# *Meet The Professor*
# Optimizing the Management of Acute Myeloid Leukemia

**Keith W Pratz, MD**
Director of Leukemia Program
Hospital of the University of Pennsylvania
Associate Professor of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

# Commercial Support

This activity is supported by educational grants from Bristol-Myers Squibb Company, Genentech, a member of the Roche Group, and Servier Pharmaceuticals LLC.

# Dr Love — Disclosures

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# Dr Pratz — Disclosures

| | |
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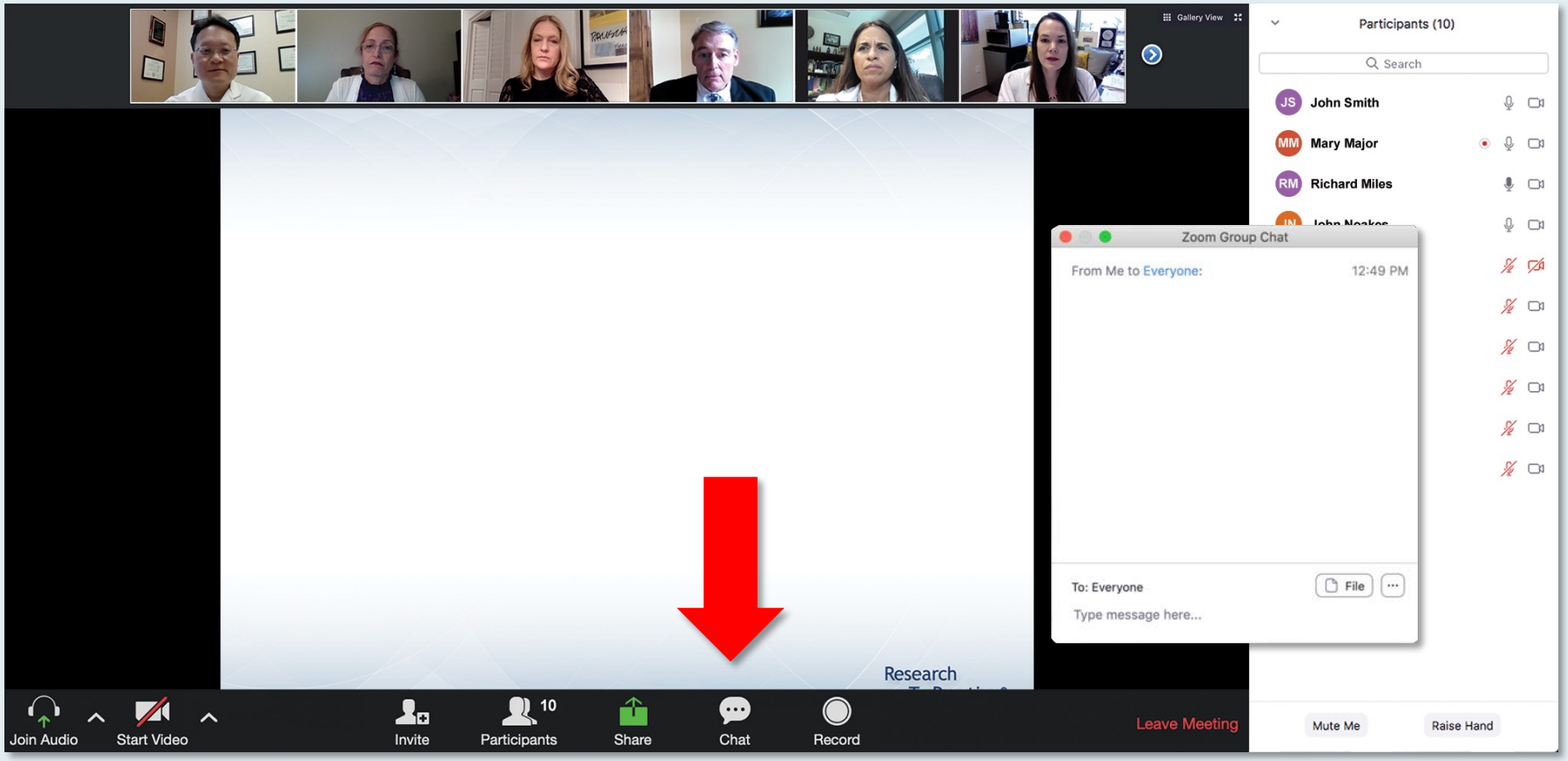
# We Encourage Clinicians in Practice to Submit Questions

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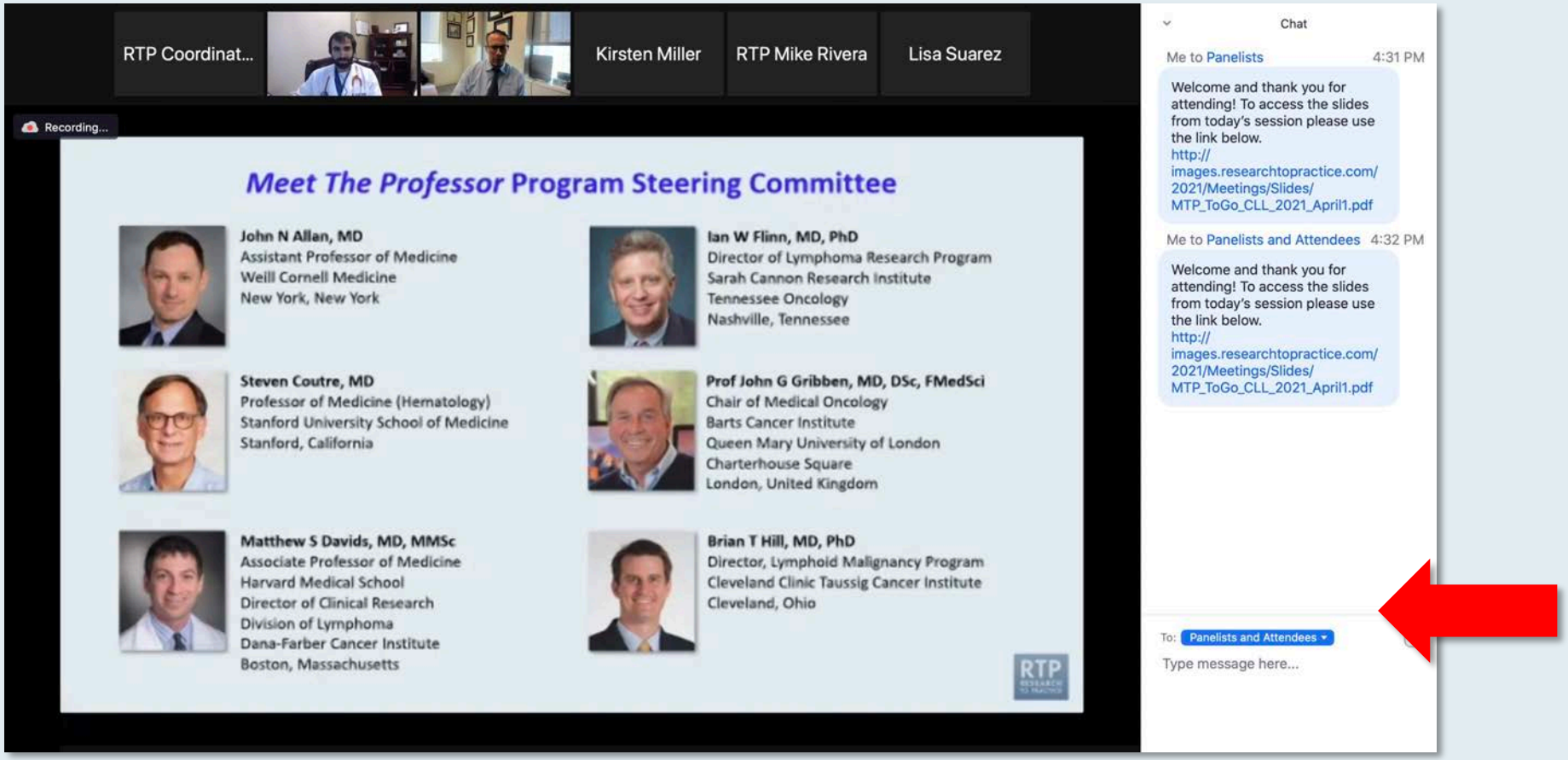
# Familiarizing Yourself with the Zoom Interface

## Expand chat submission box




**Drag the white line above the submission box up to create more space for your message.**

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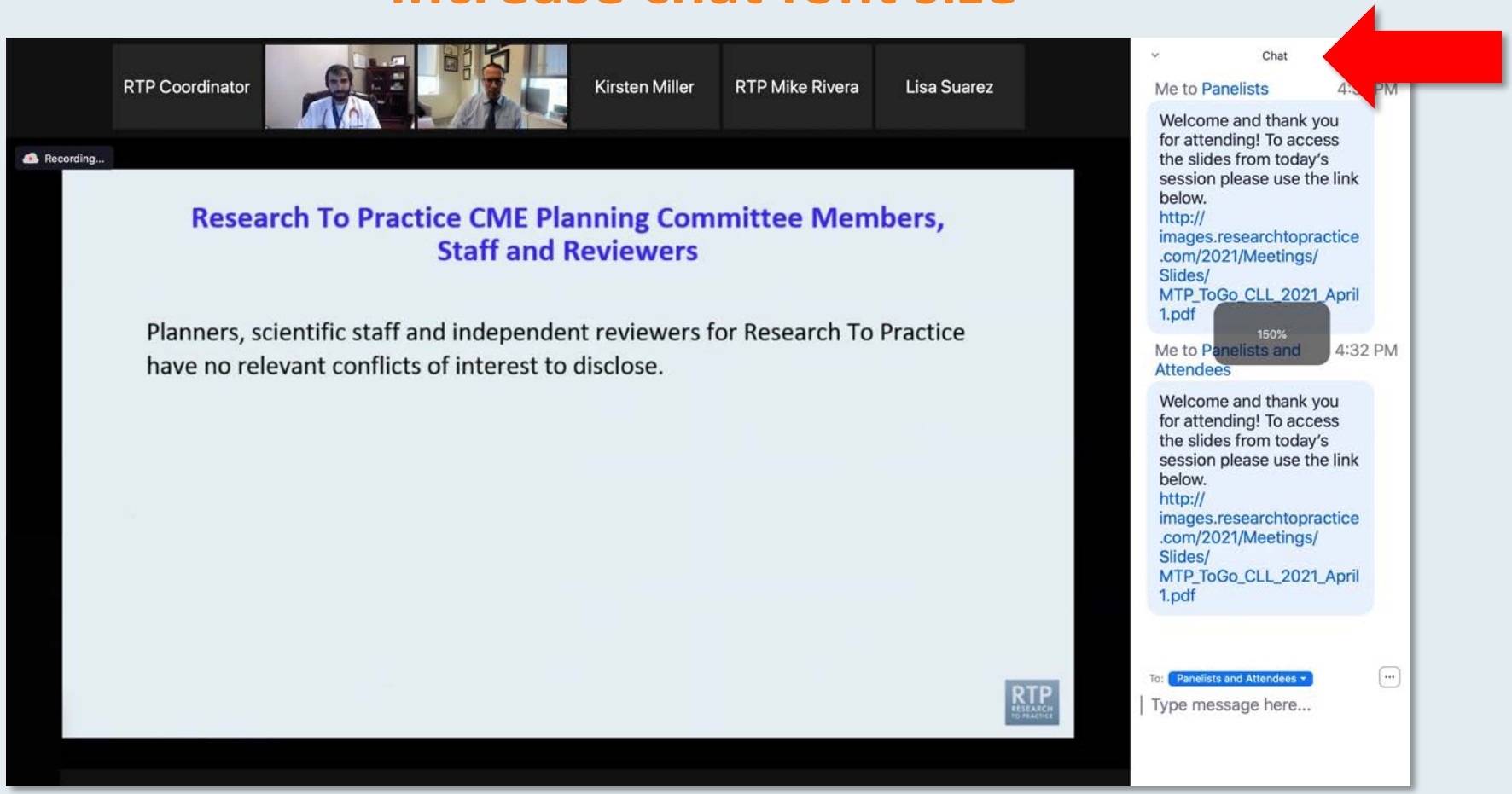
# Familiarizing Yourself with the Zoom Interface

## Increase chat font size




**Press Command (for Mac) or Control (for PC) and the + symbol.**
**You may do this as many times as you need for readability.**

# ONCOLOGY TODAY

WITH DR NEIL LOVE

# Chronic Myeloid Leukemia


DR MICHAEL MAURO

MEMORIAL SLOAN KETTERING CANCER CENTER


Listen on Apple Podcasts

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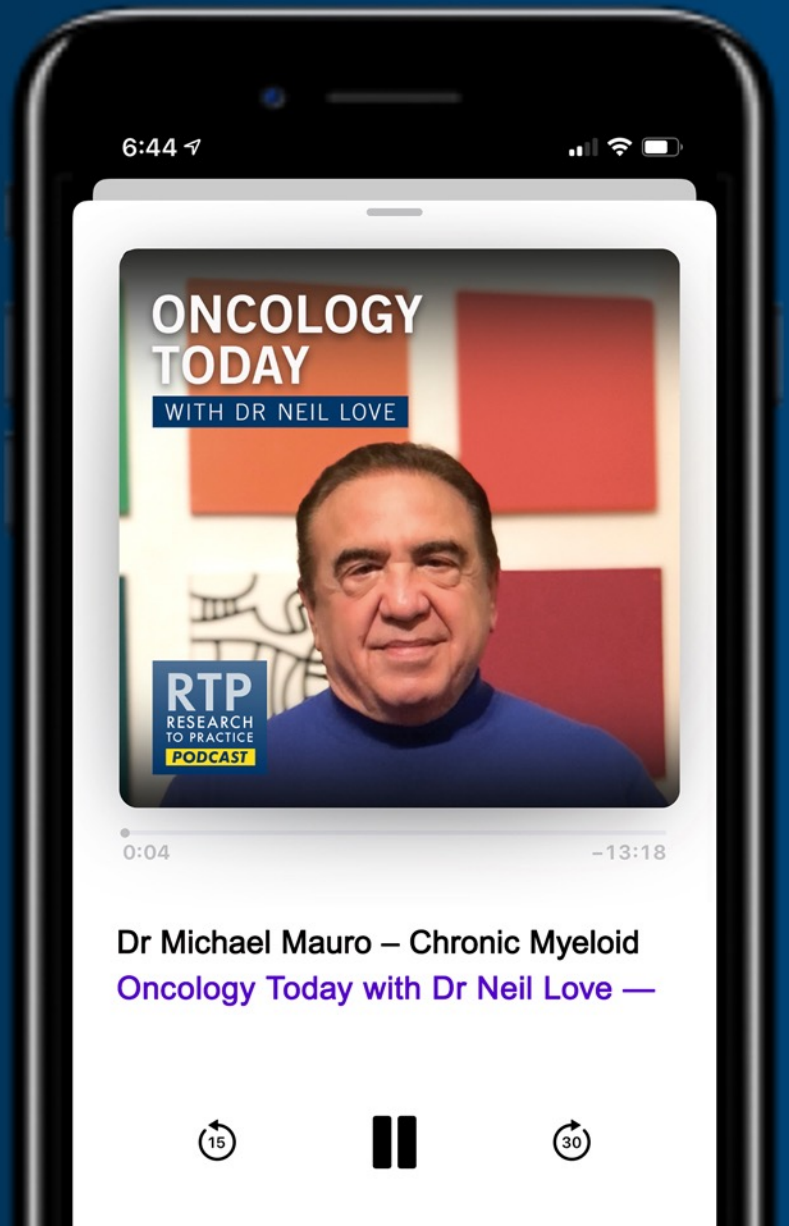

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Philip A Thompson, MB, BS (Hons)

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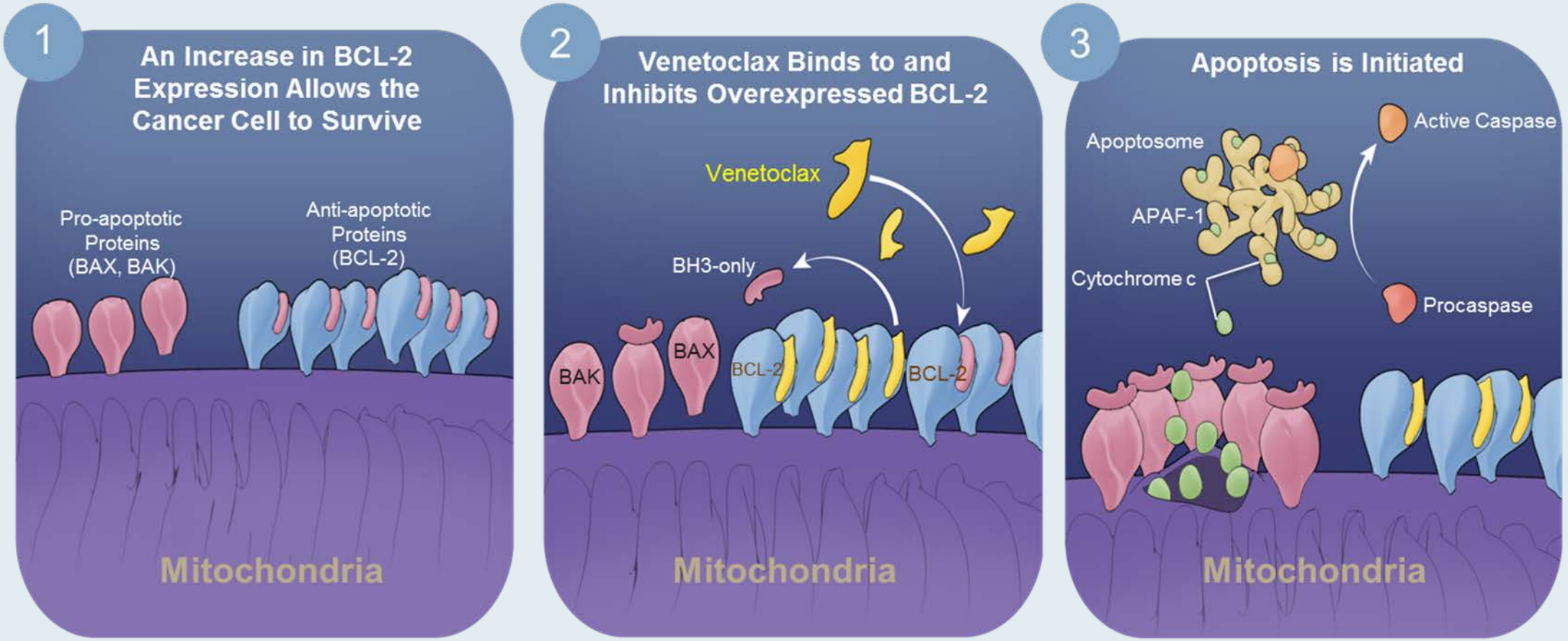
# Venetoclax Mechanism of Action




- 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 et al. ASCO 2015;Abstract 8576.

# 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 co-morbidities:
    - CHF requiring treatment or Ejection Fraction ≤50%
    - Chronic stable angina
    - DLCO ≤ 65% or FEV1 ≤ 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

## Treatment

Randomization 2:1
N=433*

**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 |

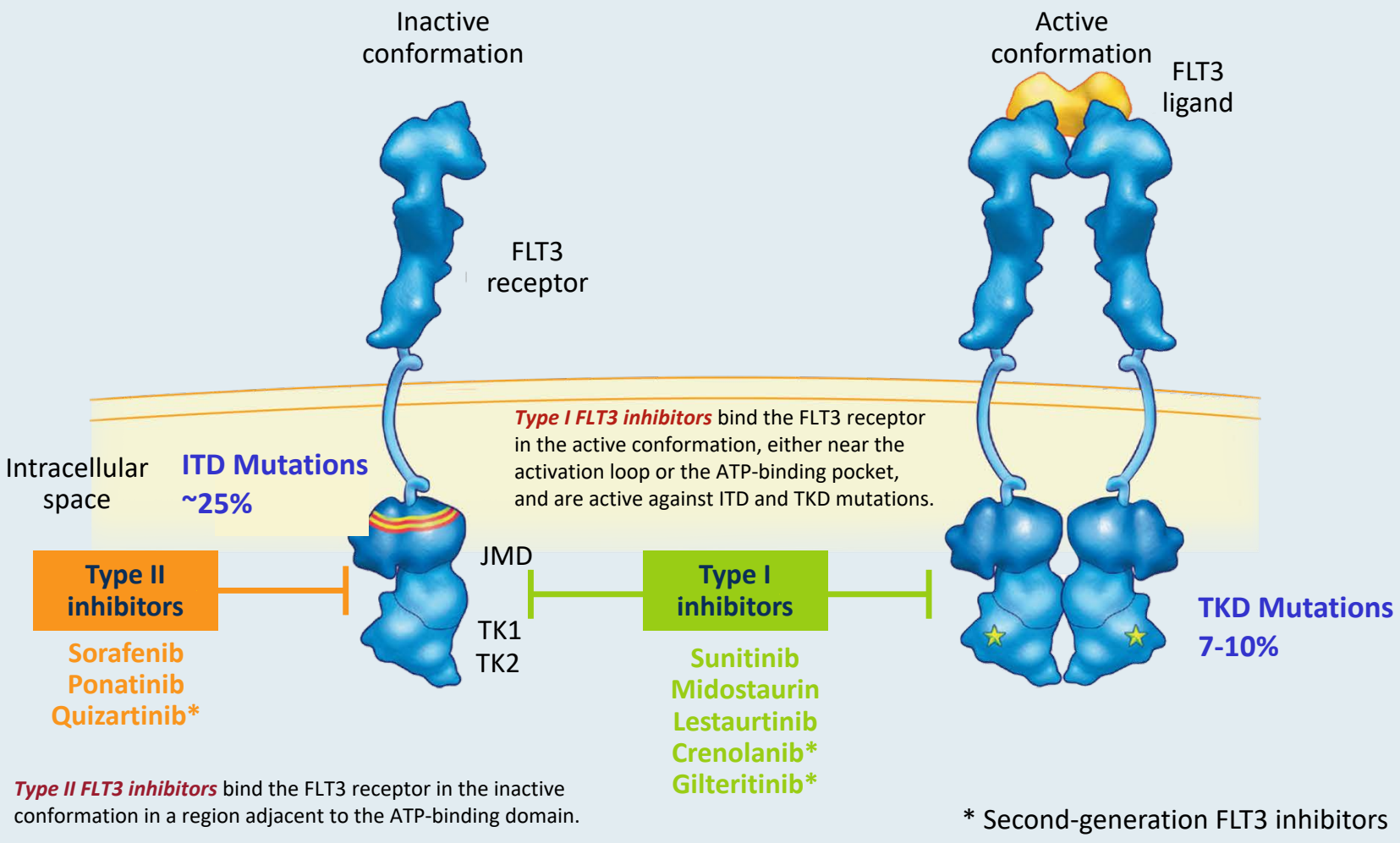
* 2 patients were not stratified by cytogenetic risk. They were excluded from efficacy analysis but included in the safety analysis. 6 patients who did not receive treatment were excluded from the safety analysis set.

AML: Acute myeloid leukemia; CHF: Congestive heart failure; CNS: Central nervous system; CR: Complete remission; CRi: CR+ incomplete marrow remission; CRh: CR+ incomplete hematologic recovery; DCLO: diffusion lung capacity for carbon monoxide; ECOG: Eastern Cooperative Oncology Group; FEV1 : Forced expiratory volume; HMA: Hypomethylating agent; NCCN: National Comprehensive Cancer Network



DiNardo C et al. EHA 2020;Abstract LB2601.

# FLT3 Mutations (ITD and TKD) Occur in Approximately 30% to 35% of Patients with AML



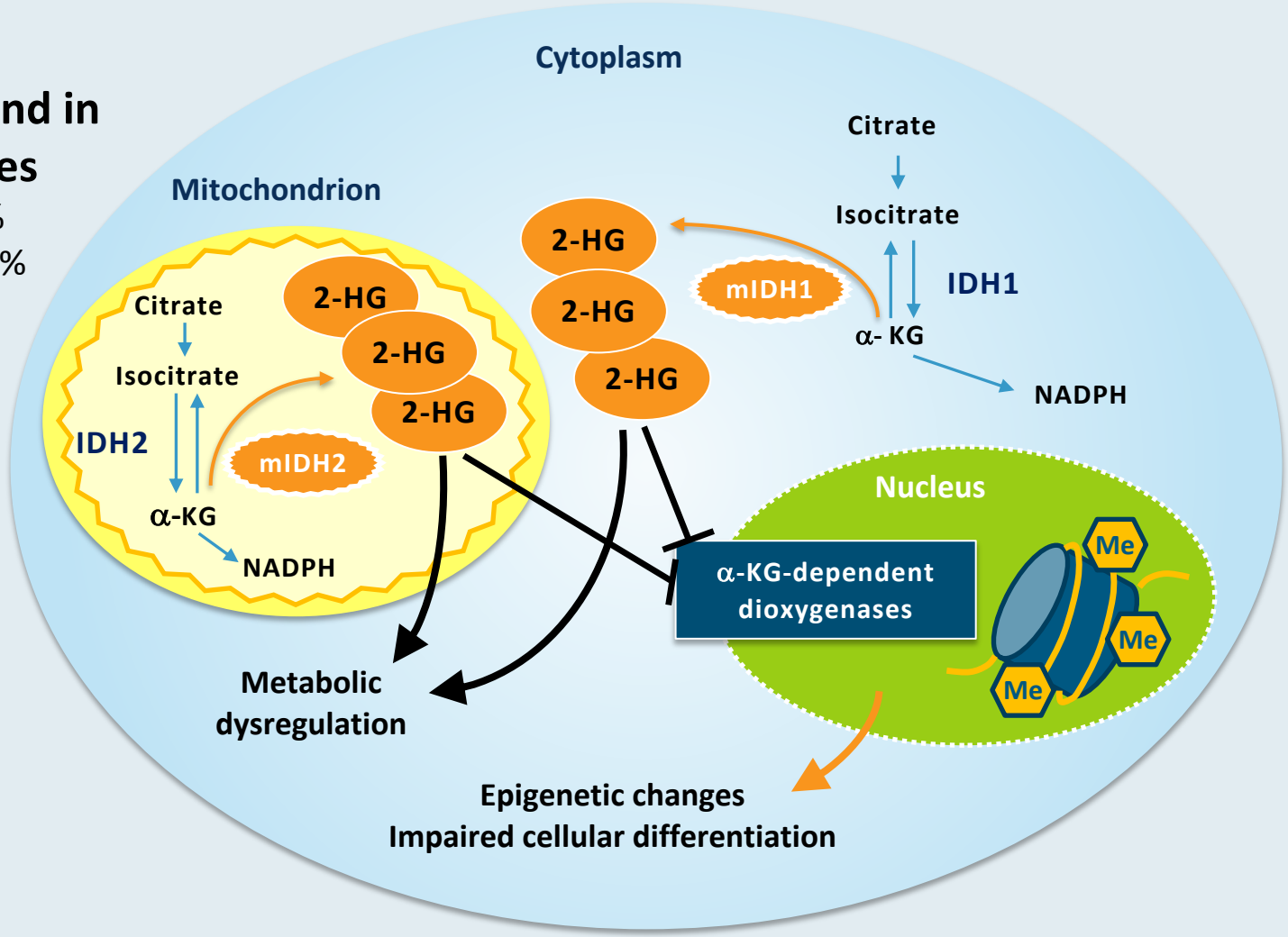

Daver N et al. *Leukemia* 2019;33:299-312.


KAHL

# IDH1 and IDH2 Mutations in AML

**IDH mutations are found in ~16%-20% of AML cases**

- IDH1 mutations in ~7.5%
- IDH2 mutations in ~8-19%




Buege MJ et al. *Cancers* 2018;10:187; Döhner H et al. *N Engl J Med* 2015;373(12):1136-52; Bullinger L et al. *J Clin Oncol* 2017;35(9):934-46.

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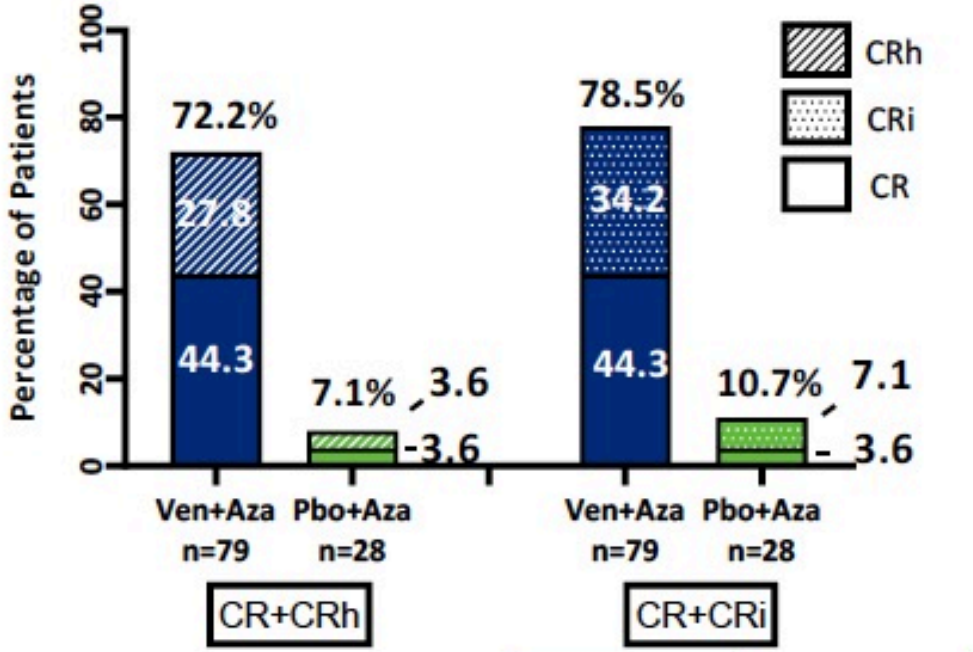
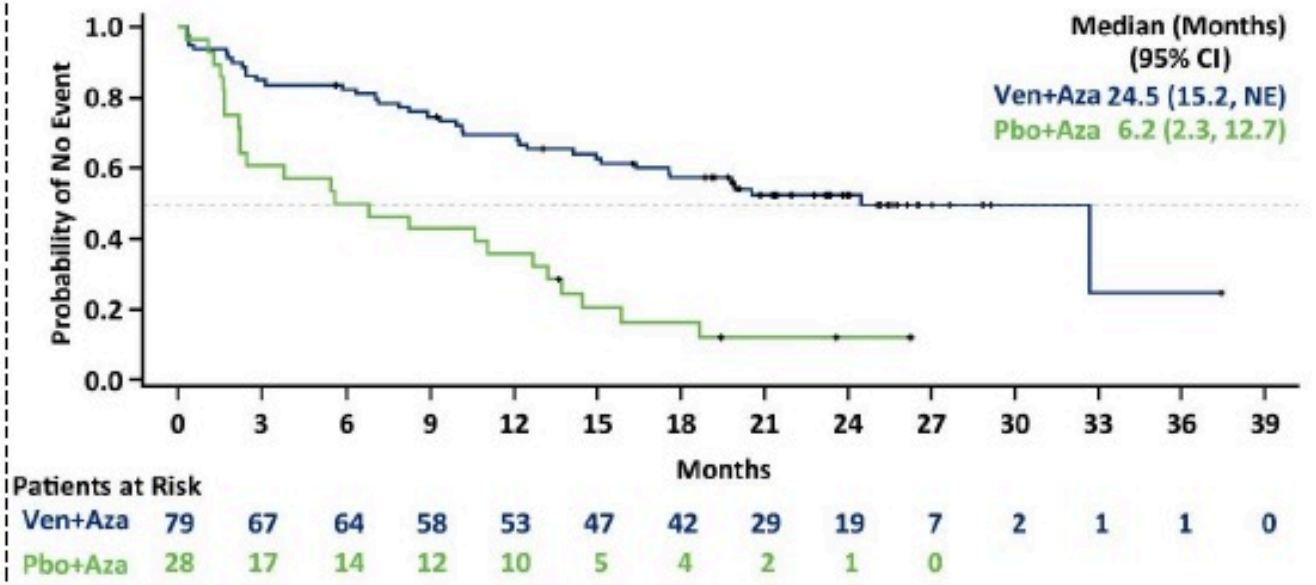
# VIALE-A: Outcomes with Venetoclax + Azacitidine for AML with IDH1/2 Mutations




| | Ven + Aza n = 79 | Pbo + Aza n = 28 |
|---|---|---|
| **CR+CRh:** | | |
| Median time to first response, mo. (min, max) | 1.0 (0.7, 9.6) | 2.6 (2.1, 3.1) |
| Median DoR, mo. (95% CI)* | 29.6 (16.7, NE) | 15.5 (NE) |
| **CR + CRi:** | | |
| Median time to first response, mo. (min, max) | 1.1 (0.7, 8.8) | 3.4 (2.1, 7.1) |
| Median DoR, mo. (95% CI)* | 29.5 (16.7, NE) | 9.5 (3.5, 15.5) |
| **Median treatment cycles (min,max)** | 8.0 (1, 37) | 2.5 (1, 18) |




Patients at Risk

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ven+Aza | 79 | 67 | 64 | 58 | 53 | 47 | 42 | 29 | 19 | 7 | 2 | 1 | 1 | 0 |
| Pbo+Aza | 28 | 17 | 14 | 12 | 10 | 5 | 4 | 2 | 1 | 0 | | | | |

**Survival Estimate (%) (95% CI)**

| | Month 6 | Month 12 | Month 24 |
|---|---|---|---|
| | 82.3 (71.9, 89.1) | 69.3 (57.8, 78.3) | 52.4 (40.4, 63.1) |
| | 50.0 (30.6, 66.6) | 35.7 (18.9, 53.0) | 12.2 (3.2, 27.8) |

Pratz K et al. ASH 2020;Abstract 1944.

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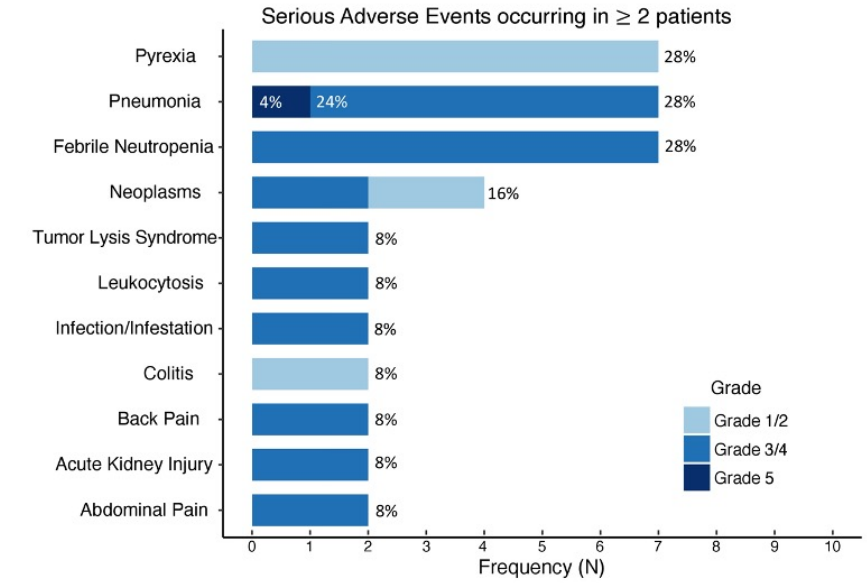
# Phase Ib/II Study of Ivosidenib with Venetoclax with or without Azacitidine in Patients with Myeloid Cancer and an IDH1 Mutation

- 3 x 3 dose escalation/de-escalation study exploring 4 dose levels in 25 patients with advanced MDS or MPN or newly diagnosed or R/R AML

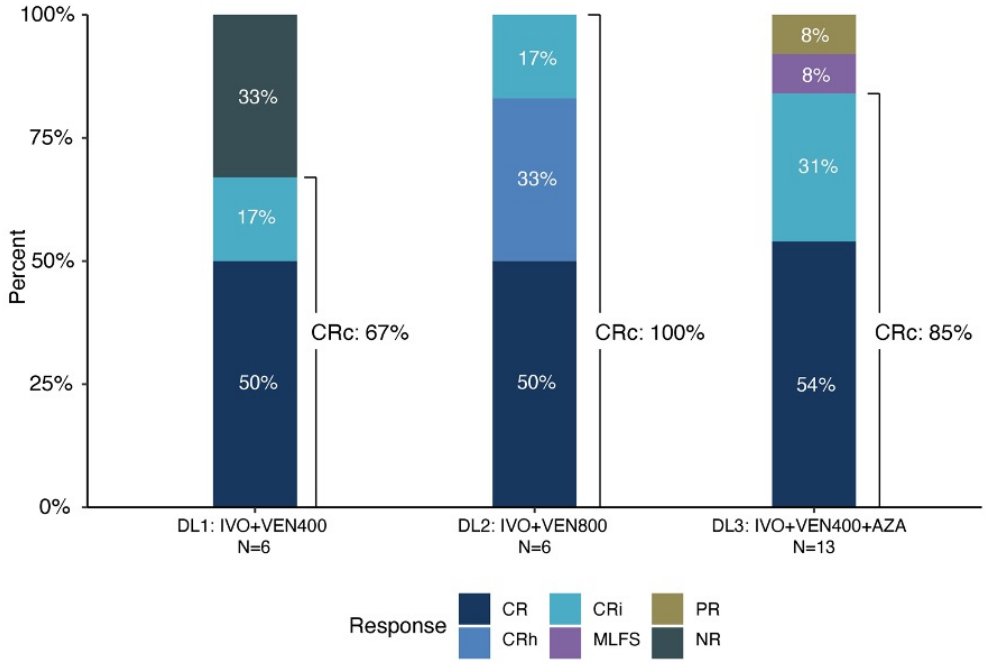
## Safety




| Mortality | Frequency |
|---|---|
| 30-day | 0% |
| 60-day | 0% |
| Study Deaths | 1 (pneumonia) |

| IDH Differentiation Syndrome N (%) | |
|---|---|
| Dose Level #1 | 2 (33%) |
| Dose Level #2 | 1 (17%) |
| Dose Level #3 | 1 (8%) |

## Efficacy




| | DL1 (n = 6) | DL2 (n = 6) | DL3 (n = 13) |
|---|---|---|---|
| 1-Year OS | 50% | 67% | 83% |

Lachowiez CA et al. ASCO 2021;Abstract 7012.

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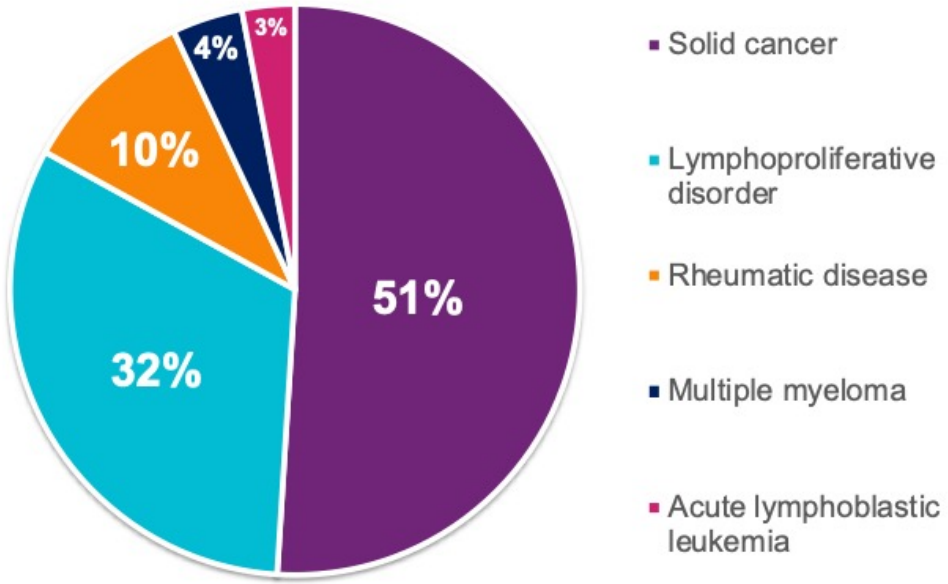
# Therapy-Related AML

**The WHO defines t-AML as AML that arises from prior cytotoxic therapy or ionizing radiotherapy for an unrelated disease. Estimated to account for 5-10% of all AML cases.**

Primary malignancy prior to tAML

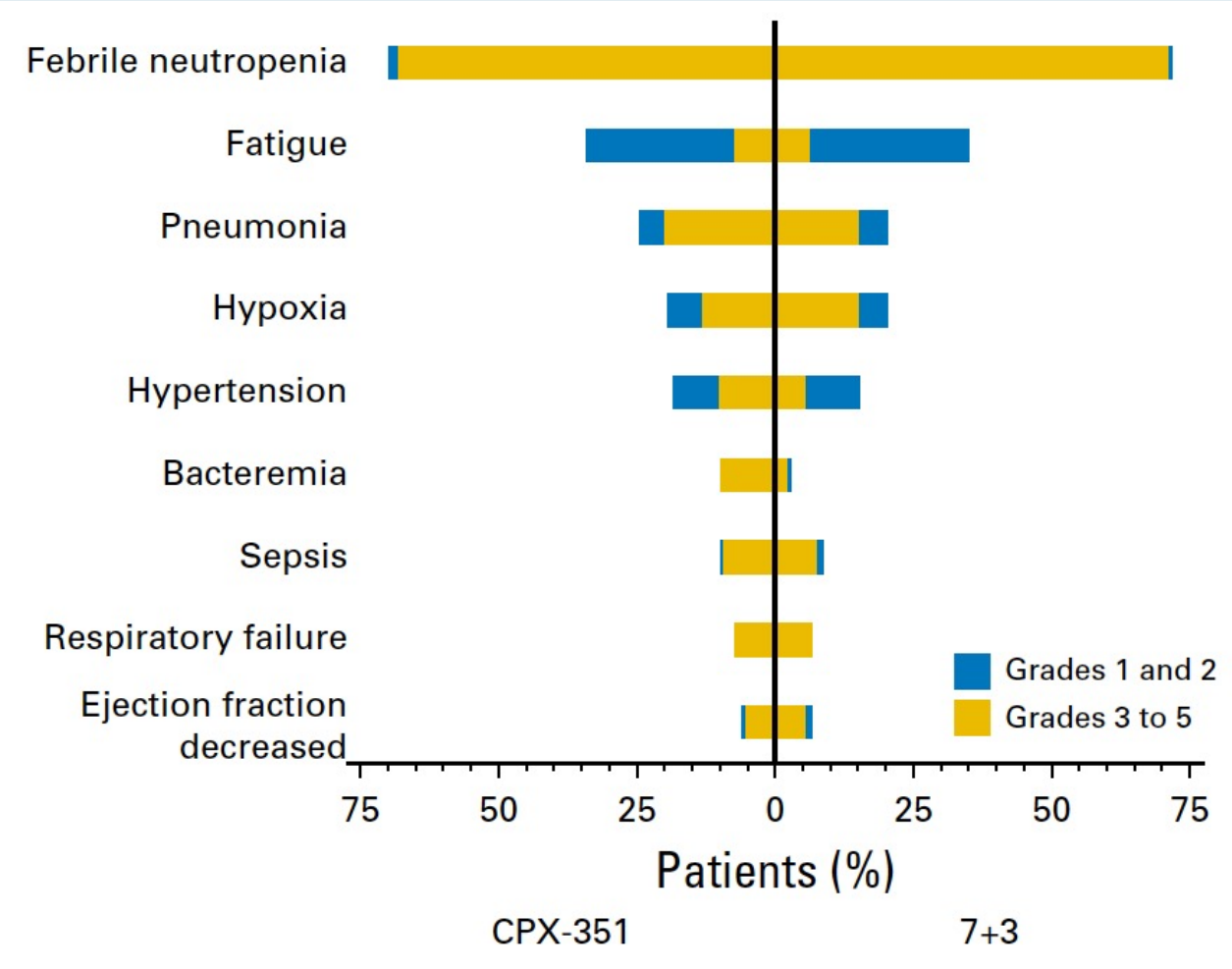



| Cytotoxic therapy[a] | MOA | Examples | Latency period |
|---|---|---|---|
| Alkylating agents and radiation | Induce chromosomal deletions, commonly in 5 and/or 7 | Cyclophosphamide, mechlorethamine, procarbazine, chlorambucil, melphalan, carmustine, busulfan | 5-10 years |
| Topoisomerase II inhibitors | Induce chromosomal translocations | Etoposide, teniposide, mitoxantrone, epirubicin, and doxorubicin | 2-3 years |

Bhatia S. *Semin Oncol.* 2013;40(6):666-675. 2. Czader M, et al. *Am J Clin Pathol.* 2009;132(3):410-425. 3. Leone G, et al. *Haematologica.* 1999;84(10):937-945.

Courtesy of Eunice S Wang, MD.

# Phase III Trial of CPX-351 versus 7 + 3 Cytarabine and Daunorubicin for Older Patients with Newly Diagnosed High-Risk or Secondary AML: Most Frequently Reported Adverse Events




Lancet JE et al. *J Clin Oncol* 2018;36(26):2684-92.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*Thank you for joining us!*

*CME and MOC credit information will be emailed to each participant within 5 business days.*

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# *Meet The Professor* Program Participating Faculty

**Amir Fathi, MD**
Director, Leukemia Program
Massachusetts General Hospital
Associate Professor of Medicine
Harvard Medical School
Boston, Massachusetts

**Rebecca L Olin, MD, MSCE**
Associate Professor of Medicine
Division of Hematology/Oncology
Department of Medicine
University of California, San Francisco
San Francisco, California

**Keith W Pratz, MD**
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Philadelphia, Pennsylvania

**Andrew H Wei, MBBS, PhD**
Professor, Department of Haematology
Alfred Hospital
Monash University
Walter and Eliza Hall Institute of Medical Research
Melbourne, Australia

**Moderator**
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Research To Practice
Miami, Florida

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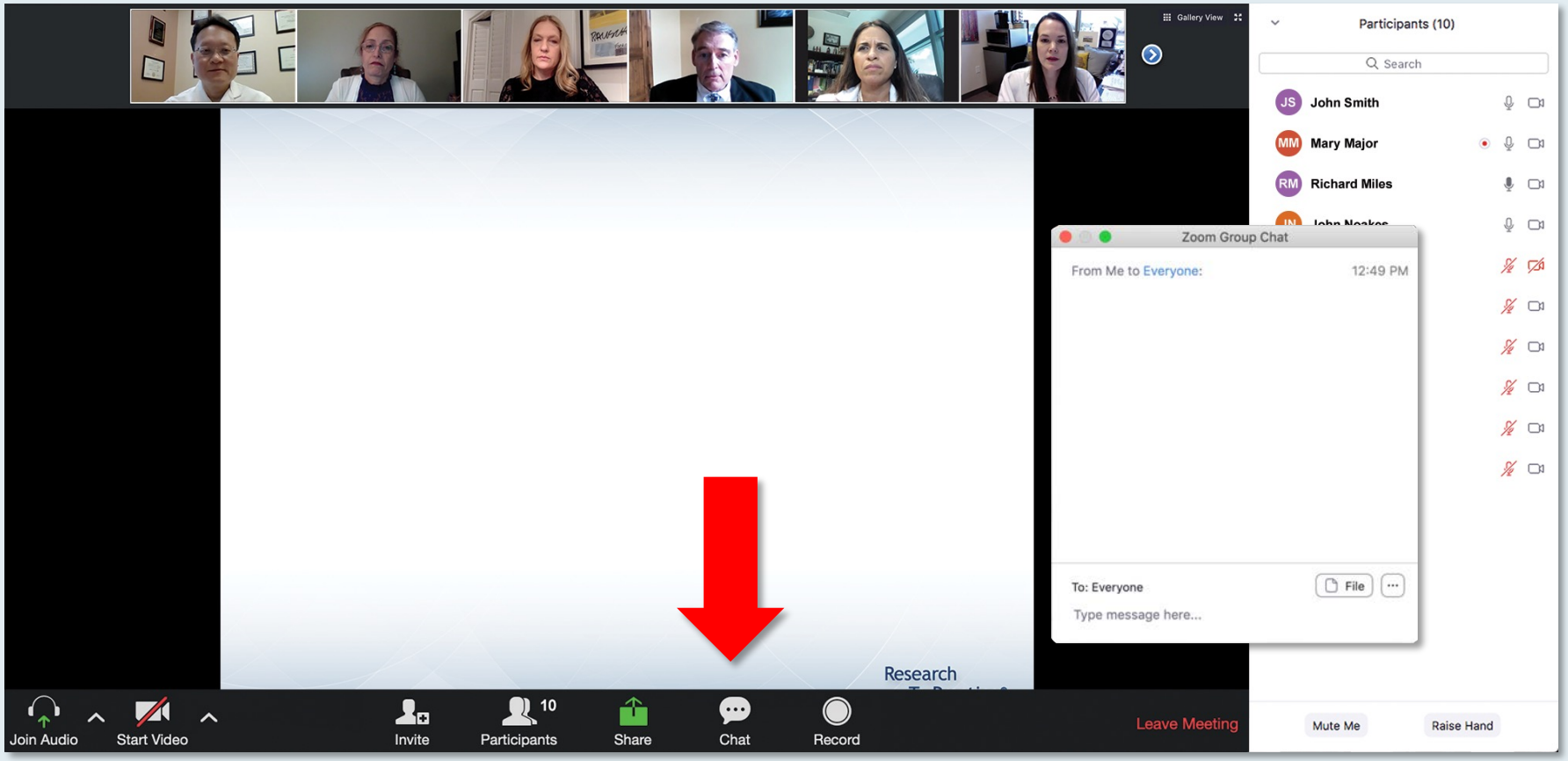


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**Raji Shameem, MD**
Florida Cancer Specialists
and Research Institute
Deland, Florida

**Shachar Peles, MD**
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Lake Worth, Florida

**John Yang, MD**
Oncologist
Fall River, Massachusetts

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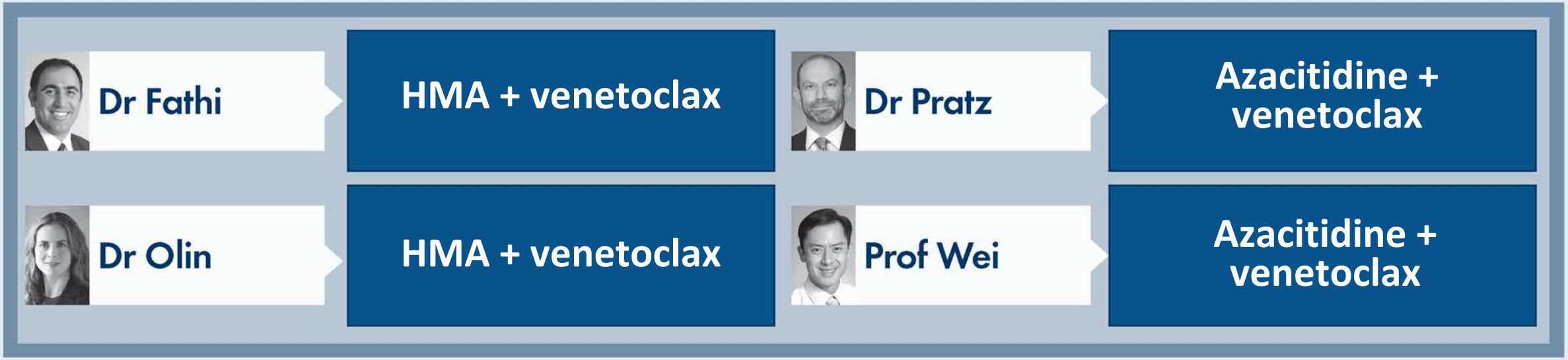
# Regulatory and reimbursement issues aside, in general, what is your preferred initial treatment for a patient with AML with no actionable mutations who is not eligible for intensive chemotherapy?




HMA: azacitidine or decitabine

# Agenda

Introduction: AML Molecular Workup

Module 1: Dr Peles — A 71-year-old woman with AML with MDS-related changes

Module 2: Dr Shameem — A 77-year-old man with AML and an IDH1 mutation

Module 3: Dr Olin — A 62-year-old man with therapy-related AML

Module 4: Dr Yang — A 71-year-old woman with AML and FLT3-ITD and WT1 mutations

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Module 6: Journal Club with Dr Pratz

Module 7: Faculty Survey

Module 8: Appendix

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# Case Presentation – Dr Peles: A 71-year-old woman with AML with MDS-related changes

Dr Shachar Peles

- Annual routine physical: WBC 1.6, ANC 2,556, Hb 11.1, Plt 77; asymptomatic
- Bone marrow biopsy: AML 40% blasts, mild dyserythropoiesis, normal karyotype
- Decitabine (IV)/venetoclax initiated
- NGS: CBL, CUX1, SRSF2, and PDGFRA mutations
- Bone marrow biopsy day 28: 4% blasts

**Questions**

- Should I have treated her with liposomal daunorubicin/cytarabine, given that this is AML with MDS-related changes? Should I have waited for the NGS results to make that decision?
- She has a 9/10 match donor for allotransplant. Is that a reasonable option for her?

# Case Presentation – Dr Peles: A 71-year-old woman with AML with MDS-related changes (continued)

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**Questions**

- ***May oral decitabine be substituted, either with the initial cycle of therapy or subsequent cycles of therapy? Can we administer decitabine/venetoclax initially, and then continue with oral azacitidine?***
- ***Do we know the efficacy in terms of adding venetoclax to an HMA in an MDS patient once they've progressed on HMA alone?***
- ***Do we have data on using venetoclax in combination with an HMA right out of the gate on patients with MDS? How would you integrate the combination?***

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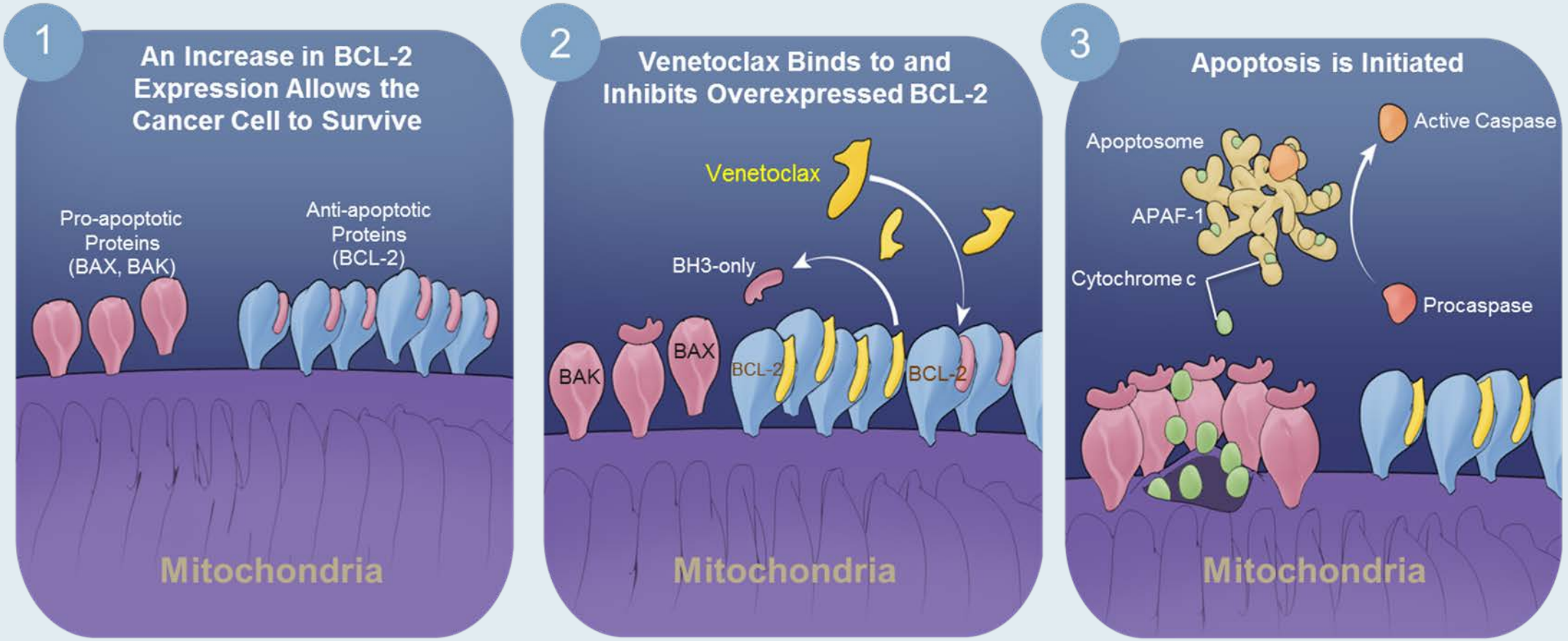


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    - CHF requiring treatment or Ejection Fraction ≤50%
    - Chronic stable angina
    - DLCO ≤ 65% or FEV1 ≤ 65%
    - ECOG 2 or 3

**Exclusion**

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

## Treatment

Randomization 2:1
N=433*

**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 |

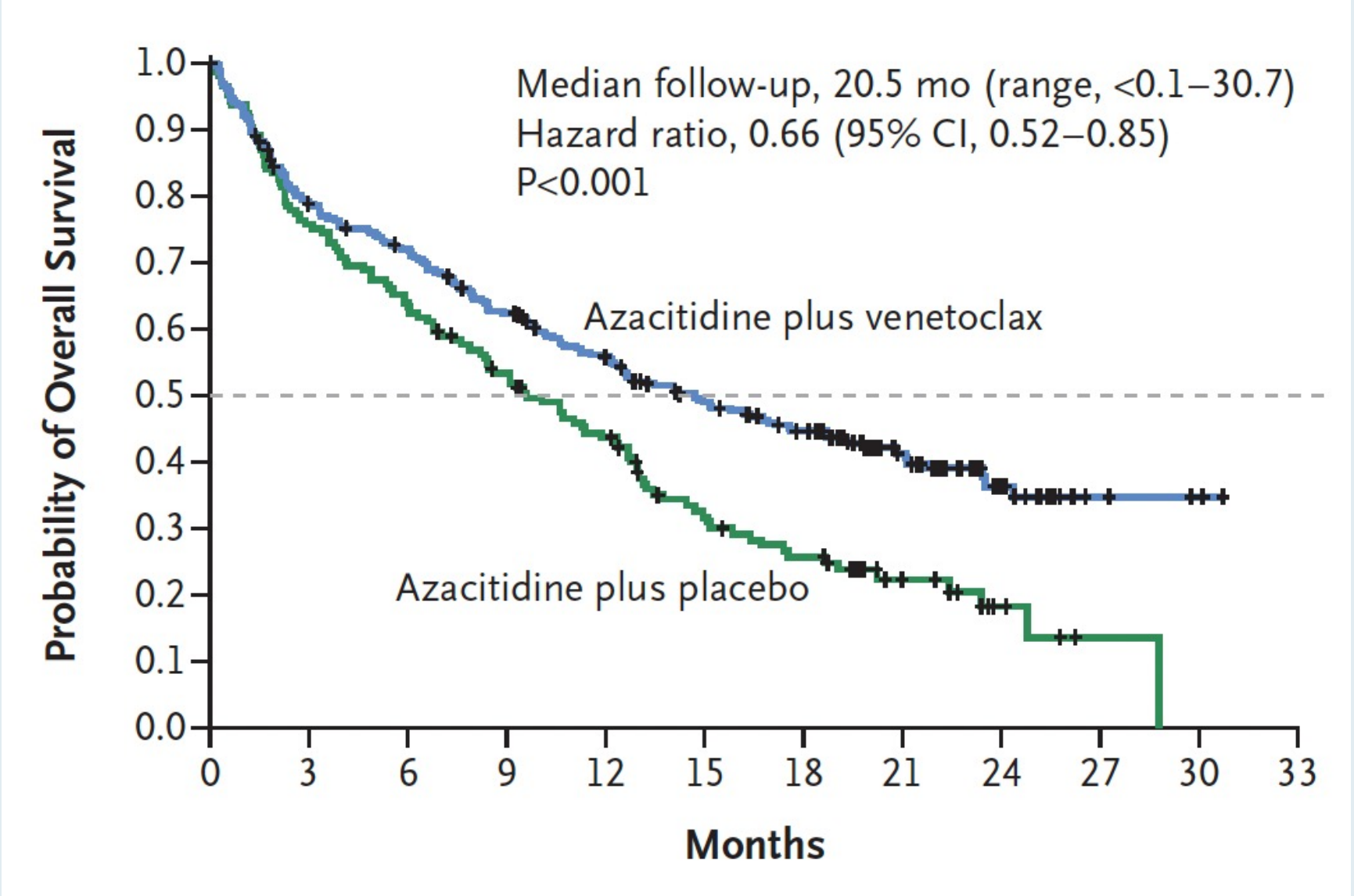
* 2 patients were not stratified by cytogenetic risk. They were excluded from efficacy analysis but included in the safety analysis. 6 patients who did not receive treatment were excluded from the safety analysis set.

AML: Acute myeloid leukemia; CHF: Congestive heart failure; CNS: Central nervous system; CR: Complete remission; CRi: CR+ incomplete marrow remission; CRh: CR+ incomplete hematologic recovery; DCLO: diffusion lung capacity for carbon monoxide; ECOG: Eastern Cooperative Oncology Group; FEV1 : Forced expiratory volume; HMA: Hypomethylating agent; NCCN: National Comprehensive Cancer Network



DiNardo C et al. EHA 2020;Abstract LB2601.

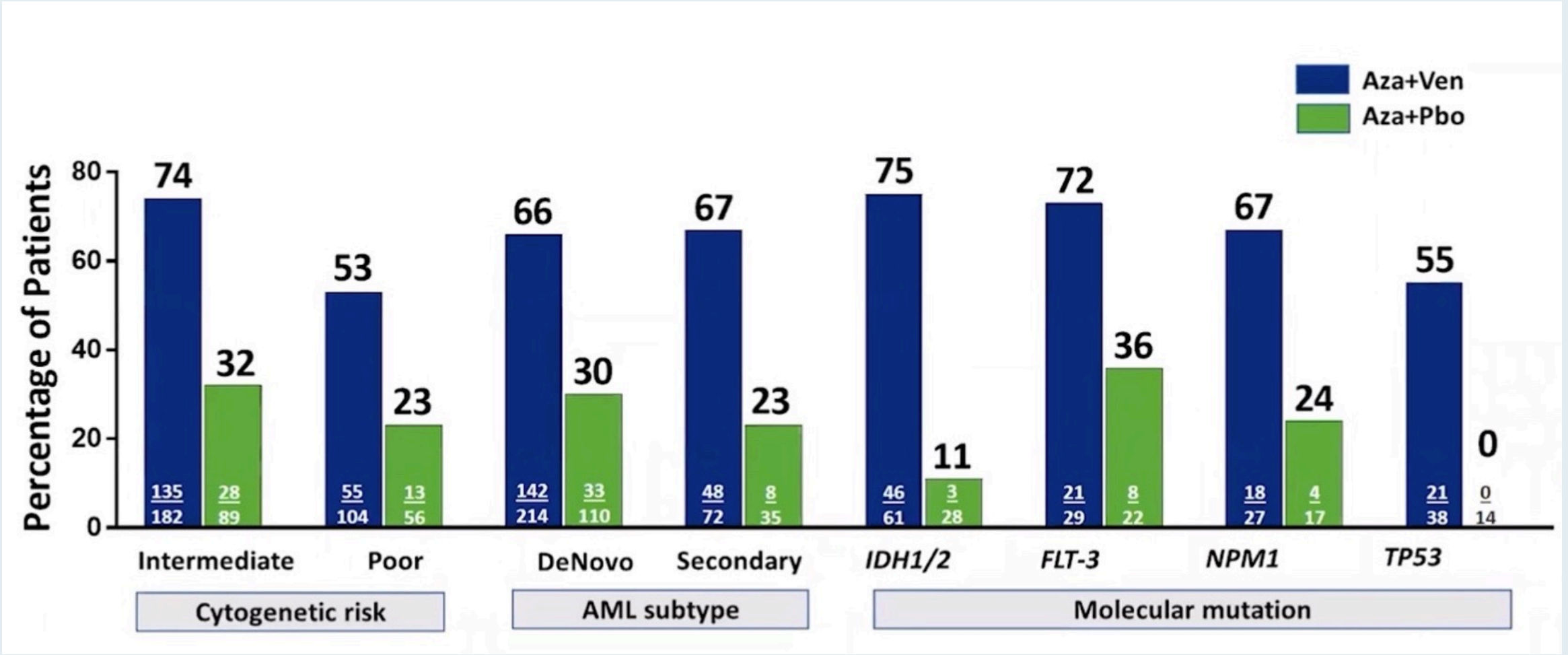
# VIALE-A: Overall Survival




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

RTP RESEARCH TO PRACTICE

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




DiNardo C et al. EHA 2020;Abstract LB2601.

# VIALE-C Phase 3 Study Design

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

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

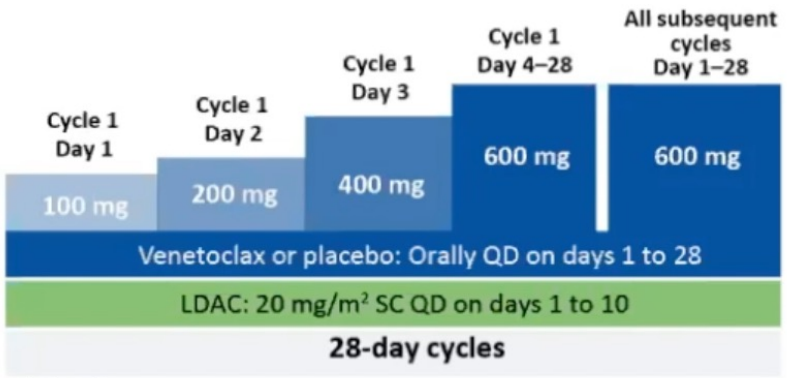
- **Venetoclax + LDAC (n=143)**
- **Placebo + LDAC (n=68)**

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**

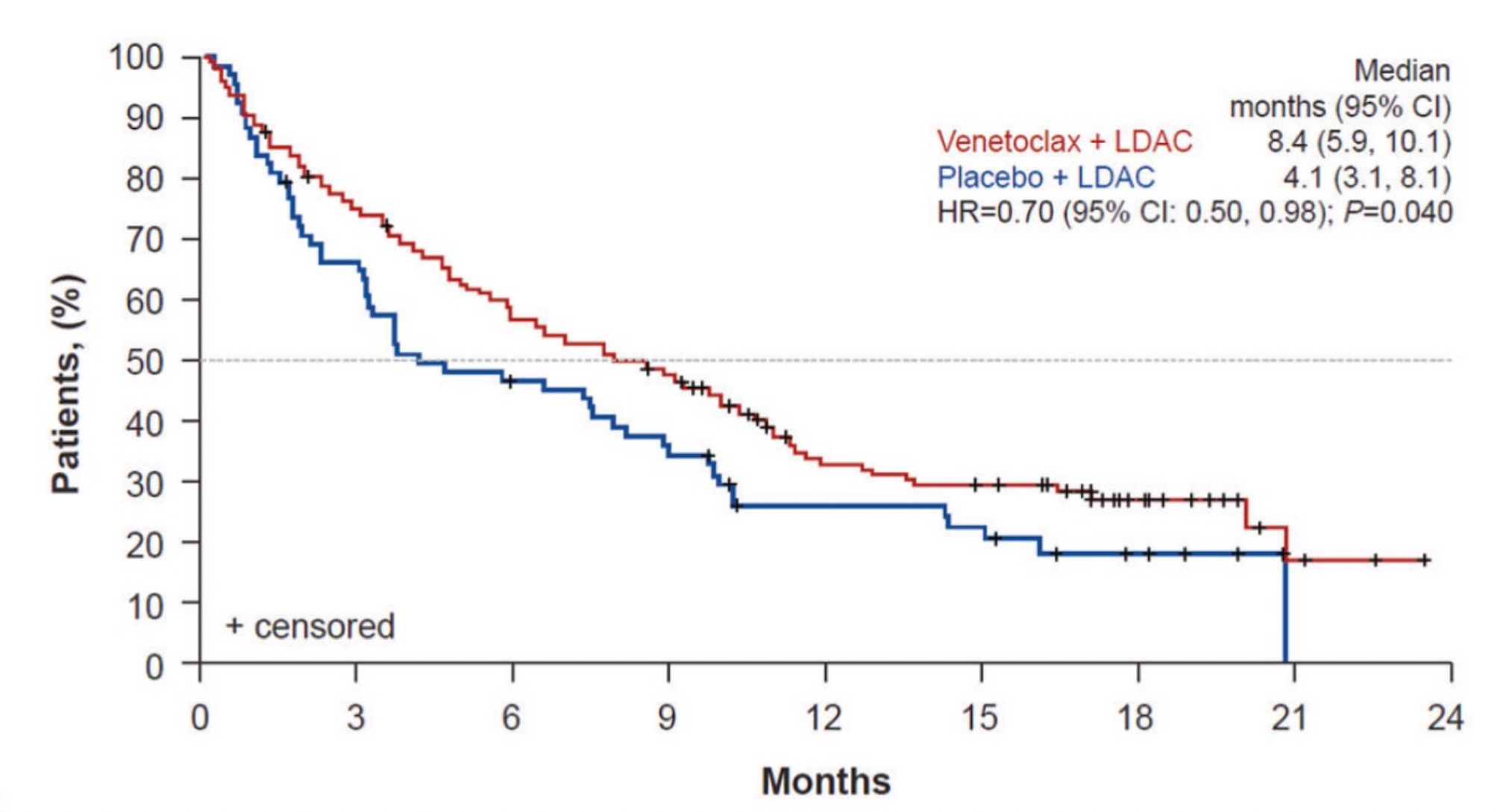
- CR, CRh, and CRi (modified IWG criteria[1])
- Rate of transfusion independence
- EFS
- MRD

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 Cancer J* 2021;11:163.

# Agenda

Introduction: AML Molecular Workup

Module 1: Dr Peles — A 71-year-old woman with AML with MDS-related changes

**Module 2: Dr Shameem — A 77-year-old man with AML and an IDH1 mutation**

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Module 8: Appendix

# Case Presentation – Dr Shameem: A 77-year-old man with AML and an IDH1 mutation

Dr Raji Shameem

- PMH: HLD, HTN, persistent pancytopenia including macrocytic anemia
- CBC on consultation showed WBC 1.1, ANC 0.10, Hb 9.7, MCV 116, Plt 91
- Peripheral blood flow cytometry: CD34+ blasts (9.9% of total cellularity)
- Bone marrow biopsy: consistent with AML with myelodysplasia changes, hypercellular bone marrow with 85% blasts, complex karyotype
- Azacitidine/venetoclax initiated as patient was anxious to start therapy
- NGS: IDH1 mutation
- Repeat bone marrow biopsy at 1 month: hypoplasia with no residual blasts

**Questions**

- In the elderly population, do you typically wait for NGS results before deciding a treatment course?
- What would be your first-line therapy of choice for a patient with an IDH1 or IDH2 mutation?
- What is your experience with differentiation syndrome associated with the use of IDH inhibitors? How do you manage it?

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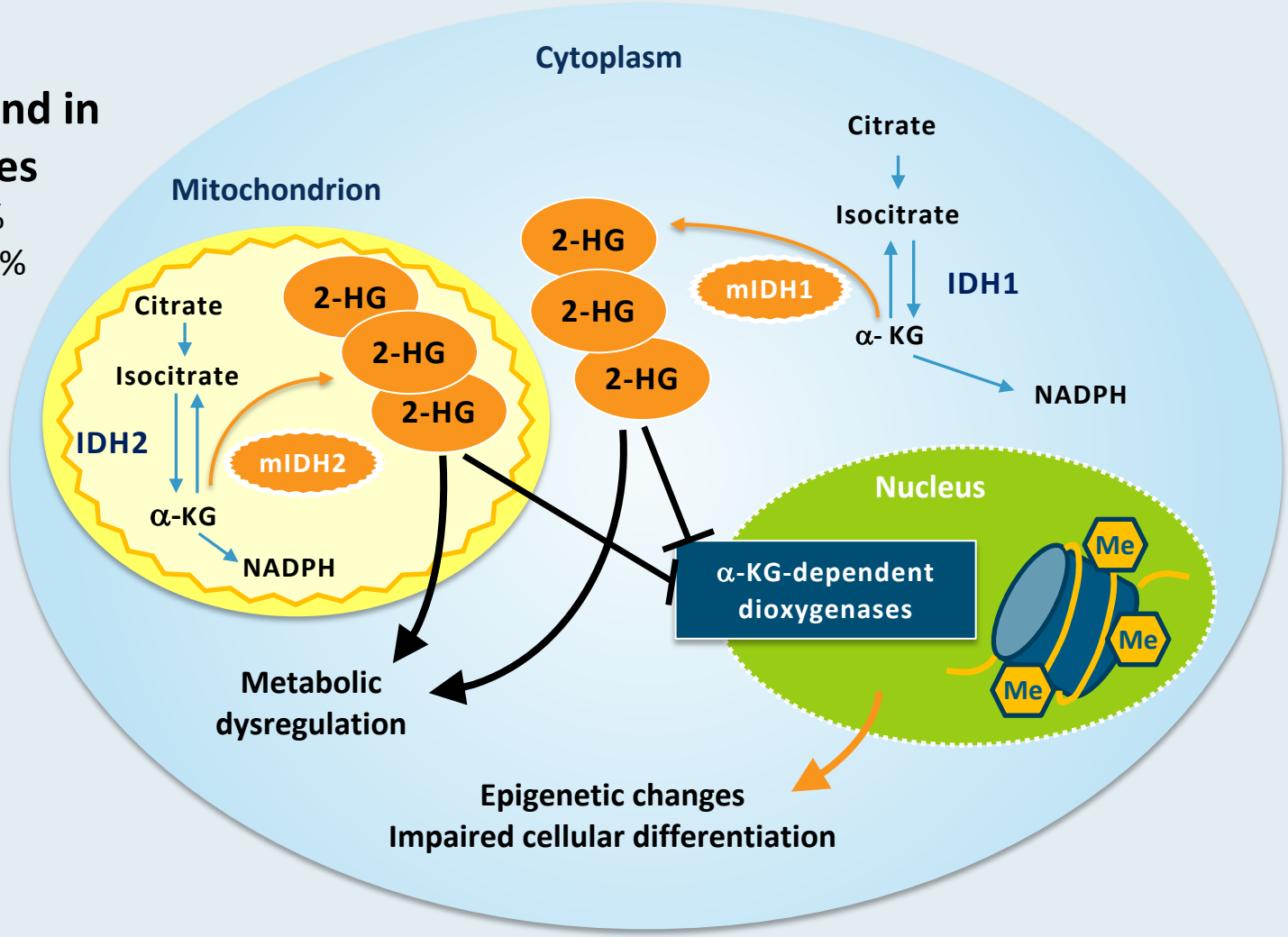
# IDH1 and IDH2 Mutations in AML

**IDH mutations are found in ~16%-20% of AML cases**

- IDH1 mutations in ~7.5%
- IDH2 mutations in ~8-19%




Buege MJ et al. *Cancers* 2018;10:187; Döhner H et al. *N Engl J Med* 2015;373(12):1136-52; Bullinger L et al. *J Clin Oncol* 2017;35(9):934-46.

RTP RESEARCH TO PRACTICE

# Pivotal Studies of IDH Inhibitor Monotherapy for AML with IDH Mutations

| IDH inhibitor | Enasidenib | Ivosidenib | |
|---|---|---|---|
| FDA approval | Aug 1, 2017 | July 20, 2018 | May 2, 2019 |
| Setting | Relapsed/refractory | Relapsed/refractory | Newly diagnosed |
| Trial | AG221-C-001 | AG120-C-001 | AG120-C-001 |
| IDH mutation | IDH2 | IDH1 | IDH1 |
| N | 109 | 179 | 28 |
| Dose | 100 mg qd | 500 mg qd | 500 mg qd |
| CR + CRh | 23% | 30.4% | 42.9% |
| Median duration of response | 8.2 mo | 8.2 mo | Not estimable |
| Median OS, ITT | 9.3 mo | 8.8 mo | 12.6 mo |
| Median OS, complete remission | 19.7 mo | Not reached | Not reported |

CRh = CR with partial hematologic recovery

Stein EM, et al. *Blood* 2017;130(6):722-731; Enasidenib PI, rev 11/2020; DiNardo CD, et al. *N Engl J Med* 2018;378(25):2386; Roboz GJ et al. *Blood* 2020;135(7)463-71; Ivosidenib PI, rev 8/2021.

# AG-221-AML-005: A Phase II Study of Enasidenib + Azacitidine for Newly Diagnosed AML with an IDH2 Mutation

| Clinical endpoint | Enasidenib + azacitidine (n = 68) | Azacitidine (n =33) |
|---|---|---|
| Overall response* | 50 (74%) | 12 (36%) |
| CR | 37 (54%) | 4 (12%) |
| CR + CRh | 39 (57%) | 6 (18%) |
| 12-month survival estimate (%) | 72% | 70% |
| **Select Grade ≥3 treatment-emergent AEs, n (%)** | | |
| Thrombocytopenia | 25 (37%) | 6 (19%) |
| Anemia | 13 (19%) | 7 (22%) |
| Febrile neutropenia | 11 (16%) | 5 (16%) |
| IDH differentiation syndrome | 7 (10%) | — |

* Overall response defined as proportion of patients with complete remission, complete remission with incomplete blood count or platelet recovery, partial remission or morphological leukemia-free state

DiNardo CD et al. *Lancet Oncol* 2021;22:1597-608.

RTP RESEARCH TO PRACTICE

# Positive Top-Line Data from the Global Phase III Study of Ivosidenib in Combination with Azacitidine for Previously Untreated AML with an IDH1 Mutation

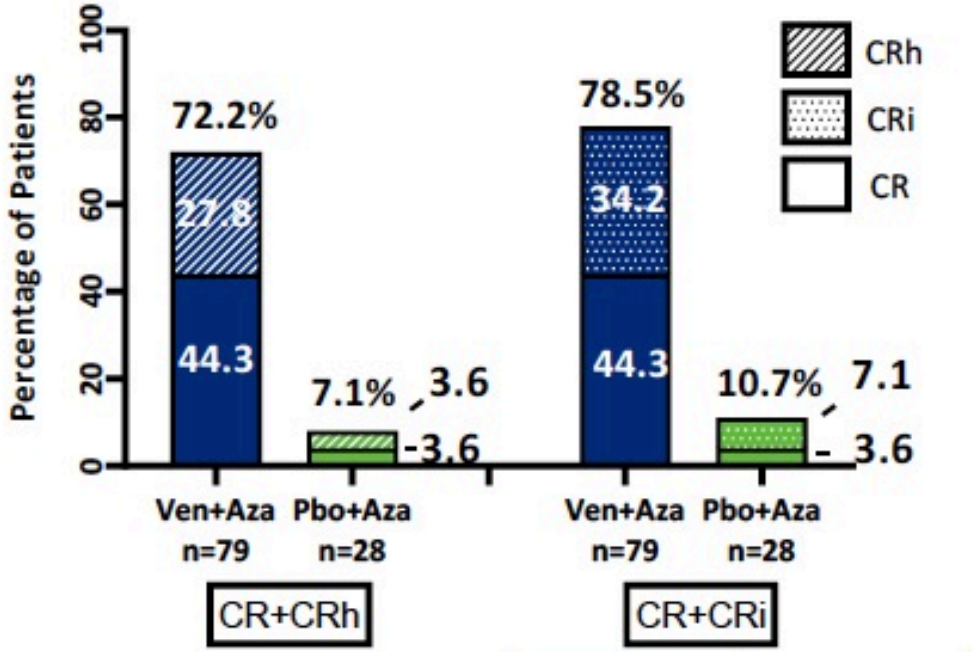
## Press Release: August 2, 2021

"The global Phase 3 double blinded placebo controlled AGILE study of ivosidenib in combination with the chemotherapy azacitidine in adults with previously untreated IDH1-mutated acute myeloid leukemia (AML) met its primary endpoint of event-free survival (EFS). Treatment with ivosidenib in combination with azacitidine compared to azacitidine in combination with placebo demonstrated a statistically significant improvement in EFS. Additionally, the trial met all of its key secondary endpoints, including complete remission rate (CR rate), overall survival (OS), CR and complete remission with partial hematologic recovery rate (CRh rate) and objective response rate (ORR).

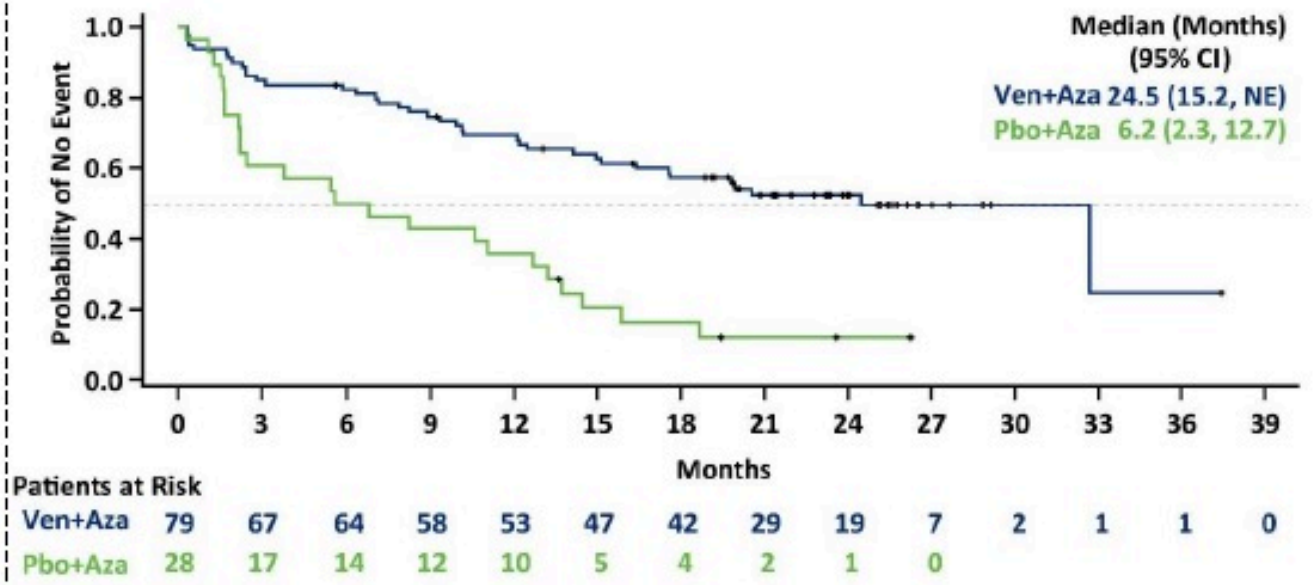
The safety profile of ivosidenib in combination with azacitidine was consistent with previously published data. The study recently halted further enrollment based on the recommendation of the Independent Data Monitoring Committee (IDMC), as a difference of clinical importance was noted between the treatment groups."

https://www.prnewswire.com/news-releases/servier-announces-positive-topline-data-from-the-global-phase-3-study-of-tibsovo-ivosidenib-tablets-in-combination-with-azacitidine-in-patients-with-previously-untreated-idh1-mutated-acute-myeloid-leukemia-301345783.html

# VIALE-A: Outcomes with Venetoclax + Azacitidine for AML with IDH1/2 Mutations




| | Ven + Aza n = 79 | Pbo + Aza n = 28 |
|---|---|---|
| **CR+CRh:** | | |
| Median time to first response, mo. (min, max) | 1.0 (0.7, 9.6) | 2.6 (2.1, 3.1) |
| Median DoR, mo. (95% CI)* | 29.6 (16.7, NE) | 15.5 (NE) |
| **CR + CRi:** | | |
| Median time to first response, mo. (min, max) | 1.1 (0.7, 8.8) | 3.4 (2.1, 7.1) |
| Median DoR, mo. (95% CI)* | 29.5 (16.7, NE) | 9.5 (3.5, 15.5) |
| **Median treatment cycles (min,max)** | 8.0 (1, 37) | 2.5 (1, 18) |




Patients at Risk

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ven+Aza | 79 | 67 | 64 | 58 | 53 | 47 | 42 | 29 | 19 | 7 | 2 | 1 | 1 | 0 |
| Pbo+Aza | 28 | 17 | 14 | 12 | 10 | 5 | 4 | 2 | 1 | 0 | | | | |

**Survival Estimate (%) (95% CI)**

| | Month 6 | Month 12 | Month 24 |
|---|---|---|---|
| | 82.3 (71.9, 89.1) | 69.3 (57.8, 78.3) | 52.4 (40.4, 63.1) |
| | 50.0 (30.6, 66.6) | 35.7 (18.9, 53.0) | 12.2 (3.2, 27.8) |

Pratz K et al. ASH 2020;Abstract 1944.

RTP RESEARCH TO PRACTICE

# Commonly Observed and Noteworthy IDH Inhibitor-Related Adverse Events (AEs)

## Commonly Observed Treatment-Emergent AEs (Any Grade, >20%)

- **Enasidenib:** Hyperbilirubinemia, nausea
- **Ivosidenib:** Diarrhea, leukocytosis, nausea, fatigue, febrile neutropenia, dyspnea, anemia, QT prolongation, peripheral edema

## Noteworthy Grade 3 and 4 AEs

- **IDH differentiation syndrome: 5%-6%**
- **Prolongation of the QT interval**
  - Enasidenib: Not reported
  - Ivosidenib: ~8%
- **Leukocytosis: 2%-3%**
- **Hyperbilirubinemia**
  - Enasidenib: 12%
  - Ivosidenib: Not reported

Stein EM et al. *Blood* 2017;130(6):722-31; DiNardo CD et al. *N Engl J Med* 2018;378:2386-98; Fathi AT et al. *JAMA Oncol* 2018;4(8):1106-10.

# IDH Differentiation Syndrome (IDH-DS)

- **Potentially fatal complication of effective leukemia treatment**
  - First described in patients with APL treated with ATRA
- **Signs and symptoms of IDH-DS not specific**
  - Fever, edema, weight gain, leukocytosis, rash, hypotension, renal dysfunction, and pleural and pericardial effusions
  - A rising leukocyte count, comprising increasing neutrophils with a parallel decrease in leukemic blasts
- **Median time to onset:** ~30 days (range: 5-340 days)
- **Frequency:** 5%-6% Grade 3 or higher
  - Frequent dose interruptions but not associated with treatment discontinuation
- **Treatment**
  - Corticosteroids for IDH-DS
  - Hydroxyurea for leukocytosis, which frequently accompanies IDH-DS
  - Hyperuricemia agents for tumor lysis syndrome, which may co-occur

Stein EM et al. *Blood* 2017;130(6):722-31; Stein EM et al. *Blood* 2019;133(7):676-87; DiNardo CD et al. *N Engl J Med* 2018;378:2386-98; Birendra KC, DiNardo CD. *Clin Lymphoma Myeloma Leuk* 2016;16(8):460-5.

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# Case Presentation – Dr Olin: A 62-year-old man with therapy-related AML

**Dr Rebecca Olin**

- PMH: FL in 2013 treated with bendamustine/rituximab and rituximab maintenance
- Recently developed progressive dyspnea, dizziness and palpitation
- Bloodwork showed neutropenia and anemia
- Bone marrow biopsy: 70% - 80% blasts
- Cytogenetics: Normal, but FISH showed monosomy 7 in 7% of cells
- NGS: TP53 and SRSF2 mutations

# Case Presentation – Dr Olin: A 62-year-old man with therapy-related AML (continued)

Dr Rebecca Olin

- PMH: FL in 2013 treated with bendamustine/rituximab and rituximab maintenance
- Cytogenetics: Normal, but FISH showed monosomy 7 in 7% of cells
- NGS: TP53 and SRSF2 mutations
- ***CPX-351→ bone marrow biopsies on d21 and d28 showed low cellularity and blast 10% - 20%***
- ***Reinduction with CPX-351, and treatment course complicated by neutropenic fevers, DVT and slow recovery counts***
- ***Bone marrow biopsy on d48 showed remission → allogeneic transplant***

***Questions***

- ***What do you do when you encounter a positive nadir bone marrow biopsy result?***
- ***What treatment would you have recommended? Would you recommend decitabine due to the presence of a TP53 mutation in this patient?***

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# Case Presentation – Dr Olin: A 62-year-old man with therapy-related AML (cont)

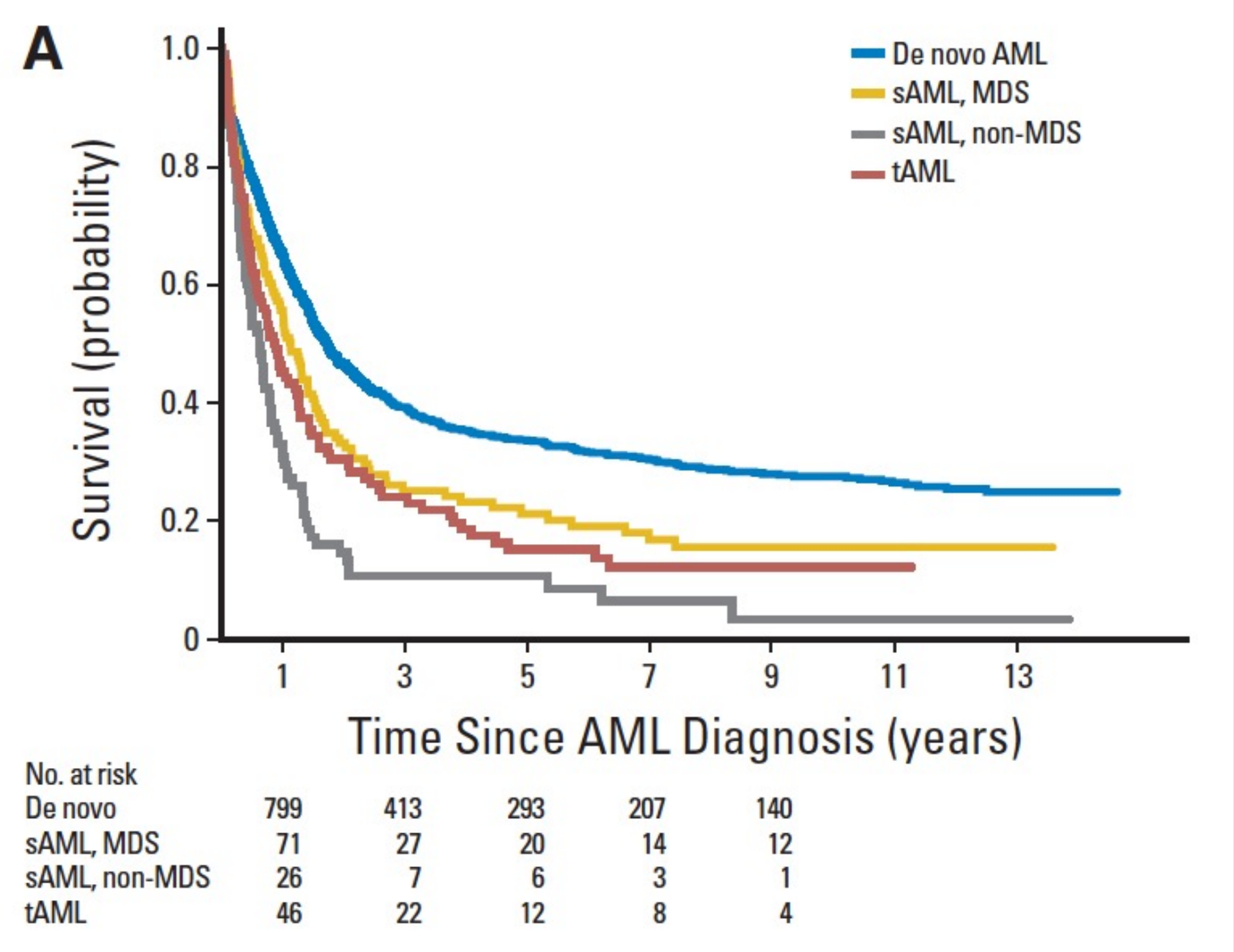
Dr Rebecca Olin

- PMH: FL in 2013 treated with bendamustine/rituximab and rituximab maintenance
- Cytogenetics: Normal, but FISH showed monosomy 7 in 7% of cells
- NGS: TP53 and SRSF2 mutations
- CPX-351→ bone marrow biopsies on d21 and d28 showed low cellularity and blast 10% - 20%
- Reinduction with CPX-351, and treatment course complicated by neutropenic fevers, DVT and slow recovery counts
- Bone marrow biopsy on d48 showed remission → allogeneic transplant

***Questions***

- ***Have you attempted to administer CPX-351 in the outpatient setting? What do you think is the future of CPX-351? Do you believe any of the novel combination trials with this agent are promising?***
- ***What do you do when you encounter a positive nadir bone marrow biopsy result?***

# Survival by AML Diagnosis




Granfeldt Østgård LS et al. *J Clin Oncol* 2015;33:3641-49.

# AML-MRC: AML with MDS-Related Changes

**Definition: AML with a history of MDS or myelodysplasia-related cytogenetic findings, specifically ≥ 20% blasts in the peripheral blood or bone marrow and any of the following:**

- Previously documented MDS or MDS/MPN
- Myelodysplasia-related **cytogenetic abnormalities**
- Morphologic detection of **multilineage dysplasia**

1. ***Complex karyotype*** *(3 or more abnormalities).*
2. ***Unbalanced abnormalities****: -7/del(7q), del(5q)/t(5q), i(17q)/t(17p), -13/del(13q), del(11q), del(12p)/t(12p), idic(X)(q13).*
3. ***Balanced abnormalities****: t(11;16)(q23.3;p13.3), t(3:21)(q26.2;q22.1), t(1;3)(p36.3;q21.2), t(2;11)(p21;q23.3), t(5;12)(q32;p13.2), t(5;7)(q32;q11.2), t(5;17)(q32;p13.2), t(5;10)(q32;q21.2), t(3;5)(q25.3;q35.1)*

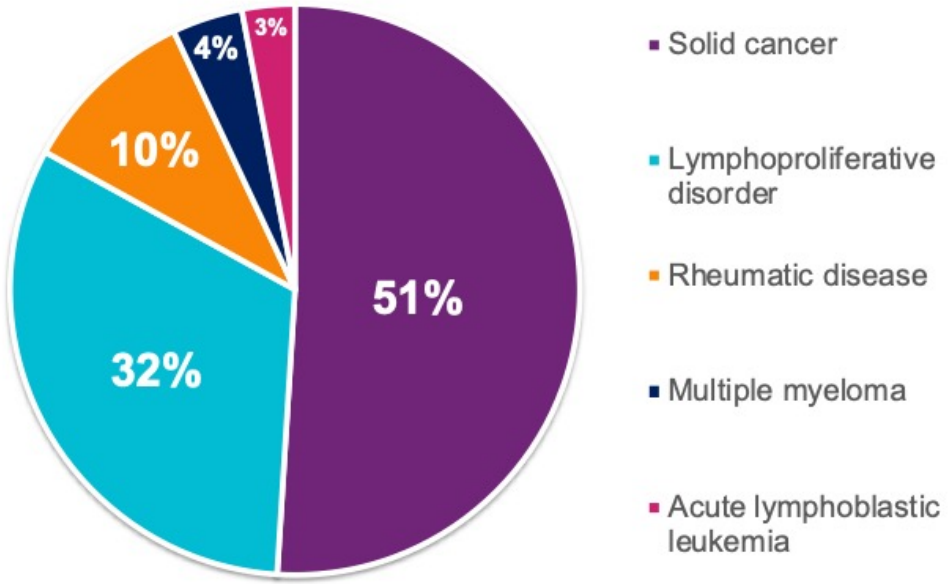
*Footnote 1. The presence of 50% or more dysplastic cells in at least 2 cell lines,* ***excluding cases when a mutation of NPM1 or biallelic mutation of CEBPA is present.***

Courtesy of Eunice S Wang, MD.

# Therapy-Related AML

**The WHO defines t-AML as AML that arises from prior cytotoxic therapy or ionizing radiotherapy for an unrelated disease. Estimated to account for 5-10% of all AML cases.**

Primary malignancy prior to tAML



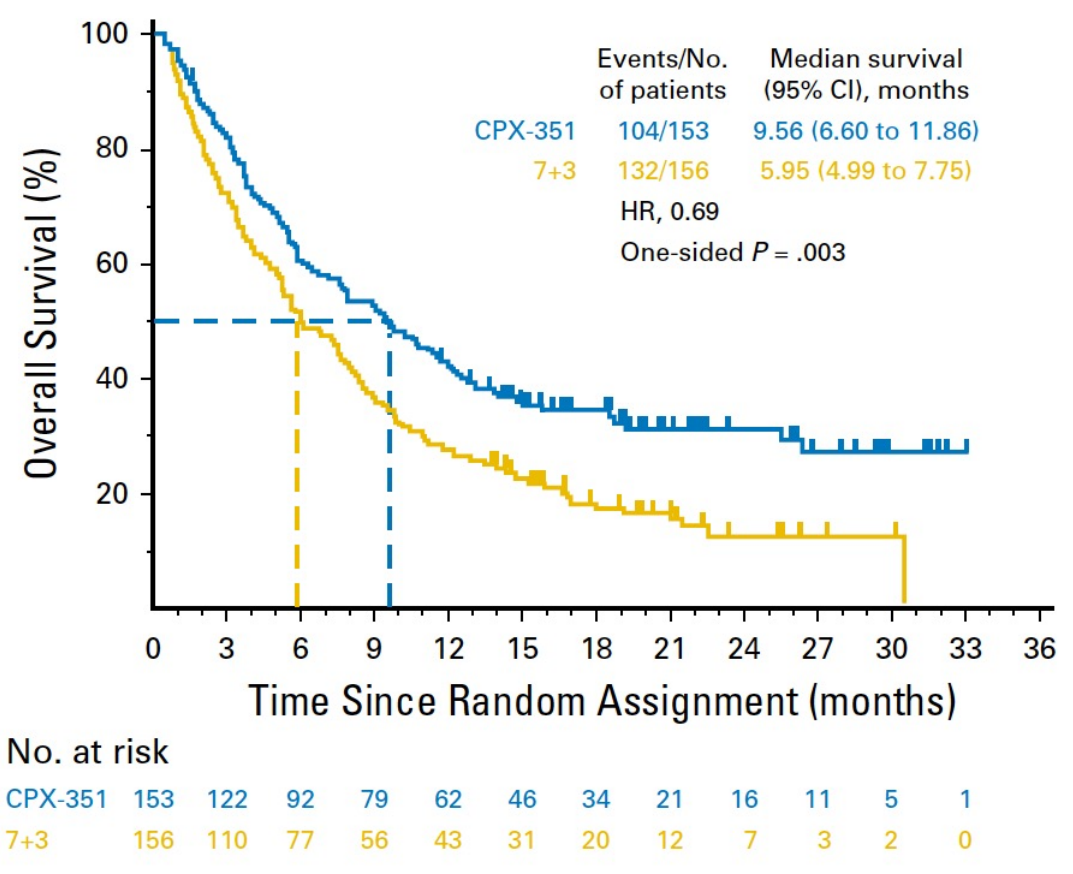

| Cytotoxic therapy[a] | MOA | Examples | Latency period |
|---|---|---|---|
| Alkylating agents and radiation | Induce chromosomal deletions, commonly in 5 and/or 7 | Cyclophosphamide, mechlorethamine, procarbazine, chlorambucil, melphalan, carmustine, busulfan | 5-10 years |
| Topoisomerase II inhibitors | Induce chromosomal translocations | Etoposide, teniposide, mitoxantrone, epirubicin, and doxorubicin | 2-3 years |

Bhatia S. *Semin Oncol.* 2013;40(6):666-675. 2. Czader M, et al. *Am J Clin Pathol.* 2009;132(3):410-425. 3. Leone G, et al. *Haematologica.* 1999;84(10):937-945.

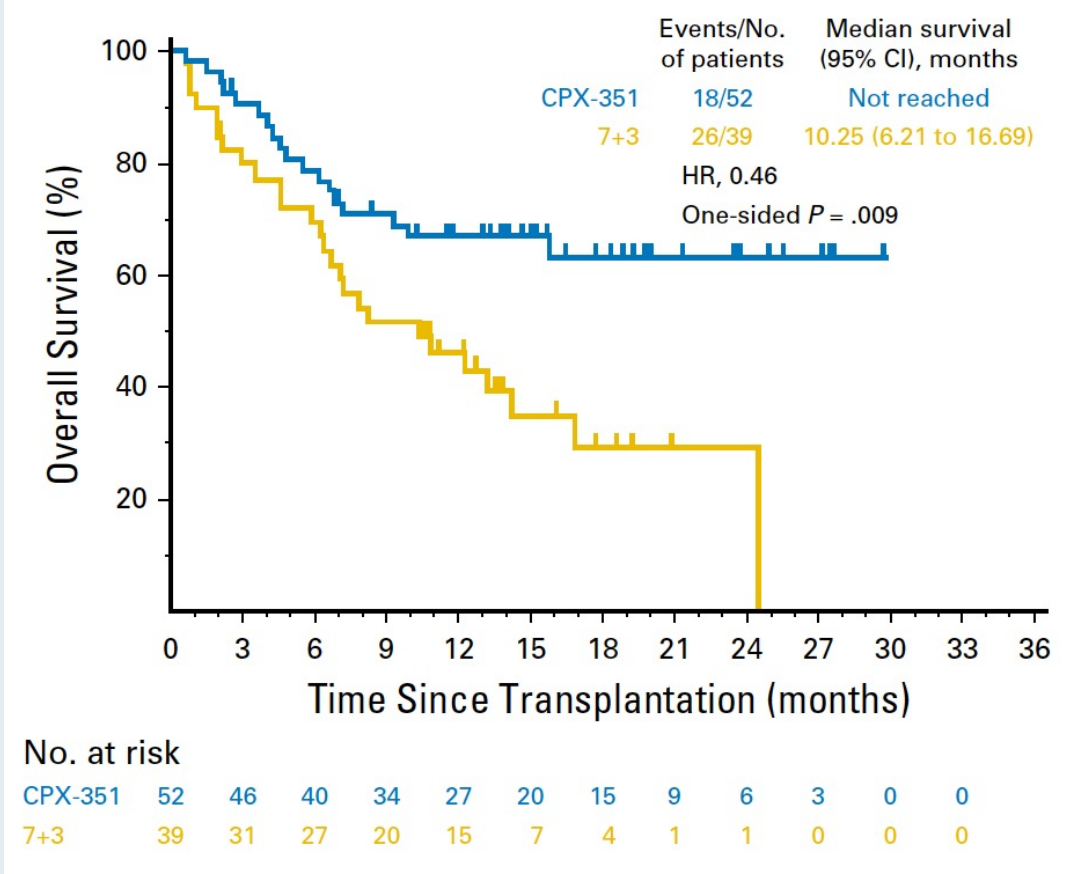
Courtesy of Eunice S Wang, MD.

# Phase III Trial of CPX-351 versus 7 + 3 Cytarabine and Daunorubicin for Older Patients with Newly Diagnosed High-Risk or Secondary AML

## OS



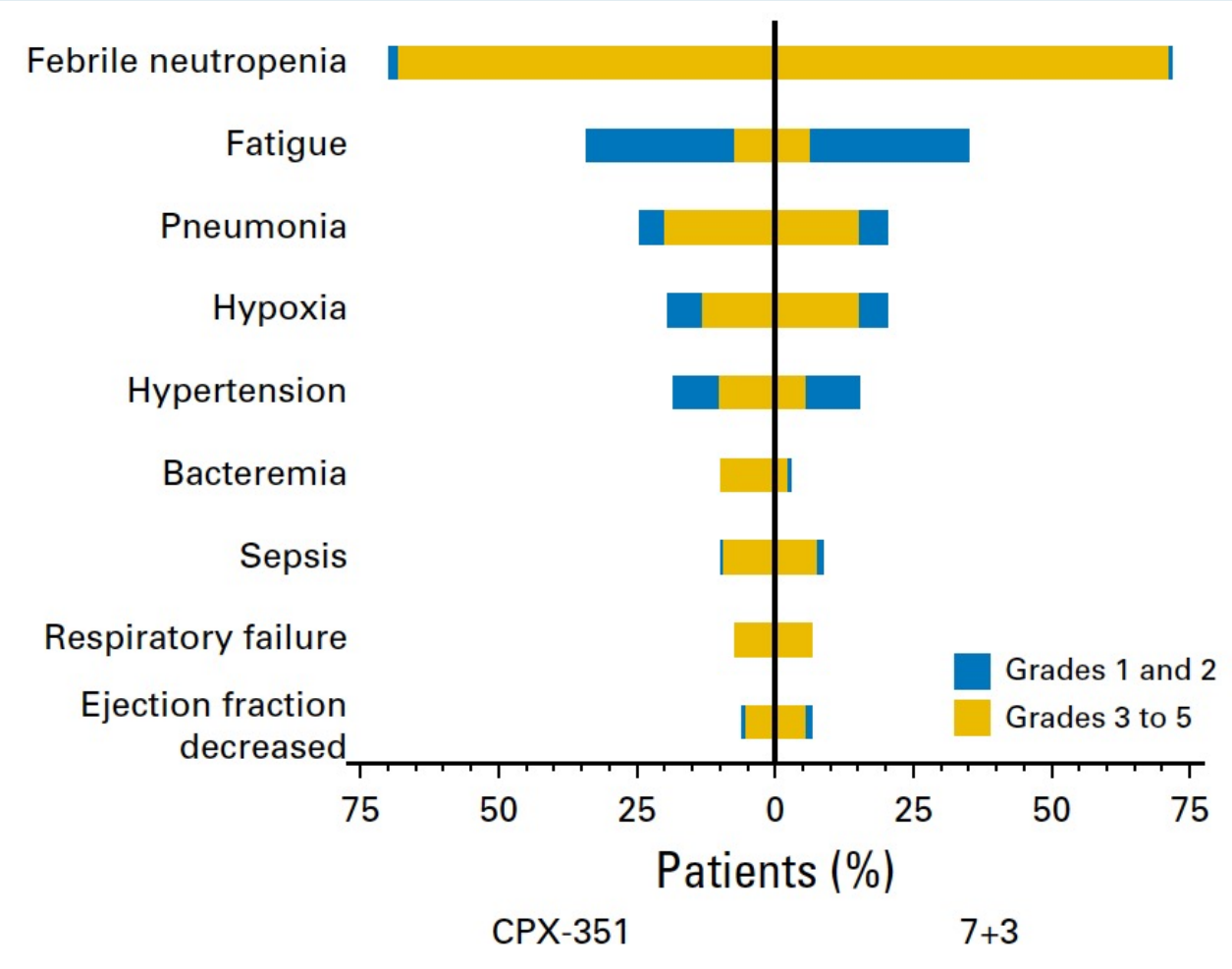

## OS landmarked from time of HSCT




Lancet JE et al. *J Clin Oncol* 2018;36(26):2684-92.

RTP RESEARCH TO PRACTICE

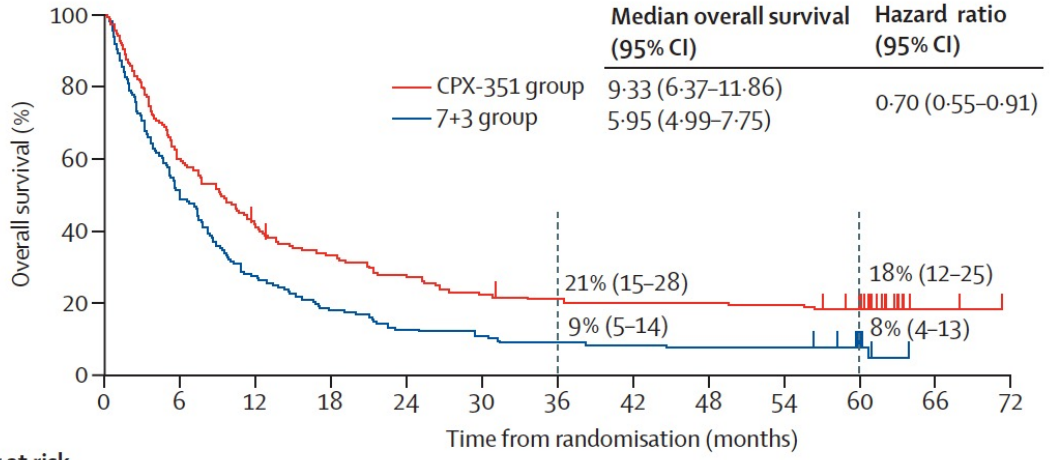
# Phase III Trial of CPX-351 versus 7 + 3 Cytarabine and Daunorubicin for Older Patients with Newly Diagnosed High-Risk or Secondary AML: Most Frequently Reported Adverse Events




Lancet JE et al. *J Clin Oncol* 2018;36(26):2684-92.

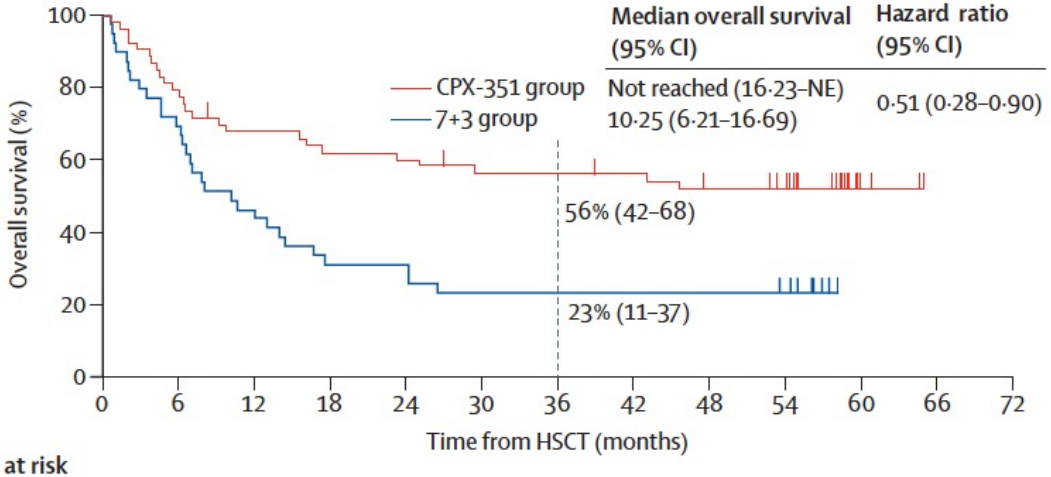
# Phase III Trial of CPX-351 versus 7 + 3 Cytarabine and Daunorubicin for Older Patients with Newly Diagnosed High-Risk or Secondary AML: 5-Year Overall Survival Results

## OS




| Number at risk (number censored) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CPX-351 group | 153 | 92 | 62 | 49 | 40 | 33 | 30 | 29 | 29 | 28 | 22 | 2 | 0 |
| | (0) | (0) | (1) | (2) | (2) | (2) | (3) | (3) | (3) | (3) | (7) | (27) | (29) |
| 7+3 group | 156 | 77 | 43 | 28 | 20 | 17 | 14 | 13 | 12 | 12 | 5 | 0 | 0 |
| | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (7) | (11) | (11) |

## OS landmarked from time of HSCT




| Number at risk (number censored) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CPX-351 group | 53 | 42 | 35 | 32 | 31 | 28 | 28 | 27 | 24 | 21 | 6 | 0 | 0 |
| | (0) | (0) | (1) | (1) | (1) | (2) | (2) | (3) | (4) | (7) | (22) | (28) | (28) |
| 7+3 group | 39 | 27 | 18 | 12 | 12 | 9 | 9 | 9 | 9 | 8 | 0 | 0 | 0 |
| | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (1) | (9) | (9) | (9) |

Lancet JE et al. *Lancet Haematol* 2021;8:e481-91.

RTP RESEARCH TO PRACTICE

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# Case Presentation – Dr Yang: A 71-year-old woman with AML and FLT3-ITD and WT1 mutations

**Dr John Yang**

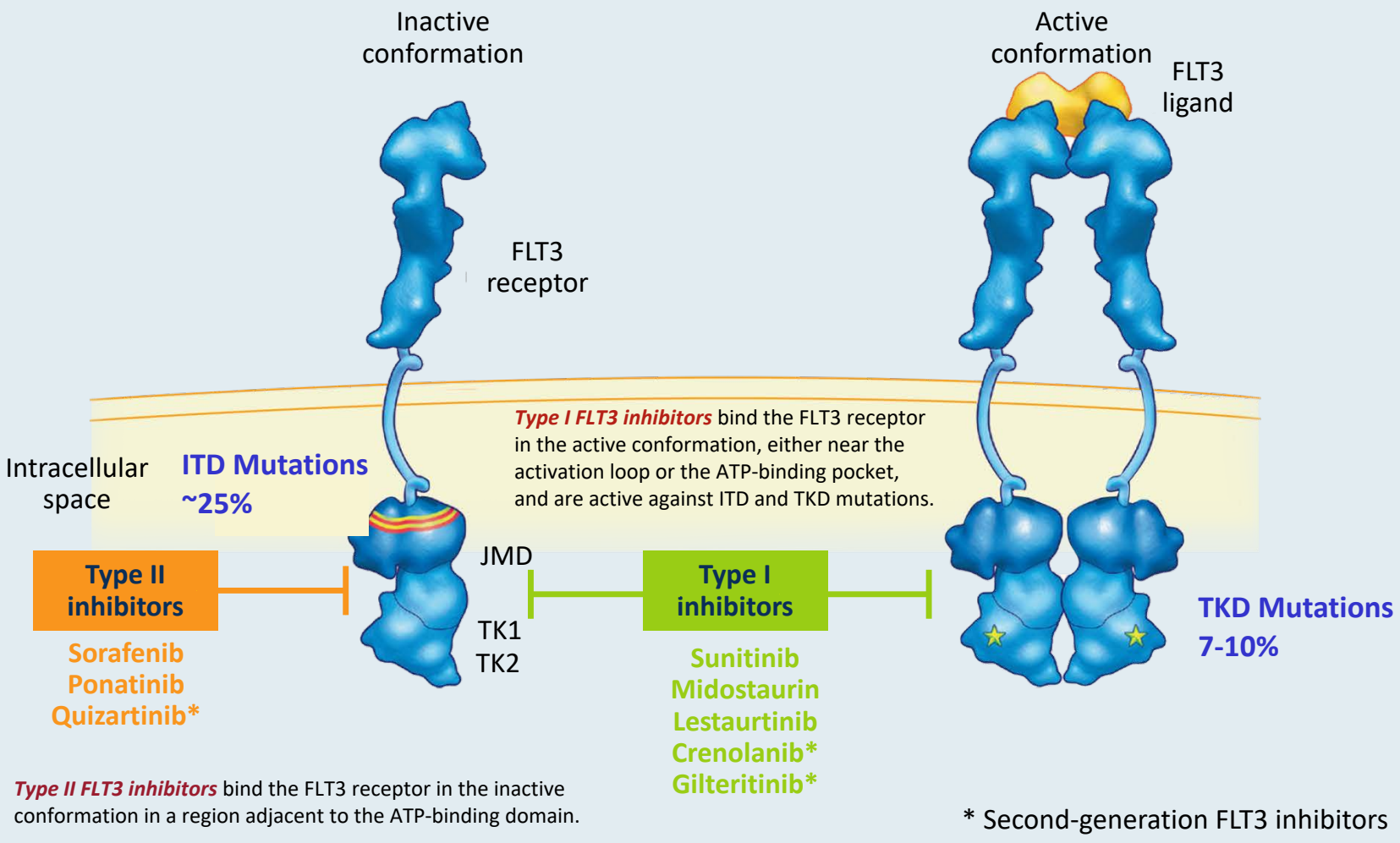
- Presented to PCP with fatigue → Severe anemia, high WBC and blast count
- Diagnosed with AML and FLT3-ITD and WT1 mutations
- 5/2021: Venetoclax/decitabine
  - Progressive cytopenias and increase in bone marrow blasts after cycle 2
- CPX-351 x 1, with bone marrow in CR
- Gilteritinib

## Question

- Would you dose-reduce venetoclax to address cytopenias?

RTP RESEARCH TO PRACTICE

# FLT3 Mutations (ITD and TKD) Occur in Approximately 30% to 35% of Patients with AML




Daver N et al. *Leukemia* 2019;33:299-312.

# Characteristics of Select FLT3 Inhibitors

| FLT3 inhibitor | Inhibitory type | FLT3 kinase inhibition IC50 (nmol/L) | Non-FLT3 targets | FLT3-TKD mutation activity | Major toxicities |
|---|---|---|---|---|---|
| Sorafenib<br>400 mg BID | II | 58 | c-KIT<br>PDGFR<br>RAF<br>VEGFR | No | Rash<br>Hemorrhage<br>Myelosuppression |
| Midostaurin<br>50 mg BID | I | 6.3 | c-KIT<br>PDGFR<br>PKC<br>VEGFR | Yes | GI toxicity<br>Myelosuppression |
| Quizartinib<br>30 – 60 mg QD | II | 1.6 | c-KIT | No | QTc prolongation<br>Myelosuppression |
| Gilteritinib<br>120 mg QD | I | 0.29 | AXL<br>LTK<br>ALK | Yes | Elevated transaminases<br>Diarrhea |

Kiyoi H et al. *Cancer Science* 2019;[Online ahead of print];
Short NJ et al. *Ther Adv Hematol* 2019;10:2040620719827310.

# Key Clinical Trials of FLT3 Inhibitors

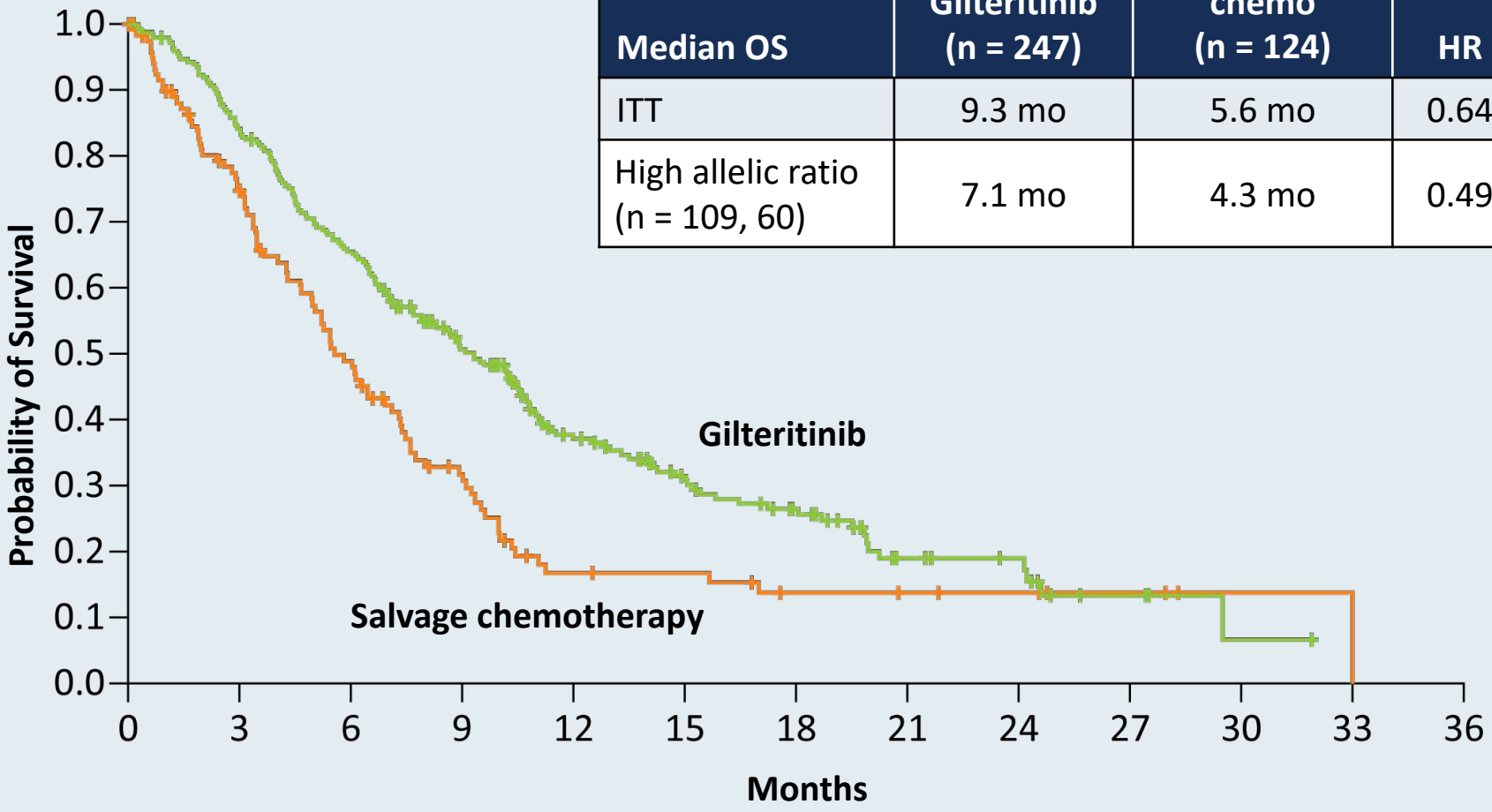
| Study | Agents | FLT3 inhibitor generation | Inhibits | N | Population | OS hazard ratio |
|---|---|---|---|---|---|---|
| SORAML<br>Ph II | Sorafenib<br>Placebo | First | ITD | 267 | Treatment naïve | 0.82, n.s. |
| RATIFY<br>Ph III | Midostaurin<br>Placebo | First | ITD, TKD | 717 | Treatment naïve | 0.78 |
| QuANTUM-First<br>Ph III | Quizartinib<br>Placebo | Second | ITD | NR | Treatment naïve | NR |
| QuANTUM-R<br>Ph III | Quizartinib<br>SC | — | — | — | R/R | 0.76 |
| ARO-021<br>Ph III | Crenolanib<br>Placebo | Second | ITD, TKD | 510 | Treatment naïve | Not yet reported |
| ADMIRAL<br>Ph III | Gilteritinib<br>SC | Second | ITD, TKD | 371 | R/R | 0.64 |

OS = overall survival; SC = salvage chemotherapy; R/R = relapsed/refractory

Novatcheva ED et al. *Clin Lymphoma, Myeloma & Leuk* 2021;[Online ahead of print].
Rollig C et al. *Leukemia* 2021;35:2517-25.

# ADMIRAL: Overall Survival

| Median OS | Gilteritinib (n = 247) | Salvage chemo (n = 124) | HR | *p*-value |
|---|---|---|---|---|
| ITT | 9.3 mo | 5.6 mo | 0.64 | <0.01 |
| High allelic ratio (n = 109, 60) | 7.1 mo | 4.3 mo | 0.49 | Not reported |




Perl AE et al. *N Engl J Med* 2019;381:1728-40.

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# Agenda

Introduction: AML Molecular Workup

Module 1: Dr Peles — A 71-year-old woman with AML with MDS-related changes

Module 2: Dr Shameem — A 77-year-old man with AML and an IDH1 mutation

Module 3: Dr Olin — A 62-year-old man with therapy-related AML

Module 4: Dr Yang — A 71-year-old woman with AML and FLT3-ITD and WT1 mutations

**Module 5: Dr Olin — A 63-year-old man with relapsed AML**

Module 6: Journal Club with Dr Pratz

Module 7: Faculty Survey

Module 8: Appendix

# Case Presentation – Dr Olin: A 63-year-old man with relapsed AML

**Dr Rebecca Olin**

- PMH: Diabetes, HTN, treated tuberculosis, chronic kidney disease, and psoriasis
- Follow-up labwork through tuberculosis clinic demonstrated new pancytopenia with some rare circulating blasts
- Bone marrow biopsy: 40% - 50% blasts by morphology; diagnosis of AML-NOS
- Cytogenetics and FISH panel: Normal
- NGS: 2 different CEBPA alpha gene mutations; no allele frequency provided

# Case Presentation – Dr Olin: A 63-year-old man with relapsed AML (continued)

Dr Rebecca Olin

- PMH: Diabetes, HTN, treated tuberculosis, chronic kidney disease, and psoriasis
- Follow-up labwork through tuberculosis clinic demonstrated new pancytopenia with some rare circulating blasts
- Bone marrow biopsy: 40% - 50% blasts by morphology; diagnosis of AML-NOS
- Cytogenetics and FISH panel: Normal
- NGS: 2 different CEBPA alpha gene mutations; no allele frequency provided
- ***7 + 3 induction → CR → 2 cycles of intermediate dose cytarabine consolidation***
- ***Maintenance with oral azacitidine***

***Questions***

- ***How quickly do you usually receive results from NGS assays that you order?***
- ***Do you choose therapy without having the NGS information on hand?***

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# Case Presentation – Dr Olin: A 63-year-old man with relapsed AML (continued)

Dr Rebecca Olin

- PMH: Diabetes, HTN, treated tuberculosis, chronic kidney disease, and psoriasis
- Bone marrow biopsy: 40% - 50% blasts by morphology; diagnosis of AML-NOS
- Cytogenetics and FISH panel: Normal
- NGS: 2 different CEBPA alpha gene mutations; no allele frequency provided
- 7 + 3 induction → CR → 2 cycles of intermediate dose cytarabine consolidation
- Maintenance with oral azacitidine

***Questions***

- ***If this patient had completed his entire course of consolidation, would you have used oral azacitidine maintenance? Would you only use it if the patient did not complete their full course of consolidation?***
- ***Would you consider using oral azacitidine for patients with good-risk disease or would you restrict it to patients with intermediate or poor risk?***

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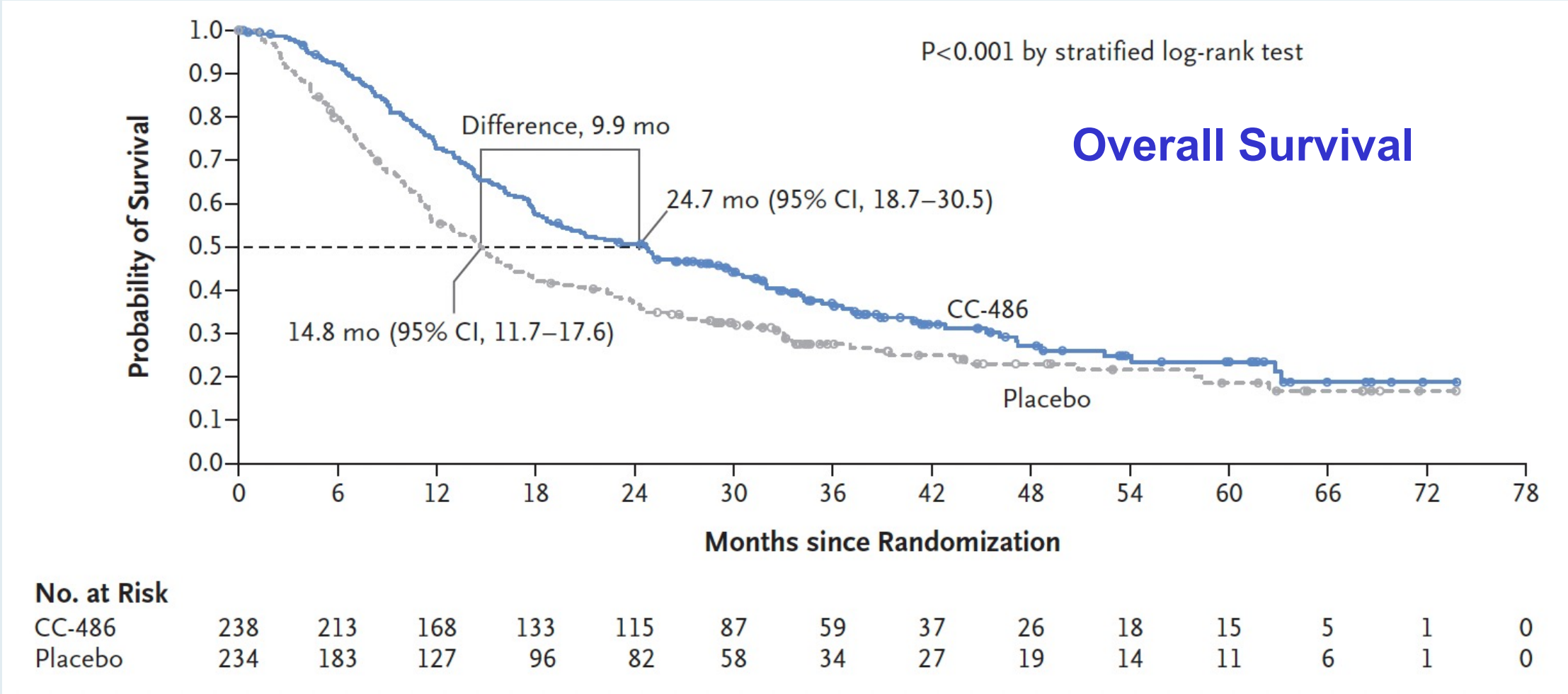
# QUAZAR AML-001: Oral Azacitidine Maintenance Therapy for AML in First Remission




| No. at Risk | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CC-486 | 238 | 213 | 168 | 133 | 115 | 87 | 59 | 37 | 26 | 18 | 15 | 5 | 1 | 0 |
| Placebo | 234 | 183 | 127 | 96 | 82 | 58 | 34 | 27 | 19 | 14 | 11 | 6 | 1 | 0 |

Wei AH et al. *N Engl J Med* 2020;383:2526-37.

# QUAZAR AML-001: Safety Summary and Select Adverse Events (AEs)

| | CC-486 (N = 236) | | Placebo (N = 233) | |
|---|---|---|---|---|
| | Any grade | Grade 3 or 4 | Any grade | Grade 3 or 4 |
| AEs leading to dose interruptions | 43% | — | 17% | — |
| AEs leading to dose reductions | 16% | — | 3% | — |
| AEs leading to discontinuation | 13% | — | 4% | — |
| Nausea | 65% | 3% | 24% | <1% |
| Vomiting | 60% | 3% | 10% | 0 |
| Diarrhea | 50% | 5% | 21% | 1% |
| Neutropenia | 44% | 41% | 26% | 24% |
| Thrombocytopenia | 33% | 22% | 27% | 21% |
| Anemia | 20% | 14% | 18% | 13% |

Wei AH et al. *N Engl J Med* 2020;383:2526-37.

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**Module 6: Journal Club with Dr Pratz**

Module 7: Faculty Survey

Module 8: Appendix

# Journal Club with Dr Pratz: ASH 2021 Preview

**Dr Pratz ASH 2021: Select Papers**

- Minehart JC et al. **Incidence and predictors of SARS-CoV-2 antibody responses following COVID-19 vaccination in allogeneic stem cell transplant recipients.** ASH 2021;Abstract 2888.
- Pollyea DA et al. **Outcomes in patients with poor-risk cytogenetics with or without TP53 mutations treated with venetoclax combined with hypomethylating agents.** ASH 2021; Abstract 224.
- Pratz KW et al. **Cost effectiveness analysis of venetoclax plus azacitidine versus azacitidine in newly diagnosed adult patients with acute myeloid leukemia who are ineligible for intensive chemotherapy from a United States payer perspective.** ASH 2021; Abstract 112.
- Matthews A et al. **Real world survival outcomes of CPX-351 versus venetoclax and azacitadine for initial therapy in adult acute myeloid leukemia.** ASH 2021;Abstract 795.

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# Journal Club with Dr Pratz: ASH 2021 Preview (Cont)

**Other ASH 2021: Select Papers**

- Montesinos P et al. **AGILE: A global, randomized, double-blind, phase 3 study of ivosidenib + azacitidine versus placebo + azacitidine in patients with newly diagnosed acute myeloid leukemia with an IDH1 mutation.** ASH 2021;Abstract 697.
- Grenet J et al. **Comparing outcomes between liposomal daunorubicin/cytarabine (CPX-351) and HMA + venetoclax as frontline therapy in acute myeloid leukemia.** ASH 2021;Abstract 32.
- Rautenberg C et al. **Real-world experience of CPX-351 as first-line treatment in 188 patients with acute myeloid leukemia.** ASH 2021;Abstract 33.
- Chen S et al. **Venetoclax plus decitabine for young adults with newly diagnosed ELN adverse-risk acute myeloid leukemia: Interim analysis of a prospective, multicenter, single-arm, phase 2 trial.** ASH 2021;Abstract 35.

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# Journal Club with Dr Pratz: ASH 2021 Preview (Cont)

**Other ASH 2021: Select Papers**

- Pollyea DA et al. **Outcomes in patients with poor-risk cytogenetics with or without *TP53* mutations treated with venetoclax combined with hypomethylating agents.** ASH 2021;Abstract 224.
- Yilmaz M et al. **Quizartinib (Quiz) with decitabine (DAC) and venetoclax (VEN) is highly active in patients (pts) with FLT3-ITD mutated acute myeloid leukemia (AML) – RAS/MAPK mutations continue to drive primary and secondary resistance.** ASH 2021;Abstract 370.
- Daver N et al. **Phase I/II study of azacitidine (AZA) with venetoclax (VEN) and magrolimab (Magro) in patients (pts) with newly diagnosed older/unfit or high-risk acute myeloid leukemia (AML) and relapsed/refractory (R/R) AM.** ASH 2021;Abstract 371.

# Journal Club with Dr Pratz: ASH 2021 Preview (Cont)

**Other ASH 2021: Select Papers**

- Borate U et al. **Comparative outcomes and molecular response predictors of IDH1/2-mutated adult acute myeloid leukemia (AML) patients (Pts) after frontline treatment with intensive induction chemotherapy (IC), targeted inhibitors, or hypomethylating agents (HMA) (Alliance).** ASH 2021;Abstract 226.
- Sekeres MA et al. **Pevonedistat (PEV) + azacitidine (AZA) versus AZA alone as first-line treatment for patients with higher-risk myelodysplastic syndromes (MDS)/chronic myelomonocytic leukemia (CMML) or acute myeloid leukemia (AML) with 20-30% marrow blasts: The randomized phase 3 PANTHER trial (NCT03268954).** ASH 2021;Abstract 370.
- Daver N et al. **Venetoclax in combination with gilteritinib demonstrates molecular clearance of *FLT3* mutation in relapsed/refractory *FLT3*-mutated acute myeloid leukemia.** ASH 2021;Abstract 691.

# Journal Club with Dr Pratz: ASH 2021 Preview (Cont)

**Other ASH 2021: Select Papers**

- Short NJ et al. **A triplet combination of azacitidine, venetoclax and gilteritinib for patients with *FLT3*-mutated acute myeloid leukemia: Results from a phase I/II study.** ASH 2021;Abstract 696.
- Yilmaz M et al. **Hypomethylating agent (HMA) therapy and venetoclax (VEN) with FLT3 inhibitor "triplet" therapy is highly active in older/unfit patients with FLT3 mutated AML.** ASH 2021;Abstract 798.
- Patel P et al. **Ivosidenib (IVO) in combination with azacitidine (AZA) in newly diagnosed (ND) older patients with IDH1 R132-mutated acute myeloid leukemia (AML) induces high response rates: A phase 2 sub-study of the Beat AML Master trial.** ASH 2021;Abstract 875.

RTP RESEARCH TO PRACTICE

*Blood* 2021;137(13):1792-803.

blood®

Regular Article

MYELOID NEOPLASIA

# Ivosidenib or enasidenib combined with intensive chemotherapy in patients with newly diagnosed AML: a phase 1 study

Eytan M. Stein,[1,*] Courtney D. DiNardo,[2,*] Amir T. Fathi,[3] Alice S. Mims,[4] Keith W. Pratz,[5] Michael R. Savona,[6] Anthony S. Stein,[7] Richard M. Stone,[8] Eric S. Winer,[8] Christopher S. Seet,[9] Hartmut Döhner,[10] Daniel A. Pollyea,[11] James K. McCloskey,[12] Olatoyosi Odenike,[13] Bob Löwenberg,[14] Gert J. Ossenkoppele,[15] Prapti A. Patel,[16] Mikhail Roshal,[17] Mark G. Frattini,[18] Frederik Lersch,[19] Aleksandra Franovic,[20] Salah Nabhan,[21] Bin Fan,[21] Sung Choe,[21] Hongfang Wang,[21] Bin Wu,[21] Lei Hua,[21] Caroline Almon,[21] Michael Cooper,[21] Hagop M. Kantarjian,[2,†] and Martin S. Tallman[1,†]

Received: 29 September 2020 | Revised: 22 October 2020 | Accepted: 25 October 2020

DOI: 10.1002/ajh.26039

RESEARCH ARTICLE

# Venetoclax with azacitidine or decitabine in patients with newly diagnosed acute myeloid leukemia: Long term follow-up from a phase 1b study

Daniel A. Pollyea[1] | Keith Pratz[2] | Anthony Letai[3] | Brian A. Jonas[4] | Andrew H. Wei[5] | Vinod Pullarkat[6] | Marina Konopleva[7] | Michael J. Thirman[8] | Martha Arellano[9] | Pamela S. Becker[10,11] | Brenda Chyla[12] | Wan-Jen Hong[13] | Qi Jiang[12] | Jalaja Potluri[12] | Courtney D. DiNardo[7]

*Am J Hematol* 2021;96(2):208-17

# Summary of Rate and Duration of Response

| All patients | N | CR n (%) | CR/CRi n (%) | DOR mos. (95% CI) |
|---|---|---|---|---|
| 400 mg venetoclax - Venetoclax + Azacitidine Patient Subgroups | | | | |
| **Mutation subgroup** | | | | |
| *TP53* | 17 | 5 (29) | 9 (53) | 6.5 (1.9-17.3) |
| *FLT3* | 12 | 6 (50) | 7 (58) | NR (2.8-NR) |
| *IDH1/2* | 22 | 10 (46) | 19 (86) | 29.5 (17.9-NR) |
| *NPM1* | 14 | 8 (57) | 11 (79) | NR (15.1–NR) |

Pollyea DA et al. *Am J Hematol* 2021;96(2):208-17.

2021 ASCO ANNUAL MEETING

## Abstract 7011

# VENETOCLAX AND AZACITIDINE COMBINATION IN CHEMOTHERAPY INELIGIBLE UNTREATED PATIENTS WITH THERAPY-RELATED ACUTE MYELOID LEUKEMIA, ANTECEDENT MYELODYSPLASTIC SYNDROMES OR CHRONIC MYELOMONOCYTIC LEUKEMIA

Vinod Pullarkat M.D.[1], Keith W. Pratz M.D.[2], Hartmut Döhner M.D.[3], Christian Recher M.D.[4], Michael J. Thirman M.D [5], Courtney D. DiNardo M.D. [6], Pierre Fenaux M.D. [7], Andre C. Schuh M.D. [8], Andrew H. Wei M.D.[9], Arnaud Pigneux M.D. [10], Jun-Ho Jang M.D. [11], Gunnar Juliusson M.D. [12], Yasushi Miyazaki M.D. [13], Dominik Selleslag M.D. [14], Martha L. Arellano M.D. [15], Kiran Naqvi M.D. [16] Jun Yu Ph.D [17], Jean A. Ridgeway DNP, NP-C [17], Jalaja Potluri M.D. [17], Marina Konopleva M.D.[6]

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RTP RESEARCH TO PRACTICE

2021 ASCO ANNUAL MEETING

Abstract 7018

# MEASURABLE RESIDUAL DISEASE RESPONSE AND PROGNOSIS IN ACUTE MYELOID LEUKEMIA WITH VENETOCLAX AND AZACITIDINE

Keith W. Pratz[1], Brian A. Jonas[2], Vinod Pullarkat[3], Christian Recher[4], Andre C. Schuh[5], Michael J. Thirman[6], Jacqueline S. Garcia[7], Courtney D. DiNardo[8], Vladimir Vorobyev[9], Nicola S. Fracchiolla[10], Su-Peng Yeh[11], Jun Ho Jang[12], Muhit Ozcan[13], Kazuhito Yamamoto[14], Arpad Illes[15], Ying Zhou[16], Monique Dail[17], Brenda Chyla[16], Jalaja Potluri[16], Hartmut Döhner[18]

[1]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA, [2]Department of Internal Medicine, Division of Hematology and Oncology, University of California Davis School of Medicine, Sacramento, CA, USA, [3]Department of Hematology and Hematopoietic Cell Transplantation and Gehr Family Center for Leukemia Research, City of Hope Comprehensive Cancer Center, Duarte, CA, USA [4]Centre Hospitalier Universitaire de Toulouse, Toulouse, France, [5]Department of Medical Oncology and Hematology, Princess Margaret Cancer Center, Toronto, Ontario, Canada, [6]Section of Hematology/Oncology, Department of Medicine, The University of Chicago Medicine, Chicago, IL, USA, [7]Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA, [8]Department of Leukemia, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [9]Department of Hematology, S. P. Botkin City Clinical Hospital, Moscow, Russia, [10]UOC Ematologia, Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico, Milan, Italy, [11]Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan, [12]Department of Hematology-Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, [13]Department of Hematology, Ankara University School of Medicine, Ankara, Turkey, [14]Department of Hematology and Cell Therapy, Aichi Cancer Center Hospital, Nagoya, Japan, [15]University of Debrecen, Faculty of Medicine, Department of Hematology, Debrecen, Hungary, [16]AbbVie Inc., North Chicago, IL, USA, [17]Genentech Inc., South San Francisco, CA, USA, [18]Department of Internal Medicine III, University Hospital, Ulm, Germany

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Module 8: Appendix

# At what age of an otherwise fit patient with AML would you not recommend intensive chemotherapy as initial treatment?


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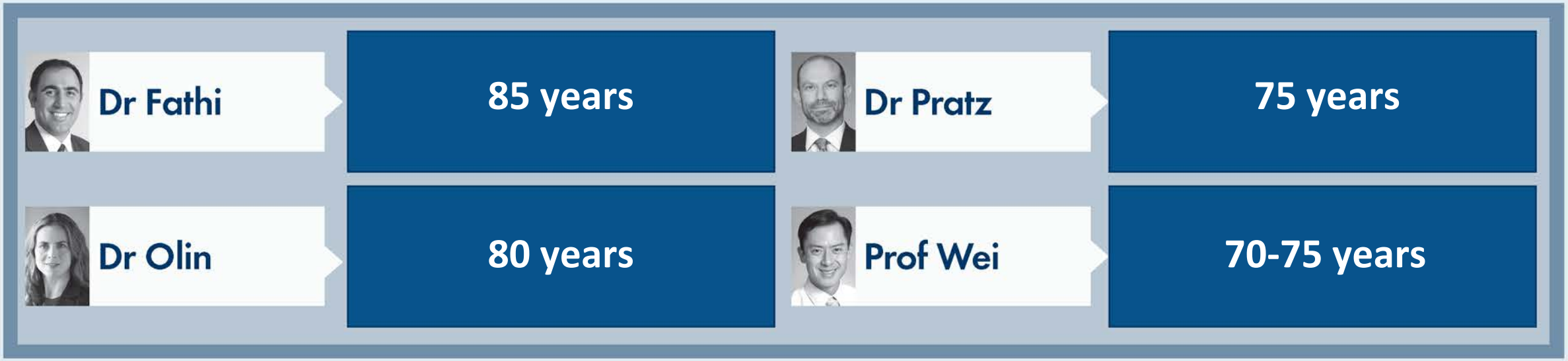
# At what age of an otherwise fit patient with AML would you not recommend allogeneic transplant?

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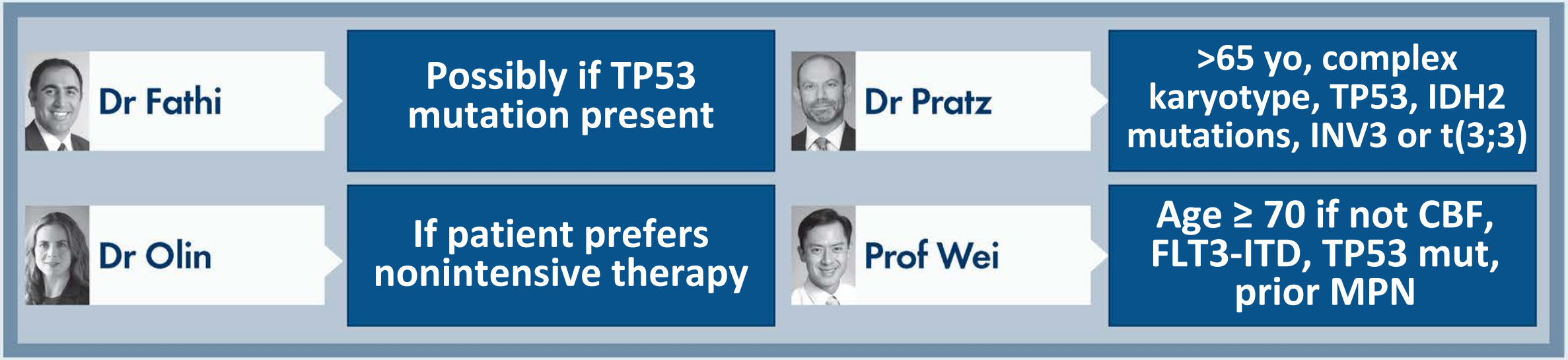
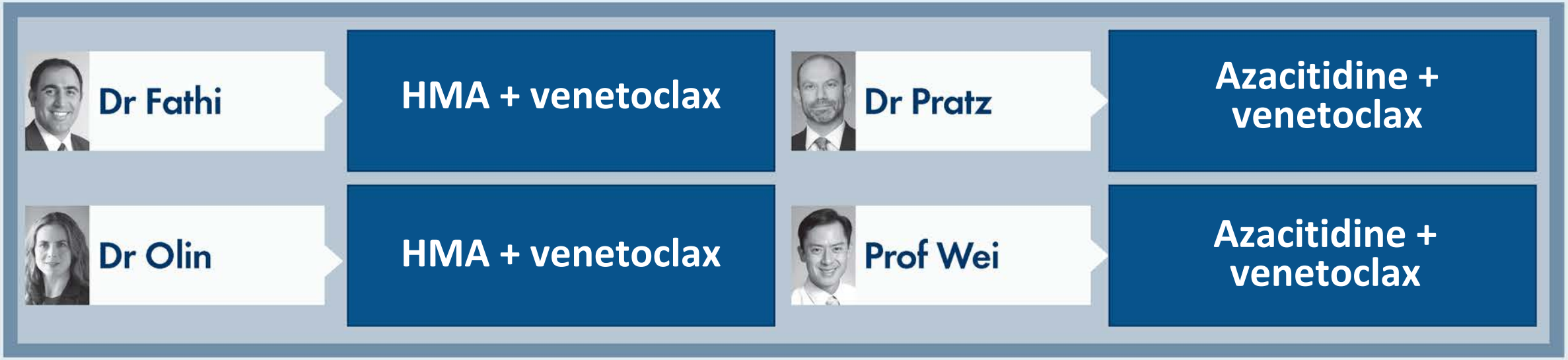
# In what clinical situations, if any, do you recommend HMA/ venetoclax for a patient with AML who is eligible for intensive chemotherapy (eg, adverse cytogenetics)?




HMA = hypomethylating agent

# Regulatory and reimbursement issues aside, in general, what is your preferred initial treatment for a patient with AML with no actionable mutations who is not eligible for intensive chemotherapy?




HMA: azacitidine or decitabine

# What prophylaxis, if any, do you generally administer to patients with AML receiving venetoclax in combination with azacitidine?

| | |
|---|---|
|  Dr Fathi | Acyclovir, allopurinol |
|  Dr Pratz | Acyclovir, extended-spectrum quinolone, allopurinol |
|  Dr Olin | Acyclovir, extended-spectrum quinolone, antifungal therapy |
|  Prof Wei | Acyclovir, antifungal if Grade 4 neutropenia, allopurinol |

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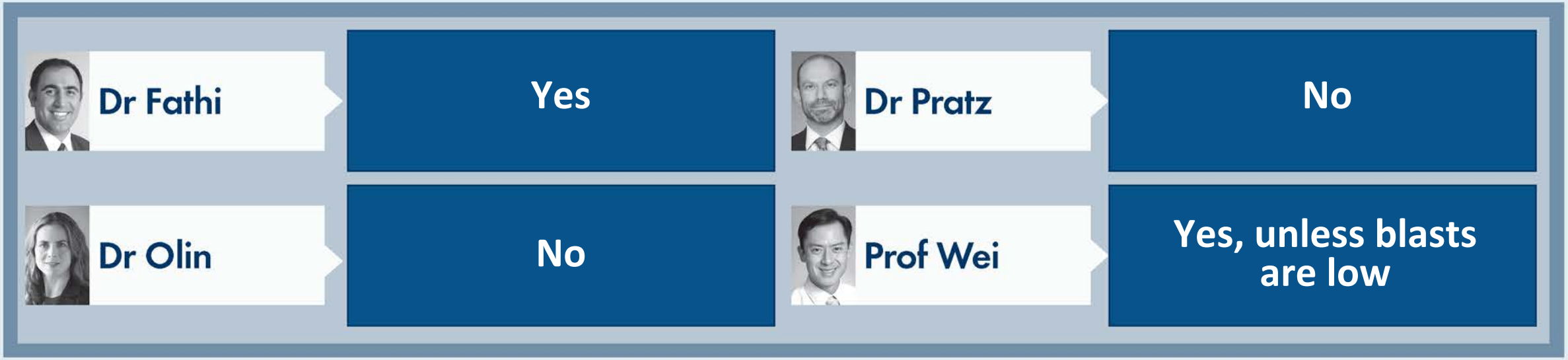
# Do you generally admit to the hospital all patients with AML who are receiving venetoclax in combination with a hypomethylating agent?

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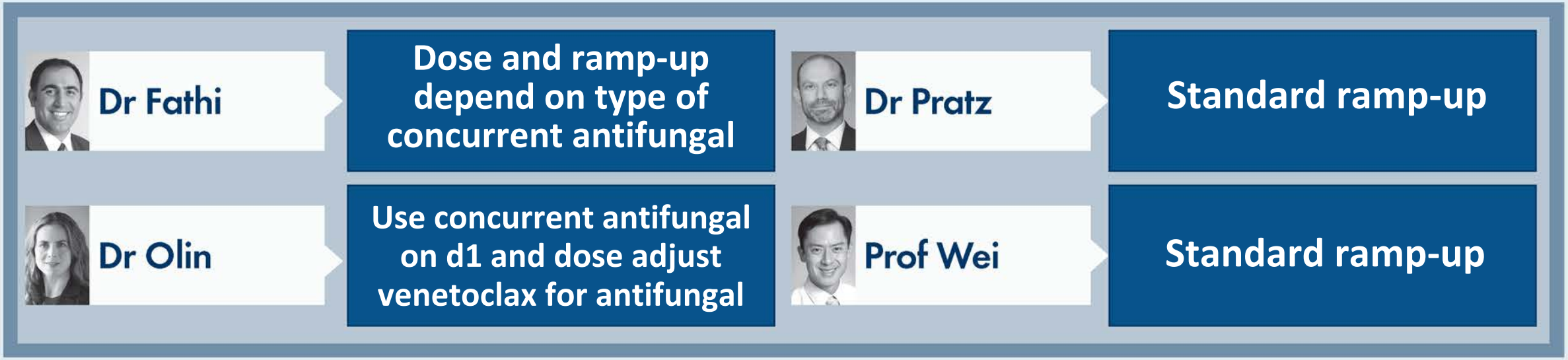
# You are about to administer venetoclax/azacitidine to an older patient with AML, a PS of 0, WBC = 15K and 50% blasts who is receiving no medications other than allopurinol. What would be your approach to venetoclax dosing?



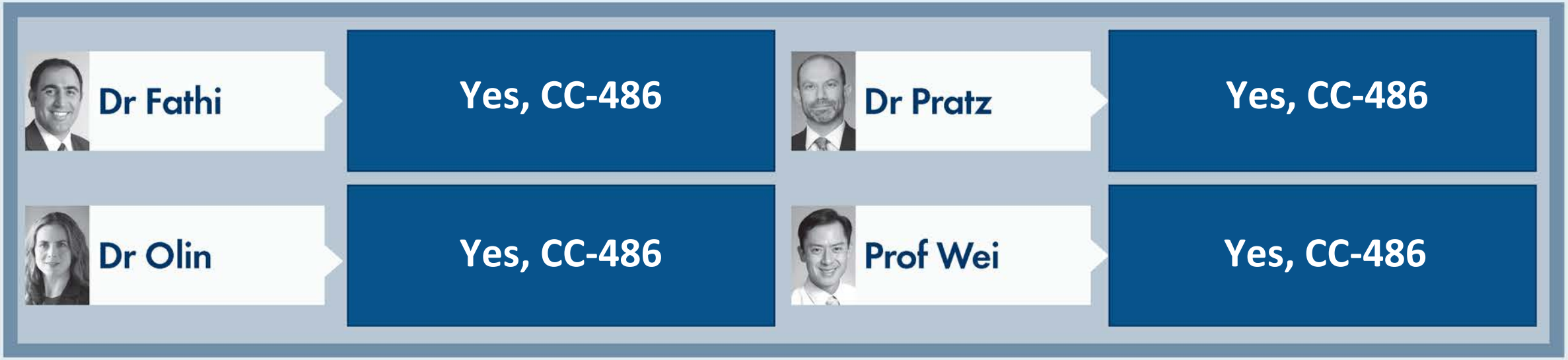
# For a patient with AML who is pancytopenic and is receiving venetoclax in combination with an HMA or low-dose cytarabine(LDAC), when do you perform the first bone marrow evaluation?

| | | | |
|---|---|---|---|
|  Dr Fathi | At end of cycle 1 |  Dr Pratz | Between days 22 and 28 |
|  Dr Olin | At end of cycle 1 |  Prof Wei | Day 21-28 if circulating blasts cleared |

# For a patient with AML who is receiving venetoclax in combination with an HMA and is responding to and tolerating treatment, for how long do you generally continue therapy?

| | | | |
|---|---|---|---|
|  Dr Fathi | Indefinitely |  Dr Pratz | Indefinitely |
|  Dr Olin | Indefinitely |  Prof Wei | 12-18 cycles; consider stopping if CR and no MRD |

# A 65-year-old patient with intermediate-risk AML, no actionable mutations, PS 0, receives 7 + 3 induction therapy, achieves a complete remission after 2 cycles and then receives 2 cycles of high-dose cytarabine consolidation but declines transplant. Would you offer this patient maintenance therapy?

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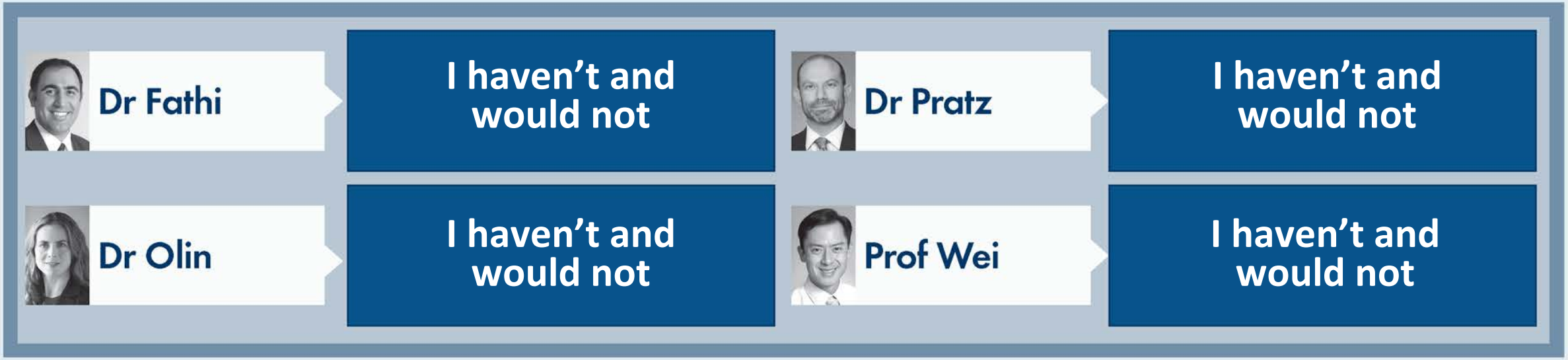
# Have you substituted or would you substitute CC-486 (oral azacitidine) for standard-administration azacitidine under any circumstances?

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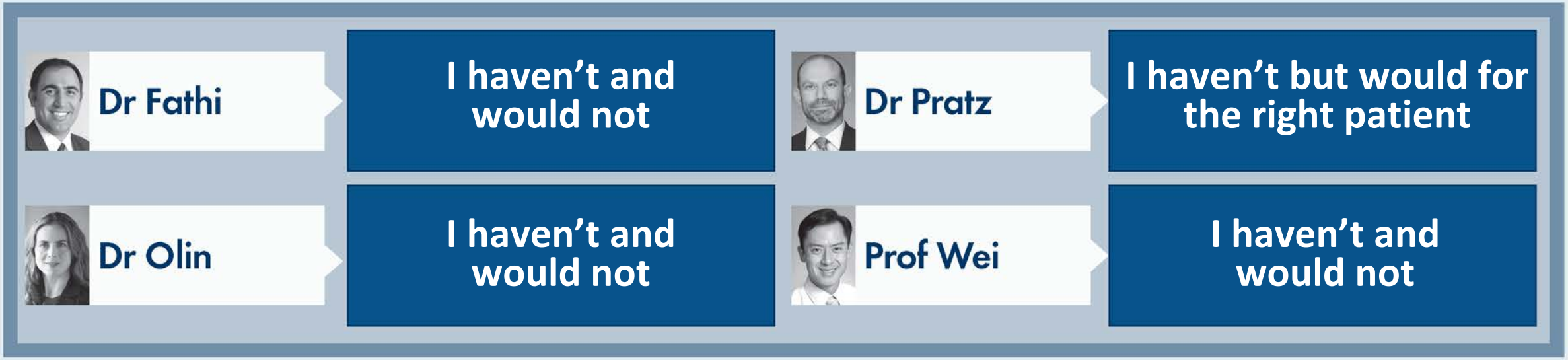
# Have you administered or would you administer CC-486 (oral azacitidine) as maintenance therapy to a patient who has undergone stem cell transplant?



# In what clinical situations, if any, do you administer CPX-351?

| | |
|---|---|
|  Dr Fathi | Therapy-related or secondary AML |
|  Dr Pratz | Failure of response to aza/ven and are intended for transplant |
|  Dr Olin | Secondary AML |
|  Prof Wei | Therapy-related and secondary AML if allo-HSCT planned |

aza = azacitidine; ven = venetoclax; HSCT = hematopoietic stem cell transplant

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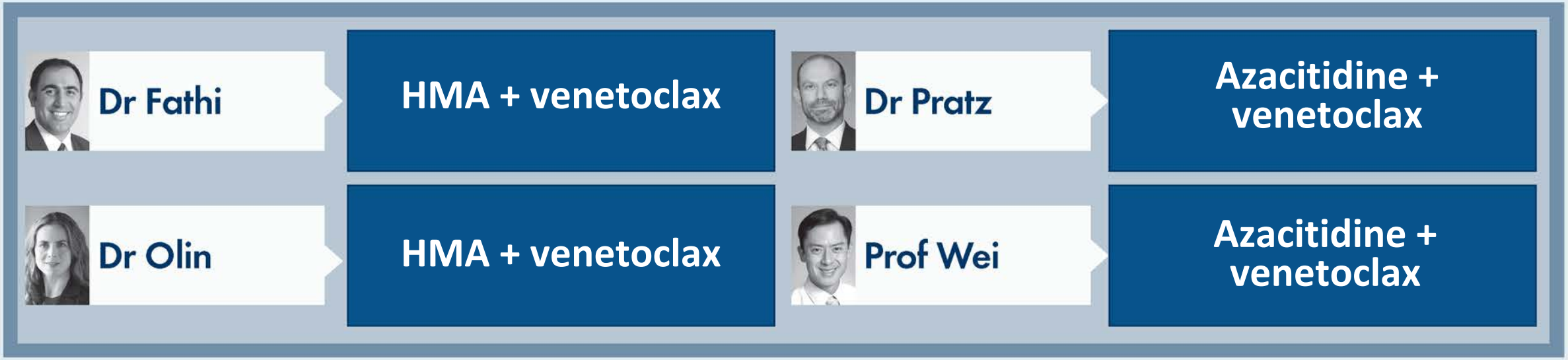
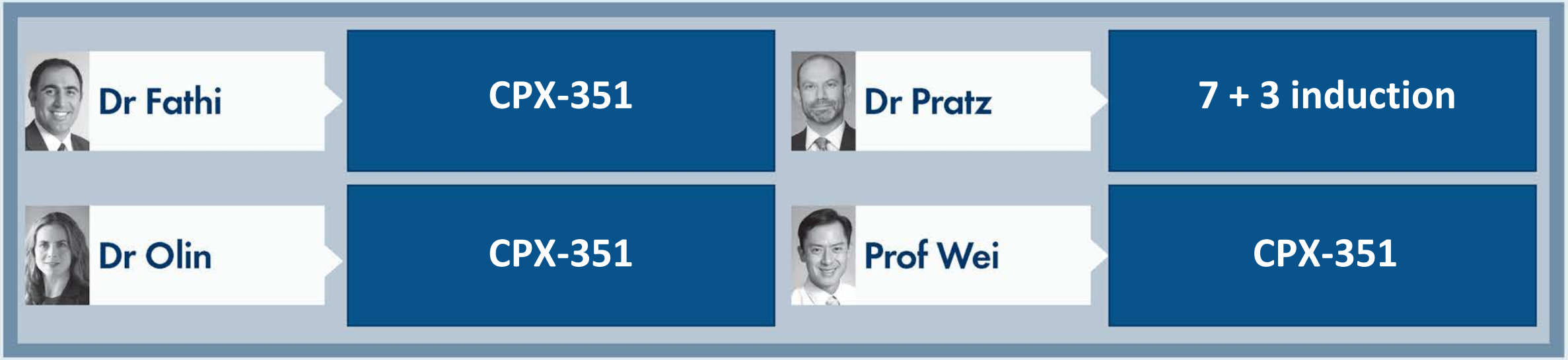
# Regulatory and reimbursement issues aside, what initial treatment would you recommend for an older patient who is not eligible for intensive chemotherapy who develops AML with no actionable mutations while receiving an erythropoietin stimulating agent (ESA) for lower-risk MDS?




MDS = myelodsyplastic syndromes
HMA: azacitidine or decitabine

RTP RESEARCH TO PRACTICE

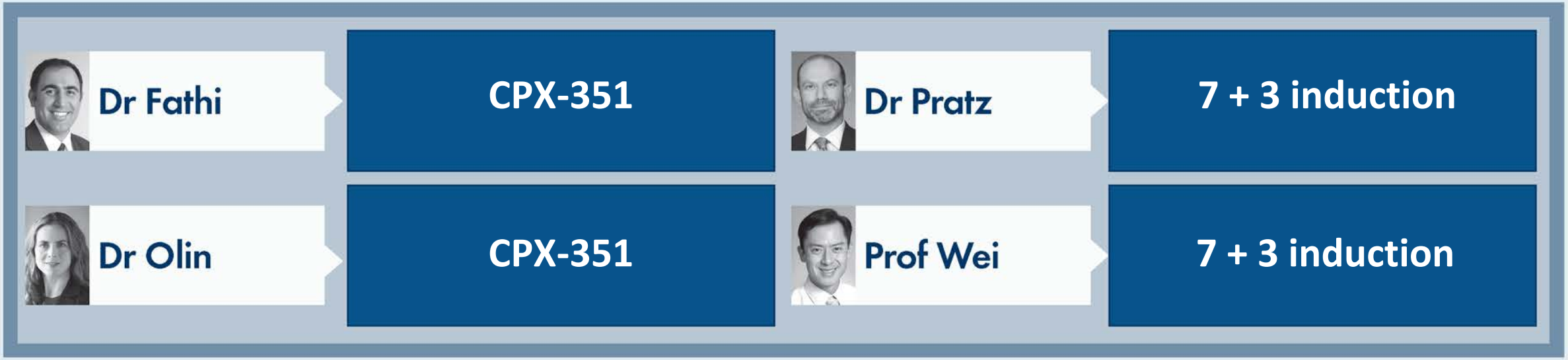
# Regulatory and reimbursement issues aside, what initial treatment would you recommend for a younger patient who is eligible for intensive chemotherapy who develops AML with no actionable mutations while receiving an ESA for lower-risk MDS?



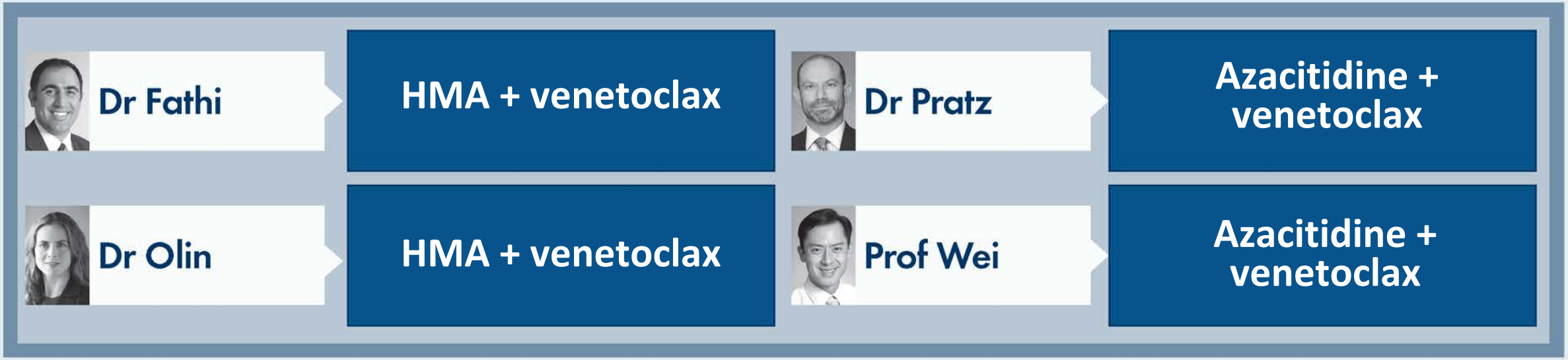
# Regulatory and reimbursement issues aside, what initial treatment would you recommend for an older patient who is not eligible for intensive chemotherapy who develops AML with no actionable mutations while receiving azacitidine for higher-risk MDS?

| | | | |
|---|---|---|---|
|  Dr Fathi | HMA + venetoclax |  Dr Pratz | Azacitidine + venetoclax |
|  Dr Olin | HMA + venetoclax<br>LDAC + venetoclax |  Prof Wei | Azacitidine + venetoclax |

# Regulatory and reimbursement issues aside, what initial treatment would you recommend for a younger patient who is eligible for intensive chemotherapy who develops AML with no actionable mutations while receiving azacitidine for higher-risk MDS?

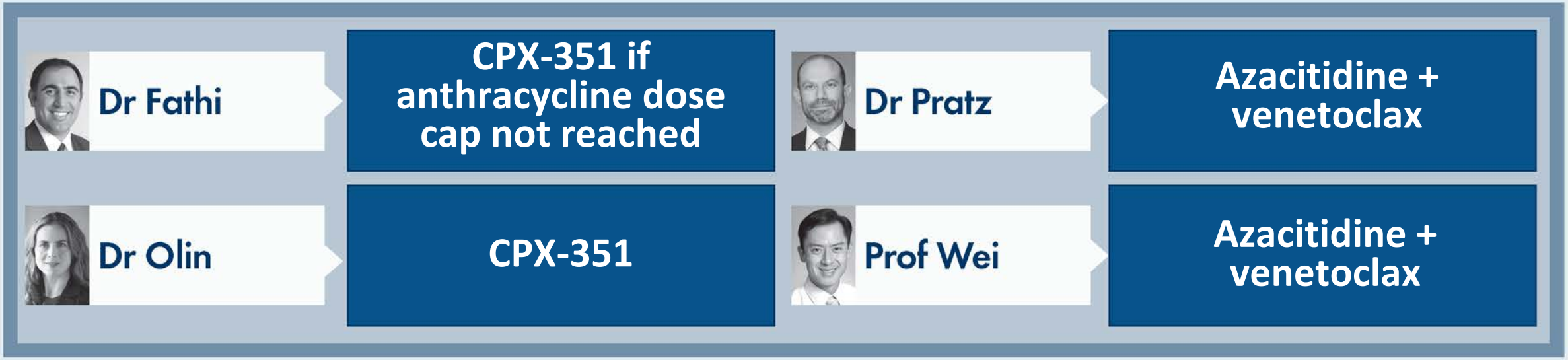


## Regulatory and reimbursement issues aside, what initial treatment would you recommend for an older woman who is not eligible for intensive chemotherapy, who has a history of breast cancer for which she received adjuvant anthracycline chemotherapy and who now presents with AML with no actionable mutations?

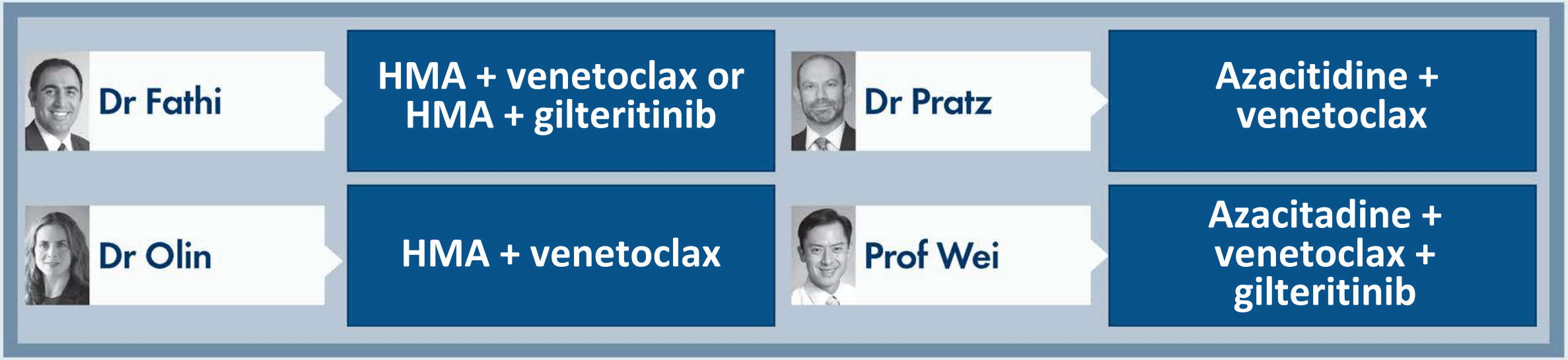



HMA: azacitidine or decitabine

**Regulatory and reimbursement issues aside, what initial treatment would you recommend for a younger woman who is eligible for intensive chemotherapy, who has a history of breast cancer for which she received adjuvant anthracycline chemotherapy and who now presents with AML with no actionable mutations?**

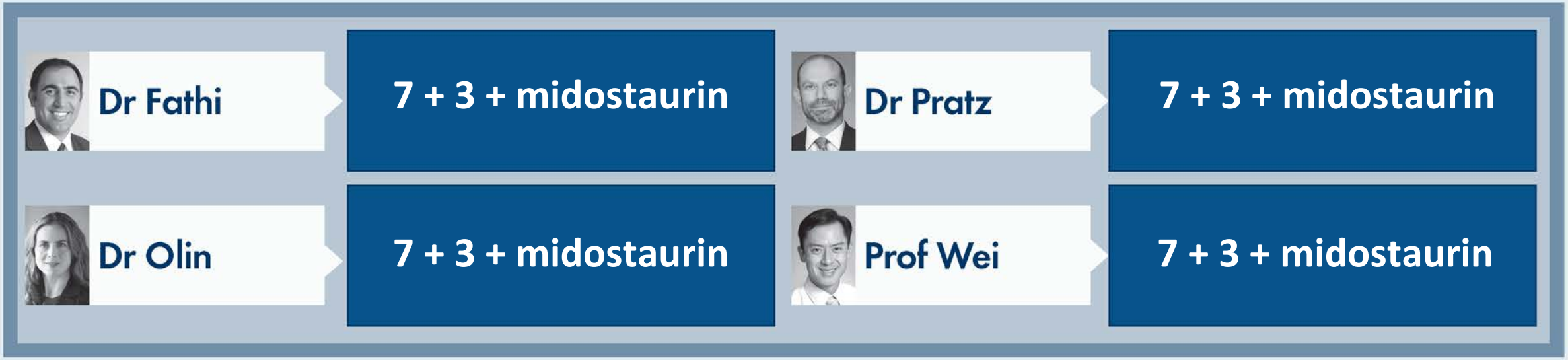


# Regulatory and reimbursement issues aside, what initial treatment would you recommend for an older patient who is not eligible for intensive chemotherapy who presents with AML and a FLT3-ITD mutation?

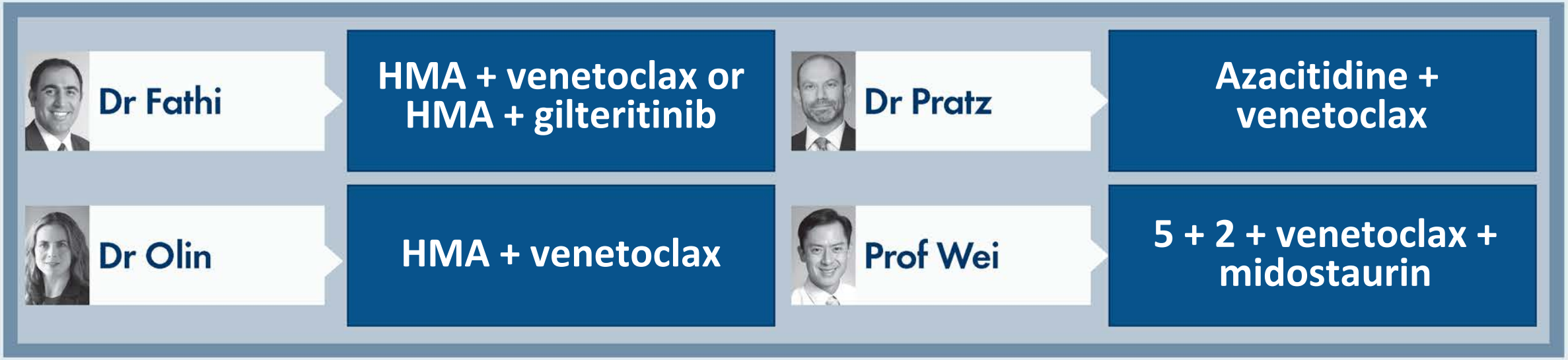



HMA: azacitidine or decitabine

# Regulatory and reimbursement issues aside, what initial treatment would you recommend for a younger patient who is eligible for intensive chemotherapy who presents with AML and a FLT3-ITD mutation?

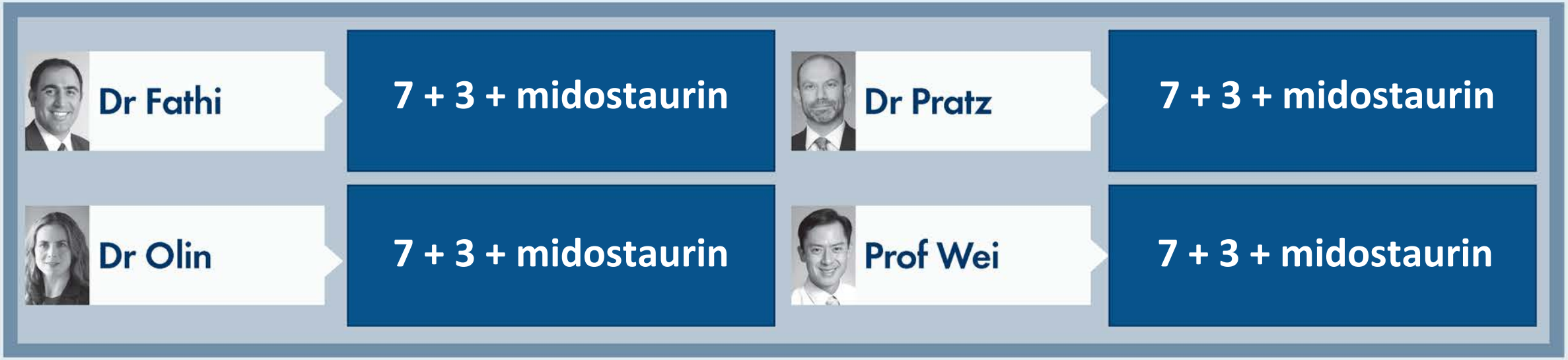


# Regulatory and reimbursement issues aside, what initial treatment would you recommend for an older patient who is not eligible for intensive chemotherapy who presents with AML and a FLT3-TKD mutation?

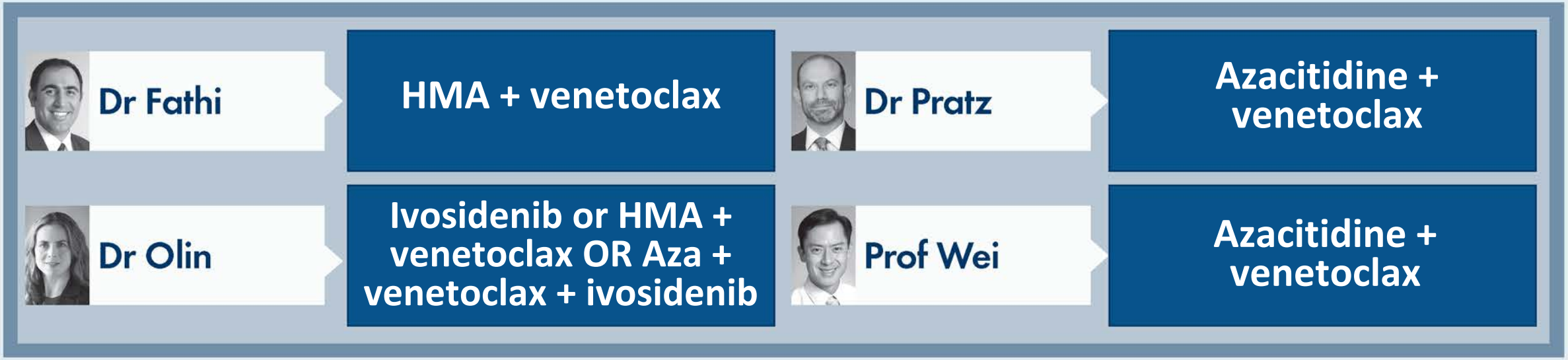



HMA: azacitidine or decitabine

**Regulatory and reimbursement issues aside, what initial treatment would you recommend for a younger patient who is eligible for intensive chemotherapy who presents with AML and a FLT3-TKD mutation?**

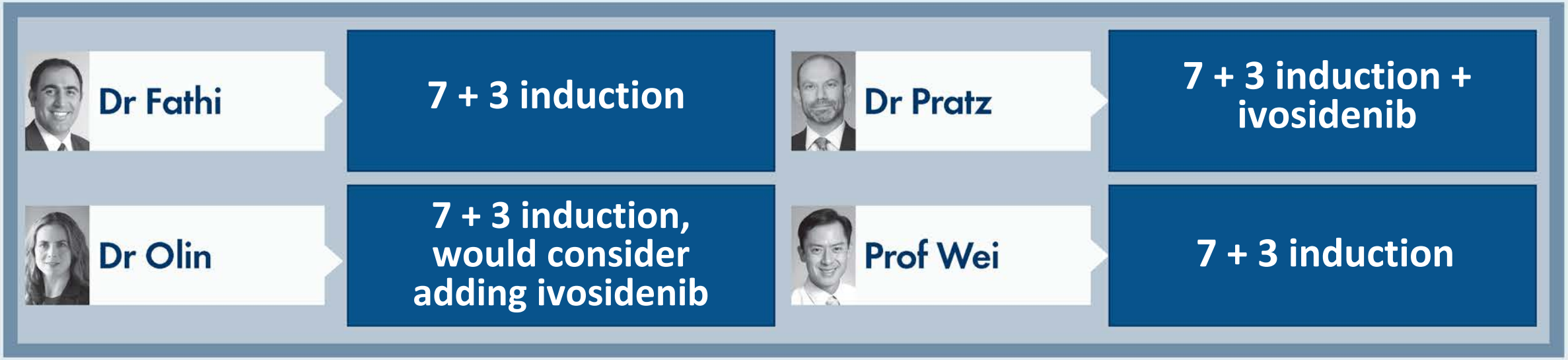


# Regulatory and reimbursement issues aside, what initial treatment would you recommend for an older patient who is not eligible for intensive chemotherapy who presents with AML and an IDH1 mutation?

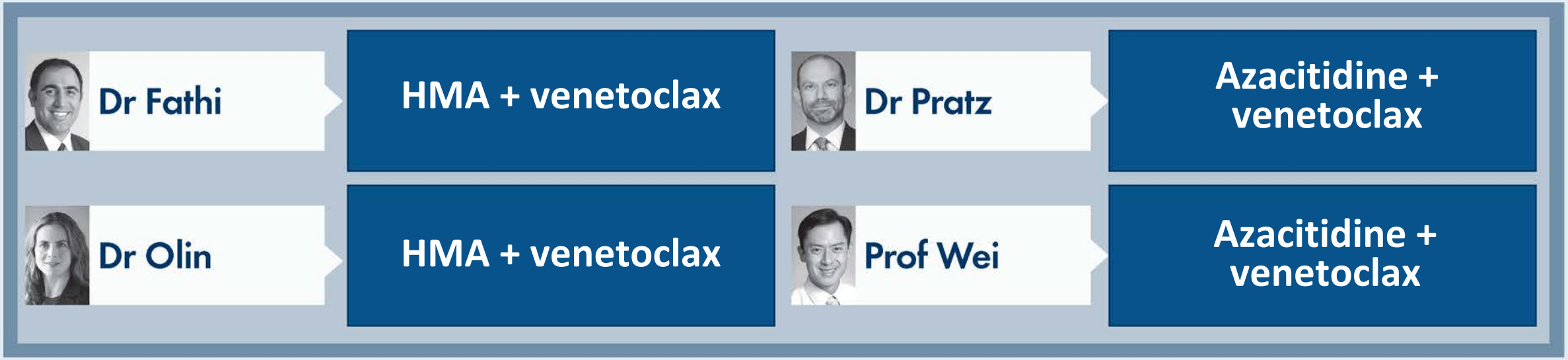



HMA: azacitidine or decitabine

# Regulatory and reimbursement issues aside, what initial treatment would you recommend for a younger patient who is eligible for intensive chemotherapy who presents with AML and an IDH1 mutation?

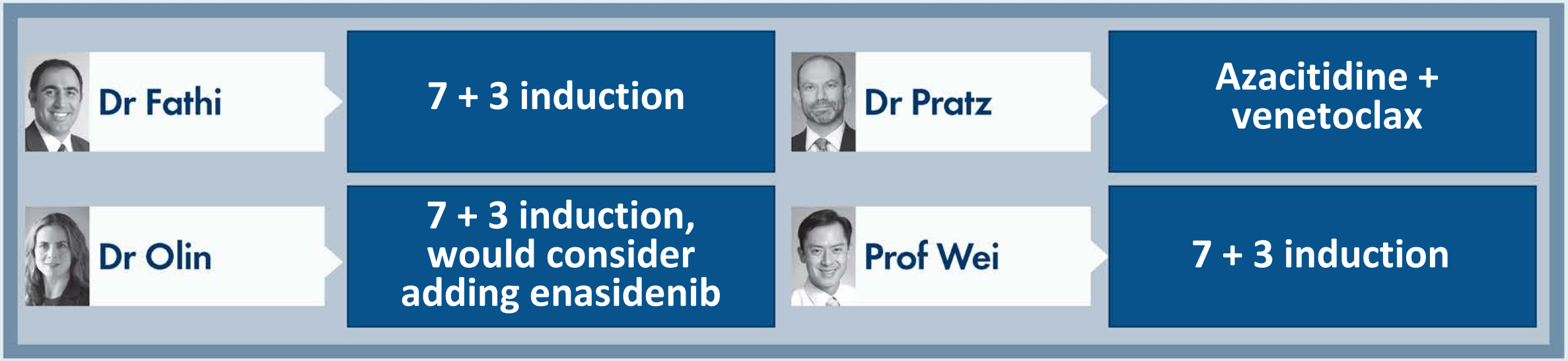


# Regulatory and reimbursement issues aside, what initial treatment would you recommend for an older patient who is not eligible for intensive chemotherapy who presents with AML and an IDH2 mutation?

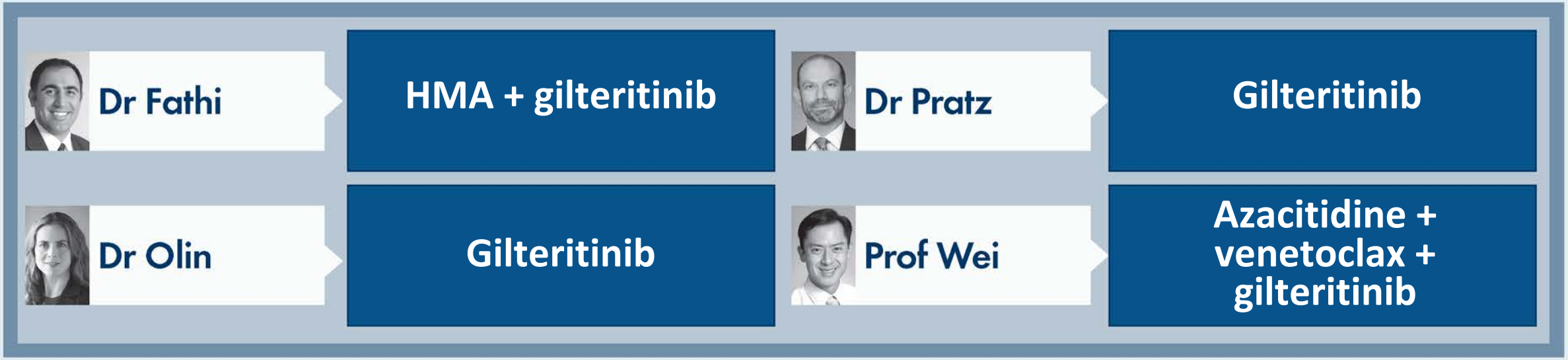



HMA: azacitidine or decitabine

# Regulatory and reimbursement issues aside, what initial treatment would you recommend for a younger patient who is eligible for intensive chemotherapy who presents with AML and an IDH2 mutation?

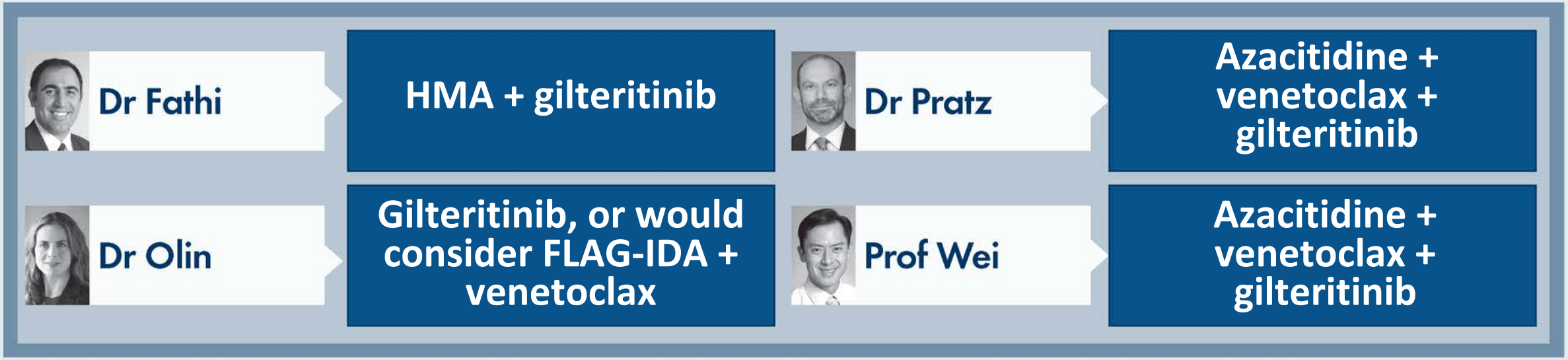


# Regulatory and reimbursement issues aside, what would you generally recommend as the next line of treatment for an older patient with AML and a FLT3-ITD mutation who is not eligible for intensive chemotherapy and has experienced disease progression after 7 + 3 with midostaurin?




RTP RESEARCH TO PRACTICE

# Regulatory and reimbursement issues aside, what would you generally recommend as the next line of treatment for a younger patient with AML and a FLT3-ITD mutation who is eligible for intensive chemotherapy and has experienced disease progression after 7 + 3 with midostaurin?



# Regulatory and reimbursement issues aside, what would you generally recommend as the next line of treatment for an older patient with AML and a FLT3-TKD mutation who is not eligible for intensive chemotherapy and has experienced disease progression after 7 + 3 with midostaurin?

| | | | |
|---|---|---|---|
|  Dr Fathi | HMA + gilteritinib |  Dr Pratz | Gilteritinib |
|  Dr Olin | Gilteritinib |  Prof Wei | Azacitidine + venetoclax + gilteritinib |

# Regulatory and reimbursement issues aside, what would you generally recommend as the next line of treatment for a younger patient with AML and a FLT3-TKD mutation who is eligible for intensive chemotherapy and has experienced disease progression after 7 + 3 with midostaurin?

| | | | |
|---|---|---|---|
|  Dr Fathi | HMA + gilteritinib |  Dr Pratz | Gilteritinib |
|  Dr Olin | Gilteritinib or would consider FLAG-IDA + venetoclax |  Prof Wei | Azacitidine + venetoclax + gilteritinib |

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# Regulatory and reimbursement issues aside, what would you generally recommend as the next line of treatment for an older patient with AML and an IDH1 mutation who is not eligible for intensive chemotherapy and has experienced disease progression after venetoclax/azacitidine?

| | | | |
|---|---|---|---|
|  Dr Fathi | Ivosidenib |  Dr Pratz | Ivosidenib |
|  Dr Olin | Ivosidenib +/- decitabine |  Prof Wei | Ivosidenib + venetoclax |

# Regulatory and reimbursement issues aside, what would you generally recommend as the next line of treatment for a younger patient with AML and an IDH1 mutation who is eligible for intensive chemotherapy and has experienced disease progression after venetoclax/azacitidine?

| | | | |
|---|---|---|---|
|  Dr Fathi | Ivosidenib |  Dr Pratz | Azacitidine + venetoclax + ivosidenib |
|  Dr Olin | 7 + 3 induction therapy or FLAG-IDA + venetoclax |  Prof Wei | Ivosidenib + venetoclax |

# Regulatory and reimbursement issues aside, what would you generally recommend as the next line of treatment for an older patient with AML and an IDH2 mutation who is not eligible for intensive chemotherapy and has experienced disease progression after venetoclax/azacitidine?

| | | | |
|---|---|---|---|
|  Dr Fathi | Enasidenib |  Dr Pratz | Enasidenib |
|  Dr Olin | Enasidenib +/- decitabine |  Prof Wei | Enasidenib + venetoclax |

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# Regulatory and reimbursement issues aside, what would you generally recommend as the next line of treatment for a younger patient with AML and an IDH2 mutation who is eligible for intensive chemotherapy and has experienced disease progression after venetoclax/azacitidine?

| | | | |
|---|---|---|---|
|  Dr Fathi | Enasidenib |  Dr Pratz | Azacitidine + venetoclax + enasidenib |
|  Dr Olin | 7 + 3 + enasidenib or FLAG-IDA + venetoclax |  Prof Wei | FLAG-IDA + venetoclax |

# In what clinical situations, if any, do you administer glasdegib to your patients with AML?

| | | | |
|---|---|---|---|
|  Dr Fathi | Perhaps older pts who have PD on HMA or HMA + venetoclax |  Dr Pratz | Have not used |
|  Dr Olin | When no other treatment options are available |  Prof Wei | None |

# Agenda

Introduction: AML Molecular Workup

Module 1: Dr Peles — A 71-year-old woman with AML with MDS-related changes

Module 2: Dr Shameem — A 77-year-old man with AML and an IDH1 mutation

Module 3: Dr Olin — A 62-year-old man with therapy-related AML

Module 4: Dr Yang — A 71-year-old woman with AML and FLT3-ITD and WT1 mutations

Module 5: Dr Olin — A 63-year-old man with relapsed AML

Module 6: Journal Club with Dr Pratz

Module 7: Faculty Survey

**Module 8: Appendix**

# Optimal Management of Newly Diagnosed Acute Myeloid Leukemia (AML) Not Eligible for Intensive Therapy

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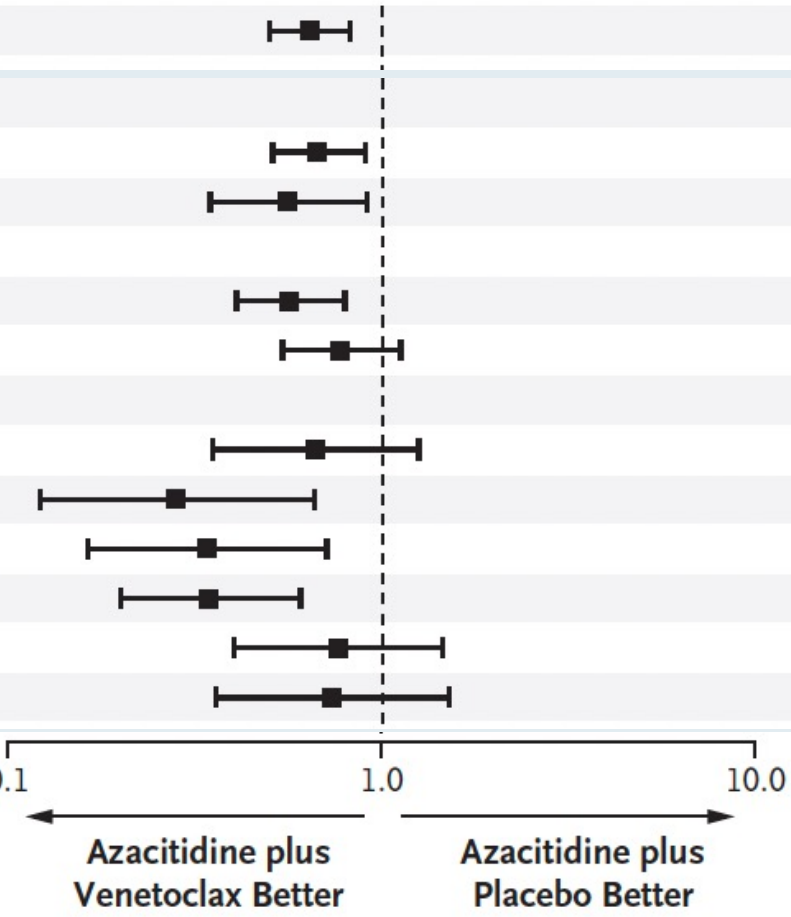
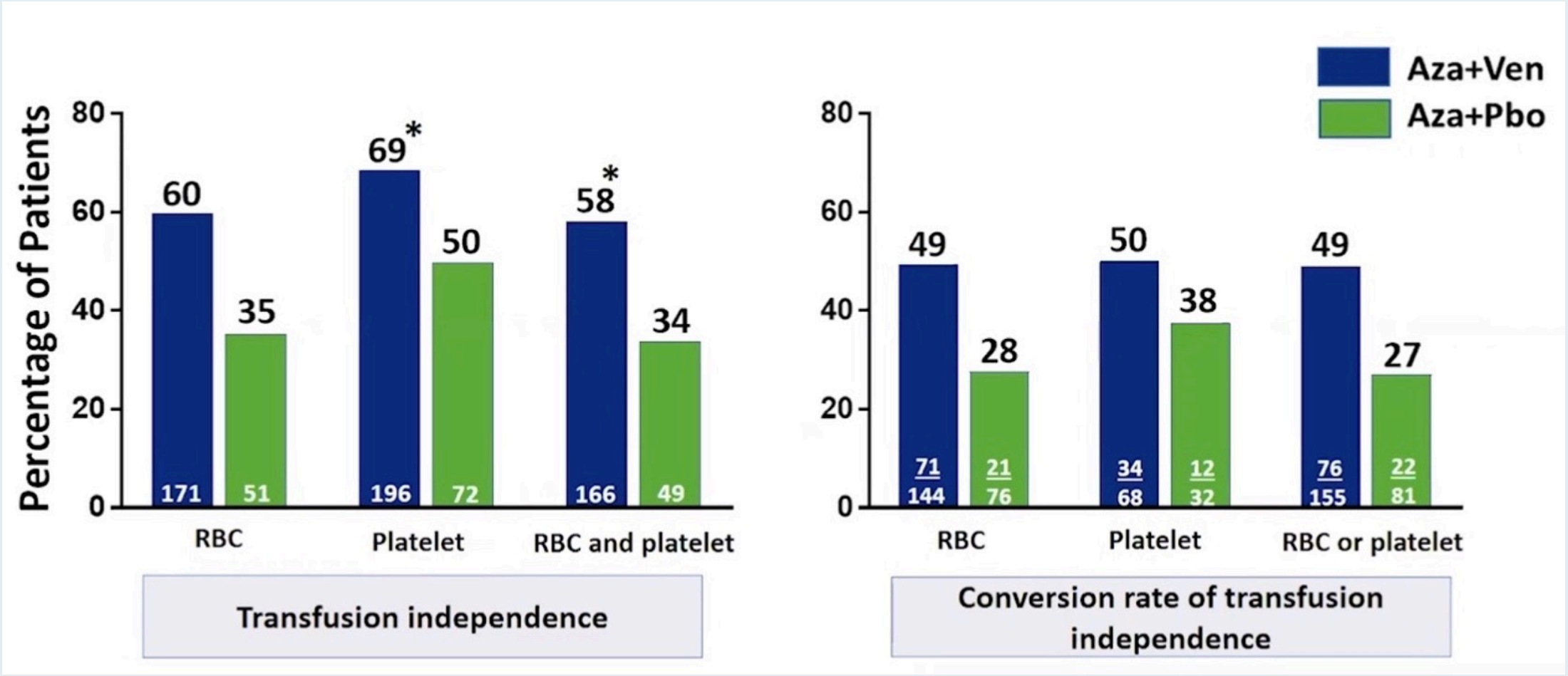
# VIALE-A: Overall Survival Subgroup Analysis

| Subgroup | Azacitidine plus Venetoclax | Azacitidine plus Placebo | Hazard Ratio for Death (95% CI) |
|---|---|---|---|
| | *no. of events/total no. (%)* | | |
| All patients | 161/286 (56.3) | 109/145 (75.2) | 0.64 (0.50–0.82) |
| Type of AML | | | |
| De novo | 120/214 (56.1) | 80/110 (72.7) | 0.67 (0.51–0.90) |
| Secondary | 41/72 (56.9) | 29/35 (82.9) | 0.56 (0.35–0.91) |
| Cytogenetic risk | | | |
| Intermediate | 84/182 (46.2) | 62/89 (69.7) | 0.57 (0.41–0.79) |
| Poor | 77/104 (74.0) | 47/56 (83.9) | 0.78 (0.54–1.12) |
| Molecular marker | | | |
| *FLT3* | 19/29 (65.5) | 19/22 (86.4) | 0.66 (0.35–1.26) |
| *IDH1* | 15/23 (65.2) | 11/11 (100.0) | 0.28 (0.12–0.65) |
| *IDH2* | 15/40 (37.5) | 14/18 (77.8) | 0.34 (0.16–0.71) |
| *IDH1* or *IDH2* | 29/61 (47.5) | 24/28 (85.7) | 0.34 (0.20–0.60) |
| *TP53* | 34/38 (89.5) | 13/14 (92.9) | 0.76 (0.40–1.45) |
| *NPM1* | 16/27 (59.3) | 14/17 (82.4) | 0.73 (0.36–1.51) |




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

# VIALE-A: Patients with ≥8 Weeks Transfusion-Free Interval




DiNardo C et al. EHA 2020;Abstract LB2601.

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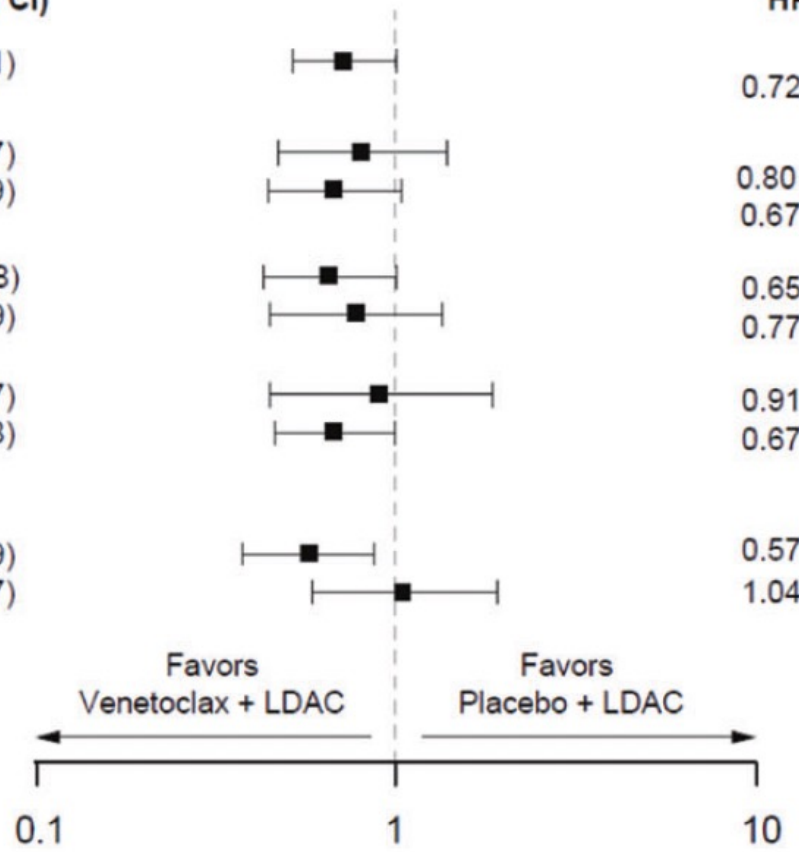
# VIALE-A: Selected Adverse Events

| Event | Azacitidine–Venetoclax Group (N=283) | | Azacitidine–Placebo Group (N=144) | |
|---|---|---|---|---|
| | All Grades† | ≥Grade 3‡ | All Grades† | ≥Grade 3‡ |
| | *number of patients (percent)* | | | |
| Hematologic adverse events | 236 (83) | 233 (82) | 100 (69) | 98 (68) |
| Thrombocytopenia | 130 (46) | 126 (45) | 58 (40) | 55 (38) |
| Neutropenia | 119 (42) | 119 (42) | 42 (29) | 41 (28) |
| Febrile neutropenia | 118 (42) | 118 (42) | 27 (19) | 27 (19) |
| Anemia | 78 (28) | 74 (26) | 30 (21) | 29 (20) |
| Leukopenia | 58 (21) | 58 (21) | 20 (14) | 17 (12) |
| 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.

# VIALE-C: Overall Survival Subgroup Analysis

| | Venetoclax + LDAC | | Placebo + LDAC | | |
|---|---|---|---|---|---|
| | n/N (%) | Median months (95% CI) | n/N (%) | Median months (95% CI) | HR (95% CI) |
| **All Subjects** | 99/143 (69.2) | 8.4 (5.9, 10.1) | 54/68 (79.4) | 4.1 (3.1, 8.1) | 0.72 (0.51, 1.00) |
| **Age (years)** | | | | | |
| 18 - < 75 | 41/61 (67.2) | 9.8 (5.6, 11.2) | 20/28 (71.4) | 6.5 (2.0, 9.7) | 0.80 (0.47, 1.37) |
| ≥ 75 | 58/82 (70.7) | 6.6 (4.6, 9.7) | 34/40 (85.0) | 3.6 (3.0, 8.9) | 0.67 (0.44, 1.03) |
| **AML Status** | | | | | |
| *De novo* | 53/85 (62.4) | 9.2 (7.2, 11.3) | 36/45 (80.0) | 6.5 (3.1, 9.8) | 0.65 (0.42, 0.99) |
| Secondary | 46/58 (79.3) | 5.6 (3.4, 9.8) | 18/23 (78.3) | 3.2 (1.8, 7.9) | 0.77 (0.45, 1.34) |
| **Prior HMA** | | | | | |
| Yes | 24/28 (85.7) | 5.6 (3.4, 9.6) | 11/14 (78.6) | 4.1 (2.2, 9.7) | 0.91 (0.44, 1.86) |
| No | 75/115 (65.2) | 8.9 (6.6, 10.9) | 43/54 (79.6) | 4.7 (2.2, 8.8) | 0.67 (0.46, 0.98) |
| **Cytogenetic Risk** | | | | | |
| Favorable | 1/1 (100.0) | NA | 2/3 ( 66.7) | NA | NA |
| Intermediate | 54/90 (60.0) | 10.9 (7.9, 16.4) | 36/43 (83.7) | 6.5 (2.2, 8.9) | 0.57 (0.37, 0.87) |
| Poor | 40/47 (85.1) | 4.4 (3.0, 6.4) | 15/20 (75.0) | 3.6 (1.2, 9.7) | 1.04 (0.58, 1.89) |

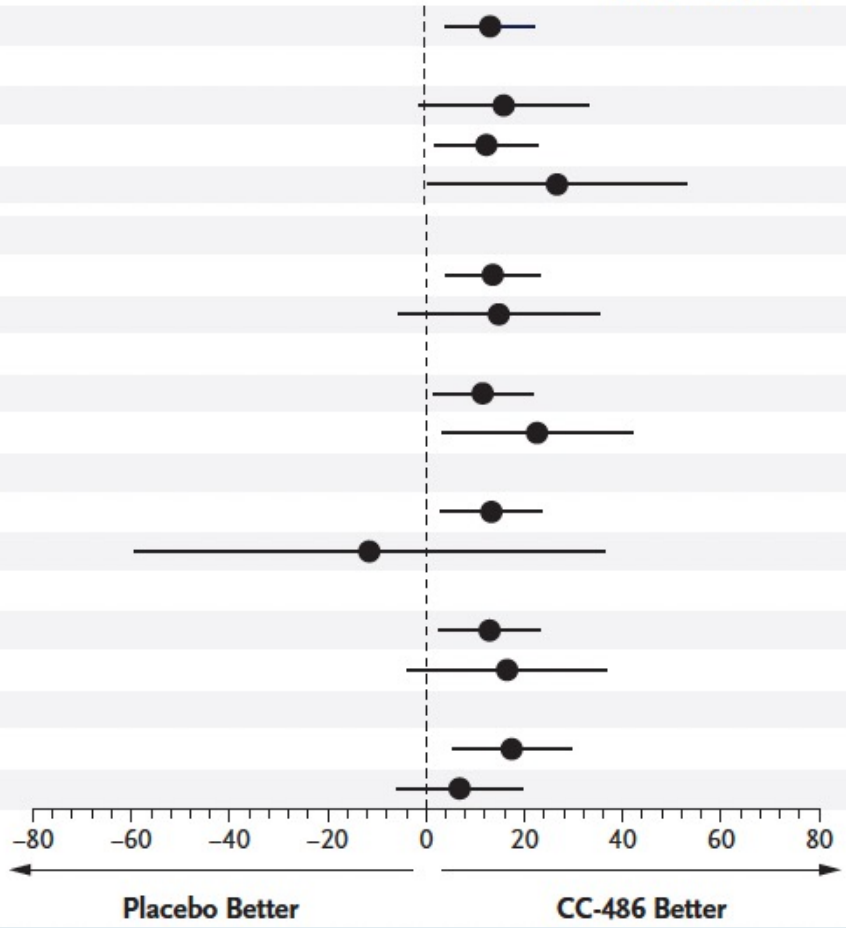



Wei AH et al. *Blood Cancer J* 2021;11:163.

# Novel Induction and Maintenance Strategies for Younger Patients with AML; Promising Agents and Strategies Under Investigation

# QUAZAR AML-001: Overall Survival Subgroup Analysis

| Subgroup | No. of Patients | | 2-Yr Survival | | 2-Yr Survival Difference (95% CI) |
|---|---|---|---|---|---|
| | CC-486 | Placebo | CC-486 | Placebo | |
| | | | % | | *percentage points* |
| Overall | 238 | 234 | 50.6 | 37.1 | 13.5 (4.5 to 22.5) |
| Age | | | | | |
| ≥55 to <65 yr | 66 | 68 | 61.3 | 45.1 | 16.2 (–0.9 to 33.4) |
| ≥65 yr | 172 | 166 | 46.7 | 33.9 | 12.8 (2.3 to 23.3) |
| ≥75 yr | 28 | 24 | 51.9 | 24.8 | 27.1 (0.7 to 53.4) |
| Cytogenetic risk at induction | | | | | |
| Intermediate | 203 | 203 | 54.1 | 40.4 | 13.6 (3.9 to 23.4) |
| Poor | 35 | 31 | 30.3 | 15.5 | 14.8 (–5.6 to 35.2) |
| Consolidation after induction | | | | | |
| Yes | 186 | 192 | 50.8 | 39.2 | 11.6 (1.4 to 21.7) |
| No | 52 | 42 | 50.0 | 27.4 | 22.6 (3.2 to 42.0) |
| Consolidation cycles | | | | | |
| 1 or 2 | 180 | 179 | 50.8 | 37.6 | 13.3 (2.9 to 23.7) |
| 3 | 6 | 13 | 50.0 | 61.5 | –11.5 (–59.5 to 36.4) |
| Response at randomization | | | | | |
| Complete remission | 183 | 177 | 49.7 | 36.7 | 13.0 (2.7 to 23.3) |
| Complete remission with incomplete blood count recovery | 50 | 44 | 55.1 | 38.6 | 16.5 (–3.8 to 36.8) |
| MRD status at randomization | | | | | |
| Positive | 103 | 116 | 39.5 | 22.0 | 17.5 (5.3 to 29.8) |
| Negative | 133 | 111 | 58.6 | 51.7 | 6.9 (–5.8 to 19.5) |

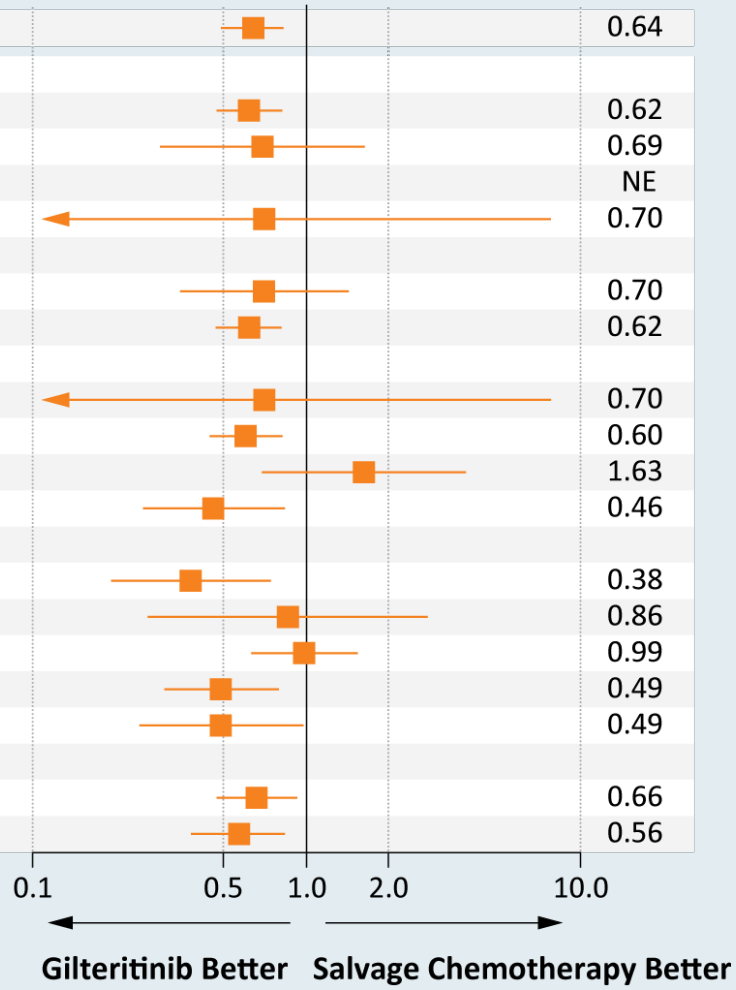



Wei AH et al. *N Engl J Med* 2020;383:2526-37.

# Current Management Approaches for Patients with AML and a FLT3 and/or IDH Mutation

# ADMIRAL: Subgroup Analysis of Overall Survival

| Subgroup | Gilteritinib | Salvage Chemotherapy | Hazard Ratio for Death |
|---|---|---|---|
| | *no. of events/total no. of patients* | | |
| All patients | 171/247 | 90/124 | 0.64 |
| FLT3 mutation type | | | |
| FLT3 ITD alone | 145/215 | 81/113 | 0.62 |
| FLT3 TKD alone | 16/21 | 8/10 | 0.69 |
| FLT3 ITD and FLT3 TKD | 6/7 | 0 | NE |
| Other | 4/4 | 1/1 | 0.70 |
| Previous use of FLT3 inhibitor | | | |
| Yes | 26/32 | 11/14 | 0.70 |
| No | 145/215 | 79/110 | 0.62 |
| Cytogenetic risk status | | | |
| Favorable | 3/4 | 1/1 | 0.70 |
| Intermediate | 119/182 | 63/89 | 0.60 |
| Unfavorable | 22/26 | 7/11 | 1.63 |
| Unknown | 27/35 | 19/23 | 0.46 |
| Response to first-line therapy per IRT | | | |
| Relapse ≤6 mo after allogeneic HSCT | 24/31 | 16/17 | 0.38 |
| Relapse >6 mo after allogeneic HSCT | 10/17 | 4/8 | 0.86 |
| Primary refractory disease without HSCT | 70/98 | 28/48 | 0.99 |
| Relapse ≤6 mo after composite complete remission and no HSCT | 47/67 | 28/34 | 0.49 |
| Relapse >6 mo after composite complete remission and no HSCT | 20/34 | 14/17 | 0.49 |
| Preselected chemotherapy per IRT | | | |
| High intensity | 96/149 | 52/75 | 0.66 |
| Low intensity | 75/98 | 38/49 | 0.56 |




Perl AE et al. *N Engl J Med* 2019;381:1728-40.

RTP RESEARCH TO PRACTICE

# ADMIRAL: Antileukemic Responses

| | Gilteritinib (n = 247) | Salvage chemo (n = 124) | HR or risk difference |
|---|---|---|---|
| Complete remission (CR) | 21.1% | 10.5% | 10.6 |
| CR or CR with partial hematologic recovery | 34.0% | 15.3% | 18.6 |
| CR with partial hematologic recovery | 13.0% | 4.8% | Not determined |
| CR with incomplete hematologic recovery | 25.5% | 11.3% | Not determined |
| CR with incomplete platelet recovery | 7.7% | 0 | Not determined |
| Composite CR* | 54.3% | 21.8% | 32.5 |
| Overall response | 67.6% | 25.8% | Not reported |

*Composite complete remission was defined as the combination of CR, CR with incomplete hematologic recovery and CR with incomplete platelet recovery

Perl AE et al. *N Engl J Med* 2019;381:1728-40.

# Phase Ib Trial of Ivosidenib in Combination with Azacitidine for Newly Diagnosed AML

| Clinical endpoint | N = 23 |
|---|---|
| CR + CRh, n (%)<br>CR<br>CRh | 16 (70%)<br>14 (61%)<br>2 (9%) |
| ORR, n (%) | 18 (73%) |
| 12-month survival estimate (%) | 82% |
| **Select Grade ≥3 treatment-emergent AEs, n (%)** | |
| Thrombocytopenia | 14 (61%) |
| Anemia | 10 (43.5%) |
| Febrile neutropenia | 10 (43.5%) |
| ECG QT prolongation | 3 (13%) |
| IDH differentiation syndrome | 2 (9%) |

CRh = CR with partial hematologic recovery

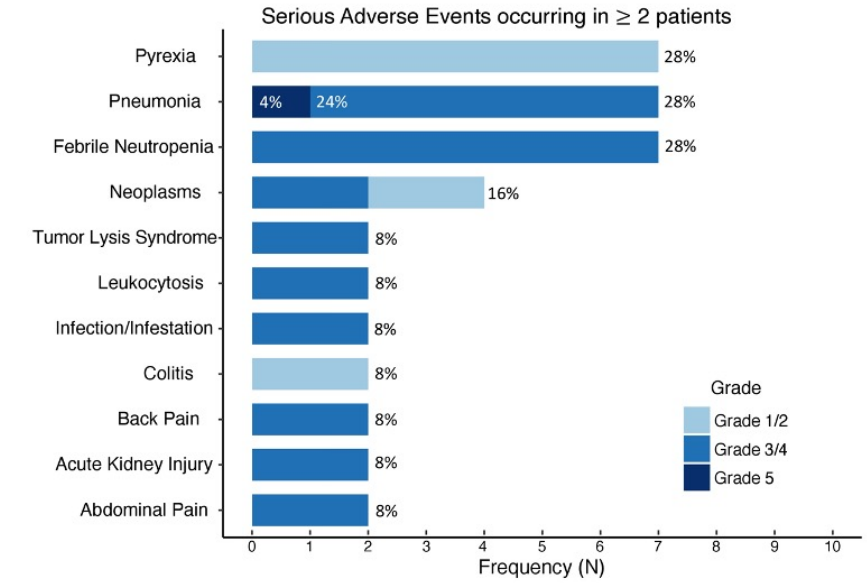
DiNardo CD et al. *J Clin Oncol* 2020;39:57-65.

RTP RESEARCH TO PRACTICE

# Phase Ib/II Study of Ivosidenib with Venetoclax with or without Azacitidine in Patients with Myeloid Cancer and an IDH1 Mutation

- 3 x 3 dose escalation/de-escalation study exploring 4 dose levels in 25 patients with advanced MDS or MPN or newly diagnosed or R/R AML

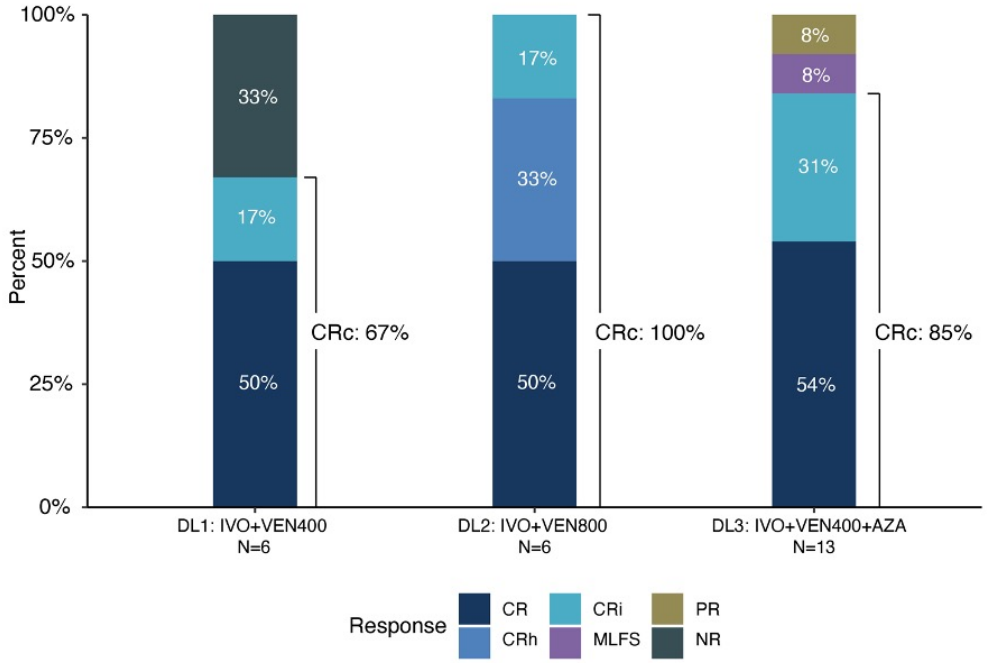
## Safety




| Mortality | Frequency |
|---|---|
| 30-day | 0% |
| 60-day | 0% |
| Study Deaths | 1 (pneumonia) |

| IDH Differentiation Syndrome N (%) | |
|---|---|
| Dose Level #1 | 2 (33%) |
| Dose Level #2 | 1 (17%) |
| Dose Level #3 | 1 (8%) |

## Efficacy




| | DL1 (n = 6) | DL2 (n = 6) | DL3 (n = 13) |
|---|---|---|---|
| 1-Year OS | 50% | 67% | 83% |

Lachowiez CA et al. ASCO 2021;Abstract 7012.

RTP RESEARCH TO PRACTICE

# Incidence and Management of Secondary AML (sAML)

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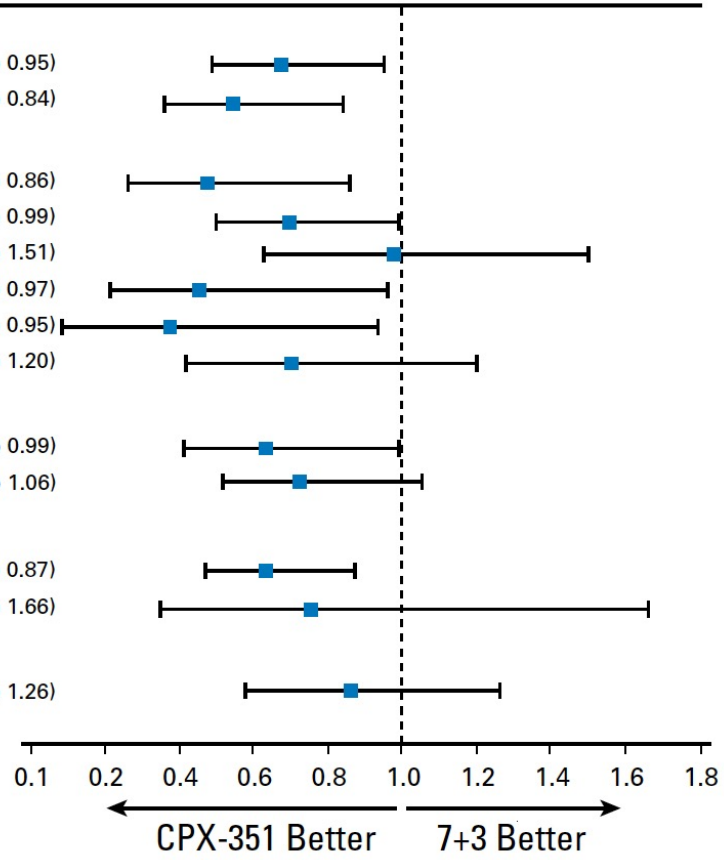
TO PRACTICE

# Phase III Trial of CPX-351 versus 7 + 3 Cytarabine and Daunorubicin for Older Patients with Newly Diagnosed High-Risk or Secondary AML: Overall Survival by Baseline Characteristics

**B**

| Subgroup | CPX-351 No. | CPX-351 Median OS, months | 7+3 No. | 7+3 Median OS, months | HR (95% CI) for Death |
|---|---|---|---|---|---|
| **Age** | | | | | |
| 60-69 years | 96 | 9.63 | 102 | 6.87 | 0.68 (0.49 to 0.95) |
| 70-75 years | 57 | 8.87 | 54 | 5.62 | 0.55 (0.36 to 0.84) |
| **Type of AML** | | | | | |
| Therapy-related AML | 30 | 12.17 | 33 | 5.95 | 0.48 (0.26 to 0.86) |
| AML with antecedent MDS or CMML | 82 | 7.38 | 86 | 5.95 | 0.70 (0.50 to 0.99) |
| MDS with prior HMA exposure | 50 | 5.65 | 55 | 7.43 | 0.98 (0.64 to 1.51) |
| MDS without prior HMA exposure | 21 | 15.74 | 19 | 5.13 | 0.46 (0.21 to 0.97) |
| CMML | 11 | 9.33 | 12 | 2.28 | 0.37 (0.14 to 0.95) |
| De novo AML with MDS karyotype | 41 | 10.09 | 37 | 7.36 | 0.71 (0.42 to 1.20) |
| **Cytogenetic risk at screening** | | | | | |
| Favorable/intermediate | 71 | 14.72 | 63 | 8.41 | 0.64 (0.41 to 0.99) |
| Unfavorable | 72 | 6.60 | 83 | 5.16 | 0.73 (0.51 to 1.06) |
| **Baseline *FLT3* mutation status** | | | | | |
| *FLT3* wild type | 116 | 9.33 | 120 | 5.98 | 0.64 (0.47 to 0.87) |
| *FLT3* mutation | 22 | 10.25 | 21 | 4.60 | 0.76 (0.34 to 1.66) |
| **Overall HMA experience** | | | | | |
| All patients with prior HMA exposure* | 62 | 5.65 | 71 | 5.90 | 0.86 (0.59 to 1.26) |




Lancet JE et al. *J Clin Oncol* 2018;36(26):2684-92.

# *Meet The Professor*

## Optimizing the Management of Metastatic Castration-Resistant Prostate Cancer

**Tuesday, November 9, 2021**
**5:00 PM – 6:00 PM ET**

### Faculty

**Simon Chowdhury, MD, PhD**

### Moderator

**Neil Love, MD**

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*Thank you for joining us!*

*CME and MOC credit information will be emailed to each participant within 5 business days.*

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