Management of Acute Myeloid Leukemia in 2020: A Paradigm Shift for Older Adults?

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Disclosures

- Honoraria: AbbVie, Agios, Celgene, Daiichi Sankyo, Genentech, Pfizer, Tolero
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- Research support: Celgene, Merck, Takeda, Tolero

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Objectives

- To discuss pathogenesis/etiology of AML
- To discuss diagnostic testing in AML
- To discuss management of AML in older patient populations in the context of recent drug approvals
- To highlight investigational agents in development and evolving treatment paradigms for older adults

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Case

- 75 yo M with PMHx of chronic myelomonocytic leukemia (CMML) & HTN presented to urgent care in 10/2017 with lower extremity edema and fatigue.
  - CMML diagnosed in December, 2016- WBC = 40,000 with monocytosis, no significant cytopenias, Bone marrow biopsy at Dx revealed 1% blasts, trilineage dysplasia (CMML-0)
- At presentation, WBC = $174x10^9$/L, Diff = range of differentiation, blasts >20%, Hb = 9.6 g/dL, Platelets = $70x10^9$/L, uric acid = 12.0 mg/dL, creatinine = 1.3 mg/dL, LDH = 1,659
- Denies any symptoms of chest pain or dyspnea.
- Bone marrow biopsy = Hypercellular (80%) marrow with 31% blasts + promonocytes consistent with AML
  - Normal cytogenetics (46,XY) and NGS Mutational Panel WNL

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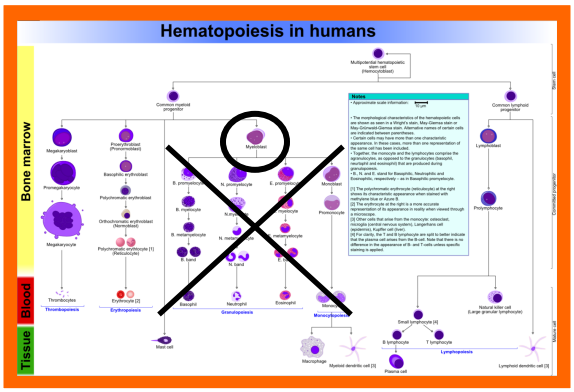
What is AML?



Adapted from commons.Wikimedia.org/wiki/file:hematopoiesis_(human)_diagram.png

- Clonal proliferation of myeloid precursors (i.e. myeloblasts)
  - Reduced capacity for differentiation
  - Reduced capacity for cell death-> uncontrolled proliferation

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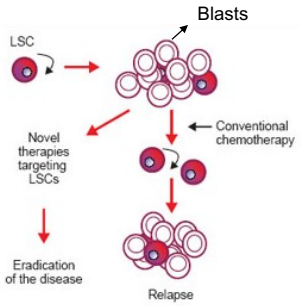
Pathogenesis of AML

- Stem Cell Hypothesis- AML arises from early hematopoietic progenitor/stem cell- LSC

- Stem cells- 3 basic properties
  - Not cell cycle-dependent
  - Capable of self-renewal
  - Produce committed progenitor cells

- Stem cells inherently chemoresistant
- Origin of LSC likely dictates prognosis and drug resistance



UNC LINEBERGER Cancer Control 2004- H. Lee Moffitt Cancer Center and Research Institute UNC CANCER CARE

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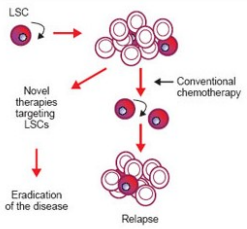
How To Cure AML?

- Holy grail of AML = Cure
- Working hypothesis is that all (or most) AML's arise from a LSC
- The more primitive LSC- harder to eradicate -> refractory and/or relapse
- Genetic features of AML provide a clue for how primitive AML is



Cancer Control 2004- H. Lee Moffitt Cancer Center and Research Institute

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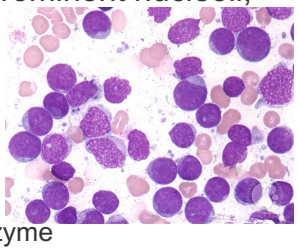
Pathology of AML

- Diagnosis: ≥20% myeloblasts in PB or BM
  - Blast % irrelevant in CBF AML [t(8;21); inv(16)] and APL
- Morphology: Smooth chromatin, prominent nucleoli, Auer Rods
- Immunophenotype:
  - Myeloid antigens:
    - MPO, CD13, CD33, CD15
  - Monocytic antigens:
    - NSE, CD11c, CD14, CD64, Lysozyme
  - Blast markers:
    - CD34, CD117



Maslak P, ASH Image Bank

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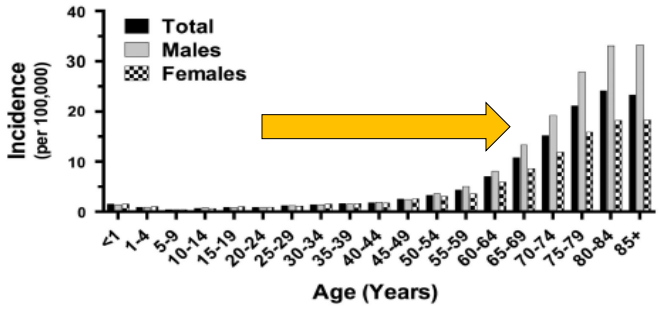
Epidemiology of AML



- 18,000 new cases of AML/year
  - > 10,000 deaths/year
- Median age- 67-68 years- high prevalence in elderly
  - All ages can be affected

SEER Data, Walter, Leukemia 2015

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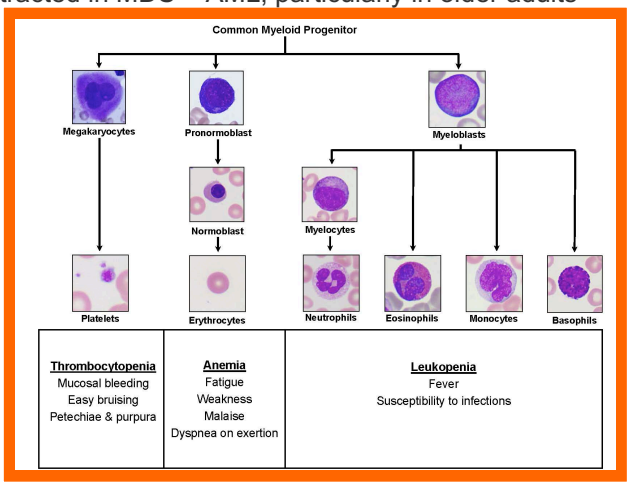
Clinical Presentation

- Rapid onset of symptoms over 1-2 weeks, can be more protracted in MDS-> AML, particularly in older adults



Duncan D et al., Acute Leukemia Textbook 2017.

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Classification/Prognostication

- FAB Classification outdated (M0-M7)
- Genetic information critical for prognostication
- European LeukemiaNet Classification 2017

ELN Risk	Cytogenetic/Molecular	Incidence-Younger pts	Incidence-Older pts
Favorable	• t(8;21); inv(16); t(16;16) • NPM1 mutation w/o FLT3-ITD mut. OR with FLT3-ITD^{low} • Biallelic mutated CEPBA	41%	20%
Intermediate	• Mutated NPM1 and FLT3-ITD^{high} • Wild-type NPM1 w/o FLT3-ITD or with FLT3-ITD^{low} • t(9;11) • Other	37%	49%
Adverse	• Inv(3); t(3;3); t(6;9); t(v;11); -5; del(5q); -7; -17/abnl(17p); complex • Wild type NPM1 & FLT3-ITD^{high} • Mutated RUNX1, ASXL1, TP53	22%	31%

Mrozek, J Clin Oncol 2012; Dohner, Blood 2017

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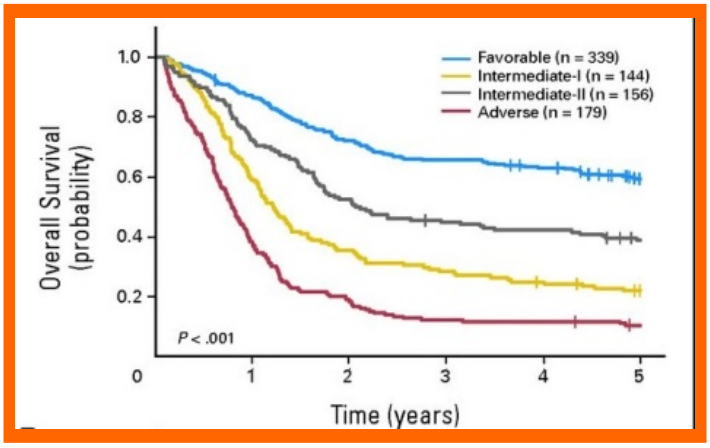
Do Risk Groups Matter?

- Risk groups validated to predict outcome



Mrozek, J Clin Oncol 2012

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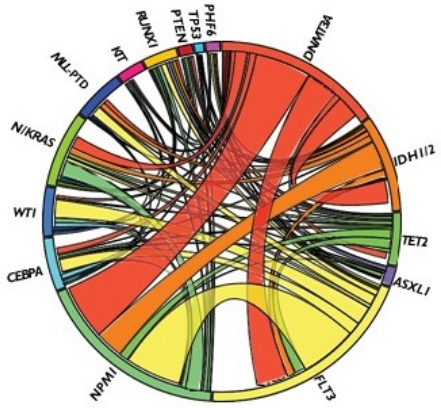
AML is a Heterogeneous Disease



Gene	Overall Frequency (%)
FLT3 (ITD, TKD)	37 (30, 7)
NPM1	29
DNMT3A	23
NRAS	10
CEBPA	9
TET2	8
WT1	8
IDH2	8
IDH1	7
KIT	6
RUNX1	5
MLL-PTD	5
ASXL1	3
PHF6	3
KRAS	2
PTEN	2
TP53	2
HRAS	0
EZH2	0

Patel, NEJM 2012

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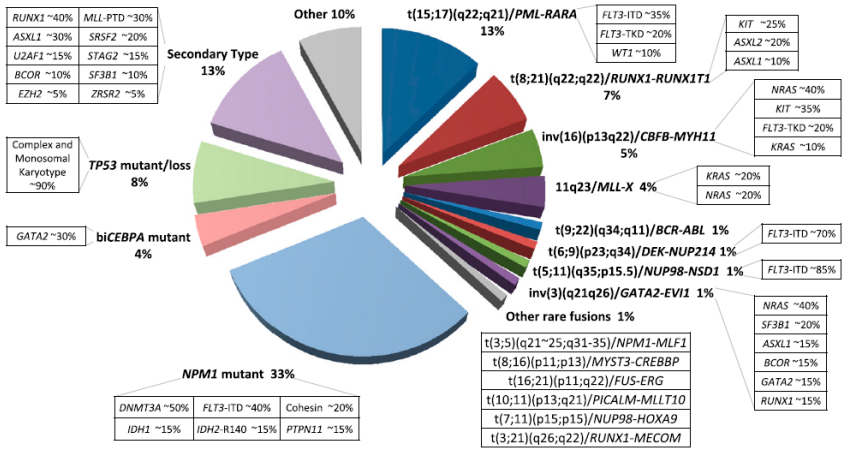
Complexity of Molecular Mutations in AML



Grimwade, Blood 2016

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11 Genomic Classes of AML

Table 1. Proposed Genomic Classification of Acute Myeloid Leukemia (AML).

Genomic Subgroup	Frequency in the Study Cohort (N=1540)	Most Frequently Mutated Genes*
	no. of patients (%)	*gene (%)*
AML with *NPM1* mutation	418 (27)	***NPM1*** (100), *DNMT3A* (54), *FLT3*^{ITD} (39), *NRAS* (19), *TET2* (16), *PTPN11* (15)
AML with mutated chromatin, RNA-splicing genes, or both†	275 (18)	***RUNX1*** (39), ***MLL***^{PTD} (25), ***SRSF2*** (22), *DNMT3A* (20), ***ASXL1*** (17), ***STAG2*** (16), *NRAS* (16), *TET2* (15), *FLT3*^{ITD} (15)
AML with *TP53* mutations, chromosomal aneuploidy, or both‡	199 (13)	**Complex karyotype** (68), **–5/5q** (47), **–7/7q** (44), ***TP53*** (44), **–17/17p** (31), **–12/12p** (17), +8/8q (16)
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB–MYH11*	81 (5)	**inv(16)** (100), *NRAS* (53), +8/8q (16), +22 (16), *KIT* (15), *FLT3*^{TKD} (15)
AML with biallelic *CEBPA* mutations	66 (4)	***CEBPA***^{biallelic} (100), *NRAS* (30), *WT1* (21), *GATA2* (20)
AML with t(15;17)(q22;q12); *PML–RARA*	60 (4)	**t(15;17)** (100), *FLT3*^{ITD} (35), *WT1* (17)
AML with t(8;21)(q22;q22); *RUNX1–RUNX1T1*	60 (4)	**t(8;21)** (100), *KIT* (38), –Y (33), –9q (18)
AML with *MLL* fusion genes; t(x;11)(x;q23)§	44 (3)	**t(x;11q23)** (100), *NRAS* (23)
AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *GATA2, MECOM(EVI1)*	20 (1)	**inv(3)** (100), –7 (85), *KRAS* (30), *NRAS* (30), *PTPN11* (30), *ETV6* (15), *PHF6* (15), *SF3B1* (15)
AML with *IDH2*^{R172} mutations and no other class-defining lesions	18 (1)	***IDH2***^{R172} (100), *DNMT3A* (67), +8/8q (17)
AML with t(6;9)(p23;q34); *DEK–NUP214*	15 (1)	**t(6;9)** (100), *FLT3*^{ITD} (80), *KRAS* (20)
AML with driver mutations but no detected class-defining lesions	166 (11)	*FLT3*^{ITD} (39), *DNMT3A* (16)
AML with no detected driver mutations	62 (4)	
AML meeting criteria for ≥2 genomic subgroups	56 (4)	

Papaemmanuil et al. NEJM 2016

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Driver Mutations With Effect on OS

Table 2. Driver Mutations with the Strongest Effect on Overall Survival and Other Clas

Variable	Frequency in Study Cohort (N=1540)	Hazard Ratio for Death (95% CI)	P Value
	no. of patients (%)		
Main effects			
inv(3), *GATA2, MECOM(EVI1)*	23 (1)	2.9 (1.8–4.7)	9×10^{-6}
TP53	98 (6)	1.7 (1.4–2.2)	7×10^{-6}
Complex karyotype	159 (10)	1.4 (1.2–1.7)	2×10^{-6}
BRAF	9 (1)	1.4 (1.1–1.8)	0.009
SRSF2	89 (6)	1.4 (1.1–1.7)	0.003
FLT3^{ITD}	341 (22)	1.4 (1.2–1.7)	0.0008
+21	39 (3)	1.3 (1.1–1.6)	0.001
–5/5q	107 (7)	1.3 (1.1–1.5)	0.0007
–17/17p	74 (5)	1.3 (1.1–1.5)	0.003
+13	21 (1)	1.3 (1.1–1.5)	0.004
–7	88 (6)	1.3 (1.1–1.5)	0.003
–9q†	53 (3)	1.2 (1.1–1.5)	0.01
+22†	26 (2)	1.2 (1.1–1.4)	0.008
NPM1	436 (28)	0.7 (0.6–0.9)	0.0004
CEBPA^{biallelic}	73 (5)	0.6 (0.4–0.7)	4×10^{-5}
t(15;17), *PML–RARA*	65 (4)	0.3 (0.2–0.4)	5×10^{-8}
inv(16), *CBFB–MYH11*	82 (5)	0.3 (0.2–0.4)	4×10^{-9}
Gene–gene interactions			
NPM1–FLT3^{ITD}*–DNMT3A*	93 (6)	1.5 (1.2–1.9)	0.0002
MLL^{PTD}*–FLT3*^{TKD}	10 (1)	1.4 (1.2–1.8)	0.0005
DNMT3A–IDH2^{R140}	47 (3)	1.4 (1.1–1.8)	0.007
STAG2–IDH2^{R140}	11 (1)	0.8 (0.6–0.9)	0.01
NPM1–FLT3^{TKD}	53 (3)	0.7 (0.6–0.9)	0.009
DNMT3A–RAD21	19 (1)	0.7 (0.5–0.9)	0.0008
Other class-defining lesions			
t(x;11), not *MLLT3–MLL*	37 (2)	1.4 (1.0–2.1)	0.06
ASXL1	70 (5)	1.3 (1.0–1.6)	0.04
ZRSR2	13 (1)	1.3 (1.0–1.7)	0.04
RUNX1	133 (9)	1.1 (0.9–1.3)	0.5
t(9;11), *MLLT3–MLL*	18 (1)	0.8 (0.4–1.4)	0.5
IDH2^{R172}	39 (3)	0.8 (0.6–1.0)	0.07
t(8;21), *RUNX1–RUNX1T1*	63 (4)	0.7 (0.4–1.0)	0.03

Papaemmanuil et al. NEJM 2016

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Myeloid Molecular Panel- UNC

- NGS Panel of 33 genes- most commonly mutated in MDS/AML
- Performed on all diagnostic bone marrow aspirates in MDS/AML
- Recheck at time of relapse- evolving area
- Mutations can be prognostic, therapeutic, and/or can monitor minimal residual disease (MRD)

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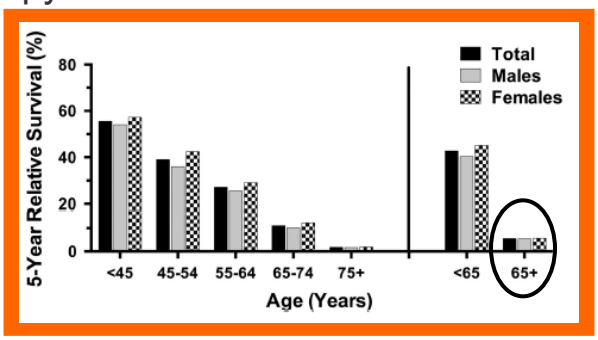
AML Outcomes

- Extremely poor prognosis with conventional therapy



- 5-year survival rates = 40% in <65 yrs and <10% in ≥65 yrs

Walter, Leukemia 2015

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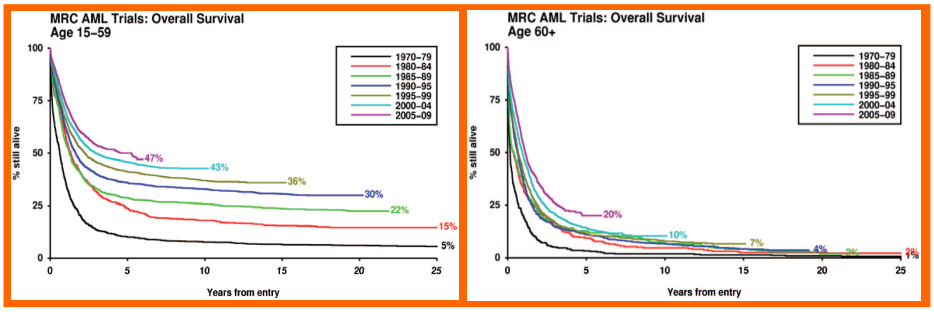
AML Outcomes Over Time



- Improvements in survival likely due to supportive care and allogeneic transplantation
- No new drugs approved in AML since 1990…UNTIL 2017!

Burnett AK, Hematology Am Soc Hematol Educ Program 2012

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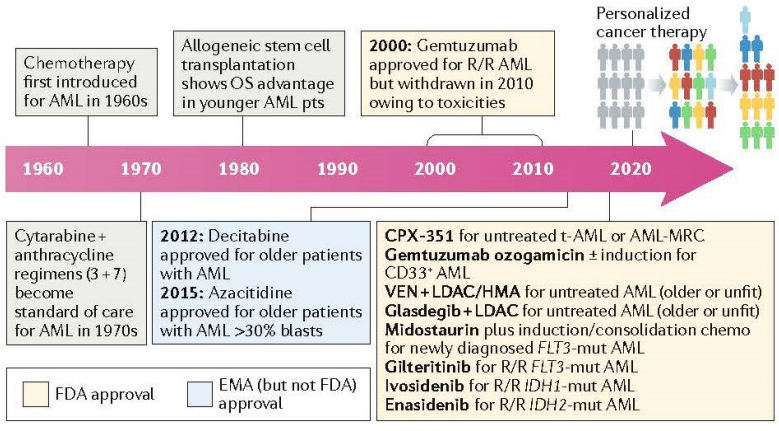
Treatment Landscape of AML since 1960



Dinardo, Nat Rev Clin Oncol 2019

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Why Do Elderly AML Have Poor Prognosis?

- Age- tend to be more frail, more comorbidities
  - Less able to tolerate intensive therapy
  - Allogeneic transplant mainly performed in ≤70-75 years
- Biology of disease
  - Increased risk of adverse-risk karyotype & mutations- TP53
- Increased incidence of secondary AML from MDS
  - Very poor prognosis
- Lack of effective Tx options, treatment nihilism?

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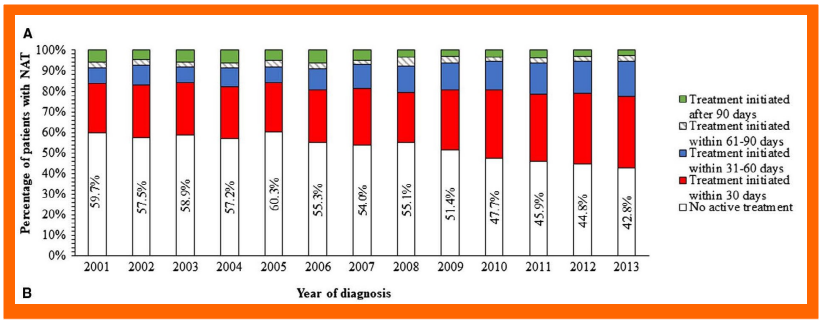
Many Elderly AML Pts Not Treated in Community



- Retrospective analysis from SEER database- 2001-2013
- 14,089 AML pts diagnosed b/w 66-99 years
- Overall trend of more pts being treated with chemotherapy agents over time- still significant proportion untreated

Zeidan, Cancer 2019

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Intensive Chemo in Elderly

- Elderly AML defined as age >60-65 years
- Intensive chemo- SOC for <60 years
- Older adults have significantly higher rates of toxicity and lower clinical efficacy with 7+3 induction

Table 5. Mortality within 30 days of initiation of induction

	Younger than 56 y	56-65 y	66-75 y	Older than 75 y
No. patients	364	242	270	79
Early deaths* by performance status, no./no. total patients (%)				
0	3/129 (2)	8/72 (11)	9/73 (12)	2/14 (14)
1	6/180 (3)	6/112 (5)	20/126 (16)	7/40 (18)
2	1/46 (2)	6/34 (18)	16/52 (31)	7/14 (50)
3	0/9 (0)	7/24 (29)	9/19 (47)	9/11 (82)

Table 6. Treatment outcomes

	Younger than 56 y	56-65 y	66-75 y	Older than 75 y
No. patients	368	246	274	80
Response, no. (%)				
CR	235 (64)	113 (46)	108 (39)	26 (33)
Resistant disease	99 (27)	91 (37)	101 (37)	29 (36)
Median overall survival, no. (95% CI)	18.8 (14.9-22.6)	9.0 (8.1-10.2)	6.9 (5.4-7.7)	3.5 (1.4-6.1)
No. patients with CR	235	113	108	26
Median disease-free survival, no. (95% CI)	21.6 (15.8-35.5)	7.4 (6.5-9.8)	9.3 (6.3-10.2)	8.9 (5.8-10.8)

- Even those with good ECOG PS have poor outcomes w/ 7+3 in elderly
- Can be done in select scenarios in >65 years (i.e. favorable-risk dz)

Appelbaum, Blood 2006

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CPX-351- Liposomal "7+3"

- Liposomal formulation of 7+3- designed to mitigate toxicity of 7+3 and improve efficacy- **true intensive chemo**
- Clinical activity noted in a randomized phase 2 study in newly Dx AML ≥60 years- CPX-351 vs. 7+3
  - CR rates = 67% vs. 51%, p=0.07
  - Median OS = 14.7 months vs. 12.9 months, lower 60-day mortality with CPX-351
  - Secondary AML appeared to have most benefit
- Data led to a randomized phase 3 study of CPX-351 vs. 7+3 in newly Dx AML with MDS-Related Changes, t-AML, or Secondary AML from MDS/CMML in pts 60-75 years
  - Older adults fit for intensive chemotherapy
  - Primary endpoint = OS

Lancet, Blood 2014; Lancet, J Clin Oncol 2018

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AML with MDS-Related Changes

- Presence of preexisting MDS OR:
- Morphology- multilineage dysplasia (≥50% dysplasia in ≥2 lineages)
  - W/O NPM1 or biallelic CEBPA mutations
- Presence of MDS-related cytogenetics
  - Complex Karyotype
  - -7/del(7q)
  - Del(5q)/t(5q)
  - i(17q)/t(17p)
  - -13/del(13q)
  - Del(11q)
  - Del(12p)/t(12p)
  - Idic(X)(q13)
  - t(11;16)
  - t(3;21)
  - t(1;3)
  - t(2;11)
  - t(5;12)
  - t(5;7)
  - t(5;17)
  - t(5;10)
  - t(3;5)

Arber, Blood 2016

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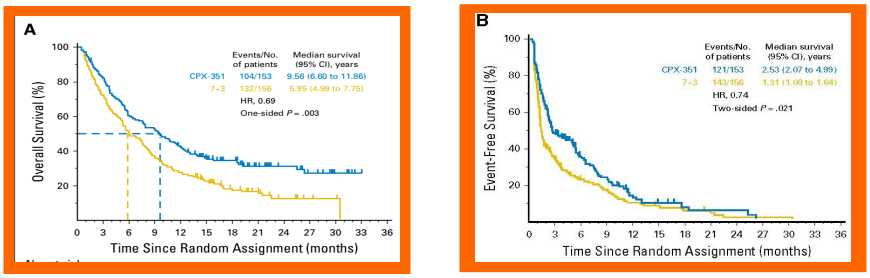
CPX-351 > 7+3 in Older Adults with AML with MRC



- CPX-351 led to superior outcomes vs. 7+3 in older, fit adults with AML with MRC
- Median OS 9.6 vs. 6 months, p = 0.003
- CR rates = 48% vs. 33%, p=0.016, similar CR duration
- CPX-351 led to superior outcomes post-BMT

Lancet, Blood 2014; Lancet, J Clin Oncol 2018

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CPX-351 Summary

- CPX-351 FDA-approved for management of AML with MRC, treatment-related AML or AML from preexisting MDS/CMML
  - No age restriction by label but studies have only conferred benefit in older adults **up to age 75 years**
  - Studies ongoing in other patient subpopulations- i.e. younger AML pts, other risk groups, combination strategies
- This study highlights that 7+3 may not be a useful comparator
  - Dismal outcomes with 7+3 and should not be used in this older adverse-risk pt population
- CPX-351 new SOC for older, **FIT** AML pts with AML with MRC- best done in pts who may be BMT candidates
  - Subsets of pts who truly benefit evolving area
- Moves the needle slightly- still need better therapies

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Low-Intensity Strategies

- Multiple studies have shown that any Tx leads to improved OS compared with best supportive care alone
- Low dose cytarabine (LDAC)- old standard- improved OS compared with best supportive care- CR rates with LDAC = 18% and median OS 6-7 months[1]
- Hypomethylating agents- Azacitidine or Decitabine- not approved for AML but generally reimbursable
  - Approved for MDS
  - Has been used as SOC in USA for >10 years
- Combination therapies now leading to superior outcomes

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1) Burnett, Cancer 2007

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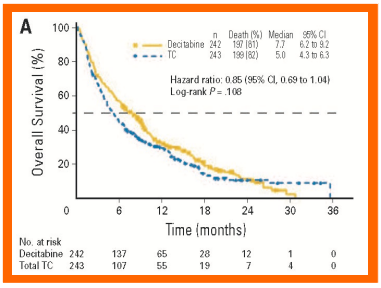
Decitabine

- Randomized Phase 3 study of Decitabine (5 days) vs. Physician choice (LDAC or Best Supportive Care) for newly Dx elderly (≥65 years) AML



- N=485 pts; Median age = 73 yrs
- Intermediate & Poor-risk cytogenetics
- CR rates = 17.8% vs. 7.8%
- Median OS = 7.7 months vs. 5.0 months- p= 0.106
- Not FDA-approved

Kantarjian, J Clin Oncol 2012

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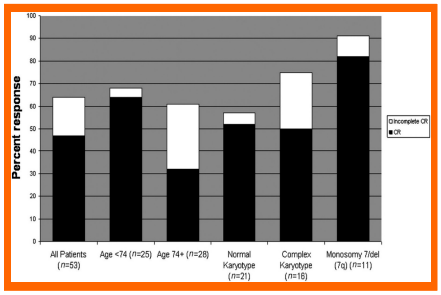
Decitabine- 10 days

- Phase II Study of newly dx AML ≥60 years not candidates for intensive chemo[1]



- N=53 pts, median age = 74 yrs
- CR/CRi rate = 64%
- Median OS ~1 year
- Subsequent studies have suggested high CR's in TP53 mut AML[2]

- Enthusiasm for 10-day tempered after randomized phase 2 study showed no improvement versus 5-days[3]

1) Blum, PNAS 2010; 2) Welch, N Engl J Med 2016; 3) Short, Lancet Haematol 2019

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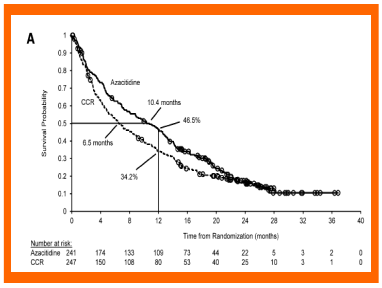
Azacitidine

- Randomized Phase 3 study of Azacitidine vs. Physician Choice (7+3, LDAC, Best Supportive Care) in newly Dx AML ≥65 years with ≥30% blasts



- N=488 pts; Median age = 75 yrs
- Intermediate & Poor-risk cytogenetics
- CR rates = 27.8% vs. 25.1%
  - 7+3 = 47.7%
- Median OS = 10.4 months vs. 6.5 months, p= 0.10 but reached significance censoring for subsequent Tx

- Pts preselected for 7+3-> N=87 randomized
- Median OS = 13.3 months vs. 12.2 months
- Despite lower CR rates, should 7+3 be used at all in elderly?

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Dombret, Blood 2015

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Summary of HMA's

- Reasonable first-line strategy in all older AML pts (≥65 years)
  - Particularly in pts who are not BMT candidates
- No data comparing HMA's to CPX-351 but no advantage to 7+3 over Azacitidine in ≥65 years
- HMA's are less toxic than intensive chemo, outpatient
- Disadvantages- Tx continues indefinitely, low CR rates- can take a few months to see response, cytopenias can persist
- How can we improve HMA's?

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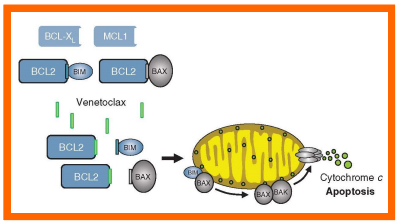
HMA's + Venetoclax

- Venetoclax- oral BCL-2 inhibitor- modest response rates as single agent in R/R AML- 20%



- Phase 1b study of HMA + Venetoclax in newly dx AML ≥65 years
- Eligibility = ineligible for intensive chemo due to:
  - Age >75 years
  - Cardiac Dz
  - Prior anthracyclines
  - High prob. Of mortality

- Arm A: Decitabine 20 mg/m^2 IV x 5 days + Venetoclax
- Arm B: Azacitidine 75 mg/m^2 IV x 5 days + Venetoclax
- Safe dose chosen- 400 mg daily

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HMA's + Venetoclax

- Median age = 74 years
- Most had de novo AML (75%)
- CR/CRi rates = 67%, median duration of CR = 11.3 months
- Similar CR rates b/w Azacitidine and Decitabine
- Median OS = 17.5 months

Subgroup	Evaluable for response/OS, n (%)	CR + CRi, n (%)	n for Median duration of CR + CRi	Median duration of CR + CRi, mo (95%CI)	Median OS, mo (95%CI)
All patients	145	97 (67)	97	11.3 (8.9, NR)	17.5 (12.3-NR)
Cytogenetic risk					
Intermediate	74 (51)	55 (74)	55	12.9 (11, NR)	NR (17.5-NR)
Poor	71 (49)	42 (60)	42	6.7 (4.1, 9.4)	9.6 (7.2-12.4)
Age					
≥75 y	62 (43)	40 (65)	40	9.2 (6.4, 12.5)	11 (9.3-NR)
<75 y	83 (57)	57 (69)	57	12.9 (9.2, NR)	17.7 (14.2-NR)
AML					
De novo	109 (75)	73 (67)	73	9.4 (7.2, 11.7)	12.5 (10.3-24.4)
Secondary	36 (25)	24 (67)	24	NR (12.5, NR)	NR (14.6-NR)
Mutations*					
FLT3†	18 (12)	13 (72)	13	11 (6.5, NR)	NR (8-NR)
IDH1 or 2‡	35 (24)	25 (71)	25	NR (6.8, NR)	24.4 (12.3-NR)
NPM1	23 (16)	21 (91)	21	NR (6.8, NR)	NR (11-NR)
TP53	36 (25)	17 (47)	17	5.6 (1.2, 9.4)	7.2 (3.7-NR)

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Venetoclax Summary

- Based on promising data from phase 1b-> Venetoclax given accelerated FDA-approval for Tx of newly Dx AML + HMA's
  - >75 years or comorbidities that preclude intensive chemo
- New SOC for elderly AML?
- How do we define fitness for intensive chemo vs. low-intensity strategies?
- 2 ongoing Randomized Phase 3 Trials- Aza + Venetoclax vs. Aza & LDAC + Venetoclax vs. LDAC
  - Primary endpoint = OS
- Unanswered questions- challenging to give in community
  - Myelosuppression frequent- how to dose in cytopenias?
  - Drug interactions with CYP3A4 inhibitors
  - Dose ramp-up over 3-5 days

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Tx Options Post-Venetoclax?

- Despite encouraging response rates-> almost all pts who respond will ultimately relapse
- Median OS = 2.4 months in pts with relapsed/refractory Dz after Aza/Ven[1]
- In pts with FLT3, IDH1 or IDH2 mutations, targeted Tx options available- majority do not have a targeted Tx option
- MCL-1- BCL-2 family member- anti-apoptotic peptide up-regulated in AML
- MCL-1 appears to be a dominant mechanism of resistance after Ven-> targeting MCL-1 rational Tx approach[2-3]
- **UNC lead site on a randomized phase 2 study of Alvocidib (CDK9 inhibitor-> MCL-1 inhibition) +/- low dose cytarabine (LDAC) in pts with relapsed/refractory AML after Venetoclax 1st line Tx**

1) Maiti, Blood[ASH Abstract] 2019; 2) Konopleva, Cancer Disc 2016; 3) Ramsey, Cancer Disc 2018

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Other Low-Intensity Tx for Newly Dx Elderly AML

- Glasdegib- Hedgehog inhibitor + LDAC
  - Randomized phase 2 study- Glasdegib + LDAC vs. LDAC[1]
  - Median OS = 8.8 months vs. 4.9 months
  - LDAC not useful comparator, not commonly used
- LDAC + Venetoclax
  - Phase 1b study- CR/CRi = 54%, Median OS = 10.1 months[2]
  - Option for prior HMA-treated secondary AML
  - Randomized phase 3 study ongoing
- Ivosidenib- IDH1 inhibitor
  - N=34 pts, CR+CRh = 42%, Median OS = 12.6 months[3]
  - How does this compare to HMA + Ven or HMA?
  - Option in prior HMA-treated pts with IDH1 mut

1) Cortes, Leukemia 2018; 2) Wei, J Clin Oncol 2019; 3) Roboz, Blood 2019

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Paradigm Shift?

- Treatment nihilism has existed for elderly AML pts in community
- Multitude of available agents- overall outcomes remain poor
- Low-intensity Tx evolving- shifting to younger pts, combination therapies to improve outcomes
- Biomarker-based approaches critical- which pts predicted to respond versus resistance?
- Genomic sequencing (NGS) critical to inform Tx decisions- future strategies will likely be based on full sequencing panels

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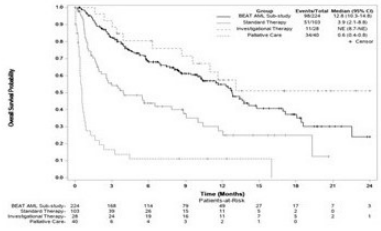
Clinical Trials

- **Despite Tx advances-> clinical trials should be 1st option**
  - Improve clinical outcomes- outcomes remain poor and CR not durable
  - Understand which pts benefit from specific Tx
  - Mitigate toxicity and improve QOL
- Beat AML- Multi-institutional precision-medicine based trial
  - >60 years, all pts receive genomic profiling w/in 1 week
  - Multiple Tx arms w/ investigational agents based on genomic profile
  - Enrolling pts at UNC



Burd, Blood [ASH Abstract] 2019

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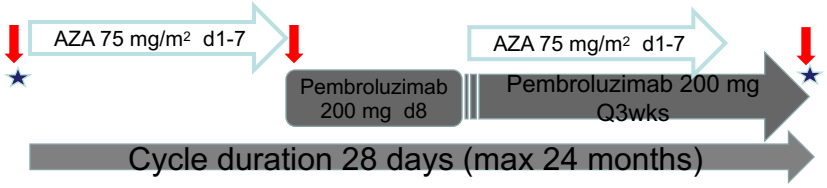
Clinical Trials- Azacitidine + Pembrolizumab

- Phase 2 Study of Azacitidine + Pembrolizumab in 1) Relapsed/Refractory AML, 2) Newly Dx AML ≥65 years



- Collaboration with Johns Hopkins (Lead PI: Ivana Gojo)
- Newly Dx AML- CR/CRi = 53% in evaluable pts
- Well tolerated but immune-related AE's can occur
- Immunogenomic biomarkers of response ongoing
- Combination strategies

Gojo, Blood[ASH abstract], 2019

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Back to Case

- After cytoreduction and management of TLS-> enrolled on Phase 2 Study of Azacitidine + Pembrolizumab
- Achieved CR after 2 cycles of Tx and has been in CR since 11/2017
- No hospitalizations after 1st being hospitalized at Dx
- Completed 2 years of therapy and now on Aza maintenance
  - Pembro-induced hypothyroidism
- Normal QOL and no limitations- currently 77 years old

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Conclusions

- AML is a challenging Dz to treat
  - Heterogeneous with diverse genetic subsets inform Tx decisions
- Elderly AML pts now have many Tx options
  - Should be referred to specialized centers
  - Targeted Tx approaches will continue to move field forward and lead to improved patient outcomes
- Venetoclax-based Tx-> Paradigm shift in management of elderly AML?
  - Can we predict who will respond best? Who will be resistant?
  - What to do after Venetoclax?
- Clinical trials are imperative in all facets of Dz

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Questions?

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