Controversies in Cancer Care: Evidence, Interpretation, & Clinical Decision Making

Intensive Induction Versus Azacitidine/Venetoclax for Older but Fit Patients With AML

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Disclosures

I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

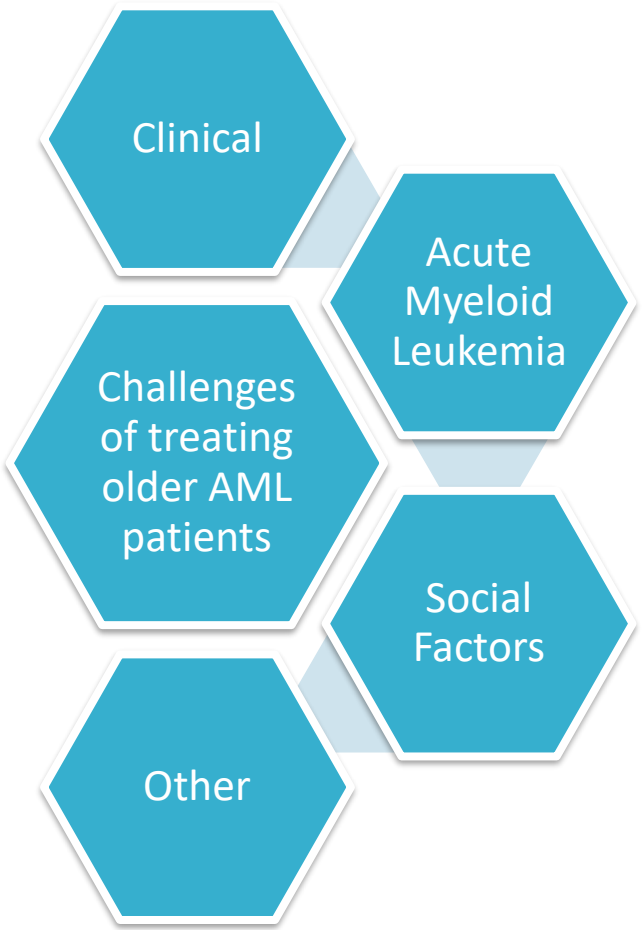
STATE LAW:
The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:
Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.

- Adults aged 65 years or older account for approximately 60% of new cases , but comprise 75% of deaths related to acute myeloid leukemia
- Historically, the treatment options for older patients were split into intensive chemotherapy and palliative approaches with low dose cytarabine, supportive care alone, or hospice.
- The development of hypomethylating agents in the mid-2000s offered a new therapeutic option for older or unfit patients with AML
- The approval in November 2018 of the oral BCL-2 inhibitor Venetoclax has substantially improved the outcomes in older or unfit AML and provided a tolerable, yet effective, therapy for patients



- **Controversy still exists regarding which older patients should be treated with HMA + Venetoclax and who may still benefit from intensive chemotherapy**

- **Clinical trial practice varies widely for patients aged between 60 and 74 years who do not have comorbidity that makes them clearly unfit for an intensive approach**

Short NJ; Kantarjian H, Lancet Haematology 2022 9:e535-45

Rationale for Intensive Chemotherapy

- Since the establishment of the combination of 7+3 schedule in the 1980s, cure rates and life expectancy in patients fit for intensive treatment have continued to improve largely d/t significant progress in supportive care and allogeneic stem cell transplant
- No alternative treatment achieving better long term remission results than intensive chemo in first line therapy
- Depending on genetic risk, more than 50% of elderly patients can be cured with a combination of intensive induction and post remission treatment including allogeneic stem cell transplant
- Disease eradication and prognostically relevant MRD reduction is quickly and profoundly achieved after 1-2 cycles of intensive induction with 60-80% of patients becoming MRD negative

Short NJ; Kantarjian H, Lancet Haematology 2022 9:e535-45

- Early mortality rates in intensively treated elderly AML patients have continually decreased throughout the past decades due to better supportive care
- Intensive chemotherapy is generally a time-limited treatment, ie, patients will become treatment-free within a few months
- Randomized comparisons suggest that 100 and 200mg of continuous daily cytarabine are of equal efficacy, most extensive body of knowledge exists for 7 day infusion
- The optimal dose of daunorubicin has been the subject of several randomized controlled trials (RCTs). Dauno 60mg/m2-90mg/m2 over 3 daus or Idarubicin 12mg/m2 as an alternative is used

- CPX-351 is a dual-drug liposomal encapsulation of cytarabine and daunorubicin that delivers a synergistic 5:1 drug ratio into leukemia cells
- CPX-351 was superior to conventional 7 + 3 chemotherapy for the treatment of older patients with newly diagnosed secondary acute myeloid leukemia who were deemed fit to receive intensive chemotherapy (median overall survival of 9·6 months for CPX-351 vs 6·0 months for 7 + 3 chemotherapy
- 2-year overall survival of 31% for CPX-351 vs 12% for 7 + 3 chemotherapy
- The most frequently reported grade 3 to 5 adverse events in the CPX-351 and 7+3 cohortswere febrile neutropenia (68.0% v 70.9%), pneumonia (19.6% v 14.6%), and hypoxia (13.1% v 15.2%)

Lancet JE, et al. *J Clin Oncol* **36**, 2684-2692(2018) Volume 36, Number 26

Potential Risks of Intensive Chemotherapy

- IC can be associated with substantial risk including treatment related morbidity and mortality
- Early mortality is substantially higher in population-based studies of older or unfit patients with AML, with 8-week mortality of 25-30% in patients aged 60-69years and more than 50% in patients aged 70 years or older
- Factors related to higher mortality
    - ❖ Age over 75 years or older
    - ❖ ECOG PS of 2 or higher
    - ❖ Complex Cytogenetics
    - ❖ Treatment outside of a laminar airflow room
    - ❖ Preceding antecedent hematological disorder
    - ❖ Creatinine of more than 1.3mg/dL

Short NJ; Kantarjian H, Lancet Haematology 2022 9:e535-45

Who is fi

- Integrating p ent decisions might help
- Evidence su has been proven use ch can help guide thera
- Screening t e prognostic utility in AM and may be able to guid ctivities of daily living (SPPB), or slow gait speed
- To assess th -specific Comorbidit ing transplant, was validat ars old

LAWTON - BRODY
INSTRUMENTAL ACTIVITIES OF DAILY LIVING SCALE (I.A.D.L.)

Scoring: For each category, circle the item description that most closely resembles the client's highest functional level (either 0 or 1).

A. Ability to Use Telephone		**E. Laundry**	
1. Operates telephone on own initiative-looks up and dials numbers, etc.	1	1. Does personal laundry completely	1
2. Dials a few well-known numbers	1	2. Launders small items-rinses stockings, etc.	1
3. Answers telephone but does not dial	1	3. All laundry must be done by others	0
4. Does not use telephone at all	0		
B. Shopping		**F. Mode of Transportation**	
1. Takes care of all shopping needs independently	1	1. Travels independently on public transportation or drives own car	1
2. Shops independently for small purchases	0	2. Arranges own travel via taxi, but does not otherwise use public transportation	1
3. Needs to be accompanied on any shopping trip	0	3. Travels on public transportation when accompanied by another	1
4. Completely unable to shop	0	4. Travel limited to taxi or automobile with assistance of another	0
		5. Does not travel at all	0
C. Food Preparation		**G. Responsibility for Own Medications**	
1. Plans, prepares and serves adequate meals independently	1	1. Is responsible for taking medication in correct dosages at correct time	1
2. Prepares adequate meals if supplied with ingredients	0	2. Takes responsibility if medication is prepared in advance in separate dosage	0
3. Heats, serves and prepares meals, or prepares meals, or prepares meals but does not maintain adequate diet	0	3. Is not capable of dispensing own medication	0
4. Needs to have meals prepared and served	0		
D. Housekeeping		**H. Ability to Handle Finances**	
1. Maintains house alone or with occasional assistance (e.g. "heavy work domestic help")	1	1. Manages financial matters independently (budgets, writes checks, pays rent, bills, goes to bank), collects and keeps track of income	1
2. Performs light daily tasks such as dish washing, bed making	1	2. Manages day-to-day purchases, but needs help with banking, major purchases, etc.	1
3. Performs light daily tasks but cannot maintain acceptable level of cleanliness	1	3. Incapable of handling money	0
4. Needs help with all home maintenance tasks	1		
5. Does not participate in any housekeeping tasks	0		
Score		**Score**	
		Total score_____	

A summary score ranges from 0 (low function, dependent) to 8 (high function, independent) for women and 0 through 5 for men to avoid potential gender bias.

Extermann, M. et al. Journal of Geriatric Oncology 15 (2024) 101626

- creatinine clearance should systematically be calculated in every patient, as renal impairment frequently exists above age 70 even in the presence of normal creatinine levels
- Effects of drug interactions between chemotherapy and non-oncologic drugs should not be neglected as the potential of severe side effects can be doubled or tripled => Minimize polypharmacy
- 30% prevalence of cognitive impairment at baseline, older patients admitted for AML are at significant risk of delirium
- poor nutritional status represents a common problem in patients with AML and is an independent prognostic parameter

Extermann, M. et al. Journal of Geriatric Oncology 15 (2024) 101626

VIALE-A

- This phase 3, multicenter, randomized, double blind, placebo-controlled trial was conducted to evaluate the efficacy and safety of azacitidine plus venetoclax, as compared with azacitidine plus placebo
- N= 431 patients (286 in the azacitidine venetoclax group and 145 in the azacitidine–placebo
- median age was 76 years in both groups (range, 49 to 91)
- At a median follow-up of 20.5 months, the median overall survival was 14.7 months in the azacitidine–venetoclax group and 9.6 months in the control group (hazard ratio for death, 0.66; 95% confidence interval, 0.52 to 0.85; P<0.001)
- The incidence of complete remission was higher with azacitidine–venetoclax than with the control regimen (36.7% vs. 17.9%; P<0.001).
- composite complete remission (complete remission or complete remission with incomplete hematologic recovery) (66.4% vs. 28.3%; P<0.001)

DiNardo, C et al. NEJM 2020:Vol 383, No 7, 617-629

- Similarly, in the phase 3, VIALE C trial , combination of low dose cytarabine and venetoclax resulted in improvement in CR and CR with incomplete hematologic recovery (48% for LDAC + Venetoclax vs. 13% for low dose cytarabine plus placebo
- Approximately 20% of the patients in VIALE-C received previous hypomethylating agents, which is a group known to have particularly poor outcomes that was excluded from VIALE-A
- Given the remarkable improvement in response rates and survival observed with the addition of venetoclax to hypomethylating agents or low-dose cytarabine therapy, the role of intensive chemotherapy in older patients who do not fit the inclusion criteria for VIALE-A or VIALE-C (ie, patients who are aged 60–74 years but without a clinically significant comorbidity) has been increasingly questioned

American Society of Hematology 2025 guidelines for treating newly diagnosed acute myeloid leukemia in older adults

- ASH formed a multidisciplinary guideline panel, including patient representatives, that minimized bias from conflicts of interest. Clarity Research Group at McMaster University supported the guideline development process, including updating or performing systematic evidence reviews
- The panel agreed on 9 critical clinical recommendations for managing AML in older adults, mirroring real-time practitioner-patient conversations:
- Including, traditional induction and post remission therapy vs hypomethylating agent or low-dose cytarabine, or combinations with venetoclax
- the role and duration of post remission therapy
- combinations with venetoclax vs monotherapy
- the use of targeted therapy, including isocitrate dehydrogenase and FMS-like tyrosine kinase 3 (FLT3) inhibitors, in appropriate patients;
- the role of hematopoietic stem cell transplantation in non-favorable prognosis AML

Sekeres, MA, et al. Blood Advances March 2026; Volume 10, No 6

Should older adults with newly diagnosed AML considered candidates for ALT receive conventional induction and post-remission therapy vs HMA-or LDAC-based induction and post-remission therapy?

- review compared the efficacy and safety of low-dose cytarabine (LDAC), azacitidine (AZA), 5- and 10-day decitabine (DEC), and gemtuzumab ozogamicin, alone or combined with drugs such as venetoclax (VEN), in older adults with AML ineligible for conventional chemotherapy
- There were 21 studies (3 RCTs and 18 NRSs) addressing this question

Recommendation 2a

- For older adults with newly diagnosed AML considered candidates for intensive ALT, the ASH guideline panel suggests conventional induction and post remission therapy over HMA or LDAC monotherapy induction and post remission therapy (conditional recommendation based on low certainty in the evidence of effects

Recommendation 2b

- For older adults with newly diagnosed AML considered candidates for intensive ALT, the ASH guideline panel suggests using either conventional induction and post remission therapy or HMA-or LDAC-based induction and post remission therapy in combination with venetoclax (conditional recommendation based on very low certainty in the evidence of effects

Recommendation 2A

- 3 RCTs enrolled 1099 older adults at least 60 years of age. The mean age across studies was 70.6 years +/- 5 yrs
- When conventional induction and post remission therapy is compared with HMA- or LDAC-based monotherapy, suggestive that patients who receive conventional therapy may have a lower risk of death at the longest follow-up (relative risk [RR], 0.94 at 48 months follow-up)
- Conventional therapy increases CR rates (OR 1.75) and may reduce recurrence at 12 months (RR, 0.69) and at the longest follow-up (RR, 0.81)
- conventional chemotherapy probably increases hospital length of stay , multiple organ and sepsis

Recommendation 2B

- A total of 18 NRs compared conventional induction and post-remission therapy with HMA- or LDAC based therapy + venetoclax
- The NRSs enrolled 6770 older adults
- The mean age across studies was 67.1 ± 5.04 suggests that patients who receive conventional therapy may have a lower risk of death at 1 year (RR, 0.72)
- conventional therapy may also be associated with a higher likelihood of undergoing allo-HCT (RR, 2.28), range, 6-60 months follow-up
- evidence suggests that patients who receive conventional therapy may have a higher risk of death at 1 month (RR, 1.34) and may have lower CR rates (RR, 0.95)
- Conventional therapy may increase hospital LOS

Improving on HMA + Venetoclax treatment backbone

- The addition of cladribine (CLAD) and LDAC with VEN has been shown to be highly effective in newly diagnosed AML
- Phase 2 clinical trial with CLAD (5mg/m2 days 1-5), LDAC (20mg SQ BID on days 1-10) and Venetoclax (400mg , d 1-21) induction therapy followed by a consolidation phase that alternates 2 courses of Aza (75mg/m2 on d 1-7) and Venetoclax with 2 courses of CLA (d 1-3), LDAC and Ven (same doses)
- N=141 , median age was 68 (47-84) and 58% were male
- Normal karyotype in 53% and 19% had complex karyotype
- According to the ELN 2022 classification, 60% were classified as adverse risk , TP53 was mutated in 17% of patients
- composite complete remission (CR) rate was 85% (120/141 pts), with 73% achieving CR and 12% achieving CR with incomplete blood count recovery (CRi). The median cycles to first and best response was 1 (range, 1-3 and 1-7, respectively). Among pts with CR/CRi, 78% achieved negative measurable residual disease (MRD-) by flow cytometry.

Bataller A, Kadia T et al. Blood (2024) 144 (Supplement 1): 56

- The median follow-up was 28 months. The 2-yr OS and event-free survival (EFS) was 62% and 55%, respectively.
- The 2-yr OS was 84%, 67% and 51% for patients allocated in the favorable, intermediate and adverse ELN 2022 classification
- Patients achieving MRD- had a better 2-yr OS (75%) compared to patients with positive MRD (32%, P < .001)
- Patients with *NPM1* or *DDX41* mutations were allocated in the very good risk group (n=43, MRD- 97%, mOS 60 months, 2-yr OS 85%)
- Patients without risk-defining genetic abnormalities were allocated in the good risk group (n=54, MRD- 84%, mOS 50 months, 2-yr OS 66%)
- Patients with *N/KRAS* without *NPM1* mutation were allocated in the intermediate risk group (n=19, MRD- 56%, mOS 18 months, 2-yr OS 43%)
- Patients with complex karyotype or multihit *TP53* mutation were allocated in the poor risk group (n=25, MRD- 56%, mOS 7 months, 2-yr OS 23%)

Bataller A, Kadia T et al. Blood (2024) 144 (Supplement 1): 56

Potential for Triplet Therapy

Fl

Author	Regimen	Study population	CR rates	OS	MRD negati
Short NJ et al. Blood Cancer J. 2023;13:142	Aza+ Ven +Gilt	N=30 Median age of 71	CRc rates of 96%	18-month OS was 61% for *FLT3*-ITD and 100% for *FLT3*-TKD	MRD negative rate was 76% by NGS
Yilmaz M, et al. Hemasphere 2025;9:e70151	Dac + Ven + Quiz	N=26 median age was 70	CRc rate was 92%, with 67%	30-day mortality was 4%; at a median follow-up of 17 months, the median OS was not reached	67% MRD-negative by multiparameter flow cytometry (MFC)
Chua CC, et al (INTERVENE, ALLG AMLM25) Blood. 2024;144:217	LDAC + VEN with midostaurin (LVM) or LDAC + VEN	N=120 in a 2:1 randomization Median age-74	CRc was obtained in 82% of LVM-treated patients, compared with 57% after LDAC + VEN	Median OS was 16.8 months, with a 1-year OS of 57%	61% cleared *FLT3*-ITD using a highly sensitive NGS assay
Altman J et al. (VICEROY) *Blood* (2025) 146 (Supplement 1): 654.	VEN + AZA + GILT	N=44	Ven 200 CRc rate was 90% and 91% for Ven 400 group	12-month OS rate was 64% (VEN200 and 77% (54–90) in Ven 400 group	MRD was achieved in 85% (11/13) of patients in VEN200 and 57% (8/14) of patients in VEN400 achieved MRD $<10^{-4}$

Jen, WY et al Blood Cancer Journal (2026) 16:6

IDH Triplets

- Mutations in isocitrate dehydrogenase 1 and 2 (*IDH1*^{mut} and *IDH2*^{mut}) occur in 8% and 12% of ND AML, respectively
- These mutations lead to the accumulation of the oncometabolite 2-hydroxyglutarate (2-HG), which promotes differentiation block and BCL2 dependence
- The mutant IDH1 inhibitors ivosidenib and olutasidenib and the mutant IDH2 inhibitor , relieve this differentiation block and are approved by the FDA as single agents
- Pooled results of two prospective phase 2 trials of AZA + VEN + ivosidenib (AZA + VEN + IVO) for ND *IDH1*^{mut} AML, and decitabine-cedazuridine (DEC-C) + VEN with ivosidenib (DEC-C + VEN + IVO, *IDH1*^{mut}) or enasidenib (DEC-C + VEN + ENA, *IDH2*^{mut}) were recently reported
- Results include a CRc rate of 92%, with 87% of responding patients attaining MRD negative status by MFC after a median of 2 cycles
- Responses appear to be durable, with a 2-year cumulative incidence of relapse of 24% and 2-year OS of 70%

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- In both reported IDH triplet studies, VEN is administered on days 1–14 of each treatment cycle, with the IDHi starting on C1D15 of AZA + VEN + IVO and C1D8 of DEC-C + VEN + IVO/ENA
- Differentiation Syndrome occurs in 10–20% of patients treated with single-agent IDHi, with a median time to onset of approximately 20 days
- Anticipated studies
  - The European HOVON/AMLSG group is now enrolling a randomized phase 3 study of AZA + IVO with VEN or placebo in *IDH1*^{mut} AML (EVOLVE-1, NCT07075016) to definitively answer the question of whether the triplet improves event-free survival (EFS) compared to AZA + IVO alone
  - olutasidenib in combination with AZA + VEN (NCT06782542) or DEC-C + VEN (NCT06445959)
  - LY3410738, a potent dual inhibitor of IDH1/2, with AZA + VEN (NCT04603001)
  - *IDH2*^{mut} AML, a phase 2 MyeloMATCH study is comparing DEC-C + VEN to DEC-C + VEN + ENA, with a primary outcome of MRD-negative CR after 2 cycles of treatment, assessed by MFC (NCT06672146)

Menin Inhibitor Triplets

- Rearrangements of *lysine methyltransferase 2A (KMT2A)*, located on chromosome 11q23, occur in 5–10% of pediatric and adult acute leukemias . *KMT2A*r confer a poor prognosis with standard therapies, especially in older patients
- Mutations in *nucleophosmin 1* (*NPM1*^{mut}) are present in up to 30% of ND AML and 12% of RR AML, and result in defective shuttling and cytoplasmic persistence of NPM1
- Both *NPM1*^{mut} and *KMT2Ar* drive leukemogenesis in part through constitutive activation of transcriptional homeobox (*HOX*) genes, which regulate cell proliferation and differentiation. Menin is a scaffold protein that interacts with such transcription factors to regulate gene expression
- Menin inhibitors are thus active in specific subtypes of acute leukemia (*KMT2A*r, *NPM1*^{mut}, *NUP98* rearrangements, etc.) by targeting the transcriptome complex and relieving differentiation arrest
    - Revumenib is the first menin inhibitor to be FDA approved for RR AML with *KMT2A*r or *NPM1*^{mut}. As a single agent, the CR/CRh (complete remission with partial hematologic recovery) rate was 23% in RR *KMT2A*r and *NPM1*^{mut} AML
    - Ziftomenib, FDA approved for RR *NPM1*^{mut} AML, is associated with a 35% CR rate in patients treated at the RP2D
    - Other menin inhibitors in clinical trials include enzomenib (NCT04988555), bleximenib (NCT04811560), and BN104 (NCT06052813),

Issa GC, Aldoss, I et al. (AUGMENT-101). J Clin Oncol. 2025;43:75–84
Jen, WY et al Blood Cancer Journal (2026) 16:6

AUTHOR	REGIMEN		Safety/ AE	ORR
Zeidner J, et al. *J Clin Oncol* **43**, 2606-2615(2025) Volume 43, No 23	Aza + Venetoclax + Revumenib	N=43	Differentiation Syndrome 19% QTc prolongation 44%	ORR was 88.4% CRc 81.4% ((80% in *NPM1*^{mut} and 89% in *KMT2A*r) and 100% MRD undetectable status by MFC (31% by *NPM1* NGS. CR rate was 67.4% (*NPM1m*: 65%; *KMT2Ar*: 78%)
Wei AH, et al. Hemasphere. 2025;9:e70151.	AZA, VEN and bleximenib (AZA + VEN + BLEXI, NCT05453903)	N=120	Most common AE: nausea (60%), thrombocytopenia (55%), and anemia (51%) DS – 4% and no QT prolongation has been reported	ORR and cCRR lower with 50mg (76% and 32%) 100mg BID ORR and cCRR (79% and 54%)
Jen, WY et al. SAVE trial ASH abstract #47	SNDX-5613 + ASTX727 + VEnetoclax (SAVE)	N=21	QTc prolonged 43% Differentiation Syndrome 19% any grade, 10% grade 3	-ORR 86% for all patients (86% for NPM1mt and 86% for KMT2Ar) -CR 81% for all patients (79% NPM1mt and 86% KMT2Ar)

Role of Allogeneic Stem Cell Transplantation

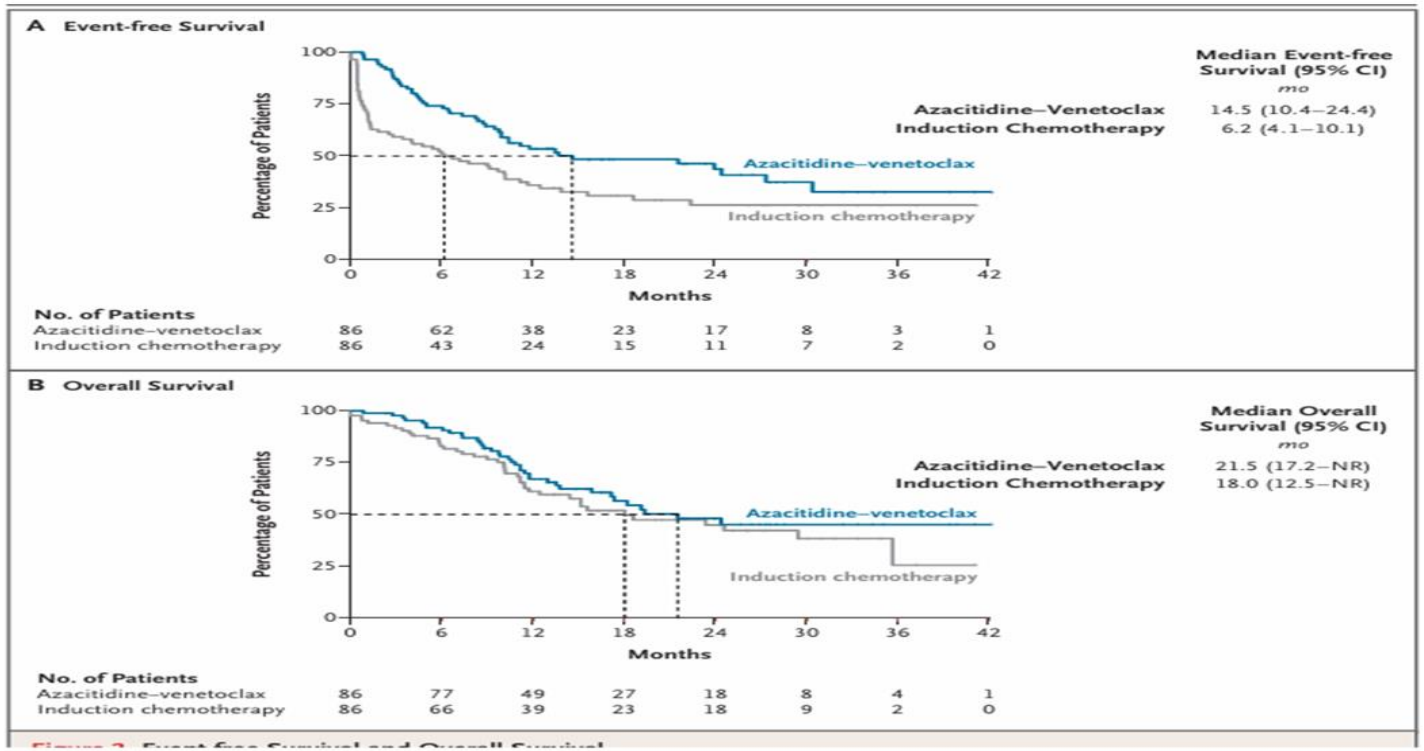
- ASH 2025 guideline recommendation is that for older patients who are candidates for allo-HCT and have non favorable prognosis based on molecular and karyotypic characteristics, the suggestion is to proceed with an allo-HCT
- 1 RCT and 13 observational studies were reviewed to address this question. Four observational studies compared allo-HCT with no transplant
- The included studies enrolled 4348 older adults, with a mean average age of 64 years
- Allo-HCT may reduce the rate of mortality over time (HR, 0.74) ; 60 months follow-up and rate of recurrence of leukemia over time (HR, 0.46) ; 60 months follow-up)
- Allo-HCT can represent a potentially curative treatment alternative that can be safely performed in an increasingly higher number of older adults after continuing improvements in patient selection, conditioning regimen intensity tailoring, and a larger alternative donor pool thorough the increased use of mismatched unrelated and haploidentical donors
- value of allo-HCT and the decision whether to recommend the procedure for older adults with AML is modulated by multiple factors including comorbidities and fitness more than a specific age threshold and the presence of a suitable social support network. Specific genetic characteristics of the disease within nonfavorable disease subgroups can also predict outcomes after allo-HCT

Sekeres, MA, et al. Blood Advances March 2026; Volume 10, No 6

PARADIGM Study

- Multicenter, investigator initiated, phase 2 trial, randomly assigned in a 1:1 ratio previously untreated adults with AML who were eligible for induction chemotherapy to receive either Azacitidine plus Venetoclax or Induction chemotherapy
- Patients with core binding factor fusions, mutations in the gene encoding FMS-like tyrosine kinase 3 (FLT3), or mutations in the gene encoding nucleophosmin-1 (NPM1; unless the patient was ≥60 years of age) were excluded
- The primary endpoint was event free survival
- N=172 who underwent randomization, with 86 patients assigned to each group.
- The median age of the patients was 64 years. A total of 72% of the patients had adverse-risk disease according to the European Leukemia Net 2022 classification
- At a median follow-up of 21.9 months, the median event-free survival was 14.5 months (95% confidence interval [CI], 10.4 to 24.4) in the azacitidine–venetoclax group, as compared with 6.2 months (95% CI, 4.1 to 10.1) in the induction chemotherapy group
- HR 0.57 (95% CI, 0.39 to 0.84; P=0.002 by the stratified log-rank test)

Fathi A, Aldoss I et al, NEJM September 2026;395:845-858



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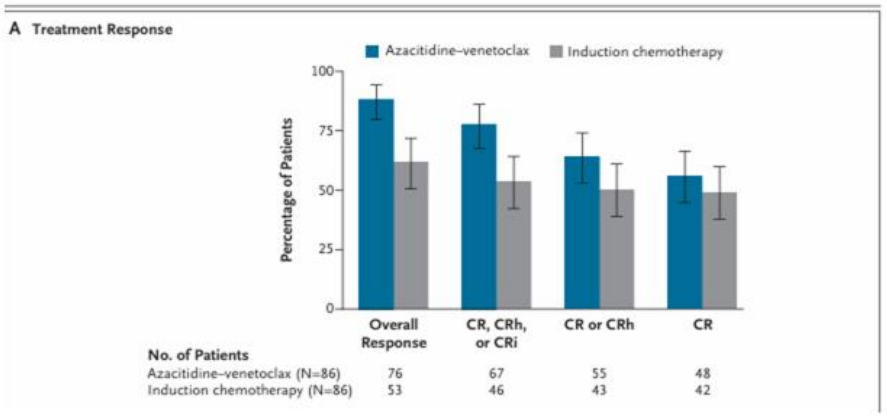

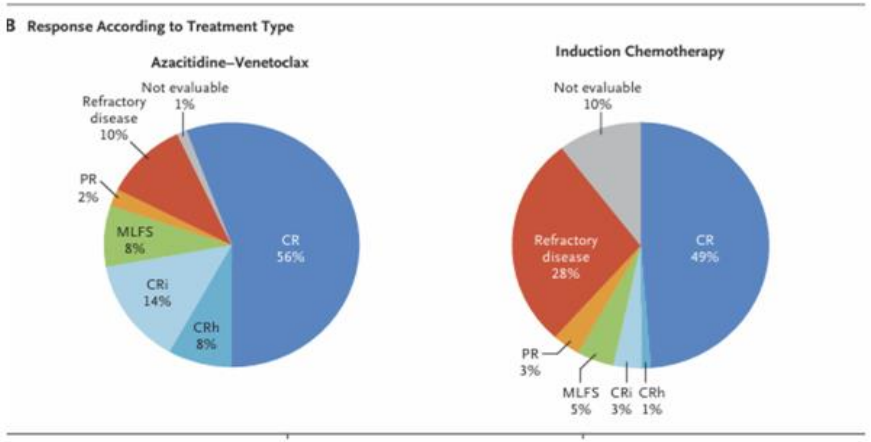

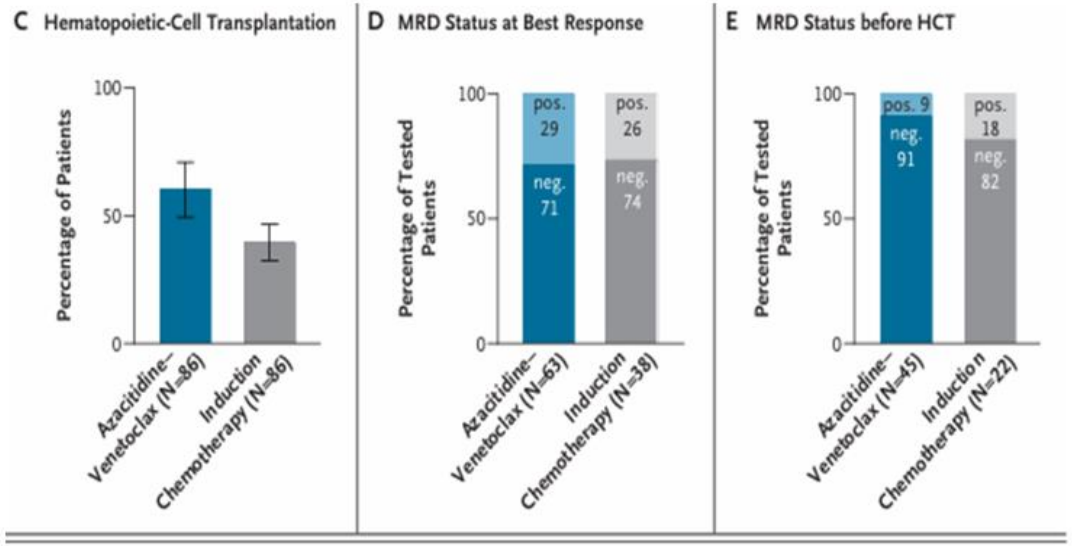

Fathi A, Aldoss I et al, NEJM September 2026;395:845-858

- Grade 3 or higher adverse events that occurred in at least 10% in either group
- AEs were primarily hematologic and incidence was similar in both groups
- Infectious adverse events of grade 3 or higher occurred in 28% of the patients who received azacitidine–venetoclax and in 41% of those who received induction chemotherapy
- hemorrhagic adverse events of grade 3 or higher occurred in 2% and 12% , respectively
- At 30 days and 60 days, no patient in the azacitidine–venetoclax group had died; in the induction chemotherapy group, 30-day mortality was 3% and 60-day mortality was 5%
- During the first 30 days after randomization, the mean number of inpatient days was 12.5 in the azacitidine–venetoclax group and 27.3 in the induction chemotherapy group
- No patient in the azacitidine–venetoclax group was admitted to the intensive care unit (ICU), and 10% of the patients in the induction chemotherapy group were admitted to the ICU

Fathi A, Aldoss I et al, NEJM September 2026;395:845-858

- For decades, our approach has been to answer a relatively simple question: Is this patient FIT enough for intensive induction?
- PARADIGM challenges us to ask a different question: Which therapy FITS the patient?
- The decision is increasingly about disease biology, molecular profile, treatment goals, toxicity, the likelihood of achieving a deep remission, and possibly a path to allogeneic stem cell transplant , rather than chronological age or fitness alone
- The real paradigm shift in treating older AML patients : not intensive versus non-intensive but choosing the right induction strategy for the right patient