



# Targeting the Un-targetable

Initial Treatment of Acute Myeloid Leukemia without Targetable Mutations

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Pharmacy Grand Rounds  
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# LEARNING OBJECTIVES

1. Describe epidemiology, pathophysiology, and prognosis of acute myeloid leukemia (AML)
2. Review literature supporting induction regimens for patients with AML without targetable mutations
3. Discuss how to select between AML induction regimens based on patient-specific factors

# 1

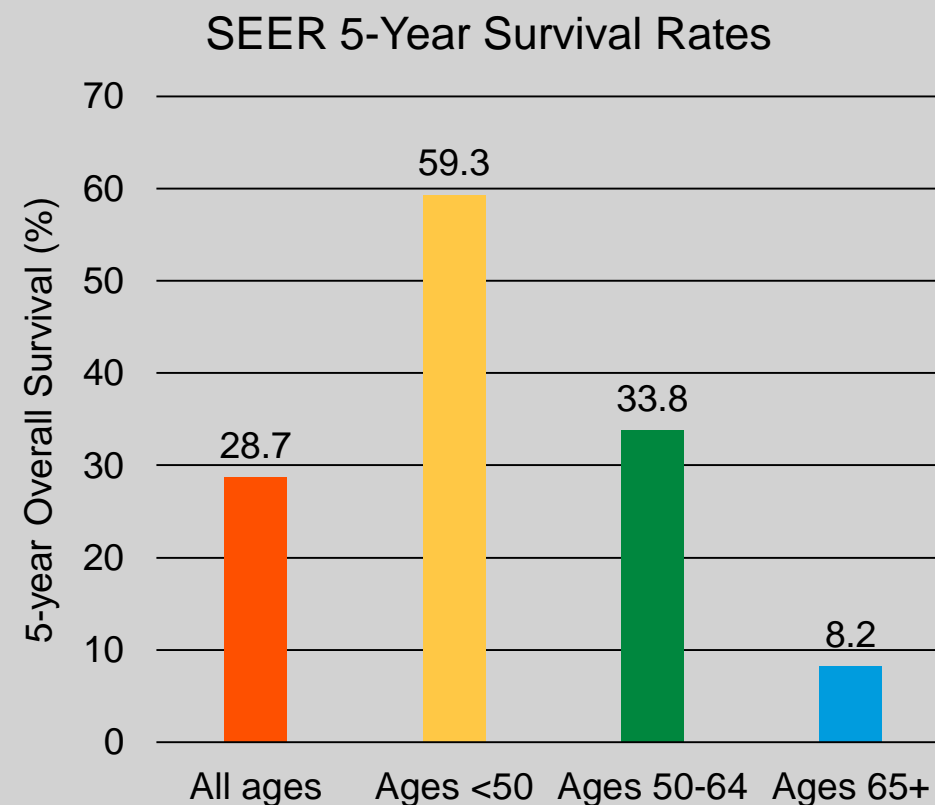
## **AML Background**

Epidemiology, Pathophysiology, and Prognosis

# Epidemiology

## Acute Myeloid Leukemia in the United States

- Estimated 19,940 new cases in 2020
  - 1.1% of all new cancer cases
- Estimated 11,180 deaths in 2020
  - 1.8% of all cancer deaths
- Lifetime risk is ~0.5%
- More common:
  - Older adults
    - Median age at diagnosis is 68
  - 1.4:1 ratio of men to women



SEER Cancer Database. 2020.

# Risk Factors

## Acute Myeloid Leukemia

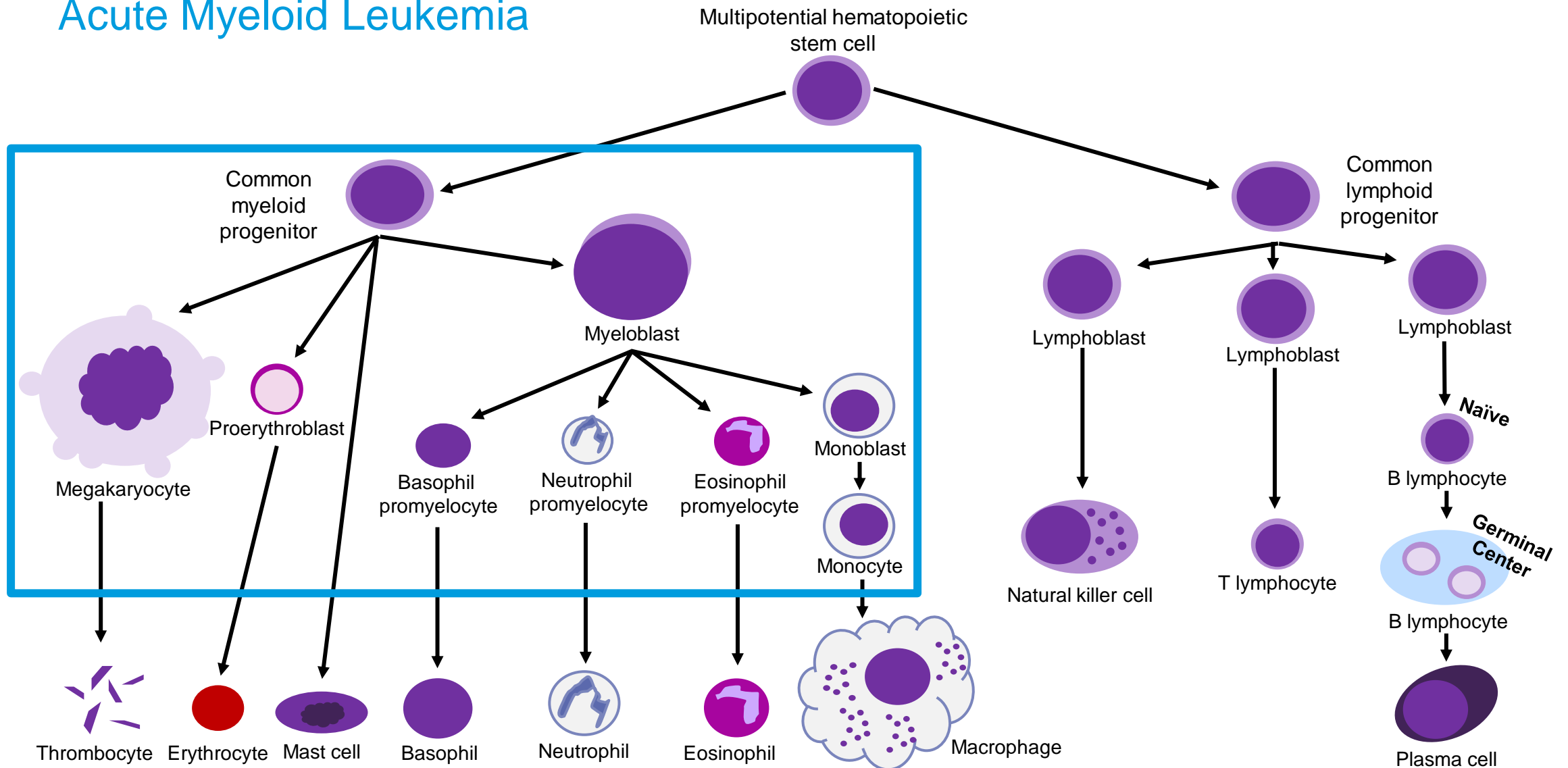
- Germline mutations in hematopoietic cells
- Prior chemotherapy
  - Topoisomerase II inhibitors – latency 1-5 years
    - Examples: doxorubicin, etoposide
  - Alkylating agents – latency 5-10 years
    - Examples: cyclophosphamide, cisplatin
- Radiation therapy
- Inherited bone marrow failure syndromes, genetic disorders, myelodysplastic disorders and myeloproliferative neoplasms



Warren JT and Link DC. Blood. 2020; 136(14):1599-1605.

# Pathogenesis

## Acute Myeloid Leukemia



# Clinical Presentation

## Signs/Symptoms

### Neutropenia

- Fever
- Infection

### Thrombocytopenia

- Bruising
- Bleeding
  - Gums
  - Epistaxis
  - Heavy menstruation

### Anemia

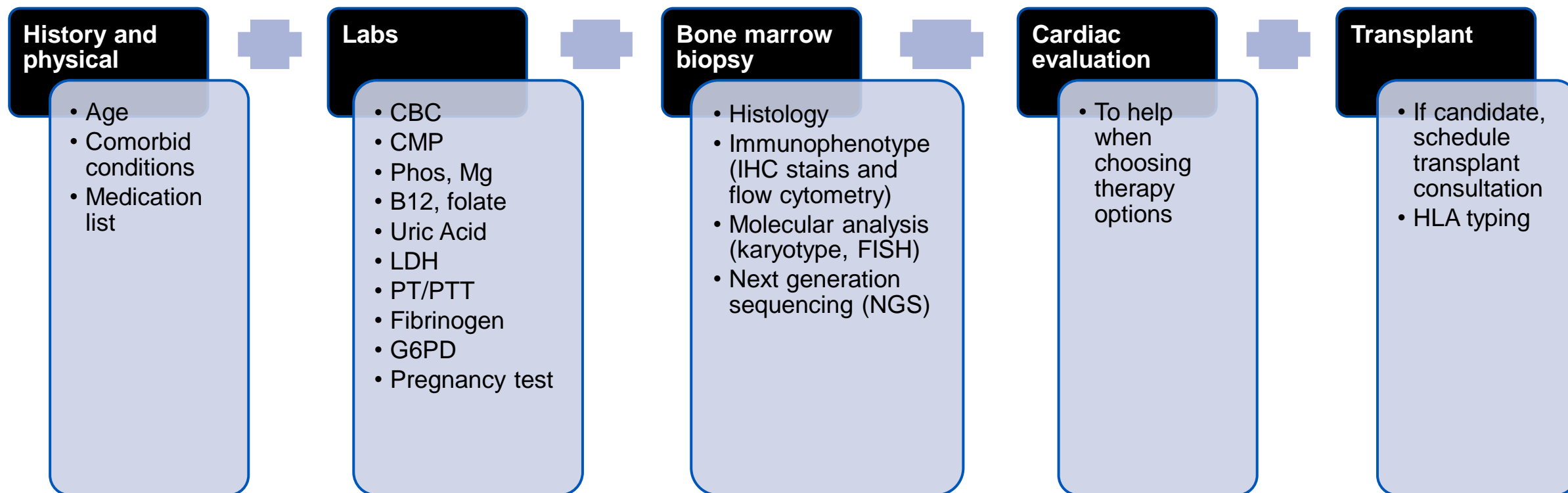
- Fatigue
- Feeling cold
- Dyspnea on exertion
- Dizziness
- Chest pain
- Pale skin

### Other

bone/joint pain, hepatosplenomegaly, leukemia cutis, myeloid sarcoma, blood clots

# Diagnostic Workup

## NCCN Recommendations



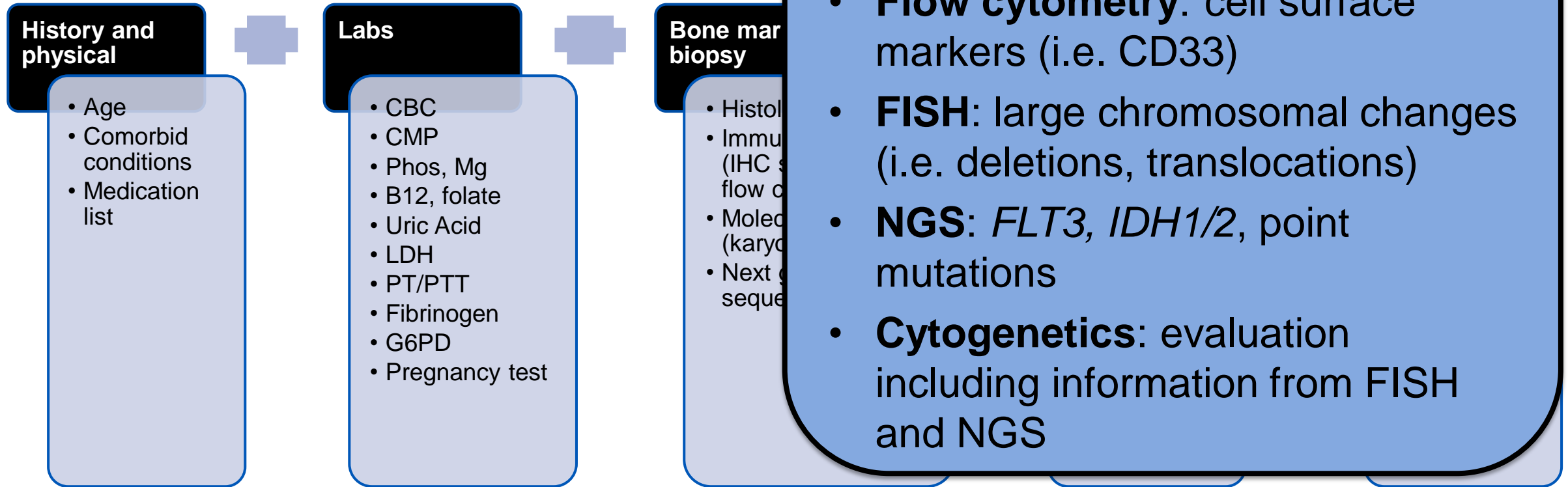
Acute Myeloid Leukemia. NCCN Guidelines, Version 1.2021.

CBC: complete blood count, CMP: complete metabolic panel, LDH: lactate dehydrogenase, PT: prothrombin time, PTT: partial thromboplastin time, IHC: immunohistochemistry, FISH: fluorescence in situ hybridization, HLA: human leukocyte antigen



# Diagnostic Workup

## NCCN Recommendations



# World Health Organization Classification

## Acute myeloid leukemia and related neoplasms

**≥20% blasts in marrow or blood OR <20% blasts with certain cytogenetic abnormalities\***

AML with recurrent  
genetic  
abnormalities

Therapy-related  
myeloid neoplasms

Myeloid sarcoma

AML with  
myelodysplasia-  
related changes

Myeloid  
proliferations  
related to Down  
Syndrome

AML, NOS

- Acute myelomonocytic leukemia
- Acute monoblastic/monocytic leukemia

Acute leukemias of  
ambiguous lineage

Blood. 2016;127(20):2391-2405.

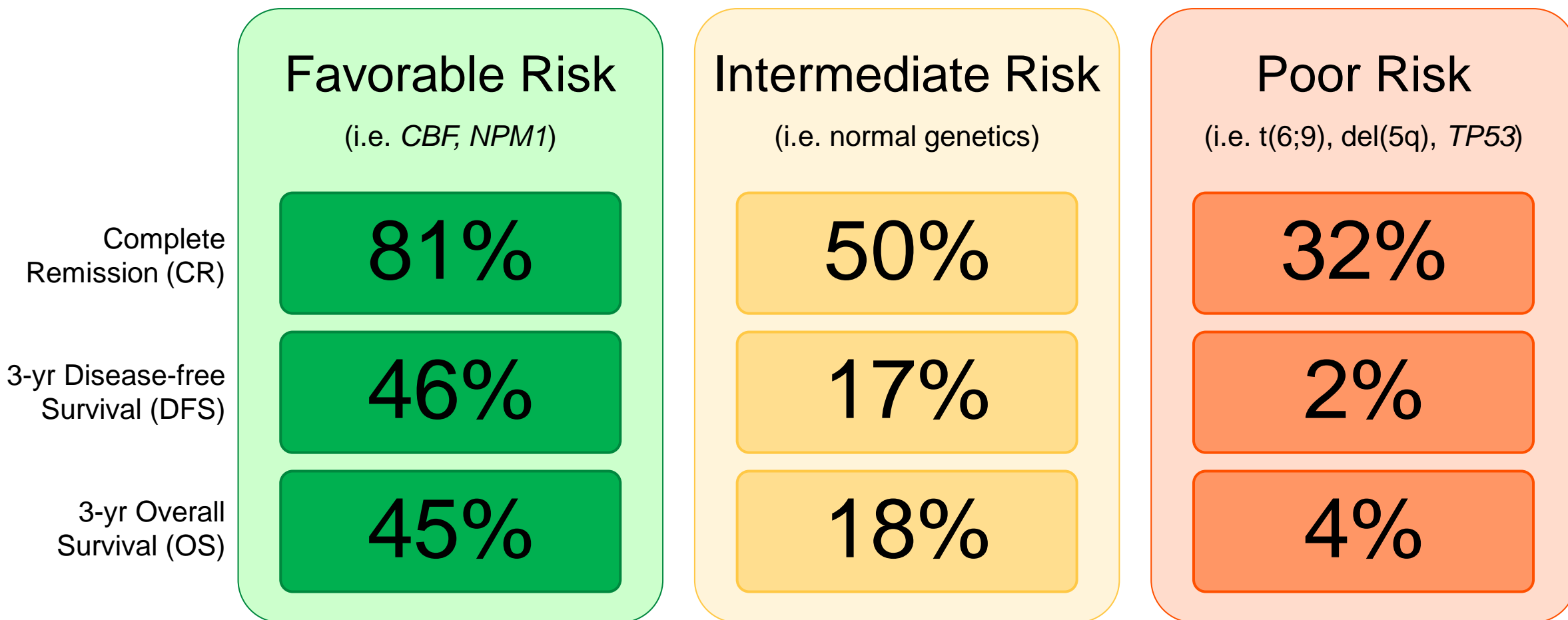
\*t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*

\*inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*

\*APL with *PML-RARA*

# Prognosis Based on Cytogenetics

Outcomes with standard chemotherapy



Leukemia. 2018;32:1338-1348.

# Question #1

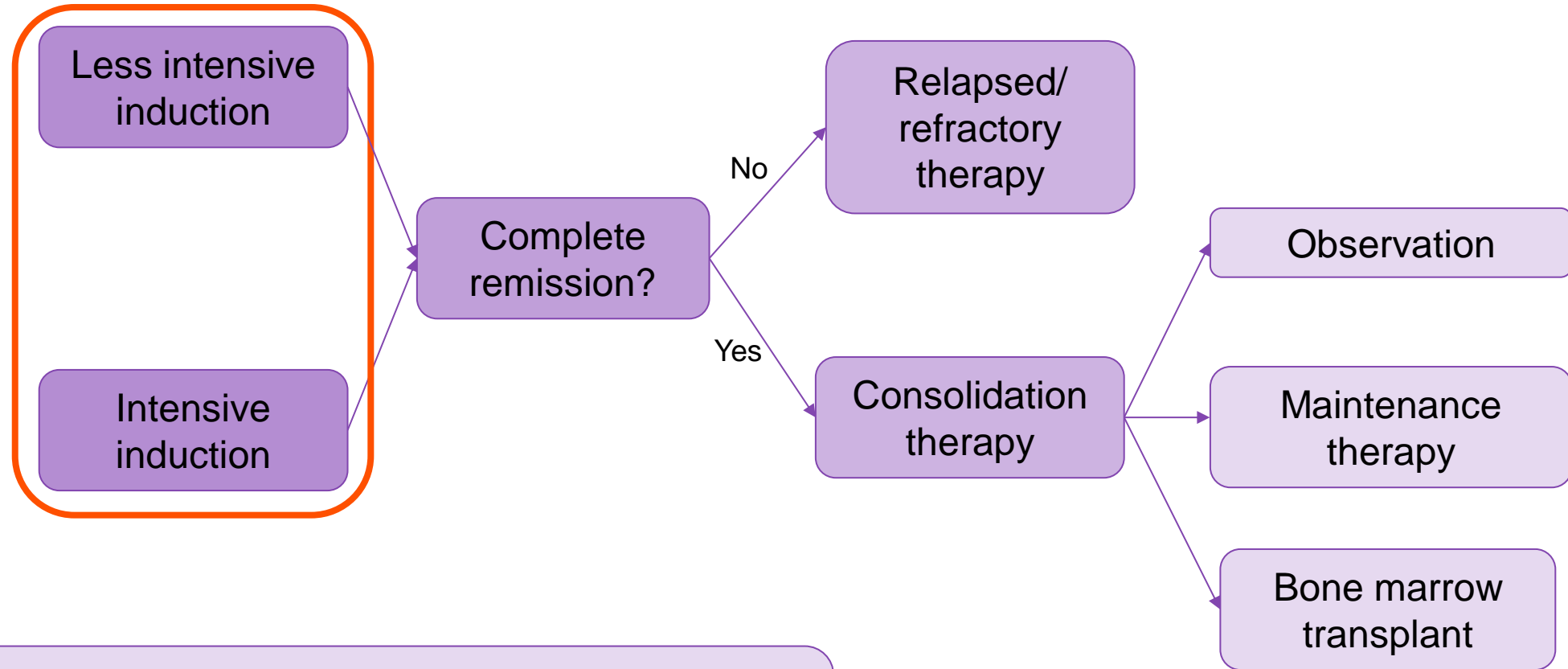
- Which of the following is true about acute myeloid leukemia (AML)?
  - A. Cytogenetics play a key role in AML prognosis
  - B. Pathogenesis of AML begins with the common lymphoid progenitor
  - C. 5-year overall survival in AML is >80%
  - D. All patients with AML should receive intensive induction chemotherapy



# 2

## **AML Induction Treatment** Literature Review

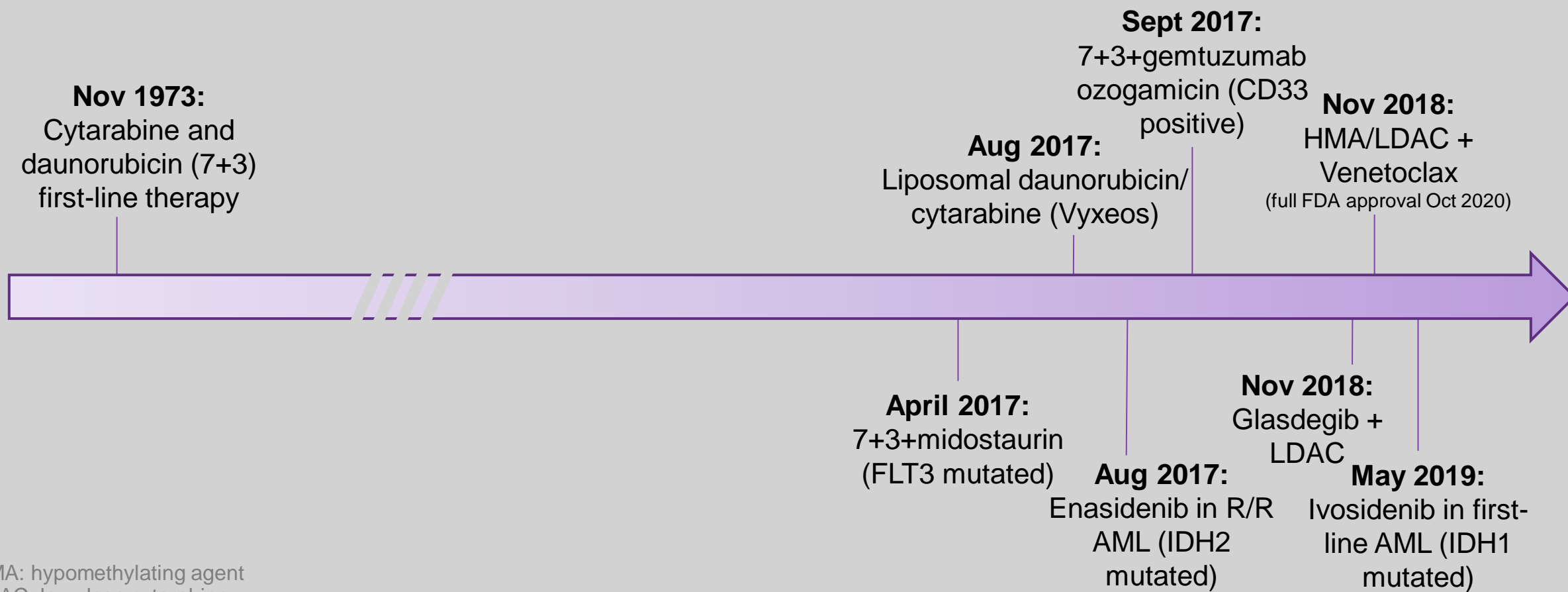
# General AML Outline of Treatment



**Complete remission:** Bone marrow blasts <5%, no circulating blasts, absence of extramedullary disease; ANC  $\geq 1.0 \times 10^9/L$ ; platelets  $\geq 100 \times 10^9/L$

# AML Induction Timeline

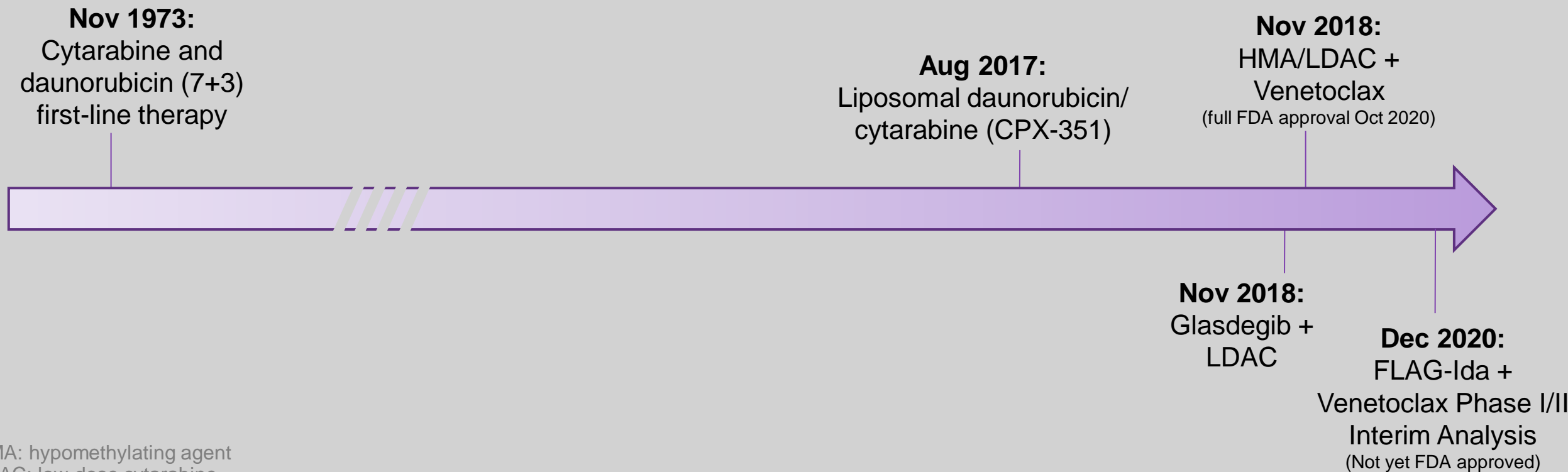
## AML Induction Therapy Breakthroughs



HMA: hypomethylating agent  
LDAC: low-dose cytarabine

# AML Induction Timeline

## AML Induction Therapy Breakthroughs



HMA: hypomethylating agent

LDAC: low-dose cytarabine

FLAG-Ida: fludarabine, cytarabine, idarubicin, growth colony stimulating factor

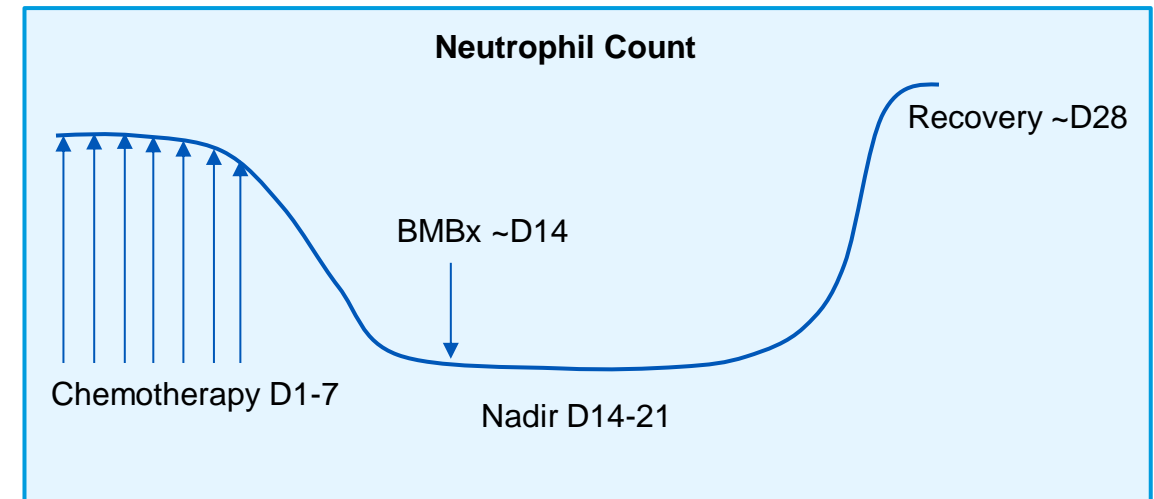


# Cytarabine and Daunorubicin (7+3)

## Regimen Pearls



- **Major adverse effects:**
  - Myelosuppression
  - Cardiomyopathy (daunorubicin)
  - Hepatotoxicity
  - Mucositis
  - Exanthematous pustulosis (cytarabine)
- **Recommended prophylaxis:**
  - Antiviral
  - Antibacterial with antipseudomonal coverage
  - Antifungal with antimold coverage



BMBx: bone marrow biopsy

# Cytarabine + Daunorubicin (7+3)

## Study Design

### Inclusion/Exclusion

- All adult patients with acute nonlymphocytic leukemia at a single institution
- No previous treatment with daunorubicin
- Not in remission

### Methods/Intervention

- Induction with cytarabine 100mg/m<sup>2</sup>/day via continuous infusion x7 days and daunorubicin 45mg/m<sup>2</sup> given on days 1, 2, and 3

### Outcomes/Results (n=17)

- 5 of 8 previously untreated patients achieved CR
- 2 CR and 3 PR among 8 previously treated patients

Yates JW, et al. Cancer Chemother Rep. 1973 (57):485-488.

# Cytarabine + Daunorubicin (7+3)

Daunorubicin 60mg/m<sup>2</sup> vs. 90mg/m<sup>2</sup>



## Study Objective

- Compare overall effectiveness of daunorubicin 90mg/m<sup>2</sup> vs. 60mg/m<sup>2</sup> for AML induction
- Given in combination with cytarabine 100mg/m<sup>2</sup>



## Included Patients

- 1206 patients were randomized to 60mg/m<sup>2</sup> vs. 90mg/m<sup>2</sup>
- Majority <60 years old



## Efficacy Results

- No difference in CR rate (73% vs. 75%, OR 1.07 [0.83-1.39]; P=0.6)



## Safety Results

- 60-day mortality increased in 90mg/m<sup>2</sup> (10% vs. 5%, HR 1.98 [1.30-3.02]; P=0.001)
- No difference in 2-year OS

Burnett AK, et al. Blood. 2015; 125(25):3878-3885.

# Liposomal Daunorubicin/Cytarabine (CPX-351)

## Drug Pearls



- ***Not interchangeable with other daunorubicin or cytarabine formulations***

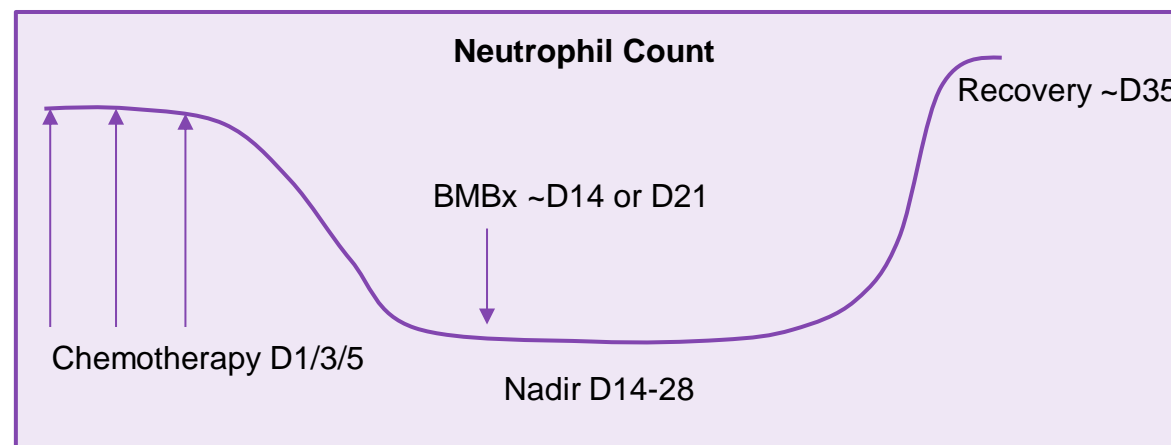
- Fixed 1:5 (daunorubicin : cytarabine) molar ratio
- Enhanced uptake liposomal uptake by leukemia cells

- **Major adverse effects:**

- Prolonged myelosuppression
- Febrile neutropenia
- GI toxicities
- Skin rash
- Cardiotoxicity

- **Recommended prophylaxis:**

- Same as 7+3



BMBx: bone marrow biopsy

# CPX-351 in Newly Diagnosed sAML

## Study Design

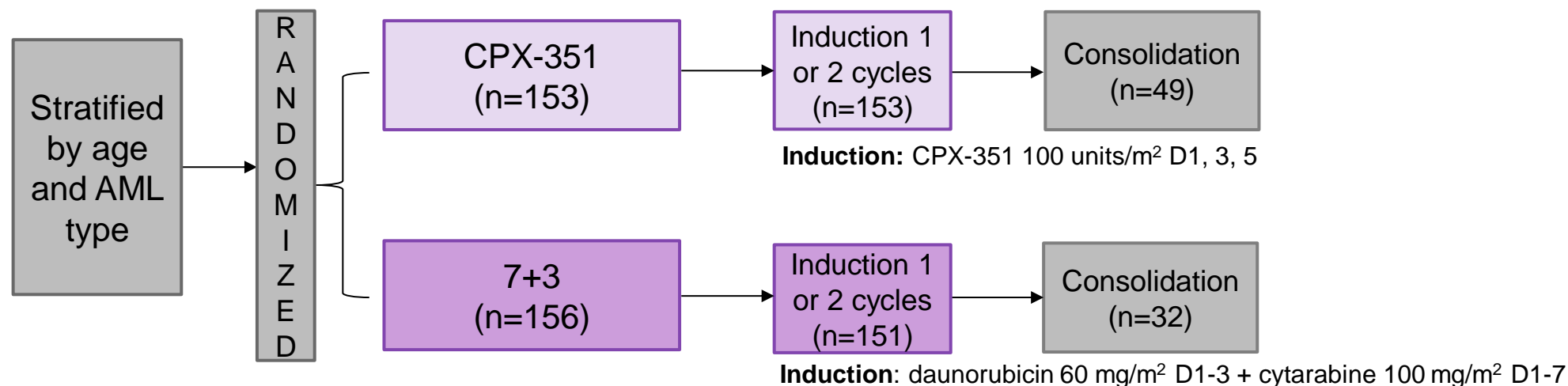
### Inclusion/Exclusion

- Patients age 60-75 years old with newly diagnosed high-risk/secondary-AML per WHO 2008 criteria

### Methods

- Multicenter, phase III, randomized, open-label study

### Intervention



Lancet JE, et al. J Clin Oncol 2018;36(26):2684-2692.

# CPX-351 in Newly Diagnosed sAML

## Results

- n=309, median age 68 years old
- Median follow up was 20.7 months

	CPX-351	7+3	Group comparison
OS	9.56 months	5.95 months	HR 0.69, 95% CI, 0.52 to 0.90; P=0.003
Overall Remission Rate (CR/CRi)	47.7%	33.3%	P=0.16
CR	37.3%	25.6%	P=0.040
EFS	2.53 months	1.31 months	HR 0.74; 95% CI, 0.58 to 0.96; P=0.021
Remission duration	6.93 months	6.11 months	P=0.291

# CPX-351 in Newly Diagnosed sAML

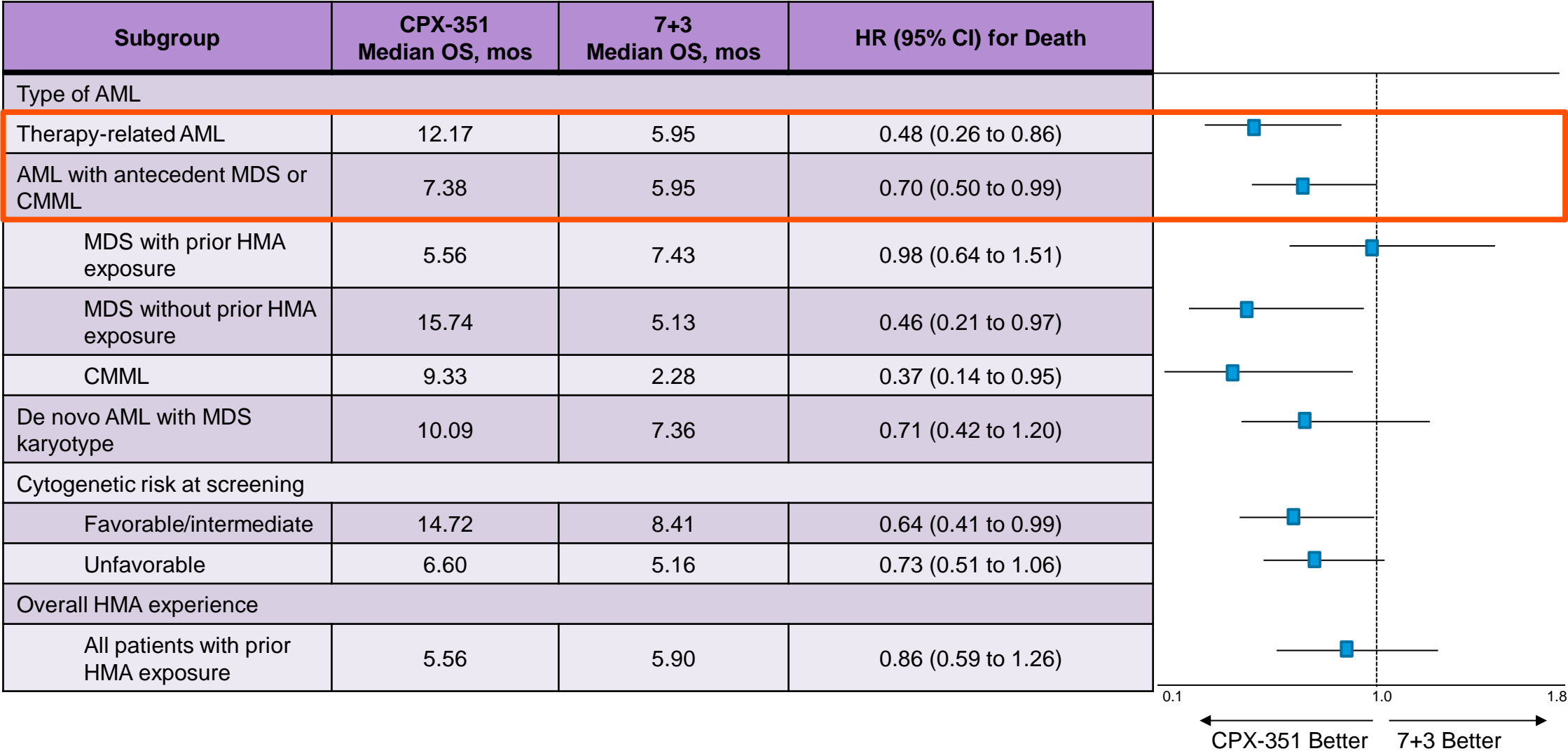
## Results

- n=309, median age 68 years old
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	CPX-351	7+3	Group comparison
OS	9.56 months	5.95 months	HR 0.69, 95% CI 0.52 to 0.90, P=0.003
Overall Remission (CR/CRi)	<b>5-year follow up data:</b> Median OS 9.33 months vs. 5.95 months (HR 0.70; 95% CI, 0.55 to 0.91)		
CR			
EFS			
Remission duration	6.93 months	6.11 months	P=0.291

# CPX-351 in Newly Diagnosed sAML

## Subgroup Analysis Results



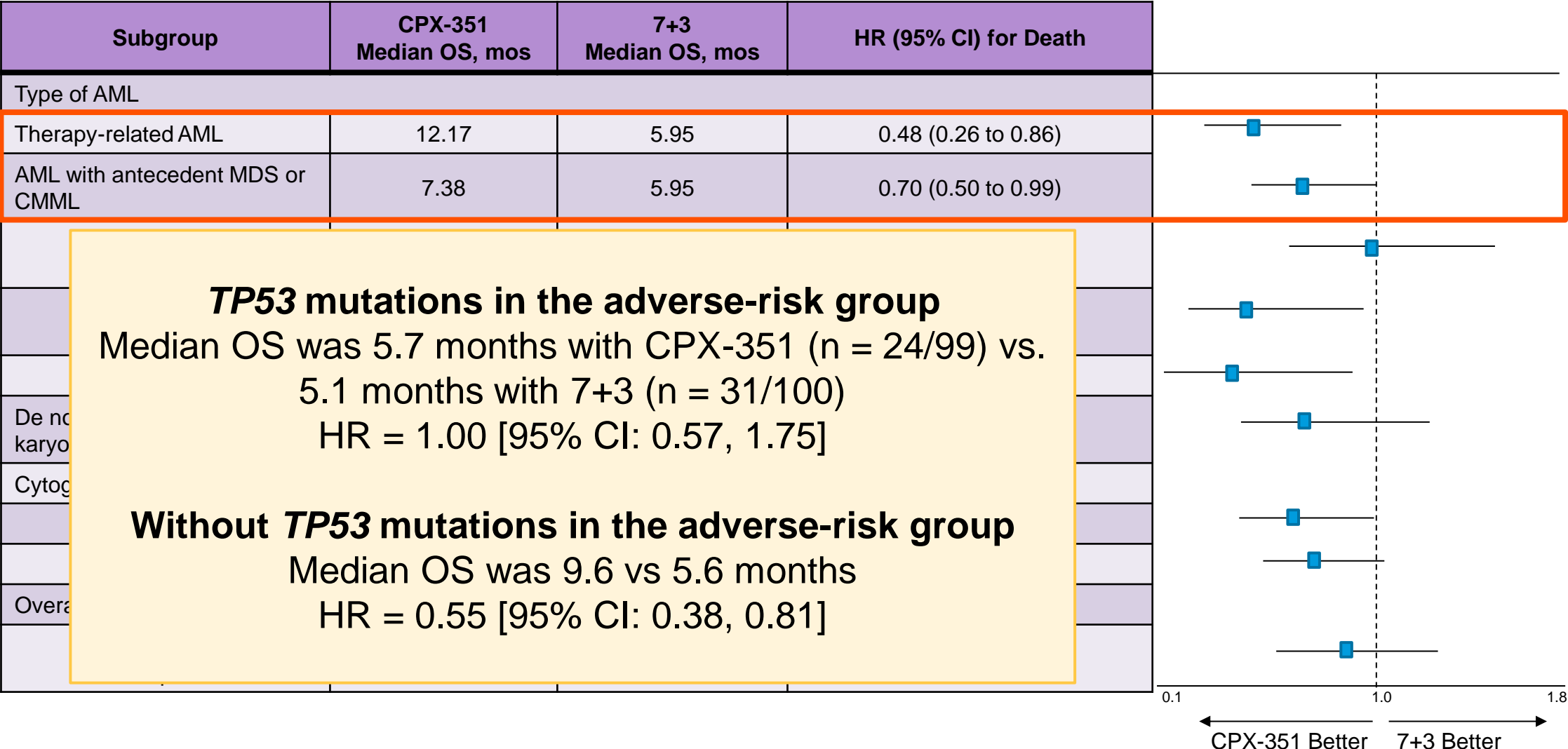
MDS: myelodysplastic syndrome, CMML: chronic myelomonocytic leukemia, HMA: hypomethylating agent, OS: overall survival

Lancet JE, et al. J Clin Oncol 2018;36(26):2684-2692.  
Prebet T, et al. Abstract 2844 in ASH Annual Meeting; Dec 5-8. 2020. <sup>8-24</sup>



# CPX-351 in Newly Diagnosed sAML

## Subgroup Analysis Results



MDS: myelodysplastic syndrome, CMML: chronic myelomonocytic leukemia, HMA: hypomethylating agent, OS: overall survival

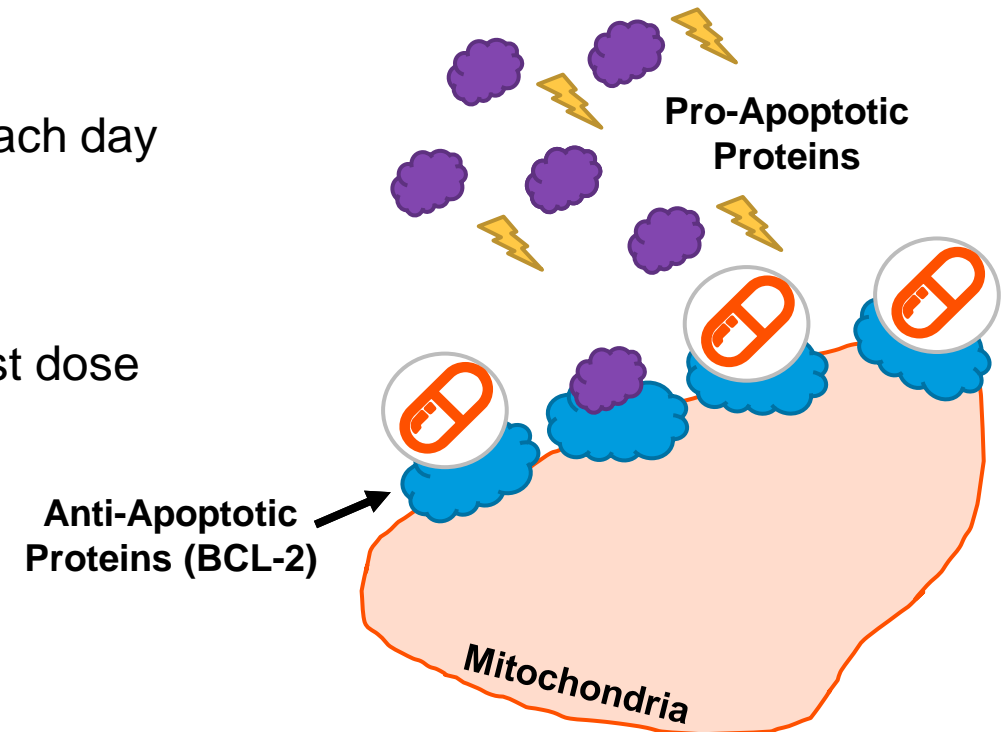
Lancet JE, et al. J Clin Oncol 2018;36(26):2684-2692.  
Prebet T, et al. Abstract 2844 in ASH Annual Meeting; Dec 5-8. 2020.<sup>8-25</sup>

# Venetoclax

## Drug Pearls



- **Mechanism:** BCL2 inhibitor
- Administer with a meal and water at the same time each day
- **Tumor lysis syndrome risk:**
  - Hydroxyurea for WBC  $\geq 25 \times 10^9/L$
  - Prophylactic hydration and allopurinol prior to first dose
  - Utilize ramp up schedule based on target dose
  - Adjust dose based on antifungal prophylaxis
- **Caution:**
  - CYP3A4 substrate (major)
  - P-glycoprotein substrate (minor)



# VIALE-A: Azacitidine + Venetoclax

## Study Design

### Inclusion/Exclusion

- Patients  $\geq 18$  years old with previously untreated AML who were ineligible for standard induction therapy
  - Due to comorbid conditions or being  $\geq 75$  years old
  - Excluded patients with favorable genetics

### Methods

- Phase III, multicenter, randomized, double-blind, placebo-controlled trial

### Intervention

- Randomized 2:1 to receive azacitidine 75mg/m<sup>2</sup> on days 1-7 + venetoclax daily (target dose 400mg) or placebo

### Outcomes

- Primary: overall survival
- Secondary: multiple efficacy and safety outcomes, patient-reported quality of life

DiNardo CD, et al. N Engl J Med 2020.383:617-629.

# VIALE-A: Azacitidine + Venetoclax

## Results

- n=431, median age 76 years old
- Median duration of follow-up was 20.5 months (range <0.1 to 30.7)

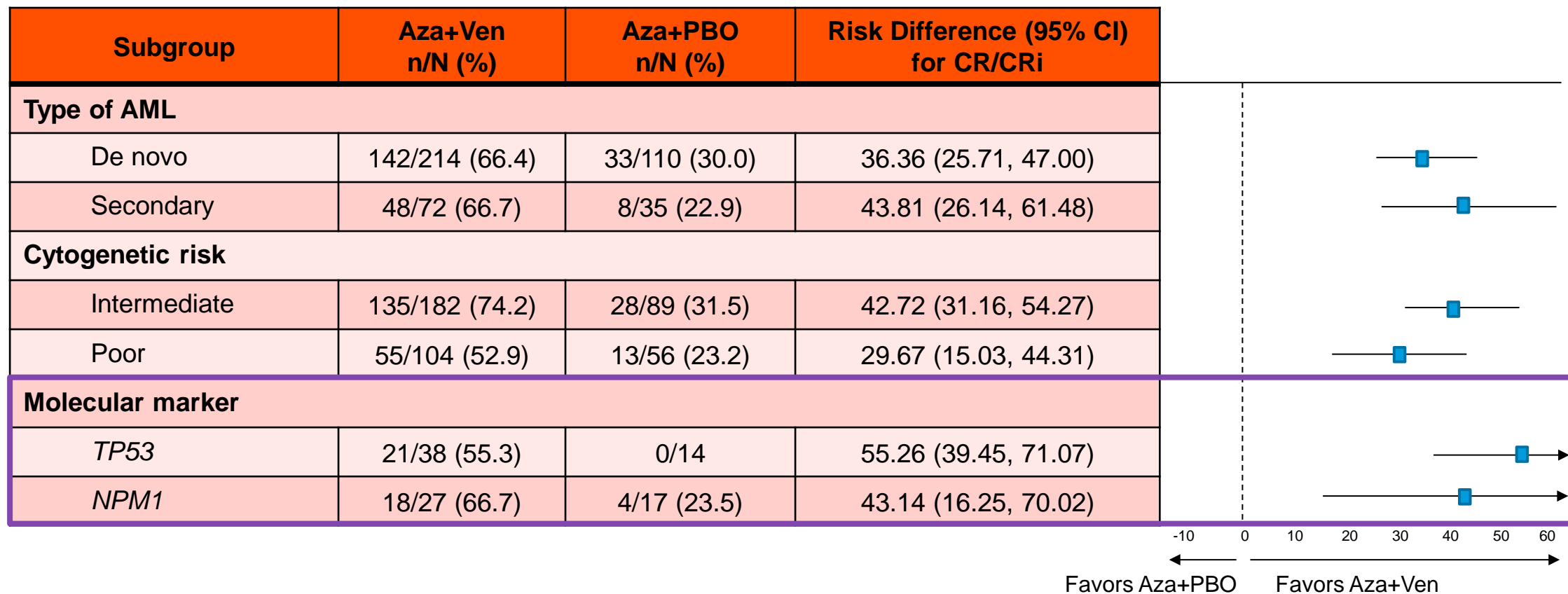
	Azacitidine-Venetoclax N=286	Azacitidine-Placebo N=145	Comparison
Median OS, months	14.7	9.6	HR death, 0.66 95% CI, 0.52 to 0.85; p<0.001
Composite CR	66.4%	28.3%	P<0.001
Median time to first response, months	1.3	2.8	
Median duration of response, months	17.5	13.4	
CR	36.7%	17.9%	P<0.001

- Rates of adverse effects were consistent with each agent used and population treated

DiNardo CD, et al. N Engl J Med 2020;383:617-629.

# VIALE-A: Azacitidine + Venetoclax

## Subgroup Analysis



DiNardo CD, et al. N Engl J Med 2020;383:617-629.

# VIALE-C: Low-dose Cytarabine + Venetoclax

## Study Design

### Inclusion/Exclusion

- Adult patients with AML ineligible for intensive chemotherapy

### Methods

- International, phase 3, randomized, double-blind, placebo-controlled trial

### Intervention

- Randomized 2:1 to receive venetoclax or placebo in 28 day cycles + low-dose cytarabine D1-10

### Outcomes

- Primary: overall survival
- Secondary: response rate, transfusion independence, event-free survival

Wei AH, et al. Blood 2020; 135(24): 2137-2145.

# VIALE-C: Low-dose Cytarabine + Venetoclax

## Results

- n=211, median age 76 years old
- Median duration of follow-up was 12.0 months (range 0.1-17.6 months)

	LDAC-Venetoclax N=143	LDAC-placebo N=68	Comparison
Median OS, months (at pre-planned analysis)	7.2	4.1	HR 0.75 (95% CI, 0.52-1.07) P=0.11
Median OS, months (additional 6 mo. follow-up)	8.4	4.1	HR 0.70 (95% CI, 0.50-0.99) P=0.04
Composite CR by initiation of cycle 2	48%	13%	P<0.001
CR	27%	7%	P<0.001

- Rates of adverse effects were consistent with each agent used and population treated

Wei AH, et al. Blood 2020; 135(24): 2137-2145.

# VIALE-C: Low-dose Cytarabine + Venetoclax

## Subgroup Analysis

Subgroup Response Rates (CR/CRi)	LDAC+Ven n/N (%)	LDAC+PBO n/N (%)
<b>Type of AML</b>		
De novo	47/85 (55)	8/45 (18)
Secondary	21/58 (36)	1/23 (4)
<b>Cytogenetic risk</b>		
Intermediate	50/90 (56)	7/43 (16)
Poor	13/47 (28)	2/20 (10)
<b>Molecular markers</b>		
<i>TP53</i>	4/22 (18)	0/9
<i>NPM1</i>	14/18 (78)	4/7 (57)

Wei AH, et al. Blood 2020; 135(24): 2137-2145.

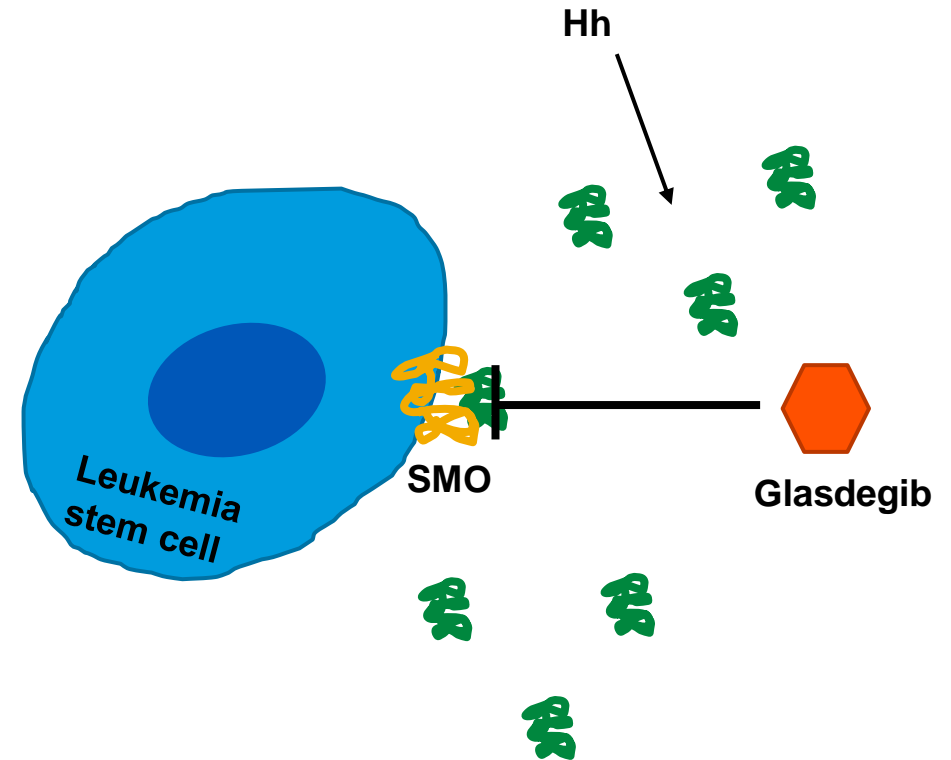


# Glasdegib

## Drug Pearls



- **Mechanism:** hedgehog inhibitor
- Take at the same time each day with or without food
- **Adverse effects:**
  - Electrolyte abnormalities
  - GI upset
  - Transaminitis, increased serum creatinine
  - Muscle pain
  - QTc prolongation
- **Other considerations:**
  - Major CYP3A4 substrate
  - Treat for minimum 6 cycles to allow time for clinical response



# BRIGHT AML 1003: Low-dose Cytarabine + Glasdegib

## Study Design

### Inclusion/Exclusion

- Adult patients with AML or high-risk MDS ineligible for intensive chemotherapy
  - Age  $\geq$  75 years
  - ECOG performance status 2+
  - Serum creatinine  $>1.3$  mg/dL
  - Severe cardiac disease

### Methods

- Phase II, open-label, multicenter trial

### Intervention

- Randomized 2:1 to received cytarabine 20mg SQ BID x10 days +/- glasdegib 100mg PO daily in 28 day cycles

### Outcomes

- Primary: overall survival

Cortes JE, et al. Leukemia 2019; 33:379-389.

# BRIGHT AML 1003: Low-dose Cytarabine + Glasdegib

## Results

- n=132, median age 76 years old
- Median duration of follow-up was 20.1-21.7 months

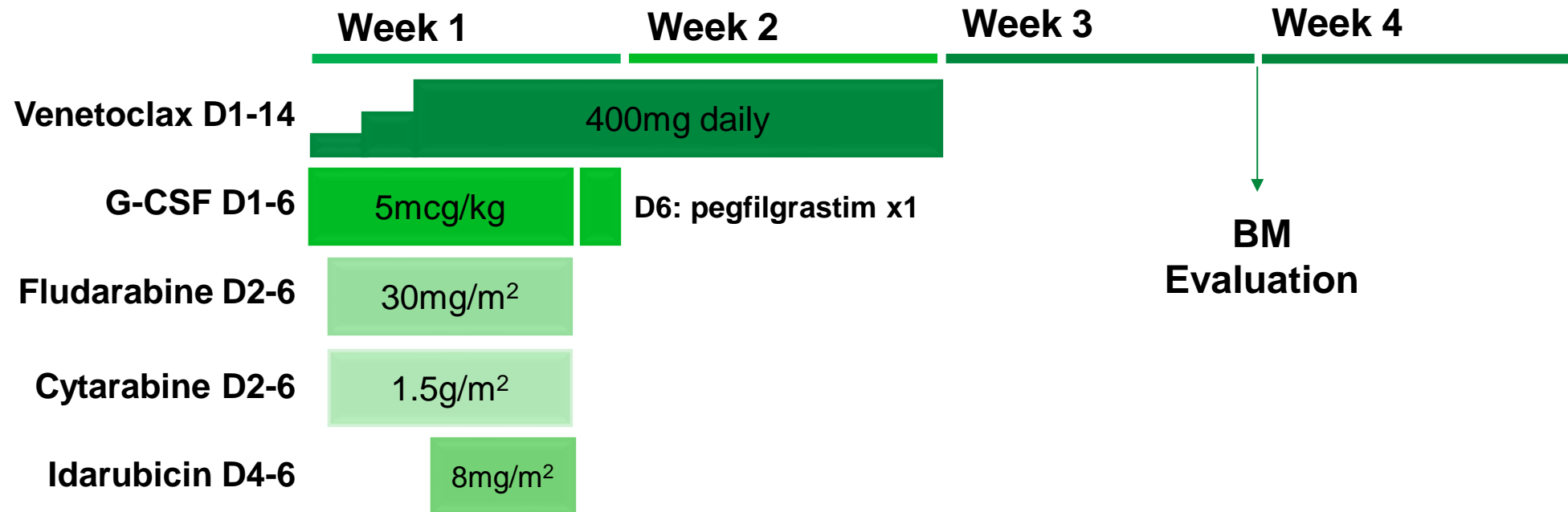
	LDAC-Glasdegib N=88	LDAC N=44	Comparison
Median OS, months	8.8	4.9	HR 0.51 (80% CI, 0.39-0.67) P=0.0004
CR	17.0%	2.3%	P<0.05
Duration of treatment, months	2.7	1.5	
Duration of response, months	9.9	NR	

- 56.0% of patients in the LDAC/glasdegib vs. 31.7% of the LDAC group temporarily discontinued treatment due to adverse effects

Cortes JE, et al. Leukemia 2019; 33:379-389.

# FLAG-Ida-Venetoclax

## Regimen Schema



G-CSF: growth-colony stimulating factor, ND: new diagnosis, R/R: relapsed/refractory, BM: bone marrow

# FLAG-Ida-Venetoclax

## Study Design

### Inclusion/Exclusion

- Adult patients with newly diagnosed (ND) or relapsed/refractory (R/R) AML

### Methods

- Phase Ib dose escalation included R/R AML
- Phase II dose expansion included 2 arms (ND and R/R)

### Outcomes

- Primary: assessment of safety and tolerability, determination of dose limiting toxicities, maximal tolerated dose
- Secondary: ORR, OS, EFS, duration of response, biomarkers predictive of response

Lachowicz C, et al. ASH Abstract 332. 2020.

# FLAG-Ida-Venetoclax

## Results

**FLAG-Ida CR Comparison:**  
*de novo* 85%  
 R/R 21%

	All patients (n=62)	Phase 2A (ND AML; N=27)	Phase 1b & Phase 2B (R/R AML; n=35)
ORR	84%	89%	66%
MRD negative CR	83%	96%	70%
1-yr OS		92%	52%
Median OS	NR	NR	11 months
EFS	16 months		

- Grade 3/4 ADRs: febrile neutropenia (37%), bacteremia (29%), hypophosphatemia (24%), pneumonia (21%), SSTI (16%), increased ALT (11%)
- 30-day mortality = 0%, 60-day mortality = 4.8%
  - Only R/R AML patients to date

Lachowicz C, et al. Abstract 332 in ASH Annual Meeting; Dec 5-8, 2020.

ORR: overall response rate, CR: complete response, MRD: minimal residual disease, OS: overall survival, EFS: event free survival, ND: newly diagnosed, NR: not reported, R/R: relapsed/refractory, SSTI: skin/soft tissue infection

# FLAG-Ida-Venetoclax

## TP53 Mutated AML

TP53 Outcomes	All patients (n=10)	ND AML (n=3)	R/R AML (n=7)
ORR	6 (60%)	3 (100%)	3 (43%)
CRc	6 (60%)	3 (100%)	3 (43%)
DOR (months, 95% CI)	3.3 (1.9 – NE)	3.4 (1.9 – NE)	3.2 (1.8 – NE)
Deceased	5 (50%)	1 (33%)	4 (57%)

Lachowicz C, et al. Abstract 332 in ASH Annual Meeting; Dec 5-8, 2020.

ORR: overall response rate, CRc: composite complete response, DOR: duration of response, ND: newly diagnosed, R/R: relapsed/refractory

# 3

## **Selecting AML Induction Regimen** Based on Patient-Specific Factors



# Factors to Consider

## When Choosing Induction Regimens

7+3	CPX-351	Flag-Ida-Ven	Aza/Ven	LDAC/Ven	Glasdegib/ LDAC
Fit Younger	Fit 60-75 years old	Fit Younger	Unfit ≥75 years old	Unfit ≥75 years old	Unfit ≥75 years old
Anthracycline eligible	Anthracycline eligible  tAML, AML-MRC  Negative <i>TP53</i> mutated data	Need more data to determine place in therapy	Positive <i>TP53</i> mutated data	Less favorable <i>TP53</i> mutated data	Poor overall response rate  <i>TP53</i> data unavailable

# Patient Case, 39 YO/M

- 39 YO/M presents to ED with complaints of SOB on exertion, fatigue, easy bruising

- PMH: HLD

- Labs:

- ANC 0.4 cells/ $\mu$ L
- 34% circulating blasts
- SCr 0.7 mg/dL
- LFTs, T. bili WNL

	7.4	
1.2		24
	23.1	

- Bone marrow biopsy: consistent with AML
  - Hypercellular marrow, 60% blasts
  - Cytogenetics: t(6;9), *FLT3* negative

Young, otherwise healthy

Good renal and hepatic function

Poor risk cytogenetics, no actionable mutations



## Question #2

- Given this patient case, what AML induction regimen would you choose for this patient?
  - A. Liposomal daunorubicin/cytarabine (CPX-351)
  - B. Cytarabine + daunorubicin (7+3)
  - C. Azacitidine/Venetoclax
  - D. Low-dose cytarabine/glasdegib

# Patient Case, 74 YO/F

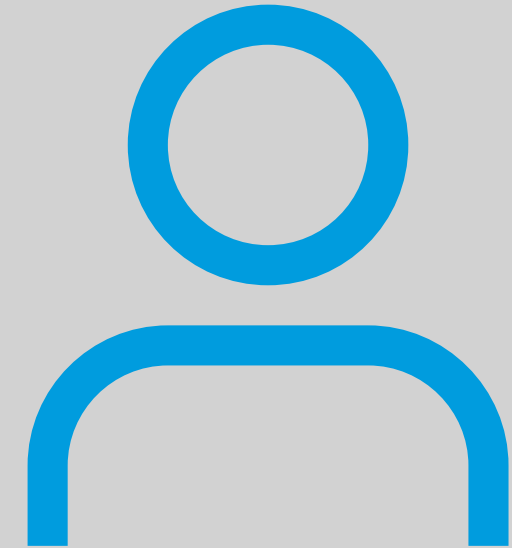
- 74 YO/F presents to ED with fevers, chest pain, and dyspnea on exertion
- PMH: hx breast cancer s/p dose-dense AC x4 cycles and bilateral mastectomy (2015), HTN, CHF with LVEF 40%, hx MI (2018), CKD stage 3
- Labs:
  - ANC 0.2 cells/ $\mu$ L
  - 5% circulating blasts
  - SCr 1.8 mg/dL
  - LFTs, T. bili WNL
- Bone marrow biopsy: consistent with therapy-related AML
  - Hypercellular marrow, 27% blasts
  - Cytogenetics: *TP53* mutated, *FLT3* negative

~~8.7  
0.6 37  
26.3~~

Older, multiple  
comorbidities

Impaired renal  
function

Poor risk cytogenetics,  
no actionable  
mutations, treatment-  
related AML



# Question #3

- Given this patient case, what AML induction regimen would you choose for this patient?
  - A. Liposomal daunorubicin/cytarabine (CPX-351)
  - B. Cytarabine + daunorubicin (7+3)
  - C. Azacitidine/Venetoclax
  - D. Low-dose cytarabine/glasdegib

# SUMMARY

- AML accounts for approximately 1.1% of all new cancer cases per year
- Recent advances in AML treatment have expanded options beyond 7+3 for patients without targetable mutations
- Considering patient-specific factors is important when choosing an AML induction regimen

# QUESTIONS & DISCUSSION

