New Agents and Strategies in the Management of Acute Myeloid Leukemia
An Interactive Grand Rounds Series

Daniel A Pollyea, MD, MS
Associate Professor of Medicine
Clinical Director of Leukemia Services
Robert H Allen, MD Chair in Hematology Research
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Aurora, Colorado

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Aurora, Colorado

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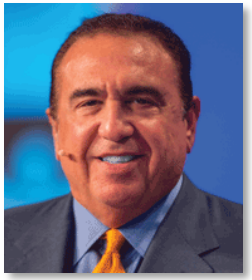

Project Chair
Neil Love, MD
Research To Practice
Miami, Florida

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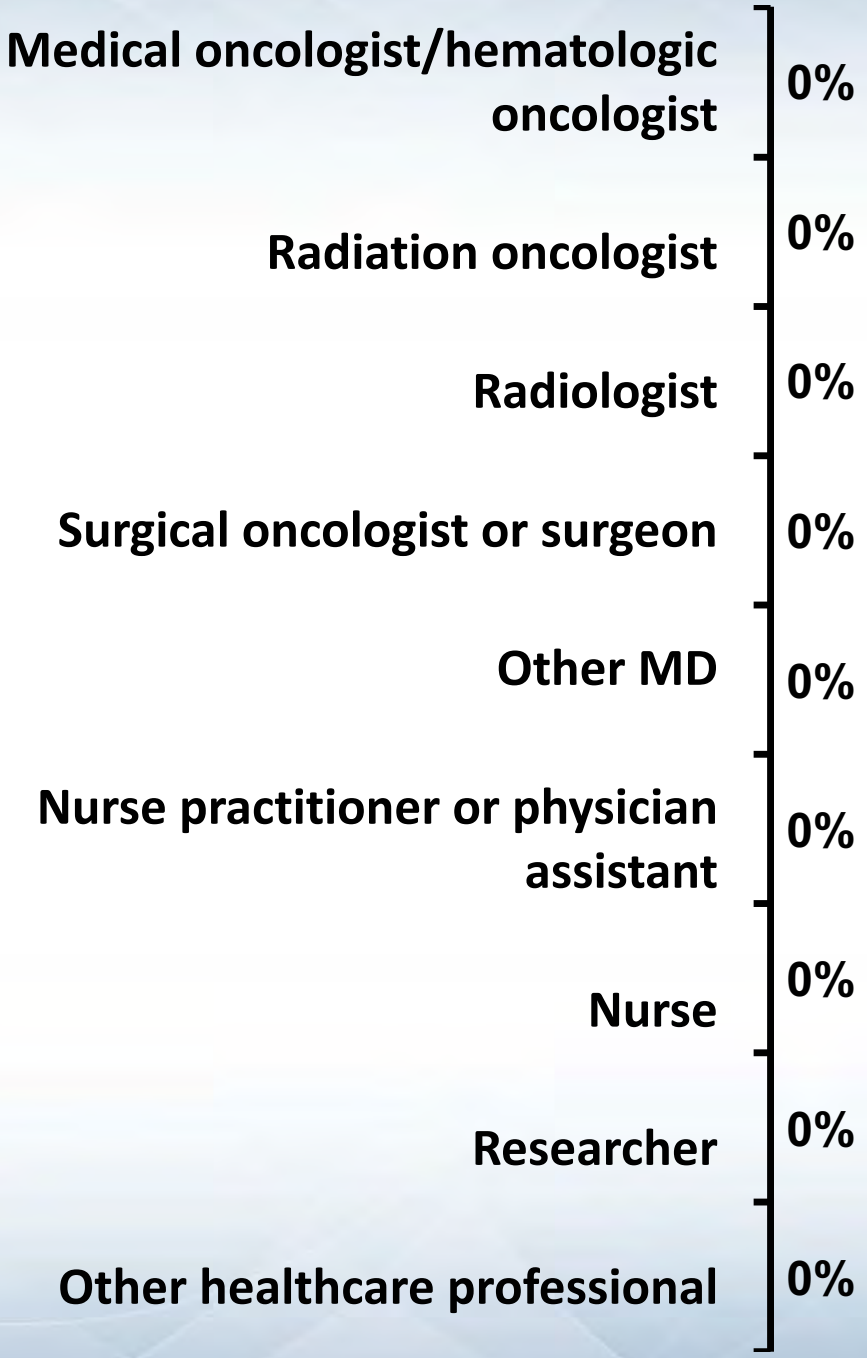
Which of the following best represents your clinical background?

1. Medical oncologist/hematologic oncologist
2. Radiation oncologist
3. Radiologist
4. Surgical oncologist or surgeon
5. Other MD
6. Nurse practitioner or physician assistant
7. Nurse
8. Researcher
9. Other healthcare professional



Management of Acute Myeloid Leukemia

Module 1: Contemporary Biomarker Assessment

- Incidence and prognostic relevance of cytogenetic and other molecular markers
- Guideline-endorsed recommendations for biomarker assessment

Module 2: Bcl-2 Inhibition as a Rational Therapeutic Strategy

- Biologic rationale for venetoclax in AML
- Safety, efficacy and patient selection for venetoclax in combination with HMAs or LDAC

Module 3: FLT3 Inhibitors in the Up-Front and Recurrent Settings

- Data supporting midostaurin in newly diagnosed AML (RATIFY)
- Efficacy and safety data with gilteritinib (ADMIRAL)

Module 4: IDH Inhibitors in the Up-Front and Recurrent Settings

- Efficacy and safety of enasidenib and ivosidenib
- Differentiation syndrome and other side effects of IDH inhibitors

Module 5: Other Novel Treatment Approaches

- Efficacy, safety and recent approval of glasdegib for newly diagnosed AML (BRIGHT 1003)
- Optimal incorporation of CPX-351 for the treatment of AML
- CC-486 as maintenance therapy for AML in complete remission
- Emerging therapeutics (CAR T-cell therapy, checkpoint inhibitors)

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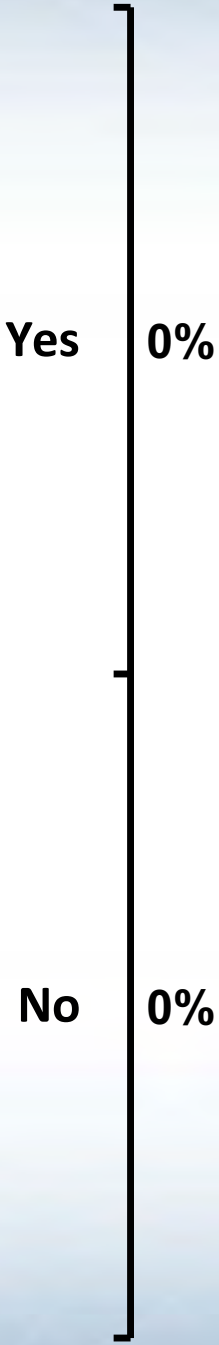
In a medically stable patient with newly diagnosed AML, do you generally wait for genomic test results before initiating treatment?

1. **Yes**
2. **No**



In a medically stable patient with newly diagnosed AML, do you generally wait for genomic test results before initiating treatment?

 HARRY P ERBA, MD, PHD	Yes
 MARK LEVIS, MD, PHD	Yes
 DANIEL A POLLYEA, MD, MS	Yes
 KEITH W PRATZ, MD	Yes
 EYTAN M STEIN, MD	Yes
 WENDY STOCK, MD	Yes
 RICHARD M STONE, MD	Yes

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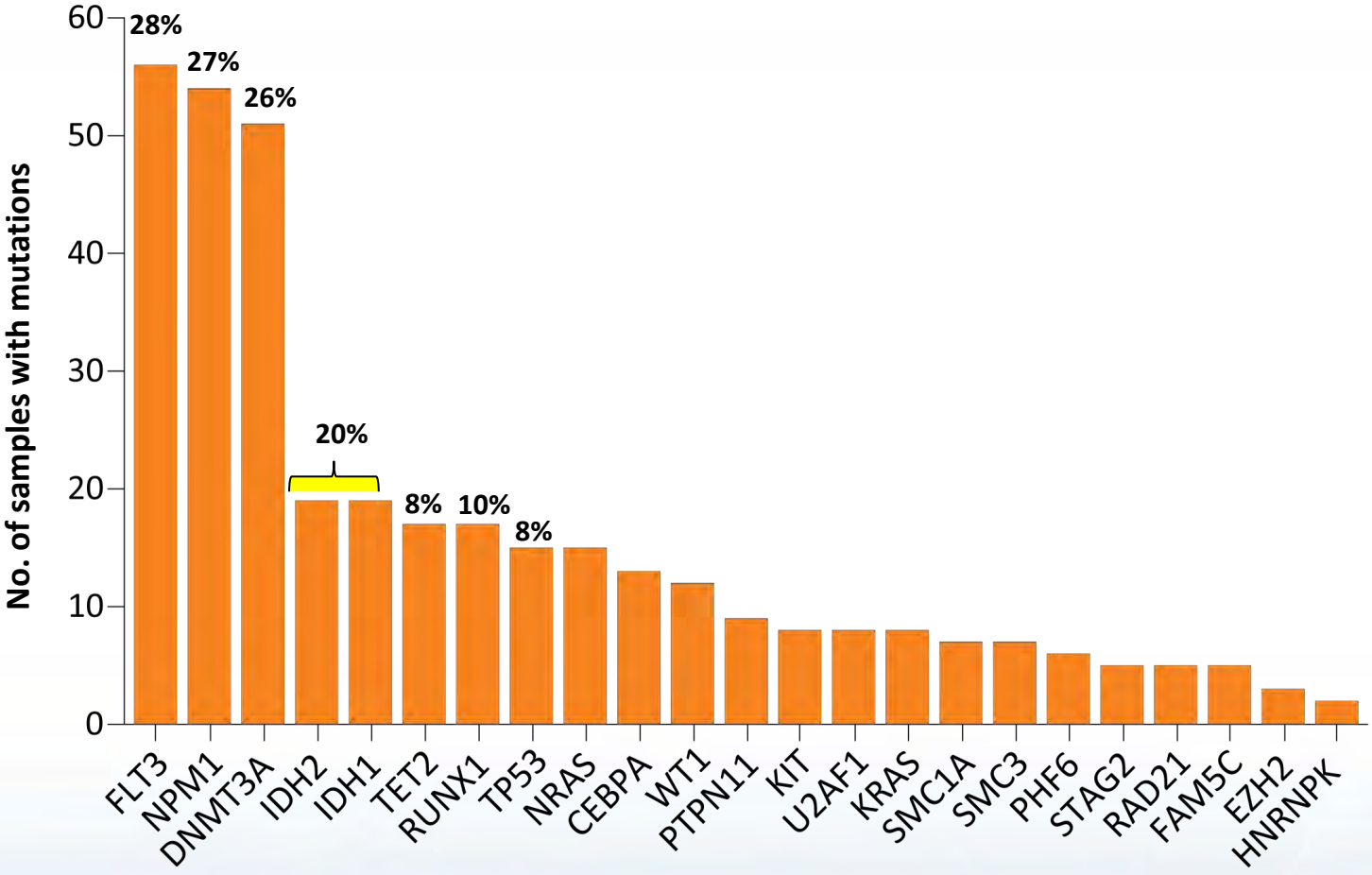
Significantly Mutated Genes in 200 Adult Patients with De Novo AML



The Cancer Genome Atlas Research Network; *N Engl J Med* 2013;368:2059-74.

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Guidelines for Risk Stratification

Risk category	Genetic abnormality
Favorable	• t(8;21)(q22;q22.1); RUNX1-RUNX1T1 • inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11 • Mutated NPM1 without FLT3-ITD or with FLT3-ITD^{low} • Biallelic mutated CEBPA
Intermediate	• Mutated NPM1 and FLT3-ITD^{high} • Wild-type NPM1 without FLT3-ITD or with FLT3-ITD^{low} • without adverse-risk genetic lesions • t(9;11)(p21.3;q23.3); MLLT3-KMT2A • Cytogenetic abnormalities not classified as favorable or adverse
Poor/Adverse	• t(6;9)(p23;q34.1); DEK-NUP214 • t(v;11q23.3); KMT2A rearranged • t(9;22)(q34.1;q11.2); BCR-ABL1 • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2,MECOM(EVI1) • -5 or del(5q); -7; -17/abn(17p) • Complex karyotype; monosomal karyotype • Wild-type NPM1 and FLT3-ITD^{high} • Mutated RUNX1* • Mutated ASXL1* • Mutated TP53

*Not used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes

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Dohner H et al. *Blood* 2017;129(4):424-47; NCCN AML v2.2020

Guideline-Recommended Genetic Analyses

- **Cytogenetics**
  - Karyotype + FISH
- **Molecular Analyses**
  - c-KIT, FLT3 (ITD and TKD), NPM1, CEBPA (biallelic), IDH1, IDH2, TP53 and other mutations
  - While the above mutations should be tested in all patients, multiplex gene panels and NGS are recommended for a comprehensive prognostic assessment

Dohner H et al. *Blood* 2017;129(4):424-47; NCCN AML v2.2020

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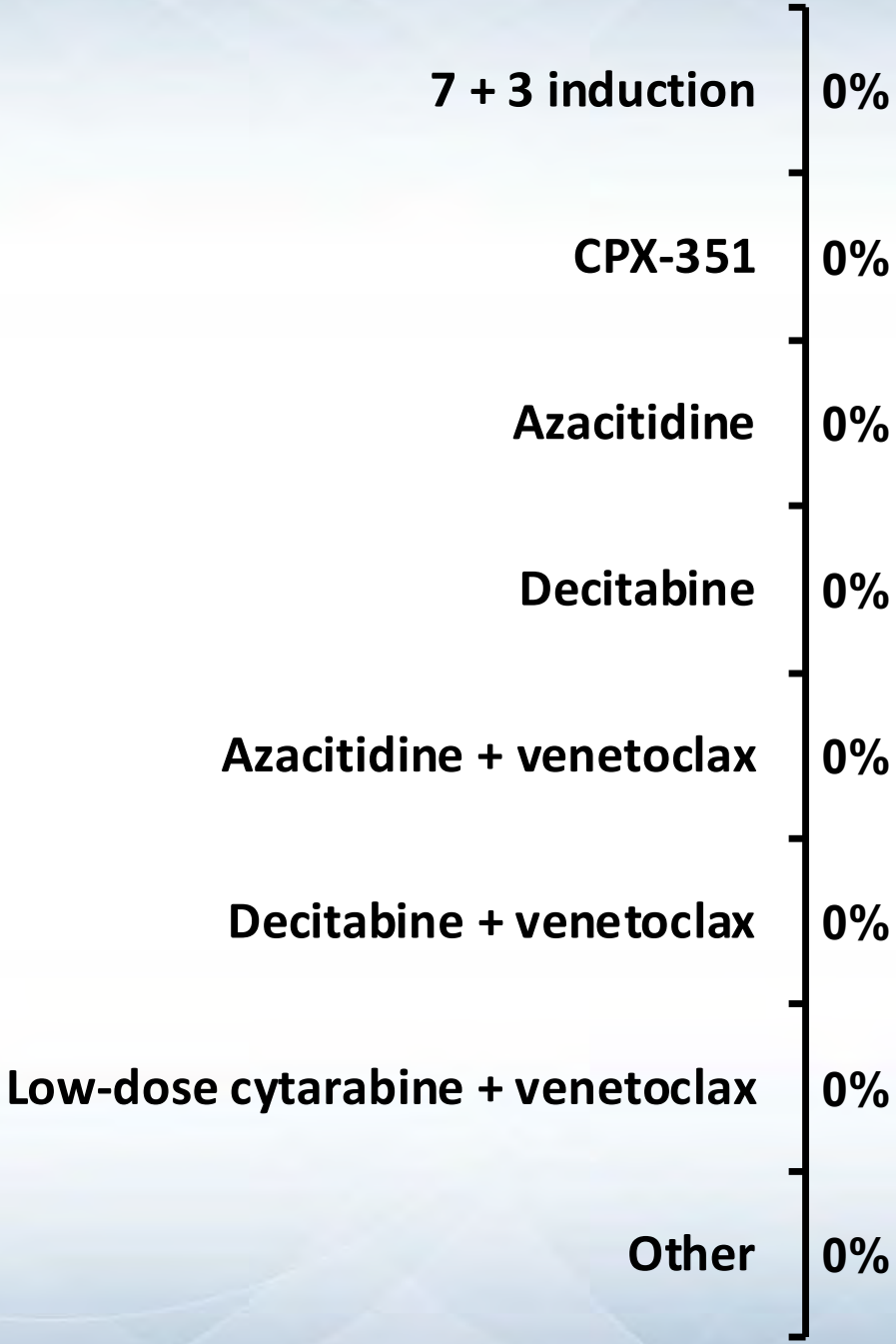
What initial treatment would you recommend for a 65-year-old man with AML with a PS of 1 and pancytopenia, 35% marrow myeloblasts, a complex karyotype and a TP53 mutation?

1. 7 + 3 induction
2. CPX-351
3. Azacitidine
4. Decitabine
5. Azacitidine + venetoclax
6. Decitabine + venetoclax
7. Low-dose cytarabine + venetoclax
8. 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?

 HARRY P ERBA, MD, PHD	Azacitidine + venetoclax
 MARK LEVIS, MD, PHD	Azacitidine + venetoclax
 DANIEL A POLLYEA, MD, MS	Azacitidine + venetoclax
 KEITH W PRATZ, MD	Azacitidine + venetoclax
 EYTAN M STEIN, MD	Azacitidine + venetoclax
 WENDY STOCK, MD	Azacitidine + venetoclax
 RICHARD M STONE, MD	Azacitidine + venetoclax

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What initial treatment would you recommend for a 68-year-old woman with AML with a performance status (PS) of 2 and a history of hypertension, coronary artery disease, anemia for 2 years with unclear etiology and diabetes mellitus, assuming organ function is normal?

 HARRY P ERBA, MD, PHD	Azacitidine + venetoclax
 MARK LEVIS, MD, PHD	Azacitidine + venetoclax
 DANIEL A POLLYEA, MD, MS	Azacitidine + venetoclax
 KEITH W PRATZ, MD	Azacitidine + venetoclax
 EYTAN M STEIN, MD	Azacitidine + venetoclax
 WENDY STOCK, MD	Azacitidine + venetoclax
 RICHARD M STONE, MD	Azacitidine + venetoclax

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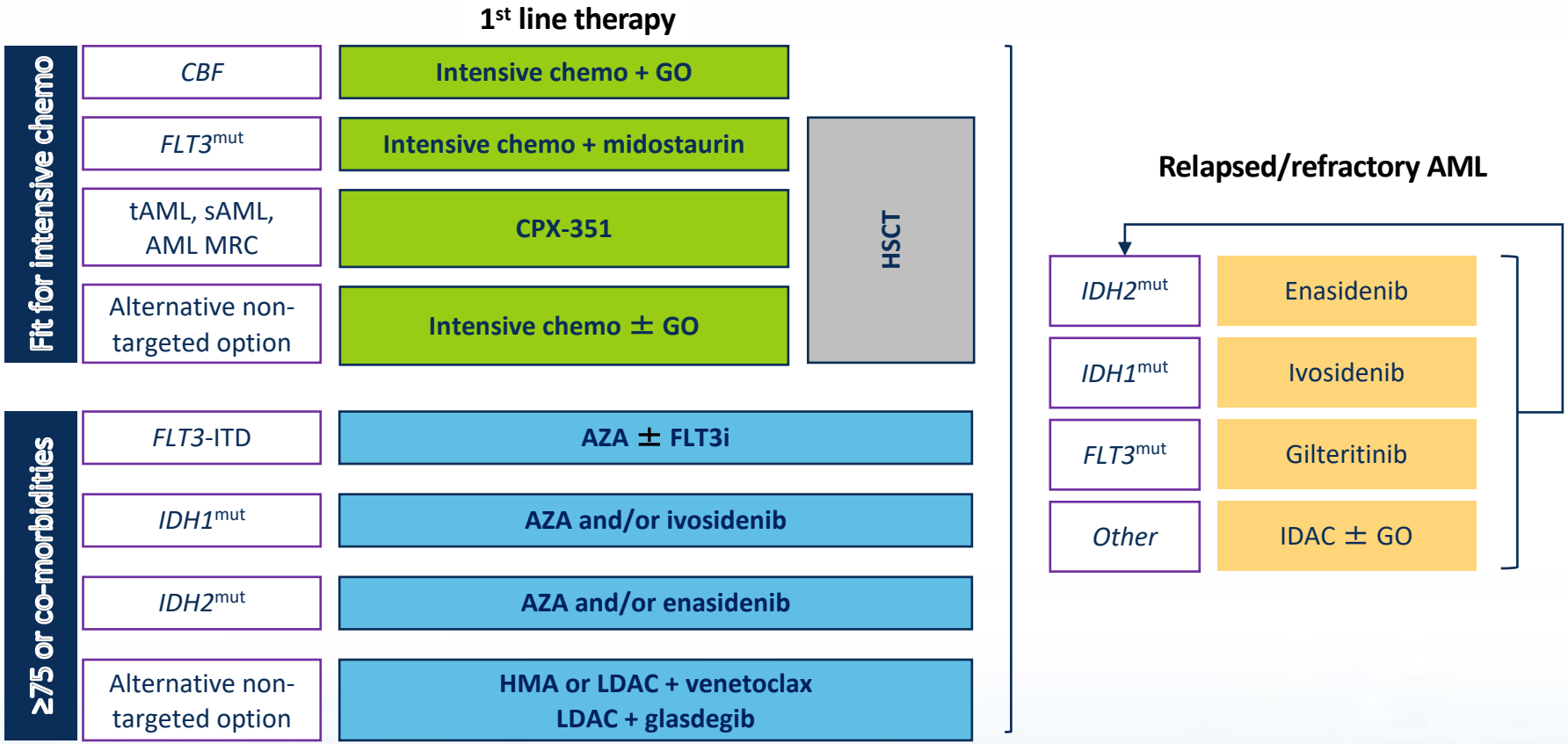
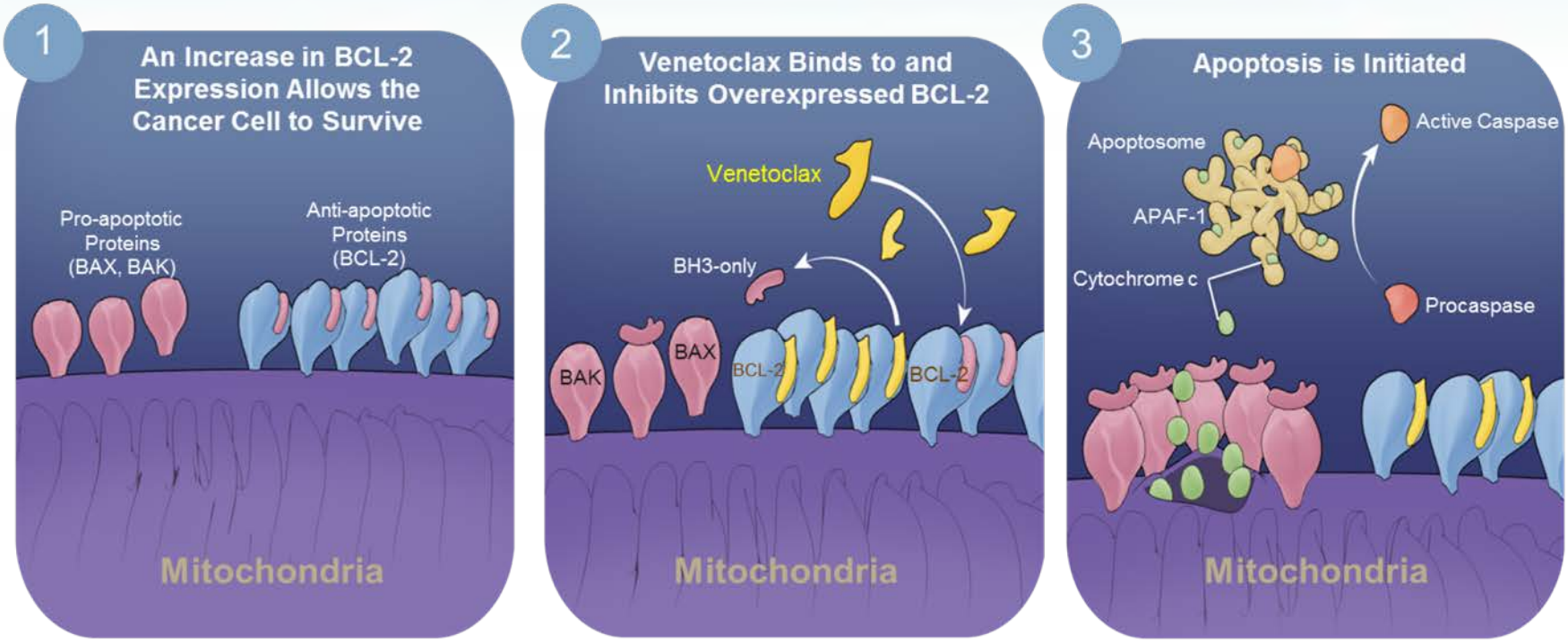
Changing Clinical Landscape in AML



Courtesy Andrew H Wei, MBBS, PhD, December 2019

Venetoclax Mechanism of Action



- Cancer cells increase the expression of anti-apoptotic proteins to offset the increase in pro-apoptotic proteins, tipping the balance toward cell survival
- The large # of pro-apoptotic proteins bound and sequestered by Bcl-2 in AML make them “primed” for death

Kumar et al. *Proc ASCO* 2015;Abstract 8576.

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FDA Approves Venetoclax Combinations for AML

Press Release – November 21, 2018

"On November 21, 2018, the Food and Drug Administration granted accelerated approval to venetoclax in combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.

Approval was based on two open-label non-randomized trials in patients with newly-diagnosed AML who were ≥ 75 years of age or had comorbidities that precluded the use of intensive induction chemotherapy. Efficacy was established based on the rate of complete remission (CR) and CR duration."

https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm626499.htm

blood

Plenary Paper

CLINICAL TRIALS AND OBSERVATIONS

Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia

Courtney D. DiNardo,[1] Keith Pratz,[2] Vinod Pullarkat,[3,4] Brian A. Jonas,[5] Martha Arellano,[6] Pamela S. Becker,[7,8] Olga Frankfurt,[9] Marina Konopleva,[1] Andrew H. Wei,[10] Hagop M. Kantarjian,[1] Tu Xu,[11] Wan-Jen Hong,[12] Brenda Chyla,[11] Jalaja Potluri,[11] Daniel A. Pollyea,[13] and Anthony Letai[14]

Blood 2019;133(1):7-17

Summary of Efficacy: Venetoclax + HMA (Azacitidine or Decitabine) in Treatment-Naïve, Elderly Patients with AML

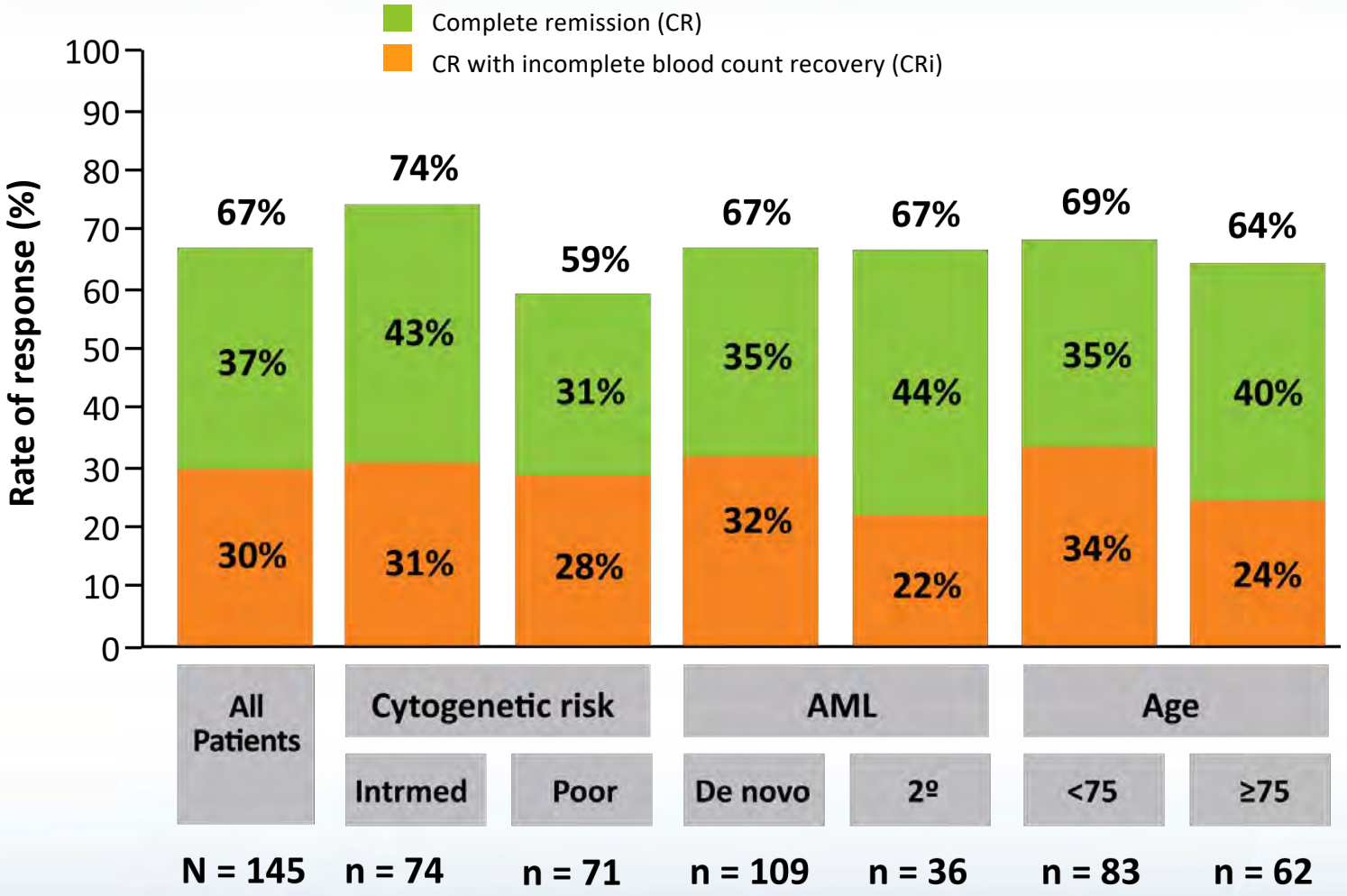
Cohort	N	CR + CRi	ORR	LRR†	Median duration of CR + CRi	Median OS
All pts*	145	67%	68%	83%	11.3 mo	17.5 mo
VEN 400 mg + HMA	60	73%	73%	82%	12.5 mo	Not reached 17+ mo

* All pts, include those receiving venetoclax 400, 800 or 1200 mg

† LRR, leukemia response rate (CR + CRi + PR + MLFS)

DiNardo CD et al. *Blood* 2019;133(1):7-17.

Venetoclax + HMA: Response by Subgroup



DiNardo CD et al. *Proc ASCO* 2018;Abstract 7010; DiNardo CD et al. *Blood* 2019;133(1):7-17.

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rapid communication

Venetoclax Combined With Low-Dose Cytarabine for Previously Untreated Patients With Acute Myeloid Leukemia: Results From a Phase Ib/II Study

Andrew H. Wei, MBBS, PhD[1]; Stephen A. Strickland Jr, MD[2]; Jing-Zhou Hou, MD, PhD[3]; Walter Fiedler, MD[4]; Tara L. Lin, MD[5]; Roland B. Walter, MD, PhD[6,7]; Anoop Enjeti, MD[8,9]; Ing Soo Tiong, MBBS[1]; Michael Savona, MD[2]; Sangmin Lee, MD[10]; Brenda Chyla, PhD[11]; Relja Popovic, PhD[11]; Ahmed Hamed Salem, PhD[11,12]; Suresh Agarwal, PhD[11]; Tu Xu, PhD[11]; Kaffa M. Fakouhi[11]; Rod Humerickhouse, MD, PhD[11]; Wan-Jen Hong, MD[13]; John Hayslip, MD[11]; and Gail J. Roboz, MD[10]

J Clin Oncol 2019;37:1277-84

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Venetoclax + LDAC: Response and Survival Summary

Patients	N	CR/CRi	Median OS
All	82	54%	10.1 mo
AML type			
De novo	42	71%	16.9 mo
Secondary	40	35%	4.0 mo
Age			
<75 years	42	48%	6.5 mo
≥75 years	40	60%	14.9 mo
Prior HMA treatment			
Yes	24	33%	4.1 mo
No	58	62%	13.5 mo

Wei A et al. *J Clin Oncol* 2019;37:1277-84.

Molecular Determinants of Outcome with Venetoclax Combinations

CR/CRi	HMA + VEN	LDAC + VEN
Intermediate CG	74%	63%
Adverse CG	60%	42%
***NPM1* mutant**	91%	89%
***IDH1/2* mutant**	71%	72%
***FLT3* mutant**	72%	44%
***TP53* mutant**	47%	30%

DiNardo CD et al. *Blood* 2019;133 (1):7-17; Wei A et al. *J Clin Oncol* 2019;37:1277-84.

Efficacy of Venetoclax in Combination with LDAC or HMA in Untreated AML by Mutation Status

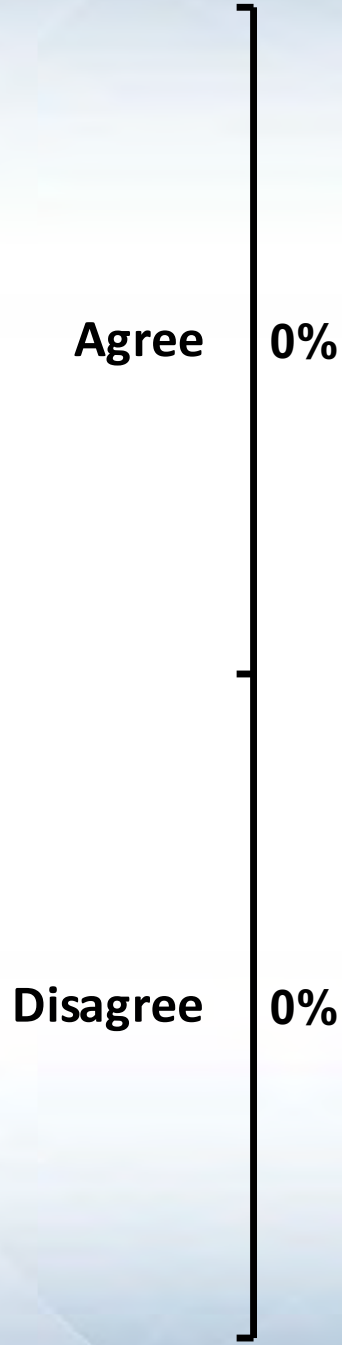
Clinical outcomes of molecularly defined patient subgroups from the Phase Ib/II studies of venetoclax with LDAC or HMA were analyzed.

	Complete Remission (CR)/CRi	Median Overall Survival	Duration of Response
Molecular Marker Cohort (n = 167)	65.3%	12.5 mo	15.0 mo
IDH1/IDH2 (n = 43)	83.7%	Not reached	Not reached
NPM1 (n = 26)	84.6%	Not reached	Not reached
TP53 (n = 37)	59.5%	8.9 mo	5.6 mo
FLT3 (n = 30)	53.3%	12.4 mo	19.9 mo

Chyla BJ et al. *Proc ASH* 2019;Abstract 546.

All patients with AML who are receiving venetoclax in combination with a hypomethylating agent should be admitted to the hospital to begin treatment and receive tumor lysis syndrome prophylaxis regardless of disease burden or performance status.

1. Agree
2. Disagree


Agree
0%
Disagree
0%

All patients with AML who are receiving venetoclax in combination with a hypomethylating agent should be admitted to the hospital to begin treatment and receive tumor lysis syndrome prophylaxis regardless of disease burden or performance status.

 HARRY P ERBA, MD, PHD	Disagree
 MARK LEVIS, MD, PHD	Agree
 DANIEL A POLLYEA, MD, MS	Agree
 KEITH W PRATZ, MD	Disagree
 EYTAN M STEIN, MD	Disagree
 WENDY STOCK, MD	Disagree
 RICHARD M STONE, MD	Disagree

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Which agents do you generally administer as prophylaxis to patients receiving venetoclax in combination with azacitidine?

 HARRY P ERBA, MD, PHD	Acyclovir, allopurinol, antifungal therapy, extended-spectrum quinolone
 MARK LEVIS, MD, PHD	Acyclovir, allopurinol, extended-spectrum quinolone
 DANIEL A POLLYEA, MD, MS	Acyclovir, allopurinol, extended-spectrum quinolone
 KEITH W PRATZ, MD	Acyclovir, allopurinol, extended-spectrum quinolone
 EYTAN M STEIN, MD	Acyclovir, allopurinol, antifungal therapy, extended-spectrum quinolone
 WENDY STOCK, MD	Acyclovir, allopurinol, antifungal therapy, extended-spectrum quinolone
 RICHARD M STONE, MD	Allopurinol

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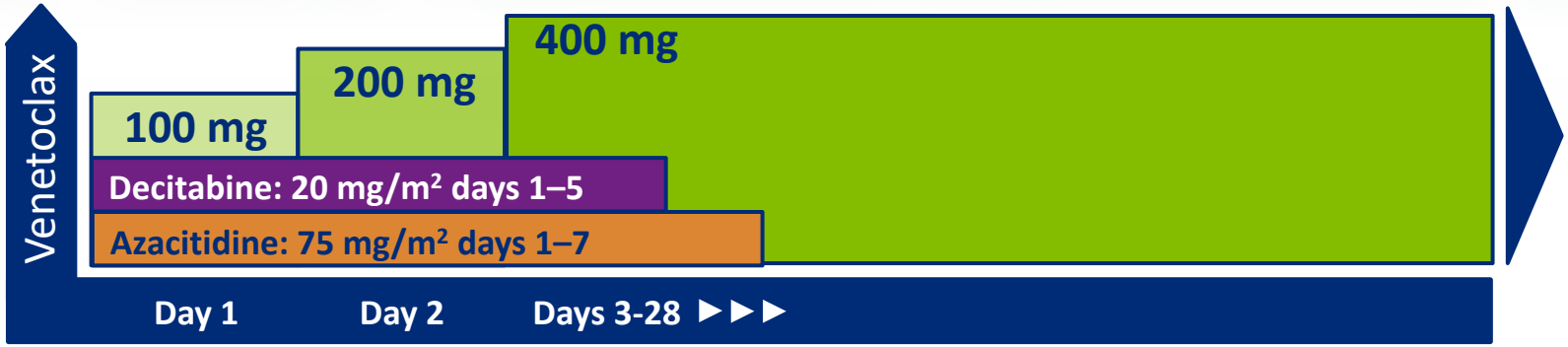
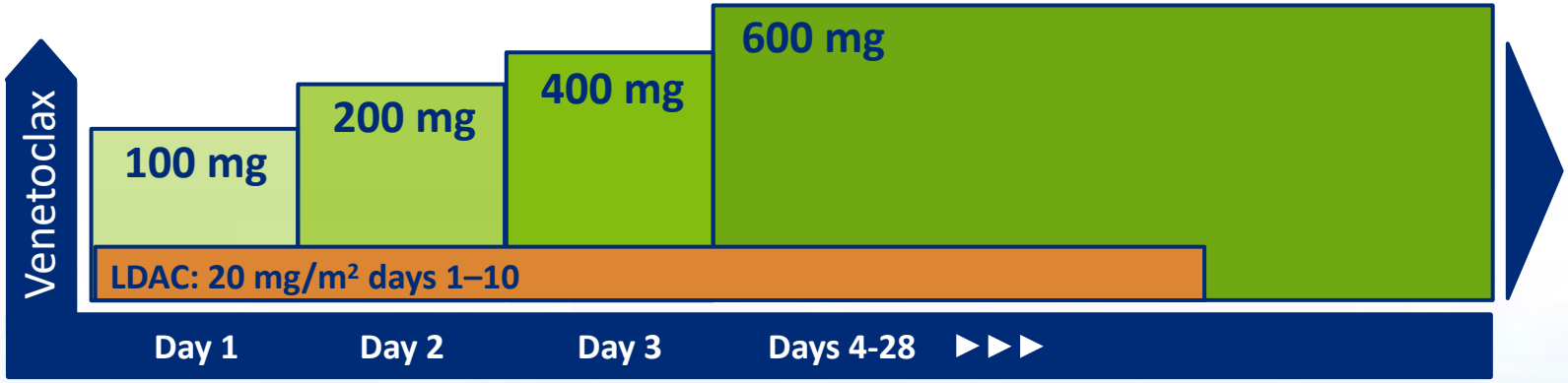
Venetoclax Dosing in AML

HMA + Venetoclax



Patients received **venetoclax** plus **decitabine** **or** **azacitidine**

LDAC + Venetoclax



DiNardo CD et al. *Lancet Oncol* 2018;19(2):226-8; Wei AH et al. *JCO* 2019;37(15):1678-85; Venetoclax package insert, July 2019.

Select Treatment-Emergent Adverse Events in Phase Ib/II Studies of Venetoclax with LDAC or HMA

Treatment-emergent AE	VEN 400 mg + HMA (n = 60)	VEN 600 mg + LDAC (n = 82)
Any event	100%	100%
AE with Grade ≥3		
Febrile neutropenia	50%	42%
Decreased WBC count	33%	34%
Anemia	27%	27%

- Patients in both studies were hospitalized and had tumor lysis syndrome (TLS) prophylaxis initiated before the first dose of venetoclax.
- There were no laboratory or clinical cases of TLS in the Phase Ib study of venetoclax with HMA.
- There were 2 cases of laboratory TLS and no cases of clinical TLS in the Phase Ib/II study of venetoclax with LDAC.

DiNardo CD et al. *Blood* 2019;133 (1):7-17; Wei A et al. *J Clin Oncol* 2019;37:1277-84.

Select Ongoing Phase III Studies of Venetoclax in AML

Study	Target accrual	Setting	Randomization
VIALE-A (NCT02993523)	443	Treatment-naïve*	• Azacitidine + venetoclax • Azacitidine
VIALE-C (NCT03069352)	211	Treatment-naïve*	• Low-dose cytarabine + venetoclax • Low-dose cytarabine
VIALE-M (NCT04102020)	360	CR/CRi after induction and consolidation†	• Azacitidine + venetoclax • Best supportive care

* Ineligible for standard induction therapy

† Intermediate- or adverse-risk cytogenetics

www.clinicaltrials.gov. Accessed October 2019.

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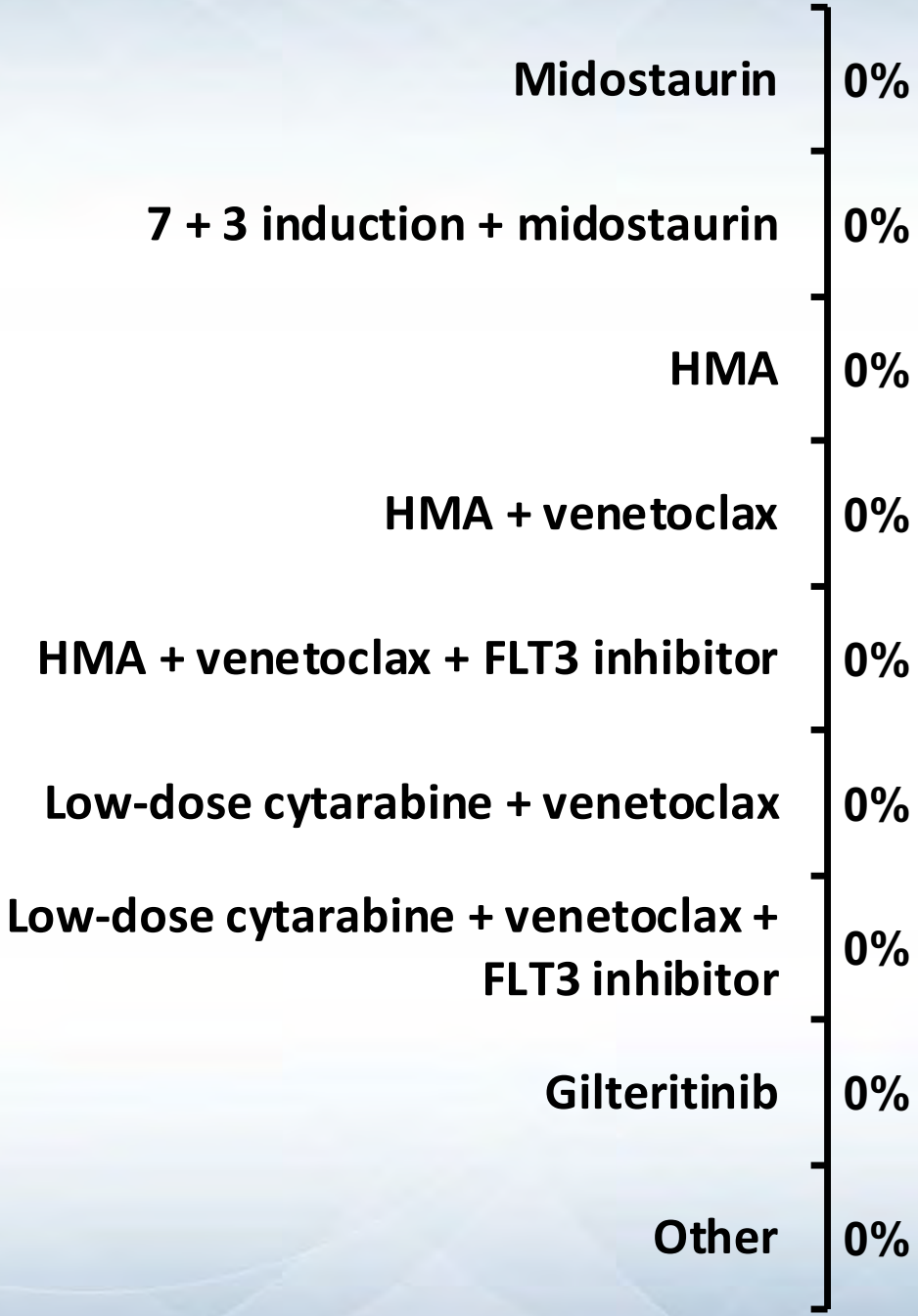
A 76-year-old otherwise healthy woman presents with mildly symptomatic AML with normal karyotype, WBC = 20K with 50% blasts, HCT = 28 and PLT = 42. A FLT3-ITD mutation is detected by PCR with an allelic burden of 0.7. What initial therapy would you recommend?

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



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 MARK LEVIS, MD, PHD	Azacitidine + venetoclax + gilteritinib
 DANIEL A POLLYEA, MD, MS	Azacitidine + venetoclax
 KEITH W PRATZ, MD	Azacitidine + venetoclax
 EYTAN M STEIN, MD	Azacitidine + venetoclax
 WENDY STOCK, MD	Azacitidine + venetoclax (followed by gilteritinib if no CR)
 RICHARD M STONE, MD	7 + 3 induction + midostaurin

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A 32-year-old man is diagnosed with AML after evaluation at an urgent care for respiratory symptoms and petechiae. WBC is 55K with circulating blasts. Bone marrow demonstrates 80% CD33+ blasts with NPM1 and FLT3-ITD mutation with an allelic ratio of 0.2. What treatment would you recommend?

 HARRY P ERBA, MD, PHD	Intensive chemotherapy + midostaurin
 MARK LEVIS, MD, PHD	Intensive chemotherapy + midostaurin
 DANIEL A POLLYEA, MD, MS	Intensive chemotherapy + midostaurin
 KEITH W PRATZ, MD	Intensive chemotherapy + midostaurin
 EYTAN M STEIN, MD	Intensive chemotherapy + midostaurin
 WENDY STOCK, MD	Intensive chemotherapy + midostaurin
 RICHARD M STONE, MD	Intensive chemotherapy + midostaurin

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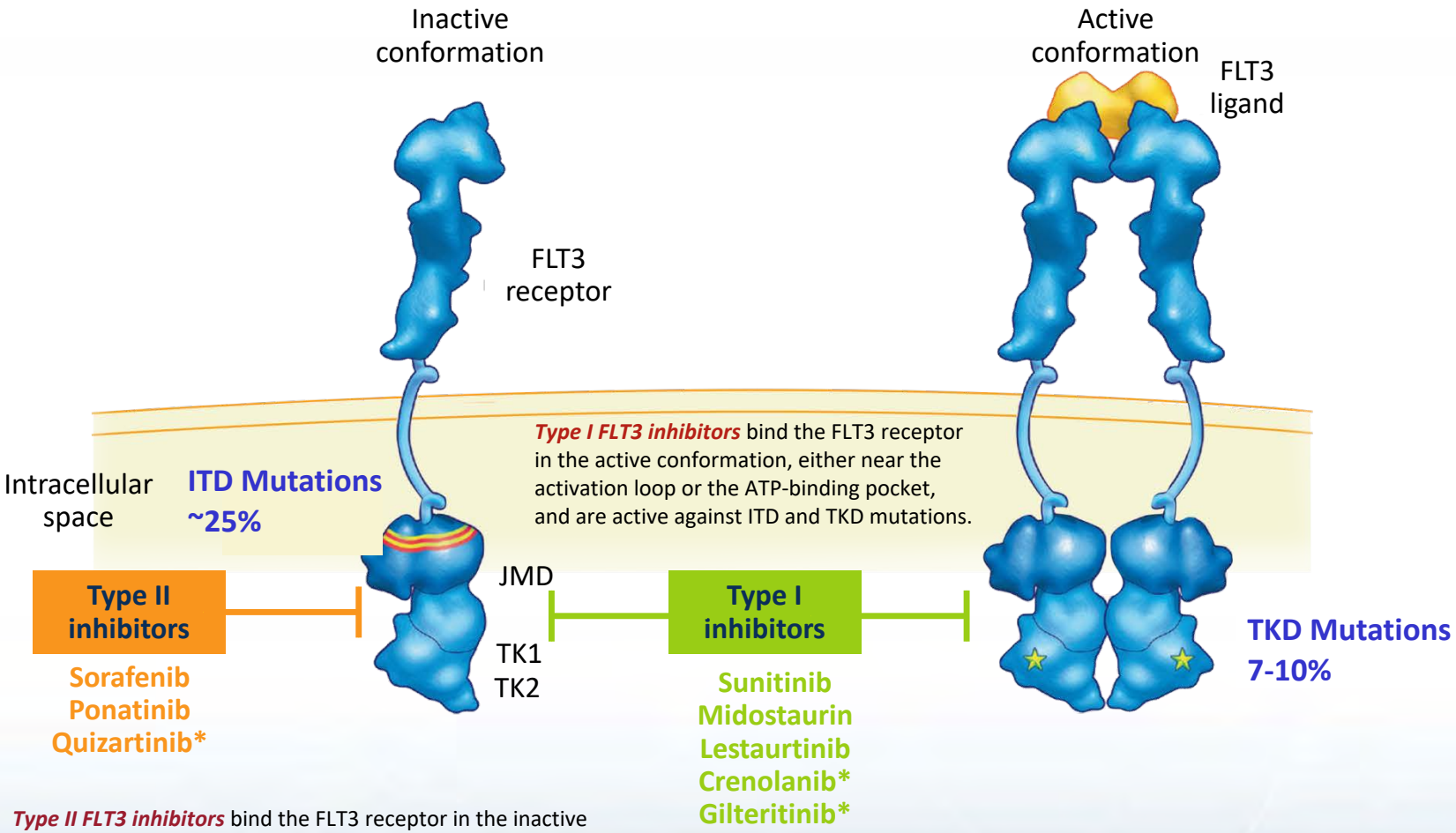
FLT3 Mutations (ITD and TKD) Occur in Approximately 30-35% of Patients with AML



Daver N et al. *Leukemia* 2019;33:299-312.

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Characteristics of Select FLT3 Inhibitors

FLT3 Inhibitor	Inhibitory Type	FLT3 Kinase Inhibition IC50 (nmol/L)	Non-FLT3 Targets	FLT3-TKD mutation activity	Major Toxicities
Sorafenib 400 mg BID	II	58	c-KIT PDGFR RAF VEGFR	No	Rash Hemorrhage Myelosuppression
Midostaurin 50 mg BID	I	6.3	c-KIT PDGFR PKC VEGFR	Yes	GI toxicity Myelosuppression
Quizartinib 30 – 60 mg QD	II	1.6	c-KIT	No	QTc prolongation Myelosuppression
Gilteritinib 120 mg QD	I	0.29	AXL LTK ALK	Yes	Elevated transaminases Diarrhea

Kiyoi H et al. *Cancer Science* 2019;[Epub ahead of print];
Short NJ et al. *Ther Adv Hematol* 2019;10:2040620719827310.

The NEW ENGLAND JOURNAL of MEDICINE

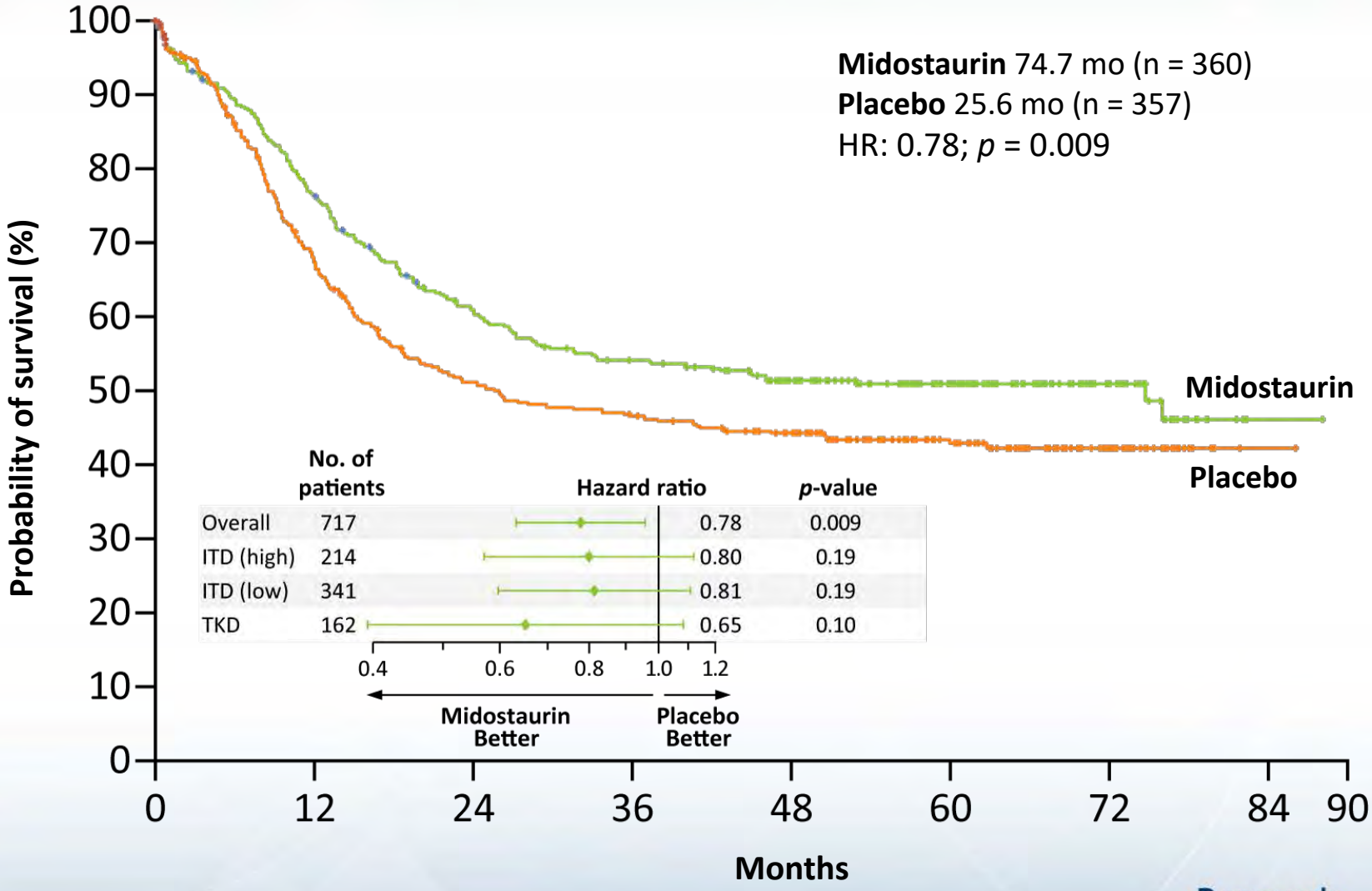
ORIGINAL ARTICLE

Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a *FLT3* Mutation

R.M. Stone, S.J. Mandrekar, B.L. Sanford, K. Laumann, S. Geyer, C.D. Bloomfield, C. Thiede, T.W. Prior, K. Döhner, G. Marcucci, F. Lo-Coco, R.B. Klisovic, A. Wei, J. Sierra, M.A. Sanz, J.M. Brandwein, T. de Witte, D. Niederwieser, F.R. Appelbaum, B.C. Medeiros, M.S. Tallman, J. Krauter, R.F. Schlenk, A. Ganser, H. Serve, G. Ehninger, S. Amadori, R.A. Larson, and H. Döhner

N Engl J Med 2017;377:454-64

RATIFY: Overall Survival Analyses



Stone RM et al. *N Engl J Med* 2017;377:454-64.

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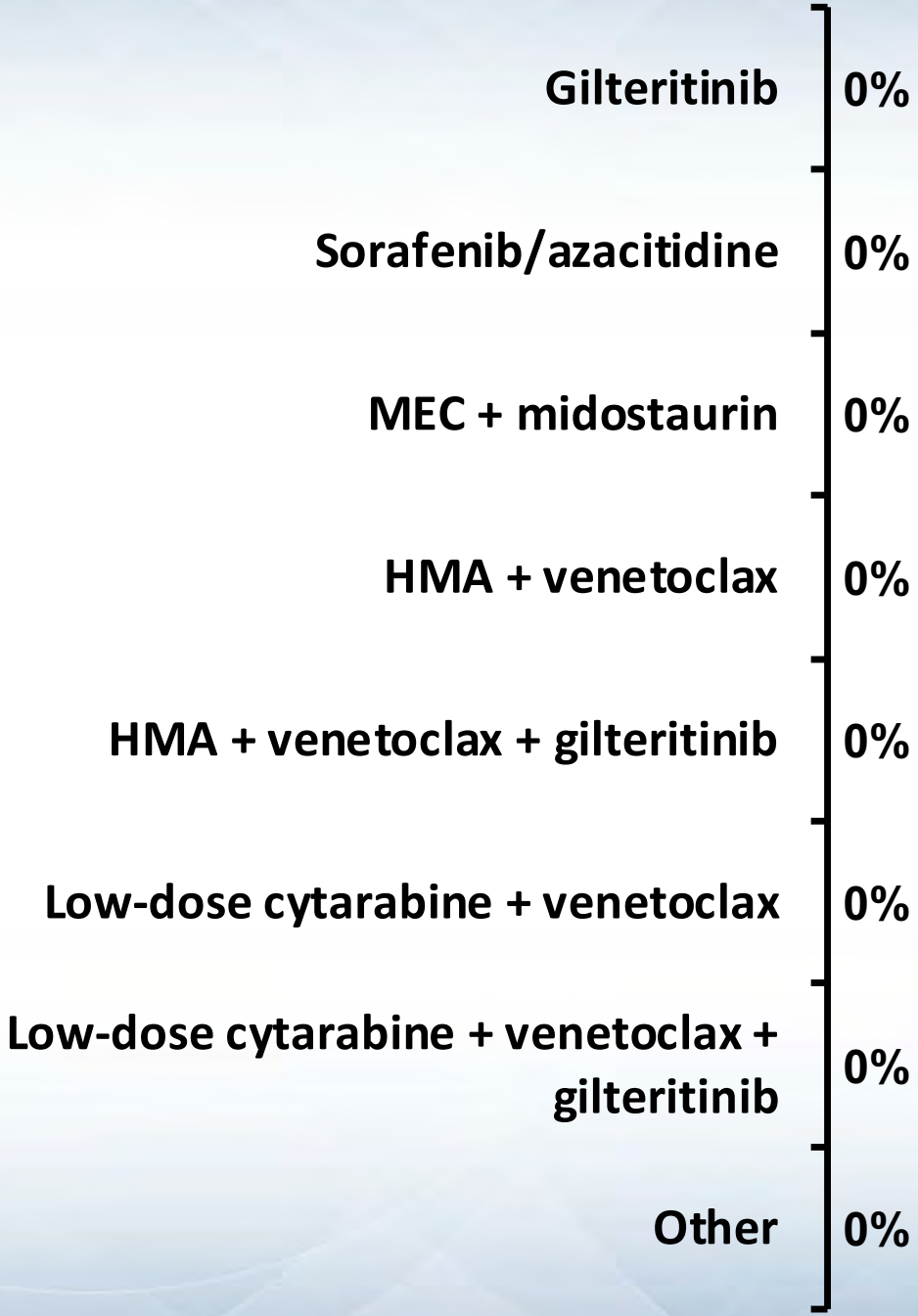
A 66-year-old otherwise healthy man with AML with a FLT3 mutation receives 7 + 3 induction and midostaurin, achieves remission and receives consolidation with 3 cycles of modified high-dose cytarabine and midostaurin. Four months after completion of therapy, he experiences disease progression and a FLT3-ITD mutation (allelic burden of 0.4) is found. What would you recommend?

1. Gilteritinib
2. Sorafenib/azacitidine
3. MEC + midostaurin
4. HMA + venetoclax
5. HMA + venetoclax + gilteritinib
6. Low-dose cytarabine + venetoclax
7. Low-dose cytarabine + venetoclax + gilteritinib
8. Other



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 HARRY P ERBA, MD, PHD	Gilteritinib
 MARK LEVIS, MD, PHD	Azacitidine + gilteritinib
 DANIEL A POLLYEA, MD, MS	Gilteritinib
 KEITH W PRATZ, MD	Azacitidine + venetoclax + gilteritinib
 EYTAN M STEIN, MD	Gilteritinib
 WENDY STOCK, MD	Gilteritinib
 RICHARD M STONE, MD	Gilteritinib

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FDA Approves Addition of Survival Data to Gilteritinib Label for Relapsed or Refractory AML with a FLT3 Mutation

Press Release – May 29, 2019

"The Food and Drug Administration approved the addition of overall survival data in labeling for gilteritinib, indicated for adult patients who have relapsed or refractory AML with a FLT3 mutation as detected by an FDA-approved test.

Approval was based on the ADMIRAL trial (NCT02421939), which included 371 adult patients with relapsed or refractory AML having a FLT3 ITD, D835, or I836 mutation by the LeukoStrat CDx FLT3 Mutation Assay. Patients were randomized (2:1) to receive gilteritinib 120 mg once daily (n = 247) over continuous 28-day cycles or prespecified salvage chemotherapy (n = 124). Salvage chemotherapy included either intensive cytotoxic chemotherapy or a low-intensity regimen. For the analysis, overall survival (OS) was measured from the randomization date until death by any cause."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-addition-survival-data-gilteritinib-label-refractory-aml-flt3-mutation

Gilteritinib Significantly Prolongs Overall Survival in Patients with FLT3-Mutated ($FLT3^{mut+}$) Relapsed/Refractory (R/R) Acute Myeloid Leukemia (AML): Results from the Phase 3 ADMIRAL Trial[1]

Effect of Gilteritinib on Survival in Patients with FLT3-Mutated ($FLT3^{mut+}$) Relapsed/Refractory (R/R) AML Who Have Common AML Co-Mutations or a High FLT3-ITD Allelic Ratio[2]

[1] Perl A et al.
Proc EHA 2019;Abstract S876.

[2] Levis MJ et al.
Proc ASCO 2019;Abstract 7000.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

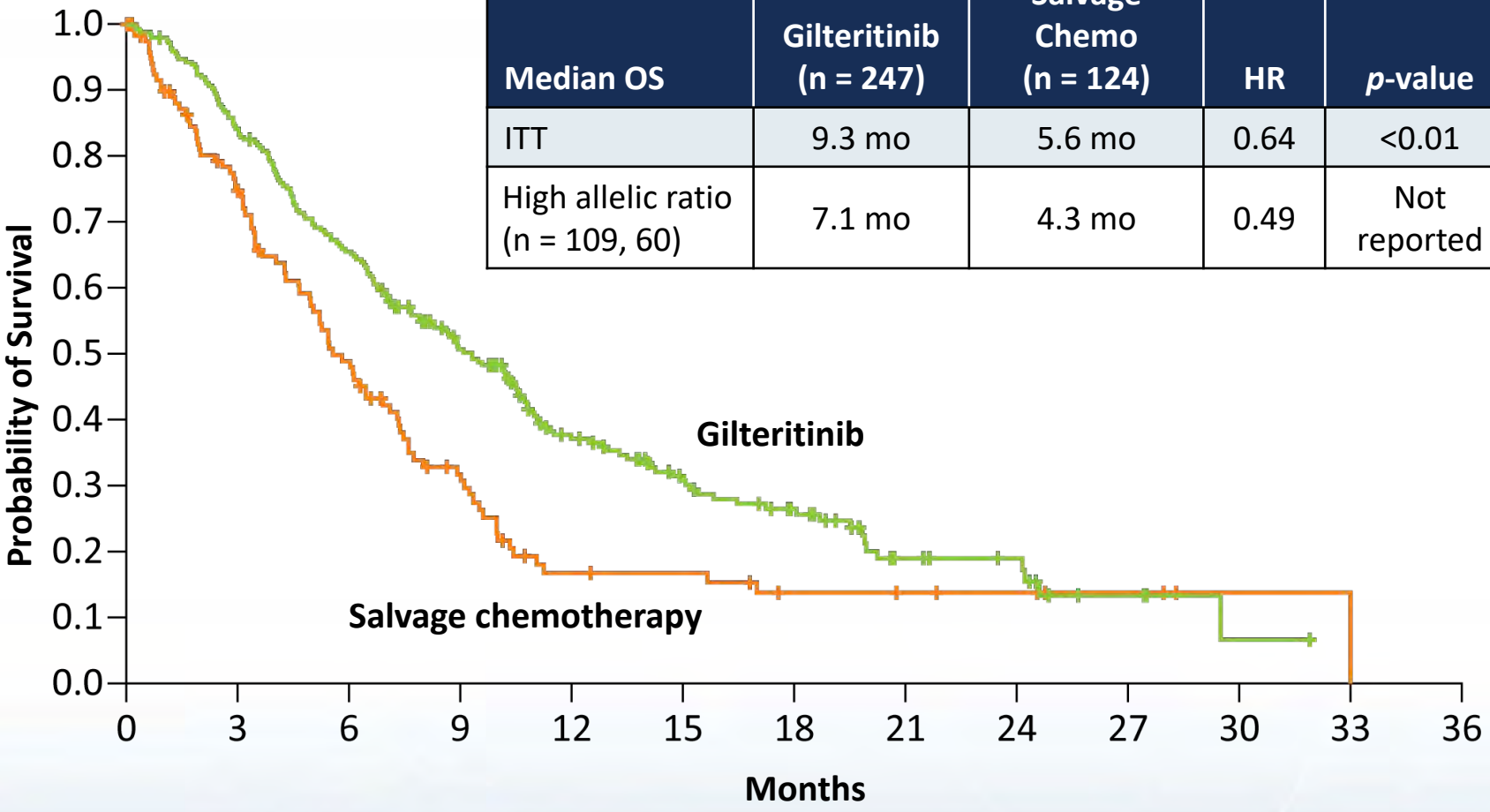
Gilteritinib or Chemotherapy for Relapsed or Refractory *FLT3*-Mutated AML

A.E. Perl, G. Martinelli, J.E. Cortes, A. Neubauer, E. Berman, S. Paolini, P. Montesinos, M.R. Baer, R.A. Larson, C. Ustun, F. Fabbiano, H.P. Erba, A. Di Stasi, R. Stuart, R. Olin, M. Kasner, F. Ciceri, W.-C. Chou, N. Podoltsev, C. Recher, H. Yokoyama, N. Hosono, S.-S. Yoon, J.-H. Lee, T. Pardee, A.T. Fathi, C. Liu, N. Hasabou, X. Liu, E. Bahceci, and M.J. Levis

N Engl J Med 2019;381:1728-40.

ADMIRAL: Overall Survival

Median OS	Gilteritinib (n = 247)	Salvage Chemo (n = 124)	HR	*p*-value
ITT	9.3 mo	5.6 mo	0.64	<0.01
High allelic ratio (n = 109, 60)	7.1 mo	4.3 mo	0.49	Not reported



Perl AE et al. *N Engl J Med* 2019;381:1728-40.

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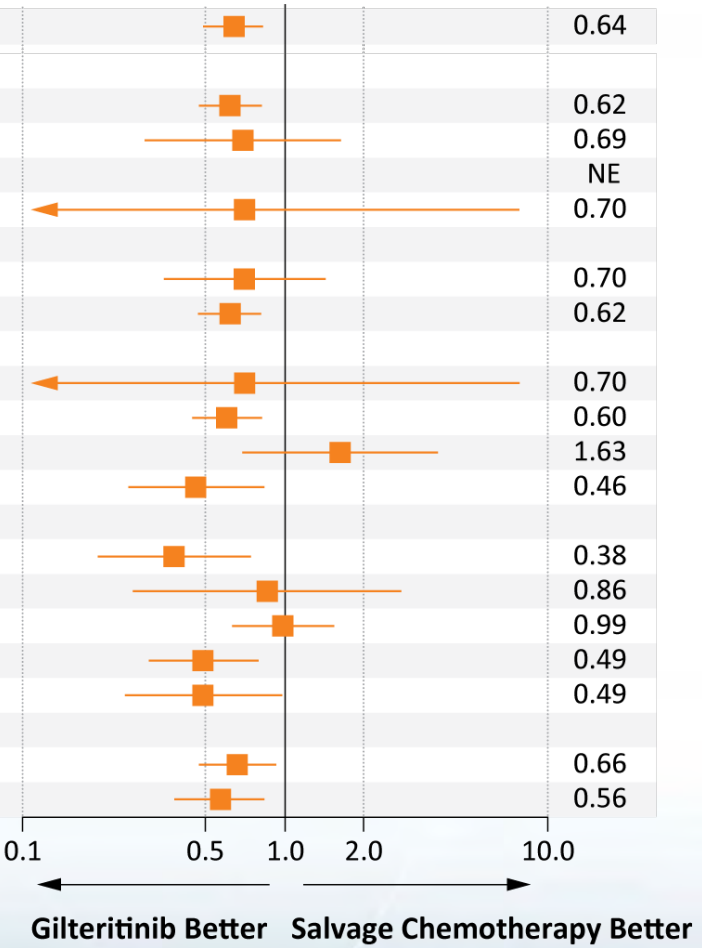
ADMIRAL: Subgroup Analysis of Overall Survival

Subgroup	Gilteritinib	Salvage Chemotherapy	Hazard Ratio for Death
	no. of events/total no. of patients		
All patients	171/247	90/124	0.64
FLT3 mutation type			
FLT3 ITD alone	145/215	81/113	0.62
FLT3 TKD alone	16/21	8/10	0.69
FLT3 ITD and FLT3 TKD	6/7	0	NE
Other	4/4	1/1	0.70
Previous use of FLT3 inhibitor			
Yes	26/32	11/14	0.70
No	145/215	79/110	0.62
Cytogenetic risk status			
Favorable	3/4	1/1	0.70
Intermediate	119/182	63/89	0.60
Unfavorable	22/26	7/11	1.63
Unknown	27/35	19/23	0.46
Response to first-line therapy per IRT			
Relapse ≤6 mo after allogeneic HSCT	24/31	16/17	0.38
Relapse >6 mo after allogeneic HSCT	10/17	4/8	0.86
Primary refractory disease without HSCT	70/98	28/48	0.99
Relapse ≤6 mo after composite complete remission and no HSCT	47/67	28/34	0.49
Relapse >6 mo after composite complete remission and no HSCT	20/34	14/17	0.49
Preselected chemotherapy per IRT			
High intensity	96/149	52/75	0.66
Low intensity	75/98	38/49	0.56



Perl AE et al. *N Engl J Med* 2019;381:1728-40.

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ADMIRAL: Antileukemic Responses

	Gilteritinib (n = 247)	Salvage Chemo (n = 124)	HR or Risk Difference
Complete remission (CR)	21.1%	10.5%	10.6
CR or CR with partial hematologic recovery	34.0%	15.3%	18.6
CR with partial hematologic recovery	13.0%	4.8%	Not determined
CR with incomplete hematologic recovery	25.5%	11.3%	Not determined
CR with incomplete platelet recovery	7.7%	0	Not determined
Composite CR*	54.3%	21.8%	32.5
Overall response	67.6%	25.8%	Not reported

*Composite complete remission was defined as the combination of CR, CR with incomplete hematologic recovery, and CR with incomplete platelet recovery

Perl AE et al. *N Engl J Med* 2019;381:1728-40.

Select Ongoing Phase III Trials of FLT3 Inhibitors

Study	Target Accrual	Setting	Randomization
NCT01371981	1,641	Newly diagnosed	• Chemotherapy • Chemotherapy + bortezomib • Chemotherapy + bortezomib + sorafenib
NCT02997202	346	Newly diagnosed/ Maintenance after transplant	• Gilteritinib • Placebo
HOVON 156 AML (NCT04027309)	768	Newly diagnosed	• Induction/consolidation chemo + midostaurin → midostaurin • Induction/consolidation chemo + gilteritinib → gilteritinib
QuANTUM-FIRST	539	Newly diagnosed	• Induction/consolidation chemo + quizartinib → quizartinib • Induction/consolidation chemo + placebo → placebo

www.clinicaltrials.gov. Accessed January 2020.

Management of Acute Myeloid Leukemia

Module 1: Contemporary Biomarker Assessment

- Incidence and prognostic relevance of cytogenetic and other molecular markers
- Guideline-endorsed recommendations for biomarker assessment

Module 2: Bcl-2 Inhibition as a Rational Therapeutic Strategy

- Biologic rationale for venetoclax in AML
- Safety, efficacy and patient selection for venetoclax in combination with HMAs or LDAC

Module 3: FLT3 Inhibitors in the Up-Front and Recurrent Settings

- Data supporting midostaurin in newly diagnosed AML (RATIFY)
- Efficacy and safety data with gilteritinib (ADMIRAL)

Module 4: IDH Inhibitors in the Up-Front and Recurrent Settings

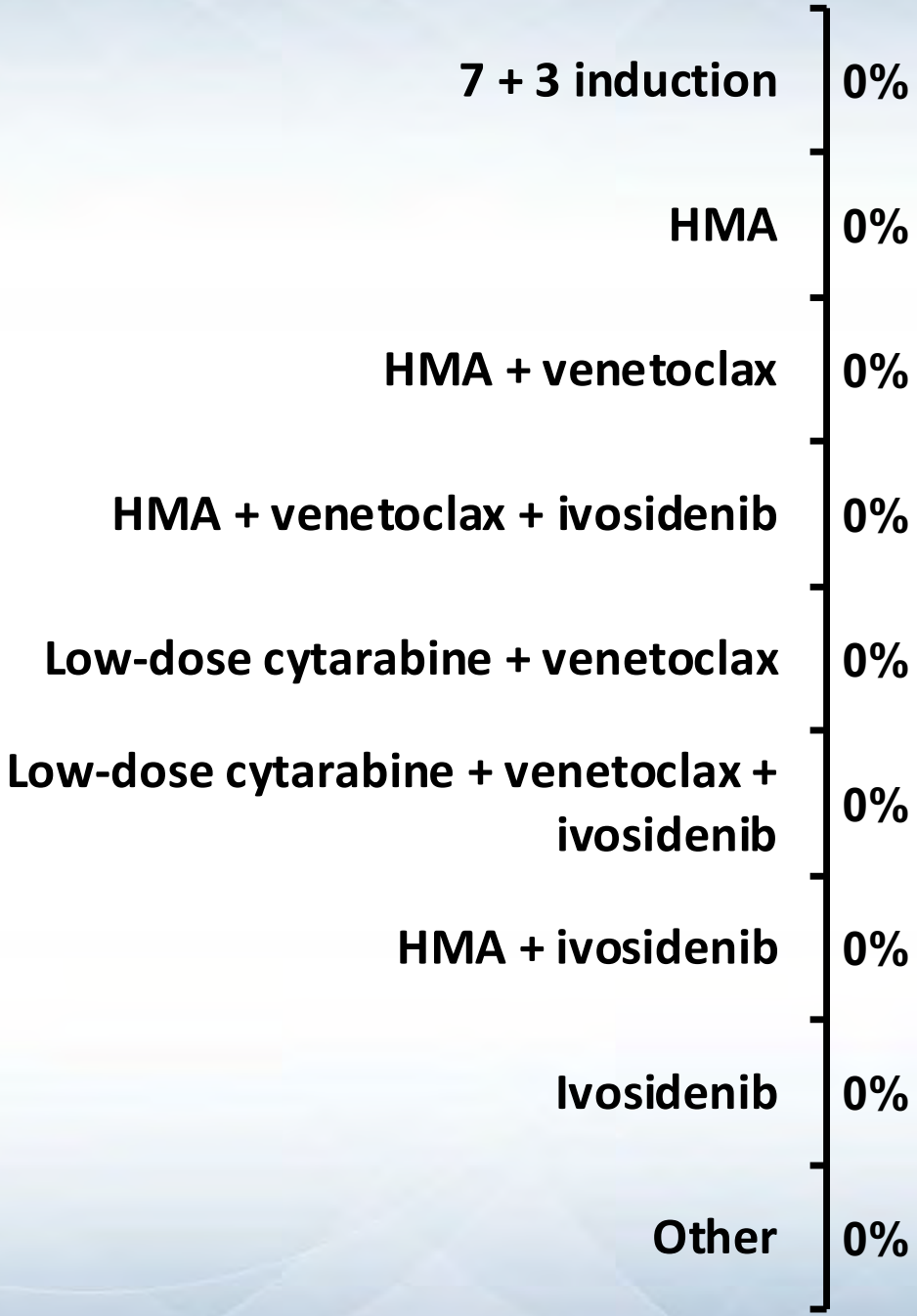
- Efficacy and safety of enasidenib and ivosidenib
- Differentiation syndrome and other side effects of IDH inhibitors

Module 5: Other Novel Treatment Approaches

- Efficacy, safety and recent approval of glasdegib for newly diagnosed AML (BRIGHT 1003)
- Optimal incorporation of CPX-351 for the treatment of AML
- CC-486 as maintenance therapy for AML in complete remission
- Emerging therapeutics (CAR T-cell therapy, checkpoint inhibitors)

What initial treatment would you recommend for a 77-year-old woman with 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 initial treatment would you recommend for a 77-year-old woman with AML with an IDH1 mutation?

 HARRY P ERBA, MD, PHD	Azacitidine + venetoclax
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 EYTAN M STEIN, MD	Azacitidine + venetoclax
 WENDY STOCK, MD	Azacitidine + venetoclax
 RICHARD M STONE, MD	Azacitidine + venetoclax

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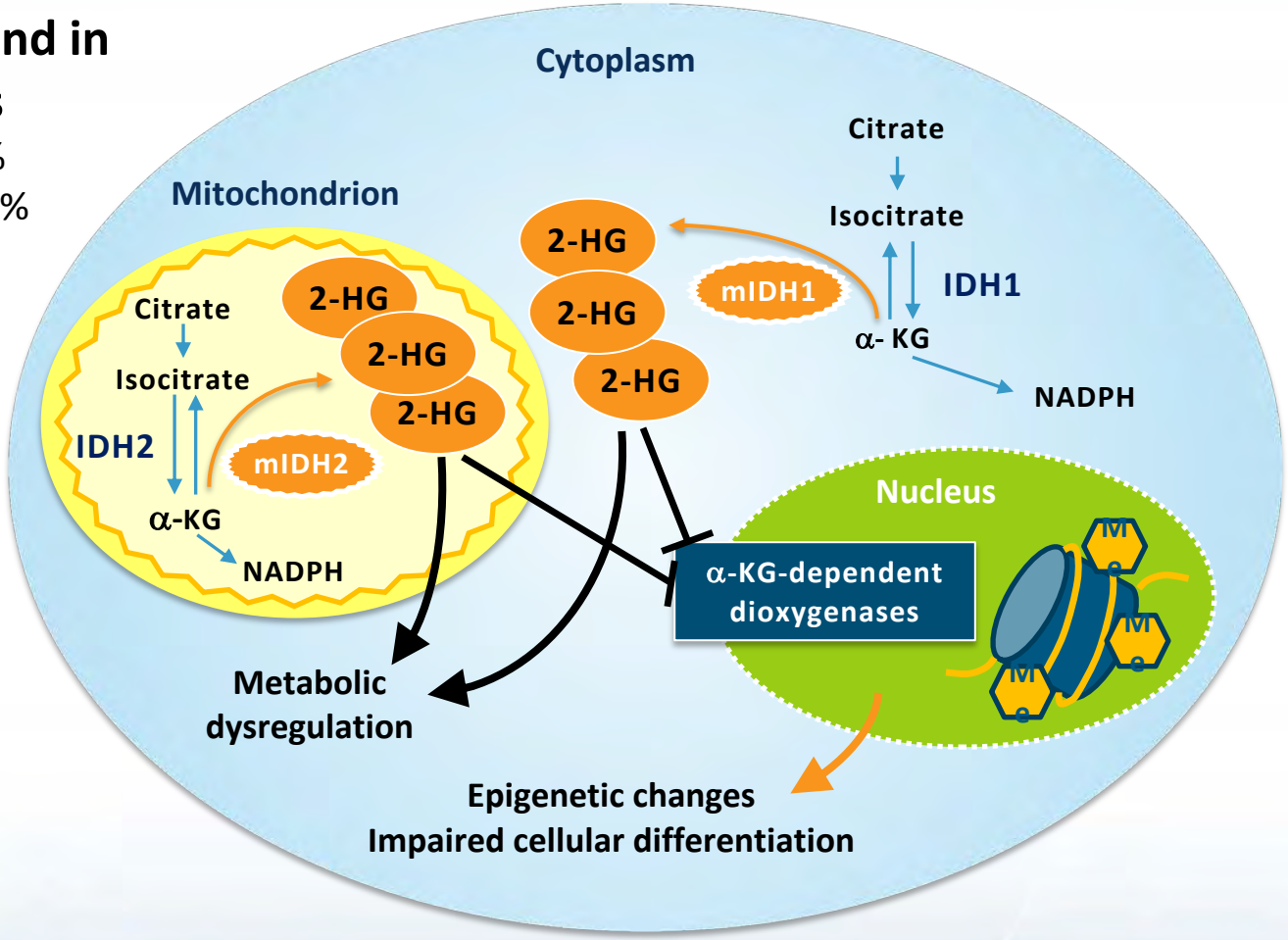
IDH1 and IDH2 Mutations in AML

IDH mutations are found in ~16-20% of AML cases

- IDH1 mutations in ~7.5%
- IDH2 mutations in ~8-19%



Buege MJ et al. *Cancers* 2018;10:187; Döhner H et al. *N Engl J Med* 2015;373(12):1136-52; Bullinger L et al. *J Clin Oncol* 2017;35(9):934-46.

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FDA Approval of Ivosidenib as First-Line Treatment for AML with IDH1 Mutation

Press Release – May 2, 2019

"On May 2, 2019, the Food and Drug Administration approved ivosidenib for newly-diagnosed AML with a susceptible IDH1 mutation, as detected by an FDA-approved test, in patients who are at least 75 years old or who have comorbidities that preclude the use of intensive induction chemotherapy. Approval was based on an open-label, single-arm, multicenter clinical trial (Study AG120-C-001, NCT02074839) of single-agent ivosidenib for newly-diagnosed AML with an IDH1 mutation.

The adverse reactions that occurred in at least 25% of patients were diarrhea, fatigue, edema, decreased appetite, leukocytosis, nausea, arthralgia, abdominal pain, dyspnea, differentiation syndrome and myalgia. Prescribing information contains a Boxed Warning alerting health care professionals and patients about the risk of differentiation syndrome which may be life-threatening or fatal."

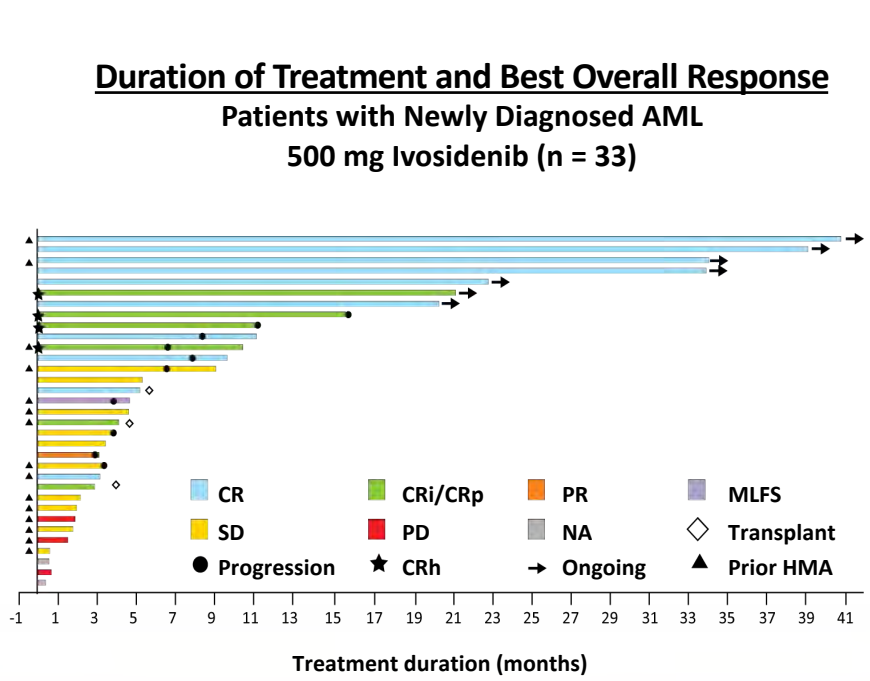
www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ivosidenib-first-line-treatment-aml-idh1-mutation

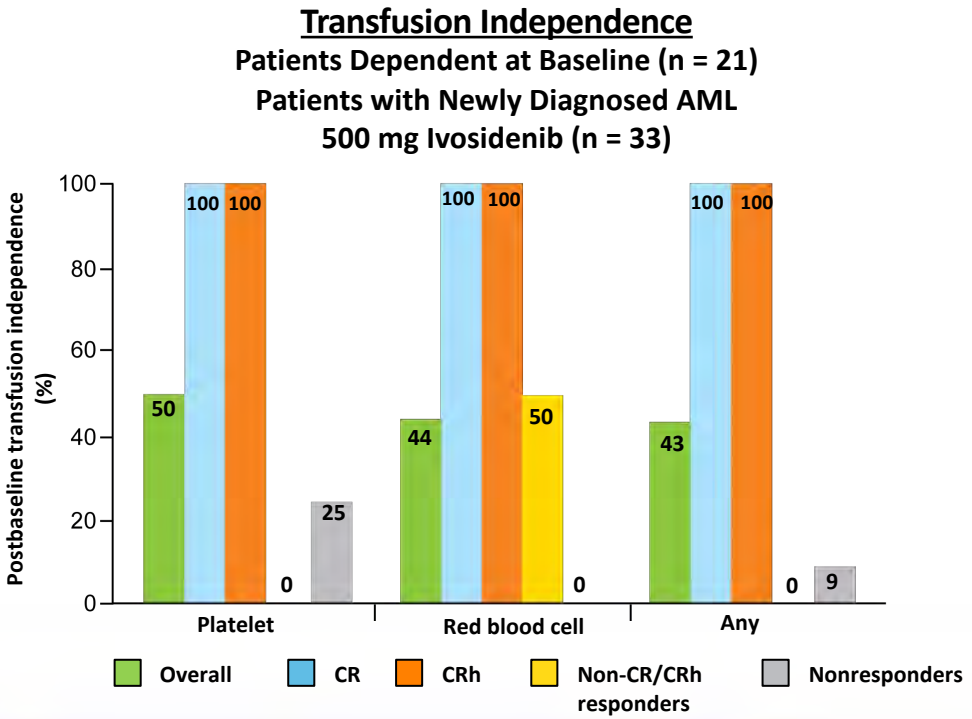
Ivosidenib (IVO; AG-120) in IDH1-Mutant Newly-Diagnosed Acute Myeloid Leukemia (ND AML): Updated Results from a Phase 1 Study

Roboz GJ et al.

Proc ASCO 2019;Abstract 7028.

Ivosidenib in Newly Diagnosed AML: Treatment Duration, Best Overall Response and Transfusion Independence





ORR = 54.4%

Roboz GJ et al. *Proc ASCO* 2019;Abstract 7028.

Research To Practice®

Mutant IDH1 Inhibitor Ivosidenib (IVO; AG-120) in Combination with Azacitidine (AZA) for Newly Diagnosed Acute Myeloid Leukemia (ND AML)[1]

Enasidenib Plus Azacitidine Significantly Improves Complete Remission and Overall Response Compared with Azacitidine Alone in Patients with Newly Diagnosed Acute Myeloid Leukemia (AML) with Isocitrate Dehydrogenase 2 (IDH2) Mutations: Interim Phase II Results from an Ongoing, Randomized Study[2]

[1]DiNardo CD et al.
Proc ASCO 2019;Abstract 7011.

[2]DiNardo C et al.
Proc ASH 2019;Abstract 643.

Clinical Efficacy of Ivosidenib or Enasidenib plus Azacitidine in Newly Diagnosed AML

Phase Ib Study of Ivosidenib	Ivosidenib + AZA (n = 23)
Overall response rate	18 (78.3%)
Median duration of response	Not estimable
Complete remission rate	14 (60.9%)

Phase II Study of Enasidenib	Enasidenib + AZA (n = 68)	AZA Monotherapy (n = 33)	*p*-value
Overall response rate	68%	42%	0.0155
Median duration of response	Not reached	10.2 mos	0.13
Complete remission rate	50%	12%	0.0002

DiNardo C et al. *Proc ASH* 2019;Abstract 643.

Ongoing Phase III Studies of IDH Inhibitors in Newly Diagnosed AML

Study	N	Setting	Randomization
HOVON 150 AML (NCT03839771)	968	• Previously untreated AML or MDS-EB2 • IDH1 or IDH mutation • Eligible for intensive chemo	• Ivosidenib or enasidenib + induction + consolidation therapy → maintenance therapy • Placebo + induction + consolidation therapy → maintenance therapy
AGILE (NCT03173248)	392	• Previously untreated AML • IDH1 mutation • Ineligible for intensive chemo	• Ivosidenib + azacitidine • Placebo + azacitidine

www.clinicaltrials.gov. Accessed December 2019.

FDA Approvals of IDH Inhibitors for R/R AML

The FDA approved **ivosidenib**, a small-molecule inhibitor of isocitrate dehydrogenase (IDH)1 on **July 20, 2018**, for treatment of adults with relapsed or refractory acute myeloid leukemia (R/R AML) with susceptible IDH1 mutation as detected by an FDA-approved test. The efficacy of ivosidenib was established on the basis of complete remission (CR) + CR with partial hematologic recovery (CRh) rate, duration of CR + CRh, and conversion from transfusion dependence (TD) to transfusion independence (TI) in **Study AG120-C-001 (NCT02074839)**

On **August 1, 2017**, the U.S. Food and Drug Administration granted regular approval to **enasidenib** for the treatment of adult patients with relapsed or refractory acute myeloid leukemia with an isocitrate dehydrogenase-2 (IDH2) mutation as detected by an FDA-approved test. The enasidenib approval was based on **Study AG221-C-001 (NCT01915498),** an open-label, single-arm, multicenter, clinical trial of enasidenib that included 199 adults with relapsed or refractory AML who had an IDH2 mutation as detected by the above assay. Patients were treated with enasidenib 100 mg orally daily. Complete response (CR) and complete response with partial hematologic recovery (CRh) rates, CR/CRh duration, and conversion from transfusion dependence to transfusion independence were the basis of approval.

Norsworthy KJ et al. *Clin Cancer Res* 2019;25(20):6021-5.

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-granted-regular-approval-enasidenib-treatment-relapsed-or-refractory-aml

blood

Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Molecular remission and response patterns in patients with mutant-*IDH2* acute myeloid leukemia treated with enasidenib

Eytan M. Stein,[1,2,*] Courtney D. DiNardo,[3,*] Amir T. Fathi,[4,5,*] Daniel A. Pollyea,[6] Richard M. Stone,[7] Jessica K. Altman,[8] Gail J. Roboz,[2,9] Manish R. Patel,[10] Robert Collins,[11] Ian W. Flinn,[12] Mikkael A. Sekeres,[13] Anthony S. Stein,[14] Hagop M. Kantarjian,[3] Ross L. Levine,[1] Paresh Vyas,[15] Kyle J. MacBeth,[16] Alessandra Tosolini,[17] Jason VanOostendorp,[17] Qiang Xu,[17] Ira Gupta,[17] Thomas Lila,[16] Alberto Risueno,[18] Katharine E. Yen,[19] Bin Wu,[19] Eyal C. Attar,[19] Martin S. Tallman,[1,2,†] and Stéphane de Botton[20,21,†]

***Blood* 2019;133(7):676-87.**

Enasidenib for IDH2-Mutated Relapsed/Refractory AML: Updated Response and Survival Outcomes

	Refractory to intensive chemotherapy (n = 40)	Refractory to lower-intensity therapy (n = 44)†	Relapsed following any prior AML therapy (n = 130)
ORR, n (%)*	15 (37.5%)	19 (43.2%)	49 (37.7%)
CR, n (%)	4 (10.0%)	12 (27.3%)	26 (20.0%)
CRi/CRp, n (%)	4 (10.0%)	2 (4.5%)	14 (10.8%)
Median OS	12.4 mo	8.0 mo	8.1 mo

* ORR included CR, CRi/CRp, MLFS and PR

† Hypomethylating agents or low-dose cytarabine

Stein EM et al. *Blood* 2019;133(7):676-87.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Durable Remissions with Ivosidenib in *IDH1*-Mutated Relapsed or Refractory AML

C.D. DiNardo, E.M. Stein, S. de Botton, G.J. Roboz, J.K. Altman, A.S. Mims, R. Swords, R.H. Collins, G.N. Mannis, D.A. Pollyea, W. Donnellan, A.T. Fathi, A. Pigneux, H.P. Erba, G.T. Prince, A.S. Stein, G.L. Uy, J.M. Foran, E. Traer, R.K. Stuart, M.L. Arellano, J.L. Slack, M.A. Sekeres, C. Willekens, S. Choe, H. Wang, V. Zhang, K.E. Yen, S.M. Kapsalis, H. Yang, D. Dai, B. Fan, M. Goldwasser, H. Liu, S. Agresta, B. Wu, E.C. Attar, M.S. Tallman, R.M. Stone, and H.M. Kantarjian

N Engl J Med 2018;378:2386-98.

Ivosidenib for IDH1-Mutated Relapsed or Refractory AML: Primary Efficacy Population (N = 125)

Efficacy endpoint	Rate	Median duration
CR or CRh	30.4%	8.2 mo
Complete remission	21.6%	9.3 mo
Overall response	41.6%	6.5 mo

Median OS: 8.8 mos

Change from red-cell transfusion-dependent → RBT-independent: 35%

DiNardo CD et al. *N Engl J Med* 2018;378:2386-98.

Commonly Observed and Noteworthy IDH Inhibitor-Related Adverse Events (AEs)

Commonly Observed Treatment-Emergent AEs (Any Grade, >20%)

- **Enasidenib:** Hyperbilirubinemia, nausea
- **Ivosidenib:** Diarrhea, leukocytosis, nausea, fatigue, febrile neutropenia, dyspnea, anemia, QT prolongation, peripheral edema

Noteworthy Grade 3/4 AEs

- **IDH-differentiation syndrome: 5-6%**
- **Prolongation of the QT interval**
  - Enasidenib: Not reported
  - Ivosidenib: ~8%
- **Leukocytosis: 2-3%**
- **Hyperbilirubinemia**
  - Enasidenib: 12%
  - Ivosidenib: Not reported

Stein EM et al. *Blood* 2017;130(6):722-31; DiNardo CD et al. *N Engl J Med* 2018;378:2386-98; Fathi AT et al. *JAMA Oncol* 2018;4(8):1106-10.

IDH Differentiation Syndrome (IDH-DS)

- **Potentially fatal complication of effective leukemia treatment**
  - First described in patients with APL treated with ATRA
- **Signs and symptoms of DS are not specific**
  - Fever, edema, weight gain, leukocytosis, rash, hypotension, renal dysfunction, and pleural and pericardial effusions
  - A rising leukocyte count, comprising increasing neutrophils with a parallel decrease in leukemic blasts
- **Median time to onset:** ~30 days (range: 5-340 days)
- **Frequency:** 5-6% Grade 3 or higher
  - Frequent dose interruptions but not associated with treatment discontinuation
- **Treatment**
  - Corticosteroids for IDH-DS
  - Hydroxyurea for leukocytosis, which frequently accompanies IDH-DS
  - Hyperuricemia agents for tumor lysis syndrome, which may co-occur

Stein EM et al. *Blood* 2017;130(6):722-31; Stein EM et al. *Blood* 2019;133(7):676-87; DiNardo CD et al. *N Engl J Med* 2018;378:2386-98; Birendra KC, DiNardo CD. *Clin Lymphoma Myeloma Leuk* 2016;16(8):460-5.

A 64-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?

 HARRY P ERBA, MD, PHD	Discontinue ivosidenib and begin antibiotics and corticosteroids
 MARK LEVIS, MD, PHD	Continue ivosidenib and begin antibiotics and corticosteroids
 DANIEL A POLLYEA, MD, MS	Continue ivosidenib and begin antibiotics and corticosteroids
 KEITH W PRATZ, MD	Continue ivosidenib and begin antibiotics and corticosteroids
 EYTAN M STEIN, MD	Continue ivosidenib and begin antibiotics and corticosteroids
 WENDY STOCK, MD	Continue ivosidenib and begin antibiotics and corticosteroids
 RICHARD M STONE, MD	Continue ivosidenib and begin antibiotics and corticosteroids

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A 65-year-old man with relapsed/refractory AML and an IDH2 R140 mutation presents with a WBC of 25K and 80% blasts and is started on enasidenib. After 3 weeks, his WBC has risen to 50K and the patient still has 80% blasts. He is clinically stable otherwise. What would you recommend?

 HARRY P ERBA, MD, PHD	Continue enasidenib and begin hydroxyurea
 MARK LEVIS, MD, PHD	Continue enasidenib and begin hydroxyurea
 DANIEL A POLLYEA, MD, MS	Continue enasidenib and begin hydroxyurea
 KEITH W PRATZ, MD	Continue enasidenib and begin hydroxyurea and corticosteroids for differentiation syndrome
 EYTAN M STEIN, MD	Continue enasidenib and begin hydroxyurea
 WENDY STOCK, MD	Continue enasidenib and begin hydroxyurea
 RICHARD M STONE, MD	Continue enasidenib and begin hydroxyurea

Research To Practice®

Management of Acute Myeloid Leukemia

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- Incidence and prognostic relevance of cytogenetic and other molecular markers
- Guideline-endorsed recommendations for biomarker assessment

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- Optimal incorporation of CPX-351 for the treatment of AML
- CC-486 as maintenance therapy for AML in complete remission
- Emerging therapeutics (CAR T-cell therapy, checkpoint inhibitors)

FDA Approves Glasdegib with Low-Dose Cytarabine for AML in Adults Aged 75 or Older or Those with Comorbidities

Press Release – November 21, 2018

"On November 21, 2018, the Food and Drug Administration approved glasdegib in combination with low-dose cytarabine (LDAC), for newly-diagnosed acute myeloid leukemia (AML) in patients who are 75 years old or older or who have comorbidities that preclude intensive induction chemotherapy. Approval was based on a multicenter, open-label, randomized study (BRIGHT AML 1003, NCT01546038)…

Efficacy was established based on an improvement in overall survival. With a median follow-up of 20 months, median survival was 8.3 months (95% CI: 4.4, 12.2) for the glasdegib + LDAC arm and 4.3 months (95% CI: 1.9, 5.7) for the LDAC alone arm and HR of 0.46 (95% CI: 0.30, 0.71; p = 0.0002)."

https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm626494.htm

ARTICLE

Acute myeloid leukemia

Randomized comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome

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Leukemia 2019;33:379-89

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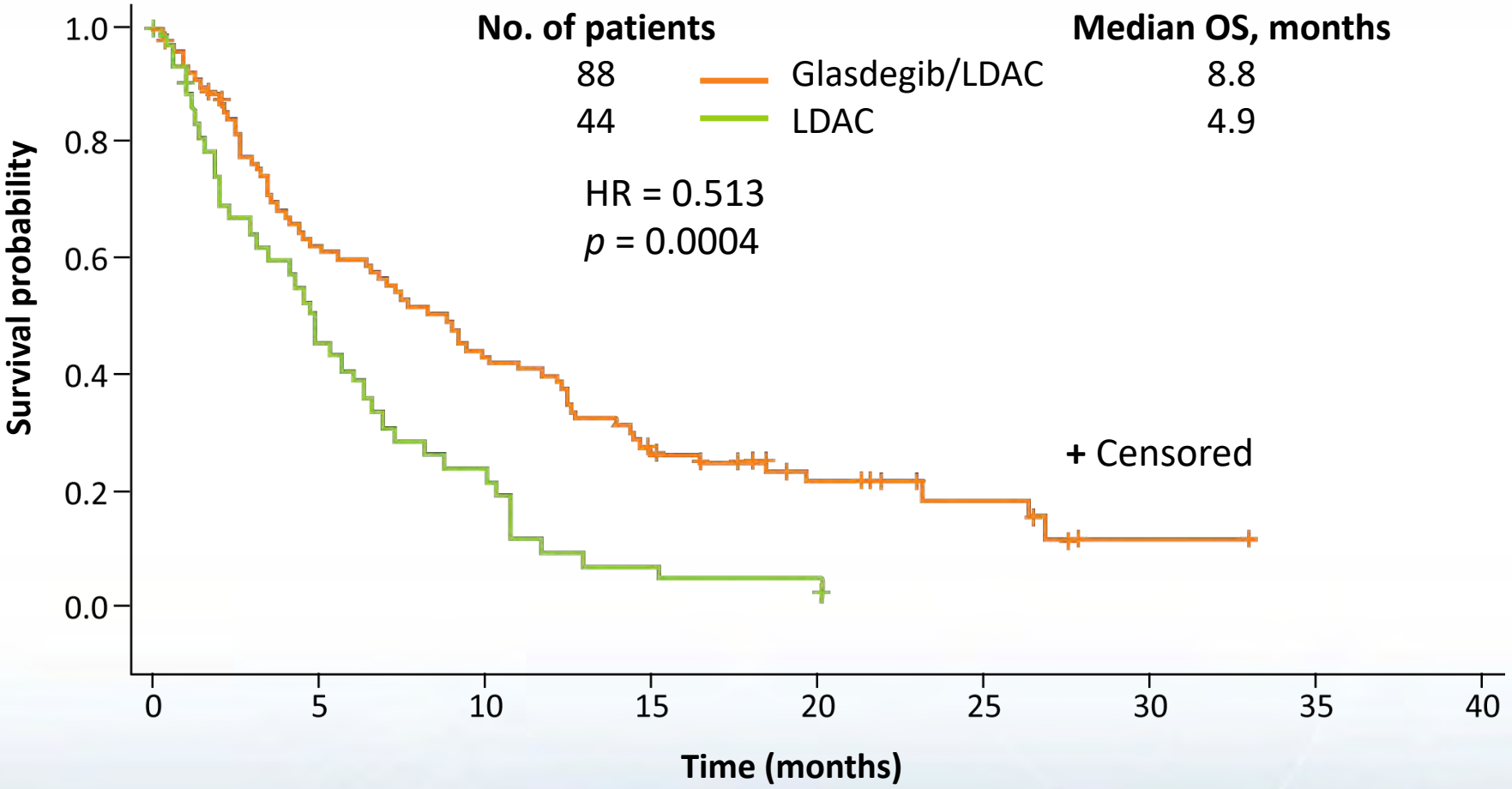
BRIGHT AML 1003: Low-Dose Cytarabine with or without Glasdegib for Untreated AML or High-Risk MDS



Cortes JE et al. *Leukemia* 2019;33:379-89.

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A 69-year-old woman with a history of myelodysplastic syndrome (MDS) 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?

 HARRY P ERBA, MD, PHD	CPX-351
 MARK LEVIS, MD, PHD	CPX-351
 DANIEL A POLLYEA, MD, MS	Continue azacitidine and add venetoclax
 KEITH W PRATZ, MD	Decitabine + venetoclax
 EYTAN M STEIN, MD	CPX-351
 WENDY STOCK, MD	CPX-351
 RICHARD M STONE, MD	CPX-351

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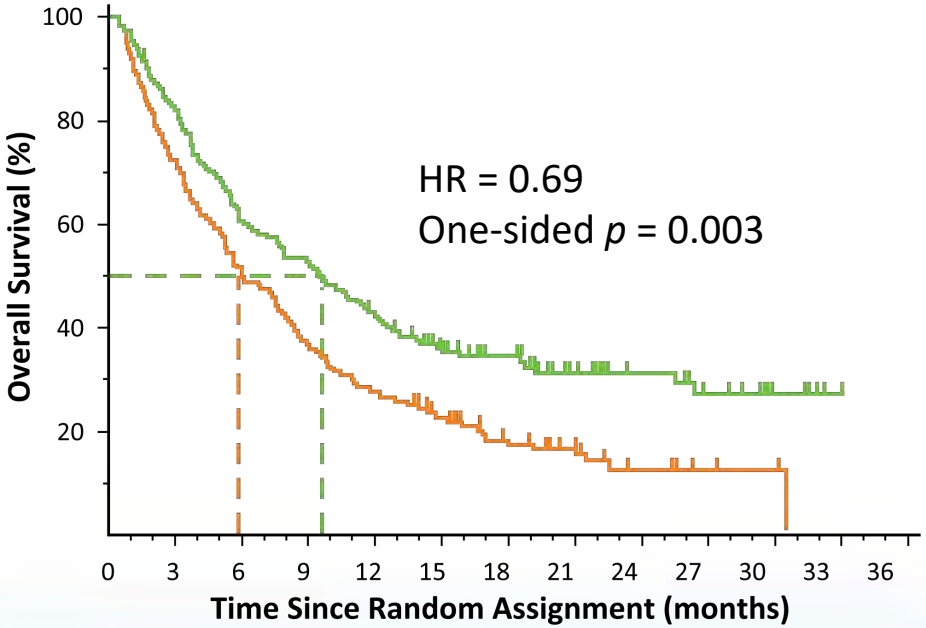
RAPID COMMUNICATION

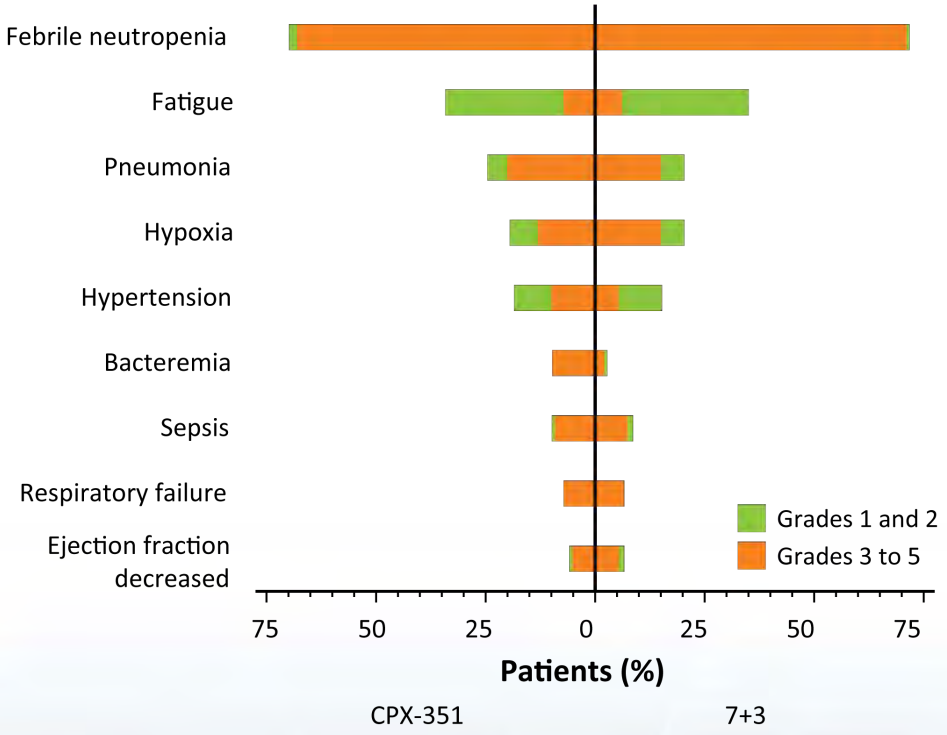
CPX-351 (cytarabine and daunorubicin) Liposome for Injection Versus Conventional Cytarabine Plus Daunorubicin in Older Patients With Newly Diagnosed Secondary Acute Myeloid Leukemia

Jeffrey E. Lancet, Geoffrey L. Uy, Jorge E. Cortes, Laura F. Newell, Tara L. Lin, Ellen K. Ritchie, Robert K. Stuart, Stephen A. Strickland, Donna Hogge, Scott R. Solomon, Richard M. Stone, Dale L. Bixby, Jonathan E. Kolitz, Gary J. Schiller, Matthew J. Wieduwilt, Daniel H. Ryan, Antje Hoering, Kamalika Banerjee, Michael Chiarella, Arthur C. Louie, and Bruno C. Medeiros

Study 301: Survival and Toxicity

Group	Events/ no. of patients	Median survival, months
CPX-351	104/153	9.56
7 + 3	132/156	5.95





Lancet JE et al. *J Clin Oncol* 2018;36(26):2684-92.

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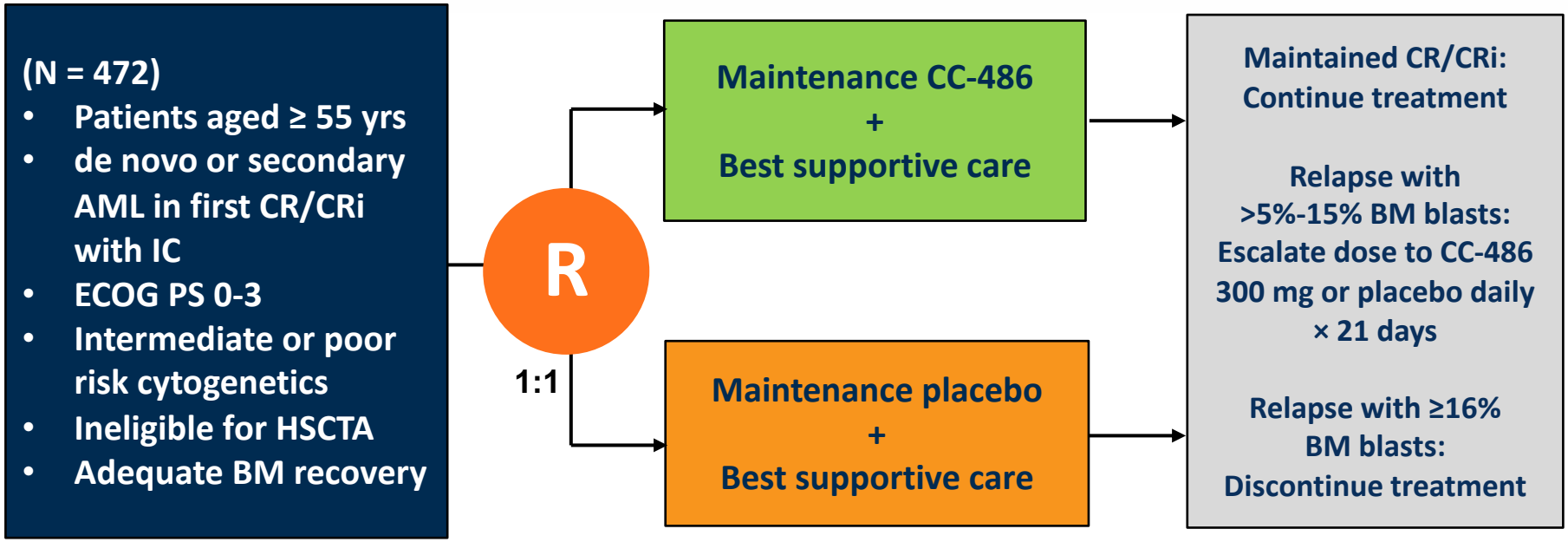
Phase III QUAZAR AML-001 Study Design

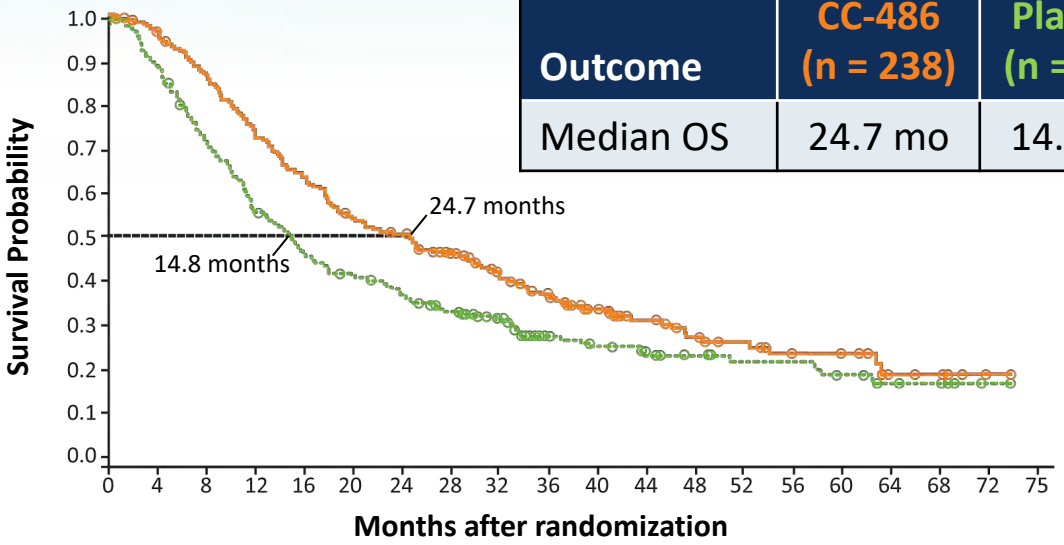


Primary endpoint: Overall survival

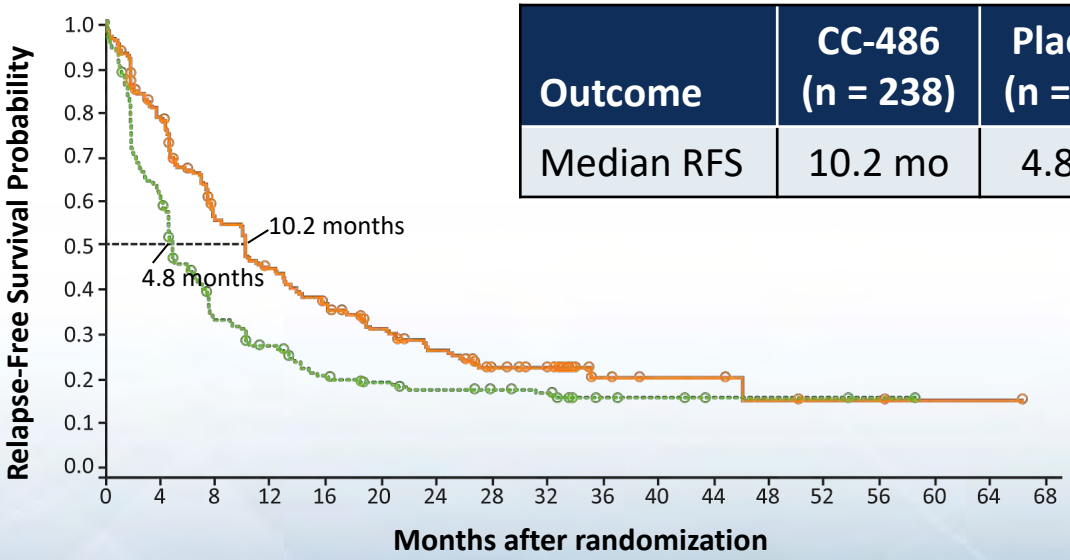
Roboz GJ et al. *Future Oncol* 2016;12(3):293-302.

QUAZAR AML-001: Overall and Relapse-Free Survival

Outcome	CC-486 (n = 238)	Placebo (n = 234)	HR	*p*-value
Median OS	24.7 mo	14.8 mo	0.69	0.0009



Outcome	CC-486 (n = 238)	Placebo (n = 234)	HR	*p*-value
Median RFS	10.2 mo	4.8 mo	0.65	0.0001



Wei AH et al. *Proc ASH* 2019;Abstract LBA-3.

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QUAZAR AML-001: GI Adverse Events, Dosing Modifications or Treatment Discontinuation

GI AEs, n (%)	CC-486 (n = 236)		Placebo (n = 233)	
	All Grades	Grades 3/4	All Grades	Grades 3/4
Discontinuation due to GI AE	4.7%		0.4%	
Nausea	153 (65)	6 (3)	55 (24)	1 (0.4)
Vomiting	141 (60)	7 (3)	23 (10)	0
Diarrhea	119 (50)	12 (5)	50 (22)	3 (1)
Constipation	91 (39)	3 (1)	56 (24)	0

	CC-486	Placebo
Dose interruptions	43%	17%
Dose reductions	16%	3%

Neutropenia was the most common reason for dose modifications.

Wei AH et al. *Proc ASH* 2019;Abstract LBA-3.

New Agents and Strategies in the Management of Acute Myeloid Leukemia
An Interactive Grand Rounds Series

Daniel A Pollyea, MD, MS
Associate Professor of Medicine
Clinical Director of Leukemia Services
Robert H Allen, MD Chair in Hematology Research
Division of Hematology
University of Colorado School of Medicine
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