State of the Art in Acute Leukemias

Brian A. Jonas, MD, PhD, FACP
Associate Professor
University of California, Davis
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Disclosures

- **Consulting/Advising**: AbbVie, Genentech/Roche, GlycoMimetics, Jazz, Takeda, Treadwell
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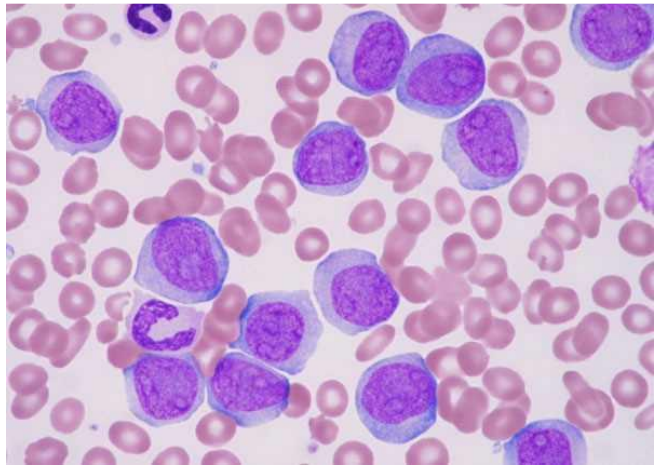
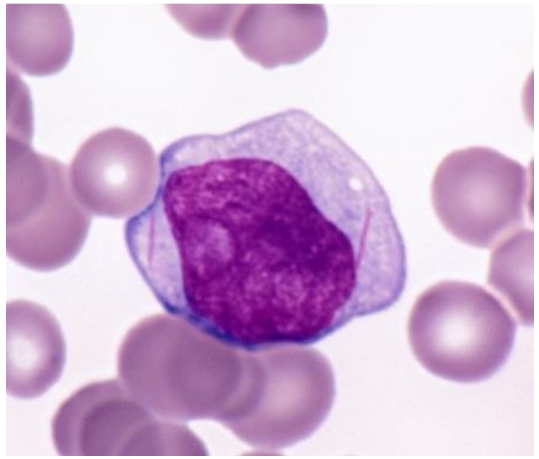
Learning Objectives

- Review key treatment options for older adults with AML
- Discuss two recent FDA approvals for AML and MDS
- Briefly highlight current strategies for R/R ALL

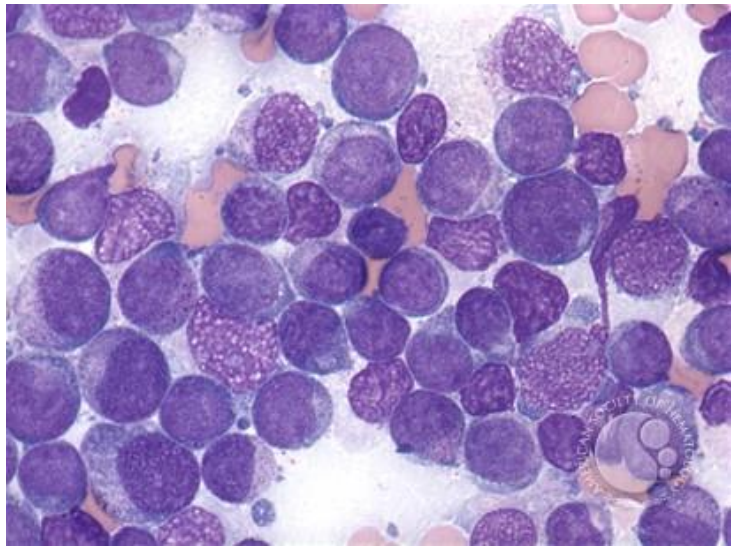
Treatment of Older Adults with Acute Myeloid Leukemia





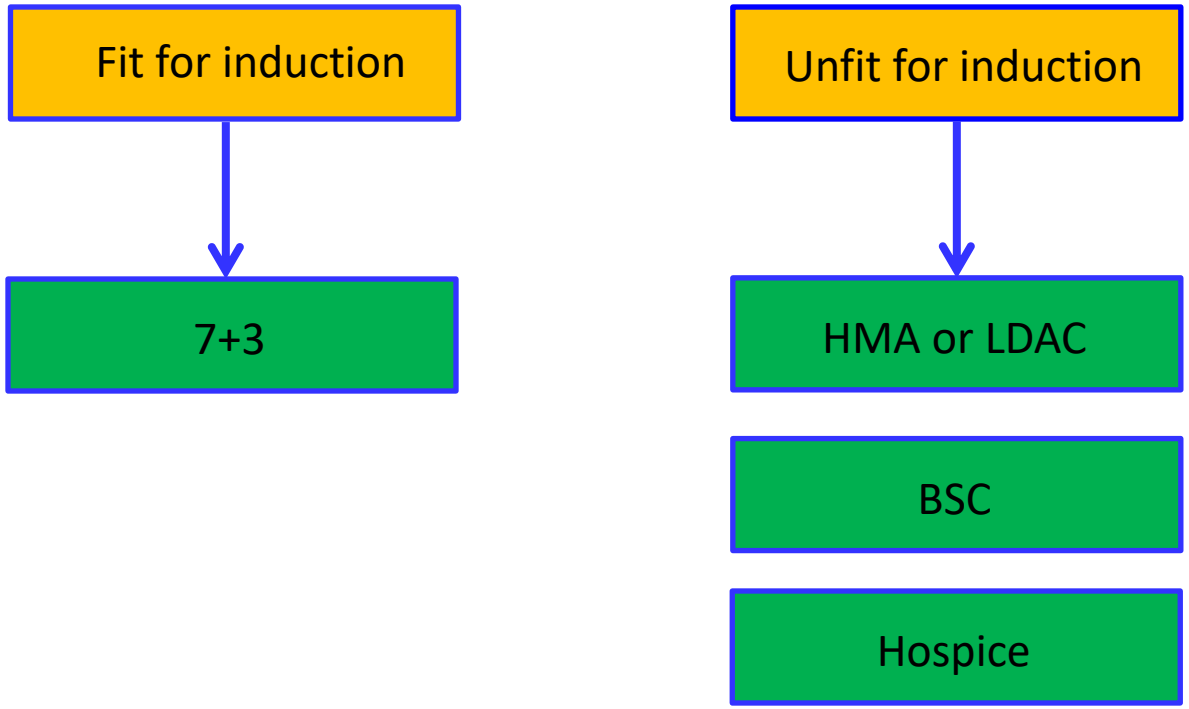
Acute Myeloid Leukemia

- Clonal expansion of immature myeloid cells
- Heterogeneous disease
- Median age 68
- 19,940 new cases (M>F) with 11,180 deaths expected in US in 2020[1]
- Bleeding, infections, anemia
- High relapse rates



[1]ACS Cancer Statistics, 2020.

Former First-Line Treatment of AML



AML Score

AML-Score

You selected the following input parameter:

Body temperature:	≤100.4˚F
Hemoglobin:	>10.3 g/dl
Platelets:	>28-53 G/l
Fibrinogen:	>150 mg/dl
LDH:	≤700 U/l
Age:	65-67 years
Type:	de novo
Cytogenetic / molecular risk:	intermediate normal (NPM1 Wildtype; Flt3 internal tandem duplication)

Based on these input parameters, the following scores were calculated:

The chance for the achievement of a complete remission after intensive induction therapy is	
Complete remission [%]	**74.2**
The risk of an early death within 60 deays after start of an intensive induction therapy is	
Early death [%]	**11.8**

AML-Score. Available online at http://aml-score.org. AML Study Alliance Group. Krug U, Müller-Tidow C. et al. Complete remission and early death after intensive chemotherapy in patients aged 60 years or older with acute myeloid leukaemia: A web-based application for prediction of outcomes. Lancet 2010; 376(9757): 2000-2008.

Ferrara Criteria to Define Unfitness for Intense Chemotherapy for AML

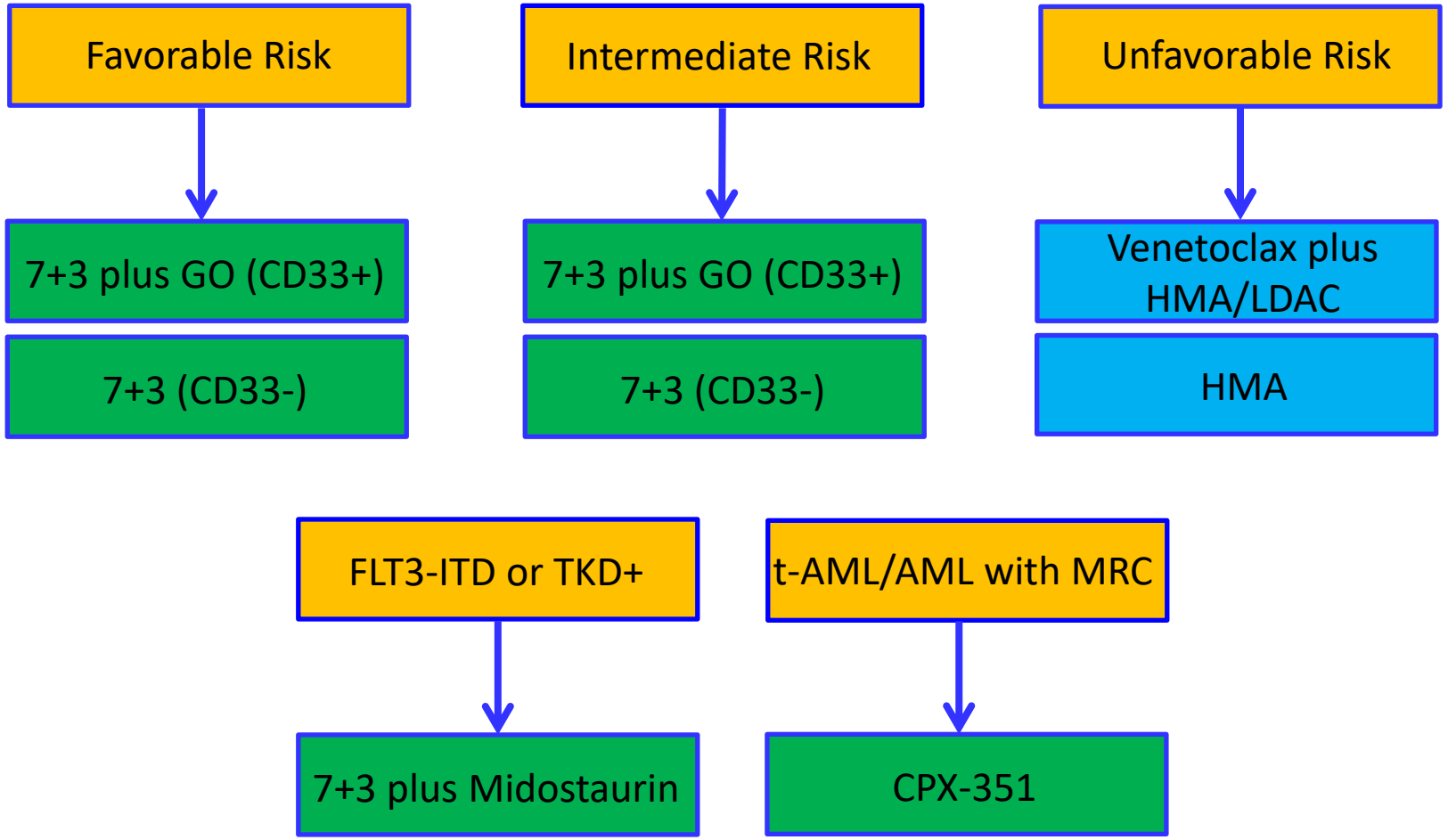
Table 3. Operation criteria to define unfitness to intensive chemotherapy in AML

1. An age older than 75 years
2. Congestive heart failure or documented cardiomyopathy with an EF $\leq$50%
3. Documented pulmonary disease with DLCO $\leq$65% or FEV1 $\leq$65%, or dyspnea at rest or requiring oxygen, or any pleural neoplasm or uncontrolled lung neoplasm
4. On dialysis and age older than 60 years or uncontrolled renal carcinoma
5. Liver cirrhosis Child B or C, or documented liver disease with marked elevation of transaminases ($>$3 times normal values) and an age older than 60 years, or any biliary tree carcinoma or uncontrolled liver carcinoma or acute viral hepatitis
6. Active infection resistant to anti-infective therapy
7. Current mental illness requiring psychiatric hospitalization, institutionalization or intensive outpatient management, or current cognitive status that produces dependence (as confirmed by the specialist) not controlled by the caregiver
8. ECOG performance status $\geq$3 not related to leukemia
9. Any other comorbidity that the physician judges to be incompatible with conventional intensive chemotherapy

Abbreviations: AML, acute myeloid leukemia; DLCO, diffusing capacity of the lungs for carbon monoxide; ECOG, Eastern Cooperative Oncology Group; EF, ejection fraction; FEV1, forced expiratory volume in 1 s.

Ferrara et al, Leukemia 2013.

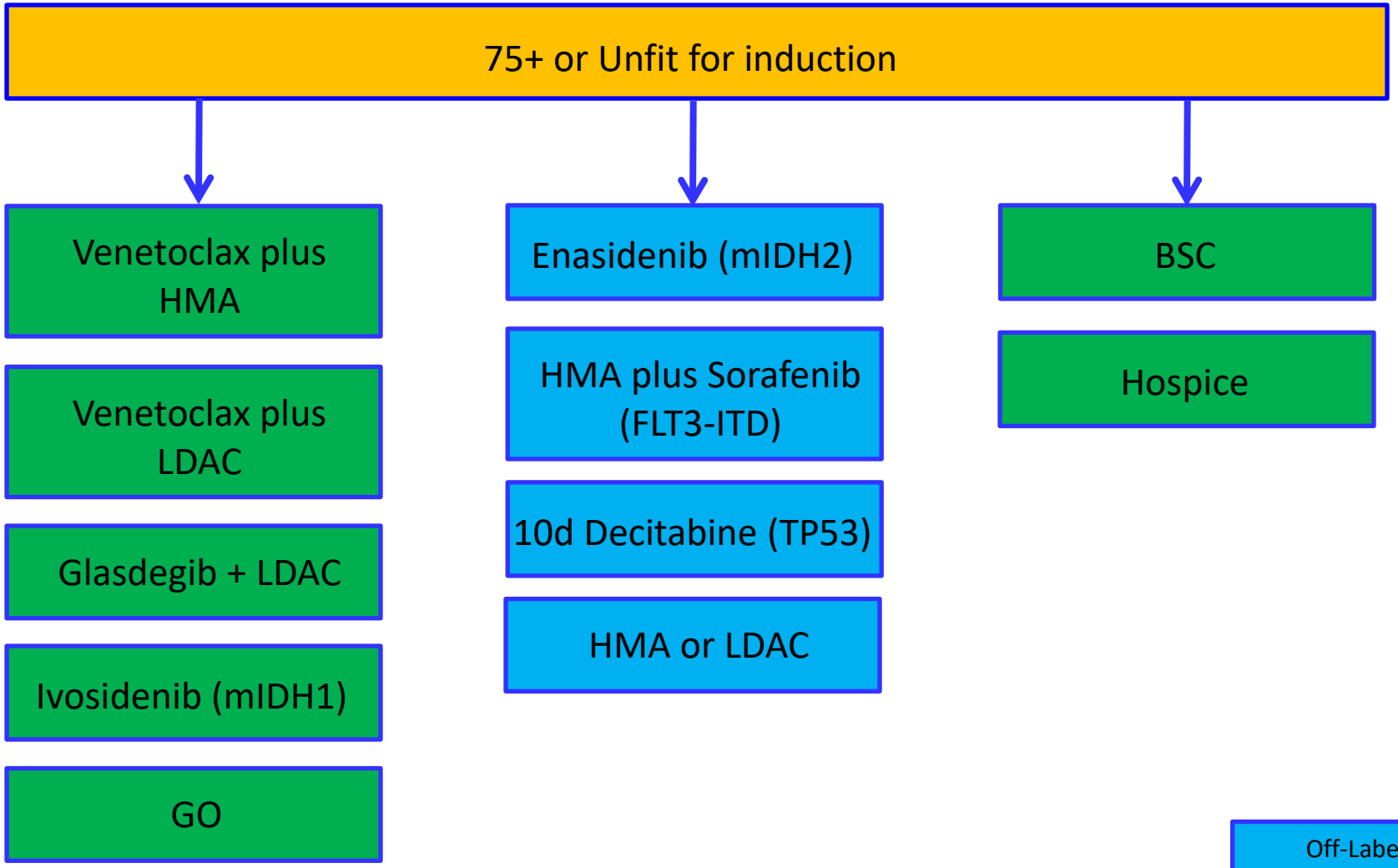
First-Line Treatment of Older Fit AML in 2020



Off-Label

Based on NCCN guidelines, AML v3.2020

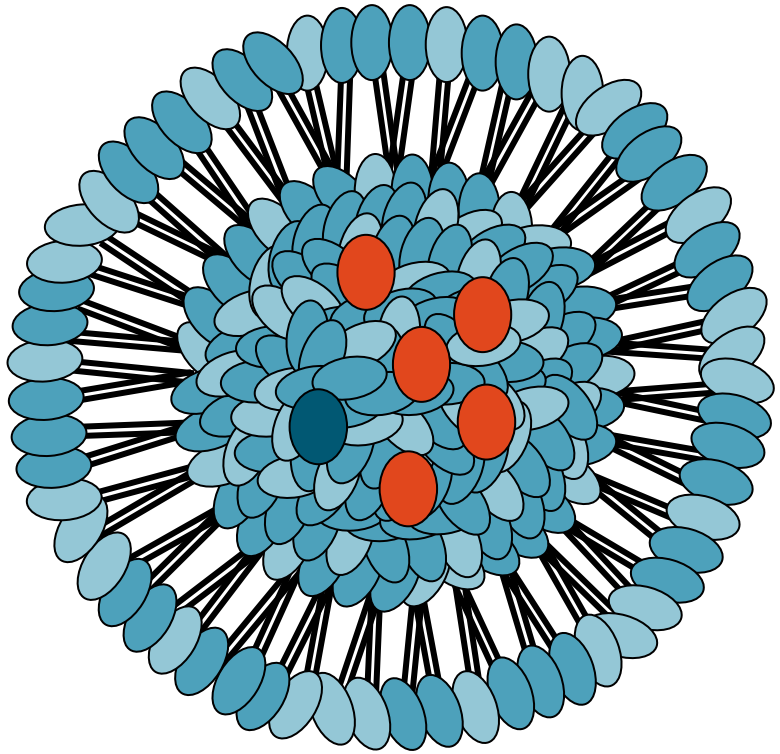
First-Line Treatment of Older Unfit AML in 2020



Based on NCCN guidelines, AML v3.2020

CPX-351

Liposomal Cytarabine and Daunoribuicin (CPX-351)



- CPX-351 a 5:1 molar ratio of cytarabine:daunorubicin
- Formulation provides synergistic leukemia cell killing in vitro[1]
- In humans
  - CPX-351 preserved delivery of the 5:1 drug ratio for > 24 hours
  - Drug exposure maintained for 7 days[2]
- Selective uptake of liposomes by bone marrow leukemia cells in xenograft models[3]

1. Tardi P, et al. *Leuk Res*. 2009;33(1):129-39. 2. Feldman. *J Clin Oncol*. 2011;29:979-85. 3. Lim. *Leuk Res*. 2010;34 (9):1214-23.

CPX-351 for Secondary AML

VOLUME 36 · NUMBER 26 · SEPTEMBER 10, 2018

JOURNAL OF CLINICAL ONCOLOGY

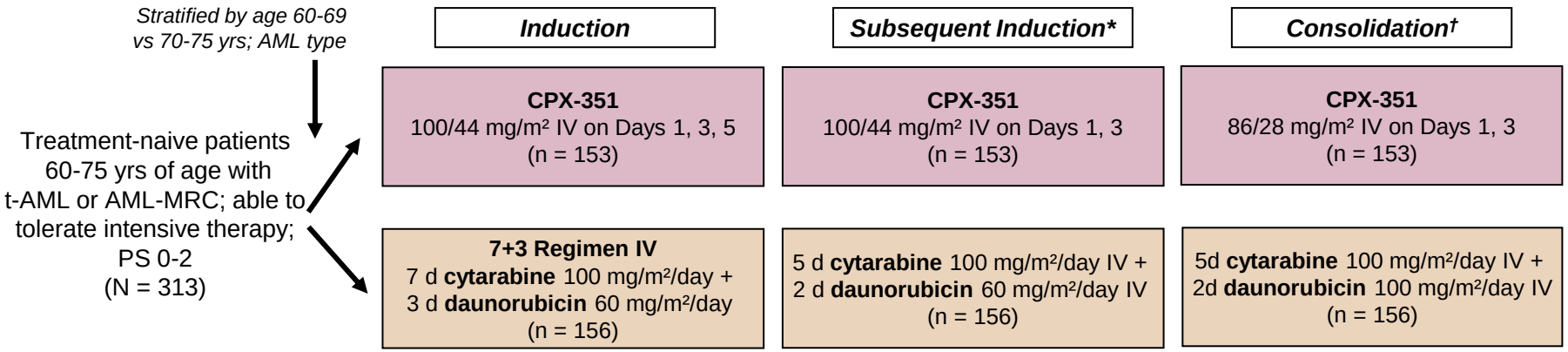
RAPID COMMUNICATION

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 vs Standard 7+3 Chemotherapy in Older Patients with Newly Diagnosed tAML or sAML

- Multicenter, open-label, randomized phase III trial

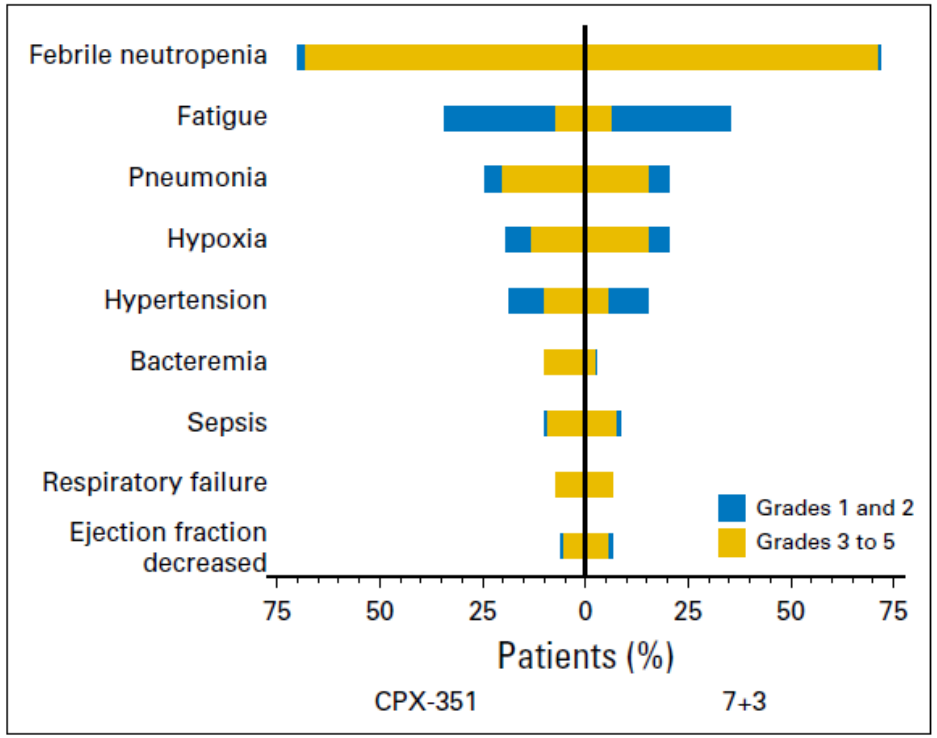


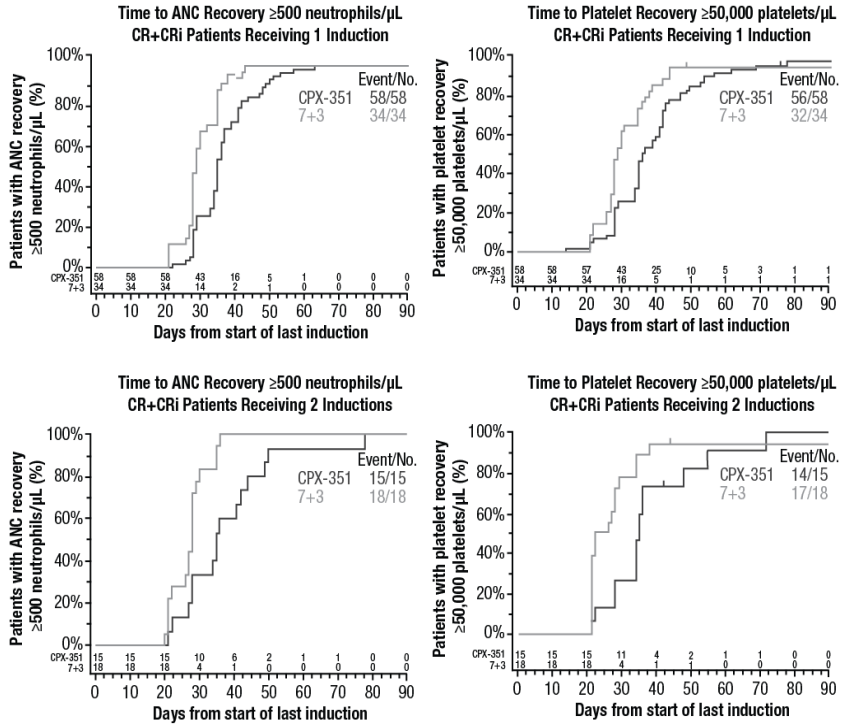
*Subsequent induction was recommended for patients who did not achieve a CR or CRi and was mandatory for patients achieving > 50% reduction in percent blasts.
†Postremission therapy with allogeneic HCT permitted either in place of or after consolidation.

- Primary endpoint: OS

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		

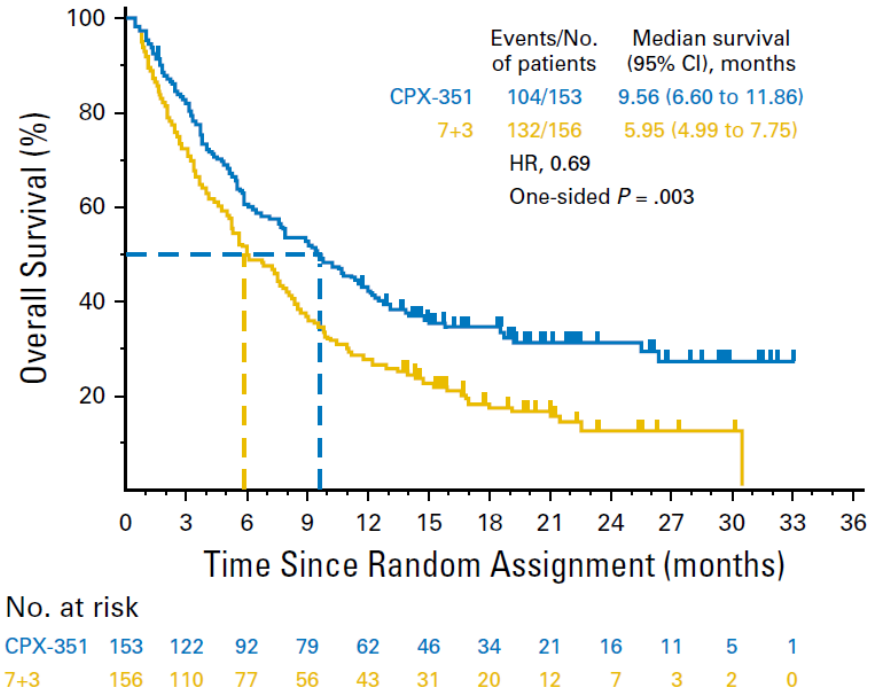




Lancet et al, ASCO 2016 Abstract #7000.
Lancet et al, JCO 2018.

CPX-351 Improved Outcomes Compared to 7+3

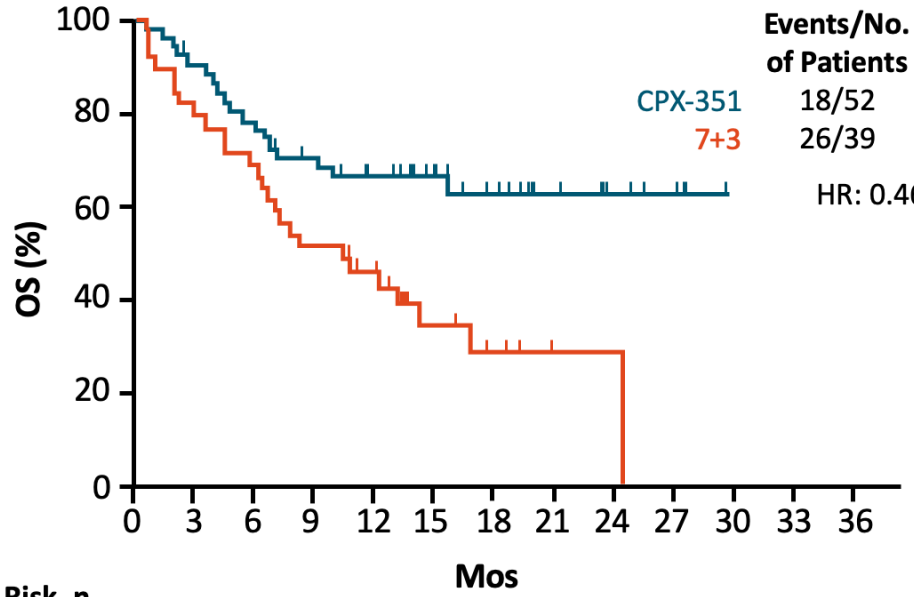
	CPX-351 n=153	7+3 n=156		
			Odds Ratio	***P* value**
CR	37.3%	25.6%	1.67 (1.02, 2.74)	0.040
CR+CRi	47.7%	33.3%	1.77 (1.11, 2.81)	0.016
Stem Cell Transplant	34.0%	25.0%	1.54 (0.92, 2.56)	0.098



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

Allo-HCT Outcomes after CPX-351 Compared to 7+3

CPX-351 in Older Patients With tAML/sAML: OS by Time Since Allogeneic Stem Cell Transplantation



	Events/No. of Patients	Median Survival, Mos (95% CI)
CPX-351	18/52	Not reached
7+3	26/39	10.25 (6.21-16.69)

HR: 0.46 (1-sided *P* = .009)

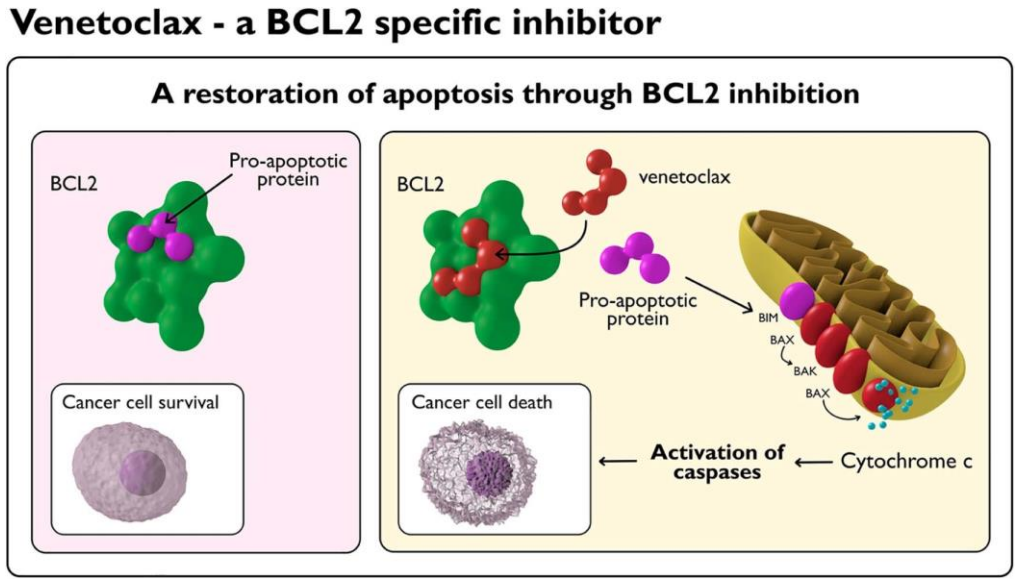
Patients at Risk, n												
CPX-351	52	46	40	34	27	20	15	9	6	3	0	0
7+3	39	31	27	20	15	7	4	1	1	0	0	0

Lancet. J Clin Oncol. 2018;36:2684.

Slide credit: clinicaloptions.com

Bcl-2 Inhibitor Combinations

Venetoclax and AML



- BCL-2 is an anti-apoptotic protein that plays key roles in the survival and therapeutic resistance of AML cells, including LSC
- Venetoclax is a potent, selective oral Bcl-2 inhibitor with significant anti-AML and anti-LSC activity in combination with hypomethylating agents (HMA) and low-dose cytarabine (LDAC)

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

Venetoclax for AML

Safety and preliminary efficacy of venetoclax with decitabine or azacitidine in elderly patients with previously untreated acute myeloid leukaemia: a non-randomised, open-label, phase 1b study

Courtney D DiNardo, Keith W Pratz, Anthony Letai, Brian A Jonas, Andrew H Wei, Michael Thirman, Martha Arellano, Mark G Frattini, Hagop Kantarjian, Relja Popovic, Brenda Chyla, Tu Xu, Martin Dunbar, Suresh K Agarwal, Rod Humerickhouse, Mack Mabry, Jalaja Potluri, Marina Konopleva, Daniel A Pollyea**

Lancet Oncol 2018; 19: 216–28

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)

Pollyea et al, Blood 2018, Abstract #285.
DiNardo et al, Lancet Oncology 2018.
DiNardo et al, Blood 2019.

P1 Study Design

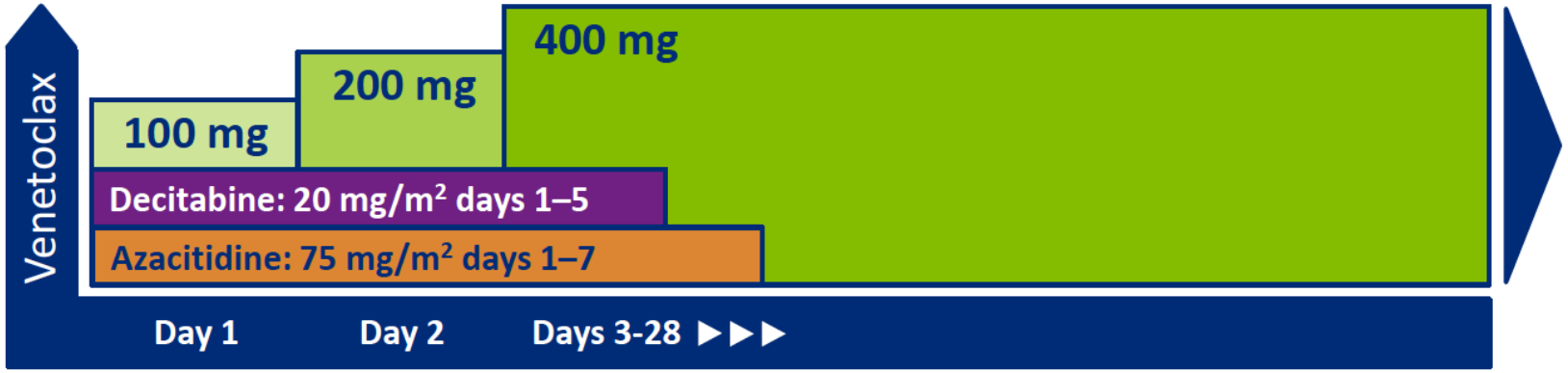
KEY INCLUSION CRITERIA

- AML by WHO criteria
- Age ≥ 60 years
- Ineligible for standard induction therapy with cytarabine and anthracycline as determined by medical criteria
- ECOG score 0–3

* Favorable risk cytogenetics (now known as non-adverse cytogenetics) is defined as: core binding factor: inv(16), t(16;16), t(8;21), or t(15;17)

KEY EXCLUSION CRITERIA

- Prior therapy for AML or any antecedent hematologic disorder
- Favorable risk cytogenetics per NCCN*
- Active CNS involvement
- WBC count >25 $\times 10^9$ per liter (hydrea was permitted)
- Known infection with HIV, HBV, or HCV



- RP2D was 400mg
- Safety demonstrated at 800mg and 1200mg
- Dose adjustments for concurrent CYP3A4 inhibitors (e.g. Azoles)

Pollyea et al, Blood 2018, Abstract #285.
DiNardo et al, Lancet Oncology 2018.
DiNardo et al, Blood 2019.

Adverse Events

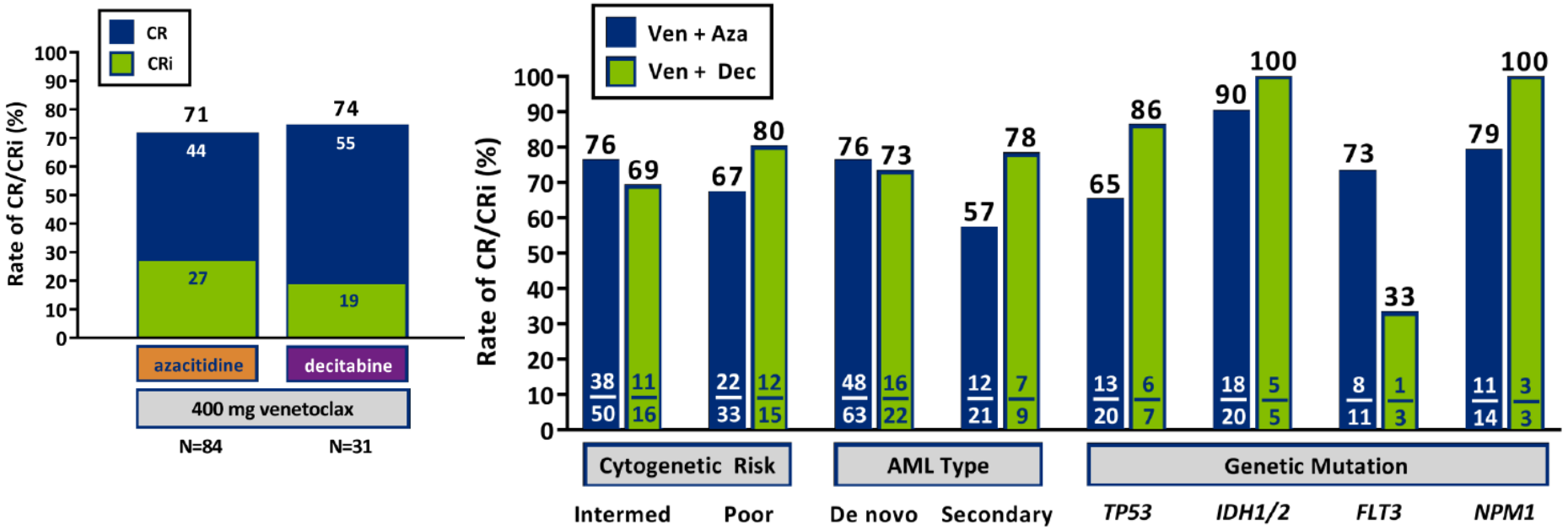
AEs in ≥30% of patients	Venetoclax + Aza (n = 84)		Venetoclax + Dec (n=31)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Anemia	26 (31)	26 (31)	8 (26)	8 (26)
Platelet count decreased	25 (30)	22 (26)	15 (48)	14 (45)
WBC count decreased	28 (33)	28 (33)	14 (45)	14 (45)
Febrile neutropenia	33 (39)	33 (39)	20 (65)	20 (65)
Pneumonia	23 (27)	23 (27)	12 (39)	10 (32)
Decreased appetite	24 (29)	2 (2)	10 (32)	1 (3)
Constipation	42 (50)	3 (4)	16 (52)	0
Diarrhea	49 (58)	2 (2)	14 (45)	2 (6)
Nausea	54 (64)	2 (2)	20 (65)	0
Vomiting	32 (38)	0	12 (39)	0
Fatigue	28 (33)	5 (6)	14 (45)	3 (10)
Edema peripheral	34 (41)	1 (1)	10 (32)	0
Hypokalemia	28 (33)	5 (6)	11 (36)	5 (16)

Early Deaths, n (%)	Venetoclax + Aza (n = 84)	Venetoclax + Dec (n=31)
≤30 days after beginning treatment	2 (2)	2 (7)
≤60 days after beginning treatment	7 (8)	3 (10)

No events of laboratory or clinical tumor lysis syndrome were reported
Most common SAEs include febrile neutropenia, pneumonia, bacteriemia, sepsis and respiratory failure

DiNardo et al, ASCO 2018, Abstract #7010.
DiNardo et al, Lancet Oncology 2018.
DiNardo et al, Blood 2019.

Responses



CR/CRi and MRD Negative:

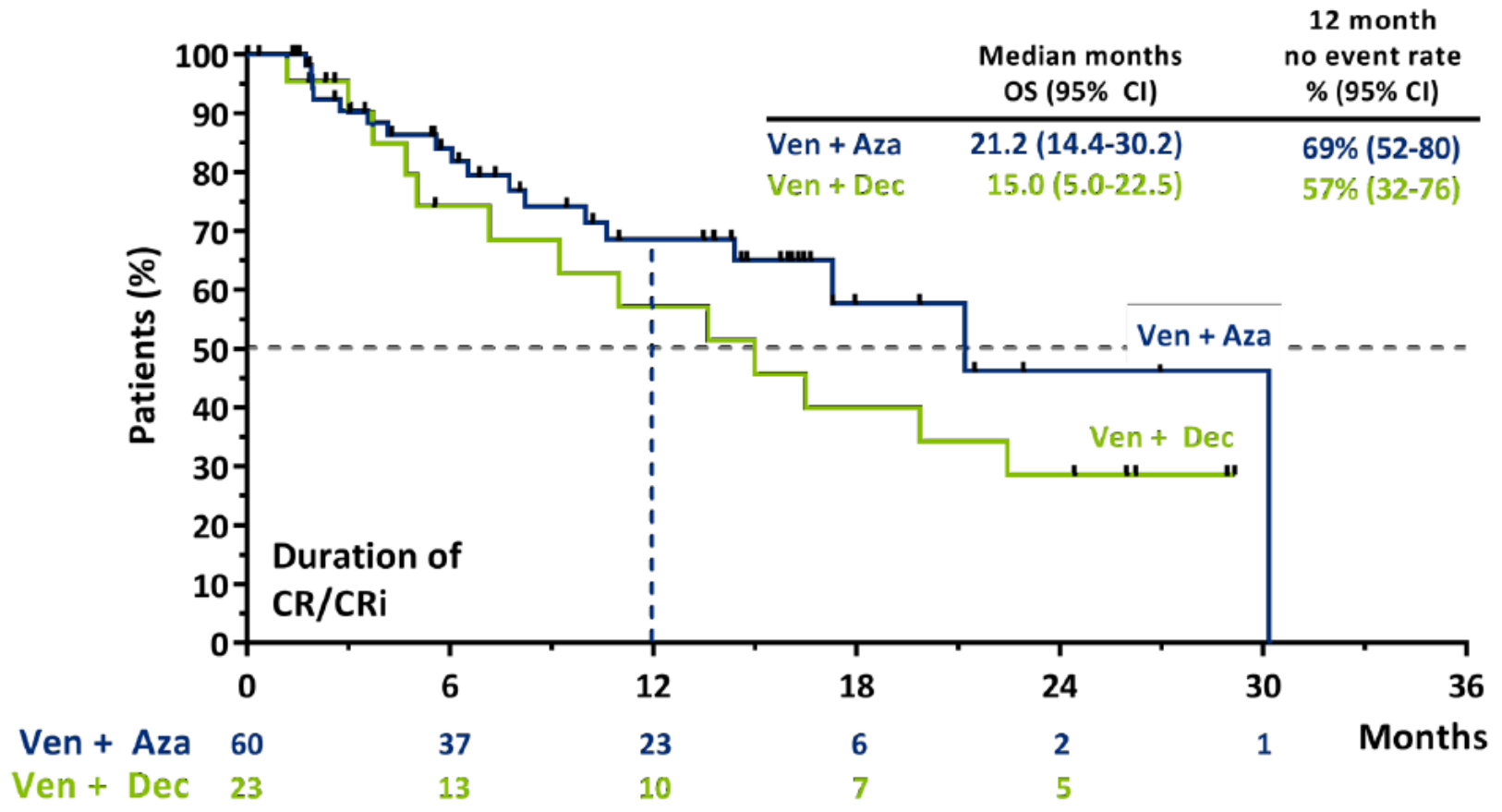
48% AZA

39% DEC

10^{-3} at any time

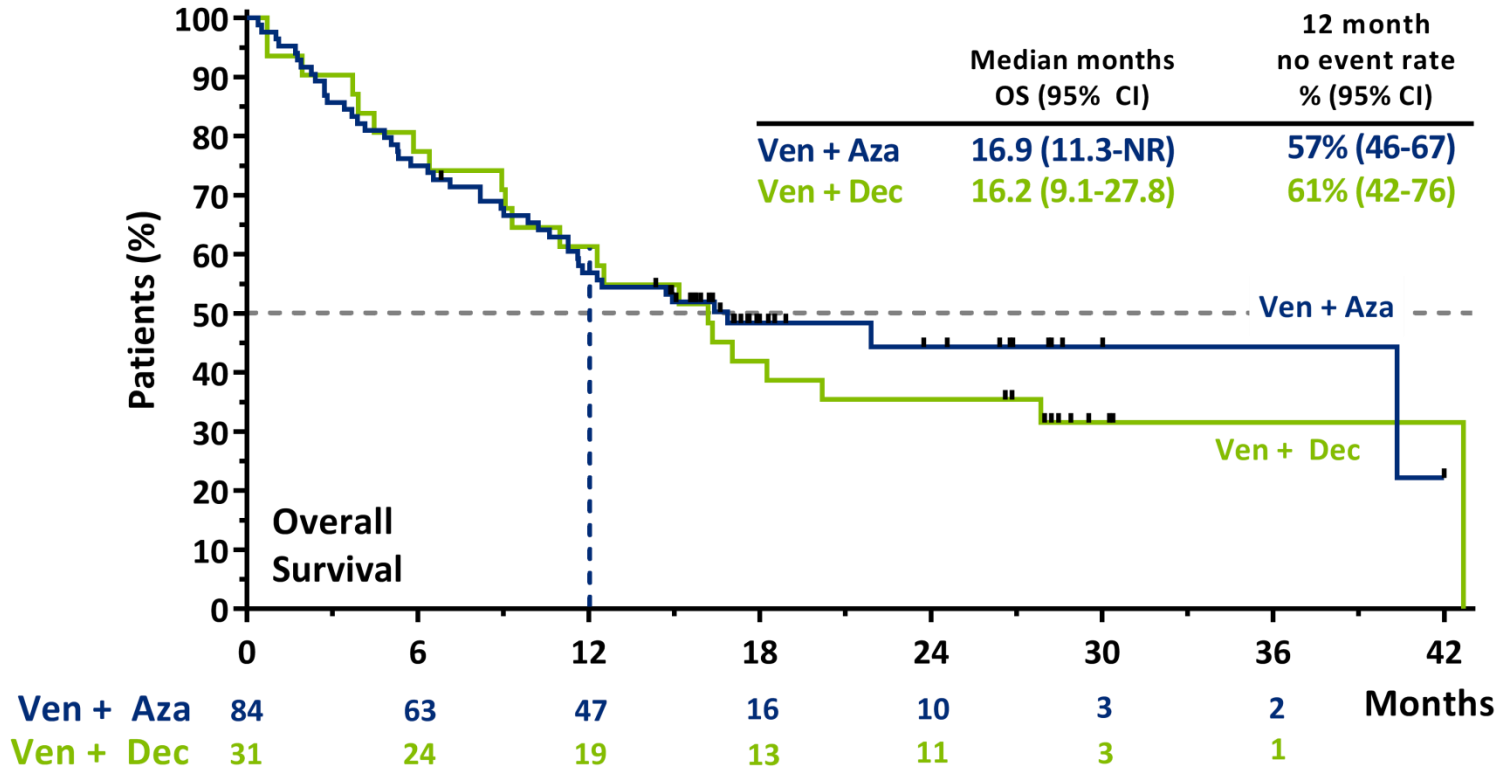
Pollyea et al, Blood 2018, Abstract #285.
DiNardo et al, Lancet Oncology 2018.
DiNardo et al, Blood 2019.

DoR after CR/CRi



Pollyea et al, Blood 2018, Abstract #285.
DiNardo et al, Lancet Oncology 2018.
DiNardo et al, Blood 2019.

Overall Survival



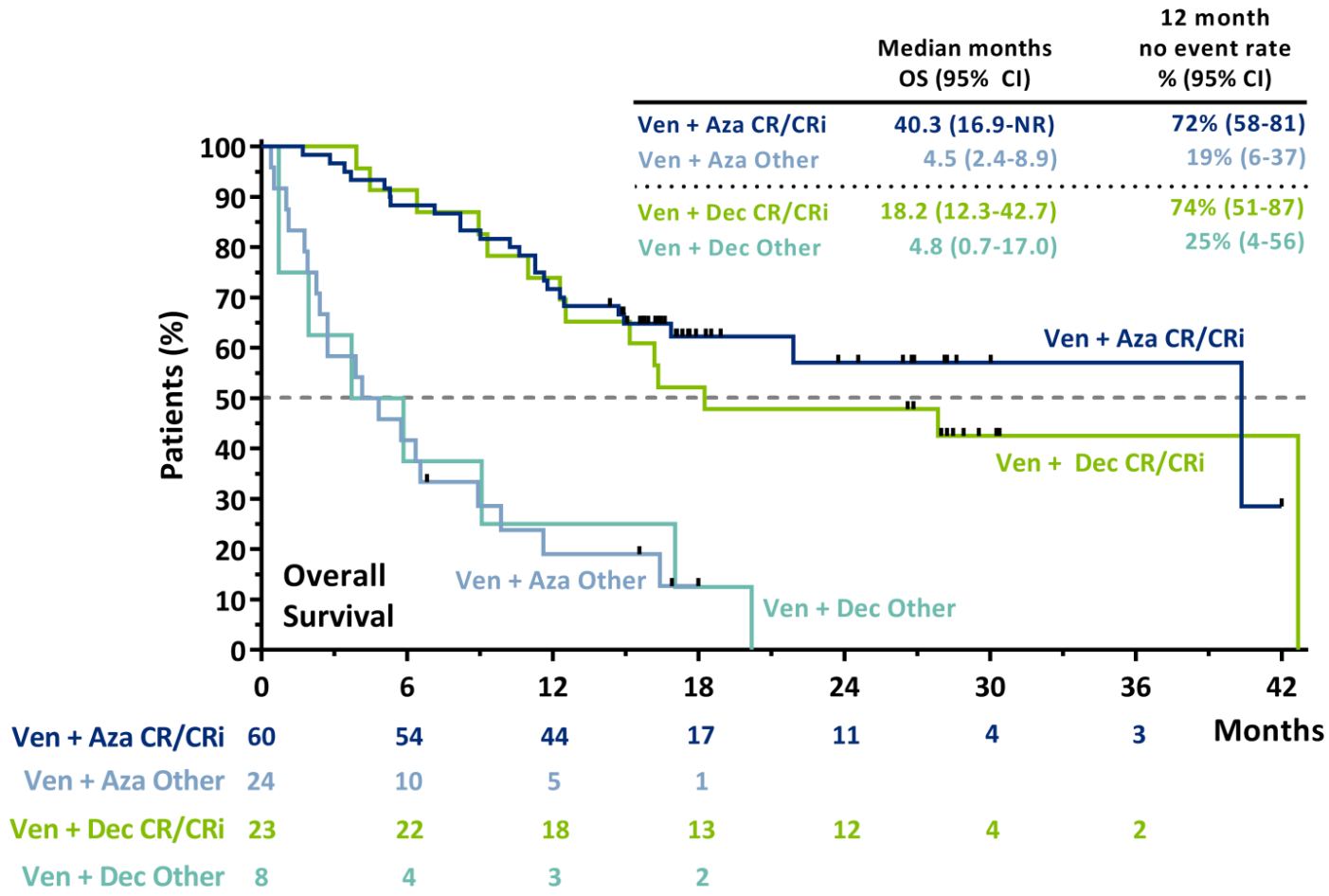
Median Survival Follow-up

Venetoclax + azacitidine
14.9 months (range 0.4–42.0)

Venetoclax + decitabine
16.2 months (range 0.7–42.7)

Pollyea et al, Blood 2018, Abstract #285.
DiNardo et al, Lancet Oncology 2018.
DiNardo et al, Blood 2019.

OS by Response



Pollyea et al, Blood 2018, Abstract #285.
DiNardo et al, Lancet Oncology 2018.
DiNardo et al, Blood 2019.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 13, 2020 VOL. 383 NO. 7

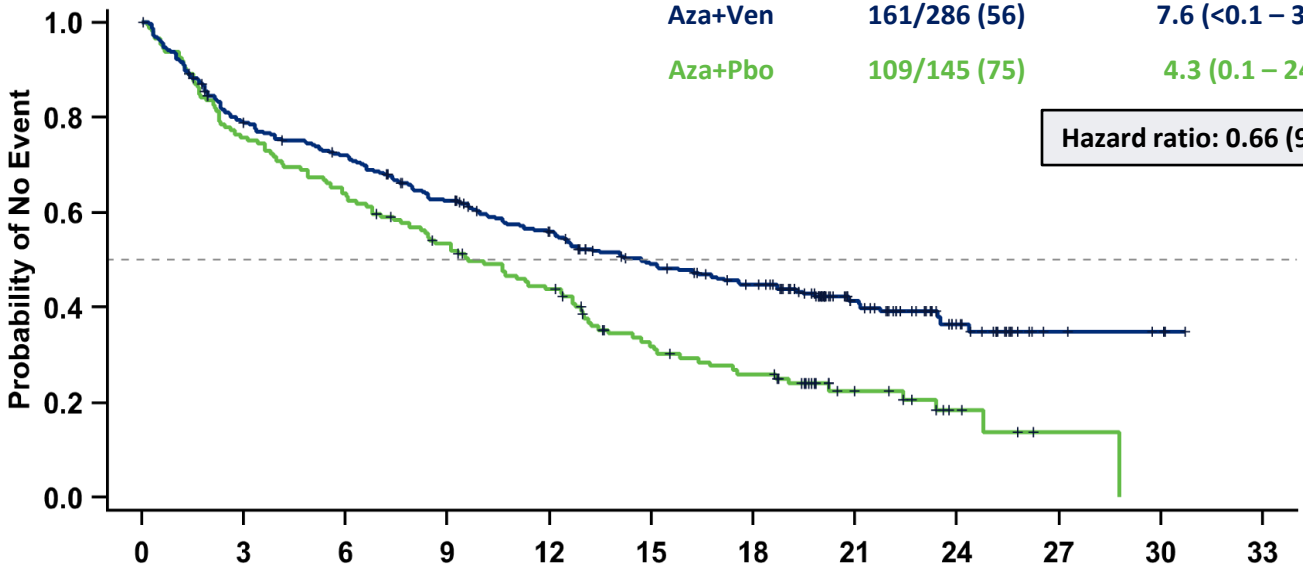
Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia

C.D. DiNardo, B.A. Jonas, V. Pullarkat, M.J. Thirman, J.S. Garcia, A.H. Wei, M. Konopleva, H. Döhner, A. Letai, P. Fenaux, E. Koller, V. Havelange, B. Leber, J. Esteve, J. Wang, V. Pejsa, R. Hájek, K. Porkka, Á. Illés, D. Lavie, R.M. Lemoli, K. Yamamoto, S.-S. Yoon, J.-H. Jang, S.-P. Yeh, M. Turgut, W.-J. Hong, Y. Zhou, J. Potluri, and K.W. Pratz

Azacitidine plus Venetoclax vs Azacitidine - OS

	No. of events/No. of patients (%)	Median duration of study treatment, months (range)	Median overall survival, months (95% CI)
Aza+Ven	161/286 (56)	7.6 (<0.1 – 30.7)	14.7 (11.9 – 18.7)
Aza+Pbo	109/145 (75)	4.3 (0.1 – 24.0)	9.6 (7.4 – 12.7)

Hazard ratio: 0.66 (95% CI: 0.52 – 0.85), p<0.001



Patients at Risk

Aza+Ven	286	219	198	168	143	117	101	54	23	5	3	0
Aza+Pbo	145	109	92	74	59	38	30	14	5	1	0	0

Median follow-up time: 20.5 months (range: <0.1 – 30.7)

DiNardo et al, NEJM 2020.

Outcomes after stem cell transplant in older patients with acute myeloid leukemia treated with venetoclax-based therapies

#264

Keith Pratz[1], Courtney D. DiNardo[2], Martha Arellano[3], Anthony Letai[4], Michael Thirman[5], Vinod Pullarkat[6], Gail J. Roboz[7], Pamela S. Becker[8], Wan-Jen Hong[9], Qi Jiang[10], John Hayslip[10], Jalaja Potluri[10], Daniel A. Pollyea[11]

[1]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, USA; [2]MD Anderson Cancer Center, Houston, TX, USA; [3]Department of Hematology and Oncology, Emory University School of Medicine, Atlanta, GA, USA; [4]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [5]University of Chicago Medical Center, Chicago, IL, USA; [6]Department of Hematology and Hematopoietic Cell Transplantation and Gehr Family Center for Leukemia Research, City of Hope National Medical Center, Duarte, CA, USA; [7]Weill Medical College of Cornell University and New York-Presbyterian Hospital, New York, NY, USA; [8]Clinical Research Division, Fred Hutchinson Cancer Research Center and Division of Hematology, Department of Medicine, University of Washington School of Medicine, Seattle, WA, USA; [9]Genentech, Inc., South San Francisco, CA, USA; [10]AbbVie Inc., North Chicago, IL, USA; [11]University of Colorado School of Medicine, Aurora, CO, USA

American Society of Hematology (ASH) – 61st Annual Meeting
Orlando, FL, USA ● December 7, 2019

Objective and Included Studies

OBJECTIVE

- To assess the clinical outcomes of SCT after venetoclax-based treatment on patients with newly diagnosed AML, ineligible for intensive chemotherapy

NCT02203773
NCT02287233

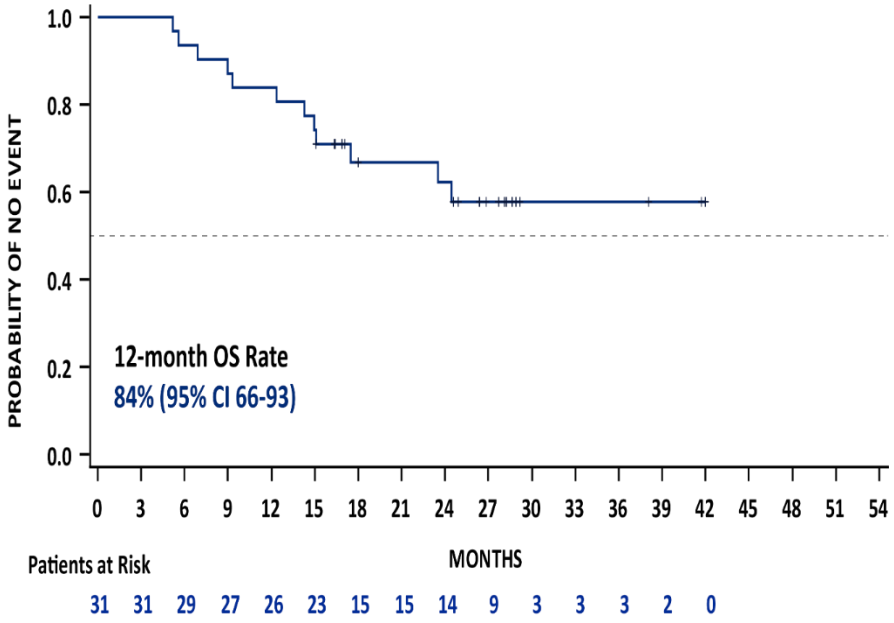
- **Studies included in secondary analysis (n=304):**
  - Open-label phase 1b: **venetoclax + azacitidine/decitabine**
  - Open-label phase 1/2: **venetoclax + LDAC**
- **Endpoints:** Best response, time to best response, time from last dose of venetoclax until SCT, and 12-month post-SCT survival

Pratz et al, ASH 2019 #264.

Outcomes of HCT in Patients After Ven-Based Regimens

- **10%** 31 of 304 patients received Allo-HCT
  - 26/31 in CR/CRi
- **68%** (21/31) of patients remained alive at 12 months post-allo-HCT
- **55%** (17/31) of all patients that had allo-HCT had posttransplant remission of ≥12 months
  - **71%** (12/17) of those patients remained in remission for ≥2 years

VEN-based regimens, even in patients deemed unfit for intensive induction, may provide a path to curative allo-HCT



Pratz et al, ASH 2019 #264.

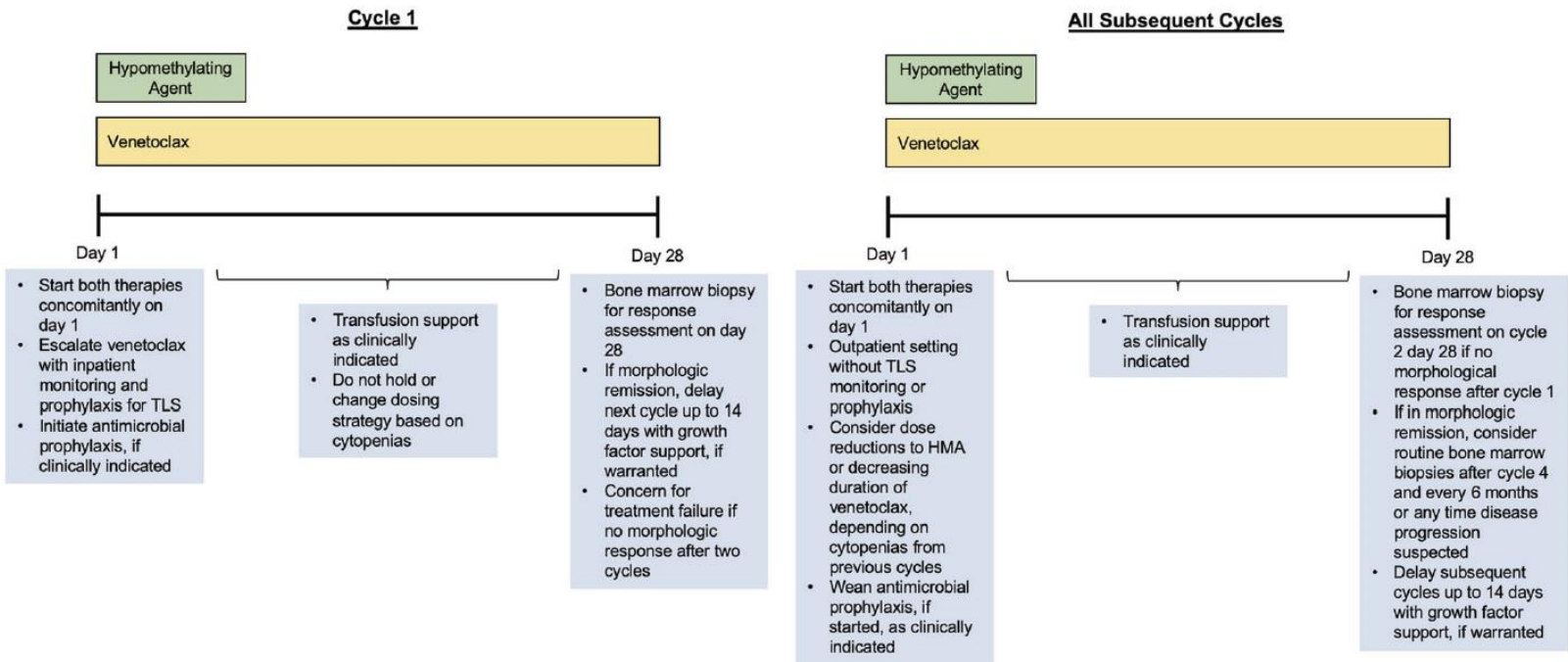
Leukemia
https://doi.org/10.1038/s41375-019-0612-8

PERSPECTIVE

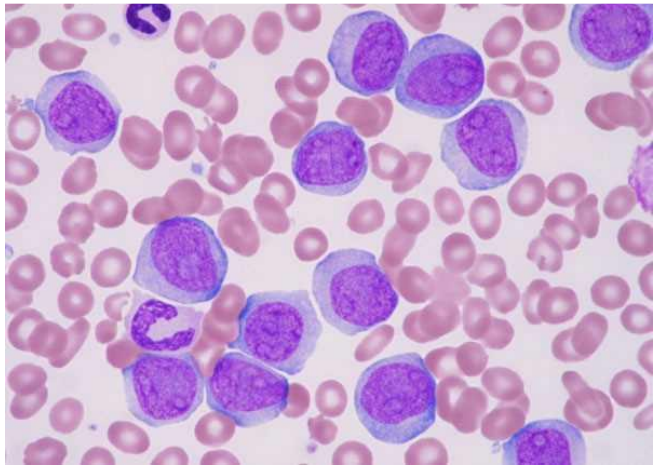
Acute myeloid leukemia

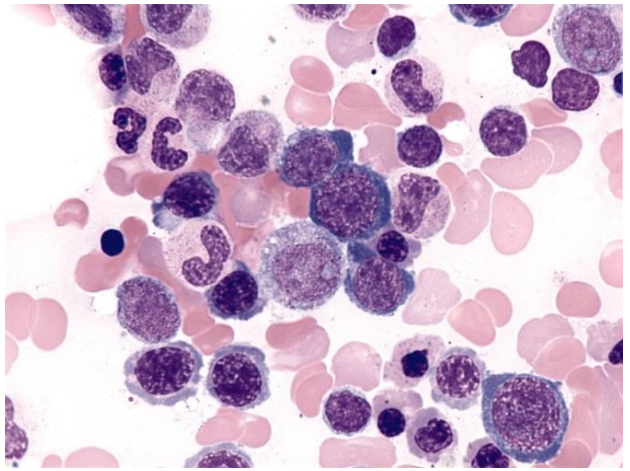
How we use venetoclax with hypomethylating agents for the treatment of newly diagnosed patients with acute myeloid leukemia

Brian A. Jonas[1] · Daniel A. Pollyea[2]



Recent Approvals of Oral HMA for AML and MDS





Oral HMA Approved by the FDA

“Oral Azacitidine”

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ONUREG safely and effectively. See full prescribing information for ONUREG.

ONUREG (azacitidine) tablets, for oral use
Initial U.S. Approval: 2004

INDICATIONS AND USAGE

ONUREG is a nucleoside metabolic inhibitor indicated for continued treatment of adult patients with acute myeloid leukemia who achieved first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following intensive induction chemotherapy and are not able to complete intensive curative therapy (1).

DOSAGE AND ADMINISTRATION

- **Do not substitute ONUREG for intravenous or subcutaneous azacitidine. The indications and dosing regimen for ONUREG differ from that of intravenous or subcutaneous azacitidine (2.1, 5.1).**
- Administer ONUREG 300 mg orally once daily on Days 1 through 14 of each 28-day cycle (2.2).
- Administer an antiemetic before each dose for at least the first 2 cycles (2.2).

“Oral Decitabine”

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use INQOVI safely and effectively. See full prescribing information for INQOVI.

INQOVI® (decitabine and cedazuridine) tablets, for oral use
Initial U.S. Approval: 2020

INDICATIONS AND USAGE

INQOVI is a combination of decitabine, a nucleoside metabolic inhibitor, and cedazuridine, a cytidine deaminase inhibitor, indicated for treatment of adult patients with myelodysplastic syndromes (MDS), including previously treated and untreated, de novo and secondary MDS with the following French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and chronic myelomonocytic leukemia [CMML]) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups. (1)

DOSAGE AND ADMINISTRATION

- The recommended dosage of INQOVI is 1 tablet (35 mg decitabine and 100 mg cedazuridine) taken orally once daily on Days 1 through 5 of each 28-day cycle. (2.2)
- Take INQOVI on an empty stomach. (2.2)

The QUAZAR AML-001 Maintenance Trial: Results of a Phase III International, Randomized, Double-Blind, Placebo-Controlled Study of CC-486 in Patients with Acute Myeloid Leukemia (AML) in First Remission

Andrew H. Wei[1,2], Hartmut Döhner[3], Christopher Pocock[4], Pau Montesinos[5,6], Boris Afanasyev[7], Hervé Dombret[8], Farhad Ravandi[9], Hamid Sayar[10], Jun Ho Jang[11], Kimmo Porkka[12], Dominik Selleslag[13], Irwindeep Sandhu[14], Mehmet Turgut[15], Valentina Giai[16], Yishai Ofran[17,18], Merih Kizil Cakar[19], Aida Botelho de Sousa[20], Justyna Rybka[21], Chiara Frairia[22], Lorenza Borin[23], Germana Beltrami[24], Jaroslav Cermak[25], Gert Ossenkoppele[26], Ignazia La Torre[27], Barry Skikne[27], Keshava Kumar[27], Qian Dong[27], CL Beach[27], Gail J. Roboz[28,29]

[1]The Alfred Hospital, Melbourne, Australia; [2]Monash University, Melbourne, Australia; [3]Ulm University Hospital, Ulm, Germany; [4]Kent and Canterbury Hospital, Canterbury, United Kingdom; [5]Hospital Universitari i Politècnic La Fe, Valencia, Spain; [6]CIBERONC, Instituto Carlos III, Madrid, Spain; [7]First I. P. Pavlov State Medical University of St. Petersburg, Saint Petersburg, Russian Federation; [8]Hôpital Saint Louis, Institut de Recherche Saint Louis, Université de Paris, Paris, France; [9]The University of Texas MD Anderson Cancer Center, Houston, TX; [10]Indiana University Cancer Center, Indianapolis, IN; [11]Samsung Medical Center, Seoul, South Korea; [12]Helsinki University Hospital Comprehensive Cancer Center, Helsinki, Finland; [13]AZ Sint-Jan Brugge-Oostende, Brugge, Belgium; [14]University of Alberta Hospital, Alberta, Canada; [15]Ondokuz Mayis University, Samsun, Turkey; [16]Antonio e Biagio e Cesare Arrigo Hospital, Alessandria, Italy; [17]Rambam Medical Center, Haifa, Israel; [18]Faculty of Medicine Technion, Haifa, Israel; [19]Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Turkey; [20]Hospital dos Capuchos (CHLC), Lisbon, Portugal; [21]Wroclaw Medical University, Wroclaw, Poland; [22]Città della Salute e della Scienza, Torino, Italy; [23]Ospedale San Gerardo Monza, Monza, Italy; [24]Ospedale Policlinico San Martino, Genoa, Italy; [25]Ústav Hematologie a Krevní Transfuze, Prague, Czech Republic; [26]Amsterdam UMC, Location VUMC, Amsterdam, Netherlands; [27]Celgene Corporation, Summit, NJ; [28]Weill Cornell Medicine, New York, NY; [29]New York Presbyterian Hospital, New York, NY

QUAZAR: Schema and Patients

Primary Endpoint: OS; Secondary Endpoints: RFS, QoL and Safety.

Screening

Key eligibility criteria:
- First CR / CRi with IC ± consolidation
- Age ≥55 years
- *de novo* or secondary AML
- ECOG PS score 0-3
- Intermediate- or poor-risk cytogenetics
- Ineligible for HSCT

Screened: N = 555

Screened but not randomized n = 83

Randomized N = 472

Randomization (1:1)

Within 4 months (±7 days) of CR/CRi

Stratified by:
- Age: 55–64 / ≥ 65
- Prior MDS/CMML: Y / N
- Cytogenetic risk: Intermediate / Poor
- Consolidation: Y / N

CC-486 QD x 14 days n = 238

Discontinued treatment: n = 193

Disease relapse	60%
Adverse events	12%
Withdrew consent	4%
Physician decision†	3%
Other	2%
Death	0.4%

Treatment ongoing* n = 45

Placebo QD x 14 days n = 234

Discontinued treatment: n = 208

Disease relapse	77%
Withdrew consent	6%
Adverse events	5%
Other	1%
Death	1%
Physician decision†	0%

Treatment ongoing* n = 26

*Still receiving study drug at data cutoff (July 15, 2019).
†Became eligible for hematopoietic stem cell transplant during treatment.

Wei et al, ASH 2019 LBA#3.

QUAZAR: Safety

- Median treatment durations:
  - CC-486: 12 cycles (range 1–80)
  - Placebo: 6 cycles (range 1–73)
- CC-486 safety profile was generally consistent with that of injectable AZA[1]
- Gastrointestinal adverse events (AEs) in the CC-486 arm were most common during the first 2 treatment cycles
- Serious AEs were reported for 34% and 25% of patients in the CC-486 and placebo arms, respectively
- No treatment-related deaths

AEs reported in ≥15% of patients in either arm

Preferred term	CC-486 n = 236		Placebo n = 233	
	All Grades	Grade 3–4	All Grades	Grade 3–4
	n (%)			
Patients with ≥1 AE	**231 (98)**	**169 (72)**	**225 (97)**	**147 (63)**
Gastrointestinal				
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
Hematologic				
Neutropenia	105 (45)	97 (41)	61 (26)	55 (24)
Thrombocytopenia	79 (34)	53 (23)	63 (27)	50 (22)
Anemia	48 (20)	33 (14)	42 (18)	30 (13)
Other				
Fatigue	70 (30)	7 (3)	45 (19)	2 (1)
Asthenia	44 (19)	2 (1)	13 (6)	1 (0.4)
Pyrexia	36 (15)	4 (2)	44 (19)	1 (0.4)
Cough	29 (12)	0	39 (17)	0

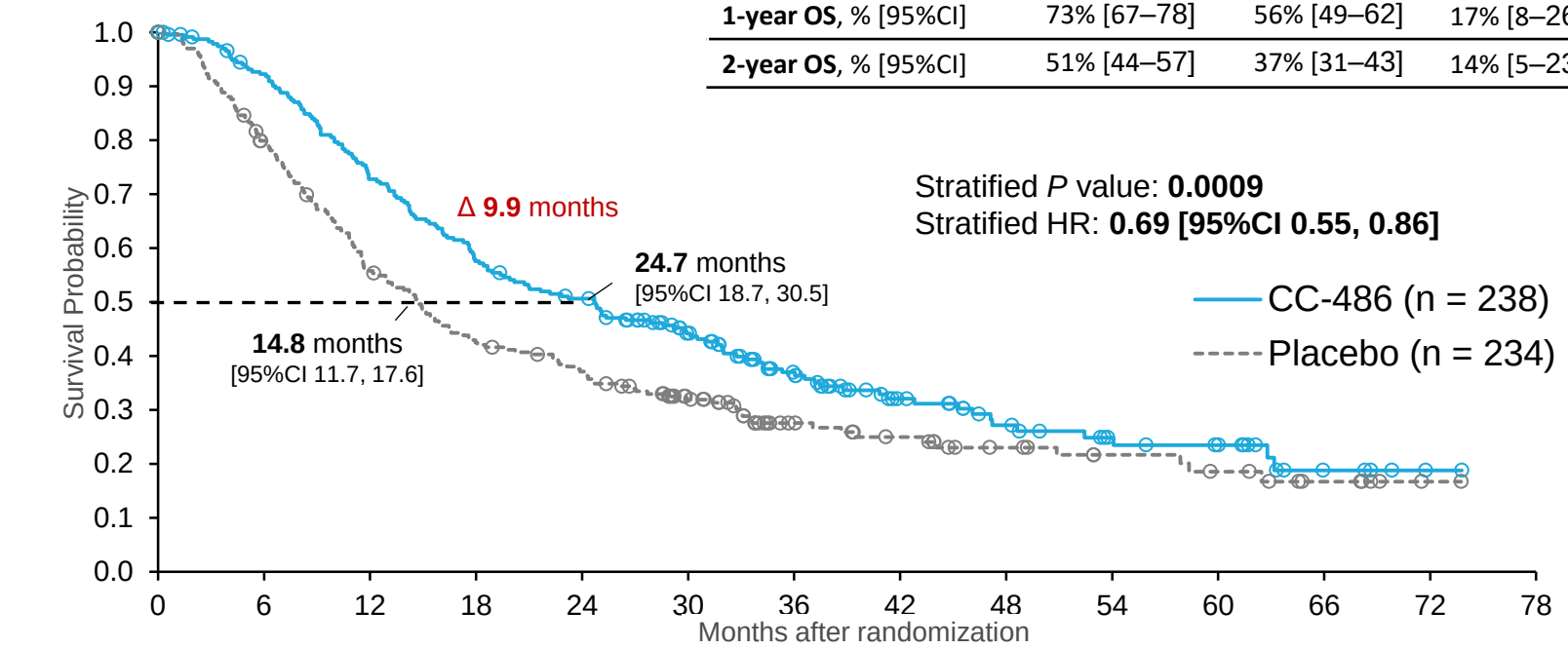
1. Dombret et al. *Blood.* 2015;126(3):291-9.
AE, adverse event; AZA, azacitidine; GI, gastrointestinal.

Wei et al, ASH 2019 LBA#3.

QUAZAR: Primary Endpoint OS

- Median follow-up: 41.2 months

	CC-486	Placebo	Difference
1-year OS, % [95%CI]	73% [67–78]	56% [49–62]	17% [8–26]
2-year OS, % [95%CI]	51% [44–57]	37% [31–43]	14% [5–23]



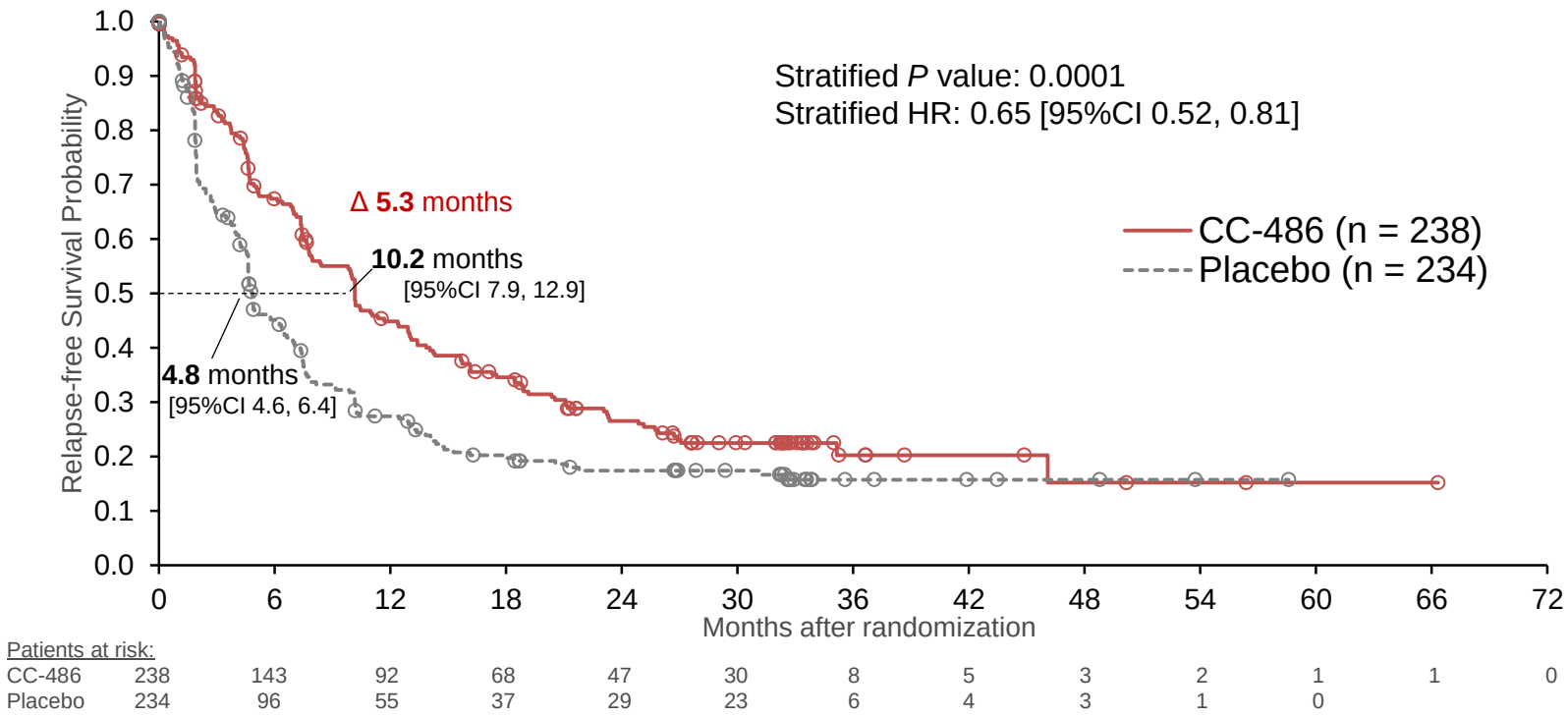
Patients at risk:

CC-486	238	213	169	133	115	87	59	37	26	18	15	5	1	0
Placebo	234	183	128	96	82	58	34	27	19	15	11	6	1	0

Data cutoff: July 15, 2019
OS was defined as the time from randomization to death by any cause. Kaplan-Meier estimated OS was compared for CC-486 vs. placebo by stratified log-rank test. HRs and 95%CIs were generated using a stratified Cox proportional hazards model.

Wei et al, ASH 2019 LBA#3.

QUAZAR: Secondary Endpoint RFS



- 1-year relapse rate was 53% in the CC-486 arm [95%CI 46, 59] and was 71% in the placebo arm [65, 77]

Data cutoff: July 15, 2019
RFS was defined as the time from randomization to relapse or death by any cause, whichever occurred first. Kaplan-Meier estimated RFS was compared for CC-486 vs. placebo by stratified log-rank test. HRs and 95%CIs were generated using a stratified Cox proportional hazards model.

Wei et al, ASH 2019 LBA#3.

Oral decitabine + cedazuridine (ASTX727)

- Current HMA treatment poses significant patient burden due to 5–7 days per month of parenteral administration in a clinic setting
- Oral bioavailability of HMAs decitabine and azacitidine is limited due to rapid degradation by CDA in the gut and liver

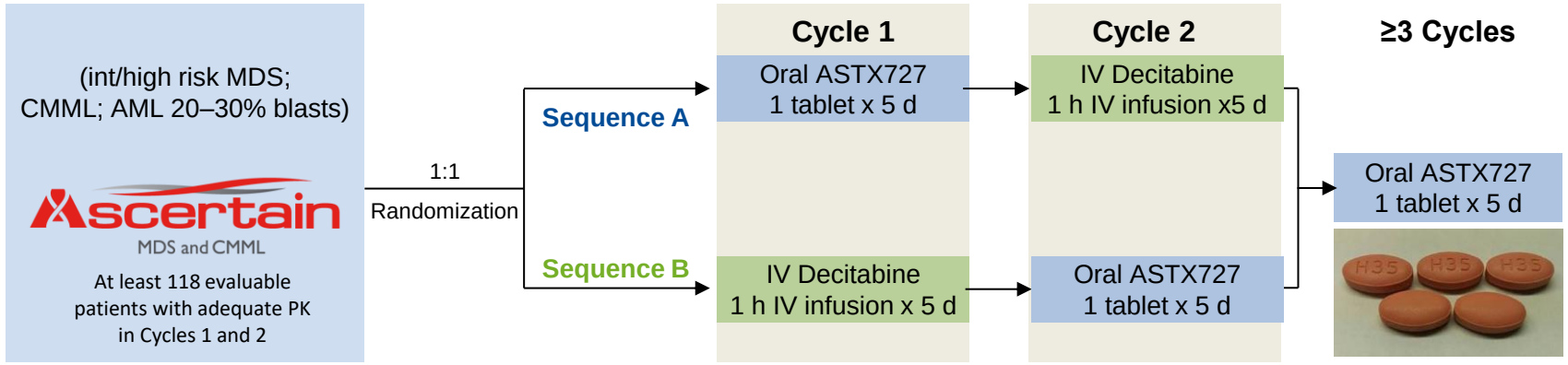
Decitabine **CDA inhibitor** **Inactive metabolite**

- Cedazuridine is a novel, potent, and safe CDA inhibitor
  - Large safety margin, with no adverse events at up to 200 mg/kg in monkeys (~2400 mg/m^2 human equivalent)

CDA, cytidine deaminase.

Savona et al. Lancet Hematogy 2019.
Garcia-Manero et al. ASH 2019 Abstract 846 .

ASTX727 Phase 3 Study (ASCERTAIN) in MDS/CMML
Trial Design: Randomized Cross-Over



Major entry criteria
- Candidates for IV decitabine
- ECOG PS 0–1
- Life expectancy of ≥3 months
- Adequate Organ Function
- One prior cycle of HMA is allowed

Primary endpoint
- Total 5-d decitabine AUC equivalence (Oral/IV 90% CI between 80% and 125%)

Secondary endpoints
- Efficacy: Response rate; Transfusion independence; duration of response; Leukemia-free and overall survival
- Safety of ASTX727
- Max LINE-1 demethylation

Garcia-Manero et al. ASH 2019 Abstract 846 .

Primary Endpoint: (5-day Decitabine AUC Equivalence)

Decitabine 5-day AUC_{0-24} (h·ng/mL)		IV DEC		Oral ASTX727		Ratio of Geo. LSM Oral/IV, % (90% CI)	Intrasubject (%CV)
		N	Geo. LSM	N	Geo. LSM		
Primary Analysis	Paired[1]	123	864.9	123	855.7	98.9 (92.7, 105.6)	31.7

[1] Paired patient population: patients who received both ASTX727 and IV decitabine in the randomized first 2 cycles with adequate PK samples.

- Study met its primary endpoint with high confidence: Oral/IV 5-day decitabine AUC ~99% with 90% CI of ~93-106%
- All Sensitivity and secondary PK AUC analyses confirmed findings from primary analysis

Garcia-Manero et al. ASH 2019 Abstract 846 .

Efficacy: Preliminary Response in MDS/CMML

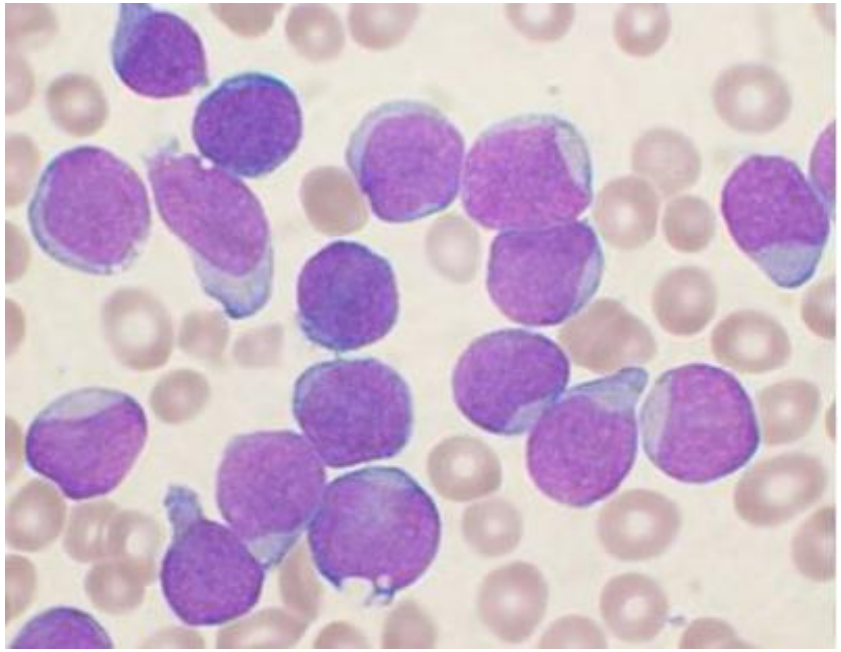
	Evaluable Patients[1] N=101 n (%)
Complete response (CR)	12 (11.9%)
Partial response (PR)	0
Marrow CR (mCR)	46 (45.5%)
mCR with hematologic improvement	14 (13.9%)
Hematologic improvement (HI)	7 (5.3%)
HI-erythroid	2 (2.0%)
HI-neutrophils	1 (1.0%)
HI-platelet	6 (5.9%)
Overall response (CR + PR + HI)	33 (31%)
Stable disease	28 (27.7%)
Progressive disease	8 (7.9%)

[1] Due to short median follow up (~ 5 months) at data cutoff, 32 patients could not be evaluated for response by the Central IRC. Response was assessed by IWG 2006 criteria

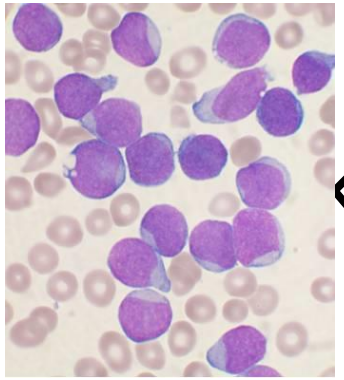
Longer term follow up response assessment and molecular/cytogenetic analyses are pending

Garcia-Manero et al. ASH 2019 Abstract 846 .

Current Approaches to the Treatment of Relapsed/Refractory Acute Lymphoblastic Leukemia (ALL)



AYA and Adult R/R ALL Treatment Algorithm



R/R ALL in AYA or Adult

Ph+

1. Clinical Trial
2. TKI -/+ Chemo or Steroids
3. Blinatumomab (TKI i/r)
4. Inotuzumab (TKI i/r)
5. Tisagenlecleucel (<26y, 2+ relapses, failure of 2 TKI)

Consider allo-HCT

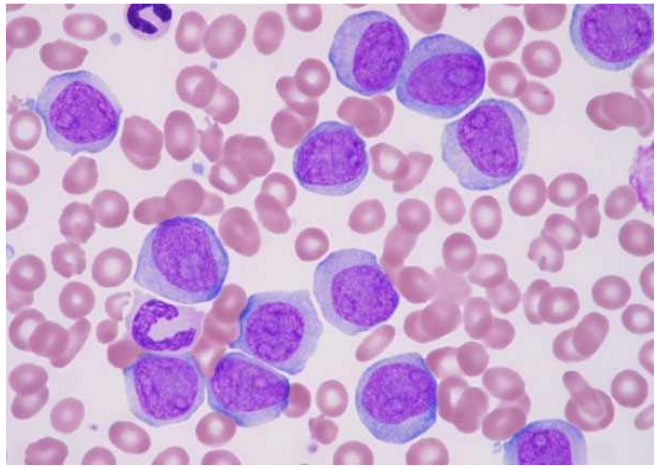
Ph-

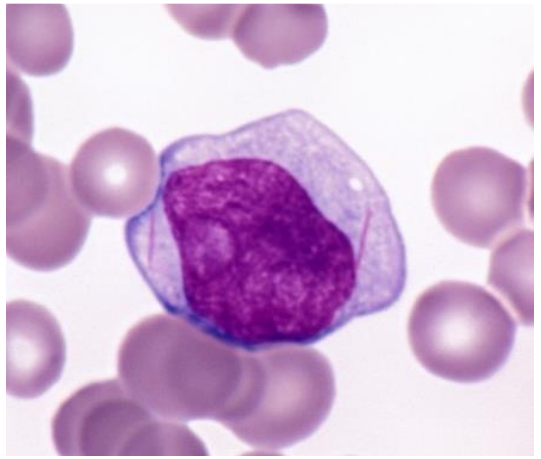
1. Clinical Trial
2. Blinatumomab
3. Inotuzumab
4. Tisagenlecleucel (<26y, 2+ relapses)
5. Chemotherapy

Consider allo-HCT

NCCN Guidelines, ALL, v1.2020.

Summary and Conclusions





Summary and Conclusions

- Exciting time for new FDA therapy approvals for AML, MDS and ALL
  - 9 new drugs approved since 4/2017
  - 2 new drugs approved for MDS in 2020
  - 3 new drugs recently approved for ALL
- Standards of care for acute leukemia are rapidly evolving
- Clinical trials continue to advance new treatments

Questions?

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