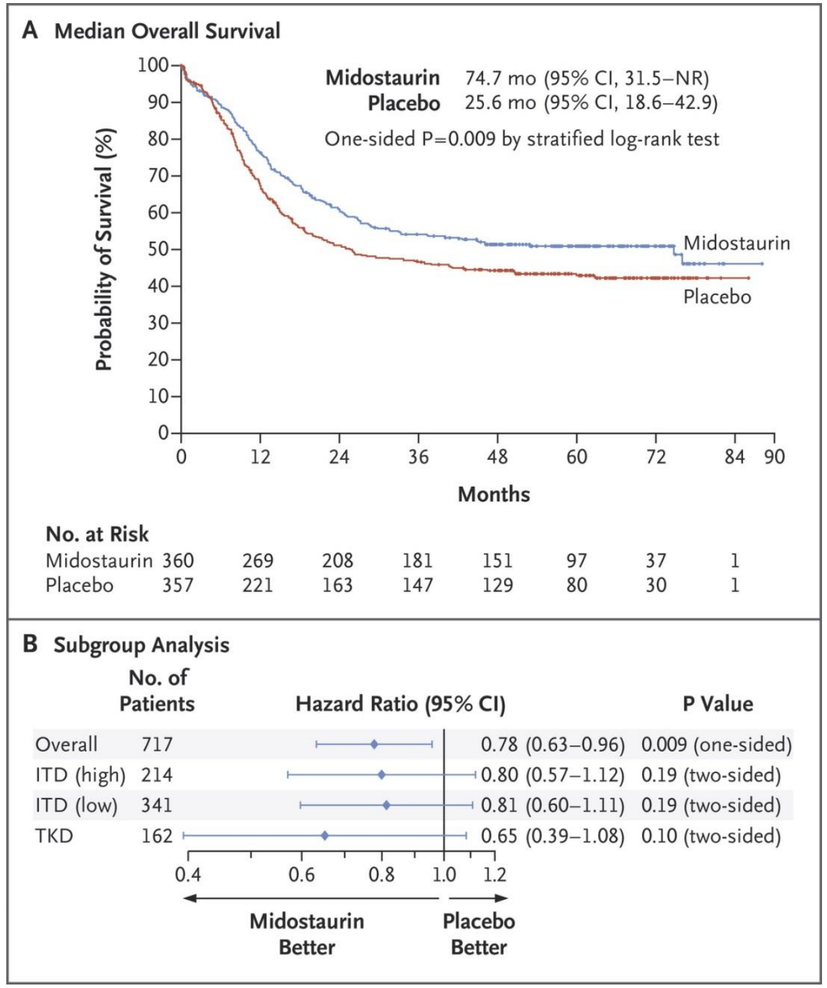
Recent drug approvals



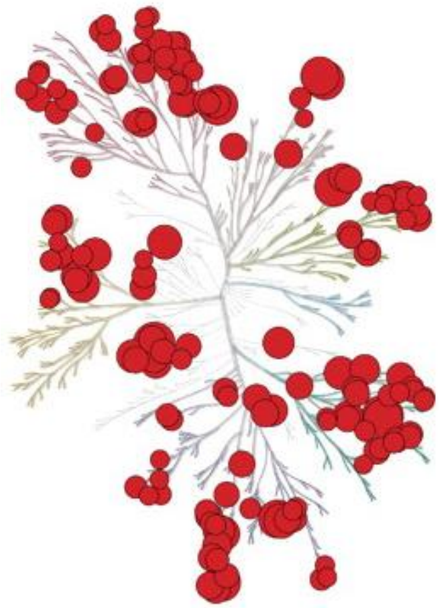
Issues with recent drug approvals

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

FDA approval 2017: midostaurin

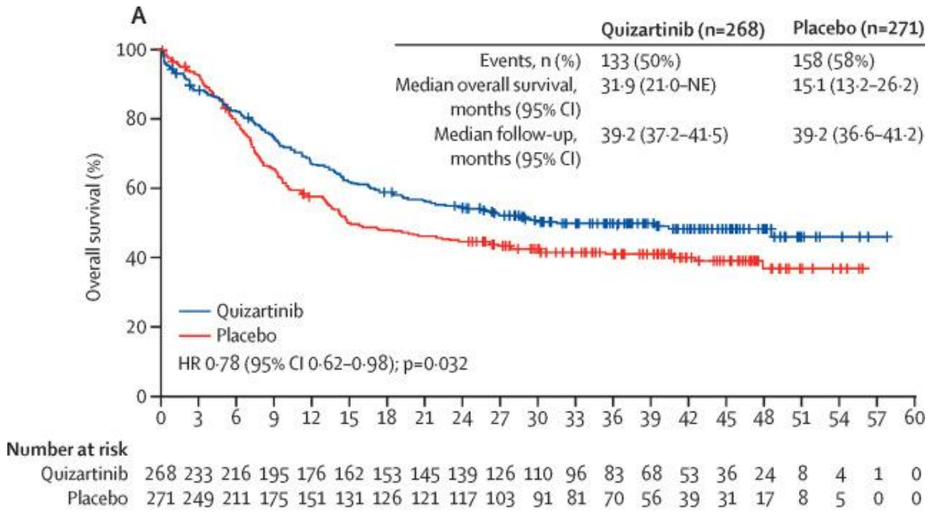


- Multikinase inhibitor
- Added to 7+3 induction, consolidation, maintenance x 1 year
- Approved for *FLT3*+ AML (both ITD and TKD mutation)
- Main toxicities: cytopenias, GI, rash

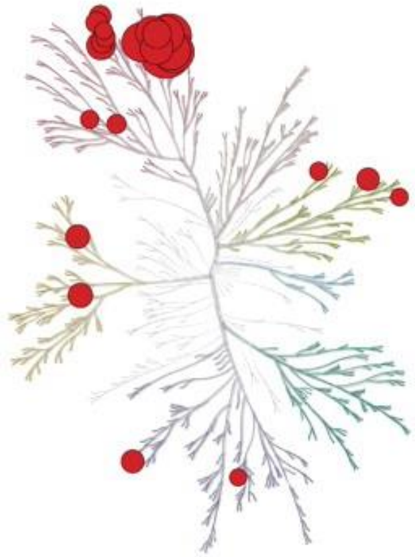


Stone RM et al. *N Engl J Med* 2017; Zarrinkar P et al *Blood* 2009

FDA approval 2023: quizartinib



- Targeted FLT3 inhibitor
- Added to 7+3 induction, consolidation, maintenance x 3 years
- Age 18-75
- Approved for *FLT3*+ AML (only ITD mutation)
- Main toxicities: cytopenias, QT prolongation



Erba H et al *Lancet* 2023; Zarrinkar P et al *Blood* 2009

FDA approval 2017: GO

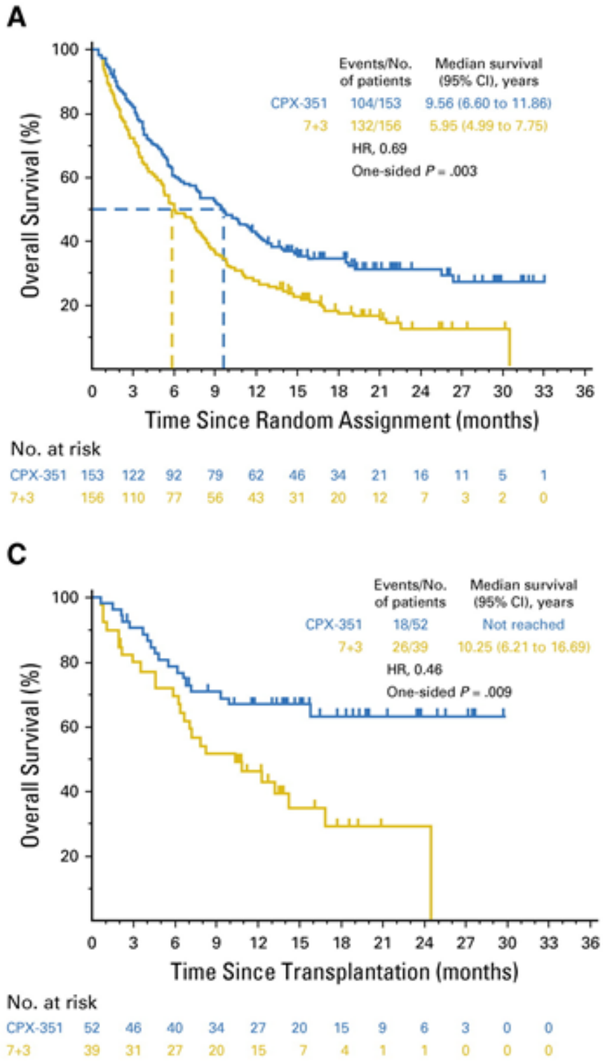
- Gemtuzumab ozogamicin, first antibody-drug conjugate ever developed
- Targets CD33 (splice variants may be important for response)
- Approved in 2000, but voluntarily removed from market in 2010
- Meta-analysis of RCTs showed benefit, particularly in favorable risk
- Induction regimens:
  - ALFA-0701: 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 increased 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 plus survival better after alloHCT



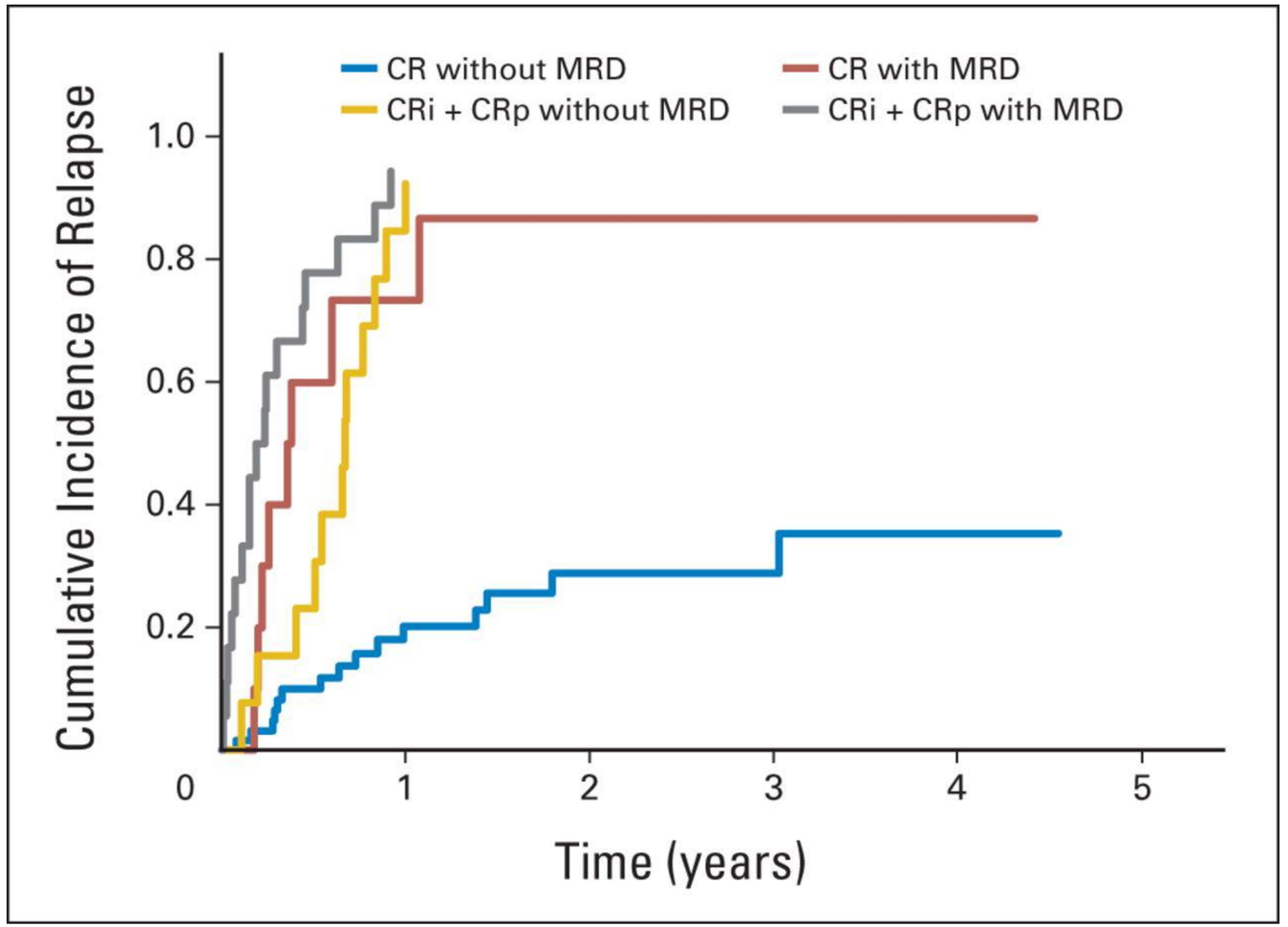
Lancet JE et al, *JCO* 2018

Response criteria (ELN 2022)

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	
CRh	All CR criteria except ANC≥500/ml; plt≥50K/ml	
CRi	All CR criteria except ANC<1000/ml 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

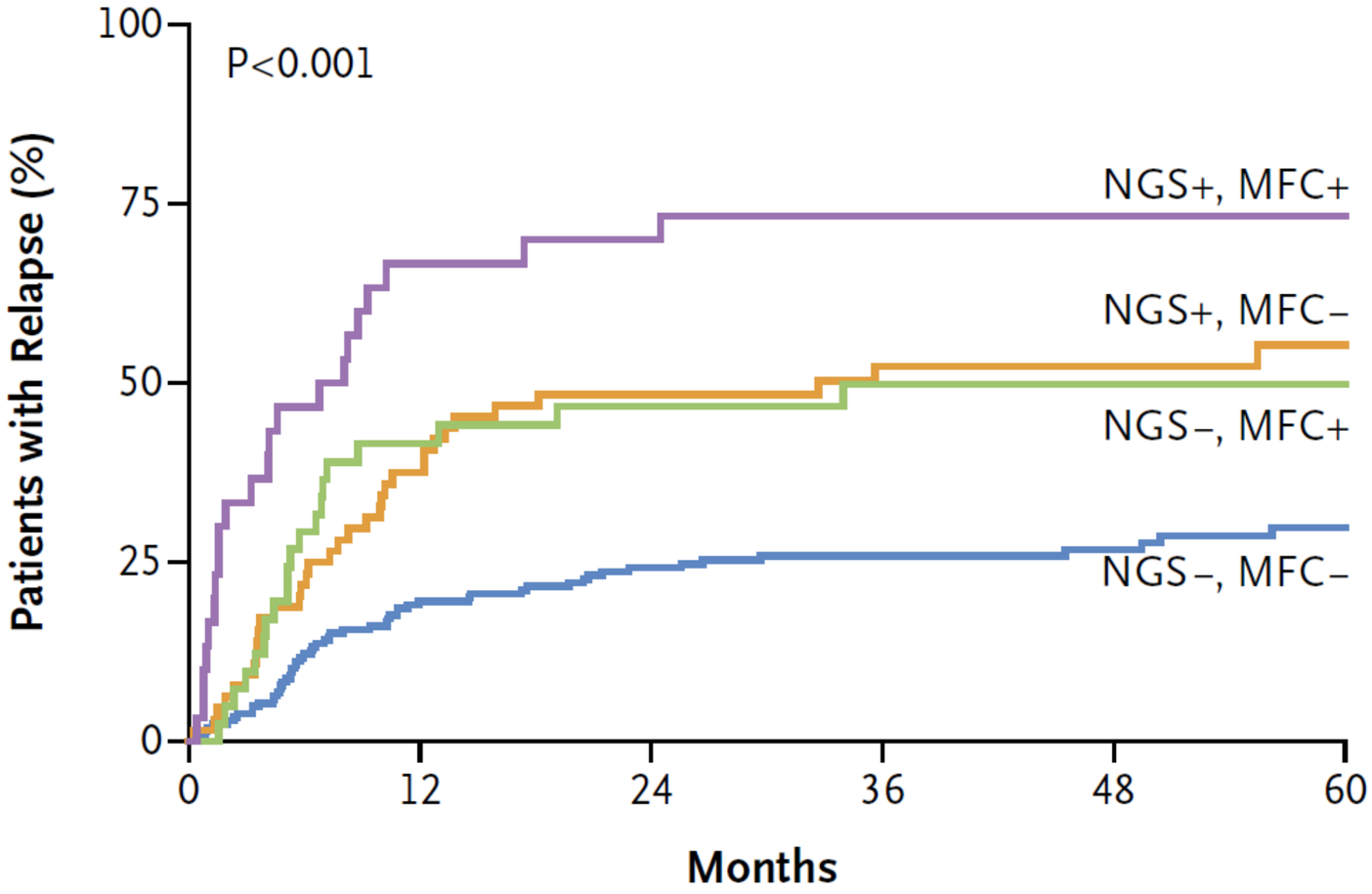
Dohner H et al, *Blood* 2022

Importance of count recovery/MRD



Chen X et al, *JCO* 2015

High relapse risk regardless of method of MRD detection



Jongen-Lavrencic et al, *NEJM* 2018

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
    - HiDAC 1g/m^2 q12hr x 12 doses
    - HiDAC 3g/m^2 q12 hr on days 1, 2, 3
  - Allogeneic transplant

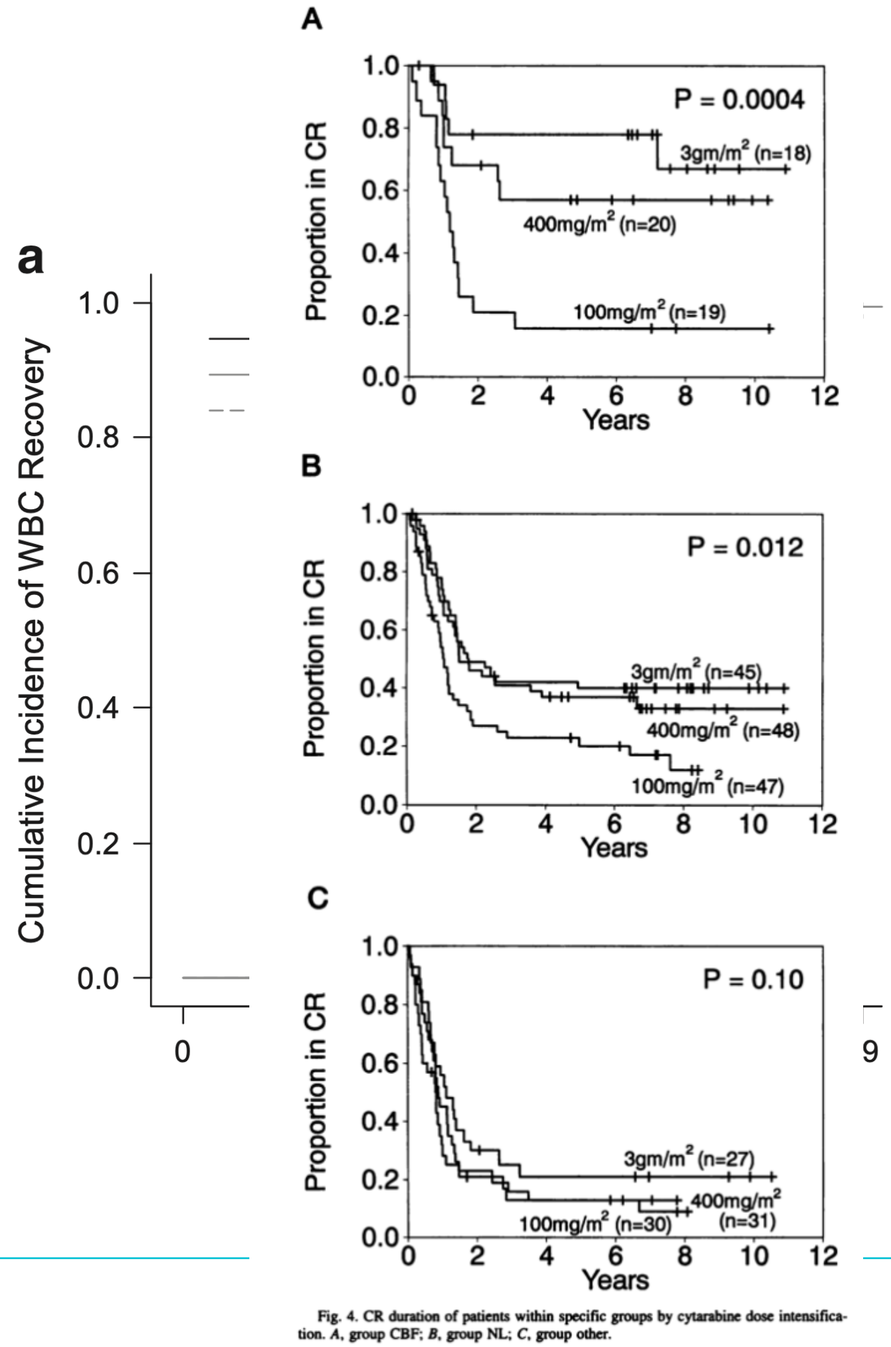


Fig. 4. CR duration of patients within specific groups by cytarabine dose intensification. *A*, group CBF; *B*, group NL; *C*, group other.

Bloomfield C et al, *Cancer Research* 1998; Jaramillo et al, *Blood Cancer J* 2017

Current maintenance options

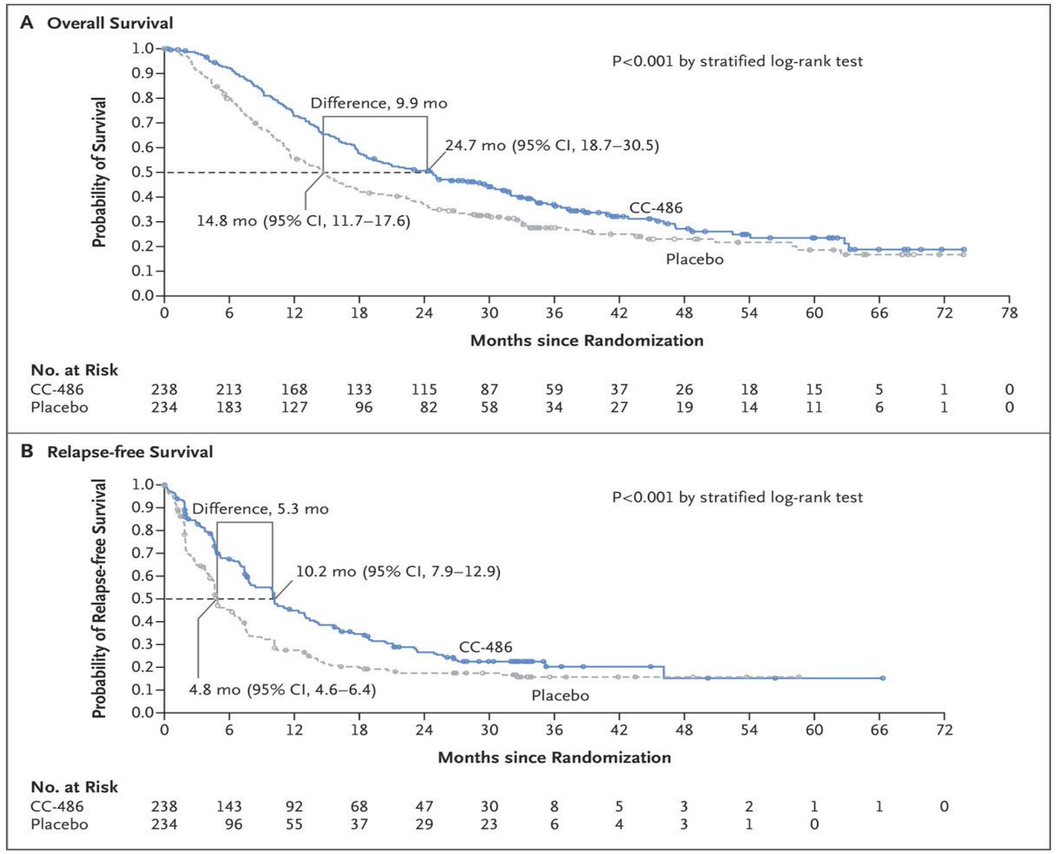
- **Midostaurin** x 12 months in *FLT3*-mutated patients who do not undergo HCT
- 5-day **azacitidine** 50mg/m^2 in patients >60 after 2 courses of intensive chemo (studied for max 12 cycles)
- **Oral azacitidine** tablets (Onureg)
- **Quizartinib** x 3 years in *FLT3*-ITD mutated patients who do or do not undergo HCT
- **Gilteritinib** x 2 years post-HCT in *FLT3*-ITD mutated patients with pre-HCT MRD

Stone RM et al, *NEJM* 2017; Huls G et al, *Blood* 2019; Wei et al *NEJM* 2020; Erba H et al *Lancet* 2023; Levis M et al *JCO* 2024

FDA approval 2020: oral 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 are not bioequivalent to subQ/IV



Wei A et al, *NEJM* 2020

FDA approval 2017/18/22: IDH inhibitors

- IDH mutations are found in 10-20% of newly diagnosed AML, and increase in frequency with age
- Mutations lead to accumulation of oncometabolite 2-HG (impairment of differentiation)
- Ivosidenib (AG-120): selective IDH1 inhibitor
  → Approved for newly diagnosed and R/R AML
- Olutasidenib: selective IDH1 inhibitor (better toxicity profile?)
  → Approved for 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; Watts JM et al *Lancet Haematol* 2023

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

- MORPHO trial (post-transplant maintenance in *FLT3*-ITD patients)

- Many ongoing trials, including randomized upfront 7+3+gilt vs. 7+3+midostaurin

NB: LACEWING with aza +/- gilteritinib for upfront AML failed to meet primary endpoint in Dec 2020

Perl A et al, *NEJM* 2019; Levis M et al *JCO* 2024

Less intensive induction

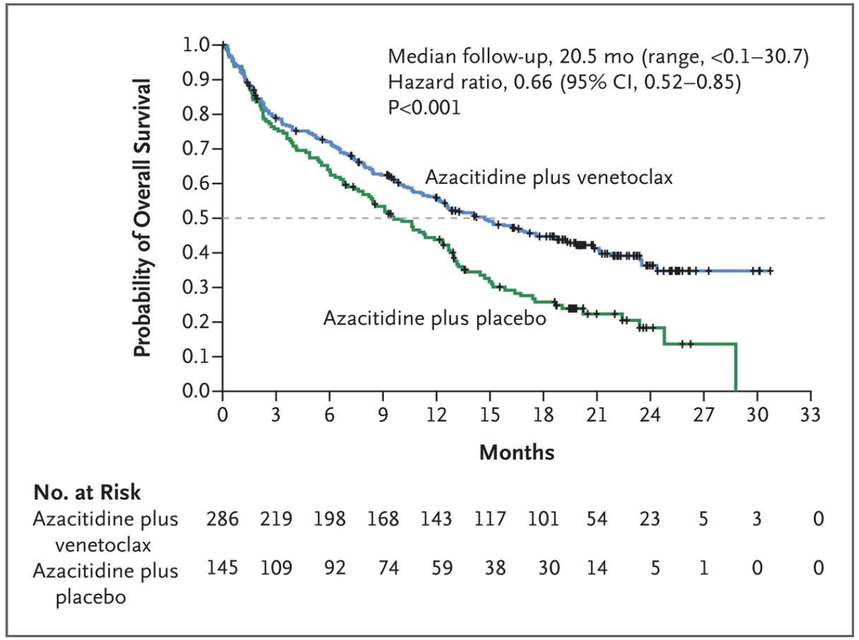
- Generally for “less fit”
- Continue less intensive treatment for as long as patients tolerate and receive clinical benefit
- ?relevance of MRD
- Retrospective analyses: older patients benefit from higher-intensity therapy
- ELN 2017: older age *plus* another factor for non-intense therapy
  - ➢ Patient-related factors, such as ECOG PS 3-4 or significant co-morbidities not related to AML
  - ➢ Disease-related factor, such as adverse-risk genetics

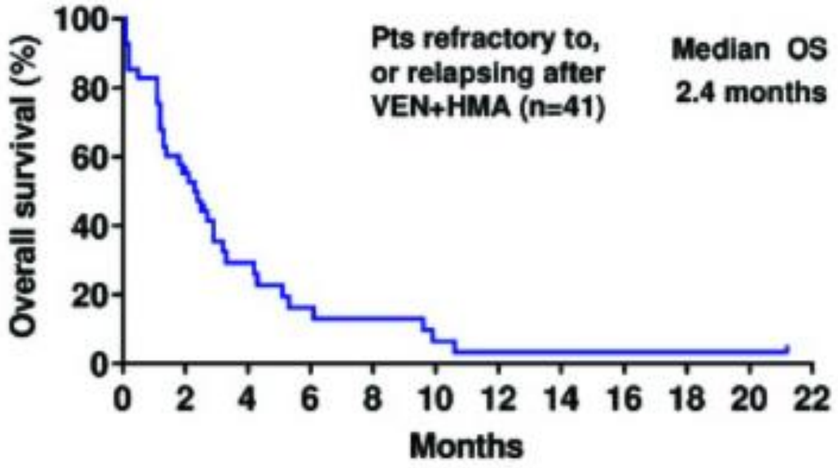
Juliusson G et al, *Blood* 2009; Dohner H et al, *Blood* 2017

FDA approval 2018: venetoclax

- Phase 3 VIALE-A trial: azacitidine +/- 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

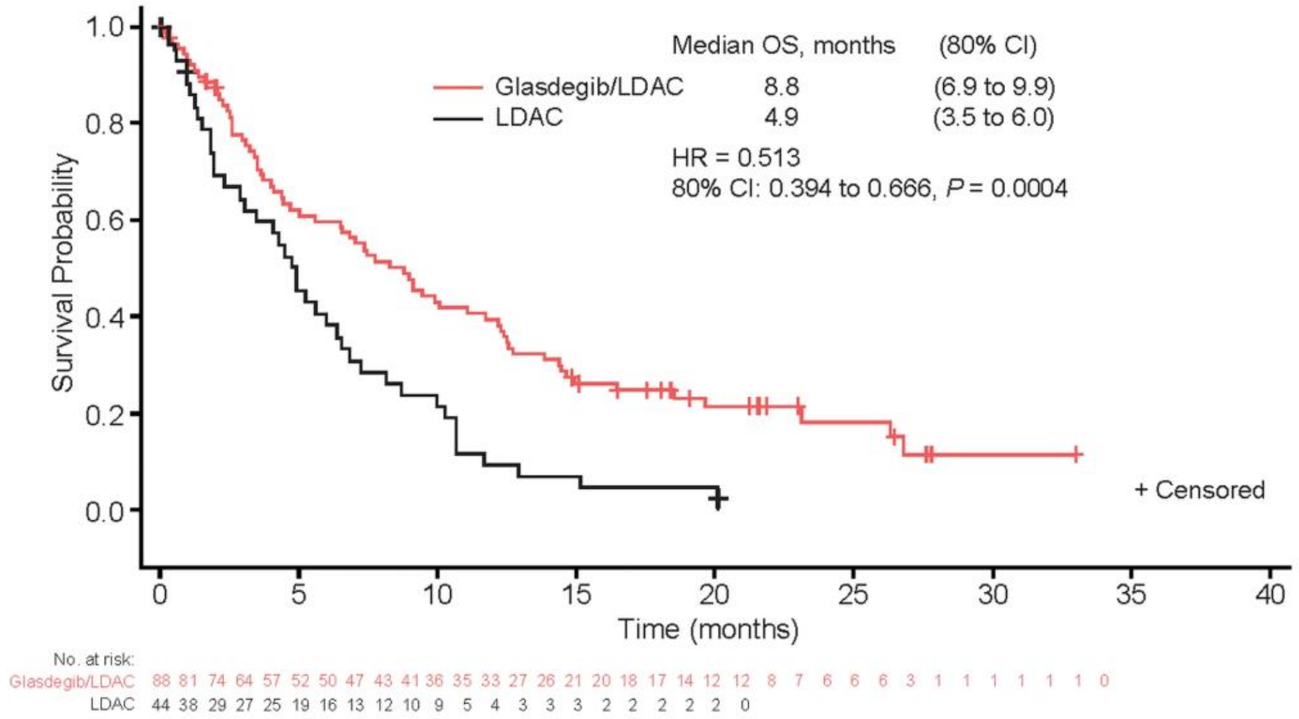




DiNardo C et al, *NEJM* 2020; Maiti A et al *Haematologica* 2021

FDA approval 2018: glasdegib

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

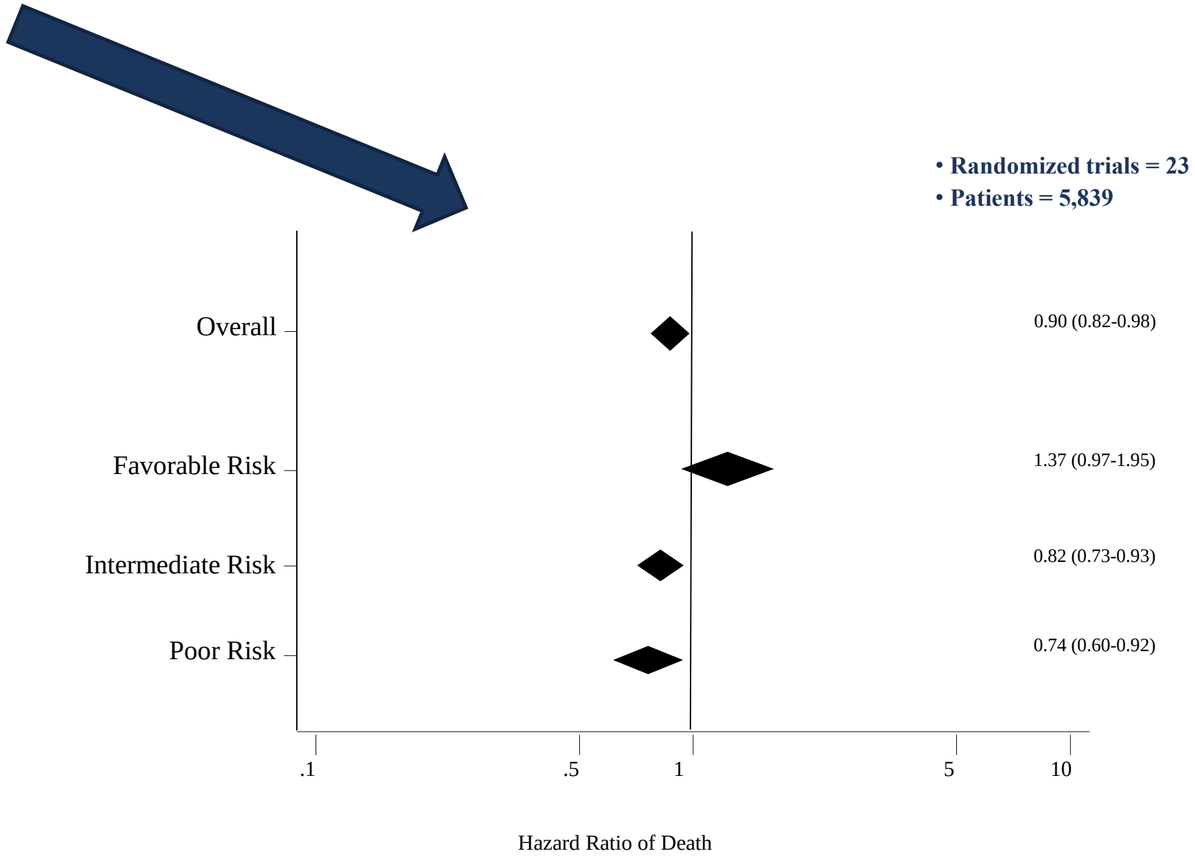


Cortes JE et al, *Leukemia* 2019

Indications for transplant referral

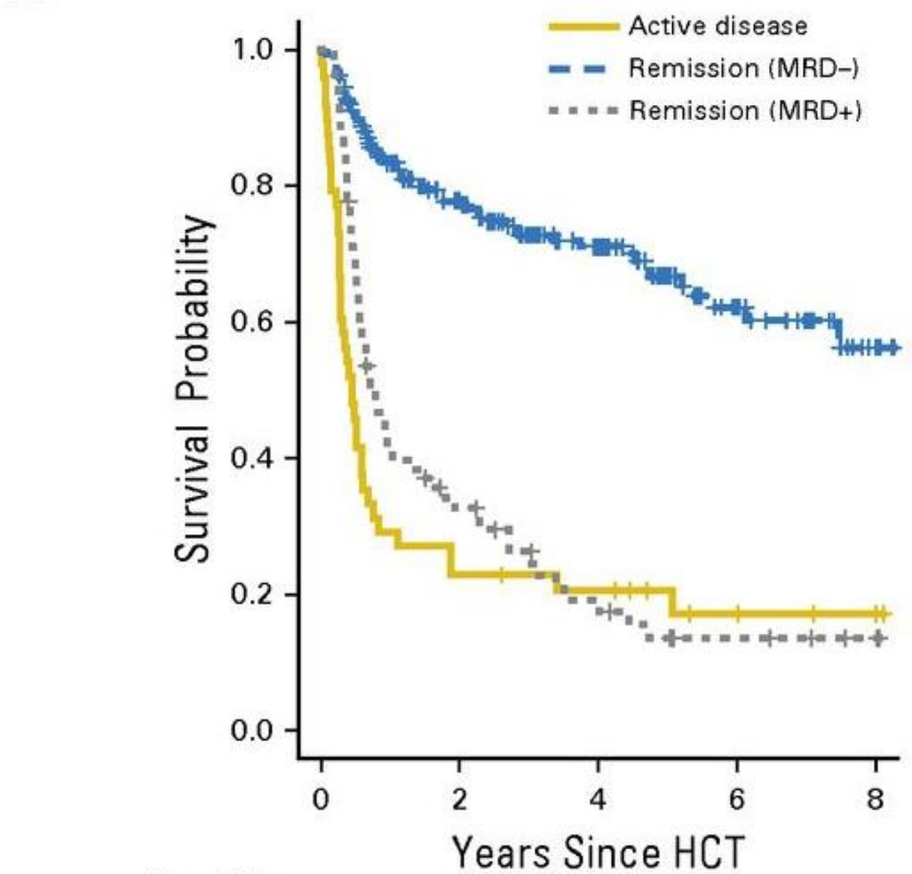
- Intermediate or adverse risk AML in CR1
- AML in CR2
- Primary refractory AML

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



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

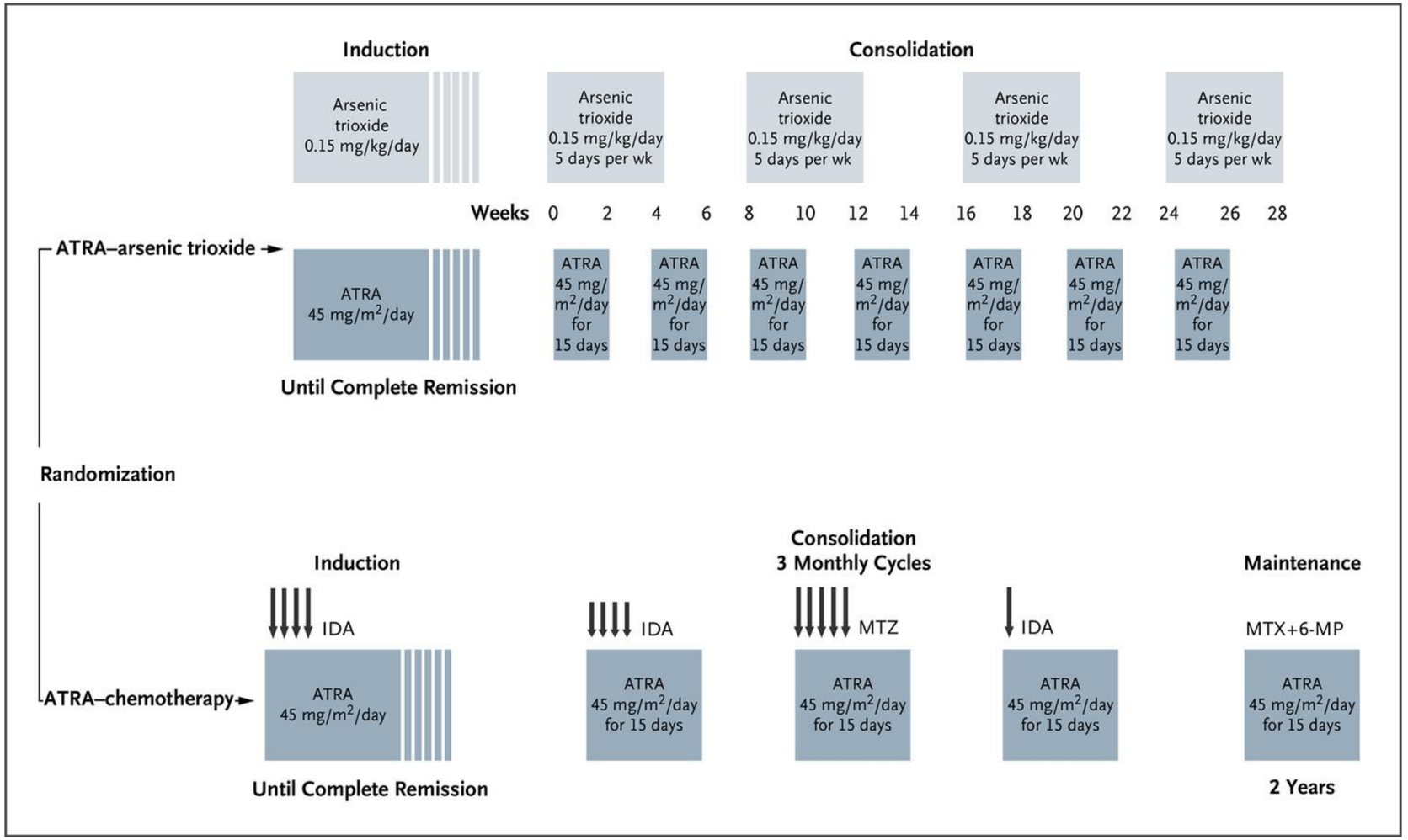
Acute promyelocytic leukemia

- ~10% of new AML (1200 pts/year in US)
- Morphology: bilobed nuclei, lots of Auer rods
- 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
- Start treatment with ATRA (all-*trans* retinoic acid) whenever you suspect APL

Differentiation syndrome

- More common in high-risk patients, suggesting mechanism is cytokine release
- Often seen when peripheral WBC is rising
- Typically occurs between days 5 and 15 after initiation of treatment
- Constellation of symptoms can be vague: fever, respiratory distress, weight gain, hypotension, pleural/pericardial effusions, LE edema, renal failure
- Decrease risk by cytoreducing with hydroxyurea +/- idarubicin
- Treat promptly with dexamethasone (some will use steroid prophylaxis)
- Can occur with ATRA or ATO

Lo-coco regimen (APL 0406 trial)

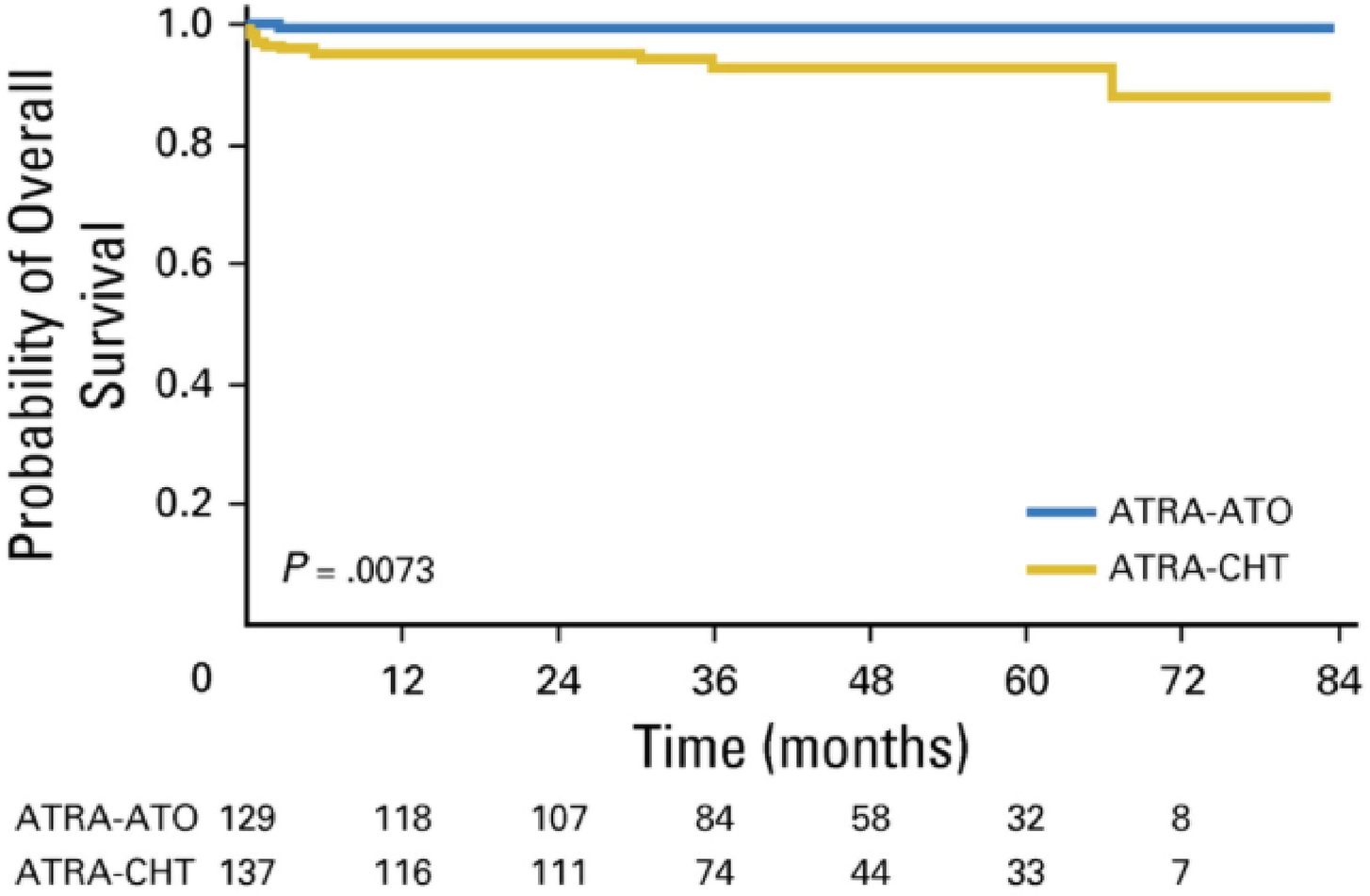


Lo-coco F et al, *NEJM* 2013

Side effects of ATRA and ATO

ATRA	ATO
Differentiation syndrome	Differentiation syndrome
Headache (sometimes pseudotumor cerebri)	Electrolyte abnormalities
Bone pain	QT prolongation
Hypertriglyceridemia	
Dry skin/mucous membranes	
Teratogen	

APL 0406 long-term outcomes



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

Summary

- Diagnosis of AML generally requires 20% or more blasts in blood or marrow
- Cytogenetic and molecular data are used to risk stratify (ELN 2022)
- 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
- Allogeneic transplant is a common component of AML treatment
- APL is a highly curable subtype of AML

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Thank you!

Contact with questions:

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