Consensus or Controversy? Investigators Discuss Clinical Practice Patterns and Available Research Data Guiding the Management of Hematologic Cancers

Acute Myeloid Leukemia

Friday, December 4, 2020
3:00 PM – 4:30 PM Pacific Time

Faculty

Mark Levis, MD, PhD
Alexander Perl, MD
Daniel A Pollyea, MD, MS
Eytan M Stein, MD
Andrew H Wei, MBBS, PhD

Moderator

Neil Love, MD

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Commercial Support

This activity is supported by educational grants from AbbVie Inc, Astellas, Bristol-Myers Squibb Company, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Helsinn Healthcare SA and Pfizer Inc.

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Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following commercial interests: AbbVie Inc, Acerta Pharma — A member of the AstraZeneca Group, Adaptive Biotechnologies Corporation, Agendia Inc, Agios Pharmaceuticals Inc, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Biodesix Inc, bioTheranostics Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Daiichi Sankyo Inc, Dendreon Pharmaceuticals Inc, Eisai Inc, EMD Serono Inc, Epizyme Inc, Exelixis Inc, Foundation Medicine, Genentech, a member of the Roche Group, Genmab, Genomic Health Inc, Gilead Sciences Inc, GlaxoSmithKline, Grail Inc, Guardant Health, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Infinity Pharmaceuticals Inc, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Lexicon Pharmaceuticals Inc, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Merrimack Pharmaceuticals Inc, Myriad Genetic Laboratories Inc, Natera Inc, Novartis, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Prometheus Laboratories Inc, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sandoz Inc, a Novartis Division, Sanofi Genzyme, Seagen Inc, Sirtex Medical Ltd, Spectrum Pharmaceuticals Inc, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Oncology, Tesaro, A GSK Company, Teva Oncology, Tokai Pharmaceuticals Inc and Verastem Inc.

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Dr Levis — Disclosures

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Contracted Research	Astellas, FUJIFILM Pharmaceuticals USA Inc

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Dr Perl — Disclosures

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Dr Pollyea — Disclosures

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Data and Safety Board/Committee	GlycoMimetics Inc, Takeda Oncology

Dr Stein — Disclosures

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Dr Wei — Disclosures

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Royalties	Former employee of the Walter and Eliza Hall Institute of Medical Research receiving a fraction of its royalty stream related to venetoclax
Speakers Bureau	AbbVie Inc, Genentech, a member of the Roche Group

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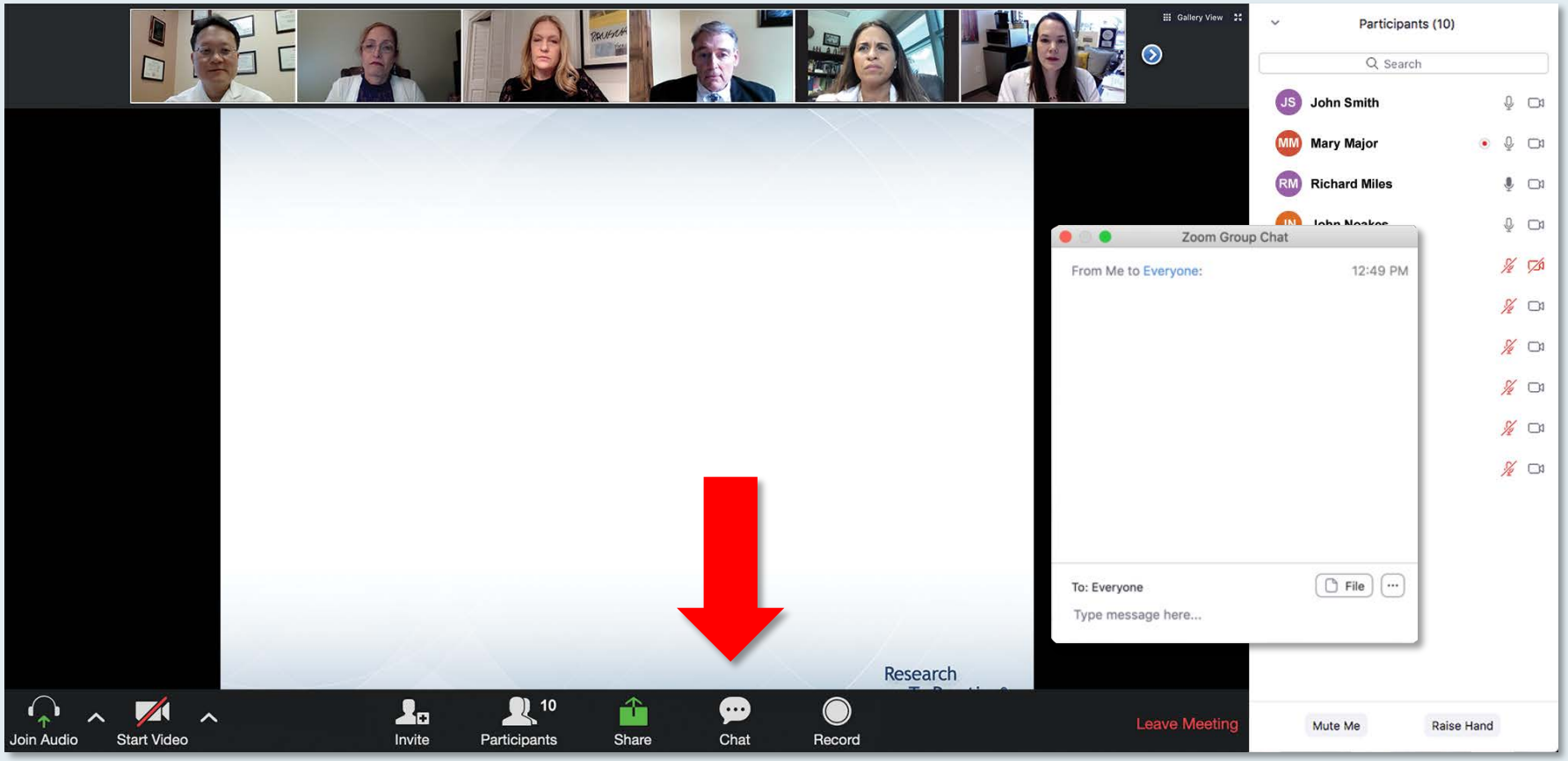

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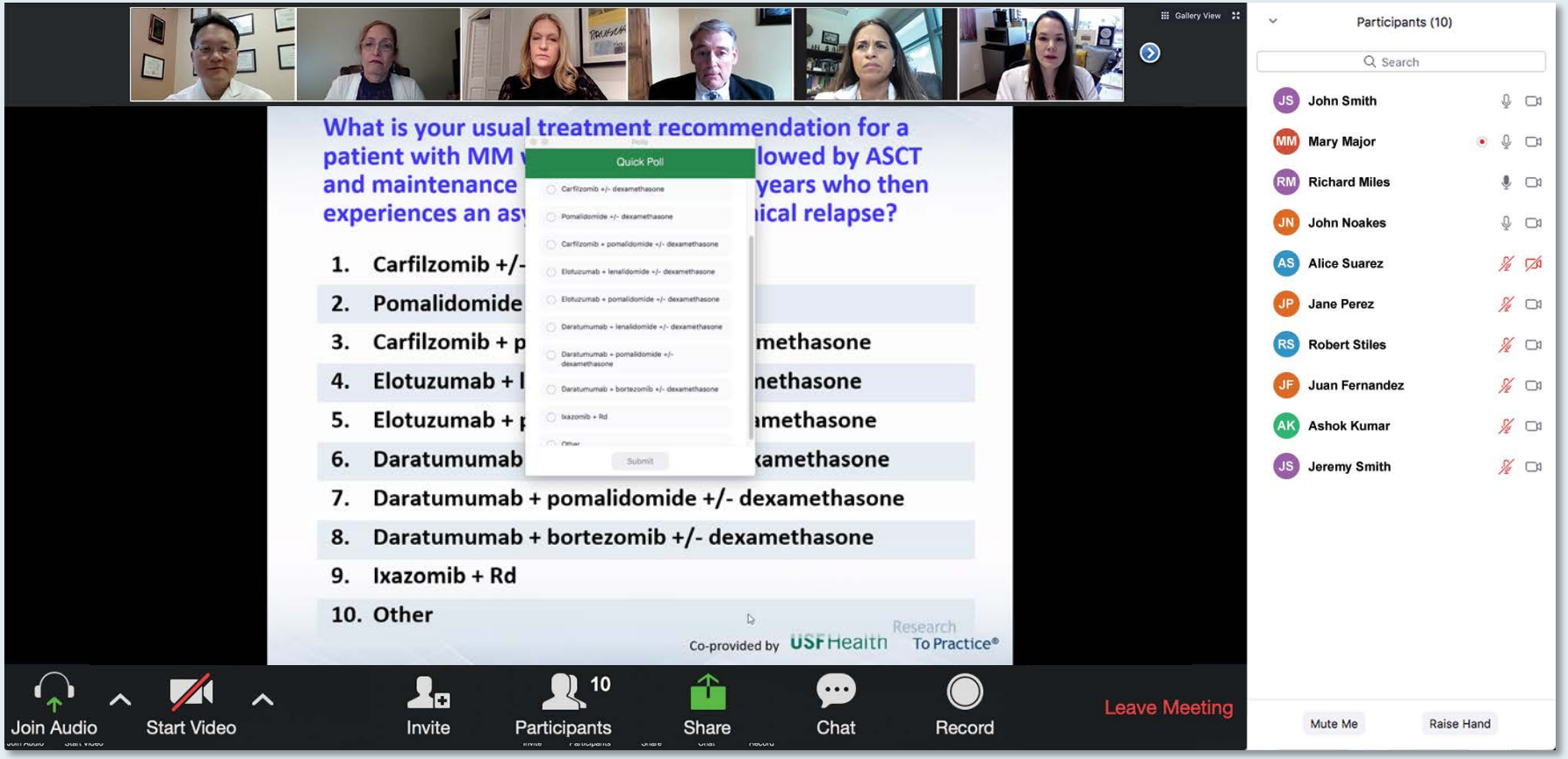

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Results will be shown after everyone has answered.

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Upcoming Webinars

Tuesday, December 8, 2020
5:00 PM – 6:00 PM ET

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

Faculty
Peter C Enzinger, MD
Zev Wainberg, MD, MSc

Moderator
Neil Love, MD

Wednesday, December 9, 2020
12:30 PM – 1:30 PM ET

Meet The Professor: Immunotherapy and Novel Agents in Gynecologic Cancers

Faculty
Gottfried E Konecny, MD

Moderator
Neil Love, MD

Upcoming Webinars

Thursday, December 10, 2020
8:30 PM – 10:00 PM ET

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of HER2-Positive Breast Cancer

Faculty

Carey K Anders, MD
Erika Hamilton, MD
Sara Hurvitz, MD
Mark D Pegram, MD
Sara M Tolaney, MD, MPH

Moderator

Neil Love, MD

Friday, December 11, 2020
8:30 PM – 10:00 PM ET

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Triple-Negative Breast Cancer

Faculty

P Kelly Marcom, MD
Joyce O'Shaughnessy, MD
Hope S Rugo, MD
Professor Peter Schmid, MD, PhD

Moderator

Neil Love, MD

Thank you for joining us!

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

ONCOLOGY TODAY

WITH DR NEIL LOVE

ACUTE MYELOID LEUKEMIA WITH FLT3 MUTATIONS

DR KEITH PRATZ
UNIVERSITY OF PENNSYLVANIA

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Consensus or Controversy? Investigators Discuss Clinical Practice Patterns and Available Research Data Guiding the Management of Hematologic Cancers

Hodgkin and Non-Hodgkin Lymphoma

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John Kuruvilla, MD
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Michael E Williams, MD, ScM

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Neil Love, MD

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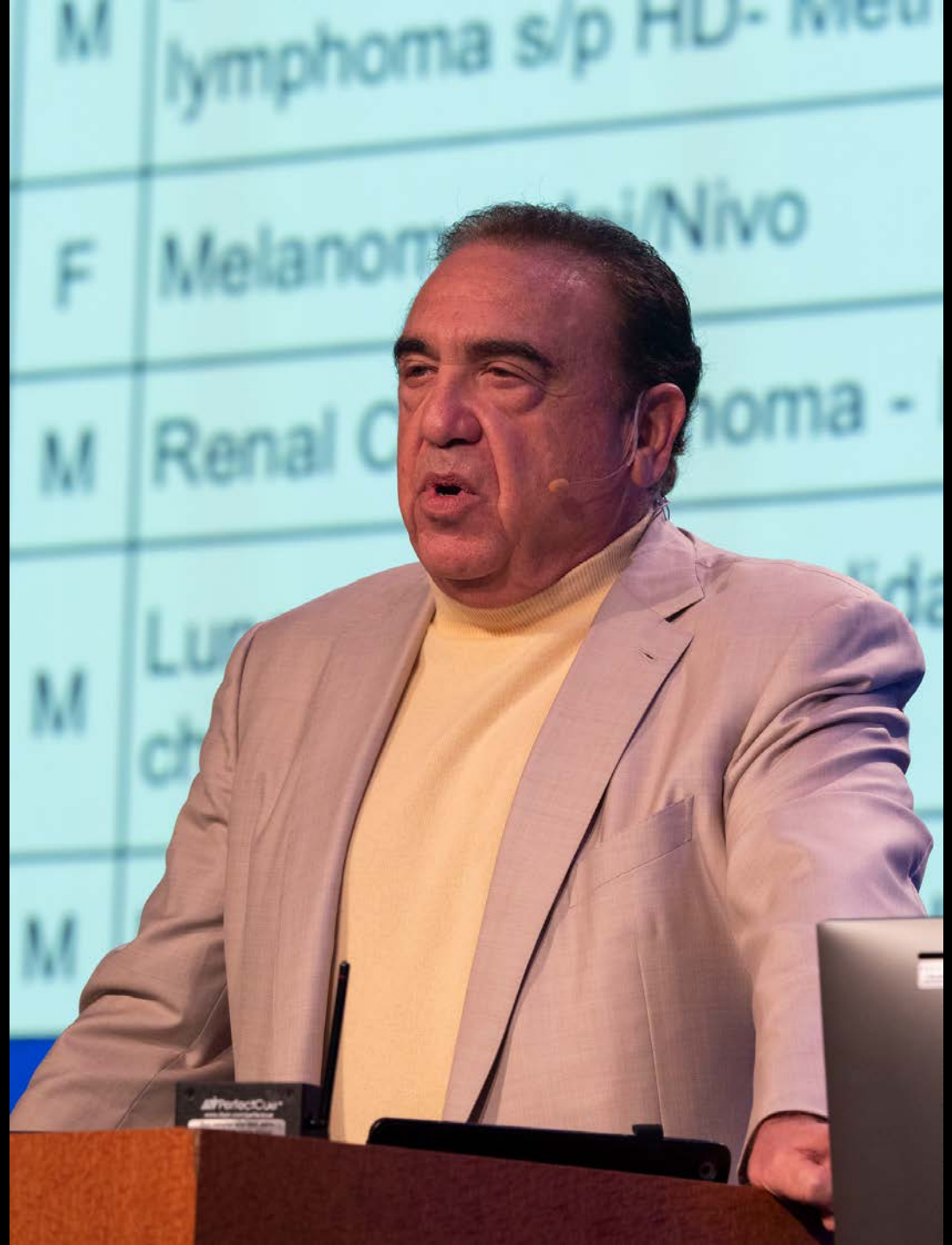
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Exploring Current Management Paradigms
for Patients with Acute Myeloid Leukemia
Not Eligible for Intensive Therapy
Friday, October 25, 2019, 1:15 PM – 3:45 PM
Orlando, Florida
Faculty
Courtney D DiNardo,
Keith W Pratz,
Richard M Ston
Moderat
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Levis,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

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Faculty

Mark Levis, MD, PhD
Director, Adult Leukemia Program
Co-Division Director, Hematologic Malignancies
Professor of Oncology
The Sidney Kimmel Comprehensive Cancer Center
Johns Hopkins Medicine
Baltimore, Maryland

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Clinical Director of Leukemia Services
Robert H Allen, MD Chair in Hematology Research
Division of Hematology
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Aurora, Colorado

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Perelman School of Medicine at the
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Member, Leukemia Program
Abramson Cancer Center of the
University of Pennsylvania
Philadelphia, Pennsylvania

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

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Faculty

Andrew H Wei, MBBS, PhD
Adjunct Professor, Department of Haematology
Alfred Hospital and Monash University
Melbourne, Australia

Moderator
Neil Love, MD
Research To Practice
Miami, Florida

Consensus or Controversy Survey Participants (in Addition to Our Faculty)

Courtney D DiNardo, MD, MSCE
The University of Texas
MD Anderson Cancer Center
Houston, Texas

Alice S Mims, MD
The James Cancer Hospital at The Ohio
State University
Columbus, Ohio

Eunice S Wang MD
Roswell Park Comprehensive Cancer Institute
Buffalo, New York

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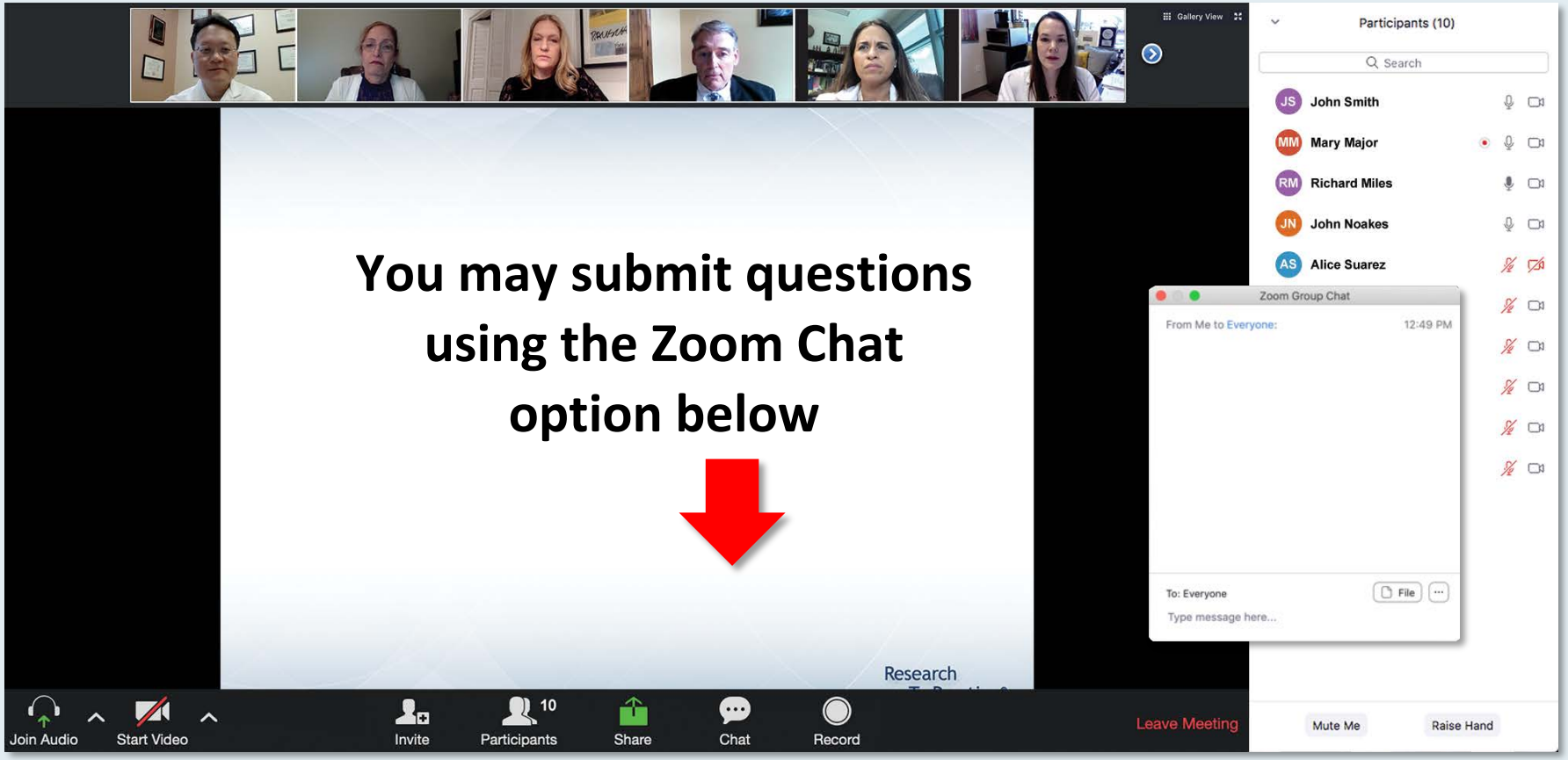

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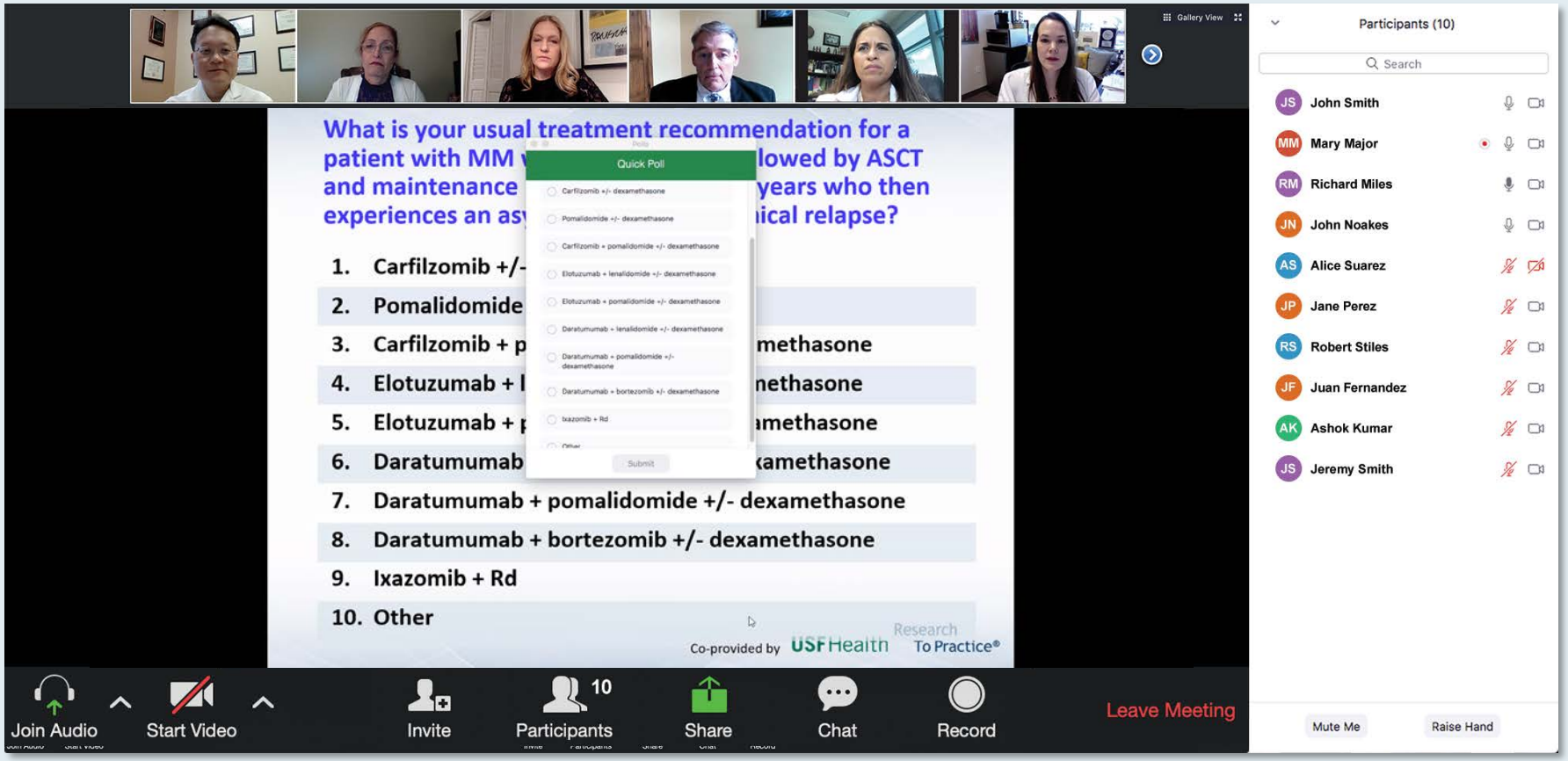

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Recent Advances in Hematologic Oncology: A 4-Part Live Webinar Series Reviewing Key Data and Presentations from the 62nd ASH Annual Meeting

Acute Myeloid Leukemia

Wednesday, January 20, 2021
5:00 – 6:00 PM ET

Faculty
Daniel A Pollyea, MD, MS
Andrew H Wei, MBBS, PhD
Additional faculty to be announced

Multiple Myeloma

Wednesday, February 10, 2021
5:00 – 6:00 PM ET

Faculty
Robert Z Orlowski, MD, PhD
Edward A Stadtmauer, MD
Additional faculty to be announced

Hodgkin and Non-Hodgkin Lymphoma

Wednesday, February 3, 2021
5:00 – 6:00 PM ET

Faculty
John Kuruvilla, MD
John P Leonard, MD
Michael E Williams, MD, ScM

Chronic Lymphocytic Leukemia

Wednesday, February 24, 2021
5:00 – 6:00 PM ET

Faculty
Matthew S Davids, MD, MMSc
Additional faculty to be announced

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ASH AML 2020 Presentation Library

Optimizing the Management of AML in Older Patients or Those Ineligible for Intensive Chemotherapy

Andrew H Wei, MBBS, PhD

Download Slides

Treatment Options for Patients with AML Harboring FLT3 Mutations

Alexander Perl, MD

Download Slides

Management of Newly Diagnosed and Previously Treated AML with IDH Mutations

Eytan M Stein, MD

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Tailoring Induction and Maintenance Therapy for Younger Patients with AML without Targetable Tumor Mutations

Mark Levis, MD, PhD

Download Slides

Other Novel Agents and Investigational Strategies for Patients with AML

Daniel A Pollyea, MD, MS

Download Slides

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Agenda

Module 1: Optimizing the Management of AML in Older Patients or Those Ineligible for Intensive Chemotherapy — Dr Wei

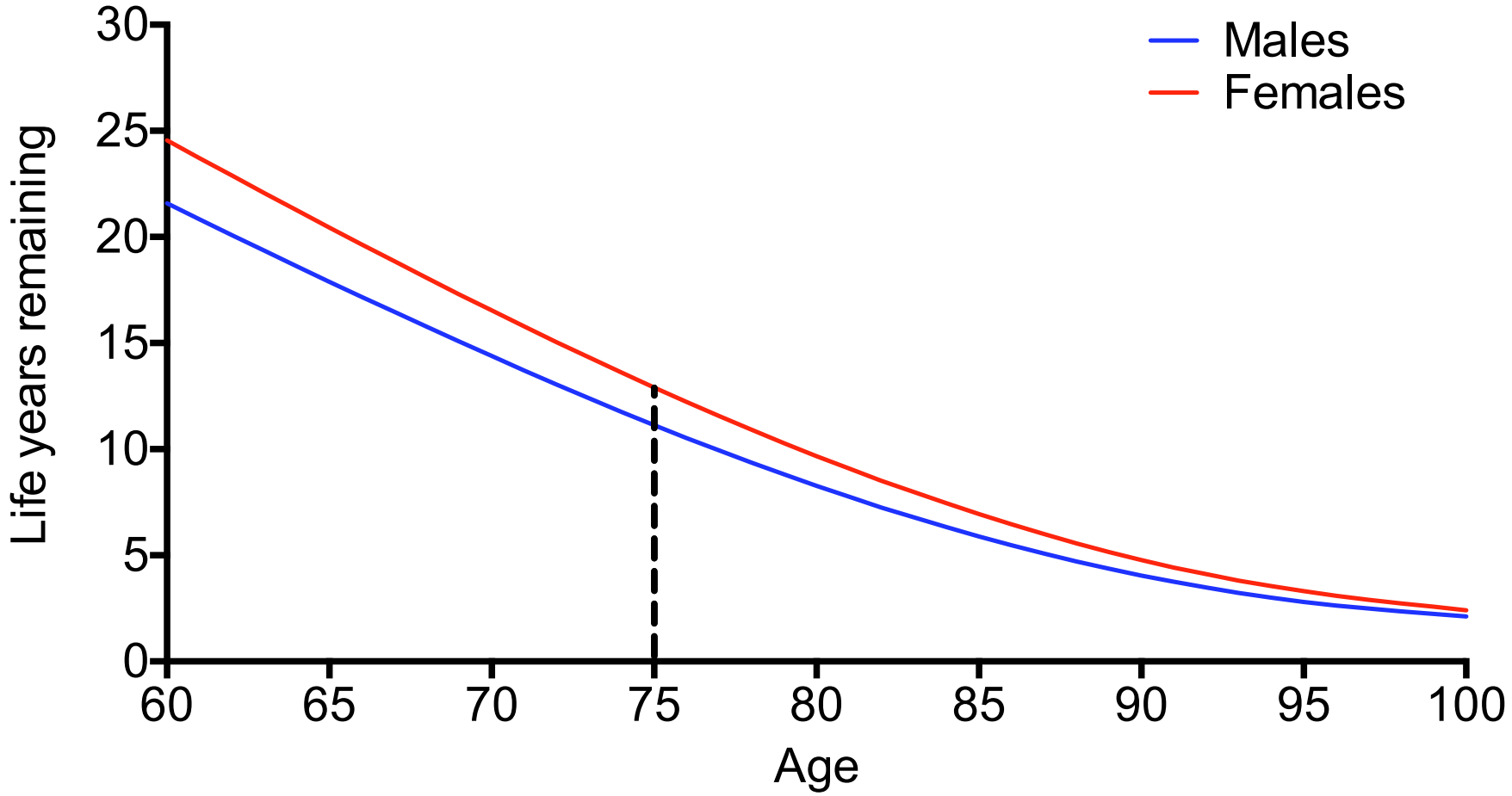
Module 2: Treatment Options for Patients with AML Harboring FLT3 Mutations — Dr Perl

Module 3: Management of Newly Diagnosed and Previously Treated AML with IDH Mutations — Dr Stein

Module 4: Tailoring Induction and Maintenance Therapy for Younger Patients with AML without Targetable Tumor Mutations — Dr Levis

Module 5: Other Novel Agents and Investigational Strategies for Patients with AML — Dr Pollyea

Life expectancy in older people

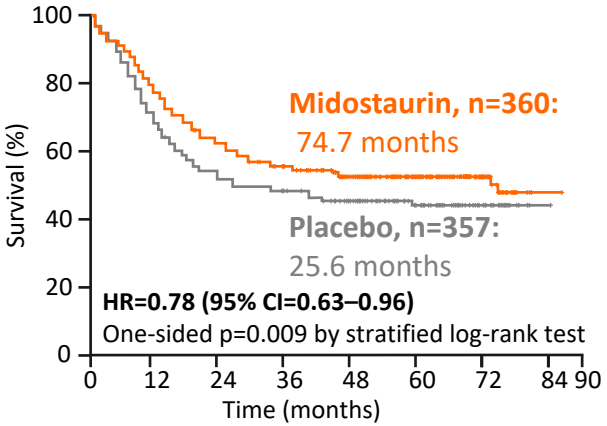


Courtesy of Andrew H Wei, MBBS, PhD

Recent FDA-approved drugs for AML (Survival Outcomes)

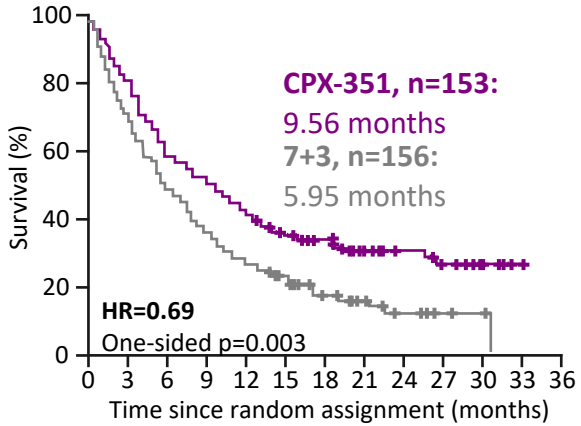
Phase III CALGB-10603 Trial

7+3 + midostaurin[1]



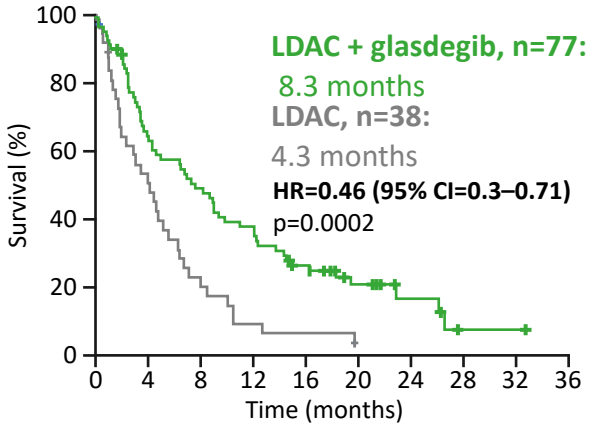
Phase III Study 301

CPX-351[2]



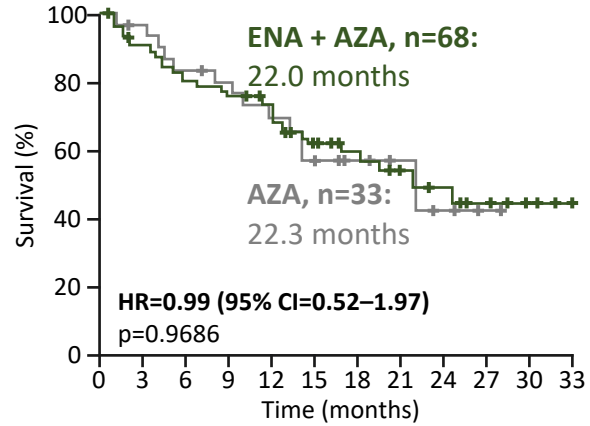
Phase II BRIGHT AML 1003 Trial

LDAC + glasdegib[3]



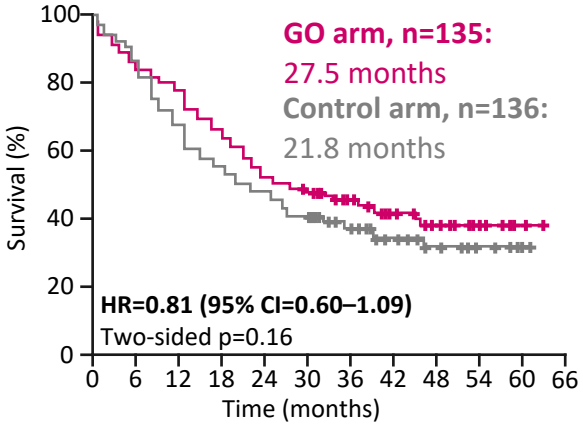
Phase I/II Trial

AZA + enasidenib[4]



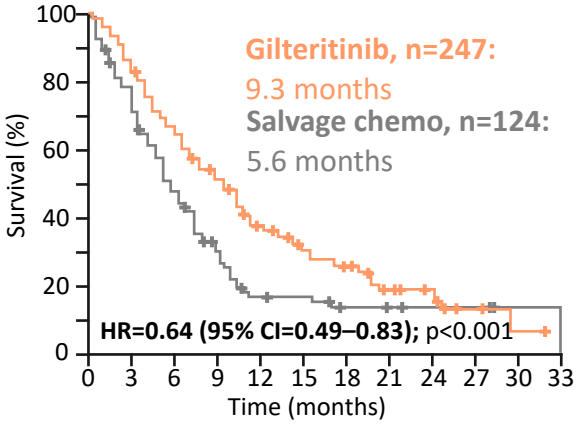
Phase III ALFA-0701 Trial

7+3 + GO[5]



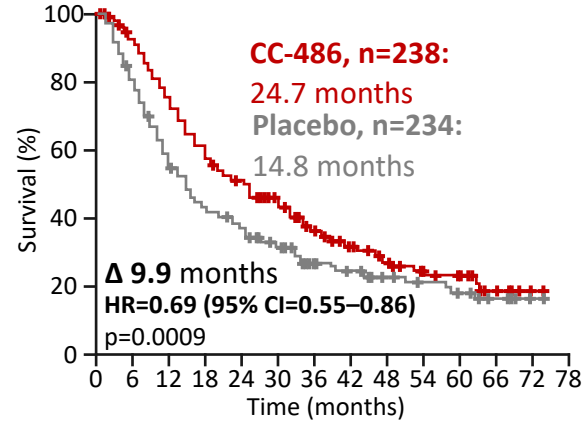
Phase III ADMIRAL Trial

Gilteritinib[6]



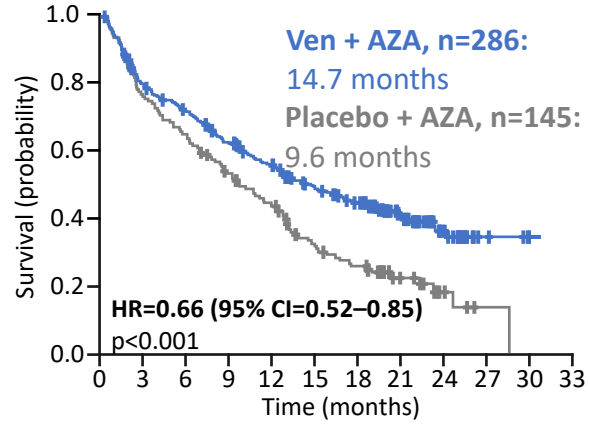
Phase III QUAZAR AML-001 Trial

CC-486[7]



Phase III VIALE-A Trial

AZA + venetoclax[8]



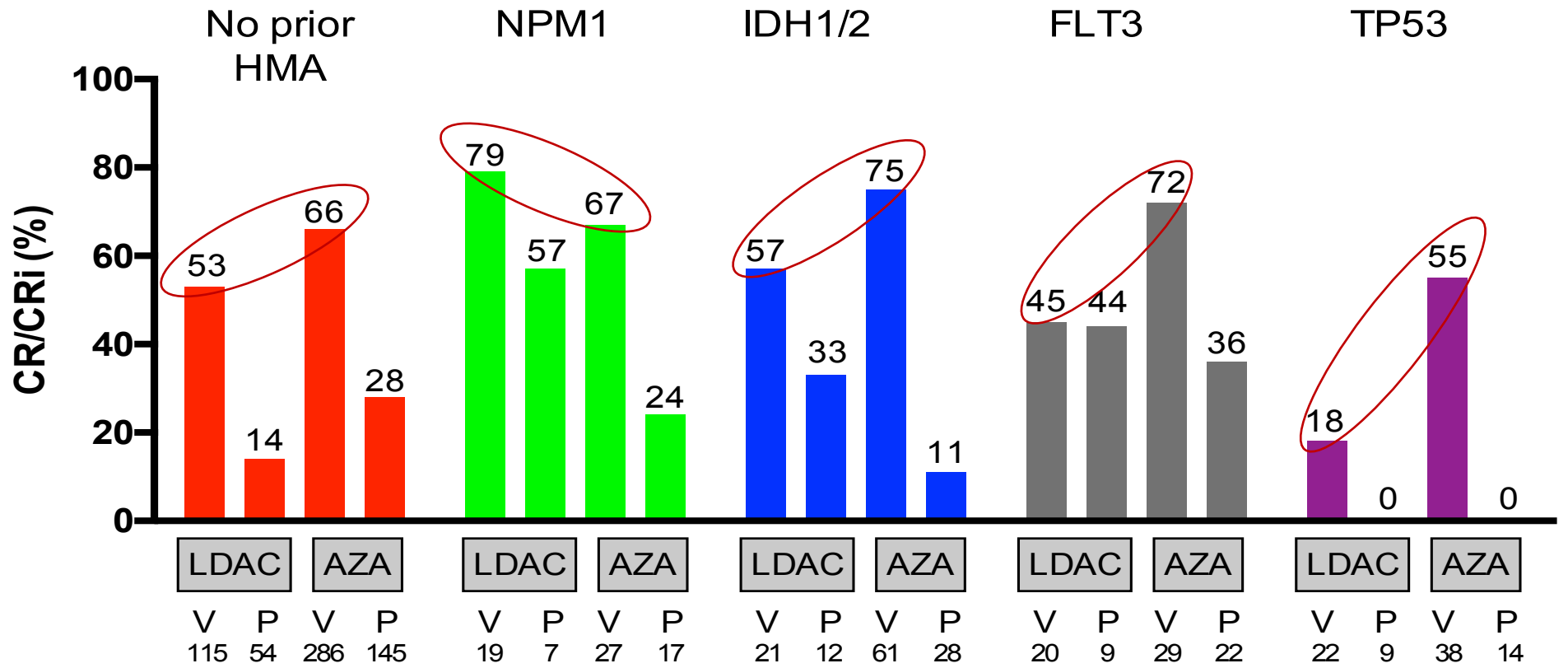
AZA, azacitidine; ENA, enasidenib; GO, gemtuzumab ozogamicin; LDAC, low-dose cytarabine; Ven, venetoclax.

1. Stone M, *et al. N Engl J Med* 2017; **377:**454–464; 2. Lancet JE, *et al. J Clin Oncol* 2018; **36**:2684–2692; 3. Norsworthy KJ, *et al. Clin Cancer Res* 2019; **25:**6021–6025;
4. DiNardo CD, *et al. EHA* 2020; oral presentation S139 5. Lambert J, *et al. Haematologica* 2019; **104**:113–119; 6. Perl AE, *et al. N Engl J Med* 2019; **381:**1728–1740;
7. Wei AH, *et al.* ASH 2019; oral presentation LBA3; 8. DiNardo CD, *et al. N Engl J Med* 2020; **383**:617–629.

Courtesy of Andrew H Wei, MBBS, PhD

Comparison of HMA or LDAC + venetoclax responses

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

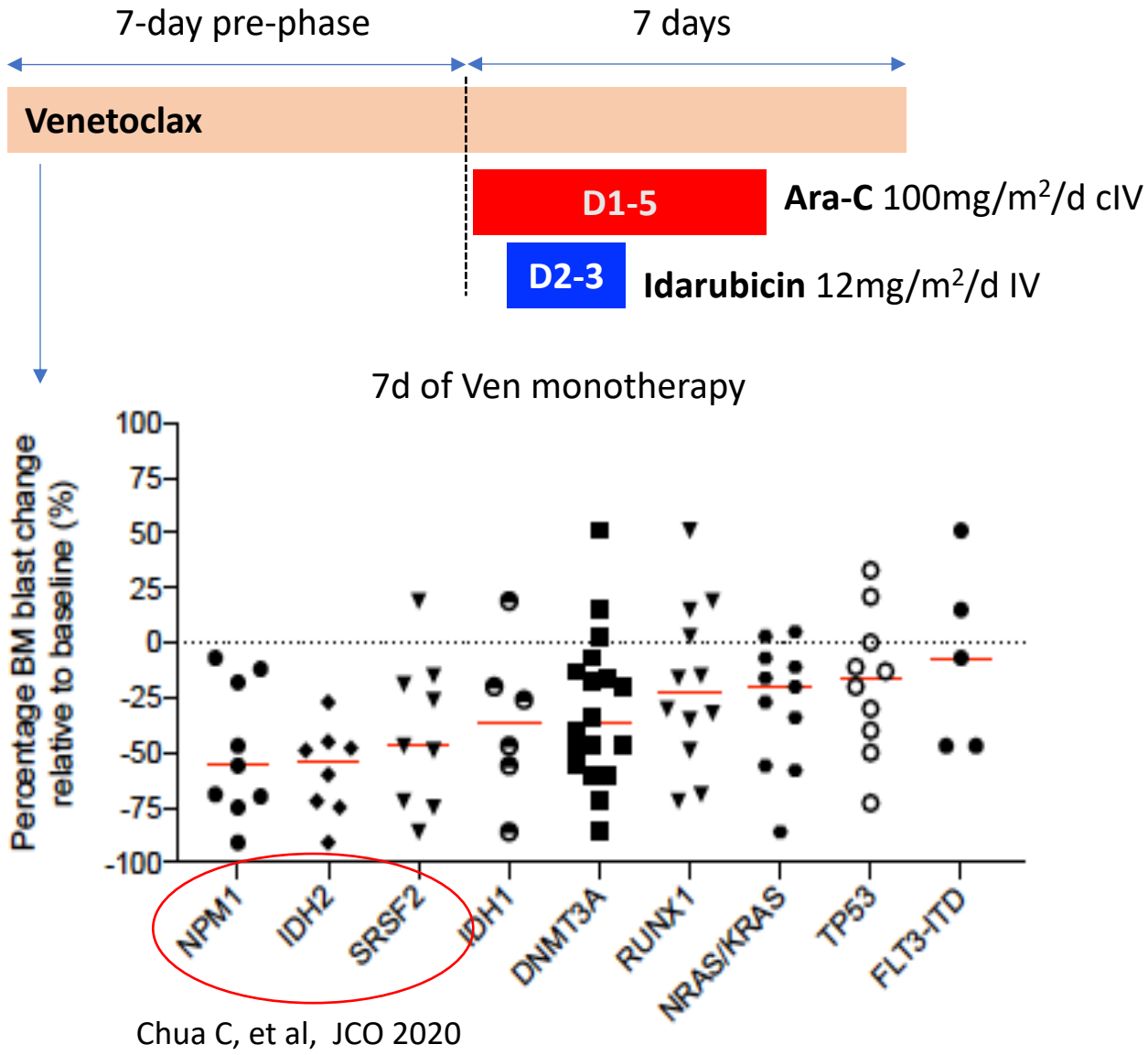


Wei et al, Blood 2020; EHA 2020, Di Nardo et al, EHA 2020

Courtesy of Andrew H Wei, MBBS, PhD

Uncertainties with targeting BCL2 in AML

- Role of monotherapy
- Safety in MF-associated AML
- Optimal dose in combination with anti-fungal agents
- Role of VEN in prior HMA failure
- Management of VEN-AZA treatment failure



Chua C, et al, JCO 2020

Courtesy of Andrew H Wei, MBBS, PhD

Future directions

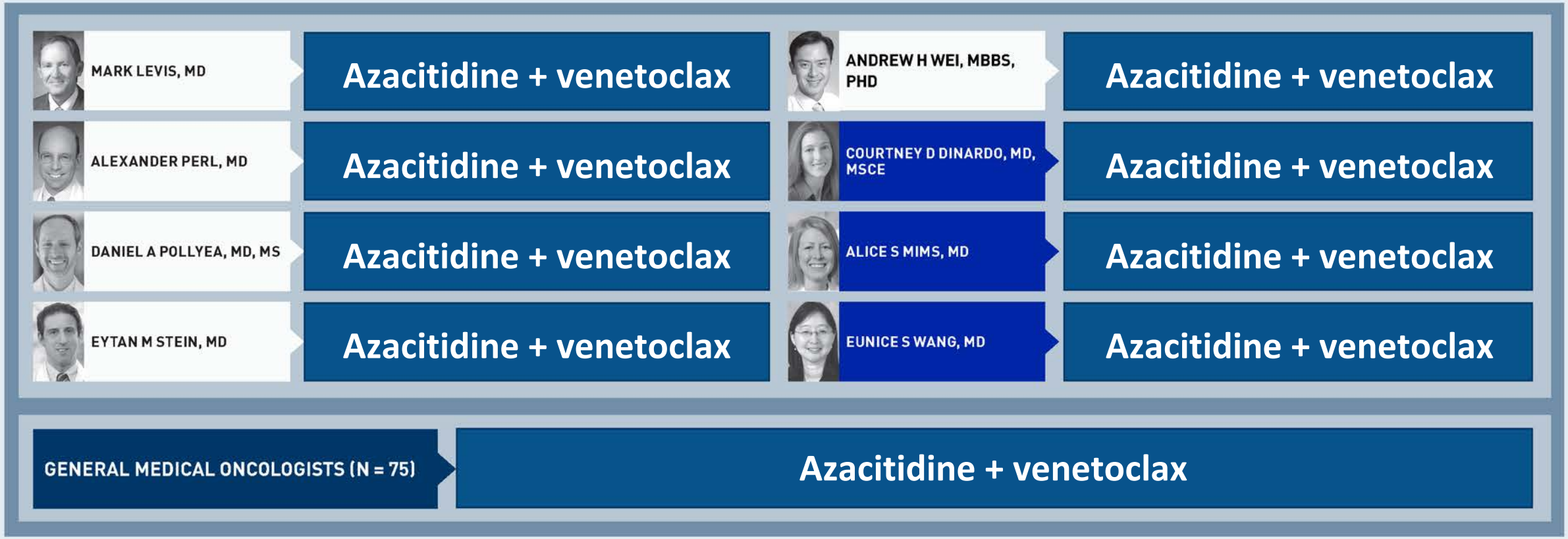
- More intensive combinations
- Combinations with targeted therapies
  - Targeted drugs
  - Immunotherapy
- Maintenance therapy
- More convenient regimens- with CC-486, ASTX727 (decitabine + cedazuridine)

Courtesy of Andrew H Wei, MBBS, PhD

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

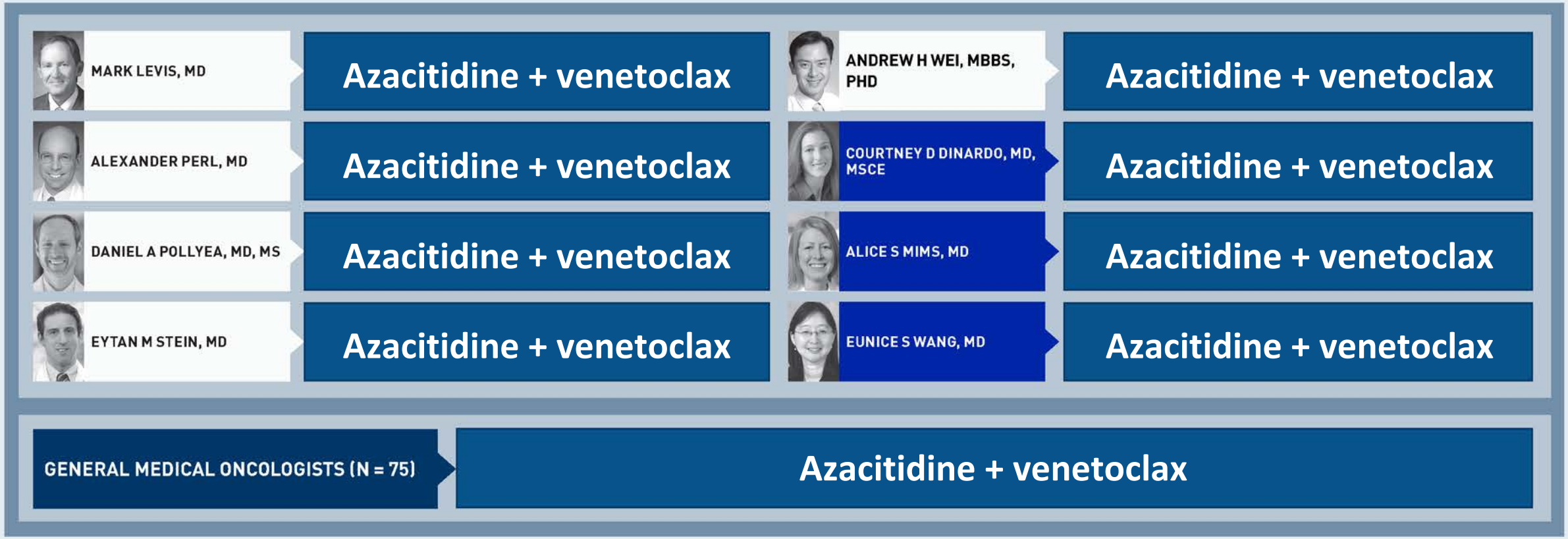
1. Azacitidine
2. Decitabine
3. Azacitidine + venetoclax
4. Decitabine + venetoclax
5. Low-dose cytarabine + venetoclax
6. Low-dose cytarabine + glasdegib
7. Other

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



LDAC, low-dose cytarabine

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



LDAC, low-dose cytarabine

What initial treatment would you recommend for a 65-year-old patient with AML with a performance status (PS) of 2 and a history of hypertension, coronary artery disease and diabetes mellitus, assuming organ function is normal?

1. 7 + 3 induction
2. Azacitidine
3. Decitabine
4. Azacitidine + venetoclax
5. Decitabine + venetoclax
6. Low-dose cytarabine + venetoclax
7. Low-dose cytarabine + glasdegib
8. Other

What initial treatment would you recommend for a 65-year-old patient with AML with a performance status (PS) of 2 and a history of hypertension, coronary artery disease and diabetes mellitus, assuming organ function is normal?

 MARK LEVIS, MD	7 + 3 induction	 ANDREW H WEI, MBBS, PHD	7 + 3 induction if non-adverse cytogenetics
 ALEXANDER PERL, MD	7 + 3 induction	 COURTNEY D DINARDO, MD, MSCE	Azacitidine + venetoclax
 DANIEL A POLLYEA, MD, MS	Azacitidine + venetoclax	 ALICE S MIMS, MD	7 + 3 induction or azacitidine + venetoclax
 EYTAN M STEIN, MD	Azacitidine + venetoclax	 EUNICE S WANG, MD	Azacitidine + venetoclax

GENERAL MEDICAL ONCOLOGISTS (N = 75)	Azacitidine + venetoclax, 7 + 3 induction

How would you compare the global efficacy of venetoclax/HMA or venetoclax/low-dose cytarabine to that of glasdegib/low-dose cytarabine in patients with AML?

 MARK LEVIS, MD	Venetoclax-based therapy is more efficacious	 ANDREW H WEI, MBBS, PHD	Venetoclax-based therapy is more efficacious
 ALEXANDER PERL, MD	Venetoclax-based therapy is more efficacious	 COURTNEY D DINARDO, MD, MSCE	Venetoclax-based therapy is more efficacious
 DANIEL A POLLYEA, MD, MS	Venetoclax-based therapy is more efficacious	 ALICE S MIMS, MD	Venetoclax-based therapy is more efficacious
 EYTAN M STEIN, MD	Venetoclax-based therapy is more efficacious	 EUNICE S WANG, MD	Venetoclax-based therapy is more efficacious

GENERAL MEDICAL ONCOLOGISTS (N = 75)	Venetoclax-based therapy is more efficacious

How would you compare the tolerability/toxicity of venetoclax/HMA or venetoclax/low-dose cytarabine to that of glasdegib/low-dose cytarabine in patients with AML?

1. About the same
2. Venetoclax-based therapy has less toxicity
3. Glasdegib/low-dose cytarabine has less toxicity
4. There are currently not enough data
5. I don’t know

How would you compare the tolerability/toxicity of venetoclax/HMA or venetoclax/low-dose cytarabine to that of glasdegib/low-dose cytarabine in patients with AML?

 MARK LEVIS, MD	Venetoclax-based therapy has less toxicity	 ANDREW H WEI, MBBS, PHD	Glasdegib/LDAC has less toxicity
 ALEXANDER PERL, MD	Venetoclax-based therapy has less toxicity	 COURTNEY D DINARDO, MD, MSCE	About the same
 DANIEL A POLLYEA, MD, MS	Not enough data to answer	 ALICE S MIMS, MD	About the same
 EYTAN M STEIN, MD	Venetoclax-based therapy has less toxicity	 EUNICE S WANG, MD	Glasdegib/LDAC has less toxicity

GENERAL MEDICAL ONCOLOGISTS (N = 75)	Venetoclax-based therapy has less toxicity

Case Presentation – Dr Wei: A 78-year-old woman with AML with 34% marrow blasts

- 78yo lady
- Dec 2014: AML 34% blasts (IDH2 R140Q)
  - Rx LDAC + VEN → CR
  - Ceased in July 2016 (15 cycles)
  - IDH2 R140Q still present
- Jan 2020: Relapse 51% blasts (IDH2 R140Q, new SRSF2)
  - Rx enasidenib → MLFS EOC4 2% blasts
- FLT3-ITD relapse
  - Rx gilteritinib

Learning points
- Patient able to cease therapy
- Relapse 3.5 years after ceasing therapy
- Important to look for targetable causes of clonal evolution with targeted therapy

Courtesy of Andrew H Wei, MBBS, PhD

Agenda

Module 1: Optimizing the Management of AML in Older Patients or Those Ineligible for Intensive Chemotherapy — Dr Wei

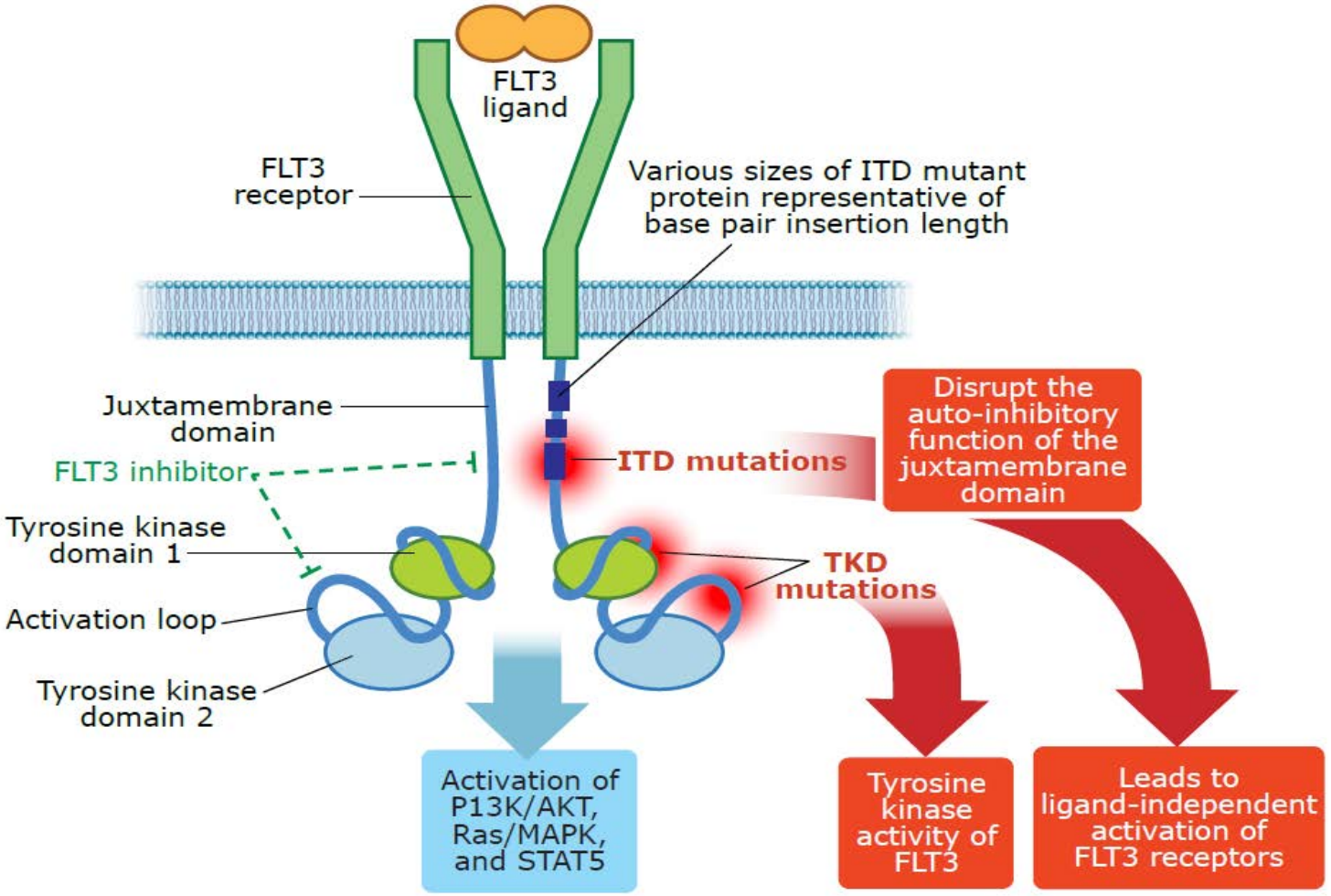
Module 2: Treatment Options for Patients with AML Harboring FLT3 Mutations — Dr Perl

Module 3: Management of Newly Diagnosed and Previously Treated AML with IDH Mutations — Dr Stein

Module 4: Tailoring Induction and Maintenance Therapy for Younger Patients with AML without Targetable Tumor Mutations — Dr Levis

Module 5: Other Novel Agents and Investigational Strategies for Patients with AML — Dr Pollyea

FLT3 mutations in AML



- Incidence
  - *FLT3*-ITD 20-25%
  - *FLT3*-TKD 5-10%
- Clinical features
  - Leukocytosis
  - High marrow blast percent
  - Proliferative disease
- Genetic associations
  - Diploid karyotype
  - NPM1 mutation
  - t(6;9)
  - t(15;17)
- Frequently subclonal
  - gained at relapse/progression
  - sometimes lost at relapse/progression

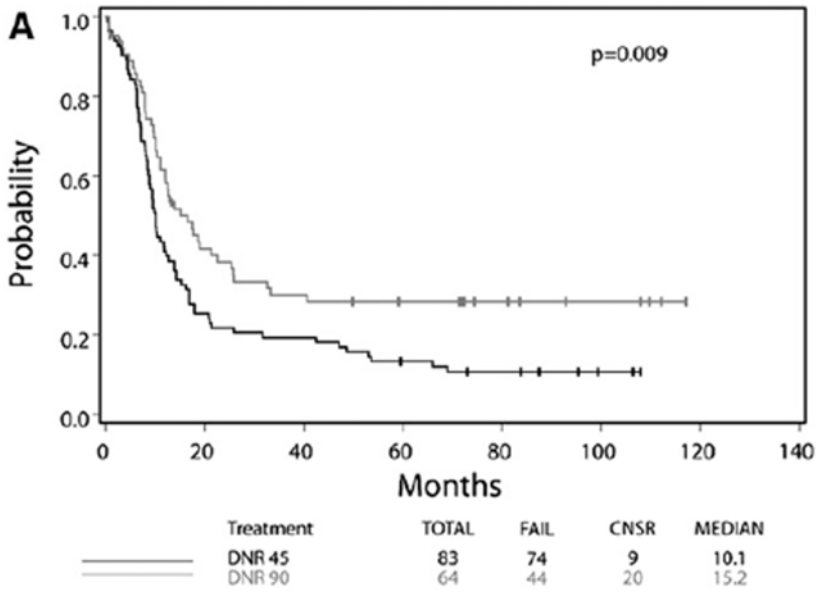
ITD= internal tandem duplication
TKD= tyrosine kinase domain

Slide courtesy of Ashkan Emadi

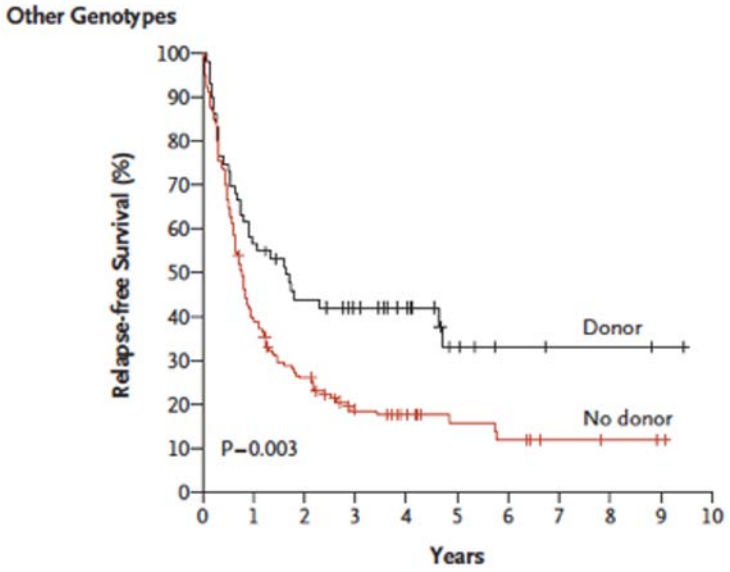
Courtesy of Alexander Perl, MD

3 therapies improve FLT3-ITD+ AML cure rates

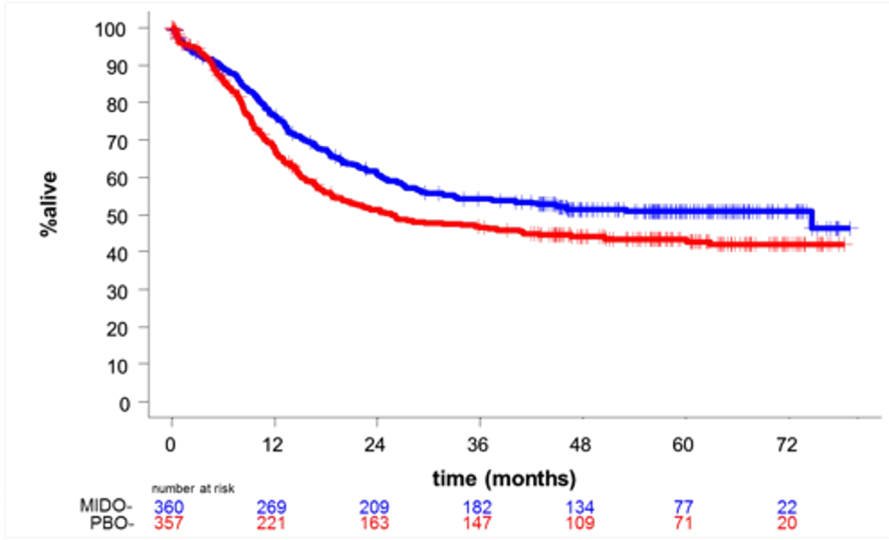
High dose daunorubicin



First remission AlloHSCT



Midostaurin



Note: includes FLT3-ITD (77%) and FLT3-D835 (23%)
57% underwent alloHSCT

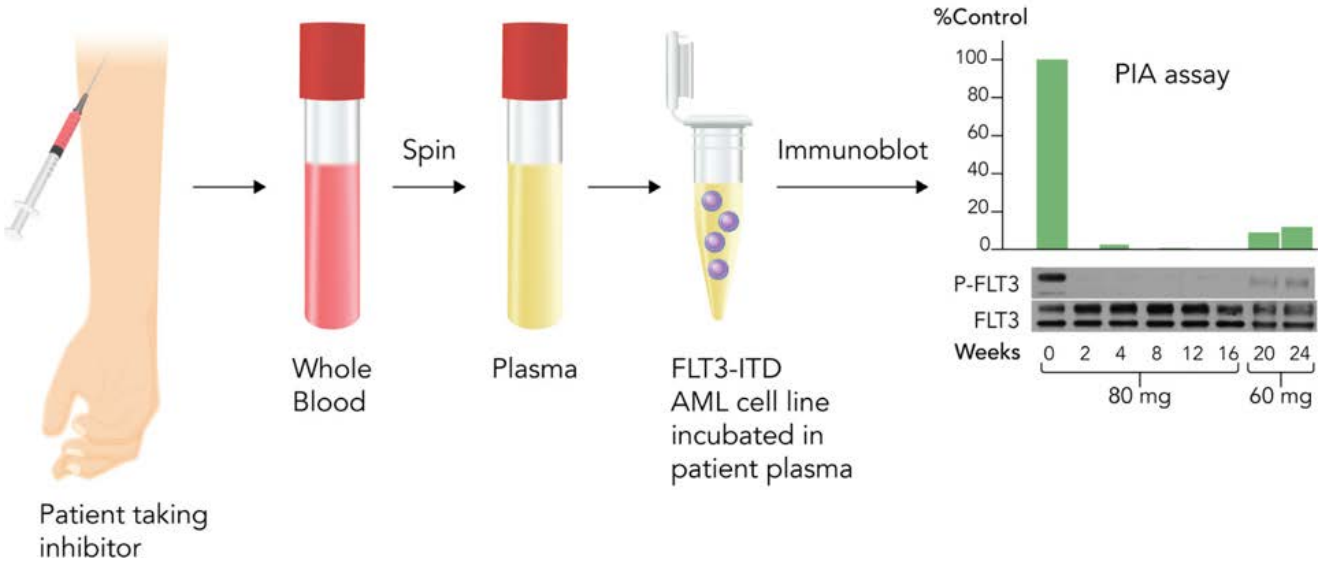
Courtesy of Alexander Perl, MD

Luskin MR, et al. *Blood*. 2016 Mar 24;127(12):1551-8
Schlenk RF, et al. N Engl J Med. 2008 May 1;358(18):1909-18.
Stone RM, et al. *N Engl J Med*. 2017 Aug 3;377(5):454-464

Potency and selectivity of FLT3 inhibitors

		IC_{50} (medium)	IC_{50} (plasma)	Single agent clinical activity	Kinase inhibition
1st gen	Lestaurtinib	2 nM	700 nM	-	**Type 1**
	Midostaurin	6 nM	~1000 nM	-	**Type 1**
	Sorafenib	3 nM	~265 nM	+/-	**Type 2**
2nd gen	Quizartinib	1 nM	18 nM	+	**Type 2**
	Crenolanib	2 nM	48 nM	+	**Type 1**
	Gilteritinib	3 nM	43 nM	+	**Type 1**

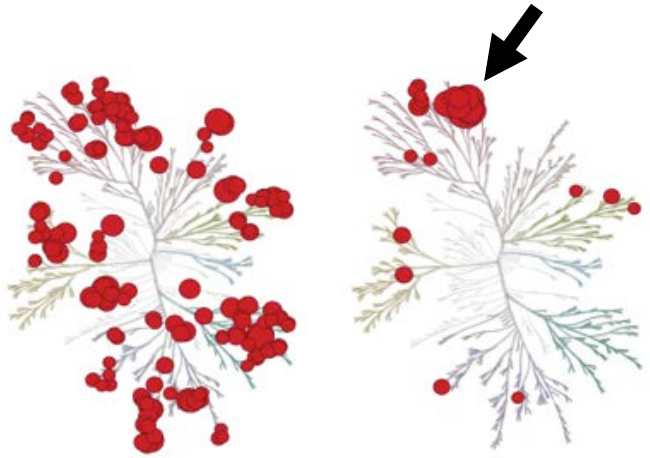
The plasma inhibitory activity (PIA) assay for FLT3



Courtesy of Alexander Perl, MD

Type 2 inhibitors: resistance due to FLT3-D835
Type 1 inhibitors: active against FLT3-D835, limited potential for on-target resistance

Class 3 RTK's:
FLT3, KIT, CSF1R, PDGFRA/B

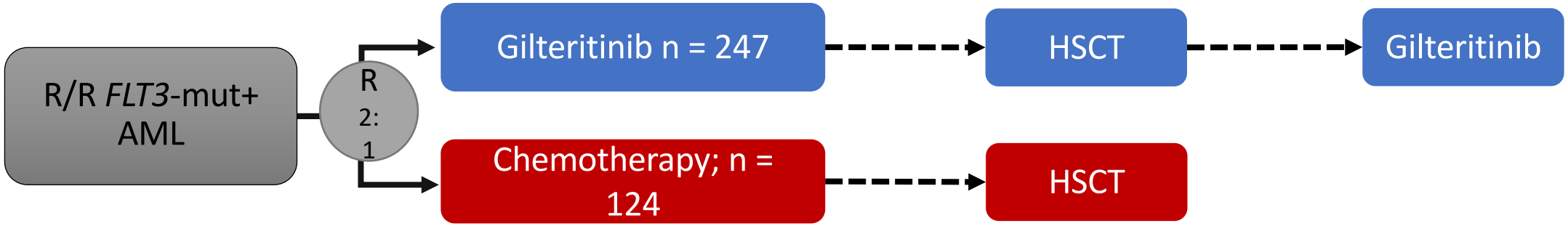


Midostaurin **Quizartinib**

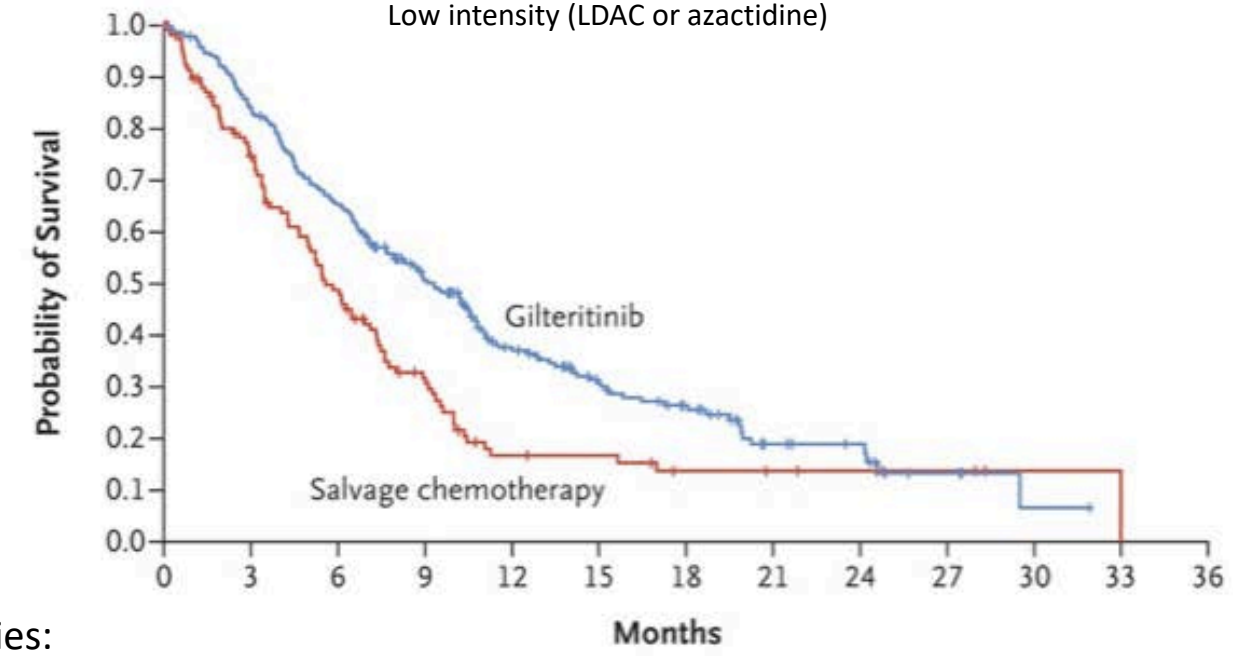
Pratz KW, et al. Blood 2010;115(7):1425-32
Zarrinkar PP, et al. Blood. 2009 Oct 1;114(14):2984-92
Galanis A, et al. Blood 2014 Jan 2;123(1):94-100
Levis M, Perl AE. Blood Adv. 2020 Mar 24;4(6):1178-1191
Smith CC, et al. Nature. 2012 Apr 15;485(7397):260-3
Tarver TC, et al. Blood Adv. 2020 Feb 11;4(3):514-524

Current relapsed/refractory standard of care: gilteritinib

Gilteritinib Phase 3 (ADMIRAL)



High intensity (MEC or FLAG-IDA)
Low intensity (LDAC or azactidine)



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

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

CR/CRh

34%
15.3%

- Gilteritinib toxicities:
  - Cytopenias, elevation of LFTs, CPK, fevers/rashes (Sweet's syndrome)
  - Uncommon toxicities: differentiation syndrome, QT prolongation

Courtesy of Alexander Perl, MD

Perl AE, et al. *N Engl J Med.* 2019;381:1728-1740.

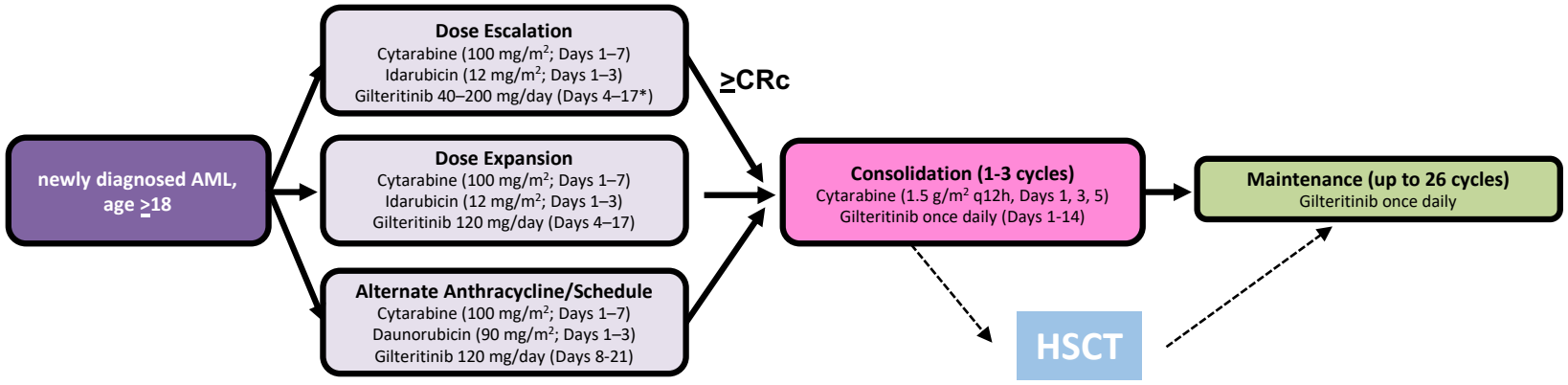
Ongoing questions in the FLT3 world

- The NCCN guidelines only recommend midostaurin for intermediate risk karyotype $FLT3^{mut+}$--does it work in other patients?
- Do FLT3-TKD+ patients benefit from midostaurin?
- Which $FLT3^{mut+}$ patients need transplant?
- Should I give TKI maintenance after transplant?
- Should I give midostaurin or a newer FLT3 inhibitor with induction?
- What should newly diagnosed $FLT3^{mut+}$ unfit patients receive?

Courtesy of Alexander Perl, MD

Newer FLT3 inhibitors in frontline intensive therapy?

Combination: gilteritinib + intensive chemotherapy for newly diagnosed FLT3mut+ AML



up to 2 induction cycles permitted; HSCT followed by maintenance allowed without leaving study

Response FLT3^{mut+} (n=33†)	N (%)
CR	22 (66.7)
CRp	1 (3.0)
CRi	8 (24.2)
PR	0
NR	2 (6.1)
CRc‡	31 (93.9)

Trial	Phase (N)	Control	Maintenance	Primary endpoint	status
Quantum-FIRST (quizartinib)[1]	3 (539)	Placebo	1-3 years	EFS, OS	Enrollment complete
ARO-021 (crenolanib)[2]	3 (510)	Midostaurin	1 year	EFS	Ongoing (US)
PrECOG 0905 (gilteritinib)[3]	2 (170)	Midostaurin	None	FLT3^{mut}(-) CRc	Ongoing (US)
HOVON 156 (gilteritinib)[4]	3 (768)	Midostaurin	1 year	EFS	Ongoing (Europe)

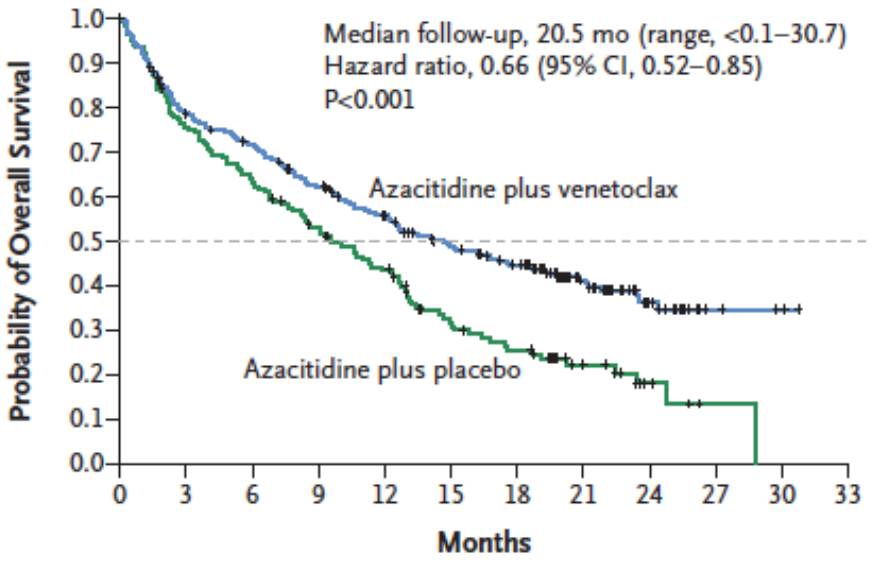
Pratz KW, et al. *Blood* 2018; 132 (Supplement 1): 564

Courtesy of Alexander Perl, MD

1. NCT02668653
2. NCT03258931
3. NCT03836209
4. NCT04027309

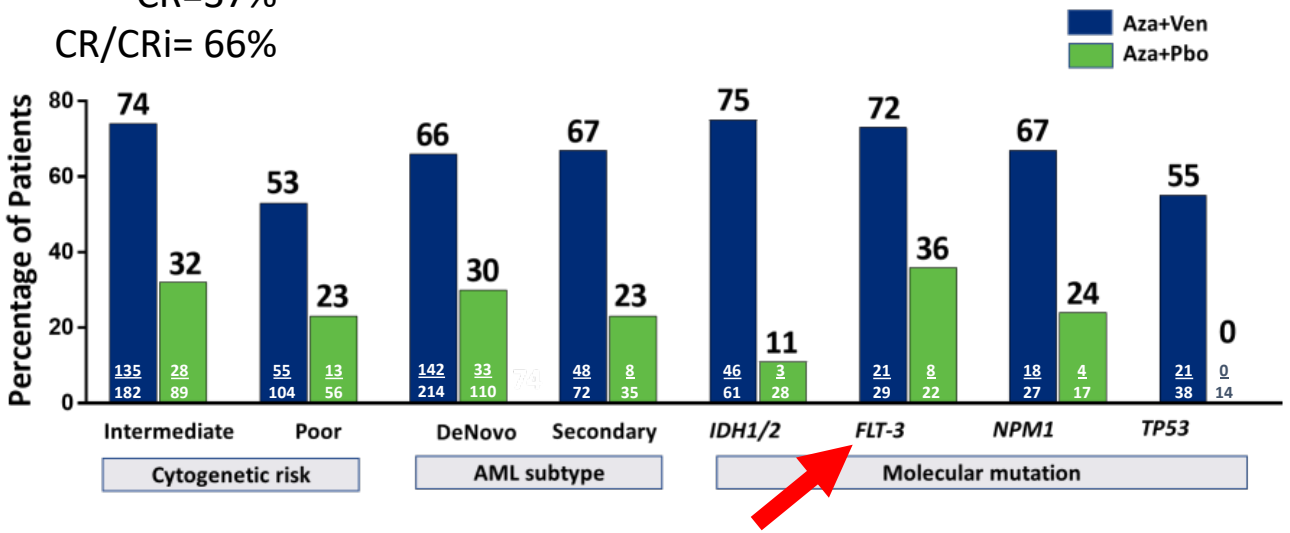
VIALE-A Response Rates (CR+CRi) by Subgroups

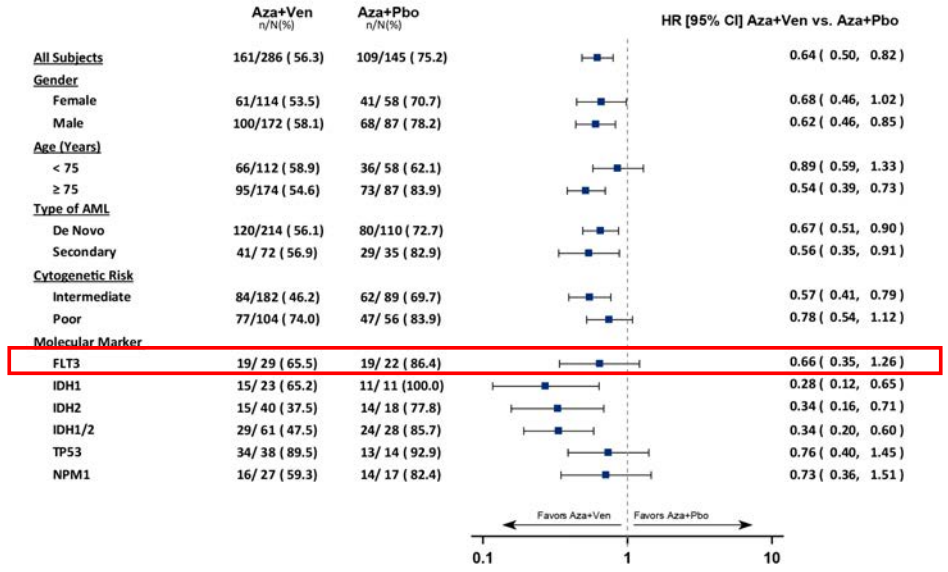
AZA + venetoclax vs. AZA/placebo



HMA + ven: median OS= 14.7 mo
HMA + PBO: median OS=9.6 mo

CR=37%
CR/CRi= 66%





Age >60 unfit or age >75 fit/unfit
All non-CBF subtypes, no prior HMA

Courtesy of Alexander Perl, MD

What would you recommend as first-line therapy to a 60-year-old patient who presents with intermediate-risk AML and a FLT3-TKD mutation?

 MARK LEVIS, MD	7 + 3 induction + midostaurin	 ANDREW H WEI, MBBS, PHD	7 + 3 induction + midostaurin
 ALEXANDER PERL, MD	7 + 3 induction + midostaurin	 COURTNEY D DINARDO, MD, MSCE	7 + 3 induction + midostaurin
 DANIEL A POLLYEA, MD, MS	7 + 3 induction + midostaurin	 ALICE S MIMS, MD	7 + 3 induction + midostaurin
 EYTAN M STEIN, MD	7 + 3 induction + midostaurin	 EUNICE S WANG, MD	7 + 3 induction + midostaurin

GENERAL MEDICAL ONCOLOGISTS (N = 75)	7 + 3 induction + midostaurin

What would you recommend as first-line therapy to a 60-year-old patient who presents with intermediate-risk AML and a FLT3-ITD mutation?

 MARK LEVIS, MD	7 + 3 induction + midostaurin	 ANDREW H WEI, MBBS, PHD	7 + 3 induction + midostaurin
 ALEXANDER PERL, MD	7 + 3 induction + midostaurin	 COURTNEY D DINARDO, MD, MSCE	7 + 3 induction + midostaurin OR 7 + 3 + gilteritinib
 DANIEL A POLLYEA, MD, MS	7 + 3 induction + midostaurin	 ALICE S MIMS, MD	7 + 3 induction + midostaurin
 EYTAN M STEIN, MD	7 + 3 induction + midostaurin	 EUNICE S WANG, MD	7 + 3 induction + midostaurin

GENERAL MEDICAL ONCOLOGISTS (N = 75)	7 + 3 induction + midostaurin

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?

1. Midostaurin
2. 7 + 3 induction + midostaurin
3. HMA
4. HMA + venetoclax
5. HMA + venetoclax + FLT3 inhibitor
6. Low-dose cytarabine + venetoclax
7. Low-dose cytarabine + venetoclax + FLT3 inhibitor
8. Gilteritinib
9. Other

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?

 MARK LEVIS, MD	Azacitidine + venetoclax x 2 → azacitidine + gilteritinib x 2 → gilteritinib	 ANDREW H WEI, MBBS, PHD	Azacitidiine + venetoclax + gilteritinib
 ALEXANDER PERL, MD	Azacitidine + venetoclax	 COURTNEY D DINARDO, MD, MSCE	Azacitidine + venetoclax + gilteritinib
 DANIEL A POLLYEA, MD, MS	Azacitidine + venetoclax	 ALICE S MIMS, MD	Azacitidine + gilteritinib
 EYTAN M STEIN, MD	Azacitidine + venetoclax	 EUNICE S WANG, MD	Azacitidine + venetoclax
GENERAL MEDICAL ONCOLOGISTS (N = 75)	Azacitidine + venetoclax		

What would you recommend as first-line therapy to a 78-year-old patient with a history of cardiac and renal abnormalities (PS 2) who presents with intermediate-risk AML with a FLT3-ITD mutation?

 MARK LEVIS, MD	Azacitidine + venetoclax x 2 → azacitidine + gilteritinib x 2 → gilteritinib	 ANDREW H WEI, MBBS, PHD	Low-dose cytarabine + venetoclax + gilteritinib
 ALEXANDER PERL, MD	Azacitidine + venetoclax	 COURTNEY D DINARDO, MD, MSCE	Gilteritinib or azacitidine + gilteritinib
 DANIEL A POLLYEA, MD, MS	Azacitidine + venetoclax	 ALICE S MIMS, MD	Azacitidine + gilteritinib
 EYTAN M STEIN, MD	Azacitidine + venetoclax	 EUNICE S WANG, MD	Azacitidine + venetoclax

GENERAL MEDICAL ONCOLOGISTS (N = 75)	Azacitidine + venetoclax

A 60-year-old with AML, FLT3 mutation receives 7 + 3 induction + midostaurin, achieves remission. Receives consolidation with 3 cycles of modified high-dose cytarabine + midostaurin. 4 months after completion of therapy, disease progression, FLT3 ITD mutation (allelic burden 0.4) confirmed. What would you recommend?

1. Gilteritinib
2. Sorafenib/azacitidine
3. FLAG-IDA
4. MEC + midostaurin
5. HMA + venetoclax
6. HMA + venetoclax + FLT3 inhibitor
7. Low-dose cytarabine + venetoclax
8. Low-dose cytarabine + venetoclax + FLT3 inhibitor
9. Other

A 60-year-old patient with AML with a FLT3 mutation receives 7 + 3 induction and midostaurin, achieves remission and receives consolidation with 3 cycles of modified high-dose cytarabine and midostaurin. Four months after completion of therapy he experiences disease progression, and a FLT3 ITD mutation (allelic burden of 0.4) is confirmed. What would you recommend?

MEC = mitoxantrone/etoposide/cytarabine

Case Presentation – Dr Perl: A 53-year-old woman with AML with a FLT3-ITD mutation

- 53 YO previously well woman presents (in early 2017) with progressive DOE of 2 weeks duration
  - laboratory tests show hyperleukocytosis (WBC= 301K) with >95% blasts and she is leukapheresed
- Marrow biopsy diagnoses her with AML with myelodysplasia-related changes
  - Karyotype: 46,XX,i(17)(q10)
  - PCR: FLT3-ITD+ (ITD:WT allelic ratio: 0.5), no other mutations on 68 gene NGS panel
- She is induced with 7 + 3 but is refractory after two cycles, genetics unchanged from dx.
- She enrolls on a phase 3 clinical trial of a FLT3 inhibitor vs. standard chemotherapy
  - randomizes to control arm and does not respond
- She receives sorafenib and azacitidine
  - peripheral blasts clear and marrow blasts decrease to <10% after two cycles.
  - FLT3-ITD remains detectable by PCR
- She undergoes a myeloablative HSCT from her HLA-identical sibling.
  - she tolerates transplant well, engrafts with full donor chimerism, and has no detectable FLT3-ITD in marrow
  - She is started on post-HSCT sorafenib maintenance on day +50.

Courtesy of Alexander Perl, MD

Case Presentation – Dr Perl: A 53-year-old woman with AML with a FLT3-ITD mutation (continued)

- Resistance to FLT3 inhibitors can be from several causes
  - Immunologic/loss of GVL
  - Clonal evolution with new on-target mutations (e.g. FLT3-D835 on sorafenib; FLT3-F691L on gilteritinib)
  - Clonal evolution with new off-target mutations (e.g. ras pathway)
  - Selection for FLT3-WT clones

- Therapy for cases with prior TKI is uncertain
  - Only 12% of patients on ADMIRAL had prior TKI
  - Ras pathway mutations commonly emerge at gilteritinib progression
  - If Ras pathway mutations were present at study gilteritinib remained active

- This patient enrolled on a clinical trial of venetoclax + gilteritinib and entered CR2.
  - She remains on study therapy at 14 months duration without relapse and with full donor chimerism

Courtesy of Alexander Perl, MD

McMahon CM, et al. Cancer Discov. 2019 Aug;9(8):1050-1063
Smith CC, et al. Blood; 134(Suppl. 1), 14
Perl AE, et al. Blood 2019; 134 : 3910

Agenda

Module 1: Optimizing the Management of AML in Older Patients or Those Ineligible for Intensive Chemotherapy — Dr Wei

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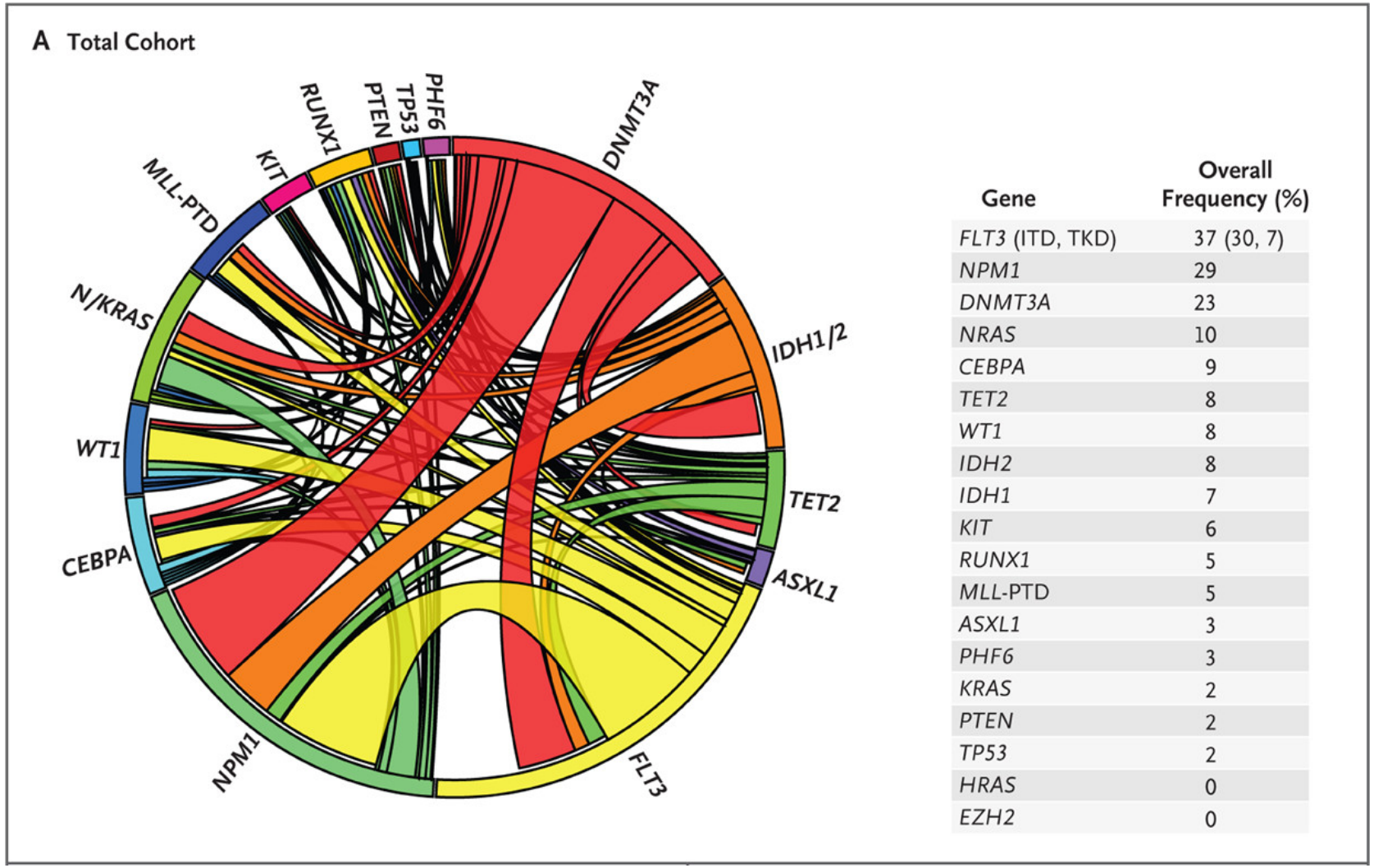
Recurring Mutations in Patients with AML



Gene	Overall Frequency (%)
FLT3 (ITD, TKD)	37 (30, 7)
NPM1	29
DNMT3A	23
NRAS	10
CEBPA	9
TET2	8
WT1	8
IDH2	8
IDH1	7
KIT	6
RUNX1	5
MLL-PTD	5
ASXL1	3
PHF6	3
KRAS	2
PTEN	2
TP53	2
HRAS	0
EZH2	0

Courtesy of Eytan M Stein, MD

Patel JP et al. N Engl J Med 2012;366:1079-1089.

IDH2m and IDH1m: Distinct Genetically Defined Populations

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

Courtesy of Eytan M Stein, MD

Efficacy of Enasidenib in R/R AML

	Relapsed/Refractory AML	
	Enasidenib 100 mg/day (n=214)	All patients (N=280)
Overall response rate, n (%)	38·8% (83/214)	39·6% (111/280)
CR + CRi/CRp	62 (29·0)	78 (27·9)
Best response, n (%)		
Complete remission	42 (19·6)	53 (18·9)
CR with incomplete count recovery (CRi/CRp)	20 (9·3)	25 (8·9)
Partial remission, n (%)	9 (4·2)	17 (6·1)
Morphologic leukemia-free state, n (%)	12 (5·6)	16 (5·7)
Stable disease, n (%)	98 (45·8)	122 (43·6)
Progressive disease, n (%)	19 (8·9)	26 (9·3)
Not evaluable, n (%)	3 (1·4)	4 (1·4)

Courtesy of Eytan M Stein, MD

Stein EM, Dinardo CD, Blood 2017

IDHentify – Randomized Enasidenib versus SOC

Update on Phase 3 IDHENTIFY Trial in Patients with Relapsed or Refractory Acute Myeloma Leukemia

08/25/2020

CATEGORY: Corporate/Financial News

PRINCETON, N.J.—(BUSINESS WIRE)– (NYSE:BMY) The Phase 3 IDHENTIFY study evaluating enasidenib plus best supportive care (BSC) versus conventional care regimens, which include best supportive care (BSC) only, azacitadine plus BSC, low-dose cytarabine plus BSC or intermediate-dose cytarabine plus BSC, did not meet the primary endpoint of overall survival (OS) in patients with relapsed or refractory acute myeloid leukemia (R/R AML) with an isocitrate dehydrogenase-2 (IDH2) mutation. The safety profile of enasidenib was consistent with previously reported findings. The company will complete a full evaluation of the enasidenib data and work with investigators to present detailed results at a future medical meeting.

Ivosidenib – Response and Response Duration

Response	Primary Efficacy Population (N=125)	Relapsed or Refractory AML (N=179)
CR or CRh		
No. of patients	38	54
% (95% CI)	30.4 (22.5–39.3)	30.2 (23.5–37.5)
Median time to CR or CRh (range) — mo	2.7 (0.9–5.6)	2.0 (0.9–5.6)
Median duration of CR or CRh (95% CI) — mo	8.2 (5.5–12.0)	6.5 (5.5–11.1)
CR		
No. of patients	27	39
% (95% CI)	21.6 (14.7–29.8)	21.8 (16.0–28.6)
Median time to CR (range) — mo	2.8 (0.9–8.3)	2.8 (0.9–8.3)
Median duration of CR (95% CI) — mo	9.3 (5.6–18.3)	9.3 (5.6–12.5)
Overall response		
No. of patients	52	70
% (95% CI)	41.6 (32.9–50.8)	39.1 (31.9–46.7)
Median time to first response (range) — mo§	1.9 (0.8–4.7)	1.9 (0.8–4.7)
Median duration of response (95% CI) — mo	6.5 (4.6–9.3)	6.5 (4.6–9.3)

Courtesy of Eytan M Stein, MD

CD Dinardo, EM Stein, S deBotton et. al. N Engl J Med 2018.

Response Among Patients With and Without IDH-DS

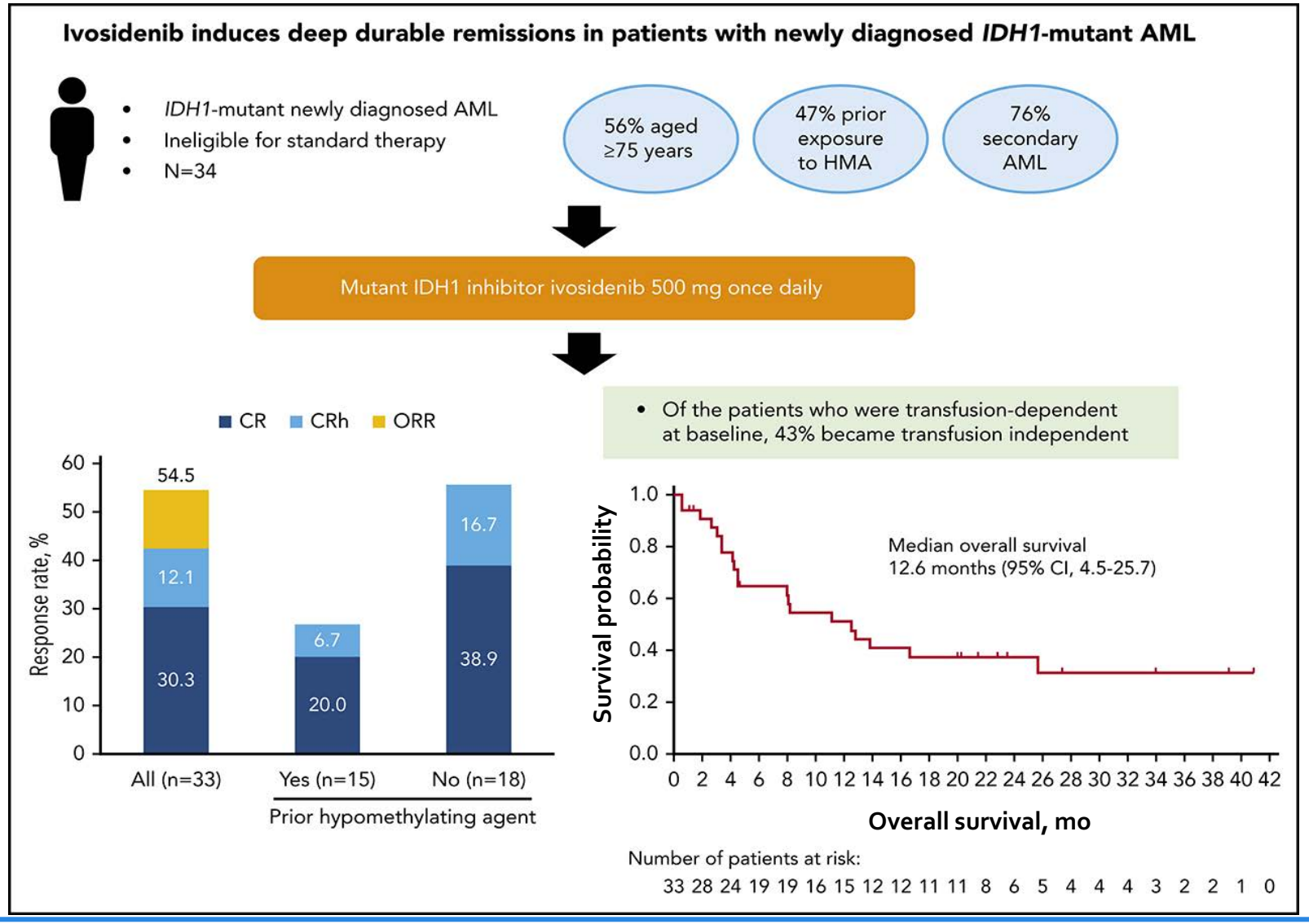
Table 2. Response Among Patients With and Without IDH-DS

Patient Response	IDH-DS, No. (%) (n = 33)[a]	No IDH-DS, No. (%) (n = 248)
Overall response[b]	15 (45.5)	93 (37.5)
CR	6 (18.2)	49 (19.8)
CRi/CRp	6 (18.2)	16 (6.5)
PR	2 (6.1)	14 (5.7)
MLFS	1 (3.0)	14 (5.7)
Stable disease[c]	16 (48.5)	121 (48.8)
Disease progression	1 (3.0)	14 (5.7)

Courtesy of Eytan M Stein, MD

Fathi A, Dinardo CD, et al, JAMA Oncology 2018

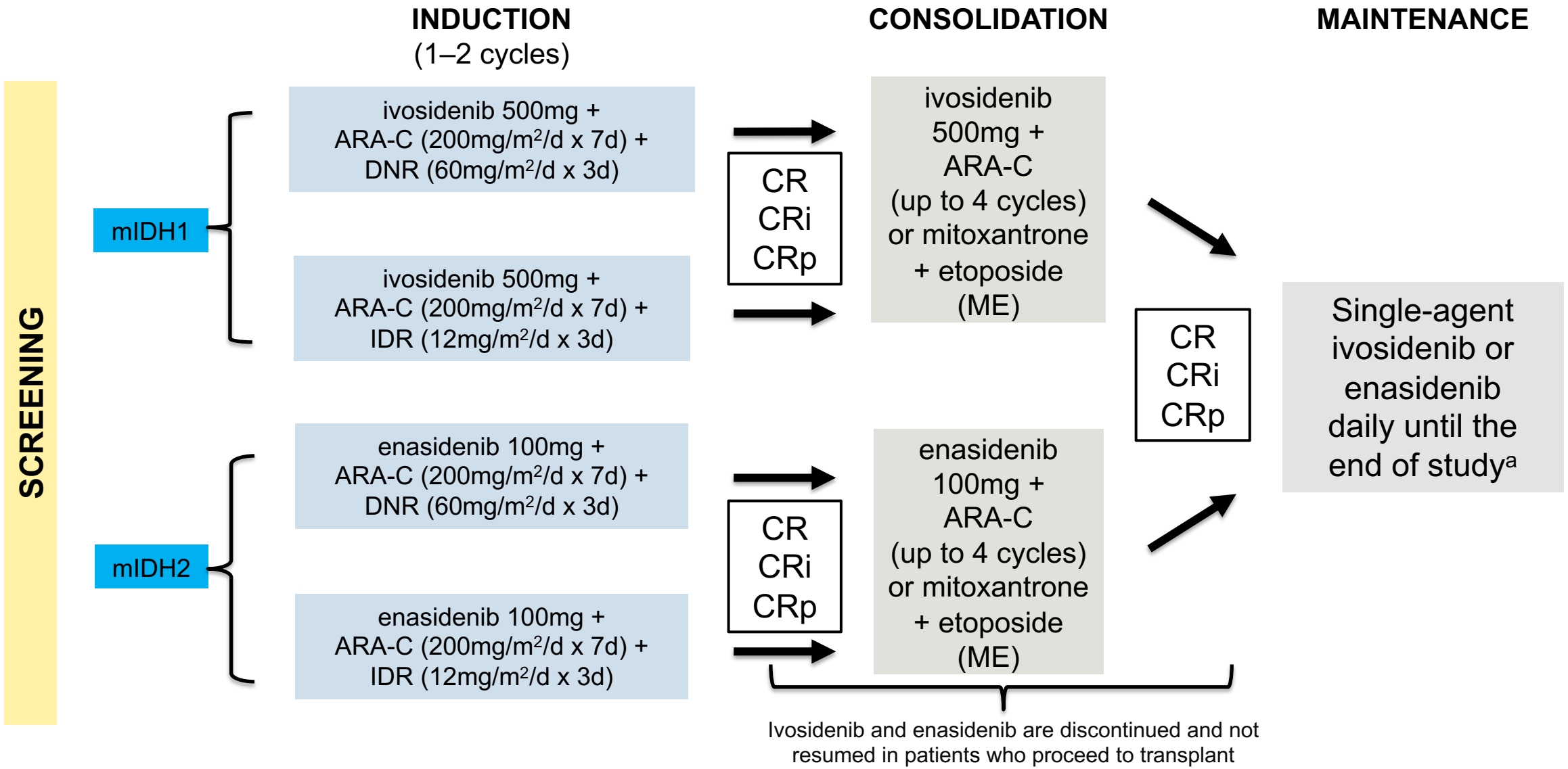
Ivosidenib – Newly Diagnosed AML



Courtesy of Eytan M Stein, MD

Roboz G, et. Al, Blood 2020

Enasidenib/Ivosidenib with Induction Chemotherapy



ARA-C = cytarabine; DNR = daunorubicin; IDR = idarubicin

Courtesy of Eytan M Stein, MD

Enasidenib/Ivosidenib with Induction Chemotherapy

Table 3. Best overall responses at any time during the study in the FAS

Response category	Ivosidenib 500 mg + chemotherapy, n (%)			Enasidenib 100 mg + chemotherapy, n (%)		
	All, N = 60	De novo AML, n = 42	Secondary AML, n = 18	All, N = 91*	De novo AML, n = 56	Secondary AML, n = 35
CR/CRi/CRp	46 (77)	37 (88)	9 (50)	67 (74)	45 (80)	22 (63)
CR	41 (68)	32 (76)	9 (50)	50 (55)	36 (64)	14 (40)
CRi/CRp	5 (8)	5 (12)	—	17 (19)	9 (16)	8 (23)
MLFS	4 (7)	3 (7)	1 (6)	10 (11)	5 (9)	5 (14)
PR	2 (3)	—	2 (11)	2 (2)	1 (2)	1 (3)
Treatment failure†	8 (13)	2 (5)	6 (33)	12 (13)	5 (9)	7 (20)

Courtesy of Eytan M Stein, MD

Stein EM, et al, Blood 2020

What would you recommend as first-line therapy to a 60-year-old patient who presents with intermediate-risk AML with an IDH1 mutation?

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?

1. 7 + 3 induction
2. HMA
3. HMA + venetoclax
4. HMA + venetoclax + ivosidenib
5. Low-dose cytarabine + venetoclax
6. Low-dose cytarabine + venetoclax + ivosidenib
7. HMA + ivosidenib
8. Ivosidenib
9. Other

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?

 MARK LEVIS, MD	Azacitidine + ivosidenib	 ANDREW H WEI, MBBS, PHD	Azacitidine + venetoclax
 ALEXANDER PERL, MD	Azacitidine + venetoclax	 COURTNEY D DINARDO, MD, MSCE	Azacitidine + ivosidenib
 DANIEL A POLLYEA, MD, MS	Azacitidine + venetoclax	 ALICE S MIMS, MD	Ivosidenib
 EYTAN M STEIN, MD	Azacitidine + venetoclax	 EUNICE S WANG, MD	Azacitidine + venetoclax

GENERAL MEDICAL ONCOLOGISTS (N = 75)	Azacitidine + venetoclax, Ivosidenib

What would you recommend as first-line therapy to a 78-year-old patient with a history of cardiac and renal abnormalities (PS = 2) who presents with intermediate-risk AML with an IDH1 mutation?

 MARK LEVIS, MD	Azacitidine + ivosidenib	 ANDREW H WEI, MBBS, PHD	Ivosidenib
 ALEXANDER PERL, MD	Azacitidine + venetoclax	 COURTNEY D DINARDO, MD, MSCE	Ivosidenib
 DANIEL A POLLYEA, MD, MS	Azacitidine + venetoclax	 ALICE S MIMS, MD	Ivosidenib
 EYTAN M STEIN, MD	Azacitidine + venetoclax	 EUNICE S WANG, MD	Ivosidenib

GENERAL MEDICAL ONCOLOGISTS (N = 75)	Ivosidenib, Azacitidine + venetoclax

What would you generally recommend as the next line of treatment for a 60-year-old patient with AML with an IDH2 mutation who has experienced disease progression after 7 + 3 induction, consolidation therapy and transplant?

1. Chemotherapy
2. HMA + venetoclax
3. HMA + venetoclax + enasidenib
4. Low-dose cytarabine
5. Low-dose cytarabine + venetoclax
6. Low-dose cytarabine + venetoclax + enasidenib
7. HMA + enasidenib
8. Enasidenib
9. Other

What would you generally recommend as the next line of treatment for a 60-year-old patient with AML with an IDH2 mutation who has experienced disease progression after 7 + 3 induction, consolidation therapy and transplant?

 MARK LEVIS, MD	Azacitidine + enasidenib	 ANDREW H WEI, MBBS, PHD	Azacitidine + venetoclax
 ALEXANDER PERL, MD	Azacitidine + venetoclax	 COURTNEY D DINARDO, MD, MSCE	Azacitidine + venetoclax
 DANIEL A POLLYEA, MD, MS	Enasidenib	 ALICE S MIMS, MD	Enasidenib
 EYTAN M STEIN, MD	Enasidenib	 EUNICE S WANG, MD	Azacitidine + venetoclax
GENERAL MEDICAL ONCOLOGISTS (N = 75)	Enasidenib		

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

 MARK LEVIS, MD	Enasidenib	 ANDREW H WEI, MBBS, PHD	Enasidenib
 ALEXANDER PERL, MD	Enasidenib	 COURTNEY D DINARDO, MD, MSCE	Azacitidine + venetoclax + enasidenib or enasidenib
 DANIEL A POLLYEA, MD, MS	Enasidenib	 ALICE S MIMS, MD	Enasidenib
 EYTAN M STEIN, MD	Enasidenib	 EUNICE S WANG, MD	Enasidenib
GENERAL MEDICAL ONCOLOGISTS (N = 75)	Enasidenib		

A 65-year-old patient presents with new-onset shortness of breath, hypoxemia and fever 3 weeks into therapy with ivosidenib for relapsed AML. Chest CT reveals diffuse ground glass infiltrates. The patient has an ANC of 600, 27% blasts in the blood and has been receiving prophylaxis with levofloxacin and acyclovir only. What would you recommend?

 MARK LEVIS, MD	Continue ivosidenib and begin antibiotics and corticosteroids
 ALEXANDER PERL, MD	Test for COVID-19; Continue ivosidenib and begin antibiotics and corticosteroids
 DANIEL A POLLYEA, MD, MS	Continue ivosidenib and begin antibiotics and corticosteroids
 EYTAN M STEIN, MD	Continue ivosidenib and begin antibiotics and corticosteroids
 ANDREW H WEI, MBBS, PHD	Continue ivosidenib and begin antibiotics and corticosteroids
 COURTNEY D DINARDO, MD, MSCE	Continue ivosidenib and begin antibiotics and corticosteroids
 ALICE S MIMS, MD	Continue ivosidenib and begin antibiotics and corticosteroids
 EUNICE S WANG, MD	Continue ivosidenib and begin antibiotics and corticosteroids
GENERAL MEDICAL ONCOLOGISTS (N = 75)	Continue ivosidenib and begin antibiotics and corticosteroids

Case Presentation – Dr Stein: An 86-year-old woman with newly diagnosed AML with an IDH2 mutation

- 86 year old woman with newly diagnosed AML associated with mutations in IDH2, RUNX1 and DNMT3A.
- Physical exam is normal. Peformance status is 1.
- Labs notable for pancytopenia with WBC of 3 (ANC of 0.5), Hgb of 8 and platelets of 13.
- Started on treatment with aza/ven. Achieves a complete remission with the presence of MRD after one cycle of therapy
- Develops COVID pneumonia, 3 week hospitalization, survives.
- Receives another cycle of aza/ven and relapses with 30% blasts
- Started on enasidenib 100 mg daily. Has brief onset of differentiation syndrome a month into therapy, with lower extremity edema and shortness of breath. Steroids given.
- Achieves an MRD negative complete remission at cycle 3 day 1.

Courtesy of Eytan M Stein, MD

Case Presentation – Dr Stein: A 76-year-old woman with AML with a IDH1 mutation

- 76 year old woman presents with fatigue, shortness of breath, petechiae.
- Exam shows scattered bruising and a petechial rash.
- Labs notable for WBC of 6, hgb of 6.4, platelets of 5.
- Bone marrow biopsy confirms a diagnosis of AML with 55% blasts and mutations in IDH1 and DNMT3A.
- Patient wants to take oral medication – does not want aza or aza/ven– and is started on ivosidenib 500mg qd.
- At cycle 4 day 1, achieves an MRD negative complete remission.
- Is now in a continuous MRD negative complete remission at cycle 60 (5 years!).

Courtesy of Eytan M Stein, MD

Agenda

Module 1: Optimizing the Management of AML in Older Patients or Those Ineligible for Intensive Chemotherapy — Dr Wei

Module 2: Treatment Options for Patients with AML Harboring FLT3 Mutations — Dr Perl

Module 3: Management of Newly Diagnosed and Previously Treated AML with IDH Mutations — Dr Stein

Module 4: Tailoring Induction and Maintenance Therapy for Younger Patients with AML without Targetable Tumor Mutations — Dr Levis

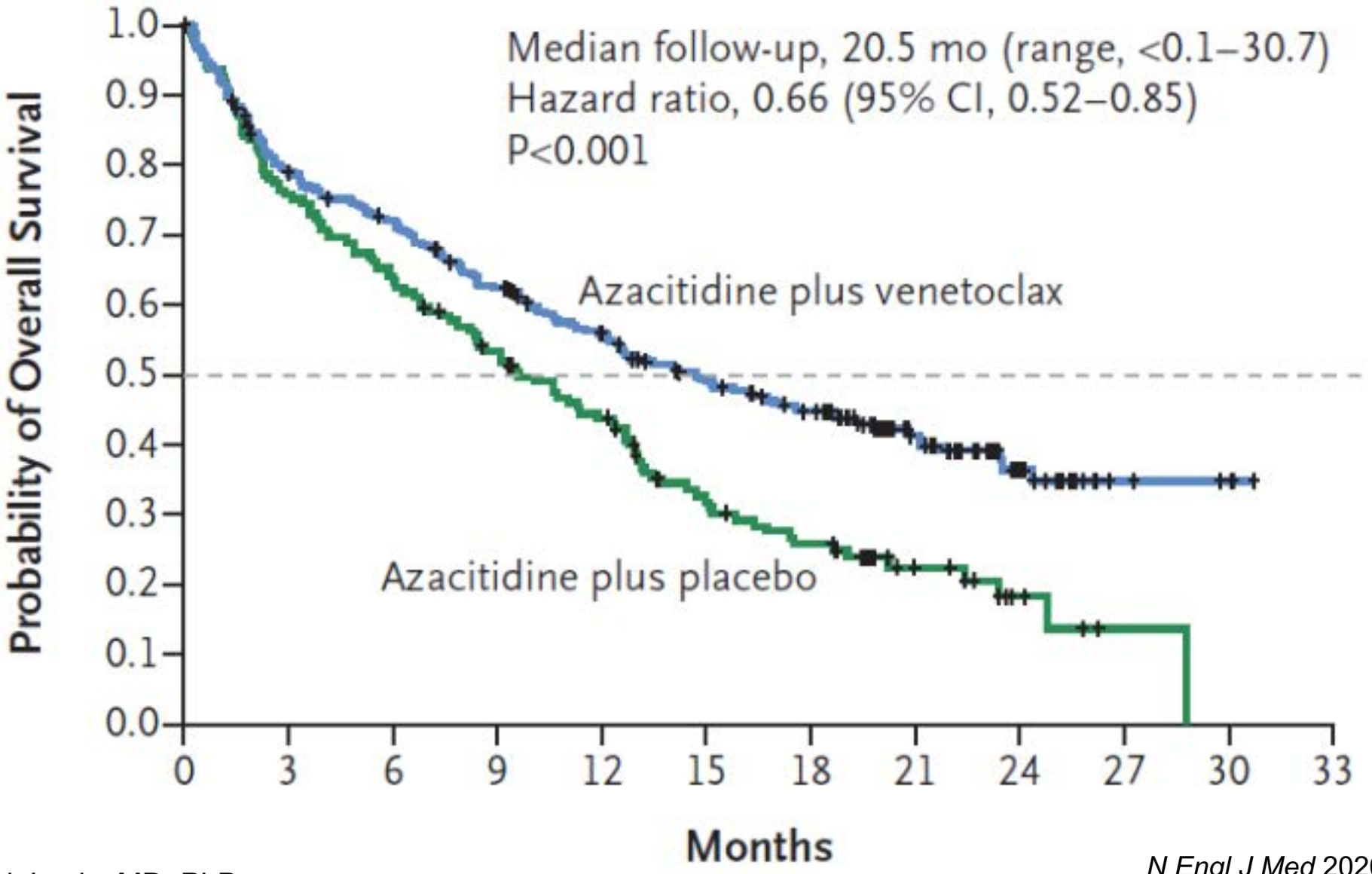
Module 5: Other Novel Agents and Investigational Strategies for Patients with AML — Dr Pollyea

Phase III VIALE-A Trial

- Patients with newly-diagnosed AML
  - Age 75 or older…or…
  - ..”unfit” for intensive chemotherapy
- Randomization (2:1):
  - Azacitidine + venetoclax
  - Azacitidine + placebo
- Primary endpoint: Overall Survival
- 431 patients enrolled from Feb 2017 to May 2019
  - Median age 76
  - Poor-risk cytogenetics in 36%

Courtesy of Mark Levis, MD, PhD

VIALE-A Trial



N Engl J Med 2020;383:617-29

Courtesy of Mark Levis, MD, PhD

What do we know about maintenance therapy for AML?

Courtesy of Mark Levis, MD, PhD

Evidence-Based Focused Review

blood

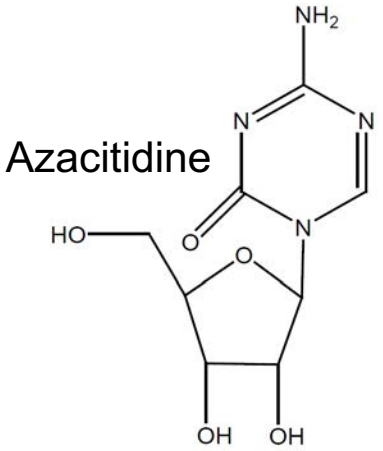
Maintenance therapy in acute myeloid leukemia: an evidence-based review of randomized trials

Armin Rashidi,[1] Roland B. Walter,[2-4] Martin S. Tallman,[5] Frederick R. Appelbaum,[2,6] and John F. DiPersio[1]

"…the benefit of maintenance seems more apparent after suboptimal induction and consolidation. This may be relevant to patients who cannot tolerate consolidation (e.g., some elderly patients or those who develop serious complications during induction)."

Courtesy of Mark Levis, MD, PhD

Blood. 2016; 128:763-773



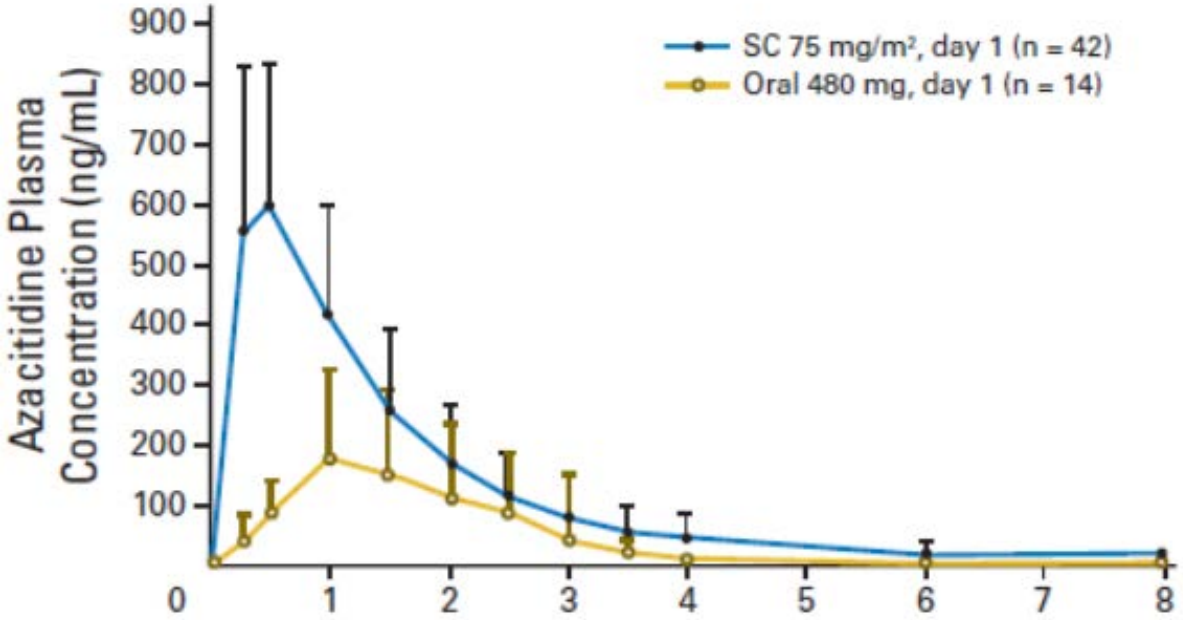
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase I Study of Oral Azacitidine in Myelodysplastic Syndromes, Chronic Myelomonocytic Leukemia, and Acute Myeloid Leukemia

Guillermo Garcia-Manero, Steven D. Gore, Christopher Cogle, Renee Ward, Tao Shi, Kyle J. MacBeth, Eric Laille, Heidi Giordano, Sarah Sakoian, Elias Jabbour, Hagop Kantarjian, and Barry Skikne

J Clin Oncol. 2011; 29:2521-2527

- 45 patients with MDS or AML
- First cycle treated with SQ aza
- Second cycle and beyond:
  - Oral azacitidine (CC-486)
- Overall response rate in untreated patients:
  - 73%



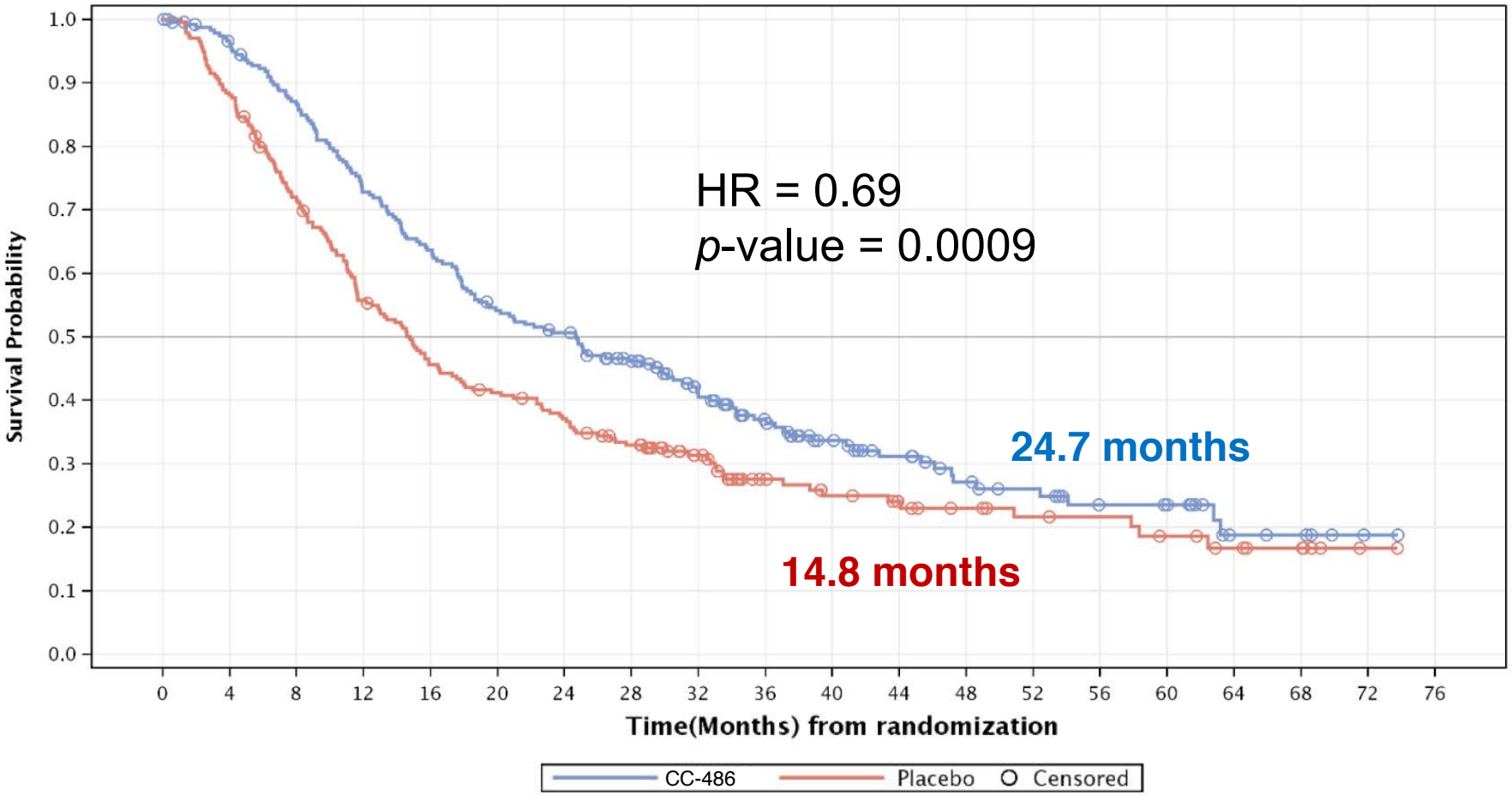
Courtesy of Mark Levis, MD, PhD

The Phase III QUAZAR AML-001 Study

- Multi-center, randomized, double-blinded, placebo-controlled
- Patients age 55+ with AML
  - Within 4 months of achieving CR or CRi after intensive induction
- 472 randomized
  - Median age 68
  - Most (65%) had received 0 or 1 cycle consolidation
- Primary endpoint:
  - Overall survival

Courtesy of Mark Levis, MD, PhD

Maintenance therapy with oral azacitidine after partially-completed intensive therapy for AML prolongs survival



On September 1, 2020, the FDA approved oral azacitidine (CC-486) for the continued treatment of AML in patients who attain first complete remission (CR) or CR with incomplete blood count recovery (CRi) after intensive induction chemotherapy and who are not able to complete intensive curative therapy.

Approval was based on the results of the QUAZAR AML-001 trial.

Courtesy of Mark Levis, MD, PhD

Conclusions

- AML patients without obvious targetable mutations can still clearly benefit from newer induction regimens with targeted drugs.
  - Venetoclax with azacitidine/decitabine is a “targeted” regimen with broad applicability.
- Maintenance therapy with a hypomethylating agent seems to be most effective in AML patients who have been unable to complete a standardized course of intensive chemotherapy
- Oral azacitidine appears to offer a more patient-friendly version of this type of maintenance.
- Question going forward:
  - Can oral azacitidine (or oral decitabine) be substituted for the SQ/IV versions in a venetoclax-based induction?

Courtesy of Mark Levis, MD, PhD

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

1. 7 + 3 induction
2. Azacitidine
3. Decitabine
4. Azacitidine + venetoclax
5. Decitabine + venetoclax
6. Low-dose cytarabine + venetoclax
7. Other

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?

 MARK LEVIS, MD	Azacitidine + venetoclax	 ANDREW H WEI, MBBS, PHD	Azacitidine + venetoclax → SCT
 ALEXANDER PERL, MD	Azacitidine + venetoclax	 COURTNEY D DINARDO, MD, MSCE	Azacitidine + APR-246 OR Azacitidine + magrolimab
 DANIEL A POLLYEA, MD, MS	Azacitidine + venetoclax	 ALICE S MIMS, MD	Azacitidine + venetoclax
 EYTAN M STEIN, MD	Azacitidine + venetoclax	 EUNICE S WANG, MD	Decitabine + venetoclax

GENERAL MEDICAL ONCOLOGISTS (N = 75)	Azacitidine + venetoclax

A 65-year-old with intermediate-risk AML, no actionable mutations and a PS of 0 receives standard 7 + 3 induction. He achieves a complete remission after 2 cycles of induction and then receives 2 cycles of high-dose cytarabine as consolidation but ultimately declines transplant. Would you offer this patient maintenance therapy?

1. Yes
2. Yes, with oral azacitidine (CC-486)
3. No

A 65-year-old patient with intermediate-risk AML, no actionable mutations and a PS of 0 receives standard 7 + 3 induction. He achieves a complete remission after 2 cycles of induction and then receives 2 cycles of high-dose cytarabine as consolidation but ultimately declines transplant. Would you offer this patient maintenance therapy?

 MARK LEVIS, MD	Yes, oral azacitidine (CC-486)	 ANDREW H WEI, MBBS, PHD	Yes, oral azacitidine (CC-486)
 ALEXANDER PERL, MD	Yes, oral azacitidine (CC-486)	 COURTNEY D DINARDO, MD, MSCE	Yes, oral azacitidine (CC-486)
 DANIEL A POLLYEA, MD, MS	Yes, oral azacitidine (CC-486)	 ALICE S MIMS, MD	Yes, oral azacitidine (CC-486)
 EYTAN M STEIN, MD	Yes, oral azacitidine (CC-486)	 EUNICE S WANG, MD	Yes, oral azacitidine (CC-486)
GENERAL MEDICAL ONCOLOGISTS (N = 75)	No		

Reimbursement issues aside, do you believe your patients with AML would prefer to receive an all-oral regimen like venetoclax/CC-486 rather than venetoclax/standard intravenous azacitidine?

 MARK LEVIS, MD	Yes, all patients	 ANDREW H WEI, MBBS, PHD	Yes, all patients
 ALEXANDER PERL, MD	Yes, select patients	 COURTNEY D DINARDO, MD, MSCE	Yes, all patients
 DANIEL A POLLYEA, MD, MS	Yes, all patients	 ALICE S MIMS, MD	Yes, all patients
 EYTAN M STEIN, MD	Yes, select patients	 EUNICE S WANG, MD	Yes, all patients
GENERAL MEDICAL ONCOLOGISTS (N = 75)	Yes, all patients		

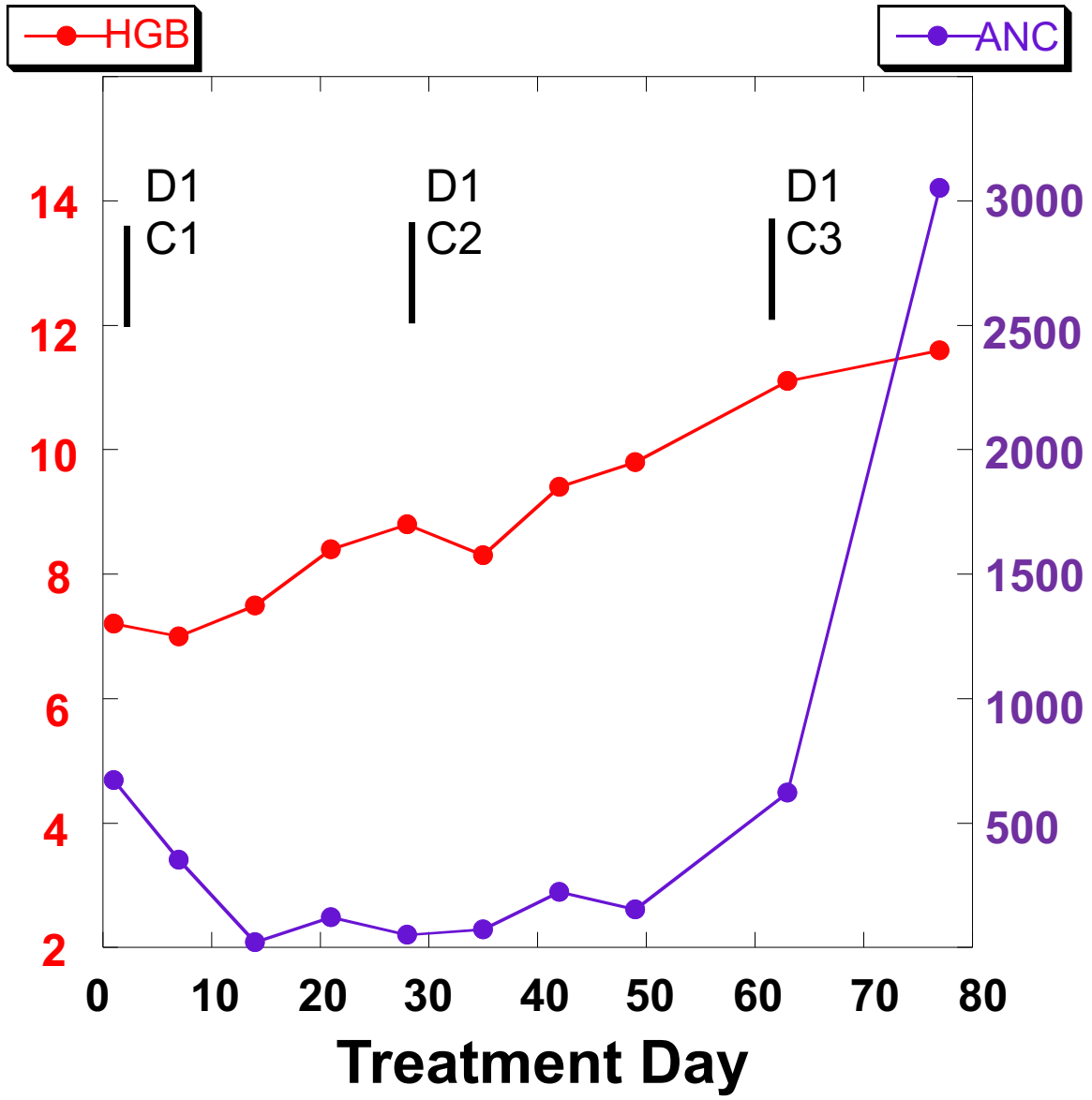
Case Presentation – Dr Levis: A 70-year-old man with AML, complex karyotype and a TP53 mutation

- 70 yo man, recently retired
  - Travelling around country with spouse
- Notices unusual fatigue while hiking...
  - …and an infected tooth not responding to antibiotics.
- Sees internist on return from trip
  - Blood work ordered:
    - WBC 2.2, ANC 670, Hgb 9.1, platelets 143
- Referred to a hematologist
- Bone marrow biopsy:
  - AML with dysplastic granulocytes
  - 60% blasts
- Molecular analysis:
  - Monosomal/complex karyotype
    - 45XY, -3; del5q22q33; t(3;6)(q26;p25); t(9;15)(p24;q22); -14; 15; add (17)(p11.2);-22
  - NGS:
    - TP53 H179Q VAF 36.8%

Courtesy of Mark Levis, MD, PhD

Case Presentation – Dr Levis: A 70-year-old man with AML, complex karyotype and a TP53 mutation (continued)

- Marrow blasts fall to 5% after cycle 1
- Marrow blasts fall to 1% after cycle 2
- Other than protocol-mandated admission on Day 1 Cycle 1, no further admissions.
  - After cycle 3, resumes active lifestyle, including travel
- Completes 12 cycles, then progresses.



Courtesy of Mark Levis, MD, PhD

Case Presentation – Dr Levis: A 73-old-man with newly diagnosed AML

- 73 yo man, still working
  - MDS (mild anemia) diagnosed three years previously, no treatment required so far
- Develops dyspnea on exertion
  - CBC shows Hgb 8.3, platelets 56K, white blood cells 26K, 40% blasts
- Diagnosed with AML
  - Normal karyotype
  - NGS: STAG2, TET2, NRAS mutations
- Initiated on azacitidine and venetoclax
- Achieves a prompt remission after 1 cycle, normalization of counts
  - Bone marrow biopsy normal, no mutations detected
- Bone marrow biopsy after 10 cycles (~14 months):
  - Mutations re-emerging, dysplasia evident
- Allogeneic transplant is offered:
  - Non-myeloablative
  - Successful engraftment

Courtesy of Mark Levis, MD, PhD

Case Presentation – Dr Levis: A 73-old-man with newly diagnosed AML (continued)

- At age 78, in early relapse 2.5 years post-transplant
- Counts normalized after 2 cycles of SQ azacitidine
- Begins therapy with oral azacitidine (CC-486)

Courtesy of Mark Levis, MD, PhD

Agenda

Module 1: Optimizing the Management of AML in Older Patients or Those Ineligible for Intensive Chemotherapy — Dr Wei

Module 2: Treatment Options for Patients with AML Harboring FLT3 Mutations — Dr Perl

Module 3: Management of Newly Diagnosed and Previously Treated AML with IDH Mutations — Dr Stein

Module 4: Tailoring Induction and Maintenance Therapy for Younger Patients with AML without Targetable Tumor Mutations — Dr Levis

Module 5: Other Novel Agents and Investigational Strategies for Patients with AML — Dr Pollyea

RTP
RESEARCH
TO PRACTICE

Definition of Secondary AML

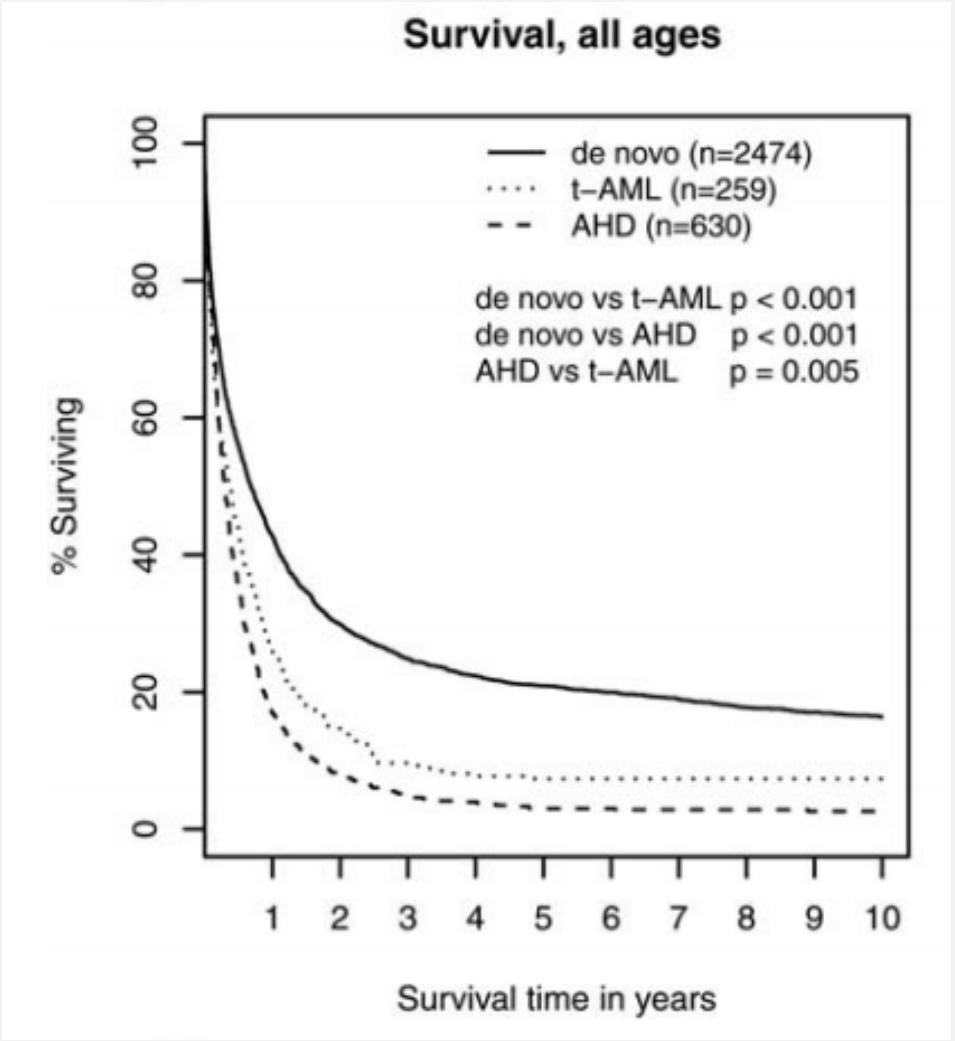
- AML from an antecedent hematological disorder
  - Most commonly MDS (1/3 of MDS patients will develop AML)
  - Could also be from MPN or a non-malignant antecedent disorder (e.g. aplastic anemia)
- Treatment-related AML
  - WHO defined as history of exposure to alkylating agents and/or topoisomerase II inhibitors and/or ionizing radiation to large fields including bone marrow
  - Other implicated therapies include antimetabolites or antitubulin agents but their relationship is less certain.

Greenberg et al, Blood 1997
Arber et al, Blood 2016

Courtesy of Daniel A Pollyea, MD, MS

De Novo AML vs Secondary AML

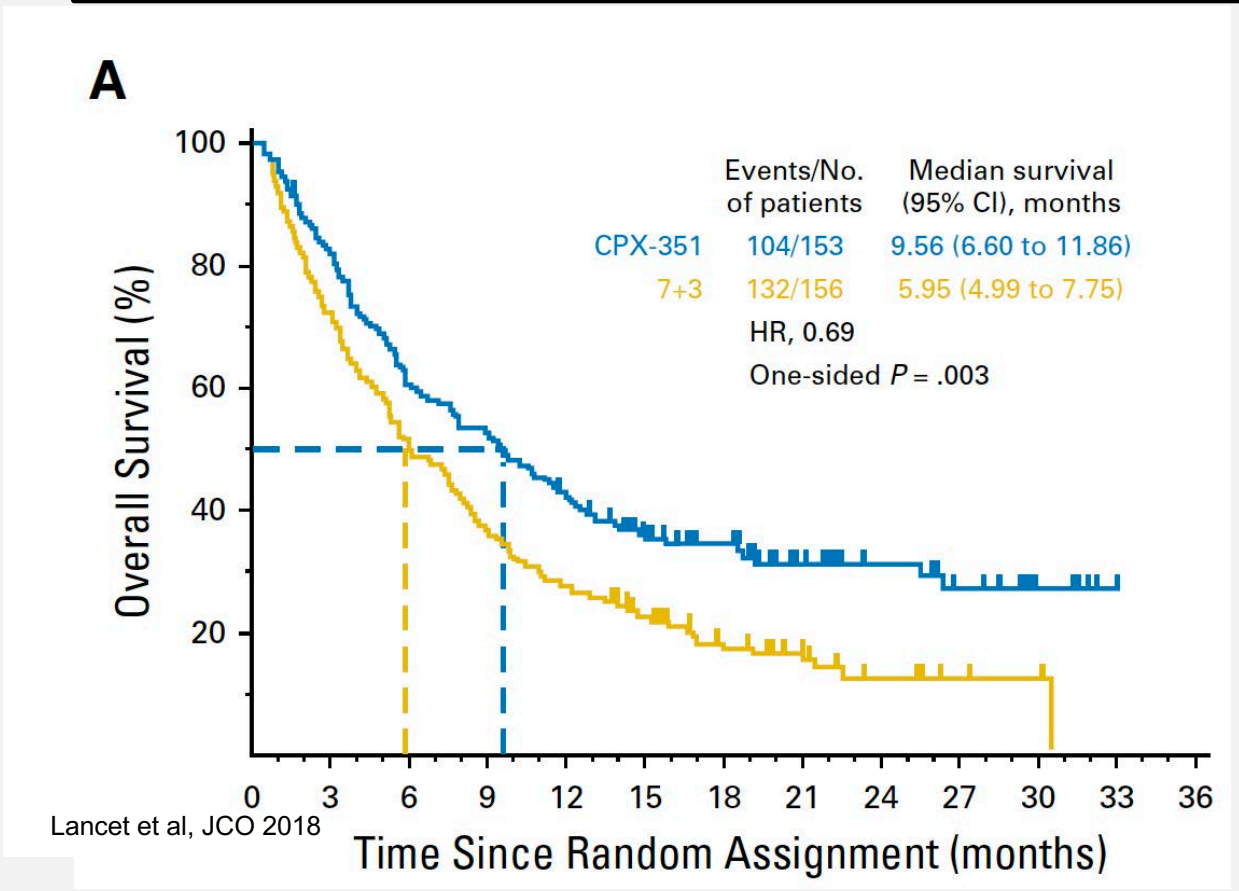
- Secondary AML patients are older, have more adverse biological risk factors (cytogenetics/TP53)
- Lower response rates to conventional treatments
- Worse overall survival
- Incurable without an allogeneic stem cell transplantation



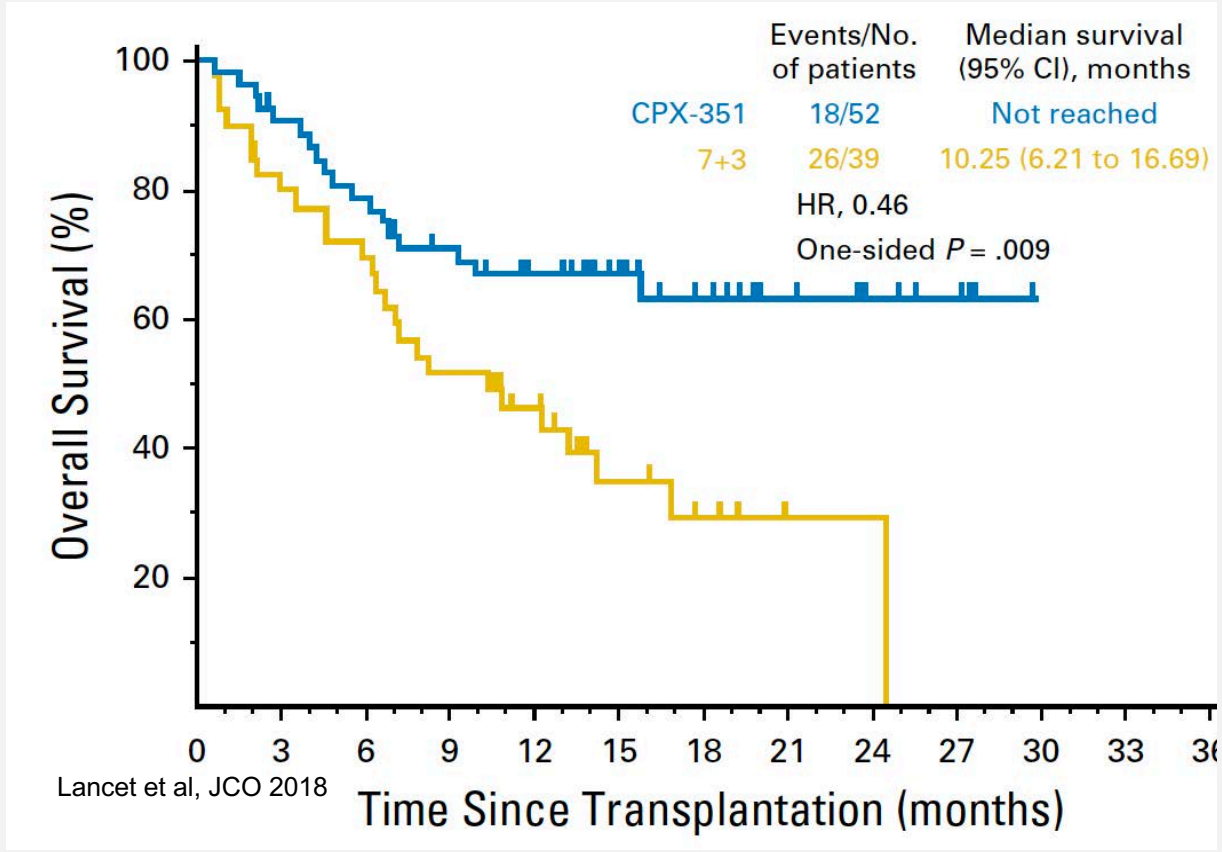
Courtesy of Daniel A Pollyea, MD, MS

Hulegardh et al, AJH 2015

Phase III Study 301: CPX-351 vs 7+3 for Older Patients with Newly Diagnosed Secondary AML



Lancet et al, JCO 2018



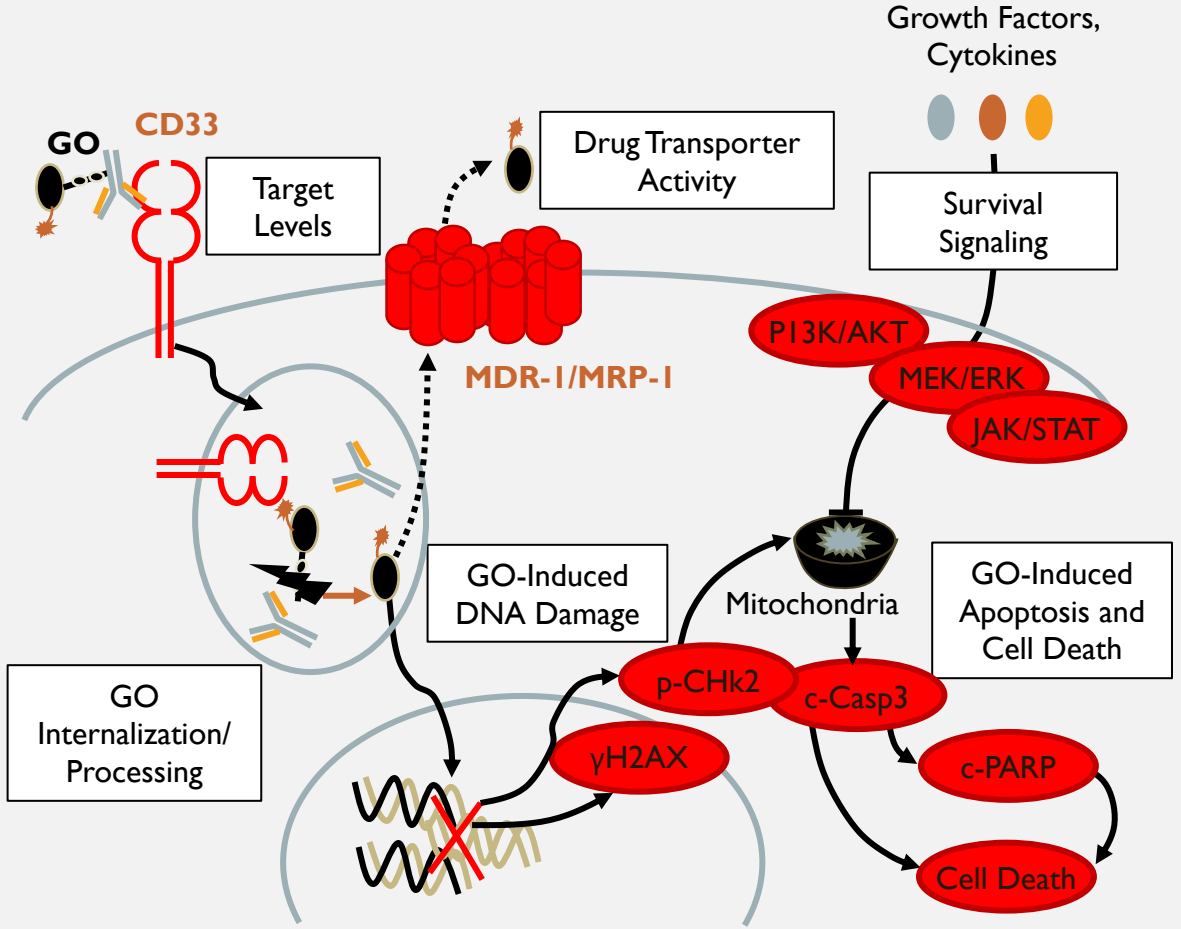
Lancet et al, JCO 2018

- Consider CPX-351 for newly diagnosed, *induction eligible* secondary AML patients, particularly if they would be suitable candidates for a transplant
- How can you tell if they have secondary AML? Probably OK to wait (up to 15 days) for marrow results (Rollig et al, Blood 2020)
- Caution if TP53+ (Lindsley et al, ASH 2019)

Courtesy of Daniel A Pollyea, MD, MS

CD33 Antibody Drug Conjugate: Gemtuzumab Ozogamicin

- Monoclonal anti-CD33 antibody linked to calicheamicin
- Internalized and cleaved in lysosomes to release calicheamicin
- Calicheamicin enters nucleus and interacts with DNA causing double-strand breaks initiating apoptosis
- Approved in 2000 based on 30% ORR in R/R AML



Rosen DB, et al. *PLoS One.* 2013;8:e53518.

Sievers et al, JCO 2001

Courtesy of Daniel A Pollyea, MD, MS

Gemtuzumab in AML: Select Phase III Results

Study	N	Treatment	Results of GO vs Comparator
MRC/NCRI AML1 (2011)	1113	GO (3 mg/m^2) + either ADE, DA, or FLAG-IDA	▪ Improved 5-yr OS for favorable-risk group ▪ No difference in ORR, TRM, relapse, survival
ALFA 0701 (2012)	280	GO (3 mg/m^2) + DA	▪ Improved 2-yr EFS, RFS, OS ▪ No difference in ORR or mortality
MRC/NCRI AML (2012)	1115	GO (3 mg/m^2) + either DA or DCLo	▪ Reduced 3-yr relapse risk, and superior DFS and OS ▪ No difference in TRM
SWOG S0106 (2013)	637	GO (6 mg/m^2) + DA induction vs DA	▪ No difference in CR, DFS, OSs

Courtesy of Daniel A Pollyea, MD, MS

Antibody-Drug Conjugates

Target	Drug(s)	Clinical Experience	Citation
CD33	Gemtuzumab ozogamicin	Extensive, previously reviewed	Multiple
	IMG779	Modest activity	Cortes et al, Blood 2018
CD123	IMGN632	Blast reduction and modest response rates	Daver et al, ASH 2019
	SGN-CD123A	Not reported	
CD25	Camidanlumab tesirine	Minimal responses, manageable toxicity	Goldberg et al, Leukemia Research 2020
CD30	Brentuximab vedotin	Used with chemotherapy for R/R AML; ~40% ORR	Narayan et al, Cancer 2020
CLL-1	Several	Pre-clinical	

Courtesy of Daniel A Pollyea, MD, MS

Immune Checkpoint Inhibitors

- PD-1/PD-L1 inhibitors with azacitidine in R/R AML

Best response	Azacitidine/nivolumab
Overall response rate	23 (33)
CR	4 (6)
CRi/CRp	11 (16)
PR	1 (1)
HI[a] (6 months+)	7 (10)
Stable disease (6 months+)[b]	6 (9)
Nonresponders	41 (58)
Median cycles to response	2 (1–13)
Median follow-up, in months	13.3 (8.2–25.5)

Daver et al, Cancer Discovery 2019

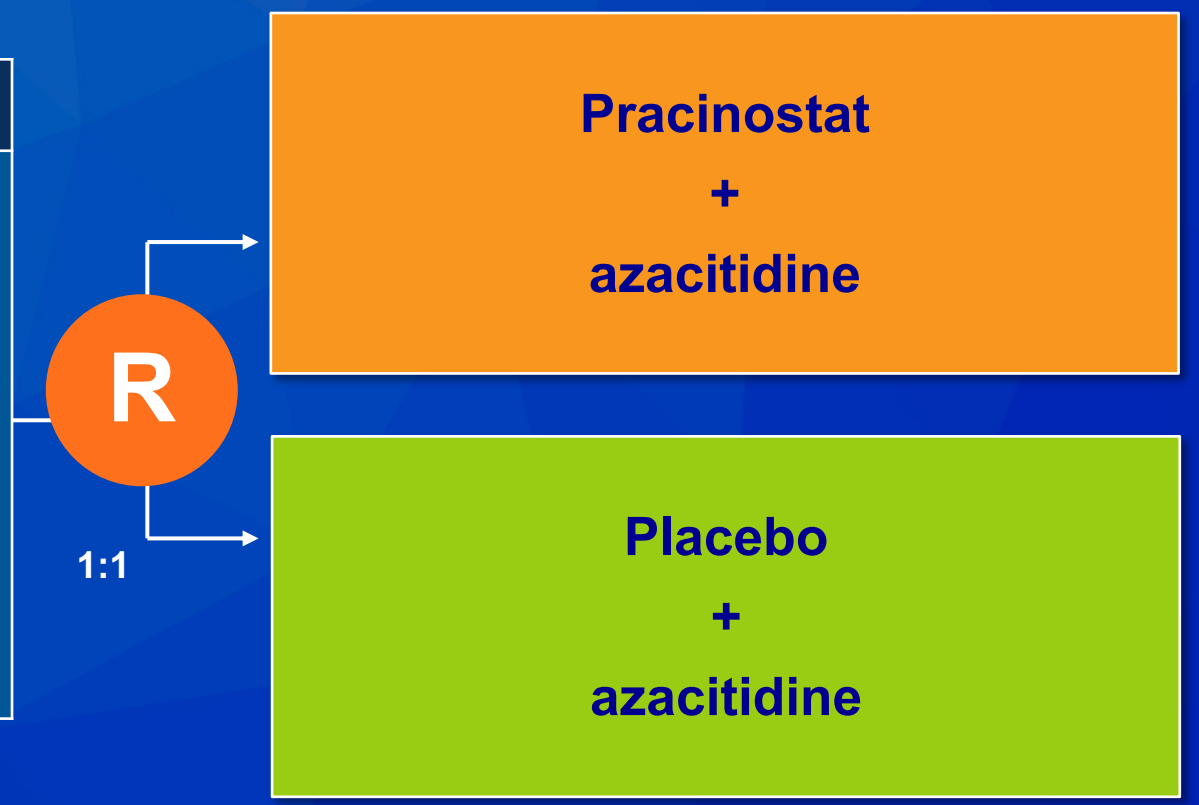
- Ongoing work with pembrolizumab and durvalumab in combinations and in various settings…

Courtesy of Daniel A Pollyea, MD, MS

Phase III PRAN-16-52 Trial Design

Eligibility (N = 406)

- Newly diagnosed AML (including de novo, secondary to hematologic disorders or treatment-related disease with intermediate or unfavorable-risk cytogenetics)
- Ineligibility for intensive chemotherapy
- ECOG PS 0-2



Primary endpoint: Overall survival

Secondary endpoints include morphologic CR rate, CR without MRD, cytogenetic CR rate and transfusion independence

www.clinicaltrials.gov (NCT03151408) – Accessed November 2020. Garcia-Manero G et al. ASCO 2018;Abstract TPS7078.

Phase III PRAN-16-52 Trial Discontinued After Completing Interim Analysis
Press Release: July 02, 2020

"An interim futility analysis of the ongoing Phase 3 study of pracinostat in combination with azacitidine in patients with AML who are unfit to receive standard intensive chemotherapy, undertaken by the study Independent Data Monitoring Committee ('IDMC'), has demonstrated it was unlikely to meet the primary endpoint of overall survival compared to the control group.

Based on the outcome of the interim analysis, the decision was made to discontinue the recruitment of patients and end the study. The decision was based on a lack of efficacy and not on safety concerns.

Pending further evaluation, patients currently enrolled in other pracinostat studies will continue treatment."

https://www.globenewswire.com/news-release/2020/07/02/2056824/0/en/Helsinn-Group-and-MEI-Pharma-Discontinue-the-Phase-3-Study-with-Pracinostat-in-AML-after-Completing-Interim-Analysis.html

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

1. 7 + 3 induction
2. CPX-351
3. Decitabine
4. Decitabine + venetoclax
5. Low-dose cytarabine + venetoclax
6. Low-dose cytarabine + glasdegib
7. Other

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 MARK LEVIS, MD	CPX-351	 ANDREW H WEI, MBBS, PHD	CPX-351 → SCT
 ALEXANDER PERL, MD	CPX-351	 COURTNEY D DINARDO, MD, MSCE	CPX-351
 DANIEL A POLLYEA, MD, MS	Azacitidine + venetoclax	 ALICE S MIMS, MD	CPX-351
 EYTAN M STEIN, MD	CPX-351	 EUNICE S WANG, MD	CPX-351

GENERAL MEDICAL ONCOLOGISTS (N = 75)	CPX-351

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?

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GENERAL MEDICAL ONCOLOGISTS (N = 75)	CPX-351, Azacitidine + venetoclax

Case Presentation – Dr Pollyea: A 79-year-old man with newly diagnosed AML and intermediate cytogenetics

79 year old healthy male with newly diagnosed AML. Had intermediate cytogenetics with a trisomy 8 and mutations in ASXL1, BCORL1, TET2 and RUNX1. He started venetoclax + azacitidine and experienced a CRi after cycle 1. He continued therapy and after 10 cycles had a routine bone marrow biopsy that showed 10% blasts. No new mutations on repeat sequencing. He stopped venetoclax and azacitidine and had two cycles of decitabine; a repeat bone marrow biopsy showed 30% blasts. No new mutations on repeat sequencing; he was CD33+. He had a course of gemtuzumab ozogamicin (three doses over 28 days) and a repeat bone marrow biopsy now showed 50% blasts. No new mutations on repeat sequencing. The patient opted for hospice and passed away 3 weeks later.

Courtesy of Daniel A Pollyea, MD, MS

Consensus or Controversy? Investigators Discuss Clinical Practice Patterns and Available Research Data Guiding the Management of Hematologic Cancers

Hodgkin and Non-Hodgkin Lymphoma

Friday, December 4, 2020
7:00 PM – 8:30 PM Pacific Time

Faculty

Jonathan W Friedberg, MD, MMSc
John Kuruvilla, MD
Ann S LaCasce, MD, MMSc
John P Leonard, MD
Michael E Williams, MD, ScM

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Thank you for joining us!

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

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