A Conversation with the Investigators: Acute Myeloid Leukemia and Myelodysplastic Syndromes

Wednesday, July 14, 2021
5:00 PM – 6:00 PM ET

Faculty

Courtney D DiNardo, MD, MSCE
Gail J Roboz, MD
Eytan M Stein, MD

Moderator

Neil Love, MD

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Faculty

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

Eytan M Stein, MD
Assistant Attending Physician
Director, Program for Drug Development in Leukemia
Leukemia Service, Department of Medicine
Memorial Sloan Kettering Cancer Center
New York, New York

Gail J Roboz, MD
Director, Clinical and Translational
Leukemia Programs
Professor of Medicine
Weill Cornell Medical College
NewYork-Presbyterian Hospital
New York, New York

Moderator

Neil Love, MD
Research To Practice
Miami, Florida

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Commercial Support

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

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Dr Love — Disclosures

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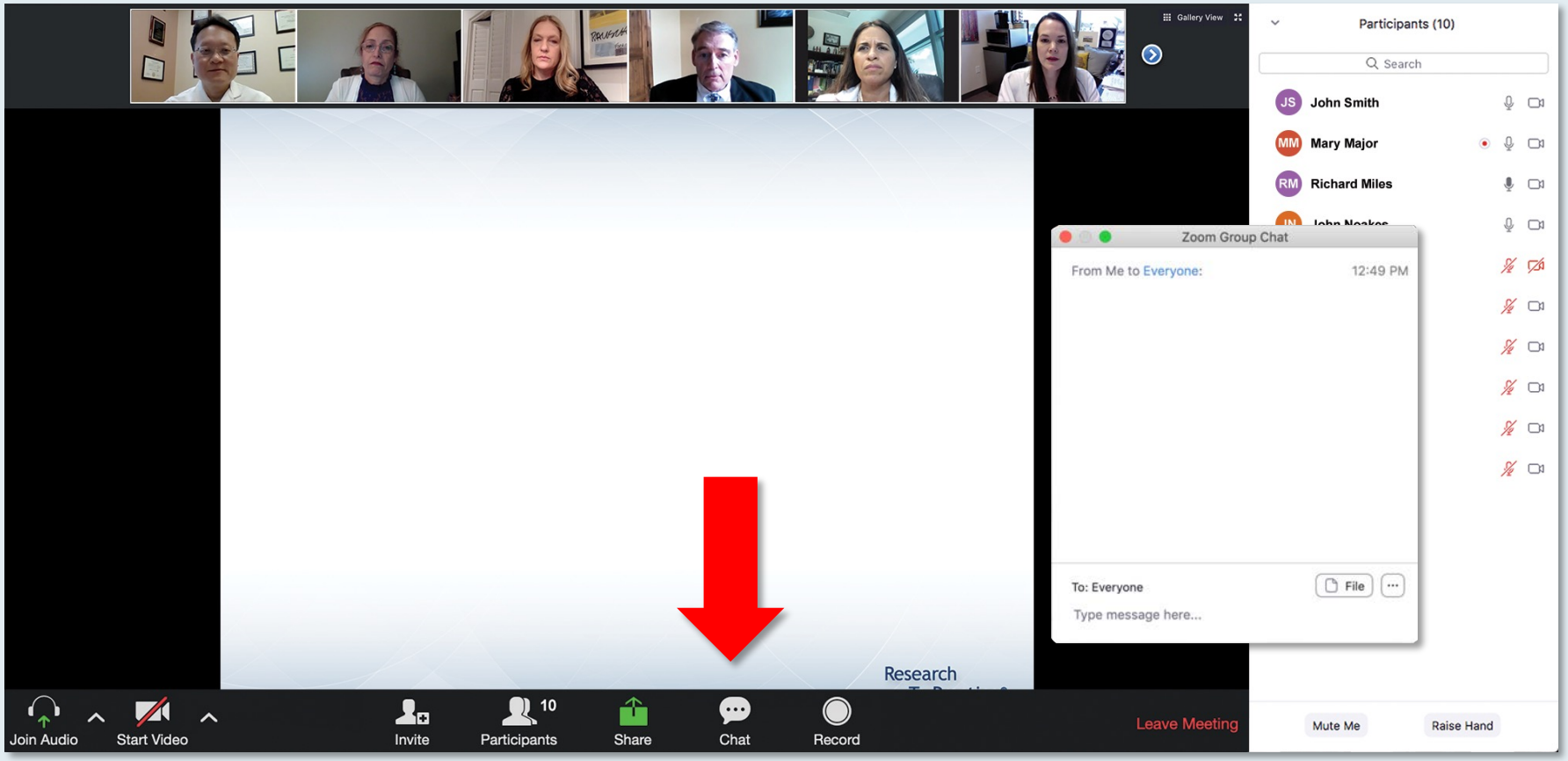
We Encourage Clinicians in Practice to Submit Questions



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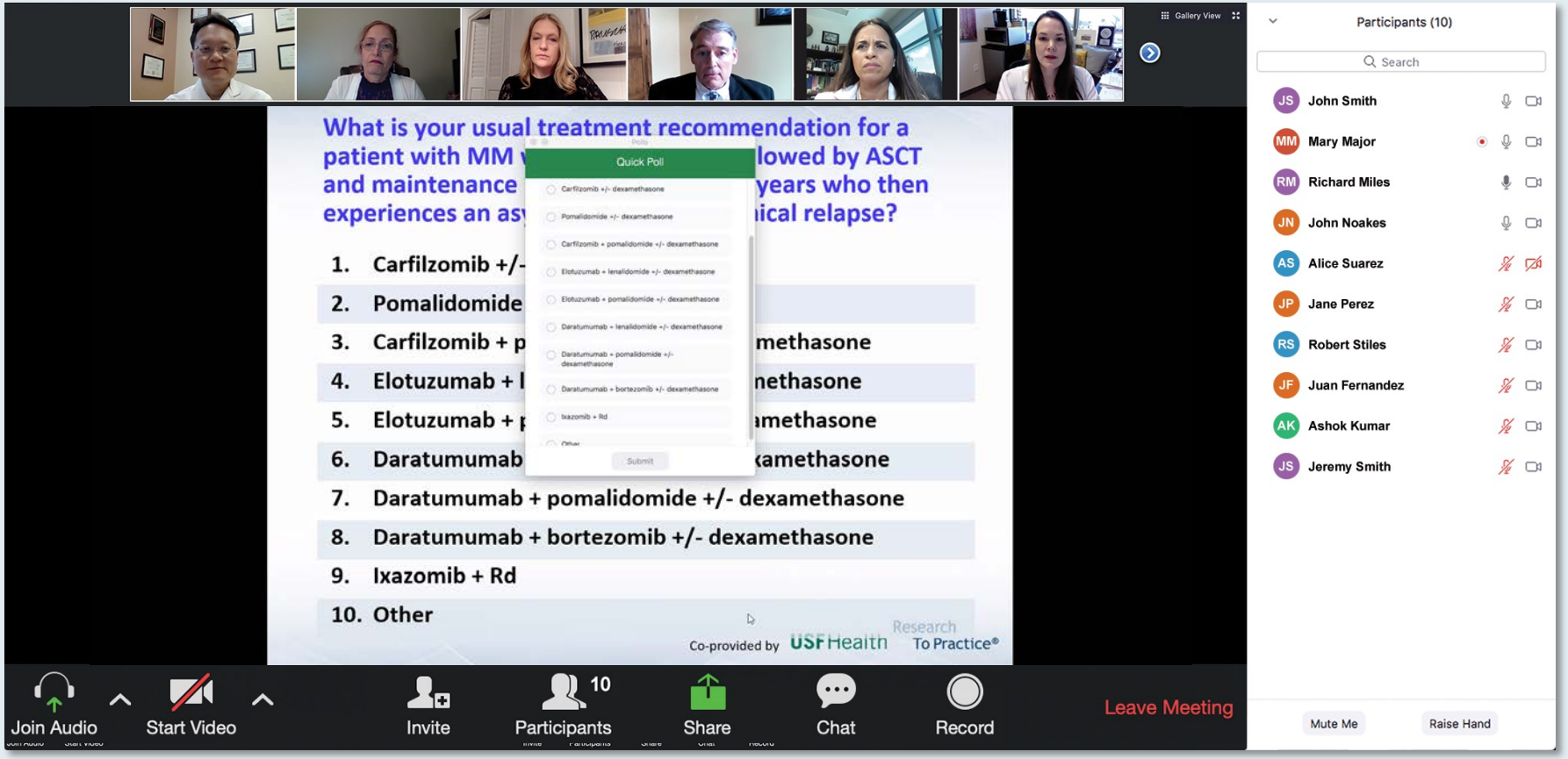
How to answer poll questions



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Familiarizing Yourself with the Zoom Interface

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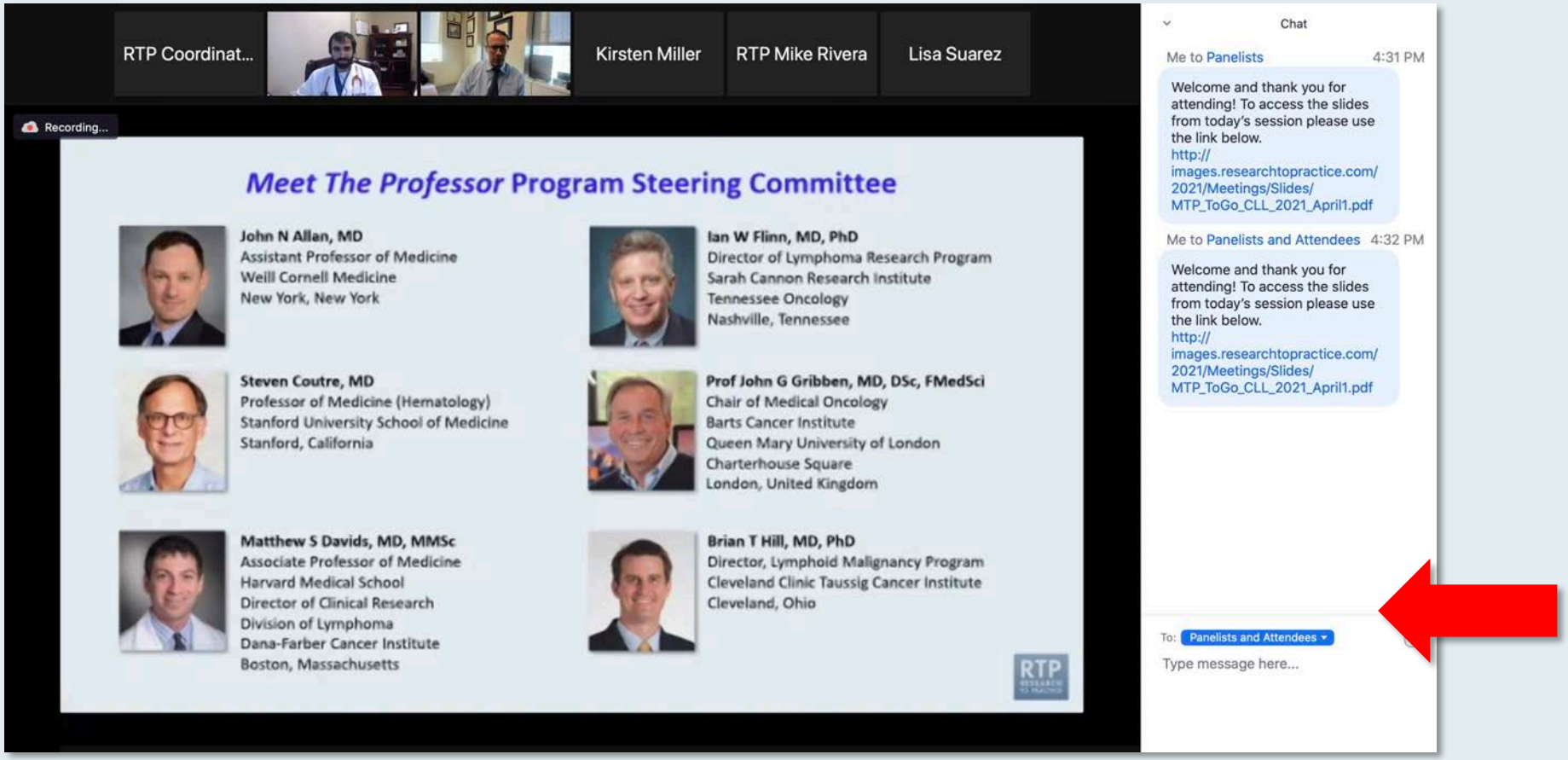

Drag the white line above the submission box up to create more space for your message.

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Familiarizing Yourself with the Zoom Interface

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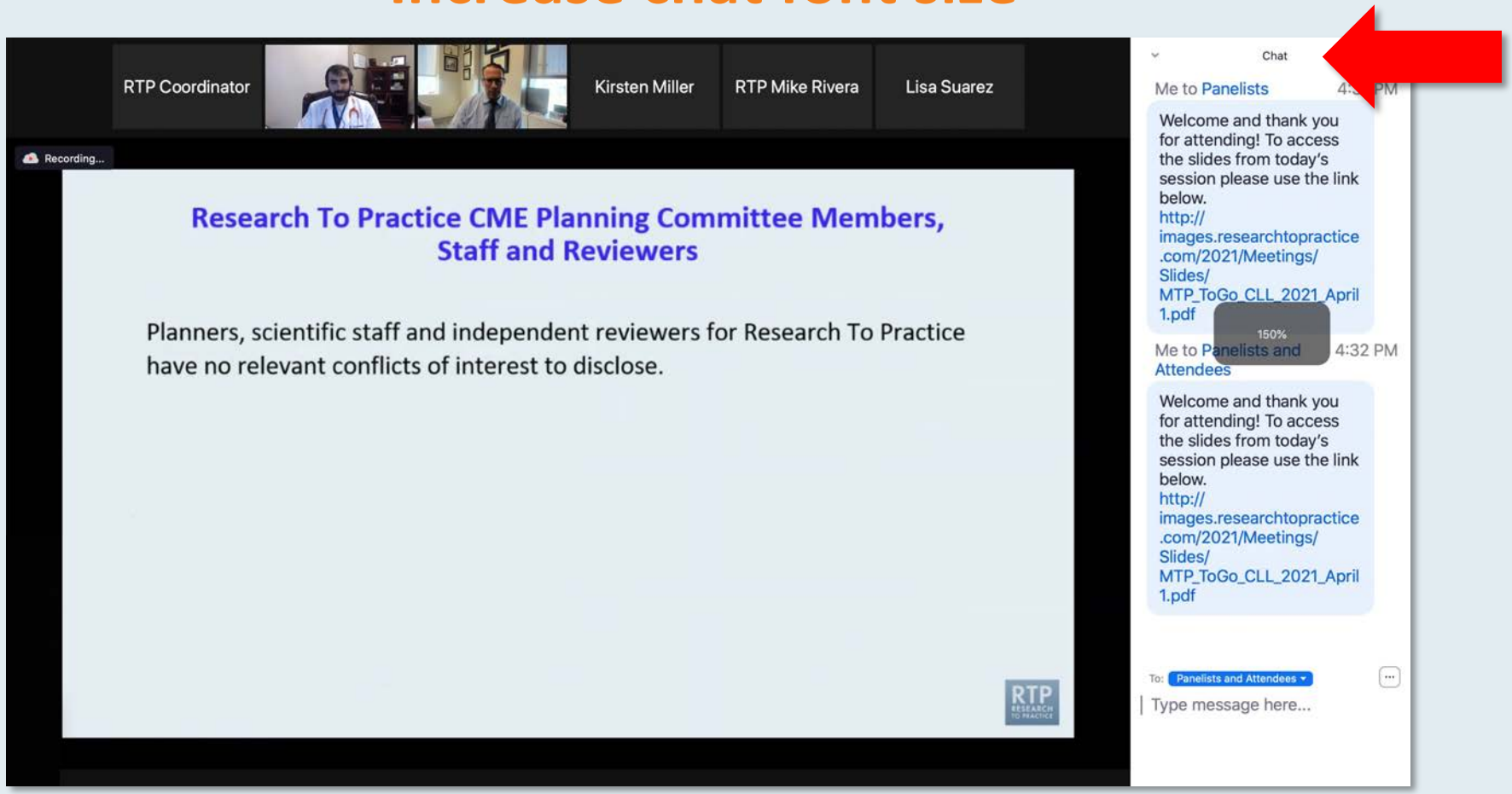

Press Command (for Mac) or Control (for PC) and the + symbol.
You may do this as many times as you need for readability.

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Progress in Myelodysplastic Syndromes

DR GUILLERMO GARCIA-MANERO

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10 Exciting CME/MOC Events You Do Not Want to Miss

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Wednesday, July 14
5:00 PM – 6:00 PM ET

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Tuesday, July 20
5:00 PM – 6:00 PM ET

Bladder Cancer
Wednesday, July 21
5:00 PM – 6:00 PM ET

Endometrial and Cervical Cancers
Monday, July 26
5:00 PM – 6:00 PM ET

Targeted Therapy for Non-Small Cell Lung Cancer
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Mantle Cell, Diffuse Large B-Cell and Hodgkin Lymphoma
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Hepatocellular Carcinoma and Pancreatic Cancer
Wednesday, August 4
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Head and Neck Cancer
Wednesday, August 11
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Meet The Professor

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

Monday, July 19, 2021
5:00 PM – 6:00 PM ET

Faculty

Tanios Bekaii-Saab, MD

Moderator

Neil Love, MD

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A Conversation with the Investigators: Metastatic Castration-Resistant Prostate Cancer

Tuesday, July 20, 2021
5:00 PM – 6:00 PM ET

Faculty

Emmanuel S Antonarakis, MD
Johann de Bono, MBChB, MSc, PhD
Julie N Graff, MD

Moderator

Neil Love, MD

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A Conversation with the Investigators: Bladder Cancer

Wednesday, July 21, 2021
5:00 PM – 6:00 PM ET

Faculty

Petros Grivas, MD, PhD
Daniel P Petrylak, MD
Arlene Siefker-Radtke, MD

Moderator

Neil Love, MD

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

Thursday, July 22, 2021
5:00 PM – 6:00 PM ET

Faculty

David F McDermott, MD

Moderator

Neil Love, MD

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A Conversation with the Investigators: Endometrial and Cervical Cancers

Monday, July 26, 2021
5:00 PM – 6:00 PM ET

Faculty

Mansoor Raza Mirza, MD
David M O'Malley, MD
Angeles Alvarez Secord, MD, MHSc

Moderator

Neil Love, MD

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What General Medical Oncologists Want to Know About Targeted Therapy for Non-Small Cell Lung Cancer

Tuesday, July 27, 2021
5:00 PM – 6:00 PM ET

Faculty

Professor Solange Peters, MD, PhD
Zofia Piotrowska, MD, MHS
Gregory J Riely, MD, PhD

Moderator

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What General Medical Oncologists Want to Know About Immunotherapy and Other Nontargeted Approaches for Lung Cancer

Wednesday, July 28, 2021
5:00 PM – 6:00 PM ET

Faculty

Mark Awad, MD, PhD
David R Spigel, MD
Heather Wakelee, MD

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Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 2 to 3 business days.

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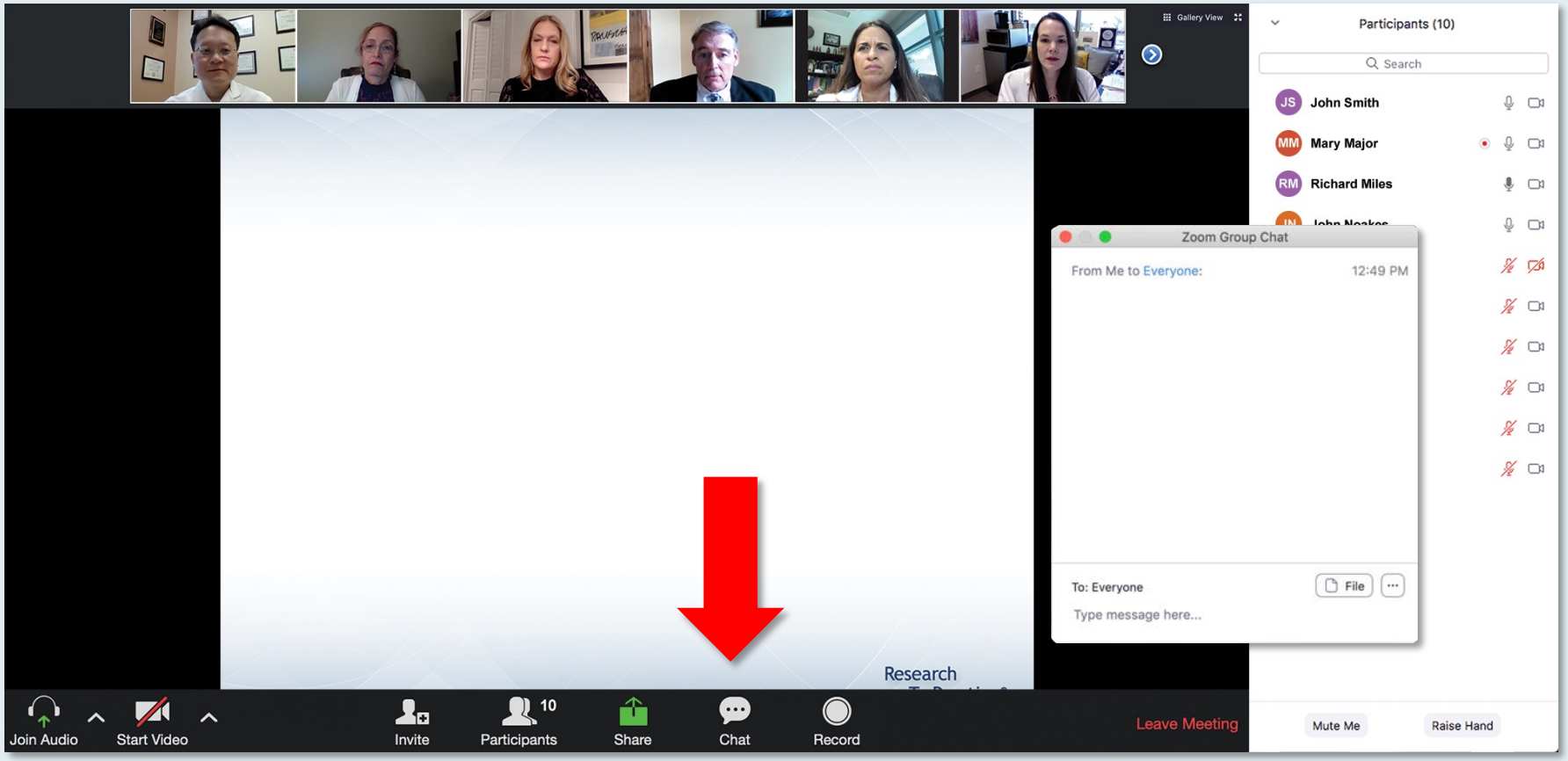

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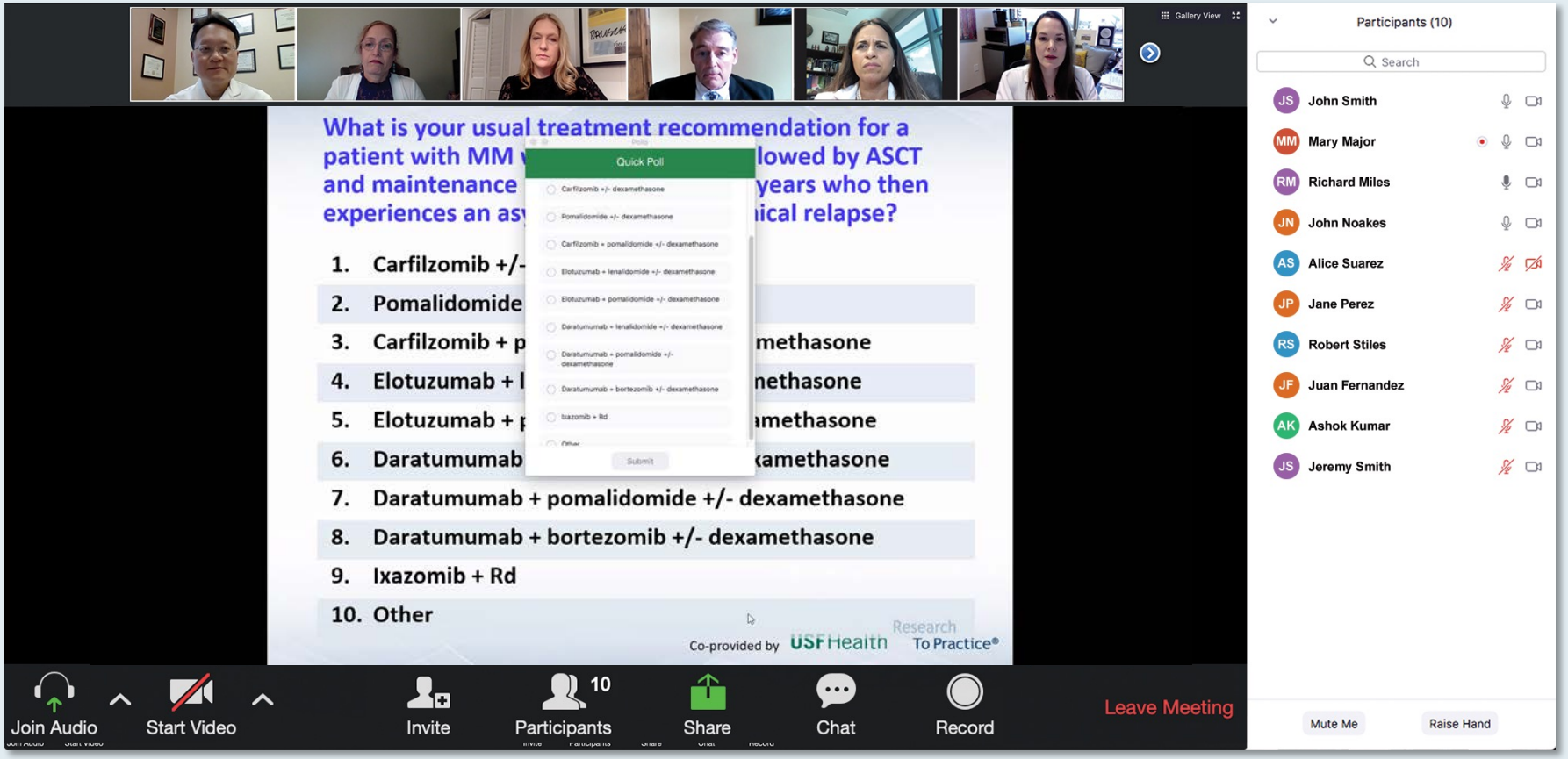

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ASCO 2021 Acute Myeloid Leukemia and Myelodysplastic Syndromes Presentation Library

Recent Advances in the Up-Front Treatment of AML

Courtney D DiNardo, MD, MSCE

Download Slides

Update on the Management of MDS

Gail J Roboz, MD

Download Slides

Secondary AML (sAML)

Eytan M Stein, MD

Download Slides

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Agenda

Module 1: Recent Advances in the Up-Front Treatment of Acute Myeloid Leukemia (AML)

- VIALE-A: Azacitidine and venetoclax in older patients with previously untreated AML
- Venetoclax-based regimens for patients with newly diagnosed AML who are or are not eligible for intensive induction therapy
- Efficacy of venetoclax-based combination regimens in patients with FLT3 or IDH1/2 mutations

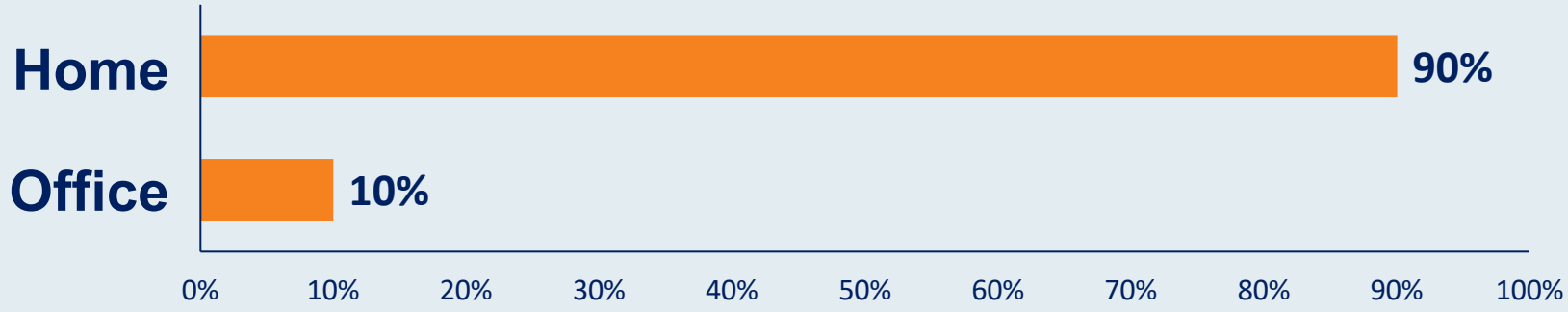
Module 2: Secondary AML (sAML)

- Mechanism of action, available data with and side effects of CPX-351 in previously untreated sAML and primary AML
- Available data with and current clinical role of venetoclax-based therapy for patients with sAML

Module 3: Myelodysplastic Syndromes (MDS)

- ASCERTAIN studies evaluating the oral combination of decitabine and cedazuridine in patients with MDS
- Available research findings for agents with established efficacy in AML for patients with MDS
- Promising novel agents (eg, magrolimab, pevonedistat, sabatolimab) in MDS

Where is the most common location that you watch oncology education webinars?



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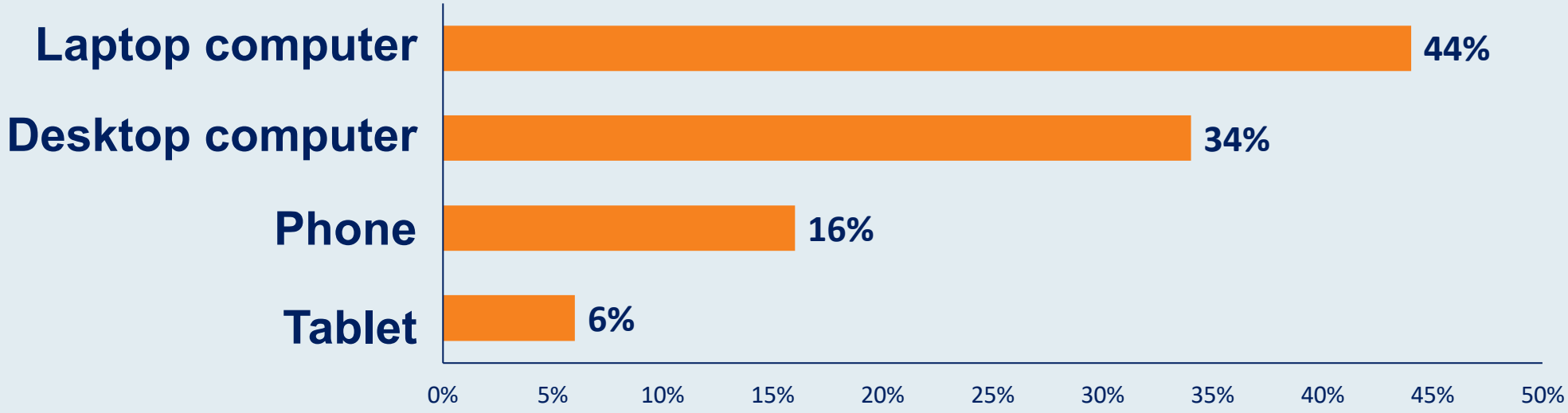

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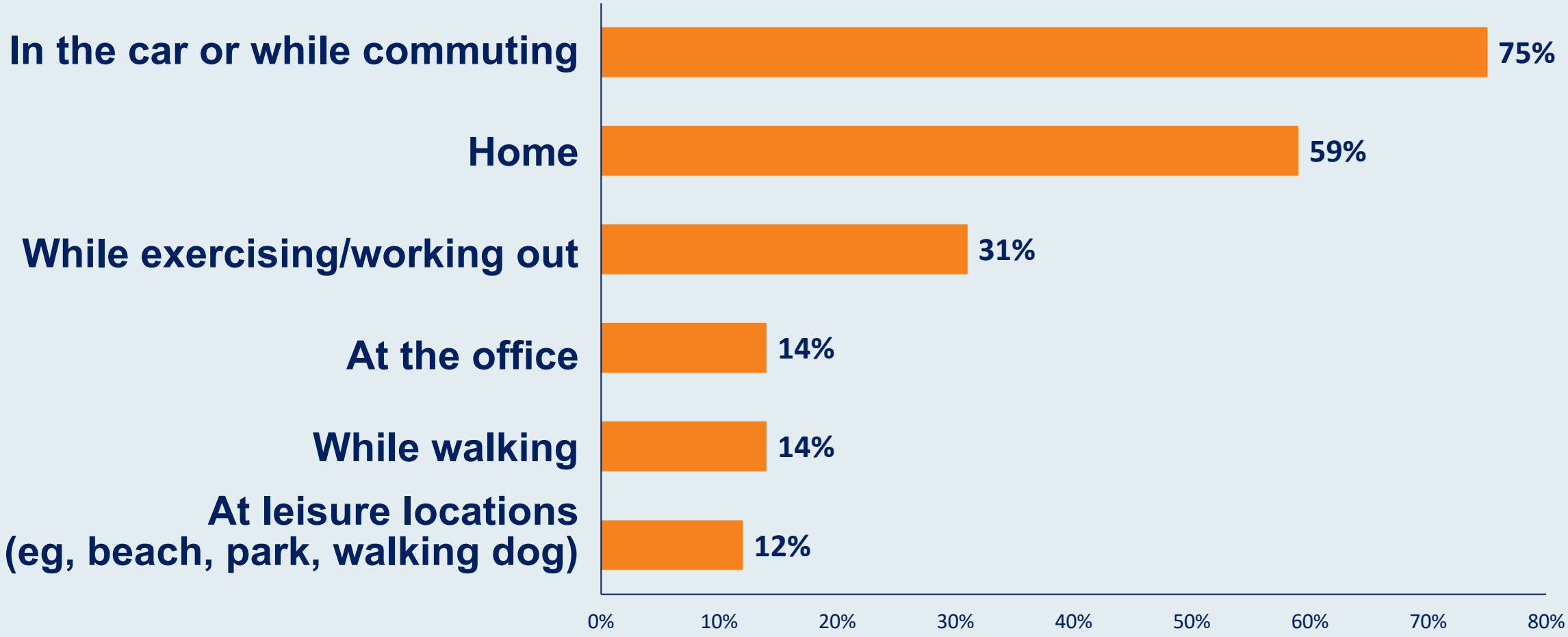
Where do you generally listen to audio podcasts? (Check all that apply)



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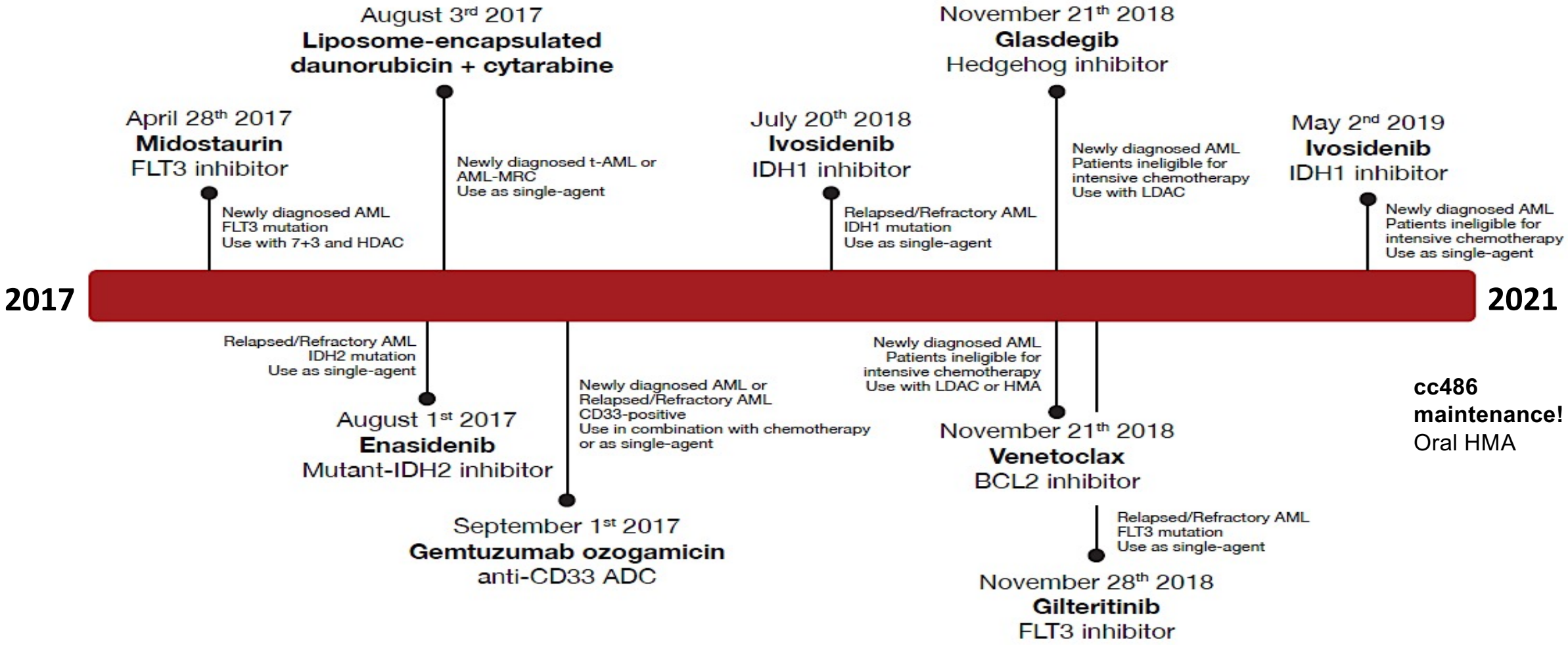
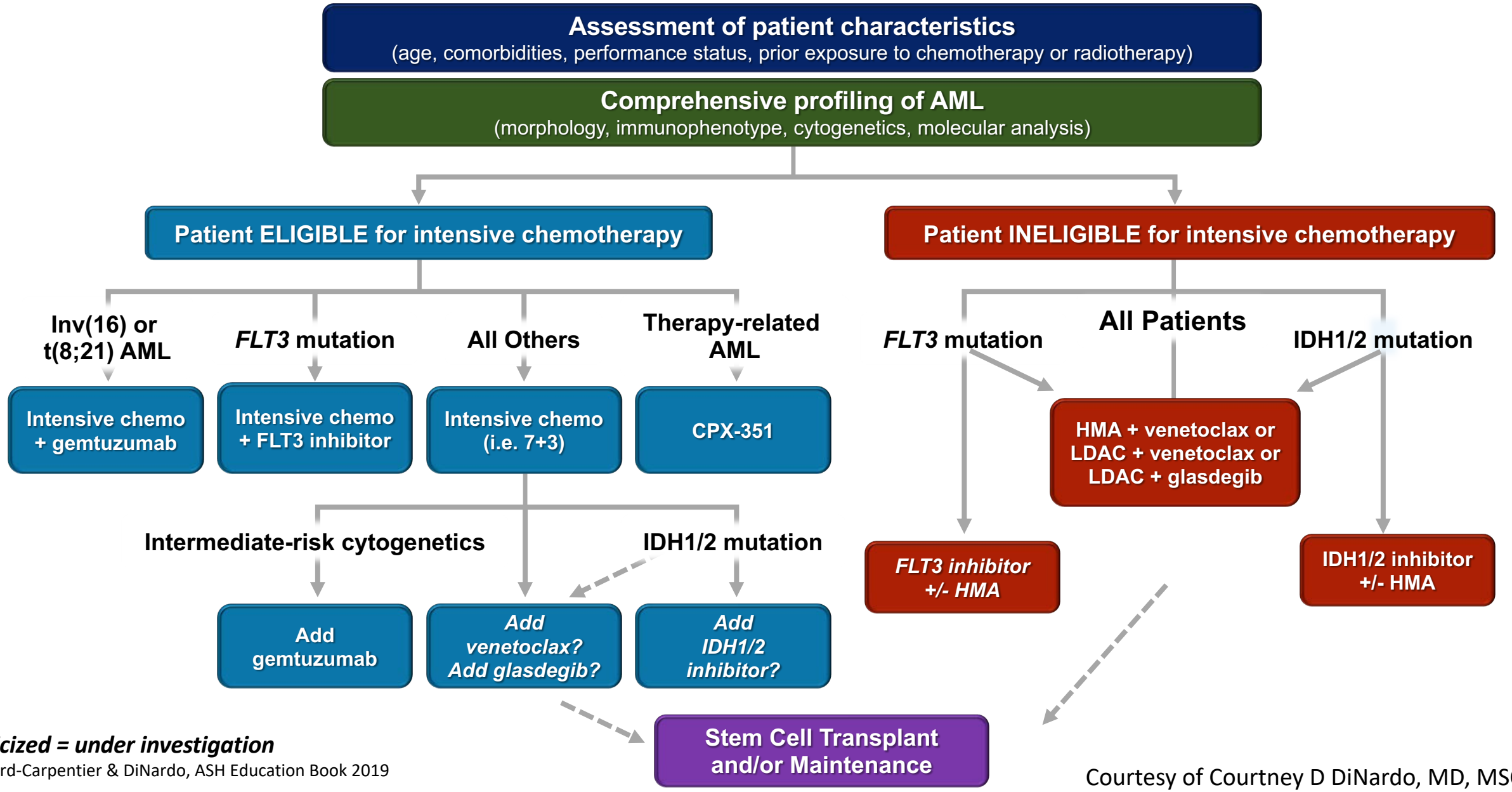
The Rapidly Evolving Treatment Landscape of AML: FDA Approvals



Richard-Carpentier G, DiNardo CD. *Hematology Am Soc Educ Program*. 2019(1):548-556.

Courtesy of Courtney D DiNardo, MD, MSCE

Evolving diagnostic and treatment paradigm for Newly Dx AML

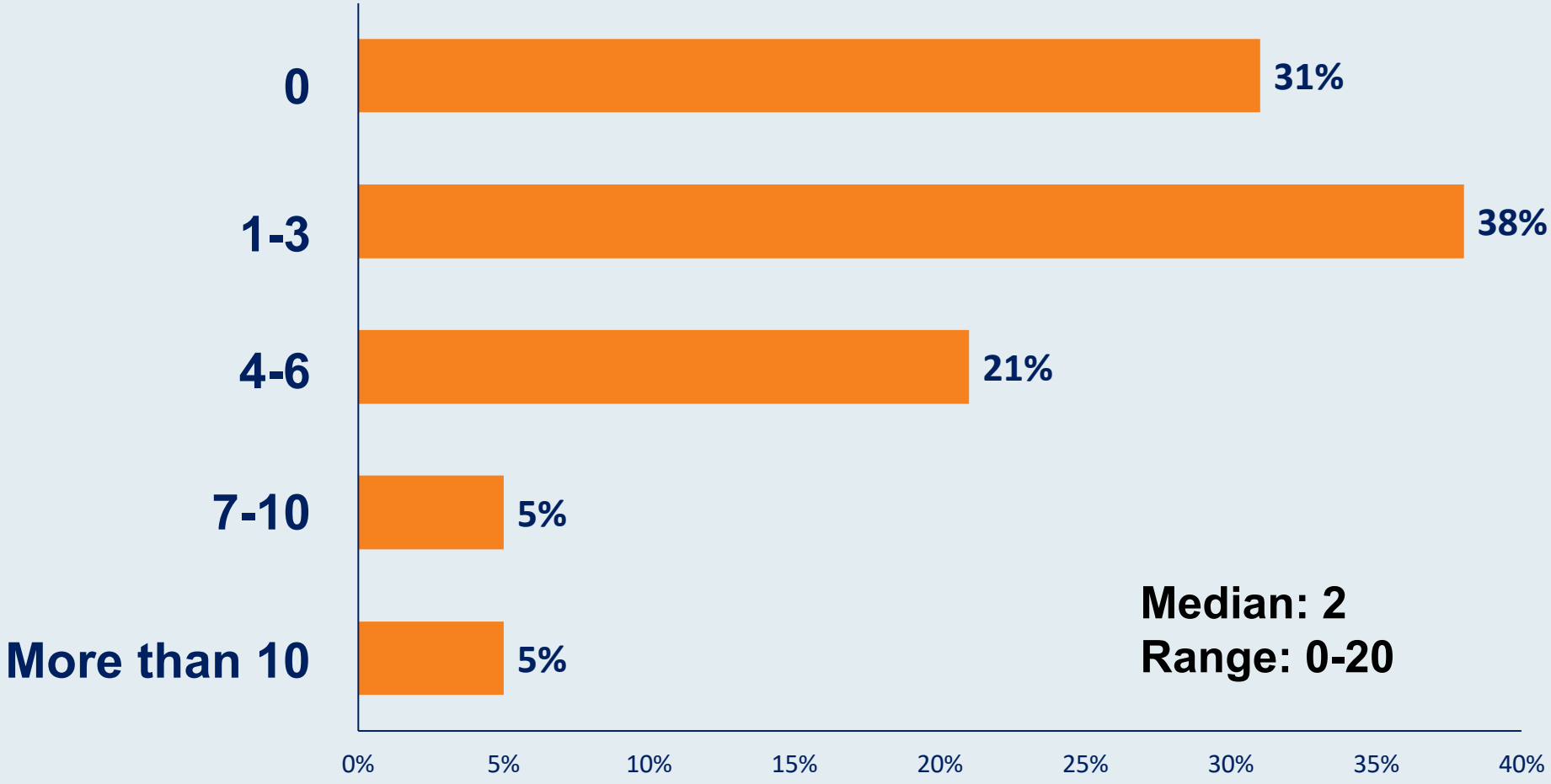


Italicized = under investigation

Richard-Carpentier & DiNardo, ASH Education Book 2019

Courtesy of Courtney D DiNardo, MD, MSCE

In the past year, to approximately how many patients with acute myeloid leukemia (AML) have you administered treatment?



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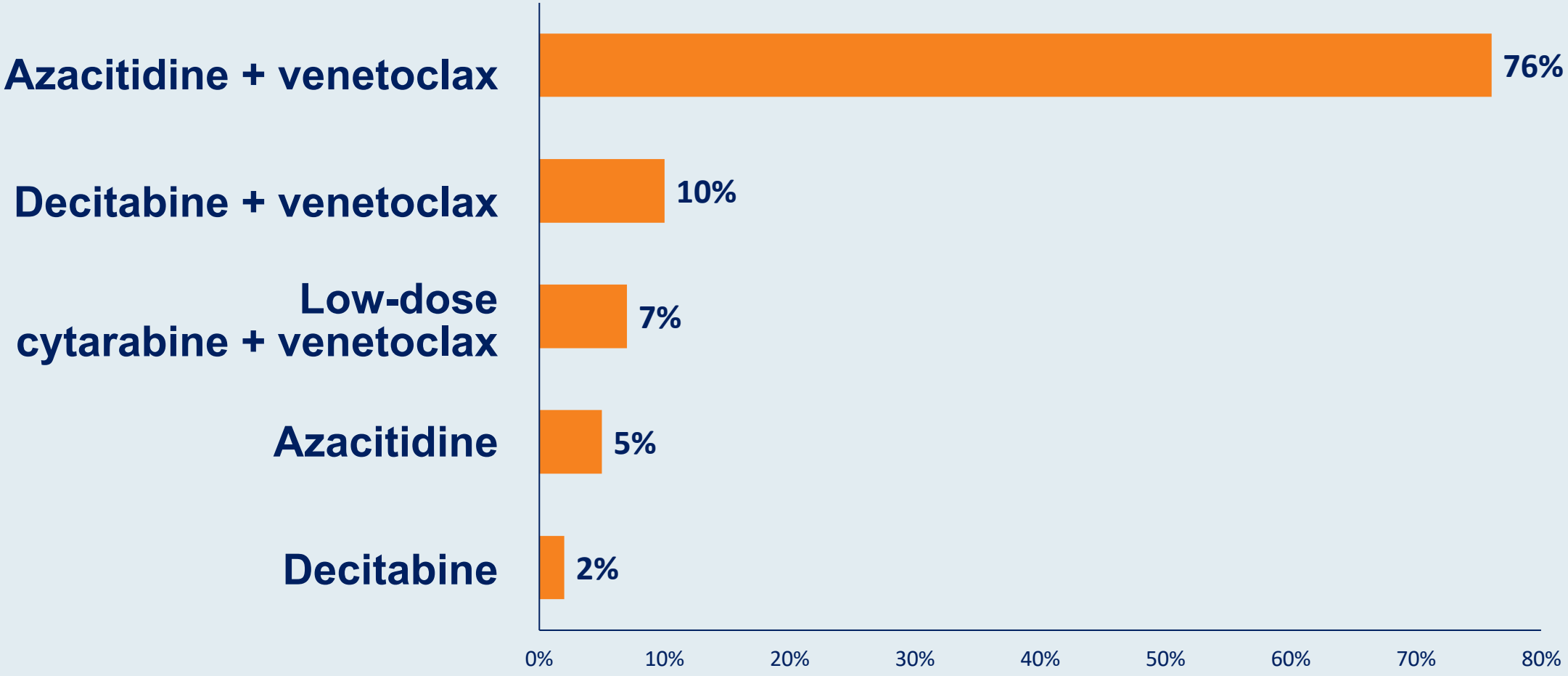
What initial treatment would you generally recommend for an 80-year-old patient with AML and intermediate-risk cytogenetics?



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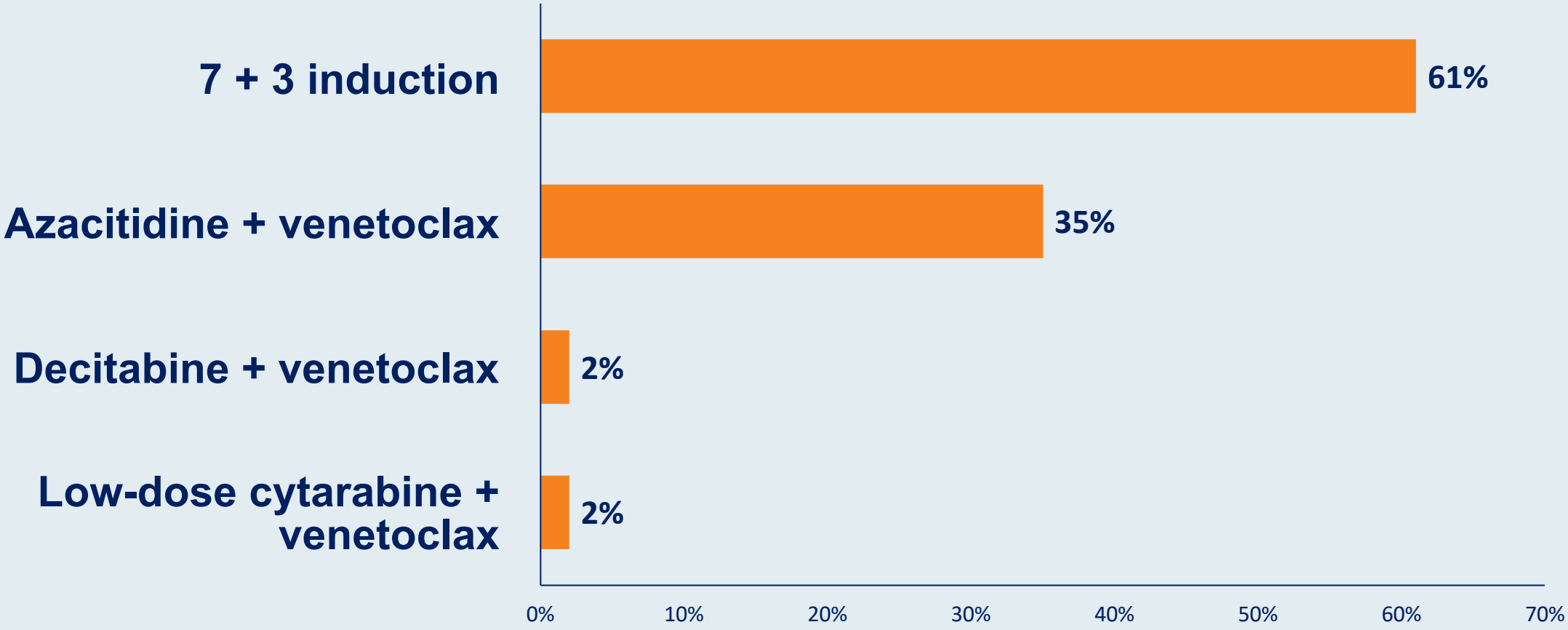
What initial treatment would you recommend for a 65-year-old man with AML with a PS of 1 and pancytopenia, 35% marrow myeloblasts, a complex karyotype and a TP53 mutation?



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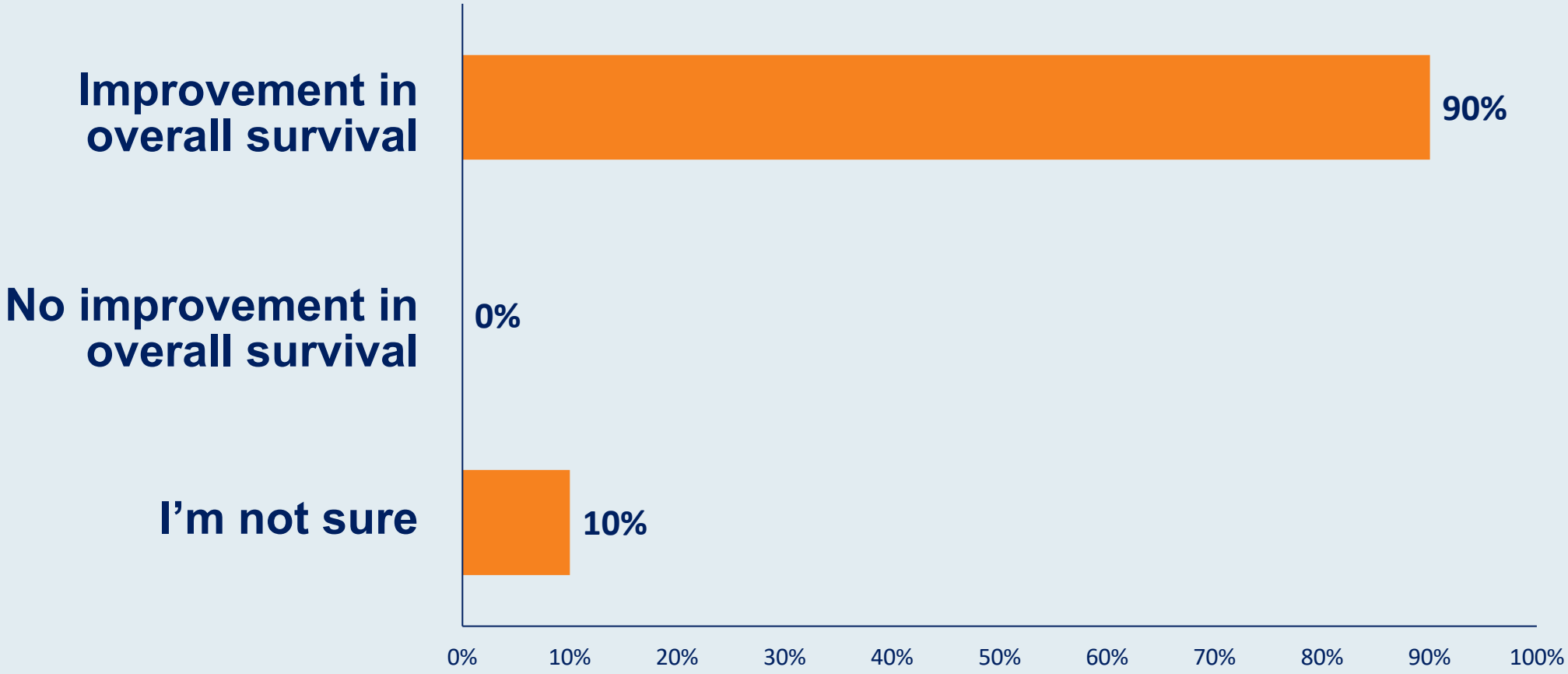
The VIALE-A trial evaluating azacitidine in combination with either venetoclax or placebo for patients with treatment-naïve AML not eligible for intensive therapy demonstrated which clinical outcome on the azacitidine/venetoclax arm?



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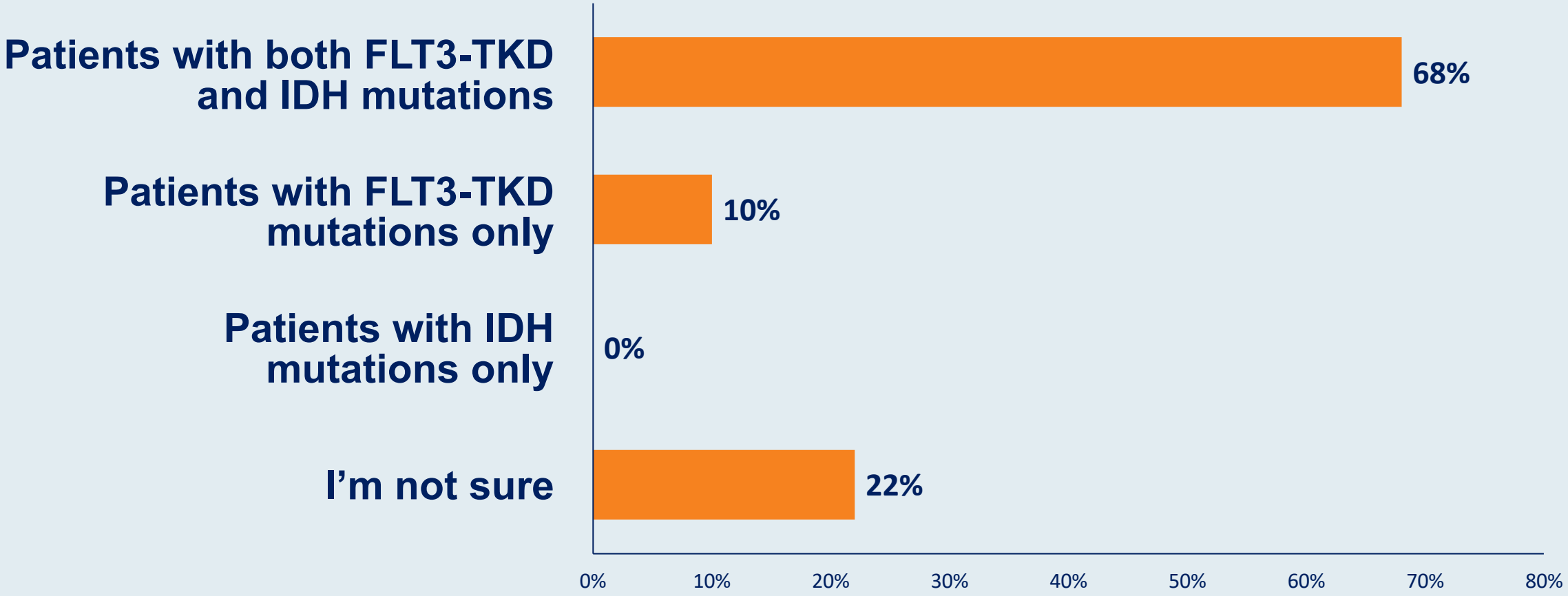
The combination of venetoclax and azacitidine is effective in which of the following types of patients with chemotherapy-ineligible, untreated AML?



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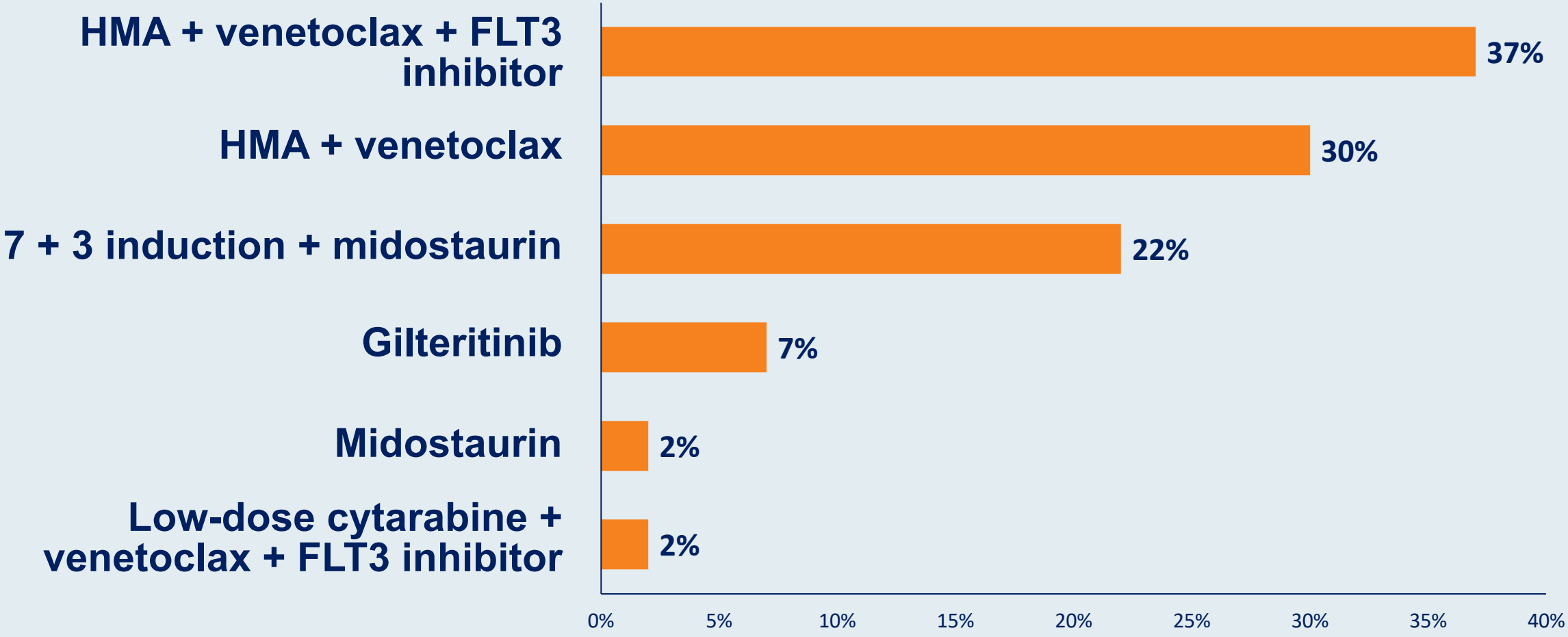
What would you recommend as first-line therapy to a 78-year-old patient (PS 0) who presents with intermediate-risk AML with a FLT3-ITD mutation?



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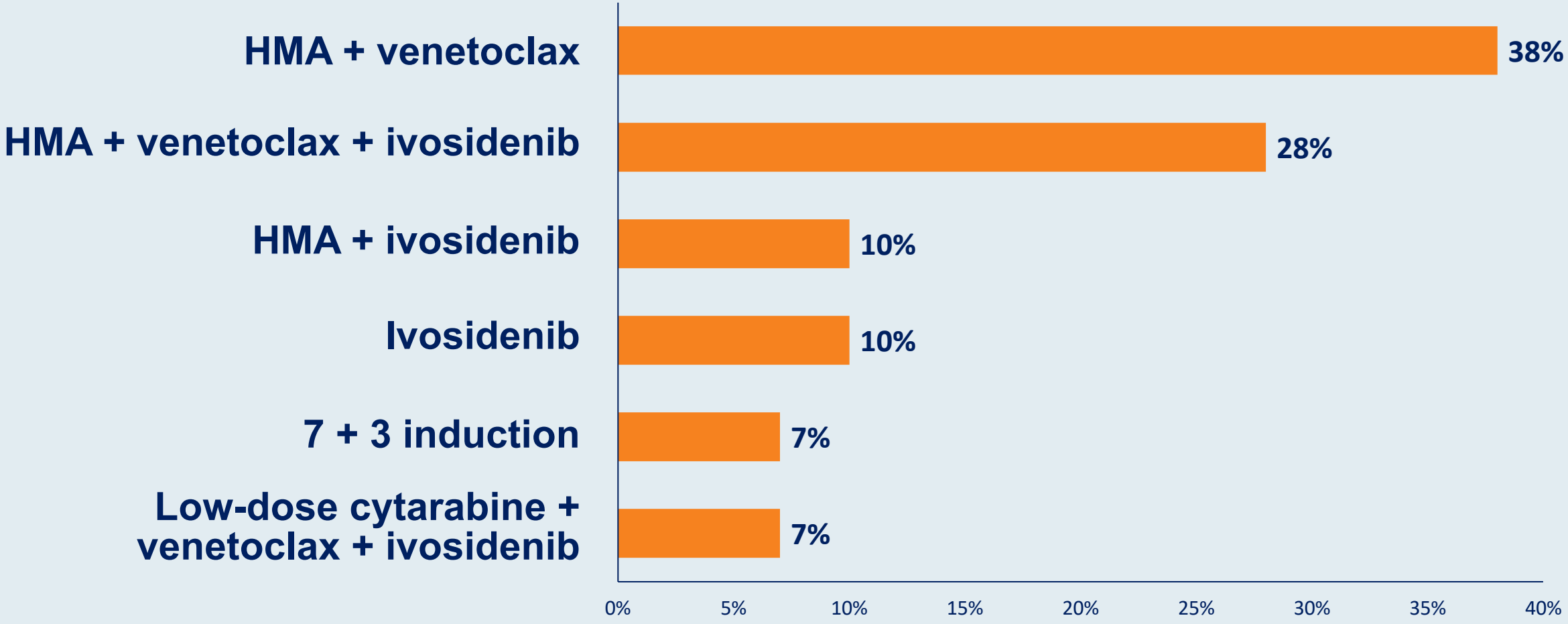
What would you recommend as first-line therapy to a 78-year-old patient (PS 0) who presents with intermediate-risk AML with an IDH1 mutation?



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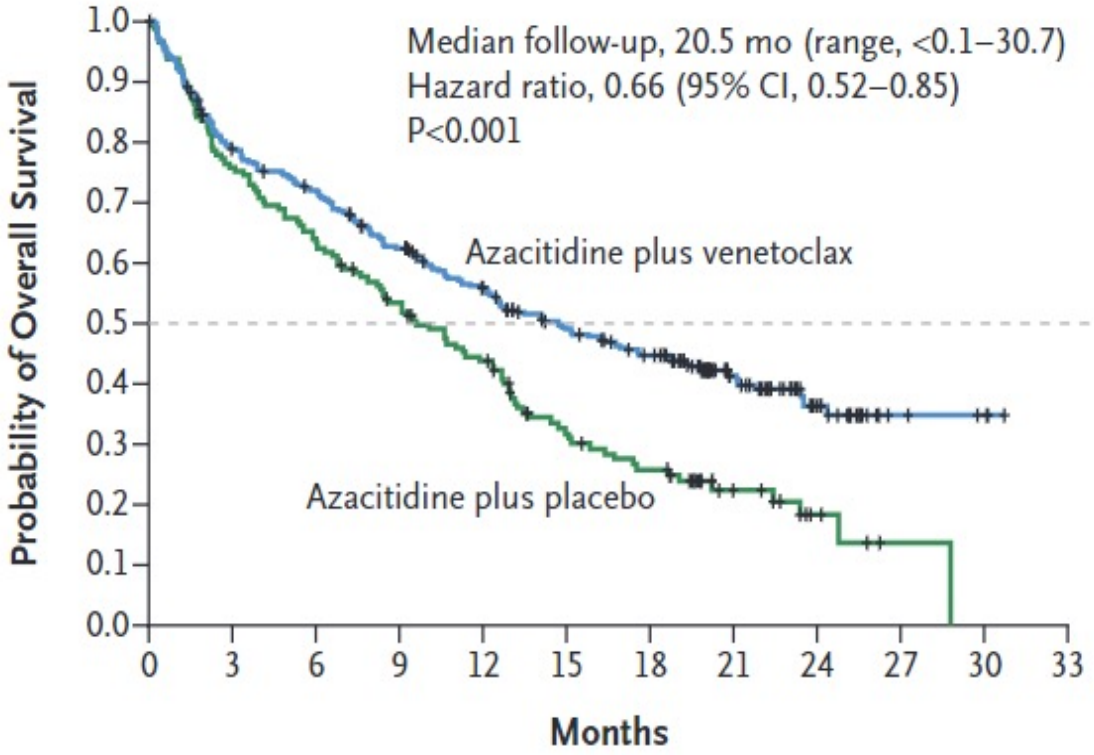
Results of VIALE-A : Azacitidine + venetoclax

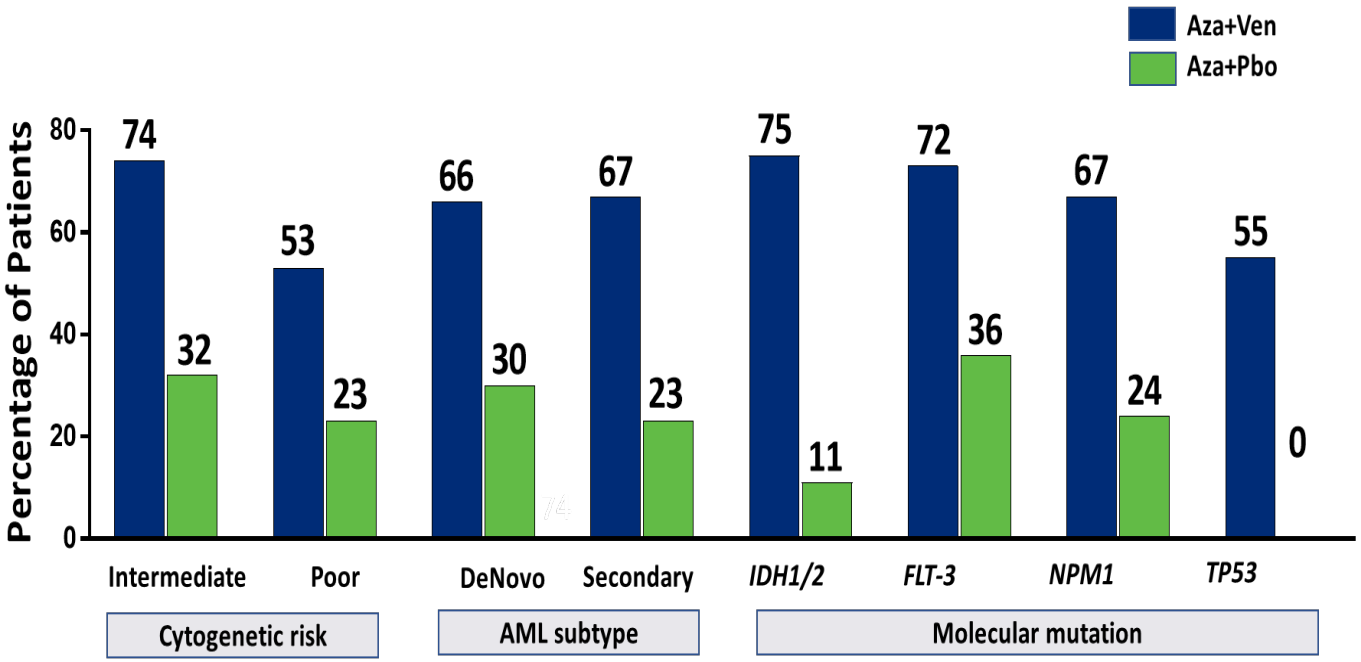
Significant OS improvement with venetoclax/azacitidine

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

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



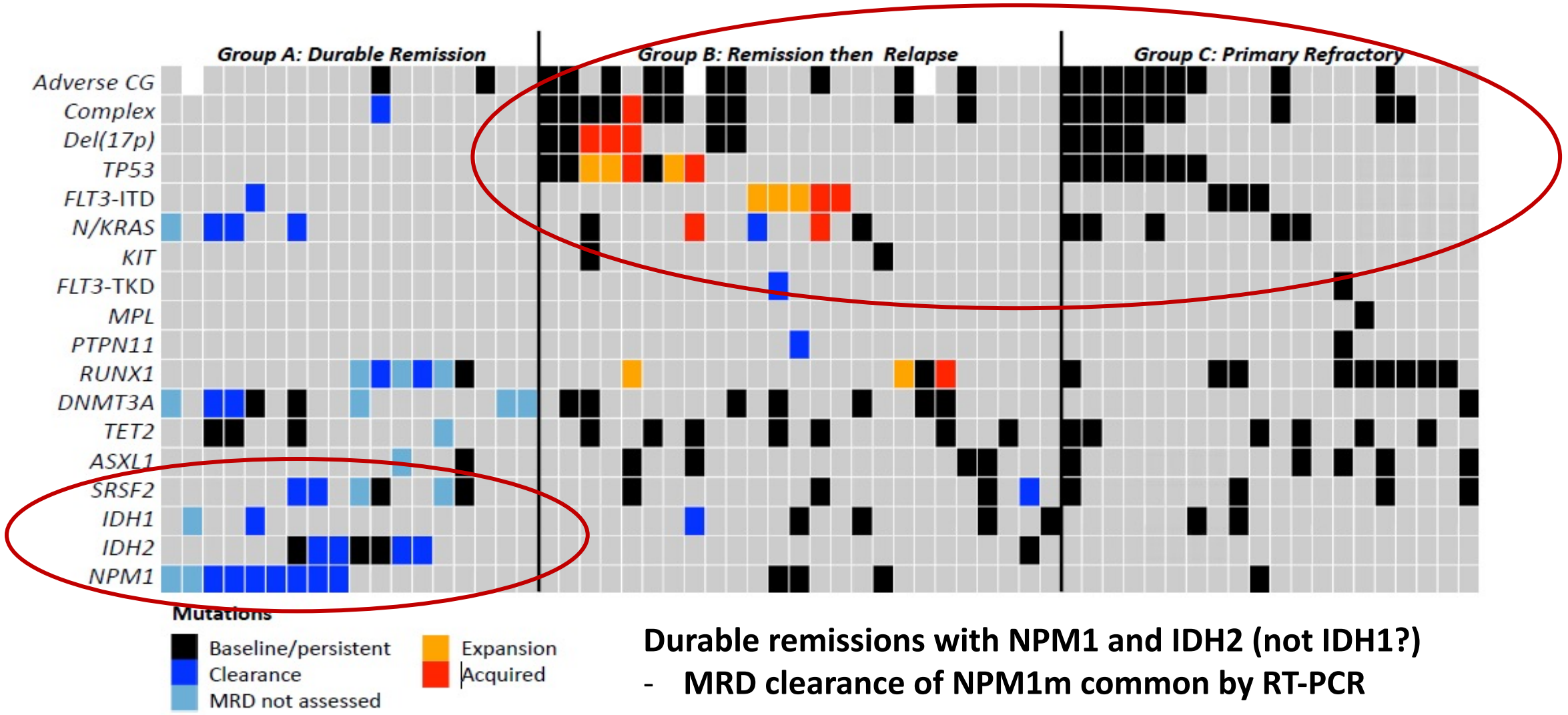
Improved responses occurred *independent* of high risk genomics



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

Courtesy of Courtney D DiNardo, MD, MSCE

Molecular determinants of outcome with venetoclax combos



Durable remissions with NPM1 and IDH2 (not IDH1?)

- **MRD clearance of NPM1m common by RT-PCR**

Resistance commonly associated with expansion or acquisition of TP53 or FLT3-ITD

Patients treated at MDACC and The Alfred (n=81)

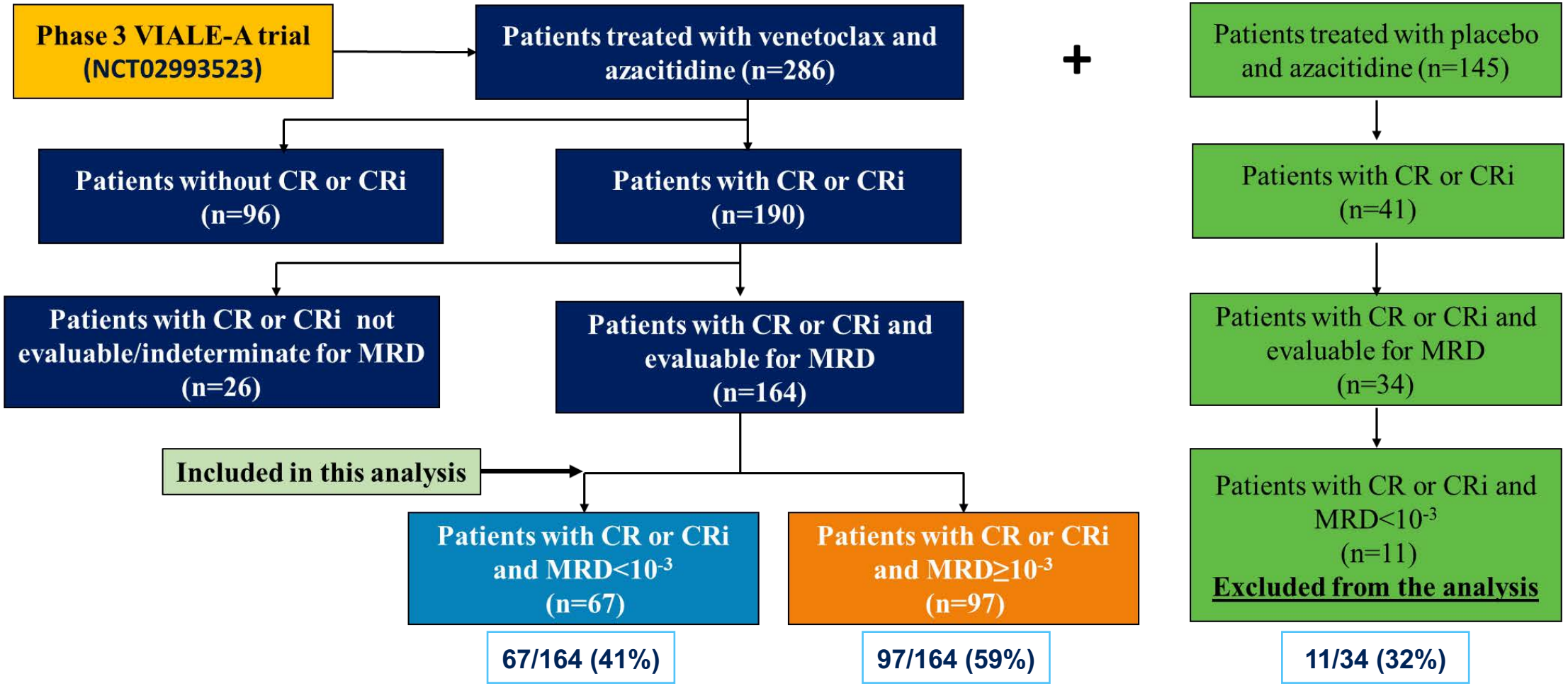
DiNardo CD, Tiong I, … Konopleva M, Wei A, Blood 2020

Courtesy of Courtney D DiNardo, MD, MSCE

VIALE-A: Flow cytometry MRD: Response and Prognosis

ASCO 21

Analyzed patient population



Data cutoff: Jan 04, 2020
CR: Complete remissions, CRi: CR with incomplete hematological recovery; MRD: Minimal residual disease
Patients were indeterminate if the BM samples had less than a hundred thousand CD45+ leukocytes

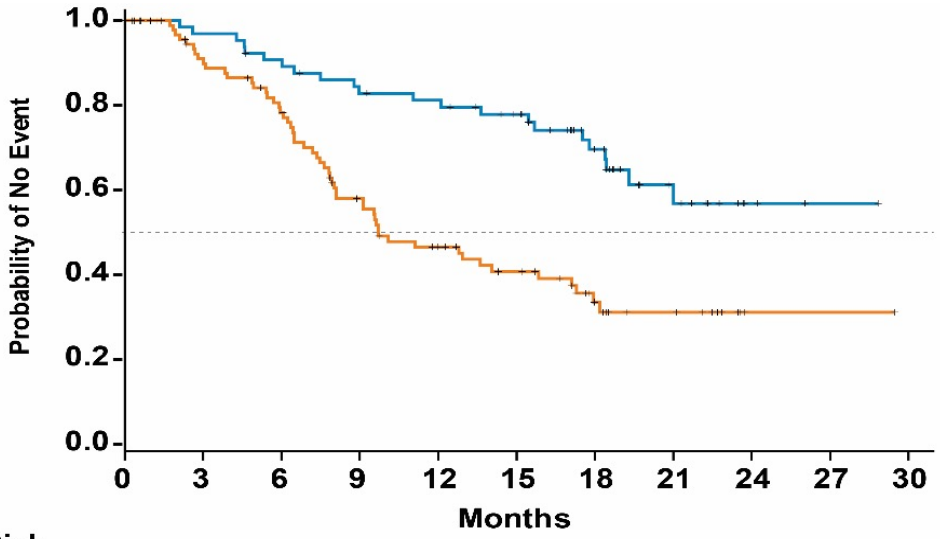
Pratz KW, et al. Abstract 7018. ASCO 2021.

Courtesy of Courtney D DiNardo, MD, MSCE

VIALE-A

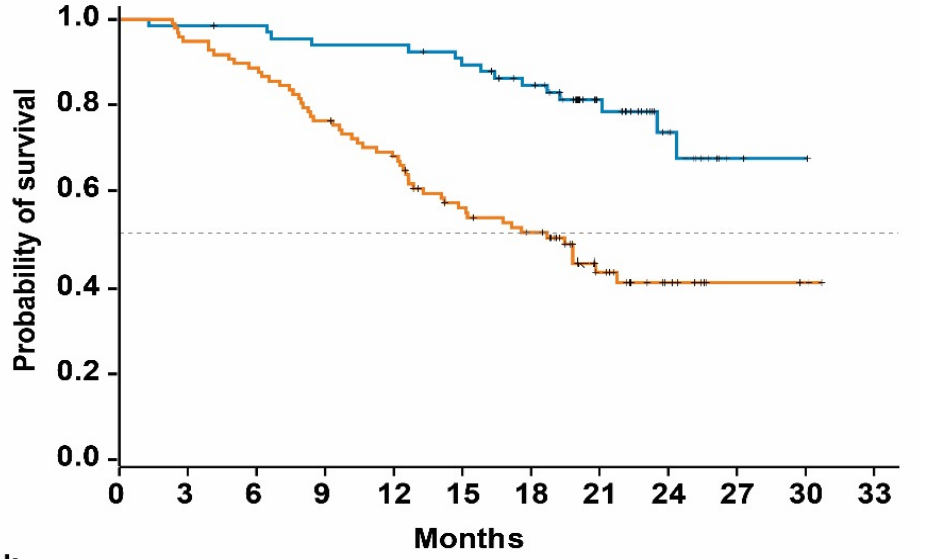
ASCO 21

Duration of remission



Patients at Risk											
CR+CRi+MRD<10^{-3}	67	63	58	52	50	44	30	14	3	1	0
CR+CRi+MRD≥10^{-3}	97	80	67	46	34	27	14	9	1	1	0

Overall Survival



Patients at Risk												
CR+CRi+MRD<10^{-3}	67	66	65	62	62	58	52	30	13	2	1	0
CR+CRi+MRD≥10^{-3}	97	92	86	74	64	49	42	21	10	3	2	0

Duration of remission	# of events	12-month, %	18-month, %	Median DoR, months
CR+CRi+MRD<10^{-3}	22	81.2	69.6	NR
CR+CRi+MRD≥10^{-3}	54	46.6	33.5	9.7

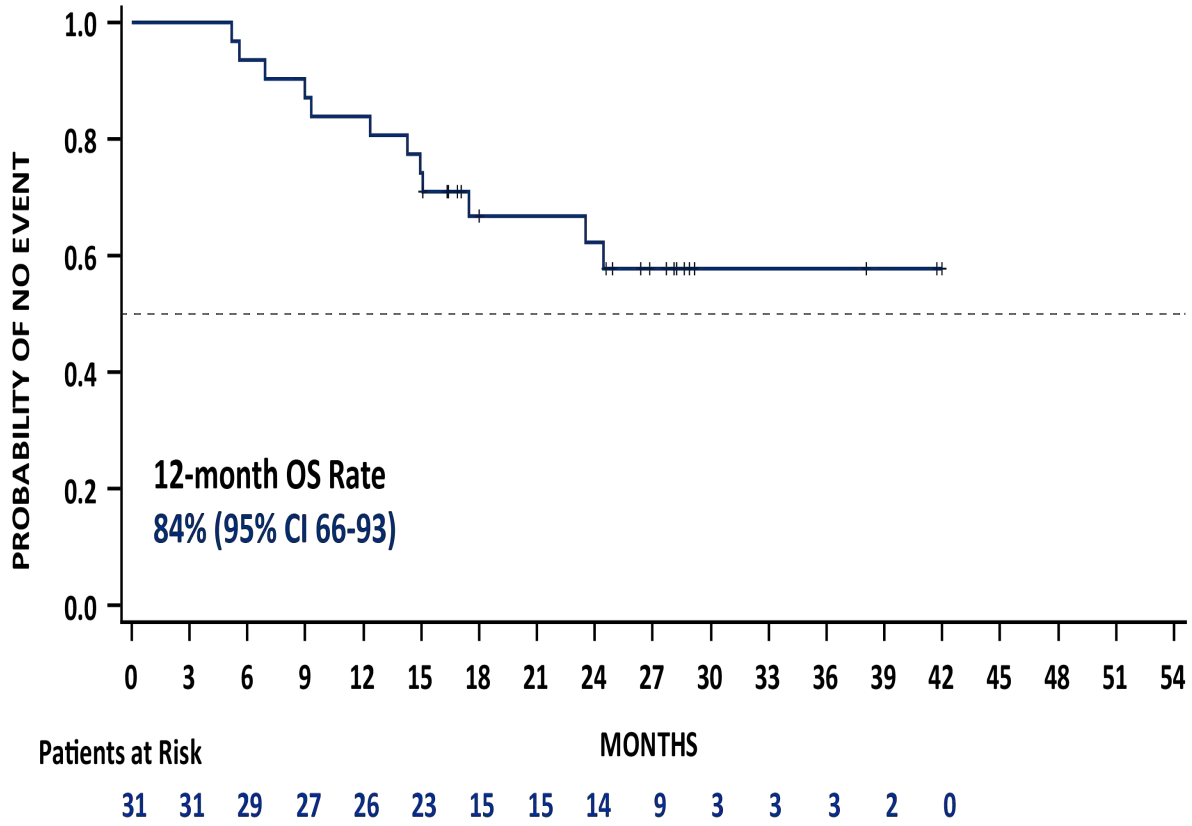
Overall survival	# of events	12-month, %	18-month, %	Median OS, months
CR+CRi+MRD<10^{-3}	15	94.0	84.6	NR
CR+CRi+MRD≥10^{-3}	52	67.9	50.1	18.7

Pratz KW, et al. Abstract 7018. ASCO 2021.

Courtesy of Courtney D DiNardo, MD, MSCE

Outcomes of SCT in patients after VEN-based regimens

- **10%** 31 of 304 patients received SCT
  - 26/31 in CR/CRi
- **68%** (21/31) of patients remained alive at 12 months post-transplant
- **55%** (17/31) of all patients that had SCT had posttransplant remission of ≥12 months
  - **71%** (12/17) of those patients remained in remission for ≥2 years

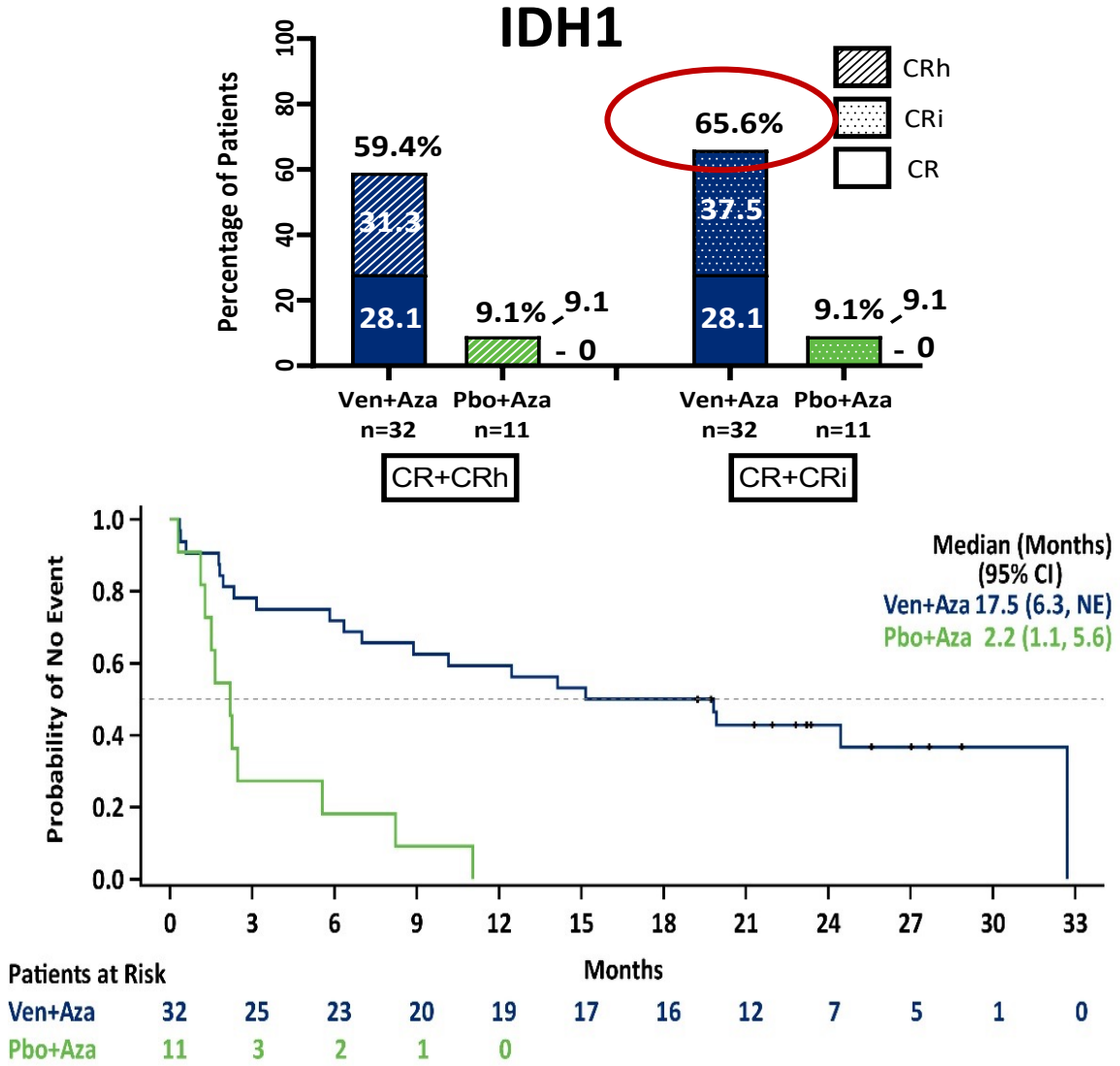


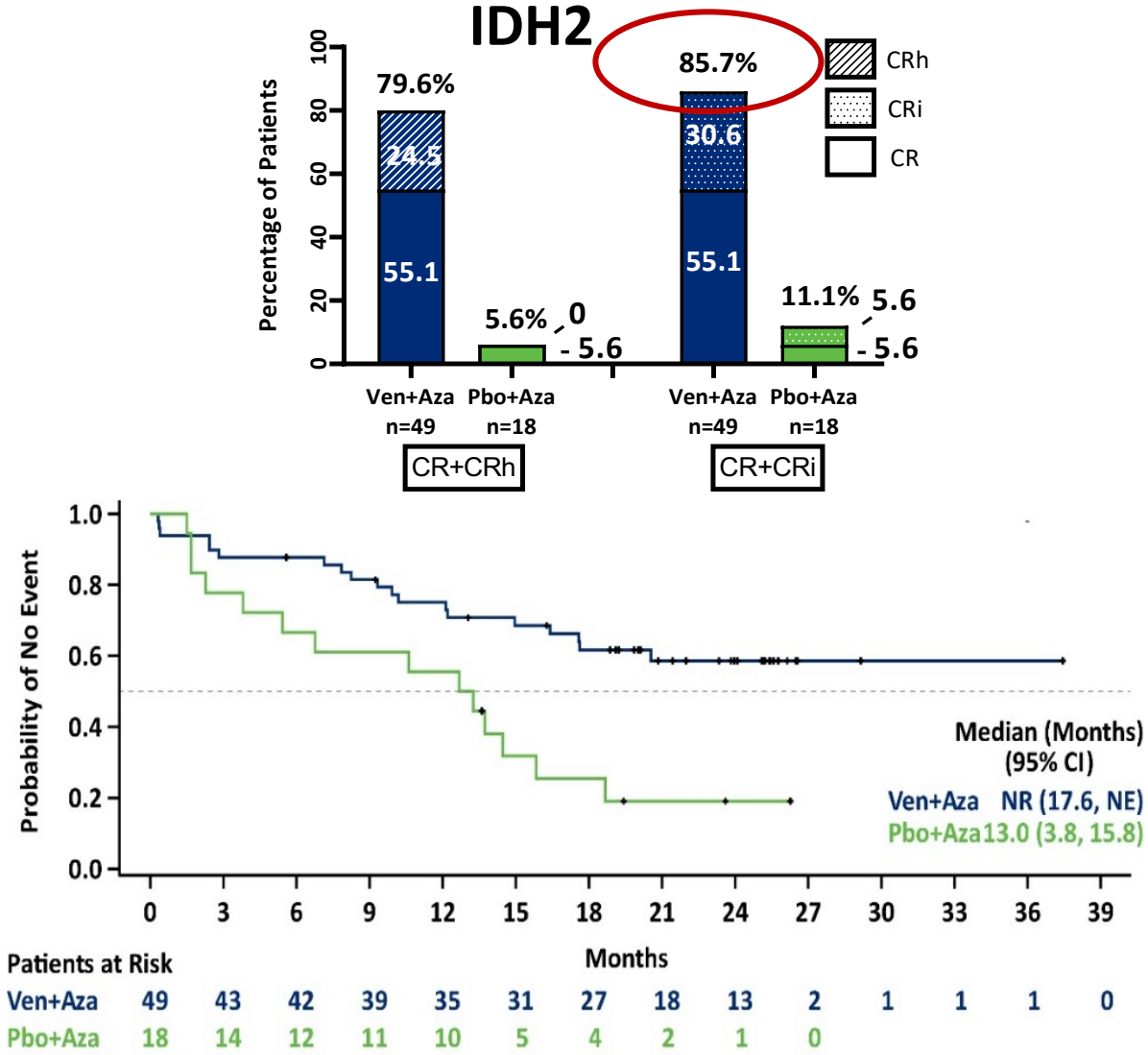
VEN-based regimens, even in patients deemed unfit for intensive induction, may provide a path to curative allogenic SCT

#264: Pratz K et al, ASH 2019

Courtesy of Courtney D DiNardo, MD, MSCE

Response Rates and OS with *IDH1 or IDH2* Mutations



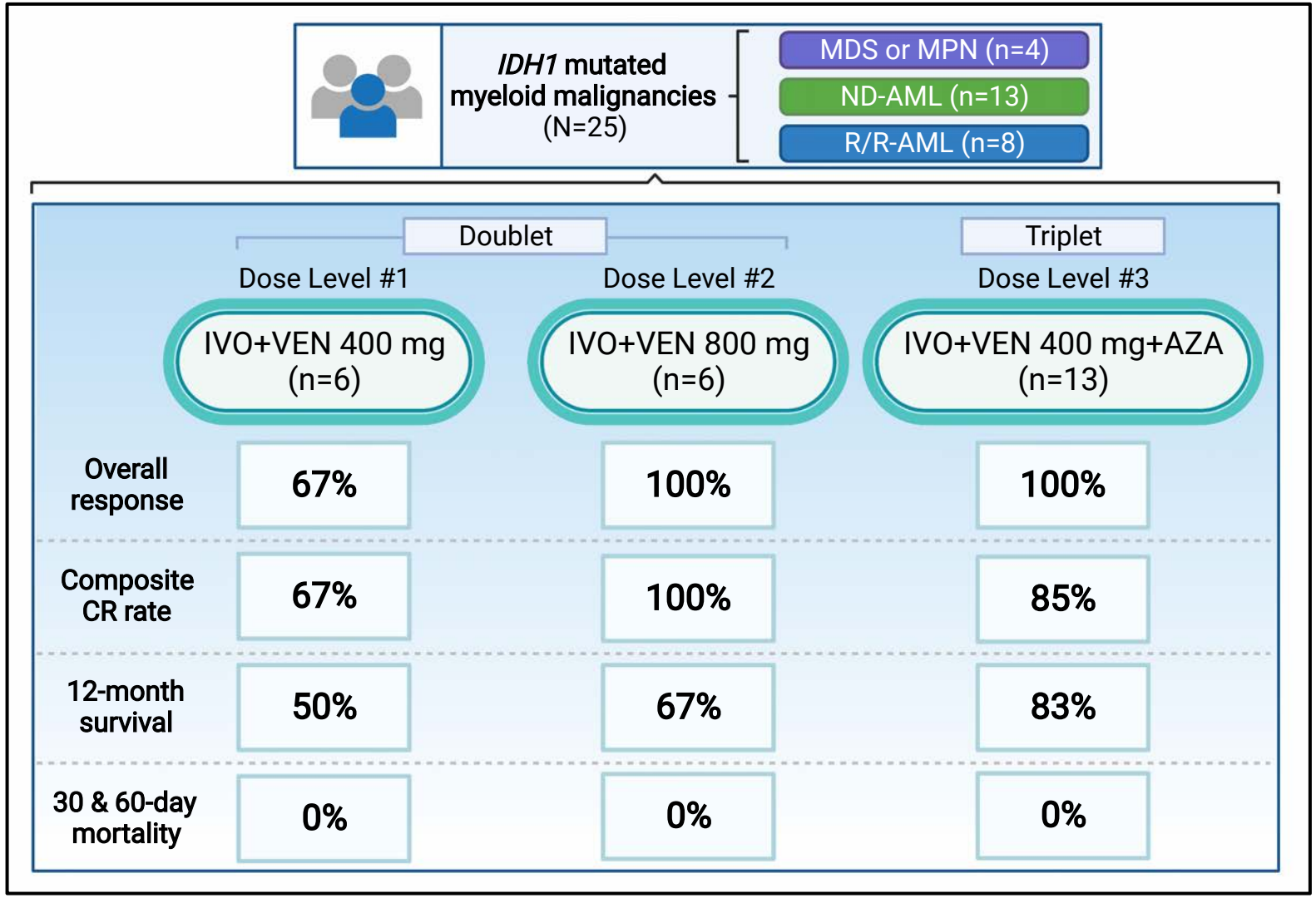


Courtesy of Courtney D DiNardo, MD, MSCE

A phase IB/II study of ivosidenib with venetoclax +/- azacitidine in *IDH1* mutated myeloid malignancies

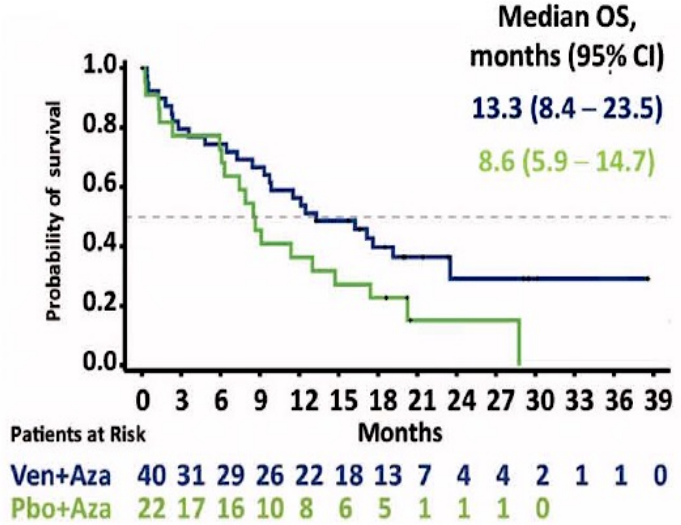
IVO+VEN +/- AZA associated with

- Expected and acceptable safety profile
- High composite CR rates in ND and R/R-AML
  - ND-AML: **92%**
  - R/R-AML: **63%**
- MRD-negative remissions in ND and R/R-AML
  - ND-AML: **60%**
  - R/R-AML: **60%**
- Durable responses and prolonged survival across disease groups

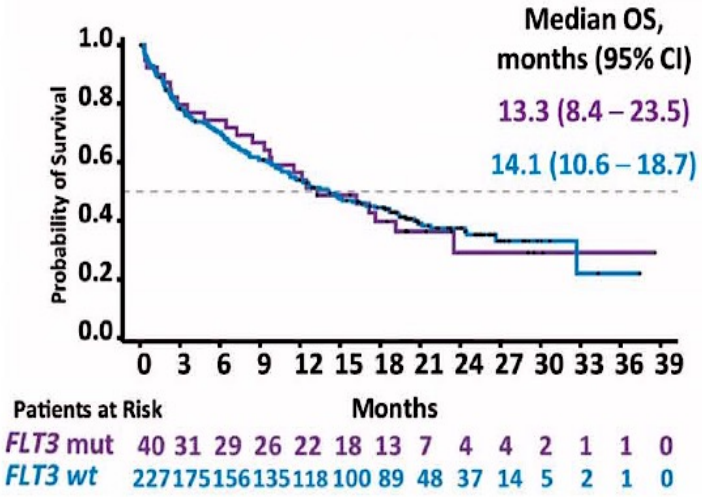


AZA + VEN for FLT3-mutated ND AML: OS

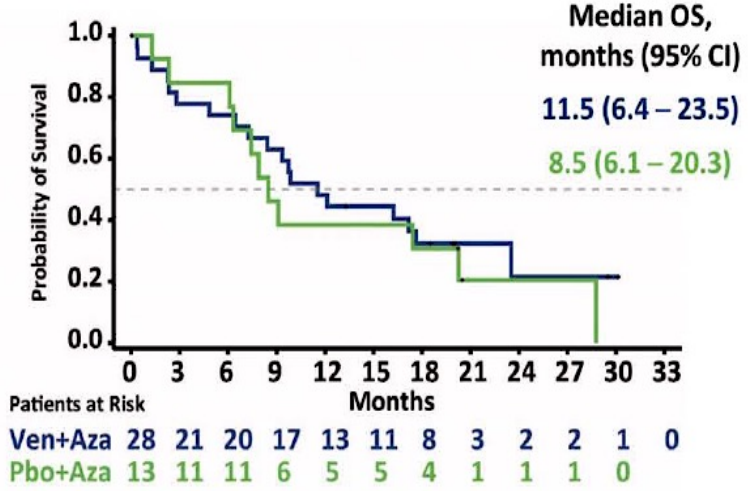
A. FLT3mut



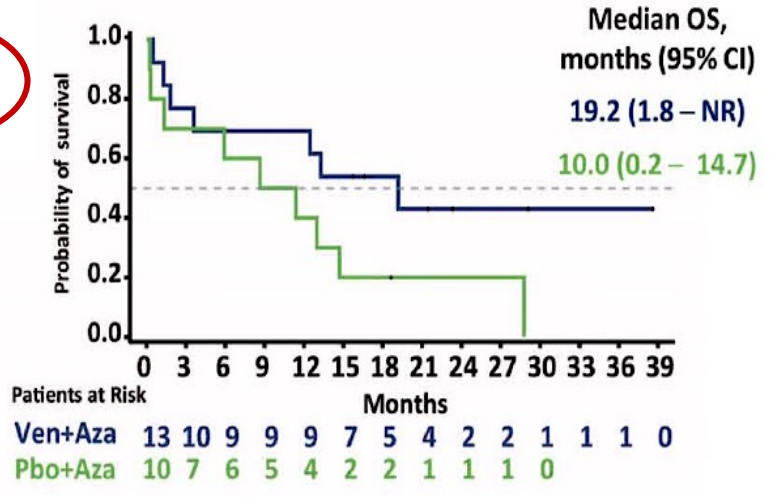
B. FLT3mut vs. wt in Ven+Aza



C. FLT3-ITD



D. FLT3-TKD



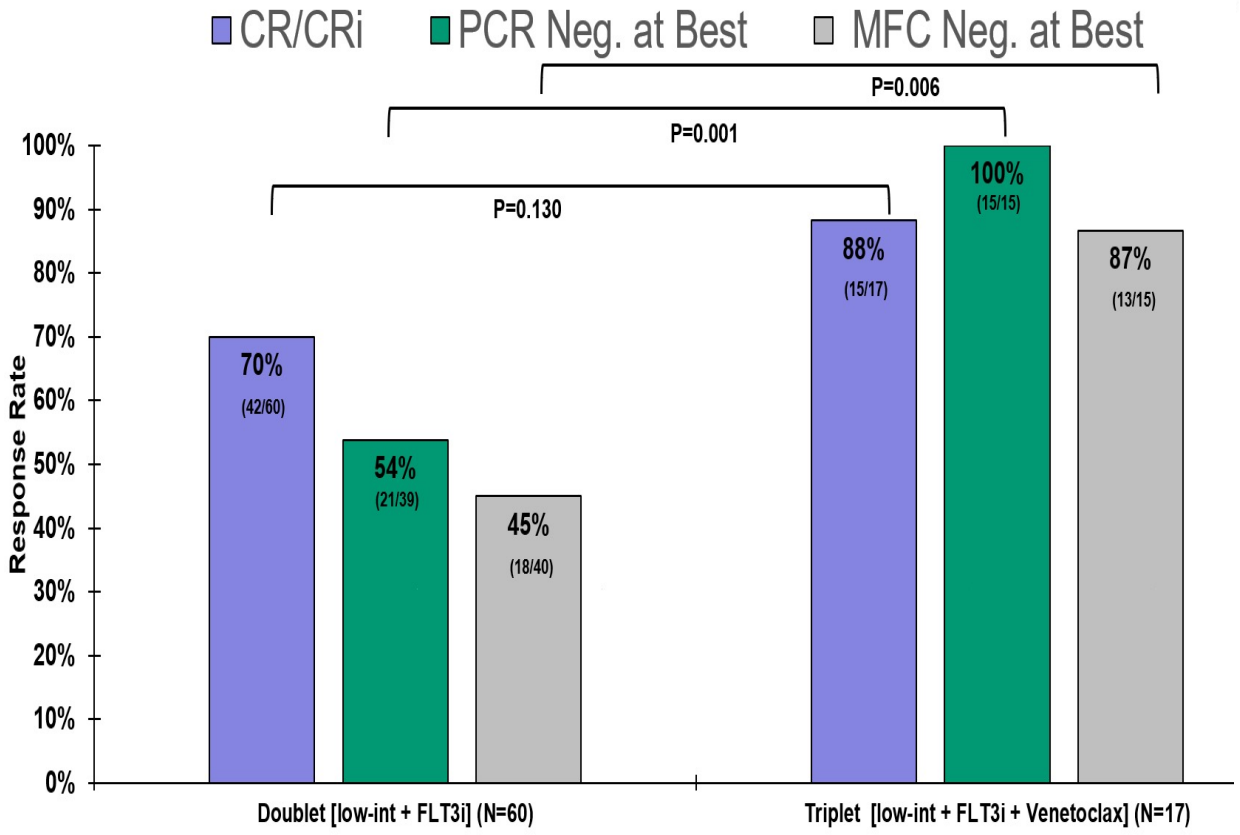
Summary

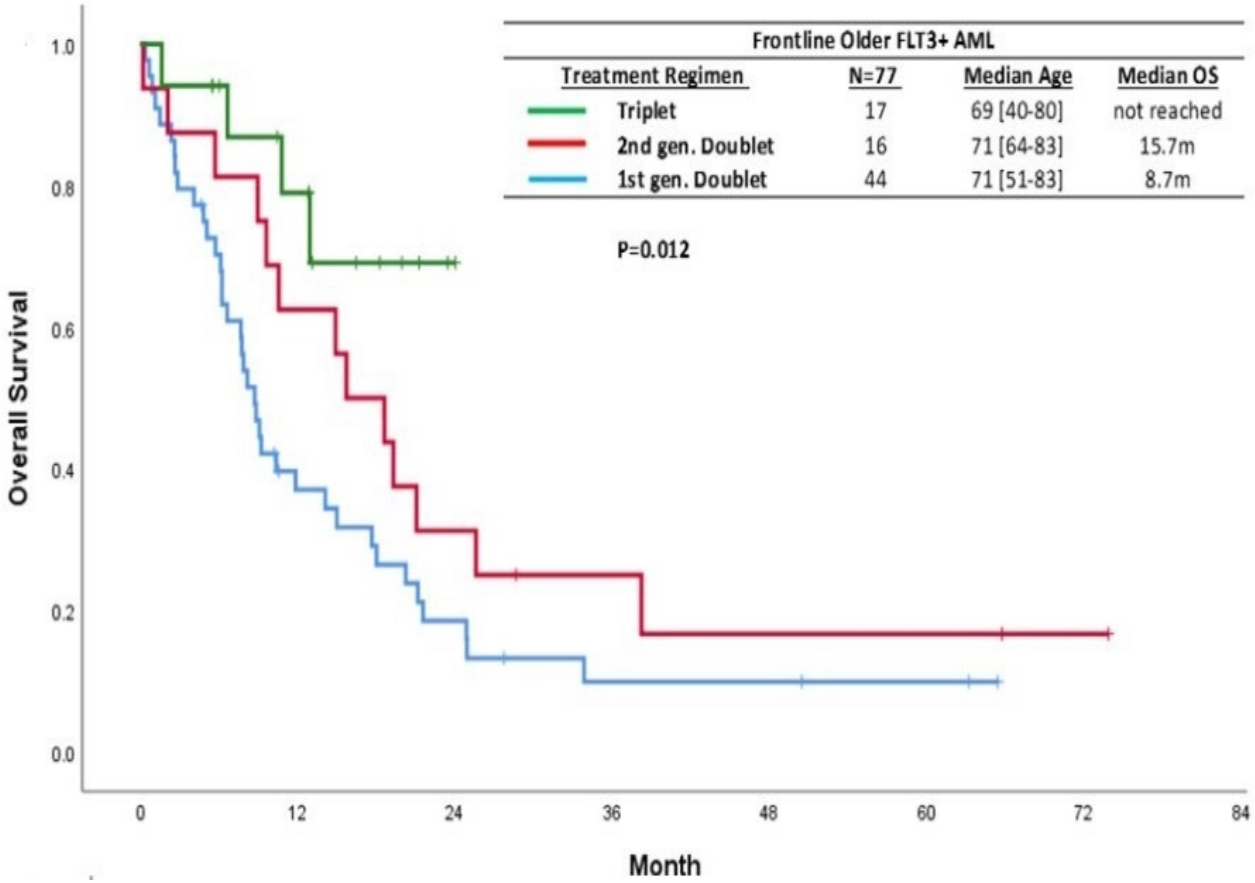
- In patients with *FLT3*$^{mut+}$ AML, response rates and OS were similar to *FLT3*^{WT} AML
- CR/CRi and OS were higher in *FLT3*$^{mut+}$ patients receiving AZA + VEN
- **FLT3-TKD patients appear to do particularly well**

Courtesy of Courtney D DiNardo, MD, MSCE

Konopleva M, et al. ASH 2020. Abstract 1904.

Lower Intensity FLT3i “doublet” vs “triplet” with VEN



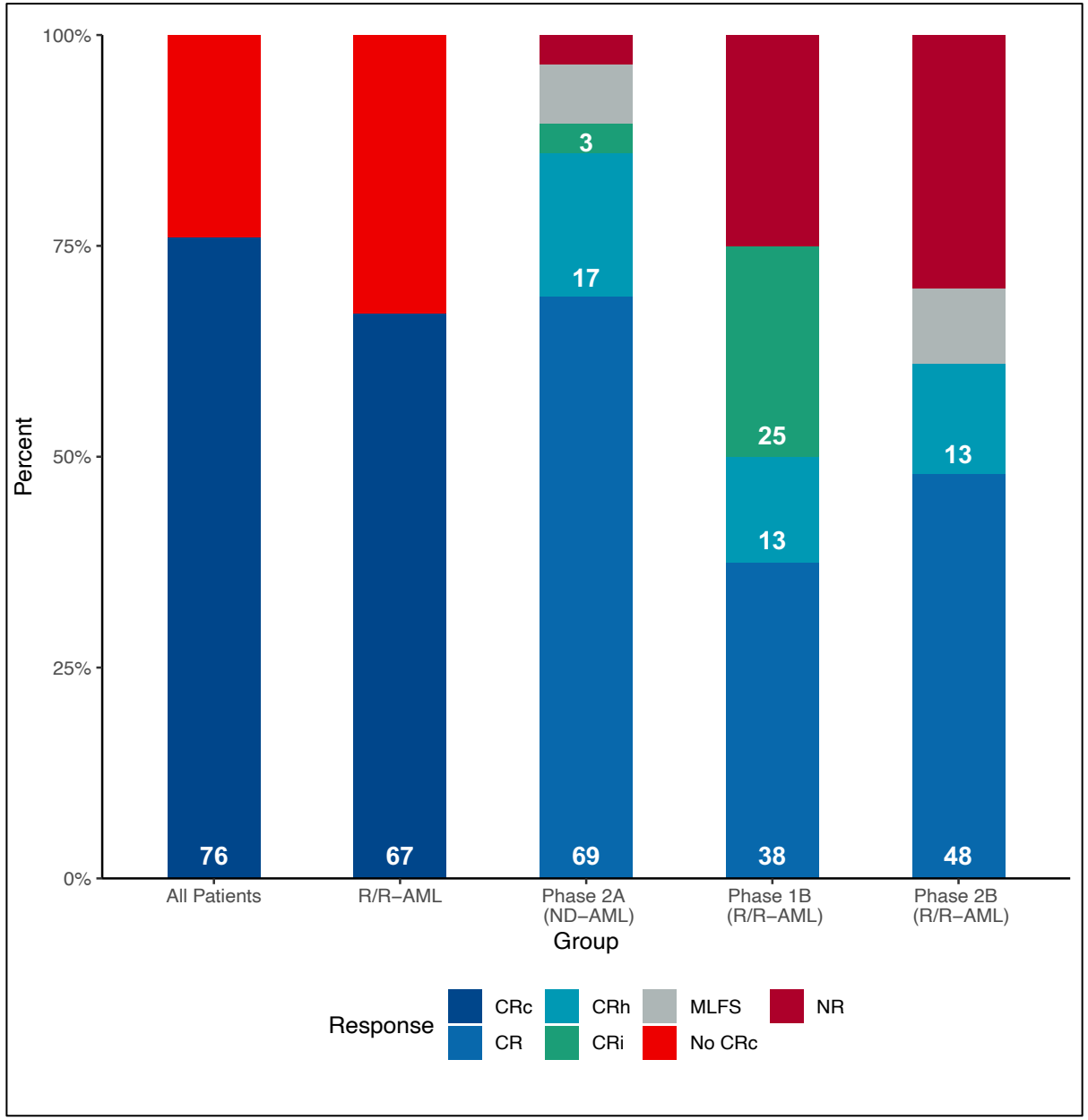


Courtesy of Courtney D DiNardo, MD, MSCE

Yilmaz M et al, EHA 2021 EP464

FLAG-IDA + VEN: Response

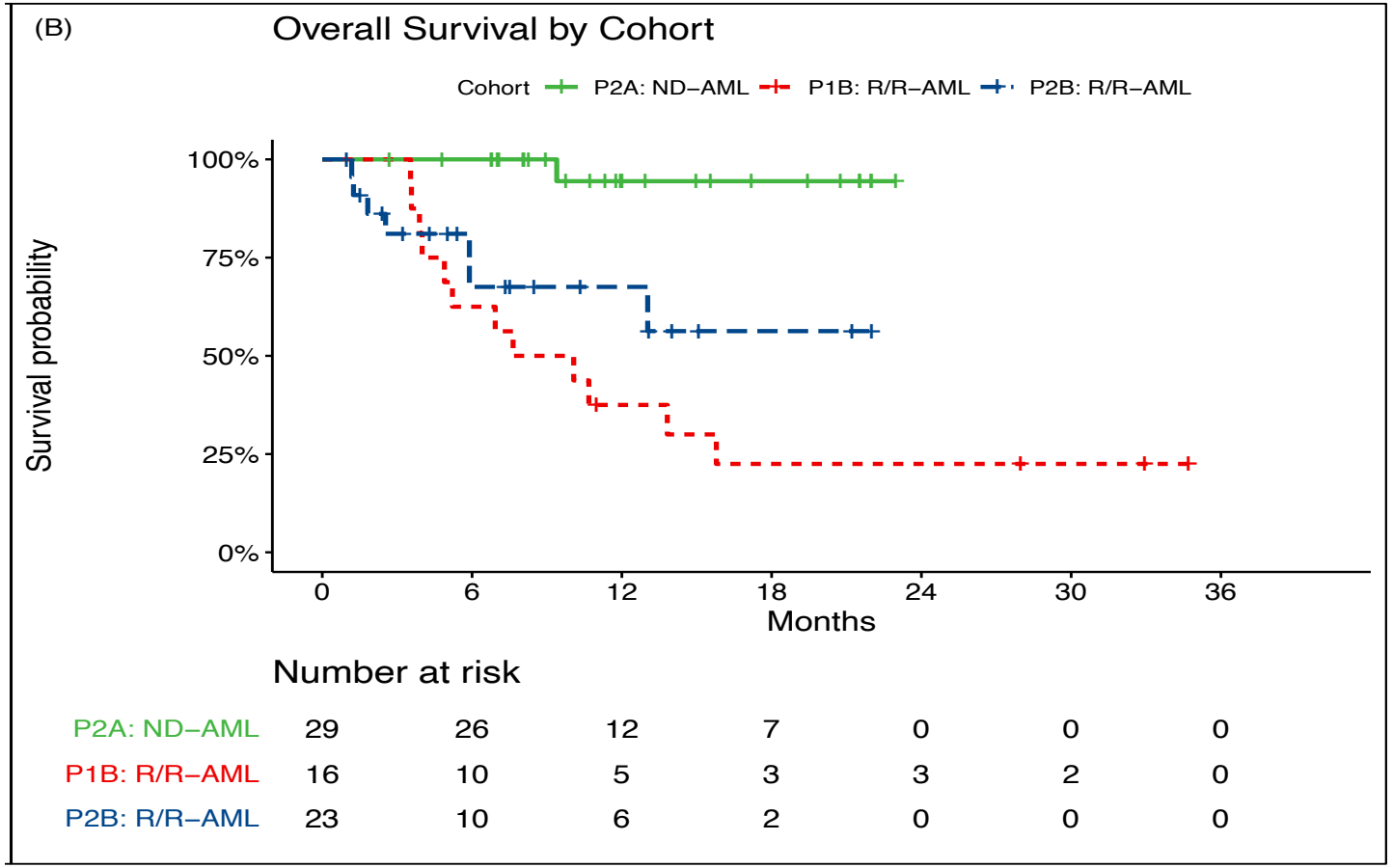
Outcome	Phase 2A ND-AML (N=29)	Phase IB R/R-AML (N=16)	Phase 2B R/R-AML (N=23)
Overall Response (ORR) N(%[CI])	**28 (97%)***	**12 (75%)**	**16 (70%)***
Composite CR (CR + CR_i + CR_h)	**26 (90%)**	**12 (75%)**	**14 (61%)**
CR	20 (69%)	6 (38%)	11 (48%)
CR_h	5 (17%)	2 (13%)	3 (13%)
CR_i	1 (3%)	4 (25%)	-
MRD Negative CR (flow cytometry)	**25 (96%)**	**7 (58%)**	**11 (79%)**
MLFS	2	-	2
Event Free Survival			
Median, months (95% CI)	NR	6 (3-NE)	11 (2-NE)
12-Month, % (95% CI)	85% (72-100)	31% (15-65)	41% (21-77)
Overall Survival			
Median, months (95% CI)	NR	9 (4.9-NE)	NR (6-NE)
12-Month, % (95% CI)	**94% (84-100)**	**38% (20-71)**	**68% (49-94)**

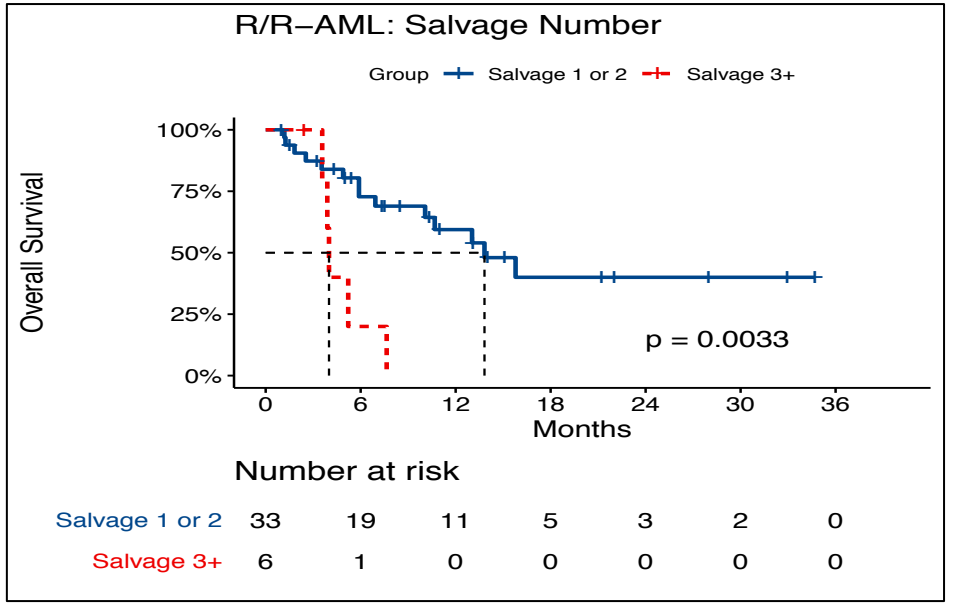


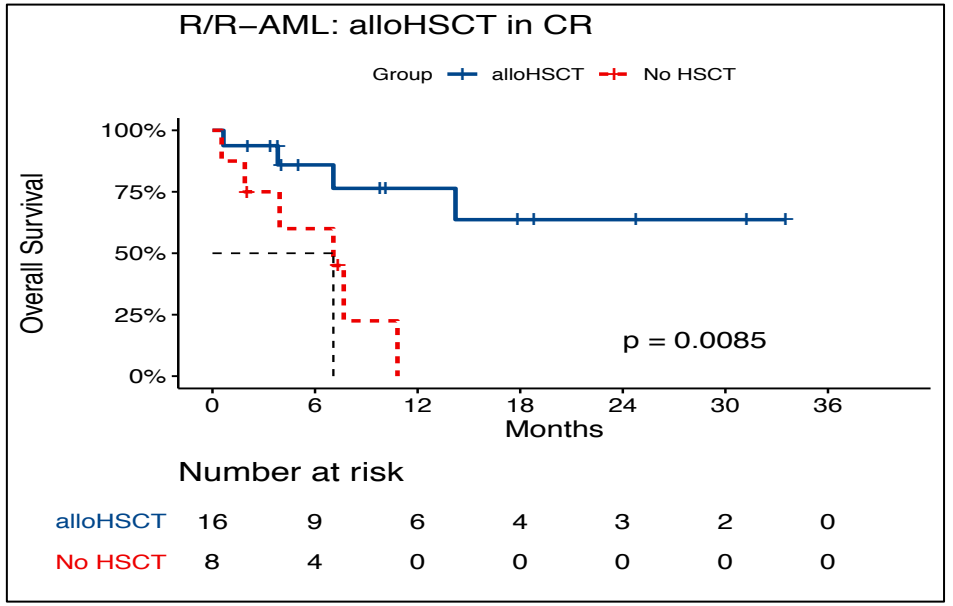
DiNardo CD, Lachowiez C, et al. JCO 2021

Courtesy of Courtney D DiNardo, MD, MSCE

FLAG-IDA + VEN: Survival Outcomes







DiNardo CD, Lachowiez C, et al. JCO 2021

Courtesy of Courtney D DiNardo, MD, MSCE

Case Presentation – Dr DiNardo: A 58-year-old man with AML and NPM1, IDH1 and FLT3-ITD mutations

- 58 year old M with gingival swelling, myalgias, fevers and epistaxis. WBC 44K, Hgb 6.8 g/dl, Plts 22K. Bone marrow with 72% MPO+, CD33+ and CD123+ blasts. Diploid cytogenetics. ECOG PS 0. **NPM1, IDH1, and FLT3-ITD** (AR 0.49) mutations.
- Started 7+3 + midostaurin, attained CR. Received 4 consolidation courses. No maintenance midostaurin.
- Noted to have WBC 27K with 37% circulating blasts 5 months after last consolidation.

- You recommend:
  - Reinduce with 7+3+midostaurin
  - Reinduce with FLAG-IDA
  - Start ivosidenib 500mg daily
  - Start gilteritinib 120mg daily
  - Start gemtuzumab 3 mg/kg (4.5 mg cap) d1,4,7
  - Rush and repeat NGS panel

Courtesy of Courtney D DiNardo, MD, MSCE

Case Presentation – Dr DiNardo: An 82-year-old woman whose disease progressed from MDS to AML

- 82yo F with history of MDS, followed expectantly
- Counts started to fall and bone marrow demonstrated progression to AML with 28% blasts
- Del(20q) cytogenetics. DNMT3A and SRSF2 and ASXL1 mutations.
- Enrolled her on our clinical trial of oral decitabine + venetoclax and she is in CR now 3 months into therapy.
- Received a dose of GCSF because her ANC is in the 500 range, getting 21 days of VEN with treatment every 5 weeks.

Courtesy of Courtney D DiNardo, MD, MSCE

Agenda

Module 1: Recent Advances in the Up-Front Treatment of Acute Myeloid Leukemia (AML)

- VIALE-A: Azacitidine and venetoclax in older patients with previously untreated AML
- Venetoclax-based regimens for patients with newly diagnosed AML who are or are not eligible for intensive induction therapy
- Efficacy of venetoclax-based combination regimens in patients with FLT3 or IDH1/2 mutations

Module 2: Secondary AML (sAML)

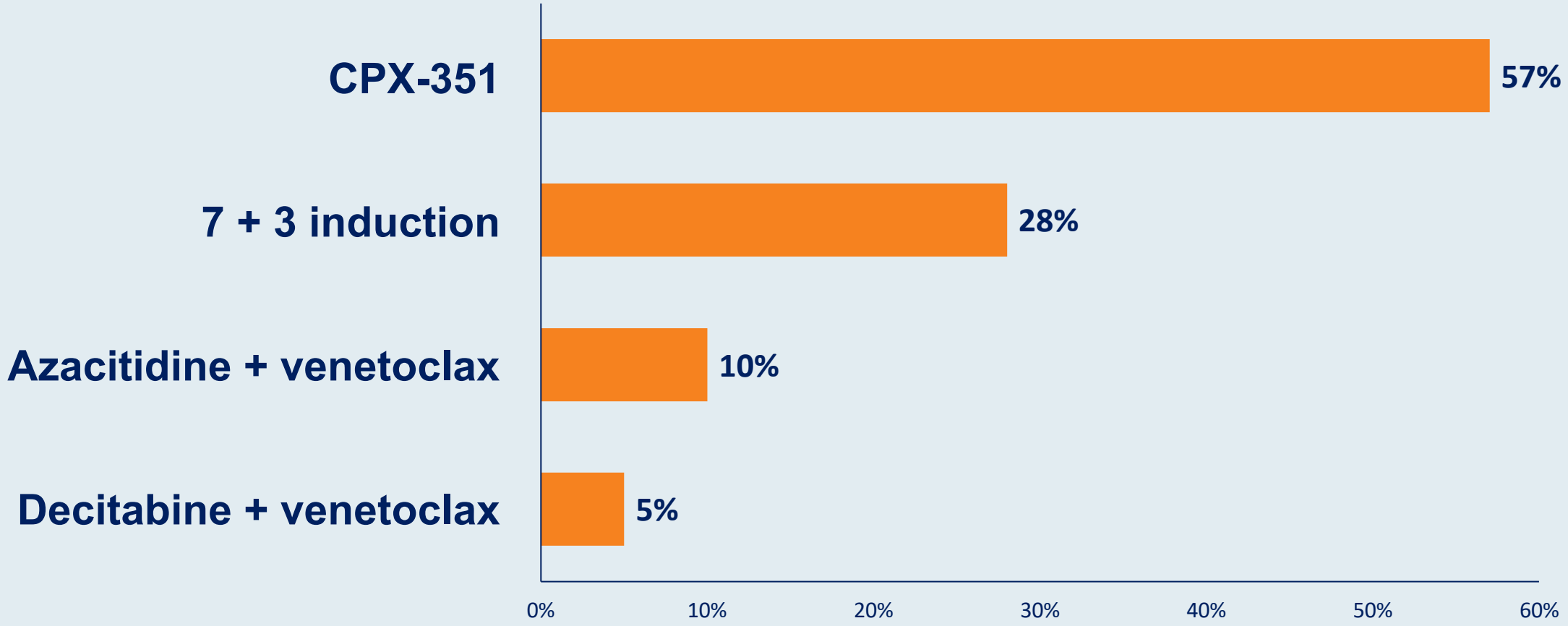
- Mechanism of action, available data with and side effects of CPX-351 in previously untreated sAML and primary AML
- Available data with and current clinical role of venetoclax-based therapy for patients with sAML

Module 3: Myelodysplastic Syndromes (MDS)

- ASCERTAIN studies evaluating the oral combination of decitabine and cedazuridine in patients with MDS
- Available research findings for agents with established efficacy in AML for patients with MDS
- Promising novel agents (eg, magrolimab, pevonedistat, sabatolimab) in MDS

RTP RESEARCH TO PRACTICE

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?



Premeeting survey: July 2021

RTP RESEARCH TO PRACTICE

What is "Secondary" Acute Myeloid Leukemia?

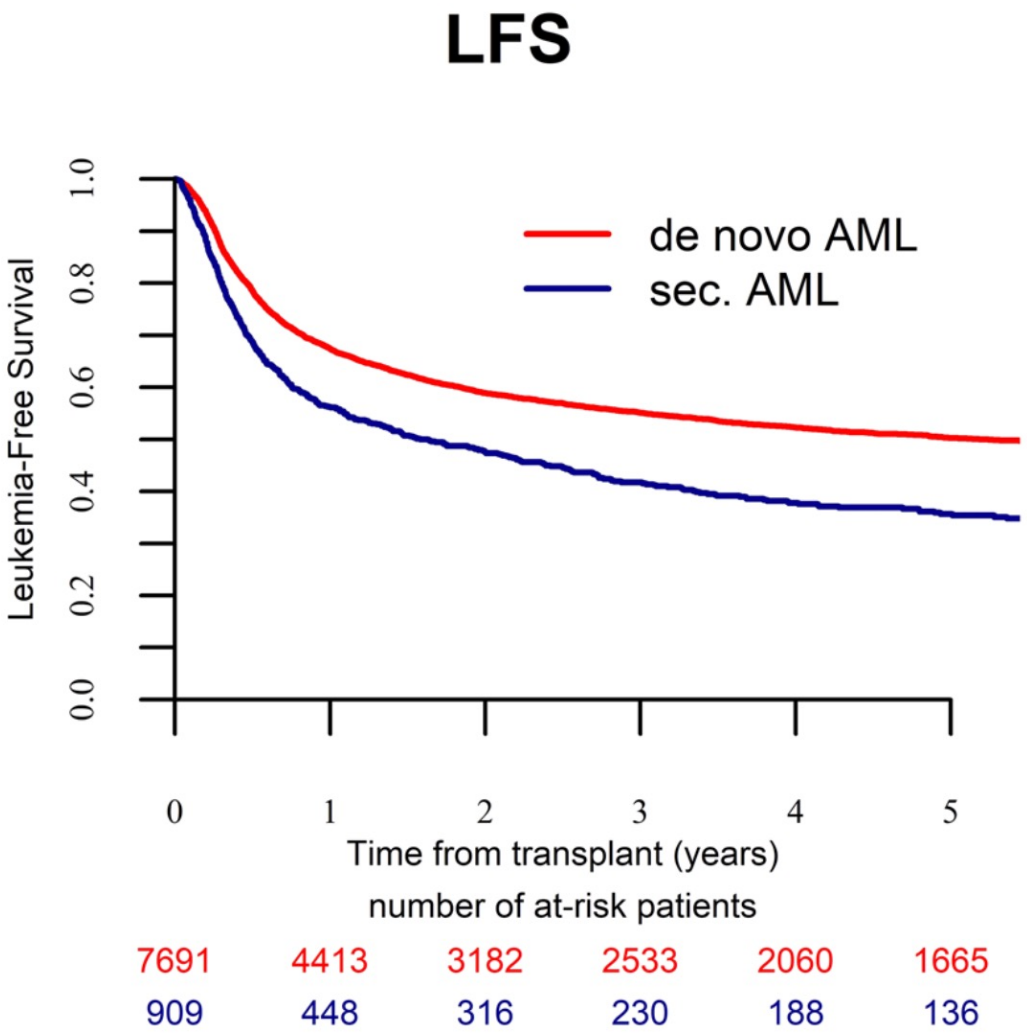
- Acute myeloid leukemia that arises from an antecedent myeloid malignancy, most commonly myelodysplastic syndrome.

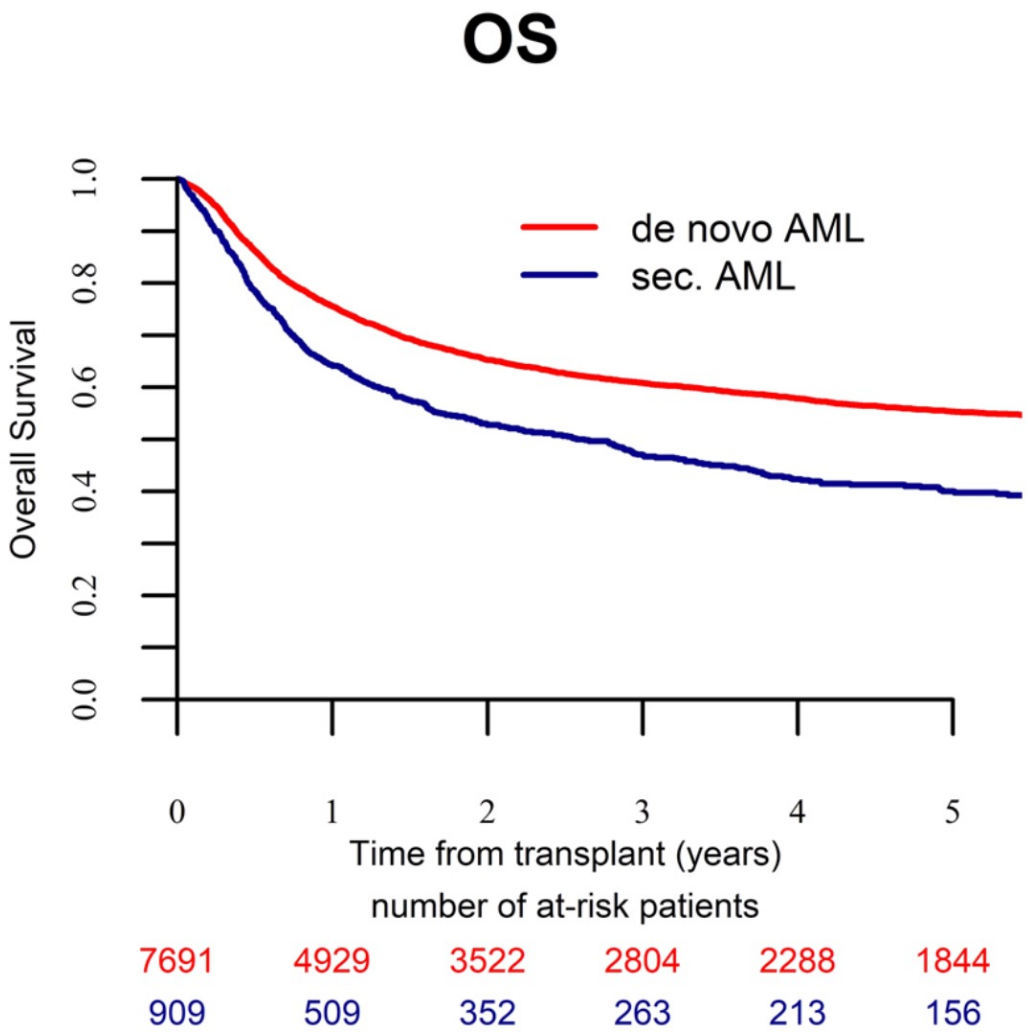
- Acute myeloid leukemia that is secondary to cytotoxic chemotherapy or radiation given for a different disease, most commonly a solid tumor or lymphoma.

- Acute myeloid leukemia where the karyotype is suggestive of a prior, undiagnosed and unrecognized myelodysplastic syndrome

Courtesy of Eytan M Stein, MD

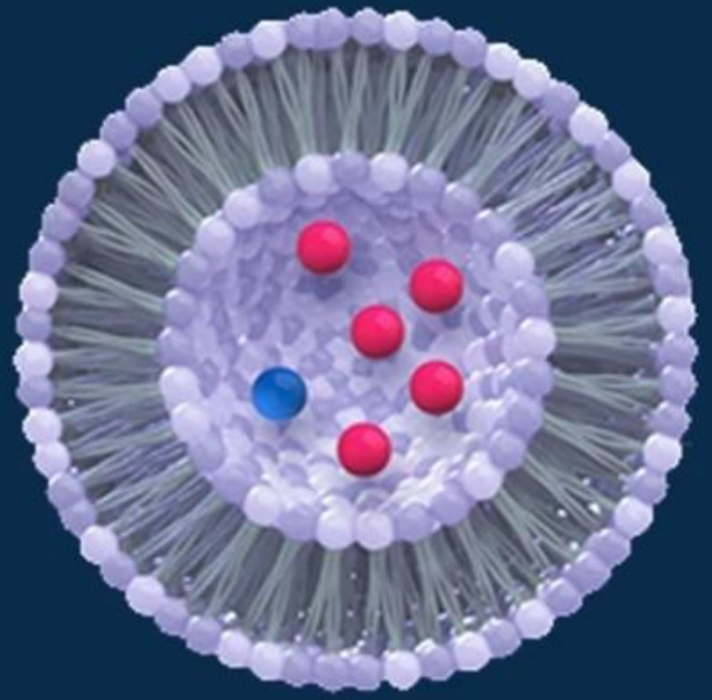
Outcomes of Patients with Secondary AML after Transplant





CPX-351 – Liposomal Formulation of 7+3

CPX-351 Uses a Nano-Scale Delivery Complex



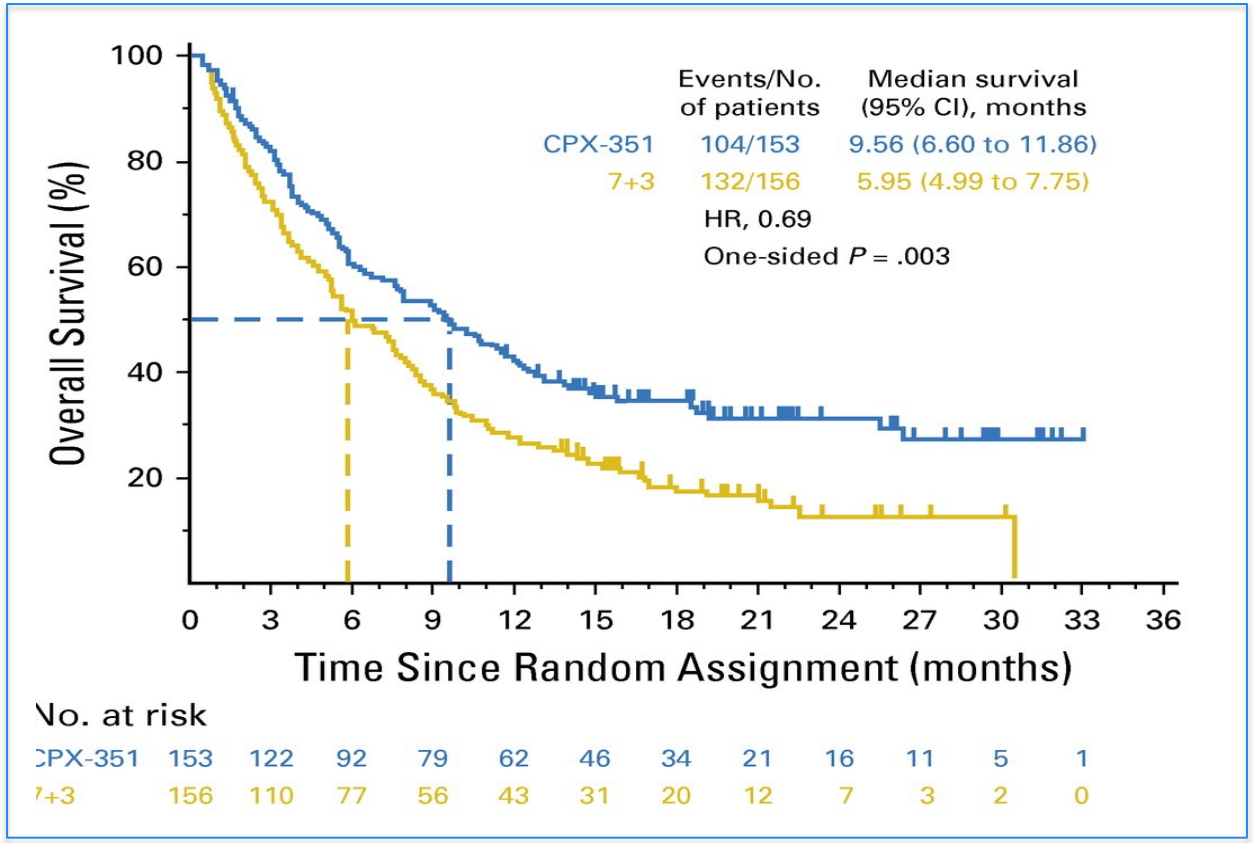
- 100 nm bilamellar liposomes
- 5:1 molar ratio of cytarabine to daunorubicin
- 1 unit = 1.0 mg cytarabine plus 0.44 mg daunorubicin

Courtesy of Eytan M Stein, MD

CPX-351 – Remission Rates and Overall Survival

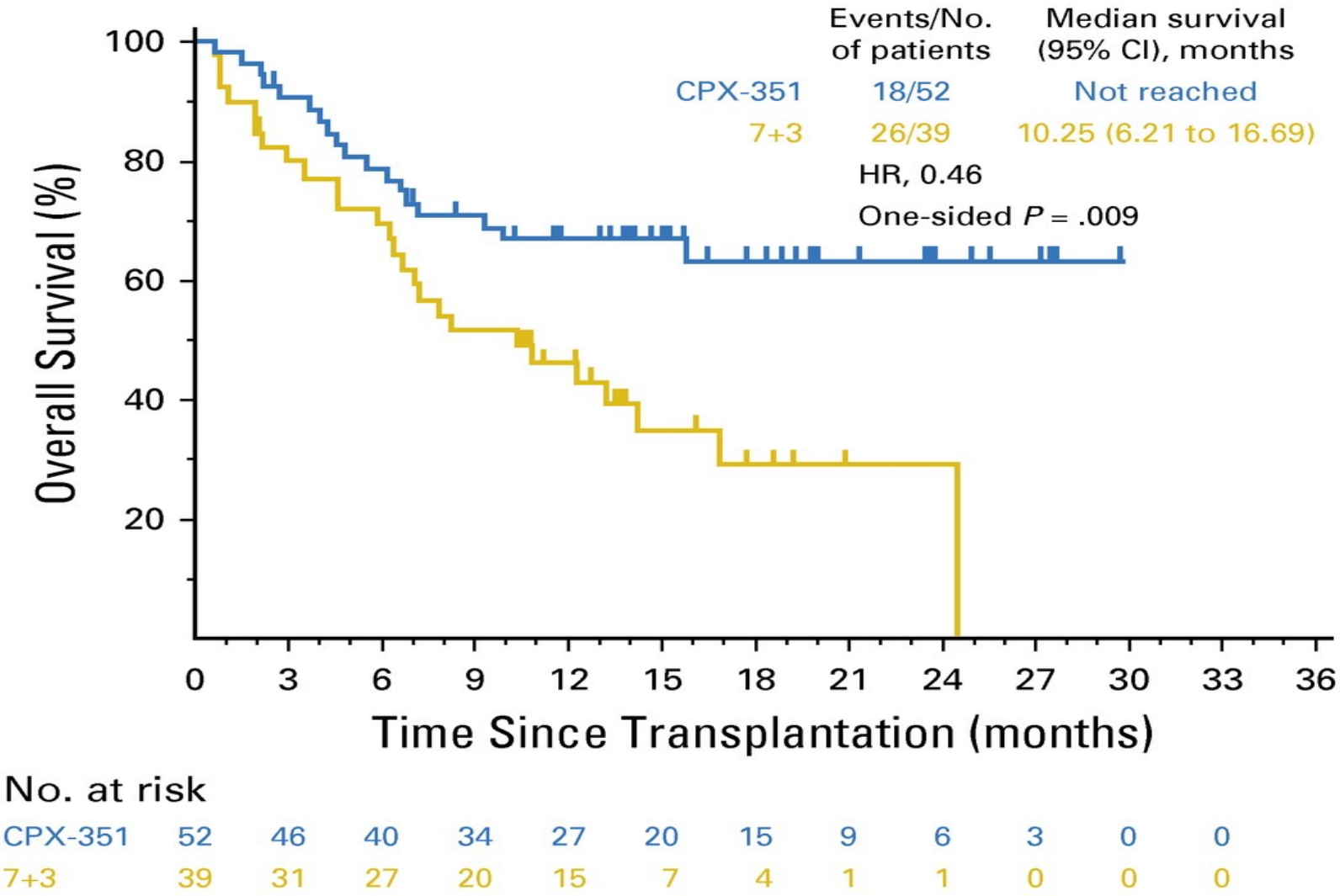
Table 2. Best Response Rates

Response	CPX-351, No. (%)	7+3, No. (%)	OR (95% CI)
No. of patients	153	156	
CR + CRi	73 (47.7)	52 (33.3)	1.77 (1.11 to 2.81)*
CR	57 (37.3)	40 (25.6)	1.69 (1.03 to 2.78)†
Age group			
No. in 60-69–year age-group	96	102	
CR + CRi	48 (50.0)	37 (36.3)	1.76 (1.00 to 3.10)
CR	38 (39.6)	27 (26.5)	1.82 (1.00 to 3.32)
No. in 70-75–year age-group	57	54	
CR + CRi	25 (43.9)	15 (27.8)	2.03 (0.92 to 4.49)
CR	19 (33.3)	13 (24.1)	1.58 (0.69 to 3.62)



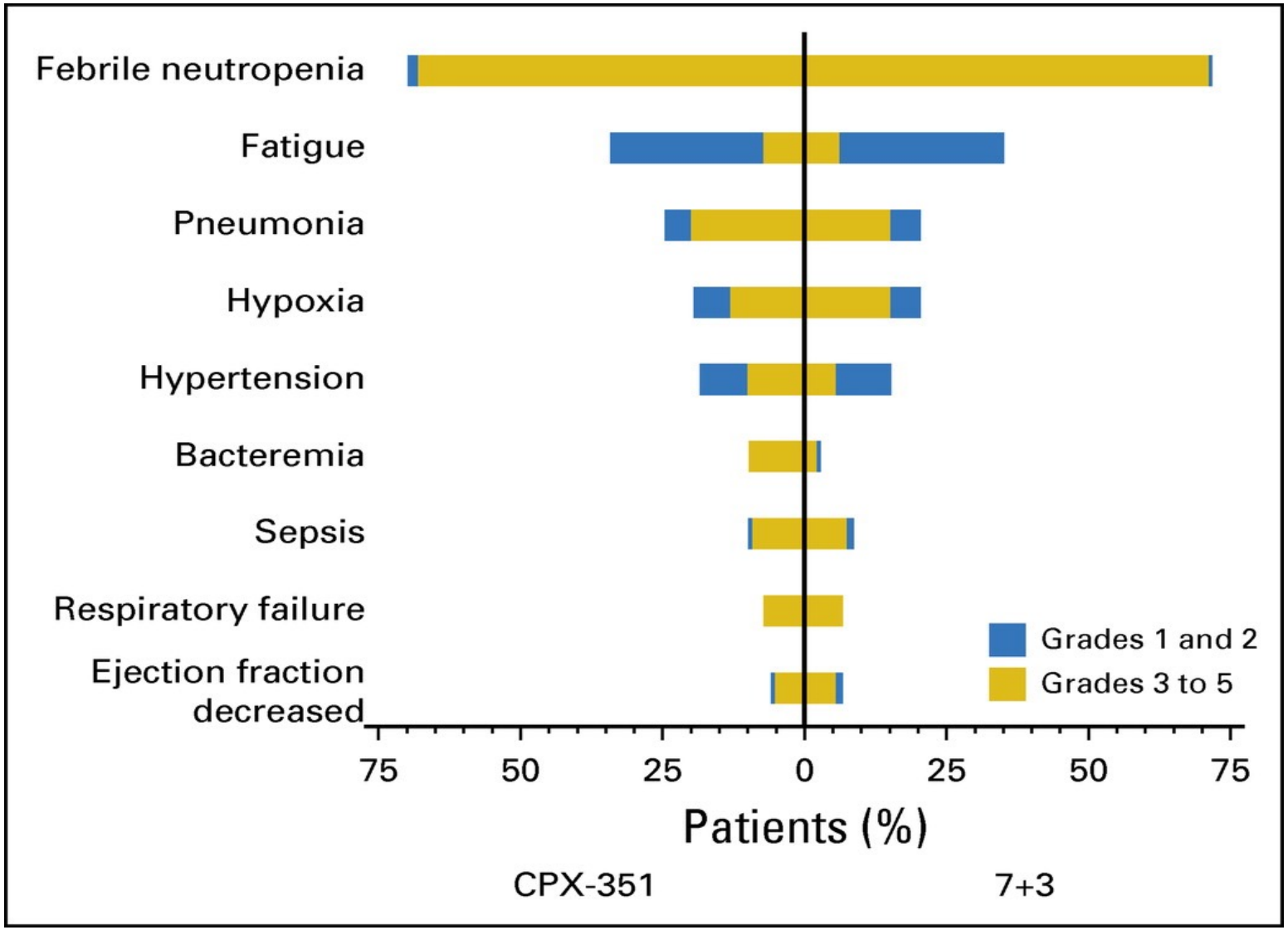
Courtesy of Eytan M Stein, MD

CPX-351 – Survival Landmarked from Day of Transplant



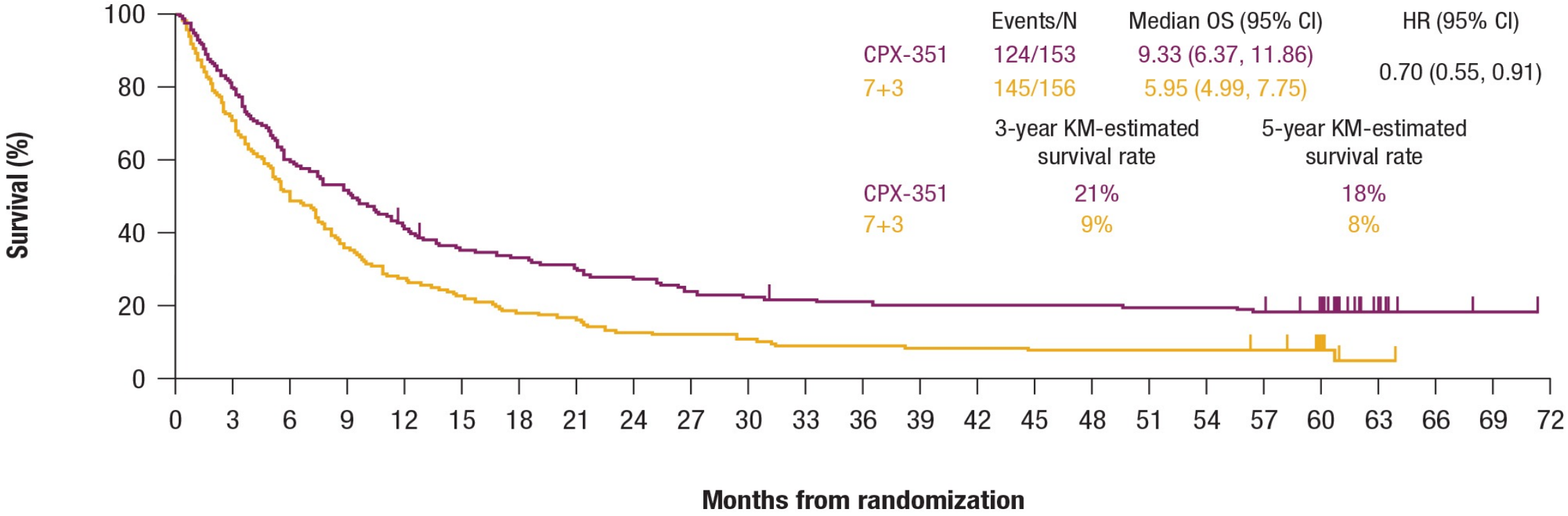
Courtesy of Eytan M Stein, MD

CPX-351 versus 7+3 – Adverse Events



Courtesy of Eytan M Stein, MD

CPX-351 – 5-year follow-up



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

Lancet, et al. ASH 2020: Abstract 635. Lancet, et al. *J Clin Oncol*. 2020 38:15_suppl, 7510-7510

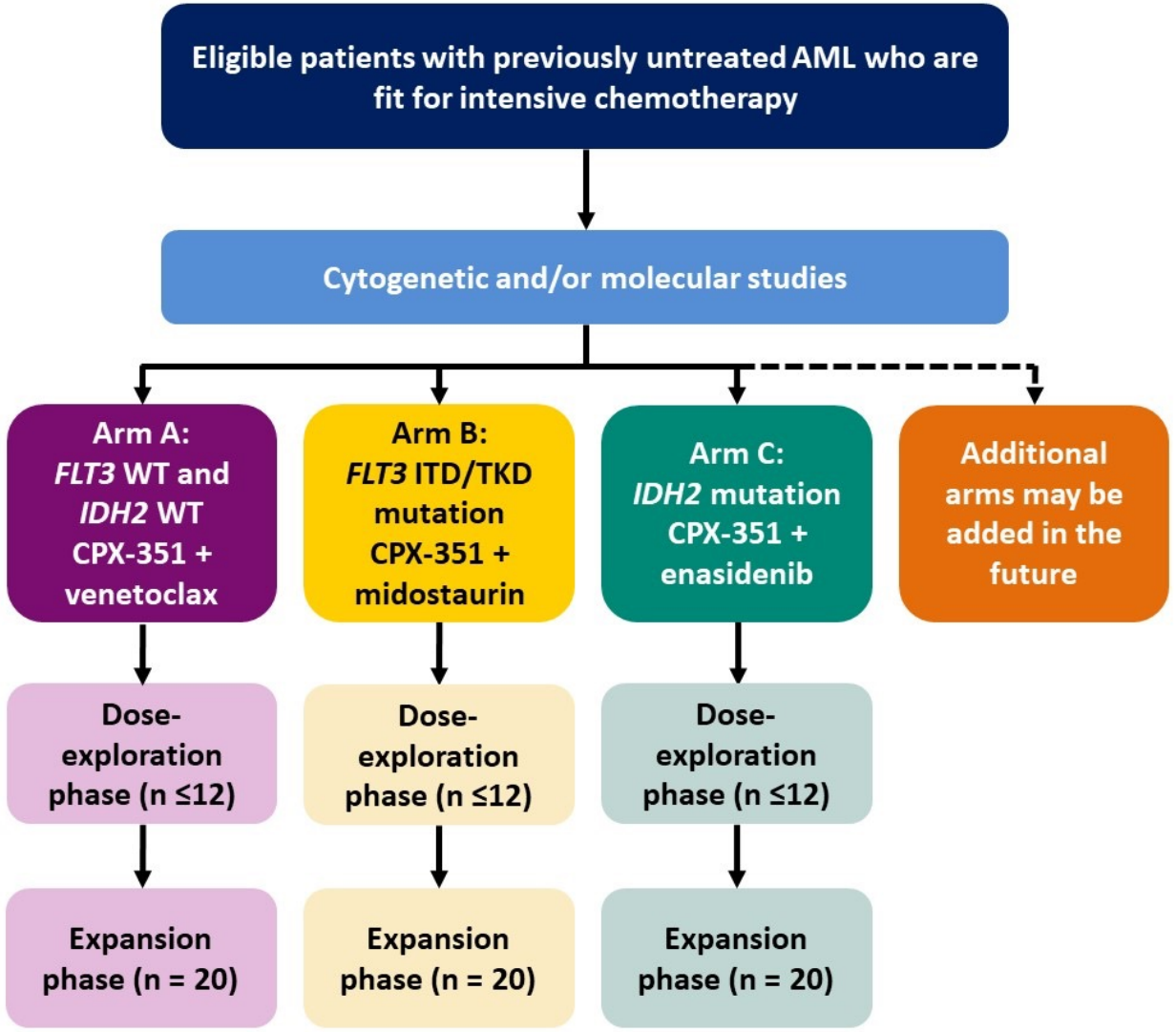
Courtesy of Eytan M Stein, MD

V-FAST Study Design

- The V-FAST (CPX-351 - First Phase ASsessment with Targeted Agents) trial aims to examine the safety and initial efficacy of CPX-351 combinations (eg, with venetoclax, midostaurin, or enasidenib) in adults with previously untreated AML who are fit for intensive chemotherapy
- V-FAST is an open-label, multicenter, multi-arm, nonrandomized, phase 1b master trial (ClinicalTrials.gov Identifier: NCT04075747)
- The flexible trial design permits additional combinations to be added in the future, under the same master protocol

Dose-exploration phase: 3+3 design to identify a RP2D and evaluate the safety of CPX-351 combination regimens

Expansion phase: Confirm the RP2D of CPX-351 combination regimens, further evaluate safety, and assess efficacy



RP2D, recommended phase 2 dose.

Courtesy of Eytan M Stein, MD

V-FAST: Safety Profile

	Arm A CPX-351 + venetoclax (N = 21)	Arm B CPX-351 + midostaurin (N = 3)	Arm C CPX-351 + enasidenib (N = 2)	Overall (N = 26)
Any TEAE (all grades), n (%)[a]	21 (100)	3 (100)	2 (100)	26 (100)
Febrile neutropenia	13 (62)	2 (67)	2 (100)	17 (65)
Neutropenia	11 (52)	2 (67)	1 (50)	14 (54)
Thrombocytopenia	11 (52)	2 (67)	1 (50)	14 (54)
Nausea	9 (43)	2 (67)	2 (100)	13 (50)
Constipation	10 (48)	1 (33)	0	11 (42)
Headache	7 (33)	3 (100)	1 (50)	11 (42)
Diarrhea	6 (29)	2 (67)	2 (100)	10 (38)
Fatigue	7 (33)	0	2 (100)	9 (35)
Hypokalemia	7 (33)	1 (33)	1 (50)	9 (35)
Maculopapular rash	6 (29)	1 (33)	2 (100)	9 (35)
Leukopenia	8 (38)	0	0	8 (31)
Pyrexia	6 (29)	1 (33)	1 (50)	8 (31)
Pain in extremity	5 (24)	2 (67)	0	7 (27)
Chills	3 (14)	2 (67)	1 (50)	6 (23)
Peripheral edema	5 (24)	1 (33)	0	6 (23)
Vomiting	4 (19)	2 (67)	0	6 (23)
Any grade ≥3 TEAE, n (%)[b]	19 (90)	3 (100)	2 (100)	24 (92)
Febrile neutropenia	13 (62)	2 (67)	2 (100)	17 (65)
Neutropenia	11 (52)	2 (67)	1 (50)	14 (54)
Thrombocytopenia	11 (52)	2 (67)	1 (50)	14 (54)
Leukopenia	8 (38)	0	0	8 (31)
Anemia	3 (14)	0	0	3 (12)
Lymphopenia	3 (14)	0	0	3 (12)
Hypoxia	3 (14)	0	0	3 (12)

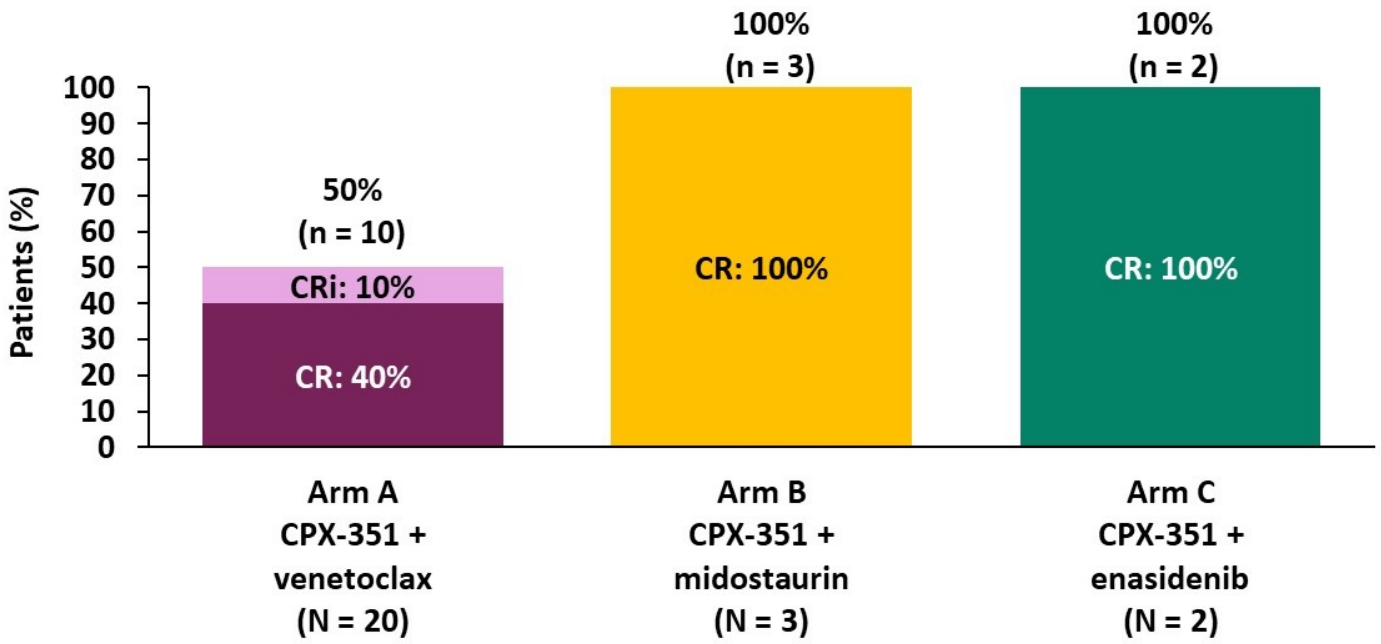
N = number of patients who received ≥1 dose of study drug and had sufficient data to be included in the analysis.
[a]Individual TEAEs occurring in >20% of the population.
[b]Individual grade ≥3 TEAEs occurring in >10% of the population.

- **Across treatment arms, 13 serious adverse events were reported; events in >1 patient included febrile neutropenia (n = 5) and sepsis (n = 2)**
- **Median hematologic recovery times for Arm A**
  - **To platelets ≥50,000/µL: 36.0 days (range: 33, 40)**
  - **To neutrophils ≥500/µL: 35.5 days (range: 33, 37)**
- **Early mortality**
  - **Arm A: 5% at Day 30 and 14% at Day 60**
  - **Arms B and C: no early mortality has been observed**

- **As of this interim analysis, the drug combinations have exhibited manageable safety profiles**

Courtesy of Eytan M Stein, MD

V-FAST: Remission Rates



N = number of patients who received ≥1 dose of study drug and had an evaluable bone marrow result.
n = number of patients who achieved CR or CRi in each treatment arm.

- **In conclusion, these results suggest CPX-351 can be combined with venetoclax and midostaurin with a manageable safety profile in patients with newly diagnosed AML**
- **Preliminary remission rates are promising, particularly given the high-risk population enrolled in Arm A**
- **The study is currently ongoing and actively enrolling patients**

Courtesy of Eytan M Stein, MD

2021 ASCO ANNUAL MEETING

VENETOCLAX AND AZACITIDINE COMBINATION IN CHEMOTHERAPY INELIGIBLE UNTREATED PATIENTS WITH THERAPY-RELATED ACUTE MYELOID LEUKEMIA, ANTECEDENT MYELODYSPLASTIC SYNDROMES OR CHRONIC MYELOMONOCYTIC LEUKEMIA

Vinod Pullarkat M.D.[1], Keith W. Pratz M.D.[2], Hartmut Döhner M.D.[3], Christian Recher M.D.[4], Michael J. Thirman M.D [5], Courtney D. DiNardo M.D. [6], Pierre Fenaux M.D. [7], Andre C. Schuh M.D. [8], Andrew H. Wei M.D.[9], Arnaud Pigneux M.D. [10], Jun-Ho Jang M.D. [11], Gunnar Juliusson M.D. [12], Yasushi Miyazaki M.D. [13], Dominik Selleslag M.D. [14], Martha L. Arellano M.D. [15], Kiran Naqvi M.D. [16] Jun Yu Ph.D [17], Jean A. Ridgeway DNP, NP-C [17], Jalaja Potluri M.D. [17], Marina Konopleva M.D.[6]

[1]Department of Hematology and Hematopoietic Cell Transplantation and Gehr Family Center for Leukemia Research, City of Hope Comprehensive Cancer Center, Duarte, CA, USA; [2]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [3] Department of Internal Medicine III, Ulm University Hospital, Ulm, Germany; [4] Centre Hospitalier Universitaire de Toulouse, Toulouse, France; [5] Section of Hematology/Oncology, Department of Medicine, The University of Chicago Medicine, Chicago, IL, USA; [6] Department of Leukemia, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [7] Hôpital St. Louis /Assistance Publique- Hôpitaux de Paris and Université de Paris, France; [8] Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, Ontario, Canada; [9] Australian Center for Blood Diseases, The Alfred Hospital and Monash University, Melbourne, Australia, [10] Department of Hematology, CHU de Bordeaux, France; [11]Department of Hematology-Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [12] Department of Hematology, Skåne University Hospital, Lund, Sweden; [13] Department of Hematology, Atomic Bomb Disease and Hibakusha Medicine Unit, Atomic Bomb Disease Institute, Nagasaki University, Nagasaki, Japan; [14] Algemeen Ziekenhuis Sint-Jan, Brugge, Belgium; [15] Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA; [16] Genentech Inc., South San Francisco, CA, USA; [17]AbbVie Inc., North Chicago, IL, USA

Methods and patient categorization

Design:
Pooled analysis of patients enrolled in the randomized phase 3 VIALE-A trial **(NCT02993523)** and a prior phase 1b trial **(NCT02203773)**

Key patient inclusion criteria:
- Treatment-naïve AML patients with co-morbidities and/or age ≥ 75 years[1]
- Ineligible for intensive chemotherapy

Key patient exclusion criteria:
- No prior exposure to hypomethylating agents
- Patients with history of myeloproliferative neoplasm including myelofibrosis, essential thrombocytosis, polycythemia vera, chronic myeloid leukemia with or without *BCR-ABL1* translocation, and AML with *BCR-ABL1* translocation
- Patients with favorable-risk cytogenetics

Key outcomes evaluated:
CR+CRi, CR+CRh, DoR, OS

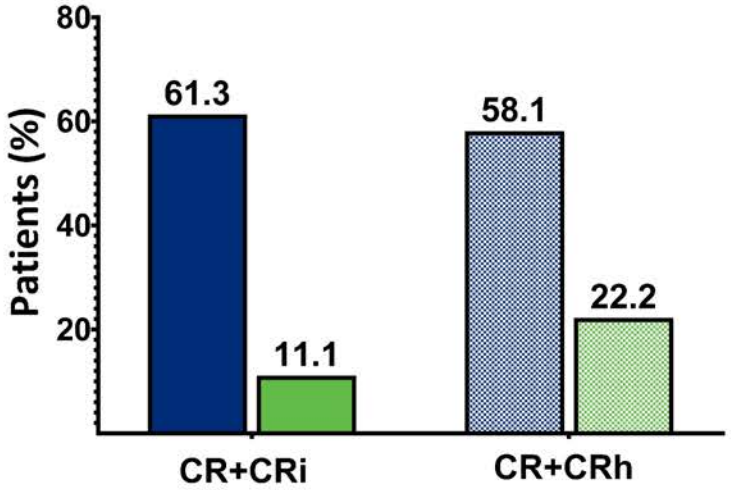
Patient categorization	Ven+Aza			Pbo+Aza
	Viale-A (N=286)	Phase 1b (N=67)	Total (N=353)	Viale-A (N=145)
			Included in this analysis	
Therapy-related AML, n (%)	26 (9.1)	5 (7.5)	**31 (8.8)**	**9 (6.2)**
Antecedent MDS/CMML, n (%)	46 (16.1)	13 (19.4)	**59 (16.7)**	**26 (17.9)**
Antecedent MDS[2]	39 (13.6)	13 (19.4)	52 (14.7)	24 (16.6)
Antecedent CMML	7 (2.4)	0	7 (2.0)	2 (1.4)

Data cutoff: Viale-A-Jan 04, 2020; phase 1b study-Jul 19, 2019
[1]Includes therapy-related patients with AML who were not previously treated for AML; [2]Antecedent MDS is any-time before transformation to AML

A-MDS/CMML: antecedent myelodysplastic syndrome or chronic myelomonocytic leukemia ; Aza: Azacitidine; CR: Complete remission; CRi: CR with incomplete hematologic recovery; CRh: CR with partial hematologic recovery; DoR: Duration of response; OS: Overall survival; Pbo: Placebo; Ven: Venetoclax; tAML: therapy-related acute myeloid leukemia;

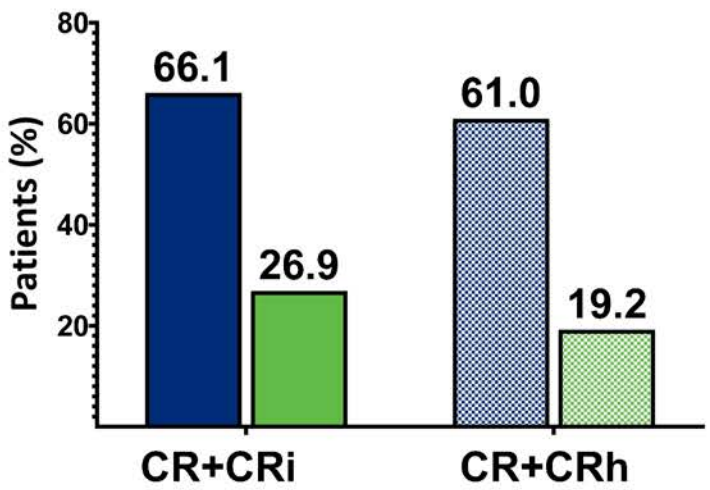
Response rates and duration of response (Pooled Analysis)

tAML



Median duration of response, months (95% CI)				
	n	CR+CRi	n	CR+CRh
Ven+Aza	19	NR (17.8, NR)	18	NR (17.8, NR)
Aza	1	8.5 (-)	2	4.6 (0.5, NR)

A-MDS/CMML



Median duration of response, months (95% CI)				
	n	CR+CRi	n	CR+CRh
Ven+Aza	39	17.3 (9.6, NR)	36	17.4 (10.6, NR)
Aza	7	5.8 (1.1, NR)	5	15.6 (1.1, NR)

CR+CRi Ven+Aza Aza
CR+CRh Ven+Aza Aza

Note: Patients with tAML received a median (Ven+Aza/Aza) of 5/4 cycles of treatment and patients with A-MDS/CMML received a median (Ven+Aza/Aza) of 9/5 cycles of treatment.

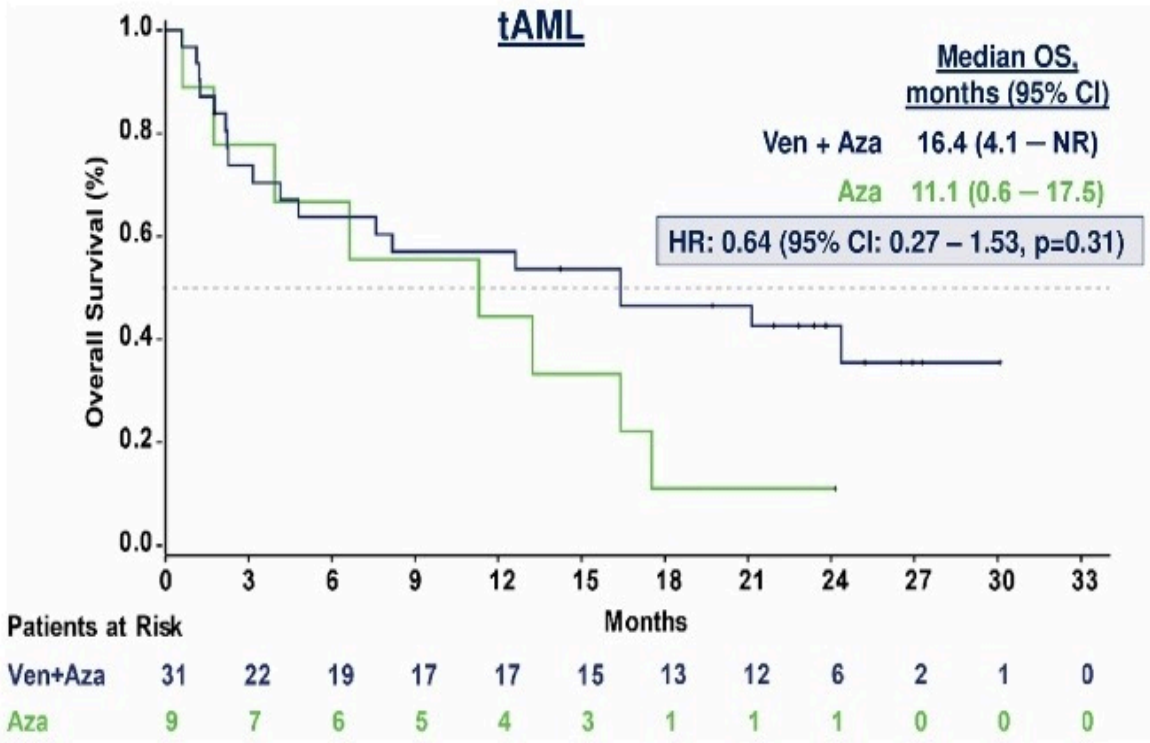
CR was defined as absolute neutrophil count >10^3/µL, platelets >10^5/µL, red cell transfusion independence (TI), and bone marrow with <5% blasts; CRi was defined as all criteria for CR, except for neutropenia ≤10^3/µL or thrombocytopenia ≤10^5/µL. CRh was defined as all the criteria for CR, except for neutropenia >0.5 X10^3/µL, and platelets >0.5 x 10^5 /µL.

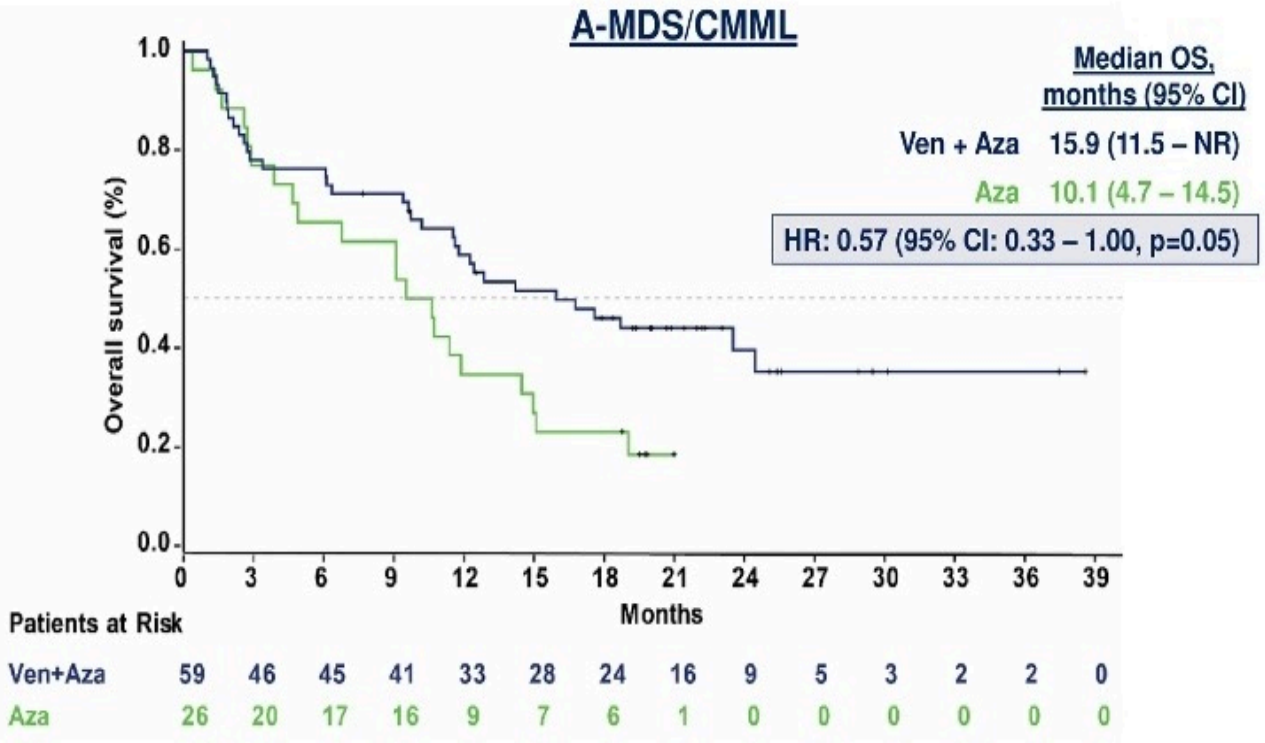
Aza: Azacitidine; CR: Complete remission; CRi: CR with incomplete hematologic recovery; CRh: CR with partial hematologic recovery; Pbo: Placebo; Ven: Venetoclax; NR: Not reached

Pullarkat V et. al ASCO. 2021

Courtesy of Eytan M Stein, MD

Overall Survival (Pooled Analysis)





Pullarkat V et. al ASCO. 2021

Courtesy of Eytan M Stein, MD

Case Presentation – Dr Stein: A 67-year-old man with secondary AML

- 67 year old man with a history of myelodysplastic syndrome (under observation – no treatment given), coronary artery disease, type 2 diabetes and hyperlipidemia develops fatigue and a rash.

- He presents to his local internist. Physical exam is normal. A CBC with differential shows a white blood count of 2.4, with an absolute neutrophil count of 0.7, Hgb of 6.8 and platelets of 8.

- He is referred to a hematologist who performs a bone marrow aspiration and biopsy. The bone marrow shows acute myeloid leukemia with 45% myeloblasts, trisomy 8 and a mutation in IDH2

- What is the optimal treatment of his secondary AML

Courtesy of Eytan M Stein, MD

Case Presentation – Dr Stein: A 67-year-old man with secondary AML (continued)

- The patient received CPX-351 induction and achieved an MRD negative complete remission
- He went on to receive an allogeneic stem cell transplant
- Remains in remission 3 years post transplant and is very likely cured.

Courtesy of Eytan M Stein, MD

Case Presentation – Dr Stein: A 79-year-old woman s/p treatment for breast cancer with secondary AML

- 79y0 woman with a prior medical history of breast cancer at the age of 71 treated with a lumpectomy, radiation and adjuvant chemotherapy
- She develops pancytopenia, a bone marrow biopsy is performed and a diagnosis of AML is confirmed.
- Cytogenetics show loss of chromosome 7 and mutations in DNMT3A and p53
- She is not a transplant candidate.
- What is the best therapy for her disease?

Courtesy of Eytan M Stein, MD

Agenda

Module 1: Recent Advances in the Up-Front Treatment of Acute Myeloid Leukemia (AML)

- VIALE-A: Azacitidine and venetoclax in older patients with previously untreated AML
- Venetoclax-based regimens for patients with newly diagnosed AML who are or are not eligible for intensive induction therapy
- Efficacy of venetoclax-based combination regimens in patients with FLT3 or IDH1/2 mutations

Module 2: Secondary AML (sAML)

- Mechanism of action, available data with and side effects of CPX-351 in previously untreated sAML and primary AML
- Available data with and current clinical role of venetoclax-based therapy for patients with sAML

Module 3: Myelodysplastic Syndromes (MDS)

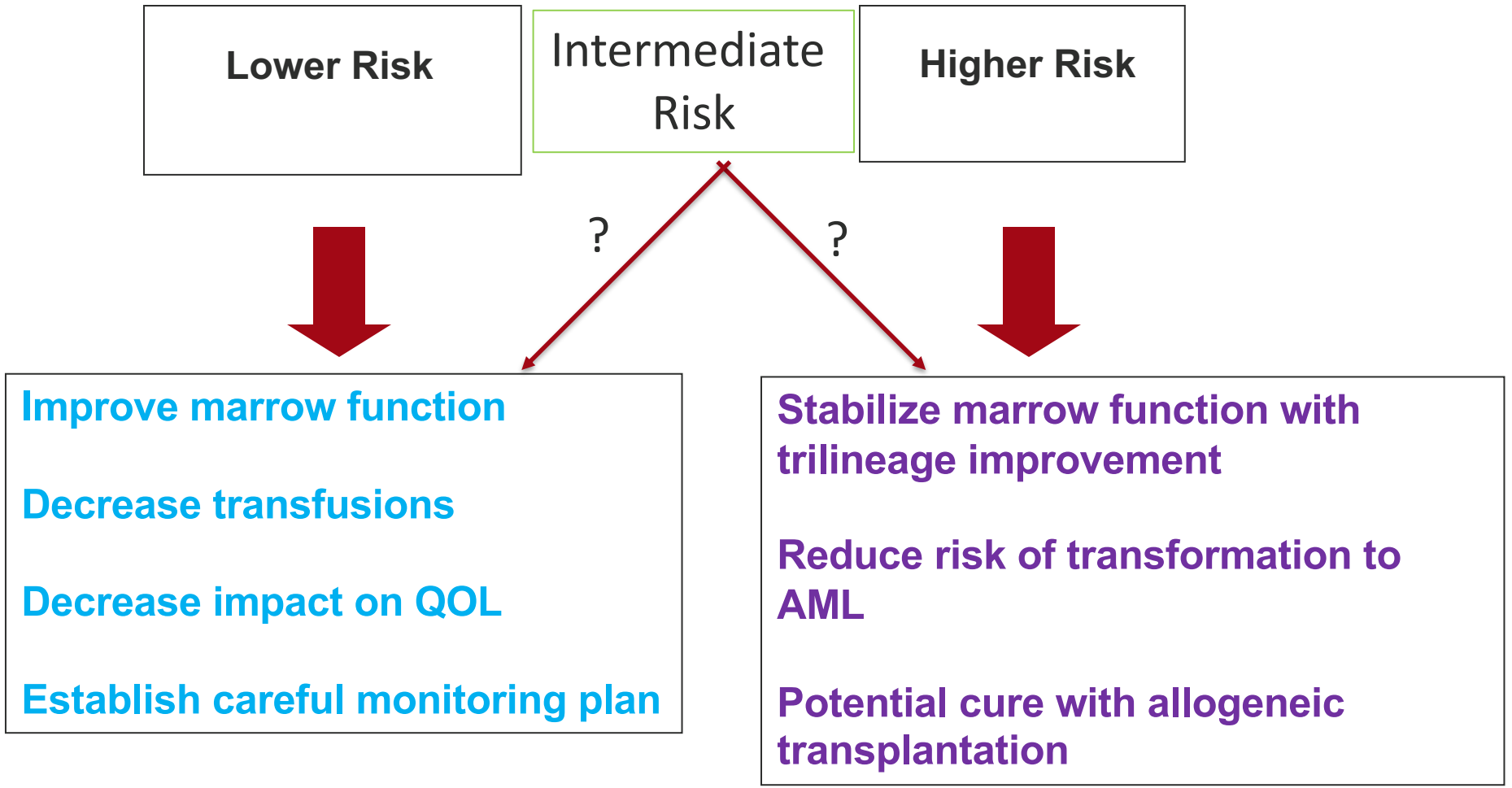
- ASCERTAIN studies evaluating the oral combination of decitabine and cedazuridine in patients with MDS
- Available research findings for agents with established efficacy in AML for patients with MDS
- Promising novel agents (eg, magrolimab, pevonedistat, sabatolimab) in MDS

RTP RESEARCH TO PRACTICE

Have you or would you use the oral combination of decitabine/ cedazuridine for a patient with MDS for whom you are planning to administer a hypomethylating agent?

1. I have
2. I have not but would for the right patient
3. I have not and would not
4. I am not familiar with this oral combination

Treatment goals in MDS



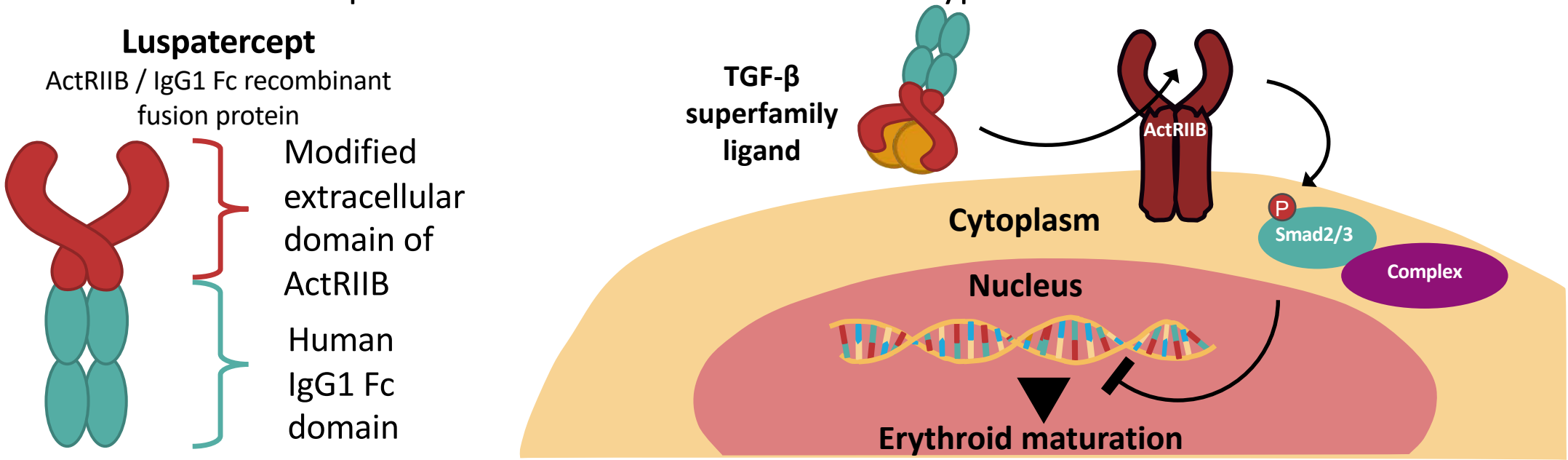
Weill Cornell Medicine NewYork-Presbyterian

Courtesy of Gail J Roboz, MD

MEDALIST Trial

Luspatercept

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

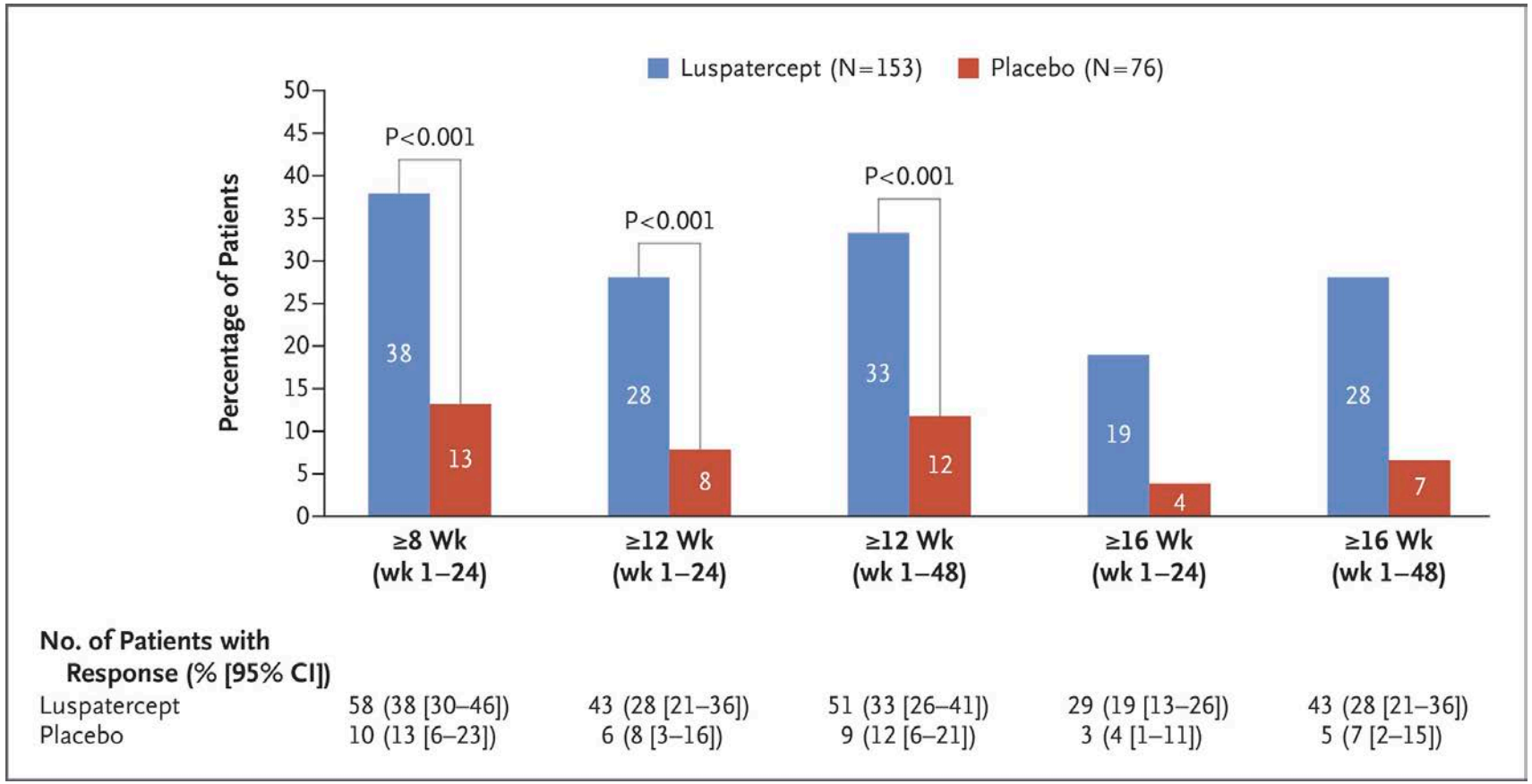


ActRIIB, human activin receptor type IIB; IgG1 Fc, immunoglobulin G1 fragment crystallizable; RBC-TI, red blood cell transfusion independence; RS, ring sideroblasts; TGF-β, transforming growth factor beta.

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

Courtesy of Gail J Roboz, MD

MEDALIST: Independence from Red-Cell Transfusion with Luspatercept



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])

Weill Cornell Medicine NewYork-Presbyterian

Courtesy of Gail J Roboz, MD

The NEW ENGLAND JOURNAL of MEDICINE

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

ASH 20-Platzbecker et al: Treatment With Imetelstat Provides Durable Transfusion Independence (TI) in Heavily Transfused Non-Del(5q) LR-MDS Relapsed/Refractory (R/R) to ESAs- Results from IMerge study

Results

Parameters	N = 38
8-week TI, n (%)	**16 (42)**
Time to onset of 8-week TI, weeks, median (range)	8.3 (0.1-40.7)
Duration of TI, weeks, median (95% CI)[a]	**88.0 (23.1 – 140.9*)**
Cumulative duration of TI ≥ 8 weeks[b], median (95% CI)[a]	92.3 (42.9, 140.9)
Hb rise ≥ 3.0 g/dL during TI[c], n (%)	12 (32)
24-week TI, n (%)	**12 (32)**
Hb rise ≥ 3.0 g/dL during TI[c], n (%)	11 (29)
1-year TI, n (%)	**11 (29)**
HI-E per IWG 2006, n (%)	26 (68)
≥1.5 g/dL increase in Hb lasting ≥ 8 weeks, n (%)	13 (34)
Transfusion reduction by ≥ 4 units/8 weeks, n (%)	26 (68)
Duration of HI-E, weeks, median (95% CI)[a]	92.7 (37.1, 149.4)

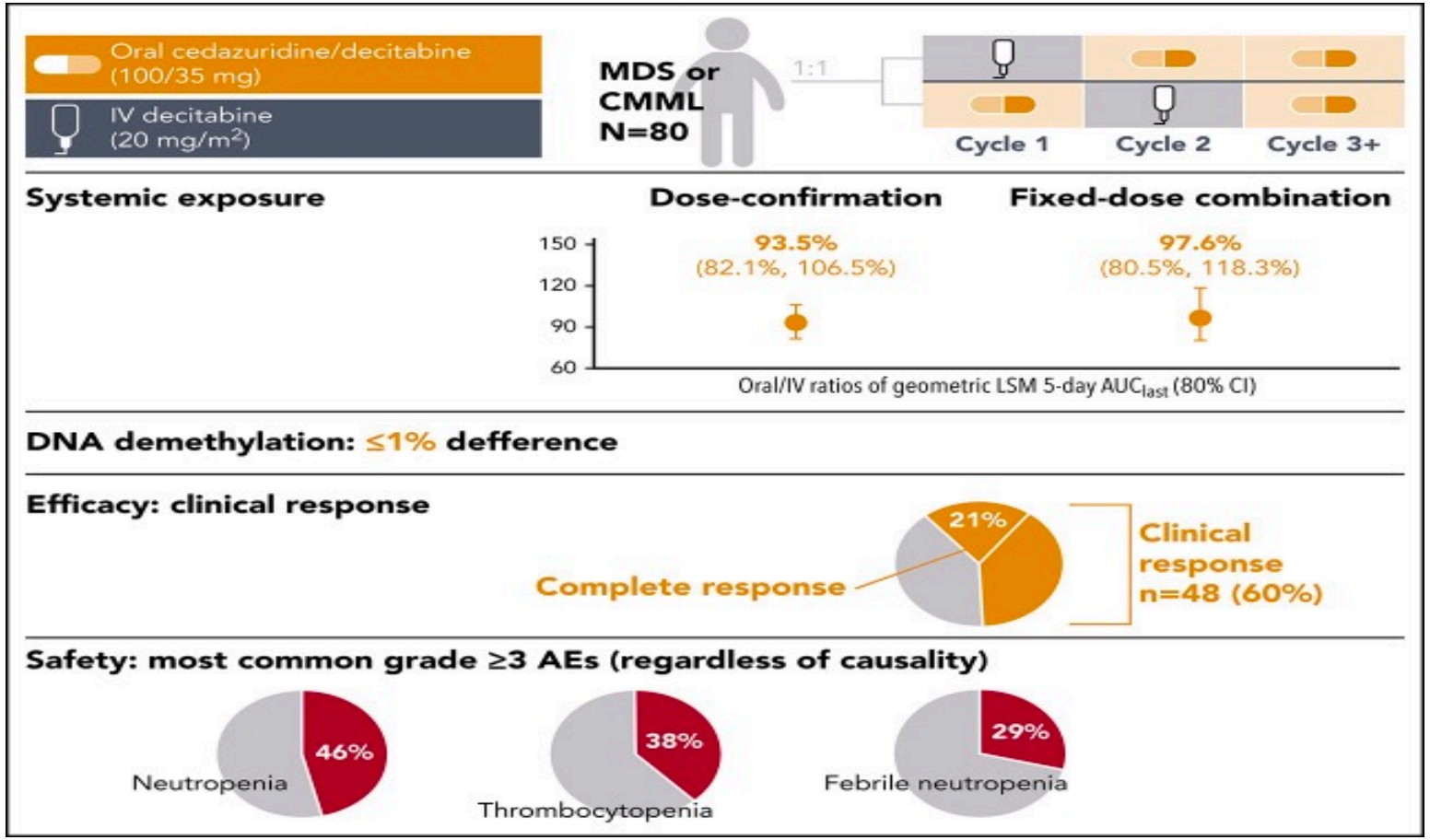
IMerge
63935937MDS3001

***Longest TI > 2.7 years**

[a] Kaplan Meier method;
[b] Cumulative Duration of TI ≥ 8 weeks is defined as the sum of all periods of TI ≥ 8 weeks during the treatment;
[c] Maximum Hb rise of ≥ 3g/dL from pretreatment level (pretreatment level defined as mean Hb/8 weeks).
CI, confidence interval; Hb, hemoglobin

Platzbecker et al, EHA 2020, S183
Platzbecker et al, ASH 2020, Abstract #658

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



FDA-approved for:

- Previously treated and untreated
- De novo and secondary MDS
- French-American-British RA, RARS, RAEB, and CMML
- Int-1, Int-2, and high-risk IPSS

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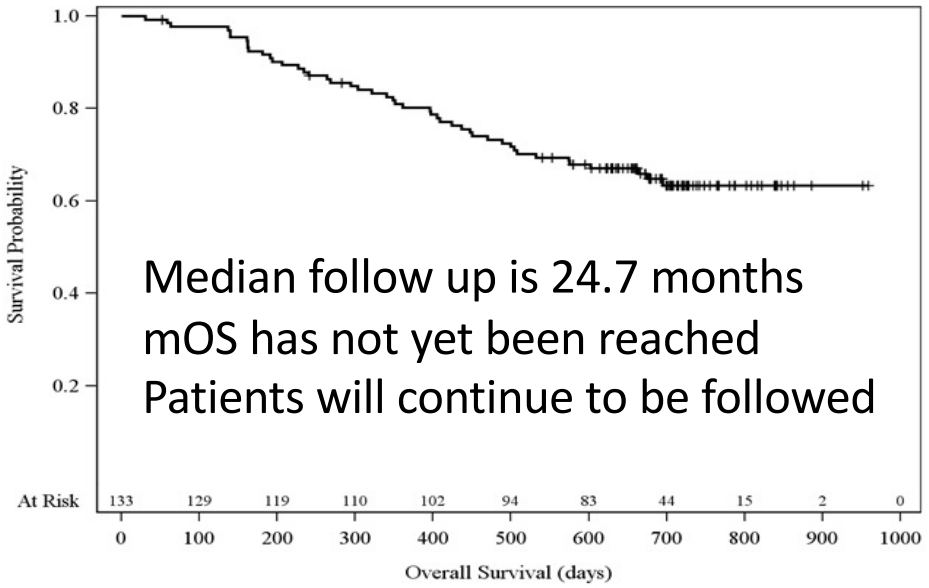
Courtesy of Gail J Roboz, MD

Garcia-Manero et al. Blood. 2020 Aug 6; 136(6): 674–683.

ASH 20-Savona et al: Clinical Efficacy and Safety of Oral Decitabine/Cedazuridine in 133 Patients with MDS and CMML-An Update of Phase 3 Study (ASCERTAIN)

Response category	Treated Patients (N=133), n (%)
Complete response (CR)	29 (22%)
Partial response (PR)	0
Marrow CR (mCR)	43 (32.3%)
mCR with hematologic improvement	22 (16.5%)
Hematologic improvement (HI)	10 (7.5%)
HI-erythroid	2 (1.5%)
HI-neutrophils	1 (0.8%)
HI-platelet	7 (5.3%)
RBC Transfusion Independence*	27/53 (51%)
Platelet Transfusion Independence*	6/12 (50%)
Overall response (CR + PR + mCR + HI)	82 (61.7%)

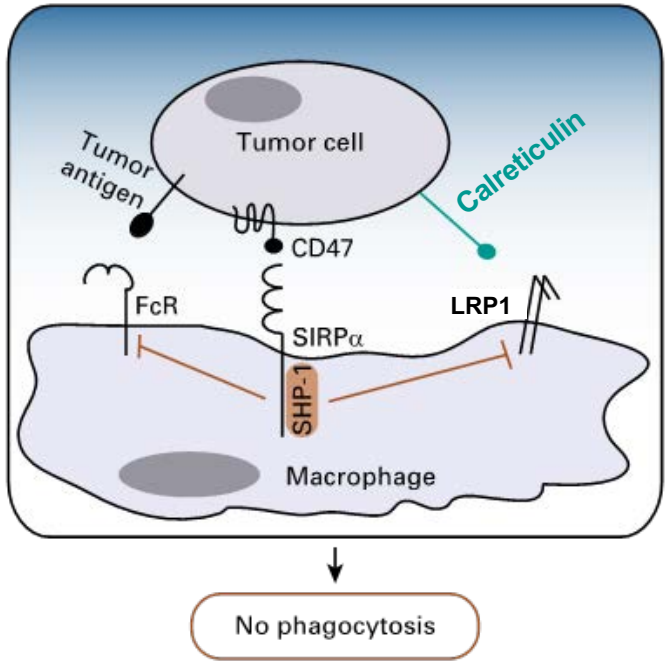
- CR (N=133): Median CR duration was 14.0 months
- Median duration of best response was 12.7 months
- 34 (26%) of subjects proceeded to HCT



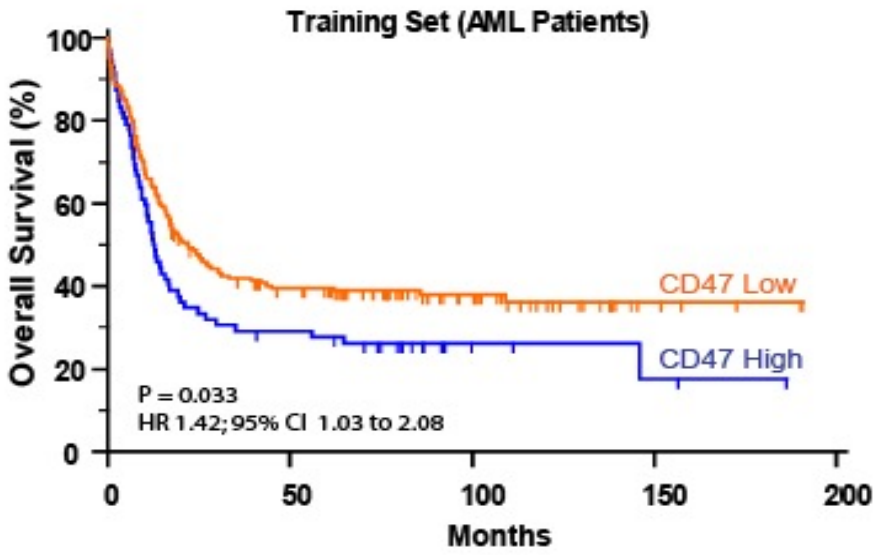
Courtesy of Gail J Roboz, MD

Savona M ,et al, ASH, 2020

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



CD47 Expression in AML Patients



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

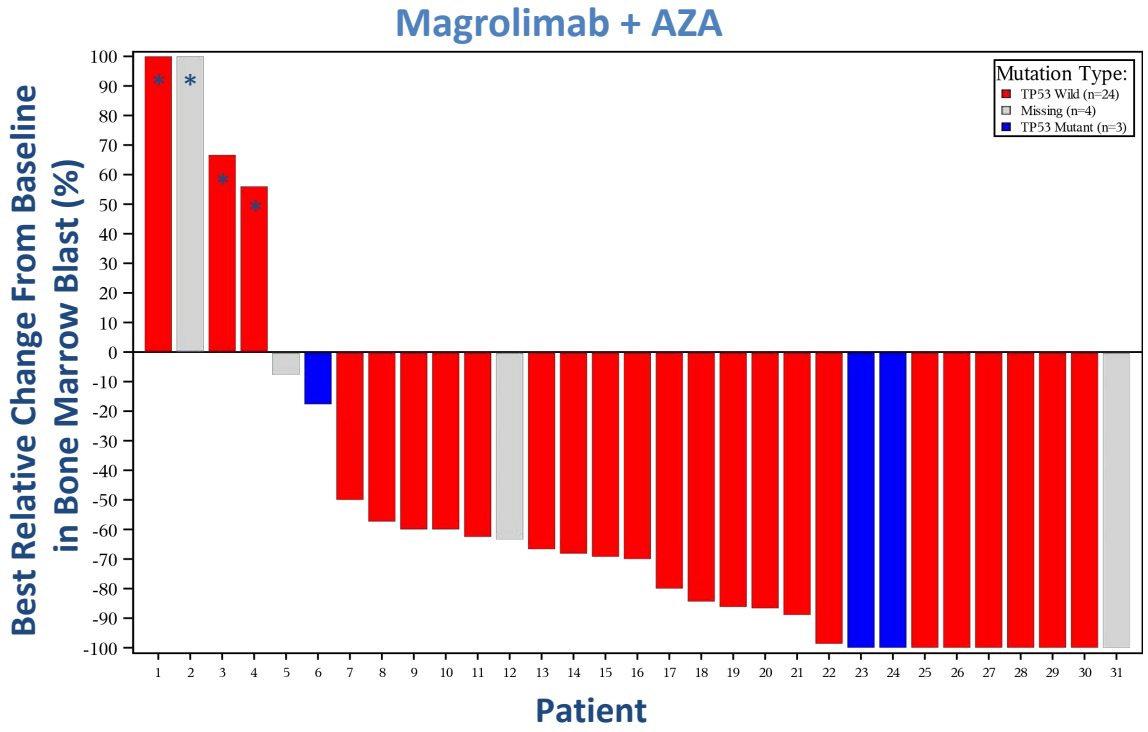
Figure at left adapted from Veillette A, Tang Z. *J Clin Onc*. 2019;37(12)1012-1014, and Chao MP, et al. *Current Opin Immunol*. 2012; 24(2):225-232.
Figure at right adapted from Majeti R, et al. *Cell*. 2009;138(2):286-299.

Courtesy of Gail J Roboz, MD

Magrolimab + AZA is Effective in Untreated Higher Risk MDS

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

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



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

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

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

Courtesy of Gail J Roboz, MD

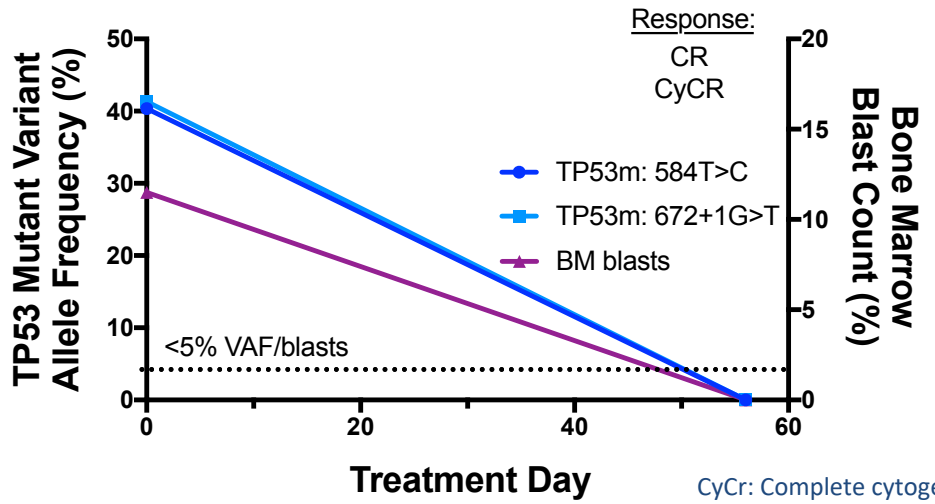
Magrolimab + AZA Has Activity in *TP53*-Mutant MDS

Efficacy in *TP53*-Mutant MDS Patients

Best Overall Response	MDS *TP53* Mutant (N=4)
ORR	3 (75%)
CR	2 (50%)
Marrow CR	1 (25%)
Complete cytogenetic response in responders*	3/3 (100%)
MRD negative of responders	0
Median duration of response (months)	Not reached (0.03+ – 5.2+)
Median overall survival (months)	100%
Median follow-up (range) (months)	7 (4.2 - 12.2)

*For patients with abnormal cytogenetics at baseline.

77M very high risk, complex karyotype, and double *TP53*-mutant MDS: Achieved a CR, CyCr, and clearance of both *TP53* mutations at Cycle 3



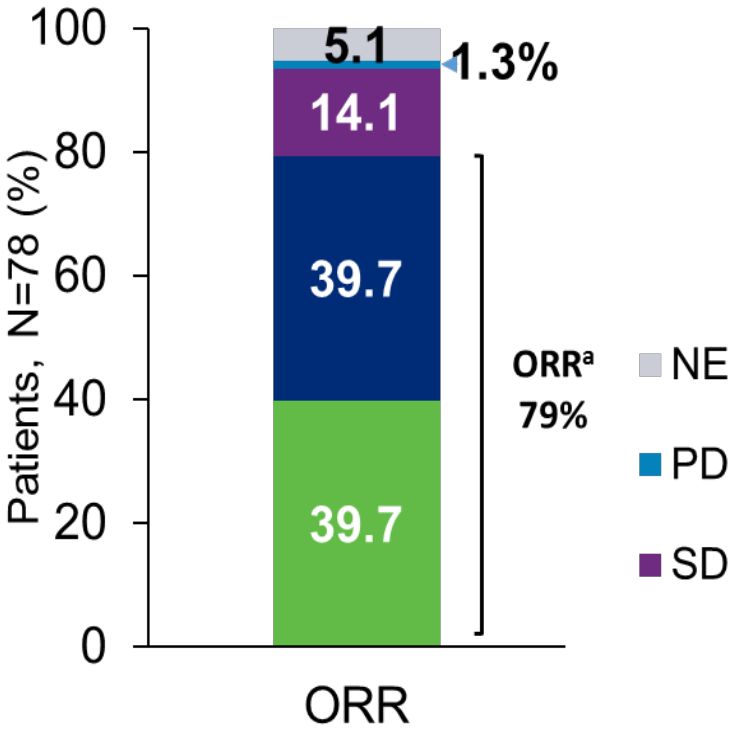
CyCr: Complete cytogenetic response

- In small patient numbers, magrolimab + AZA has a high response rate and encouraging durability
- Magrolimab + AZA has also shown a 75% CR/CRi rate with no median duration reached in 12 untreated *TP53*-mutant AML patients who are unfit for intensive chemo (Daver N, et al., EHA 2020)

Courtesy of Gail J Roboz, MD

ASH20-Garcia et al: Safety, Efficacy, and Patient-Reported Outcomes of Venetoclax in Combination With Azacitidine for the Treatment of Patients With HR-MDS: A Phase 1b Study

Results

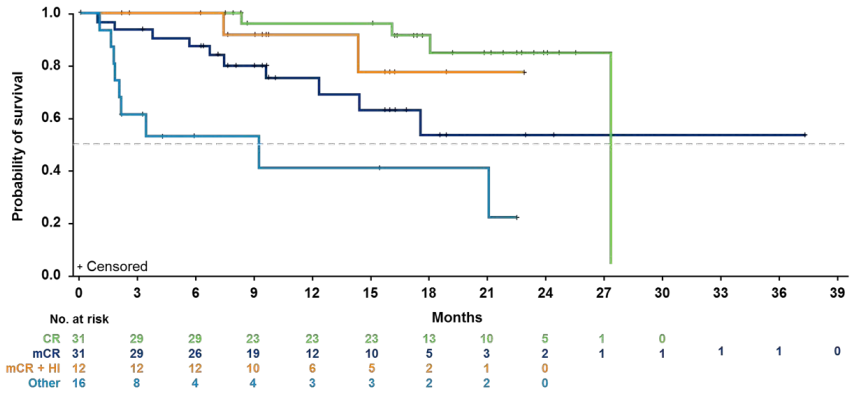


- **Median DoR: 12.9 months (min–max, 12.1–16.8)**
- **Median DoR after CR: 13.8 months (min–max, 6.5–20.9)**
- **Median time to CR: 2.6 months (min–max, 1.2–19.6)**
- **For patients receiving Ven 400 mg (RP2D; n=51)[b]**
  - **84% of patients achieved ORR[a]**
    - **47% achieved ORR by Cycle 2; 78%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

- Median F/U: 16.4 months
- Median OS 27 months



OS, median (95% CI), months	
CR	27.5 (NR, NR)
mCR	NR (12.4, NR)
mCR + HI	NR (14.5, NR)
Other	9.3 (1.7, NR)

Data cutoff: June 30, 2020

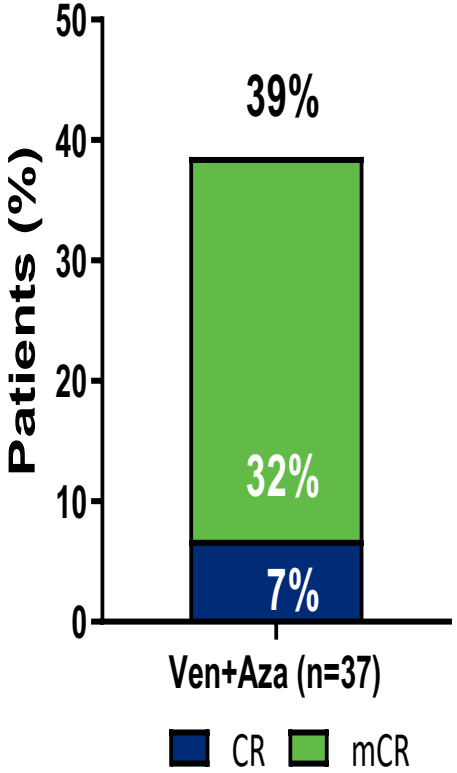
Courtesy of Gail J Roboz, MD

Garcia J et al, ASH 2020

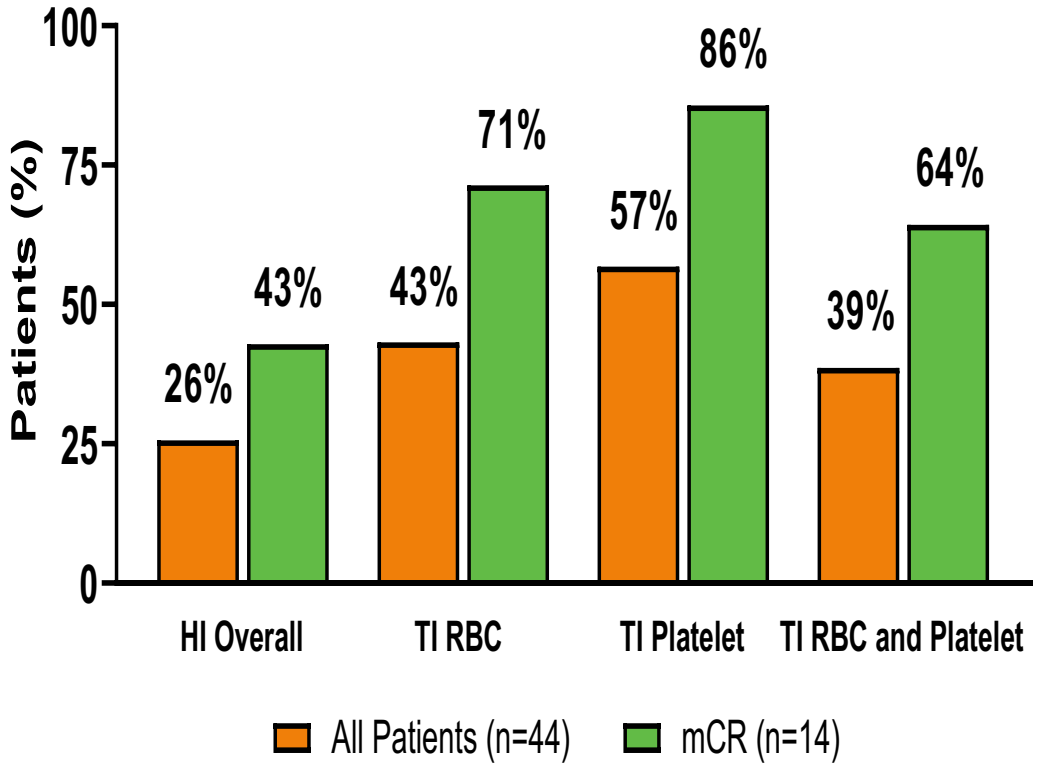
ASH20-Zeidan et al: A Phase 1b Study Evaluating the Safety and Efficacy of Venetoclax in Combination with Azacitidine for the Treatment of Relapsed/Refractory MDS

Results

Objective Response Rate



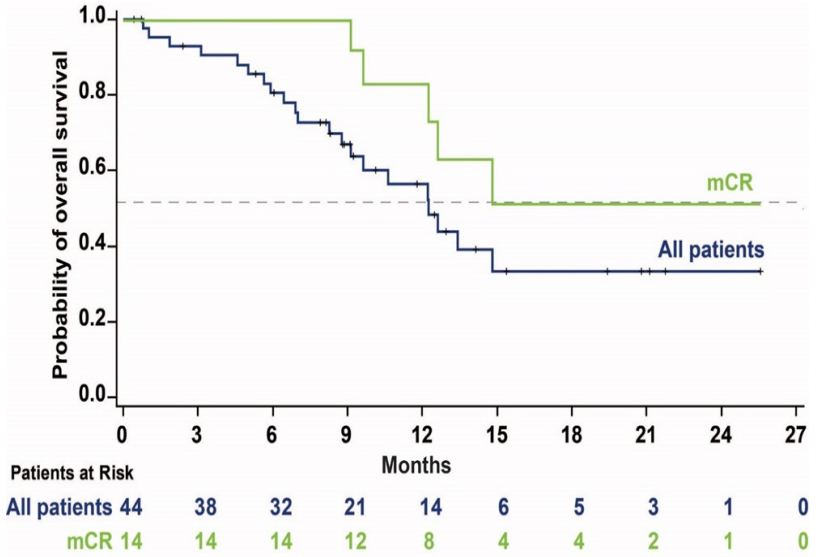
Hematological Improvement



Median OS, Months (95%CI)

All patients: 12.3 (8.8 – NR)

mCR: 14.8 (9.6 –NR)



37/44 patients were evaluable for response; HI: hematological improvement; HI-E: erythroid response; HI-N: neutrophil response; HI-P: platelet response; mCR: marrow complete remission; RBC: red blood cell; TI: transfusion independence; Aza: Azacitidine; Ven: Venetoclax; Overall HI response rate included subjects who were eligible for the HI assessment at baseline and achieved any component of HI-E + HI-P + HI-N: Transfusion dependent on packed red blood cells or whole blood 8 weeks prior to C1D1 or hemoglobin level < 11 g/dL. HI-P: Transfusion dependent on platelet 8 weeks prior to C1D1 or platelet counts < 100 X 10^9/L; HI-N: Neutrophil counts < 1.0 X 10^9/L at baseline.

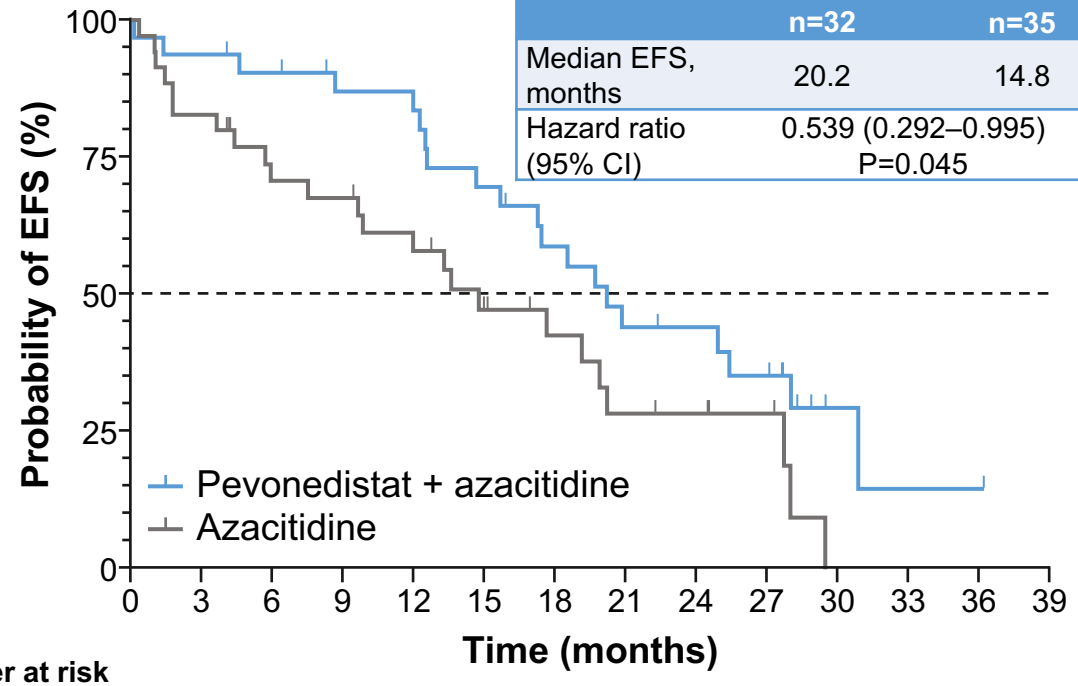
Courtesy of Gail J Roboz, MD

Zeidan A et al, ASH 2020

ASH20-Sekeres et al: Efficacy and Safety of Pevonedistat plus Azacitidine vs Azacitidine Alone in Higher-Risk MDS from Study P-2001

Results

EFS*



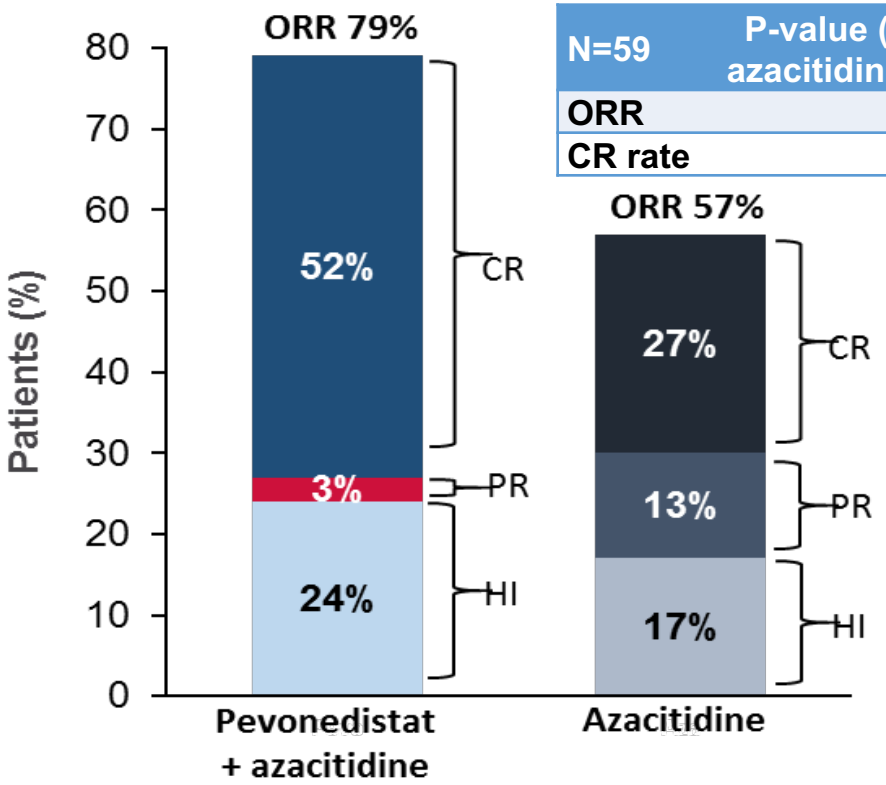
	Pevonedistat + azacitidine n=32	Azacitidine n=35
Median EFS, months	20.2	14.8
Hazard ratio (95% CI)	0.539 (0.292–0.995) P=0.045	

Number at risk

Pevonedistat + azacitidine	32	30	28	25	24	20	16	11	10	8	2	1	1	0
Azacitidine	35	29	23	22	18	12	9	6	5	4	0	0	0	0

- Longer EFS was particularly evident in patients with IPSS-R-defined very-high-risk MDS (n=26; HR: 0.47; 95% CI: 0.19–1.18) and high-risk MDS (n=21; HR: 0.53; 95% CI: 0.17–1.72)

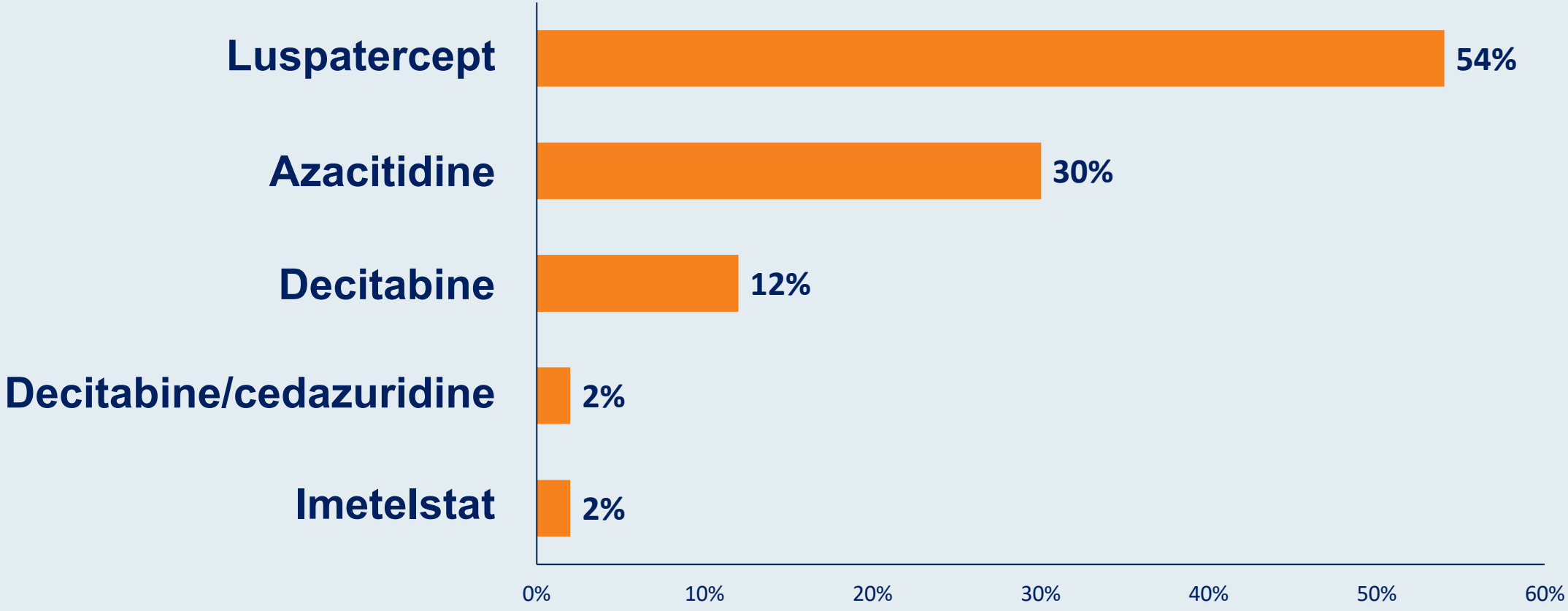
*EFS defined as time to death or transformation to AML in higher-risk MDS.



N=59	P-value (pevonedistat + azacitidine vs azacitidine)
ORR	0.065
CR rate	0.050

	Pevonedistat + azacitidine n=32	Azacitidine n=35
Median OS, months	**23.9**	**19.1**
Hazard ratio (95% CI)	**0.701 (0.386–1.273) P=0.240**	

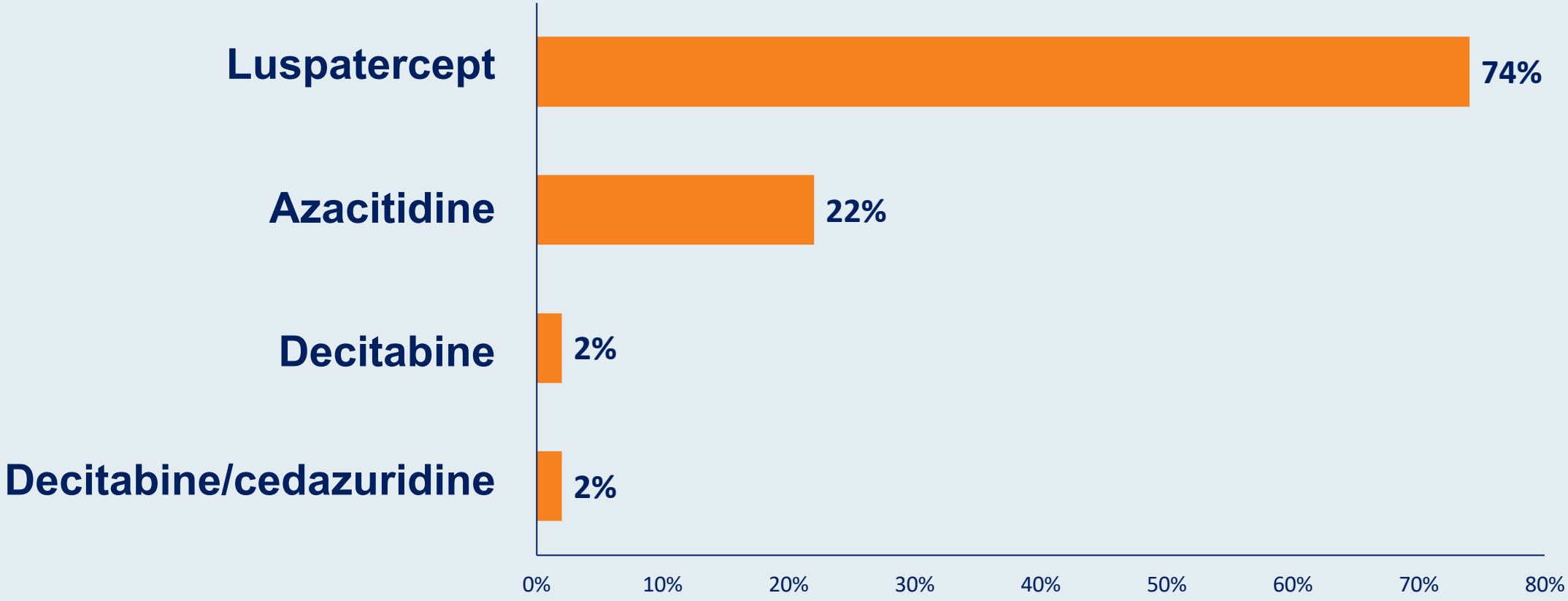
Regulatory and reimbursement issues aside, what is your preferred treatment for an otherwise healthy 72-year-old patient with lower-risk MDS with no del(5q), ring sideroblasts <15% and transfusion-dependent anemia who responds to darbepoetin alfa but then develops a new transfusion requirement?



Premeeting survey: July 2021

RTP RESEARCH TO PRACTICE

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



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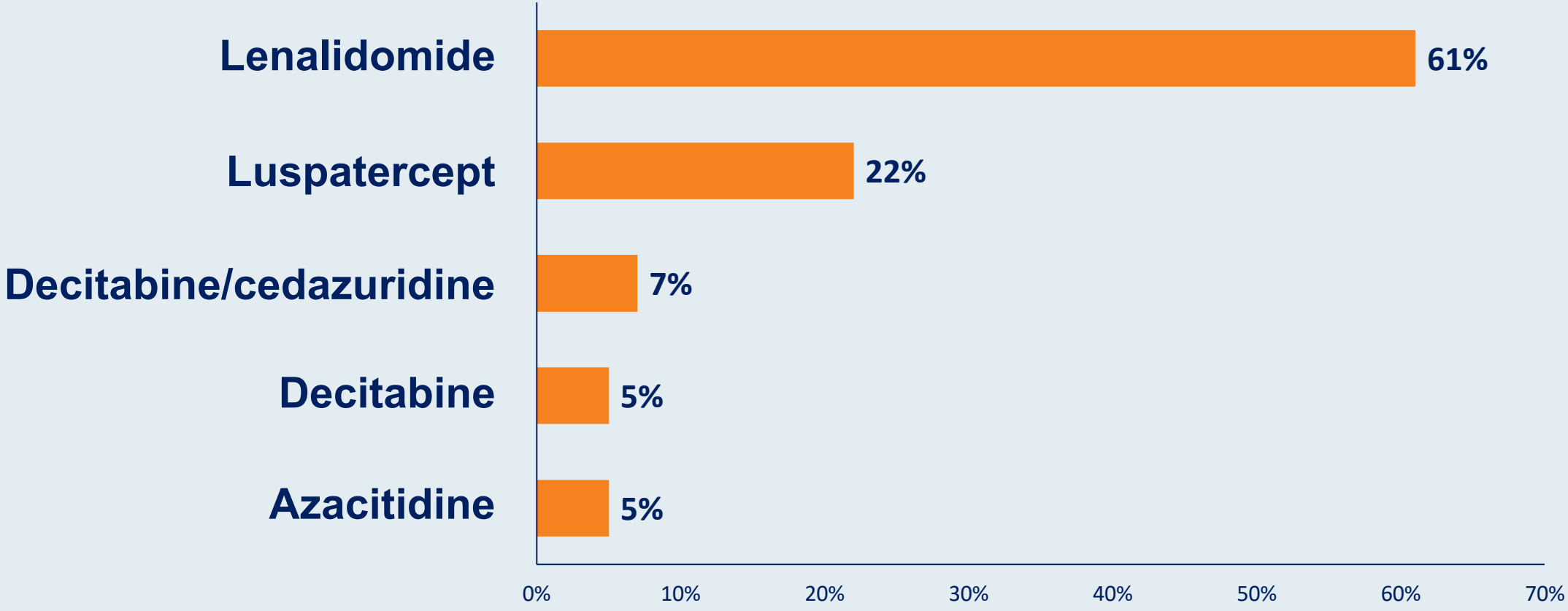

Premeeting survey: July 2021

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Roboz: A 56-year-old man with CMML

- 56 year-old generally healthy man diagnosed with CMML in Oct 2020 after presenting with shortness of breath
- Leukocytosis, thrombocytopenia, transfusion-dependent anemia
- Normal cytogenetics, 14% blasts
- TET2, U2AF1, DNMT3 mutations
- Treated with 1 cycle azacitidine, transferred to my care
- Treated with 2 cycles decitabine/cedazuridine
- Bone marrow biopsy with 3% blasts
- Allo transplant planning

Courtesy of Gail J Roboz, MD

Case Presentation – Dr Roboz: A 72-year-old man with RCMD MDS and ringed sideroblasts

- 72 year old man with low-grade MDS diagnosed Feb 2010 (RARS; anemia, normal cytogenetics, <5% blasts in marrow)
- Bone marrow biopsy from Jun 2013 with loss of Y in 8 metaphases and marrow with RCMD and ringed sideroblasts, no increased blasts, SF3B1 mutation.
- Started ESA support 2013
- GCSF added 2015
- Loss of response with worsening anemia and requiring transfusions 2020
- Started luspatercept 2020
- Transfusion independent and hgb>10 starting after 3rd dose

Weill Cornell Medicine NewYork-Presbyterian

Courtesy of Gail J Roboz, MD

Faculty Case Appendix

Case Presentation – Dr DiNardo: A 68-year-old man with AML and SRSF2 and TET2 mutations

A 68-year old man with newly diagnosed AML is being evaluated for treatment recommendations. His WBC is 3K with 7% circulating blasts, and his BM blasts are 35% with MDS-related morphological changes. Cytogenetics show monosomy 7. Mutation panel shows *SRSF2* and *TET2* mutations. His ECOG PS is 1.

What would be your preferred frontline treatment regimen?

1. CPX-351
2. Hypomethylating agent (HMA) alone
3. HMA + venetoclax
4. LDAC + venetoclax
5. LDAC + glasdegib

Courtesy of Courtney D DiNardo, MD, MSCE

Case Presentation – Dr DiNardo: A 72-year-old man with AML and RUNX1 and IDH2 mutations

72 year old M presenting with fatigue and dyspnea on exertion

- PMHx: coronary artery disease s/p CABG, atrial fibrillation, EF 50%, Type 2 DM
- WBC 15K, Hgb 7.5 g/dl, Plts 85K. 27% circulating blasts.
- ECOG PS 1.
- Interested in leukemia-directed therapy.

Diagnosis:

- AML with 32% CD33+ blasts.
- Diploid cytogenetics
- RUNX1 and IDH2 mutations

Courtesy of Courtney D DiNardo, MD, MSCE

Case Presentation – Dr DiNardo: A 72-year-old man with AML and RUNX1 and IDH2 mutations (continued)

You decide to treat the patient with azacitidine plus venetoclax. He is started on prophylaxis with levofloxacin, caspofungin, and valacyclovir. Venetoclax is given at a dose of 400 mg daily. On day 12 of therapy, he develops neutropenic fever, and a CT of his chest shows 2 nodular opacities concerning for fungal infection, including a 1.5-cm lesion with halo sign. He is on room air and otherwise clinically stable.

How would you manage his current therapy?

1. Hold therapy and treat with voriconazole or posaconazole until infection has resolved
2. Continue current regimen and wait until venetoclax is completed on day 28, then start voriconazole or posaconazole
3. Add posaconazole or voriconazole and continue same dose of venetoclax
4. Add posaconazole or voriconazole but reduce the dose of venetoclax

Courtesy of Courtney D DiNardo, MD, MSCE

Case Presentation – Dr DiNardo: A 72-year-old man with AML and RUNX1 and IDH2 mutations (continued)

The patient's BM examination is performed on day 28 of therapy. BM blasts are 2% in a sufficient sample. Flow cytometry for MRD is negative. His WBC is 0.3 (no differential performed), and he is still RBC- and platelet-transfusion dependent.

What would you do next?

1. Continue venetoclax at same dose and await count recovery before restarting azacitidine
2. Reduce the dose of venetoclax and await count recovery before restarting azacitidine
3. Hold venetoclax and await count recovery before beginning cycle 2
4. Start cycle 2 of azacitidine plus venetoclax at full dose
5. Start cycle 2 of azacitidine plus venetoclax at reduced dose

Courtesy of Courtney D DiNardo, MD, MSCE

Case Presentation – Dr Roboz: An 86-year-old man with newly diagnosed TP53-mutated MDS

- 86 year-old man referred for consultation re newly diagnosed TP53 mutated MDS with pancytopenia and complex cytogenetics, no increased blasts.
- Has a history of sarcoma treated with XRT and doxorubicin, also with psoriatic arthritis, atrial fibrillation, Type 2 DM
- Enrolled onto azacitidine/APR-246 randomized trial, treated on control arm
- CR with azacitidine
- Treated with 3-day cycles throughout COVID pandemic to minimize cytopenias and MD visits
- Recently with return of cytopenias
- Ongoing consideration of alternatives

Courtesy of Gail J Roboz, MD

Meet The Professor

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

Monday, July 19, 2021
5:00 PM – 6:00 PM ET

Faculty

Tanios Bekaii-Saab, MD

Moderator

Neil Love, MD

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Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 2 to 3 business days.

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