Acute Myeloid Leukemia in 2024

James M. Foran, MD FRCPC
Professor of Medicine & Consultant Hematologist
Chair, *Acute Leukemia & Myeloid Neoplasm* Disease Group,
Mayo Clinic Comprehensive Cancer Center
Division of Hematology & Medical Oncology, Mayo Clinic, Jacksonville, FL

Disclosures - JMF

- Research Support   Astellas, Astex, Celgene, Chordia, Novartis, Actinium, Gilead, H3Biosciences (Roivant/Hemavant), Kura, Sellas, and Takeda

- Advisory Board   Intrinsiq (AmeriSouce Bergen), Lava Therapeutics, Targeted Oncology, Treadwell, National Cancer Institute & NHLBI

- Off-Label Use I^{131}-Apamistamab & AlloHCT for rel/ref AML; Magrolimab for $TP53_{mut}$ AML
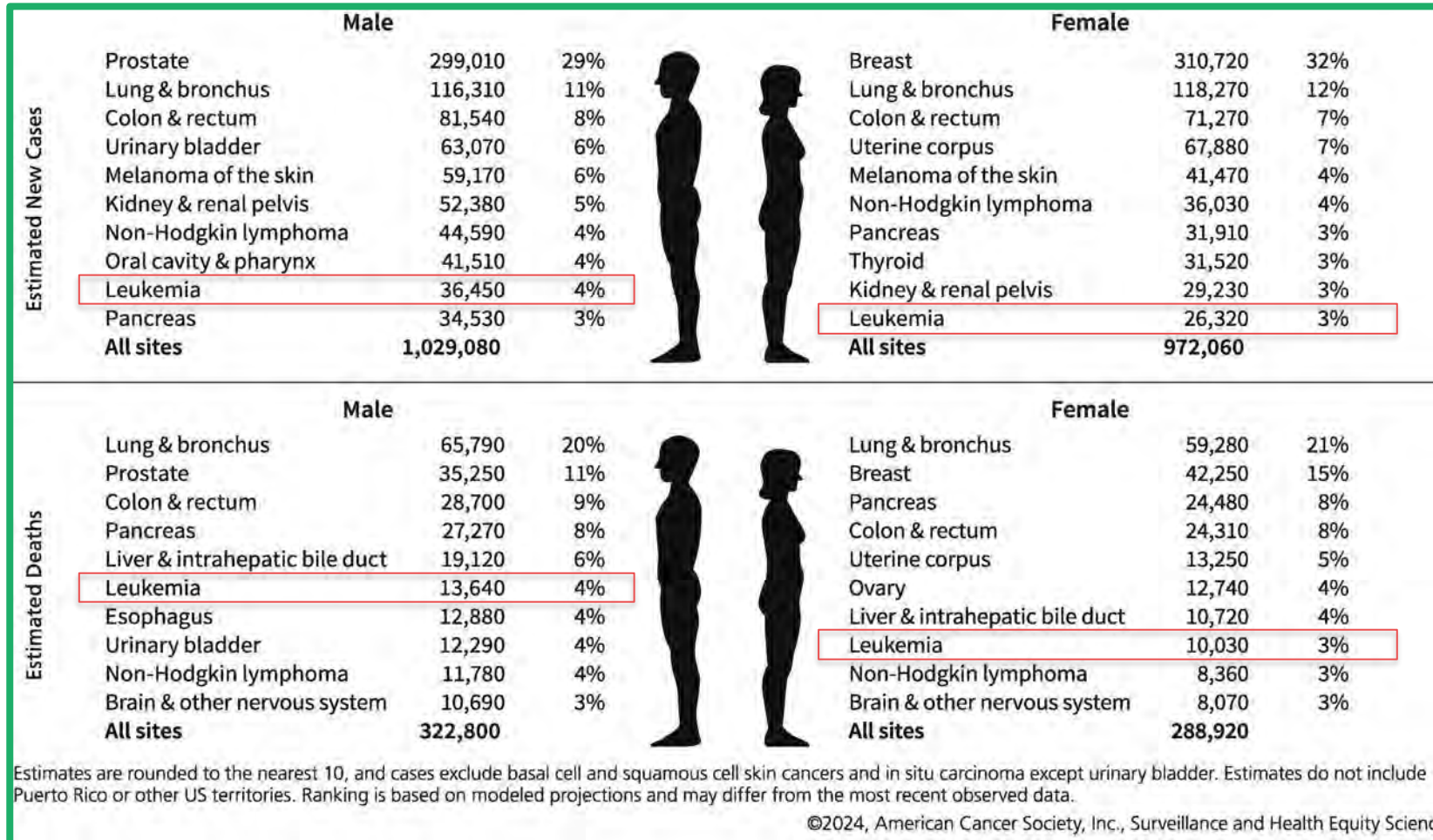
Happy Groundhog Day!

Alas, 6 more weeks of winter…

AML Updates in 2024

- Evolving Treatment Landscape

- Advances with Lower Intensity Therapy

- High quality remission & *Measurable Residual Disease*

- New Targeted Strategies
  - Mutation-based   Menin inhibitors for KMT2A & NPM1
  - Radioimmunotherapy   I^{131}-Apamistamab
  - Targeting TP53   Magrolimab, Allogeneic Transplantation

2024 AML Estimates in United States

Estimated New Cases

Male			Female		
Prostate	299,010	29%	Breast	310,720	32%
Lung & bronchus	116,310	11%	Lung & bronchus	118,270	12%
Colon & rectum	81,540	8%	Colon & rectum	71,270	7%
Urinary bladder	63,070	6%	Uterine corpus	67,880	7%
Melanoma of the skin	59,170	6%	Melanoma of the skin	41,470	4%
Kidney & renal pelvis	52,380	5%	Non-Hodgkin lymphoma	36,030	4%
Non-Hodgkin lymphoma	44,590	4%	Pancreas	31,910	3%
Oral cavity & pharynx	41,510	4%	Thyroid	31,520	3%
Leukemia	36,450	4%	Kidney & renal pelvis	29,230	3%
Pancreas	34,530	3%	Leukemia	26,320	3%
All sites	1,029,080		All sites	972,060	

Estimated Deaths

Male			Female		
Lung & bronchus	65,790	20%	Lung & bronchus	59,280	21%
Prostate	35,250	11%	Breast	42,250	15%
Colon & rectum	28,700	9%	Pancreas	24,480	8%
Pancreas	27,270	8%	Colon & rectum	24,310	8%
Liver & intrahepatic bile duct	19,120	6%	Uterine corpus	13,250	5%
Leukemia	13,640	4%	Ovary	12,740	4%
Esophagus	12,880	4%	Liver & intrahepatic bile duct	10,720	4%
Urinary bladder	12,290	4%	Leukemia	10,030	3%
Non-Hodgkin lymphoma	11,780	4%	Non-Hodgkin lymphoma	8,360	3%
Brain & other nervous system	10,690	3%	Brain & other nervous system	8,070	3%
All sites	322,800		All sites	288,920	

Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates do not include Puerto Rico or other US territories. Ranking is based on modeled projections and may differ from the most recent observed data.

©2024, American Cancer Society, Inc., Surveillance and Health Equity Science

Cases: n=20,800
- Male   11,600
- Female   9,200

Deaths: n=11,220
- Male   6,290
- Female   4,930

Myeloid Classification: from 2016 to 2023

Arber DA et al. Blood 2016;127(20): 2391-2405

## The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia

Daniel A. Arber,[1] Attilio Orazi,[2] Robert Hasserjian,[3] Jürgen Thiele,[4] Michael J. Borowitz,[5] Michelle M. Le Beau,[6] Clara D. Bloomfield,[7] Mario Cazzola,[8] and James W. Vardiman[9]

[1]Department of Pathology, Stanford University, Stanford, CA; [2]Department of Pathology, Weill Cornell Medical College, New York, NY; [3]Department of Pathology, Massachusetts General Hospital, Boston, MA; [4]Institute of Pathology, University of Cologne, Cologne, Germany; [5]Department of Pathology, Johns Hopkins Medical Institutions, Baltimore, MD; [6]Section of Hematology/Oncology, University of Chicago, Chicago, IL; [7]Comprehensive Cancer Center, James Cancer Hospital and Solove Research Institute, The Ohio State University, Columbus, OH; [8]Department of Molecular Medicine, University of Pavia, and Department of Hematology Oncology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; and [9]Department of Pathology, University of Chicago, Chicago, IL

WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues

Steven H. Swerdlow, Elias Campo, Nancy Lee Harris, Elaine S. Jaffe, Stefano A. Pileri, Harald Stein, Jürgen Thiele, Daniel A. Arber, Robert P. Hasserjian, Michelle M. Le Beau, Attilio Orazi, Reiner Siebert
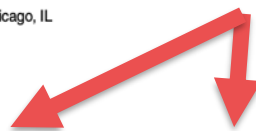
International Agency for Research on Cancer

Lyon, 2017

Arber DA et al. Blood 2022;140(11): 1200-

International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data

Daniel A. Arber,[1] Attilio Orazi,[2] Robert P. Hasserjian,[3] Michael J. Borowitz,[4] Katherine R. Calvo,[5] Hans-Michael Kvasnicka,[6] Sa A. Wang,[7] Adam Bagg,[8] Tiziano Barbui,[9] Susan Branford,[10] Carlos E. Bueso-Ramos,[7] Jorge E. Cortes,[11] Paola Dal Cin,[12] Courtney D. DiNardo,[7] Hervé Dombret,[13] Eric J. Duncavage,[14] Benjamin L. Ebert,[15] Elihu H. Estey,[16] Fabio Facchetti,[17] Kathryn Foucar,[18] Naseema Gangat,[19] Umberto Gianelli,[20] Lucy A. Godley,[1] Nicola Gökbuget,[21] Jason Gotlib,[22] Eva Hellström-Lindberg,[23] Gabriela S. Hobbs,[3] Ronald Hoffman,[24] Elias J. Jabbour,[7] Jean-Jacques Kiladjian,[13] Richard A. Larson,[1] Michelle M. Le Beau,[1] Mignon L.-C. Loh,[25] Bob Löwenberg,[26] Elizabeth Macintyre,[27] Luca Malcovati,[28] Charles G. Mullighan,[29] Charlotte Niemeyer,[30] Olatoyosi M. Odenike,[1] Seishi Ogawa,[31] Alberto Orfao,[32] Elli Papaemmanuil,[33] Francesco Passamonti,[28] Kimmo Porkka,[34] Ching-Hon Pui,[29] Jerald P. Radich,[35] Andreas Reiter,[36] Maria Rozman,[37] Martina Rudelius,[38] Michael R. Savona,[39] Charles A. Schiffer,[40] Annette Schmitt-Graeff,[41] Akiko Shimamura,[15,42] Jorge Sierra,[43] Wendy A. Stock,[1] Richard M. Stone,[15] Martin S. Tallman,[44] Jürgen Thiele,[45] Hwei-Fang Tien,[46] Alexandar Tzankov,[47] Alessandro M. Vannucchi,[48] Paresh Vyas,[49] Andrew H. Wei,[50] Olga K. Weinberg,[51] Agnieszka Wierzbowska,[52] Mario Cazzola,[28] Hartmut Döhner,[53] and Ayalew Tefferi[19]

Khoury JD et al. Leukemia 2022;36(7):1703-1719

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms

Joseph D. Khoury[1], Eric Solary[2], Oussama Abla[3], Yassmine Akkari[4], Rita Alaggio[5], Jane F. Apperley[6], Rafael Bejar[7], Emilio Berti[8], Lambert Busque[9], John K. C. Chan[10], Weina Chen[11], Xueyan Chen[12], Wee-Joo Chng[13], John K. Choi[14], Isabel Colmenero[15], Sarah E. Coupland[16], Nicholas C. P. Cross[17], Daphne De Jong[18], M. Tarek Elghetany[19], Emiko Takahashi[20], Jean-Francois Emile[21], Judith Ferry[22], Linda Fogelstrand[23], Michaela Fontenay[24], Ulrich Germing[25], Sumeet Gujral[26], Torsten Haferlach[27], Claire Harrison[28], Jennelle C. Hodge[29], Shimin Hu[1], Joop H. Jansen[30], Rashmi Kanagal-Shamanna[1], Hagop M. Kantarjian[31], Christian P. Kratz[32], Xiao-Qiu Li[33], Megan S. Lim[34], Keith Loeb[35], Sanam Loghavi[1], Andrea Marcogliese[19], Soheil Meshinchi[36], Phillip Michaels[37], Kikkeri N. Naresh[35], Yasodha Natkunam[38], Reza Nejati[39], German Ott[40], Eric Padron[41], Keyur P. Patel[1], Nikhil Patkar[42], Jennifer Picarsic[43], Uwe Platzbecker[44], Irene Roberts[45], Anna Schuh[46], William Sewell[47], Reiner Siebert[48], Prashant Tembhare[42], Jeffrey Tyner[49], Srdan Verstovsek[31], Wei Wang[1], Brent Wood[50], Wenbin Xiao[51], Cecilia Yeung[35] and Andreas Hochhaus[52]

- **ICC – MDS/AML (10-19% blasts, replaces RAEB-2)**

Despite a Wealth of Innovative Options, More Work Needs to Be Done to Expose Patients to Effective Therapy

RW analysis of 629 newly diagnosed AML patients from a comprehensive health system in the Midwest United States, including metropolitan and rural populations (2011-2018)

- 66% of patients aged ≥75 years did not receive any chemotherapy or alternative treatment
- Only 13% of patients had evidence of a genomic report, although it has been used for prognostication for at least the last decade

EMR data from 2,133 AML patients to determine the effect of COVID-19 on AML care

- Compared with the pre-COVID-19 cohort, post-COVID-19 patients were significantly less likely to receive HCT
- Longer HCT waiting times suggest the pandemic affected access to timely transplantation

Byrd JC et al. (ASH 2021). Abstract 3383.　　　Chen C et al. (ASH 2021). Abstract 4139.
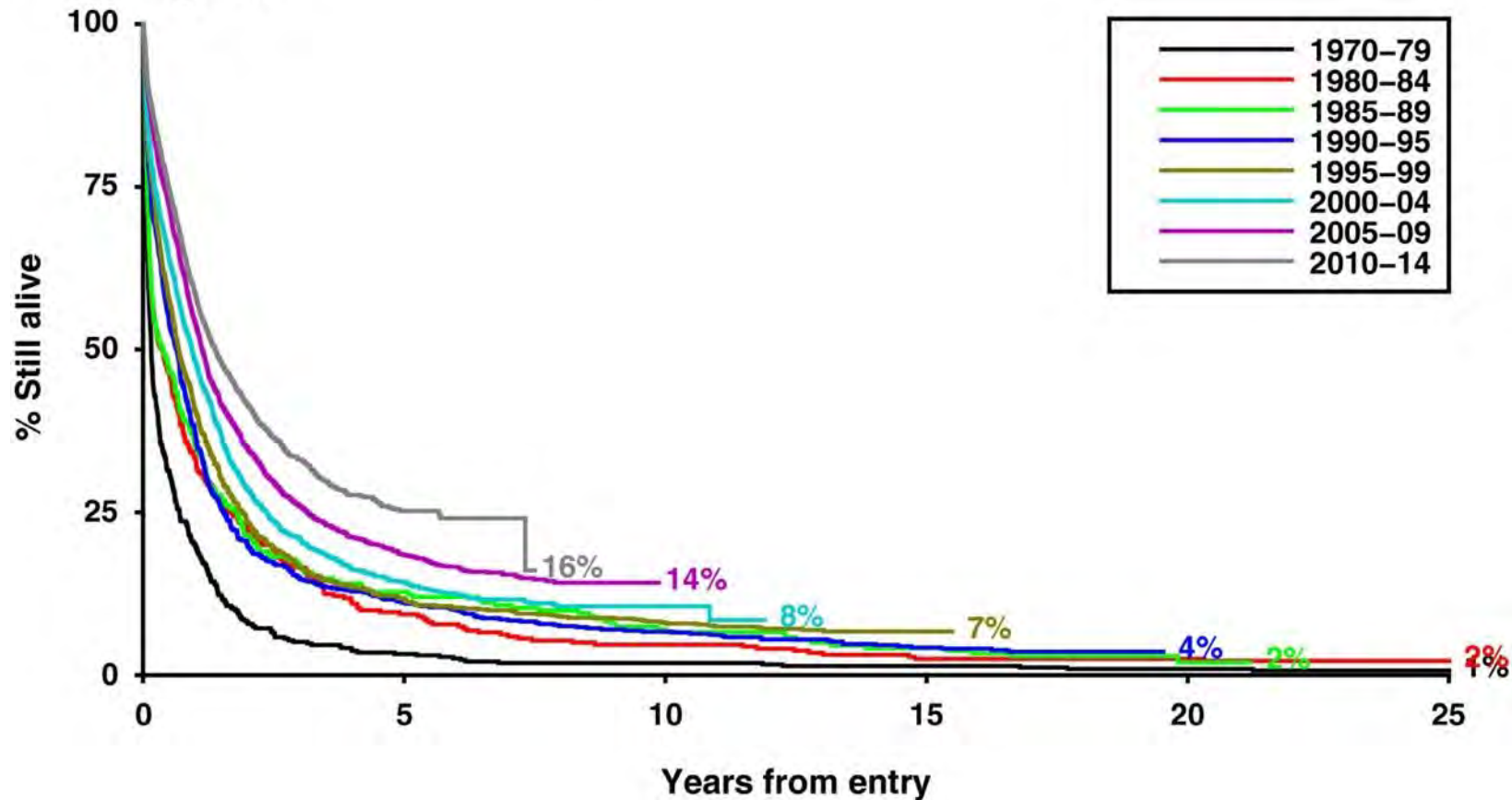
- *More intensive chemotherapy combinations have been facilitated by better supportive care, including support from other medical disciplines, and nursing expertise.*

Twenty five years of UK trials in acute myeloid leukaemia: what have we learned?
Burnett AK, British Journal of Haematology, 188:86-100, 2020

E2906 Randomized Study in Fit Older Adults with AML

Log Rank Test p<0.001

Induction Response	TOTAL	FAIL	CNSR	MEDIAN
CR	280	148	132	20.1
CRi	31	23	8	14.9
LFS	26	18	8	7.4
Treatment-failure	271	187	84	9.0
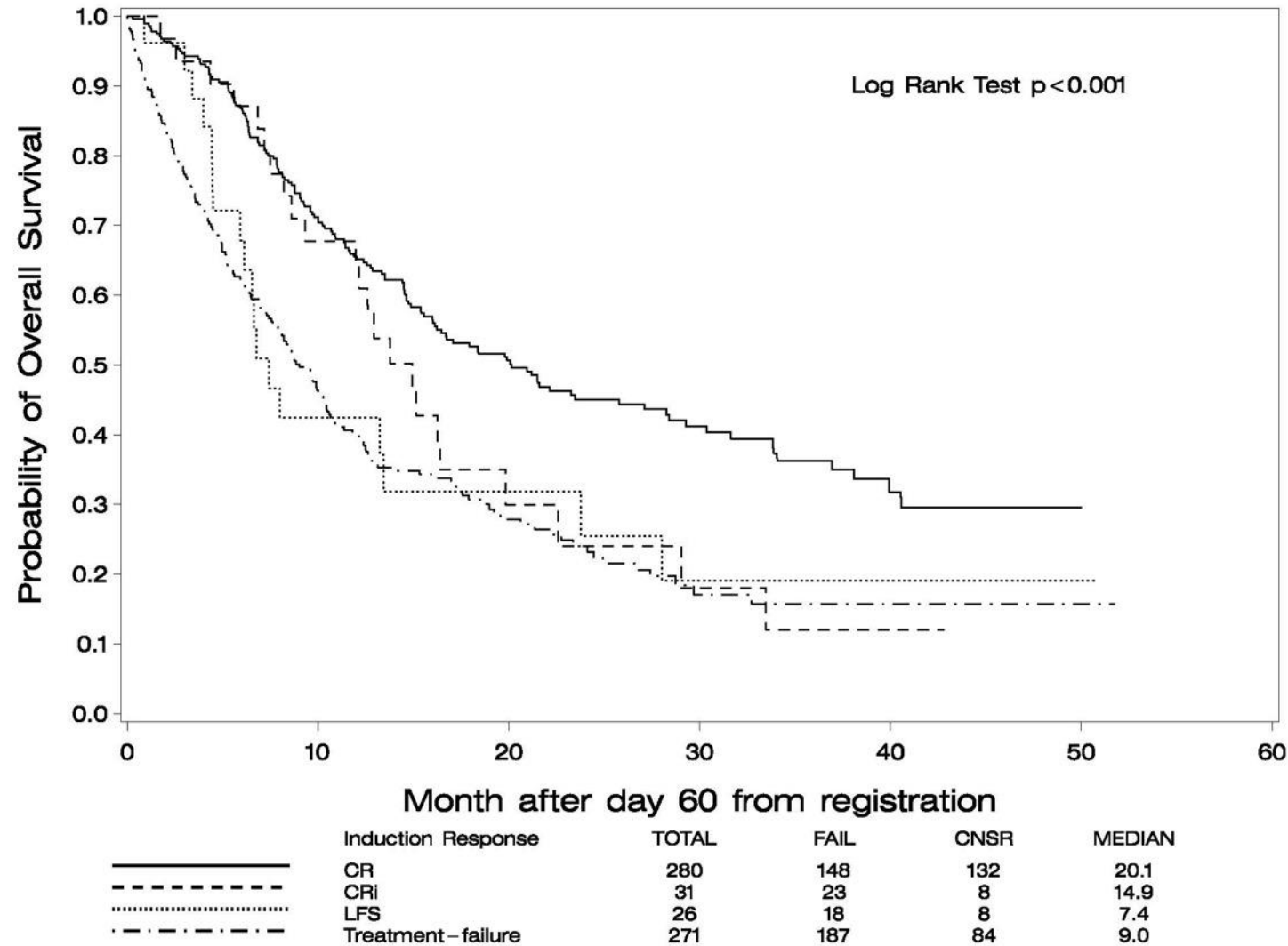
Randomized 1:1 to Intensive therapy ("7&3", HiDAC x2 consolidation), vs. single agent Clofarabine

* **Superior OS with 7&3**

Advantage in achieving CR vs. CR/CRi
- Diminished Benefit CRi after 12 months
- MLFS survival is similar to treatment failure

Landmark Analysis: Overall Survival According to Quality of Response

Foran et al, ASH 2016

Prospective MRD Evaluation in E2906 using Multiparameter Flow Cytometry
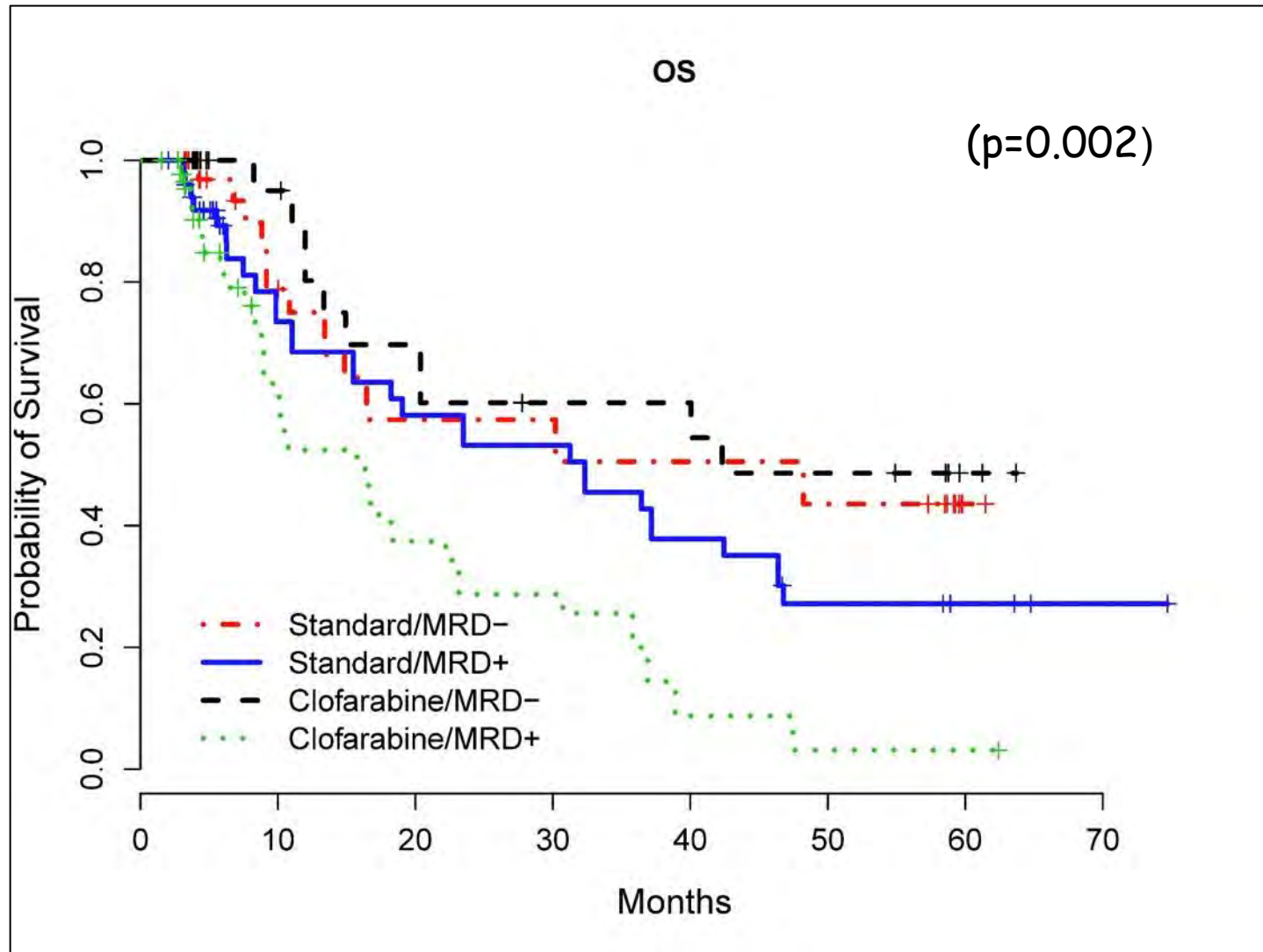
- CR/CRi 50%

- MRD-negative remission in 41% (n=161 evaluable)
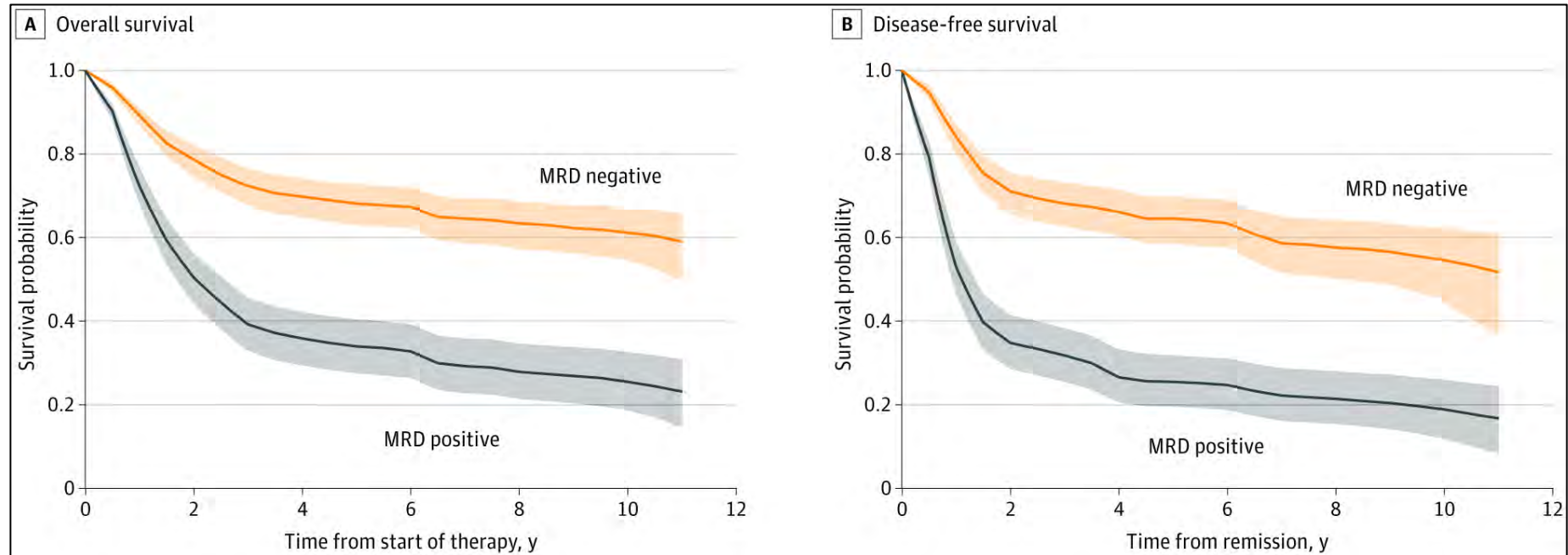
- N=11,151 from 81 publications
- MRD by PCR, MFC, NGS, cytogenetics and/or FISH, or others
- Average Hazard Ratio for achieving MRD negativity:
  - OS   **HR 0.36** (95% Bayesian credible interval [CrI], 0.33-0.39)
  - DFS   **HR 0.37** (95% CrI, 0.34-0.40)

Mechanism of action of Venetoclax
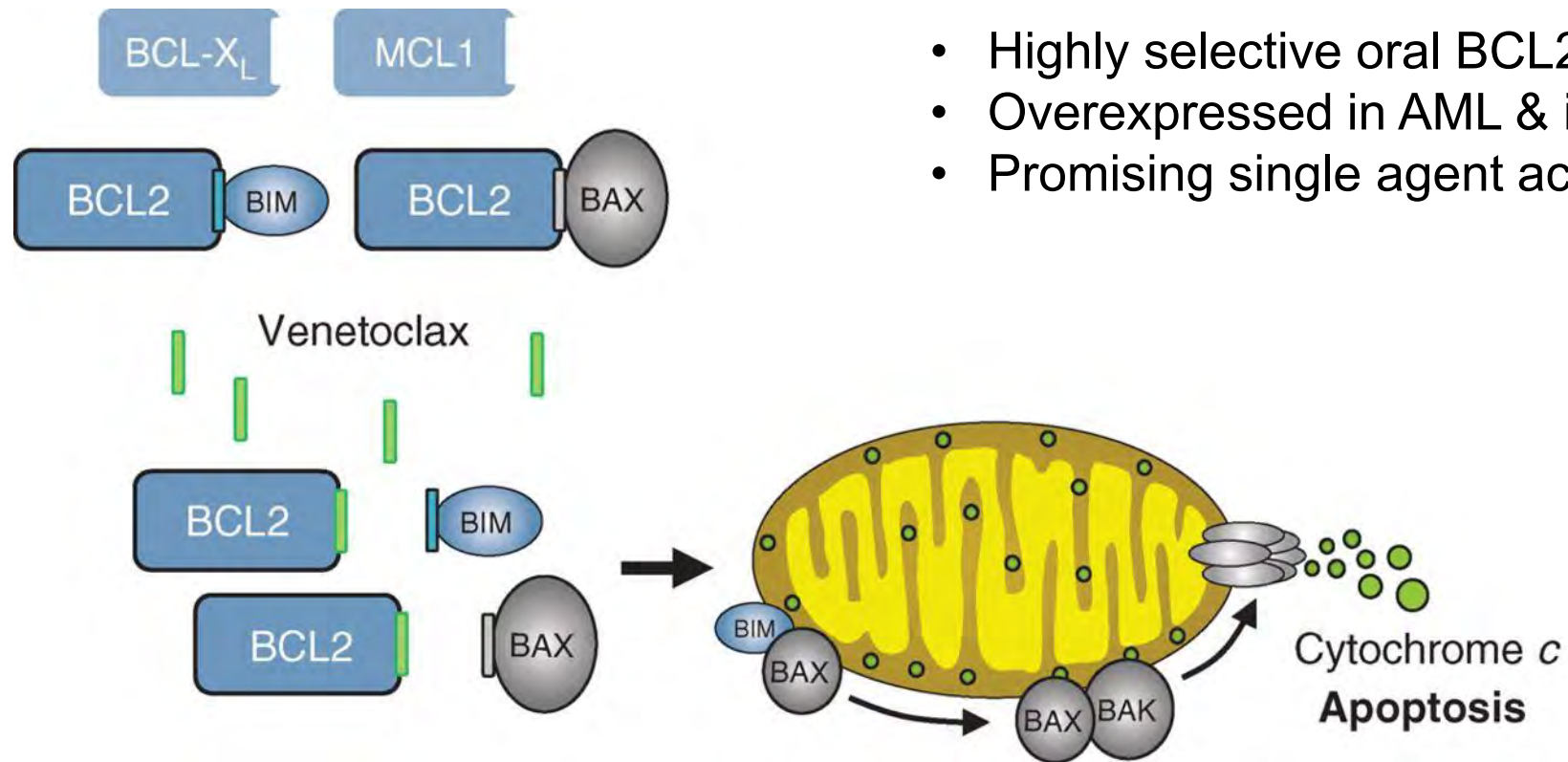
- Highly selective oral BCL2 inhibitor
- Overexpressed in AML & in Leukemia Stem Cells
- Promising single agent activity

Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia

Courtney D. DiNardo, M.D., Brian A. Jonas, M.D., Ph.D., Vinod Pullarkat, M.D., Michael J. Thirman, M.D., Jacqueline S. Garcia, M.D., Andrew H. Wei, M.B., B.S., Ph.D., Marina Konopleva, M.D., Ph.D., Hartmut Döhner, M.D., Anthony Letai, M.D., Ph.D., Pierre Fenaux, M.D., Ph.D., Elizabeth Koller, M.D., Violaine Havelange, M.D., Ph.D., Brian Leber, M.D., Jordi Esteve, M.D., Ph.D., Jianxiang Wang, M.D., Vlatko Pejsa, M.D., Ph.D., Roman Hájek, M.D., Ph.D., Kimmo Porkka, M.D., Ph.D., Arpád Illés, M.D., D.Sci., David Lavie, M.D., Roberto M. Lemoli, M.D., Kazuhito Yamamoto, M.D., Ph.D., Sung-Soo Yoon, M.D., Ph.D., Jun-Ho Jang, M.D., Su-Peng Yeh, M.D., Mehmet Turgut, M.D., Wan-Jen Hong, M.D., Ying Zhou, Ph.D., Jalaja Potluri, M.D., and Keith W. Pratz, M.D.

- Patients age >75 years, or *ineligible* for standard induction therapy
  - CHF or chronic stable angina
  - Pulmonary Disease (DLCO or FEV1 <65%)
  - ECOG performance-status score >1

- n=431, 2:1 randomization

Viale A: Phase 3 randomized study AZA-Venetoclax vs. AZA-Placebo
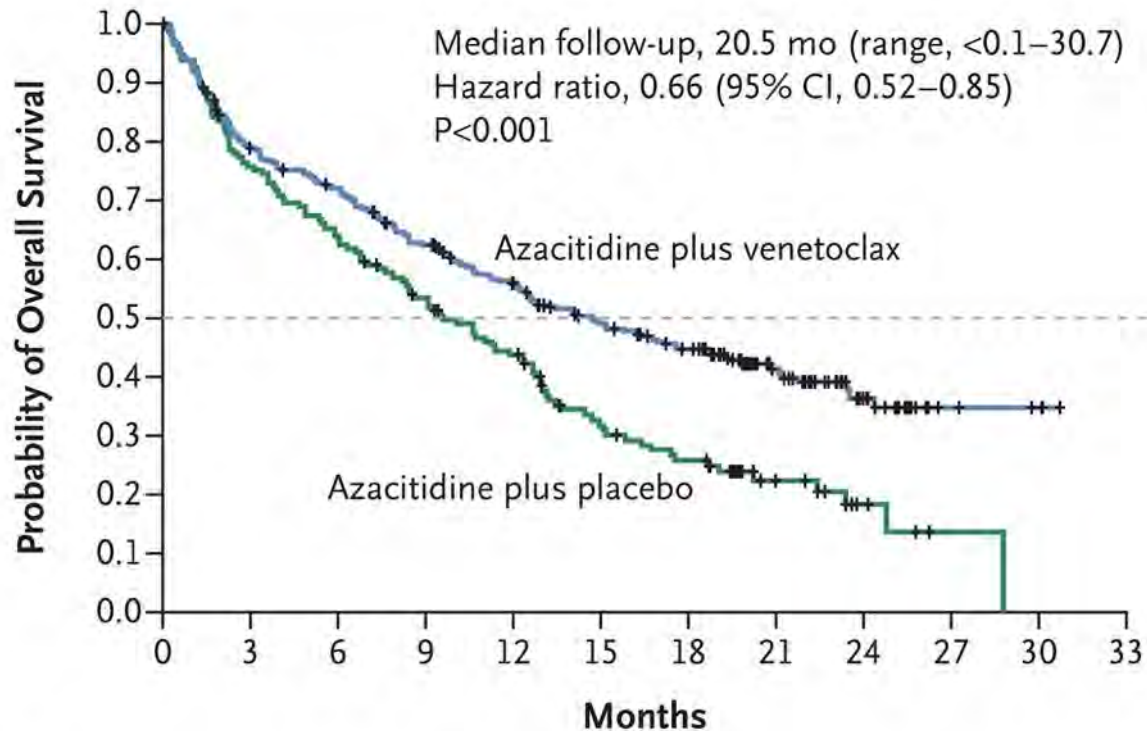
- Improved OS overall
- Higher CR rates across all subgroups
- Some able to proceed to 'curative' AlloHCT

* Venetoclax Dosing recommendations:
DiNardo & Wei, Blood 135:85, 2020
"How I treat AML in the era of new drugs"

Viale-A SubGroup Analysis
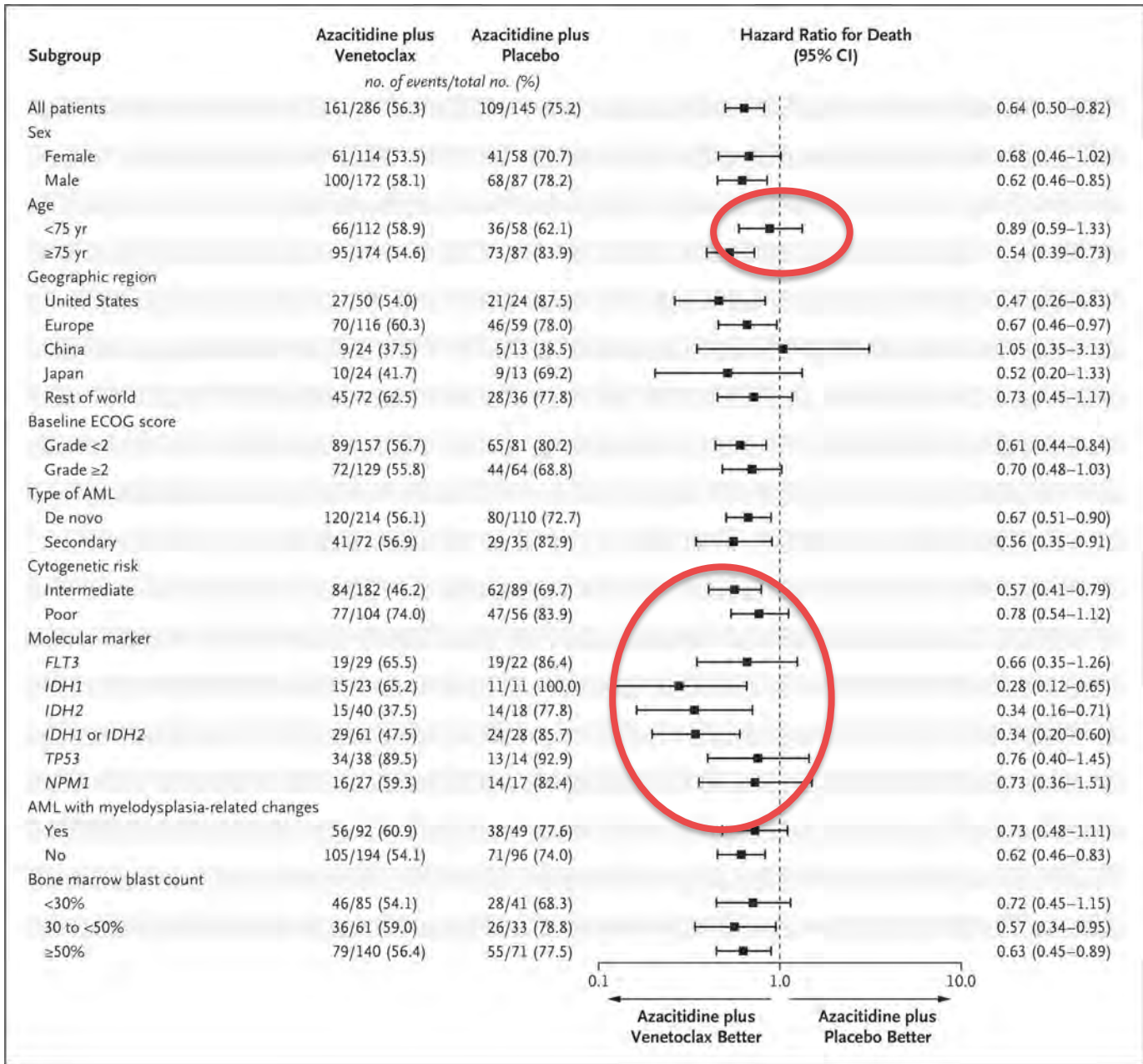
- Significantly higher CR rates in all subgroups

- Some subgroups not significant for OS (post hoc)

  - Age <75 years
  - Poor Risk cytogenetics
  - Some mutation groups (e.g. TP53, NPM1, FLT3)

Original Study

Check for updates

Induction Therapy and Survival for Acute Myeloid Leukemia in Hispanic Adults from Puerto Rico

Maira A. Castaneda-Avila,[1,#] Tonatiuh Suárez Ramos,[2,#]
Carlos R. Torres-Cintrón,[2,#] Luis A. Cotto-Santana,[3] Guillermo Tortolero-Luna,[2,4,#]
Karen J. Ortiz-Ortiz[2,4,5,#]

Maira A. Castaneda-Avila et al

Abstract

We described the first-line therapy and survival of Hispanics from Puerto Rico with acute myeloid leukemia. Age, risk, and comorbidities were associated with induction therapy type. Among patients who received intensive therapy, those of ≥60 years had a higher risk of death. The low survival and the disparities observed highlight the need to examine further new treatment options for older and comorbid patients.

Background: Acute myeloid leukemia (AML) is the most common type of leukemia in adults. There are no previous studies evaluating AML treatment patterns in Puerto Rico. We describe the first-line therapy patterns and survival of patients diagnosed with AML in Puerto Rico using the Puerto Rico Central Cancer Registry Health Insurance Linkage Database (2011-2015). **Methods:** We describe patient characteristics according to intensive, non-intensive, and non-treatment status. We used Cox proportional hazard models to evaluate the factors associated with the risk of death stratified by intensive and non-intensive therapy. For this study, 385 patients with AML were included. **Results:** The mean age was 67 years old and 50.1% were female. Nearly half of AML patients (46.8%) received intensive treatment, 23.6% received non-intensive treatment, and 26.2% did not receive treatment. The overall 3-year survival rate was 17.9%. Among those who received intensive therapy, the risk of death among females was lower than males (hazard ratio [HR]: 0.64, 95% confidence interval [CI]: 0.44-0.93). Patients 60 years or older who received intensive treatment had a higher risk of death than younger patients (HR: 1.67, 95% CI: 1.09-2.55). Patients with poor/adverse risk receiving intensive (HR: 3.43, 95% CI: 1.76-6.69) or non-intensive (HR: 4.32, 95% CI: 1.66-11.28) treatment had a higher risk of death than patients with a favorable risk category. **Conclusion:** Our findings are the first step to monitor the quality of care of patients with AML in Puerto Rico, particularly related to the administration of appropriate induction therapies, which is one of the most important predictors of AML survival.

Figure 2 Survival probabilities for patients who were given (A) intensive treatments and (B) non-intensive treatments
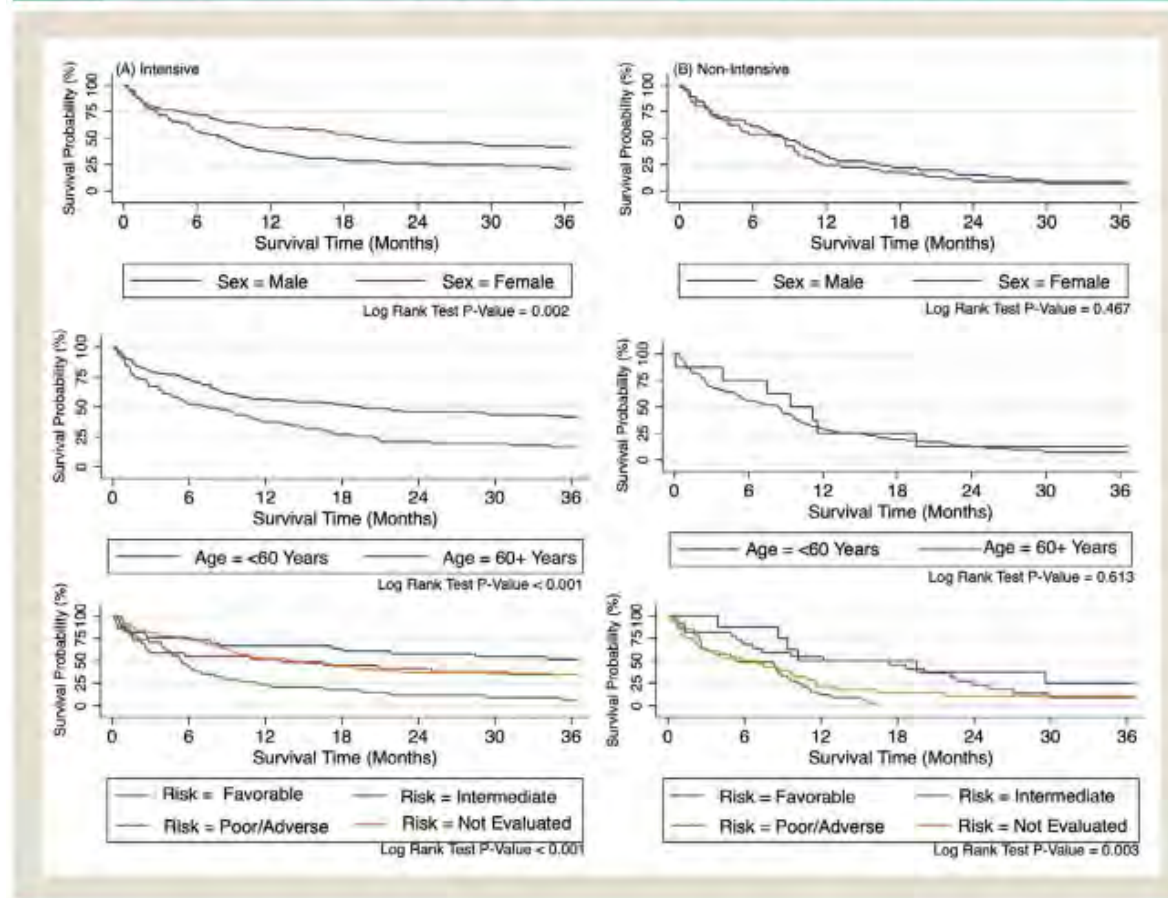
MRD with Azacitidine & Venetoclax in Viale-A Trial
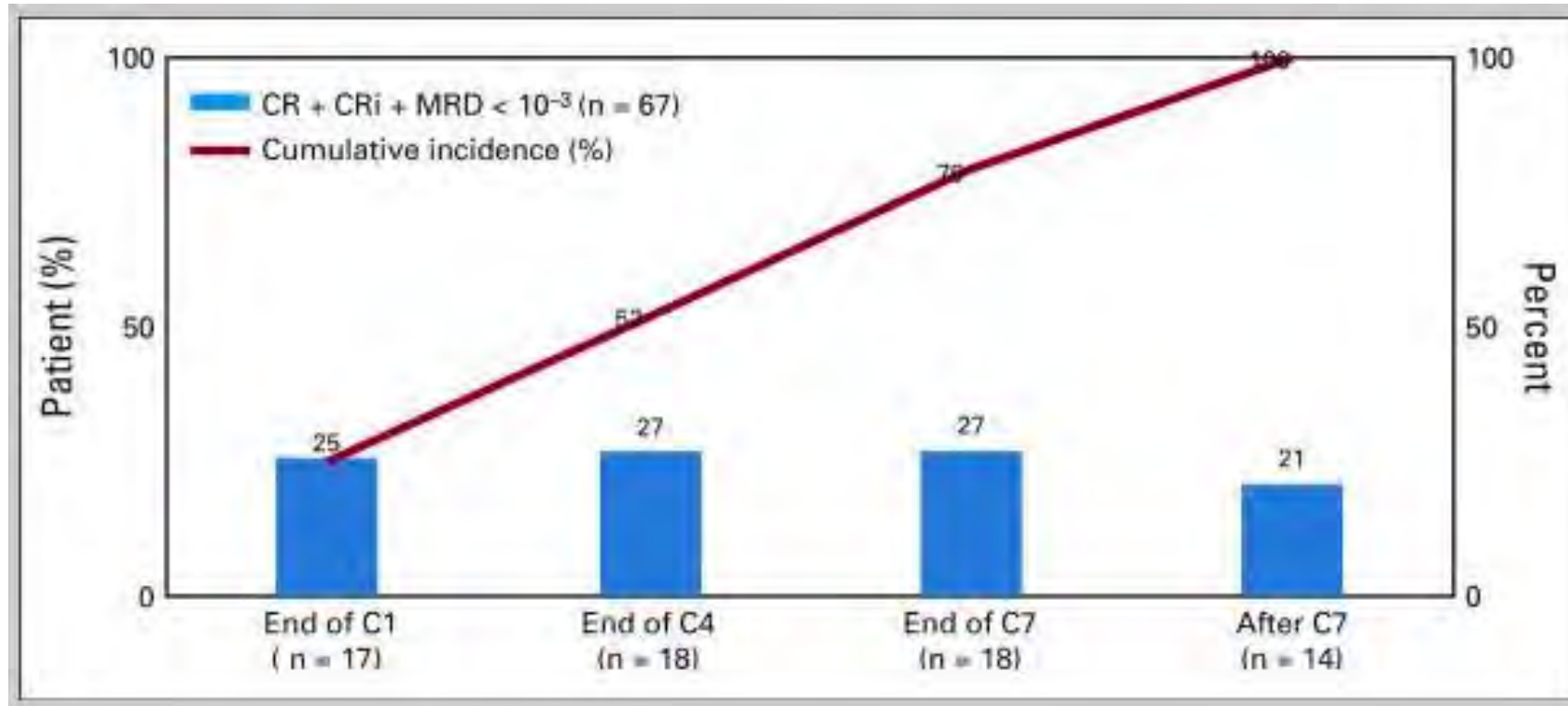
- Prospective central (LabCorp) MRD testing by MFC
  - 86% of CRc patients evaluable
- Threshold 10^{-3} (i.e. <0.1%) residual leukemia blasts
- **41% MRD-neg CR/CRi**

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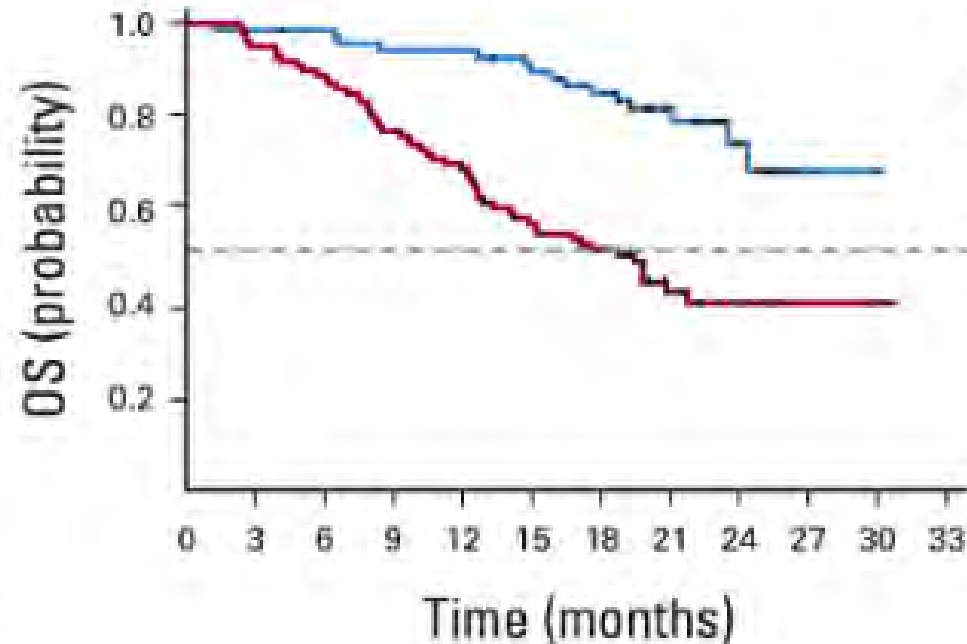
OS	No. of Events	12 Months, % (95% CI)	18 Months, % (95% CI)	Median OS, Months (95% CI)
CR + CRi + MRD < 10^{-3}	15	94.0 (84.7 to 97.7)	84.6 (73.3 to 91.4)	NR (24.4 to NR)
CR + CRi + MRD ≥ 10^{-3}	52	67.9 (57.6 to 76.2)	50.1 (39.6 to 59.8)	18.7 (12.9 to NR)

No. at risk:

CR + CRi + MRD < 10^{-3}	67	66	65	62	62	58	52	28	12	2	1	0
CR + CRi + MRD ≥ 10^{-3}	97	92	86	74	64	48	42	21	10	3	2	0

Multivariate analysis showed CRc with MRD <10^{-3} was strong predictor of OS
[**HR 0.285** (95% CI, 0.159 - 0.510), *p*<0.001]

Pre-MEASURE Observational Study of FLT3$_m$ and NPM1$_m$ in Remission Prior to Allogeneic Transplantation
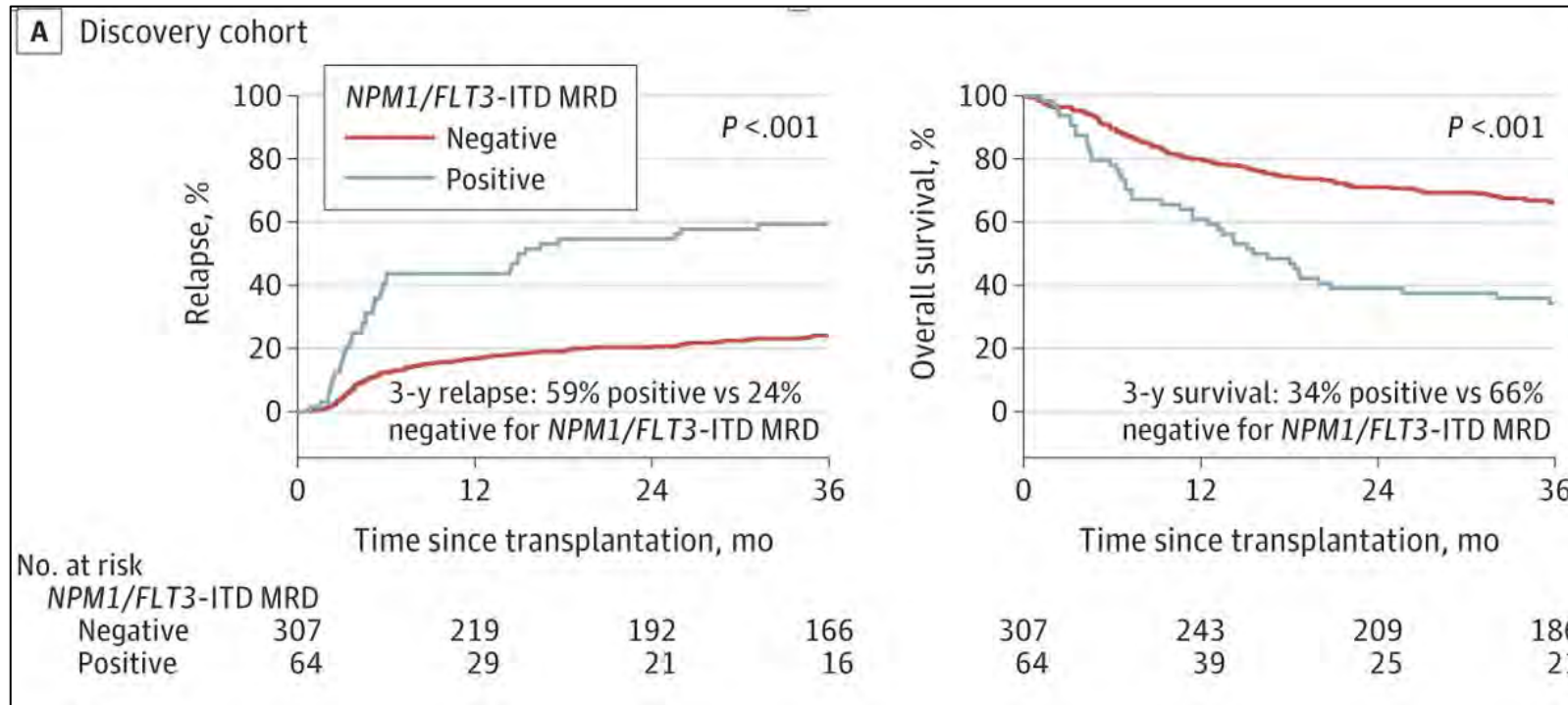
- 17.3% with residual *NPM1* and/or *FLT3*-ITD variants

- Higher rates of relapse at 3 years 68% vs 21%
- HR 4.32 [95% CI, 2.98-6.26]; *P* < .001)

- Decreased survival at 3 years 39% vs 63%
- HR, 2.43 [95% CI, 1.71 - 3.45]; *P* < .001).

- Variants in *FLT3 & NPM1 from* Blood from AML patients
- 111 CIBMTR sites from 2013 through 2019. Clinical data were collected through May 2022
- Targeted error–corrected DNA sequencing at a variant allele fraction (VAF) of 0.01%

Evaluating MRD in AML

Timing	Platform
CR/CRi; Later if low intensity…	MFC (LAIP, DFN, both)
Prior to Transplant	PCR (NPM1, FLT3, CBF), or NGS
Surveillance	PCR (NPM1, CBF), or NGS

- **Goals & Challenges**:
  - *Increase MRD-negative CR rate*
    - Addition targeted inhibitors, immunotherapy (clinical trials)
  - *Improve outcomes in MRD-positive remission*
    - e.g. intensify HiDAC consolidation (older adults); maintenance with oral azacitidine (e.g. $NPM1_m$); addition of targeted agents (Gilteritinib in MRD+ AML with FLT3-ITD after AlloHCT), etc.

Advances Since 2017, and the Rapidly Developing Future of AML Care

Since 2017, we have seen FDA approval of
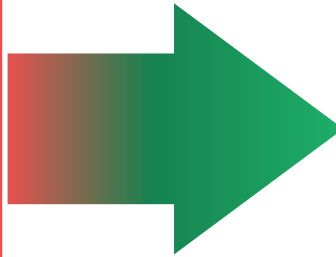
- ✓ CPX-351 (sAML, AML-MRC)
- ✓ Midostaurin, Gilteritinib & Quizartinib
- ✓ Ivosidenib, Olutasidenib, and Enasidenib
- ✓ Ivosidenib + azacitidine combo
- ✓ Re-emergence of gemtuzumab-ozogamicin
- ✓ Venetoclax
- ✓ Oral azacitidine as maintenance
- ✓ Glasdegib

Emerging advances center on

- Integrating novel targeted doublets and triplets

- Development novel targeted agents, and strategies for challenging subgroups (*e.g TP53*-mutated AML)

- Determining role for immunotherapy in AML and increasing benefit of allogeneic transplantation

Sept 10, 2009

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Recurring Mutations Found by Sequencing an Acute Myeloid Leukemia Genome

Mar 16, 2010

Cancer Cell
Article

The Common Feature of Leukemia-Associated IDH1 and IDH2 Mutations Is a Neomorphic Enzyme Activity Converting α-Ketoglutarate to 2-Hydroxyglutarate

**First patient treated
Sept 2013**

Aug 1, 2017

FDA approves new targeted treatment for relapsed or refractory acute myeloid leukemia

APPROVED

July 20, 2018

FDA approves first targeted treatment for patients with relapsed or refractory acute myeloid leukemia who have a certain genetic mutation

APPROVED

Enasidenib

Ivosidenib
*2022 Olutasidenib

Ivosidenib and Azacitidine in IDH1-Mutated Acute Myeloid Leukemia

Pau Montesinos, M.D., Ph.D., Christian Recher, M.D., Ph.D., Susana Vives, M.D., Ewa Zarzycka, M.D., Jianxiang Wang, M.D., Giambattista Bertani, M.D., Michael Heuser, M.D., Rodrigo T. Calado, M.D., Ph.D., Andre C. Schuh, M.D., Su-Peng Yeh, M.D., Scott R. Daigle, M.S., Jianan Hui, Ph.D., et al.
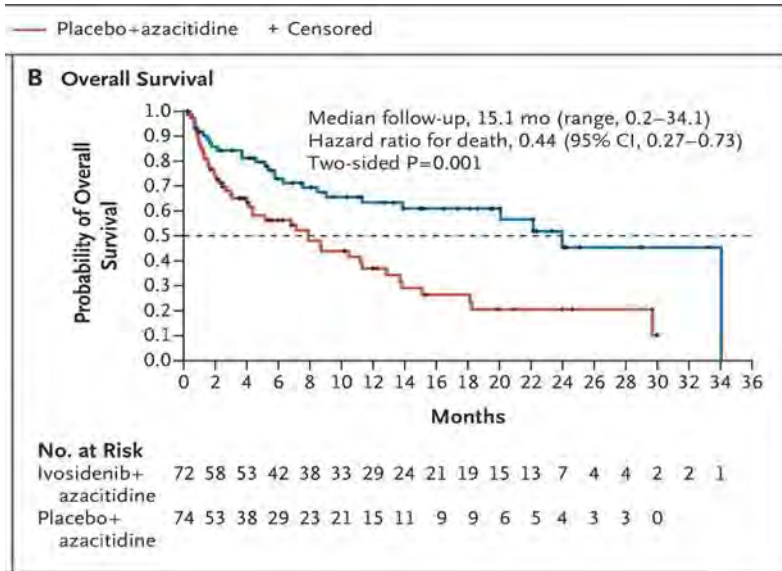
- Median survival 24.0 vs. 7.9 months

  - HR 0.44 (95% CI, 0.27-o 0.73; p=0.001)

- CR/CRh 53% vs.18% (p<0.001)

- DS 14 %

- FDA Approval 1st line Aza combination 12/22

Differentiation Syndrome

Auer rods

Citrate
↓
Isocitrate
↓ IDH1/2
α-KG → ↓2-HG
IDH1/2^{mut}

Ivosidenib   Enasidenib

Leukemia cell with *IDH1/2* mutation
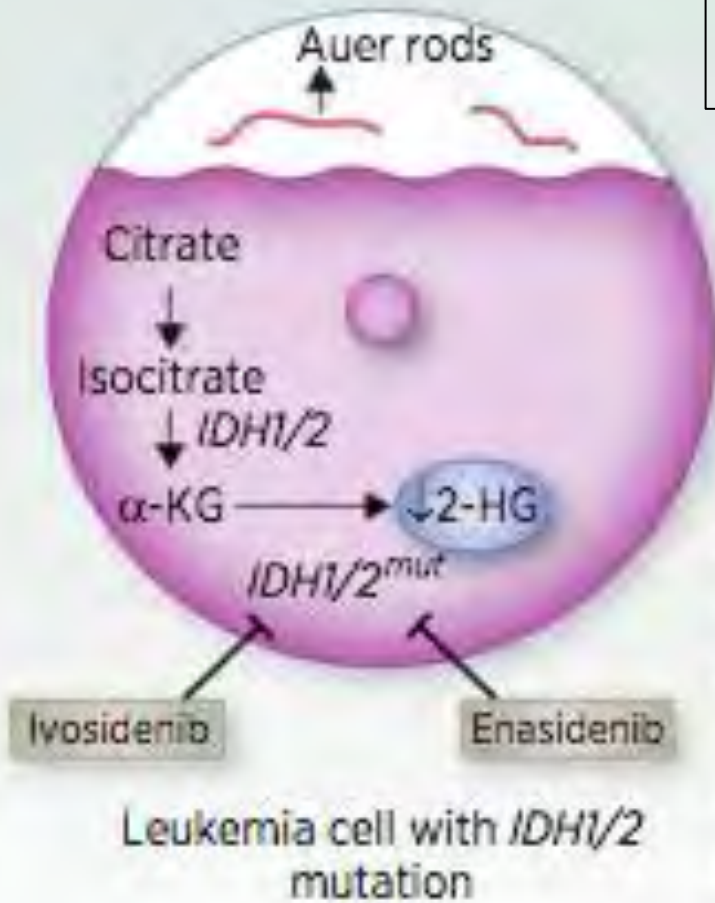
Differentiation syndrome   19%

Symptoms ≥2
1) Dyspnea   68–76%
2) Pulm. infiltrates/effusions   61–76%
3) Weight gain   41–53%
4) Fever   44–57%
5) Acute renal failure   17–24%
6) Hypotension   7–18%

Neutrophil

Risk factors
≥48% blasts in bone marrow
≥15–25% blasts in blood

- Concomitant TET2, SRSF2

- **Dexamethasone 10mg IV BID**
- **Hydroxyurea**
- **Continue Agent if possible**

New Oral agents in AML
Menin Inhibitors - NPM1$_{mut}$ & MLL rearrangement

- Target HOXA9/Meis1 overexpression in AML, which leads to AML proliferation/renewal

- AML with NPM1$_{mut}$ or MLLr
- Promising agents in clinical development (KO-539, SNDX-5613, BMF-219, others…)

- DS as a clinical toxicity/concern

FIGURE. Targeting Menin-MLL Interactions

Targeting the menin-KMT2A(MLL) interaction to reverse epigenetic dysregulation in MLL-rearranged AML

A central role for menin-KMT2A(MLL) interaction in epigenetic dysregulation in NPM1-mutant AML
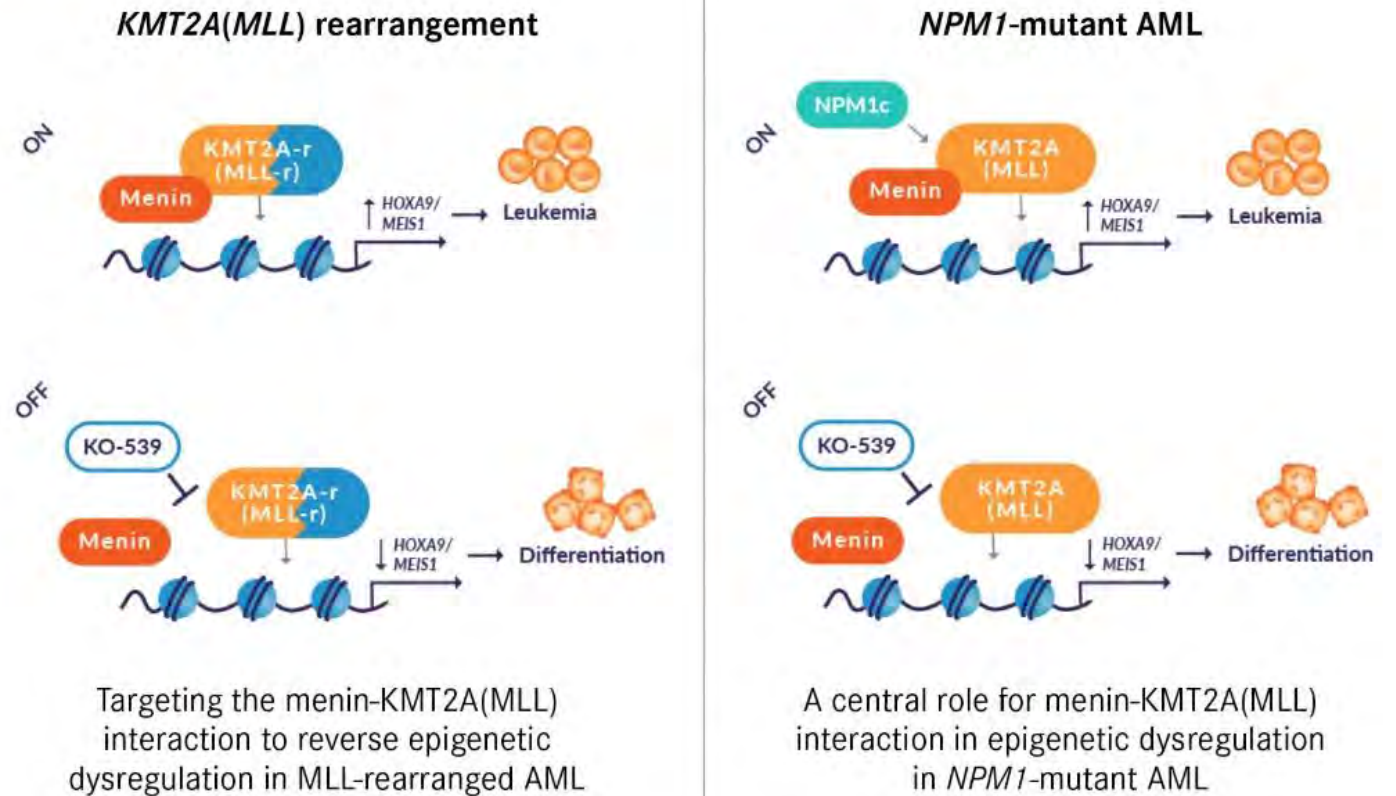
Ziftomenib Monotherapy Drives Durable Responses

- Median DoR **8.2 months** (med. follow up 8.8 months)

- **35% CR rate** (7/20) at 600mg dose (RP2D)
  - 33% (2/6) with FLT3 co-mutations, and 50% (4/8) with IDH co-mutations achieved CR

- DS: 15% (grade 1/2) and 5% (grade 3)

- Ziftomenib less likely to induce Menin resistance mutations

Ph. 1a/b *NPM1*-m Duration of Ziftomenib and CRc up to 12 mo.

Legend:
- 200 mg
- 600 mg
- CR
- CRc

- → Ongoing in Response
- AE Adverse Event
- DTH Death
- PI Physician Decision
- WD Withdrawal by Subject
- PD Disease Progression as Assessed by Investigator
- HSCT Stem Cell Transplant
- OTH Other
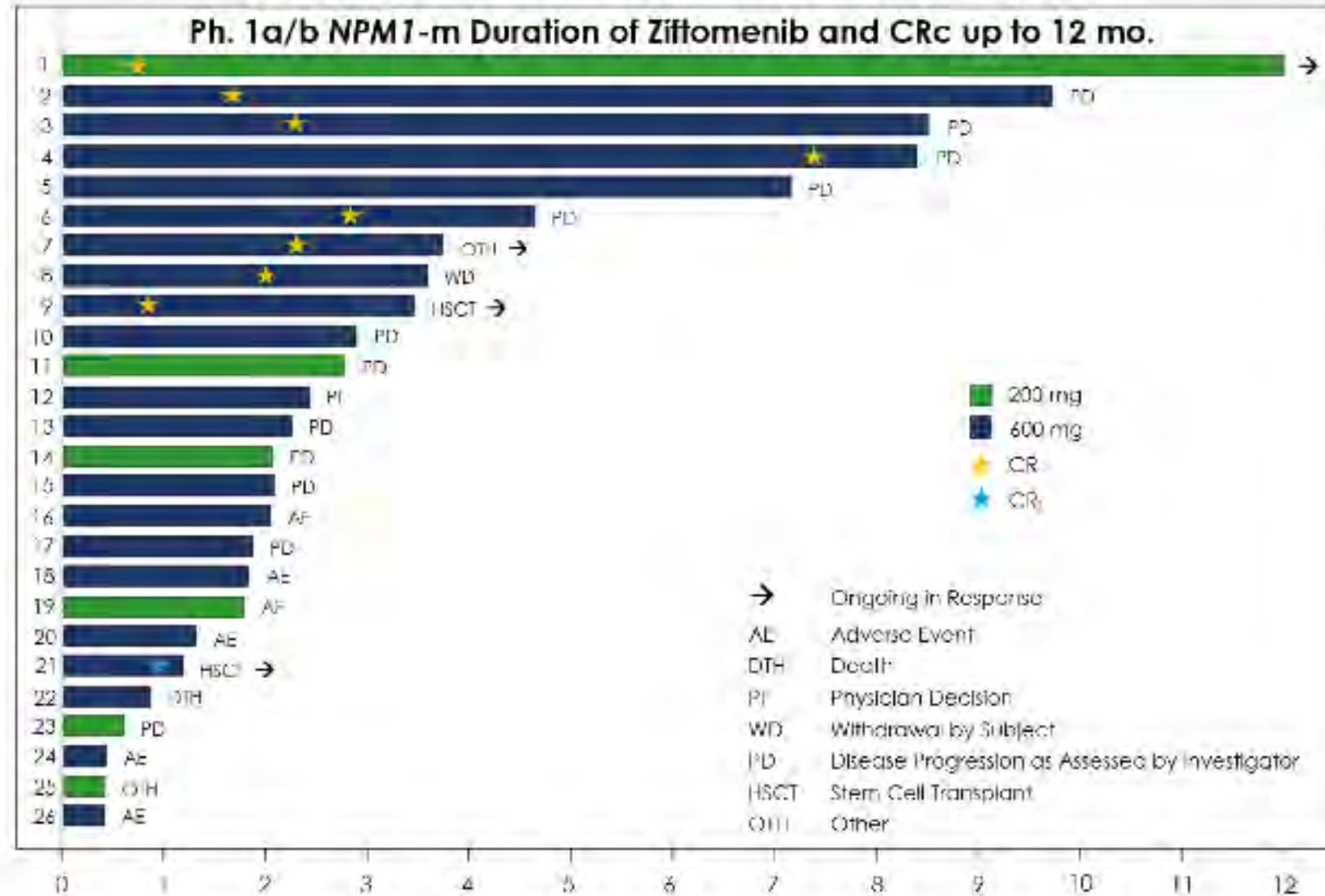
AML with TP53 Mutation

- Despite surge in use of venetoclax-based therapy, no improvement in duration response or overall survival in "Real World" dataset   (Badar, ASH 2023)
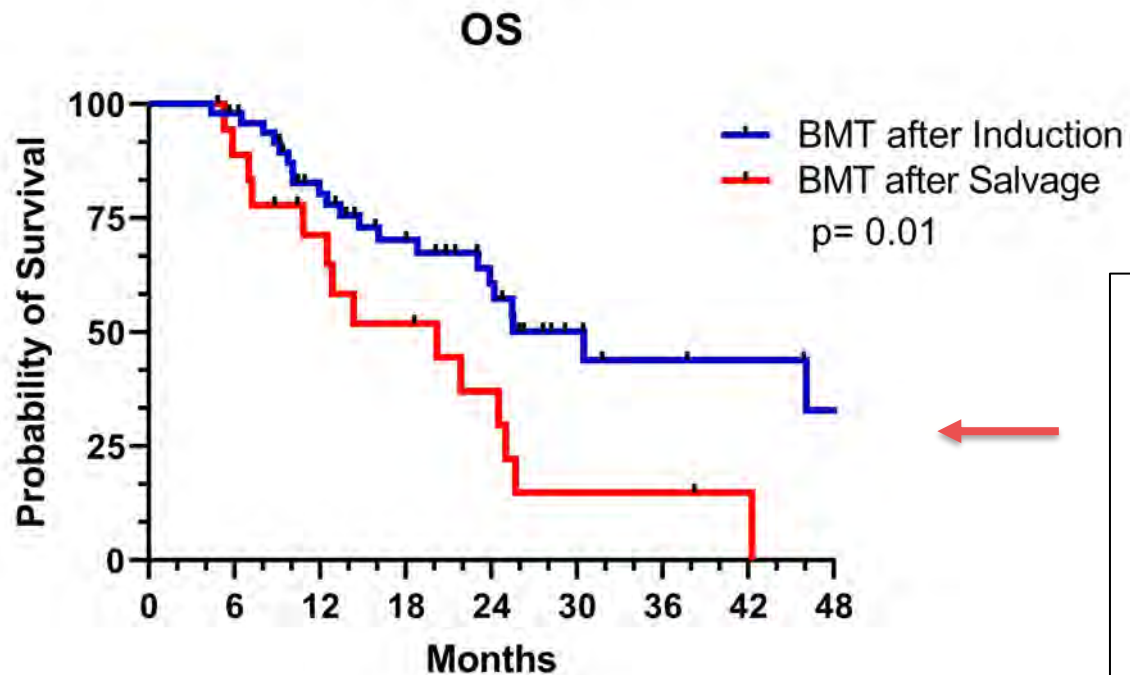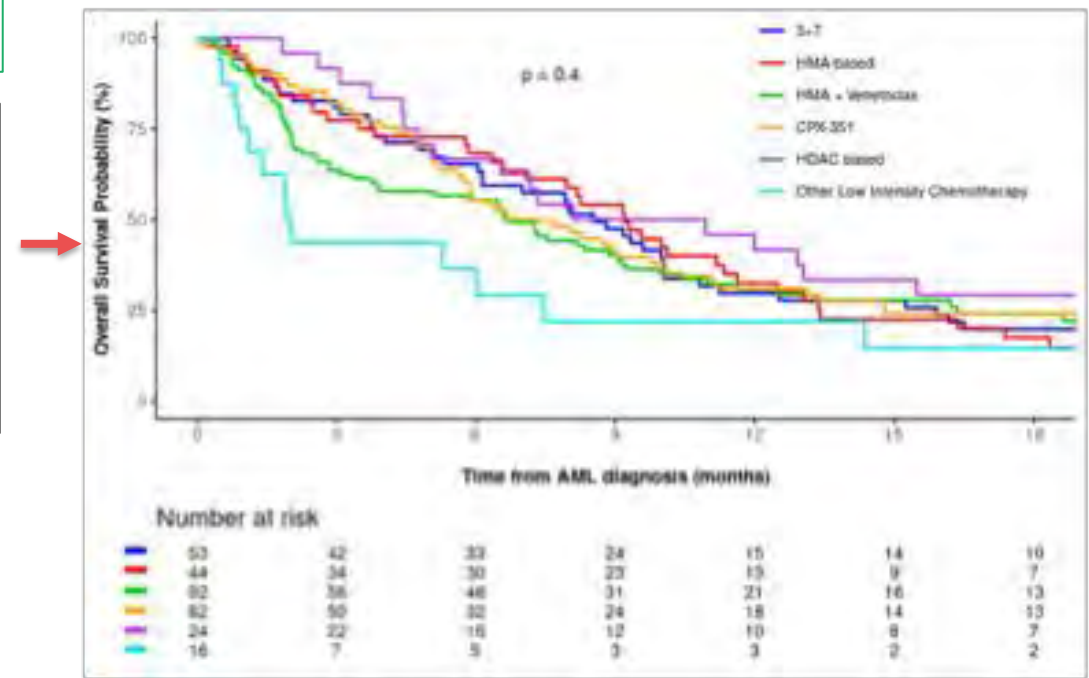
- Impact of Allogeneic Transplantation, esp. in 1st line (Med. OS 30.5 mos. vs. 20.2 mos.), again demonstrated in RWD analysis   (Badar, ASH 2023)
HR: 0.15 (95% CI 0.04-0.40), p=0.002

Mechanism of Action of CD47-Blocking Antibodies as Novel Checkpoint Inhibitors
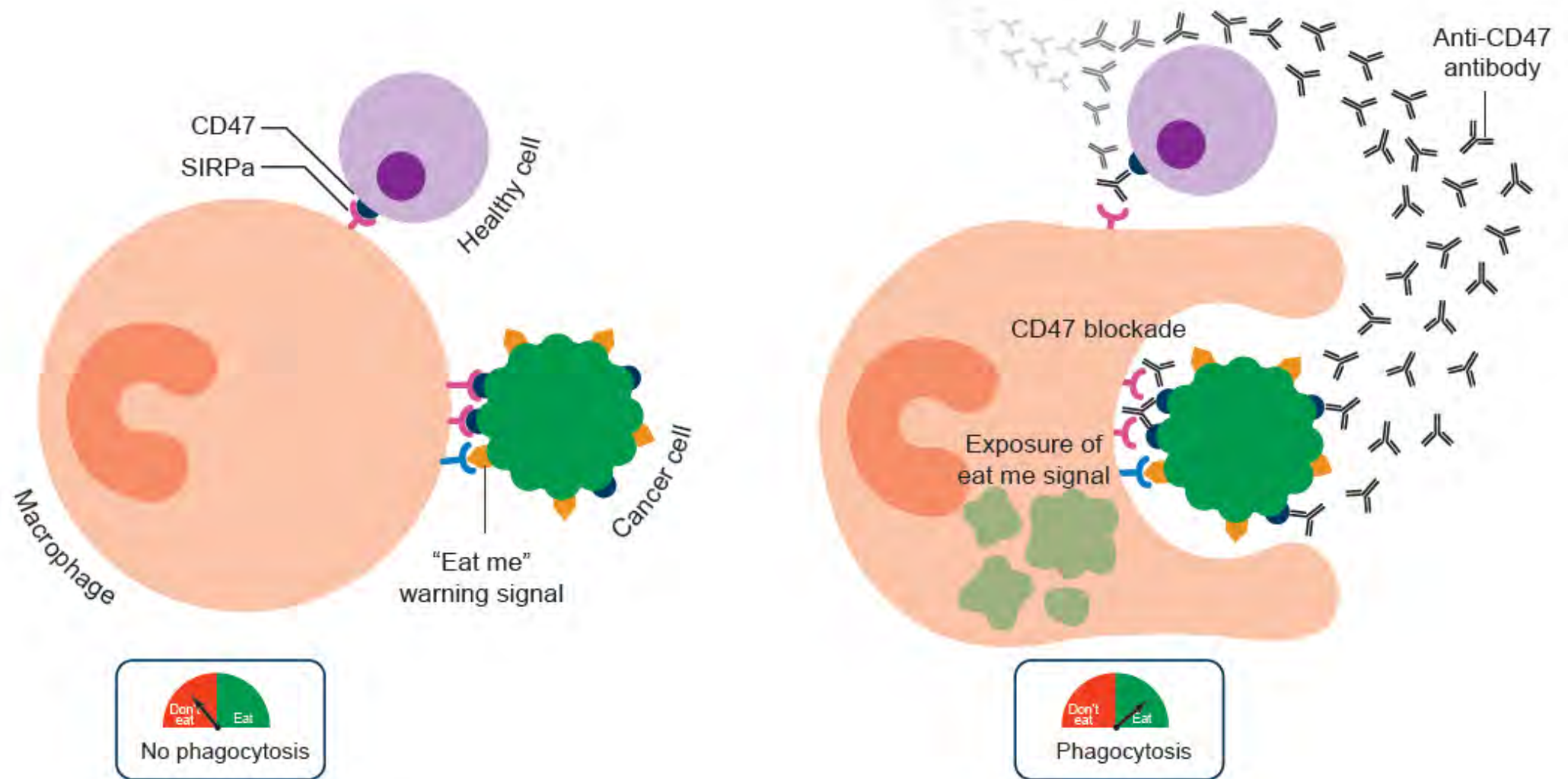
Magrolimab + Azacitidine Appeared "Efficacious" Against TP53 AML in Early Phase Trial

- No significant cytopenias, infections, or immune-related AEs observed

- **On-target hemolytic anemia**

- Median OS - 10.8 months

Outcome	Patients With *TP53* AML (N = 72)
ORR, % (95% CI)	**48.6 (36.7, 60.7)**
CR, % (95% CI)	**33.3 (22.7, 45.4)** (n = 24/72)
MRD- CR[a], % (95% CI)	50.0 (29.1, 70.9) (n = 12/24)
CRi/CRh, n (%)	6 (8.3)
PR, n (%)	4 (5.6)
MLFS, n (%)	1 (1.4)
DOR, median (95% CI), mo	**8.7 (6.5, 10.4)**

Frontline *TP53*-mutated AML in the Phase 3 ENHANCE-2 trial (currently recruiting; NCT04778397)

Best Change From Baseline in % Bone Marrow Blasts (N = 50)

Daver N. EHA2022 Hybrid Congress. Abstract S132.
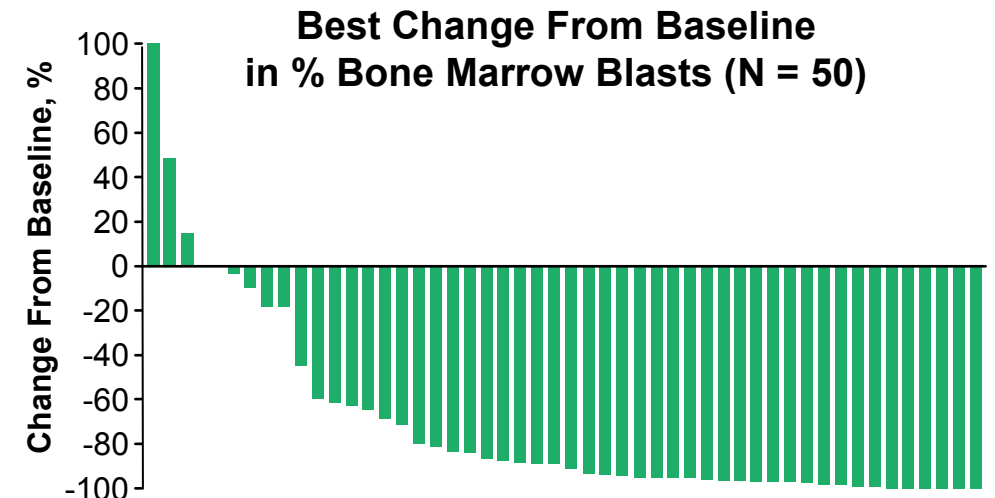
Gilead Statement on the Discontinuation of Magrolimab Study in AML with TP53 Mutations

Foster City, Calif., September 26, 2023 – Gilead Sciences has stopped its ENHANCE-2 study in acute myeloid leukemia (AML) with TP53 mutations. Based on an ad hoc analysis, and following review by an independent data monitoring committee, Gilead concluded that magrolimab is unlikely to demonstrate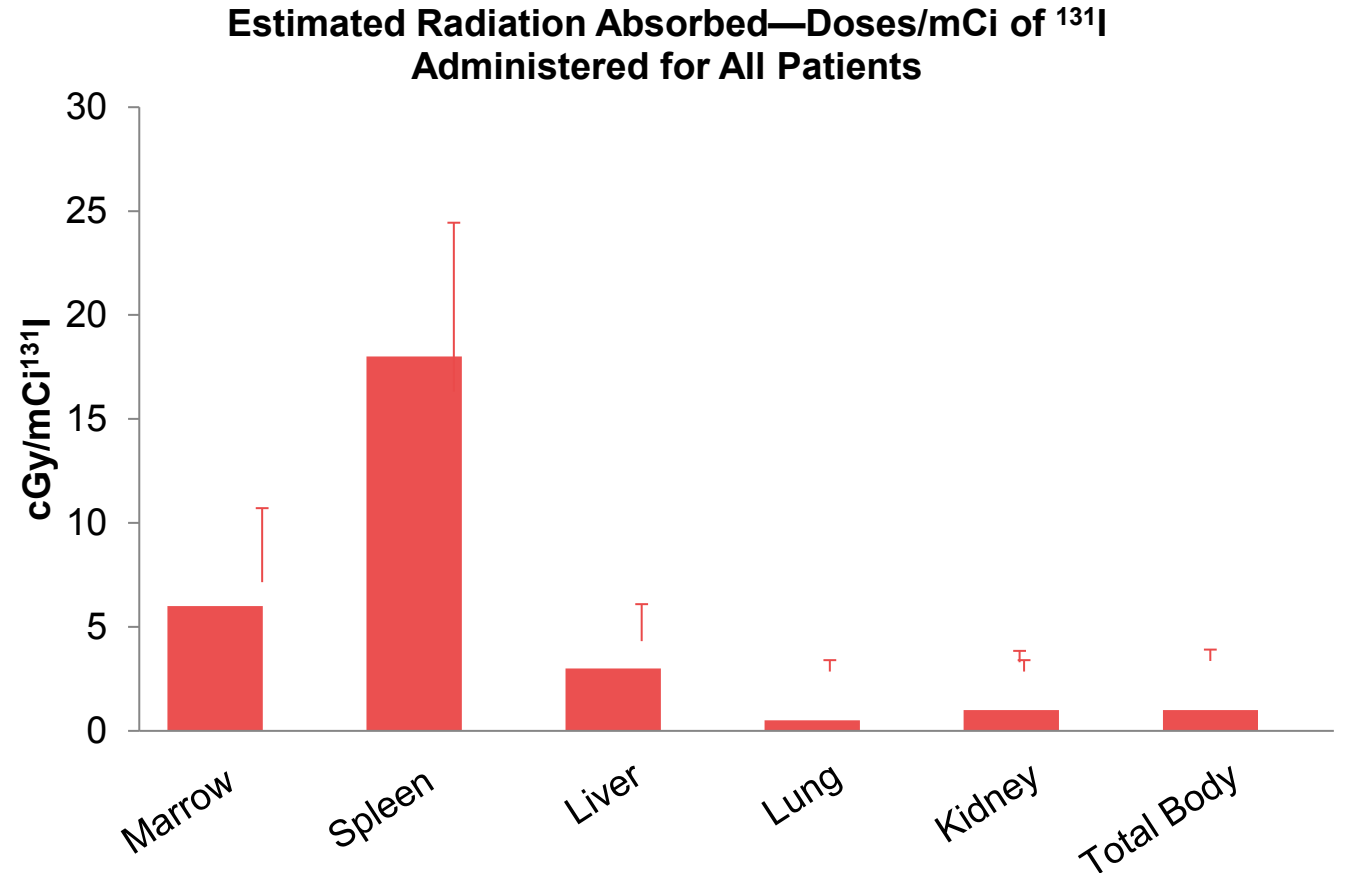 a survival benefit in AML with TP53 mutations compared to standard of care. There were no new safety signals identified and the safety profile was comparable between treatment arms. ENHANCE-2 is a randomized, open-label, Phase 3 trial to determine if magrolimab plus azacitidine improves overall survival, compared to physician's choice of venetoclax plus azacitidine or intensive chemotherapy in previously untreated AML with TP53 mutations. Gilead is working with study investigators on appropriate next steps for patients enrolled in this study. This decision follows the previously announced partial clinical hold placed on the ENHANCE-2 study.

AML with TP53 mutation remains an area of pressing need for novel therapies that improve outcome

Iomab-B (I[131]-Apamistamab) & CD45: Mechanisms and Biodistribution

- CD45 antigen expressed on virtually all lymphocytes, and 85%-90% of acute leukemias

- Iomab-B (^{131}I apamistamab): anti-CD45 mAb targeting lympho-hematopoietic cells with β-particle–emitting radionuclide[131]I

- Offers target-specific ablation as HCT conditioning regimen

- Does not bind other normal tissues; directs radiation to leukemic and immune cells

Estimated Radiation Absorbed—Doses/mCi of [131]I Administered for All Patients

y-axis: cGy/mCi[131]I (0, 5, 10, 15, 20, 25, 30)

x-axis: Marrow, Spleen, Liver, Lung, Kidney, Total Body

Pagel JM et al. *Blood*. 2009;114:5444-5453.

Phase 3 SIERRA Trial: Iomab-B Prior to HCT vs Chemotherapy in R/R AML

Inclusion Criteria

- Aged ≥55 years, KPS ≥70 with active, R/R AML
  - Primary induction fail ≥2 cycles Chemo
  - 1st early relapse <6m
  - Refractory to salvage chemotherapy with high-dose cytarabine
  - ≥ 2nd Relapse
- **8/8 HCT donor match**
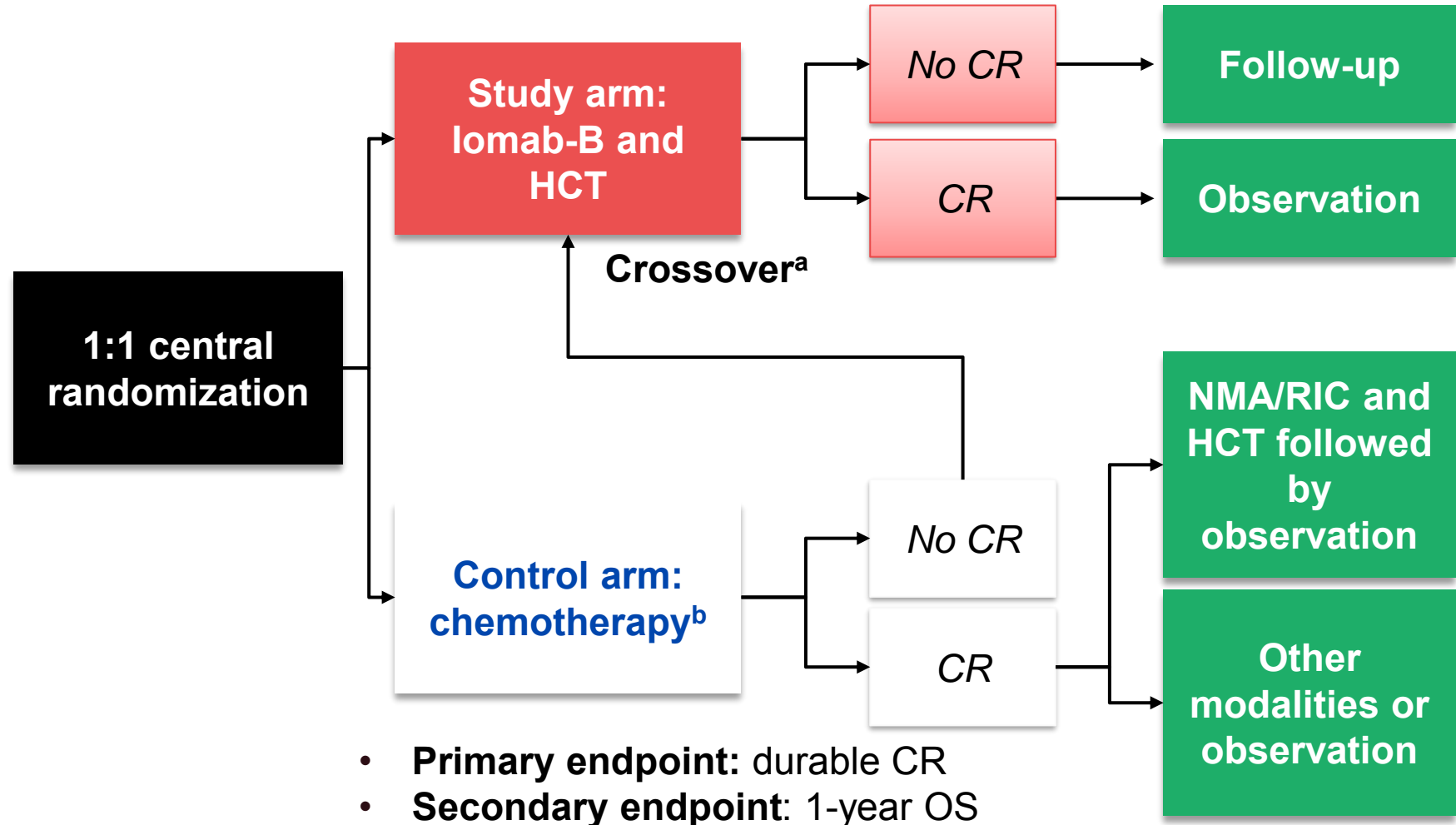
1:1 central randomization

Study arm: Iomab-B and HCT

→ *No CR* → **Follow-up**

→ *CR* → **Observation**

Crossover[a]

Control arm: chemotherapy[b]

→ *No CR* → **NMA/RIC and HCT followed by observation**

→ *CR* → **Other modalities or observation**

- **Primary endpoint:** durable CR
- **Secondary endpoint**: 1-year OS

MAYO CLINIC

SIERRA: Iomab-B Treatment Schedule

Iomab-B Specific

Standard Transplant Procedure

~7 days

~12 days

Dosimetry

Iomab-B
(~10-20 mCi)

Therapy Dose

Iomab-B
(24 Gy to liver,
mean ~600 mCi)

NMA

FLU
30 mg/m^2/day

HCT

TBI
200 cGy

-12 days
to HCT

-4 -3 -2 -1 0

Imaging

Immunosuppression

Therapy dose individualized and calculated
based on upper limit of 24 Gy liver exposure
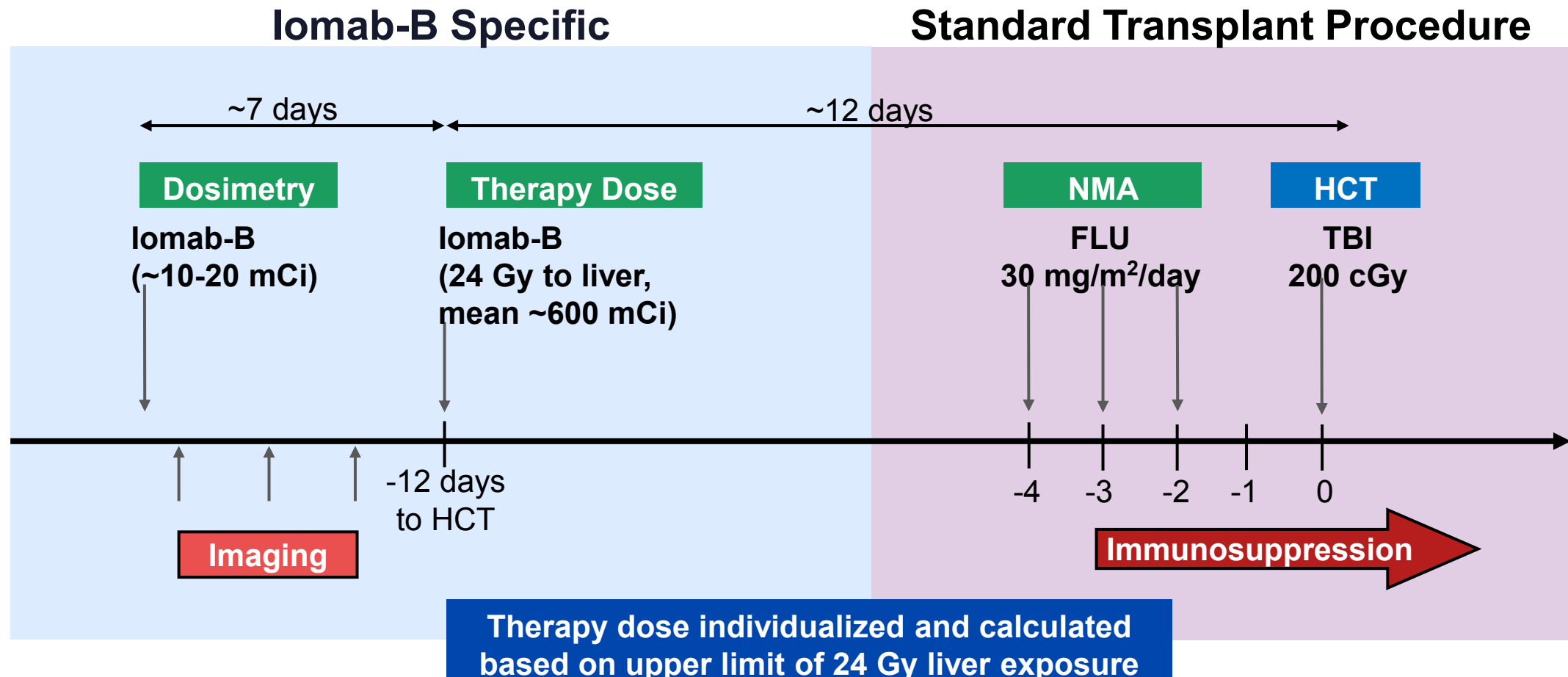
^{131}-Apamistamab vs. Conventional Care

D. EFS in ITT population

	No. of patients	Events, n (%)	Median EFS (95% CI), months
^{131}I-apamistamab	76	66 (86.8)	3.2 (0-4.0)
Conventional care	77	77 (100.0)	0 (NE-NE)
+ Censored			HR, 0.29 (0.20-0.42); P<0.0001
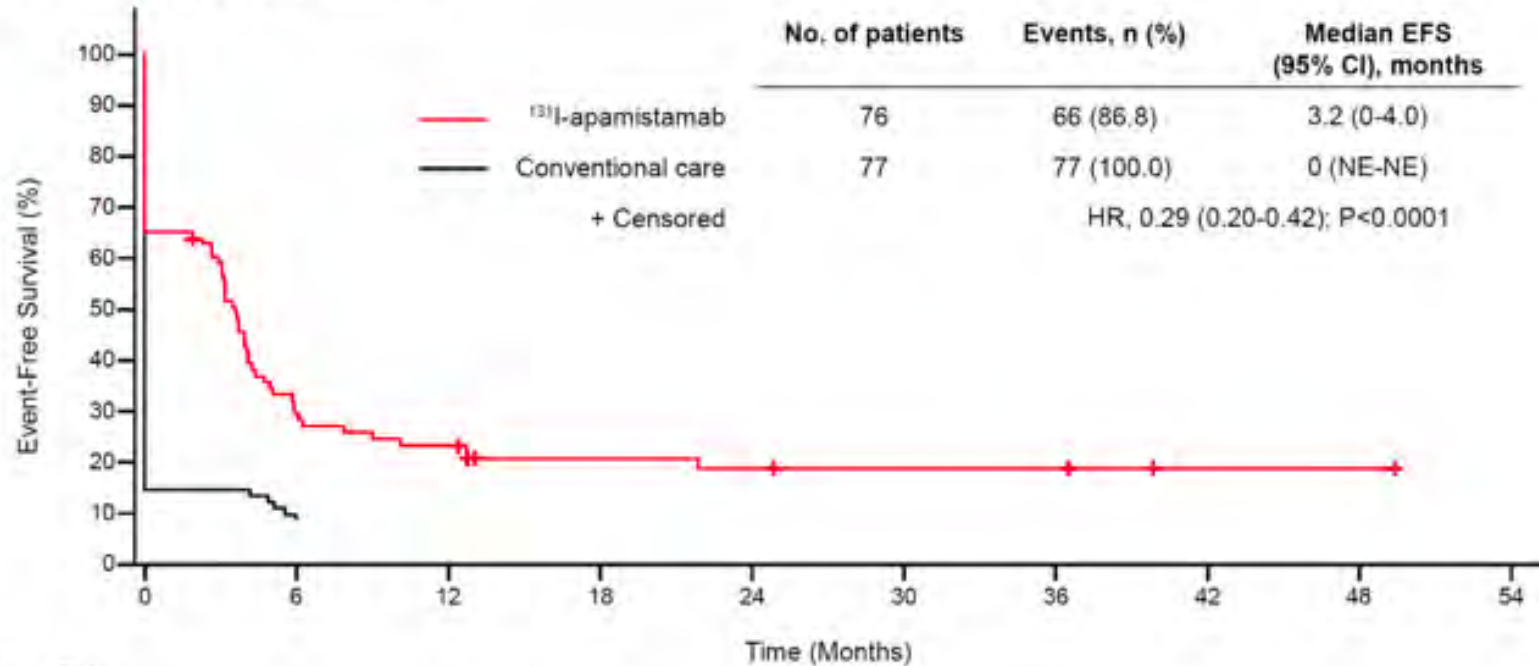
No. at Risk:

^{131}I-apamistamab	76	17	12	5	4	3	3	1	1	0
Conventional care	77	0	0	0	0	0	0	0	0	0

Iomab-B conditioning

Well-tolerated

- Low NRM rates <10%

- Lower incidence of sepsis compared to the CC group (p=0.002)

|	^{131}-Apamistamab(n=76)	Conventional Care (n=77)	Crossover (n=44)
CR/CRp	60.5%	6.5%	52.3%
*Durable CR	17.1%	0% (*p<0.0001)	

^{131}-Apamistamab vs. Conventional Care in TP53$_{mut}$

Table 2: CR and dCR rates by TP53 mutation status and treatment received

Response Type	Iomab-B + Crossover			Conventional Care		
	N	%	95% CI	N	%	95% CI
TP53 Positive	N = 27			N = 10		
CR	15	55.56	(35.33, 74.52)	0	0	–
Durable CR	4	14.81	(4.19, 33.73)	0	0	–
Wildtype	N = 93			N = 23		
CR	54	58.06	(47.38, 68.22)	4	17.39	(4.95, 38.78)
Durable CR	15	16.13	(9.32, 25.20)	0	0	–

Figure 1. Effect of ^{131}I-apamistamab on Survival for Pts with TP53 Mutation

- 24.2% with TP53 mutation in trial
  - Similar CR and dCR with TP53$_{mut}$ vs. TP53$_{wt}$
- Excluding CO, Median OS **5.49** mos. vs. **1.66** mos.in pts who did not receive Iomab-B (Figure)
  - HR=0.23; 95% CI [0.10, 0.52]; (p=0.0002)

Foran et al. TCT (Tandem), San Antonio, TX, Feb. 2024

©2011 MFMER | slide-35
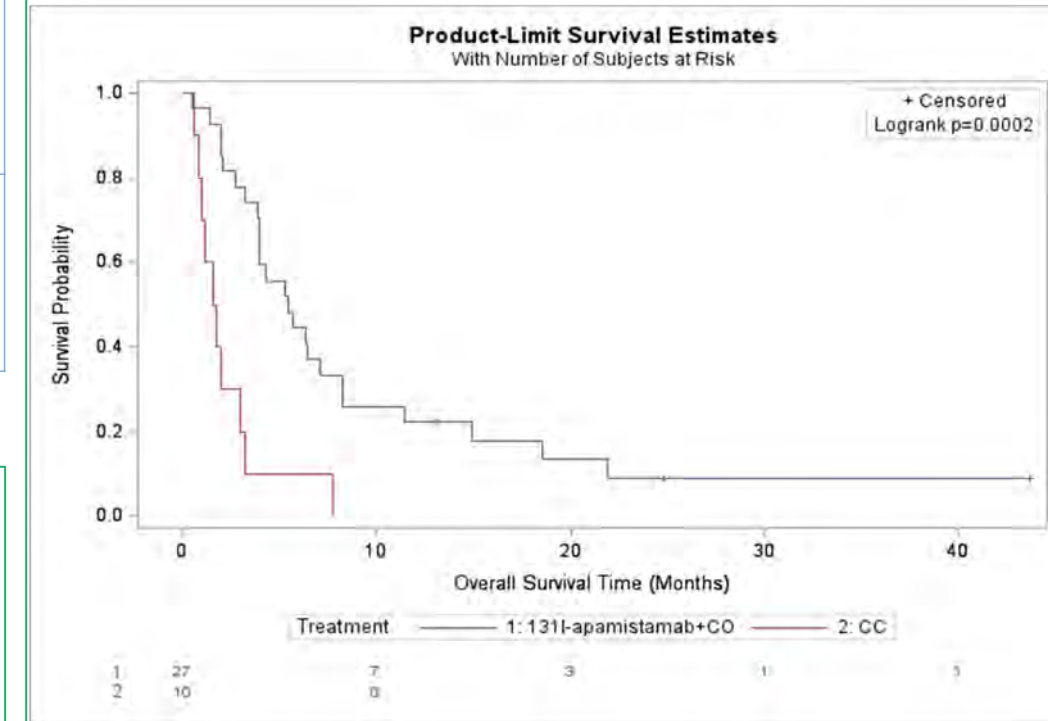
Conclusions

- Goal - Achievement high quality (MRD-negative) remission

- Novel targeted agents, novel toxicities (DS, AIHA)

- Targeting TP53 remains a pressing clinical need
  - Allogeneic transplantation improves OS for eligible patients, although long-term DFS rates remain poor

- Advances in relapsed & refractory AML, including matched donor AlloHCT for high-risk populations

- Importance of supporting clinical trials in diverse clinical populations

"The best interest of the patient is the only interest to be considered, and in order that the sick may have the benefit of advancing knowledge, a union of forces is necessary."

1910: Dr. William J. Mayo   Rush Medical College, commencement address

MAYO CLINIC