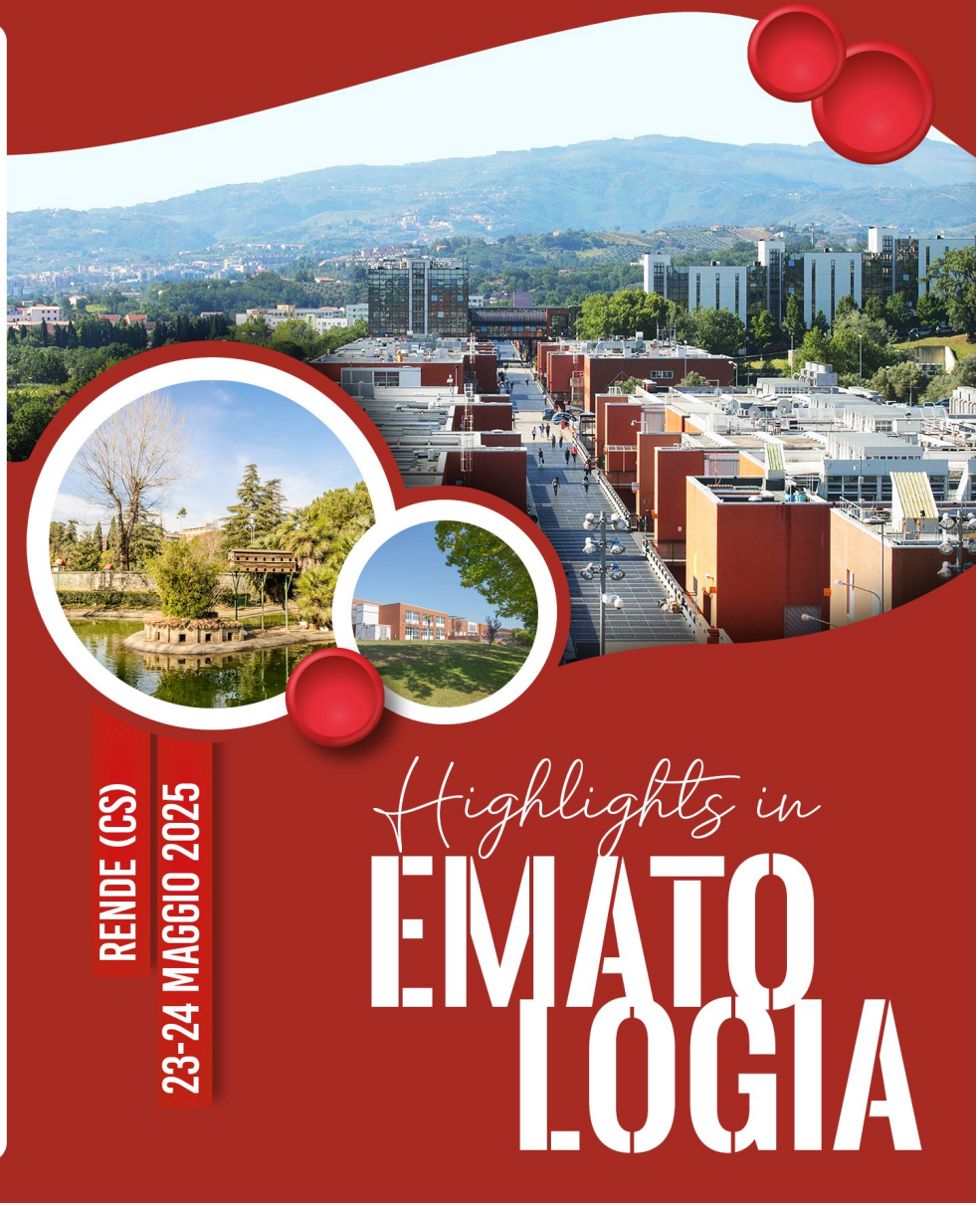
AML in very frail patients: a case report

Antonella Bruzzese
AO Cosenza



♂ M.G.(dn 28/09/1934)

27/01/2025

- Hb 8.3 g/dl, plts 34.000/mmc, **WBC 68040/mmc**, N 2360/mmc, L 51480/mmc, M 14010/mmc
- **Crea 2,15**
- INR 1, aPTT 26,3 sec, FBG 318 mg/dl

Anamnesi

- Atrial fibrillation
- Chronic renal impairment
- Chronic obstructive pulmonary disease
- Obesity
- Retired (ex company manager)
- Married
- Lives near to the hospital with his wife and a son that works as a manager

♂ M.G.(dn 28/09/1934)

Diagnosis

- Peripheral blood smear: 75% di blasti CD34+/CD13+
- Cytogenetic: not valuable
- Molecular analysis: FLT3-ITD^{mut}, NPM1^{mut}, IDH1/2^{wt}

Acute myeloid leukemia

- Patient started HU

03/02/2025

- Emocromo: Hb 8.8 g/dl, plts 1800/mmc, WBC 78300/mmc, N 2380/mmc, L 53010/mmc, M 22690/mmc

Vinblastine 5 mg ev

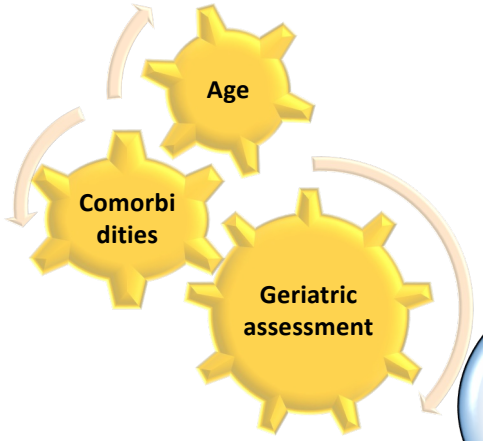
Which choice?

- **Very elderly patient**
- **Good quality of life**
- **Relevant comorbidities**
- **Easy access to the hospital**

What is fitness?

Or even better fitness for?

Every hematologist should be a good geriatric to choose the best treatment for elderly patients



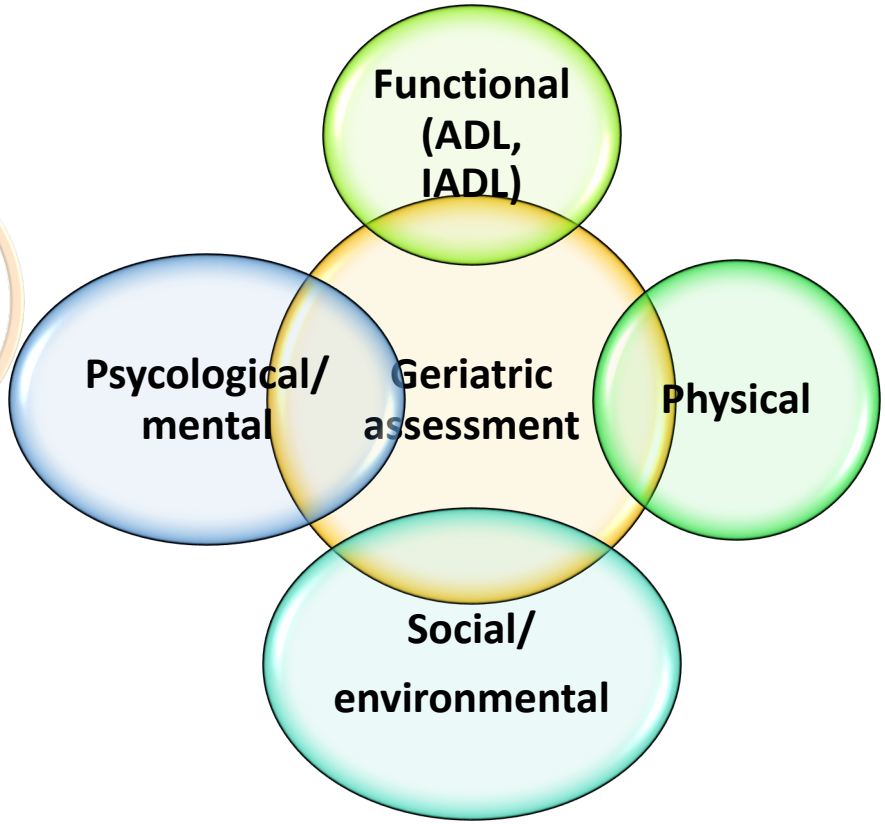


Table 1 – Dimensions used for the development of the GAH scale.

Dimension	Measurement	Range of score	Cut-off point (1 point)
No. of drugs	Medication count of drugs of current use.	Continuous	≥5[17]
Gait speed	Double determination of gait speed at usual pace over a 4 meter course[19,20]	Continuous	<0.8 m/s[21]
Mood	Single item from the CES-D[22]: *In the last week, did you feel depressed?*	Never, rarely, or occasionally (no more than 2 days); frequently, most of the time or all time (3–7 days)	Frequently, most of the time or all time (3–7 days)
Activities of daily living	• Item no. 4 of the VES-13 Instrument[24]: *Do you have any difficulty in …?* • Do you need any help in your daily living? • Do you have a caregiver?	Yes/no	Needs help in at least one area
Subjective health status	Single item from the VES-13 Instrument[24]: *Compared to other people your age, would you say your health is…?*	Poor, fair, good, very good, or excellent	Poor and fair
Nutrition	Four items from the MNA-SF[30]: *BMI, weight loss during the last 3 months, food intake decline over the past 3 months, and psychological stress or acute disease.*	0–10	≤8
Mental status	SPMSQ[31]	Right/wrong	≥3 errors
Comorbidities	Prognostic Index for 4-year Mortality in Older Adults[35]	0, for absence; 1 point for DM or BMI < 25 kg/m^2; 2 points for cancer, lung disease, heart failure, or smoking habit.	≥3

Abbreviations: BMI, body mass index; CES-D, Centre for Epidemiological Studies Depression Scale; DM, diabetes mellitus; MNA-SF, Mini-Nutritional Assessment questionnaire; SPMSQ, Short Portable Mental Status Questionnaire; VES-13, 13-item Vulnerable Elders Survey.

Bonanad S. J Geriatr Oncol. 2015 Sep;6(5):353-61

Criteria for fitness

Operation criteria to define unfitness to intensive chemotherapy in AML
Age older than 75 years old
Congestive heart failure or documented cardiomyopathy with an EF ≤50%
Documented pulmonary disease with DLCO ≤65% or FEV1 ≤65%, or dyspnea at restor requiring oxygen or any pleural neoplasm or uncontrolled lung neoplasm
On dialysis and age ≥60 years or uncontrolled renal carcinoma
Liver cirrhosis Child B or C, or documented liver disease with marked elevation of transaminases (> 3times normal values) and an age >60 years, or any biliary tree carcinoma or uncontrolled liver carcinoma or acute viral hepatitis
Active infection resistant to anti-infective therapy
Current mental illness requiring psychiatrich ospitalization, institutionalization or intensive out patient management, or current cognitive status that produces dependence (as confirmed by the specialist) not controlled by the caregiver
ECOG performance status ≥3 not related to leukemia
Any other comorbidity that the physician judges to be incompatible with conventional intensive chemotherapy

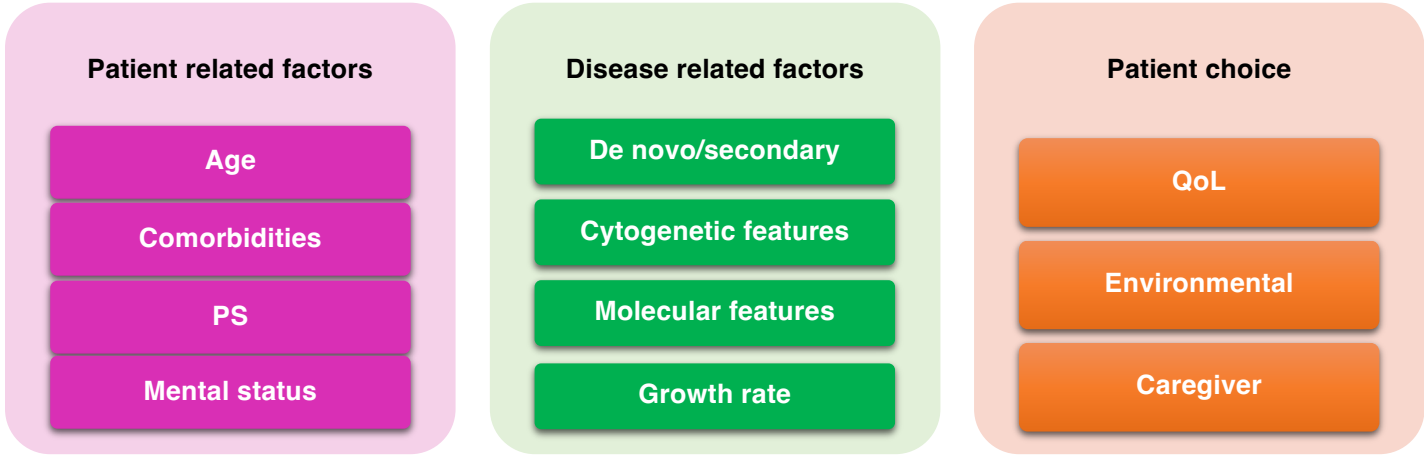
Operation criteria to define unfitness to non-intensive chemotherapy in AML
Refractory congestive heart failure
Documented pulmonary disease with DLCO <65% or FEV1 <65%, or dyspnea at rest or requiring oxygen, or any pleural neoplasm or uncontrolled lung neoplasm
Liver cirrhosis Child B or C or acute viral hepatitis
Active infection resistant to anti-infective therapy
Current mental illness requiring psychiatric hospitalization, institutionalization or intensive out patient management, or current cognitive status that produces dependence (as confirmed by the specialist) not controlled by the caregiver
Uncontrolled neoplasia

Ferrara F et al. Leukemia. 2013 Apr;27(5):997-9

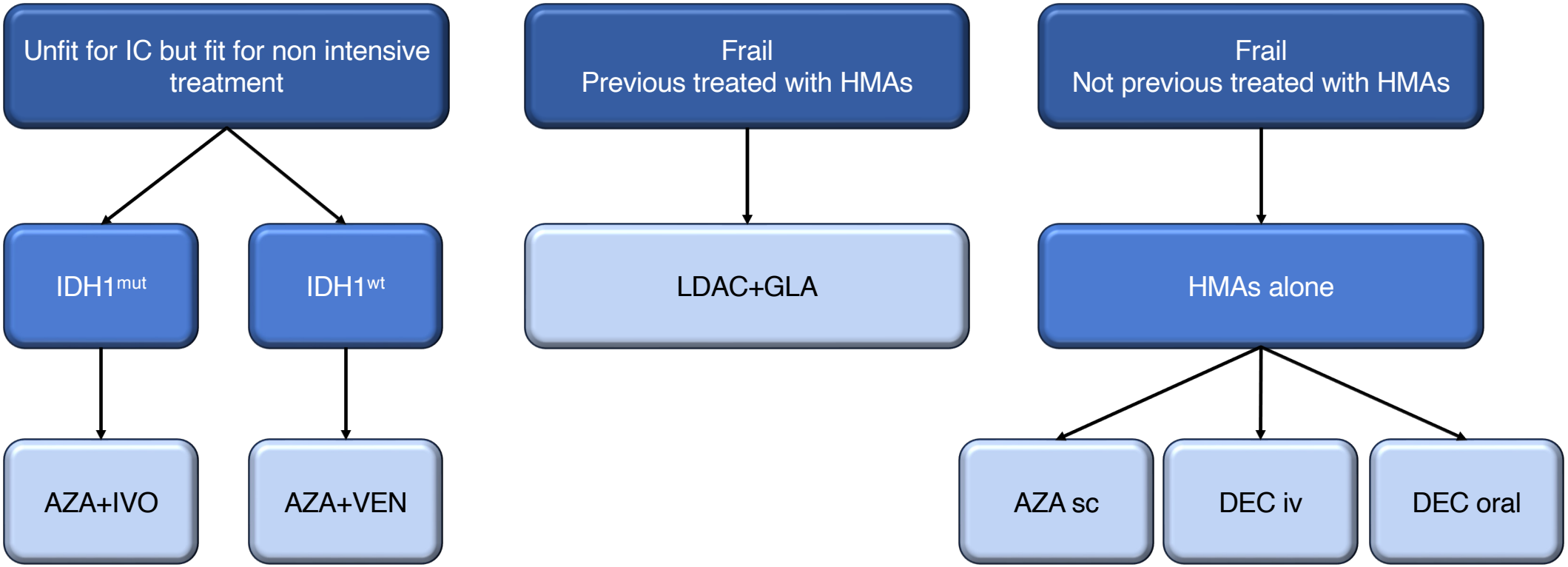
Criteria for fitness

Fitness assessment in acute myeloid leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet

Venditti A. Blood Adv. 2025 May 13;9(9):2207-2220



Therapeutic algorytm



ELN guidelines 2022

Treatment option for patients unfit for intensive treatment	
HMAs plus Venetoclax	Azacitidine 75 mg/m2 SC/IV d1-7 (alternatively d1-5 1 d8-9) or decitabine 20 mg/m2 IV d1-5; venetoclax dose ramp up: 100 mg d1, 200 mg d2, 400 mg PO QD d3-28 Adjust venetoclax dose if concurrent strong CYP3A4 inhibitors
HMAs alone	Azacitidine 75 mg/m2 SC/IV d1-7 (alternatively d1-5 1 d8-9) or decitabine 20 mg/m2 IV d1-5; venetoclax dose ramp up: 100 mg d1, 200 mg d2, 400 mg PO QD d3-28
Azacitidine plus Ivosidenib (IDHmut)	Azacitidine 75 mg/mq SC/IV d1-7 (alternatively d1-5 1 d8-9); ivosidenib 500 mg PO QD d1-28; both q4 wk, until progression
Oral decitabine/cetazuridine	Decitabine/catezuridine 35 mg/day oral d1-5
Glasdegib plus low dose cytarabine	Glasdegib 100 mg/day oral d1-28; cytarabine 20 mg/mq d1-10
Best supportive care	Transfusion, prophylaxis, HU

Döhner H et al. Blood. 2022 Sep 22;140(12):1345-1377

Non-intensive chemotherapy: AZA-VEN

Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia

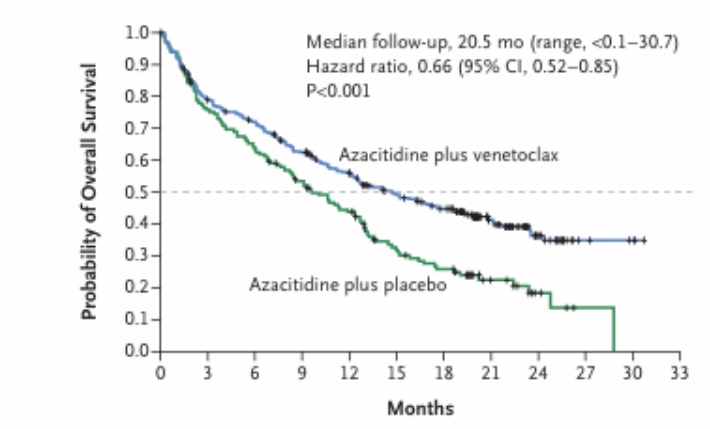
431 patients
286 in the AZA-VEN group
145 in the AZA-PLACEBO group

OS
- ***AZA/VEN*** 14,7 months
- ***AZA/Placebo*** 9,6 months

P<0.001

cCR
- ***AZA/VEN*** 66,4%
- ***AZA/Placebo*** 28,3%

P<0.001



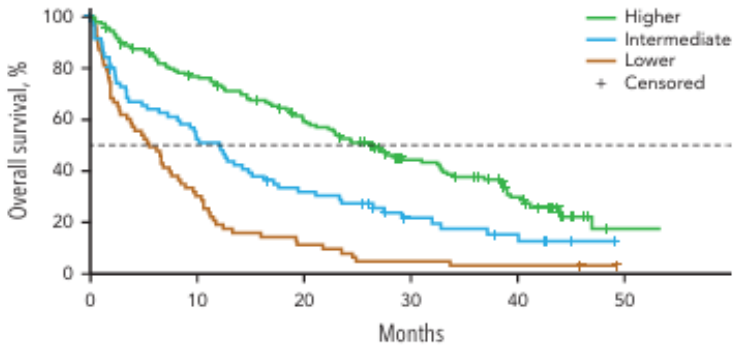
Serious adverse events	N Pts (%)
Febrile neutropenia	84 (30)
Anaemia	14 (5)
Neutropenia	13 (5)
Atrial fibrillation	13 (5)
Pneumoniae	47 (17)
Sepsis	16 (6)

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

Non-intensive chemotherapy: AZA-VEN

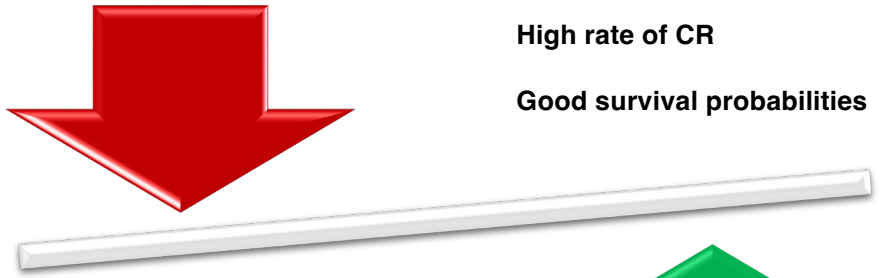
Genetic risk stratification and outcomes among treatment-naive patients with AML treated with venetoclax and azacitidine

Döhner H et al. Blood. 2024 Nov 21;144(21):2211-2222.



Prognostic outcome after AZA-vEN could be defined by the mutational status of only 4 genes.

- *higher-benefit group* had WT TP53 and KRAS/NRAS and lacked FLT3 internal tandem duplication (FLT3-ITD);
- *intermediate-benefit group* had WT TP53 but had FLT3-ITD and/or KRAS/NRAS mutation;
- *lower-benefit group* was positive for TP53 mutation



High rate of CR

Good survival probabilities

Intermediate risk molecular group

Daily sc administration

High percentage of severe cytopenias

ELN guidelines 2022

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Best supportive care	Transfusion, prophylaxis, HU

Döhner H et al. Blood. 2022 Sep 22;140(12):1345-1377

Non intensive chemotherapy: LDAC-GLA

Randomized comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome

OS
- ***LDAC/GLA*** 8.8 months
- ***LDAC alone*** 4.9 months

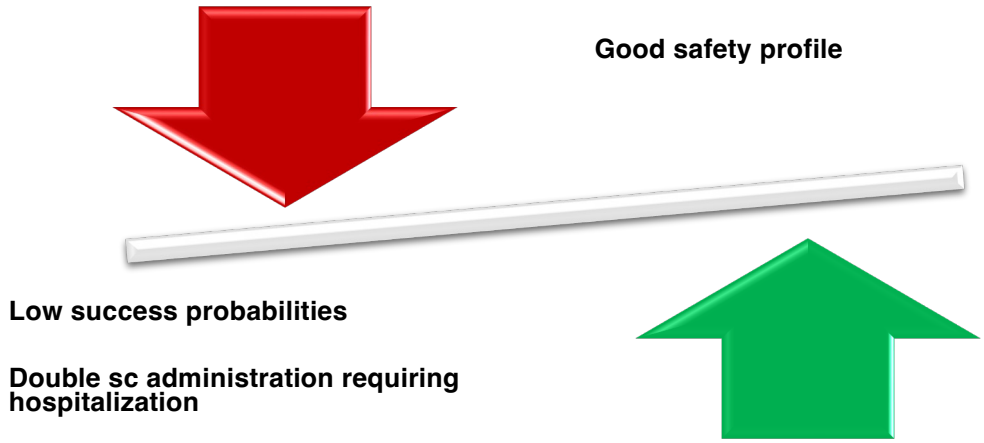
P = 0.0004

CR
- ***LDAC/GLA*** 17%
- ***LDAC alone*** 2,3%

P < 0.05

Cortes JE. Leukemia. 2019 Feb;33(2):379-389.

Nonhematologic grade 3/4 adverse events included **pneumonia (16.7%)** and **fatigue (14.3%)** with glasdegib/LDAC and pneumonia (14.6%) with LDAC.



ELN guidelines 2022

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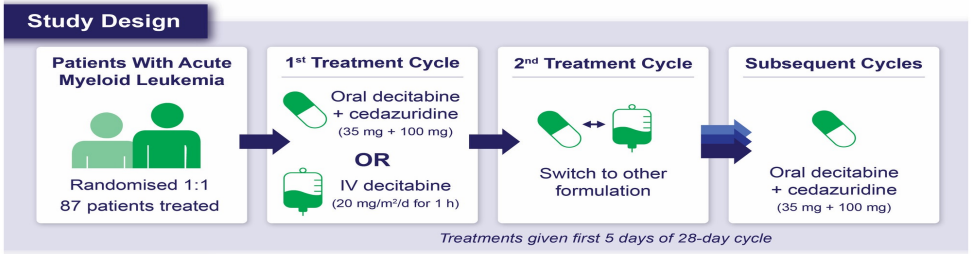
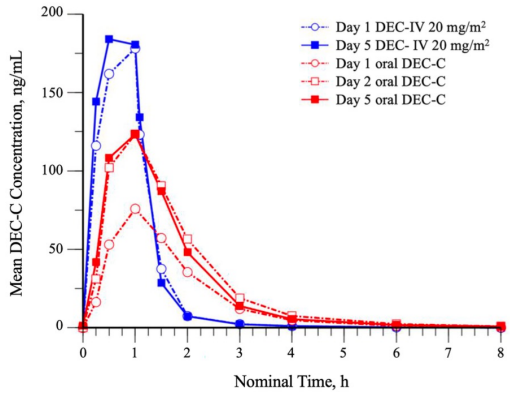
Döhner H et al. Blood. 2022 Sep 22;140(12):1345-1377

Non intensive chemotherapy: oral decitabine/cedazuridine

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

Geissler K. Br J Haematol. 2024 Nov;205(5):1734-1745

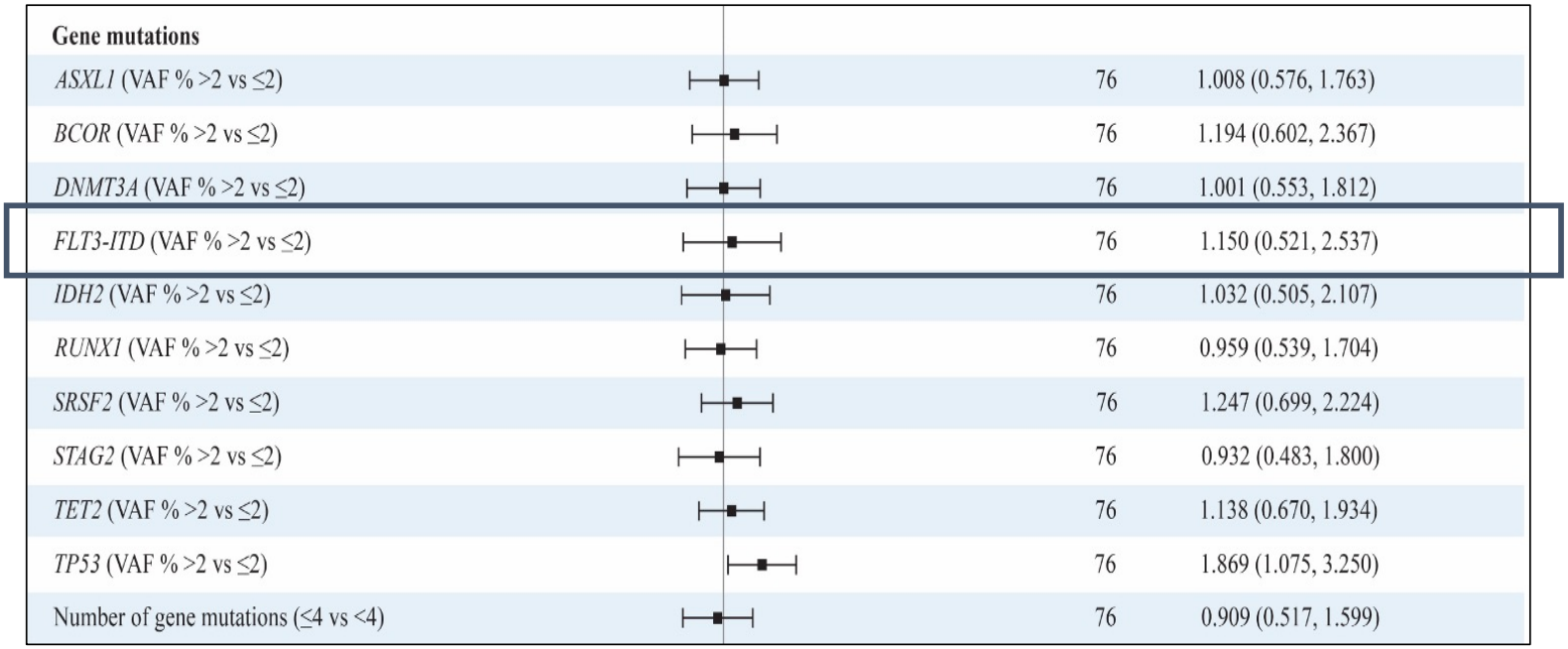




- 87 patients were treated
- 7 received only DEC-IV
- 8 received only oral DEC-C
- 80 received ≥1 dose of oral DEC-C.

	Efficacy set (n=87)		Oral DEC-C (n=80)	
Analysis	***n*** **(%)**	**95% CI**	***n*** **(%)**	**95% CI**
Best response				
CR	19 (21.8)	13.7, 32.0	19 (23.8)	14.9, 34.6
CRi	5 (5.7)	1.9, 12.9	5 (6.3)	2.1, 14.0
CRp	2 (2.3)	0.3, 8.1	2 (2.5)	0.3, 8.7
PR	4 (4.6)	1.3, 11.4	4 (5.0)	1.4, 12.3
SD	33 (37.9)	27.7, 49.0	32 (40.0)	29.2, 51.6
NE	26 (29.9)	20.5, 40.6	20 (25.0)	16.0, 35.9
Composite response rates				
CR+CRi+PR	28 (32.2)	22.6, 43.1	28 (35.0)	24.7, 46.5
CR+CRh	21 (24.1)	15.6, 34.5	21 (26.3)	17.0, 37.3
CRh	2 (2.3)	0.3, 8.1	2 (2.5)	0.3, 8.7

Non intensive chemotherapy: oral decitabine/cedazuridine



TEAE regardless of relation to treatment	n. Pts (%)
Thrombocitopenia	47 (59)
Anemia	44(55)
Neutropenia	28 (35)
Febrile neutropenia	25 (31)
Asthenia	22 (28)
Pneumoniae	19 (24)
Pyrexia	19 (24)
Diarrhoea	18 (23)
Nausea	17 (21)
Peripheral oedema	16 (20)
Costipation	15 (19)
Hypokaliemia	15 (19)
Decreased appetite	12 (15)

Geissler K. Br J Haematol. 2024 Nov;205(5):1734-1745

Non intensive chemotherapy: oral decitabine/cedazuridine

Patients' perspectives on oral decitabine/cedazuridine for the treatment of myelodysplastic syndromes/neoplasms

Zeidan AM. Ther Adv Hematol. 2024 Jul 30;15:20406207241257313.

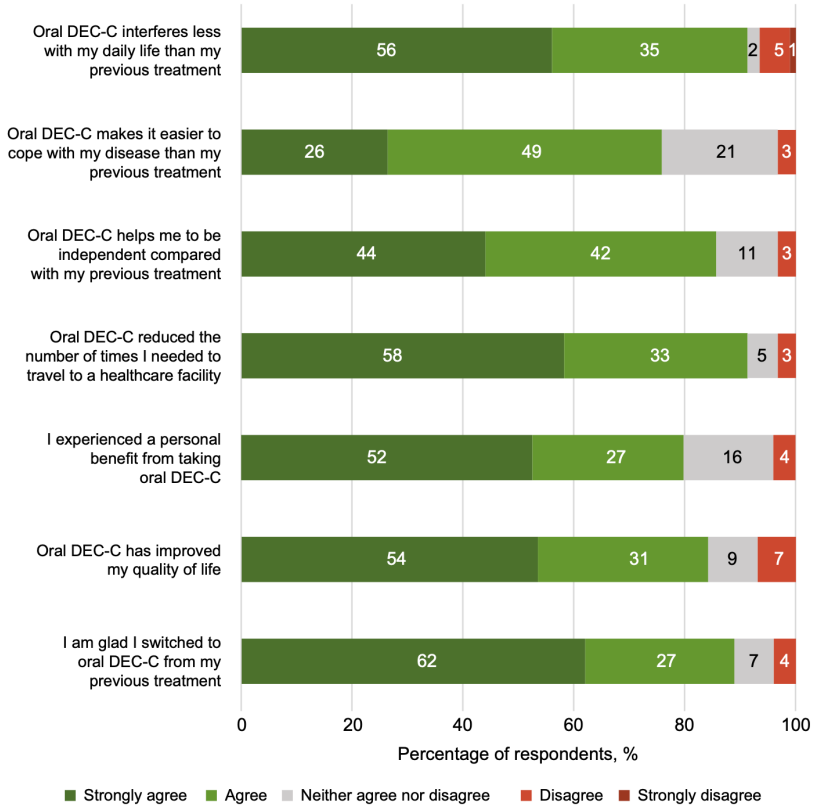
Good safety profile

Tretament administered only outpatient

High treatment aderence

Low rate of hospitalization

Lower rate of CR compared to combination strategies



♂ M.G.(dn 28/09/1934)

05/02/2025	***Started therapy with oral DECITABINE (35 mg/100 mg)/day on days 1-5 28day cycles***
22/05/2025	<u>Day+23 4th cycle of oral DECITABINE</u> None ospitalizatation RBC transfusion dependency (1U every 10 day) Platelets transfusion independency form day 14 2nd cycle **Bone marrow evalutation (22/4/25): CR, FLT3 and NPM1 positive**

Conclusion

- *Nowadays with the availability of new agents almost every AML patients could be treated*
- *Beyond clinical consideration also biological features must be taken into account*
- *Long term quality of life must be considered expecially in patients with a short life expectancy*

Non vivere bonum est, sed bene vivere