Data + Perspectives: Clinical Investigators Discuss the Current and Future Management of Acute Myeloid Leukemia and Myelodysplastic Syndromes

A Virtual CME Satellite Symposium During the Society of Hematologic Oncology 2021 Annual Meeting

Wednesday, September 8, 2021
7:30 PM – 9:00 PM Central Time

Faculty

Courtney D DiNardo, MD, MSCE
Daniel A Pollyea, MD, MS
David Sallman, MD
Eunice S Wang, MD

Moderator

Neil Love, MD

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Faculty

Courtney D DiNardo, MD, MSCE
Associate Professor, Department of Leukemia
Division of Cancer Medicine
The University of Texas
MD Anderson Cancer Center
Houston, Texas

Daniel A Pollyea, MD, MS
Associate Professor of Medicine
Clinical Director of Leukemia Services
Robert H Allen, MD Chair in Hematology Research
Division of Hematology
University of Colorado School of Medicine
Aurora, Colorado

David Sallman, MD
Assistant Member
Malignant Hematology
Moffitt Cancer Center
Tampa, Florida

Eunice S Wang, MD
Chief, Leukemia Service
Professor of Oncology
Roswell Park Comprehensive Cancer Center
Buffalo, New York

Moderator

Neil Love, MD
Research To Practice
Miami, Florida

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Commercial Support

This activity is supported by educational grants from AbbVie Inc, Astellas, Bristol-Myers Squibb Company, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc and Jazz Pharmaceuticals Inc.

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Dr Love — Disclosures

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Dr DiNardo — Disclosures

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Dr Sallman — Disclosures

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Speakers Bureau	Bristol-Myers Squibb Company, Incyte Corporation

Dr Wang — Disclosures

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Speakers Bureau	Astellas, DAVA Oncology, Kura Oncology, Stemline Therapeutics Inc

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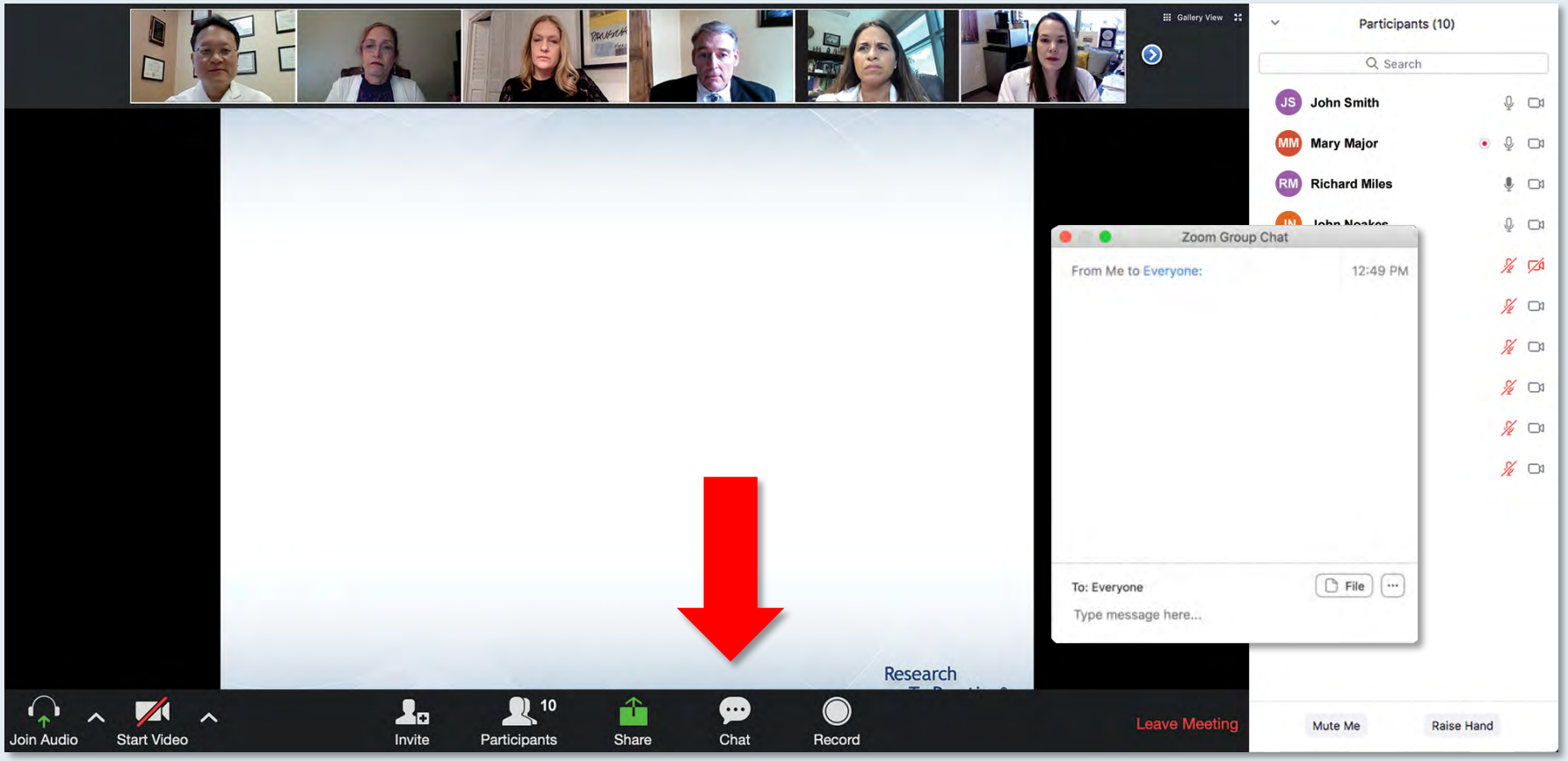
We Encourage Clinicians in Practice to Submit Questions



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

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Familiarizing Yourself with the Zoom Interface

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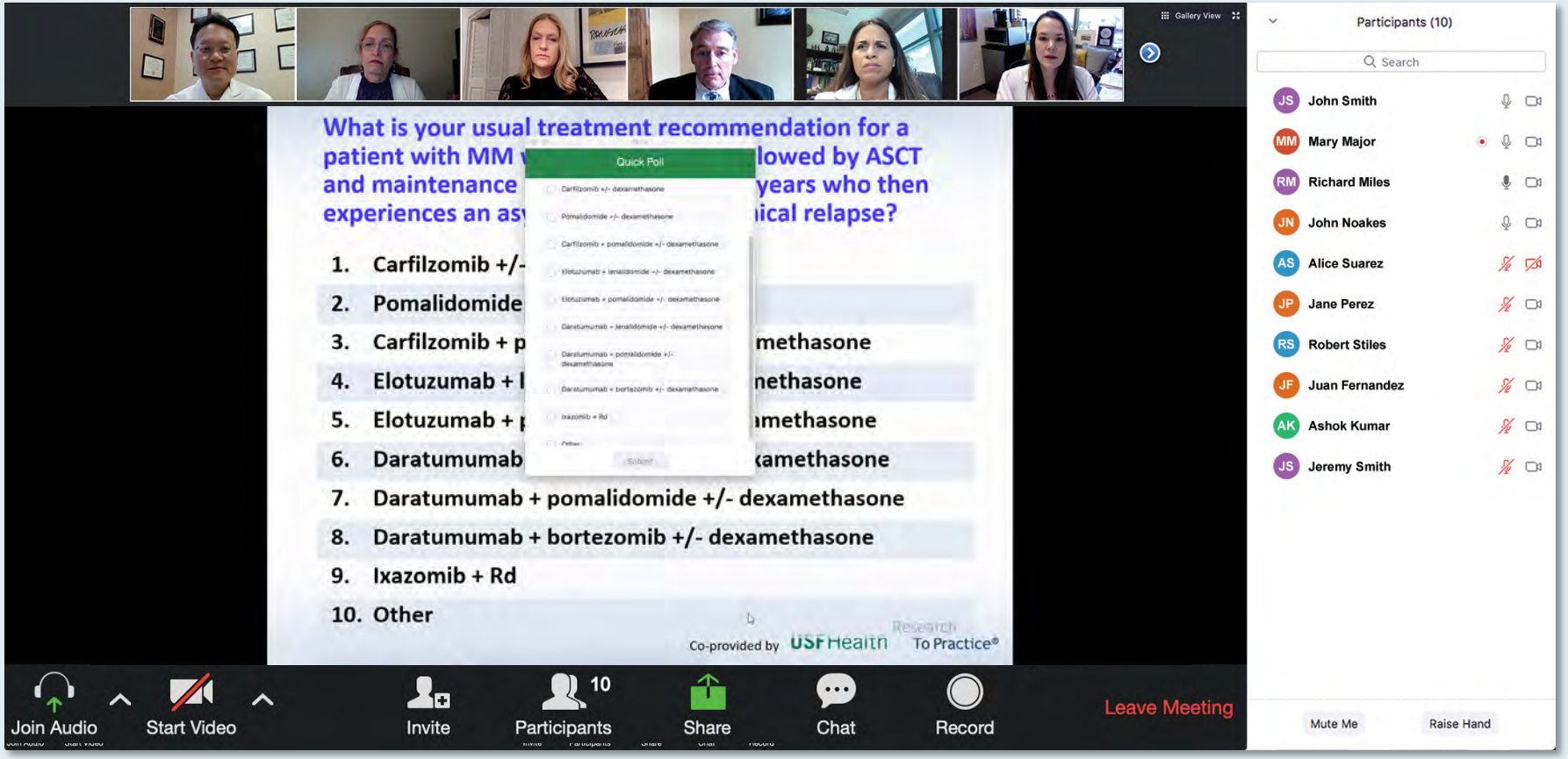

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Familiarizing Yourself with the Zoom Interface

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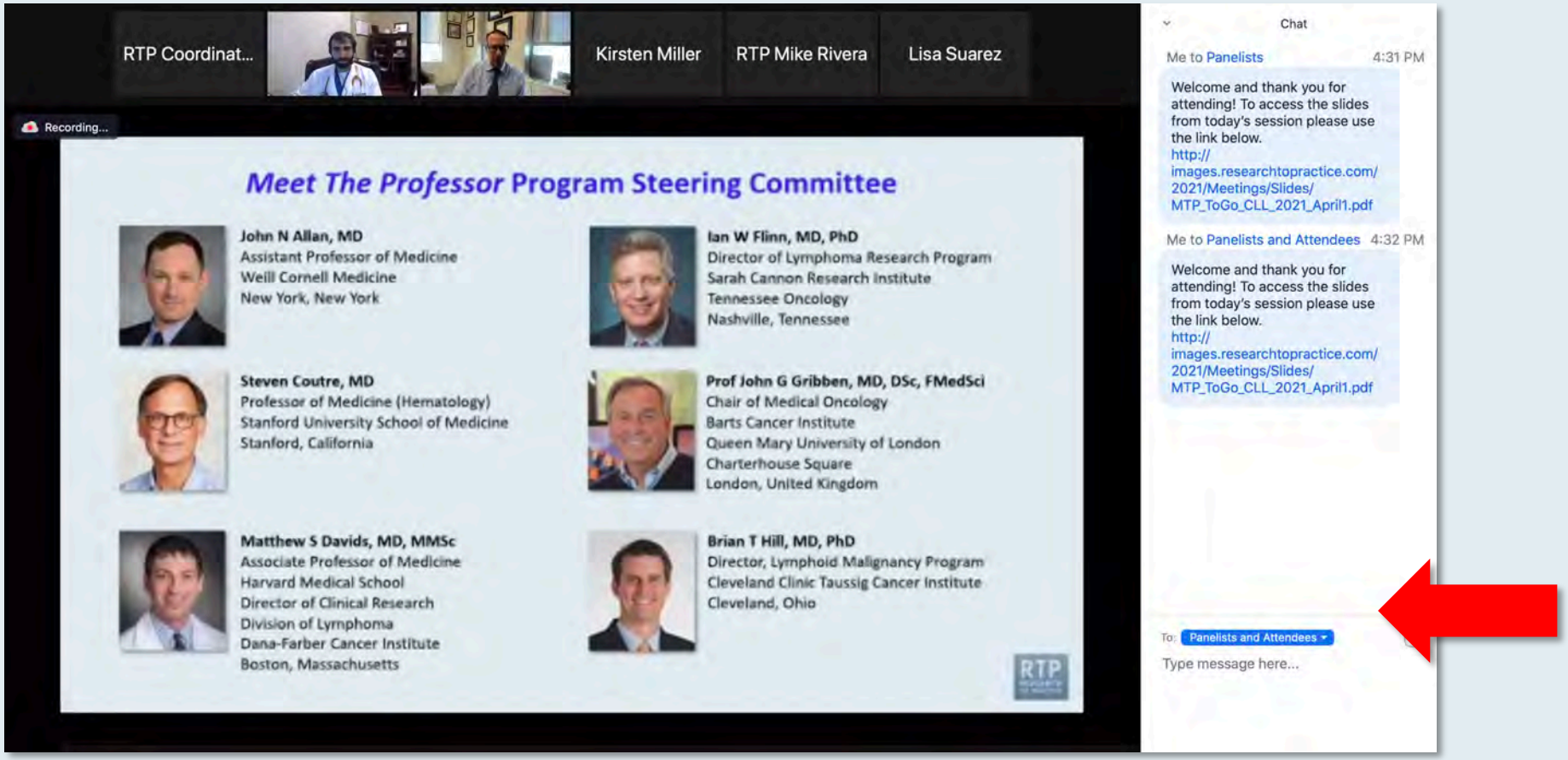

Drag the white line above the submission box up to create more space for your message.

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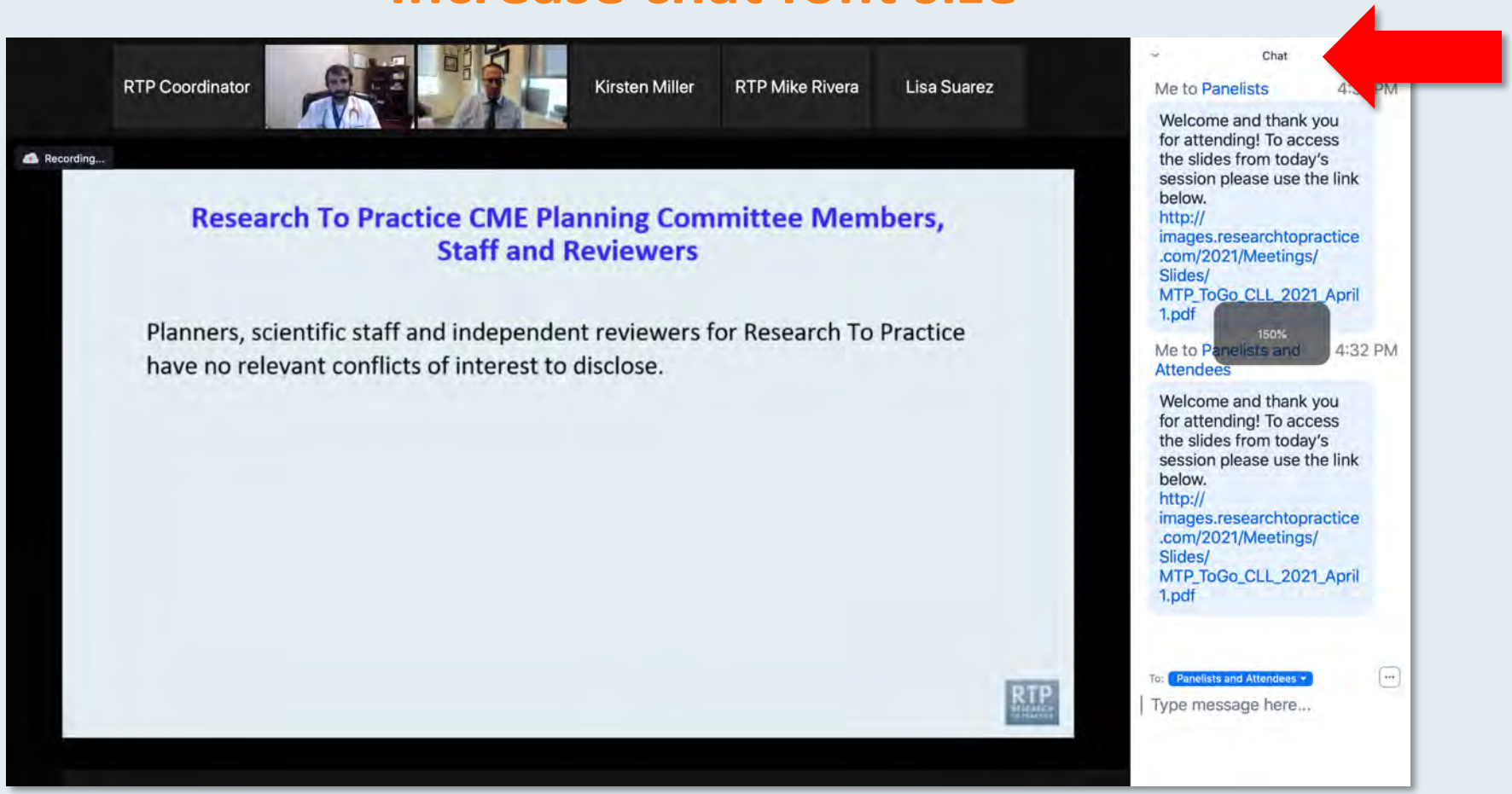
Increase chat font size



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

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WITH DR NEIL LOVE

Progress in Myelodysplastic Syndromes

DR GUILLERMO GARCIA-MANERO

MD ANDERSON CANCER CENTER

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Exploring Key Issues Affecting the Care of Patients with Metastatic Colorectal Cancer with BRAF Mutations

A CME/MOC-Accredited Virtual Event

Thursday, September 9, 2021
5:00 PM – 6:00 PM ET

Faculty
Scott Kopetz, MD, PhD

Consulting Clinical Investigator
Wells A Messersmith, MD

Moderator
Neil Love, MD

RTP RESEARCH TO PRACTICE

Expert Second Opinion: Investigators Discuss Available Clinical Research in the Care of Patients with Non-Small Cell Lung Cancer and Validated Targets Beyond EGFR

A Live Webinar Held as a Satellite CME/MOC Symposium During the IASLC 2021 World Conference on Lung Cancer Worldwide Virtual Event

Friday, September 10, 2021
5:45 AM – 6:45 AM MDT / 7:45 AM – 8:45 AM ET

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Alexander E Drilon, MD
Justin F Gainor, MD

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Sunday, September 12, 2021
9:15 PM – 10:15 PM MDT / 11:15 PM – 12:15 AM ET

Faculty

Edward B Garon, MD, MS
Harvey I Pass, MD
Heather Wakelee, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

What Urologists Want To Know: Addressing Current Questions and Controversies in the Management of Bladder Cancer

A Virtual CME Satellite Symposium During the American Urological Association (AUA) 2021 Annual Meeting

Monday, September 13, 2021
11:00 AM – 12:30 PM ET / 8:00 AM – 9:30 AM PT

Faculty

Arjun Balar, MD
Ashish M Kamat, MD, MBBS
Guru Sonpavde, MD
Robert Svatek, MD

Moderator

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Maha Hussain, MD, FACP, FASCO
A Oliver Sartor, MD
Neal D Shore, MD

Moderator

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RTP RESEARCH TO PRACTICE

Meet The Professor

Optimizing the Clinical Management of Hodgkin and Non-Hodgkin Lymphomas

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

Faculty

Loretta J Nastoupil, MD

Moderator

Neil Love, MD

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

Friday, September 17, 2021
12:00 PM – 1:00 PM ET

Faculty

Philip A Philip, MD, PhD, FRCP

Moderator

Neil Love, MD

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RESEARCH TO PRACTICE

Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with HER2-Positive Breast Cancer

Wednesday, September 22, 2021
5:00 PM – 6:00 PM ET

Faculty

Sara M Tolaney, MD, MPH

Moderator

Neil Love, MD

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Thank you for joining us!

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

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Robert H Allen, MD Chair in Hematology Research
Division of Hematology
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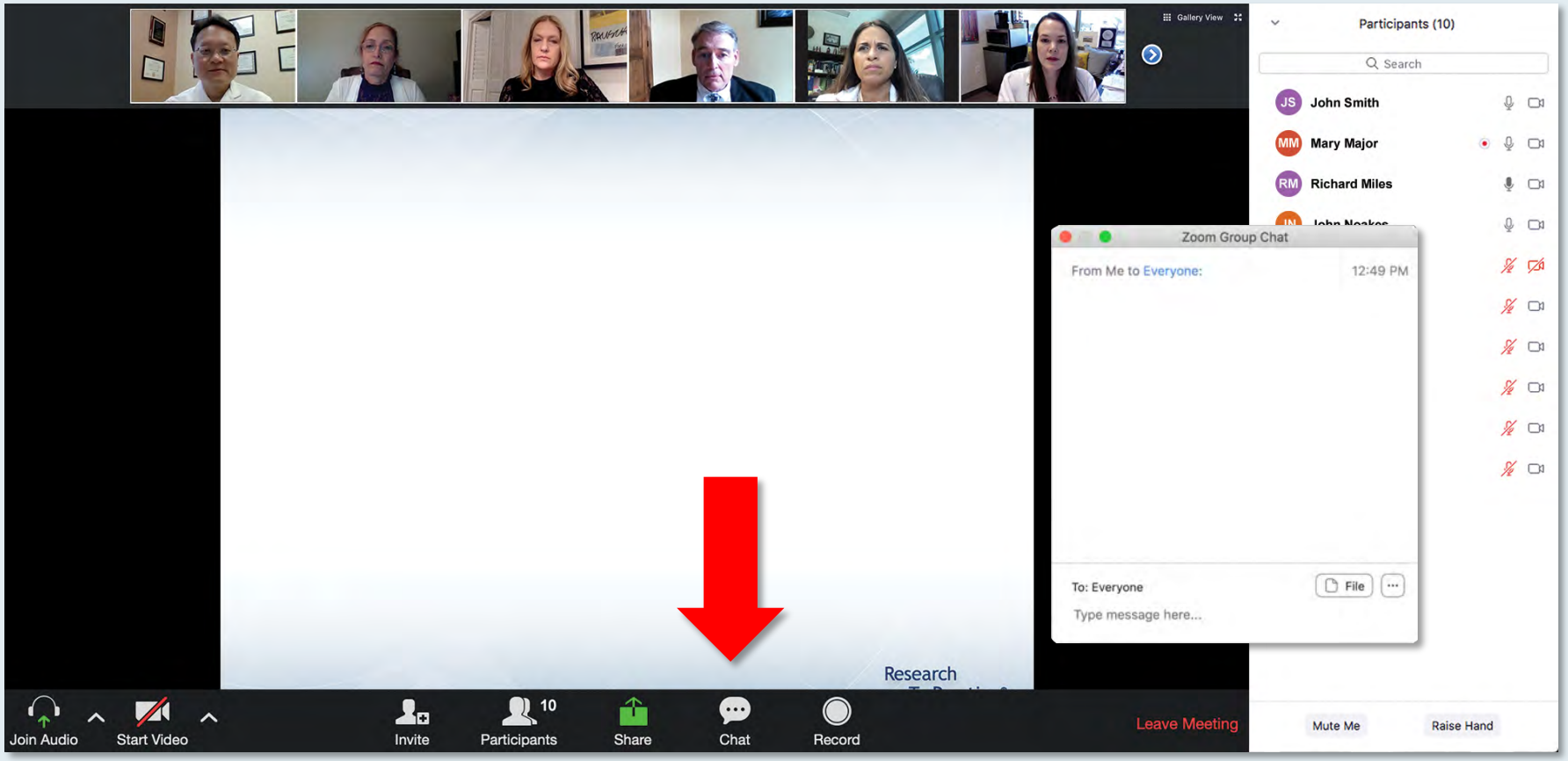

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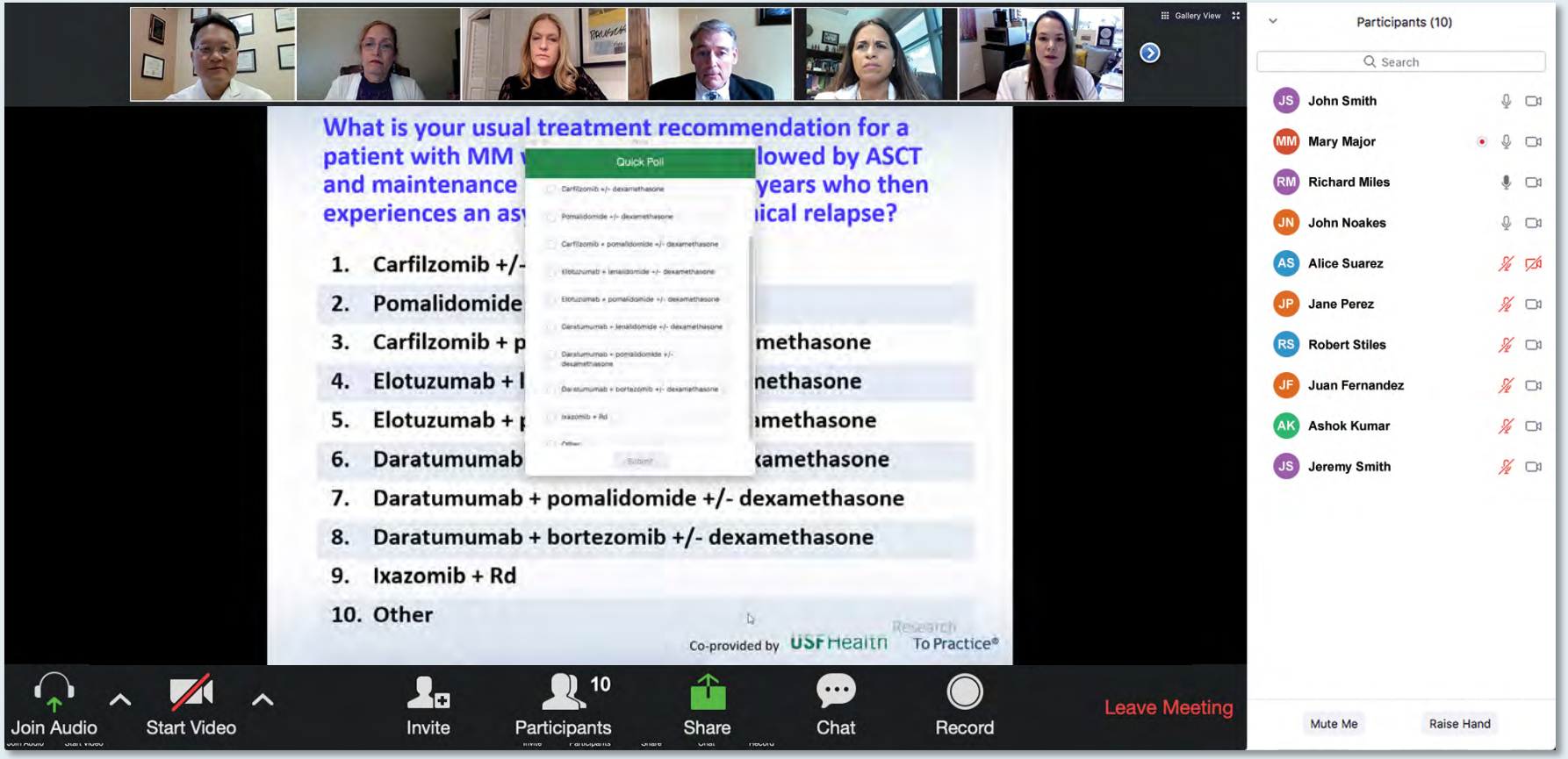

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Agenda

Prologue: A Personal Reflection on Acute Myeloid Leukemia (AML)

Module 1: Up-Front Treatment of AML in Patients Who Are Not Eligible for Intensive Therapy

Module 2: Management of AML with Targetable Mutations

Module 3: Other Currently Available and Investigational Treatment Strategies for AML

Module 4: Management of Myelodysplastic Syndromes

Agenda

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Module 3: Other Currently Available and Investigational Treatment Strategies for AML

Module 4: Management of Myelodysplastic Syndromes

At what point in your oncology career were you in December 2014?

1. Clinical practice
2. Residency or fellowship
3. Medical school
4. College
5. High school
6. Before high school
7. Other

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A Personal Reflection on AML

PLENARY SCIENTIFIC SESSION | DECEMBER 6, 2014

Sorafenib Versus Placebo in Addition to Standard Therapy in Younger Patients with Newly Diagnosed Acute Myeloid Leukemia: Results from 267 Patients Treated in the Randomized Placebo-Controlled SAL-Soraml Trial

Christoph Röllig, MD, Carsten Müller-Tidow, MD, Andreas Hüttmann, MD, Richard Noppeney, MD, Volker Kunzmann, MD, Claudia D Baldus, MD, Christian H. Brandts, MD, Alwin Krämer, MD, Kerstin Schäfer-Eckart, MD, Andreas Neubauer, MD, Stefan W. Krause, MD, Aristoteles Giagounidis, MD PhD, Walter E. Aulitzky, MD, Martin Bornhäuser, MD, Markus Schaich, MD, Stefani B Parmentier, MD, Christian Thiede, MD, Malte von Bonin, MD, Johannes Schetelig, MD M. Sc., Michael Kramer, PhD, Hubert Serve, MD, Wolfgang E Berdel, MD, Gerhard Ehninger, MD

Blood (2014) 124 (21): 6.

https://doi.org/10.1182/blood.V124.21.6.6

The NEW ENGLAND JOURNAL of MEDICINE

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

Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia

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

Case Presentation – Dr Pollyea: An 84-year-old woman with newly diagnosed AML

- 84 YO F with history of COPD, PE, aortic aneurysm, breast cancer with new diagnosis of AML
  - 46,XX,inv(16)(p13.1q22)[1]/48,sl,+8,+22[15]/47,sl,+add(8)(q22)[4]
  - Mutations in TET2 and PTPN11

Case Presentation – Dr Pollyea: An 84-year-old woman with newly diagnosed AML (continued)

Not a candidate for intensive induction chemotherapy despite having CBF

- Used venetoclax + azacitidine
- Achieved a CR
- Continued therapy in remission
- Patient died of recurrent breast cancer 18 months later, in an ongoing AML remission

Agenda

Prologue: A Personal Reflection on Acute Myeloid Leukemia (AML)

Module 1: Up-Front Treatment of AML in Patients Who Are Not Eligible for Intensive Therapy

Module 2: Management of AML with Targetable Mutations

Module 3: Other Currently Available and Investigational Treatment Strategies for AML

Module 4: Management of Myelodysplastic Syndromes

What initial treatment would you generally recommend for an 80-year-old patient with AML and intermediate-risk cytogenetics?

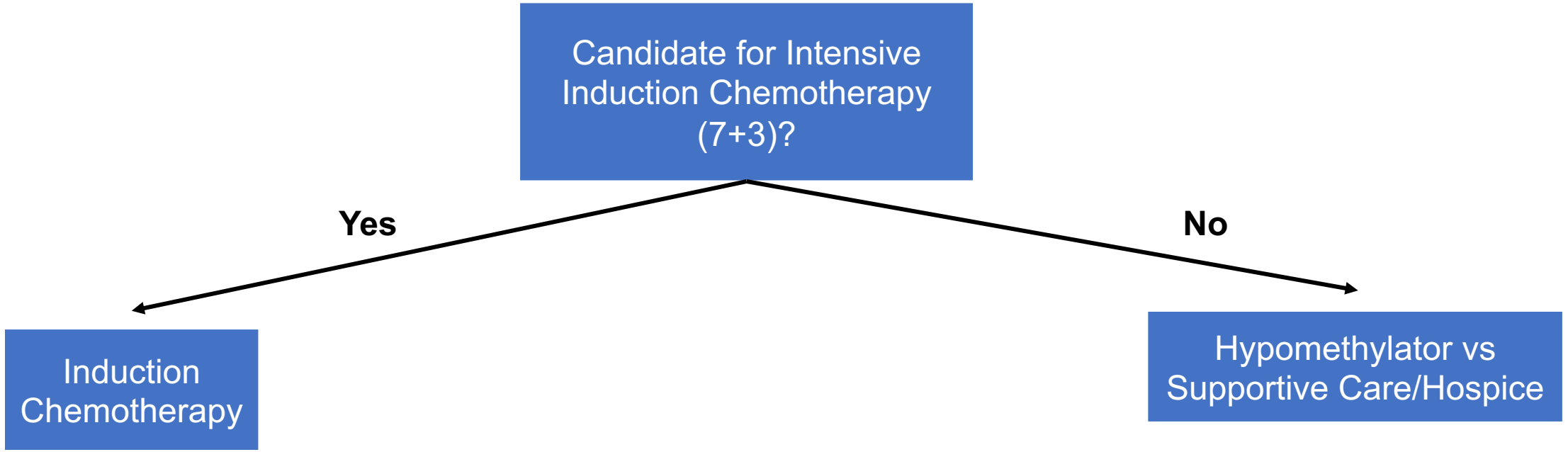
1. Azacitidine + venetoclax
2. CC-486 (oral azacitidine) + venetoclax
3. Decitabine + venetoclax
4. Decitabine/cedazuridine (oral decitabine) + venetoclax
5. Low-dose cytarabine + venetoclax
6. Low-dose cytarabine + glasdegib
7. Other

What initial treatment would you recommend for a 65-year-old man with AML with a PS of 1 and pancytopenia, 35% marrow myeloblasts, a complex karyotype and a TP53 mutation?

1. 7 + 3 induction
2. Azacitidine + venetoclax
3. CC-486 (oral azacitidine) + venetoclax
4. Decitabine + venetoclax
5. Decitabine/cedazuridine (oral decitabine) + venetoclax
6. Low-dose cytarabine + venetoclax
7. Other

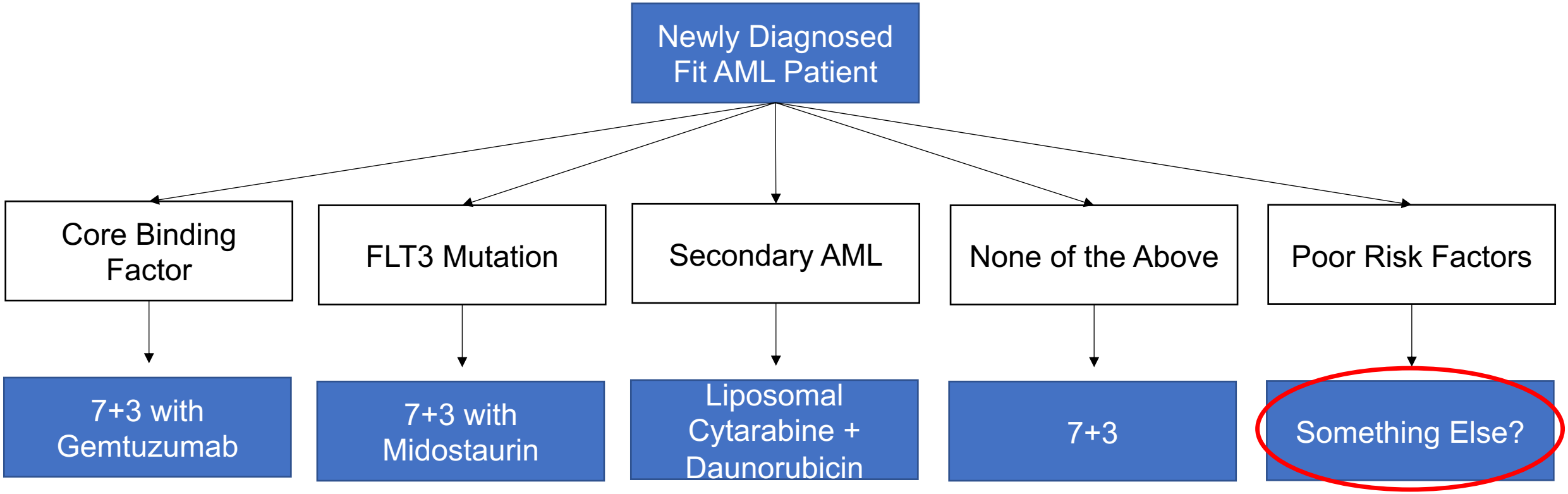
Flashback to March 2017

Binary treatment approach to newly diagnosed older AML patient



Courtesy of Daniel A Pollyea, MD, MS

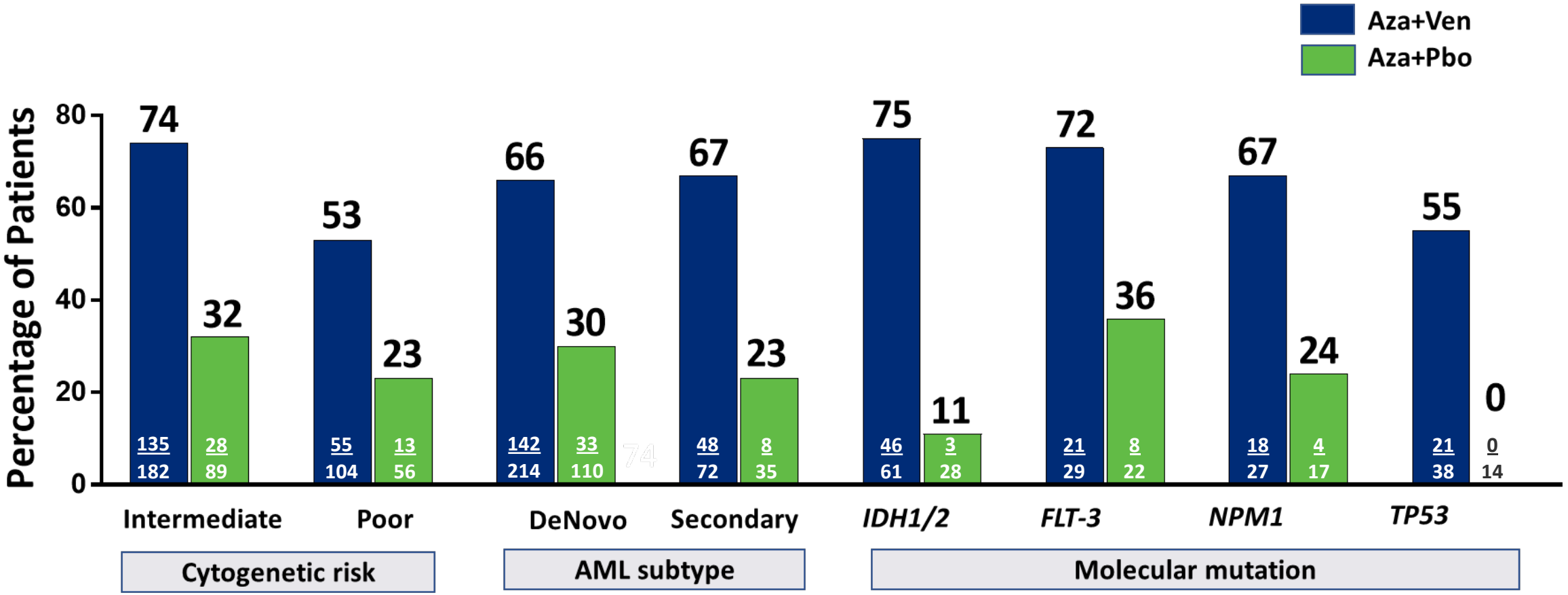
Current Treatment Landscape for Newly Diagnosed "Fit" AML Patients



Source: The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Acute Myeloid Leukemia (Version 3.2021). © 2021 National Comprehensive Cancer Network, Inc. Available at: NCCN.org.

Courtesy of Daniel A Pollyea, MD, MS

VIALE-A Study of Venetoclax + Azacitidine vs Azacitidine by Subset



DiNardo et al, EHA 2020

Courtesy of Daniel A Pollyea, MD, MS

Intensive Chemotherapy + Venetoclax in Newly Diagnosed AML

	Venetoclax and Cladribine+Idarubicin+ Cytarabine	Venetoclax and Fludarabine+Cytarabine+ Idarubicin
N	41	29
Overall Response Rate	95%	97%
Complete Response Rate	85%	69%

Kadia et al, Lancet Haematology 2021
DiNardo et al, JCO 2021

Courtesy of Daniel A Pollyea, MD, MS

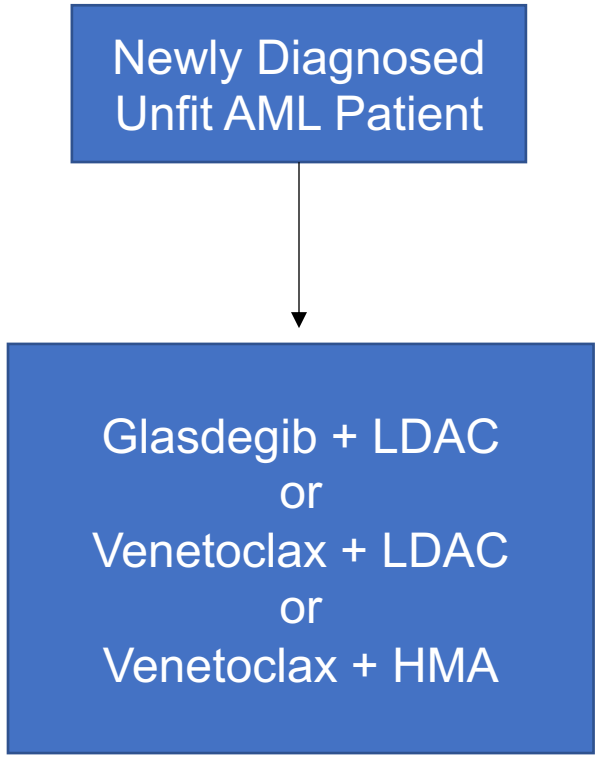
Ongoing or Planned Studies

- Venetoclax + Azacitidine for younger newly diagnosed AML patients who are candidates for induction and have adverse risk biology (NCT03573024)

- Randomized trial of induction chemotherapy vs venetoclax + HMA (coming soon)

Courtesy of Daniel A Pollyea, MD, MS

Current Treatment Landscape for Newly Diagnosed "Unfit" AML Patients Without Targetable Mutations

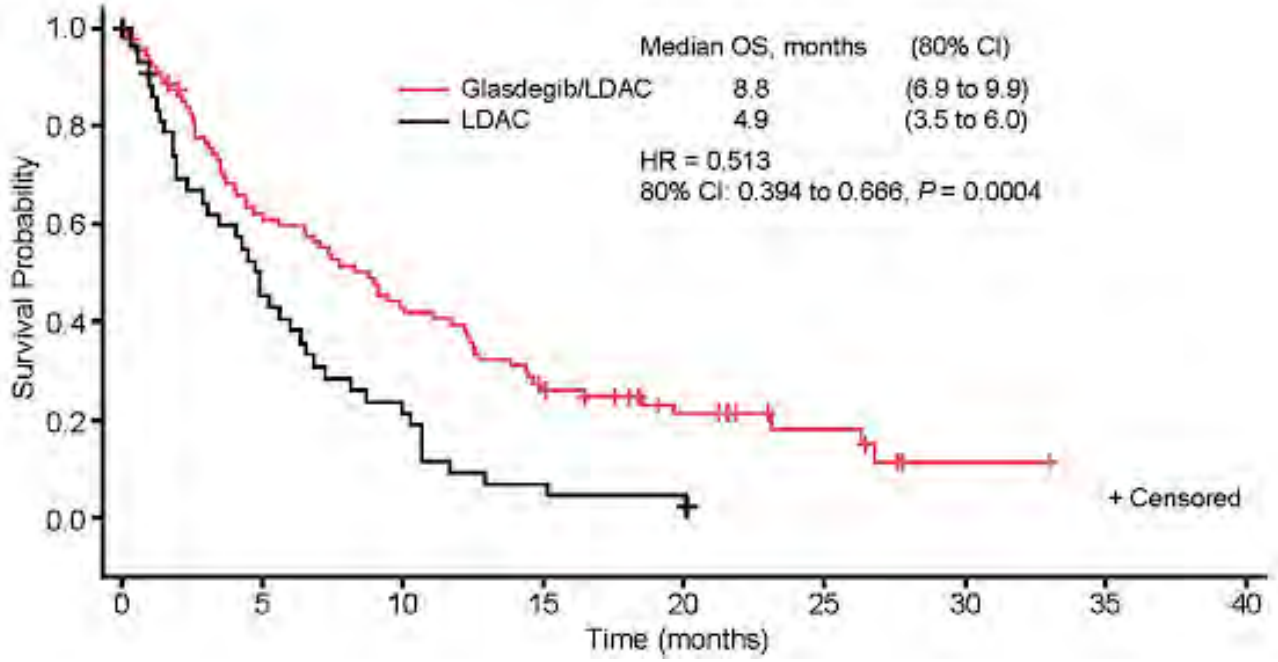


Source: The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Acute Myeloid Leukemia (Version 3.2021). © 2021 National Comprehensive Cancer Network, Inc. Available at: NCCN.org.

Courtesy of Daniel A Pollyea, MD, MS

Glasdegib + LDAC

	Glasdegib 100 mg + LDAC, $N = 88$	LDAC, $N = 44$
Patients with CR, *n* (%)	15 (17.0)	1 (2.3)
80% CI*	11.9–22.2	0.0–5.2

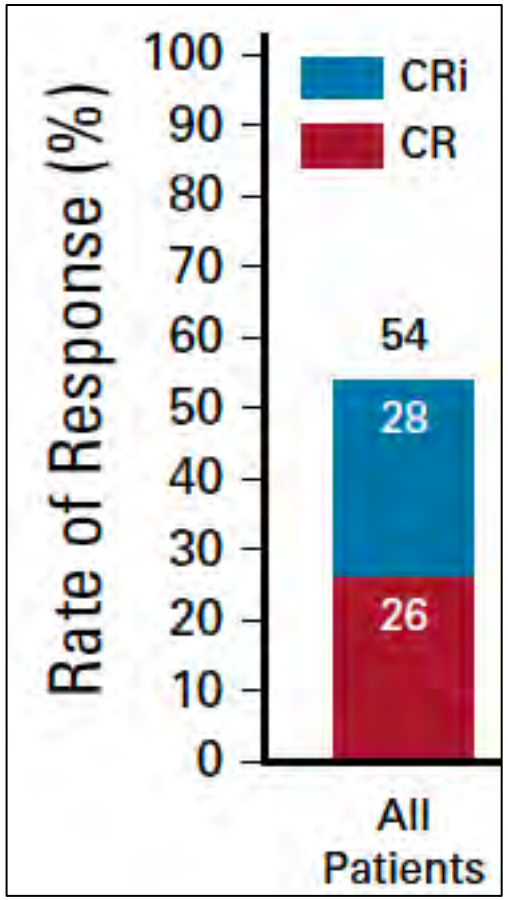


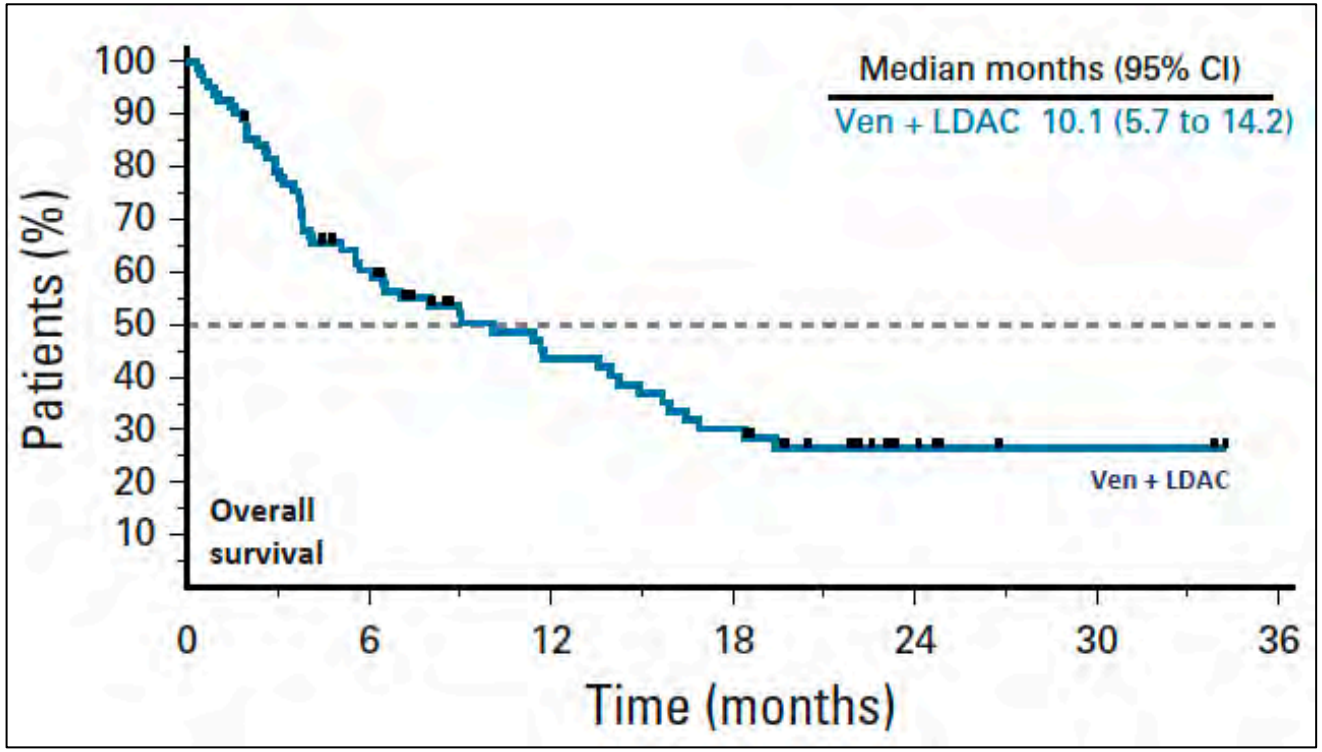
Cortes et al, Leukemia 2019

Courtesy of Daniel A Pollyea, MD, MS

Early Phase Study of Venetoclax + LDAC

- Previously untreated AML patients unfit for induction chemotherapy (N=82)



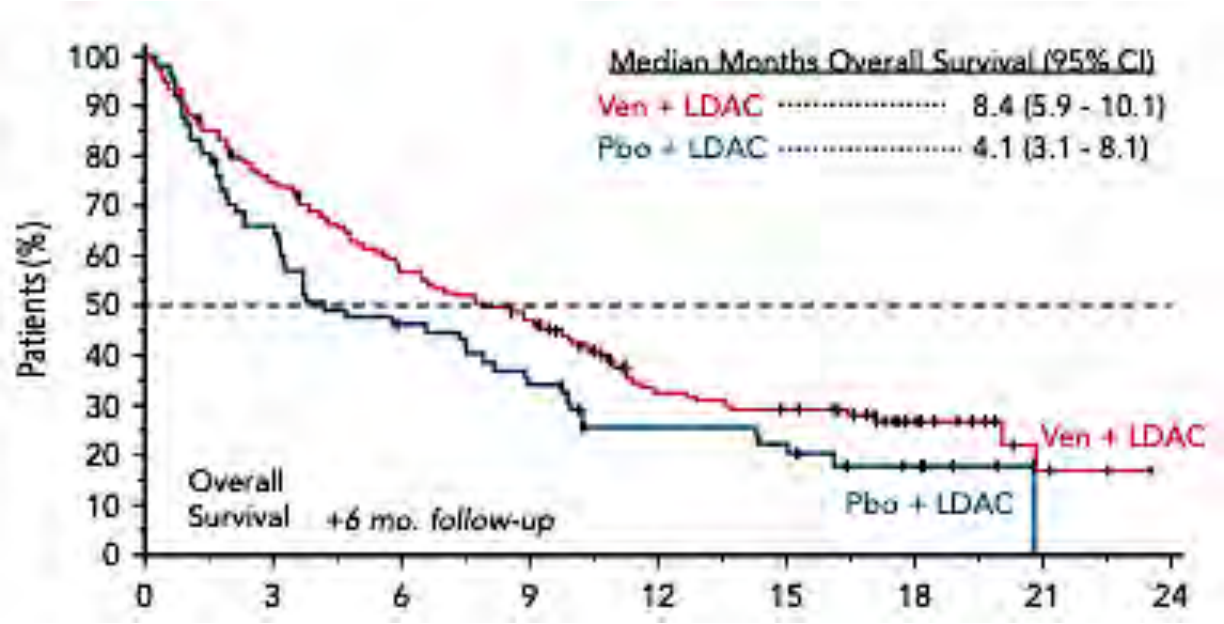


Wei et al, JCO 2019

Courtesy of Daniel A Pollyea, MD, MS

Phase 3 Study of Venetoclax + LDAC vs LDAC Alone

End point	% (95% CI)		P
	Placebo + LDAC (n = 68)	Venetoclax + LDAC (n = 143)	
Remission rate			
CR*	7 (2-16)	27 (20-35)	<.001
CR/CRi†	13 (6-24)	48 (39-56)	<.001
By initiation of cycle 2	3 (0-10)	34 (27-43)	<.001
CR/CRh‡	15 (7-25)	47 (39-55)	<.001
By initiation of cycle 2	4 (1-12)	31 (23-39)	<.001



Wei et al, Blood 2020

Courtesy of Daniel A Pollyea, MD, MS

Early Phase Study of Venetoclax + HMA

All patients	N	CR n (%)	CR/CRi n (%)	DOR mos. (95% CI)
400 mg venetoclax				
Venetoclax + Azacitidine	84	37 (44)	60 (71)	21.9 (15.1-30.2)
Response by cycle two start[a]	84	17 (20)	39 (46)	–
Venetoclax + Decitabine	31	17 (55)	23 (74)	15.0 (7.2–30.0)
Response by cycle two start[b]	31	1 (3)	10 (32)	-
800 mg venetoclax				
Venetoclax + Azacitidine	37	15 (41)	22 (59)	16.1 (10.9-31.0)
Response by cycle two start	37	10 (27)	15 (41)	–
Venetoclax + Decitabine	37	17 (46)	27 (73)	9.2 (6.7–NR)
Response by cycle two start	37	8 (22)	20 (54)	-

Pollyea et al, AJH 2020

Courtesy of Daniel A Pollyea, MD, MS

Early Phase Study of Venetoclax + HMA

All patients	N	CR n (%)	CR/CRi n (%)	DOR mos. (95% CI)
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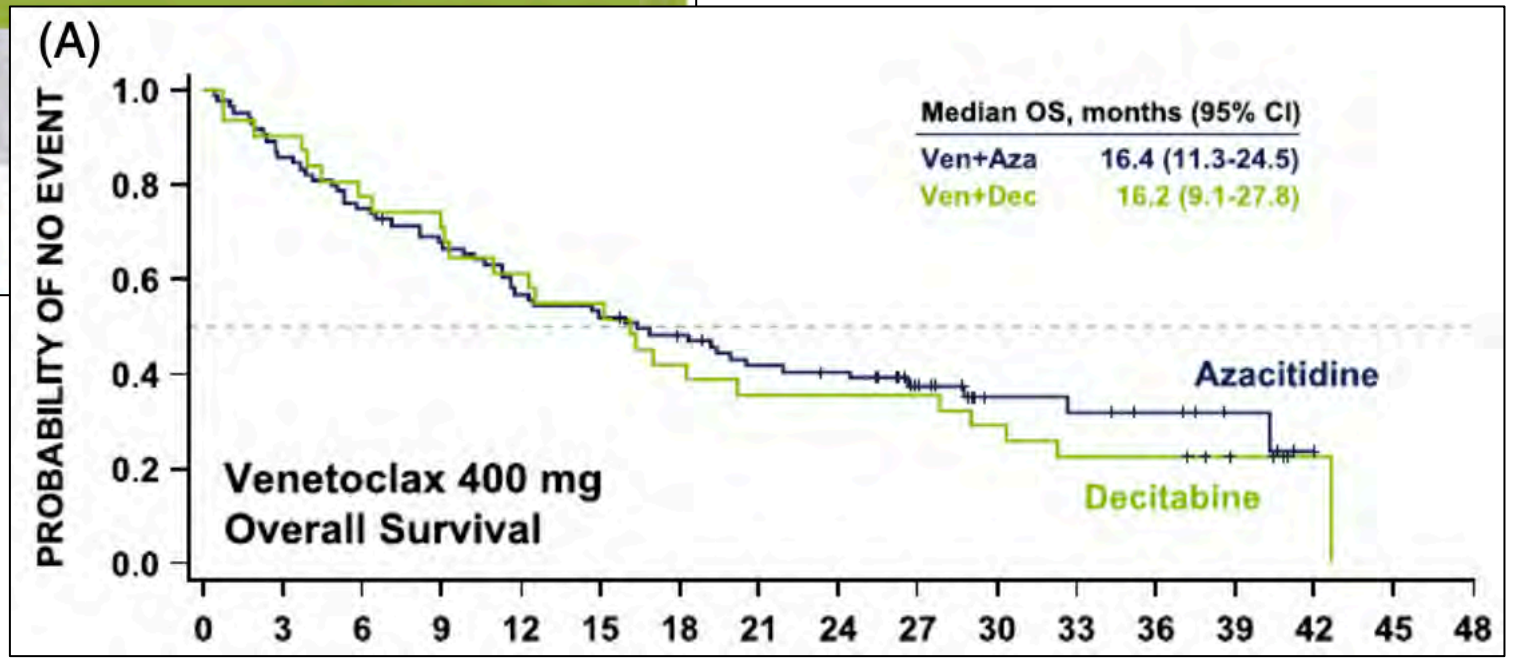
Response by cycle two start[b]	31	1 (3)	10 (32)	-
800 mg venetoclax				
Venetoclax + Azacitidine	37	15 (41)		
Response by cycle two start	37	10 (27)		
Venetoclax + Decitabine	37	17 (46)		
Response by cycle two start	37	8 (22)		

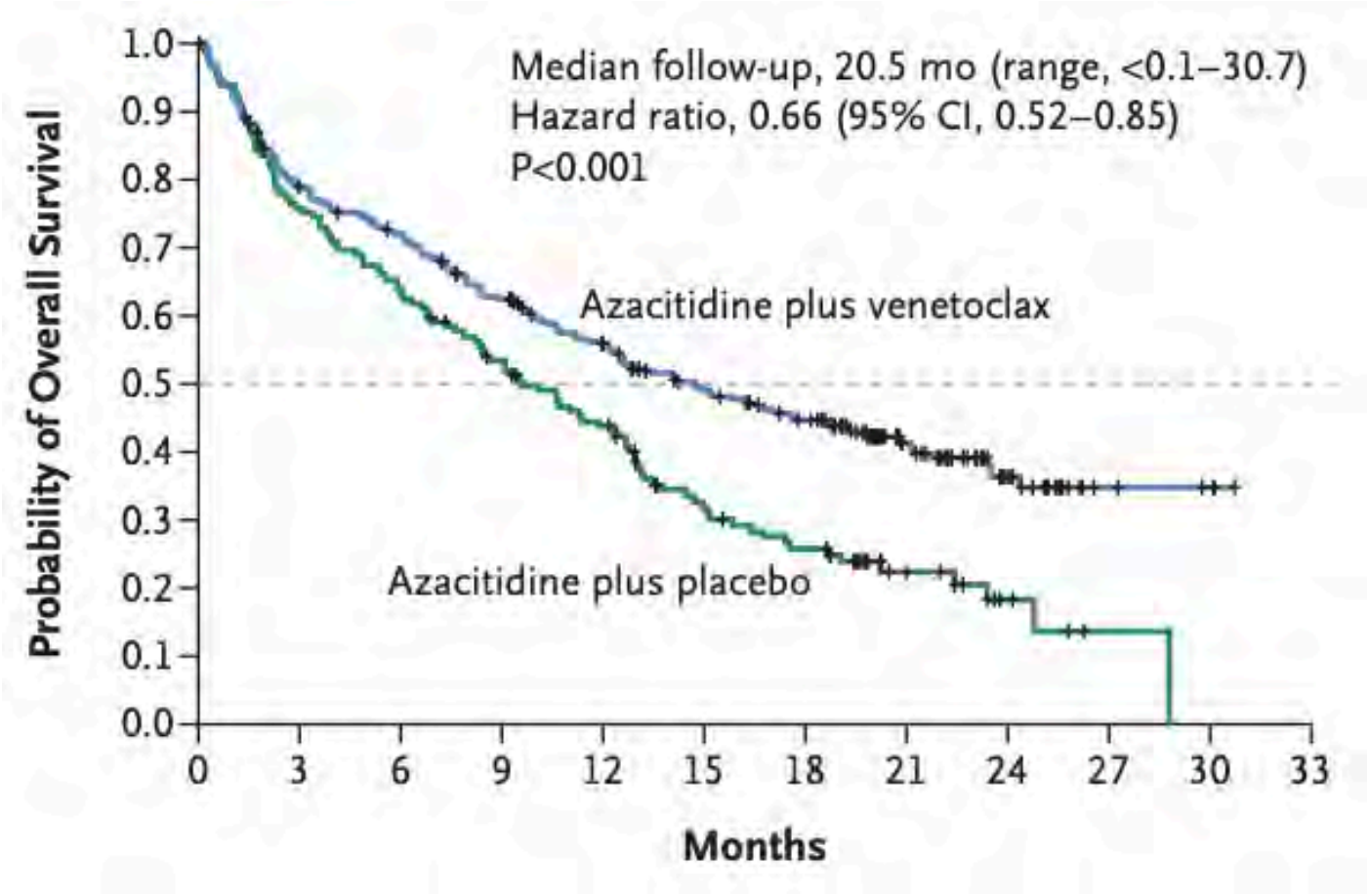


Pollyea et al, AJH 2020

Courtesy of Daniel A Pollyea, MD, MS

Phase 3 Study of Venetoclax + Azacitidine vs Azacitidine Alone

	Venetoclax + Azacitidine	Placebo + Azacitidine
Composite Complete Remission	66.4%	28.3%



DiNardo et al, NEJM 2020

Courtesy of Daniel A Pollyea, MD, MS

Main Toxicity Concern: Myelosuppression

Grade ≥3 AEs in >2 patients in the Ven arm, n (%)	Ven+Aza n=283	Pbo+Aza n=144
Hematologic AEs		
Thrombocytopenia	126 (45)	55 (38)
Neutropenia	119 (42)	41 (28)
Febrile neutropenia	118 (42)	27 (19)
Anemia	74 (26)	29 (20)
Leukopenia	58 (21)	17 (12)

Grade ≥3 AEs in ≥20% of patients in either arm, n (%)	Ven+LDAC n=142	Pbo+LDAC n=68
Hematologic AEs		
Thrombocytopenia	64 (45)	25 (37)
Neutropenia	66 (46)	11 (16)
Febrile neutropenia	45 (32)	20 (29)
Anemia	36 (25)	15 (22)

- Mitigation:
  - Post cycle 1 bone marrow biopsy
  - Breaks between cycles when in morphologic remission
  - Growth factors
  - Dose reductions of venetoclax or backbone

DiNardo et al, NEJM 2020
Wei et al, Blood 2020

Courtesy of Daniel A Pollyea, MD, MS

Venetoclax and Tumor Lysis Syndrome

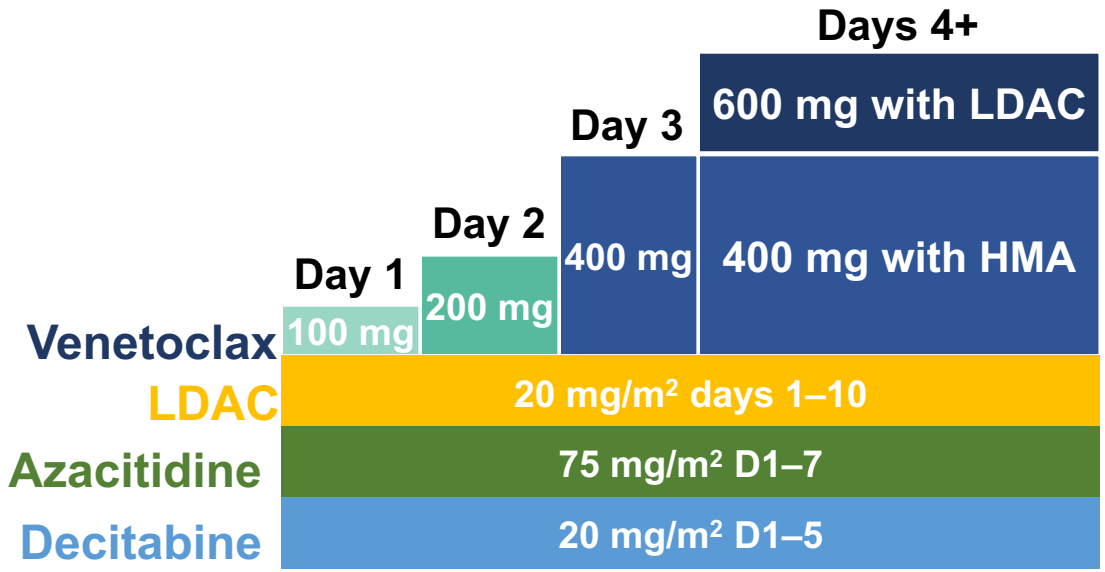
Rate of TLS in Phase 3 Studies

Trial	Laboratory TLS, n (%)	Clinical TLS, n (%)
Ven+Aza (n=283)	3 (1)	0
Ven+LDAC (n=142)	4 (3)	4 (3)

DiNardo et al, NEJM 2020
Wei et al, Blood 2020

Courtesy of Daniel A Pollyea, MD, MS

Mitigation Strategies



AND

- Hydration
- Anti-hyperuricemics
- Monitor chemistries every 6-8 hours
- Reduce WBC to <25 x 10^9 prior to initiation

Case Presentation – Dr Pollyea: A 72-year-old man with AML and a complex monosomal karyotype

- 72 YO M with AML and a complex, monosomal karyotype with a TP53 mutation achieves CRi after cycle 1 of venetoclax + azacitidine
- After second cycle had ongoing remission with evidence of MRD
- Patient went to allogeneic stem cell transplantation
- Relapsed 8 months after transplant

Case Presentation – Dr Pollyea: A 74-year-old woman with newly diagnosed AML

- 74-year-old woman with severe aortic stenosis diagnosed with AML with trisomy 21 and mutations in ASXL1 and RUNX1
- Prescribed venetoclax + azacitidine
- Prophylaxis with levofloxacin and acyclovir
- Achieved CR but became neutropenic with each cycle
- Cycle 5 day 15 developed pneumonia, concerning for fungal process

Case Presentation – Dr Pollyea: A 74-year-old woman with newly diagnosed AML (continued)

Prophylaxis for Antifungals with Venetoclax?

- We do not do this, but most others do
- If using an azole must dose reduce the venetoclax

Agenda

Prologue: A Personal Reflection on Acute Myeloid Leukemia (AML)

Module 1: Up-Front Treatment of AML in Patients Who Are Not Eligible for Intensive Therapy

Module 2: Management of AML with Targetable Mutations

Module 3: Other Currently Available and Investigational Treatment Strategies for AML

Module 4: Management of Myelodysplastic Syndromes

What would you recommend as first-line therapy to a 78-year-old patient (PS 0) who presents with intermediate-risk AML with a FLT3-ITD mutation?

1. 7 + 3 induction + midostaurin
2. HMA + venetoclax
3. HMA + FLT3 inhibitor
4. HMA + venetoclax + FLT3 inhibitor
5. Low-dose cytarabine + venetoclax
6. Low-dose cytarabine + venetoclax + FLT3 inhibitor
7. Gilteritinib
8. Other

A 60-year-old with AML, FLT3 mutation receives 7 + 3 induction + midostaurin, achieves remission. Receives consolidation with 3 cycles of modified high-dose cytarabine + midostaurin. Four months after completion of therapy, disease progression, FLT3-ITD mutation (allelic burden 0.4) confirmed. What would you recommend?

1. Gilteritinib
2. MEC + midostaurin
3. Venetoclax + FLT3 inhibitor
4. HMA + venetoclax
5. HMA + venetoclax + FLT3 inhibitor
6. Low-dose cytarabine + venetoclax
7. Low-dose cytarabine + venetoclax + FLT3 inhibitor
8. Other

What would you recommend as first-line therapy to a 78-year-old patient (PS 0) who presents with intermediate-risk AML with an IDH1 mutation?

1. Ivosidenib
2. HMA
3. HMA + venetoclax
4. HMA + ivosidenib
5. HMA + venetoclax + ivosidenib
6. Low-dose cytarabine + venetoclax
7. Low-dose cytarabine + venetoclax + ivosidenib
8. Other

What would you generally recommend as the next line of treatment for a 60-year-old patient with AML with an IDH2 mutation who has experienced disease progression after 7 + 3 induction, consolidation therapy and transplant?

1. Enasidenib
2. HMA + venetoclax
3. HMA + enasidenib
4. HMA + venetoclax + enasidenib
5. Low-dose cytarabine
6. Low-dose cytarabine + venetoclax
7. Low-dose cytarabine + venetoclax + enasidenib
8. Other

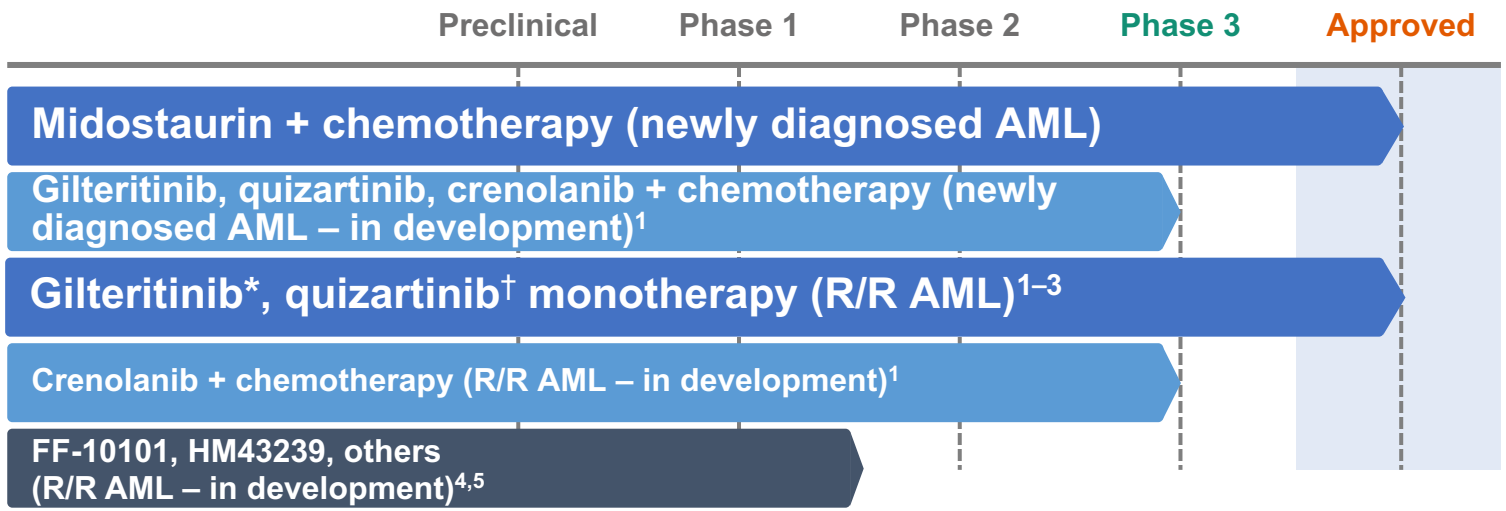
Case Presentation – Dr DiNardo: A 77-year-old woman with AML and a FLT3-ITD mutation

- 77yo Female NPM1, DNMT3A and FLT3-ITD mutated AML
- Started on frontline AZA + VEN and attained a CR1. Received 5 cycles and then relapsed
- FLT3-ITD confirmed at relapse; started on gilteritinib 120 mg daily
  - Transaminitis led to dose reduction to 80 mg daily
- Responded with count normalization for ~ 4 months; then WBC rose with circulating blasts
- FLT3-ITD and NPM1 again confirmed
- Treated with decitabine + venetoclax + quizartinib triplet trial
- Responded then relapse
- Screening for Menin inhibitor

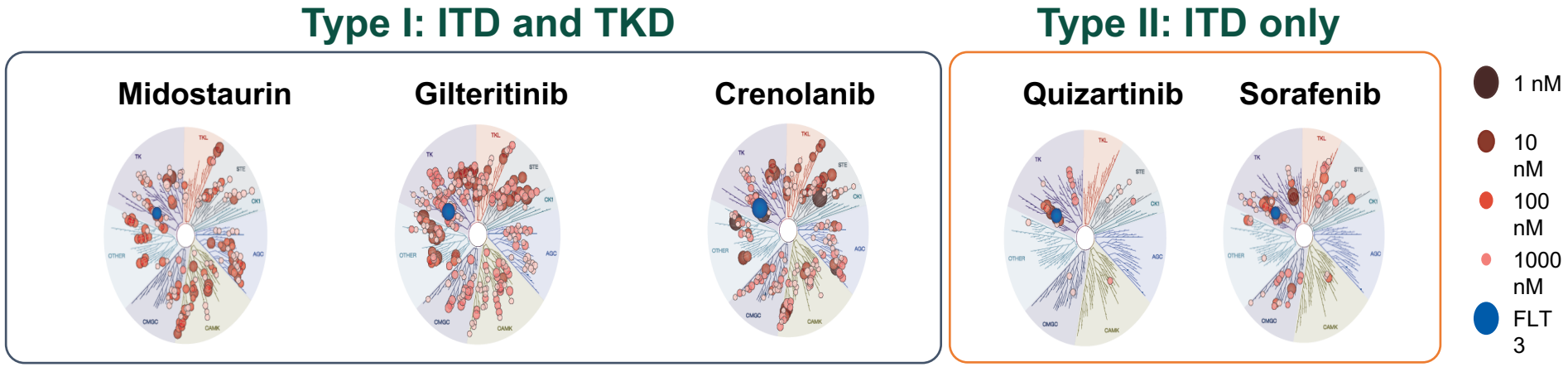
Case Presentation – Dr DiNardo: A 61-year-old man with AML and a FLT3-TKD mutation

- 61yo Male with URI symptoms -> PCP -> bloodwork with leukocytosis and thrombocytopenia
- AML with +8 and +21 cytogenetics and FLT3-TKD mutation at diagnosis in January 2019
- Received 7+3 + midostaurin, and 3 cycles of HIDAC + midostaurin.
- Came in late 2019 to MDACC for SCT and maintenance considerations
  - Intermediate risk, declined SCT, received gilteritinib maintenance ~ 1 year
- Now 2.5 years in continuous CR1 with MRD negative status by flow, cytogenetics and FLT3 mutation status testing

Improving Outcomes in FLT3-ITD Mutated AML



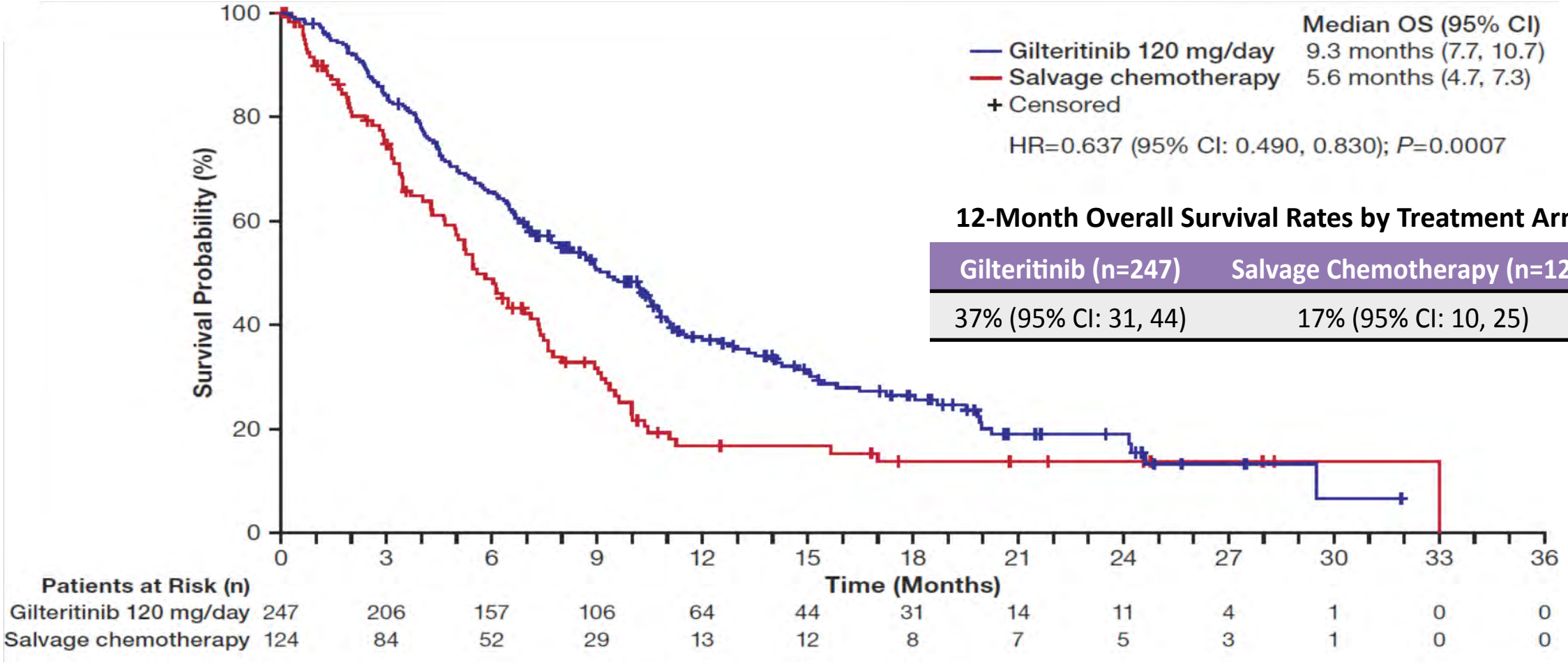
*Approved in the US and Japan
†Approved in Japan



- 1. Short NJ, et al. *Ther Adv Hematol.* 2019. doi: 10.1177/2040620719827310; 2. Daiichi Sankyo. Press release. Available at: https://www.daiichisankyo.com/media_investors/media_relations/press_releases/detail/007030.html; 3. Astellas. Press release. Available at: https://www.astellas.com/en/news/14271; 4. ClinicalTrials.gov. NCT03194685. Available from: https://clinicaltrials.gov/ct2/show/NCT03194685; 5. ClinicalTrials.gov. NCT03850574. Available from: https://clinicaltrials.gov/ct2/show/NCT03850574; 5. Aikawa T, et al. Presented at the 2019 Annual Meeting of the AACR; March 29–April 03, 2019; Atlanta, GA. Abstract 1318

Courtesy of Courtney D DiNardo, MD, MSCE

ADMIRAL Trial: Overall Survival (n=371) and Safety Outcomes



12-Month Overall Survival Rates by Treatment Arm

Gilteritinib (n=247)	Salvage Chemotherapy (n=124)
37% (95% CI: 31, 44)	17% (95% CI: 10, 25)

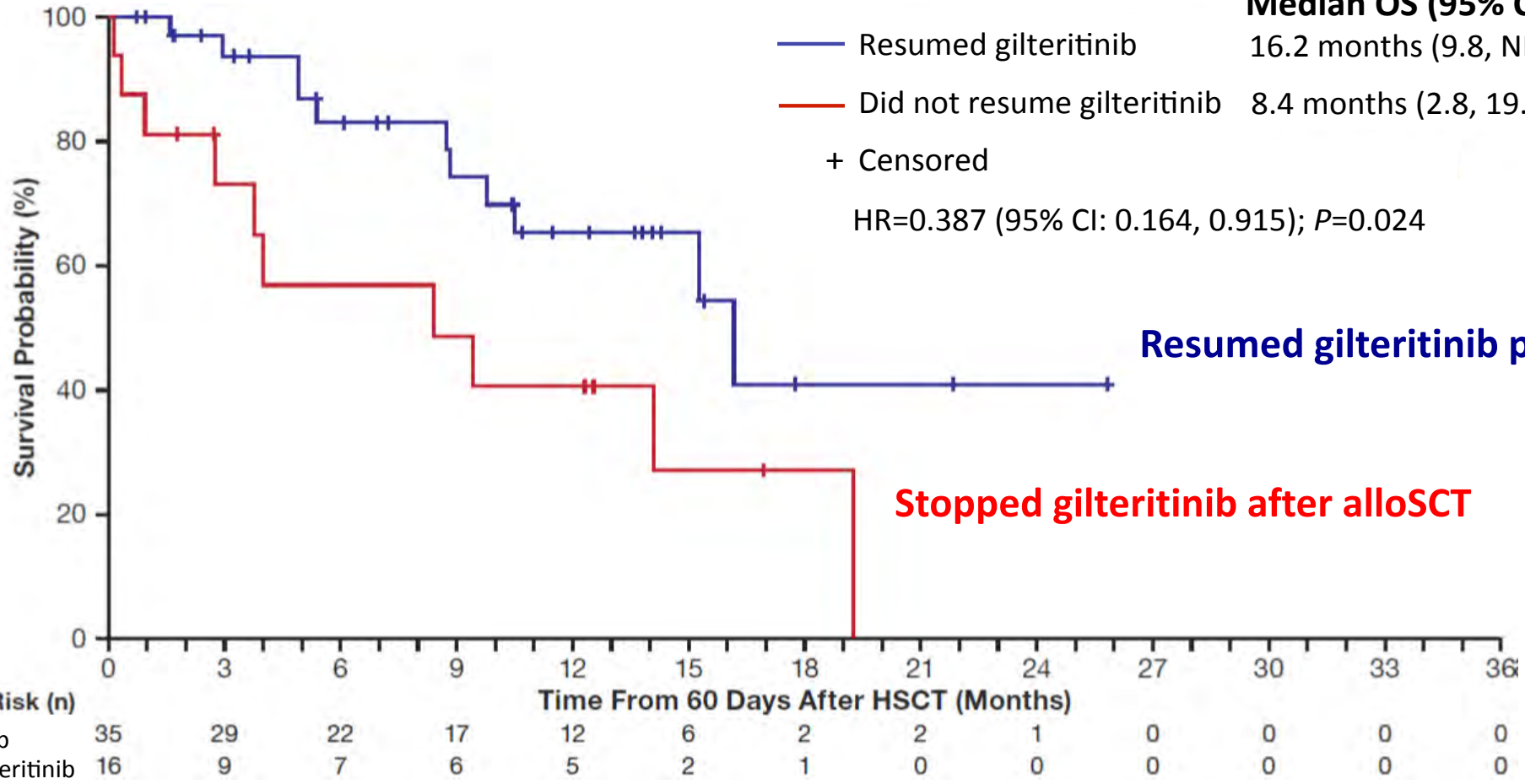
- Grade ≥3 AEs and serious AEs occurred less frequently in the gilteritinib group than in the chemotherapy group
- The most common Grade ≥3 AEs in the gilteritinib group were febrile neutropenia (45.9%), anemia (40.7%), and thrombocytopenia (22.8%)

Courtesy of Courtney D DiNardo, MD, MSCE

Perl A et al NEJM 2019

ADMIRAL Trial: Post-HSCT Survival in the Gilteritinib Arm

Effect of Maintenance Therapy (Landmark Analysis Day 60 Post-HSCT; n=51)



Two-sided *P*-values were determined according to the log-rank test; the Kaplan-Meier method in combination with the Greenwood formula were used to determine overall survival and corresponding 95% confidence intervals.
Abbreviations: CI, confidence interval; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; ITT, intention-to-treat; NE, not estimable; OS, overall survival.

Courtesy of Courtney D DiNardo, MD, MSCE

Overall Survival Endpoint Met in the COMMODORE Trial of Gilteritinib for Patients with Relapsed or Refractory AML with a FLT3 Mutation

Press Release: March 30, 2021.

A Phase 3 confirmatory trial of gilteritinib in patients with relapsed or refractory FLT3 mutation-positive (FLT3mut+) acute myeloid leukemia (AML) met its primary endpoint of overall survival (OS) compared to chemotherapy at a planned interim analysis.

COMMODORE is an open-label, randomized study of gilteritinib versus salvage chemotherapy in adult patients who have relapsed or refractory AML in China and other countries.

Enrollment has stopped in the trial and patients in the chemotherapy arm will be offered the opportunity to receive gilteritinib.

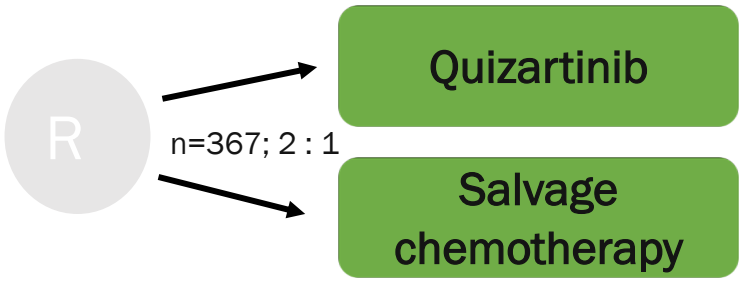
https://www.astellas.com/en/news/16781

Courtesy of Courtney D DiNardo, MD, MSCE

Quizartinib in R/R *FLT3*-ITD AML: *QuANTUM-R Study*

Eligibility

- Adults ≥ 18 yrs
- R/R AML (relapse ≤ 6 mos)
- *FLT3*-ITD positive

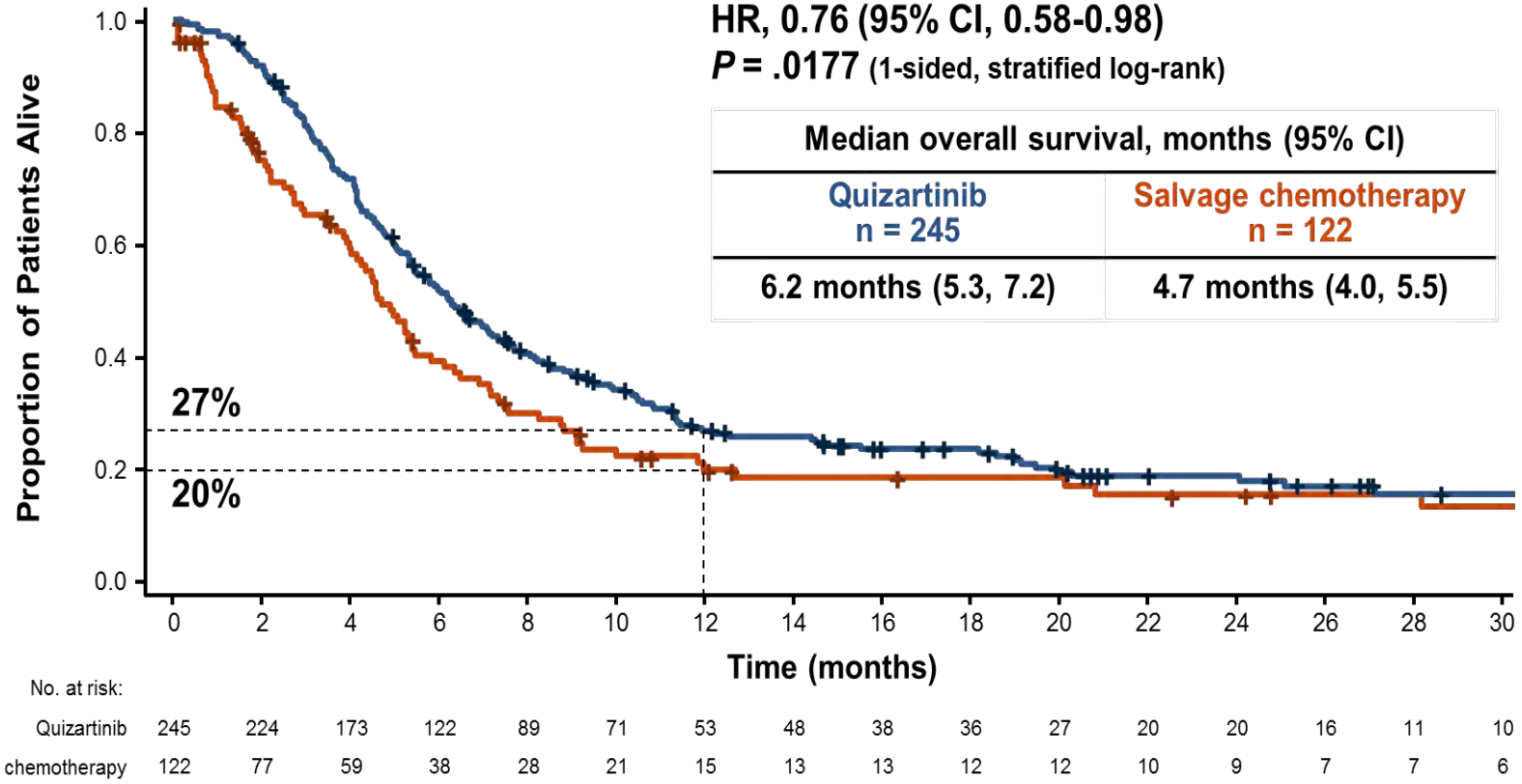


Primary endpoint

- Overall survival

Secondary / exploratory endpoints

- CRc: 48% vs 27%
- EFS: HR = 0.9 (*P* =.107; IIT analysis)
- HCT: 32% vs 12%



- Median follow-up: 23.5 months

- Cortes J, et al. *Lancet Oncol.* 2019;20:984-997.

Courtesy of Courtney D DiNardo, MD, MSCE

Quizartinib and Gilteritinib Phase III Trial Summaries

	Percentage	
	Quizartinib	Gilteritinib
Phase 1/2		
CRc	47	41*
CR	4	11*
Phase 3	**QuANTUM-R**	**ADMIRAL**
CRc	48	54
CR	4	21
CRi	44	26
CRh	NR	13
Eligibility	• Refractory or relapsed (**duration of remission of ≤6 months**) to anthracycline containing chemotherapy • **FLT3-ITD**	• Refractory or relapsed to anthracycline containing chemotherapy or optimum choice of therapy to induce remission for this subject • **FLT3-ITD or TKD**

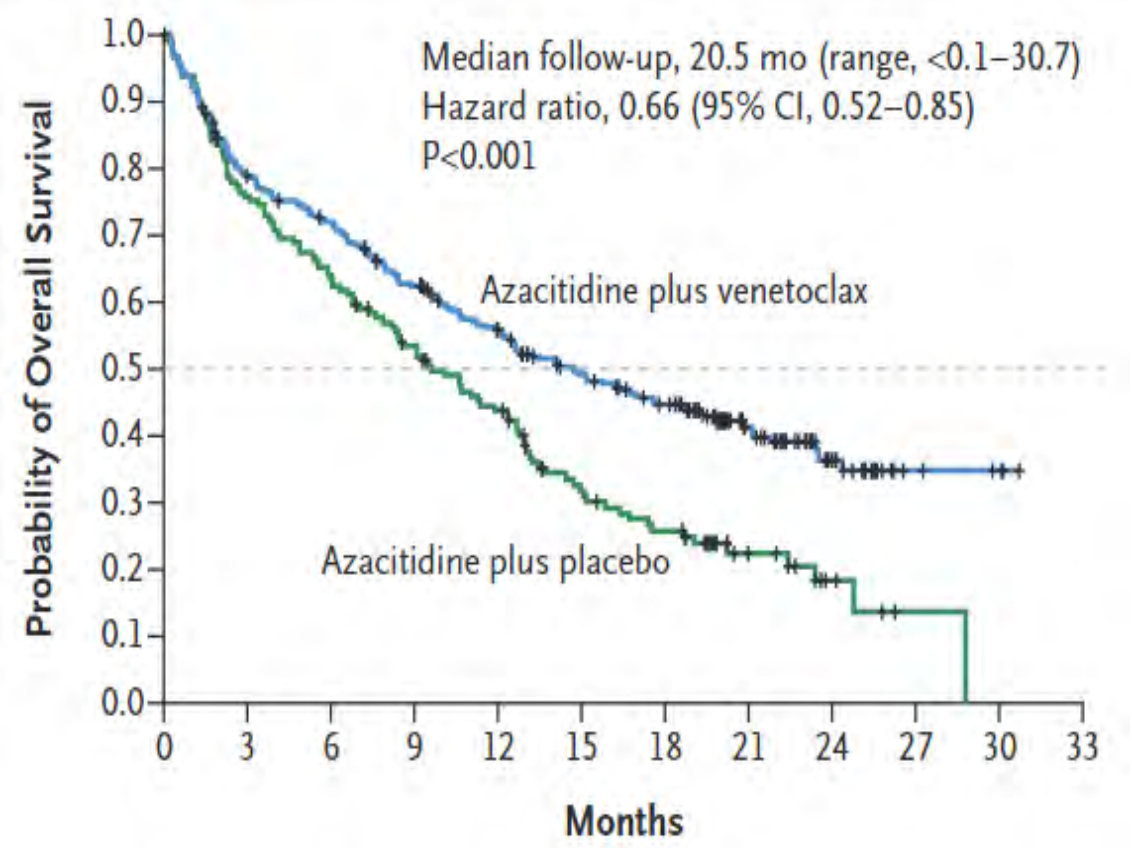
*** Pts treated at ≥80 mg/d**

Cortes, et al. Blood 2018; 132: 598-607; Perl A, et al. AACR 2019; Gilteritinib Prescribing Information

Courtesy of Courtney D DiNardo, MD, MSCE

VIALE-A: Azacitidine + venetoclax for newly diagnosed IC-Ineligible AML

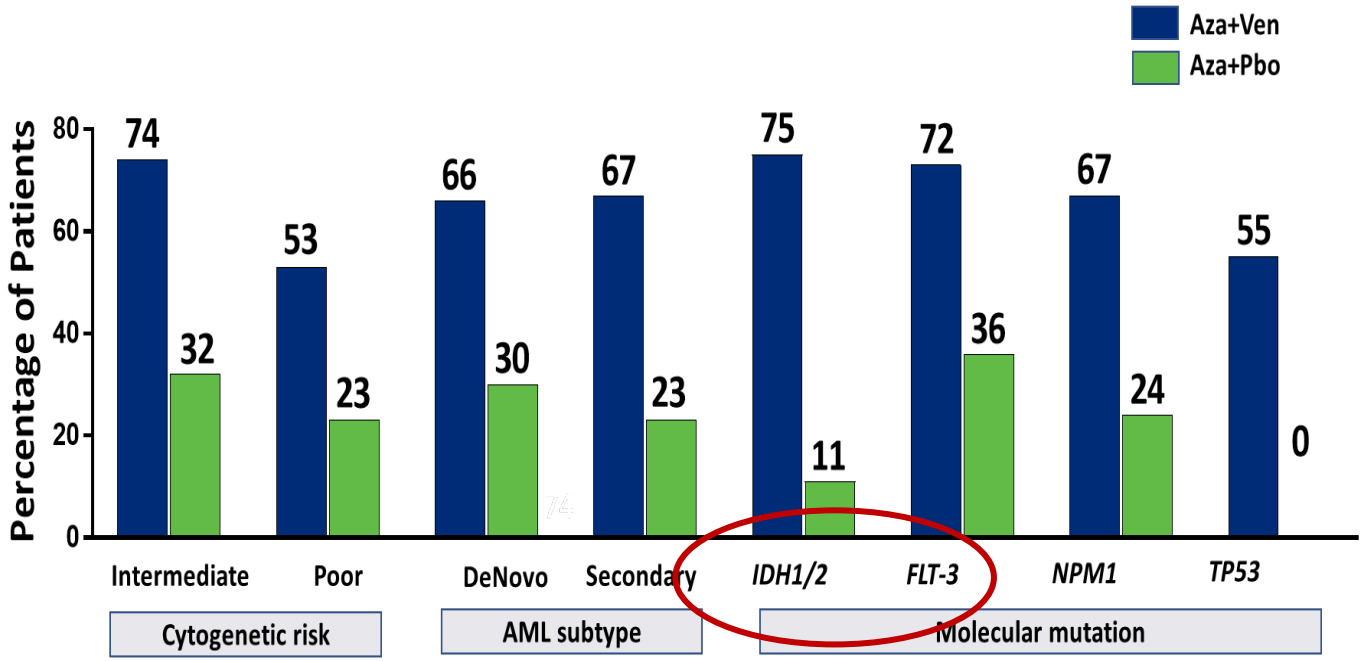
Significant OS improvement with venetoclax/azacitidine



CR rate: 36.7% vs 17.9% (*P* < .001)

CR/CRi rate: 66.4% vs 28.3% (*P* < .001)

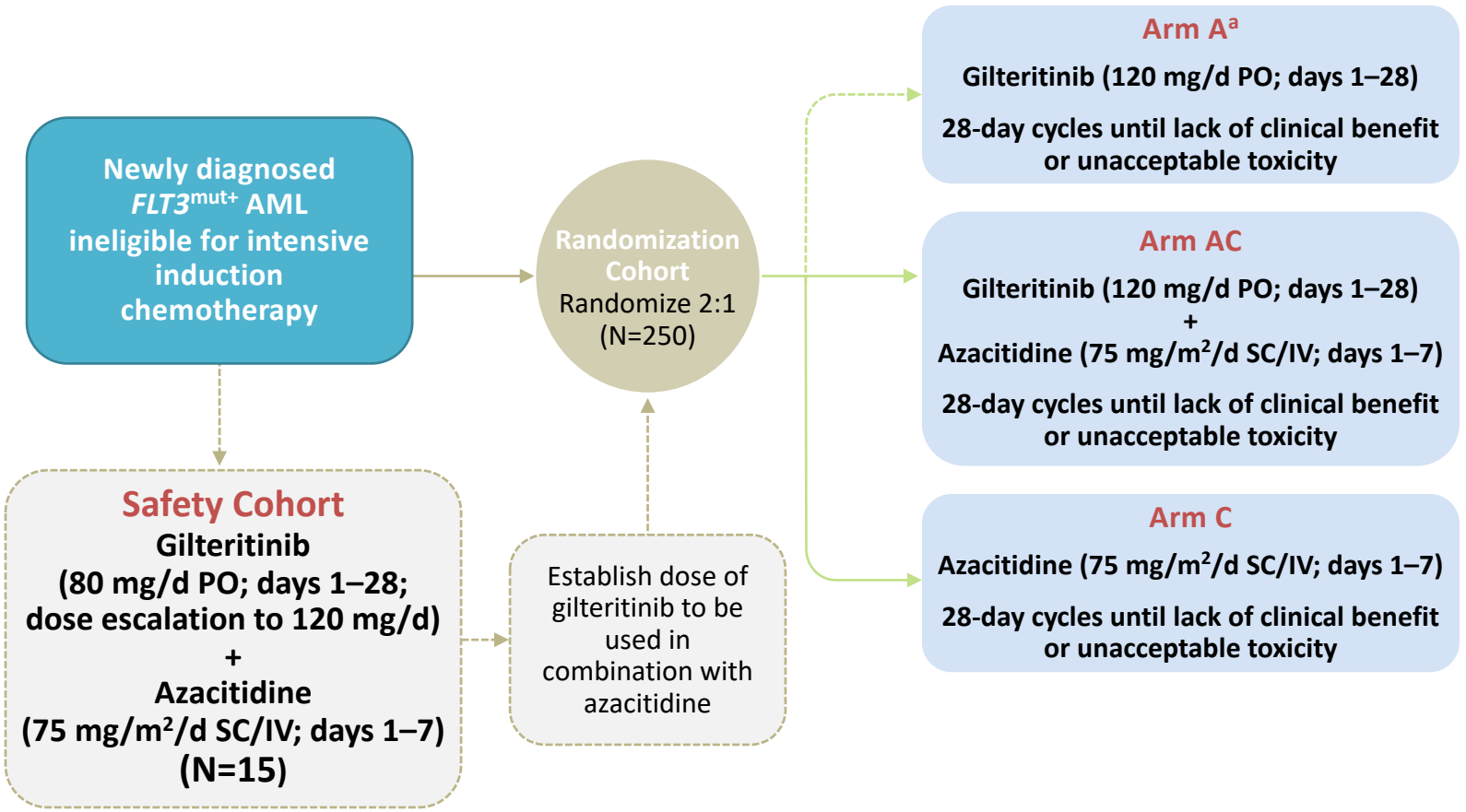
Improved responses occurred *independent* of high-risk genomics



DiNardo C, et al. *N Engl J Med*. 2020;383:617-629.

Courtesy of Courtney D DiNardo, MD, MSCE

LACEWING 2020: Study Design and Update



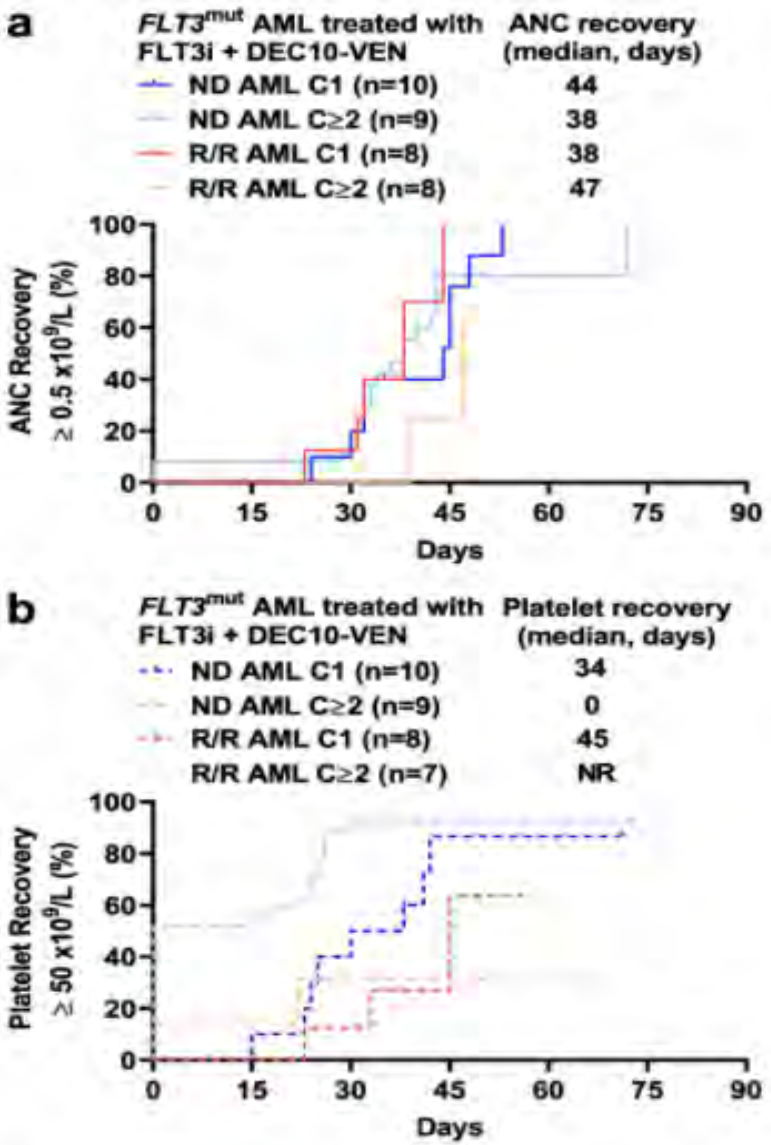
Characteristic	Safety Cohort (N=15)
Age, y	
Median (range)	75 (65–86)
≥75, n (%)	9 (60)
FLT3 status, n (%)	
ITD alone	10 (67)
TKD alone	3 (20)
ITD/TKD	1 (7)
Wild type	1 (7)
ECOG PS ≤1, n (%)	6 (40)
CR	**5/15 (33)**
CRc	**10/15 (67)**
DOR (n=10)	**10.4 mo**

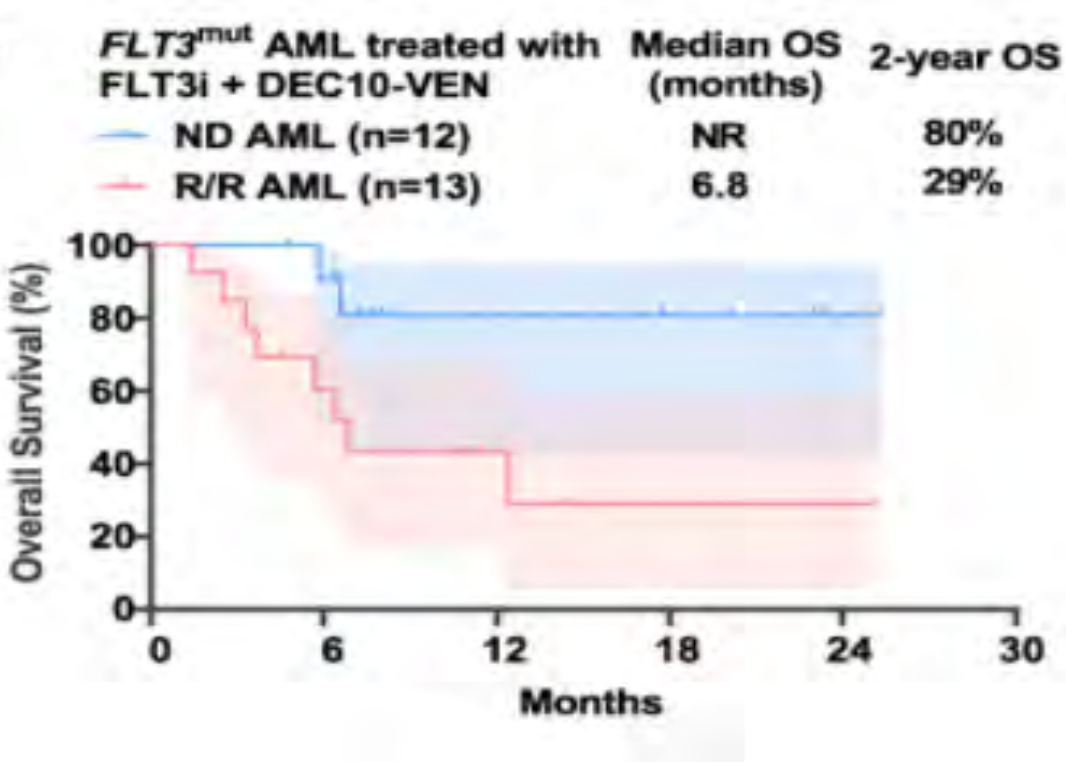
Post-ASH press release reported that trial failed to meet primary endpoint

Courtesy of Courtney D DiNardo, MD, MSCE

Wang E, et al. ASH 2020. Abstract 27.

Newly Dx and R/R AML FLT3i + DEC10-VEN (Triplet Therapy): Phase II Trial Outcomes



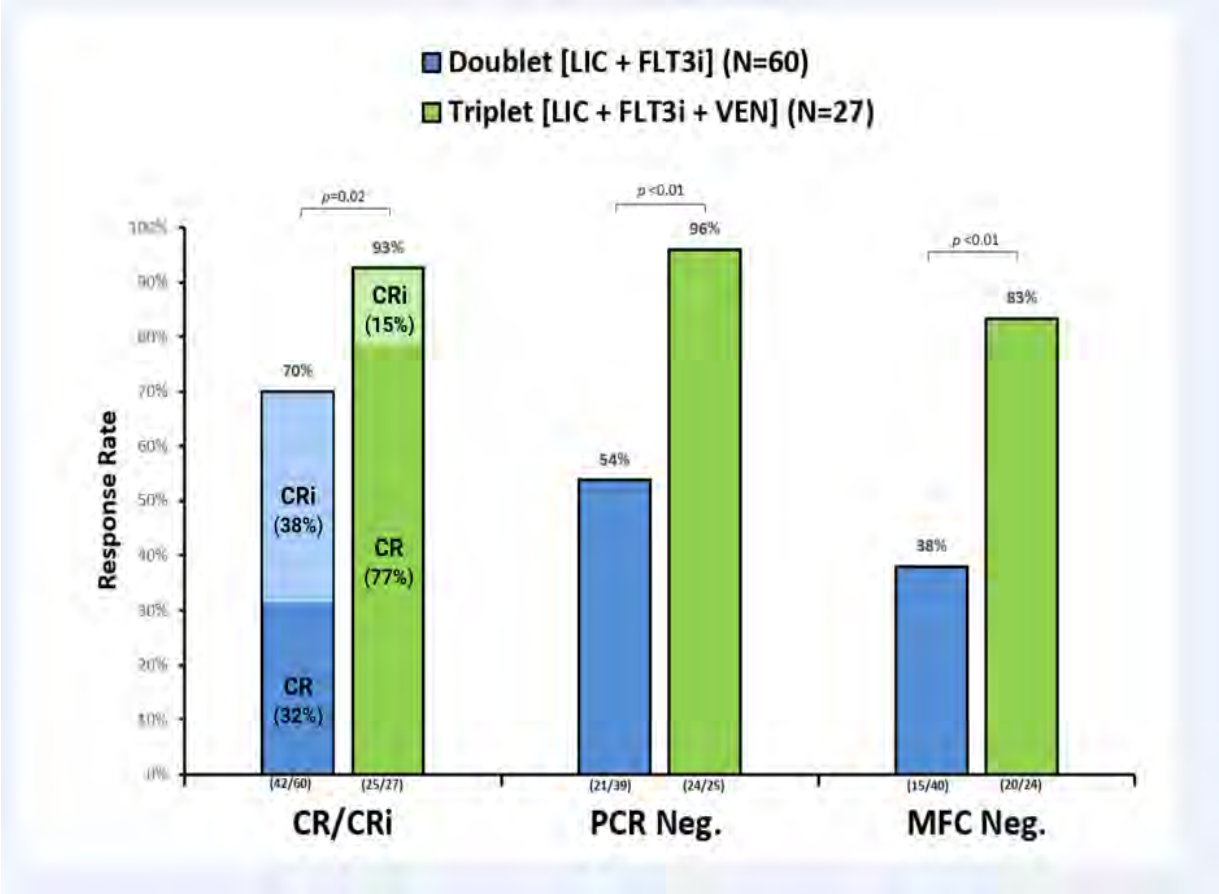


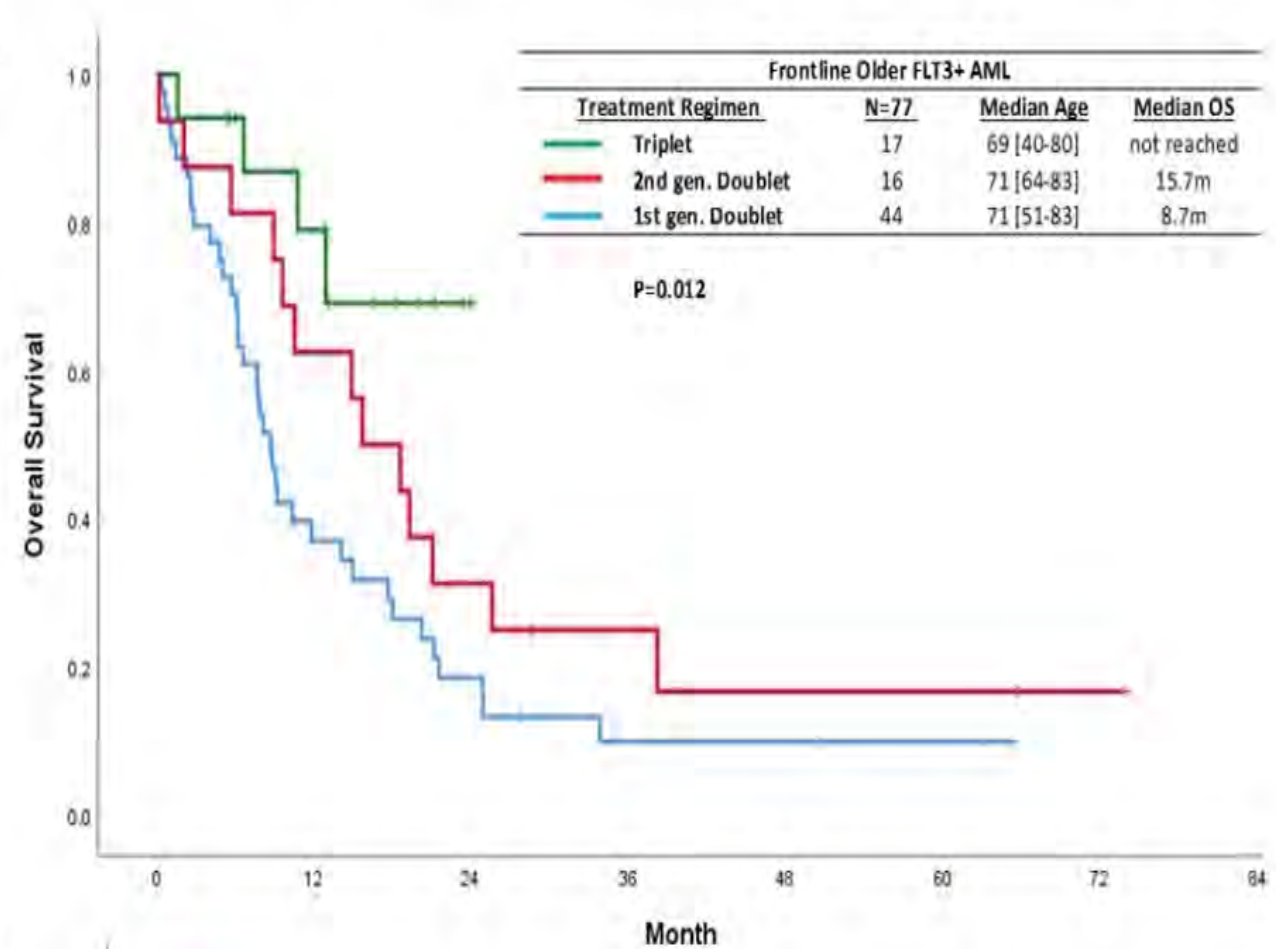
Additional Outcomes	
60-d mortality	0% ND 7% R/R (n=1)
Median course duration	**Cycle 1: 46 days** Cycle 2+: 40 days

Courtesy of Courtney D DiNardo, MD, MSCE

Maiti et al, Blood Cancer J 2021

Lower intensity FLT3i "doublet" vs "triplet" with the addition of venetoclax (Phase I/II trial)

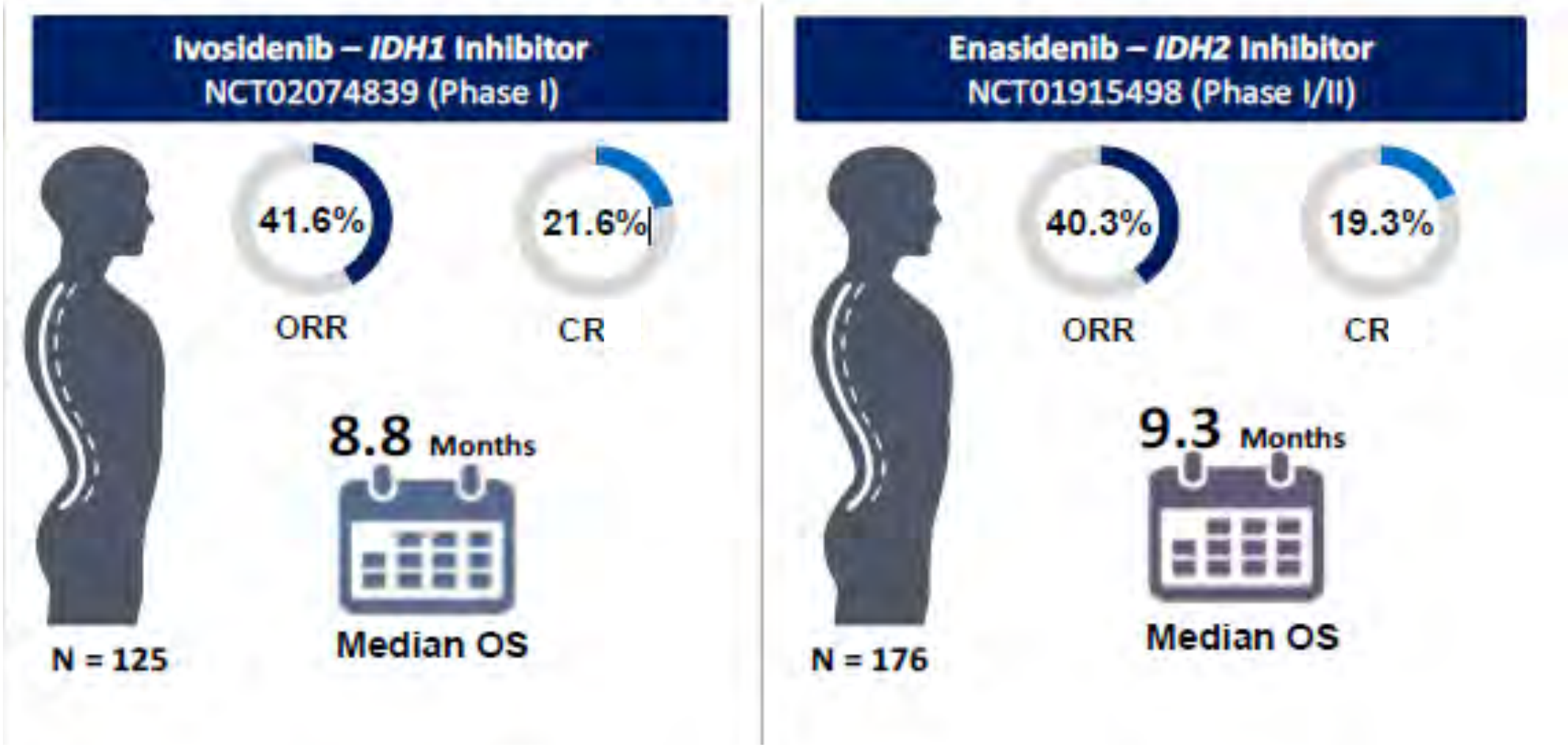




Courtesy of Courtney D DiNardo, MD, MSCE

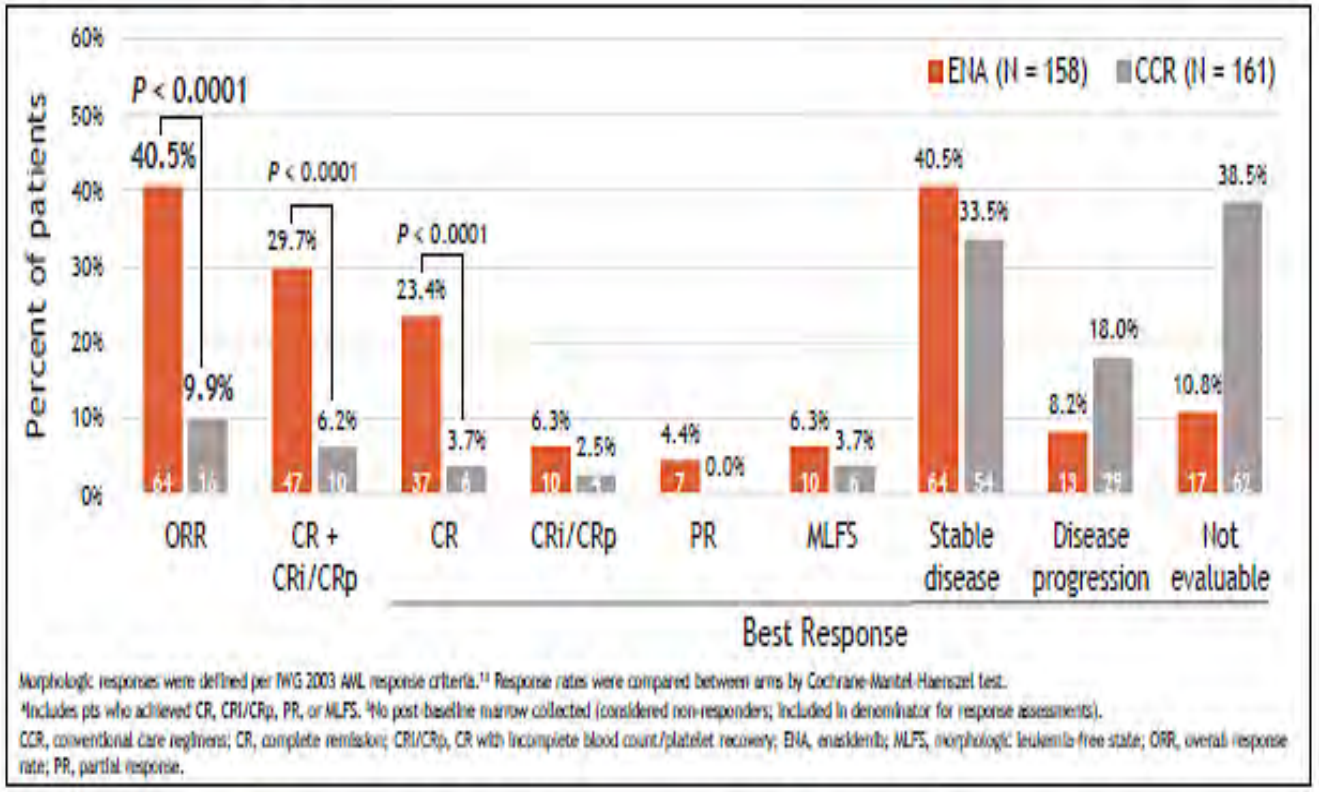
Yilmaz M et al, ASH 2020

IDH1/2 Inhibitors for R/R AML



Courtesy of Courtney D DiNardo, MD, MSCE

IDHentify: Responses with Enasidenib



Morphologic responses were defined per IWG 2003 AML response criteria.[13] Response rates were compared between arms by Cochrane-Mantel-Haenszel test.
[a]Includes pts who achieved CR, CRi/CRp, PR, or MLFS. [b]No post-baseline marrow collected (considered non-responders; included in denominator for response assessments).
CCR, conventional care regimens; CR, complete remission; CRi/CRp, CR with incomplete blood count/platelet recovery; ENA, enasidenib; MLFS, morphologic leukemia-free state; ORR, overall response rate; PR, partial response.

	ENA N = 158	CCR N = 161
Overall response rate (ORR)[a]	**40.5% (64/158)**	**9.9% (16/161)**
ENA vs. CCR	OR 6.1 [95% CI 3.3-11.1]; *P* < 0.0001	
Duration of response, mo[95% CI]	7.3 [5.6-11.1]	NE [2.5- NE]
Morphologic CR rate	**23.4% (37/158)**	**3.7% (6/161)**
ENA vs. CCR	*P* < 0.0001	
Composite CR rate (CR+CRi/CRp)	29.7% (47/158)	6.2% (10/161)
ENA vs. CCR	*P* < 0.0001	
RBC TI, n/N (%)		
RBC-TD at BL, became TI	33/104 (31.7)	9/97 (9.3)
RBC-TI at BL, remained TI	32/53 (60.4)	7/44 (15.9)
Platelet TI, n/N (%)		
Platelet-TD at BL, became TI	26/88 (29.5)	8/74 (10.8)
Platelet-TI at BL, remained TI	48/69 (69.6)	22/67 (32.8)
Any HI, n (%)	67 (42.4)	18 (11.2)
HI-Erythroid	21 (13.3)	9 (5.6)
HI-Neutrophil	57 (36.1)	13 (8.1)
HI-Platelet	31 (19.6)	7 (4.3)

Morphologic responses were defined per IWG 2003 AML response criteria,[13] and HI and TI were defined according to IWG 2006 MDS criteria.[14].
[a]Includes pts who achieved CR, CRi/CRp, PR, or MLFS.

Courtesy of Courtney D DiNardo, MD, MSCE

AZA +/- ENA for Newly Dx IC-Ineligible IDH2-mutated AML

Azacitidine

N = 33

42%

ORR

12%

CRR

10.4 Months

Median EFS

Enasidenib + Azacitidine

N = 68

71%

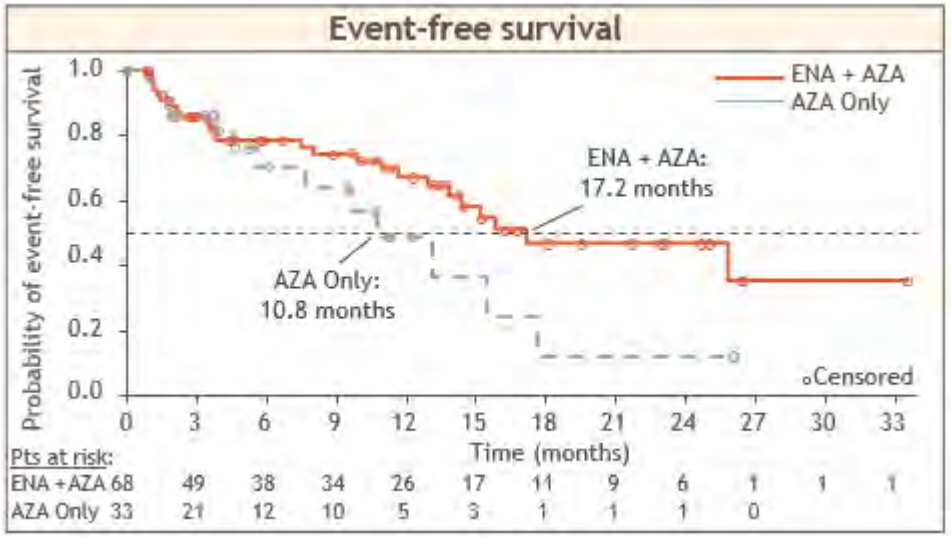
ORR

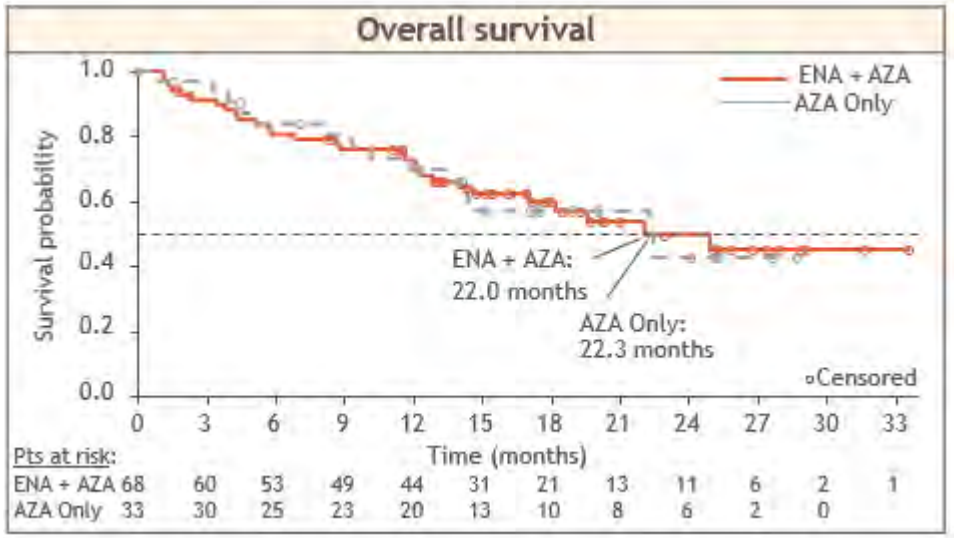
53%

CRR

17.4 Months

Median EFS



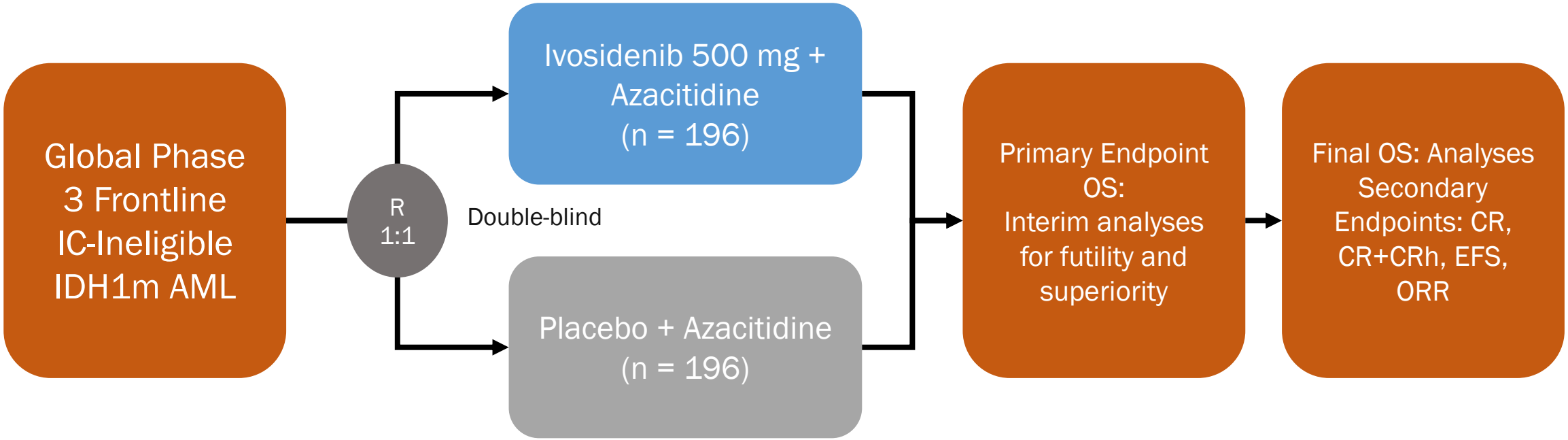


****Non-Blinded Study**, In the AZA Only arm,
8 patients (24%) received subsequent treatment with enasidenib monotherapy

DiNardo CD et al, ASCO 2020

Courtesy of Courtney D DiNardo, MD, MSCE

AGILE Study: AZA +/- Ivosidenib for Newly Dx AML



*155 sites worldwide, enrolling primarily ex-US due to AZA + VEN approval in the US for front-line treatment.

*Amendment has modified primary endpoint to event-free survival (EFS)

****Press release Aug 8 2020: AGILE study is positive for primary and secondary endpoints***

Courtesy of Courtney D DiNardo, MD, MSCE

Case Presentation – Dr DiNardo: A 79-year-old man with AML and diploid cytogenetics

- 79yo Male with MDS/AML with 24% blasts at diagnosis
- Diploid cytogenetics and ASXL1, IDH2 R140, NRAS, SRSF2 and STAG2 mutations
- Treated with azacitidine + venetoclax (x 14 days) + enasidenib triplet
- Obtained CR, but took 10 weeks for full count recovery
- Now receiving AZA x 3 days and enasidenib continuously with full count recovery
- Currently quarantining with COVID-19 (despite vaccination x 2) at home; low-grade fevers but doing OK

Agenda

Prologue: A Personal Reflection on Acute Myeloid Leukemia (AML)

Module 1: Up-Front Treatment of AML in Patients Who Are Not Eligible for Intensive Therapy

Module 2: Management of AML with Targetable Mutations

Module 3: Other Currently Available and Investigational Treatment Strategies for AML

Module 4: Management of Myelodysplastic Syndromes

A 65-year-old patient with a history of myelodysplastic syndrome treated with azacitidine for 10 months presents 1 year later with AML with 35% marrow blasts, trisomy 8 and ASXL1, NRAS and U2AF1 mutations (VAFs 45, 20 and 45, respectively). What would you recommend?

1. 7 + 3 induction
2. CPX-351
3. Decitabine
4. Decitabine + venetoclax
5. Low-dose cytarabine + venetoclax
6. Low-dose cytarabine + glasdegib
7. Other

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

1. Yes
2. Yes, with oral azacitidine (CC-486)
3. No

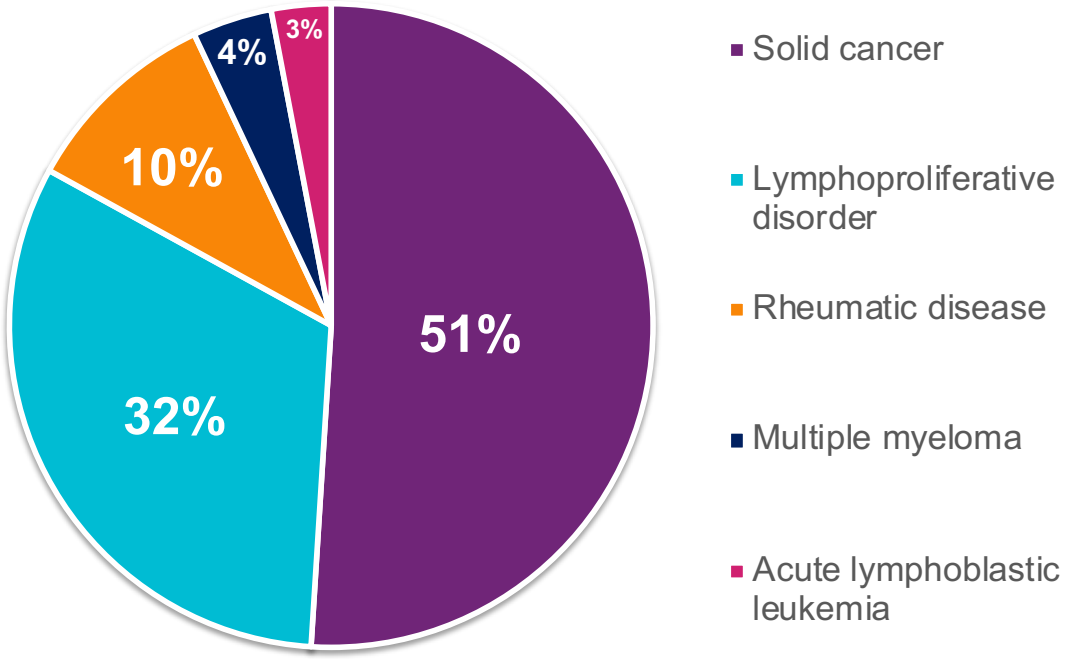
Case Presentation – Dr Wang: A 64-year-old man with secondary AML and DNMT3A and FLT3-ITD mutations

- 64 yo man with new onset pancytopenia. He was diagnosed with COVID-19 in Dec 2020 and received the second dose of the Moderna vaccine in Feb 2021. After the second vaccine he felt tired with exertional dyspnea and thought he was having a side effect of the vaccine. In the ER, his labs showed WBC 12.7, hgb 5.1, plts 15K. BMBX done in March 2021 showed markedly hypercellular BM (>95%) with dysplasia with <5% blasts. Normal cytogenetics. Vitamin B12 levels were low and he was started on B12 supplementation.
- April 2021: Platelets persistently <10K. Repeat BMBX showed hypercellular BMBX (98%) with marked erythroid hyperplasia and 6% blasts consistent with MDS with excess blasts. NGS: DNMT3A mutation.
- June 2021: Presented to clinic with 27% peripheral blasts c/w secondary AML transformation from prior MDS. Repeat NGS showed DNMT3A and FLT3-ITD mutations.
- Admitted to inpatient service and started on treatment with liposomal cytarabine/daunorubicin. On day 15 of therapy, he underwent nadir BMBX showing a hypercellular BMBX (70%) with scattered clusters of myeloblasts c/w persistent refractory AML. Normal cytogenetics.
- Started on Gilteritinib 120 mg daily. Over time, achieved count recovery and awaiting repeat BMBX prior to planned stem cell transplant.

Therapy related AML (tAML)

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

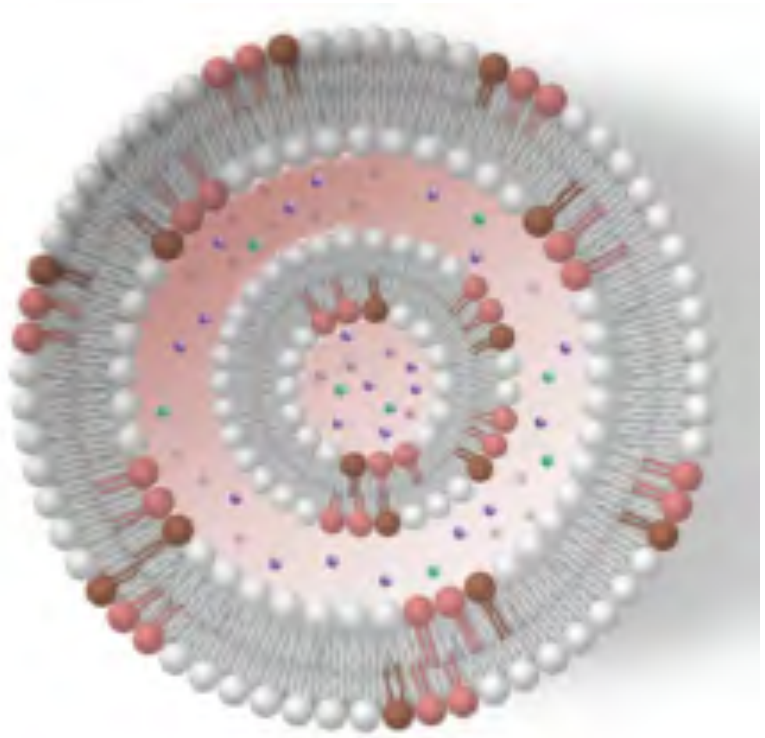


Cytotoxic therapy[a]	MOA	Examples	Latency period
Alkylating agents and radiation	Induce chromosomal deletions, commonly in 5 and/or 7	Cyclophosphamide, mechlorethamine, procarbazine, chlorambucil, melphalan, carmustine, busulfan	5-10 years
Topoisomerase II inhibitors	Induce chromosomal translocations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

Liposomal 7+3 (CPX-351): Drug formulation

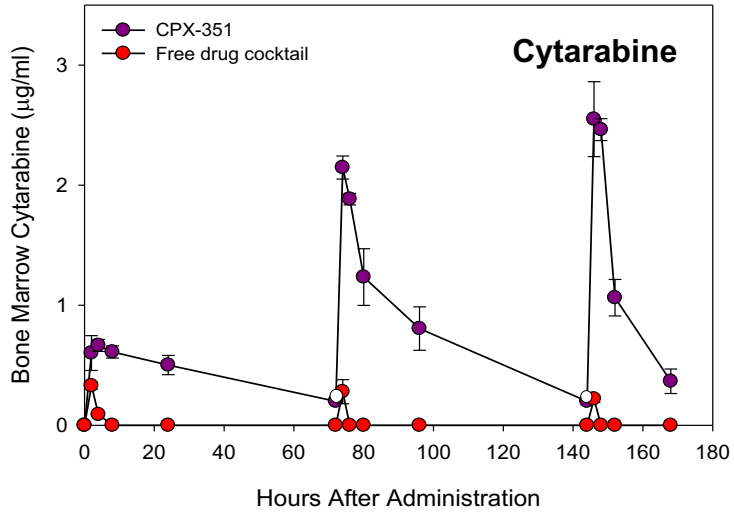


Liposomal formulation of cytarabine and daunorubicin

Fixed 5:1 molar ratio of cytarabine: daunorubicin provides synergistic leukemia cell killing *in vitro*

In patients, CPX-351 preserved delivery of the 5:1 drug ratio for over 24 hours, with drug exposure maintained for 7 days

Selective uptake of liposomes by bone marrow leukemia cells in xenograft models[3]

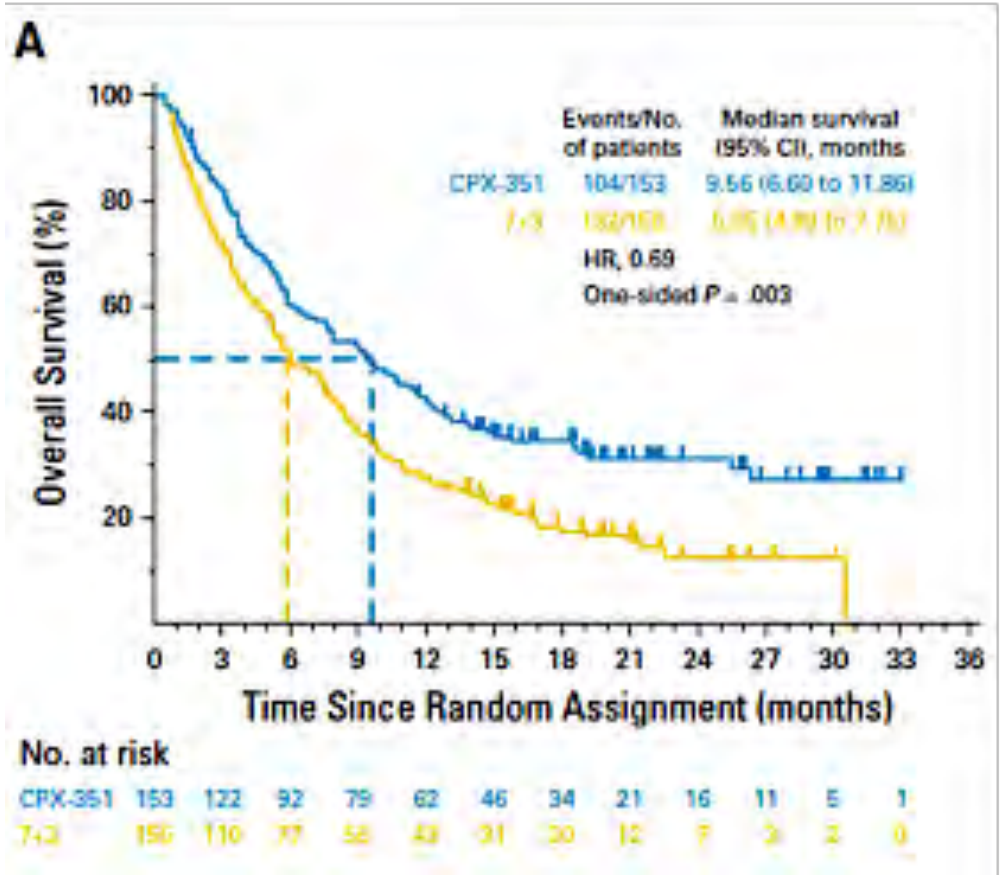


Lancet JE, et al. J Clin Oncol. 2018;36:2684-2692.

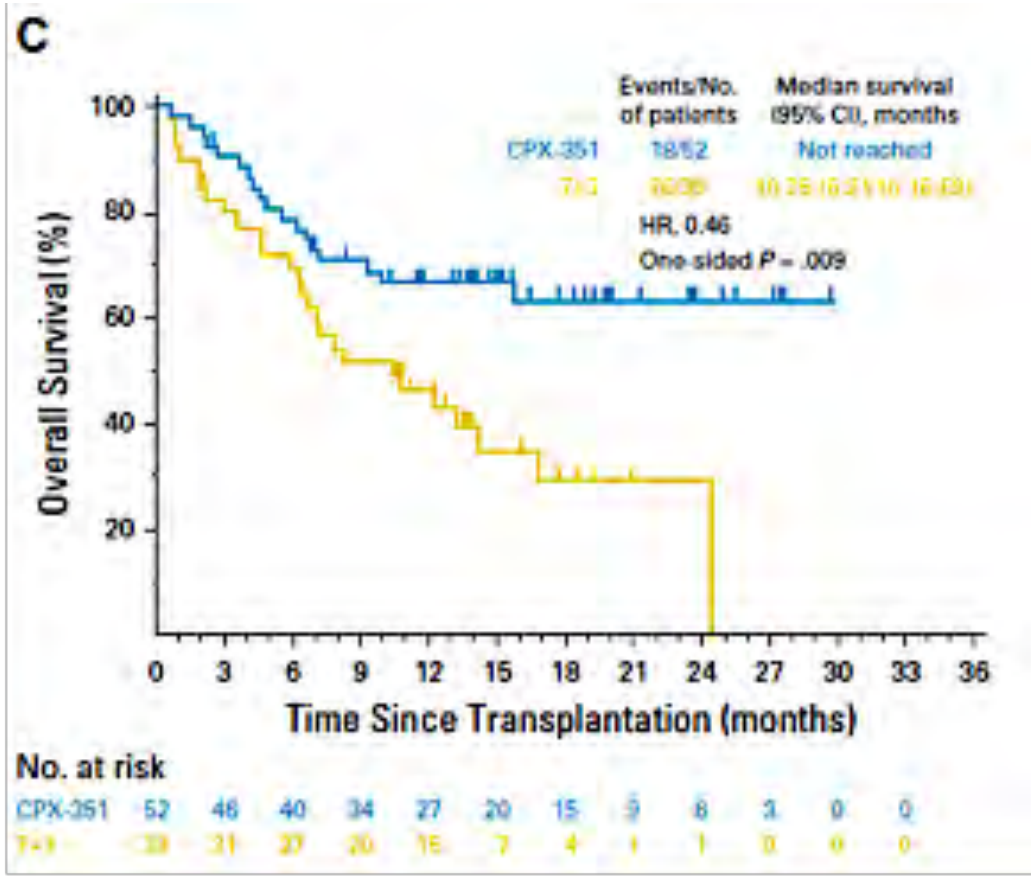
Courtesy of Eunice S Wang, MD

CPX-351 in Older Pts with AML-MRC and t-AML

Overall survival



OS landmarked for transplant



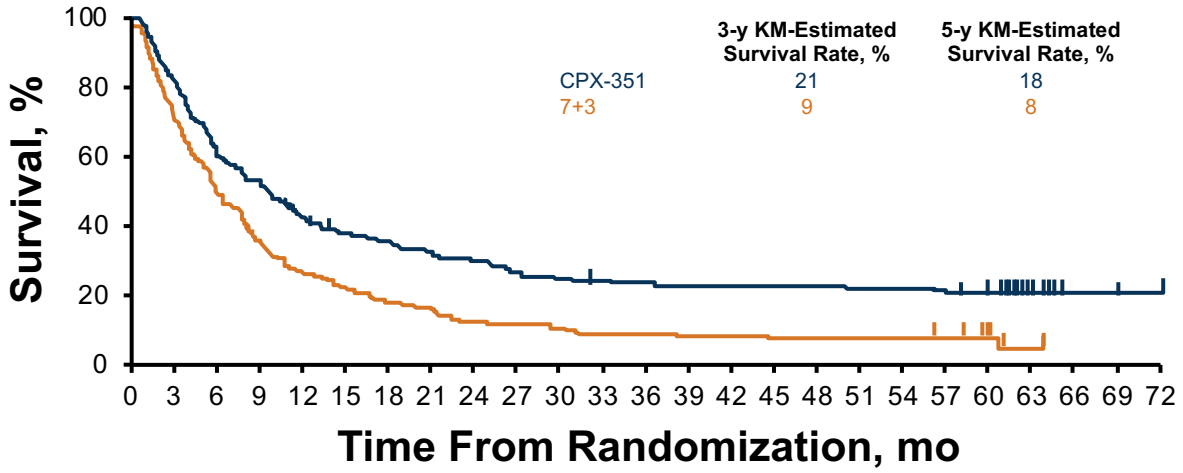
Lancet JE, et al. J Clin Oncol. 2018;36:2684-2692.

Courtesy of Eunice S Wang, MD

Five-year outcomes of CPX-351 vs 7+3

OS improvement maintained, showing that CPX-351 has the ability to produce or contribute to long-term remission and survival in older patients with newly diagnosed high-risk/secondary AML

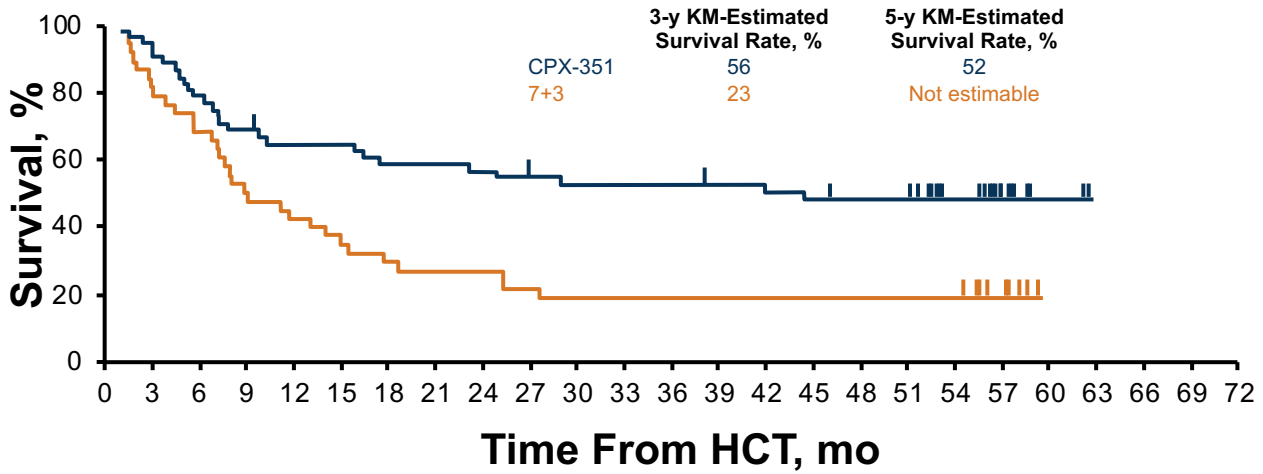
	Events/N	Median OS (95% CI)	HR (95% CI)
CPX-351	124/153	9.33 (6.37-11.86)	0.70 (0.55-0.91)
7+3	145/156	5.95 (4.99-7.75)	



CPX-351	153	122	92	79	62	52	49	45	40	35	33	31	30	29	29	29	29	28	28	26	22	6	2	1	0
7+3	156	110	77	56	43	35	28	25	20	19	17	14	14	13	13	12	12	12	12	11	5	1	0	0	0

Survival Landmarked From Time of HCT

	Events/N	Median OS (95% CI)	HR (95% CI)
CPX-351	25/53	Not reached	0.51 (0.28-0.90)
7+3	30/39	10.25 (6.21-16.69)	



CPX-351	53	48	42	37	35	35	32	32	31	29	28	28	28	27	27	26	24	24	21	15	6	2	0	0	0
7+3	39	31	27	20	18	14	12	12	12	9	9	9	9	9	9	9	9	9	8	2	0	0	0	0	0

1. Lancet JE et al. ASCO 2020 Annual Meeting (ASCO 2020). Abstract 7510

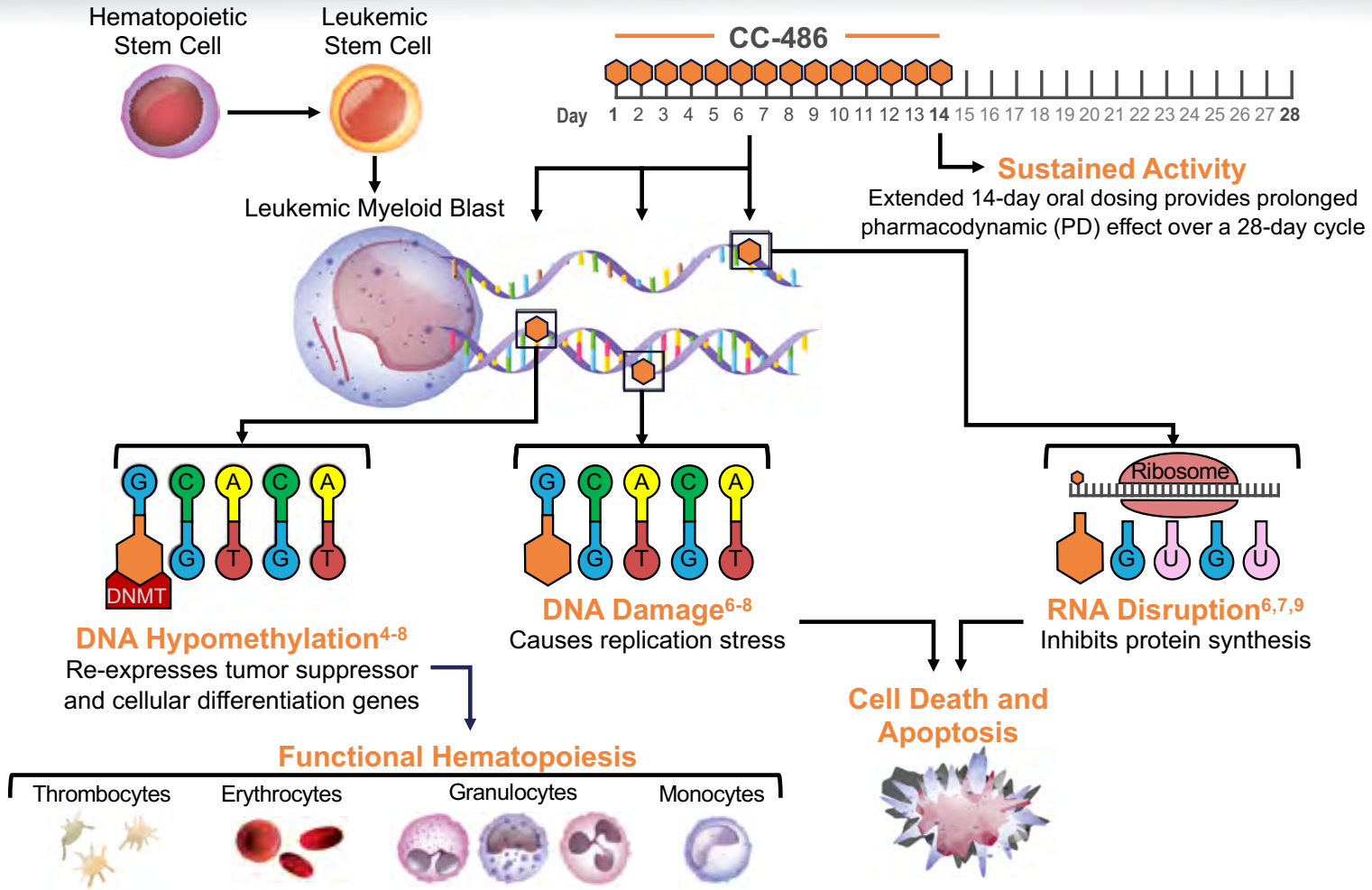
Courtesy of Eunice S Wang, MD

Ongoing clinical trials with CPX-351 in AML

- **CPX-351 compared with standard therapy**
  - Randomized trial of standard intensive chemo vs CPX-351 in newly diagnosed AML with intermediate/adverse cytogenetics
  - CPX-351 or CLAG-M in AML/high grade myeloid neoplasms
- **CPX-351 combined with targeted/non-targeted agents for AML**
  - CPX-351 + palbociclib in AML
  - CPX-351 + glasdegib for newly dx AML-MRC or tAML
  - Low intensity CPX-351 + venetoclax as first line therapy for AML
  - CPX-351 + GO in AML aged ≥ 55 yrs or relapsed AML
  - CPX-351 + enasidenib in relapsed IDH2 mutant AML
  - CPX-351 + venetoclax in RR and newly dx AML
  - CPX-351 + gilteritinib in FLT3 mutant/wildtype AML
- **CPX-351 in other indications**
  - CPX-351 in AML secondary to MPN

Courtesy of Eunice S Wang, MD

CC-486 (Oral Aza): First drug for AML maintenance



1. Garcia-Manero et al. *J Clin Oncol.* 2011;29(18):2521–7. 2. Laille et al. *PLoS One*. 2015;10(8):e0135520. 3. Garcia-Manero et al. *Leukemia*. 2016;30(4):889–96. 4. Savona et al. *Am J Hematol.* 2018;93(10):1199–206. 5. Streseman et al. *Mol Cancer Ther*. 2008;7:2998–3005. 6. Hollenbach et al. *PLoS One*. 2010;5(2):e9001. 7. Scott LJ. *Drugs*. 2016;76(8):889–900. 8. Stresemann C, Lyko F. *Int J Cancer*. 2008;123(1):8–13. 9. Aimiuwu et al. *Blood*. 2012;119(22):5229–38.
AML, acute myeloid leukemia; DNMT, DNA methyltransferase; PD, pharmacodynamic; PK, pharmacokinetic.

Courtesy of Eunice S Wang, MD

QUAZAR AML trial: CC-486 vs placebo

International, multicenter, placebo-controlled, double-blind, randomized, phase III study that enrolled patients from 148 sites in 23 countries (NCT01757535)

PRE-RANDOMIZATION

Screening

Key eligibility criteria:

- First CR / CRi with IC ± consolidation
- Age ≥55 years
- *de novo* or secondary AML
- ECOG PS score 0-3
- Intermediate- or poor-risk cytogenetics
- Ineligible for HSCT
- Adequate bone marrow recovery (ANC ≥0.5 × 10^9/L, platelet count ≥20 × 10^9/L)

RANDOMIZATION

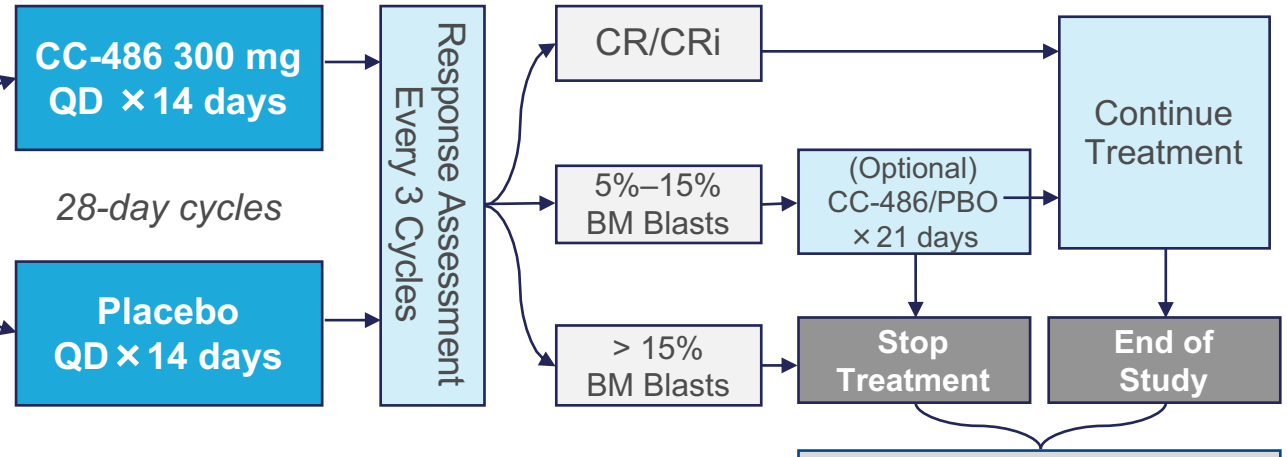
Randomization (1:1)

Within 4 months (±7 days) of CR/CRi

Stratified by:

- Age: 55–64 / ≥ 65
- Prior MDS/CMML: Y / N
- Cytogenetic risk: Intermediate / Poor
- Consolidation: Y / N

TREATMENT PHASE



MRD evaluable cohort was 463/472 randomized patients (98.1%)

- **Oral Aza: 44% (n=103) MRD+ at BL**
- **Placebo: 51% (n=116) MRD+ at BL**

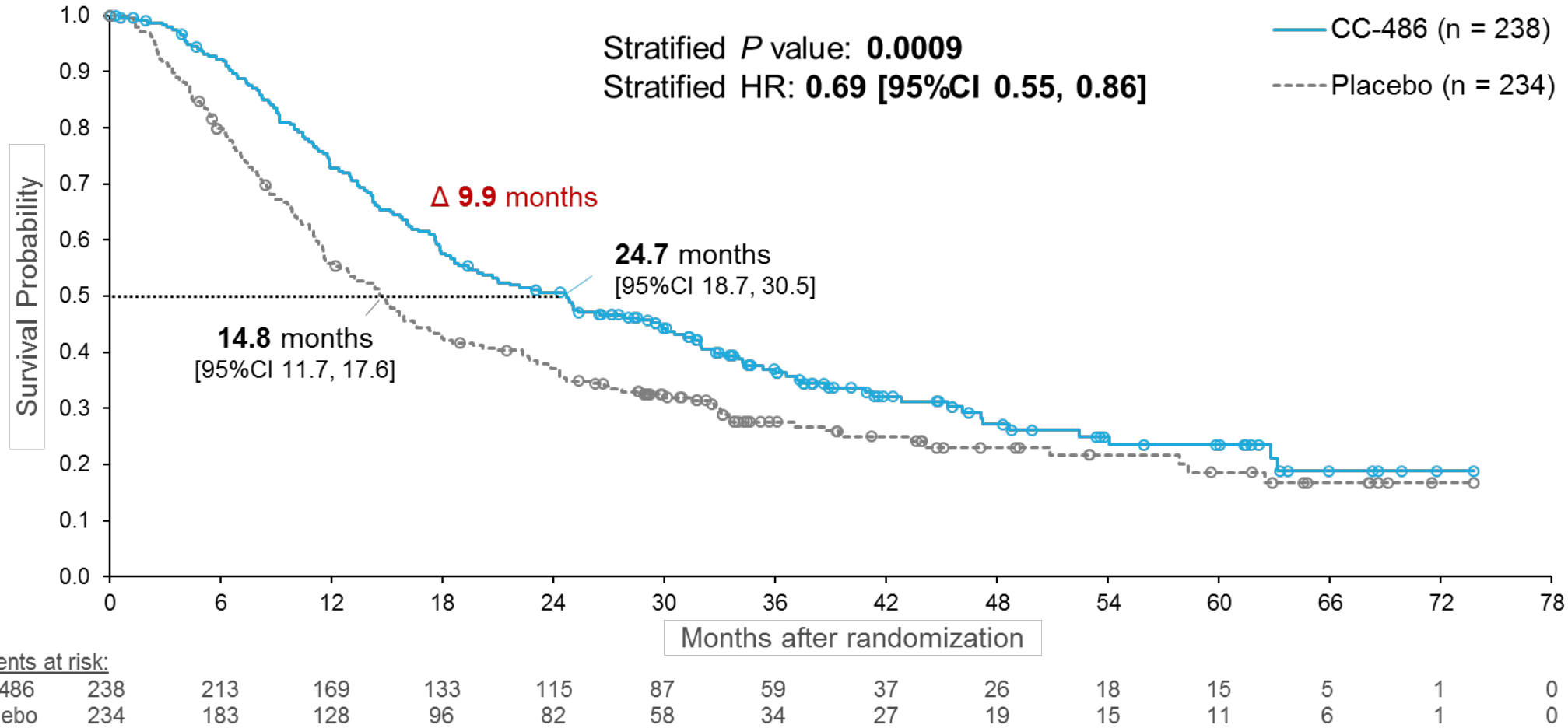
FOLLOW-UP

- Follow until death, withdrawal of consent, study termination, or loss to follow-up

Courtesy of Eunice S Wang, MD

QUAZAR AML-001: Overall survival from randomization

- Median follow-up: 41.2 months

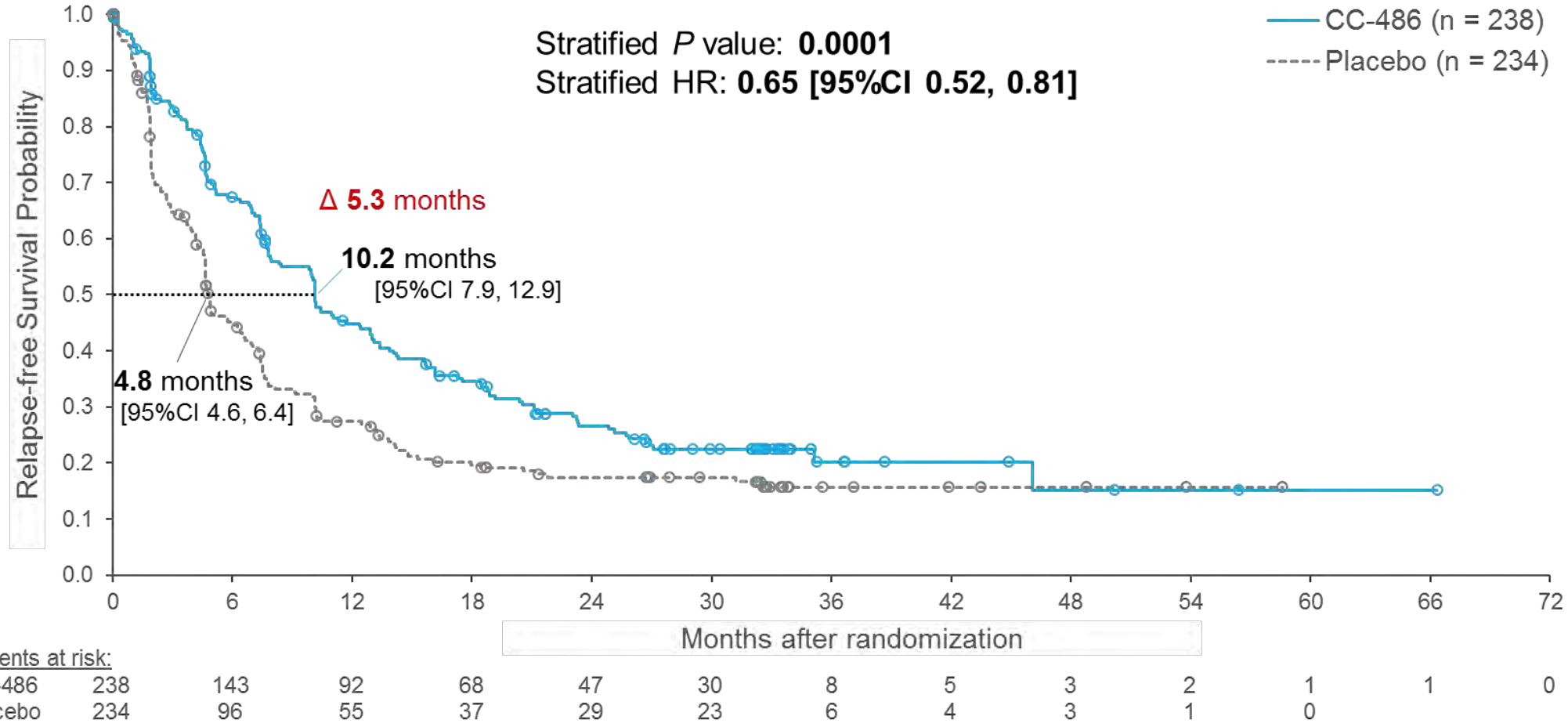


Patients at risk:

CC-486	238	213	169	133	115	87	59	37	26	18	15	5	1	0
Placebo	234	183	128	96	82	58	34	27	19	15	11	6	1	0

Courtesy of Eunice S Wang, MD

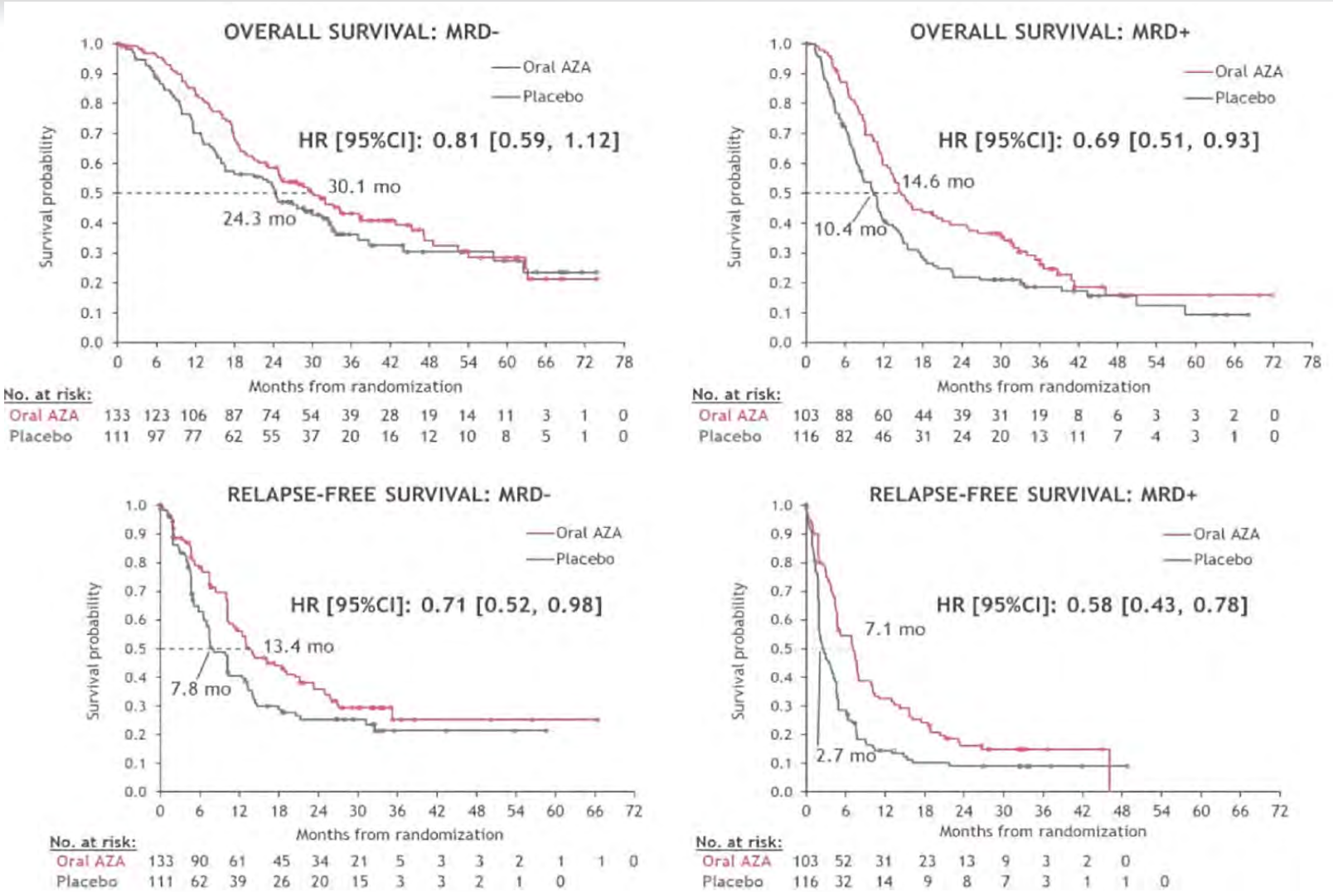
QUAZAR AML trial: Relapse-free survival



- 1-year relapse rate was 53% in the CC-486 arm [95%CI 46, 59] and was 71% in the placebo arm [65, 77]

Courtesy of Eunice S Wang, MD

CC-486: OS and RFS by baseline MRD status and treatment arm



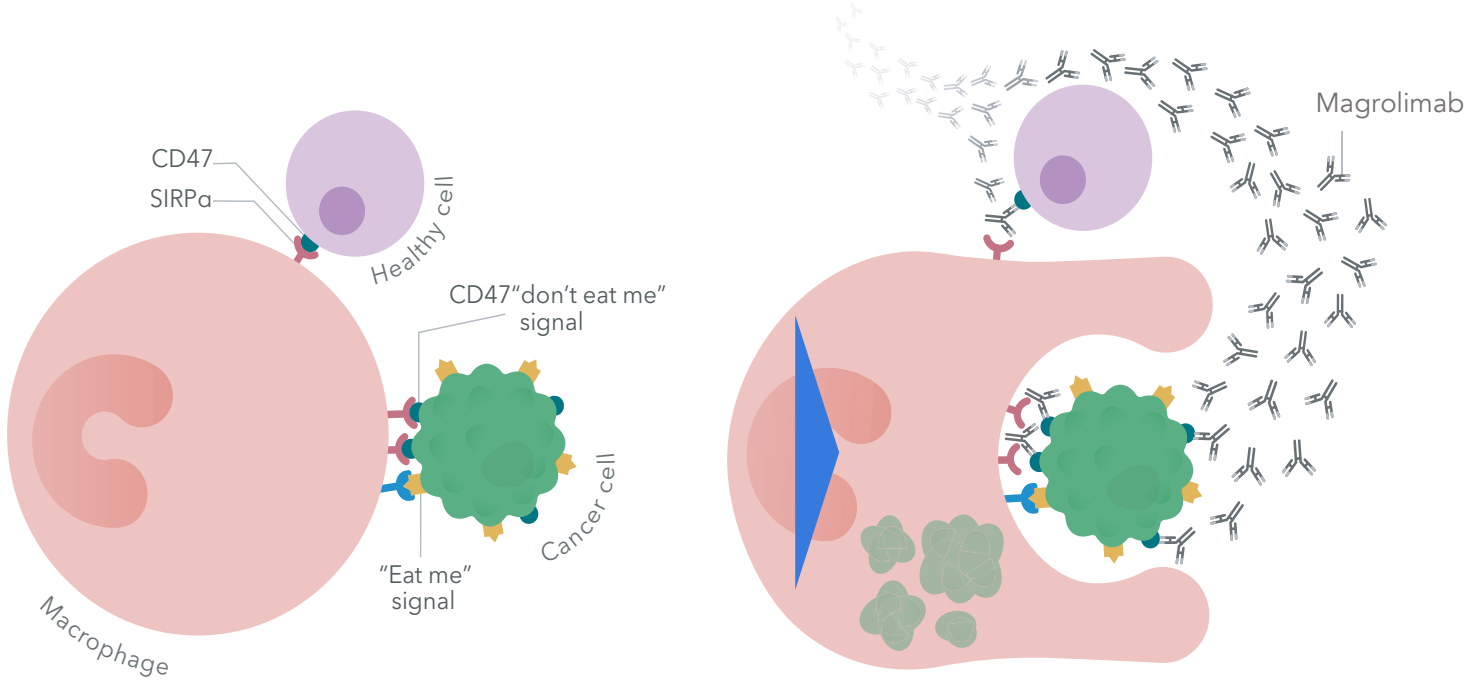
Summary

- MRD+ status was associated with shorter OS and RFS vs patients with MRD- AML
- Oral aza maintenance improved OS and RFS independent of MRD status at baseline
- **Oral AZA was associated with a higher rate of MRD response** (i.e. MRD+ at start, became MRD- on study): **37% vs 19%**

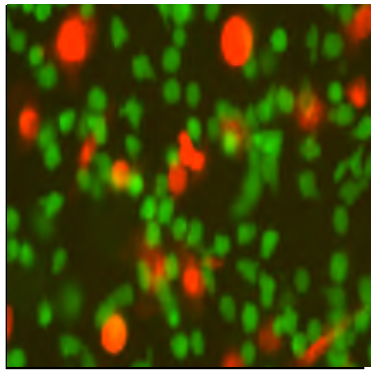
Roboz GJ, et al. ASH 2020. Abstract 692

Courtesy of Eunice S Wang, MD

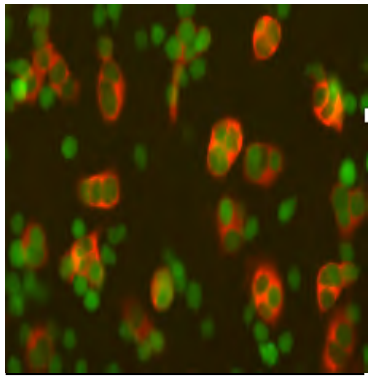
Magrolimab (anti-CD47) induces macrophage phagocytosis



Control mAb: No Phagocytosis



Anti-CD47 mAb: Phagocytosis



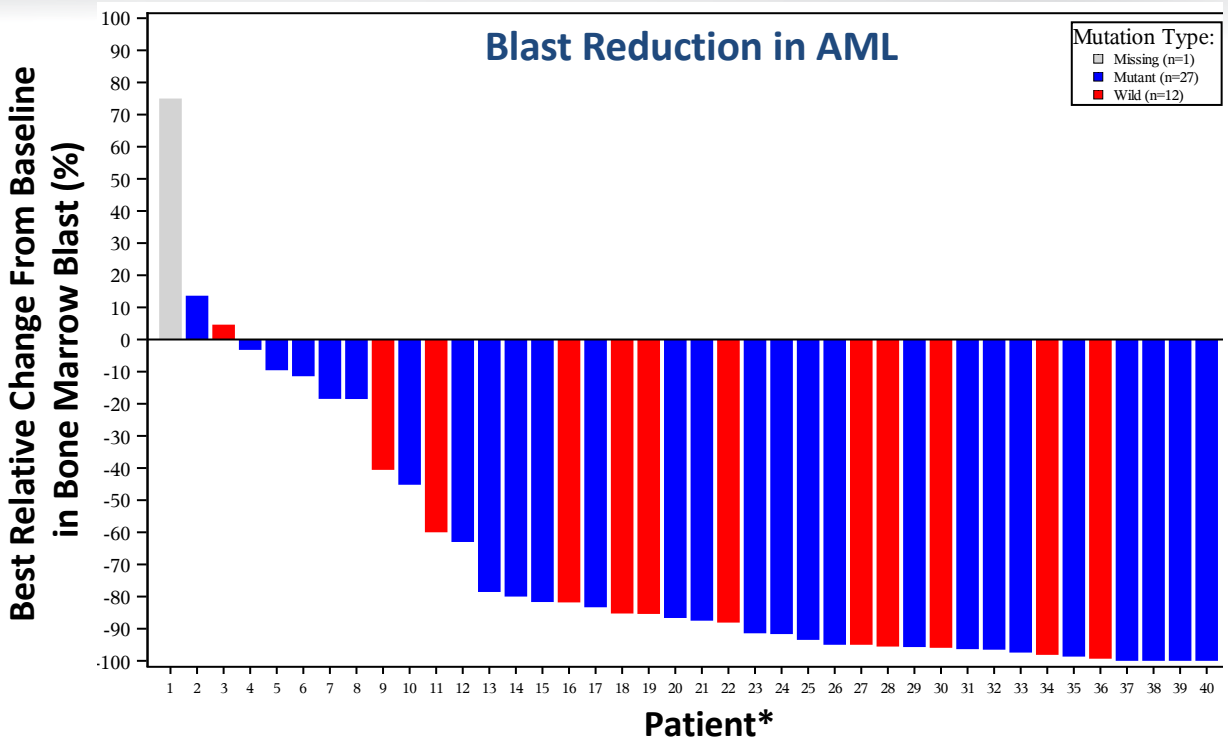
Macrophages
Cancer cells

- Magrolimab is an IgG4 anti-CD47 monoclonal antibody that eliminates tumor cells through macrophage phagocytosis
- Magrolimab is being investigated in multiple cancers with >500 patients dosed

Courtesy of Eunice S Wang, MD

Outcomes of Magrolimab + Azacitidine in de novo AML

Best Overall Response	All AML (N=43)	*TP53*-mutant AML (29)
ORR	**27 (63%)**	**20 (69%)**
CR	**18 (42%)**	**13 (45%)**
CRi	5 (12%)	4 (14%)
PR	1 (2%)	1 (3%)
MLFS	3 (7%)	2 (7%)
SD	14 (33%)	8 (28%)
PD	2 (5%)	1 (3%)



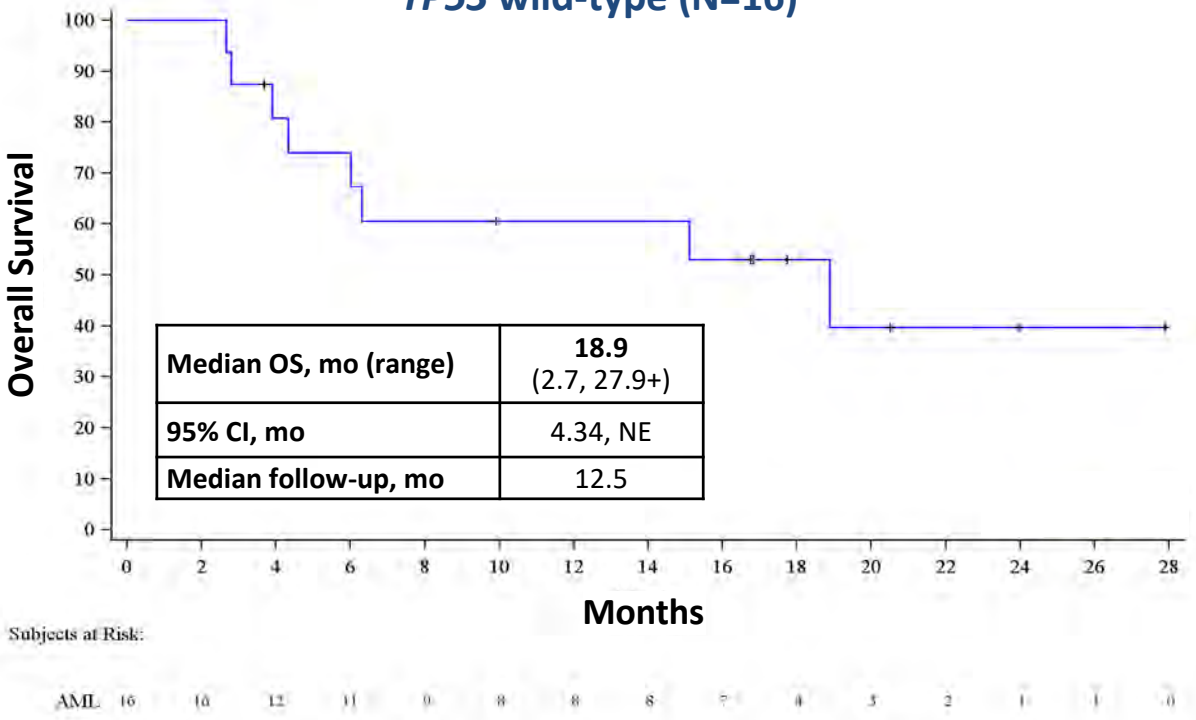
- **Magrolimab + AZA induces a 63% ORR and 42% CR rate in AML, including similar responses in *TP53*-mutant patients**
- Median time to response is **1.95 months** (range 0.95 to 5.6 mo), more rapid than AZA monotherapy
- 9.6% of patients proceeded to bone marrow stem cell transplantation
- Magrolimab + AZA efficacy compares favorably to AZA monotherapy (CR rate 18%–20%)[1,2]

Sallman D et al, ASH 2020, abstract #330

Courtesy of Eunice S Wang, MD

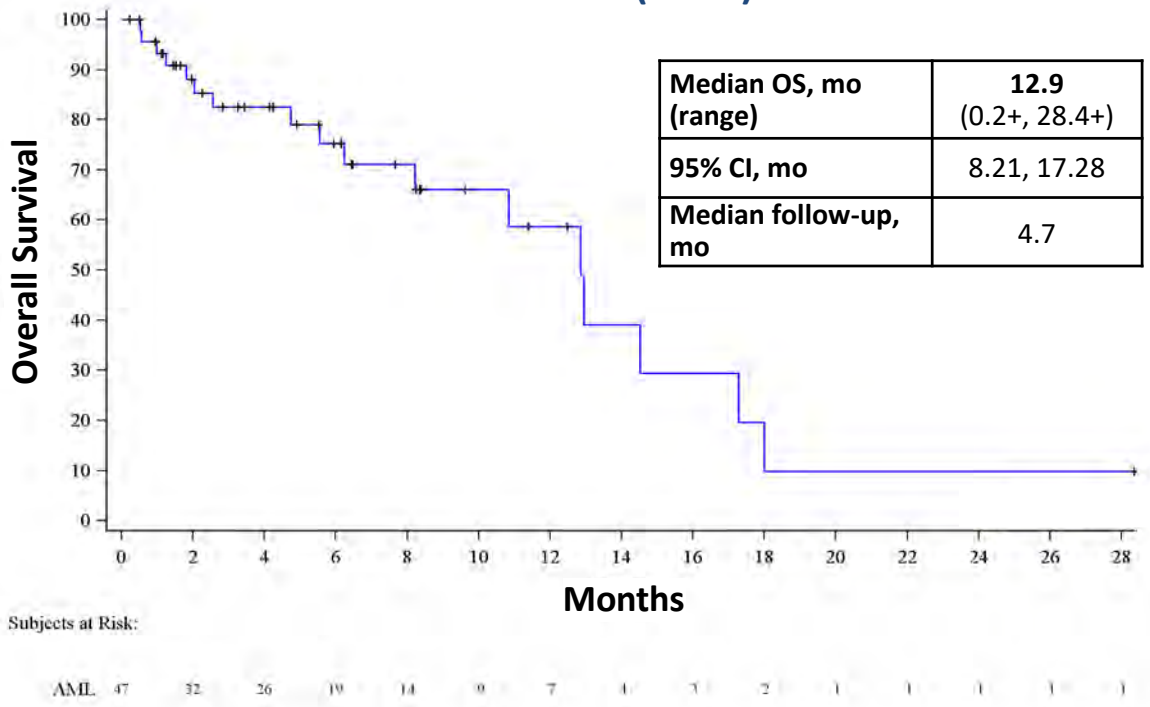
Survival of unfit AML patients after Magrolimab + Aza

TP53 wild-type (N=16)



Median OS, mo (range)	**18.9** (2.7, 27.9+)
95% CI, mo	4.34, NE
Median follow-up, mo	12.5

TP53 mutant (N=47)



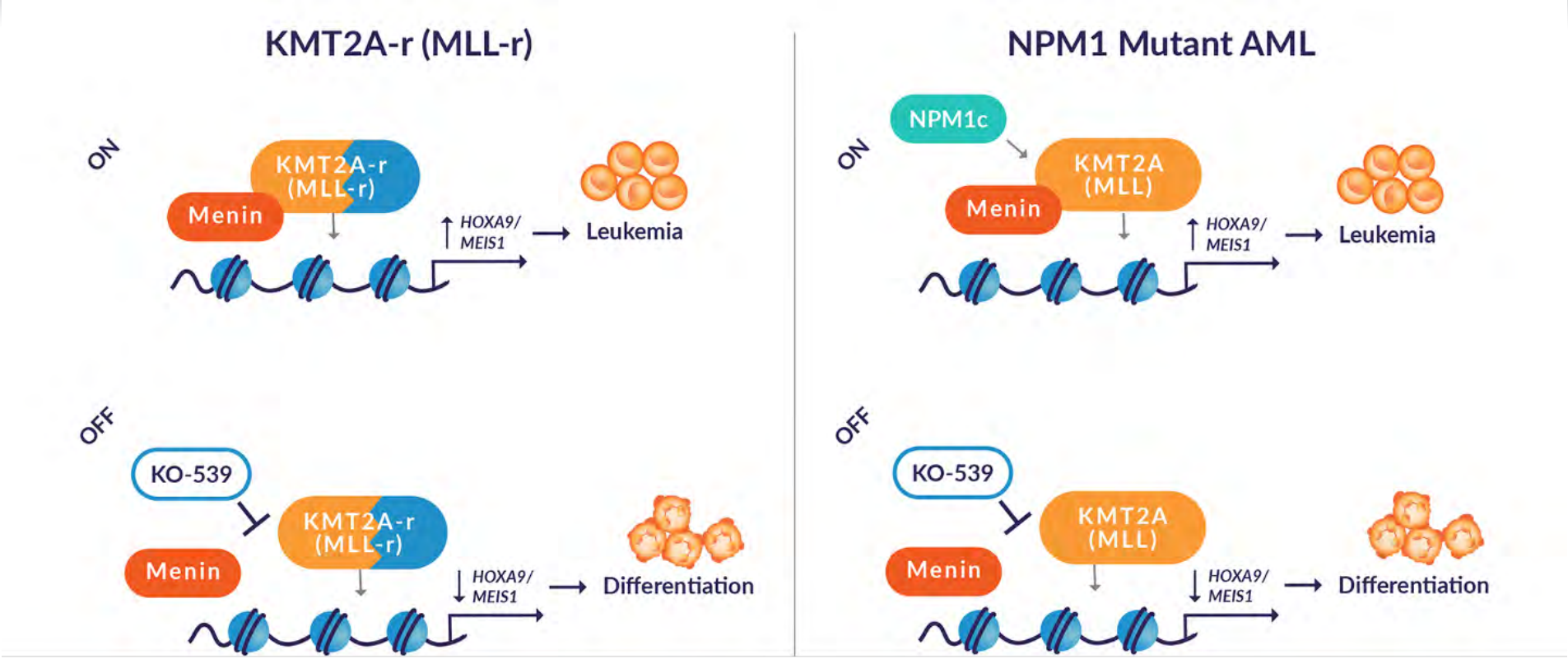
Median OS, mo (range)	**12.9** (0.2+, 28.4+)
95% CI, mo	8.21, 17.28
Median follow-up, mo	4.7

- The median OS is 18.9 months in *TP53* wild-type patients and 12.9 months in *TP53*-mutant patients
- This initial median OS data may compare favorably to venetoclax + hypomethylating agent combinations (**14.7-17.5 mo** in all-comers,[1,3] **5.2–7.2 mo** in patients who are *TP53* mutant[2,3])
- Additional patients and longer follow-up are needed to further characterize the survival benefit

Sallman D et al, ASH 2020, abstract #330

Courtesy of Eunice S Wang, MD

Menin inhibitors target KMT2A-r and NPM-1 mutant AML



Targeting the menin-KMT2A(MLL) interaction to reverse epigenetic dysregulation in MLL-rearranged AML

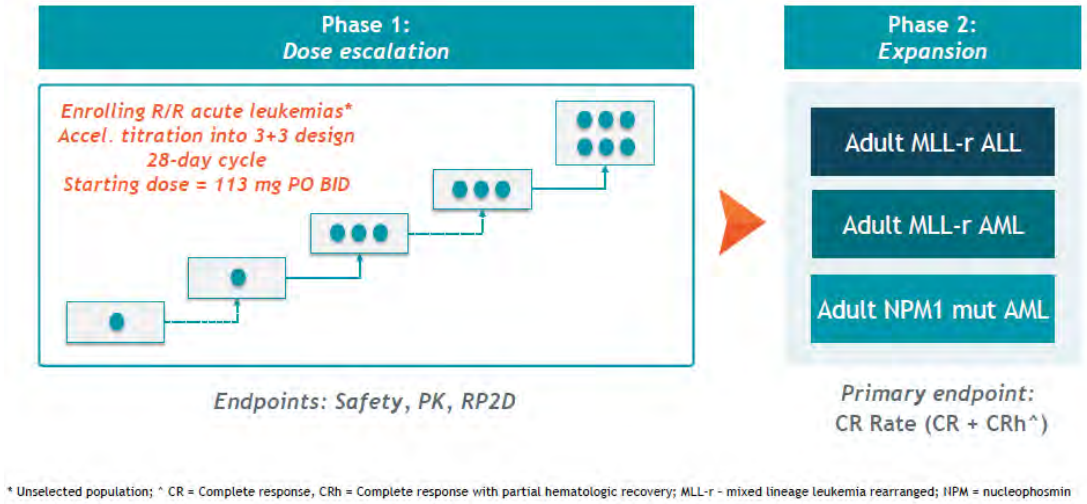
A central role for menin-KMT2A(MLL) interaction in epigenetic dysregulation in NPM1-mutant AML

Kühn MW, *et al. Cancer Discov.* 2016;6(10):1166; Thorsteinsdottir U, *et al. MCB* 2001;21(1):224; Patel SS, *et al. Curr Hematol Malig Rep.* 2020;15(4):350; Brunetti L, *et al. Cancer Cell.* 2018;34(3):499-512

Courtesy of Eunice S Wang, MD

AUGMENT-101: Phase 1/2 Trials of SNDX-5613

AUGMENT-101 schema: ALL & AML pts



* Unselected population; ^ CR = Complete response, CRh = Complete response with partial hematologic recovery; MLL-r - mixed lineage leukemia rearranged; NPM = nucleophosmin

PK: QTC prolongation, interactions with Azoles (CYP inhibitors)

Patient outcomes (4/20/21)

43 pts (median 3 prior lines of Rx) with RR-AML
31 pts efficacy evaluable
- **ORR 48% (n=15)**
- **2/3rd of responses (67%, n=10) MRDneg**

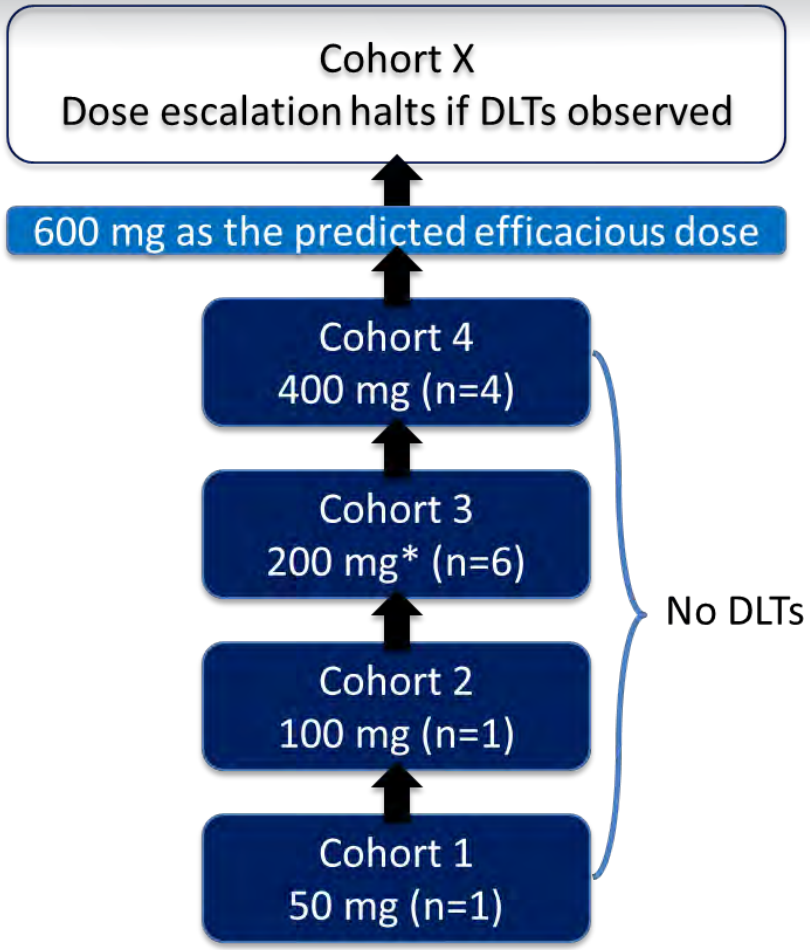
MLL-r AML (n=24): 54% ORR (n=13)
NPM-c AML (n=7): 29% ORR (n=2)

RP2D: 226 mg q12h (strong CYP3A4 inhibitor)
113 mg q12h (no strong CYP3A4 inhibitor)
TAEs >5%: QTc prolongation (9%), anemia, DS

McGeehan J. 2020 AACR Virtual Annual Meeting Abstract DDT01-01; Syndax press release 4/20/21

Courtesy of Eunice S Wang, MD

KOMET-1: Phase 1 schema and results of KO-539



*Expanded to characterize PK

Clinical activities observed in 6 patients (efficacy evaluable = 8)				
Dose	Mutational Profile	CYP3A4 inhibitor	# of prior regimens	Clinical Activity
400 mg	RUNX1, SRSF2, ASXL1, TET2, STAG2, BCOR, PTPN11	Yes	3	Decreased peripheral blasts
200 mg	U2AF1, TET2, p53, DNMT3A, PTPN11	No	4	Stable disease
	NPM1, FLT3-ITD, TET2, CUX1	Yes	4	Morphological leukemia-free state
	NPM1, DNMT3A, KMT2D	Yes	7	CR, MRD-
100 mg	SETD2, RUNX1	Yes	2	CR, MRD+
50 mg	KMT2A-r	Yes	2	Decreasing hydrea requirement

No doses discontinued due to Rx-related AEs.
No ECG changes or interactions with azoles.

Wang ES et al ASH 2020: abstract

Courtesy of Eunice S Wang, MD

Case Presentation – Dr Wang: A 59-year-old woman with leukemia cutis

- 59 yo woman with prior medical history of COPD who noted one spot on her face and then developed multiple spots on the left side of her face. She went to the dermatologist for a skin biopsy in May 2020 revealing leukemia cutis. Flow cytometry demonstrated an abnormal myeloid population expressing CD34 + CD123 + HLA-DR positive cells.

- Based on this result, she was admitted to the leukemia inpatient service at our center. BMBx showed no morphologic evidence of AML with no abnormalities on NGS and normal karyotype. She was treated with 7 + 3 (cytarabine and daunorubicin) with complete resolution of all the skin lesions and negative PET scan for extramedullary disease following therapy.

Case Presentation – Dr Wang: A 59-year-old woman with leukemia cutis (continued)

- She then went on to receive cycle 1 of high dose cytarabine consolidation chemotherapy complicated by multiple admissions for fevers and low platelet counts refractory to transfusions (<5k). Following cycle 1 consolidation, she had prolonged time to count recovery with platelet count <100K over 52 days following initiation of last therapy. Patient not interested in allogeneic stem cell transplant due to lack of social and family support.

- She started on oral azacitidine therapy in Dec 2020. Repeat BMBX following 6 months of therapy demonstrated no evidence of AML with 1% blasts and MRD negative disease by flow cytometry. She continues to complain of drug related nausea requiring multiple prophylactic anti-emetic drugs. After completing 10 cycles of therapy, she reported to clinic with a new "spot" on her cheek. Awaiting skin biopsy result to rule out dermatitis vs recurrent leukemia cutis.

Case Presentation – Dr Wang: A 64-year-old man with secondary AML and TET2, JAK2, CBL, CUX1 and SRSF2 mutations

- 64 yo man noted to have leukopenia and thrombocytopenia in 2013. Marrow done in 2014 showed hypercellular marrow with normal cytogenetics consistent with MDS/MPN. He was followed observantly until 2019 when leukocytosis was noted on labs. Repeat BMBx continued to demonstrate profibrotic stage of MPN with JAK2V617F mutation. Given his age and the marrow findings, he was started on ruxolitinib 15 mg po BID.

- Over the next few months, however, he develops progressive anemia and back pain and is found to have AML transformation with WBC of 49K. BMBX demonstrated AML with monocytic differentiation with 80% blasts in a packed (>95%) marrow. NGS reveals TET2, JAK2, CBL, CUX1, SRSF2 mutations.

Case Presentation – Dr Wang: A 64-year-old man with secondary AML and TET2, JAK2, CBL, CUX1 and SRSF2 mutations (cont)

- Ruxolitinib is tapered off and he received induction therapy with liposomal cytarabine and daunorubicin in May 2021. Bone marrow biopsy at nadir demonstrates no evidence of AML. However at count recovery BMBX was consistent with persistent JAK2 mutant MPN with no increased blasts.
- Due to lack of platelet recovery, the patient initiated azacitidine maintenance therapy in combination with ruxolitinib 10 mg bid. Counts remain low (WBC 1.2, hgb 8.0, plts 59K) and workup for allogeneic stem cell transplant as next therapy is under way.

Agenda

Prologue: A Personal Reflection on Acute Myeloid Leukemia (AML)

Module 1: Up-Front Treatment of AML in Patients Who Are Not Eligible for Intensive Therapy

Module 2: Management of AML with Targetable Mutations

Module 3: Other Currently Available and Investigational Treatment Strategies for AML

Module 4: Management of Myelodysplastic Syndromes (MDS)

Regulatory and reimbursement issues aside, what is your preferred treatment for an otherwise healthy 72-year-old patient with lower-risk MDS with no del(5q), ring sideroblasts <15% and transfusion-dependent anemia who responds to darbepoetin alfa but then develops a new transfusion requirement?

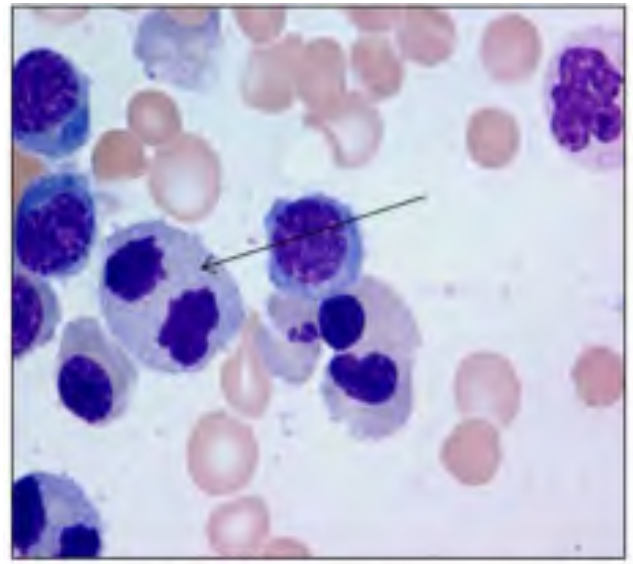
1. Luspatercept
2. Azacitidine
3. Decitabine
4. Decitabine/cedazuridine (oral decitabine)
5. Imetelstat
6. Other

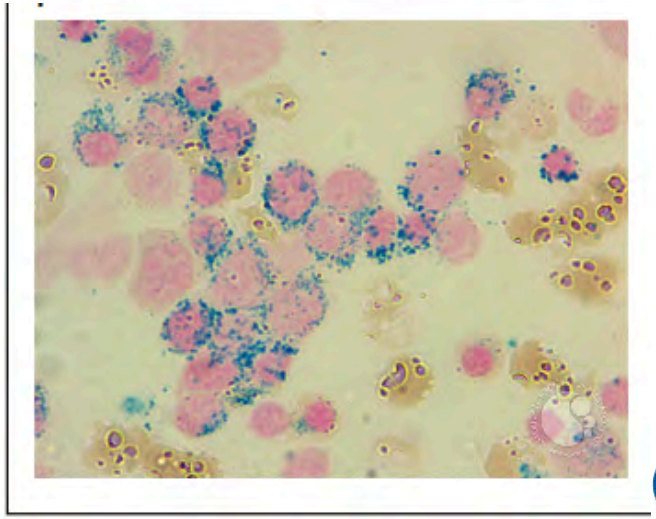
Regulatory and reimbursement issues aside, what is your preferred treatment for an otherwise healthy 72-year-old patient with lower-risk MDS with no del(5q), ring sideroblasts >15% and transfusion-dependent anemia who responds to darbepoetin alfa but then develops a new transfusion requirement?

1. Luspatercept
2. Azacitidine
3. Decitabine
4. Decitabine/cedazuridine (oral decitabine)
5. Imetelstat
6. Other

Case Presentation – Dr Sallman: A 68-year-old woman with lower-risk MDS

- 68 yo female with transfusion dependent anemia with MDS-RS with an isolated SF3B1 mutation and an IPSS-R of low presents for evaluation.
- CBC at baseline with hgb of 8gm/dl (2U PRBC 2 weeks prior) and nl ANC/platelets. BM biopsy showed 25% ringed sideroblasts with unilineage dysplasia and no increase in BM blasts.
- Patient had failed a 4-month trial of epoetin at 60,000U weekly





Case Presentation – Dr Sallman: A 68-year-old woman with lower-risk MDS (continued)

- Patient was started on luspatercept 1 mg/kg every 3 weeks and patient had decreased transfusion requirement to 2 units monthly
- Patient increased up to 1.75mg/kg and patient achieved transfusion independence that has been ongoing x 36 weeks to date.

Risk Stratification – Revised IPSS (IPSS-R)

Parameter	IPSS-R				
	Categories and associated scores				
Cytogenetic risk group	Very good	Good	Intermediate	Poor	Very poor
	0	1	2	3	4
Marrow blast proportion	<2%	2%-<5%	5%-10%	>10%	
	0	1	2	3	
Hemoglobin	≥10 g/dL	8-<10 g/dL	<8 g/dL		
	0	1	1.5		
Absolute neutrophil count	$\geq 0.8 \times 10^9$/L	$<0.8 \times 10^9$/L			
	0	0.5			
Platelet count	$\geq 100 \times 10^9$/L	$50\text{-}100 \times 10^9$/L	$<50 \times 10^9$/L		
	0	0.5	1		

Overall Survival

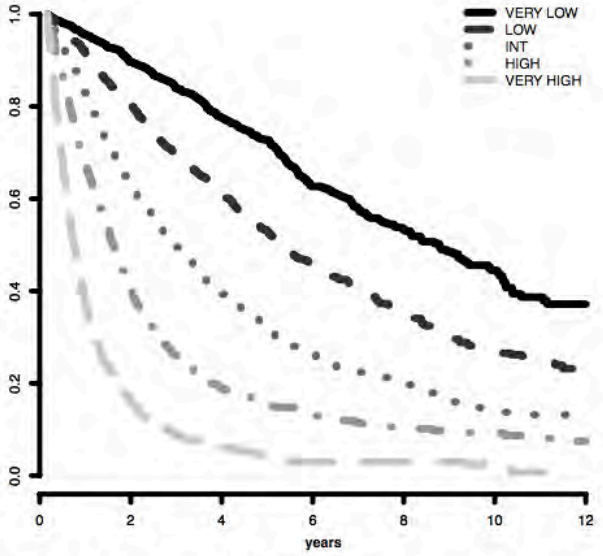


Figure 3. Survival based on IPSS-R prognostic risk-based categories. Survival related to MDS patients' prognostic risk categories (Kaplan-Meier curves, n = 7012; Dxy 0.43, $P < .001$). The number of patients in each category and their proportional representation are shown in Table 1.

Progression to AML

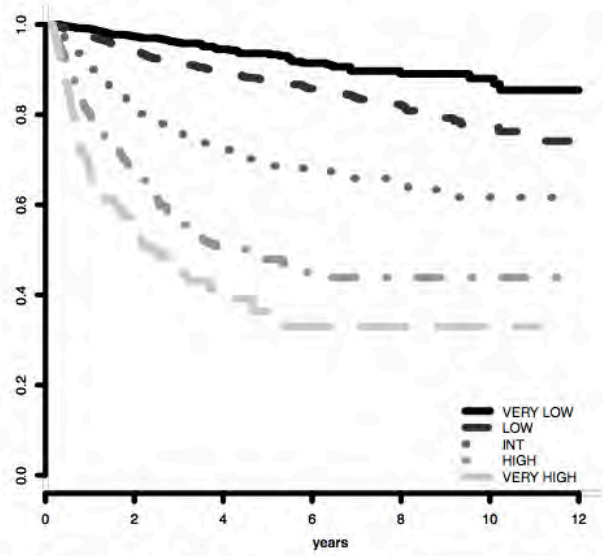


Figure 4. AML evolution based on IPSS-R prognostic risk-based categories. Progression to AML related to MDS patients' prognostic risk categories (Kaplan-Meier curves, n = 6485; Dxy 0.52, $P < .001$). The number of patients in each category and their proportional representation are shown in Table 1.

Greenberg P et al. *Blood 2012.*

Courtesy of David Sallman, MD

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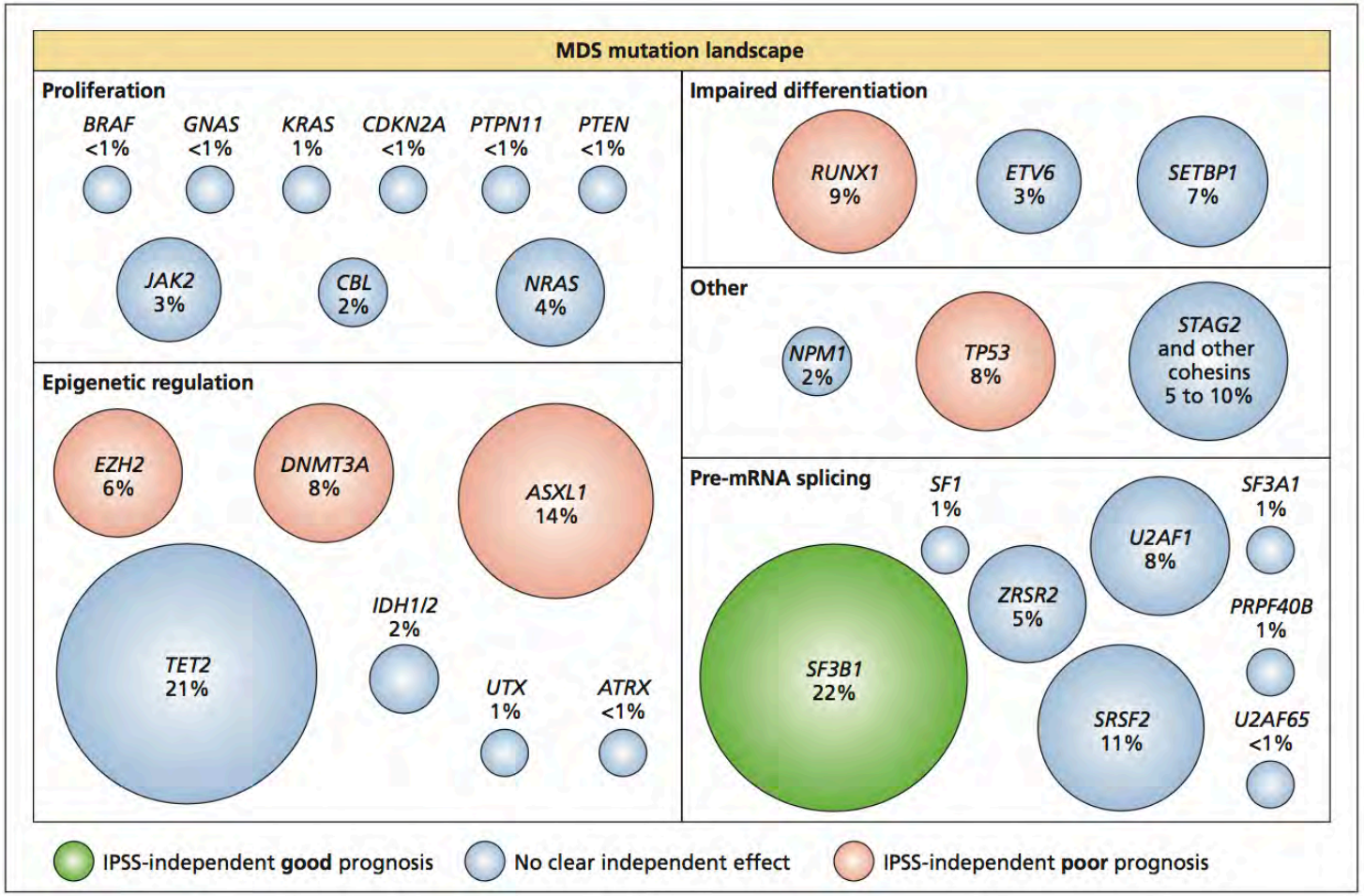
NGS Further Refines Prognosis



IPSS-independent

GOOD prognosis:

- **SF3B1**

IPSS-independent

POOR prognosis:

- **TP53**
- ASXL1
- **EZH2**
- RUNX1
- ETV6
- CBL
- U2AF1

Steensma D et al. *Mayo Clinic Proceedings* 2015; Nazha A, et al. *Leukemia*. 2016.

Courtesy of David Sallman, MD

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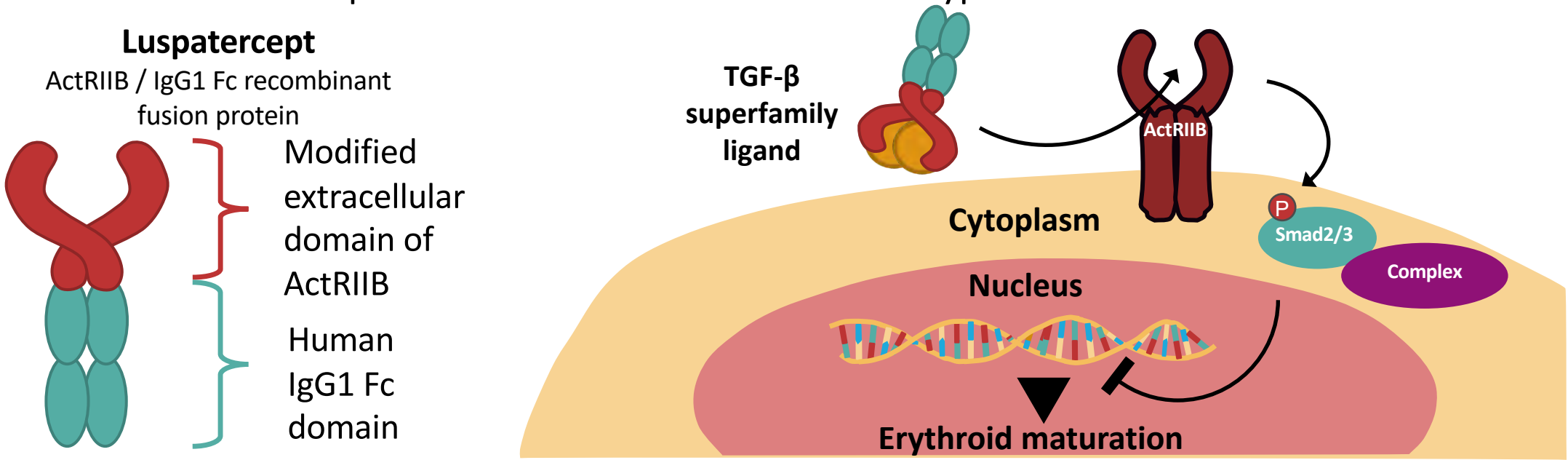
MEDALIST Trial

Luspatercept

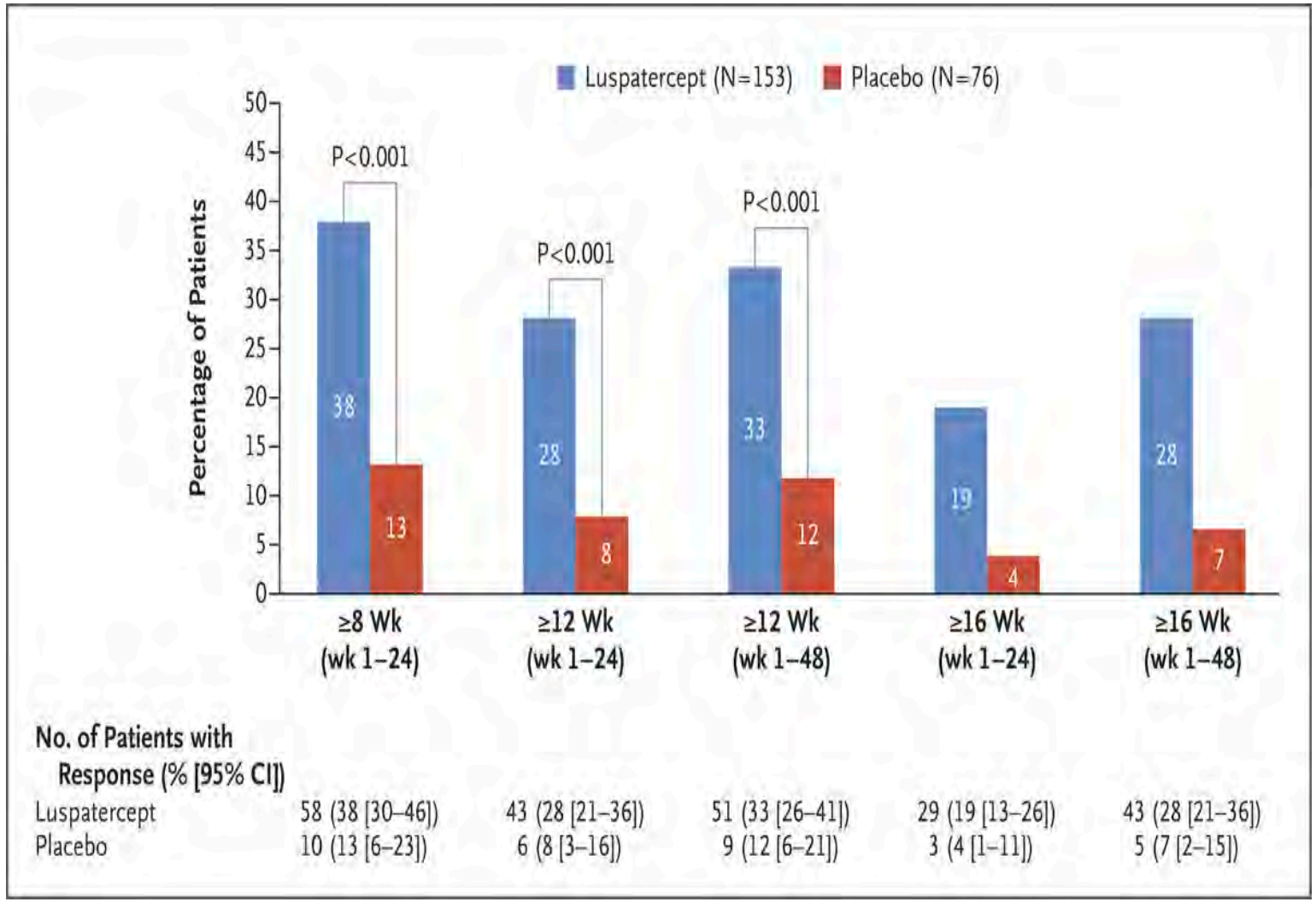
- Luspatercept is an investigational first-in-class erythroid maturation agent that neutralizes select TGF-β superfamily ligands to inhibit aberrant Smad2/3 signaling and enhance late-stage erythropoiesis in MDS models[1]
- In a phase 2 study in LR, non-del(5q) MDS, luspatercept yielded a high frequency of transfusion reduction or RBC-TI in patients with MDS-RS vs other subtypes[2]



ActRIIB, human activin receptor type IIB; IgG1 Fc, immunoglobulin G1 fragment crystallizable; RBC-TI, red blood cell transfusion independence; RS, ring sideroblasts; TGF-β, transforming growth factor beta.

1. Suragani RN, et al. Nat Med. 2014;20:408-414;
2. Platzbecker U, et. A. Lancet Oncol. 2017; 18:1338.

Luspatercept in MDS-RS - MEDALIST



P3 COMMANDS STUDY ONGOING IN FRONTLINE LR-MDS

Courtesy of David Sallman, MD

P Fenaux et al. N Engl J Med 2020;382:140-151.

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Luspatercept in MDS-RS - MEDALIST

Table 2. Erythroid Response and Increase in Mean Hemoglobin Levels.

End Point	Luspatercept (N=153)	Placebo (N=76)
Erythroid response during wk 1–24*		
No. of patients (% [95% CI])	81 (53 [45–61])	9 (12 [6–21])
Reduction of ≥4 red-cell units/8 wk — no./total no. (%)†	52/107 (49)	8/56 (14)
Mean increase in hemoglobin level of ≥1.5 g/dl — no./total no. (%)‡	29/46 (63)	1/20 (5)
Erythroid response during wk 1–48*		
No. of patients (% [95% CI])	90 (59 [51–67])	13 (17 [9–27])
Reduction of ≥4 red-cell units/8 wk — no./total no. (%)†	58/107 (54)	12/56 (21)
Mean increase in hemoglobin level of ≥1.5 g/dl — no./total no. (%)‡	32/46 (70)	1/20 (5)
Mean increase in hemoglobin level of ≥1.0 g/dl — no. (% [95% CI])§		
During wk 1–24	54 (35 [28–43])	6 (8 [3–16])
During wk 1–48	63 (41 [33–49])	8 (11 [5–20])

P3 COMMANDS STUDY ONGOING IN FRONTLINE LR-MDS

Courtesy of David Sallman, MD

P Fenaux et al. N Engl J Med 2020;382:140-151.

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AZA + Ven Frontline Study

Any AEs, n (%)	78 (100)
Neutropenia[a]	65 (83)
Febrile neutropenia	38 (49)
Nausea	43 (55)
Constipation	42 (54)
Diarrhea	38 (49)
Thrombocytopenia[b]	38 (49)
Vomiting	32 (41)
Leukopenia[c]	30 (38)
Anemia[d]	23 (29)
Fatigue	20 (26)
Hypokalemia	16 (21)

Grade 3/4 AEs, n (%)	75 (96)
Neutropenia[a]	64 (82)
Febrile neutropenia	38 (49)
Thrombocytopenia[b]	33 (42)
Leukopenia[c]	30 (38)
Anemia[d]	18 (23)

Any SAEs, n (%)	57 (73)
Neutropenia[a]	38 (49)
Febrile neutropenia	35 (45)
Pneumonia	5 (6)
Diverticulitis	4 (5)

- Overall, 74 patients (95%) required a cycle delay; median time to delay 15.0 days (range 3–99)
- 43 patients (55%) had ≥2 Ven dose interruptions
  - AEs 59 (80%); hematologic toxicity 27 (37%); logistics/scheduling 19 (26%), other 41 (55%)
- A total of 35% of patients required ≥1 Ven dose reduction[e]
  - AEs 6 (21%); starting CYP3A inhibitor 20 (71%); other 7 (25%)
- A total of 33% of patients required ≥1 Aza dose reduction[e]
- 30-day mortality after first dose was 1%

Ven Schedule for MDS is days 1-14 on a 28 day Cycle

Courtesy of David Sallman, MD

Garcia JS et al., ASH 2020

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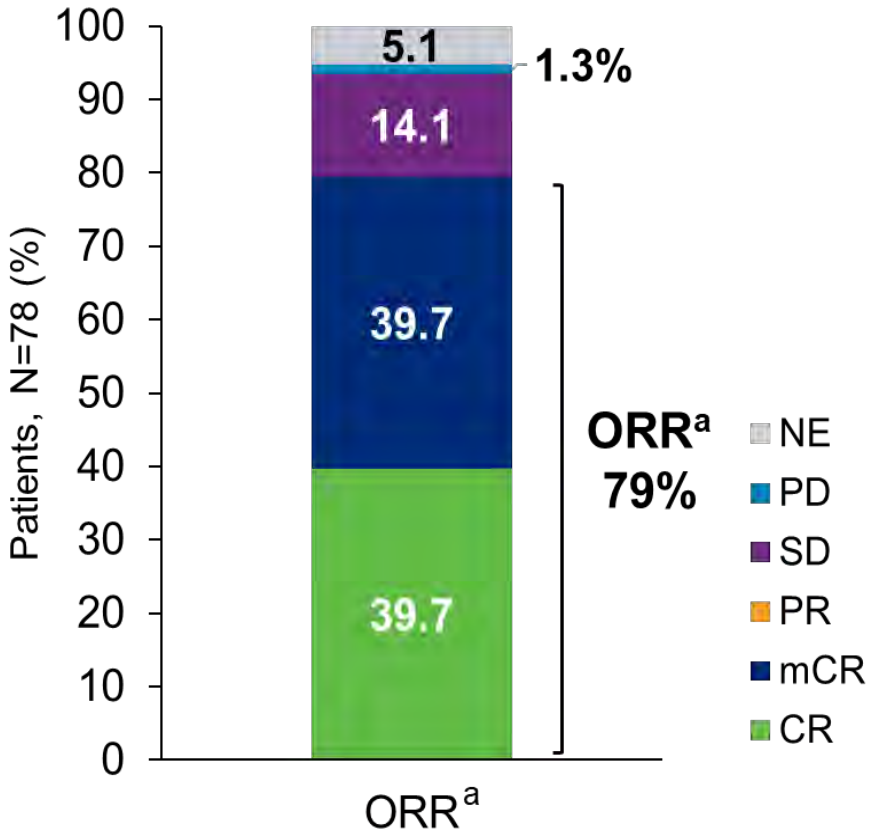
AZA + Ven Frontline Study



- Median DoR: 12.9 months (min–max, 12.1–16.8)
- Median DoR after CR: 13.8 months (min–max, 6.5–20.9)
- Median time to CR: 2.6 months (min–max, 1.2–19.6)
- For patients receiving Ven 400 mg (RP2D; n=51)[b]
  - 84% of patients achieved ORR[a]
    - 47% achieved ORR by Cycle 2; 78% achieved ORR by Cycle 3
  - 35% of patients achieved CR

Transfusion independence rate	n (% of N=78)
RBC and platelet	51 (65)
RBC	52 (67)
Platelet	60 (77)

- A total of 16 patients (21%) went on to receive poststudy transplants; 7 received bone marrow transplant; and 9 received stem cell transplant

Garcia JS et al., ASH 2020

Courtesy of David Sallman, MD

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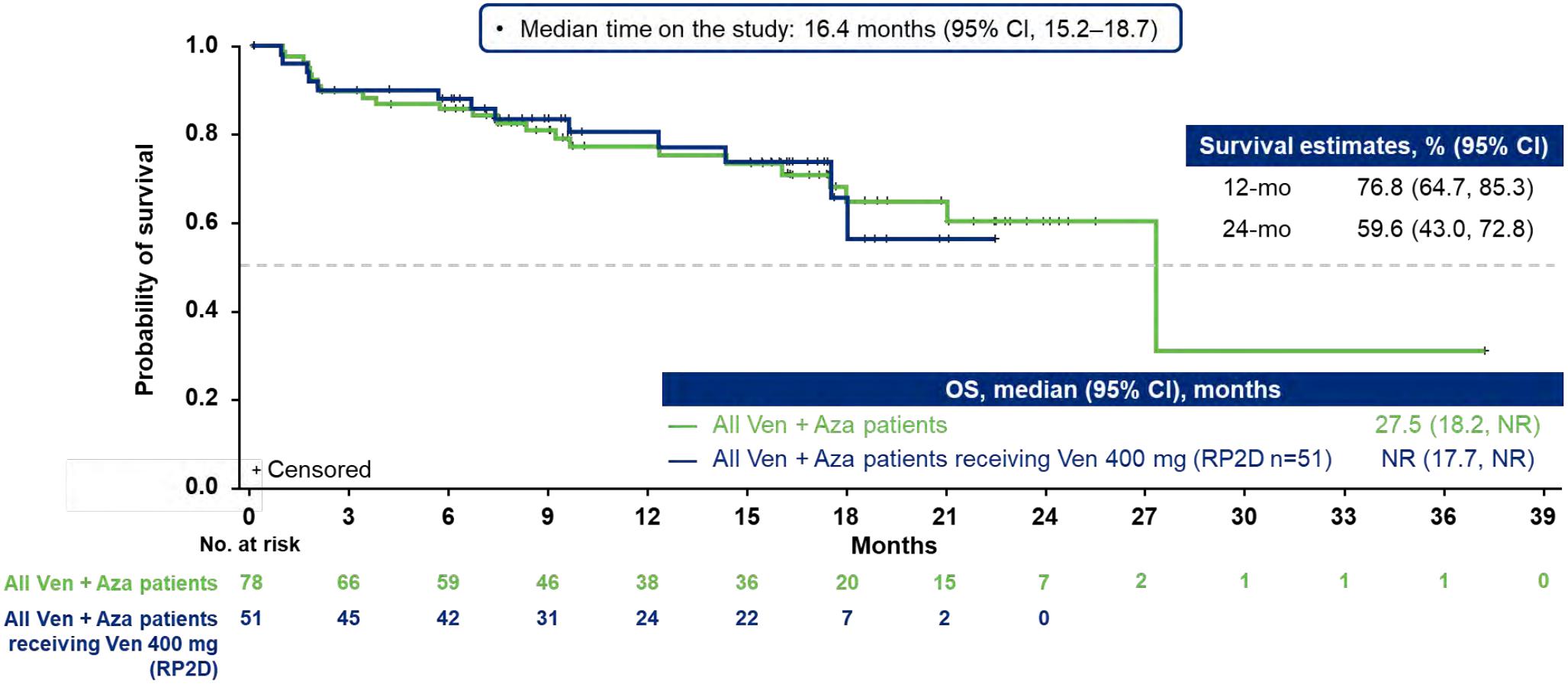
AZA + Ven Frontline Study



Courtesy of David Sallman, MD

Garcia JS et al., ASH 2020

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FDA Grants Breakthrough Therapy Designation for Venetoclax in Combination with Azacitidine for the Treatment of MDS

Press Release: July 21, 2021

"[Today it was announced] that venetoclax in combination with azacitidine has been granted Breakthrough Therapy Designation (BTD) by the US Food and Drug Administration (FDA) for the treatment of adult patients with previously untreated intermediate, high- and very high-risk myelodysplastic syndromes (MDS) based on the revised International Prognostic Scoring System (IPSS-R).

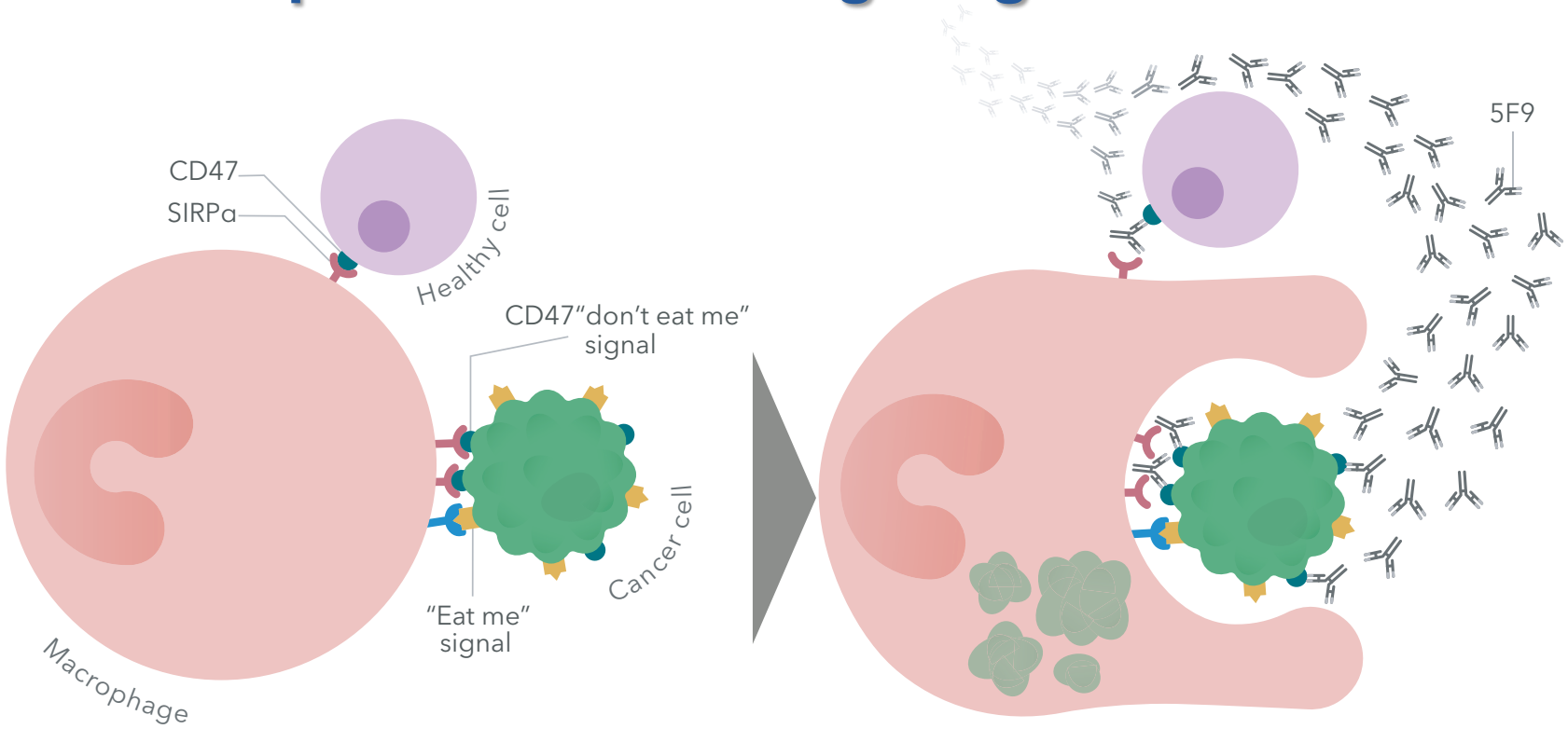
MDS are a rare group of blood cancers that gradually affect the ability of the bone marrow to produce normal blood cells. This can lead to weakness, frequent infections, anaemia and debilitating fatigue. In some cases, MDS can also progress into acute myeloid leukaemia (AML). Every year in the US, approximately 10,000 people are diagnosed with MDS, and the median survival for those with higher-risk MDS is approximately 18 months.

This designation was granted based on interim results from the phase Ib M15-531 study investigating venetoclax plus azacitidine in people with previously untreated, higher-risk MDS. BTD is designed to accelerate the development and review of medicines intended to treat serious or life-threatening conditions with preliminary evidence that indicates they may demonstrate a substantial improvement over existing therapies."

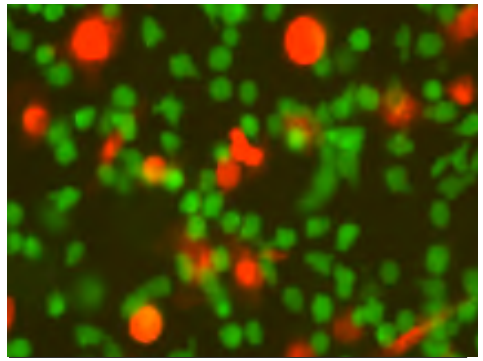
https://www.roche.com/investors/updates/inv-update-2021-07-21.htm

RTP RESEARCH TO PRACTICE

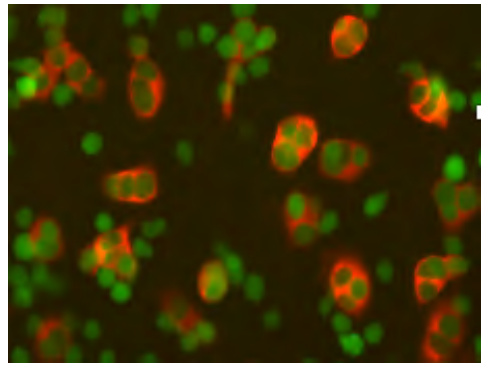
Magrolimab (Formerly 5F9) Is a First-in-class Macrophage Immune Checkpoint Inhibitor Targeting CD47



Control mAb: No Phagocytosis



Anti-CD47 mAb: Phagocytosis



Macrophages Cancer cells

- Magrolimab is an IgG4 anti-CD47 monoclonal antibody being investigated in multiple cancers
- Magrolimab was well tolerated in a UK Phase 1 trial in r/r AML with no MTD reached (Vyas et al., EHA abs 2018)

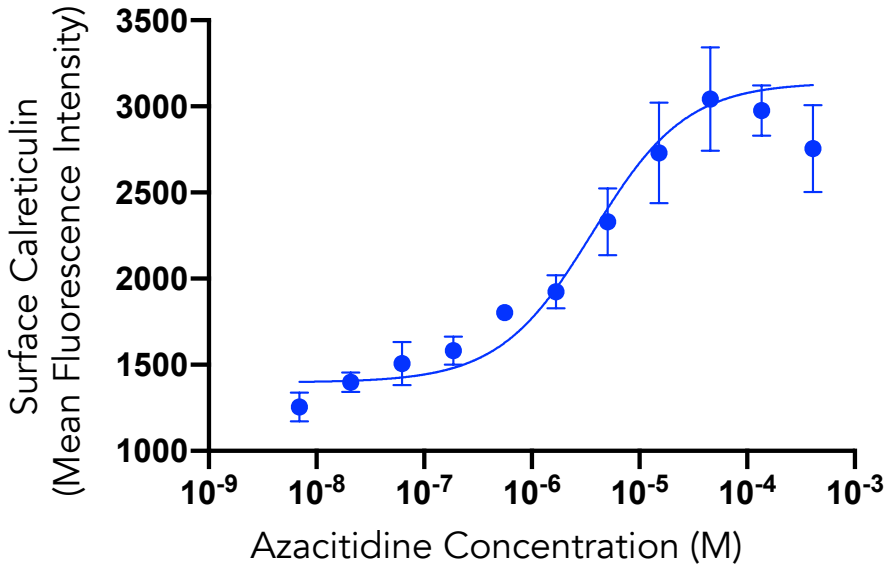
Sallman et al., EHA 2020

Courtesy of David Sallman, MD

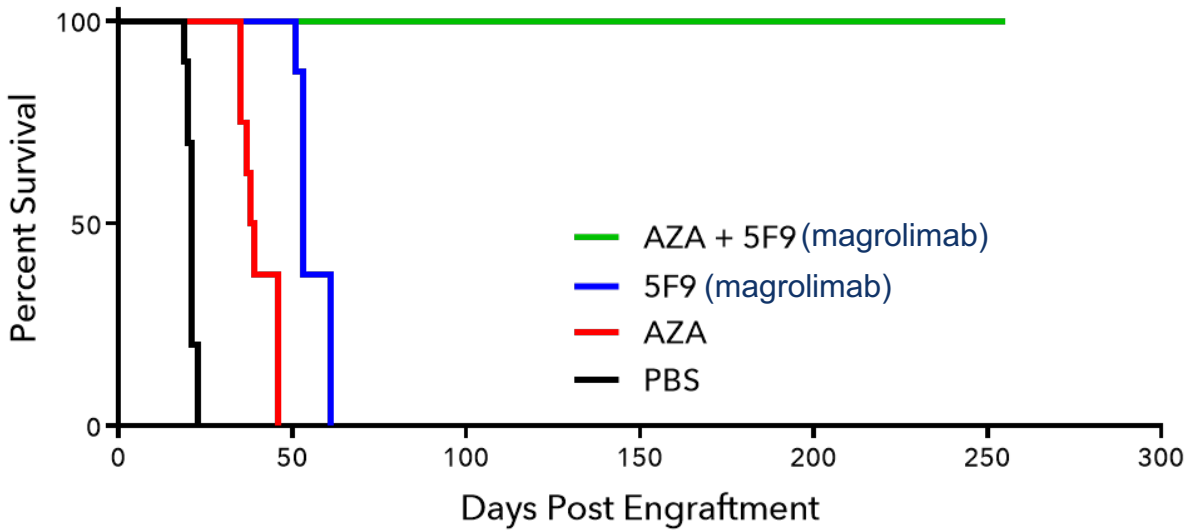
Magrolimab Synergizes With Azacitidine to Induce Remissions in AML Xenograft Models

- Azacitidine (AZA) induces prophagocytic “eat me” signals, like calreticulin on cancer cells
- Increased “eat me” signals induced by AZA synergize with CD47 blockade of the “don’t eat me” signal, leading to enhanced phagocytosis

Calreticulin expression in AML



AML xenograft model



- Feng D, et al. Poster presented at 60th ASH Annual Meeting and Exposition, December 1-4, 2018, San Diego, CA. Abstract no. 616 (with adaptations).

Courtesy of David Sallman, MD

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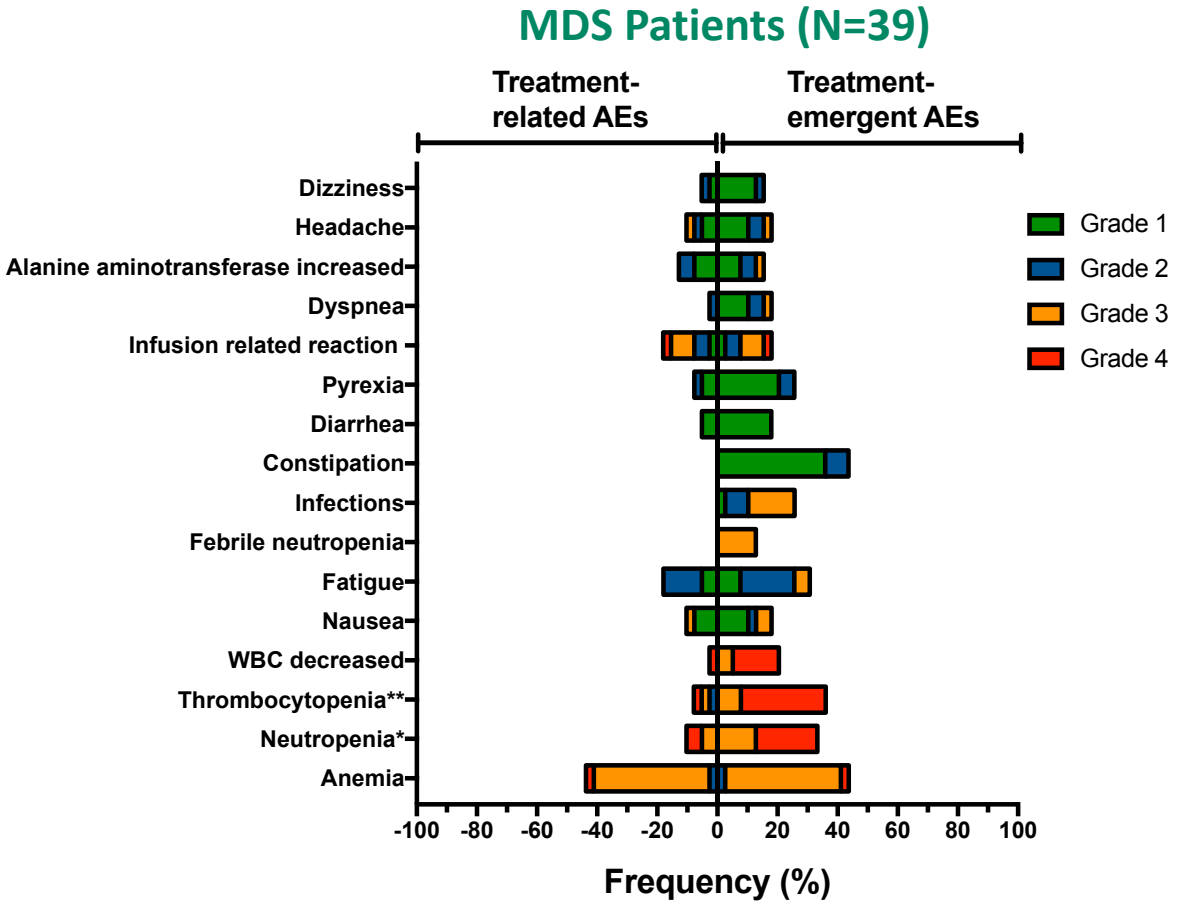
Magrolimab in Combination With AZA Is Well Tolerated



- No maximum tolerated dose was reached; magrolimab + AZA profile consistent with AZA monotherapy
- No significant cytopenias, infections, or autoimmune AEs were observed (most patients were cytopenic at baseline)
- No deaths were observed in the first 60 days on therapy
- No treatment discontinuations due to drug-related AEs

AEs ≥15% or AEs of interest are shown. All patients with at least 1 magrolimab dose are shown. AE, adverse event.
*Includes neutropenia and neutrophil count decreased. **Includes thrombocytopenia and platelet count decreased

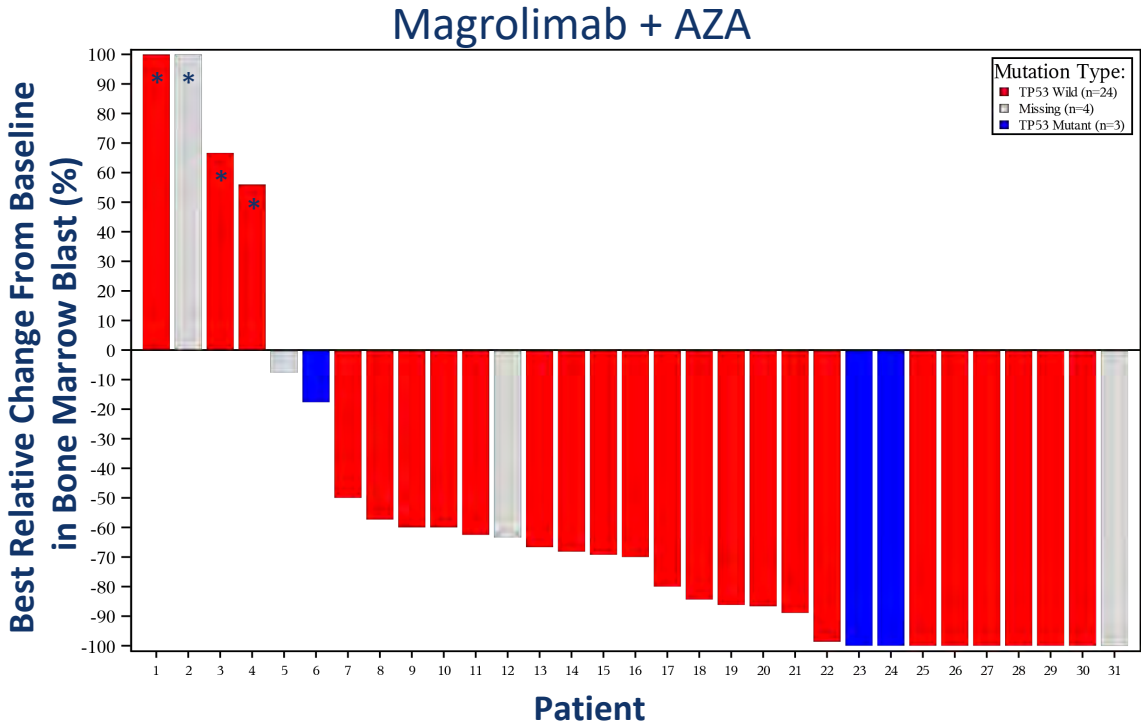
Sallman et al., EHA 2020

Courtesy of David Sallman, MD

Deep and Durable Responses Are Seen in Magrolimab + AZA Treated Patients

Best Overall Response	1L MDS, N=33
ORR	30 (91%)
CR	14 (42%)
PR	1 (3%)
Marrow CR	8 (24%) 4 with marrow CR + HI
Hematologic improvement (HI)	7 (21%)
SD	3 (9%)
PD	0

Response assessments per 2006 IWG MDS criteria. Patients with at least 1 post-treatment response assessment are shown; all other patients are on therapy and are too early for first response assessment, except for 2 MDS patients not evaluable (withdrawal of consent).



<5% blasts imputed as 2.5%. *Baseline bone marrow blasts ≤5%.

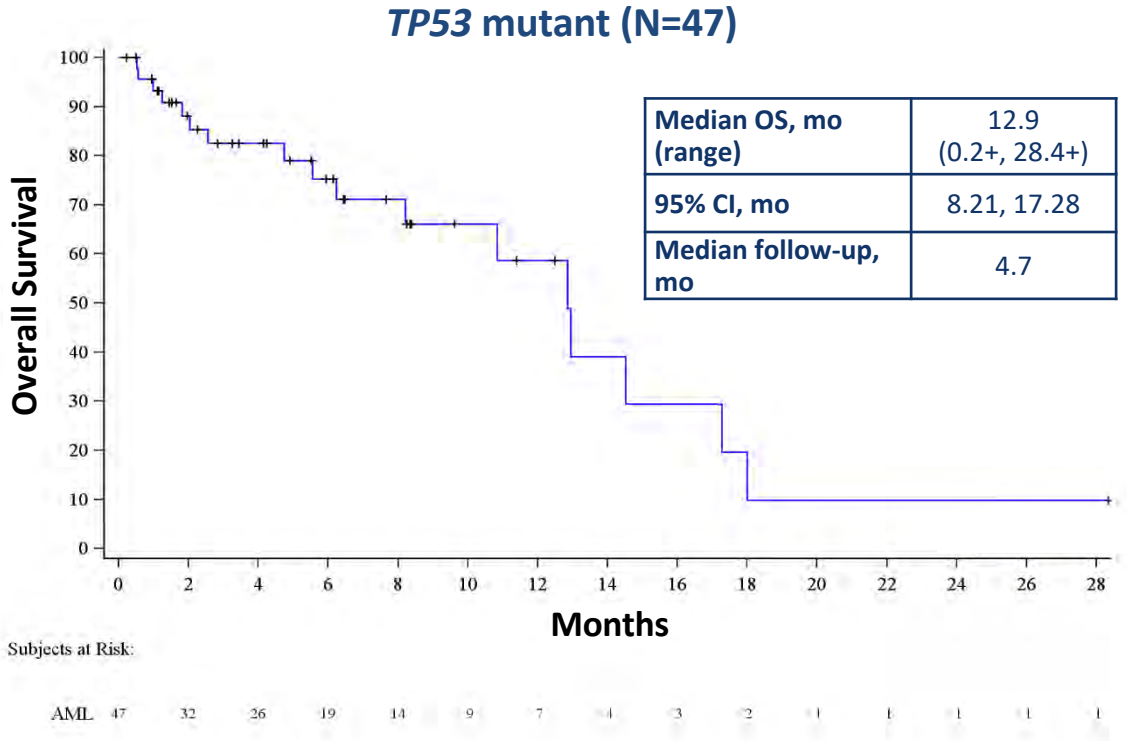
- Magrolimab + AZA induces a 91% ORR (42% CR)
- Responses deepened over time with a 56% 6-month CR rate (assessed in all patients 6 months after initial treatment)
- Median time to response is 1.9 months, more rapid than AZA alone
- Magrolimab + AZA efficacy compares favorably to AZA monotherapy (CR rate 6%–17%[1,2])
- No median duration of response (.03-10.4+ months) with median f/u of 5.8 months (2-15)
- No median OS reached (0.1-14.3+ months) with 6 month survival estimate of 100%.

Sallman et al., EHA 2020

Courtesy of David Sallman, MD

Magrolimab + AZA Induces High Response Rates in AML

Best Overall Response	All AML (N=43)	*TP53*-mutant AML (29)
ORR	27 (63%)	20 (69%)
CR	18 (42%)	13 (45%)
CRi	5 (12%)	4 (14%)
PR	1 (2%)	1 (3%)
MLFS	3 (7%)	2 (7%)
SD	14 (33%)	8 (28%)
PD	2 (5%)	1 (3%)



- Magrolimab + AZA induces a 63% ORR and 42% CR rate in AML, including similar responses in *TP53*-mutant patients
- Median time to response is 1.95 months (range 0.95 to 5.6 mo), more rapid than AZA monotherapy
- 9.6% of patients proceeded to bone marrow stem cell transplantation
- Magrolimab + AZA efficacy compares favorably to AZA monotherapy (CR rate 18%–20%)[1,2]

Response assessments per 2017 AML ELN criteria. Patients with at least 1 post-treatment response assessment are shown. *Three patients not shown due to missing values; <5% blasts imputed as 2.5%.

1. Fenaux P, et al. *J Clin Oncol*. 2010;28(4):562-569. 2. Dombret H, et al. *Blood*. 2015;126(3):291-299.

Sallman D et al., ASH 2020

Courtesy of David Sallman, MD

Phase 3 Studies in HR-MDS

- P3 VERONA Study (AZA+VEN), 500 pts, CR and OS
- P3 ENHANCE Study (AZA+MAGRO), 520 pts, CR and OS
- P3 PANTHER Study (Aza+Pevo), 454 pts, allows CMML (<13k WBC) and oligoblastic AML, EFS
- P3 STIMULUS-MDS2 Study (Aza+Saba), allows CMML-2, 500 pts, OS
- P3 SY-1425 +Aza for RARA-positive MDS patients, 190 pts, CR

- Future Directions of Triplets and Oral Substitution of HMA backbone

Courtesy of David Sallman, MD

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Phase III PANTHER (Pevonedistat-3001) Trial Does Not Achieve Primary Endpoint of Event-Free Survival

Press Release: September 1, 2021

"[Today it was announced] that the Phase 3 PANTHER (Pevonedistat-3001) study did not achieve pre-defined statistical significance for the primary endpoint of event-free survival (EFS). The trial evaluated whether the combination of pevonedistat plus azacitidine as first-line treatment for patients with higher-risk myelodysplastic syndromes (MDS), chronic myelomonocytic leukemia (CMML) and low-blast acute myeloid leukemia (AML) improved EFS versus azacitidine alone. An event in the trial is defined as death or transformation to AML in participants with higher-risk MDS or CMML, whichever occurs first, and death in participants with AML.

Pevonedistat is a NEDD8-activating enzyme (NAE) inhibitor that leads to cancer cell death by disrupting protein homeostasis. Pevonedistat is an investigational drug for which safety and efficacy have not been established. Full data results will be submitted for presentation at an upcoming medical congress. Investigators have been informed of the outcome so they can discuss the potential impact with study participants. [The company] will work with investigators who will determine the most appropriate action for each individual patient enrolled in the study."

https://www.takeda.com/newsroom/newsreleases/2021/takeda-provides-update-on-phase-3-panther-pevonedistat-3001-trial/

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Sallman: A 78-year-old man with high-risk MDS

- 78 yo male with PMH of hypertension presents with severe fatigue, dyspnea on exertion and easy bruising.
- CBC shows ANC of 0.3 k/µl; Hgb 7gm/dl; Platelets 45 k/ µl
- Patient has no history of gastrointestinal bleeding or other blood loss.
- BM Biopsy is performed and shows a hypercellular bone marrow (80%) with RAEB-2 MDS with 14% BM blasts, trilineage dysplasia and no increase in marrow fibrosis.
- Cytogenetics show Trisomy 8 and NGS myeloid panel shows an *ASXL1* and a *U2AF1* mutation
- IPSS-R Classification is Very High

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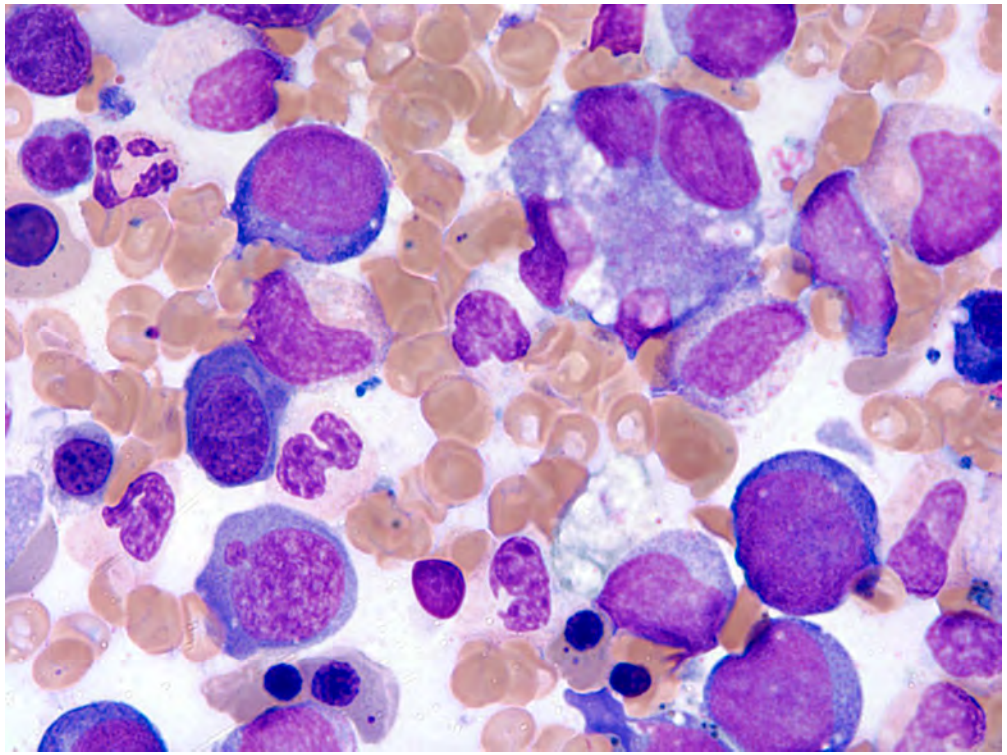
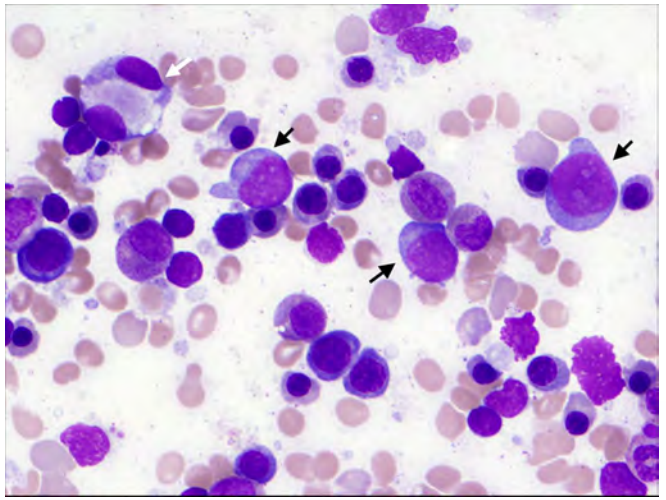
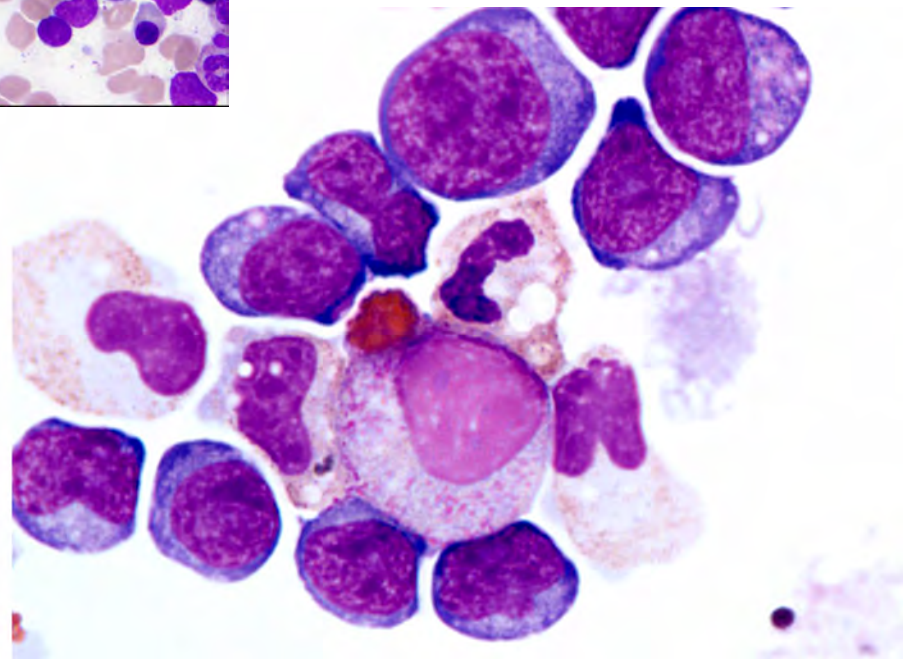
Case Presentation – Dr Sallman: A 78-year-old man with high-risk MDS (continued)

Trilineage Dypslasia



Increased BM Blasts





Case Presentation – Dr Sallman: A 78-year-old man with high-risk MDS (continued)

- Patient was treated with Azacitidine 7 day schedule + venetoclax 14 day schedule (antibacterial/antimicrobial/antiviral ppx were utilized).
  - Day +21 BM biopsy with < 5% blasts, therapy held until day 42 at which point ANC was 1.1, Hgb 10gm/dl, Platelets 155; ppx d/c
  - Patient continued on same schedule C1, but ANC dropped to 0.4 mid-cycle
  - Patient dropped to 7 day schedule of venetoclax with 7 day azacitidine and CBC with ANC 1.6, Hgb 11.2 gm/dl, Platelets 160

Case Presentation – Dr Sallman: An 85-year-old man with high-risk MDS

- 85 yo male with multiple co-morbidities including CKD III, HTN presents for evaluation of a very high risk, complex karyotype MDS with 9% blasts and pancytopenia. NGS shows biallelic *TP53* mutation. The patient has significant transportation issues and is not a candidate for clinical trials as burdensome to get to local oncologist.

- What options could be considered?

Case Presentation – Dr Sallman: An 85-year-old man with high-risk MDS (continued)

- The patient was ultimately started on oral Cedazuridine/decitabine
- Based on **ASCERTAIN - PHASE III Cedazuridine/decitabine PO 5 day dosing for MDS and CMML met primary endpoint of equivalent decitabine exposure with fixed dose combination (ASTX727)**

Faculty Cases Appendix

Module 1: Up-Front Treatment of AML in Patients Who Are Not Eligible for Intensive Therapy

RTP
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Case Presentation – Dr Pollyea: A 66-year-old man with intermediate-risk AML

- 66-year-old male with no significant past medical history
- Presents with 2 weeks of fatigue and exertional dyspnea
- Workup reveals pancytopenia with WBC $0.9x10^9$/L with ANC $0.1x10^9$/L, hemoglobin $8.6x10^9$/L and platelets $53x10^9$/L
- Bone marrow biopsy reveals AML with 44% blasts
- Categorized as AML with myelodysplasia related changes
- Cytogenetics 47,XY,+8[14]/46,XY[6] (intermediate risk)
- Next generation sequencing shows mutations in RUNX1, ASXL1 and U2AF1 (adverse risk per ELN)
- What treatment should we recommend?

Module 2: Management of AML with Targetable Mutations

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Case Presentation – Dr DiNardo: A 63-year-old man with AML and diploid cytogenetics

- 63yo Male diagnosed in June 2021 with AML with diploid cytogenetics and IDH2, BCOR, ASXL1 and STAG2 mutations
- Received 7+3 induction, complicated by strep mitis bacteremia
- Recovered with persistent/primary refractory disease
- Declined reintensive reinduction, presented to MDACC for trial considerations
- Started on oral decitabine + venetoclax + enasidenib (all oral triplet)
- End of cycle 1 marrow with variably cellular marrow (30-70%) with 1% blasts
- SCT work-up and transition in progress (has fully matched sibling)

Case Presentation – Dr DiNardo: An 82-year-old man with AML and an IDH1 mutation

- 82yo Male with a hx of CKD (baseline Cr 1.3-1.5), atrial fibrillation, PE/DVT
- Dx low risk MDS in 2018; observed but progressed rapidly to AML
- Treated with azacitidine in mid-2018; CR1 x 1 year
- In 2019, due to falling counts and rising blasts (13%) venetoclax was added with start of AZA cycle #14. Bacteremia and myelosuppression; received 3 cycles only and then stopped all treatment with CR2 sustained for 1 year.
- Oct 2020, relapse with IDH1 mutation. Started on ivosidenib and attained CR3 x 9 months.
- Came to MDACC; started on oral decitabine + venetoclax + ivosidenib all oral triplet. EOC1 confirmed CR4. Full count recovery by C1D43. Now in cycle 2.

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

- 78-year-old male with history of diabetes, hypertension and obesity presents with relapsed AML
- Was diagnosed about 2 years prior
- Had a normal karyotype and mutations in IDH2 and SRSF2
- Started venetoclax + azacitidine and had a morphologic remission after the first cycle
- Achieved a complete remission and continued therapy

Case Presentation – Dr Pollyea: A 78-year-old man with relapsed AML and an IDH2 mutation (continued)

Six Months Into Therapy

- Patient has worsening anemia and neutropenia
- Disease relapse is ruled out with a bone marrow biopsy
- Breaks between cycles extended from 2 weeks to 3 weeks and azacitidine reduced from 7 days to 5 days
- Counts improve; do not normalize but patient clinically asymptomatic and without any infectious complications
- This schedule of venetoclax and azacitidine continues

Case Presentation – Dr Pollyea: A 78-year-old man with relapsed AML and an IDH2 mutation (continued)

Two Years Into Therapy

- Blood counts again significantly decrease, now requiring blood transfusions
- Bone marrow biopsy shows 15% blasts, consistent with relapsed AML
- Normal karyotype and IDH2 and SRSF2 still detected; new mutation in PTPN11
- Enasidenib is prescribed

Case Presentation – Dr Pollyea: A 78-year-old man with relapsed AML and an IDH2 mutation (continued)

Three Weeks Later

- WBC significantly rising
- Patient develops fevers, rash and shortness of breath
- CXR shows new pleural effusions bilaterally
- Concern for differentiation syndrome is raised and dexamethasone 10 mg BID is started along with broad spectrum antibiotics
- Enasidenib is continued

Case Presentation – Dr Pollyea: A 72-year-old woman with AML and a FLT3-ITD mutation

- 72 YO F with history of rheumatoid arthritis and CVA, presents with AML with WBC of 240,000
- Bone marrow biopsy shows AML
- Normal cytogenetics
- Molecular positive for DNMT3A, NPM1 and FLT3 ITD

Case Presentation – Dr Pollyea: A 72-year-old woman with AML and a FLT3-ITD mutation (continued)

- Not an induction candidate so no role for a FLT3 inhibitor in the up-front setting
- Aggressively cytoreduced with hydrea and apharesis to get the WBC to ~25K
- Started venetoclax+azacitidine with aggressive TLS mitigation
- No TLS observed
- Patient achieved a remission
- Relapsed after 1 year

Case Presentation – Dr Pollyea: A 52-year-old woman with AML and a FLT3-ITD mutation

- MM is a 52 year-old female with a past medical history of hypothyroidism and hypertension managed on 1 anti-hypertensive agent
- At baseline she is very active but for the past month she has noted dyspnea on exertion and fatigue
- Visit to the ED after two months showed stable vital signs and a normal CXR; she was reassured and told to follow up with her PCP
- 2 weeks later she sees her PCP who draws labs

Case Presentation – Dr Pollyea: A 52-year-old woman with AML and a FLT3-ITD mutation (continued)

Lab Results

- WBC 85x10^9/L
- Hgb 8.2 g/dL
- Platelets 33x10^9/L
- Differential shows 80% circulating blasts

Case Presentation – Dr Pollyea: A 52-year-old woman with AML and a FLT3-ITD mutation (continued)

Workup Begins

- Peripheral blood flow cytometry confirms blasts are myeloid with expression of CD33, MPO and CD117
- Hydroxyurea 1000mg BID is begun and coagulation studies (PT, PTT, INR, D-Dimer, fibrinogen) are sent and come back within normal limits
- Bone marrow biopsy is performed; cytogenetics and genomic sequencing tests are ordered

Case Presentation – Dr Pollyea: A 52-year-old woman with AML and a FLT3-ITD mutation (continued)

24 Hours Later

- AML confirmed in the bone marrow by morphology and immunohistochemical stains
- WBC now 45
- Patient is stable, on 1L supplemental O2
- FISH comes back without evidence of a t(8;21) or inv(16)
- Induction chemotherapy with 7+3 is initiated

Case Presentation – Dr Pollyea: A 52-year-old woman with AML and a FLT3-ITD mutation (continued)

5 Days Later

- The patient is tolerating chemotherapy with minimal nausea, on daily anti-emetic regimen
- Genomic testing shows evidence of FLT3 ITD
- Midostaurin begins on day 8

Case Presentation – Dr Wang: An 83-year-old man with recurrent AML and an IDH2 mutation

83 yo man who initially presented with pancytopenia in March 2018. BMBX showed AML with 23% blasts by morphology and 20% by flow cytometry on background of prior myelodysplasia. Cytogenetics showed trisomy 8. Patient was started on decitabine monotherapy in April 2018. Repeat BMBX in July 2018 demonstrated persistent AML with 19% blasts and persistent trisomy 8. NGS demonstrated IDH2 mutation. Patient was started on enasidenib in Sept 2018 with followup marrow showing improvement (4% blasts) with persistent trisomy 8 and emergence of new trisomy 11 clone. Patient was then initiated on therapy with azacitidine in addition to enasidenib. However treatment was complicated by persistent transfusion dependent severe pancytopenia: WBC 0.8, hgb 8.1, plts 38K. BMBX in Jan 2019 showed recurrent AML with 20% blasts. Referred to our academic center.

Given prior exposure to multiple cycles of HMA therapy, decision made to start therapy on venetoclax and LDAC. After two cycles of therapy, marrow showed no blasts and normal karyotype with no evidence of trisomy 8 or 11 consistent with CR with incomplete count recovery. He has subsequently continued on outpatient therapy with the same agents, now truncated to LDAC x 7 (from 10) days and venetotclax 400 mg daily x 7 days per month. He now returns for cycle 19 of therapy with WBC 2.8, ANC 1.4, hgb 11.3, plts 247K.

Case Presentation – Dr Wang: A 46-year-old woman with recurrent AML and TET2, WT1, FLT3-ITD and IDH1 mutations

46 yo with no prior medical history presented in April 2019 with abnormal counts. She was found to have a diagnosis of AML with normal karyotype and mutational profile showing TET2 and WT1 mutations. As she was living in the UK at the time, she received double induction therapy with cytarabine and daunorubicin based therapy followed by two cycles of consolidation chemotherapy with high dose cytarabine. The patient and her physicians opted for no transplant in CR. Four months later, her disease relapsed and she received salvage re-induction chemotherapy with mitoxantrone, etoposide, and cytarabine (MEC). Her disease unfortunately was refractory to treatment (42% blasts) and she received clinical trial therapy with venetoclax/azacitidine backbone plus experimental drug. She achieved a CR with incomplete count recovery and proceeded onto haploidentical peripheral blood stem cell transplant from her sister in April 2020.

One year later, she presented with bilateral hip and back pain as well as new paresthesias of the lip and chin. Labs demonstrated relapsed AML with 12% peripheral blasts. She was started on hydrea for control of leukocytosis and initiated therapy with venetoclax and 10 day decitabine. Repeat NGS from the relapsed AML cells surprisingly demonstrated FLT3-ITD and IDH1 mutations in addition to TET2 and WT1 mutations. Given these results, gilteritinib was added to the decitabine and venetoclax. She received two cycles of therapy and proceeded onto a second allogeneic transplant from the same donor (haploidentical sister).

Module 3: Other Currently Available and Investigational Treatment Strategies for AML

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Case Presentation – Dr Wang: An 88-year-old man with recurrent AML and multiple mutations including FLT3-IDT, IDH2 and RUNX1

88 yo retired general surgeon who previously practiced in Buffalo, NY and currently divides his time between NY and Florida. While in Florida in June 2020, he noted that he was progressively short of breath and had generalized weakness during his almost daily golfing excursions. He presented to local hospital and was found to have elevated WBC 249K, hgb 5, plts 90K, ANC 5000, 47% peripheral blasts. BMBx confirmed diagnosis of AML with 84% blasts and normal karyotype. NGS showed multiple mutations: ASXL1, BCOR, IDH2, RUNX1, SRFS2, STAG2.

Initially treated with venetoclax and azacitidine in the hospital for 11 days and complicated but left upper extremity DVT and bilateral pneumonia. He completed 3 cycles of therapy in the outpatient setting with subsequent BMBX in Sept 2020 showing markedly hypocellular marrow with no evidence of AML. Normal karyotype. Persistent IDH2 mutation. Due to cytopenias, venetoclax was omitted and the patient continued on single agent Aza for an additional 2 cycles, at which time all therapy was halted.

Repeat BMBX in Jan 2021 showed recurrent AML with 45% blasts. Karyotype was now abnormal with 46, XY, additional 21 abnormality (add (21)(q11.2). NGS showed FLT3-ITD (VAF <0.5%), IDH2 (VAF 0.36), RUNX1 (VAF 0.27). He was started on gilteritinib 120 mg qd and cleared peripheral blasts within a few weeks.

Case Presentation – Dr Wang: An 88-year-old man with recurrent AML and multiple mutations including FLT3-IDT, IDH2 and RUNX1 (continued)

However, three months later (April 2021), repeat BMBX again showed relapsed AML with 65% blasts, FLT3 wildtype but IDH2 mutation. Started on enasidenib 100 mg qd in addition to the gilteritinib (dose reduced to 80 mg qd). His disease remained relatively stable with dual enasidenib and gilteritinib. In July 2021, BMBx showed evidence of residual AML with 3-5% myeloblasts. Repeat NGS now showed wild-type FLT3 but mutations in both IDH1 and IDH2.

Three weeks later, the patient presented to clinic with increased generalized weakness and fatigue not improving despite transfusion. WBC now markedly elevated to 63.4K with LDH 2195 with 1% circulating blasts. Repeat BMBX showed 18% Cd33+ blasts with wildtype FLT3 and normal karyotype. Unfortunately the patient's course was complicated by acute renal failure, rendering him ineligible for clinical trial. He is now receiving salvage gemtuzumab ozogamicin.

Module 4: Management of MDS

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Case Presentation – Dr Sallman: A 72-year-old man with lower-risk MDS

- 72 yo male presents with ESA failure lower risk MDS (IPSS-R low risk). There is no increase in ring sideroblasts. Cytogenetics shows normal male karyotype (46XY) and NGS shows an isolated *TET2* mutation.

- What options could be considered next?

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Case Presentation – Dr Sallman: A 72-year-old man with lower-risk MDS (continued)

- Patient was considered for a clinical trial but deferred secondary to distance from center
- Patient was ultimately started on lenalidomide 10mg PO on a 21 out of 28 day schedule along with Epoetin 60,000U weekly.
  - Patient achieved TI that lasted approximately 12 months

Case Presentation – Dr Sallman: A 77-year-old man with MDS and HMA failure

- 77 yo male with h/o of RAEB-2 MDS who achieved CR x 12 months on single agent azacitidine now has progressive disease.

- What options can be considered?

Case Presentation – Dr Sallman: A 77-year-old man with MDS and HMA failure (continued)

- All patients should be considered for clinical trials as lack of efficacious therapy in this setting and change to alternative HMA with little activity.

- A repeat NGS was performed and showed a hotspot *IDH1* mutation.

Case Presentation – Dr Sallman: A 77-year-old man with MDS and HMA failure (continued)

- Patient was started on off-label ivosidenib 500mg PO daily and tolerated well without differentiation syndrome. Patient achieved a CR and remains on therapy x 6 months.

Case Presentation – Dr Sallman: A 60-year-old man with high-risk MDS

- 60 yo male with no PMH presents for evaluation of a very high risk, complex karyotype MDS with 12% blasts and pancytopenia. NGS shows *TP53* hot spot mutation with a VAF of 80%. The patient is highly interested in clinical trials.

- What options could be considered?

Case Presentation – Dr Sallman: A 60-year-old man with high-risk MDS (continued)

- The patient was started on 7-day azacitidine + investigational agent and after 2 cycles BM blasts were down to 4% with a partial cytogenetic remission and repeat NGS showing TP53 VAF of 10%. Patient has an 8/8 MUD available

- Would you proceed with allo-HSCT vs continue on trial at this time?

Case Presentation – Dr Sallman: A 60-year-old man with high-risk MDS (continued)

- Patient was continued for 2 more cycles at which point patient had achieved CR, CCR, and serial NGS was negative. Patient was bridged to allo-HSCT and is currently in remission post-transplant.

Case Presentation – Dr Pollyea: A 77-year-old woman with MDS

- 77-year-old woman with MDS diagnosed 7 years prior
- Watched for 6 years with no intervention
- 1 year prior began to require regular blood transfusions
- Bone marrow biopsy confirmed MDS with hypercellularity and no increased blasts
- Initiated with azacitidine 75 mg/m^2 IV every 7 days/28 day cycle
- After three cycles transfusion burden decreased significantly
- Now 12 months later with continuous therapy, worsened cytopenias and requiring blood and now platelet transfusions
- Bone marrow biopsy performed and now shows AML with 25% blasts
- What treatment should we recommend?

Case Presentation – Dr DiNardo: A 65-year-old man with del(20q) MDS with an IDH1 mutation

- 65yo Male with del(20q) MDS with IDH1 mutation
- Received azacitidine x 19 cycles with response and then progression
- Received ivosidenib on trial for MDS, with remission lasting ~ 16 months
- Progressed to AML and received cladribine/LDAC + venetoclax on MDACC trial, remission lasting ~10 months
- Now on a clinical trial of a novel IDH1 inhibitor

Exploring Key Issues Affecting the Care of Patients with Metastatic Colorectal Cancer with BRAF Mutations

A CME/MOC-Accredited Virtual Event

Thursday, September 9, 2021
5:00 PM – 6:00 PM ET

Faculty
Scott Kopetz, MD, PhD

Consulting Clinical Investigator
Wells A Messersmith, MD

Moderator
Neil Love, MD

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