How I Treat Acute Myeloid Leukemia

Brian A. Jonas, MD, PhD, FACP
Associate Professor of Medicine
University of California, Davis
August 17, 2019

UCDAVIS
COMPREHENSIVE
CANCER CENTER

Disclosures

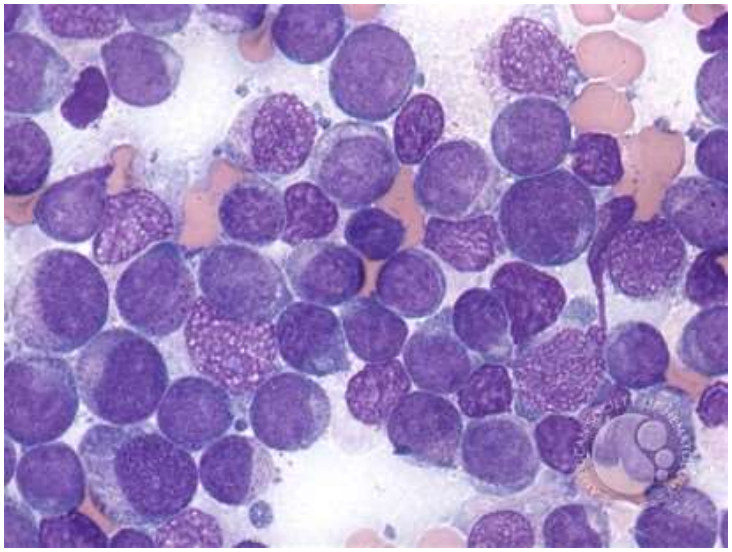
- Consulting/Advising:
  - AbbVie, Amgen, Celgene, GlycoMimetics, Jazz, Pharmacyclics, Tolero
- Travel Support:
  - AbbVie, Amgen, GlycoMimetics
- Grant/Research Support:
  - AbbVie, AROG, Celgene, Daiichi Sankyo, Esanex, Forma, Genentech/Roche, GlycoMimetics, Incyte, Pharmacyclics, Accelerated Medical Diagnostics, LP Therapeutics

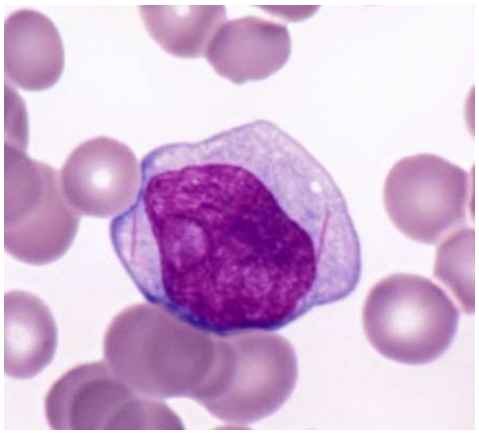
Learning Objectives

- Review some of the recent FDA approved drugs for acute myeloid leukemia
- Discuss the evolving standard of care for acute myeloid leukemia and state of the art in 2019, *with a focus on first-line treatment*

Acute Myeloid Leukemia

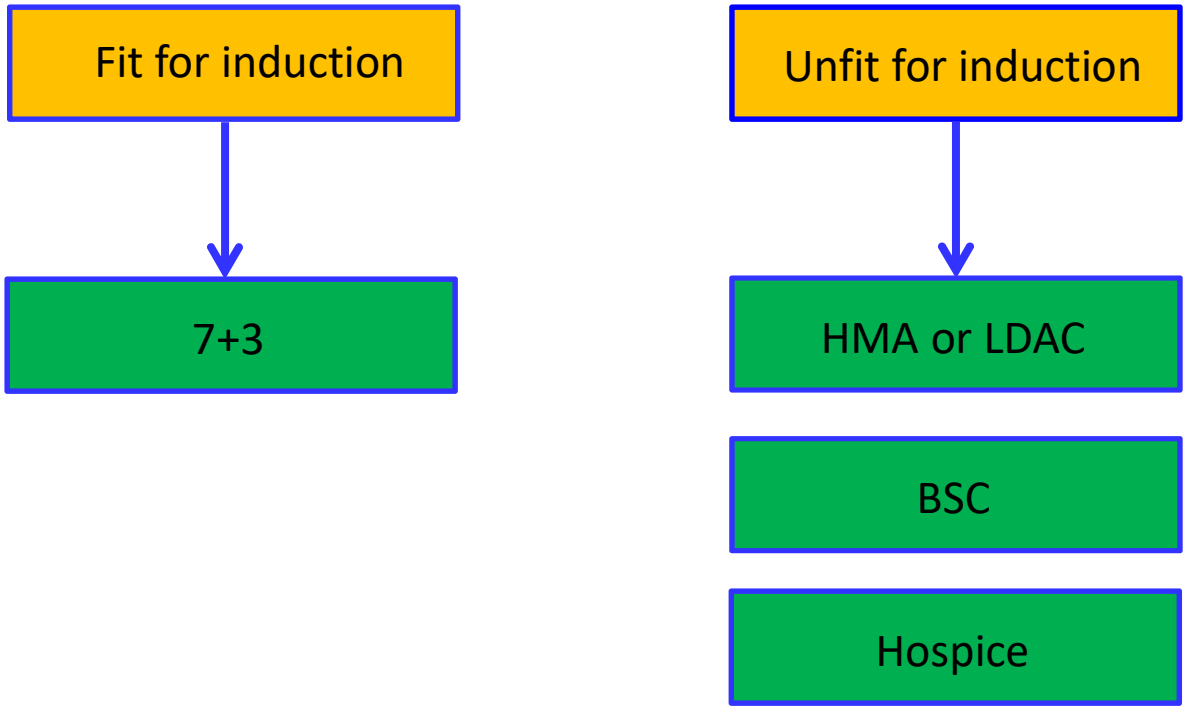
- Clonal expansion of immature myeloid cells
- Heterogeneous disease
- Median age 68
- 21,450 new cases (M>F) with 10,920 deaths expected in US in 2019[1]
- Bleeding, infections, anemia
- High relapse rates





[1]ACS Cancer Statistics, 2019.

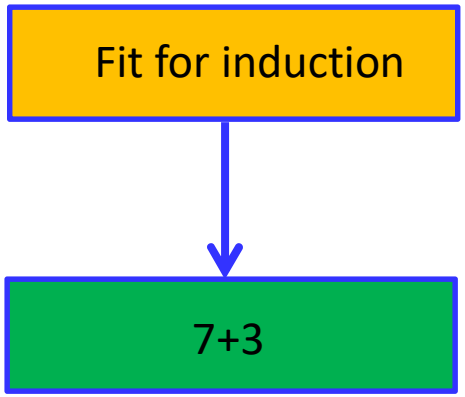
Prior First-Line Treatment of AML



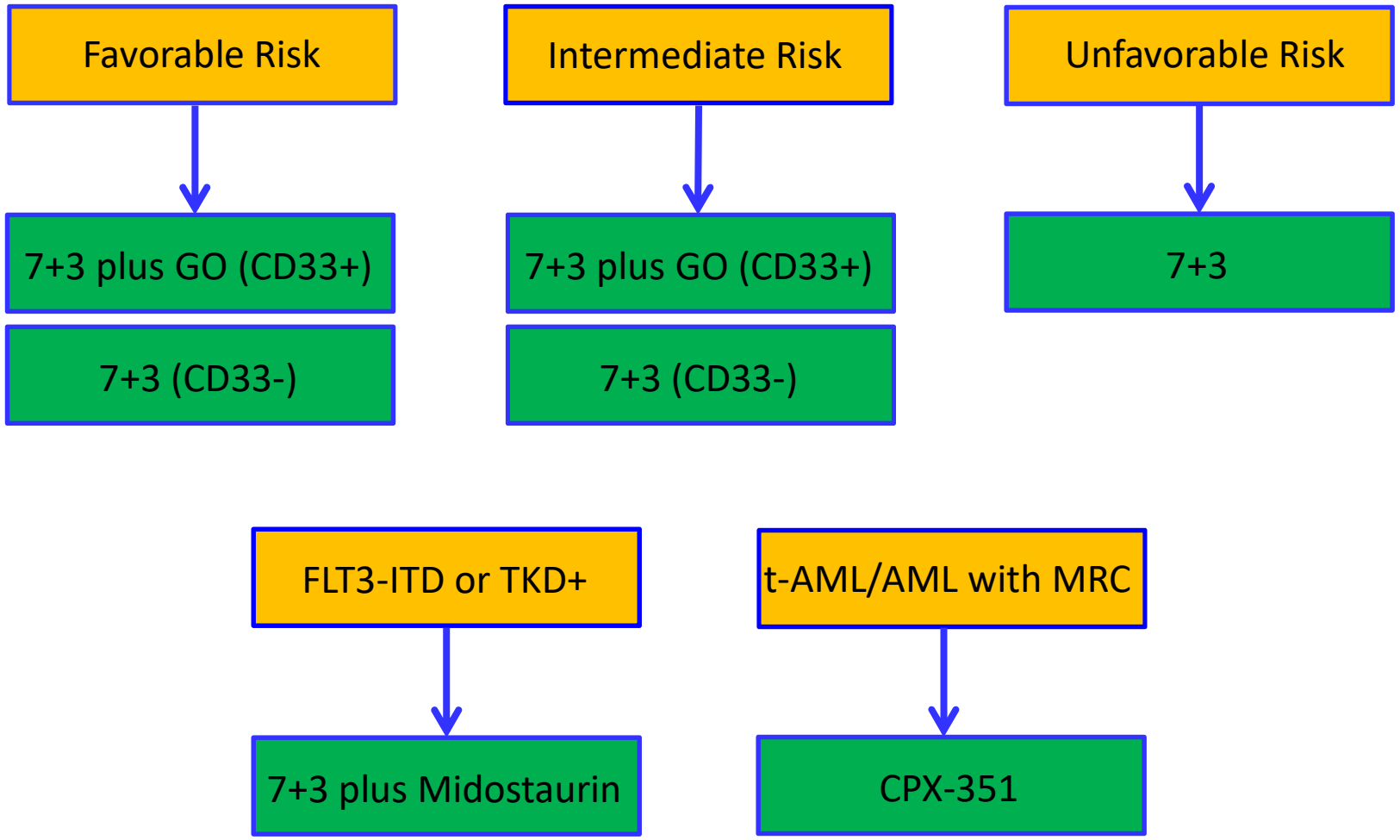
Recent FDA Approvals for AML

- Standard of care 7+3 treatment established in 1972…
- 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
  - 5/2/19 first line for 75+ or unfit treatment naïve AML with mutated IDH1
- 11/21/18 – **Venetoclax** plus Aza/Dec/LDAC for 75+ or unfit treatment naïve AML
- 11/21/18 – **Glasdegib** plus LDAC for 75+ or unfit treatment naïve AML
- 11/28/18 – **Gilteritinib** for R/R FLT3-mutated AML

Prior First-Line Treatment of AML

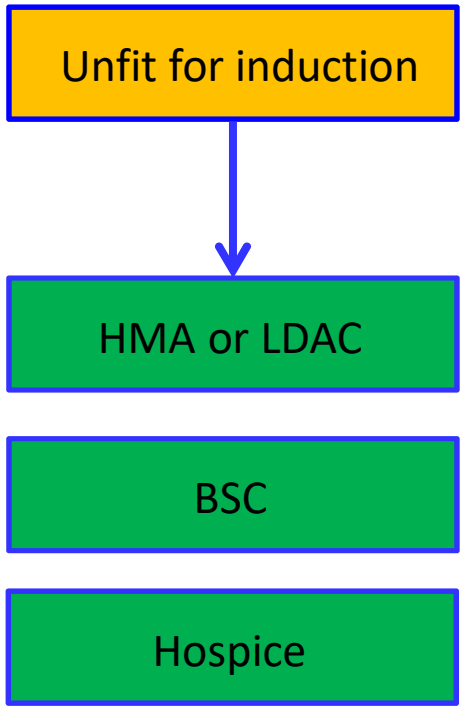


First-Line Treatment of Fit AML in 2019

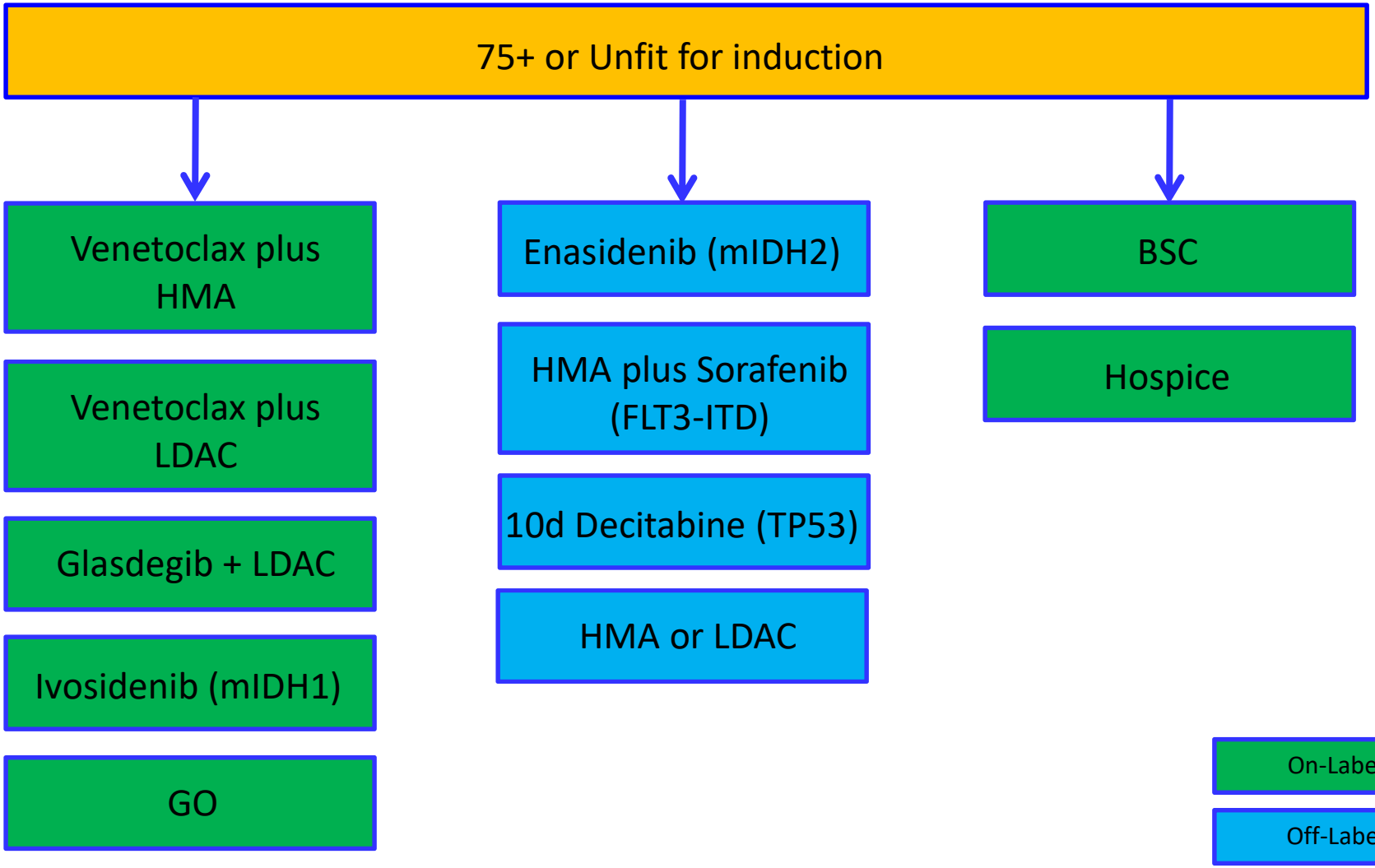


Based on NCCN guidelines, AML v3.2019

Prior First-Line Treatment of AML



First-Line Treatment of Unfit AML in 2019

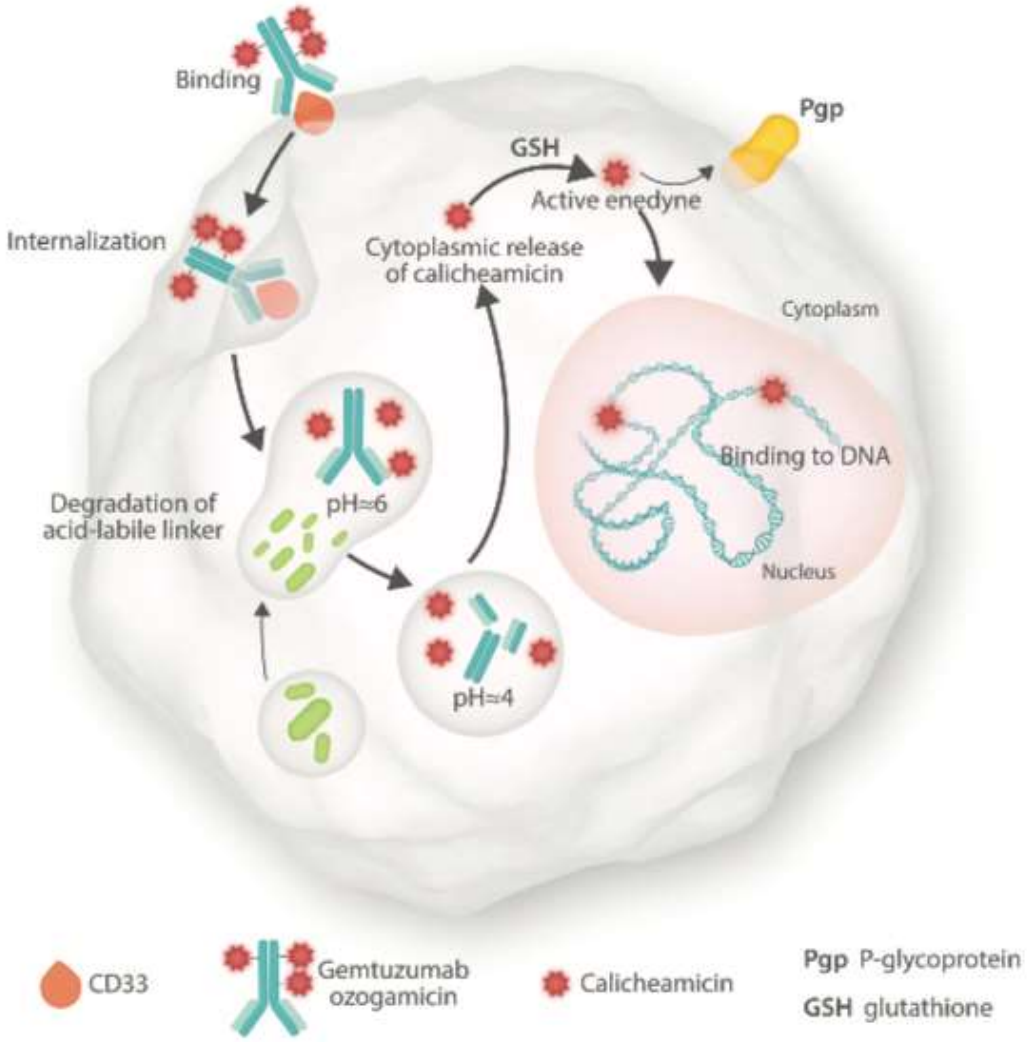


Based on NCCN guidelines, AML v3.2019

Recently FDA Approved Agents and Regimens for First-Line Treatment of AML

Gemtuzumab ozogamicin (GO)

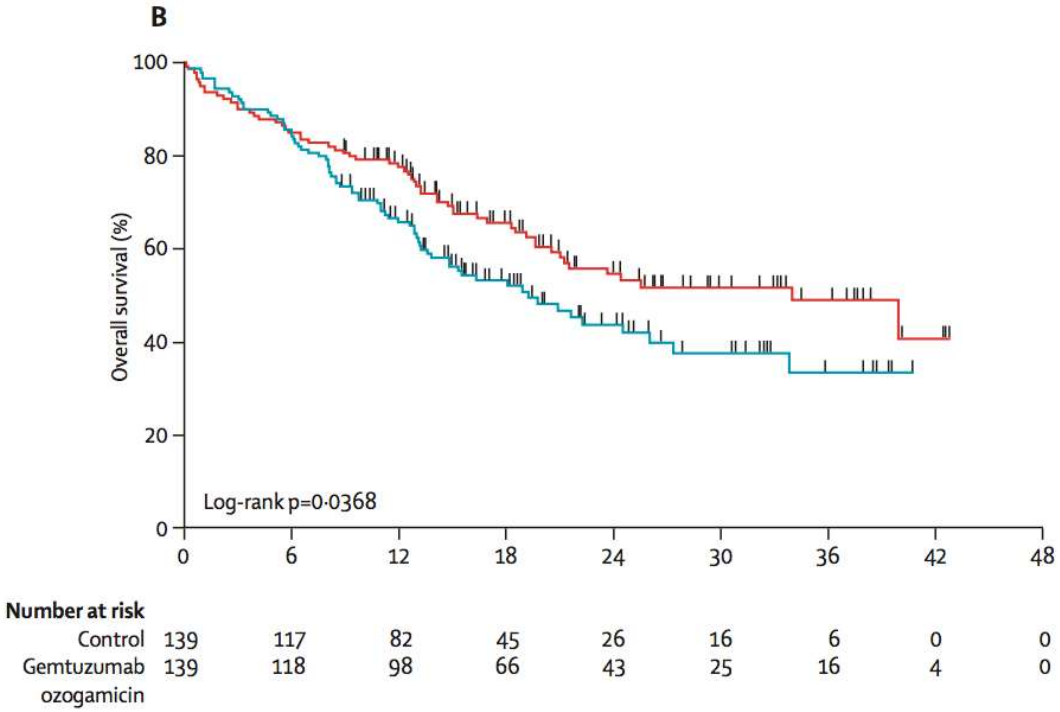
- CD33 antibody-drug conjugate (calicheamicin derivative)
- CD33 on >80% of AML



Hitzler and Estey, Haematologica 2019.

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
- 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

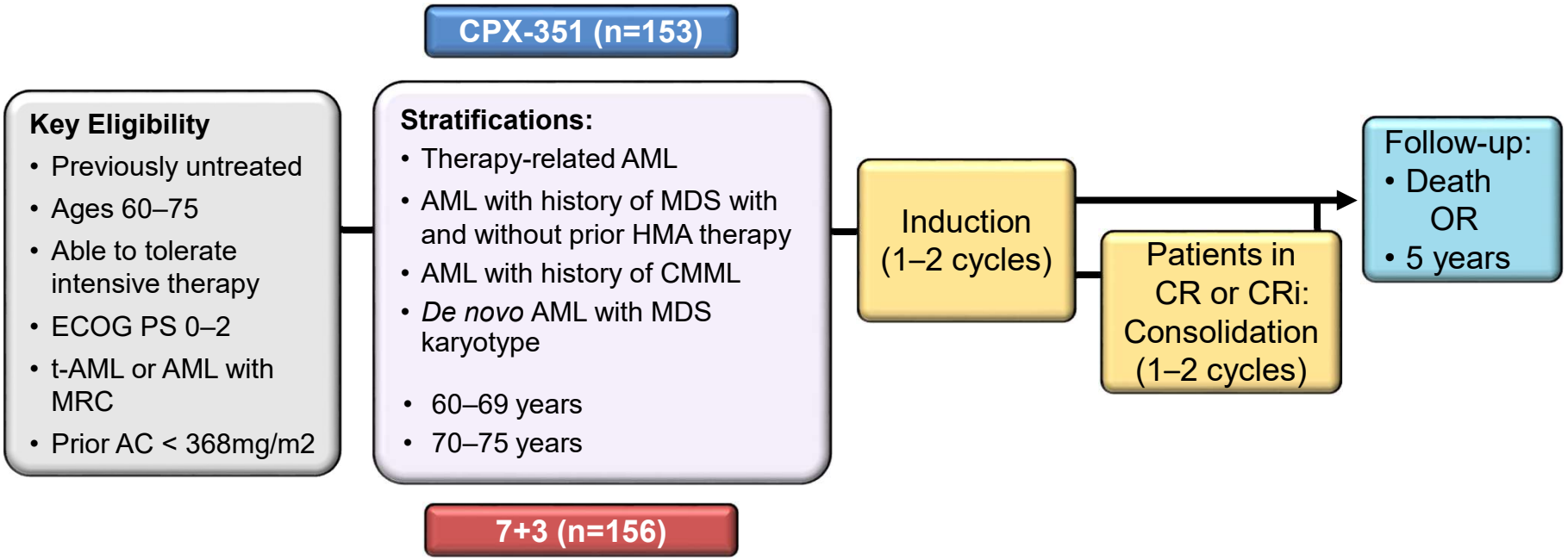
- Independent patient data meta-analysis of 5 randomized trials (3325 pts): ALFA-0701, MRC AML15, NCRI AML16, SWOG-0106, GOELAMS AML2006IR
- No difference in CR/CRi rate
- Doses of 3mg/m2 associated with fewer early deaths than 6mg/m2 with equal efficacy
- Addition of GO significantly reduced relapse 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.

CPX-351 Phase 3 Study Design

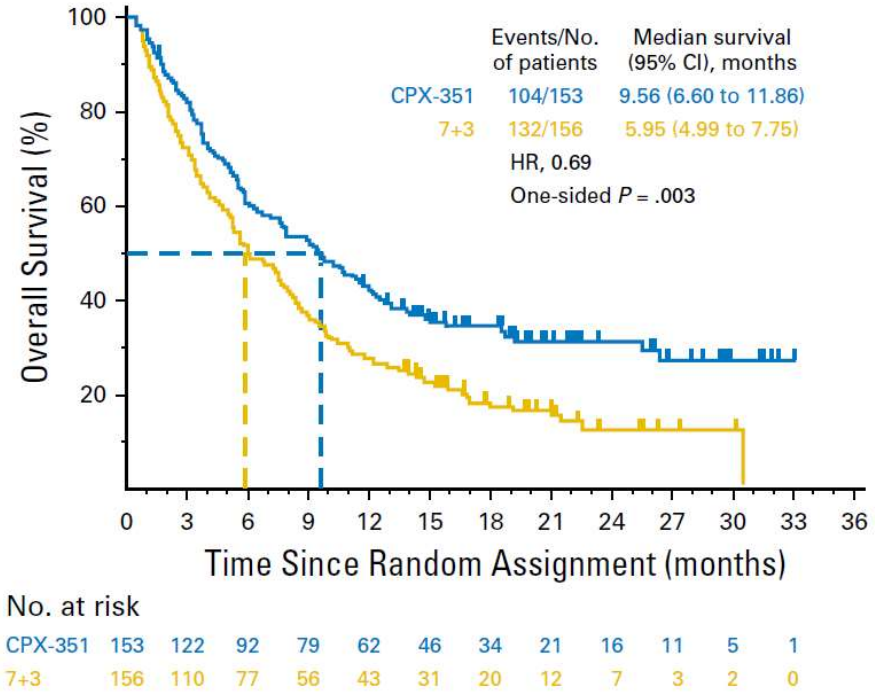
- Liposomal formulation of cytarabine and daunorubicin encapsulated at a 5:1 molar ratio
  - Prolonged fixed molar ratio in plasma, prolonged drug exposure, selective uptake by leukemic cells



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

CPX-351 Improved Outcomes Compared to 7+3

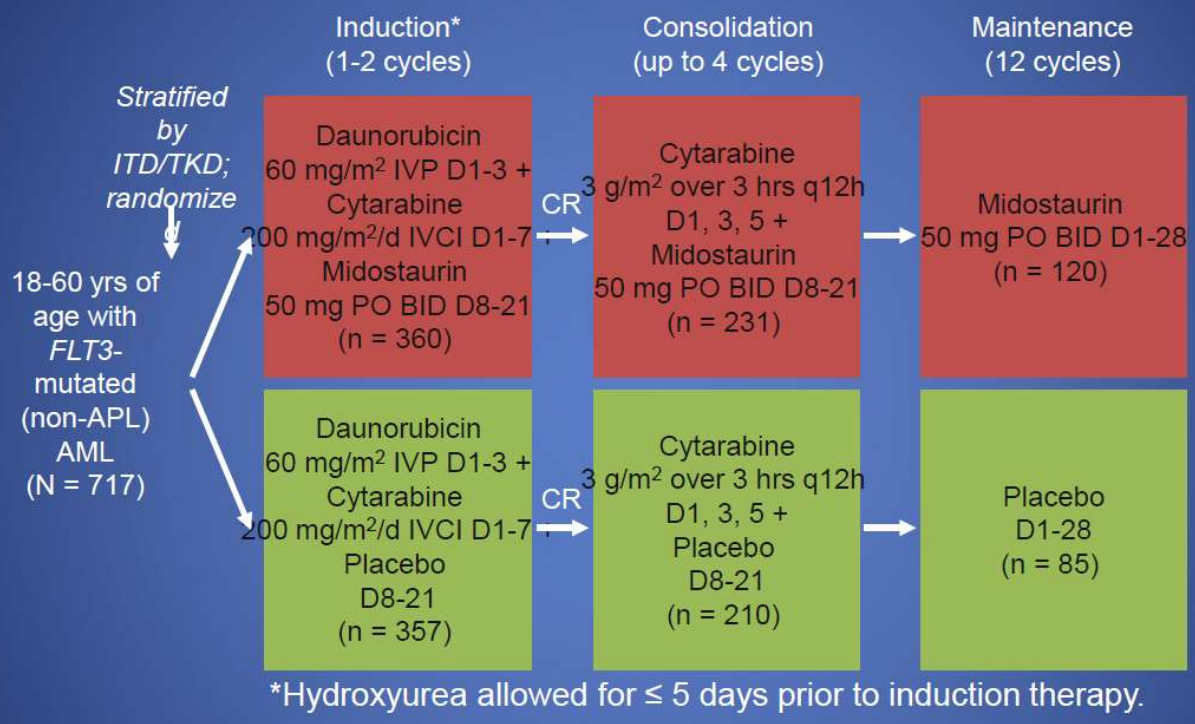
	CPX-351 n=153	7+3 n=156		
			Odds Ratio	***P* value**
CR	37.3%	25.6%	1.67 (1.02, 2.74)	0.040
CR+CRi	47.7%	33.3%	1.77 (1.11, 2.81)	0.016
Stem Cell Transplant	34.0%	25.0%	1.54 (0.92, 2.56)	0.098



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

CALGB10603 – RATIFY TRIAL

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

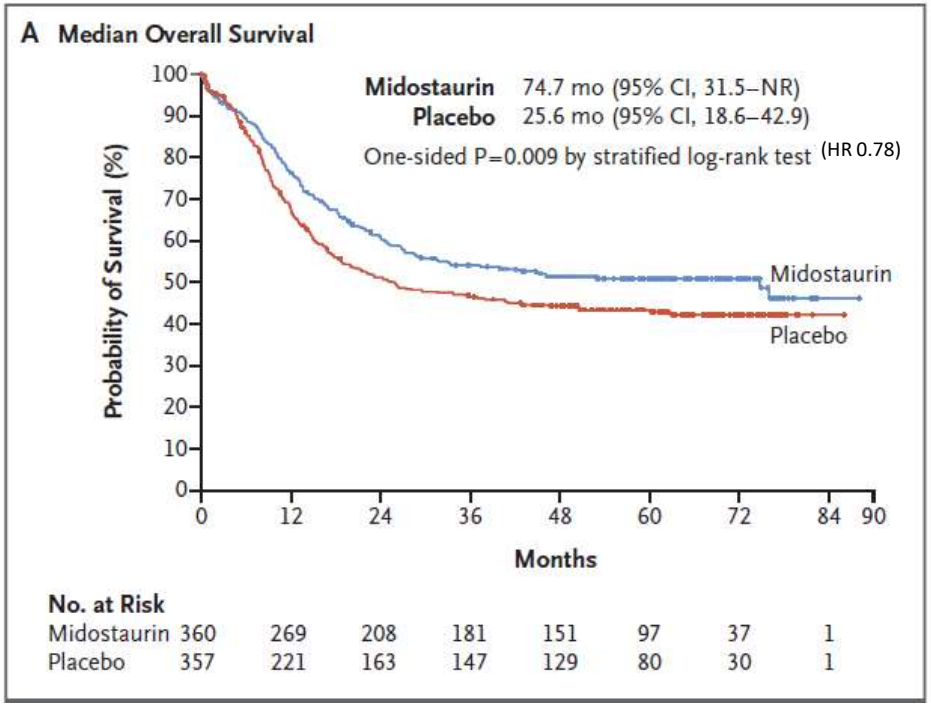


*Hydroxyurea allowed for ≤ 5 days prior to induction therapy.

- 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



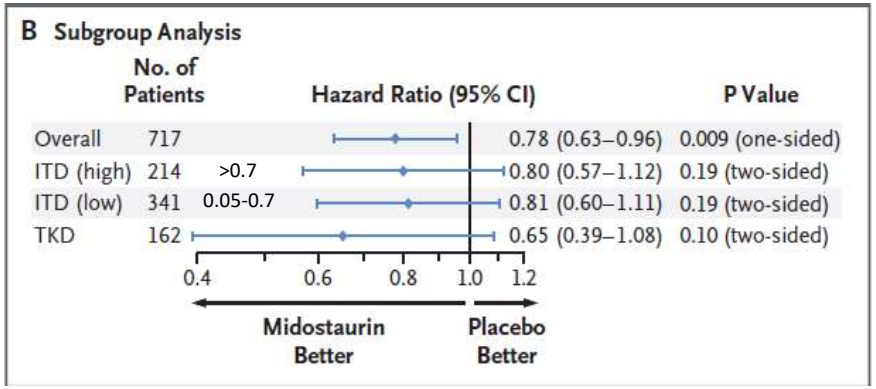


Table 3. Summary of Complete Remission.*

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	

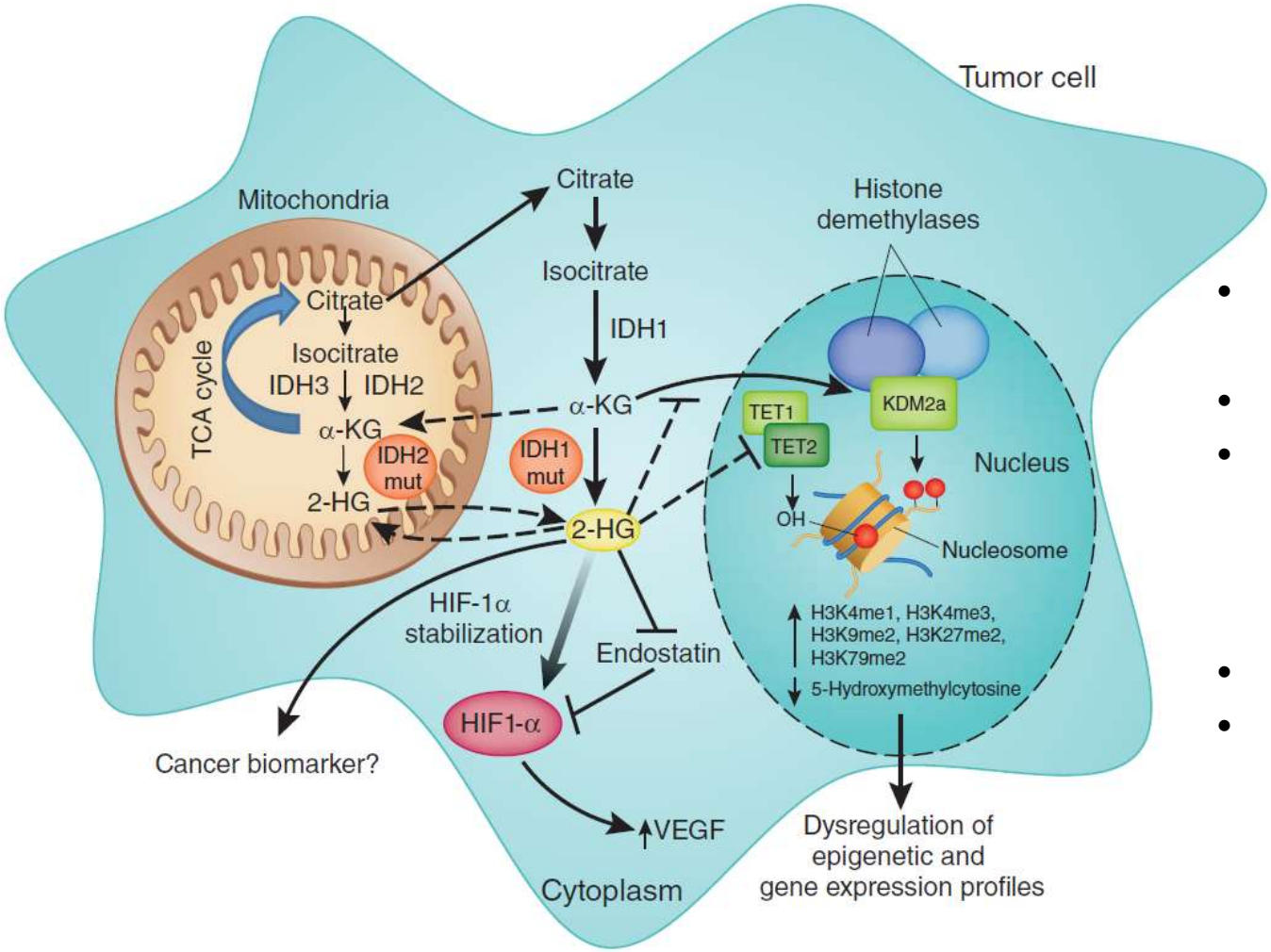
* Complete remission was defined as the presence of less than 5% blasts in the marrow or extramedullary leukemia, an absolute neutrophil count of more than 1000 per microliter, a platelet count of more than 100,000 per microliter, and the absence of blasts in the peripheral blood; in addition, per protocol, 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.

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.

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

*On May 2, 2019, the FDA approved Ivosidenib for newly diagnosed AML with an IDH1 mutation that are 75 or older or unfit for induction.

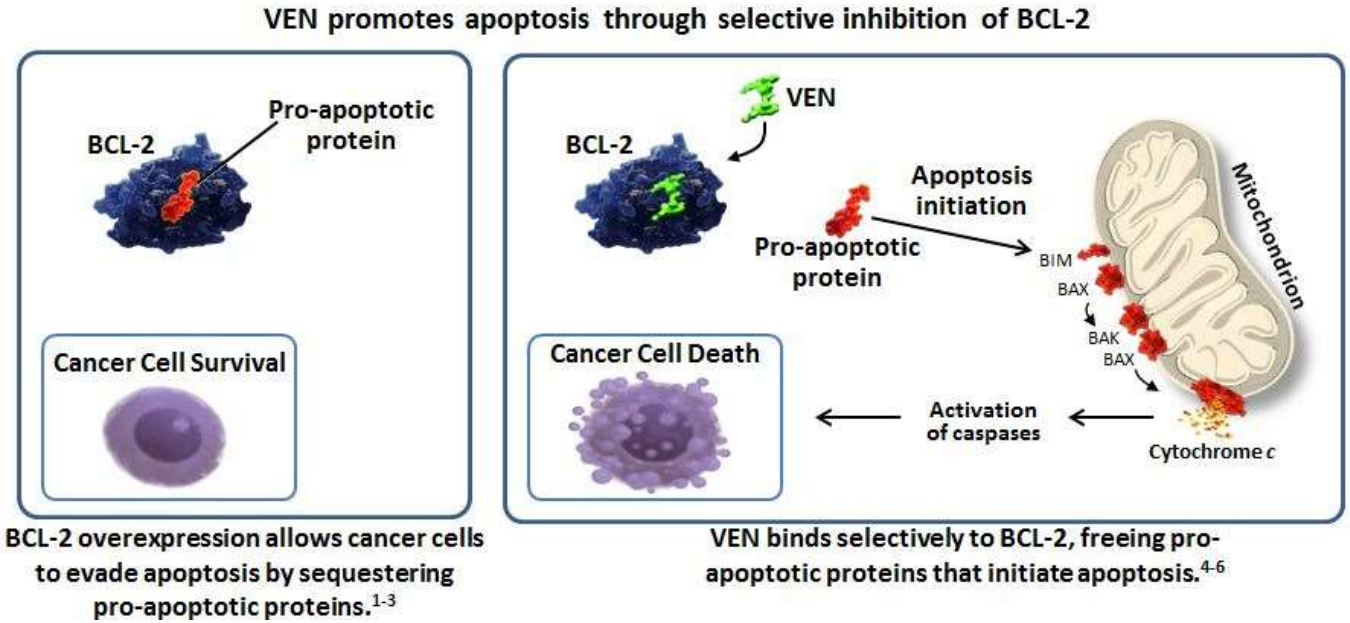
Based on NCT02074839 arm two.

CR+CRh rate of 42.9% (95% CI: 24.5-62.8)

Transfusion-independence rate of 41.2% (among transfusion-dependent patients).

Pollyea et al, ASCO 2018, Abstract #7000.
DiNardo et al, NEJM 2018.

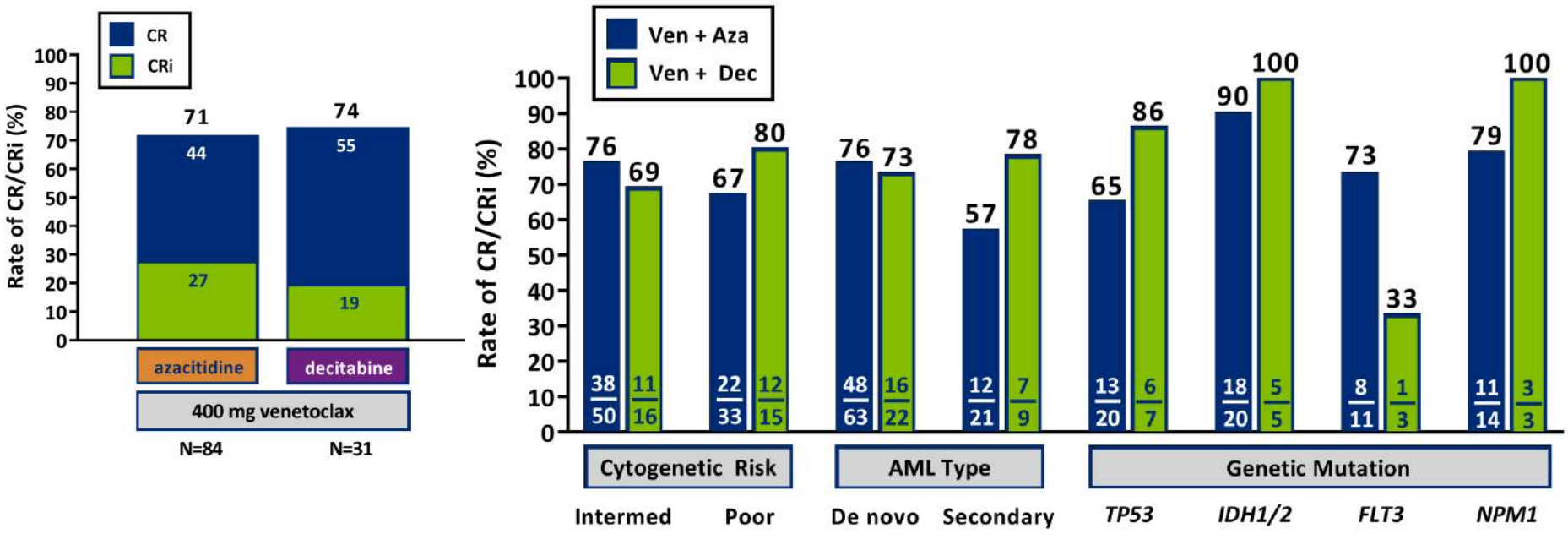
Venetoclax and AML



- 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.

Venetoclax plus HMA is Highly Active Overall and Across AML Subtypes



CRs in 1-2 cycles

CR/CRi and MRD Negative:

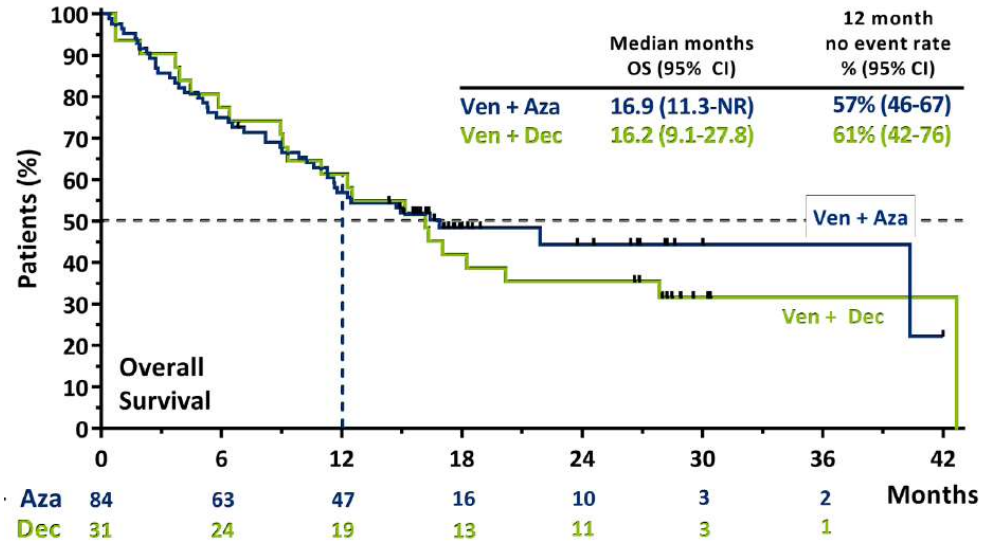
48% AZA

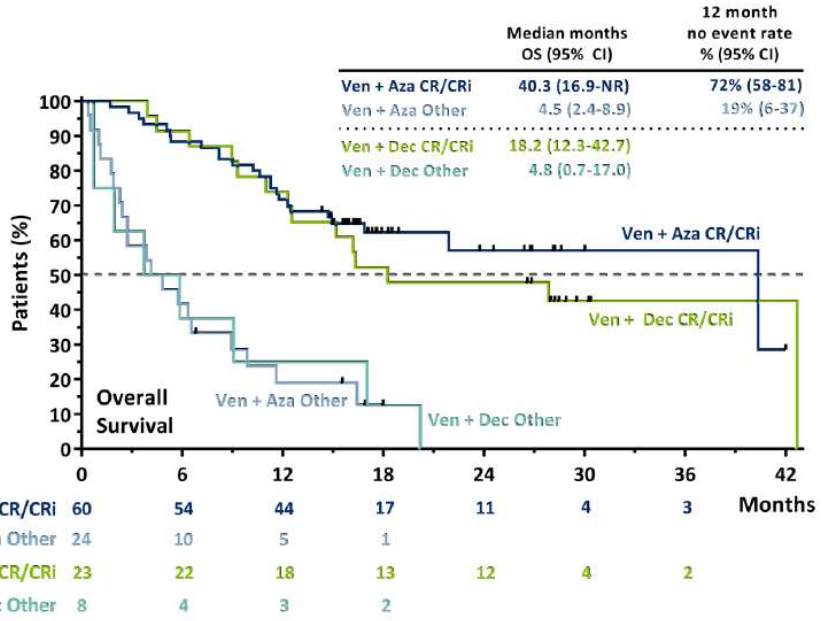
39% DEC

10^{-3} at any time

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

Venetoclax for AML – OS





Median Survival Follow-up

Venetoclax + azacitidine
14.9 months (range 0.4–42.0)

Venetoclax + decitabine
16.2 months (range 0.7–42.7)

- Phase 3 study ongoing
- Follow-up studies evaluating triplets, using the regimen earlier, etc.

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

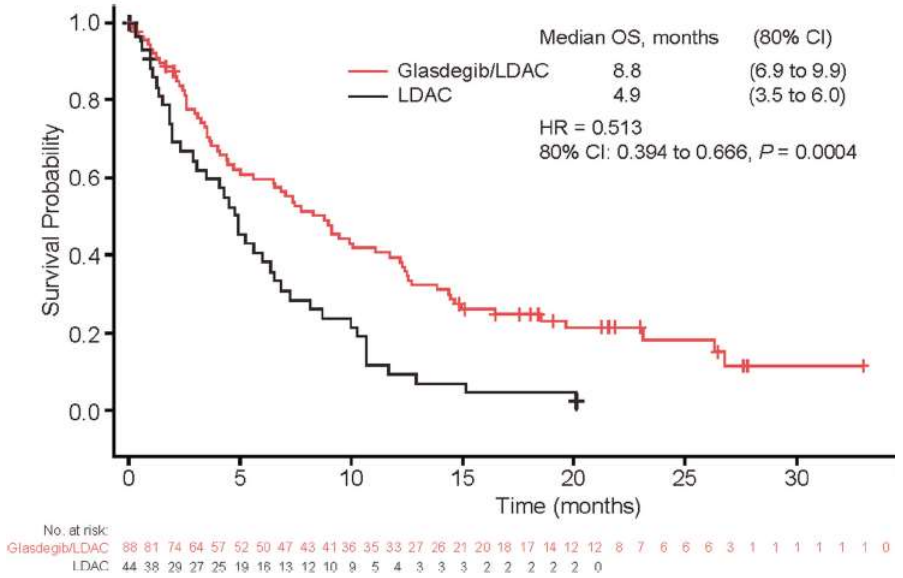
Venetoclax plus LDAC for Elderly AML

- 65+yo untreated AML patients
- Venetoclax 600mg plus LDAC
- 61 subjects, median age 74 (66-87)
- Deaths <30 days 3%
- CR+CRi **54**%, most CR/CRi in C1-2
- Median OS **NR**, estimated **1yr OS ~65%**
- Most common G3/4 AE >10%: febrile neutropenia, hypokalemia, hypophosphatemia, HTN

Wei et al, ASH 2016 Abstract# 7009.

Glasdegib plus LDAC for Elderly AML

- Oral HH pathway (Smoothened) inhibitor with anti-LSC activity
- 75 or older or unfit for induction
- Glasdegib 100mg daily plus LDAC 20mg SQ BID for 10d every 28 days
- Randomization of 88 pts to glasdegib/LDAC and 44 pts to LDAC
- CR rate was 17% for glasdegib/LDAC vs 2.3% in LDAC (p<0.05)
- G3+ AE in more than 10% included anemia, febrile neutropenia, fatigue, thrombocytopenia and pneumonia.



Cortes et al, Leukemia 2019.

How I Treat AML in 2019: Precision and Imprecision Medicine

Effects of Time To Treatment on AML Outcomes

Effect of Time to Treatment (TTT) on Overall Survival among Hospitalized Acute Myeloid Leukemia Patients

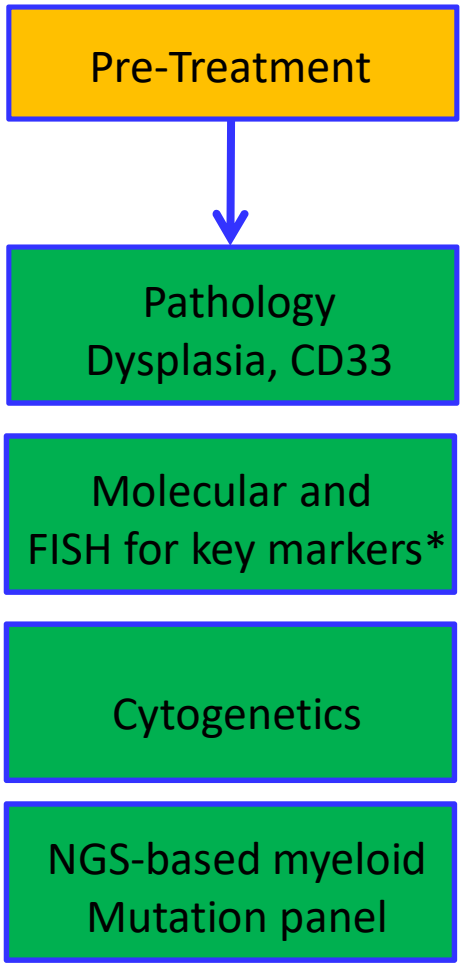
	Overall Survival	
	HR	**95% CI**
Patients age <60		
TTT 1-5 days	REF	-
TTT 6-7 days	1.10	(0.94, 1.29)
TTT 8-10 days	1.24	(1.04, 1.49)
TTT > 10 days	1.26	(1.11, 1.42)
Patients age ≥60		
TTT 1-5 days	REF	-
TTT 6-7 days	1.10	(0.96, 1.26)
TTT 8-10 days	1.06	(0.92, 1.23)
TTT > 10 days	1.16	(1.06, 1.28)

Hazard ratios (HR) and 95% confidence intervals (CI) adjusted for time to treatment, age, sex, race/ethnicity, year of diagnosis, number of comorbidities, marital status, neighborhood socioeconomic status, health insurance type, treatment at National Cancer Institute designated (NCI) vs non-NCI designated facility, and receipt of leukapheresis.

- There is sufficient time in most patients to gather baseline data to recommend optimal therapy.
- BEAT AML trial
  - Treatment assignment within 7 days in 95.2% of patients (200/210)
  - Showed feasibility of assigning treatment prospectively based on mutation profiling in older patients

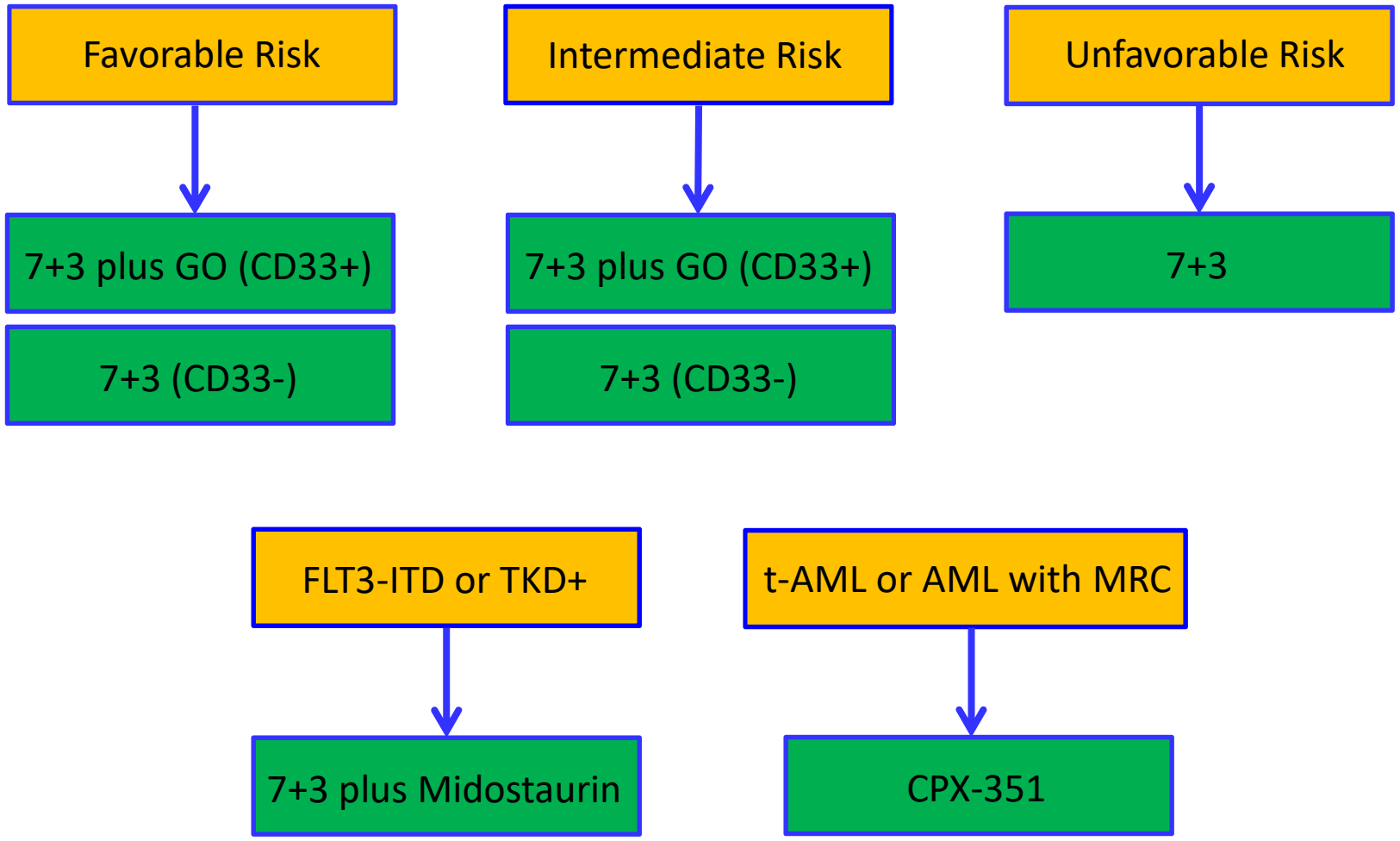
Datta T, Jonas BA et al, ASH 2016 Abstract #3982.
Burd A, Levine RL et al., ASH 2018 Abstract #559.

How I Use Diagnostic Testing for AML in 2019



*Goal turnaround time of <5-7 days
Key markers include:
Molecular: FLT3, NPM1, CEBPA, IDH1/2 and TP53
FISH: t(8;21), inv(16)/t(16;16), t(15;17), -5/del(5q), -7/del(7q), -17/del(17p)

How I Treat AML Fit for Induction in 2019 – Precision Medicine



Venetoclax plus HMA – An Argument for Imprecision Medicine in AML

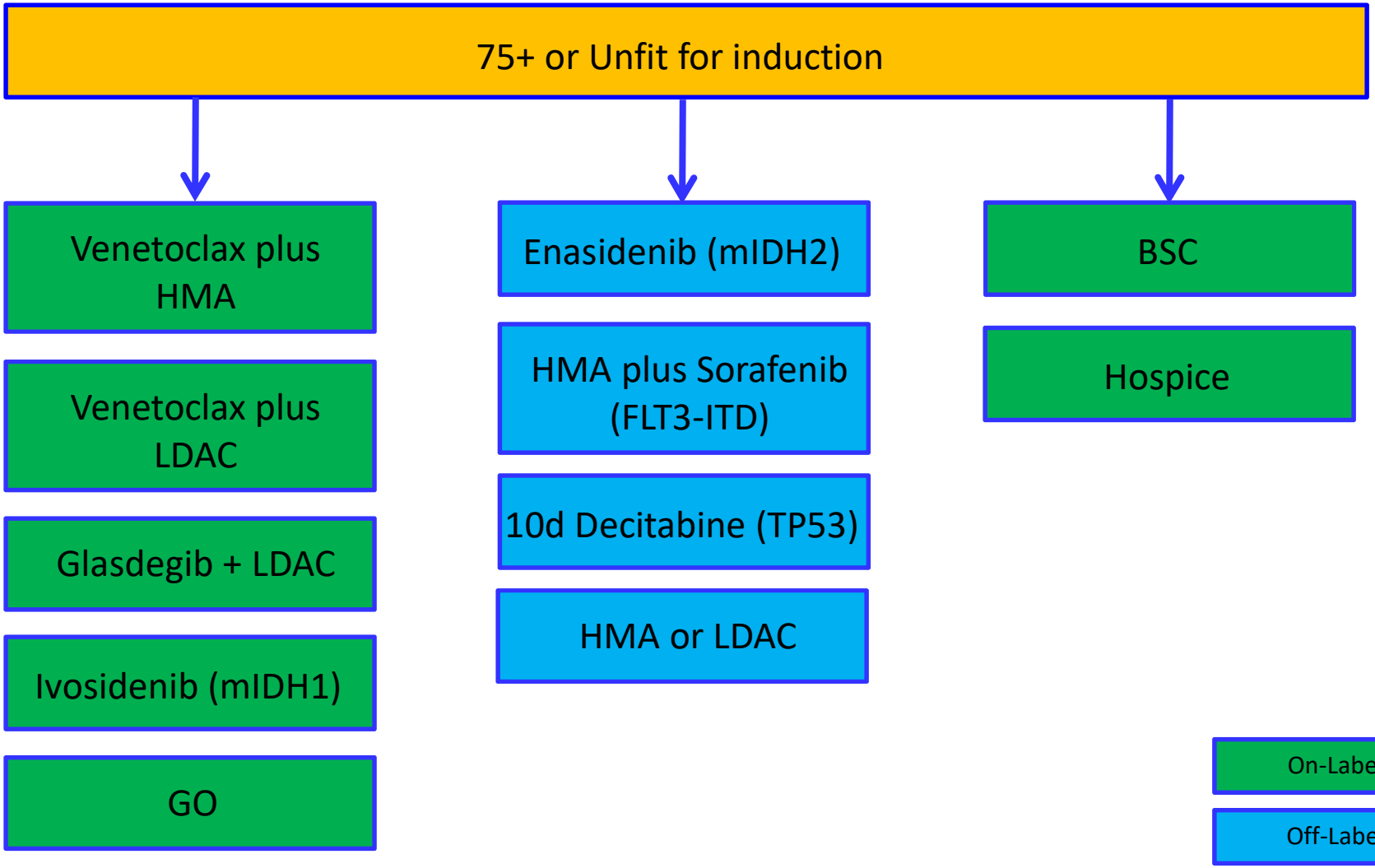
	Regimen						
	Venetoclax 400 mg plus HMA (Overall)	**Glasdegib plus LDAC**	**GO Monotherapy**	**7+3 plus GO**	**CPX-351**	**Venetoclax 400 mg plus HMA (Secondary AML, N=30)**	**Venetoclax 400 mg plus HMA (TP53 mutated, N=27)**
Response Rate	**71.8% CR/CRi**	**26.9% CR/CRi/MLFS**	**27% CR/CRh**	**81% CR/CRi**	**47.7% CR/CRi**	**63% CR/CRi**	**70% CR/CRi**
Median Overall Survival (months)	17.5	8.8	4.9	34	9.56	Not available	Not available
Citation	Pollyea et al, ASH 2018; Dinardo et al, Blood 2019	Cortes et al, Leukemia 2019	Amadori et al, JCO 2016	Castaigne et al, Lancet 2012	Lancet et al, JCO 2018	Pollyea et al, ASH 2018; Dinardo et al, Blood 2019	Pollyea et al, ASH 2018; Dinardo et al, Blood 2019

= ?

Venetoclax plus HMA – Further Support for Imprecision Medicine in AML

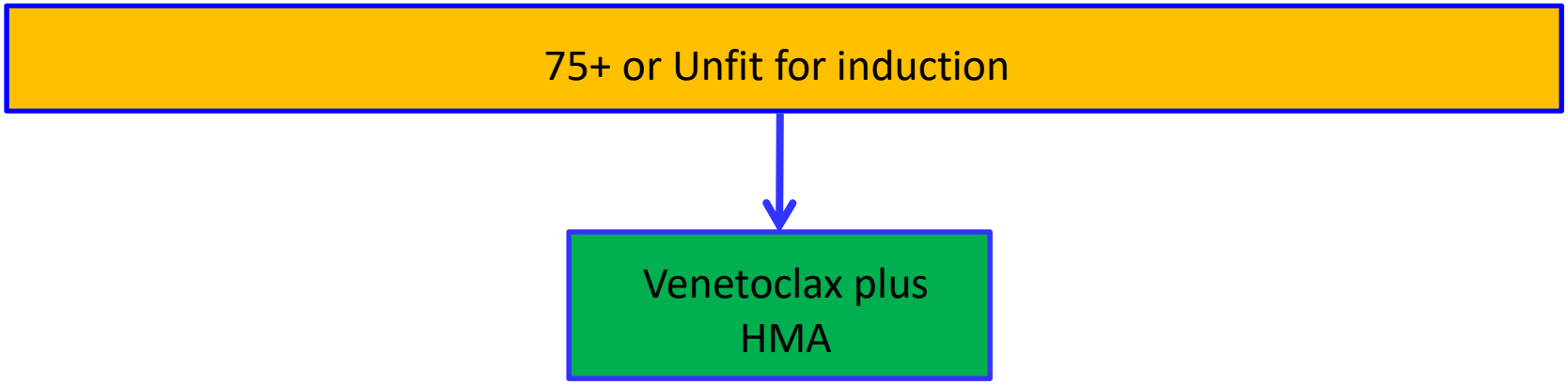
	Isocitrate Dehydrogenase				FLT3	
	Enasidenib (N=39)	Enasidenib -/+ Azacitidine (N=23)	Ivosidenib (N=33)	**Venetoclax 400 mg plus HMA (N=25)**	Sorafenib plus Azacitidine (N=6)	**Venetoclax 400 mg plus HMA (N=14)**
Response Rate	**21% CR/CRi**	**43% CR/CRi**	**42% CR/CRh**	**92% CR/CRi**	**50% CR/CRi**	**64% CR/CRi**
Median Overall Survival (months)	11.3	Not available	12.6	Not available (17.5 months for the entire study population)	Not available	Not available (17.5 months for the entire study population)
Citation	Pollyea et al, Leukemia 2019	Stein et al, ASH 2018	Roboz et al, ASCO 2019	Pollyea et al, ASH 2018; Dinardo et al, Blood 2019	Ravandi et al, Blood 2013	Pollyea et al, ASH 2018; Dinardo et al, Blood 2019

First-Line Treatment of Unfit AML in 2019

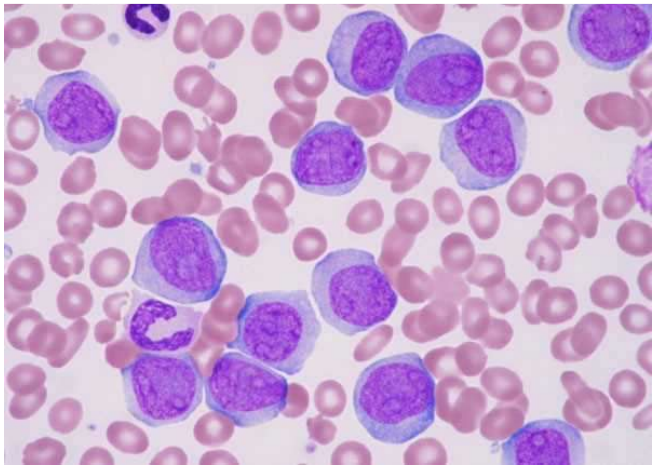


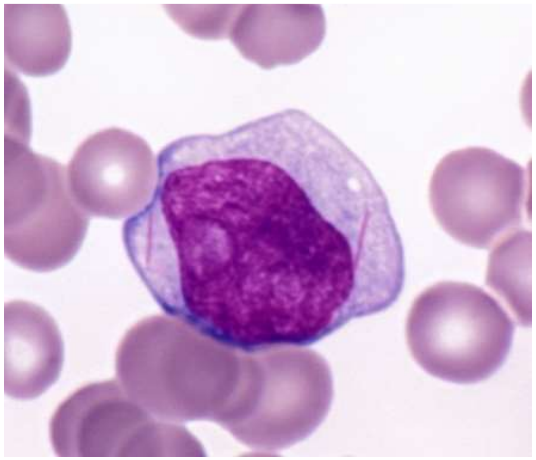
Based on NCCN guidelines, AML v3.2019

How I Treat AML Unfit for Induction in 2019 – Imprecision Medicine



Summary and Conclusions





Summary and Conclusions

- Exciting time for new FDA therapy approvals for AML
  - 8 new drugs approved since 4/2017 including 6 for first-line
- Standards of care for AML are rapidly evolving
- Additional challenges are arising, such as need for rapid assessment of select mutation and FISH markers to allow for optimal initial therapy
- Clinical trial designs need to evolve as trials continue to advance new treatments
- Apologies to those interested in updates on other AML treatment subjects, including MRD, post-remission therapy, maintenance and treatment of R/R AML, due to time constraints

Questions?

UCDAVIS
COMPREHENSIVE
CANCER CENTER