Meet The Professor
Optimizing the Management of Acute Myeloid Leukemia

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

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

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: AbbVie Inc, Adaptive Biotechnologies Corporation, ADC Therapeutics, Agios Pharmaceuticals Inc, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, BeyondSpring Pharmaceuticals Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Coherus BioSciences, CTI BioPharma Corp, Daiichi Sankyo Inc, Eisai Inc, EMD Serono Inc, Epizyme Inc, Exact Sciences, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Genmab, Gilead Sciences Inc, GlaxoSmithKline, Grail Inc, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Mersana Therapeutics Inc, Natera Inc, Novartis, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sanofi Genzyme, Seagen Inc, Servier Pharmaceuticals LLC, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, Tesaro, A GSK Company, TG Therapeutics Inc, Turning Point Therapeutics Inc, Verastem Inc and Zymeworks Inc.

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Dr Fathi — Disclosures

Consulting Agreements	AbbVie Inc, Agios Pharmaceuticals Inc, Amgen Inc, Blueprint Medicines, Bristol-Myers Squibb Company, Celgene Corporation, Daiichi Sankyo Inc, Foghorn Therapeutics, FORMA Therapeutics, Forty Seven Inc, Genentech, a member of the Roche Group, Ipsen Biopharmaceuticals Inc, Kite, A Gilead Company, Kura Oncology, MorphoSys, NewLink Genetics, Novartis, Pfizer Inc, Seagen Inc, Servier Pharmaceuticals LLC, Takeda Pharmaceuticals USA Inc, Trillium Therapeutics Inc, Trovagene
Contracted Research	AbbVie Inc, Agios Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Servier Pharmaceuticals LLC
Data and Safety Monitoring Board/Committee	Takeda Pharmaceuticals USA Inc

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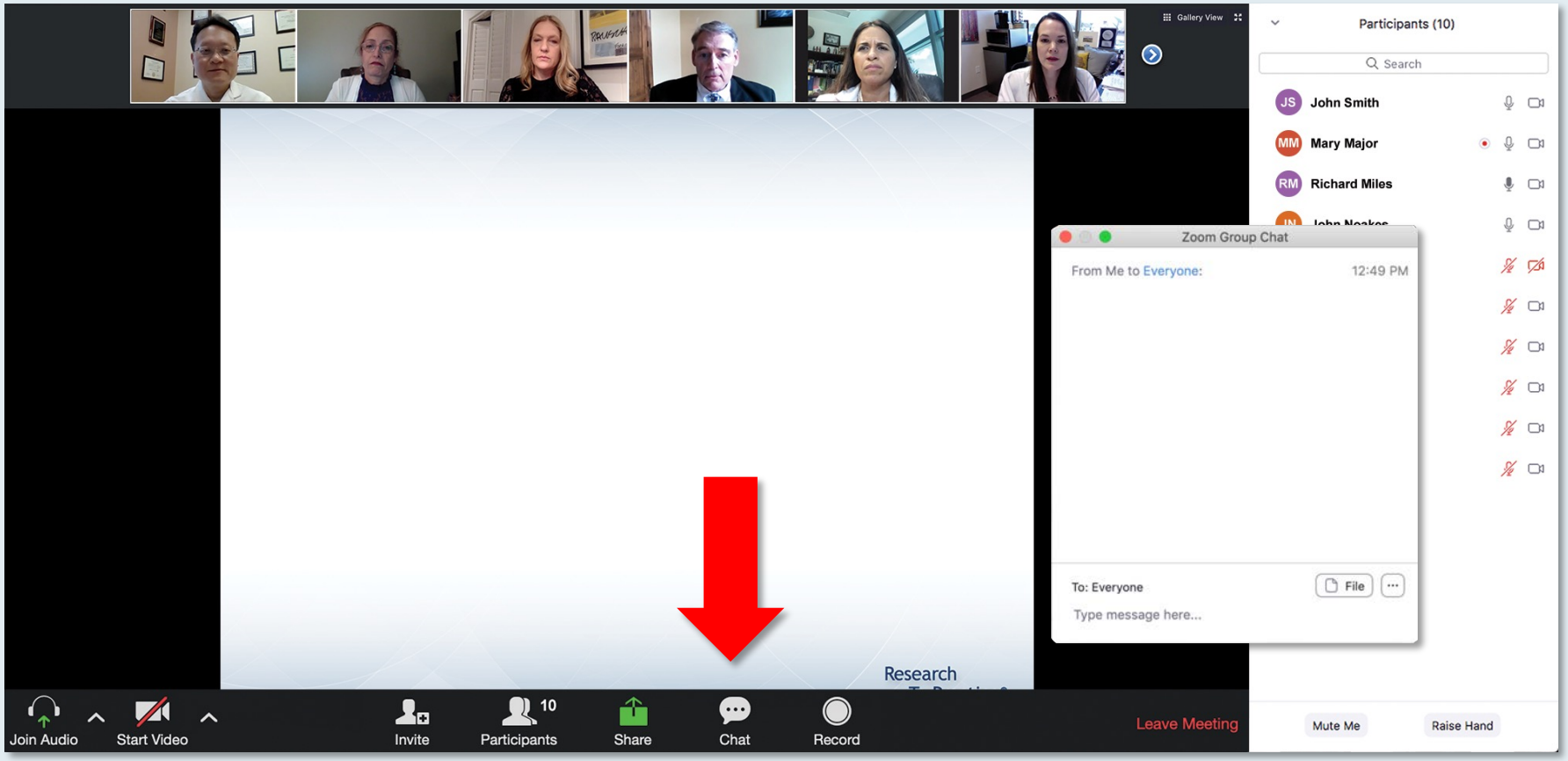
We Encourage Clinicians in Practice to Submit Questions



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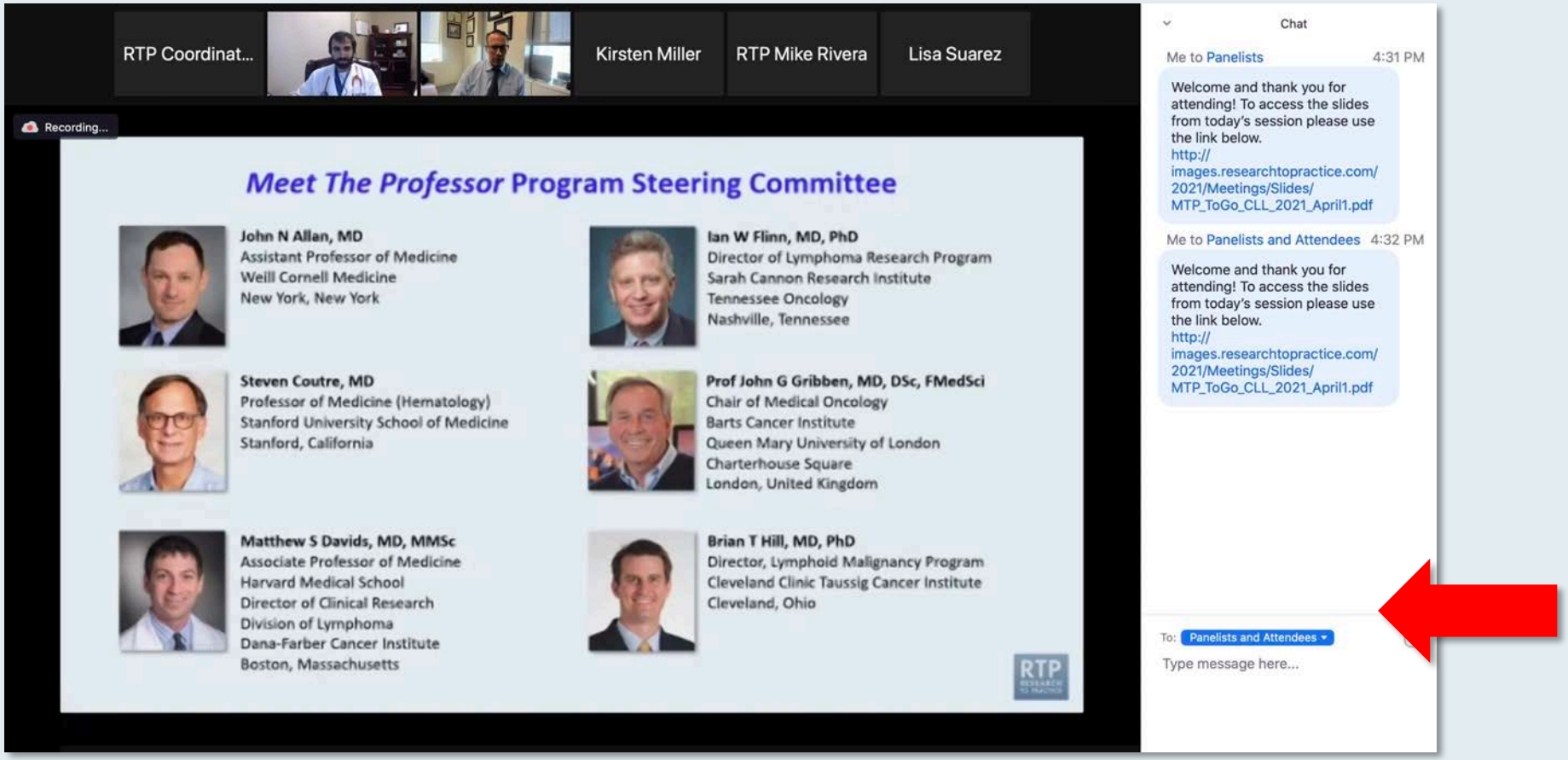

Drag the white line above the submission box up to create more space for your message.

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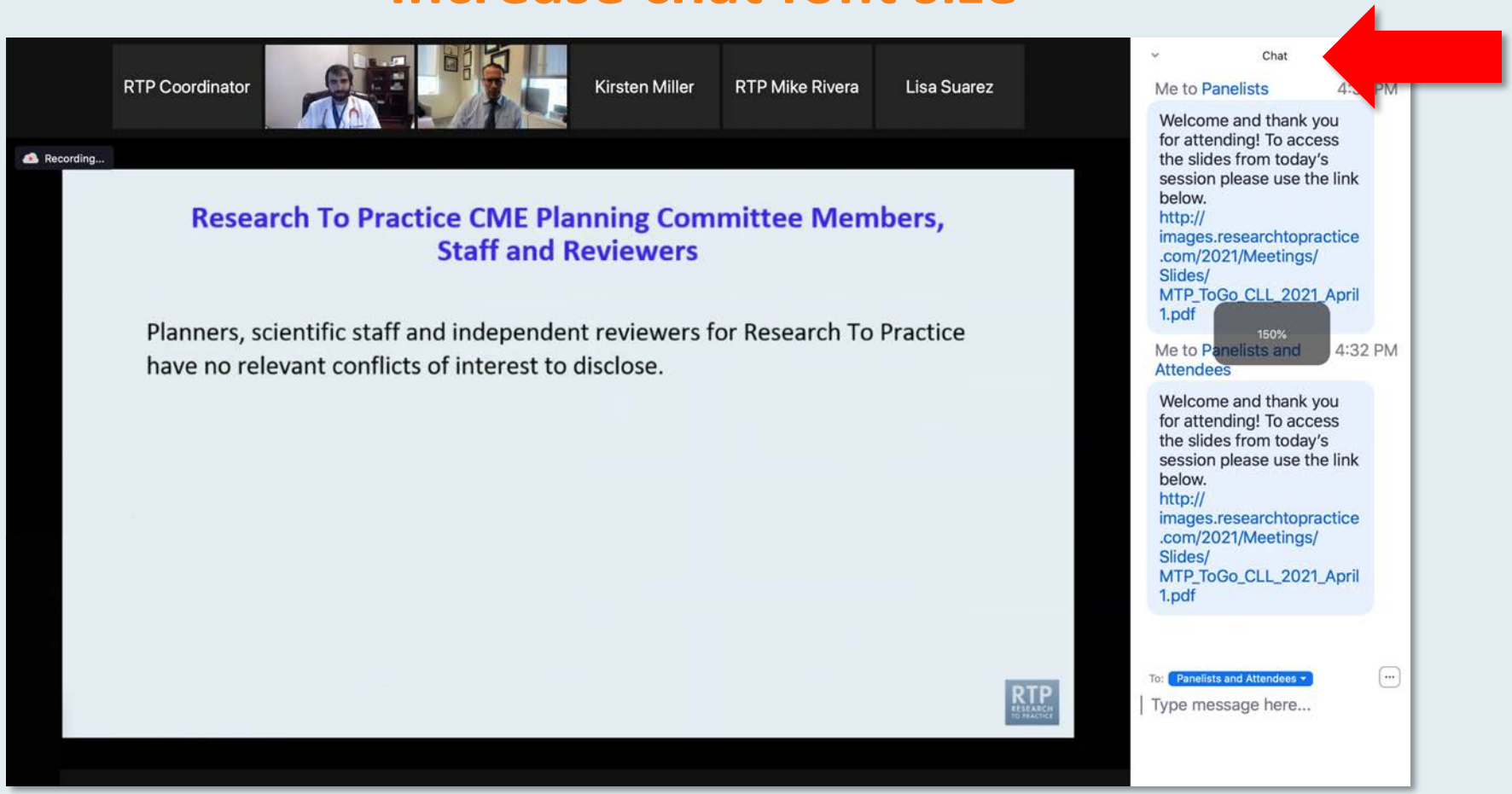

Press Command (for Mac) or Control (for PC) and the + symbol.
You may do this as many times as you need for readability.

ONCOLOGY TODAY

WITH DR NEIL LOVE

Key Presentations on Acute Myeloid Leukemia and Myelodysplastic Syndromes from ASH 2021

DR ANDREW BRUNNER

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

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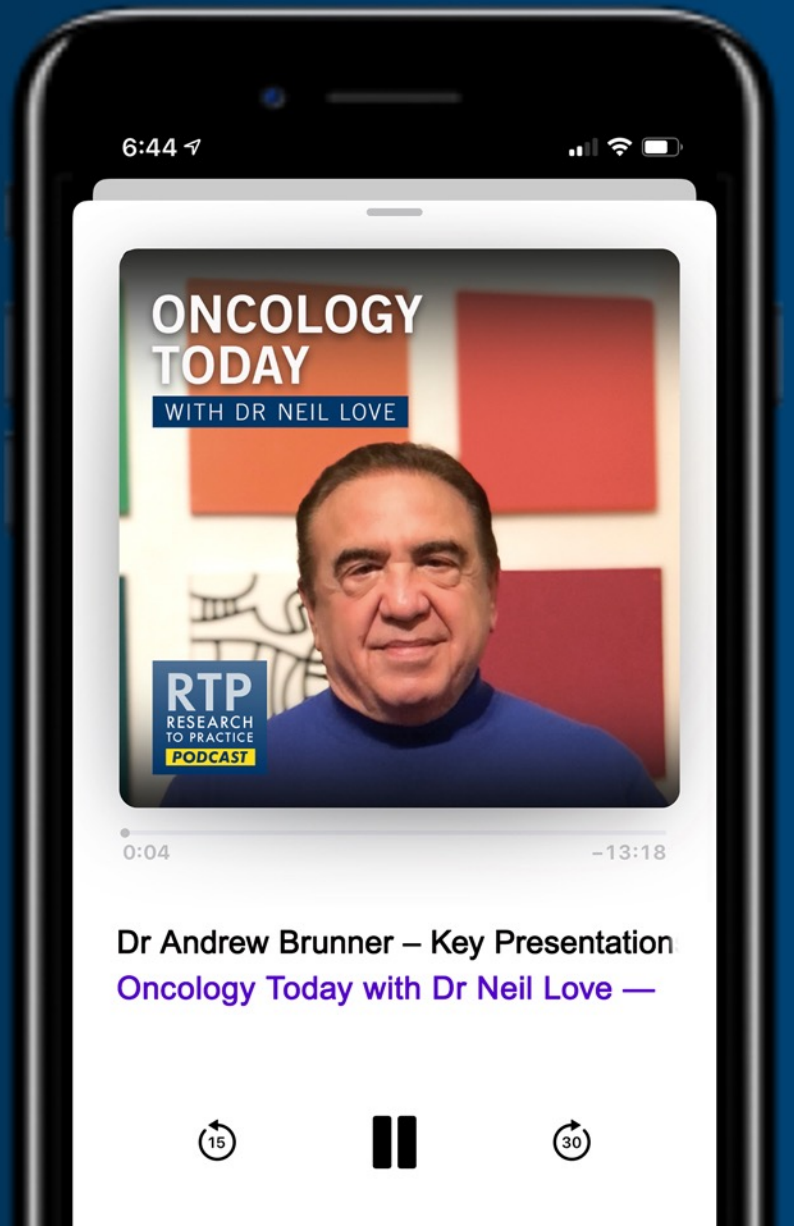

The Great Adjuvant Debate — Exploring the Role of Novel Therapies in the Management of Localized Cancer

Monday, February 28, 2022

5:00 PM – 6:00 PM ET

Faculty

Jeffrey S Weber, MD, PhD
Roy S Herbst, MD, PhD
Sara M Tolaney, MD, MPH

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Clinical Management of Hodgkin and Non-Hodgkin Lymphomas

Tuesday, March 1, 2022
5:00 PM – 6:00 PM ET

Faculty

Michael E Williams, MD, ScM

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Management of Metastatic Castration-Resistant Prostate Cancer

Wednesday, March 2, 2022
5:00 PM – 6:00 PM ET

Faculty

Andrew J Armstrong, MD, ScM

Moderator

Neil Love, MD

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Meet The Professor

Current and Future Management of Chronic Lymphocytic Leukemia

Thursday, March 3, 2022
5:00 PM – 6:00 PM ET

Faculty

William G Wierda, MD, PhD

Moderator

Neil Love, MD

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Meet The Professor

Current and Future Role of Immunotherapy in the Management of Lung Cancer

Monday, March 7, 2022
5:00 PM – 6:00 PM ET

Faculty

Charu Aggarwal, MD

Moderator

Neil Love, MD

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Year in Review:
Kidney and Bladder Cancer

Tuesday, March 8, 2022
5:00 PM – 6:00 PM ET

Faculty

Elizabeth R Plimack, MD, MS

Thomas Powles, MBBS, MRCP, MD

Moderator

Neil Love, MD

RTP Year in Review 2022

Meet The Professor

Optimizing the Management of Acute Myeloid Leukemia

Wednesday, March 9, 2022
5:00 PM – 6:00 PM ET

Faculty

Rebecca L Olin, MD, MSCE

Moderator

Neil Love, MD

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Meet The Professor

Current and Future Management of Myelofibrosis

Thursday, March 10, 2022
5:00 PM – 6:00 PM ET

Faculty

Srdan Verstovsek, 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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Meet The Professor
Optimizing the Management of Acute Myeloid Leukemia

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

Meet The Professor Program Participating Faculty

Naval Daver, MD
Director, Leukemia Research Alliance Program
Associate Professor
Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, Texas

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

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

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

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Meet The Professor Program Participating Faculty

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

Moderator
Neil Love, MD
Research To Practice
Miami, Florida

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

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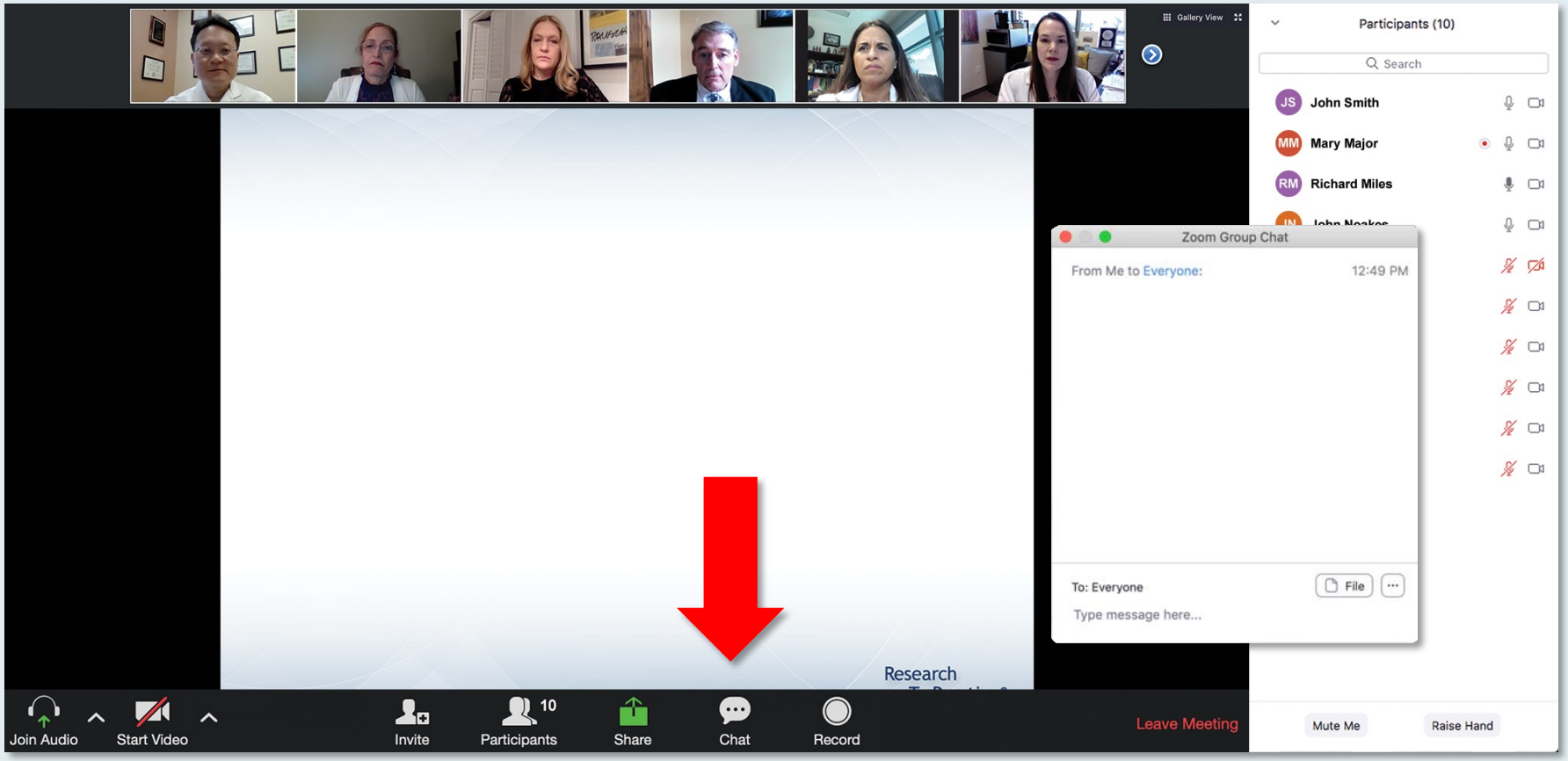

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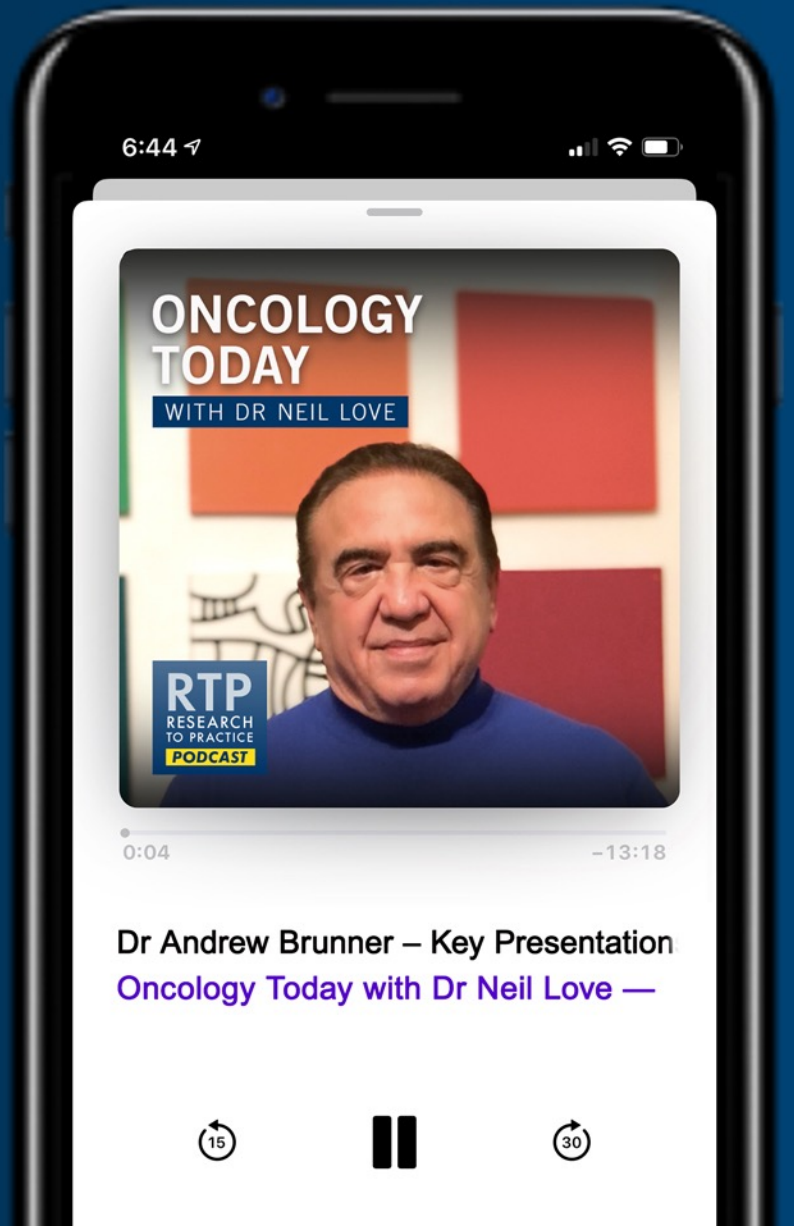

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Dr Fathi — Disclosures

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Data and Safety Monitoring Board/Committee	Takeda Pharmaceuticals USA Inc

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Bhavana (Tina) Bhatnagar, DO
West Virginia University Cancer Institute Schiffler Cancer Center
Wheeling, West Virginia

Jeanne Palmer, MD
Mayo Clinic, Arizona
Phoenix, Arizona

Agenda

Introduction: Differentiation Syndrome

Module 1: Case Presentations

- Dr Bhatnagar: A 77-year-old woman who received decitabine/venetoclax for acute myeloid leukemia (AML)
- Dr Palmer: A 33-year-old man with AML harboring a FLT3-ITD mutation with an allelic ratio of 0.6 and NPM1 and IDH2 mutations
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Module 2: Faculty Survey

Module 3: Journal Club with Dr Fathi

Module 4: Appendix – Key Data Sets

RTP RESEARCH TO PRACTICE

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DOI: 10.1002/ajh.26142

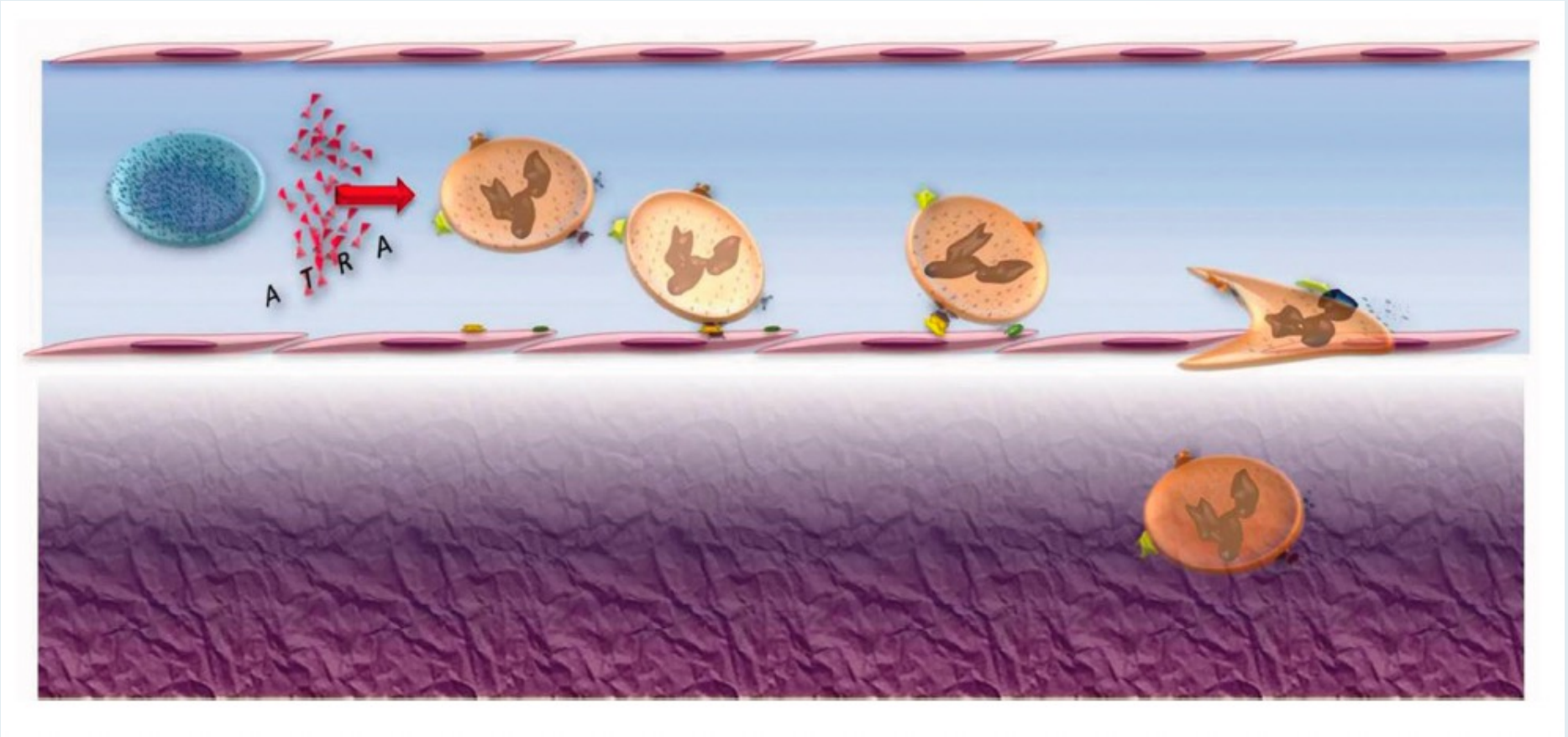
CRITICAL REVIEW

Am J Hematol 2021;96(6):735-46.

Differentiation syndrome with lower-intensity treatments for acute myeloid leukemia

Amir T. Fathi[1,2] | Eytan M. Stein[3,4] | Courtney D. DiNardo[5] | Mark J. Levis[6] | Pau Montesinos[7] | Stéphane de Botton[8]

Development of Differentiation Syndrome

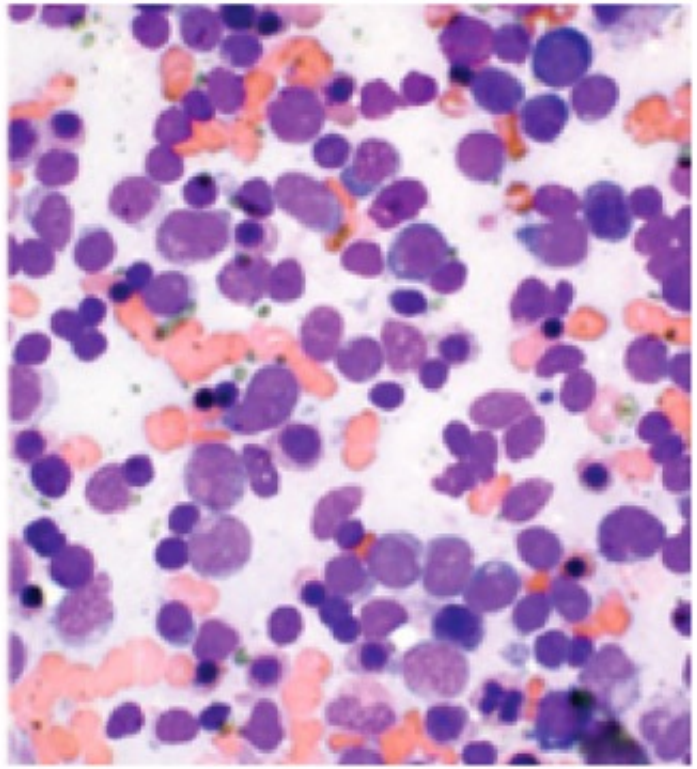


Cellular and molecular mechanisms participate in DS development. ATRA treatment induces increased expression of adhesion molecules such as CD11b, CD18 and CAM-1, which increase the adhesion of myeloid to endothelial cells, facilitating migration into tissues.

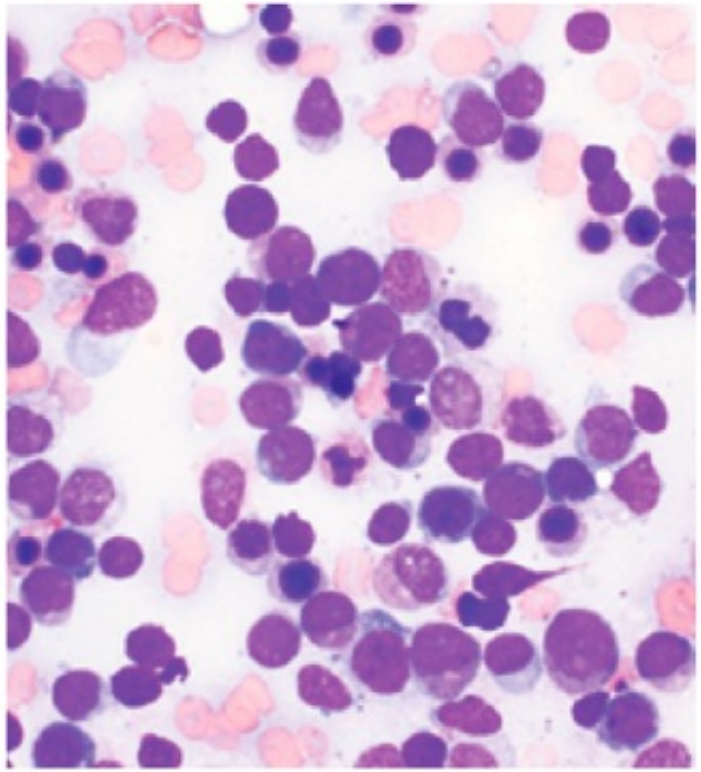
Fathi AT et al. *Am J Hematol* 2021;96(6):735-46.

Cytomorphological Evidence of Cellular Differentiation in Patients Receiving Enasidenib

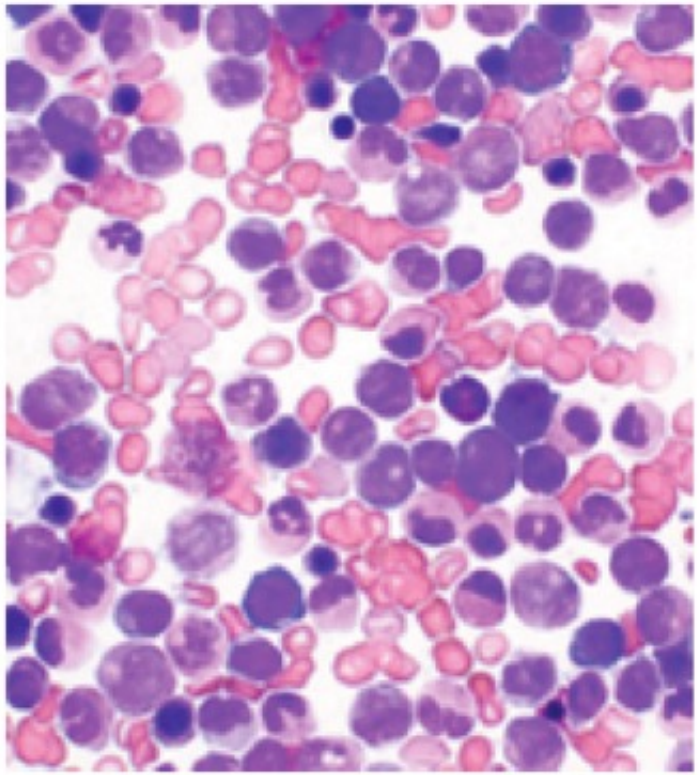
Screening
37% BM blasts



Cycle 1 Day 15
Evidence of cellular differentiation

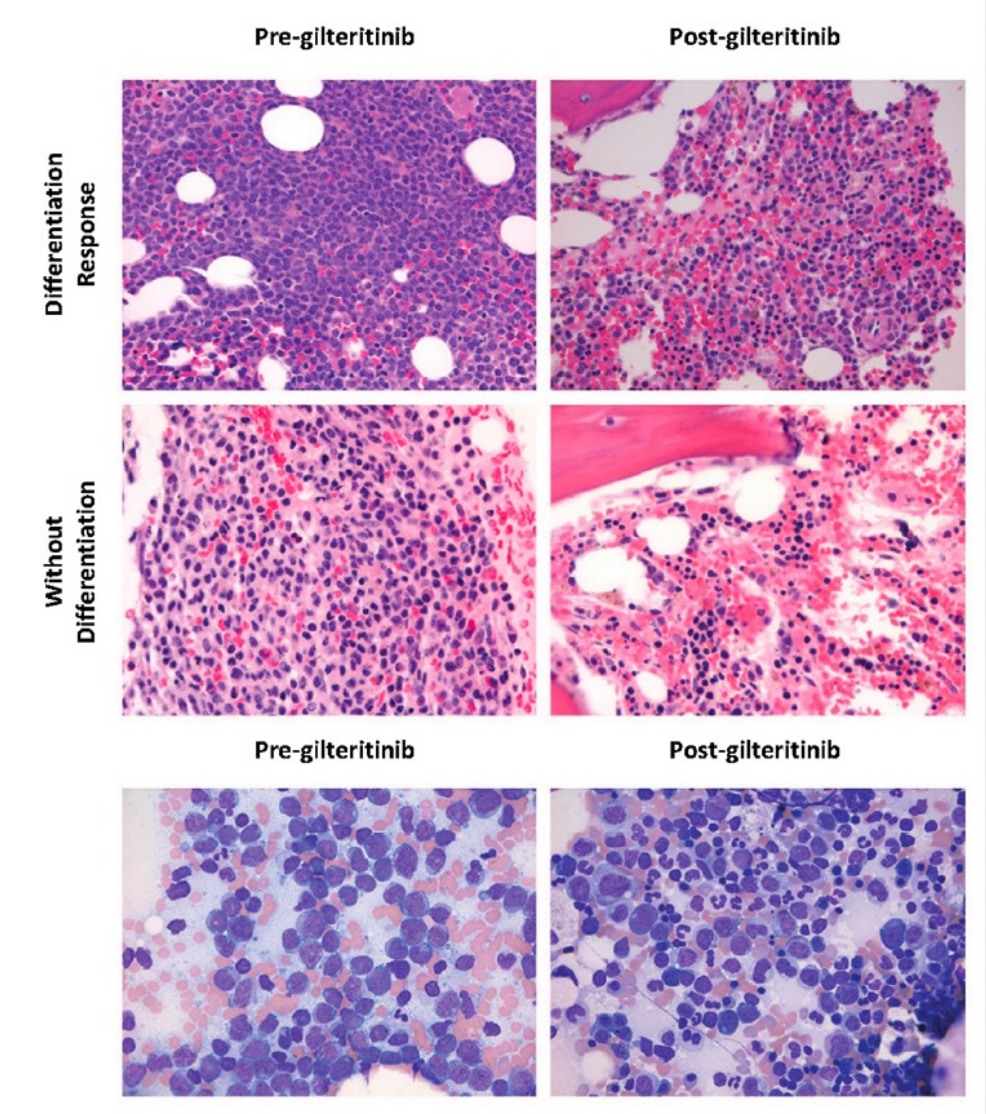


Cycle 3 Day 1
4% BM blasts



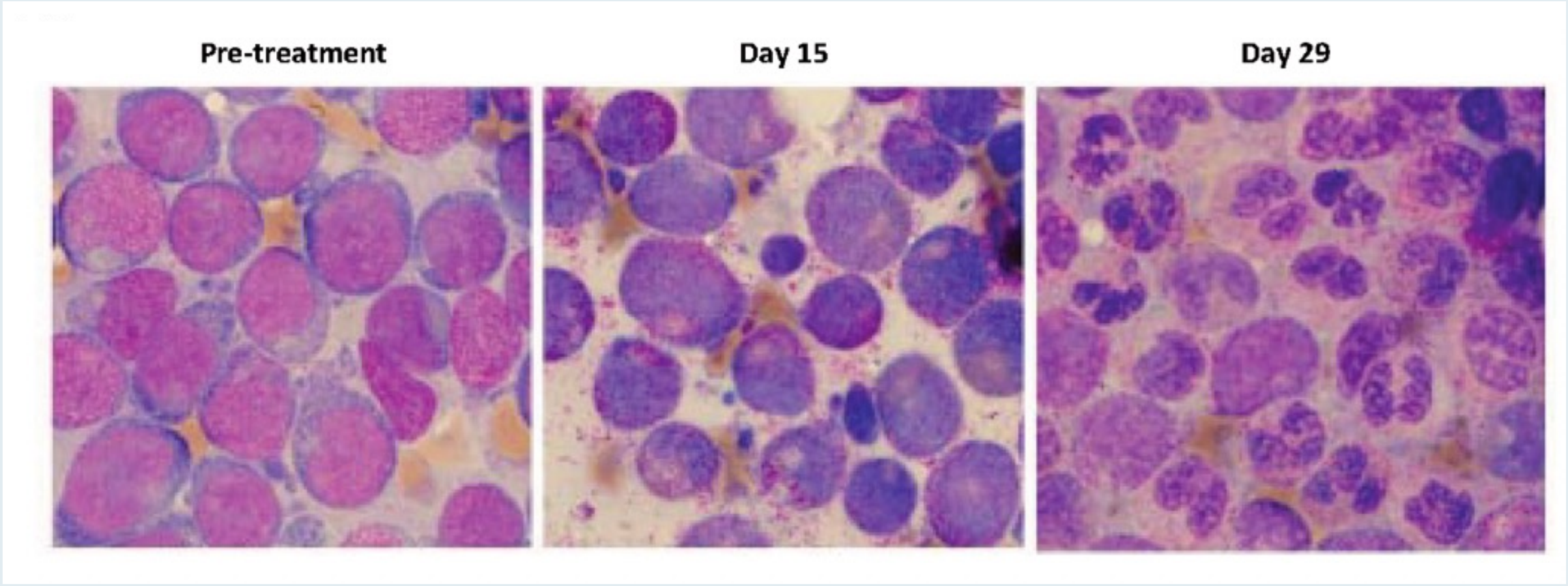
Fathi AT et al. *Am J Hematol* 2021;96(6):735-46.

Cytomorphological Evidence of Cellular Differentiation in Patients Receiving Gilteritinib



Fathi AT et al. *Am J Hematol* 2021;96(6):735-46.

Cytomorphological Evidence of Cellular Differentiation in Patients Receiving Quizartinib



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Module 2: Faculty Survey

Module 3: Journal Club with Dr Fathi

Module 4: Appendix – Key Data Sets

Management of the cytopenias associated with venetoclax/hypomethylating agent is a major issue and is the most challenging aspect of administering this regimen.

1. Strongly agree
2. Agree
3. Neutral
4. Disagree
5. Strongly disagree

Case Presentation: A 77-year-old woman who received decitabine/venetoclax for AML

Dr Tina Bhatnagar (Wheeling, West Virginia)

Case Presentation: A 33-year-old man with AML harboring a FLT3-ITD mutation with an allelic ratio of 0.6 and NPM1 and IDH2 mutations

Dr Jeanne Palmer (Phoenix, Arizona)

Case Presentation: A 77-year-old woman with ovarian cancer who develops AML with a TP53 mutation and a complex karyotype

Dr Tina Bhatnagar (Wheeling, West Virginia)

Case Presentation: A 77-year-old woman with ovarian cancer who develops AML with a TP53 mutation and a complex karyotype (continued)

Dr Tina Bhatnagar (Wheeling, West Virginia)

Case Presentation: A 35-year-old woman with inversion 16 AML

Dr Jeanne Palmer (Phoenix, Arizona)

Case Presentation: A 58-year-old man with therapy-related AML and a KMT2A rearrangement

Dr Tina Bhatnagar (Wheeling, West Virginia)

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

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RTP RESEARCH TO PRACTICE

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

RTP RESEARCH TO PRACTICE

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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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

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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

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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

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 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

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

Agenda

Introduction: Differentiation Syndrome

Module 1: Case Presentations

- Dr Bhatnagar: A 77-year-old woman who received decitabine/venetoclax for acute myeloid leukemia (AML)
- Dr Palmer: A 33-year-old man with AML harboring a FLT3-ITD mutation with an allelic ratio of 0.6 and NPM1 and IDH2 mutations
- Dr Bhatnagar: A 77-year-old woman with ovarian cancer who develops AML with a TP53 mutation and a complex karyotype
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Module 2: Faculty Survey

Module 3: Journal Club with Dr Fathi

Module 4: Appendix – Key Data Sets

RTP RESEARCH TO PRACTICE

blood

Regular Article

Blood 2021;138(5):387-400.

MYELOID NEOPLASIA

Multisite 11-year experience of less-intensive vs intensive therapies in acute myeloid leukemia

Mohamed L. Sorror,[1,2] Barry E. Storer,[3,4] Amir T. Fathi,[5] Andrew Brunner,[5] Aaron T. Gerds,[6] Mikkael A. Sekeres,[6] Sudipto Mukherjee,[6] Bruno C. Medeiros,[7] Eunice S. Wang,[8] Pankit Vachhani,[8] Paul J. Shami,[9] Esteban Peña,[9] Mahmoud Elsawy,[1,10] Kehinde Adekola,[11] Selina Luger,[12] Maria R. Baer,[13] David Rizzieri,[14] Tanya M. Wildes,[15] Jamie Koprivnikar,[16] Julie Smith,[17] Mitchell Garrison,[17] Kiarash Kojouri,[18] Wendy Leisenring,[3] Lynn Onstad,[3] Jennifer E. Nyland,[19] Pamela S. Becker,[1,20] Jeannine S. McCune,[1,21] Stephanie J. Lee,[1,2] Brenda M. Sandmaier,[1,2] Frederick R. Appelbaum,[1,2] and Elihu H. Estey[1,20]

Phase 1 First-in-Human Study of Irreversible FLT3 Inhibitor FF-10101-01 in Relapsed or Refractory Acute Myeloid Leukemia

Levis MJ et al.

ASCO 2021;Abstract 7008.

CASE REPORT

Clinical Case Reports Open Access WILEY

Arsenic toxicity manifesting as profuse watery diarrhea during induction therapy for acute promyelocytic leukemia

Ashley Ott[1] | Vinayak Venkataraman[1] | Yousef R. Badran[2] | Rose Goldman[3,4] | Smiljana Spasic[5] | Darshali A. Vyas[1] | Philip Amrein[6] | Steven McAfee[6] | Andrew Brunner[6] | Amir T. Fathi[6] | Rupa Narayan[6]

Clin Case Rep 2021;9(5):e04115.

Updated Survival and Response Analyses from a Phase 1 Study of Ivosidenib or Enasidenib Combined with Induction and Consolidation Chemotherapy in Patients with Newly Diagnosed AML with an IDH1 or IDH2 Mutation

Stein EM et al.

ASH 2021;Abstract 1276.

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Blood. 2021 Apr 1; 137(13): 1792–1803.
PMCID: PMC8020270
Prepublished online 2020 Oct 5. doi: 10.1182/blood.2020007233: 10.1182/blood.2020007233
PMID: 33024987

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,†]

REVIEW ARTICLE

Monoclonal Antibodies in Acute Myeloid Leukemia—Are We There Yet?

Yasmin Abaza, MD, and Amir T. Fathi, MD†*

***Cancer J* 2022;28(1):37-42**

The Associations Between Coping Strategy Use and Patient-Reported Outcomes in Patients with Acute Myeloid Leukemia

Reynolds MJ et al.

ASH 2021;Abstract 4131.

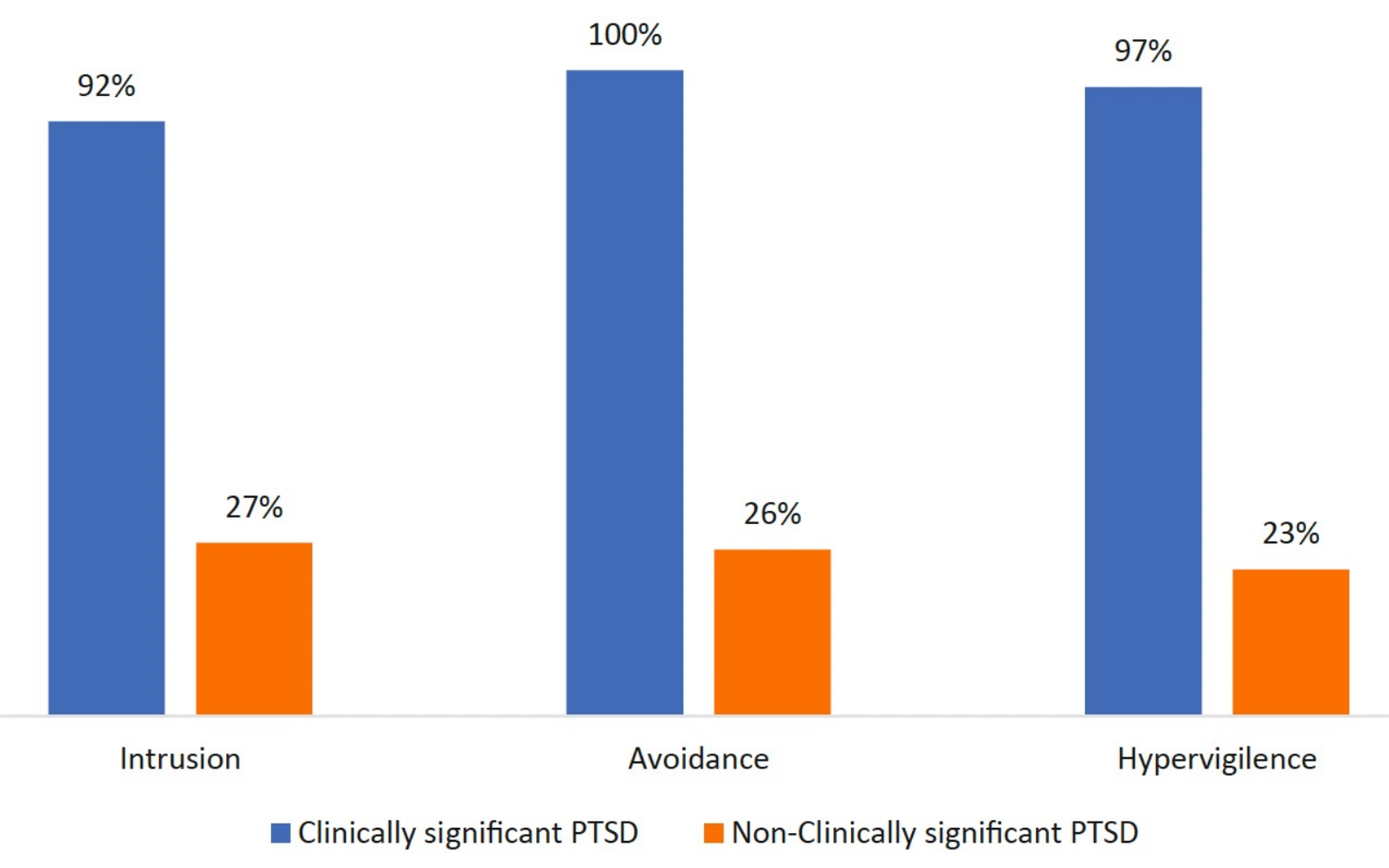
Cancer 2021;127(14):2500-6.

Original Article

Posttraumatic Stress Disorder Symptoms in Patients With Acute Myeloid Leukemia

Hermioni L. Amonoo, MD, MPP [1,2,3]; Thomas W. LeBlanc, MD [4]; Alison R. Kavanaugh, NP[3,5]; Jason A. Webb, MD[6]; Lara N. Traeger, PhD[3,7]; Annemarie D. Jagielo, BSc, BA[8]; Dagny M. Vaughn, BA [8,9]; Madeleine Elyze, BA[8]; Regina M. Longley, BA[7]; Amir T. Fathi, MD [3,8]; Gabriela S. Hobbs, MD[3,8]; Andrew M. Brunner, MD[3,8]; Nina R. O'Connor, MD[10]; Selina M. Luger, MD[11]; Jillian L. Gustin, MD[12]; Bhavana Bhatnagar, DO[13]; Nora K. Horick, MS[3,14]; and Areej El-Jawahri, MD [3,8]

Distribution of Post-Traumatic Stress Disorder Symptom Domains in Patients with AML



The distribution of posttraumatic stress disorder (PTSD) symptom domains is illustrated in patients who had acute myeloid leukemia with or without clinically significant PTSD symptoms 1 month after their intensive acute myeloid leukemia hospitalization. Among patients with clinically significant PTSD symptoms, 92%, 100%, and 97% reported intrusion, avoidance, and hypervigilance symptoms, respectively. Among patients without clinically significant PTSD symptoms, 27%, 26%, and 23% reported intrusion, avoidance, and hypervigilance symptoms, respectively.

Amonoo HL et al. *Cancer* 2021;127(14):2500-6.

Research

JAMA Oncol 2021;7(2):238-45.

JAMA Oncology | Original Investigation

Effectiveness of Integrated Palliative and Oncology Care for Patients With Acute Myeloid Leukemia
A Randomized Clinical Trial

Areej El-Jawahri, MD; Thomas W. LeBlanc, MD; Alison Kavanaugh, NP; Jason A. Webb, MD; Vicki A. Jackson, MD; Toby C. Campbell, MD; Nina O'Connor, MD; Selina M. Luger, MD; Ellin Gafford, MD; Jillian Gustin, MD; Bhavana Bhatnagar, DO; Alison R. Walker, MD; Amir T. Fathi, MD; Andrew M. Brunner, MD; Gabriela S. Hobbs, MD; Showly Nicholson, BS; Debra Davis, RN, BSN; Hilena Addis, BS; Dagny Vaughn, BA; Nora Horick, MS; Joseph A Greer, PhD; Jennifer S. Temel, MD

J Palliat Med 2021;[Online ahead of print].

Original Article

Factors Associated with Health Care Utilization at the End of Life for Patients with Acute Myeloid Leukemia

Dagny M. Vaughn, MS,[1] P. Connor Johnson, MD,[1,2,i] Annemarie D. Jagielo, BA,[1] Carlisle E.W. Topping, BA,[1] Matthew J. Reynolds, BA,[1] Alison R. Kavanaugh, NP,[1,2] Jason A. Webb, MD,[3] Amir T. Fathi, MD,[1,2] Gabriela Hobbs, MD,[1,2] Andrew Brunner, MD,[1,2] Nina O'Connor, MD,[4] Selina Luger, MD,[5] Bhavana Bhatnagar, DO,[6] Thomas W. LeBlanc, MD,[7] and Areej El-Jawahri, MD[1,2]

Agenda

Introduction: Differentiation Syndrome

Module 1: Case Presentations

- Dr Bhatnagar: A 77-year-old woman who received decitabine/venetoclax for acute myeloid leukemia (AML)
- Dr Palmer: A 33-year-old man with AML harboring a FLT3-ITD mutation with an allelic ratio of 0.6 and NPM1 and IDH2 mutations
- Dr Bhatnagar: A 77-year-old woman with ovarian cancer who develops AML with a TP53 mutation and a complex karyotype
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- Dr Bhatnagar: A 58-year-old man with therapy-related AML and a KMT2A rearrangement
- Dr Palmer: A 78-year-old man with AML and a TP53 mutation

Module 2: Faculty Survey

Module 3: Journal Club with Dr Fathi

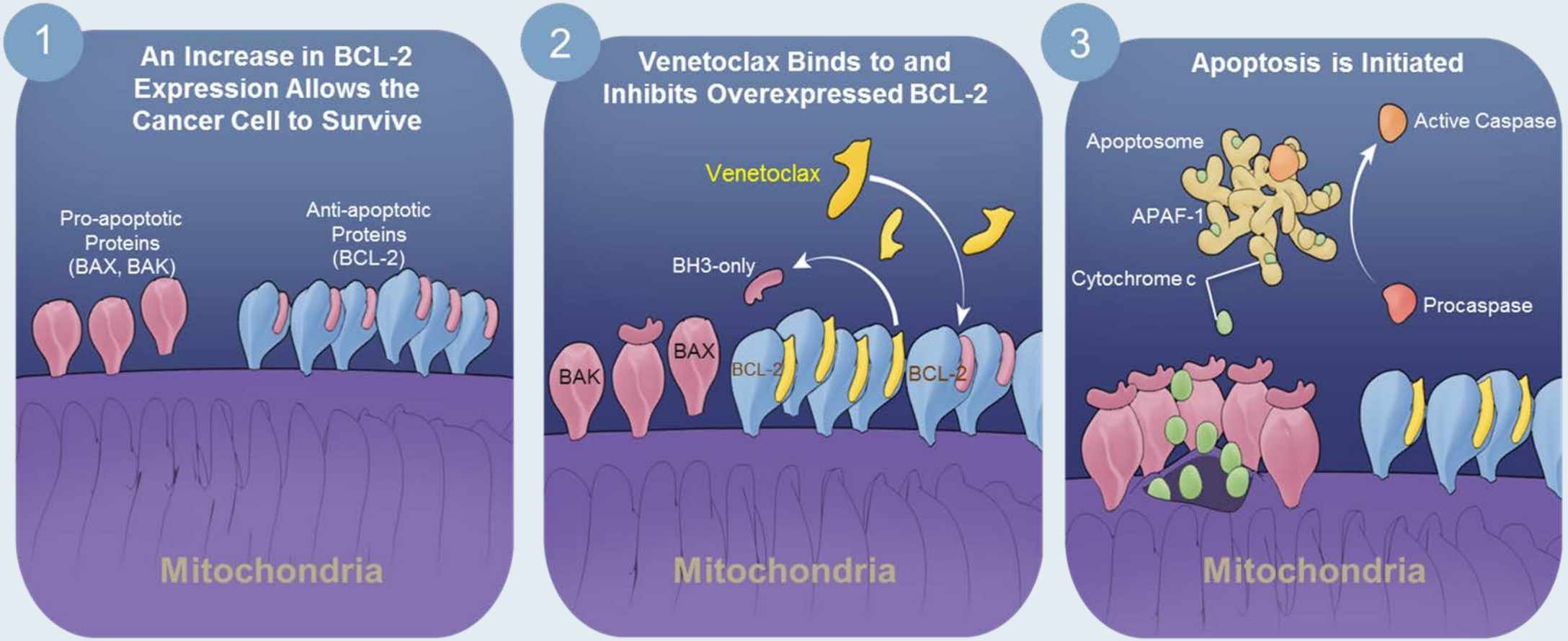
Module 4: Appendix – Key Data Sets

RTP RESEARCH TO PRACTICE

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

RTP
RESEARCH
TO PRACTICE

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

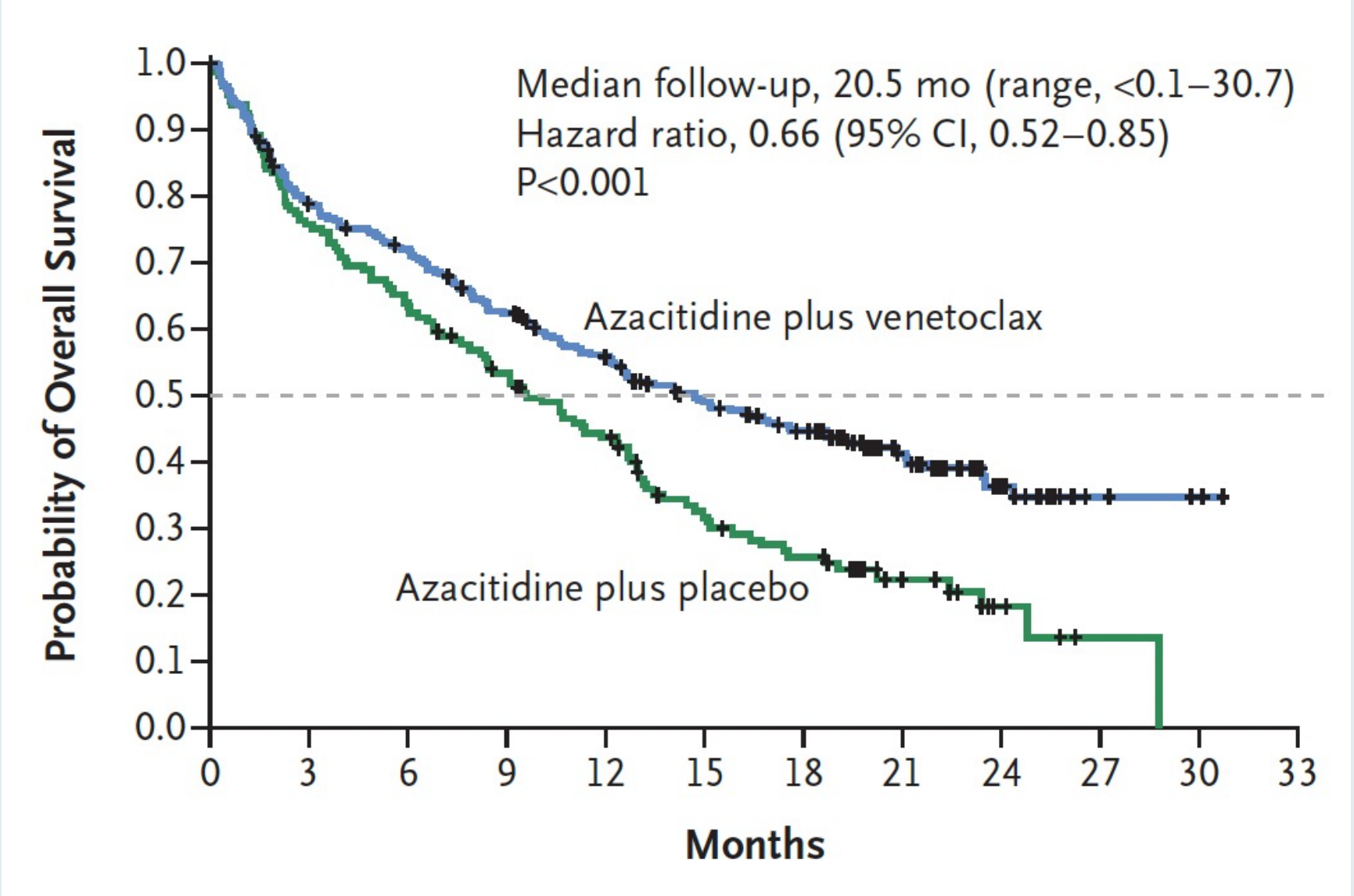
Randomization Stratification Factors	Age (<75 vs. ≥75 years); Cytogenetic Risk (intermediate, Poor); Region
Venetoclax dosing ramp-up	**Cycle 1 ramp-up** Day 1: 100 mg, Day 2: 200 mg, Day 3 - 28: 400 mg **Cycle 2** → Day 1-28: 400 mg

* 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

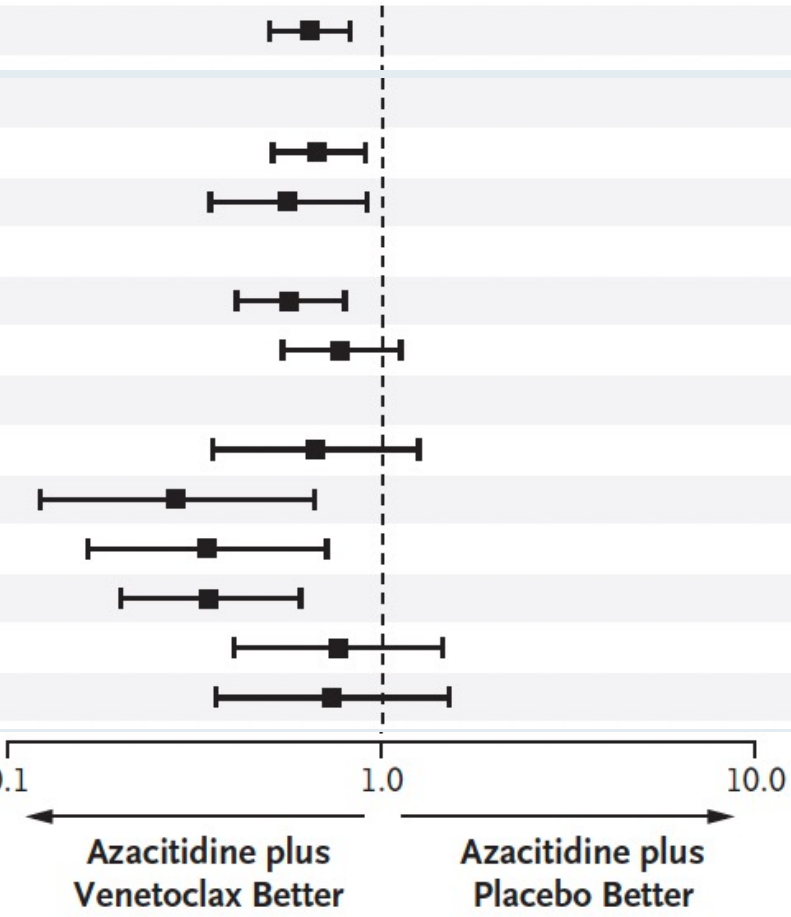


DiNardo CD et al. *N Engl J Med* 2020;383:617-29.

RTP RESEARCH TO PRACTICE

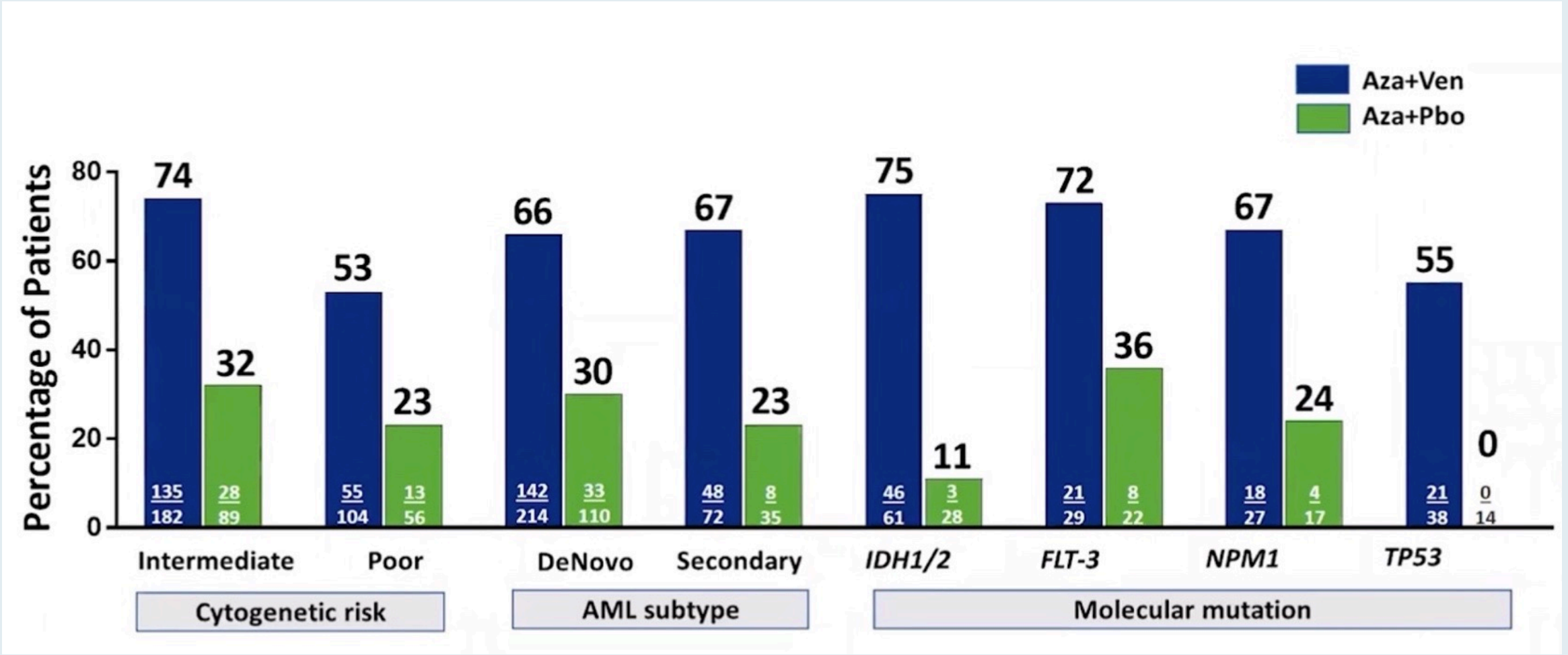
VIALE-A: Overall Survival Subgroup Analysis

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)



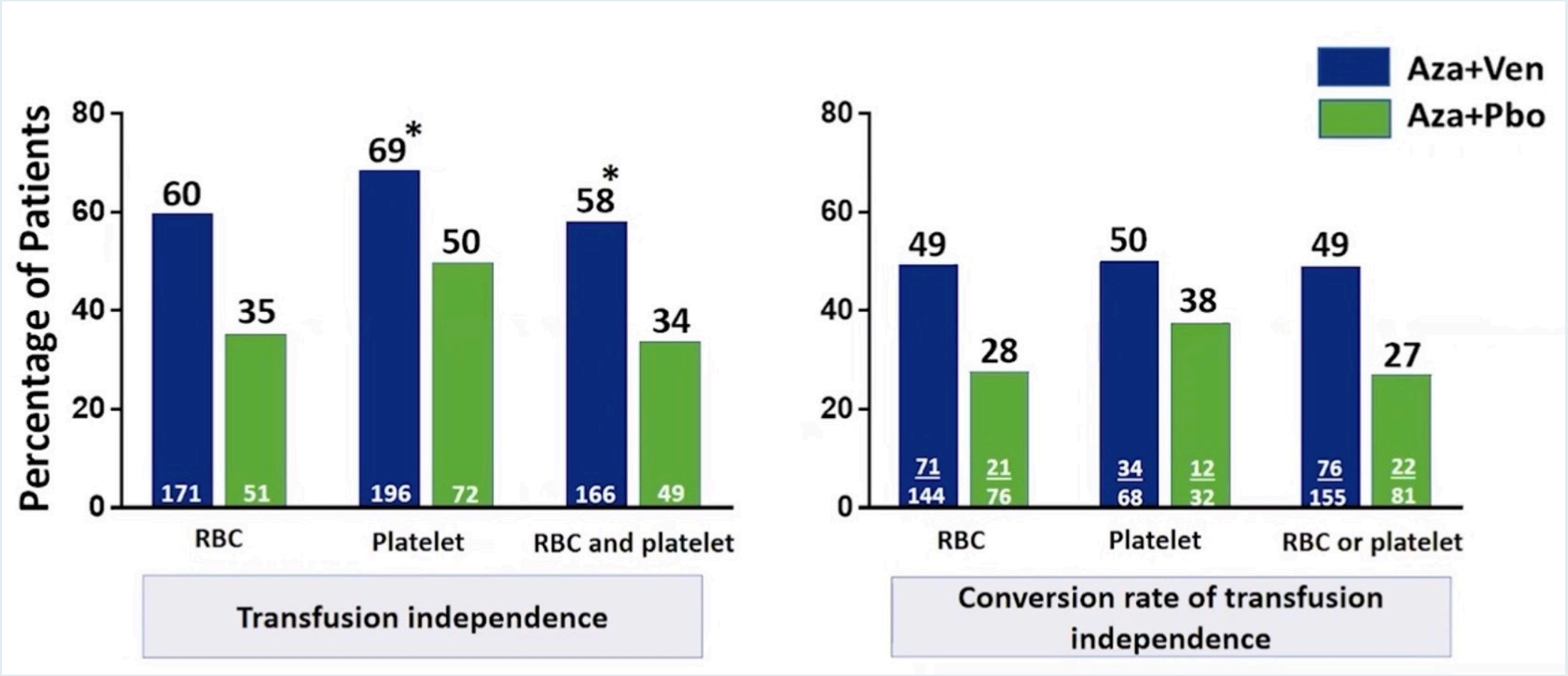
DiNardo CD et al. *N Engl J Med* 2020;383:617-29.

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)

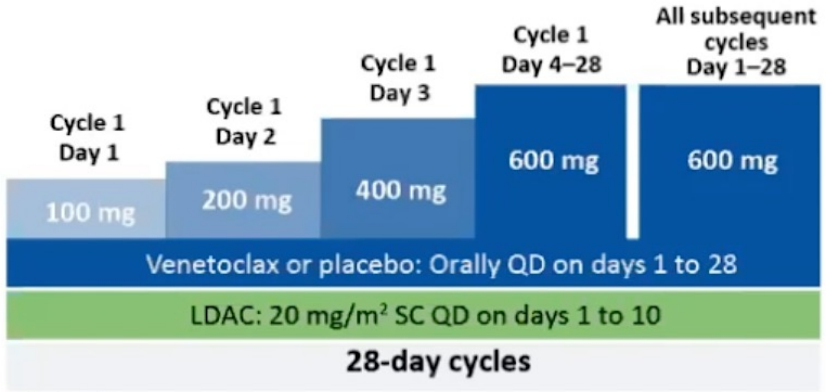
DiNardo CD et al. *N Engl J Med* 2020;383:617-29.

VIALE-C Phase 3 Study Design

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

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

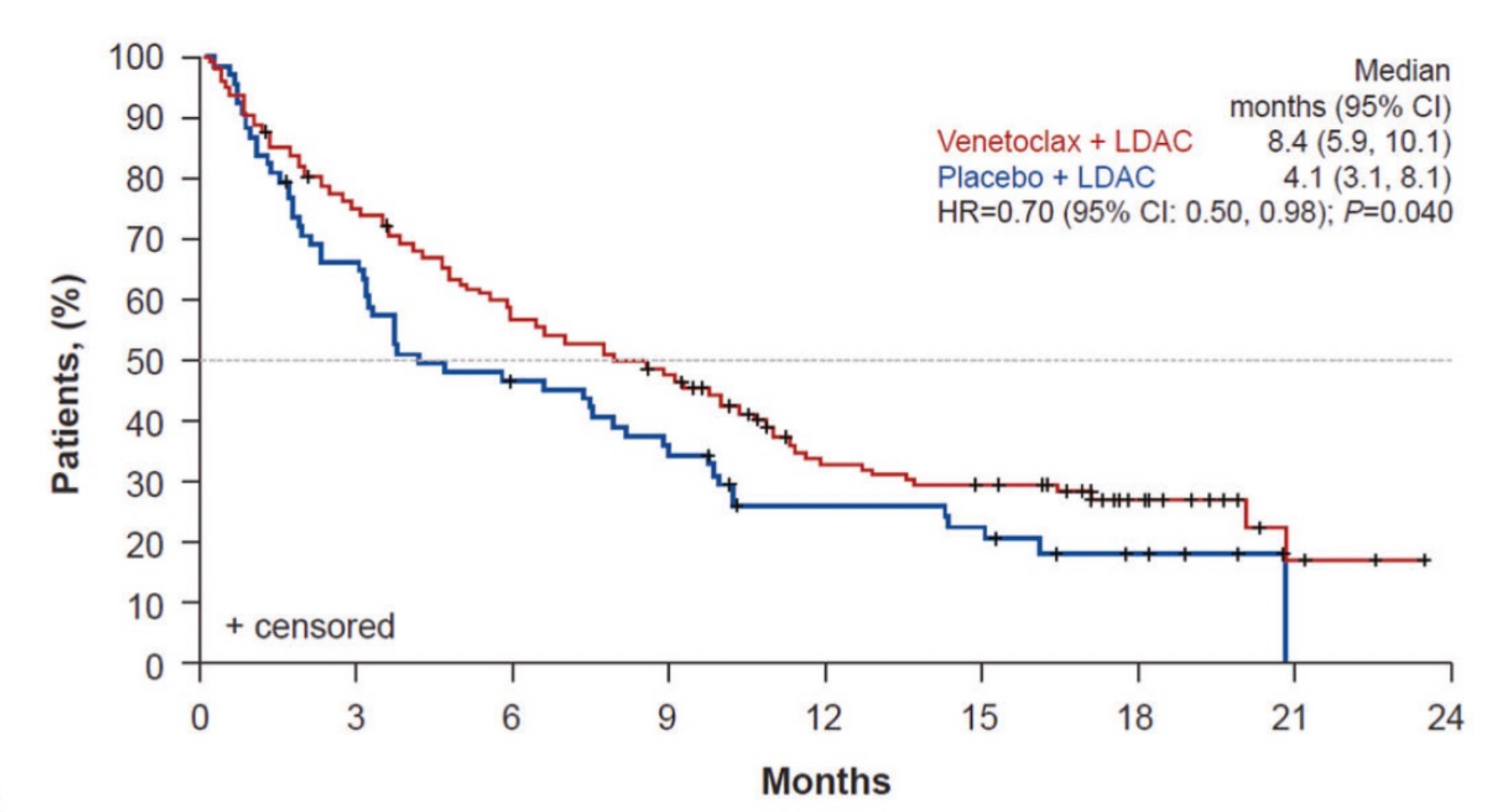
- CR, CRh, and CRi (modified IWG criteria[1])
- Rate of transfusion independence
- EFS
- MRD

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.

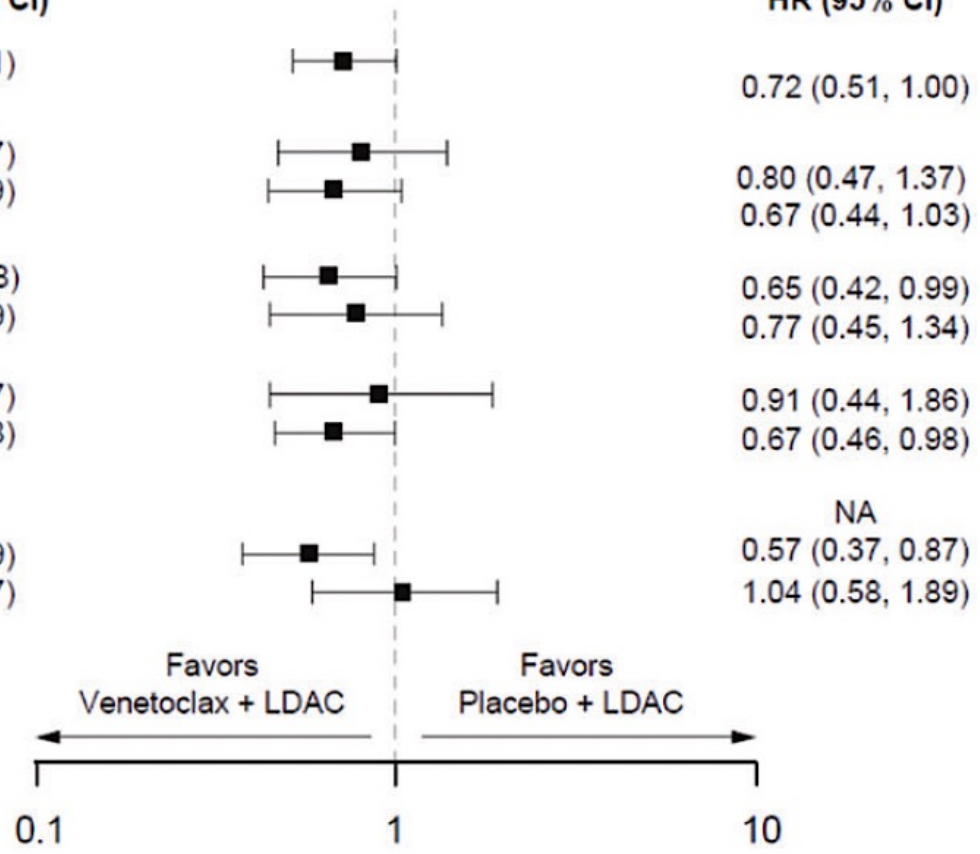
VIALE-C: Overall Survival



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)

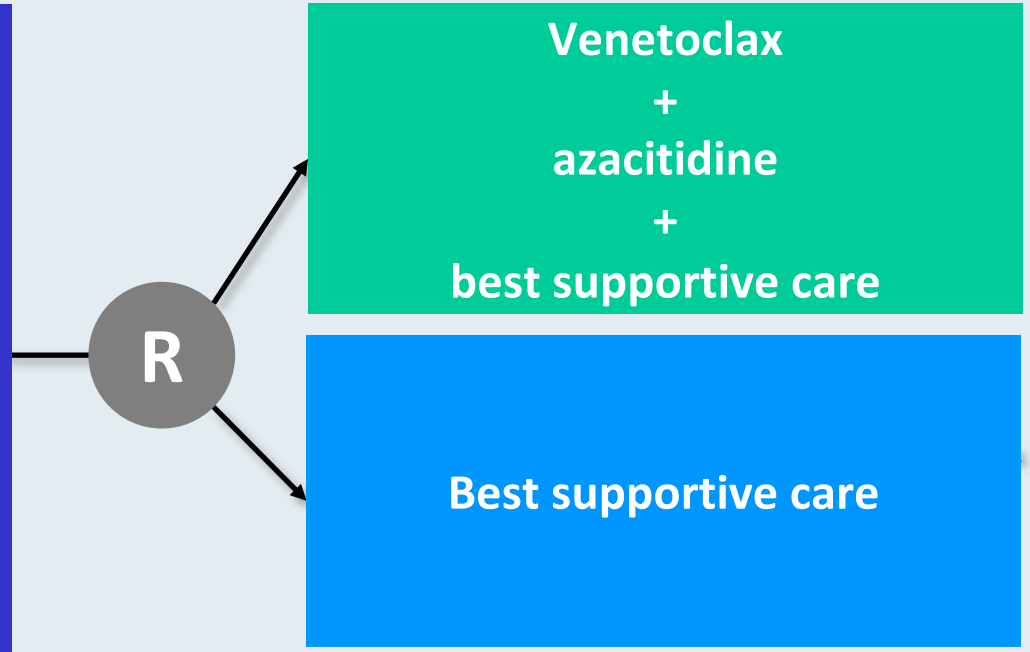


Wei AH et al. *Blood Cancer J* 2021;11:163.

VIALE-T: Phase III Trial Design

Key eligibility criteria (N = 424)

- Newly diagnosed AML
- *ASCT within the past 30 days or planned*
- Adequate renal, hepatic and hematologic criteria
- KPS score >50
- Age ≥17 years



- **Primary endpoints: Dose-limiting toxicities (Part 1), relapse-free survival (Part 2)**
- **Select secondary endpoints: Overall survival (Part 2), graft versus host disease-free survival (Part 2)**

www.clinicaltrials.gov. NCT04161885. Accessed February 2022.

RTP RESEARCH TO PRACTICE

Long-term overall survival with oral azacitidine in patients with acute myeloid leukemia in first remission after intensive chemotherapy: updated results from the phase 3 QUAZAR AML-001 trial

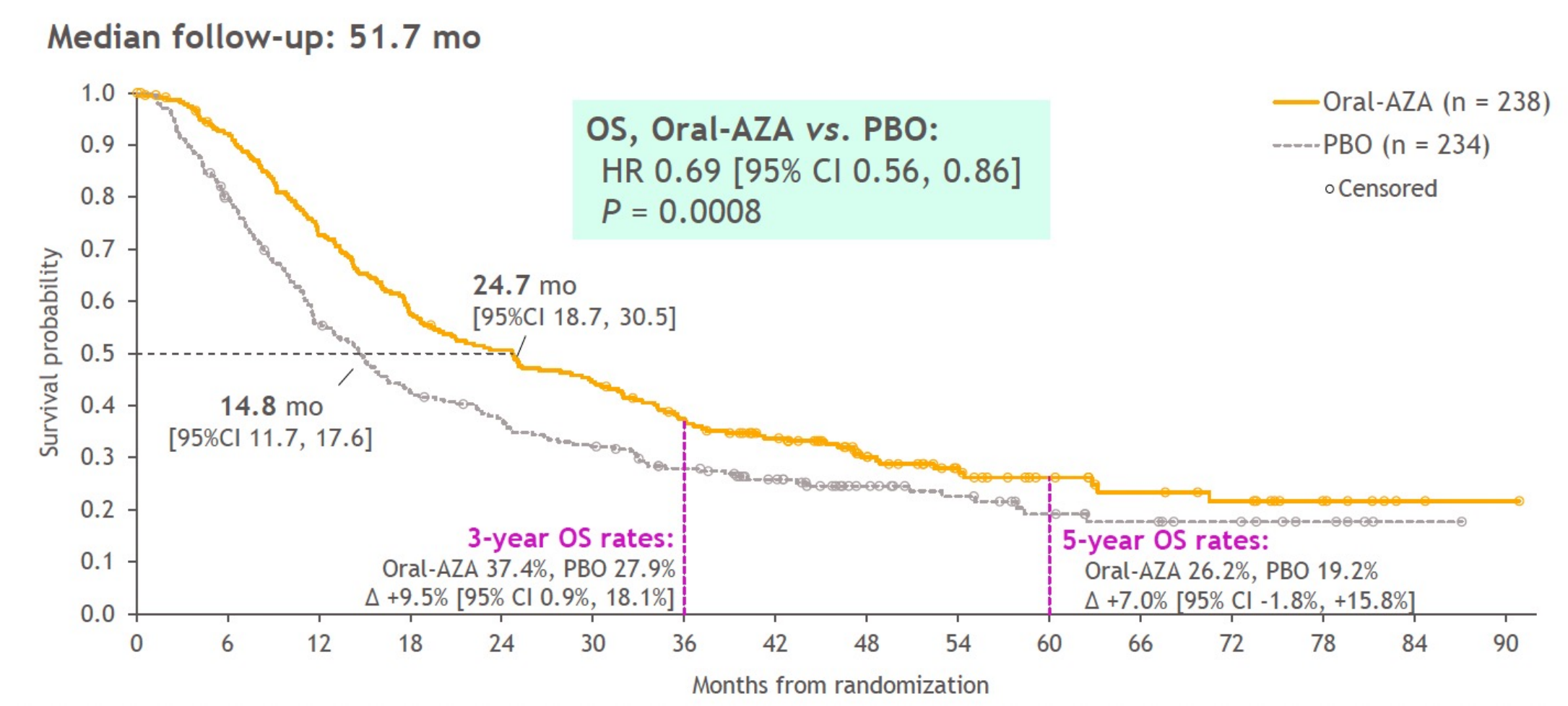
Andrew H Wei,[1,2] Hartmut Döhner,[3] Hamid Sayar,[4] Farhad Ravandi,[5] Pau Montesinos,[6] Hervé Dombret,[7,8] Dominik Selleslag,[9] Kimmo Porkka,[10,11] Jun-Ho Jang,[12] Barry Skikne,[13,14] CL Beach,[14] Olivia Yu Tian,[14] and Gail J Roboz[15,16]

[1]The Alfred Hospital, Melbourne, Australia; [2]Australian Centre for Blood Diseases, Monash University, Melbourne, Australia; [3]Ulm University Hospital, Ulm, Germany; [4]Indiana University Cancer Center, Indianapolis, IN; [5]The University of Texas MD Anderson Cancer Center, Houston, TX; [6]Hospital Universitario La Fe de Valencia, Valencia, Spain; [7]Institut de Recherche Saint Louis, Université de Paris, Paris, France; [8]Hôpital Saint-Louis, Assistance Publique - Hôpitaux de Paris (AP-HP), Paris, France; [9]AZ Sint-Jan Brugge-Oostende AV, Brugge, Belgium; [10]iCAN Digital Precision Cancer Medicine Flagship, University of Helsinki, Helsinki, Finland; [11]Helsinki University Hospital Comprehensive Cancer Center, Helsinki, Finland; [12]Samsung Medical Center, Seoul, Republic of Korea; [13]University of Kansas Medical Center, Kansas City, KS; [14]Bristol Myers Squibb, Princeton, NJ; [15]Weil Cornell Medical College, New York, NY; [16]New York Presbyterian Hospital, New York, NY

Presentation 871

ASH 2021

QUAZAR AML-001: Long-Term Overall Survival with Oral Azacitidine in AML in First-Remission after Intensive Chemotherapy

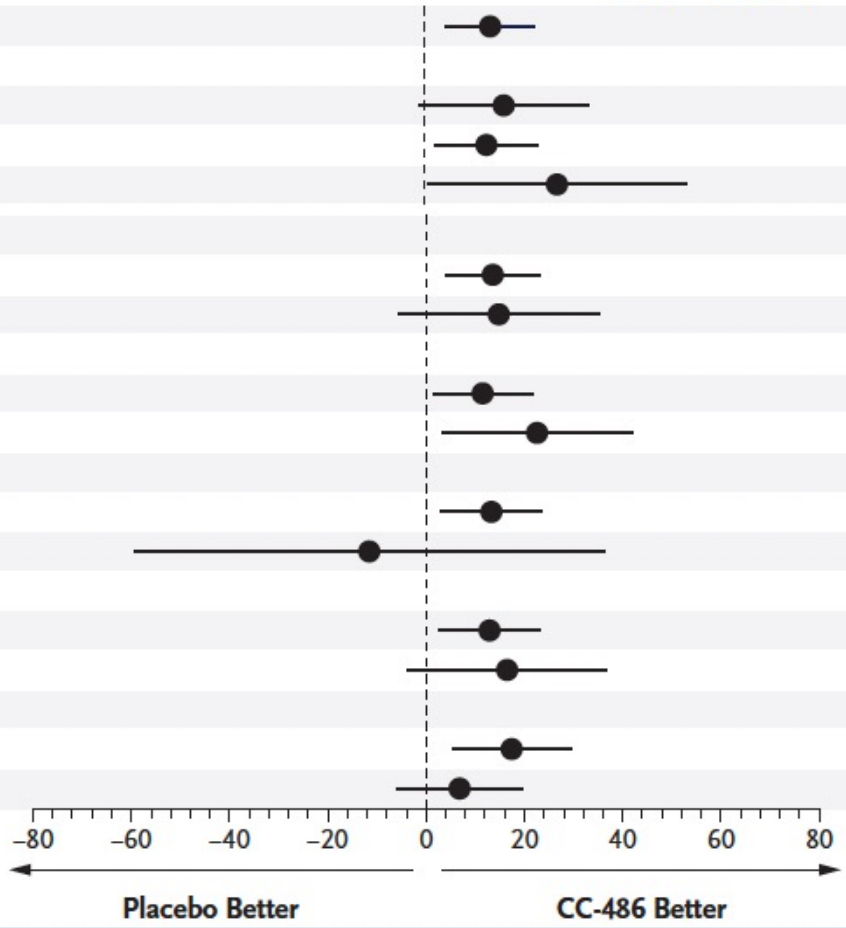


Wei AH et al. ASH 2021;Abstract 871.

RTP RESEARCH TO PRACTICE

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.

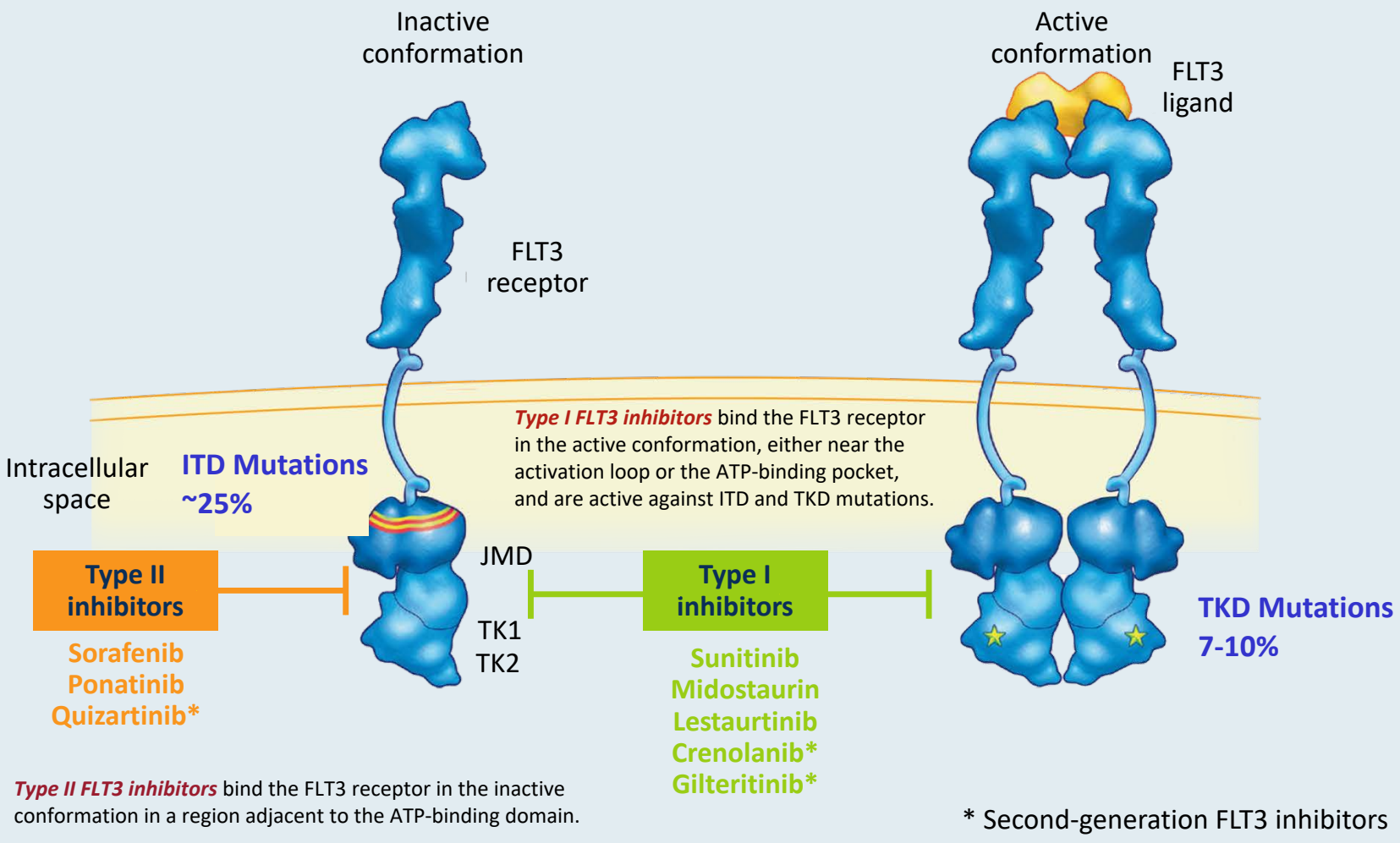
QUAZAR AML-001: Safety Summary and Select Adverse Events (AEs)

	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.

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

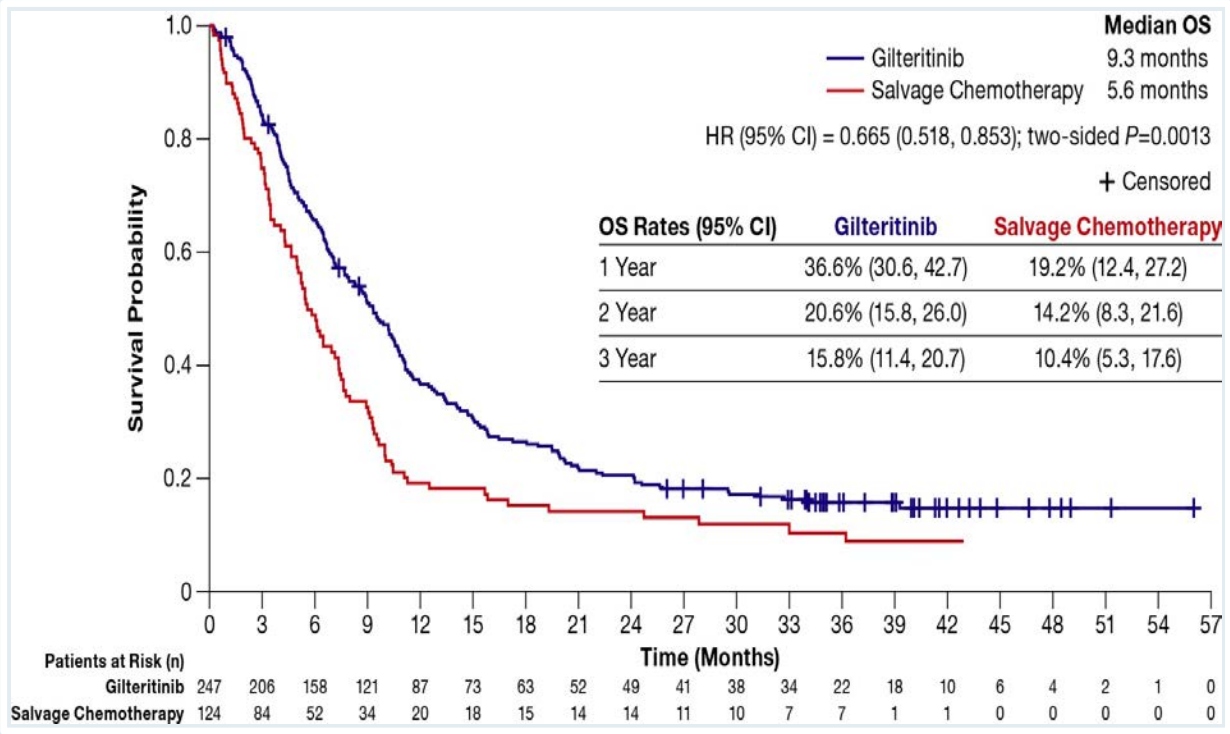
Follow-Up of Patients with *FLT3*-Mutated R/R AML in the Phase 3 ADMIRAL Trial

Perl AE et al.

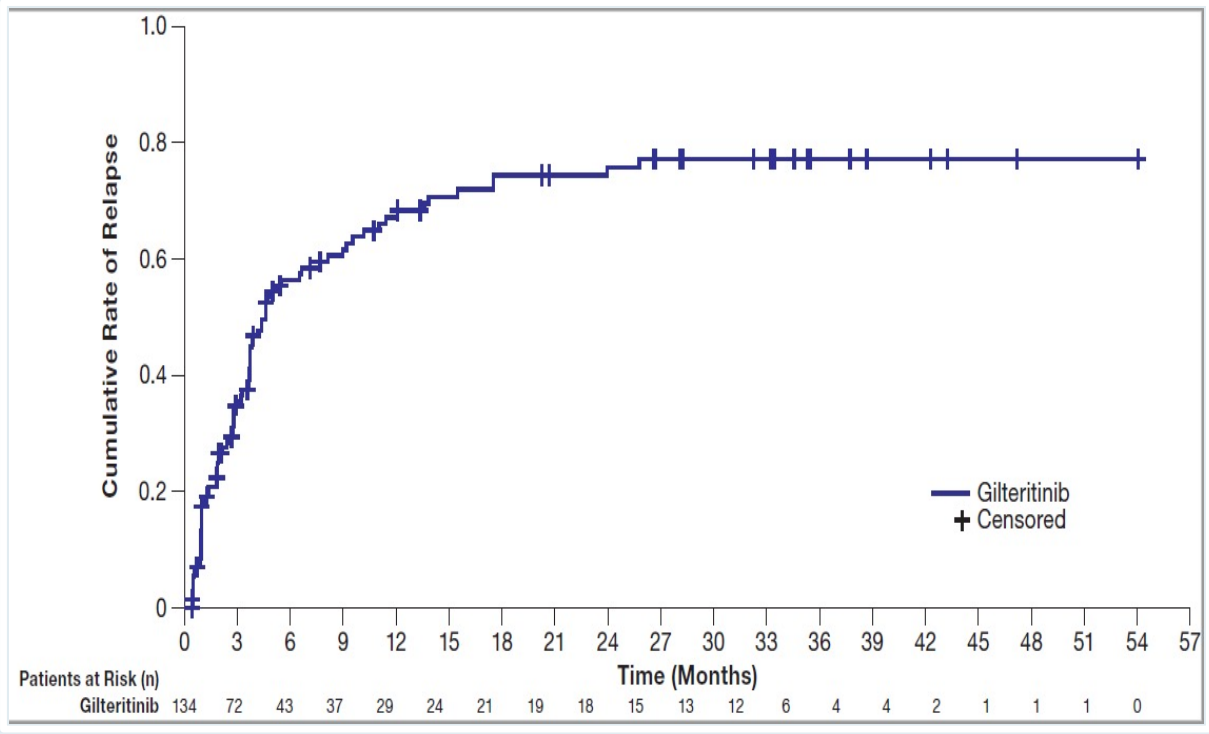
ASCO 2021;Abstract 7013.

ADMIRAL: Updated Overall Survival and Cumulative Relapse Rate

Overall Survival in R/R *FLT3*$^{mut+}$ AML Patients (ITT Population; N=371)



Cumulative Incidence of Relapse in Patients Achieving CRc With Gilteritinib



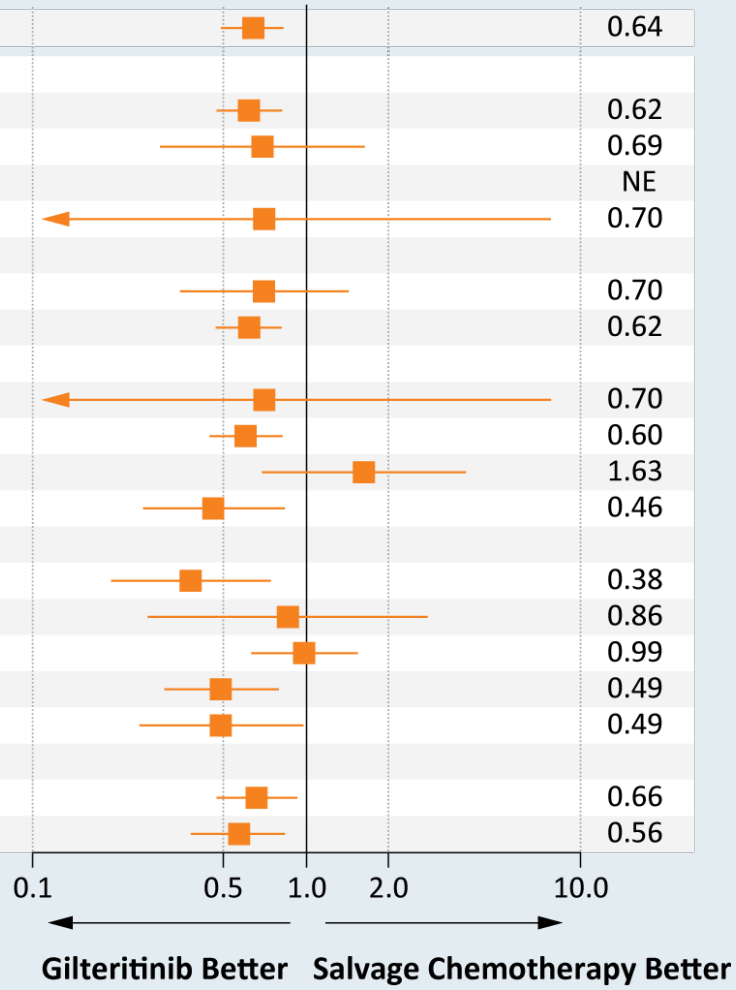
- With a median follow-up of 37.1 months, the median OS remained longer with gilteritinib than with salvage chemotherapy
- Most relapses after CRc occurred within 12 months and rarely occurred after 18 months

Perl AE et al. ASCO 2021;Abstract 7013.

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



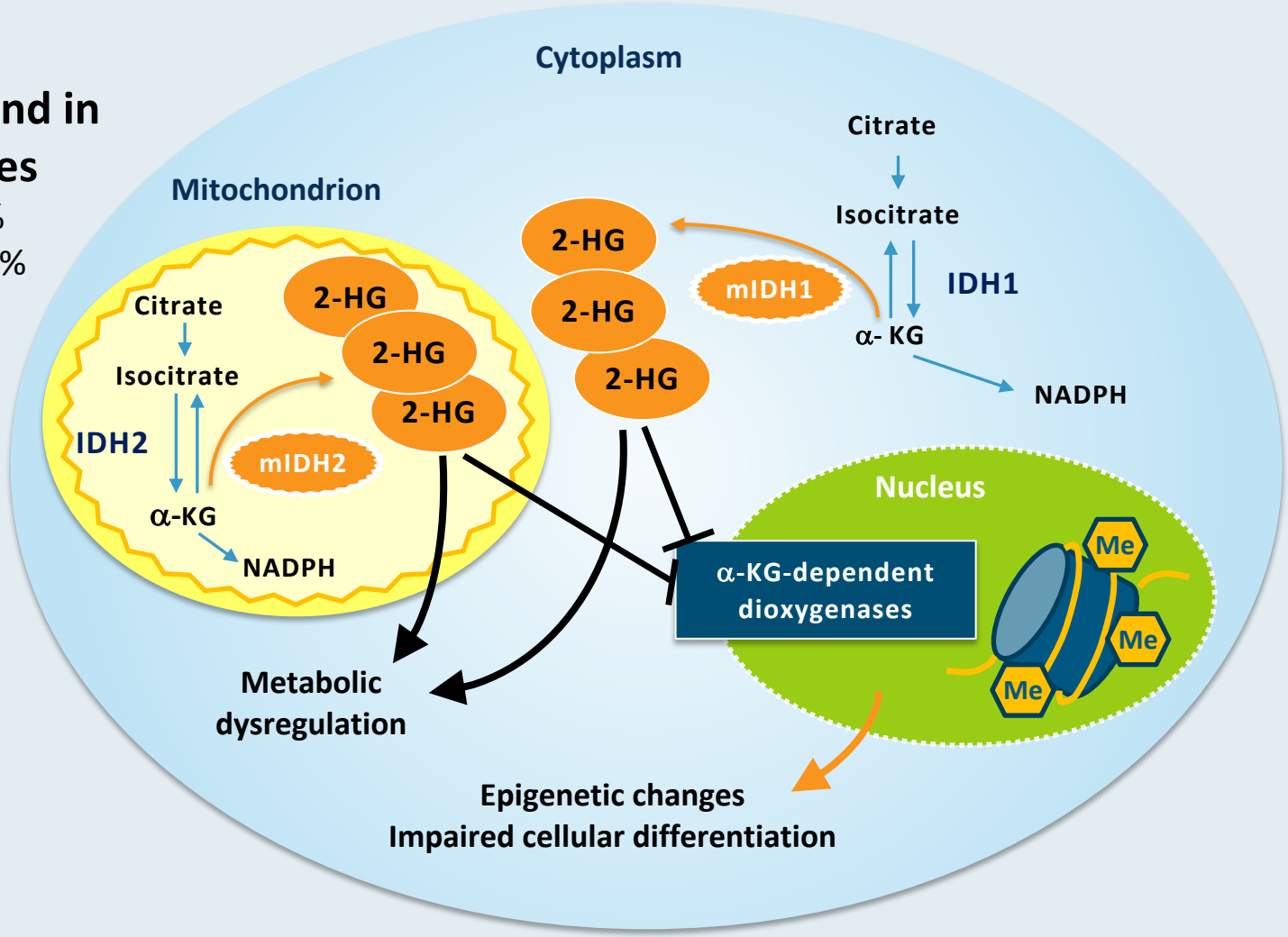
Perl AE et al. *N Engl J Med* 2019;381:1728-40.

RTP RESEARCH TO PRACTICE

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

ASH 2021; Abstract 697

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

Pau Montesinos,[1a] Christian Recher,[2a] Susana Vives,[3] Ewa Zarzycka,[4] Jianxiang Wang,[5] Giambattista Bertani,[6] Michael Heuser,[7] Rodrigo T Calado,[8] Andre C Schuh,[9] Su-Peng Yeh,[10] Scott R Daigle,[11] Jianan Hui,[11] Vickie Zhang,[11] Shuchi S Pandya,[11] Diego A Gianolio,[11] Stephane de Botton,[12b] Hartmut Döhner[13b]

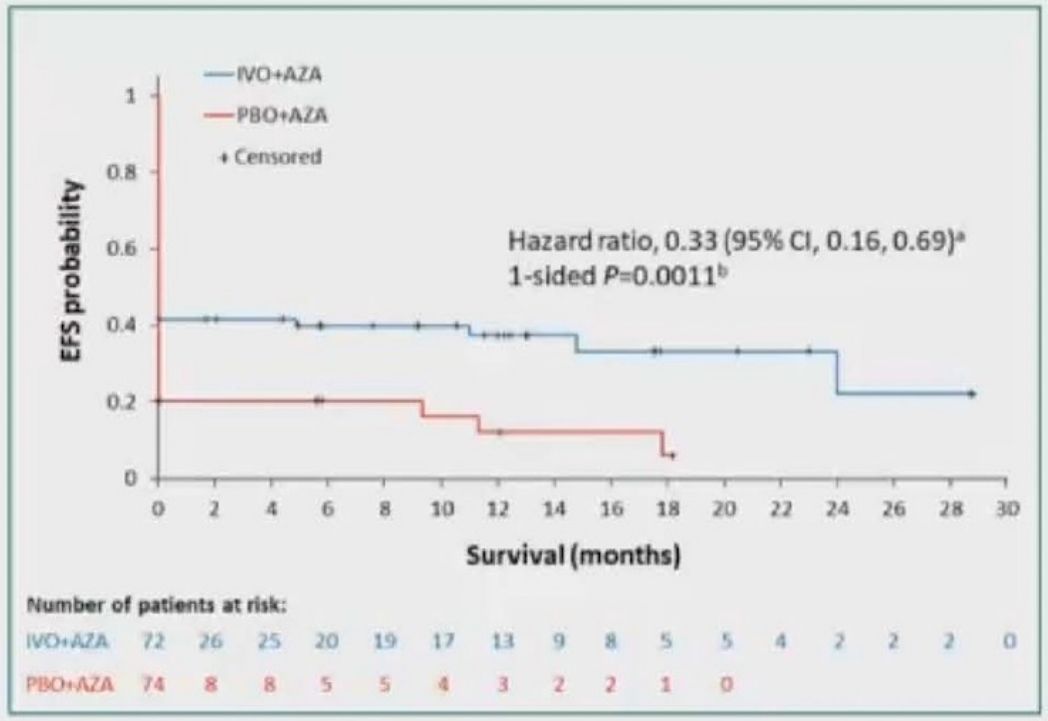
[1]Hospital Universitari i Politècnic La Fe, Valencia, Spain; [2]Institut Universitaire du Cancer de Toulouse Oncopole, CHU de Toulouse, Toulouse, France; [3]Hospital Universitario Germans Trias i Pujol-ICO Badalona, Josep Carreras Research Institute, Universitat Autònoma de Barcelona, Badalona, Spain; [4]Klinika Hematologii i Transplantologii, Uniwersyteckie Centrum Kliniczne, Gdansk, Poland; [5]Institute of Hematology & Hospital of Blood Disease – Peking Union Medical College, Tianjin, China; [6]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [7]Hannover Medical School, Hannover, Germany; [8]Ribeirão Preto School of Medicine, University of São Paulo, São Paulo, Brazil; [9]Princess Margaret Cancer Centre, Toronto, ON, Canada; [10]China Medical University, Taichung, Taiwan; [11]Servier Pharmaceuticals, Boston, MA, USA; [12]Institut Gustave Roussy, Villejuif, France; [13]Ulm University Hospital, Ulm, Germany

[a]Co-first authors; [b]Co-senior authors

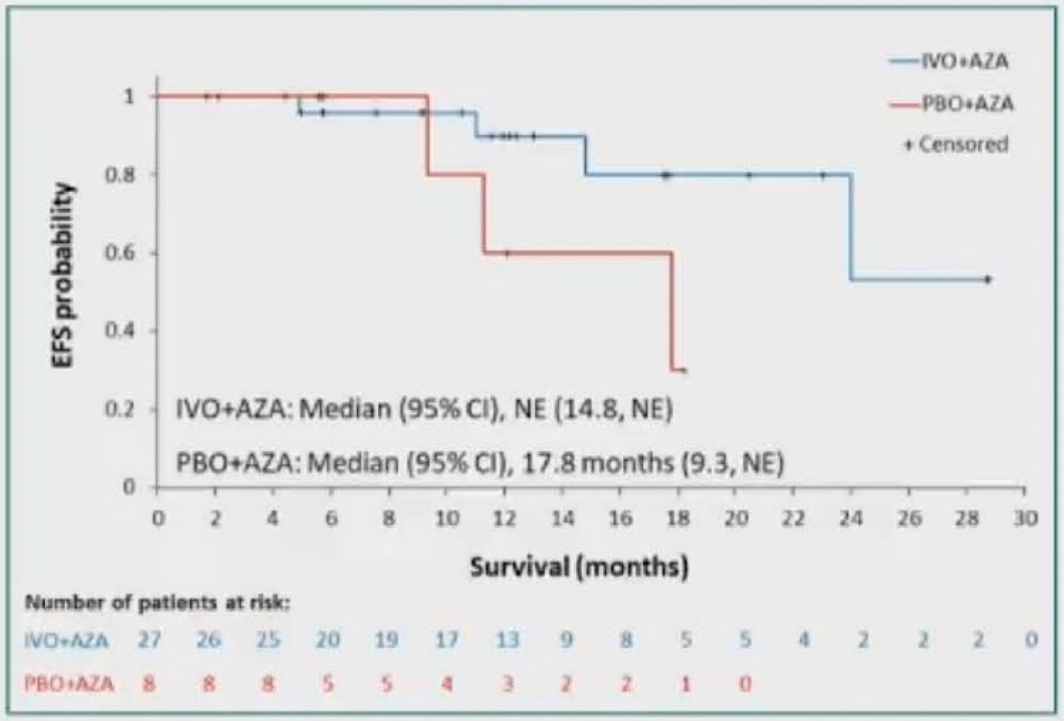
Presented at the 63rd American Society of Hematology (ASH) Annual Meeting, December 11–14, 2021, Atlanta, GA, USA (Hybrid)

AGILE: Event-Free Survival

EFS in the intent-to-treat population



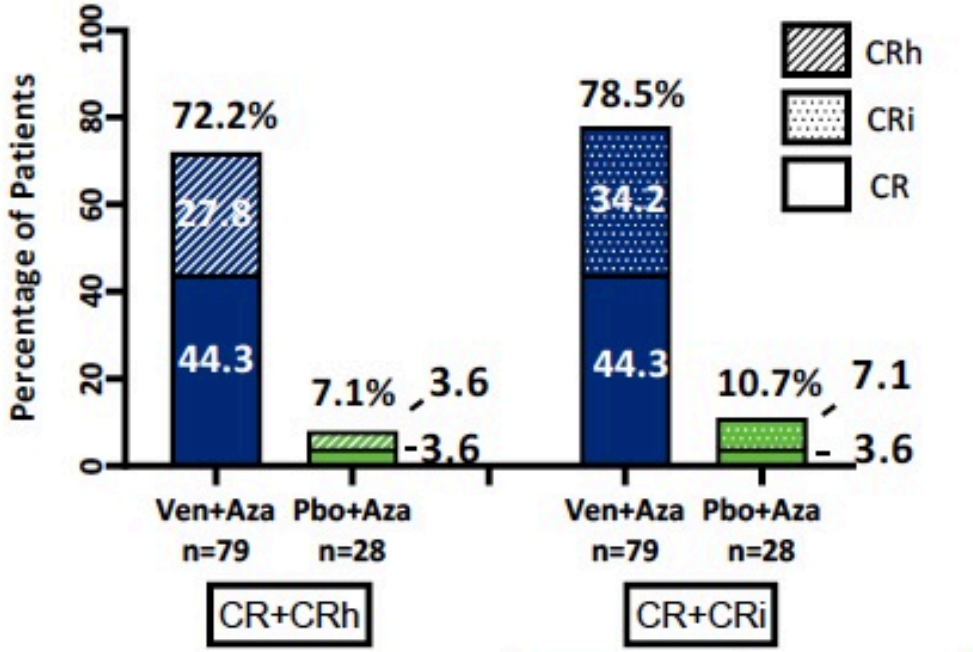
EFS among patients who achieved CR by 24 weeks



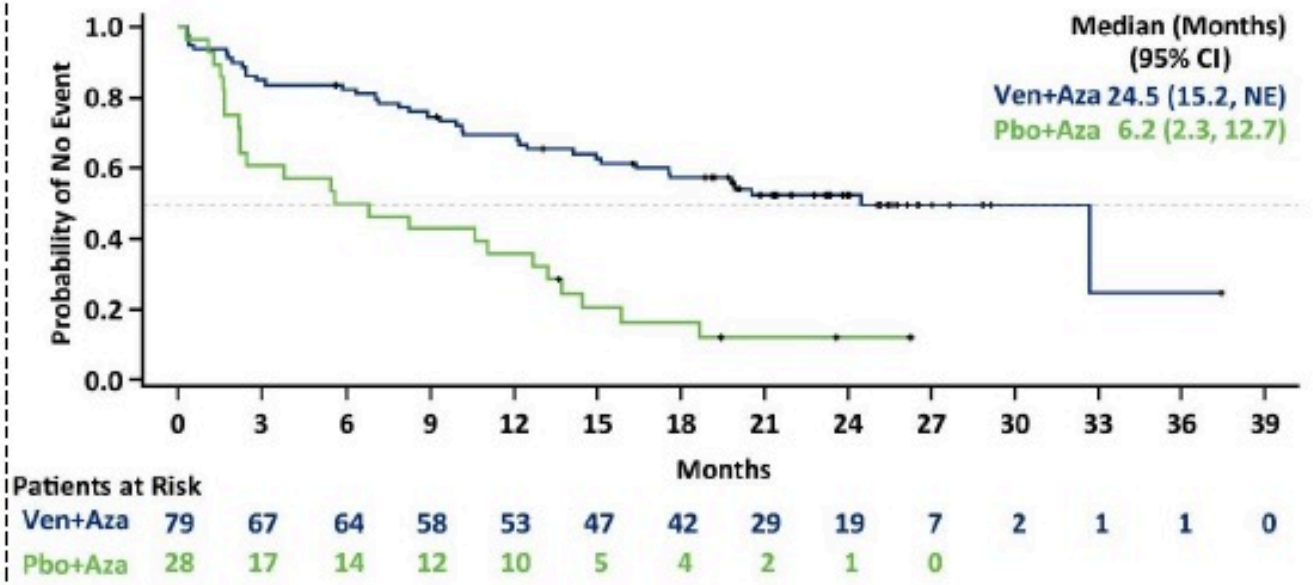
- Patients who did not achieve CR by week 24 were considered to have had an event at day 1 of randomization.
- EFS benefit was consistent across subgroups: de novo status, region, age, baseline ECOG PS score, sex, race, baseline cytogenetic risk status, WHO classification of AML, baseline white blood cell count, baseline percentage of bone marrow blasts.

Montesinos P et al. ASH 2021;Abstract 697.

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
Ven+Aza	82.3 (71.9, 89.1)	69.3 (57.8, 78.3)	52.4 (40.4, 63.1)
Pbo+Aza	50.0 (30.6, 66.6)	35.7 (18.9, 53.0)	12.2 (3.2, 27.8)

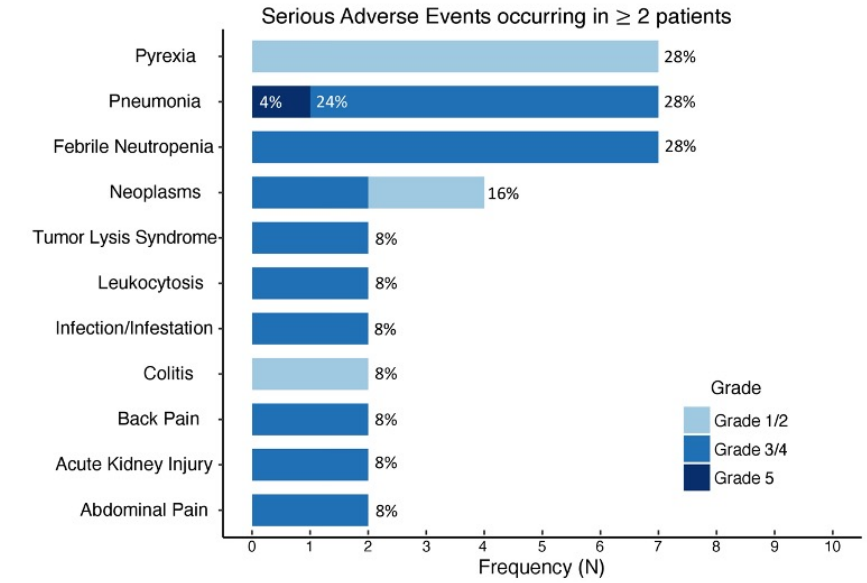
Pratz K et al. ASH 2020;Abstract 1944.

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

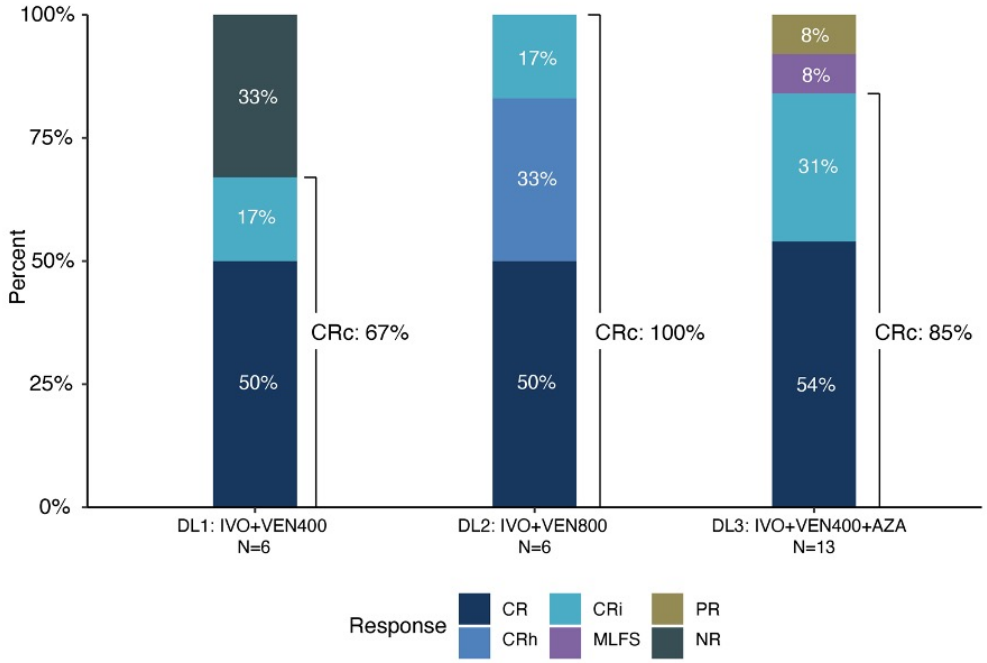
Safety



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)

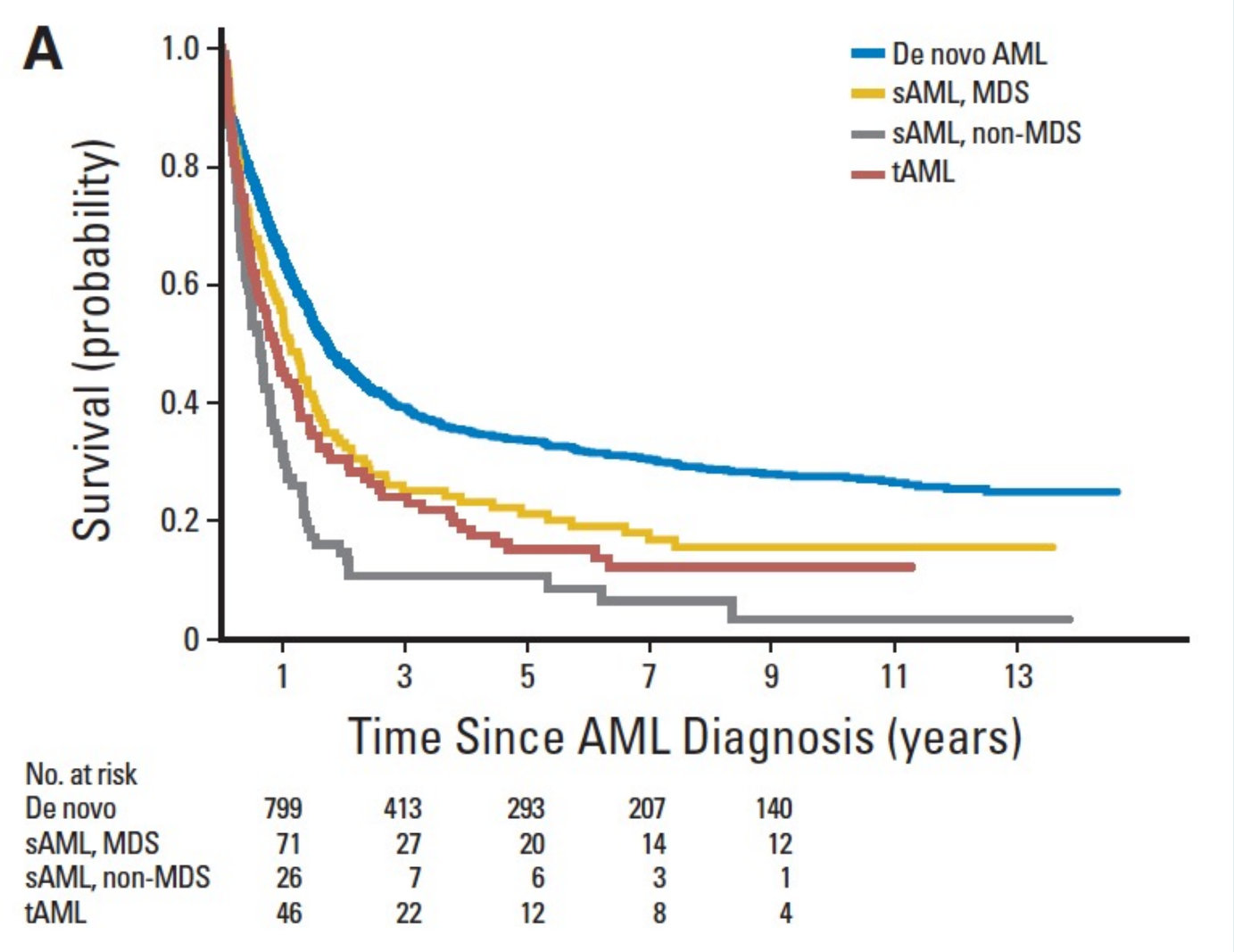
- **Potentially fatal complication of effective leukemia treatment**
  - First described in patients with APL treated with ATRA
- **Signs and symptoms of IDH-DS not specific**
  - Fever, edema, weight gain, leukocytosis, rash, hypotension, renal dysfunction, and pleural and pericardial effusions
  - 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)

RTP
RESEARCH
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)*

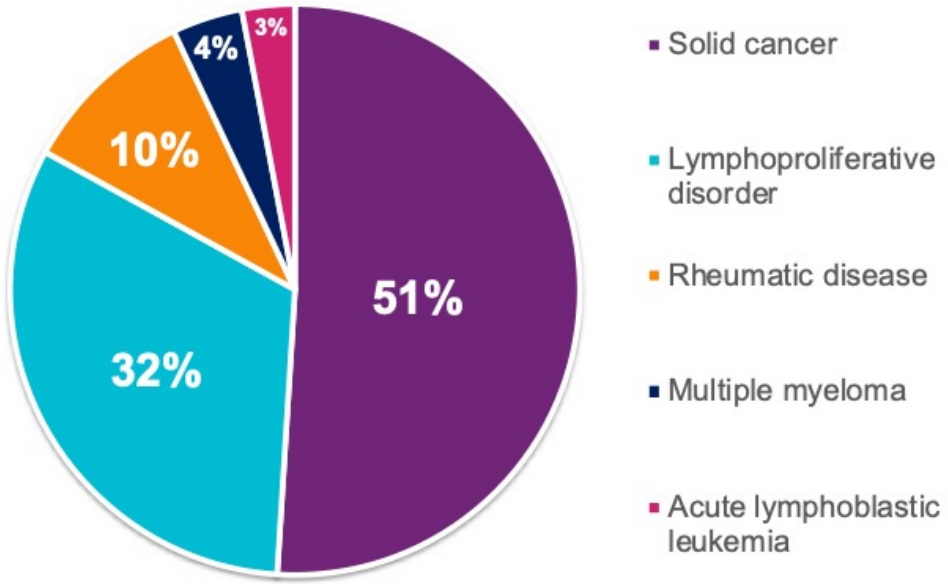
Footnote 1. The presence of 50% or more dysplastic cells in at least 2 cell lines, ***excluding cases when a mutation of NPM1 or biallelic mutation of CEBPA is present.***

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



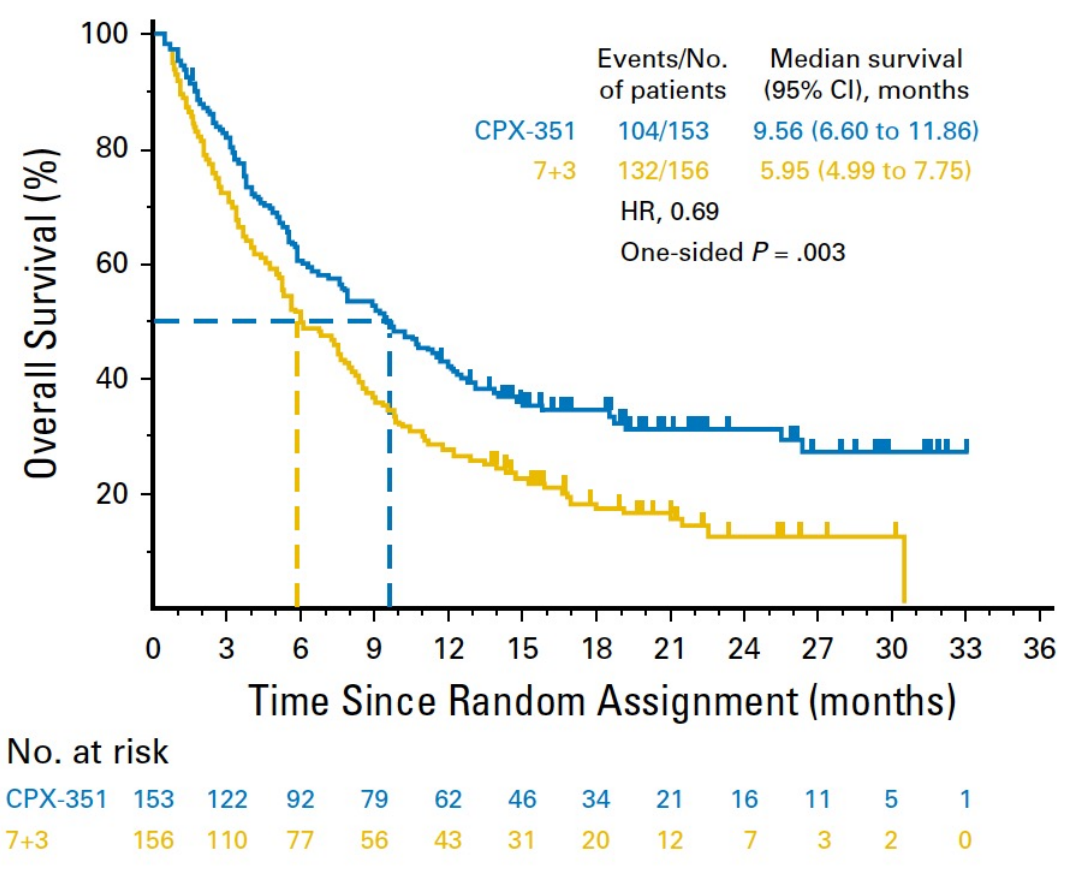
Cytotoxic therapy[a]	MOA	Examples	Latency period
Alkylating agents and radiation	Induce chromosomal deletions, commonly in 5 and/or 7	Cyclophosphamide, mechlorethamine, procarbazine, chlorambucil, melphalan, carmustine, busulfan	5-10 years
Topoisomerase II inhibitors	Induce chromosomal translocations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

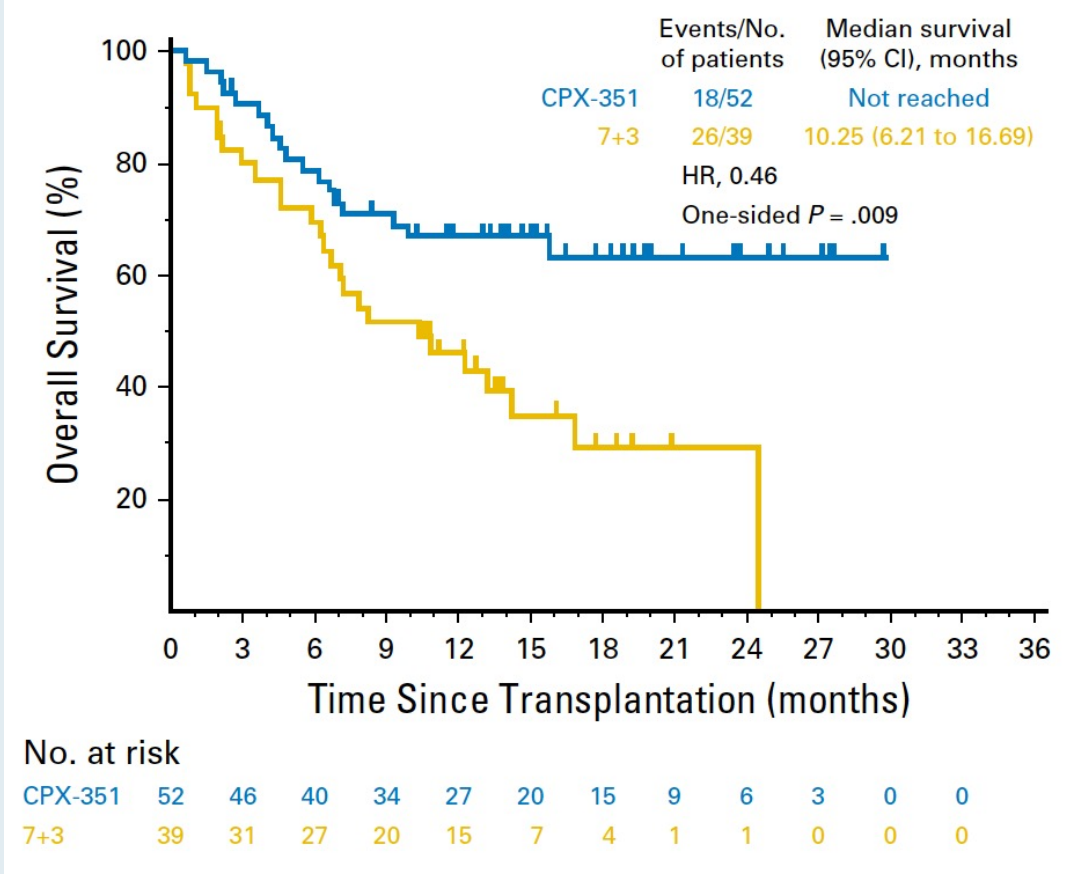
Courtesy of Eunice S Wang, MD.

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



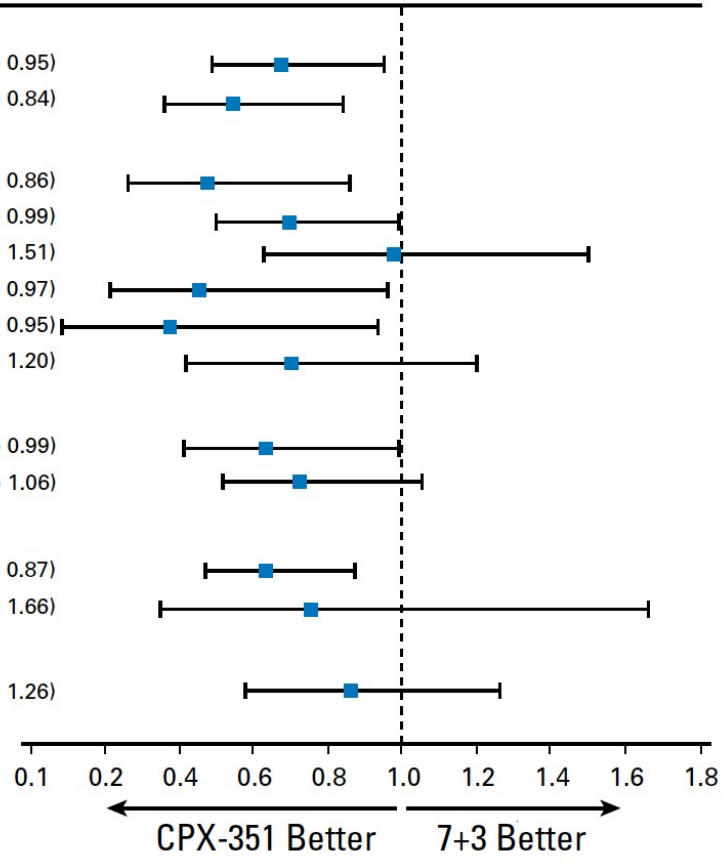
Lancet JE et al. *J Clin Oncol* 2018;36(26):2684-92.

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

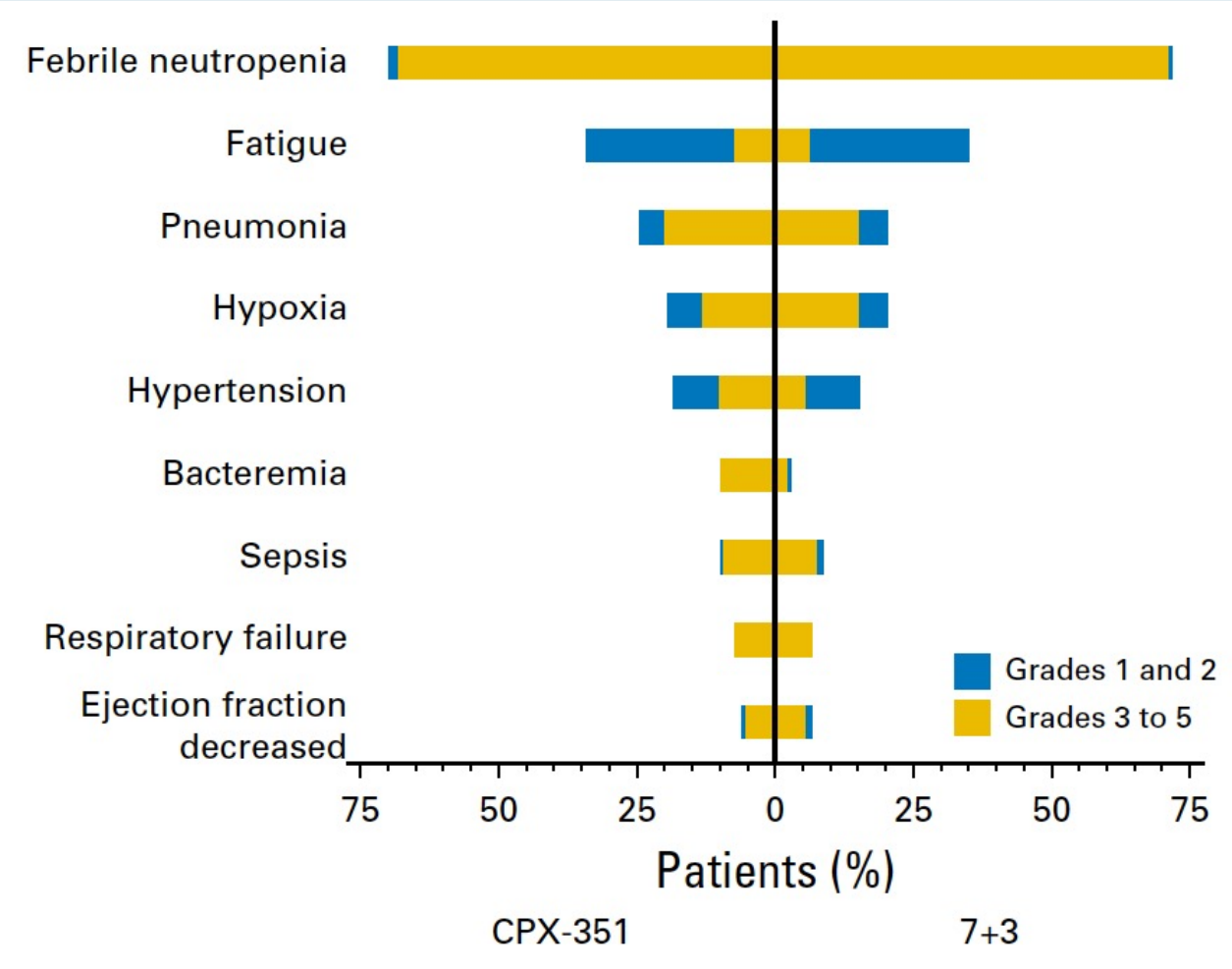
B

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.

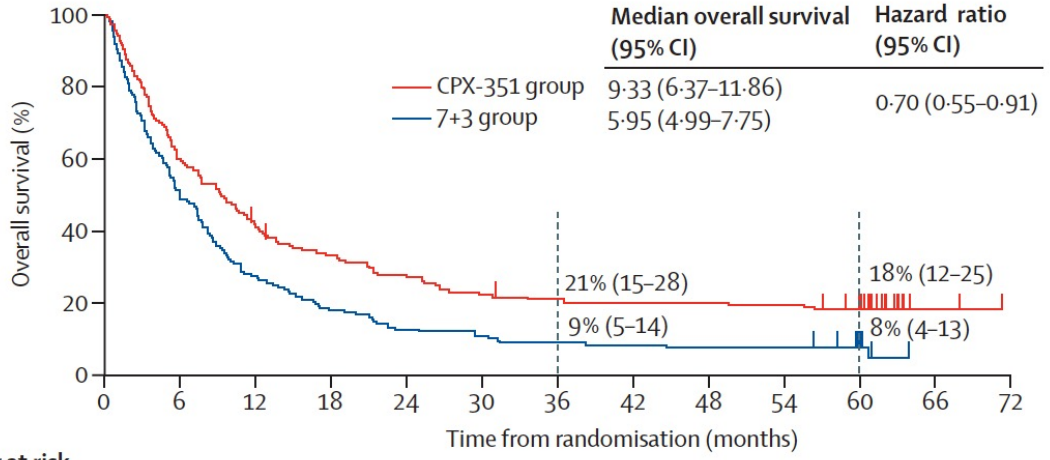
Phase III Trial of CPX-351 versus 7 + 3 Cytarabine and Daunorubicin for Older Patients with Newly Diagnosed High-Risk or Secondary AML: Most Frequently Reported Adverse Events



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

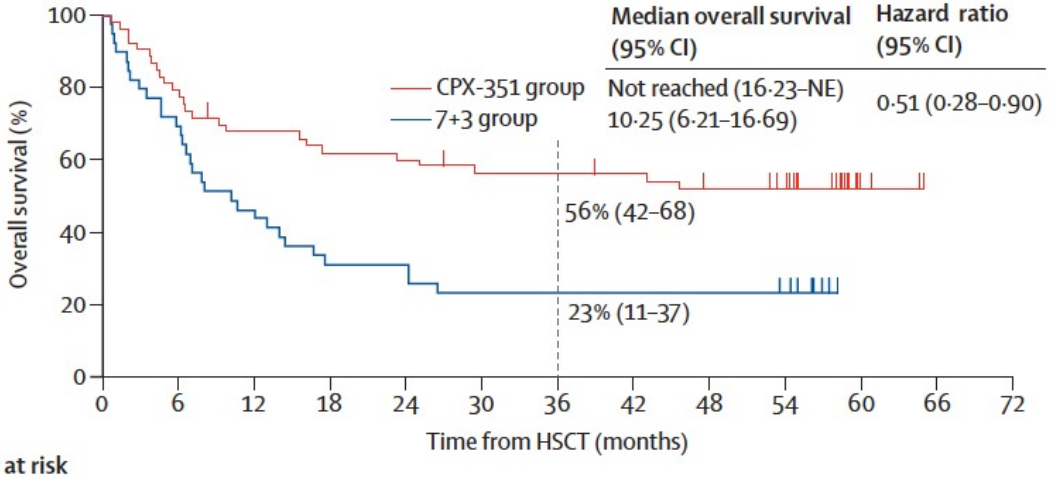
Phase III Trial of CPX-351 versus 7 + 3 Cytarabine and Daunorubicin for Older Patients with Newly Diagnosed High-Risk or Secondary AML: 5-Year Overall Survival Results

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.

RTP RESEARCH TO PRACTICE

The Great Adjuvant Debate — Exploring the Role of Novel Therapies in the Management of Localized Cancer

Monday, February 28, 2022

5:00 PM – 6:00 PM ET

Faculty

Jeffrey S Weber, MD, PhD
Roy S Herbst, MD, PhD
Sara M Tolaney, MD, MPH

Moderator

Neil Love, MD

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