Acute Myeloid Leukemia Trials in Older Adults

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Disclosures- Richard M. Stone, MD

- **Consulting relationships past three years:**
  - **AbbVie*; Actinium, Agios*; Amgen; Argenix (DSMB); Arog*; Astellas; AztraZenaca; BerGenBio; Biolinerx, Celgene (includes DSMB and steering committee);Daiici-Sanko; Elevate Bio; Fujifilm; GemoAb; Janssen; Jazz; Juno; Lilly* (only clin res support); Macrogenics; Novartis*; Ortsuka; Pfizer; Roche; Stemline; Syndax; Syntrix (DSMB only); Syros; Takeda (DSMB), Trovagene**
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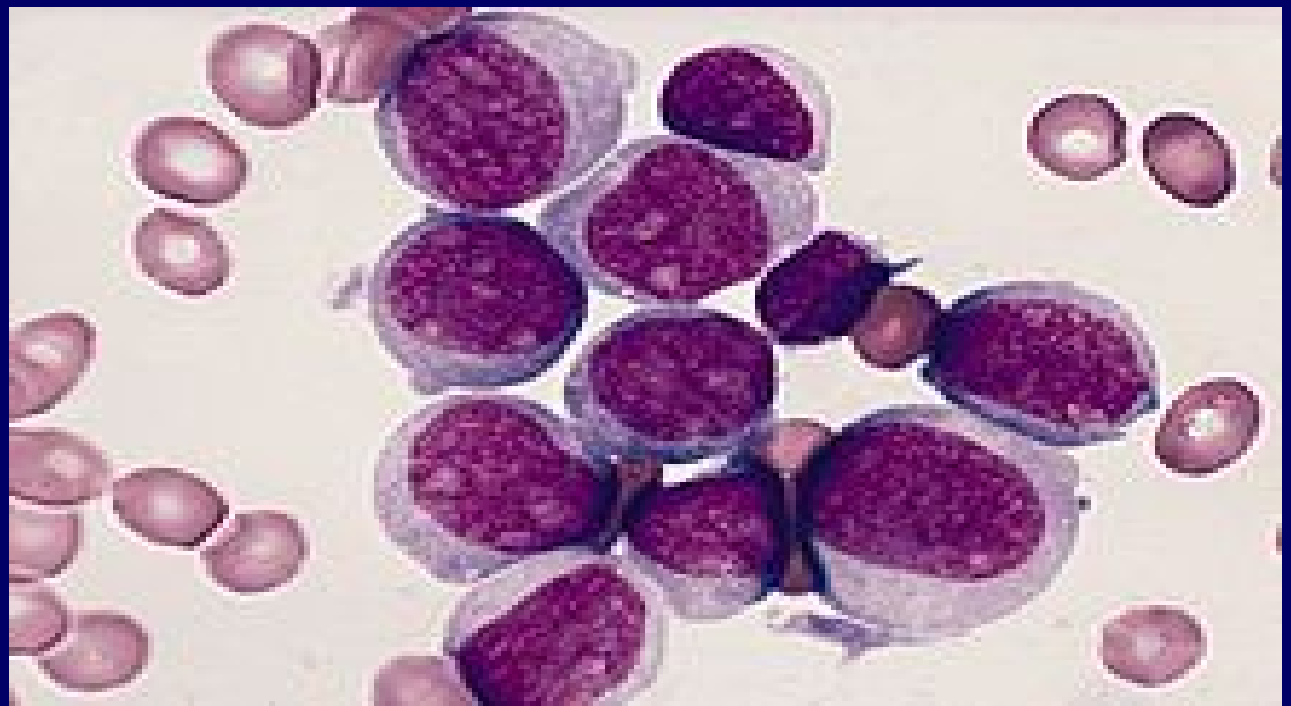
  - **None**

AML: What is it and how did it get there?

- Unbridled proliferation of hematopoietic stem cells (myeloid lineage) resulting in marrow failure and patient death unless successfully treated
- Risk factors: AGE, prior chemo for other cancers, ionizing radiation, industrial solvents (last 3 probably <10% of incidence=15K new US cases annually); unusual but kindreds exist w germ-line mutations in >10 genes



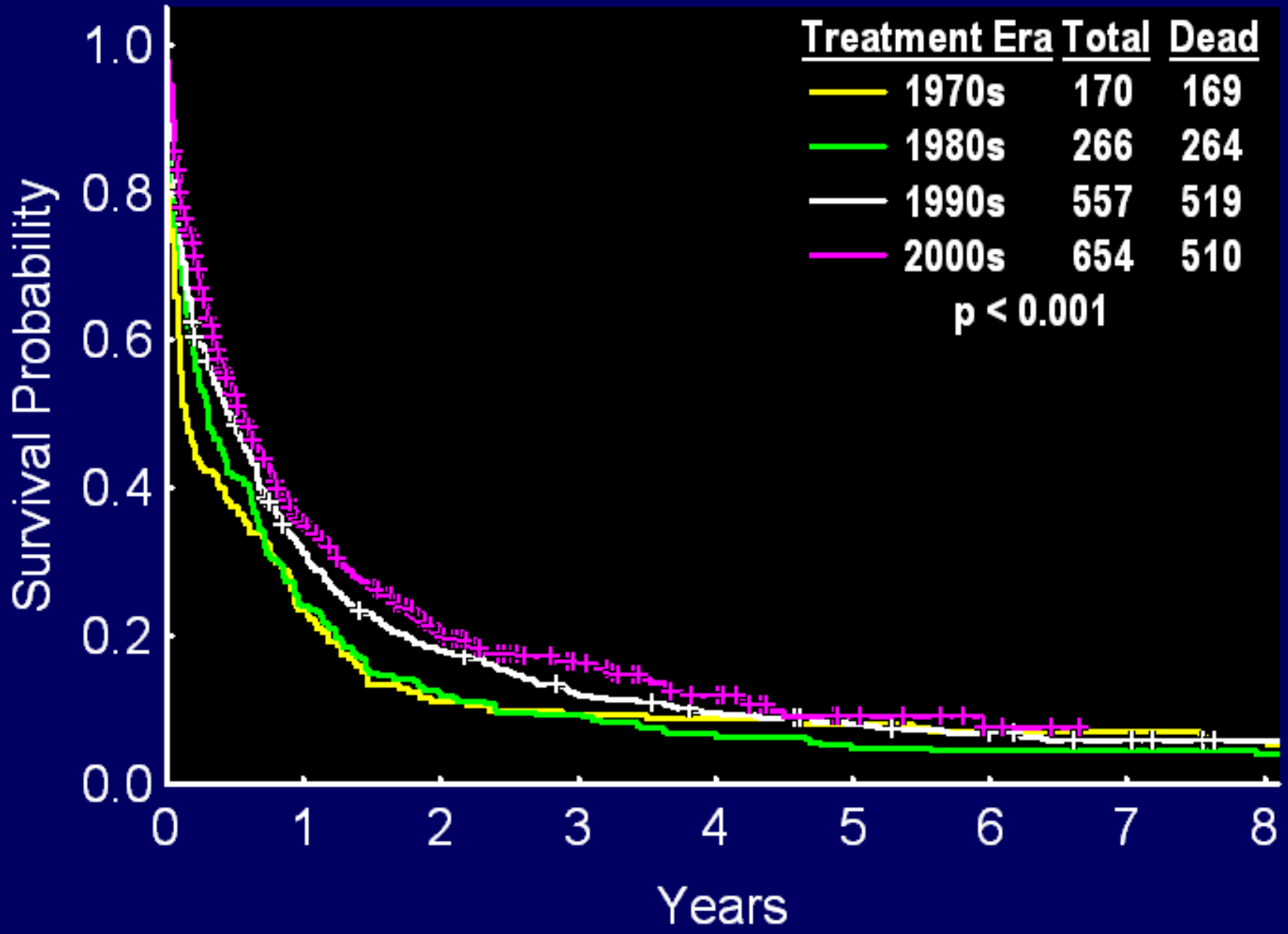
Current Risk Assessment in AML

Key Prognostic Data in AML in 2021

Patient **age (** FH, bleeding hx; **?Therapy related; ?Prior MDS**)	
Cytogenetics / fusion mRNA (screen for APL, MLL, Ph+, CBF)	
Multiparameter flow	
Molecular studies:	
• ***FLT3*** **ITD (internal tandem duplication) mutation**	*Unfavorable*
• ***NPM1*** **mutation**	*Favorable*
• ***CEBPA*** **biallelic mutation**	*Favorable*
• *RUNX1, TP53, ASXL1 (? KIT in CBF)*	*Unfavorable*

Of Future Importance: mutation status of ***IDH1/2, DNMT3A, TET2***, etc.

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

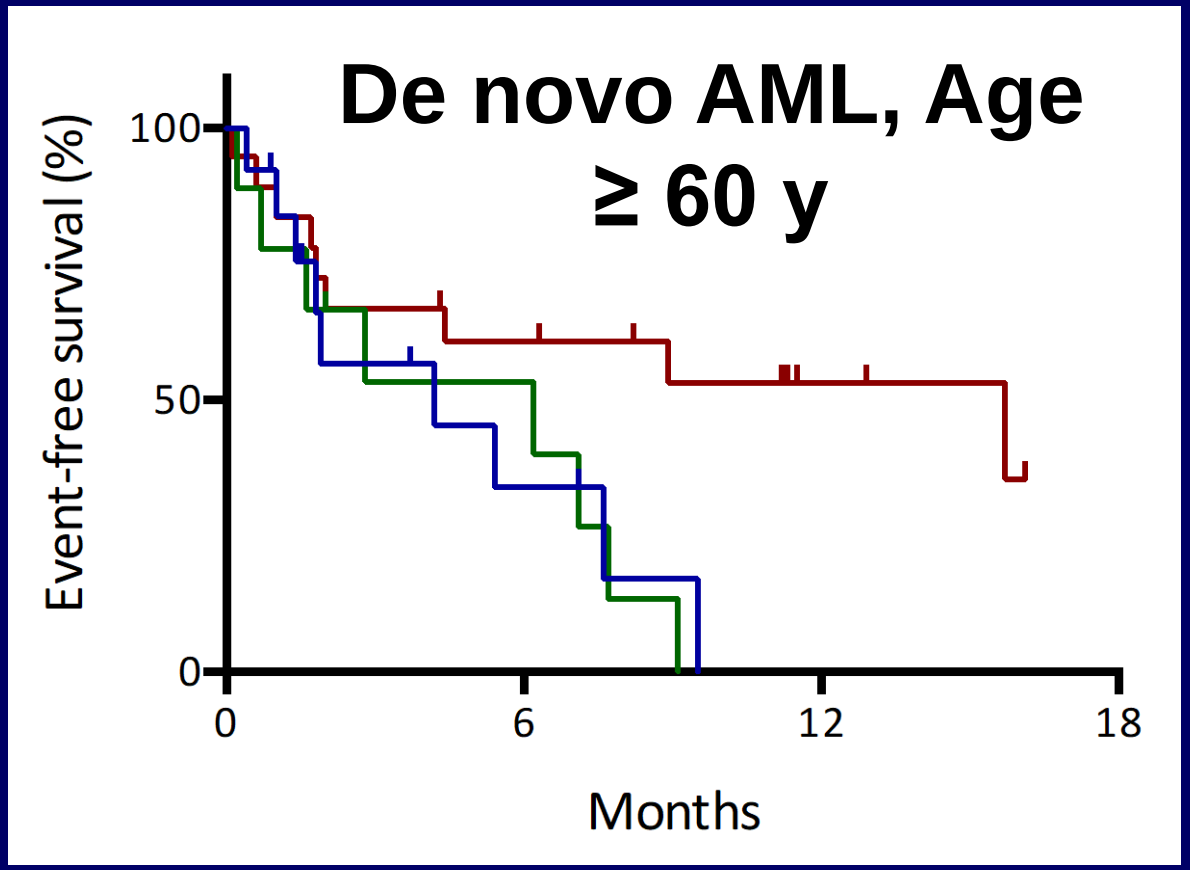


Why Do Older Patients With AML Experience Inferior Outcomes?

- 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.

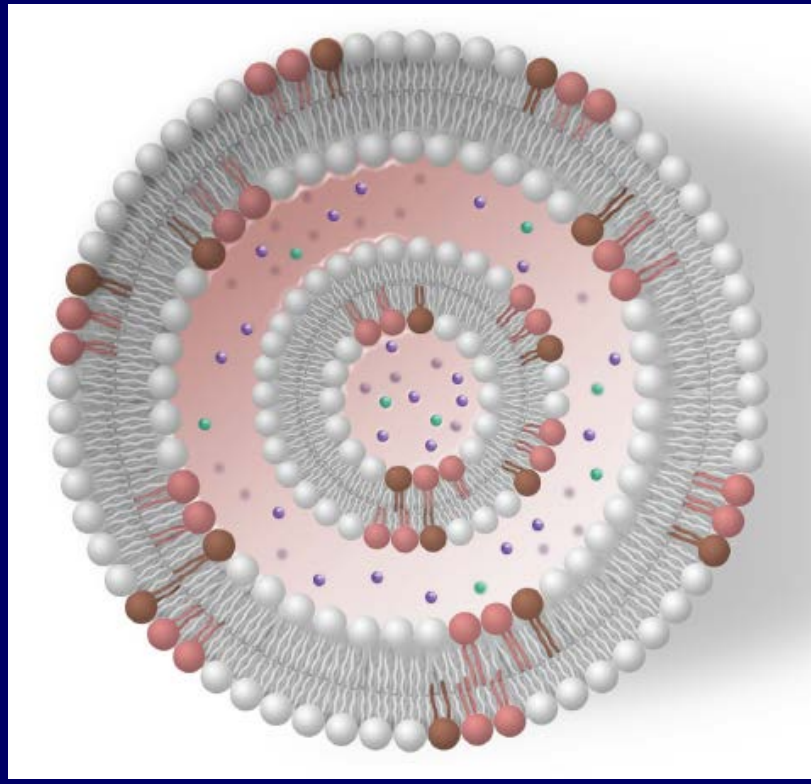
Heterogeneity and Hope in Older Adults with AML

- Host Factors: Fitness (Geriatric Assessment [Klepin H et al, J Geriatr Oncol, 2020]), comorbidities, age
- Disease Features: Cytogenetic and Molecular features

- 3 new recently approved drugs based on trials for older adults
  - AZA/VEN, upfront age>75, unfit
  - CPX-351, upfront, age 60-75, fit
  - CC-486 (oral aza) , maintenance, age >55, fit

CPX-351

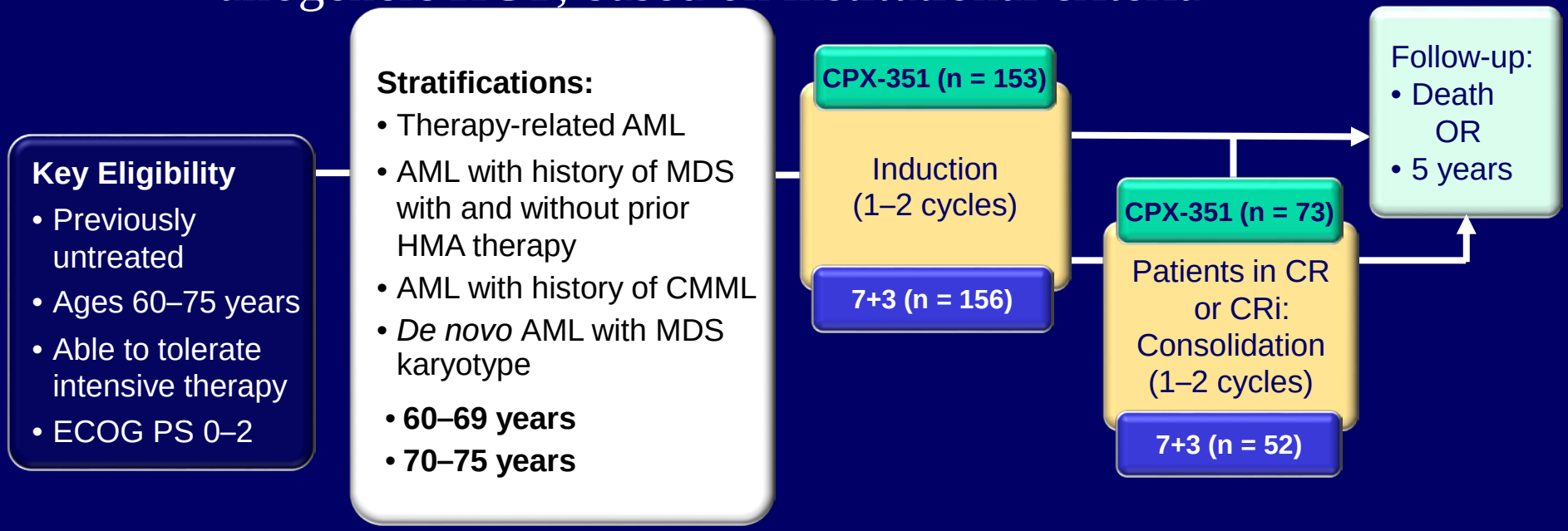
- CPX-351 is a liposomal co-formulation of cytarabine and daunorubicin designed to achieve synergistic antileukemia activity
  - 5:1 molar ratio of cytarabine:daunorubicin provides synergistic leukemia cell killing *in vitro*[1]
  - In patients, CPX-351 preserved delivery of the 5:1 drug ratio for over 24 hours, with drug exposure maintained for 7 days[2]
  - Selective uptake of liposomes by bone marrow leukemia cells in xenograft models[3]



. Tardi P et al. *Leuk Res.* 2009;33(1):129–139.
2. Feldman EJ et al. *J Clin Oncol.* 2011;29(8):979–985;
3. Lim WS et al. *Leuk Res.* 2010;34(9):1245–1223.

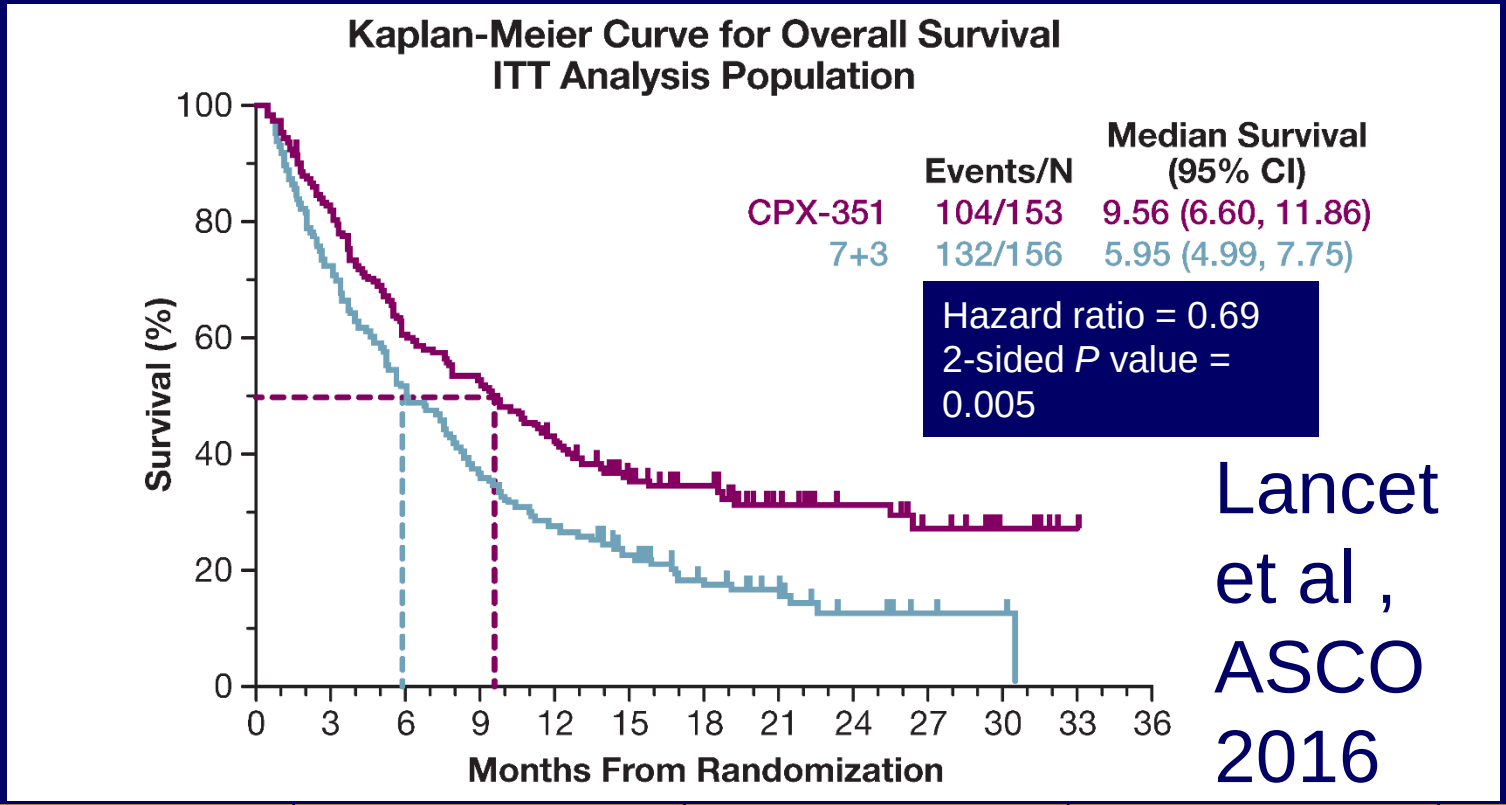
CPX-351 Phase III Study Design

- Randomized, open-label, parallel-arm, standard therapy–controlled
  - 1:1 randomization, enrolled from December 2012 to November 2014
  - Patients with CR or CRi could be considered for allogeneic HCT, based on institutional criteria



recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; HMA, hypomethylating agents; MDS, myelodysplastic syndrome.

1. World Health Organization. *WHO Classification of Tumours of Haematopoitic and Lymphoid Tissues*. Swerdlow S et al (ed). Lyon, IRAC Press, 2008.



Lancet et al , ASCO 2016

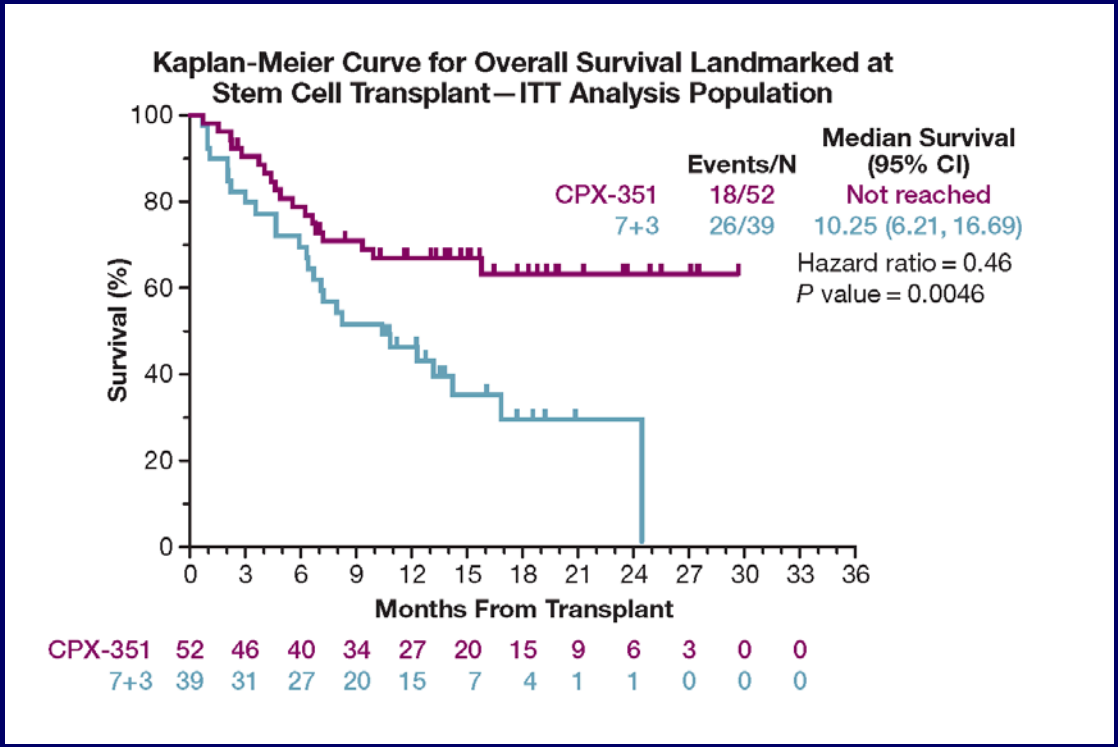
	CPX-351 (n = 153)	7+3 (n = 156)	Odds ratio	*P* value
CR+CRi	47.7%	33.3%	1.77 (1.11, 2.81)	0.016
HSCT rate	34.0%	25.0%	1.54 (0.92, 2.56)	0.098
Deaths ≤30 days*	5.9%	10.3%		
Deaths ≤60 days*	13.7%	21.2%		

were alive: CPX-351 (n = 49): 589 days (range: 44-1007); 7+3 (n = 24): 601 days (range: 417-917).

CI, confidence interval; CR, complete response; CRi, CR with incomplete platelet or neutrophil recovery; HSCT, hematopoietic stem cell transplant.

Survival Landmarked from Time of Transplant

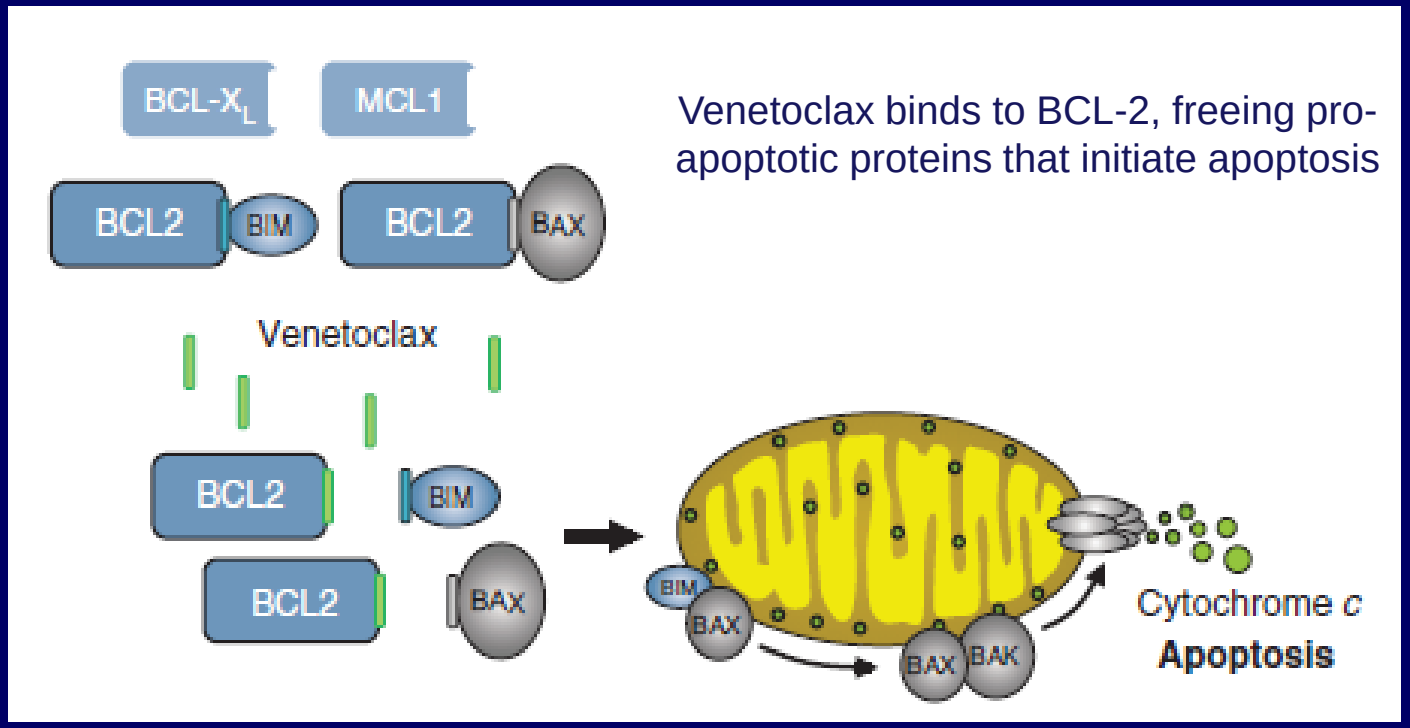
- CPX-351 median OS not reached vs 10.25 months for 7+3
  - HR of 0.46 favoring CPX-351 (*P*=0.0046)
  - Cox proportional hazards HR, including transplant as a time-dependent covariate, was 0.51 (95% CI, 0.35–0.75; *P*=0.0007), favoring CPX-351



Lancet et al, ASH 2016

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.

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

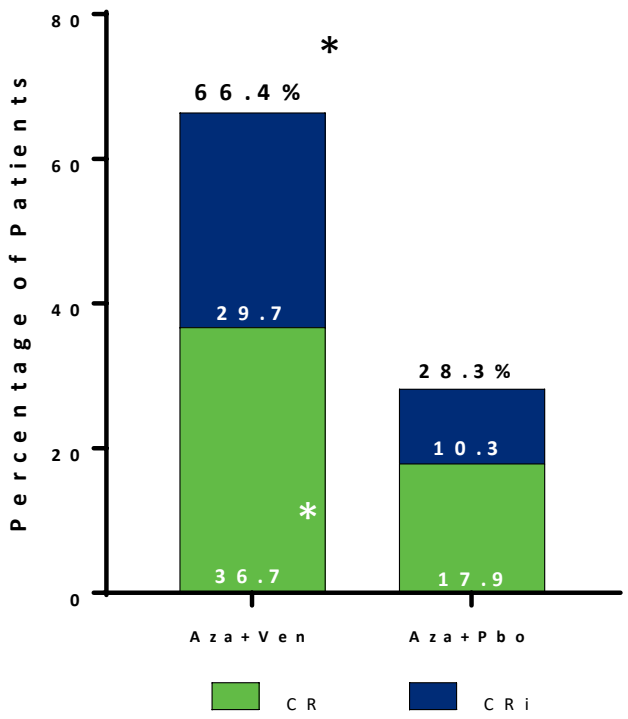
- CR+CRi rate
- CR+CRh rate
- CR+CRi and CR+CRh rates by initiation of cycle 2
- CR rate
- Transfusion independence
- CR+CRi rates and OS in molecular subgroups
- Event-free survival

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

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

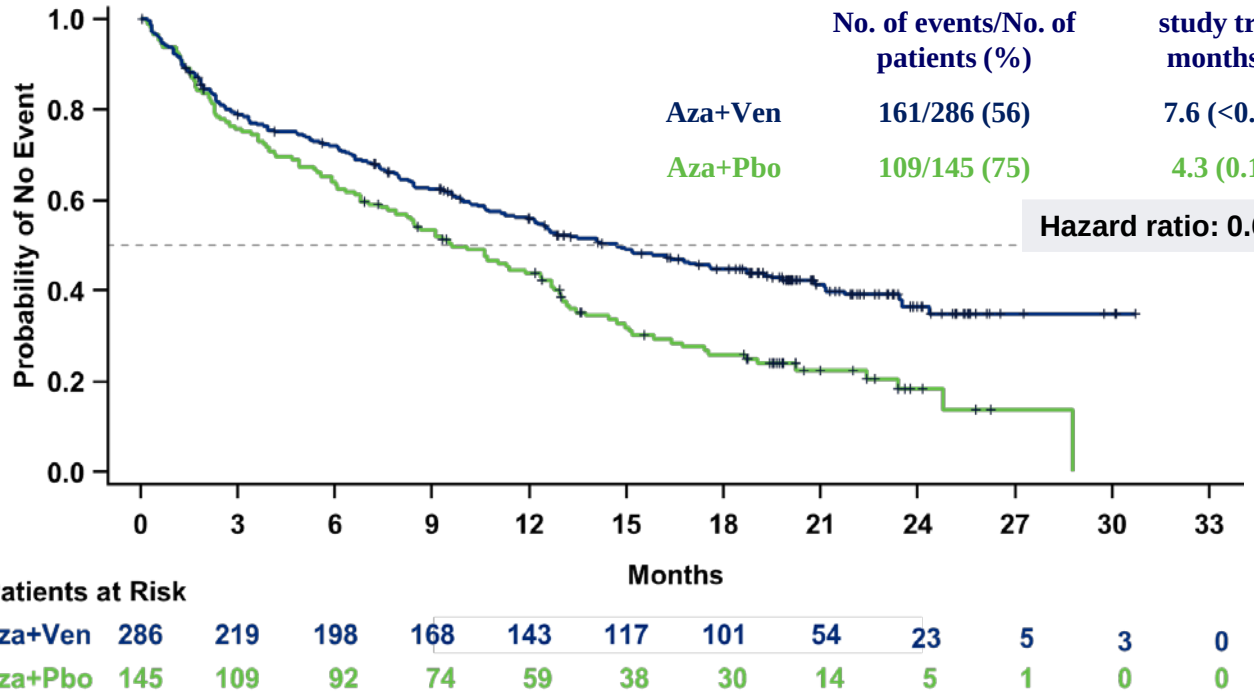


	No. of treatment cycles, median (range)	Median time to CR/CRi, Months (range)	*CR+CRi by initiation of Cycle 2, n (%)
Aza + Ven (n = 286)	7.0 (1.0 – 30.0)	1.3 (0.6 – 9.9)	124 (43.4)
Aza + Pbo (n = 145)	4.5 (1.0 –26.0)	2.8 (0.8 – 13.2)	11 (7.6)

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

DiNardo CD et al. NEJM 2020

AZA ± VEN in AML: Overall Survival



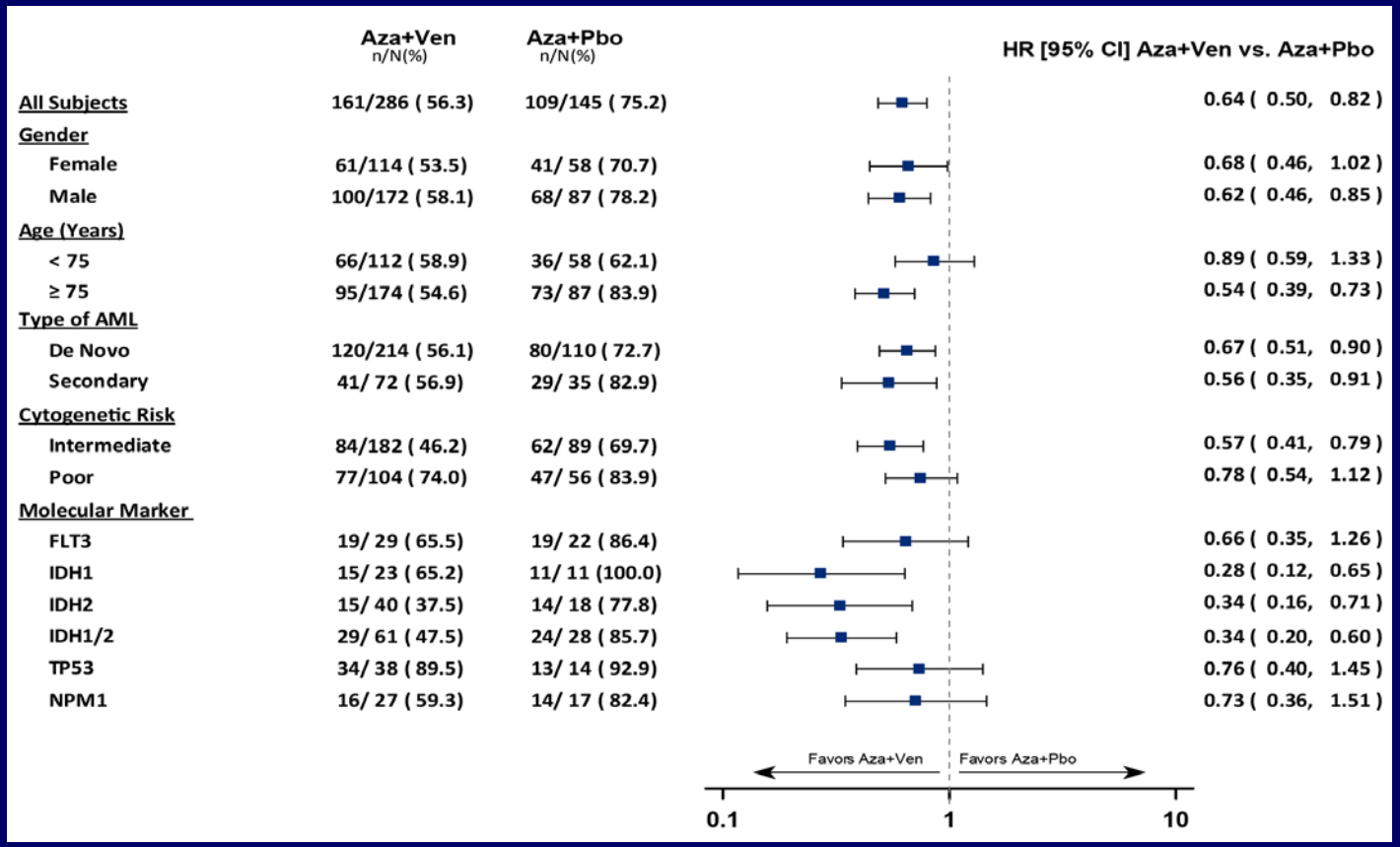
	No. of events/No. of patients (%)	Median duration of study treatment, months (range)	Median overall survival, months (95% CI)
Aza+Ven	161/286 (56)	7.6 (<0.1 – 30.7)	14.7 (11.9 – 18.7)
Aza+Pbo	109/145 (75)	4.3 (0.1 – 24.0)	9.6 (7.4 – 12.7)

Hazard ratio: 0.66 (95% CI: 0.52 – 0.85), *P* <.001

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

DiNardo CD et al. NEJM 2020

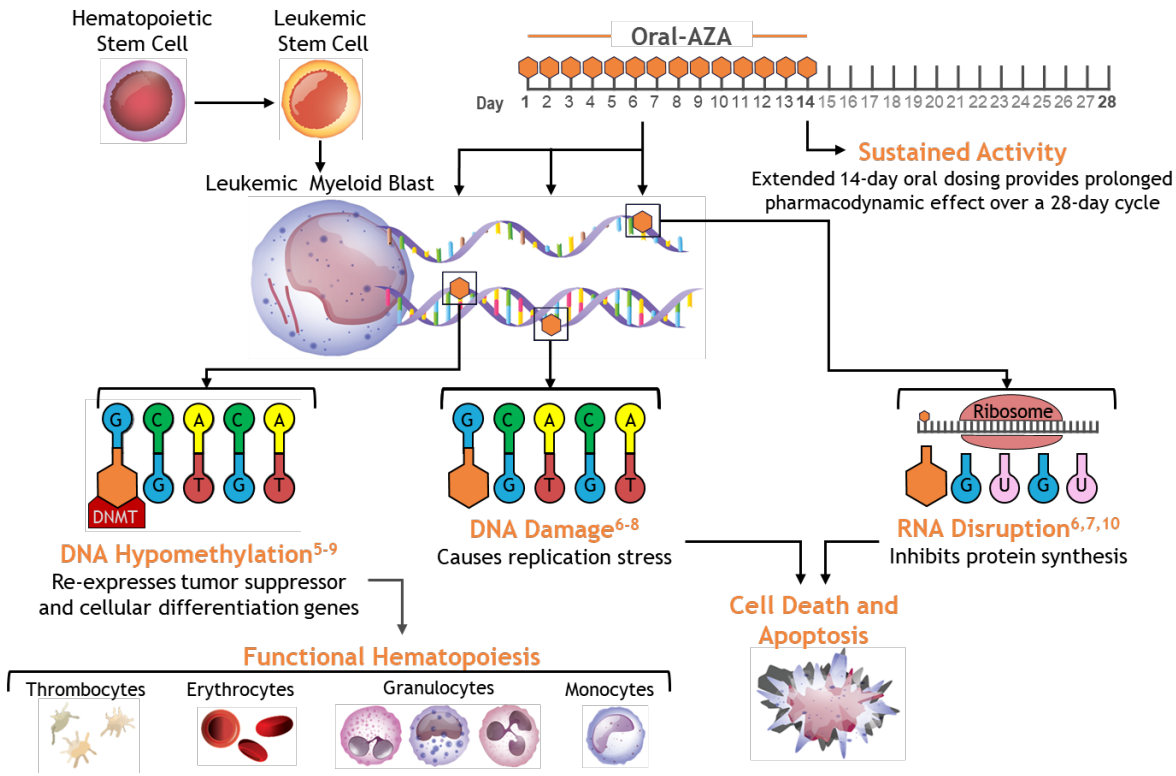
AZA ± VEN in AML: Survival by Subgroups



DiNardo CD et al. NEJM 2020

Oral azacitidine

- Oral azacitidine (Oral-AZA [CC-486]):
  - Oral HMA with a distinct PK/PD profile from injectable AZA; the two are not bioequivalent[1,2]
  - Approved in the United States for continued Tx of adult pts with AML in first CR/CRi post-IC and not able to complete intensive curative therapy (eg, HSCT)[3]
- Oral dosing allows for extended drug exposure during each Tx cycle to prolong AZA activity[1,2]

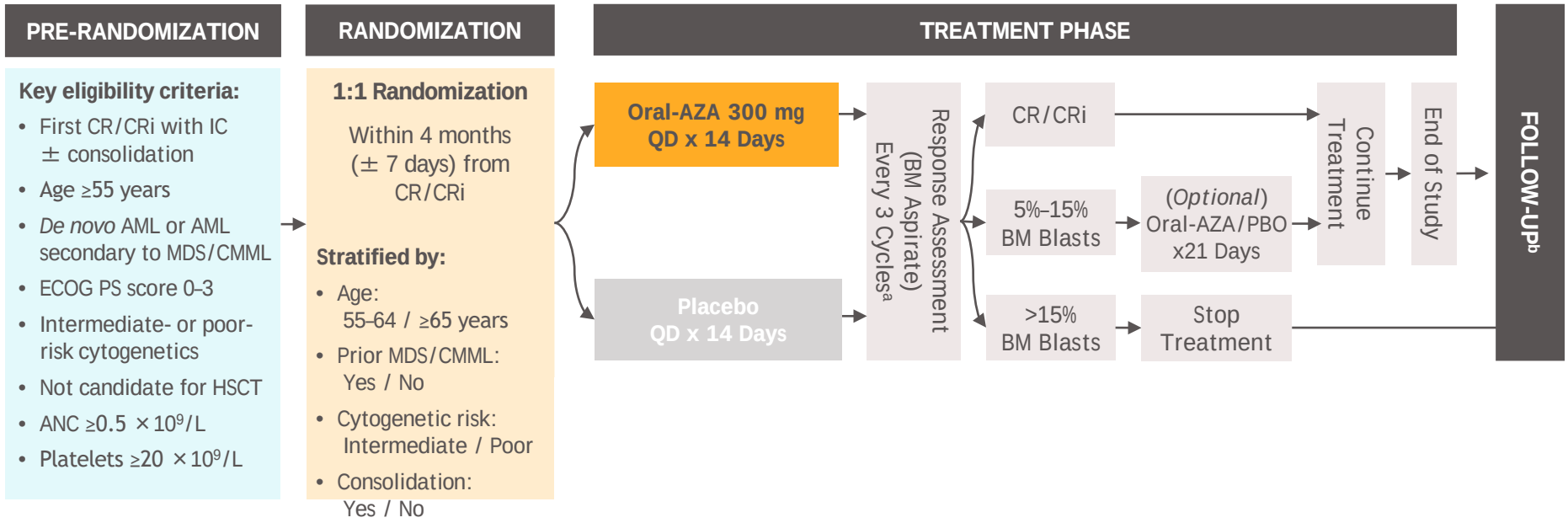


Garcia-Manero et al. *J Clin Oncol*. 2011;29(18):2521–7. 2. Laille et al. *PLoS One*. 2015;10(8):e0135520. 3. ONUREG® (azacitidine) tablets [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; Rev. 9/2020. 4. Savona et al. *Am J Hematol*. 2018;93(10):1199–206. 5. Stresemann et al. *Mol Cancer Ther*. 2008;7:2998–3005. 6. Hollenbach et al. *PLoS One*. 2010;5(2):e9001. 7. Scott LJ. *Drugs*. 2016;76(8):889–900. 8. Stresemann C, Lyko F. *Int J Cancer*. 2008;123(1):8–13. 9. Aimiuwu et al. *Blood*. 2012;119(22):5229–38.

AML, acute myeloid leukemia; AZA, azacitidine; CR, complete remission; CRi, CR with incomplete blood count recovery; HMA, hypomethylating agent; HSCT, hematopoietic stem cell transplant; IC, intensive chemotherapy; PD, pharmacodynamic; PK, pharmacokinetic; pts, patients; Tx, treatment.

QUAZAR AML-001: Study design and eligibility criteria

International, multicenter, placebo (PBO)-controlled, double-blind, randomized, phase III study of Oral-AZA as maintenance Tx in pts with AML in first remission post-IC

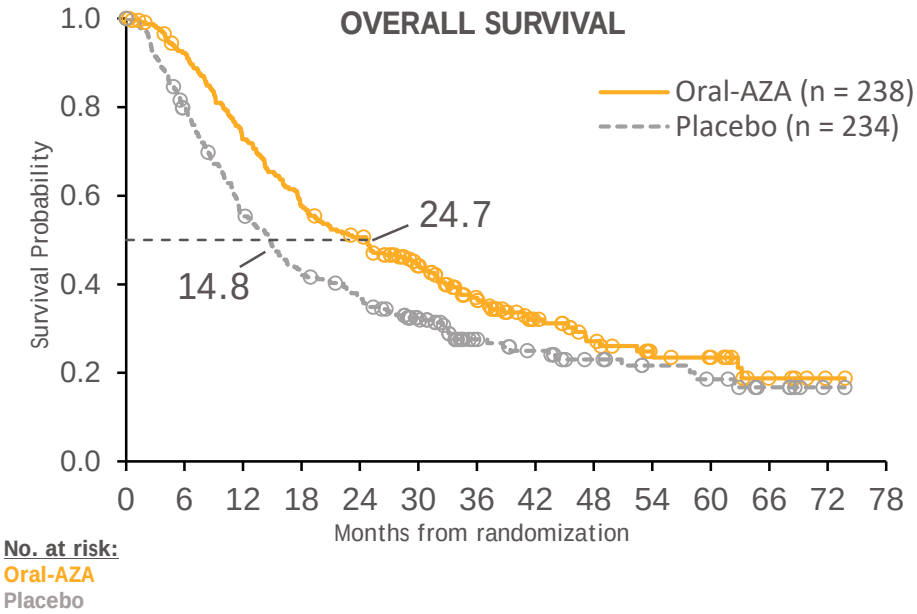


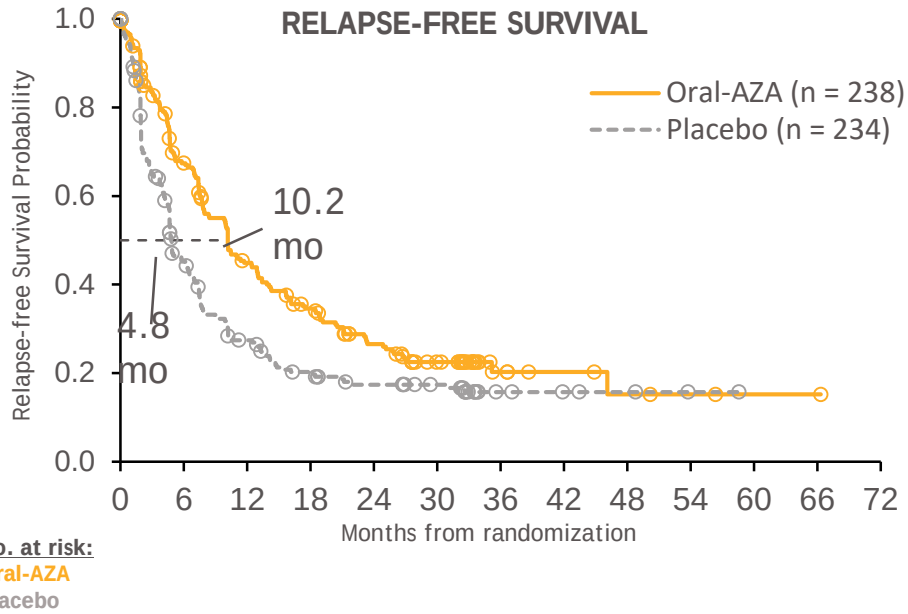
[a]BM aspirates were collected every 3 cycles through cycle 24, at cycle 30 and cycle 36, and as clinically indicated thereafter. BM assessments were also performed as clinically indicated. [b]Patients were followed until death, withdrawal of consent, study termination, or loss to follow-up.

AML, acute myeloid leukemia; ANC, absolute neutrophil count; AZA, azacitidine; BM, bone marrow; CMML, chronic myelomonocytic leukemia; CR, complete remission; CRi, CR with incomplete blood count recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; HSCT, hematopoietic stem cell transplant; IC, induction chemotherapy; IWG, International Working Group; MDS, myelodysplastic syndromes; PBO, placebo. Wei A, et al , NEJM, 2020.

Overall and relapse-free survival

- Oral-AZA 300 mg QD was associated with significantly improved overall survival (OS) (*P* = 0.0009) and relapse-free survival (RFS) (*P* = 0.0001) vs. PBO[1]





Wei A, et al NEJM, 2020

New RX Algorithm in Older Adults with AML

- FIT, FLT3 mutation (TKD or ITD): 3+7+mido
- FIT, CBF: 3+7+GO
- FIT, MRC-related cytogenetics, h/o MDS, prior rx for CA: CPX-351
- FIT, NOS: 3+7
- UNFIT, or >75 yo: aza (7d) +venetoclax
- UNFIT, IDH1 or IDH2 mut: ivo- or enasidenib
- Post CR
  - alloSCT if poss (Devine et al , JCO 2015)
  - Cont low dose rx (Dinardo et al, NEJM 2020)
  - Maint oral aza (Wei, et al , NEJM 2020)

New CTEP/NCTN Approach in Myeloid Malignancies: MyeloMatch

- 3 Working groups: younger AML, older AML, MDS
- 1 Master screening protocol will assign pts based on age, fitness, AML subtype (rapid cytogenetic and molecular screening)
  - MRD-driven endpoints
    - A fit older adult could be assigned to 3+7 +/- drug X (currently X = the E-selectin inhibitor uproleselan) or to CPX351+ mido v novel FLT3 inhib or CPX v aza/ven (adverse risk)
    - An unfit older adult could be assigned to aza/ven+/- IDH inhibitor or aza/ven +/- anti CD47 or Aza/ven+/- TP53 refolding agent

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