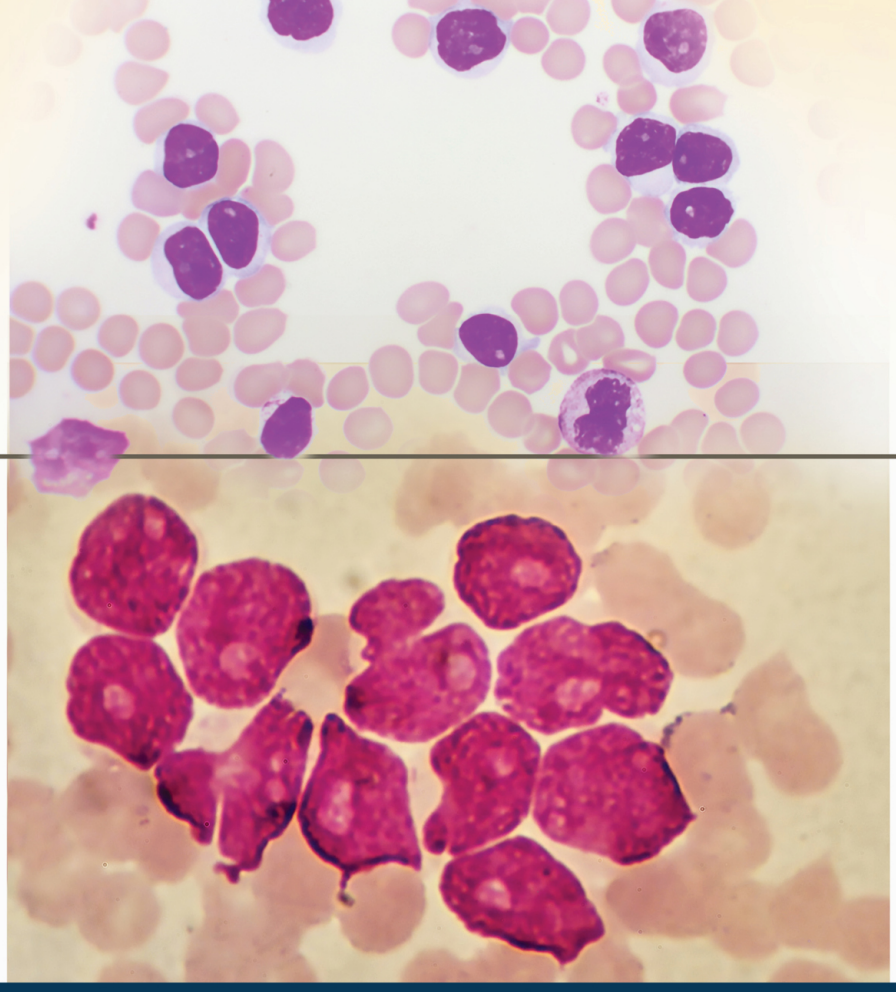

# catalyst:

## A 3D VIEW of Genomics, Targeted Therapeutic Options, and Treatment Sequencing for the Management of Hematologic Malignancies

*This activity is provided by Med Learning Group.*
*This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM).*

*Supported by educational grants from AbbVie Inc. and Celgene Corporation.*

# *CATALYST: A 3D View of Genomics, Targeted Therapeutic Options, and Treatment Sequencing for the Management of Hematologic Malignancies*

**FACULTY**

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

**Ryan Jacobs, MD**
Director of CLL Clinical Trials
Department of Hematology, Lymphoma Section
Levine Cancer Institute/Atrium Health
Charlotte, NC
Clinical Assistant Professor of Medicine
UNC-Chapel Hill School of Medicine
Chapel Hill, NC

**FACULTY PRESENTERS**

**Farrukh T. Awan, MD**
Associate Professor of Medicine
Director of Lymphoid Malignancies Program
Harold C. Simmons Comprehensive Cancer Center
University of Texas Southwestern Medical Center
Dallas, TX

**Michael R. Grunwald, MD**
Chief, Leukemia Division
Associate Professor, Atrium Health
Department of Hematologic Oncology and Blood Disorders
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Director of CLL Clinical Trials
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Levine Cancer Institute/Atrium Health
Charlotte, NC
Clinical Assistant Professor of Medicine
UNC-Chapel Hill School of Medicine
Chapel Hill, NC

## PROGRAM OVERVIEW

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

## EDUCATIONAL AUDIENCE

This activity is designed to meet the education needs of US-based hematologists, medical oncologists, and other healthcare providers involved in the treatment of CLL and AML.

## LEARNING OBJECTIVES

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

- Explain how common mutations and abnormalities in patients with previously untreated and R/R CLL and AML affect treatment decision-making
- Describe available and emerging therapeutic approaches for patients with previously untreated and R/R CLL and AML
- Review methods for measuring and analyzing MRD in CLL and clinical trial data providing insight into the use of MRD status in the management of CLL
- Design evidence-based therapeutic strategies for patients with previously untreated and R/R CLL and AML based on patient characteristics
- Discuss the benefits of effective communication between healthcare providers and patients with previously untreated and R/R CLL and AML.

## ACCREDITATION STATEMENT

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This CME activity was planned and produced in accordance with the ACCME Essentials.

## CREDIT DESIGNATION STATEMENT

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## NURSING CREDIT INFORMATION

Purpose: This program would be beneficial for nurses involved in the treatment and management of patients with AML and CLL. CNE Credits: 1.0 ANCC Contact Hour

CNE Accreditation Statement:
Ultimate Medical Academy/CCM is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.
Awarded 1.0 contact hour of continuing nursing education of RNs and APNs.

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**Dr. Ryan Jacobs** has served on the speakers' bureau for AbbVie, AstraZeneca, Pharmacyclics, Genentech, Janssen, and Verastem. He has received consultant fees from AbbVie, Pharmacyclics, Verastem, and AstraZeneca. He has received research funding from Pharmacyclics and TG Therapeutics.

**Dr. Michael Grunwald** has received consultant fees from Incyte, BMS/Celgene, Pfizer, Cardinal Health, Amgen, Merck, Agios, AbbVie, Daiichi Sankyo, Trovagene, Astellas, and Premier, and received fees for non-CME services from Incyte. He has been contracted for research for Amgen, Incyte, Genentech/Roche, Janssen, Forma Therapeutics, and Novartis. He has ownership interest in Medtronic.

**Dr. Farrukh T. Awan** has received consulting fees from Genentech, Astrazeneca, AbbVie, Janssen, Pharmacyclics, Gilead Sciences, Kite Pharma, Dava Oncology, Celgene, Blueprint medicines, Sunesis, Karyopharm, and MEI Pharma.

**CME Content Review**

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The reviewer of this activity has nothing to disclose.

**CNE Content Review**

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The reviewer of this activity has nothing to disclose.

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Christina Gallo, SVP Educational Development for Med Learning Group has nothing to disclose.

Marcello A. Morgan, MD, MPH, Director of Medical and Scientific Services for Med Learning Group has nothing to disclose.

Brianna Hanson, Accreditation and Outcomes Coordinator has nothing to disclose.

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1. Read the CME/CNE information and faculty disclosures.
2. Participate in the live activity.
3. Complete the online evaluation form.

You will receive your certificate as a downloadable file.

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**AGENDA**

Acute Myeloid Leukemia (AML)

1. **AML: An Overview**
   - Review of epidemiology, disease pathophysiology, and course
   - Economic burden and effects on quality of life

2. **The Genomics of AML**
   - Common genetic aberrations
     - **i.** Diagnostic and prognostic value
     - **ii.** Role in treatment decision-making

3. **Current and Emerging Treatments in AML: Pathways and Targets**
   - VIDEO presentation
   - Targeting apoptotic pathways in the management of AML
   - FLT-3 inhibition
   - Targeting IDH1 and IDH2 mutations
   - Other targets and pathways

4. **Case Studies: Individualizing Care for Patients with AML**

5. **The Role of Clinician-Patient Communication**
   - Strategies to improve clinician-patient interactions
     - **i.** Avenues of engagement for patients with AML and their families
     - **ii.** Incorporating shared decision-making practices into a value-based approach to high-quality care

6. **Conclusions**

7. **Questions and Answers**

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

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

# *Updates in Acute Myeloid Leukemia (AML): An Overview*

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

## Disclosures

- Please see Program Overview for specific speaker disclosure information.
- 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

- Explain how common mutations and abnormalities in patients with previously untreated and R/R CLL and AML affect treatment decision-making
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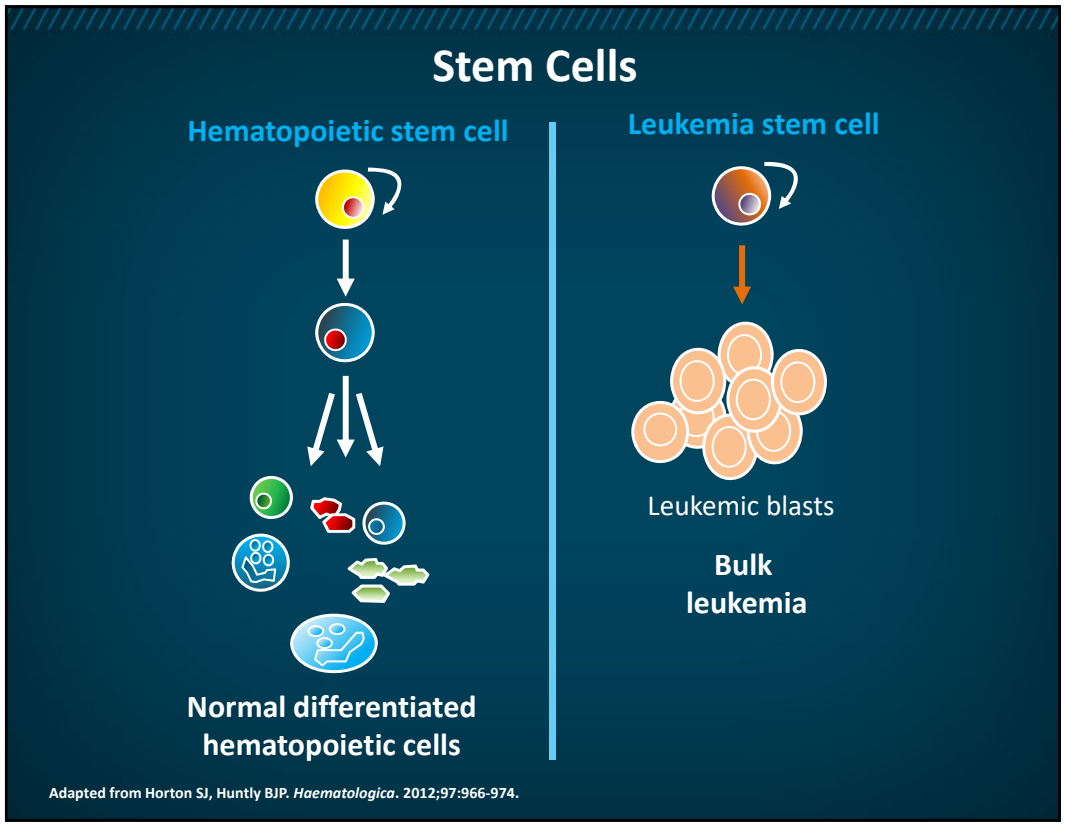
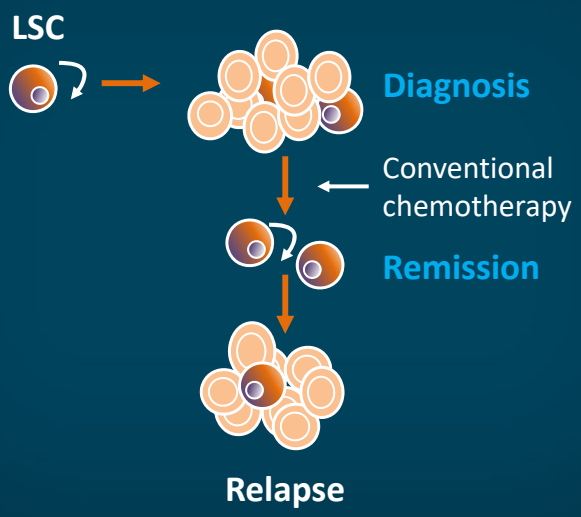
# Stem Cells




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

# Leukemia Stem-Cell Theory

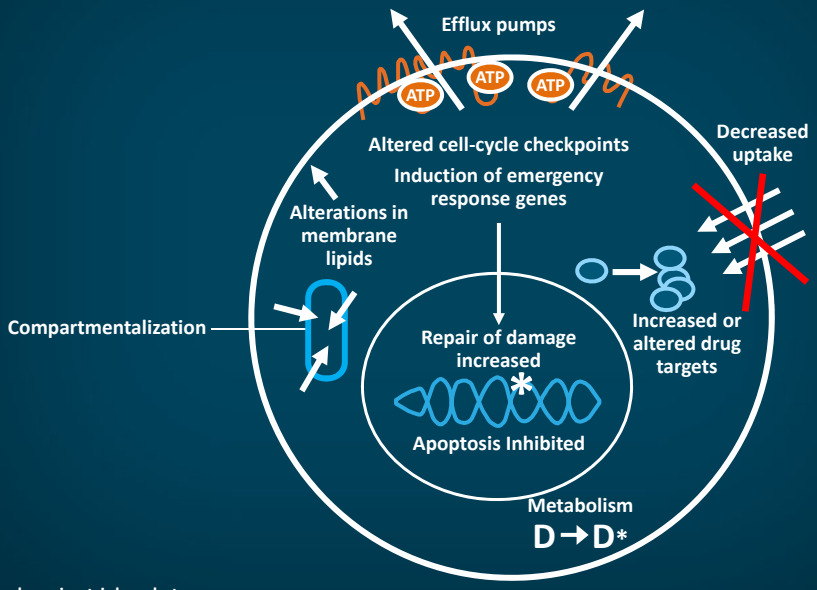
## Relapse results from resistant LSCs




LSC = leukemia stem cell.

Adapted from Zeijlemaker W, Schuurhuis GJ. (www.intechopen.com/books/leukemia/minimal-residual-disease-and-leukemic-stem-cells-in-acute-myeloid-leukemia). Accessed May 5, 2020.

# How Cultured Cancer Cells Become Resistant to Cytotoxic Cancer Drugs

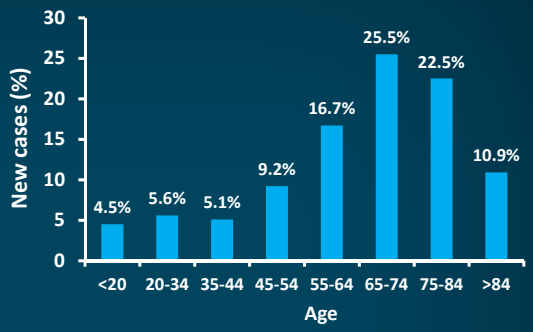


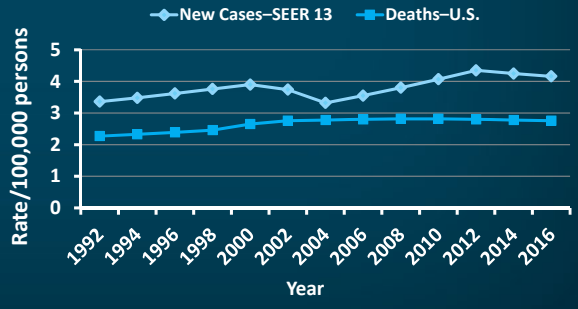

ATP = adenosine triphosphate.

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

# Acute Myeloid Leukemia (AML)

- 19,940 estimated new cases in 2020
  - 1.1% of all new cancer cases
  - 1.8% 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
- 28.7% of patients survive ≥5 years




National Cancer Institute (NCI). Cancer Stat Facts: AML, SEER database (https://seer.cancer.gov/statfacts/html/amyl.html). Accessed May 5, 2020.

# 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 May 5, 2020. 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 and the Veteran Population

- Increased risk of development in the following populations:[1,2]
  - Exposure to benzene is well established as a risk factor for myeloid malignancy
  - Both ground troops and onboard support personnel were at risk for significant exposure to dioxin, benzene, and Agent Orange herbicide during the Vietnam war
  - More recently, veterans stationed at Camp Lejeune between 1953 and 1987 were found to have potential exposure to industrial solvents in well water associated with increased risk for myeloid malignancy
- Military Disability Rating Code(s): Code 7703 and 7719[3]
- Patient resources for veterans include:
  - www.cancercare.org/tagged/veterans
  - www.cancercare.org/publications/340-veterans_living_with_cancer_resources_and_support
  - www.publichealth.va.gov/exposures/agentorange/

1. Defense Health Research Programs (June 2017) (www.aplu.org/members/councils/governmental-affairs/cga-miscellaneous-documents/2017-Defense-Health-Research-Military-Relevance-inc.%20endnotes.pdf). 2. ACS. (www.cancer.org/cancer/acute-myeloid-leukemia/causes-risks-prevention/risk-factors.html). 3. Military Disability Made Easy (blood cell disorders). (www.militarydisabilitymadeeasy.com/theblood.html#red). All URLs accessed May 5, 2020.

# AML: Comorbidities and Effect on QoL

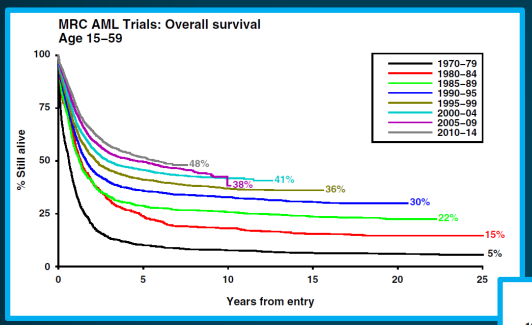
- Comorbidities are an independent predictor of all-cause mortality and negatively impact prognosis in AML patients
  - Age, gender, and socioeconomic status are associated with comorbidity, which may explain the impact of comorbidities on prognosis
    - Link between increased comorbidity burden and 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.**

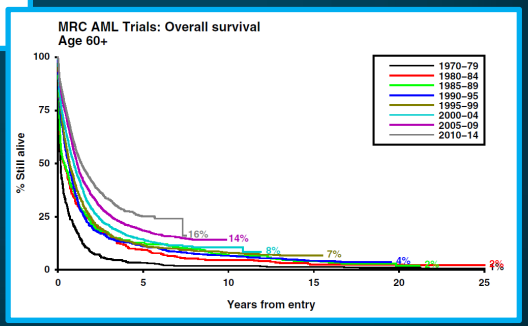
Storey S, et al. *Curr Geriatr Rep.* 2017;6:247-254. Buckley SA, et al. *Cancer.* 2018;124:145-152.

# MRC AML Trials: OS

## Ages 15–59 years

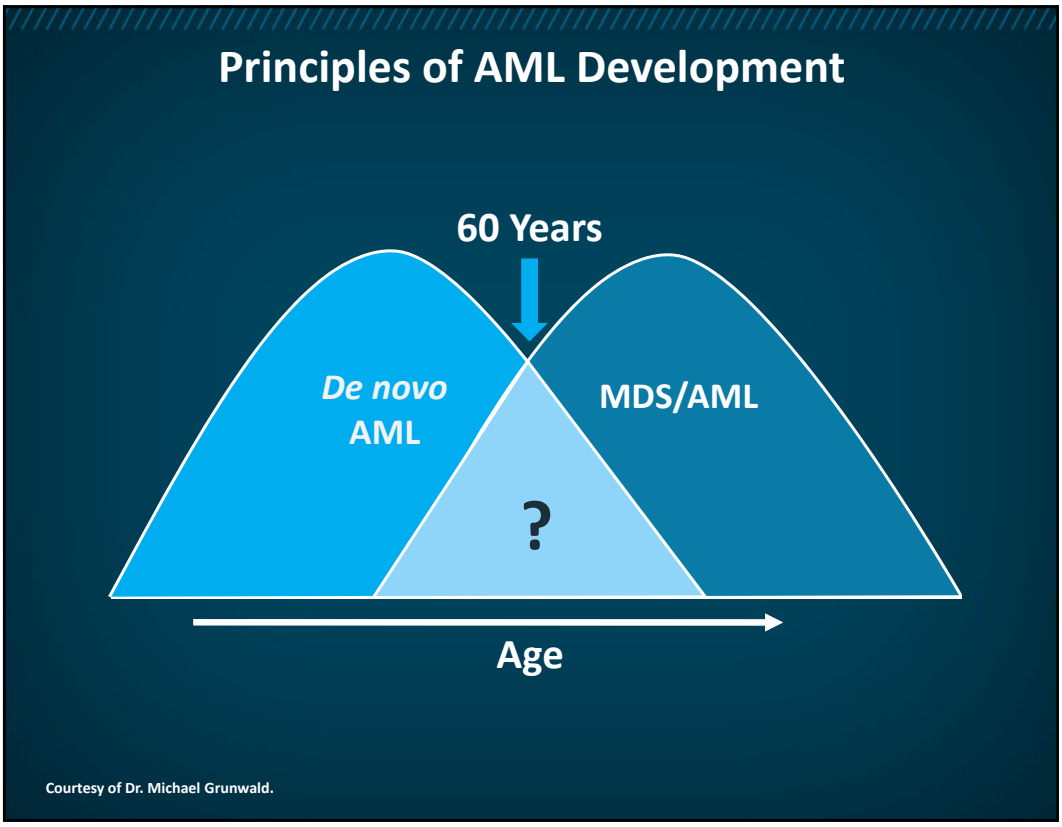


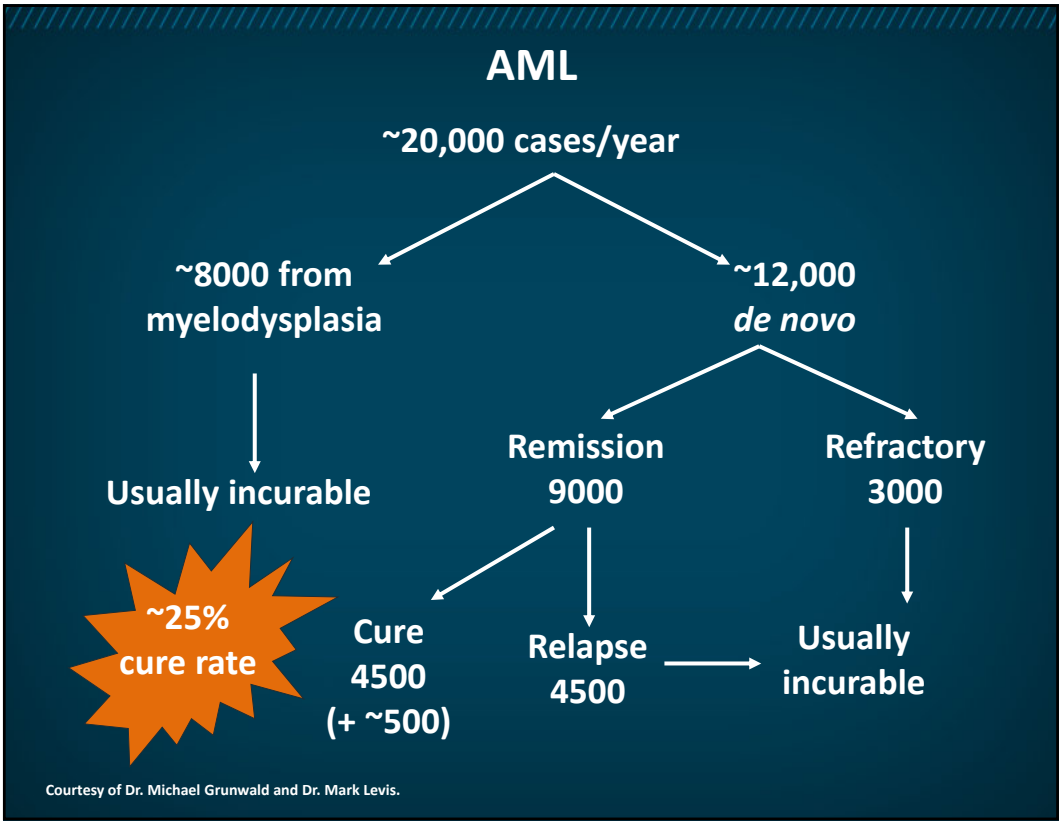

## Age 60+ years




**MRC = Medical Research Council (UK).**

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


Principles of AML Development
60 Years
De novo AML
MDS/AML
?
Age
Courtesy of Dr. Michael Grunwald.


AML
~20,000 cases/year
~8000 from myelodysplasia
~12,000 de novo
Usually incurable
Remission 9000
Refractory 3000
~25% cure rate
Cure 4500 (+ ~500)
Relapse 4500
Usually incurable
Courtesy of Dr. Michael Grunwald and Dr. Mark Levis.

## Acute Leukemia: Signs/Symptoms

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

**WBC = white blood (cell) count.**

**ACS. AML signs and symptoms (www.cancer.org/cancer/acute-myeloid-leukemia/detection-diagnosis-staging/signs-symptoms.html). Accessed May 5, 2020.**

## 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

**CBC = complete blood count; CMP = comprehensive metabolic panel; 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). Accessed May 5, 2020.**

# Initial Workup—Bone Marrow

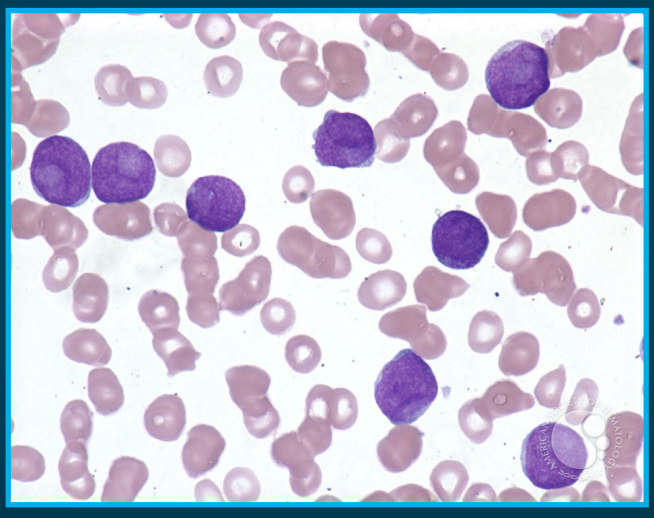
- Aspirate and core biopsy
  - Aspirate lets you see the morphology
  - Core gives cellularity
- Flow cytometry
- Cytogenetics
- FISH
- Molecular studies
- Research specimen

FISH = fluorescent in situ hybridization.

ACS. AML diagnosis (www.cancer.org/cancer/acute-myeloid-leukemia/detection-diagnosis-staging/how-diagnosed.html). Accessed May 5, 2020.

# AML

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



O'Donnell MR, et al. *J Natl Compr Canc Netw.* 2017;15:926-957. National Comprehensive Cancer Network (NCCN). AML. V3.2020. (www.nccn.org/professionals/physician_gls/pdf/aml.pdf). Accessed May 5, 2020.

# Initial Workup—Other

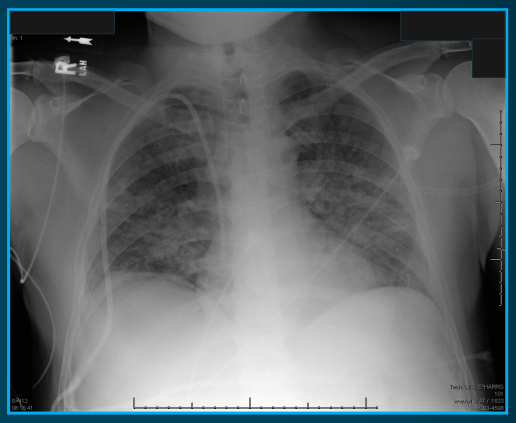
- Non-contrast CT chest and sinuses
  - Avoid IV contrast to prevent renal toxicity
  - Fungal pneumonia may be missed on CXR
- 12-lead EKG
- Interventional radiology for central line
- Echocardiogram
  - Assess EF prior to chemotherapy
- Lumbar puncture
  - WBC >50 K, neurologic symptoms, M4Eo (Inv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

**CT = computed tomography; 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 May 5, 2020.**

# 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

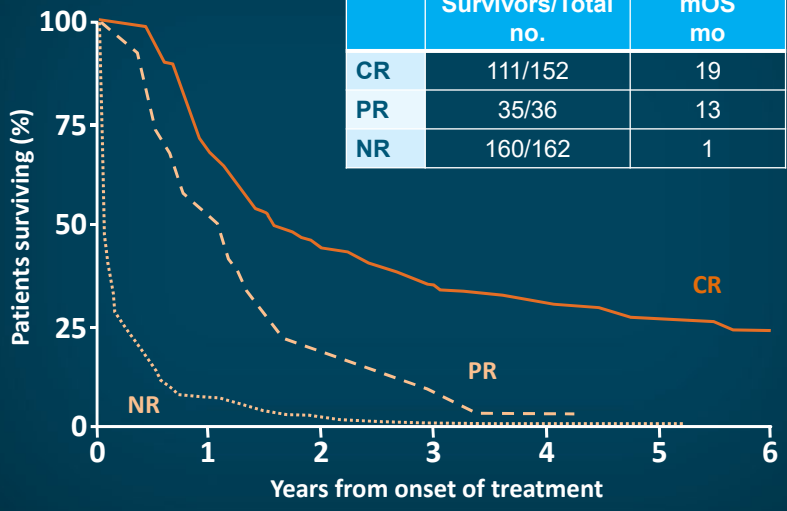
**IWG = International Working Group; ANC = absolute neutrophil count.**

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

# Survival: All Patients

## 4 Regimens Used for Remission Induction

| | Survivors/Total no. | mOS mo |
|---|---|---|
| CR | 111/152 | 19 |
| PR | 35/36 | 13 |
| NR | 160/162 | 1 |




mOS = median overall survival; mo = month(s); PR = partial remission/response; NR = 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
  - 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. V3.2020 (www.nccn.org/professionals/physician_gls/pdf/aml.pdf). Accessed May 5, 2020.

# Post-remission Therapy: "Consolidation"

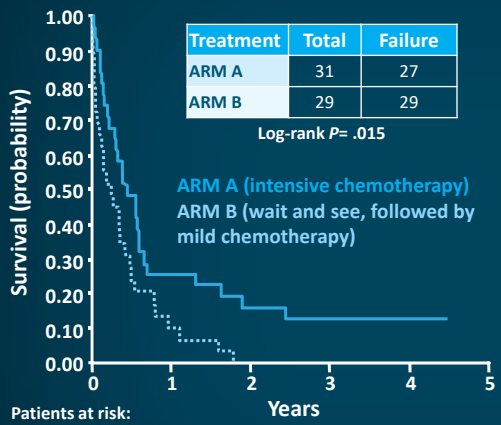
- High-dose cytarabine (HiDAC)[1]
  - 3 g/m$^2$ IV BID days 1, 3, and 5 for 3–4 cycles[1,2]
  - Several alternates (eg, 1.5 g IV BID Days 1, 3, and 5)[1]
- Sometimes etoposide or anthracycline is added to HiDAC
- Allogeneic HCT

BID = twice daily; HCT = hematopoietic cell transplantation.

1. NCCN. AML. V3.2020 (www.nccn.org/professionals/physician_gls/pdf/aml.pdf). Accessed May 5, 2020. 2. Mayer RJ, et al. *N Engl J Med.* 1994;331:896-903.

# AML in Elderly (Age >60 Years)

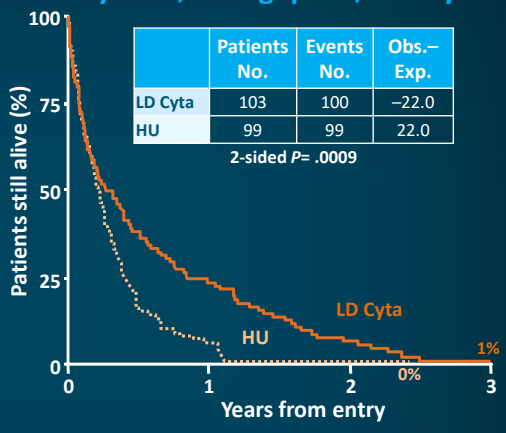
## 7+3 induction[1]




| Treatment | Total | Failure |
|---|---|---|
| ARM A | 31 | 27 |
| ARM B | 29 | 29 |

Log-rank *P*= .015

## Cyta SC, 20 mg q12 h, 10 days[2]




| | Patients No. | Events No. | Obs.–Exp. |
|---|---|---|---|
| LD Cyta | 103 | 100 | –22.0 |
| HU | 99 | 99 | 22.0 |

2-sided *P*= .0009

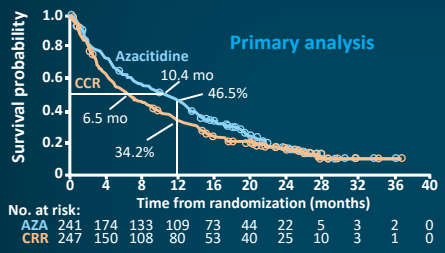
- Median survival = 575 days for patients with CR and 66 days for refractory patients
- CR rate for patients with poor cytogenetics = 0%

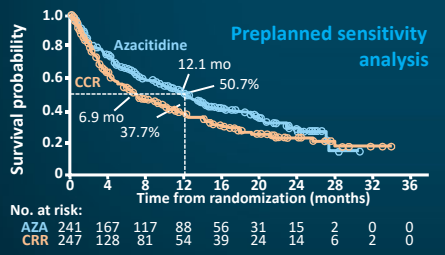
LD = low dose; Cyta = cytarabine; SC = subcutaneous; HU = hydroxyurea; Obs = observed; Exp = expected.

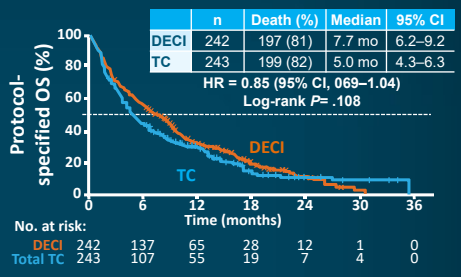
1. Löwenberg B, et al. *J Clin Oncol.* 1989;7:1268-1274. 2. Burnett AK, et al. *Cancer.* 2007;109:1114-1124.

# Treatment of AML in Elderly

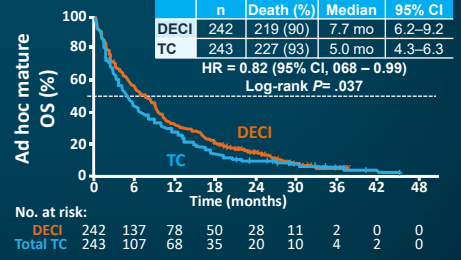
- Some patients can benefit from intensive therapy, but "first do no harm"
- Consider gentler therapies, eg, hypomethylating agents
- Preference is clinical trial




| | n | Death (%) | Median | 95% CI |
|---|---|---|---|---|
| DECI | 242 | 197 (81) | 7.7 mo | 6.2–9.2 |
| TC | 243 | 199 (82) | 5.0 mo | 4.3–6.3 |

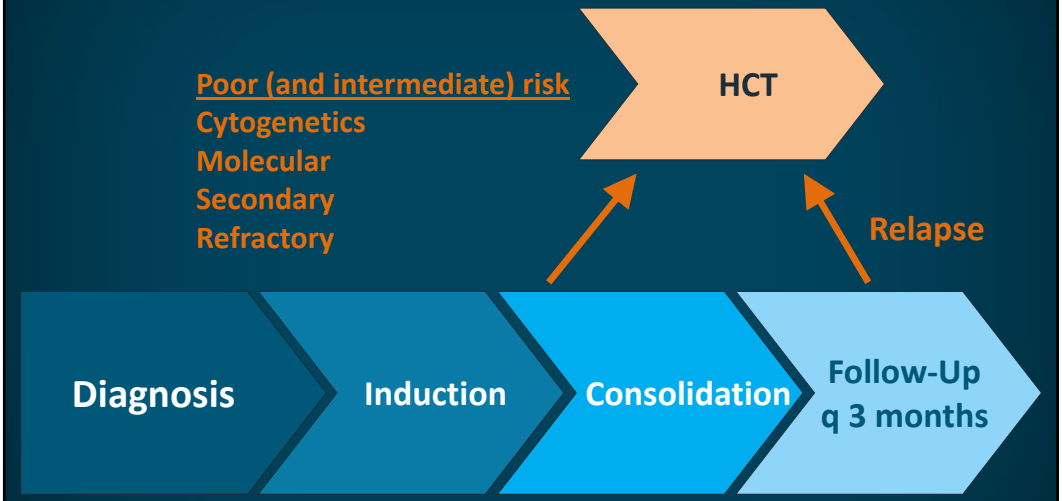



| | n | Death (%) | Median | 95% CI |
|---|---|---|---|---|
| DECI | 242 | 219 (90) | 7.7 mo | 6.2–9.2 |
| TC | 243 | 227 (93) | 5.0 mo | 4.3–6.3 |

AZA = azacitidine; CCR = conventional care regimen; DECI = decitabine; TC = treatment choice; HR = hazard ratio; CI = confidence interval.

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

# AML: Course of the Disease




q = every.

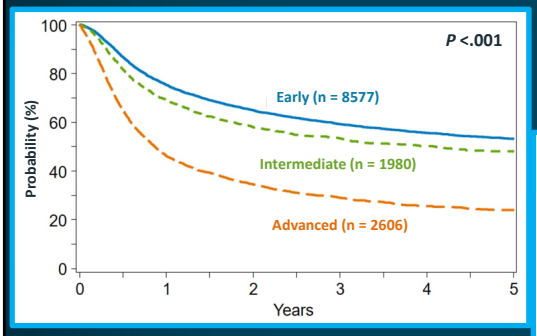
# Allogeneic HCT

- 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

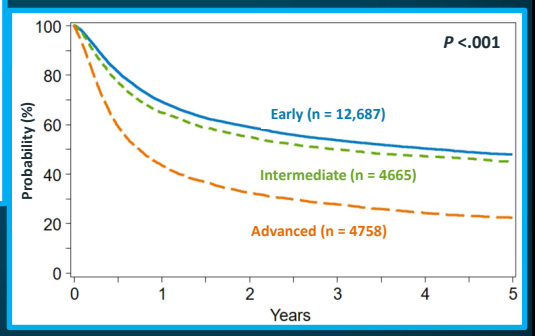
VOD = veno-occlusive disease.; GVHD = graft-versus-host disease.

# Survival After Hematopoietic Stem-Cell Transplantation

**Survival after HLA-matched sibling donor HCT for AML, 2007–2017**




**Survival after unrelated donor HCT for AML, 2007–2017**




D'Souza A, Fretham C. Current uses and outcomes of HCT: Center for International Blood & Marrow Transplant Research (CIBMTR) summary slides, 2019. (www.cibmtr.org/ReferenceCenter/SlidesReports/SummarySlides/pages/index.aspx). Accessed May 5, 2020.

# 2017 European LeukemiaNet (ELN) Risk Stratification

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

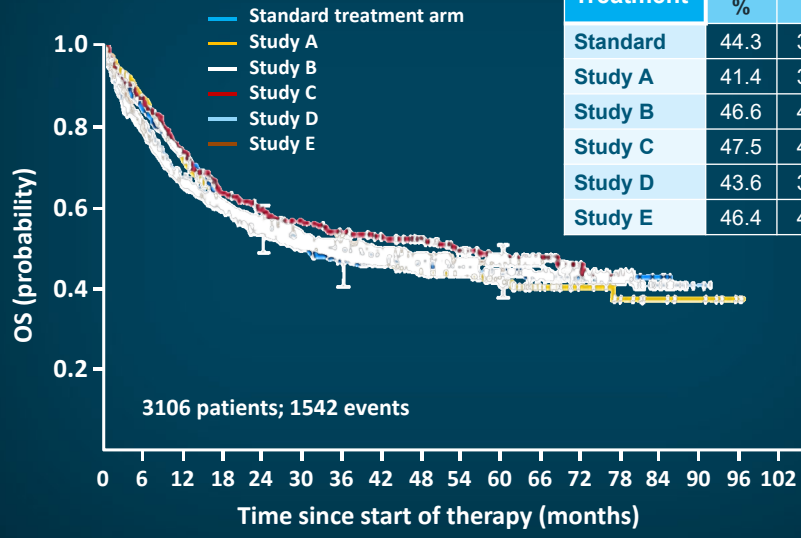
*Frequencies, response rates, and outcome measures should be reported by risk category, and, if sufficient numbers are available, by specific genetic lesions indicated.

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

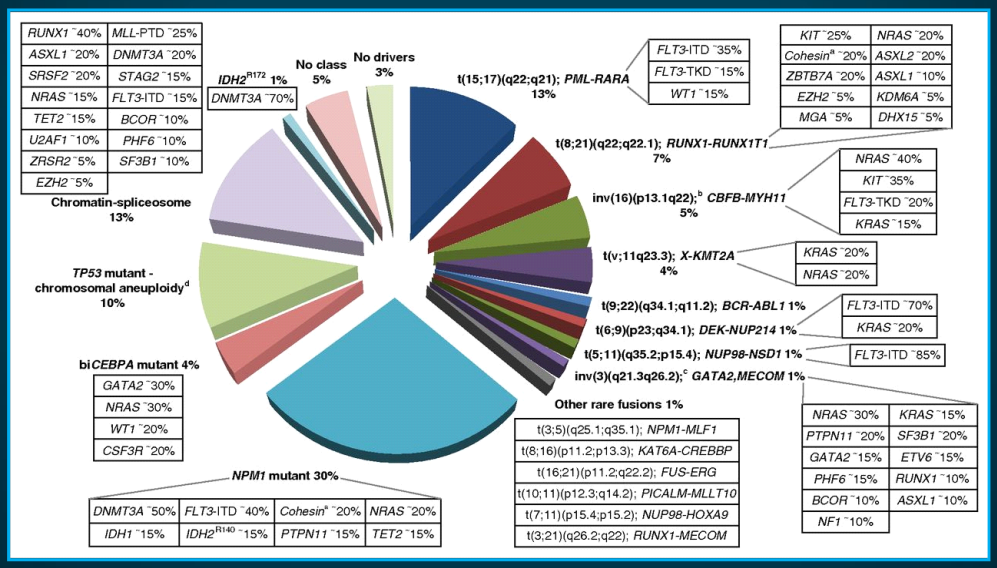



| Treatment | 5-Year Survival | |
|---|---|---|
| | % | 95% CI |
| Standard | 44.3 | 37.7–50.7 |
| Study A | 41.4 | 36.9–45.8 |
| Study B | 46.6 | 41.1–51.8 |
| Study C | 47.5 | 40.1–54.6 |
| Study D | 43.6 | 39.6–47.6 |
| Study E | 46.4 | 41.0–51.7 |

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 the age of ~65 years




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

# AML 360 animation

https://youtu.be/boXjdlQiFig

# Novel Therapies in AML

## BCL-2 inhibitor

- Venetoclax—FDA approved in combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly diagnosed AML in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.

## Hedgehog pathway inhibitor

- Glasdegib—FDA approved in combination with low-dose cytarabine, 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 with newly diagnosed therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC).

**CD = cluster of differentiation; BCL = B-cell lymphoma; FDA = US Food and Drug Administration.**

Venetoclax (Venclexta®) prescribing information (PI) 2019 (www.rxabbvie.com/pdf/venclexta.pdf). Glasdegib (Daurismo™) PI 2020 (http://labeling.pfizer.com/ShowLabeling.aspx?id=11336). Daunorubicin + cytarabine (Vyxeos®) PI 2019 (http://pp.jazzpharma.com/pi/vyxeos.en.USPI.pdf). All URLs accessed May 5, 2020.

# Novel Therapies in AML (continued)

## 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

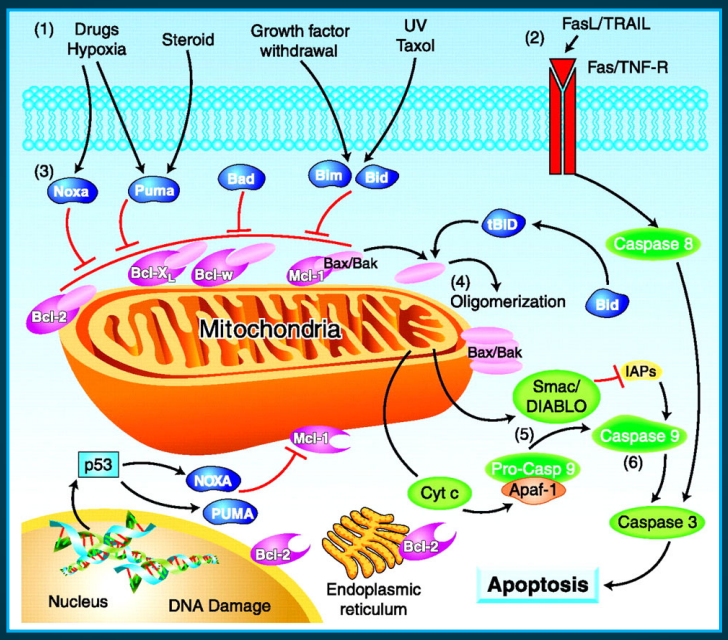
- Enasidenib—FDA approved for treatment of adult patients with R/R IDH2-mutated AML.

## CD33 antibody-drug conjugate

- Gemtuzumab ozogamicin—FDA approved for treatment of newly diagnosed CD33-positive AML in adults and treatment of R/R refractory CD33-positive AML in adults and in pediatric patients 2 years and older.

Midostaurin (Rydapt®) PI 2020 (www.novartis.us/sites/www.novartis.us/files/rydapt.pdf). Gilteritinib (Xospata®) PI 2019 (https://astellas.us/docs/xospata.pdf). Ivosidenib (Tibsovo®) PI (www.tibsovopro.com/pdf/prescribinginformation.pdf). Enasidenib (Idhifa®) PI 2019 (www.idhifa.com/prescribing-information/). Gemtuzumab ozogamicin (Mylotarg™) PI 2020 (http://labeling.pfizer.com/ShowLabeling.aspx?id=9548). All URLs accessed May 5, 2020.

# Apoptotic Pathway

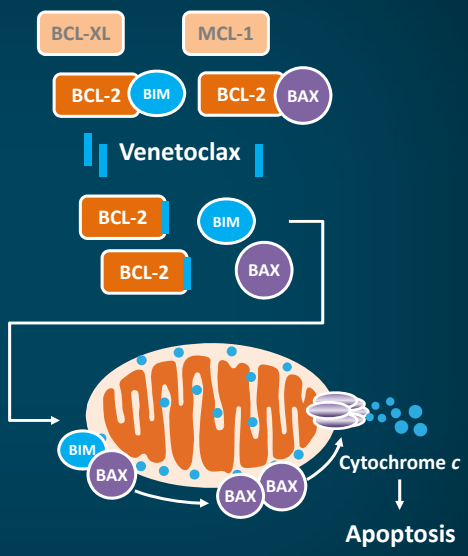



DNA = deoxynucleic acid; TNF = tumor-necrosis factor.

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

# Venetoclax + HMA—Phase 1b

- Multicenter, phase 1b dose-escalation and expansion study
- 145 patients were ≥65 years with treatment-naive AML ineligible for intensive chemotherapy
- Oral venetoclax was administered at 400, 800, or 1200 mg daily in combination with either decitabine or azacitidine
- In expansion phase, 400 mg or 800 mg venetoclax was administered with HMA




HMA = hypomethylating agent; BIM = BCL-2–like 11; BAX = BCL-2–associated X protein; BAK = BCL-2 antagonist/killer 1.

DiNardo CD, et al. *Blood*. 2019;133:7-17. Konopleva M, et al. *Cancer Discov.* 2016;6:1106-1117.

# Venetoclax + HMA—Phase 1b (continued)

- Median age 74 years
- Poor-risk cytogenetics in 49% of patients
- Common AEs (>30%) included nausea, diarrhea, constipation, febrile neutropenia, fatigue, hypokalemia, decreased appetite, and decreased white blood cell count
- 67% of patients (all doses) achieved CR + CR with incomplete hematologic (count) recovery (CRi)
  - CR+CRi rate of 73% in the venetoclax 400 mg + HMA cohort

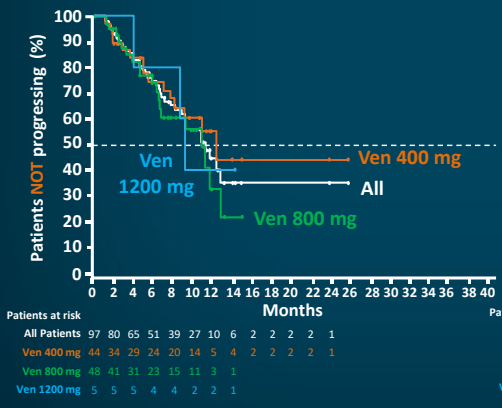
**AE = adverse event.**

DiNardo CD, et al. *Blood*. 2019;133:7-17.

# Venetoclax + HMA—Phase 1b: Results

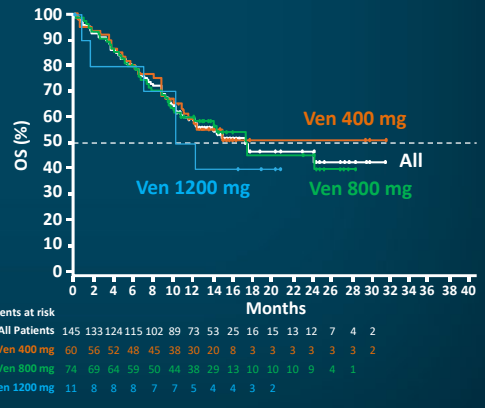
**Duration of CR+CRi by venetoclax dose levels (dose escalation + dose expansion cohorts)**

| | n | Events n (%) | Median Duration of CR/Cri mo (95% CI) |
|---|---|---|---|
| All Patients | 97 | 37 (38) | 11.3 (8.9–NR) |
| Ven 400 mg | 44 | 15 (34) | 12.5 (7.8–NR) |
| Ven 800 mg | 48 | 19 (40) | 11.0 (6.5–12.9) |
| Ven 1200 mg | 5 | 3 (60) | 9.4 (4.1–NR) |




**OS by venetoclax dose levels (dose escalation + dose expansion cohorts)**

| | n | Events n (%) | mOS mo (95% CI) | 2-year OS % (95% CI) |
|---|---|---|---|---|
| All Patients | 145 | 68 (47) | 17.5 (12.3–NR) | 46 (35–56) |
| Ven 400 mg | 60 | 27 (45) | NR (11.0–NR) | 51 (36–64) |
| Ven 800 mg | 74 | 35 (47) | 17.5 (10.3–NR) | 45 (30–59) |
| Ven 1200 mg | 11 | 6 (55) | 11.4 (0.9–NR) | N/A |




**NR = not reached; N/A = not applicable.**

DiNardo CD, et al. *Blood*. 2019;133:7-17.

# VIALE-A

- Phase 3 study comparing venetoclax+azacitidine with azacitidine alone (2:1 randomization)
- Venetoclax was administered at a dose of 400 mg daily
- Population consisted of 433 previously untreated AML patients who were ineligible for intensive induction therapy
- Statistically significant differences in primary endpoints of OS and cCR (CR+CRi), favoring the combination arm

**cCR = composite complete response rate.**

**AbbVie press release (PR), 3/23/2020 (https://news.abbvie.com/news/press-releases/abbvie-announces-positive-topline-results-from-phase-3-trial-venclexta-venetoclax-in-combination-with-azacitidine-in-patients-with-acute-myeloid-leukemia-aml.htm). Accessed May 5, 2020.**

# VIALE-C

- Phase 3 study comparing venetoclax+LDAC to LDAC alone
- No statistically significant improvement in primary endpoint of OS (HR = 0.75; [95% CI 0.52–1.07], *P*= .11)
- Median OS = 7.2 months with combination vs 4.1 months in control arm

**Select Secondary Endpoint Outcomes***

| Outcome | Venetoclax plus LDAC (n=143) | Placebo plus LDAC (n=68) |
|---|---|---|
| Complete Remission | 27.3% | 7.4% |
| Complete Remission or Complete Remission with Incomplete Blood Count Recovery (CR + CRi) | 47.6% | 13.2% |
| Complete Remission or Complete Remission with Partial Hematologic Recovery (CR + CRh) | 46.9% | 14.7% |
| Complete Remission or Complete Remission with Incomplete Blood Count (CR + CRi) by Initiation of Cycle 2 | 34.3% | 2.9% |

*Nominal p values <0.001

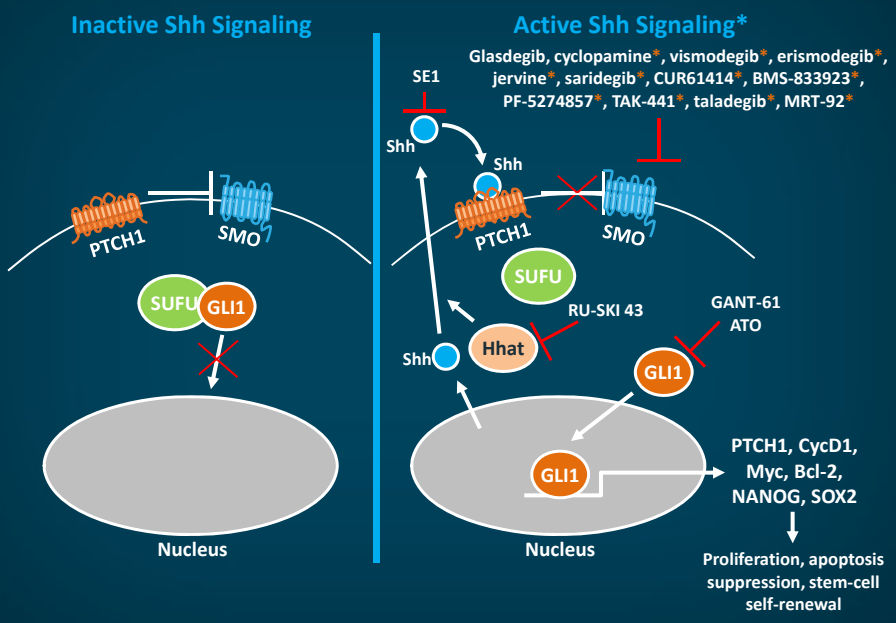
**Serious and Non-Serious Adverse Events**

| | Venetoclax plus LDAC (n=142) | | Placebo plus LDAC (n=68) | |
|---|---|---|---|---|
| AE's | Non-Serious | Serious | Non-Serious | Serious |
| Febrile neutropenia | 15.5% | 16.9% | 11.8% | 17.7% |
| Neutropenia | 45.8% | 2.8% | 17.7% | 0 |
| Thrombocytopenia | 40.9% | 4.9% | 36.8% | 2.9% |
| Anemia | 26.1% | 2.8% | 22.1% | 0 |

**LDAC = low-dose cytarabine.**

**AbbVie PR, 2/28/2020 (https://news.abbvie.com/news/press-releases/abbvie-provides-update-from-phase-3-study-evaluating-venclexta-venetoclax-in-combination-with-low-dose-cytarabine-in-newly-diagnosed-patients-with-acute-myeloid-leukemia-aml.htm. Accessed May 5, 2020.**

# Sonic Hedgehog (Shh) Signaling Pathway




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

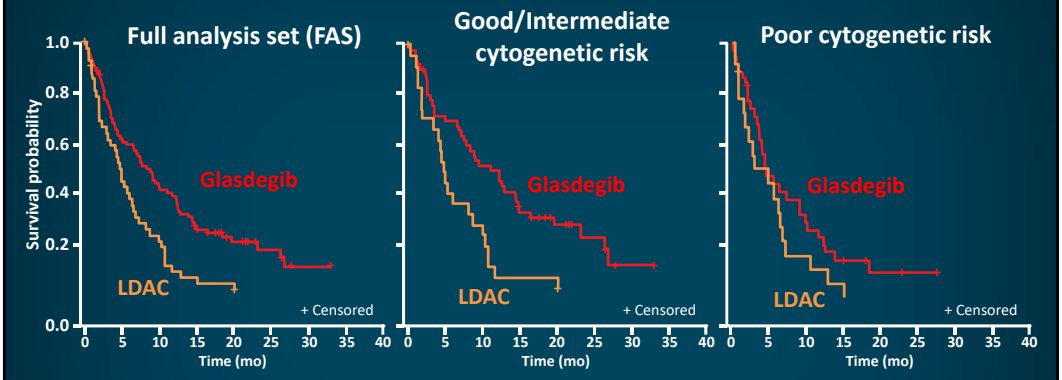
Rimkus TK, et al. *Cancers (Basel)*. 2016;8:22.

# 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 mo vs 4.9 mo 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 QT prolongation with glasdegib

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

# Low-Dose Cytarabine + Glasdegib (continued)




| FAS | mOS mo (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 mo (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

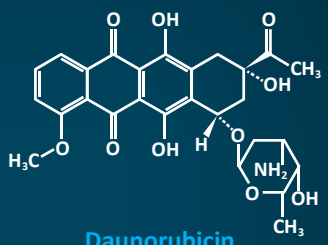
| Poor | mOS mo (80% CI) |
|---|---|
| Glasdegib/LDAC | 4.7 (4.0–7.4) |
| LDAC | 4.9 (2.3–6.4) |

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

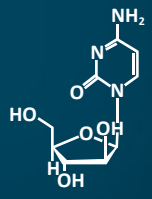
Cortes JE, et al. *Leukemia*. 2019;33:379-389.

# 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 2019 (http://pp.jazzpharma.com/pi/vyxeos.en.USPI.pdf). Accessed May 5, 2020. Lancet JE, et al. *Blood*. 2014;123:3239-3246. Mayer LD, et al. *Mol Cancer Ther*. 2006;5:1854-1863.

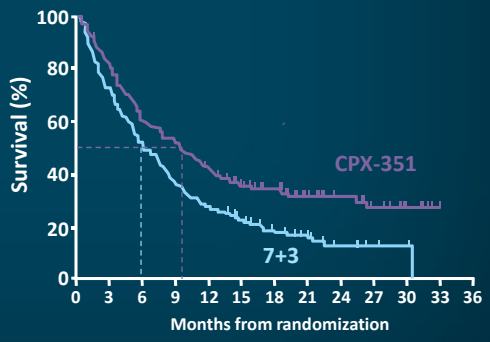
# Liposomal "7+3" (CPX-351): Results

- Phase 3 trial: patients 60 to 75 years old with untreated AML
  - Hx 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 overall survival
  - 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%)

**Kaplan-Meier Curve for OS ITT Analysis Population**

| | Events N | 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*=0.003




CMML = chronic myelomonocytic leukemia; WHO = World Health Organization.

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)

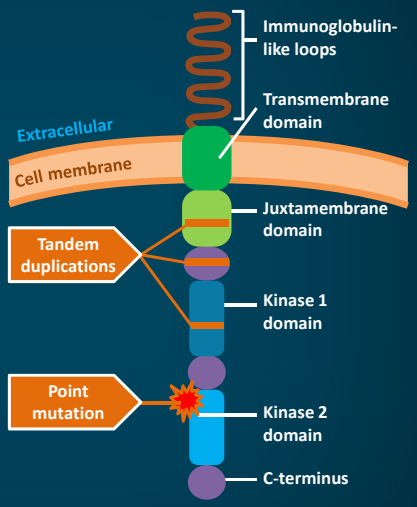
- FDA approved in August 2017
  - Adults with newly diagnosed t-AML
  - Adults with AML with myelodysplasia-related changes (AML-MRC)
- Induction
  - Liposomal encapsulation of cytarabine 100 mg/m$^2$ and daunorubicin 44 mg/m$^2$ on days 1, 3, and 5
  - Subsequent cycles of induction, if needed, at dose of cytarabine 100 mg/m$^2$ and daunorubicin 44 mg/m$^2$ on days 1 and 3
- Post-remission therapy
  - Cytarabine 65 mg/m$^2$ and daunorubicin 29 mg/m$^2$ on days 1 and 3
- NCCN guidelines
  - Category 1 recommendation for patients ≥60 years with t-AML or AML-MRC
  - Category 2B recommendation for patients <60 years with t-AML (other than CBF AML or APL) or AML-MRC

MRC = myelodysplasia-related changes; CBF = core-binding factor; APL = acute promyelocytic leukemia.

Daunorubicin + cytarabine (Vyxeos™) PI 2019 (http://pp.jazzpharma.com/pi/vyxeos.en.USPI.pdf). NCCN. AML. V3.2020. (www.nccn.org/professionals/physician_gls/pdf/aml.pdf). Both URLs accessed May 5, 2020.

# FLT3

- FLT3 mutations result in survival and proliferation of leukemic blasts
- FLT3/ITD mutations confer a 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 an oral multikinase inhibitor that has activity with regard to the FLT3 receptor

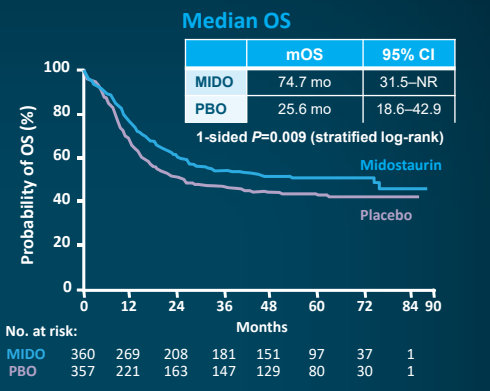


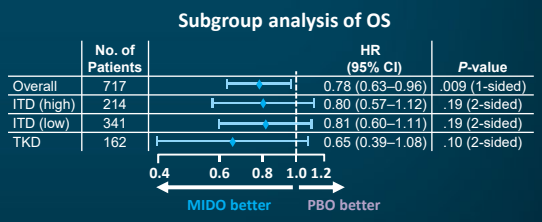

TKD = tyrosine kinase domain.

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



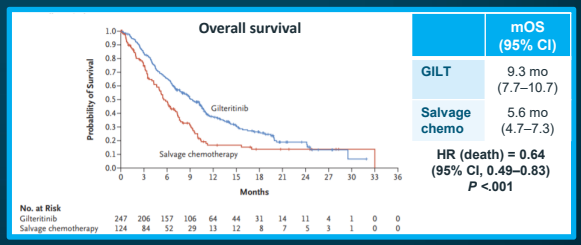

Stone RM, et al. *N Engl J Med.* 2017;377:454-464. Midostaurin (Rydapt®) PI 2020 (www.novartis.us/sites/www.novartis.us/files/rydapt.pdf). Accessed May 5, 2020.

# Gilteritinib—ADMIRAL Trial

- 371 adult patients with R/R FLT3 mutated AML randomized 2:1 to gilteritinib or salvage chemotherapy
- 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, thrombocytopenia, edema, vomiting, dyspnea
- Gilteritinib can prolong QT interval
- PRES (1%), pancreatitis (4%), differentiation syndrome (3%)

**Antileukemic Responses (Intention-to-Treat Population)**

| Variable | Gilteritinib (N=247) | Salvage Chemotherapy (N=124) | Hazard Ratio or Risk Difference (95% CI)† |
|---|---|---|---|
| Median overall survival (95% CI) — mo | 9.3 (7.7–10.7) | 5.6 (4.7–7.3) | 0.64 (0.49–0.83) |
| Median event-free survival (95% CI) — mo | 2.8 (1.4–3.7) | 0.7 (0.2–NE) | 0.79 (0.58–1.09) |
| Response — no. (%) | | | |
| Complete remission | 52 (21.1) | 13 (10.5) | 10.6 (2.8–18.4) |
| Complete remission or complete remission with partial hematologic recovery | 84 (34.0) | 19 (15.3) | 18.6 (9.8–27.4) |
| Complete remission with partial hematologic recovery | 32 (13.0) | 6 (4.8) | ND |
| Complete remission with incomplete hematologic recovery | 63 (25.5) | 14 (11.3) | ND |
| Complete remission with incomplete platelet recovery | 19 (7.7) | 0 | ND |
| Partial remission | 33 (13.4) | 5 (4.0) | ND |
| No response | 66 (26.7) | 43 (34.7) | ND |
| Composite complete remission‡ | 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) — mo§ | 11.0 (4.6–NE) | NE (NE–NE) | NE |
| Time to composite complete remission — mo | 2.3±1.9 | 1.3±0.5 | NA |
| Median leukemia-free survival (95% CI) — mo | 4.4 (3.6–5.2) | 6.7 (2.1–8.5) | NE |



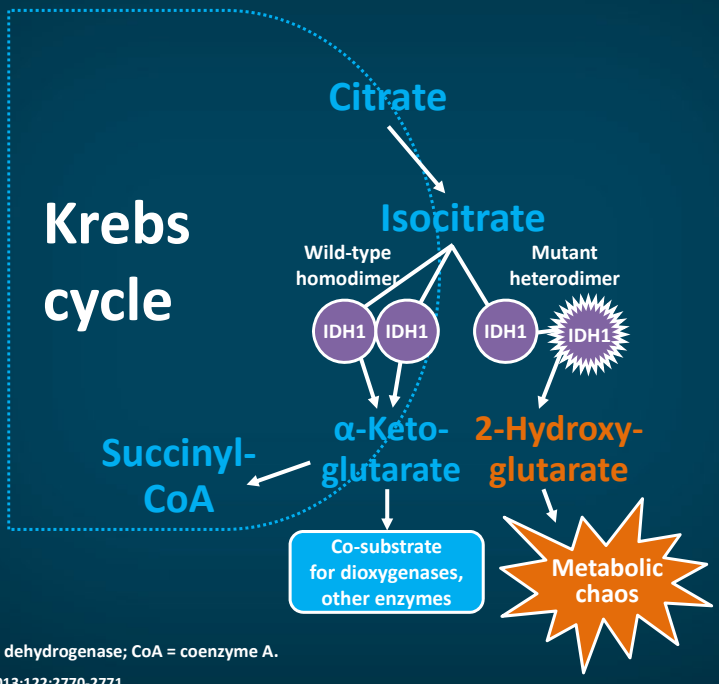

| | mOS (95% CI) |
|---|---|
| GILT | 9.3 mo (7.7–10.7) |
| Salvage chemo | 5.6 mo (4.7–7.3) |

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

CRh = hematologic CR; CRp = CR, incomplete platelet recovery; PRES = posterior reversible encephalopathy syndrome.

Perl AE, et al. *N Engl J Med*. 2019;381:1728-1740. Gilteritinib (Xospata®) PI 2019 (https://astellas.us/docs/xospata.pdf). Accessed May 5, 2020.

# IDH1 and IDH2 Mutations in AML




IDH = isocitrate dehydrogenase; CoA = coenzyme A.

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

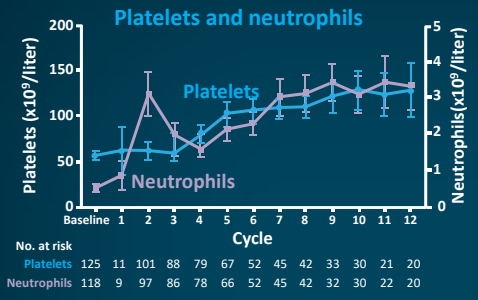
# Ivosidenib—IDH1 Inhibitor

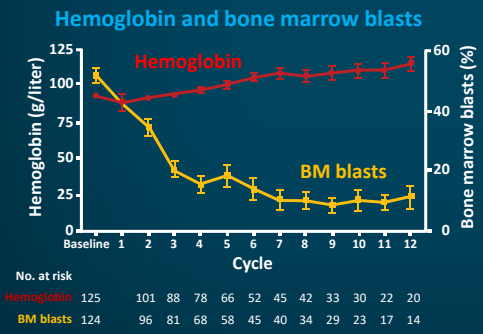
- IDH1 mutations occur in approximately 6–10% of AML patients
- Phase 1 dose escalation and expansion study
  - 258 pts with R/R AML or other advanced hematologic malignancies with IDH1 mutations
- Efficacy population = 125 R/R AML patients
  - ORR = 41.6%
  - CR+CRh = 30.4% (CR = 21.6% and CRh = 8.8%)
  - 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

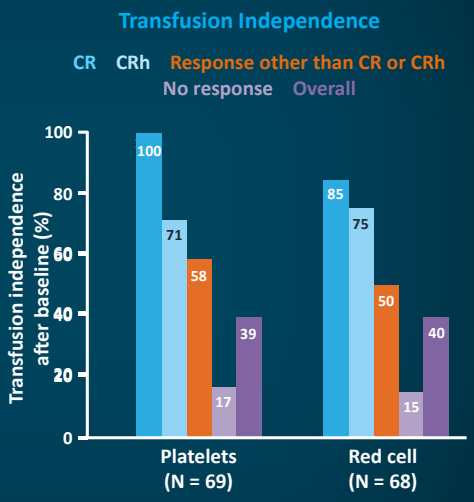
**ORR = overall/objective response rate.**

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 (www.tibsovopro.com/pdf/prescribinginformation.pdf). URLs accessed May 5, 2020.

# Ivosidenib—IDH1 Inhibitor: Results



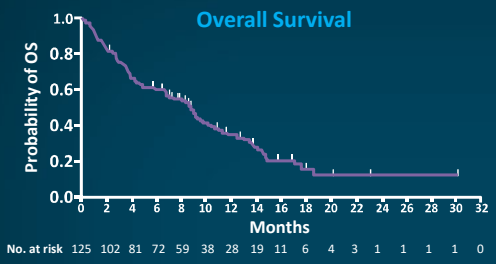



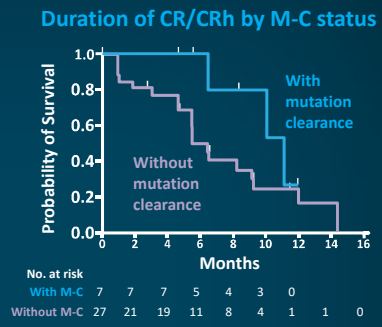



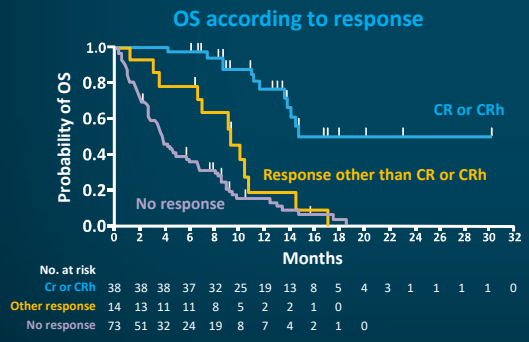

**BM = bone marrow.**

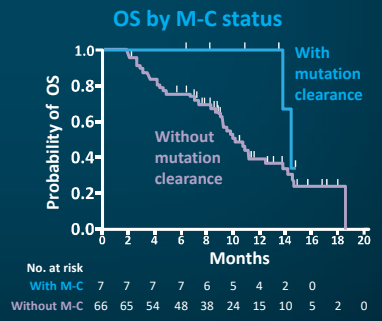
DiNardo CD, et al. *N Engl J Med* 2018;378:2386-2398.

# Ivosidenib—IDH1 Inhibitor: OS and Duration



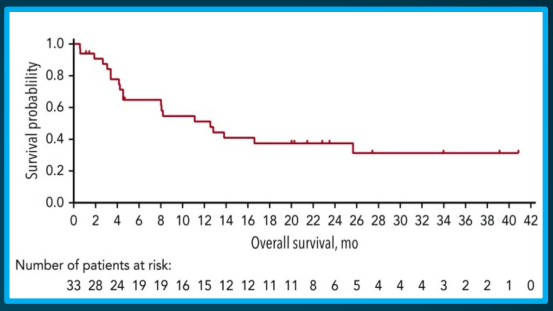




M-C = mutation clearance.

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

# Ivosidenib—IDH1 Inhibitor

- Phase 1, IDH1-mutated AML
- 34 patients
  - Median age 77 years (range, 64–87 years)
  - 21 (62%) with t-AML or AML-MRC
- CR+CRh = 42.9% (12 patients)



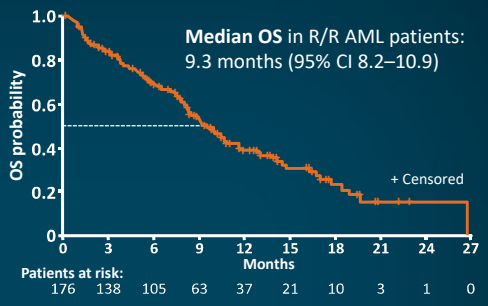

- Adverse reactions occurring in at least 25% of patients include:

  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

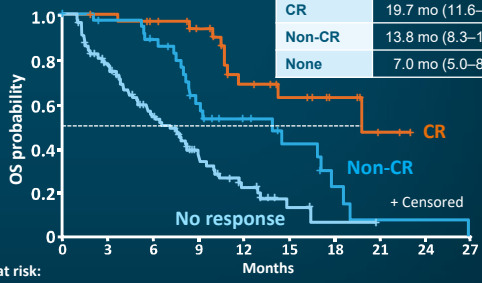
Roboz GJ, et al. *Blood.* 2020;135:463-471. Ivosidenib (Tibsovo®) PI 2019 (www.tibsovopro.com/pdf/prescribinginformation.pdf). Accessed May 5, 2020.

# Enasidenib—IDH2 inhibitor

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




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




Patients at risk:

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| CR | 34 | 34 | 31 | 25 | 15 | 11 | 6 | 2 | 0 |
| Non-CR | 37 | 34 | 30 | 17 | 11 | 7 | 3 | 1 | 1 |
| No response | 97 | 68 | 43 | 20 | 10 | 3 | 1 | 0 | |

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

# IDH-Inhibitor Combinations*

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

- 23 patients were reported at ASCO 2019
- ORR = 78% (CR = 57%, CRi/CRp = 13%, MLFS = 9%)
- 10/16 patients with CR/Crh achieved mIDH1 clearance
- AEs included thrombocytopenia, anemia, febrile neutropenia, sepsis, QT prolongation (26%; 13% Grade 3/4), and differentiation syndrome (17%).

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

**Table. Clinical efficacy with enasidenib plus azacitidine versus azacitidine monotherapy**

| | Enasidenib + Azacitidine (N=68) | Azacitidine Monotherapy (N=33) |
|---|---|---|
| **Overall response rate,*** n (%) | **46 (68)** | **14 (42)** |
| [95%CI] | [55, 79] | [26, 61] |
| *P* value | 0.0155 | |
| **Best response, n (%)** | | |
| Complete remission (CR) | 34 (50) | 4 (12) |
| [95%CI] | [38, 62] | [3, 28] |
| *P* value | 0.0002 | |
| CR with incomplete recovery (CRi/CRp) | 6 (9) | 4 (12) |
| Partial remission | 3 (4) | 4 (12) |
| Morphologic leukemia-free state | 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 (months)**, median (range) | 1.9 (1–9) | 2.0 (1–6) |
| **Duration of response (months)**, median [95%CI] | NR [11, NR] | 10.2 [3, NR] |
| **Time to CR (months)**, median (range) | 5.0 (1–20) | 3.7 (3–4) |

*Overall response comprises complete remission (CR), CR with incomplete hematologic recovery, CR with incomplete platelet recovery, partial remission, or morphologic leukemia-free state, per IWG 2003 AML response criteria.

†Absence of hematologic response and not meeting criteria for disease progression, sustained for a period of ≥8 weeks.

*P* values are from Chi-square test.

95%CI, 95% confidence interval; AML, acute myeloid leukemia; CR, complete remission; CRi, CR with incomplete blood count recovery; CRp, CR with incomplete platelet count recovery; IWG, International Working Group; NR, not reached.

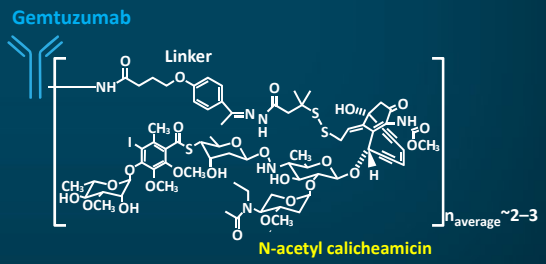
*Not currently approved by the FDA.

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

DiNardo CD, et al. *J Clin Oncol*. 2019;37(15 suppl): abstract 7011. DiNardo CD, et al. *Blood*. 2019;134(suppl 1): abstract 643.

# Gemtuzumab Ozogamicin (GO)

- Gemtuzumab ozogamicin is a CD33-directed antibody-drug conjugate
- Initially granted accelerated approval by the FDA in 2000 for adults with relapsed AML.
- Withdrawn from US market in 2010 and was re-approved 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 the 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)



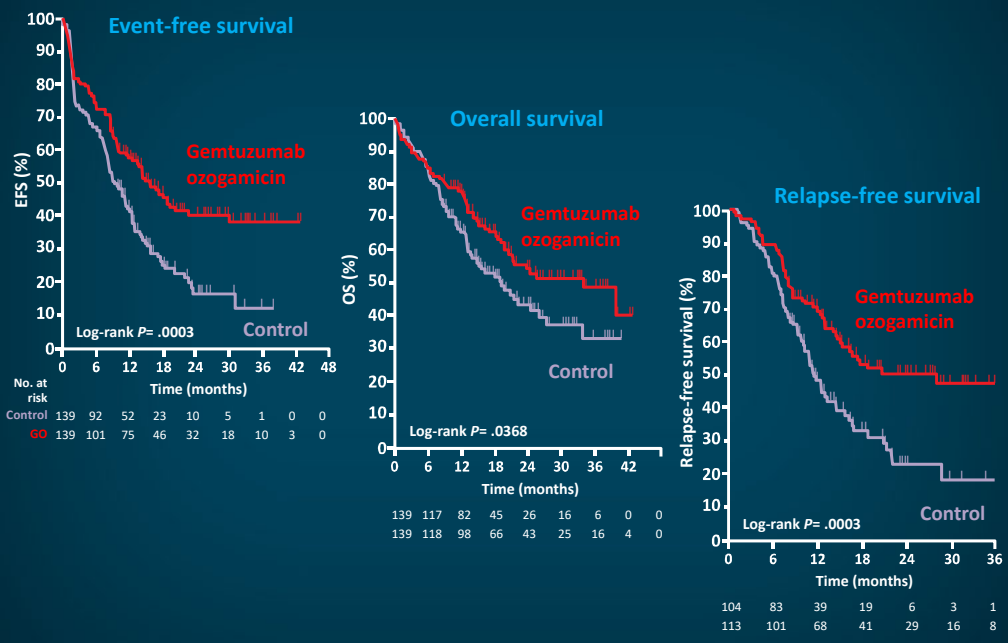

Gemtuzumab ozogamicin (Mylotarg™) PI 2020 (http://labeling.pfizer.com/ShowLabeling.aspx?id=9548). GO overview (www.ncbi.nlm.nih.gov/books/NBK548438/pdf/Bookshelf_NBK548438.pdf). FDA PR (www.fda.gov/newsevents/newsroom/pressannouncements/ucm574507.htm. Ingram I. Cancer Network, 2017. (www.cancernetwork.com/acute-myeloid-leukemia/fda-approves-gemtuzumab-ozogamicin-acute-myeloid-leukemia). All URLs accessed May 5, 2020.

# 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
    - 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 the GO group

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

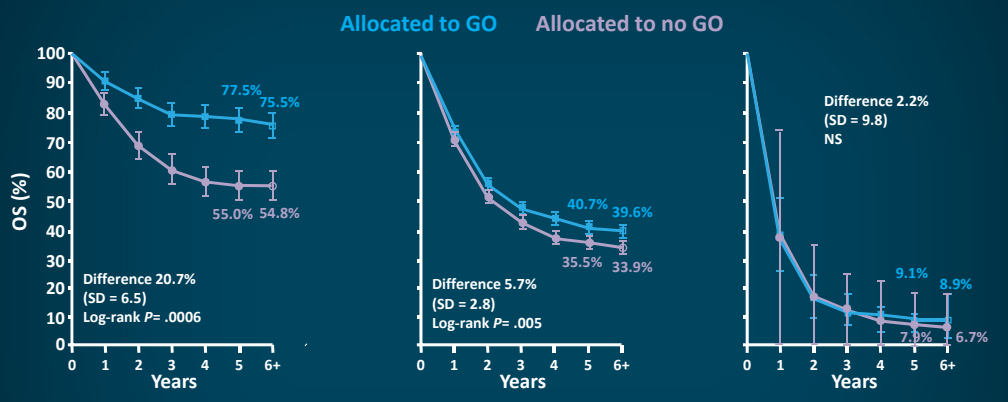
# Gemtuzumab Ozogamicin: ALFA-0701: Results




EFS = event-free survival.

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

# Gemtuzumab Ozogamicin: Meta-analysis




| 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) |

| 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) |

| 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; NS = not significant.

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

# When to Use GO

- Also investigated as single agent for elderly/unfit AML and for R/R AML (AML-19 and MyloFrance-1)
- FDA approved in September 2017
  - Treatment of newly diagnosed CD33-positive AML in adults
  - Treatment of R/R CD33-positive AML in adults and in pediatric patients 2 years and older
- 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 pts as well as in relapsed APL

**----------DOSAGE AND ADMINISTRATION----------**

- Newly-diagnosed, de novo AML (combination regimen):
  - *Induction:* 3 mg/m$^2$ (up to one 4.5 mg vial) on Days 1, 4, and 7 in combination with daunorubicin and cytarabine (2.2).
  - *Consolidation:* 3 mg/m$^2$ on Day 1 (up to one 4.5 mg vial) in combination with daunorubicin and cytarabine. (2.2).
- Newly-diagnosed AML (single-agent regimen):
  - *Induction:* 6 mg/m$^2$ on Day 1 and 3 mg/m$^2$ on Day 8 (2.2).
  - *Continuation:* For patients without evidence of disease progression following induction, up to 8 continuation courses 2 mg/m$^2$ on Day 1 every 4 weeks (2.2).
- Relapsed or refractory AML(single-agent regimen):
  - 3 mg/m$^2$ on Days 1, 4, and 7 (2.2).
- Premedicate with a corticosteroid, antihistamine, and acetaminophen 1 hour prior (2.1).

**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. V3.2020. (www.nccn.org/professionals/physician_gls/pdf/aml.pdf). All URLs accessed May 5, 2020.

# 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 |

MDS = myelodysplastic syndrome; HMA = hypomethylating agent; LDAC = low dose cytarabine.

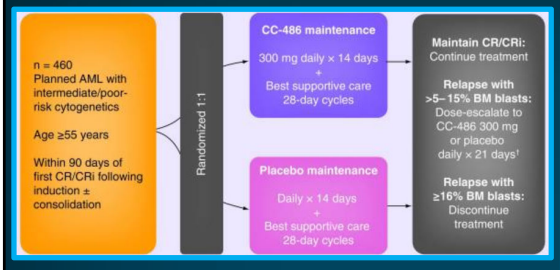
# Summary of Therapies
## Relapsed/Refractory AML

| 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:<br>— HMAs<br>— Combination chemotherapy (ie, MEC, HiAC, FLAG, etc) | | |

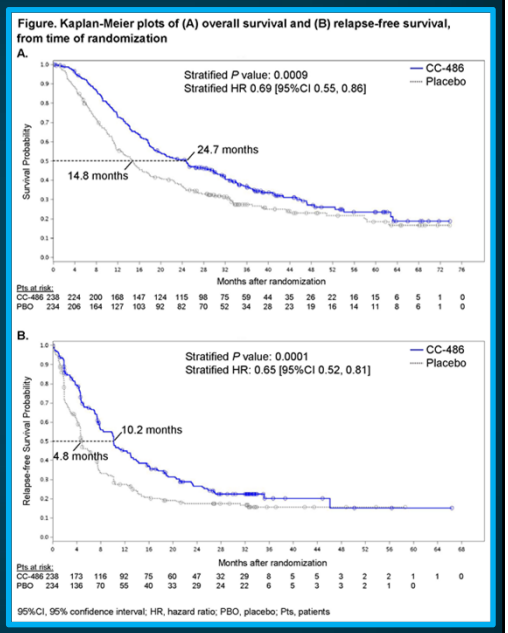
**MEC = mitoxantrone, etoposide, and cytarabine; FLAG = fludarabine, high-dose cytarabine, and granulocyte colony-stimulating factor.**

# QUAZAR AML-001: Maintenance with CC-486*

*Oral formulation of azacitidine.




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




Wei AH, et al. *Blood.* 2019;134(suppl 2): abstract LBA-3. Roboz GJ, et al. *Future Oncol.* 2016;12:293-302. 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 September 18, 2020.

## Some Emerging Therapeutic Strategies

- Bispecific therapies*
  - CD123/CD3
    - Flotetuzumab
    - XmAb14045
    - JNJ-63709178
  - CD33/CD3
    - AMG 330
- CAR T cells
  - CD123
  - FLT3
- MDM2 inhibition*
- Aurora kinase inhibition*
- BET inhibition*
- MCL-1 inhibition*
- CDK9 kinase inhibition*
- ADC*
  - CD123
    - IMGN632
  - CD33
    - IMGN779
- Immune checkpoint inhibition†
  - Nivolumab
  - Pembrolizumab
  - Ipilimumab
- Others

*Investigational; †Not FDA-approved, off-label use.

CAR = chimeric antigen receptor; MDM = murine double minute; BET = bromodomain and extra-terminal motif; CDK = cyclin-dependent kinase; ADC = antibody-drug conjugate.

## Case Studies

## Patient Case 1

- 78-year-old male with history of coronary artery disease and chronic kidney disease presents with pancytopenia.
- BM biopsy reveals AML with complex karyotype
- ECOG PS 1
- The patient is interested in being treated but does not desire a prolonged hospitalization.

- ***Among the options below, what is the optimal treatment?***

  A) Liposomal cytarabine and daunorubicin (liposomal 7+3)

  B) Low-dose cytarabine

  C) 7+3

  D) Venetoclax + azacitidine

**ECOG = Eastern Cooperative Oncology Group; PS = performance status.**

## Patient Case 2

- A 77-year-old male with well-compensated cardiomyopathy (EF = 40%) and MDS achieves a response to azacitidine but develops progressive cytopenia after 1 year of therapy.
- BM biopsy now reveals 28% blasts.
- The patient does not have a FLT3 ITD or TKD mutation.

- ***Which therapy is most appropriate for this patient?***

  A. Decitabine

  B. Gilteritinib

  C. Low-dose cytarabine and glasdegib

  D. Liposomal cytarabine and daunorubicin (liposomal 7+3)

  E. Midostaurin

## Patient Case 3

- An otherwise healthy 64-year-old female with history of anal cancer s/p treatment with 5-FU and mitomycin C 3 years ago presents with fatigue.
- She is found to have a WBC of 20K with circulating blasts.
- The patient is diagnosed with AML and is found to have complex cytogenetics
- EF = 60%

- ***What is the preferred induction treatment?***
  - A. 7+3
  - B. Decitabine
  - C. Liposomal cytarabine and daunorubicin
  - D. 7+3 + gemtuzumab ozogamicin
  - E. Midostaurin

**s/p = status post.**

## Patient Case 4

- 57-year-old female presents with WBC 70K with circulating blasts.
- She is discovered to have monocytic AML.
  - Normal cytogenetics
  - Molecular panel shows presence of FLT3/ITD, NPM1, and IDH2 mutations.
  - Blasts express CD33.
- Patient's medical history is significant for hypertension, diabetes, and depression.
- TTE shows EF of 60%.

- ***After cytoreduction, what is the optimal treatment for this patient?***
  - A. 7+3
  - B. 7+3 + midostaurin
  - C. 7+3 + enasidenib
  - D. 7+3 + gemtuzumab ozogamicin
  - E. Liposomal 7+3

**TTE = transthoracic echocardiogram.**

## Patient Case 5

- 75-year-old male was diagnosed 1.5 years ago with normal karyotype AML with an NPM1 mutation.
- He is not a transplant candidate due to stage 3/4 chronic kidney disease.
- He has been treated with azacitidine since his diagnosis but has now relapsed.
- The patient has ECOG PS of 1.

- ***Among the options below, what is the next step in the patient's care?***
  - A) Allogeneic hematopoietic cell transplantation (HCT)
  - B) 7+3
  - C) Lenalidomide
  - D) Continue azacitidine
  - E) Send molecular studies on bone marrow aspirate

## 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

## Shared Decision-Making

- Shared decision-making (SDM) is a process of communication in which clinicians and patients work together to make optimal healthcare decisions that align with what matters most to patients.

- SDM requires 3 components:
  1. Clear, accurate, and unbiased medical evidence about reasonable alternatives—including no medical intervention—and the risks and benefits of each
  2. Clinician expertise in communicating and tailoring that evidence for individual patients
  3. Patient values, goals, informed preferences, and concerns, which may include treatment burdens

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

## Shared Decision-Making (continued)

- Provides a **patient-centered approach** to decision-making when multiple options (including no intervention) may be medically reasonable
- Utilizes **decision aids** that present organized, evidence-based, and unbiased information to *assist with communication* with each patient
- Engages the **patient's *values, goals, concerns, expertise*** (of living with the condition) ***and preferences*** (including treatment burdens)
- Involves **"choice-awareness,"** which enhances execution of the SDM process
- Benefits include enhanced patient satisfaction, heightened patient therapeutic adherence, and enriched provider/patient relationships.

SHARE (www.ahrq.gov/professionals/education/curriculum-tools/shareddecisionmaking/workshop/module1/shareworkshop-mod1slides.html). Accessed May 9, 2020. Kunneman M, et al. *Mayo Clin Proc Innov Qual Outcomes*. 2018;2:60-68.

## 5 Essential Steps of SDM
## SHARE Approach


**It's all about Communication!**

AHRQ Share Approach (www.ahrq.gov/sites/default/files/publications/files/share-approach_factsheet.pdf). Accessed May 5, 2020.

## 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.

## Concepts to Consider: SDM in Oncology

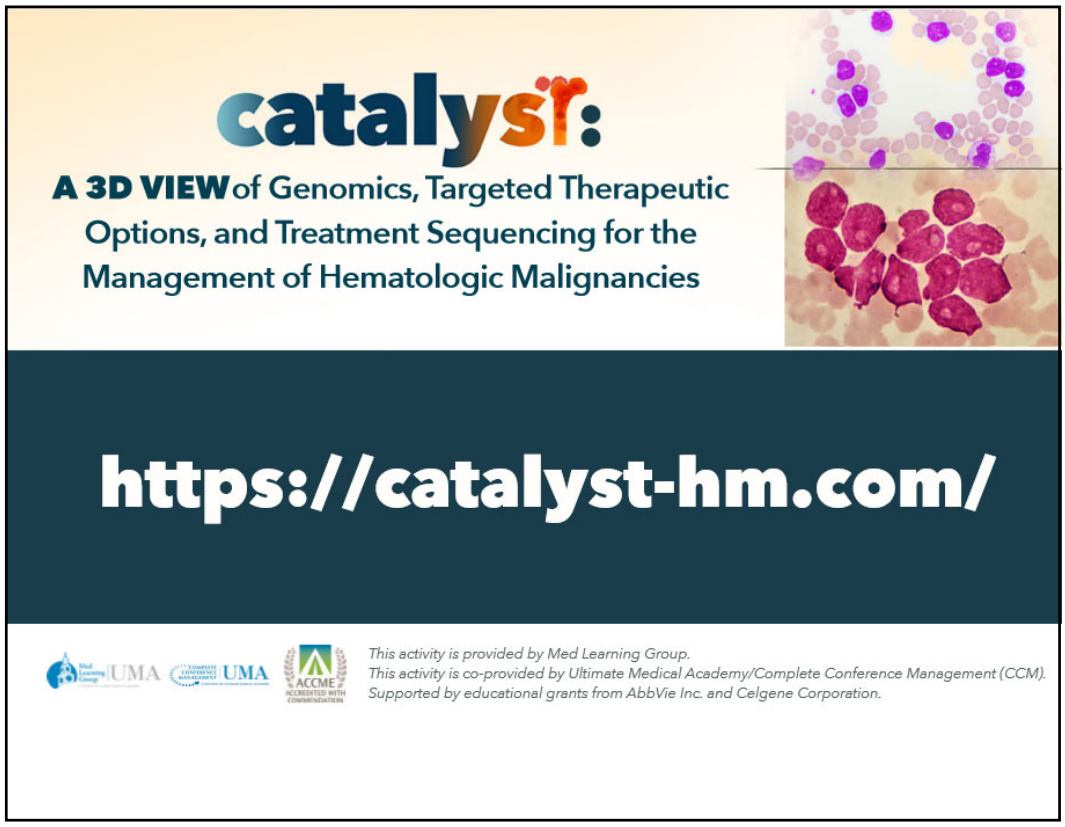
| |
|---|
| Stage of cancer |
| Available treatments |
| Treatment type (chemotherapy vs immunotherapy) |
| Sociodemographic characteristics |
| Preference for involvement (high- vs low-input patients) |
| Goals of treatment(s) |
| Complex data delivered in a patient-centered manner |
| Maintain and update knowledge |

### SDM goals

- Ensure that each patient understands the risks and benefits of his/her options
- Incorporate patient preference(s) and goals to reach clinical decisions

## Summary Points

- Outcomes are gradually improving in AML
  - 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


catalyst:
A 3D VIEW of Genomics, Targeted Therapeutic Options, and Treatment Sequencing for the Management of Hematologic Malignancies
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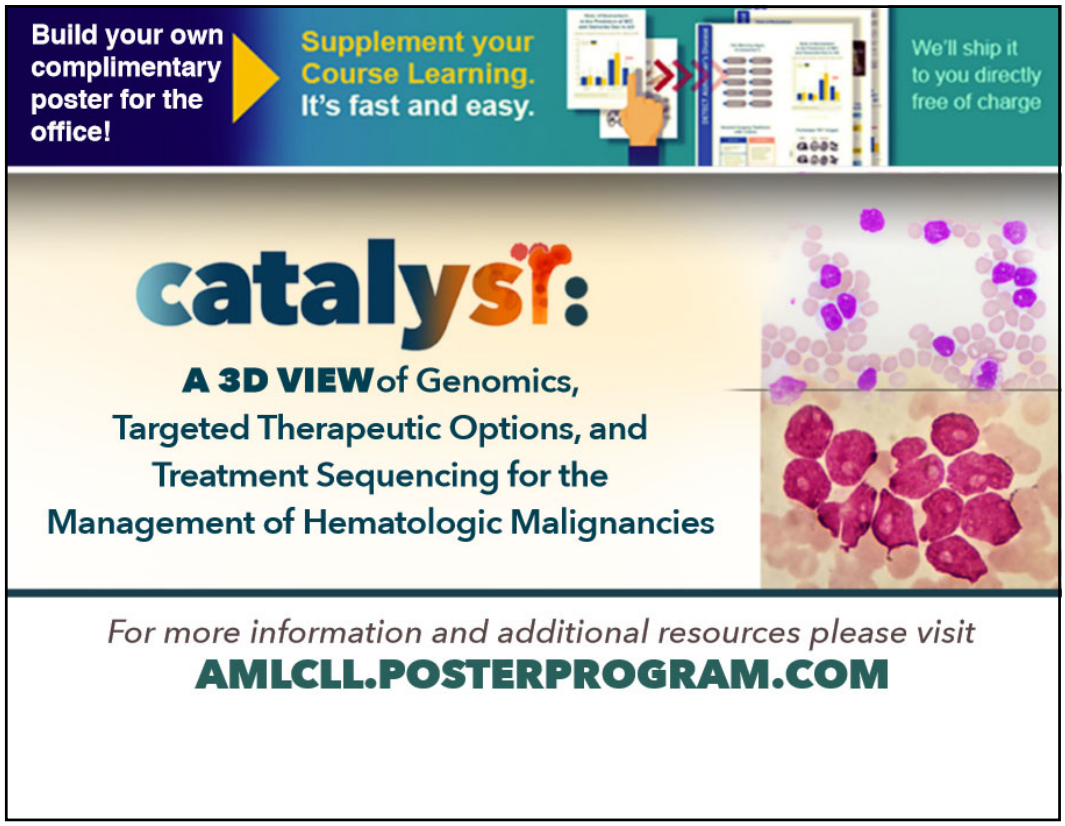
Build your own complimentary poster for the office!
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catalyst:
A 3D VIEW of Genomics, Targeted Therapeutic Options, and Treatment Sequencing for the Management of Hematologic Malignancies
For more information and additional resources please visit
AMLCLL.POSTERPROGRAM.COM

# THANK YOU


# AGENDA

Chronic Lymphocytic Leukemia (CLL)

1. **CLL: An Overview**
   - Assessing clinical stage of the disease, the symptoms of the patient, the fitness and concomitant diseases of the patient, genetic risks, line of treatment, and response to previous therapy

2. **First-Line Treatment of Patients with CLL**
   - CASE consideration
   - Treatment guidelines and rationale
   - Risks and benefits of therapies

3. **Advances in First-Line Treatments for CLL**
   - VIDEO presentation
   - Targeting apoptotic pathways in the management of CLL

4. **Treatment Options for Relapsed/Refractory CLL**
   - CASE consideration
   - Treatment guidelines and rationale
   - Risks and benefits of therapies

5. **Monitoring and Managing Adverse Events in Collaboration with Patients and Families**

6. **Conclusions**

7. **Questions and Answers**

# *CATALYST: A 3D View of Genomics, Targeted Therapeutic Options, and Treatment Sequencing for the Management of Hematologic Malignancies*

**Ryan Jacobs, MD**
Clinical Assistant Professor of Medicine
UNC-Chapel Hill School of Medicine
Chapel Hill, NC
Director of CLL Clinical Trials
Department of Hematology, Lymphoma Section
Levine Cancer Institute/Atrium Health
Charlotte, NC

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

# *Updates in Chronic Lymphocytic Leukemia (CLL): An Overview*

**PROGRAM CHAIR**
**Ryan Jacobs, MD**
Clinical Assistant Professor of Medicine
UNC-Chapel Hill School of Medicine
Chapel Hill, NC
Director of CLL Clinical Trials
Department of Hematology, Lymphoma Section
Levine Cancer Institute/Atrium Health
Charlotte, NC

## Disclosures

- Please see Program Overview for specific speaker disclosure information.
- During the course of this lecture, the faculty may mention the use of medications for both FDA-approved and non-approved indications.

**This activity is supported by educational grants from AbbVie Inc. and Celgene Corporation.**

## Learning Objectives

- Explain how common mutations and abnormalities in patients with previously untreated and R/R CLL and AML affect treatment decision-making
- Describe available and emerging therapeutic approaches for patients with previously untreated and R/R CLL and AML
- Review methods for measuring and analyzing MRD in CLL and clinical trial data providing insight into the use of MRD status in the management of CLL
- Design evidence-based therapeutic strategies for patients with previously untreated and R/R CLL and AML based on patient characteristics
- Discuss the benefits of effective communication between health care providers and patients with previously untreated and R/R CLL and AML
-

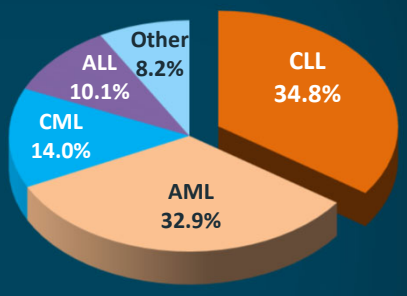
# Assessment of Chronic Lymphocytic Leukemia in the Treatment-Naïve Setting

## 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

### 2020 expected new cases of leukemia in the US by type[2]




- In the US in 2020, an estimated **21,040** patients will be diagnosed with CLL[2]
- Average age of CLL diagnosis = 70 years[3]

IWCLL = International Workshop on Chronic Lymphocytic Leukaemia; CD = cluster designation (antigenic marker on helper/inducer T-cells); ALL = acute lymphocytic leukemia; AML = acute myeloid leukemia; CML = chronic myeloid leukemia.

1. Hallek M, et al; IWCLL. *Blood.* 2008;111:5446-5456. 2. American Cancer Society (ACS). Cancer Facts & Figures 2020 (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 February 27, 2020.

# Staging Systems for CLL

| Rai System | | |
|---|---|---|
| Stage | Description | Modified Risk Status |
| 0 | Lymphocytosis, lymphocytes in blood >5 x $10^9$/L clonal B cells and >40% lymphocytes in the bone marrow | Low |
| I | Stage 0 with enlarged node(s) | Intermediate |
| II | Stage 0–I with splenomegaly, hepatomegaly, or both | Intermediate |
| III | Stage 0–II with hemoglobin <11.0 g/dL or hematocrit <33% | High |
| IV | Stage 0–III with platelets <100,000/mcL | High |

| Binet System | |
|---|---|
| Stage | Description |
| A | Hemoglobin ≥10 g/dL and platelets ≥100,000/$mm^3$ and <3 enlarged areas |
| B | Hemoglobin ≥10 g/dL and platelets ≥100,000/$mm^3$ and ≥3 enlarged areas |
| C | Hemoglobin <10 g/dL and/or platelets <100,000/$mm^3$ and any number of enlarged areas |

National Comprehensive Cancer Network (NCCN). Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Version 4.2020. (www.nccn.org/professionals/physician_gls/pdf/cll.pdf).

# CLL and the Veteran Population

- Evidence associates an increased risk for CLL to Vietnam War service and exposure to herbicides such as Agent Orange[1–3]
  - Other studies have suggested that farming and long-term exposure to certain pesticides may be linked to an increased risk[2]
  - Radon exposure at home has been linked to an increased risk[2]
  - More research is needed[2]
- Military Disability Rating Code(s): Code 7703[4]
- Patient resources for veterans include:
  - www.cancercare.org/tagged/veterans
  - www.cancercare.org/publications/340-veterans_living_with_cancer_resources_and_support
  - www.publichealth.va.gov/exposures/agentorange/

1. Frumkin H. *CA Cancer J Clin*. 2003;53:245-255. 2. ACS. CLL risks (www.cancer.org/cancer/chronic-lymphocytic-leukemia/causes-risks-prevention/risk-factors.html). 3. Defense Health Research Programs (June 2017). (www.aplu.org/members/councils/ governmental-affairs/cga-miscellaneous-documents/2017-Defense-Health-Research-Military-Relevance-inc.%20endnotes.pdf). 4. Military disability made easy (www.militarydisabilitymadeeasy.com/theblood.html). URLs accessed February 27, 2020.

# 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

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.

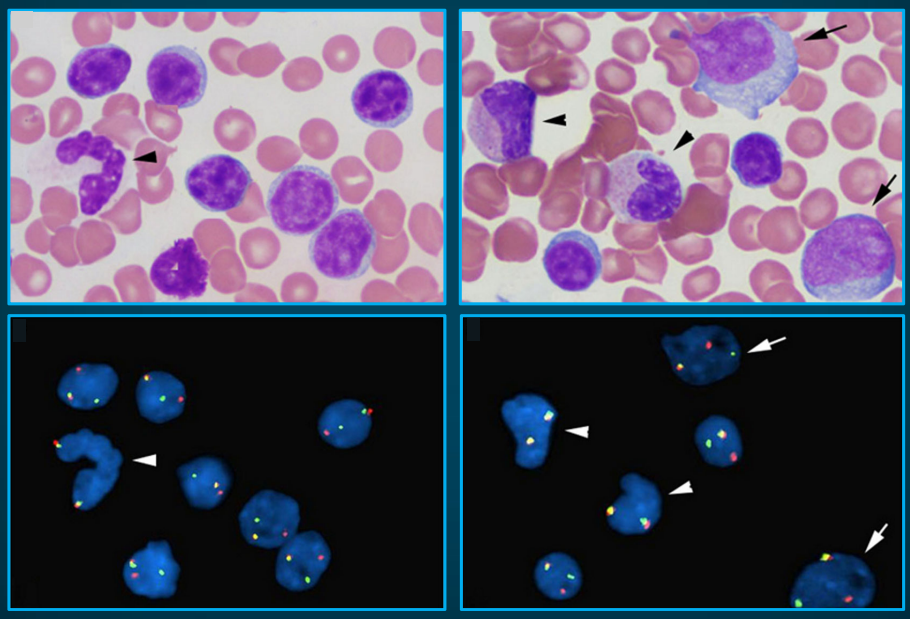
# Prognostic Markers in CLL

## Prognostic Markers

- **Interphase cytogenetics by FISH**
- IgHV mutational status
- Tp53 mutation analysis

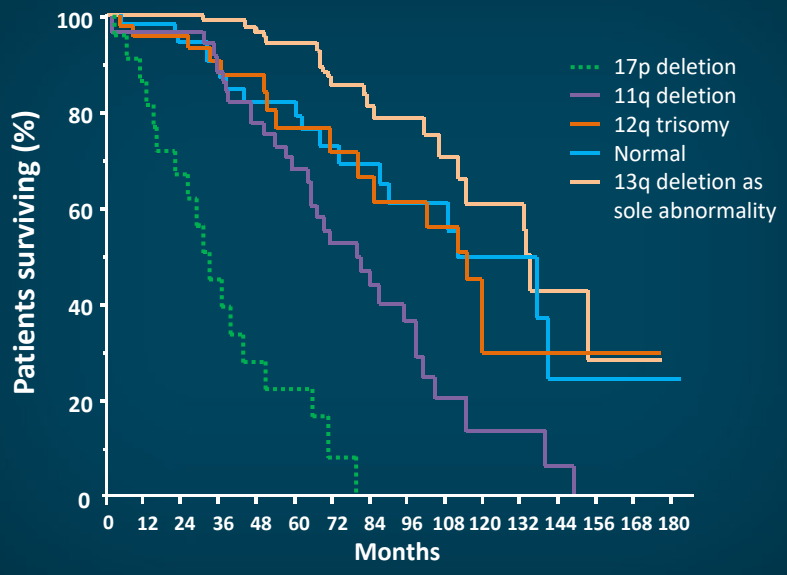
## FISH Analysis—An Example

### Combined Morphologic-FISH Analysis



Shaikh F, et al. *Cureus*. 2017;9:e968.

# 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 |

OS = overall survival; del = deletion; mos = months.

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

## Prognostic Markers

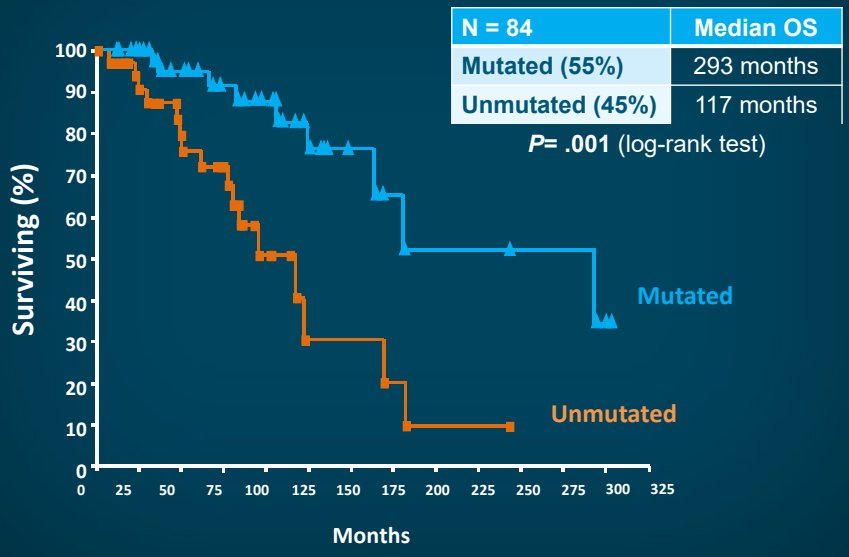
- Interphase cytogenetics by FISH
- **IgHV mutational status**
- Tp53 mutation analysis

## Significance of IgHV

- IgHV undergoes hypermutation during B-cell development[1]
- 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




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

# Prognostic Markers

- Interphase cytogenetics by FISH
- IgHV mutational status
- **Tp53 mutation analysis**

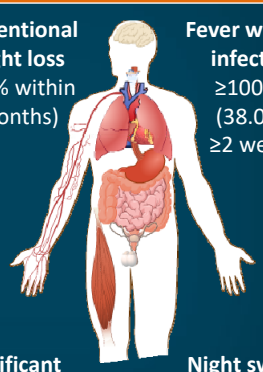
# Criteria for Initiation of Treatment

## 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.

# Case 1: Introduction and Questions to Consider

## Case description

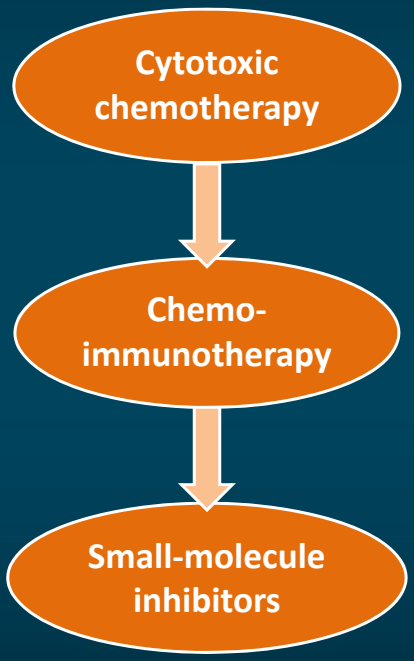
- 63-year-old woman presents with painful lymphadenopathy
- Laboratory findings:
  - WBC: 117.3 X $10^9$/L
  - Lymphocytes: 109.2 X $10^9$/L
  - Hgb: 9.6 g/dL
  - Platelets: 174 X $10^9$/L
  - ANC: 1950/$mm^3$
  - LDH: 160 U/L
  - Flow cytometry: CD19++, CD5+, CD20+, CD23++, CD38+
  - BM: CLL in 86% of cells
  - IgHV unmutated
  - Cytogenetics by FISH: normal

## Questions to consider

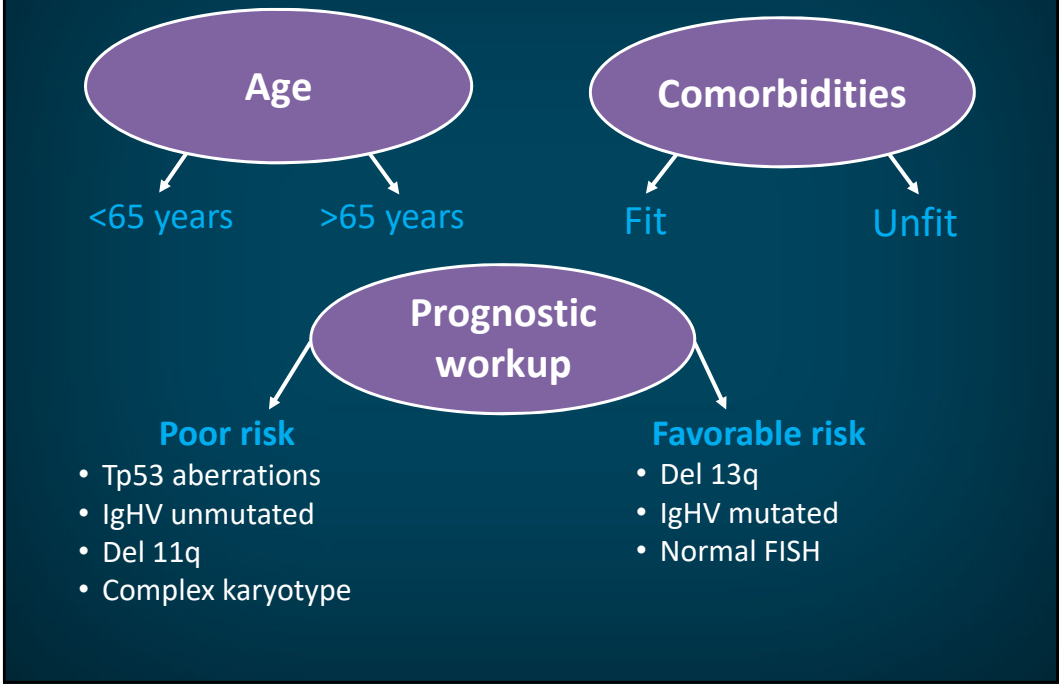
- What would you do to manage this patient?
- How would you discuss treatment options and potential adverse events with the patient and/or her family?

WBC = white blood count; Hgb = hemoglobin; ANC = absolute neutrophil count; BM = bone marrow.

## Advances in Therapeutic Paradigms




## Stratification of CLL Patients




## FCR vs BR—CLL-10 GCLLSG Trial

| | FCR n = 282 | BR n = 279 | *P* value |
|---|---|---|---|
| ORR (%) | 98 | 98 | NS |
| CR (%) | 41 | 32 | 0.026 |
| Median PFS (months) | 54 | 43 | 0.001 |
| OS at 3 years (%) | 91 | 92 | NS |
| Severe neutropenia (%) | 88 | 68 | <0.001 |
| Severe infections (%) | 40 | 25 | 0.001 |
| TRM (%) | 4 | 2 | — |

FCR = fludarabine + cyclophosphamide + rituximab; BR = bendamustine + rituximab; GCLLSG = German CLL Study Group; ORR = overall/objective response rate; CR = complete response; PFS = progression-free survival; TRM = treatment-related mortality.

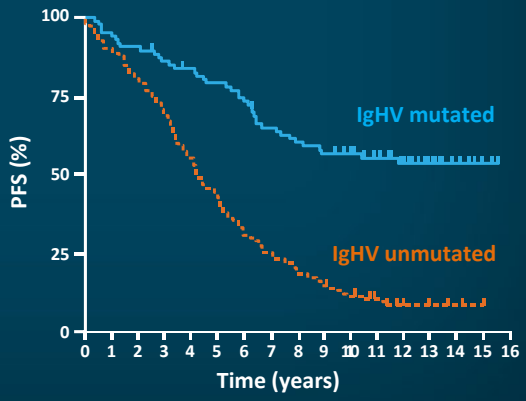
Eichhorst B, et al. *Blood*. 2014;124(21):abstract 19.

# FCR: A Possible Cure for CLL?

- Median PFS was not reached at 12.8 years in IgHV-mutated group
- Approximately 50% 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?

| | Patients n | PFS % |
|---|---|---|
| IgHV mutated | 88 | 49 |
| IgHV unmutated | 126 | 12 |

*P* <.0001



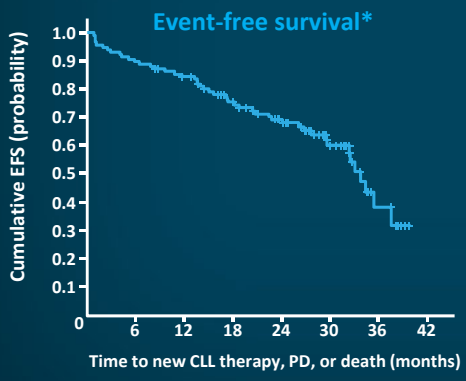

MRD = minimal residual disease.

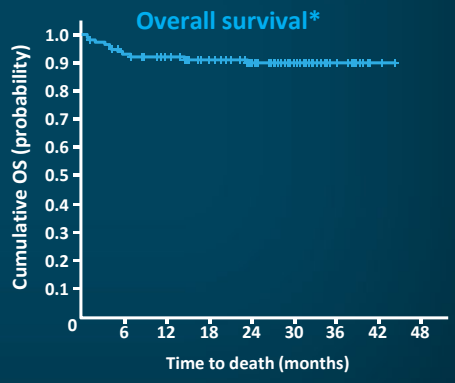
Thompson PA, et al. *Blood.* 2016;127:303-309.

# Chemotherapy Options in Fit Elderly Patients

## Bendamustine + Rituximab

- Avoid fludarabine-based regimens
- Bendamustine + rituximab
  - Slightly higher adverse event rate



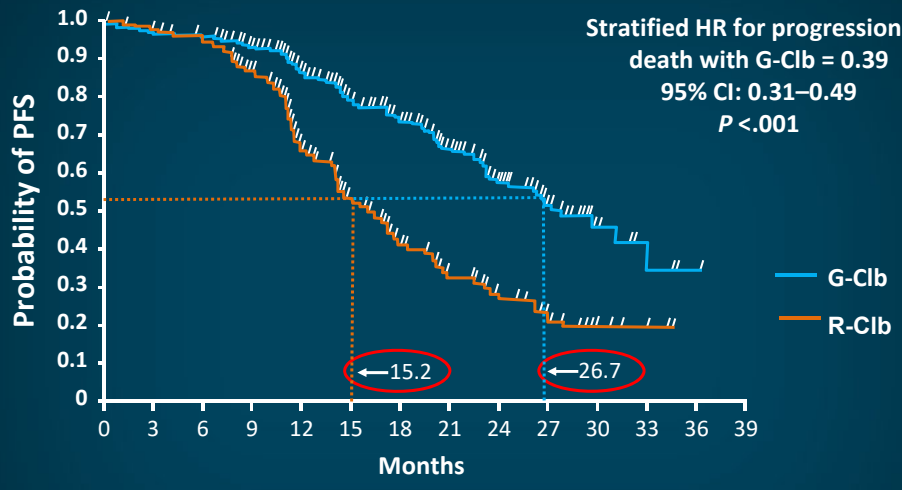




*All patients in the intent-to-treat group.

EFS = event-free survival; PD = progression of disease.

Fischer K, et al. *J Clin Oncol.* 2012;30:3209-3216.

# Obinutuzumab + Chlorambucil—CLL-11 Trial

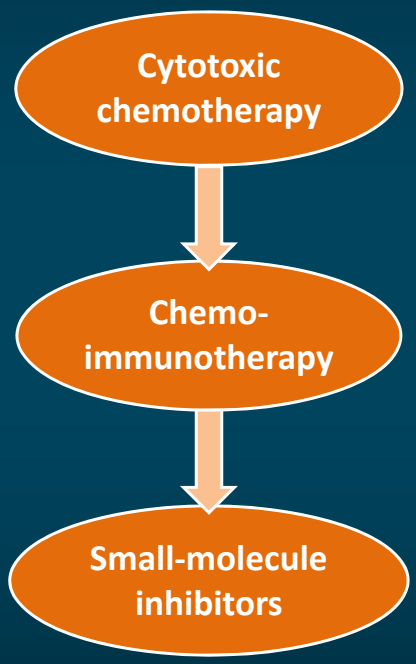



- Obinutuzumab is an engineered anti-CD20 monoclonal antibody
- It is well tolerated in patients with comorbidities and median age of 73

HR = hazard ratio; CI = confidence interval; G-Clb = obinutuzumab + chlorambucil; R-Clb = rituximab + chlorambucil; PR = partial response.

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

# Advances in Therapeutic Paradigms

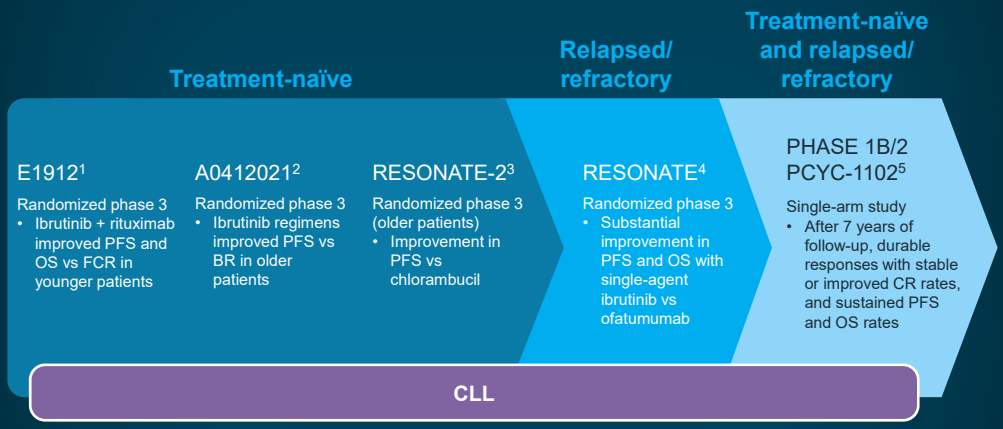


## CLL 360 animation

https://youtu.be/mybD0VOmM-4

## Treatment with Ibrutinib

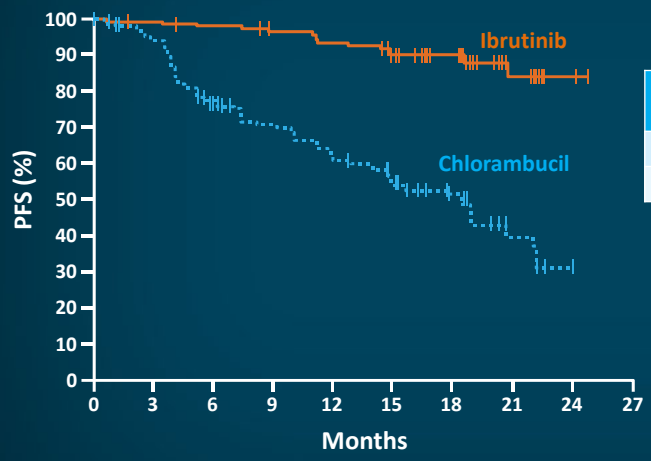
# Summary of Major Studies With Ibrutinib in CLL




1. Shanafelt TD, et al. American Society of Hematology (ASH) 2018:abstract LBA-4. 2. Woyach J, et al. *N Engl J Med*. 2018;379:2517-2528. 3. Burger JA, et al. European Hematology Association (EHA) 2018: abstract PF343. 4. Byrd JC, et al. American Society of Clinical Oncology (ASCO) 2017:abstract 7510. 5. Byrd JC, et al. ASH 2018:abstract 3133.

# Ibrutinib vs Chlorambucil—Resonate-2

- Ibrutinib is superior to chlorambucil in patients aged >65 years of age with previously untreated CLL[1]



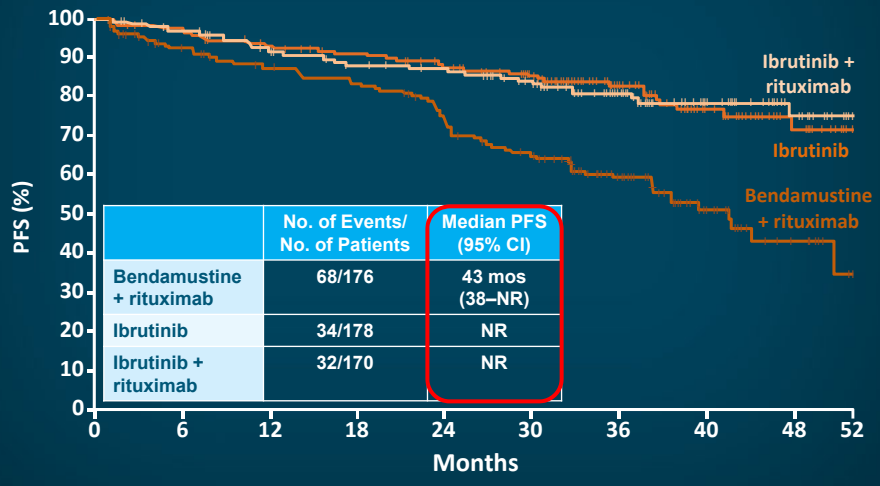

| Agent | Median PFS (months) |
|---|---|
| Chlorambucil | 18.9 |
| Ibrutinib | Not reached |

HR = 0.16 (95% CI, 0.09–0.28)
***P* <.001**

- **FDA approval for all untreated CLL patients (March 2016)[2]**

1. Burger JA, et al. *N Engl J Med*. 2015;373:2425-2437. 2. Ibrutinib (Imbruvica®) expanded labeling (www.prnewswire.com/news-releases/imbruvica-ibrutinib-approved-by-us-fda-for-the-first-line-treatment-of-chronic-lymphocytic-leukemia-300231107.html/). Accessed February 29, 2020.

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



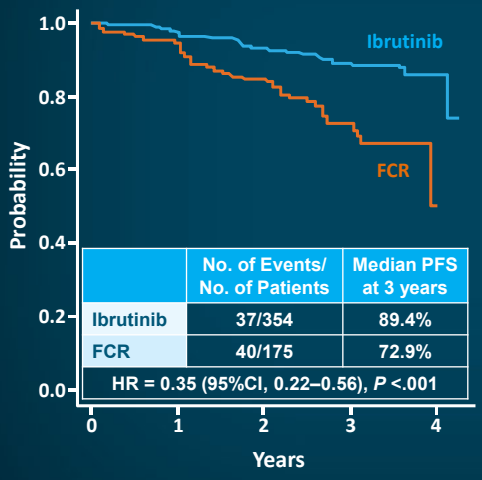

| | No. of Events/ No. of Patients | Median PFS (95% CI) |
|---|---|---|
| Bendamustine + rituximab | 68/176 | 43 mos (38–NR) |
| Ibrutinib | 34/178 | NR |
| Ibrutinib + rituximab | 32/170 | NR |

NR = not reached.

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

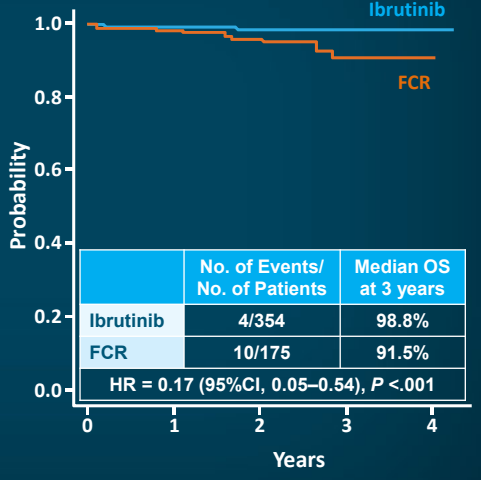
# Ibrutinib vs FCR in Untreated Younger Patients with CLL (ECOG)

PFS (all randomized)




| | No. of Events/ No. of Patients | Median PFS at 3 years |
|---|---|---|
| Ibrutinib | 37/354 | 89.4% |
| FCR | 40/175 | 72.9% |
| HR = 0.35 (95%CI, 0.22–0.56), *P* <.001 | | |

OS (all randomized)



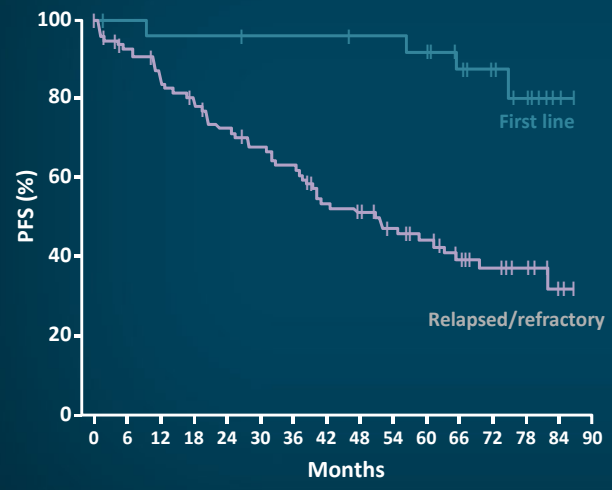

| | No. of Events/ No. of Patients | Median OS at 3 years |
|---|---|---|
| Ibrutinib | 4/354 | 98.8% |
| FCR | 10/175 | 91.5% |
| HR = 0.17 (95%CI, 0.05–0.54), *P* <.001 | | |

ECOG = Eastern Cooperative Oncology Group.

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

# PFS with Long-Term Ibrutinib Use

PFS for all treated first-line and relapsed/refractory patients with CLL



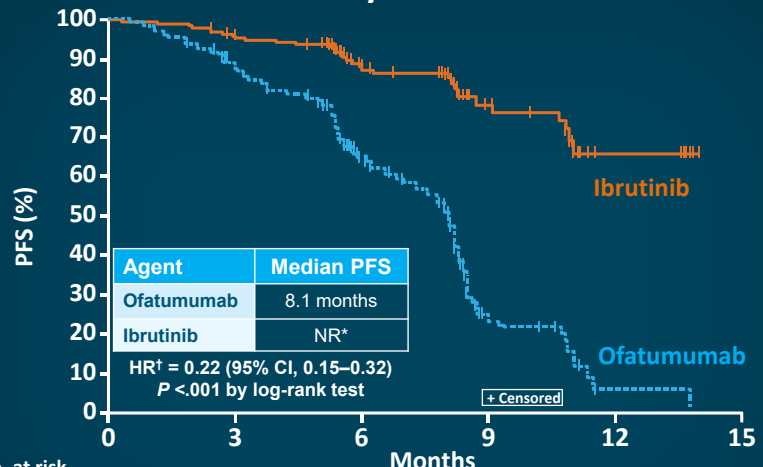

| | Median PFS | 7-year PFS |
|---|---|---|
| Treatment-naïve (n = 31) | NR | 80% |
| R/R (n = 101) | 51 mos | 32% |

R/R = relapsed/refractory.

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

# Resonate Trial: Ibrutinib vs Ofatumumab

## Previously Treated CLL




| Agent | Median PFS |
|---|---|
| Ofatumumab | 8.1 months |
| Ibrutinib | NR* |

HR† = 0.22 (95% CI, 0.15–0.32)
*P* <.001 by log-rank test

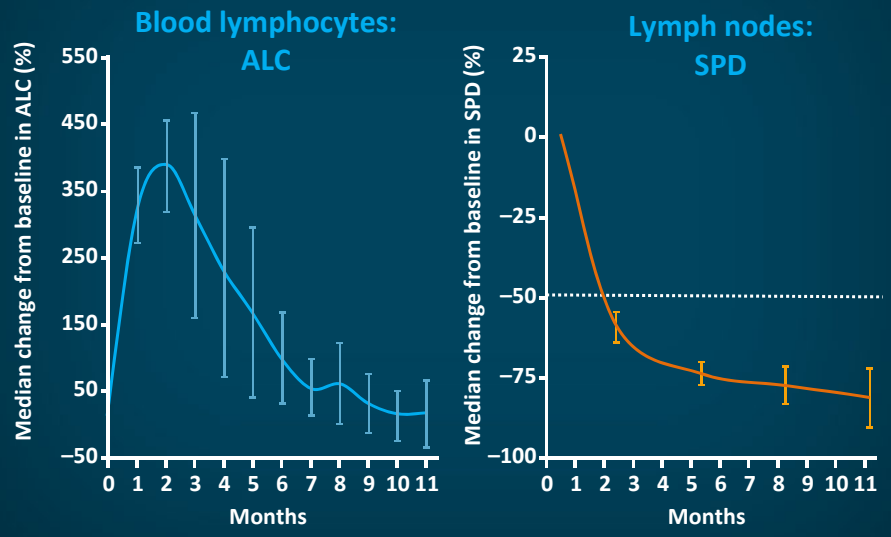
| No. at risk | | | | | | |
|---|---|---|---|---|---|---|
| Ibrutinib | 195 | 183 | 116 | 38 | 7 | |
| Ofatumumab | 196 | 161 | 83 | 15 | 1 | 0 |

**FDA approval in 2014 for all previously treated CLL patients**

*Not reached at median follow-up of 9.4 months; †HR for progression or death.

Byrd JC, et al. *N Engl J Med.* 2014;371:213-223. FDA. Ibrutinib (www.cancernetwork.com/chronic-lymphocytic-leukemia/fda-approves-ibrutinib-chronic-lymphocytic-leukemia). Accessed March 1, 2020.

# Pattern of Response: Blood Lymphocytes vs Lymph Nodes




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.

# Understanding the Spectrum of Grade 3/4 AEs With Ibrutinib

| AE, % | 0–6 Mos | 6–12 Mos | 1–2 Years | 2–3 Years | 3–4 Years | 4–5 Years |
|---|---|---|---|---|---|---|
| Hypertension | 2 | 8 | 8 | 18 | 15 | 16 |
| Pneumonia | 9 | 4 | 10 | 7 | 10 | 6 |
| Neutropenia | 10 | 4 | 3 | 2 | 3 | 2 |
| Thrombocytopenia | 5 | 1 | 3 | 2 | 1 | 0 |
| Atrial fibrillation | 2 | 1 | 3 | 1 | 5 | 3 |
| Diarrhea | 3 | 1 | 3 | 1 | 3 | 2 |
| Cellulitis | 2 | 0 | 1 | 6 | 3 | 0 |
| Sepsis | 1 | 1 | 5 | 0 | 3 | 2 |
| Fatigue | 2 | 1 | 2 | 0 | 3 | 0 |
| Decreased lymphocyte count | 0 | 0 | 2 | 6 | 4 | 3 |

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)

O'Brien S, et al. *Blood*. 2018:131:1910-1919 and supplement.

# Real-World Experience of Incidence of Dose Modification and Interruption of Ibrutinib

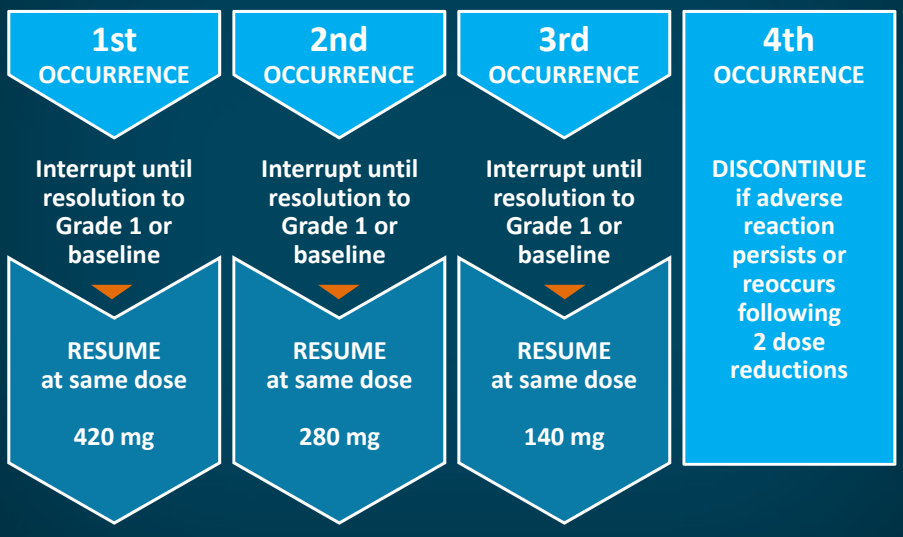
| Dosing Information for Ibrutinib | |
|---|---|
| Patients, no. | 143 |
| Median time on KI, mos (95% CI) | 5 (0.25–41) |
| Proportion requiring dose modification, n (%) | 141 (18) |
| Proportion requiring dose interruption, n (%) | 96 (43) |

| Most Common Reasons for Discontinuing Ibrutinib | |
|---|---|
| Adverse event, n (%) | 73 (51) |
| CLL progression, n (%) | 40 (28) |
| Richter's transformation, n (%) | 11 (8) |
| Cellular therapies, n (%) | 3 (2) |
| Unrelated death/other, n (%) | 16 (11) |

KI = kinase inhibitor.

Mato AR, et al. *Blood.* 2016;128:2199-2205.

# Dosing Modifications for Managing Adverse Reactions with Ibrutinib




Ibrutinib (Imbruvica®) prescribing information (PI) 2019 (https://imbruvica.com/files/prescribing-information.pdf). Accessed February 27, 2020.

## 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% relapsed/refractory
  - Up to 29% in previously untreated
- Response deepens over time
  - Median time to response: 4 mos
  - Median time to best response: 12 mos
- Del17p responds, but PFS is shorter

Slide courtesy of Dr. Ryan Jacobs.

## Treatment with Acalabrutinib

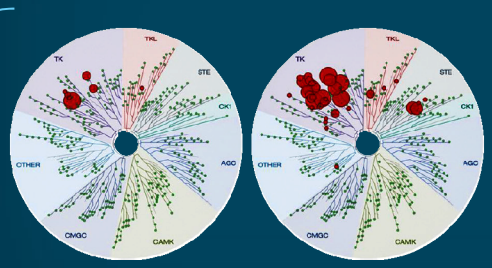
# Acalabrutinib (ACP-196)

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

**Kinase Inhibition Average $IC_{50}$ (nM)**

| 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 |

Kinase selectivity profiling at 1 µM



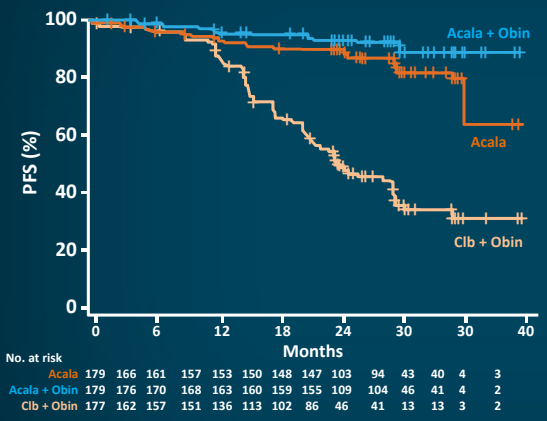

*Larger red circles represent stronger inhibition*

BTK = Bruton's tyrosine kinase; 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.

Byrd JC, et al. *N Engl J Med*. 2016;374:323-332 and supplement.

# ELEVATE-TN: Phase 3 Study of Acalabrutinib Improved PFS in Treatment-Naive CLL

**PFS assessed by independent review committee**




- Previously untreated CLL (N=535)
- 3 treatment arms:
  - Acalabrutinib + obinutuzumab
  - Acalabrutinib monotherapy
  - Obinutuzumab + chlorambucil

**HR for PFS at 28.3 months**

- Acalabrutinib + Obin vs Obin + Clb = 0.10 (95% CI: 0.06–0.18); *P* <.0001
- Acalabrutinib vs Obin + Clb = 0.20 (95% CI: 0.13–0.31); *P* <.0001

**Acalabrutinib ± obinutuzumab: FDA approval for all previously untreated CLL patients (November 2019)**

Acala = acalabrutinib; Obin = obinutuzumab; Clb = chlorambucil.

Sharman JP, et al. *Blood*. 2019;134(suppl 1):abstract 31. FDA approves acalabrutinib (www.drugs.com/newdrugs/fda-approves-calquence-adults-chronic-lymphocytic-leukemia-5110.html). Accessed February 28, 2020.

# Acalabrutinib Safety and Adverse Event Profile

**SAEs occurred at any grade in 22–39% of patients in any arm or at grade ≥3 in 20–33% of patients in any arm.**

| | Acalabrutinib + Obinutuzumab (n = 178) | | Acalabrutinib (n = 179) | | Obinutuzumab + Chlorambucil (n = 169) | |
|---|---|---|---|---|---|---|
| | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| Any, n (%) | 171 (96) | 125 (70) | 170 (95) | 89 (50) | 167 (99) | 118 (70) |
| Serious, n (%) | 69 (39) | 58 (33) | 57 (32) | 53 (30) | 37 (22) | 33 (20) |
| Common AEs, n (%) | | | | | | |
| Headache | 71 (40) | 2 (1) | 66 (37) | 2 (1) | 20 (12) | 0 |
| Diarrhea | 69 (39) | 8 (4) | 62 (35) | 1 (1) | 36 (21) | 3 (2) |
| Neutropenia | 56 (31) | 53 (30) | 19 (11) | 17 (9) | 76 (45) | 70 (41) |
| Nausea | 36 (20) | 0 | 40 (22) | 0 | 53 (31) | 0 |
| infusion-related reaction | 24 (13) | 4 (2) | 0 | 0 | 67 (40) | 9 (5) |
| Thrombocytopenia | 23 (13) | 15 (8) | 13 (7) | 5 (3) | 24 (14) | 20 (12) |
| Anemia | 21 (12) | 10 (6) | 25 (14) | 12 (7) | 20 (12) | 12 (7) |
| Pneumonia | 19 (11) | 10 (6) | 13 (7) | 4 (2) | 5 (3) | 3 (2) |
| Tumor lysis syndrome[a] | 3 (2) | 2 (1) | 0 | 0 | 15 (9) | 13 (8) |
| Febrile neutropenia | 3 (2) | 3 (2) | 2 (1) | 2 (1) | 9 (5) | 9 (5) |

- Acalabrutinib monotherapy dose reduction rate = 4%; discontinuation rate = 9%
- Acalabrutinib + Obin dose reduction rate = 7% ; discontinuation rate = 11%

[a]By clinical assessment.

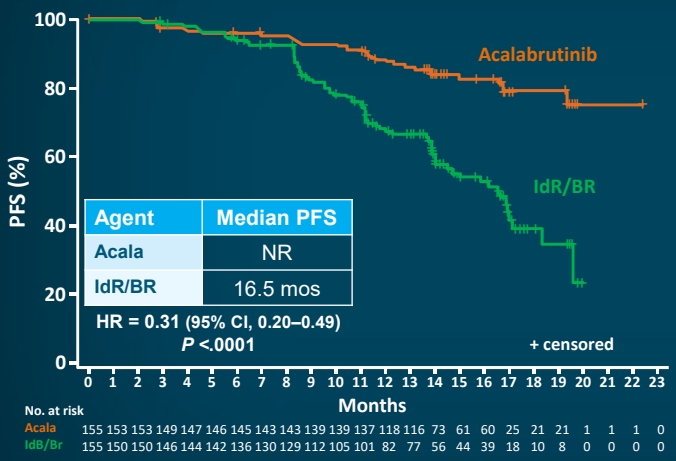
SAE = serious AE.

Sharman JP, et al. *Blood*. 2019;134(suppl 1):abstract 31.

# ASCEND: Phase 3 Study of Acalabrutinib

## Improved PFS in R/R CLL

**Acalabrutinib vs rituximab + idelalisib or bendamustine (investigator's choice); N = 310**




- 12-mo PFS: 88% with acalabrutinib vs 68% with rituximab + idelalisib or bendamustine
- 12-mo OS: 94% with acalabrutinib and 91% with rituximab + idelalisib or bendamustine
- Similar toxicity profile to use in frontline (11% discontinuation rate due to AEs)

**Acalabrutinib: FDA approval for all previously treated CLL patients (November 2019)**

IdR/BR = rituximab + idelalisib or bendamustine.

Ghia P, et al. EHA Library. 2019;273259:LB2606. FDA approves acalabrutinib (www.drugs.com/newdrugs/fda-approves-calquence-adults-chronic-lymphocytic-leukemia-5110.html). The ASCO Post. https://www.ascopost.com/News/60168. Accessed February 28, 2020.

## Acalabrutinib

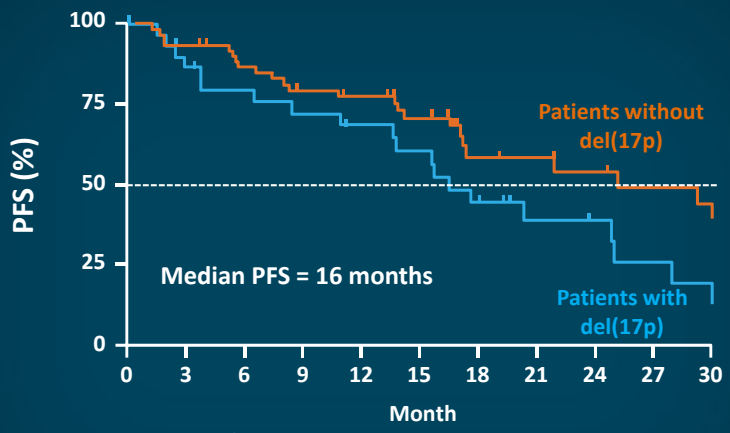
- Second generation BTK inhibitor with higher selectivity to BTK
- No head-to-head comparative data vs ibrutinib at this time
  - ? Lower incidence of all-grade adverse reactions noted in ibrutinib
    - Bruising: 10%
    - Rash: 9%
    - Afib/flutter: 5%
    - Hypertension: 3.2%
- Effective in ibrutinib-intolerant patients but not in ibrutinib resistance

**Afib = atrial fibrillation.**
**Slide courtesy of Dr. Ryan Jacobs.**

## Treatment with Venetoclax

# Venetoclax—Response

## 17p Deletion




Patients with 17p deletion had[1]:

- Overall response rate: 71%
- Complete response rate: 16%

**Approved by FDA for previously treated CLL patients ± 17p deletion (June 2018)[2]**

1. Roberts AW, et al. *N Engl J Med.* 2016;374:311-322. 2. FDA 2018 (www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-venetoclax-cll-or-sll-or-without-17-p-deletion-after-one-prior-therapy). Accessed February 29, 2020.

# Venetoclax Monotherapy in R/R Del 17 CLL

## International Phase 2 Study

| Best response (n = 107) | IRC Assessment | Investigator Assessment |
|---|---|---|
| ORR, n (%) | **85 (79.4%)** | **79 (73.8%)** |
| CR or CRi | 8 (7.5%) | 17 (15.9%) |
| Nodular PR (nPR) | 3 (2.8%) | 4 (3.7%) |
| PR | 74 (69.2%) | 58 (54.2%) |
| Non-responder* | 22 (20.6%) | 28 (26.2%) |
| Stable disease | — | 24 (22.4%) |
| PD | — | 2 (1.9%) |
| Incomplete data | — | 2 (1.9%) |

*Patients with SD, PD, or incomplete data were all considered non-responders by the IRC and not subcategorized.

| Duration of response | N | Maintained Response at 12 months by IRC (%)† |
|---|---|---|
| All responders | 85 | 84.7 |
| Responder subgroups | | |
| Deep responders (CR, Cri, nPR) | 11 | 100 |
| PR | 74 | 82.6 |
| MRD negative* | 18 | 94.4 |

*MRD-negative in PB, and 6 also negative in BM; †Based on Kaplan-Meier estimate.

IRC = independent review committee; CRi = complete remission with incomplete bone marrow recovery; PD = progressive disease; PB = peripheral blood.

Stilgenbauer S, et al. *Blood.* 2015;126:abstract LBA-6.

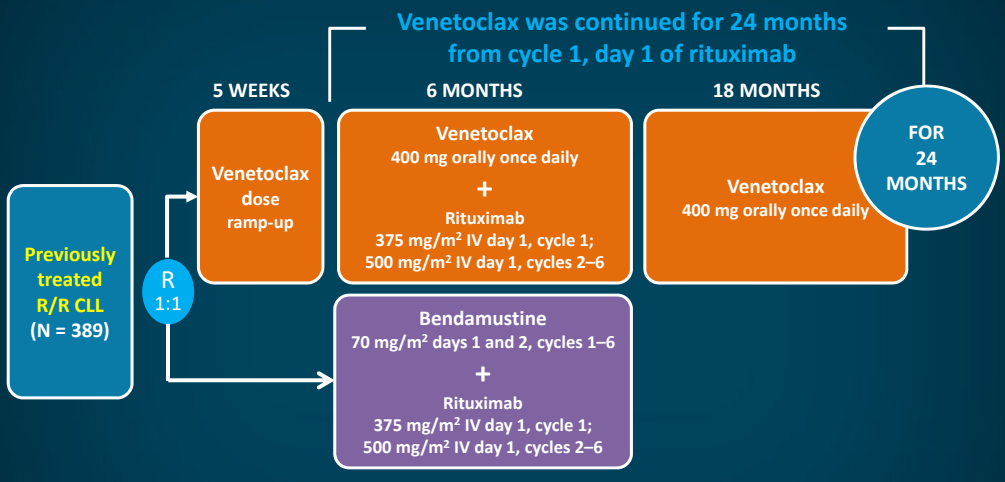
# Venetoclax in Kinase-Inhibitor Failure

| Response to Venetoclax by Prior Treatment | | | | |
|---|---|---|---|---|
| Best Response, n (%) | Prior Ibrutinib Arm (n = 43) | | Prior Idelalisib Arm (n = 21) | |
| | Assessed by | | Assessed by | |
| | IRC | Investigator | IRC | Investigator |
| ORR | 30 (70) | 29 (67) | 10 (48) | 12 (57) |
| CR/CRi | 0/1 (2) | 2 (5)/1 (2) | 0/0 | 2 (10)/1 (5) |
| nPR | 0 | 2 (5) | 0 | 0 |
| PR | 29 (67) | 24 (56) | 10 (47) | 9 (43) |
| Stable disease | — | 9 (21) | — | 8 (38) |
| Disease progression | — | 1 (2) | — | 1 (5) |
| Non-responder* | 13 (30) | — | 11 (52) | — |

*Non-responder was a category specific to assessments by the IRC and indicates a response less than PR (ie, stable disease or disease progression).

Jones J, et al. *Blood*. 2016;128: abstract 637.

# MURANO Study

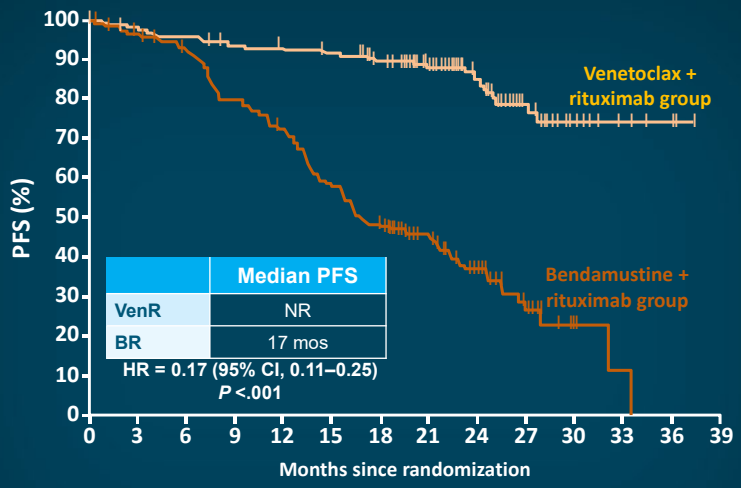



**First published phase 3 trial involving treatment of CLL with novel small-molecule inhibitors delivered over a defined treatment timeline**

IV = intravenous.

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

# MURANO Study: PFS



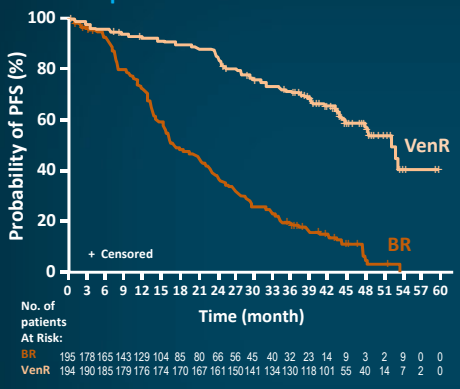

**Venetoclax + rituximab: FDA approval for all previously treated CLL patients (June 2018)**

VenR = venetoclax + rituximab.

Seymour JF, et al. *N Engl J Med*. 2018;378:1107-1120. FDA—venetoclax (https://news.abbvie.com/news/abbvie-announces-us-fda-approval-venclexta-venetoclax-tablets-in-combination-with-rituximab-as-fixed-duration-treatment-for-chronic-lymphocytic-leukemia-or-small-lymphocytic-lymphoma-patients-who-have-received-one-prior-therapy.htm). Accessed Febraury 29, 2020.

# MURANO Study—ASH 2019 Update

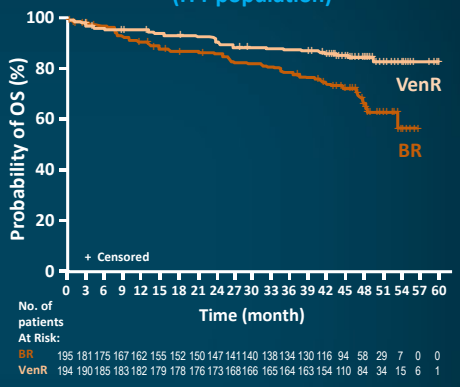
Kaplan-Meier Assessments of PFS




| | 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% |

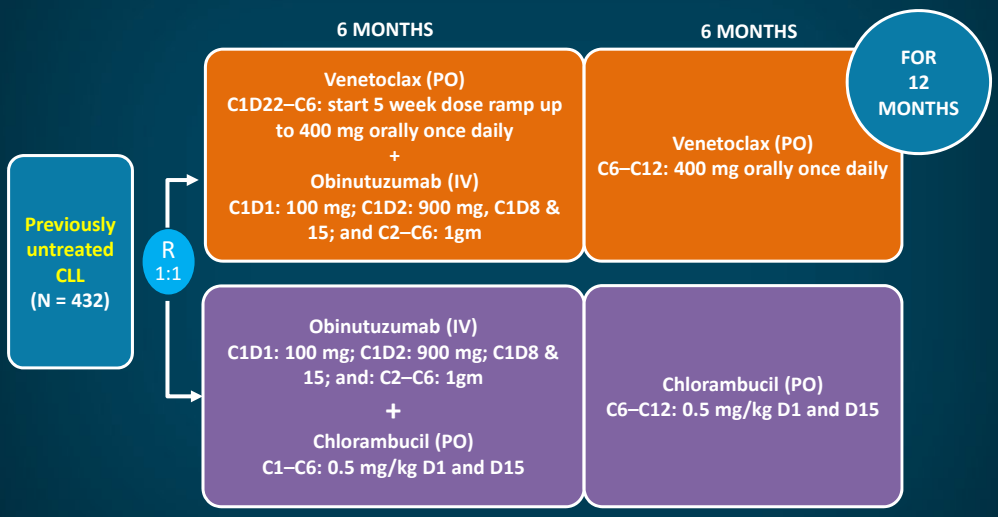
HR = 0.41 (95% CI, 0.26–0.65)
*P* <.0001

ITT = intention to treat.

Seymour JF, et al. *ASH* 2019:abstract 642.

# CLL14 Trial

## Treatment-Naïve Patients with Coexisting Conditions

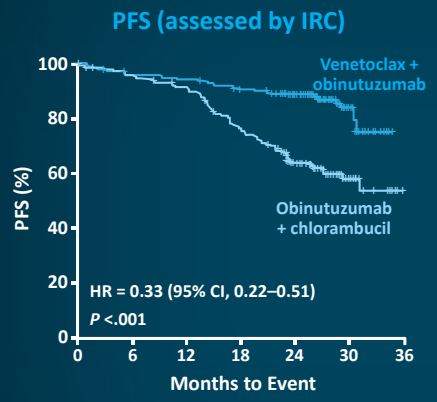


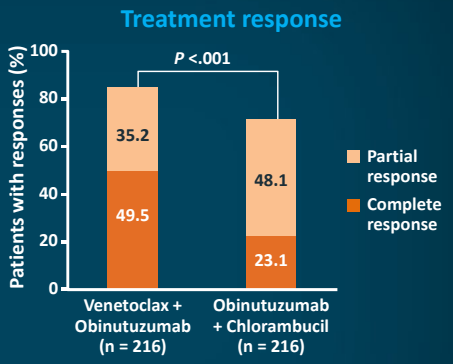

1 cycle = 28 days.

PO = by mouth; C = cycle; D = day.

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

# CLL14: Venetoclax + Obinutuzumab for Untreated CLL




**PB MRD:**

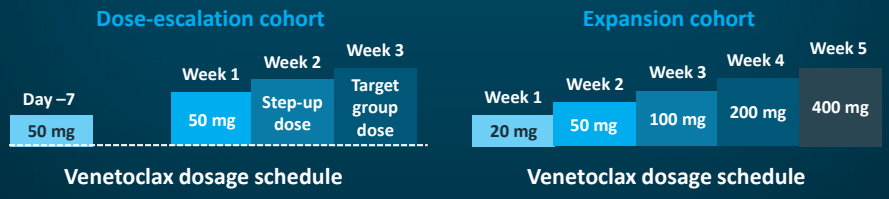
- Venetoclax + Obinutuzumab = 76%
- Obinutuzumab + Chlorambucil = 35%

**Venetoclax + obinutuzumab: FDA approval for all previously untreated CLL patients (May 2019)**

Fischer K, et al. *N Engl J Med*. 2019;380:2225-2236. FDA—venetoclax (news.abbvie.com/news/press-releases/abbvie-announces-us-fda-approval-venclexta-venetoclax-as-chemotherapy-free-combination-regimen-for-previously-untreated-chronic-lymphocytic-leukemia-patients.htm). Accessed February 29, 2020.

# Venetoclax—Tumor Lysis Syndrome (TLS)

- First 3 patients received 200 mg as the initial dose
  - All 3 developed tumor lysis
- Stepwise ramp-up dosing was developed in response
- Amendment to protocol included TLS prophylaxis closer monitoring
- Patients with bulky disease require inpatient observation for dose escalations on day 1 and 2
- No clinical TLS has been observed on trial since dose ramp-up was implemented



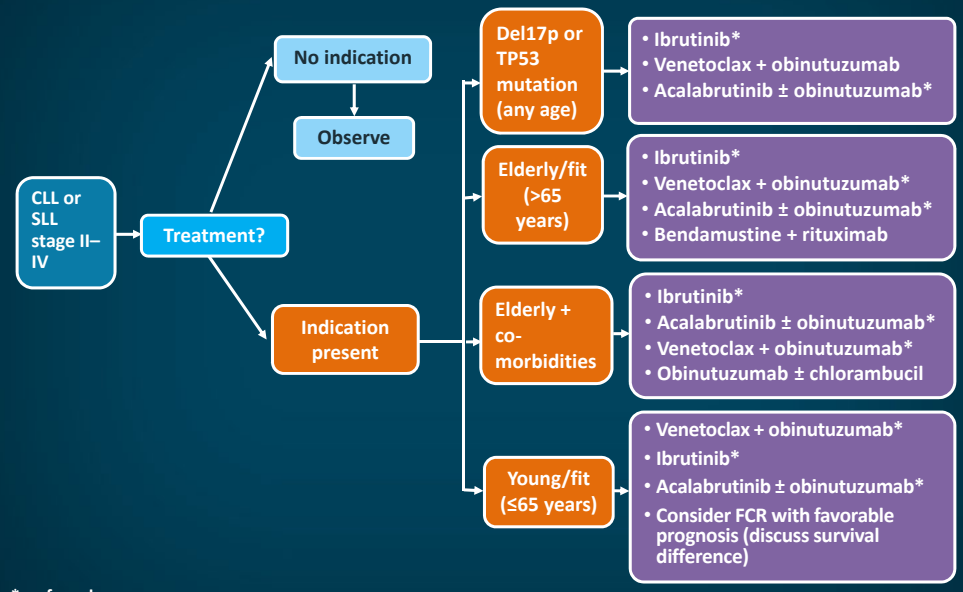

Roberts AW, et al. *N Engl J Med.* 2016;374:311-322.

# Venetoclax—Other Adverse Events

| Event | VenR (n = 194) | BR (n = 188) |
|---|---|---|
| Grade 3 or 4 AE—no. of patients (%) | 159 (82.0) | 132 (70.2) |
| Total no. of AEs | 335 | 255 |
| Grade 3 or 4 AEs with at least 2% difference in incidence between groups—no. of patients (%) | 130 (67.0) | 104 (55.3) |
| Neutropenia | 112 (57.7) | 73 (38.8) |
| Infections and infestations | 34 (17.5) | 41 (21.8) |
| Anemia | 21 (10.8) | 26 (13.8) |
| Thrombocytopenia | 11 (5.7) | 19 (10.1) |
| Febrile neutropenia | 7 (3.6) | 18 (9.6) |
| Pneumonia | 10 (5.2) | 15 (8.0) |
| Infusion-related reaction | 3 (1.5) | 10 (5.3) |
| Tumor lysis syndrome | 6 (3.1) | 2 (1.1) |
| Hypotension | 0 | 5 (2.7) |
| Hyperglycemia | 4 (2.1) | 0 |
| Hypogammaglobulinemia | 4 (2.1) | 0 |
| SAEs with at least 2% incidence in either group—no. of patients (%) | 90 (46.4) | 81 (43.1) |
| Pneumonia | 16 (8.2) | 15 (8.0) |
| Febrile neutropenia | 7 (3.6) | 16 (8.5) |
| Pyrexia | 5 (2.6) | 13 (6.9) |
| Anemia | 3 (1.5) | 5 (2.7) |
| Infusion-related reaction | 1 (0.5) | 6 (3.2) |
| Sepsis | 1 (0.5) | 4 (2.1) |
| Tumor lysis syndrome | 4 (2.1) | 1 (0.5) |
| Hypotension | 0 | 5 (2.7) |
| Fatal AEs—no. of patients (%) | 10 (5.2) | 11 (5.9) |

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

# Summary of Front-Line Therapy




*preferred.

SLL = small lymphocytic lymphoma.

Adapted from: NCCN. CLL/SLL V4.2020 (www.nccn.org/professionals/physician_gls/pdf/cll.pdf). Accessed February 20, 2020.

# Case 2: Introduction and Questions to Consider

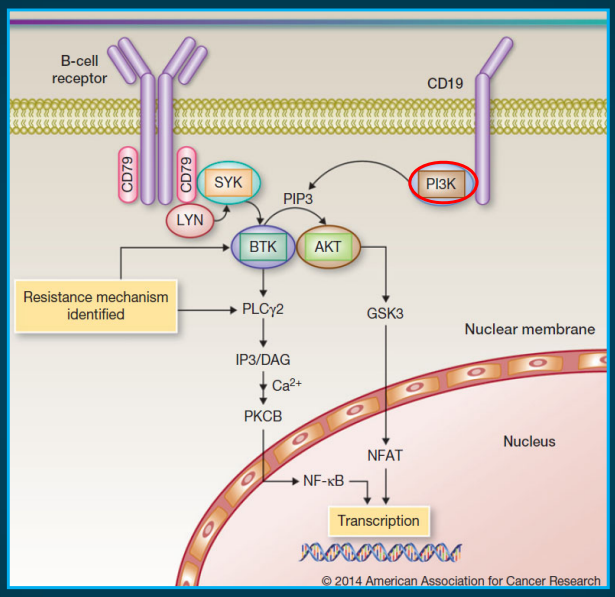
## Case description

- 74-year-old man with diagnosed CLL presents for follow-up
- He received chemotherapy, then ibrutinib, which he discontinued after 3 years due to atrial fibrillation
- During routine follow-up, the patient reported increasing fatigue
- He has cervical lymphadenopathy ~4 cm, his spleen is palpable 8 cm below the costal margin, and he has normal kidney function
- Laboratory results:
  - ALC: 112,000 cells/mL
  - Hgb: 10.8 g/dL
  - Platelets: 105,000 cells/mm$^3$

## Questions to consider

- What would you do to treat this patient?
- How would you discuss options with the patient and/or his family?
- How would you discuss potential adverse events?

# Targeting PI3K in CLL




PI3K = phosphoinositide 3-kinase; SYK = spleen tyrosine kinase; PIP3 = phosphatidylinositol–3,4,5,-triphosphate; DAG = diacylglycerol; PKC = protein kinase C; GSK = glycogen synthase kinase; NFAT = nuclear receptor of activated T cells; NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells.

Awan FT, Byrd JC. *Clin Cancer Res.* 2014;20:5869-5874.

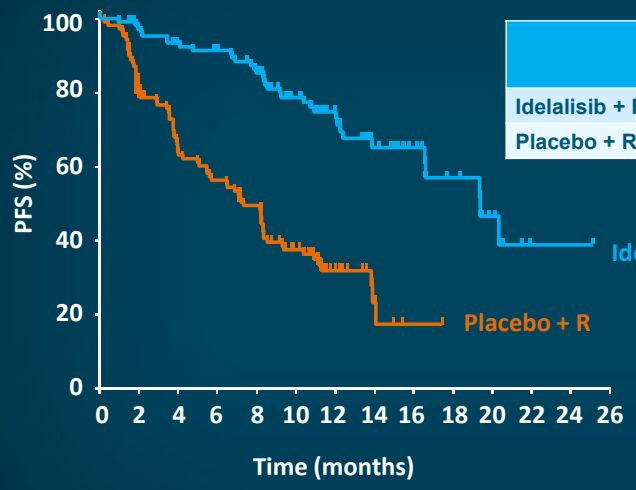
# Idelalisib

- Selective PI3K delta inhibitor
- Single-agent ORR of 72%
- 39% PR and 33% PR+L

PI3K = phosphatidylinositol 3- kinase; PR+L = partial response with treatment-induced lymphocytosis.

Brown JR, et al. *Blood*. 2014;123:3390-3397.

## Phase 3 Study: Idelalisib and Rituximab for Previously Treated Patients With CLL[1]




| | No. | Median PFS |
|---|---|---|
| Idelalisib + Ritux | 110 | 19 mos |
| Placebo + Ritux | 110 | 7 mos |

**Approved by FDA for treatment of relapsed CLL (July 2014)[2]**

Ritux = rituximab.

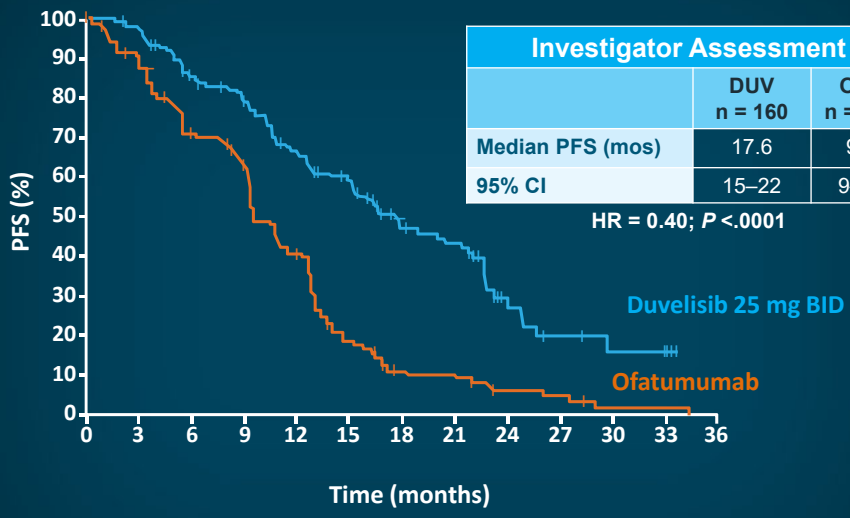
1. Sharman JP, et al. *Blood.* 2014;124(21): abstract 330. 2. FDA: idelalisib (www.cancernetwork.com/hematologic-malignancies/fda-approves-idelalisib-zydelig-three-types-blood-cancer). Accessed March 1, 2020.

## Duvelisib

- Dual PI3-K gamma + delta inhibitor
- Delta inhibition blocks the survival and proliferation of malignant B cells
- Gamma inhibition disrupts the recruitment and differentiation within the tumor microenvironment that support malignant B-cells

Flinn IW, et al. *Blood.* 2018;132:2446-2455.

# DUO Trial




| Investigator Assessment | DUV n = 160 | OFA n = 159 |
|---|---|---|
| Median PFS (mos) | 17.6 | 9.7 |
| 95% CI | 15–22 | 9–11 |

HR = 0.40; *P* <.0001

**Duvelisib was approved by FDA for treatment of relapsed CLL (September 2018)**

DUV = duvelisib; OFA = ofatumumab.

Flinn IW, et al. *Blood*. 2018;132:2446-2455. FDA: duvelisib approval (www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm621503.htm).

# Adverse Events with Idelalisib and Duvelisib

- Severe pneumonitis
  - Distinguish from infectious issues
    - Idelalisib: 4%
    - Duvelisib: 3%
- 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: 15%‡; 8%/2% 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; ‡includes both AST and ALT.

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

Idelalisib (Zydelig®) PI 2018 (www.gilead.com/~/media/Files/pdfs/medicines/oncology/zydelig/zydelig_pi.pdf). Flinn IW, et al. *Blood.* 2018;132: 2446-2455. Duvelisib (Copiktra®) PI 2019 (www.verastem.com/wp-content/uploads/2018/08/prescribing-information.pdf). FDA. 2016 (www.fda.gov/drugs/drug-safety-and-availability/fda-alerts-healthcare-professionals-about-clinical-trials-zydelig-idelalisib-combination-other). Accessed March 1, 2020.

## Summary of Therapeutic Options for *Relapsed/Refractory* CLL

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

## Patient Management and Shared Decision-Making

## 5 Essential Steps of Shared Decision-Making
## SHARE Approach


**It's all about communication!**

AHRQ Share Approach (www.ahrq.gov/sites/default/files/publications/files/share-approach_factsheet.pdf). Accessed March 1, 2020.

## 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

# THANK YOU

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

**TOOLKIT**

## Chronic Lymphocytic Leukemia (CLL)

### *Selected Guidelines, Recommendations, and Articles*

| Resource | Web Address |
|---|---|
| **National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Version 4.2020.** | https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf |
| **American Cancer Society: Cancer Facts and Figures 2020.** | https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2020.html |
| **American Cancer Society. Chronic Lymphocytic Leukemia (CLL).** | https://www.cancer.org/cancer/chronic-lymphocytic-leukemia.html |
| **National Cancer Institute. Chronic Lymphocytic Leukemia Treatment (PDQ®) – Health Professional Version.** | https://www.cancer.gov/types/leukemia/hp/cll-treatment-pdq |
| **Hallek M, et al; IWCLL. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood*. 2008;111:5446-5456.** | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2972576/ |
| **Döhner H, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. *N Engl J Med.* 2000;343:1910-1916.** | https://www.ncbi.nlm.nih.gov/pubmed/11136261 |
| **Hamblin TJ, et al. Unmutated Ig V(H) genes are associated with a more aggressive form of chronic lymphocytic leukemia. *Blood.* 1999;94:1848-1854.** | https://www.ncbi.nlm.nih.gov/pubmed/10477713 |
| **Byrd JC, et al. Up to 7 Years of Follow-up of Single-Agent Ibrutinib in the Phase 1b/2 PCYC-1102 Trial of First Line and Relapsed/Refractory Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. *Blood.* 2018;132(suppl 1):3133.** | https://ashpublications.org/blood/article/132/Supplement%201/3133/263863/Up-to-7-Years-of-Follow-up-of-Single-Agent |

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|---|---|
| **Byrd JC, et al. Acalabrutinib (ACP-196) in Relapsed Chronic Lymphocytic Leukemia. *N Engl J Med*. 2016;374:323-332.** | https://www.ncbi.nlm.nih.gov/pubmed/26641137 |
| **Sharman JP, et al. ELEVATE TN: Phase 3 study of acalabrutinib combined with obinutuzumab (O) or alone vs O plus chlorambucil in patients with treatment-naive chronic lymphocytic leukemia (CLL). *Blood*. 2019;134(suppl 1):31.** | https://ashpublications.org/blood/article/134/Supplement_1/31/427832/ELEVATE-TN-Phase-3-Study-of-Acalabrutinib-Combined |
| **Seymour JF, et al. Venetoclax-Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. *N Engl J Med*. 2018;378:1107-1120.** | https://www.ncbi.nlm.nih.gov/pubmed/29562156 |
| **Fischer K, et al. Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions. *N Engl J Med*. 2019;380:2225-2236.** | https://www.nejm.org/doi/full/10.1056/NEJMoa1815281 |
| **Sharman JP, et al. Second Interim Analysis of a Phase 3 Study of Idelalisib (ZYDELIG®) Plus Rituximab (R) for Relapsed Chronic Lymphocytic Leukemia (CLL): Efficacy Analysis in Patient Subpopulations with Del(17p) and Other Adverse Prognostic Factors. *Blood.* 2014;124(21):330.** | https://ashpublications.org/blood/article/124/21/330/97718/Second-Interim-Analysis-of-a-Phase-3-Study-of |
| **Flinn IW, et al. The phase 3 DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL. *Blood*. 2018;132:2446-2455.** | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6284216/ |

## *Selected Ongoing Clinical Trials*

| Resource | Web Address |
|---|---|
| **Standard Chemoimmunotherapy (FCR/BR) Versus Rituximab + Venetoclax (RVe) Versus Obinutuzumab (GA101) + Venetoclax (GVe) Versus Obinutuzumab + Ibrutinib + Venetoclax (GIVe) in Fit Patients With Previously Untreated Chronic Lymphocytic Leukemia (CLL) Without Del(17p) or TP53 Mutation (GAIA)**<br><br>**NCT02950051** | https://clinicaltrials.gov/ct2/show/NCT02950051 |

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|---|---|
| **A Study to Evaluate the Efficacy of Venetoclax in Relapsed/Refractory Participants With Chronic Lymphocytic Leukemia (CLL) Including Those With 17p Deletion or TP53 Mutation or Those Who Have Received a Prior B-cell Receptor Inhibitor. (VENICE I)**<br><br>**NCT02756611** | https://clinicaltrials.gov/ct2/show/NCT02756611 |
| **Acalabrutinib Safety Study in Untreated and Relapsed or Refractory Chronic Lymphocytic Leukemia Patients (ASSURE)**<br><br>**NCT04008706** | https://clinicaltrials.gov/ct2/show/NCT04008706 |
| **Testing The Addition of a New Anti-cancer Drug, Venetoclax, to the Usual Treatment (Ibrutinib and Obinutuzumab) in Untreated, Older Patients With Chronic Lymphocytic Leukemia**<br><br>**Ibrutinib and Obinutuzumab With or Without Venetoclax in Treating Patients With Chronic Lymphocytic Leukemia**<br><br>**NCT03737981; NCT03701282** | https://clinicaltrials.gov/ct2/show/NCT03737981<br><br>https://clinicaltrials.gov/ct2/show/NCT03701282 |
| **A Study of Zanubrutinib (BGB-3111) Versus Ibrutinib in Participants With Relapsed/Refractory Chronic Lymphocytic Leukemia (ALPINE)**<br><br>**NCT03734016** | https://clinicaltrials.gov/ct2/show/NCT03734016 |
| **A Study of the Combination of Ibrutinib Plus Venetoclax Versus Chlorambucil Plus Obinutuzumab for the First-line Treatment of Participants With Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)**<br><br>**NCT03462719** | https://clinicaltrials.gov/ct2/show/NCT03462719 |
| **Duvelisib and Venetoclax in Relapsed or Refractory CLL or SLL or RS**<br><br>**NCT03534323** | https://clinicaltrials.gov/ct2/show/NCT03534323 |

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|---|---|
| **Intermittent Duvelisib Dosing in Treating Patients With Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma**<br><br>**NCT03961672** | https://clinicaltrials.gov/ct2/show/NCT03961672 |

### *Resources for Patients*

| Resource | Address |
|---|---|
| **Lymphoma Research Foundation (LRF)—CLL/SLL.** | https://www.lymphoma.org/aboutlymphoma/cll/ |
| **Leukemia and Lymphoma Society (LLS)—CLL.** | https://www.lls.org/leukemia/chronic-lymphocytic-leukemia |
| **CLL Society.** | https://cllsociety.org/ |
| **American Cancer Society (ACS). CLL.** | https://www.cancer.org/cancer/chronic-lymphocytic-leukemia.html |
| **American Society of Clinical Oncology (ASCO)—Cancer.net. CLL.** | https://www.cancer.net/cancer-types/leukemia-chronic-lymphocytic-cll/view-all |
| **National Organization for Rare Disorders—CLL.** | https://rarediseases.org/rare-diseases/chronic-lymphocytic-leukemia/ |
| **CANCERcare.org. Veterans.** | https://www.cancercare.org/tagged/veterans |
| **National Cancer Institute. CLL – Patient Version.** | https://www.cancer.gov/types/leukemia/patient/cll-treatment-pdq |

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

**Acute Myeloid Leukemia (AML)**

**TOOLKIT**

## *Guidelines, Recommendations, and Articles*

| Resource | Web Address |
|---|---|
| **National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Acute Myeloid Leukemia. Version 3.2019.** | https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf |
| **American Cancer Society: Cancer Facts and Figures 2020.** | https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2020.html |
| **American Cancer Society. Acute Myeloid Leukemia (AML) in Adults.** | https://www.cancer.org/cancer/acute-myeloid-leukemia.html |
| **National Cancer Institute. Adult Acute Myeloid Leukemia Treatment (PDQ®) – Health Professional Version.** | https://www.cancer.gov/types/leukemia/hp/adult-aml-treatment-pdq |
| **O'Donnell MR, et al. Acute Myeloid Leukemia, Version 3.2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2017;15:926-957.** | https://jnccn.org/view/journals/jnccn/15/7/article-p926.xml |
| **Döhner H, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood.* 2017;129:424-447.** | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5291965/ |
| **DiNardo CD, et al. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. *Blood*. 2019;133:7-17.** | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6318429/ |
| **Lancet JE, et al. Final results of a phase III randomized trial of CPX-351 versus 7+3 in older patients with newly diagnosed high risk (secondary) AML. *J Clin Oncol.* 2016;34(15_suppl):7000.** | https://ascopubs.org/doi/abs/10.1200/JCO.2016.34.15_suppl.7000 |
| **Cortes JE, et al. Randomized comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome. *Leukemia*. 2019;33:379–389.** | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6365492/ |

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|---|---|
| **Stone RM, et al. Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a FLT3 Mutation. *N Engl J Med.* 2017;377:454-464.** | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5754190/ |
| **Perl AE, et al. Selective inhibition of FLT3 by gilteritinib in relapsed or refractory acute myeloid leukaemia: a multicentre, first-in-human, open-label, phase 1-2 study. *Lancet Oncol.* 2017;18:1061-1075.** | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5572576/ |
| **DiNardo CD, et al. Durable Remissions with Ivosidenib in IDH1-Mutated Relapsed or Refractory AML. *N Engl J Med.* 2018;378:2386-2398.** | https://www.ncbi.nlm.nih.gov/pubmed/29860938 |
| **Stein EM, et al. Enasidenib in mutant *IDH2* relapsed or refractory acute myeloid leukemia. *Blood.* 2017;130:722-731.** | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5572791/ |
| **Hills RK, et al. Addition of gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukaemia: a meta-analysis of individual patient data from randomised controlled trials. *Lancet Oncol.* 2014;15:986-996.** | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4137593/ |

## *Selected Ongoing Clinical Trials*

| Resource | Web Address |
|---|---|
| **A Global Study of the Efficacy and Safety of Midostaurin + Chemotherapy in Newly Diagnosed Patients With FLT3 Mutation Negative (FLT3-MN) Acute Myeloid Leukemia (AML)**<br><br>**NCT03512197** | https://clinicaltrials.gov/ct2/show/NCT03512197 |
| **A Trial of the FMS-like Tyrosine Kinase 3 (FLT3) Inhibitor Gilteritinib Administered as Maintenance Therapy Following Allogeneic Transplant for Patients With FLT3/Internal Tandem Duplication (ITD) Acute Myeloid Leukemia (AML)**<br><br>**NCT02997202** | https://clinicaltrials.gov/ct2/show/NCT02997202 |
| **Study of AG-120 (Ivosidenib) vs. Placebo in Combination With Azacitidine in Patients** | https://clinicaltrials.gov/ct2/show/NCT03173248 |

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|---|---|
| **With Previously Untreated Acute Myeloid Leukemia With an IDH1 Mutation (AGILE)**<br><br>**NCT03173248** | |
| **A Study Evaluating Intensive Chemotherapy With or Without Glasdegib or Azacitidine With or Without Glasdegib In Patients With Previously Untreated Acute Myeloid Leukemia (BRIGHT AML1019)**<br><br>**NCT03416179** | https://clinicaltrials.gov/ct2/show/NCT03416179 |
| **A Study of ASP2215 (Gilteritinib) by Itself, ASP2215 Combined With Azacitidine or Azacitidine by Itself to Treat Adult Patients Who Have Recently Been Diagnosed With Acute Myeloid Leukemia With a FLT3 Gene Mutation and Who Cannot Receive Standard Chemotherapy**<br><br>**NCT02752035** | https://clinicaltrials.gov/ct2/show/NCT02752035 |
| **Study of Crenolanib vs Midostaurin Following Induction Chemotherapy and Consolidation Therapy in Newly Diagnosed FLT3 Mutated AML**<br><br>**NCT03258931** | https://clinicaltrials.gov/ct2/show/NCT03258931 |
| **CD123/CLL1 CAR-T Cells for R/R AML (STPHI_0001)**<br><br>**NCT03631576** | https://clinicaltrials.gov/ct2/show/NCT03631576 |

### *Resources for Patients*

| Resource | Address |
|---|---|
| **National Cancer Institute. Adult AML Treatment (PDQ®)– Patient Version.** | https://www.cancer.gov/types/leukemia/patient/adult-aml-treatment-pdq |
| **Leukemia and Lymphoma Society—AML.** | https://www.lls.org/leukemia/acute-myeloid-leukemia |
| **American Cancer Society (ACS). AML in Adults.** | https://www.cancer.org/cancer/acute-myeloid-leukemia.html |
| **American Society of Clinical Oncology (ASCO)—Cancer.net. AML.** | https://www.cancer.net/cancer-types/leukemia-acute-myeloid-aml |
| **National Organization for Rare Disorders—AML.** | https://rarediseases.org/rare-diseases/acute-myeloid-leukemia/ |

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|---|---|
| **CANCERcare.org. Veterans.** | https://www.cancercare.org/tagged/veterans |
| **MedLinePlus. AML.** | https://medlineplus.gov/acutemyeloidleukemia.html |