New Therapeutic Options in Acute Myeloid Leukemia

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Relevant financial relationships in the past twelve months by presenter or spouse/partner.

Grant/research support: AbbVie, Celgene, Daiichi Sankyo, Esanex, Forma, Genentech/Roche, Glycomimetics, Incyte, Kalobios, Pharmacyclics, AMD, LP Therapeutics
Consultant: AbbVie, Amgen, Tolero

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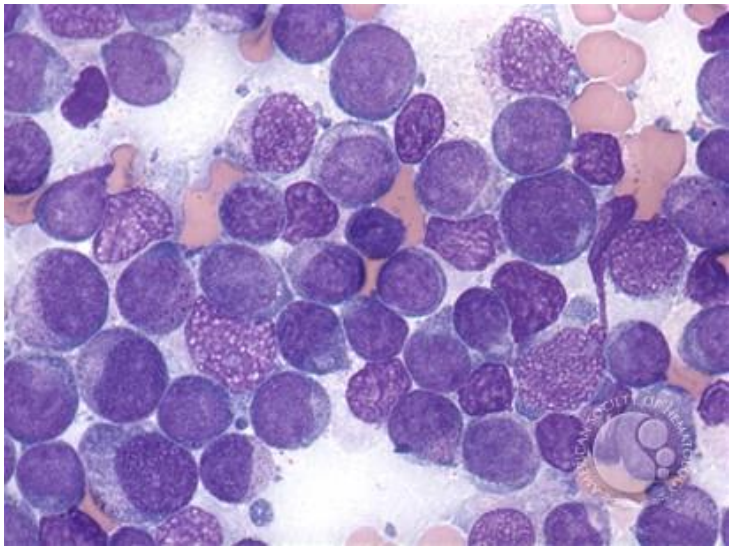
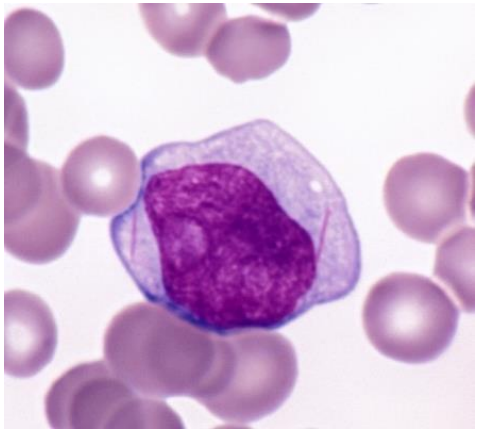
Learning Objectives

- Review the recent FDA approvals for acute myeloid leukemia
- Discuss the evolving standard of care for acute myeloid leukemia

Acute Myeloid Leukemia

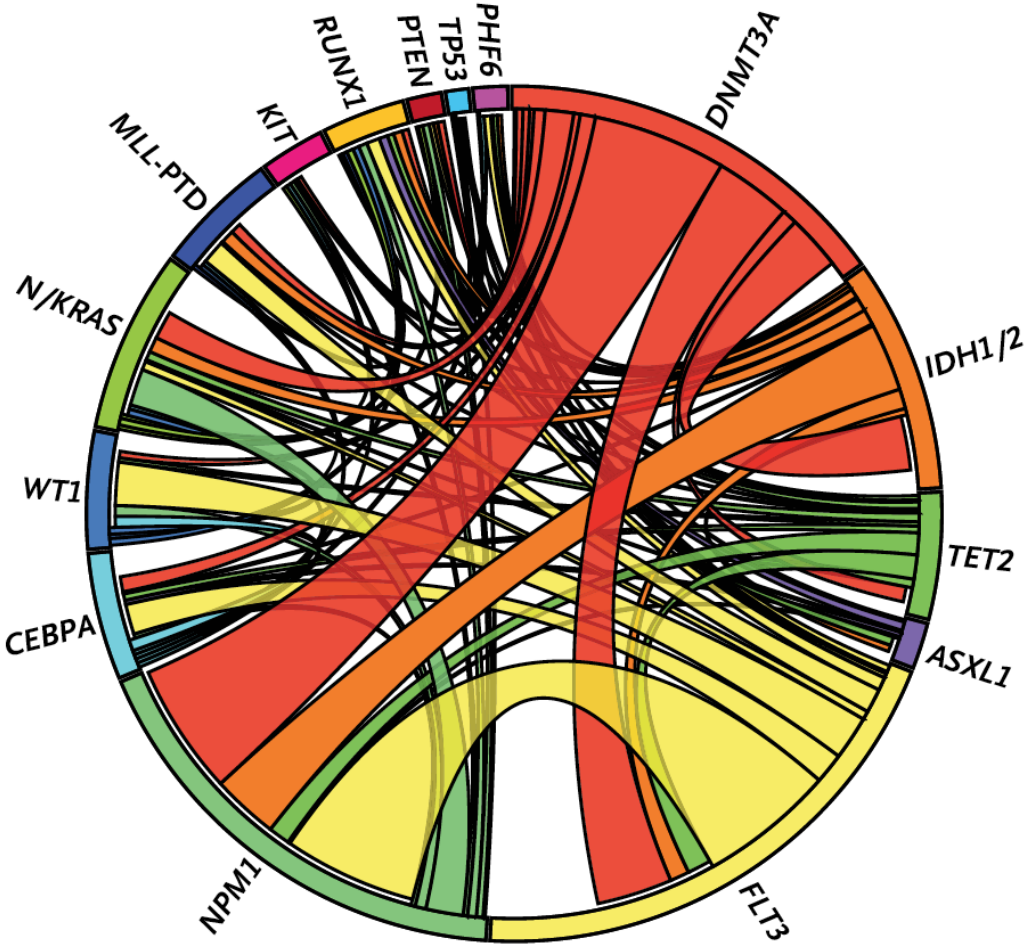
- Heterogeneous disease
- Median age 67
- ~21,000 new cases (M>F) expected in US in 2018 with ~11,000 deaths[1]
- Clonal expansion of immature myeloid cells
- Bleeding, infections, anemia
- High relapse rates





[1]ACS Cancer Statistics, 2018.

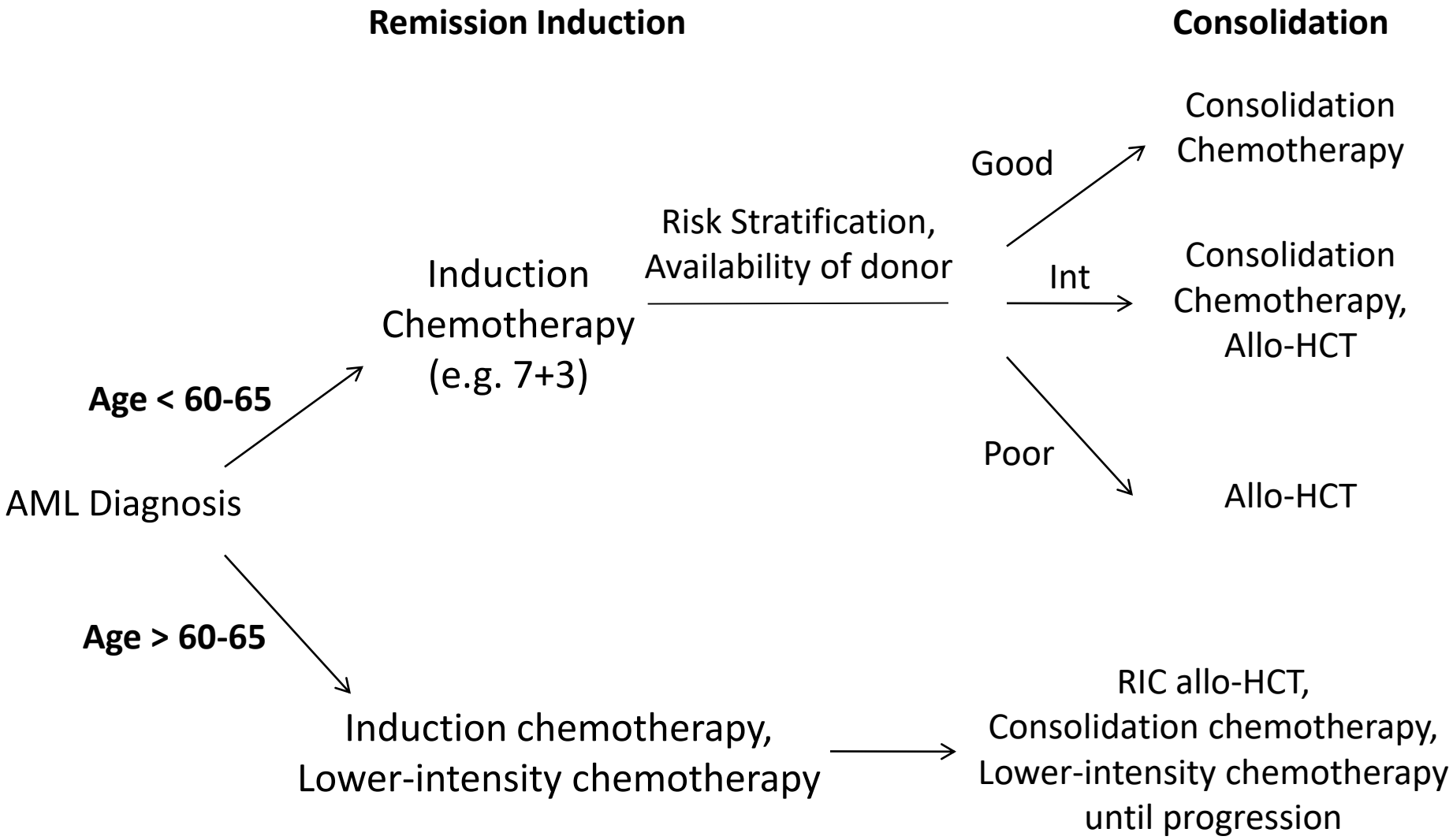
Recurrent Mutations in AML



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

Patel et al. NEJM 2012.

General Treatment Algorithm for AML



Recent FDA Approvals for AML

- 4/28/17 – ***Midostaurin*** for newly diagnosed FLT3-mutated AML in combination with 7+3
- 8/1/17 – ***Enasidenib*** for R/R AML with mutated IDH2
- 8/3/17 – ***Daunorubicin and cytarabine liposome for injection*** (CPX-351) for newly diagnosed t-AML and AML with MRC
- 9/1/17 – ***Gemtuzumab ozogamicin*** for newly diagnosed or R/R CD33-positive AML
- 7/20/18 – **Ivosidenib** for R/R AML with mutated IDH1

Midostaurin for FLT3-mutated AML

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

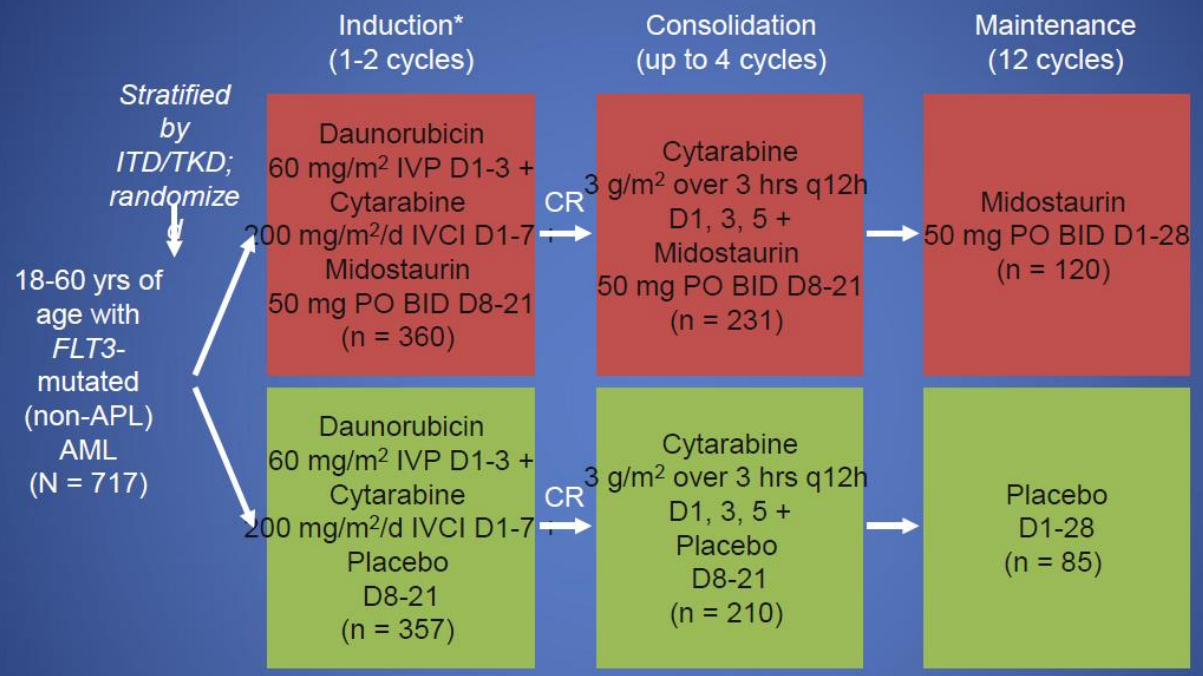
Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a *FLT3* Mutation

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 377;5 NEJM.ORG AUGUST 3, 2017

CALGB10603 – RATIFY TRIAL

Phase III RATIFY Trial of Midostaurin + Daunorubicin and Cytarabine in AML

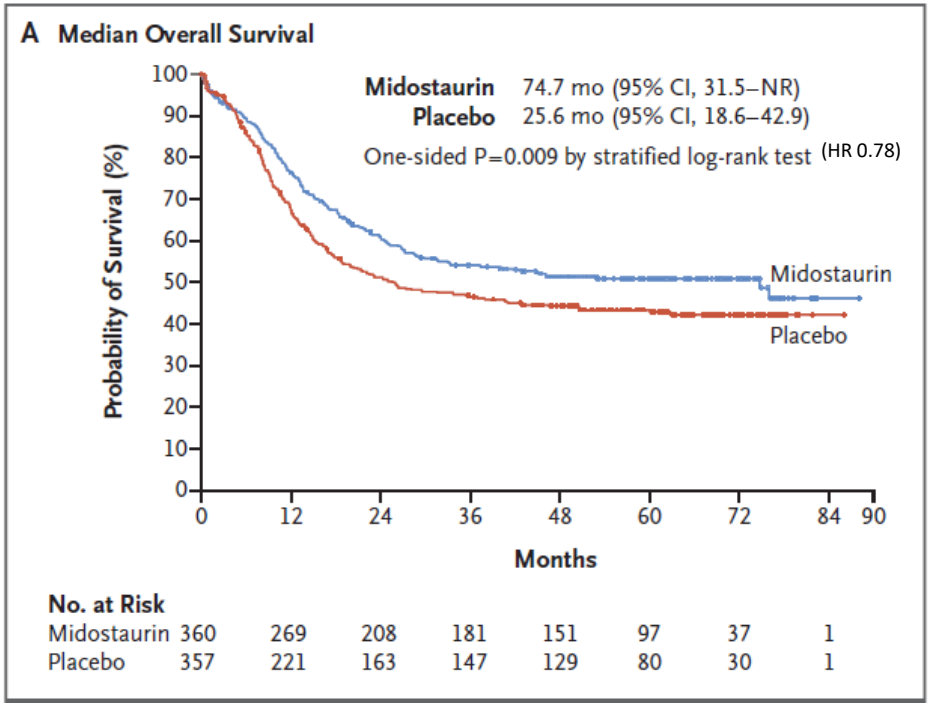


*Hydroxyurea allowed for ≤ 5 days prior to induction therapy.

- Double-blind, placebo-controlled, randomized phase III study
  - Primary endpoint: OS (not censored for SCT)
  - Secondary endpoint: EFS

Stone et al, NEJM 2017.

RATIFY TRIAL - Efficacy



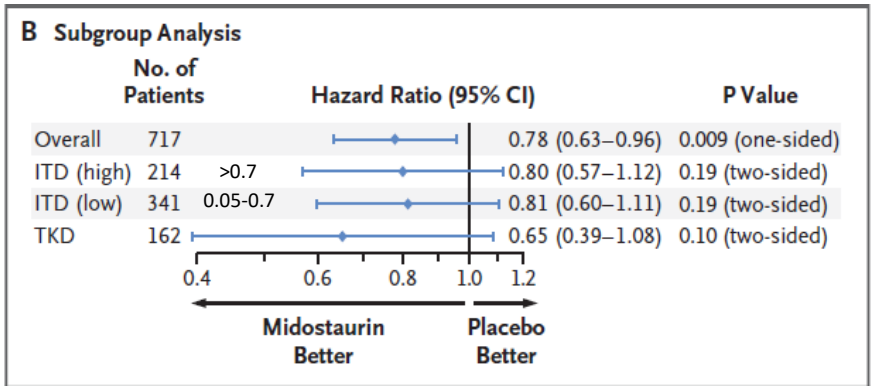


Table 3. Summary of Complete Remission.*

Variable	Midostaurin Group (N=360)	Placebo Group (N=357)	P Value†
Protocol-specified complete remission — no. (%)	212 (59)	191 (54)	0.15
Kaplan–Meier estimate of time to complete remission — days			
Median	35	35	
Range	20–60	20–60	

* Complete remission was defined as the presence of less than 5% blasts in the marrow or extramedullary leukemia, an absolute neutrophil count of more than 1000 per microliter, a platelet count of more than 100,000 per microliter, and the absence of blasts in the peripheral blood; in addition, per protocol, complete remission had to occur by day 60.
† P value is two-sided and was calculated with the use of Fisher's exact test.

For CR patients, no difference in median time to ANC or Plt recovery

Med EFS 8.2 vs 3.0 months (p=0.002)
Med DFS 26.7 vs 15.5 months (p=0.01)
57% of patients had HSCT
4yr OS (censored for HSCT) 63.7% vs 55.7% (p=0.08)

Stone et al, NEJM 2017.

RATIFY TRIAL – Adverse Events

Table 2. Summary of Grade 3, 4, or 5 Adverse Events.

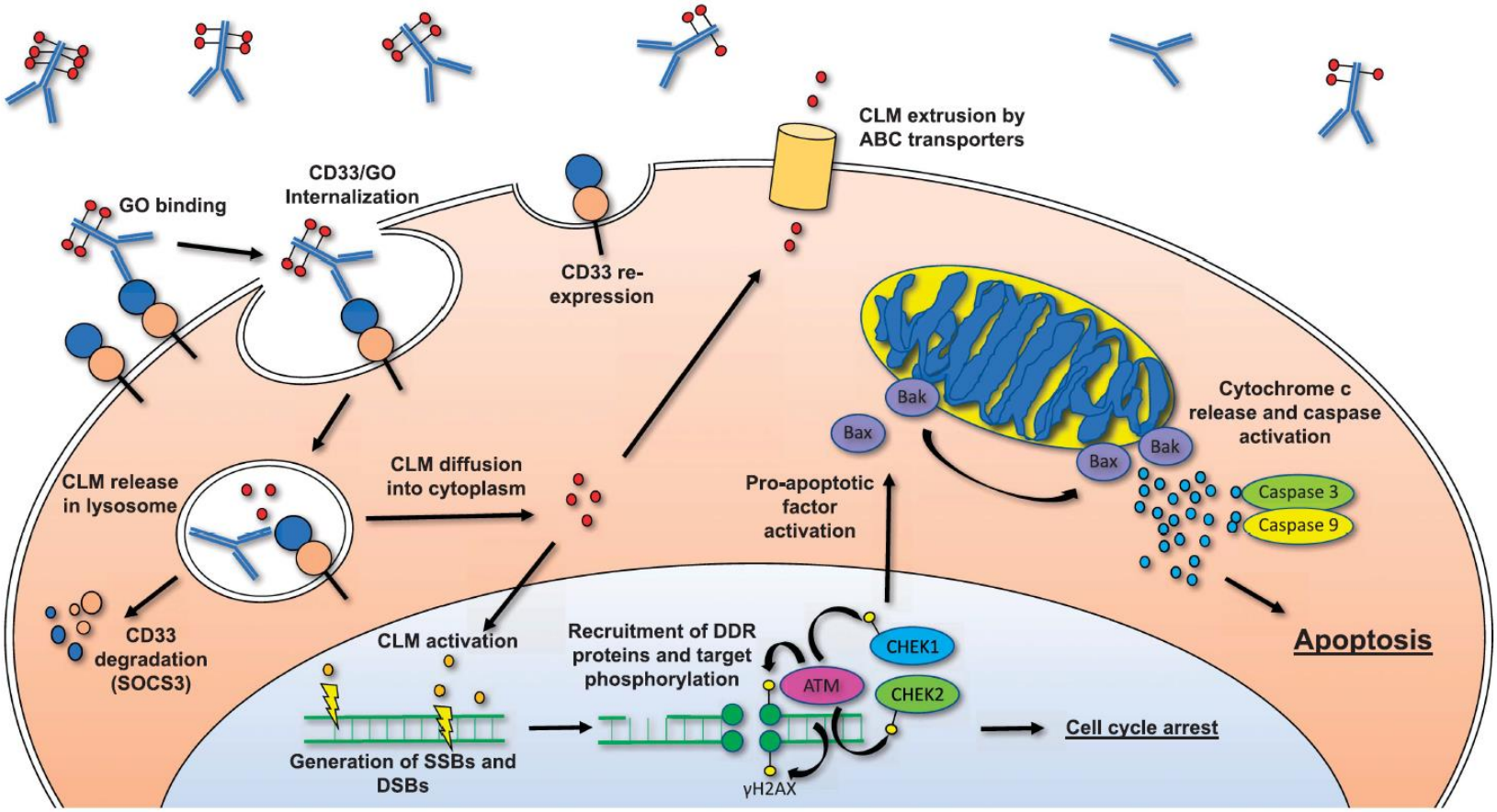
Adverse Event	Midostaurin Group (N=355)	Placebo Group (N=354)	P Value*
	no. of patients (%)		
Hematologic			
Thrombocytopenia	346 (97)	342 (97)	0.52
Neutropenia	338 (95)	339 (96)	0.86
Anemia	329 (93)	311 (88)	0.03
Leukopenia	93 (26)	105 (30)	0.32
Lymphopenia	68 (19)	78 (22)	0.35
Other blood or bone marrow event	1 (<1)	4 (1)	0.22
Bone marrow hypocellularity	0	1 (<1)	0.50
Nonhematologic			
Febrile neutropenia	290 (82)	292 (82)	0.84
Infection	186 (52)	178 (50)	0.60
Lymphopenia	68 (19)	78 (22)	0.35
Diarrhea	56 (16)	54 (15)	0.92
Hypokalemia	49 (14)	60 (17)	0.25
Pain	47 (13)	44 (12)	0.82
Increased alanine aminotransferase	45 (13)	33 (9)	0.19
Rash or desquamation	50 (14)	27 (8)	0.008
Fatigue	32 (9)	37 (10)	0.53
Pneumonitis or pulmonary infiltrates	28 (8)	29 (8)	0.89
Nausea	20 (6)	34 (10)	0.05
Hyponatremia	31 (9)	23 (6)	0.32
Hyperbilirubinemia	25 (7)	28 (8)	0.67
Mucositis or stomatitis	22 (6)	28 (8)	0.38
Hypophosphatemia	19 (5)	29 (8)	0.14
Hypocalcemia	24 (7)	21 (6)	0.76

* P values are two-sided and were calculated with the use of Fisher's exact test.

Stone et al, NEJM 2017.

Gemtuzumab ozogamicin (GO)

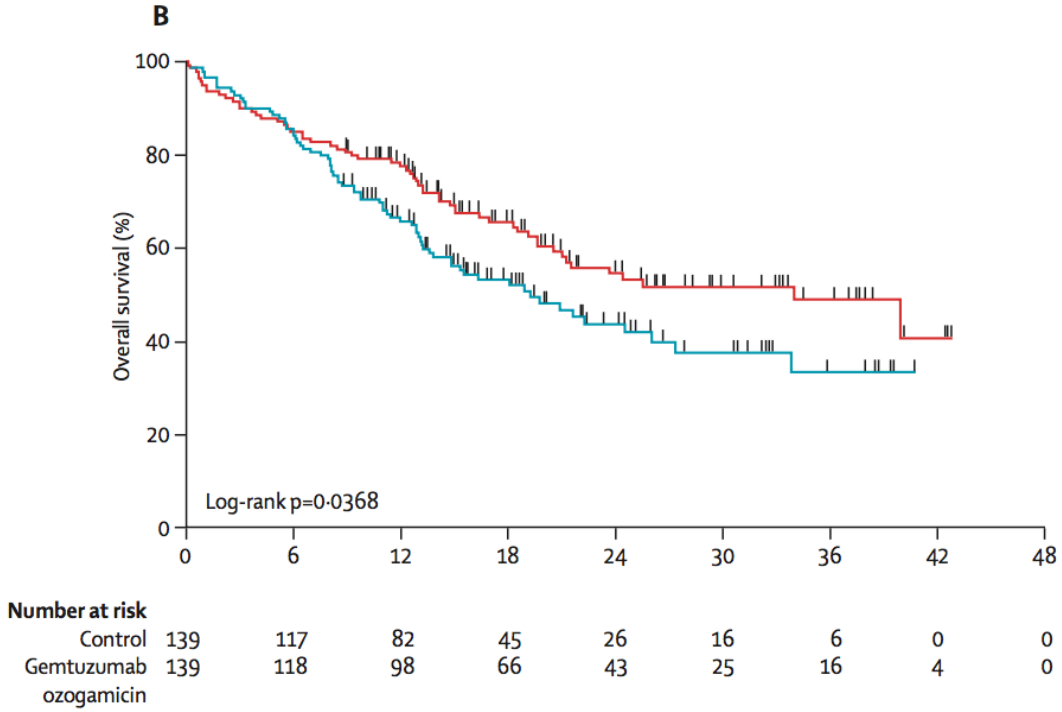
CD33 antibody-drug conjugate (calicheamicin derivative)
CD33 on >80% of AML



Godwin et al, Leukemia 2017.

ALFA-0701 Trial – Addition of GO to 7+3 improved OS

- 7+3 (DNR 60, AraC 200) vs 7+3 plus fractionated gemtuzumab ozogamicin (3mg/m2 days 1, 4 and 7)
- 280 patients randomized 1:1, age 50-70, 17% favorable, 71% intermediate
- Up to 2 cycles of induction and 2 cycles of consolidation
- CR 75% (control) vs 81% (GO), p=0.25



Med OS
Control: 19.2mo (13.8-26.0)
GO: 34.0mo (20.5-NR)
HR 0.69 (0.49-0.98)
p=0.0368

EFS HR 0.58 (0.43-0.78)
p=0.0003
RFS HR 0.52 (0.36-0.75)
p=0.0003

Castaigne et al, Lancet 2012.

ALFA-0701 Trial – Subgroup and Safety Data

- Benefit more pronounced in Fav/Int risk, FLT3-ITD+
- More hematologic toxicity
  - Longer duration of neutropenia and thrombocytopenia
- Non-heme toxicity similar
- 31 patients in GO arm had subsequent allo-HCT
  - Recommended 2 month interval between GO and allo-HCT
  - 6 cases of VOD (5%) in GO arm
    - 3 without HSCT (3%)
      - Two fatal
    - 3 post-transplant (9.7%)
      - All three non-fatal

	Control group (n=139)	Gemtuzumab ozogamicin group (n=139)	Relative risk (95% CI)	p value
Induction death	5/139 (4%)	9/139 (6%)	0·56 (0·20–1·54)	0·41
Transfer to intensive-care unit	17/139 (12%)	20/139 (14%)	0·85 (0·47–1·54)	0·72
Treatment-related death during CR or CRp	8/104* (8%)	2/113 (2%)	4·35 (1·07–17·84)	0·051
Grade 3 and 4 adverse events				
Haemorrhage	4/139 (3%)	12/139 (9%)	0·33 (0·12–0·95)	0·068
Cardiac	9/139 (6%)	11/139 (8%)	0·82 (0·36–1·87)	0·82
Liver	9/139 (6%)	18/139 (13%)	0·50 (0·24–1·05)	0·10
Skin or mucosa	25/139 (18%)	32/139 (23%)	0·11 (0·03–0·42)	0·37
Gastrointestinal	14/139 (10%)	22/139 (16%)	0·64 (0·34–1·18)	0·21
Pulmonary	16/139 (12%)	16/139 (12%)	1·00 (0·53–1·90)	1·00
Grade 3 and 4 infections				
During induction	50/131 (38%)	59/129 (46%)	0·83 (0·62–1·11)	0·26
During first consolidation	38/95 (40%)	48/97 (49%)	0·80 (0·59–1·11)	0·19
During second consolidation	38/82 (46%)	38/81 (47%)	0·99 (0·71–1·37)	0·99

Data are n/N (%), unless otherwise indicated. CR=complete remission. CRp=complete remission with incomplete platelet recovery. *Includes five deaths after stem-cell transplantation.

Table 4: **Non-haematological toxicity**

Castaigne et al, Lancet 2012.

Meta-Analysis of Trials Adding Gemtuzumab to Induction Chemo in AML

- Independent patient data meta-analysis of 5 randomized trials (3325 pts): ALFA-0701, MRC AML15, NCRI AML16, SWOG-0106, GOELAMS AML2006IR
- No difference in CR/CRi rate
- Doses of 3mg/m2 associated with fewer early deaths than 6mg/m2 with equal efficacy
- Addition of GO significantly reduced relapse risk (HR: 0.81 [0.73-0.90]; *p* = 0.0001) and improved OS (HR: 0.90 [0.82-0.98]; *p = 0.01*)
  - Benefit limited to patients with favorable- or intermediate-risk cytogenetics (HR: 0.47 and 0.84; *p* = .0006 and 0.005, respectively)

6-Yr OS, %	GO + Chemo	Chemo	*P* Value
All patients	34.6	30.7	.01
Cytogenetic risk			
▪ Favorable	76.3	55.0	.005
▪ Intermediate	39.4	34.1	.007
▪ Adverse	9.2	6.7	> .10

Hills R, et al. ASH 2013. Abstract 356.
Hills et al, Lancet Oncology 2014.

AML-19 and MyloFrance-1 Trials

AML-19

- Unfit for induction
- GO monotherapy (n=118) vs BSC (n=119)
- CR/CRi 27%
- HR for OS 0.69 (0.53-0.90, p=005)
- Med OS 4.9 vs 3.6mo
- No VOD

MyloFrance-1

- First relapse
- GO 3mg/m2 d1,4,7 (n=57)
- HSCT allowed 90d after GO
- CR/CRp 33%
- Med OS 8.4mo, med RFS 11mo
- No VOD including 7 who had subsequent transplant

Amadori et al, JCO 2016.
Taksin et al, Leukemia 2007.

CPX-351 for Secondary AML

VOLUME 36 · NUMBER 26 · SEPTEMBER 10, 2018

JOURNAL OF CLINICAL ONCOLOGY

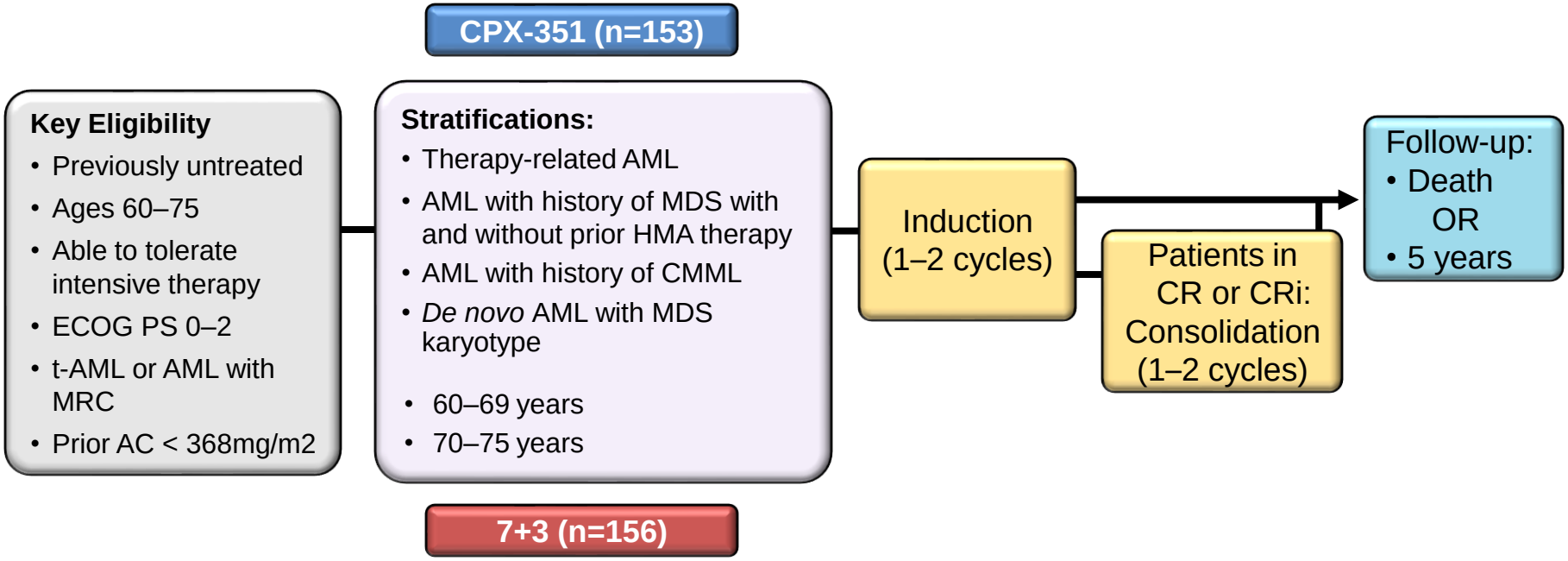
RAPID COMMUNICATION

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

CPX-351 Phase 3 Study Design

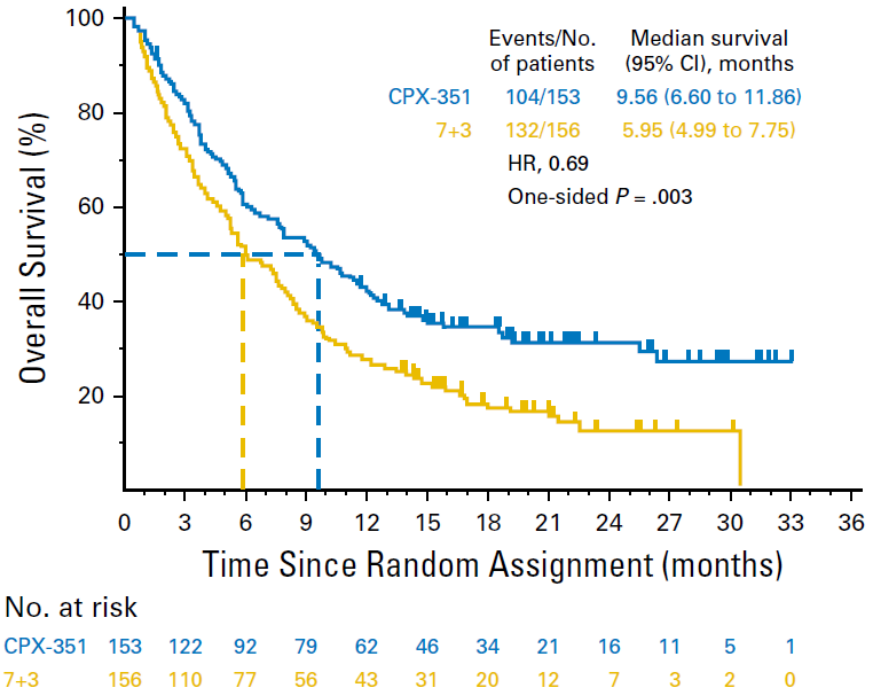
- Liposomal formulation of cytarabine and daunorubicin encapsulated at a 5:1 molar ratio
  - Prolonged fixed molar ratio in plasma, prolonged drug exposure, selective uptake by leukemic cells



Lancet et al, ASCO 2016 Abstract #7000.
Lancet et al, JCO 2018.

CPX-351 Improved Outcomes Compared to 7+3

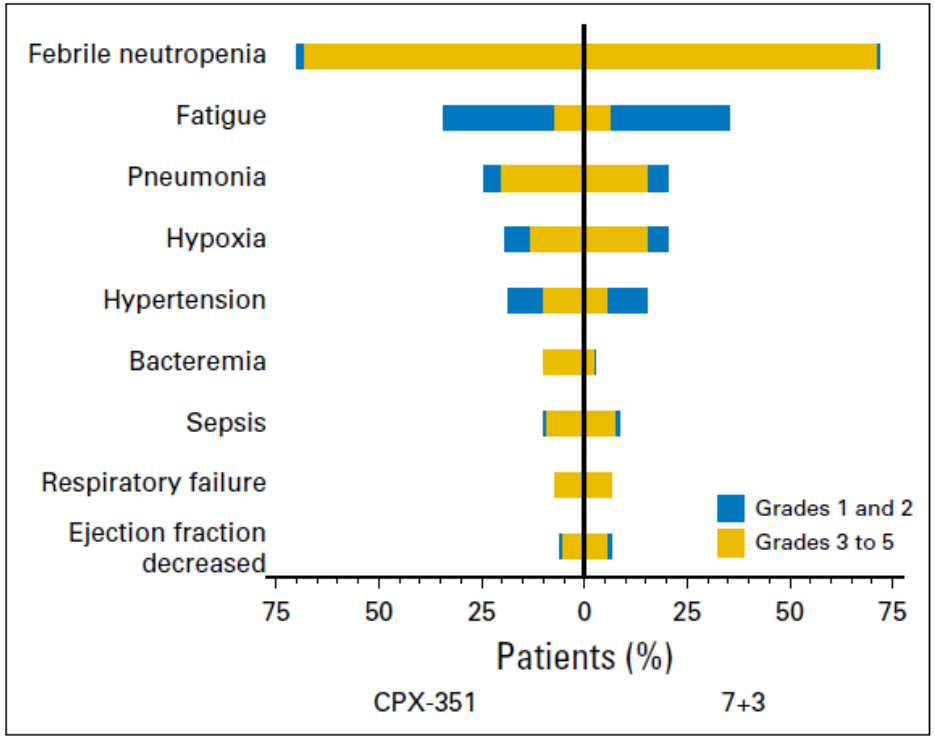
	CPX-351 n=153	7+3 n=156		
	Median Survival in Months (95% CI)		**Hazard Ratio**	***P* value**
Event-Free Survival	2.53 (2.07, 4.99)	1.31 (1.08, 1.64)	0.74	0.021
Remission Duration	6.93 (4.60, 9.23)	6.11 (3.45, 8.71)	0.77	0.291
			Odds Ratio	***P* value**
CR	37.3%	25.6%	1.67 (1.02, 2.74)	0.040
CR+CRi	47.7%	33.3%	1.77 (1.11, 2.81)	0.016
Stem Cell Transplant	34.0%	25.0%	1.54 (0.92, 2.56)	0.098

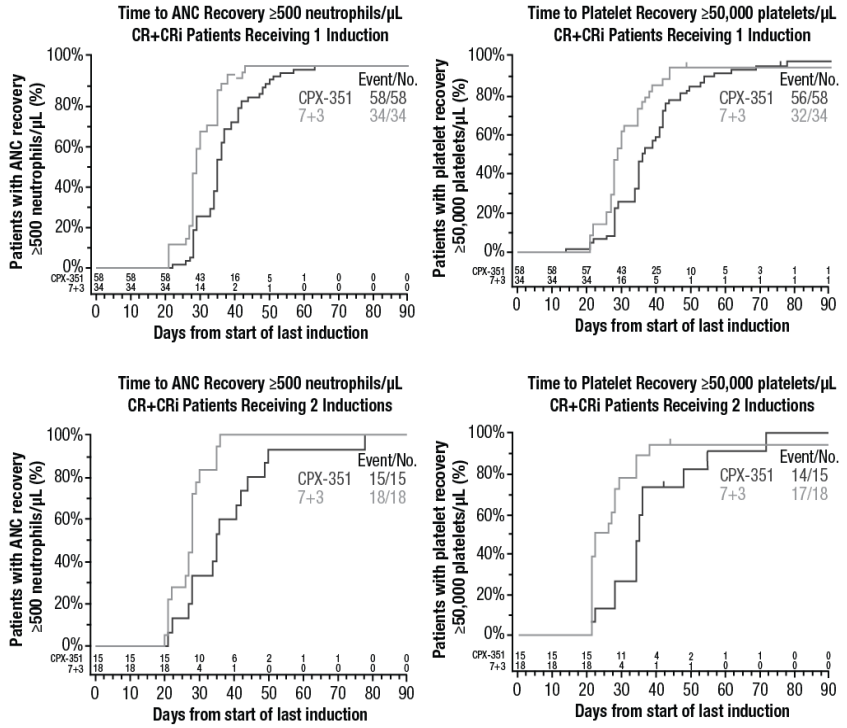


Lancet et al, ASCO 2016 Abstract #7000.
Lancet et al, JCO 2018.

Safety of CPX-351 Compared to 7+3

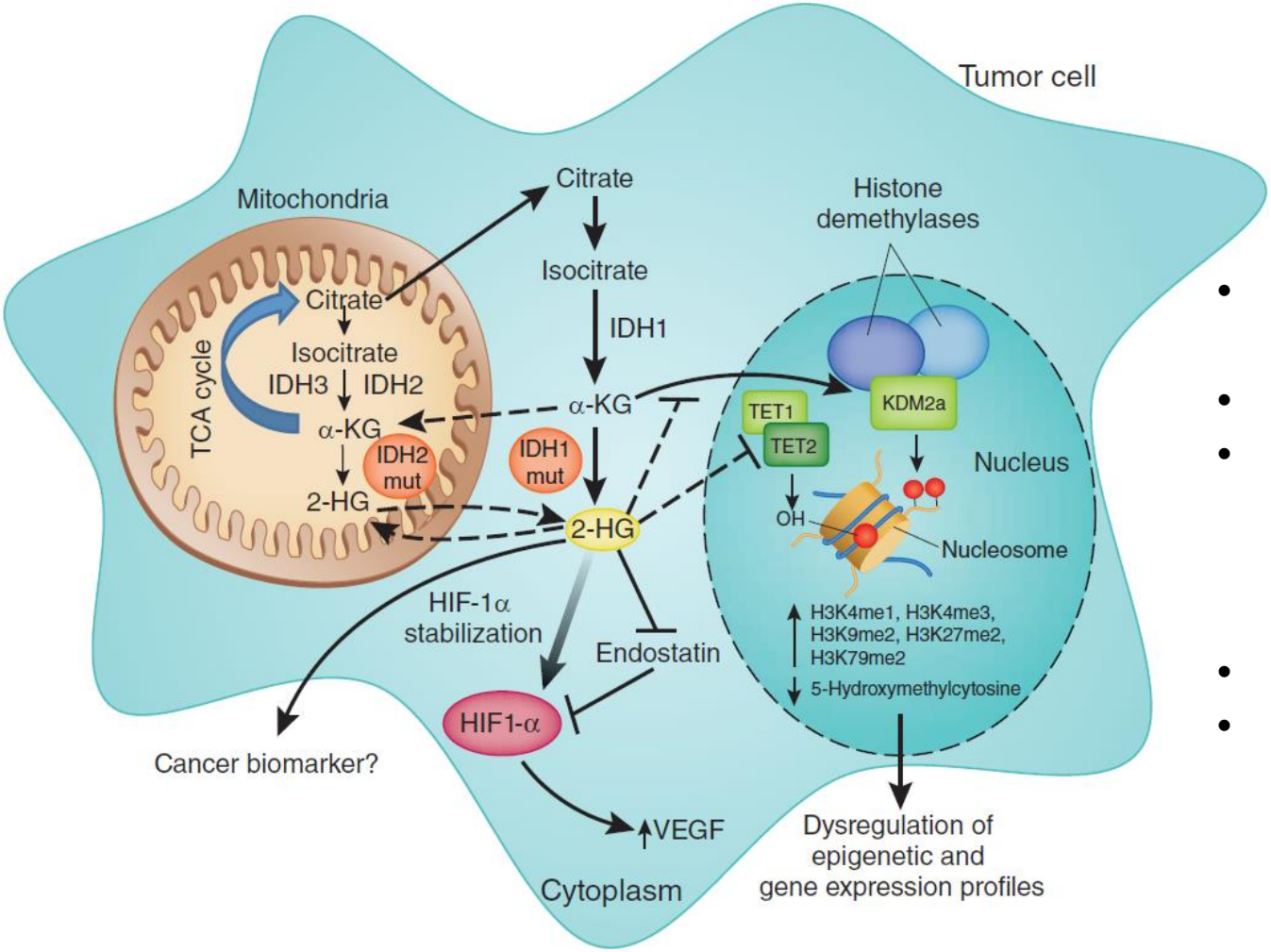
	CPX-351 n=153	7+3 n=156		*P* value
Deaths ≤ 30 Days	5.9%	10.6%		0.149
Deaths ≤ 60 Days	13.8%	21.8%		0.097
Median Time to ANC Recovery	35/35	29/28		
Median Time to Plt Recovery	36.5/35	29/24		





Lancet et al, ASCO 2016 Abstract #7000.
Lancet et al, JCO 2018.

Targeting Mutated IDH



- Mutation frequency = ~15-20%
- Neomorphic activity
- Cooperates with FLT3, RAS, DNMT3A mutations to drive leukemia
- **Ivosidenib** (IDH1i)
- **Enasidenib** (IDH2i)

Prensner et al, Nature Med, 2011.

Ivosidenib for IDH1 mutated AML

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

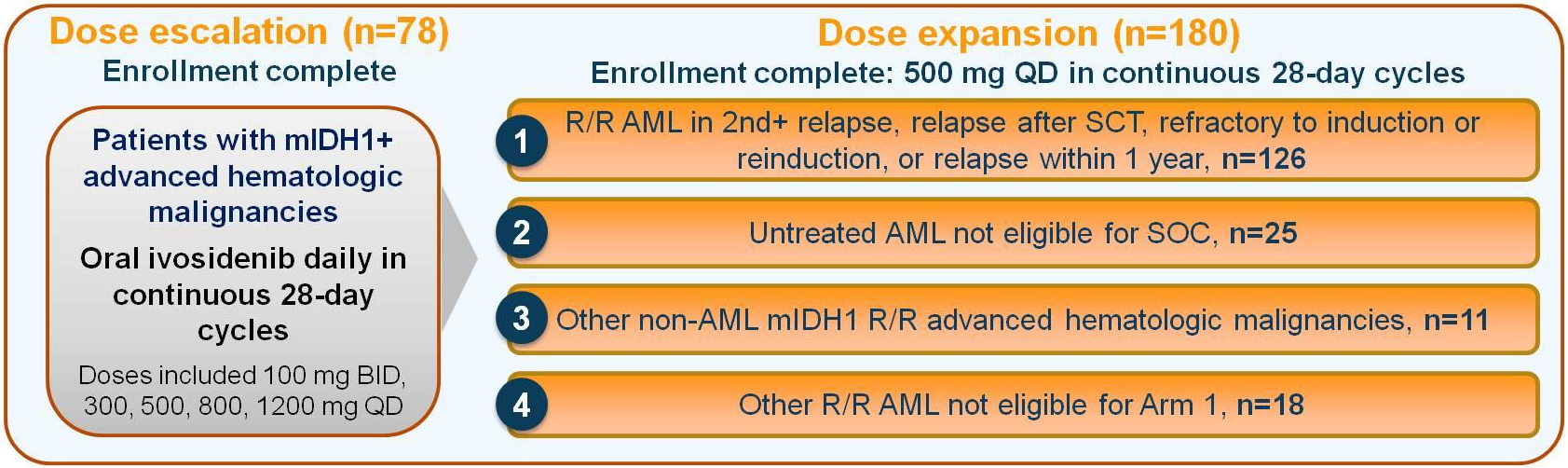
Durable Remissions with Ivosidenib in *IDH1*-Mutated Relapsed or Refractory AML

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

Ivosidenib: first-in-class, oral, potent, reversible, selective inhibitor of mutant IDH1

Study Design and Objectives

Single-arm, open-label, phase 1, multicenter trial



Study objectives

Primary	Safety and tolerability, MTD and/or RP2D, clinical activity in mIDH1 R/R AML enrolled in expansion Arm 1
Secondary	DLTs, pharmacokinetics and pharmacodynamics (including 2-HG), preliminary clinical activity in advanced hematologic malignancies
Exploratory	Determination of comutations and mIDH1 variant allele frequency (VAF)

ClinicalTrials.gov NCT02074839. DLTs, dose limiting toxicities; MTD, maximum tolerated dose; RP2D, recommended phase 2 dose

Data reported on R/R AML 500mg (n=179) from escalation and Arm 1

Response in R/R AML 500 mg (n=179)

	R/R AML 500 mg (n=179)
CR+CRh rate, n (%) [95% CI]	**57 (31.8) [25.1, 39.2]**
Time to CR/CRh, median (range) months	2.0 (0.9, 5.6)
Duration of CR/CRh, median [95% CI] months	8.2 [5.6, 12.0]
CR rate, n (%) [95% CI]	43 (24.0) [18.0, 31.0]
Time to CR, median (range) months	2.8 (0.9, 8.3)
Duration of CR, median [95% CI] months	10.1 [6.5, 22.2]
CRh rate, n (%)	14 (7.8)
Duration of CRh, median [95% CI] months	3.6 [1.0, 5.5]

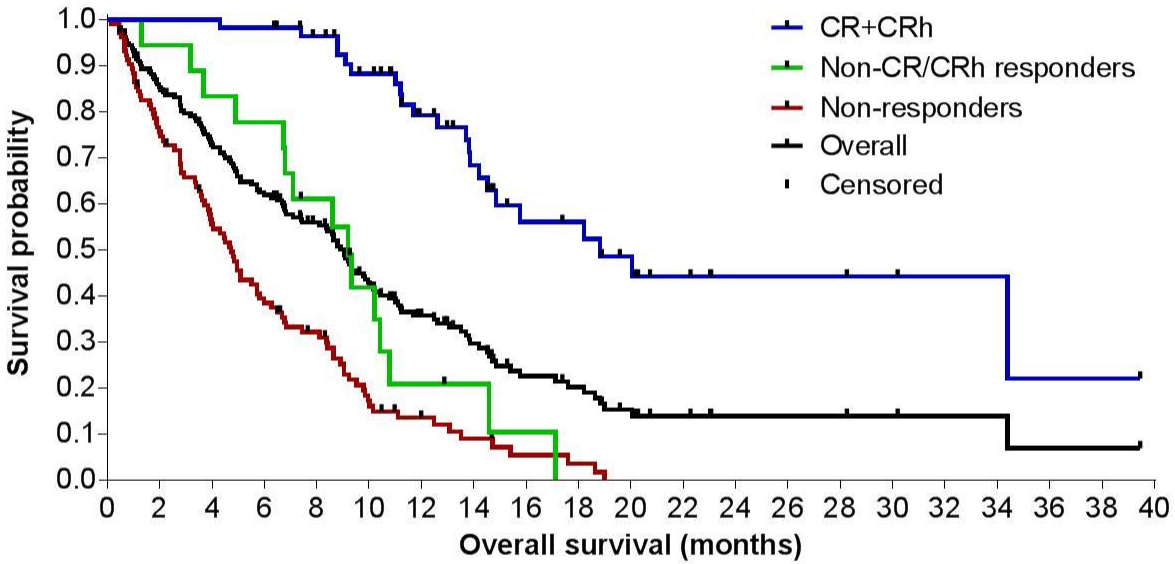
	R/R AML 500 mg (n=179)
Overall Response Rate, n (%) [95% CI]	**75 (41.9) [34.6, 49.5]**
Time to first response, median (range) months	1.9 (0.8, 4.7)
Duration of response, median [95% CI] months	6.5 [5.5, 10.1]
Best response, n (%)	
CR	43 (24.0)
CRi or CRp	21 (11.7)
MLFS	11 (6.1)
SD	68 (38.0)
PD	15 (8.4)
NA	21 (11.7)

CRh = 9 patients with investigator-assessed responses of CRi/CRp and 5 with MLFS

Among the 179 patients with R/R AML, 5 from dose escalation and 1 from dose expansion were not positive for mIDH1 by the companion diagnostic test and none of these 6 patients achieved a CR or CRh
CR+CRh was consistent across baseline age groups, including patients who were > 65 years of age
Overall response rate includes CR, CRi/CRp, MLFS and PR

Data cutoff: 10Nov2017. PD, progressive disease; PR, partial response

Overall Survival by Best Response in R/R AML 500 mg (n=179)



Number of patients at risk:

57	57	57	56	50	43	32	25	16	15	11	7	4	4	4	3	2	2	1	1
18	17	15	14	10	6	3	2	1	0										
104	77	55	38	29	15	9	6	3	2	0									

CR+CRh
Non-CR/CRh responders
Non-responders

	Months
Overall survival, median [95% CI]	
CR+CRh	18.8 [14.2, NE]
Non-CR/CRh responders	9.2 [6.7, 10.8]
Non-responders	4.7 [3.7, 5.7]
All	9.0 [7.1, 10.0]
Overall follow-up, median (range)	15.3 (0.2–39.5)

Non-CR/CRh responders include CRi, CRp, and MLFS who are not CRh
Non-responders = all others including those with best responses of SD, PD, or not evaluable

Data cutoff: 10Nov2017 NE, not estimable

Overall transfusion independence: Platelet 38.5%, RBC 42.3%

AEs of Interest: R/R AML 500 mg (n=179)

- **Leukocytosis[a]**
  - Grade ≥ 3 leukocytosis reported in 14/179 patients (8%)
  - Managed with hydroxyurea
  - None were fatal
- **ECG QT prolongation**
  - Grade ≥ 3 QT prolongation reported in 18/179 patients (10%)
  - Study drug was reduced in 2 patients and held in 13 patients (all grades)
  - None were fatal
  - QT prolonging medications such as antifungals and fluoroquinolone anti-infectives were allowed on study with monitoring
- **IDH differentiation syndrome (IDH-DS)**
  - All grade reported in 19/179 patients (10.6%)
  - Resolved in 17 patients, ongoing in 2 patients at data cut
  - Grade ≥ 3 IDH-DS in 9 (5.0%)
  - 7/19 IDH-DS patients had co-occurring leukocytosis
  - Study drug held in 6 patients (3.4%)
  - No instances of IDH-DS led to dose reduction, permanent treatment discontinuation, or death
  - Managed with corticosteroids and diuretics, and hydroxyurea if accompanied by leukocytosis
  - Best response for the 19 patients with IDH-DS:

Best Response	CR	CRh	CRi/CRp	MLFS	SD	NE
n=19	5	0	3	2	8	1

These events were managed using standard of care treatments and ivosidenib dose modifications as required

[a]Grade 3 = WBC > 100,000/mm^3; Grade 4 = clinical manifestations of leukostasis, urgent intervention indicated

Data cutoff: 10Nov2017 CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; MLFS, morphologic leukemia-free state; NE, not evaluable; SD, stable disease

Other G3+ TEAE in >1 patient – febrile neutropenia (29.1%), anemia (20.1%), diarrhea (2.2%), fatigue (1.7%), dyspnea (3.9%), pyrexia 1.1%)

Presented By Daniel Pollyea at 2018 ASCO Annual Meeting

Enasidenib for IDH2 mutated AML

CLINICAL TRIALS AND OBSERVATIONS

Enasidenib in mutant *IDH2* relapsed or refractory acute myeloid leukemia

Eytan M. Stein,[1,2,*] Courtney D. DiNardo,[3,*] Daniel A. Pollyea,[4] Amir T. Fathi,[5,6] Gail J. Roboz,[2,7] Jessica K. Altman,[8] Richard M. Stone,[9] Daniel J. DeAngelo,[9] Ross L. Levine,[1] Ian W. Flinn,[10] Hagop M. Kantarjian,[3] Robert Collins,[11] Manish R. Patel,[12] Arthur E. Frankel,[11] Anthony Stein,[13] Mikkael A. Sekeres,[14] Ronan T. Swords,[15] Bruno C. Medeiros,[16] Christophe Willekens,[17,18] Paresh Vyas,[19,20] Alessandra Tosolini,[21] Qiang Xu,[21] Robert D. Knight,[21] Katharine E. Yen,[22] Sam Agresta,[22] Stephane de Botton,[17,18,†] and Martin S. Tallman[1,2,†]

BLOOD, 10 AUGUST 2017 • VOLUME 130, NUMBER 6

Enasidenib for IDH2 mutated AML

Enasidenib: first-in-class, oral, potent, reversible, selective inhibitor of mutant IDH2, triggers blast differentiation

P1 study (NCT01915498) Advanced IDH2 mutant heme malignancies (R140Q and R172K)

	RR-AML (n = 159)	Untreated AML (n = 24)	MDS (n = 14)	All (N = 209)
Overall Response (CR, CRp, CRi, mCR, PR)	59 (37%)	10 (42%)	7 (50%)	79 (38%)
CR	29 (18%)	4 (17%)	3 (21%)	37 (18%)
CRp	1 (1%)	1 (4%)	1 (7%)	3 (1%)
CRi	3 (2%)	0	0	3 (1%)
mCR	9 (6%)	1 (4%)	3 (21%)	14 (7%)
PR	17 (11%)	4 (17%)	0	22 (11%)
SD	72 (45%)	9 (38%)	6 (43%)	96 (46%)
PD	10 (6%)	1 (4%)	0	11 (5%)
Not evaluable	18 (11%)	4 (17%)	1 (7%)	23 (11%)

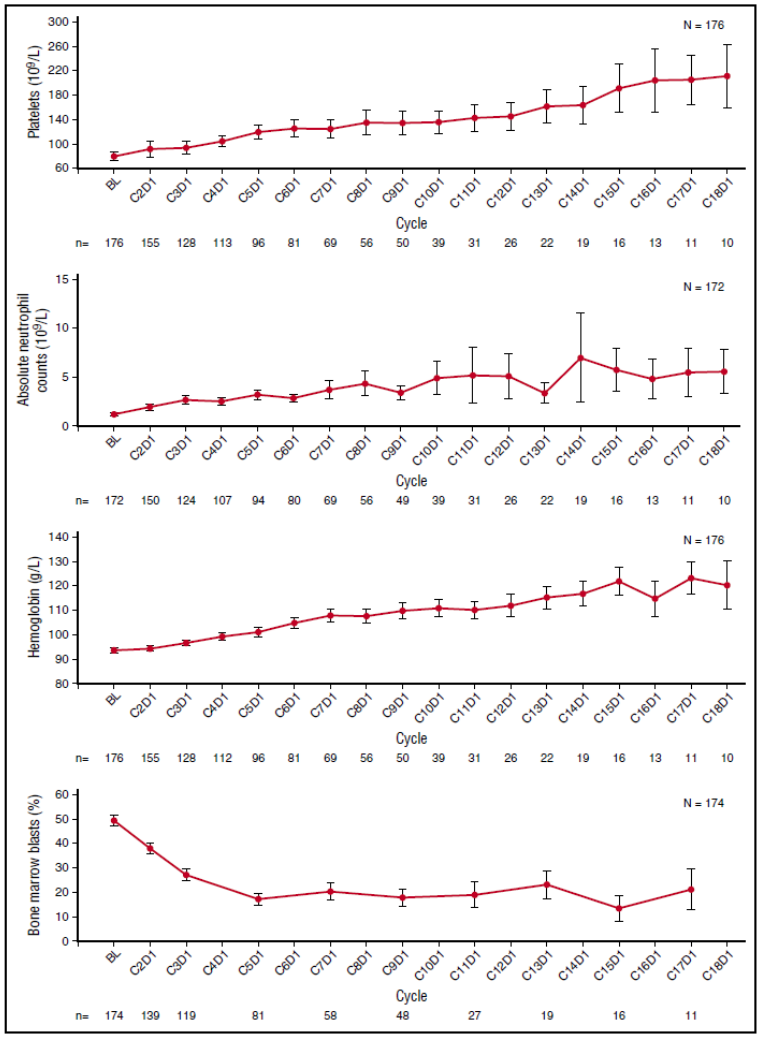
TR AE G3+: hyperbilirubinemia (8%), **IDH differentiation syndrome** (7%), anemia (7%), low plts (5%), **leukocytosis** (1%), TLS (3%), nausea (1%)

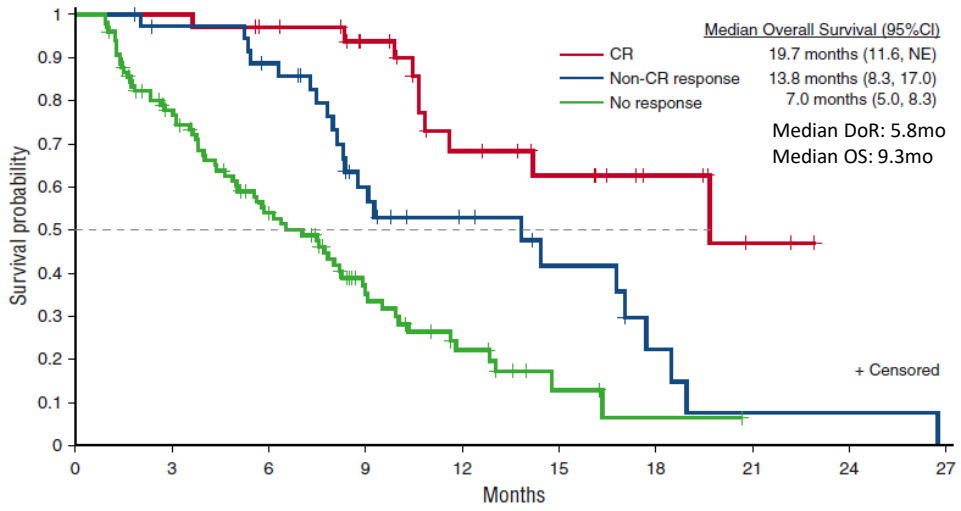
- **Overall response by IDH mutation type: R140Q 36% / R172K 42%**

Sustained plasma 2-HG inhibition

Stein et al, ASH 2014 Abstract# 115.
DiNardo et al, ASH 2015 Abstract# 1306.
Stein et al, ASH 2016 Abstract# 343.
Stein et al, Blood 2017.

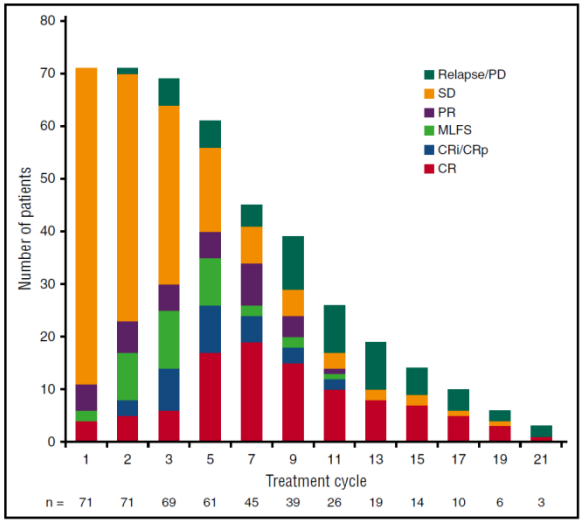
Enasidenib for IDH2 mutated AML





Patients at risk:

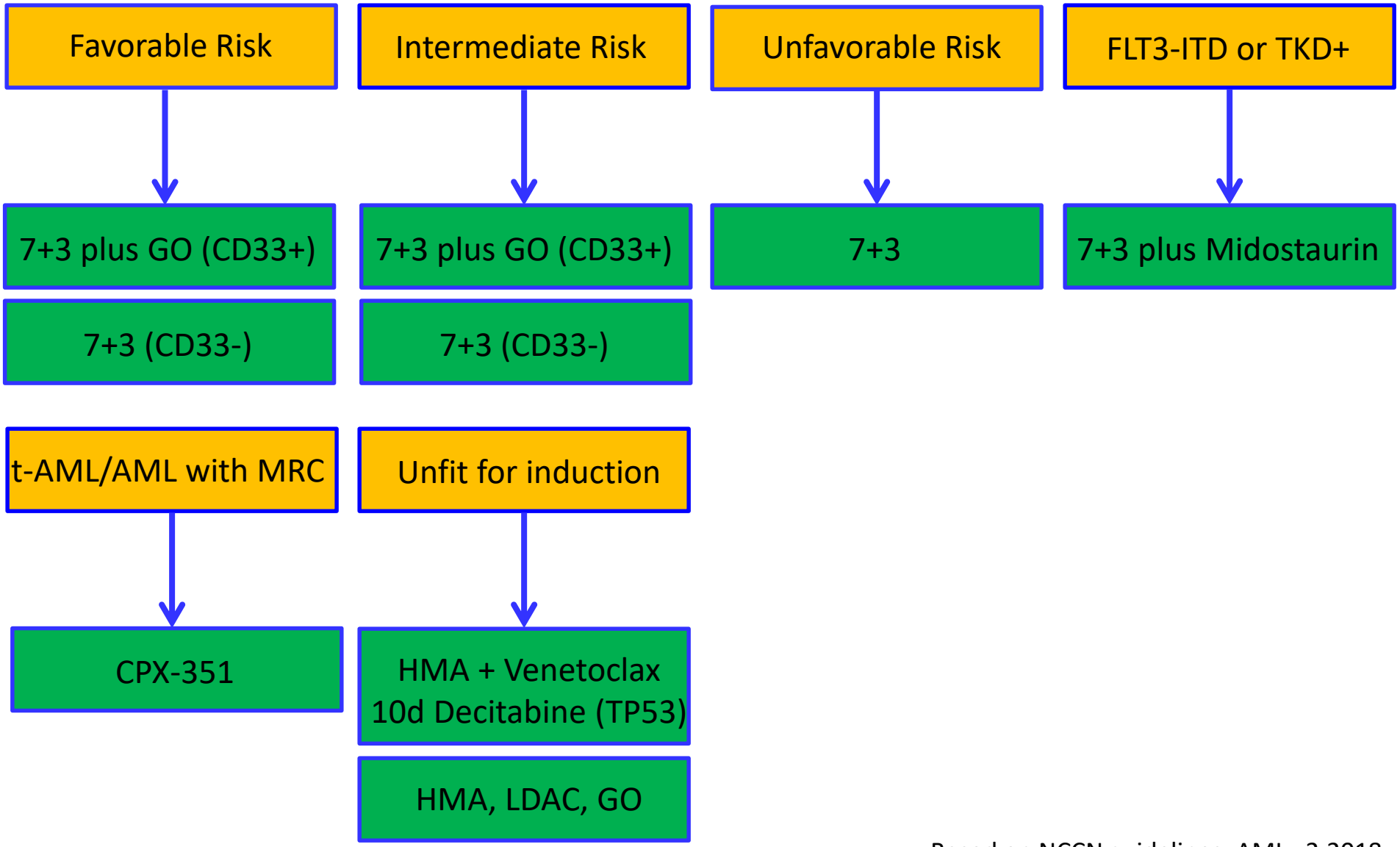
CR	34	34	31	25	15	11	6	2	0	
Non-CR response	37	34	30	17	11	7	3	1	1	0
No response	97	68	43	20	10	3	1	0		



Stein et al, Blood 2017.

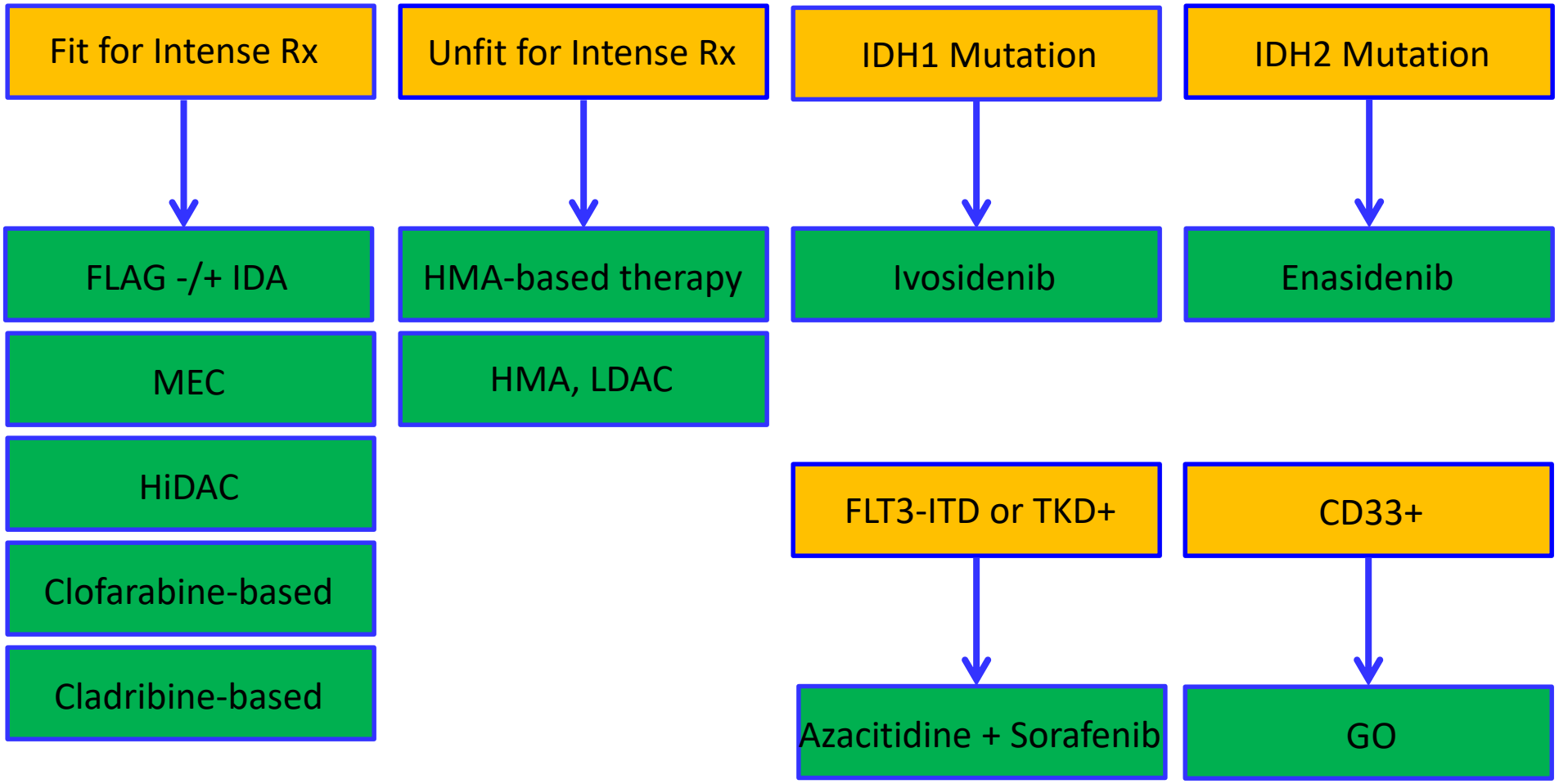
Evolving Standards of Care for AML

First-Line Treatment of AML Off Trial



Based on NCCN guidelines, AML v2.2018

Treatment of Relapsed or Refractory AML Off Trial



Based on NCCN guidelines, AML v2.2018

Summary

- Exciting time for new FDA therapy approvals for AML
  - 5 new approvals since 4/2017
- SOC for AML is rapidly evolving
- Clinical trials continue to advance new treatments

Questions?

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Extra Slides

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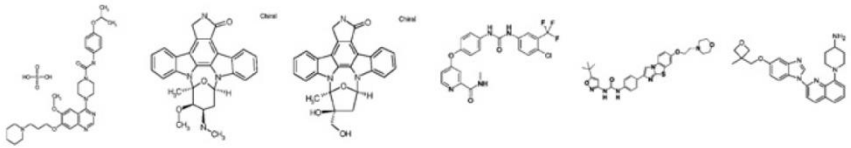
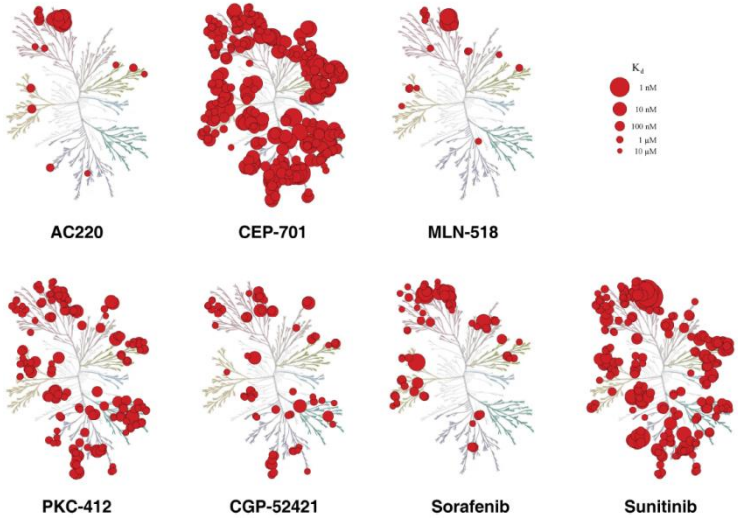
Upcoming AML Drugs in Development

Other FLT3 Inhibitors in Development

FLT3 inhibitors	Tandutinib	Lestaurtinib	Midostaurin	Sorafenib	Quizartinib	Crenolanib
FLT3 inhibition (IC50, nM)	220	3	<10	58	1.1	0.15
Structure						

Gilteritinib – FLT3/AXL inhibitor active against FLT3-ITD and FLT3-D835 mutations

Crenolanib – active against FLT3-ITD and FLT3-TKD mutations

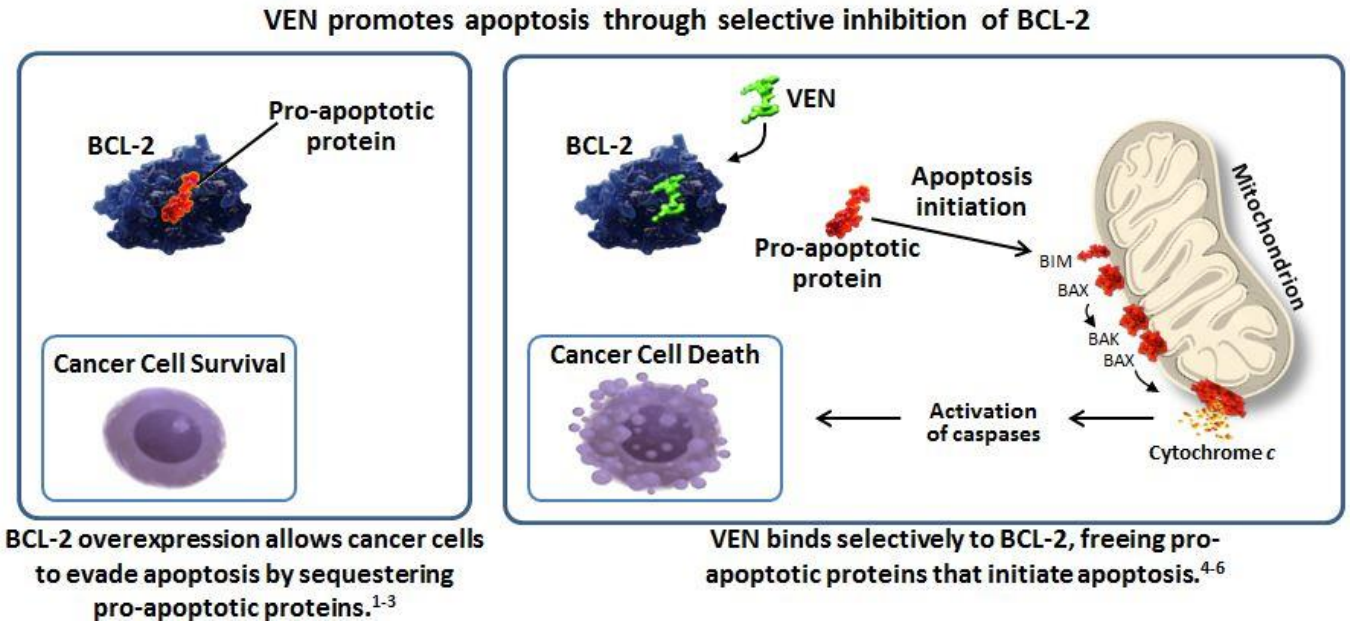


Quizartinib, Gilteritinib and Crenolanib are all in P3 trials

Quantum-R (Quizartinib vs SOC for R/R FLT3-ITD+ AML) showed improved OS vs SOC
EHA 2018 Abstract #LB2600

Fathi AT, Blood, 2015.
Smith et al, Leukemia, 2015.
Kiyoi et al. Nag J Med Sci, 2015.
Zarrinkar et al. Blood, 2009.

Venetoclax and AML



- AML – median age at diagnosis 68 and pts are often ineligible for or refractory to intense chemotherapy
- BCL-2 is highly expressed in AML and is associated with poor outcomes
- Ven is an oral BCL-2 inhibitor with activity in AML

Pratz et al, BSH, #BSH18-OR-007.
Mihalyova et al, Exp Hematol 2018.

Abstract 7010

Durable Response with Venetoclax in Combination with Decitabine or Azacitidine in Elderly Patients with Acute Myeloid Leukemia

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

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Presented By Courtney Dinardo at 2018 ASCO Annual Meeting

Study Design and Objectives

- **Design:** Phase 1b, open label, multicenter dose escalation and expansion
- **Endpoints:** Safety, Rates of CR/CRi, Overall Survival (OS), and Duration of Response (DOR)

PRIMARY OBJECTIVE

To assess the safety of venetoclax in combination with decitabine or azacitidine in patients ≥65 years of age with untreated AML who are ineligible for standard induction chemotherapy

SECONDARY OBJECTIVE

To assess CR, CRi, DOR, and OS

EXPLORATORY OBJECTIVE

To assess the impact of venetoclax on minimal residual disease (MRD)

***Venetoclax dose ramped up from 100mg to 400mg or 800mg over 3-4 days**

Treatment Emergent Adverse Events (AE)

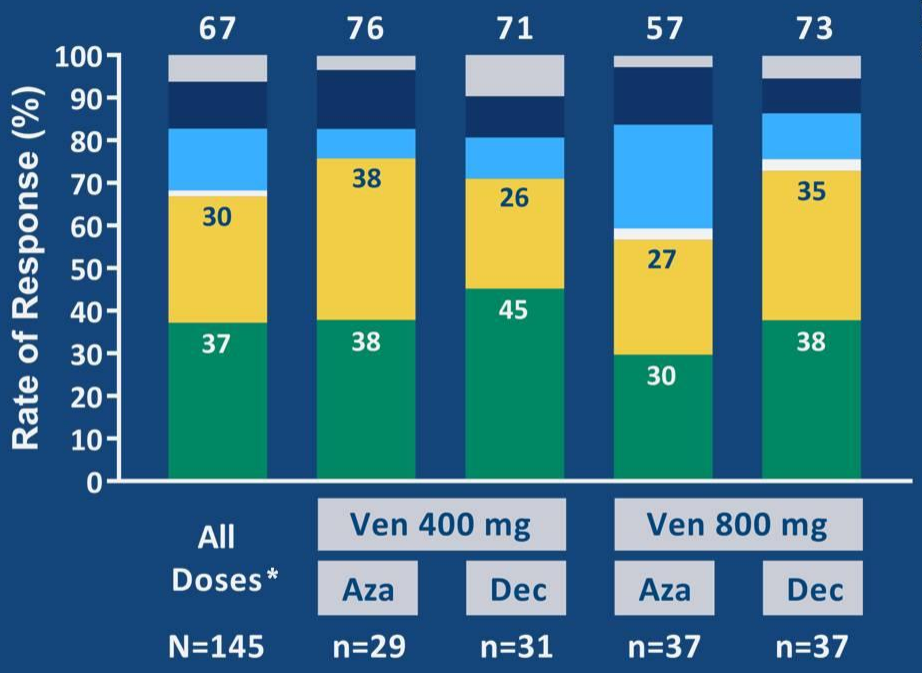
AEs in ≥25% of patients	Any grade	Grade 3/4
Any event, n (%)	145 (100)	141 (97)
Nausea	88 (61)	2 (1)
Diarrhea	76 (52)	7 (5)
Constipation	70 (48)	2 (1)
Febrile neutropenia	63 (43)	63 (43)
Fatigue	54 (37)	8 (6)
Hypokalemia	49 (34)	15 (10)
Decreased appetite	48 (33)	3 (2)
Decreased WBC count	45 (31)	45 (31)
Vomiting	44 (30)	0
Platelet count decreased	42 (30)	35 (24)
Anemia	40 (28)	36 (25)
Cough	41 (28)	0
Peripheral edema	41 (28)	0

Serious AEs in ≥3% of patients	N = 145
Any event, n (%)	102 (70)
Febrile neutropenia	46 (32)
Pneumonia	17 (12)
Bacterial Infection	9 (6)
Lung Infection	7 (5)
Sepsis	6 (4)
Hypotension	5 (3)
Mental Status Changes	4 (3)
Gastrointestinal Hemorrhage	4 (3)
Mucosal Inflammation	4 (3)

Patient Disposition	N=145
Deaths, n (%)	
≤30 days after Ven start	5 (3)
≤60 days after Ven start	11 (8)

- Rates of AEs between patients treated with Dec or Aza were similar at respective Ven doses
- No events of laboratory or clinical tumor lysis syndrome (TLS) were observed

Response Rates by Treatment



* All doses includes 11 patients that received 1200 mg venetoclax

Patients (%) with CR/CRi shown at the top of each bar

- Other
- RD
- MLFS
- PR
- CRi
- CR

CR/CRi and MRD Negative:
29% overall
45% Aza 400

Abbreviations: CR, complete remission; CRi, CR with incomplete blood count recovery; PR, partial remission; MLFS, morphogenic leukemia free state; RD, resistant disease.

Other, disease progression, or discontinued prior to assessment

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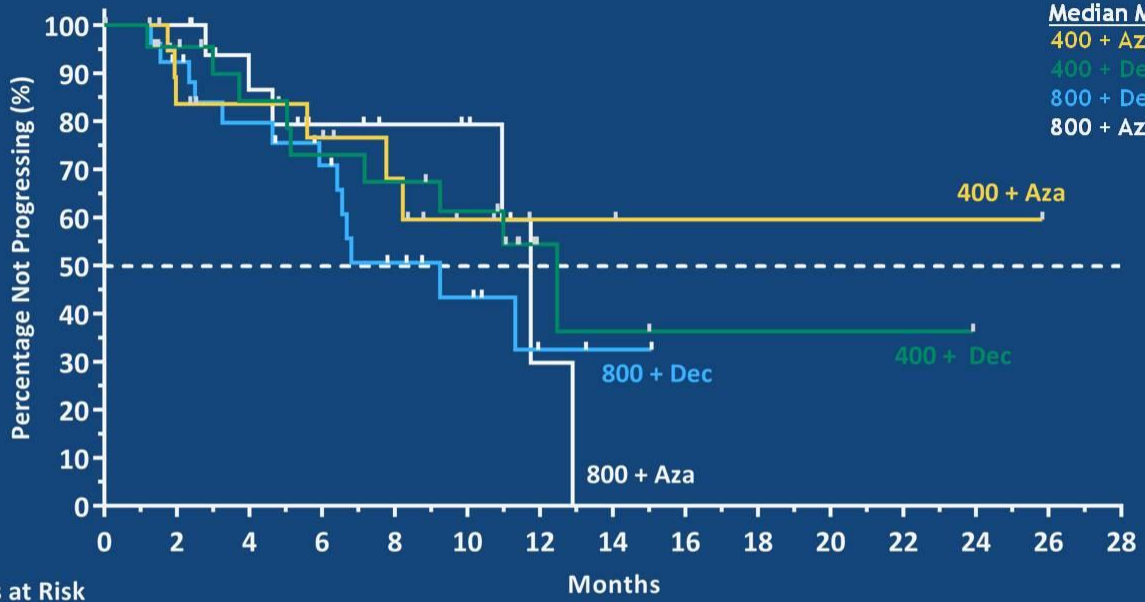
Duration of Response after CR/CRi



Median Months of Response (95% CI)	
400 + Aza	NR (5.6 – NR)
400 + Dec	12.5 (5.1 – NR)
800 + Dec	9.2 (5.9 – NR)
800 + Aza	11.7 (4.6 – 12.9)

Patients at Risk													
400 + Dec	22	19	15	13	12	10	3	2	1	1	1	1	
400 + Aza	22	15	13	11	8	4	2	2	1	1	1	1	1
800 + Dec	27	23	19	15	9	6	2	1					
800 + Aza	21	18	12	8	6	5	1						

Abbreviations:
400, 400 mg venetoclax;
800, 800 mg venetoclax
NR, not reached
NA, not available

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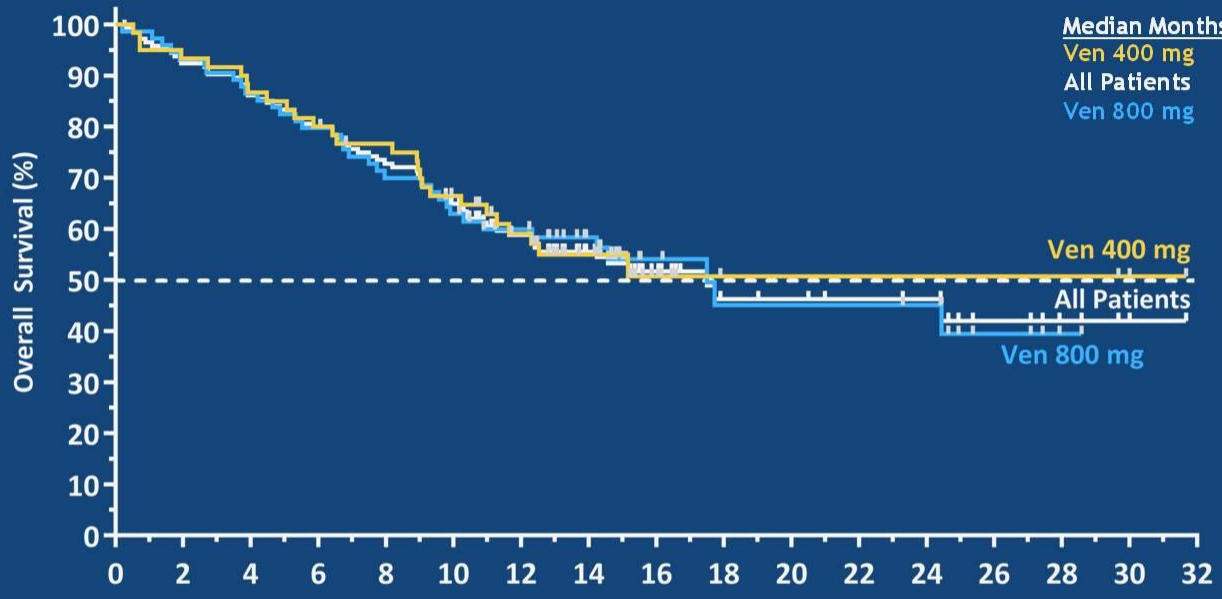
Overall Survival



Patients at Risk

All patients	145	133	124	115	102	89	73	53	25	16	15	13	12	7	4	2
Ven 400 mg	60	56	52	48	45	38	30	20	8	3	3	3	3	3	3	2
Ven 800 mg	74	69	64	59	50	44	38	29	13	10	10	10	9	4	1	

Presented By Courtney Dinardo at 2018 ASCO Annual Meeting