Meet The Professor
Optimizing the Management of Acute Myeloid Leukemia

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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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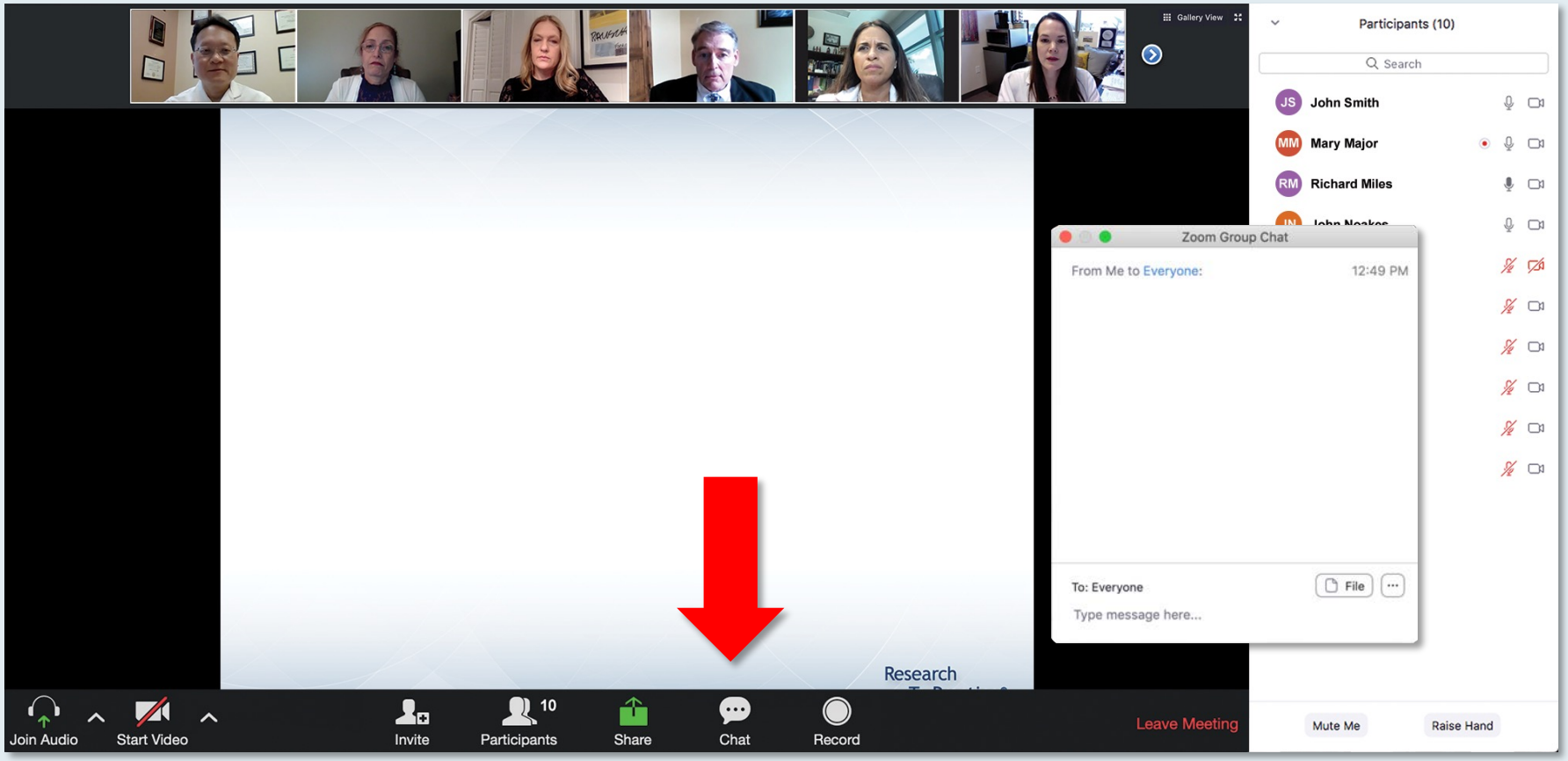

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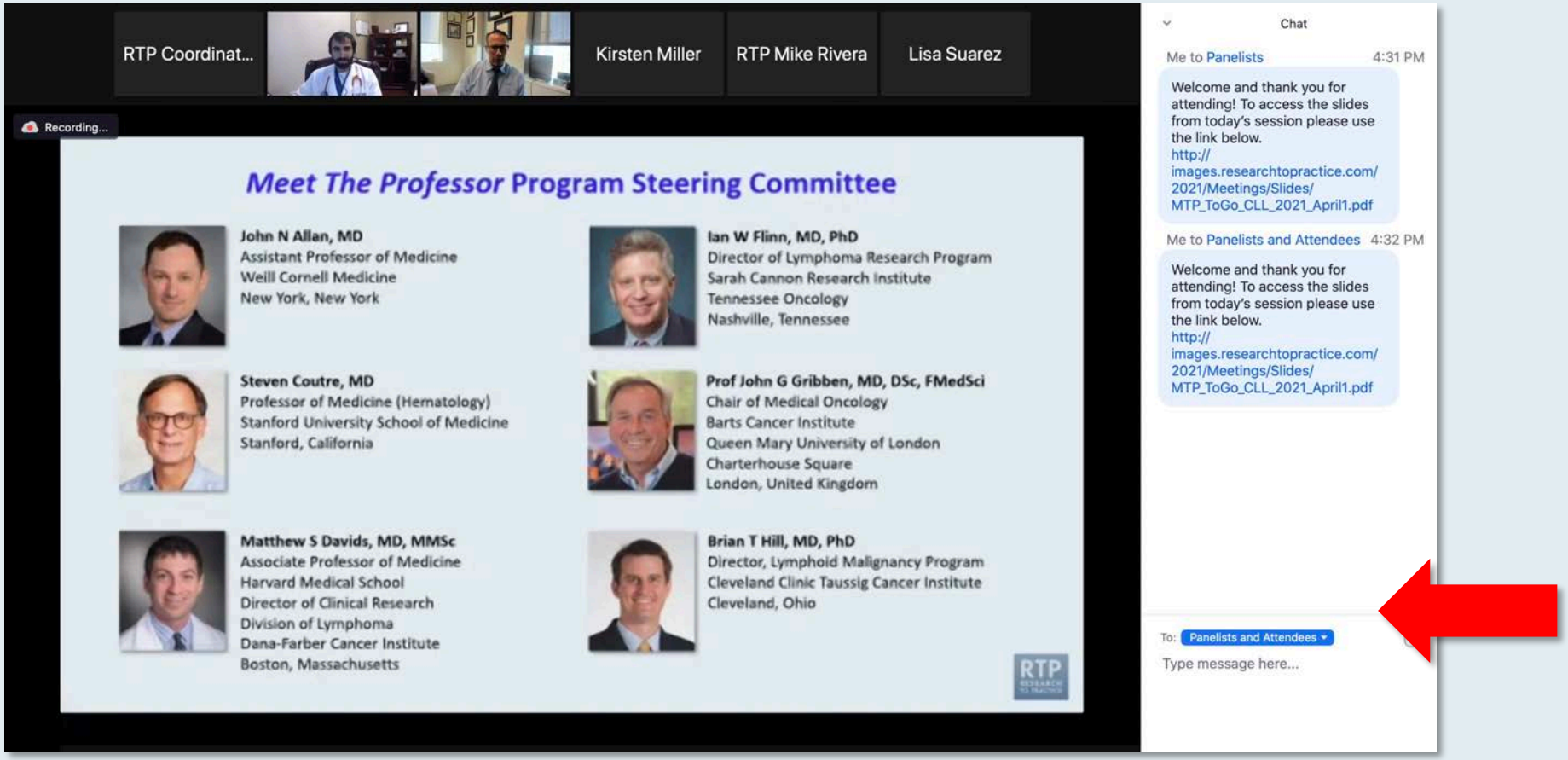

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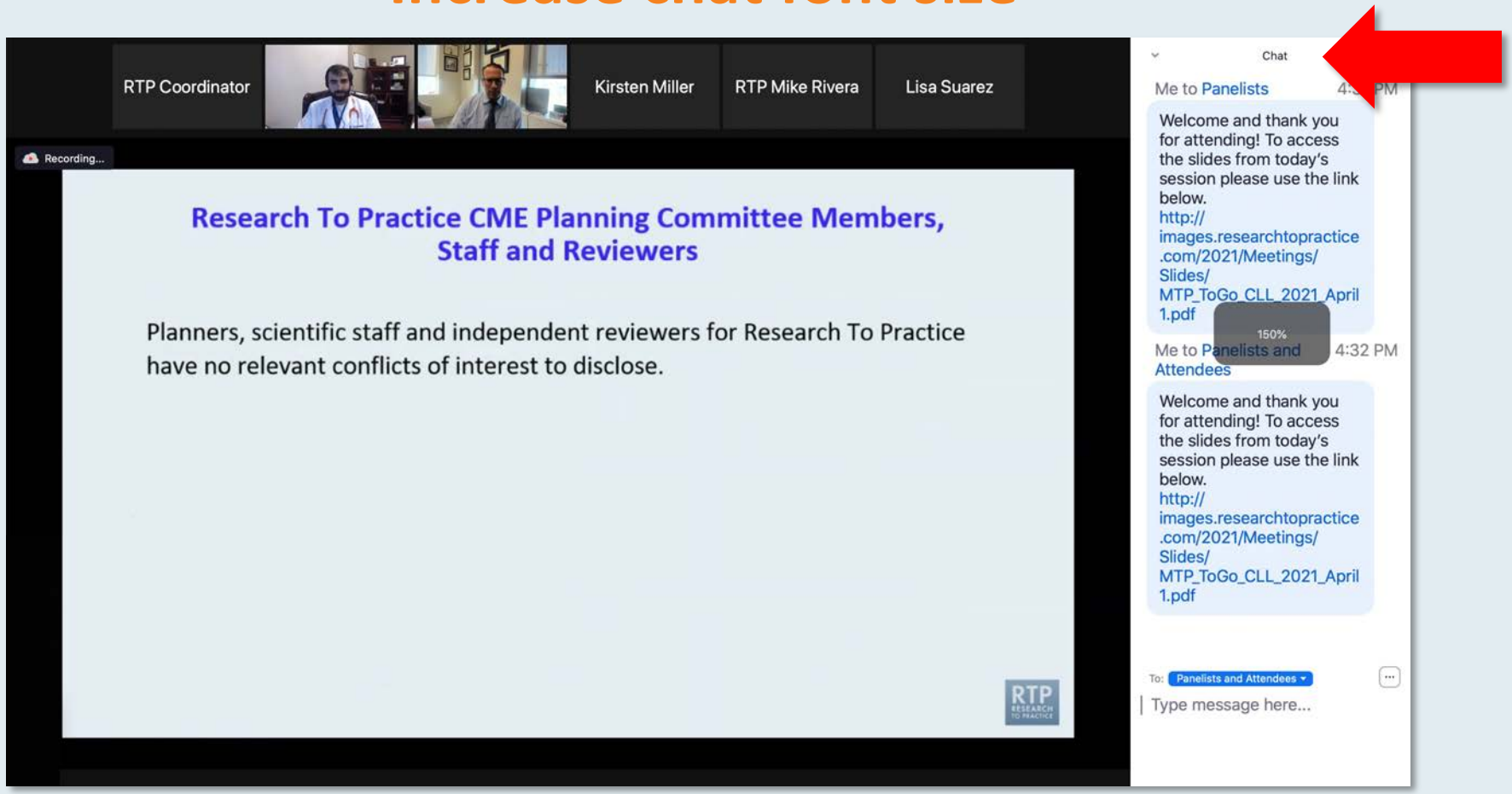

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Chronic Myeloid Leukemia

DR MICHAEL MAURO

MEMORIAL SLOAN KETTERING CANCER CENTER

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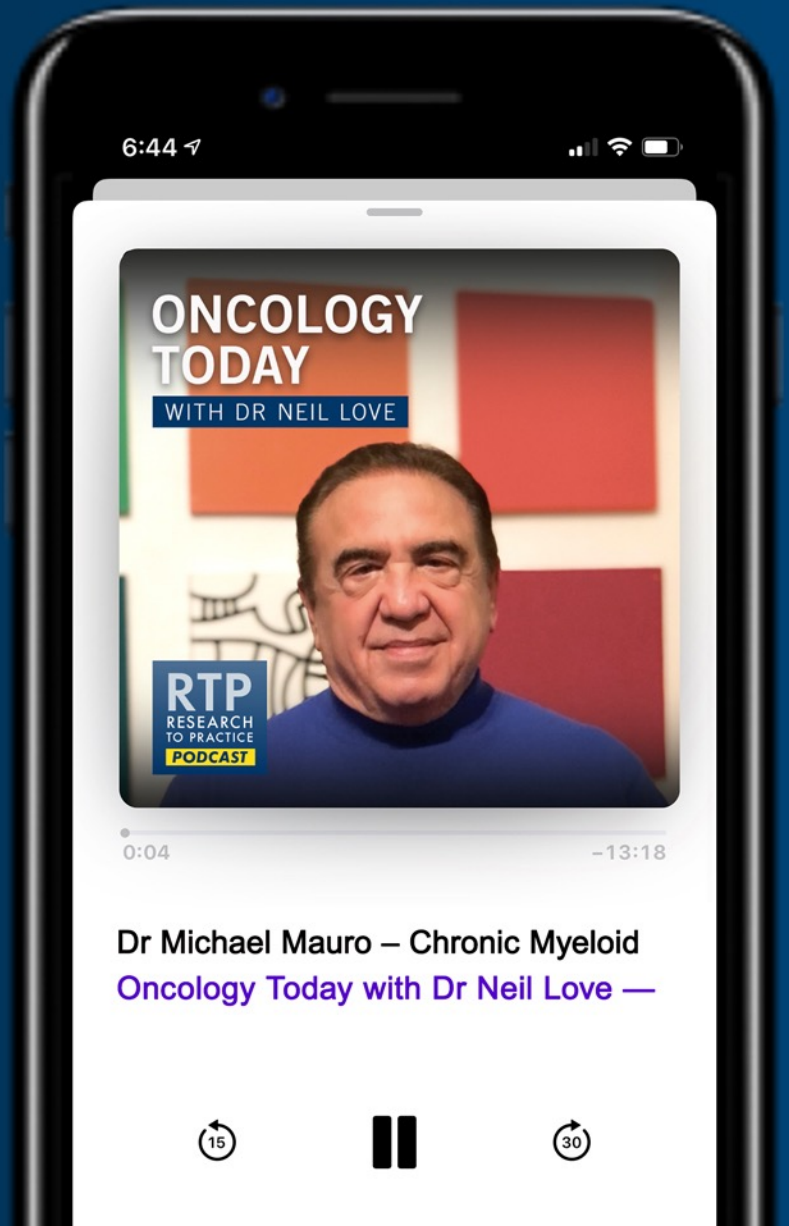

Meet The Professor

Optimizing the Clinical Management of Hodgkin and Non-Hodgkin Lymphomas

Wednesday, December 15, 2021
5:00 PM – 6:00 PM ET

Faculty

Brian T Hill, MD, PhD

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with ER-Positive Breast Cancer

Thursday, December 16, 2021
5:00 PM – 6:00 PM ET

Faculty

Ruth O'Regan, MD

Moderator

Neil Love, MD

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Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

Follicular Lymphoma

Tuesday, January 4, 2022
5:00 PM – 6:00 PM ET

Faculty

Laurie H Sehn, MD, MPH
Additional faculty to be announced.

Moderator

Neil Love, MD

RTP Year in Review 2022

Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

Breast Cancer

Thursday, January 6, 2022
5:00 PM – 6:00 PM ET

Faculty

Harold J Burstein, MD, PhD
Additional faculty to be announced.

Moderator

Neil Love, MD

RTP Year in Review 2022

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Colorectal Cancer (Part 1 of a 3-Part Series)

Wednesday, January 19, 2022
10:15 PM – 11:45 PM ET

Faculty

Alan P Venook, MD

Additional faculty to be announced.

Moderator

To be announced.

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Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Gastroesophageal Cancers (Part 2 of a 3-Part Series)

Thursday, January 20, 2022
9:15 PM – 10:45 PM ET

Faculty

Yelena Y Janjigian, MD
Eric Van Cutsem, MD, PhD
Additional faculty to be announced.

Moderator

Samuel J Klempner, MD

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Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Hepatobiliary Cancers (Part 3 of a 3-Part Series)

Friday, January 21, 2022
9:15 PM – 10:45 PM ET

Faculty

Ghassan Abou-Alfa, MD, MBA
Richard S Finn, MD
Robin K Kelley, MD

Moderator

Tanios Bekaii-Saab, 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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Houston, Texas

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

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Clinical Director of Leukemia Services
Robert H Allen, MD Chair in Hematology Research
Division of Hematology
University of Colorado School of Medicine
Aurora, Colorado

Keith W Pratz, MD
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Associate Professor of Medicine
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Philadelphia, Pennsylvania

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Meet The Professor Program Participating Faculty

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Assistant Attending Physician
Director, Program for Drug Development in Leukemia
Leukemia Service, Department of Medicine
Memorial Sloan Kettering Cancer Center
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Andrew H Wei, MBBS, PhD
Professor, Department of Haematology
Alfred Hospital
Monash University
Walter and Eliza Hall Institute of Medical Research
Melbourne, Australia

Wendy Stock, MD
Anjuli Seth Nayak Professor of
Leukemia Research
University of Chicago Medicine and
Comprehensive Cancer Center
Chicago, Illinois

Moderator

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Research To Practice
Miami, Florida

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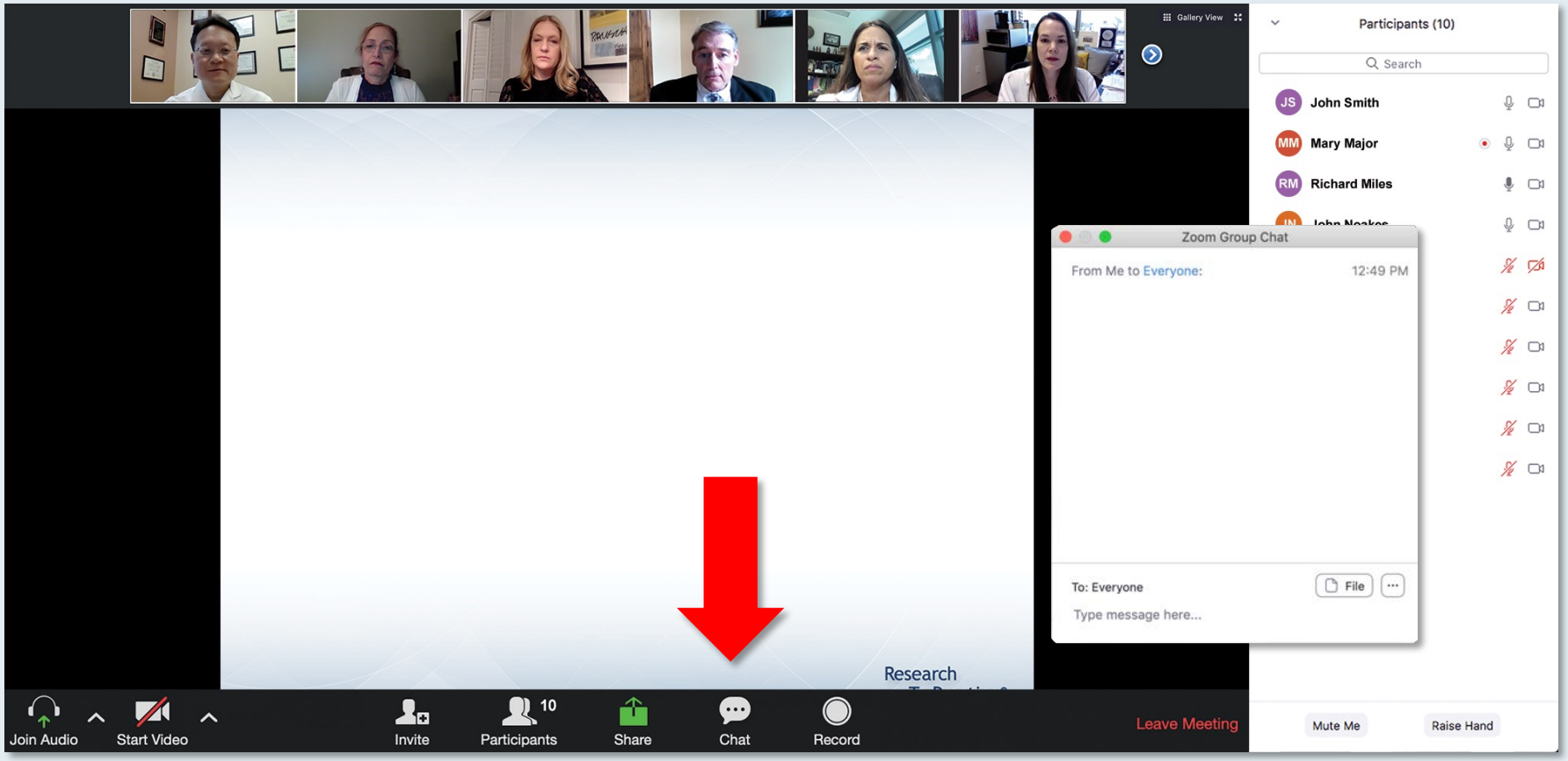

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Ranju Gupta, MD
LVPG Hematology Oncology Associates
Lehigh Valley Health Network
Bethlehem, Pennsylvania

Erik J Rupard, MD
Drexel University College of Medicine
West Reading, Pennsylvania

Shaachi Gupta, MD, MPH
Florida Cancer Specialists and
Research Institute
Lake Worth, Florida

Prashant Sharma, MD
Intermountain Healthcare
Salt Lake City, Utah

Rebecca L Olin, MD, MSCE
University of California, San Francisco
San Francisco, California

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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 (HMA)?

 Dr Daver	Yes	 Dr Pratz	No
 Dr Fathi	Yes	 Dr Stein	No
 Dr Olin	No	 Dr Stock	No
 Dr Pollyea	Yes	 Prof Wei	Yes, unless blasts are low

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Agenda

Module 1: Introduction

Module 2: Case Presentations

- Dr S Gupta: A 78-year-old man with AML and a TP53 mutation
- Dr Olin: A 40-year-old woman with relapsed AML
- Dr Sharma: A 33-year-old woman with therapy-related core binding factor (CBF) AML
- Dr Rupard: A 71-year-old man with AML and an IDH2 mutation
- Dr Sharma: A 67-year-old woman with AML and a FLT3-ITD mutation
- Dr R Gupta: A 78-year-old man with AML and an IDH2 mutation

Module 3: ASH 2021 Review

Module 4: Faculty Survey

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Lancet Haematol 2021;8:e922-33

Review

Harnessing the benefits of available targeted therapies in acute myeloid leukaemia

Hagop Kantarjian, Nicholas J Short, Courtney DiNardo, Eytan M Stein, Naval Daver, Alexander E Perl, Eunice S Wang, Andrew Wei, Martin Tallman

Quizartinib Added to Chemotherapy Demonstrates Superior Overall Survival Compared to Chemotherapy Alone for Adult Patients with Newly Diagnosed FLT3-ITD Positive AML

Press Release: November 18, 2021

"Positive topline results [were announced] from the global pivotal QuANTUM-First phase 3 trial evaluating quizartinib, a highly potent and selective FLT3 inhibitor, in patients with newly diagnosed *FLT3*-ITD positive acute myeloid leukemia (AML).

QuANTUM-First met its primary endpoint, demonstrating that patients who received quizartinib in combination with standard induction and consolidation chemotherapy and then continued with single agent quizartinib had a statistically significant and clinically meaningful improvement in overall survival (OS) compared to those who received standard treatment alone. The safety of quizartinib was shown to be manageable and consistent with the known safety profile."

https://www.businesswire.com/news/home/20211118006328/en/Quizartinib-Added-to-Chemotherapy-Demonstrates-Superior-Overall-Survival-Compared-to-Chemotherapy-Alone-in-Adult-Patients-with-Newly-Diagnosed-FLT3-ITD-Positive-AML

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Case Presentation – Dr Gupta: A 78-year-old man with AML and a TP53 mutation

Dr Shaachi Gupta

- WBC borderline: 3.5, low hemoglobin, macrocytosis
- BMB: 60% blasts
- FISH and NGS: Complex cytogenetics, including TP53 mutation
- Decitabine/venetoclax 200 mg/d
- BMB on C1, d22: 10%
- Fluconazole

Questions

- Even though he is not receiving the full dose of venetoclax, should I further dose reduce when starting fluconazole?
- Should I have waited until day 28 to repeat the bone marrow biopsy?
- How do you approach treatment for patients with TP53 mutations, knowing that they may not respond for very long?

Case Presentation – Dr Olin: A 40-year-old woman with relapsed AML

Dr Rebecca Olin

- 2017: Diagnosed with AML and t(6;11) without actionable mutations
- 7 + 3 → Consolidation HiDAC x 4
- Late 2020: Increasing pancytopenia
- BMB: Relapsed AML and t(6;11)
- Molecular genetics: NRAS, PTPN11, KRAS, WT1 mutations

Case Presentation – Dr Olin: A 40-year-old woman with relapsed AML (continued)

Dr Rebecca Olin

- 2017: Diagnosed with AML and t(6;11) without actionable mutations
- 7 + 3 → Consolidation HiDAC x 4
- Late 2020: Increasing pancytopenia
- BMB: Relapsed AML and t(6;11)
- Molecular genetics: NRAS, PTPN11, KRAS, WT1 mutations
- ***FLAG-IDA + venetoclax, with CR → Allogeneic SCT***

Questions

- ***What are your thoughts about the FLAG-IDA/venetoclax regimen?***
- ***Are you using this regimen more often or waiting for more data to emerge?***

Case Presentation – Dr Sharma: A 33-year-old woman with therapy-related core binding factor (CBF) AML

Dr Prashant Sharma

- PMH: Right breast IDC, s/p lumpectomy, SLNB, adjuvant TC → ACT, RT, tamoxifen in 2019
- 4/2020: Presented with a "boil" on left axilla
- CBC: WBC 17,000, ANC 900, Hgb 6.5, Plts 55,000
- BMB: CBF t-AML, with 28% blasts, INV16, NRAS-positive, JAK2 mutation
- Thrombocytopenia, transfusion dependent
- 7 + 3 due to refractory thrombocytopenia, with morphological CR → Consolidation HiDAC
  - Gemtuzumab ozogamicin (GO) not added due to thrombocytopenia
- Due to complications, she was not transplant eligible → Continue HiDAC consolidation x 2 → CC-486

Questions

- What is the best approach to treatment in a younger patient with CBF AML, particularly therapy-related AML?

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Case Presentation – Dr Rupard: A 71-year-old man with AML and an IDH2 mutation

Dr Erik Rupard

- Presents with fatigue, weakness and WBC 40,000
- BMB: 90% cellular, with 30% blasts
- Cytogenetics and FISH: WNL
- NGS: IDH2 mutation, RUNX1, SRSF2 and ASXL1 mutations
- Liposomal daunorubicin/cytarabine, with CR in 2 months, but relapses 8 months later
- Enasidenib, with a durable partial response

Questions

- What has been your experience with liposomal daunorubicin/cytarabine?
- Is this typical for AML to relapse in 8 months?
- What is the role of targeted agents, such as enasidenib, in treating these patients?

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Case Presentation – Dr Sharma: A 67-year-old woman with AML and a FLT3-ITD mutation

Dr Prashant Sharma

- Presents with fatigue, pancytopenia
- AML, FLT3-ITD mutation
- 7 + 3 + midostaurin → Consolidation HiDAC + midostaurin c/b severe cytopenias, sepsis, FTT, CMV viremia
- Patient declines further chemotherapy and transplant
- EOT BMB: NED, with negative flow
- Gilteritinib 120 mg/d → Cytopenias → Dose reduced to 80 mg/d x 7 months
- BMB: Relapse
- Azacitidine/venetoclax, with CR

Question

- Would you have treated the patient differently?
- What is your opinion on gilteritinib in combination with induction chemotherapy for patients with FLT3-positive ITD mutation? How would you manage these patients post-transplant? Would you use gilteritinib?

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Case Presentation – Dr Gupta: A 78-year-old man with AML and an IDH2 mutation

Dr Ranju Gupta

- PMH: Rectal cancer
- Newly diagnosed with AML (ECOG PS 1)
- Azacitidine/venetoclax
- Molecular testing: IDH2 mutation

Questions

- Would you continue azacitidine/venetoclax and only consider IDH2 inhibitors at relapse?
- Are there guidelines for IDH inhibitor-related differentiation syndrome? What happens if the patient continues to have differentiation syndrome despite maximal supportive care?

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ASH 2021 Review

- Venugopal S et al. **NPM1 Mutations Do Not Retain a Favorable Prognostic Impact in Adults with Advanced Relapsed or Refractory (R/R) Acute Myeloid Leukemia (AML).** ASH 2021;Abstract 2287. 
- Schaefer-Eckart K et al. **Immediate Allogeneic Hematopietic Stem Cell Transplantation for Patients with NPM1-Mutated AML in Molecular Relapse.** ASH 2021;Abstract 2288.
- Vachhani P et al. **Real World Treatment Patterns and Outcomes of Venetoclax (Ven) and Hypomethylating Agents (HMA) in Patients with Newly Diagnosed Acute Myeloid Leukemia (AML) in the United States.** ASH 2021;Abstract 2290.

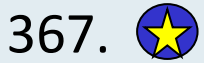
ASH 2021 Review

- Lachowiez C et al. **Venetoclax Combined with FLAG-IDA Induction and Consolidation in Newly Diagnosed Acute Myeloid Leukemia.** ASH 2021;Abstract 701.
- Maiti A et al. **Phase II Trial of Ten-Day Decitabine with Venetoclax (DEC10-VEN) in Acute Myeloid Leukemia: Updated Outcomes in Genomic Subgroups.** ASH 2021;Abstract 694.
- 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) AML.** ASH 2021;Abstract 371.
- Bazinet A et al. **A Phase II Study of 5-Azacytidine (AZA) and Venetoclax as Maintenance Therapy in Patients with Acute Myeloid Leukemia (AML) in Remission.** ASH 2021;Abstract 2326.

ASH 2021 Review

- Kim K et al. **A Phase II Study of CPX-351 plus Venetoclax in Patients with Relapsed/Refractory (R/R) or Newly Diagnosed Acute Myeloid Leukemia (AML).** ASH 2021;Abstract 1275. 
- 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.
- 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.

ASH 2021 Review

- Reville PK et al. **Phase II Study of Venetoclax Added to Cladribine (CLAD) and Low Dose AraC (LDAC) Alternating with 5-Azacytidine (AZA) in Older and Unfit Patients with Newly Diagnosed Acute Myeloid Leukemia (AML).** ASH 2021;Abstract 367. 
- 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.
- 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.

ASH 2021 Review

- 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.
- 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.

ASH 2021 Review

- 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. **Venetoclax in Combination with Gilteritinib Demonstrates Molecular Clearance of *FLT3* Mutation in Relapsed/Refractory *FLT3*-Mutated Acute Myeloid Leukemia.** ASH 2021;Abstract 691.
- 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.

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ASH 2021 Review

- Rivera D et al. **Liposomal Cytarabine and Daunorubicin (CPX-351) in Combination with Gemtuzumab Ozogamicin (GO) in Relapsed Refractory (R/R) Acute Myeloid Leukemia (AML) and Post-Hypomethylating Agent (Post-HMA) Failure High-Risk Myelodysplastic Syndrome (HR-MDS).** ASH 2021;Abstract 2323. 

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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)?

 Dr Daver	TP53 mut, adverse cytogenetics, PS ≥3, severe cardiac, renal or other comorbidity	 Dr Pratz	Age >65, complex karyotype, TP53, IDH2 mutations, INV3 or t(3;3)
 Dr Fathi	Possibly if TP53 mutation present	 Dr Stein	Adverse-risk AML, anticipated response to induction tx < 30%
 Dr Olin	If patient prefers nonintensive therapy	 Dr Stock	Adverse cytogenetics/ molecular genetics, TP53 mutation
 Dr Pollyea	Age >65, ELN adverse risk, secondary or tAML, IDH mutations	 Prof Wei	Age ≥70 if not CBF, FLT3-ITD, TP53 mut, prior MPN

HMA = hypomethylating agent; tAML = treatment-related AML

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?

 Dr Daver	Yes, azacitidine + venetoclax or CC-486	 Dr Pratz	Yes, CC-486
 Dr Fathi	Yes, CC-486	 Dr Stein	Yes, CC-486
 Dr Olin	Yes, CC-486	 Dr Stock	Yes, CC-486
 Dr Pollyea	Yes, CC-486	 Prof Wei	Yes, CC-486

RTP RESEARCH TO PRACTICE

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

 Dr Daver	I have	 Dr Pratz	I haven't but would for the right patient
 Dr Fathi	I haven't and would not	 Dr Stein	I haven't and would not
 Dr Olin	I haven't and would not	 Dr Stock	I haven't but might for the right patient
 Dr Pollyea	I haven't and would not	 Prof Wei	I haven't and would not

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 presents with AML and a FLT3-ITD mutation?

 Dr Daver	CLIA + gilteritinib FLAG-IDA + gilteritinib	 Dr Pratz	7 + 3 + midostaurin
 Dr Fathi	7 + 3 + midostaurin	 Dr Stein	7 + 3 + midostaurin
 Dr Olin	7 + 3 + midostaurin	 Dr Stock	7 + 3 + midostaurin
 Dr Pollyea	7 + 3 + midostaurin	 Prof Wei	7 + 3 + midostaurin

CLIA = trial regimen, cladribine, high-dose cytarabine and idarubicin

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?

 Dr Daver	Azacitadine + venetoclax + gilteritinib	 Dr Pratz	Azacitidine + venetoclax
 Dr Fathi	HMA + venetoclax + gilteritinib	 Dr Stein	Azacitadine + venetoclax
 Dr Olin	HMA + venetoclax	 Dr Stock	Azacitadine + venetoclax (add gilteritinib if no response at day 21)
 Dr Pollyea	Azacitadine + venetoclax	 Prof Wei	Azacitadine + venetoclax + gilteritinib

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 presents with AML and an IDH1 mutation?

 Dr Daver	FLAG-IDA + venetoclax or CLIA + venetoclax	 Dr Pratz	7 + 3 induction + ivosidenib
 Dr Fathi	7 + 3 induction	 Dr Stein	7 + 3 induction
 Dr Olin	7 + 3 induction, would consider adding ivosidenib	 Dr Stock	Azacitidine + venetoclax
 Dr Pollyea	7 + 3 induction	 Prof Wei	7 + 3 induction

RTP RESEARCH TO PRACTICE

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?

 Dr Daver	HMA + venetoclax or azacitidine + venetoclax + ivosidenib	 Dr Pratz	Azacitidine + venetoclax
 Dr Fathi	HMA + venetoclax	 Dr Stein	Azacitidine + venetoclax
 Dr Olin	Ivosidenib or HMA + venetoclax OR Aza + venetoclax + ivosidenib	 Dr Stock	Azacitidine + venetoclax
 Dr Pollyea	Azacitidine + venetoclax	 Prof Wei	Azacitidine + venetoclax

HMA: azacitidine or decitabine

RTP RESEARCH TO PRACTICE

Agenda

Module 1: Introduction

Module 2: Case Presentations

- Dr S Gupta: A 78-year-old man with AML and a TP53 mutation
- Dr Olin: A 40-year-old woman with relapsed AML
- Dr Sharma: A 33-year-old woman with therapy-related core binding factor (CBF) AML
- Dr Rupard: A 71-year-old man with AML and an IDH2 mutation
- Dr Sharma: A 67-year-old woman with AML and a FLT3-ITD mutation
- Dr R Gupta: A 78-year-old man with AML and an IDH2 mutation

Module 3: ASH 2021 Review

Module 4: Faculty Survey

Module 5: Journal Club with Dr Daver

Module 6: Appendix

RTP RESEARCH TO PRACTICE

Journal Club with Dr Daver

- Alwash Y et al. **Development of TP53 mutations over the course of therapy for acute myeloid leukemia.** *Am J Hematol* 2021;96(11):1420-28.
- Kim K et al. **Outcomes of TP53-mutant acute myeloid leukemia with decitabine and venetoclax.** *Cancer* 2021;127(20):3772-81.
- Venugopal S et al. **Outcomes in patients with newly diagnosed TP53-mutated acute myeloid leukemia with or without venetoclax-based therapy**. *Cancer* 2021;127(19):3541-51.

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TO PRACTICE

Journal Club with Dr Daver

Maiti A et al. **Ten-day decitabine with venetoclax versus intensive chemotherapy in relapsed or refractory acute myeloid leukemia: A propensity score-matched analysis.** *Cancer* 2021; 127(22):4213-20.

Sasaki K et al. **Prediction of early (4-week) mortality in acute myeloid leukemia with intensive chemotherapy**. *Am J Hematol* 2021;[Online ahead of print].

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TO PRACTICE

Journal Club with Dr Daver

- Lachowiez CA et al. **A phase Ib/II study of ivosidenib with venetoclax +/- azacitidine in IDH1-mutated myeloid malignancies**. ASCO 2021;Abstract 7012.
- Venugopal S et al. **Phase II study of the IDH2-inhibitor enasidenib in patients with high-risk IDH2-mutated myelodysplastic syndromes (MDS).** ASCO 2021;Abstract 7010.
- Yilmaz M et al. **Quizartinib with decitabine and venetoclax (triplet) is highly active in patients with FLT3-ITD mutated acute myeloid leukemia (AML).** ASCO 2021;Abstract e19019.

Journal Club with Dr Daver

- Abou Dalle I et al. **Phase II study of single-agent nivolumab in patients with myelofibrosis.** *Ann Hematol* 2021;100(12):2957-60.
- Abbas HA et al. **Single-cell polyfunctional proteomics of CD4 cells from patients with AML predicts responses to anti-PD-1-based therapy.** *Blood Adv* 2021;5(22):4569-74.

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TO PRACTICE

Journal Club with Dr Daver

- Tambaro FP et al. **Autologous CD33-CAR-T cells for treatment of relapsed/refractory acute myelogenous leukemia**. *Leukemia* 2021;35(11):3282-6.
- Tanaka T et al. **Clonal dynamics and clinical implications of postremission clonal hematopoiesis in acute myeloid leukemia**. *Blood* 2021;138(18):1733-9.

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TO PRACTICE

Agenda

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Module 3: ASH 2021 Review

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RTP RESEARCH TO PRACTICE

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?

 Dr Daver	HMA + venetoclax	 Dr Pratz	Azacitidine + venetoclax
 Dr Fathi	HMA + venetoclax	 Dr Stein	Azacitidine + venetoclax
 Dr Olin	HMA + venetoclax	 Dr Stock	Azacitidine + venetoclax
 Dr Pollyea	Azacitidine + venetoclax	 Prof Wei	Azacitidine + venetoclax

HMA: azacitidine or decitabine

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

 Dr Daver	Yes	 Dr Pratz	No
 Dr Fathi	Yes	 Dr Stein	No
 Dr Olin	No	 Dr Stock	No
 Dr Pollyea	Yes	 Prof Wei	Yes, unless blasts are low

RTP RESEARCH TO PRACTICE

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 Daver	Between days 21 and 28 of cycle 1	 Dr Pratz	Between days 22 and 28
 Dr Fathi	At end of cycle 1	 Dr Stein	Day 28
 Dr Olin	At end of cycle 1	 Dr Stock	Around day 21
 Dr Pollyea	Cycle 1, day 28	 Prof Wei	Day 21-28 if circulating blasts cleared

RTP RESEARCH TO PRACTICE

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 Daver	Indefinitely	 Dr Pratz	Indefinitely
 Dr Fathi	Indefinitely	 Dr Stein	Indefinitely
 Dr Olin	Indefinitely	 Dr Stock	Indefinitely
 Dr Pollyea	Indefinitely	 Prof Wei	12-18 cycles; consider stopping if CR and no MRD

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?

 Dr Daver	Venetoclax + gilteritinib +/- azacitidine or FLAG-IDA + gilteritinib	 Dr Pratz	Azacitidine + venetoclax + gilteritinib
 Dr Fathi	HMA + gilteritinib	 Dr Stein	Gilteritinib
 Dr Olin	Gilteritinib, or would consider FLAG-IDA + venetoclax	 Dr Stock	Gilteritinib
 Dr Pollyea	Gilteritinib	 Prof Wei	Azacitidine + venetoclax + gilteritinib

RTP RESEARCH TO PRACTICE

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?

 Dr Daver	Venetoclax + gilteritinib +/- azacitidine	 Dr Pratz	Gilteritinib
 Dr Fathi	HMA + gilteritinib	 Dr Stein	Gilteritinib
 Dr Olin	Gilteritinib	 Dr Stock	Gilteritinib
 Dr Pollyea	Gilteritinib	 Prof Wei	Azacitidine + venetoclax + gilteritinib

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 an IDH1 mutation who is eligible for intensive chemotherapy and has experienced disease progression after venetoclax/azacitidine?

 Dr Daver	Azacitidine + venetoclax + ivosidenib or FLAG-IDA + venetoclax	 Dr Pratz	Azacitidine + venetoclax + ivosidenib
 Dr Fathi	Ivosidenib	 Dr Stein	Chemotherapy
 Dr Olin	7 + 3 induction therapy or FLAG-IDA + venetoclax	 Dr Stock	Possibly ivosidenib + venetoclax
 Dr Pollyea	Ivosidenib	 Prof Wei	Ivosidenib + venetoclax

RTP RESEARCH TO PRACTICE

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 Daver	Azacitidine + venetoclax +/- ivosidenib	 Dr Pratz	Ivosidenib
 Dr Fathi	Ivosidenib	 Dr Stein	Ivosidenib
 Dr Olin	Ivosidenib +/- decitabine	 Dr Stock	Ivosidenib
 Dr Pollyea	Ivosidenib	 Prof Wei	Ivosidenib + venetoclax

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 presents with AML and an IDH2 mutation?

 Dr Daver	FLAG-IDA + venetoclax or CLIA + venetoclax	 Dr Pratz	Azacitidine + venetoclax
 Dr Fathi	7 + 3 induction	 Dr Stein	7 + 3 induction
 Dr Olin	7 + 3 induction, would consider adding enasidenib	 Dr Stock	Azacitidine + venetoclax
 Dr Pollyea	7 + 3 induction	 Prof Wei	7 + 3 induction

RTP RESEARCH TO PRACTICE

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?

 Dr Daver	HMA + venetoclax or azacitidine + venetoclax + enasidenib	 Dr Pratz	Azacitidine + venetoclax
 Dr Fathi	HMA + venetoclax	 Dr Stein	Azacitidine + venetoclax
 Dr Olin	HMA + venetoclax	 Dr Stock	Azacitidine + venetoclax
 Dr Pollyea	Azacitidine + venetoclax	 Prof Wei	Azacitidine + venetoclax

HMA: azacitidine or decitabine

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 an IDH2 mutation who is eligible for intensive chemotherapy and has experienced disease progression after venetoclax/azacitidine?

 Dr Daver	Azacitidine + venetoclax + enasidenib or FLAG-IDA + venetoclax	 Dr Pratz	Azacitidine + venetoclax + enasidenib
 Dr Fathi	Enasidenib	 Dr Stein	Chemotherapy
 Dr Olin	7 + 3 + enasidenib or FLAG-IDA + venetoclax	 Dr Stock	Azacitidine + venetoclax + enasidenib
 Dr Pollyea	Enasidenib	 Prof Wei	FLAG-IDA + venetoclax

RTP RESEARCH TO PRACTICE

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 Daver	Azacitidine + enasidenib +/- venetoclax	 Dr Pratz	Enasidenib
 Dr Fathi	Enasidenib	 Dr Stein	Enasidenib
 Dr Olin	Enasidenib +/- decitabine	 Dr Stock	Enasidenib
 Dr Pollyea	Enasidenib	 Prof Wei	Enasidenib + venetoclax

RTP RESEARCH TO PRACTICE

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?

 Dr Daver	CPX-351 or FLAG-IDA + venetoclax	 Dr Pratz	Azacitidine + venetoclax
 Dr Fathi	CPX-351 if anthracycline dose cap not reached	 Dr Stein	CPX-351
 Dr Olin	CPX-351	 Dr Stock	CPX-351
 Dr Pollyea	CPX-351	 Prof Wei	Azacitidine + venetoclax

RTP RESEARCH TO PRACTICE

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?

 Dr Daver	Azacitidine + venetoclax or CC-486 + venetoclax	 Dr Pratz	Azacitidine + venetoclax
 Dr Fathi	HMA + venetoclax	 Dr Stein	Azacitidine + venetoclax
 Dr Olin	HMA + venetoclax	 Dr Stock	Azacitidine + venetoclax
 Dr Pollyea	Azacitidine + venetoclax	 Prof Wei	Azacitidine + venetoclax

HMA: azacitidine or decitabine

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

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RESEARCH
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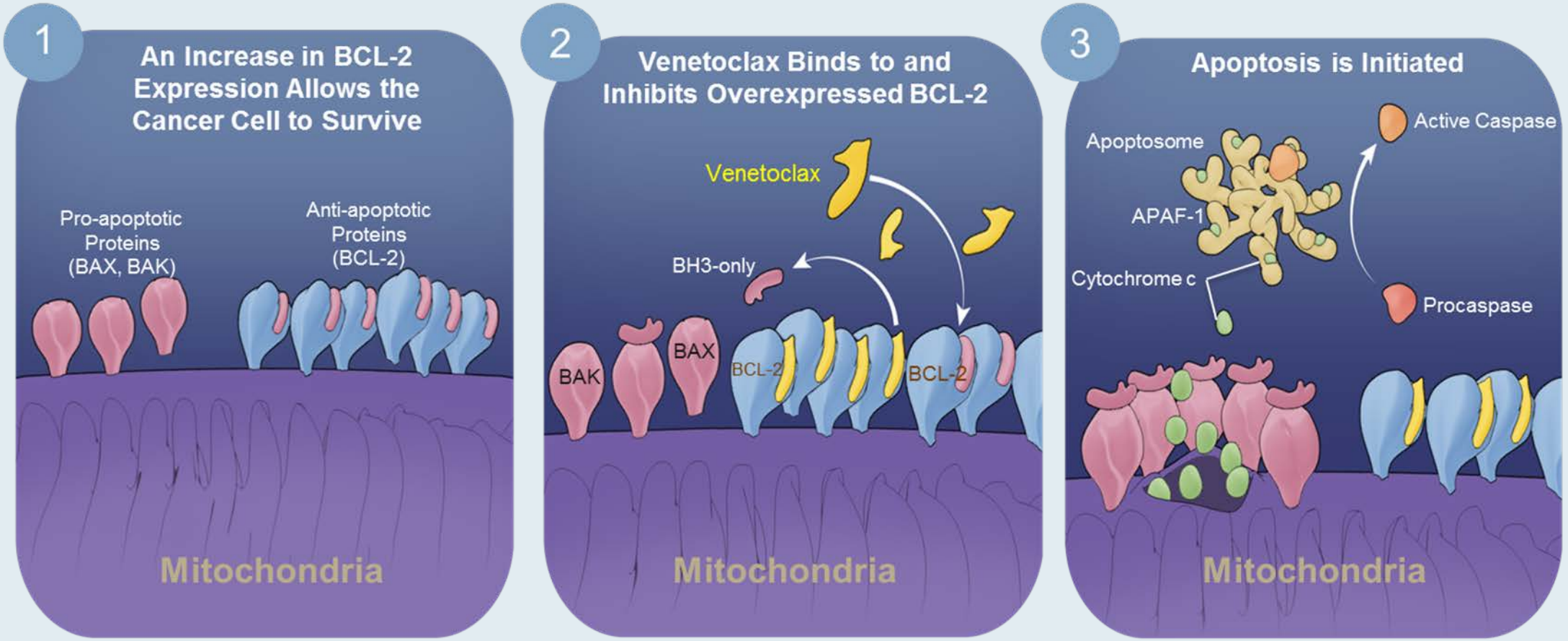
Venetoclax Mechanism of Action



- 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

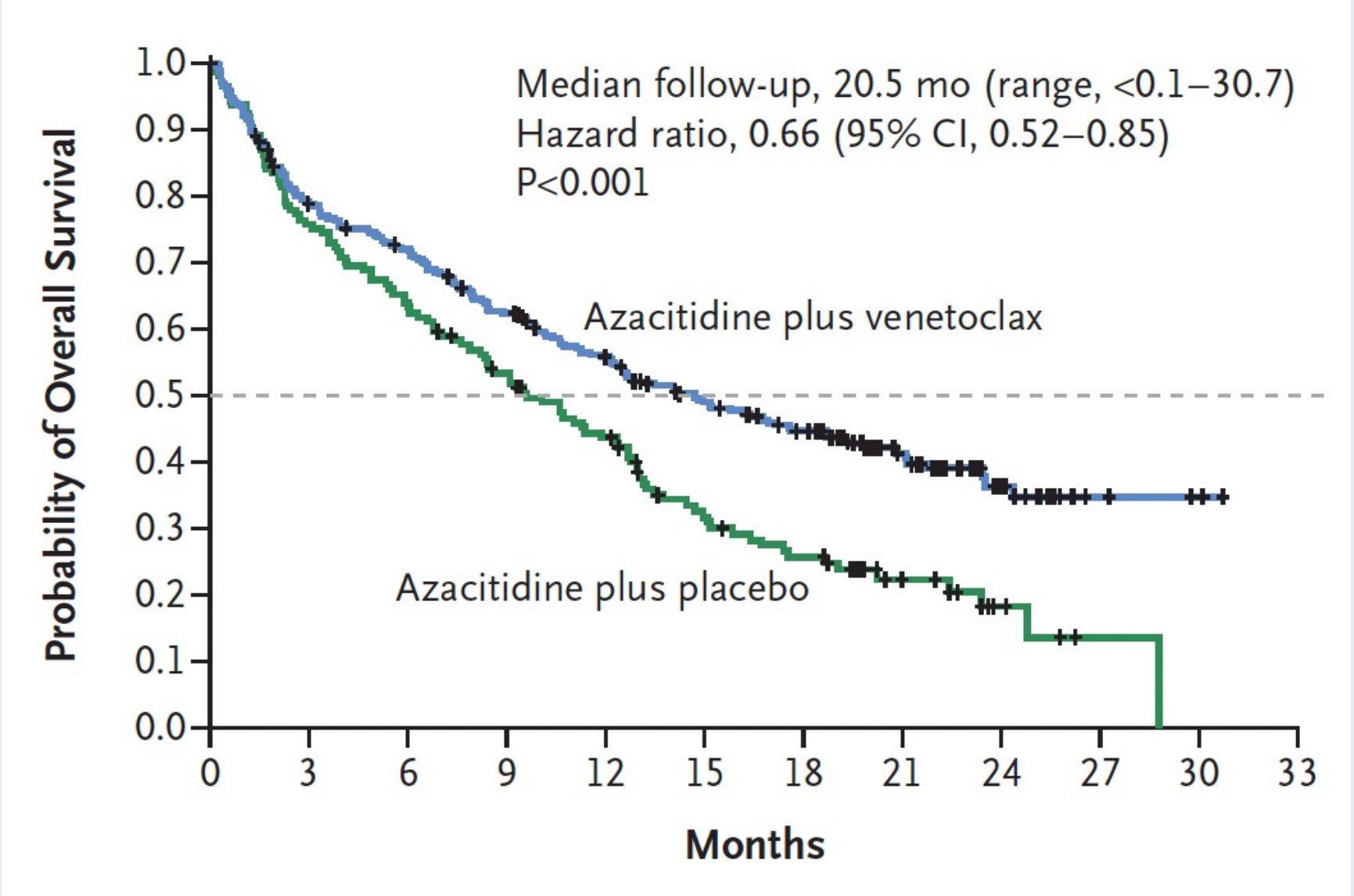
Randomization Stratification Factors	Age (<75 vs. ≥75 years); Cytogenetic Risk (intermediate, Poor); Region
Venetoclax dosing ramp-up	**Cycle 1 ramp-up** Day 1: 100 mg, Day 2: 200 mg, Day 3 - 28: 400 mg **Cycle 2** → Day 1-28: 400 mg

* 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

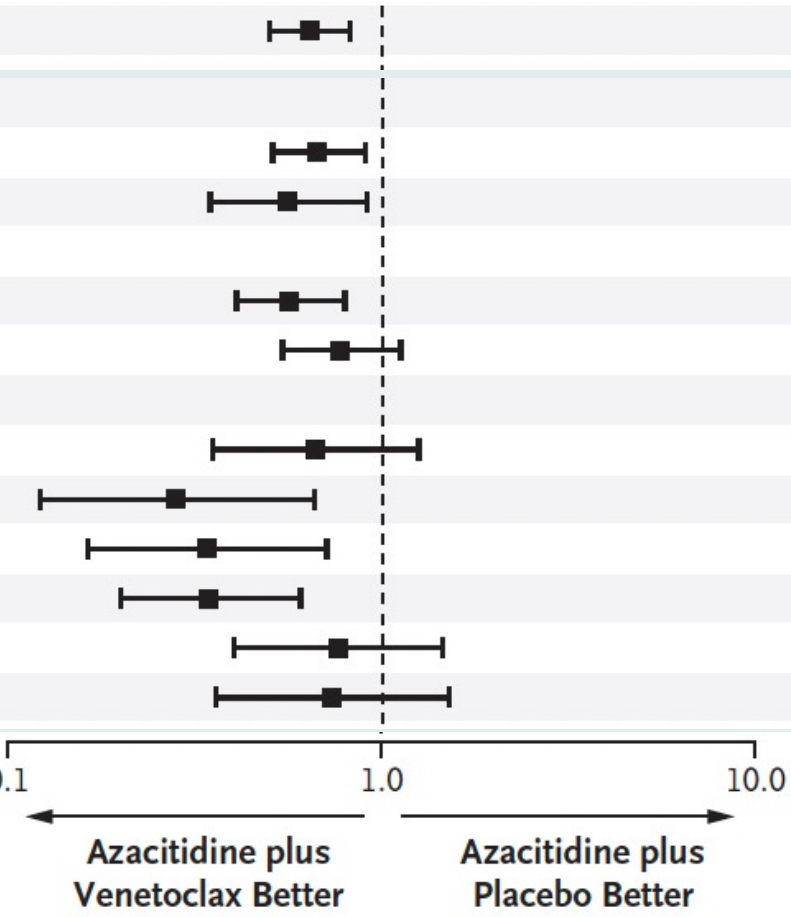


DiNardo CD et al. *N Engl J Med* 2020;383:617-29.

RTP RESEARCH TO PRACTICE

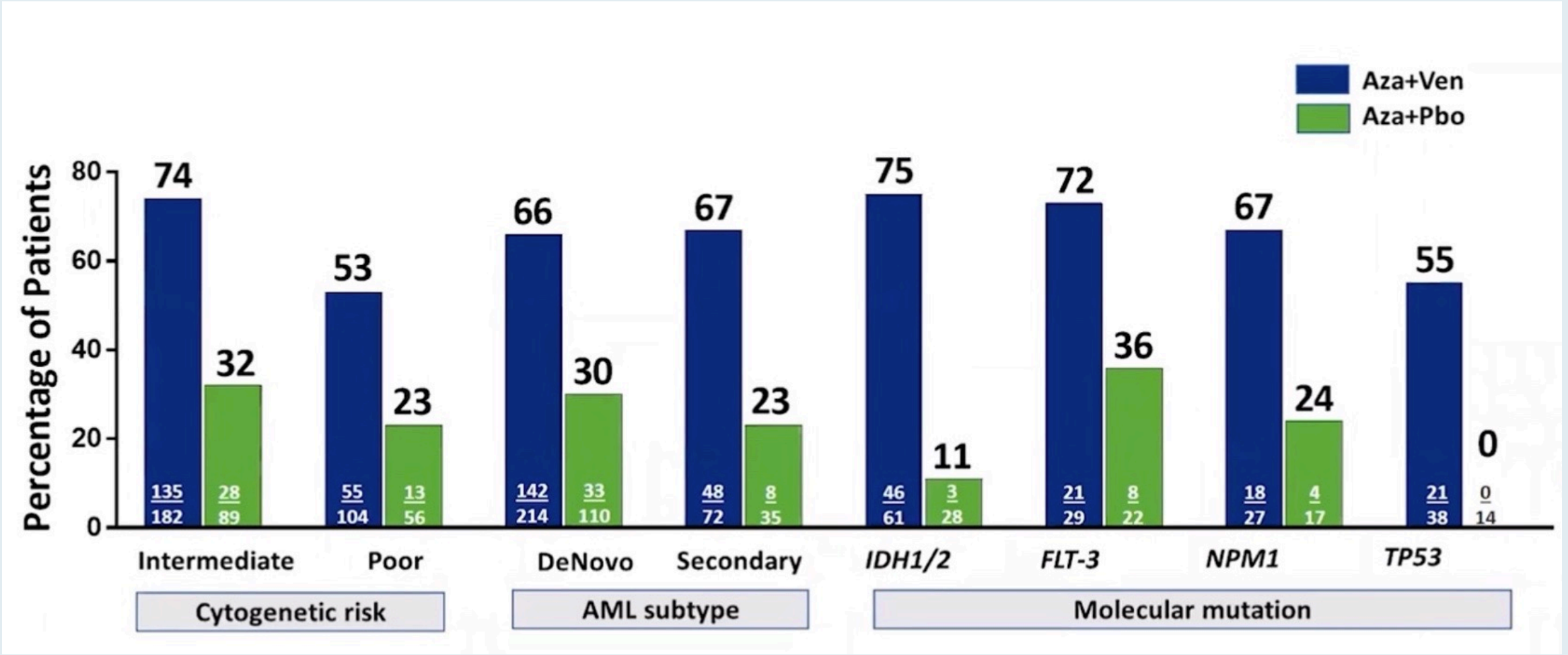
VIALE-A: Overall Survival Subgroup Analysis

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)



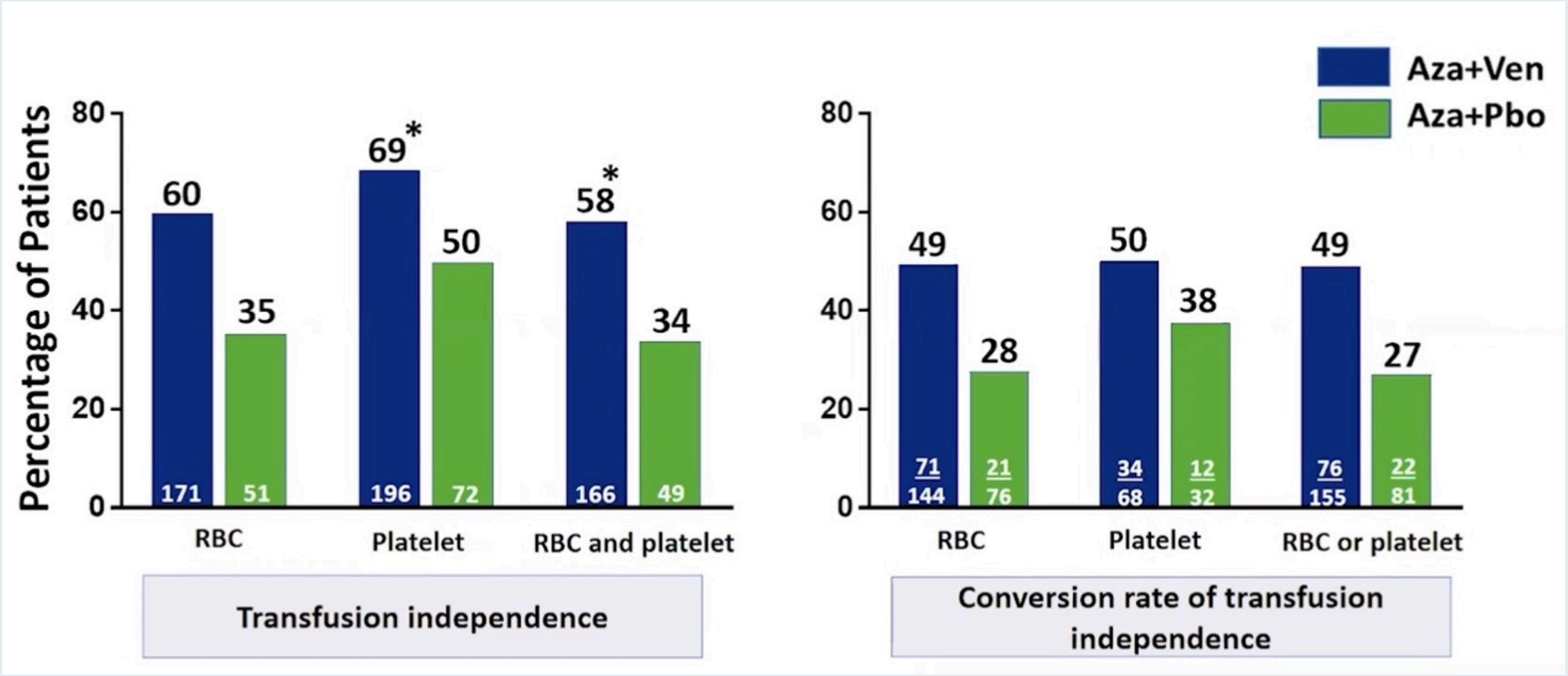
DiNardo CD et al. *N Engl J Med* 2020;383:617-29.

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



DiNardo C et al. EHA 2020;Abstract LB2601.

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



DiNardo C et al. EHA 2020;Abstract LB2601.

RTP RESEARCH TO PRACTICE

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 Phase 3 Study Design

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

2:1 Randomization via IRT
N=211

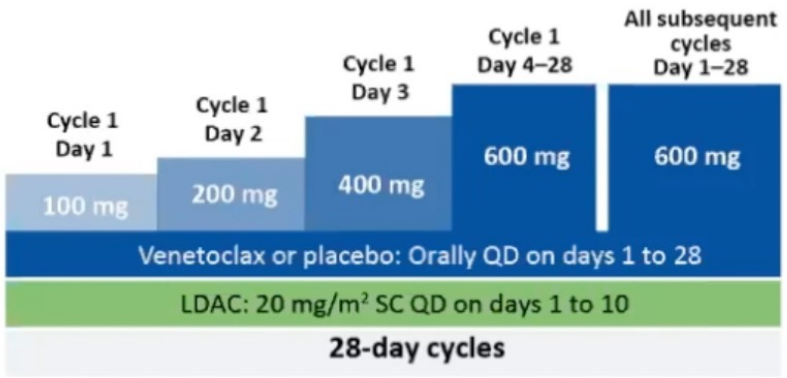
- **Venetoclax + LDAC (n=143)**
- **Placebo + LDAC (n=68)**

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

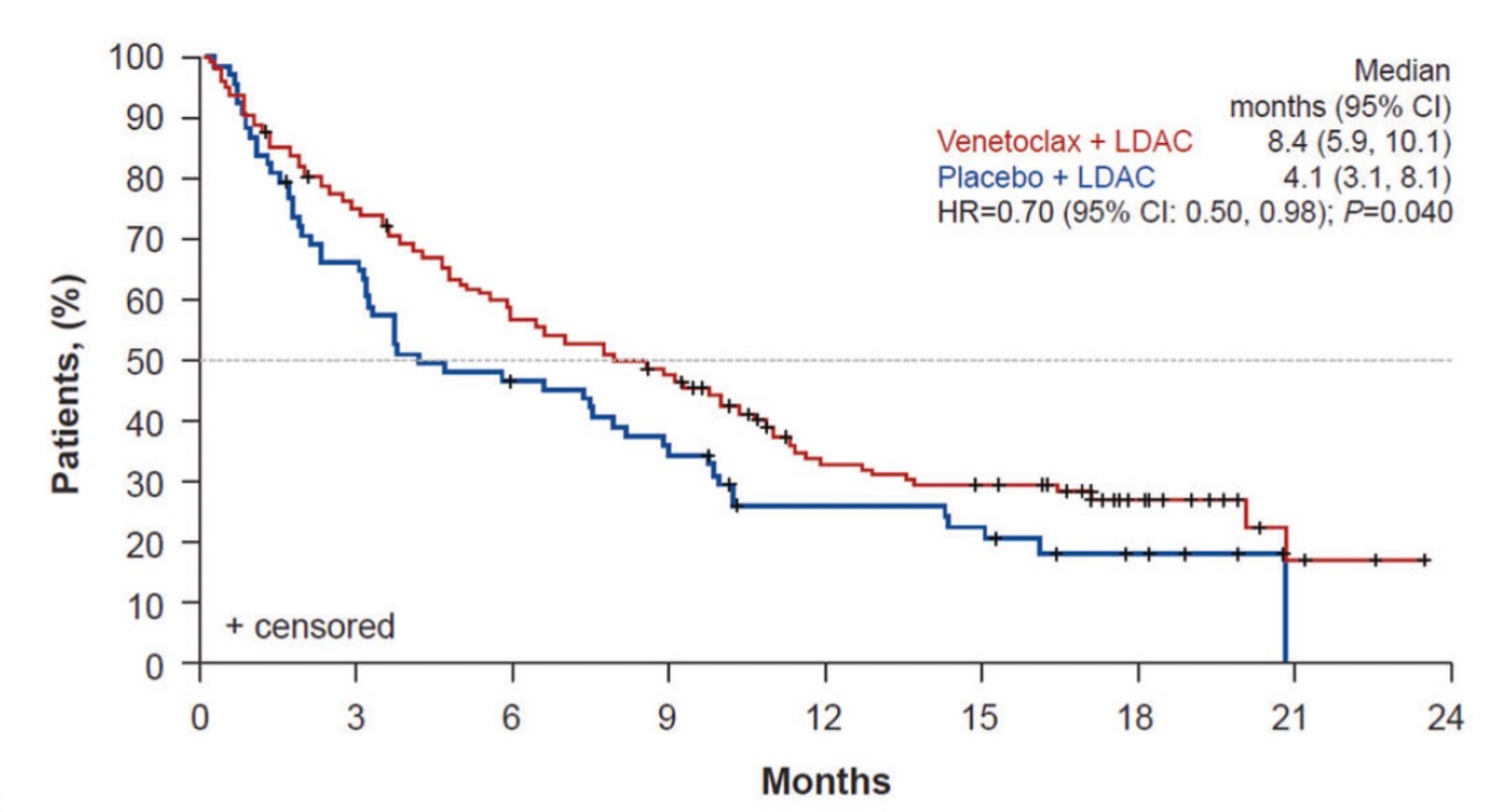
- CR, CRh, and CRi (modified IWG criteria[1])
- Rate of transfusion independence
- EFS
- MRD

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.

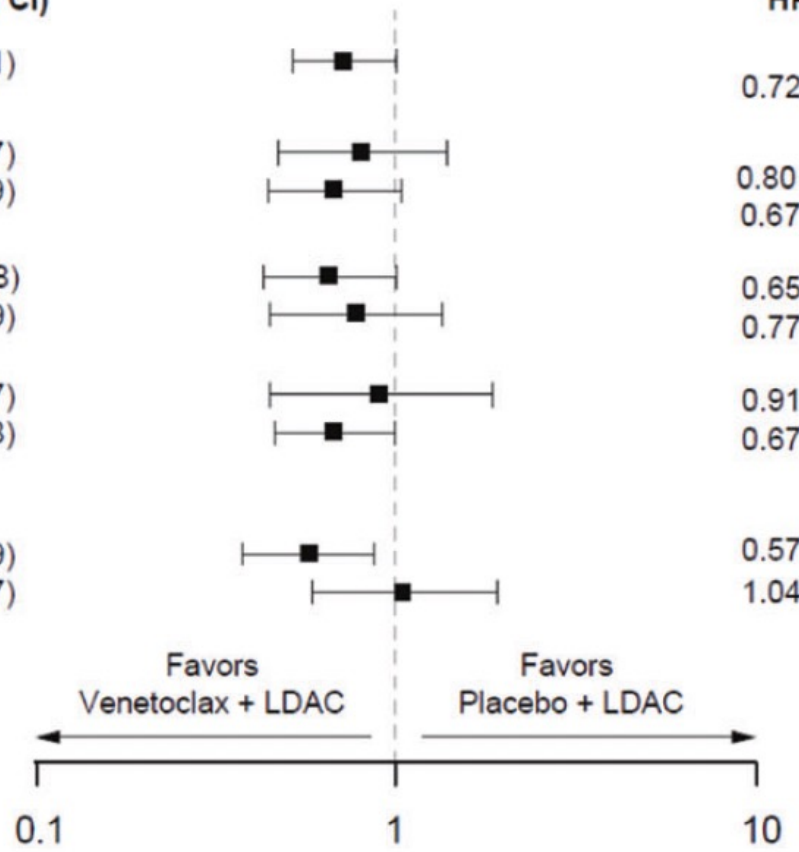
VIALE-C: Overall Survival



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

VIALE-C: Overall Survival Subgroup Analysis

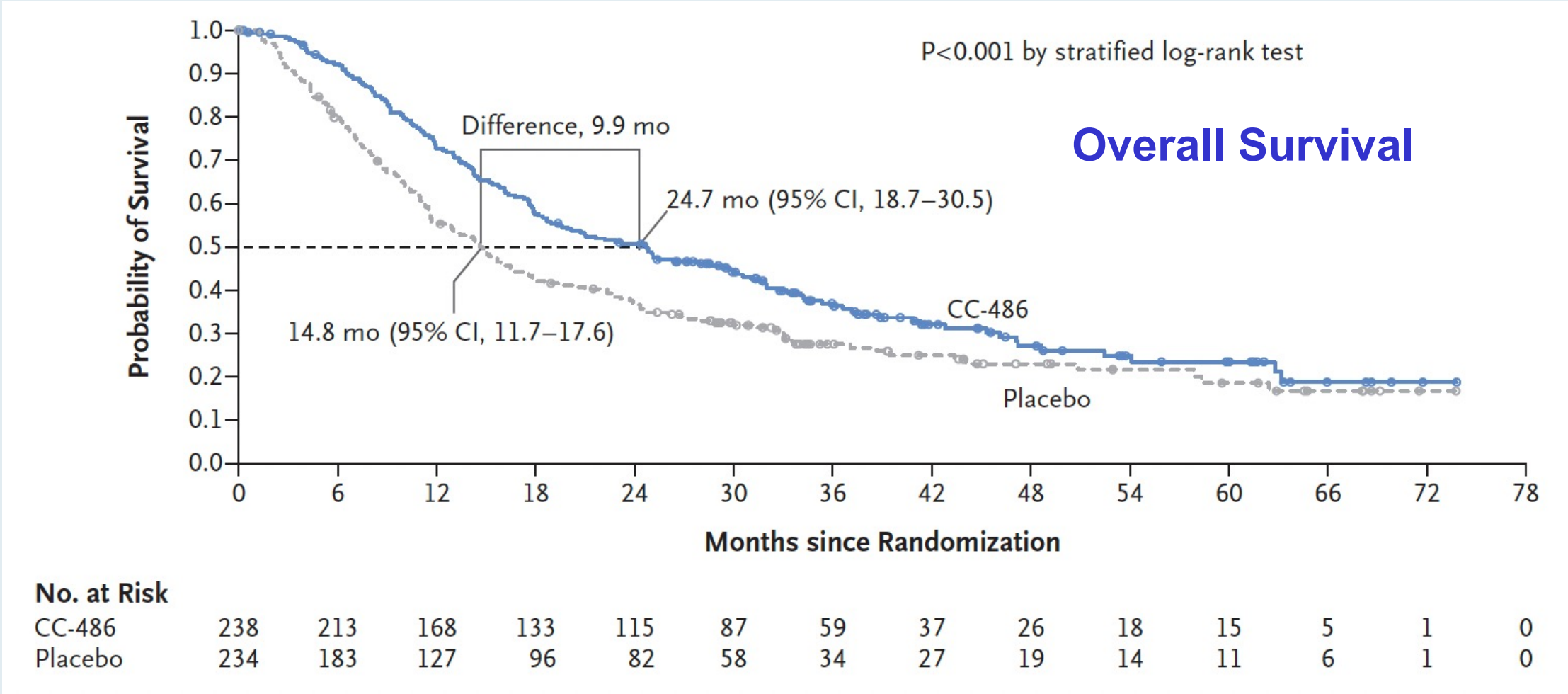
	Venetoclax + LDAC		Placebo + LDAC		
	n/N (%)	Median months (95% CI)	n/N (%)	Median months (95% CI)	HR (95% CI)
All Subjects	99/143 (69.2)	8.4 (5.9, 10.1)	54/68 (79.4)	4.1 (3.1, 8.1)	0.72 (0.51, 1.00)
Age (years)					
18 - < 75	41/61 (67.2)	9.8 (5.6, 11.2)	20/28 (71.4)	6.5 (2.0, 9.7)	0.80 (0.47, 1.37)
≥ 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: Oral Azacitidine Maintenance Therapy for AML in First Remission

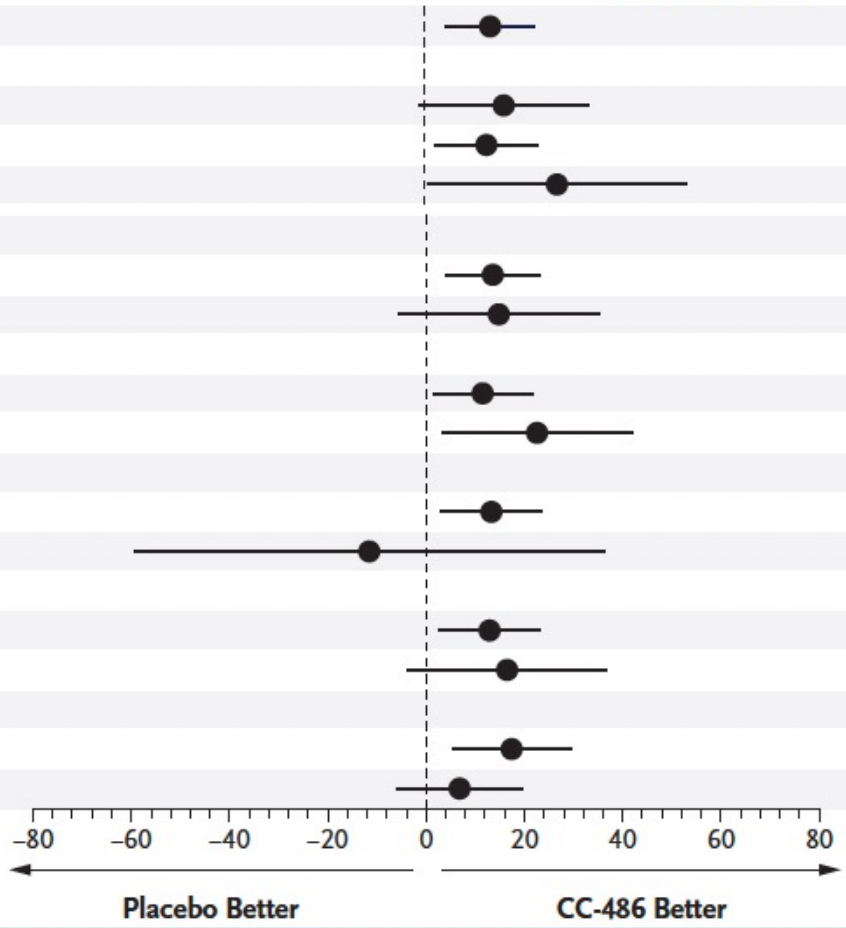


No. at Risk													
CC-486	238	213	168	133	115	87	59	37	26	18	15	5	1	0
Placebo	234	183	127	96	82	58	34	27	19	14	11	6	1	0

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

QUAZAR AML-001: 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.

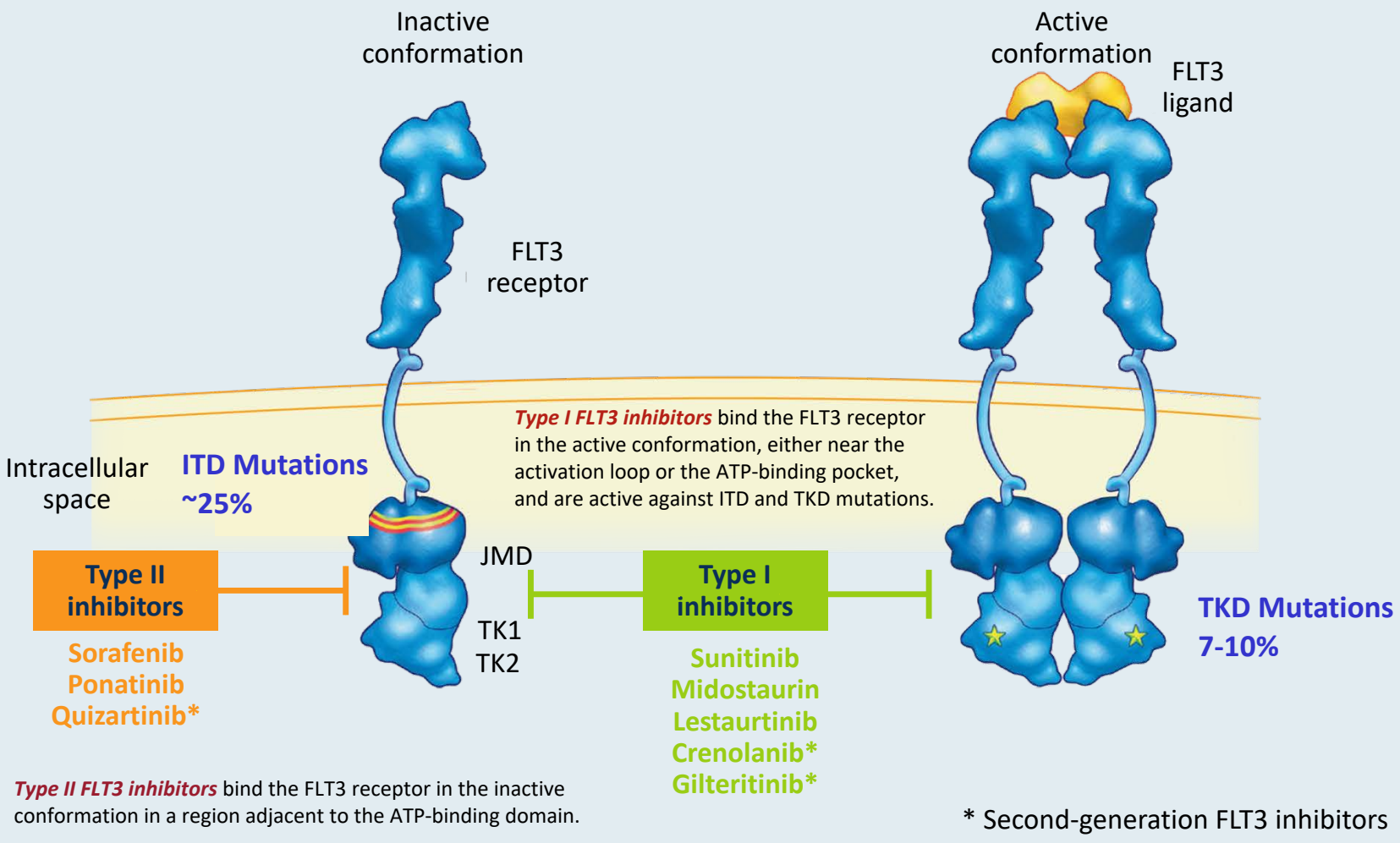
QUAZAR AML-001: Safety Summary and Select Adverse Events (AEs)

	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.

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

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 400 mg BID	II	58	c-KIT PDGFR RAF VEGFR	No	Rash Hemorrhage Myelosuppression
Midostaurin 50 mg BID	I	6.3	c-KIT PDGFR PKC VEGFR	Yes	GI toxicity Myelosuppression
Quizartinib 30 – 60 mg QD	II	1.6	c-KIT	No	QTc prolongation Myelosuppression
Gilteritinib 120 mg QD	I	0.29	AXL LTK ALK	Yes	Elevated transaminases 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

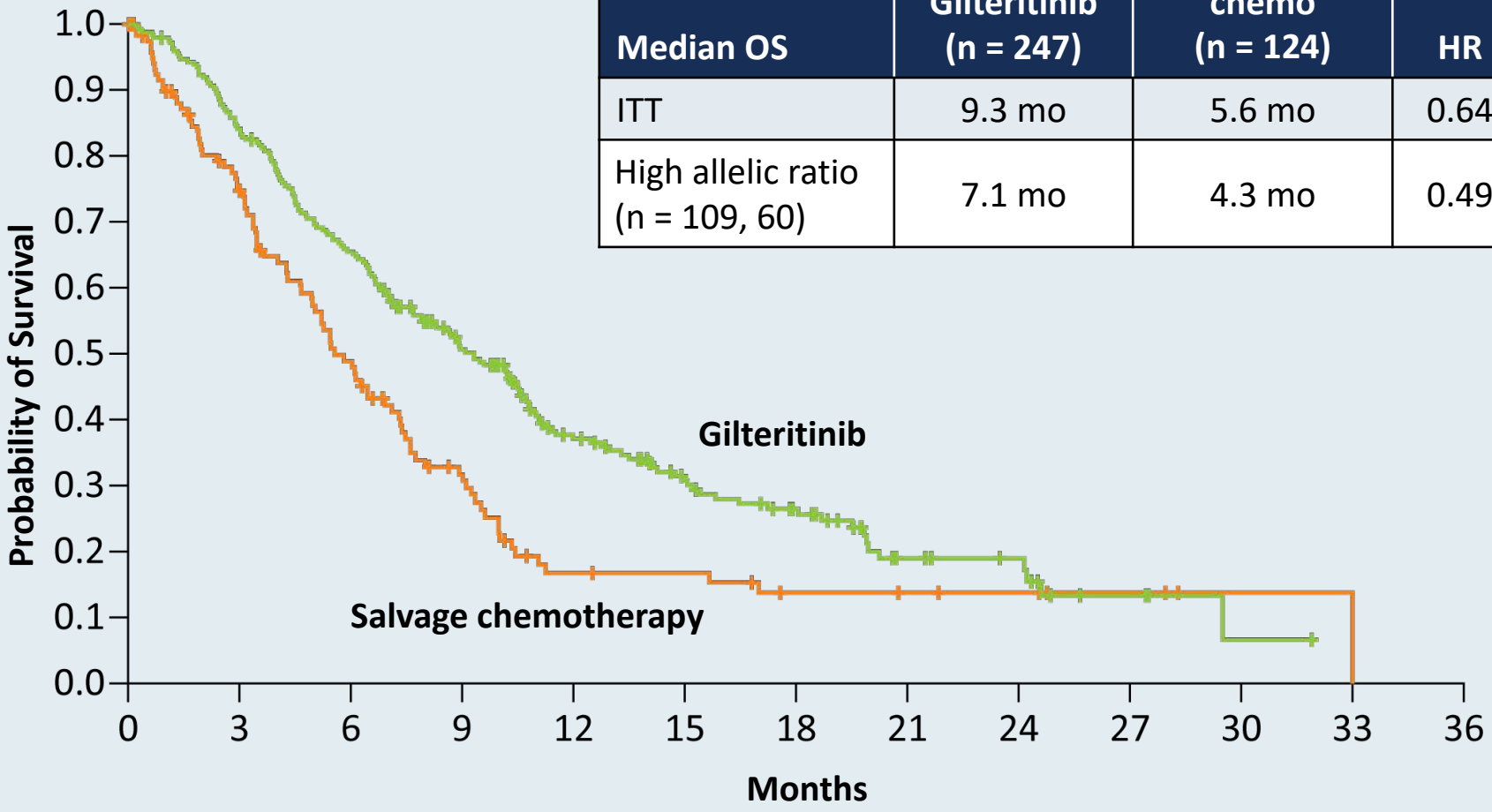
Study	Agents	FLT3 inhibitor generation	Inhibits	N	Population	OS hazard ratio
SORAML Ph II	Sorafenib Placebo	First	ITD	267	Treatment naïve	0.82, n.s.
RATIFY Ph III	Midostaurin Placebo	First	ITD, TKD	717	Treatment naïve	0.78
QuANTUM-First Ph III	Quizartinib Placebo	Second	ITD	NR	Treatment naïve	NR
QuANTUM-R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

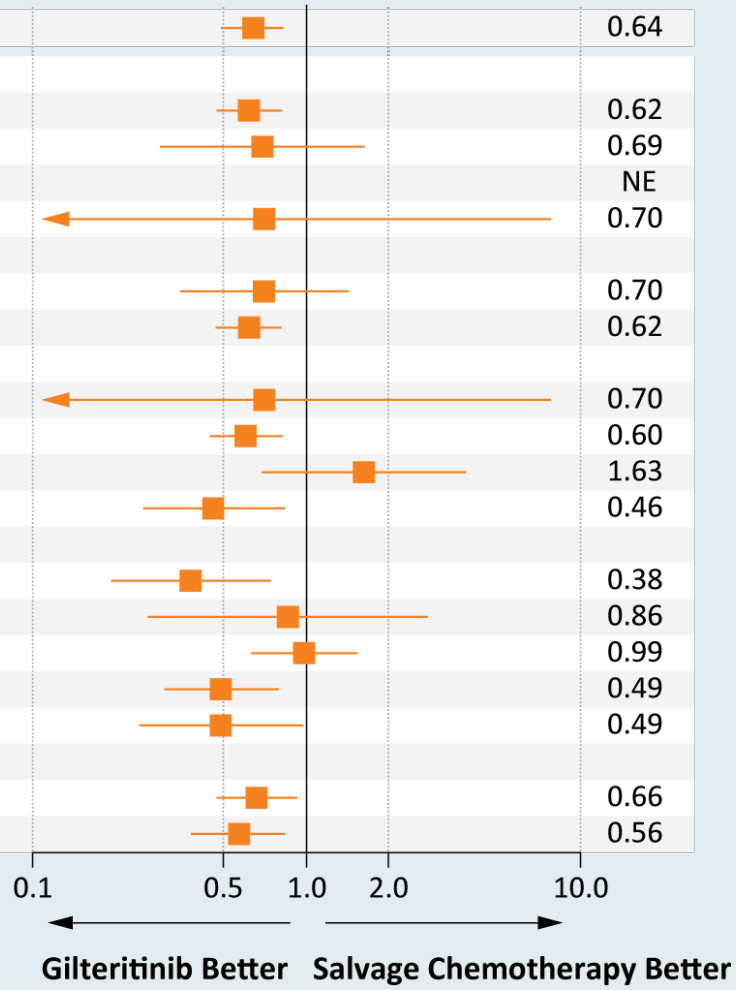


Perl AE et al. *N Engl J Med* 2019;381:1728-40.

RTP RESEARCH TO PRACTICE

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

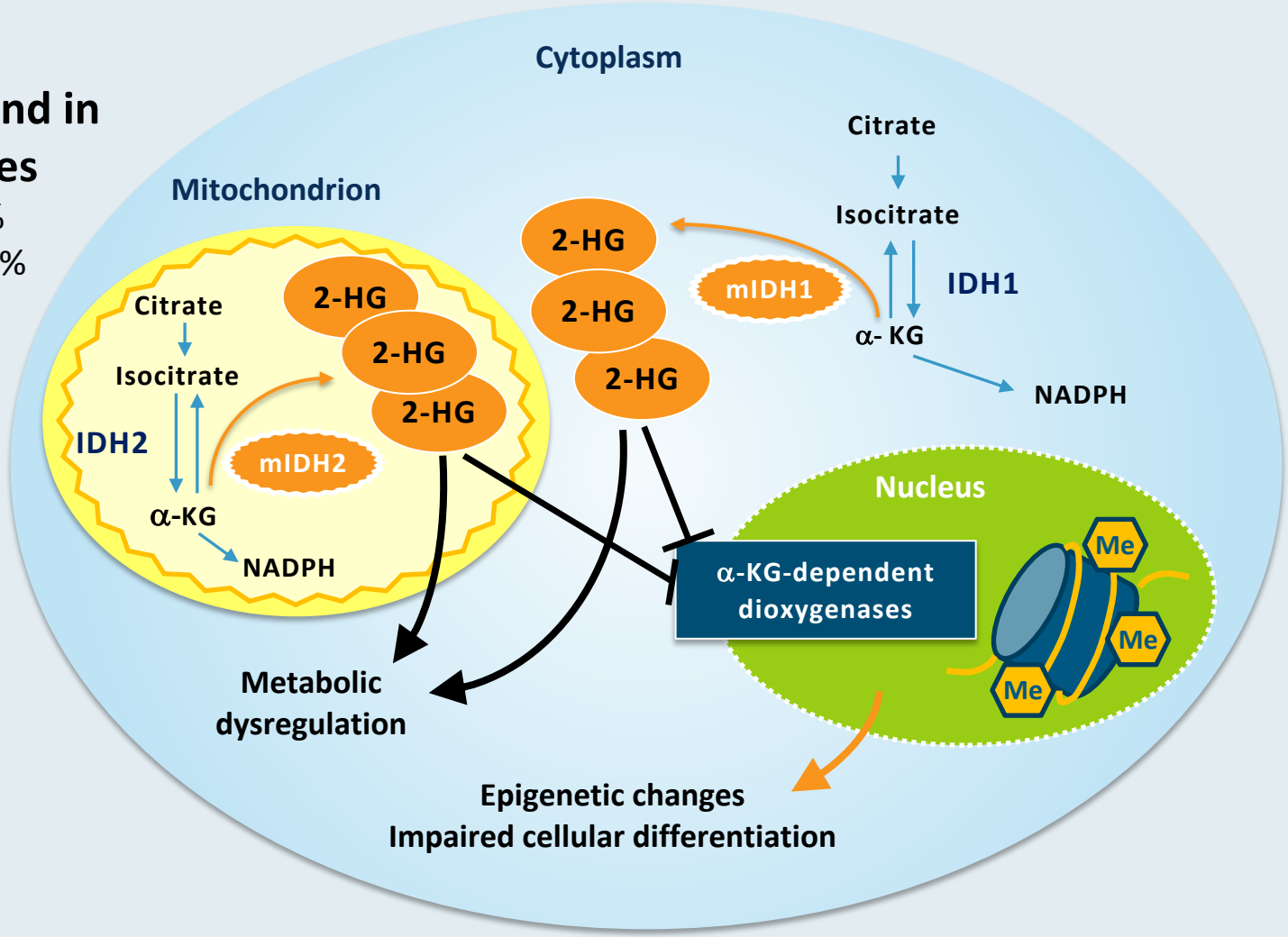
*Composite complete remission was defined as the combination of CR, CR with incomplete hematologic recovery and CR with incomplete platelet recovery

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

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

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

Clinical endpoint	N = 23
CR + CRh, n (%) CR CRh	16 (70%) 14 (61%) 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

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

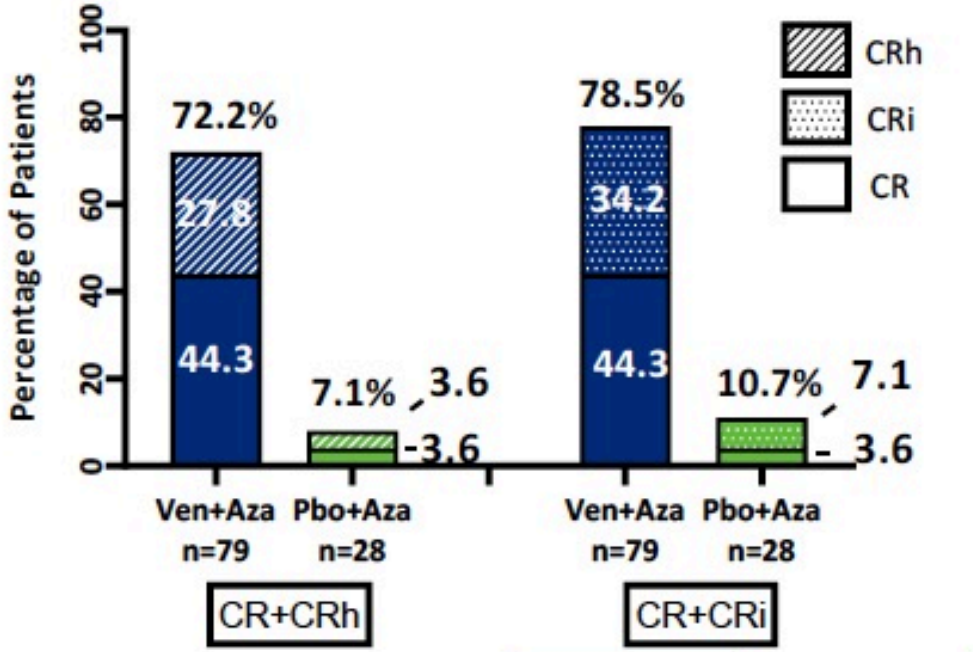
Press Release: August 2, 2021

"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).

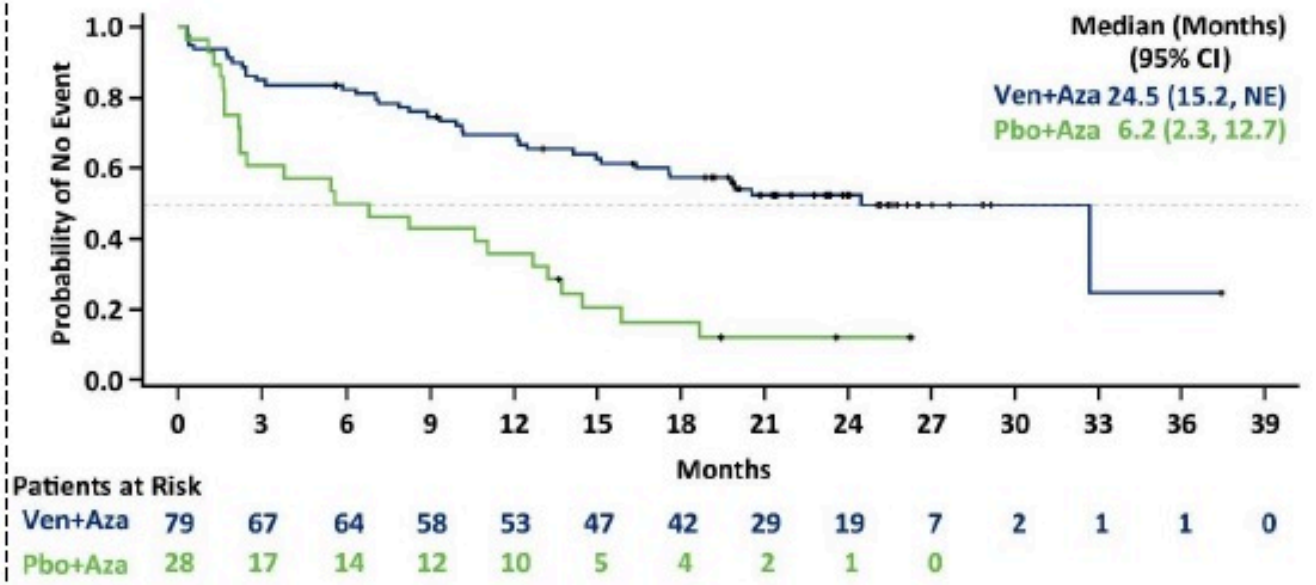
The safety profile of ivosidenib in combination with azacitidine was consistent with previously published data. The study recently halted further enrollment based on the recommendation of the Independent Data Monitoring Committee (IDMC), as a difference of clinical importance was noted between the treatment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

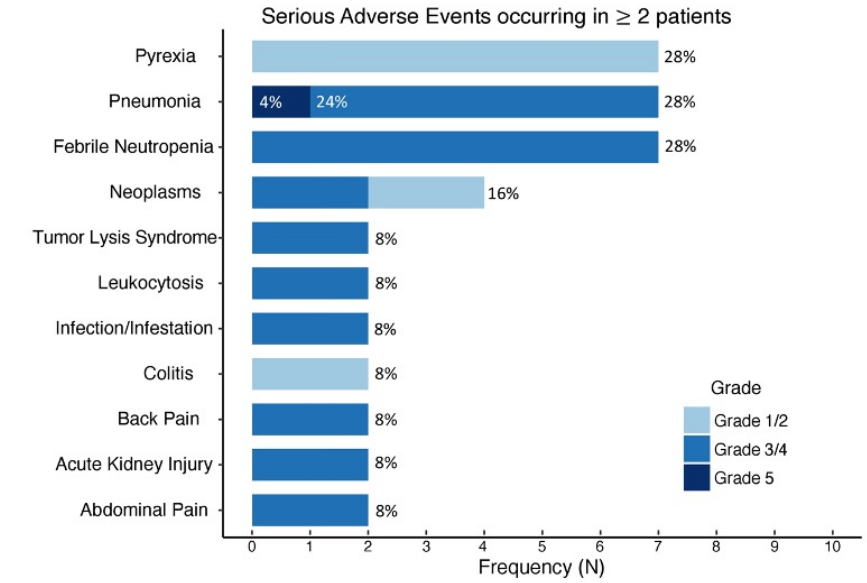
Pratz K et al. ASH 2020;Abstract 1944.

RTP RESEARCH TO PRACTICE

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

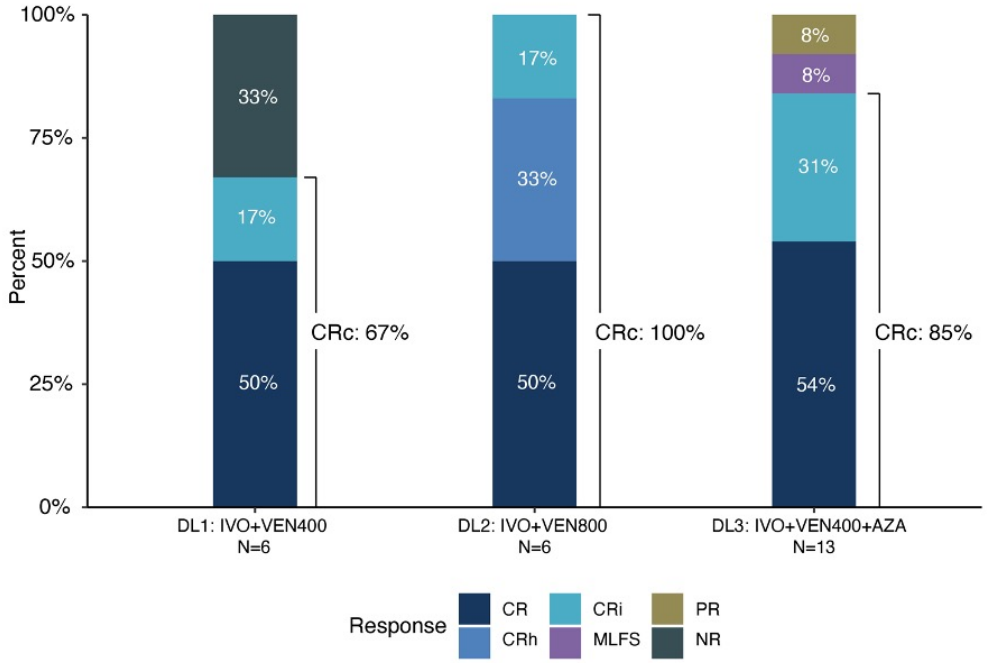
Safety



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

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.

Incidence and Management of Secondary AML (sAML)

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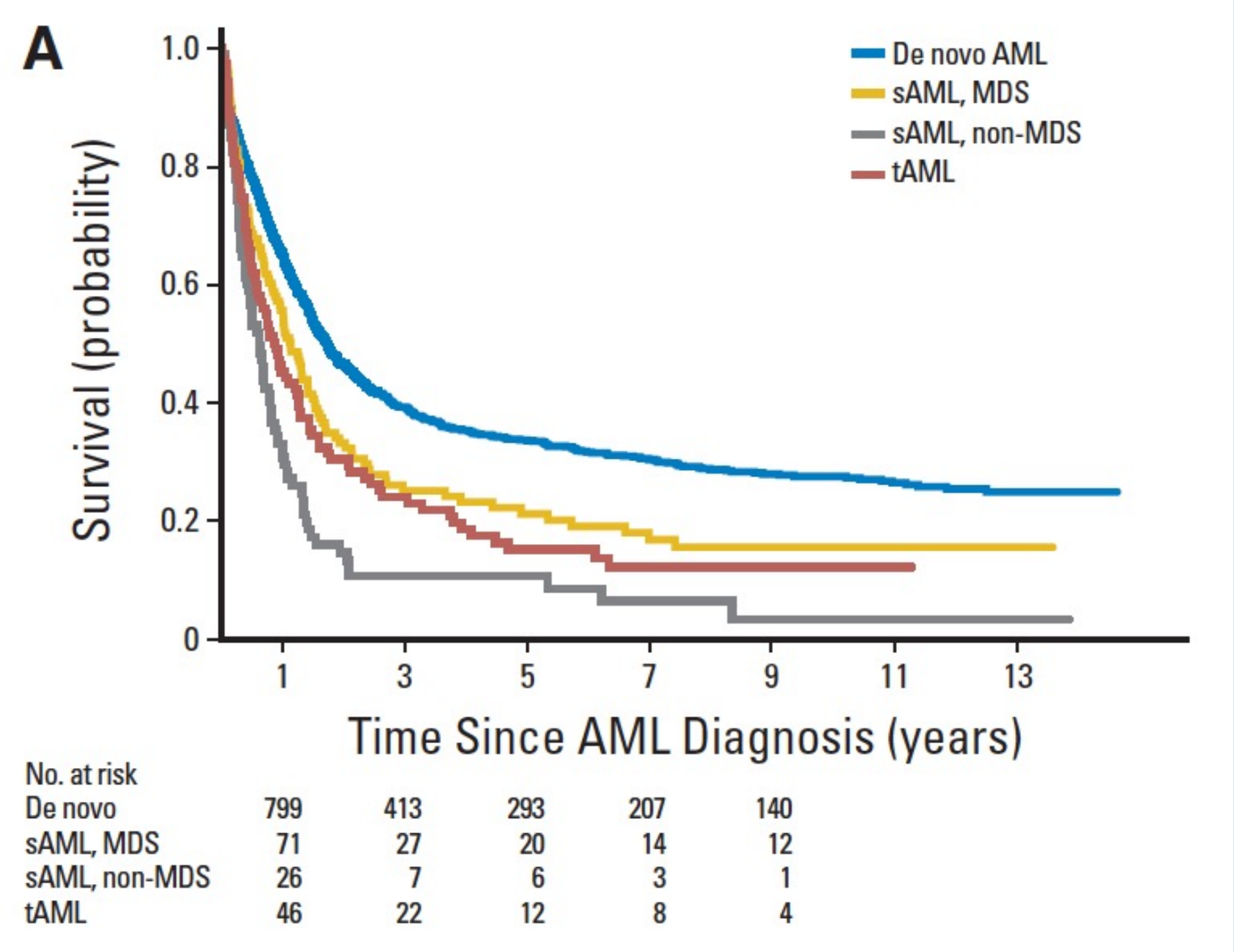
TO PRACTICE

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)*

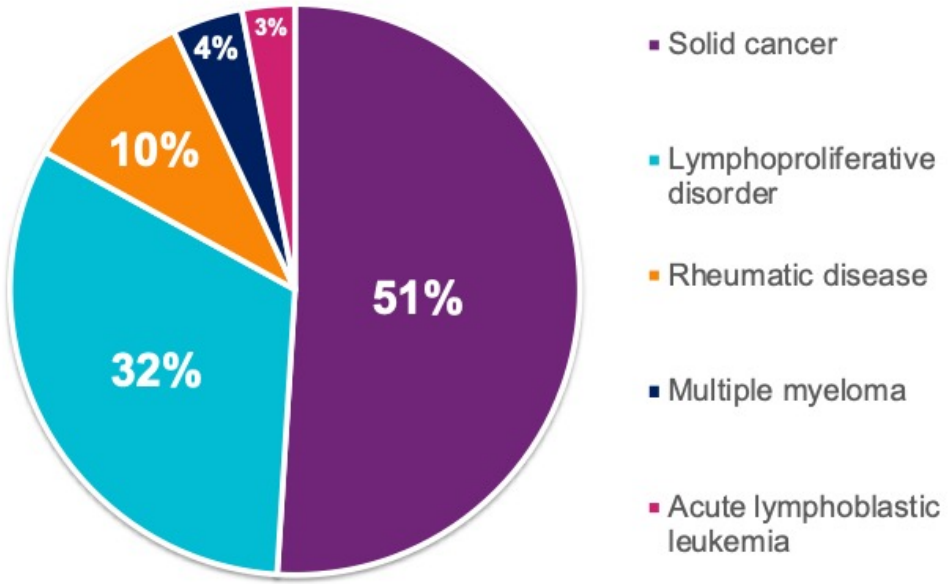
Footnote 1. The presence of 50% or more dysplastic cells in at least 2 cell lines, ***excluding cases when a mutation of NPM1 or biallelic mutation of CEBPA is present.***

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



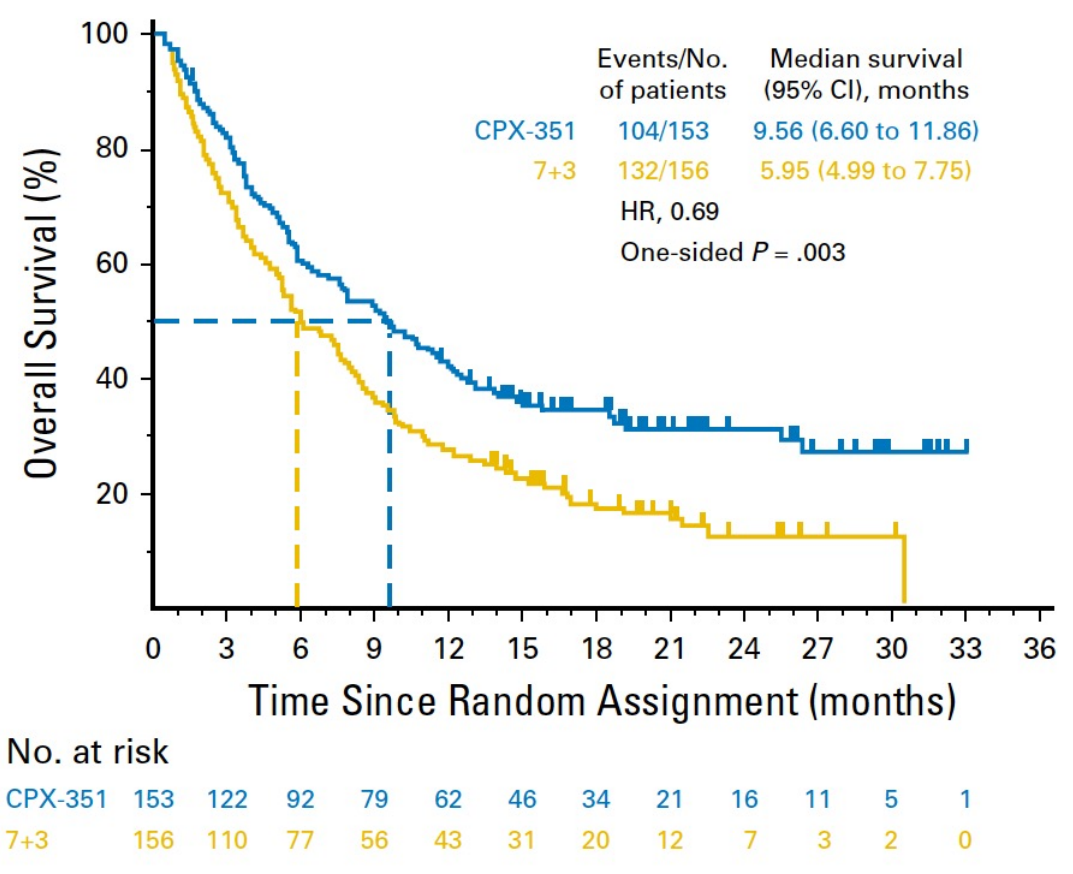
Cytotoxic therapy[a]	MOA	Examples	Latency period
Alkylating agents and radiation	Induce chromosomal deletions, commonly in 5 and/or 7	Cyclophosphamide, mechlorethamine, procarbazine, chlorambucil, melphalan, carmustine, busulfan	5-10 years
Topoisomerase II inhibitors	Induce chromosomal translocations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

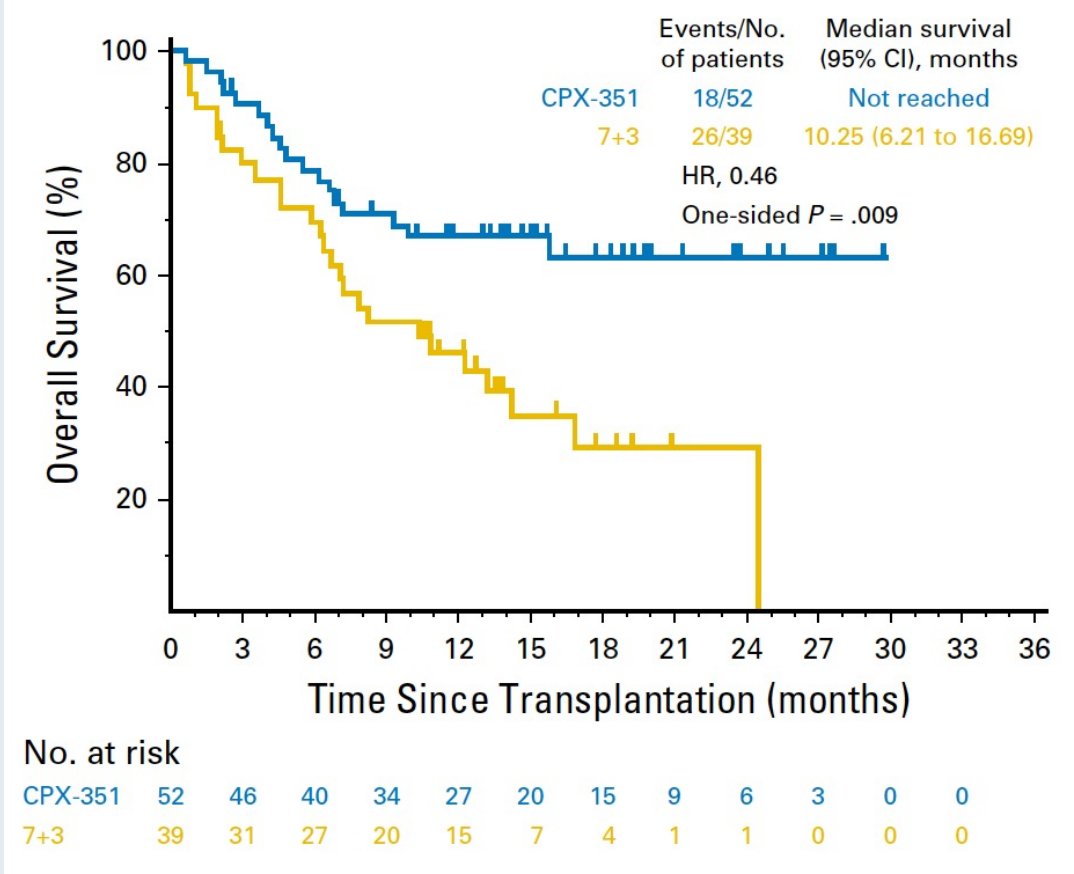
Courtesy of Eunice S Wang, MD.

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



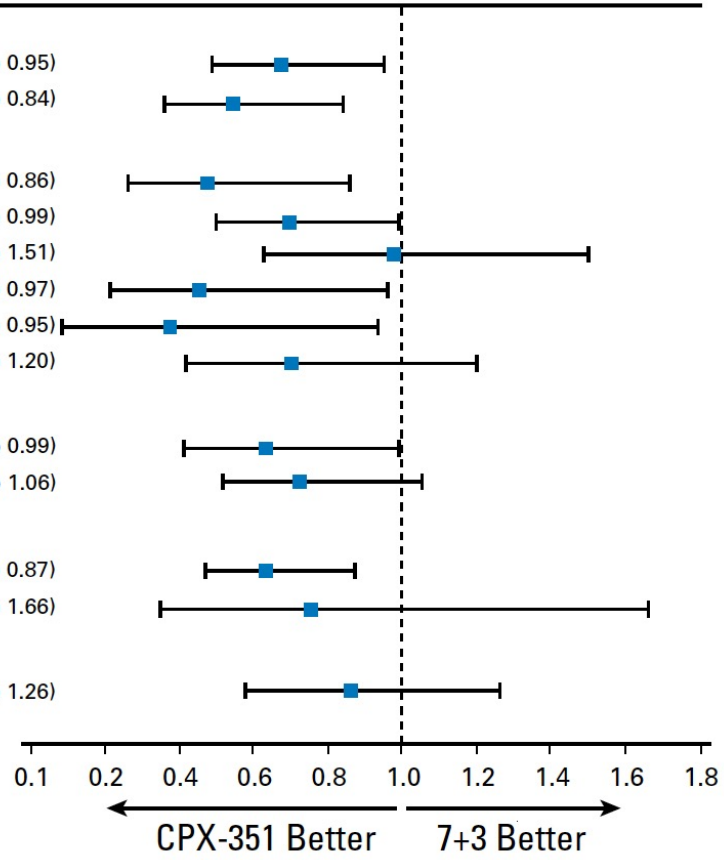
Lancet JE et al. *J Clin Oncol* 2018;36(26):2684-92.

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: Overall Survival by Baseline Characteristics

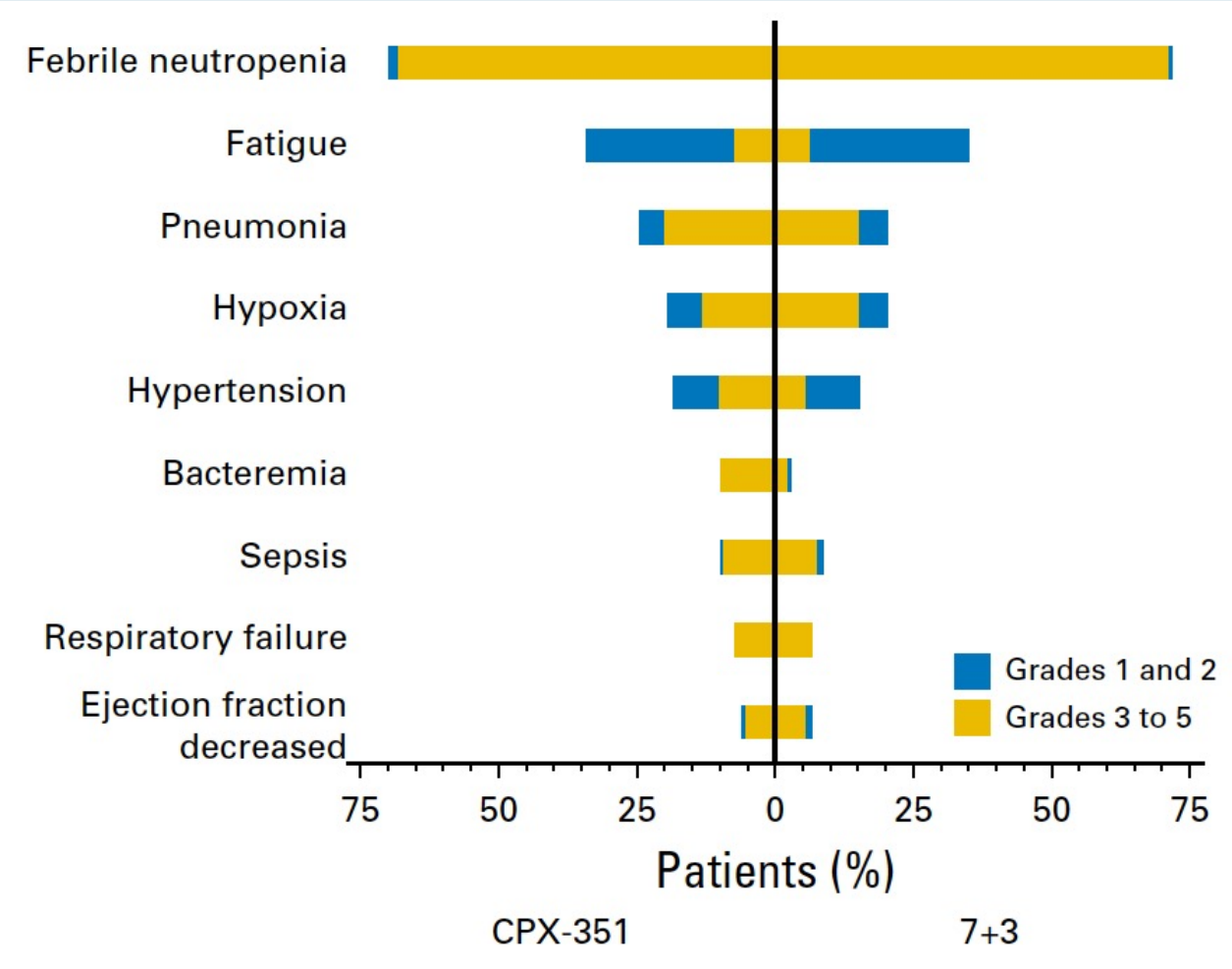
B

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.

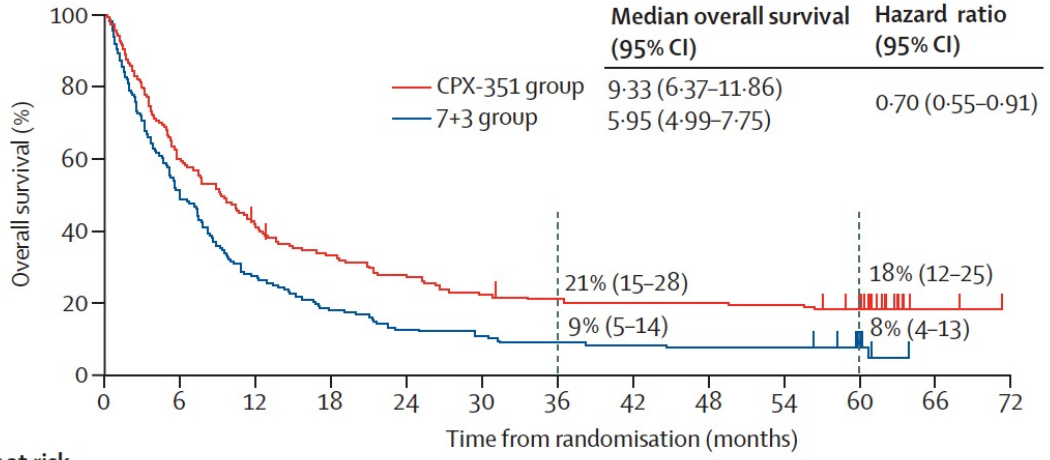
Phase III Trial of CPX-351 versus 7 + 3 Cytarabine and Daunorubicin for Older Patients with Newly Diagnosed High-Risk or Secondary AML: Most Frequently Reported Adverse Events



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

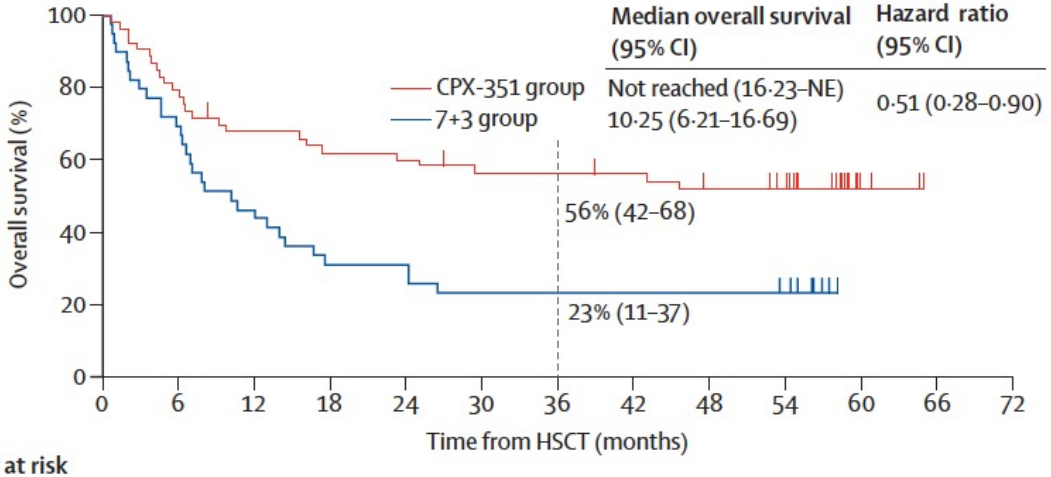
Phase III Trial of CPX-351 versus 7 + 3 Cytarabine and Daunorubicin for Older Patients with Newly Diagnosed High-Risk or Secondary AML: 5-Year Overall Survival Results

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.

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Wednesday, December 15, 2021
5:00 PM – 6:00 PM ET

Faculty

Brian T Hill, MD, PhD

Moderator

Neil Love, MD

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