Management of Newly Diagnosed Acute Myeloid Leukemia (AML) in Patients Ineligible for Intensive Induction Therapy

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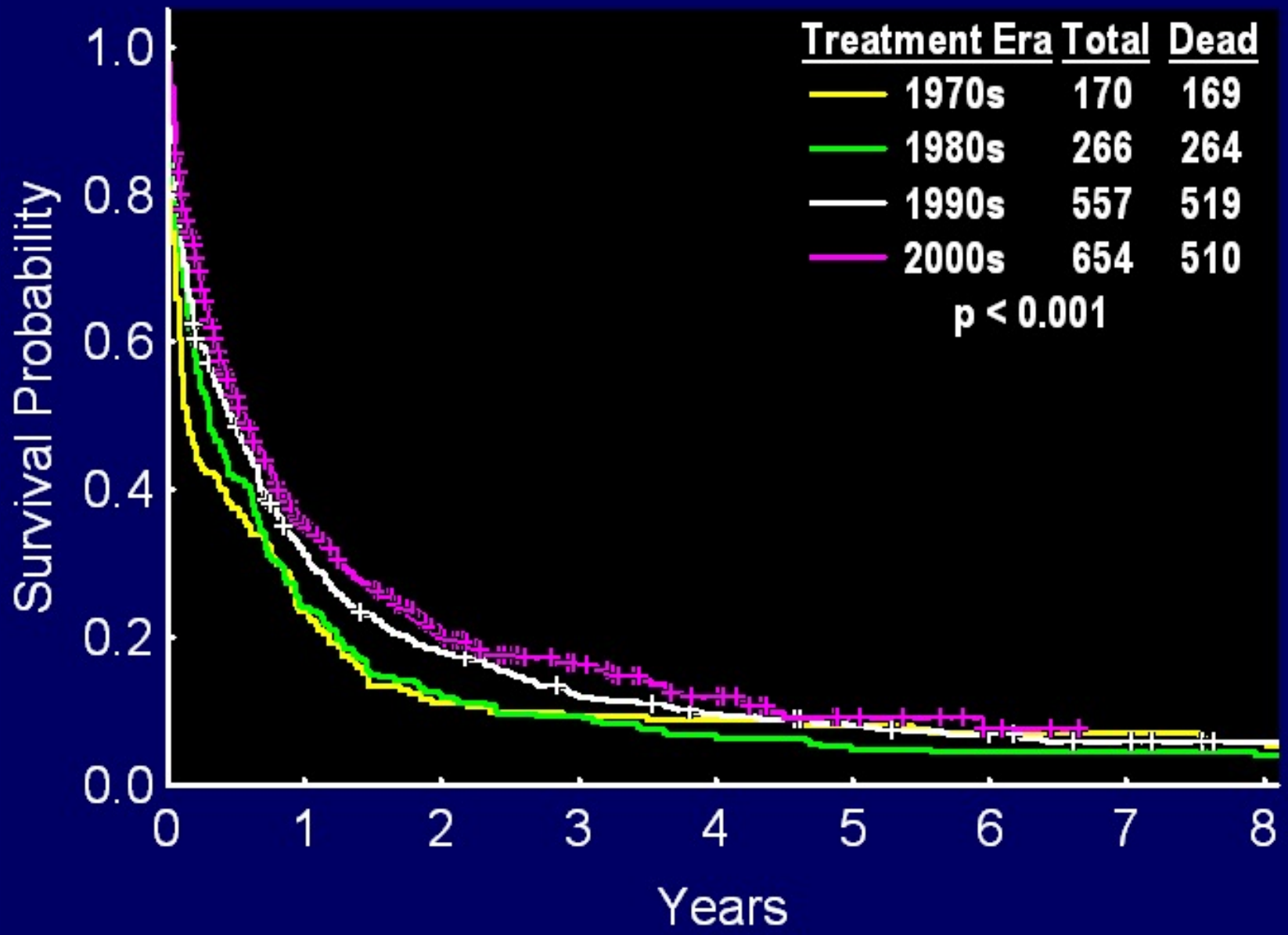
AML: What is unfit?

- **Prefer: Unlikely to benefit for induction chemo**
- **Accounts for disease biology, this would include younger pts with adverse biology (e.g. complex karyotype, t (6;9), inv 3, muts in *TP53, RUNX1, ASXL1*; not *NPM1* WT/*FLT3* ITD high allelic ratio) (Dohner H, et al, Blood 2017)**

AML: What is unfit?

- **Current (FDA) definition: age >74 and/or significant co-morbid dx (Ferrara Criteria, see VIALE-A eligibility; Ferrara et al. Leukemia, 2013)**
- **Perhaps: use geriatric assessment to define who will benefit (Klepin H, et al, J Geri Oncol 2019)**

Survival in AML in Age ≥ 60 Years (MDACC, 1973-Present, n=1647)

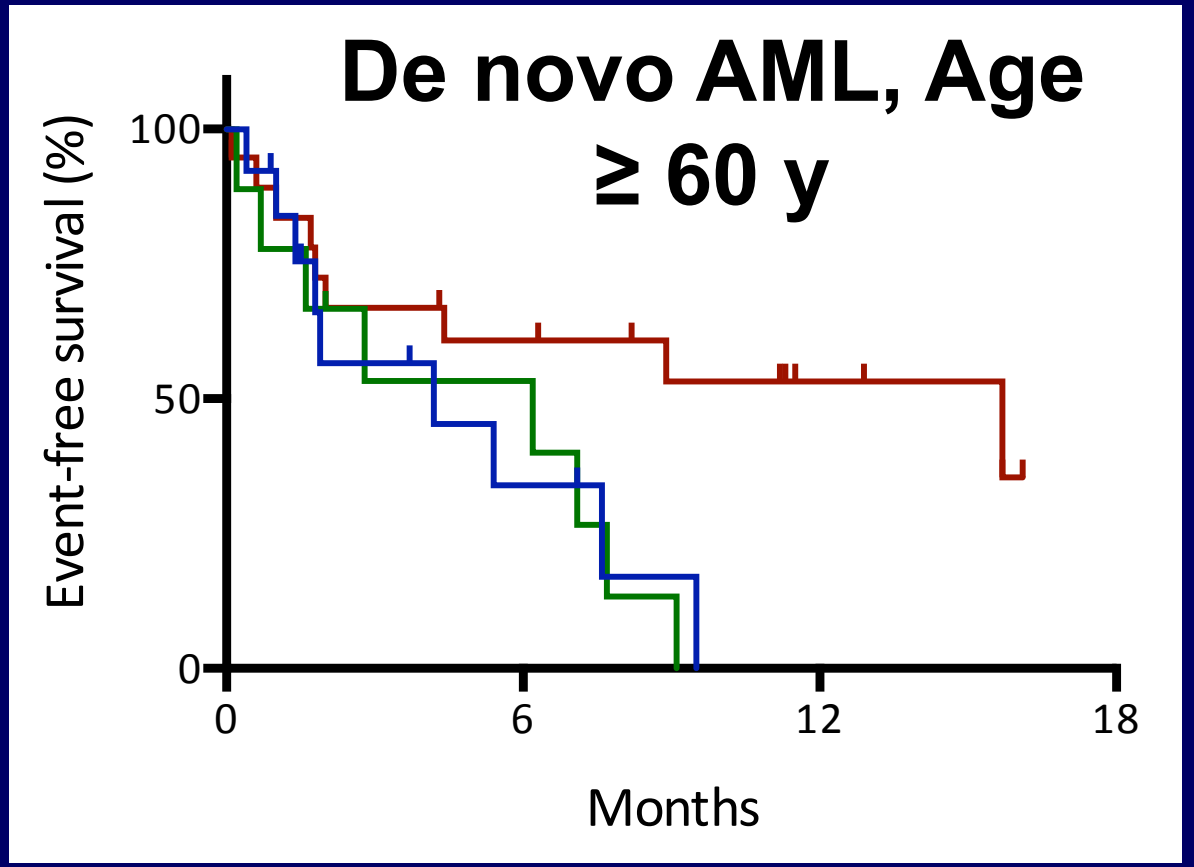


Why Do Older Patients With AML Experience Inferior Outcomes?

- Decreased host tolerance of intensive therapy
  - Impaired hematopoietic stem cell reserve
  - Presence of comorbid diseases
  - Decreased chemotherapy clearance
- Increased resistance of disease to therapy
  - Ratio of favorable (eg, t[8;21]) to unfavorable (eg, -7) cytogenetics is lower than for younger patients
  - Higher expression of drug resistance proteins (eg, PGP)
  - Higher incidence of antecedent hematologic disorders

PGP = p-glycoprotein.

In Elderly de novo AML, Secondary-Type Mutations Are Associated With Adverse Outcomes



Genetic Subtype

- De novo/pan-AML
- Secondary-type
- *TP53* mutated

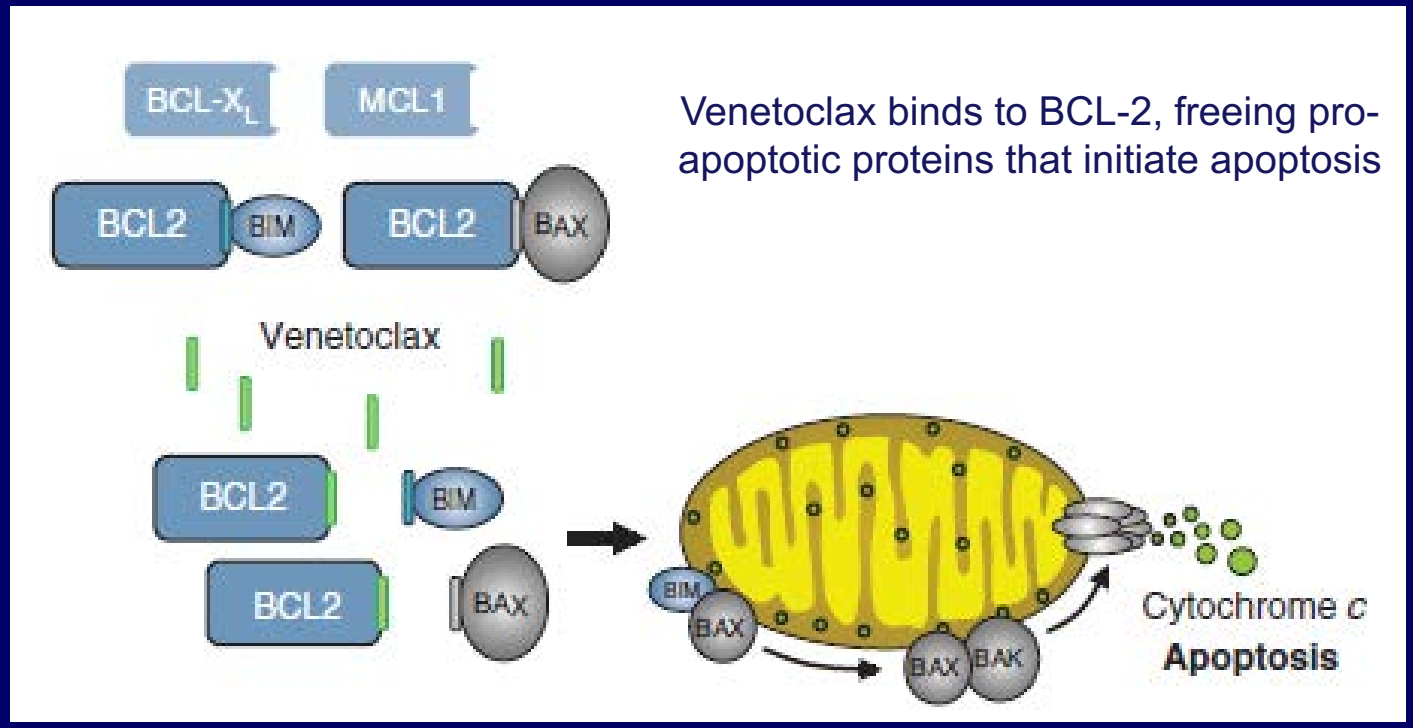
Lindsley RC et al. Blood. 2015;125:1367-1376.

Therapy for older and/or ‘unfit’ patients with AML

- Induction
  - fit, de novo, likely to benefit:
    - daunorubicin 60-90 mg/m^2/d x 3d + cytosine arabinoside 100-200 mg/m^2/d by IVCI for 7 d
      - Add midostaurin days 8-21 if FLT3 mutation
      - ? Add GO 3 mg/m^2 days 1, 4, and 5
  - Fit, secondary (s/p MDS or w MDS-type cytogenetics):
    - CPX-351
  - Unfit (age>70-75, PS>2, co-morbid dx; regardless of molecular status)
    - HMA/VEN or ara-C/VEN
- Post-remission therapy
  - Keep going with HMA/VEN
  - RIC allo SCT if feasible
  - ?Repeat induction for others
  - Maintenance oral AZA (for intensively treat non-tx pts)

Venetoclax: BCL-2 Selective Inhibitor

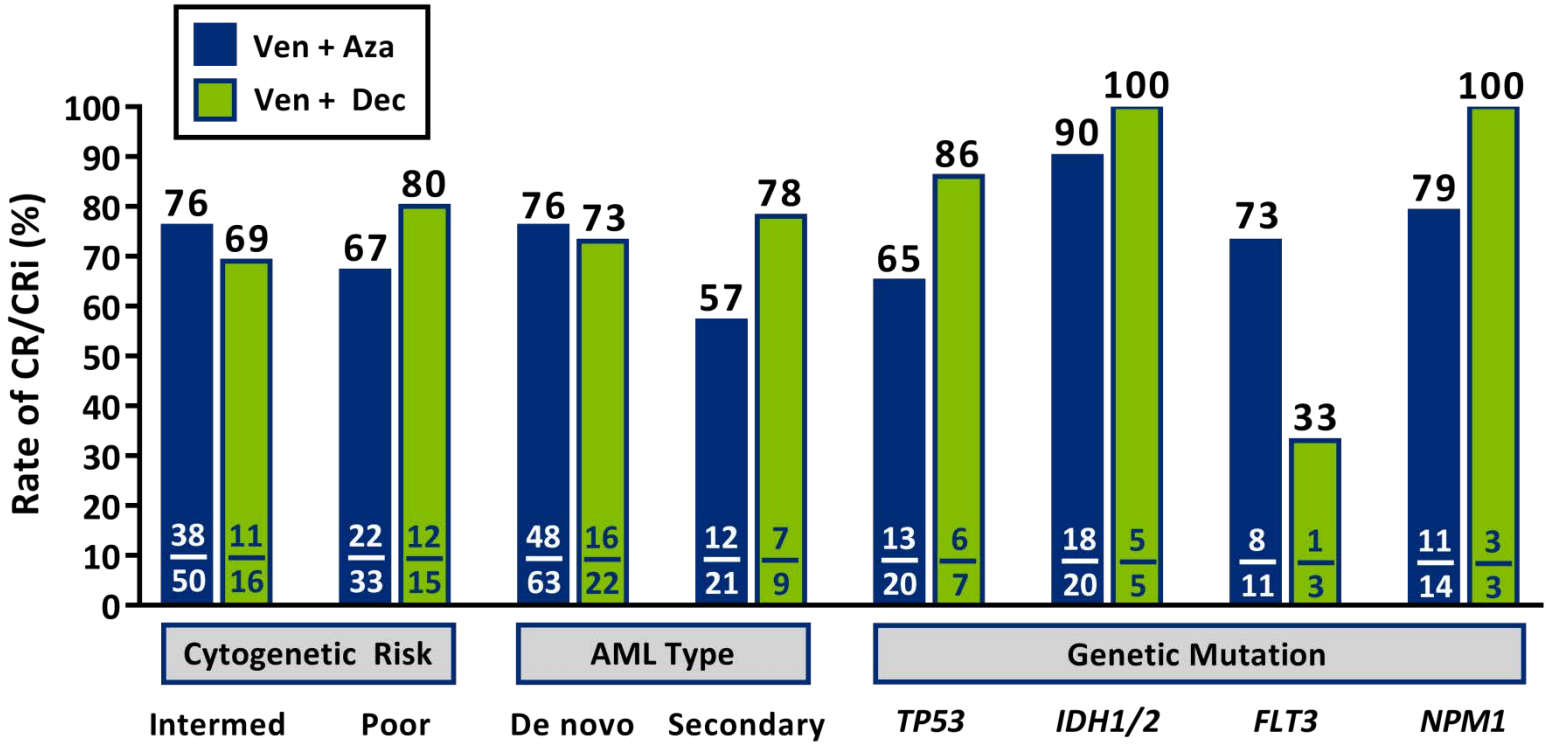
BCL-2 overexpression allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins



Venetoclax binds to BCL-2, freeing pro-apoptotic proteins that initiate apoptosis

Konopleva M, et al. *Cancer Discov*. 2016. Epub ahead of print. Lin T, et al. ASCO 2016. Abstract 7007.

Phase I Trial of VEN/HMA: Response Rates of CR/CRi by Patient Subgroups



Venetoclax with HMAs induces rapid, deep, and durable responses in older patients with AML | ASH 2018

Pollyea D, et al , ASH 2018, DiNardo C, Blood, 2019

Azacitidine ± Venetoclax (VIALE-A) Study Design

(NCT02993523)

Eligibility

Inclusion

- Patients with newly diagnosed confirmed AML
- Ineligible for induction therapy defined as **either**
  - ❖ ≥75 years of age
  - ❖ 18 to 74 years of age with at least one of the co-morbidities:
    - CHF requiring treatment or Ejection Fraction ≤50%
    - Chronic stable angina
    - DLCO ≤65% or FEV_1 ≤65%
    - ECOG 2 or 3

Exclusion

- Prior receipt of any HMA, venetoclax, or chemotherapy for myelodysplastic syndrome
- Favorable risk cytogenetics per NCCN
- Active CNS involvement

Treatment

Randomization 2:1
N = 433*

Venetoclax + Azacitidine
(n = 286)
Venetoclax 400 mg PO, daily, days 1–28
+ Azacitidine 75 mg/m² SC /IV days 1–7

Placebo + Azacitidine
(n = 145)
Placebo daily, days 1–28
+ Azacitidine 75 mg/m² SC /IV days 1–7

Endpoints

Primary

- Overall survival

Secondary

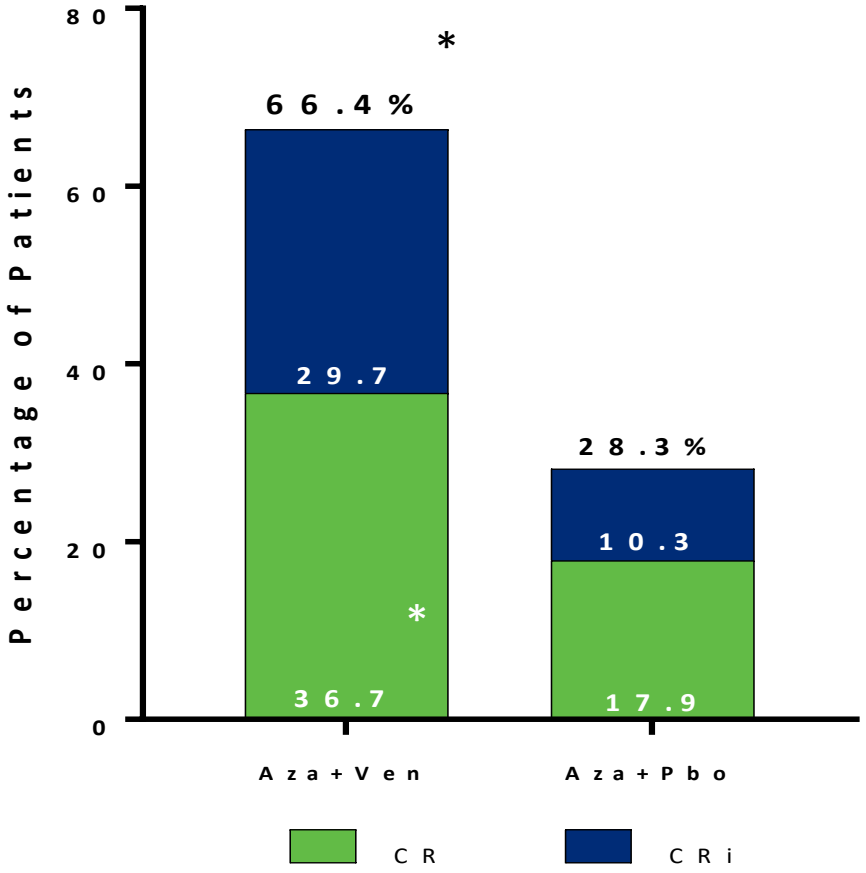
- CR+CRi rate
- CR+CRh rate
- CR+CRi and CR+CRh rates by initiation of cycle 2
- CR rate
- Transfusion independence
- CR+CRi rates and OS in molecular subgroups
- Event-free survival

Randomization Stratification Factors: Age (<75 vs. ≥75 years); Cytogenetic Risk (intermediate, Poor); Region

Venetoclax dosing ramp-up: **Cycle 1 ramp-up** Day 1: 100 mg, Day 2: 200 mg, Day 3 - 28: 400 mg
Cycle 2 → Day 1-28: 400 mg

DiNardo CD et al. NEJM 2020

VIALE-A
AZA ± VEN in AML: Composite Response Rate (CR+CRi)



	No. of treatment cycles, median (range)	Median time to CR/CRi, Months (range)	*CR+CRi by initiation of Cycle 2, n (%)
Aza + Ven (n = 286)	7.0 (1.0 – 30.0)	1.3 (0.6 – 9.9)	124 (43.4)
Aza + Pbo (n = 145)	4.5 (1.0 –26.0)	2.8 (0.8 – 13.2)	11 (7.6)

*CR+CRi rate, CR rate, and CR+CRi by initiation of cycle 2 are statistically significant with *P* <.001 by CMH test

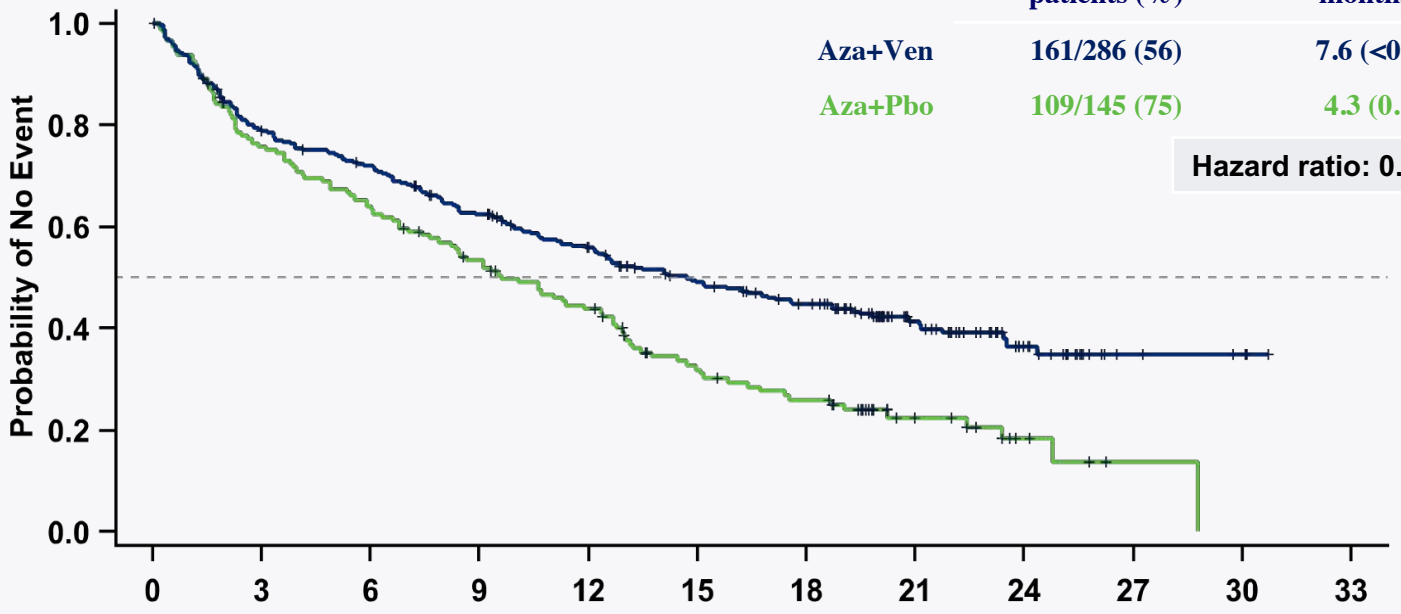
Tox: myelosupression; TLS not seen with mitigation via ramp-up, allopurinol, monitoring

DiNardo CD et al. NEJM 2020

VIALE-A
AZA ± VEN in AML: Overall Survival

	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* <.001



Patients at Risk

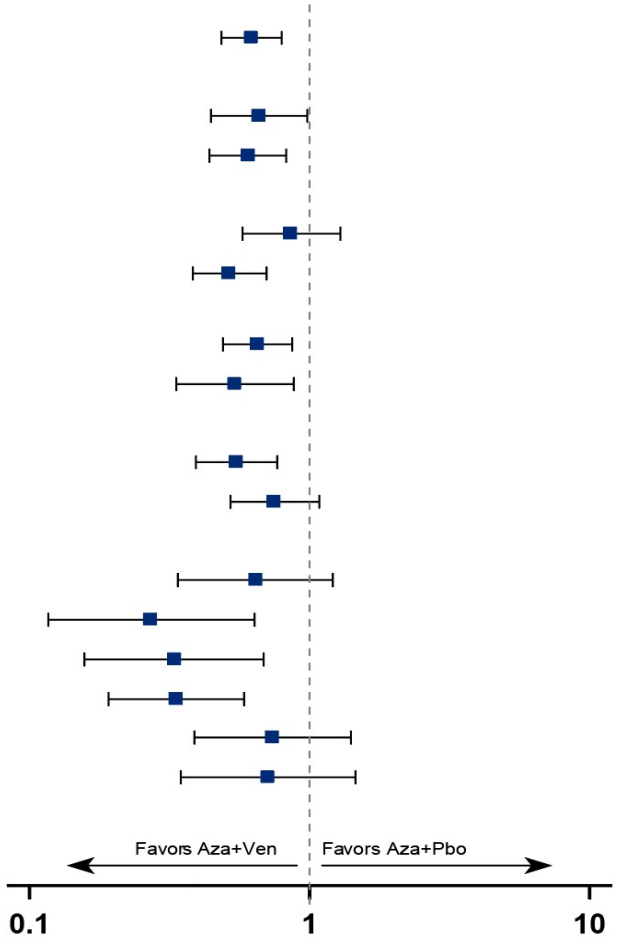
Aza+Ven	286	219	198	168	143	117	101	54	23	5	3	0
Aza+Pbo	145	109	92	74	59	38	30	14	5	1	0	0

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

DiNardo CD et al. NEJM 2020

VIALE-A
AZA ± VEN in AML: Survival by Subgroups

	Aza+Ven n/N(%)	Aza+Pbo n/N(%)	HR [95% CI] Aza+Ven vs. Aza+Pbo
All Subjects	161/286 (56.3)	109/145 (75.2)	0.64 (0.50, 0.82)
Gender			
Female	61/114 (53.5)	41/ 58 (70.7)	0.68 (0.46, 1.02)
Male	100/172 (58.1)	68/ 87 (78.2)	0.62 (0.46, 0.85)
Age (Years)			
< 75	66/112 (58.9)	36/ 58 (62.1)	0.89 (0.59, 1.33)
≥ 75	95/174 (54.6)	73/ 87 (83.9)	0.54 (0.39, 0.73)
Type of AML			
De Novo	120/214 (56.1)	80/110 (72.7)	0.67 (0.51, 0.90)
Secondary	41/ 72 (56.9)	29/ 35 (82.9)	0.56 (0.35, 0.91)
Cytogenetic Risk			
Intermediate	84/182 (46.2)	62/ 89 (69.7)	0.57 (0.41, 0.79)
Poor	77/104 (74.0)	47/ 56 (83.9)	0.78 (0.54, 1.12)
Molecular Marker			
FLT3	19/ 29 (65.5)	19/ 22 (86.4)	0.66 (0.35, 1.26)
IDH1	15/ 23 (65.2)	11/ 11 (100.0)	0.28 (0.12, 0.65)
IDH2	15/ 40 (37.5)	14/ 18 (77.8)	0.34 (0.16, 0.71)
IDH1/2	29/ 61 (47.5)	24/ 28 (85.7)	0.34 (0.20, 0.60)
TP53	34/ 38 (89.5)	13/ 14 (92.9)	0.76 (0.40, 1.45)
NPM1	16/ 27 (59.3)	14/ 17 (82.4)	0.73 (0.36, 1.51)



DiNardo CD et al. EHA 2020. Abstract LB2601.

DiNardo CD et al. NEJM 2020

VIALE-A: Select Adverse Events

Event	Azacitidine–Venetoclax Group (N=283)		Azacitidine–Placebo Group (N=144)	
	All Grades†	≥Grade 3‡	All Grades†	≥Grade 3‡
	number of patients (percent)			
All adverse events	283 (100)	279 (99)	144 (100)	139 (97)
Serious adverse events	235 (83)	232 (82)	105 (73)	102 (71)
Febrile neutropenia	84 (30)	84 (30)	15 (10)	15 (10)
Anemia	14 (5)	14 (5)	6 (4)	6 (4)
Neutropenia	13 (5)	13 (5)	3 (2)	3 (2)
Atrial fibrillation	13 (5)	10 (4)	2 (1)	2 (1)
Pneumonia	47 (17)	46 (16)	32 (22)	31 (22)
Sepsis	16 (6)	16 (6)	12 (8)	12 (8)

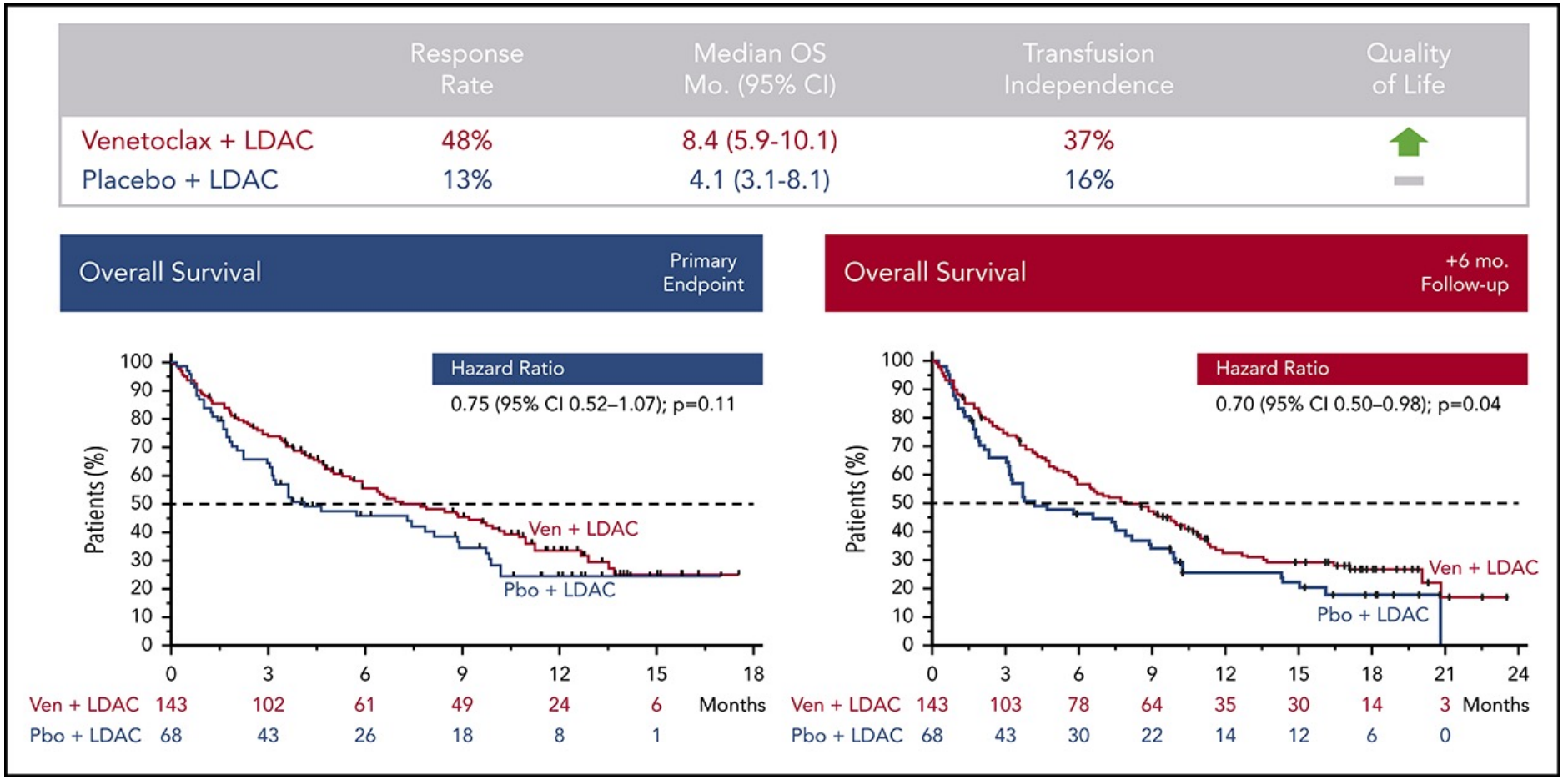
- Tumor lysis syndrome (TLS) reported during the ramp-up period (on d1 through d3 when the dose of venetoclax was increased) in 3 pts (1%) in the Aza/Ven group and in none of the pts in the control group;
  - All 3 pts had transient biochemical changes that resolved with uricosuric agents and calcium supplements without interruption of Aza/Ven or Aza/Placebo

DiNardo CD et al. NEJM 2020;383(7):617-629.

LDAC plus VENETOCLAX vs PLACEBO for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial (VIALE-C)

Similar eligibility c/w VIALE-A but prior rx for MDS allowed

	Response Rate	Median OS Mo. (95% CI)	Transfusion Independence	Quality of Life
Venetoclax + LDAC	48%	8.4 (5.9-10.1)	37%	↑
Placebo + LDAC	13%	4.1 (3.1-8.1)	16%	–



Wei A, et al. Blood, 135: 2137-2145, 2020.

LDAC plus VENETOCLAX vs PLACEBO for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial (VIALE-C)

Multivariable Cox regression of preplanned OS analysis

Covariate	**HR (95% CI)**	***P***
Treatment arm (venetoclax vs placebo)	0.67 (0.47-0.96)	.03
Age (<75 vs ≥75 y)	0.56 (0.37-0.84)	.005
AML status (de novo vs secondary)	0.59 (0.41-0.85)	.004
ECOG performance status (<2 vs ≥2)	0.48 (0.33-0.70)	<.001
Cytogenetic risk (intermediate vs poor)	0.57 (0.40-0.82)	.003

Wei A, et al. Blood, 135: 2137-2145, 2020.

Venetoclax Dose Adjustments

Antifungal	Package Insert Recommendation (Ven mg/D)	MDACC Dose Adjustment (Ven mg/D)
Posaconazole	70	50
Voriconazole	100	100
Isavuconazole, fluconazole	200	200
Caspofungin, echinocandins	400	400

Concomitant use of venetoclax with strong CYP3A inhibitors increases venetoclax exposure and may increase the risk for tumor lysis syndrome (TLS) at initiation and during ramp-up phase[1].

[1]Venetoclax package insert (12/2020)

Controversies (beyond min age to give aza/ven)

- Rx of pts with *TP53* mutations (any fitness)
- Rx of pts with *FLT3* mutations: HMA/Ven vs HMA/FLT3 inhib vs ?triplet
- Rx of pts with IDH mutations: HMA/VEN vs single-agent inhib vs HMA/IDHinh vs ?triplet
- How long to rx/role of allorx
- Rx of relapsed disease
  - Aza/ven if not already given (Stahl, *Blood Adv* 2021)
  - Fractionated gemtuzumab ozogamicin (Taksin, *Leukemia* 2007)
  - Targeted tx (FLT3i +/- VEN or IDHi or ?Menin inhib trial) if relevant target present

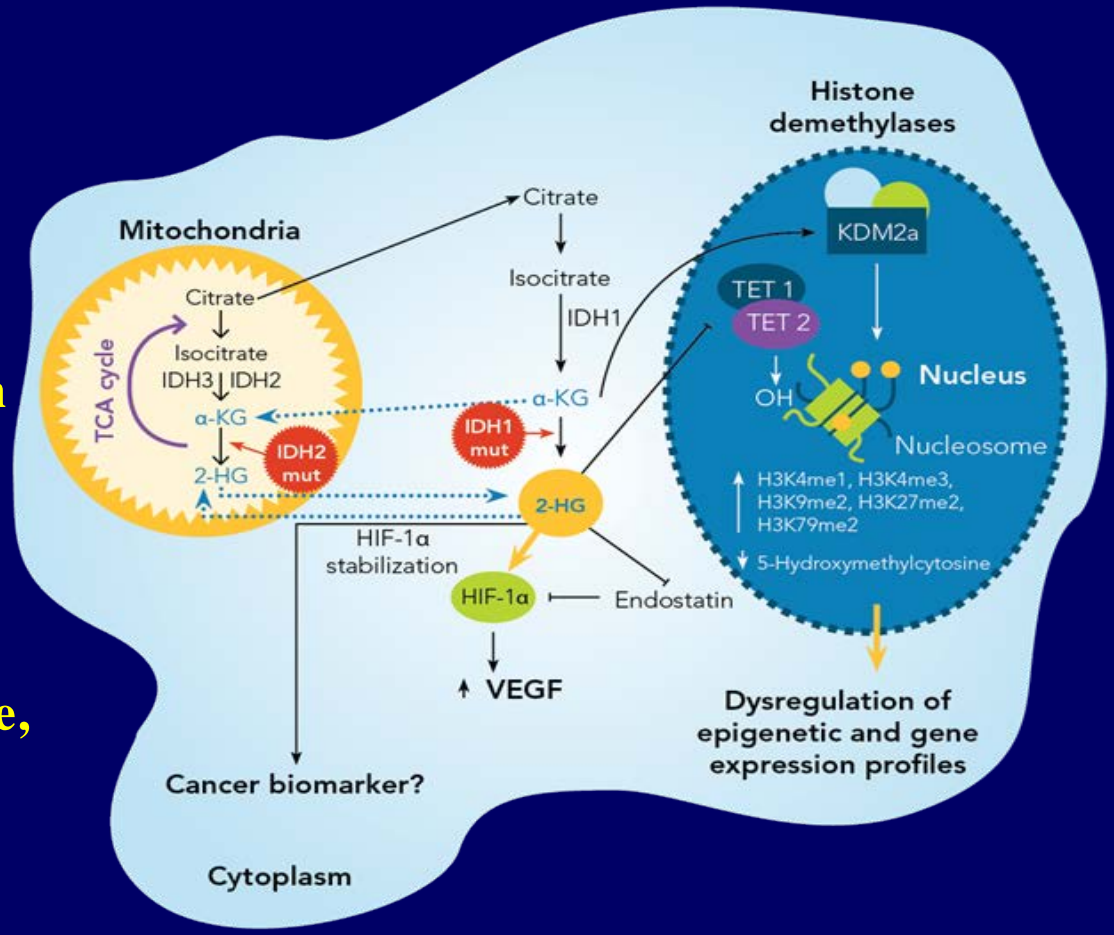
Response Rates of CR/CRi by Patient Subgroups

Abstract	Results; AZ+V v AZA+P	Notes
Pollyea, abst 461 IDH1/2 N=107	CR/CRh : 72 v 7% Med DOR: 30 v 16 mo Med OS : 25 v 6 mo	RR favored IDH2, esp in IDH2 R172 Single agent ivosidenib[1], enasidenib[2], median OS 12.6 mo
Konopleva, abst 1904 FLT3 mut N=62	CR/CRh : 65 v 18% Med DOR: 18 v 15 mo Med OS : 13 v 9 mo	AZA/FLT3i trials promising[3] but Gilt/aza not better than aza (LACEWING press release)

[1]Roboz et al, *Blood* 2020. [2]Pollyea et al, *Leukemia* 2019. [3]Swaminathan et al, *Hematologica* 2021

Isocitrate Dehydrogenase (IDH) Mutations as a Target in AML

- **IDH is an enzyme of the citric acid cycle**
- **Mutant *IDH2* produces 2-hydroxyglutarate (2-HG), which alters DNA methylation and leads to a block in cellular differentiation**
- **AG-221 (CC-90007) is a selective, oral, potent inhibitor of the mutant *IDH2* (m*IDH2*) enzyme**



IDH Inhibitor Data

AG120=ivosidenib (IDH1 inhibitor)

- Most common AEs: diarrhea, fatigue, and pyrexia
- **Overall response rate of 35**% and a complete remission rate of 15%
- **In all response evaluable patients, an estimated 55% had treatment duration of at least 33%**
- **Differentiation syndrome**

AG221=enasidenib (IDH2 inhibitor)

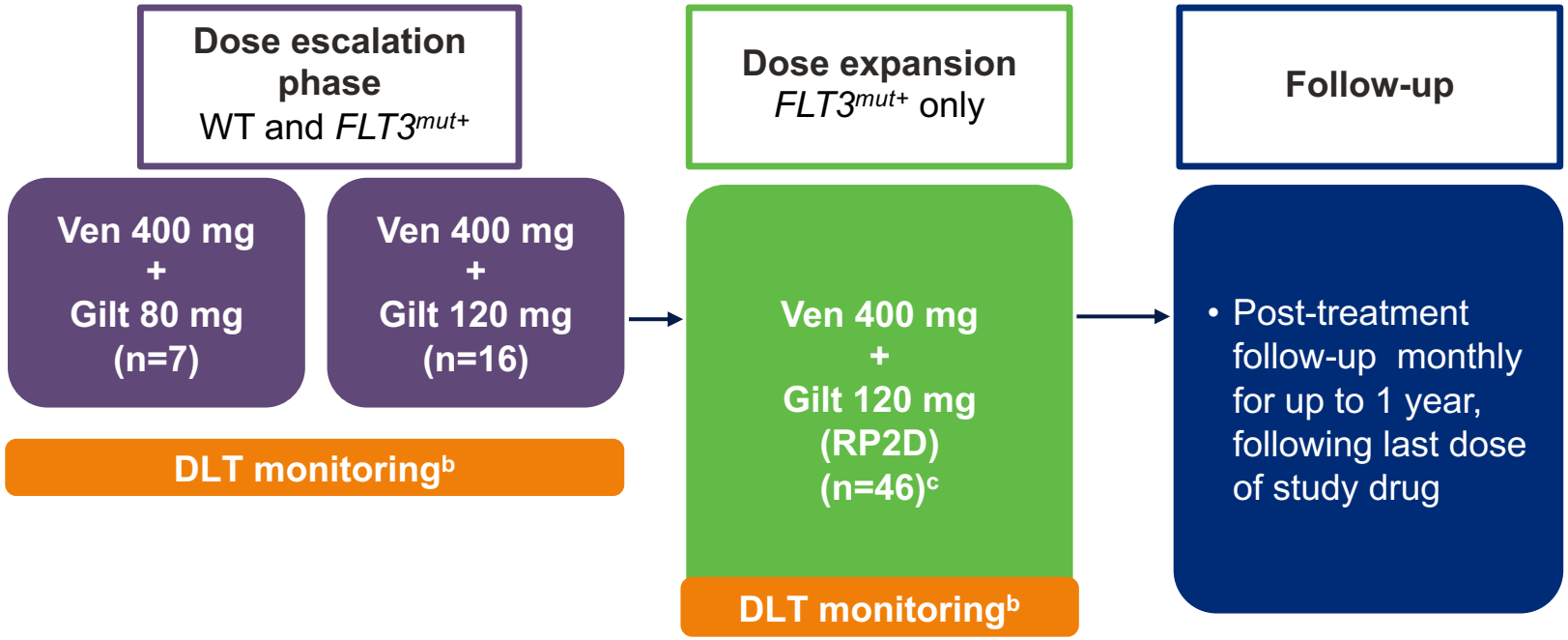
- Most common AEs: nausea, fatigue, increase in bilirubin, diarrhea
- ORR 37% in 159 adults w R/R AML
  - CR 18%
  - Median duration of response of 6.9 months
- Differentiation syndrome

DiNardo C, et al. NEJM 2018. Stein E, et al. Blood 2019

VEN/GILT in R/R AML (Daver et al, ASH 2020)

Key Eligibility Criteria

- R/R AML
- WT or *FLT3*$^{mut+}$ (dose escalation) and *FLT3*$^{mut+}$ (dose expansion)
- ≥1 prior line of therapy[a]
- WBC count ≤ 25 x 10^9 /L at start of study drug
- ECOG PS 0–2



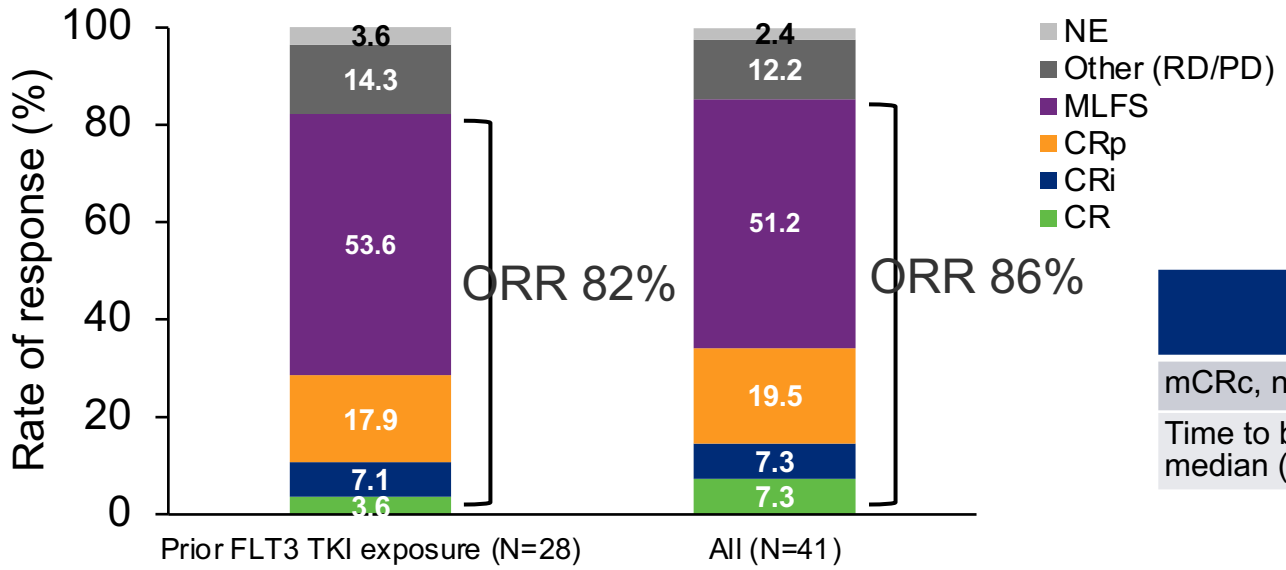
Prior exposure to Ven was permitted in a protocol amendment (unless received as part of a randomized controlled trial); FLT3 inhibitors including Gilt were allowed during dose escalation; FLT3 inhibitors except Gilt were permitted during dose expansion; prior stem cell transplant was permitted

[b]DLT evaluation period defined as first 28 days of Cycle 1

[c]Of the N=43 *FLT3*$^{mut+}$ patients presented 31 were from the expansion phase

AEs, adverse events; AML, acute myeloid leukemia; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; FLT3, FMS-like tyrosine kinase 3; *FLT3*$^{mut+}$,FLT3-mutated; mCRc, modified composite complete remission; RP2D, recommended phase two dose; R/R, relapsed/refractory; TKD, tyrosine kinase domain; WT, wild type

VEN/GILT in R/R AML (Daver et al, ASH 2020)



	All (N=41)
mCRc, n (%)	35 (85.4%)
Time to best response (mCRc), median (range), months	0.9 (0.7–4.2)

% mCRc rate compares favorably to the 52% CRc rate (using the same response parameters), with single agent Gilt in the ADMIRAL phase 3 study[1]

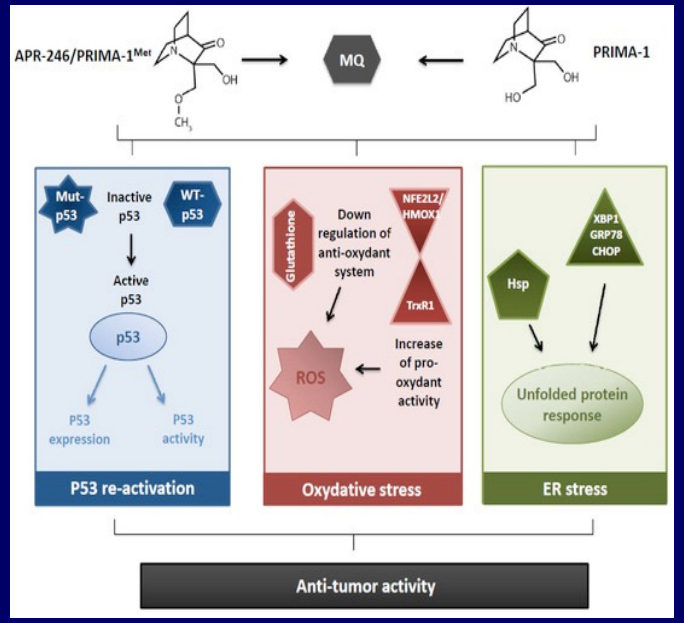
including patients who received non-RP2D dose during dose expansion phase. Two on-treatment patients did not have their first disease assessment at the cutoff date and were not included in the efficacy analyses. No patients achieved partial remission. One patient (TKD only) discontinued with no response data

AML, acute myeloid leukemia; CI, confidence interval; CR, complete remission; CRi, CR with incomplete blood count recovery; CRp, CR with incomplete platelet recovery; FLT3, FMS-like tyrosine kinase 3; Gilt, gilteritinib; ITD, internal tandem duplications; mCRc, ITT, intention to treat; modified composite complete remission; MLFS, morphologic leukemia free state; NE, not estimable; PD, progressive disease; RD, resistant disease; TKI, tyrosine kinase inhibitor; TKD, tyrosine kinase domain

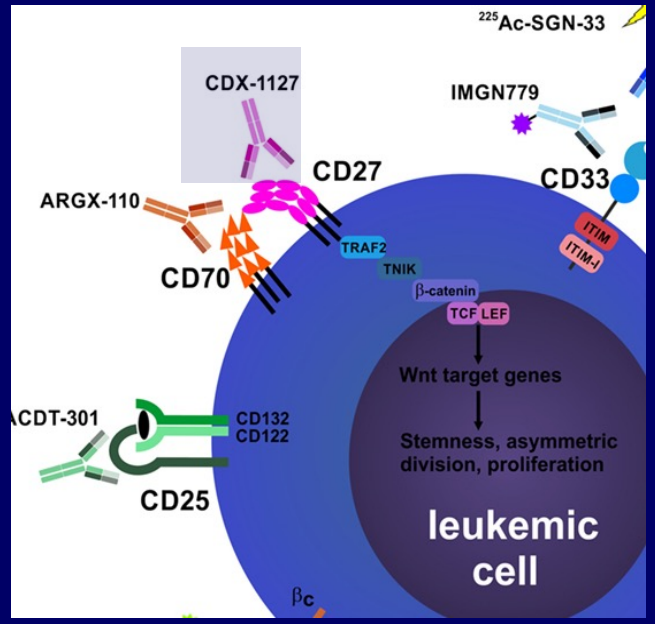
1. Perl AE, et al. N Engl J Med. 2019;381(18):1728–1740

AML: Novel Promising Strategies

APR-246 for p53 mutant AML

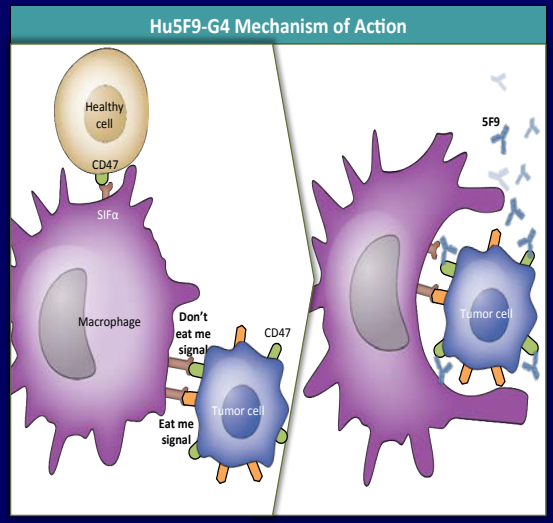


Anti-CD70 Ab



Anti-CD47 antibody (5F9)

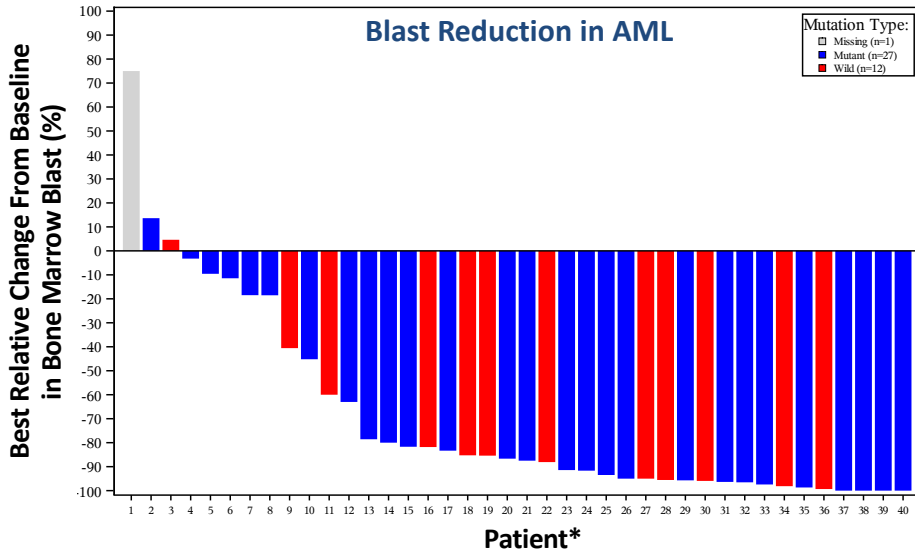
macrophage phagocytosis



Schurch CM. *Front Oncol*. 2018;8:152.

Phase I Trial of Magrolimab + AZA Induces High Response Rates in AML (Sallman et al, ASH 2020)

Best Overall Response	All AML (N=43)	*TP53*-mutant AML (29)
ORR	27 (63%)	20 (69%)
CR	18 (42%)	13 (45%)
CRi	5 (12%)	4 (14%)
PR	1 (2%)	1 (3%)
MLFS	3 (7%)	2 (7%)
SD	14 (33%)	8 (28%)
PD	2 (5%)	1 (3%)



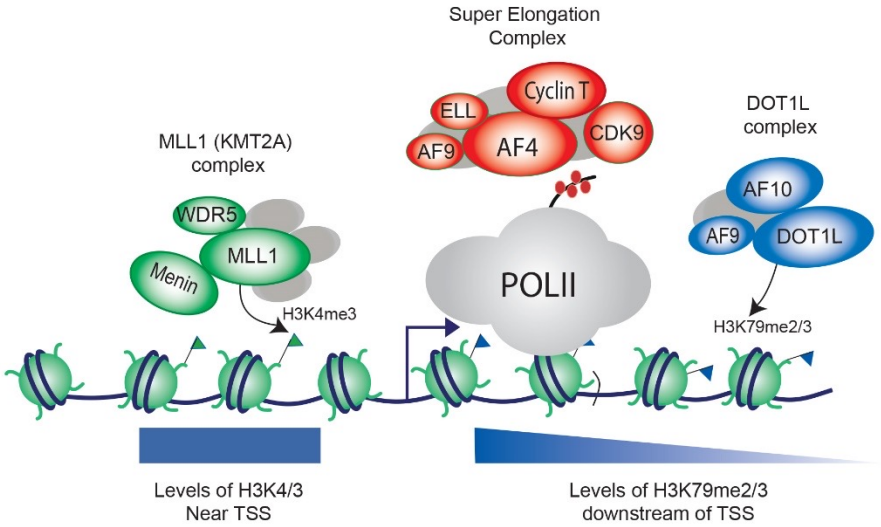
- Magrolimab + AZA induces a 63% ORR and 42% CR rate in AML, including similar responses in *TP53*-mutant patients
- Median time to response is 1.95 months (range 0.95 to 5.6 mo), more rapid than AZA monotherapy
- 9.6% of patients proceeded to bone marrow stem cell transplantation
- Magrolimab + AZA efficacy compares favorably to AZA monotherapy (CR rate 18%–20%)[1,2]

Response assessments per 2017 AML ELN criteria. Patients with at least 1 post-treatment response assessment are shown. *Three patients not shown due to missing values; <5% blasts imputed as 2.5%.

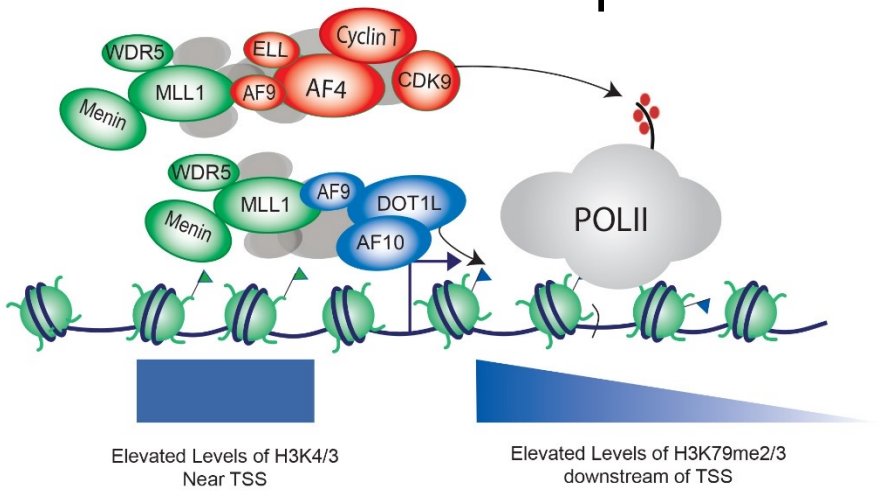
1. Fenaux P, et al. *J Clin Oncol*. 2010;28(4):562-569. 2. Dombret H, et al. *Blood*. 2015;126(3):291-299.

Regulatory Complexes Control *HOX/MEIS1* Gene Expression in both *MLL*-R and *NPM1* mut leukemia

Developmental Gene Expression (Hox/Meis1)



Leukemia Gene Expression



Potential Therapeutic Opportunities

Enzymes

1. DOT1L
2. CDK9
3. WDR5
4. NEDD8 (Pevonedistat an NEDD8 inhibitor)

Protein:Protein

1. MLL-Menin*
2. BRD4-Acetyl Lysine

Dana-Farber Cancer Institute

Responses in ongoing clin trials, e.g., Wang E , ASH 2020

Case 1: 78 yo married F, PS = 1

PMHx psoriatic arthritis rx with biologic, and IDC/DCIS rt breast rx with excision/anastrozole in 2018. No other co-morbidities. Active.

2018 High MCV noted, NGS panel: *SF3B1* K700C mut, VAF 7%
2020 New anemia. Marrow exam: no EB, 5q- in 7/28 mets
2020 Rx with darbepoetin alfa and lenalidomide
2020 Could not tolerate lenalidomide due to rash

12/31/20 More profound pancytopenia, new right knee effusion

1/21: Tap of knee: calcium pyrophosphate crystals
Marrow exam: 62% myeloblasts, complex karyotype, SF3B1 mut still with low VAF

Case 1: 78 yo married F, PS = 1 cont'd

1/10/21 Rx with full dose aza/ven
course c/b *B. cereus* bacteremia. Recovered
2/14/21: marrow: 2% blasts
2/21/21: C1 D41 CBC nl: rx aza/ven course 2
course c/b f/n
C2D36 CBC nl rx aza/ven course 3 decr ven to 21 d
C3D29 CBC nl rx aza/ven course 4, decr ven to 21 d
C4 D36 CBC nl rx aza/ven course 5, decr ven to 21 d
C5 D36 CBC nl: aza ven course 6, decr ven to 14d due to nadirs and low count on day

Meds: amoxicillin-clavulanate, statin, amlodipine

Note: nl CBC means ANC 750-1K on rx day, nadir around 200, Plt always >100K
PS has improved to 0

Issues:
If and when to re-marrow?
How long to keep going with aza/ven?
Role of further dose modifications?
What to do when disease progresses?