Data + Perspectives: Investigators Discuss the Effects of Emerging Research on the Care of Patients with Acute Myeloid Leukemia

Wednesday, March 10, 2021
7:00 PM – 8:00 PM ET

Faculty

Alexander Perl, MD
Eunice S Wang, MD

Moderator

Neil Love, MD

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Faculty

Alexander Perl, MD
Associate Professor of Medicine
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Member, Leukemia Program
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Commercial Support

This activity is supported by an educational grant from Astellas.

Dr Love — Disclosures

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Dr Wang — Disclosures

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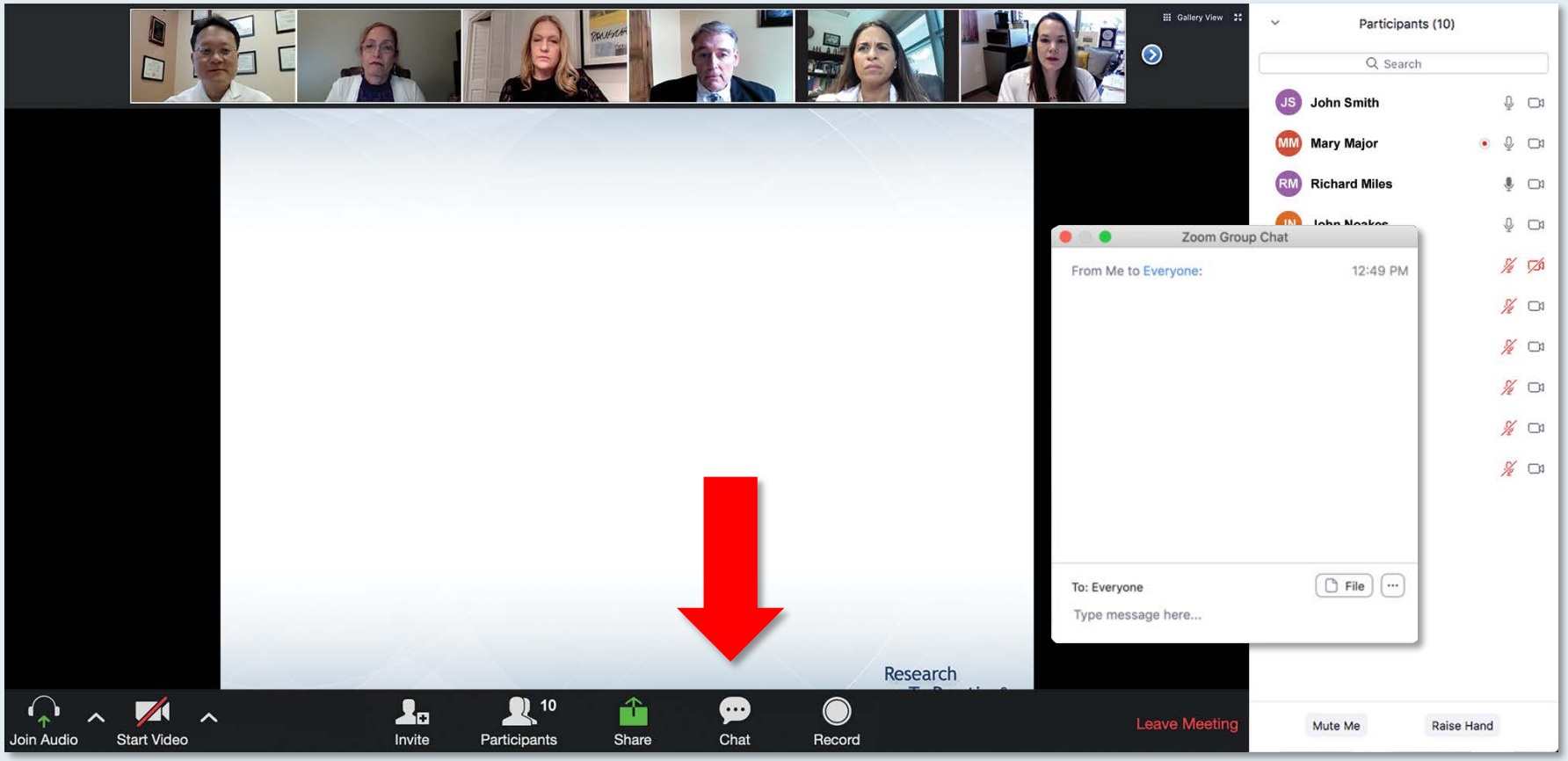
We Encourage Clinicians in Practice to Submit Questions



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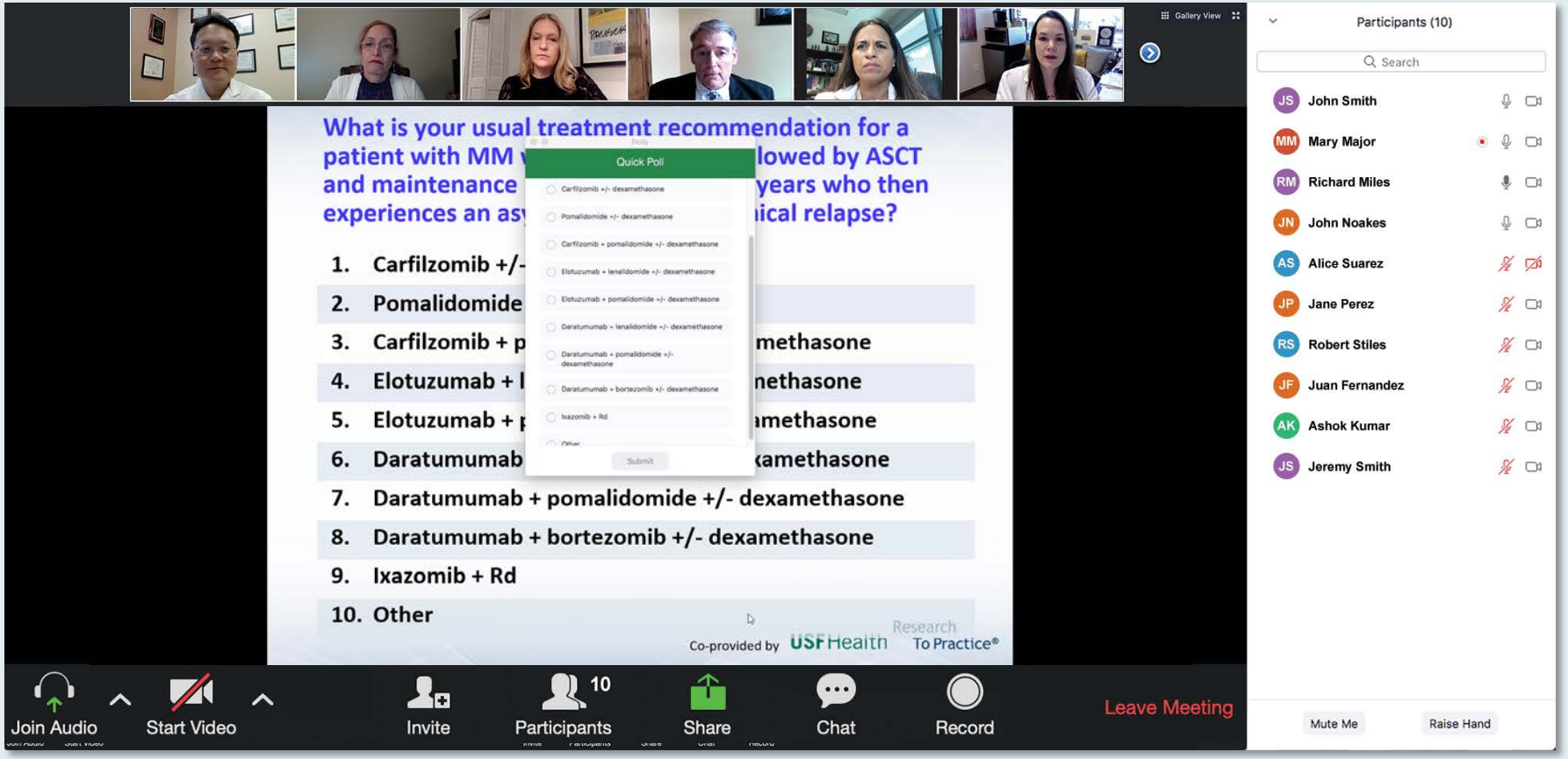

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WITH DR NEIL LOVE

ACUTE MYELOID LEUKEMIA WITH FLT3 MUTATIONS

DR KEITH PRATZ
UNIVERSITY OF PENNSYLVANIA

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Meet The Professor

Management of Chronic Lymphocytic Leukemia

Thursday, March 11, 2021
5:00 PM – 6:00 PM ET

Faculty

Steven Coutre, MD

Moderator

Neil Love, MD

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

Part 1 — Acute Myeloid Leukemia

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

Faculty

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

Moderator

Neil Love, MD

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Meet The Professor

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

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

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Alan P Venook, MD

Moderator

Neil Love, MD

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

Part 2 — HER2-Positive Breast Cancer

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

Faculty

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

Moderator

Neil Love, MD

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TO PRACTICE

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

Saturday, March 20, 2021
3:00 PM – 4:00 PM CT (4:00 PM – 5:00 PM ET)

Faculty

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

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Meet The Professor

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

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

Faculty

Robert J Motzer, MD

Moderator

Neil Love, MD

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Thank you for joining us!

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

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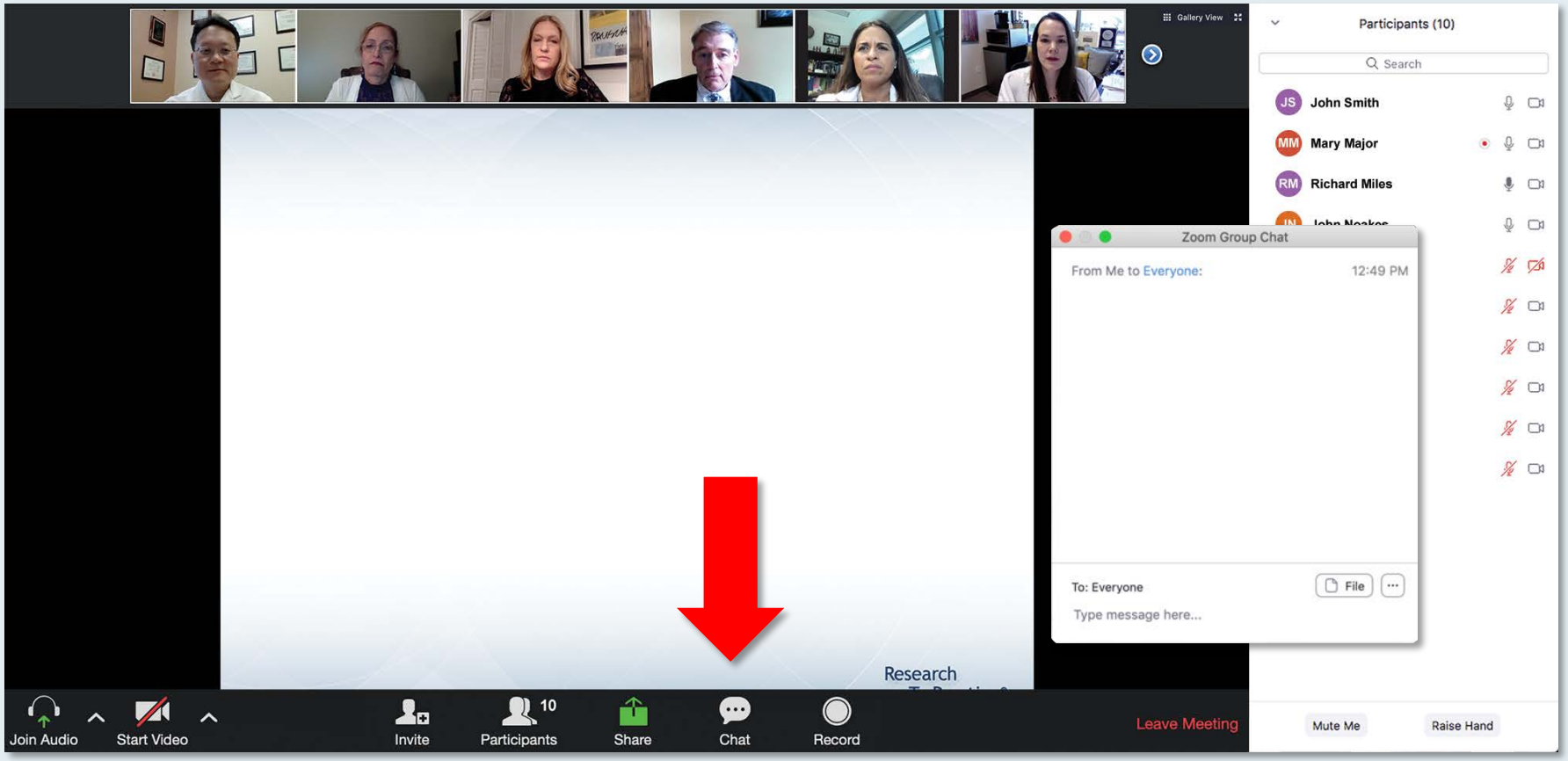

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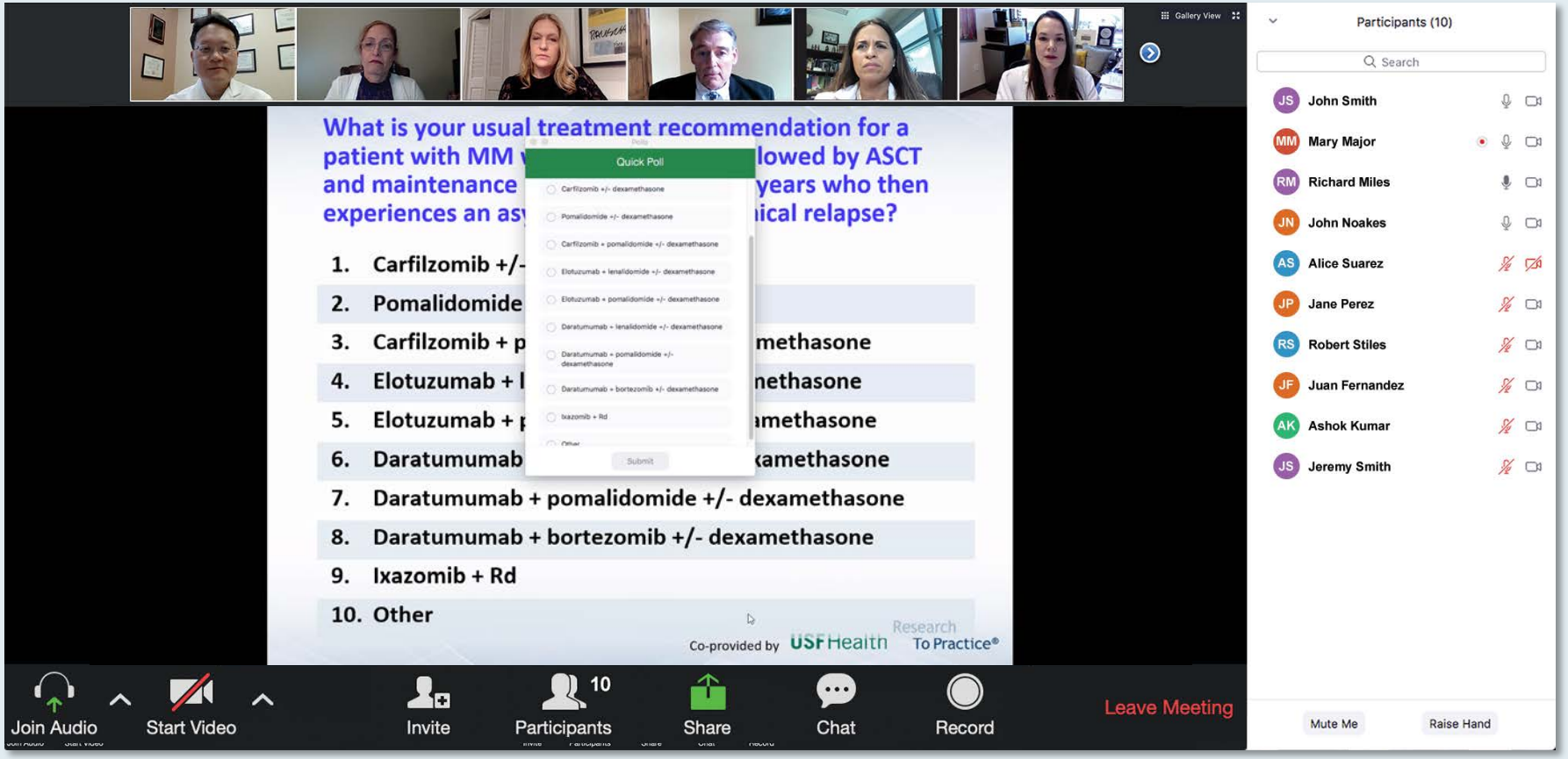

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Module 1: Venetoclax combinations

Module 2: FLT3 inhibitors

Module 3: IDH inhibitors

Module 4: Oral azacitidine (CC-486)

Module 5: Secondary AML — CPX-351

Module 6: Novel agents and strategies

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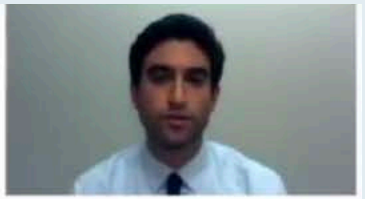


Interim Analysis of the Phase 1b/2 Study of the BCL-2 Inhibitor Venetoclax in Combination with AML Induction/Consolidation Therapy with FLAG-IDA in Patients with Newly Diagnosed or Relapsed/Refractory AML

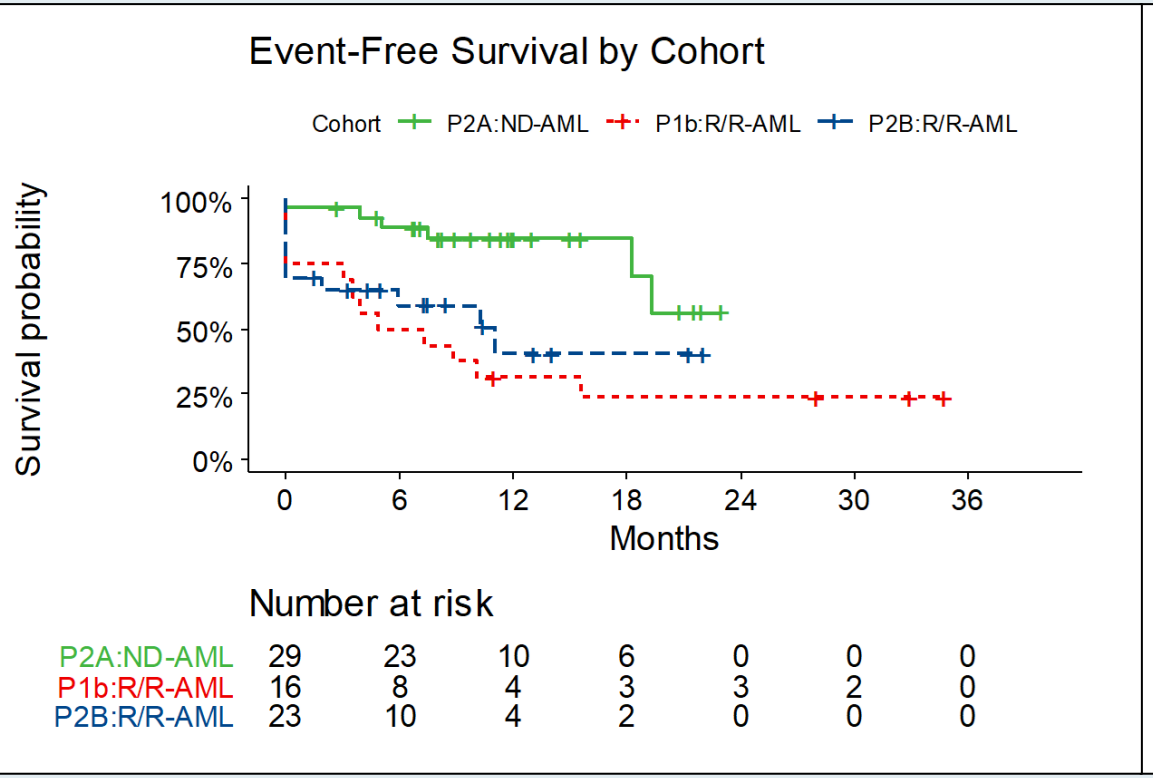
Curtis A. Lachowiez, M.D.[1], Marina Konopleva, M.D.[1], PhD., Tapan Kadia, M.D.[1], Naval Daver, M.D.[1], Sanam Loghavi, M.D.[2], Sa A. Wang, M.D.[2], M.D., Maria Adeoti, R.N.[1], Sherry Pierce, B.S.N., B.A.[1], Koichi Takahashi, M.D., Ph.D.[1], Nicholas Short, M.D.[1], Koji Sasaki, M.D., Ph.D.[1], Gautam Borthakur, M.D.[1], Ghayas Issa, M.D[1]., William Wierda, M.D., Ph.D.[1], Naveen Pemmaraju, M.D.[1], Guillermo Montalban Bravo, M.D.[1], Alessandra Ferrajoli, M.D.[1], Nitin Jain, M.D.[1], Lucia Masarova, M.D.[1], Musa Yilmaz, M.D.[1], Elias Jabbour, M.D.[1], Guillermo Garcia-Manero, M.D.[1], Steven Kornblau, M.D.[1], Farhad Ravandi, M.D.[1], Hagop Kantarjian, M.D.[1], Courtney D. DiNardo, M.D., MSc. [1]

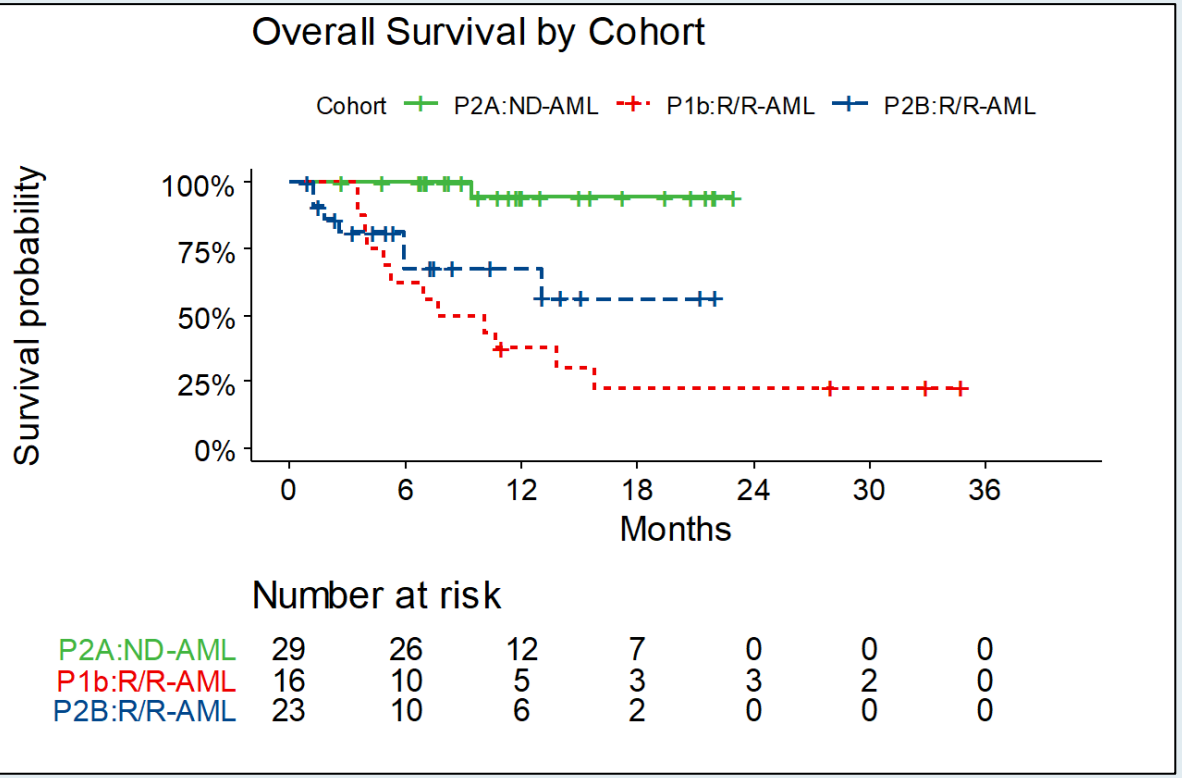
University of Texas M.D. Anderson Cancer Center

[1] Department of Leukemia, [2] Department of Hematopathology

Abstract 332

Phase 1b/2 Study of Venetoclax in Combination with FLAG-IDA

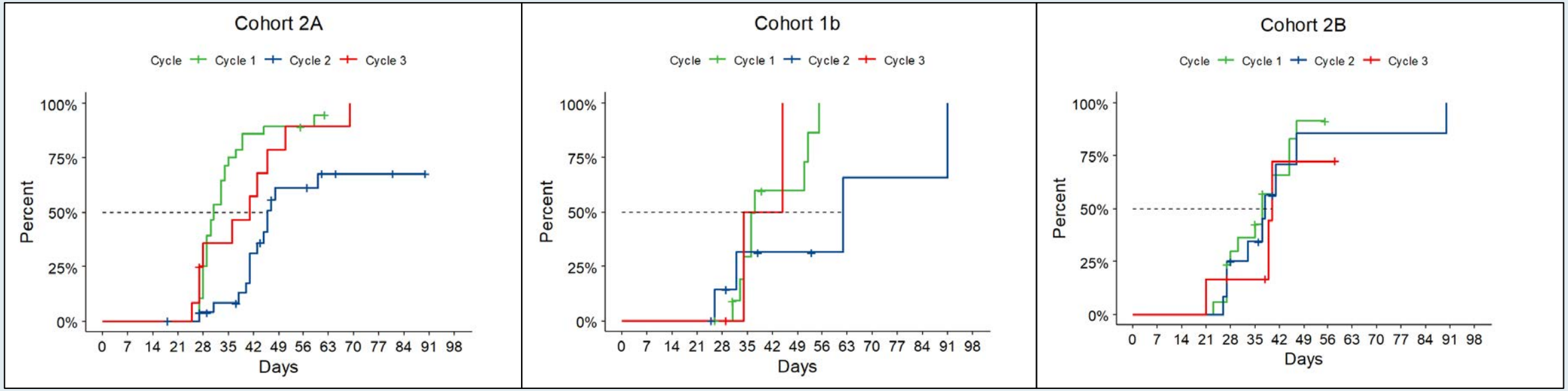




Variable	Phase 2A	Phase 1b	Phase 2B
Event-Free Survival	NR	6 (3-NE)	11 (2-NE)
Overall Survival	NR	9 (4.9-NE)	NR
1-year OS	94%	38%	68%

Lachowiez CA et al. ASH 2020;Abstract 332.

Phase 1b/2 Study of Venetoclax in Combination with FLAG-IDA



	Phase 2A ND-AML (N=29)	Phase Ib R/R-AML (N=16)	Phase 2B R/R-AML (N=23)
Cycle #1	31 days	37 days	37 days
Cycle #2	46 days	62 days	38 days
Cycle #3	41 days	40 days	40 days

* Count recovery: ANC ≥500 and platelet count ≥ 50,000 /μL

Lachowiez CA et al. ASH 2020;Abstract 332.

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Abstract 25

Phase II Study of Venetoclax added to Cladribine + LDAC Alternating with 5-AZA in Older Patients with Newly Diagnosed AML

Tapan M. Kadia, Gautam Borthakur, Naveen Pemmaraju, Naval Daver, Courtney Dinardo, Koji Sasaki, Ghayas Issa, Maro Ohanian, Guillermo Montalban-Bravo, Nicholas Short, Nitin Jain, Alessandra Ferrajoli, Kapil Bhalla, Elias Jabbour, Rashmi Kanagal, Koichi Takahashi, Rashmi Malla, Kelly Marek, Mark Brandt, Uday Popat, Michael Andreeff, Jorge Cortes, Guillermo Garcia-Manero, Marina Konopleva, Farhad Ravandi, and Hagop Kantarjian.

Cladribine/LDAC + Venetoclax in Older AML

Responses

Response / Outcome	N	%	MRD(-)
Evaluable for Response	54	98	
CR	42	78	39 (93)
CRi	8	15	3 (38)
CR + CRi (CRc)	50	93	42 (84)
No Response	4	7	
Died ≤ 4 weeks	1	2	
Died ≤ 8 weeks	2	4	
Median # of cycles given (Range)	2 (1 – 14)		
Median # of cycles to response (Range)	1 (1 – 3)		

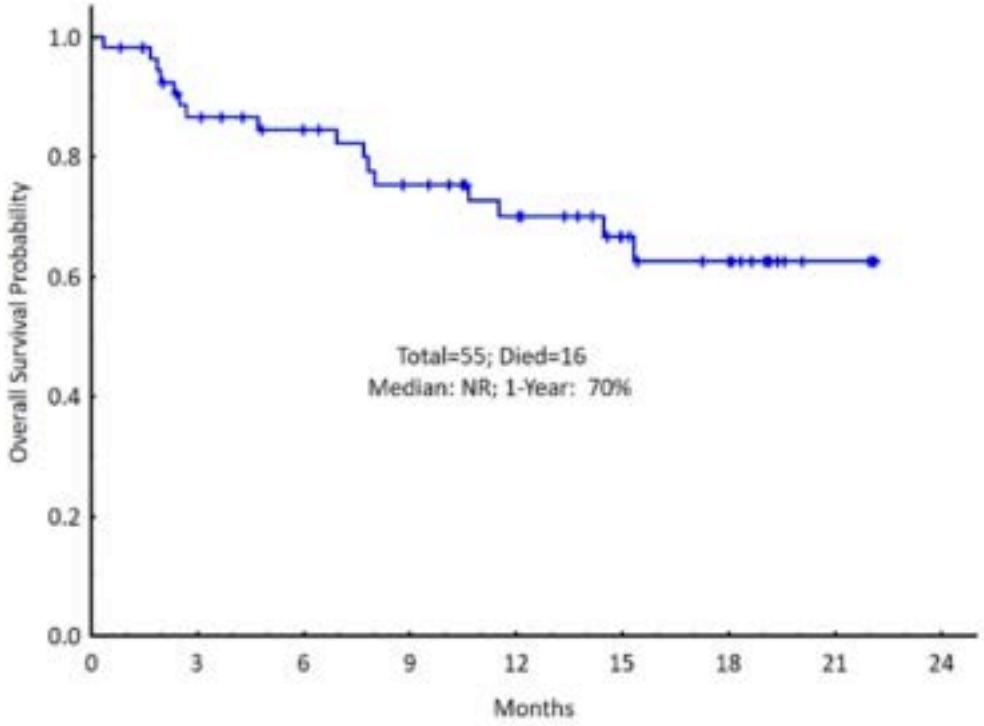
Median follow-up in Surviving Patients : 14.2 months

Kadia TM et al. ASH 2020;Abstract 25.

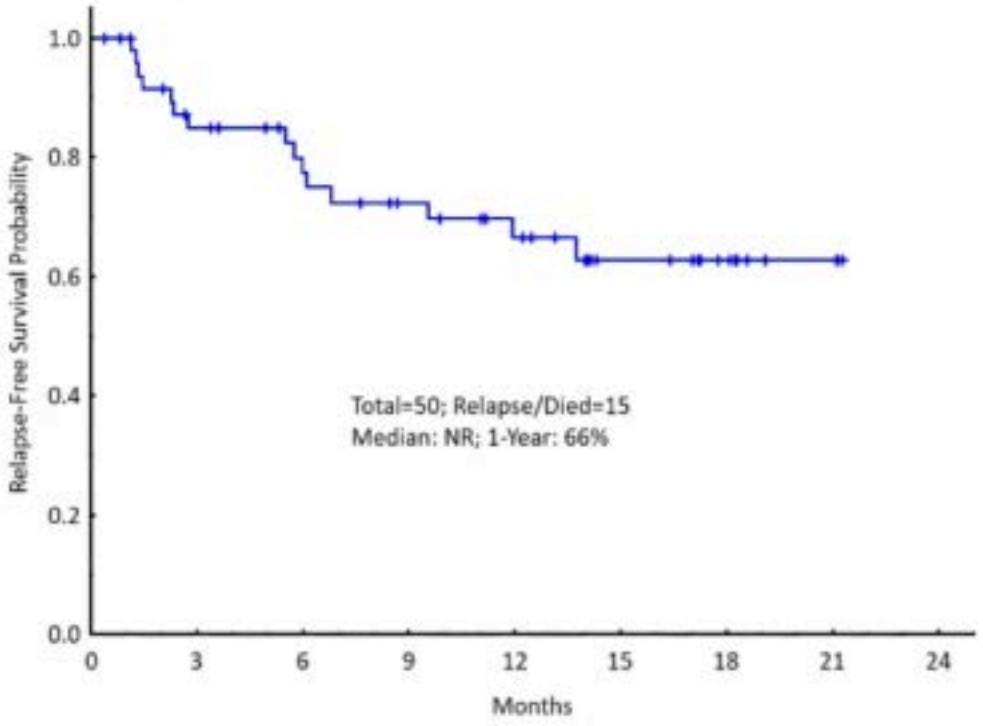
Cladribine/LDAC + Venetoclax in Older AML

Outcomes

Overall Survival



Relapse-Free Survival



Median follow-up in Surviving Patients : **14.2** months

Kadia TM et al. ASH 2020;Abstract 25.

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

1. Azacitidine
2. Decitabine
3. Azacitidine + venetoclax
4. 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
3. Decitabine
4. Azacitidine + venetoclax
5. Decitabine + venetoclax
6. Low-dose cytarabine + venetoclax
7. Other

Case Presentation – Dr Wang: An older patient with newly diagnosed AML who is not eligible for intensive induction chemotherapy

- An 89 yo woman with prior medical history of COPD, hypertension and polymyalgia rheumatica who was noted to have new onset of abnormal blood counts beginning in March 2018.
- In Dec 2018, she underwent bone marrow for progressive pancytopenia which demonstrated a hypercellular marrow consistent with myelodysplastic syndrome with excess blasts (10%). Karyotype was normal. She was started on darbepoetin alfa and remained relatively transfusion independent until March 2019.
- At that time, she was started on Azacitidine monthly until July 2019 when she presented to a local ER for shortness of breath and was found to have hemoglobin of 5.1 gm/dl with circulating blasts.
- Repeat bone marrow biopsy demonstrates AML with 20% blasts and MDS-related morphologic changes. Cytogenetics shows a normal karyotype (XX) with no evidence of FLT3, IDH1 or IDH2 mutations.

Case Presentation – Dr Wang: An older patient with newly diagnosed AML who is not eligible for intensive induction chemotherapy (continued)

- Given her advanced age, her local oncologist referred her for second opinion. Treatment options discussed included venetoclax + low dose cytarabine (LDAC), glasdegib + LDAC, gemtuzumab ozogamicin, or supportive care with hydroxyurea and transfusions only.
- The patient opted for treatment with venetoclax + LDAC and was subsequently admitted to the inpatient service to initiate therapy given the long distance between our center (4+ hours) and per our institutional standard.
- Her hospitalization was complicated by an episode of upper GI bleeding and back pain. Repeat bone marrow evaluation after 21 days of therapy revealed hypocellular marrow with <1% blasts. She was discharged home on growth factor with local oncology follow-up.
- She now completed 17 cycles of Ven/LDAC in the outpatient setting with LDAC given every 5 weeks with Ven 400 mg daily for 7 days per month. She remains transfusion independent (last WBC 10, hgb 10.3, plts 196K) and recently completed both doses of the COVID19 vaccine without issues.

Agenda

Module 1: Venetoclax combinations

Module 2: FLT3 inhibitors

Module 3: IDH inhibitors

Module 4: Oral azacitidine (CC-486)

Module 5: Secondary AML — CPX-351

Module 6: Novel agents and strategies

American Society *of* Hematology

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Place video here

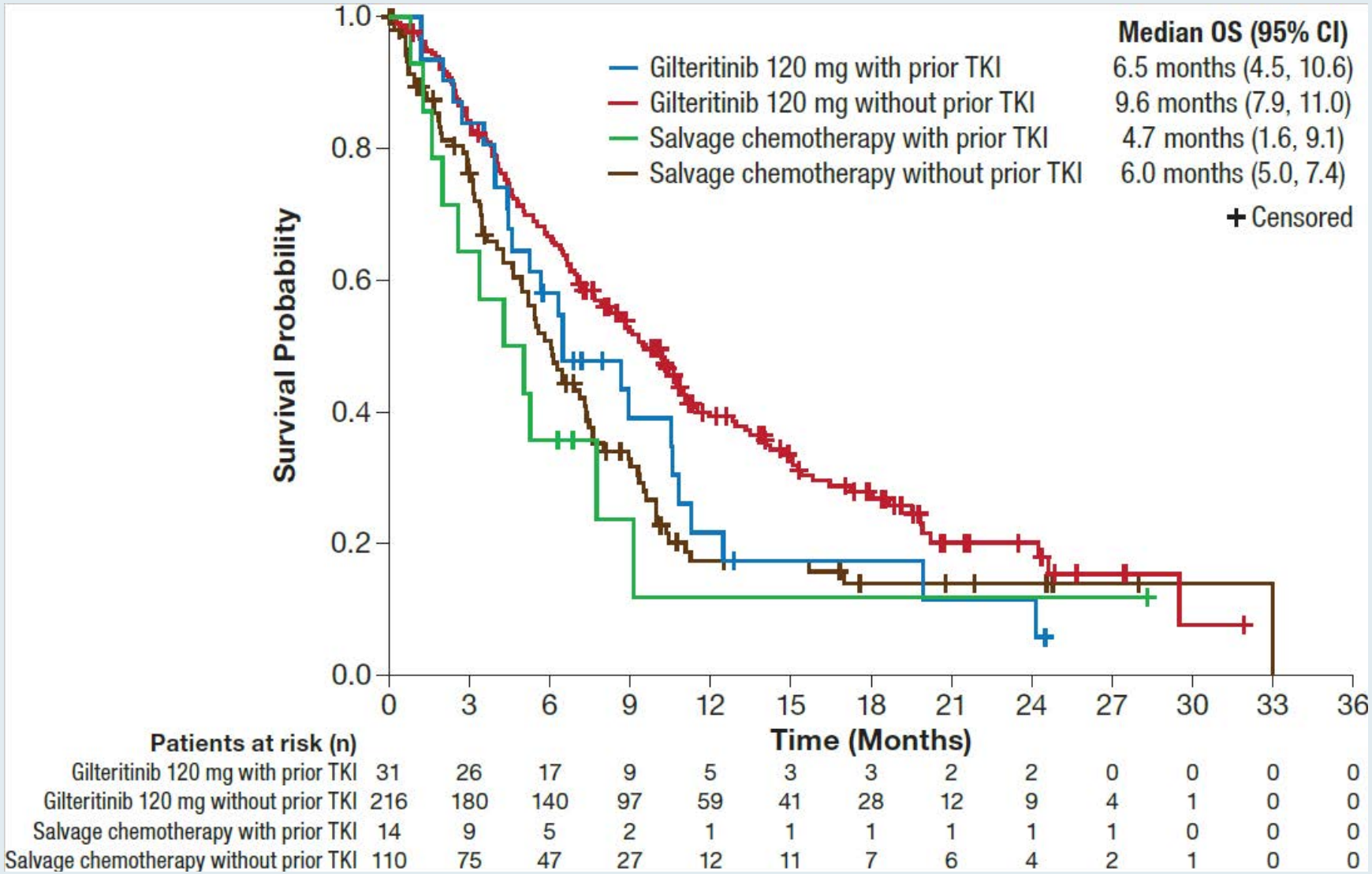
Clinical Outcomes in Patients With Relapsed/Refractory Acute Myeloid Leukemia Treated With Gilteritinib Who Received Prior Midostaurin or Sorafenib

Alexander E Perl, MD[1]; Jessica K Altman, MD[2]; Naoko Hosono, MD, PhD[3]; Pau Montesinos, MD, PhD[4]; Nikolai Podoltsev, MD, PhD[5]; Giovanni Martinelli, MD[6]; Catherine C Smith, MD[7]; Mark J Levis, MD[8]; Christoph Röllig, MD MSC[9]; Marco Groß-Langenhoff, PhD[10]; Nahla Hasabou, MD[11]; Qiaoyang Lu, MS[11]; Ramon V Tiu, MD[11]

[1]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [2]Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [3]University of Fukui, Fukui, Japan; [4]Hospital Universitario y Politécnico La Fe, Valencia, Spain; [5]Yale School of Medicine, New Haven, CT, USA; [6]Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori IRST IRCCS, Meldola, Italy; [7]University of California-San Francisco, San Francisco, CA, USA; [8]The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, USA; [9]Universitätsklinikum Carl Gustav Carus, Dresden, Germany; [10]Astellas Pharma GmbH, Munich, Germany; [11]Astellas Pharma US, Northbrook, IL, USA

Abstract 334

Gilteritinib vs Salvage Chemo in FLT3m AML Receiving Prior FLT3i



Median OS, mos (95% CI)	Gilteritinib	
	Prior TKI	No Prior TKI
***FLT3* Mutation Type**		
FLT3-ITD	6.5 (4.4, 10.8)	10.2 (7.7, 11.1)
FLT3-TKD	4.6 (1.2, 24.1)	8.0 (3.0, 24.6)
FLT3-ITD and -TKD	13.2 (4.0, NE)	10.2 (8.9, 20.2)
Relapsed or Refractory Status		
Relapsed	6.5 (4.0, 11.3)	8.9 (6.7, 10.8)
Refractory	10.5 (2.4, 24.1)	10.3 (7.9, 13.5)

Perl AE et al. ASH 2020;Abstract 334.

RTP RESEARCH TO PRACTICE

Phase III LACEWING Trial Fails to Meet Its Primary Endpoint of Overall Survival in Newly Diagnosed AML with FLT3 Mutation

Press Release – December 21, 2020

"The phase 3 LACEWING trial of the FMS-like tyrosine kinase 3 (FLT3) inhibitor gilteritinib plus azacitidine versus azacitidine alone in patients with newly diagnosed *FLT3* mutation-positive acute myeloid leukemia (AML) who were ineligible for intensive induction chemotherapy did not meet its primary end point of overall survival (OS) at a planned interim analysis, according to… the developer of the agent.

Based on these results, an independent data monitoring committee recommended the study be terminated for futility, citing that the results are unlikely to demonstrate a statistically significant increase in OS. [The developer] has since halted enrollment in the trial and is reviewing the results for other action as needed."

https://www.cancernetwork.com/view/phase-3-lacewing-trial-fails-to-meet-primary-end-point-of-os-in-newly-diagnosed-flt3-aml

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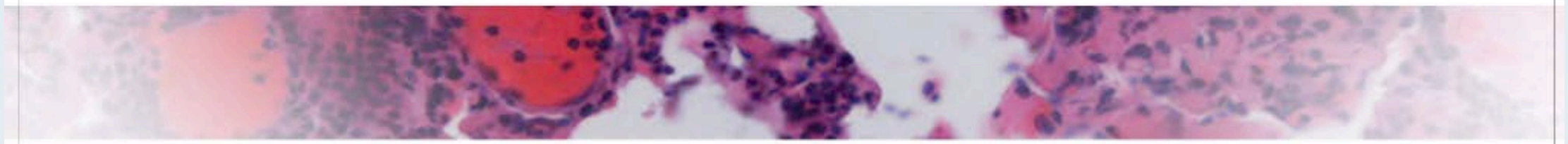

Phase 3, Multicenter, Open-Label Study of Gilteritinib, Gilteritinib Plus Azacitidine, or Azacitidine Alone in Newly Diagnosed *FLT3*-Mutated (*FLT3*$^{mut+}$) Acute Myeloid Leukemia (AML) Patients Ineligible for Intensive Induction Chemotherapy

Eunice S. Wang,[1] Pau Montesinos,[2] Mark D. Minden,[3] Je-Hwan Lee,[4] Michael Heuser,[5] Tomoki Naoe,[6] Wen-Chien Chou,[7] Shufang Liu,[8] Ruishan Wu,[8] Nisha Philipose,[8] Elizabeth Shima Rich,[8] Ramon V. Tiu[8]

[1]Department of Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [2]Hospital Universitari i Politècnic La Fe, Valencia & CIBERONC, Instituto Carlos III, Madrid, Spain; [3]Princess Margaret Hospital, Toronto, Ontario, Canada; [4]Department of Hematology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [5]Department of Hematology, Hemostasis, Oncology and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany; [6]National Hospital Organization Nagoya Medical Center, Nagoya, Japan; [7]Division of Hematology, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; [8]Astellas Pharma Global Development, Northbrook, IL, USA

Abstract 27

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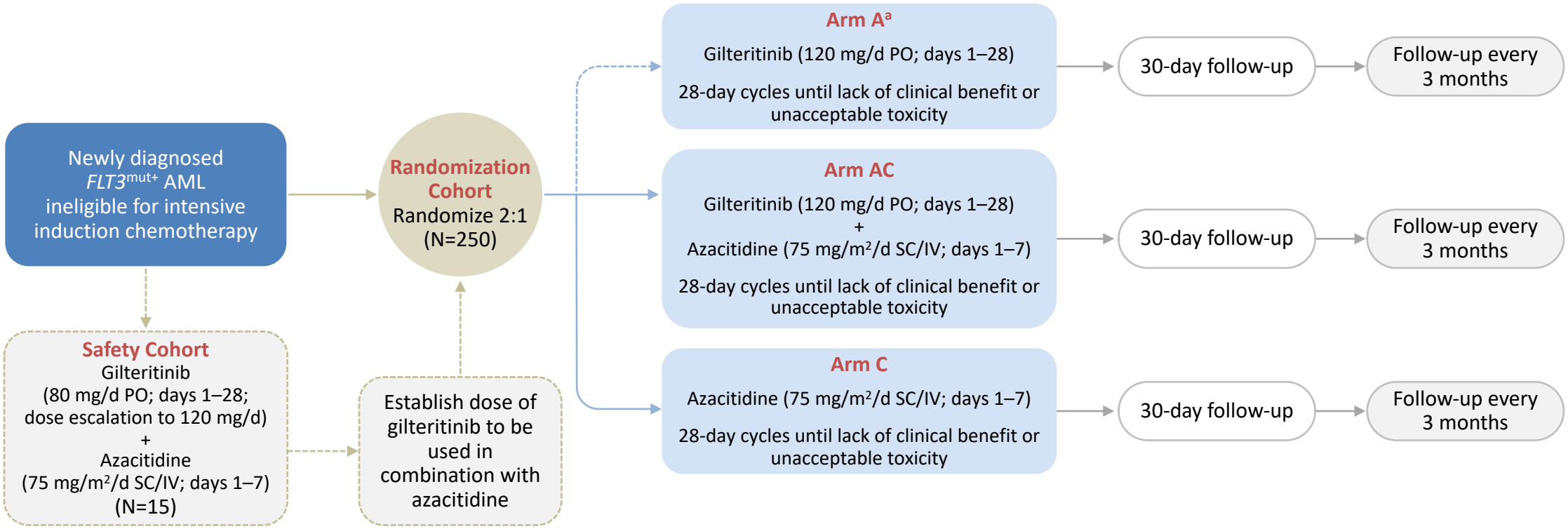
LACEWING Study Design

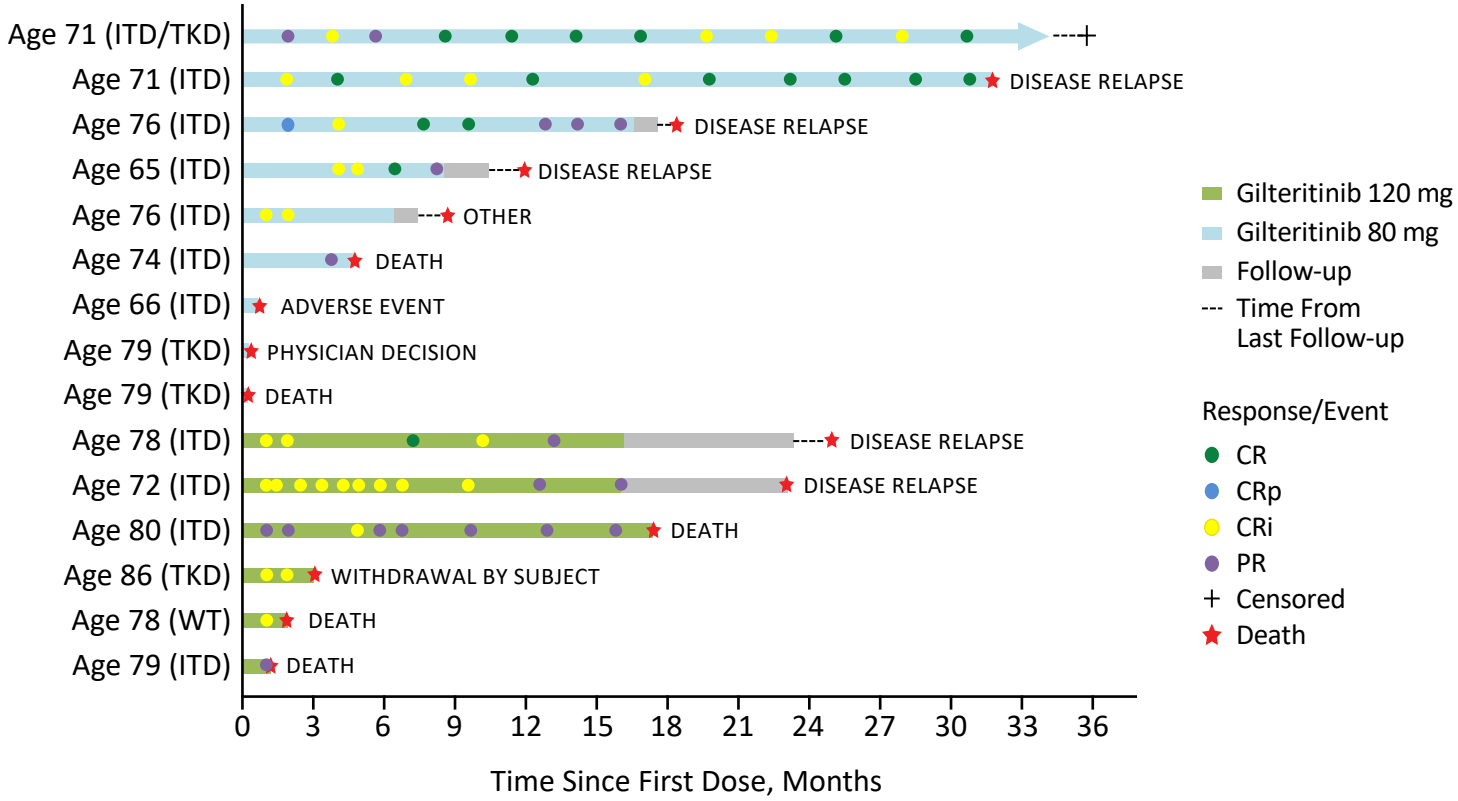


[a]Protocol versions 6.0 and earlier included a 1:1:1 randomization ratio to receive Arm A (gilteritinib monotherapy), AC (gilteritinib + azacitidine), or C (azacitidine monotherapy). Randomization to Arm A was removed in protocol version 7.0. Patients previously randomized to Arm A should continue following treatment and assessments as outlined in the protocol.
AML, acute myeloid leukemia; *FLT3*mut+, FMS-like tyrosine kinase 3 mutation-positive; IV, intravenously; PO, orally; SC, subcutaneously.

Wang ES et al. ASH 2020;Abstract 27.

Type and Duration of Response of Gilteritinib in Combination With AZA and End of Treatment Reasons

Safety Cohort (N=15)



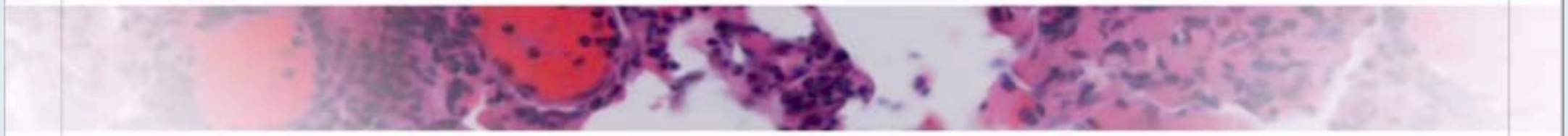
- CR and CRc were achieved by 33% (n=5/15) and 67% (n=10/15) of patients in the Safety Cohort, respectively.
- Among the 10 patients with CRc, the median (95% CI) duration of remission was 10.4 (0.95–NR) months, with 5 patients being censored

AZA, azacitidine; CR, complete remission; CRc, composite complete remission; CRi, complete remission with incomplete hematologic recovery; CRp, complete remission with incomplete platelet recovery; ITD, internal tandem duplication; NR, not reached; PR, partial remission; TKD, tyrosine kinase domain; WT, wild type.

Wang ES et al. ASH 2020;Abstract 27.

American Society *of* Hematology

Helping hematologists conquer blood diseases worldwide



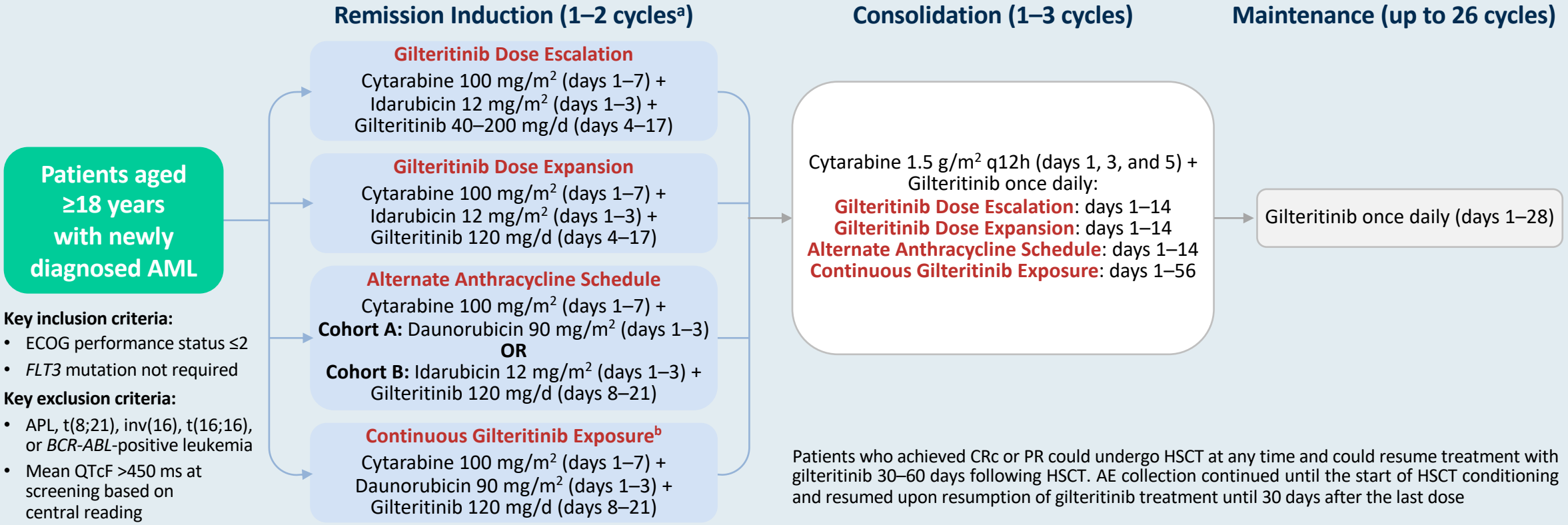
A Phase 1 Study of Gilteritinib in Combination With Induction and Consolidation Chemotherapy in Patients With Newly Diagnosed AML: Final Results

Keith W. Pratz,[1] Mohamad Cherry,[2] Jessica K. Altman,[3] Brenda W. Cooper,[4] Jose Carlos Cruz,[5] Joseph G. Jurcic,[6] Mark J. Levis,[1] Tara L. Lin,[7] Alexander E. Perl,[8] Nikolai A. Podoltsev,[9] Gary J. Schiller,[10] Jason E. Hill,[11] Angela James,[11] Qiaoyang Lu,[11] Ramon V. Tiu[11]

[1]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD; [2]Stephenson Cancer Center, University of Oklahoma, Oklahoma City, OK; [3]Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL; [4]University Hospitals, Cleveland Medical Center, Cleveland, OH; [5]Methodist Physician Practices, San Antonio, TX; [6]Columbia University Medical Center, New York, NY; [7]University of Kansas Medical Center, Kansas City, KS; [8]Abramson Comprehensive Cancer Center, University of Pennsylvania, Philadelphia, PA; [9]Yale School of Medicine, New Haven, CT; [10]David Geffen School of Medicine at UCLA, Los Angeles, CA; [11]Astellas Pharma Global Development, Northbrook, IL.

Publication No. 24

Phase Ib Study of Gilteritinib with Intensive Chemotherapy



Patients who achieved CRc or PR could undergo HSCT at any time and could resume treatment with gilteritinib 30–60 days following HSCT. AE collection continued until the start of HSCT conditioning and resumed upon resumption of gilteritinib treatment until 30 days after the last dose

- Both the maximally tolerated and expansion doses were established at 120 mg/day

[a]If day 21 bone marrow evaluation shows residual blasts and the bone marrow is not aplastic, a second induction cycle with the same regimen could be started ≥7 days after the last dose of gilteritinib but no later than day 28 (gilteritinib dose-escalation and dose-expansion cohorts) or day 35 (alternate anthracycline schedule and continuous gilteritinib exposure cohorts) of the first induction cycle; [b]During the second induction cycle, the dosage of daunorubicin was reduced to 45 mg/m².

AE, adverse event; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; *BCR-ABL*, breakpoint cluster region-Abelson murine leukemia viral oncogene homolog; CRc, composite complete remission; ECOG, Eastern Cooperative Oncology Group; *FLT3*, FMS-like tyrosine kinase 3; HSCT, hematopoietic stem cell transplant; PR, partial remission; q12h, every 12 hours; QTcF, Fridericia-corrected QT interval.

Pratz KW et al. ASH 2020;Abstract 24.

Efficacy and Safety of Venetoclax in Combination With Gilteritinib for Relapsed/Refractory *FLT3*-Mutated Acute Myeloid Leukemia in the Expansion Cohort of a Phase 1b Study

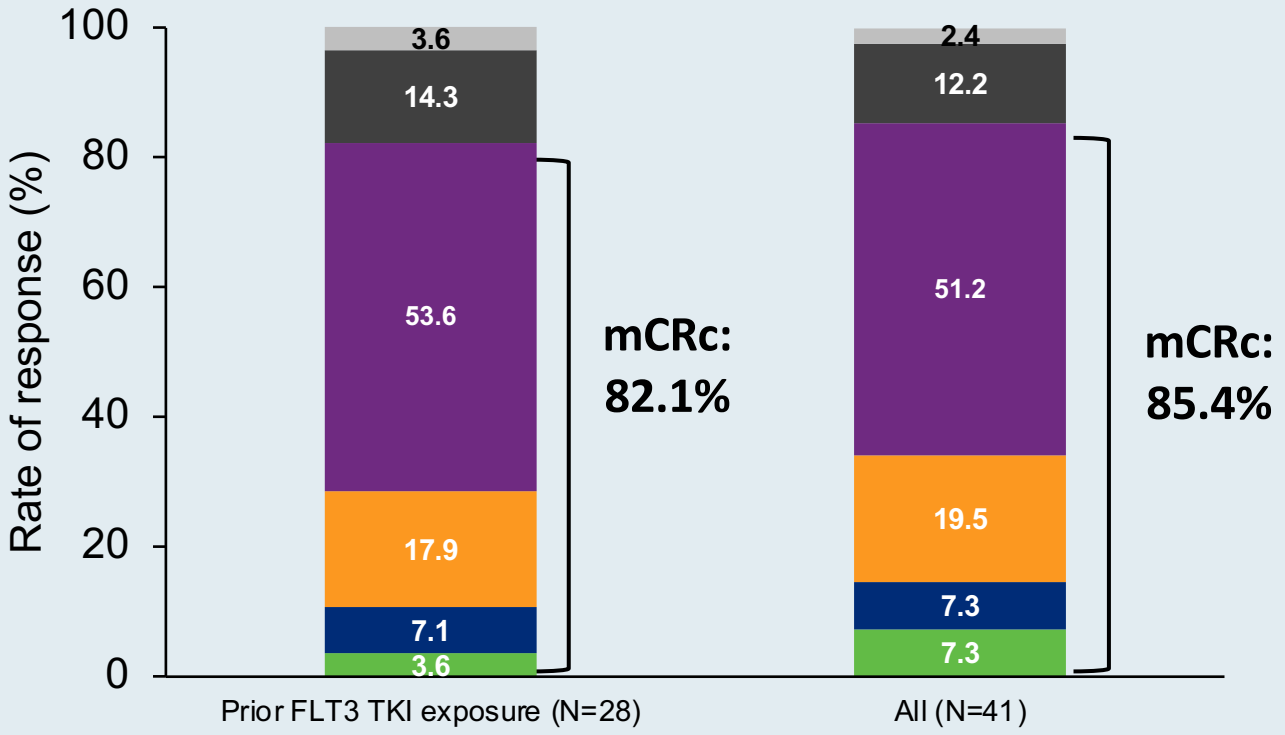
333

Naval Daver,[1] Jessica K. Altman,[2] Joseph Maly,[3] Mark Levis,[4] Ellen Ritchie,[5] Mark Litzow,[6] James McCloskey,[7] Catherine Smith,[8] Gary Schiller,[9] Terrence Bradley,[10,11] Ramon V. Tiu,[12] Wan-Jen Hong,[13] Bo Tong,[14] Qin Qin,[14] Alexander E. Perl[15]

[1]Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX, USA [2]Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL, USA [3]Norton Cancer Institute, Louisville, KY, USA [4]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, USA [5]Department of Carcinogenesis, University of Texas, MD Anderson Cancer Center, Science Park-Research Division, Smithville, TX, USA [6]Division of Hematology, Mayo Clinic, Rochester, MN, USA [7]John Theurer Cancer Center at Hackensack Meridian Health, Hackensack, NJ, USA [8]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA [9]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA [10]University of Miami, Department of Medicine, Miami, FL, USA [11]Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, USA [12]Astellas Pharma US, Northbrook, IL, USA [13]Genentech, South San Francisco, CA, USA [14]AbbVie, Inc., North Chicago, IL, USA [15]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA

American Society of Hematology (ASH) – 62nd Annual Meeting
December 5–8, 2020

Phase Ib Gilteritinib with Venetoclax: Best Responses



	All (N=41)
mCRc, n (%)	35 (85.4%)
Time to best response (mCRc), median (range), months	0.9 (0.7–4.2)

The 85% mCRc rate compares favorably to the 52% CRc rate (using the same response parameters), with single agent Gilteritinib in the ADMIRAL phase 3 study

Daver N et al. ASH 2020;Abstract 333.

Patterns of Secondary Resistance Differ in Patients with Acute Myeloid Leukemia Treated with Type I versus Type II FLT3-inhibitors

Ahmad S. Alotaibi, Musa Yilmaz, Rashmi Kanagal-Shamanna, Sanam Loghavi, Tapan Kadia, Courtney DiNardo, Gautam Borthakur, Sherry Pierce, Sa Wang, Guilin Tang, Veronica Guerra, Bachar Samra, Naveen Pemmaraju, Elias Jabbour, Nicholas Short, Ghayas Issa, Maro Ohanian, Guillermo Garcia-Manero, Kapil Bhalla, Keyur Patel, Koichi Takahashi, Michael Andreeff, Jorge Cortes, Marina Konopleva, Farhad Ravandi, Hagop Kantarjian, Naval Daver

Department of Leukemia, The University of Texas MD Anderson Cancer Center

Abstract 335

Patterns of Resistance in FLT3+ AML, abstr #335

FLT3-TKD emergent mutations common after Type-II FLT3i-based therapies

Emergent mutations	Total (N=67) N (%)	Type I *FLT3*i (N=21) N (%)	Type II *FLT3*i (N=46) N (%)
FLT3-D835	14 (21)	0	14 (30)*
FLT3-ITD	1 (1)	1 (5)	0
FLT3-N676K	2 (3)	1 (5)	1 (2)
FLT3-N841K	1 (1)	0	1 (2)

* 13 pts had received type II FLT3*i* + Low Intensity Rx, 1 pt type II FLT3*i* + Intensive Rx

FLT3-mutation was no longer detectable at relapse in 18/67 (26%) patients treated with FLT3i based therapies: 12 /46 (26%) Type II FLT3i, and 6/21 (28%) Type I FLT3i based therapies.

Alotaibi AS et al. ASH 2020;Abstract 335.

RTP RESEARCH TO PRACTICE

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. Midostaurin
2. 7 + 3 induction + midostaurin
3. HMA + FLT3 inhibitor
4. HMA + venetoclax
5. HMA + venetoclax + FLT3 inhibitor
6. Low-dose cytarabine + venetoclax
7. Low-dose cytarabine + venetoclax + FLT3 inhibitor
8. Gilteritinib
9. 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

Case Presentation – Dr Perl: A patient with relapsed/refractory AML with a FLT3 mutation

- 75 YO woman with a h/o carotid stenosis, type 2 diabetes, and hypertension presents with fever, cough, and sore throat, and is found to have a WBC of 52K with monocytosis and circulating blasts.
- She is sent to the ER and COVID-19 is ruled out.
- She is admitted and undergoes bone marrow biopsy, which confirms a diagnosis of AML not otherwise specified; she is cytoreduced with hydroxyurea until her WBC is <25K. Her karyotype is 46, XX and PCR identifies FLT3-ITD (ITD:WT allelic ratio 2:1) and NGS finds mutations in DNMT3A, NPM1, and FLT3-ITD.
- She is started on venetoclax + azacitidine and sent home after no infection is identified and her fevers defervesce on oral antibiotics.
- Her chemotherapy is well tolerated other than neutropenic fevers, requiring re-hospitalization prior to count recovery. No source is identified and the fevers abate with count recovery.

Case Presentation – Dr Perl: A patient with relapsed/refractory AML and a FLT3 mutation (continued)

- Marrow biopsy done during the fourth week of cycle 1 shows complete remission. She receives 7 more cycles before developing acute loss of vision associated with new thrombocytopenia and again circulating blasts are seen.
- Ophthalmology finds vitreous hemorrhage due to relapsed leukemia. She again tests positive for FLT3-ITD in the blood.
- Azacitidine is stopped and venetoclax continued along with gilteritinib.
- Within 72 hours of starting gilteritinib her circulating blasts clear. However, she has difficulty keeping platelets transfused adequately to achieve the target recommended by ophthalmology (>50K) and venetoclax is stopped after 3 weeks and not restarted.
- She is ultimately sent home but returns about five weeks into gilteritinib therapy with high grade fevers that persist despite broad spectrum antibiotics.

Case Presentation – Dr Perl: A patient with relapsed/refractory AML and a FLT3 mutation (continued)

- Cultures of the blood and urine are negative and CT scanning of chest, abdomen, pelvis, and sinuses fails to identify an occult infection site. She develops a piled-up erythematous rash on her arm where she had blood cultures drawn without surrounding cellulitis or fluid collection.
- A skin biopsy of the rash shows a dense neutrophilic infiltrate without bacteria or fungus in the biopsy specimen consistent with Sweet's syndrome.
- She is treated with 20 mg of prednisone daily with resolution of fevers and her rash. She is given insulin to manage hyperglycemia.
- Within 2 weeks her neutrophils start to rise and her platelet transfusions decrease from three times a week to once weekly.
- A bone marrow biopsy is performed and shows a hypocellular marrow (10% cellularity) with erythroid-dominant trilineage hematopoiesis but no increase in blasts.
- Her vision remains impaired but follow up with ophthalmology shows some resorption of the blood.

Case Presentation – Dr Wang: An older patient with newly diagnosed AML with a FLT3 mutation

- An 84-year-old woman with a prior history of rheumatoid arthritis on oral methotrexate therapy for several years, coronary artery disease s/p catheterization and stent placement, and longstanding hypertension.
- She reported increased fatigue and unintentional weight loss in 2019. Lab work done in Jan 2020 showing WBC 7.1, hgb 6.5, plts 16K with 18% peripheral blasts. She was admitted to the hospital and underwent bone marrow biopsy showing AML with 82% blasts. Cytogenetics showed trisomy 13 and deletion of 5q.
- Mutational profile showed FLT3-ITD and FLT3-D8351 mutations as well as RUNX1 and TET2 mutations. The patient received upfront therapy with azacitidine alone but was noted to have rising WBC and peripheral blasts count after 2 weeks of therapy.
- She was then started on gilteritinib monotherapy 120 mg daily with rapid cytoreduction in WBC. Repeat bone marrow after 1 month of therapy demonstrated only 1% blasts.

Case Presentation – Dr Wang: An older patient with newly diagnosed AML with a FLT3 mutation (continued)

- She remained on gilteritinib therapy from Feb-July 2021, at which time she was noted to have progressive thrombocytopenia (plts <20K). Bone marrow at this time showed relapsed AML with 30% blasts, now FLT3 negative.
- She was initiated on a clinical trial of a novel tyrosine kinase inhibitor and achieved a CR without platelet recovery and reduction in marrow blasts to 3%. Unfortunately, her disease once again relapsed in Dec 2020 and she was enrolled on a new clinical trial awaiting repeat evaluation.
- She was recently hospitalized for suspected bacteremia and severe thrombocytopenia requiring daily platelet transfusions.

Agenda

Module 1: Venetoclax combinations

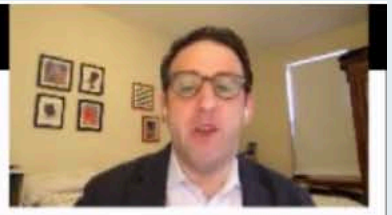
Module 2: FLT3 inhibitors

Module 3: IDH inhibitors

Module 4: Oral azacitidine (CC-486)

Module 5: Secondary AML — CPX-351

Module 6: Novel agents and strategies

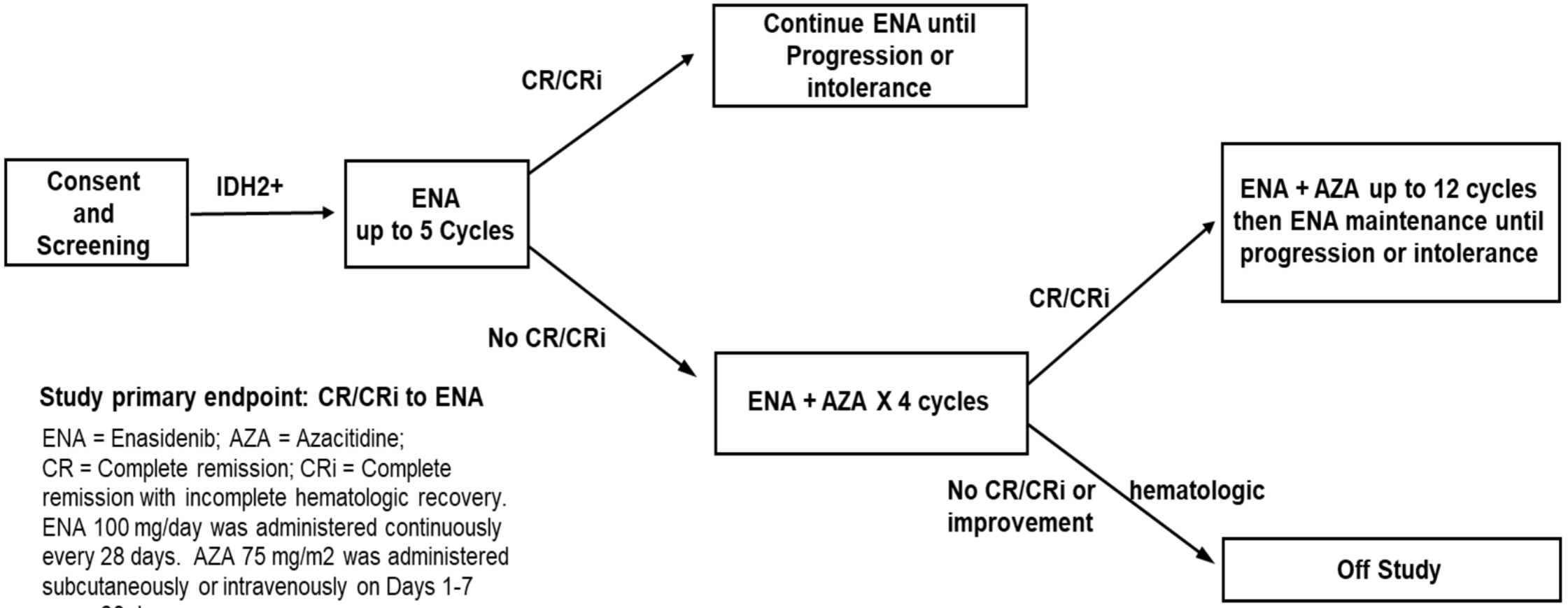


Enasidenib Monotherapy is Effective in Older Patients with Newly Diagnosed IDH2 Mutated Acute Myeloid Leukemia and Addition of Azacitidine Rescues Enasidenib Monotherapy Failures: A Phase 2/1B Study of the BEAT AML Master Trial

LEUKEMIA & LYMPHOMA SOCIETY®

RTP RESEARCH TO PRACTICE

S3 - STUDY DESIGN AND OBJECTIVES



Study primary endpoint: CR/CRi to ENA

ENA = Enasidenib; AZA = Azacitidine;
CR = Complete remission; CRi = Complete remission with incomplete hematologic recovery.
ENA 100 mg/day was administered continuously every 28 days. AZA 75 mg/m2 was administered subcutaneously or intravenously on Days 1-7 every 28 days.

Stein EM et al. ASH 2020;Abstract 636.

RESPONSE

Parameter	Phase 2 Enasidenib 100 mg/day (n=60)	Phase 1b Enasidenib + Azacitidine (n=17)
Duration of Response in months Median, 95% CI	NR, 7.1-NR	NR, 2.5 – NR
Overall Survival Median in months, 95% CI	24.4, 10.6-NE	8.9, 5.2-NE
Median Follow-up in months (range)	14.6 (6.2-33.5)	12.7 (1.1-31.4)

Stein EM et al. ASH 2020;Abstract 636.

Phase III IDHENTIFY Study Fails to Meet Its Primary Endpoint of OS in Relapsed/Refractory AML with an IDH2 Mutation

Press Release – August 25, 2020

"The phase 3 IDHENTIFY study evaluating enasidenib plus best supportive care versus conventional care regimens did not meet the primary end point of overall survival (OS) in patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation, according to… the developer of the agent. Notably, the safety profile of enasidenib was consistent with previously reported findings.

The international, multicenter, open-label, randomized, phase 3 IDHENTIFY study compared the efficacy and safety of enasidenib versus conventional care regimens, including continuous 28-day cycles of best supportive care only, azacitidine subcutaneously plus best supportive care, low-dose cytarabine subcutaneously plus best supportive care, or intermediate-dose cytarabine intravenously plus best supportive care, in patients aged 60 years or older with AML refractory to or relapsed after second- or third-line AML therapy and positive for an *IDH2* mutation. The primary end point of the study was OS, and key secondary end points included overall response rate, event-free survival, duration of response, and time to response."

https://www.cancernetwork.com/view/phase-3-idhentify-study-fails-to-meet-primary-end-point-of-overall-survival

RTP RESEARCH TO PRACTICE

Ivosidenib improves overall survival relative to standard therapies in relapsed or refractory mutant *IDH1* AML: results from matched comparisons to historical controls

Peter Paschka, MD,[1*] Hervé Dombret, MD,[2] Xavier Thomas, MD, PhD,[3] Christian Recher, MD, PhD,[4] Sylvain Chantepie, MD,[5] Pau Montesinos, MD, PhD,[6,7] Evelyn Acuña-Cruz, MD,[7] Paresh Vyas, MRCP FRCP FRCPath,[8] Karl-Anton Kreuzer, MD,[9] Michael Heuser, MD,[10] Klaus H. Metzeler, MD,[11] Michael Dennis, MD,[12] Bruno Quesnel, MD, PhD,[13] Mathilde Hunault-Berger, MD, PhD,[14] Mohamad Mohty, MD, PhD,[15] Arnaud Pigneux, MD, PhD,[16] Stéphane de Botton, MCU-PH,[17] Daniela Weber, MSc,[1] Konstanze Döhner, MD,[1] Gary Milkovich, PharmD,[18] John Reitan, PharmD,[18] Sarah C. MacDonald, SD,[19] Deborah Casso, MPH,[20] Michael Storm, MSc,[21] Hua Liu, PhD,[21] Stephanie M. Kapsalis, OTR,[21] Eyal C. Attar, MD,[21] Thomas Winkler, MD,[21] Hartmut Döhner, MD[1]

[1]Ulm University Hospital Ulm, Germany; [2]Hôpital Saint-Louis, Paris, France; [3]Centre Hospitalier Lyon-Sud, Pierre-Benite, France; [4]IUCT-Oncopole, Centre Hospitalier Universitaire de Toulouse, Toulouse, France; [5]Institut d'Hématologie de Basse-Normandie, Centre Hospitalier Universitaire de Caen, Caen, France; [6]CIBERONC, Instituto Carlos III, Madrid, Spain; [7]Hospital Universitario y Politécnico La Fe, Valencia, Spain; [8]University of Oxford, Oxford, United Kingdom; [9]Uniklinik Köln, Köln, Germany; [10]Department of Hematology, Hemostasis, Oncology and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany; [11]Department of Medicine III, University Hospital, LMU Munich, Munich, Germany; [12]The Christie NHS Foundation Trust, Manchester, United Kingdom; [13]Centre Hospitalier Régional Universitaire de Lille, Lille, France; [14]CRCINA Centre Hospitalier Universitaire d'Angers, Angers, France; [15]Sorbonne University, Hôpital Saint-Antoine, Paris, France; [16]CHU Bordeaux, Université de Bordeaux, Bordeaux, France; [17]Institut Gustave Roussy, Villejuif, France; [18]RJM Group, LLC, Washington, DC, United States; [19]IQVIA, Kirkland, QC, Canada; [20]IQVIA, Seattle, WA, United States; [21]Agios Pharmaceuticals, Inc., Cambridge, MA, United States

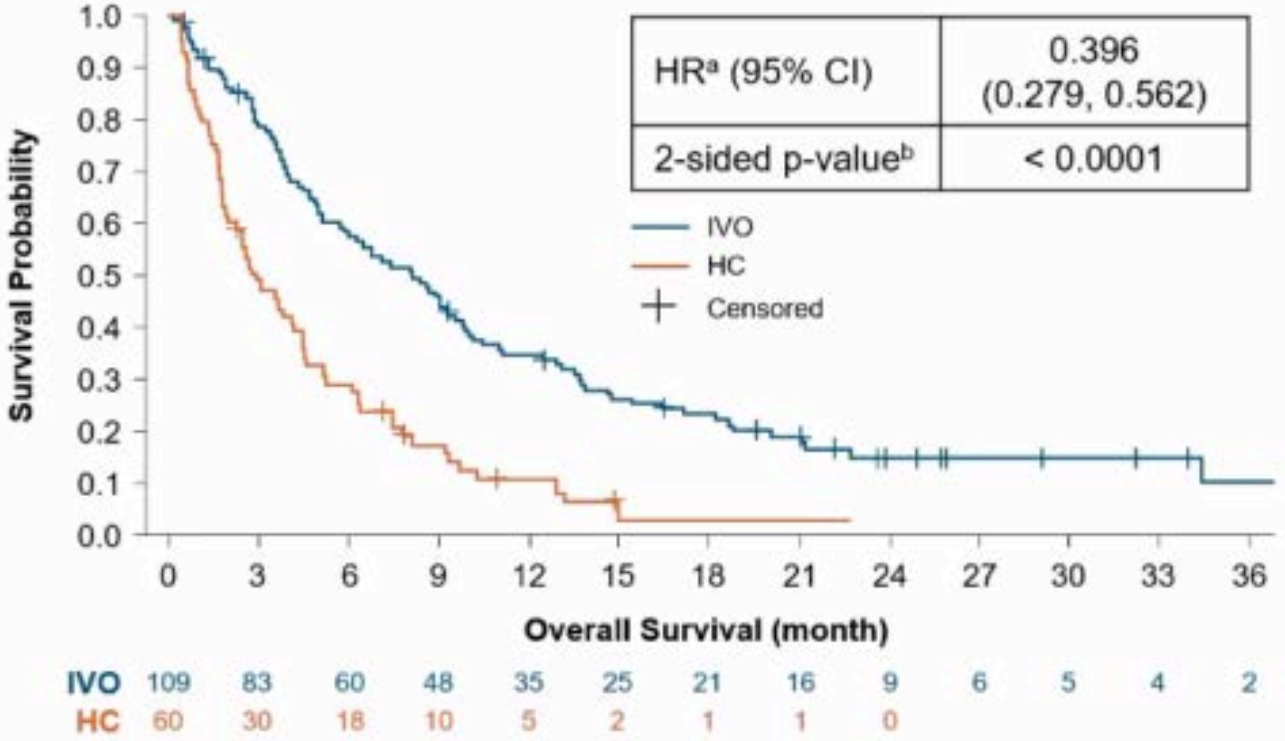
**Current address: Klinikum Ludwigshafen, Ludwigshafen am Rhein, Germany*

This study was funded by Agios Pharmaceuticals, Inc.

Presented at the 62nd American Society of Hematology Annual Meeting and Exposition 2020 (ASH 2020) 5 – 8 December 2020 (Virtual)

Kaplan–Meier curves demonstrate significant OS benefit for IVO

IPTW



HR[a] (95% CI)	0.396 (0.279, 0.562)
2-sided p-value[b]	< 0.0001

IVO
HC
Censored

- Clear separation of the IVO and HC KM curves demonstrates that patients in the last line setting benefit from IVO treatment
- KM curves were comparable for unmatched and optimal full matching

[a]Cox regression analysis, using the key prognostic factors as covariates, was applied to estimate HR and the corresponding 95% CI was estimated using the sandwich estimator. [b]P-value based on 2-sided log-rank test.
CI = confidence interval; HC = historical control; HR = hazard ratio; IPTW = inverse probability of treatment weighting method; IVO = ivosidenib; KM = Kaplan-Meier; OS = overall survival

Paschka P et al. ASH 2020;Abstract 625.

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Results of Venetoclax and Azacitidine Combination in Chemotherapy Ineligible Untreated Patients with Acute Myeloid Leukemia with *IDH 1/2* mutations

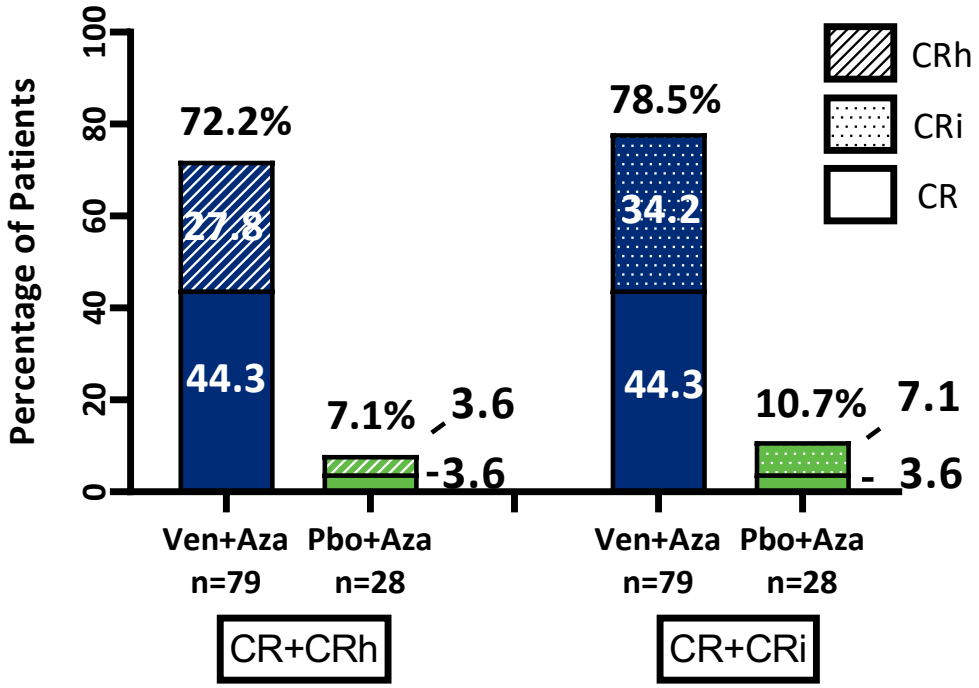
Daniel A. Pollyea [1], Courtney D. DiNardo [2], Martha L. Arellano [3], Arnaud Pigneux [4], Walter Fiedler [5], Marina Konopleva [2], David A. Rizzieri [6], B. Douglas Smith [7], Atsushi Shinagawa [8], Roberto M. Lemoli [9], Monique Dail [10], Yinghui Duan [11], Brenda Chyla [11], Jalaja Potluri [11], Jean A. Ridgeway [11], Hagop M. Kantarjian [2]

[1]Division of Hematology, School of Medicine, University of Colorado, Aurora, CO, USA; [2]Department of Leukemia, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [3]Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA; [4]Department of Hematology, CHU de Bordeaux, France; [5]Department of Hematology, University Medical Center Hamburg-Eppendorf, Germany; [6]Department of Hematology, Duke University School of Medicine, Durham, NC, USA; [7]Department of Oncology, Johns Hopkins Medicine, Baltimore, MD, USA; [8]Department of Hematology, Hitachi General Hospital, Hitachi-shi, Japan; [9]Clinic of Hematology, Department of Internal Medicine (DiMI), University of Genoa, San Martino Hospital IRCCS, Genoa, Italy; [10]Genentech Inc., South San Francisco, CA, USA; [11]AbbVie Inc., North Chicago, IL, USA

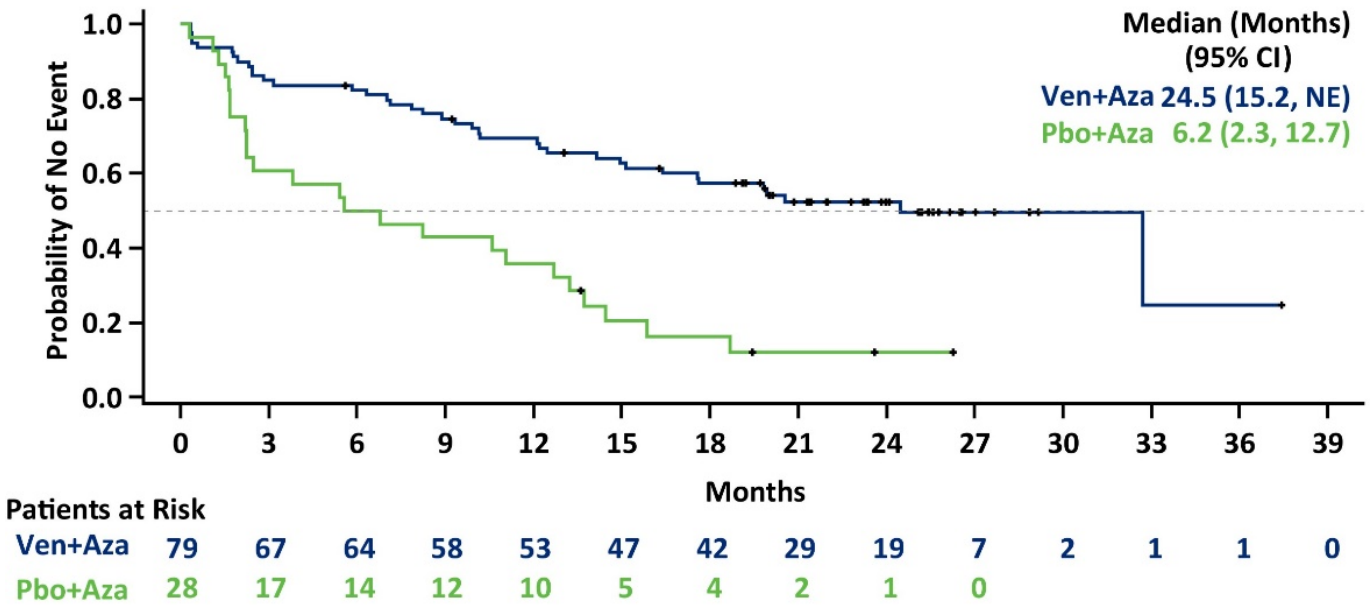
Abstract 461

American Society of Hematology (ASH) – 62nd Annual Meeting
December 5-8, 2020

Response Rates with Ven/AZA for Patients with IDH1m/IDH2m AML



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



Survival Estimate (%) (95% CI)

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

Pollyea DA et al. ASH 2020;Abstract 461.

RTP RESEARCH TO PRACTICE

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

Case Presentation – Dr Perl: A patient with AML and an IDH1 or IDH2 mutation

- 67 YO retired mailman complains of progressive dyspnea on exertion and feels faint after mowing his lawn.
- He sees the doctor and is found to have hemoglobin=4.8. He is sent to the ER and admitted.
- Labs there show a WBC=2.7 (33% blasts, ANC 600) and platelets=35. Prior CBC from 6 months prior is notable for plts =100K.
- CXR is notable for RUL infiltrate and a small pleural effusion. A marrow biopsy shows a 90% cellular marrow with 61% myeloblasts and genetic studies show a karyotype 47,XY,+8 and NGS finds mutations in ASXL1, U2AF1, and IDH2.
- He is treated with IV antibiotics and induced with 7+3 (cytarabine 100 mg/m^2/d; d1-7 CIVI, daunorubicin 60 mg/m^2/d IV; d1-3).
- Over the next two weeks, he develops progressive hypoxemia and near resolution of the R upper lobe infiltrate but new bilateral nodular infiltrates concerning for angio-invasive fungal infection and persistent mediastinal lymphadenopathy.

Case Presentation – Dr Perl: A patient with AML and an IDH1 or IDH2 mutation (continued)

- A bone marrow biopsy on day 14 shows a 60% cellular marrow with 84% blasts.
- His therapy is changed to venetoclax (dose reduced to 100 mg for concurrent voriconazole) and azacitidine.
- 21 days later a bone marrow shows erythroid hyperplasia, trilineage dysplasia, scattered non-caseating granulomas but no increase in blasts.
- He has an unremarkable recovery of blood counts with GCSF and becomes transfusion independent.
- He continues on monthly cycles of venetoclax 100 mg/d; days 1-14 + azacitidine 75 mg/m^2/d; days 1-5 as an outpatient after discharge (dosing adjusted to avoid prolonged neutropenia).
- 3 months later, his chest CT has normalized and he is being worked up for allogeneic transplant from his HLA-identical brother.

Agenda

Module 1: Venetoclax combinations

Module 2: FLT3 inhibitors

Module 3: IDH inhibitors

Module 4: Oral azacitidine (CC-486)

Module 5: Secondary AML — CPX-351

Module 6: Novel agents and strategies

Oral Azacitidine (CC-486) Prolongs Survival for Patients with Acute Myeloid Leukemia (AML) in Remission after Intensive Chemotherapy (IC) Independent of the Presence of Measurable Residual Disease (MRD) at Study Entry: Results from the QUAZAR AML-001 Trial

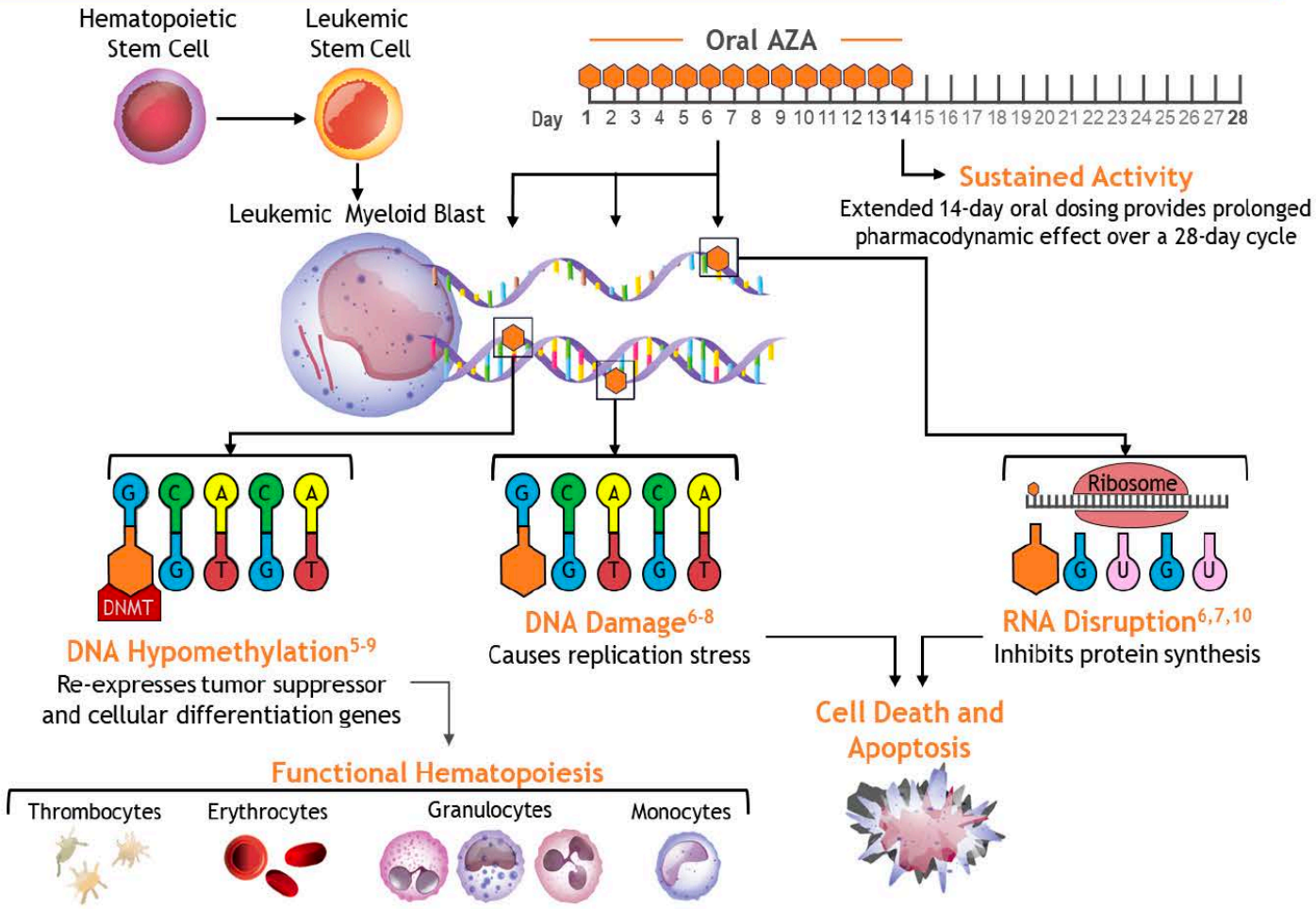
Gail J. Roboz,[1] Farhad Ravandi,[2] Andrew H Wei,[3,4] Hervé Dombret,[5,6] Hartmut Döhner,[7] Felicitas Thol,[8] Maria Teresa Voso,[9] Andre C. Schuh,[10] Kimmo Porkka,[11,12] Ignazia La Torre,[13] Barry Skikne,[14,15] Keshava Kumar,[15] Qian Dong,[15] C.L. Beach,[15] Alberto Risueño,[16] Daniel Lopes de Menezes,[15] and Gert Ossenkoppele[17]

[1]Division of Hematology and Oncology, Weill Cornell Medicine and The New York Presbyterian Hospital, New York, NY; [2]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX; [3]The Alfred Hospital, Melbourne, Australia; [4]Monash University, Melbourne, Australia; [5]Hôpital Saint-Louis, Assistance Publique - Hôpitaux de Paris (AP-HP), Paris, France; [6]Institut de Recherche Saint Louis, Université de Paris, Paris, France; [7]Ulm University Hospital, Ulm, Germany; [8]Medizinische Hochschule Hannover, Hannover, Germany; [9]University of Rome Tor Vergata, Rome, Italy; [10]Princess Margaret Cancer Centre, Toronto, ON, Canada; [11]iCAN Digital Precision Cancer Medicine Flagship, University of Helsinki, Helsinki, Finland; [12]Hematology Research Unit Helsinki, Helsinki University Hospital Comprehensive Cancer Center, Helsinki, Finland; [13]Celgene, a Bristol-Myers Squibb Company, Boudry, Switzerland; [14]Kansas University Medical Center, Kansas City, KS; [15]Bristol Myers Squibb, Princeton, NJ; [16]BMS Center for Innovation and Translational Research Europe (CITRE), a Bristol Myers Squibb Company, Seville, Spain; [17]Amsterdam UMC, Location VU University Medical Center, Amsterdam, Netherlands

Publication #692

Oral azacitidine

- Oral azacitidine (Oral AZA [CC-486]):
  - Oral HMA with a distinct PK/PD profile from injectable AZA; the two are not bioequivalent[1,2]
  - Oral AZA was recently approved in the US for continued Tx of adult pts with AML in first CR/CRi post-IC and not able to complete intensive curative therapy (eg, HSCT)[3]
- Oral dosing allows for extended drug exposure during each Tx cycle to prolong AZA activity[1,2,4]



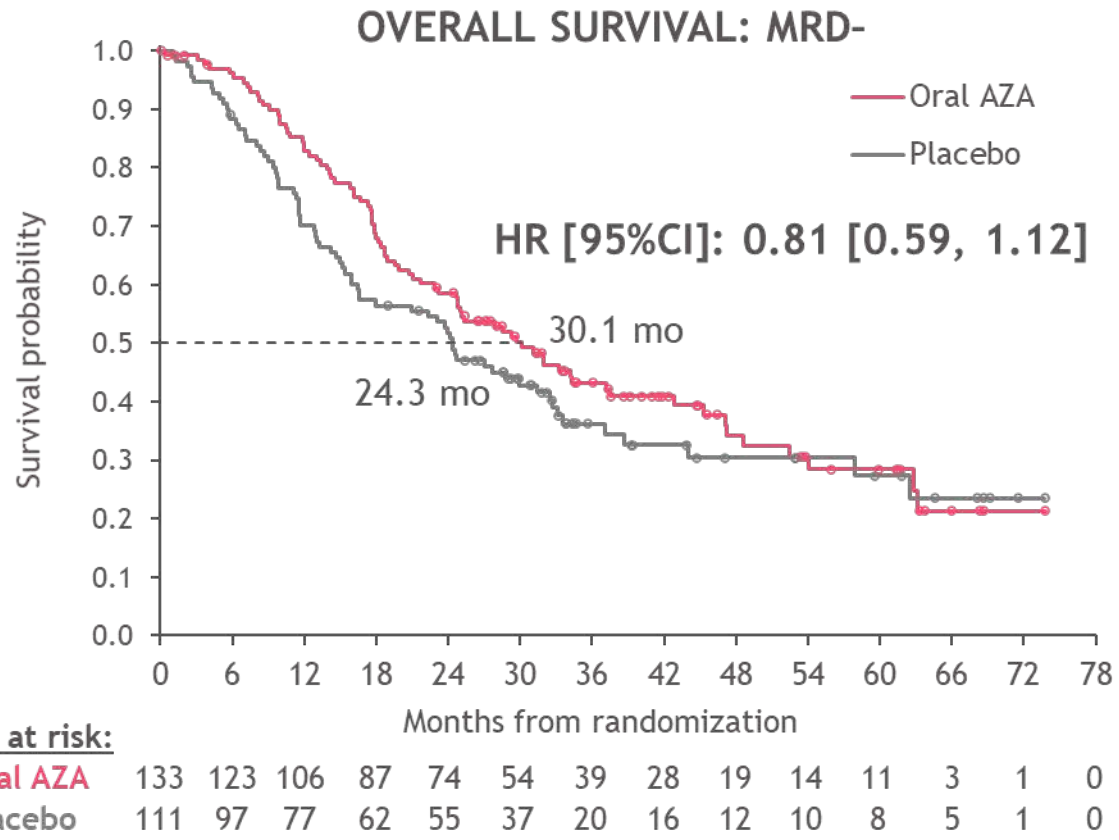
1. Garcia-Manero et al. *J Clin Oncol*. 2011;29(18):2521-7. 2. Laille et al. *PLoS One*. 2015;10(8):e0135520. 3. ONUREG® (azacitidine) tablets [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; Rev. 9/2020. 4. Savona et al. *Am J Hematol*. 2018;93(10):1199-206. 5. Stresemann et al. *Mol Cancer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

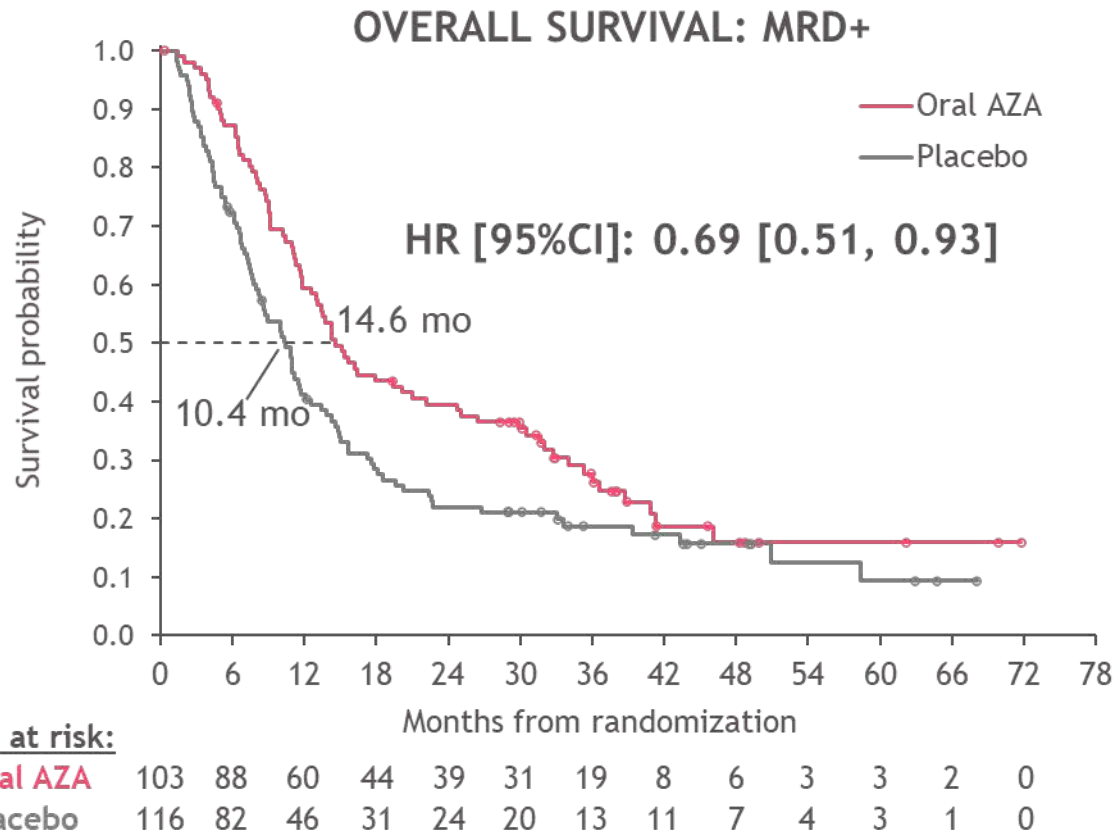
AML, acute myeloid leukemia; AZA, azacitidine; CR, complete remission; CRi, CR with incomplete blood count recovery; HMA, hypomethylating agent; HSCT, hematopoietic stem cell transplant; IC, intensive chemotherapy; PD, pharmacodynamic; PK, pharmacokinetic; pts, patients; Tx, treatment.

Roboz GJ et al. ASH 2020;Abstract 692.

QUAZAR: Overall survival by baseline MRD status and treatment arm

- **Treatment with Oral AZA (CC-486) resulted in improved OS from time of randomization compared with PBO in pts who were MRD+ or MRD- at study entry**





Roboz GJ et al. ASH 2020;Abstract 692.

Escalated Dosing Schedules of Oral Azacitidine (CC-486) are Effective and Well Tolerated for Patients Experiencing First Acute Myeloid Leukemia (AML) Relapse: Results from the Phase III QUAZAR AML-001 Trial

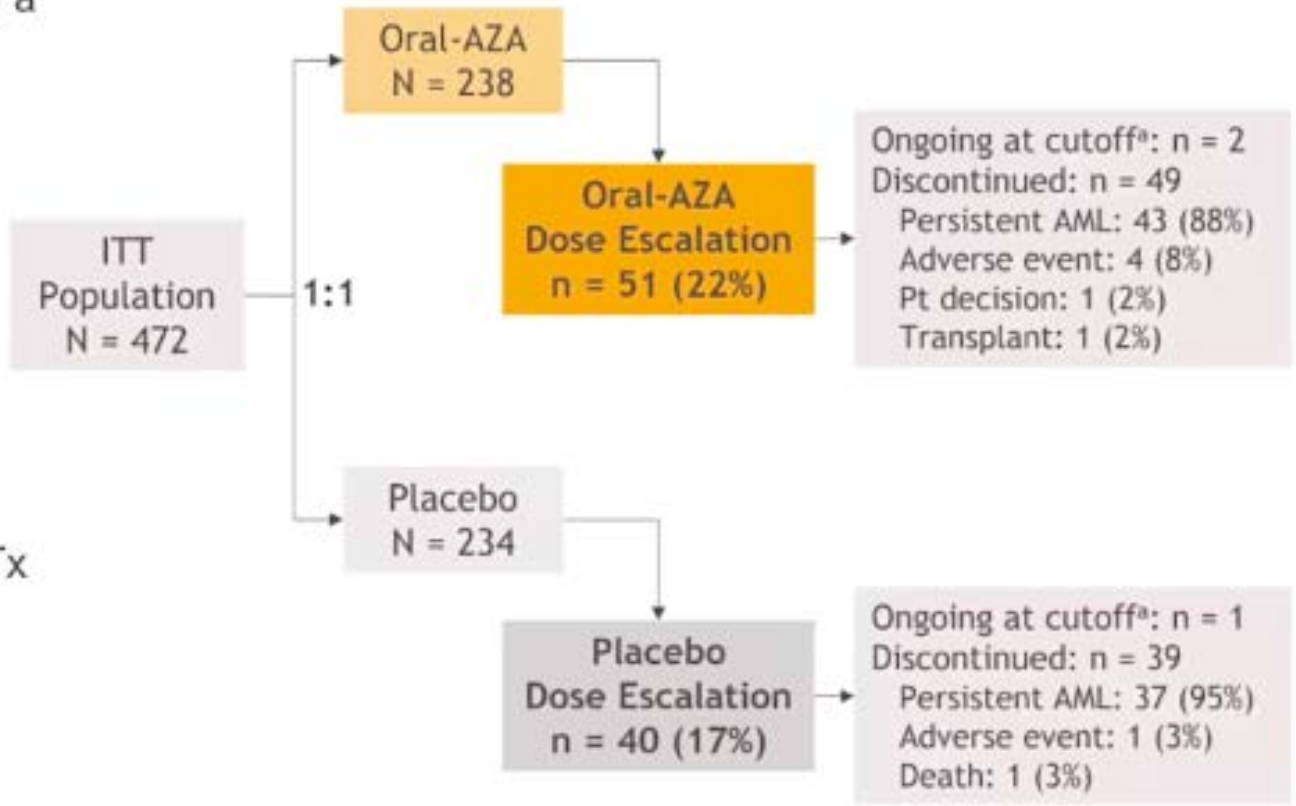
Hartmut Döhner,[1] Andrew H Wei,[2,3] Pau Montesinos,[4,5] Hervé Dombret,[6,7] Farhad Ravandi,[8] Hamid Sayar,[9] Kimmo Porkka,[10,11] Irwindeep Sandhu,[12] Francesco Passamonti,[13] Fabrizio Pane,[14] Tadeusz Robak,[15] José F. Falantes,[16] Andre C. Schuh,[17] Gert Ossenkoppele,[18] Ignazia La Torre,[19] Barry Skikne,[20,21] Keshava Kumar,[21] Qian Dong,[21] C.L. Beach,[21] and Gail J. Roboz[22]

[1]Ulm University Hospital, Ulm, Germany; [2]The Alfred Hospital, Melbourne, Australia; [3]Australian Centre for Blood Diseases, Monash University, Melbourne, Australia; [4]CIBERONC, Instituto de Salud Carlos III, Madrid, Spain; [5]Hematology and Hemotherapy Department, Hospital Universitari i Politècnic La Fe, Valencia, Spain, Spain; [6]Institut de Recherche Saint Louis, Université de Paris, Paris, France; [7]Hôpital Saint-Louis, Assistance Publique - Hôpitaux de Paris (AP-HP), Paris, France; [8]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX; [9]Indiana University Cancer Center, Indianapolis, IN; [10]iCAN Digital Precision Cancer Medicine Flagship, University of Helsinki, Helsinki, Finland; [11]Hematology Research Unit Helsinki, Helsinki University Hospital Comprehensive Cancer Center, Helsinki, Finland; [12]University of Alberta Hospital, Edmonton, Canada; [13]Department of Medicine and Surgery, University of Insubria, Varese, Italy; [14]Azienda Ospedaliera Universitaria Federico II, Naples, Italy; [15]Department of Hematology, Medical University of Lodz, Copernicus Memorial Hospital, Lodz, Poland; [16]Hospital Virgen del Rocío. Hematología, Seville, Spain; [17]Princess Margaret Cancer Centre, Toronto, ON, Canada; [18]Amsterdam UMC, Location VU University Medical Center, Amsterdam, Netherlands; [19]Celgene, a Bristol-Myers Squibb Company, Boudry, Switzerland; [20]Kansas University Medical Center, Kansas City, KS; [21]Bristol Myers Squibb, Princeton, NJ; [22]Division of Hematology and Oncology, Weill Cornell Medicine and The New York-Presbyterian Hospital, New York, NY

Abstract # 111

Dose-escalation cohort

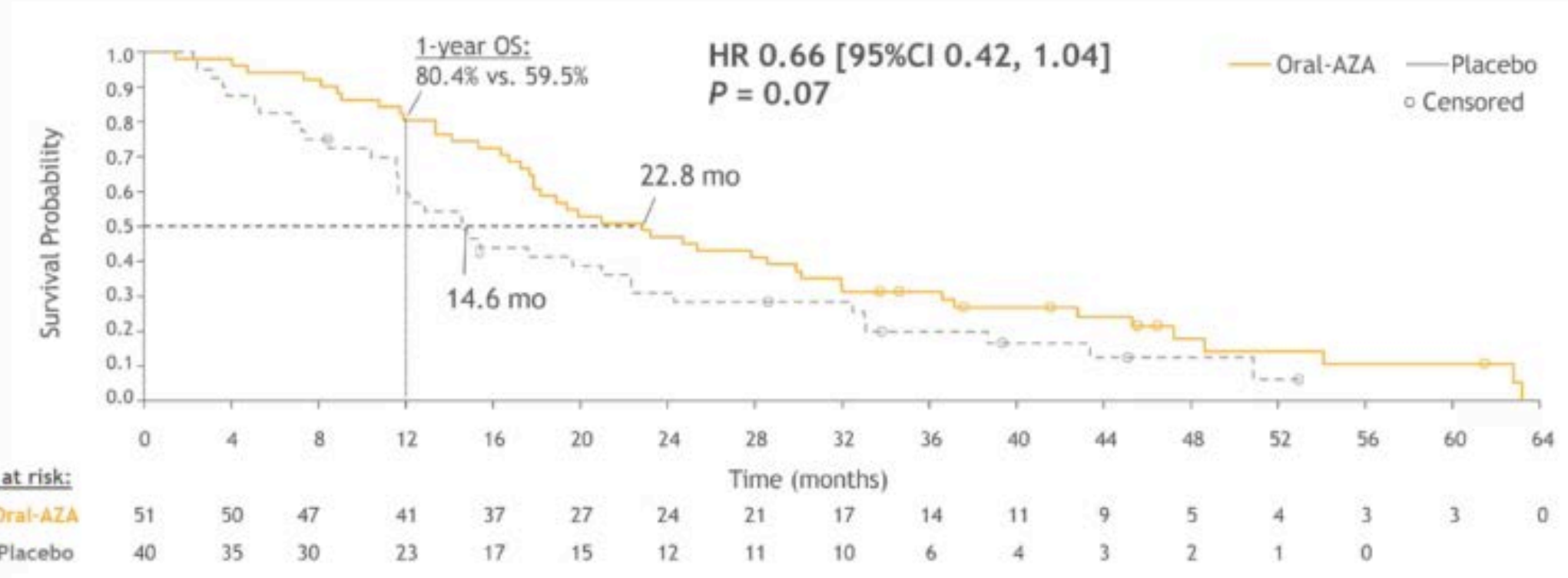
- 91/472 (19.3%) randomized pts received a 21-day escalated dosing schedule
- Median time to dose escalation:
  - Oral-AZA: 9.2 months (range 1.0–52.7)
  - PBO: 6.0 months (range 0.5–19.3)
- Duration of escalated dosing:
  - Median (range) number of cycles: Oral-AZA 2 (1–45), PBO 2 (1–16)
  - Received > 3 escalated dosing cycles: Oral-AZA 43% (22/51); PBO 18% (7/40)
- Most pts (88%) ultimately discontinued Tx due to persistent AML



[a]Data cutoff: July 15, 2019.
AML, acute myeloid leukemia; AZA, azacitidine; PBO, placebo; pt(s), patient(s); Tx, treatment.

Döhner H et al. ASH 2020;Abstract 111.

Escalated dosing cohort: Overall survival



Overall survival estimated using Kaplan-Meier methods. The hazard ratio (HR) and 95% confidence intervals comparing Oral-AZA vs. placebo are from a Cox proportional hazards model, and the *P* value is from an unstratified log-rank test.

95%CI, 95% confidence interval; AZA, azacitidine; HR, hazard ratio; mo, months; OS, overall survival; No., number.

Döhner H et al. ASH 2020;Abstract 111.

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

Agenda

Module 1: Venetoclax combinations

Module 2: FLT3 inhibitors

Module 3: IDH inhibitors

Module 4: Oral azacitidine (CC-486)

Module 5: Secondary AML — CPX-351

Module 6: Novel agents and strategies

Five-year Final Results of a Phase 3 Study of CPX-351 Versus 7+3 in Older Adults with Newly Diagnosed High-risk/Secondary Acute Myeloid Leukemia (AML): Outcomes by Age Subgroup and Among Responders

Presenter: Jeffrey E. Lancet

H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL

Jeffrey E. Lancet,[1] Geoffrey L. Uy,[2] Laura F. Newell,[3] Tara L. Lin,[4] Donna Hogge,[5] Scott R. Solomon,[6] Gary J. Schiller,[7] Matthew J. Wieduwilt,[8] Daniel H. Ryan,[9] Stefan Faderl,[10] Yu-Lin Chang,[10] Jorge E. Cortes[11,12]

[1]H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA; [2]Washington University School of Medicine, St. Louis, MO, USA; [3]Oregon Health & Science University, Portland, OR, USA; [4]University of Kansas Medical Center, Kansas City, KS, USA; [5]Leukemia/BMT Program of British Columbia, Vancouver, BC, Canada; [6]Leukemia Program, Northside Hospital Cancer Center Institute, Atlanta, GA, USA; [7]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [8]University of California – San Diego Moores Cancer Center, La Jolla, CA, USA; [9]University of Rochester, Rochester, NY, USA; [10]Jazz Pharmaceuticals, Palo Alto, CA, USA; [11]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [12]Georgia Cancer Center, Augusta University, Augusta, GA, USA.

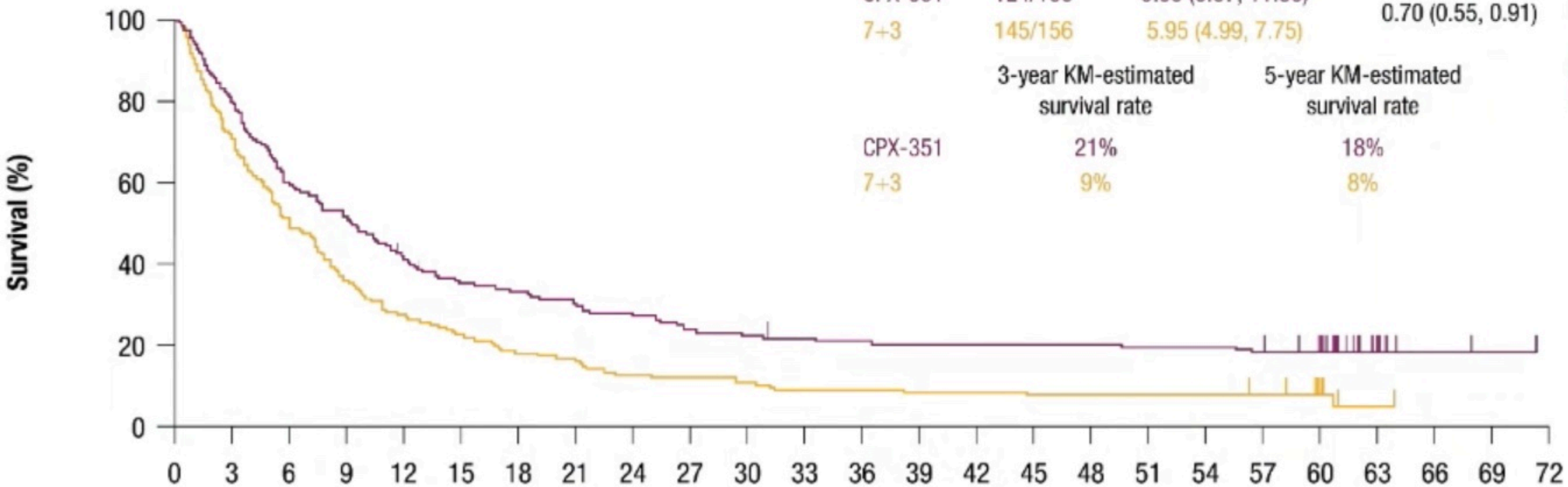
62nd ASH Annual Meeting & Exposition; December 5-8, 2020

Abstract 635

Overall Survival

	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)	

	3-year KM-estimated survival rate	5-year KM-estimated survival rate
CPX-351	21%	18%
7+3	9%	8%



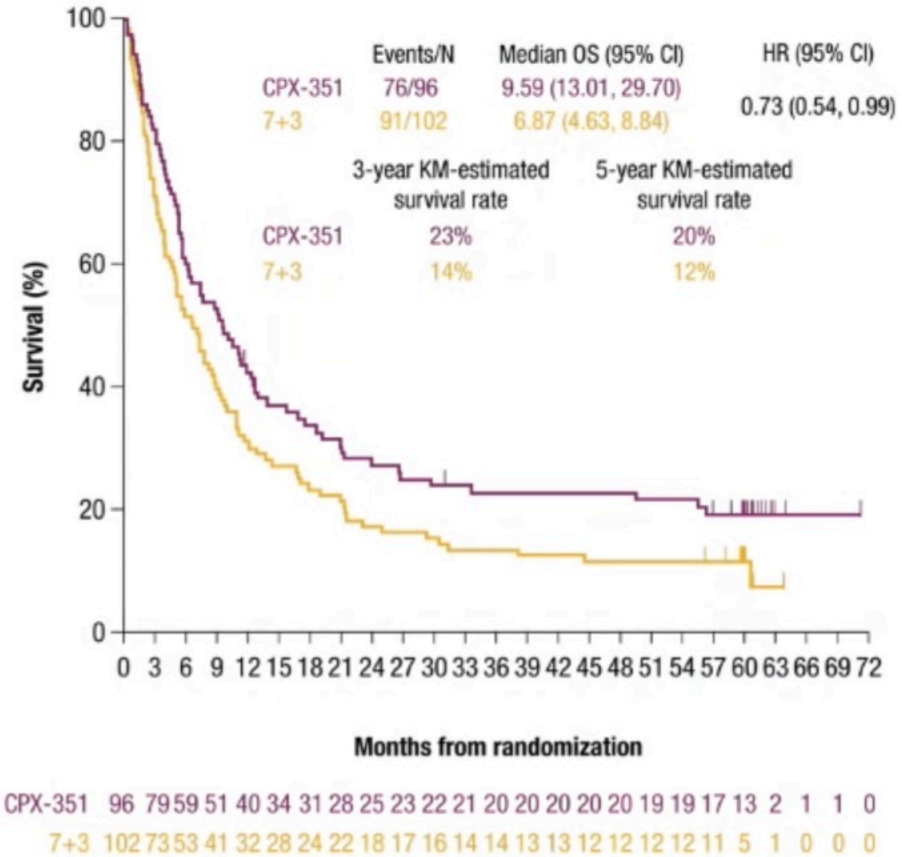
CPX-351	153	122	92	79	62	52	49	45	40	35	33	31	30	29	29	29	29	28	28	26	22	6	2	1	0
7+3	156	110	77	56	43	35	28	25	20	19	17	14	14	13	13	12	12	12	12	11	5	1	0	0	0

- **After a median follow-up of 60.65 months, improved median OS with CPX-351 vs 7+3 was maintained, with an HR that was very stable and consistent with the prior primary analysis**

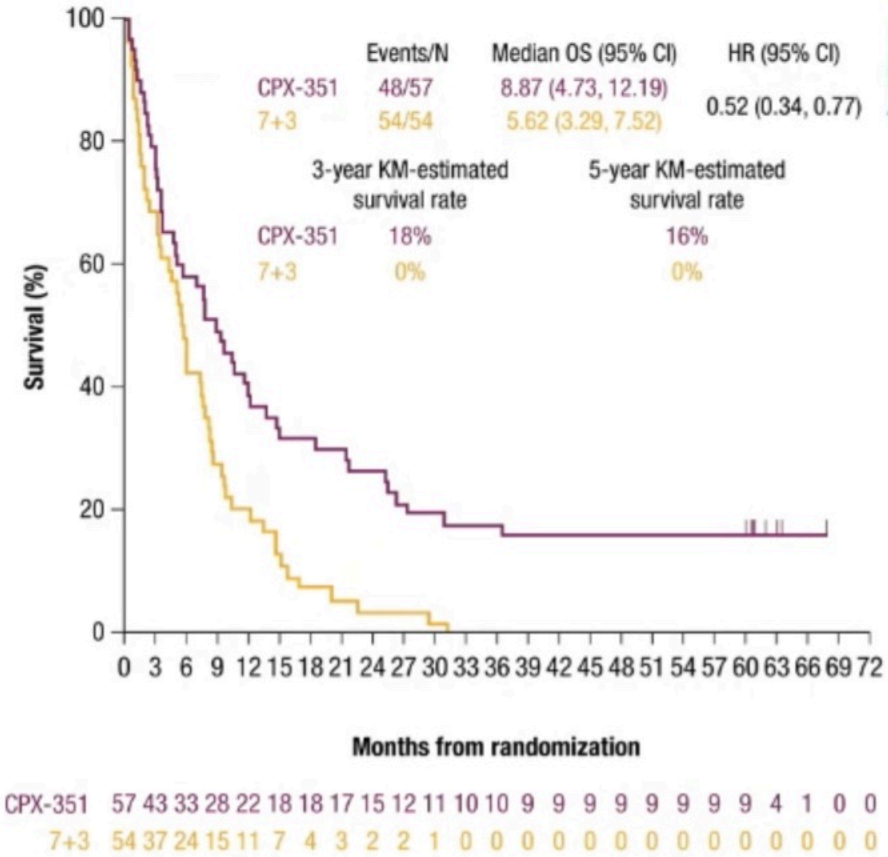
Lancet JE et al. ASH 2020;Abstract 635.

Overall Survival by Age Subgroup

Ages 60 to 69 Years



Ages 70 to 75 Years



- **Improved median OS and higher Kaplan-Meier–estimated survival rates at 3 and 5 years for CPX-351 vs 7+3 were maintained in patients aged 60 to 69 years and in those aged 70 to 75 years**

Lancet JE et al. ASH 2020;Abstract 635

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Abstract # 28

Phase II Study of CPX-351 Plus Venetoclax in Patients with Acute Myeloid Leukemia (AML)

Tapan M. Kadia, Gautam Borthakur, Koichi Takahashi, Courtney Dinardo, Naval Daver, Naveen Pemmaraju, Elias Jabbour, Nitin Jain, Nicholas Short, Wei Qiao, Lade Adewale, Caitlin Rausch, Sherry Pierce, Yesid Alvarado, Amin Alousi, Uday Popat, Issa Khouri, Guillermo Garcia-Manero, Marina Konopleva, Jorge Cortes, Farhad Ravandi, and Hagop Kantarjian.

58:13

CPX351 + Venetoclax in AML

Responses

Response / Outcome	N	%
Evaluable for Response	18	90
CR	1	6
CRi	6	33
MLFS	1	6
ORR	8	44
Died ≤ 4 weeks	2	10
Died ≤ 8 weeks	4	20
Median # of cycles given [Range]	1 [1 – 2]	
Median # of cycles to response	1 [1 – 2]	
No. of Responding Pts Receiving SCT	7	88
Median time to count recover (days)	41 [23 – 60]	

Kadia TM et al. ASH 2020;Abstract 28.

Agenda

Module 1: Venetoclax combinations

Module 2: FLT3 inhibitors

Module 3: IDH inhibitors

Module 4: Oral azacitidine (CC-486)

Module 5: Secondary AML — CPX-351

Module 6: Novel agents and strategies

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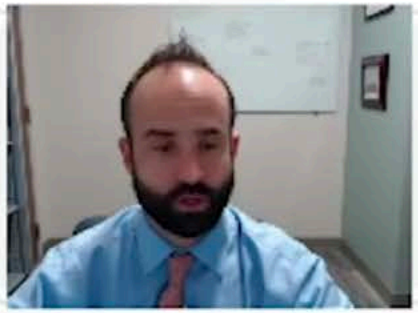
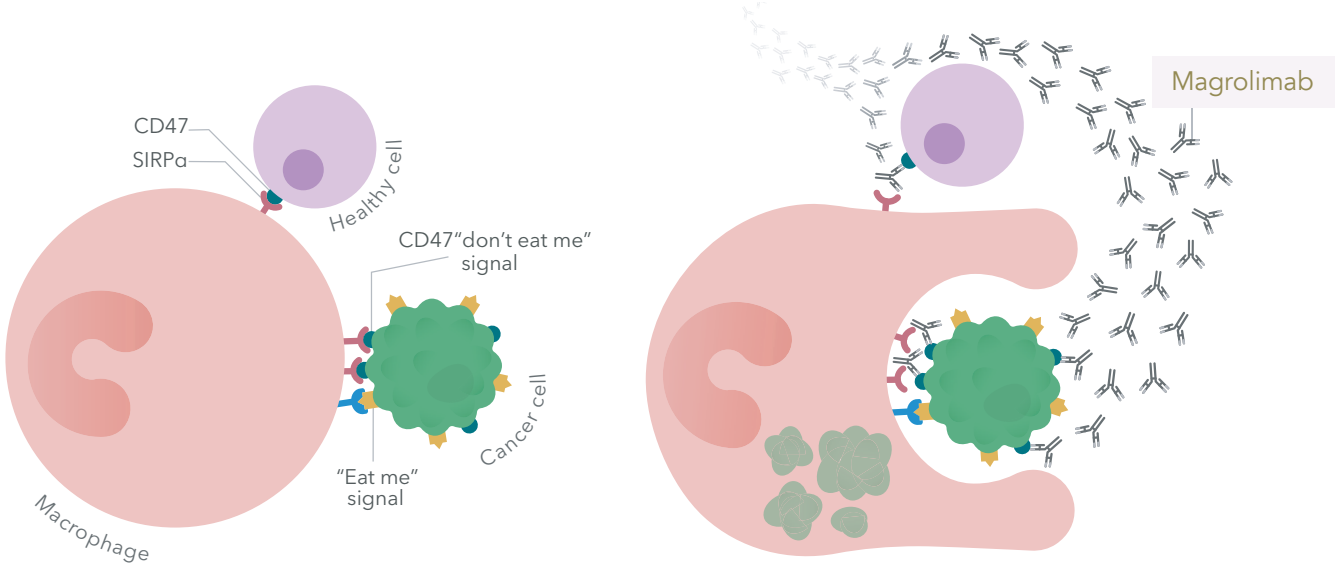


The First-in-Class Anti-CD47 Antibody Magrolimab Combined With Azacitidine Is Well Tolerated and Effective in AML Patients: Phase 1b Results

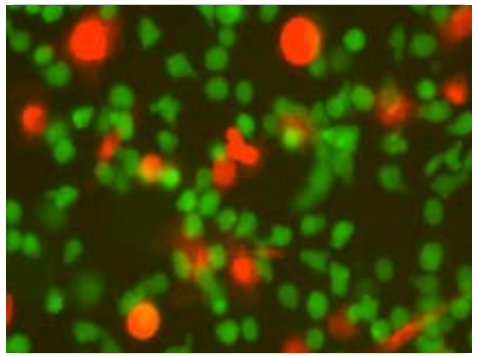
David A. Sallman[1], Adam S. Asch[2], Suman Kambhampati[3], Monzr M. Al Malki[4], Joshua F. Zeidner[5], William Donnellan[6], Daniel J. Lee[7], Paresh Vyas[8], Deepa Jeyakumar[9], Gabriel N. Mannis[10], Tiffany N. Tanaka[11], Wanxing Chai-Ho[12], Richard A. Larson[13], Andrew R. Whiteley[14], Guido Marcucci[4], Rami S. Komrokji[1], Guillermo Garcia-Manero[15], Joanna Van Elk[16], Ming Lin[16], Roy Maute[16], Jens-Peter Volkmer[16], Chris H. Takimoto[16], Mark P. Chao[16], and Naval G. Daver[15]

Abstract 330

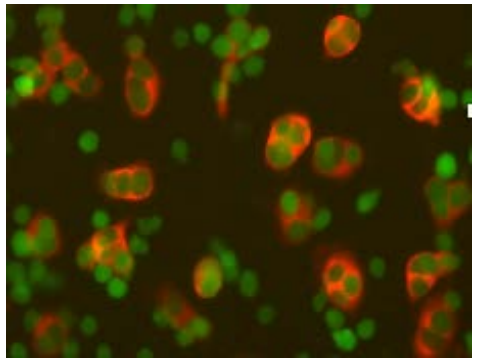
Magrolimab (Formerly 5F9) Is a First-in-Class Macrophage Immune Checkpoint Inhibitor Targeting CD47



Control mAb: No Phagocytosis



Anti-CD47 mAb: Phagocytosis



Macrophages
Cancer cells

CD47 is a "do not eat me" signal that is overexpressed in multiple cancers, including acute myeloid leukemia, leading to macrophage immune evasion

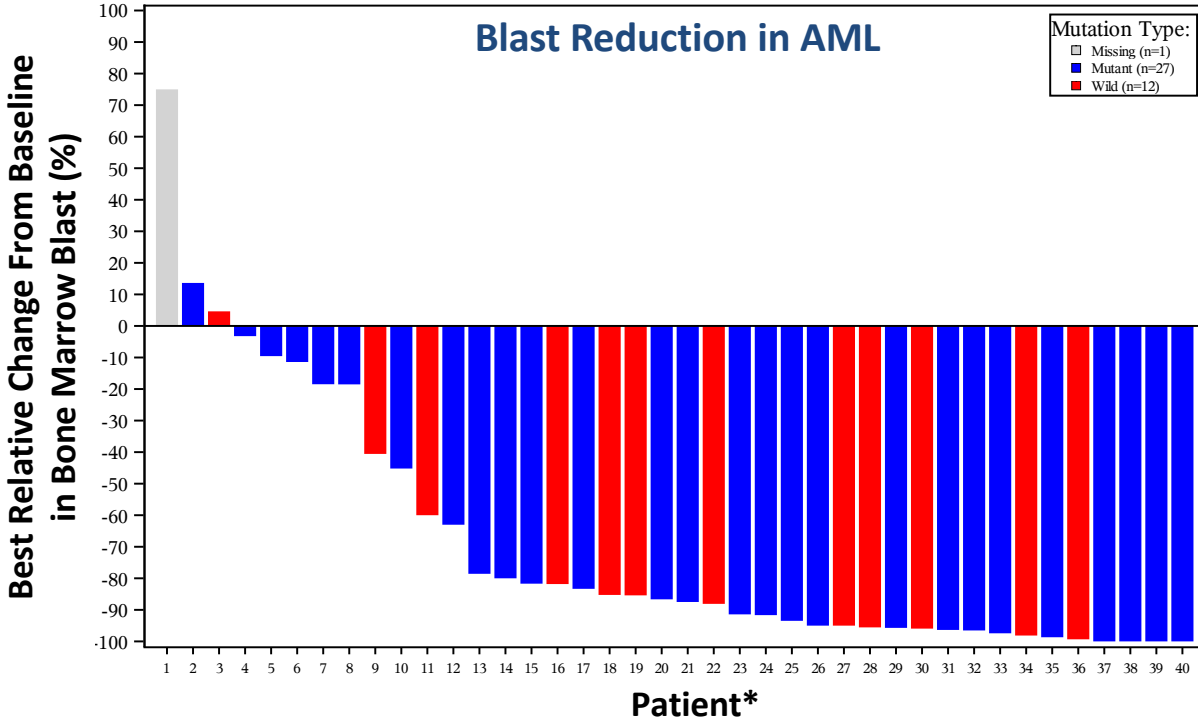
Magrolimab, an IgG4 anti-CD47 monoclonal antibody (mAb), eliminates tumor cells through macrophage phagocytosis

Magrolimab is being investigated in multiple cancers with >500 patients dose

Sallman DA et al. ASH 2020;Abstract 330.

Magrolimab + AZA in ND AML Ineligible for Intensive Chemotherapy: Responses

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.

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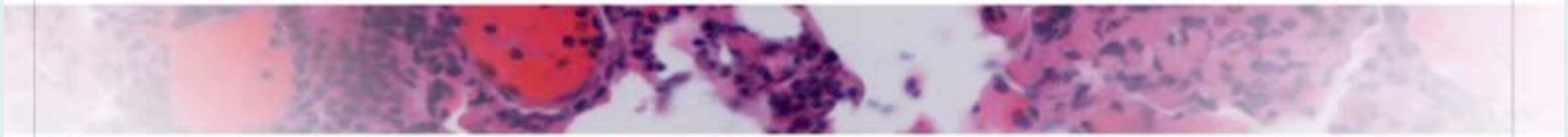


Preliminary Data Report on a Phase 1/2A First in Human Study of the Menin-KMT2A (MLL) inhibitor KO-539 in patients with relapsed or refractory acute myeloid leukemia

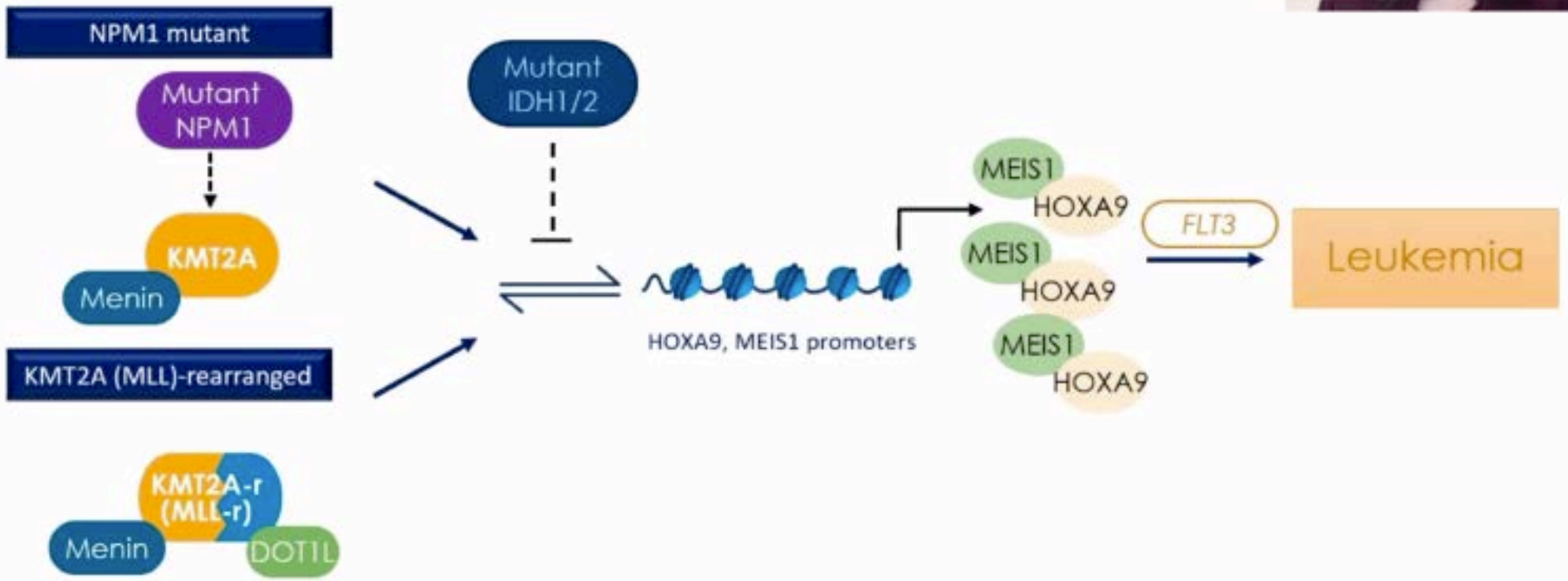
Eunice S. Wang[1], Jessica Altman[2], Kristen Pettit[3], Stephane DeBotton[4], Roland Walter[5], Pierre Fenaux[6], Francis Burrows[7], Blake Tomkinson[7], Bridget Martell[7] and Amir T Fathi[8]

[1]Roswell Park Comprehensive Cancer Center, Buffalo, NY; [2]Northwestern Medical Faculty Foundation, Chicago IL; [3]University of Michigan, Ann Arbor, MI; [4]Institut Gustave Roussy Service d'Hématologie Clinique, France; [5]Fred Hutchinson Cancer Research Center, Seattle, WA; [6]Hospital Saint Louis, France; [7]Kura Oncology, San Diego, CA; [8]Massachusetts General Hospital, Harvard Medical School, Boston, MA

Abstract 115

RTP RESEARCH TO PRACTICE

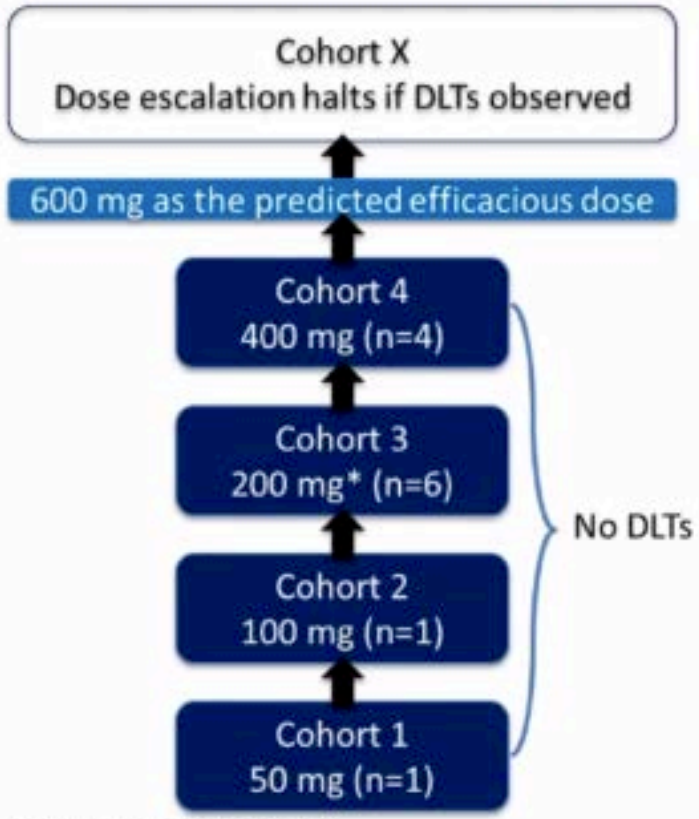
KO-539 is a Potent and Selective Oral Inhibitor of the Menin-KMT2A (MLL) Complex



American Society *of* Hematology

Wang ES et al. ASH 2020;Abstract 115.

KO-539 Demonstrates Encouraging Early Clinical Activity



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

*Expanded to characterize PK

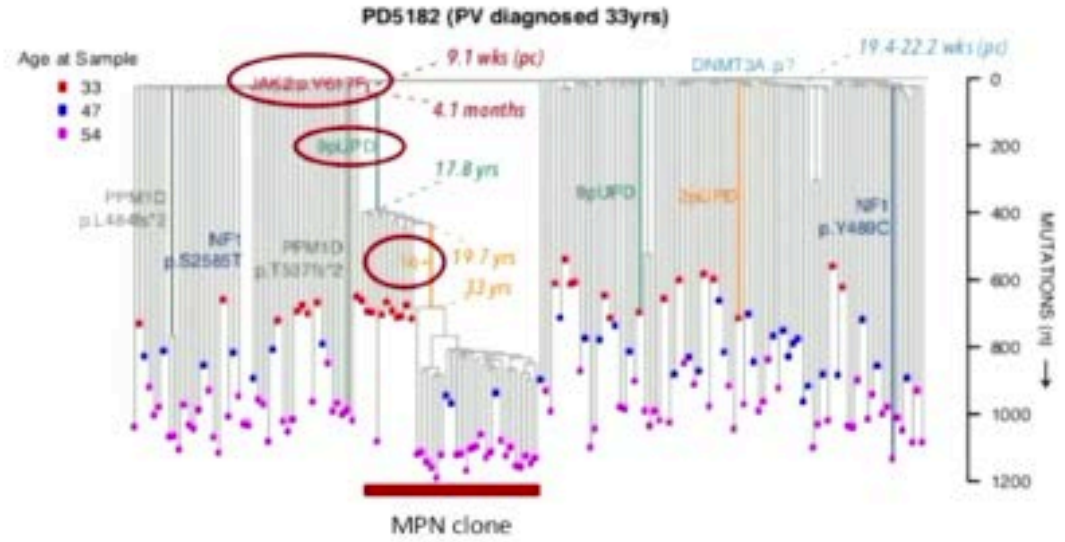
Data as of 02 November 2020

American Society of Hematology

Wang ES et al. ASH 2020;Abstract 115.

Abstract LBA-1

JAK2 and *DNMT3A* mutations can be acquired *in utero*



- Rich driver mutation landscape
- *JAK2* and *DNMT3A* mutations acquired very early in life – including *in utero*
- Additional driver mutation acquisitions separated by decades

62nd ASH® Annual Meeting and Exposition

Williams N et al. ASH 2020;Abstract LBA-1.

RTP RESEARCH TO PRACTICE

Meet The Professor

Management of Chronic Lymphocytic Leukemia

Thursday, March 11, 2021
5:00 PM – 6:00 PM ET

Faculty

Steven Coutre, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Thank you for joining us!

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