FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

CONVEGNO FISiM

Firenze, CSF Montedomini
"Il Fuligno"
24-25 ottobre 2025

Attività di decitabina nelle LMA secondarie

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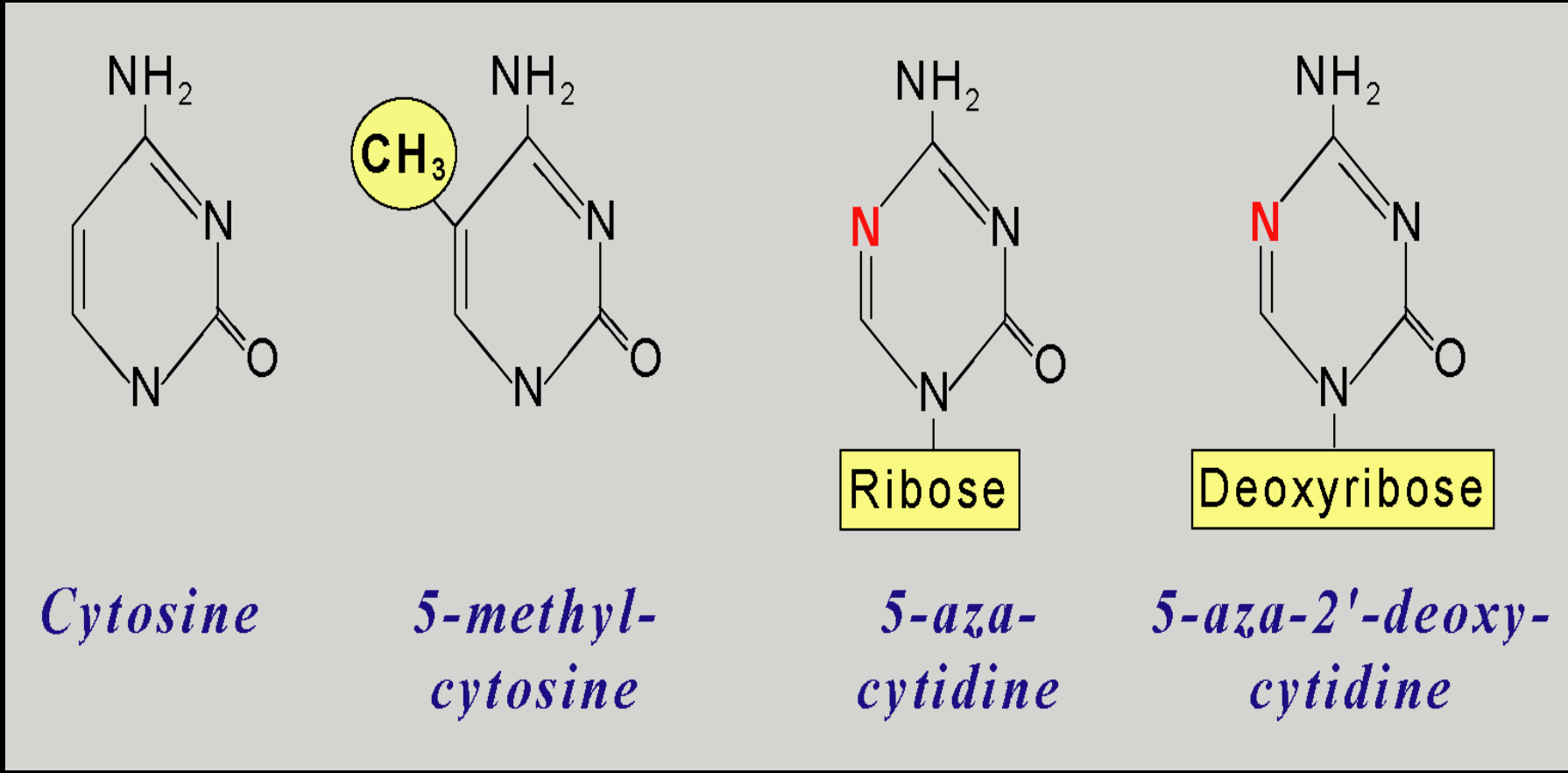
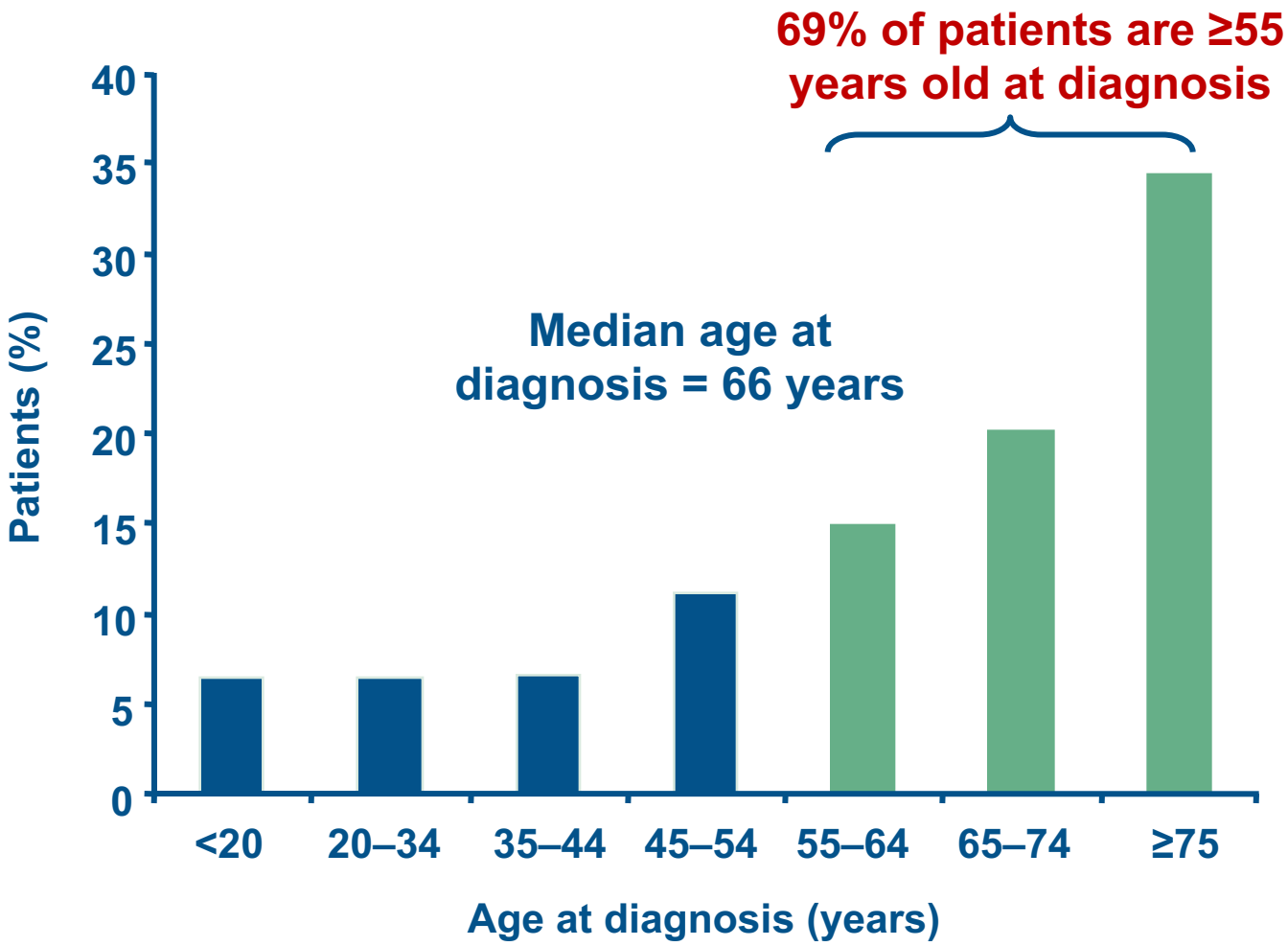
Hypomethylating Cytosine Analogs

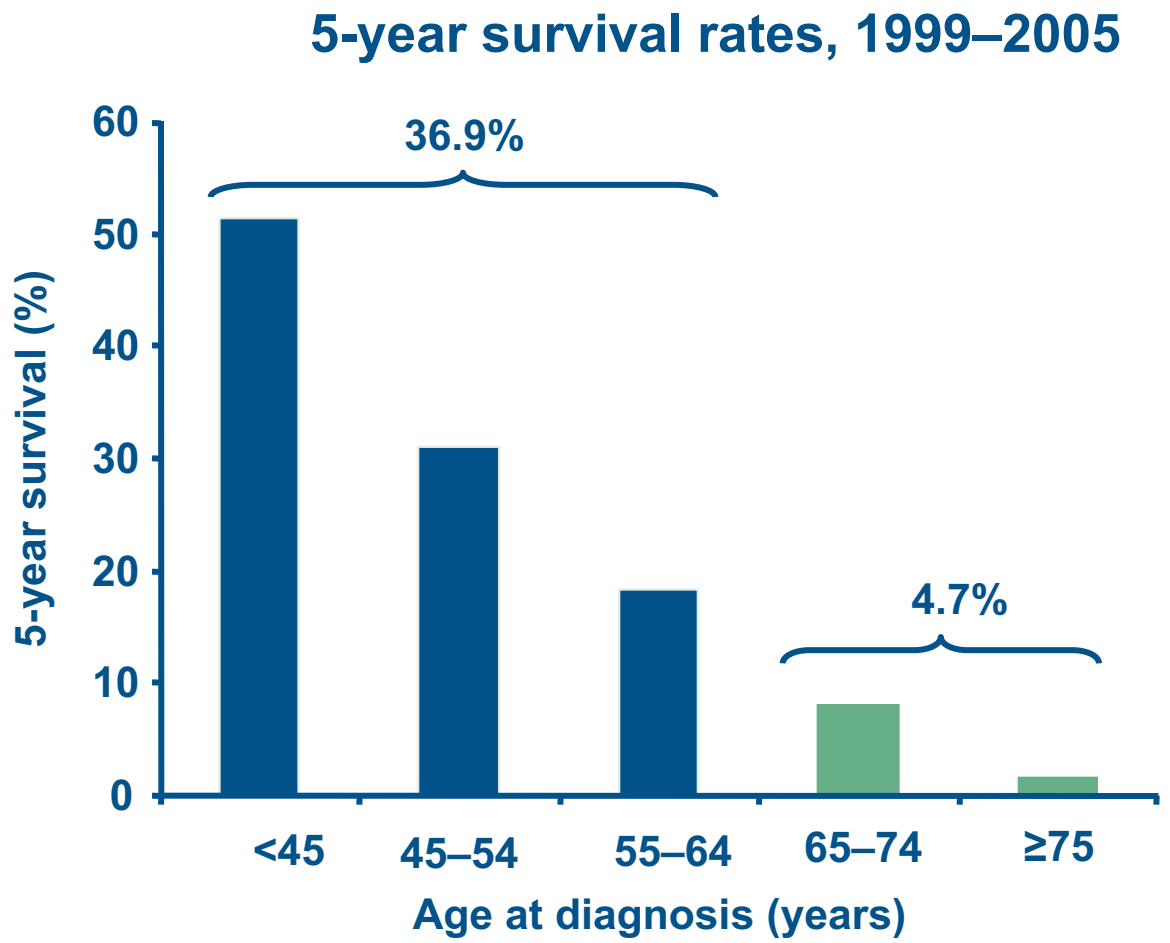


AML is predominantly a disease of the elderly



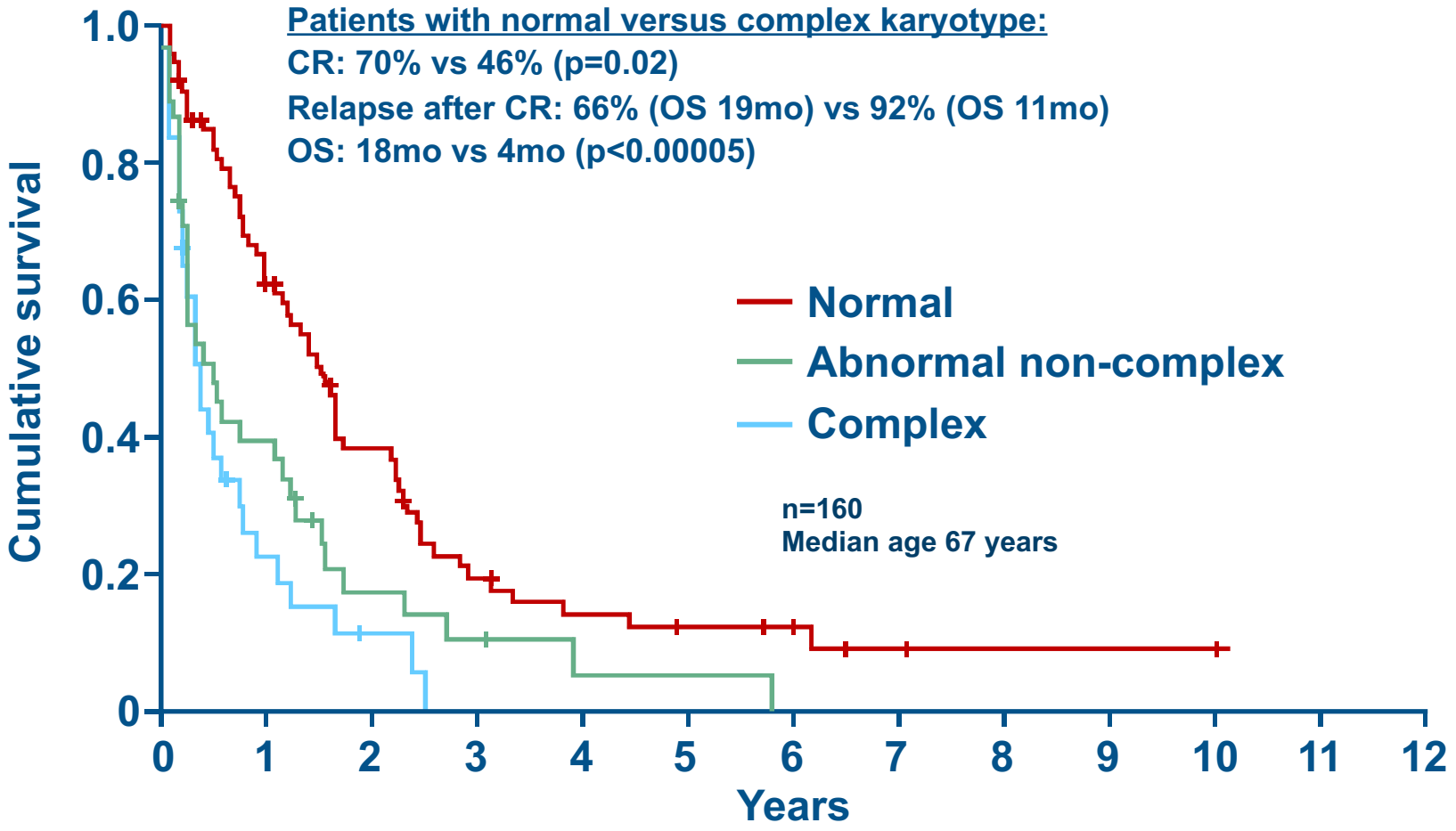
SEER Cancer Statistics, National Cancer Institute, USA 2002–2006
Available at http://seer.cancer.gov/statfacts/html/amyl.html

AML in the elderly is associated with poor survival rates



SEER Cancer Statistics, National Cancer Institute, USA 1999–2005.
Available at http://seer.cancer.gov/csr/1975_2006/browse_csr.php?section=13&page=sect_13_table.15.html#table3

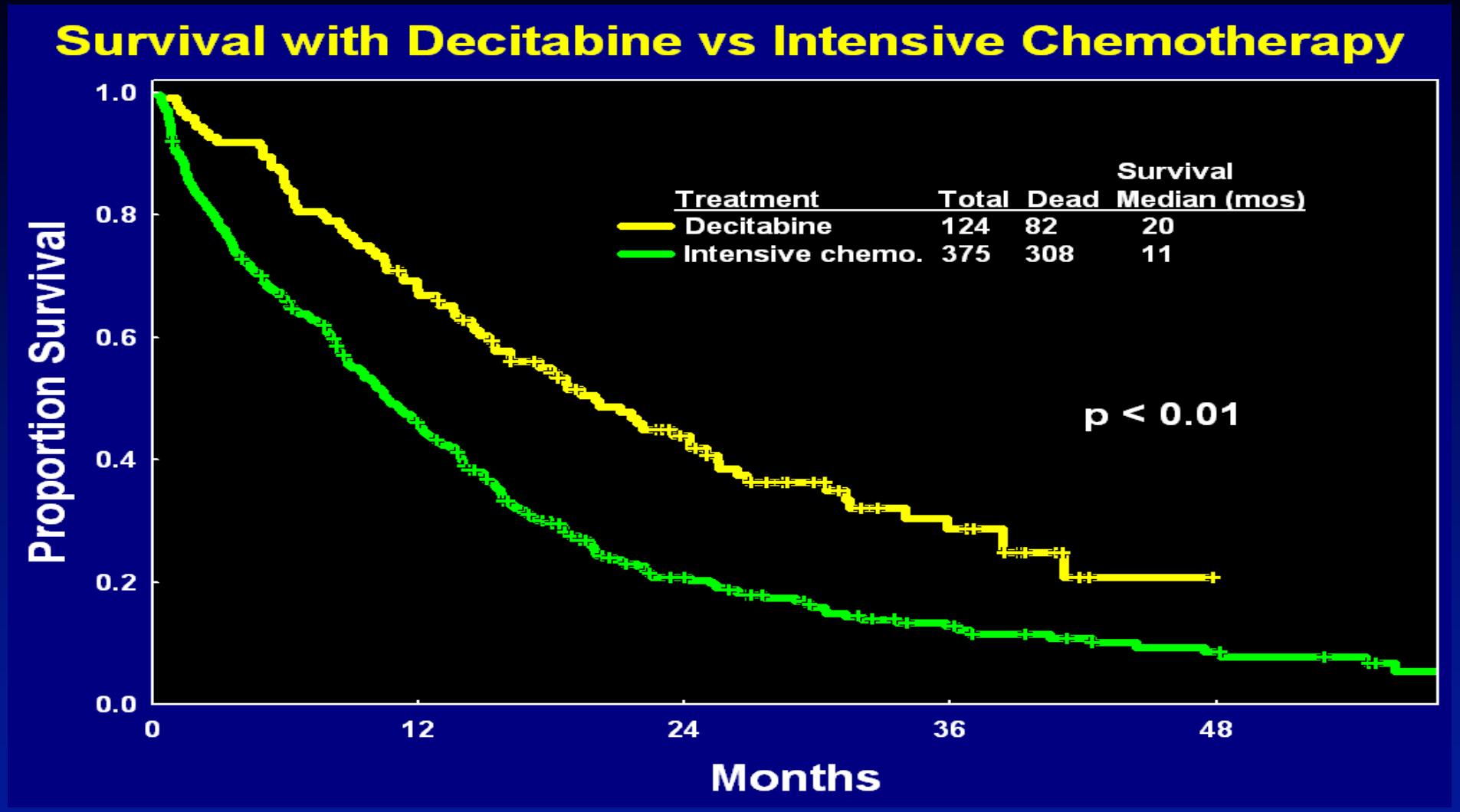
Intensive chemotherapy is associated with poor survival in patients with AML aged >60 years



Survival is particularly poor in patients with abnormal cytogenetic profiles

Knipp S, et al. Cancer 2007;110:345–52

Survival with Decitabine vs Intensive Chemotherapy



Kantarjian. Cancer 109: 1133, 2007

DAC in elderly AML pts with > 30% BM blasts

227 AML patients
median age 72 yrs
40% with comorbidities
32% adverse cytogenetics

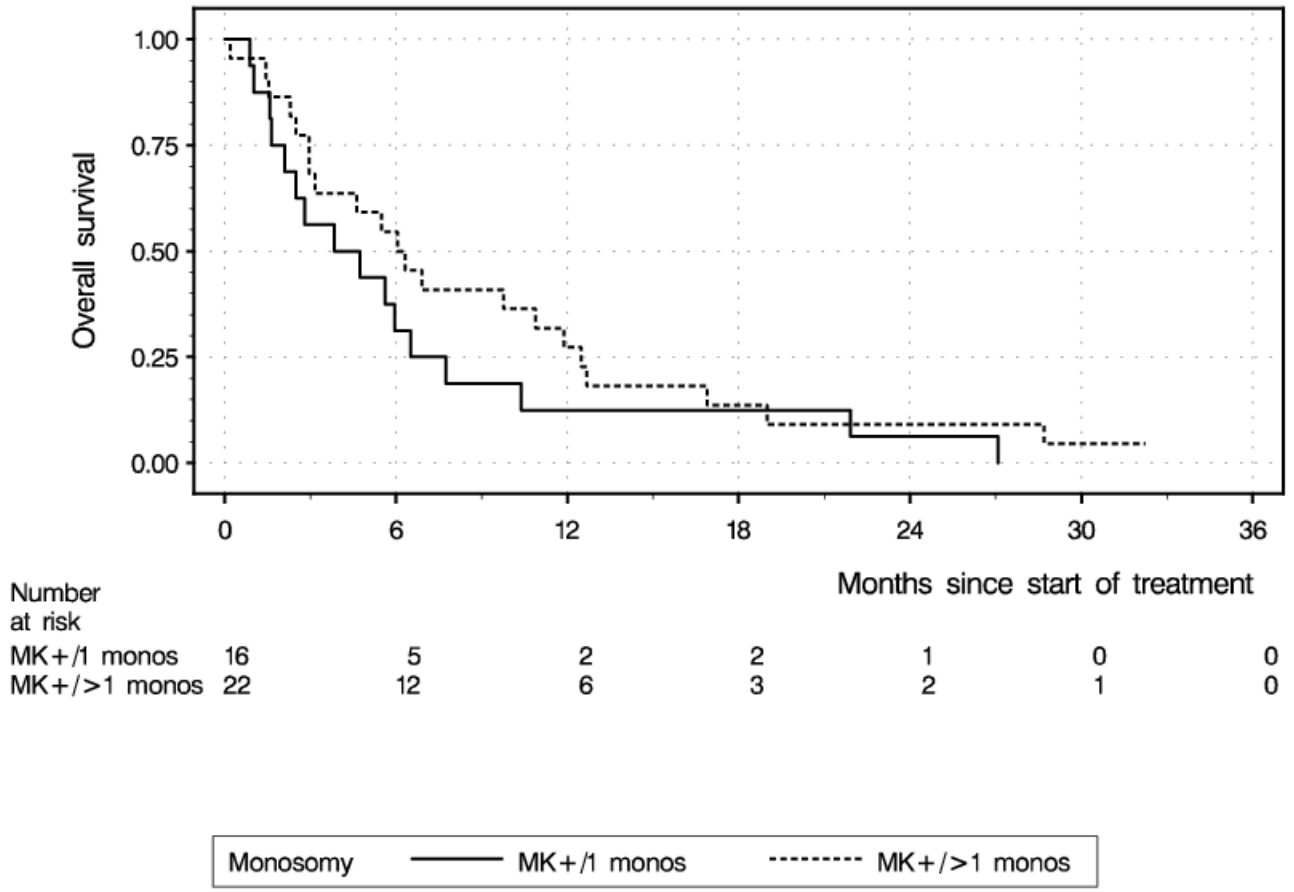
DAC 135 mg/m2 total dose IV over 72 hours every 6 weeks

CR + PR rate 26%, 95% CI (20%, 32%)

OS median 5.5 mos; 28% at 1yr

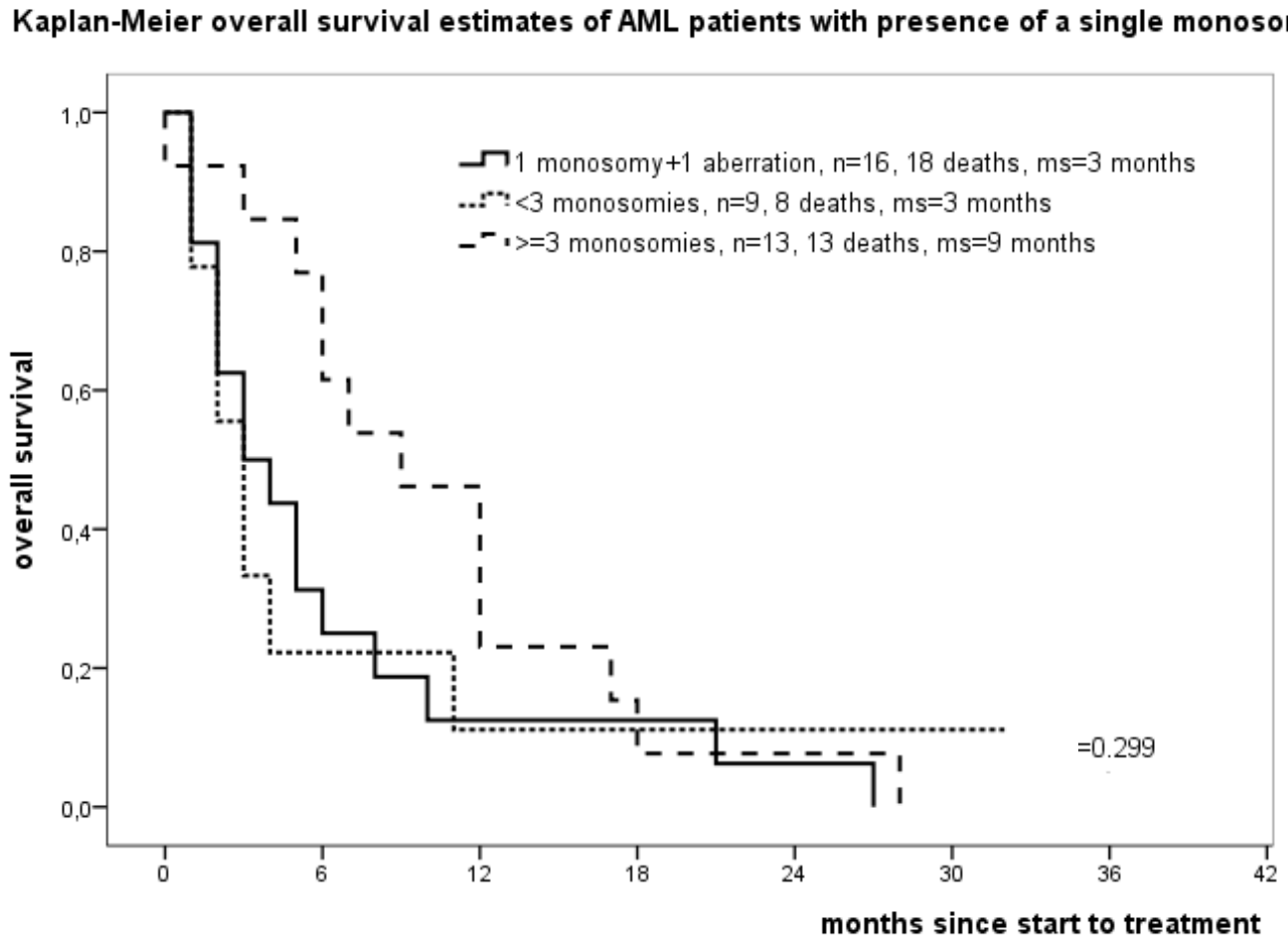
Lübbert et al, Haematologica 2012

Patients with multiple monosomies treated with DAC do not have worse outcome than those with single monosomy



Lübbert et al, Haematologica 2012

AML patients with at least 3 monosomies treated with DAC have better outcome than those with 1 or 2 monosomies



CR/PR rate (%)

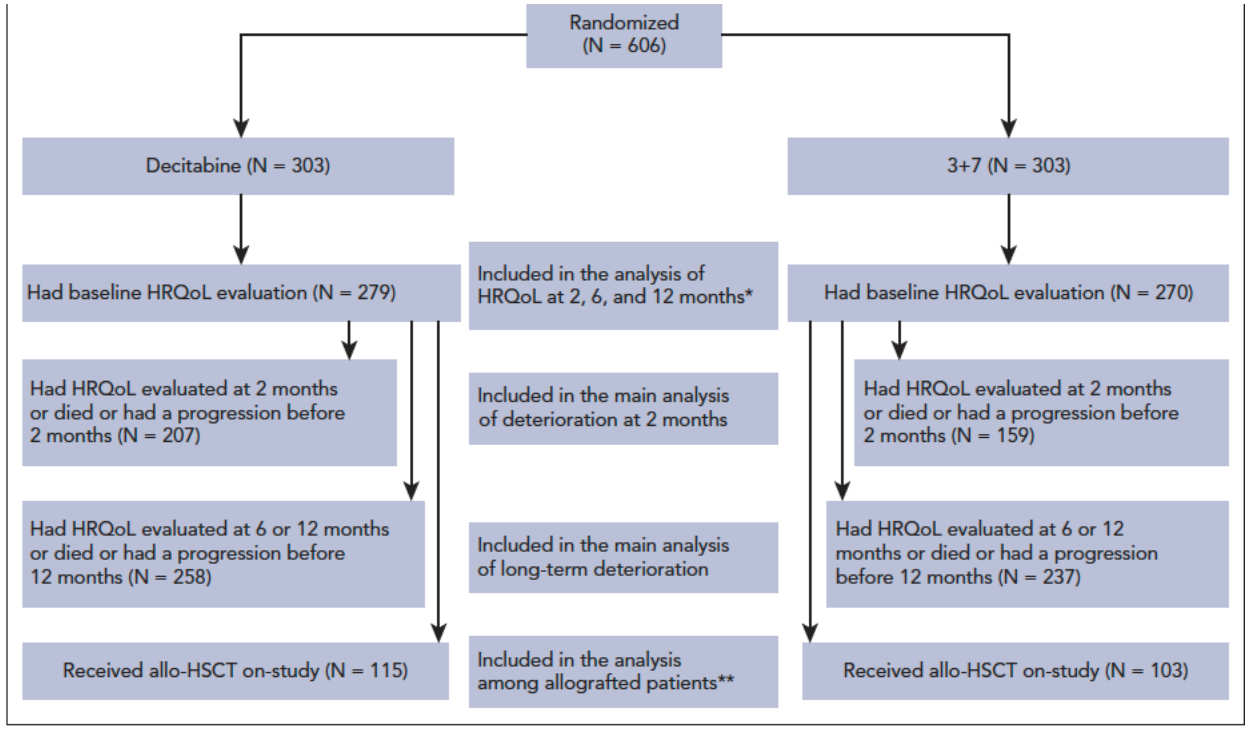
MK-1 25

MK-2 22

MK≥3 63

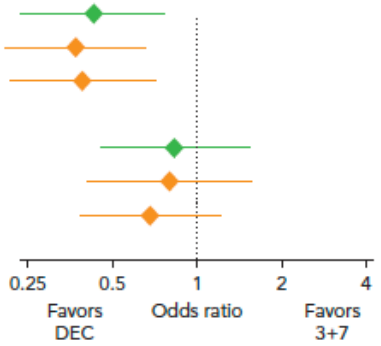
Lübbert et al, Haematologica 2012

Quality of life and treatement with decitabine



Health-related quality of life deterioration by treatment arm

	Decitabine		3+7		
Deterioration at 2 months	N/Total	% (95% CI)	N/Total	% (95% CI)	OR (95% CI)
Main analysis	157/207	76 (69-82)	140/159	88 (82-93)	0.43 (0.24, 0.76)
Including discontinuation	199/248	80 (75-85)	210/229	92 (87-95)	0.37 (0.21, 0.65)
Excluding progression	143/194	74 (67-80)	135/154	88 (81-92)	0.39 (0.22, 0.70)
Deterioration at long-term					
Main analysis	231/258	90 (85-93)	216/237	91 (87-94)	0.83 (0.46, 1.52)
Including discontinuation	252/274	92 (88-95)	244/261	93 (90-96)	0.80 (0.41, 1.54)
Excluding progression	212/245	87 (82-91)	207/229	90 (86-94)	0.68 (0.39, 1.21)



- **Limited data are available on HRQoL of patients with AML treated with decitabine.**
- **Current HRQoL findings suggest that decitabine, may be preferable to intensive chemotherapy in fit older patients with AML.**

Efficace et al, Blood 2024

Oral HMAs: Introduction

- HMAs (azacitidine, decitabine) standard of care for MDS and older AML
- Both drugs require 3 to 7 days of IV/SC administration per cycle
- Treatment needs to be maintained for as long as possible
  - Interruptions associated with failure
  - Important impact in quality of life
- Oral DEC has potential for multiple oral combinations
- Therefore: importance of DEC-C

Fenaux et al, *Lancet Oncology* 2009; Kantarjian et al, *Cancer* 2006, Cabrero et al, *Leuk Res* 2015

Oral HMAs in MDS: introduction

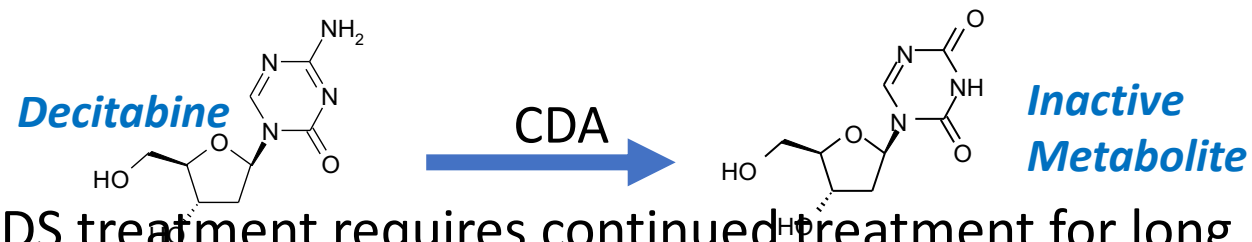
Two approaches to oral HMA

- **Combined with cytidine deaminase inhibitor**
  - **Cedazuridine (ASTX727 DEC-C)**
  - **Tetrahydrouridine**
- **Single agent uncombined (CC-486)**
- **Significant differences in PK profile**

Garcia-Manero: Blood 2020; Molokie: Plos Med 2017; Garcia-Manero: JCO 2011

Oral decitabine/cedazuridine

- Intravenous (IV) Decitabine(DAC) is an approved therapy for MDS
- Oral bioavailability of DAC is low due to degradation in the gut by cytidine deaminase (CDA)



- MDS treatment requires continued treatment for long periods.
- An oral decitabine would provide significant benefit
- Development of a potent safe CDA inhibitor should enable decitabine oral bioavailability

Garcia-Manero et al, ASH 2016; Savona et al, *Lancet Hematology*, 2019

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BRITISH JOURNAL OF HAEMATOLOGY

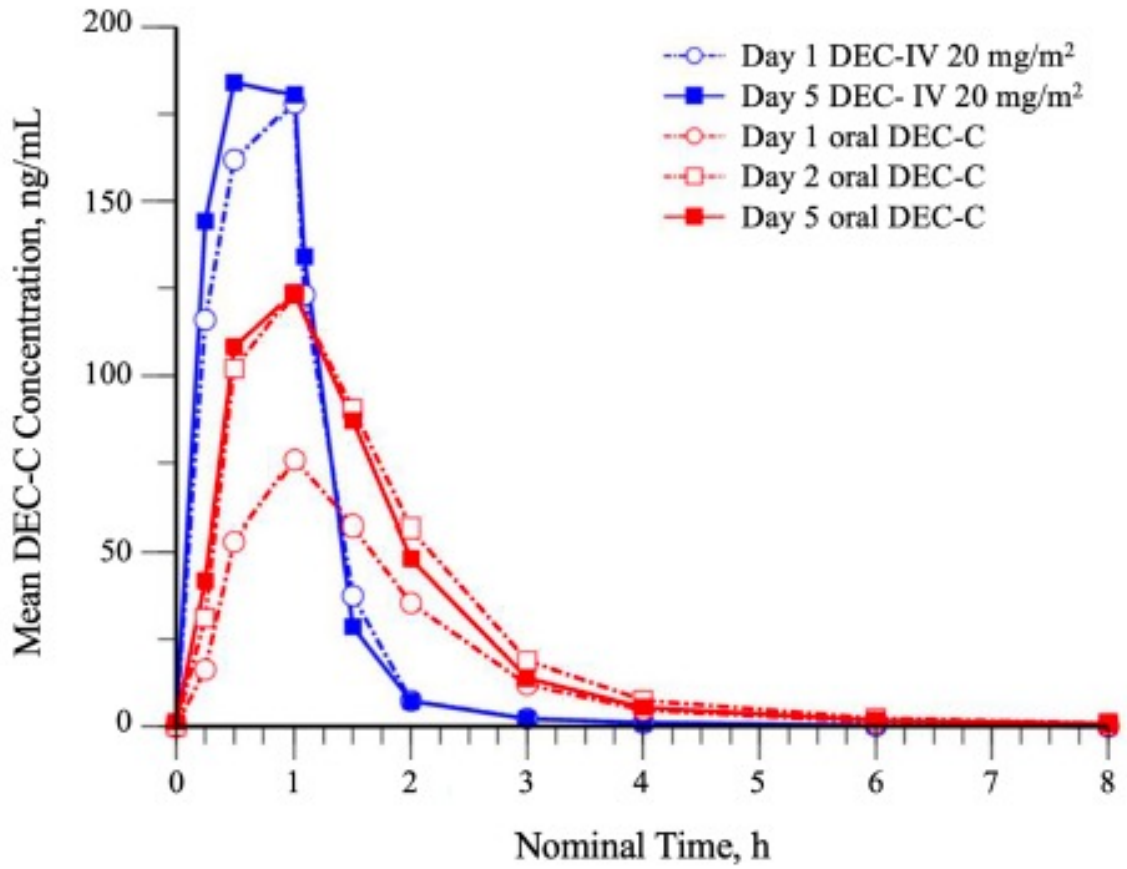
ORIGINAL PAPER

Haematological Malignancy – Clinical

Oral decitabine/cedazuridine versus intravenous decitabine for acute myeloid leukaemia: A randomised, crossover, registration, pharmacokinetics study

Klaus Geissler[1] | Zdenek Koristek[2] | Teresa Bernal del Castillo[3] | Jan Novák[4] | Gabriela Rodríguez-Macías[5] | Stephan K. Metzelder[6] | Arpad Illes[7] | Jiří Mayer[8] | Montserrat Arnan[9] | Mary-Margaret Keating[10] | Jürgen Krauter[11] | Monia Lunghi[12] | Nicola Stefano Fracchiolla[13] | Uwe Platzbecker[14] | Valeria Santini[15] | Yuri Sano[16] | Aram Oganesian[16] | Harold Keer[16] | Michael Lübbert[17]

DEC-C vs decitabine IV plasma concentrations

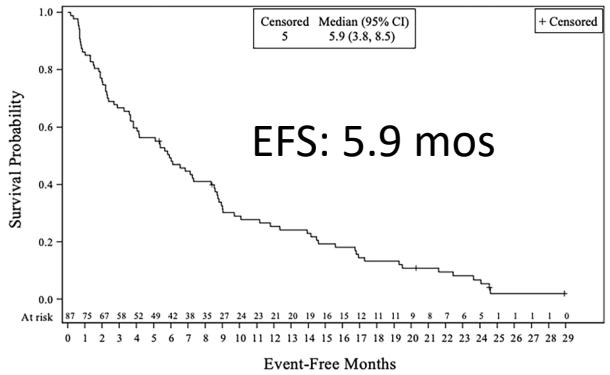


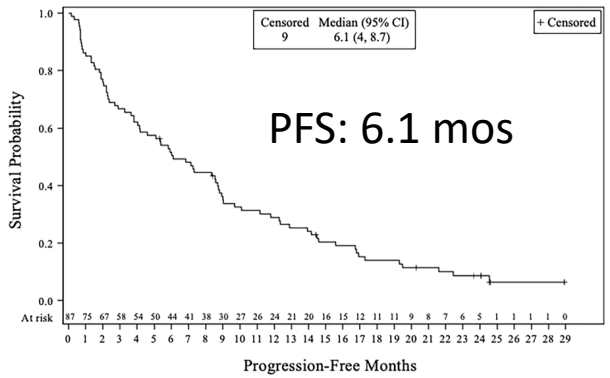
Baseline AML pts characteristics

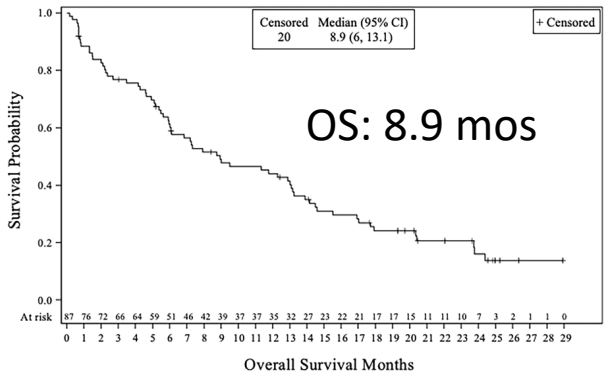
Baseline characteristic	Oral DEC-C (*n*=80)	All treated patients (*N*=87)
Age, *n*		
Mean (SD)	76.3 (6.77)	76.7 (6.71)
Median (range)	76.5 (61, 92)	78.0 (61, 92)
Age ≥75 years, *n* (%)	23 (62.2)	56 (64)
Study disease, *n* (%)		
De novo AML	51 (64)	55 (63)
Secondary AML	29 (36)	32 (37)
MDS	17 (21)	18 (21)
Other haematological disorder	6 (8)	7 (8)
Therapy-related AML	6 (8)	7 (8)
ECOG performance status, *n* (%)		
0	33 (41)	35 (40)
1	46 (58)	51 (59)
2	1 (1)	1 (1)
>30% Bone marrow blasts, *n* (%)	39 (49)	45 (52)
2022 ELN risk category, *n* (%)		
Favourable	4 (5)	4 (5)
Intermediate	18 (23)	19 (22)
Adverse	57 (71)	63 (72)
Not evaluable	1 (1)	1 (1)

TP53mut AML 16 + 18

DEC-C in AML :
event-free, progression-free and overall survival







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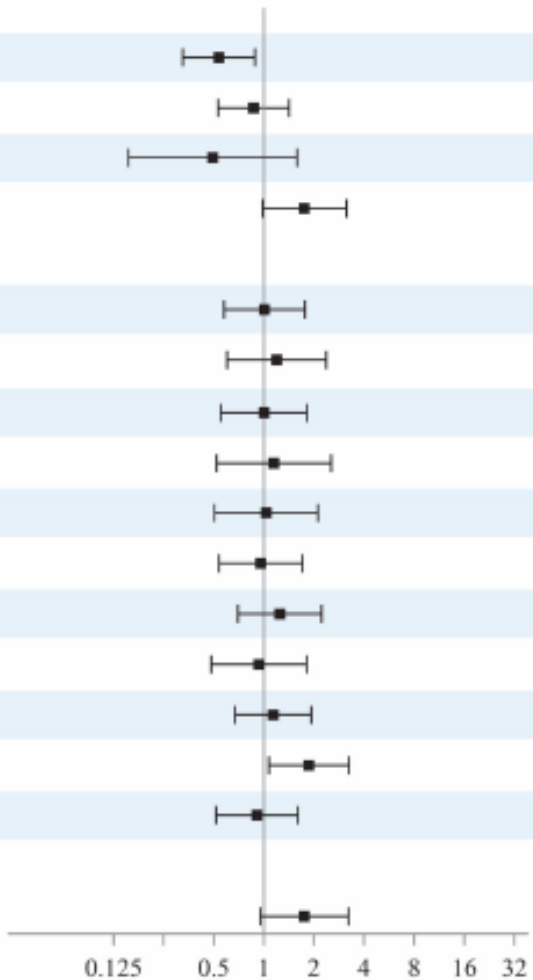
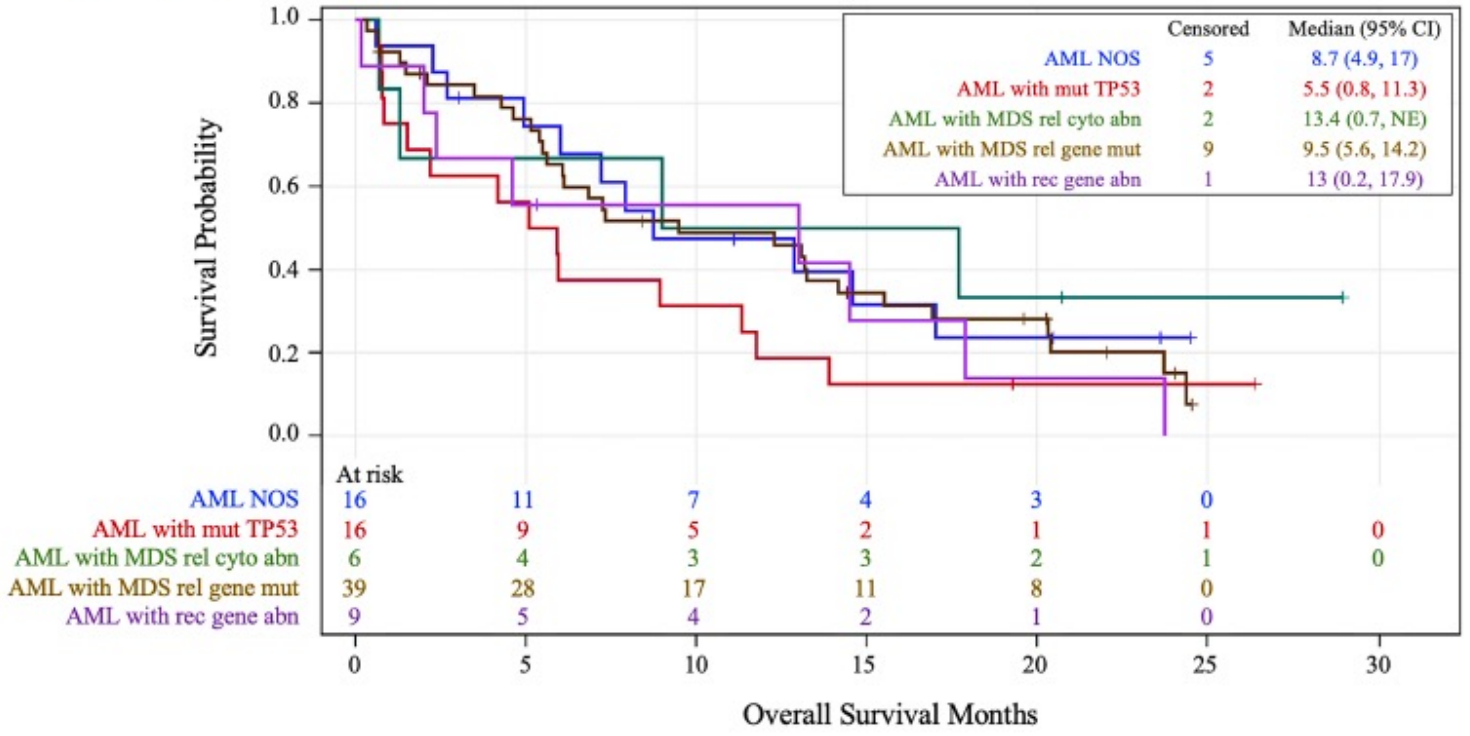


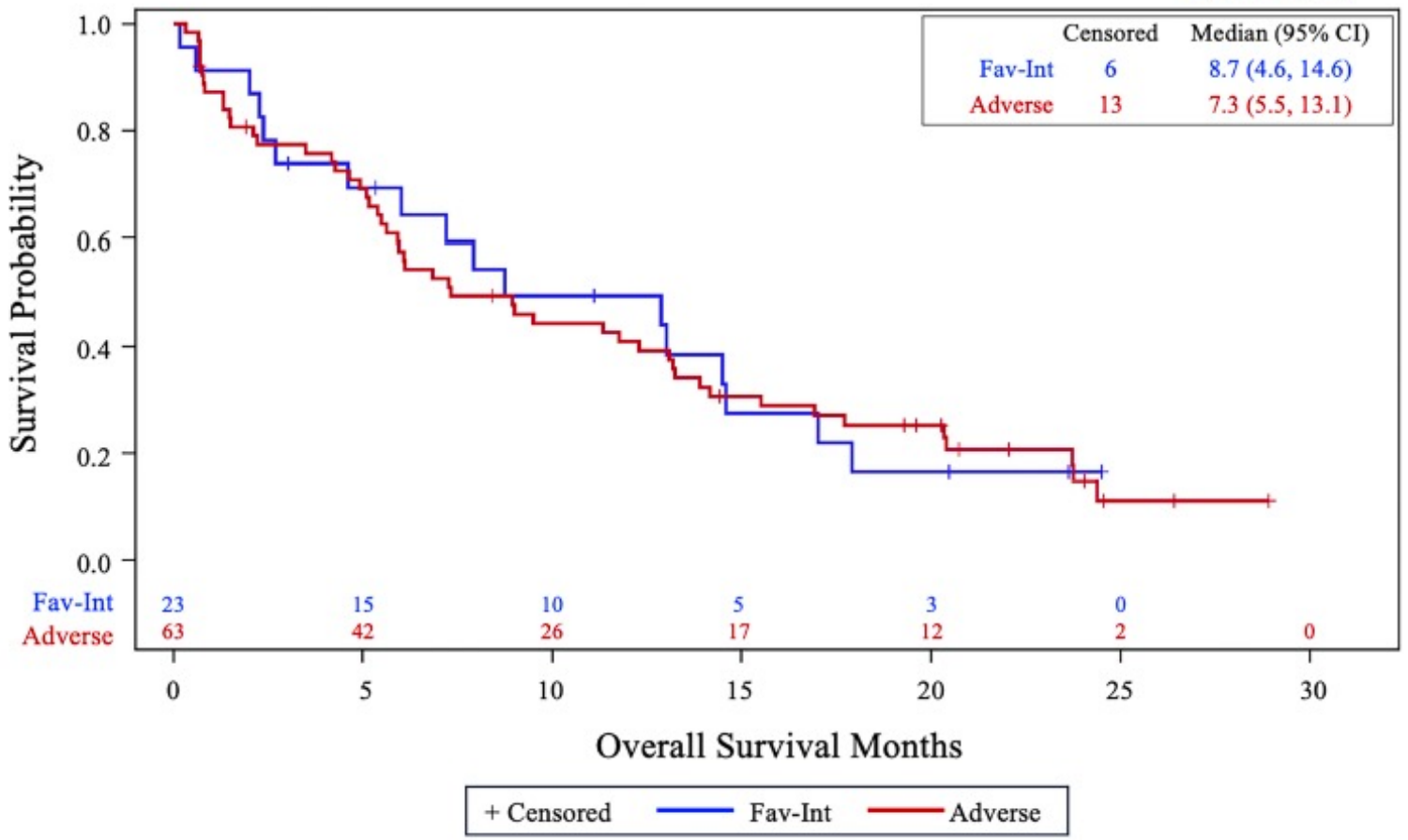
	Hazard Ratio (95% CI)	n	Hazard Ratio (95% CI)
Baseline			
Platelet count (>50x10⁹/L vs ≤50x10⁹/L)		87	0.536 (0.327, 0.881)
ECOG baseline (0 vs 1)		87	0.866 (0.529, 1.418)
Treatment-related AML (yes vs no)		87	0.493 (0.154, 1.577)
Complex karyotype (yes vs no)		87	1.753 (0.980, 3.137)
Gene mutations			
ASXL1 (VAF % >2 vs ≤2)		76	1.008 (0.576, 1.763)
BCOR (VAF % >2 vs ≤2)		76	1.194 (0.602, 2.367)
DNMT3A (VAF % >2 vs ≤2)		76	1.001 (0.553, 1.812)
FLT3-ITD (VAF % >2 vs ≤2)		76	1.150 (0.521, 2.537)
IDH2 (VAF % >2 vs ≤2)		76	1.032 (0.505, 2.107)
RUNX1 (VAF % >2 vs ≤2)		76	0.959 (0.539, 1.704)
SRSF2 (VAF % >2 vs ≤2)		76	1.247 (0.699, 2.224)
STAG2 (VAF % >2 vs ≤2)		76	0.932 (0.483, 1.800)
TET2 (VAF % >2 vs ≤2)		76	1.138 (0.670, 1.934)
TP53 (VAF % >2 vs ≤2)		76	1.869 (1.075, 3.250)
Number of gene mutations (≤4 vs <4)		76	0.909 (0.517, 1.599)
Adverse event			
Neutropenia Grade 4 (no vs yes)		87	1.750 (0.952, 3.216)

Overall survival per AML subtype



ICC AML Type	n†	Median OS, mo	Time	Survival, %	95% CI
NOS	16	8.8	1-year OS	47	22, 69
			2-year OS	24	6, 48
Mutated *TP53**	16	5.5	1-year OS	19	5, 40
			2-year OS	13	2, 33
MD-rel cyto abn	6	13.4	1-year OS	50	11, 80
			2-year OS	33	5, 68
MD-rel gene mut	39	9.5	1-year OS	49	32, 64
			2-year OS	15	5, 31
Rec gene abn	9	13.0	1-year OS	56	20, 80
			2-year OS	0	

Overall survival according to ELN risk



DEC-C safety

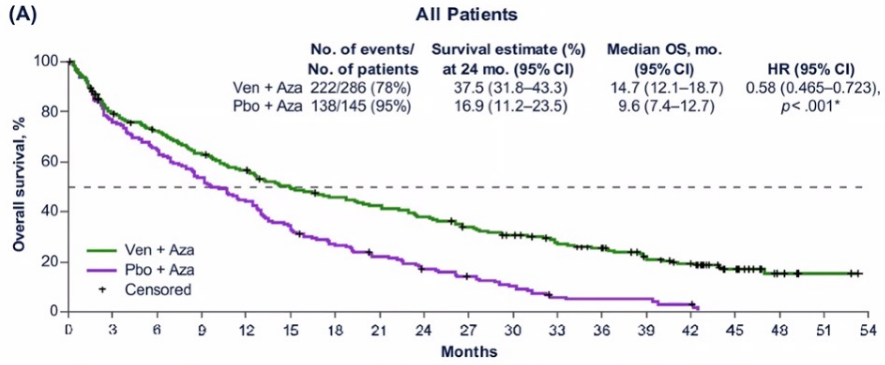
Patients, *n* (%)	Efficacy set (*n* = 87)	Oral DEC-C (*n* = 80)
≥1 TEAE regardless of relation to treatment[b]	86 (99)	80 (100)
Thrombocytopenia	50 (58)	47 (59)
Anaemia	45 (52)	44 (55)
Neutropenia	28 (32)	28 (35)
Febrile neutropenia	26 (30)	25 (31)
Asthenia	22 (25)	22 (28)
Pneumonia	22 (25)	19 (24)
Pyrexia	19 (22)	19 (24)
Diarrhoea	18 (21)	18 (23)
Nausea	17 (20)	17 (21)
Peripheral oedema	16 (18)	16 (20)
Constipation	17 (20)	15 (19)
Hypokalaemia	15 (17)	15 (19)
Decreased appetite	12 (14)	12 (15)
≥1 Grade ≥3 TEAE regardless of relation to treatment[b]	52 (66)	43 (55)
Thrombocytopenia	43 (49)	41 (51)
Anaemia	33 (38)	33 (41)
Neutropenia	26 (30)	26 (32)
Febrile neutropenia	24 (28)	23 (29)
Pneumonia	21 (24)	18 (23)
Treatment-related TEAEs[b]		
≥1 TEAE	60 (69)	57 (71)
Thrombocytopenia	27 (31)	26 (33)
Neutropenia	20 (23)	20 (25)
Anaemia	17 (20)	17 (21)

Future possible combinations of DEC-C in AML

But we know that the standard of care for unfit AML is a combination:

Azacitidine/Venetoclax (Aza/Ven) for Newly Dx Older/Unfit AML

- **VIALE-A: Randomized Phase 3 study of Azacitidine + Venetoclax vs. Azacitidine + Placebo**
- Eligibility: Newly Dx AML ≥75 years or unfit for intensive chemo (Median Age = 76 years)



CR/CRi rates: 67% vs. 29% (p<0.001)

Paradigm shift in management of older adults with AML

- **Long-term outcomes remain poor- 2 year OS <40%**
- **Full CR rates are low (37%) and ~1/3 of pts will not respond to treatment**
- **Dismal outcomes in *KMT2Ar***
  - **Mayo Clinic Analysis: CR/CRi rates = 43%, median OS = 2.5 months in *KMT2Ar* Tx with Aza/Ven**
- **~50% of *NPM1m* AML have Intermediate-risk ELN-2024 (*FLT3-ITD*, *NRAS* or *KRAS* mut)**
  - **Poor outcomes (CR/CRi = 57%, median OS <10 months)**

BEAT AML® MASTER CLINICAL TRIAL

DiNardo, *N Engl J Med* 2020; Pratz, *Am J Hematol* 2024; Gangat, *Am J Hematol* 2024, Dohner, *Blood* 2024

LEUKEMIA & LYMPHOMA SOCIETY®

Oral decitabine and cedazuridine plus venetoclax for older or unfit patients with acute myeloid leukaemia: a phase 2 study

62 pts, median age 78 yrs

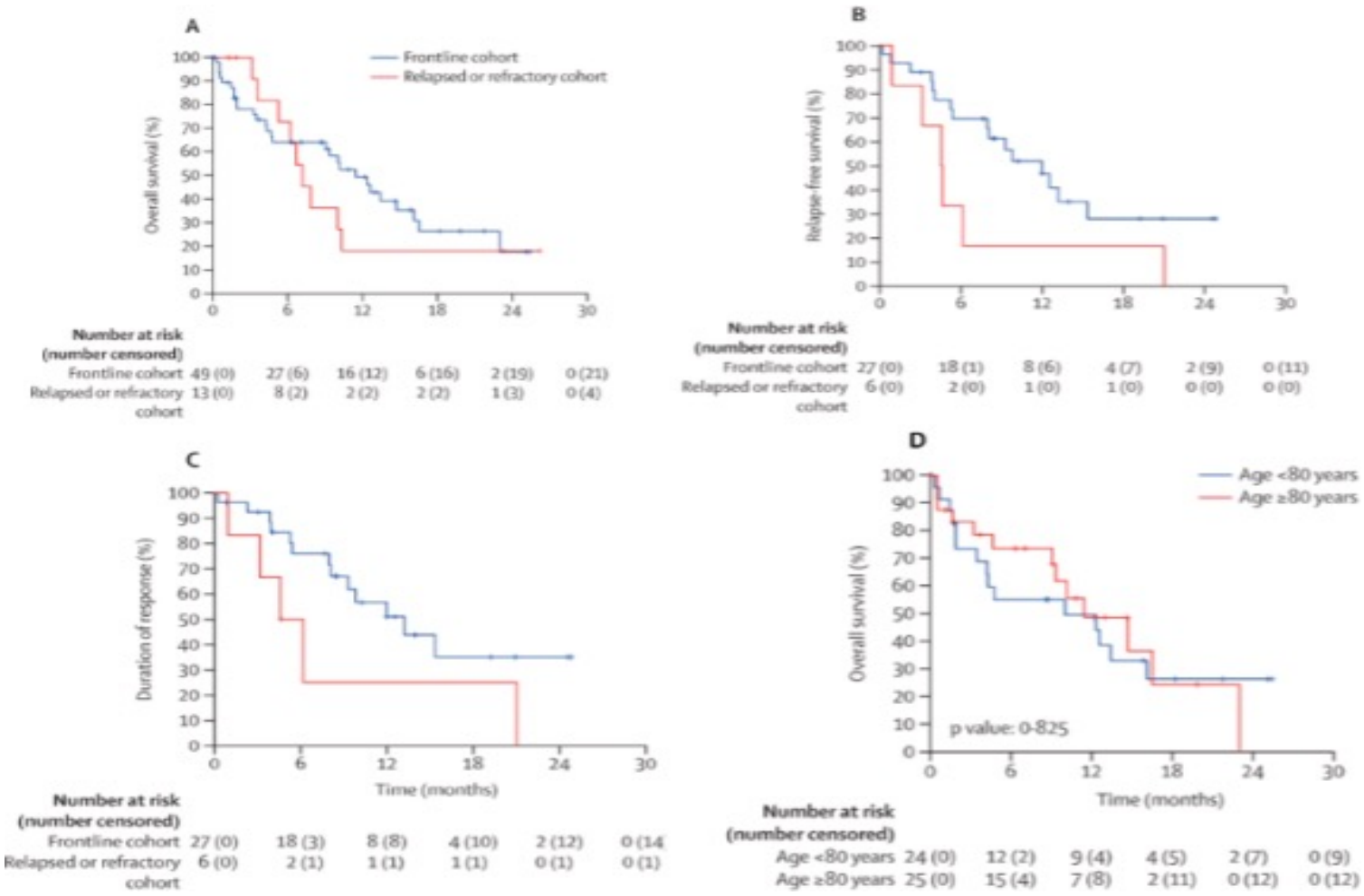
	Frontline treatment cohort (n=47)	Relapsed or refractory disease treatment cohort (n=13)
Overall response rate†	30 (64%; 49–77)	6 (46%; 19–75)
Complete remission	16 (34%; 21–49)	4 (31%; 9–61)
Complete remission with incomplete blood count recovery	11 (23%; 12–38)	2 (15%; 2–45)
Partial remission	0 (0%; 0–8)	0 (0%; 0–25)
Morphologic leukaemia-free state	3 (6%; 1–18)	0 (0%; 0–25)
Cycles given	3 (1–7)	3 (2–4)
Cycles to first response	1 (1–1)	1 (1–1)
Cycles to best response	1 (1–1)	2 (1–2)
4-week mortality	5 (11%; 4–23)	0 (0%; 0–25)
8-week mortality	8 (17%; 8–31)	0 (0%; 0–25)

Data are n (%; 95% CI) or median (IQR). *Two patients in the frontline cohort have not yet completed cycle one. †Overall response rate is the sum of complete remission, complete remission with incomplete blood count recovery, partial remission, and morphologic leukaemia-free state.

Table 2: **Responses in evaluable patients***

Bazinet et al , Lancet Haematol 2024

Overall survival after DEC-C + VEN



Bazinet et al , Lancet Haematol 2024

Future possible combinations of DEC-C in AML

News from EHA 2025

S135 – All-Oral Decitabine-Cedazuridine (DEC-C) + Venetoclax (VEN) in Patients With Newly Diagnosed Acute Myeloid Leukemia (AML) Ineligible for Induction Chemotherapy: Phase 1/2 Clinical Trial Results. Roboz R. (Oral Presentation)

ASCERTAIN-V: Background

- In patients with AML aged ≥75 years and ineligible for intensive induction chemotherapy (IIC), the combinations VEN with AZA, DEC, or LDAC received accelerated approvals in the United States and the European Union based on phase 1/2 trials[1,2]
- Clinical outcomes with AZA and DEC were comparable in newly-diagnosed patients with AML ineligible for IIC[3]
- The regimen of parenteral DEC or AZA is associated with a significant treatment burden[4] and questions remain regarding optimal duration of VEN dosing[5]
- Oral DEC-C (decitabine 35 mg and cedazuridine 100 mg) demonstrated equivalent PK AUC exposure to intravenous DEC in an AML population, which led to monotherapy approval in the EU. However, survival remains limited (mOS 9.0 mos.)[6,a]

5-day decitabine AUC_{0-24} for oral and IV formulations

	5-day DEC AUC_{0-24} LSM, h × ng/mL (n)			
Analysis	**IV DEC**	**Oral DEC-C**	**Ratio, % (90% CI)**	**Intrapatient CV (%)**
Primary endpoint Paired	907.39 (69)	904.13 (69)	99.64 (91.23, 108.8)	31.55

Reproduced from Geissler K, Koristek Z, Del Castillo TB, et al., "Oral decitabine/cedazuridine versus intravenous decitabine for acute myeloid leukaemia: A randomised, crossover, registration, pharmacokinetics study," *British Journal of Haematology*, 205(5), 1734–1745, 2024, with permission from John Wiley & Sons.
[a]Oral DEC-C is approved in European Union for patients with newly diagnosed AML who are ineligible for standard induction chemotherapy.
ASCERTAIN-V, AStx727-07: decitabine + CEdazuRidine TreAtment In Newly diagnosed AML adding Venetoclax; AML, acute myeloid leukemia; AUC, area under the curve; AUC_{0-24}, area under the curve from 0 to 24 hours; AZA, azacitidine; CI, confidence interval; CV, coefficient of variation; DEC, decitabine; DEC-C, decitabine-cedazuridine; IIC, intensive induction chemotherapy; IV, intravenous; LDAC, low-dose cytarabine; LSM, least squares mean; mOS, median overall survival; PK, pharmacokinetics; VEN, venetoclax.
1. DiNardo CD et al. *Lancet Oncol.* 2018;19:216–28. 2. Wei AH et al. *J Clin Oncol.* 2019;37:1277–84. 3. Zeidan AM et al. *Blood*. 2022;140:285–9. 4. DiNardo CD et al. *Blood*. 2019;133:7–17. 5. Wei A et al. *Blood*. 2025;145:1237-50. 6. Geissler et al. *Br J Haematol*. 2024;205(5):1734–45.

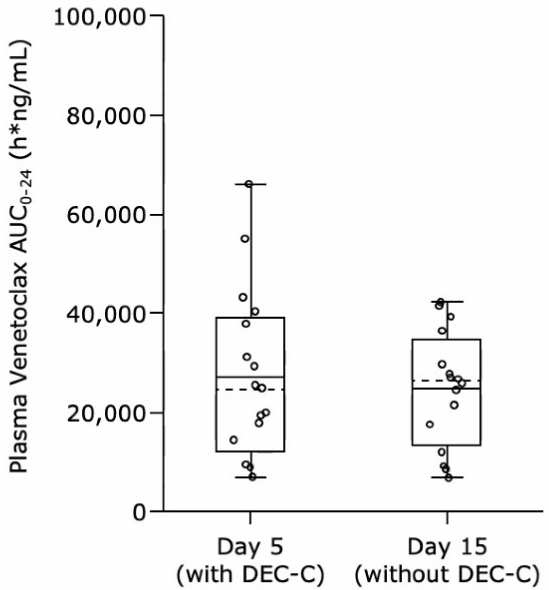
ASCERTAIN-V: Results
Pharmacokinetics

Plasma VEN DDI Assessment: DEC-C and VEN, and VEN Alone – Combined Phase 1 and Phase 2A

PK Parameter	Units	DEC-C + VEN Geo LSM (n=54)	VEN Geo LSM (n=49)	Ratio of Geo LSM (%)	90% CI
AUC_{0-24}	h*ng/mL	26,310[a]	25,780[b]	102.0	(87.25–119.3)
C_{max}	ng/mL	1879	1931	97.30	(85.31–111.0)

- PK data confirmed no DDIs between DEC-C and VEN
  - No DDI effect from DEC-C on VEN in phase 1 and 2A
  - No effect from VEN on DEC-C (DEC-C data compared to ASCERTAIN-AML)
- **Primary objective for phase 1 and secondary objective from phase 2 were met (no DDIs)**

VEN C2D5 and C2D15 AUC_{0-24h} boxplot (Phase 1)



[a]n=52; [b]n=45.
Reference treatment = VEN alone (Cycle 2 Day 15); Test treatment = DEC-C + VEN (Cycle 2 Day 5). ASCERTAIN-V, AStx727-07: decitabine + CEdazuRidine TreAtment In Newly diagnosed AML adding Venetoclax; AUC_{0-24}, area under the curve from 0 to 24 hours; CI, confidence interval; DDI, drug-drug interactions; DEC-C, decitabine-cedazuridine; Geo LSM, geometric least square means; PK, pharmacokinetics; VEN, venetoclax.

ASCERTAIN-V: Results
Best Overall Response and Duration of Response

	Phase 1 (n=30)	Phase 2A (n=58)	Phase 2B (n=101)
Best overall response, %			
CR,% (95% CI)	40.0 (22.7–59.4)	37.9 (25.5–51.6)	46.5 (36.5–56.7)
CRi, %	23.3	27.6	16.8
CRh, %	16.7	20.7	5.0
CR+CRi, % (95% CI)	63.3 (43.9–80.1)	65.5 (51.9–77.5)	63.4 (53.2–72.7)
CR+CRh, % (95% CI)	56.7 (37.4–74.5)	58.6 (44.9–71.4)	51.5 (41.3–61.6)
CR+CRi+CRh, % (95% CI)	63.3 (43.9, 80.1)	65.5 (51.9, 77.5)	63.4 (53.2–72.7)
Median time to complete response, months	1.9 (0.9–9.6)	2.4 (0.8–12.2)	2.4 (0.7–15.3)
CR duration, %[a]			
Responders continuing CR at 9 months	75.0 (40.8–91.2)	76.2 (51.9–89.3)	80.0 (63.9–89.5)
Median duration of follow-up, months	34.3	26.0	11.2

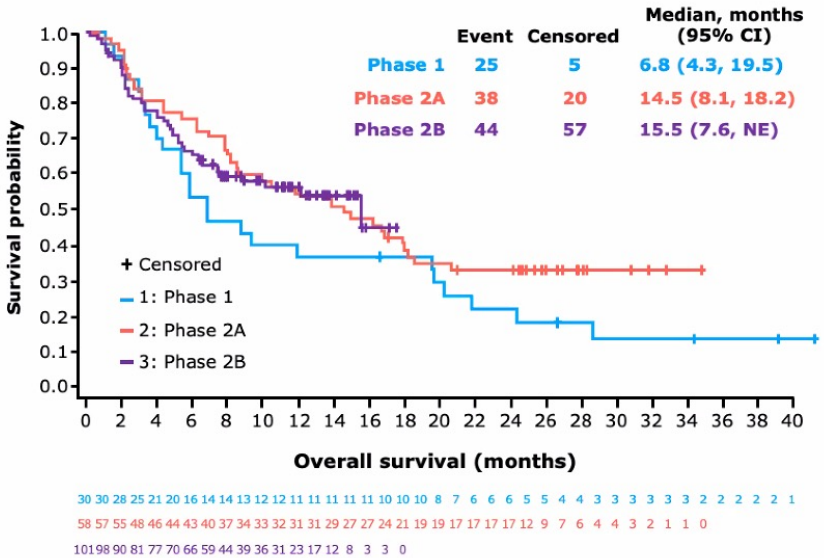
- A subgroup analysis of phase 2B demonstrated consistency in CR rate across age, sex, region, baseline ECOG PS, prior systemic therapy, and cytogenetic classification

[a]Median CR duration was not reached. CR duration defined as the time from the first documentation of CR to the first documentation of disease progression or death due to any cause, whichever occurs first.
ASCERTAIN-V, AStx727-07: decitabine + CEdazuRidine TreAtment In Newly diagnosed AML adding Venetoclax; CI, confidence interval; CR, complete response; CRh, complete response with partial hematologic recovery; CRi, complete response with incomplete hematologic recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; MRD, minimal residual disease.

ASCERTAIN-V: Results
Overall Survival

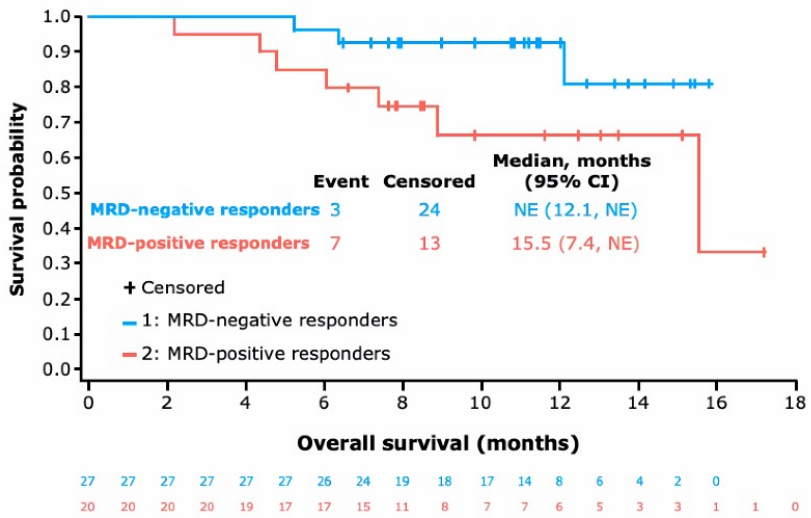
Median OS:

- Phase 1: 6.8 (95% CI, 4.3–19.5) months
- Phase 2A: 14.5 (95% CI, 8.1–18.2) months
- Phase 2B: 15.5 (95% CI, 7.6–NE) months



In phase 2B, 49 patients with CR/CRh/CRi had MRD evaluated by local multi-parameter flow cytometry[a]:

- 27 (55.1%) of patients achieved MRD negativity at any time
- mOS MRD-negative: NE (95% CI 12.1–NE)
- mOS MRD-positive: 15.5 months (95% CI 7.4–NE)



[a]MRD negativity was assessed according to local site standards.
ASCERTAIN-V, AStx727-07: decitabine + CEdazuRidine TreAtment In Newly diagnosed AML adding Venetoclax; CI, confidence interval; m, median; MFC, multi-parameter flow cytometry; NE, not estimable; OS, overall survival.

ASCERTAIN-V: Conclusions

- No drug-drug interactions were observed between DEC-C and VEN
- The pivotal phase 2B trial met its primary endpoint of complete response
  - CR rate: 46.5% [95% CI: 36.5%–56.7%]
  - Median OS: 15.5 months
  - Durable responses, with 75% ongoing at 12 months
- Most frequent Grade ≥3 AEs were anemia (25.9%), neutropenia (21.2%), and febrile neutropenia (20.6%); 30- and 60-day mortality rates were as expected in this clinical setting
- Earlier bone marrow assessment allowed reduced dosing days of VEN and/or DEC-C after clearance of bone marrow blasts in some patients without compromising efficacy
- DEC-C + VEN resulted in comparable safety, response, and survival rates to parenteral AZA + VEN as described in VIALE-A,[1] though cross-trial comparisons cannot be made

In newly diagnosed patients with AML ineligible for intensive chemotherapy, the all-oral regimen of DEC-C + VEN represents a potential new standard of care.

ASCERTAIN-V, AStx727-07: decitabine + CEdazuRidine TreAtment In Newly diagnosed AML adding Venetoclax; AE, adverse event; AML, acute myeloid leukemia; AZA, azacitidine;

DAC + VEN + Quizartinib in FLT-ITD mutated AML

Primary Objective:

- To establish RP2D of quizartinib in combination with DAC + VEN in pts with FLT3m AML

Secondary Objective:

- To determine complete remission (CR), CR with incomplete count recovery (CRi), minimal residual disease (MRD), and overall survival (OS)

Patients	Induction	Consolidation
•Relapsed/Refractory FLT3-mutated* AML or high-risk MDS (≥10% blasts) *or* •Newly diagnosed FLT3-mutated* AML unfit for intensive chemoRx	Decitabine 20 mg/m^2 IV on D1-10 Venetoclax** 400 mg/day D1-D21 (BM biopsy on D14) Quizartinib 30-40 mg/day on D1-28#	Decitabine 20 mg/m^2 IV on D1-5 Venetoclax*** 400 mg/day D1-D14 Quizartinib 30-40 mg/day on D1 to 28

*FLT3-ITD with/without TKD mutations allowed

**Venetoclax discontinued on D14 in pts with BM blasts ≤5% or hypoplastic BM
#Amendment - reduced quizartinib to 14 days in C1

Up to 12 cycles. ***Venetoclax duration reduced to 14 > 10 >7 days in subsequent cycles for pts in CR based on count recovery durations. Quizartinib dose reduced to 14 days in pts with prolonged count recovery