What I Tell My Patients:
New Treatments and Clinical Trial Options

An NCPD Hybrid Symposium Series
Held During the 47th Annual ONS Congress

Acute Myeloid Leukemia and Myelodysplastic Syndromes

Friday, April 29, 2022
8:20 PM – 9:20 PM PT

Faculty

Ilene Galinsky, NP
Eunice S Wang, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Faculty

Ilene Galinsky, NP
Senior Adult Leukemia Program Research Nurse Practitioner
Dana-Farber Cancer Institute
Boston, Massachusetts

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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Ms Galinsky — Disclosures

Advisory Committee	AbbVie Inc, Bristol-Myers Squibb Company, Jazz Pharmaceuticals Inc, Novartis, Pfizer Inc
Consulting Agreements	AbbVie Inc, Bristol-Myers Squibb Company, Pfizer Inc

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Dr Wang — Disclosures

Advisory Committee	AbbVie Inc, Amgen Inc, Astellas, Bristol-Myers Squibb Company, Genentech, a member of the Roche Group, Gilead Sciences Inc, GlaxoSmithKline, Jazz Pharmaceuticals Inc, Kite, A Gilead Company, Kura Oncology, Novartis, PharmaEssentia, Stemline Therapeutics Inc
Consulting Agreements	Mana Therapeutics, Rafael Pharmaceuticals Inc
Data and Safety Monitoring Board/Committee	AbbVie Inc, Rafael Pharmaceuticals Inc
Speakers Bureau	Astellas, DAVA Oncology, Kura Oncology, Stemline Therapeutics Inc

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Commercial Support

This activity is supported by educational grants from AbbVie Inc and Genentech, a member of the Roche Group.

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Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.

Answer Survey Questions: Complete the premeeting survey before the meeting. Survey results will be presented and discussed throughout the meeting.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

Complete Your Evaluation: Tap the CME Evaluation button to complete your evaluation electronically to receive credit for your participation.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

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Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.

Answer Survey Questions: Complete the premeeting survey before the meeting. Survey results will be presented and discussed throughout the meeting.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get CME Credit: A CME credit link will be provided in the chat room at the conclusion of the program.

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

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"What I Tell My Patients"
14th Annual RTP-ONS NCPD Symposium Series
ONS Congress, Anaheim, California — April 27 - May 1, 2022

Thursday April 28	**Prostate Cancer** 6:00 AM – 7:30 AM PT (9:00 AM – 10:30 AM ET)
	Ovarian Cancer 12:15 PM – 1:45 PM PT (3:15 PM – 4:45 PM ET)
	Non–Small Cell Lung Cancer 6:00 PM – 8:00 PM PT (9:00 PM – 11:00 PM ET)
	Hepatobiliary Cancers 8:20 PM – 9:20 PM PT (11:20 PM – 12:20 AM ET)
Friday April 29	**Small Cell Lung Cancer** 6:00 AM – 7:30 AM PT (9:00 AM – 10:30 AM ET)
	Chronic Lymphocytic Leukemia 12:15 PM – 1:45 PM PT (3:15 PM – 4:45 PM ET)
	Breast Cancer 6:00 PM – 8:00 PM PT (9:00 PM – 11:00 PM ET)
	Acute Myeloid Leukemia and Myelodysplastic Syndromes 8:20 PM – 9:20 PM PT (11:20 PM – 12:20 AM ET)
Saturday April 30	**Cervical and Endometrial Cancer** 6:00 AM – 7:30 AM PT (9:00 AM – 10:30 AM ET)
	Bladder Cancer 12:15 PM – 1:45 PM PT (3:15 PM – 4:45 PM ET)

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Prostate Cancer

Thursday, April 28, 2022

6:00 AM – 7:30 AM PT (9:00 AM – 10:30 AM ET)

Faculty

Kathy D Burns, RN, MSN, AGACNP-BC, OCN
Robert Dreicer, MD, MS
Sandy Srinivas, MD
Ronald Stein, JD, MSN, NP-C, AOCNP

Non-Small Cell Lung Cancer

Thursday, April 28, 2022

6:00 PM – 8:00 PM PT (9:00 PM – 11:00 PM ET)

Faculty

Edward B Garon, MD, MS
Kelly EH Goodwin, MSN, RN, ANP-BC
Tara Plues, APRN, MSN
Anne S Tsao, MD, MBA

Ovarian Cancer

Thursday, April 28, 2022

12:15 PM – 1:45 PM PT (3:15 PM – 4:45 PM ET)

Faculty

Jennifer Filipi, MSN, NP
Kathleen N Moore, MD, MS
Krishnansu S Tewari, MD
Deborah Wright, MSN, APRN, AGCNS-BC

Hepatobiliary Cancers

Thursday, April 28, 2022

8:20 PM – 9:20 PM PT (11:20 PM – 12:20 AM ET)

Faculty

Richard S Finn, MD
Amanda K Wagner, APRN-CNP, AOCNP

What I Tell My Patients: Expert Insights into Patient Education on New Treatments and Clinical Trial Participation

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Small Cell Lung Cancer

Friday, April 29, 2022

6:00 AM – 7:30 AM PT (9:00 AM – 10:30 AM ET)

Faculty

Marianne J Davies, DNP, MSN, RN, APRN
Matthew Gubens, MD, MS
Lowell L Hart, MD
Chaely J Medley, MSN, AGNP

Breast Cancer

Friday, April 29, 2022

6:00 PM – 8:00 PM PT (9:00 PM – 11:00 PM ET)

Faculty

Jamie Carroll, APRN, MSN, CNP
Sara A Hurvitz, MD
Kelly Leonard, MSN, FNP-BC
Hope S Rugo, MD

Chronic Lymphocytic Leukemia

Friday, April 29, 2022

12:15 PM – 1:45 PM PT (3:15 PM – 4:45 PM ET)

Faculty

Lesley Camille Ballance, MSN, FNP-BC
Amy Goodrich, CRNP
Lowell L Hart, MD
Anthony R Mato, MD, MSCE

Acute Myeloid Leukemia and Myelodysplastic Syndromes

Friday, April 29, 2022

8:20 PM – 9:20 PM PT (11:20 PM – 12:20 AM ET)

Faculty

Ilene Galinsky, NP
Eunice S Wang, MD

What I Tell My Patients: Expert Insights into Patient Education on New Treatments and Clinical Trial Participation

An NCPD Hybrid Symposium Series Held During the 47th Annual ONS Congress

Cervical and Endometrial Cancer

Saturday, April 30, 2022
6:00 AM – 7:30 AM PT (9:00 AM – 10:30 AM ET)

Faculty
Paula J Anastasia, MN, RN, AOCN
Robert L Coleman, MD
David M O'Malley, MD
Jaclyn Shaver, MS, APRN, CNP, WHNP

Bladder Cancer

Saturday, April 30, 2022
12:15 PM – 1:45 PM PT (3:15 PM – 4:45 PM ET)

Faculty
Monica Averia, MSN, AOCNP, NP-C
Shilpa Gupta, MD
Brenda Martone, MSN, NP-BC, AOCNP
Sumanta Kumar Pal, MD

Join Us After ONS for Our Series Continuation

What I Tell My Patients —
A 2-Part NCPD Webinar Series

Hodgkin and Non-Hodgkin Lymphomas

Date and time to be announced

Gastroesophageal Cancers

Wednesday, May 18, 2022

5:00 PM – 6:00 PM ET

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How often, if at all, do you exercise?

1. Frequently or daily
2. Occasionally
3. Rarely
4. Never

Faculty

Ilene Galinsky, NP
Senior Adult Leukemia Program Research Nurse Practitioner
Dana-Farber Cancer Institute
Boston, Massachusetts

Eunice S Wang, MD
Chief, Leukemia Service
Professor of Oncology
Roswell Park Comprehensive Cancer Center
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Miami, Florida

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RTP RESEARCH TO PRACTICE

Agenda

Module 1 – Younger Patients with Acute Myeloid Leukemia (AML)

Module 2 – Older Patients with AML

Module 3 – Myelodysplastic Syndromes

Agenda

Module 1 – Younger Patients with Acute Myeloid Leukemia (AML)

Module 2 – Older Patients with AML

Module 3 – Myelodysplastic Syndromes

SELF-ASSESSMENT QUIZ

A 65-year-old man with relapsed/refractory AML and an IDH2 mutation is started on enasidenib and after 8 weeks is responding well to treatment but now has fever, shortness of breath and rapid weight gain. Which therapy will likely be used?

1. Infliximab
2. Corticosteroids
3. Diuretics
4. I don't know

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SELF-ASSESSMENT QUIZ

CPX-351 (liposomal cytarabine-daunorubicin) is approved for…

1. AML with a FLT3 mutation
2. Secondary AML
3. CD33-positive AML
4. I don’t know

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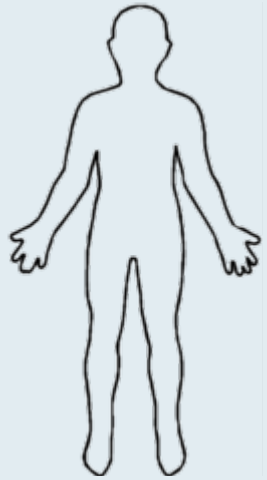
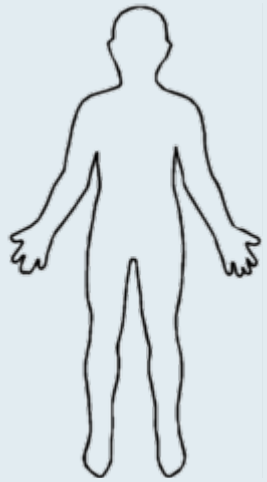
Management of AML in 2022



"Fit," younger patients



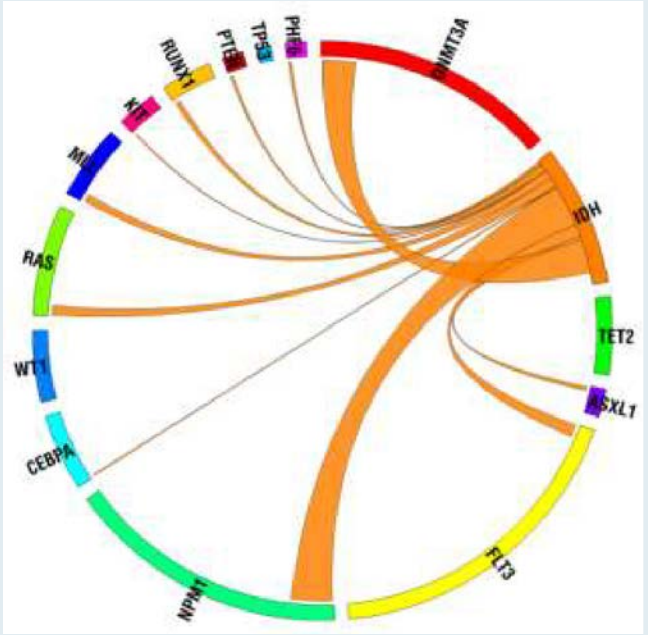
"Frail," older patients

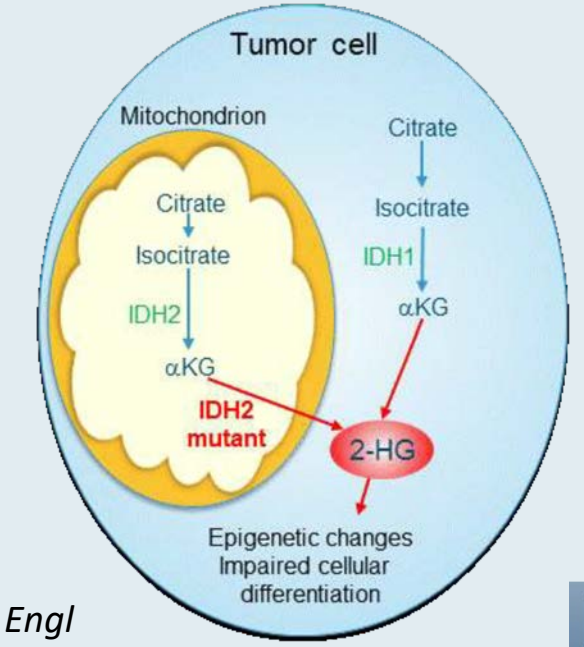
	Initial Treatment	Relapsed/Refractory
FLT3	7+3+midostaurin	FLT3i ± Reinduction
Fav Cyto	7+3+GO	Reinduction
Int Cyto	7+3 → HCT	HMA+IDHi
sAML	CPX-351 → HCT	
TP53	DAC 10d → ?HCT	HMA+Ven
TP53	HMA+Ven	GO monotherapy
FLT3	HMA + FLT3i	FLT3i
"Other"	HMA+Ven	Low Intensity/Palliative
IDH1/2	GO monotherapy	Enasidenib/Ivosidenib
	Enasidenib/Ivosidenib	HMA monotherapy
	HMA monotherapy	

Courtesy of Andrew M Brunner, MD

IDH in Leukemia

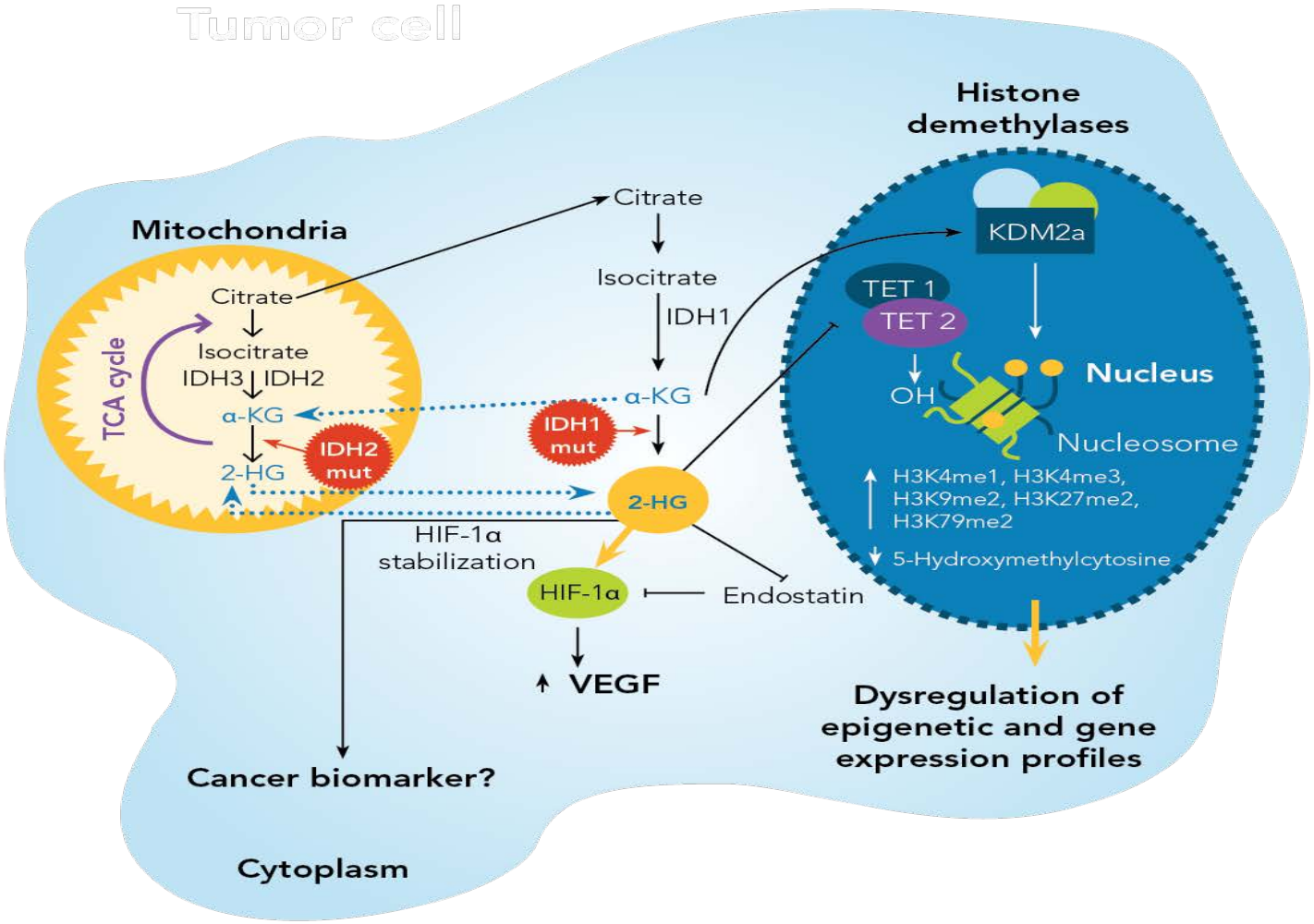
- **IDH mutations occur in ~20% of AML**
  - **Frequency: 6%-16% IDH1 and 8%-18% IDH2**
  - **Majority (85%) with diploid or +8 cytogenetics**
  - **↑ prevalence with ↑ patient age**
  - **Prognostic effect in AML remains controversial**
  - **IDH1 and IDH2 mutations may have different effects on prognosis**





Dang L et al. *Trends Mol Med* 2010;16(9):387-97. Chou WC et al. *Leukemia* 2011;25(2):246-53. Patel JP et al. *N Engl J Med* 2012;366(2):1079-89. Medeiros BC et al. *Leukemia* 2017;31:272-81.

IDH in AML



- IDH1 in cytoplasm and IDH2 in mitochondria
- Cancer-associated IDHm produces 2-hydroxyglutarate (R-2-HG)
- IDH1/IDH2 mutations induce BCL-2 dependence (Majeti, Nature Medicine, 2015)
- R-2HG suppresses homologous recombination (Bindra, Science Translational Medicine, 2017)

Prensner and Chinnaiyan Nature, 2011

IDH2m and IDH1m: Distinct Genetically Defined Populations

IDH Mutations Seen in Multiple Cancer Types		
Target	Indication	IDHm (%)
IDH2m	AML	15%
	MDS/MPN	5%
	Angio-immunoblastic NHL	25%
	Others (melanoma, glioma, chondro)[2]	3-5%
	Type II D-2HG Aciduria (inborn error of metabolism)	100%
IDH1m	Low-grade glioma & 2^{ary} GBM[1]	70%
	Chondrosarcoma	>50%
	AML	7.5%
	MDS/MPN	5%
	Intrahepatic cholangiocarcinoma	20%
	Others (colon, melanoma, lung)[2]	1-2%

[1]Includes 8.5% of Primary GBM
[2]Includes "basket" of emerging unconfirmed indications

Approved IDH Inhibitors for AML

- **Enasidenib – IDH2 inhibitor. Approved for relapsed and refractory IDH2 mutant AML.**
  - **Oral, given once daily, continuous 28 day cycles**
  - **Indirect hyperbilirubinemia**

- **Ivosidenib – IDH1 inhibitor. Approved for relapsed and refractory and newly diagnosed IDH1 mutant AML.**
  - **Oral, once daily, continuous 28 day cycles**
  - **QT prolongation**

- **In R/R AML, complete remission rates with IDH inhibitors are about 21%**

Courtesy of Eytan M Stein, MD

The NEW ENGLAND JOURNAL of MEDICINE

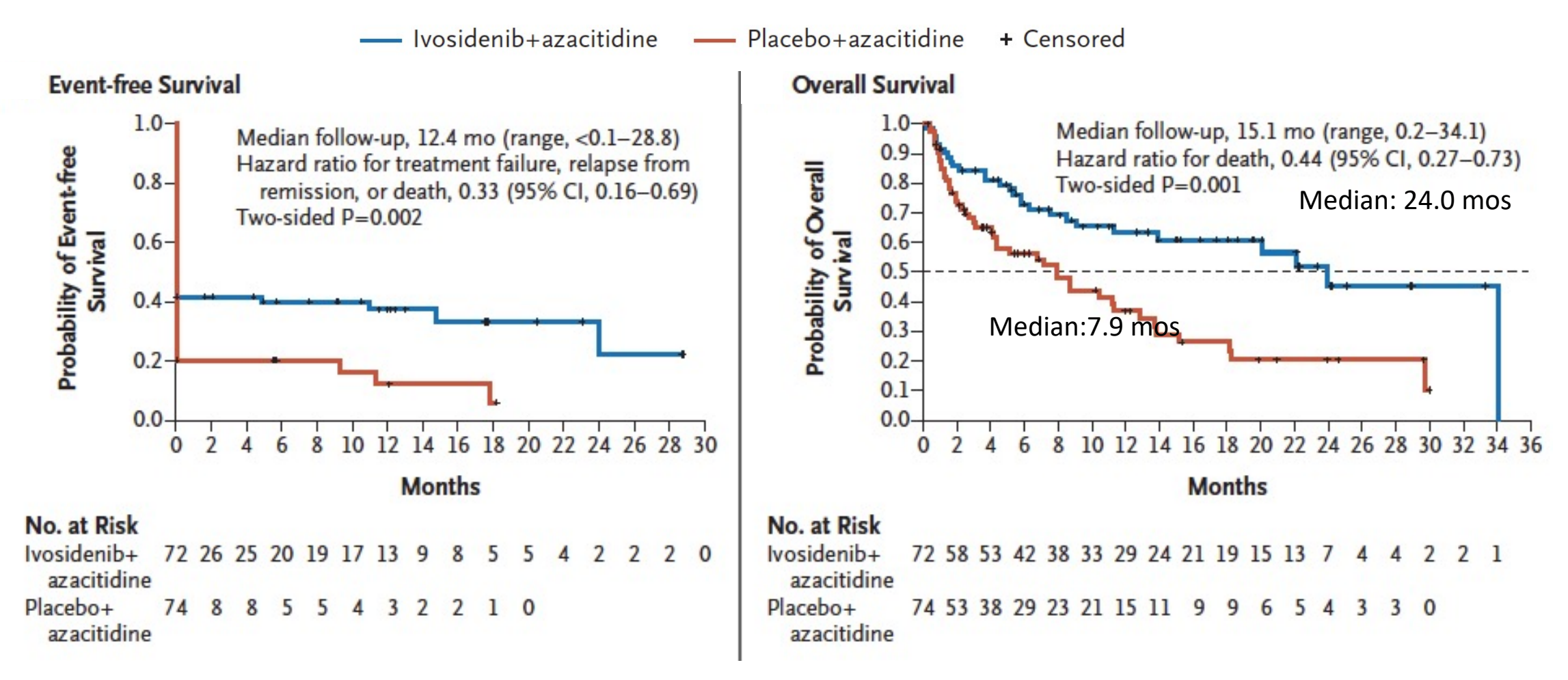
ORIGINAL ARTICLE

Ivosidenib and Azacitidine in *IDH1*-Mutated Acute Myeloid Leukemia

Pau Montesinos, M.D., Ph.D., Christian Recher, M.D., Ph.D., Susana Vives, M.D., Ewa Zarzycka, M.D., Jianxiang Wang, M.D., Giambattista Bertani, M.D., Michael Heuser, M.D., Rodrigo T. Calado, M.D., Ph.D., Andre C. Schuh, M.D., Su-Peng Yeh, M.D., Scott R. Daigle, M.S., Jianan Hui, Ph.D., Shuchi S. Pandya, M.D., Diego A. Gianolio, Ph.D., Stephane de Botton, M.D., Ph.D., and Hartmut Döhner, M.D.

N Engl J Med 2022;386(16):1519-31.

AGILE: Event-Free and Overall Survival



Montesinos P et al. *N Engl J Med* 2022;386(16):1519-31.

Differentiation Syndrome

Frequency of Signs and Symptoms Consistent With IDH-DS[a]

Sign or Symptom	Patients With IDH-DS, No. (%) (n = 33)[b]
Dyspnea	28 (85)
Unexplained fever (body temperature of 38.0°C for 2 d)	26 (79)
Pulmonary infiltrates	24 (73)
Hypoxia	19 (58)
Acute kidney injury (CTCAE grade ≥2)	14 (42)
Pleural effusion	14 (42)
Bone pain or arthralgia	9 (27)
Lymphadenopathy	8 (24)
Rash	8 (24)
Disseminated intravascular coagulopathy	7 (21)
Edema or weight gain of >5 kg from screening	7 (21)
Pericardial effusion	5 (15)

[a] Signs and symptoms are based on retrospective differentiation syndrome review committee review of clinical records.

[b] Patients may have had multiple symptoms.

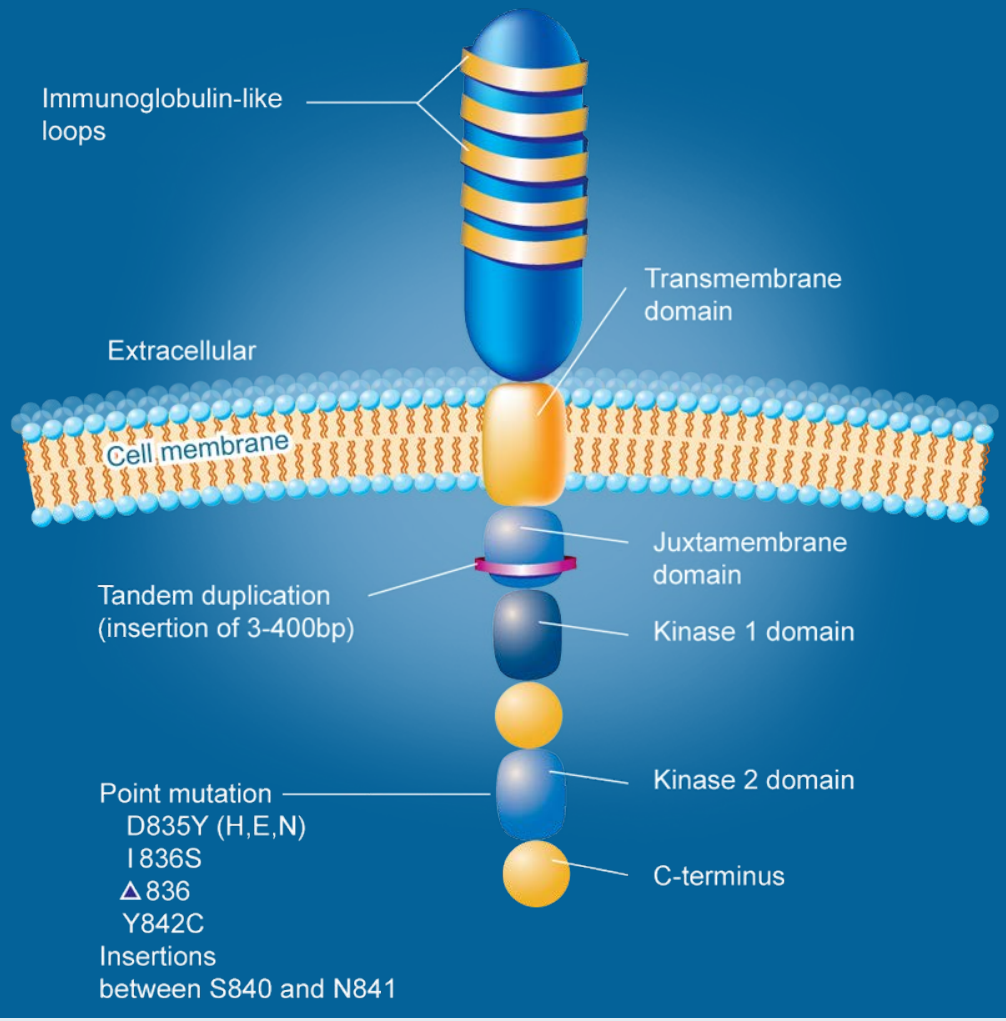
Fathi A et al, JAMA Oncology 2018

FLT3 Mutations in AML

Approximately 30% of patients with AML have a FLT3 mutation

FLT3-ITD: 25% of patients with AML

FLT3-TKD: 5% of patients with AML



- **FLT3 ligand (FL) binding activates downstream pathways (↑ cell proliferation)**
- **FLT3 mutations associated with a poor prognosis**

Litzow MR. *Blood* 2005;106:3331-2; Small D. *Hematology Am Soc Hematol Educ Program* 2006:178-84; Swords R et al. *Leukemia* 2012;26(10):2176-85; Griffith J et al. *Mol Cell* 2004;13(2):169-78; Levis M. *Hematology Am Soc Hematol Educ Program* 2013;2013:220-6.

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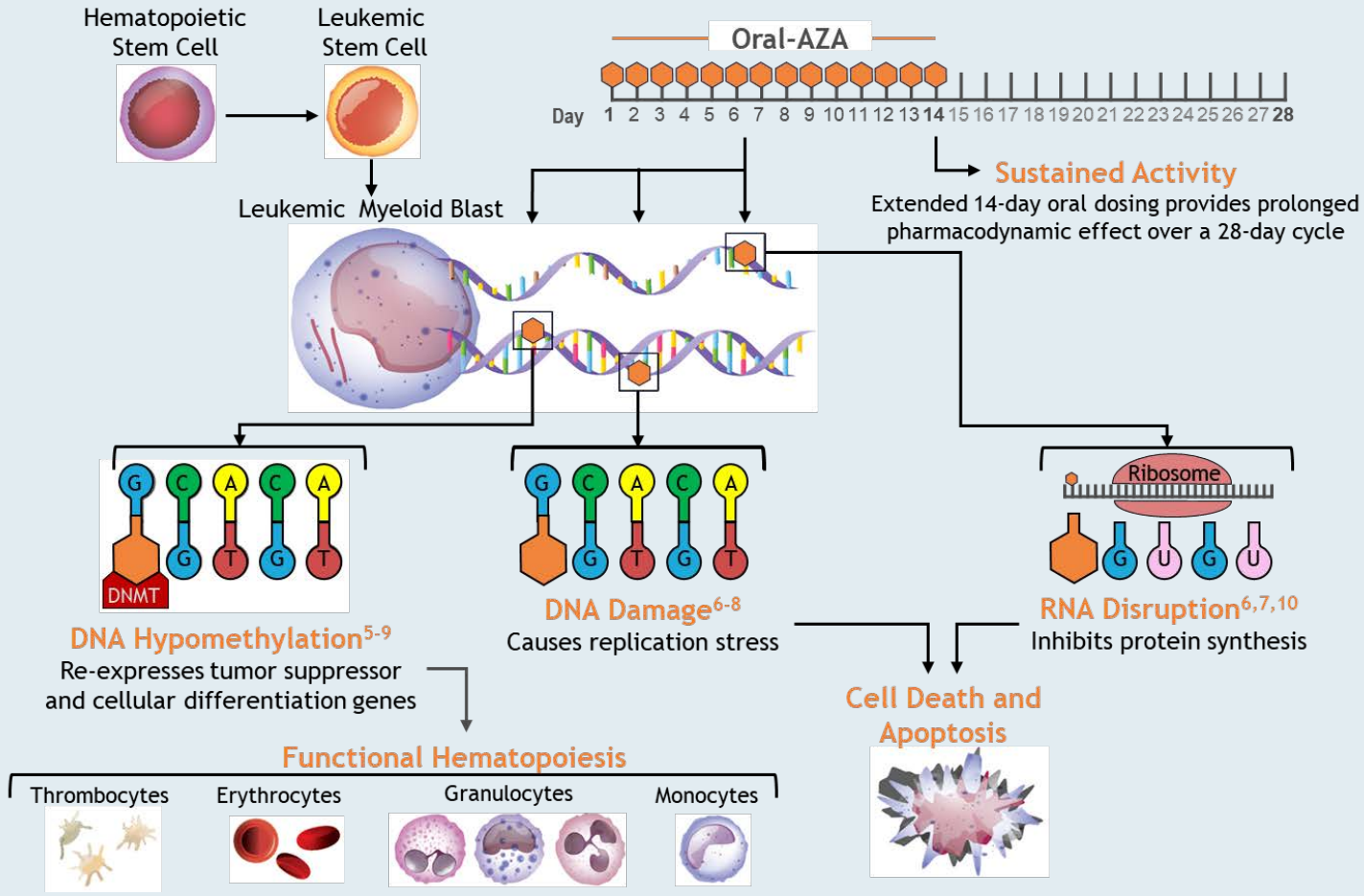
Characteristics of Select FLT3 Inhibitors

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

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

Oral Azacitidine (Oral-AZA, CC-486)

- **Oral HMA with a distinct PK/PD profile from injectable AZA; the two are not bioequivalent[1,2]**
- **Approved in the United States 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]**



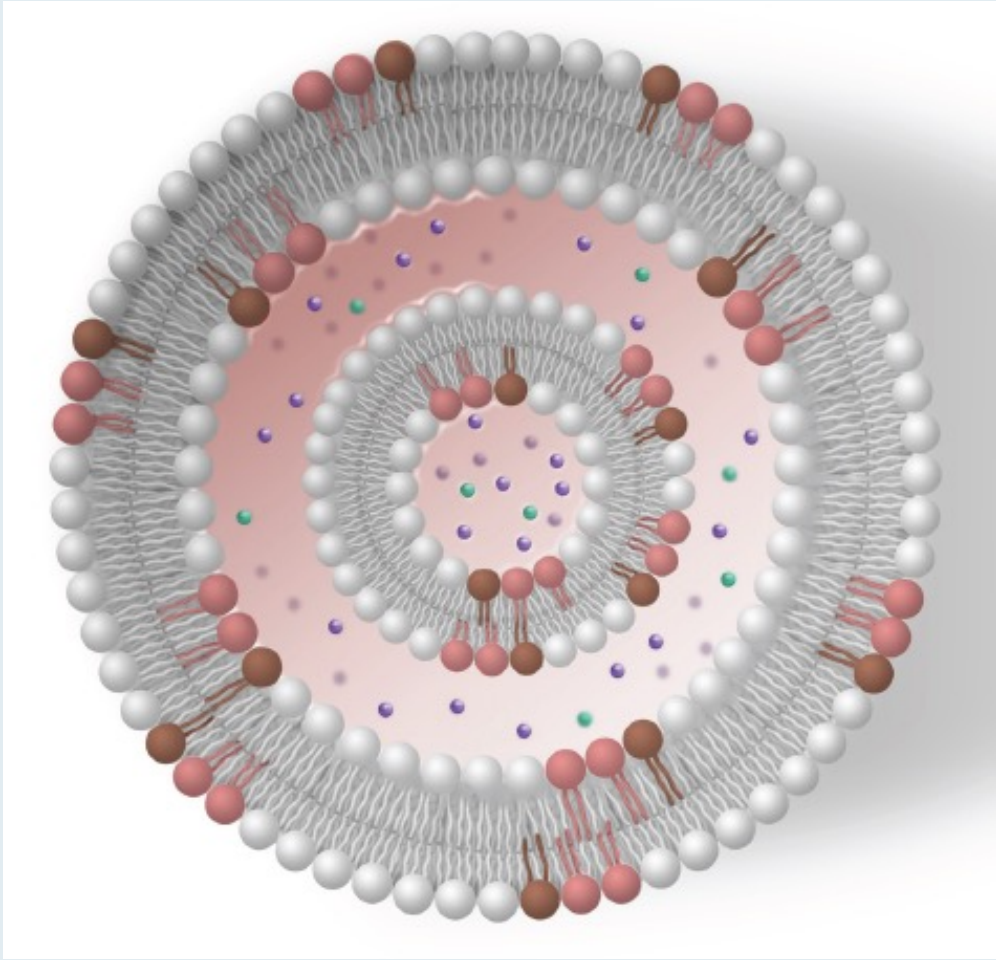
1. Garcia-Manero et al. *J Clin Oncol*. 2011;29(18):2521–7. 2. Laille et al. *PLoS One*. 2015;10(8):e0135520. 3. ONUREG® (azacitidine) tablets [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; Rev. 9/2020. 4. Savona et al. *Am J Hematol*. 2018;93(10):1199–206. 5. Stresemann et al. *Mol Cancer 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.

Courtesy of Richard M Stone, MD

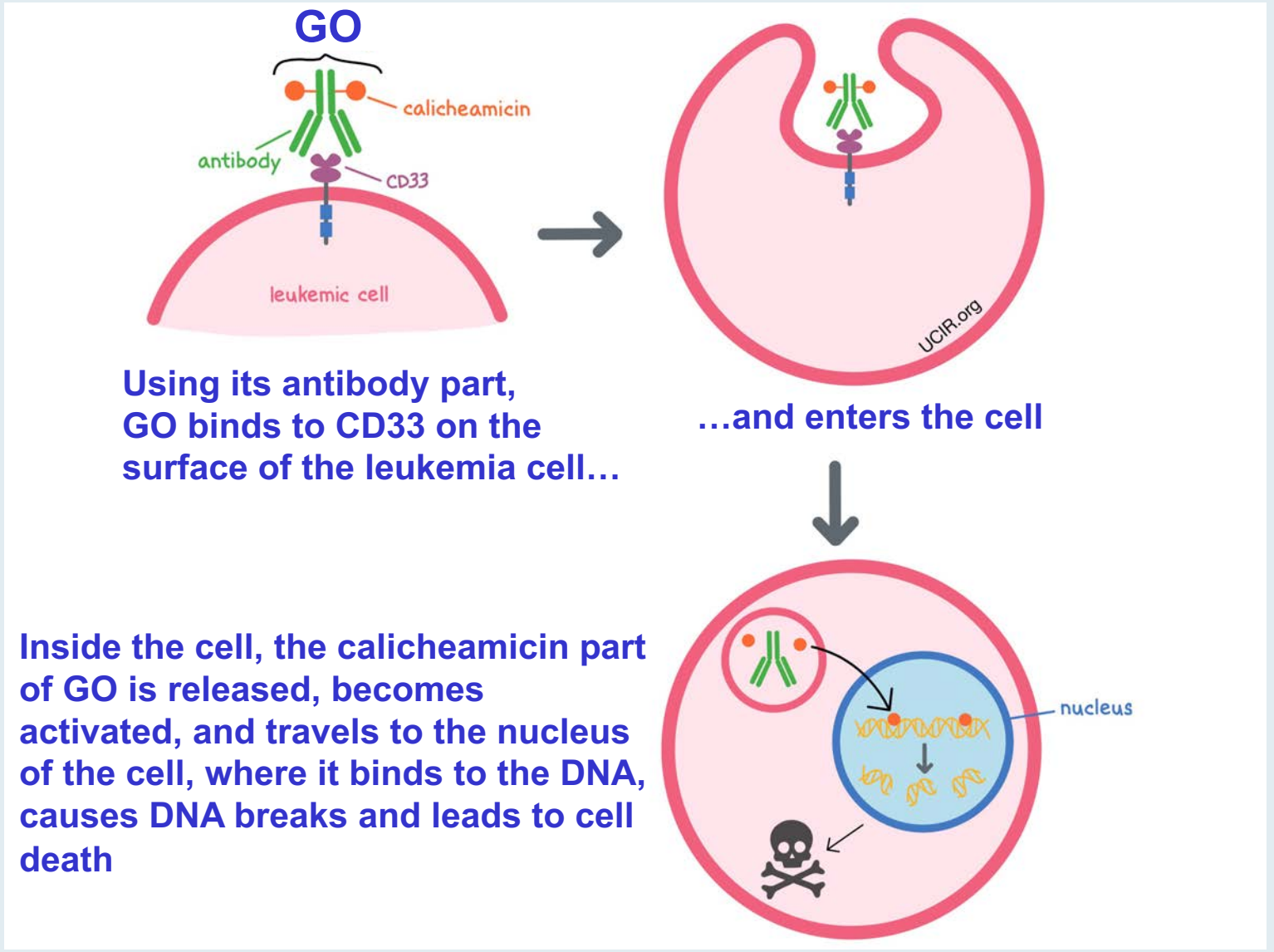
CPX-351

- CPX-351 is a liposomal co-formulation of cytarabine and daunorubicin designed to achieve synergistic antileukemia activity
  - 5:1 molar ratio of cytarabine to daunorubicin provides synergistic leukemia cell killing in vitro[1]
  - In patients, CPX-351 preserved delivery of the 5:1 drug ratio for over 24 hours, with drug exposure maintained for 7 days[2]
  - Selective uptake of liposomes by bone marrow leukemia cells in xenograft models[3]



1. Tardi P et al. *Leuk Res* 2009;33(1):129-39. 2. Feldman EJ et al. *J Clin Oncol* 2011;29(8):979-85;
3. Lim WS et al. *Leuk Res* 2010;34(9):1214-23.

Gemtuzumab Ozogamicin (GO): Mechanism of Action



www.ucir.org/immunotherapy-drugs/gemtuzumab-ozogamicin

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Questions — Eunice S Wang, MD

Younger, fit patients with AML who are eligible for intensive chemotherapy

- **What are the available treatments for these patients, and how do you select which one to use as initial therapy?**

Commentary — Eunice S Wang, MD

Younger, fit patients with AML who are eligible for intensive chemotherapy

Scenario:
Younger fit patients with AML who are eligible for Intensive Chemotherapy

Treatment Options

- **7+3**
- **7+3 plus GO**
- **7+3 plus FLT3 inhibitor**
- **CPX-351**
- **High intensity regimens (CLAG-M, FLAG-Ida)**

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Commentary — Eunice S Wang, MD

Younger, fit patients with AML who are eligible for intensive chemotherapy

7+3 plus GO

- **Case presentation**
  - **41 yo man PMH HTN and chronic kidney disease (solitary kidney s/p donation to father), presented with painless lump in left inguinal regions. Referred for surgical evaluation for possible hernia. Preop labs demonstrated normal WBC with 10% blasts. Underwent surgical excision of a left inguinal mass.**
  - **Pathology showed myeloid sarcoma.**
  - **WBC 5.60, hgb 12.7, plts 137K, 38% peripheral blasts, ANC 0.90.**
  - **Bone marrow: AML with t(8;21) (q22;q22.1).**
  - **Flow cytometry: 92.8% of blasts expressed CD33.**
  - **Mutational profile: RUNX1-RUNX1T1 fusion, IDH2+ KRAS+ ASXL1+ FLT3 wildtype CKIT wildtype.**

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Commentary — Eunice S Wang, MD

7+3 plus FLT3 inhibitor

- **Case presentation**
  - **34 yo wm h/o substance abuse in remission on methadone maintenance x 14y, h/o back injuries with multiple disc disease. Presented to local ER with shortness of breath and worsening fatigue over several days.**
  - **Labs: WBC 140k and hgb 6. Started on IVF and transferred to local cancer center.**
  - **Repeat WBC 114.9, hgb 5.7, plts 26K, 61% peripheral blasts.**
  - **Bone marrow: AML with Auer rods.**
  - **Mutational profile: FLT3 ITD+, WT1+.**
  - **Karyotype: Normal XY.**

Commentary — Eunice S Wang, MD

CPX-351

- **Case presentation**
  - **59 year-old man with Hx a-fib, MM s/p multiple chemotherapies (RVD) and autologous stem cell transplant 3 yrs ago who was found incidentally on routine bloodwork by PCP to have new pancytopenia with 2% blasts.**
  - **Repeat CBC showed WBC 1.6, hgb 9.7, plts 23K, ANC 0.75, 10% unclassified cells.**
  - **BMBX demonstrated hypercellular marrow with severely dysplastic myeloid cells, significant reticulin fibrosis and 24% blasts with no evidence of plasma cell disorder.**
  - **Cytogenetics: complex karyotype with numerous structural and numerical rearrangements.**
  - **Mutational profile: TP53 mutant, DNMT3A mutant.**

Questions — Ilene Galinsky, NP

Younger, fit patients with AML who are eligible for intensive chemotherapy

- **What are some of the clinical issues that arise with younger, fit patients with AML who are beginning treatment, and what are some key points you address with them prior to starting treatment?**
- **What are some of the psychosocial issues that arise in these situations?**

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Commentary — Ilene Galinsky, NP

Younger, fit patients with AML who are eligible for intensive chemotherapy

- **Side effects of the therapy — prolonged hospitalizations, hair loss, "loss of control," myelosuppression**
- **Change in personal relationships (sexual, missing out on things due to restrictions)**
- **Discuss sperm banking and egg harvesting, fertility issues**
- **Tailor discussions to the patient, their age, support network, where they are in the life cycle**
- **Funny story about sperm banking with a 17 year old — parents present**

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Agenda

Module 1 – Younger Patients with Acute Myeloid Leukemia (AML)

Module 2 – Older Patients with AML

Module 3 – Myelodysplastic Syndromes

SELF-ASSESSMENT QUIZ

The short-term response to treatment and survival for patients in their 80s with AML is similar to that observed for patients with pancreatic cancer.

1. Agree
2. Disagree
3. I don’t know

RTP RESEARCH TO PRACTICE

SELF-ASSESSMENT QUIZ

Which of the following agents is FDA approved in combination with venetoclax for AML?

1. Decitabine
2. Azacitidine
3. Low-dose cytarabine
4. All of the above
5. Both decitabine and azacitidine
6. I don’t know

SELF-ASSESSMENT QUIZ

All patients with AML who are receiving venetoclax in combination with a hypomethylating agent (HMA) should be admitted to the hospital to begin treatment and receive tumor lysis syndrome prophylaxis, regardless of disease burden or performance status.

1. Agree
2. Disagree
3. I don’t know

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SELF-ASSESSMENT QUIZ

Patients with AML receiving venetoclax/HMA generally undergo first repeat bone marrow examination after…

1. 1 cycle of treatment
2. 2 cycles of treatment
3. 3 cycles of treatment
4. 4 cycles of treatment
5. I don’t know

SELF-ASSESSMENT QUIZ

What is the most common side effect associated with venetoclax that leads to dose reduction or withholding therapy?

1. GI toxicity
2. Cytopenias
3. Renal dysfunction
4. Peripheral neuropathy

SELF-ASSESSMENT QUIZ

The usual approach to a patient with asymptomatic AML who has successfully been receiving venetoclax/HMA therapy is to…

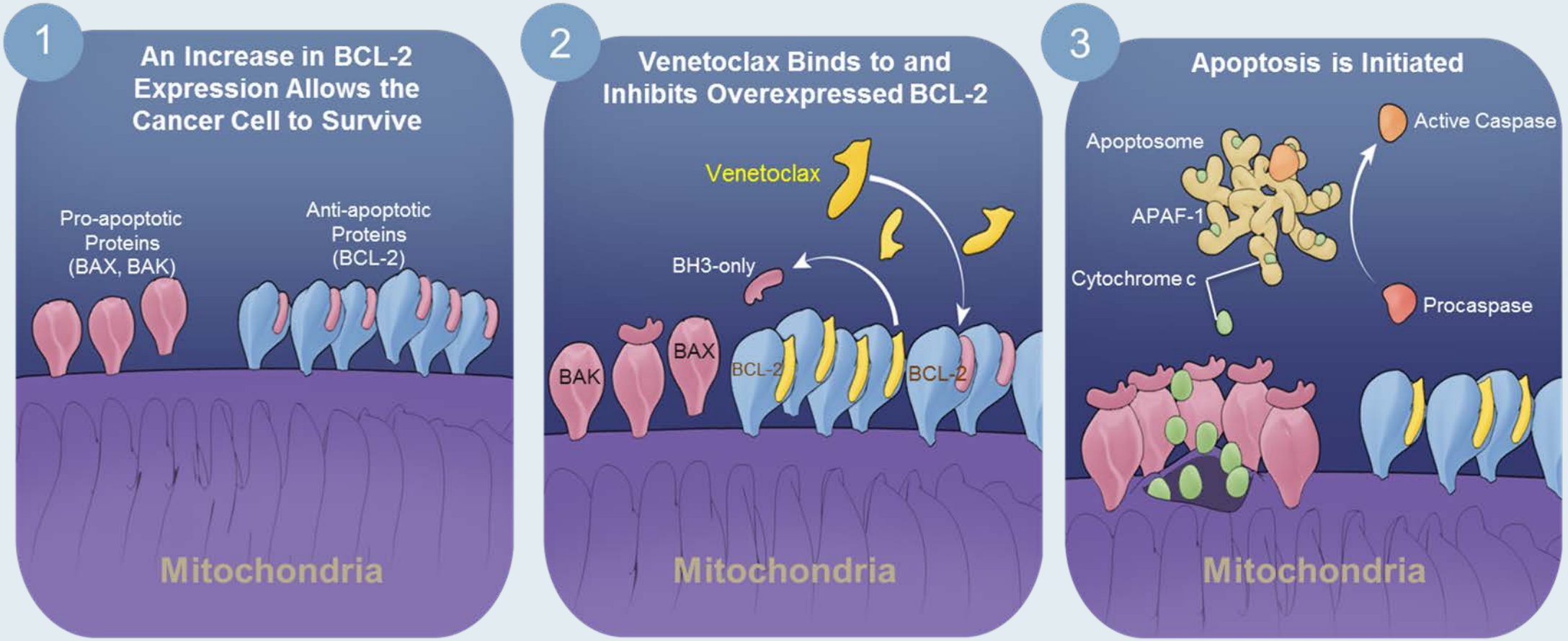
1. Discontinue treatment
2. Continue treatment
3. I don’t know

SELF-ASSESSMENT QUIZ

Is it safe and effective to use an oral HMA in combination with venetoclax?

1. Yes, oral azacitidine
2. Yes, oral decitabine
3. Yes, either oral azacitidine or oral decitabine
4. No, neither oral azacitidine nor oral decitabine
5. I don’t know

Venetoclax Mechanism of Action



- Cancer cells increase the expression of anti-apoptotic proteins to offset the increase in pro-apoptotic proteins, tipping the balance toward cell survival
- The large # of pro-apoptotic proteins bound and sequestered by Bcl-2 in AML make them “primed” for death

Kumar et al. ASCO 2015;Abstract 8576.

VIALE-A Study Design (NCT02993523)

Eligibility

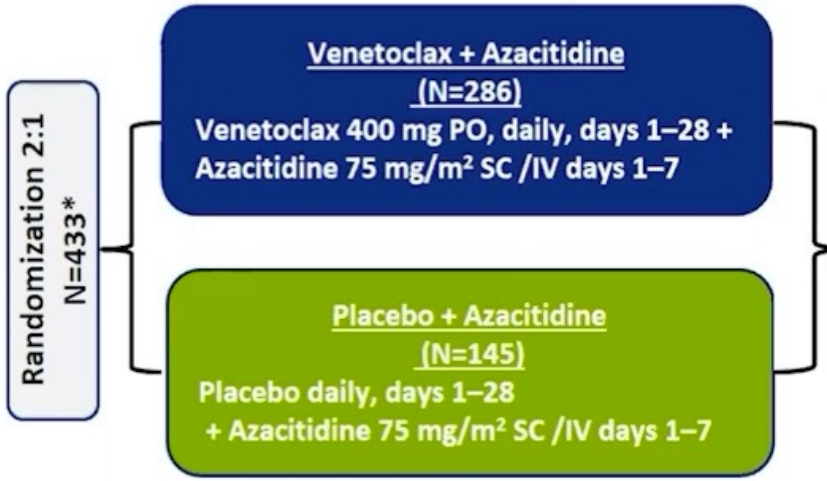
Inclusion

- Patients with newly diagnosed confirmed AML
- Ineligible for induction therapy defined as **either**
  - ≥75 years of age
  - 18 to 74 years of age with at least one of the co-morbidities:
    - CHF requiring treatment or Ejection Fraction ≤50%
    - Chronic stable angina
    - DLCO ≤ 65% or FEV1 ≤ 65%
    - ECOG 2 or 3

Exclusion

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

Treatment



Randomization Stratification Factors Age (<75 vs. ≥75 years); Cytogenetic Risk (intermediate, Poor); Region

Venetoclax dosing ramp-up **Cycle 1 ramp-up** Day 1: 100 mg, Day 2: 200 mg, Day 3 - 28: 400 mg
Cycle 2 → Day 1-28: 400 mg

Endpoints

Primary

- Overall survival

Secondary

- CR+CRi rate
- CR+CRh rate
- CR+CRi and CR+CRh rates by initiation of cycle 2
- CR rate
- Transfusion independence
- CR+CRi rates and OS in molecular subgroups
- Event-free survival

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

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

DiNardo C et al. EHA 2020;Abstract LB2601.

The NEW ENGLAND JOURNAL of MEDICINE

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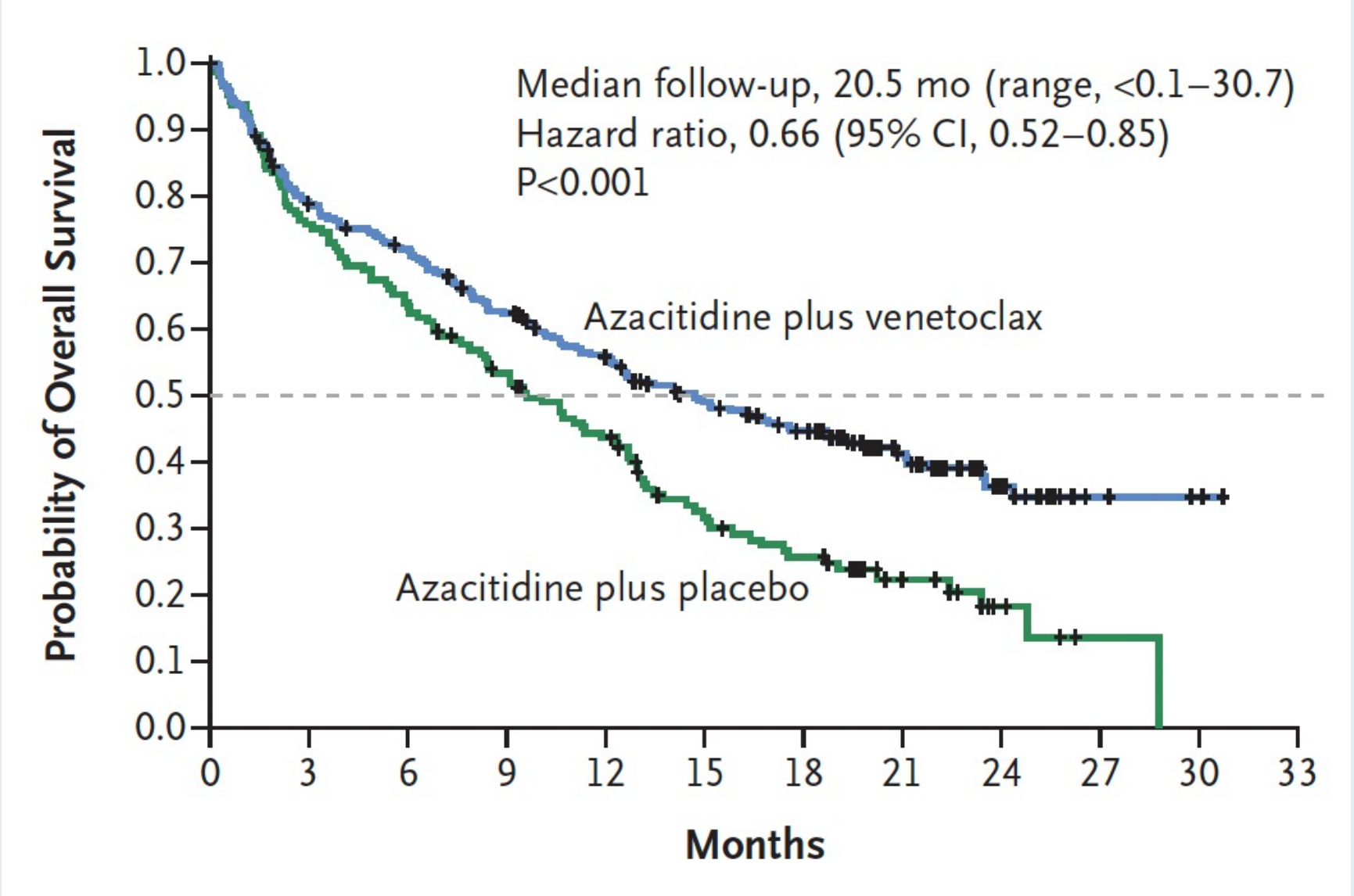
Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia

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

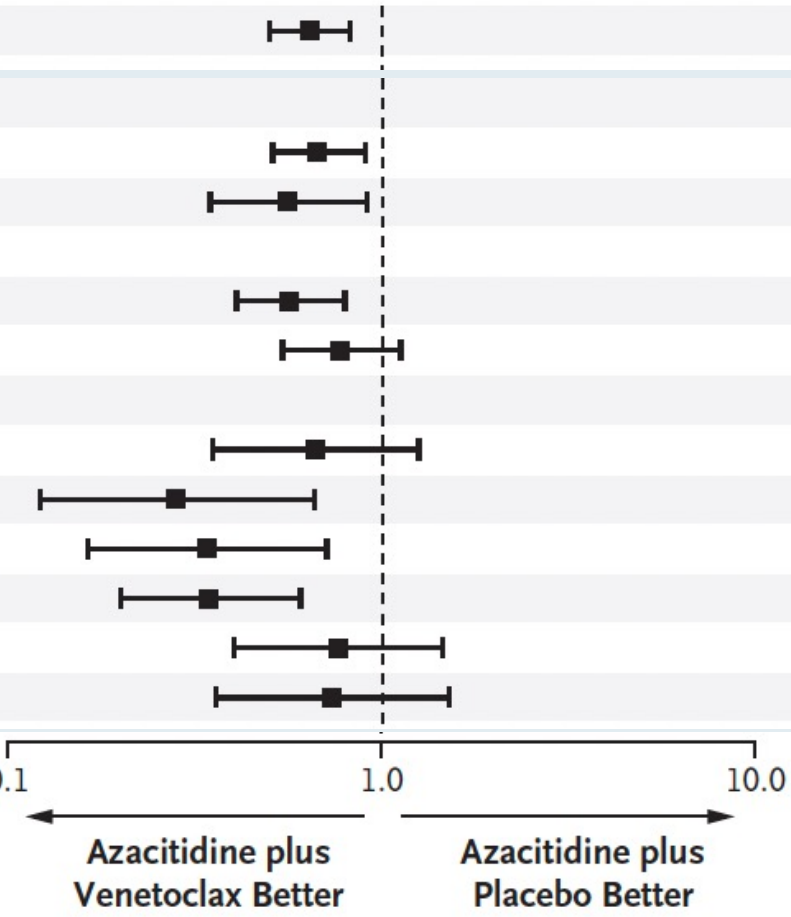
VIALE-A: Overall Survival



DiNardo CD et al. *N Engl J Med* 2020;383(7):617-29.

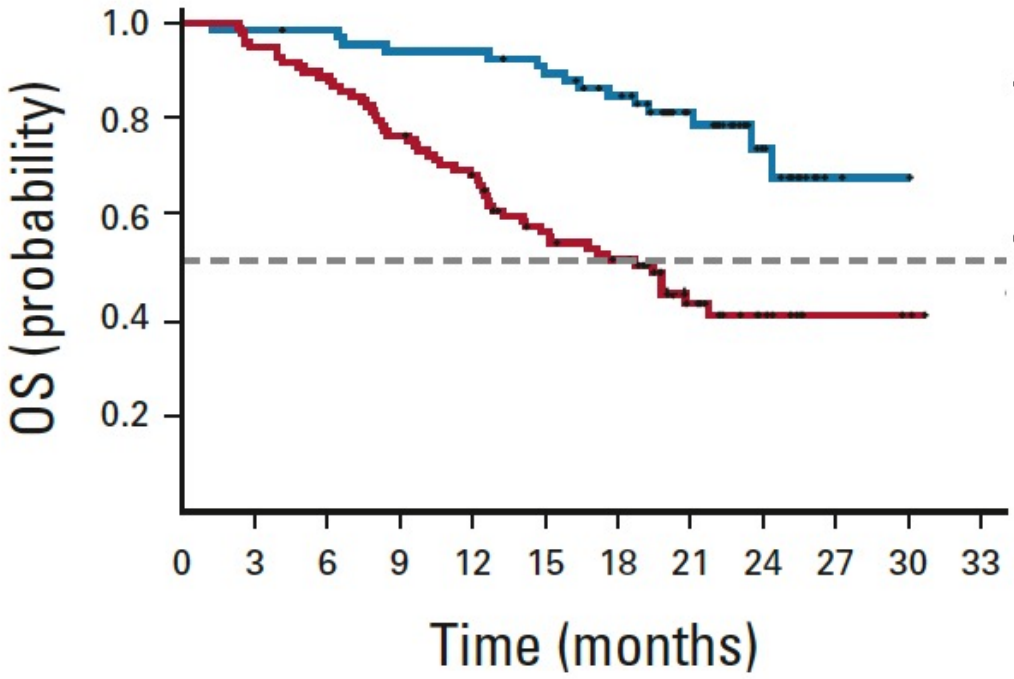
VIALE-A: Overall Survival Subgroup Analysis

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



DiNardo CD et al. *N Engl J Med* 2020;383(7):617-29.

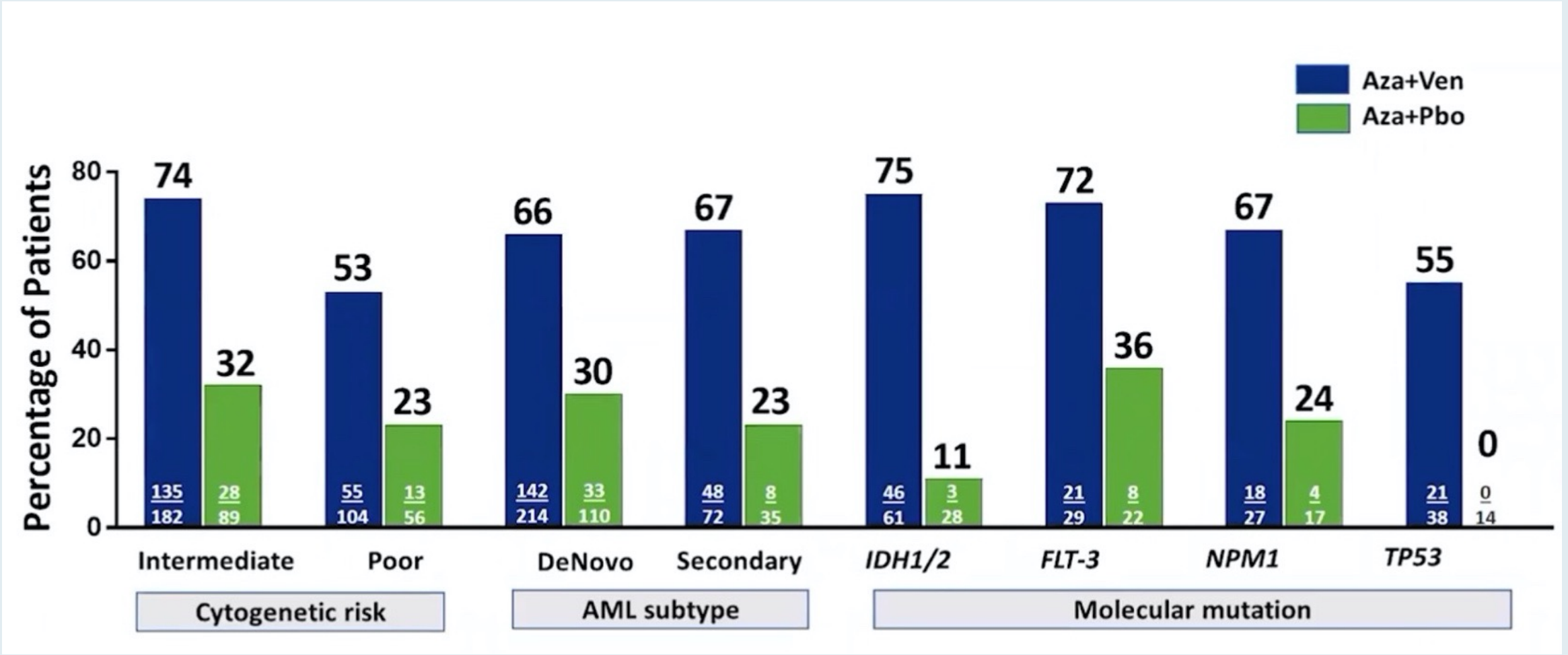
VIALE-A: Overall Survival by Minimal Residual Disease (MRD) Status



OS	No. of Events	12 Months, % (95% CI)	18 Months, % (95% CI)	Median OS, Months (95% CI)
CR + CRi + MRD < 10^{-3}	15	94.0 (84.7 to 97.7)	84.6 (73.3 to 91.4)	NR (24.4 to NR)
CR + CRi + MRD ≥ 10^{-3}	52	67.9 (57.6 to 76.2)	50.1 (39.6 to 59.8)	18.7 (12.9 to NR)

Pratz KW et al. *J Clin Oncol* 2022;40:855-65.

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



CR = complete response; CRi = CR with incomplete blood-count recovery

DiNardo C et al. EHA 2020;Abstract LB2601.

VIALE-A: Serious Adverse Events

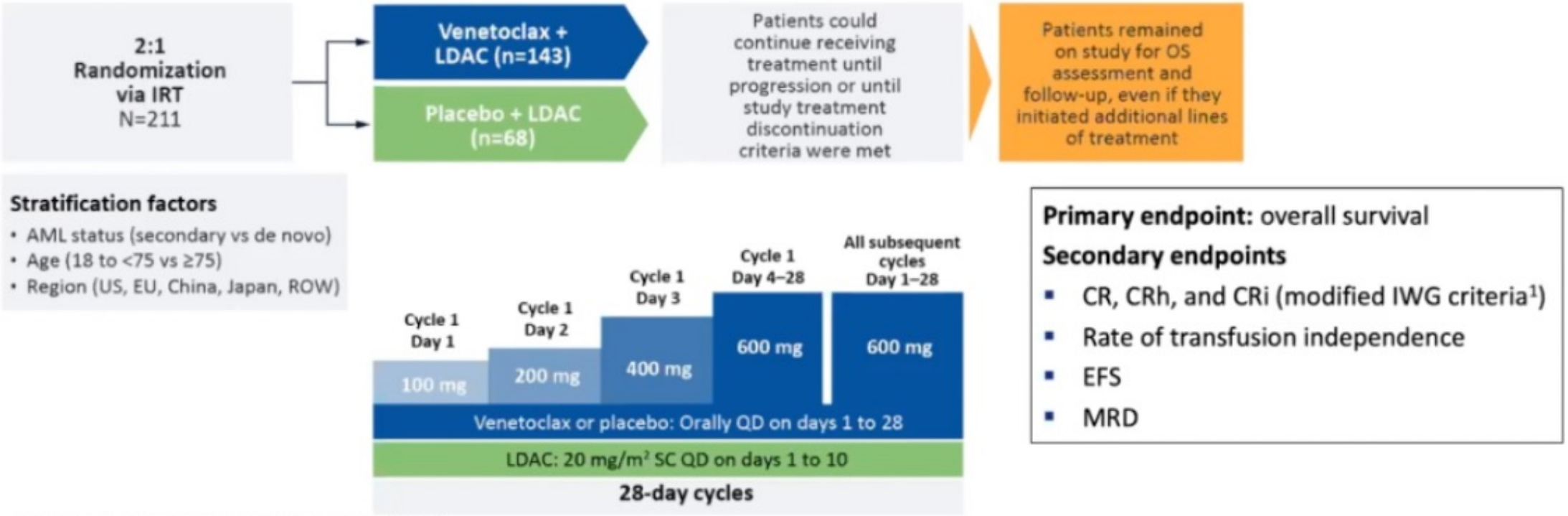
Adverse event	Azacitidine/venetoclax (N = 283)		Azacitidine/placebo (N = 144)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Serious adverse events	83%	82%	73%	71%
Febrile neutropenia	30%	30%	10%	10%
Anemia	5%	5%	4%	4%
Neutropenia	5%	5%	2%	2%
Atrial fibrillation	5%	4%	1%	1%
Pneumonia	17%	16%	22%	22%
Sepsis	6%	6%	8%	8%

Tumor lysis syndrome observed during ramp-up (days 1-3) in 3 patients (1%) receiving azacitidine/venetoclax, without interruption of treatment

DiNardo CD et al. *N Engl J Med* 2020;383(7):617-29.

VIALE-C: Phase III Trial of Venetoclax Plus Low-Dose Cytarabine in Previously Untreated Older Patients with AML

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



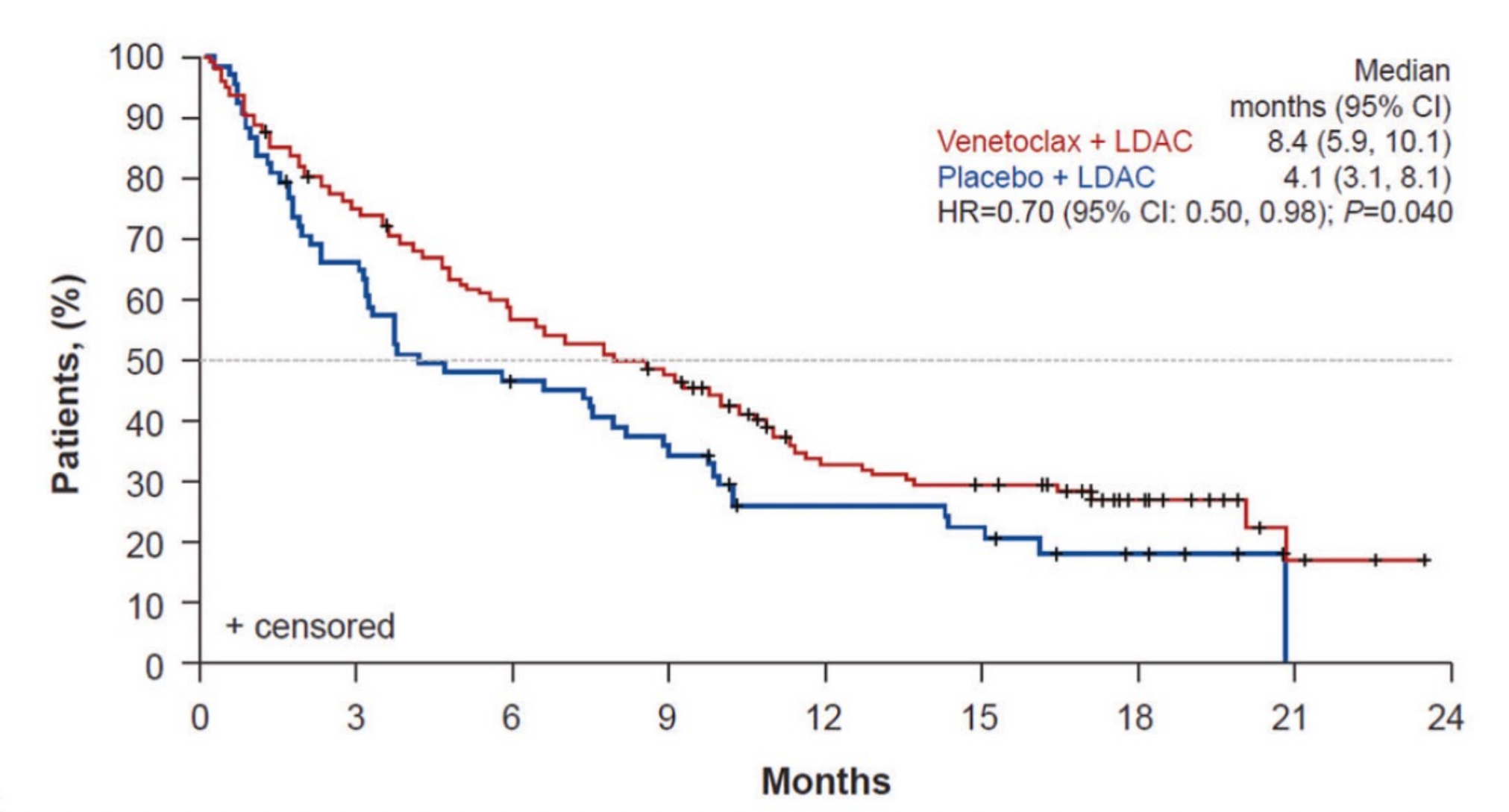
Progressive disease was defined per ELN recommendations.[2]

AML, acute myeloid leukemia; CR, complete remission; CRh, CR with partial hematologic recovery; CRi, CR with incomplete blood count recovery; EFS, event-free survival; ELN, European LeukemiaNet; IRT, Interactive Response Technology; IWG, International Working Group; LDAC, low-dose cytarabine; MRD, minimal residual disease; OS, overall survival; QD, once a day; ROW, rest of world; SC, subcutaneous.

1. Cheson BD, et al. *J Clin Oncol.* 2003;21:4642-4649; 2. Döhner H, et al. *Blood.* 2017;129:424-447.

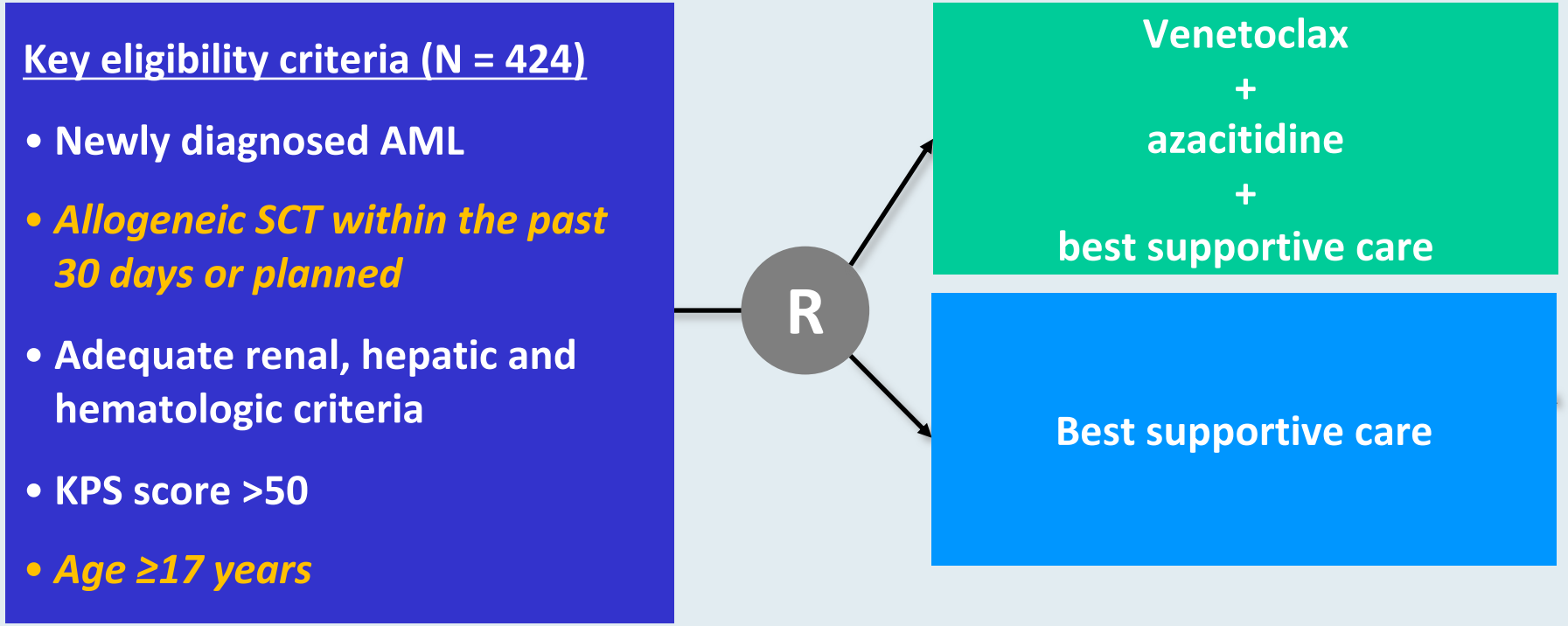
Wei AH et al. *EHA* 2020;Abstract S136.

VIALE-C: Overall Survival



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

VIALE-T: Phase III Trial of Venetoclax with Azacitidine and Best Supportive Care Compared to Best Supportive Care Alone for Newly Diagnosed AML



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

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

Questions — Eunice S Wang, MD

Older patients with AML who are not eligible for intensive chemotherapy

- **What are the available treatments for these patients, and how do you select which one to use as initial therapy?**

Commentary — Eunice S Wang, MD

Older patients with AML who are not eligible for intensive chemotherapy

Scenario:
Older patients with AML who are not eligible for Intensive Chemotherapy

Treatment Options

- **Venetoclax + Azacitidine**
- **Venetoclax + LDAC**
- **IDH1 inhibitor (ivosidenib)**
- **IDH2 inhibitor (enasidenib)**
- **Glasdegib + LDAC**
- **Gemtuzumab ozogamicin**

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Commentary — Eunice S Wang, MD

Older patients with AML who are not eligible for intensive chemotherapy

Venetoclax + Azacitidine

- **Case presentation**
  - **75 yo woman hx HTN, hyperlipidemia, DM, neuropathy, gout, adrenal insufficiency, ulcerative colitis presented with persistent upper respiratory infections, extreme fatigue, chills, gum bleeding, intermittent blurred vision.**
  - **WBC 3.61, hgb 11, plts 48K with 76% blasts.**
  - **BMBx consistent with AML.**
  - **Normal karyotype.**
  - **Mutational profile: No mutations. FLT3/IDH1/IDH2 wildtype.**

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Commentary — Eunice S Wang, MD

Venetoclax + LDAC

- **Case presentation**
  - **90 yo woman PMHx COPD, HTN, polymyalgia rheumatica presented with pancytopenia 4 yrs ago and diagnosed with MDS (10% blasts). Received EPO growth factor (progressive anemia) followed by 4 cycles of azacitidine therapy.**
  - **Presented to local ER with worsening SOB and found to have anemia (hgb 5.1).**
  - **Repeat BMBX: AML with MDS related changes (21% blasts).**
  - **Karyotype: Normal XX.**
  - **Mutational profile: TET2+ NRAS+ AXSL1+ EZH2+ MLL2+, RUNX1.**

Commentary — Eunice S Wang, MD

IDH inhibitor

- **Case presentation**
  - **74 yo man hx cardiomyopathy s/p heart transplant 2006 and hypothyroidism who was admitted to outside hospital with new right sided heart failure and hyponatremia.**
  - **WBC noted to be 150K, hgb 7.9, plts 74K.**
  - **BMBX showed AML with monocytic features.**
  - **Karyotype: trisomy 8.**
  - **Mutational profile: DNMT3A+ NPM1+ U2AF1+ EZH2+. IDH1+.**

Questions — Ilene Galinsky, NP

Older patients with AML who are not eligible for intensive chemotherapy

- **What are some of the clinical issues that arise with older patients with AML that are beginning treatment, and what are some key points you address with them prior to starting treatment?**
- **What are some of the psychosocial issues that arise in these situations?**

Commentary — Ilene Galinsky, NP

Older patients with AML who are not eligible for intensive chemotherapy

- **Quality of life, end of life, caretaking, family support, friends?**
- **Change in lifestyle — feeling they are a burden; transportation issues — as most therapy is an outpatient treatment — azacitidine + ven for example**
- **Clinical trials, supportive care, vs no care**
- **Bone marrow examinations, line care, frequent visits**
- **Comorbidities — "Is it worth it?" "Why go through this if I am not going to be cured?" "I don't want to be a burden to my family," "I can't ask them to take time away from their children to bring me to the MDs."**
- **Discussions between family members and their parent — "Who wants the therapy?" and why do they want it — fear of death? I'm going to do it because my daughter wants me to?**

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Commentary — Ilene Galinsky, NP

- **89-year-old male with newly dx AML on a clinical trial — in remission now, stopped trial because he felt schedule too much, so now on soc azacitidine still in remission, great quality of life — I want to stop the trial, because it is working, so why not?**
- **I try to say it is a chronic disease — like HTN: you treat it, control it, but don't stop it**

Questions — Eunice S Wang, MD

Supportive care issues that arise during HMA/venetoclax treatment for older patients

- **What are some of the potential side effects associated with HMA/venetoclax?**
- **How do you approach prevention and management of tumor lysis syndrome?**

Commentary — Eunice S Wang, MD

Supportive care issues that arise during treatment of older patients with HMA/venetoclax

- **Most common side effects are myelosuppression (neutropenia, leukopenia, anemia, thrombocytopenia), risk of infection/pneumonia/bacteremia in addition to GI side effects (constipation, nausea/vomiting, skin rash at injection site).**
- **We admit patients for the first cycle of ven/HMA to manage TLS with daily IVF, allopurinol, rasburicase as needed for uric acid >9 and monitor renal function.**
- **Actual side effects include severe cytopenia, (particularly single digit thrombocytopenia requiring daily platelets), neutropenic fever, pneumonia, cellulitis, bacteremia.**

Commentary — Eunice S Wang, MD

- **First case: 82 yo woman with COPD on oxygen, hypertension, thyroid cancer, 50 pack year smoker who was diagnosed with AML (TET2, NRAS, ASXL1, SRSF2). Course complicated by acalculous cholecystitis (gallbladder infection) with sepsis presenting with neutropenic fever and abdominal pain. Improved on broad spectrum antibiotics, not surgical candidate. Also developed urinary tract infection (UTI) with enterococcus identified in the urine and treated with linezolid.**

- **Second case: 73 yo woman with prior history of ET on hydrea for 2.5 years now diagnosed with secondary AML with TP53 and CALR mutations. Platelet transfusion dependent with daily single digit platelet counts refractory to transfusions, Developed headache last week and CT showed a small subdural bleed which is stable. Also deconditioning s/p total knee replacement 10 weeks ago and working with PT. Also completed cefepime/azithromycin for neutropenic fever with pulmonary infiltrates.**

Questions — Ilene Galinsky, NP

Supportive care issues that arise during HMA/venetoclax treatment for older patients

- **What are some of the supportive care issues that arise for older patients receiving HMA/venetoclax?**
- **What are some of the key points you address with older patients who are receiving HMA/venetoclax in terms of what to expect related to side effects?**
- **What are some of the psychosocial issues that arise in this situation?**

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Commentary — Ilene Galinsky, NP

Supportive care issues that arise during HMA/venetoclax treatment for older patients

- **Fluid issues; constipation from the ven and antiemetics; fatigue; sleep disturbance; decrease in PO intake**
- **Comorbidities, drug-drug interactions; polypharmacy; “too many pills to take”**
- **Myelosuppression, SOB, fatigue, anemia, bleeding issues**
- **Similar to previous, burden, frequent visits, why can’t I stop, it is working**
- **My children have their lives, they shouldn’t need to help me — but they do, how to let loved ones help? For those that outlived their friends, this is difficult for them to want to be treated**

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Agenda

Module 1 – Younger Patients with Acute Myeloid Leukemia (AML)

Module 2 – Older Patients with AML

Module 3 – Myelodysplastic Syndromes

Defining MDS Risk

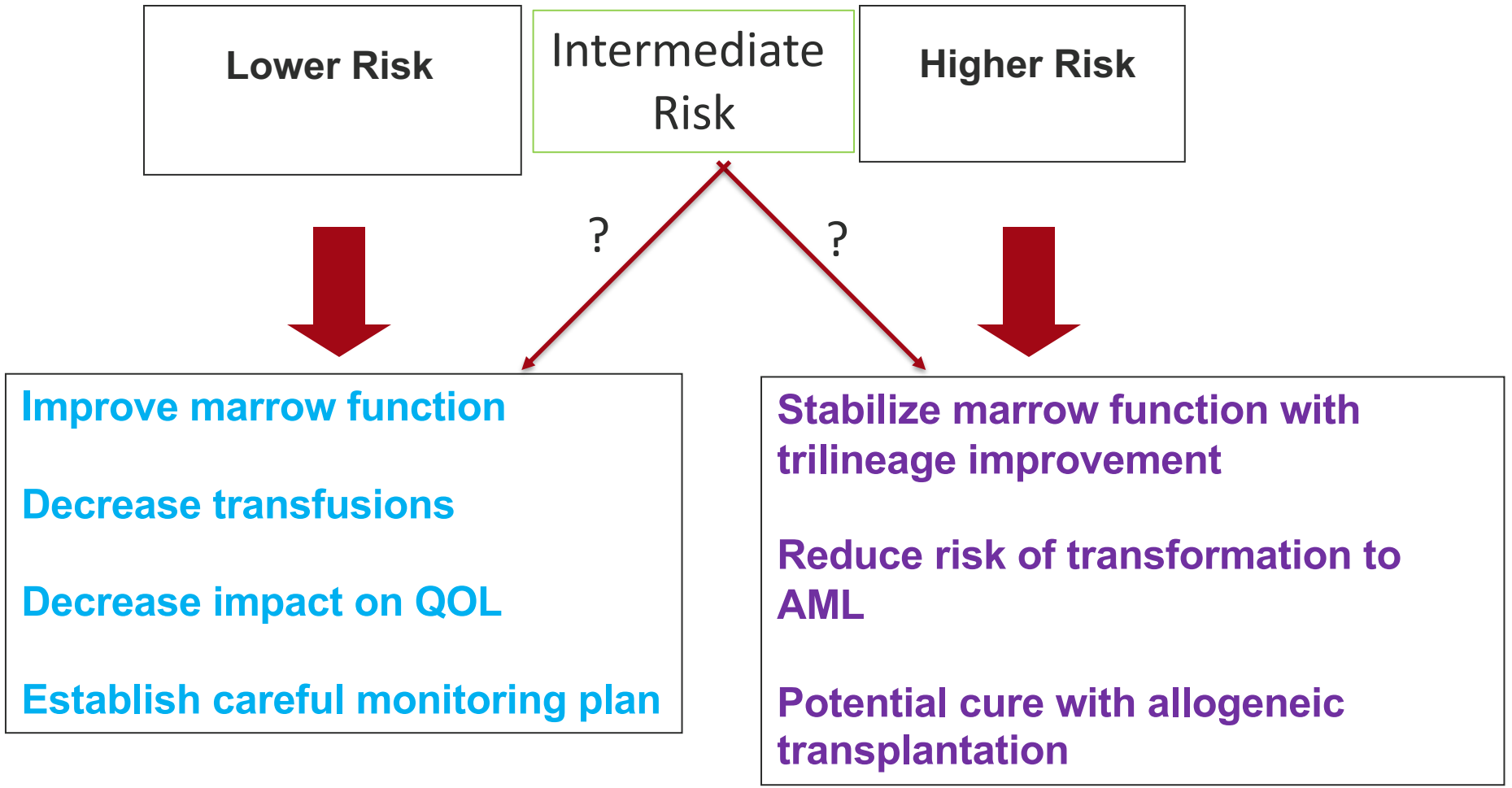
Goal: Identify patients whose disease, left untreated, is high risk of:

- Death (most often from infection/bleed/cardiac disease) or
- Leukemic progression within months (generally <18 months)

IPSS	IPSS-R	Disease History	Molecular*
INT-2 Risk High Risk	Score > 3.5 Intermediate High Very High	Progression after prior therapies e.g. formerly low risk	TP53 EZH2, RUNX1, ASXL1 “AML-like” mutations

Courtesy of Andrew M Brunner, MD

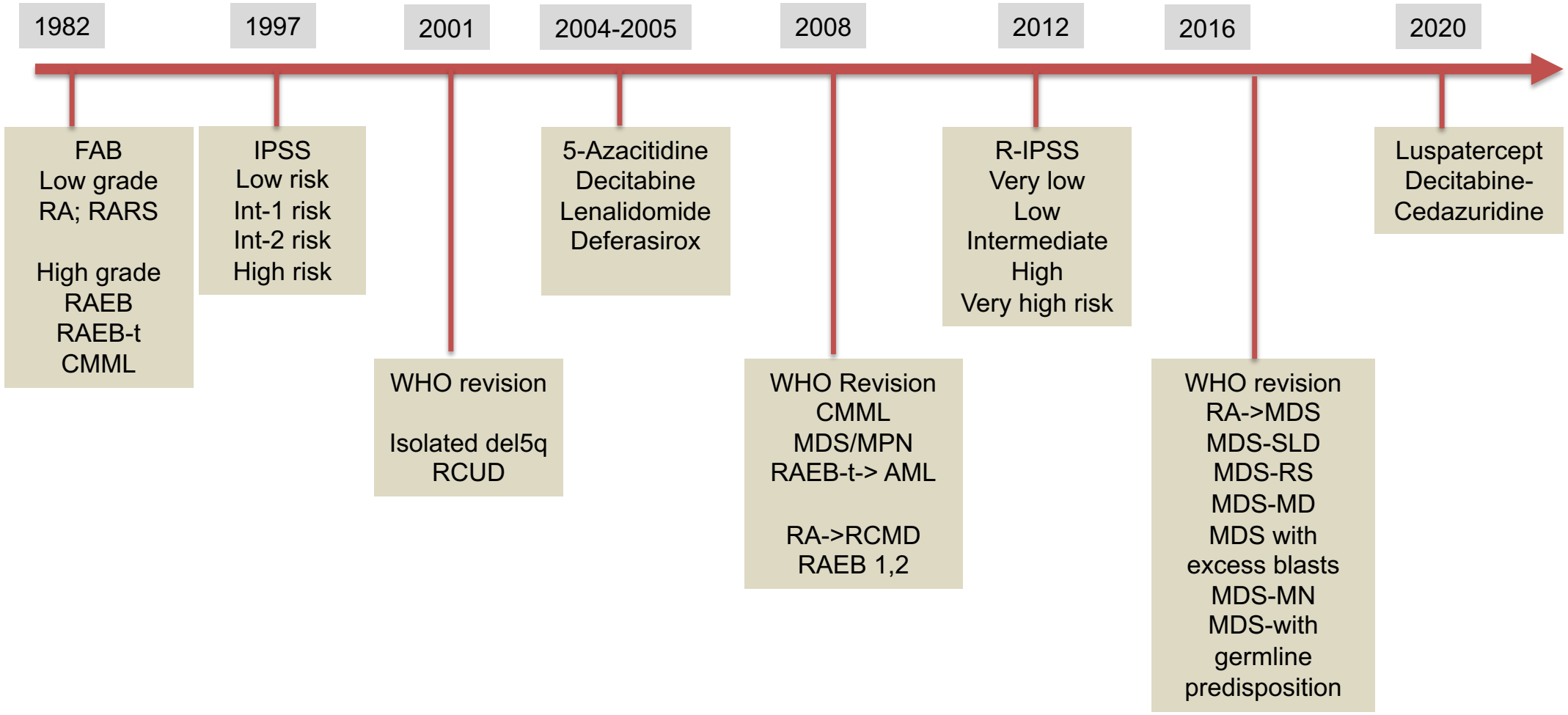
Treatment goals in MDS



Weill Cornell Medicine NewYork-Presbyterian

Courtesy of Gail J Roboz, MD

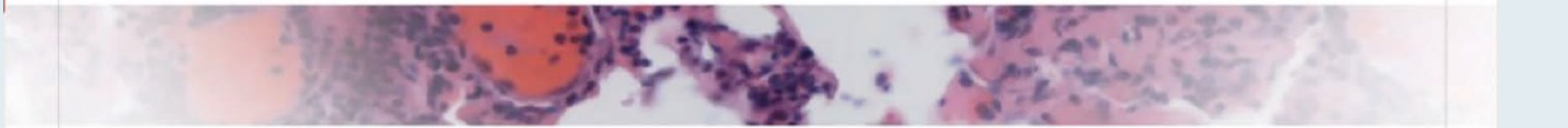
Timeline in MDS



Courtesy of Krishna Gundabolu, MD

ASH 2021;Abstract 66.

American Society of Hematology
Helping hematologists conquer blood diseases worldwide



Oral Decitabine/Cedazuridine in Patients with Lower Risk Myelodysplastic Syndrome: a Longer-Term Follow-Up of from the ASCERTAIN Study

On behalf of the ASCERTAIN Investigators Team

Guillermo Garcia-Manero, MD[1], James K. McCloskey, MD[2], Elizabeth A. Griffiths, MD[3], Karen W.L. Yee, MD[4], Amer M. Zeidan, MBBS, MHS[5], Aref Al-Kali, MD[6], , H. Joachim Deeg, MD[7], Prapti A. Patel, MD[8], Mitchell Sabloff, MSc, MD, FRCPC[9], Mary-Margaret Keating, MD, FRCPC[10], Kim-Hien Dao, DO, PhD[11,26], Nancy Zhu, MD[12*], Nashat Gabrail, MD[13*], Salman Fazal, MD[14], Joseph Maly, MD[15], Olatoyosi Odenike, MD[16], Hagop M. Kantarjian, MD[17], Amy E. DeZern, MD[18], Casey L. O'Connell, MD[19], Gail J. Roboz, MD[20], Lambert Busque, MD[21], Richard A. Wells, MD, DPhil[22*], Harshad Amin, MD[23*], Jasleen K. Randhawa, MD[24], Brian Leber, MD[25], Yong Hao, MD, PhD[26*], Harold N. Keer, MD, PhD[26], Mohammad Azab, MD[26] and Michael R. Savona, MD[25]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]John Theurer Cancer Center at Hackensack Meridian Health, Hackensack, NJ; [3]Roswell Park Comprehensive Cancer Center, Buffalo, NY; [4]Princess Margaret Cancer Centre, Toronto, Canada; [5]Yale University and Yale Cancer Center, New Haven, CT; [6]Mayo Clinic, Rochester, MN; [7]Fred Hutchinson Cancer Research Center, Seattle, WA; [8]University of Texas Southwestern Medical Center, Dallas, TX; [9]Division of Hematology, Department of Medicine, University of Ottawa and The Ottawa Hospital Research Institute, Ottawa, ON, Canada; [10]Queen Elizabeth II Health Sciences Centre, Halifax, NS, Canada; [11]Astex Pharmaceuticals, Inc., Pleasanton, CA; [12]University of Alberta, Edmonton, AB, Canada; [13]Gabrail Cancer Center Research, Canton, OH; [14]West Penn Hospital, Allegheny Health Network, Pittsburgh, PA; [15]Norton Cancer Institute, Louisville, KY; [16]University of Chicago, Chicago, IL; [17]Johns Hopkins University Hospital, Baltimore, MD; [18]USC Keck School of Medicine, University of Southern California, Los Angeles, CA; [19]Weill Cornell Medicine and The New York-Presbyterian Hospital, New York, NY; [20]Research Center, Maisonneuve-Rosemont Hospital, Montreal, QC, Canada; [21]Sunnybrook Health Sciences Centre, Toronto, Canada; [22]Boca Raton Clinical Research, Boca Raton, FL; [23]Houston Methodist Cancer Center, Houston; [24]Department of Medicine, McMaster University, Hamilton, ON, Canada; [25]Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN

RTP RESEARCH TO PRACTICE

N Engl J Med 2020;382:140-51.

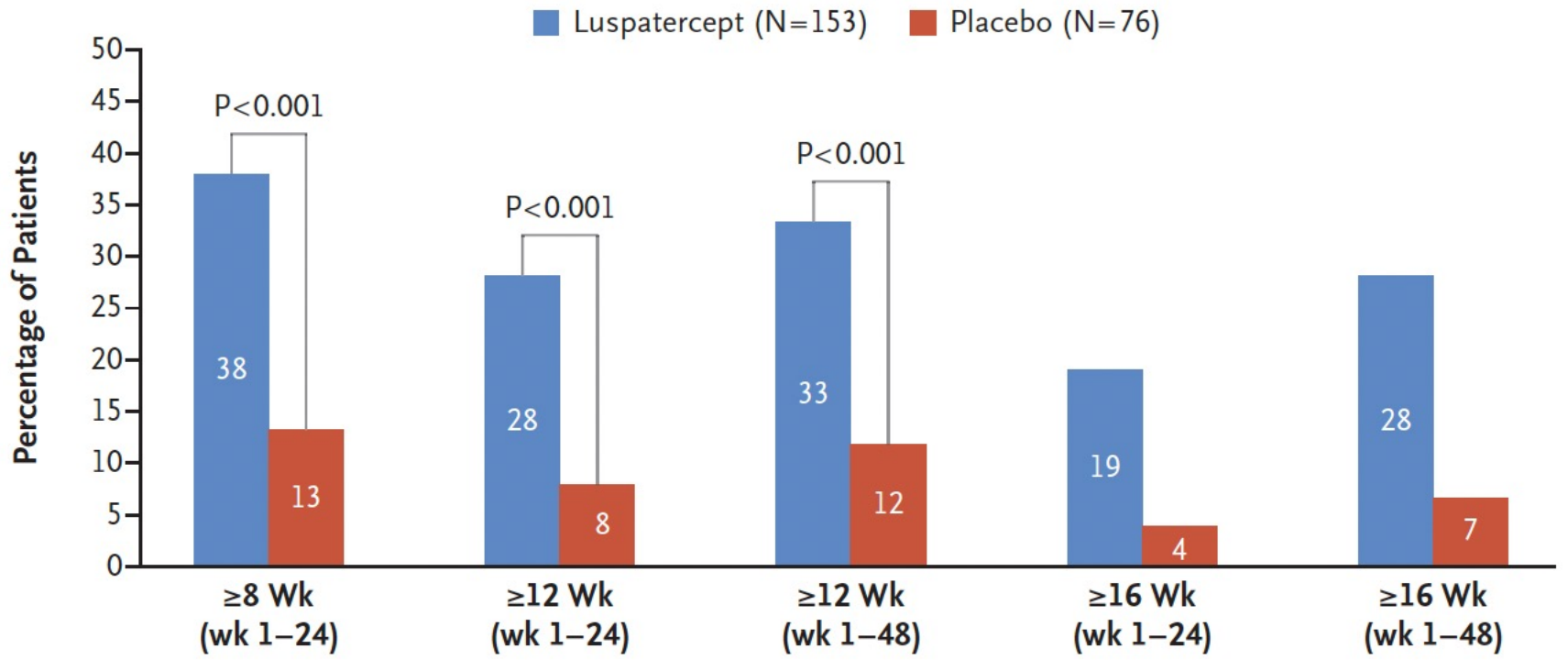
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Luspatercept in Patients with Lower-Risk Myelodysplastic Syndromes

P. Fenaux, U. Platzbecker, G.J. Mufti, G. Garcia-Manero, R. Buckstein, V. Santini, M. Díez-Campelo, C. Finelli, M. Cazzola, O. Ilhan, M.A. Sekeres, J.F. Falantes, B. Arrizabalaga, F. Salvi, V. Giai, P. Vyas, D. Bowen, D. Selleslag, A.E. DeZern, J.G. Jurcic, U. Germing, K.S. Götze, B. Quesnel, O. Beyne-Rauzy, T. Cluzeau, M.-T. Voso, D. Mazure, E. Vellenga, P.L. Greenberg, E. Hellström-Lindberg, A.M. Zeidan, L. Adès, A. Verma, M.R. Savona, A. Laadem, A. Benzohra, J. Zhang, A. Rampersad, D.R. Dunshee, P.G. Linde, M.L. Sherman, R.S. Komrokji, and A.F. List

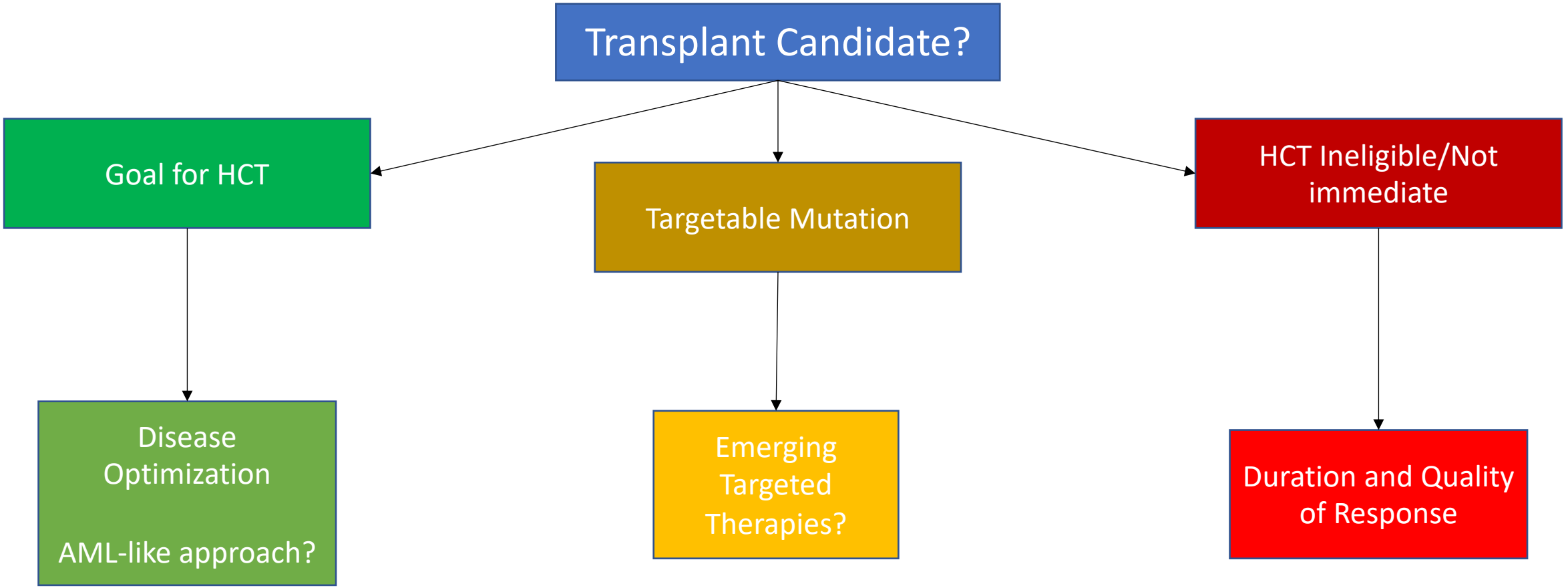
MEDALIST: Independence from Red Blood Cell Transfusion



No. of Patients with Response (% [95% CI])					
Luspatercept	58 (38 [30–46])	43 (28 [21–36])	51 (33 [26–41])	29 (19 [13–26])	43 (28 [21–36])
Placebo	10 (13 [6–23])	6 (8 [3–16])	9 (12 [6–21])	3 (4 [1–11])	5 (7 [2–15])

Fenaux P et al. *N Engl J Med* 2020;382:140-51.

Approaching Higher Risk MDS



Courtesy of Andrew M Brunner, MD

Higher-Risk MDS: Improving Response and Duration of Response Is an Unmet Medical Need

AZACITIDINE (HMA) +

- Magrolimab
- APR246
- Pevonedistat
- Ivosidenib
- Gilteritininb
- Enasidenib
- Venetoclax
- Immune Checkpoint Inhibitors
  - MBG453
  - Ipilimumab
  - Nivolumab
  - Durvalumab
- Rigosertib
- Others……

Buckstein R. Education Session. ASCO 2021.

Venetoclax in Combination with Azacitidine Granted FDA Breakthrough Therapy Designation for Higher-Risk MDS

Press Release: July 21, 2021

"…the US Food and Drug Administration (FDA) granted a Breakthrough Therapy Designation (BTD) to venetoclax in combination with azacitidine for the potential treatment of adult patients with previously untreated intermediate-, high- and very high-risk myelodysplastic syndromes (MDS) based on revised International Prognostic Scoring System (IPSS-R).

This designation is supported by data from the Phase 1b M15-531 study. In addition to the Phase 1b M15-531 study, venetoclax is being investigated in combination with azacitidine for the treatment of MDS in the Phase 1b M15-522 study in patients with relapsed or refractory disease, and the Phase 3 randomized VERONA study in patients with newly diagnosed higher-risk MDS."

https://www.prnewswire.com/news-releases/venetoclax-venclexta-granted-us-fda-breakthrough-therapy-designation-btd-in-higher-risk-myelodysplastic-syndrome-mds-301338030.html

Molecular Responses Are Observed Across Mutational Spectrum in Treatment-Naïve Higher-Risk Myelodysplastic Syndrome Patients Treated With Venetoclax Plus Azacitidine

ASH 2021;Abstract 241

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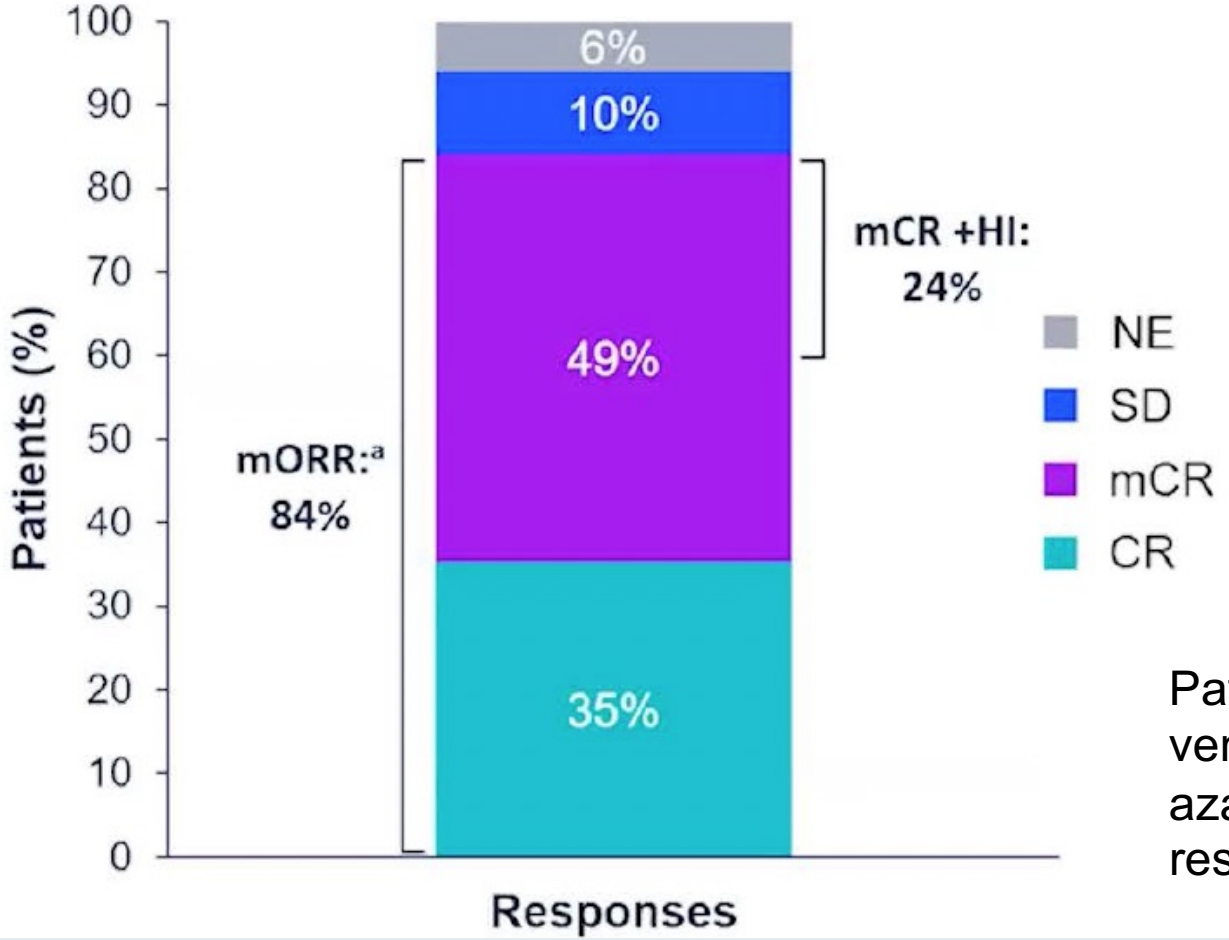
American Society of Hematology Annual Meeting, December 11–14, 2021, Atlanta, Georgia

Response to Venetoclax with Azacitidine

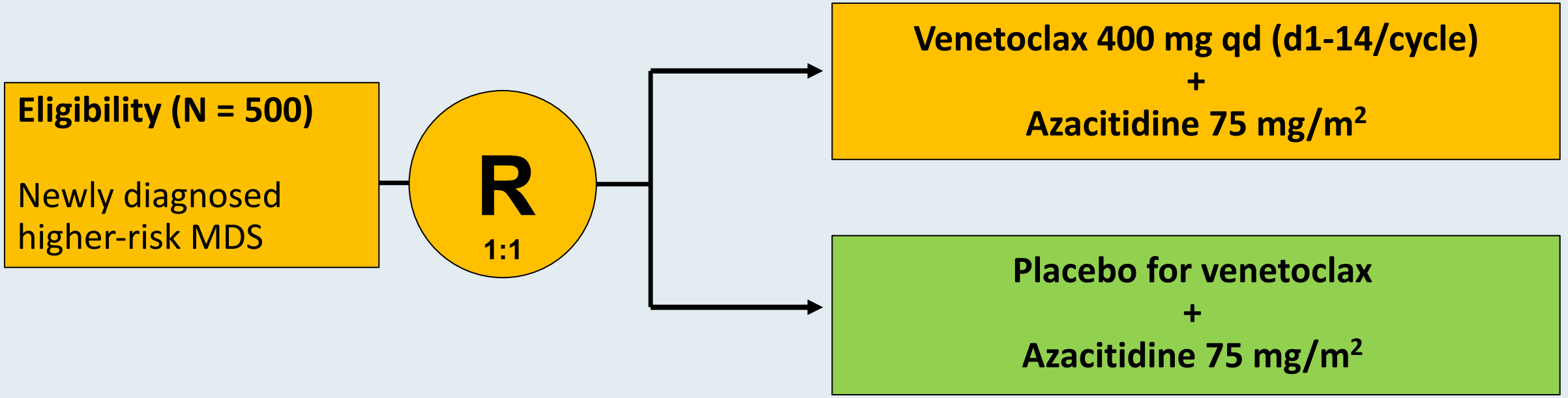


- Median time to response:
  0.9 months (95% CI, 0.7–5.8)
- Median duration of response:
  12.4 months (95% CI, 9.9–NR)

Patients with HR-MDS treated with venetoclax (400 mg D1-14) and azacitidine (75 mg/m^2) had rapid, durable responses with high remission rates

Garcia JS et al. ASH 2021;Abstract 241.

VERONA Phase III Trial of Venetoclax with Azacitidine Compared to Azacitidine with Placebo for Newly Diagnosed Higher-Risk MDS



Until relapse, progression or unacceptable toxicity

Dual primary endpoints: Complete remission and overall survival

Secondary endpoints: RBC and platelet transfusion independence for patients who are transfusion dependent at baseline, change from baseline in fatigue, time to deterioration of physical functioning and overall response

Zeidan AM et al. ASCO 2021;Abstract TPS7054.

Appendix

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

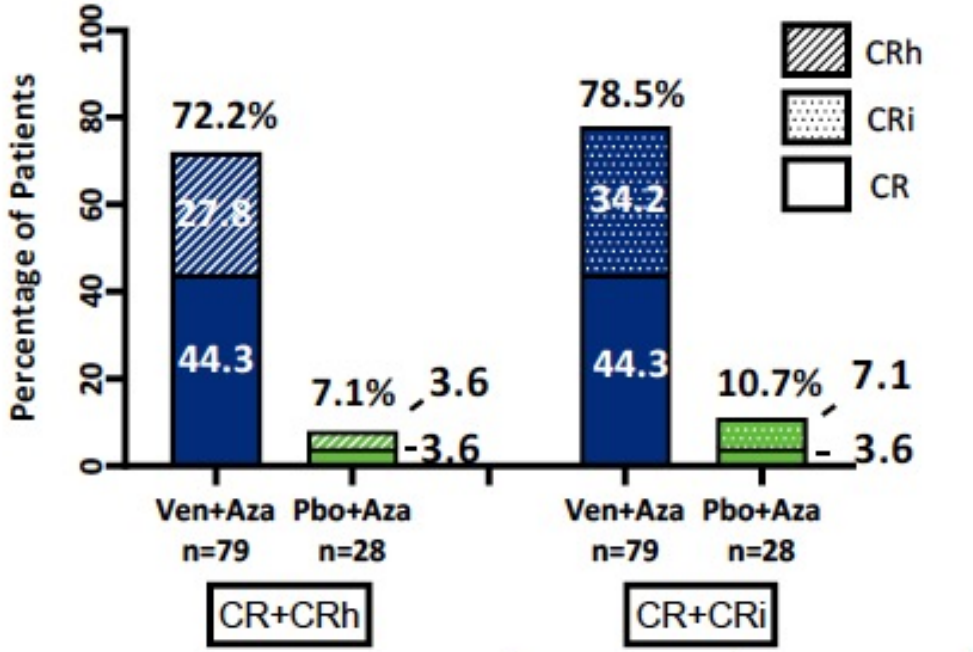
C.D. DiNardo, B.A. Jonas, V. Pullarkat, M.J. Thirman, J.S. Garcia, A.H. Wei, M. Konopleva, H. Döhner, A. Letai, P. Fenaux, E. Koller, V. Havelange, B. Leber, J. Esteve, J. Wang, V. Pejsa, R. Hájek, K. Porkka, Á. Illés, D. Lavie, R.M. Lemoli, K. Yamamoto, S.-S. Yoon, J.-H. Jang, S.-P. Yeh, M. Turgut,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

VIALE-A: Baseline Characteristics of Patients

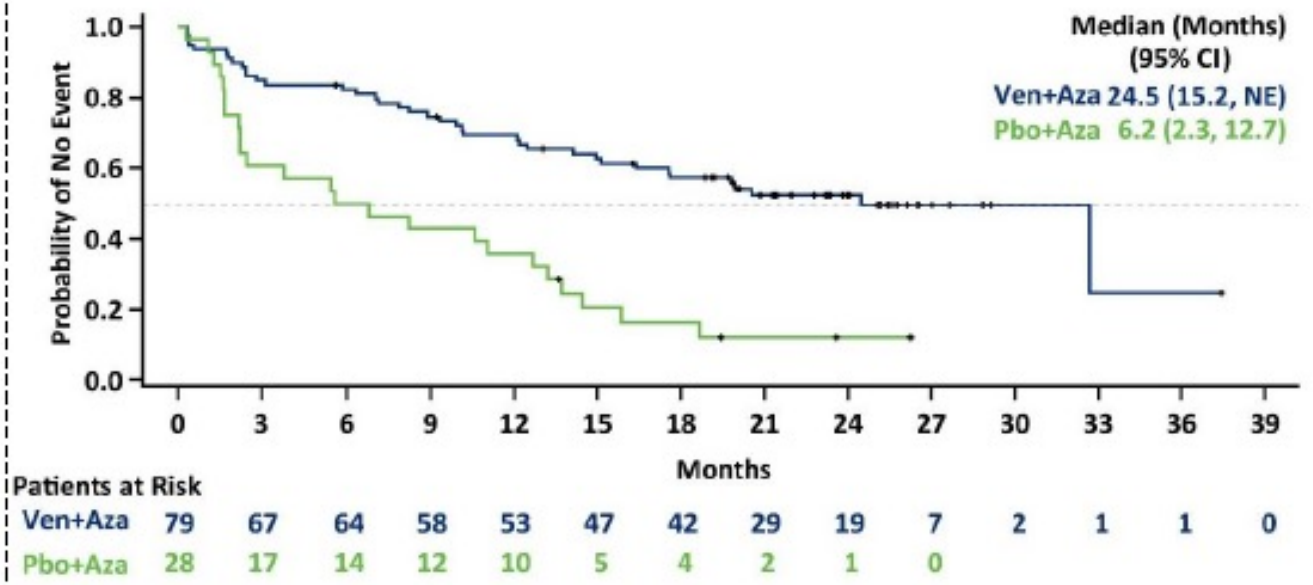
Characteristic	Azacitidine–Venetoclax Group (N=286)	Azacitidine–Placebo Group (N=145)
Age		
Median (range) — yr	76 (49–91)	76 (60–90)
≥75 yr — no. (%)	174 (61)	87 (60)
Somatic mutations — no./total no. (%)		
IDH1 or *IDH2*	61/245 (25)	28/127 (22)
FLT3 ITD or TKD	29/206 (14)	22/108 (20)
NPM1	27/163 (17)	17/86 (20)
TP53	38/163 (23)	14/86 (16)
Baseline cytopenia grade ≥3¶		
Anemia — no. (%)	88 (31)	52 (36)
Neutropenia — no./total no. (%)	206/286 (72)	90/144 (62)
Thrombocytopenia — no. (%)	145 (51)	73 (50)
Baseline transfusion dependence — no. (%)‖		
Red cells	144 (50)	76 (52)
Platelets	68 (24)	32 (22)
≥2 Reasons for ineligibility to receive intensive therapy — no. (%)	141 (49)	65 (45)

DiNardo CD et al. *N Engl J Med* 2020;383(7):617-29.

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



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



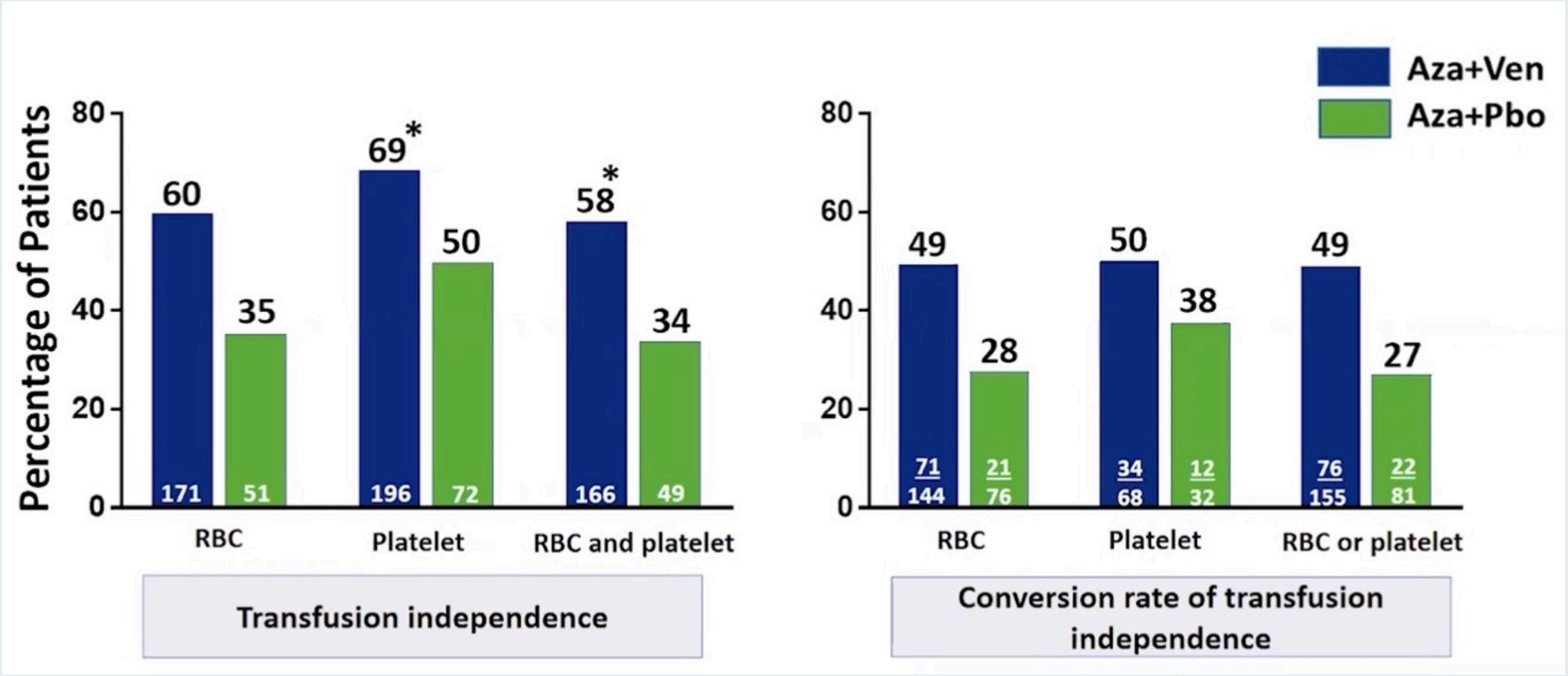
Survival Estimate (%) (95% CI)

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

Pratz K et al. ASH 2020;Abstract 1944.

RTP RESEARCH TO PRACTICE

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



DiNardo C et al. EHA 2020;Abstract LB2601.

VIALE-A: Common Hematologic Adverse Events

Adverse event (AE)	Azacitidine/venetoclax (N = 283)		Azacitidine/placebo (N = 144)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Hematologic AEs	83%	82%	69%	68%
Thrombocytopenia	46%	45%	40%	38%
Neutropenia	42%	42%	29%	28%
Febrile neutropenia	42%	42%	19%	19%
Anemia	28%	26%	21%	20%
Leukopenia	21%	21%	14%	12%

DiNardo CD et al. *N Engl J Med* 2020;383(7):617-29.

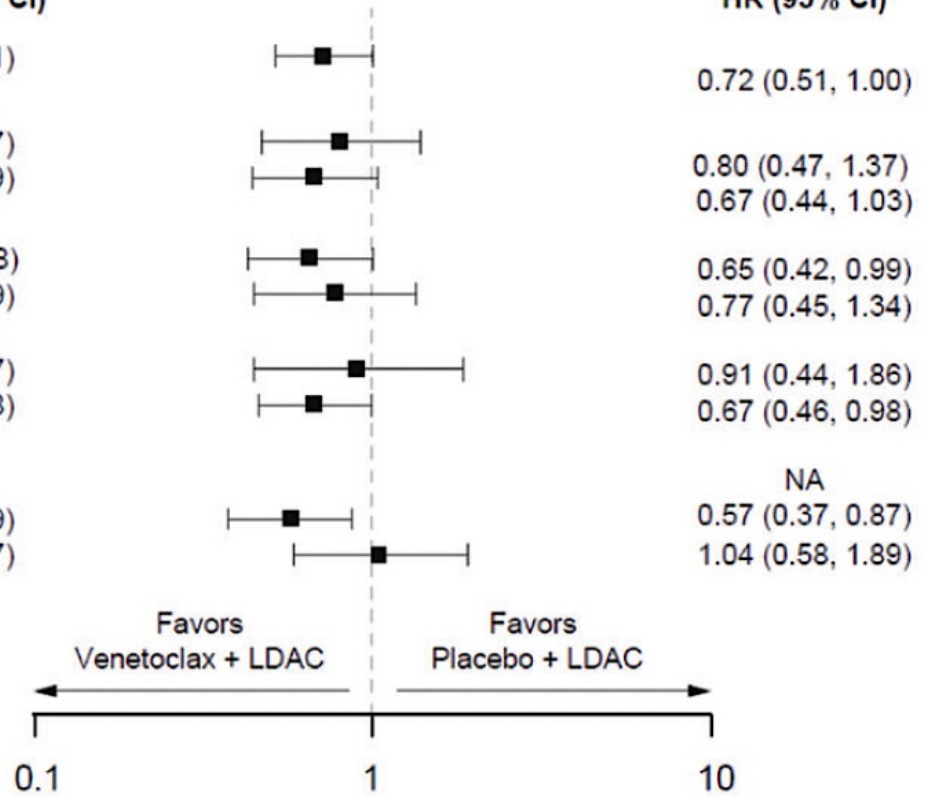
VIALE-A: Common Gastrointestinal Adverse Events

Adverse event	Azacitidine/venetoclax (N = 283)		Azacitidine/placebo (N = 144)	
	All Grades	Grade ≥3	All grades	Grade ≥3
Nausea	44%	2%	35%	1%
Constipation	43%	1%	39%	1%
Diarrhea	41%	5%	33%	3%
Vomiting	30%	2%	23%	1%
Decreased appetite	25%	4%	17%	1%

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

VIALE-C: Overall Survival Subgroup Analysis with Venetoclax and Low-Dose Cytarabine for Previously Untreated Older Patients with AML

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



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

VIALE-C: Selected Serious Adverse Events

Adverse event	Placebo + LDAC (N = 68)	Venetoclax + LDAC (N = 142)
Febrile neutropenia	18%	16%
Pneumonia	10%	13%
Sepsis	6%	6%
Thrombocytopenia	3%	5%
Anemia	0	3%
Neutropenia	0	3%

Wei AH et al. *Blood* 2020;135(24):2137-45.

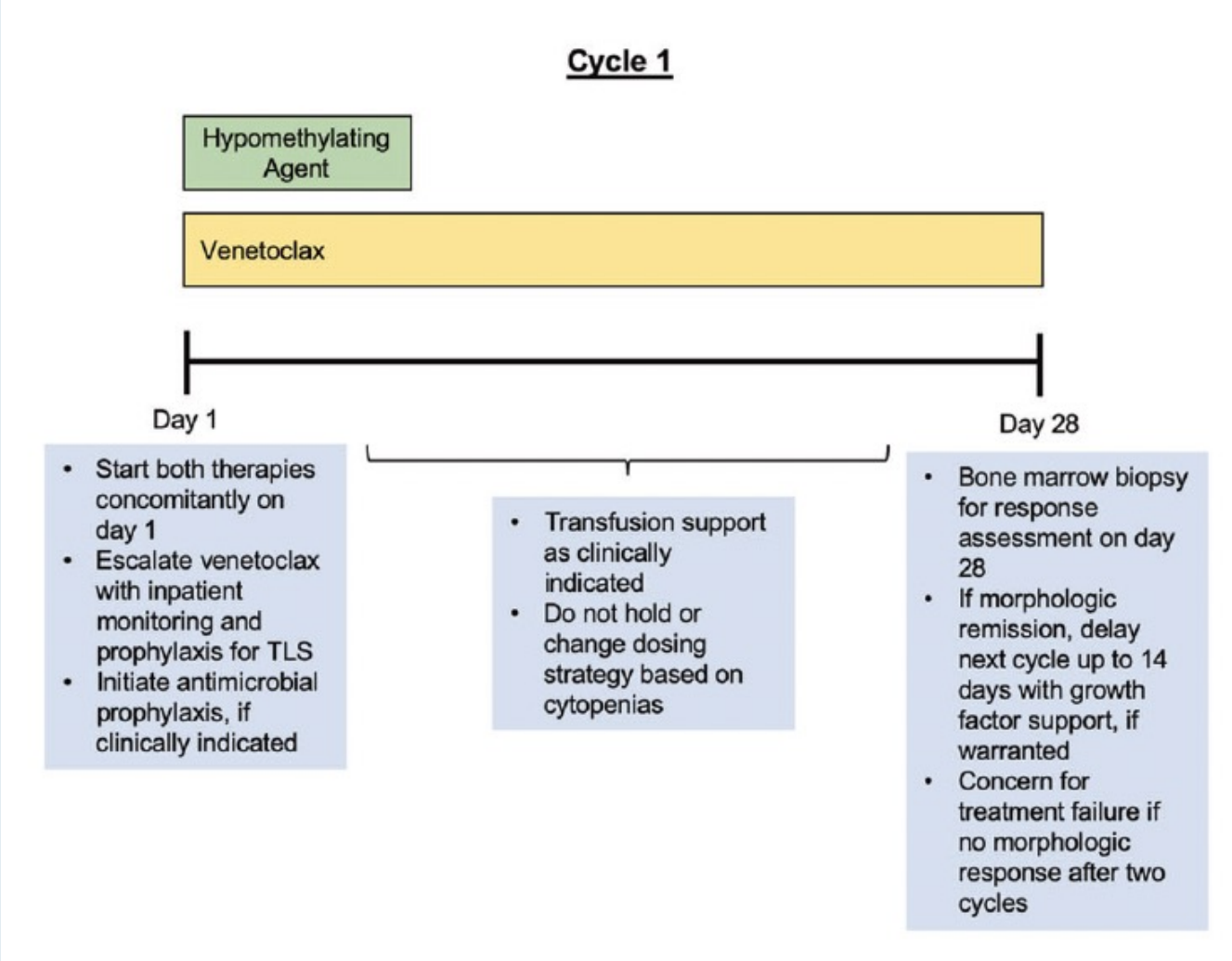
Venetoclax Dosing Schedule for 3- or 4-Day Ramp-Up Phase for Patients with AML

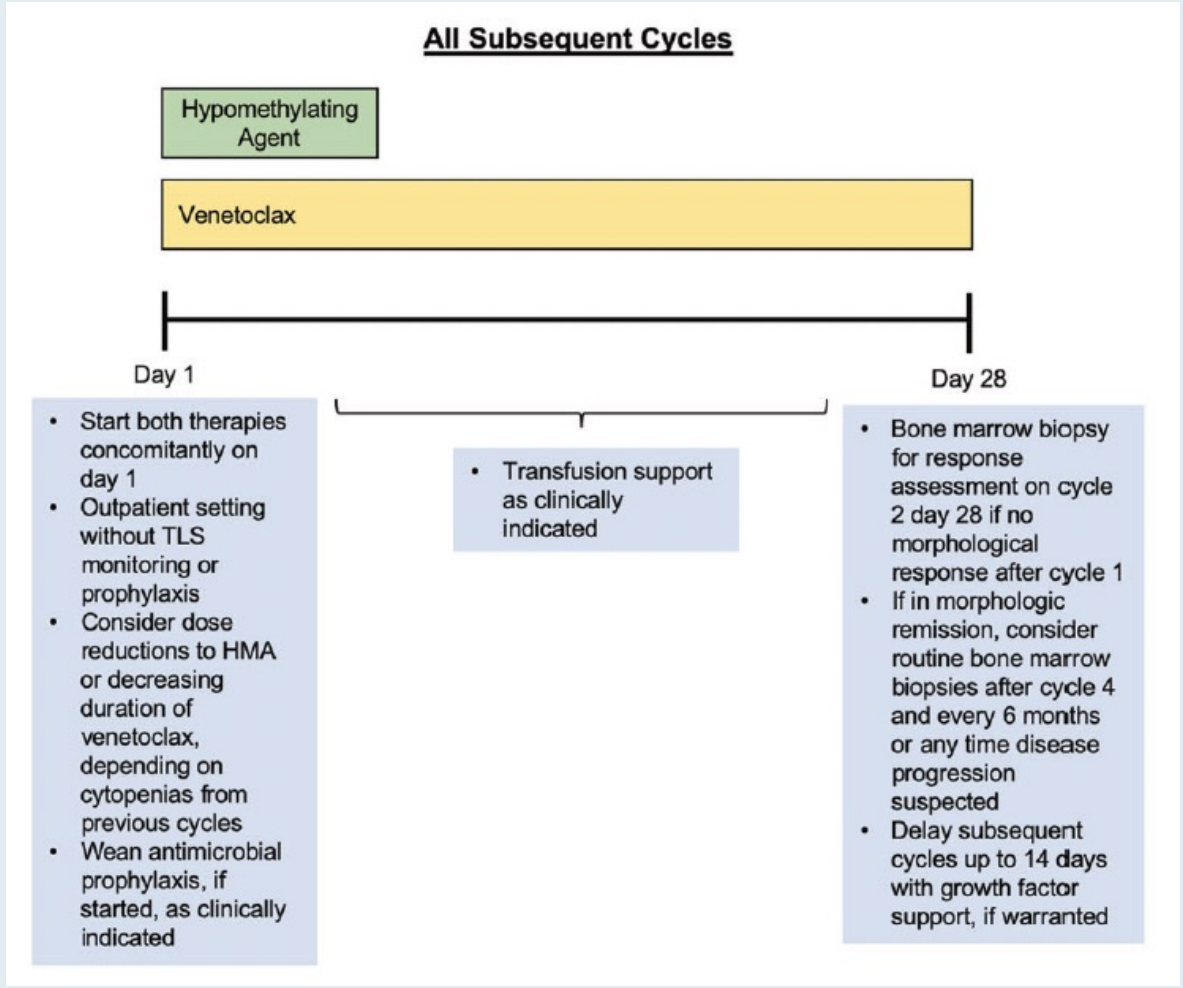
Day	Venetoclax oral daily dose	
Day 1	100 mg	
Day 2	200 mg	
Day 3	400 mg	
Day 4 and beyond	400 mg qd of each 28-day cycle in combination with **azacitidine or decitabine**	600 mg qd of each 28-day cycle in combination with **low-dose cytarabine**

- Assess patient-specific factors for level of risk of tumor lysis syndrome (TLS)
- Provide prophylactic hydration and antihyperuricemics to patients prior to first dose of venetoclax to reduce risk of TLS

Venetoclax prescribing information: www.rxabbvie.com/pdf/venclexta.pdf, Revised 12/2021

Venetoclax/HMA Treatment Schema for Cycle 1 and Subsequent Cycles

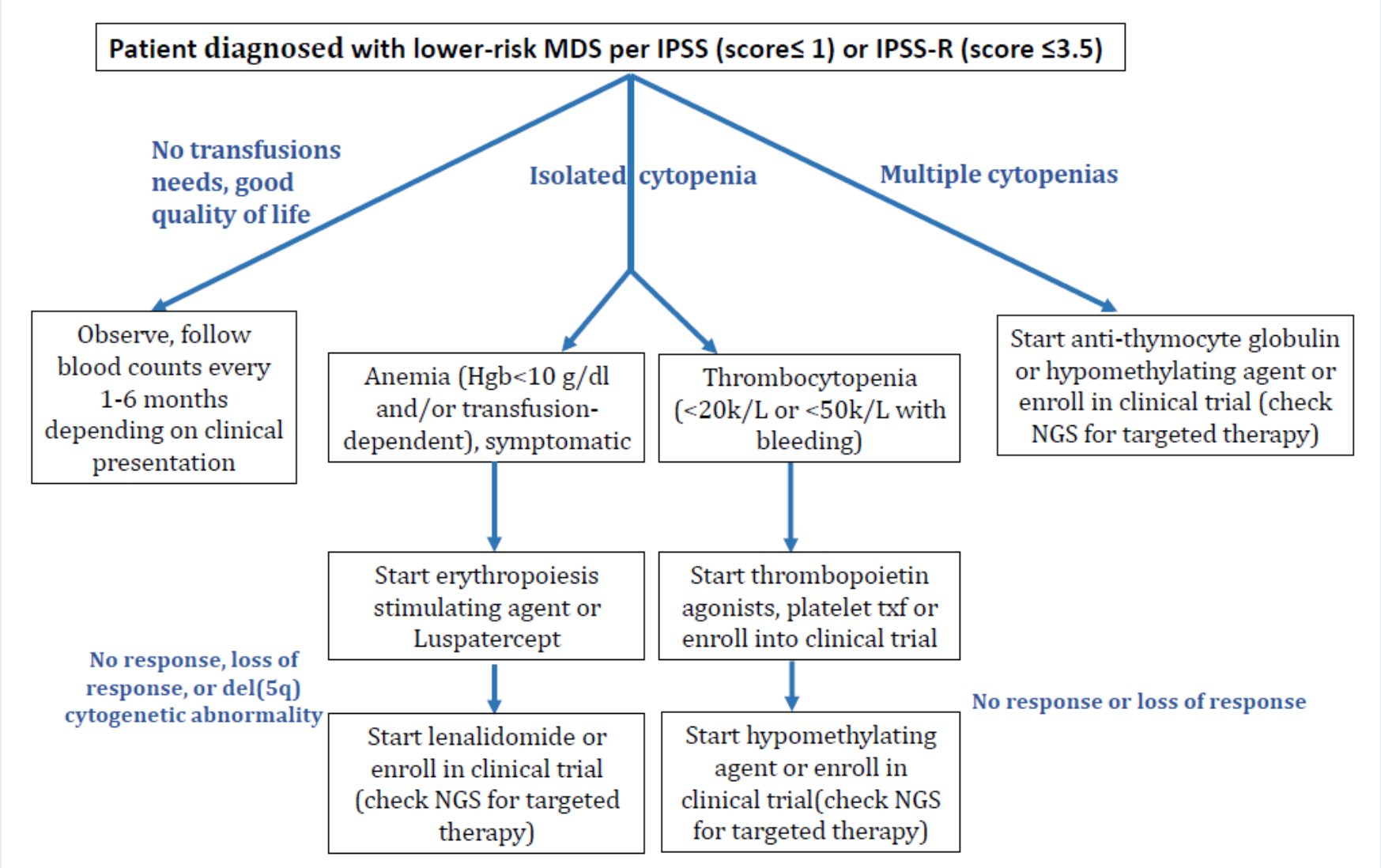




Jonas BA, Pollyea DA. *Leukemia* 2019;33(12):2795-804.

RTP RESEARCH TO PRACTICE

Treating MDS: Lower-Risk Disease



Sekeres and Patel. Hematology (ASH Educ Book) 2019.

Courtesy of Mikkael A Sekeres, MD, MS

RTP RESEARCH TO PRACTICE

ASCERTAIN: Efficacy of Decitabine/Cedazuridine in Patients with Lower-Risk MDS

Response Category	Treated Patients (N=69[a]), n (%)	95% CI
Complete response (CR)	16 (23.2%)	(13.9, 34.9)
Partial response (PR)	0	
Marrow CR (mCR)	18 (26.1%)	(16.3, 38.1)
mCR with hematologic improvement	9 (13.0%)	(6.1, 23.3)
Hematologic improvement (HI)	5 (7.2%)	(2.4, 16.1)
HI-erythroid[3]	1 (1.4%)	(0.0, 7.8)
HI-neutrophils[3]	0	
HI-platelet[3]	4 (5.8%)	(1.6, 14.2)
Overall response (CR + PR + mCR + HI)	39 (56.5)	(44.0, 68.4)

[1]Responses adjudicated by independent review committee per IWG 2006
[a] Includes 3 subjects who did not receive ASTX727 (received IV decitabine cycle 1 and did not continue)

For subjects with ≥ 5% bone marrow blasts (n=26):

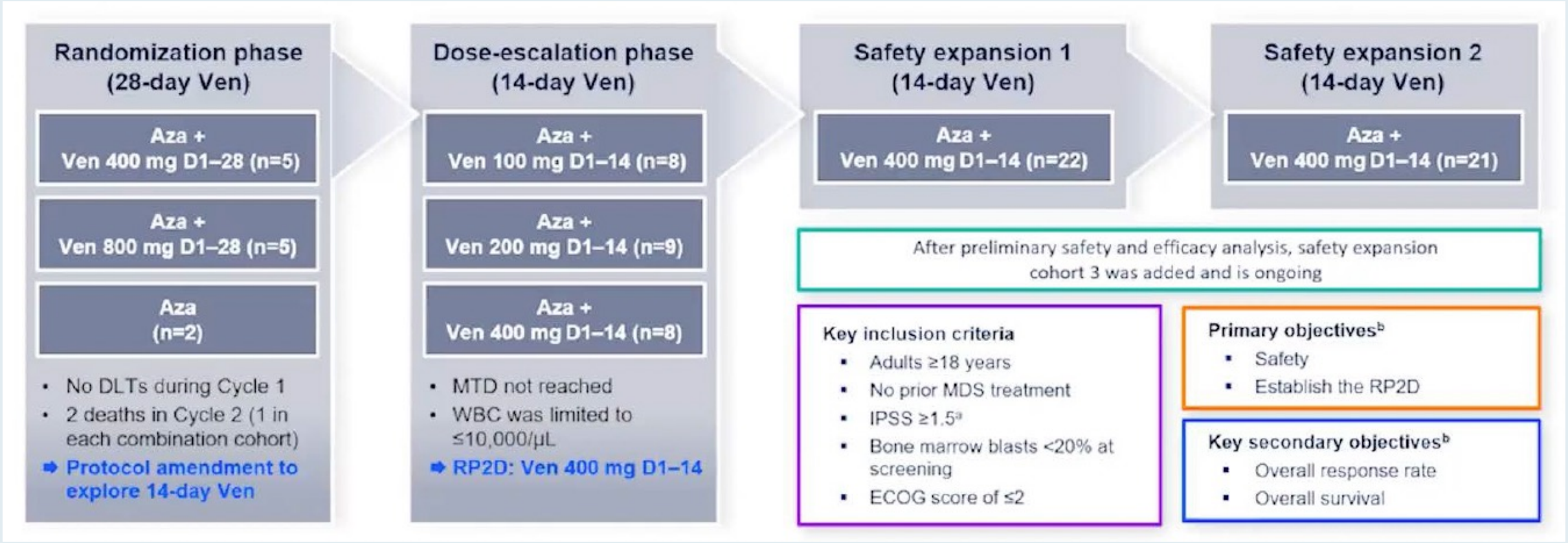
- CR 7 (26.9%)
- mCR 11 (42.3%)

For the entire group (n=69):

- Median CR duration was 15.3 months
- Median duration of best response was 13.4 months
- Median time to first and best response were 3.0 months and 4.3 months, respectively
- 18 (26.0%) subjects proceeded to HCT

Garcia-Manero G et al. ASH 2021;Abstract 66.

Phase Ib Study of Venetoclax with Azacitidine for Patients with Treatment-Naïve High-Risk MDS



Garcia JS et al. ASH 2021;Abstract 241.

What I Tell My Patients:
New Treatments and Clinical Trial Options

An NCPD Hybrid Symposium Series
Held During the 47th Annual ONS Congress

Cervical and Endometrial Cancer

Saturday, April 30, 2022
6:00 AM – 7:30 AM PT

Faculty

Paula J Anastasia, MN, RN, AOCN
Robert L Coleman, MD
David M O'Malley, MD
Jaclyn Shaver, MS, APRN, CNP, WHNP

Moderator

Neil Love, MD

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Thank you for joining us!

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Online attendees: NCPD credit information will be emailed to each participant within 3 business days.

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