catalyst:

Insights from the Experts to Navigate a Complex and Evolving Landscape in CLL and AML Management

LIVE VIRTUAL SUMMIT

WEDNESDAY, OCTOBER 6, 2021

This activity is provided by Med Learning Group.
This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM).
This activity is supported by an educational grant from AbbVie Inc.

Agenda

Part 1: Chronic Lymphocytic Leukemia

1. Introduction to CLL
    a. Epidemiology of CLL
    b. Prognosis and clinical course of the disease
    c. Pathophysiology of CLL
    d. Quality of life

2. Prognostication and Prediction
    a. Conventional staging systems
    b. Clinical and phenotypic markers
    c. Molecular and genomic markers

3. Treatment Paradigms in CLL
    a. Chemoimmunotherapy
    b. Treatment-naïve CLL
        i. Novel agents
            1) BTK inhibitors
            2) BCL2 inhibitors
        ii. Efficacy and safety data for targeted therapies
        iii. Managing adverse events
    c. Relapsed/refractory (R/R) CLL
        i. PI3K inhibitors
            1) Managing adverse events
        ii. Revisiting BTK and BCL2 inhibitors in the R/R setting
    d. Role of Allo-SCT

4. Choose the Appropriate Therapy: A Lightning Round of 5 Short Cases

5. Applying Shared Decision-Making in CLL: (Selected Case Studies from the Lightning Round)
    a. Considering goals of care and patient preferences in the management of CLL
    b. Patient education on CLL and therapy options
    c. Applying shared decision making to clinical practice

6. Conclusions: CLL

Part 2: Acute Myeloid Leukemia

7. AML: An Overview
    a. Review of epidemiology, disease pathophysiology, and course
    b. Effects on QoL
    c. Treatment options and standard of care

8. The Genomics of AML and the Role of Biomarkers in AML
    a. Common genetic aberrations
        i. Diagnostic and prognostic value
        ii. Role in treatment decision-making
        iii. Guidelines and recommendations for testing

9. *De novo*, secondary, and relapsed/refractory (R/R) AML
    a. Role of HSCT
    b. Currently Approved Novel Agents for the Management of Patients with AML
        i. Indications and efficacy and safety studies
            1) Liposomal 7+3/CPX-351
            2) BCL-2 inhibitor
            3) Hedgehog pathway inhibitor
            4) FLT3 inhibitor
            5) IDH1 inhibitor
            6) IDH2 inhibitor
            7) CD33 drug-antibody conjugate
            8) CC-486

10. Choose the Appropriate Therapy: A Lightning Round of 5 Short Cases

11. Personalizing Therapy: Applying Shared Decision Making in AML

12. Conclusions: AML

Part 3:

Questions and answers

Adjournment

CATALYST: Insights from the Experts to Navigate a Complex and Evolving Landscape in CLL and AML Management

FACULTY

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PROGRAM OVERVIEW

This live activity will cover the treatment and management of patients with AML and CLL.

TARGET AUDIENCE

This activity is intended for US-based hematologists, medical oncologists, and other healthcare providers involved in the management of patients with CLL and/or AML.

LEARNING OBJECTIVES

Upon completion of the program, attendees should be able to:

- Determine how genetic and molecular markers aid in determining treatment strategies for patients with either CLL or AML
- Differentiate therapy for the treatment of newly diagnosed or relapsed/refractory (R/R) CLL or AML based on disease- and patient-specific factors and communicate treatment plans using shared decision-making strategies
- Distinguish adverse events associated with either CLL or AML treatment to appropriately prevent and/or manage potential effects

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Purpose: This program would be beneficial for nurses involved in the care of patients with AML and CLL.
Credits: 2.0 ANCC Contact Hours.

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Ryan Jacobs, MD serves on a speaker bureau for AbbVie, AstraZeneca, Janssen, Pharmacyclics, Secura Bio and TG Therapeutics; serves as consultant for Adaptive, AstraZeneca, Genentech, Secura Bio, and TG Therapeutics; and receives research funding from MEI Pharma Pharmacyclics, Teneobio and TG Therapeutics.

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The content of this activity was independently peer reviewed.
The reviewer of this activity has nothing to disclose.

CNE Content Review
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Douglas Cox, MSN, MHA, RN
Ultimate Medical Academy/CCM – Lead Nurse Planner

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CATALYST: Insights from the Experts to Navigate a Complex and Evolving Landscape in CLL and AML Management

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- During the course of this lecture, the faculty may mention the use of medications for both FDA-approved and non-approved indications

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Learning Objectives

- Determine how genetic and molecular markers aid in determining treatment strategies for patients with either chronic lymphocytic leukemia (CLL) or acute myeloid leukemia (AML)
- Differentiate therapy for the treatment of newly diagnosed or relapsed/refractory CLL or AML based on disease- and patient-specific factors and communicate treatment plans using shared decision-making strategies
- Distinguish adverse events associated with either CLL or AML treatment to appropriately prevent and/or manage potential effects

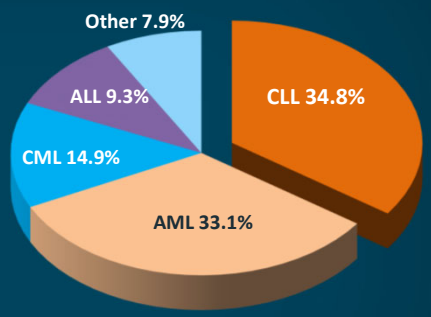
Assessment of Chronic Lymphocytic Leukemia in the Treatment-Naïve Setting

Chronic Lymphocytic Leukemia (CLL)

Definition of CLL—IWCLL (2008)[1]

- Small, monomorphic, mature B-cells
- At least 5000/µL B-cells
- Co-express CD5 and CD23

2021 expected new cases of leukemia in the US by type[2]



- In the US in 2021, an estimated **21,250** patients will be diagnosed with CLL[2]
- Average age of CLL at diagnosis = ~70 years[3]

IWCLL = International Workshop on Chronic Lymphocytic Leukaemia; CD = cluster of differentiation; ALL = acute lymphocytic leukemia; CML = chronic myeloid leukemia.

1. Hallek M, et al; IWCLL. *Blood.* 2008;111:5446-5456. 2. American Cancer Society (ACS). Cancer Facts & Figures 2021 (www.cancer.org/content/ dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2020/cancer-facts-and-figures-2020.pdf). 3. ACS CLL key statistics (www.cancer.org/cancer/chronic-lymphocytic-leukemia/about/key-statistics.html). Accessed 7/7/2021.

What Do We Do at Initial Presentation?

All patients undergo—

- History and physical
- CBC with differential
- CMP
- Quantitative immunoglobulins
- Infectious serology
- Peripheral blood flow cytometry
- ± CT scan of CAP
- ± bone marrow biopsy

Prognostic markers

- Conventional karyotyping
- Interphase FISH
- *IgHV* mutational analysis
- Beta-2 microglobulin
- LDH

Staging?

- Rai
- Binet

CLL-IPI?

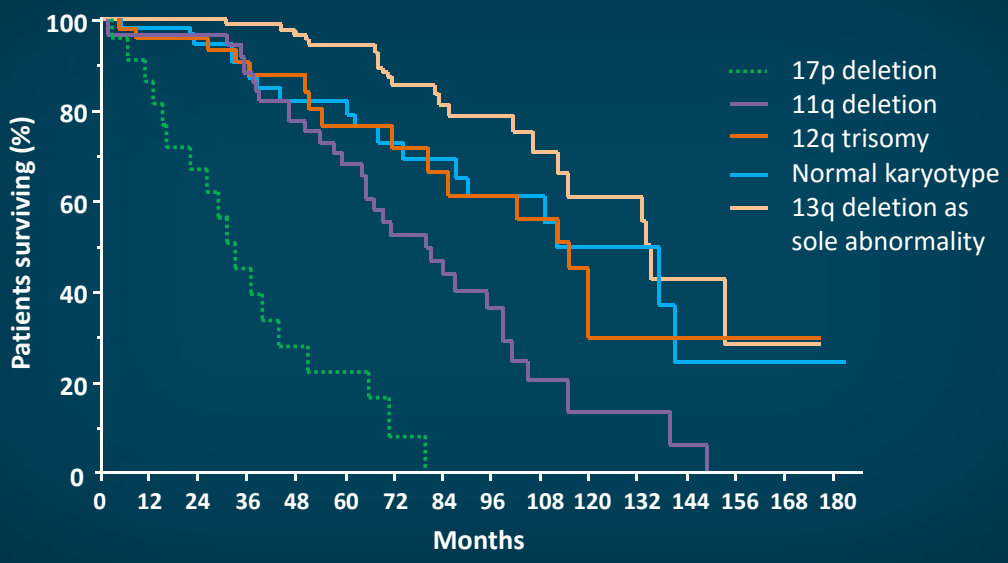
CBC = complete blood count; CMP = comprehensive metabolic panel; CT = computed tomography; CAP = chest/abdomen/pelvis; FISH = fluorescence in situ hybridization; *IgHV* = immunoglobulin heavy-chain variable region (gene); LDH = lactate dehydrogenase; CLL-IPI = International Prognostic Index for CLL.

Prognostic Markers in CLL

Prognostic Markers

- **Interphase cytogenetics by FISH**
- *IgHV* mutational status
- *TP53* mutation analysis

Interphase FISH Correlates With Overall Survival



Döhner H, et al. *N Engl J Med.* 2000;343:1910-1916.

Outcome by Interphase FISH Abnormalities

Abnormality detected by FISH	Median Time to Treatment (mos)	Median OS (mos)	Patients (%)
Del 17p	9	32	7
Del 11q	13	79	18
Trisomy 12q	33	114	16
Del 13q*	92	133	55
Normal	49	111	18

*sole abnormality.

OS = overall survival; del = deletion; mo(s) = month(s).

Döhner H, et al. *N Engl J Med.* 2000;343:1910-1916.

Prognostic Markers

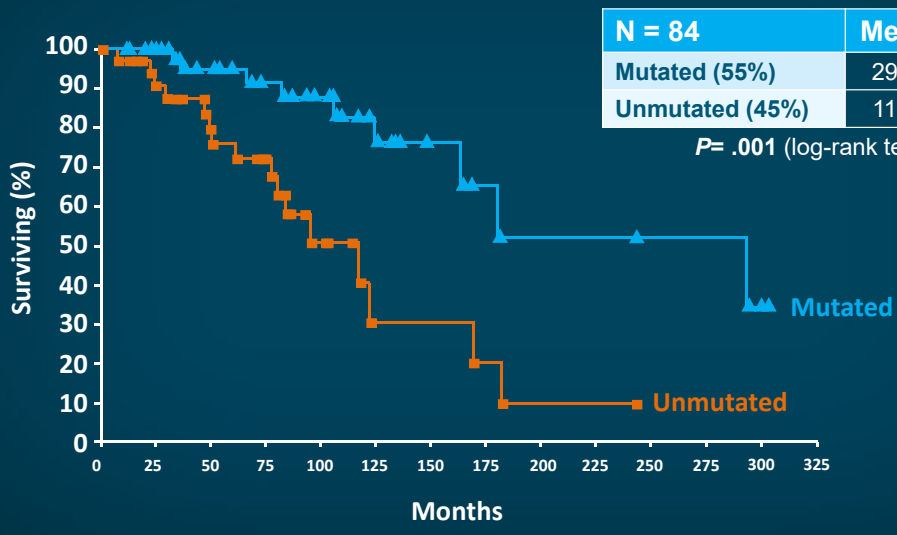
- Interphase cytogenetics by FISH
- ***IgHV* mutational status**
- *TP53* mutation analysis

Significance of *IgHV*

- *IgHV* undergoes hypermutation during B-cell development[1,2]
- Mutational status of *IgHV* predicts clinical outcome in CLL[1]
- Mutated *IgHV* is defined as <98% sequence homology to established germline sequence[2]
- Unmutated *IgHV* predicts earlier therapy, poorer response, inferior survival, and risk of transformation[1,2]

1. Damle RN, et al. *Blood.* 1999:94:1840-1847. 2. Rozovski U, et al. *Acta Haematol*. 2018;140:51-54.

IgHV Mutational Status Predicts Survival



N = 84	Median OS
Mutated (55%)	293 months
Unmutated (45%)	117 months

***P*= .001** (log-rank test)

Hamblin TJ, et al. *Blood*. 1999;94:1848-1854.

Prognostic Markers

- Interphase cytogenetics by FISH
- *IgHV* mutational status
- ***TP53* mutation analysis**

Criteria for Initiation of Treatment

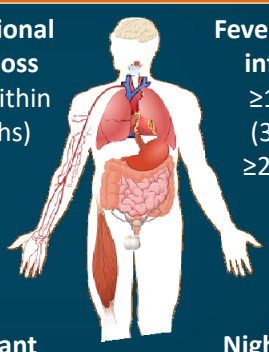
Active Disease

Active disease is defined as having ≥1 of the following:

- Hemoglobin <10 g/dL
- Platelet count <100 x 10^9/L
- Symptomatic or functional extranodal involvement
- Autoimmune anemia or thrombocytopenia poorly responsive to corticosteroids
- Lymphocyte doubling time ≤6 months
- Bulky disease (spleen ≥6 cm beneath costal margin, lymph nodes ≥10 cm)

Symptoms

Unintentional weight loss (≥10% within 6 months)



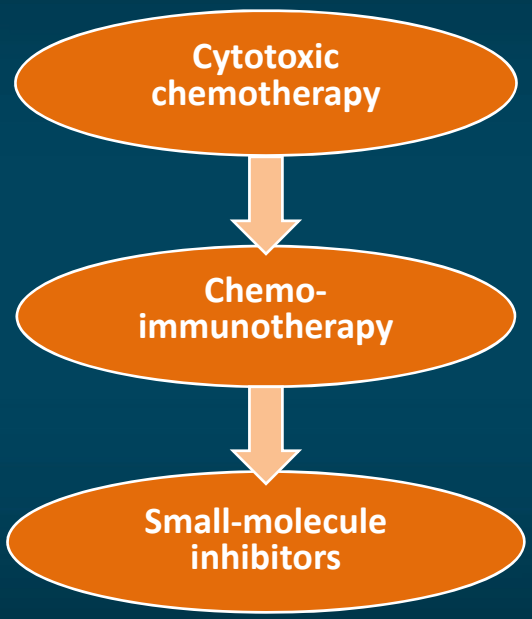
Fever without infection ≥100.5°F (38.0°C) ≥2 weeks

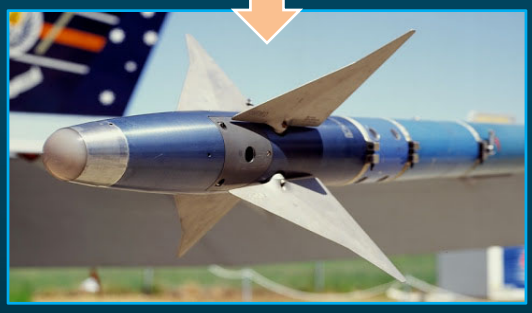
Significant fatigue

Night sweats (≥1 month)

Hallek M, et al. *Blood*. 2018;131:2745-2760.

Advances in Therapeutic Paradigms





FCR vs BR—CLL10 GCLLSG Trial

	FCR n = 282	BR n = 279	*P* value
ORR (%)	95	96	NS
CR (%)	40	31	.034
Median PFS (months)	55.2	41.7	.003
OS at 3 yrs (%)	91	92	NS
Severe neutropenia (%)	84	59	<.001
Severe infections (%)	39	25	.001
TRM (%)	5	2	—

FCR = fludarabine + cyclophosphamide + rituximab; BR = bendamustine + rituximab; GCLLSG = German CLL Study Group; ORR = overall/objective response rate; CR = complete response/remission; PFS = progression-free survival; yr(s) = year(s); TRM = treatment-related mortality; NS = not significant.

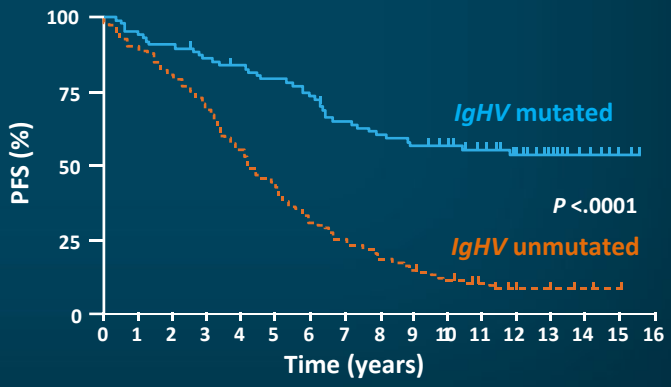
Eichhorst B, et al. *Lancet Oncol.* 2016;17:928-942. Eichhorst B, et al. *Blood.* 2014;124(21): abstract 19.

FCR: A Possible Cure for CLL?

- Median PFS was not reached at 12.8 years in *IgHV*-mutated group
- Almost 51% of *IgHV*-mutated patients achieved MRD negativity
- No relapses have been seen beyond 10 years in *IgHV*-mutated patients
- FCR vs ibrutinib as preferred front-line therapy?

12.8-year result	Patients n	PFS %
IgHV-m	88	55.9
IgHV-u	126	8.7

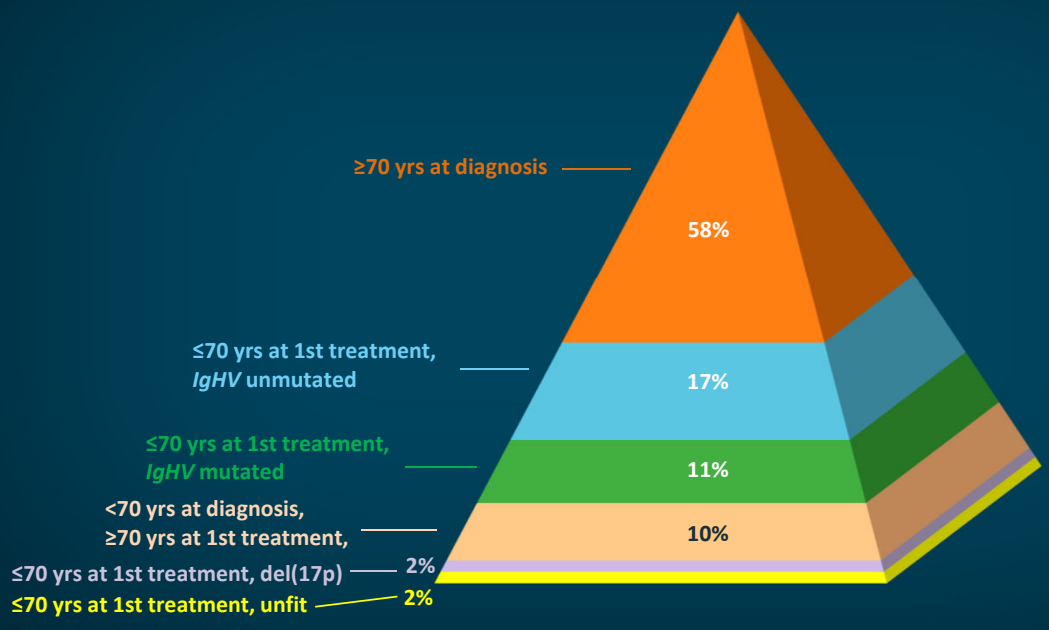
P <.0001



IgHV-m = *IgHv*-mutated; *IgHV*-u = *IgHV*-unmutated; MRD = minimal residual disease.

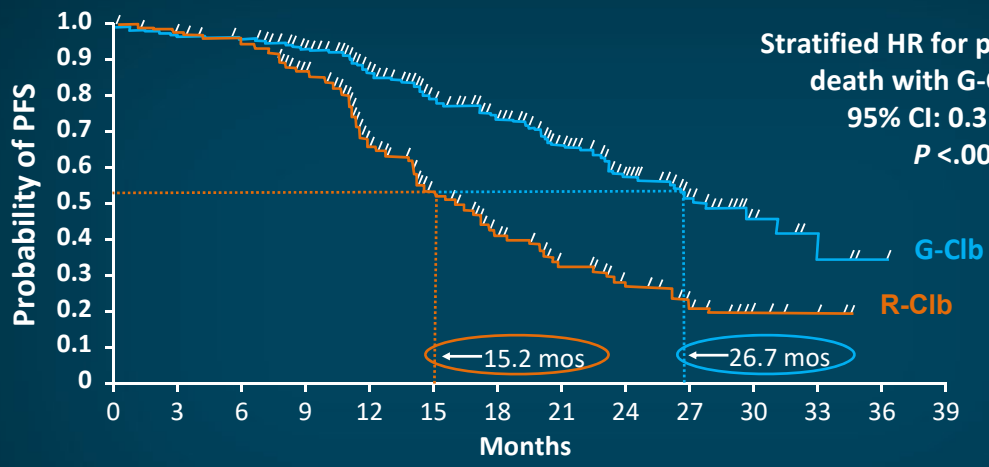
Thompson PA, et al. *Blood.* 2016;127:303-309.

Proportion of Patients According to Age and *IgHV* Status



Slide courtesy of Dr. Alessandra Tedeschi.

Obinutuzumab + Chlorambucil—CLL-11 Trial

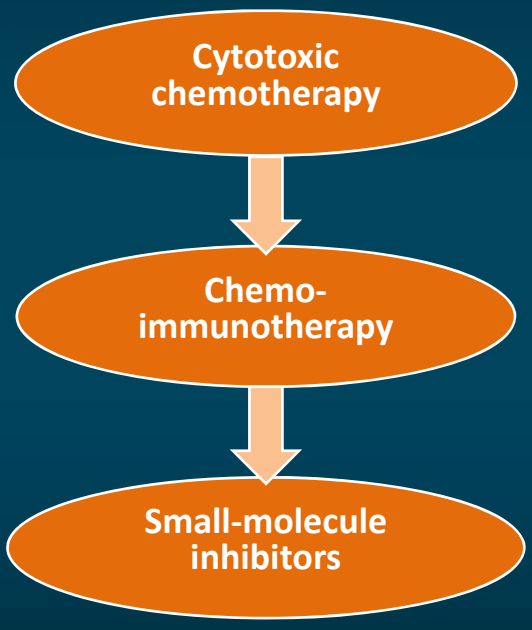


- Obinutuzumab is an engineered anti-CD20 mAb
- It is well tolerated in patients with comorbidities and median age of 73

HR = hazard ratio; CI = confidence interval; Clb = chlorambucil; G-Clb = obinutuzumab + chlorambucil; R-Clb = rituximab + chlorambucil; mAb = monoclonal antibody.

Goede V, et al. *N Engl J Med.* 2014;370:1101-1110.

Advances in Therapeutic Paradigms

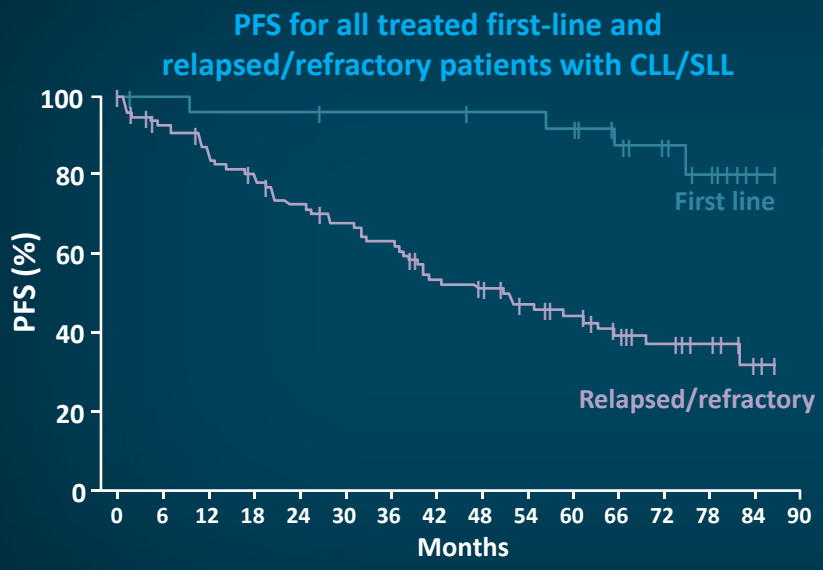


CLL MOA

https://youtu.be/mybD0VOmM-4

Treatment with BTK Inhibition

PFS With Long-Term Ibrutinib Use

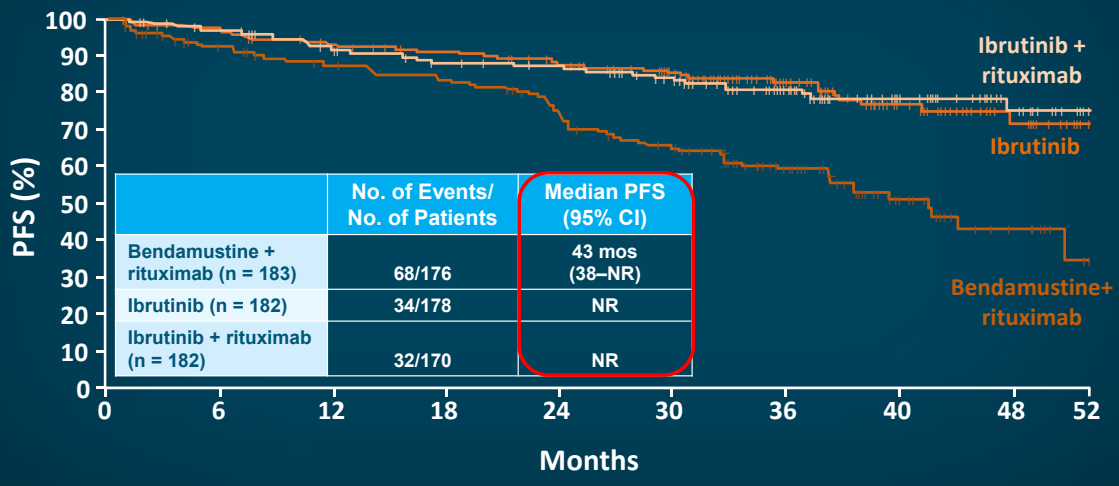


	Median PFS	7-year PFS
Treatment-naïve (n = 31)	NR	80%
R/R (n = 101)	51 mos	32%

SLL = small lymphocytic lymphoma; R/R = relapsed/refractory; NR = not reached.

Byrd JC, et al. *Blood.* 2018;132(suppl 1):abstract 3133.

ALLIANCE: Ibrutinib Regimens vs Chemoimmunotherapy in Older Patients with Untreated CLL

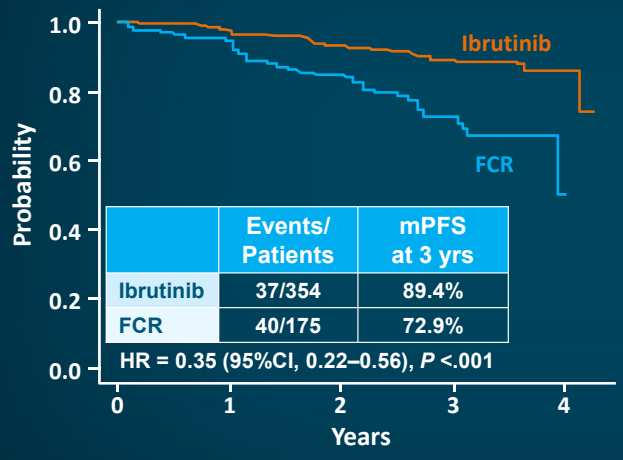


	No. of Events/ No. of Patients	Median PFS (95% CI)
Bendamustine + rituximab (n = 183)	68/176	43 mos (38–NR)
Ibrutinib (n = 182)	34/178	NR
Ibrutinib + rituximab (n = 182)	32/170	NR

Woyach JA, et al. *N Engl J Med*. 2018;379:2517-2528.

Ibrutinib vs FCR in Untreated Younger Patients with CLL (ECOG)

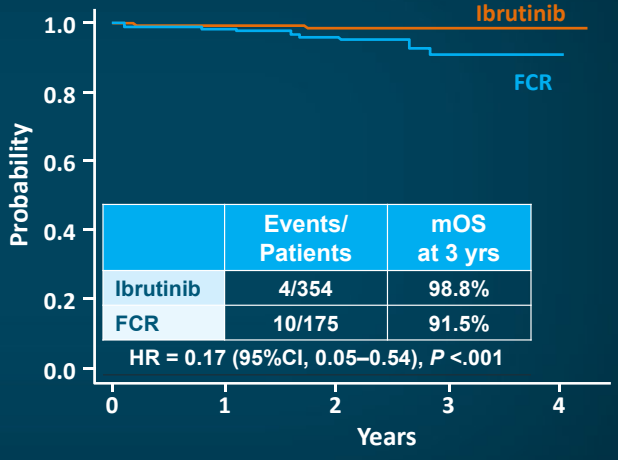
PFS (all randomized)



	Events/ Patients	mPFS at 3 yrs
Ibrutinib	37/354	89.4%
FCR	40/175	72.9%

HR = 0.35 (95%CI, 0.22–0.56), *P* <.001

OS (all randomized)



	Events/ Patients	mOS at 3 yrs
Ibrutinib	4/354	98.8%
FCR	10/175	91.5%

HR = 0.17 (95%CI, 0.05–0.54), *P* <.001

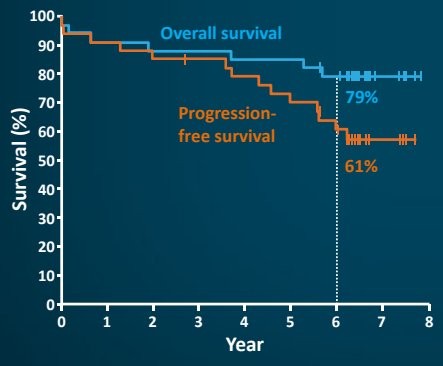
ECOG = Eastern Cooperative Oncology Group; mPFS = median PFS; mOS = median OS.

Shanafelt TD, et al. *N Engl J Med.* 2019;381:432-443.

First-Line BTK Inhibition in Del(17p)/*TP53*^{mut} CLL

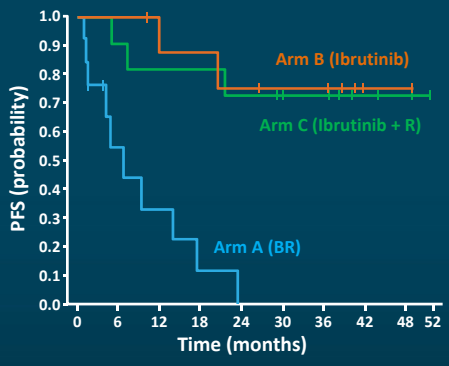
Phase 2 study: ibrutinib for CLL With *TP53*^{mut}[1]

6.5-year FU



ALLIANCE: ibrutinib vs ibrutinib + rituximab vs BR[2]

38-mo FU



iLLUMINATE: O-Clb vs ibrutinib + obinutuzumab[3]

31.3-mo FU

Median PFS
Ibrutinib + Obinutuzumab = NR
O-Clb = 19.0 mos

BTK = Bruton's tyrosine kinase; O-Clb = obinutuzumab + chlorambucil; FU = follow-up.

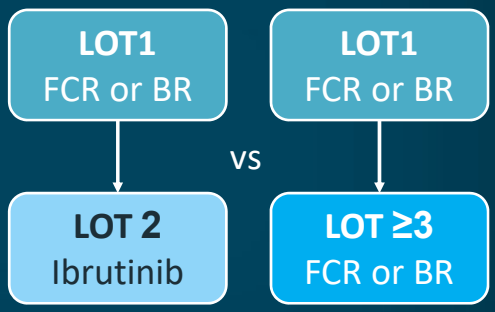
1. Ahn IE, et al. *N Engl J Med.* 2020;383:498-500. 2. Woyach JA, et al. *N Engl J Med.* 2018;379:2517-2528 and supplement. 3. Moreno C, et al. *Lancet Oncol.* 2019;20:43-56.

Real-World Evidence: Use of Ibrutinib in R/R CLL

Connect CLL Registry

- US-based multicenter prospective observational cohort study
- N = 1494 patients between 2010 and 2014 from predominantly community-based settings
- Patients were grouped by line of therapy (LOT) at enrollment

Treatment with ibrutinib in the R/R setting improved OS

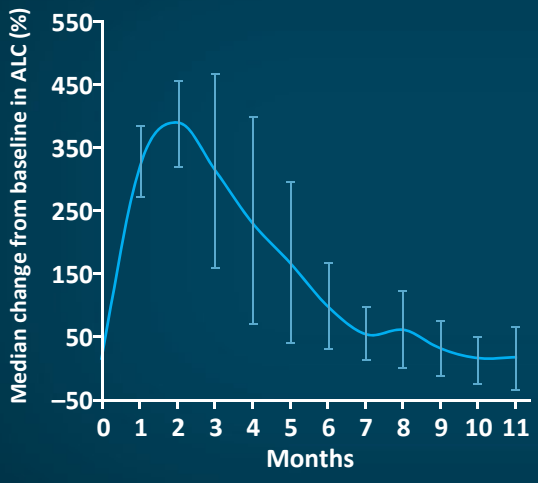


HR = 0.461
95% CI, 0.214–0.998
P= .049

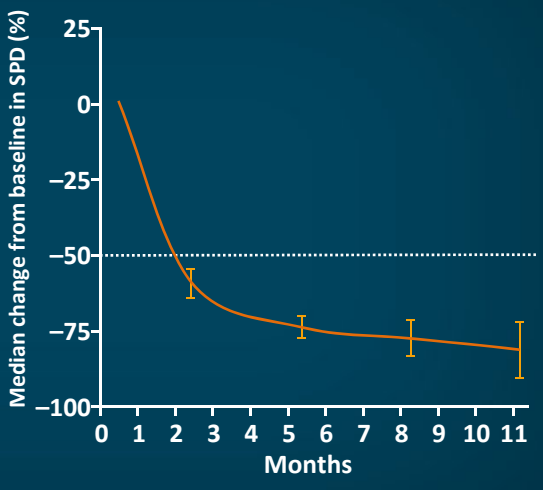
Mato A, et al. *Blood Adv.* 2020;4:1407-1418.

Pattern of Response: Blood Lymphocytes vs Lymph Nodes

Blood lymphocytes: ALC



Lymph nodes: SPD

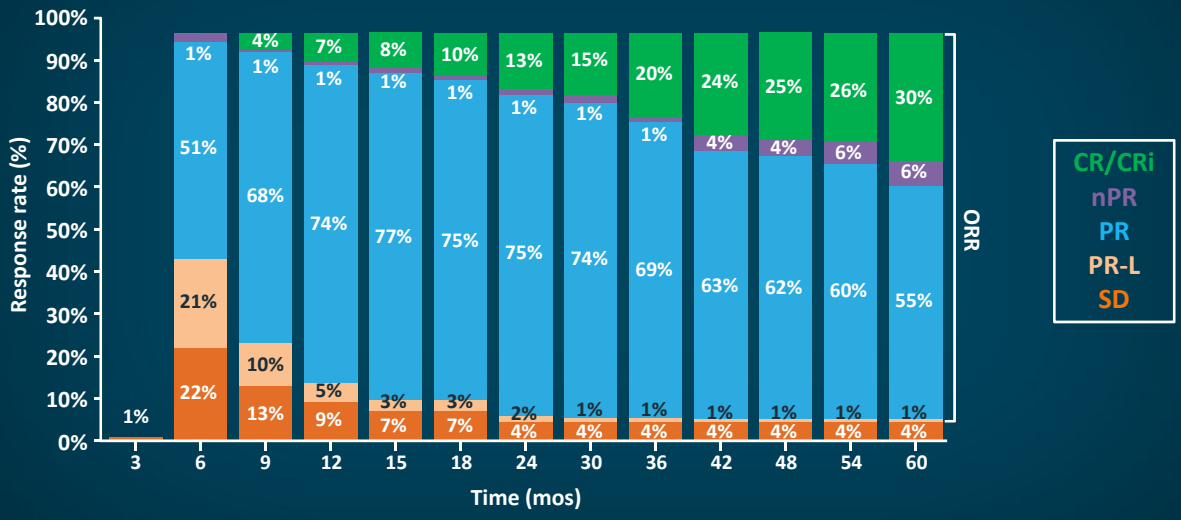


ALC = absolute lymphocyte count; SPD = sum of the products of perpendicular diameters of lymph nodes.

Byrd JC, et al. *N Engl J Med*. 2013;369:32-42.

Response Deepens Over Time

RESONATE-2 (ibrutinib monotherapy): cumulative best response over time on study



CR = complete response; CRi = CR with incomplete marrow recovery; PR = partial response/remission; nPR = nodular PR, PR-L = PR with lymphocytosis; SD = stable disease; ORR = overall/objective response rate.

Burger JA, et al. *Leukemia*. 2020;34:787-798.

Understanding Spectrum of Grade 3/4 AEs With Ibrutinib

Extended Follow-Up

Adverse event, %	≤1 year	>1–2 years	>2–3 years	>3–4 years	>4–5 years	>5–6 years	>6–7 years	Overall study
Hypertension	9	8	19	15	16	16	5	28
Pneumonia	11	10	7	10	6	6	3	24
Neutropenia	11	3	2	1	2	2	0	18
Thrombocytopenia	6	3	2	1	0	0	0	9
Atrial fibrillation	2	3	1	5	5	0	0	9
Diarrhea	3	3	1	3	2	2	0	7
Cellulitis	2	1	6	3	0	2	0	7
Sepsis	2	5	0	3	2	2	0	8
Fatigue	3	2	0	3	0	0	0	6
Decreased lymphocyte count	0	2	6	4	3	6	0	7

Dose reductions due to AEs = 14%; discontinuation due to AEs = 26%

Consider risks and benefits in patients on anticoagulants; monitor for bleeding, fever, infections (evaluate promptly)

AE = adverse event.

O'Brien S, et al. *Blood*. 2018:131:1910-1919 and supplement. Byrd JC, et al. *Clin Cancer Res*. 2020;26:3918-3927.

Dosing Modifications for Managing Adverse Reactions with Ibrutinib

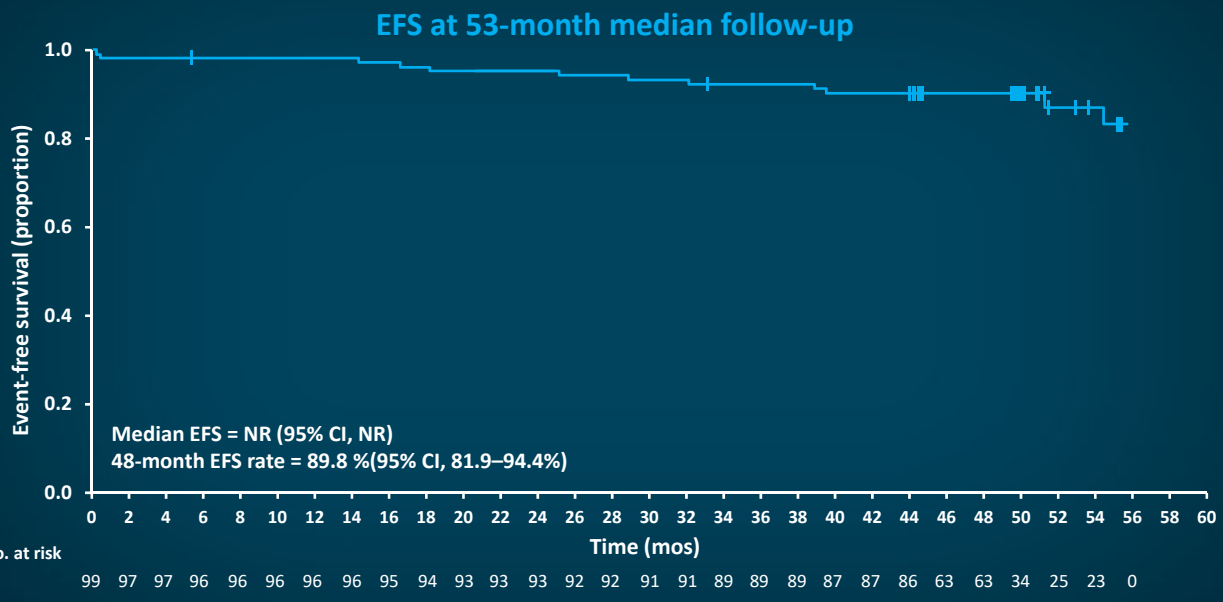
Ibrutinib (Imbruvica®) prescribing information (PI) 2019 (https://imbruvica.com/files/prescribing-information.pdf). Accessed 7/7/2021.

Ibrutinib

- Approved for front-line and relapsed therapy for all CLL
- Promising responses: ~90%
- Functions as a disease modulator—low incidence of complete responses
  - 2–7% in relapsed/refractory CLL
  - Up to 29% in previously untreated CLL
- Response deepens over time
  - Median time to response is 4 mos
  - Median time to best response is 12 mos
- Del17p responds, but PFS is shorter

Slide courtesy of Dr. Ryan Jacobs.

ACE-CL-001: Acalabrutinib in Treatment-Naïve Cohort



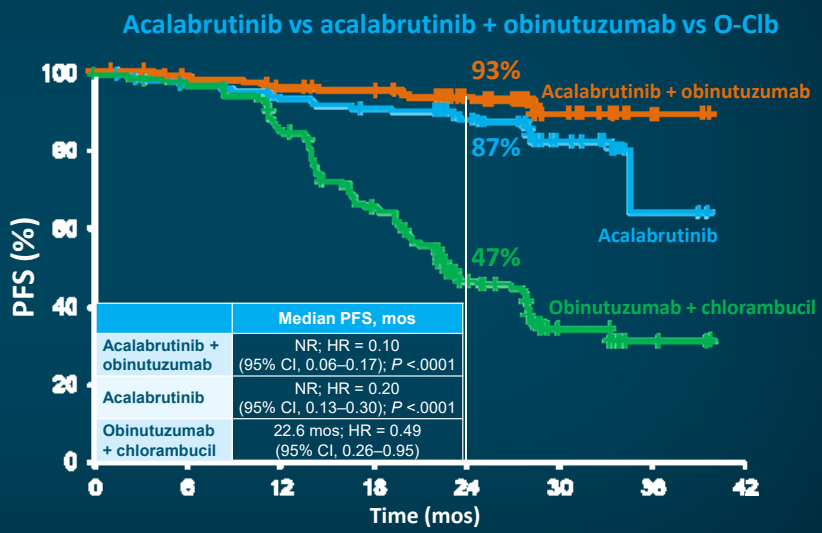
EFS = event-free survival.

Byrd JC, et al. *Blood.* 2021;137:3327-3338.

ELEVATE-TN: Acalabrutinib ± Obinutuzumab in Treatment-Naïve Patients With Coexisting Medical Conditions

- Phase 3, open-label trial
- Untreated CLL
- Eligible patients were either ≥65 years or 18 to <65 years with comorbidities
- Median FU = 28.3 mos

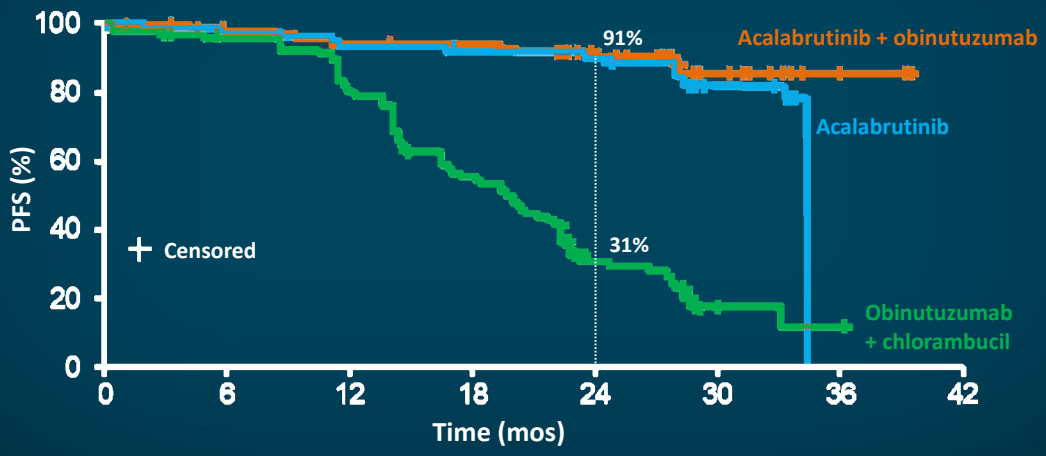
Post hoc analysis
HR for PFS between acalabrutinib + obinutuzumab and acalabrutinib monotherapy = 0.49 (95% CI, 0.26–0.95)



Sharman JP, et al. *Lancet*. 2020;395:1278-1291.

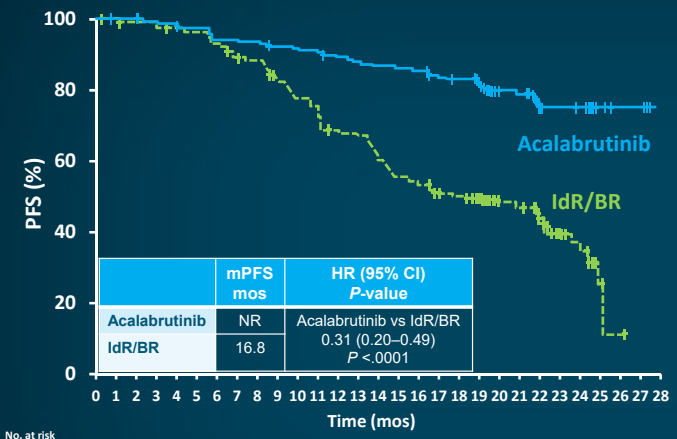
ELEVATE-TN: Acalabrutinib ± Obinutuzumab in Treatment-Naïve Patients With Coexisting Medical Conditions

PFS in *IgHV*-unmutated patients

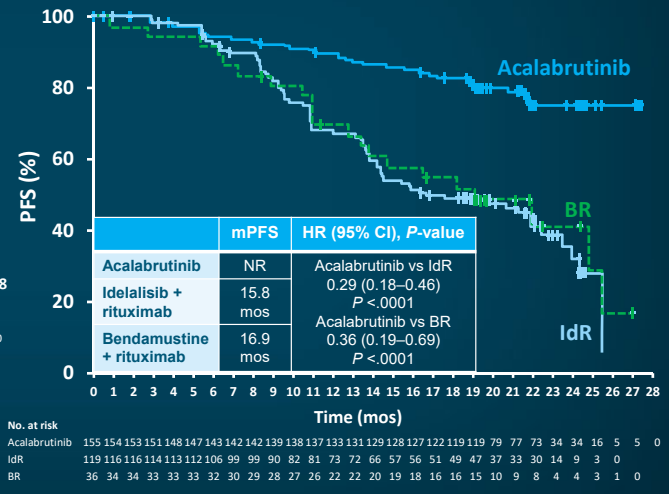


Modified from Sharman JP, et al. *Lancet*. 2020;395:1278-1291.

Phase 3 ACE-CL-309/ASCEND: Acalabrutinib Improves PFS in R/R CLL



	mPFS mos	HR (95% CI) *P*-value
Acalabrutinib	NR	Acalabrutinib vs IdR/BR 0.31 (0.20–0.49) *P* <.0001
IdR/BR	16.8	



	mPFS	HR (95% CI), *P*-value
Acalabrutinib	NR	Acalabrutinib vs IdR 0.29 (0.18–0.46) *P* <.0001
Idelalisib + rituximab	15.8 mos	
Acalabrutinib vs BR 0.36 (0.19–0.69) *P* <.0001		
Bendamustine + rituximab	16.9 mos	

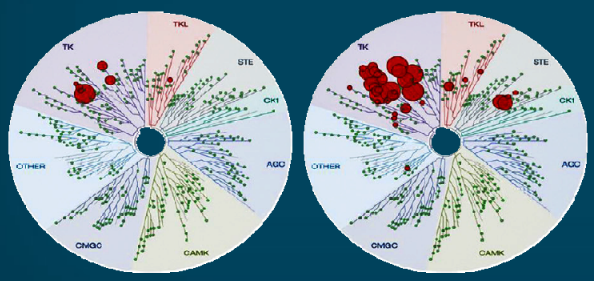
R = rituximab; IdR = idelalisib + R; BR = bendamustine + R.

Ghia P, et al. *J Clin Oncol*. 2020;38:2849-2861. Ghia P, et al. *J Clin Oncol*. 2020;38(15 suppl): abstract 8015.

Acalabrutinib (ACP-196)

Acalabrutinib is more selective for BTK with less off-target kinase inhibition compared with ibrutinib *in vitro*

Kinase selectivity profiling at 1 µM



Larger red circles represent stronger inhibition

Recombinant Kinase Inhibition Assays		
Kinase	IC_{50} (nM)	
	Acalabrutinib	Ibrutinib
BTK	5.1	1.5
TEC	93.0	7.0
ITK	>1000	4.9
BMX	46	0.8
TXK	368	2.0
EGFR	>1000	5.3
ErbB2	~1000	6.4
ErbB4	16	3.4
BLK	>1000	0.1
JAK3	>1000	32

IC_{50} = half-maximal inhibitory concentration; TEC = tyrosine kinase (TK) expressed in hepatocellular cancer; ITK = IL2-inducible T-cell kinase; BMX = bone marrow TK on chromosome X; TXK = tyrosine-protein kinase; EGFR = epidermal growth factor receptor; ErbB = erythroblastic oncogene B; BLK = B lymphocyte tyrosine kinase; JAK = Janus kinase.

Herman SEM, et al. *Clin Cancer Res*. 2017;23:2831-2841. Byrd JC, et al. *N Engl J Med*. 2016;374:323-332 and supplement.

Acalabrutinib Safety

	Phase 1b/2[1] Acalabrutinib N = 99	ELEVATE-TN[2] Acalabrutinib n = 179	ELEVATE-TN[2] Acalabrutinib + O n = 179
Acalabrutinib exposure	53 mos	28.3 mo	28.3 mo
Patients remaining on acalabrutinib treatment	86%	79%	79%
Primary reasons for discontinuation • PD while on treatment • Adverse events	 3% 6%	 3.9% 8.9%	 3.4% 11.2%

ELEVATE-TN: Most Common AEs[2]				
AEs, n (%)	Acalabrutinib + O		Acalabrutinib	
	Any	Grade ≥3	Any	Grade ≥3
Headache	71 (39.9)	2 (1.1)	66 (36.9)	2 (1.1)
Diarrhea	69 (38.8)	8 (4.5)	62 (34.6)	1 (0.6)
Neutropenia	56 (31.5)	53 (29.8)	19 (10.6)	17 (9.5)
Fatigue	50 (28.4)	3 (1.7)	33 (18.4)	2 (1.1)
Contusion	42 (23.6)	0	27 (15.1)	0
Arthralgia	39 (21.9)	2 (1.1)	28 (15.6)	1 (0.6)

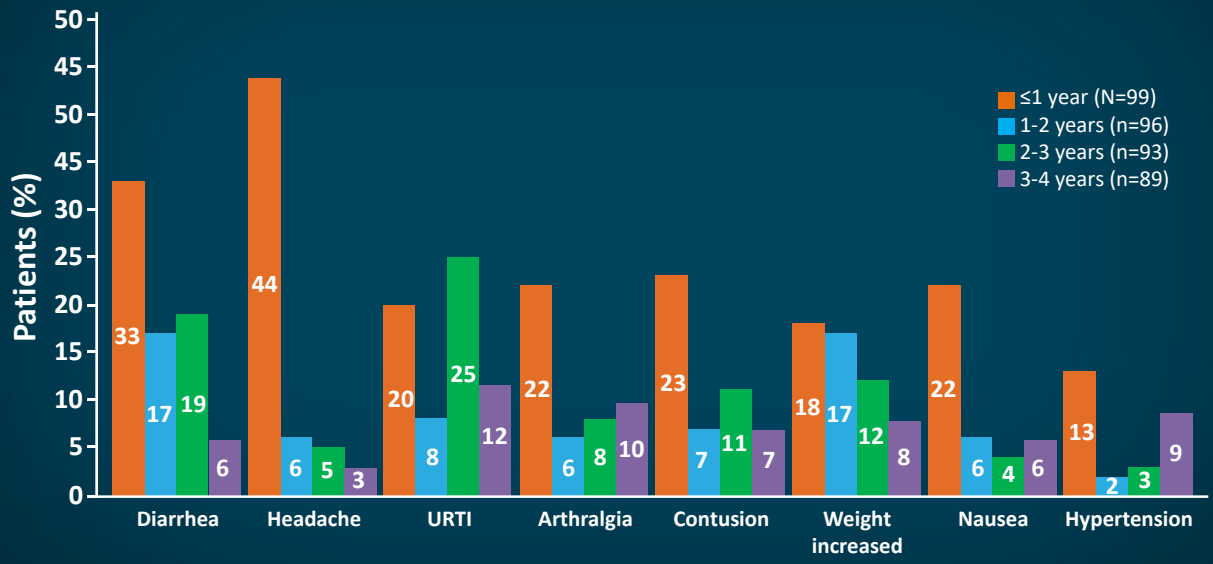
ELEVATE-TN: AEs of Interest[2]		
	Acalabrutinib + O	Acalabrutinib
Atrial fibrillation Any grade	3%	4%
Bleeding Any grade Grade ≥3	 43% 2%	 39% 2%
Hypertension Grade ≥3	3%	2%

O = obinutuzumab; PD = progressive disease.

1. Byrd JC, et al. *Blood*. 2021;137:3327-3338. 2. Sharman JP, et al. *Lancet*. 2020;395:1278-1291.

Incidence of AEs on Acalabrutinib by Year

AEs were generally more common within the first year of acalabrutinib treatment

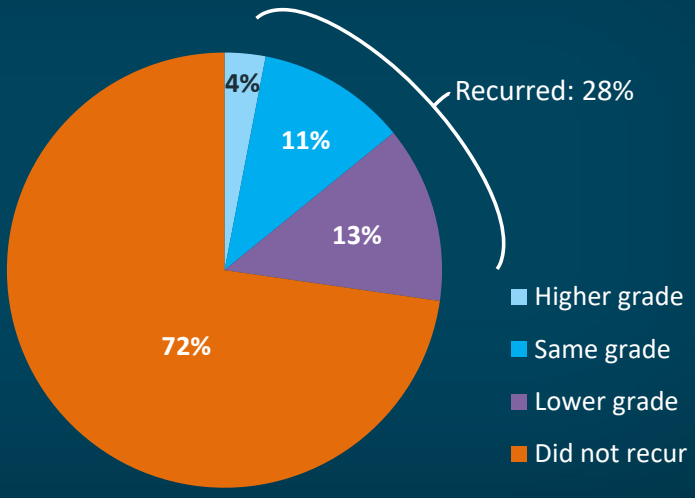


URTI = upper respiratory tract infection.

Byrd JC, et al. *Blood.* 2021;137:3327-3338. Byrd JC, et al. *Blood.* 2018;132(suppl 1): abstract 692.

Acalabrutinib for Ibrutinib-Intolerant CLL Patients (N = 33)

Recurrence of Ibrutinib-related AEs during acalabrutinib treatment



Awan FT, et al. *Blood Adv*. 2019;3:1553-1562.

ELEVATE-RR: Phase 3 Randomized Non-inferiority Open-Label Trial

Key inclusion criteria

- Adults with previously treated CLL requiring therapy per IWCLL 2008
- Presence of del(17p) or del(11q)
- ECOG PS of ≤2
- No significant CV disease
- No prior treatment with ibrutinib or BTK, PI3K, Syk, or BCL-2 inhibitors

N = 533

RANDOMIZE

1:1

Acalabrutinib 100 mg PO BID

Ibrutinib[b] 420 mg PO QD

Continue until PD or unacceptable toxicity

Primary endpoint: PFS as assessed by IRC
Secondary endpoints: incidence of any grade atrial fibrillation/flutter; incidence of grade ≥3 infection; incidence of Richter transformation; OS
Stratification by del(17p) status (yes or no), ECOG PS (2 vs ≤1), and number of prior therapies (1–3 vs ≥4)

PS = performance status; IRC = independent review committee; OS = overall survival; PO = by mouth; BID = twice daily; QD = once daily.

Byrd JC, et al. *J Clin Oncol.* 2021;39(15 suppl): abstract 7500.

ELEVATE-RR: Patient Disposition

	Acalabrutinib (n = 268)	Ibrutinib (n = 265)
Duration of follow-up, median (range), mos	41.1 (0.0–58.2)	40.7 (0.2–59.1)
Patients who received treatment	265 (98.9)	264 (99.6)
Patients continuing to receive treatment at data cutoff	124 (46.3)	109 (41.1)
Patients who discontinued treatment	141 (52.6)	155 (58.5)
Reasons for treatment discontinuation		
Disease progression*	82 (30.6)	68 (25.7)
Adverse event	40 (14.9)	59 (22.3)
Consent withdrawn	7 (2.6)	7 (2.6)
Death	5 (1.9)	6 (2.3)
Investigator decision	5 (1.9)	5 (1.9)
Other	2 (0.7)	10 (3.8)

Data cutoff date: September 15, 2020.
*Disease progression includes Richter's transformation.

Byrd JC, et al. *J Clin Oncol.* 2021;39(15 suppl): abstract 7500.

ELEVATE-RR: Most Common AEs

Events, n (%)	Any grade		Grade ≥3	
	Acalabrutinib (n = 266)	Ibrutinib (n = 263)	Acalabrutinib (n = 266)	Ibrutinib (n = 263)
Diarrhea	92 (34.6)	**121 (46.0)**	3 (1.1)	**13 (4.9)**
Headache	**92 (34.6)**	53 (20.2)	**4 (1.5)**	0
Cough	**77 (28.9)**	56 (21.3)	2 (0.8)	1 (0.4)
URTI	71 (26.7)	65 (24.7)	5 (1.9)	1 (0.4)
Neutropenia	56 (21.1)	65 (24.7)	52 (19.5)	60 (22.8)
Pyrexia	62 (23.3)	50 (19.0)	8 (3.0)	2 (0.8)
Arthralgia	42 (15.8)	**60 (22.8)**	0	2 (0.8)
Hypertension	23 (8.6)	**60 (22.8)**	11 (4.1)	**23 (8.7)**
Anemia	58 (21.8)	49 (18.6)	31 (11.7)	34 (12.9)
Fatigue	54 (20.3)	44 (16.7)	**9 (3.4)**	0
Nausea	41 (17.7)	49 (18.6)	0	1 (0.4)
Confusion	31 (11.7)	**48 (18.3)**	0	1 (0.4)
Pneumonia	47 (17.7)	43 (16.3)	28 (10.5)	23 (8.7)
Atrial fibrillation	24 (9.0)	**41 (15.6)**	12 (4.5)	9 (3.4)
Thrombocytopenia	40 (15.0)	35 (13.3)	26 (9.8)	18 (6.8)

Higher incidence in bold yellow for terms with statistical difference *P* <.05.

Byrd JC, et al. *J Clin Oncol.* 2021;39(15 suppl): abstract 7500.

Acalabrutinib

- Second-generation BTK inhibitor with higher selectivity to BTK
- No head-to-head comparative data vs ibrutinib at this time
- Lower incidence of all-grade adverse reactions noted in ibrutinib
  - Bruising: 15%
  - Rash: 14%
  - Afib: 4%
  - Hypertension: 2% (grade 3/4)
- Effective in ibrutinib-intolerant patients but not in ibrutinib resistance

Afib = atrial fibrillation.

1. Byrd JC et al. European Hematology Association (EHA) 2019: abstract S163 (https://library.ehaweb.org/eha/2020/eha25th/294983/john.c.byrd.acalabrutinib.in.treatment-nave.chronic.lymphocytic.leukemia.html). Accessed 7/19/2021. 2. Sharman JP, et al. *Lancet*. 2020;395:1278-1291 and supplement.

Treatment Paradigm in CLL

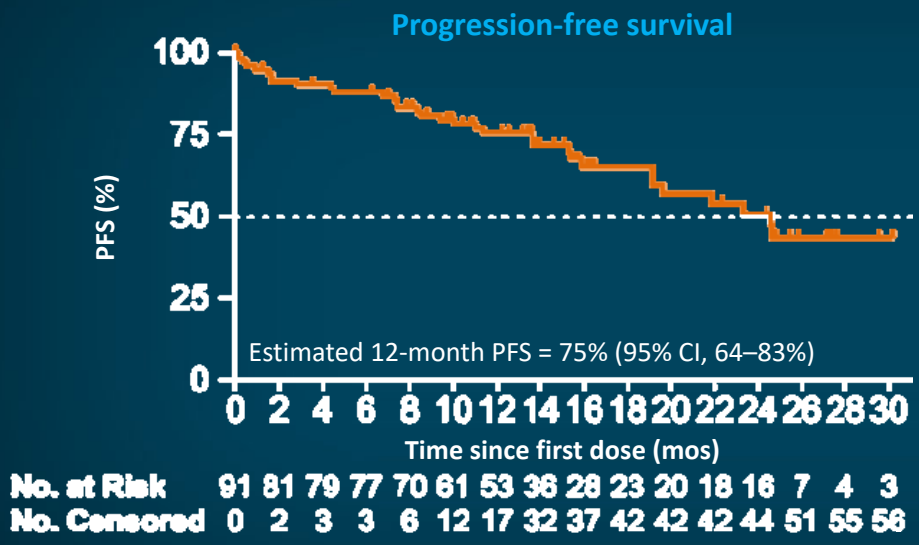
Continuous therapy	Goal of therapy
• BTK inhibitors	• Disease control • Prolonged PFS • Independent from response, MRD

Fixed duration	Goal of therapy
• Venetoclax + obinutuzumab	• Disease eradication • Prolonged PFS • Undetectable MRD

MRD = minimal residual disease.

Treatment with Venetoclax

Venetoclax in Ibrutinib-Refractory/Intolerant Patients

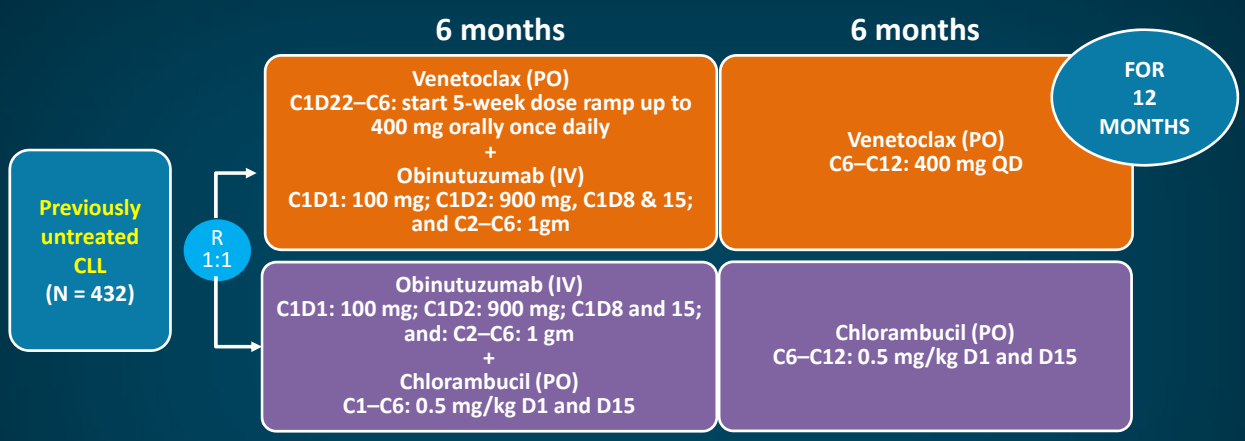


- Median of 4 prior therapies
- 47% del(17p)
- ORR* = 70%

*in main cohort.

Jones JA, et al. *Lancet Oncol*. 2018;19:65-75.

CLL14 Trial: Treatment-Naïve Patients with Coexisting Conditions



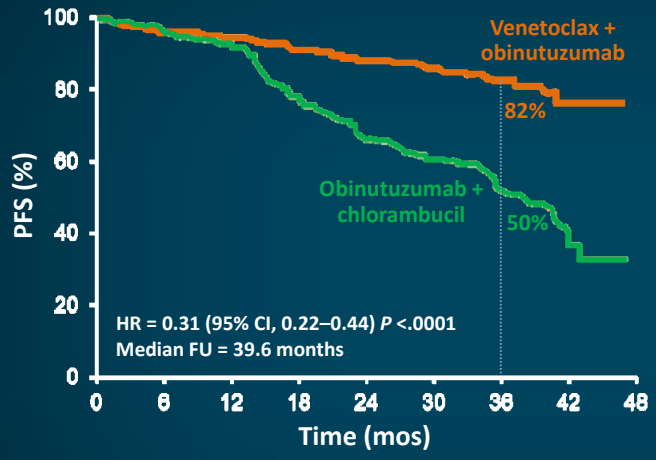
- **Primary endpoint:** investigator assessed PFS
- **Key secondary endpoints:** IRC assessed PFS, MRD negativity, ORR, CR, and OS
- **Stratification** according to Binet stage and geographic region

1 cycle = 28 days.

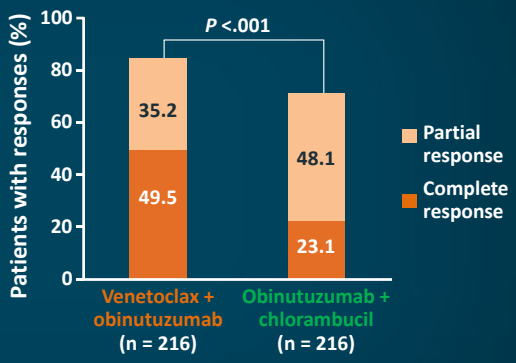
C = cycle; D = day; IV = intravenous.

Fischer K, et al. *N Engl J Med*. 2019;380:2225-2236.

CLL14: Venetoclax + Obinutuzumab for Untreated CLL



Treatment response



MRD

- Venetoclax + obinutuzumab = 75.5% PB (56.9% BM)
- Obinutuzumab + chlorambucil = 35.2% PB (17.1% BM)

PB = peripheral blood; BM = bone marrow.

Al-Sawaf O, et al. *Lancet Oncol*. 2020;21:1188-1200. Fischer K, et al. *N Engl J Med*. 2019;380:2225-2236.

CLL14: Fixed-Duration Venetoclax + Obinutuzumab in Treatment-Naïve Patients With Coexisting Medical Conditions

Eligible patients

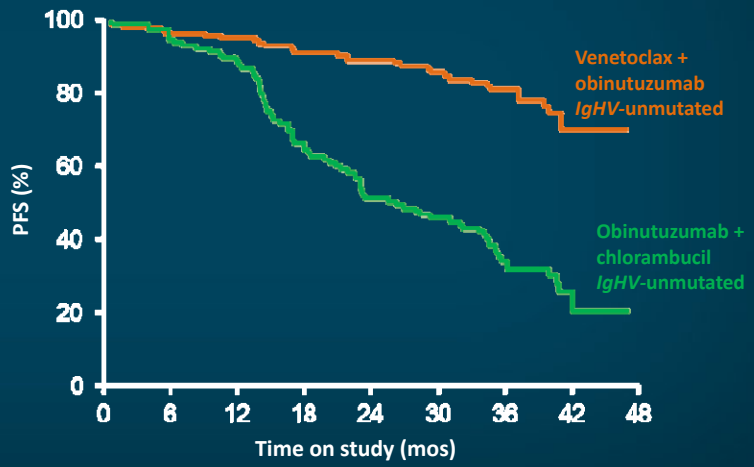
- ≥18 years
- CIRS >6 and/or CrCL <70 mL/min

Median FU = 39.6 months

Study arms	mPFS
Venetoclax + obinutuzumab	NR
O-Clb	35.6 mos

HR = 0.31 (95% CI, 0.22–0.44)
P <.0001

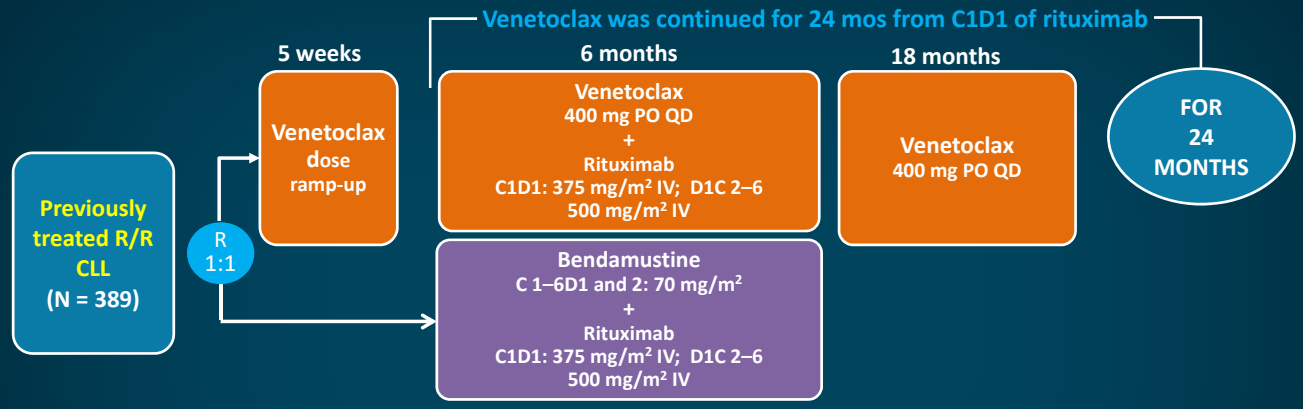
Improved PFS in *IgHV*-unmutated patients with fixed-duration venetoclax + obinutuzumab



CIRS = cumulative illness rating scale; CrCL = creatinine clearance.

Al-Sawaf O et al. *Lancet Oncol*. 2020;21:1188-1200 and supplement.

MURANO Study



- **Primary endpoint:** investigator-assessed PFS
- **Secondary endpoints:** IRC-assessed PFS, PFS in patients with del(17p), ORR, CR, OS, duration of response
- **Stratification** by presence/absence of del(17p), responsiveness to prior therapy, and geographic region

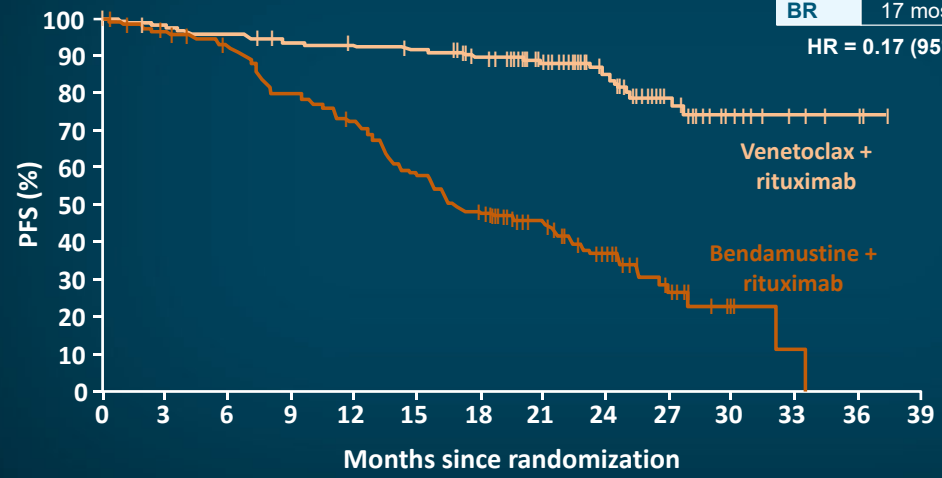
First published phase 3 trial involving treatment of CLL with novel small-molecule inhibitors delivered over defined treatment timeline

Seymour JF, et al. *N Engl J Med*. 2018;378:1107-1120.

MURANO Study: PFS

	mPFS	2-year PFS	PB MRD
VenR	NR	84.9%	–62.4%
BR	17 mos	36.3%	–13.3%

HR = 0.17 (95% CI, 0.11–0.25), *P* <.001

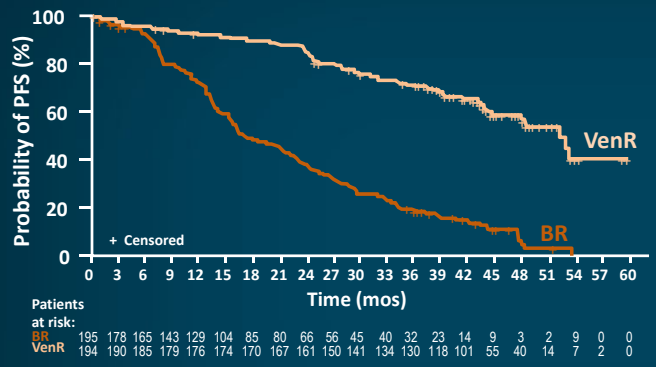


VenR = venetoclax + rituximab.

Seymour JF, et al. *N Engl J Med*. 2018;378:1107-1120.

MURANO Study—ASH 2019 Update

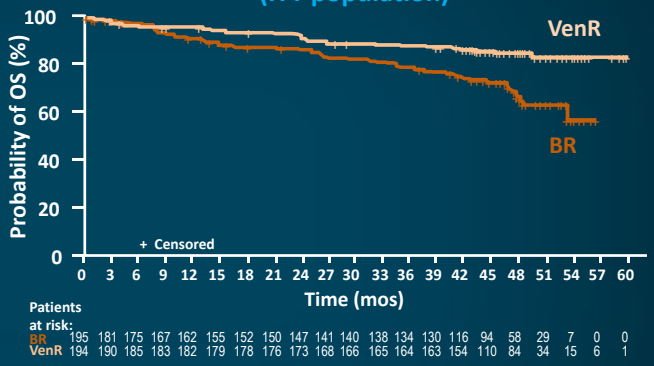
Kaplan-Meier assessments of PFS



	4-year PFS
VenR (n = 194)	57.3%
BR (n = 195)	4.6%

HR = 0.19 (95% CI, 0.14–0.25)
P <.0001

Kaplan-Meier assessments of OS (ITT population)



	4-year OS
VenR (n = 194)	85.3%
BR (n = 195)	66.8%

HR = 0.41 (95% CI, 0.26–0.65)
P <.0001

ITT = intention to treat.

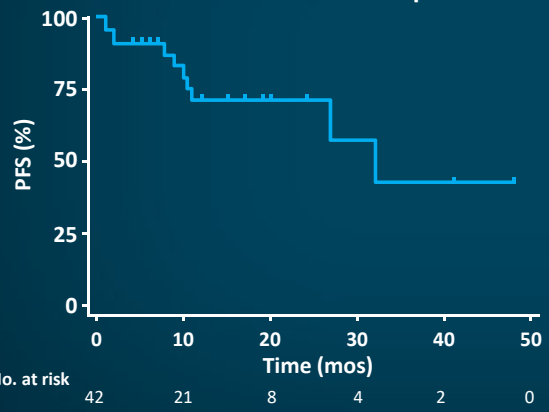
Kater AP, et al. *J Clin Oncol.* 2020;38:4042-4054.

Post-Venetoclax Use of BTKi in CLL

Patients Sequencing to Subsequent Treatment (N = 326)

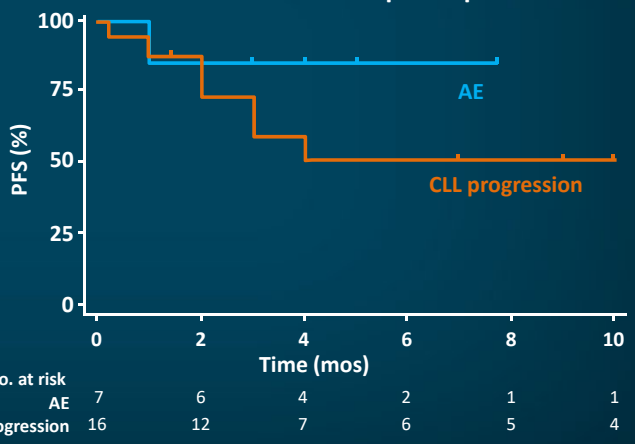
BTKi-naïve patients: BTKi therapy results in high ORR and durable remissions

PFS for BTKi in BTKi-naïve patients



For BTKi-exposed patients, BTK inhibition is NOT effective in setting of BTKi resistance

PFS for BTKi in BTKi-exposed patients



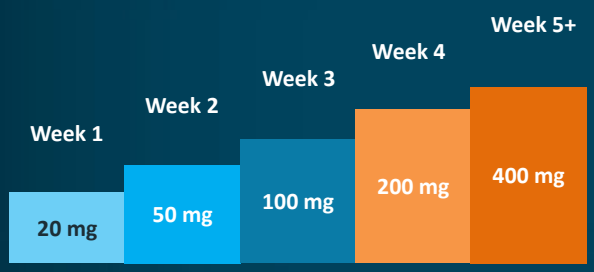
BTKi = BTK inhibitor.

Mato AR, et al. *Clin Cancer Res.* 2020;26:3589-3596.

Venetoclax

Tumor lysis syndrome and Other AEs

5-week dose escalation



- Assess TLS risk in all patients preparing for venetoclax therapy
- Premedicate with antihyperuricemics and ensure adequate hydration
- As overall TLS risk increases, employ more intensive measures
  1. IV hydration
  2. Frequent monitoring
  3. Hospitalization

TLS = tumor-lysis syndrome.

National Community Oncology Dispensing Association (NCODA) Positive quality intervention: venetoclax risk stratification, dosing, and dispensing procedure (www.ncoda.org/wp-content/uploads/2018/05/PQI-Venetoclax-12-2019.pdf). Accessed 7/19/2021.

Venetoclax + Obinutuzumab: Safety

164/212 patients (77.4%) completed study treatments

Venetoclax dose reductions due to AEs: 43 patients (20%) → Most common was neutropenia

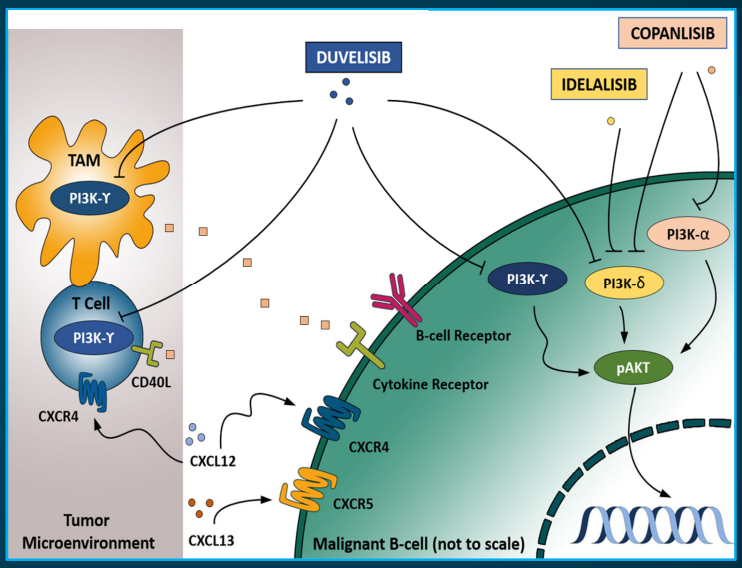
Discontinuation due to AEs: 33 patients (16%) → Most common was neutropenia

Most Frequent ≥Grade 3 AEs		
	During treatment	After treatment
Neutropenia	51.9%	4%
Thrombocytopenia	13.7%	0.5%
Anemia	7.5%	1.5%
Febrile neutropenia	4.2%	1.0%
Infusion-related reactions	9.0%	—
TLS	1.4%	—
Neoplasms	1.4%	6.4%

Al-Sawaf O, et al. *Lancet Oncol*. 2020;21:1188-1200.

Targeting PI3K in CLL

- The phosphatidylinositol-3-kinase (PI3K) pathway is aberrantly activated in many cancers, including NHL, contributing to proliferation and resistance to therapy
- The delta isoform of p110 catalytic subunit is of particular interest in lymphoma
- Several PI3K inhibitors are approved for R/R FL and ≥2 prior therapies



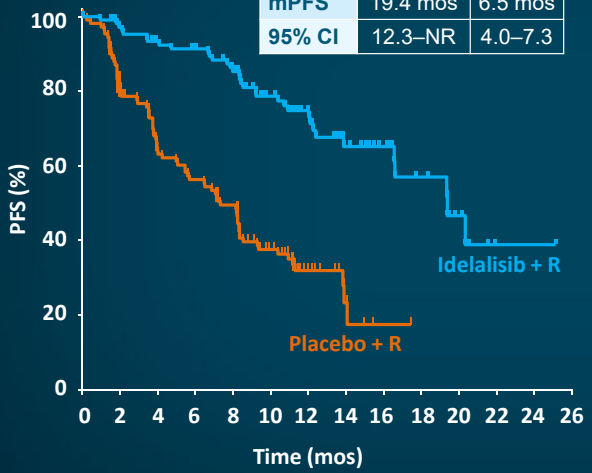
NHL = non-Hodgkin lymphoma; FL = follicular lymphoma; TAM = tumor-associated macrophage; CD = cluster of differentiation; CXCL = C-X-C motif chemokine ligand; CXCR = α-chemokine receptor; AKT = serene/threonine-protein kinase; pAKT = phosphorylated AKT.

Westin JR. *Clin Lymphoma Myeloma Leuk*. 2014;14:335-342. von Keudell G, Moskowitz AJ. *Curr Hematol Malig Rep*. 2019;14:405-413. Patel K, et al. *Blood*. 2019;134:1573-1577.

Trials of PI3K Inhibitors in CLL

Phase 3 trial of idelalisib + R vs R[1]

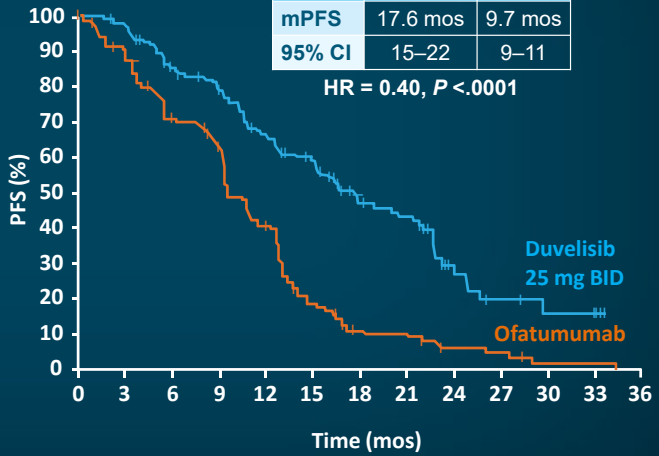
	IR	R
mPFS	19.4 mos	6.5 mos
95% CI	12.3–NR	4.0–7.3



Phase 3 DUO trial of duvelisib vs ofatumumab[2]

	DUV	OFA
mPFS	17.6 mos	9.7 mos
95% CI	15–22	9–11

HR = 0.40, *P* <.0001



IR = idelalisib + rituximab; DUV = duvelisib; OFA = ofatumumab.

1. Sharman JP, et al. *J Clin Oncol*. 2019;37:1391-1402. 2. Flinn IW, et al. *Blood*. 2018;132:2446-2455.

Adverse Events with Idelalisib and Duvelisib

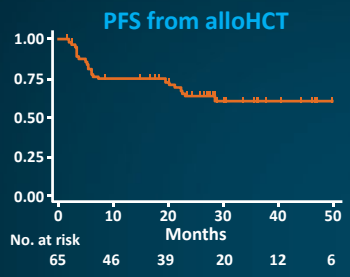
- Severe pneumonitis
  - Distinguish from infectious issues
    - Idelalisib: 4%
    - Duvelisib: 5%
- Diarrhea
  - Can be early and/or late onset
    - Idelalisib: 32%; 11% Gr 3/4
    - Duvelisib: 50%; 23% Gr 3/4*
  - Colitis (secondary to T-cell activation)
    - Idelalisib: 14–20%†
    - Duvelisib: 50%; 23% Gr 3/4*
- AST/ALT elevations
  - Idelalisib: 28%/39%; 5%/9% Gr 3/4
  - Duvelisib: 37%/40%; 6%/8% Gr 3/4
- Infections
  - Frontline idelalisib trials discontinued due to increased deaths
  - PJP and CMV prophylaxis now considered standard
    - Occurs in <1%

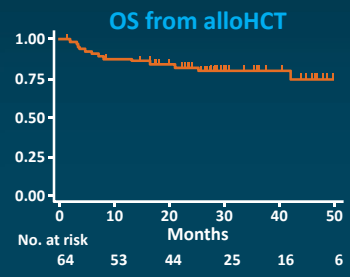
*reported as diarrhea OR colitis; †did not report separately from severe diarrhea.

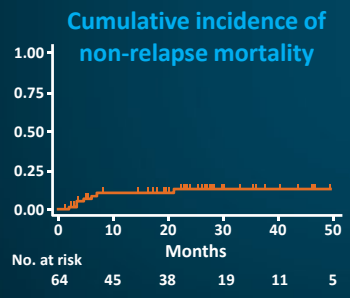
Gr = grade; AST = aspartate aminotransferase; ALT = alanine aminotransferase; PJP = *Pneumocystis jirovecii* pneumonia; CMV = cytomegalovirus.

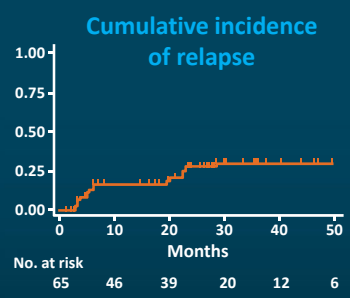
Idelalisib (Zydelig®) PI 2020 (www.gilead.com/~/media/Files/pdfs/medicines/oncology/zydelig/zydelig_pi.pdf FDA. 2016 (www.fda.gov/drugs/drug-safety-and-availability/ fda-alerts-healthcare-professionals-about-clinical-trials-zydelig-idelalisib-combination-other). Duvelisib (Copiktra®) PI 2019 (https://copiktra.com/pdf/verastem/COPIKTRA-PI-072019.pdf). Accessed 7/19/2021.

Allogeneic Stem-Cell Transplantation for CLL in Era of Novel Agents







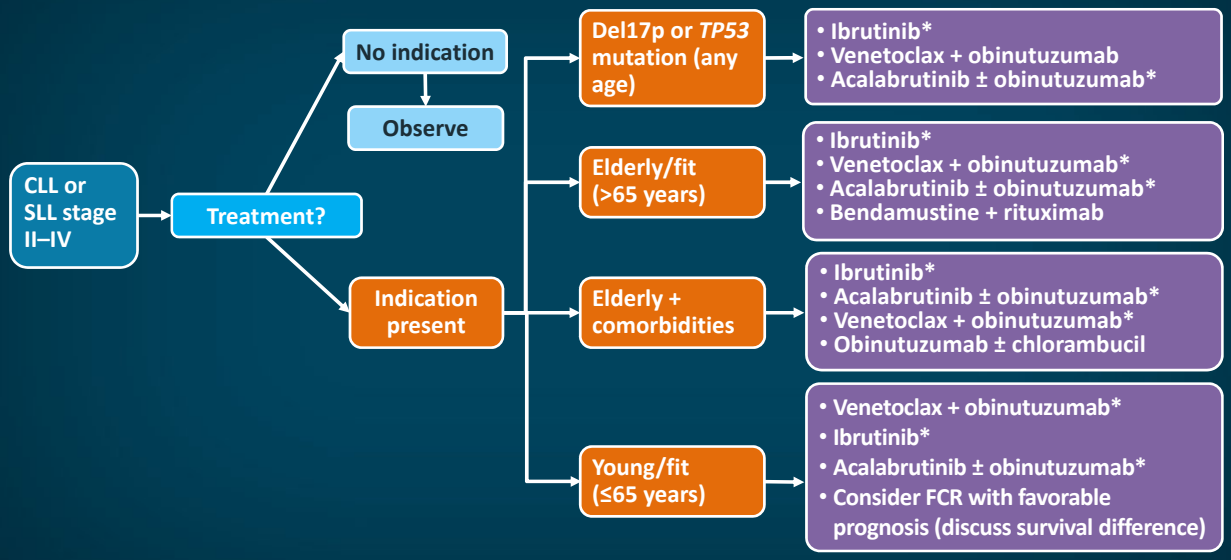


- N = 65, median age at allo-HCT = 60 years
- CLL status prior to transplant:
  - CR = 26%
  - PR = 66%
  - SD = 5%
  - PD = 3%
- RIC = 95%; ablative = 5%
- Lines of therapy = 3 (1–9); 1 (1–3) novel
- 82% progression on ≥1 novel agent
- Median PFS and OS not reached after allo-HCT (median FU = 27 mos)
- 24-mo PFS = 63%; 24-mo OS = 81%

alloHCT = allogeneic hematopoietic stem-cell transplantation; RIC = reduced-intensity conditioning.

Roeker LE, et al. *Blood Adv*. 2020;4:3977-3989.

Summary of Front-Line Therapy



*preferred.

SLL = small lymphocytic lymphoma.

Adapted from National Comprehensive Cancer Network (NCCN). CLL/SLL. V4.2021. (www.nccn.org/professionals/physician_gls/pdf/cll.pdf). Accessed 7/19/2021.

Summary of Therapeutic Options for Relapsed/Refractory CLL

Ibrutinib
Venetoclax + rituximab
Acalabrutinib
Idelalisib + rituximab
Duvelisib
Obinutuzumab + chlorambucil
Allo-HCT

Quick-Fire Cases of 5 Symptomatic CLL Patients

- 77-year-old female, previously untreated, *IgHV*-unmutated, commutes 1.5 hours to cancer center
- 77-year-old female, previously untreated, *IgHV*-unmutated, commutes 1.5 hours to cancer center, on a PPI
- 64-year-old male, previously untreated, *IgHV*-mutated, FISH + del(11q)
- 70-year-old male, previously treated with BR and then ibrutinib but discontinued after 2 years due to rash
- 68-year-old female, del(17p) FISH, treated with ibrutinib 4 years and now progressing (BTK mutation +)

PPI = proton-pump inhibitor.

Patient Management and Shared Decision-Making

5 Essential Steps of Shared Decision-Making
SHARE Approach

1. **S**eek your patient's participation
2. **H**elp your patient explore and compare treatment options
3. **A**ssess your patient's values and preferences
4. **R**each a decision with your patient
5. **E**valuate your patient's decision

It's all about communication!

AHRQ Share Approach (www.ahrq.gov/sites/default/files/publications/files/share-approach_factsheet.pdf). Accessed 7/7/2021.

Shared Decision-Making (SDM) in Oncology

Collaborative care

- Interconnection of essential players
- Patient-centered
- Communication is **KEY!**

Adapted from National Quality Forum (NQF). National Quality Partners Playbook™: Shared Decision Making in Healthcare. Washington, DC: NQF;2018.

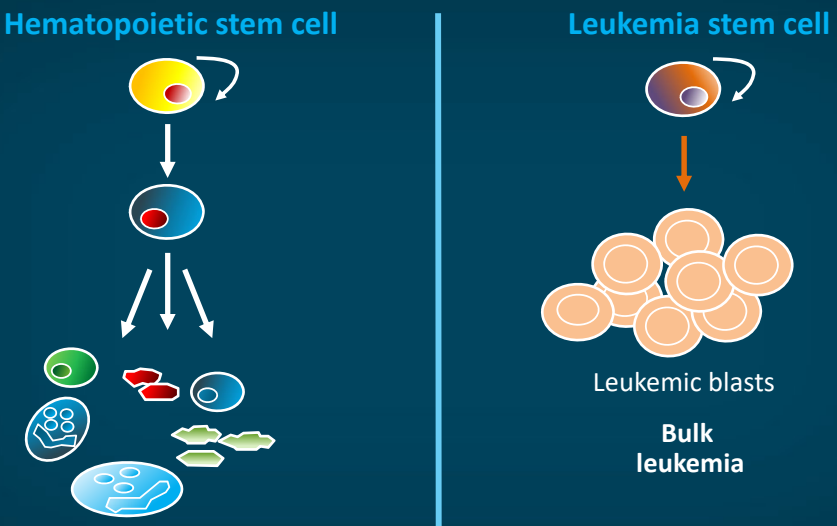
Summary Points

- Early results with small-molecule inhibitors are extremely promising
- Small-molecule inhibitors provide favorable treatment options for majority of CLL patients, most notably high-risk, elderly, and/or comorbid patients and those with relapsed disease
- Cost, prescription coverage, and long-term side effects may be issues
- Novel combinations delivered over defined treatment timelines offer hope for deep responses and long treatment-free intervals
- Important to incorporate SDM components when developing care plans with patients, family members, and/or caregivers

Updates in Acute Myeloid Leukemia (AML): An Overview

Michael R. Grunwald, MD
Chief, Leukemia Division
Associate Professor, Atrium Health
Department of Hematologic Oncology and Blood Disorders
Levine Cancer Institute
Charlotte, NC

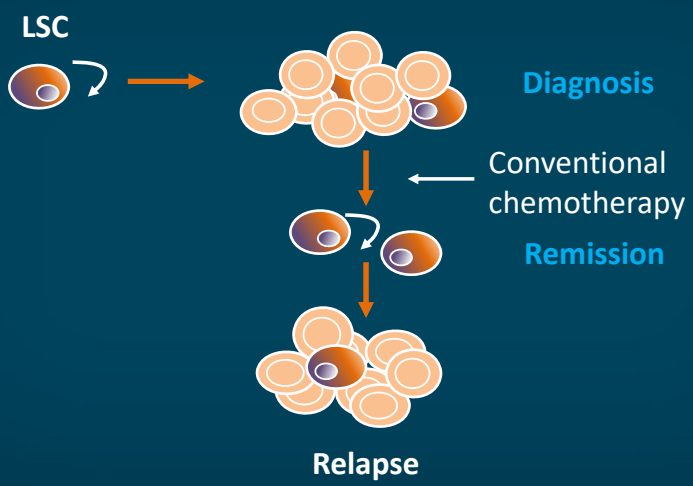
Stem Cells



Modified from Horton SJ, Huntly BJP. *Haematologica*. 2012;97:966-974.

Leukemia Stem-Cell Theory

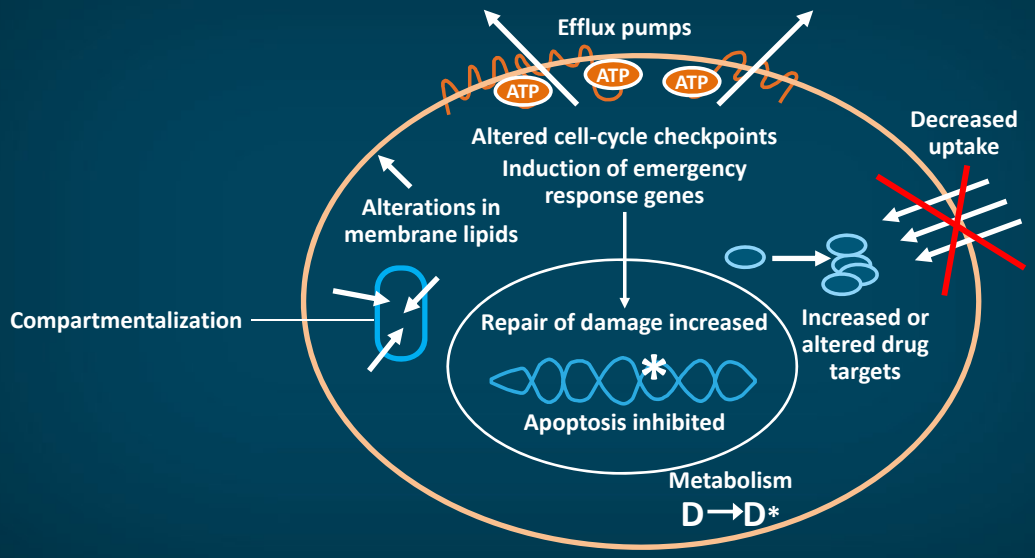
Relapse results from resistant LSCs



LSC = leukemia stem cell.

Modified from Zeijlemaker W, Schuurhuis GJ. (www.intechopen.com/books/leukemia/minimal-residual-disease-and-leukemic-stem-cells-in-acute-myeloid-leukemia). Accessed 7/7/2021.

How Cultured Cancer Cells Become Resistant to Cytotoxic Cancer Drugs

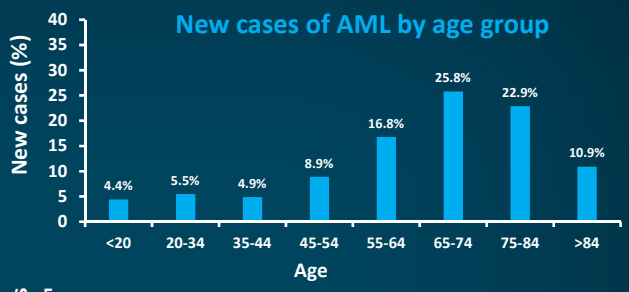


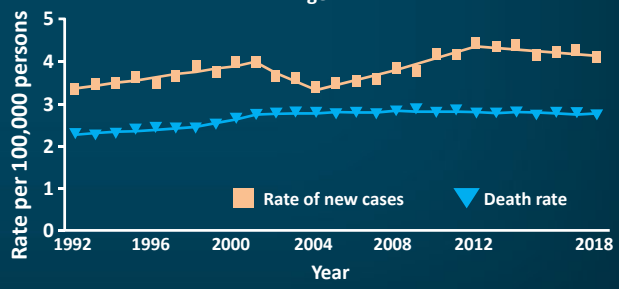
ATP = adenosine triphosphate.

Gottesman MM. *Annu Rev Med.* 2002;53:615-627.

Acute Myeloid Leukemia (AML)

- 20,240 estimated new cases in 2021
  - 1.1% of all new cancer cases
  - 1.9% of all cancer deaths
- 4.3 cases per 100,000 population
- 2.8 deaths per 100,000 population
- Median age at diagnosis is 68 years
- 29.5% of patients survive ≥5 years





New cases come from SEER 13. Deaths come from US mortality. Data include all races and both sexes; rates are age-adjusted.

National Cancer Institute (NCI). *Cancer Stat Facts: AML*, Surveillance, Epidemiology, and End Results Program (SEER) database (https://seer.cancer.gov/statfacts/html/amyl.html). Accessed 7/7/2021.

AML Epidemiology

- AML is more common in older adults and among men compared with women
- Other risk factors include:
  - Smoking
  - Prior treatment with chemotherapy or radiation therapy
  - Exposure to radiation or benzene
  - History of antecedent blood disorder, eg, myelodysplastic syndrome (MDS)
- AML poses a significant healthcare burden during induction and relapse treatment phases
- Among older adults, AML is associated with high costs, particularly during the few remaining months of life

NCI. Cancer Stat Facts: AML, SEER database (https://seer.cancer.gov/statfacts/html/amyl.html). ACS. AML risk factors (www.cancer.org/cancer/acute-myeloid-leukemia/causes-risks-prevention/risk-factors.html). Both URLs accessed 7/7/2021. Menzin J, et al. *Arch Intern Med*. 2002;164:1597-1603. Irish W, et al. *Curr Med Res Opin*. 2017;33:519-527. Redaelli A, et al. *Cancer Treat Rev*. 2004;30:237-247.

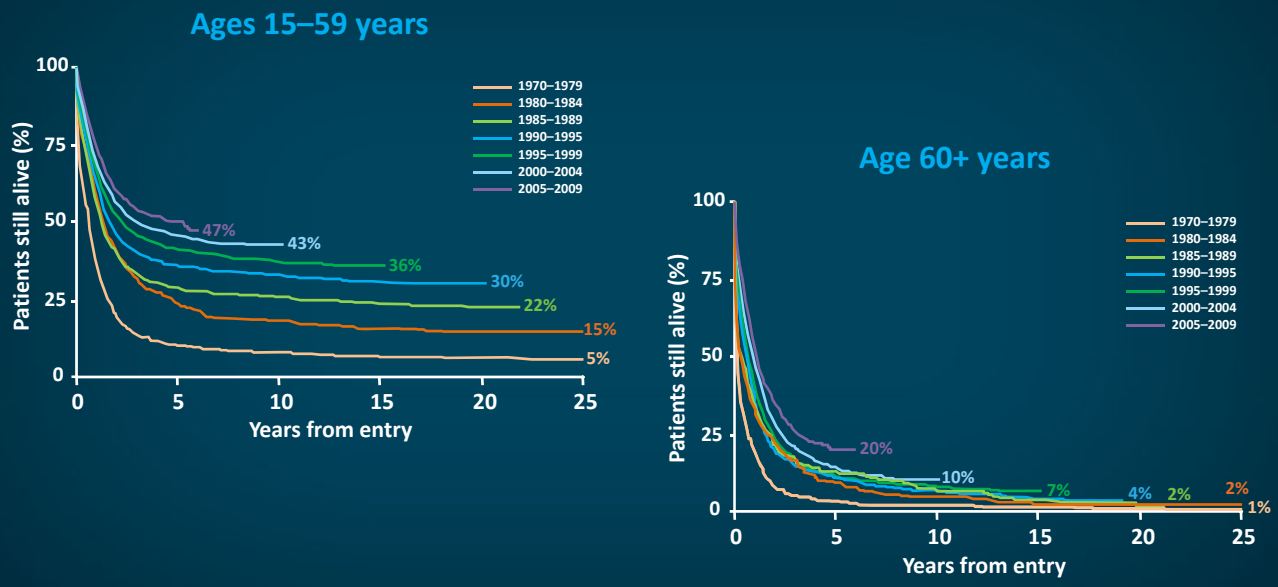
AML: Comorbidities and Effect on QoL

- Comorbidities are an independent predictor of all-cause mortality and negatively impact prognosis in AML patients
  - Age, gender, and socioeconomic status are associated with comorbidity, which may explain impact of comorbidities on prognosis
    - Link between increased comorbidity burden and worse outcomes (eg, toxicity, readmission rates, worse OS)
- Data on QoL impact are lacking, but here is what we **do know**:
  - 97% of AML patients >60 years report QoL is more important than length of life
  - QoL scores are associated with treatment stage
  - Individuals differ in what they think will impact their QoL
    - For instance, bruising and low libido may impact one patient's QoL, while another patient may be less seriously affected
  - Impact and factors influencing QoL may change throughout the patient's journey
  - Maximizing QoL is an important treatment goal

QoL = quality of life; OS = overall survival.

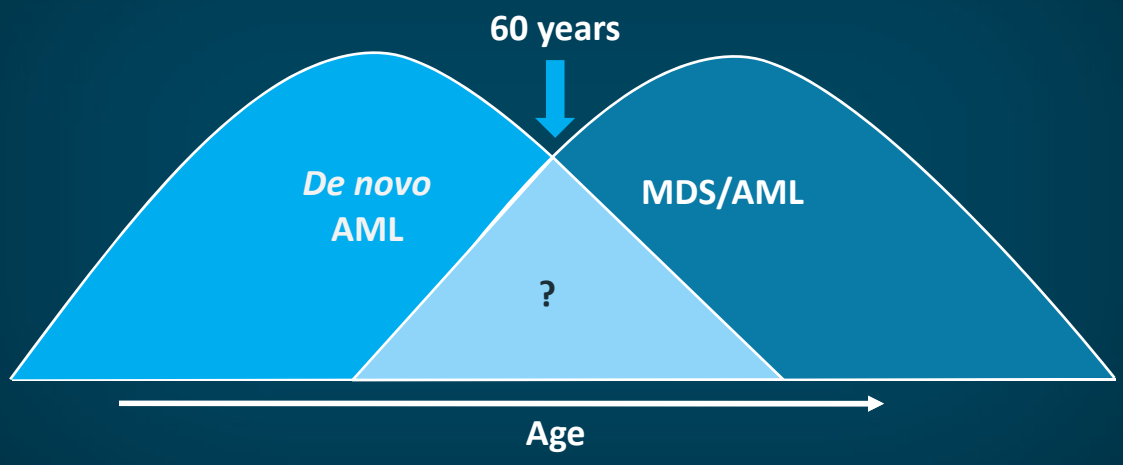
Storey S, et al. *Curr Geriatr Rep*. 2017;6:247-254. Buckley SA, et al. *Cancer*. 2018;124:145-152.

Medical Research Council (UK) AML Trials: OS

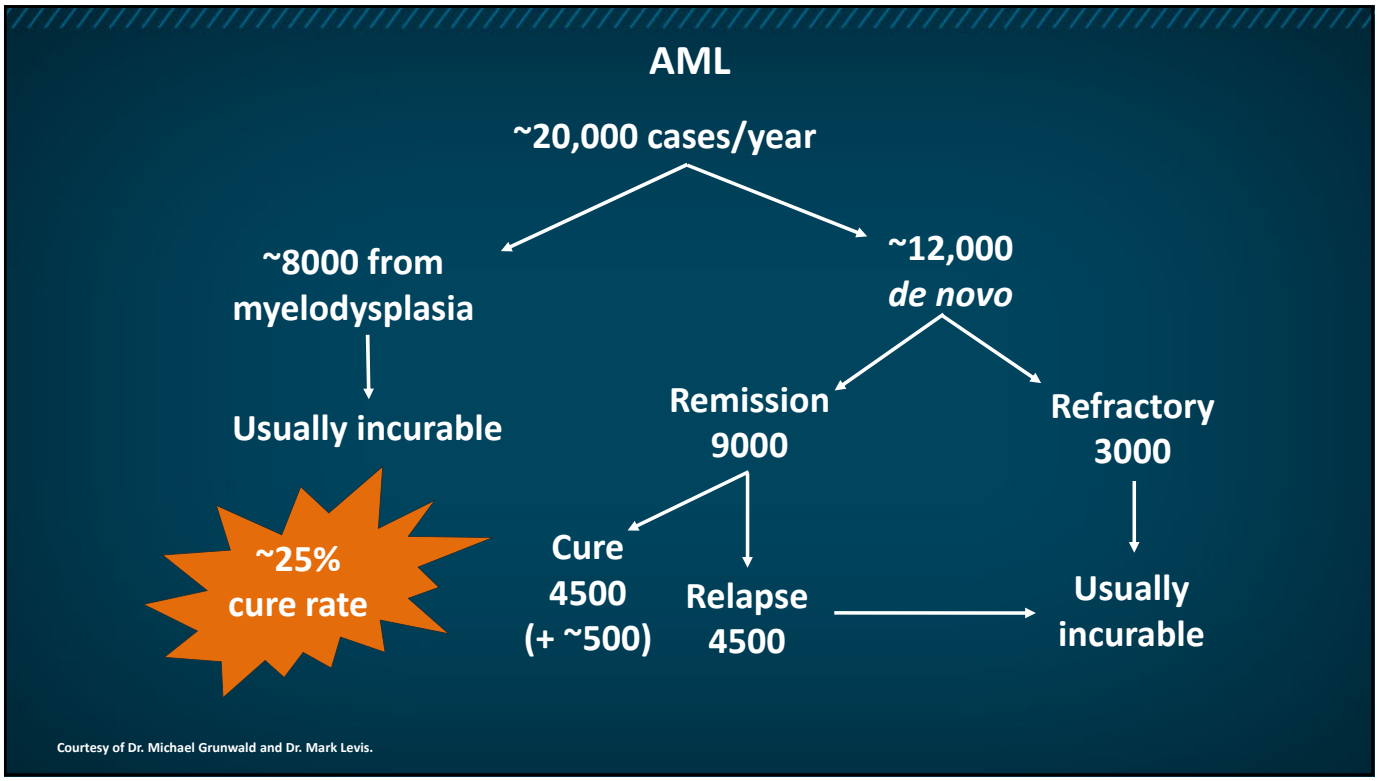


Burnett AK, et al. *Br J Haematol*. 2020;188:86-100.

Principles of AML Development



Courtesy of Dr. Michael Grunwald.



Courtesy of Dr. Michael Grunwald and Dr. Mark Levis.

Case 1: Introduction and Questions to Consider

Case description

- 64-year-old female presents with fatigue and pallor
  - History of anal cancer s/p treatment with 5-FU, mitomycin C, and radiation 5 years ago
  - The patient is active and works full-time as a consultant
  - TTE reveals LVEF 60%
- Laboratory findings:
  - WBC = 20 X 10^9/L
  - 80% peripheral blasts
  - ANC = 0.3 X 10^9/L
  - Hgb = 5.7 g/dL
  - Platelets = 19 X 10^9/L
  - BM = 70% cellular marrow with greater than 90% myeloid blasts
  - Cytogenetics by FISH: Positive for deletion 7q and deletion 5q

Questions to consider

- What would you do to manage this patient?
- How would you discuss treatment options and potential adverse events with patient and/or her family?

s/p = status post; 5-FU = fluorouracil; TTE = transthoracic echocardiogram; LVEF = left ventricular ejection fraction; WBC = white blood (cell) count; ANC = absolute neutrophil count; BM = bone marrow.

Acute Leukemia: Signs/Symptoms

- Fatigue, weakness
- Weight loss
- Fever
- Bruising
- Bleeding
- Bone pain
- Recurrent infections
- Abnormal WBC
- Anemia
- Low platelets
- Pallor
- Petechiae

ACS. AML signs and symptoms (www.cancer.org/cancer/acute-myeloid-leukemia/detection-diagnosis-staging/signs-symptoms.html). Accessed 7/7/2021.

Initial Workup—Labs

- CBC w/differential
- Peripheral blood smear
- CMP
- Tumor lysis panel: uric acid, phosphate (+ K, Cr)
- DIC panel: PT, aPTT, fibrinogen, d-dimer (+ CBC)
- Type and cross
  - Consider HLA typing for platelets
- Blood, urine, and surveillance cultures
- Flow cytometry (peripheral blood)
  - Can be used to quickly determine myeloid from lymphoid, determine likelihood of acute promyelocytic leukemia

K = potassium; Cr = chromium; DIC = disseminated intravascular coagulation; PT = prothrombin time; PTT = partial thromboplastin time; HLA = human leukocyte antigen.

ACS. AML diagnosis (www.cancer.org/cancer/acute-myeloid-leukemia/detection-diagnosis-staging/how-diagnosed.html). NCCN. AML. V3.2021. (www.nccn.org/professionals/physician_gls/pdf/aml.pdf). Accessed 7/7/2021.

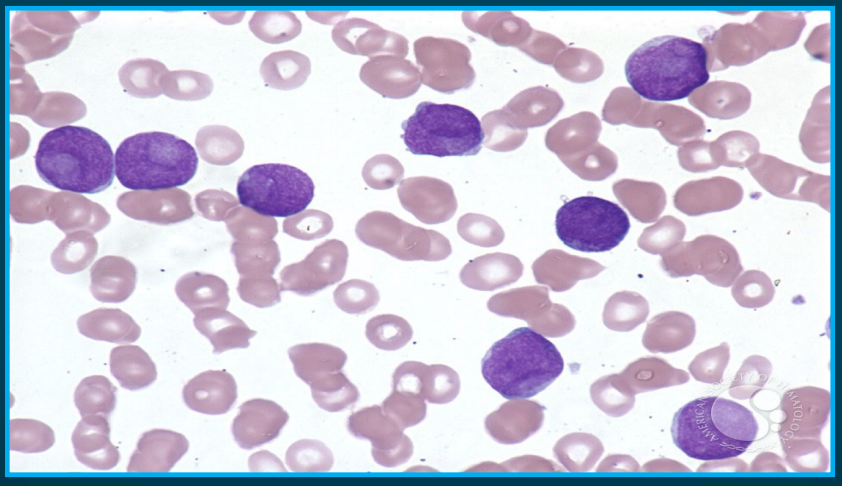
Initial Workup—Bone Marrow

- Aspirate and core biopsy
  - Aspirate lets you see the morphology
  - Core gives cellularity
- Flow cytometry
- Cytogenetics
- FISH
- Molecular studies
- Research specimen

ACS. AML diagnosis (www.cancer.org/cancer/acute-myeloid-leukemia/detection-diagnosis-staging/how-diagnosed.html). NCCN. AML. V3.2021. (www.nccn.org/professionals/physician_gls/pdf/aml.pdf). Accessed 7/7/2021.

AML

≥20% myeloid blasts in blood or marrow;
can be <20% if t(8;21), inv(16), t(16;16), or t(15;17) is present



O'Donnell MR, et al. *J Natl Compr Canc Netw.* 2017;15:926-957. NCCN. AML. V3.2021. (www.nccn.org/professionals/physician_gls/pdf/aml.pdf). Accessed 7/7/2021.

Initial Workup—Other

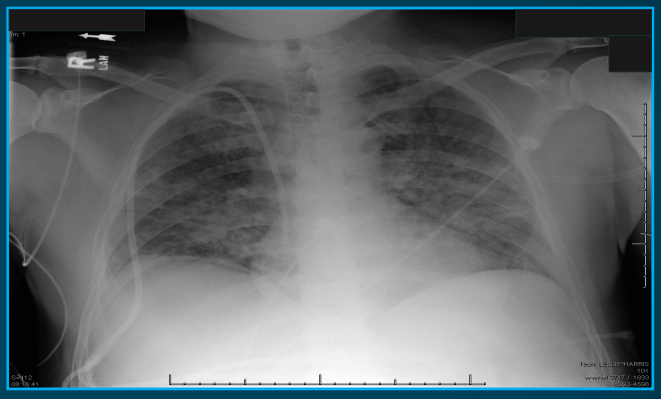
- Non-contrast CT chest and sinuses
  - Avoid IV contrast to prevent renal toxicity
  - Fungal pneumonia may be missed on CXR
- 12-lead EKG
- Interventional radiology for central line
- Echocardiogram
  - Assess EF prior to chemotherapy
- Lumbar puncture
  - WBC >50 K, neurologic symptoms, M4Eo (Inv 16), M5 (monocytic AML)
  - Perform once peripheral blasts have cleared
  - Prophylactic IT chemotherapy

IV = intravenous; CXR = chest x-ray; EKG = electrocardiogram; EF = ejection fraction; IT = intrathecal.

ACS. AML diagnosis (www.cancer.org/cancer/acute-myeloid-leukemia/detection-diagnosis-staging/how-diagnosed.html). Accessed 7/7/2021.

Complications of Acute Leukemia

- Leukostasis
- Bleeding (DIC)
- Infection
  - Antimicrobial prophylaxis
  - Neutropenic fever
  - Sepsis
  - Fungal infections
- Tumor lysis syndrome
- Other: mucositis, nausea/vomiting, diarrhea



AML Therapy: Goals

- Achieve a complete remission (CR)
  - Induction
- Prevent relapse
  - Post-remission therapy ("consolidation")

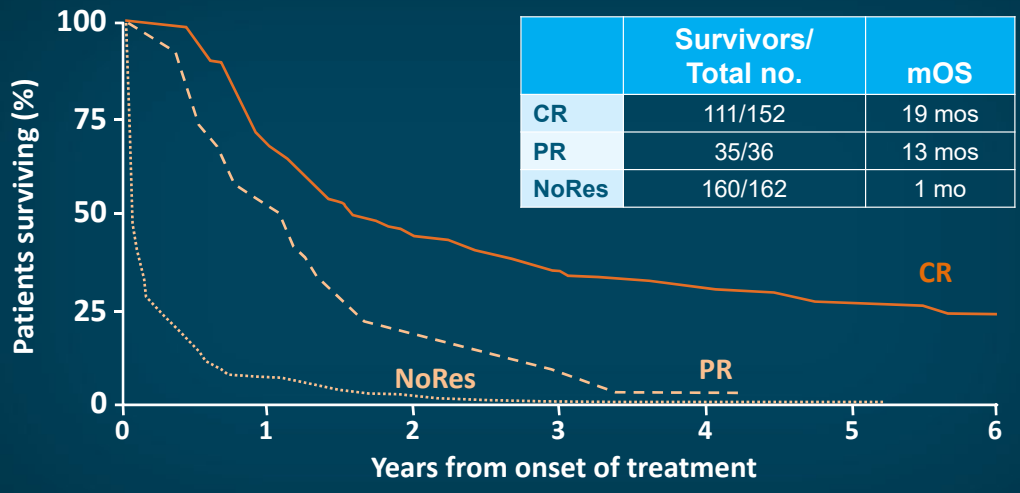
Complete Remission
IWG ("Cheson") Criteria

- Morphologic leukemia-free state
  - No microscopic or flow-cytometric evidence of leukemia in marrow or peripheral blood
- No extra-medullary leukemia
- ANC >1000 cells/µL
- Platelets ≥100,000/µL
- Transfusion independent
- We are now able to assess for deeper levels of remission
  - Flow cytometry, cytogenetics/FISH, molecular

IWG = International Working Group.

Cheson BD, et al. *J Clin Oncol.* 2003;21:4642-4649.

Survival: All Patients



	Survivors/ Total no.	mOS
CR	111/152	19 mos
PR	35/36	13 mos
NoRes	160/162	1 mo

NoRes = no response.

Rai KR, et al. *Blood*. 1981;58:1203-1212.

"7+3"—a "Traditional" Regimen…

- Cytarabine—7 days
  - 100 or 200 mg/m^2/day IV continuous infusion
- Anthracycline—3 days
  - 45–90 mg/m^2/day daunorubicin OR 12 mg/m^2/day idarubicin IV push
- Day-14 marrow—no longer performed universally
  - If aplasia (marrow <5% cellularity), wait for recovery
  - If residual leukemia, can give 5+2, starting on day 21
  - If after counts are recovered and still residual leukemia, can give a second course of 7+3
- CR rate ≈75% (includes those needing 2 courses)

NCCN. AML. V3.2021 (www.nccn.org/professionals/physician_gls/pdf/aml.pdf). Accessed 7/7/2021.

Post-remission Therapy: "Consolidation"

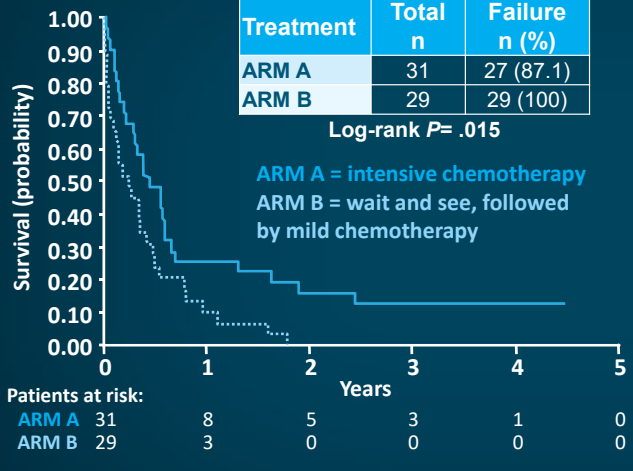
- High-dose cytarabine (HiDAC)[1]
  - 3 g/m^2 IV BID days 1, 3, and 5 for 3–4 cycles[1,2]
  - Several alternates (eg, 1.5 g IV BID days 1, 3, and 5) [1]
- Sometimes etoposide or anthracycline is added to HiDAC
- Allogeneic HCT

HCT = hematopoietic cell transplantation.

1. NCCN. AML. V3.2021 (www.nccn.org/professionals/physician_gls/pdf/aml.pdf). Accessed 7/7/2021. 2. Mayer RJ, et al. *N Engl J Med.* 1994;331:896-903.

AML in Elderly (Age >60 Years)

7+3 induction[1]

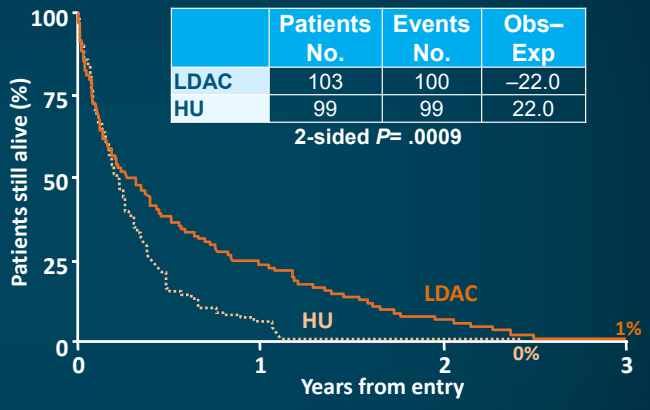


Treatment	Total n	Failure n (%)
ARM A	31	27 (87.1)
ARM B	29	29 (100)

Log-rank *P*= .015

ARM A = intensive chemotherapy
ARM B = wait and see, followed by mild chemotherapy

Cytarabine SC, 20 mg Q12H x 10 days[2]



	Patients No.	Events No.	Obs–Exp
LDAC	103	100	–22.0
HU	99	99	22.0

2-sided *P*= .0009

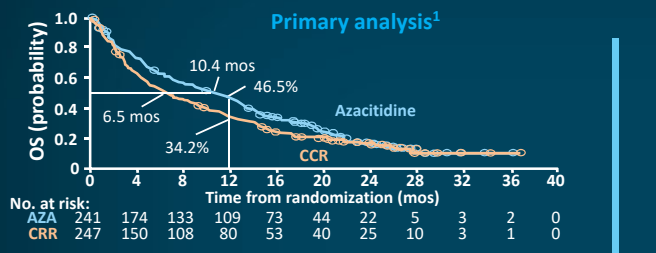
- Median survival = 575 days for patients with CR and 66 days for refractory patients
- CR rate for patients with poor cytogenetics = 0%

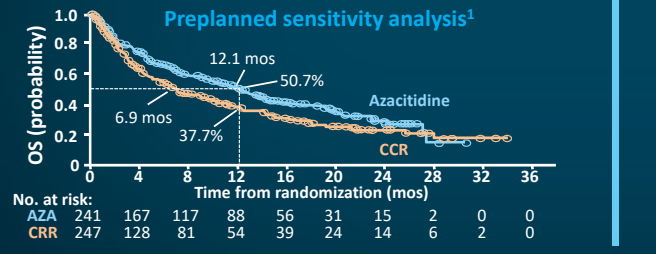
LDAC = low-dose cytarabine; SC = subcutaneous; HU = hydroxyurea; Obs = observed; Exp = expected; Q12H = every 12 hours.

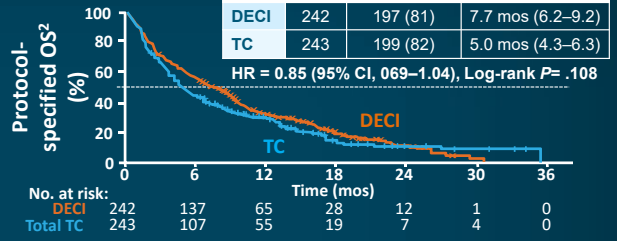
1. Löwenberg B, et al. *J Clin Oncol.* 1989;7:1268-1274. 2. Burnett AK, et al. *Cancer.* 2007;109:1114-1124.

Treatment of AML in Elderly

- Some patients can benefit from intensive therapy, but "first do no harm"
- Consider gentler therapies, eg, hypomethylating agents

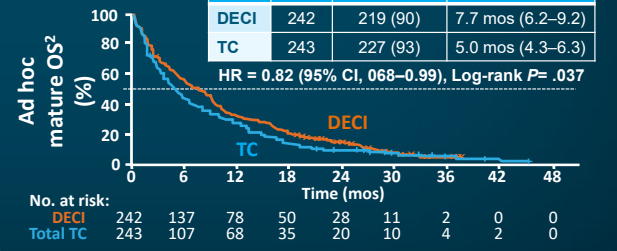






	n	Death (%)	mOS (95% CI)
DECI	242	197 (81)	7.7 mos (6.2–9.2)
TC	243	199 (82)	5.0 mos (4.3–6.3)

HR = 0.85 (95% CI, 069–1.04), Log-rank *P*= .108



	n	Death (%)	mOS (95% CI)
DECI	242	219 (90)	7.7 mos (6.2–9.2)
TC	243	227 (93)	5.0 mos (4.3–6.3)

HR = 0.82 (95% CI, 068–0.99), Log-rank *P*= .037

AZA = azacitidine; CCR = conventional care regimen; DECI = decitabine; TC = treatment choice.

1. Dombret H, et al. *Blood.* 2015;126:291-299. 2. Kantarjian HM, et al. *J Clin Oncol.* 2012;30:2670-2677.

AML: Course of the Disease

Young, Fit Patients

Poor (and intermediate) risk
Cytogenetics
Molecular
Secondary
Refractory

HCT

Relapse

Diagnosis → Induction → Consolidation → Follow-up Q3M

Q3M = every 3 months.

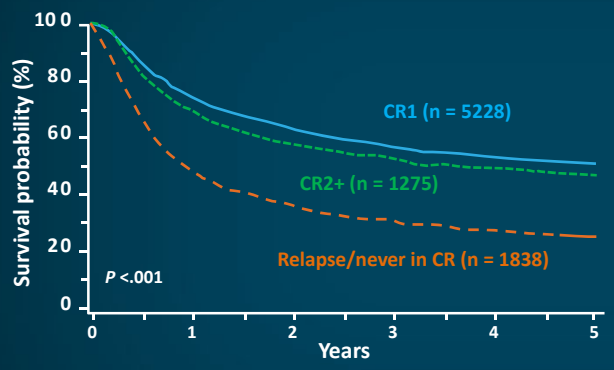
Allogeneic HCT

- Conditioning regimen—goals
  - Immunosuppression
  - Cytoreduction/stem-cell space
- Graft-versus-leukemia (GVL) effect
- Toxicities
  - Conditioning regimen
    - Idiopathic pneumonia syndrome
    - Sinusoidal obstruction syndrome/VOD of the liver
  - Infection
  - GVHD

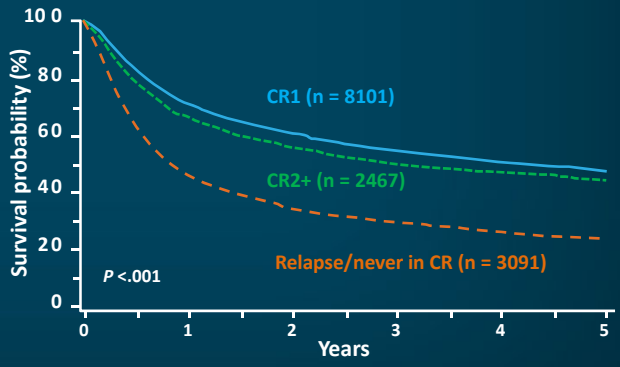
VOD = veno-occlusive disease.; GVHD = graft-versus-host disease.

Survival After Hematopoietic Stem-Cell Transplantation

Survival after matched related donor HCT for AML, age ≥18 years, in US, 2008–2018



Survival after unrelated donor HCT for AML, age ≥18 Years, in US, 2008–2018

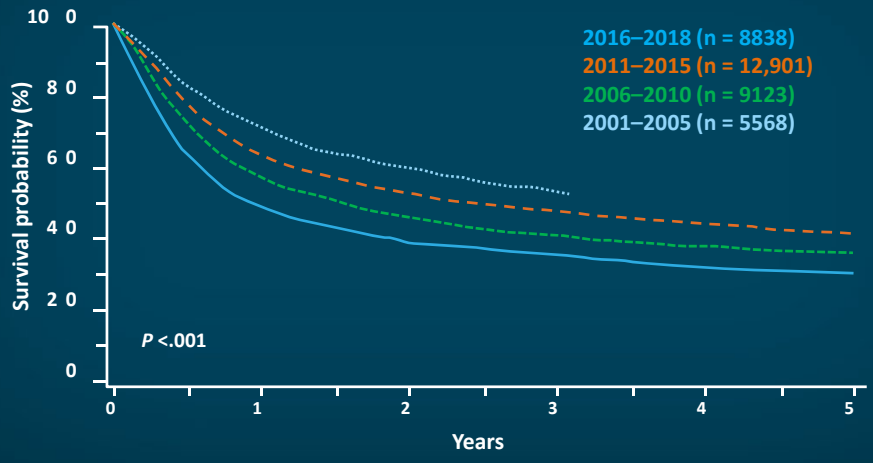


CR1 = first CR; CR2 = second CR.

Phelan R, et al. Current uses and outcomes of HCT: Center for International Blood & Marrow Transplant Research (CIBMTR) summary slides, 2020. (www.cibmtr.org/ReferenceCenter/SlidesReports/SummarySlides/pages/index.aspx). Accessed 7/7/2021.

Trends in Survival After Hematopoietic Stem-Cell Transplantation

Trends in survival after allogeneic HCT for AML, age ≥18 Years, in US, 2001–2018



Phelan R, et al. Current uses and outcomes of HCT: Center for International Blood & Marrow Transplant Research (CIBMTR) summary slides, 2020. (www.cibmtr.org/ReferenceCenter/SlidesReports/SummarySlides/pages/index.aspx). Accessed 7/7/2021.

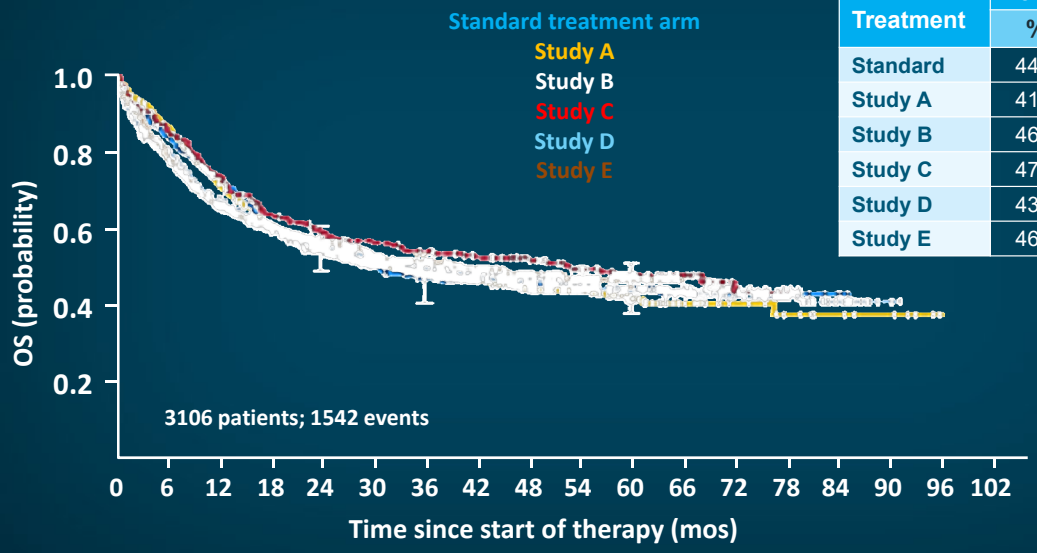
2017 European LeukemiaNet (ELN) Risk Stratification

Risk category	Genetic abnormality
Favorable	• t(8;21)(q22:q22.1); *RUNX1-RUNX1T1* • inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* • Biallelic mutated *CEBPA* • Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}
Intermediate	• Mutated *NPM1* and *FLT3*-ITD^{high} • Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low} (without adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3); *MLLT3-KMT2A* • Cytogenetic abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23;q34.1); *DEK-NUP214* • t(v;11q23.3); *KMT2A* rearranged • t(9;22)(q34.1:q11.2); *BCR-ABL1* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2*, *MECOM(EVI1)* –5 or del(5q); –7; –17/abn(17p) • Complex karyotype, monosomal karyotype • Wild-type *NPM1* and *FLT3*-ITD^{high} • Mutated *RUNX1* • Mutated *ASXL1* • Mutated *TP53*

FLT3 = Fms-like tyrosine kinase 3; ITD = internal tandem duplications.

Döhner H, et al. *Blood.* 2017;129:424-447.

Rearranging Chemotherapy: A Decade of Futility

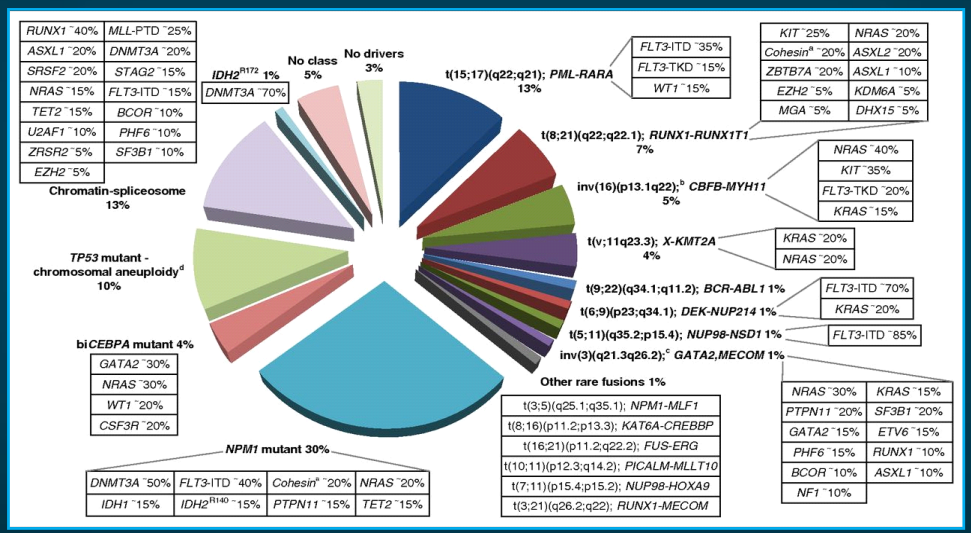


Treatment	5-Year Survival	
	%	95% CI
Standard	44.3	37.7–50.7
Study A	41.4	36.9–45.8
Study B	46.6	41.1–51.8
Study C	47.5	40.1–54.6
Study D	43.6	39.6–47.6
Study E	46.4	41.0–51.7

Büchner T, et al. *J Clin Oncol.* 2012;30:3604-3610.

Genetic Abnormalities in AML

Molecular classes of AML and concurrent gene mutations in adult patients up to age of ~65 years



Döhner H, et al. *Blood.* 2017;129:424-447.

AML Video
Novel Therapies

https://youtu.be/boXjdlQiFig

Novel Therapies in AML

BCL-2 inhibitor

- Venetoclax—FDA approved in combination with azacitidine or decitabine or LDAC for treatment of newly diagnosed AML in adults ≥75 years old, or who have comorbidities that preclude use of intensive induction chemotherapy

Hedgehog pathway inhibitor

- Glasdegib—FDA approved in combination with LDAC for the treatment of newly diagnosed AML in adult patients who are ≥75 years old or who have comorbidities that preclude use of intensive induction chemotherapy

Liposomal 7+3

- Liposomal 7+3 (CPX-351)—FDA approved for the treatment of adults and pediatric patients ≥1 year old with newly diagnosed t-AML or AML with MRC (AML-MRC)

BCL = B-cell lymphoma; t-AML = therapy-related AML; MRC = myelodysplasia-related changes.

Venetoclax (Venclexta®) PI 2020 (www.rxabbvie.com/pdf/venclexta.pdf). Glasdegib (Daurismo™) PI 2020 (http://labeling.pfizer.com/ShowLabeling.aspx?id=11336). Daunorubicin + cytarabine (Vyxeos®) PI 2021 (http://pp.jazzpharma.com/ pi/vyxeos.en.USPI.pdf). All URLs accessed 7/7/2021.

Novel Therapies in AML
(continued 1)

FLT3 inhibitors

- Midostaurin—FDA approved tyrosine kinase inhibitor (TKI) for *FLT3*-mutated AML in combination with standard 7+3 induction and cytarabine consolidation
- Gilteritinib—FDA approved TKI for relapsed/refractory (R/R) *FLT3*-mutated AML

IDH1 inhibitor

- Ivosidenib—FDA approved for treatment of adult patients with newly diagnosed AML with susceptible *IDH1* mutation who are ≥75 years old or who have comorbidities that preclude use of intensive induction chemotherapy and adults with R/R *IDH1*-mutated AML

IDH2 inhibitor

- Enasidenib—FDA approved for treatment of adult patients with R/R *IDH2*-mutated AML

Midostaurin (Rydapt®) PI 2021 (www.novartis.us/sites/www.novartis.us/files/rydapt.pdf). Gilteritinib (Xospata®) PI 2019 (https://astellas.us/docs/xospata.pdf). Ivosidenib (Tibsovo®) PI 2019 (www.tibsovopro.com/pdf/prescribinginformation.pdf). Enasidenib (Idhifa®) PI 2020 (www.idhifa.com/prescribing-information/). URLs accessed 7/7/2021.

Novel Therapies in AML
(continued 2)

CD33 antibody-drug conjugate

- Gemtuzumab ozogamicin—FDA approved for treatment of newly diagnosed CD33-positive AML in adults and in pediatric patients ≥1 month and treatment of R/R CD33-positive AML in adults and in pediatric patients ≥2 years

Hypomethylating agent

- CC-486 (oral azacitidine)—FDA approved for continued treatment of adult patients with AML who achieved first CR or CRi following intensive induction chemotherapy and are not able to complete intensive curative therapy

Gemtuzumab ozogamicin (Mylotarg™) PI 2020 (http://labeling.pfizer.com/ShowLabeling.aspx?id=9548). Azacitidine (Onureg®) PI 2021 (https://packageinserts.bms.com/pi/pi_onureg.pdf). URLs accessed 7/7/2021.

Case 2: Introduction and Questions to Consider

Case description

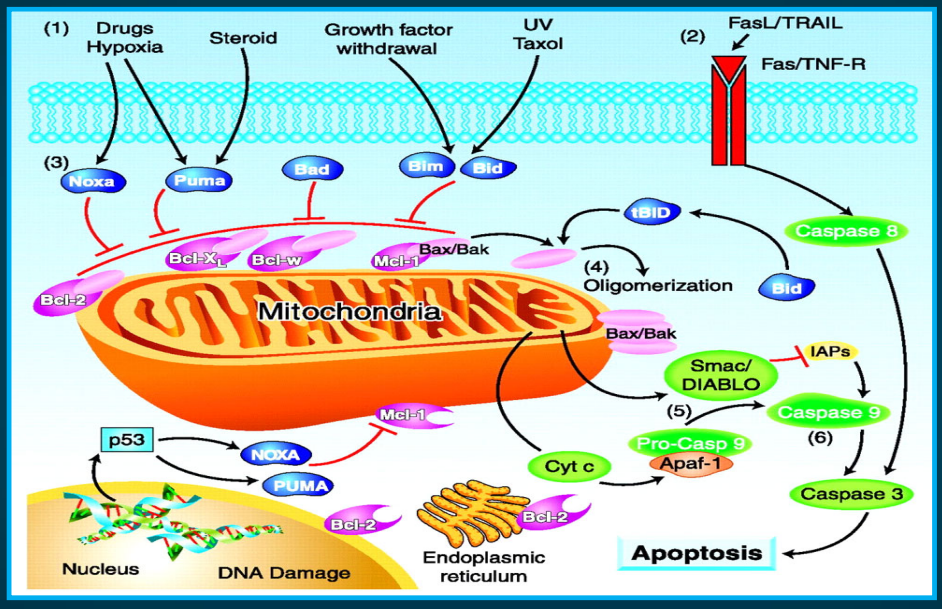
- Previously healthy 75-year-old man with history of DM, CAD, and stage 2 CKD presents with pancytopenia
  - He is diagnosed with AML
  - ECOG PS of 1
  - TTE: LVEF = 45–50%
  - He is interested in being treated but does not desire a prolonged hospitalization
- Laboratory findings:
  - WBC = 0.9 X 10^9/L
  - ANC = 0.2 X 10^9/L
  - Hgb = 7.1 g/dL
  - Platelets = 21 X 10^9/L
  - BM = 50% cellular marrow with 40% myeloid blasts
  - Cytogenetics by FISH: positive for deletion 7q

Questions to consider

- How do comorbidities and patient preferences inform decisions about the patient's treatment?
- How would you speak with the patient about his treatment options?

DM = diabetes mellitus; CAD = coronary artery disease; CKD = chronic kidney disease; PS = performance status.

Apoptotic Pathway



DNA = deoxynucleic acid; TNF = tumor-necrosis factor; Mcl-1 = myeloid cell leukemia-1; UV = ultraviolet; FasL = Fas ligand.

Kang MH, Reynolds CP. *Clin Cancer Res.* 2009;15:1126-1132.

Venetoclax

- Venetoclax is a selective oral BCL-2 inhibitor
- A phase 1b study of azacitidine and venetoclax showed CR/CRi rate of 71% in newly diagnosed AML patients ineligible for intensive chemotherapy
  - Median duration of CR/CRi was 21.9 months.
  - Median overall survival was 16.4 months
- VIALE-A is a phase 3 study comparing azacitidine + venetoclax with azacitidine + placebo (randomized 2:1)
  - Venetoclax was administered at dose of 400 mg daily, with a 3-day dose ramp-up
  - Azacitidine was administered at 75 mg/m^2/day on days 1–7 of a 28-day cycle
  - Population consisted of 431 previously untreated AML patients who were ineligible for intensive induction therapy
  - Median age was 76 years

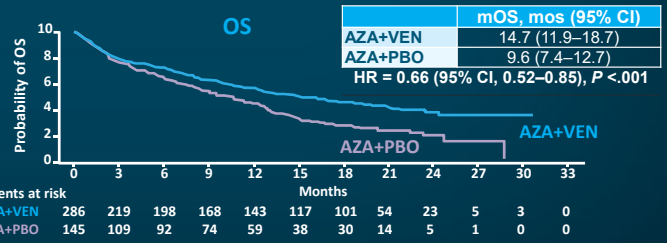
Pollyea DA, et al. *Am J Hematol.* 2021;96:208-217. DiNardo CD, et al. *N Engl J Med.* 2020;383:617-629.

VIALE-A Study

- Grade 3 thrombocytopenia 45% with AZA/VEN vs 38% with control
- Grade 3 neutropenia: 42% vs 28%
- Grade 3 febrile neutropenia: 42% vs 19%
- Grade 3 anemia: 26% vs 20%
- Nausea, vomiting, constipation, diarrhea
- Tumor lysis syndrome in 3 patients (1%) during ramp-up

Patient responses in treatment groups

		AZA + VEN (n = 286)	AZA + PBO (n = 145)	*P*-value
CR + CRi ratio, % (95% CI)		66.4 (60.6–71.9)	28.3 (21.1–36.3)	<.001
CR+CRi by initiation of cycle 2, % (95% CI)		43.4 (37.5–49.3)	7.6 (3.8–13.2)	<.001
CR rate, % (95% CI)		36.7 (31.1–42.6)	17.9 (12.1–25.2)	<.001
TI, % (95% CI)	Red blood cells	59.8 (53.9–65.5)	35.2 (27.4–43.5)	<.001
	Platetets	68.5 (62.8–73.9)	49.7 (41.3–58.1)	<.001
CR+CRi rates in molecular subgroups, % (95% CI)	*IDH1/2*	75.4 (62.7–85.5)	10.7 (2.3–28.2)	<.001
	FLT3	72.4 (52.8–87.3)	36.4 (17.2–59.3)	.020
	NPM1	66.7 (46.0–83.5)	23.5 (6.8–49.9)	.012
	TP53	55.3 (38.3–71.4)	0	<.001
EFS, mos (95% CI)		9.8 (8.4–11.8)	7.0 (5.6–9.5)	<.001



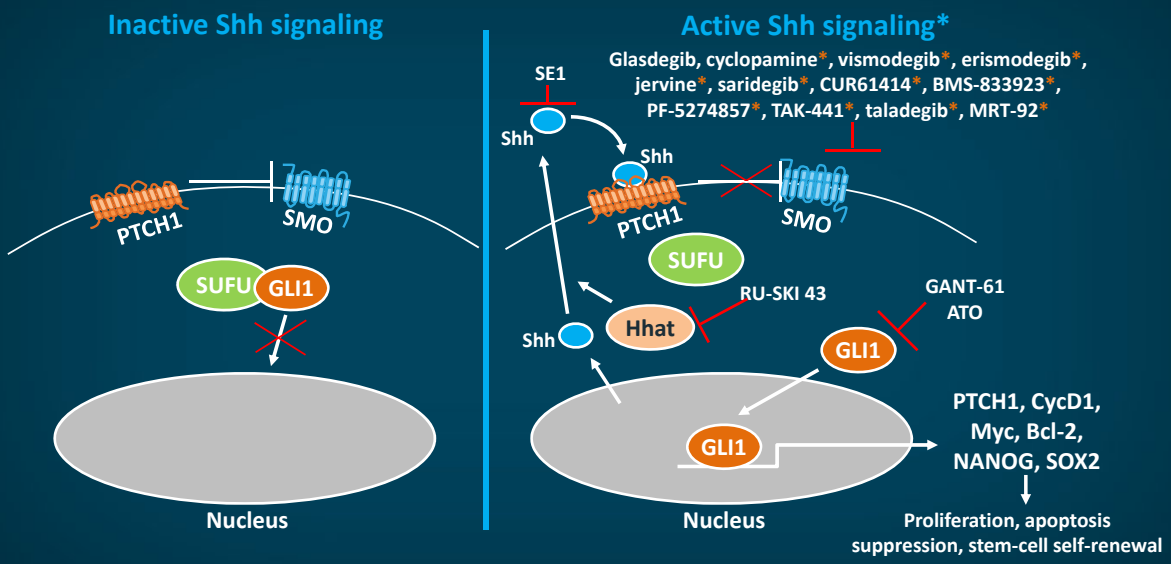
	mOS, mos (95% CI)
AZA+VEN	14.7 (11.9–18.7)
AZA+PBO	9.6 (7.4–12.7)

HR = 0.66 (95% CI, 0.52–0.85), *P* <.001

AZA = azacitidine; VEN = venetoclax; PBO = placebo; TI: Transfusion independence (≥56 days with no red blood cell or platelet transfusion between first and last day of treatment); EFS = event-free survival.

DiNardo CD, et al. *N Engl J Med.* 2020;383:617-629. DiNardo C, et al. Hematology Association (EHA) Annual Congress; June 2020: abstract LB2601.

Sonic Hedgehog (Shh) Signaling Pathway



*Investigational agents that are not FDA-approved for use in treatment of AML.

PTCH1 = patched 1; SMO = smoothened; SUFU = Suppressor of fused; GLI = glioma-associated oncogene homolog.

Rimkus TK, et al. *Cancers (Basel)*. 2016;8:22.

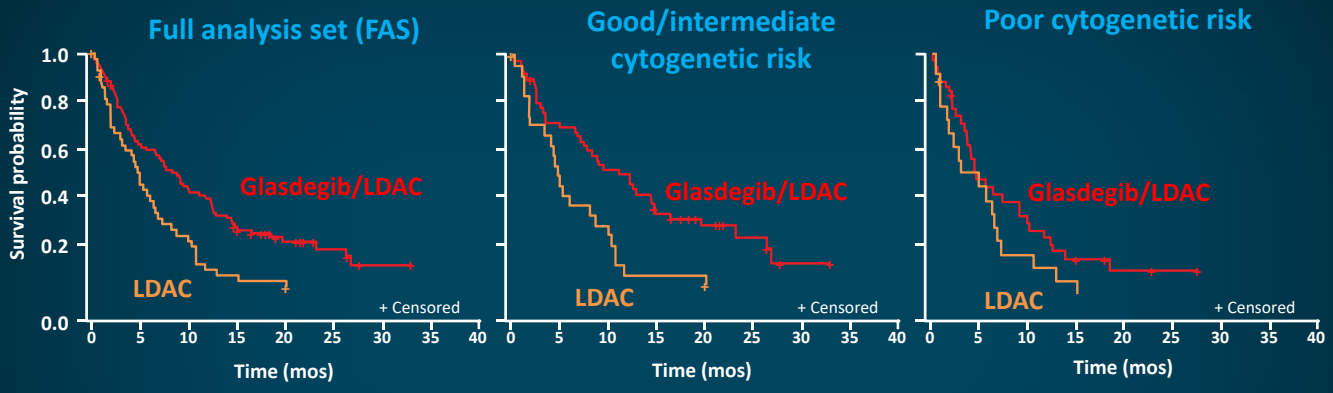
Low-Dose Cytarabine + Glasdegib

- Phase 2, open-label, multicenter study
- Patients with AML or high-risk MDS unsuitable for intensive therapy were randomized 2:1 to LDAC+glasdegib vs LDAC alone
- Glasdegib 100 mg by mouth daily was administered continuously
- LDAC 20 mg SC BID was given for 10 of 28 days
- Median OS = 8.8 mos vs 4.9 mos with LDAC+glasdegib vs LDAC (*P*= .0004)
- CR achieved in 15 (17.0%) vs 1 (2.3%) patient(s) (*P* <.05)
- Nonhematologic grade 3/4 AEs included pneumonia and fatigue
- Risk of abnormal QTc findings more frequent and QTcF prolongation less frequent with glasdegib

LDAC = low-dose

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

Low-Dose Cytarabine + Glasdegib: Overall Survival



	mOS mos (80% CI)
Glasdegib/LDAC	8.8 (6.9–9.9)
LDAC	4.9 (3.5–6.0)

HR = 0.513 (80% CI, 0.394–0.666)
P= .0004

Good/ intermediate	mOS mos (80% CI)
Glasdegib/LDAC	12.2 (8.3–14.4)
LDAC	4.8 (4.1–6.0)

HR = 0.427 (80% CI, 0.300–0.609)
P= .0008

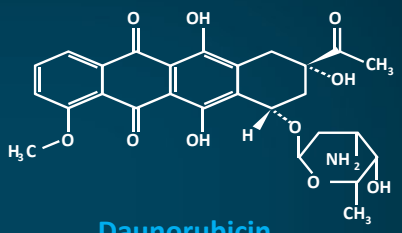
Poor	mOS mos (80% CI)
Glasdegib/LDAC	4.7 (4.0–7.4)
LDAC	4.9 (2.3–6.4)

HR = 0.633 (80% CI, 0.430–0.934)
P= .0640

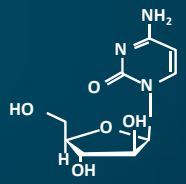
Cortes JE, et al. *Leukemia*. 2019;33:379-389.

Liposomal "7+3" (CPX-351)

- "7+3" has been the mainstay of AML induction therapy for decades
- CPX-351 is a liposomal combination of daunorubicin (anthracycline topoisomerase inhibitor) and cytarabine (nucleoside metabolic inhibitor)
- Fixed 1:5 molar ratio of daunorubicin to cytarabine
- Hypothesis, supported by laboratory studies, is that efficacy of daunorubicin and cytarabine depends upon molar ratio of these two medications
  - Synergy
  - Low level of antagonism



Daunorubicin



Cytarabine

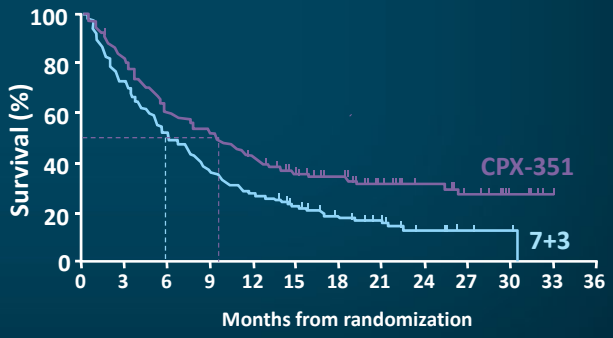
Daunorubicin + cytarabine (Vyxeos™) PI 2011 (http://pp.jazzpharma.com/pi/vyxeos.en.USPI.pdf). Accessed 7/7/2021. Lancet JE, et al. *Blood*. 2014;123:3239-3246. Mayer LD, et al. *Mol Cancer Ther*. 2006;5:1854-1863.

Liposomal "7+3" (CPX-351): Results

- Phase 3 trial: patients 60–75 years old with untreated high-risk secondary AML
  - History of prior cytotoxic treatment
  - Antecedent MDS or CMML
  - With WHO-defined MDS-related cytogenetic abnormalities
- 309 patients randomized 1:1 to CPX-351 or 7+3
- CPX-351 resulted in superior OS
  - Median OS = 9.56 vs 5.95 months (*P*= .003)
  - CR+CRi response = 47.7% vs 33.3% (*P*= .016)
  - Grade 3–5 AEs similar (92% vs 91%)

OS: ITT Analysis Population		
	Events/ patients	mOS (95% CI)
CPX-351	104/153	9.56 (6.60–11.86)
7+3	132/156	5.95 (4.99–7.75)

HR = 0.69 (95% CI, 0.52–0.90), 1-sided *P*= .003



CMML = chronic myelomonocytic leukemia; WHO = World Health Organization; ITT = intention-to-treat.

Lancet JE, et al. *J Clin Oncol.* 2018;36:2684-2692. Lancet JE, et al. *J Clin Oncol.* 2016;34(suppl): abstract 7000.

Liposomal "7+3" (CPX-351)

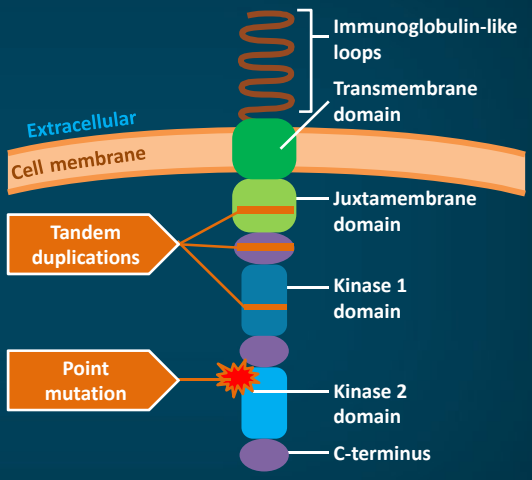
- FDA approved in August 2017
- FDA approved for adults and pediatric patients aged ≥1 year
  - With newly diagnosed t-AML
  - With AML with myelodysplasia-related changes (AML-MRC)
- Induction
  - Liposomal encapsulation of cytarabine 100 mg/m^2 and daunorubicin 44 mg/m^2 on days 1, 3, and 5
  - Subsequent cycles of induction, if needed, use same doses on days 1 and 3
- Post-remission therapy
  - Cytarabine 65 mg/m2 and daunorubicin 29 mg/m^2 on days 1 and 3
- NCCN guidelines: recommendations
  - Category 1 for patients ≥60 years with t-AML, AML-MRC, or known antecedent MDS or CMML
  - Category 2B for patients <60 years with t-AML (other than CBF AML or APL) or AML-MRC

CBF = core-binding factor; APL = acute promyelocytic leukemia.

Daunorubicin + cytarabine (Vyxeos®) PI 2021 (https://pp.jazzpharma.com/pi/vyxeos.en.USPI.pdf). NCCN. AML. V3.2021. (www.nccn.org/ professionals/physician_gls/pdf/aml.pdf). Accessed 7/7/2021.

FLT3

- *FLT3* mutations result in survival and proliferation of leukemic blasts
- *FLT3*/ITD mutations confer poor prognosis in AML
- *FLT3* mutations (which can be FLT3/ITD and/or *FLT3*/TKD) occur in ~30% of *de novo* AML patients
  - Remission rates for AML patients with *FLT3* mutations are similar to remission rates in other AML patients
  - However, relapse rates are high
- Midostaurin is oral multikinase inhibitor with activity with regard to *FLT3* receptor

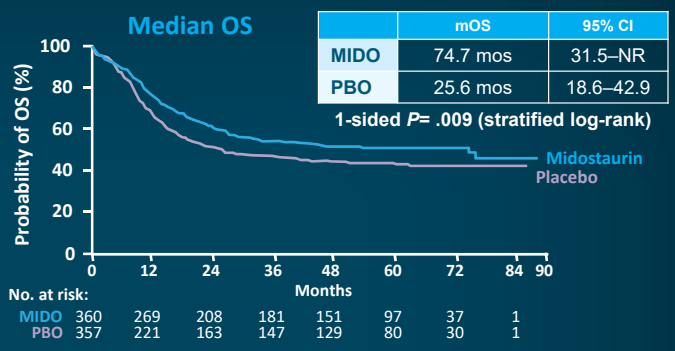


TKD = tyrosine kinase domain.

Pemmaraju N, et al. *Cancer.* 2011;117:3293-3304.

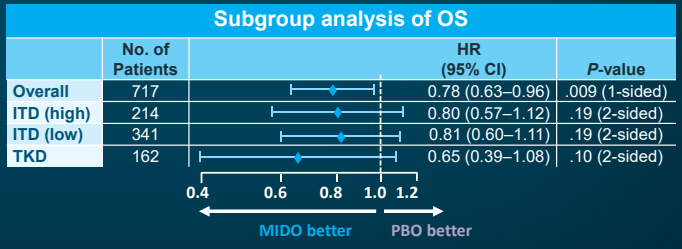
Midostaurin

- 3277 patients tested for *FLT3* mutations
- 717 FLT3-mutated patients randomized
  - 360 to midostaurin (MIDO) group
  - 357 to placebo (PBO) group
- Patients received induction with 7+3 and consolidation with high-dose cytarabine + MIDO or PBO
- In primary analysis and analysis in which data for transplanted patients were censored, benefit of MIDO was consistent across all *FLT3* subtypes
- Common AEs included nausea, mucositis, vomiting, headache, musculoskeletal pain, hyperglycemia



	mOS	95% CI
MIDO	74.7 mos	31.5–NR
PBO	25.6 mos	18.6–42.9

1-sided *P*= .009 (stratified log-rank)



Stone RM, et al. *N Engl J Med.* 2017;377:454-464. Midostaurin (Rydapt®) PI 2020 (www.novartis.us/sites/www.novartis.us/files/rydapt.pdf). Accessed 7/7/2021.

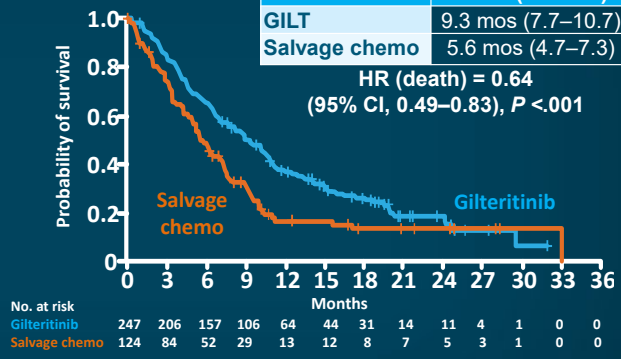
Gilteritinib—ADMIRAL Trial

- 371 adult patients with R/R *FLT3*-mutated AML randomized 2:1 to gilteritinib or salvage chemo
- CR/CRh rate = 34.0%, CRi = 25.5%, CRp = 7.7%, PR = 13.4%
- Toxicity included elevated ALT/AST/alkaline phosphatase, neutropenic fever, constipation, fatigue, cough, headache, edema thrombocytopenia, vomiting, dyspnea
- Gilteritinib can prolong QT interval
- PRES (1%), pancreatitis (4%), differentiation syndrome (3%)

Overall survival

Arms	mOS (95% CI)
GILT	9.3 mos (7.7–10.7)
Salvage chemo	5.6 mos (4.7–7.3)

HR (death) = 0.64
(95% CI, 0.49–0.83), *P* <.001



No. at risk													
Gilteritinib	247	206	157	106	64	44	31	14	11	4	1	0	0
Salvage chemo	124	84	52	29	13	12	8	7	5	3	1	0	0

GILT = gilteritinib; CRh = complete remission with partial hematologic recovery; CRp = CR with incomplete platelet recovery; PR = partial remission/response; ALT = alanine aminotransferase; AST = aspartate aminotransferase; PRES = posterior reversible encephalopathy syndrome; chemo = chemotherapy.

Perl AE, et al. *N Engl J Med*. 2019;381:1728-1740. Gilteritinib (Xospata®) PI 2019 (https://astellas.us/docs/xospata.pdf). Accessed 7/7/2021

Gilteritinib—ADMIRAL Trial
(continued)

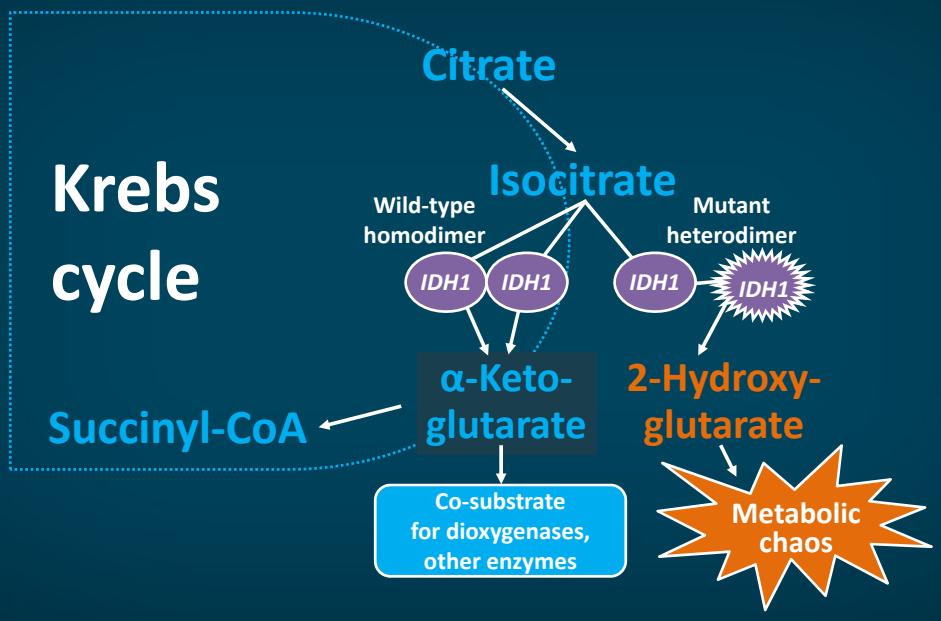
Antileukemic Responses (Intention-to-Treat Population)

Variable	Gilteritinib (n = 247)	Salvage Chemo (n = 124)	HR/Risk Difference (95% CI)
Median OS (95% CI), mos	9.3 (7.7–10.7)	5.6 (4.7–7.3)	0.64 (0.49–0.83)
Median EFS (95% CI), mos	2.8 (1.4–3.7)	0.7 (0.2–NE)	0.79 (0.58–1.09)
Response, no. (%)			
CR	52 (21.1)	13 (10.5)	10.6 (2.8-18.4)
CR/CRh	84 (34.0)	19 (15.3)	18.6 (9.8–2.4)
CRh	32 (13.0)	6 (4.8)	ND
CRi	63 (25.5)	14 (11.3)	ND
CRp	19 (7.7)	0	ND
PR	33 (13.4)	5 (4.0)	ND
No response	66 (26.7)	43 (34.7)	ND
Composite CR	134 (54.3)	27 (21.8)	32.5 (22.3–42.6)
Overall response	167 (67.6)	32 (25.8)	
Median duration of remission (95% CI), mos	11.0 (4.6–NE)	NE (NE–NE)	NE
Time to composite CR, mos	2.3±19	1.3±0.5	NA
Median leukemia-free survival (95% CI), mos	4.4 (3.6–5.2)	6.7 (2.1–8.5)	NE

NA = not applicable; ND = not determined.

Perl AE, et al. *N Engl J Med*. 2019;381:1728-1740.

IDH1 and *IDH2* Mutations in AML



CoA = coenzyme A.

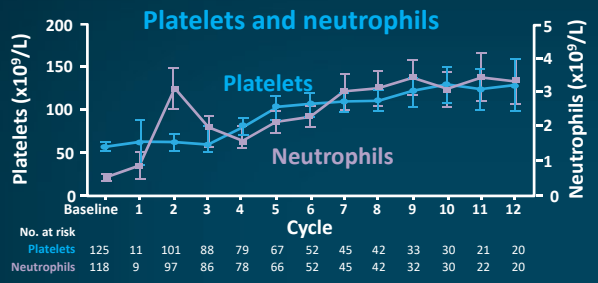
Levis M. *Blood.* 2013;122:2770-2771.

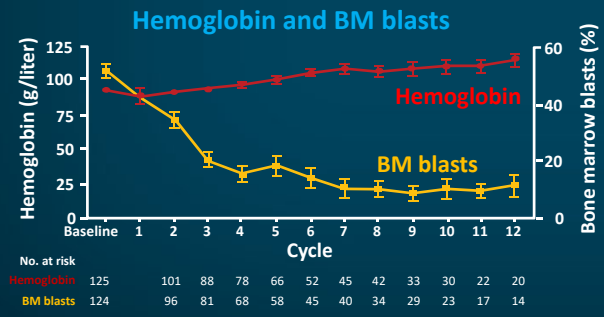
Ivosidenib—*IDH1* Inhibitor

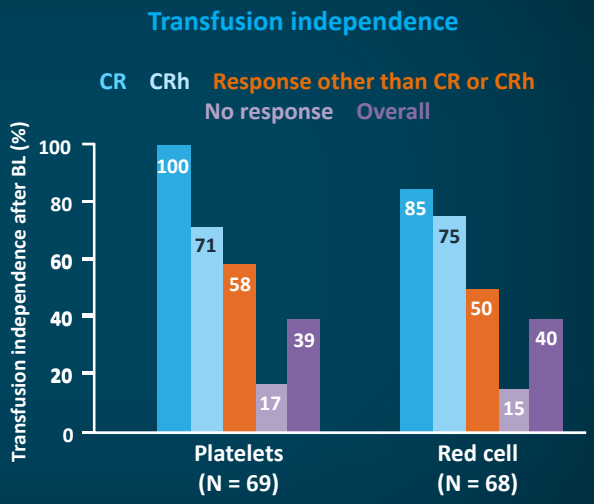
- *IDH1* mutations occur in approximately 6–10% of AML patients
- Phase 1 dose escalation and expansion study
  - 258 patients with R/R AML or other advanced hematologic malignancies with *IDH1* mutations
- Efficacy population = 125 R/R AML patients
  - ORR = 41.6%
  - CR+CRh = 30.4% (CR = 21.6% and CRh = 8.8%)
  - Median duration of CR+CRh was 8.2 months
- 12% of patients received HCT following treatment
- Differentiation syndrome was reported in 10.6% of patients
- Common AEs (≥20%): diarrhea, leukocytosis, nausea, fatigue, febrile neutropenia, dyspnea, anemia, long QT, peripheral edema, pyrexia, decreased appetite

DiNardo CD, et al. *N Engl J Med.* 2018;378:2386-2398. Stein E, et al. *J Clin Oncol.* 2018;36(15 suppl): abstract TPS7074. FDA. www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm614128.htm. Ivosidenib (Tibsovo®) PI 2019 (www.tibsovopro.com/pdf/prescribinginformation.pdf). URLs accessed 7/7/2021.

Ivosidenib—*IDH1* Inhibitor: Results

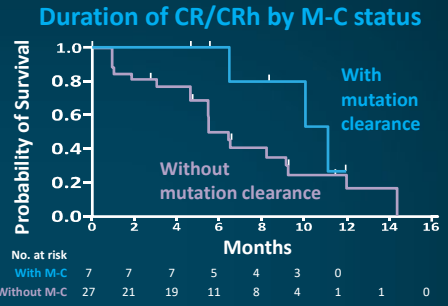


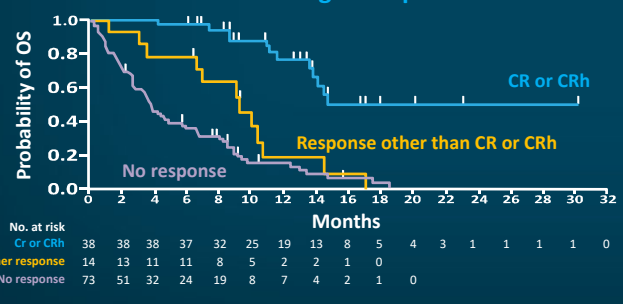


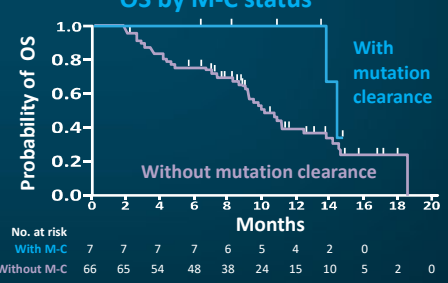


DiNardo CD, et al. *N Engl J Med* 2018;378:2386-2398.

Ivosidenib—*IDH1* Inhibitor: OS and Duration





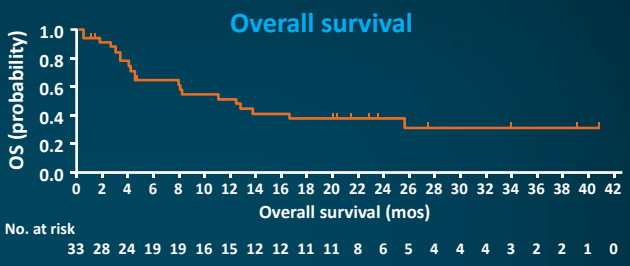


M-C = mutation clearance.

DiNardo CD, et al. *N Engl J Med* 2018;378:2386-2398.

Ivosidenib (*IDH1* Inhibitor) in *IDH1*-Mutated Patients

- Phase 1, *IDH1*-mutated AML
- 34 patients
  - Median age 76.5 yrs (range, 64–87 yrs)
  - 21 (62%) with t-AML or AML-MRC
- CR+CRh = 42.4% (14 patients)

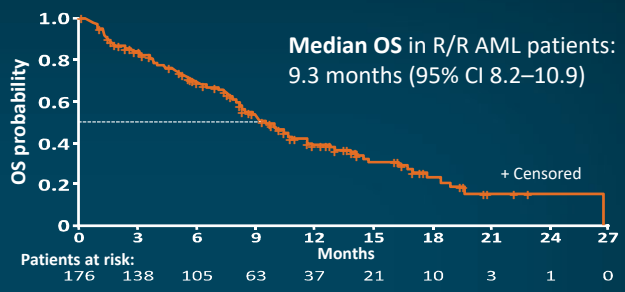


- Adverse reactions occurring in at least 25% of patients include:
  - Diarrhea, fatigue, edema, decreased appetite, leukocytosis, nausea, arthralgia, abdominal pain, dyspnea, differentiation syndrome (18%)
- 2018—FDA approved for adult patients with R/R AML with *IDH1* mutation
- 2019—FDA approved for adult patients with newly-diagnosed AML with susceptible *IDH1* mutation who are ≥75 years old or who have comorbidities that preclude use of intensive induction chemotherapy

Roboz GJ, et al. *Blood.* 2020;135:463-471. Ivosidenib (Tibsovo®) PI 2019 (www.tibsovopro.com/pdf/prescribinginformation.pdf). Accessed 7/7/2021.

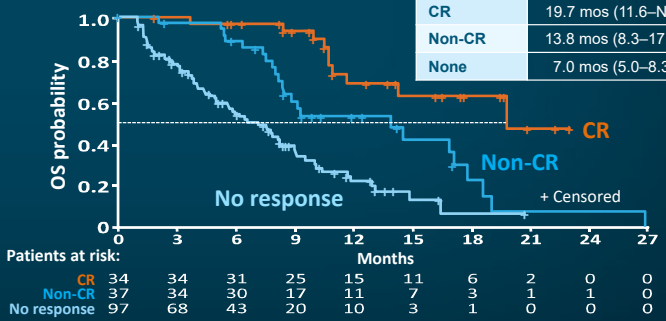
Enasidenib—*IDH2* inhibitor

- *IDH2* mutations occur in ~12% of AML patients
- Enasidenib efficacy in R/R *IDH2*-mutated AML studied in 176 patients
  - ORR = 40.3%; median response duration = 5.8 mos
  - Responses associated with cellular differentiation and maturation, typically without aplasia
  - Median OS in R/R patients = 9.3 mos
  - Among 34 patients (19.3%) who achieved CR, OS = 19.7 mos
  - Differentiation syndrome reported in 7% of patients using enasidenib
  - 10% of patients proceeded to transplant



Median OS in R/R AML patients: 9.3 months (95% CI 8.2–10.9)

Response	mOS (95% CI)
CR	19.7 mos (11.6–NE)
Non-CR	13.8 mos (8.3–17.0)
None	7.0 mos (5.0–8.3)



Stein EM, et al. *Blood.* 2017;130:722-731.

IDH-Inhibitor Combinations*

Ivosidenib + azacitidine in newly diagnosed *IDH1*-mutated AML (Phase 1b)

- 23 patients
- ORR = 78.3% (CR = 60.9%, CRh = 8.7%, MLFS = 8.7%)
- 11/16 patients (69%) with CR/CRh achieved mIDH1 clearance
- AEs included thrombocytopenia, anemia, febrile neutropenia, neutropenia, sepsis, QT prolongation (13% Grade 3/4), and differentiation syndrome (17% all grades; 8.7% grade 3/4)

Enasidenib + azacitidine in newly diagnosed *IDH2*-mutated AML (Phase 2)

Clinical efficacy: enasidenib + azacitidine vs azacitidine monotherapy

	Enasidenib + azacitidine (n = 68)	Azacitidine monotherapy (n = 33)
Overall response rate,*n (%) [95% CI]	**46 (68)** [55–79]	**14 (42)** [26–61]
P value	0.0155	
Best response/CR, n (%) [95% CI]	34 (50) [38–62]	4 (12) [3–28]
P value	0.0002	
CR with incomplete recovery (CRi/CRp), n (%)	6 (9)	4 (12)
Partial remission, n (%)	3 (4)	4 (12)
MLFS, n (%)	3 (4)	2 (6)
Stable disease n (%)	15 (22)	13 (39)
Progressive disease, n (%)	2 (3)	1 (3)
Not evaluable, n (%)	1 (2)	0
Missing, n (%)	4 (6)	5 (15)
Time to first response (mos), median (range)	1.9 (1–9)	2.0 (1–6)
Duration of response (mos), median (95% CI)	NR (11–NR)	10.2 (3–NR)
Time to CR (mos), median (range)	5.0 (1–20)	3.7 (3–4)

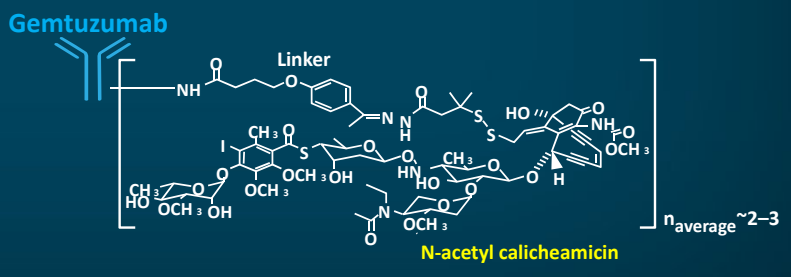
*Not currently approved by the FDA.

ASCO = American Society of Clinical Oncology; MLFS = morphologic leukemia-free state.

DiNardo CD, et al. *J Clin Oncol*. 2021;39:57-65. DiNardo CD, et al. *Blood*. 2019;134(suppl 1): abstract 643.

Gemtuzumab Ozogamicin (GO)

- Gemtuzumab ozogamicin is a CD33-directed antibody and cytotoxic drug conjugate
- Initially granted accelerated approval by the FDA in 2000 for adults with relapsed AML
- Withdrawn from US market in 2010 and was reapproved in 2017
  - Preliminary data analysis from phase 3 study (which evaluated GO incorporated into induction therapy for AML) showed GO did not improve survival
  - Increased risk of death from treatment toxicity
  - Risk of veno-occlusive disease (VOD) of liver
- Continued investigation
  - ALFA-0701 (newly diagnosed AML age 50–70 years)
  - AML-19 (elderly/unfit newly diagnosed AML)
  - MyloFrance-1 (R/R CD33-positive AML)



Gemtuzumab ozogamicin (Mylotarg™) PI 2020 (http://labeling.pfizer.com/ShowLabeling.aspx?id=9548&format=PDF). GO overview (www.ncbi.nlm.nih.gov/books/NBK548438/pdf/Bookshelf_ NBK548438.pdf). FDA PR (www.fda.gov/newsevents/newsroom/pressannouncements/ucm574507.htm). Ingram I. Cancer Network, 2017. (www.cancernetwork.com/acute-myeloid-leukemia/fda-approves-gemtuzumab-ozogamicin-acute-myeloid-leukemia). URLs accessed 7/7/2021.

Gemtuzumab Ozogamicin: ALFA-0701

- Phase 3, open-label study
- 280 patients 50–70 years old with untreated de novo AML
- 1:1 randomization
  - 7+3
  - 7+3 + GO (3 mg/m^2)
    - GO days 1, 4, and 7 of induction
    - GO day 1 of consolidation (2 cycles)
- At 2 years, OS = 53.2% in GO group vs 41.9% in control group (*P*= .0368)
- Hematologic toxicity, especially thrombocytopenia, was more common in GO group

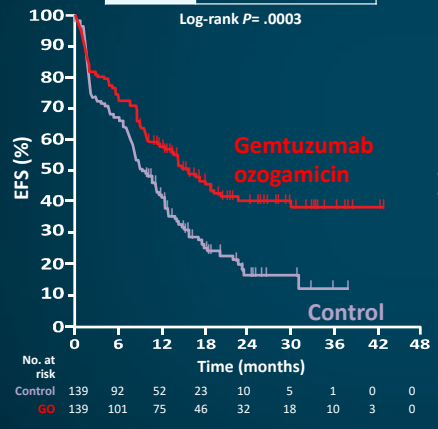
Castaigne S, et al. *Lancet*. 2012;379:1508-1516.

Gemtuzumab Ozogamicin: ALFA-0701: Results at 2 Years

Event-free survival

Arms	EFS rate (95% CI)
GO	40.8% (32.8–50.8)
Control	17.1% (10.8–27.1)

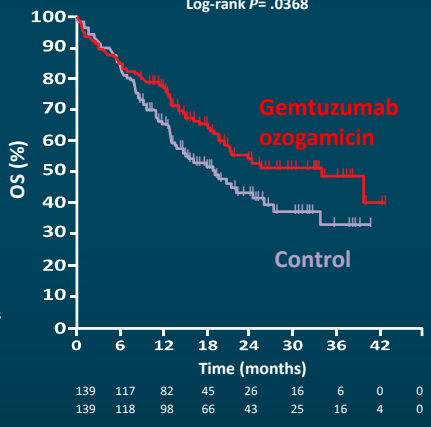
Log-rank *P*= .0003



Overall survival

Arms	OS rate (95% CI)
GO	53.2% (44.6–63.5)
Control	41.9% (33.1–53.1)

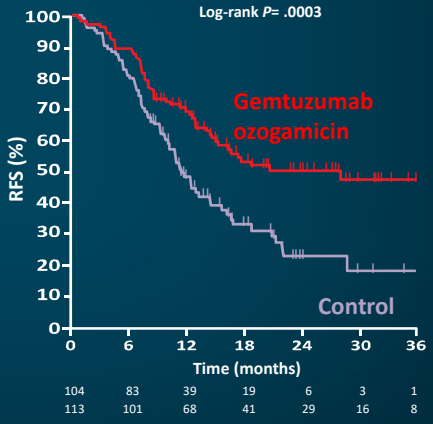
Log-rank *P*= .0368



Relapse-free survival

Arms	RFS rate (95% CI)
GO	50.3% (41.0–61.6)
Control	22.7% (14.5–35.7)

Log-rank *P*= .0003

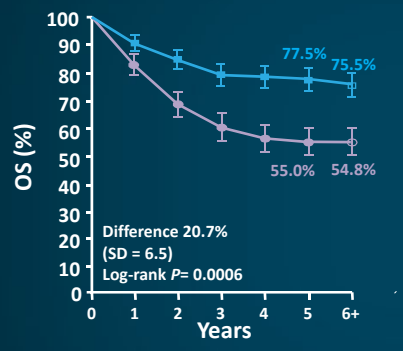


RFS = relapse-free survival.

Castaigne S, et al. *Lancet*. 2012;379:1508-1516.

Gemtuzumab Ozogamicin: Meta-analysis

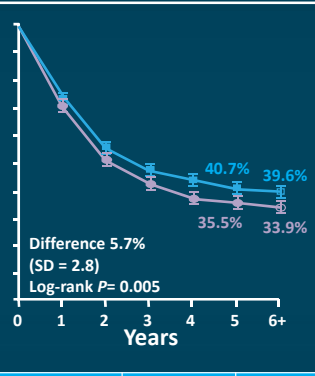
Favorable



Annual event rates	Years 1–5 % (SD)	Years 6+ % (SD)
GO	5.8 (1.1)	2.3 (1.3)
No GO	14.1 (1.9)	0.0 (0.0)

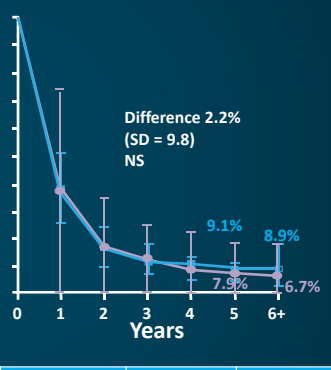
Intermediate

Allocated to GO Allocated to no GO



Annual event rates	Years 1–5 % (SD)	Years 6+ % (SD)
GO	22.4 (1.0)	2.7 (0.9)
No GO	26.2 (1.1)	4.9 (1.3)

Adverse



Annual event rates	Years 1–5 % (SD)	Years 6+ % (SD)
GO	73.8 (4.6)	2.4 (2.4)
No GO	76.7 (4.8)	21.1 (10.5)

SD = standard deviation.

Hills RK, et al. *Lancet Oncol.* 2014;15:986-996.

When to Use GO

- FDA approved in September 2017
  - Treatment of newly diagnosed CD33-positive AML in adults and in pediatric patients aged ≥1 month
  - Treatment of R/R CD33-positive AML in adults and in pediatric patients aged ≥2 years
- Also investigated as single agent for elderly/unfit AML and R/R AML (AML-19 and MyloFrance-1)
- VOD in 6/131 (5%) of patients
- NCCN
  - Induction/consolidation option for patients <60 and ≥60 years
  - Option for R/R AML
  - Option for APL induction and consolidation in high-risk and/or cardiac patients and relapsed APL

WARNING: HEPATOTOXICITY

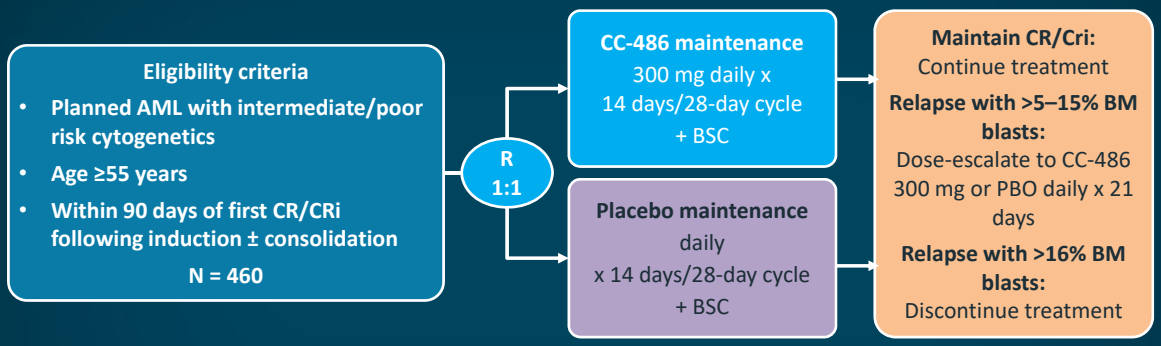
See full prescribing information for complete boxed warning.

Hepatotoxicity, including severe or fatal hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), has been reported in association with the use (5.1, 6.1)

Gemtuzumab ozogamicin (Mylotarg™) PI 2020 (http://labeling.pfizer.com/ShowLabeling.aspx?id=9548). Ingram I. Cancer Network. 2017. (www.cancernetwork.com/acute-myeloid-leukemia/fda-approves-gemtuzumab-ozogamicin-acute-myeloid-leukemia). NCCN. AML. V3.2021. (www.nccn.org/professionals/physician_gls/pdf/aml.pdf). All URLs accessed 7/7/2021.

QUAZAR AML-001: Maintenance With CC-486*

Study Design



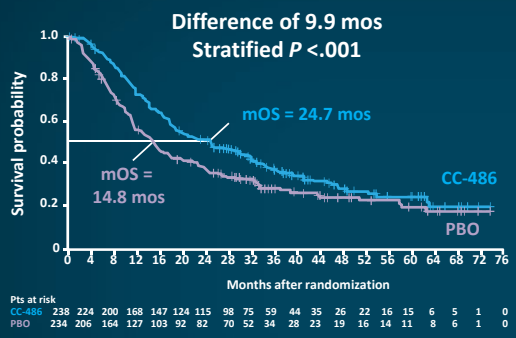
Primary endpoint: OS
Secondary endpoints: RFS, safety, HRQoL, healthcare resource utilization
Stratification: age, history of MDS, cytogenetic risk category, consolidation therapy following induction

*Oral formulation of azacitidine.
BSC = best supportive care; HRQoL = health-related quality of life.

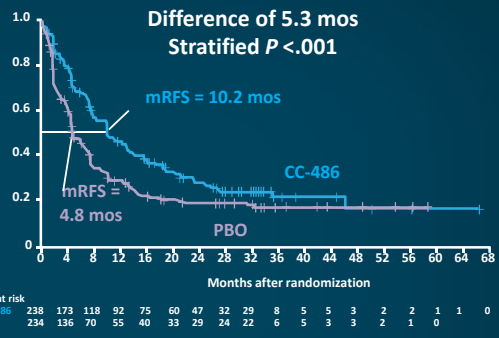
Roboz GJ, et al. *Future Oncol*. 2016;12:293-302.

QUAZAR AML-001: Maintenance with CC-486: OS and RFS

Overall survival



Relapse-free survival



- 472 AML patients with intermediate- or poor-risk cytogenetics who had achieved CR or CRi after intensive chemotherapy
- Randomized 1:1 to CC-486 (oral azacitidine) vs placebo
- CC-486 had a safety profile consistent with that of parenteral azacitidine
- Received FDA approval September 2020 at 300-mg dose for adults with AML who achieve complete first remission

Wei AH, et al. *N Engl J Med.* 2020;383:2526-2537. Solis-Moreira J. JNCCN 360 (https://jnccn360.org/aml/news/azacitidine-tablets-approved-by-fda-for-patients-with-aml-in-first-remission/?bc_md5=ab23334ef76a2e69802649e75e321b67&utm_medium= email&utm_source=JNCCN-360_AML+%2b+Balance_091520). Accessed 7/7/2021.

Summary of Therapies: Newly Diagnosed AML

Fit patients	Specific populations
• 7+3	
• 7+3 + midostaurin	→ *FLT3*-mutated AML
• 7+3 + gemtuzumab ozogamicin	→ Consider in favorable-risk CD33- positive AML
• Liposomal 7+3 (CPX-351)	→ Consider in AML arising from MDS and therapy-related AML
Unfit patients	
• Venetoclax + HMA (or LDAC)	
• Glasdegib + LDAC	
• Ivosidenib	→ Can consider in *IDH1*-mutated AML
• Gemtuzumab ozogamicin	→ Can consider in CD33-positive AML
Maintenance therapy	
• CC-486	→ Patients in CR/CRi who cannot complete intensive curative therapy

HMA = hypomethylating agent.

Summary of Therapies: Relapsed/Refractory AML

Therapies	Specific populations
• Gilteritinib	→ *FLT3*-mutated AML
• Ivosidenib	→ *IDH1*-mutated AML
• Enasidenib	→ *IDH2*-mutated AML
• Gemtuzumab ozogamicin	→ CD33-positive AML
• Can still consider previously existing therapies:	
– HMAs	
– Combination chemotherapy (ie, MEC, HiAC, FLAG, etc)	

MEC = mitoxantrone, etoposide, and cytarabine; FLAG = fludarabine, high-dose cytarabine, and granulocyte colony-stimulating factor.

Case 3: Introduction and Questions to Consider

Case description

- 71-year-old man was diagnosed nearly 2 years ago with normal karyotype AML with an *NPM1* mutation
- He is not a transplant candidate due to stage 4 CKD
- He has been treated with azacitidine since his diagnosis, with an excellent response, but has now relapsed
  - He is interested in continuing treatment for his AML
  - ECOG PS of 1
- Laboratory results:
  - WBC = 2.1 X 10^9/L
  - ANC = 0.7 X 10^9/L
  - Hgb = 8.8 g/dL
  - Platelets = 46 X 10^9/L

Questions to consider

- What are the next steps in the management of this patient?
- How would you discuss potential treatment options with the patient?

Personalizing Treatment

Selection and Sequencing of Care for AML Patients

- Established treatment algorithms and clinical practice: choosing appropriate patient populations
- Analysis of patient-specific factors that affect outcomes
  - Genetic characteristics
  - Treatment history
  - Comorbidities
  - Common adverse effects
  - Age
  - Patient preferences

Role of Clinician-Patient Communication in AML

- Avenues of engagement for patients with AML and their families
  - Increasing opportunities with more available therapies
- Incorporating shared decision-making (SDM) practices
  - Value-based approach to high-quality care

Summary Points

- Outcomes in AML are gradually improving
  - Increasing array of treatment options
  - Many patients can achieve long-term survival with allogeneic transplant
- AML therapy is no longer “one size fits all”
- Care should be individualized, based on a number of factors
  - Karyotype and molecular features are important, as are patient characteristics
- Other promising agents are in clinical studies

Thank You!

Questions & Answers

Use your device's QR code scanner to view this 360° content in the **YOUTUBE APP!**

CATALYST: Insights from the Experts to Navigate a Complex and Evolving Landscape in CLL and AML Management

Chronic Lymphocytic Leukemia (CLL)
TOOLKIT

Resource	Web Address
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CATALYST: A Virtual Reality View of Genomics, Targeted Therapeutic Options, and Treatment Sequencing for the Management of Hematologic Malignancies

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