Penn Medicine
Abramson Cancer Center
Leukemia Program

Front-Line Treatment for Patients with Newly Diagnosed Acute Myeloid Leukemia (AML) Ineligible for Intensive Induction Therapy

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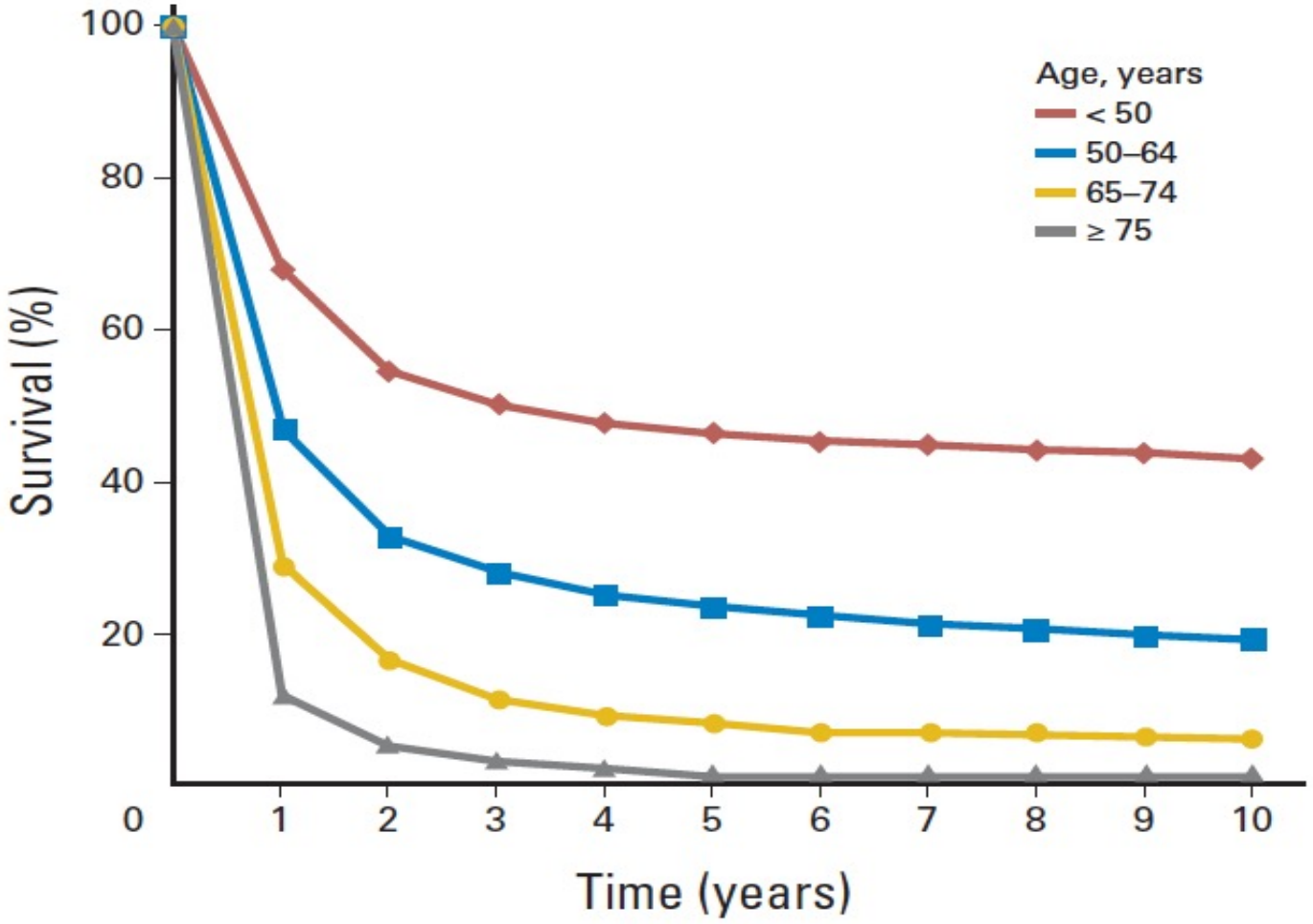
Intensive treatment of older patients: inferior survival, high early mortality

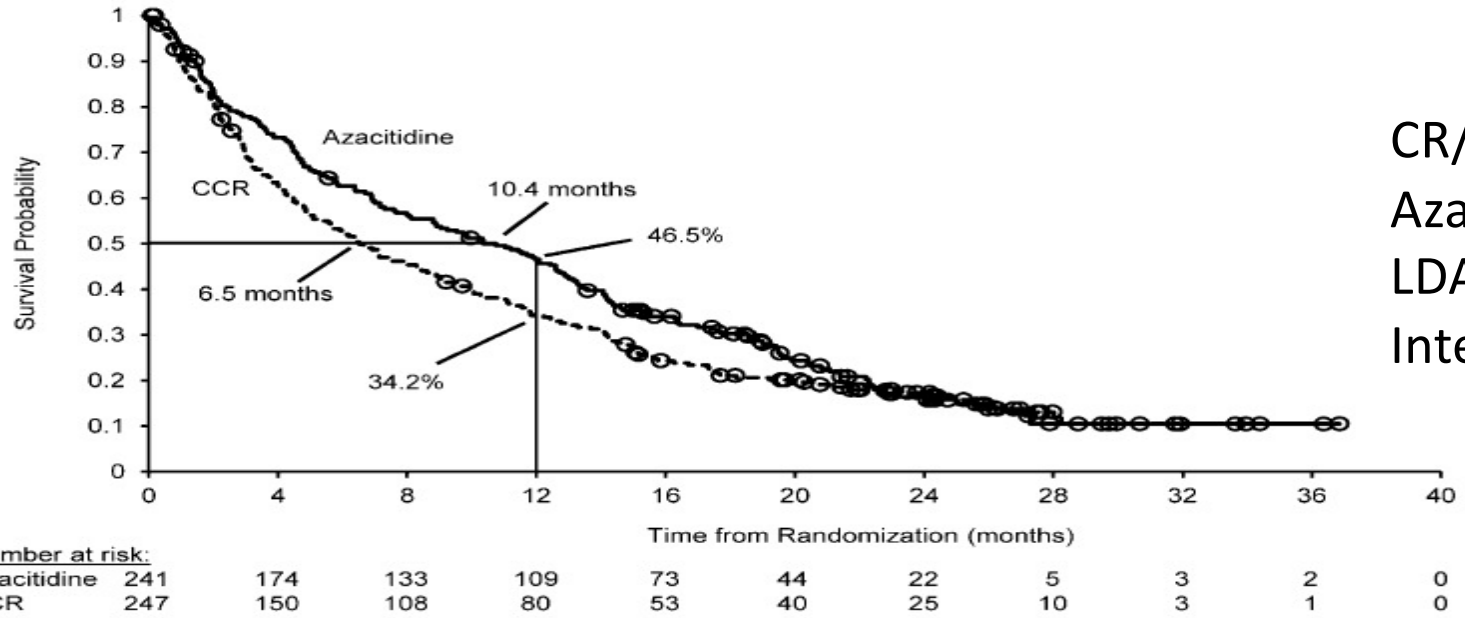
- Induction mortality risk factors, age ≥70
  - Extremes of age (esp. over age 80)
  - ECOG PS of 2 or higher
  - Abnormal creatinine (>1.3)
  - Complex karyotype (e.g. TP53 mutation)

  8 week mortality of >50% if 2 or more present



Klepin HD, et al. *J Clin Oncol.* 2014 Aug 20;32(24):2541-52
Kantarjian H, et al. *Blood*. 2010 Nov 25;116(22):4422-9.

Age >65: to induce or not to induce?



CR/CRi rates:
Azacitidine: 28%
LDAC: 26%
Intensive chemo (IC): 48%

Table 3. Kaplan-Meier estimated median OS and 1-y survival comparisons within preselected treatment subgroups

		OS							1-y survival			
		Median		Difference								
	No. of patients	Months	95% CI	Months	95% CI	HR	95% CI	*P*	%	95% CI	Difference	95% CI
Preselected for BSC only	89											
Azacitidine	44	5.8	3.6-9.7	2.1	–1.0-5.2	0.60	0.38-0.95	.0288	30.3	17.5-44.2	11.7	–6.3-29.8
BSC	45	3.7	2.8-5.7						18.6	8.7-31.4		
Preselected for LDAC	312											
Azacitidine	154	11.2	8.8-13.4	4.8	1.7-7.9	0.90	0.70-1.16	.4270	48.5	40.3-56.2	14.5	3.5-25.5
LDAC	158	6.4	4.8-9.1						34.0	26.6-41.6		
Preselected for IC	87											
Azacitidine	43	13.3	7.2-19.9	1.1	–5.4-7.6	0.85	0.52-1.38	.5032	55.8	39.8-69.1	4.9	–16.2-26.0
IC	44	12.2	7.5-15.1						50.9	35.2-64.6		

Dombret H, et al. *Blood*. 2015 Jul 16;126(3):291-9

2017: a turning point in AML history

1973
7+3 initially reported to produce high CR rates in AML

Sep 27, 1990
Idarubicin approved for AML

May 17, 2000
Gemtuzumab ozogamicin receives accelerated approval in CD33 AML for older adults in 1st relapse

Oct 15, 2010
Gemtuzumab withdrawn from market

2017-2021 FDA Approvals

April 28, 2017
midostaurin approved for new dx FLT3-mut+ AML (with chemotherapy)

August 1, 2017
enasidenib approved for rel/ref IDH2-mut AML

August 3, 2017
CPX-351 approved for new dx therapy-related AML or AML with MDS-related changes

September 1, 2017
gemtuzumab ozogamicin re-approved for new dx CD33+ AML in adults and rel/ref CD33+ AML in adults and children

July 20, 2018
ivosidenib approved for rel/ref IDH1-mut AML, On May 2, 2019 approved for unfit newly diagnosed IDH1-mut AML

Nov 21, 2018
venetoclax approved for newly diagnosed patients unsuitable for intensive induction (with HMA or LDAC)

Nov 21, 2018
glasdegib approved for newly diagnosed patients unsuitable for intensive induction (with LDAC)

Nov 28, 2018
gilteritinib approved for relapsed/refractory FLT3 mutated patients

Sep 1, 2020
Oral azacitidine approved as continuation therapy for intensively treated AML patient in CR1, unable to receive further therapy or HSCT

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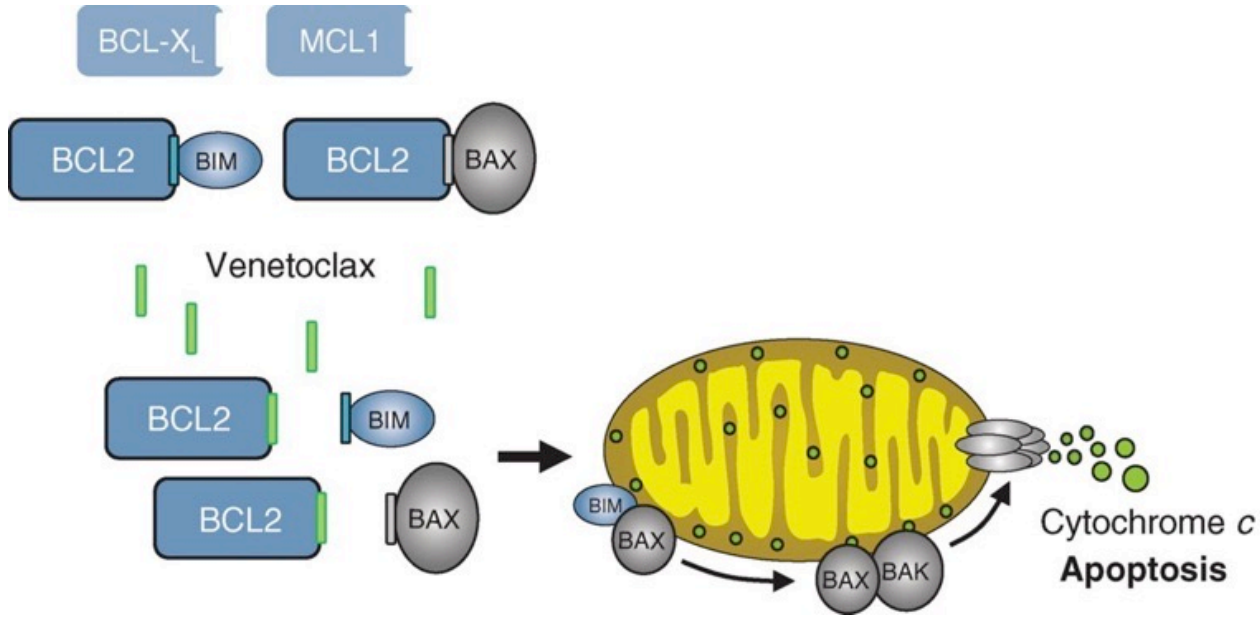
BCL2 in AML

- BCL2 inhibits apoptosis in normal and malignant cells
- BCL2 is overexpressed in AML cells
- Early BCL2 inhibitors (navitoclax) also inhibited BCL_{XL}
  - BCL_{XL} inhibition contributed to toxicity (thrombocytopenia)
- Oral BCL-2 inhibitor venetoclax is a BH-3 mimetic without activity against BCL_{XL}
- single-agent venetoclax ph1 in R/R AML showed modest efficacy, enriched in mIDH+ patients



Konopleva M, et al. Cancer Discov 2016;6:1106-1117

Venetoclax doublets in unfit, newly diagnosed AML

- Two multicenter, single-arm studies performed
  - Ph1b: Venetoclax + HMA (azacitidine or decitabine), prior HMA for MDS prohibited
  - Ph1/2: Venetoclax + low dose cytarabine (LDAC), prior HMA for MDS allowed

- Inpatient hospitalization mandated
  - Ramp up venetoclax over 3-5 days
  - WBC <25K at initiation of regimen
  - TLS ppx/monitoring x 24h after target venetoclax dose

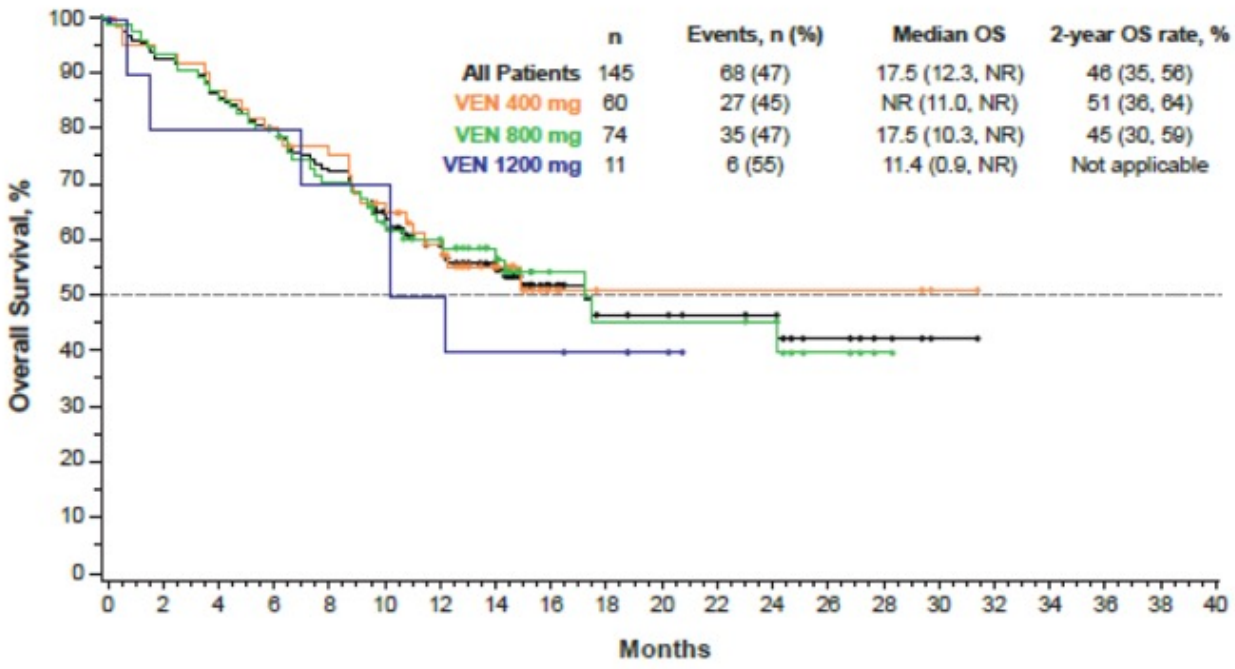
- Ineligible for induction defined as:
  - Age $\geq$75
  - Age >65 with comorbidity (poor PS, low EF/active CHF, pulmonary, renal, hepatic dysfunction, etc.)

- Primary endpoints: safety, efficacy

DiNardo CD, *Blood*. 2019 Jan 3;133(1):7-17
Wei et al. *J Clin Oncol* 2019, 37: 1277-84

Venetoclax + HMA phase 1b

Cohort	N (%)	CR + CRi	Median CR/CRi duration (95% CI)	Median OS (95% CI)
All patients	145	67%	11.3 mo.	17.5 mo.
VEN 400/HMA	44 (73)	73%	12.5 mo.	NR (11-NR)
Age 65-74	83 (57)	69%	12.9 mo.	17.7 mo.
Age ≥75	62 (43)	65%	9.2 mo.	11 mo.
De Novo AML	109 (75)	67%	9.4 mo.	12.5 mo.
Secondary AML	36 (25)	67%	NR (12.5, NR)	NR (14.6, NR)



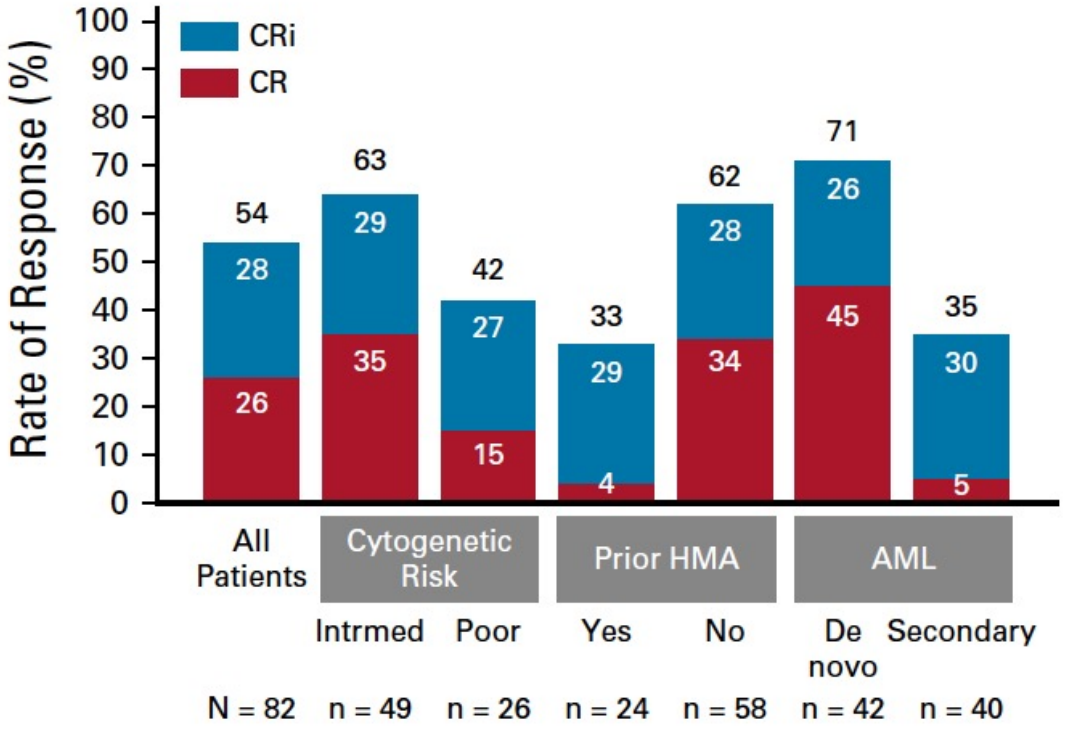
Better outcomes with NPM1 or IDH1/2 mutation (71-91% CR/CRi, median OS NR)
TP53 mutation did worse (47% CR/CRi, 5.6 mo median OS)

- 3-5 day ramp up from 100 mg to target venetoclax dose (400-1200 mg)
- Azacitidine 75 mg/m^2 SQ/IV days 1-7 or Decitabine 20 mg/m^2 IV days 1-5, repeat Q28 days

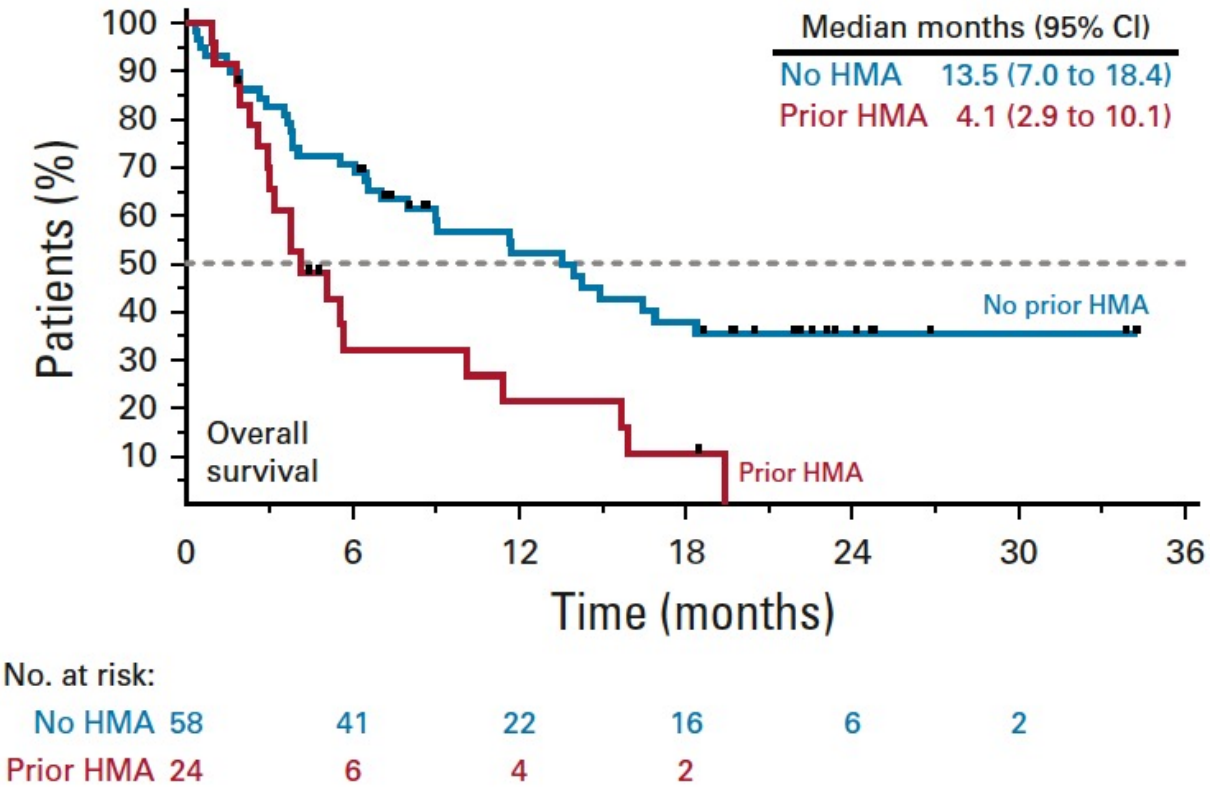
DiNardo CD, *Blood*. 2019 Jan 3;133(1):7-17

Venetoclax + LDAC

Median duration of response: 8.1 months



Median OS for all patients= 10.1 mo



- 3-5 day ramp up from 100 mg to target VEN dose (MTD= 600 mg/d)
- LDAC 20 mg/m^2 SQ, once daily d1-10, repeat Q28 days

Wei AH et al. *J Clin Oncol* 2019, 37: 1277-84

Venetoclax doublets: toxicity management

- Watch for myelosuppression and infections
  - Perform marrow biopsy after 3-4 weeks of venetoclax
    - hold chemo for recovery if MLFS
    - in responding patients, consider GCSF support for persistent neutropenia
  - Patients can take up to 4 cycles to respond
  - 30-day mortality 3%, 60 day 8% (sepsis, pneumonia, AML)

- Venetoclax dose reductions required for concurrent azole antifungals
  - 200 mg if moderate CYP3A4 inhibitors (fluconazole, isavuconazole)
  - 70-100 mg if strong CYP3A4 inhibitors (posaconazole, voriconazole)

- TLS not seen on trials, does occur rarely in practice
  - label recommends inpatient hospitalization for initiation/ramp up
  - cytoreduction prior to initiation
  - allopurinol, oral or IV hydration
  - lab monitoring within hours of first dose and each increase

DiNardo CD, *Blood*. 2019 Jan 3;133(1):7-17
Jonas BA and Pollyea DA, Leukemia. 2019 Dec;33(12):2795-2804
DiNardo CD and Wei AH, Blood. 2020 Jan 9;135(2):85-96.

VIALE-A Study Design

Eligibility

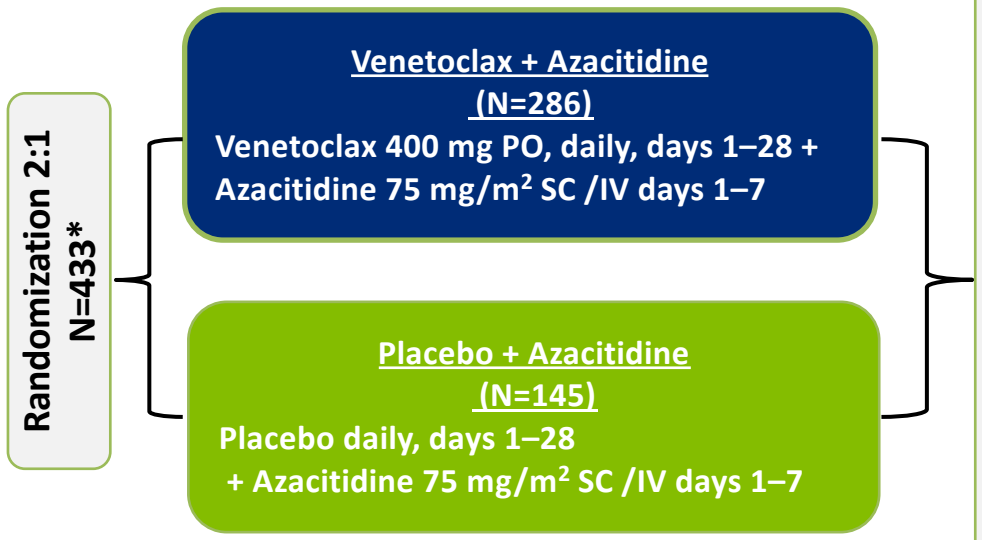
Inclusion

- 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 FEV1 ≤ 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 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

Endpoints

Primary

- Overall survival

Secondary

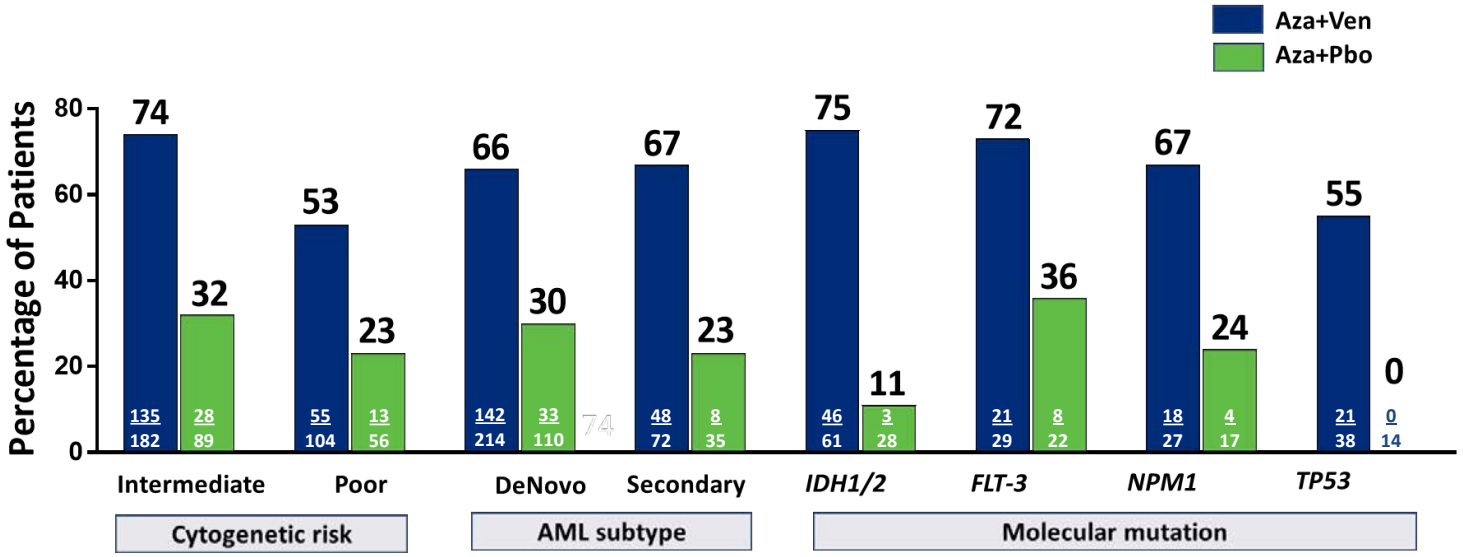
- CR+CRi rate
- CR+CRh rate
- CR+CRi and CR+CRh rates by initiation of cycle 2
- CR rate
- Transfusion independence
- CR+CRi rates and OS in molecular subgroups
- Event-free survival

DiNardo CD, et al. N Engl J Med. 2020 Aug 13;383(7):617-629

VIALE-A Response Rates

	VEN + AZA	AZA + placebo	P value
CR	27%	18%	<0.001
CR/CRi	66%	28%	<0.001
CR/CRh	65%	23%	<0.001
EFS	9.8 mo	7 mo.	<0.001
Transfusion independence	59.8%	35.2%	<0.001

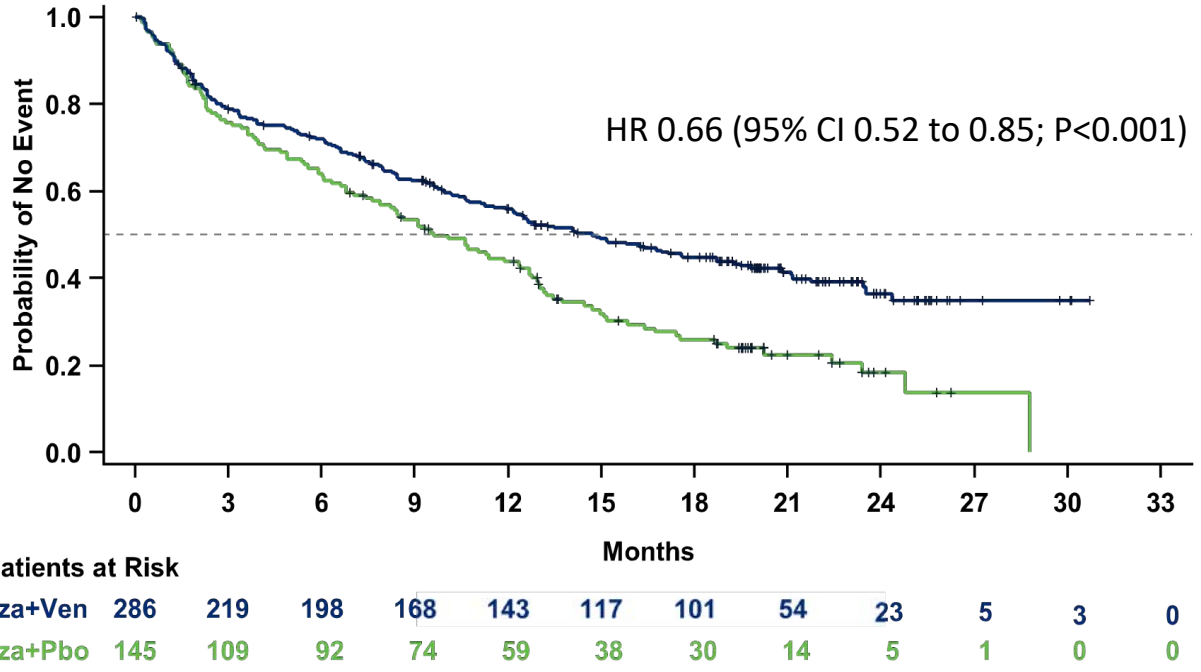
CR/CRi by treatment arm:



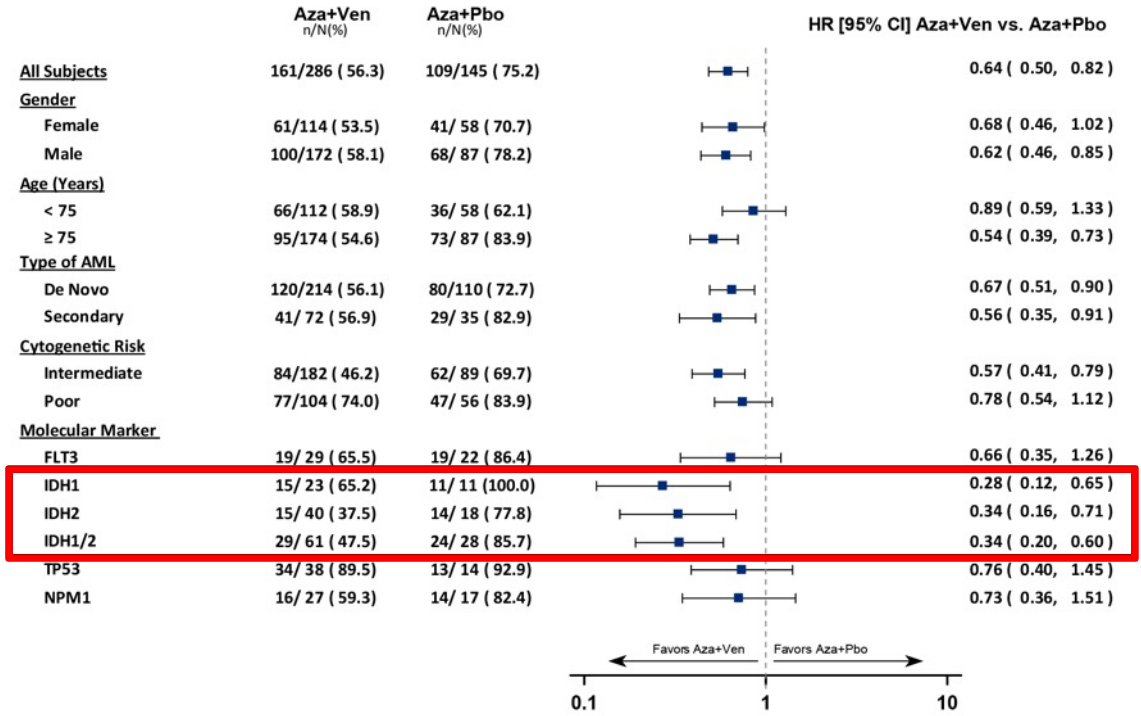
DiNardo CD, et al. N Engl J Med. 2020 Aug 13;383(7):617-629

VIALE-A Overall Suvival (primary endpoint)

	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)

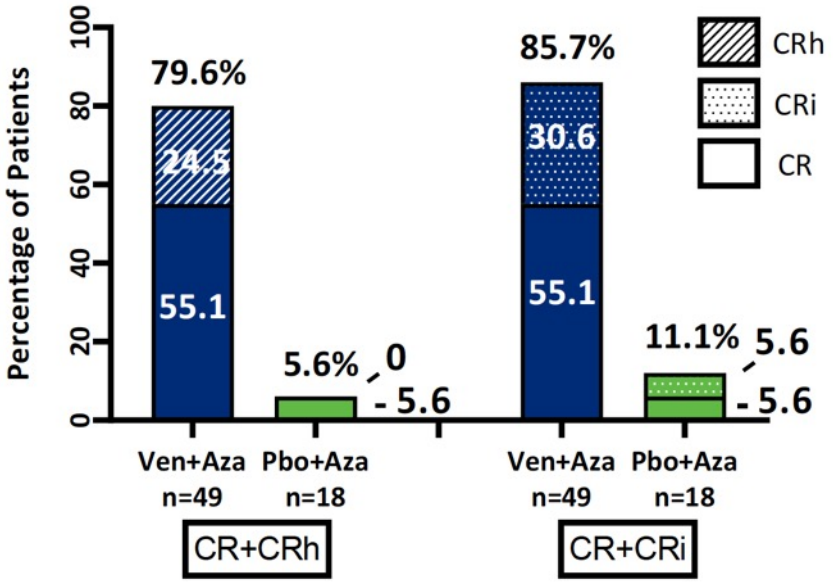


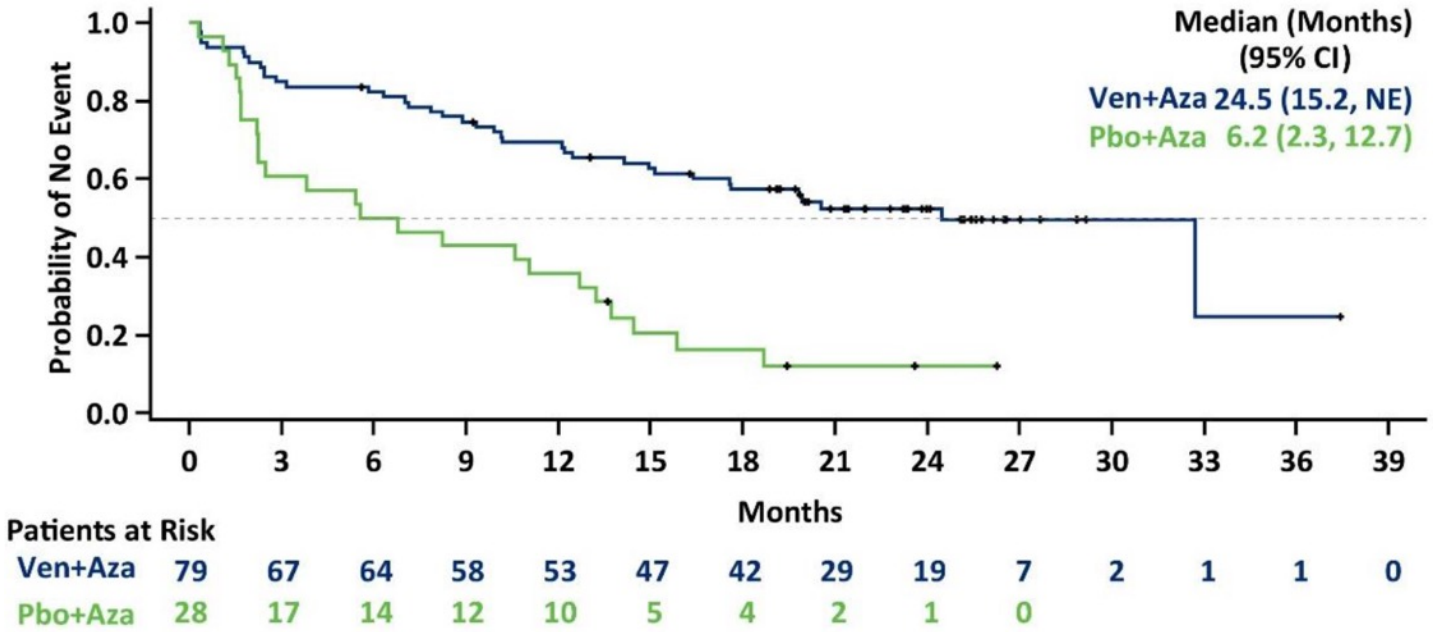
Median follow-up time: 20.5 months (range: <0.1 – 30.7)



DiNardo CD, et al. N Engl J Med. 2020 Aug 13;383(7):617-629

Ven/AZA Response and survival in mIDH1/2





Pooled analysis from IDH1/IDH2 mutation+ patients on phase 1b and VIALE-A

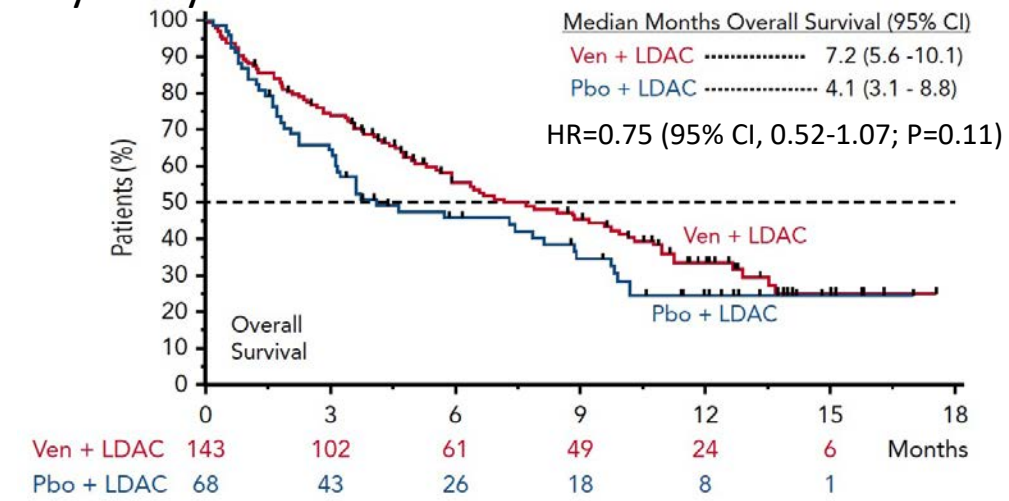
Pollyea DA, et al. ASH 2020 abstract #461

VIALE-C: Phase 3 LDAC + VEN/Placebo

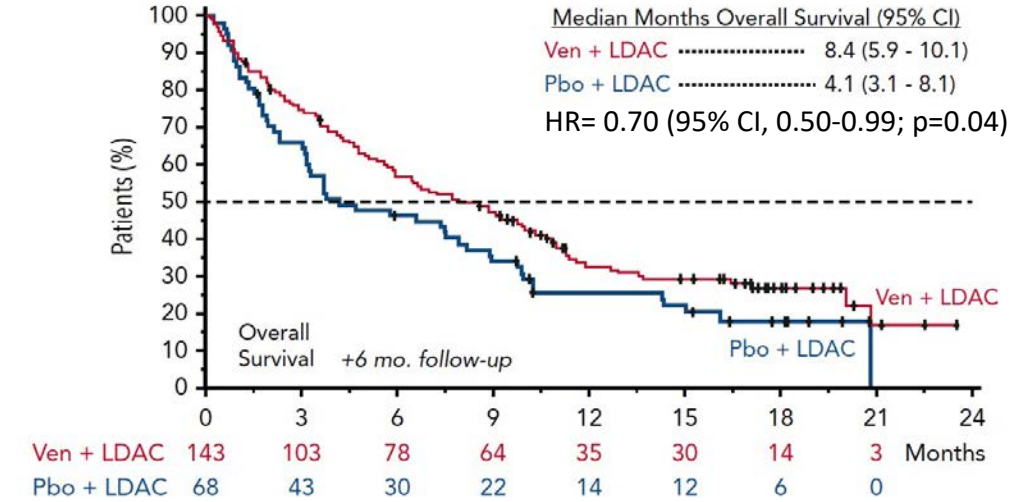
	VEN + LDAC	LDAC + placebo	P value
CR	27%	7%	<0.001
CR/CRi	48%	13%	<0.001
CR/CRh	47%	15%	<0.001
EFS	4.7 mo	2 mo.	0.002
Transfusion independence	41%	18%	0.002

- Phase 3 RCT for newly diagnosed AML, ineligible for intensive induction
- Prior HMA allowed
- Randomized 2:1 to LDAC 20 mg/m2 qd days 1-10 + 600 mg VEN/placebo
- 28 day cycles until progression or intolerance
- Primary endpoint: OS

Primary analysis



6 months longer follow-up



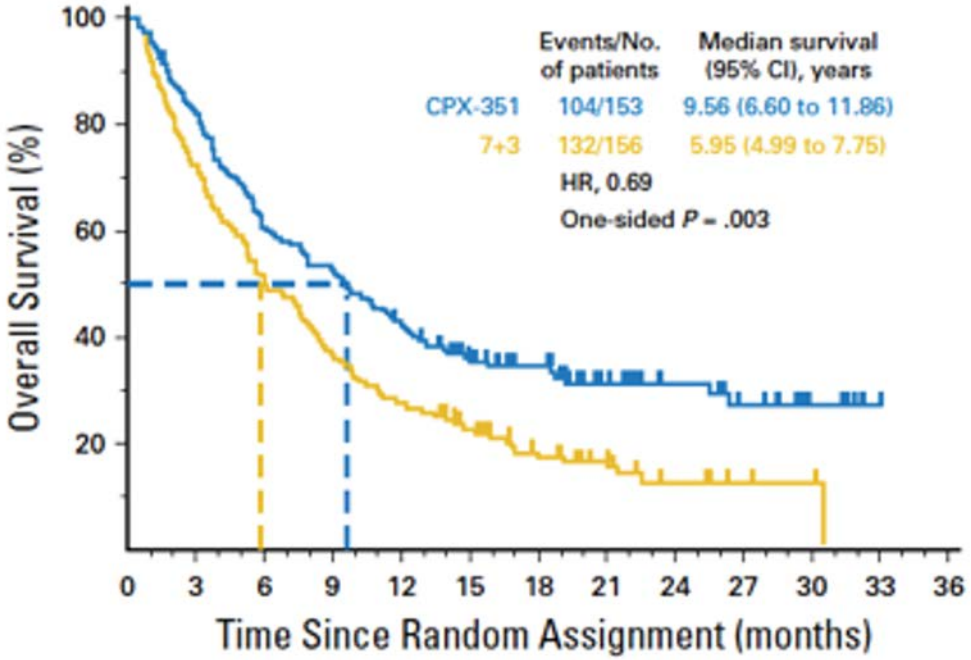
Wei AH, et al. Blood. 2020 Jun 11;135(24):2137-2145

Ongoing questions:

- Will ven/aza potentially replace intensive induction in older, fit patients?
- Can/should we ever stop ven/aza in responders?
- What is second line therapy for patients who relapse after or are refractory to VEN doublets?
- Can we use ven/aza prior to transplant?
- How do we combine ven with other agents?
  - Intensive chemo
  - Targeted agents (FLT3i, IDHi, etc.)

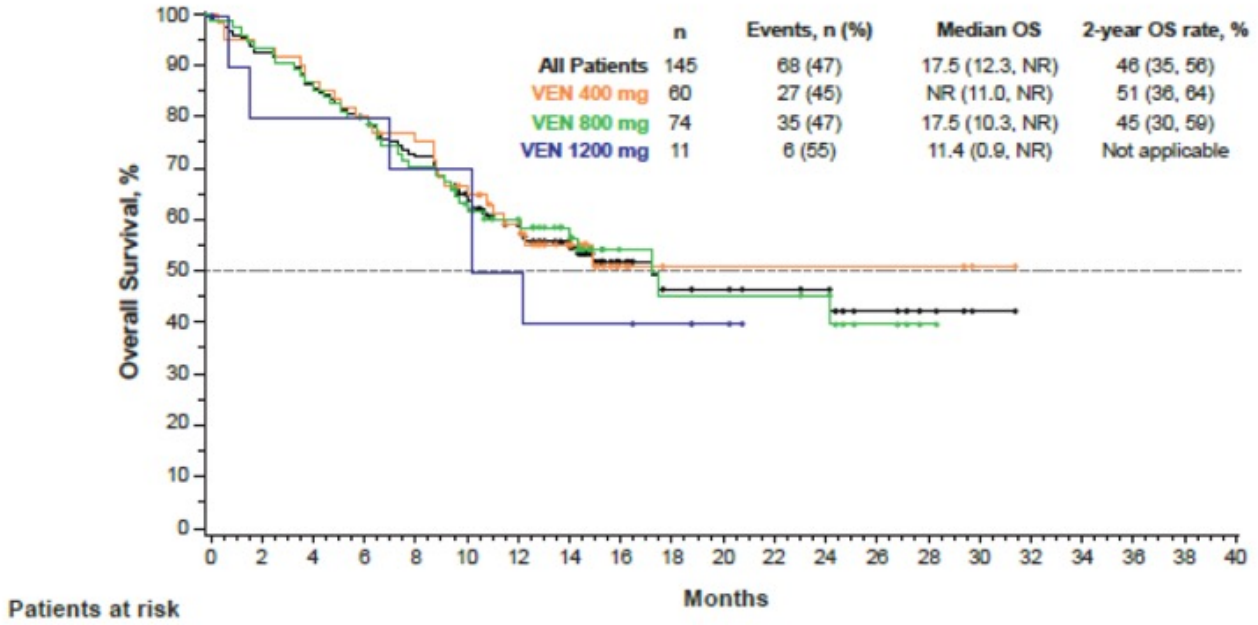
Age >65: to induce or not to induce?

Fit patients, age 60-75 with t-AML or AML-MRC



CPX-351 vs. 7+3

Unfit patients, age >65



Venetoclax+ HMA

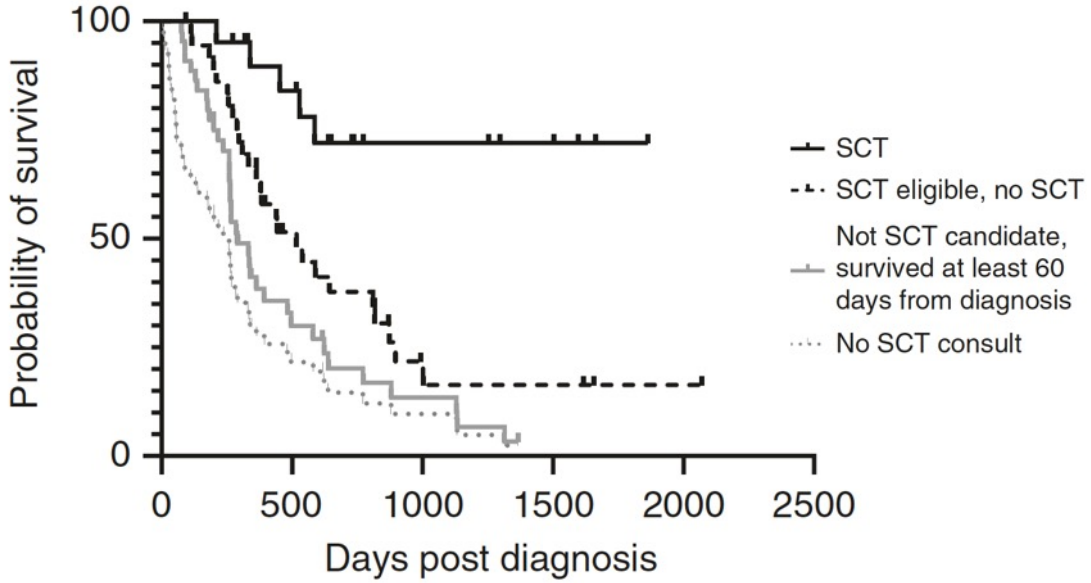
Lancet J, et al. J Clin Oncol. 2018 Sep 10;36(26):2684-2692
DiNardo CD, *Blood*. 2019 Jan 3;133(1):7-17

Transplant after frontline venetoclax + azacitidine

- 119 newly diagnosed AML, age ≥60, non-CBF, at single center

- 58 (49%) referred for SCT consult
- 21 (18%) received SCT
  - 17/21 (81%) in CR/CRi at SCT
  - Median age 65 (range 60-73)
- 31 (31%) found eligible but deferred SCT

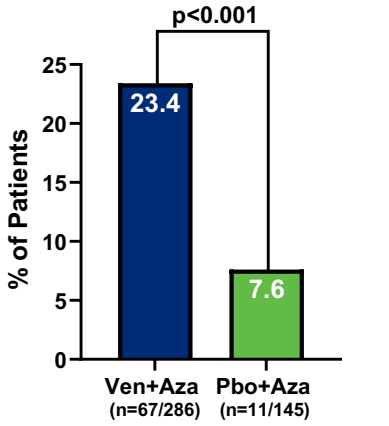
- SCT and SCT-eligible/non-transplanted groups had similar comorbidity
- SCT occurred at a median of 176 days from dx
  - 2 MAC preparative regimens, remainder RIC/NMA
  - Only 5 relapses post-SCT (24%) and 2 TRM deaths (10%)



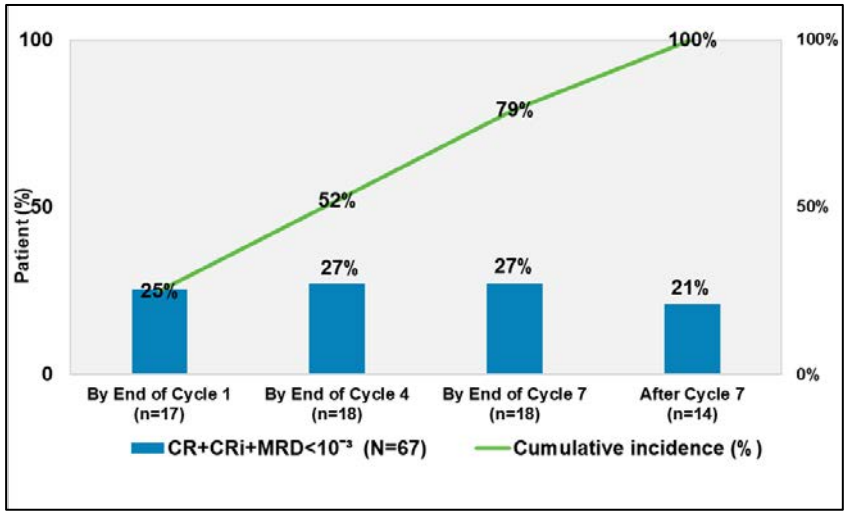
SCT vs. SCT-eligible, no SCT p=0.002
Median follow up 24.1 months

Pollyea DA, et al. Bone Marrow Transplant. 2021 Oct 13 epub

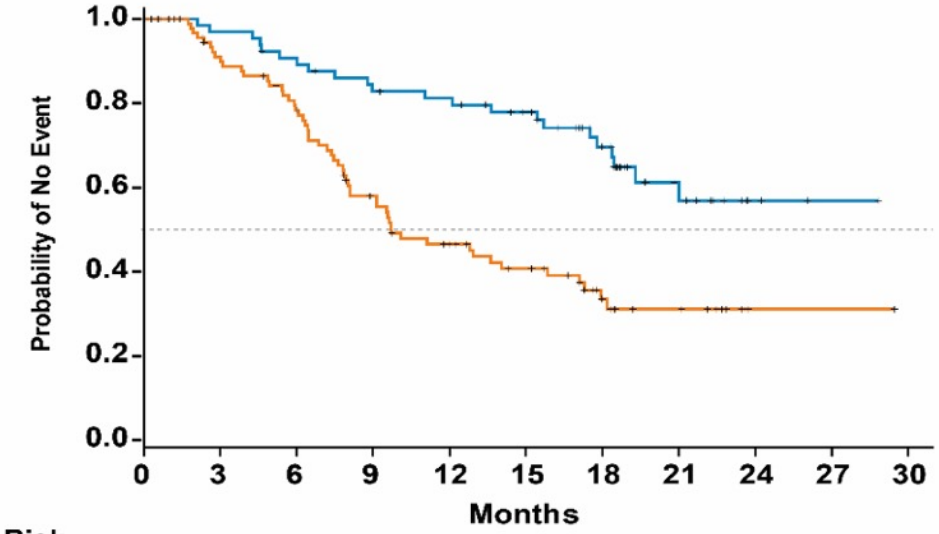
How long is optimal therapy with ven/HMA?



CR+CRi+MRD<10^{-3}



Duration of remission



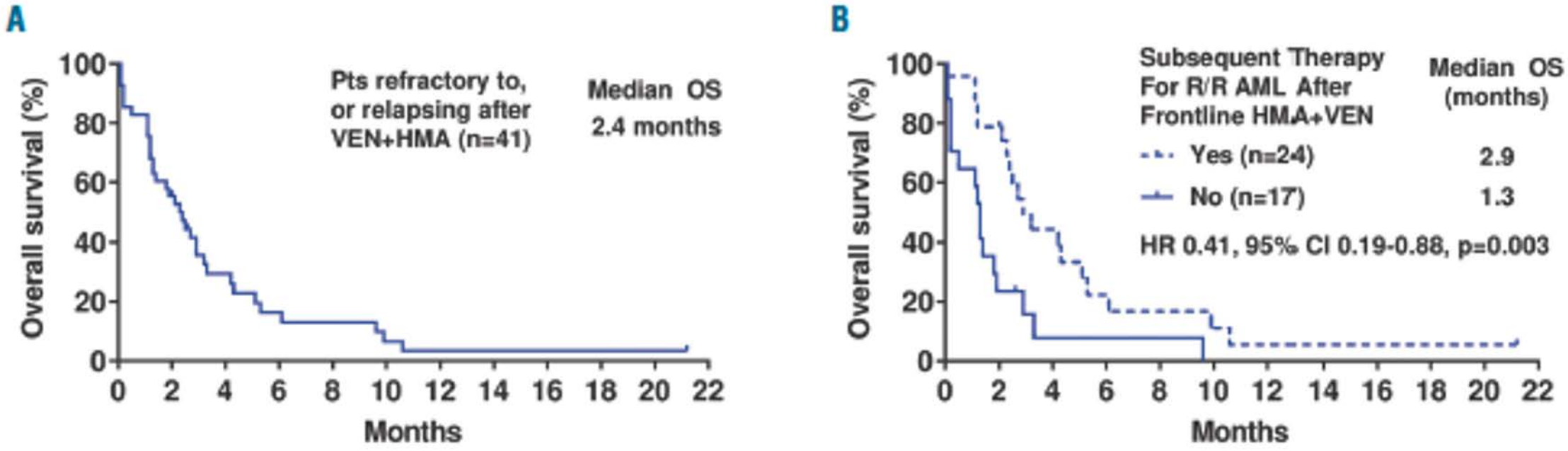
Patients at Risk											
CR+CRi+MRD<10^{-3}	67	63	58	52	50	44	30	14	3	1	0
CR+CRi+MRD≥10^{-3}	97	80	67	46	34	27	14	9	1	1	0

No difference in OS among patients who became MRD(-) post cycle 1 and those who became MRD(-) thereafter

Duration of remission	# of events	12-month, % (95% CI)	18-month % (95% CI)	Median DoR, months (95% CI)
CR+CRi+MRD<10^{-3}	22	81.2 (69.3, 88.9)	69.6 (55.9, 79.8)	NR (19.3 – NR)
CR+CRi+MRD≥10^{-3}	54	46.6 (35.6, 56.8)	33.5 (22.9, 44.5)	9.7 (8.0 – 15.8)

Pratz KW, et al. EHA 2021 Abstract S137

Survival after progression to venetoclax doublets



Maiti A, et al. Haematologica. 2021 Mar 1;106(3):894-898

Conclusions

- Venetoclax doublets have opened up new treatment options and improved outlook for many patients with AML
- There is a learning curve to giving this regimen
- Future studies will clarify role of this regimen in fit, which may obviate the question of whether fitness should determine treatment choice
- Validation of transplant outcomes especially important for those considering curative options
- Patients with IDH mutation derive particular benefit from frontline ven/aza
- Role of MRD to be defined but may allow shorter course ven/HMA therapy for optimal responders.