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New Therapies for Acute Myeloid Leukemia

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Learning Objectives

- Identify risk stratification schema for AML to guide t/t selection and prognosis
  - Diagnostic workup
- Describe management for specific AML types
  - FLT3 AML
  - Elderly/ Poor risk AML
  - Secondary/ therapy related AML/ AML with targetable mutations
  - Good risk: Core binding factor AML
- Summarize the treatment for AML in 2021

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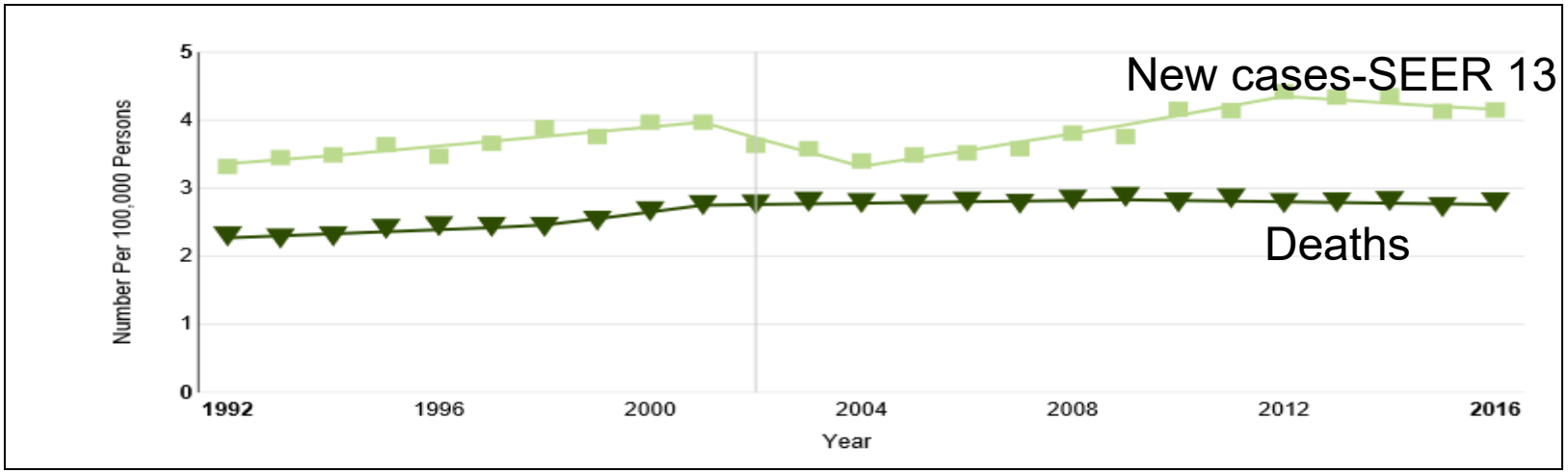
Epidemiology of AML



At a Glance….	
Estimated New Cases in 2019 (% of all cancers)	21,450 (1.2%)
Median age at diagnosis	68 years
Estimated Deaths in 2019 (% of all cancer deaths)	10,920 (1.8%)
Percent Surviving 5 Years (2009 to 2016)	28%

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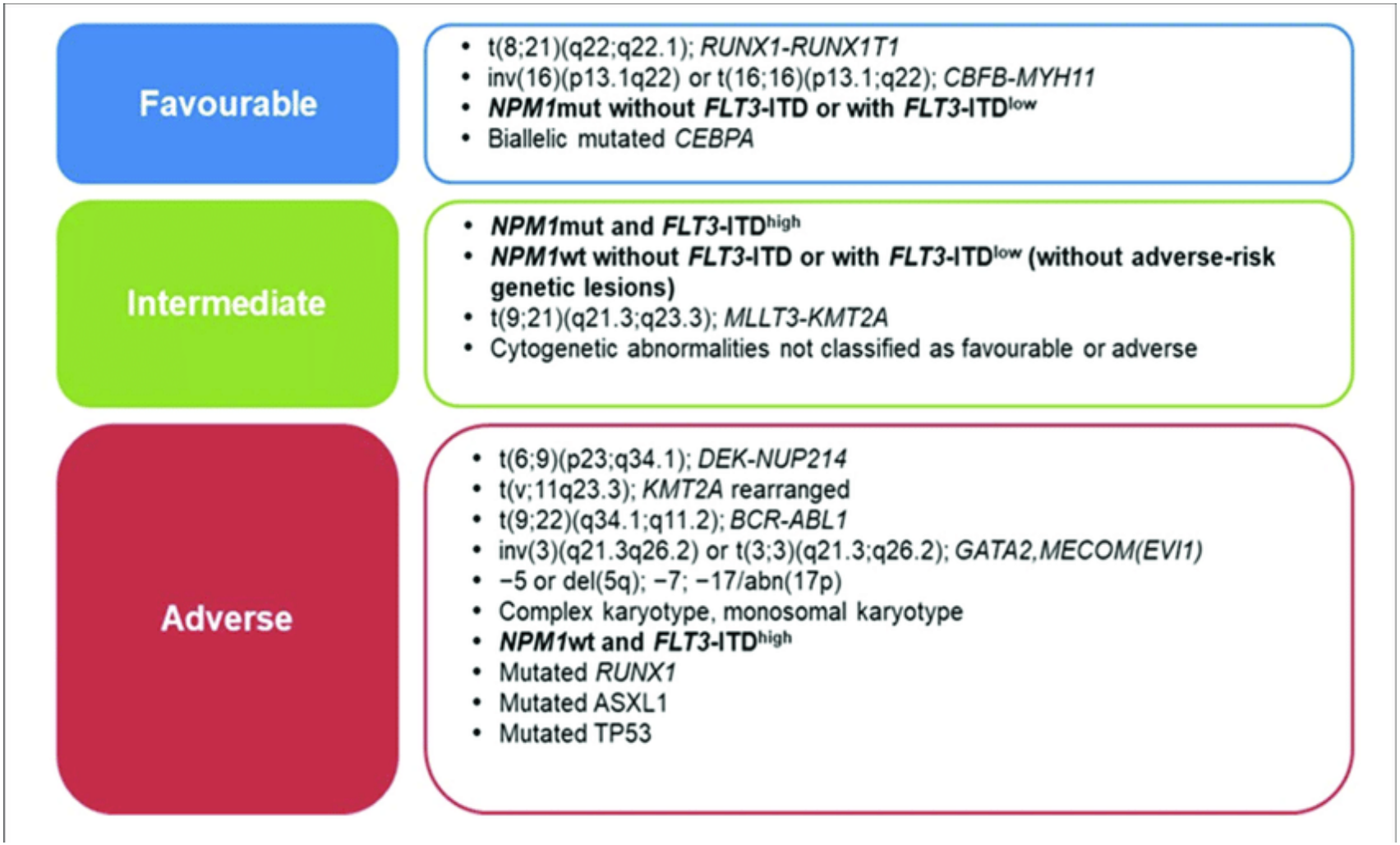
Risk Stratification for AML



Dohner et al. Blood 2017

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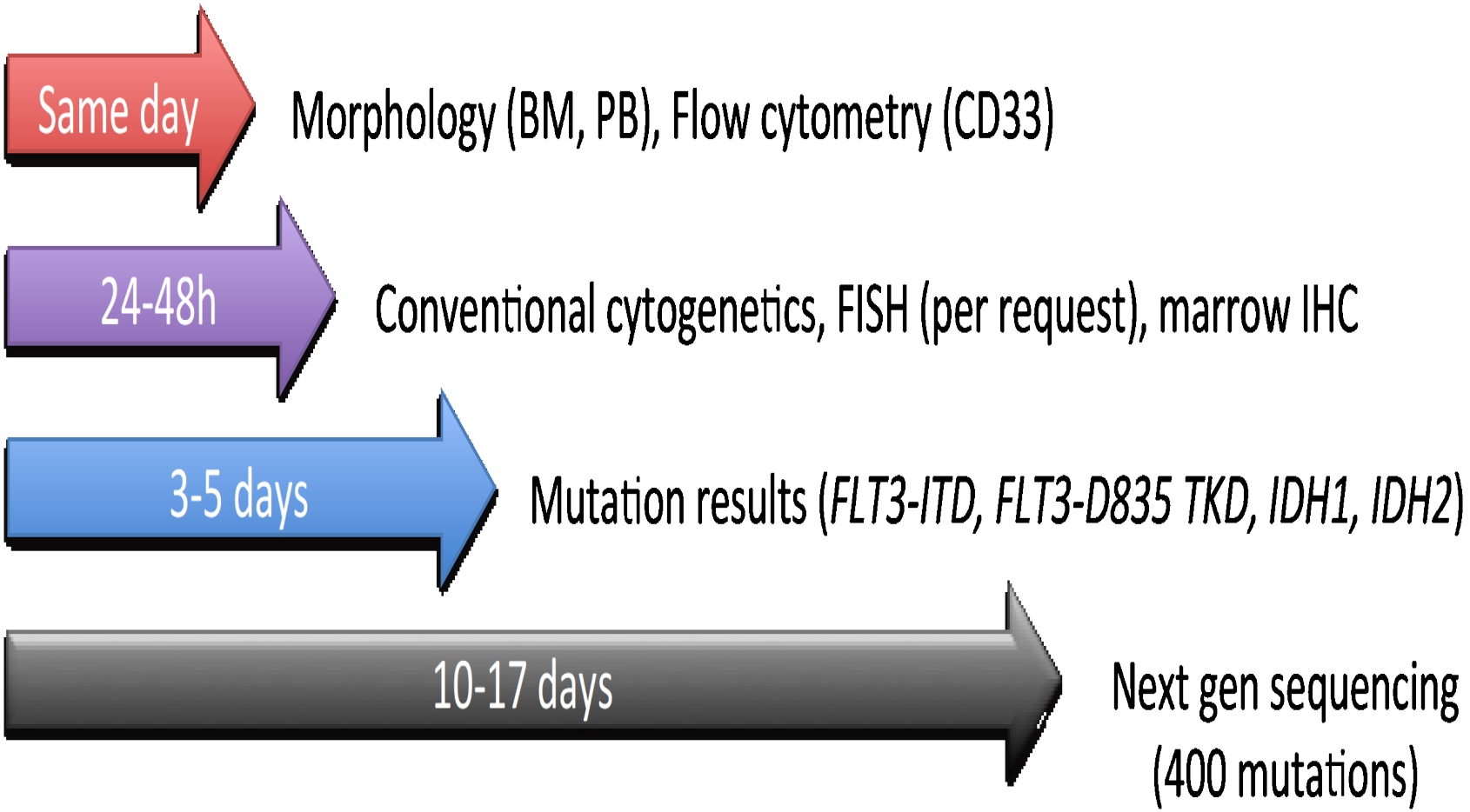
Diagnostic Workup for AML in 2021



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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Genome Sequencing as an Alternative to Cytogenetic Analysis in Myeloid Cancers

N Engl J Med 2021;384:924-35.
DOI: 10.1056/NEJMoa2024534

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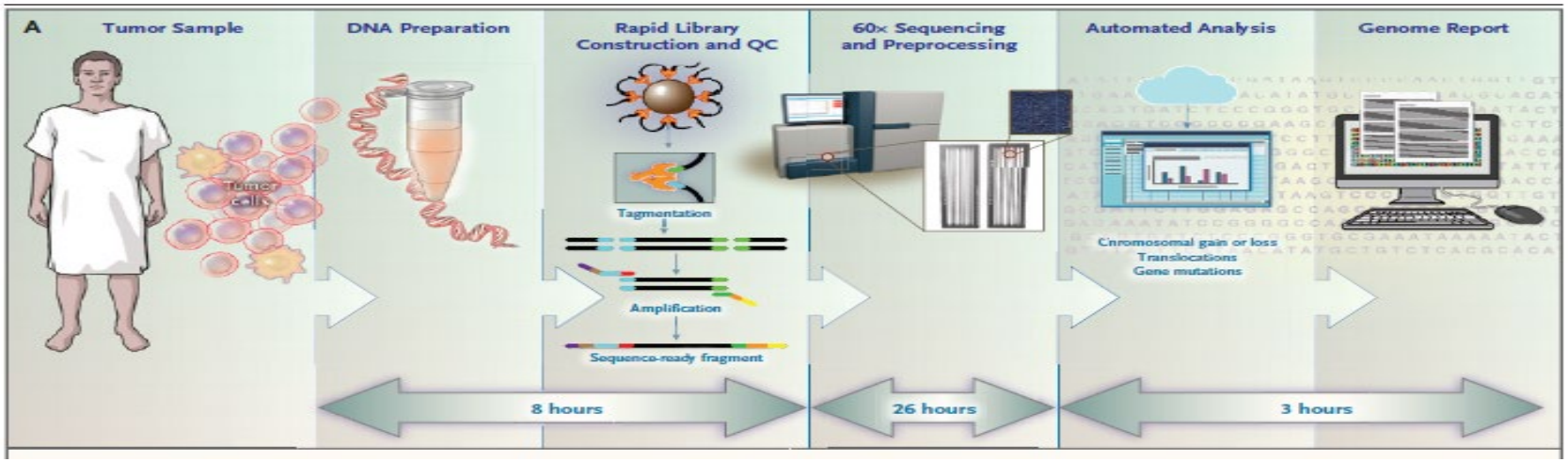
Workflow and processing time for each step of WGS and Cost



Estimated costs for current tests: $2000 (CG and targeted molecular test)
Rough cost range for WGS: $1284-$ 2523

Duncavage E et al. NEJM 2021

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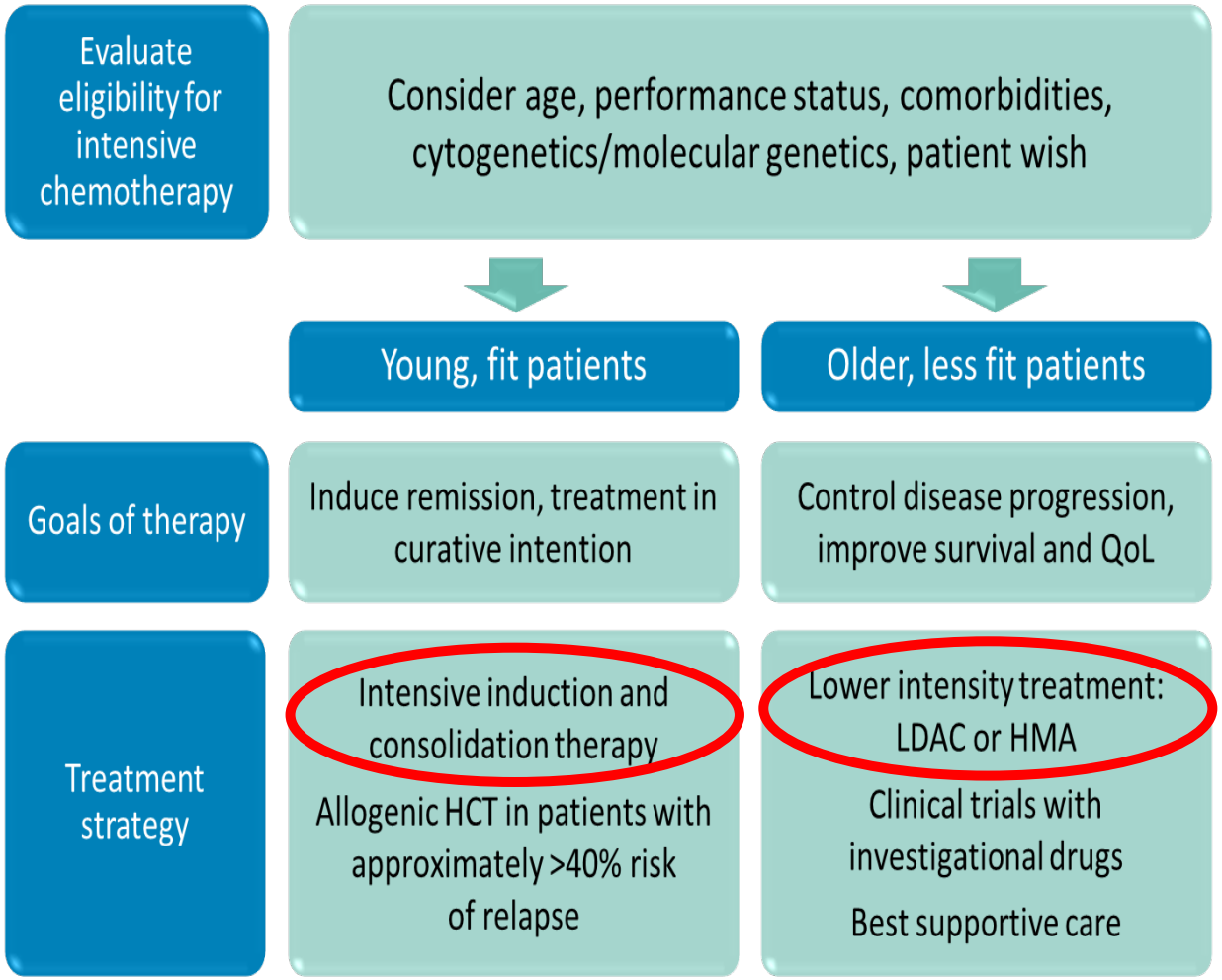
Algorithm of AML Therapy (*circa* 2017)



Dohner et al. Blood 2017

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Changing paradigm of AML treatment

Induction treatment	• Cytotoxic chemotherapy • Hypomethylating agents • Targeted agents
Consolidation	• High dose cytarabine • Allogeneic HCT

Maintenance (with or without HCT)	• Targeted agents
	• Hypomethylating agents
	  • Iv or Sc Decitabine/ Azacitidine
	  • Oral Azacitidine

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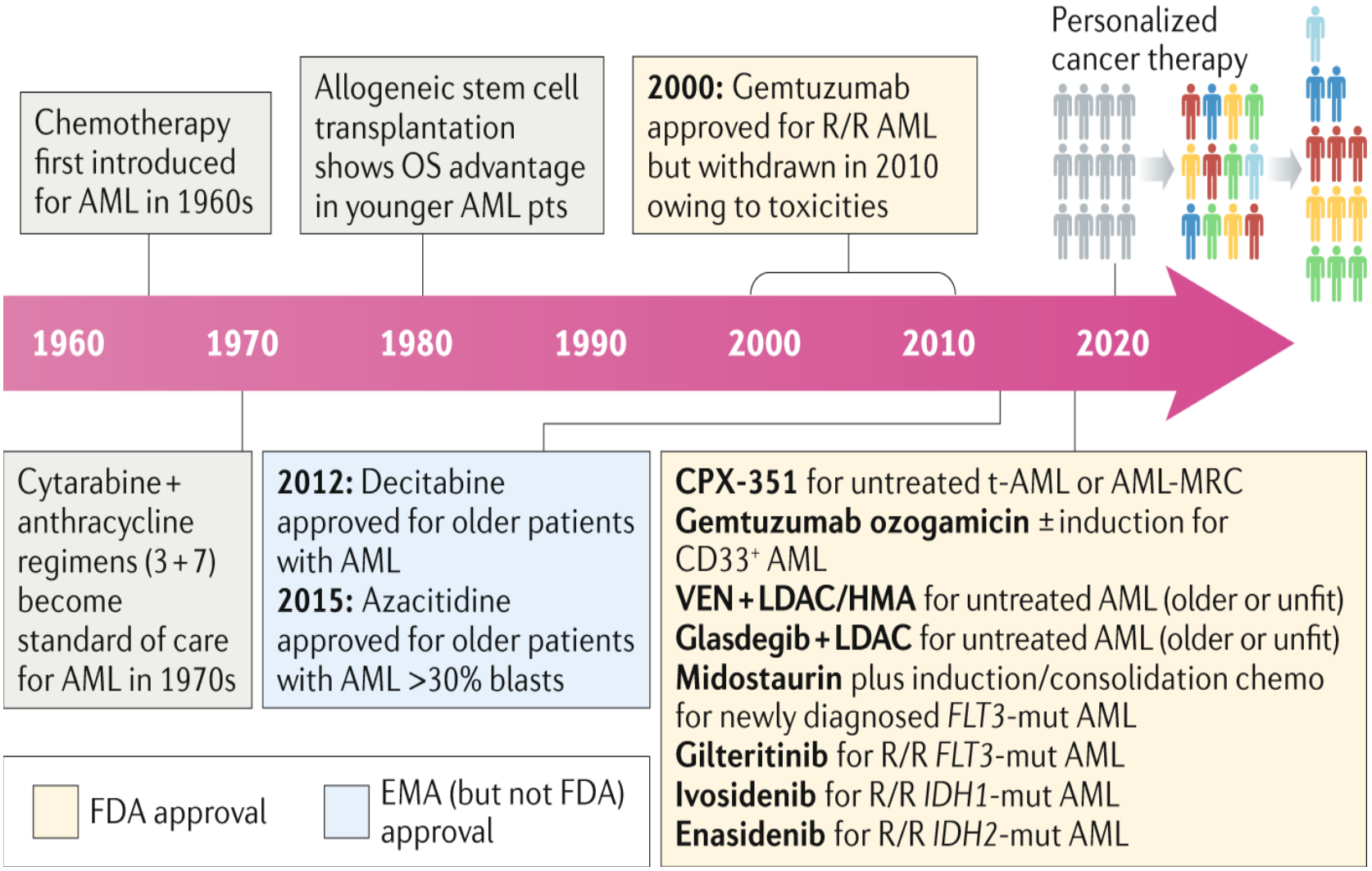
Drugs for treatment of AML



DiNardo and Perl. Nat Rev Clin Onc 2019

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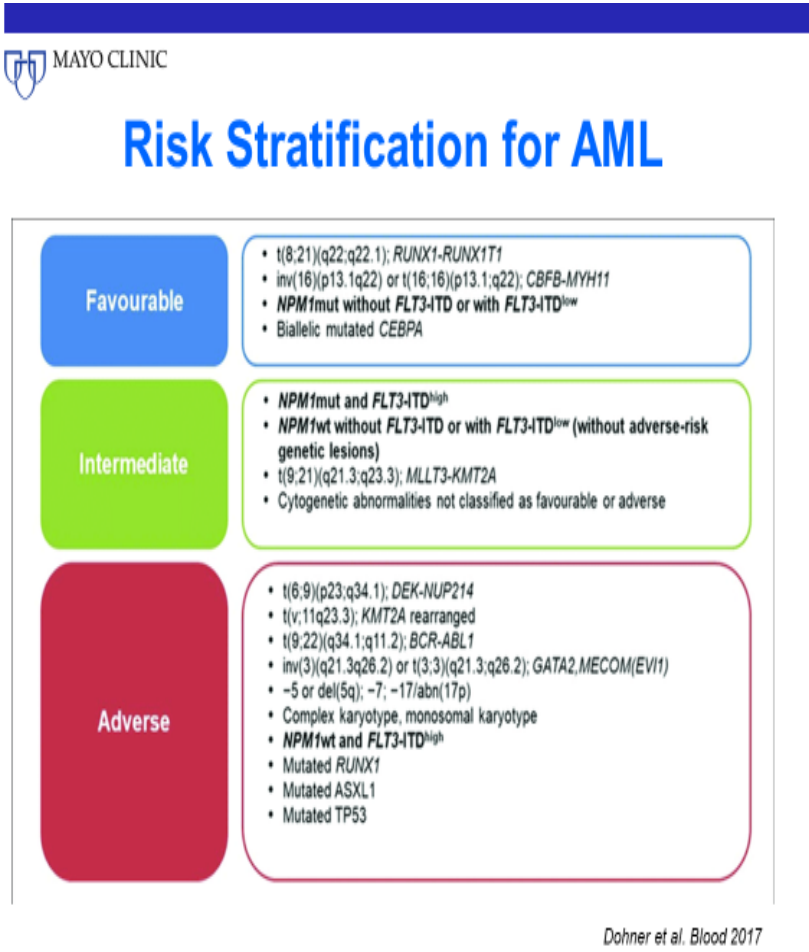
Patient case 1

- 60y/M with h/o Crohn's disease found to have a WBC of 43K with Blasts at 15K, Hb of 10.2 and platelets of 41 at annual labs
- BM biopsy showed 99% cellularity with 73% blasts.
  - Cytogenetics and FISH were normal
  - NGS showed FLT3 ITD (allelic ratio 0.3)
- Induction chemo with 7+3 with idarubicin and cytarabine with midostaurin from D8 to D21
  - D21 marrow showed no e/o AML
  - Recovery marrow: hypocellular with 3% blasts ; FLT3 +ve



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Patient case 1 (contd)-

- Received one cycle of consolidation with high dose cytarabine and midostaurin
- Underwent 10/10 Matched Unrelated donor hematopoietic cell transplant
- Enrolled on BMT CTN 1506 study for Gilteritinib maintenance post HCT
- 15 months out from HCT-doing well

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FLT 3 POSITIVE AML

- Newly Diagnosed AML
- Relapsed Refractory AML
- Maintenance post allogeneic HCT

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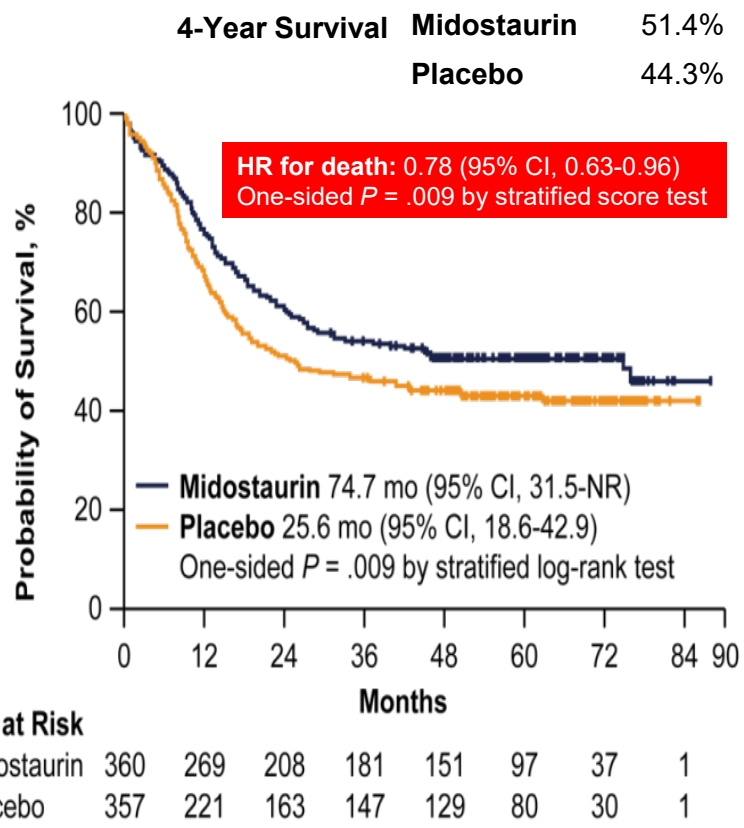
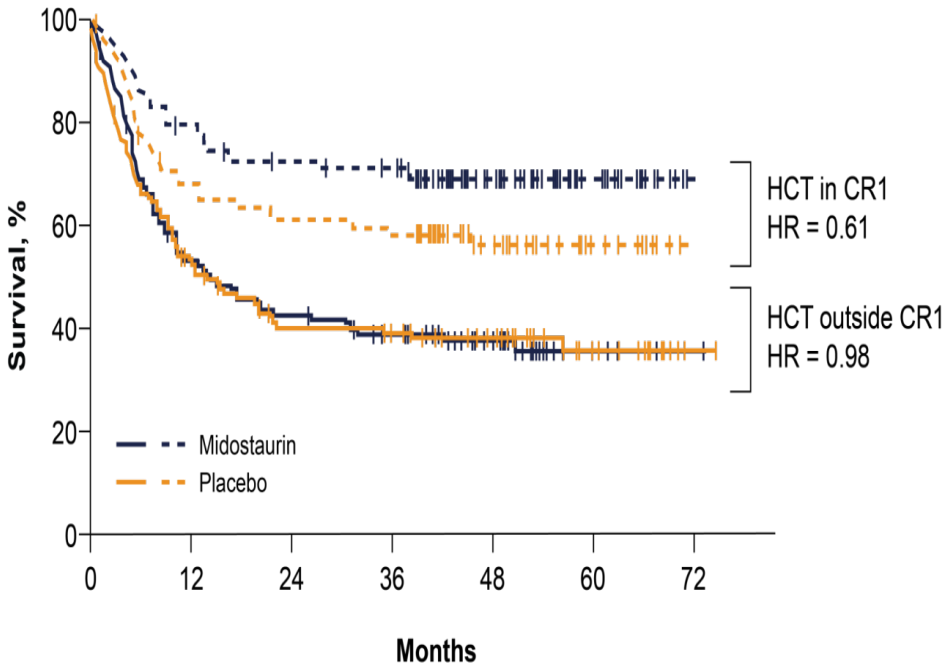
RATIFY Trial: Midostaurin plus Chemotherapy for AML with a *FLT3* Mutation

All Patients[1]



Transplanted Patients[2]



Stone et al. NEJM 2017

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FLT3 inhibitors in upfront setting

- **Phase I study: Gilteritinib plus induction and consolidation chemotherapy**
  - **well tolerated in patients with newly diagnosed AML**
- **PrE0905: A Randomized Trial of Gilteritinib vs Midostaurin in FLT3 Mutated Acute Myeloid Leukemia**
- **QUANTUM-First: Ph III randomized study of 7+3 vs. 7+3 +Quizartinib**

Pratz et al. ASH Abstract 2020

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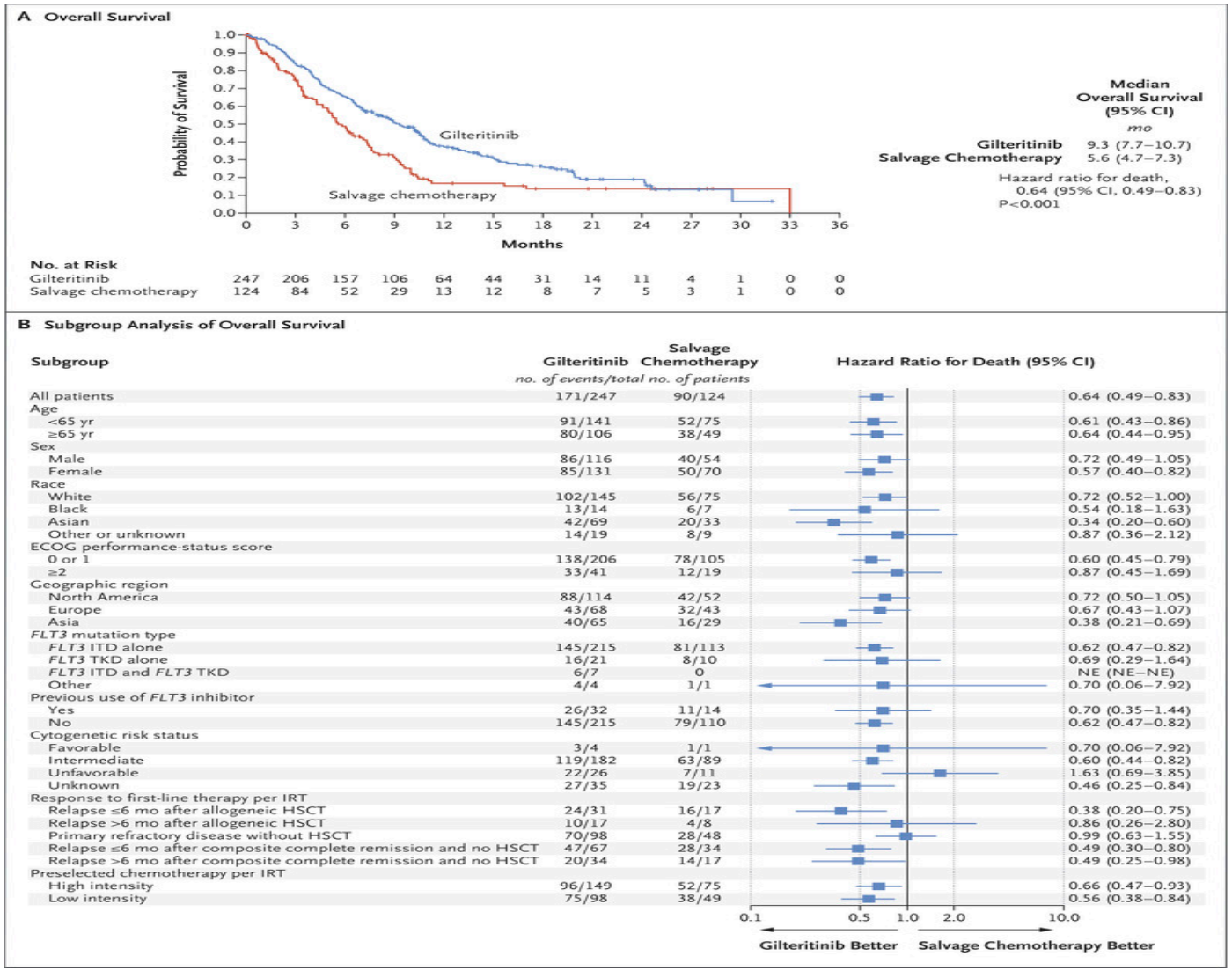
ADMIRAL Trial: Gilteritinib vs. Salvage Chemo in Relapsed AML



Perl et al. NEJM 2019

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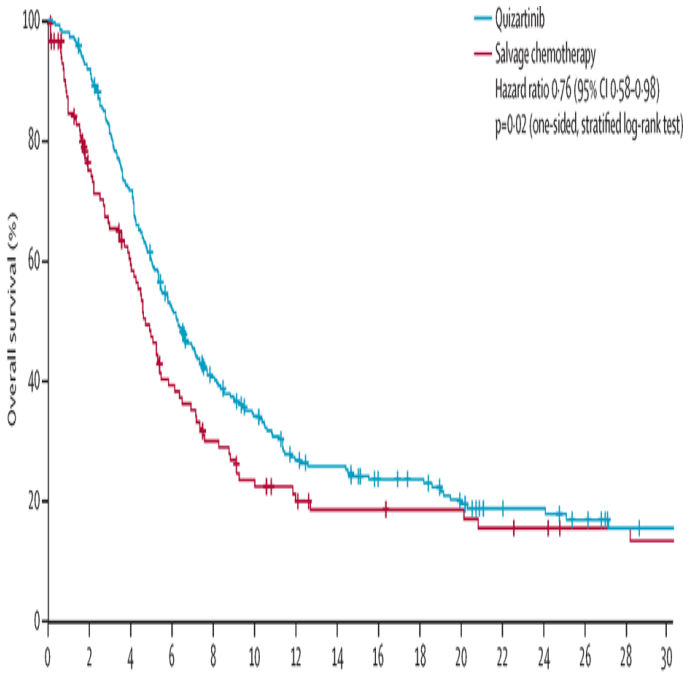
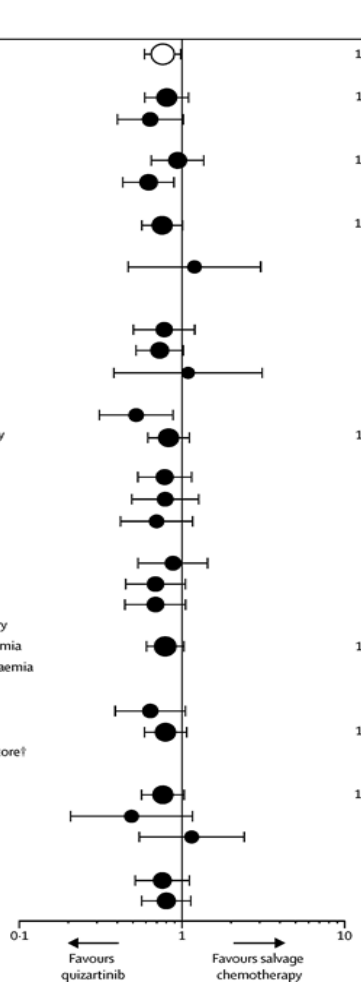
QuANTUM-R: Quizartinib vs. salvage chemo in relapsed/ refractory AML



Number at risk (number censored)

Quizartinib	245 (0)		224 (1)		173 (3)		122 (6)		89 (13)		71 (17)		53 (20)		48 (23)		38 (29)		36 (31)		27 (34)		20 (40)		20 (40)		16 (42)		11 (46)		10 (47)
Salvage chemotherapy	122 (0)		77 (18)		59 (20)		38 (21)		28 (22)		21 (23)		15 (26)		13 (27)		13 (27)		12 (28)		12 (28)		10 (28)		9 (29)		7 (31)		7 (31)		6 (31)



	Quizartinib		Salvage chemotherapy		Hazard ratio (95% CI)
	n/N	Median overall survival (95% CI), months	n/N	Median overall survival (95% CI), months	
Intention-to-treat population	190/245	6·2 (5·3–7·2)	86/122	4·7 (4·0–5·5)	0·76 (0·59–0·98)
Age					
<65 years	134/180	7·0 (5·9–8·2)	60/89	5·0 (4·0–7·1)	0·81 (0·59–1·09)
≥65 years	56/65	4·7 (4·1–6·3)	26/33	3·9 (1·8–5·2)	0·64 (0·40–1·02)
Sex					
Female	109/132	6·0 (4·9–7·1)	38/58	4·9 (4·0–8·8)	0·94 (0·65–1·36)
Male	81/113	6·9 (5·1–8·5)	48/64	4·5 (3·0–5·4)	0·62 (0·43–0·89)
Race					
White	146/184	6·3 (5·3–7·3)	69/93	4·7 (4·0–5·8)	0·75 (0·57–1·01)
Black or African-American	5/9	NA	3/3	NA	NA
Asian	17/24	7·9 (6·1–10·5)	6/16	8·7 (0·8–NR)	1·19 (0·47–3·04)
Other	5/9	NA	0/2	NA	NA
Region					
North America	79/100	6·5 (5·0–8·5)	28/41	4·6 (2·5–7·3)	0·78 (0·50–1·20)
Europe and Australia	99/127	5·8 (4·7–7·0)	53/68	4·7 (3·7–5·4)	0·73 (0·52–1·02)
Asia	12/18	9·0 (4·5–10·8)	5/13	8·8 (0·1–NR)	1·09 (0·38–3·12)
Preselected salvage therapy					
Low-intensity chemotherapy	45/57	5·0 (4·2–6·4)	22/29	3·7 (1·6–4·6)	0·52 (0·31–0·88)
High-intensity* chemotherapy	145/188	6·6 (5·5–7·9)	64/93	5·4 (4·3–7·2)	0·83 (0·62–1·11)
Response to previous therapy					
Relapsed, no HSCT	86/109	6·5 (5·0–8·1)	39/54	4·7 (2·5–7·2)	0·78 (0·53–1·14)
Refractory	56/80	7·9 (5·5–10·4)	25/41	5·4 (4·2–9·2)	0·79 (0·49–1·26)
Relapsed, post-HSCT	48/56	5·1 (3·5–5·8)	22/27	4·0 (2·2–4·9)	0·70 (0·42–1·16)
FLT3-ITD VAF					
3% to ≤25%	47/66	7·2 (6·0–11·4)	24/37	6·1 (4·6–8·8)	0·88 (0·54–1·44)
>25% to ≤50%	67/86	5·7 (4·5–7·1)	32/42	4·7 (2·1–7·6)	0·69 (0·45–1·05)
>50%	74/90	5·4 (4·1–7·3)	30/43	3·5 (1·9–4·9)	0·69 (0·45–1·05)
Acute myeloid leukaemia history					
De novo acute myeloid leukaemia	179/229	6·2 (5·3–7·2)	79/114	4·7 (4·0–5·5)	0·79 (0·61–1·03)
Secondary acute myeloid leukaemia	11/16	NA	7/8	NA	NA
Previous allogeneic HSCT					
Yes	51/60	5·3 (3·5–6·0)	23/28	4·0 (2·2–4·9)	0·64 (0·39–1·05)
No	139/185	6·9 (5·8–8·4)	63/94	5·2 (4·1–7·2)	0·79 (0·59–1·07)
Acute myeloid leukaemia risk score†					
Favourable	10/12	NA	6/8	NA	NA
Intermediate	149/191	6·2 (5·3–7·1)	59/81	4·6 (3·8–5·4)	0·76 (0·56–1·03)
Unfavourable	14/23	9·4 (4·2–27·1)	9/14	5·8 (1·0–8·8)	0·49 (0·21–1·16)
Unknown	17/19	4·1 (3·1–9·0)	12/19	4·9 (1·3–20·8)	1·15 (0·55–2·41)
Blast count at baseline					
Less than median	90/124	7·2 (6·1–9·5)	37/52	5·3 (4·0–8·3)	0·76 (0·52–1·11)
Median or above	99/119	5·3 (4·2–6·6)	47/68	4·6 (2·7–5·8)	0·80 (0·57–1·14)

Cortes et al. Lancet Oncol 2019

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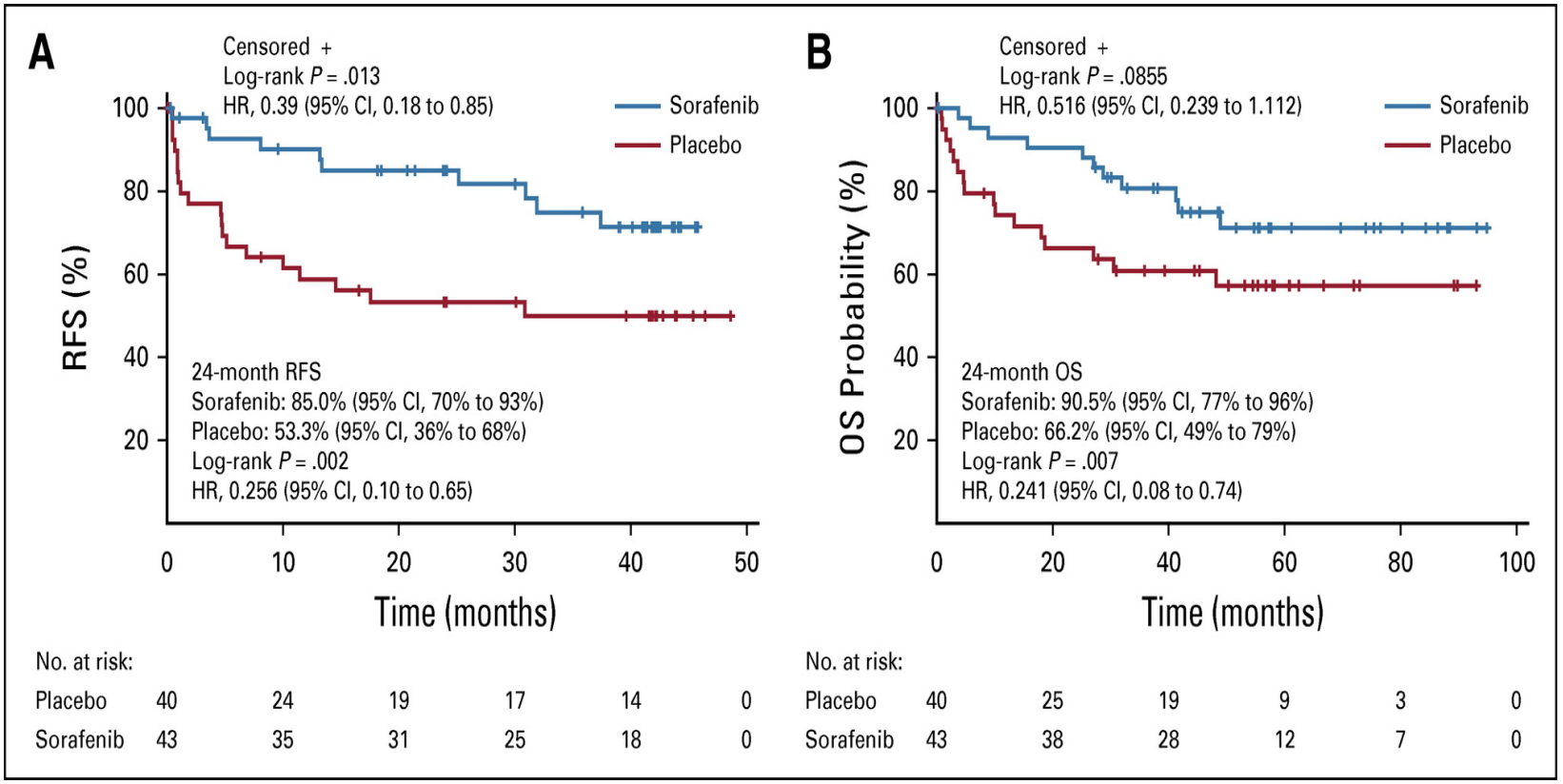
SORMAIN Trial: Sorafenib Maintenance After Allogeneic HCT for FLT3 AML



Burchert et al. JCO 2020

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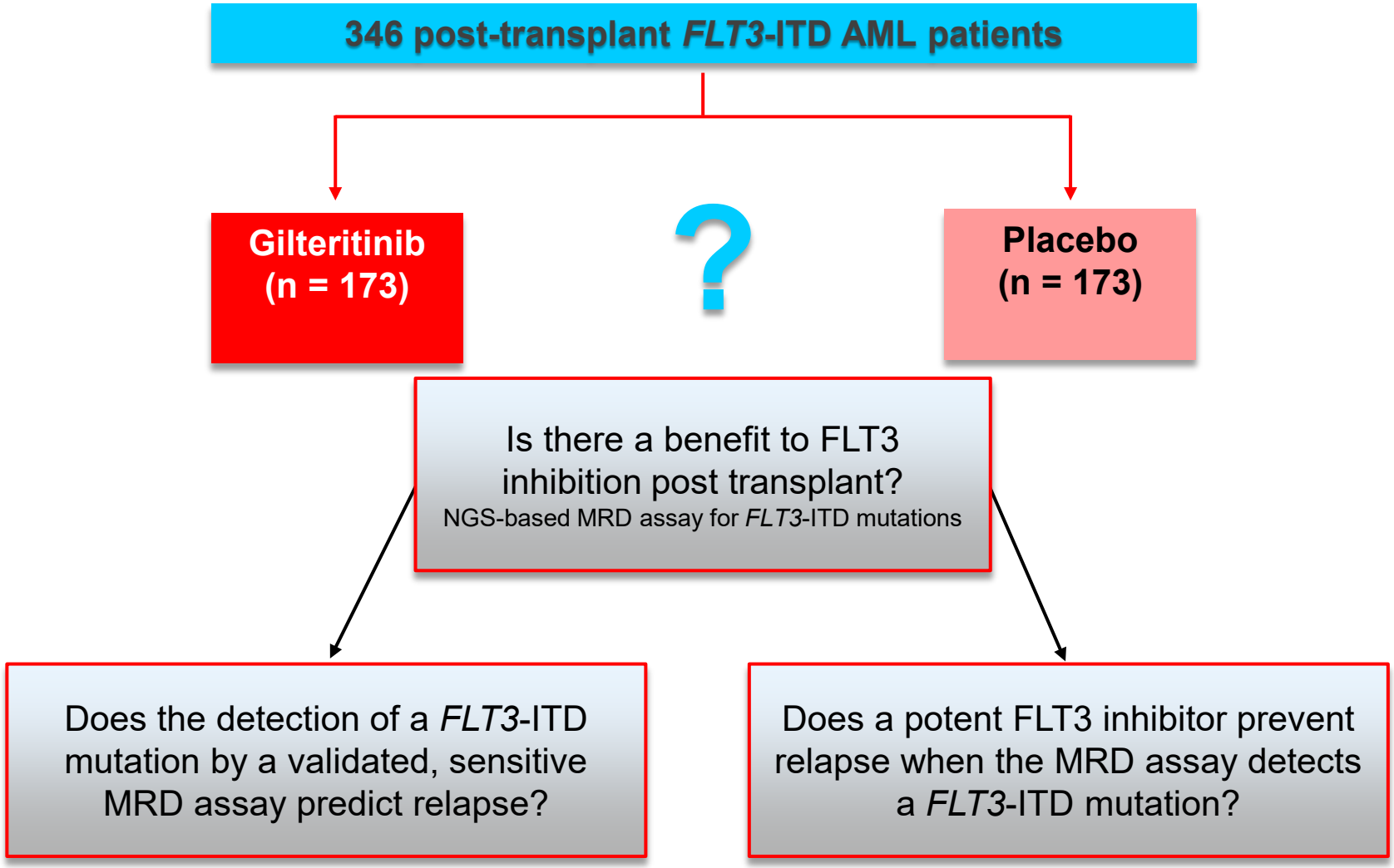
BMT-CTN 1506/Morpho Trial



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Patient case 2

- 73 y/o M with a h/o Atrial fibrillation, HTN, DM II, and GERD diagnosed with AML with 50% blasts
  - Cytogenetics-complex karyotype
  - NGS with p53 and KRAS
- Critically ill at diagnosis-intubated for acute respiratory failure, A Fib with RVR
- Options discussed
  - Supportive care
  - Hypomethylating agents (5 days vs. 10 days)+/- venetoclax
  - Low dose cytarabine+ venetoclax
  - Low dose cytarabine + Glasdegib

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Patient case 2 (contd)-

- Started on decitabine; venetoclax ordered
- Multiple complications with sepsis, renal failure requiring dialysis, continued ventilator dependent respiratory failure
- Despite aggressive care, he deteriorated and was made comfort care

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POOR RISK AML (COMPLEX KARYOTYPE/ TP53)/ ELDERLY AML

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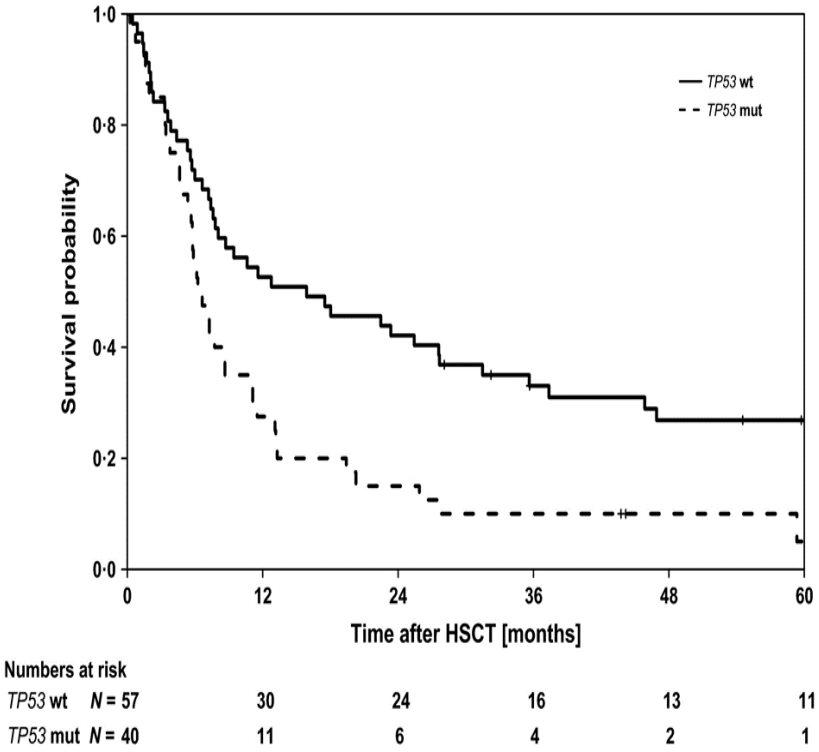
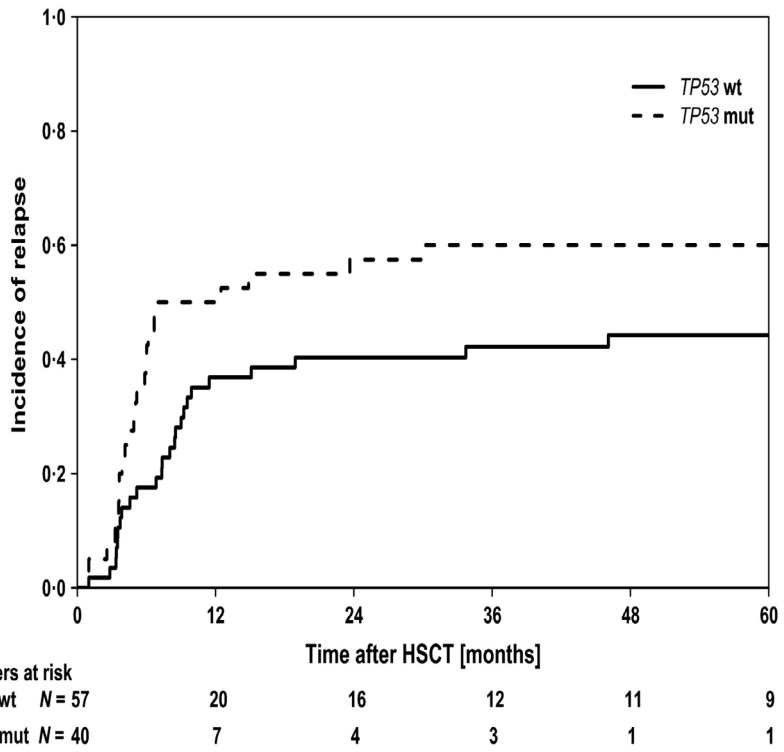
TP53- The villain in the AML drama!



Numbers at risk						
TP53 wt	*N* = 57	30	24	16	13	11
TP53 mut	*N* = 40	11	6	4	2	1



Numbers at risk						
TP53 wt	*N* = 57	20	16	12	11	9
TP53 mut	*N* = 40	7	4	3	1	1

Middeke et al. BJH 2016

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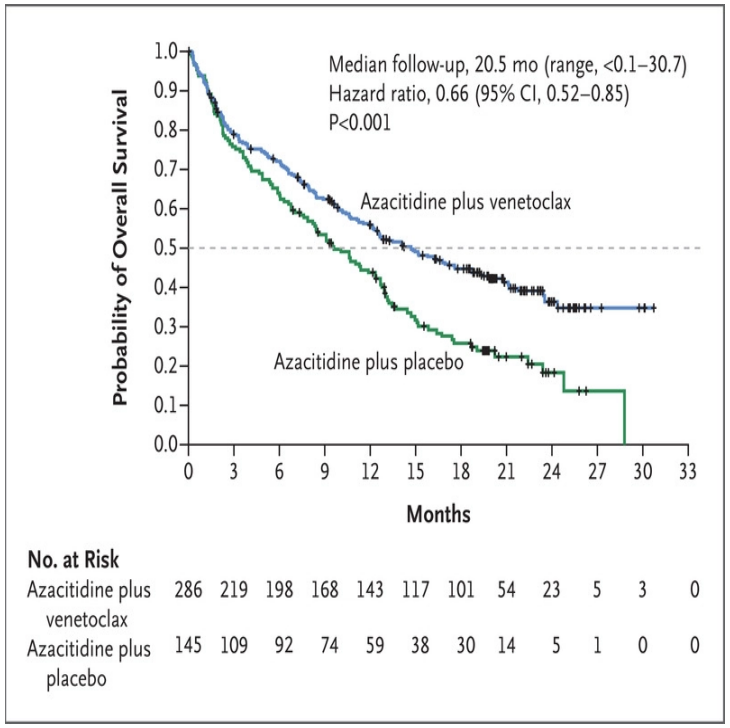
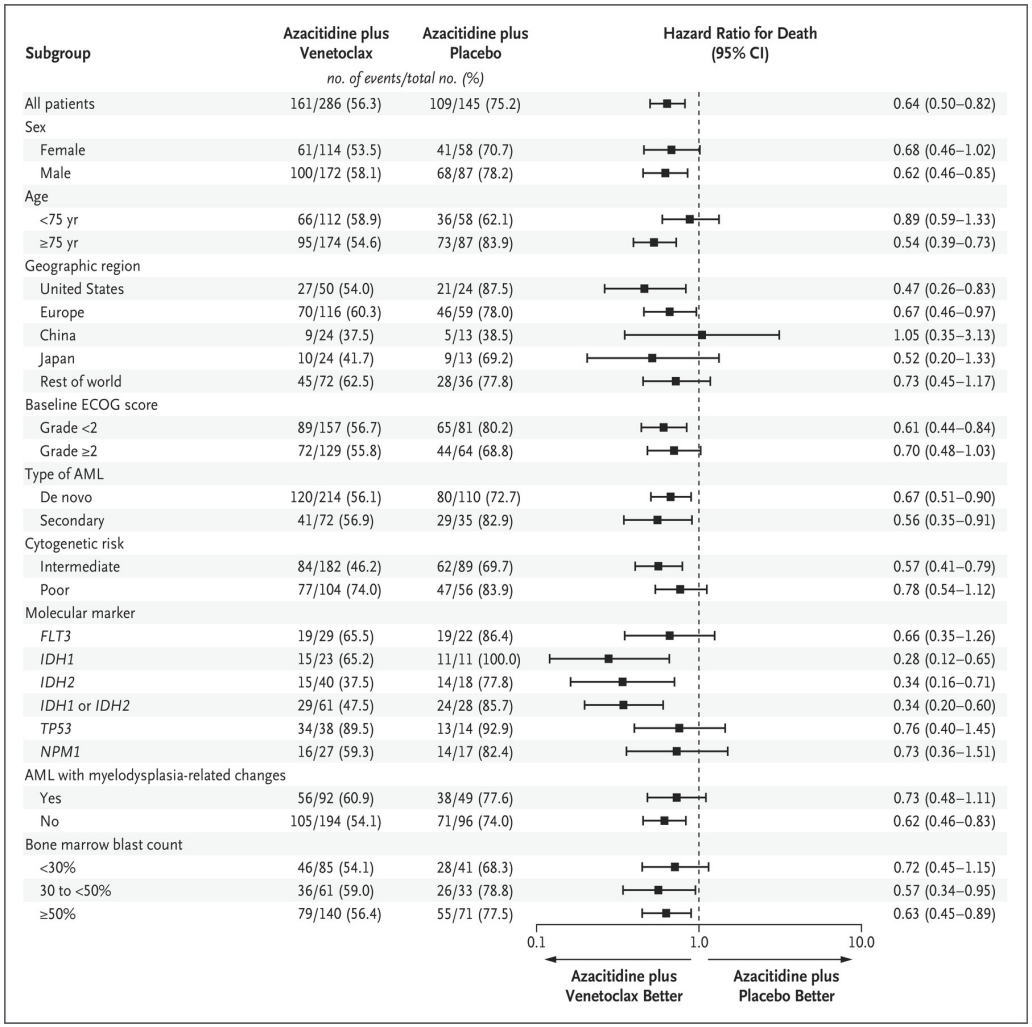
VIALE-A: Azacitidine and Venetoclax in Previously Untreated AML





DiNardo et al. NEJM 2020

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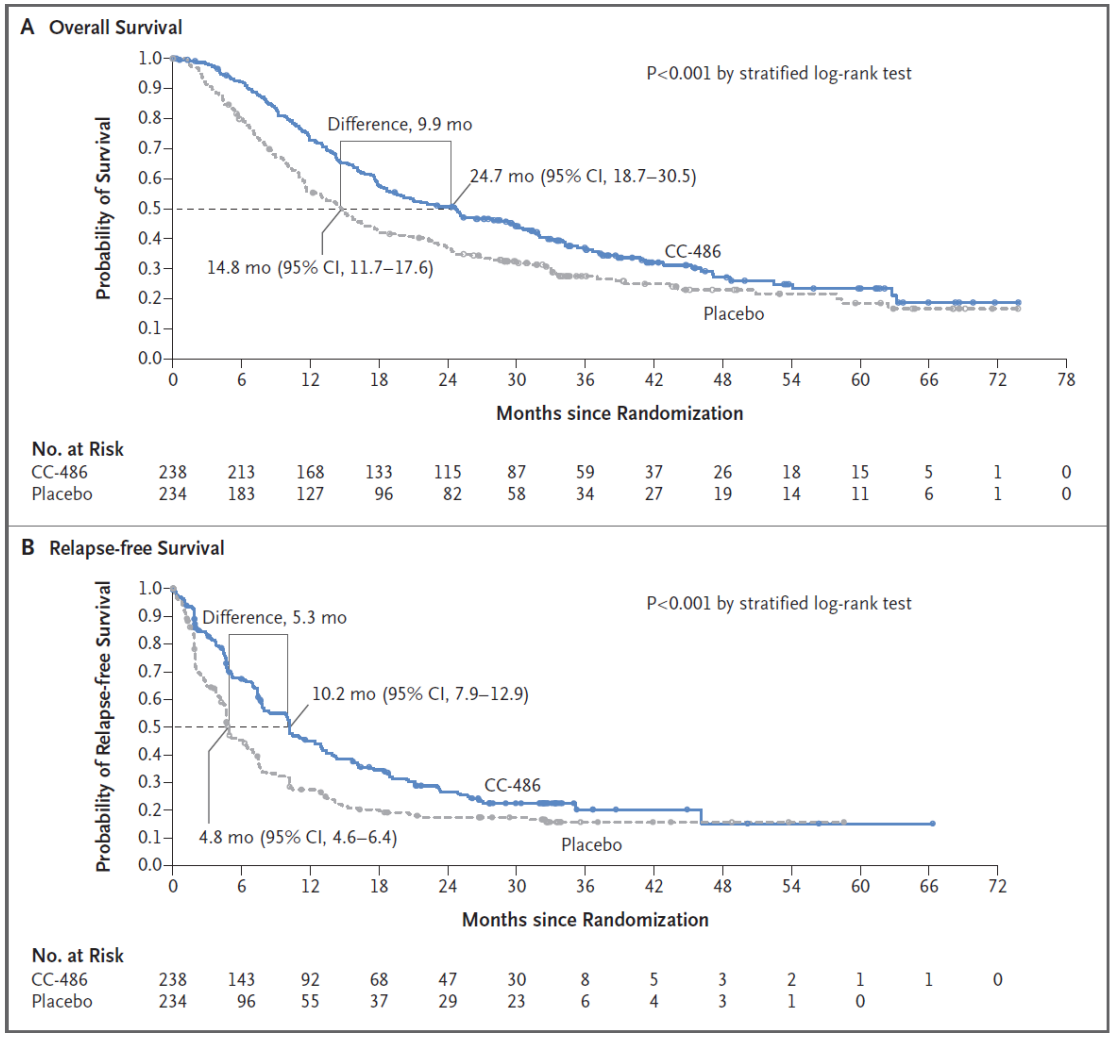
QUAZAR AML-001 trial: Oral Azacitidine maintenance in AML



Wei et al. NEJM 2020

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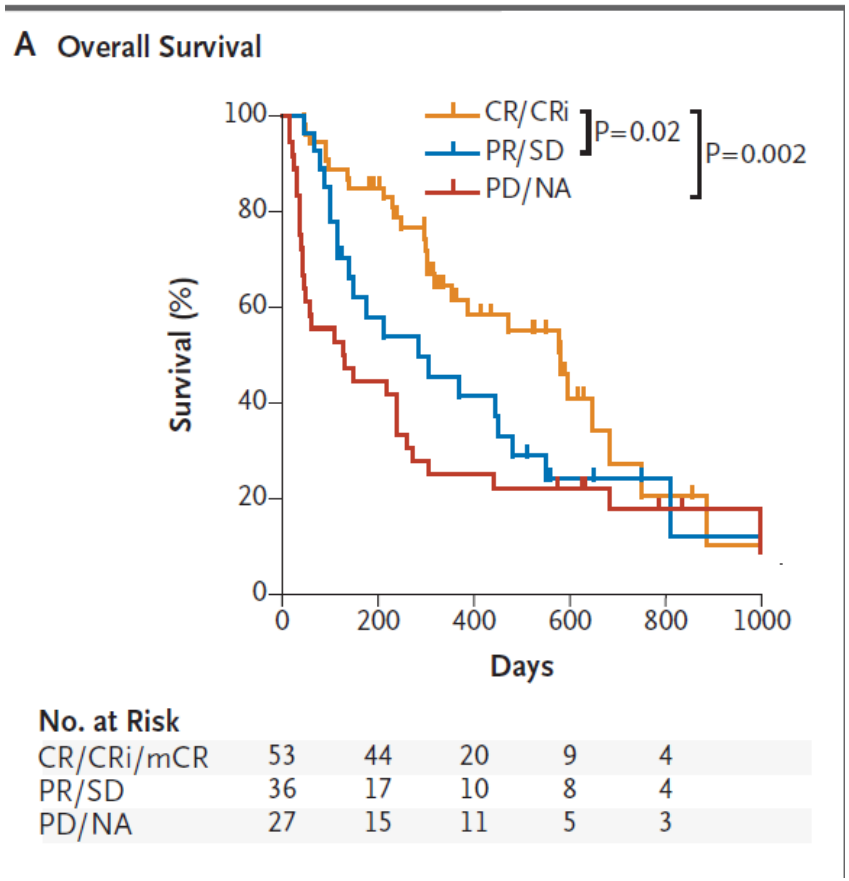
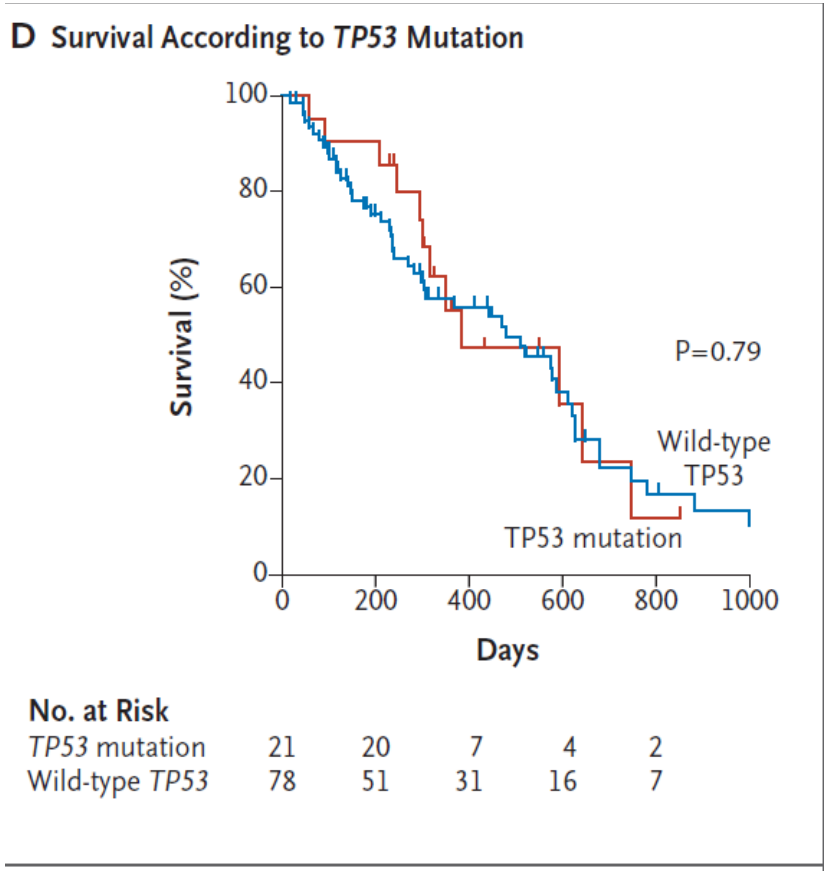
10 day Decitabine





Welch et al. NEJM 2016

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Combination of venetoclax with 10 day Decitabine

- **Pts with TP53mut**
  - **lower rate of CR/CRi at 54% vs. 76% in pts with TP53WT (p=.015)**
  - **lower median OS at 5.2 months vs.19.4 mo in *TP53*^{WT} AML (HR 4.68, p <.001)**

Kim et al. ASH Abstract 2020

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APR-246 in TP53 mutated AML

- **APR-246: novel agent that may restore the transcriptional activity of mutant p53 and induce apoptosis**
- **Ph I/II studies showed CR rates of 60 to 80% with deep molecular remission in CR patients**
- **Phase III trial: APR-246 with azacitidine (AZA) vs. AZA alone in TP53 mutant MDS**
  - **The trial failed to meet its primary endpoint of complete remission rate**
  - **CR rate 53% higher in APR-246 with AZA arm vs. AZA alone, but not statistically significant**

Sallman et al. JCO 2021

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Magrolimab in TP53 mutated AML

- **Magrolimab: monoclonal antibody against CD47 that blocks the "don't eat me" signal used by cancer cells to avoid being ingested by macrophages**
- **Ph I b study: Magrolimab with Aza:**
  - **75% CR+CRi**
  - **6 mo OS 91% in TP53 mutant AML**
- **Ongoing ENHANCE study: A Randomized, Double-blind, Multicenter Study Comparing Magrolimab and Aza Vs. Aza Plus Placebo Higher Risk MDS**

Sallman et al. ASCO abstract 2020

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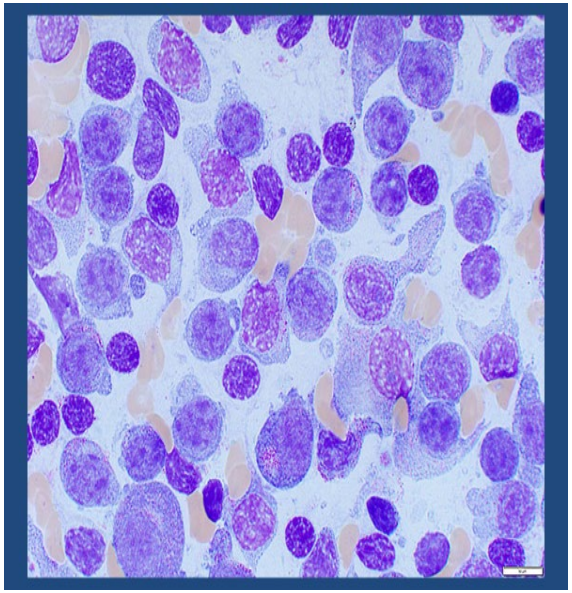
Patient case 3

- 68 y/M with multiple myeloma s/p an autologous HCT; on lenalidomide maintenance
- H/o Type II DM, HTN and Renal dysfunction (creatinine 2)
- BM biopsy for evaluation of cytopenias
  - 29% blasts by flow, AML with MRC
  - Cytogenetics-Normal Male
  - Next generation sequencing- IDH 1 and SRSF2



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Patient case 3 (contd)-

- Options discussed:
  - Induction chemotherapy
  - CPX351
  - Hypomethylating agent+/- venetoclax
- Started on Decitabine d/t poor performance status; continued to have circulating blasts 60 to 70%
- Developed systolic heart failure and sepsis
- Switched to ivosidenib after 2 cycles: response for 2 months followed by rapid increase in WBC count; possible differentiation syndrome
- Declined rapidly-enrolled in hospice

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SECONDARY AND THERAPY RELATED AML/ AML WITH TARGETABLE MUTATIONS

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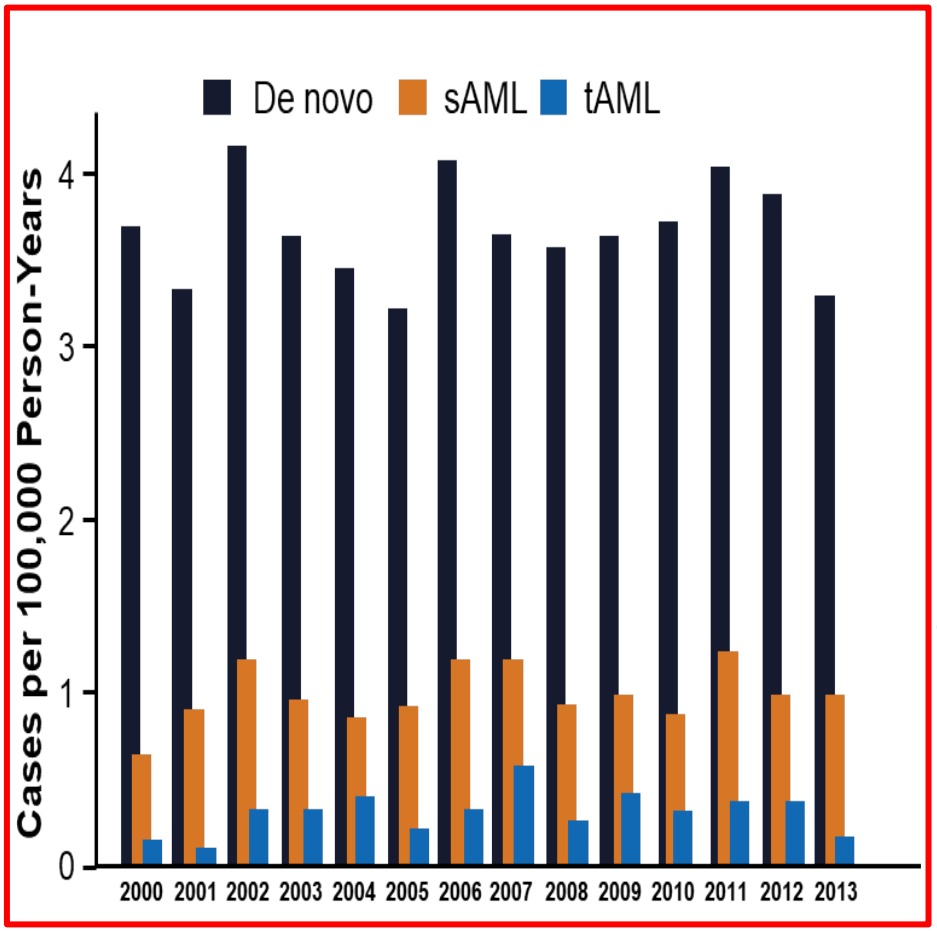
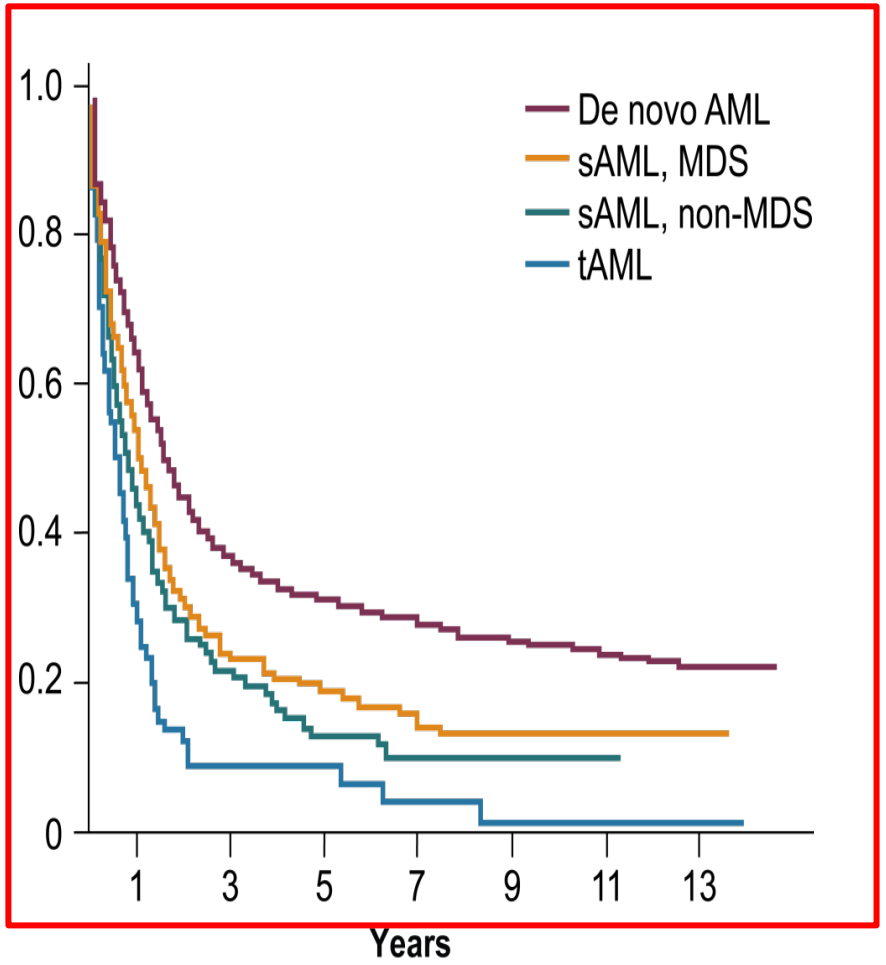
Need for Additional Options in Secondary and Treatment-Related AML





Granfeldt Østgård LS et al. JCO 2015

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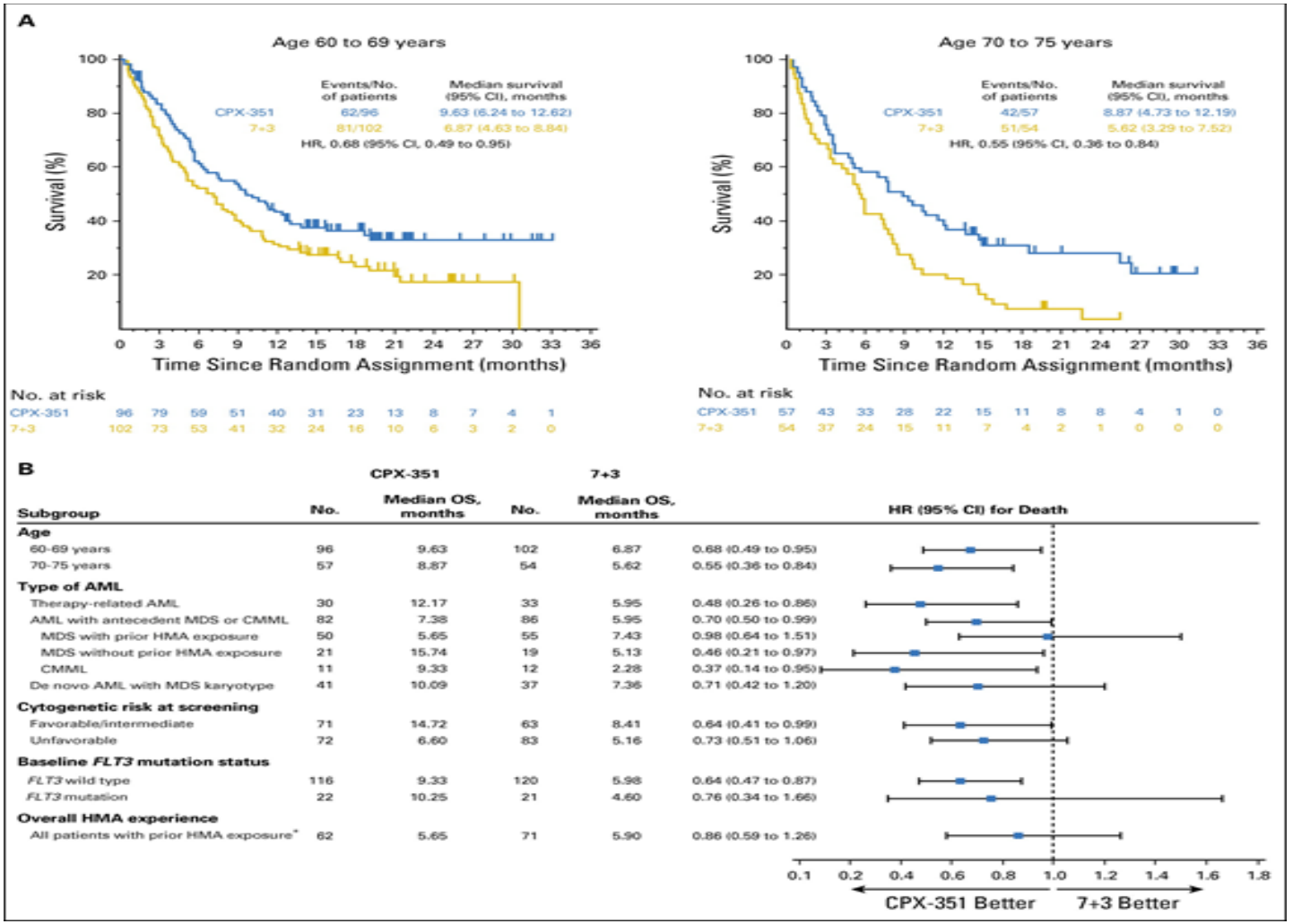
CPX-351 vs. 7+3 in Older Patients With Newly Diagnosed Secondary AML



Lancet JE et al. JCO 2018

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IDH1/2 Targeted therapy

- **Ivosidenib and Enasidenib**
  - **monotherapy for the treatment of newly diagnosed (elderly/unfit) and relapsed/refractory IDH1 or IDH2 mutant AML, respectively**
    - **Differentiation syndrome: potentially fatal AE that produces a rapid increase in the differentiation of neutrophils after the removal of the differentiation block in the malignant clone**
    - **managed by discontinuation and treatment with glucocorticoids and/or hydroxyurea**
  - **Ongoing trials adding them to 7+3 for induction in fit patients or hypomethylating agents in older patients**

DiNardo C et al. NEJM 2018
Stein EM et al. Blood 2017

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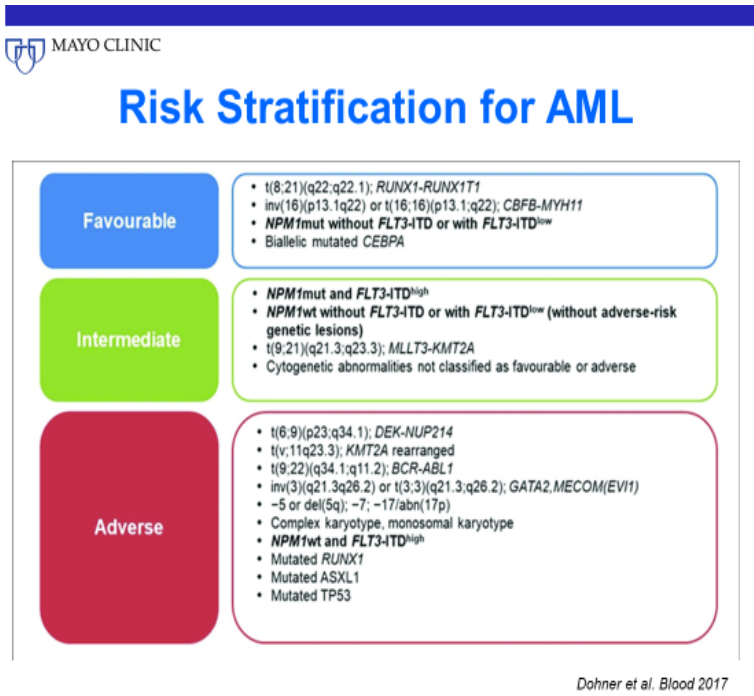
Patient case 4

- 20 y/F with shortness of breath and dry cough
  - CT scan with patchy opacities
  - cytopenic with Platelets 55 and Hb 7.8 with normal WBC
  - BM biopsy showed AML with 24% blasts with t(8;21); RUNX1-RUNX1T1 ; Kit mutation negative
- Plan to treat her with 7+3 +Gemtuzumab Ozogamicin



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FAVORABLE RISK/ CORE BINDING FACTOR AML

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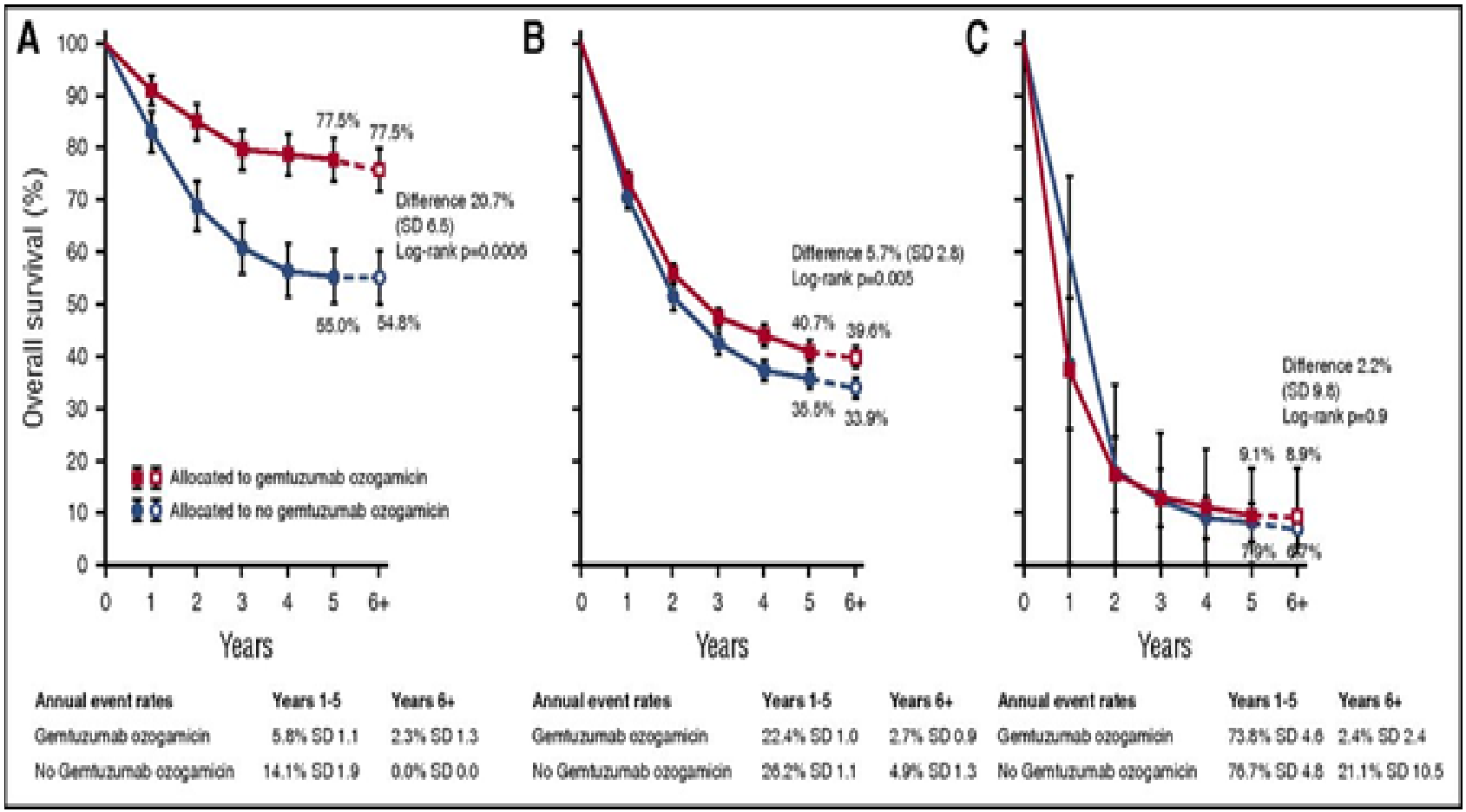
Addition of Gemtuzumab Ozogamicin (CD33 antibody) to induction chemo



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

Hills RK et al. Lancet Oncology 2014

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Consolidation in CBF Leukemias

- **Most patients will not need allogeneic HCT for consolidation**
  - **Possible exceptions:**
    - **Kit mutation +**
    - **MRD+ disease by PCR**
    - **Additional mutations +**
    - **Therapy related CBF AML**
- **Consolidation is usually anthracycline and cytarabine with GO**

Borathakur. Clinical Advances in Hematology & Oncology 2020
Litzow. Haematologica 2020

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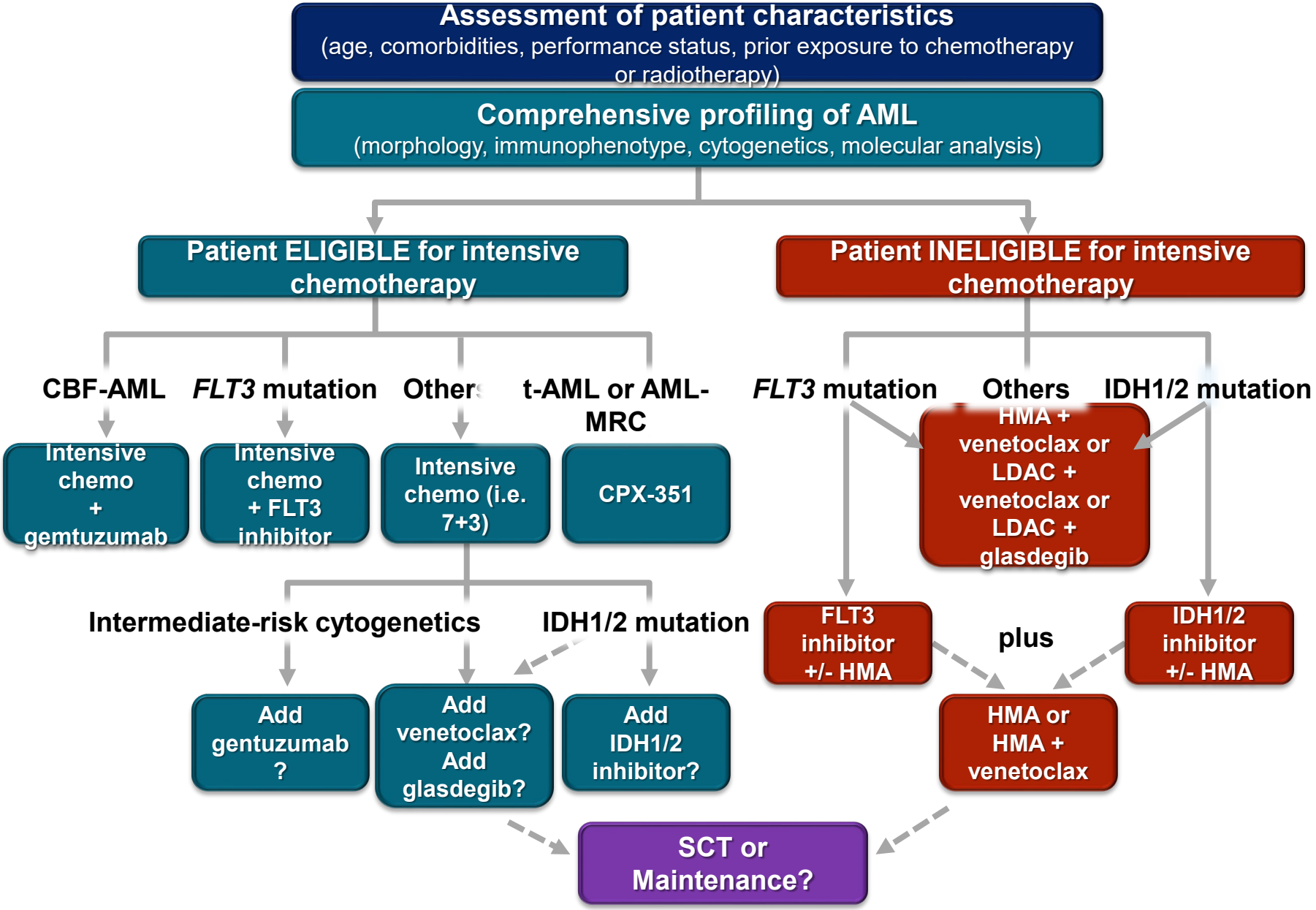
Evolving algorithm for AML



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Summary

- Improvement in outcomes of AML though certain groups still have poor outcomes
- Rapidly evolving diagnostics and therapeutics
  - Combination of conventional chemo + targeted therapies+/- immunotherapy (Bispecific antibodies)+/- cell therapies
- Complicated therapy and requires special expertise
  - Better treated in specialized academic centers
  - Individualized management based on comorbidity and molecular/ genetic subtype

Questions??

Extra slides

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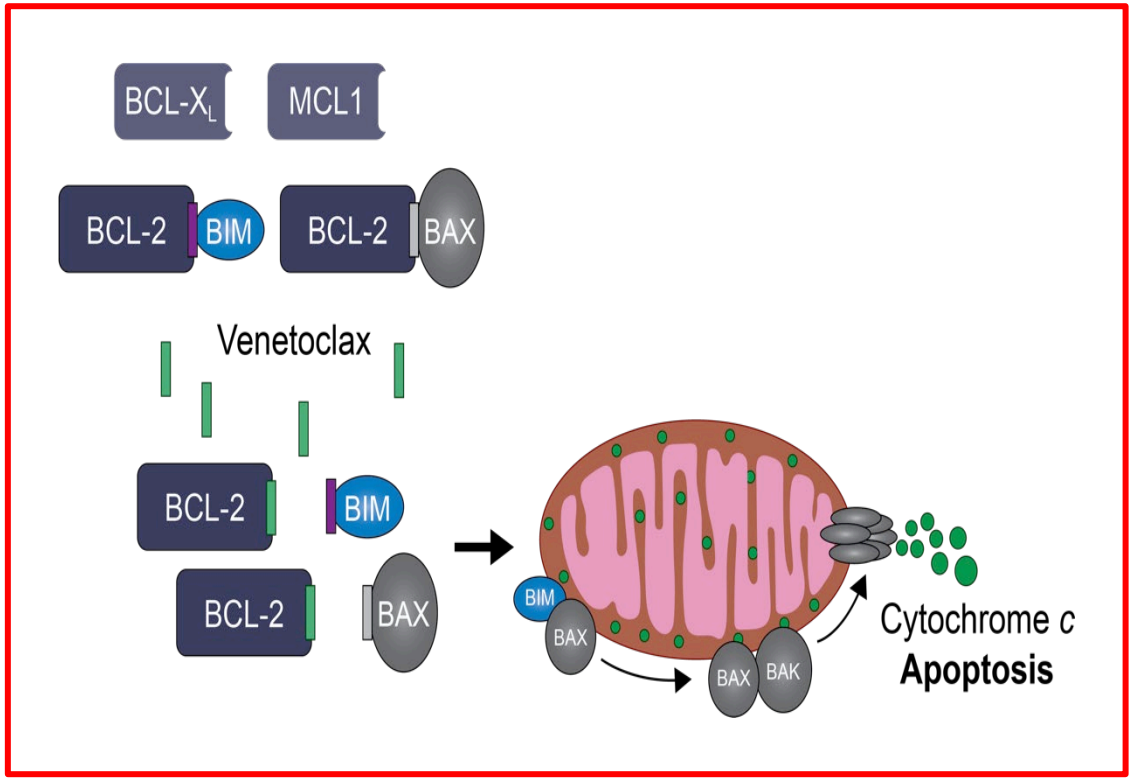
BCL2 in AML

- BCL2 inhibits apoptosis in normal and malignant cells
- BCL2 is overexpressed in AML cells
- Early BCL2 inhibitors (navitoclax) also inhibited BCL_{XL}, which contributed to toxicity (thrombocytopenia)
- BCL2 inhibitor venetoclax is a BH3 mimetic without activity against BCL_{XL}



Konopleva M et al. Cancer Discov. 2016

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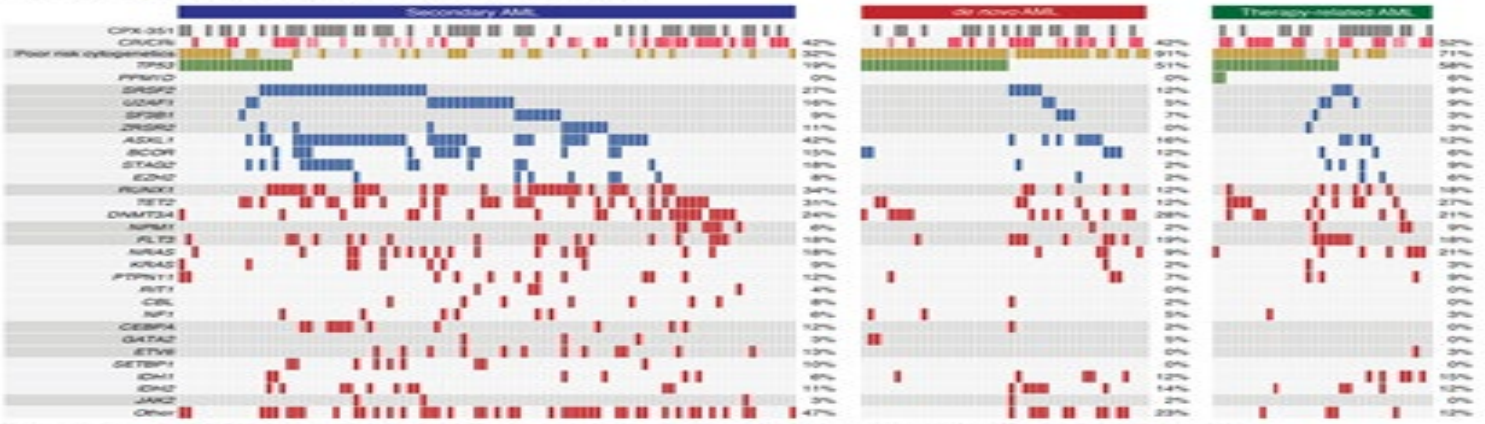
Figure. Frequency of Mutations by AML Subgroups



Nonsynonymous mutations in individual genes as labeled on the left. Mutations are depicted by colored bars and each column represents 1 of the 169 patients included in the analysis.

Table. Outcomes for Patients with the Most Frequently Occurring Mutations[a]

	ASXL1		*DNMT3A*		*RUNX1*		*TET2*		*TP53*	
Outcome	**CPX-351 (n = 30)**	**7+3 (n = 20)**	**CPX-351 (n = 20)**	**7+3 (n = 21)**	**CPX-351 (n = 21)**	**7+3 (n = 22)**	**CPX-351 (n = 26)**	**7+3 (n = 17)**	**CPX-351 (n = 24)**	**7+3 (n = 35)**
CR, n (%)	5 (17)	4 (20)	7 (35)	11 (52)	5 (24)	6 (27)	5 (19)	7 (41)	7 (29)	12 (34)
OR (95% CI)	0.80 (0.19-3.43)		0.49 (0.14-1.72)		0.83 (0.21-3.29)		0.34 (0.09-1.34)		0.79 (0.26-2.43)	
CR+CRi, n (%)	11 (37)	7 (35)	12 (60)	12 (57)	7 (33)	7 (32)	9 (35)	8 (47)	7 (29)	14 (40)
OR (95% CI)	1.08 (0.33-3.50)		1.13 (0.32-3.90)		1.07 (0.30-3.84)		0.60 (0.17-2.08)		0.62 (0.20-1.87)	
Median remission duration,[b] mo	6.37	4.11	9.89	4.32	8.05	3.45	6.37	3.45	8.05	3.45
HR (95% CI)	0.69 (0.18-2.58)		0.33 (0.10-1.06)		0.56 (0.17-1.87)		0.43 (0.13-1.38)		0.63 (0.24-1.65)	
Transplant, n (%)	8 (27)	6 (30)	11 (55)	8 (38)	6 (29)	4 (18)	6 (23)	3 (18)	3 (13)	11 (31)
OR (95% CI)	0.85 (0.24-2.97)		1.99 (0.57-6.90)		1.80 (0.43-7.59)		1.40 (0.30-6.56)		0.31 (0.08-1.27)	
Median OS,[b] mo	9.10	6.29	12.62	5.49	8.87	4.09	9.10	3.68	4.53	5.13
HR (95% CI)	0.67 (0.35-1.27)		0.41 (0.19-0.89)		0.58 (0.30-1.11)		0.47 (0.23-0.93)		1.19 (0.70-2.05)	
Median EFS,[b] mo	1.58	1.41	5.98	3.58	2.00	1.22	1.59	1.64	0.97	1.64
HR (95% CI)	0.79 (0.42-1.48)		0.45 (0.21-0.95)		0.57 (0.30-1.08)		0.93 (0.49-1.77)		1.13 (0.66-1.93)	

[a]Mutations reported for ≥20% of patients overall.
[b]Median remission duration, OS, and EFS are based on Kaplan-Meier estimates.

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Azacitidine Maintenance post HCT

Azacitidine Maintenance after Allogeneic Hematopoietic Stem Cell Transplantation in High Risk AML and MDS Patients: Outcomes of a phase III Randomized Clinical Trial

Screening period:
Days 40-100 after alogeneic transplant.

Patient population:
High risk AML/MDS
CMML
Aged 18-75
CR after allo-HSCT

R
1:1

5-azacitidine 32mg/m2/dayX5

observation

Follow up until:
Completion of 12 cycles of maintenance
Relapse/death
Discontinuation of maintenance

Population:
187 enrolled and randomized:
94 observation
93 5-azacitidine
87 started the 5-azacitidine maintenance
Median number of cycles=4

Statistics:
Primary outcome: RFS
Secondary outcomes: OS, aGvHD and toxicity

Efficacy endpoint	5-azacitidine, n=87	Observation, n=94	HR, 95%CI, p
RFS	2.07 yr	1.28 yr	0.77, 0.51-1.14, 0.19
OS	2.52 yr	3.56 yr	0.84, 0.56-1.28, 0.43

Conclusion:
- 5-azacitidine given as 32 mg/m2/dayX5 did not lead to improved RFS or OS.
- There was no safety concern.

Oran et al. Blood Advances 2020

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Options for relapsed refractory disease

- Salvage chemotherapy
- Gemtuzumab Ozogamicin
- Hypomethylating agents+/-venetoclax
- LDAC with venetoclax
- Targeted agents (if not used earlier)

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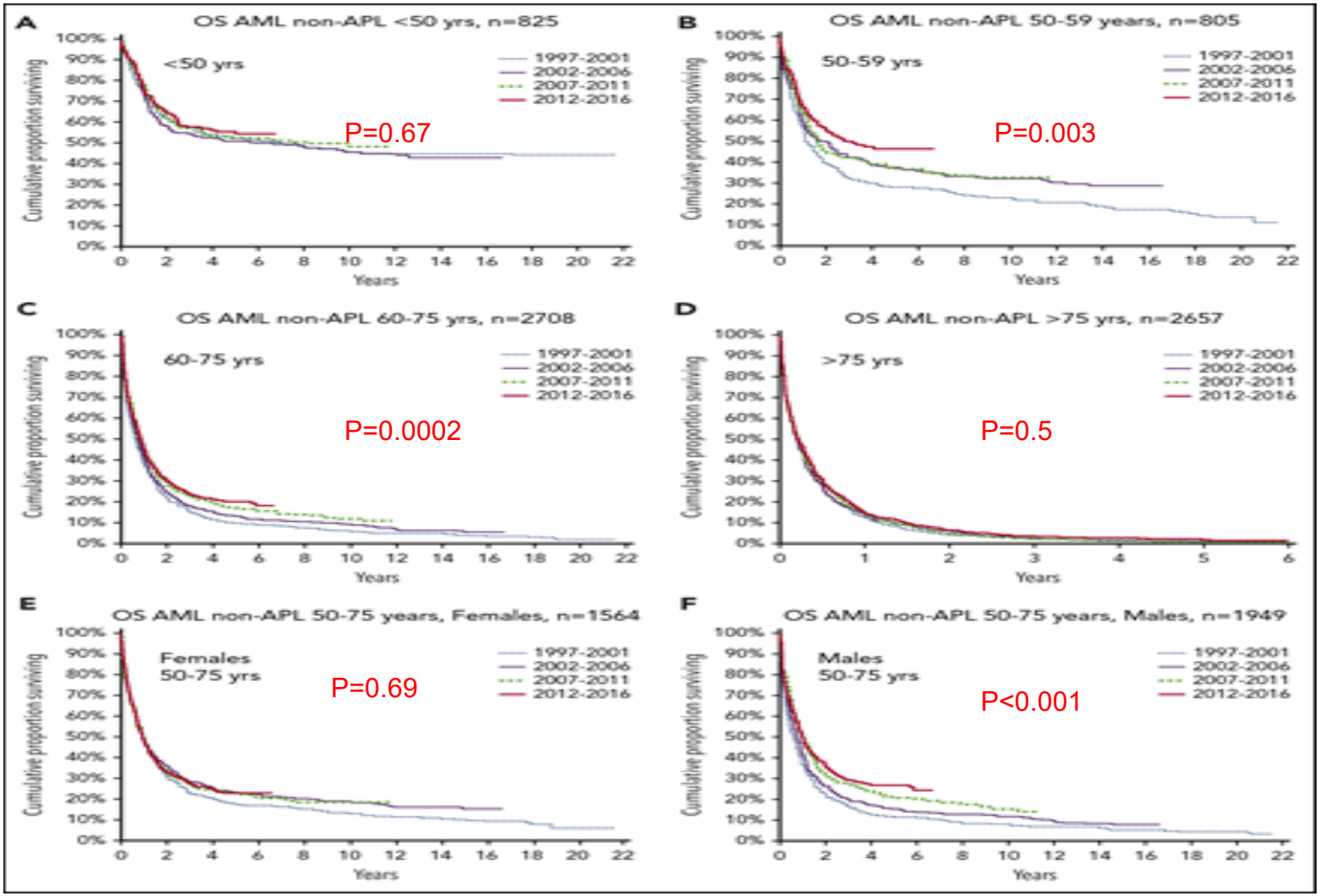
Survival for AML over the years



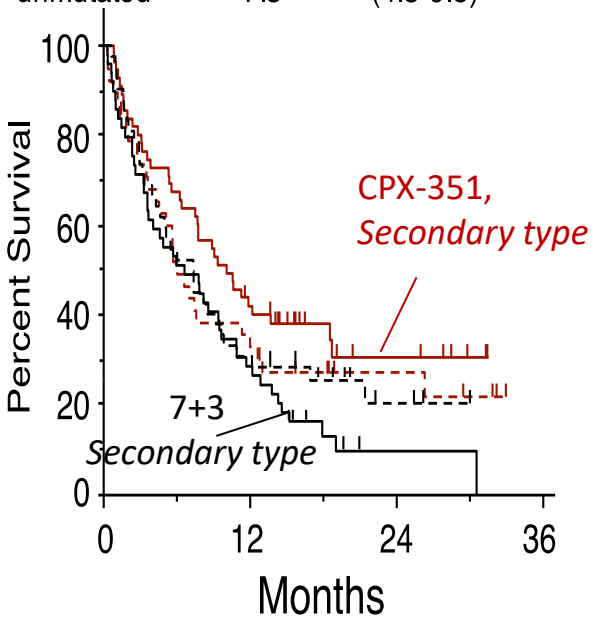
Juliusson et al. Blood 2019

Overall survival in Secondary-type and activated signaling mutations

Secondary-Type

SRSF2, U2AF1, SF3B1, ZRSR2, ASXL1, BCOR, EZH2, STAG2

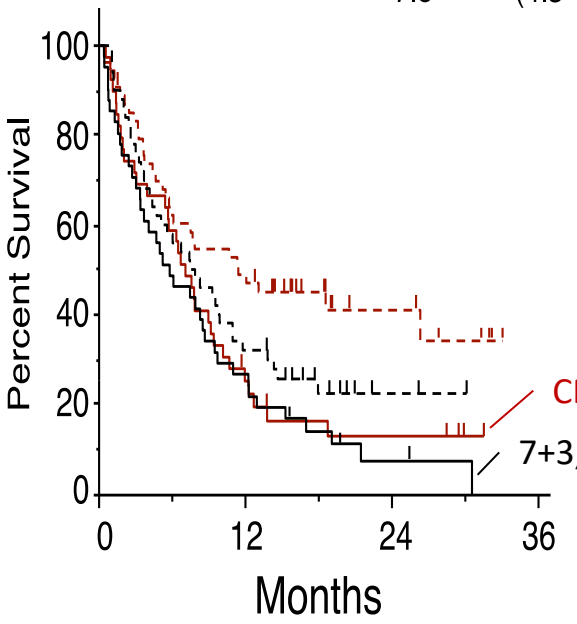
		Median Survival	(95% CI)
CPX-351	mutated	10.1	(6.4-18.5)
	unmutated	6.0	(4.3-12.0)
7+3	mutated	6.6	(3.6-9.5)
	unmutated	7.3	(4.3-9.8)



Activated Signaling

FLT3, NRAS, KRAS, PTPN11, NF1, CBL, RIT1

		Median Survival	(95% CI)
CPX-351	mutated	7.0	(3.8-9.3)
	unmutated	11.3	(5.6-NR)
7+3	mutated	5.7	(3.2-8.6)
	unmutated	7.6	(4.3-10.9)



Lindsley RC et al. ASH 2019. Abstract 15.

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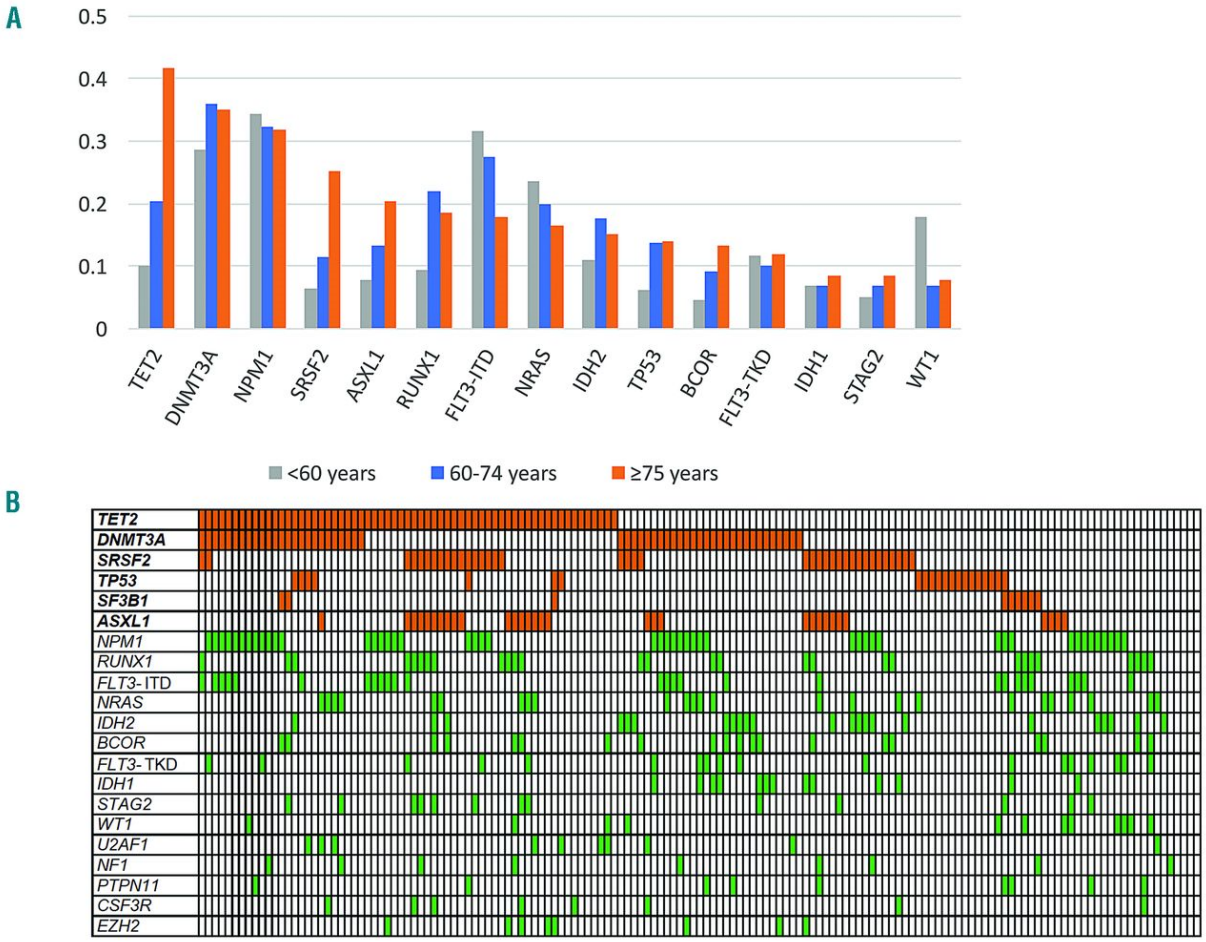
Genetic landscape of old AML patients



Prassek et al. Haematologica 2018

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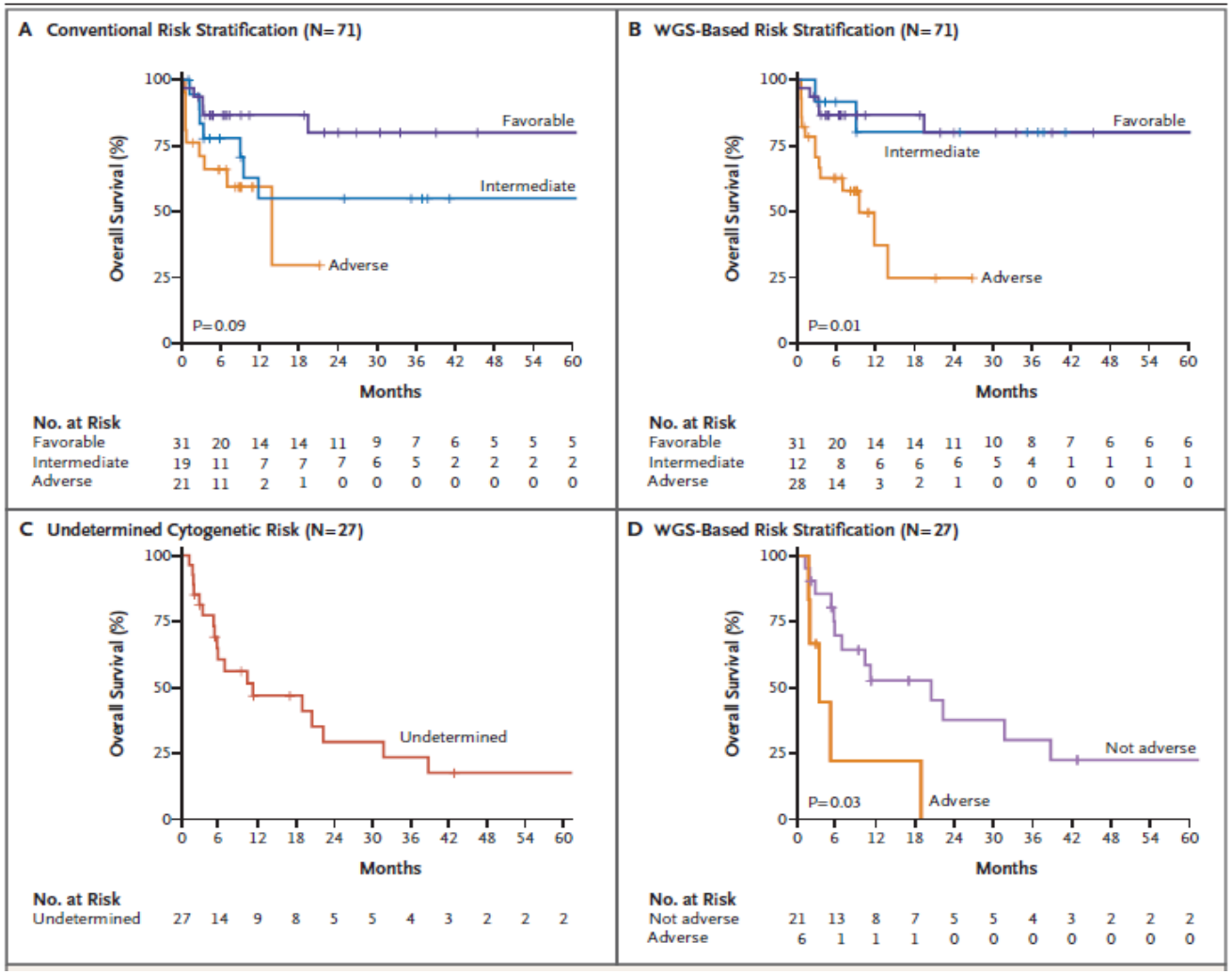
Risk Assessment by WGS



Duncavage E etal. NEJM 2021

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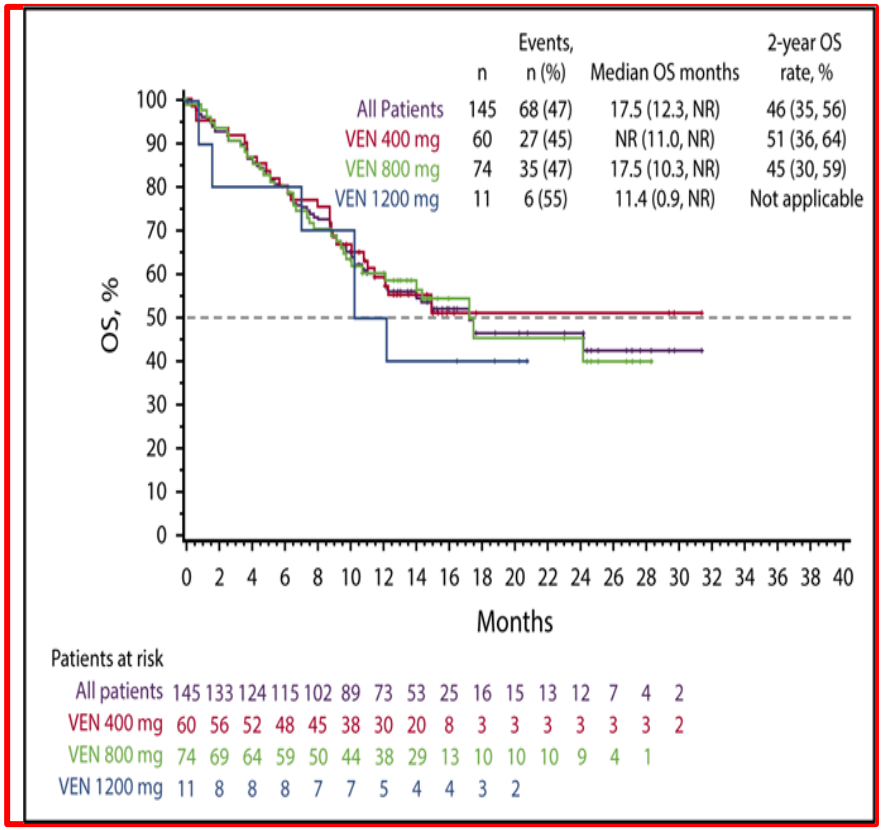
Venetoclax Plus HMA Phase 2 Trial

Cohort	n	CR + Cri, %	Median CR/CRi Duration, mo (95% CI)	Median OS, mo (95% CI)
All patients	145	67	11.3	17.5
Venetoclax 400 mg/HMA	**60**	**73**	**12.5**	**NR (11.0-NR)**
Aged 65-74 y	83	69	12.9	17.7
Aged ≥75 y	62	65	9.2	11
De novo AML	109	67	9.4	12.5
Secondary AML	**36**	**67**	**NR (12.5-NR)**	**NR (14.6-NR)**



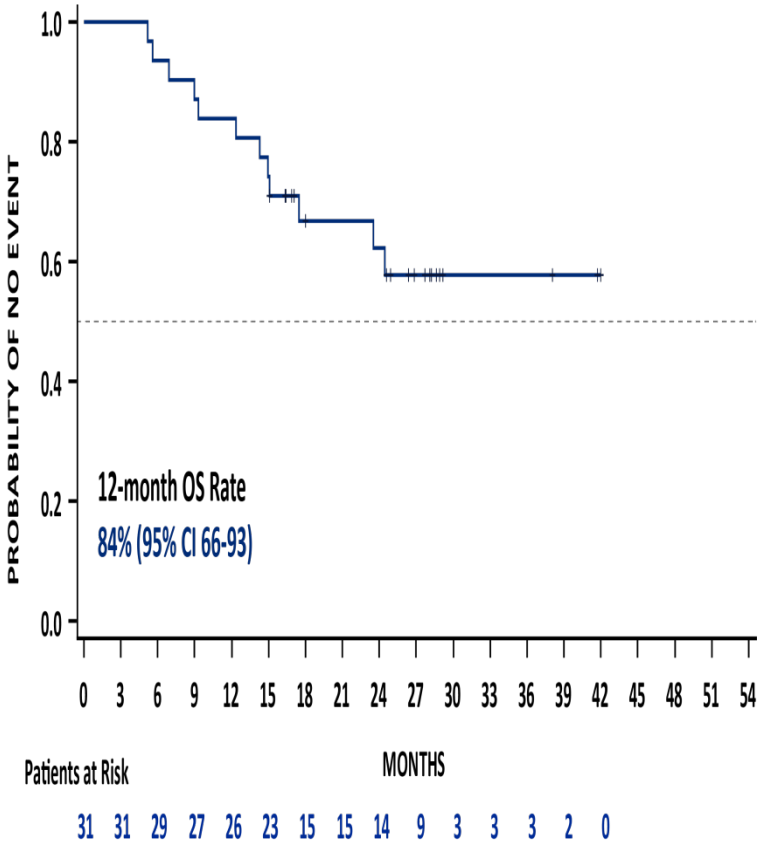
DiNardo CD et al. Blood. 2019

Outcomes of HCT in patients after venetoclax based regimens

Secondary analysis (n=304)

- Open-label phase 1b: **venetoclax + azacitidine/decitabine**
- Open-label phase 1/2: **venetoclax + LDAC**

- **10 %** (31/304)patients received HCT
  - **68%** (21/31) of patients remained alive at 12 months post-transplant
  - **55%** (17/31) of all patients that had HCT had posttransplant remission of ≥12 months
  - **71%** (12/17) of those patients remained in remission for ≥2 years



Pratz K et al. ASH 2019; Abstract 264

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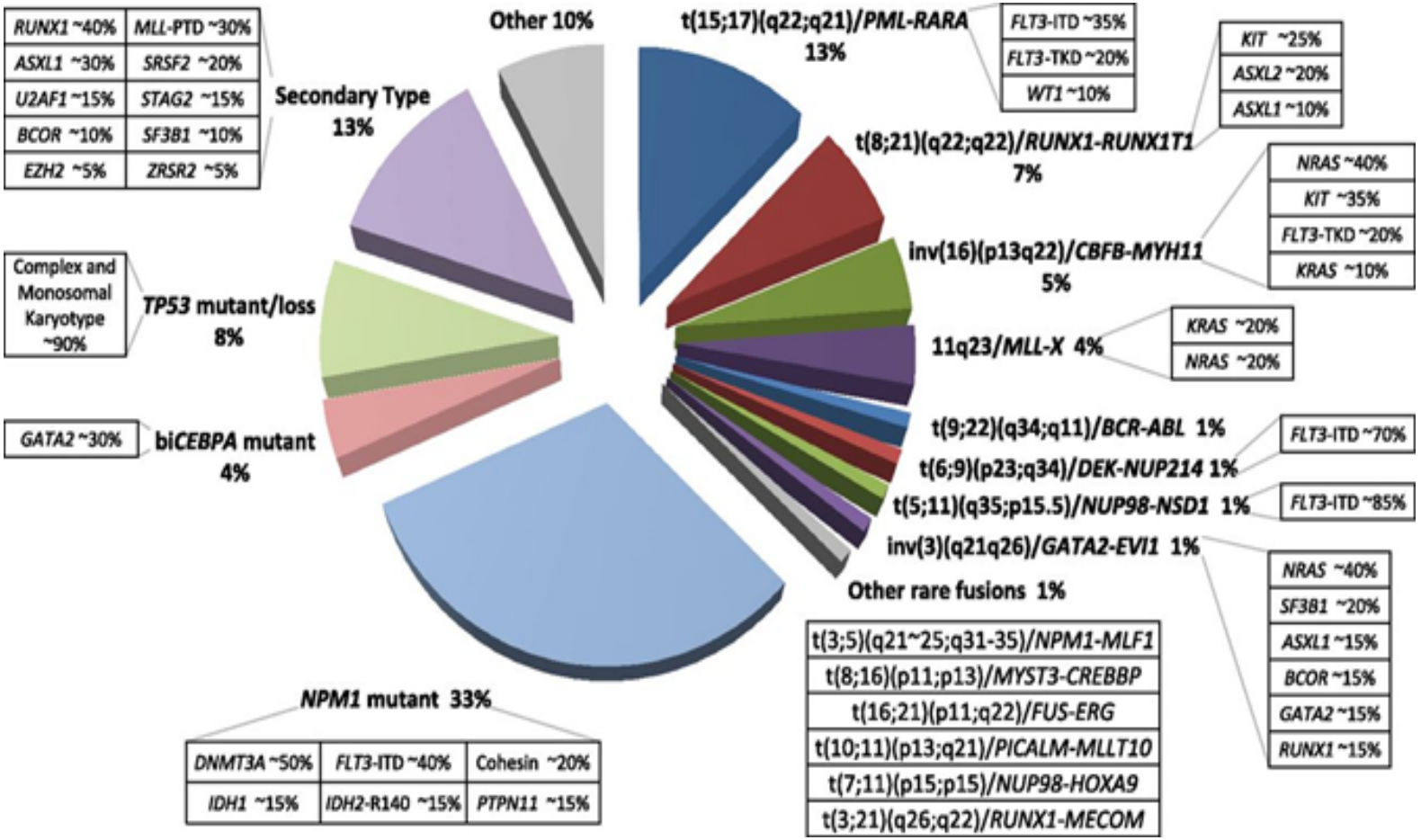
Molecular landscape of AML in younger adults



Grimwade et al. Blood 2016

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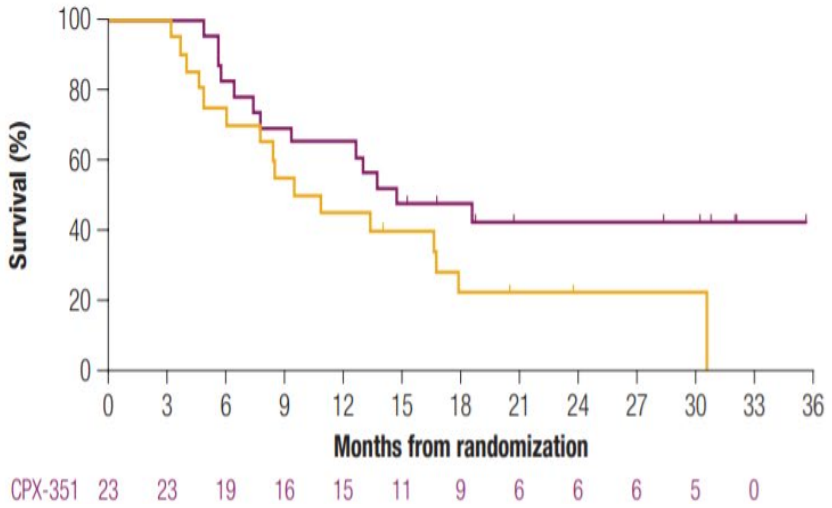
Improved OS in Patients With sAML and Prior HMA Exposure[1]

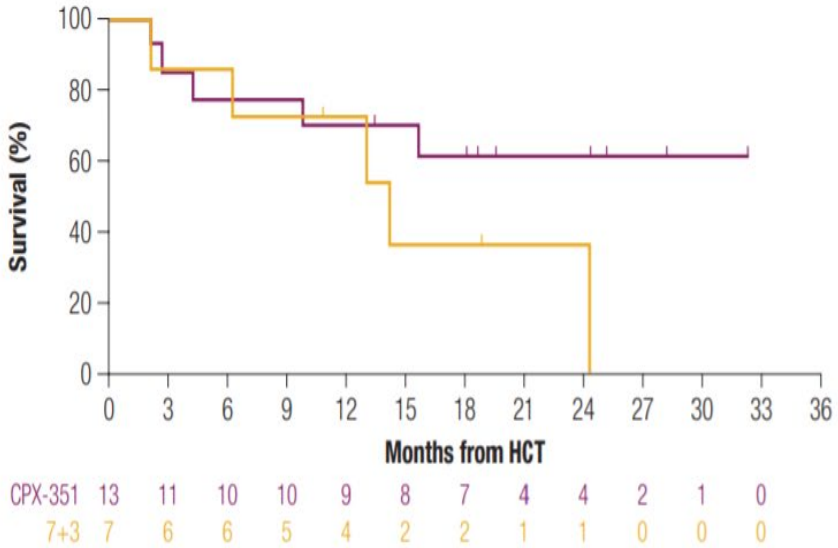
OS in AML Pts With Prior HMA Exposure Who Achieved CR or CRi



	Events/N	Median OS (95% CI)	HR (95% CI)
CPX-351	13/23	14.72 (7.75-NR)	0.55 (0.26-1.15)
7+3	16/20	10.17 (4.86-16.79)	

	1-year KM-estimated survival rate (95% CI)	2-year KM-estimated survival rate (95% CI)
CPX-351	65% (42%-81%)	40% (19%-60%)
7+3	45% (23%-65%)	23% (7%-43%)

OS Landmarked From the Date of HCT in AML Patients With Prior HMA Exposure Who Achieved CR or CRi



	Events/N	Median OS (95% CI)	HR (95% CI)
CPX-351	5/13	NR (4.30-NR)	0.43 (0.12-1.15)
7+3	5/7	14.09 (2.14-24.28)	

Lin T et al TCT 2020. Abstract 137.