Year in Review:

Acute Myeloid Leukemia and Myelodysplastic Syndromes

Thursday, January 27, 2022
5:00 PM – 6:00 PM ET

Faculty

Daniel A Pollyea, MD, MS
Gail J Roboz, MD

Moderator

Neil Love, MD

RTP Year in Review 2022

YiR Acute Myeloid Leukemia and Myelodysplastic Syndromes Faculty

Daniel A Pollyea, MD, MS
Associate Professor of Medicine
Clinical Director of Leukemia Services
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Commercial Support

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Dr Love — Disclosures

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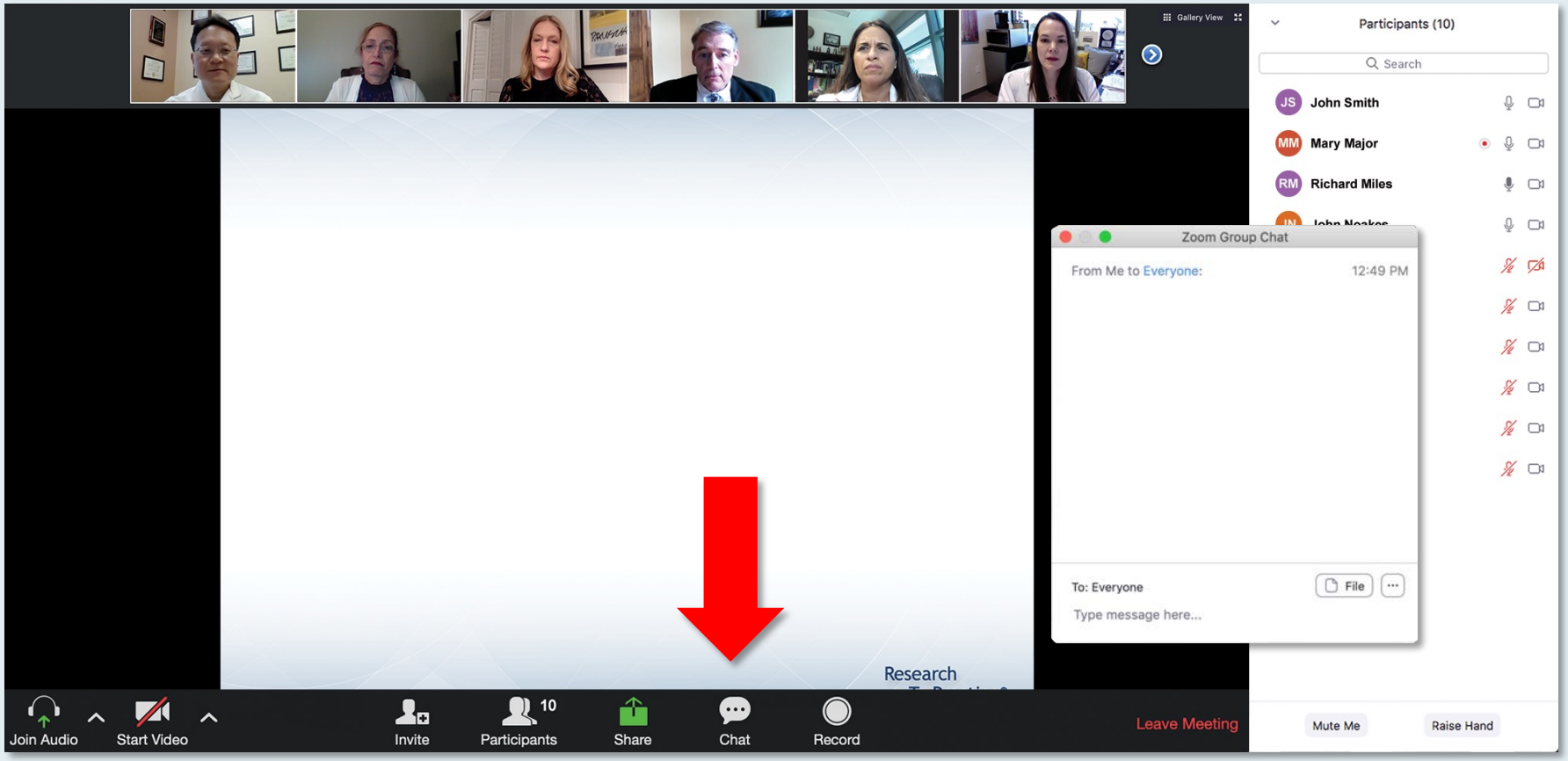
We Encourage Clinicians in Practice to Submit Questions



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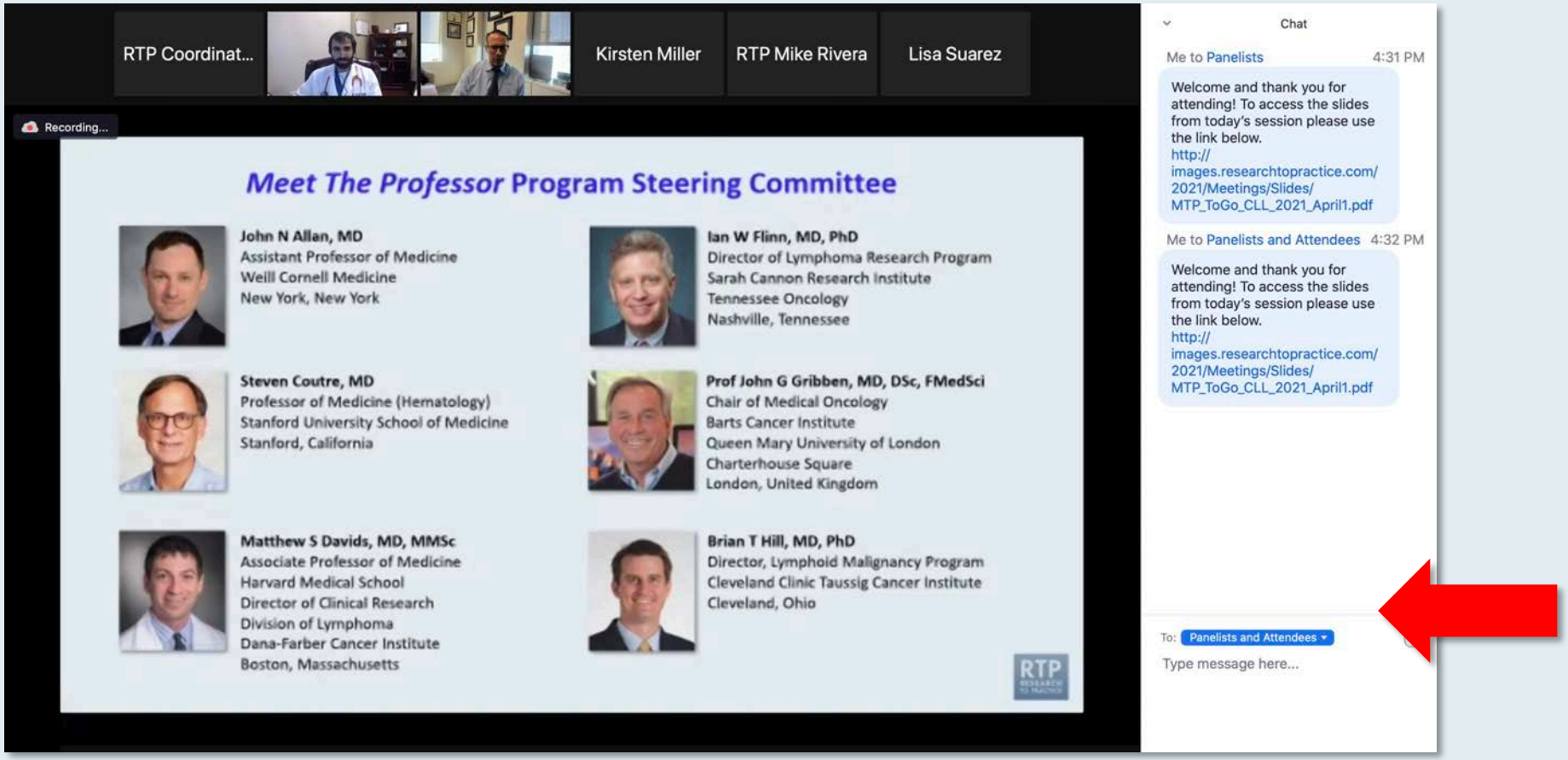

Drag the white line above the submission box up to create more space for your message.

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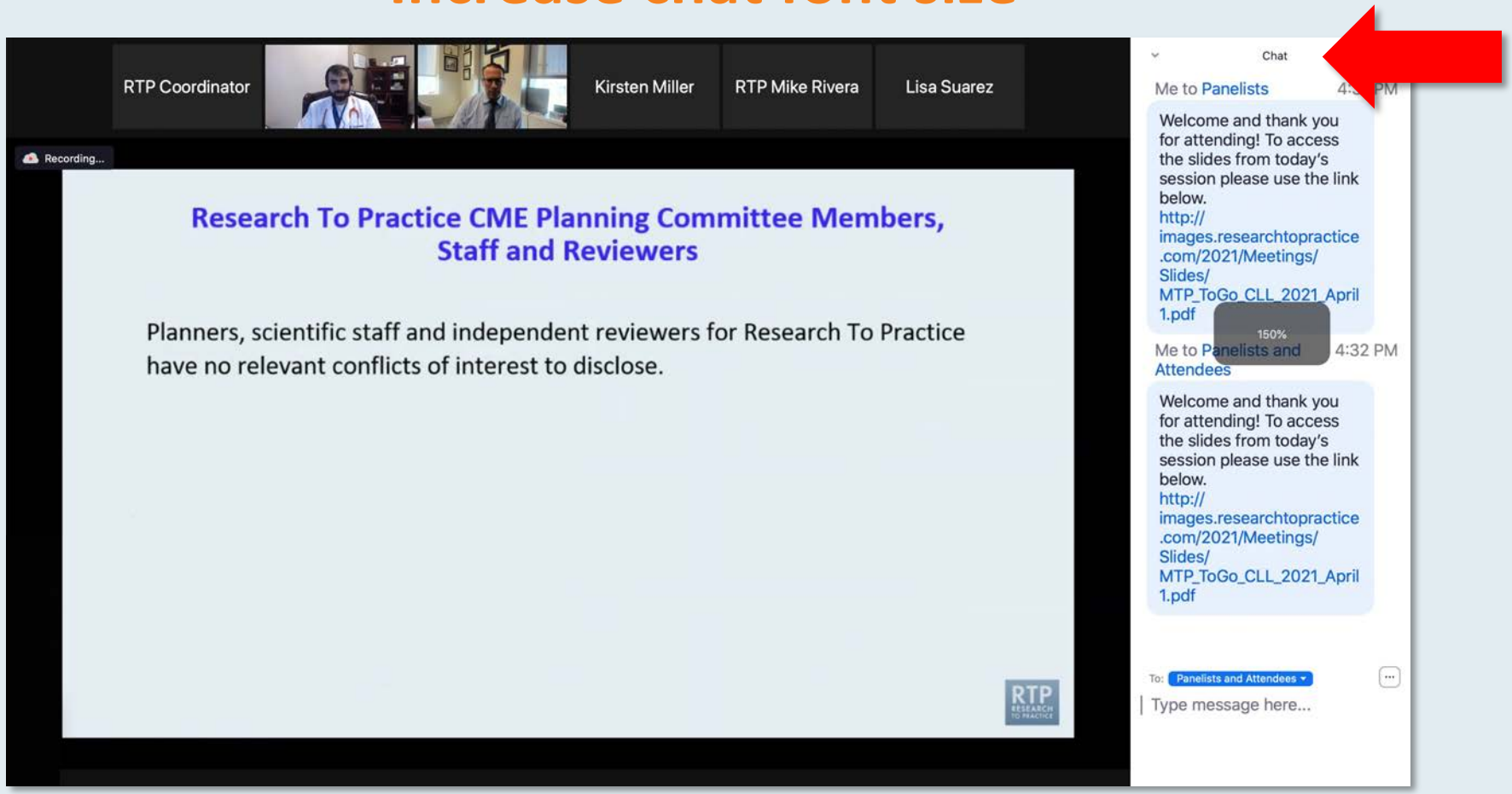

Press Command (for Mac) or Control (for PC) and the + symbol.
You may do this as many times as you need for readability.

ONCOLOGY TODAY

WITH DR NEIL LOVE

Myelodysplastic Syndromes

DR MICHAEL SAVONA
VANDERBILT UNIVERSITY SCHOOL OF MEDICINE

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Year in Review: Gastric, Gastroesophageal Junction and Esophageal Cancer

Tuesday, February 1, 2022
5:00 PM – 6:00 PM ET

Faculty

David H Ilson, MD, PhD

Zev Wainberg, MD, MSc

Moderator

Neil Love, MD

RTP Year in Review 2022

Exploring the Current and Changing Paradigm for the Management of Newly Diagnosed Diffuse Large B-Cell Lymphoma

Wednesday, February 2, 2022
5:00 PM – 6:00 PM ET

Faculty

Christopher R Flowers, MD, MS
Neha Mehta-Shah, MD, MSCI
Grzegorz Nowakowski, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Exploring the Current and Future Role of B-Cell Maturation Antigen-Directed Therapy in the Management of Multiple Myeloma

Monday, February 7, 2022
5:00 PM – 6:00 PM ET

Faculty

Jesús G Berdeja, MD
Noopur Raje, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Key Considerations in the Optimal Clinical Care of Patients with Small Cell Lung Cancer

Wednesday, February 9, 2022
5:00 PM – 6:00 PM ET

Faculty

Luis Paz-Ares, MD, PhD
Jared Weiss, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Recent Advances and Real-World Implications in Medical Oncology: A Daylong Multitumor Educational Symposium in Partnership with the North Carolina Oncology Association and the South Carolina Oncology Society

Saturday, February 12, 2022
8:30 AM – 4:00 PM ET

RTP
RESEARCH
TO PRACTICE

Recent Advances and Real-World Implications in Medical Oncology: Agenda

Module 1	**Chronic Lymphocytic Leukemia and Lymphomas** 8:35 AM – 9:40 AM
Module 2	**Multiple Myeloma** 9:40 AM – 10:45 AM
Module 3	**Genitourinary Cancers** 10:45 AM – 11:50 AM
Module 4	**Breast Cancer** 12:30 PM – 1:35 PM
Module 5	**Gastrointestinal Cancers** 1:35 PM – 2:40 PM
Module 6	**Lung Cancer** 2:40 PM – 3:45 PM

RTP
RESEARCH TO PRACTICE

Year in Review:
Kidney and Bladder Cancer

Tuesday, March 8, 2022
5:00 PM – 6:00 PM ET

Faculty

Elizabeth R Plimack, MD, MS
Thomas Powles, MBBS, MRCP, MD

Moderator

Neil Love, MD

RTP Year in Review 2022

Thank you for joining us!

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

RTP Year in Review 2022

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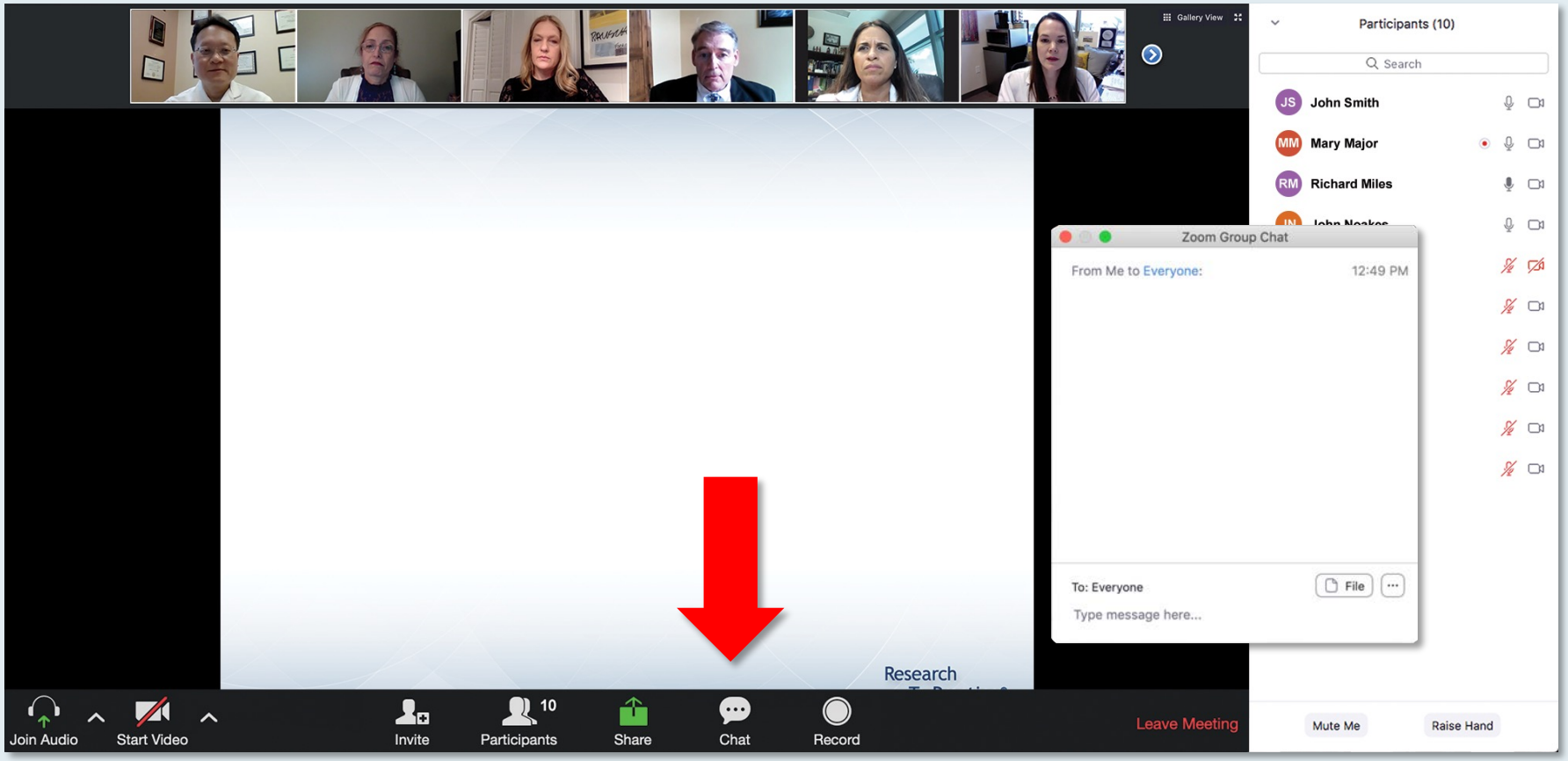

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RTP Year in Review 2022

Agenda

Module 1: Acute Myeloid Leukemia – *Dr Pollyea*

Module 2: Myelodysplastic Syndromes – *Dr Roboz*

When did you finish your oncology fellowship/enter clinical practice?

1. Less than 5 years ago
2. 5-10 years ago
3. 11-20 years ago
4. 21-30 years ago
5. 31-40 years ago
6. More than 40 years ago

Richard M Stone, MD

RTP Year in Review 2022

Agenda

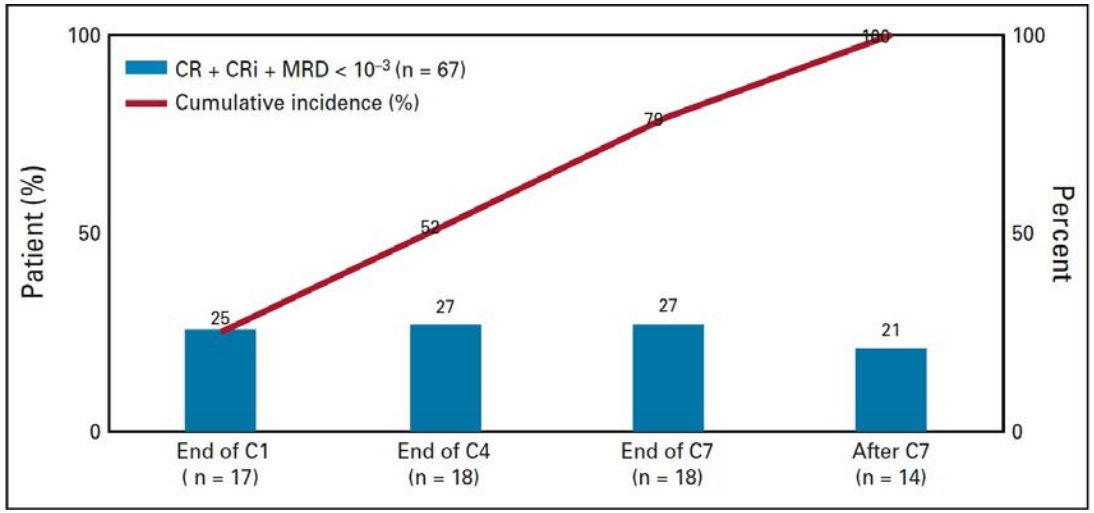
Module 1: Acute Myeloid Leukemia

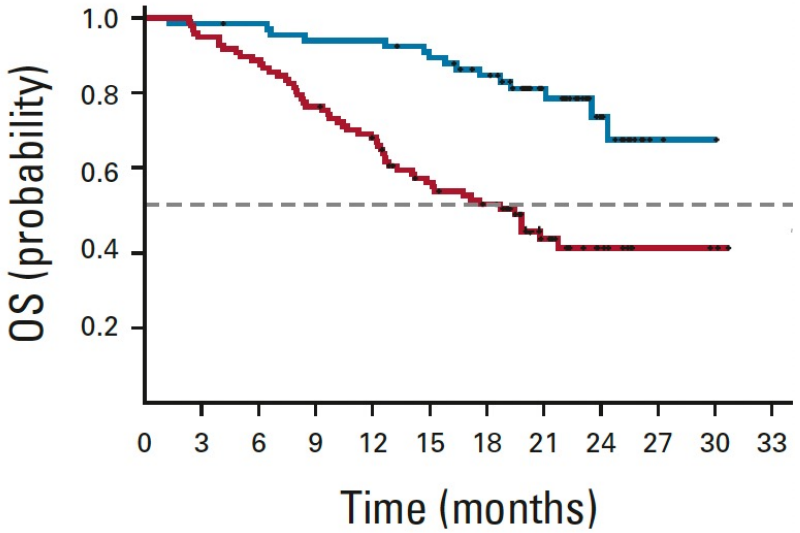
- Measurable residual disease response in VIALE-A
- Venetoclax and intensive chemotherapy
- Venetoclax/decitabine for high-risk younger patients
- Venetoclax/hypomethylating agents/magrolimab
- Future of venetoclax
- FLT3 mutations
- IDH1 versus IDH2 mutations
- Combination therapy for IDH1/2

Module 2: Myelodysplastic Syndromes

Can MRD Negativity be Achieved with a Lower Intensity Regimen?

- 41% of responding patients in VIALE-A were MRD<10^{-3}
  - Higher rates in the NPM1+ group
- Occurred early and late
- Longer remission duration (not reached vs 9.7 mos)
- Better event free survival (not reached vs 10.6 mos)
- Better OS (not reached vs 18.7 mos)





Pratz et al, JCO 2021

Courtesy of Daniel A Pollyea, MD, MS

Measurable Residual Disease

- Possible to get to MRD negative state with venetoclax
- Important to understand/predict these patients so that we can apply transplantation more judiciously
- Understanding the mechanism of a deep remission may help us treat those who have relatively poor responses

Courtesy of Daniel A Pollyea, MD, MS

Venetoclax + Intensive Chemotherapy

- High response rates
- High MRD negative rates
- Will it be better than intensive chemotherapy alone?
- Would it be better than venetoclax+HMA alone?

Courtesy of Daniel A Pollyea, MD, MS

Venetoclax + Decitabine for Younger Newly Diagnosed Patients with ELN Adverse Risk AML

- Standard venetoclax/decitabine
- If FLT3+ added sorafenib in some
- Those who responded had 1-2 cycles of HIDAC followed by allo SCT
- 14 evaluable patients, compared to historical controls with 7+3

Chen S et al. ASH 2021 #35

Courtesy of Daniel A Pollyea, MD, MS

The End of Chemotherapy?

- Ultimately will require randomized study
- We are doing this with ven/aza and no HIDAC (Gutman et al, ASH 2020)
- Preliminary results presented last year
  - 8 patients
  - 75% response rate
- NCT03573024

Courtesy of Daniel A Pollyea, MD, MS

What Does it Mean to Be Adverse Risk?

- Adverse risk factors all defined in relation to intensive chemotherapy

- Do they still apply when you are using a novel regimen?

Courtesy of Daniel A Pollyea, MD, MS

Triple Combination of Venetoclax with a Non-Genomically Targeted Therapy

Courtesy of Daniel A Pollyea, MD, MS

Manufacturer Announces Partial Clinical Hold for Studies Evaluating Magrolimab in Combination With Azacitidine — January 25, 2022

“The U.S. Food and Drug Administration (FDA) has placed a partial clinical hold on studies evaluating the combination of magrolimab plus azacitidine due to an apparent imbalance in investigator-reported suspected unexpected serious adverse reactions (SUSARs) between study arms. While no clear trend in the adverse reactions or new safety signal has been identified at this time, the partial clinical hold is being implemented by the manufacturer across all ongoing magrolimab and azacitidine combination studies worldwide in the best interests of patients as additional data is gathered and analyzed to address the concerns raised by FDA.

During the partial clinical hold, screening and enrollment of new study participants will be paused in any study investigating the combination of magrolimab with azacitidine. Patients already enrolled in these clinical studies may continue to receive magrolimab and azacitidine, or placebo, and continue to be closely monitored according to the current study protocol. Other magrolimab studies, or cohorts, that are not studying the combination of magrolimab plus azacitidine, will continue without any impact by the partial clinical hold.”

Magrolimab with Ven/Aza

- Randomized phase 3 study for up-front patients ongoing (ENHANCE-3)
- Too soon to tell if it adds anything in the R/R setting
- Will watch to see the signal in TP53+ patients

Courtesy of Daniel A Pollyea, MD, MS

Future for Venetoclax

- Learning more about its mechanism
- Re-assessing risk AML risk factors…adverse is not necessarily adverse!
- Understanding who it doesn't work for and overcoming this resistance

Courtesy of Daniel A Pollyea, MD, MS

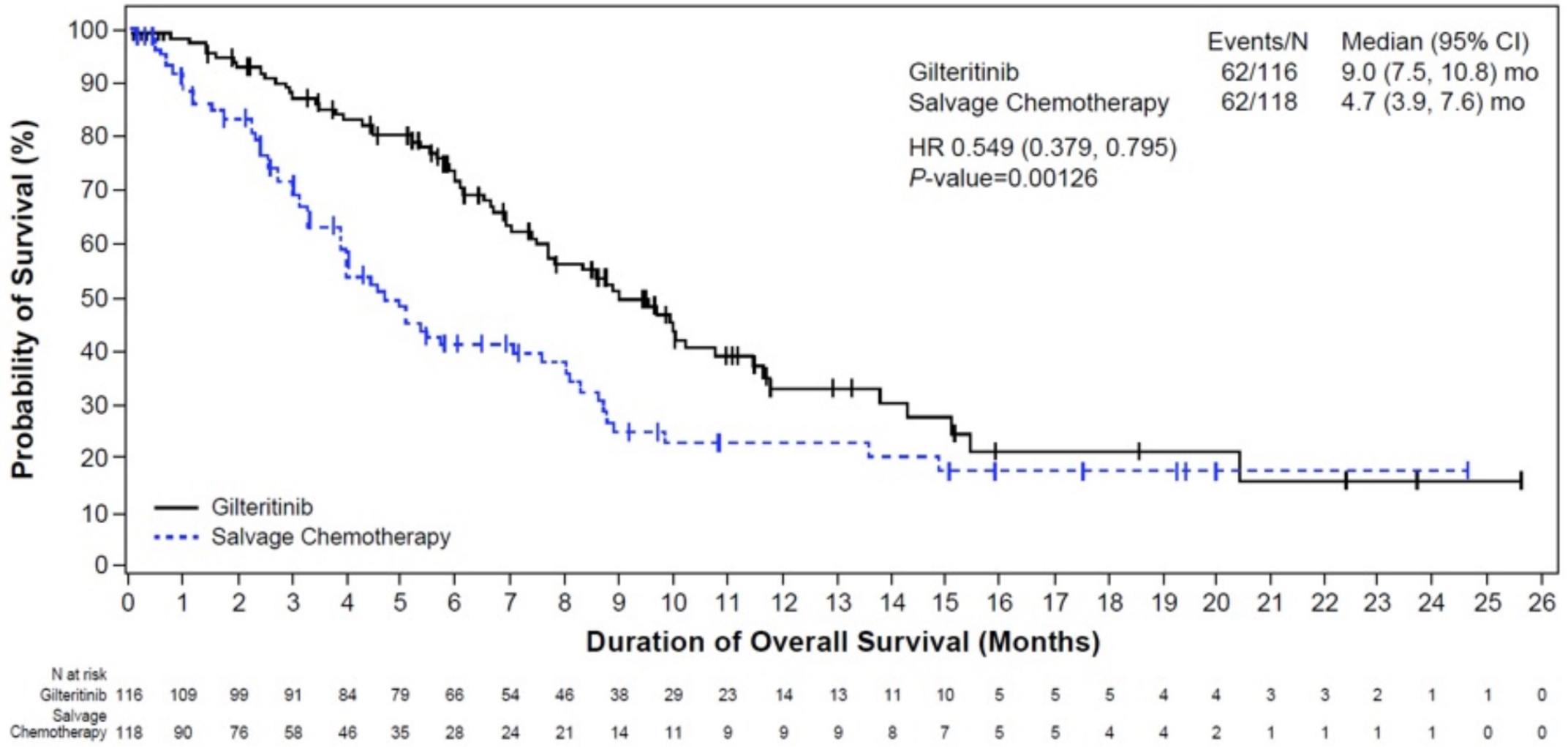
Targeting FLT3

- Based on the ADMIRAL trial, gilteritinib is approved for R/R AML due to its superiority compared with standard salvage chemotherapy

- Similar findings from a Phase 3 study in Asians with 234 patients reported at ASH

Courtesy of Daniel A Pollyea, MD, MS

Figure



Wang J et al, ASH 2021 #695

Courtesy of Daniel A Pollyea, MD, MS

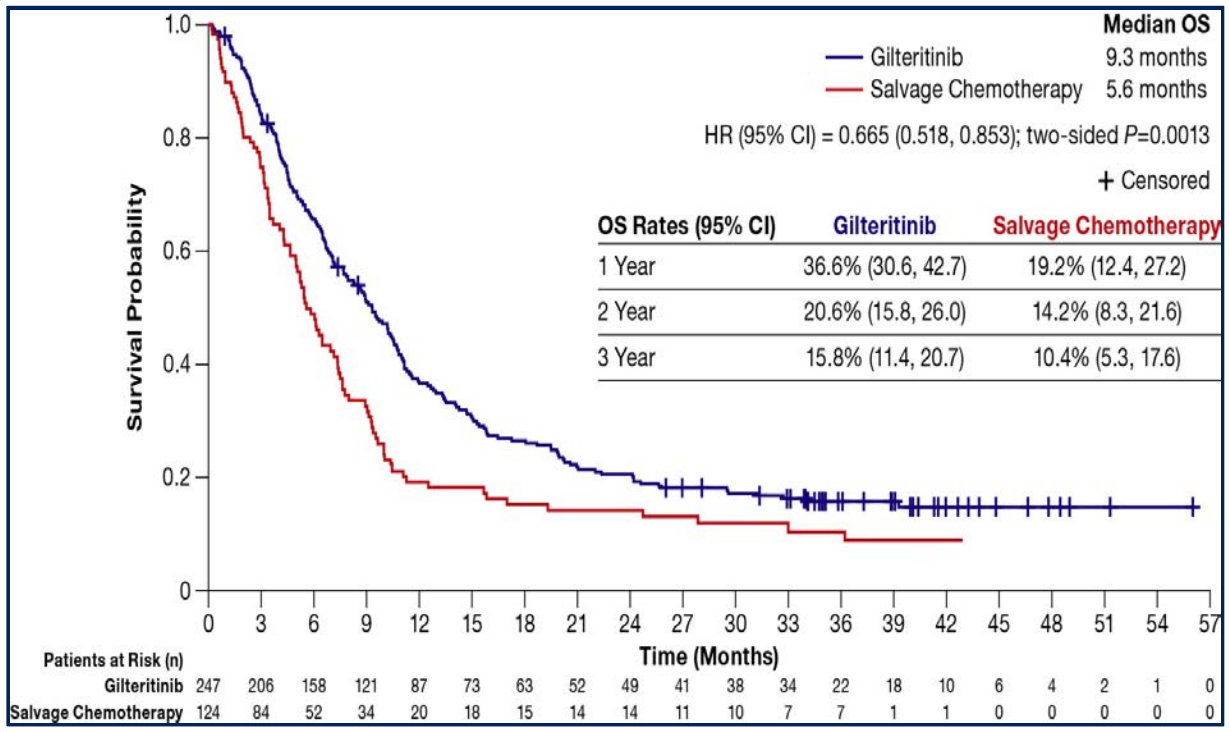
Do These Results Hold Up Over Time?

- ASCO abstract from Perl et al updates the ADMIRAL study after 2 years

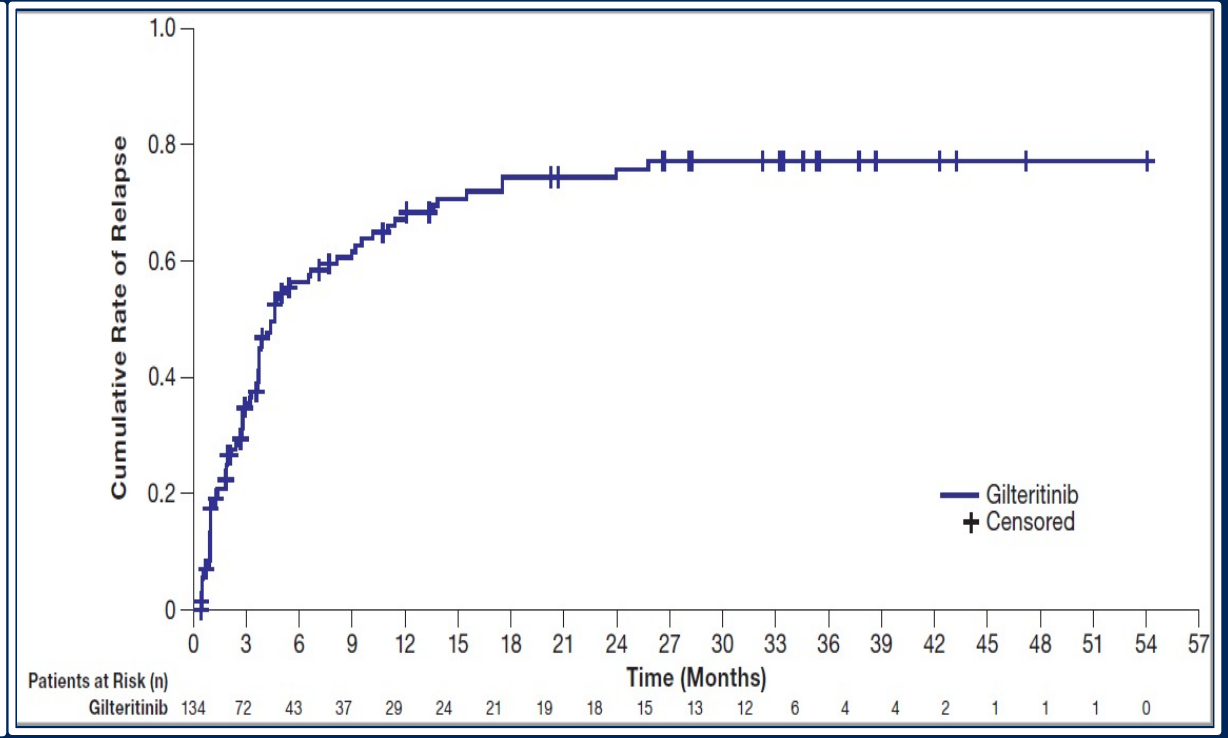
Courtesy of Daniel A Pollyea, MD, MS

Overall Survival and Cumulative Relapse Rate

Overall Survival in R/R *FLT3*$^{mut+}$ AML Patients (ITT Population; N=371)



Cumulative Incidence of Relapse in Patients Achieving CRc With Gilteritinib



With a median follow-up of 37.1 months, the median OS remained longer with gilteritinib than with salvage chemotherapy

Most relapses after CRc occurred within 12 months and rarely occurred after 18 months

Abbreviations: CI, confidence interval; CRc, composite complete remission; HR, hazard ratio; ITT, intention-to-treat.

Take Aways

- Gilteritinib is the standard of care for R/R FLT3 AML
- Outcomes remain poor and better strategies are needed
- How about adding to venetoclax?

Courtesy of Daniel A Pollyea, MD, MS

Aza+Ven+Gilteritinib in FLT3-mutated AML: Regimen

- Relapsed/refractory *FLT3*-mutated* AML or high-risk MDS or CMML

or

- Newly diagnosed *FLT3*-mutated* AML unfit for intensive chemotherapy

Induction

Azacitidine
75 mg/m² IV/SC on D1-7

Venetoclax#
D1-28 (bone marrow on D14)%

Gilteritinib
80-120 mg on D1-28

Consolidation (up to 24 cycles)

Azacitidine
75 mg/m² IV/SC on D1-5

Venetoclax
400mg on D1-7

Gilteritinib
80-120 mg on D1-28

* FLT3-ITD or FLT3 D835 mutations allowed

Venetoclax ramp-up during cycle 1: 100mg on D1, 200mg on D2, 400mg on D3+

% If <5% blasts or insufficient on C1D14, venetoclax held (both cohorts) and gilteritinib held (frontline only)

- Primary endpoints: MTD of gilteritinib in combination (phase I), CR/CRi rate (phase II)
- Secondary endpoints: CR rate, MRD negativity rate, duration of response, OS, safety

Courtesy of Daniel A Pollyea, MD, MS

Short et al, ASH 2021

Gilteritinib “Triple Combination”

- In newly diagnosed patients, high response rate but do we need FLT3 inhibitors up-front with venetoclax?
- Doesn’t contribute much to R/R who have had venetoclax
- Toxicity must be managed

Courtesy of Daniel A Pollyea, MD, MS

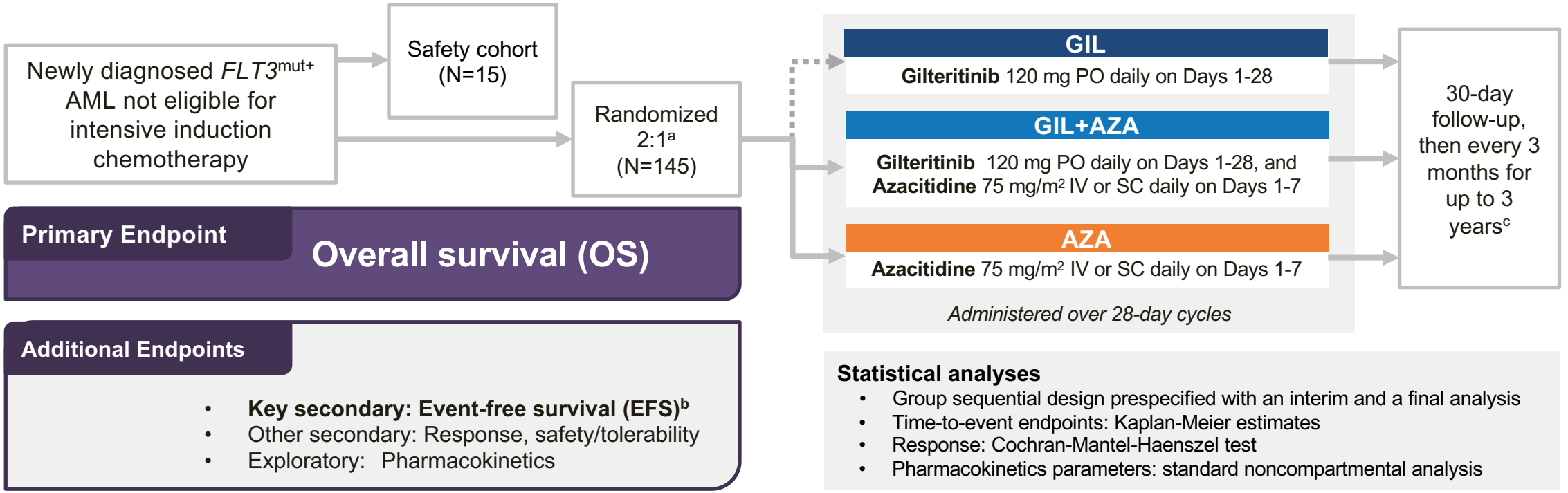
Should FLT3 be Targeted in the Newly Diagnosed “Unfit” Setting?

- Ven/HMA is standard of care here and better than HMA

- What if you use gilteritinib+aza vs aza alone?

Courtesy of Daniel A Pollyea, MD, MS

LACEWING (NCT02752035) Study Design



[a]Randomization (stratified by age, ≥75 years or <75 years) was initially 1:1:1 until the gilteritinib arm was removed due to preferred therapy changes.
[b]EFS is time from date of randomization until date of documented relapse from CR, treatment failure (randomization date), or death from any cause. Treatment failure was failure to achieve CR after completing six cycles, permanent discontinuation of treatment without achieving CR prior to completing six cycles, or lack of post-baseline disease assessment. The randomization date was used as the treatment failure date.
[c]Data from long-term follow-up ≤3 years were obtained, including subsequent AML therapy.
Abbreviations: AML, acute myeloid leukemia; AZA, azacitidine; CR, complete remission; EFS, event-free survival; *FLT3*, FMS-like tyrosine kinase; GIL, gilteritinib; IV, intravenous; OS, overall survival; PO, by mouth; SC, subcutaneous.

Courtesy of Daniel A Pollyea, MD, MS

Take Aways

- No change in OS despite higher response rates for gilteritinib
- Maybe because aza alone patients more likely to be salvaged (10 vs 2 patients) or more patients in gilteritinib group with worse ECOG PS (47% vs 33%)
- Even if positive this study would likely not have changed the standard of care

Courtesy of Daniel A Pollyea, MD, MS

Up-Front FLT3 Inhibitors in “Fit” Patients

- Current standard of care is to use midostaurin with 7+3
- Quizartinib is a more specific “next generation” FLT3 inhibitor
- Only active against FLT3 ITD (not TKD)
- Was not approved for R/R AML
- Compared to 7+3 for FLT3+ newly diagnosed AML

Passion for Innovation.
Compassion for Patients.™

Daiichi-Sankyo

Press Release

Quizartinib Added to Chemotherapy Demonstrates Superior Overall Survival Compared to Chemotherapy Alone in Adult Patients with Newly Diagnosed *FLT3*-ITD Positive AML

- Global pivotal QuANTUM-First phase 3 trial meets primary endpoint for overall survival
- There is a high unmet medical need for patients with *FLT3*-ITD positive AML, which is associated with poor prognosis

Tokyo, Munich, and Basking Ridge, N.J. – (**November 18, 2021**) – Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) today announced positive topline results from the global pivotal QuANTUM-First phase 3 trial evaluating quizartinib, a highly potent and selective FLT3 inhibitor, in patients with newly diagnosed *FLT3*-ITD positive acute myeloid leukemia (AML).[1]

Courtesy of Daniel A Pollyea, MD, MS

Future Landscape

- Will quizartinib (or another FLT3 inhibitor) displace midostaurin in up-front AML?
- Could either benefit newly diagnosed “unfit” patients with venetoclax?
- Should triplet combinations be standard in R/R FLT3+ AML?

Courtesy of Daniel A Pollyea, MD, MS

Targeting IDH

- Established strategy in the R/R setting as a single agent…or is it?
- Can we do better with combinations?
- Can we move it up-front?

Courtesy of Daniel A Pollyea, MD, MS

IDH Inhibitors in IDH+ R/R AML are Standard of Care

- FDA approved
- Listed in NCCN
- Based on single arm uncontrolled studies
- What would you see in a randomized study?

Courtesy of Daniel A Pollyea, MD, MS

Ivosidenib + Azacitidine for Newly Diagnosed “Unfit” AML

- Ivo/aza clearly superior
- How does this (or should it) impact the current treatment landscape with venetoclax?
- Different finding than seen with IDH2…

Courtesy of Daniel A Pollyea, MD, MS

Different Outcomes for IDH1 and IDH2?

- Ivosidenib and enasidenib seem equivalent in the R/R setting
- Differences in salvage or crossover for the control arm of these two studies?

Courtesy of Daniel A Pollyea, MD, MS

Triple Combinations with IDH Inhibitors and Venetoclax

- Ivosidenib + venetoclax + azacitidine
- Newly diagnosed and R/R
- Small numbers

Courtesy of Daniel A Pollyea, MD, MS

Agenda

Module 1: Acute Myeloid Leukemia

Module 2: Myelodysplastic Syndromes (MDS)

- IPSS-M: New MDS prognostic score
- PANTHER trial: Pevonedistat/azacitidine
- ENHANCE trial: Magrolimab/azacitidine
- Venetoclax/azacitidine for treatment naïve MDS
- Venetoclax/hypomethylating agents (HMA) for higher-risk MDS
- ASCERTAIN trial: Oral decitabine/cedazuridine
- Sabatolimab/HMA for higher-risk MDS
- IDH2 mutations
- IDIOME trial: Ivosidenib for MDS with an IDH1 mutation

International Working Group for the Prognosis of MDS (IWG-PM)

Study objective: **Integrate gene mutations into the International Prognostic Scoring System (IPSS/IPSS-R)**

mds foundation
the myelodysplastic syndromes foundation, inc.

Greenberg et al. Blood 1997;2012

Courtesy of Gail J Roboz, MD

Development of IPSS-M: Conclusions

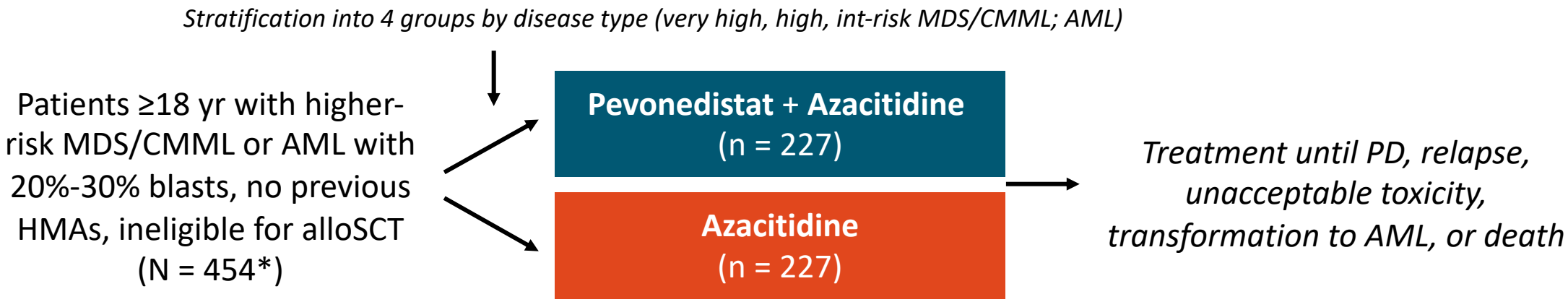
- IPSS-M combines conventional parameters with mutations in 31 key genes to improve MDS risk stratification
- Risk score is personalized as a continuous score, reproducible, and interpretable, as 1-unit increase in score doubles risk
- 6-category risk schema developed
- Includes a strategy to handle missing data and a web calculator

Bernard. ASH 2021. Abstr 61.

Courtesy of Gail J Roboz, MD

PANTHER: Study Design

- Global, multicenter, randomized, open-label phase III trial



*n = 324 with higher-risk MDS; n = 27 with CMML; n = 103 w/ low blast AML. Dosing in 28-day cycles: pevonedistat, 20 mg/m^2 IV on Days 1, 3, 5; azacitidine 75 mg/m^2 IV or SC on Days 1-5, 8, 9.

- Primary endpoint: EFS (time from randomization to death or transformation to AML for patients with higher-risk MDS/CMML, or time to death for patients with AML)
- Key secondary endpoint: OS
- EFS and OS tested sequentially in higher-risk MDS cohort and ITT population using separate hierarchical testing procedures, with subsequent OS testing in AML cohort

Sekeres. ASH 2021. Abstr 242.

Courtesy of Gail J Roboz, MD

PANTHER: Conclusions

- PANTHER did not meet the primary endpoint of EFS in patients with higher-risk MDS/CMML or AML with 20% to 30% blasts
- Post-hoc analysis showed greater OS benefit with pevonedistat + azacitidine vs azacitidine alone in patients with higher-risk MDS who received >3 treatment cycles; benefit even more pronounced with >6 cycles
- No new safety signals with pevonedistat + azacitidine; azacitidine dose intensity maintained in both arms
- Investigators concluded that results underscore the importance of large, randomized controlled trials in heterogeneous myeloid diseases
- Longitudinal clonal evolution studies ongoing to identify treatment effects on specific clones

Sekeres. ASH 2021. Abstr 242.

Courtesy of Gail J Roboz, MD

Magrolimab + Azacitidine versus Azacitidine + Placebo in Untreated Higher Risk Myelodysplastic Syndrome: The Phase 3, Randomized, Double-Blind ENHANCE Study

Guillermo Garcia Manero[1], Naval G. Daver[1], Jin Xu[2], Mark Chao[2], Trisha Chung[2], Anderson Tan[2], Yan V. Wang[2], Andrew H. Wei[3], Paresh Vyas[4], and David A. Sallman[5]

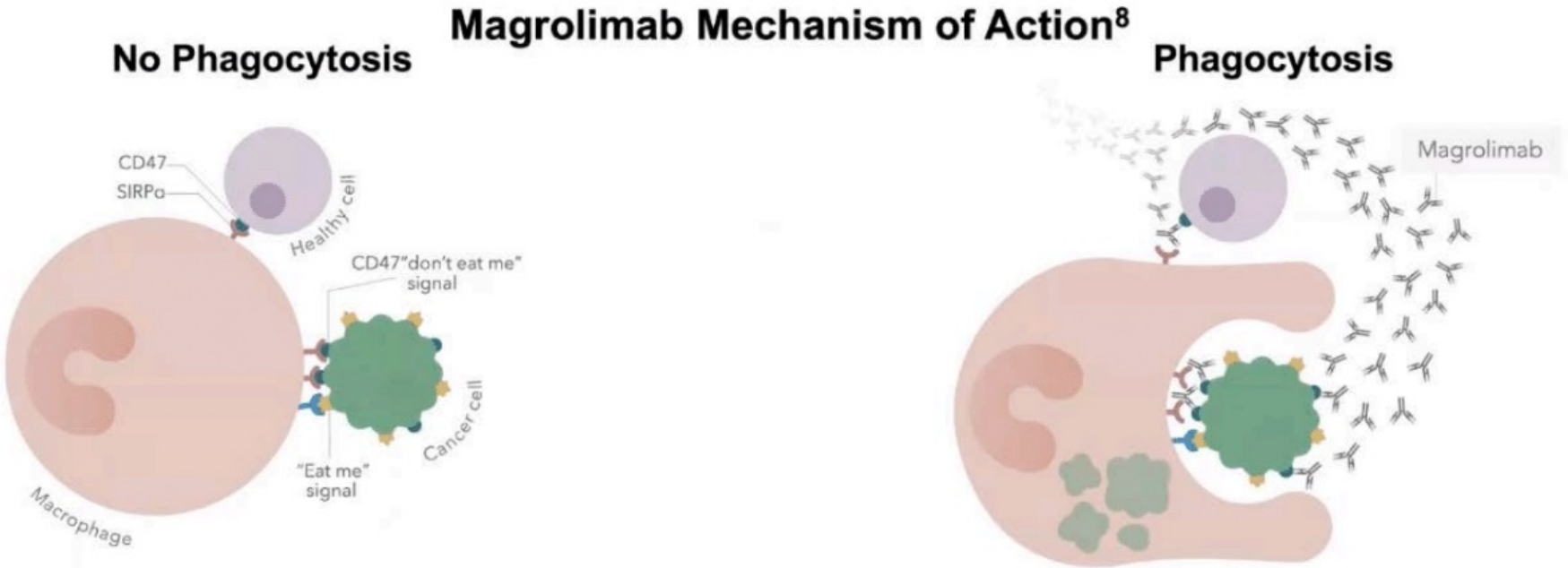
[1]The University of Texas MD Anderson Cancer Center, Houston TX, USA; [2]Gilead Sciences, Inc., Foster City, CA, USA; [3]The Alfred Hospital and Monash University, Melbourne, Australia; [4]University of Oxford, Oxford, United Kingdom; [5]Moffitt Cancer Center, Tampa, FL, USA

Presented at American Society of Hematology (ASH) Annual Meeting 2021
December 11-14, 2021

Courtesy of Gail J Roboz, MD

Background (2 of 3)

Magrolimab Mechanism of Action[8]



- Magrolimab is a first-in-class monoclonal antibody that blocks the macrophage inhibitory immune checkpoint cluster of differentiation (CD)47, a "do not eat me" signal overexpressed on tumor cells[6].
- Binding of magrolimab to CD47 leads to phagocytosis of tumor cells[6].
- Azacitidine increases expression of prophagocytic "eat me" signals, facilitating synergy with magrolimab[7].

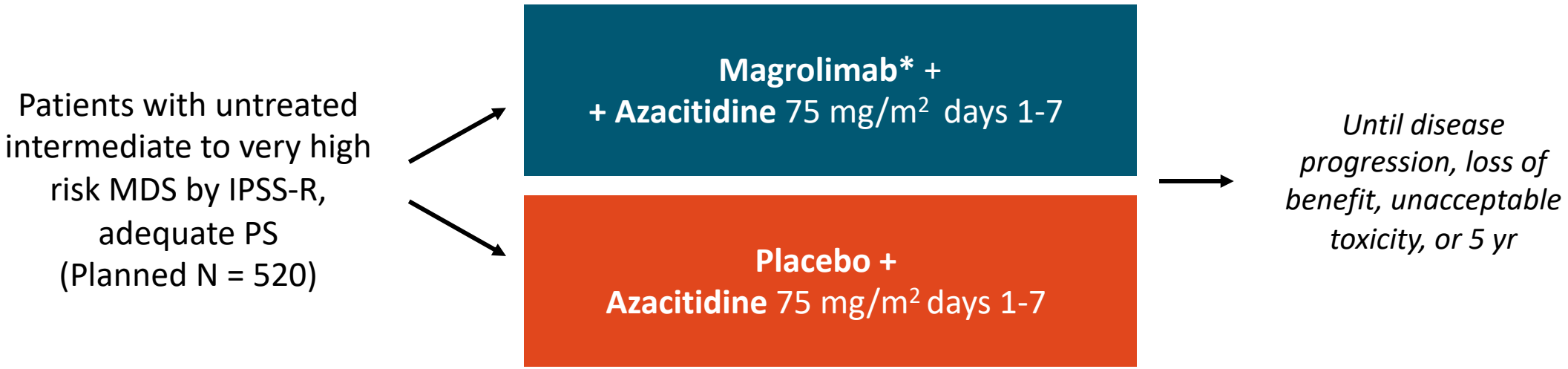
6. Liu J, et al. *PLOS One*. 2015;10(9): e0137345.
7. Feng D, et al. Poster presented at: 60th ASH Annual Meeting and Exposition; 01-04 December 2018; San Diego, CA. Abstract 616.

Garcia Manero, et al. ASH 2021.

Courtesy of Gail J Roboz, MD

ENHANCE: Magrolimab + Azacitidine vs Placebo + Azacitidine in Treatment Naive Higher-risk MDS

- Randomized, double-blind, phase III trial



*Cycle 1: 1mg/kg priming dose on D1, D4; 15 mg/kg on D8; 30 mg/kg on D11, 15, 22. Cycle 2: 30 mg/kg once weekly (D1, 8, 15, 22). Cycle ≥3: 30 mg/kg Q2W on D1, D15.

- Primary endpoints: CR, OS
- Secondary endpoints: Duration of CR, ORR, DoR, RBC TI, PFS, EFS, MRD negative RR, time to transformation to AML, safety, PK

Garcia-Manero. ASCO 2021. Abstr TPS7055. NCT04313881.

Courtesy of Gail J Roboz, MD

Venetoclax/Azacitidine in Treatment-Naive HR-MDS: Background

- The BCL-2 inhibitor venetoclax has shown synergy with hypomethylating agents such as azacitidine in preclinical studies and in clinical trials in patients with myeloid malignancies[1-4]
  - Mechanism of action: Azacitidine targets BCL-X_L and MCL-1, and venetoclax targets BCL-2; all 3 targets are expressed on HR-MDS blast cells
- Current study undertaken to evaluate combination of venetoclax and azacitidine in patients with treatment-naive HR-MDS[5]

1. Jin. Clin Cancer Res. 2020;26:3371. 2. Jilg. Exp Hematol Oncol. 2019;8:9.
3. DiNardo. Am J Hematol. 2018;93:4014. 4. DiNardo. NEJM. 2020;383:617. 5. Garcia. ASH 2021. Abstr 241.

Courtesy of Gail J Roboz, MD

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

Jacqueline S. Garcia[1], Andrew H. Wei[2], Meagan A. Jacoby[3], Chun Yew Fong[4], Uma Borate[5], Maria R. Baer[6], Ilona Cunningham[7], Olatoyosi Odenike[8], Joseph G. Jurcic[9], Daniel Nowak[10], Pierre Peterlin[11], Uwe Platzbecker[12], Diana Dunshee[13], Ying Zhou[14], David Hoffman[14], Yan Sun[14], Relja Popovic[14], Barrett Ainsworth[14], Kiran Naqvi[13], Steve Kye[14], Leah Hogdal[14], Guillermo Garcia-Manero[15]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Alfred Hospital and Monash University, Melbourne, VIC, Australia; [3]Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine, St Louis, MO, USA; [4]Olivia Newton John Cancer Research Institute, Austin Health, Melbourne, VIC, Australia; [5]Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA; [6]Greenebaum Comprehensive Cancer Center, University of Maryland School of Medicine, Baltimore, MD, USA; [7]Concord Repatriation General Hospital, University of Sydney, Sydney, Australia; [8]University of Chicago Medicine and Comprehensive Cancer Center, Chicago, IL, USA; [9]Herbert Irving Comprehensive Cancer Center, New York-Presbyterian Hospital/Columbia University Irving Medical Center, New York, NY, USA; [10]Medical Faculty Mannheim of the Heidelberg University, Mannheim, Germany; [11]Nantes University Hospital, Nantes, France; [12]Medical Clinic and Policlinic 1, Hematology and Cellular Therapy, University Hospital Leipzig, Germany; [13]Genentech Inc., South San Francisco, CA, USA; [14]AbbVie Inc., North Chicago, IL, USA; [15]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

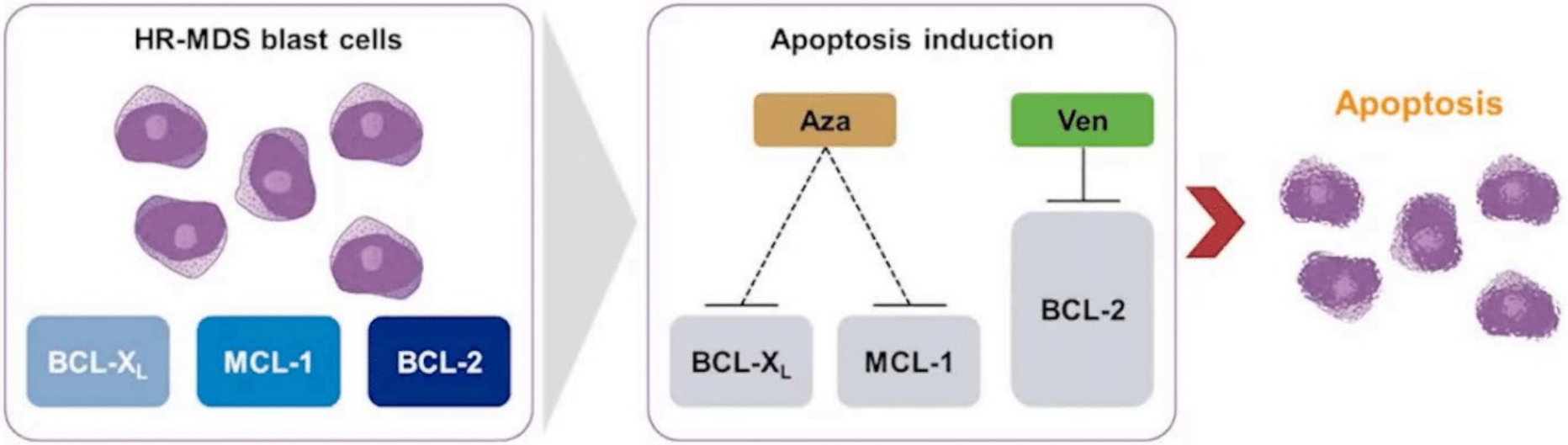
American Society of Hematology Annual Meeting, December 11–14, 2021, Atlanta, Georgia

Courtesy of Gail J Roboz, MD

Ven + Aza mechanism of action

- Venetoclax is a selective, potent, orally bioavailable BCL-2 inhibitor, which has demonstrated synergy with hypomethylating agents in preclinical and clinical studies of myeloid malignancies[1-4]

Ven + Aza Mechanism of Action



Size of rectangles indicates relative dependency on specific protein for survival
Dotted lines indicate an indirect therapeutic effect on BCL-2 family member dependency

Courtesy of Gail J Roboz, MD

Aza, azacitidine; BCL-2, B-cell lymphoma 2; HR-MDS, higher-risk myelodysplastic syndrome; MCL-1, myeloid cell leukemia 1; Ven, venetoclax.

1. DiNardo CD, et al. *Lancet Oncol.* 2018;19(2):216–28. 2. DiNardo CD, et al. *Am J Hematol.* 2018;93(3):401–7. 3. Jilg S, et al. *Exp Hematol Oncol.* 2019;8:9. 4. Jin S, et al. *Clin Cancer Res.* 2020;26(13):3371–83.

Venetoclax/Azacitidine in Treatment-Naive HR-MDS (Phase Ib): Investigator Conclusions

- In this phase Ib trial, venetoclax/azacitidine had an acceptable safety profile in patients with treatment-naive higher-risk MDS
- RP2D venetoclax 400 mg on D1-14 + azacitidine 75 mg/m^2 induced rapid, durable responses and a high remission rate
- Clinical and molecular responses were observed across mutational profiles, including in patients with poor prognostic mutations

Garcia. ASH 2021. Abstr 241.

Courtesy of Gail J Roboz, MD

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Abstract # 536

Assessing the role of Venetoclax in combination with hypomethylating agents in higher risk Myelodysplastic syndromes

Rami S. Komrokji, MD, *Najla Al Ali, MS, Onyee Chan, MD, Eric Padron, MD, Kendra Sweet, MD, Andrew T. Kuykendall, MD, Jeffrey E. Lancet, MD and David A. Sallman, MD*

63rd ASH® Annual Meeting and Exposition

Courtesy of Gail J Roboz, MD

Venetoclax and HMA in Higher-Risk MDS: Conclusions

- In this retrospective analysis, treatment with first-line HMA + venetoclax was associated with significantly higher CR rates vs HMA alone in patients with higher-risk MDS, including those with *ASXL-1*–mutant MDS
  - Investigators suggested promising clinical activity of first-line HMA + venetoclax in patients who proceed to AHSCT
  - Caveats: small population, short follow-up of combination therapy group
  - No adverse event or dose adjustment data available
- Adding venetoclax to HMA after relapse may prolong OS
- Prospective, randomized trial needed to confirm findings

Komrokji. ASH 2021. Abstr 536.

Courtesy of Gail J Roboz, MD

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Place video here

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

On behalf of the ASCERTAIN Investigators Team

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

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

Abstract # 66 presented at the American Society of Hematology Annual Meeting, Atlanta, GA, Dec 11 – 14, 2021

Courtesy of Gail J Roboz, MD

Conclusions

- **In IPSS Int-1/LR MDS patients, oral decitabine/cedazuridine:**
  - Demonstrated a safety profile consistent with decitabine
    - No noteworthy new safety signals emerged
    - Treatment-emergent events were typically related to myelosuppression
  - Produced clinical efficacy similar to IV decitabine
    - With almost 32 months of follow up, median survival for this population has not been reached
    - CR rate of 26.9%, ORR of 51%, 26% of subjects were able to proceed to transplant
- **Oral decitabine and cedazuridine (35 mg/100 mg tablets) can be given safely to MDS patients with lower risk disease, though care must be taken to avoid infectious complications**
- **The activity of a lower dose of oral decitabine/cedazuridine is being studied in a low-risk population**

Courtesy of Gail J Roboz, MD

Efficacy and Safety of Sabatolimab in Combination with Hypomethylating Agents in Patients with Very High/High-Risk Myelodysplastic Syndrome and Acute Myeloid Leukemia: Final Analysis from a Phase Ib Study

Andrew M. Brunner,[1] Jordi Esteve,[2] Kimmo Porkka,[3] Steve Knapper,[4] Elie Traer,[5] Sebastian Scholl,[6] Guillermo Garcia-Manero,[7] Norbert Vey,[8] Martin Wermke,[9] Jeroen Janssen,[10] Rupa Narayan,[1] Sun Loo,[11] Natalia Tovar,[2] Mika Kontro,[3] Oliver Ottmann,[4] Purushotham Naidu,[12] Marc Pelletier,[13] Andrew Lewandowski,[13] Na Zhang,[13] Anisa Mohammed,[12] Mikael L. Rinne,[13] Uma Borate,[5]* Andrew H. Wei[14]*

*Co-senior authors Uma Borate and Andrew H. Wei contributed equally to this work.

[1]Massachusetts General Hospital, Boston, MA, USA; [2]Hospital Clínic, Barcelona, Spain; [3]Helsinki University Hospital Comprehensive Cancer Center, Helsinki, Finland; [4]Cardiff University, Cardiff, UK; [5]Oregon Health & Science University, Portland, OR, USA; [6]University Hospital Jena, Jena, Germany; [7]MD Anderson Cancer Center, Houston, TX, USA; [8]Institut Paoli-Calmettes, Marseille, France; [9]University Hospital Dresden, Dresden, Germany; [10]Amsterdam University Medical Centers, location VUmc, Amsterdam, The Netherlands; [11]The Alfred Hospital, Melbourne, Victoria, Australia; [12]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [13]Novartis Institutes for BioMedical Research, Cambridge, MA, USA; [14]The Alfred Hospital and Monash University, Melbourne, Australia

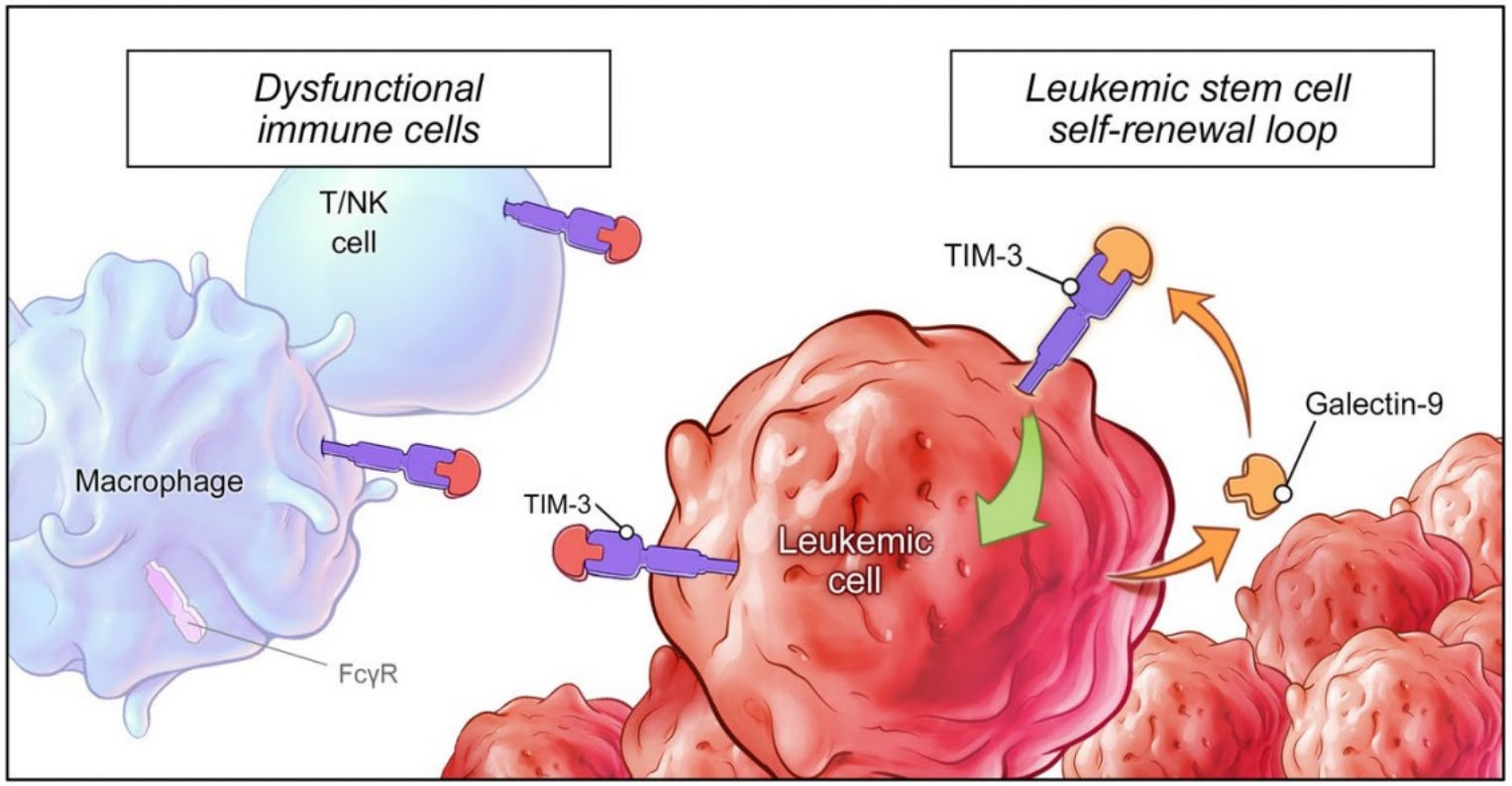
Scan to obtain

- Presentation slides
- Supplementary material

https://bit.ly/Brunner244

Courtesy of Gail J Roboz, MD

TIM-3 is an immuno-myeloid regulator expressed on immune and leukemic cells



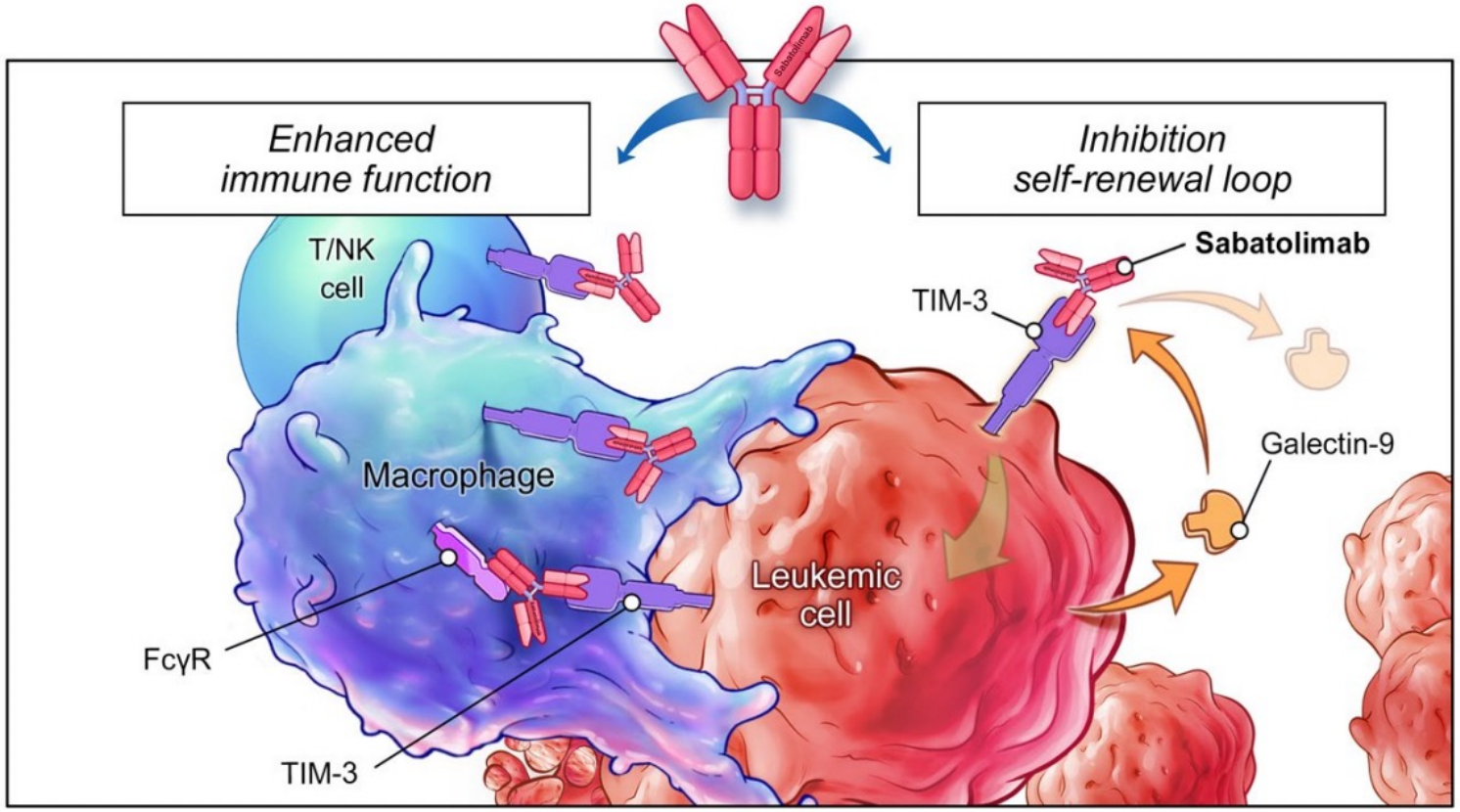
- TIM-3 plays a key role in regulating innate and adaptive immune responses[1,2]
- TIM-3 is aberrantly expressed on LSCs and blasts, but not on normal HSCs,[1-5] which makes it a promising target in treatment for MDS and AML[2,4,6]
- TIM-3/galectin-9 interaction forms an autocrine stimulatory loop, which promotes LSC self-renewal[2,7,8]

FcγR, Fc gamma receptor; HSC, hematopoietic stem cell; LSC, leukemic stem cell; NK, natural killer; TIM-3, T-cell immunoglobulin domain and mucin domain-3.

1. Pardoll DM. *Nat Rev Cancer.* 2012;12(4):252-264; 2. Das M, et al. *Immunol Rev.* 2017;276(1):97-111; 3. Kikushige Y, Miyamoto T. *Int J Hematol.* 2013;98(6):627-633; 4. Kikushige Y, et al. *Cell Stem Cell.* 2010;7(6):708-717; 5. Ngiow SF. *Cancer Res.* 2011;71(10):3540-3551; 6. Sakuishi K, et al. *Trends Immunol.* 2011;32(8):345-349; 7. Sabatos-Peyton C. AACR 2016. Oral presentation; 8. Borate U, et al. ASH 2019. Oral presentation.

Courtesy of Gail J Roboz, MD

Sabatolimab targets TIM-3 on immune and leukemic cells: A novel immuno-myeloid therapy



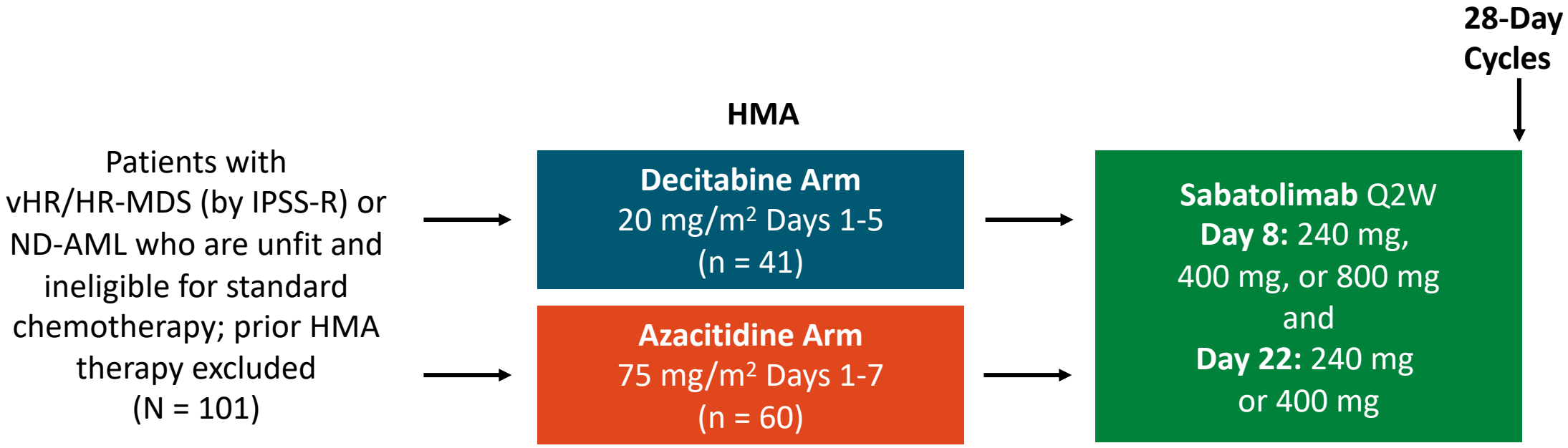
- Sabatolimab binds TIM-3 on immune cells, which enhances antileukemic immune function and phagocytic killing of LSCs and blasts[1-4]
- Sabatolimab directly targets TIM-3 on LSCs, inhibiting TIM-3/galectin-9–driven self-renewal[1,2]

1. Acharya N, et al. *J Immunother Cancer*. 2020;8(1):e000911; 2. Sabatos-Peyton C, et al. SITC 2020. Abstract 439; 3. Borate U, et al. *HemaSphere*. 2020;4(suppl 1):Abstract S185; 4. Borate U, et al. EHA 2020. Oral presentation.

Courtesy of Gail J Roboz, MD

Sabatolimab + HMA for vHR/HR-MDS and ND-AML: Study Design

- Multiarm, open-label phase Ib dose escalation and dose expansion study

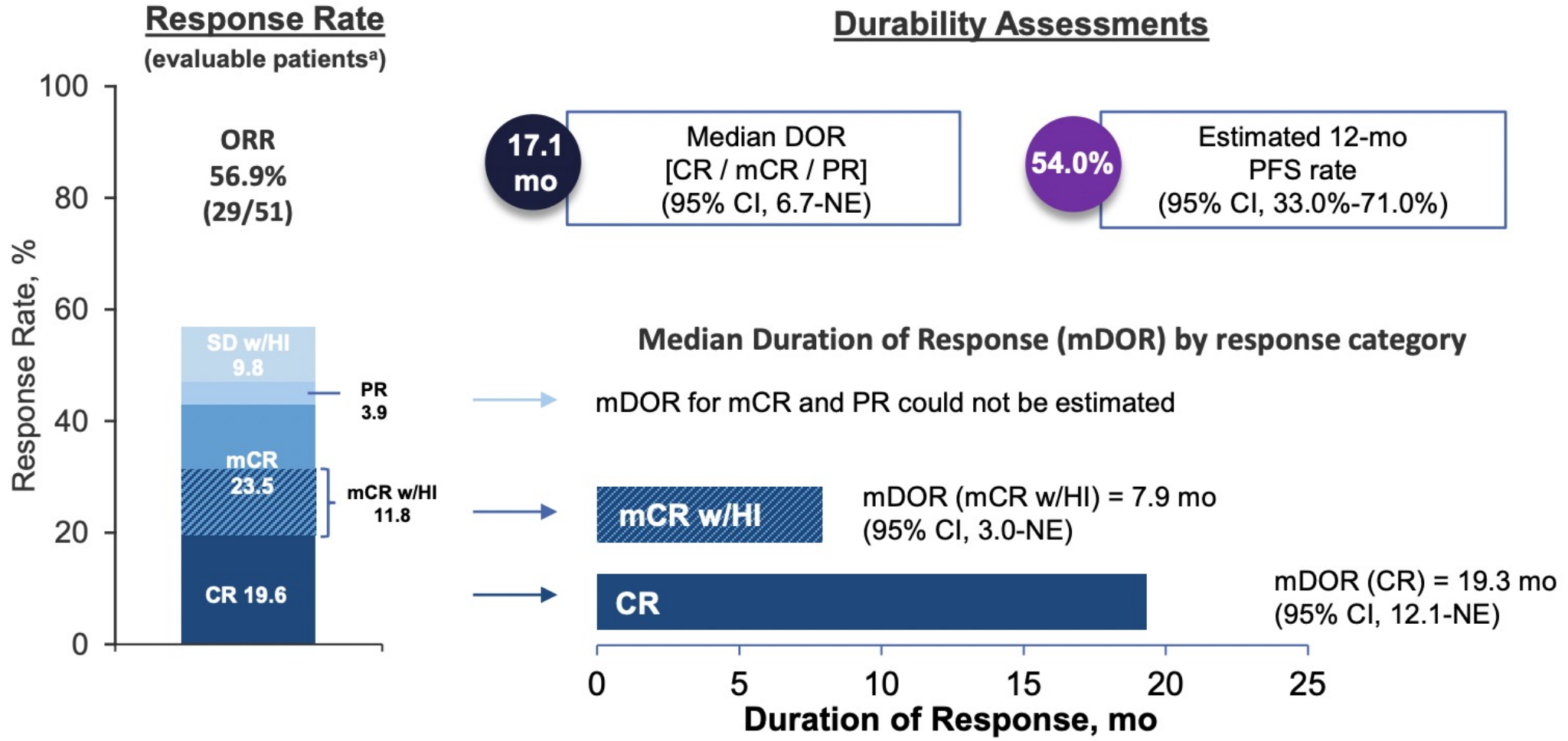


- Primary endpoints: MTD, recommended dose, safety, tolerability
- Secondary endpoints: ORR, DoR

Brunner. ASH 2021. Abstr 244.

Courtesy of Gail J Roboz, MD

Sabatolimab + HMA demonstrates durable clinical responses in vHR/HR-MDS



[a]Evaluable patients, including patients with a valid baseline and at least 1 postbaseline bone marrow assessment or if they had disease progression or disease-related death prior to the first marrow assessment.

CR, complete remission; DOR, duration of response; HI, hematologic improvement; mCR, bone marrow CR; mDOR, median duration of response; NE, not estimable; ORR, overall response rate; PFS, progression-free survival; PR, partial remission; SD, stable disease.

Courtesy of Gail J Roboz, MD

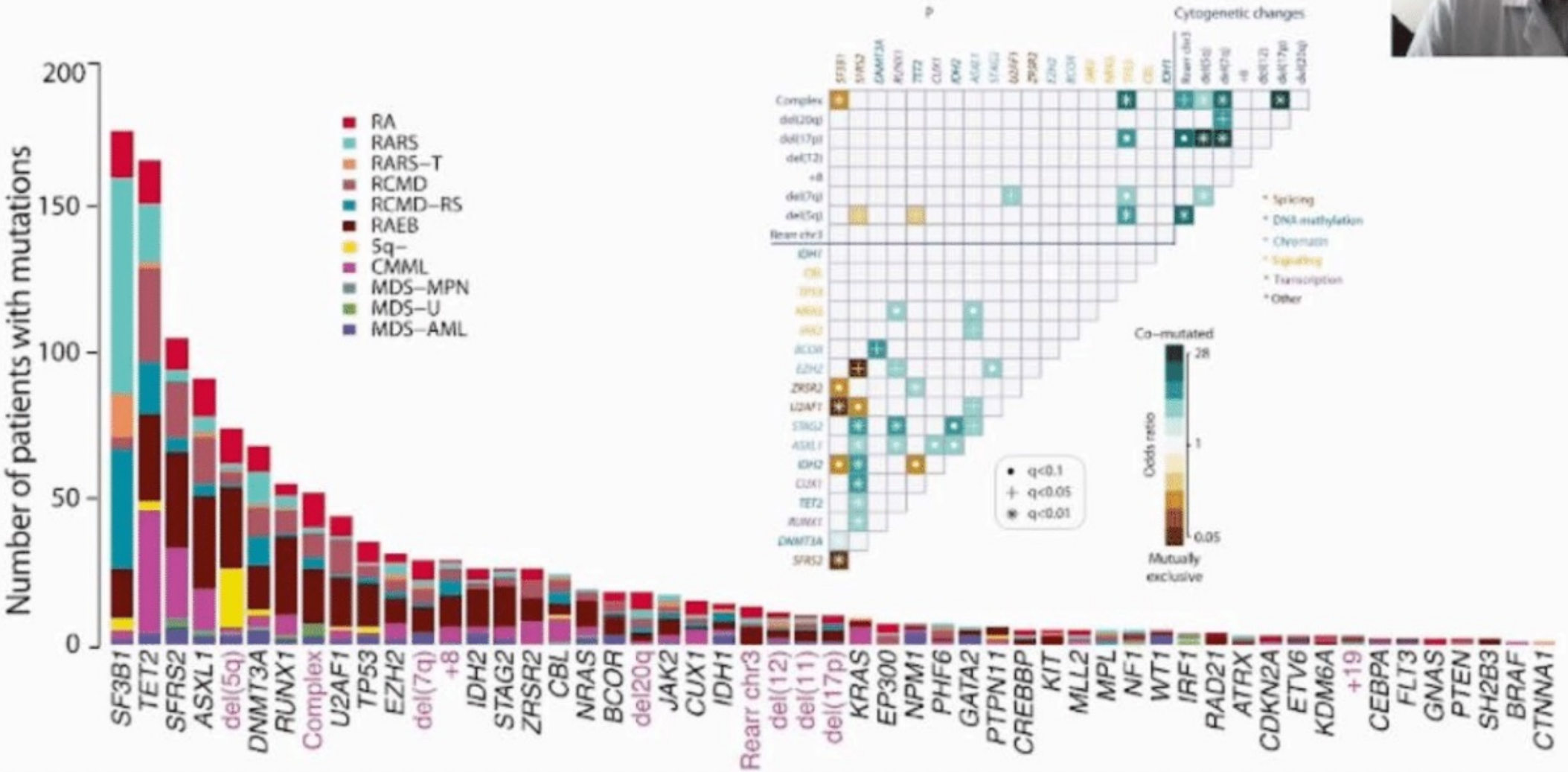
Sabatolimab + HMA for vHR/HR-MDS and ND-AML: Conclusions

- In patients with vHR/HR-MDS or newly diagnosed AML, sabatolimab in combination with HMA was generally well tolerated
  - Common AEs similar to HMA alone, immune-mediated AEs uncommon
- Treatment resulted in durable clinical benefit, including in patients with adverse risk factors
  - vHR/HR-MDS: ORR, 56.9%; median DoR, 17.1 mo (95% CI: 6.7-NE)
  - ND-AML: ORR, 42.5%; median DoR, 12.6 mo (95% CI: 5.2-18.0)
- Evaluation of sabatolimab-based therapy in patients with MDS and AML ongoing in phase II/III STIMULUS clinical trial program

Brunner. ASH 2021. Abstr 244.

Courtesy of Gail J Roboz, MD

IDH2 mutation among patients with MDS



Courtesy of Gail J Roboz, MD

Papaemmanuil E, et al. Blood 2013

Conclusions

- Results from the first 26 patients included in this study show that enasidenib can provide responses in 42% of patients with IDH2^{m} MDS
- No safety signal was observed and 3 patients experienced a differentiation syndrome that resolved without sequelae.
- Among the 11 responses, 9 were sustained at the time of analysis
- Median OS of 17.3 months
- This suggests that enasidenib can produce profound and durable responses in these patients.
- More patients and longer follow-up will be needed to confirm these results.
- Correlative studies are ongoing to investigate the impact of minimal residual disease and clonal architecture on response.

Courtesy of Gail J Roboz, MD

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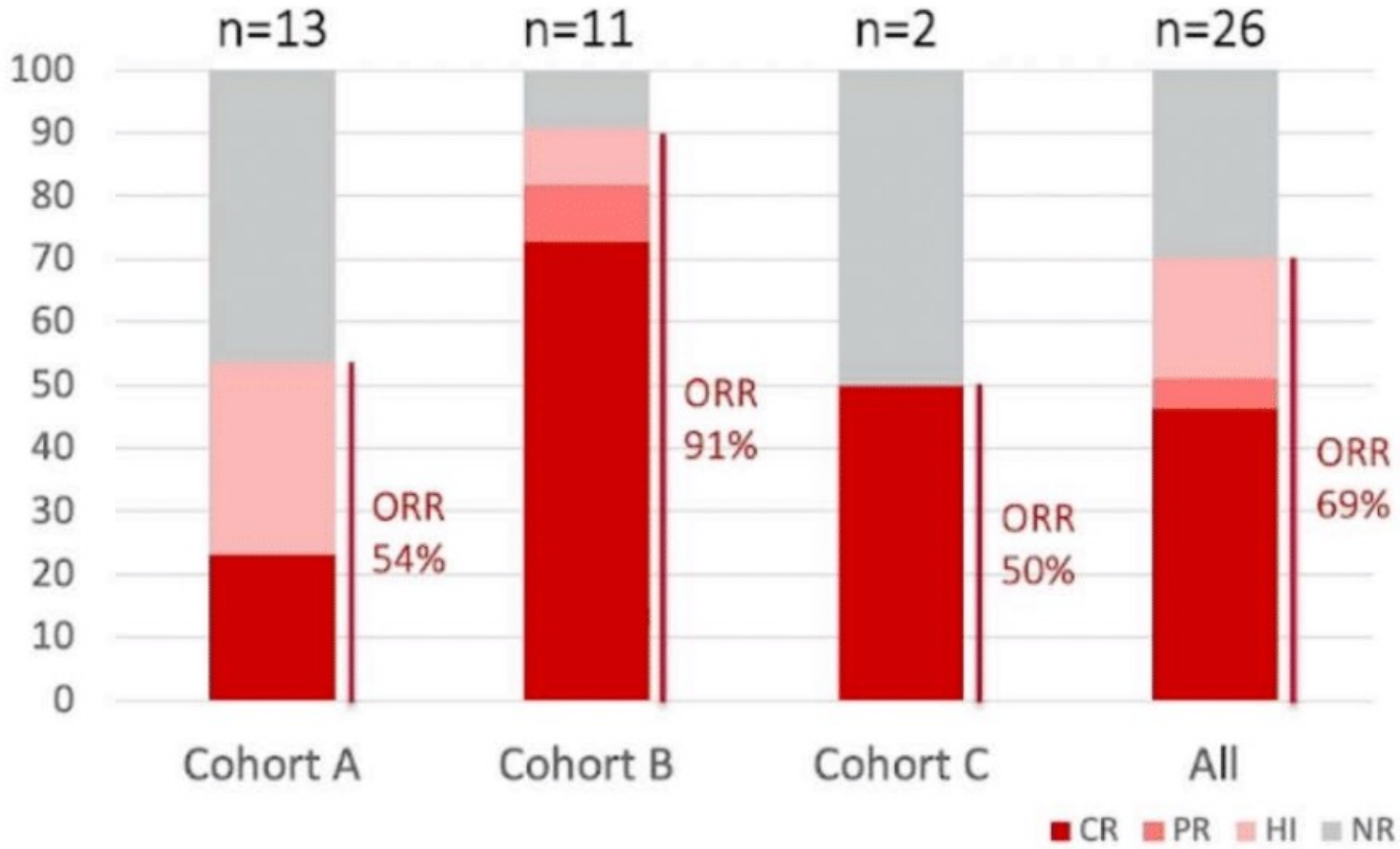
Ivosidenib Monotherapy Is Effective in Patients with IDH1 Mutated Myelodysplastic Syndrome : The IDIOME Phase 2 Study By the GFM Group

Groupe Francophone des Myélodysplasies

Marie Sébert, *Thomas Cluzeau, Odyle Beyne-Rauzy, Aspasia Stamatoullas, Sophie Dimicoli-Salazar, Sylvain Thepot, Pierre Peterlin, Sophie Park, Marie-Pierre Gourin, Oana Brehar, Cécile Bally, Sébastien Maury, Gaelle Fossard, Lamya Ait Si Selmi, Cendrine Chaffaut, Emmanuelle Clappier, Raphaël Itzykson, Fatiha Chermat, Sylvie Chevret, Pierre Fenaux and Lionel Adès.*

Courtesy of Gail J Roboz, MD

Overall response rate



- 46% of CR (including 73% in cohort B)
- 94,4% of the responders achieved response at 3 cycles
- Only one patient received azacitidine in association with Ivo after three cycles of Ivo in cohort B, without additional response

Courtesy of Gail J Roboz, MD

Year in Review: Gastric, Gastroesophageal Junction and Esophageal Cancer

Tuesday, February 1, 2022
5:00 PM – 6:00 PM ET

Faculty

David H Ilson, MD, PhD

Zev Wainberg, MD, MSc

Moderator

Neil Love, MD

RTP Year in Review 2022

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RTP Year in Review 2022