# Dissecting the Decision: Clinical and Nursing Investigators Provide Practical Perspectives on Key Issues in Cancer Care

# Part 1 — Acute Myeloid Leukemia

**Tuesday, March 16, 2021**
**5:00 PM – 6:00 PM ET**

## Faculty

**Rhonda Hewitt, MSN, ANP, AOCNP**
**Mark Levis, MD, PhD**

## Moderator

**Neil Love, MD**

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Hematology Advanced Practice Provider
Stanford Health Care
Palo Alto, California

**Mark Levis, MD, PhD**
Director, Adult Leukemia Program
Co-Division Director, Hematologic Malignancies
Professor of Oncology
The Sidney Kimmel Comprehensive Cancer Center
Johns Hopkins Medicine
Baltimore, Maryland

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# Commercial Support

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# Dr Love — Disclosures

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# Ms Hewitt — Disclosures

No relevant conflicts of interest to disclose

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# Dr Levis — Disclosures

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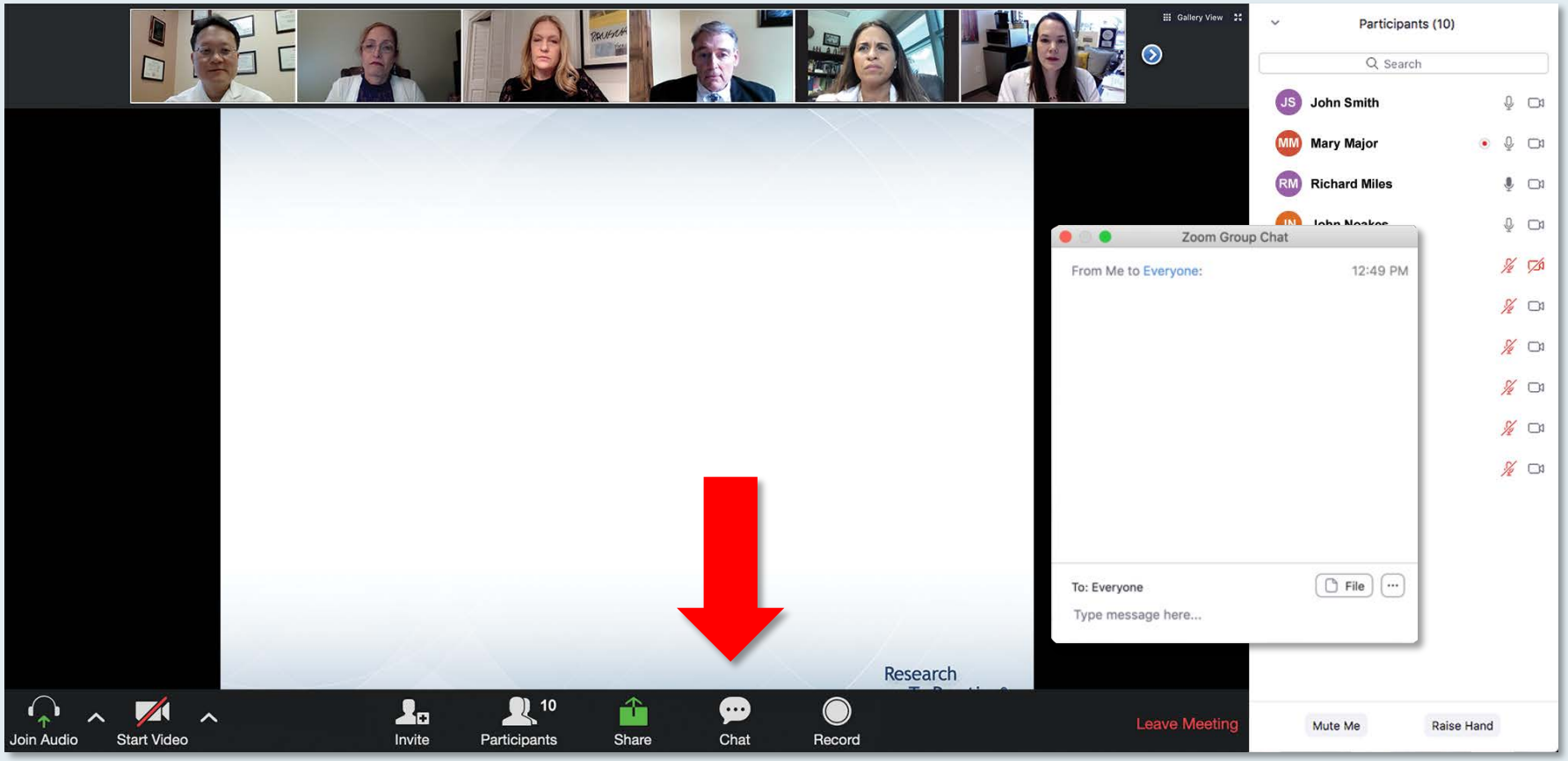
# We Encourage Clinicians in Practice to Submit Questions




**Feel free to submit questions now before the program begins and throughout the program.**

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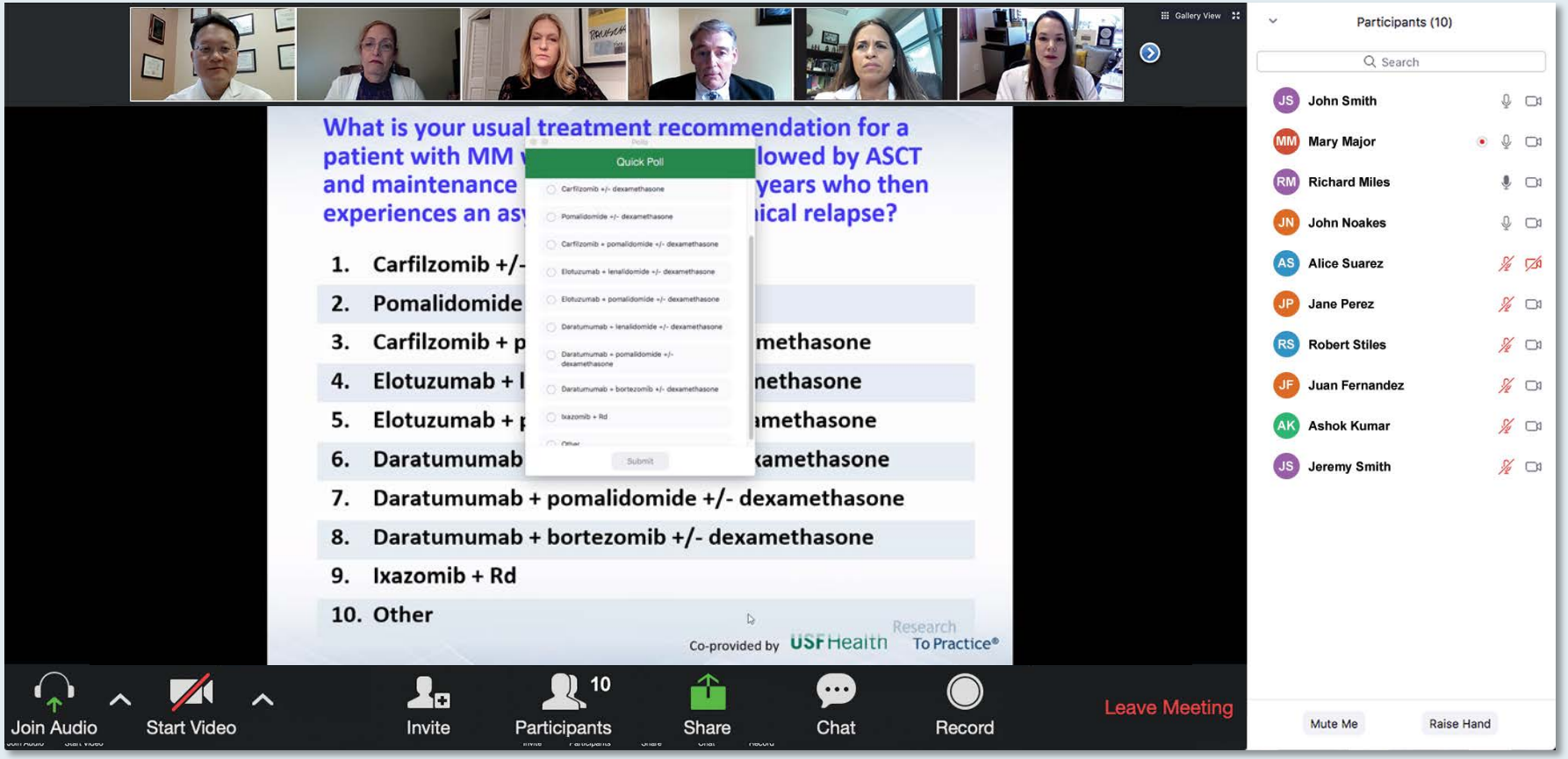
# Familiarizing Yourself with the Zoom Interface

## How to answer poll questions

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# ONCOLOGY TODAY

WITH DR NEIL LOVE

## ACUTE MYELOID LEUKEMIA WITH FLT3 MUTATIONS

DR KEITH PRATZ
UNIVERSITY OF PENNSYLVANIA

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# *Meet The Professor*

# Optimizing the Selection and Sequencing of Therapy for Patients with Advanced Gastrointestinal Cancers

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# Dissecting the Decision: Clinical and Nursing Investigators Provide Practical Perspectives on Key Issues in Cancer Care

# Part 2 — HER2-Positive Breast Cancer

**Thursday, March 18, 2021**
**5:00 PM – 6:00 PM ET**

## Faculty

**Jamie Carroll, APRN, MSN, CNP**
**Sara Hurvitz, MD**

## Moderator

**Neil Love, MD**

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# Cases from the Community: Investigators Discuss the Role of PARP Inhibition in the Care of Actual Patients with Ovarian Cancer

**Saturday, March 20, 2021**
**4:00 PM – 5:00 PM ET**

## Faculty

**Susana Banerjee, MBBS, MA, PhD**
**Richard T Penson, MD, MRCP**
**Shannon N Westin, MD, MPH**

## Moderator

**Neil Love, MD**

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# Optimizing the Selection and Sequencing of Therapy for Patients with Renal Cell Carcinoma

**Thursday, March 25, 2021**
**5:00 PM – 6:00 PM ET**

## Faculty

**Robert J Motzer, MD**

## Moderator

**Neil Love, MD**

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# *Meet The Professor*

# Management of Chronic Lymphocytic Leukemia

**Monday, March 29, 2021**
**5:00 PM – 6:00 PM ET**

## Faculty

**Philip A Thompson, MB, BS**

## Moderator

**Neil Love, MD**

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# *Meet The Professor*

# Immunotherapy and Novel Agents in Gynecologic Cancers

**Monday, April 5, 2021**
**5:00 PM – 6:00 PM ET**

## Faculty

**Bradley J Monk, MD**

## Moderator

**Neil Love, MD**

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*Thank you for joining us!*

*NCPD credit information will be emailed to each participant within 3 business days.*

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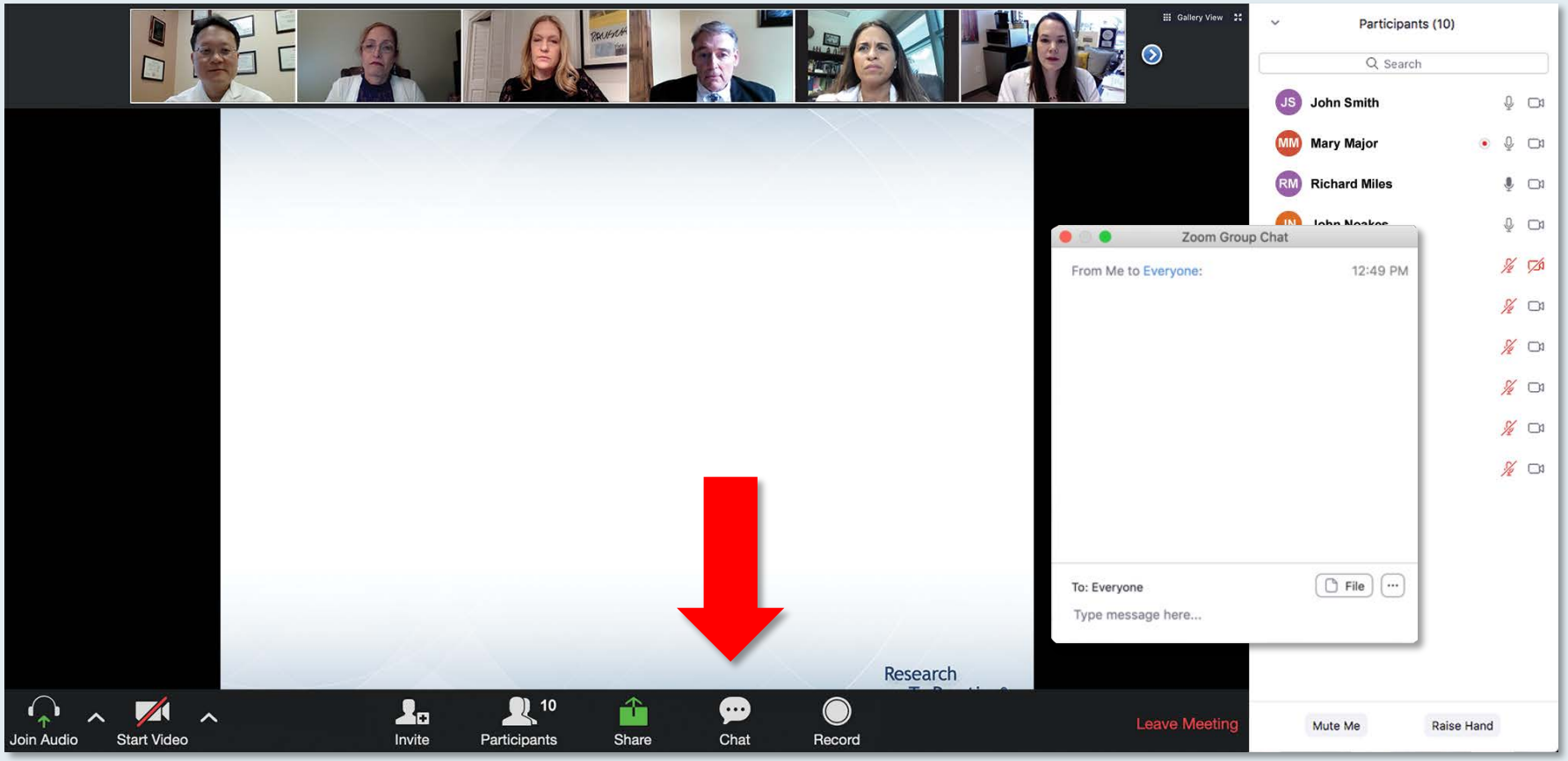


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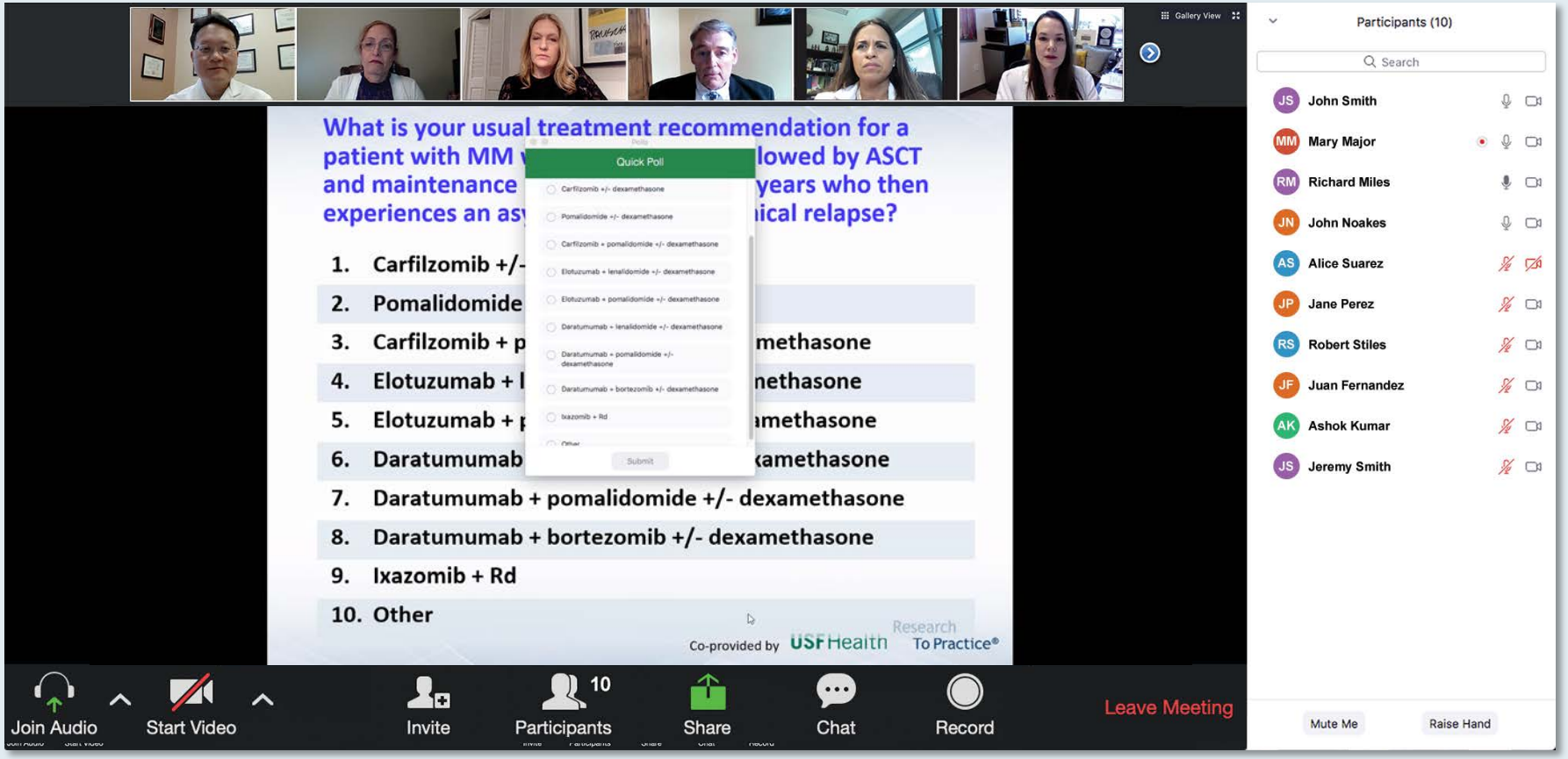


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# Agenda

Case Presentation: Ms Hewitt — An 81-year-old man with newly diagnosed poor-risk AML

Module 1: Molecular Evaluation of Patients with Newly Diagnosed AML

Module 2: Venetoclax Combinations; Management of Tumor Lysis Syndrome

Case Presentation: Dr Levis — An 82-year-old man with AML and a FLT3 ITD mutation

Module 3: Management of AML with FLT3 Mutation

Module 4: Management of AML with IDH Mutation

Module 5: Other Novel Agents and Strategies

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# Research To Practice
# First Annual Oncology Nursing Retreat

## Friday, November 8, 2019

**Moderator**
Neil Love, MD

**Keynote Panel: AML**
**Rhonda Hewitt, MSN, RN, ANP-BC, AOCNP**
**Daniel A Pollyea, MD, MS**
**Eytan M Stein, MD**
**Lauren Ziskind, APN, NP-C, OCN**


combination

*“Completely game changing. I mean, I like to say the outpatient management of AML almost used to not exist. There was no place for it. You were seeing people in long-term remission or they were in the hospital. So we actually have an AML clinic now and it's a place where instead of having end-of-life discussions and talking about hospice and goals of care, you're talking about the future and their 38 grandchildren and their vacation. So it's completely changed everything.”*

Daniel A Pollyea, MD, MS

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# Ms Hewitt Case #1

- 81 yo man with poor-risk AML (complex karyotype & p53/TET2 mutations) presents with his wife & 2 adult children to Hematology Clinic to discuss options for his newly diagnosed AML
- HPI Summary
  - 5.5 yr h/o mild thrombocytopenia
  - Increasing fatigue & SOBOE over past month
  - PCP orders fatigue w/u with CBCD, thyroid studies, iron studies
  - CBCD with pancytopenia
  - BMBx reveals AML evolving from MDS

# Ms Hewitt Case #1

- Impression/Plan
  - Poor-risk AML (complex karyotype & p53/TET2 mutations)
  - We discussed the diagnosis, natural history, prognosis, & treatment of AML
  - We discussed that AML is an incurable, life threatening, aggressive disease
  - We explained that our goal would be to control the disease the best we can
  - We explained that high-dose chemotherapy would not be an option given his age & comorbidities
  - Treatment options included low-intensity therapy with HMA/venetoclax, clinical trial, supportive care

# Ms Hewitt Case #1

- Important to patient & his family
  - Patient feels he is still contributing to society
  - Wants to continue to work as CPA
  - Not ready for/interested in supportive care only option
  - Not interested in clinical trial as it would necessitate he receive therapy at a different medical center which is farther from home
  - Prefers the “known” expected responses & SEs with SOC decitabine + venetoclax
  - Hoping to maintain his active lifestyle including hobby of bridge photography for which he has an upcoming trip planned

# Ms Hewitt Case #1

- He decides to proceed with decitabine + venetoclax
- When starting a patient on therapy we educate about potential SE's
  - Cytopenias requiring transfusion support & dose adjustments/interruptions
  - Risk of life threatening infections +/- bleeding complications
  - Fatigue from therapy
  - GI toxicities
  - Need to protect & monitor for TLS, AKI, other organ toxicities
  - Medication adherence with oral therapies
- Patients generally get a little sicker before they get better → unique to our area of medicine
- I also like to stress the importance of communication, open dialogue so we can help get patients through therapy

# Ms Hewitt Case #1

- 6/6/19 C1D1 5-day decitabine + venetoclax. Complicated by prolonged neutropenia
- 7/1/19 BMBx no morphologic evidence of leukemia, 0.2% abnormal blasts by MRD flow consistent with morphologic leukemia-free state
- 7/3/19 C2D1 Dec/Ven with 25% dose reduction due to cytopenias & MLFS
  - → received only 3 days due to neutropenic fever hospitalization
- 8/1/19 C3D1 dose reduced Dec + Ven
- 9/5/19 C4D1 with further dose reduction due to recurrent neutropenia → Dec 5 to 4 days & Ven 28 to 14 days

# Ms Hewitt Case #1

Key management points with patient & family:

- Balancing disease control and toxicities of therapy
  - Fatigue, nausea, myelosuppression, RLE cellulitis
- Much support through necessary dose reductions
  - Ongoing discussions re cause of myelosuppression → therapy vs disease progression
    - Possible BMBx if persists/worsens
  - Education/scheduling of labs & transfusion support
- Education on neutropenia & reportable symptoms/problems
- Maintaining roles while undergoing therapy → very important to patient to continue to work part time
- Ongoing participation in important life events → patient has upcoming vacation plans to go on a photography trip. C5D1 delayed to accommodate this important event

# Agenda

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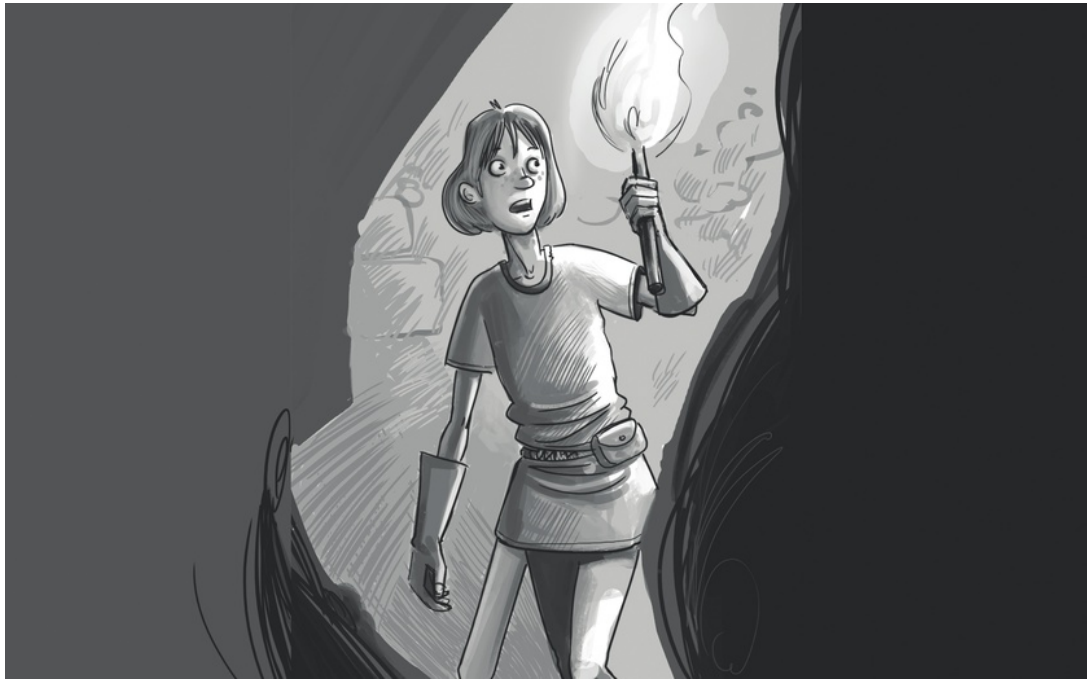
Module 5: Other Novel Agents and Strategies

# Interpreting Bone Marrow Biopsy Tests

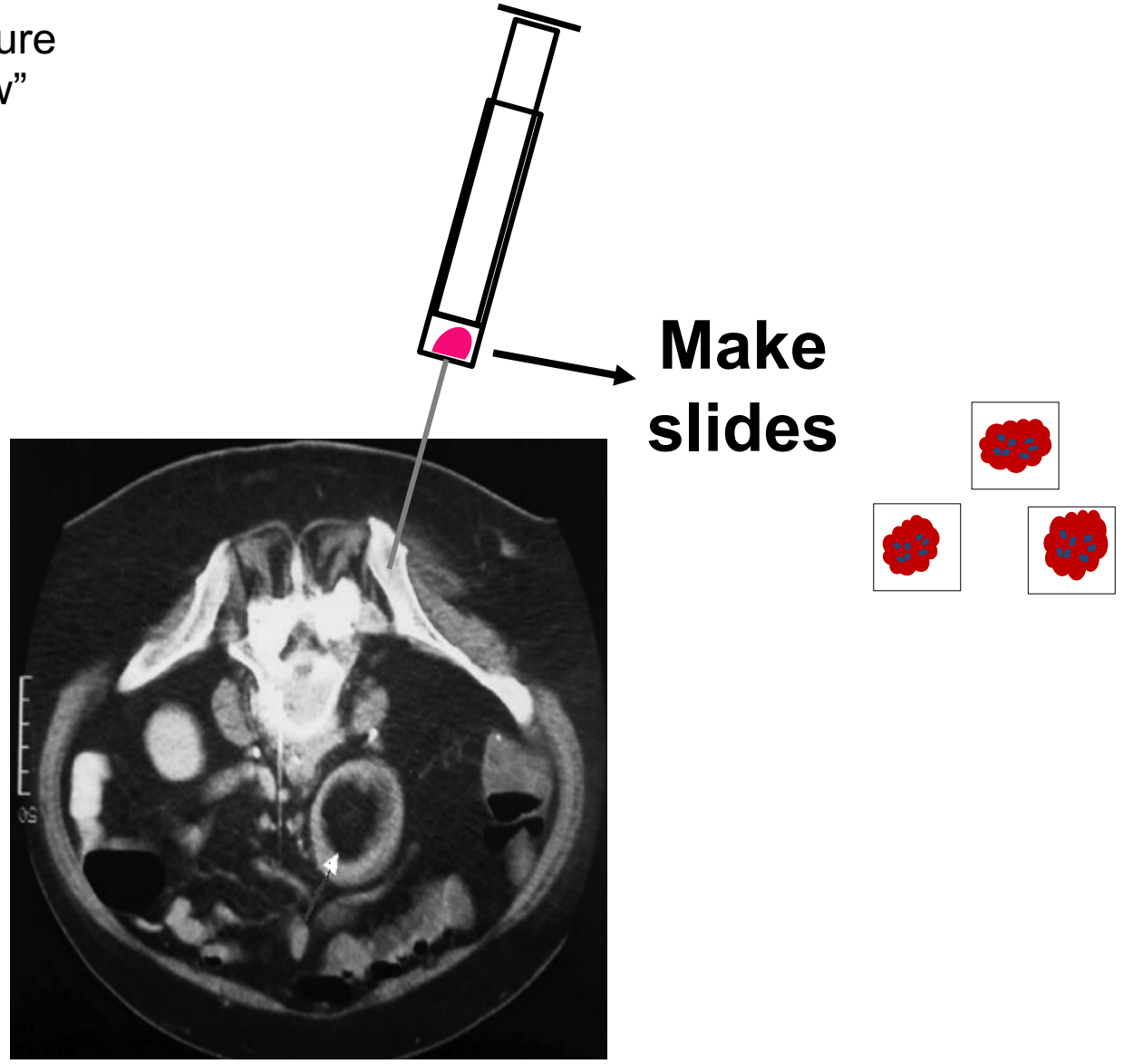


*Into a murky world. . . . .*

Courtesy of Mark Levis, MD, PhD

# First pull:

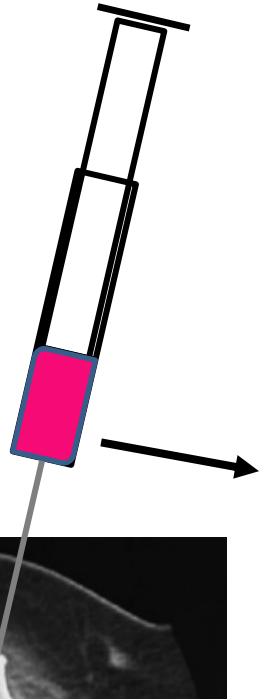
"The pure marrow"

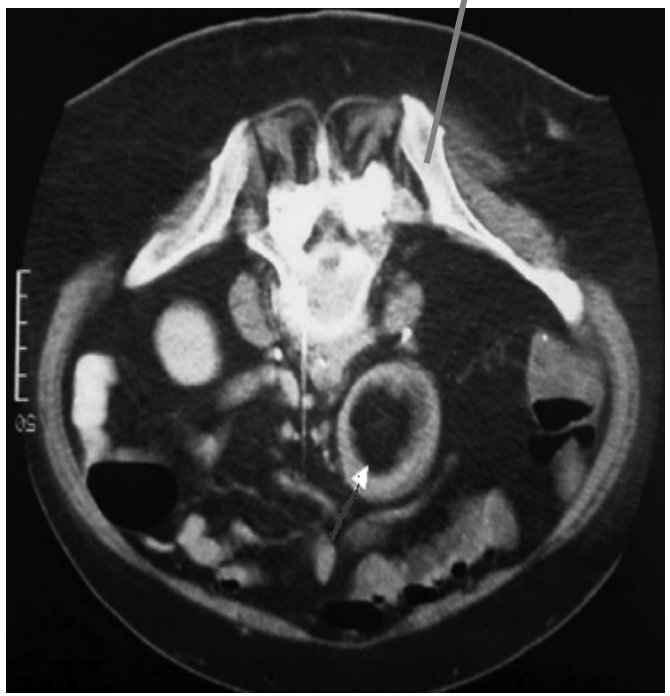



Courtesy of Mark Levis, MD, PhD

# Second pull:

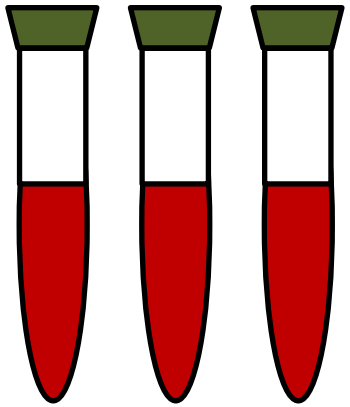
(Usually minimal contamination with peripheral blood)





## ~10-15 cc liquid marrow aspirate

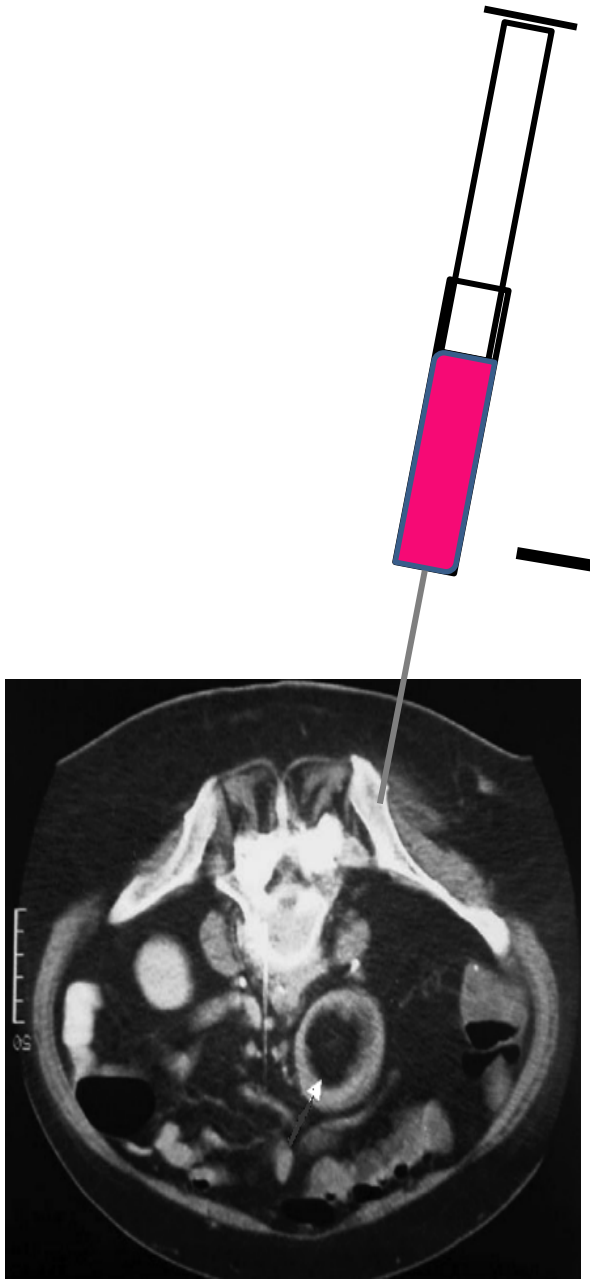
This is usually for standard clinical studies.



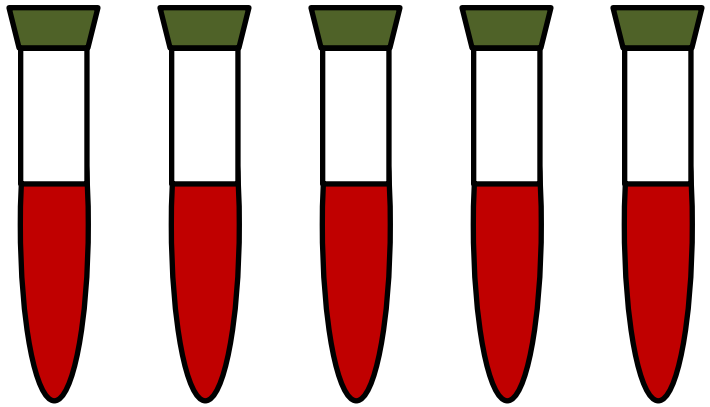
Courtesy of Mark Levis, MD, PhD

# Third pull:

(Usually LOTS of contamination
with peripheral blood)

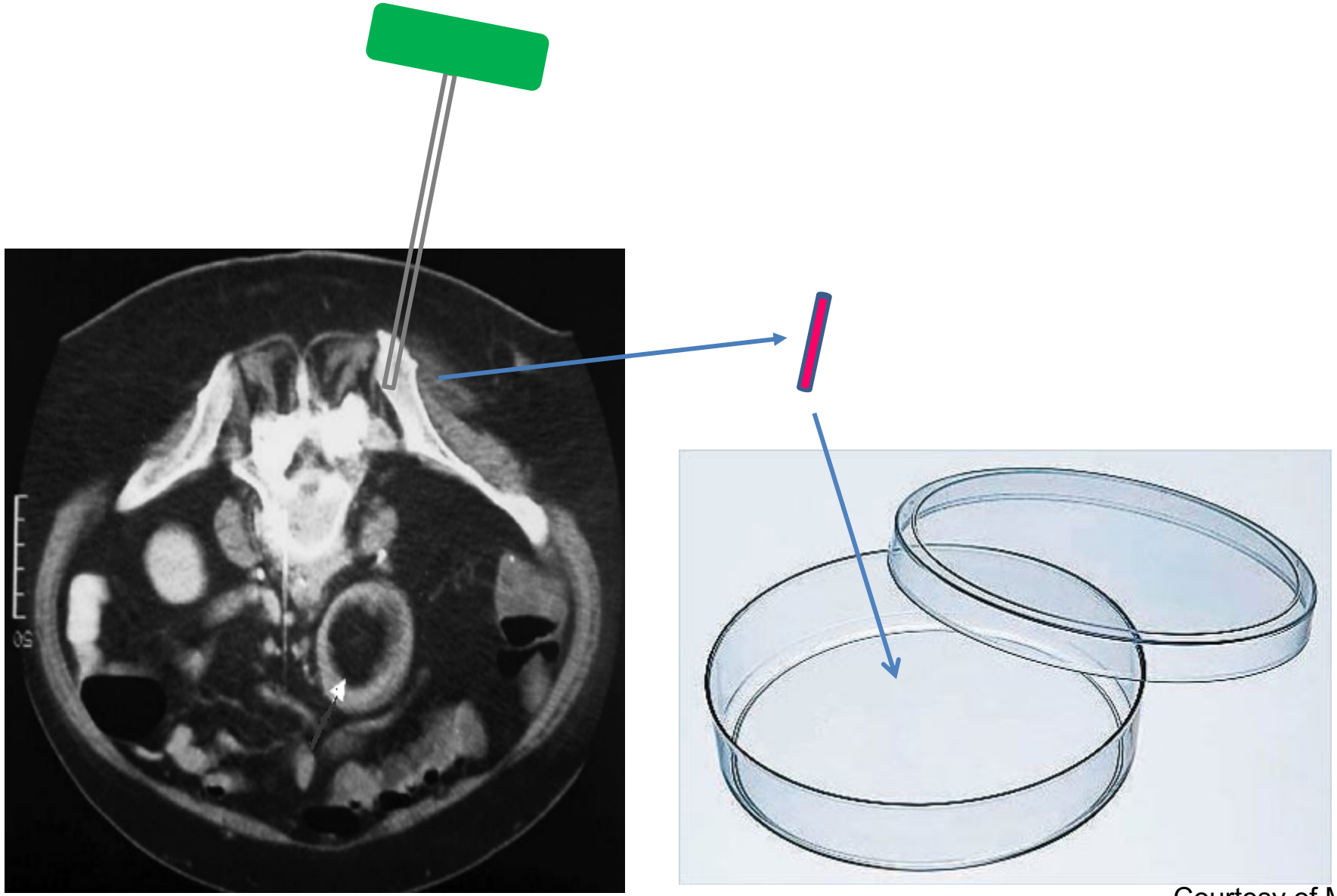


**“Research studies”**



Courtesy of Mark Levis, MD, PhD

# The core biopsy

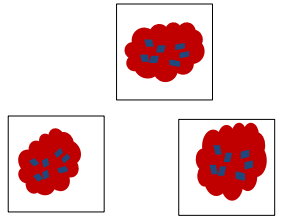


Courtesy of Mark Levis, MD, PhD

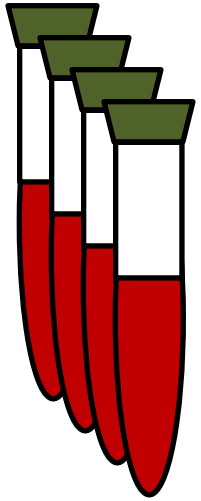
# What do we get when the procedure is over?

- A small cylinder of bone…

- A few glass coverslips with marrow aspirate…



- Vacutainer tubes with marrow aspirate…

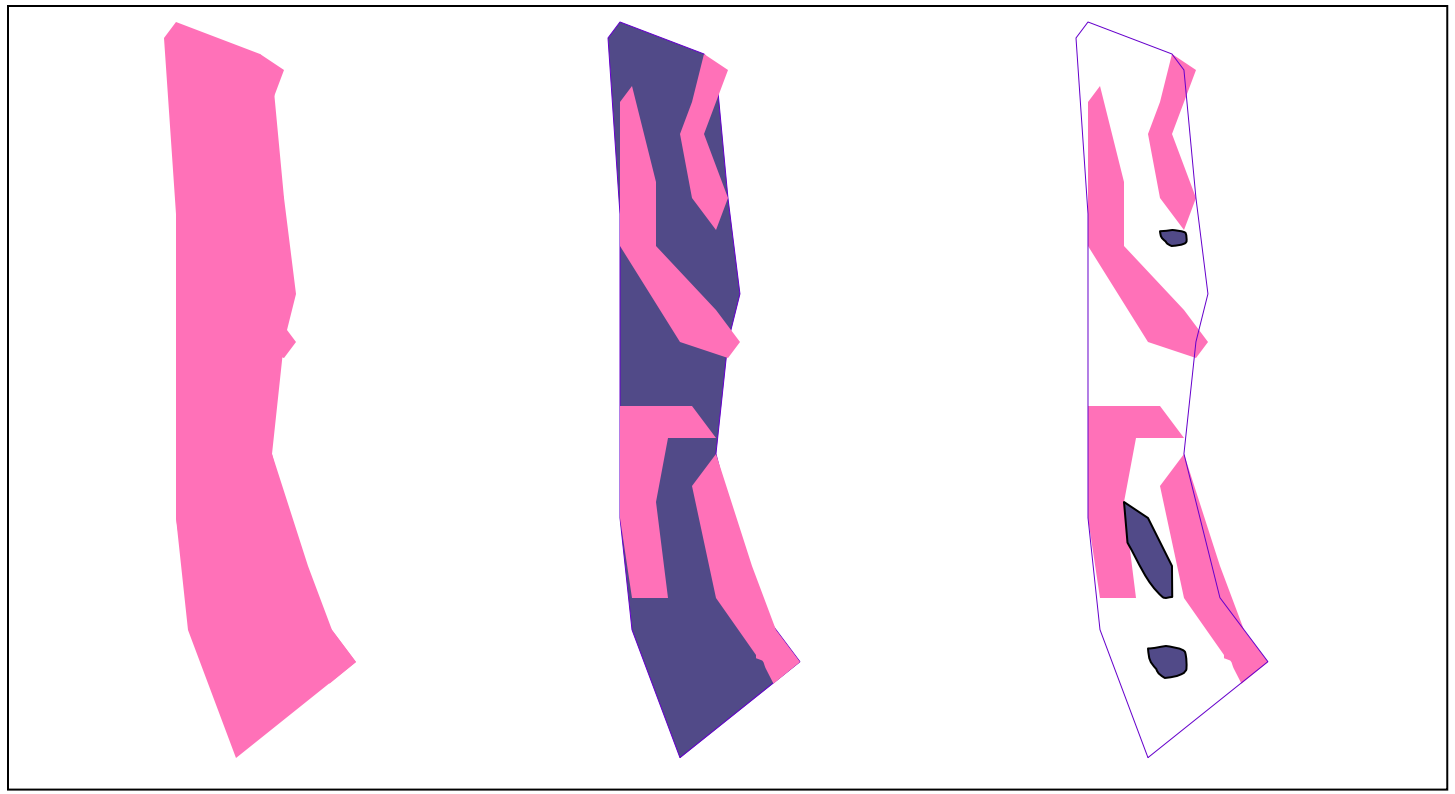


- An angry/frightened/over-sedated patient…

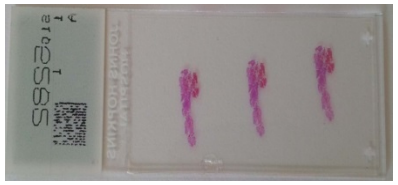
- The bone marrow tech shaking their head as they push the cart out of the room.

Courtesy of Mark Levis, MD, PhD

# Core Biopsy:

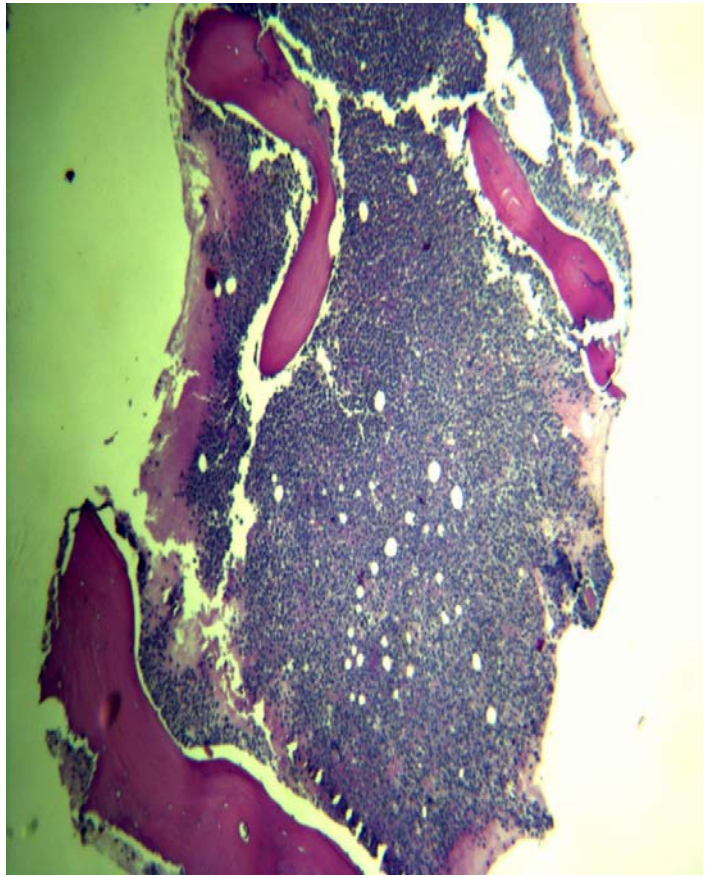


Cellular or Hypercellular  Hypocellular

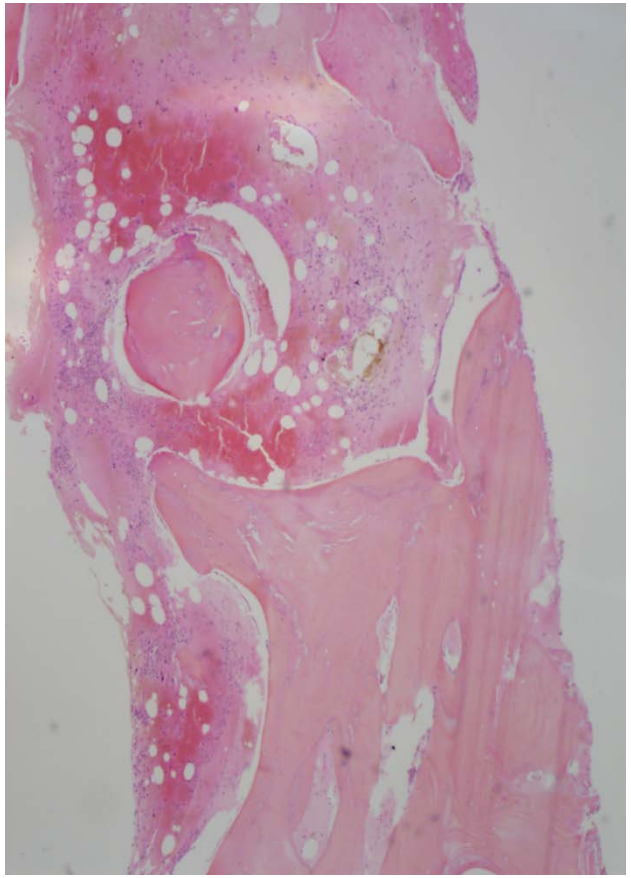


Courtesy of Mark Levis, MD, PhD

# The core biopsy sample is used to estimate the cellularity of the marrow.



**Hypercellular (i.e., packed)**

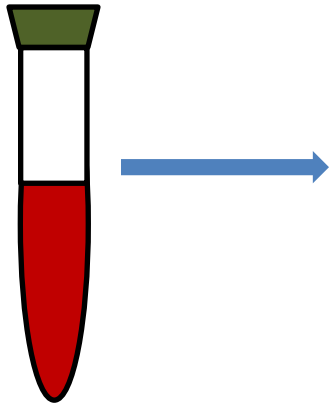


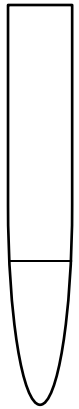
**Hypocellular (i.e., empty)**

Courtesy of Mark Levis, MD, PhD

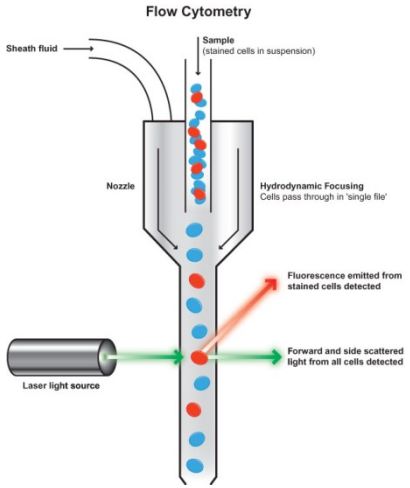
# Next: Flow cytometry

Freshly obtained aspirate





Isolate the white blood cells and stain with antibodies.

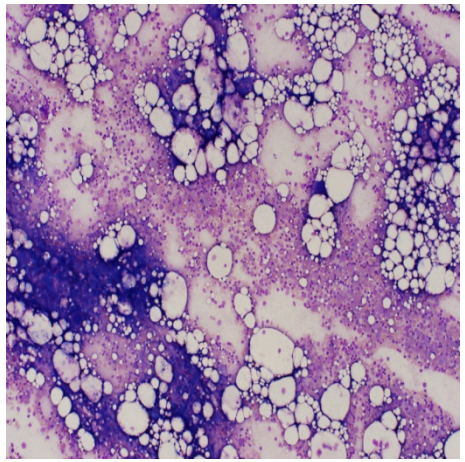


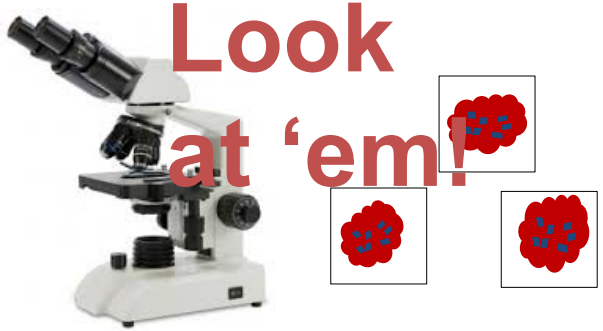

Analyze the results

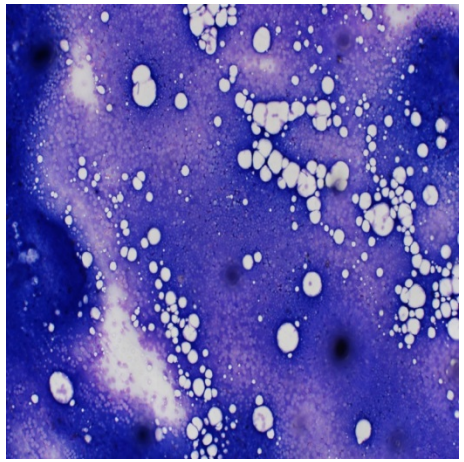
The entire process takes 1-2 hours…

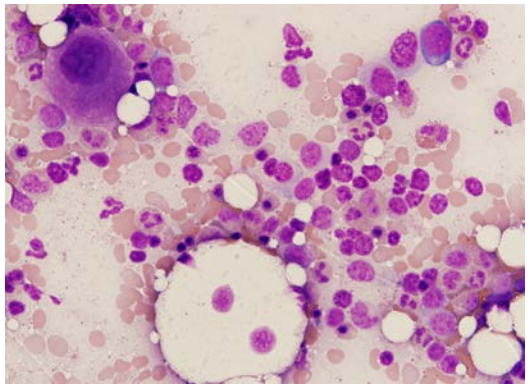
Courtesy of Mark Levis, MD, PhD

# What do we do with the aspirate slides?



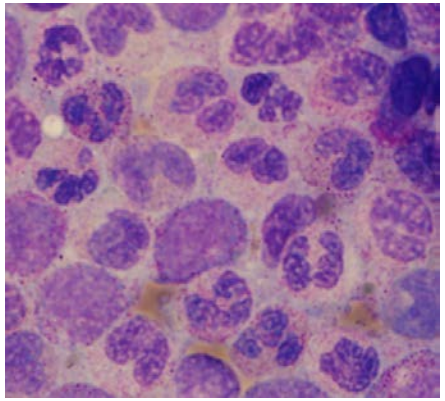


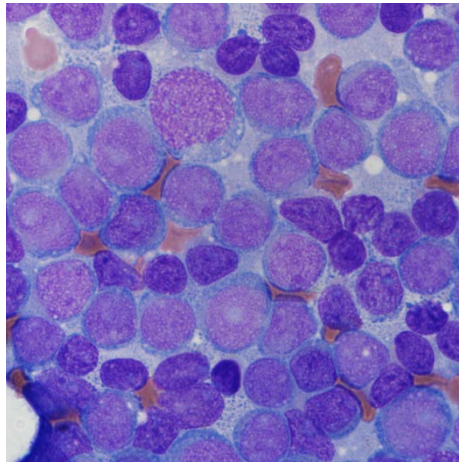


Good!

Bad…



- Visually inspect the aspirate to make sure it really is bone marrow and not blood.
- Count the number of blasts as a percentage (this is termed a "Differential").
- Compare what you see with the results of the core biopsy and flow cytometry.



Courtesy of Mark Levis, MD, PhD

# Three reasons for improvements in survival for AML patients

- Supportive care improved
- Therapy is tailored to fit the patient and the disease
- Improvements in allogeneic transplant techniques

Courtesy of Mark Levis, MD, PhD

# Targeted agents to treat AML

- Gemtuzumab ozogamicin
- IDH inhibitors
- FLT3 inhibitors
- Venetoclax
- Glasdegib

Courtesy of Mark Levis, MD, PhD

# Agenda

Case Presentation: Ms Hewitt — An 81-year-old man with newly diagnosed poor-risk AML

Module 1: Molecular Evaluation of Patients with Newly Diagnosed AML

**Module 2: Venetoclax Combinations; Management of Tumor Lysis Syndrome**

Case Presentation: Dr Levis — An 82-year-old man with AML and a FLT3 ITD mutation

Module 3: Management of AML with FLT3 Mutation

Module 4: Management of AML with IDH Mutation

Module 5: Other Novel Agents and Strategies

# Which of the following agents is FDA approved in combination with venetoclax for acute myeloid leukemia (AML)?

1. Decitabine
2. Azacitidine
3. Low-dose cytarabine
4. All of the above
5. Only 1 and 2
6. I don’t know

# Venetoclax-based combination regimens are currently approved for AML in…

1. All patients
2. Patients who are not candidates for intensive chemotherapy
3. I don’t know

**All patients with AML who are receiving venetoclax in combination with a hypomethylating agent should be admitted to the hospital to begin treatment and receive tumor lysis syndrome prophylaxis, regardless of disease burden or performance status.**

1. Agree
2. Disagree
3. I don't know

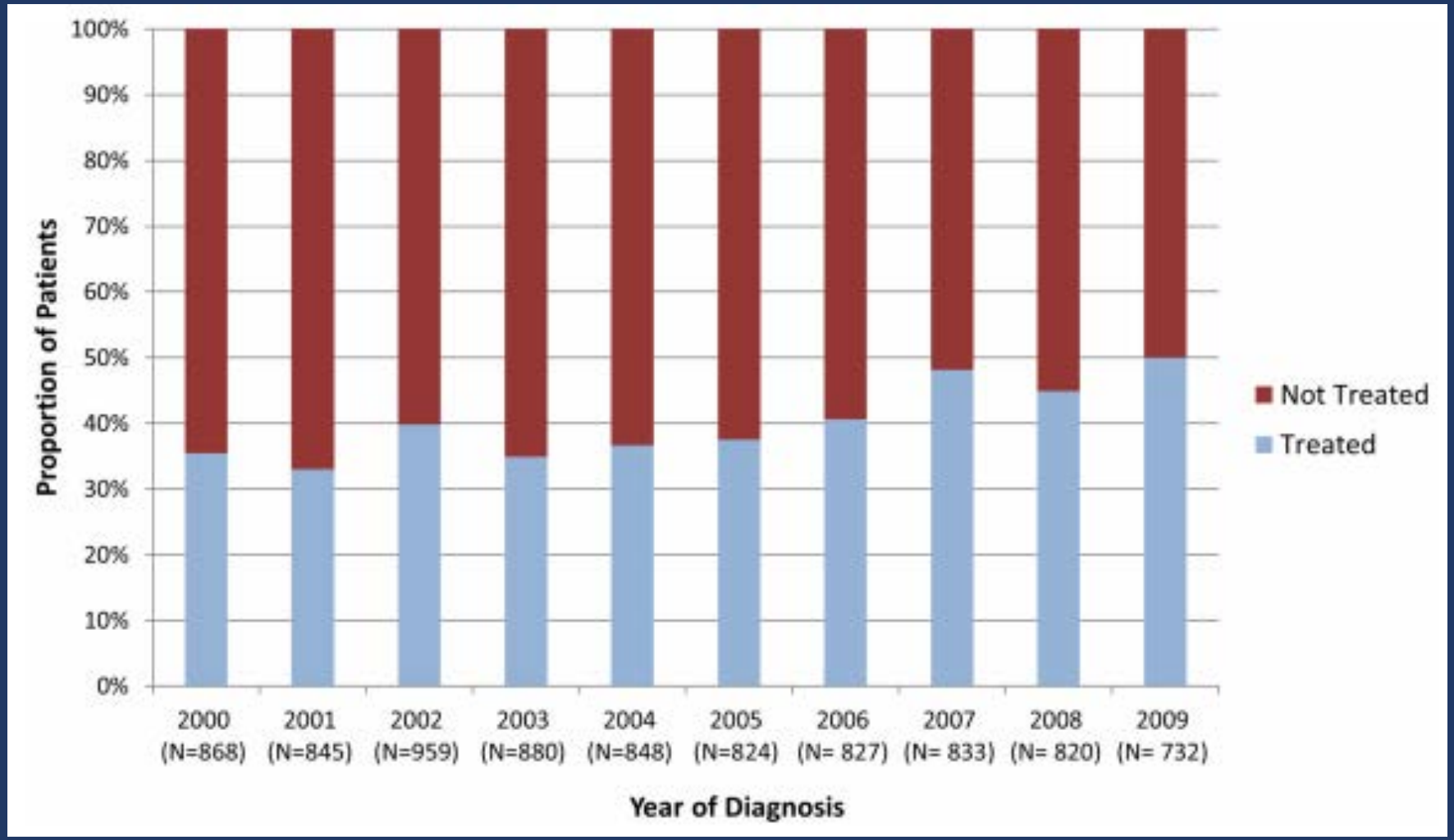
RTP
RESEARCH
TO PRACTICE

# Treating the older acute leukemia patient

Testa di Vecchio; Camillo Boccaccino; 1530

Courtesy of Mark Levis, MD, PhD

# The Reality for Older Patients with AML




Medeiros et al, Ann Hematol 2015

# Rationale for BCL-2 Inhibition in AML

- Targeting BCL-2 may allow for apoptosis to be restored
- BCL-2 overexpression associated with worse outcomes in AML, and higher resistance to conventional therapy
- But BCL-2 overexpression not universal in AML

**Additional rationale for targeting BCL-2 in AML?**

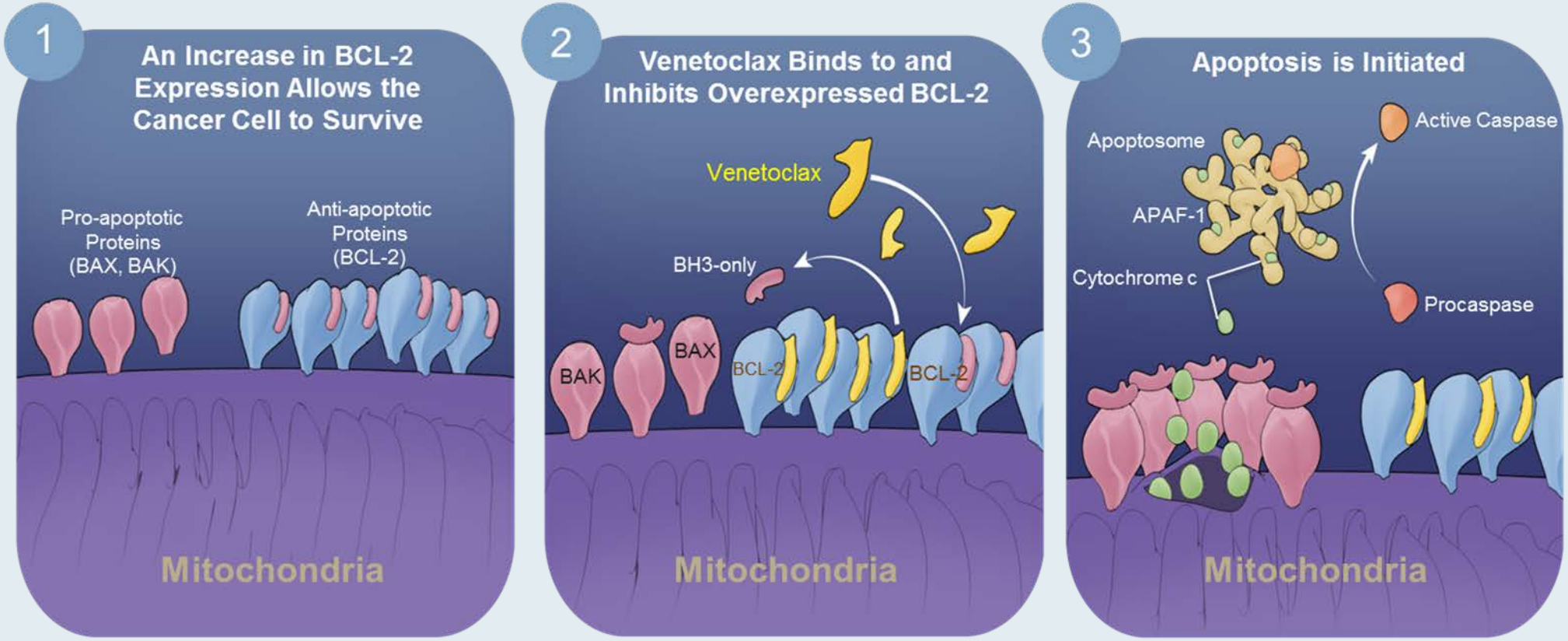
Karakas et al. Annals of Oncology 1998
Lauria et al. Leukemia 1997
Campos et al. Blood 1993
Certo, Letai et al. Cancer Cell 2006

Courtesy of Daniel A Pollyea, MD, MS

# Venetoclax

Courtesy of Mark Levis, MD, PhD

# Venetoclax Mechanism of Action




- Cancer cells increase the expression of anti-apoptotic proteins to offset the increase in pro-apoptotic proteins, tipping the balance toward cell survival
- The large # of pro-apoptotic proteins bound and sequestered by Bcl-2 in AML make them “primed” for death

Kumar S et al. ASCO 2015;Abstract 8576.

# FDA Grants Regular Approval to Venetoclax in Combination for Untreated Acute Myeloid Leukemia

## Press Release – October 16, 2020

"The Food and Drug Administration granted regular approval to venetoclax in combination with azacitidine, decitabine, or low-dose cytarabine (LDAC) for newly-diagnosed acute myeloid leukemia (AML) in adults 75 years or older, or who have comorbidities precluding intensive induction chemotherapy.

Venetoclax was initially granted accelerated approval for this indication in November 2018.

Efficacy was confirmed in two randomized, double-blind, placebo-controlled trials in patients with AML described above.

In VIALE-A (NCT02993523), patients were randomized to receive venetoclax plus azacitidine (n=286) or placebo plus azacitidine (n=145). Efficacy was established based on an improvement in overall survival (OS).

In VIALE-C (NCT03069352), patients were randomized to receive venetoclax plus LDAC (n=143) or placebo plus LDAC (n=68). Efficacy was based on CR rate and duration of CR."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-regular-approval-venetoclax-combination-untreated-acute-myeloid-leukemia

*N Engl J Med* 2020;383:617-29.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 13, 2020 VOL. 383 NO. 7

# Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia

C.D. DiNardo, B.A. Jonas, V. Pullarkat, M.J. Thirman, J.S. Garcia, A.H. Wei, M. Konopleva, H. Döhner, A. Letai, P. Fenaux, E. Koller, V. Havelange, B. Leber, J. Esteve, J. Wang, V. Pejsa, R. Hájek, K. Porkka, Á. Illés, D. Lavie, R.M. Lemoli, K. Yamamoto, S.-S. Yoon, J.-H. Jang, S.-P. Yeh, M. Turgut, W.-J. Hong, Y. Zhou, J. Potluri, and K.W. Pratz

# VIALE-A Study Design

(NCT02993523)

## Eligibility

**Inclusion**

- Patients with newly diagnosed confirmed AML
- Ineligible for induction therapy defined as **either**
  - ❖ ≥75 years of age
  - ❖ 18 to 74 years of age with at least one of the comorbidities:
    - CHF requiring treatment or Ejection Fraction ≤50%
    - Chronic stable angina
    - DLCO ≤65% or $FEV_1$ ≤65%
    - ECOG 2 or 3

**Exclusion**

- Prior receipt of any HMA, venetoclax or chemotherapy for myelodysplastic syndrome
- Favorable risk cytogenetics per NCCN
- Active CNS involvement

**Randomization 2:1**
**N = 433***

## Treatment

**Venetoclax + Azacitidine**
**(n = 286)**
**Venetoclax 400 mg PO, daily, days 1–28 +**
**Azacitidine 75 mg/m² SC /IV days 1–7**

**Placebo + Azacitidine**
**(n = 145)**
**Placebo daily, days 1–28**
**+ Azacitidine 75 mg/m² SC /IV days 1–7**

## Endpoints

**Primary**

- Overall survival

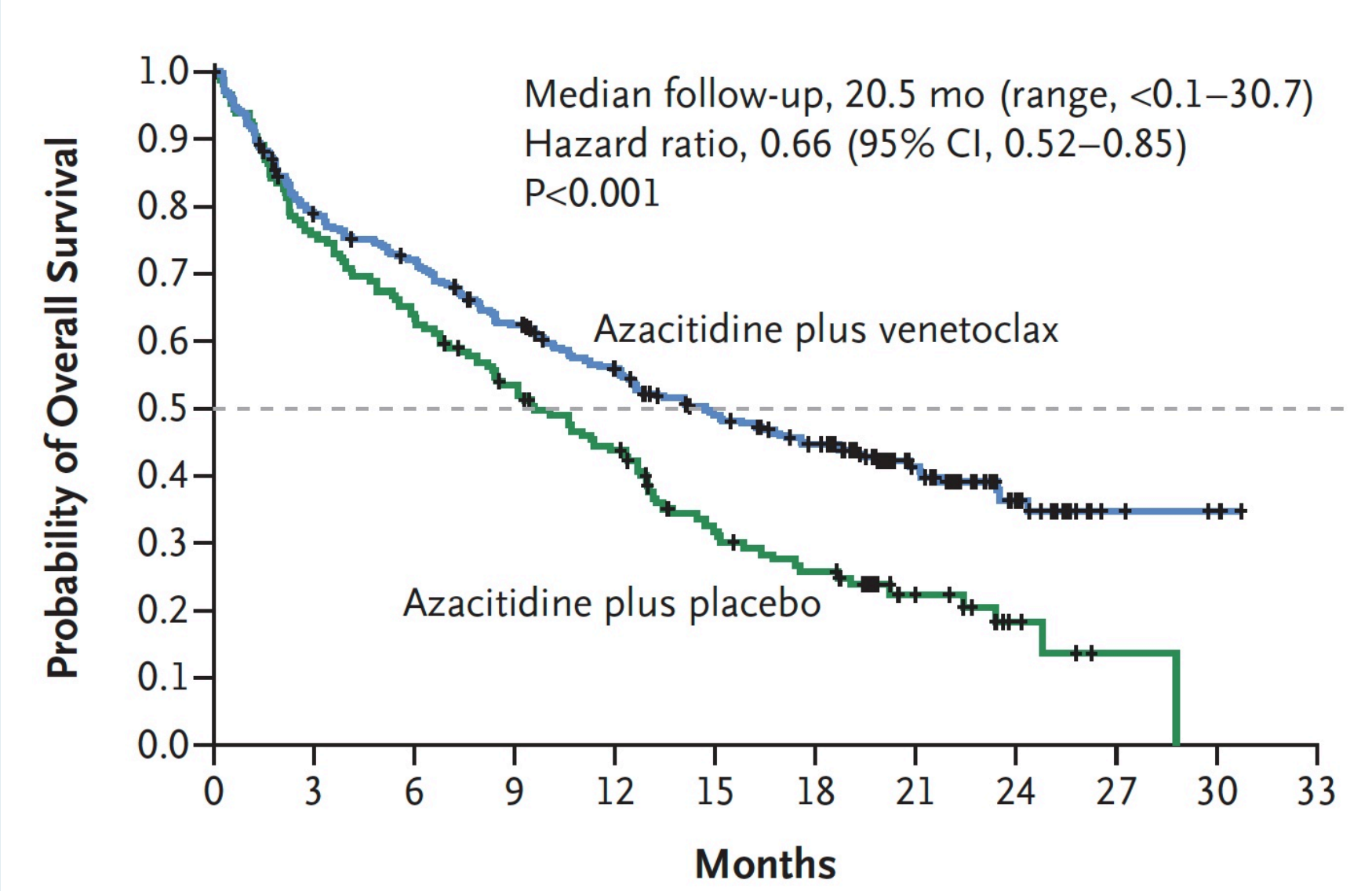
**Secondary**

- CR+CRi rate
- CR+CRh rate
- CR+CRi and CR+CRh rates by initiation of cycle 2
- CR rate
- Transfusion independence
- CR+CRi rates and OS in molecular subgroups
- Event-free survival

| | |
|---|---|
| **Randomization stratification factors** | Age (<75 vs ≥75 years); Cytogenetic risk (intermediate, poor); Region |
| **Venetoclax dosing ramp-up** | **Cycle 1 ramp-up** Day 1: 100 mg, Day 2: 200 mg, Day 3-28: 400 mg<br>**Cycle 2** Day 1-28: 400 mg |

DiNardo CD et al. *N Engl J Med* 2020;383:617-29.

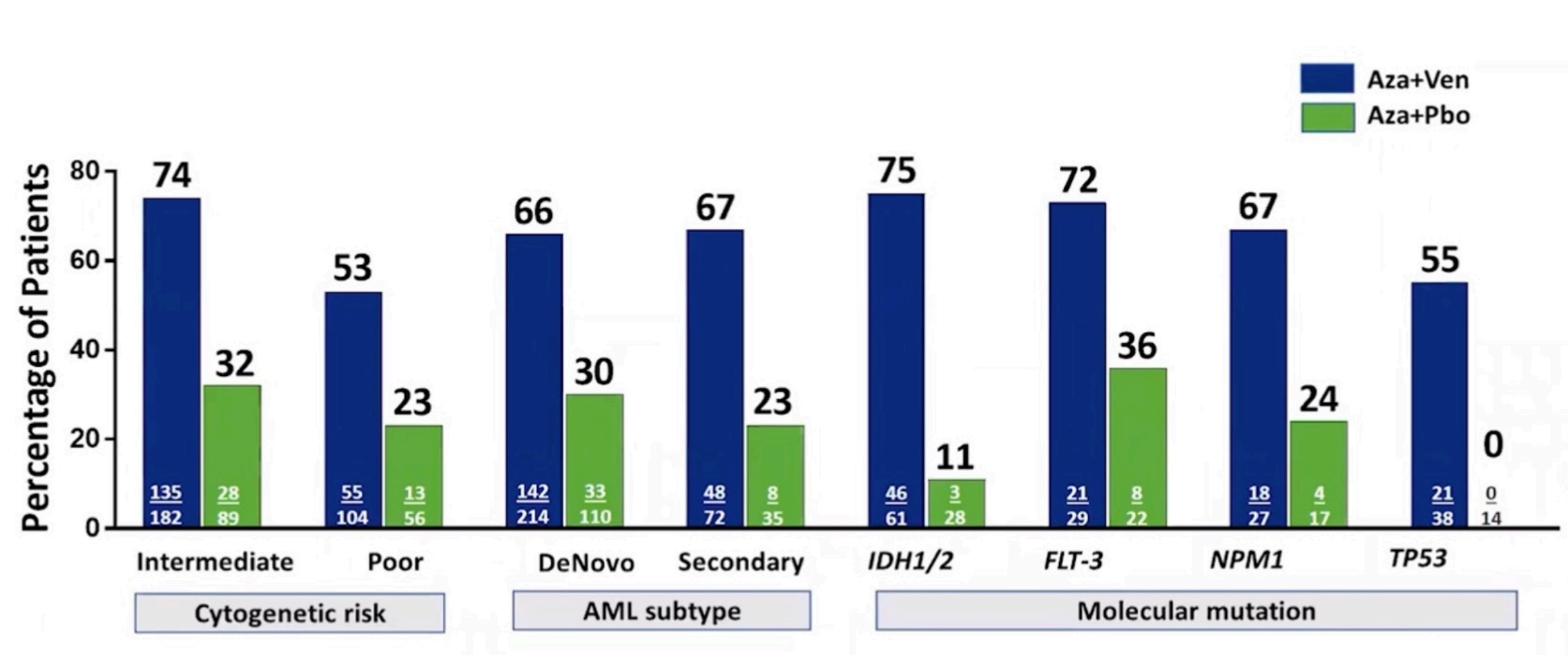
# VIALE-A: Overall Survival (N = 431)




DiNardo CD et al. *N Engl J Med* 2020;383:617-29.

RTP RESEARCH TO PRACTICE

# VIALE-A: Response Rates (CR + CRi) Subgroups




DiNardo C et al. EHA 2020;Abstract LB2601.

# VIALE-A: Selected Key AML Serious Adverse Events

| Event | Azacitidine–Venetoclax Group (N = 283) | | Azacitidine–Placebo Group (N = 144) | |
|---|---|---|---|---|
| | All Grades† | ≥Grade 3‡ | All Grades† | ≥Grade 3‡ |
| | *number of patients (percent)* | | | |
| Serious adverse events§ | 235 (83) | 232 (82) | 105 (73) | 102 (71) |
| Febrile neutropenia | 84 (30) | 84 (30) | 15 (10) | 15 (10) |
| Anemia | 14 (5) | 14 (5) | 6 (4) | 6 (4) |
| Neutropenia | 13 (5) | 13 (5) | 3 (2) | 3 (2) |
| Atrial fibrillation | 13 (5) | 10 (4) | 2 (1) | 2 (1) |
| Pneumonia | 47 (17) | 46 (16) | 32 (22) | 31 (22) |
| Sepsis | 16 (6) | 16 (6) | 12 (8) | 12 (8) |

DiNardo CD et al. *N Engl J Med* 2020;383:617-29.

blood®
Regular Article

CLINICAL TRIALS AND OBSERVATIONS

# Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial

Andrew H. Wei,[1,2] Pau Montesinos,[3,4] Vladimir Ivanov,[5] Courtney D. DiNardo,[6] Jan Novak,[7,8] Kamel Laribi,[9] Inho Kim,[10] Don A. Stevens,[11] Walter Fiedler,[12] Maria Pagoni,[13] Olga Samoilova,[14] Yu Hu,[15] Achilles Anagnostopoulos,[16] Julie Bergeron,[17] Jing-Zhou Hou,[18] Vidhya Murthy,[19] Takahiro Yamauchi,[20] Andrew McDonald,[21] Brenda Chyla,[22] Sathej Gopalakrishnan,[22] Qi Jiang,[22] Wellington Mendes,[22] John Hayslip,[22] and Panayiotis Panayiotidis[23]

*Blood* 2020;135(24):2137-45.

# VIALE-C Phase 3 Study Design

- Randomized 2:1, double-blind, placebo-controlled trial

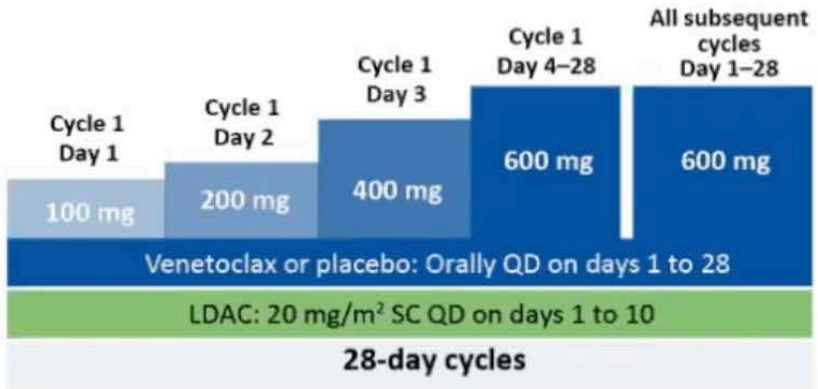
**2:1 Randomization via IRT**
N=211

- **Venetoclax + LDAC (n=143)**
- **Placebo + LDAC (n=68)**

Patients could continue receiving treatment until progression or until study treatment discontinuation criteria were met

Patients remained on study for OS assessment and follow-up, even if they initiated additional lines of treatment

**Stratification factors**
- AML status (secondary vs de novo)
- Age (18 to <75 vs ≥75)
- Region (US, EU, China, Japan, ROW)




**Primary endpoint:** overall survival

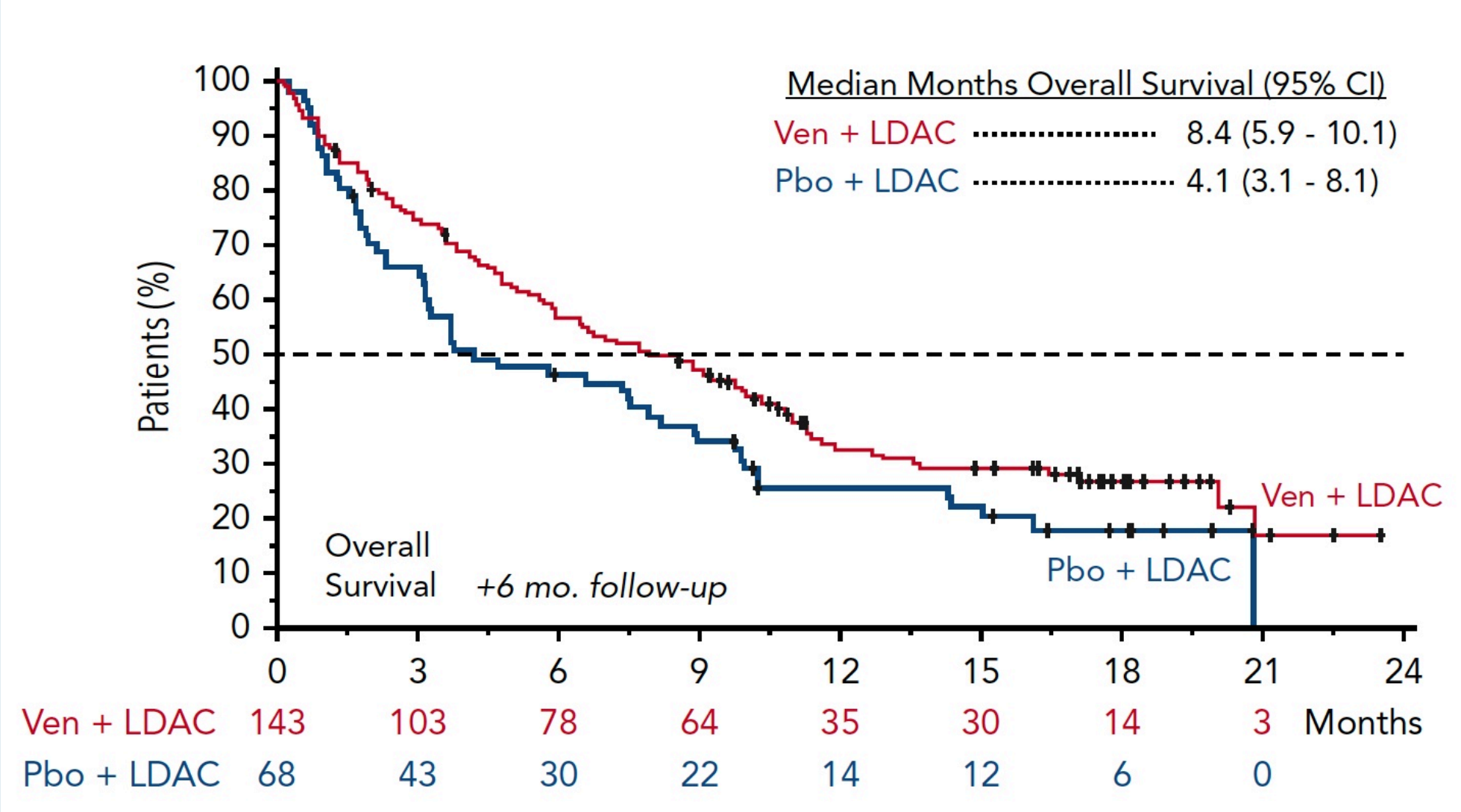
**Secondary endpoints**
- CR, CRh, and CRi (modified IWG criteria[1])
- Rate of transfusion independence
- EFS
- MRD

Progressive disease was defined per ELN recommendations.[2]

AML, acute myeloid leukemia; CR, complete remission; CRh, CR with partial hematologic recovery; CRi, CR with incomplete blood count recovery; EFS, event-free survival; ELN, European LeukemiaNet; IRT, Interactive Response Technology; IWG, International Working Group; LDAC, low-dose cytarabine; MRD, minimal residual disease; OS, overall survival; QD, once a day; ROW, rest of world; SC, subcutaneous.

1. Cheson BD, et al. *J Clin Oncol.* 2003;21:4642-4649; 2. Döhner H, et al. *Blood.* 2017;129:424-447.

# VIALE-C: Overall Survival




Wei AH et al. *Blood* 2020;135(24):2137-45.

# VIALE-C: Response Rates and Other Efficacy Endpoints

| End point | % (95% CI) | | P |
|---|---|---|---|
| | Placebo + LDAC (n = 68) | Venetoclax + LDAC (n = 143) | |
| **Remission rate** | | | |
| CR* | 7 (2-16) | 27 (20-35) | <.001 |
| CR/CRi† | 13 (6-24) | 48 (39-56) | <.001 |
| By initiation of cycle 2 | 3 (0-10) | 34 (27-43) | <.001 |
| CR/CRh‡ | 15 (7-25) | 47 (39-55) | <.001 |
| By initiation of cycle 2 | 4 (1-12) | 31 (23-39) | <.001 |
| **Other** | | | |
| EFS, mo | | | .002 |
| Median | 2.0 | 4.7§ | |
| 95% CI | 1.6-3.1 | 3.7-6.4 | |
| Transfusion independence | | | |
| Red blood cells | 18 (10-29) | 41 (32-49) | .001 |
| Platelets | 32 (22-45) | 48 (39-56) | .040 |
| Both | 16 (8-27) | 37 (29-46) | .002 |

Wei AH et al. *Blood* 2020;135(24):2137-45.

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# VIALE-C: Selected Key AML Serious Adverse Events

| AE | n (%) | |
|---|---|---|
| | Placebo + LDAC (n = 68) | Venetoclax + LDAC (n = 142) |
| **Selected key AML serious AEs** | | |
| Febrile neutropenia | 12 (18) | 23 (16) |
| Pneumonia | 7 (10) | 18 (13) |
| Sepsis | 4 (6) | 8 (6) |
| Thrombocytopenia | 2 (3) | 7 (5) |
| Anemia | 0 | 4 (3) |
| Neutropenia | 0 | 4 (3) |

Wei AH et al. *Blood* 2020;135(24):2137-45.

# Future Directions: Combination Therapies

- Low Intensity Triplets
  - With other genomically defined targeted therapies
  - With other BCL-2 family members
- With intensive chemotherapy
  - Up front
  - Salvage

Courtesy of Daniel A Pollyea, MD, MS

# Future Directions: New Settings

- Older “fit” patients
- Younger “fit” patients
- Relapsed AML
- Maintenance strategies

Courtesy of Daniel A Pollyea, MD, MS

# Agenda

Case Presentation: Ms Hewitt — An 81-year-old man with newly diagnosed poor-risk AML

Module 1: Molecular Evaluation of Patients with Newly Diagnosed AML

Module 2: Venetoclax Combinations; Management of Tumor Lysis Syndrome

**Case Presentation: Dr Levis — An 82-year-old man with AML and a FLT3 ITD mutation**

Module 3: Management of AML with FLT3 Mutation

Module 4: Management of AML with IDH Mutation

Module 5: Other Novel Agents and Strategies

# Gilteritinib has been associated with responses in patients with relapsed/refractory AML and…

1. An IDH2 mutation
2. A FLT3 mutation
3. Myelodysplasia-related changes
4. I don’t know

# Case Presentation – Dr Levis: An 82-year-old man with AML and a FLT3 ITD mutation

***Patient Circumstances***

- Very fit, British, independent contractor working full time
- Admitted to the hospital emergently in the COVID-19 era
- Contact with spouse and other family members solely via Zoom, telephone

***Clinical Presentation and Treatment Course***

- 6/2020 Presents to urgent care with fatigue: WBC 100,000, PLT 30, Hgb 8 → Emergency room
- Peripheral blood flow to assess for leukostasis, AML
- Hydroxyurea
- Patient mildly hypoxic due to DVT/PE and leukostasis
- Gemtuzumab, with decrease in WBC
- Azacitidine/venetoclax, with dramatic improvement in counts by day 20, hospital release by day 24
- Bone marrow biopsy: morphologic remission but FLT3 detectable, counts normalized
- Switched to azacitidine/gilteritinib
- Currently, back to working full time, with plan to transition to single-agent gilteritinib

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**Module 3: Management of AML with FLT3 Mutation**

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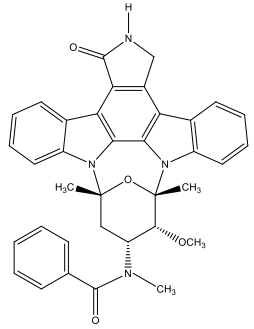
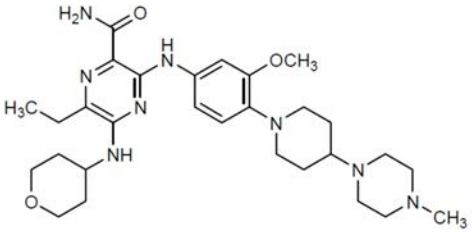
Module 5: Other Novel Agents and Strategies

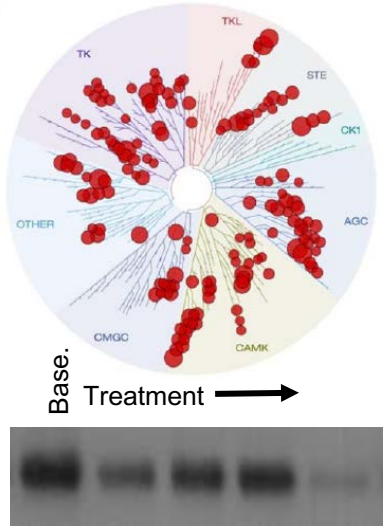
# Two FLT3 inhibitors



Midostaurin



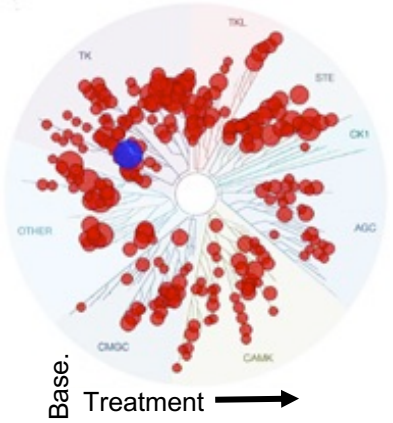
Gilteritinib



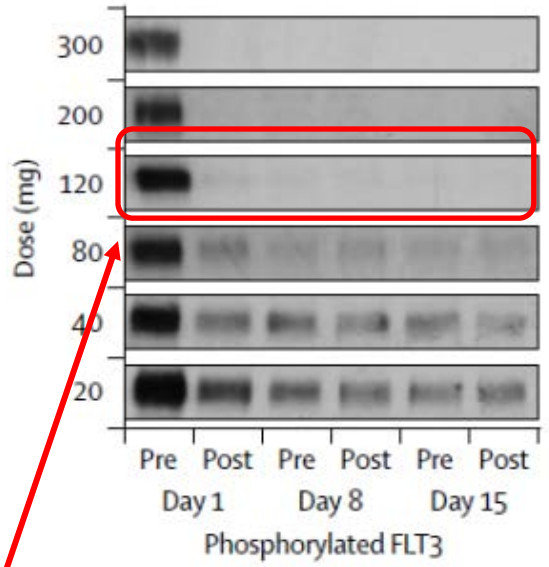

P-FLT3



Dose defined (and limited) by tolerability




**Dose defined by in vivo FLT3 inhibition**




Lancet Oncol 2017;18:1061-75

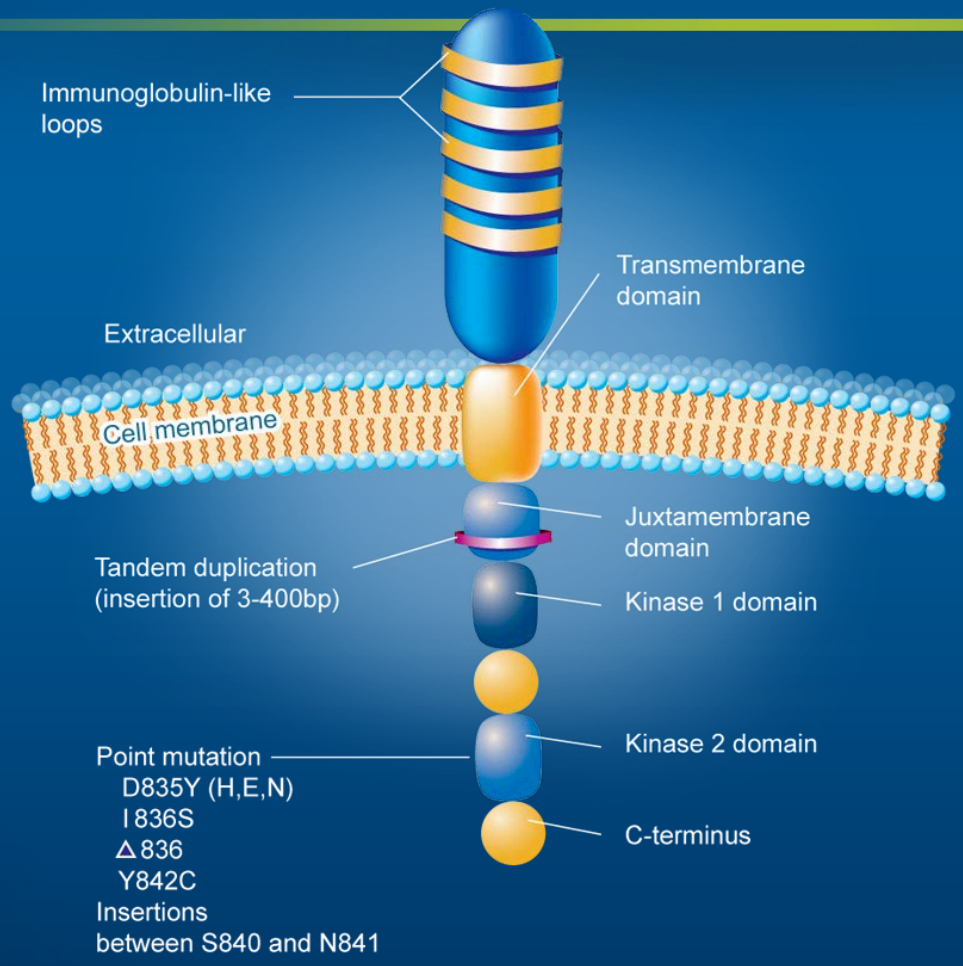
Courtesy of Mark Levis, MD, PhD

# FLT3 Mutations in AML

Approximately 30% of patients with AML have a FLT3 mutation

**FLT3-ITD: 25% of patients with AML**

**FLT3-TKD: 5% of patients with AML**




- FLT3 ligand (FL) binding activates downstream pathways (↑ cell proliferation)
- FLT3 mutations associated with a poor prognosis

Litzow MR. *Blood* 2005;106:3331-2; Small D. *Hematology Am Soc Hematol Educ Program* 2006:178-84; Swords R et al. *Leukemia* 2012;26(10):2176-85; Griffith J et al. *Mol Cell* 2004;13(2):169-78; Levis M. *Hematology Am Soc Hematol Educ Program* 2013;2013:220-6.

# Midostaurin

**Mechanism of action:**

- A multitargeted inhibitor of FLT3

**Indication:**

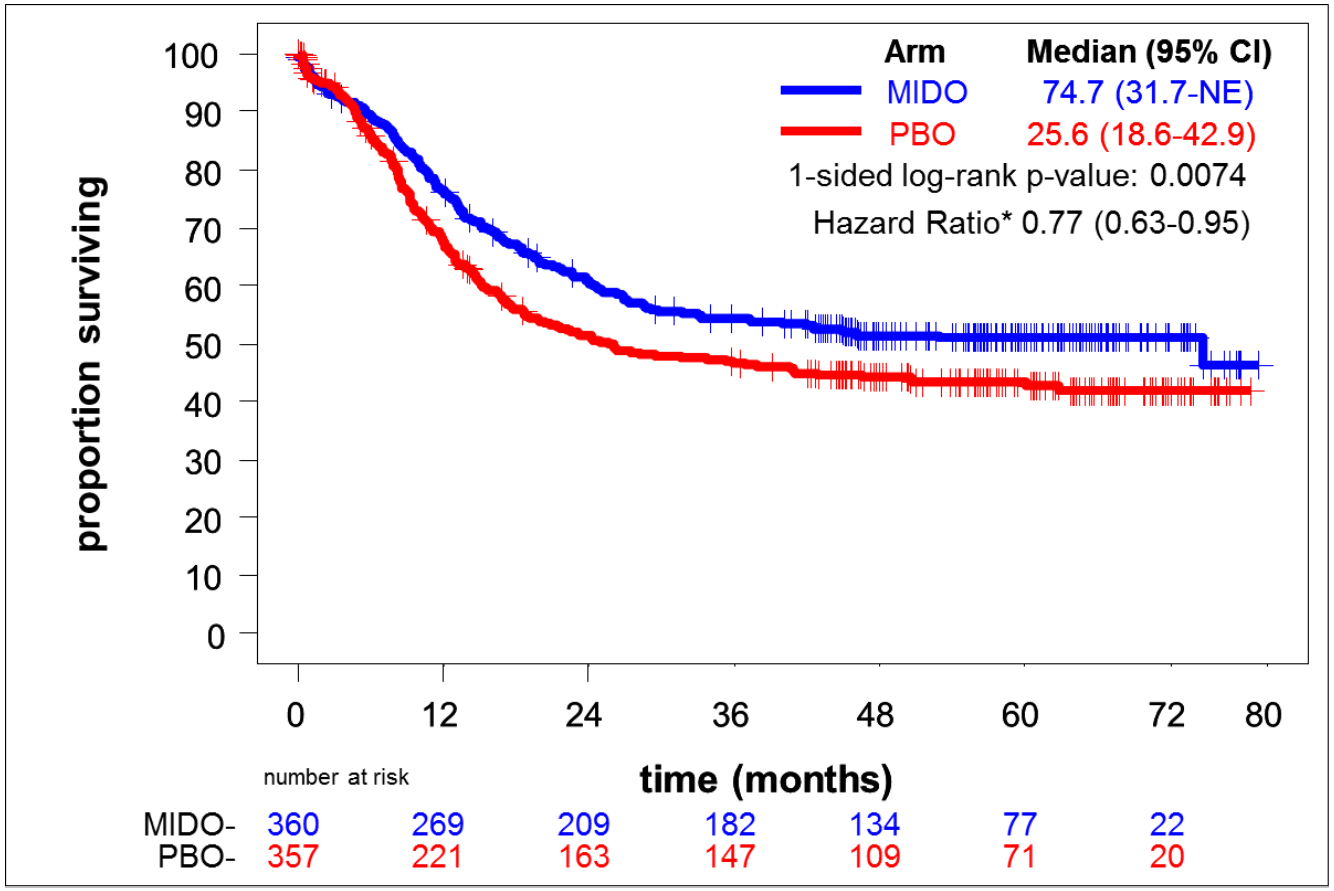
- For the treatment of patients with newly diagnosed AML that is FLT3 mutation-positive, as detected by an FDA-approved test, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation.

**Recommended dose:**

- 50 mg twice daily on days 8 to 21 of each cycle of induction and consolidation chemotherapy followed by 50 mg as a single agent for up to 12 months. Administer with food.

https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm555756.htm
Midostaurin package insert, April 2017

# Midostaurin prolongs survival for patients with newly diagnosed FLT3-mutant AML when added to induction chemotherapy



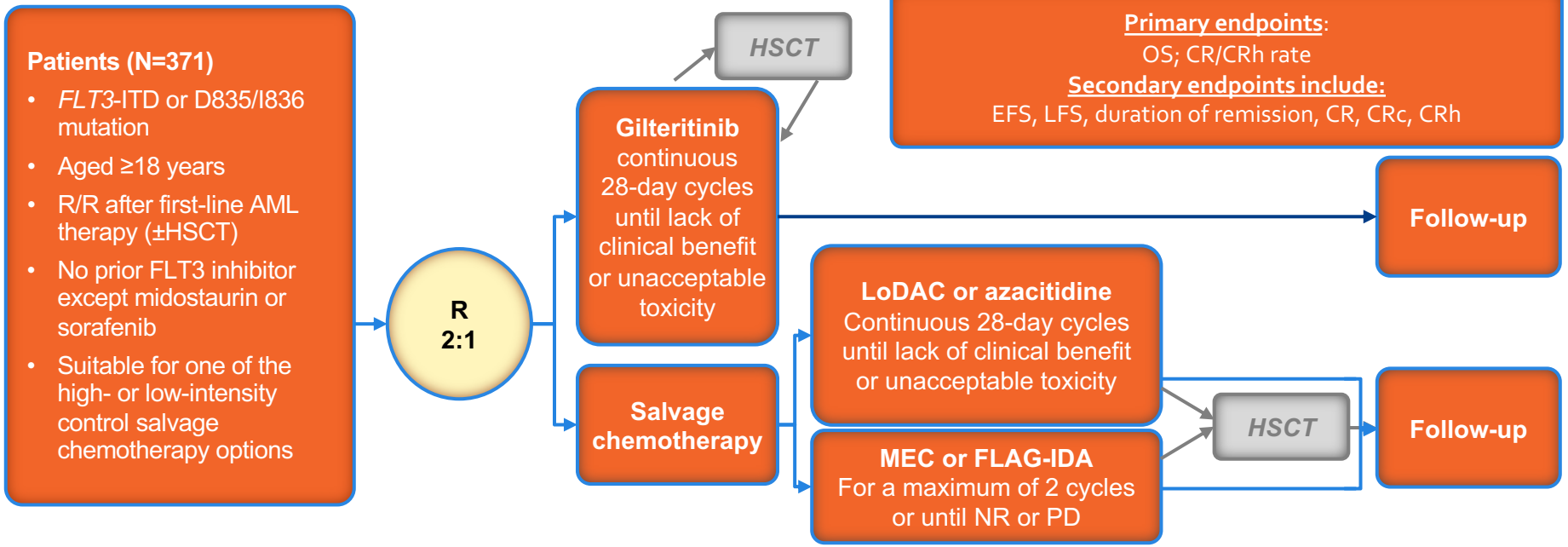

- 5 year survival rate:
  - Midostuarin 50.9% vs. Placebo 43.3%

Courtesy of Mark Levis, MD, PhD

Stone *et al.* N Engl J Med. 2017; 377:454

# Gilteritinib – Phase III ADMIRAL Study

## Monotherapy vs salvage chemotherapy (ADMIRAL; NCT02421939)

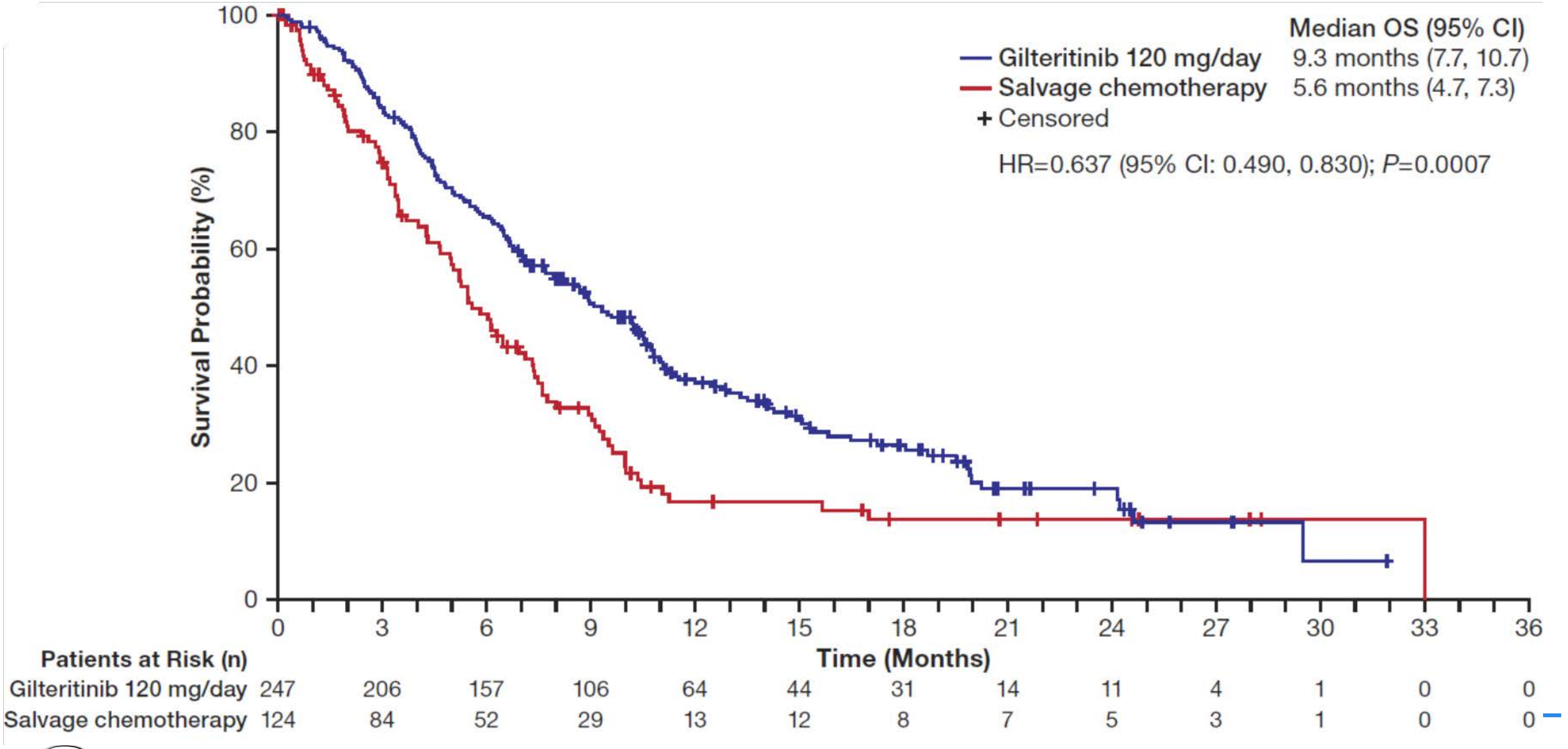



- ADMIRAL addresses gilteritinib efficacy in the R/R disease setting compared with salvage chemotherapy; the study includes patients who are and are not fit for high intensity chemotherapy
- Based on data from the ongoing ADMIRAL study, gilteritinib is approved in Japan and US for treatment of adults with *FLT3*-mutated R/R AML



Courtesy of Eytan M Stein, MD

# ADMIRAL: Overall Survival (ITT Population, N = 371)




Memorial Sloan Kettering Cancer Center

Courtesy of Eytan M Stein, MD

Perl A, et al, NEJM, Oct 31, 2019

# Relapsed FLT3-ITD AML

- Disease is typically driven by FLT3
  - If FLT3-ITD mutation still present…
  - 50% of patients treated with midostaurin during induction lose FLT3-ITD mutation at relapse
- Monotherapy with gilteritinib = 50% response rate
  - …but most patients will ultimately succumb
- Combinations are preferable
  - HiDAc + gilteritinib
  - Aza + gilteritinib
  - IDH1/2 inhibitor + gilteritinib

Courtesy of Mark Levis, MD, PhD

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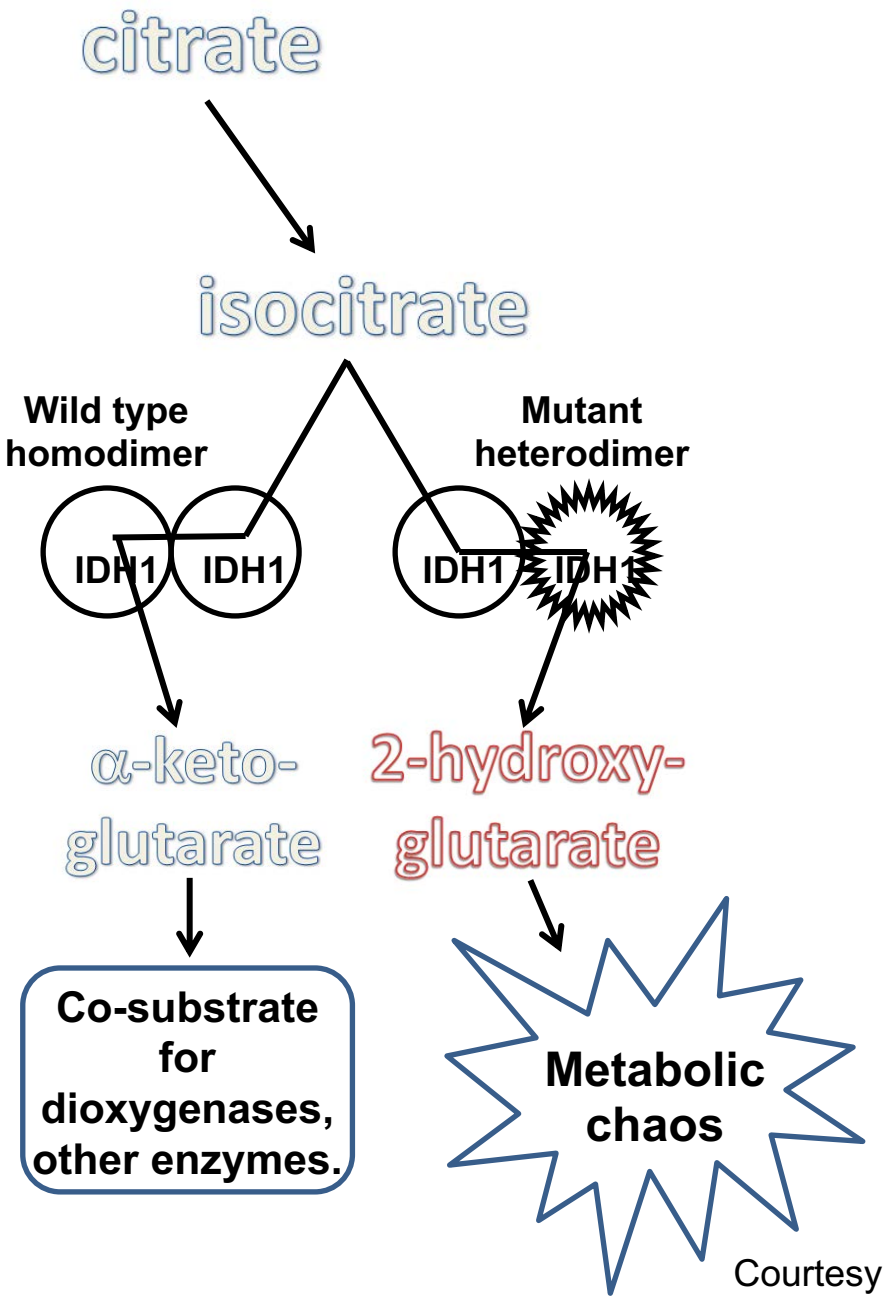
# IDH mutations

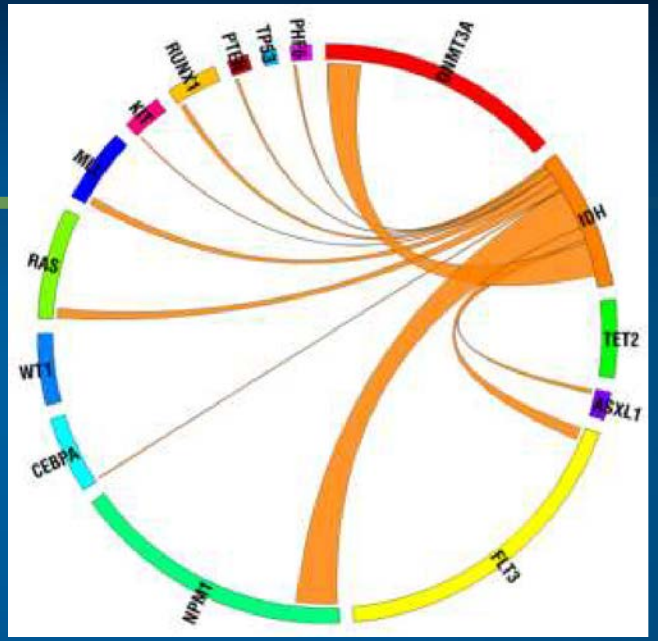
- 10-15% of AML
- Result in the generation of an “onco-metabolite
  - 2 hydroxyglutarate (2-HG)
- IDH1 mutations
  - R132
- IDH2 mutations
  - R140
  - R172

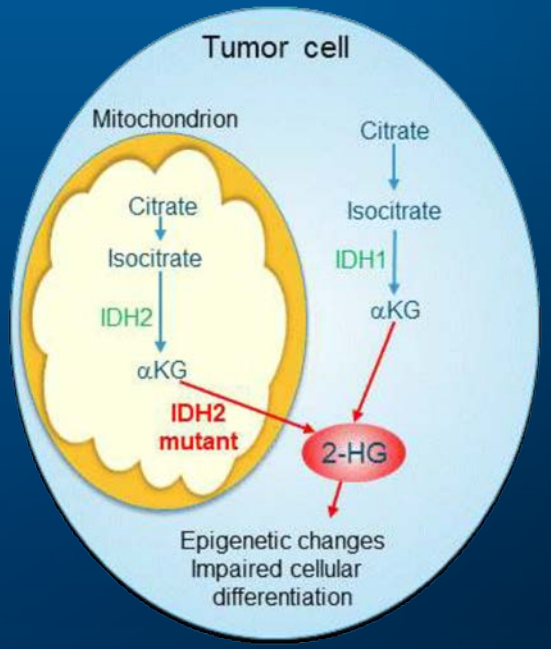



Courtesy of Mark Levis, MD, PhD

# IDH in Leukemia

- IDH mutations occur in ~20% of AML
  - Frequency: 6%-16% IDH1 and 8%-18% IDH2
  - Majority (85%) with diploid or +8 cytogenetics
  - ↑ prevalence with ↑ patient age
  - Prognostic effect in AML remains controversial
  - IDH1 and IDH2 mutations may have different effects on prognosis




Dang L et al. *Trends Mol Med* 2010;16(9):387-97. Chou WC et al. *Leukemia* 2011;25(2):246-53. Patel JP et al. *N Engl J Med* 2012;366(2):1079-89. Medeiros BC et al. *Leukemia* 2017;31:272-81.

# IDH2m and IDH1m: Distinct Genetically Defined Populations

| IDH Mutations Seen in Multiple Cancer Types | | |
|---|---|---|
| Target | Indication | IDHm (%) |
| IDH2m | AML | 15% |
| | MDS/MPN | 5% |
| | Angio-immunoblastic NHL | 25% |
| | Others (melanoma, glioma, chondro)[2] | 3-5% |
| | Type II D-2HG Aciduria (inborn error of metabolism) | 100% |
| | | |
| IDH1m | Low-grade glioma & 2$^{ary}$ GBM[1] | 70% |
| | Chondrosarcoma | >50% |
| | AML | 7.5% |
| | MDS/MPN | 5% |
| | Intrahepatic cholangiocarcinoma | 20% |
| | Others (colon, melanoma, lung)[2] | 1-2% |



Courtesy of Eytan M Stein, MD

[1]Includes 8.5% of Primary GBM
[2]Includes "basket" of emerging unconfirmed indications

# Approved IDH Inhibitors in AML

- **Enasidenib – IDH2 inhibitor. Approved for relapsed and refractory IDH2 mutant AML.**
  - **Oral, given once daily, continuous 28 day cycles**
  - **Indirect hyperbilirubinemia**

- **Ivosidenib – IDH1 inhibitor. Approved for relapsed and refractory and newly diagnosed IDH1 mutant AML.**
  - **Oral, once daily, continuous 28 day cycles**
  - **QT prolongation**

- **In R/R AML, complete remission rates with IDH inhibitors is about 21%**



Courtesy of Eytan M Stein, MD

# Differentiation Syndrome

**Frequency of Signs and Symptoms Consistent With IDH-DS[a]**

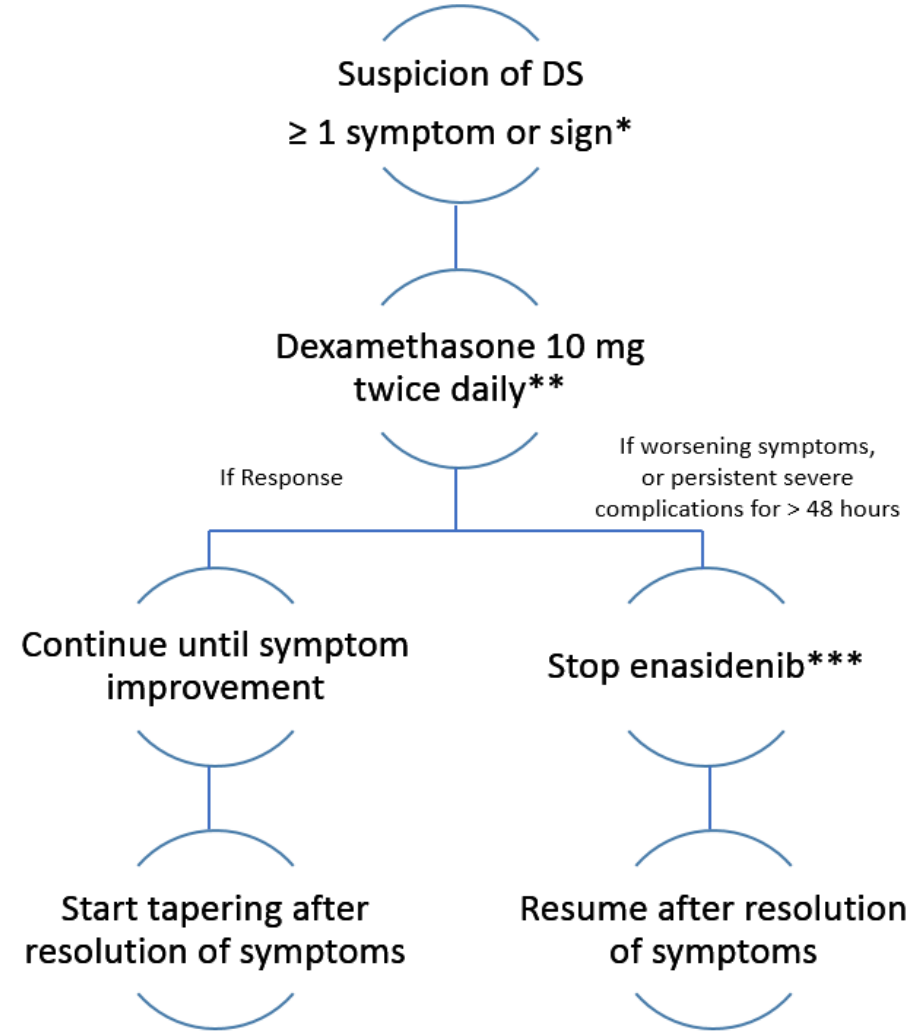
| Sign or Symptom | Patients With IDH-DS, No. (%) (n = 33)[b] |
|---|---|
| Dyspnea | 28 (85) |
| Unexplained fever (body temperature of 38.0°C for 2 d) | 26 (79) |
| Pulmonary infiltrates | 24 (73) |
| Hypoxia | 19 (58) |
| Acute kidney injury (CTCAE grade ≥2) | 14 (42) |
| Pleural effusion | 14 (42) |
| Bone pain or arthralgia | 9 (27) |
| Lymphadenopathy | 8 (24) |
| Rash | 8 (24) |
| Disseminated intravascular coagulopathy | 7 (21) |
| Edema or weight gain of >5 kg from screening | 7 (21) |
| Pericardial effusion | 5 (15) |

[a] Signs and symptoms are based on retrospective differentiation syndrome review committee review of clinical records.

[b] Patients may have had multiple symptoms.

**Fathi A et al, JAMA Oncology 2018**

# Management of IDH-DS




*DS: Differentiation syndrome*

*Main symptoms and signs:
Dyspnea, fever, rash, pulmonary infiltrates, pleural effusion, renal dysfunction.
**With other supportive measures:
-Broad spectrum antibiotics for possible underlying infection.
-Cytoreductive therapy if leukocytosis.
-Hyperuricemia management if tumor lysis syndrome.
***Symptoms will last several days until improvement due the long half-life of enasidenib.



**Abou Dalle I et al, Ther Adv Heme 2018**

Courtesy of Eytan M Stein, MD

# Case Presentation – Dr Levis: A 78-year-old man with AML and an IDH1 mutation

***Patient Circumstances***

- Worked for US government agency, traveled the world
- Supportive wife
- Has not seen grandchildren in the past year due to COVID-19 pandemic

***Clinical Presentation and Treatment Course***

- Essential thrombocythemia for years → transfusion-dependent MDS
- Azacitidine x 4
- 12/2017: Bone marrow transplant
- 12/2018: AML, with IDH1 mutation
- Ivosidenib, with CR but remains transfusion-dependent (every 2 weeks)
- 10/2018 and 12/2018: Added azacitidine to ivosidenib
  - Counts worsened, neutrophils dropped to zero, skin infection → meropenem antibiotics
  - Discontinued antibiotic → Counts normalized, Hgb: 13.6, PLT > 100, transfusion not required past 6 months

# Agenda

Case Presentation: Ms Hewitt — An 81-year-old man with newly diagnosed poor-risk AML

Module 1: Molecular Evaluation of Patients with Newly Diagnosed AML

Module 2: Venetoclax Combinations; Management of Tumor Lysis Syndrome

Case Presentation: Dr Levis — An 82-year-old man with AML and a FLT3 ITD mutation

Module 3: Management of AML with FLT3 Mutation

Module 4: Management of AML with IDH Mutation

**Module 5: Other Novel Agents and Strategies**

# CPX-351 (liposomal cytarabine-daunorubicin) is approved for…

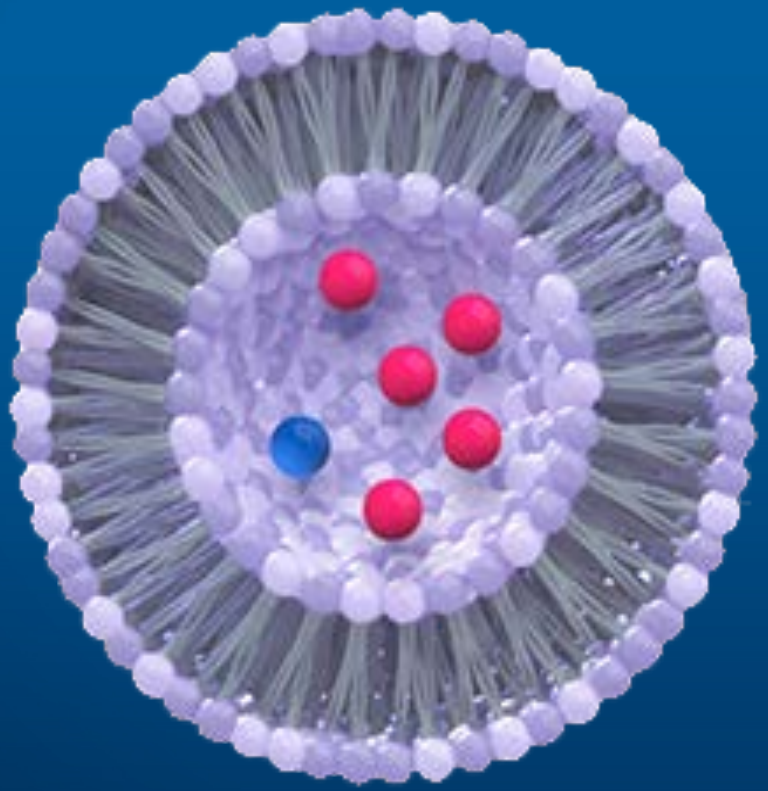
1. AML with a FLT3 mutation
2. Secondary AML
3. CD33-positive AML
4. I don’t know

# Secondary AML:
## AML evolving out of myelodysplasia or a myeloproliferative disorder

- Antecedent hematologic disorder (e.g., MDS or MPN)
  - Often, patient has a history of unexplained anemia or thrombocytopenia
  - Can be diagnosed when patient presents with AML: “AML with trilineage dysplasia”
  - Patient may have 2-3 year h/o MDS, treated with various agents
  - Patient might have h/o Polycythemia Vera, etc…
- Increasing age (a continuous variable)
  - Age usually > 65
  - Usually a different spectrum of mutations compared to AML lacking an antecedent hematologic disorder
  - Outcomes poor

Courtesy of Mark Levis, MD, PhD

# Liposomal Daunorubicin and Cytarabine (CPX-351)



- 1:5 molar ratio of daunorubicin to cytarabine
- Synergistic activity in both in vitro and animal models
- 100 nm bilamellar liposomes
- 1 unit = 0.44 mg daunorubicin and 1.0 mg cytarabine (1:5 molar ratio) complexed with copper
- Targets bone marrow and preferentially targets leukemic compared to normal marrow progenitors

# CPX-351

**Mechanism of action:**

- Liposome-encapsulated fixed ratio of daunorubicin and cytarabine

**Indication:**

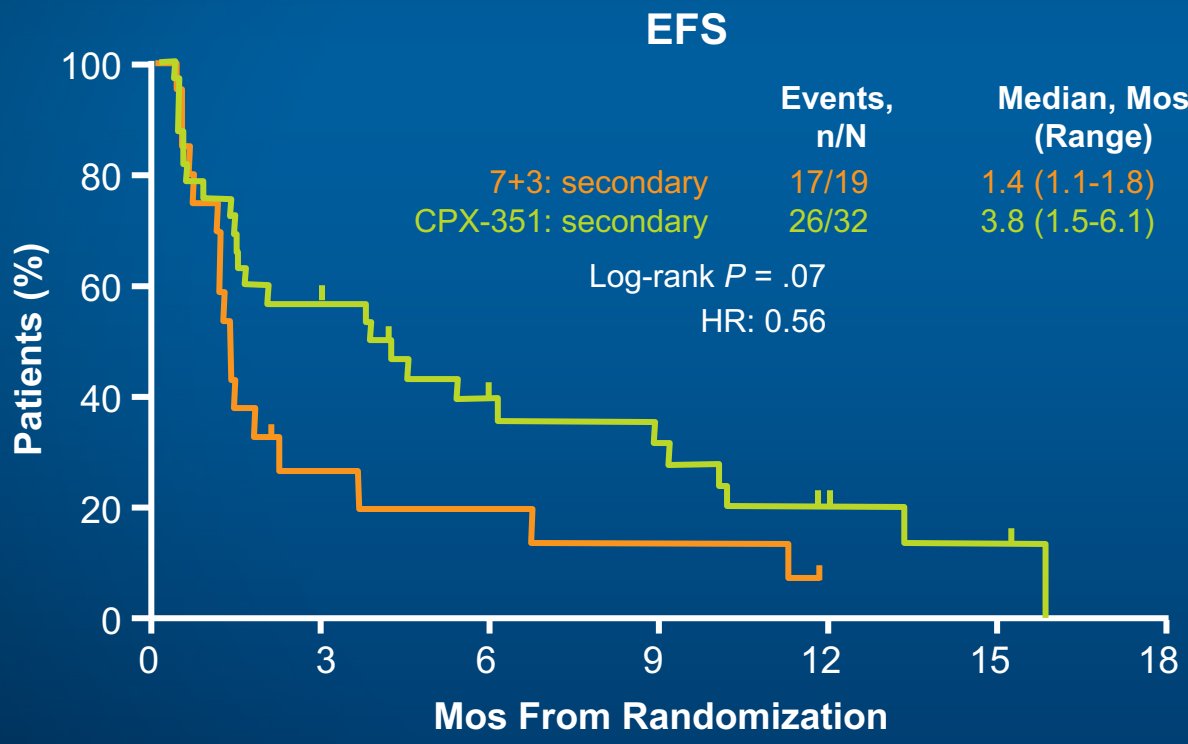
- For the treatment of newly diagnosed therapy-related AML or AML with myelodysplasia-related changes

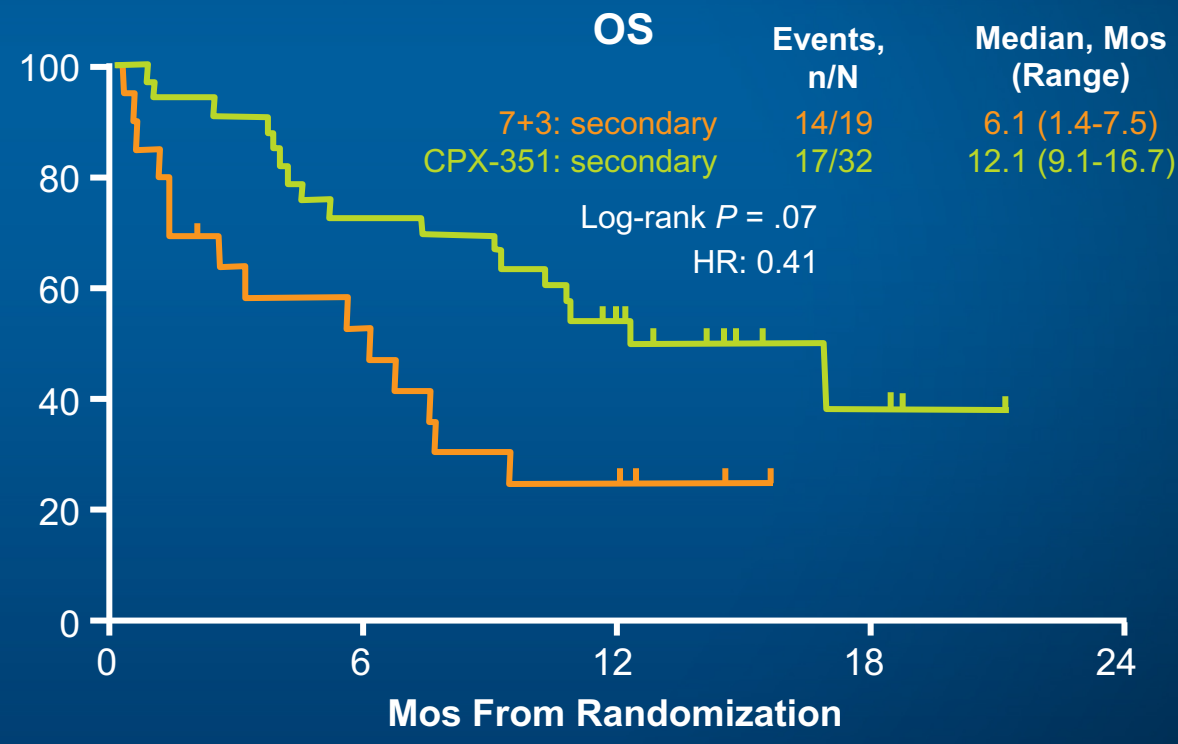
**Recommended dose:**

- Induction: (daunorubicin 44 mg/m$^2$ and cytarabine 100 mg/m$^2$) liposome via intravenous infusion over 90 minutes on days 1, 3, and 5 and on days 1 and 3 for subsequent cycles of induction, if needed
- Consolidation: (daunorubicin 29 mg/m$^2$ and cytarabine 65 mg/m$^2$) liposome via intravenous infusion over 90 minutes on days 1 and 3

https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm569950.htm
(Daunorubicin and cytarabine) liposome package insert, April 2017

# CPX-351 in Secondary AML




| Pts at Risk, n | | | | | | |
|---|---|---|---|---|---|---|
| 7+3: | 4 | 3 | 2 | 0 | 0 | 0 |
| CPX-351: | 17 | 10 | 8 | 3 | 2 | 0 |

| Pts at Risk, n | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 7+3: | 11 | 9 | 5 | 3 | 1 | 0 | 0 | 0 |
| CPX-351: | 29 | 23 | 22 | 13 | 6 | 3 | 0 | 0 |

Lancet JE et al. ASCO 2011;Abstract 6519.

# Case Presentation – Dr Levis: A 78-year-old woman with secondary AML

***Patient Circumstances***

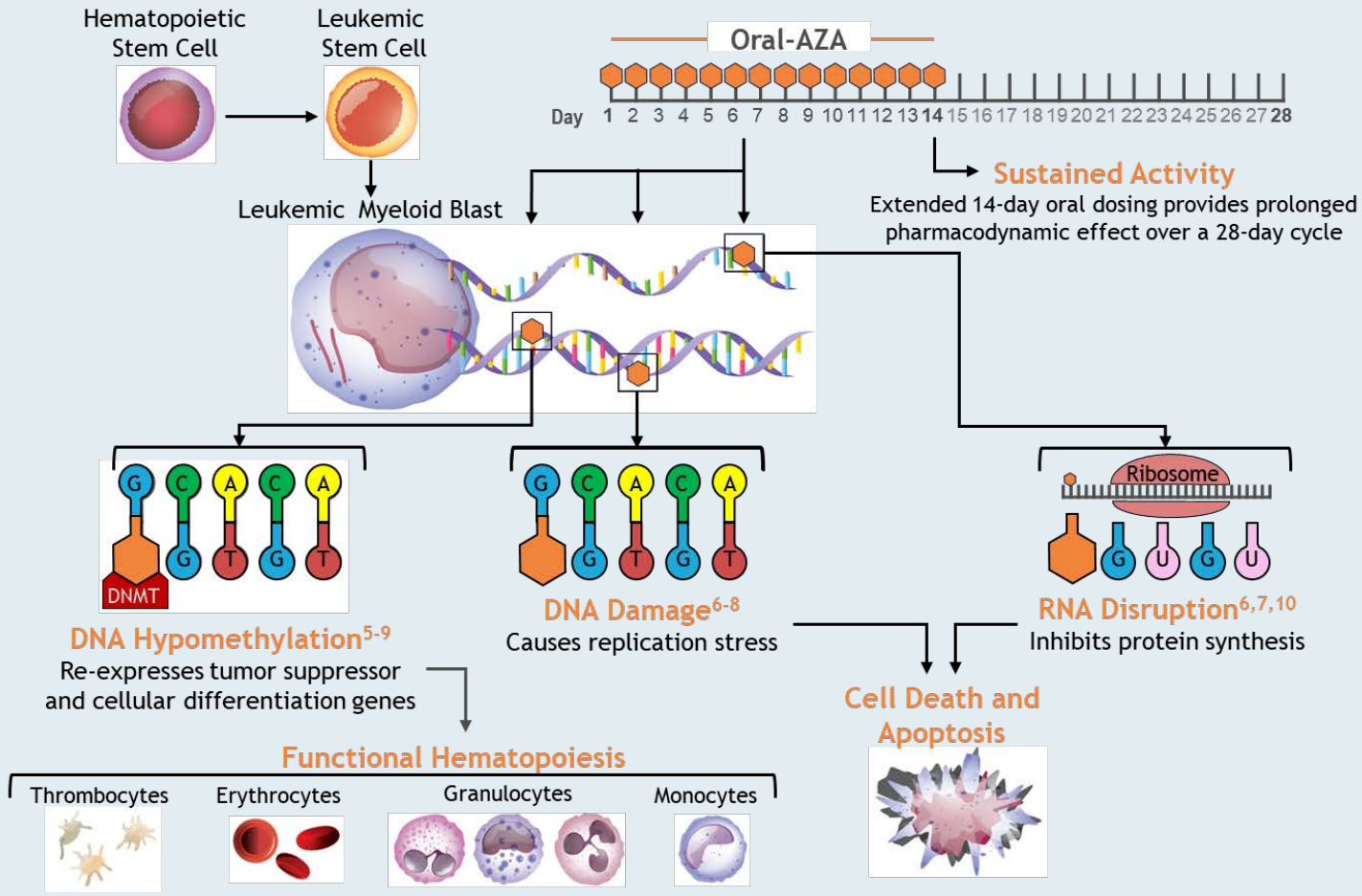
- Recreational tomato farmer
- Prior history of bladder cancer s/p surgery and chemotherapy 10 years ago
- Recent death (3/2021) of two adult sons in their 50s weeks apart
- COVID-19 pandemic
- National shortage of azacitidine

***Clinical Presentation and Treatment Course***

- 12/2017 Diagnosed with AML, presumed secondary to prior chemotherapy, with TET2 and NPM1 mutations
- CPX-351, with remission, c/b C. difficile
- 8/2018 Blood counts falling → BMB: TET2, NPM1 readily detectable, blast < 5%
- Subcutaneous azacitidine/venetoclax on outpatient basis, with rapid normalization of counts
  - Substitution of subcutaneous decitabine during shortage

# Oral Azacitidine (Oral-AZA, CC-486)

- **Oral HMA with a distinct PK/PD profile from injectable AZA; the two are not bioequivalent[1,2]**
- **Approved in the United States for continued Tx of adult pts with AML in first CR/CRi post-IC and not able to complete intensive curative therapy (eg, HSCT)[3]**
  - **Oral dosing allows for extended drug exposure during each Tx cycle to prolong AZA activity[1,2]**




1. Garcia-Manero et al. *J Clin Oncol*. 2011;29(18):2521–7. 2. Laille et al. *PLoS One*. 2015;10(8):e0135520. 3. ONUREG® (azacitidine) tablets [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; Rev. 9/2020. 4. Savona et al. *Am J Hematol*. 2018;93(10):1199–206. 5. Stresemann et al. *Mol Cancer Ther*. 2008;7:2998–3005. 6. Hollenbach et al. *PLoS One*. 2010;5(2):e9001. 7. Scott LJ. *Drugs*. 2016;76(8):889–900. 8. Stresemann C, Lyko F. *Int J Cancer*. 2008;123(1):8–13. 9. Aimiuwu et al. *Blood*. 2012;119(22):5229–38.

AML, acute myeloid leukemia; AZA, azacitidine; CR, complete remission; CRi, CR with incomplete blood count recovery; HMA, hypomethylating agent; HSCT, hematopoietic stem cell transplant; IC, intensive chemotherapy; PD, pharmacodynamic; PK, pharmacokinetic; pts, patients; Tx, treatment.

Courtesy of Richard M Stone, MD

# FDA Approves Azacitidine Tablets for Acute Myeloid leukemia

## Press Release – September 1, 2020

"The Food and Drug Administration approved azacitidine tablets for continued treatment of patients with acute myeloid leukemia who achieved first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following intensive induction chemotherapy and are not able to complete intensive curative therapy.

Efficacy was investigated in QUAZAR (NCT01757535), a multicenter, randomized, double-blind, placebo-controlled trial. Patients (n=472) who achieved CR or CRi with intensive induction chemotherapy with or without receiving subsequent consolidation therapy were randomized 1:1 to receive azacytidine tablets 300 mg (n=238) or placebo (n=234) orally on days 1 to 14 of each 28-day cycle."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-onureg-azacitidine-tablets-acute-myeloid-leukemia

RTP RESEARCH TO PRACTICE

ORIGINAL ARTICLE

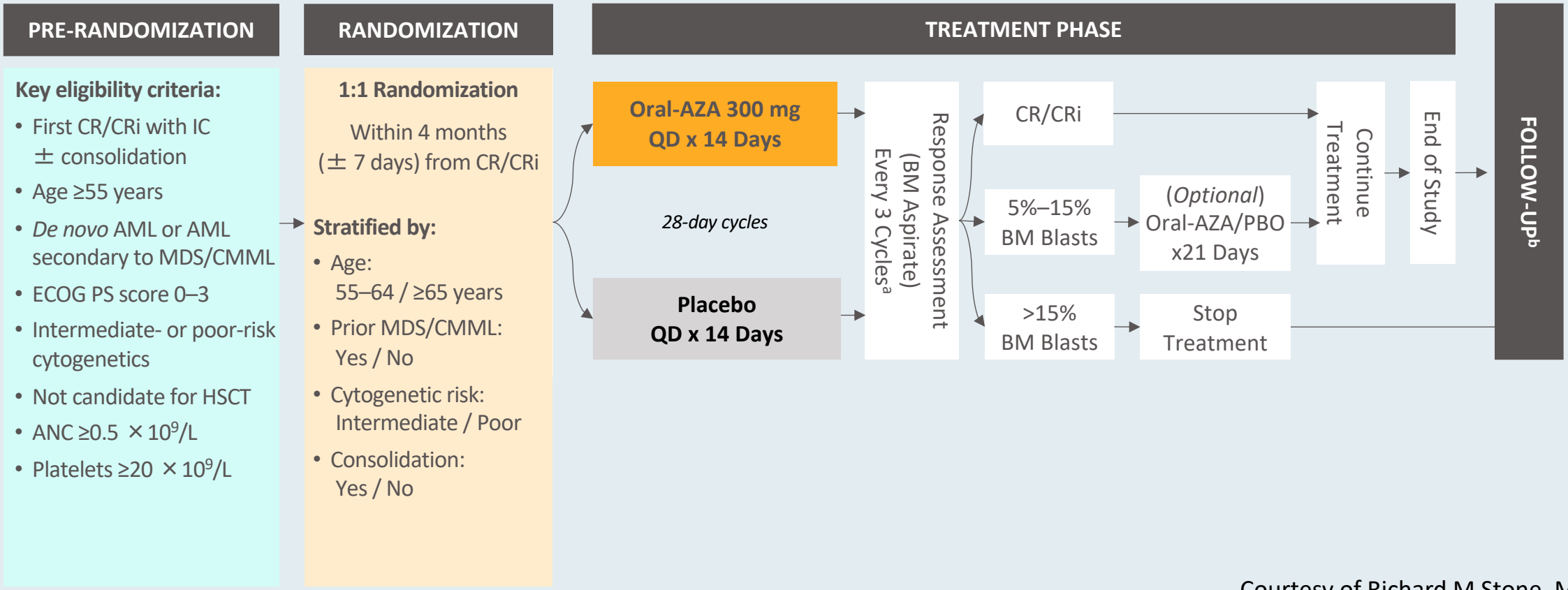
# Oral Azacitidine Maintenance Therapy for Acute Myeloid Leukemia in First Remission

A.H. Wei, H. Döhner, C. Pocock, P. Montesinos, B. Afanasyev,* H. Dombret, F. Ravandi, H. Sayar, J.-H. Jang, K. Porkka, D. Selleslag, I. Sandhu, M. Turgut, V. Giai, Y. Ofran, M. Kizil Çakar, A. Botelho de Sousa, J. Rybka, C. Frairia, L. Borin, G. Beltrami, J. Čermák, G.J. Ossenkoppele, I. La Torre, B. Skikne, K. Kumar, Q. Dong, C.L. Beach, and G.J. Roboz, for the QUAZAR AML-001 Trial Investigators†

N Engl J Med 2020;383:2526-37.

# QUAZAR AML-001: Study Design and Eligibility Criteria

**International, multicenter, placebo (PBO)-controlled, double-blind, randomized, phase III study of Oral-AZA as maintenance Tx in pts with AML in first remission post-IC**




Courtesy of Richard M Stone, MD

[a]BM aspirates were collected every 3 cycles through cycle 24, at cycle 30 and cycle 36, and as clinically indicated thereafter. BM assessments were also performed as clinically indicated. [b]Patients were followed until death, withdrawal of consent, study termination, or loss to follow-up.

AML, acute myeloid leukemia; ANC, absolute neutrophil count; AZA, azacitidine; BM, bone marrow; CMML, chronic myelomonocytic leukemia; CR, complete remission; CRi, CR with incomplete blood count recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; HSCT, hematopoietic stem cell transplant; IC, induction chemotherapy; IWG, International Working Group; MDS, myelodysplastic syndromes; PBO, placebo.

# Gemtuzumab Ozogamicin

**Mechanism of action:**

- Antibody-drug conjugate targeted to CD33

**Indication:**

- For the treatment of newly diagnosed CD33-positive acute myeloid leukemia (AML) in adults and for the treatment of relapsed or refractory CD33-positive AML in adults and in pediatric patients 2 years and older

**Recommended dose:**

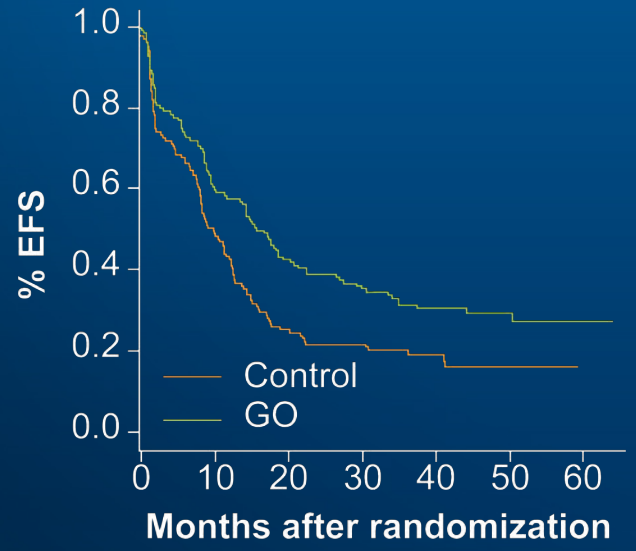
- Newly diagnosed de novo AML (in combination with daunorubicin and cytarabine): 3 mg/m$^2$ on days 1, 4 and 7 for induction and 3 mg/m$^2$ on day 1 for consolidation
- Newly diagnosed AML (single agent): 6 mg/m$^2$ on day 1 and 3 mg/m$^2$ on day 8 for induction, followed by up to 8 continuation cycles of 2 mg/m$^2$ on day 1 every 4 weeks
- Relapsed or refractory AML (single agent): 3 mg/m$^2$ on days 1, 4 and 7

https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm574518.htm
Gemtuzumab ozogamicin package insert, September 2017

# Gemtuzumab Ozogamicin (GO)
# Antibody-Drug Conjugate: CD33 Antibody Linked to Calicheamicin

**History:**

- 2000: Granted FDA accelerated approval
- 2010: Voluntarily removed from the market when confirmatory trials did not show a clinical benefit but did show higher chance of death and association with veno-occlusive disease of the liver (VOD)
- 2017: GO received FDA approval in 3 settings, including in combination with induction chemotherapy at a lower dose after review of Phase III results of ALFA 0701 study



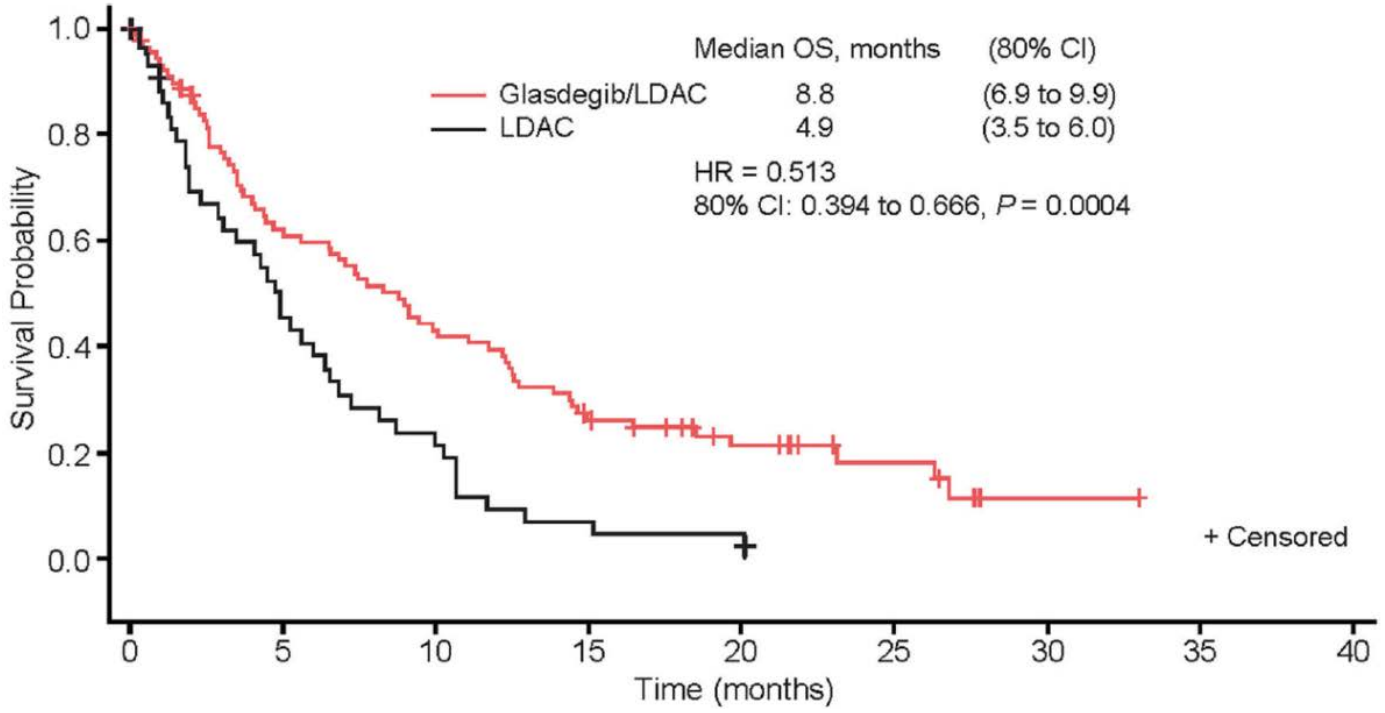

ALFA 0701

- Median EFS: 9.7 vs 15.6 months; $p = 0.0026$
- No difference in OS
- SAEs higher in GO arm

http://www.bloodjournal.org/content/124/21/376?sso-checked=true

# Glasdegib

- Oral hedgehog inhibitor
- Minimal single agent activity, but combined with low-dose araC, improved survival
- FDA approved for newly diagnosed AML in patients unfit for intensive therapy




Courtesy of Mark Levis, MD, PhD

# The field of AML therapy is rapidly changing…

- Sequencing and stem cell biology studies have advanced our understanding of the disease:
  - “Driver/founder/cooperating” mutations
  - “CHIP”
  - Leukemic stem cells
- New agents added to our arsenal:
  - Midostaurin
  - Liposomal cytarabine and daunorubicin
  - Gemtuzumab ozogamicin
  - Enasidenib
  - Gilteritinib
  - Venetoclax + HMA
  - Glasdegib
- Personalized therapy for AML is here!

Courtesy of Mark Levis, MD, PhD

# *Meet The Professor*

# Optimizing the Selection and Sequencing of Therapy for Patients with Advanced Gastrointestinal Cancers

**Wednesday, March 17, 2021**
**5:00 PM – 6:00 PM ET**

## Faculty

**Alan P Venook, MD**

## Moderator

**Neil Love, MD**

RTP
RESEARCH
TO PRACTICE

*Thank you for joining us!*

*NCPD credit information will be emailed to each participant within 3 business days.*