Year in Review: Clinical Investigators Provide Perspectives on the Most Relevant New Publications, Data Sets and Advances in Oncology

Acute Myeloid Leukemia and Myelodysplastic Syndromes

Tuesday, January 5, 2021
5:00 PM – 6:00 PM ET

Faculty

Mikkael A Sekeres, MD, MS
Richard M Stone, MD

Moderator

Neil Love, MD

RTP Year in Review 2020

Commercial Support

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Dr Love — Disclosures

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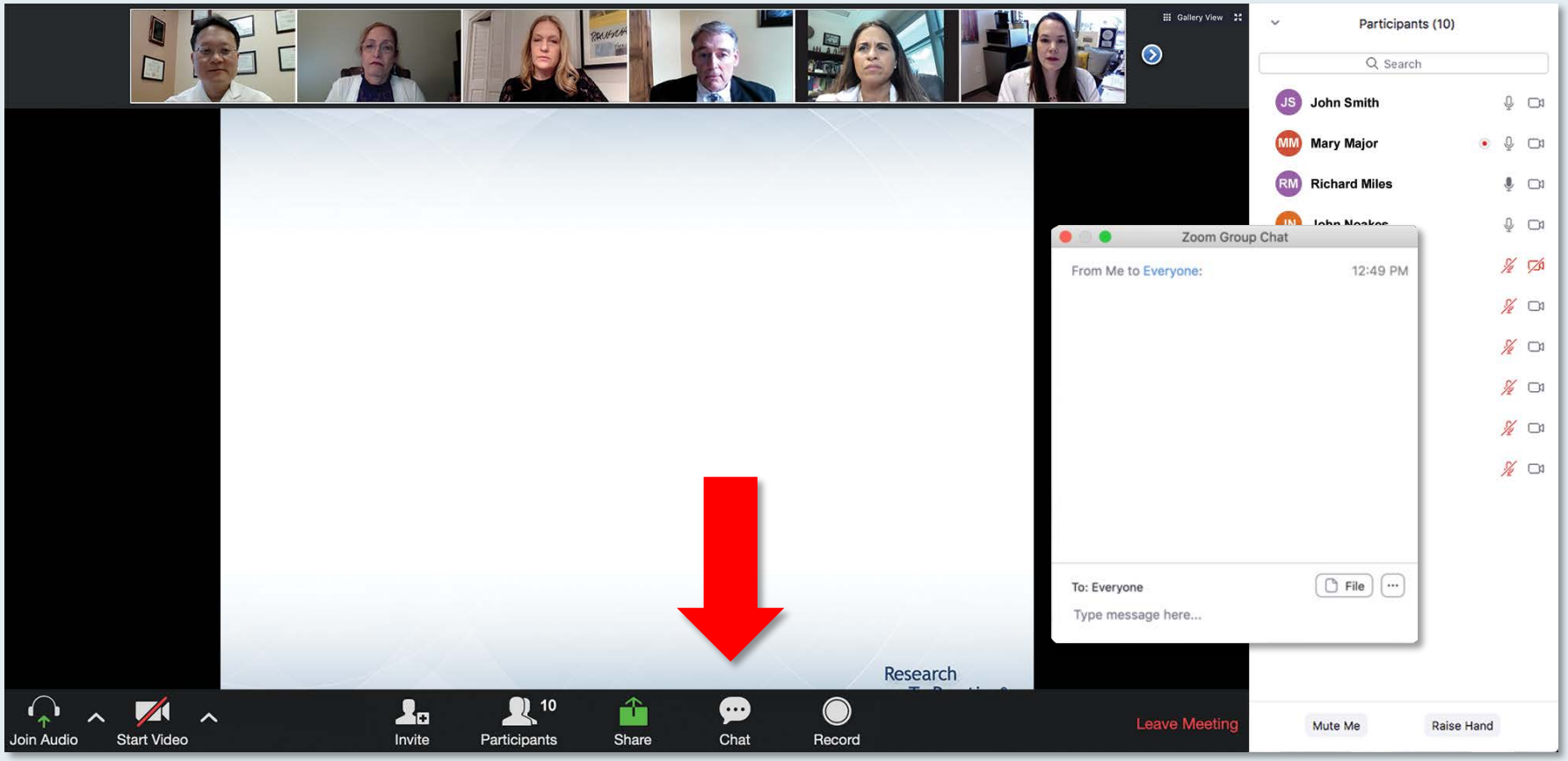

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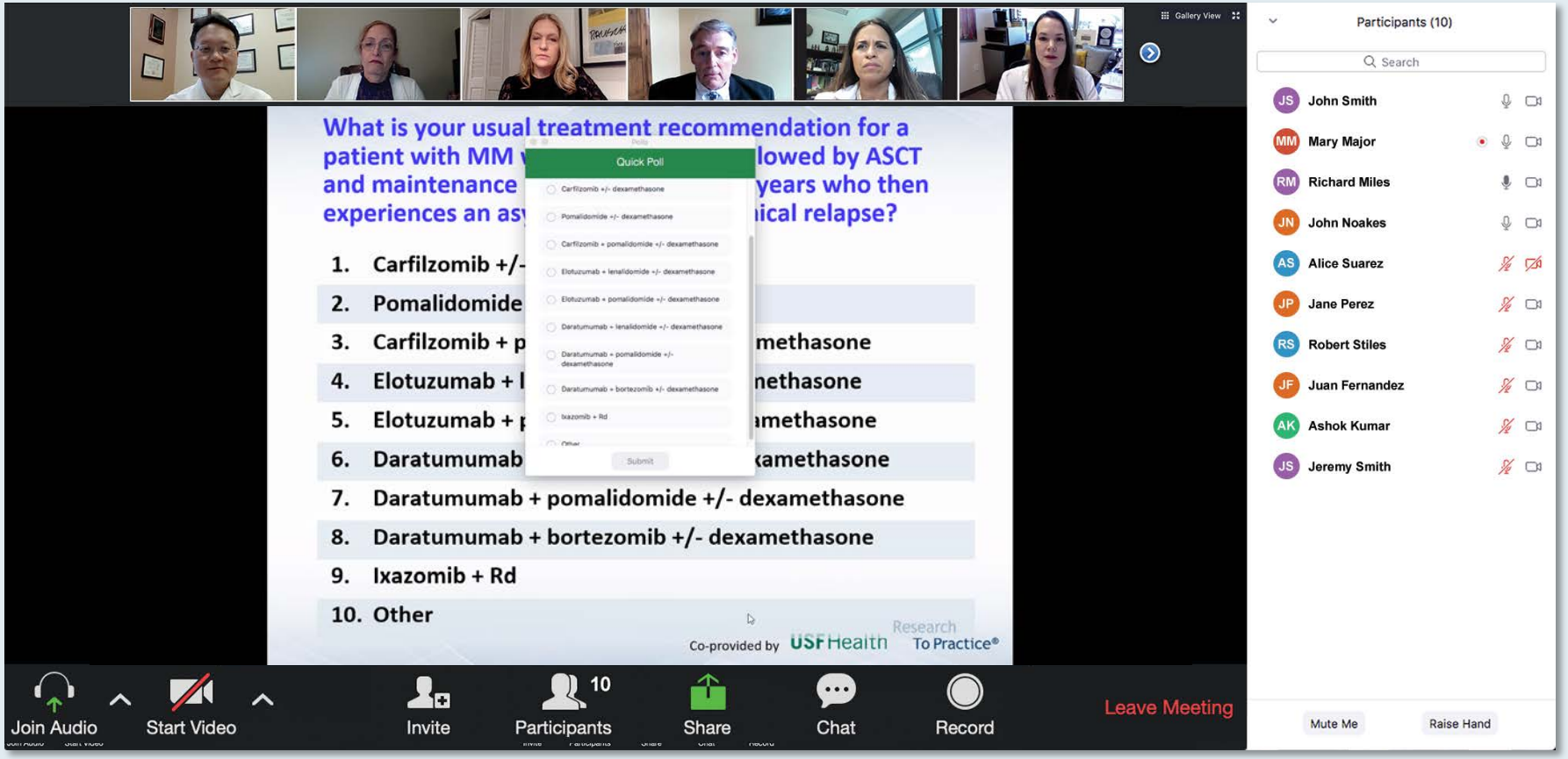

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Cancer Conference Update: What Happened at the 2020 San Antonio Breast Cancer Symposium

Session 1: Triple-Negative Breast Cancer

Monday, January 11, 2021
5:00 PM – 6:00 PM ET

Faculty

P Kelly Marcom, MD

Moderator

Neil Love, MD

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Gynecologic Cancers

Tuesday, January 12, 2021
5:00 PM – 6:00 PM ET

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Richard T Penson, MD, MRCP

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Lymphomas

Thursday, January 14, 2021
5:00 PM – 6:00 PM ET

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Christopher R Flowers, MD, MS
Sonali M Smith, MD

Moderator

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ONCOLOGY TODAY

WITH DR NEIL LOVE

ACUTE MYELOID LEUKEMIA WITH FLT3 MUTATIONS

DR KEITH PRATZ
UNIVERSITY OF PENNSYLVANIA

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

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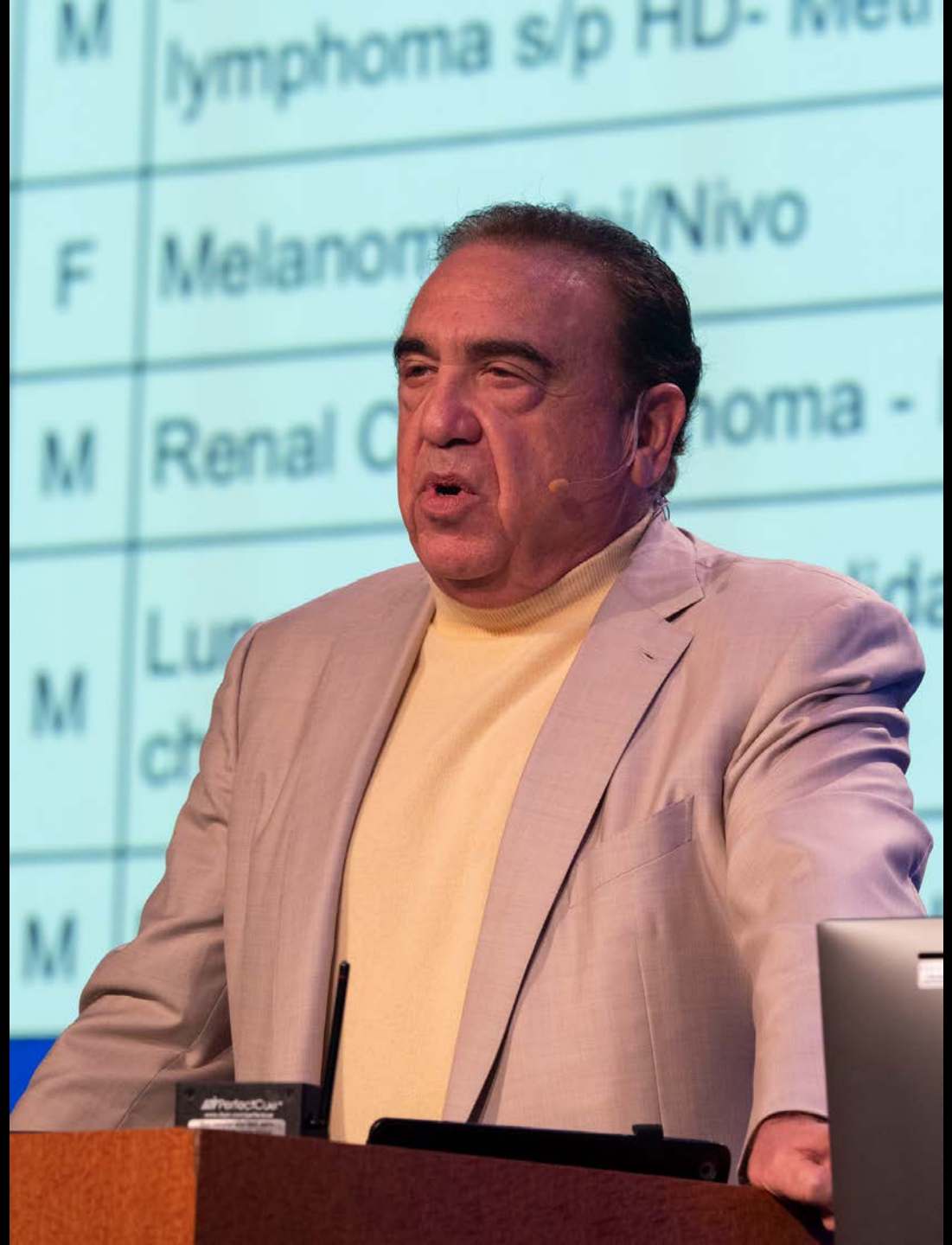
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Exploring Current Management Paradigms
for Patients with Acute Myeloid Leukemia
Not Eligible for Intensive Therapy
Friday, October 25, 2019, 1:15 PM – 3:45 PM
Orlando, Florida
Faculty
Courtney D DiNardo,
Keith W Pratz,
Richard M Ston
Moderat
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Levis, MD, PhD
el A Pollyea, MD,

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YiR Acute Myeloid Leukemia and Myelodysplastic Syndromes Faculty

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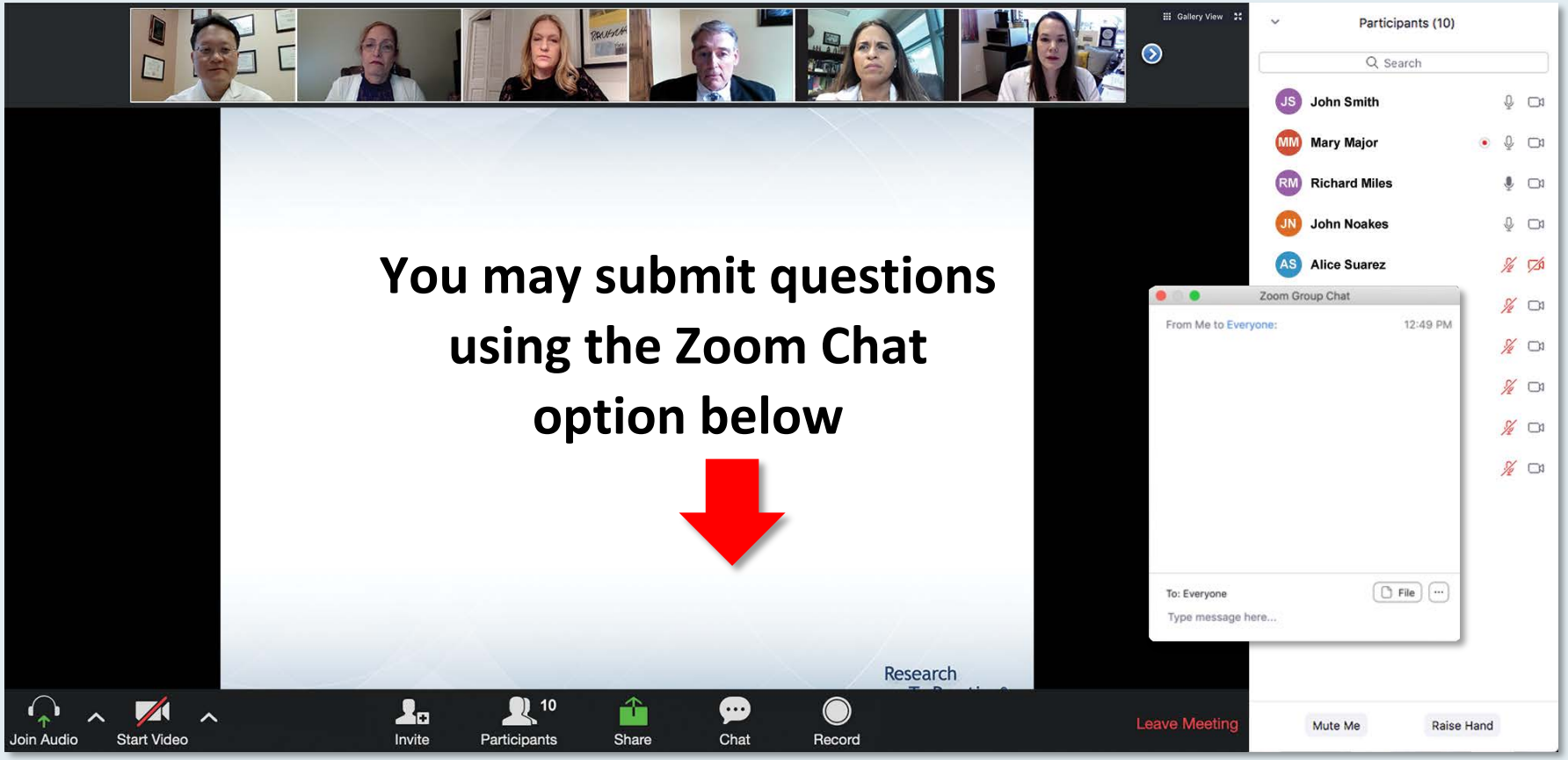
We Encourage Clinicians in Practice to Submit Questions



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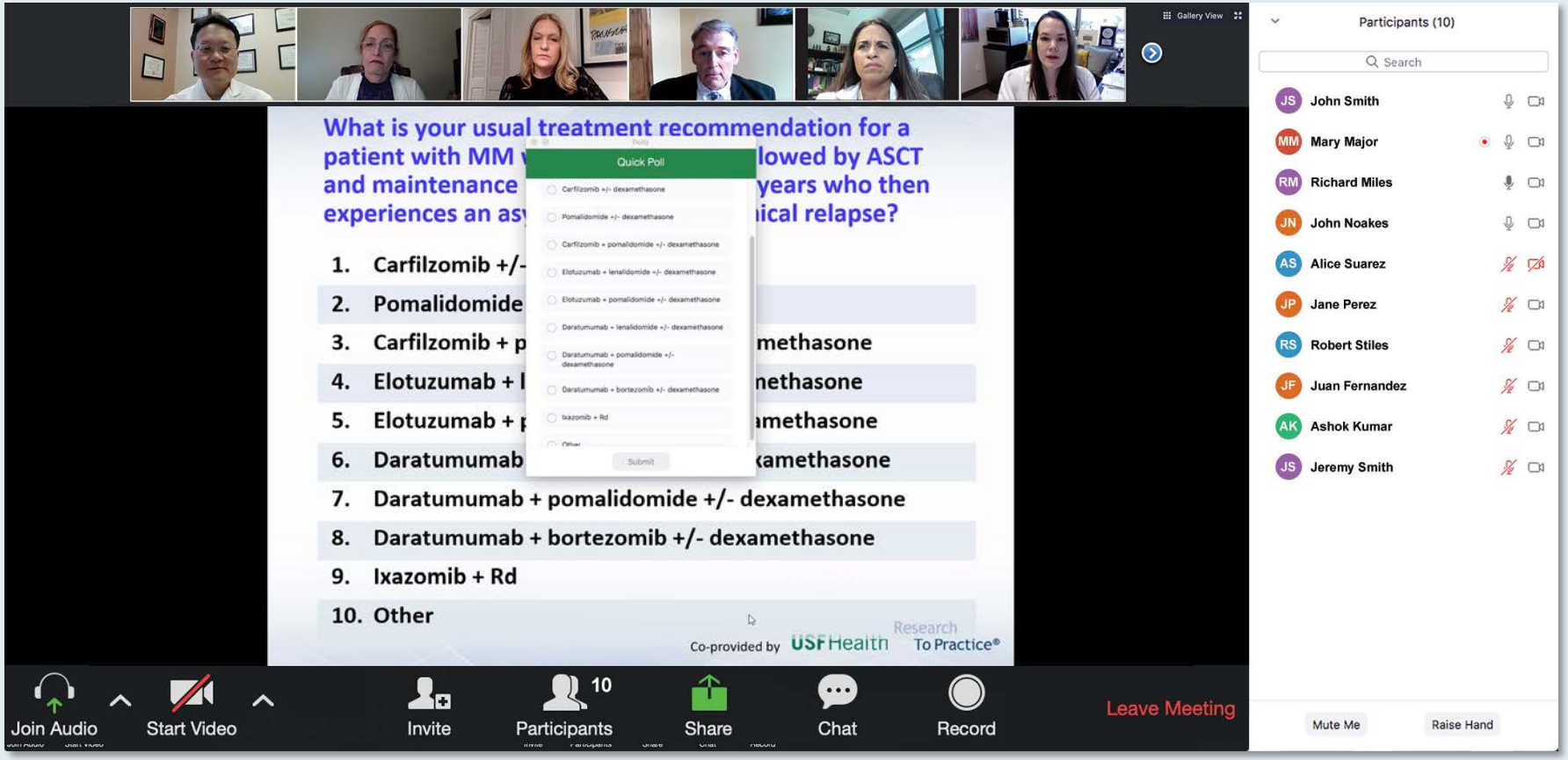

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Module 2: FLT3 inhibitors — Midostaurin, gilteritinib

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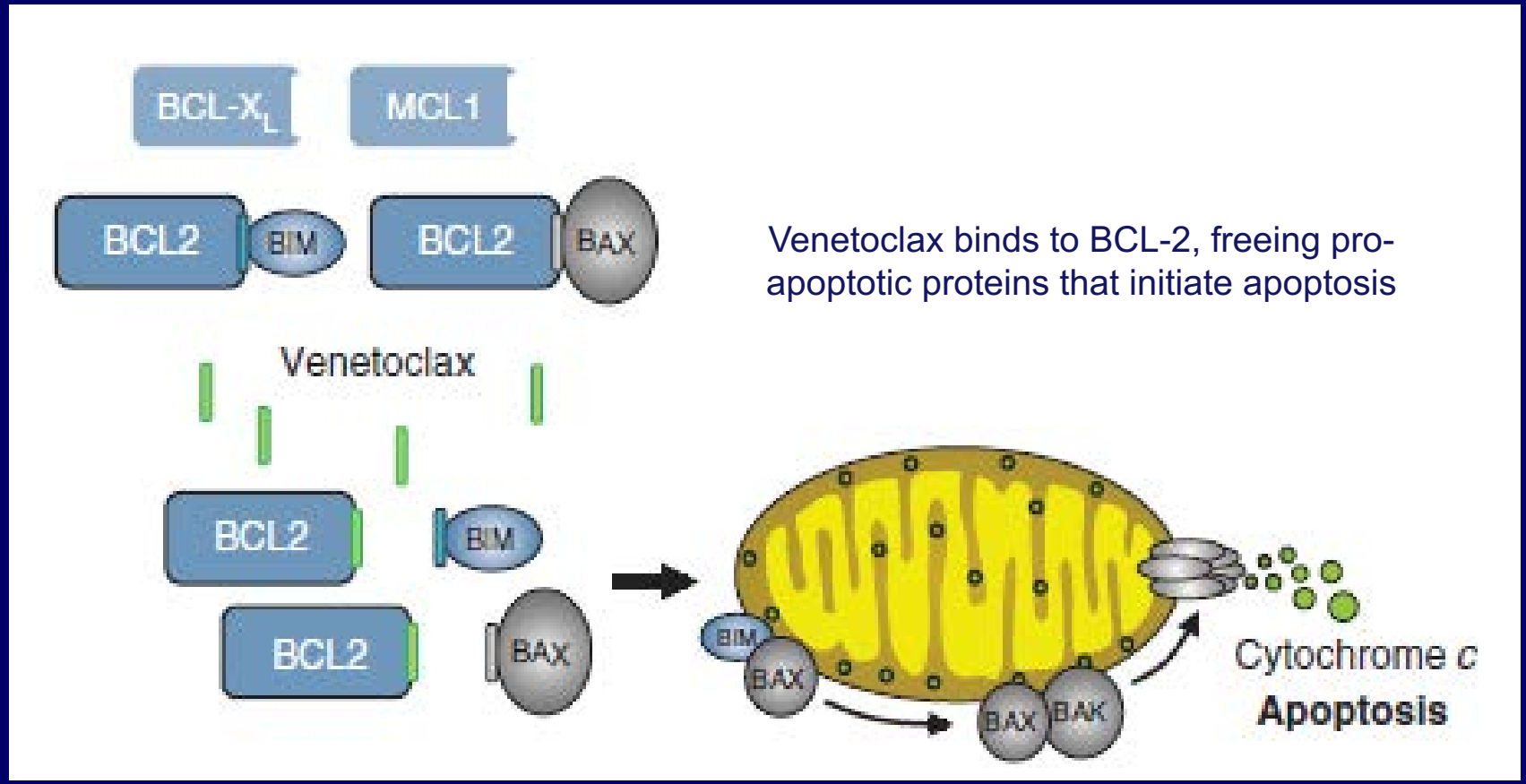
Module 1: Venetoclax combinations — Azacitidine, LDAC

- **Key Relevant Data Sets**
  - VIALE-A: Azacitidine + venetoclax for previously untreated AML
  - VIALE-C: Venetoclax + LDAC for newly diagnosed AML ineligible for intensive chemotherapy
  - Cladribine/LDAC + venetoclax in older patients with AML
  - Acquired mutations in BAX confer resistance to BH3 mimetics in AML

Venetoclax: BCL-2 Selective Inhibitor

BCL-2 overexpression allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins



Venetoclax binds to BCL-2, freeing pro-apoptotic proteins that initiate apoptosis

Courtesy of Richard M Stone, MD

Konopleva M, et al. *Cancer Discov*. 2016. Epub ahead of print. Lin T, et al. ASCO 2016. Abstract 7007.

Azacitidine ± Venetoclax (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 FEV_1 ≤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

Randomization 2:1
N = 433*

Treatment

Venetoclax + Azacitidine
(n = 286)
Venetoclax 400 mg PO, daily, days 1–28
+ Azacitidine 75 mg/m² SC /IV days 1–7

Placebo + Azacitidine
(n = 145)
Placebo daily, days 1–28
+ Azacitidine 75 mg/m² SC /IV days 1–7

Endpoints

Primary

- Overall survival

Secondary

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

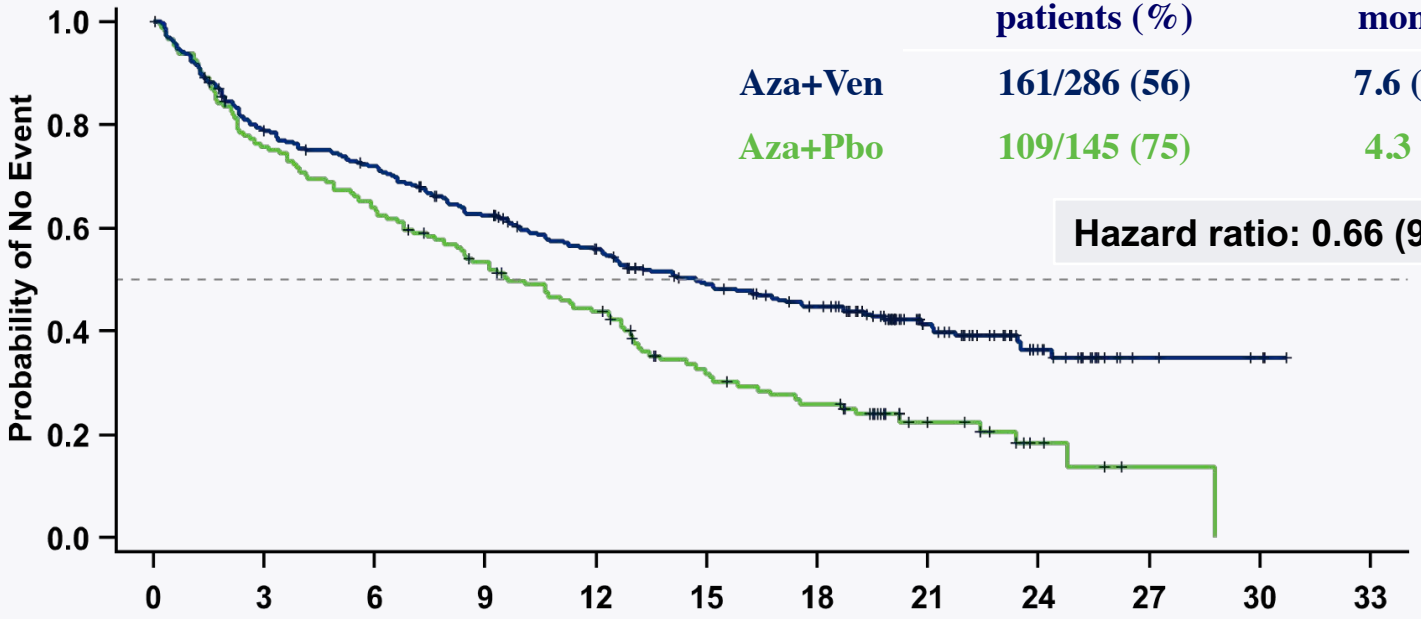
Randomization Stratification Factors	Age (<75 vs. ≥75 years); Cytogenetic risk (intermediate, poor); region
Venetoclax dosing ramp-up	**Cycle 1 ramp-up** Day 1: 100 mg, Day 2: 200 mg, Day 3 - 28: 400 mg **Cycle 2** Day 1-28: 400 mg

DiNardo CD et al. EHA 2020. Abstract LB2601; DiNardo CD et al. NEJM 2020

Courtesy of Richard M Stone, MD

VIALE-A: AZA ± VEN in AML — Overall Survival

	No. of events/No. of patients (%)	Median duration of study treatment, months (range)	Median overall survival, months (95% CI)
Aza+Ven	161/286 (56)	7.6 (<0.1 – 30.7)	14.7 (11.9 – 18.7)
Aza+Pbo	109/145 (75)	4.3 (0.1 – 24.0)	9.6 (7.4 – 12.7)



Hazard ratio: 0.66 (95% CI: 0.52 – 0.85), *P* <.001

Patients at Risk

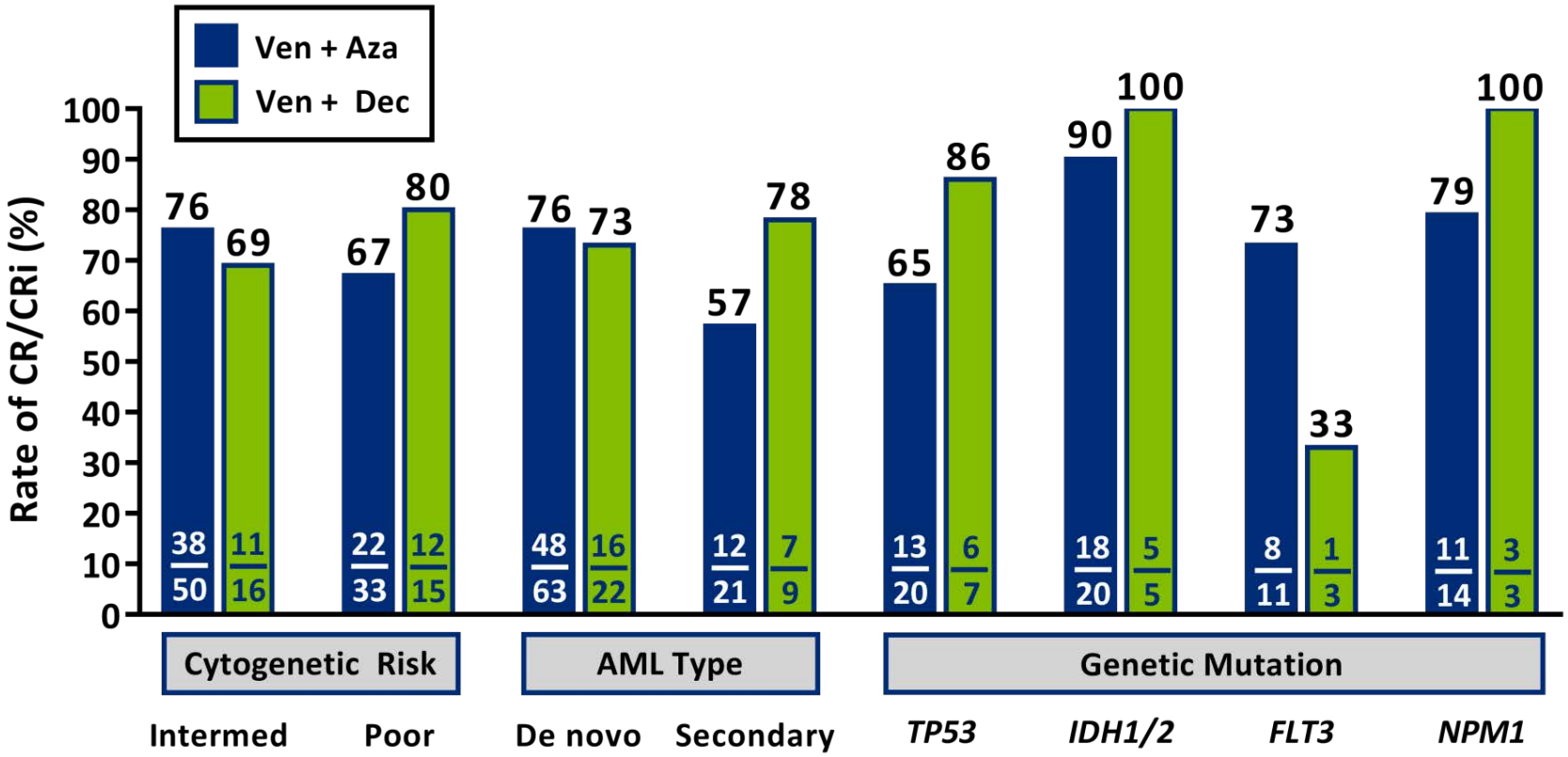
Aza+Ven	286	219	198	168	143	117	101	54	23	5	3	0
Aza+Pbo	145	109	92	74	59	38	30	14	5	1	0	0

Median follow-up time: 20.5 months (range: <0.1 – 30.7)

DiNardo CD et al. NEJM 2020

Courtesy of Richard M Stone, MD

Response Rates of CR/CRi by Patient Subgroups

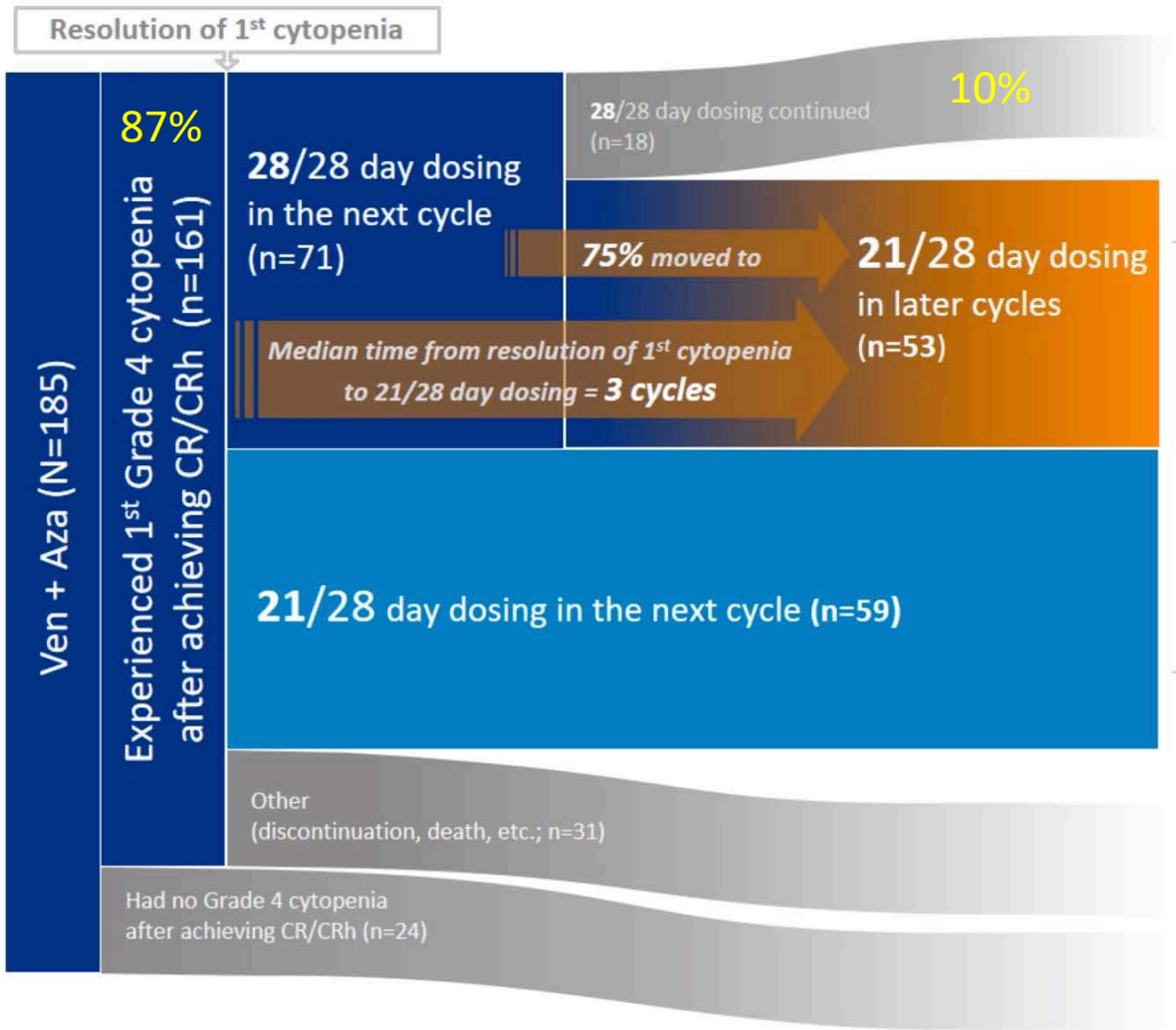


Venetoclax with HMAs induces rapid, deep, and durable responses in older patients with AML | ASH 2018

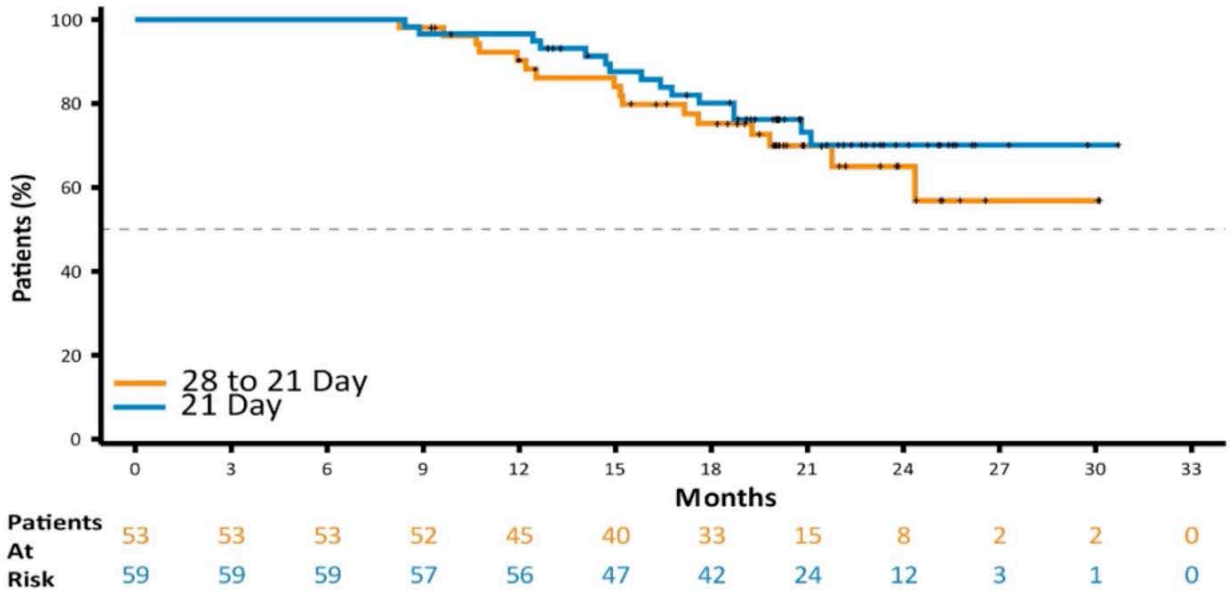
Pollyea D, et al, ASH 2018; Dinardo C, Blood, 2019

Courtesy of Richard M Stone, MD

A Sub-group of Patients in the Ven + Aza Arm Received a 21/28 Day Schedule After Their 1st Grade 4 Cytopenia*



Overall Survival Among Patients Who Achieved CR/CRh in VIALE-A (Converted to 21-Day Dosing After 1st Grade 4 Cytopenia)



- VIALE-A was not designed to evaluate differences between 21/28-day and 28/28-day dosing per cycle

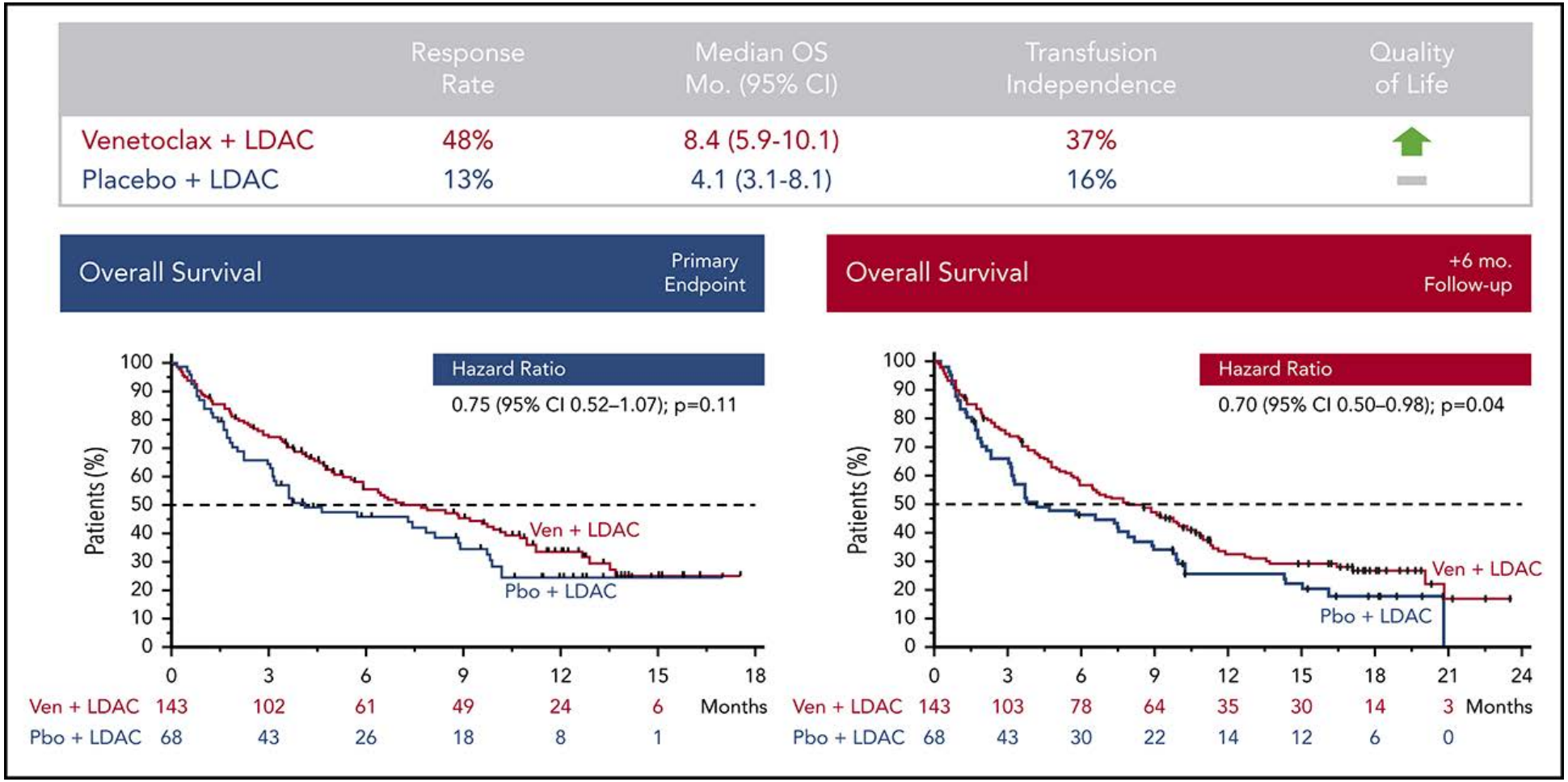
* Grade 4 cytopenia lasting ≥7 days

Keith Pratz #1944

Courtesy of Andrew H Wei, MBBS, PhD

VIALE-C: Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy — a phase 3 randomized placebo-controlled trial

	Response Rate	Median OS Mo. (95% CI)	Transfusion Independence	Quality of Life
Venetoclax + LDAC	48%	8.4 (5.9-10.1)	37%	↑
Placebo + LDAC	13%	4.1 (3.1-8.1)	16%	—



Andrew H. Wei, Blood, 2020.

Courtesy of Richard M Stone, MD

VIALE-C trial (Wei et al, EHA, 2020)

Median f/u 17.5 mo* (OS and EFS difference statistically significant)
Note: prior HMA allowed

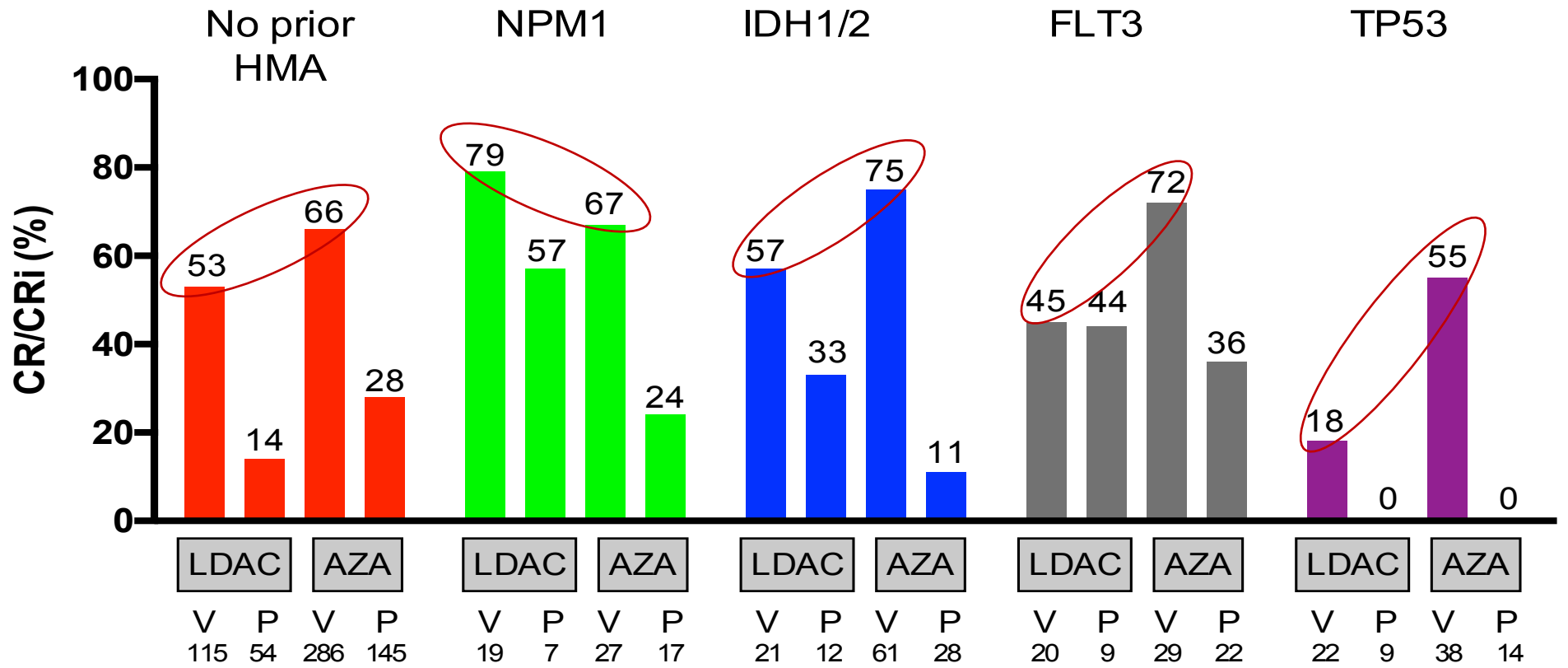
	Ven (600 mg/d) + cytarabine 20 mg/^{2}/d d1-10	Cytarabine 20 mg/m^2/d d1-10
n	143	60
CR/CRh	48%	15%
Overall survival (months)	8.4	4.1
Event-free survival (months)	4.9	2.1

*w 6 add'n f/u months, OS diff became significant

Courtesy of Richard M Stone, MD

Comparison of HMA or LDAC + venetoclax responses

		VIALE-C		VIALE-A	
		VEN (n=143)	**PBO (n=68)**	**VEN (n=286)**	**PBO (n=145)**
Response	CR/CRi	48%	13%	66%	28%
	CR	28%	7%	37%	18%
	Duration of CR	**17 mo**	8 mo	**17.5 mo**	13.5 mo



Wei et al, Blood 2020; EHA 2020, Di Nardo et al, EHA 2020

Courtesy of Andrew H Wei, MBBS, PhD

Practical issues in managing venetoclax-based therapy

Management during cycle 1 of VEN-AZA or VEN-LDAC

Cycle 1	Action
Day 21 bone marrow	If blasts ≥5%, proceed to next cycle
	If blasts <5%, start next cycle when CRh: neutrophils ≥0.5 x 10^9/L and platelets ≥50 x 10^9/L. Use 21-day VEN for next cycle
By day 35, if neutrophils <0.5 x 10^9/L	Commence G-CSF 3x/wk until recovery
By day 42	If neutrophils ≥0.5 x 10^9/L and platelets ≥25 x 10^9/L. Proceed to next cycle using 14-day VEN.
	If neutrophils <0.5 x 10^9/L and/or platelets <25 x 10^9/L. Defer next cycle.
If prolonged grade 4 cytopenia despite bone marrow blast clearance	Consider allogeneic hematopoietic stem cell transplant

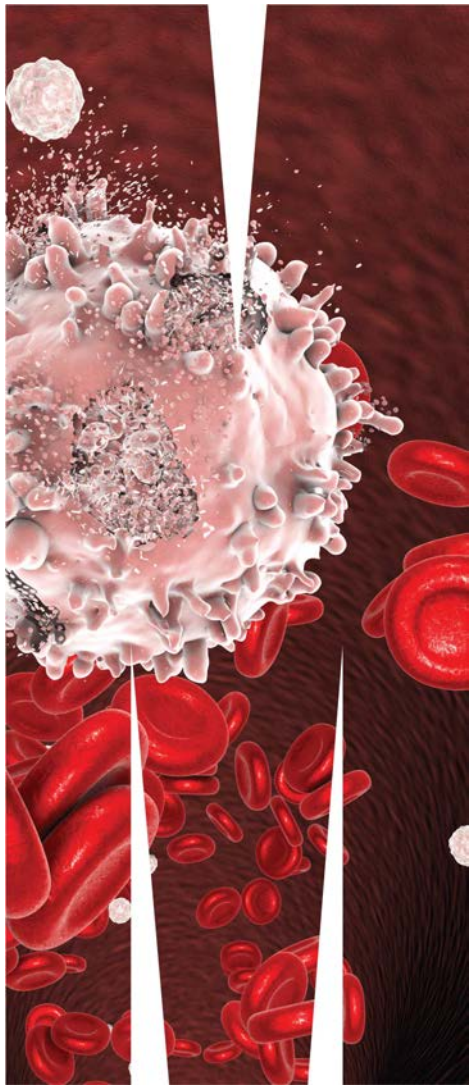
Courtesy of Andrew H Wei, MBBS, PhD

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?

a. 7 + 3 induction
b. Azacitidine
c. Decitabine
d. Azacitidine + venetoclax
e. Decitabine + venetoclax
f. Low-dose cytarabine + venetoclax
g. Other

MONASH University

Acquired mutations in BAX confer resistance to BH3-mimetics in Acute Myeloid Leukemia



Donia M. Moujalled[1,2], Fiona C. Brown[1,2], Michael Dengler[3], Giovanna Pomilio[1,2], Natasha Anstee[1,2], Veronique Litalien[2], Ella Thompson[5,6], Thomas Morley[2], Sarah Macraild[2], Chyn Chua,[1,7] Sebastien Banquet[4], Maia Chanrion[4], Ana Leticia Maragno[4], Marie Schoumacher[4], Marco J. Herold[3,7], Guillaume Lessene[3,7], Jerry Adams[3,], Olivier Geneste[4], David C.S. Huang[3], Andrew W. Roberts[3,5,6] Piers Blombery,[5,6] Andrew H. Wei[1,2]

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5. University of Melbourne, Parkville, Melbourne, Australia
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7. Department of Medical Biology, Department of Pharmacology and Therapeutics University of Melbourne, Melbourne, Australia

Abstract #263

Courtesy of Andrew H Wei, MBBS, PhD

ACBD Australian Centre for Blood Diseases

theAlfred

AML patients evaluated on venetoclax-based therapies

VEN-based therapy	VEN dose	Time to failure (months)							
		1	2	3	4	5	6	6 - 12	>12
Low intensity	100								
	ND								
	ND								
	100								
	600								
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	ND								
	100			*					
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High intensity	50								
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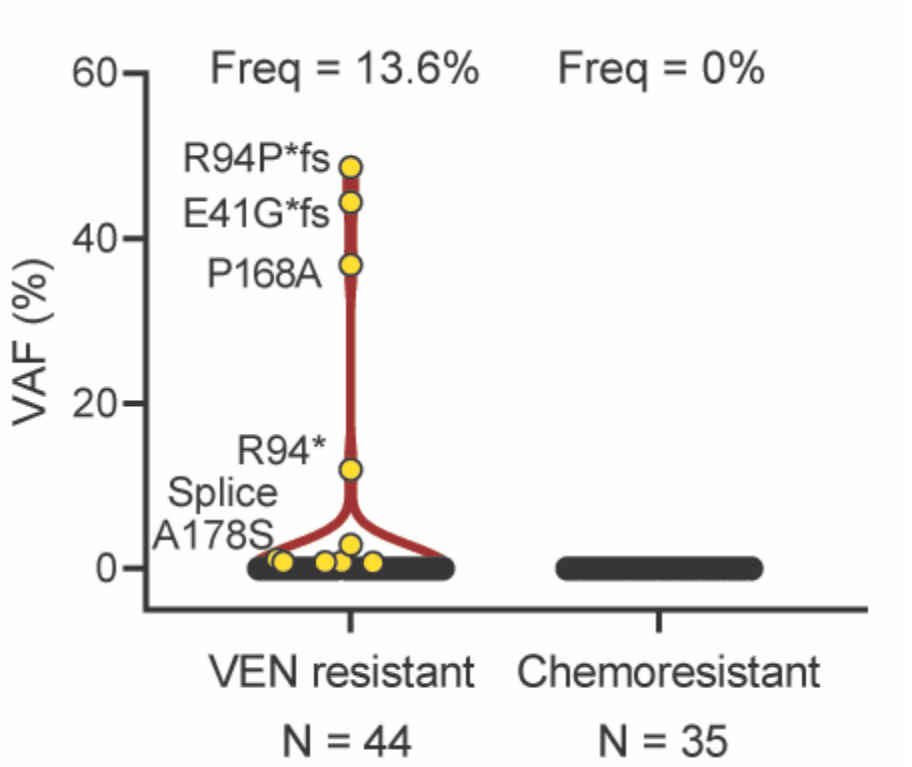

= *time in remission* = *relapsed disease* *= *BAX* variant

Courtesy of Andrew H Wei, MBBS, PhD

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

a. 7 + 3 induction
b. CPX-351
c. Decitabine
d. Decitabine + venetoclax
e. Azacitidine + venetoclax
f. Low-dose cytarabine + venetoclax
g. Other

Agenda

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Module 1: Venetoclax combinations — Azacitidine, LDAC

Module 2: FLT3 inhibitors — Midostaurin, gilteritinib

Module 3: IDH inhibitors — Ivosidenib, enasidenib

Module 4: Oral azacitidine (CC-486)

Module 5: Secondary AML — CPX-351

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Module 6: Lower-risk MDS — Luspatercept, imetelstat

Module 7: Higher-risk MDS — Decitabine + cedazuridine, azacitidine + venetoclax, magrolimab, APR-246, pevonedistat

Module 2: FLT3 inhibitors — Midostaurin, gilteritinib

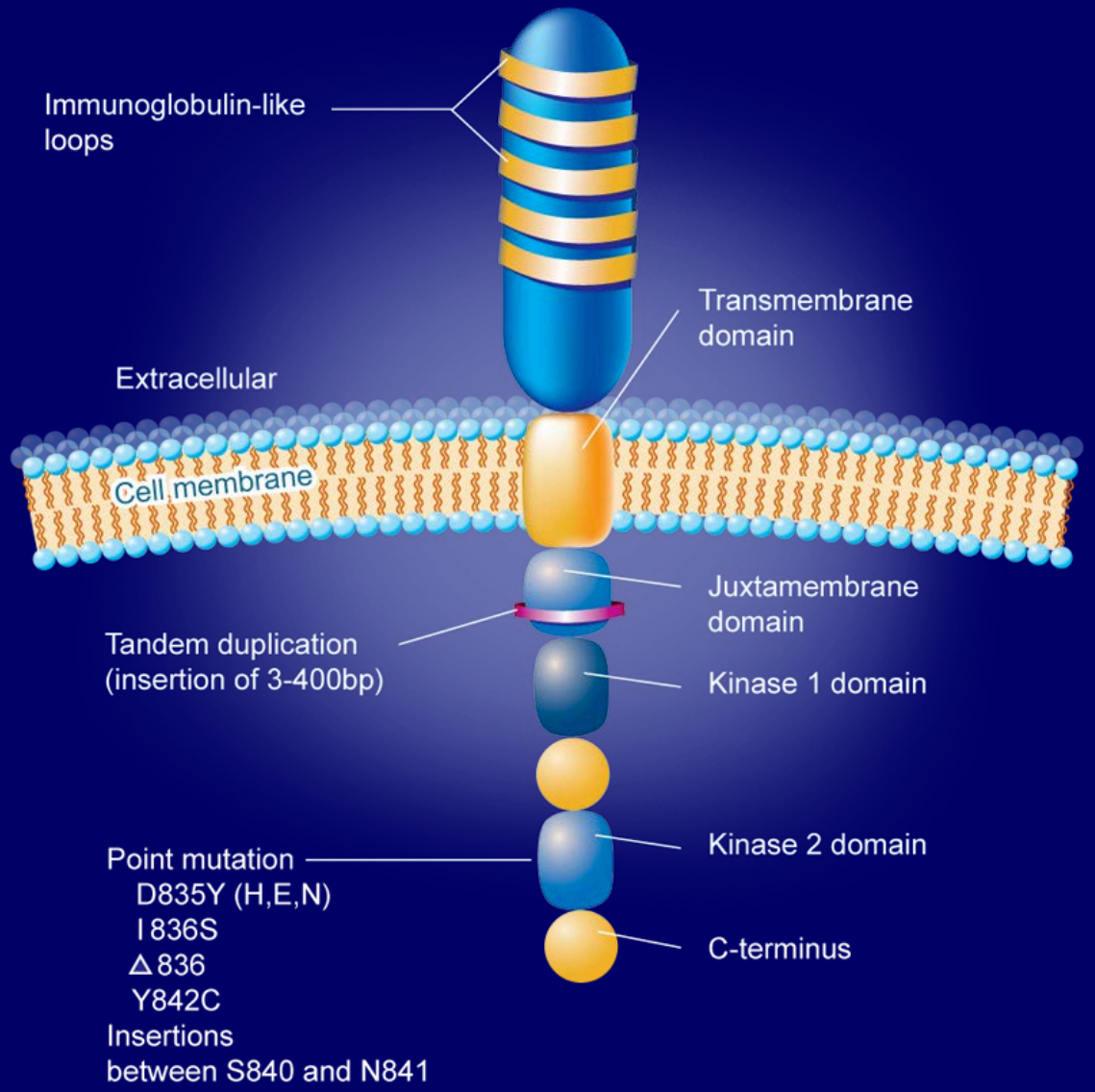
- **Key Relevant Data Sets**
  - ADMIRAL: Gilteritinib or chemotherapy for R/R FLT3-mutated AML
  - LACEWING: Gilteritinib +/- azacitidine vs azacitidine in patients newly diagnosed with FLT3 mutations ineligible for intensive induction chemotherapy

FLT3 Structure and Activating Mutations

Over-expression is common

25-30%

5-10%



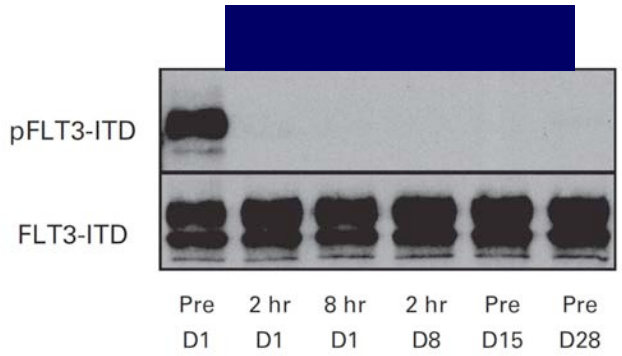
Both mutations cause spont dimerization,

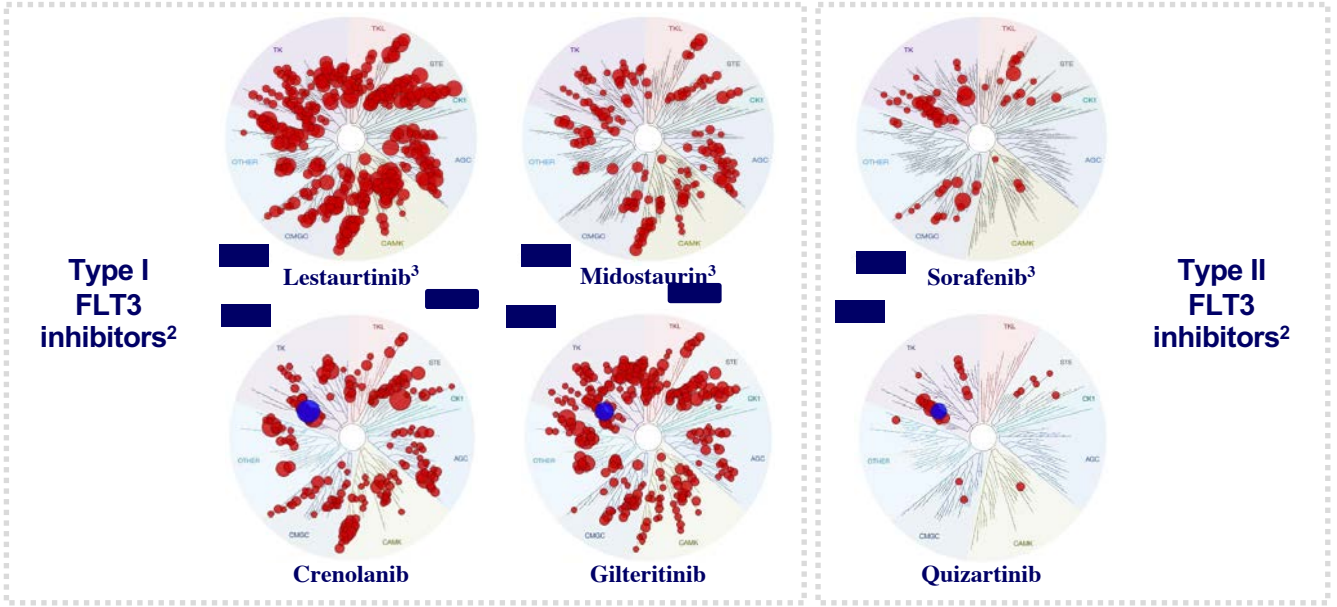
ligand independent growth, and MPD in murine model

Litzow MR. *Blood*. 2005;106:3331-3332.

Courtesy of Richard M Stone, MD

Quizartinib and Gilteritinib: Second Generation FLT3 Inhibitors



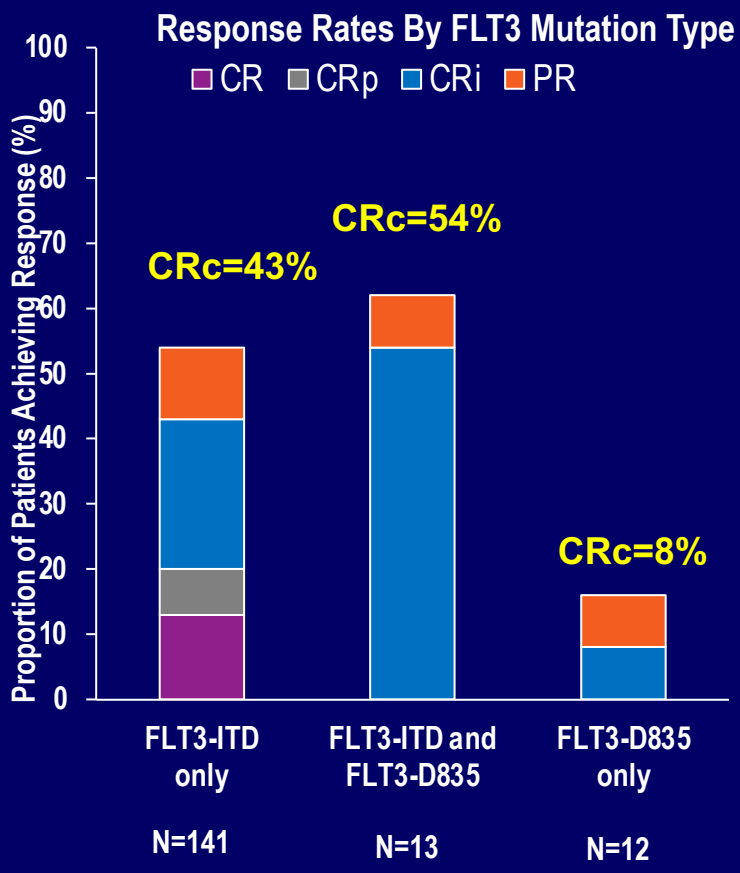


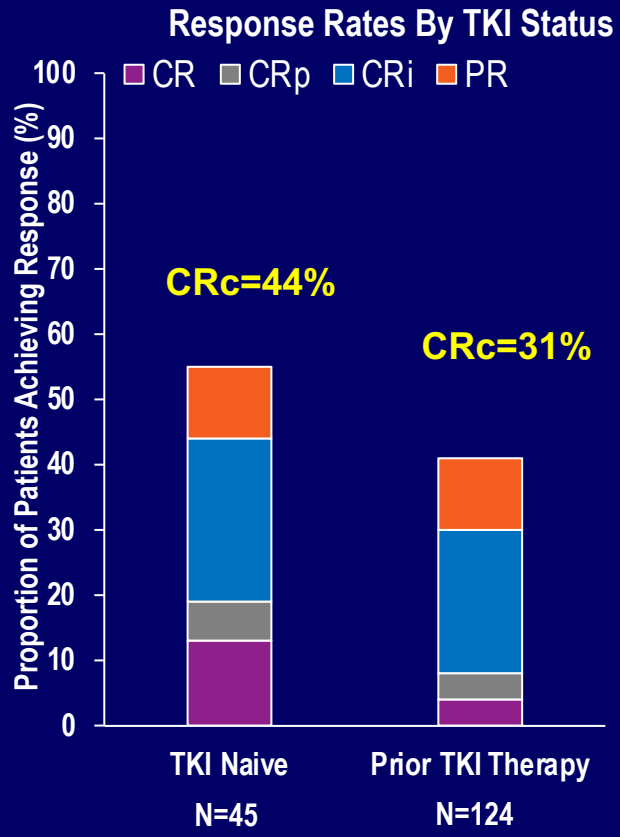
- Quizartinib is potent in vivo than any other FLT3 inhibitor to date[4,5]
- But selection of resistance with FLT3-TKD mutations
- Possible QT prolongation at higher doses

- Gilteritinib 'hits' both ITD and TKD subtypes
- Well tolerated

Courtesy of Richard M Stone, MD

Antileukemic Response to ≥80 mg/day Gilteritinib in FLT3^{mut+} Patients by Mutation Type and TKI Status

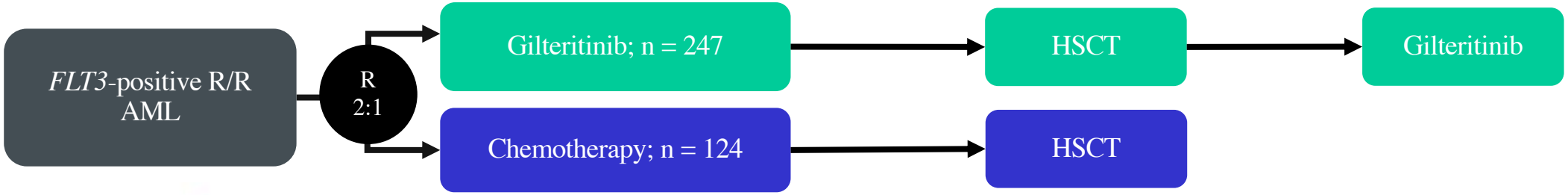


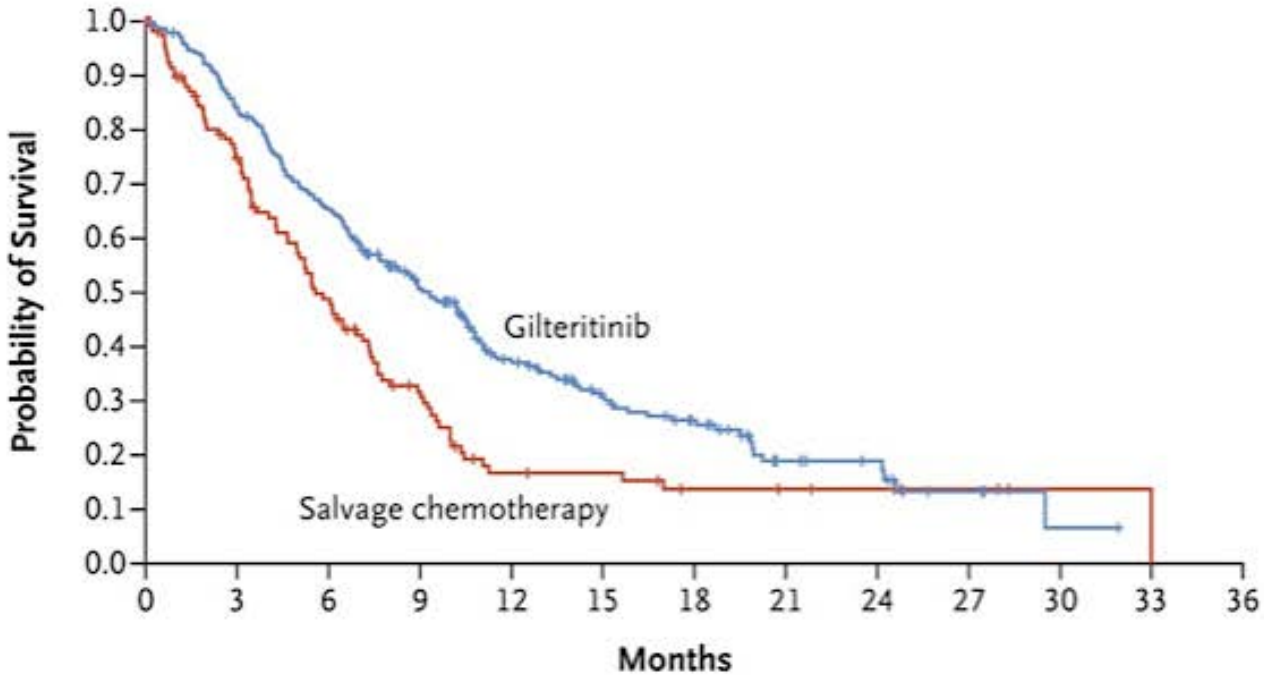


Perl et al, Lancet Oncology , 2017

Courtesy of Richard M Stone, MD

Gilteritinib: Phase 3 ADMIRAL Trial





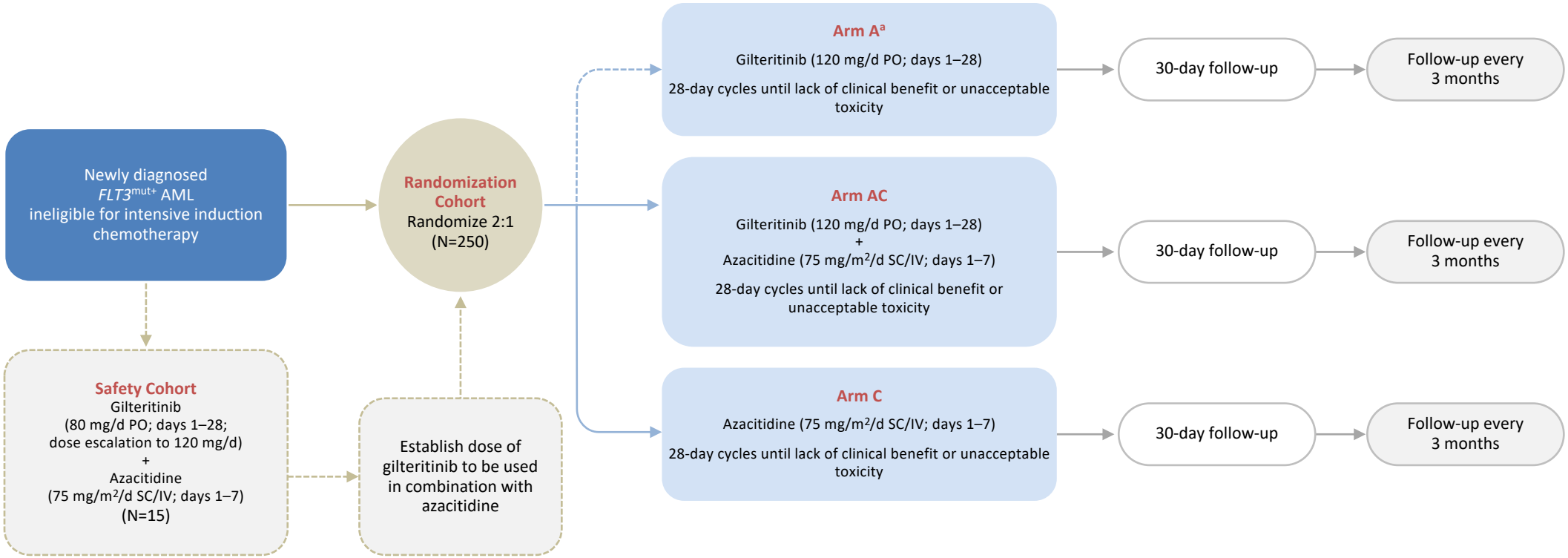
	Median Overall Survival (95% CI)
	mo
Gilteritinib	9.3 (7.7–10.7)
Salvage Chemotherapy	5.6 (4.7–7.3)

Hazard ratio for death, 0.64 (95% CI, 0.49–0.83)
P<0.001

Perl, A et al , NEJM, 2019

Courtesy of Richard M Stone, MD

LACEWING Study Design (Wang E, et al, ASH #27, 2020)



[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.

Courtesy of Richard M Stone, MD

Gilteritinib in Combination with Azacitidine Did Not Meet Endpoint of Overall Survival in Newly Diagnosed FLT3 Mutation-Positive Acute Myeloid Leukemia Patients Ineligible for Intensive Induction Chemotherapy

TOKYO, Dec. 21, 2020 The Phase 3 trial of gilteritinib plus azacitidine versus azacitidine alone in newly diagnosed FLT3 mutation-positive (FLT3mut+) acute myeloid leukemia (AML) patients who were ineligible for intensive induction chemotherapy did not meet its primary endpoint of overall survival at a planned interim analysis of the LACEWING trial. An independent Data Monitoring Committee recommended terminating the study for futility, concluding results are unlikely to show a statistically significant increase in overall survival. The trial has stopped enrollment and results are being reviewed for other action as needed.

Courtesy of Andrew H Wei, MBBS, PhD

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?

a. 7 + 3 induction + midostaurin
b. Hypomethylating agent (HMA)
c. HMA + venetoclax
d. HMA + venetoclax + FLT3 inhibitor
e. Low-dose cytarabine + venetoclax
f. Low-dose cytarabine + venetoclax + FLT3 inhibitor
g. Gilteritinib
h. Other

Agenda

Management of AML

Module 1: Venetoclax combinations — Azacitidine, LDAC

Module 2: FLT3 inhibitors — Midostaurin, gilteritinib

Module 3: IDH inhibitors — Ivosidenib, enasidenib

Module 4: Oral azacitidine (CC-486)

Module 5: Secondary AML — CPX-351

Treatment Strategies for MDS

Module 6: Lower-risk MDS — Luspatercept, imetelstat

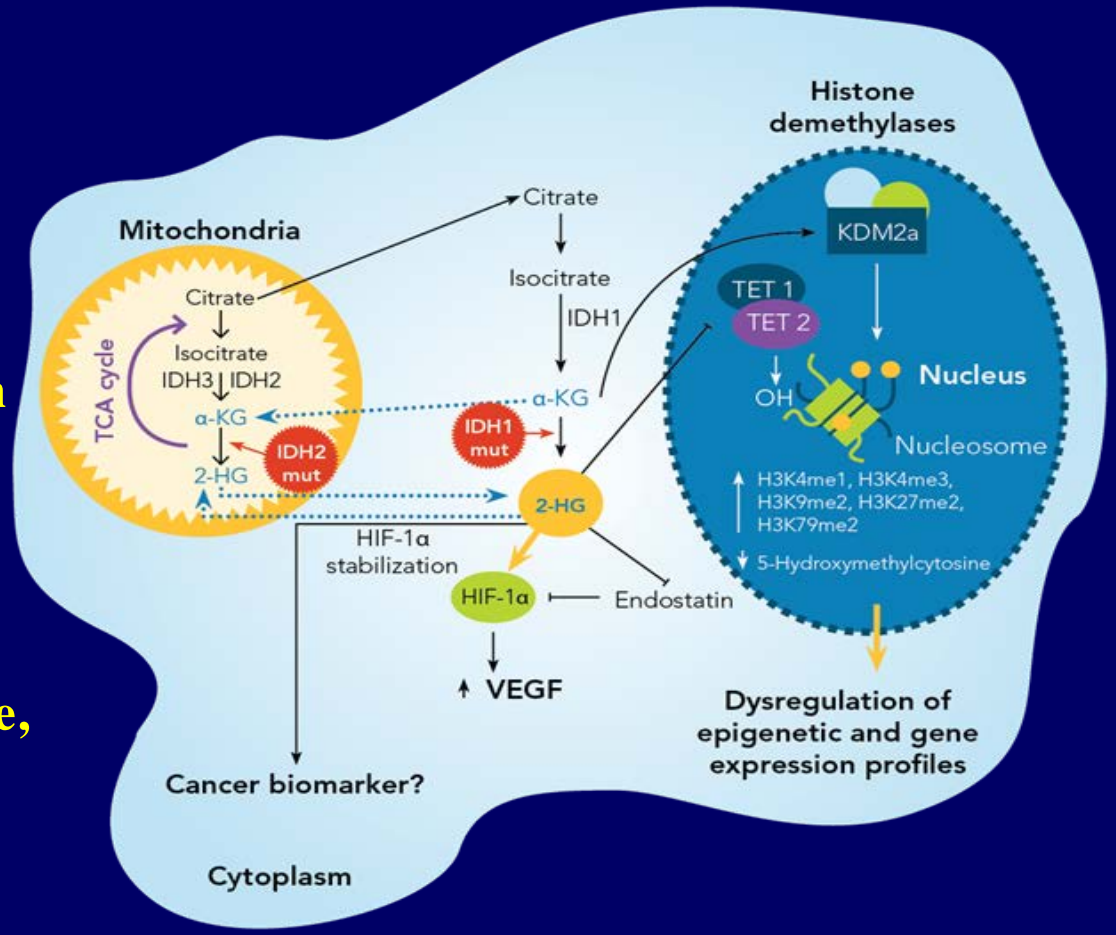
Module 7: Higher-risk MDS — Decitabine + cedazuridine, azacitidine + venetoclax, magrolimab, APR-246, pevonedistat

Module 3: IDH inhibitors — Ivosidenib, enasidenib

- **Key Relevant Data Sets**
  - Single-agent IDH1/2 inhibition for R/R AML
  - AG-221-AML-005: Enasidenib + azacitidine vs azacitidine alone for newly diagnosed AML
  - Ivosidenib or enasidenib in combination with 7 + 3 for newly diagnosed AML

Isocitrate Dehydrogenase (IDH) Mutations as a Target in AML

- **IDH is an enzyme of the citric acid cycle**
- **Mutant *IDH2* produces 2-hydroxyglutarate (2-HG), which alters DNA methylation and leads to a block in cellular differentiation**
- **AG-221 (CC-90007) is a selective, oral, potent inhibitor of the mutant *IDH2* (m*IDH2*) enzyme**



Courtesy of Richard M Stone, MD

IDH Single Agent Inhibitor Data in R/R Mut IDH AML

AG120=ivosidenib

- Most common AEs: diarrhea, fatigue, and pyrexia
- **Overall response rate of 35%** and a complete remission rate of 15%
- **In all response evaluable patients, an estimated 55% had treatment duration of at least 33%**
- **Differentiation syndrome**

AG221=enasidenib

- Most common AEs: nausea, fatigue, increase in bilirubin, diarrhea
- ORR 37% in 159 adults w R/R AML
  - CR 18%
  - Median duration of response of 6.9 months
- Differentiation syndrome

DiNardo C, et al. NEJM 2018. Stein E, et al. Blood 2019

Courtesy of Richard M Stone, MD

AG-221-AML-005: ENASIDENIB/AZACITIDINE VS AZACITIDINE – RESPONSE

- ORR and CR rate were both significantly higher with ENA + AZA *vs.* AZA Only

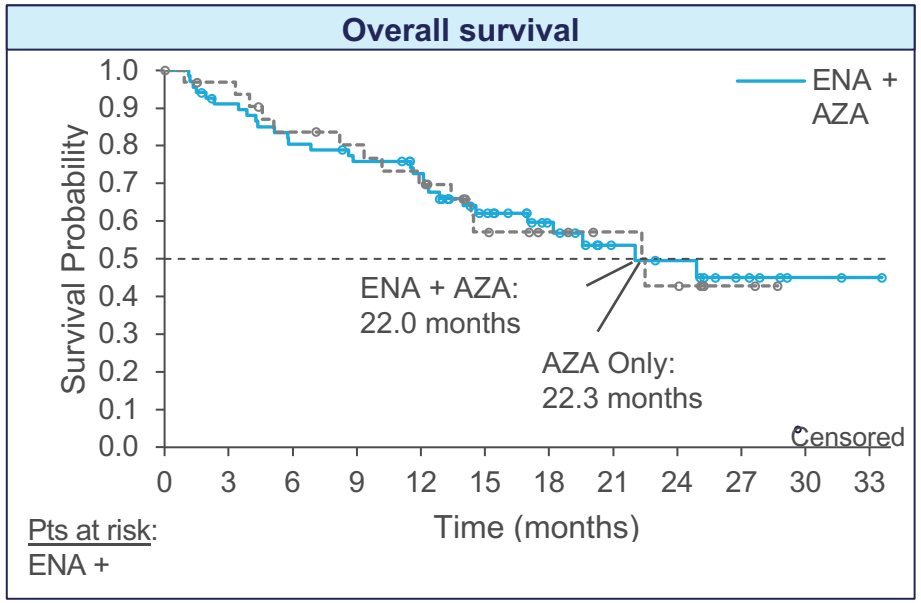
	ENA + AZA (n=68)		AZA Only (n=33)
Overall response (CR, CRi/CRp, PR, MLFS), n (%)	**48 (71)**		**14 (42)**
[ORR 95%CI]	[58, 81]		[26, 61]
***P* value**		**0.0064**	
CR, n (%)	**36 (53)**		**4 (12)**
[CR rate 95%CI]	[41, 65]		[3, 28]
***P* value**		**0.0001**	
CRi/CRp, n (%)	7 (10)		4 (12)
PR, n (%)	3 (4)		4 (12)
MLFS, n (%)	2 (3)		2 (6)
Stable disease, n (%)	13 (19)		13 (39)
Disease progression, n (%)	2 (3)		1 (3)
Not evaluable / Missing, n (%)	5 (7)		5 (15)
Time to first response, months, median (range)	1.9 (0.7–9.0)		2.0 (0.8–5.8)
Time to CR, months, median (range)	5.5 (0.7–19.5)		3.7 (3.0–4.1)
Duration of response, months, median [95%CI]	24.1 [11.1, NR]		12.1 [2.8, 14.6]

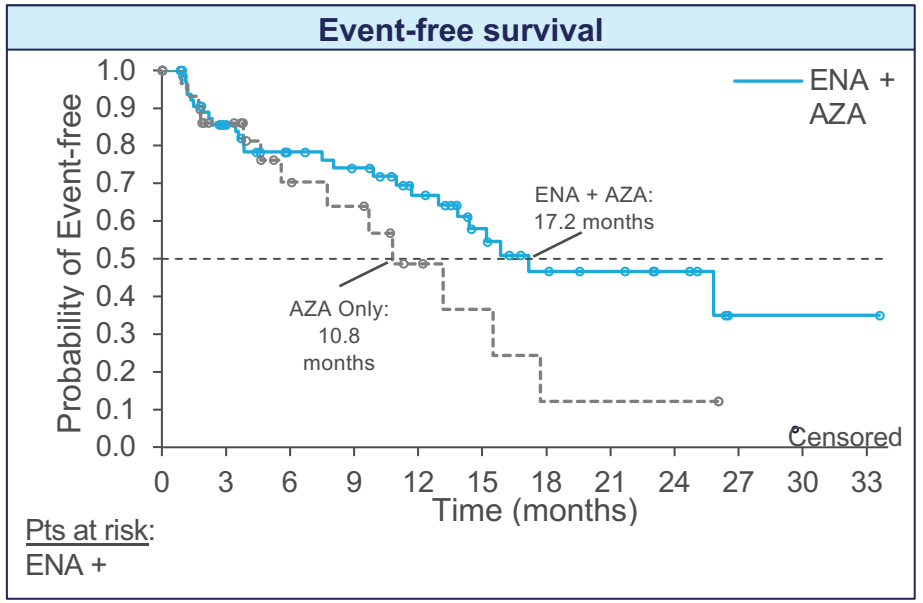
Data cutoff: August 19, 2019.
95%CI, 95% confidence interval; AZA, azacitidine; CR, complete remission; CRi/CRp, CR with incomplete hematologic or platelet recovery; ENA, enasidenib; MLFS, morphologic leukemia-free state; NR, not reached; ORR, overall response rate; PR, partial remission.

Courtesy of Richard M Stone, MD

AG-221-AML-005: ENASIDENIB/AZACITIDINE VS AZACITIDINE – SURVIVAL

- Median follow-up was 14 months in both treatment arms
- Median OS in the ENA + AZA group was 22.0 months, and in the AZA Only group was 22.3 months (HR 0.99 [95%CI 0.52, 1.87], *P*=0.9686)
  - Among pts in the ENA + AZA arm who achieved CR, median OS was not reached and estimated 1-year survival was over 90%
- Median EFS was 17.2 months in the ENA + AZA group, vs. 10.8 months in the AZA Only group (HR 0.59 [95%CI 0.30, 1.17], *P*=0.1278)
- In the AZA Only arm, 7 patients (21%) received subsequent treatment with enasidenib monotherapy





Data cutoff: August 19, 2019
EFS: time from randomization to AML relapse, disease progression (IWG AML 2003 criteria), or death from any cause, whichever occurred first.

Courtesy of Richard M Stone, MD

3+7 + IDH inhib (Stein et al, Blood, 2020)

Phase I trial: No safety signal

	Chemo+ ivosidenib (500 mg/d for mut IDH1)	Chemo + enasidenib (100 mg/d for mutant IDH2)
n	60	91
CR/CRh	55%	47%
IDH mut clearance in responders	39%	23%
Flow MRD neg in responders	80%	67%

Courtesy of Richard M Stone, MD

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?

a. 7 + 3 induction
b. HMA + venetoclax
c. HMA + venetoclax + ivosidenib
d. Low-dose cytarabine + venetoclax
e. Low-dose cytarabine + venetoclax + ivosidenib
f. HMA + ivosidenib
g. Ivosidenib
h. Other

What would you generally recommend as the next line of treatment for a 78-year-old patient with AML with an IDH2 mutation who has experienced disease progression after venetoclax/azacitidine?

a. Chemotherapy
b. HMA + venetoclax
c. HMA + venetoclax + enasidenib
d. Low-dose cytarabine + venetoclax
e. Low-dose cytarabine + venetoclax + enasidenib
f. HMA + enasidenib
g. Enasidenib
h. Other

Agenda

Management of AML

Module 1: Venetoclax combinations — Azacitidine, LDAC

Module 2: FLT3 inhibitors — Midostaurin, gilteritinib

Module 3: IDH inhibitors — Ivosidenib, enasidenib

Module 4: Oral azacitidine (CC-486)

Module 5: Secondary AML — CPX-351

Treatment Strategies for MDS

Module 6: Lower-risk MDS — Luspatercept, imetelstat

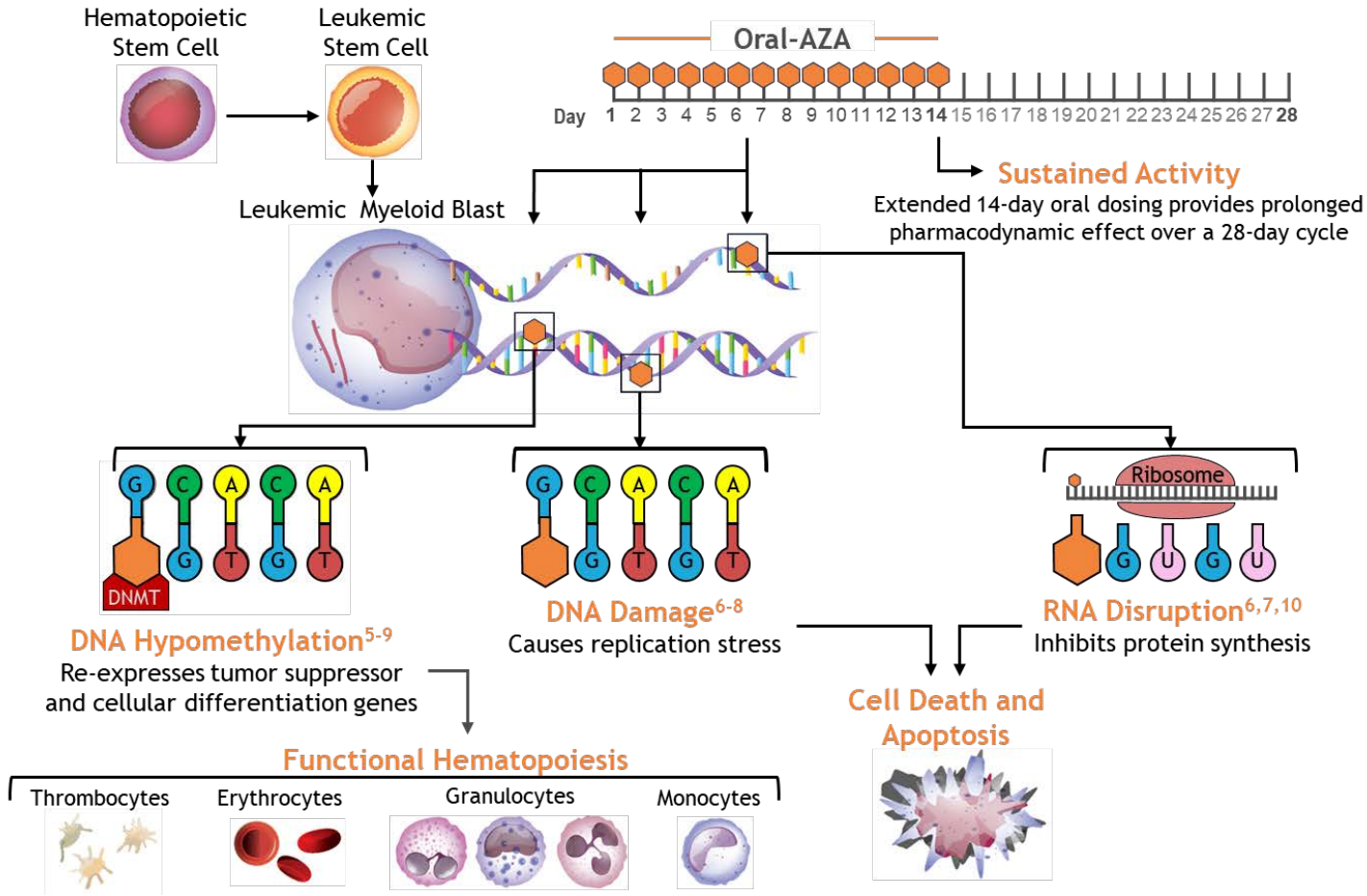
Module 7: Higher-risk MDS — Decitabine + cedazuridine, azacitidine + venetoclax, magrolimab, APR-246, pevonedistat

MODULE 4: Oral azacitidine (CC-486)

- **Key Relevant Data Sets**
  - QUAZAR AML-001 maintenance trial: CC-486 (oral azacitidine) in patients with AML in first remission
  - Escalated dosing schedules of CC-486 for patients experiencing first acute AML relapse: QUAZAR AML-001 maintenance trial

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]
  - 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

ORIGINAL ARTICLE

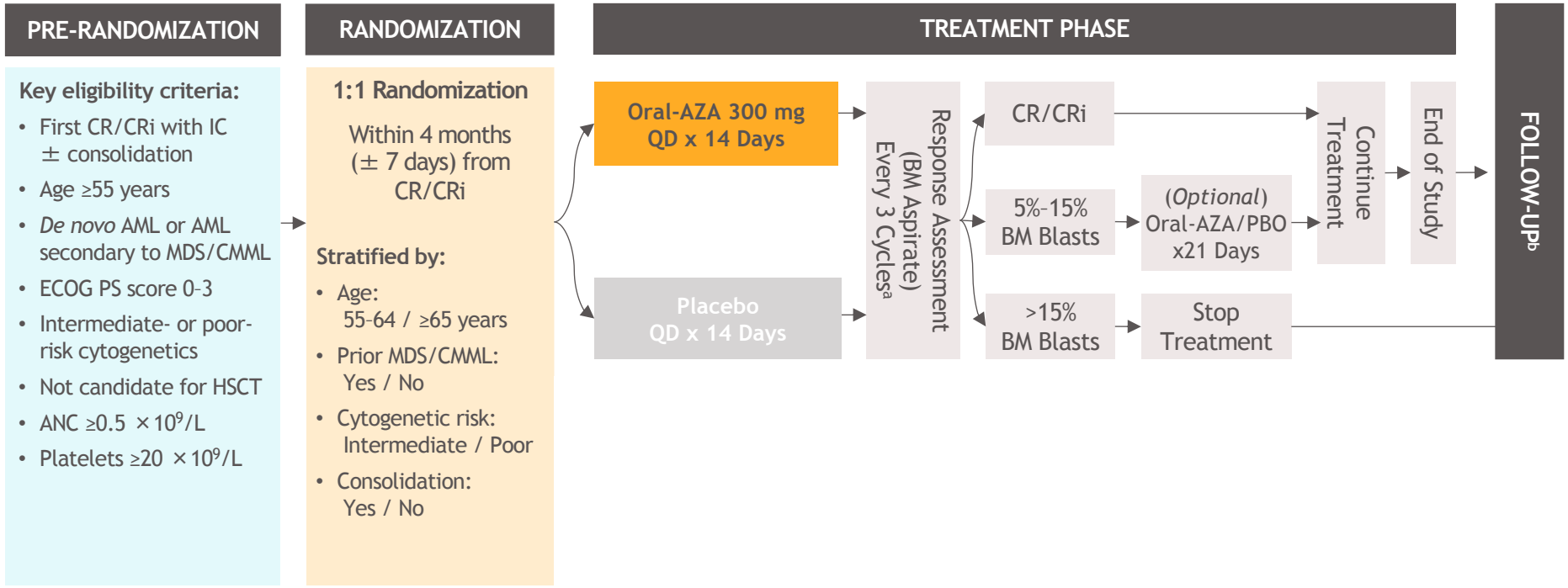
Oral Azacitidine Maintenance Therapy for Acute Myeloid Leukemia in First Remission

A.H. Wei, H. Döhner, C. Pocock, P. Montesinos, B. Afanasyev,* H. Dombret, F. Ravandi, H. Sayar, J.-H. Jang, K. Porkka, D. Selleslag, I. Sandhu, M. Turgut, V. Giai, Y. Ofran, M. Kizil Çakar, A. Botelho de Sousa, J. Rybka, C. Frairia, L. Borin, G. Beltrami, J. Čermák, G.J. Ossenkoppele, I. La Torre, B. Skikne, K. Kumar, Q. Dong, C.L. Beach, and G.J. Roboz, for the QUAZAR AML-001 Trial Investigators†

N Engl J Med 2020;383:2526-37.

QUAZAR AML-001: Study design and eligibility criteria

International, multicenter, placebo (PBO)-controlled, double-blind, randomized, phase III study of Oral-AZA as maintenance Tx in pts with AML in first remission post-IC

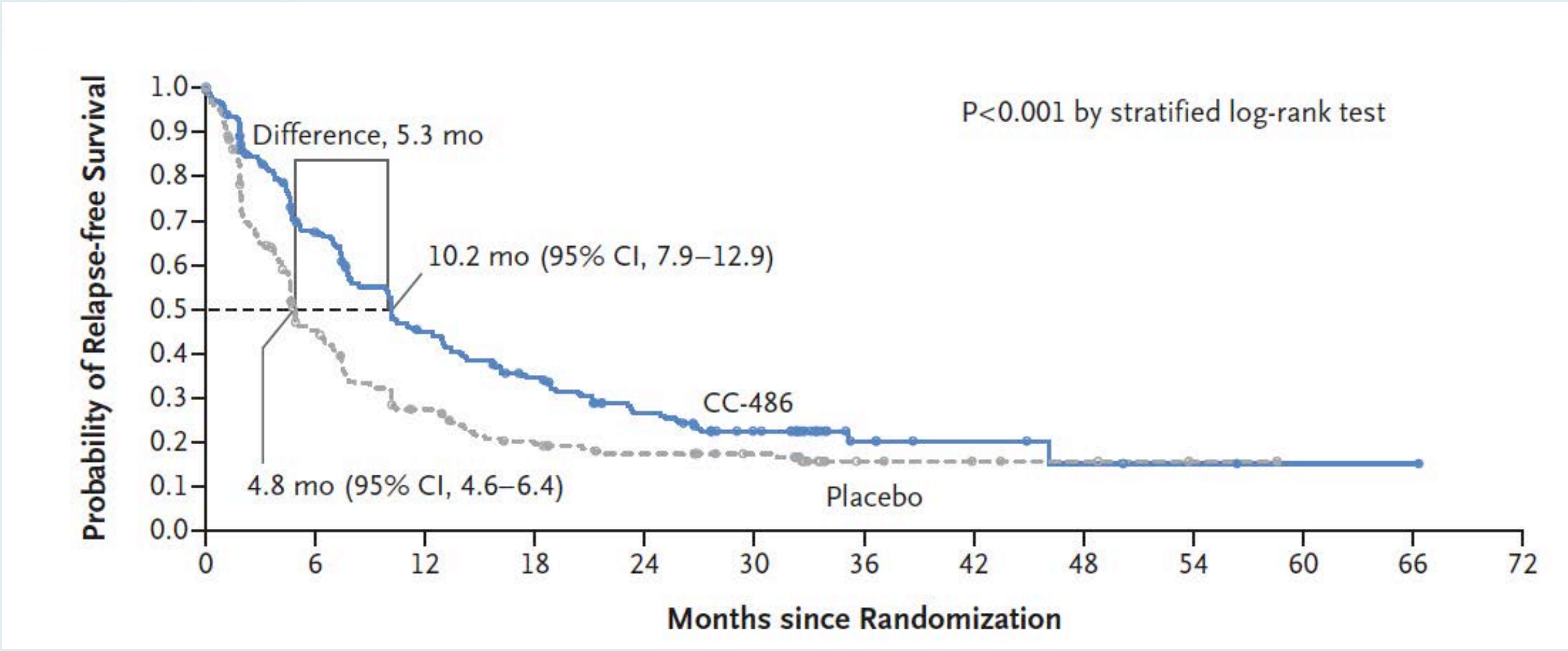


Courtesy of Richard M Stone, MD

[a]BM aspirates were collected every 3 cycles through cycle 24, at cycle 30 and cycle 36, and as clinically indicated thereafter. BM assessments were also performed as clinically indicated. [b]Patients were followed until death, withdrawal of consent, study termination, or loss to follow-up.

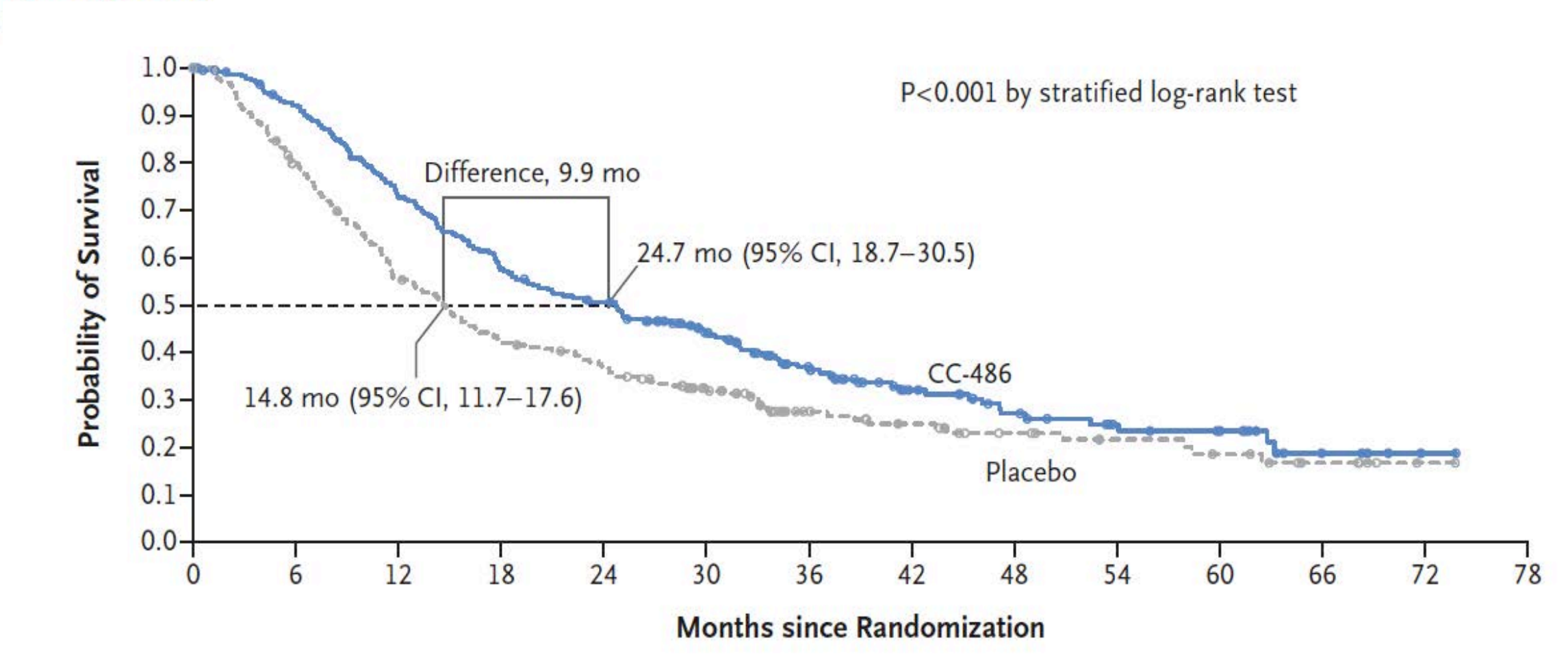
AML, acute myeloid leukemia; ANC, absolute neutrophil count; AZA, azacitidine; BM, bone marrow; CMML, chronic myelomonocytic leukemia; CR, complete remission; CRi, CR with incomplete blood count recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; HSCT, hematopoietic stem cell transplant; IC, induction chemotherapy; IWG, International Working Group; MDS, myelodysplastic syndromes; PBO, placebo.

QUAZAR AML-001: Relapse-Free Survival



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

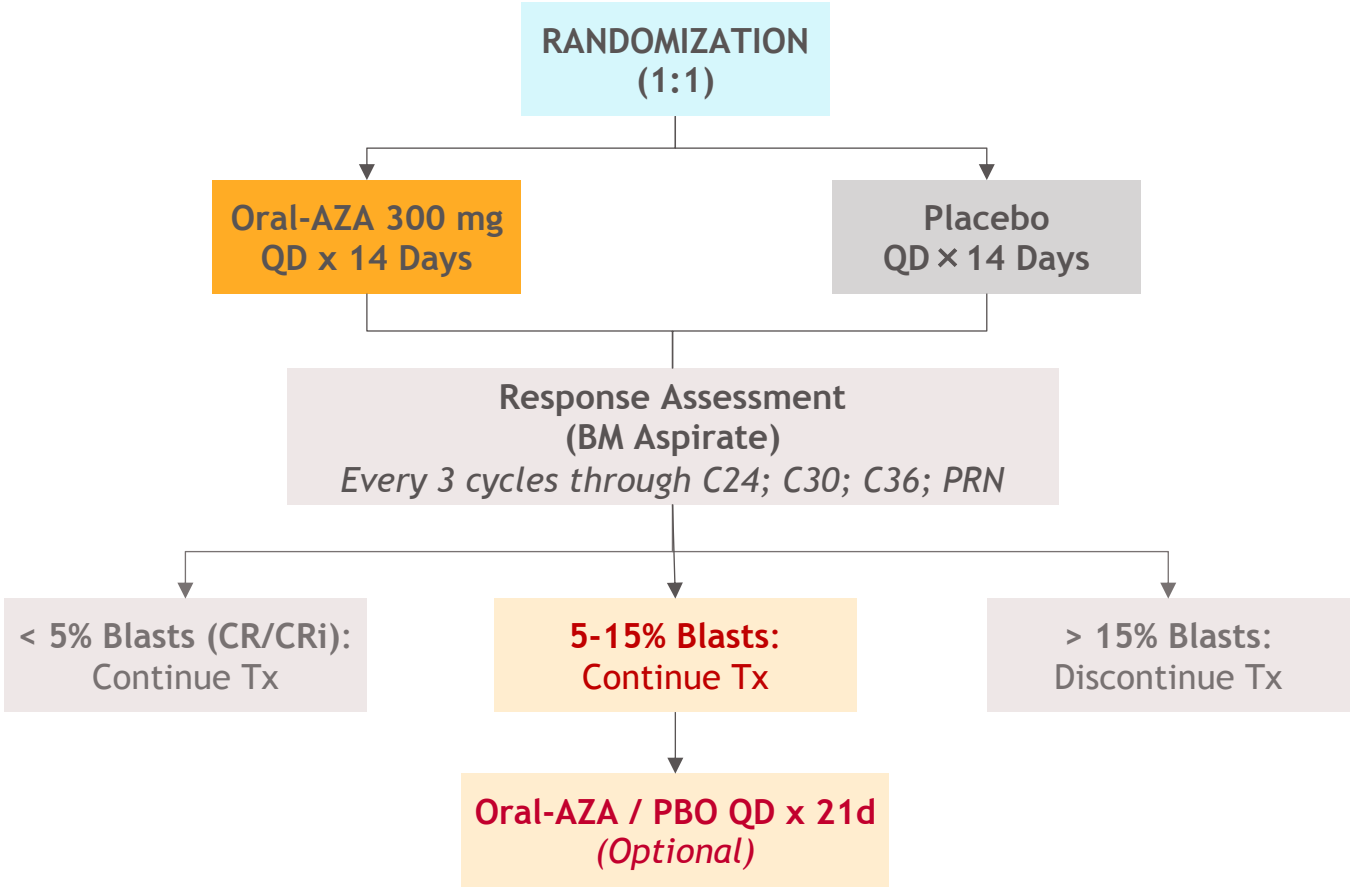
QUAZAR AML-001: Overall Survival



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

QUAZAR AML-001: Escalated dosing (Dohner H et al, Abs #111, ASH 2020)

- BM aspirates and PB smears were reviewed centrally to assess CR/CRi status (IWG 2003 criteria[1])
  - Unscheduled BM assessments allowed for pts who exhibited signs of relapse at routine clinic visits (every 2 weeks)
- Pts who had 5–15% blasts in BM or blood could receive study drug for **21 days per cycle** at the investigator's discretion

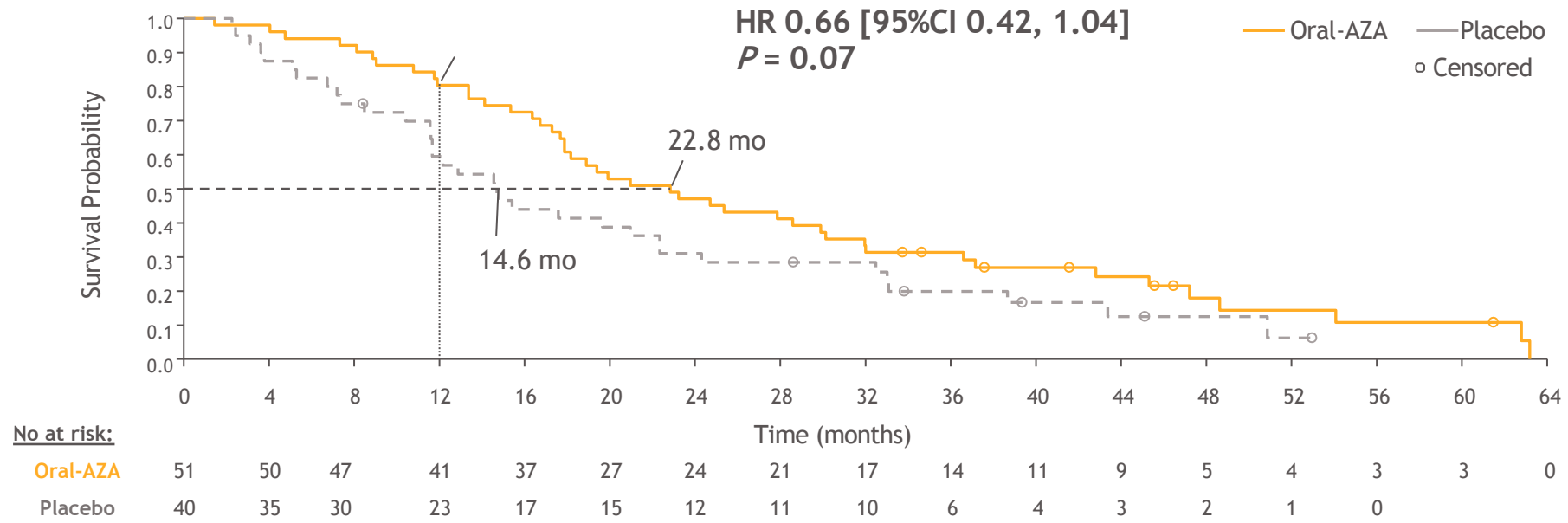


Courtesy of Richard M Stone, MD

1. Cheson et al. *J Clin Oncol*. 2003;21(24):4642-9.

AML, acute myeloid leukemia; AZA, azacitidine; BM, bone marrow; CR, complete remission; CRi, CR with incomplete blood count recovery; IWG, International Working Group; PB, peripheral blood; pts, patients; Tx, treatment.

QUAZAR AML-001: 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.

Dohner H et al, Abs #111, ASH 2020

Courtesy of Richard M Stone, MD

Have you or would you substitute oral azacitidine (CC-486) for standard-administration azacitidine in combination with venetoclax for an elderly patient who prefers to minimize office visits?

a. I haven’t and would not

b. I haven’t but would for the right patient

c. I have

Agenda

Management of AML

Module 1: Venetoclax combinations — Azacitidine, LDAC

Module 2: FLT3 inhibitors — Midostaurin, gilteritinib

Module 3: IDH inhibitors — Ivosidenib, enasidenib

Module 4: Oral azacitidine (CC-486)

Module 5: Secondary AML — CPX-351

Treatment Strategies for MDS

Module 6: Lower-risk MDS — Luspatercept, imetelstat

Module 7: Higher-risk MDS — Decitabine + cedazuridine, azacitidine + venetoclax, magrolimab, APR-246, pevonedistat

MODULE 5: Secondary AML — CPX-351

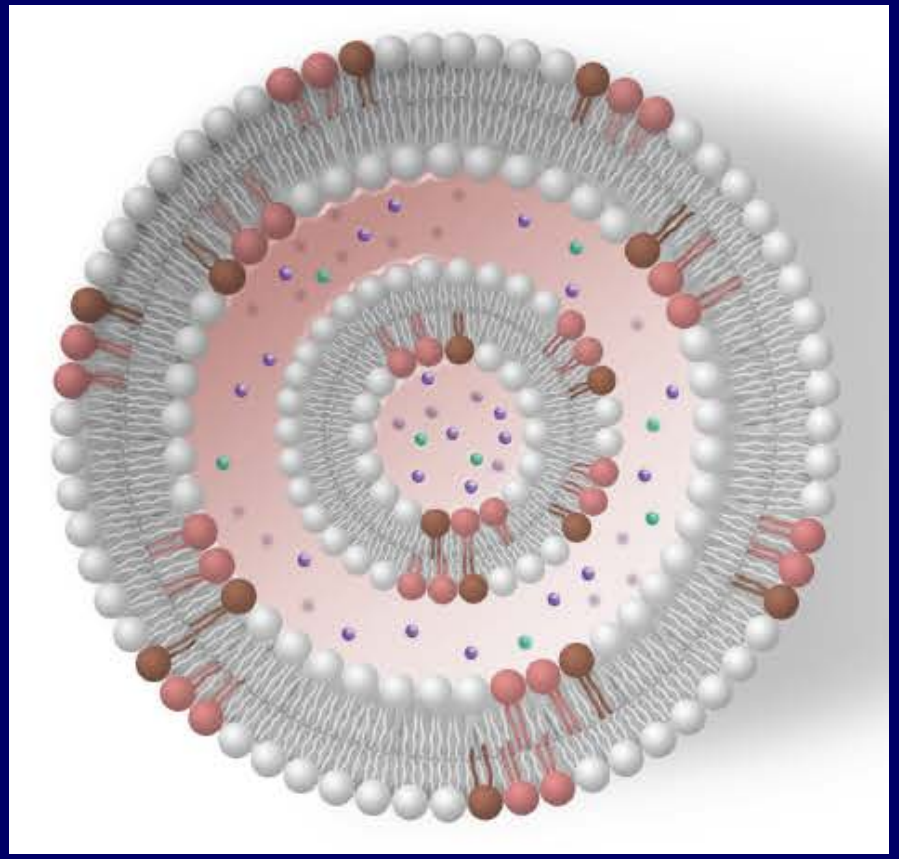
- **Key Relevant Data Sets**
  - Phase III study of CPX-351 vs 7 + 3 in older patients with newly diagnosed high-risk or secondary AML
  - CPX-351 early access program for older patients with high-risk or secondary AML
  - Phase II study of CPX-351 + venetoclax in patients with AML

What initial treatment would you recommend for a 64-year-old woman with a history of breast cancer, for which she received adjuvant chemotherapy, who now presents with bone marrow findings consistent with therapy-related AML?

a. 7 + 3 induction
b. CPX-351
c. Decitabine
d. Decitabine + venetoclax
e. Azacitidine + venetoclax
f. Low-dose cytarabine + venetoclax
g. Other

CPX-351

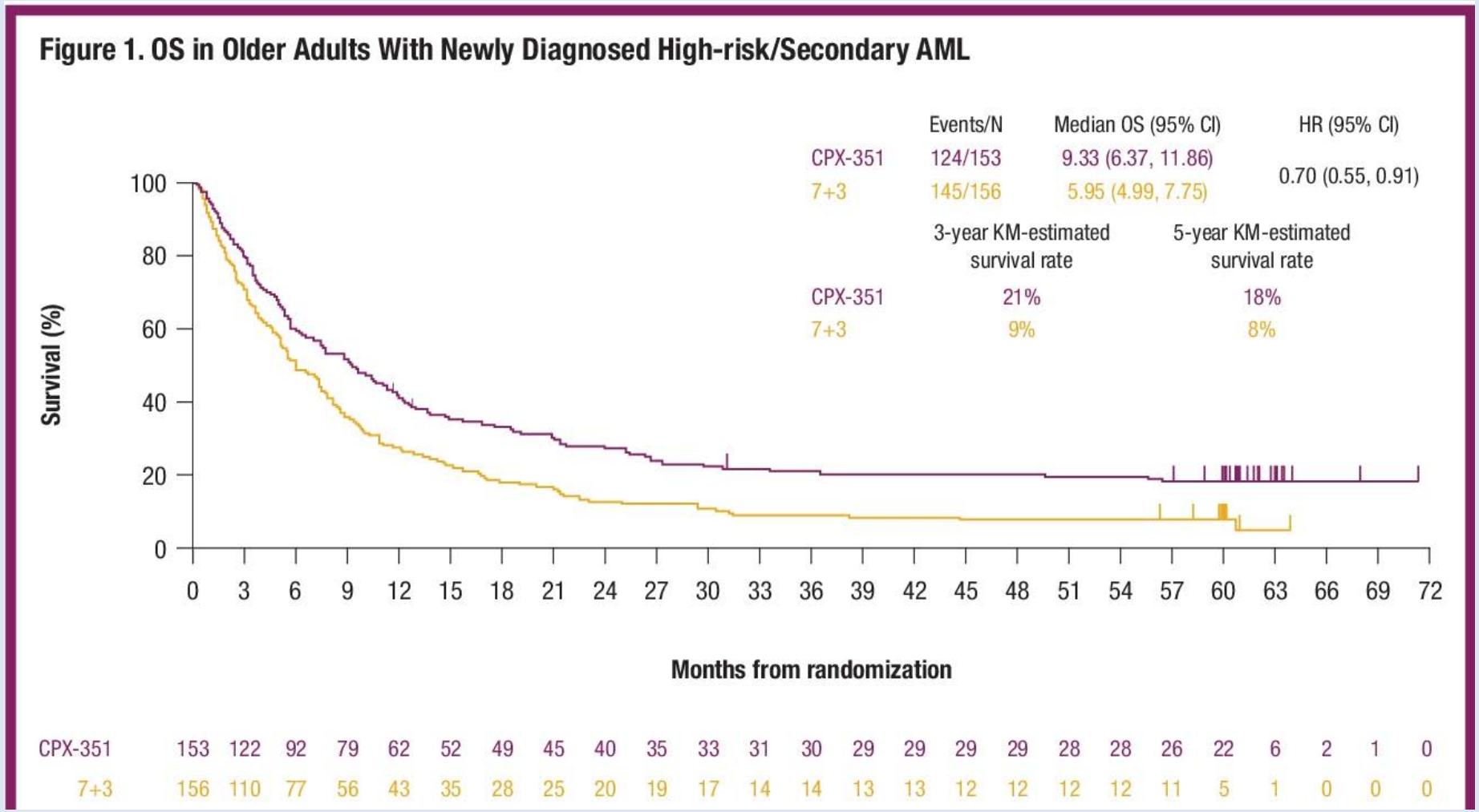
- CPX-351 is a liposomal co-formulation of cytarabine and daunorubicin designed to achieve synergistic antileukemia activity
  - 5:1 molar ratio of cytarabine:daunorubicin provides synergistic leukemia cell killing *in vitro*[1]
  - In patients, CPX-351 preserved delivery of the 5:1 drug ratio for over 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):129–139.
2. Feldman EJ et al. *J Clin Oncol.* 2011;29(8):979–985;
3. Lim WS et al. *Leuk Res.* 2010;34(9):1245–1223.

Courtesy of Richard M Stone, MD

Treating sAML| CPX-351



Lancet et al. ASCO 2020; 7510a; ASH 2020; 635a

Courtesy of Mikkael A Sekeres, MD, MS

Treating sAML| CPX-351

	$N = 52$
Best response	
CR	
n (%)	15 (29)
95% CI	17.1–43.1
CRi	
n (%)	8 (15)
95% CI	6.9–28.1
CR + CRi	
n (%)	23 (44)
95% CI	30.5–58.7
Time to CR or CRi	
n	23
Median (range), d	37.0 (15–72)
Mean (SD), d	41.5 (15.24)

Roboz et al. Leuk Lymph 2020;61:1188-94.

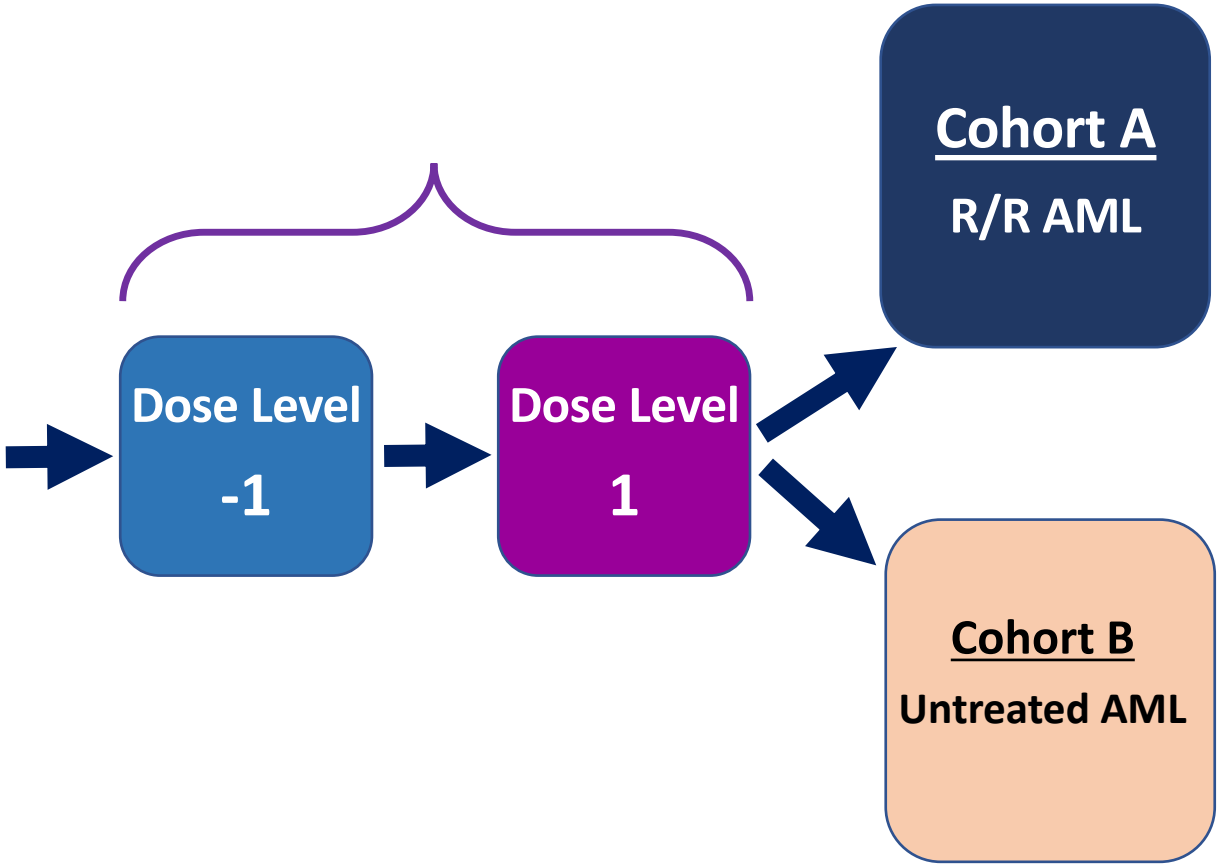
Courtesy of Mikkael A Sekeres, MD, MS

CPX351 + Venetoclax in AML (Kadia Abst #28, ASH 2020)

Study Design

Patient Selection

- **Lead in phase:** Patients ≥ 18 years of age with relapsed and/or refractory AML will be eligible.
- **Cohort A (R/R AML):** Patients ≥ 18 years of age with R/R AML .
- **Cohort B (de novo AML):** Patients ≥ **18 to 65** years of age Patients in this cohort must have received no prior therapy for AML.
- Adequate organ function :
  - Bilirubin ≤ 2mg/dL, AST / ALT ≤3 x ULN or ≤5 x ULN if related to leukemic involvement)
  - creatinine ≤ 1.5 x ULN
  - known cardiac ejection fraction of ≥45% within the past 3 months
- ECOG performance status of ≤ 2.
- Prior Venetoclax allowed in R/R cohorts



Courtesy of Richard M Stone, MD

CPX-351 + Venetoclax in AML

Treatment Plan

- **Induction**
  - **CPX-351** IV daily on D1, 3, 5
  - **Venetoclax** PO daily on D2-21
- **Consolidation** (Up to 4 consolidation cycles):
  - **CPX-351** IV daily on D1,3
  - **Venetoclax** PO daily on D2-21

Dose-Escalation Table (Planned 28 day cycle)				
	CPX-351 [mg/m^2]	Venetoclax Dosing (PO on D 2 – 21)		
Dose Level	All Patients	Patients on strong CYP3A inhibitor	Patients on moderate CYP3A inhibitor	Patients not on moderate or strong CYP3A inhibitor
-1	44 [dauno] / 100 [araC] (induction); 29 [dauno] / 65 [araC] (consolidation)	50 mg	150 mg	300 mg
1	44 [dauno] / 100 [araC] (induction); 29 [dauno] / 65 [araC] (consolidation)	100 mg	200 mg	400 mg

Day 2	Day 3	Up	Day 4	Target Dose
100mg	200 mg		400 mg	400 mg

Kadia Abst #28, ASH 2020

Courtesy of Richard M Stone, MD

CPX-351 + Venetoclax in AML (shortened ven schedule)

Treatment Plan

- **Induction**
  - **CPX-351** IV daily on D1, 3, 5
  - **Venetoclax** PO daily on D2-21
- **Consolidation** (Up to 4 consolidation cycles):
  - **CPX-351** IV daily on D1,3
  - **Venetoclax** PO daily on D2-21

Dose-Escalation Table (Planned 28 day cycle)

	CPX-351 [mg/m²]	Venetoclax Dosing (PO)		
Dose Level	**All Patients**	**Patients on strong CYP3A inhibitor**	**Patients on moderate CYP3A inhibitor**	**Patients not on moderate or strong CYP3A inhibitor**
-2	**44** (induction); **22** (consolidation)	50 mg **on D 2 – 8**	150 mg **on D 2 – 8**	300 mg **on D 2 – 8**
-1	**44** (induction); **29** (consolidation)	**50 mg on D 2 – 21**	**150 mg on D 2 – 21**	**300 mg D 2 – 21**
1	**44** (induction); **29** (consolidation)	**100 mg on D 2 – 21**	**200 mg on D 2 – 21**	**400 mg on D 2 – 21**

Day 2	Day 3	Day 4	Target Dose
100mg	200 mg	300 mg	300 mg

Kadia Abst #28, ASH 2020

Courtesy of Richard M Stone, MD

CPX-351 + Venetoclax in AML

Responses

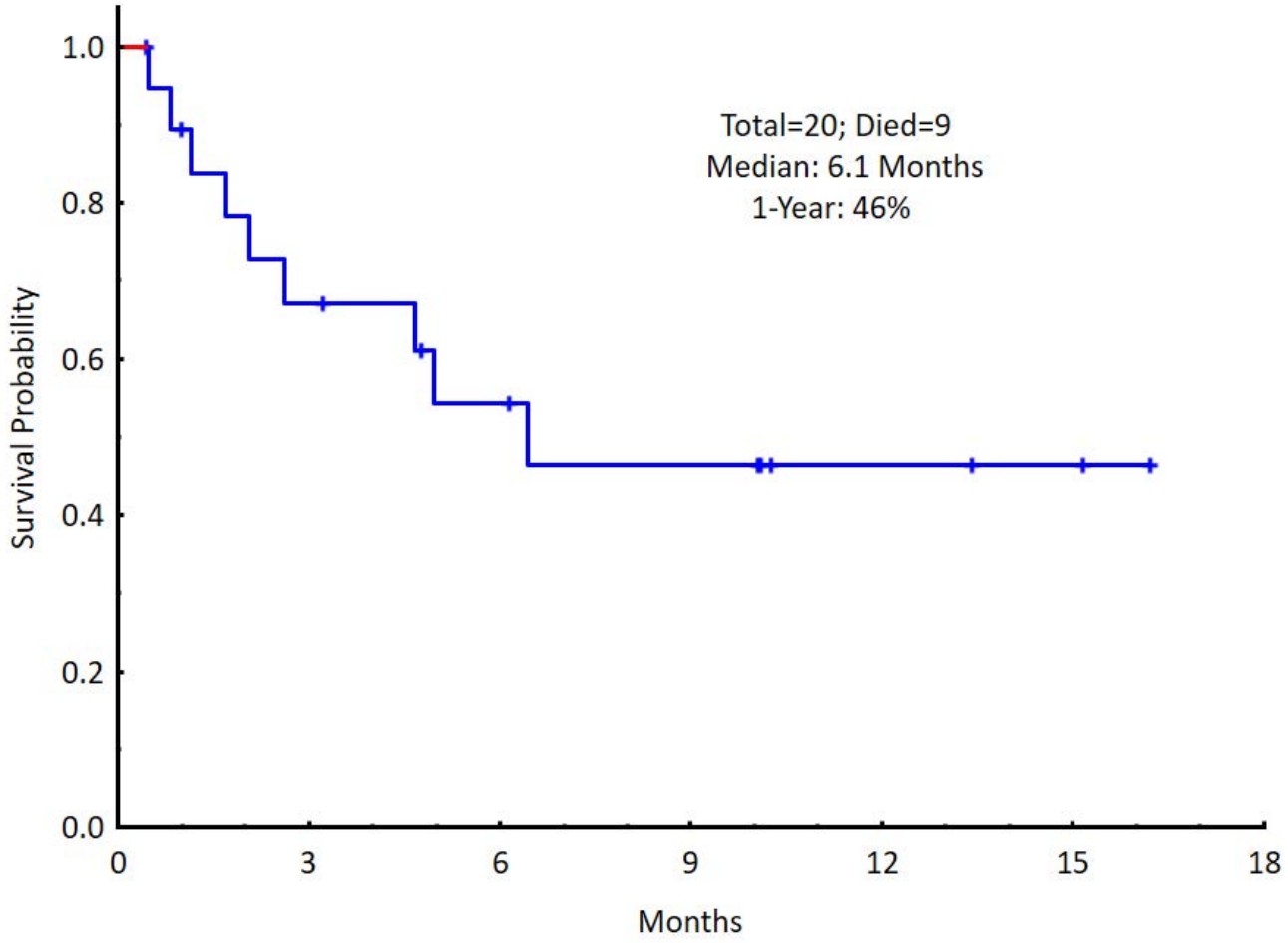
Response / Outcome	N	%
Evaluable for Response	18	90
CR	1	6
CRi	6	33
MLFS	1	6
ORR	8	44
Died ≤ 4 weeks	2	10
Died ≤ 8 weeks	4	20
Median # of cycles given [Range]	1 [1 – 2]	
Median # of cycles to response	1 [1 – 2]	
No. of Responding Pts Receiving SCT	7	88
Median time to count recover (days)	41 [23 – 60]	

Kadia Abst #28, ASH 2020

Courtesy of Richard M Stone, MD

CPX-351 + Venetoclax in AML

Overall Survival



Kadia Abst #28, ASH 2020

Courtesy of Richard M Stone, MD

CPX-351 + Venetoclax in AML

Serious Adverse Events

ADVERSE EVENT	TOTAL SAEs	GRADE 3 / 4	GRADE 5
INFECTIONS, NOT OTHERWISE SPECIFIED	7	7	
NAUSEA	4	4	
PNEUMONIA	4	3	1
PROLONGED THROMBOCYTOPENIA	3	3	
PROLONGED NEUTROPENIA	3	3	
VOMITING	2	2	
RASH	2	2	
BONE PAIN	1	1	
HYPOTENSION	1	1	
THRUSH	1	1	
STROKE	1	1	
RESPIRATORY FAILURE	1		1
CHOLECYSTITIS	1	1	
ELECTROLYTE ABNORMALITY	1	1	
SEPSIS	1		1
DIVERTICULITIS	1	1	

Kadia Abst #28, ASH 2020

Courtesy of Richard M Stone, MD

Agenda

Management of AML

Module 1: Venetoclax combinations — Azacitidine, LDAC

Module 2: FLT3 inhibitors — Midostaurin, gilteritinib

Module 3: IDH inhibitors — Ivosidenib, enasidenib

Module 4: Oral azacitidine (CC-486)

Module 5: Secondary AML — CPX-351

Treatment Strategies for MDS

Module 6: Lower-risk MDS — Luspatercept, imetelstat

Module 7: Higher-risk MDS — Decitabine + cedazuridine, azacitidine + venetoclax, magrolimab, APR-246, pevonedistat

MODULE 6: Lower-risk MDS — Luspatercept, imetelstat

- **Key Relevant Data Sets**
  - Luspatercept in patients with lower-risk MDS
  - Imetelstat in high transfusion burden, lower-risk MDS

Treating MDS| Disease Biology

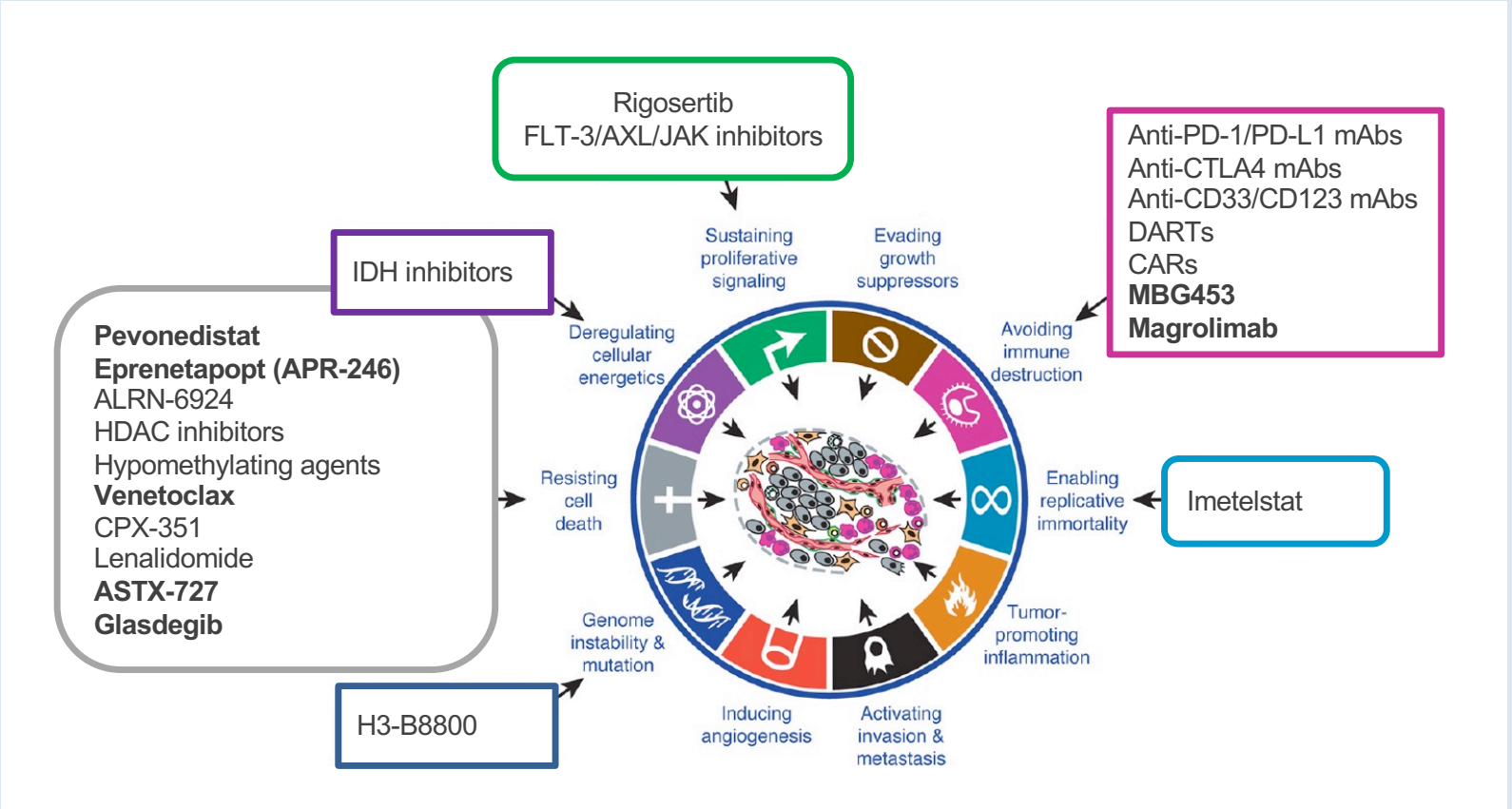
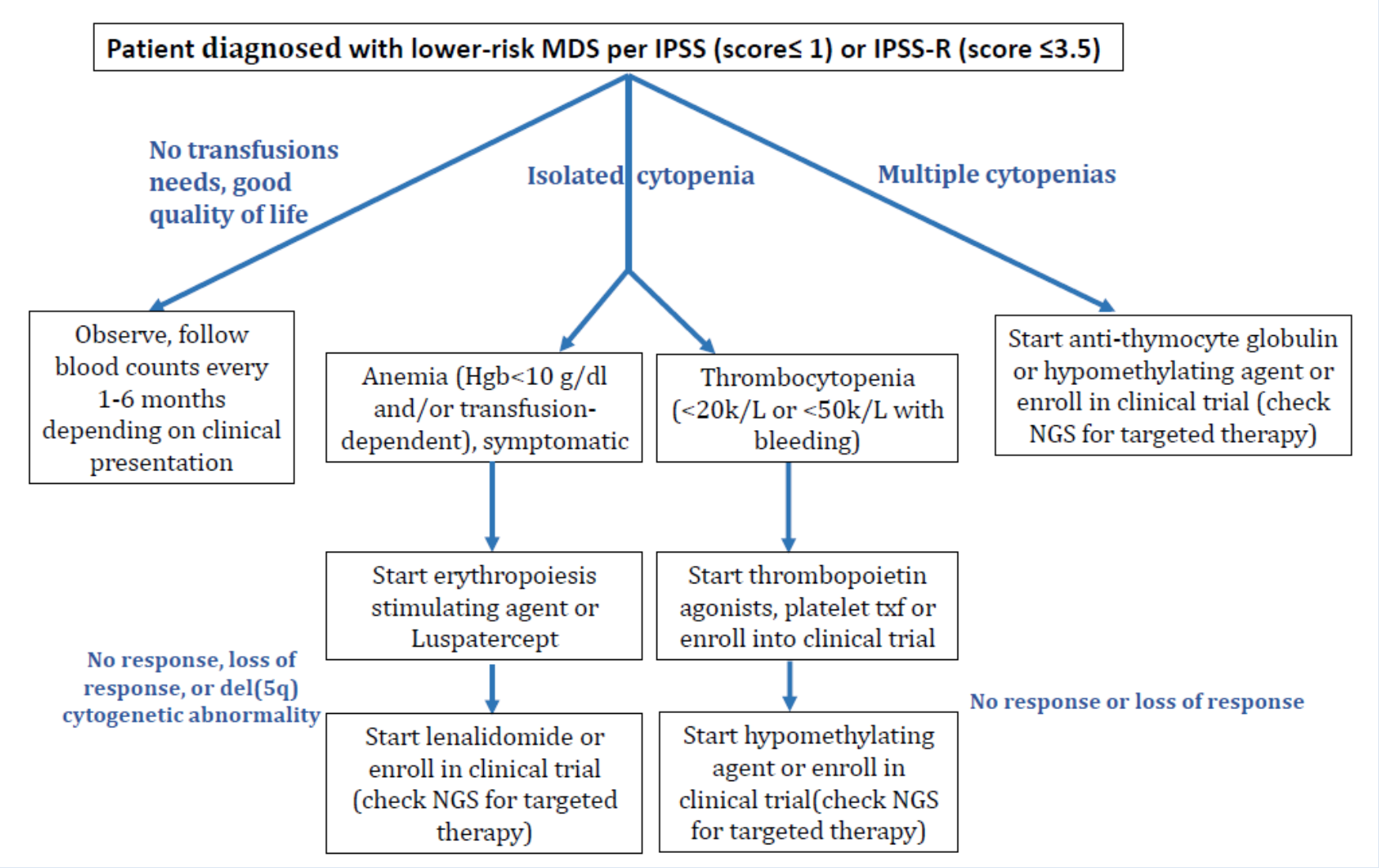


Figure adapted from Hanahan D, Weinberg RA. *Cell* 2011;144:646–74

Courtesy of Mikkael A Sekeres, MD, MS

BH3, bcl homology domain 3; CTLA4, cytotoxic T-lymphocyte-associated protein 4; DARTs, dual affinity retargeting agents; EGFR, epidermal growth factor receptor; HGF, hepatocyte growth factor; mAb, monoclonal antibody; PARP, poly adenosine diphosphate ribose polymerase; VEGF, vascular endothelial growth factor

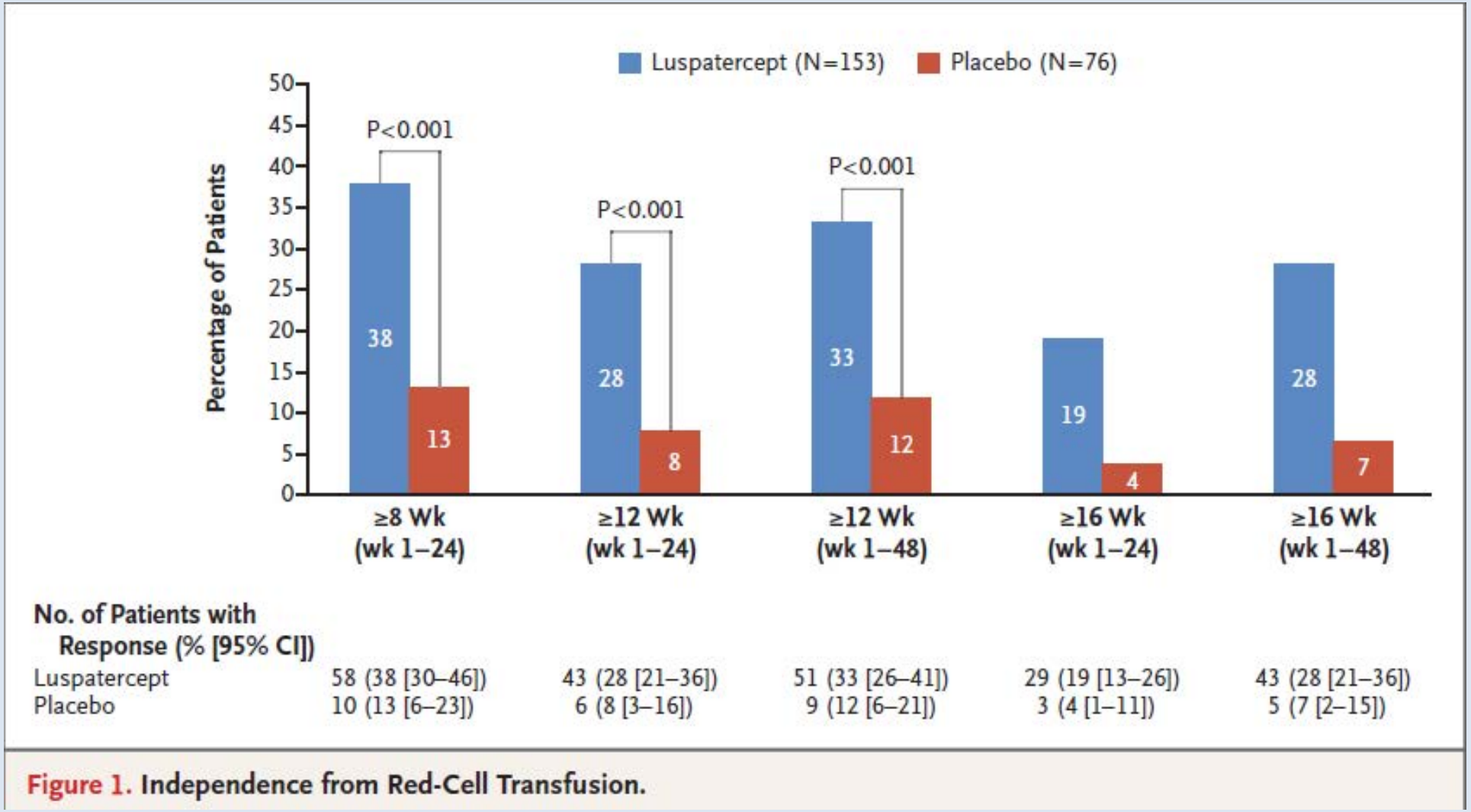
MDS | Treatment – Lower-risk



Sekeres and Patel Hematology (ASH Educ Book) 2019.

Courtesy of Mikkael A Sekeres, MD, MS

MDS | Ameliorating Anemia: LUSPAT



No. of Patients with Response (% [95% CI])	≥8 Wk (wk 1–24)	≥12 Wk (wk 1–24)	≥12 Wk (wk 1–48)	≥16 Wk (wk 1–24)	≥16 Wk (wk 1–48)
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])

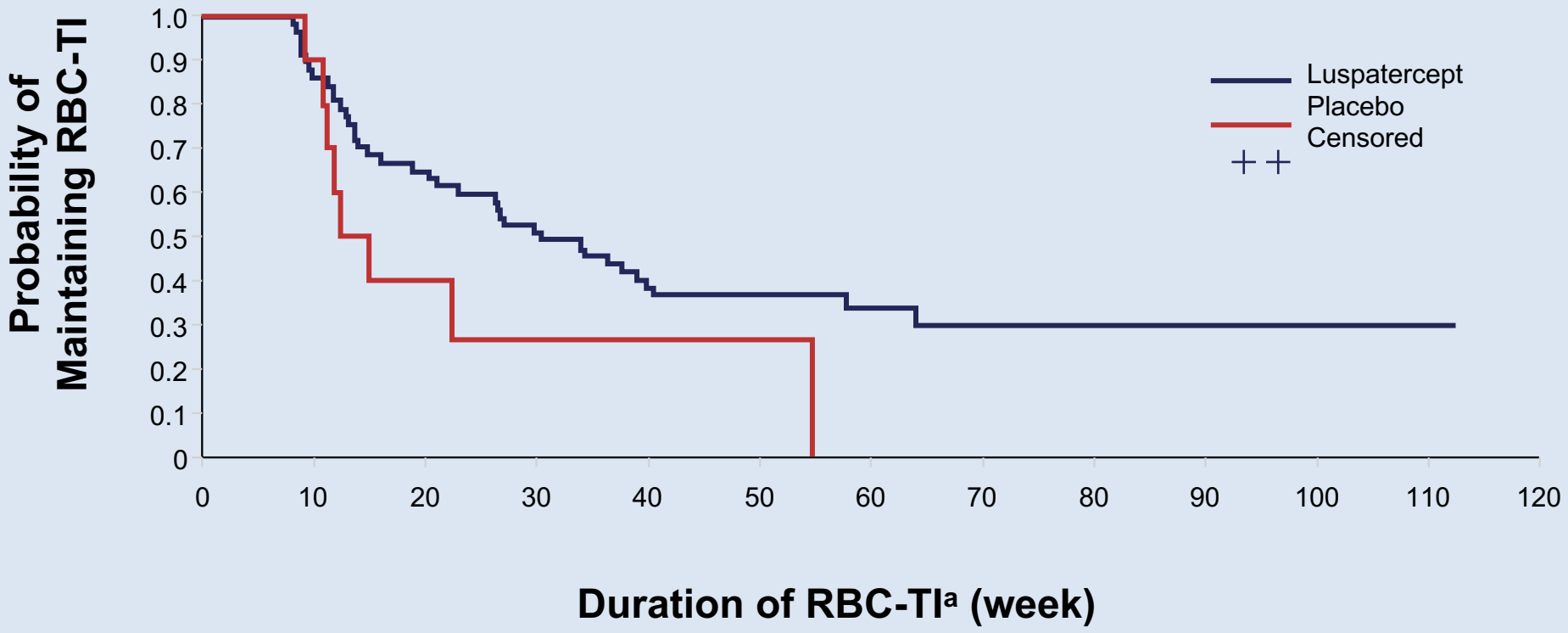
Figure 1. Independence from Red-Cell Transfusion.

Fenaux et al. NEJM 2020;382:140-151.

Courtesy of Mikkael A Sekeres, MD, MS

MDS | Ameliorating Anemia: LUSPAT

Median duration (weeks) (95% CI): 30.6 (20.6–40.6) vs 13.6 (9.1–54.9)



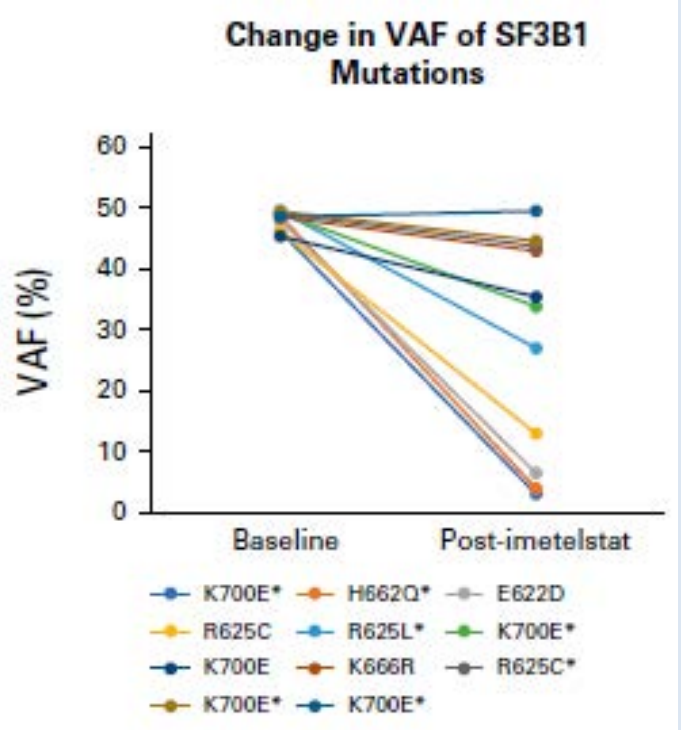
Fenaux et al. NEJM 2020;382:140-151.

Courtesy of Mikkael A Sekeres, MD, MS

MDS | Ameliorating Anemia: Imetel

Imetelstat in HTB Lower-risk MDS

Parameter	Overall Population (n = 57)
8-week TI[a], No. (%)	21 (37)
Median time to onset, weeks (range)	8.3 (0.1-100.6)
Median duration of TI[b], weeks (range)	65 (17.0-140.9)
24-week TI[a], No. (%)	13 (23)
HI-E per IWG 2006, No. (%)	37 (65)
≥ 1.5 g/dL increase in Hgb lasting ≥ 8 weeks	15 (26)
Transfusion reduction by ≥ 4 units/8 weeks	37 (65)
Response per IWG 2018, No. (%)	
Major response: 16-week TI	16 (28)
Major response: 8-week TI	21 (37)
Minor response[c]	28 (49)



Steensma et al. JCO 2020

Courtesy of Mikkael A Sekeres, MD, MS

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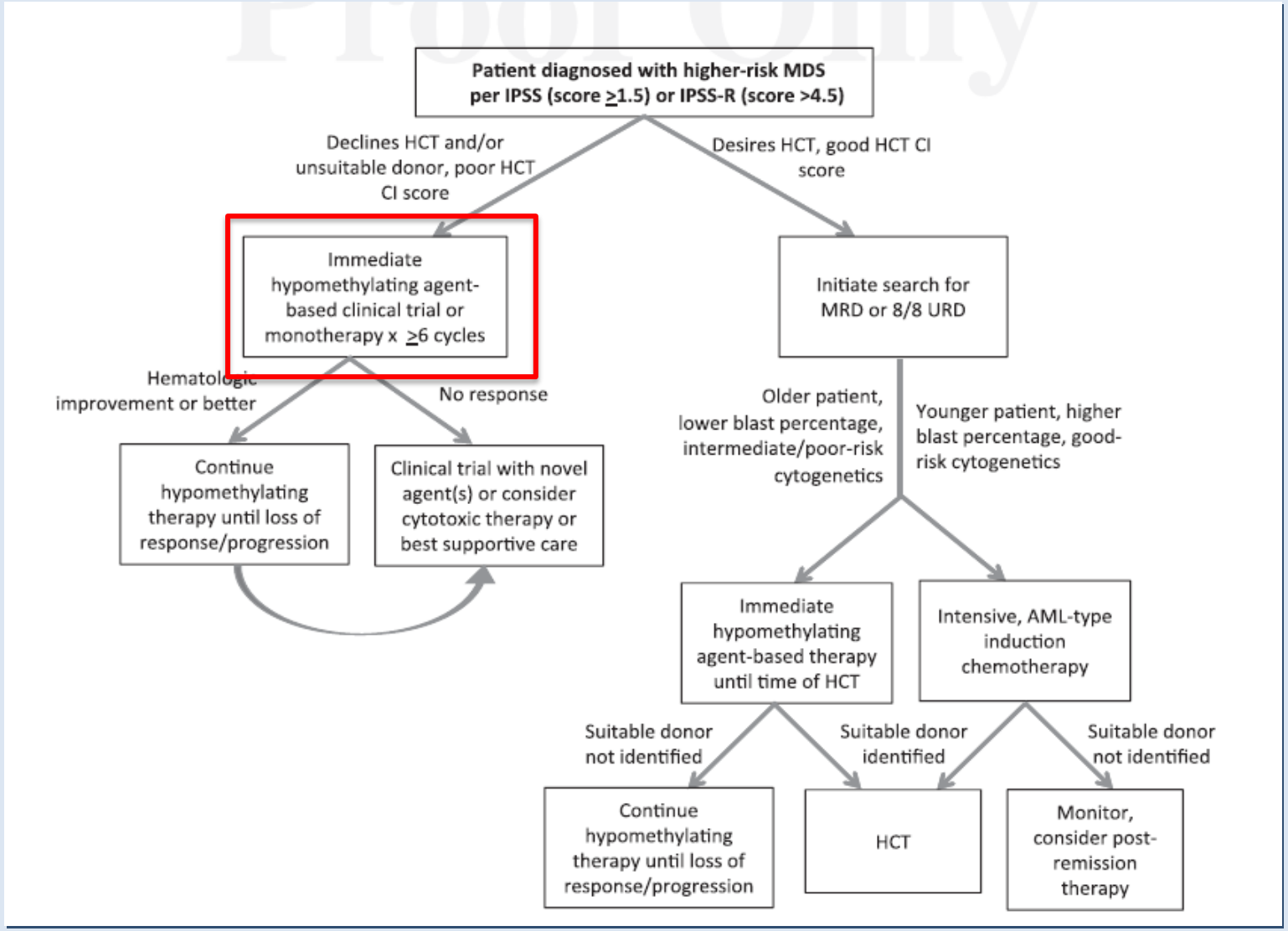
Module 7: Higher-risk MDS — Decitabine + cedazuridine, azacitidine + venetoclax, magrolimab, APR-246, pevonedistat

- **Key Relevant Data Sets**
  - Oral cedazuridine/decitabine for MDS and CMML (chronic myelomonocytic leukemia)
  - Venetoclax + azacitidine for higher-risk MDS
  - Magrolimab + azacitidine for patients with MDS
  - Targeting TP53 for high-risk MDS
  - Azacitidine +/- pevonedistat for high-risk MDS

Higher-risk MDS | HMA and HCT



Sekeres and Cutler Blood 2014;123:829.

Courtesy of Mikkael A Sekeres, MD, MS

Oral cedazuridine/decitabine for MDS and CMML: a phase 2 pharmacokinetic/pharmacodynamic randomized crossover study

Guillermo Garcia-Manero,[1] Elizabeth A. Griffiths,[2] David P. Steensma,[3] Gail J. Roboz,[4] Richard Wells,[5] James McCloskey II,[6] Olatoyosi Odenike,[7] Amy E. DeZern,[8] Karen Yee,[9] Lambert Busque,[10] Casey O'Connell,[11] Laura C. Michaelis,[12] Joseph Brandwein,[13] Hagop Kantarjian,[1] Aram Oganesian,[14] Mohammad Azab,[14] and Michael R. Savona[15]

Blood **2020;136(6):674-83.**

Higher-risk MDS | HMAs: DAC/CED

Oral Cedazuridine/Decitabine Phase 2
In Int-1, Int-2, High, CMML

Type of response	Phase 2 overall (N=80)	
	n (%)	95% CI
CR	17 (21)	13, 32
PR	0	
mCR	18 (22)	14, 33
With HI	6 (7)	3, 16
HI	13 (16)	9, 26
HI-E	8 (10)	4, 19
HI-N	2 (2)	0, 9
HI-P	11 (14)	7, 23
Overall response (CR + PR + mCR + HI)	48 (60)	48, 71
No response	32 (40)	29, 52

Garcia-Manero et al. Blood 2020.

Courtesy of Mikkael A Sekeres, MD, MS

Venetoclax/azacitidine has been evaluated in a Phase I study

Ongoing Phase 1b, open-label, dose-escalation,* multicenter study[1,2]

Higher-risk MDS
No prior therapy, not eligible for intensive chemotherapy or HSCT

N=82

Dose-escalation phase | Safety expansion phase

Venetoclax + azacitidine
Venetoclax: escalating doses (oral) 100–400 mg/day
Azacitidine: 75 mg/m^2 (IV or SC) on Days 1–7

Venetoclax + azacitidine
Venetoclax: 400 mg/day (oral)
Azacitidine: 75 mg/m^2 (IV or SC) on Days 1–7

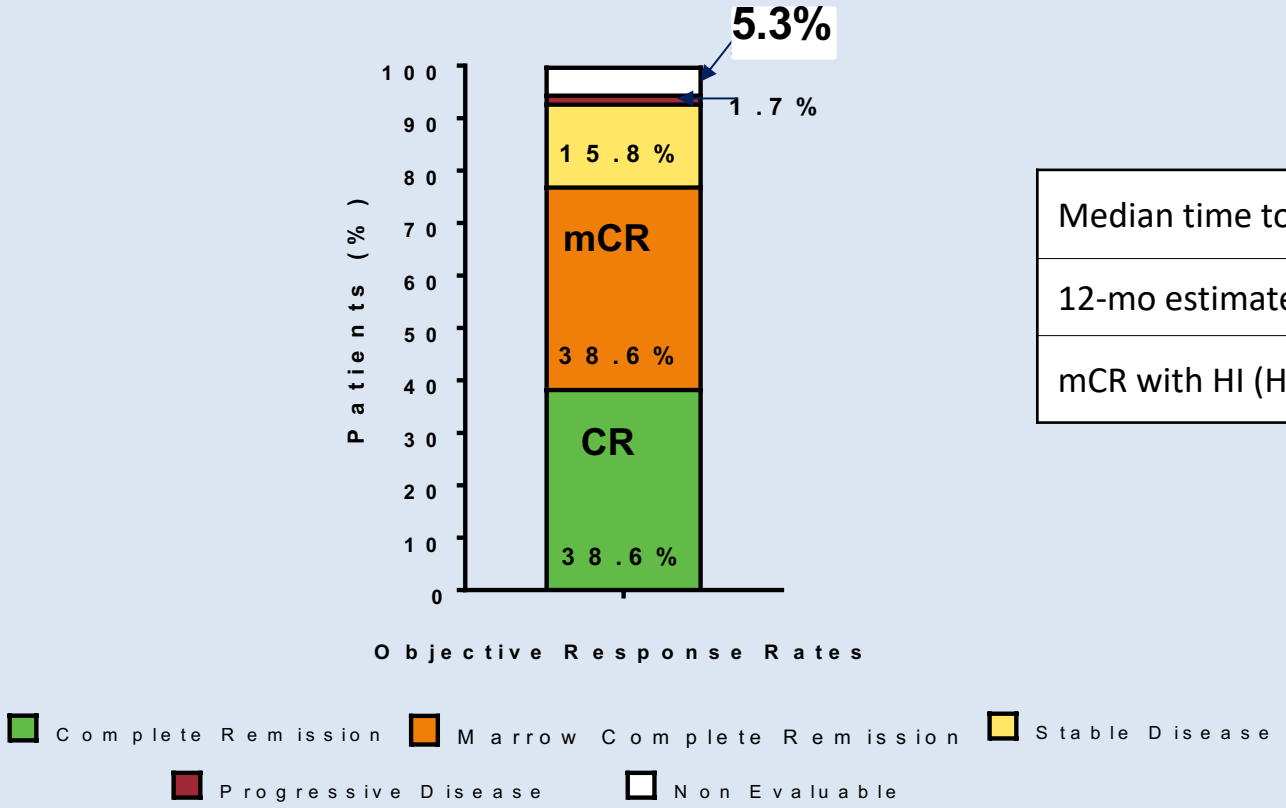
Primary endpoints:
- Safety
- RP2D

Secondary endpoints include:
- ORR
- PFS
- TTR
- DoR
- OS

1. Wei AH, *et al*. *Blood* 2019;134 (Suppl. 1):Abstract #568; 2. ClinicalTrials.gov, NCT02942290
*Originally a 3-arm, randomized study; amended to dose-escalation safety study after two deaths
TTR, time to response

Courtesy of Mikkael A Sekeres, MD, MS

Wei et al, Abstract 568 – AZA plus Venetoclax for HR-MDS: Response Rates



Median time to CR, months (range)	2.2 (1.2-11.1)
12-mo estimate of DoR after CR, % (95% CI)	83.3 (2.3, 97.5)
mCR with HI (HI-E, HI-P or HI-N), n/N (%)	10/22 (45.5)

Excludes patients of arm C (Aza only); Objective response rate (ORR) includes [complete remission (CR) + marrow complete remission (mCR) + partial remission (PR)]; # of patients with PR=0; per IWG (Cheson et al., *Blood* 2006;108:419-425)
DoR: Duration of response; HI: hematological improvement; HI-E: hematologic improvement in erythroids; HI-N: hematologic improvement in neutrophils; HI-P: hematologic improvement in platelet count; n: patients with favorable outcomes; N: patients eligible for evaluating outcomes

Wei et al. ASH 2019 Abstract #568.

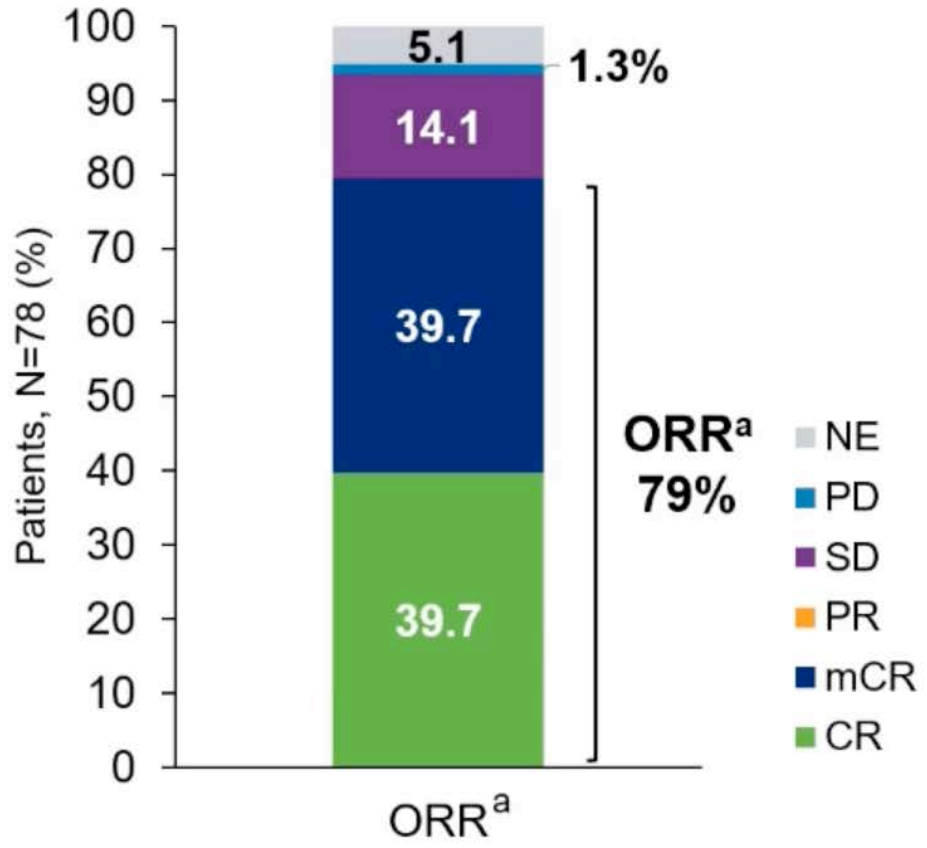
Courtesy of Mikkael A Sekeres, MD, MS

Safety, Efficacy, and Patient-Reported Outcomes of Venetoclax in Combination with Azacitidine for the Treatment of Patients with Higher-Risk Myelodysplastic Syndrome: A Phase 1b Study

Garcia JS et al.

ASH 2020;Abstract 656.

Response Rates and Transfusion Dependence with Venetoclax/Azacitidine in Higher-Risk MDS



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

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

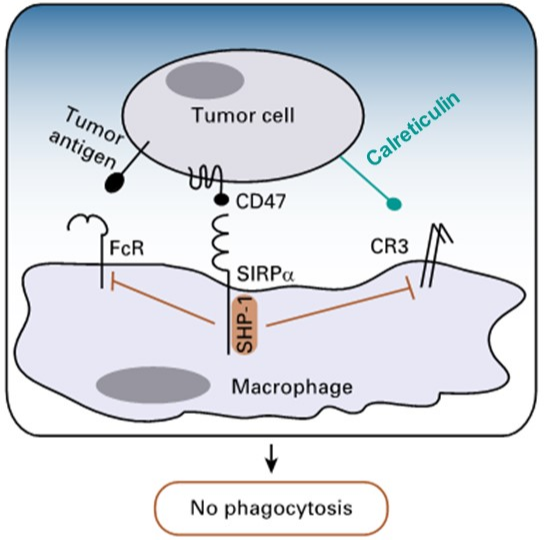
- A total of 16 patients (21%) went on to receive poststudy transplants; 7 received bone marrow transplant; and 9 received stem cell transplant

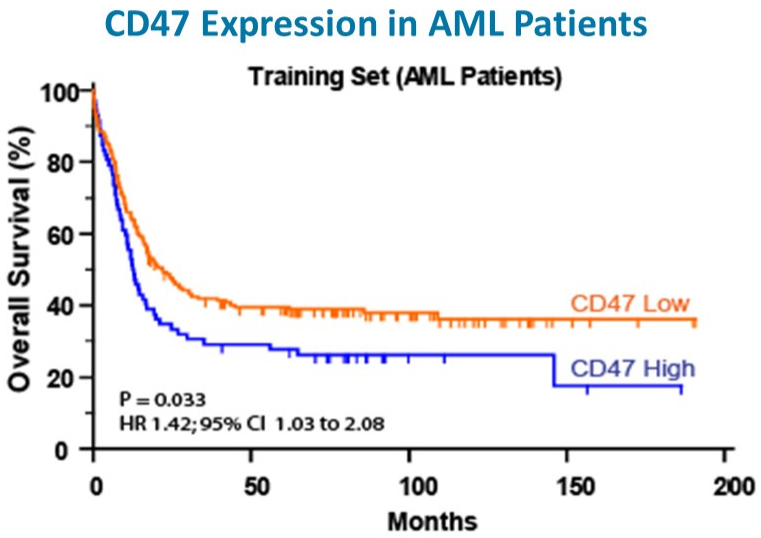
[a]Excludes patients of Arm C (Aza only); ORR includes CR + mCR + PR; PR n=0; per IWG 2006 (Cheson BD, et al. *Blood*. 2006;108(2):419–25);
[b]Excludes 5 patients from the randomization phase who received 28-day Ven

Garcia JS et al. ASH 2020;Abstract 656.

Higher-risk MDS | Combinations

CD47 Is a Major Macrophage Immune Checkpoint and 'Do Not Eat Me' Signal in Myeloid Malignancies Including MDS and AML





- CD47 is a "do not eat me" signal on cancers that enables macrophage immune evasion
- Increased CD47 expression predicts worse prognosis in AML patients

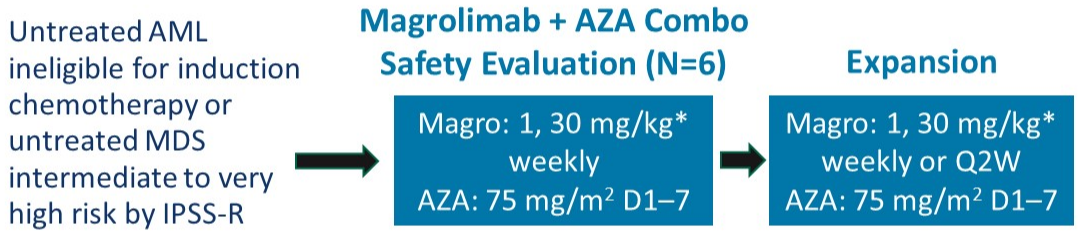
Figure at left adapted from Veillette A, Tang Z. *J Clin Onc.* 2019;37(12)1012-1014, and Chao MP, et al. *Current Opin Immunol.* 2012; 24(2):225-232.
Figure at right adapted from Majeti R, et al. *Cell.* 2009;138(2):286-299.

Sallman et al. ASCO 2020;7507a.

Courtesy of Mikkael A Sekeres, MD, MS

Higher-risk MDS | Combinations

5F9005 Study Design: Magrolimab in Combination With AZA in MDS and AML



Primary objectives

1. Safety of magrolimab alone or with AZA
2. Efficacy of magrolimab + AZA in untreated AML/MDS

Secondary objectives

1. Pharmacokinetics, pharmacodynamics, and immunogenicity of 5F9
2. Additional measures of efficacy (DOR, PFS, OS)

Exploratory objective

To assess CD47 receptor occupancy, markers of immune cell activity, and molecular profiling in AML/MDS

- A magrolimab priming dose (1 mg/kg) and dose ramp-up was utilized to mitigate on-target anemia
- Data from the expansion cohort is presented

*Dose ramp-up from 1 mg/kg to 30 mg/kg by week 2, then 30 mg/kg maintenance dosing or 30 mg/kg Q2W starting Cycle 3+.
IPSS-R: Revised International Prognostic Scoring System.

Sallman et al. ASCO 2020;7507a.

Courtesy of Mikkael A Sekeres, MD, MS

Higher-risk MDS | Combinations

Patient Characteristics (N=68): Magrolimab + AZA in Untreated (1L) MDS and AML

Characteristic	1L MDS 5F9+AZA (N=39)	1L AML 5F9+AZA (N=29)
Median age (range)	70 (47–80)	74 (60–89)
ECOG Performance Status: 0	11 (28%)	7 (24%)
1	26 (67%)	20 (69%)
2	2 (5%)	2 (7%)
Cytogenetic Risk: Favorable	0	0
Intermediate	11 (28%)	2 (7%)
Poor	25 (64%)	21 (72%)
Unknown/missing	3 (8%)	6 (21%)
WHO AML classification: MRC		19 (66%)
Recurrent genetic abnormalities	NA	2 (7%)
Therapy related		3 (10%)
Not otherwise specified		5 (17%)
WHO MDS classification:		
RS and single/multilineage dysplasia	1 (3%)	
Multilineage dysplasia	7 (18%)	NA
RS with multilineage dysplasia	3 (8%)	
Excess blasts	22 (56%)	
Unclassifiable/unknown/missing	6 (15%)	
IPSS-R (MDS): Intermediate	13 (33%)	
High	19 (49%)	NA
Very High	6 (15%)	
Unknown/missing	1 (3%)	
Therapy related MDS	12 (31%)	
Unknown/missing	1 (3%)	
Harboring a TP53 mutation	5 (13%)	13 (45%)

MRC, myelodysplasia-related changes; NA, not applicable; all patients enrolled on study are shown; WHO, World Health Organization.

- 64%–72% of MDS and AML patients were poor cytogenetic risk
- 66% of AML patients had underlying myelodysplasia (MRC)
- 31% of MDS patients were therapy related
- 45% of AML patients were *TP53* mutant

Sallman et al. ASCO 2020;7507a.

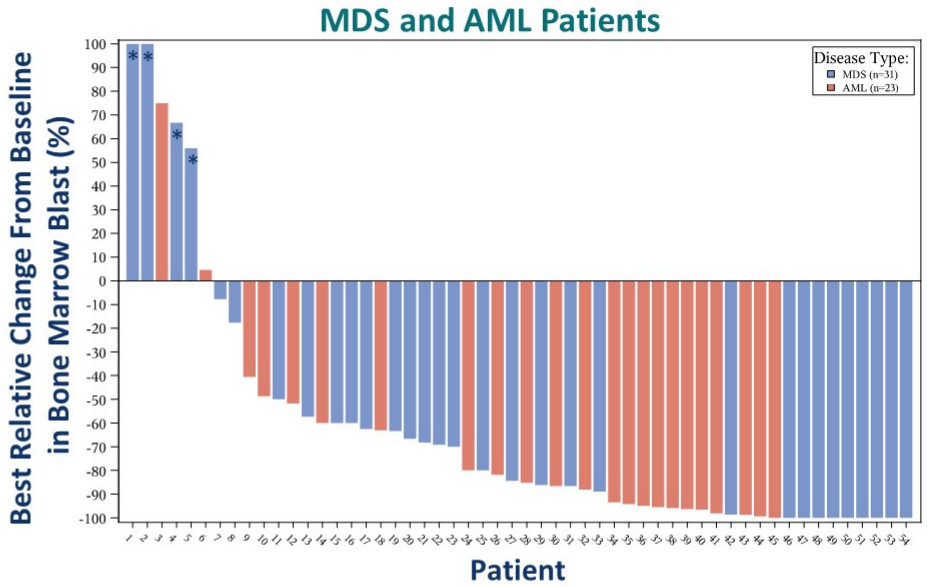
Courtesy of Mikkael A Sekeres, MD, MS

Higher-risk MDS | Combinations

Magrolimab + AZA Induces High Response Rates in MDS and AML

Best Overall Response	1L MDS N=33	1L AML N=25
ORR	30 (91%)	16 (64%)
CR	14 (42%)	10 (40%)
CRi	NA	4 (16%)
PR	1 (3%)	1 (4%)
MLFS/marrow CR	8 (24%) 4 with marrow CR + HI	1 (4%)
Hematologic improvement (HI)	7 (21%)	NA
SD	3 (9%)	8 (32%)
PD	0	1 (4%)

Response assessments per 2006 IWG MDS criteria and 2017 AML ELN criteria. Patients with at least 1 post-treatment response assessment are shown; all other patients are on therapy and are too early for first response assessment, except for 2 MDS patients not evaluable (withdrawal of consent) and 3 AML patients (1 AE, 2 early withdrawal).



Four patients not shown due to missing values; <5% blasts imputed as 2.5%. *Baseline bone marrow blasts ≤5%.

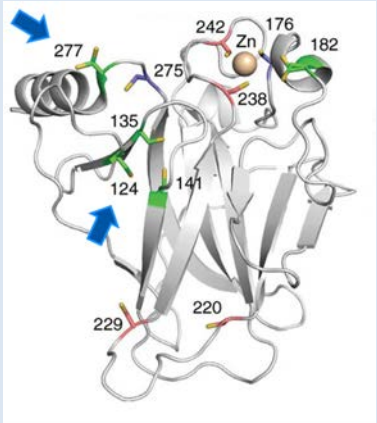
- Magrolimab + AZA induces a 91% ORR (42% CR) in MDS and 64% ORR (56% CR/CRi) in AML
- Responses deepened over time with a 56% 6-month CR rate in MDS patients (assessed in all patients 6 months after initial treatment)
- Median time to response is 1.9 months, more rapid than AZA alone
- Magrolimab + AZA efficacy compares favorably to AZA monotherapy (CR rate 6-17%[1,2])

1. Azacitidine USPI. 2. Fenaux P, et al. *Lancet Oncol.* 2009 ;10(3):223-232.

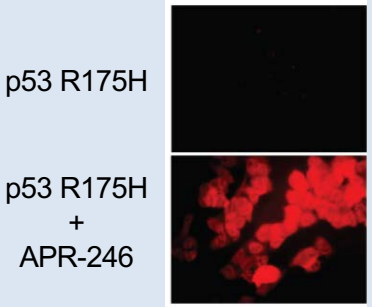
Sallman et al. ASCO 2020;7507a.

Courtesy of Mikkael A Sekeres, MD, MS

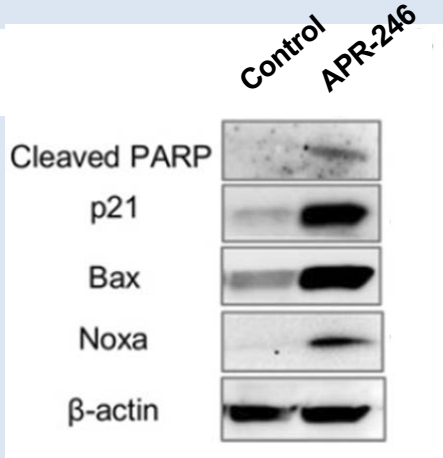
Higher-risk MDS | Targeting *TP53*



APR-246 binds covalently to p53…



…restores wt p53 conformation & activity…



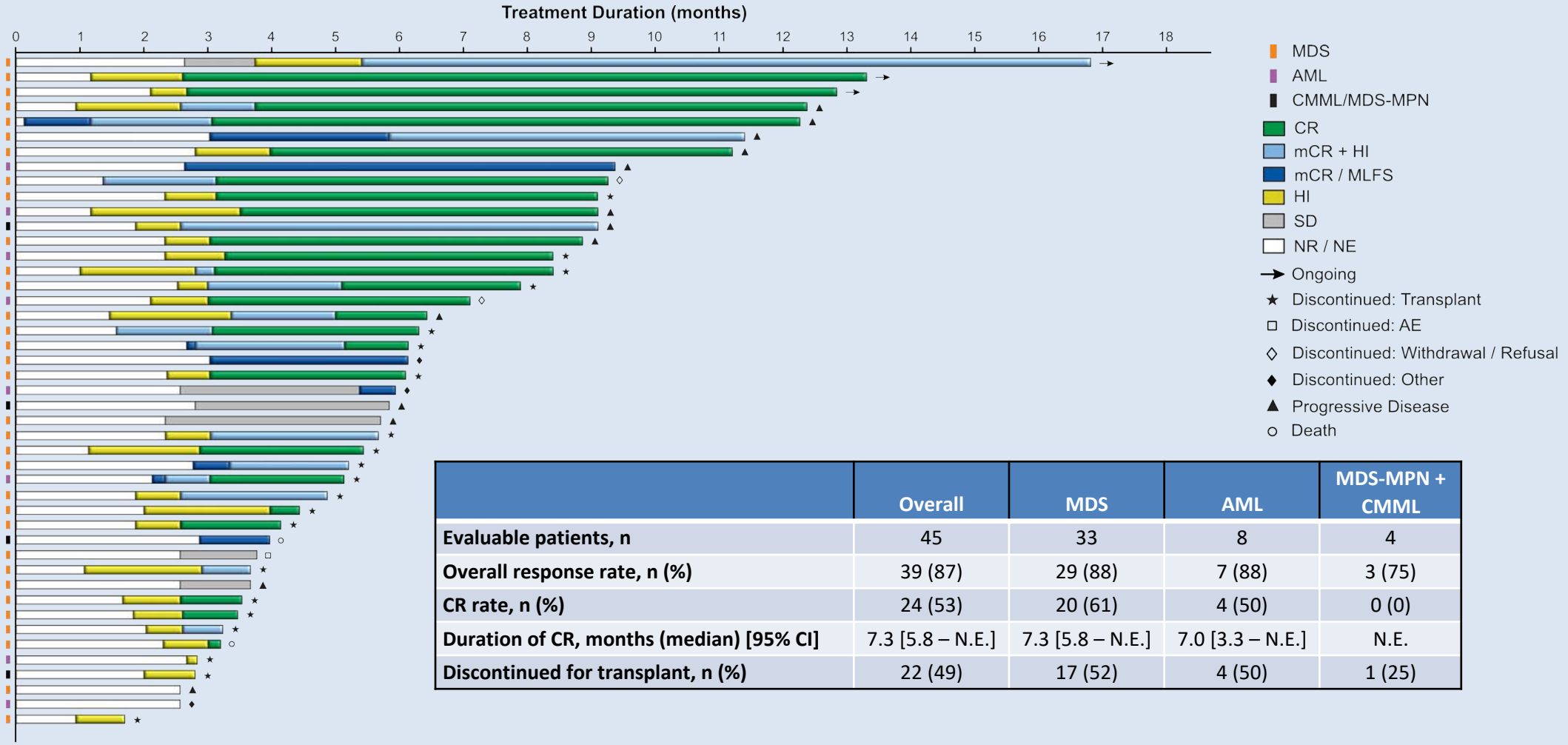
…and triggers cell cycle arrest and apoptosis

A. Fersht et al. (2010) Prot. Sci; Q. Zhang et al, (2018) Cell Death Disease; H. Furukawa et al, (2018) Cancer Sci.

Sallman et al, Cluzeau et al. ASH 2019, Abstract 676-7.

Courtesy of Mikkael A Sekeres, MD, MS

Higher-risk MDS | Targeting *TP53*



	Overall	MDS	AML	MDS-MPN + CMML
Evaluable patients, n	45	33	8	4
Overall response rate, n (%)	39 (87)	29 (88)	7 (88)	3 (75)
CR rate, n (%)	24 (53)	20 (61)	4 (50)	0 (0)
Duration of CR, months (median) [95% CI]	7.3 [5.8 – N.E.]	7.3 [5.8 – N.E.]	7.0 [3.3 – N.E.]	N.E.
Discontinued for transplant, n (%)	22 (49)	17 (52)	4 (50)	1 (25)

Median duration of follow-up = 10.8 months

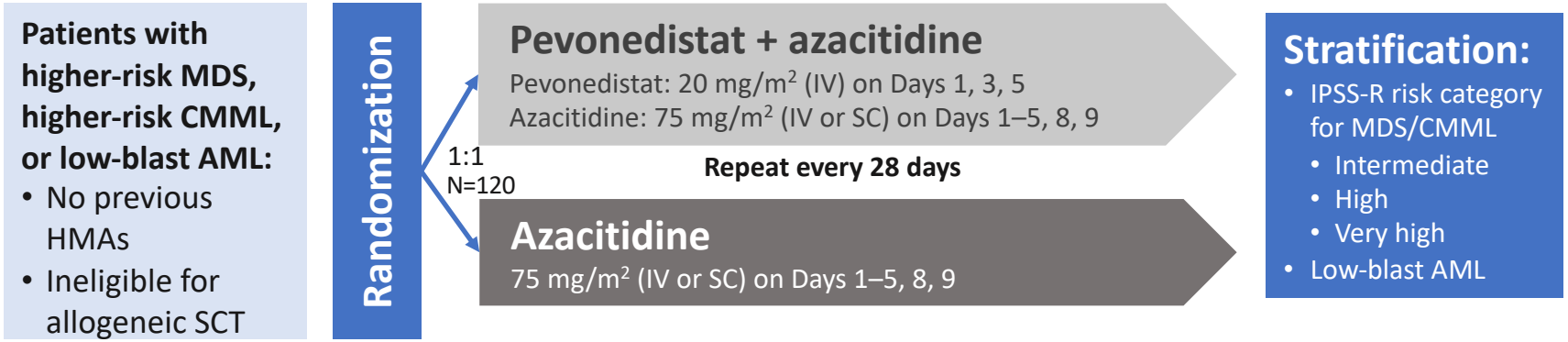
Sallman et al, Cluzeau et al. ASH 2019, Abstract 676-7.

Courtesy of Mikkael A Sekeres, MD, MS

Higher-risk MDS | Combinations

Study design: AZA +/- Pevonedistat

NCT02610777: Phase 2, randomized, open-label, global, multicenter study [proof of concept]



Study endpoints

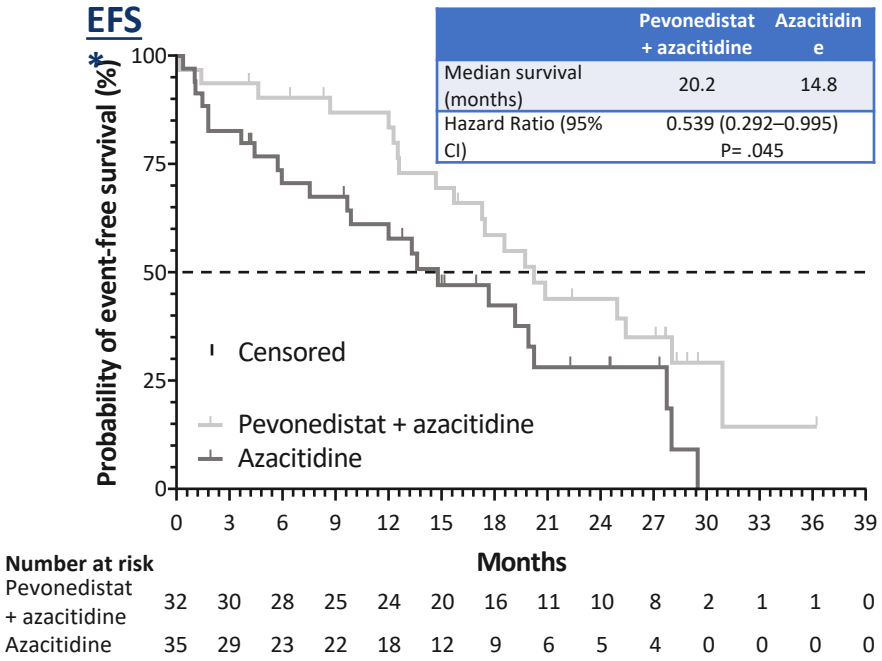
- **EFS** (defined as time to death or transformation to AML in higher-risk MDS/CMML or death in low-blast AML): Trial was powered on EFS as the original primary endpoint
- **OS**: Original secondary endpoint, changed to primary endpoint based on regulatory feedback after enrollment
- **ORR**: Secondary endpoint

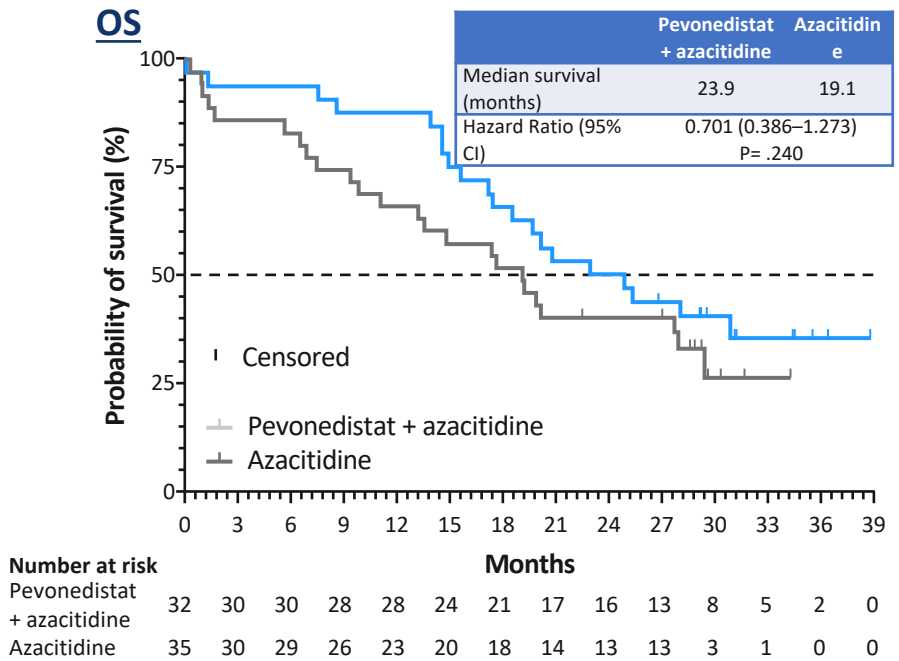
EFS, event-free survival; HMAs, hypomethylating agents; IPSS-R, Revised International Prognostic Scoring System; IV, intravenous; ORR, objective response rate; SC, subcutaneous; SCT, stem cell transplant

Courtesy of Mikkael A Sekeres, MD, MS

Higher-risk MDS | Combinations

EFS and OS: Higher-risk MDS





*EFS defined as time to death or transformation to AML in higher-risk MDS/CMML or death in low-blast AML.

Courtesy of Mikkael A Sekeres, MD, MS

Cancer Conference Update: What Happened at the 2020 San Antonio Breast Cancer Symposium

Session 1: Triple-Negative Breast Cancer

Monday, January 11, 2021
5:00 PM – 6:00 PM ET

Faculty

P Kelly Marcom, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Thank you for joining us!

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