Organizado por:

Clínica Universidad de Navarra

PUESTA AL DÍA

HEMATOLOGÍA EN 48H [LO QUE DEBES CONOCER PARA TU PRÁCTICA CLÍNICA]

X EDICIÓN

ACTUALÍZATE 48 HORAS

Abordaje Terapéutico de la Leucemia Mieloblástica Aguda en el 2025

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Clínica Universidad de Navarra, Pamplona

Disclaimers

- **Honoraria from lectures**: BMS, Novartis, Abbvie, Jazz Pharma, Janssen, Astellas
- **Participation in Ad Board meetings**: BMS, Syros, Jazz Pharma, Otsuka, Ascentage Pharma, Janssen.
- **Consultant**: Astellas, Jazz Pharma; Janssen
- **Research Founding**: Astra Zeneca

Newly diagnosed

Newly diagnosed I **Fit vs Unfit vs Frail**

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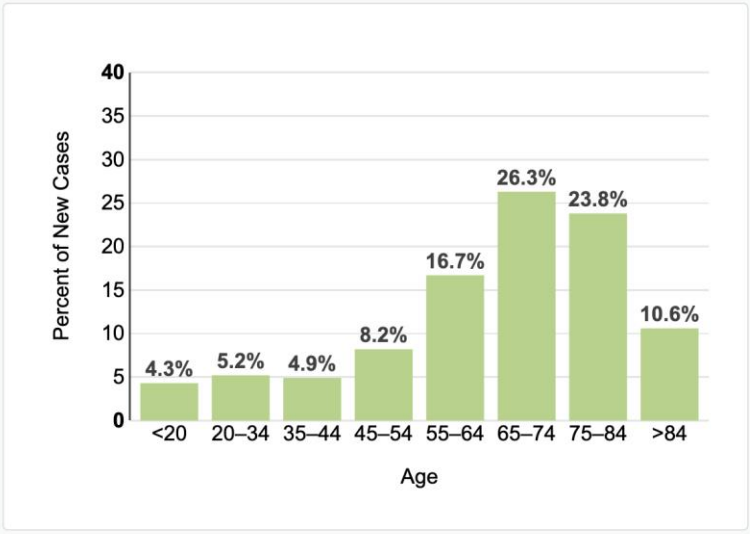
Percent of New Cases by Age Group: Acute Myeloid Leukemia



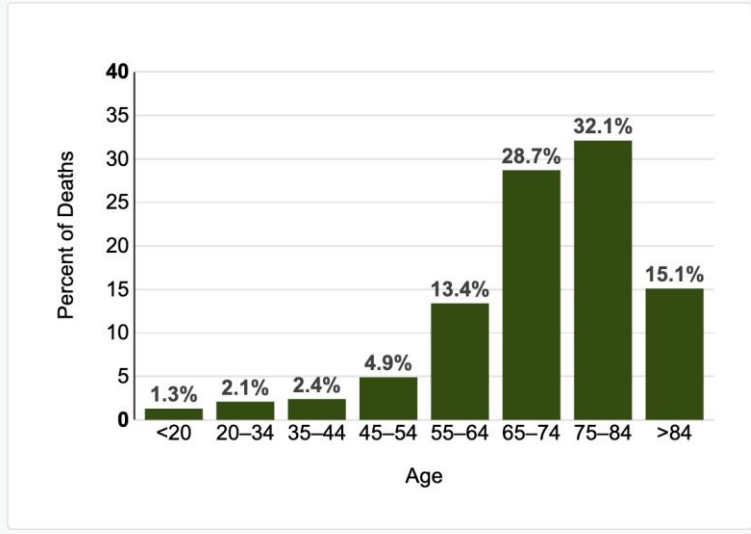
Acute myeloid leukemia is most frequently diagnosed among people aged 65–74.

Median Age At Diagnosis

69

SEER 22 2017–2021, All Races, Both Sexes

Percent of Deaths by Age Group: Acute Myeloid Leukemia



The percent of acute myeloid leukemia deaths is highest among people aged 75–84.

Median Age At Death

74

U.S. 2018–2022, All Races, Both Sexes

NIH, National Institute of Health; SEER, Surveillance, Epidemiology, and End Results Program seer.cancer.gov/statfacts/html/nhl.html. Accessed 8Mar2025

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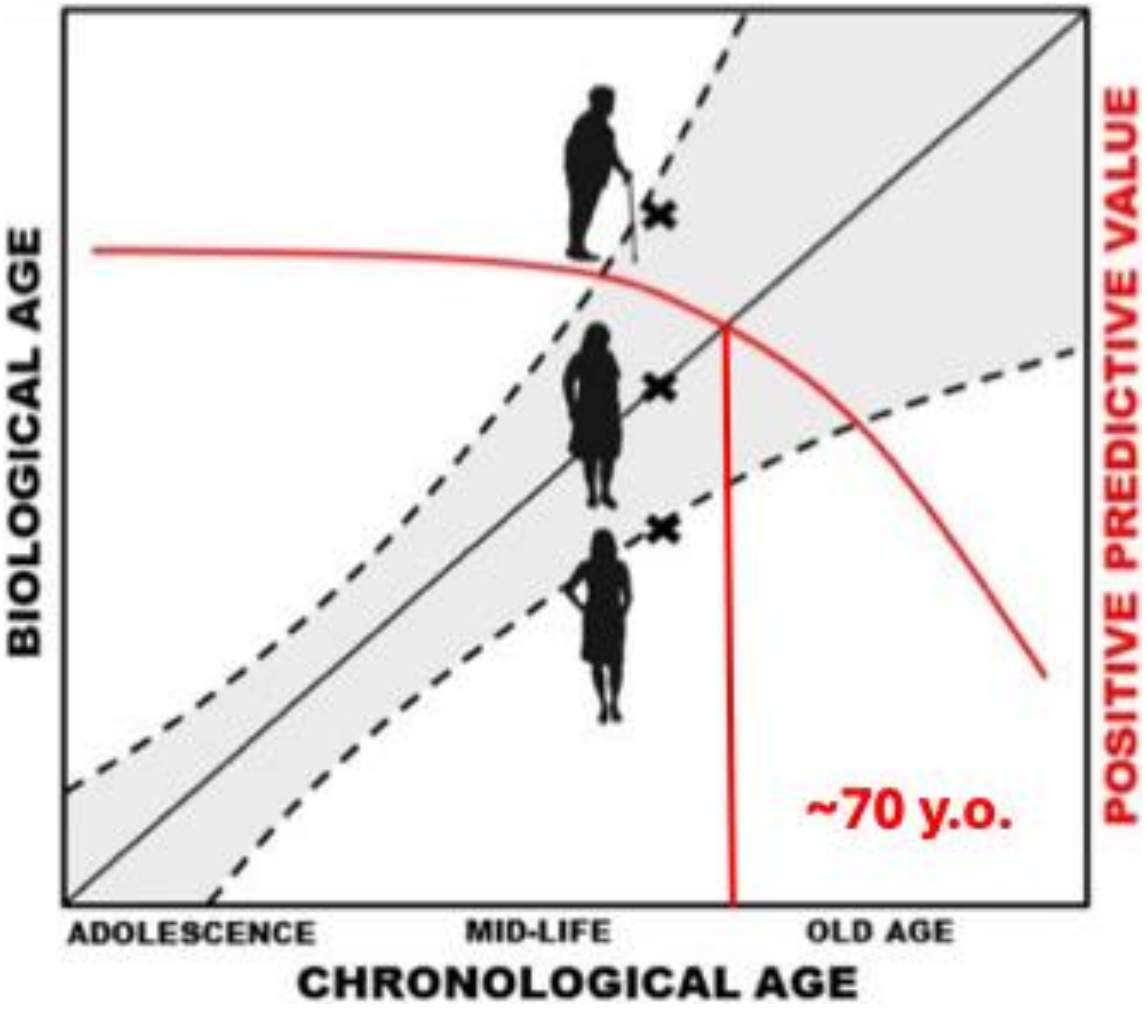

Jylhävä J et al. EBioMedicine. 2017 Jul;21:29-36.

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Definitions

- **Comorbidity**: the concurrent presence of multiple medically diagnosed diseases in the same individual

- **Frailty**: state of high vulnerability for adverse health outcomes, including disability, dependency, falls, need for long-term care, and mortality

Fried LP, et al. J Gerontol A Biol Sci Med Sci 2004;59:255–263

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Commorbidity

- Charlson Comorbidity Index (CCI)

Comorbidity	Points	Examples
Myocardial infarction	1	Prior heart attack
Congestive heart failure	1	Chronic heart failure
Peripheral vascular disease	1	Claudication, arterial disease
Cerebrovascular disease	1	Stroke, transient ischemic attack
Dementia	1	Alzheimer's disease
Chronic pulmonary disease	1	COPD, chronic bronchitis
Connective tissue disease	1	Rheumatoid arthritis, lupus
Peptic ulcer disease	1	Gastric or duodenal ulcers
Mild liver disease	1	Chronic hepatitis, cirrhosis
Diabetes without complications	1	Type 1 or Type 2 diabetes
Diabetes with complications	2	Diabetes with retinopathy, nephropathy
Hemiplegia or paraplegia	2	Spinal cord injury, stroke with hemiparesis
Moderate/severe kidney disease	2	Chronic renal failure, dialysis
Cancer (localized)	2	Non-metastatic solid tumor
Moderate/severe liver disease	3	Cirrhosis with portal hypertension
Metastatic cancer	6	Lung, liver, or bone metastases
AIDS/HIV	6	HIV/AIDS diagnosed and treated

- Comorbidity Index (HCT-CI)

Comorbidity	Points	Examples
Arrhythmia	1	Atrial fibrillation, ventricular arrhythmias
Cardiac disease	1	Heart failure, coronary artery disease
Inflammatory bowel disease	1	Crohn's disease, ulcerative colitis
Cerebrovascular disease	1	Stroke, transient ischemic attack
Diabetes mellitus	1	Type 1 or 2 diabetes requiring medication
Liver disease	1	Cirrhosis, chronic hepatitis
Pulmonary disease	1	COPD, interstitial lung disease
Renal disease	2	Chronic kidney disease, dialysis
Rheumatologic disease	2	Lupus, rheumatoid arthritis
Peptic ulcer disease	2	Gastric or duodenal ulcers
Prior malignancy	3	History of treated cancer
Moderate/severe obesity	2	BMI ≥ 35 kg/m²

J Chronic Dis. 1987;40(5):373-83. doi: 10.1016/0021-9681(87)90171-8. Clinical Lymphoma, Myeloma & Leukemia, Vol. 20, No. 12, 804-12; Biol Blood Marrow Transplant. 2016 Oct 24;23(1):67–74. doi: 10.1016/j.bbmt.2016.10.017; Biol Blood Marrow Transplant. 2018 May;24(5):964-972.

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Frailty - Comprehensive Geriatric Assessment

Domain	Assessment Tools	Examples
Functional Status	Activities of Daily Living (ADL), Instrumental ADL (IADL)	Evaluates independence in daily activities
Cognitive Function	Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA)	Detects cognitive impairment and dementia
Psychological Health	Geriatric Depression Scale (GDS), Patient Health Questionnaire (PHQ-9)	Assesses depression, anxiety, and psychological distress
Comorbidities	Charlson Comorbidity Index (CCI), Cumulative Illness Rating Scale (CIRS)	Quantifies the impact of multiple diseases on health
Nutritional Status	Body Mass Index (BMI), Mini Nutritional Assessment (MNA)	Identifies malnutrition or risk of poor nutrition
Polypharmacy	Medication review, Beers Criteria, STOPP/START Criteria	Evaluates inappropriate medication use in older adults
Social Support	Social support networks, caregiver burden assessment	Assesses family, community, and institutional support
Geriatric Syndromes	Falls, frailty, incontinence, pressure ulcers, delirium	Identifies common aging-related conditions requiring intervention

- Ferrara Criteria – Unfit for Intensive Chemotherapy

Criteria	Threshold for Unfitness	Examples
Age	≥75 years	Elderly patients
ECOG Performance Status	≥3 (severe impairment)	Bedridden, requires assistance
Cardiac Disease	Heart failure NYHA ≥3, EF <50%	Severe coronary artery disease
Lung Disease	Severe COPD, FEV1 <65%	Severe obstructive lung disease
Liver Disease	Bilirubin >2 mg/dL, AST/ALT >3x ULN	Cirrhosis, severe liver damage
Renal Disease	Creatinine clearance <45 mL/min	Advanced kidney failure
Comorbidities	≥2 severe comorbidities	Charlson Comorbidity Index ≥3
Cognitive Impairment	Dementia, severe cognitive dysfunction	Alzheimer's, vascular dementia

Biol Blood Marrow Transplant. 2016 Oct 24;23(1):67–74. doi: 10.1016/j.bbmt.2016.10.017; Biol Blood Marrow Transplant. 2018 May;24(5):964-972. Leukemia. 2013 Apr;27(5):997-9. doi: 10.1038/leu.2012.303.

Newly diagnosed I **Fit vs Unfit vs Frail**

Frailty

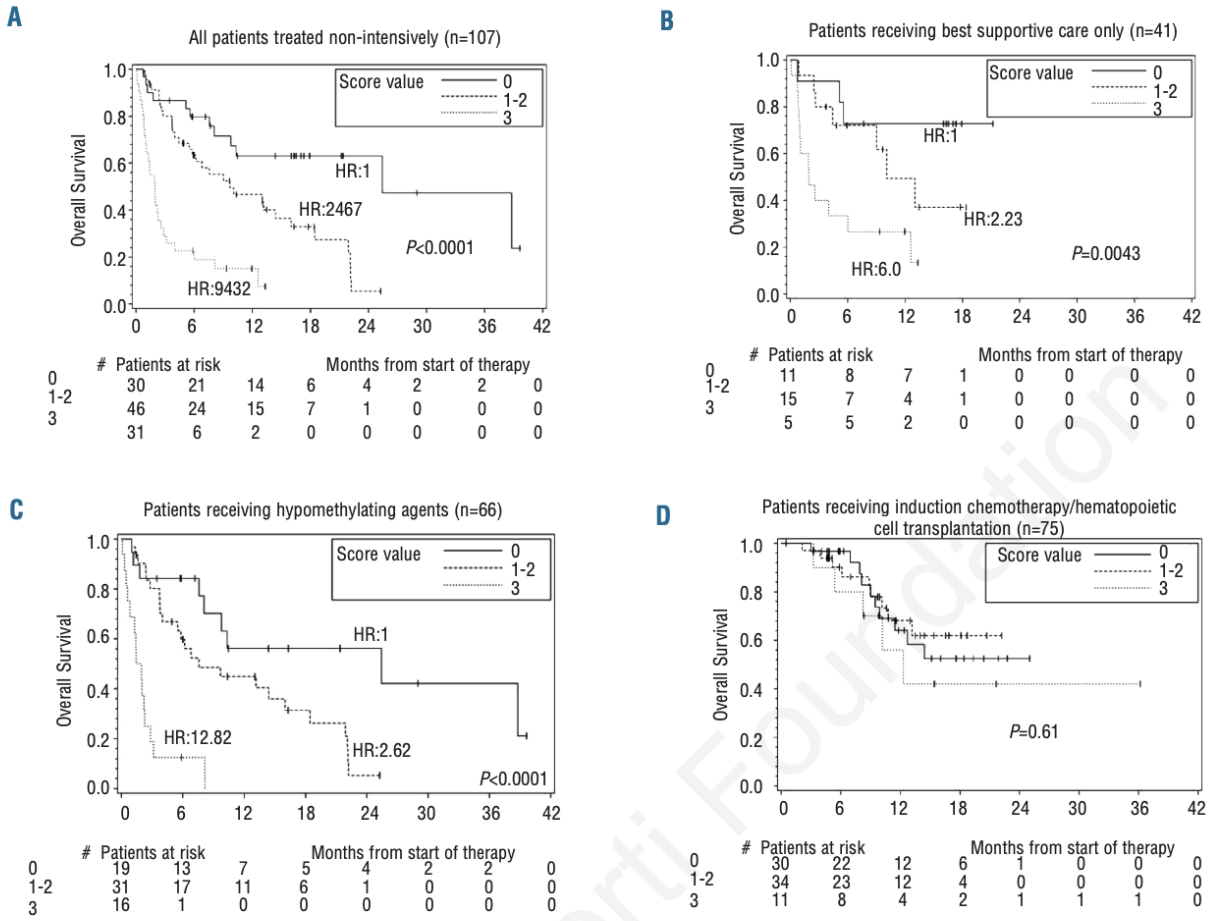

Figure 2. Overall survival (OS) according to frailty score risk groups and treatment (evaluable patients) (A). All patients treated non-intensively (n=107). (B). Patients receiving best supportive care only (n=41). (C). Patients receiving hypomethylating agents (n=66). (D). Patients receiving induction chemotherapy/hematopoietic cell transplantation (n=75).

Haematologica. 2013 Feb;98(2):208-16. doi: 10.3324/haematol.2012.067892. Epub 2012 Aug 8.

Newly diagnosed I **Fit vs Unfit vs Frail**

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Fit

Unfit

Frail

Newly diagnosed I **Fit vs Unfit vs Frail**

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Fit

Unfit

Frail

Newly diagnosed I **Fit**

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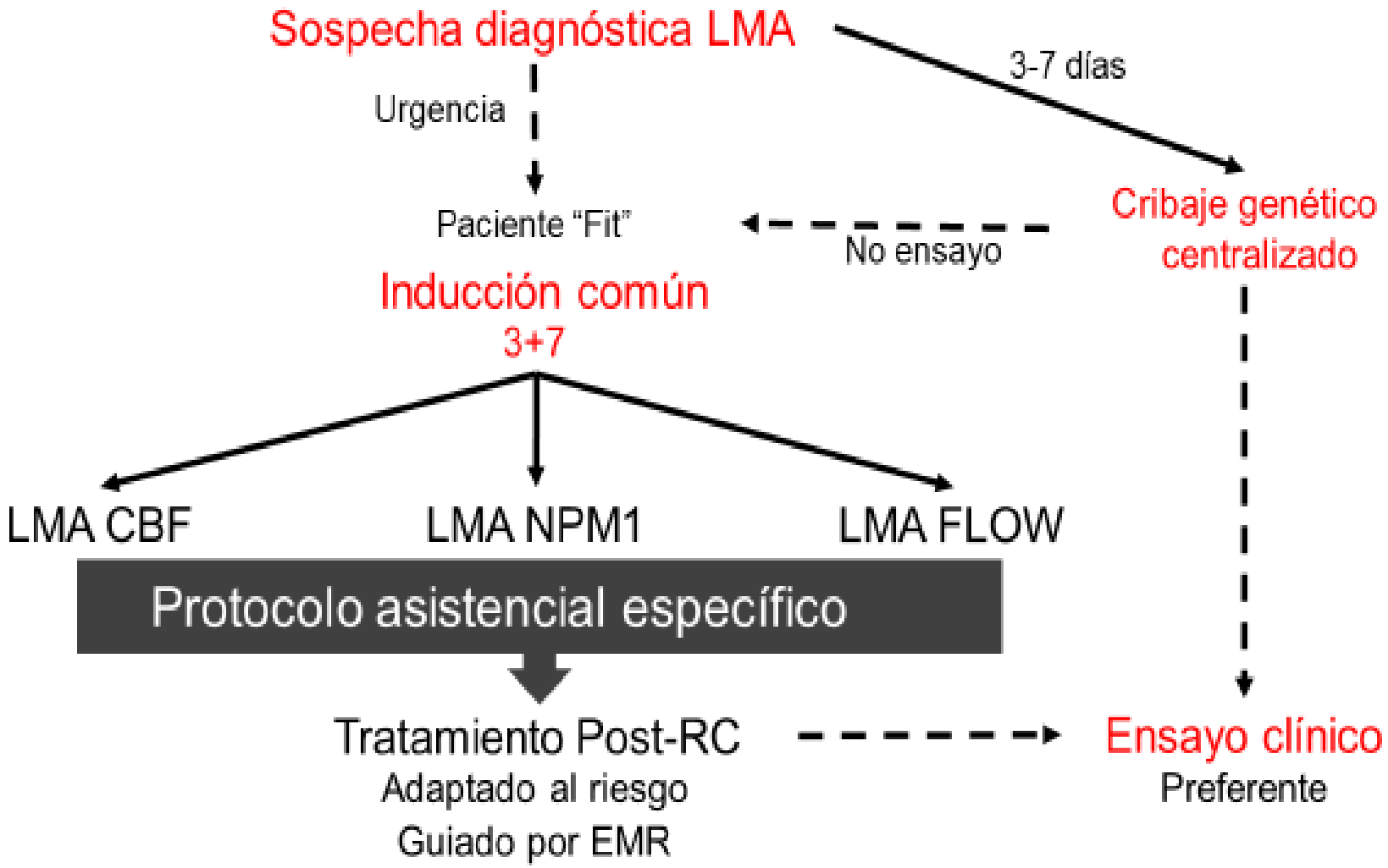
Risk category†	Genetic abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*†,‡ • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*†,‡ • Mutated *NPM1*†,§ without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*‖
Intermediate	• Mutated *NPM1*†,§ with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*†,¶ • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23.3;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged# • t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* • t(8;16)(p11.2;p13.3)/*KAT6A*::*CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2*, *MECOM(EVI1)* • t(3q26.2;v)/*MECOM*(*EVI1*)-rearranged • −5 or del(5q); −7; −17/abn(17p) • Complex karyotype,** monosomal karyotype†† • Mutated *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, and/or *ZRSR2*‡‡ • Mutated *TP53*[a]

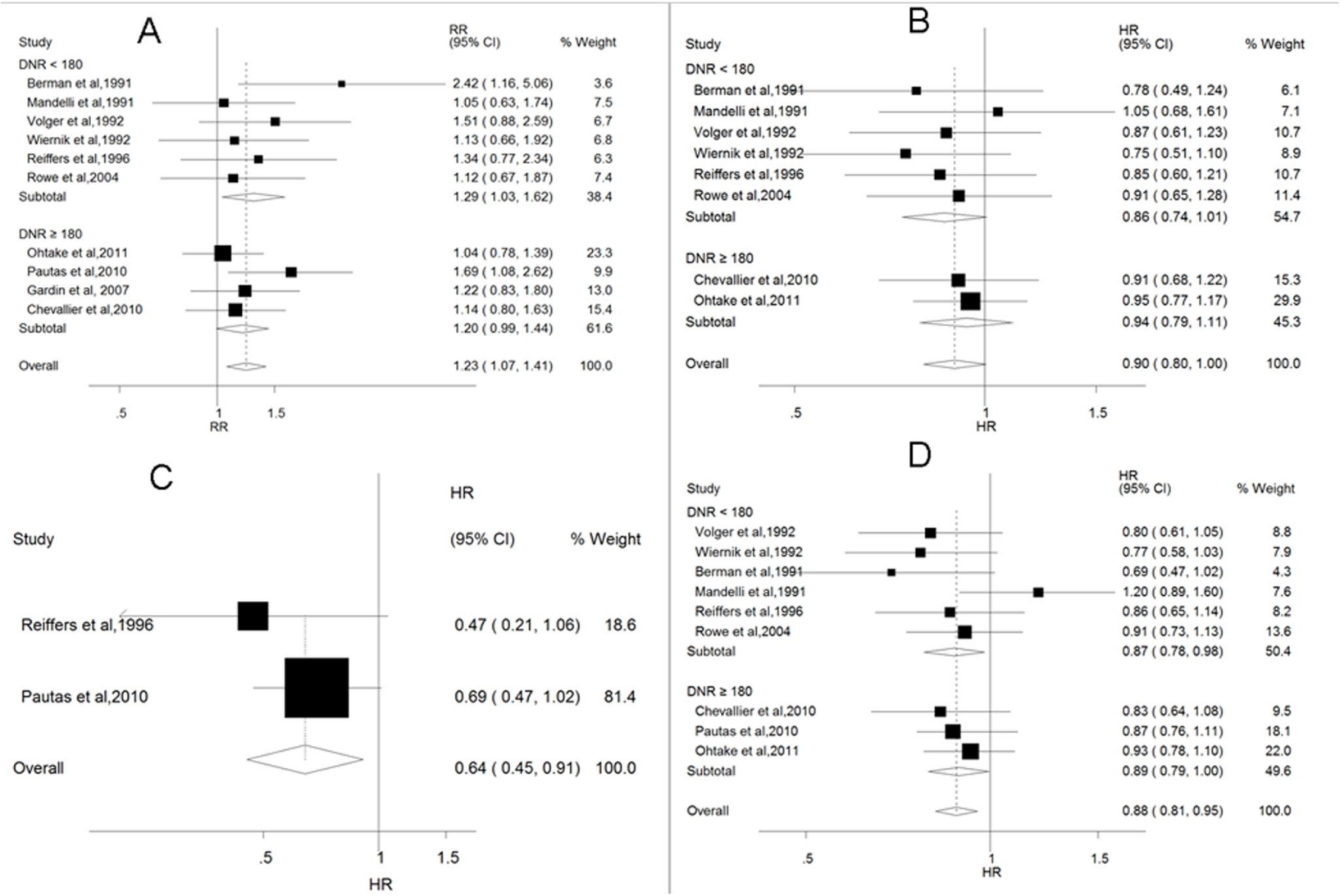
Döhner H. *Blood* (2022) 140 (12): 1345–1377.

Newly diagnosed I **Fit**



Guias de Pethema- LMA.Versión 2, 1 de Octubre de 2022

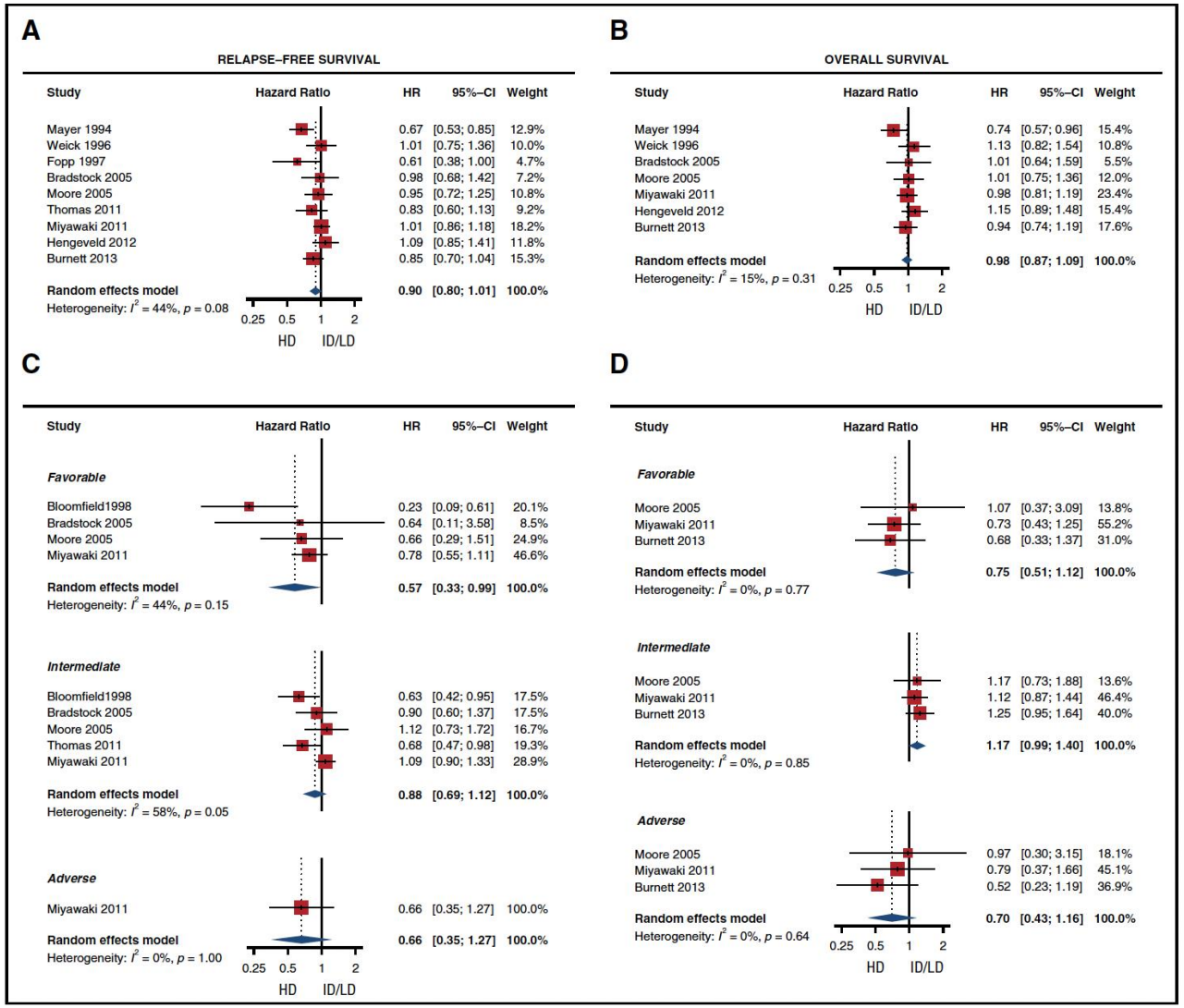
Newly diagnosed I **Fit - Induction**



Induction treatment:
Meta-Analysis of Randomised Clinical Trials Comparing Idarubicin + Cytarabine with Daunorubicin + Cytarabine

Wang J. PLoS One. 2013 Apr 5;8(4):e60699.

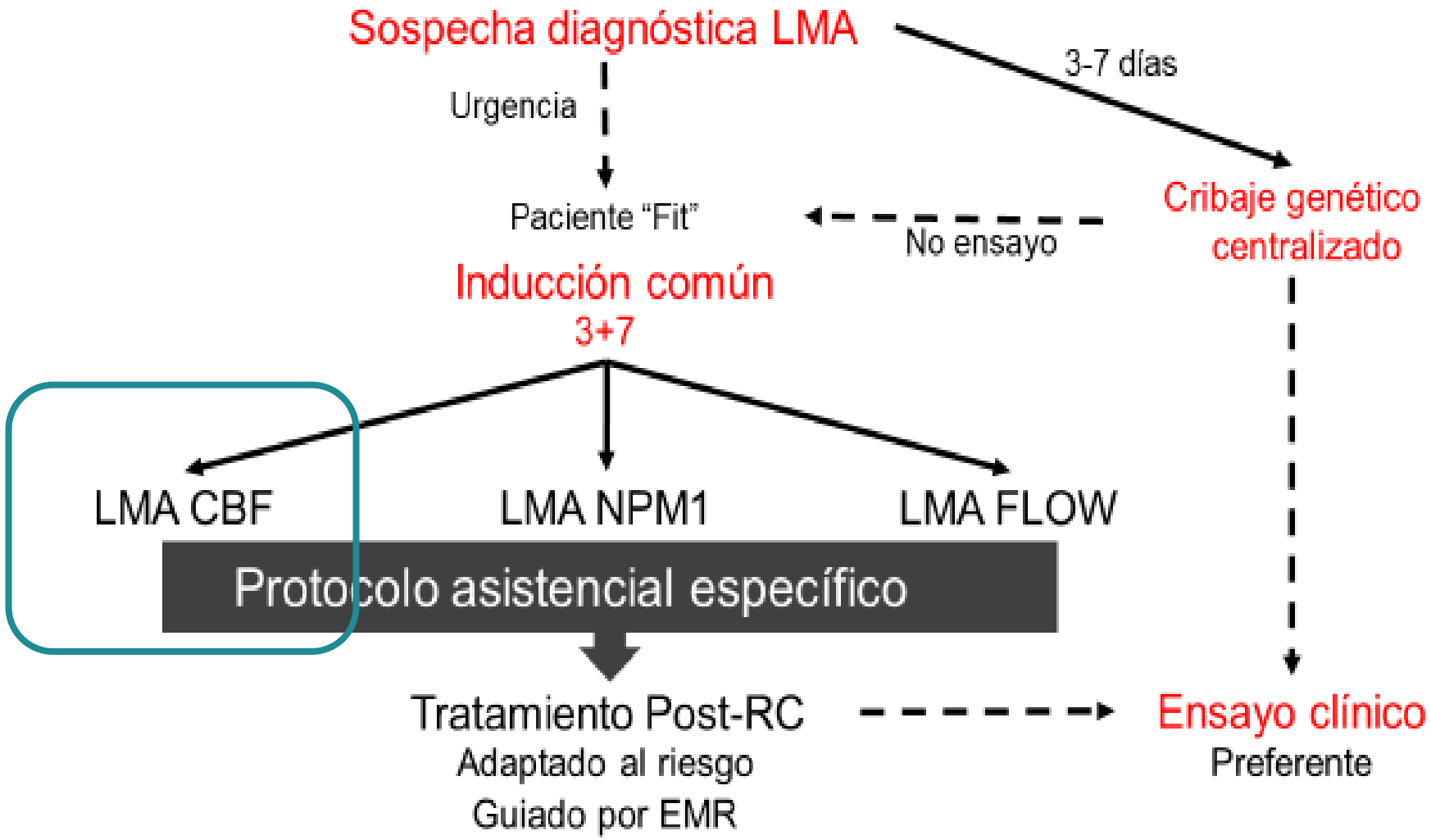
Newly diagnosed I **Fit - Consolidation**



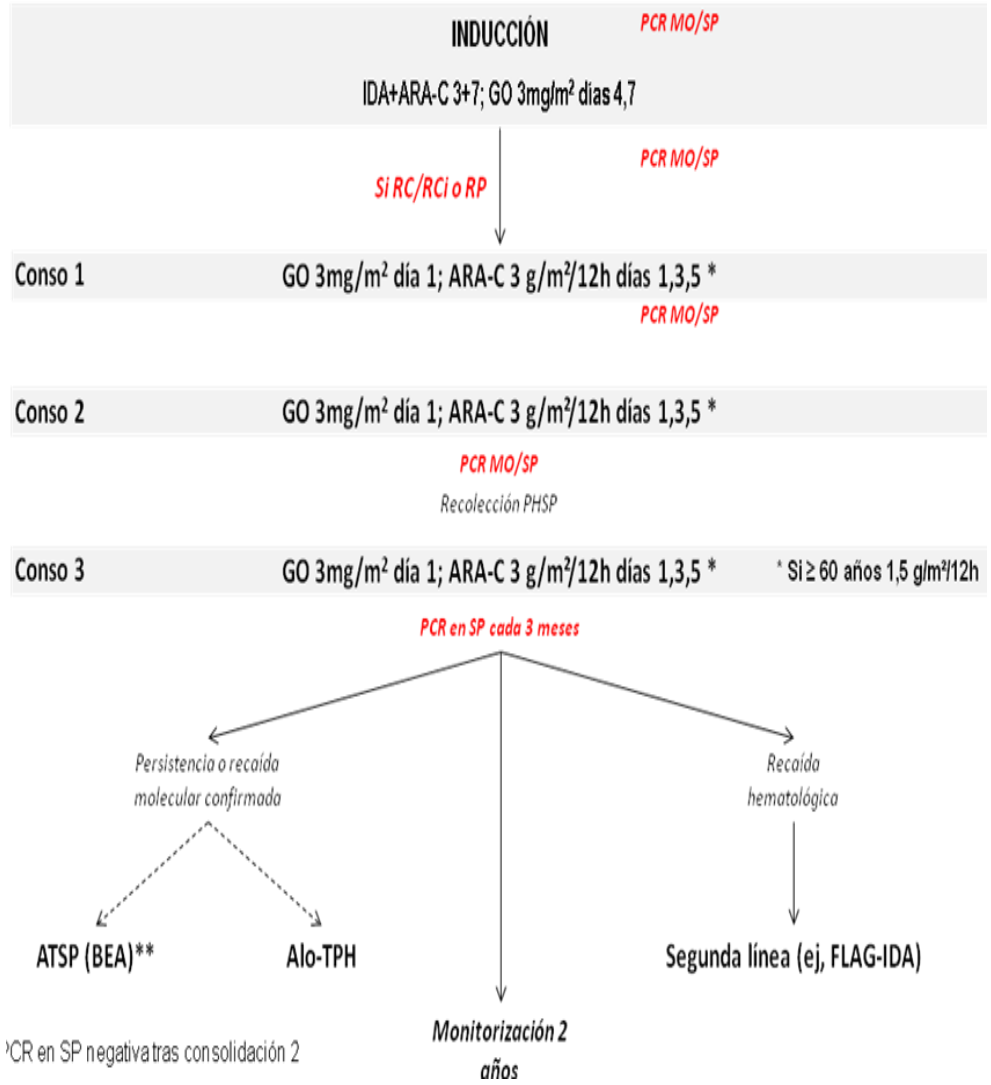
Cytarabine dose in the consolidation treatment of AML: meta-analysis

Magina K. Blood (2017) 130 (7): 946–948.

Newly diagnosed I **Fit - Induction**



Newly diagnosed I **Fit - Induction**



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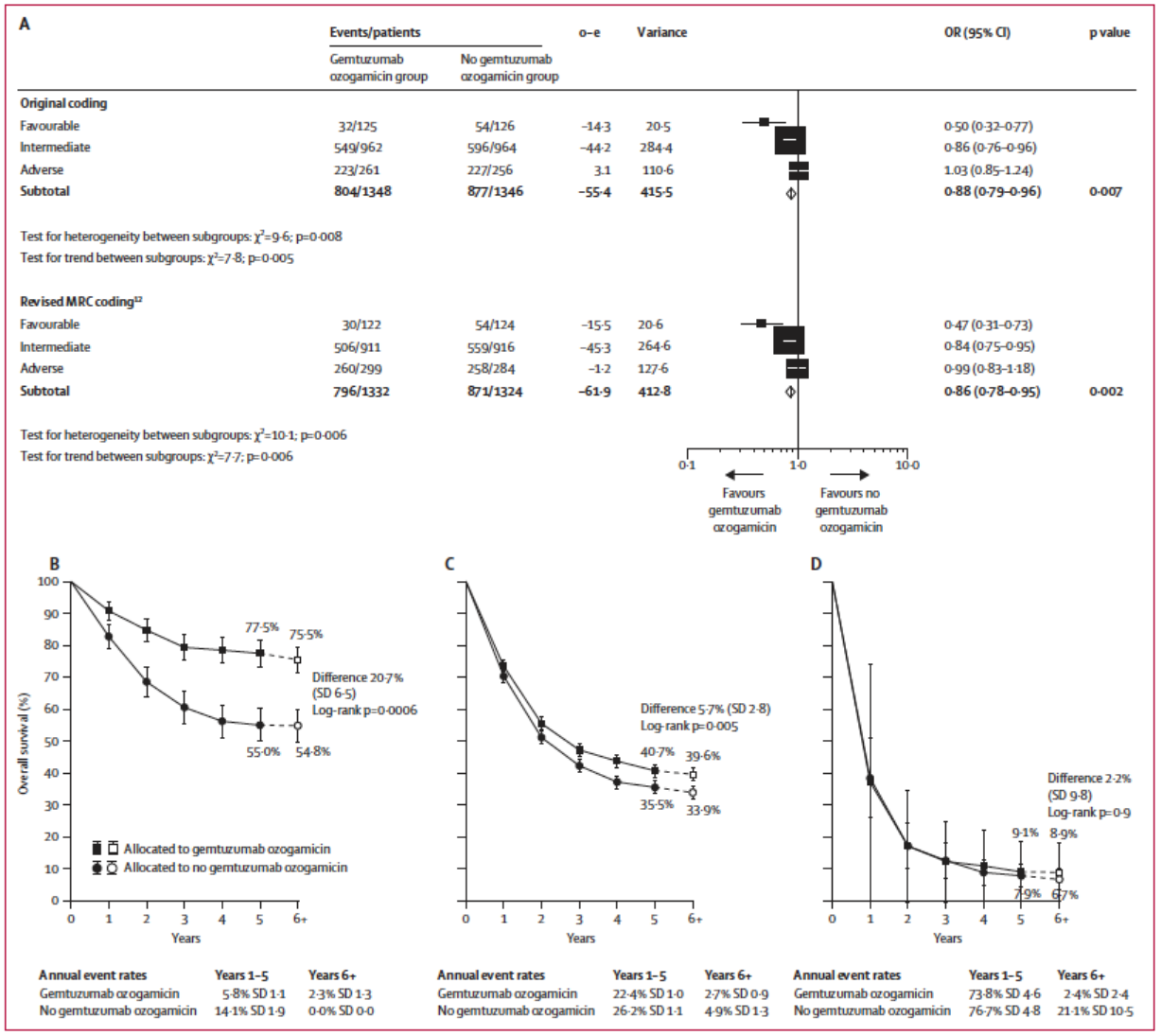


A	Events/patients: Gemtuzumab ozogamicin group	Events/patients: No gemtuzumab ozogamicin group	o–e	Variance	OR (95% CI)	p value
Original coding						
Favourable	32/125	54/126	−14·3	20·5	0·50 (0·32–0·77)	
Intermediate	549/962	596/964	−44·2	284·4	0·86 (0·76–0·96)	
Adverse	223/261	227/256	3·1	110·6	1·03 (0·85–1·24)	
Subtotal	**804/1348**	**877/1346**	**−55·4**	**415·5**	**0·88 (0·79–0·96)**	**0·007**
Test for heterogeneity between subgroups: χ^2=9·6; p=0·008						
Test for trend between subgroups: χ^2=7·8; p=0·005						
Revised MRC coding[12]						
Favourable	30/122	54/124	−15·5	20·6	0·47 (0·31–0·73)	
Intermediate	506/911	559/916	−45·3	264·6	0·84 (0·75–0·95)	
Adverse	260/299	258/284	−1·2	127·6	0·99 (0·83–1·18)	
Subtotal	**796/1332**	**871/1324**	**−61·9**	**412·8**	**0·86 (0·78–0·95)**	**0·002**
Test for heterogeneity between subgroups: χ^2=10·1; p=0·006						
Test for trend between subgroups: χ^2=7·7; p=0·006						

Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	5·8% SD 1·1	2·3% SD 1·3
No gemtuzumab ozogamicin	14·1% SD 1·9	0·0% SD 0·0

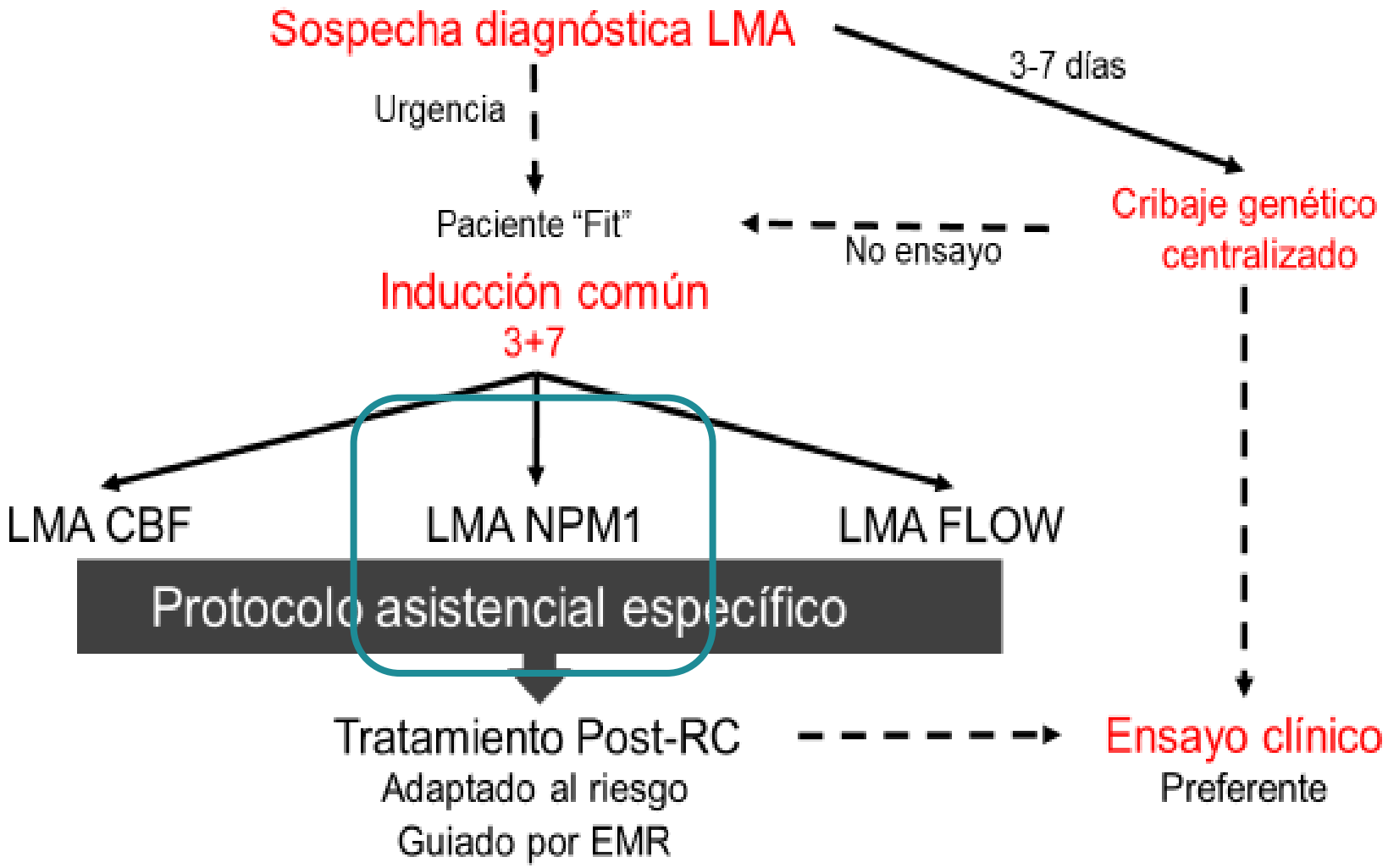
Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	22·4% SD 1·0	2·7% SD 0·9
No gemtuzumab ozogamicin	26·2% SD 1·1	4·9% SD 1·3

Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	73·8% SD 4·6	2·4% SD 2·4
No gemtuzumab ozogamicin	76·7% SD 4·8	21·1% SD 10·5

Addition of gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukaemia: a meta-analysis of individual patient data from randomised controlled trials

Hills R. The Lancet Oncology. 2014;15(9):986

Newly diagnosed I **Fit - Induction**



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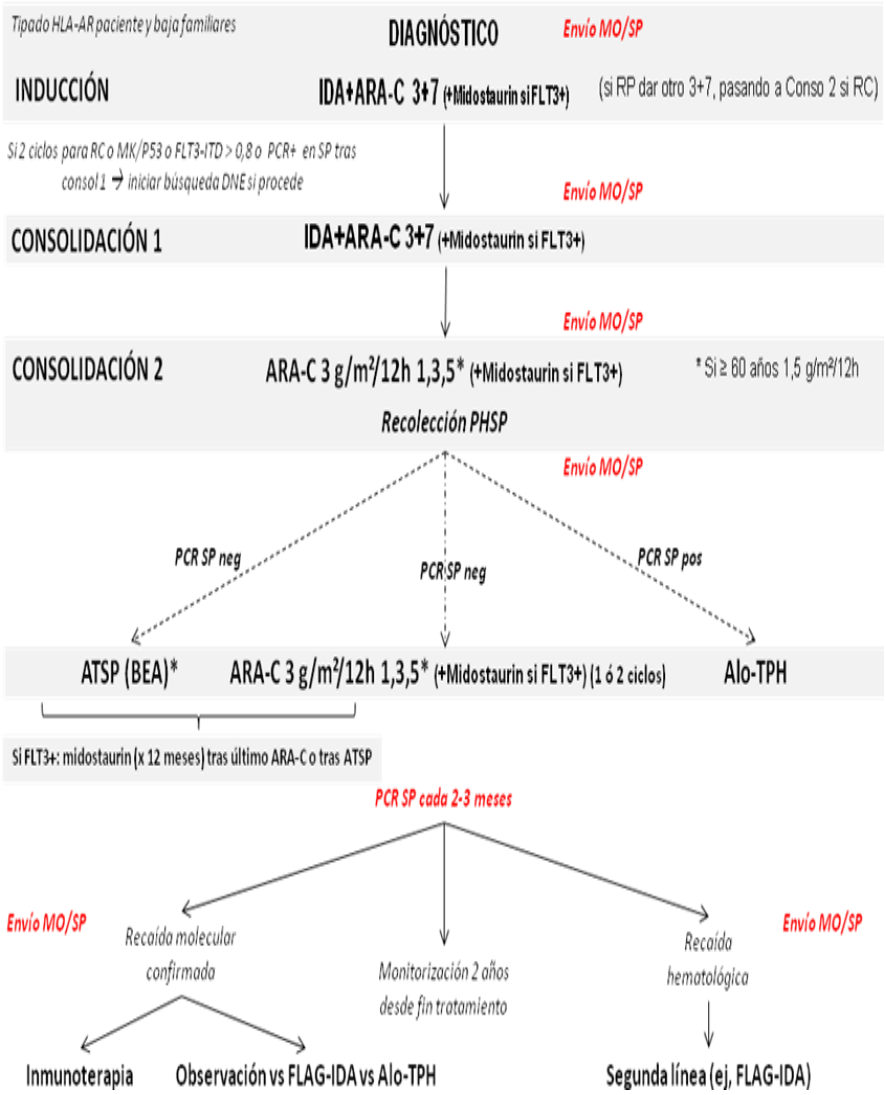
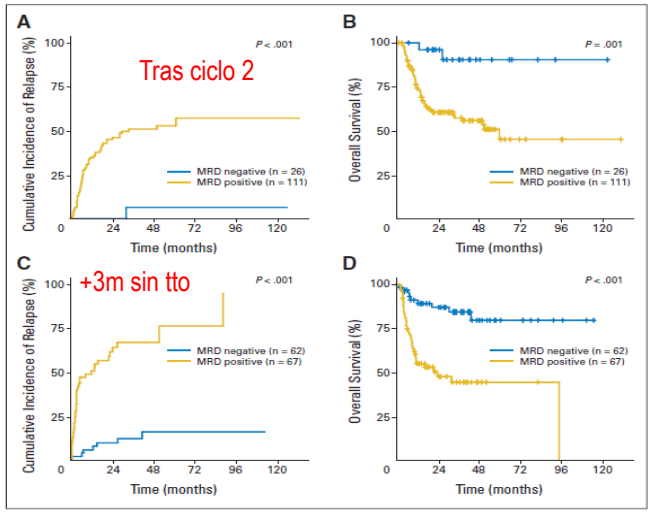
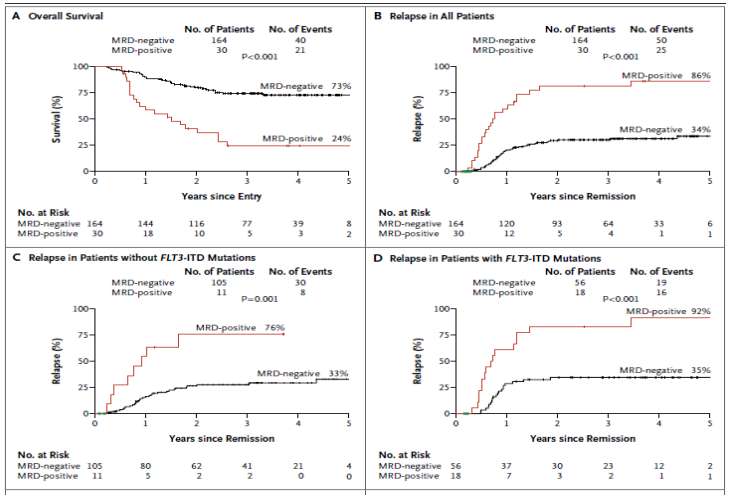


MRD - MO

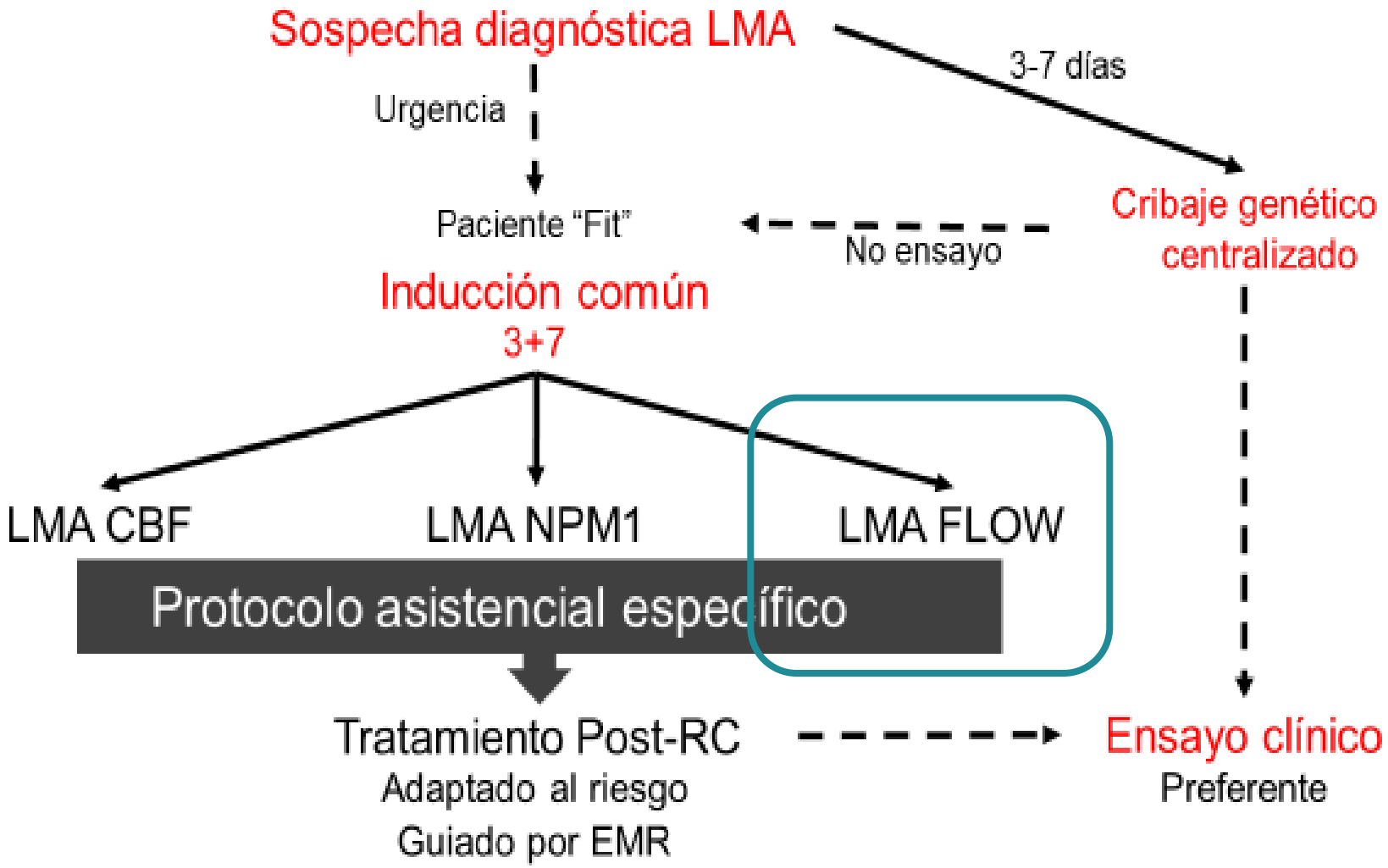


MRD - SP



Guias de Pethema- LMA. LMA-NPM1-17. Versión 23 de julio de 2019. Krönke J J Clin Oncol. 2011;29(19):2709-2716. Ivey A N Engl J Med. 2016 Feb 4;374(5):422-33.

Newly diagnosed I **Fit - Induction**



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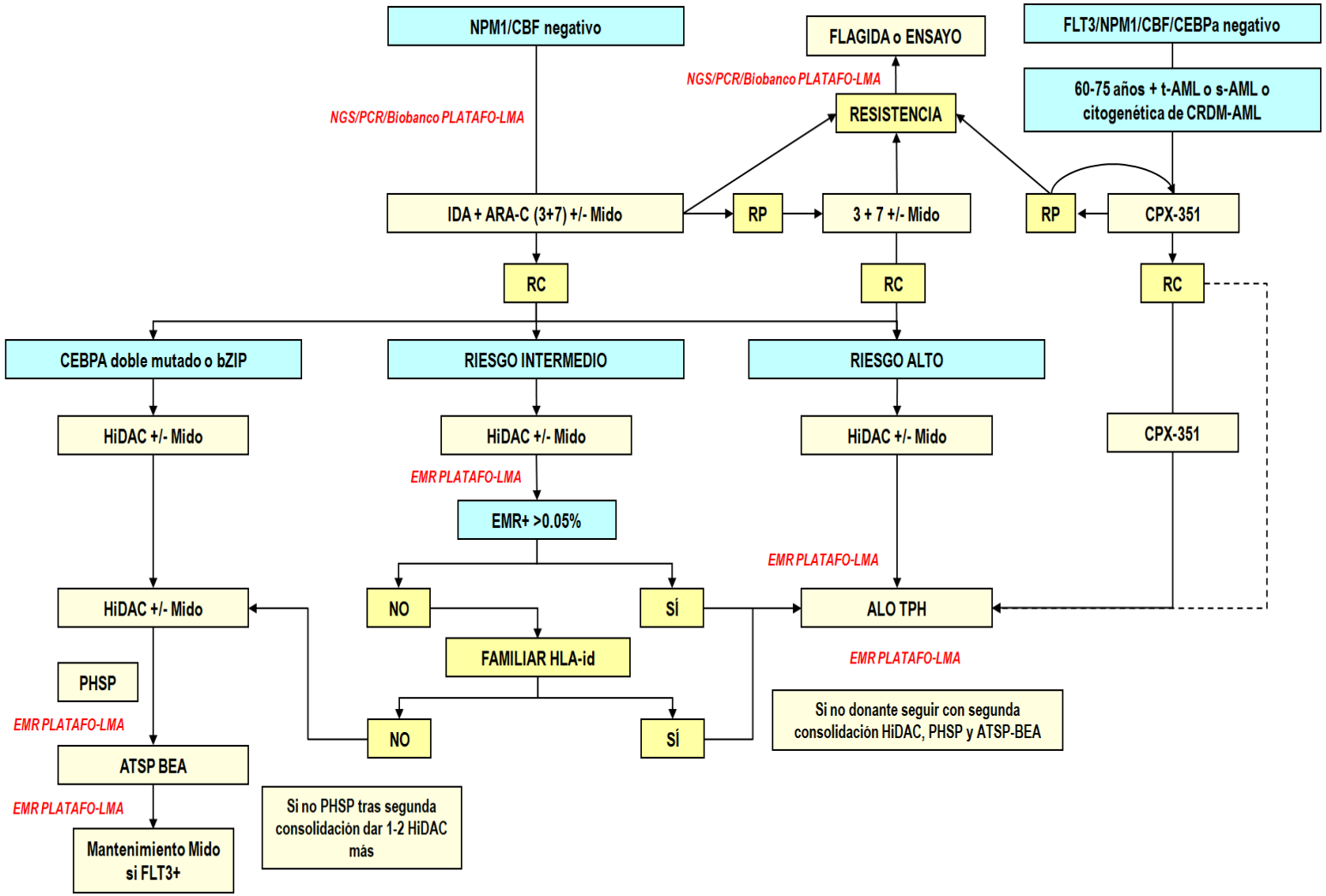

Guias de Pethema- LMA.Versión 2, 1 de Octubre de 2022

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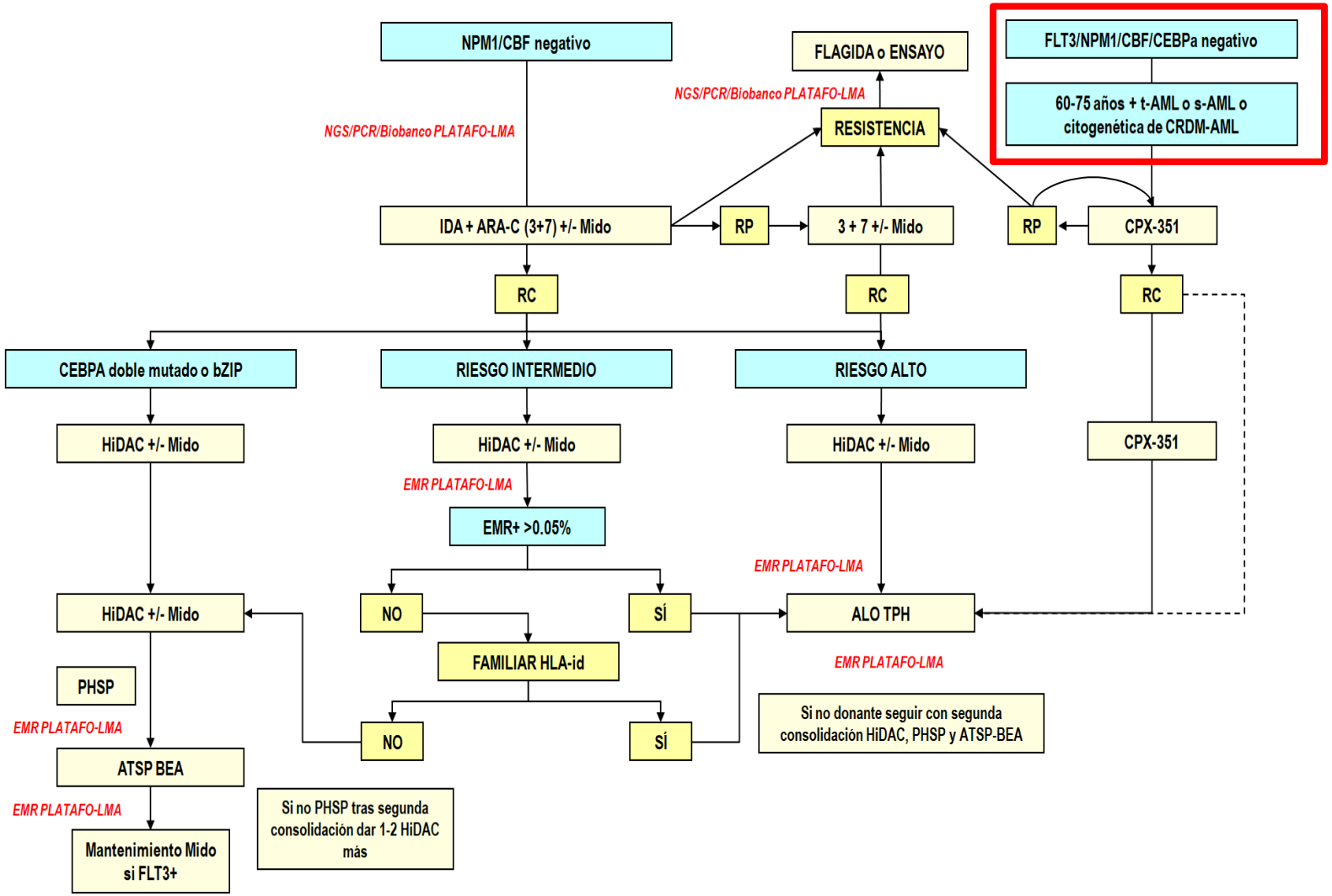


Guias de Pethema- LMA.Versión 2, 1 de Octubre de 2022

Newly diagnosed I **Fit - Induction**

Phase 3 Pivotal Study of CPX-351 in AML

- Age 60-75 years
- Able to tolerate intensive therapy
- Newly diagnosed t-AML or AML-MRC
- Prior HMA therapy for MDS or CMML
- ECOG 0-2

R 1:1
by age & subtype of AML

N=309

CPX-351
C1: 100 units/m² D1, D3, D5
Reinduction: 100 units/m² IV D1, D3
If no CR on D14 BM
(n=153)

CPX-351
65 units/m² IV D1, D3

7+3
Cytarabine: 100 mg/m² IV D1-7
Daunorubicin 60 mg/m² IV D1-3
(n=156)

5+2
Cytarabine: 100 mg/m² IV D1-5
Daunorubicin 60 mg/m² IV D1-2

Re-induction
CPX-351: 31.4%
7+3: 33.8%

Study Design
Phase III, open label, RCT

Primary Endpoint
OS

Secondary Endpoint
Remission rate (CR, CR+CRi) and duration EFS

Lancet et al J Clin Oncol 2018

Newly diagnosed I **Fit - Induction**

Phase 3 Pivotal Study of CPX-351 in AML

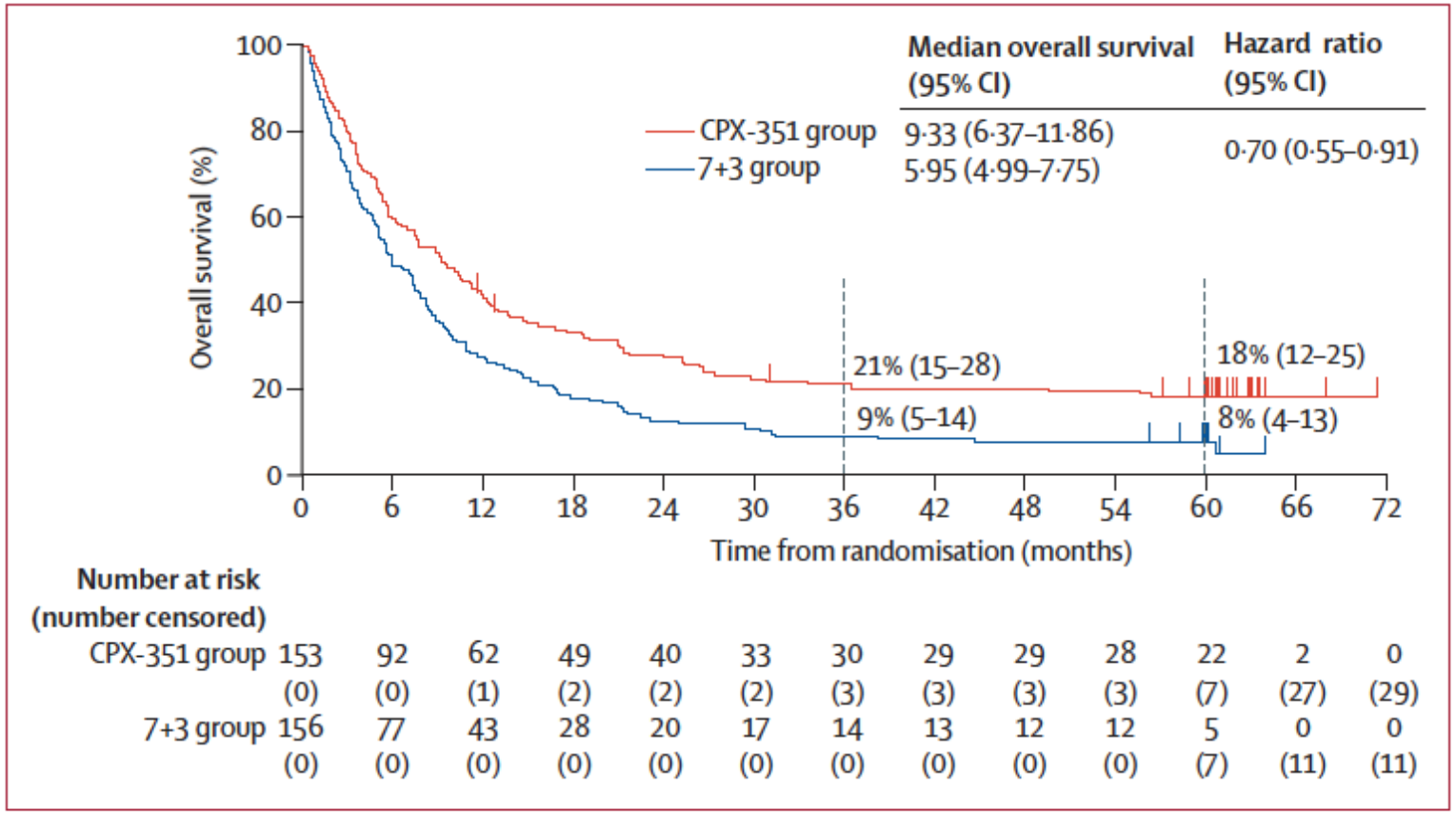


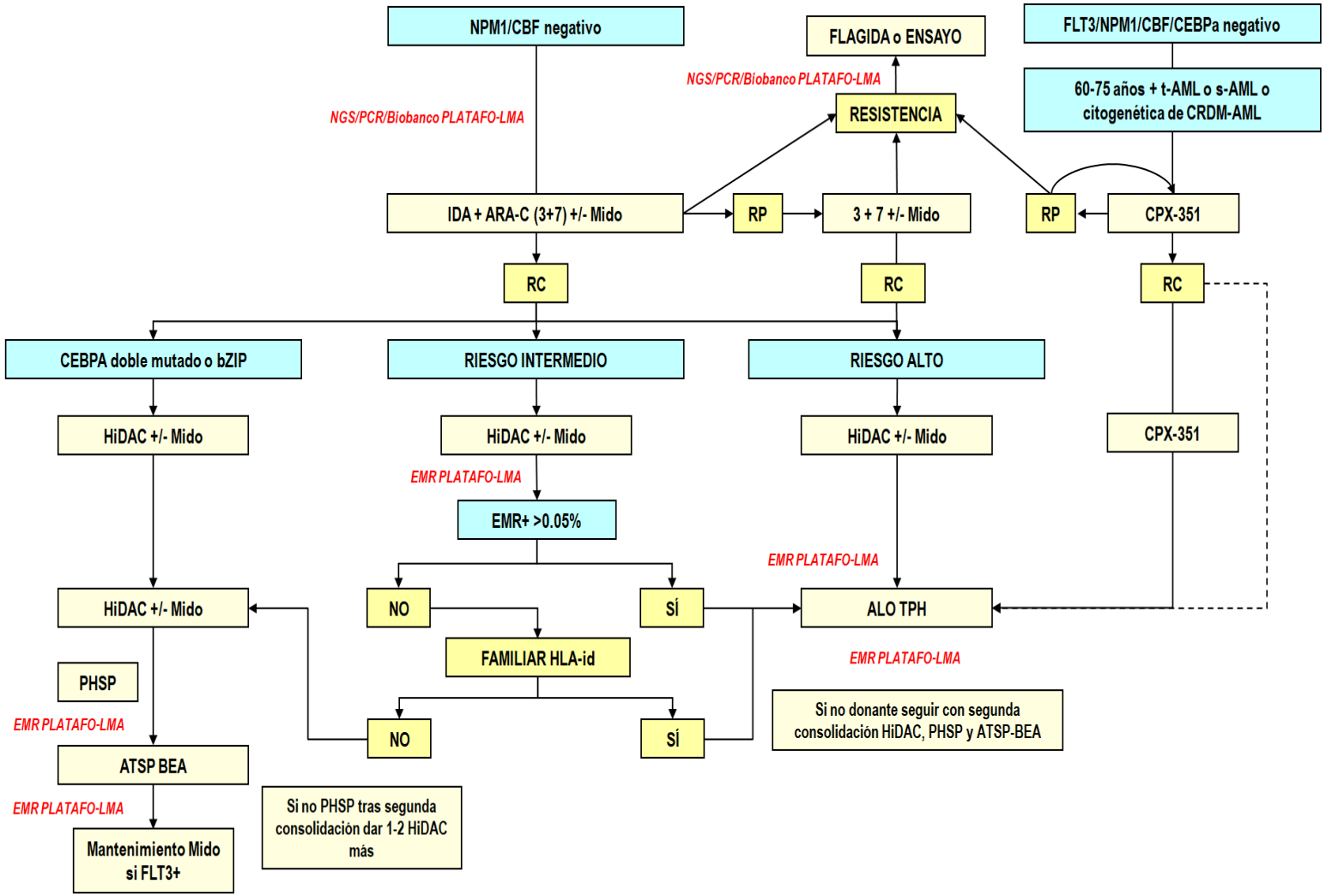
Figure 2: **Overall survival**

3-year and 5-year Kaplan-Meier-estimated survival rates are shown with 95% CI. 7+3=cytarabine and daunorubicin.

Response	CPX-351, No. (%)	7+3, No. (%)	OR (95% CI)
No. of patients	153	156	
CR + CRi	73 (47.7)	52 (33.3)	1.77 (1.11 to 2.81)*
CR	57 (37.3)	40 (25.6)	1.69 (1.03 to 2.78)†
Age group			
No. in 60-69–year age-group	96	102	
CR + CRi	48 (50.0)	37 (36.3)	1.76 (1.00 to 3.10)
CR	38 (39.6)	27 (26.5)	1.82 (1.00 to 3.32)
No. in 70-75–year age-group	57	54	
CR + CRi	25 (43.9)	15 (27.8)	2.03 (0.92 to 4.49)
CR	19 (33.3)	13 (24.1)	1.58 (0.69 to 3.62)
AML subtype			
No. with therapy-related AML	30	33	
CR + CRi	14 (46.7)	12 (36.4)	1.53 (0.56 to 4.20)
CR	11 (36.7)	10 (30.3)	1.33 (0.47 to 3.81)
No. with AML with antecedent MDS with prior HMA exposure	50	55	
CR + CRi	18 (36.0)	18 (32.7)	1.16 (0.52 to 2.59)
CR	13 (26.0)	10 (18.2)	1.58 (0.62 to 4.02)
No. with AML with antecedent MDS without prior HMA exposure	21	19	
CR + CRi	14 (66.7)	7 (36.8)	3.43 (0.93 to 12.59)
CR	12 (57.1)	7 (36.8)	2.29 (0.64 to 8.15)
No. with AML with antecedent CMML	11	12	
CR + CRi	4 (36.4)	3 (25.0)	1.71 (0.29 to 10.30)
CR	2 (18.2)	3 (25.0)	0.67 (0.09 to 4.99)
No. with de novo AML with MDS karyotype	41	37	
CR + CRi	23 (56.1)	12 (32.4)	2.66 (1.06 to 6.71)
CR	19 (46.3)	10 (27.0)	2.33 (0.90 to 6.03)

Lancet et al J Clin Oncol 2018, Lancet et al. Lancet Haematol 2021; 8: e481–91

Newly diagnosed I **Fit - Induction**



Guias de Pethema- LMA.Versión 2, 1 de Octubre de 2022

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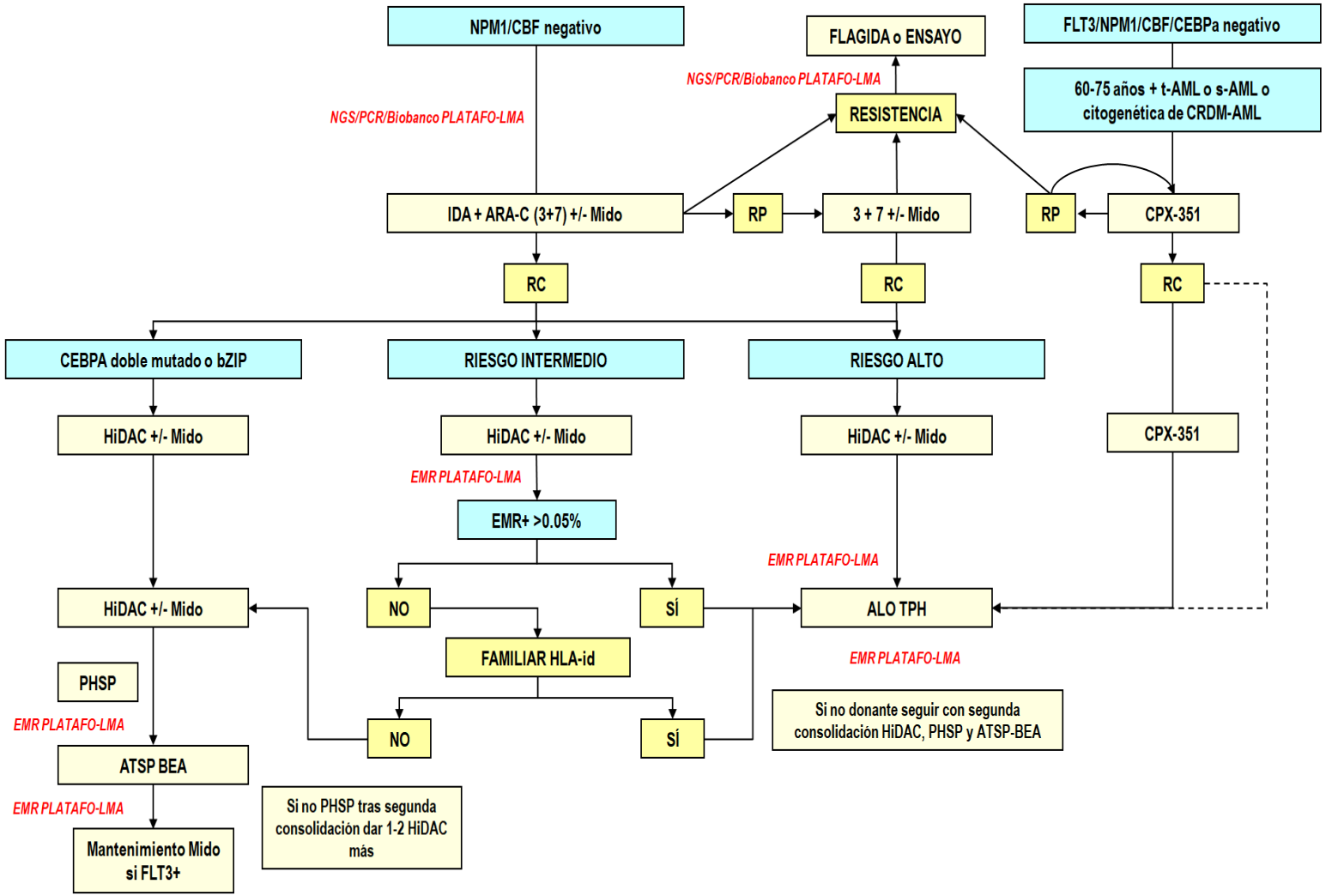

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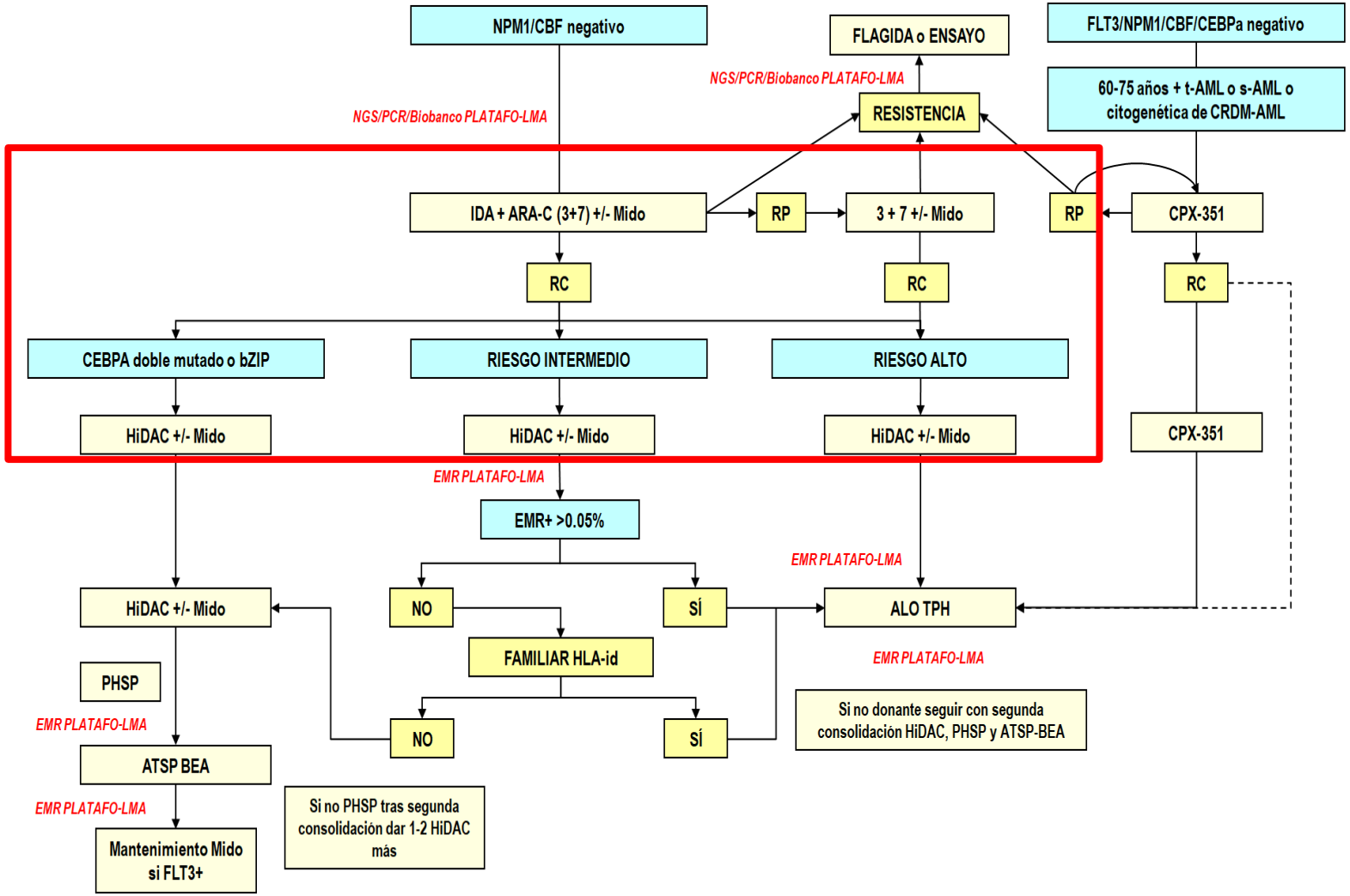
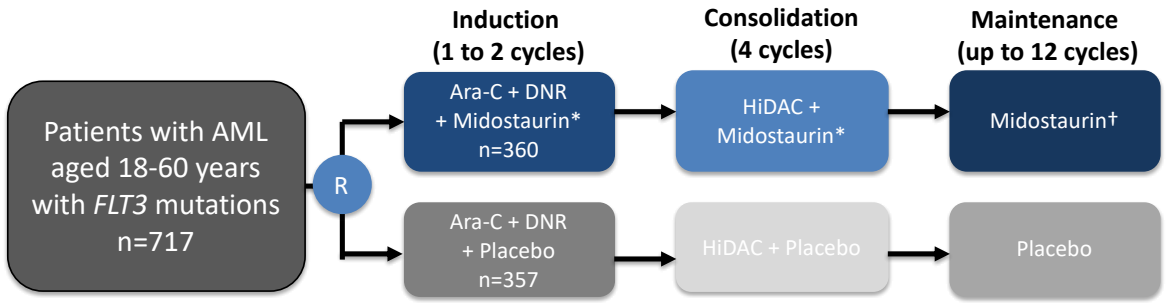


Newly diagnosed I **Fit - Induction**

RATIFY: Ph III Midostaurin + Chemotherapy for FLT3 AML patient



Primary endpoint: OS

* Midostaurin 50 mg or placebo orally twice daily, day 8-21, with each cycle.
† Midostaurin 50 mg or placebo orally twice daily for twelve 28-day cycles.

Table 3. Summary of Complete Remission.*

Variable	Midostaurin Group (N=360)	Placebo Group (N=357)	P Value†
Protocol-specified complete remission — no. (%)	212 (59)	191 (54)	0.15
Kaplan–Meier estimate of time to complete remission — days			
Median	35	35	
Range	20–60	20–60	

* Complete remission was defined as the presence of less than 5% blasts in the marrow or extramedullary leukemia, an absolute neutrophil count of more than 1000 per microliter, a platelet count of more than 100,000 per microliter, and the absence of blasts in the peripheral blood; in addition, per protocol, complete remission had to occur by day 60.
† P value is two-sided and was calculated with the use of Fisher's exact test.

Table 1. Baseline Characteristics of the Patients.

Characteristic	All Patients (N=717)	Midostaurin Group (N=360)	Placebo Group (N=357)	P Value*
Age at trial entry — yr				0.22
Median	47.9	47.1	48.6	
Range	18.0–60.9	19.0–59.8	18.0–60.9	
Female sex — no. (%)	398 (55.5)	186 (51.7)	212 (59.4)	0.04
Race — no./total no. (%)†				0.74
White	275/309 (89.0)	147/165 (89.1)	128/144 (88.9)	
Other	34/309 (11.0)	18/165 (10.9)	16/144 (11.1)	
Subtype of *FLT3* mutation — no. (%)‡				1.00
TKD	162 (22.6)	81 (22.5)	81 (22.7)	
ITD with low allelic ratio	341 (47.6)	171 (47.5)	170 (47.6)	
ITD with high allelic ratio	214 (29.8)	108 (30.0)	106 (29.7)	
Modified European LeukemiaNet classification — no./total no. (%)§				0.15
Favorable	29/547 (5.3)	16/269 (5.9)	13/278 (4.7)	
Normal	375/547 (68.6)	172/269 (63.9)	203/278 (73.0)	
Intermediate II	104/547 (19.0)	59/269 (21.9)	45/278 (16.2)	
Adverse	39/547 (7.1)	22/269 (8.2)	17/278 (6.1)	
White-cell count per μl¶				0.72
Median	34,900	35,600	33,000	
Range	600–421,800	600–421,800	800–329,800	
Platelet count per μl‖				0.58
Median	50,000	50,000	50,000	
Range	2000–461,000	2000–461,000	8000–444,000	
Absolute neutrophil count per mm^3**				0.65
Median	2.2	2.2	2.3	
Range	0–55.9	0–55.9	0–55.9	

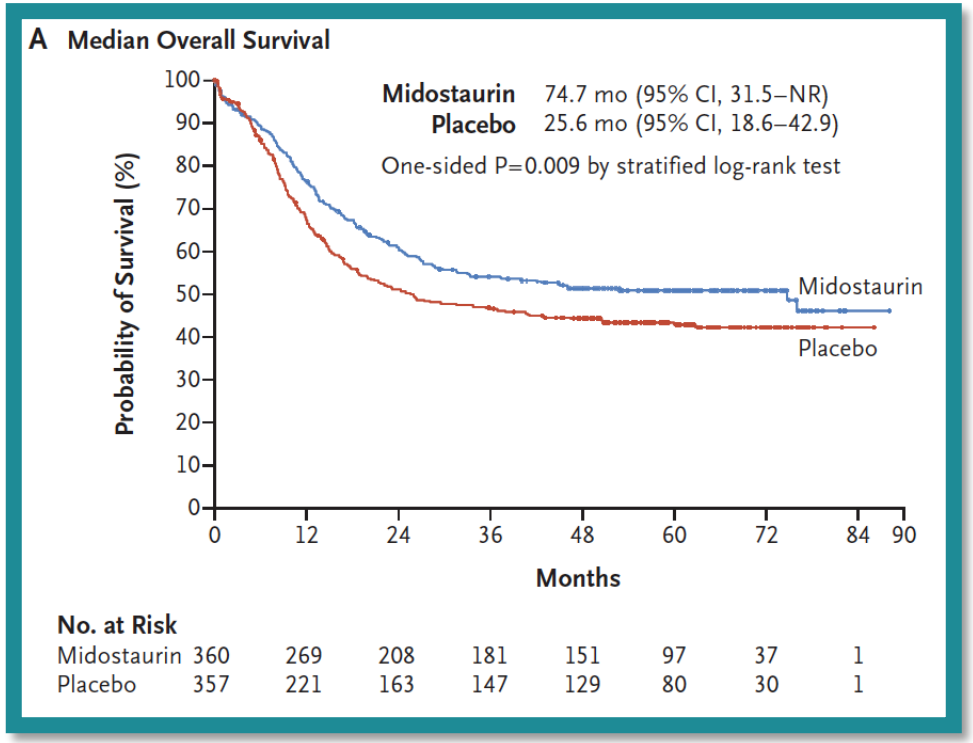
Stone, R. M. et al. N Engl J Med 377, 454–464 (2017).

Newly diagnosed I **Fit - Induction**

RATIFY: Ph III Midostaurin + Chemotherapy for FLT3 AML patient

Table 2. Summary of Grade 3, 4, or 5 Adverse Events.

Adverse Event	Midostaurin Group (N=355)	Placebo Group (N=354)	P Value*
	no. of patients (%)		
Hematologic			
Thrombocytopenia	346 (97)	342 (97)	0.52
Neutropenia	338 (95)	339 (96)	0.86
Anemia	329 (93)	311 (88)	0.03
Leukopenia	93 (26)	105 (30)	0.32
Lymphopenia	68 (19)	78 (22)	0.35
Other blood or bone marrow event	1 (<1)	4 (1)	0.22
Bone marrow hypocellularity	0	1 (<1)	0.50
Nonhematologic			
Febrile neutropenia	290 (82)	292 (82)	0.84
Infection	186 (52)	178 (50)	0.60
Lymphopenia	68 (19)	78 (22)	0.35
Diarrhea	56 (16)	54 (15)	0.92
Hypokalemia	49 (14)	60 (17)	0.25
Pain	47 (13)	44 (12)	0.82
Increased alanine aminotransferase	45 (13)	33 (9)	0.19
Rash or desquamation	50 (14)	27 (8)	0.008
Fatigue	32 (9)	37 (10)	0.53
Pneumonitis or pulmonary infiltrates	28 (8)	29 (8)	0.89
Nausea	20 (6)	34 (10)	0.05
Hyponatremia	31 (9)	23 (6)	0.32
Hyperbilirubinemia	25 (7)	28 (8)	0.67
Mucositis or stomatitis	22 (6)	28 (8)	0.38
Hypophosphatemia	19 (5)	29 (8)	0.14
Hypocalcemia	24 (7)	21 (6)	0.76



October 2017. EMA approved midostaurin for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation-positive:

- with standard 7+3 induction and HiDAC consolidation chemotherapy,
- patients in CR as a single agent maintenance therapy

Stone, R. M. et al. N Engl J Med 377, 454–464 (2017).

Newly diagnosed I **Fit - Induction**

QuANTUM-First: Ph III Quizartinib + Chemotherapy for FLT3-ITD AML patient

- Age 18-75 years
- Newly diagnosed *FLT3*-ITD AML
- ≥ 3% *FLT3*-ITD allelic frequency
- Patients begin 7+3 during screening

7+3: Cytarabine D1-7 + Daunorubicin or Idarubicin D1-3 + Quizartinib (40 mg) D8-21

HiDAC D1, 3 & 5 + Quizartinib (40 mg) D6-19 and/or allo-HCT

Quizartinib (30 then 60 mg) once daily

7+3: Cytarabine D1-7 + Daunorubicin or Idarubicin D1-3 + Placebo

HiDAC D1, 3 & 5 + Placebo D6-19 and/or allo-HCT

Placebo once daily

Study Design
Phase III, open label, RCT

Primary Endpoint
OS

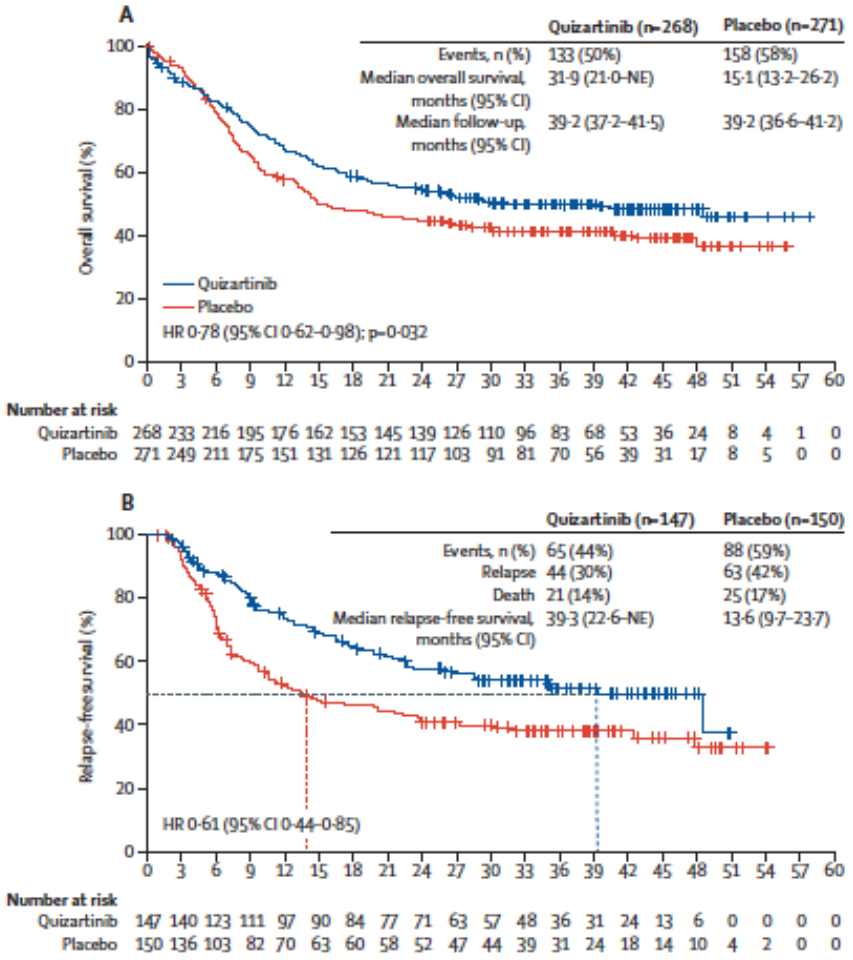
Secondary Endpoint
EFS, CR, CRc, CR/CRc with MRD- end of induction, safety

Herba HP. Lancet 2023; 401: 1571–83

Newly diagnosed I **Fit - Induction**

QuANTUM-First: Ph III Quizartinib + Chemotherapy for FLT3-ITD AML patient

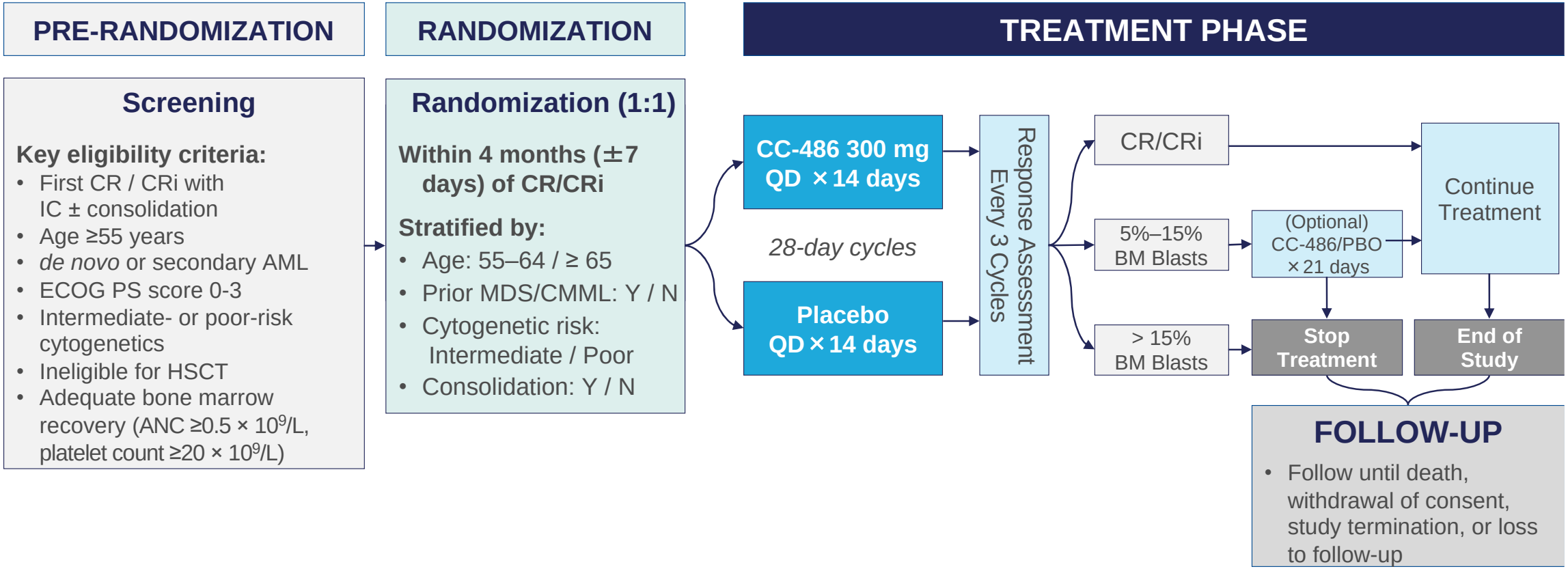
	Quizartinib (n=268)*	Placebo (n=271)*
Age, years		
Median (IQR)	56·0 (44·5–65·0)	56·0 (47·0–64·0)
Range	23–75	20–75
≥60 years	107 (40%)	109 (40%)
Sex		
Male	124 (46%)	121 (45%)
Female	144 (54%)	150 (55%)
Race		
Asian	80 (30%)	78 (29%)
Black or African American	2 (1%)	5 (2%)
American Indian or Alaska Native	0	1 (<1%)
White	159 (59%)	163 (60%)
Other	27 (10%)	24 (9%)
Region		
Europe	163 (61%)	163 (60%)
Asia or other regions	89 (33%)	90 (33%)
North America	16 (6%)	18 (7%)
ECOG performance status†		
0	87 (32%)	98 (36%)
1	134 (50%)	136 (50%)
2	47 (18%)	36 (13%)
AML type		
De novo AML	243 (91%)	255 (94%)
Secondary AML	25 (9%)	16 (6%)
Cytogenetic risks‡		
Favourable	14 (5%)	19 (7%)
Intermediate	197 (74%)	193 (71%)
Unfavourable	19 (7%)	27 (10%)
Unknown	38 (14%)	31 (11%)
Missing	0	1 (<1%)
Mutated *NPM1*§	142 (53%)	140 (52%)
Mutated *CEBPA*§¶	61 (23%)	65 (24%)
VAF‖		
≥3% to ≤25%	94 (35%)	98 (36%)
>25% to ≤50%	143 (53%)	138 (51%)
>50%	30 (11%)	35 (13%)
WBC count at diagnosis of AML		
<40 × 10⁹/L	135 (50%)	137 (51%)
≥40 × 10⁹/L	133 (50%)	134 (49%)



Herba HP. Lancet 2023; 401: 1571–83

Newly diagnosed I **Fit - Maintenance**

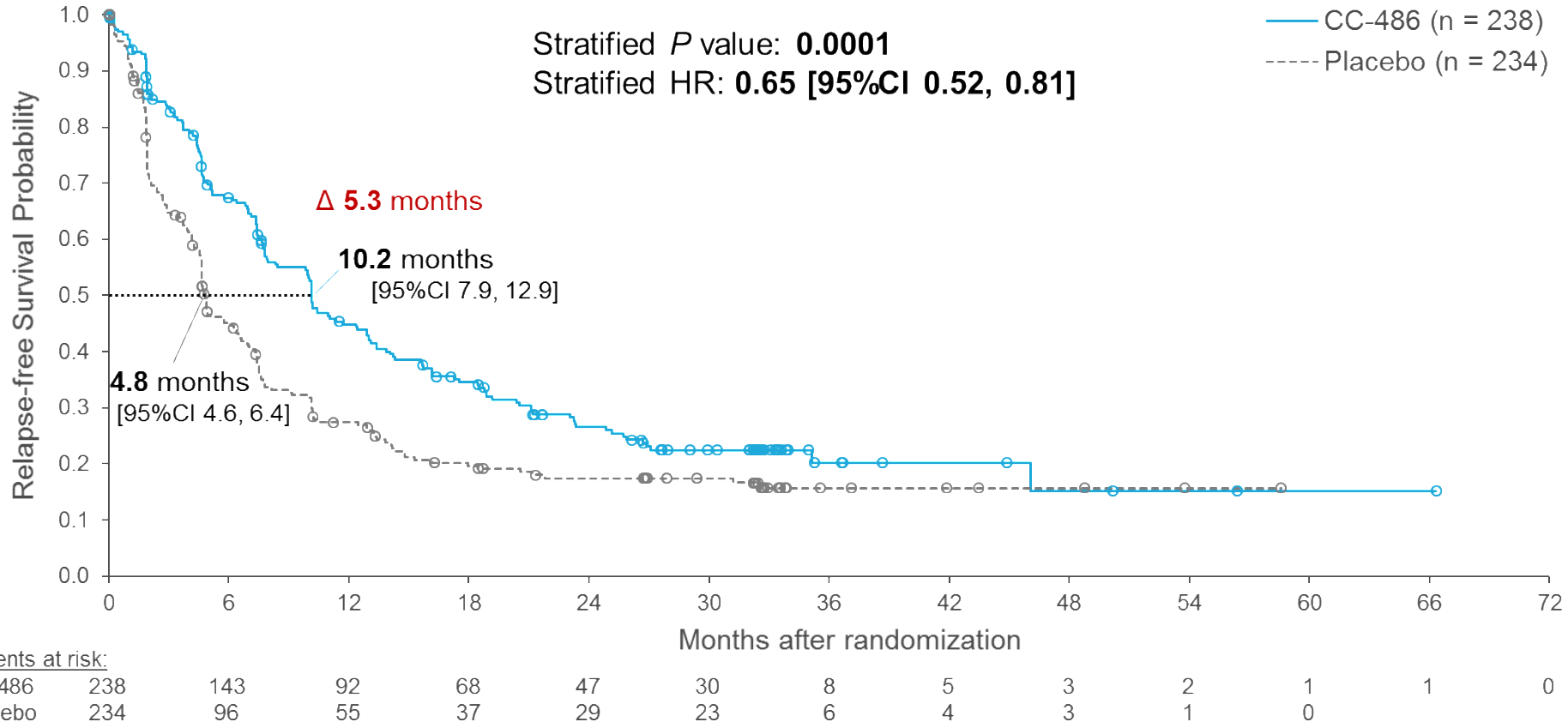
QUAZAR AML-001: Ph III randomized, CC-486 vs Pbo in AML in first remission



Wei H, et al. ASH 2019

Newly diagnosed I **Fit - Maintenance**

QUAZAR AML-001: Ph III randomized, CC-486 vs Pbo in AML in first remission



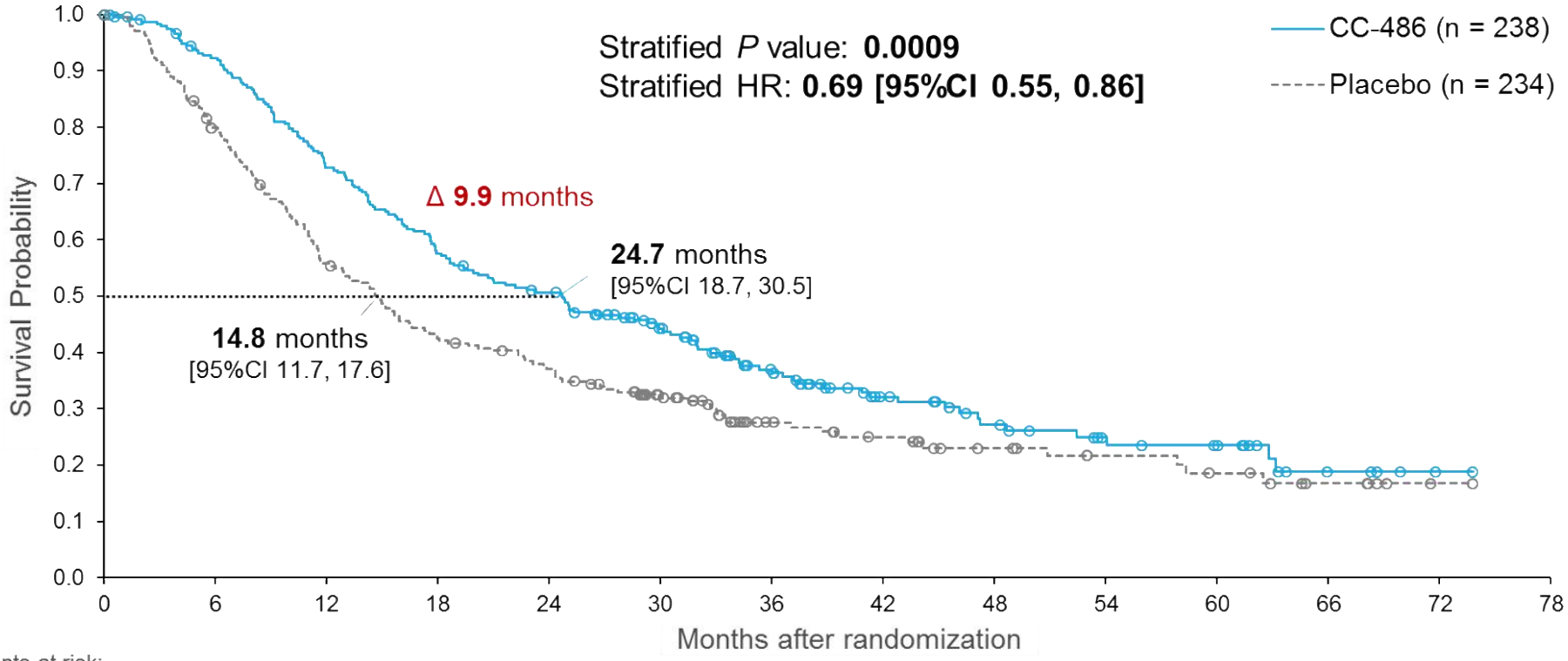
- 1-year relapse rate was 53% in the CC-486 arm [95%CI 46, 59] and was 71% in the placebo arm [65, 77]

Wei H, et al. ASH 2019

Newly diagnosed I **Fit - Maintenance**

QUAZAR AML-001: Ph III randomized, CC-486 vs Pbo in AML in first remission

- Median follow-up: 41.2 months



Patients at risk:

CC-486	238	213	169	133	115	87	59	37	26	18	15	5	1	0
Placebo	234	183	128	96	82	58	34	27	19	15	11	6	1	0

Wei H, et al. ASH 2019

Newly diagnosed I **Fit vs Unfit vs Frail**

Clínica Universidad de Navarra | Cancer Center

Fit

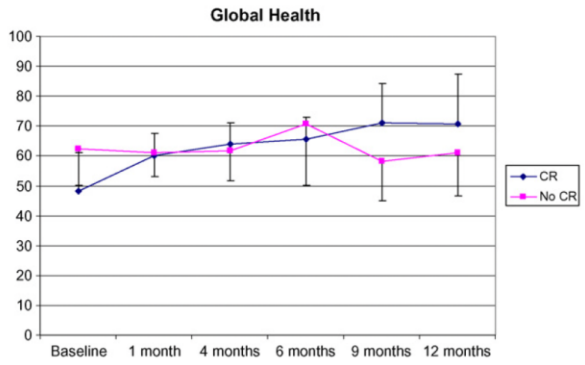
Unfit

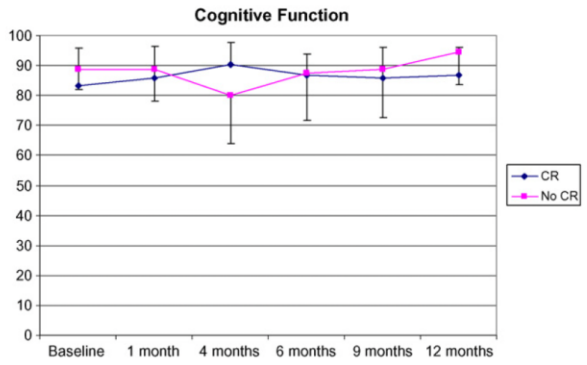
Frail

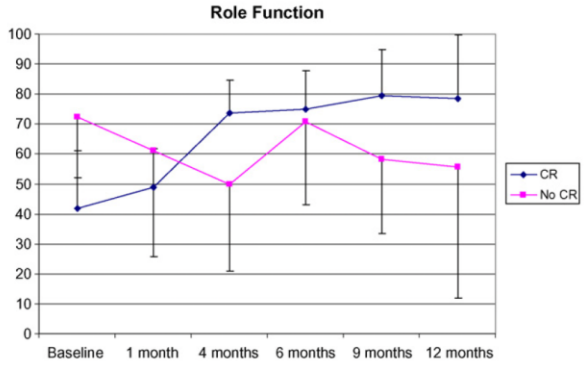
Newly diagnosed I **Unfit**

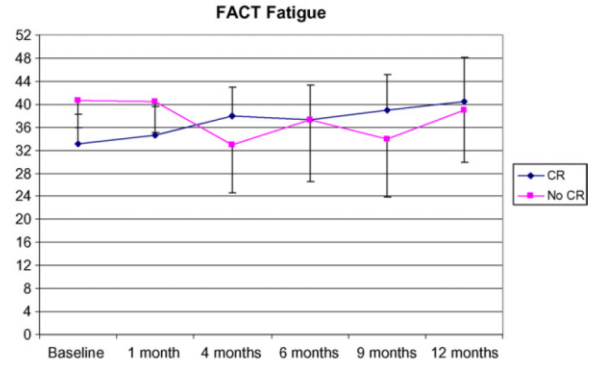
Clínica Universidad de Navarra | Cancer Center

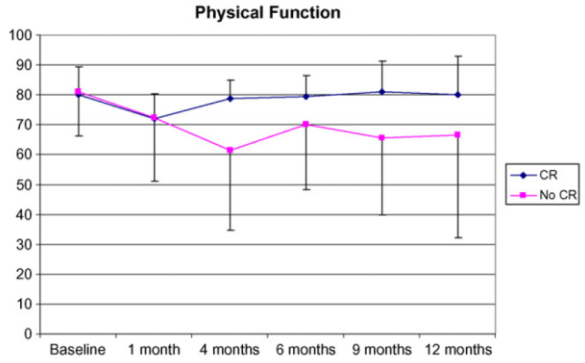
CR has an impact in QoL

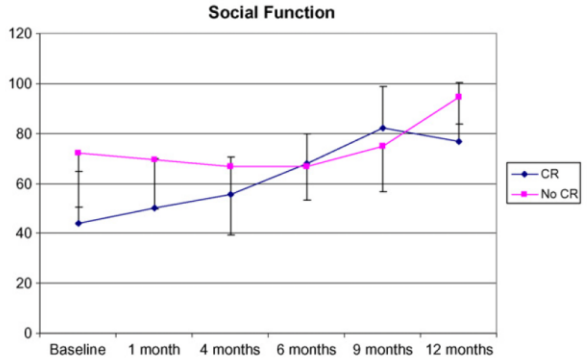


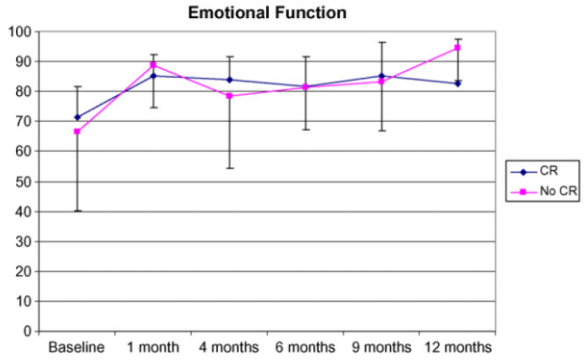












Crit Rev Oncol Hematol. 2009 Feb;69(2):168-74. doi: 10.1016/j.critrevonc.2008.07.015.

Döhner H. Blood (2024) 144 (21): 2169–2173.

Newly diagnosed I **Unfit**

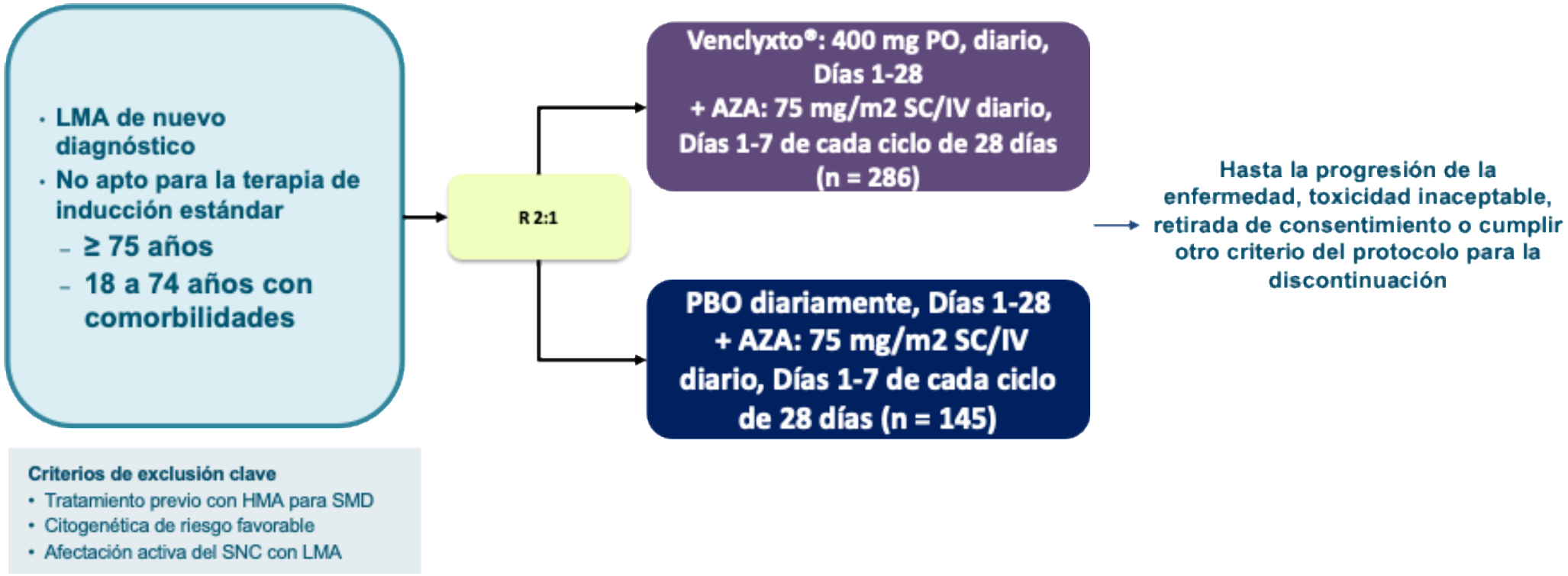
Clínica Universidad de Navarra | Cancer Center

Risk category	Genetic abnormality
Favorable	Mutated *NPM1* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt}) Mutated *IDH2* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt}) Mutated *IDH1** (*TP53*^{wt}) Mutated *DDX41*† Other cytogenetic and/or molecular abnormalities‡ (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt})
Intermediate	Other cytogenetic and molecular abnormalities‡ (*FLT3*-ITD^{pos} and/or *NRAS*^{mut} and/or *KRAS*^{mut}; *TP53*^{wt})
Adverse	Mutated *TP53*

Döhner H. Blood (2024) 144 (21): 2169–2173.

Newly diagnosed I **Unfit**

Viale-A: VEN + AZA frente a PBO + AZA LMA no son elegibles para QT



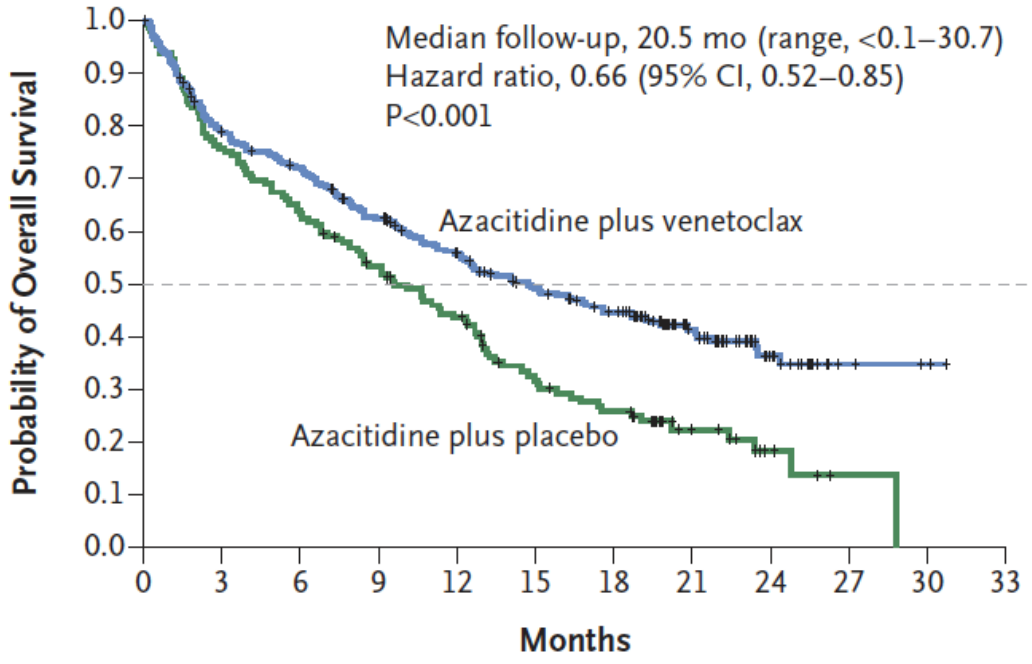
Criterios de exclusión clave
- Tratamiento previo con HMA para SMD
- Citogenética de riesgo favorable
- Afectación activa del SNC con LMA

Study Design	**Primary Endpoint**	**Secondary Endpoint**
Phase III, open label, RCT	OS, CRc (RC+Rci)	RC, RC+RCh, IT, SLE

1. ClinicalTrials.gov. NCT02993523 (consultado en noviembre de 2022). 2. DiNardo CD, et al. N Engl J Med. 2020;383(7):617-629. 3. 1. Ficha Técnica Venclyxto® (venetoclax). Disponible en CIMA https://cima.aemps.es/cima/publico/lista.html

Newly diagnosed I **Unfit**

Viale-A: VEN + AZA frente a PBO + AZA LMA no son elegibles para QT



No. at Risk

Azacitidine plus venetoclax	286	219	198	168	143	117	101	54	23	5	3	0
Azacitidine plus placebo	145	109	92	74	59	38	30	14	5	1	0	0

	Nº eventos/ Nº pacientes (%)	mSG (meses) (IC 95%)
VEN + AZA	22/286 (77,6)	14,7 (12,1 – 18,7)
PBO + AZA	138/145 (95,2)	9,6 (7,4 – 12,7)

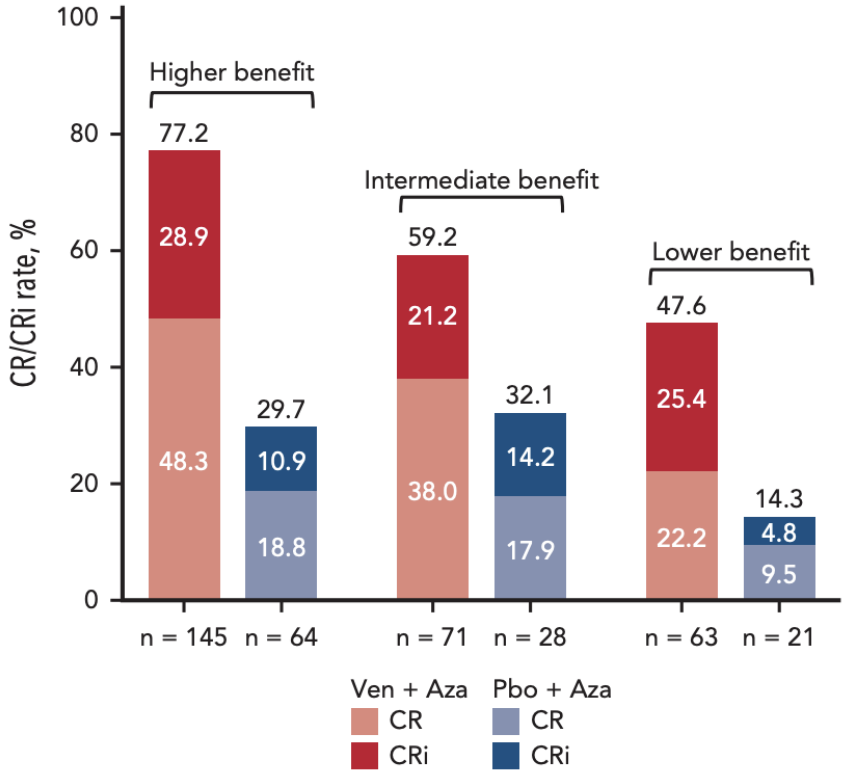
HR: 0,58 (95% CI, 0,465 – 0,723); P < 0,001

1. ClinicalTrials.gov. NCT02993523 (consultado en noviembre de 2022). 2. DiNardo CD, et al. N Engl J Med. 2020;383(7):617-629. 3. 1. Ficha Técnica Venclyxto® (venetoclax). Disponible en CIMA https://cima.aemps.es/cima/publico/lista.html

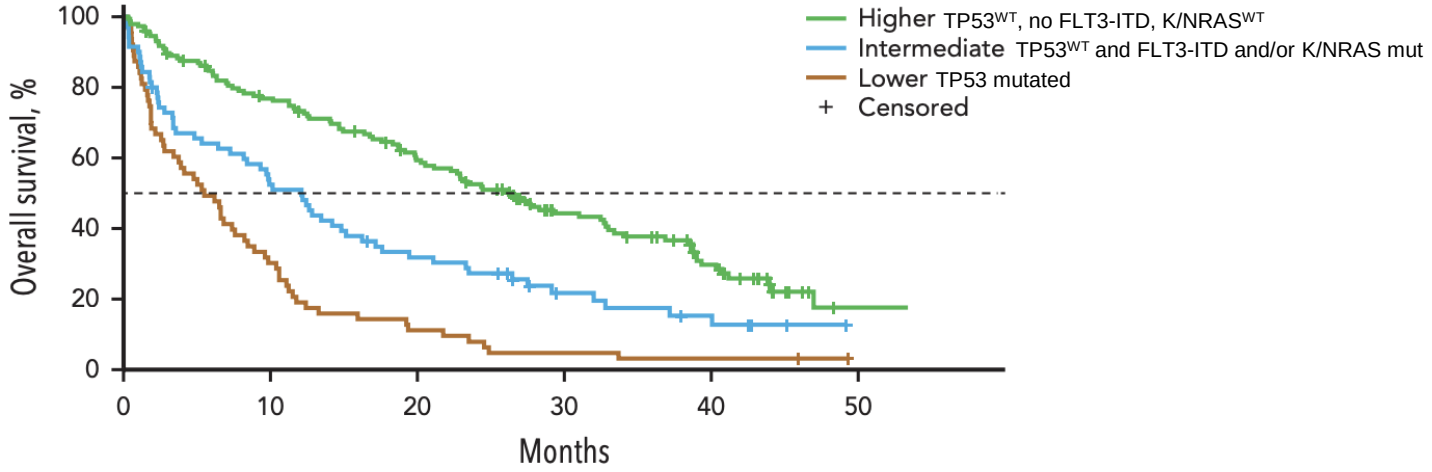
Newly diagnosed I **Unfit**

Viale-A: VEN + AZA frente a PBO + AZA LMA no son elegibles para QT

A



B



Patients at Risk

145	107	79	47	25	2
71	36	21	10	6	0
63	19	7	3	2	0

Ven + Aza (N = 279)	n	Events	Median OS, months (95% CI)
Higher benefit	145	96	26.5 (20.2, 32.7)
Intermediate benefit	71	57	12.1 (7.3, 15.2)
Lower benefit	63	61	5.5 (2.8, 7.6)

1. ClinicalTrials.gov. NCT02993523 (consultado en noviembre de 2022). 2. DiNardo CD, et al. N Engl J Med. 2020;383(7):617-629. 3. 1. Ficha Técnica Venclyxto® (venetoclax). Disponible en CIMA https://cima.aemps.es/cima/publico/lista.html

Newly diagnosed I **Unfit**

AGILE: IVO + AZA frente a PBO + AZA LMA IDH1 mutada no elegibles para QT

- LMA de nuevo diagnóstico
- IDH1 mutado
- ≥ 18 a
- No apto para la terapia de inducción estándar

R 1:1
By region, de novo status

Ivosidenib 500 mg diario, D 1-28
+ AZA: 75 mg/m2 SC/IV diario, Días 1-7 de cada ciclo de 28 días (n = 72)

PBO diariamente, Días 1-28
+ AZA: 75 mg/m2 SC/IV diario, Días 1-7 de cada ciclo de 28 días (n = 74)

Study Design
Phase III, double-blind, RCT

Primary Endpoint
EFS with 173 events (52 months)

Secondary Endpoint
CRR, OS, CR+CRh, ORR

Montesinos P. N Engl J Med 2022;386:1519-31.

Newly diagnosed I **Unfit**

AGILE: IVO + AZA frente a PBO + AZA LMA IDH1 mutada no elegibles para QT

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Ivosidenib + Azacitidine (N=72)	Placebo + Azacitidine (N=74)
Median age (range) — yr	76.0 (58.0–84.0)	75.5 (45.0–94.0)
Sex — no. (%)		
Male	42 (58)	38 (51)
Female	30 (42)	36 (49)
Race or ethnic group — no. (%)†		
Asian	15 (21)	19 (26)
White	12 (17)	12 (16)
Black	0	2 (3)
Other or not reported	45 (62)	41 (55)
ECOG performance-status score — no. (%)‡		
0	14 (19)	10 (14)
1	32 (44)	40 (54)
2	26 (36)	24 (32)
Disease history according to investigator — no. (%)		
Primary AML	54 (75)	53 (72)
Secondary AML§	18 (25)	21 (28)
History of myeloproliferative neoplasms	4 (6)	8 (11)
World Health Organization classification — no. (%)		
AML with recurrent genetic abnormalities	16 (22)	24 (32)
AML with myelodysplasia-related changes	28 (39)	26 (35)
Therapy-related myeloid neoplasms	1 (1)	1 (1)
IDH1 mutation type — no. (%)¶		
R132C	45 (62)	51 (69)
R132H	14 (19)	12 (16)
R132G	6 (8)	4 (5)
R132L	3 (4)	0
R132S	2 (3)	6 (8)
Median variant allele frequency of *IDH1* mutations in bone marrow aspirate (range) — %‖	36.8 (3.1–50.5)	35.5 (3.0–48.5)
Cytogenetic risk status — no. (%)**		
Favorable	3 (4)	7 (9)
Intermediate	48 (67)	44 (59)
Poor	16 (22)	20 (27)
Median bone marrow blast level (range) — %	54.0 (20.0–95.0)	48.0 (17.0–100)

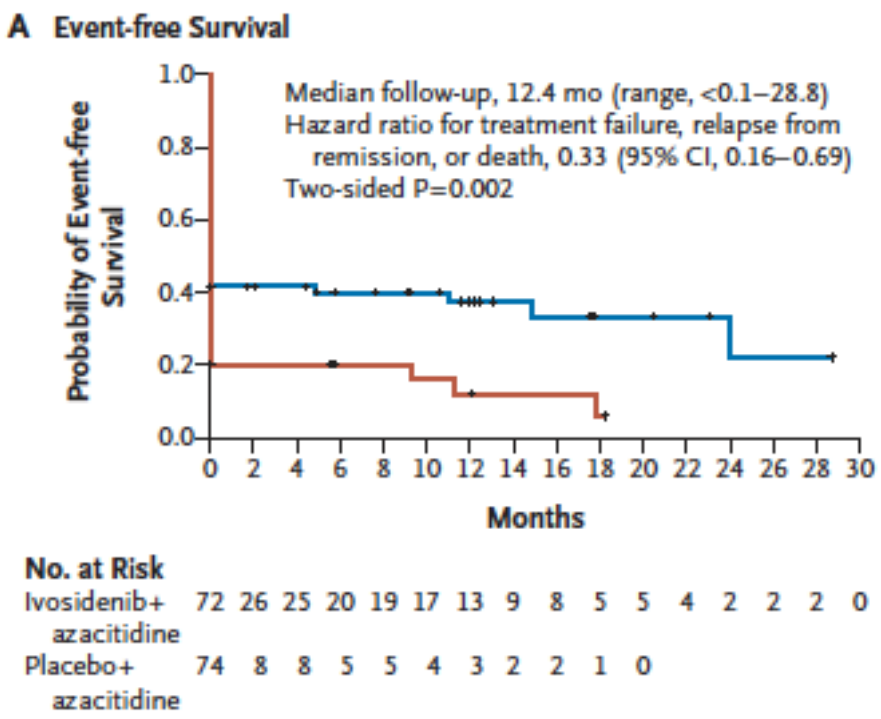
Table 2. Hematologic Response, Response Duration, and Time to Response (Intention-to-Treat Population).*

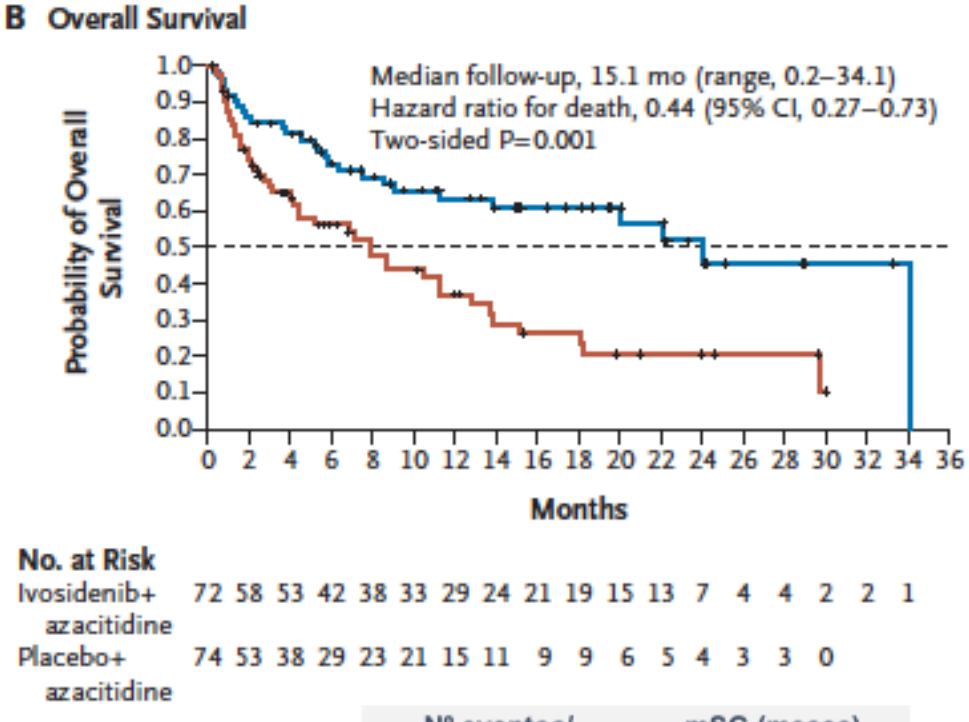
Response Category	Ivosidenib + Azacitidine (N=72)	Placebo + Azacitidine (N=74)
Best response — no. (%)		
Complete remission	34 (47)	11 (15)
Complete remission with incomplete hematologic or platelet recovery	5 (7)	1 (1)
Partial remission	4 (6)	2 (3)
Morphologic leukemia-free state	2 (3)	0
Stable disease	7 (10)	27 (36)
Progressive disease	2 (3)	4 (5)
Could not be evaluated	1 (1)	2 (3)
Not assessed	17 (24)	27 (36)
Complete remission		
Percentage of patients (95% CI)	47 (35–59)	15 (8–25)
Odds ratio vs. placebo (95% CI); P value	4.8 (2.2–10.5); two-sided P<0.001	
Median duration of complete remission (95% CI) — mo	NE (13.0–NE)	11.2 (3.2–NE)
Median time to complete remission (range) — mo	4.3 (1.7–9.2)	3.8 (1.9–8.5)
Complete remission or complete remission with partial hematologic recovery		
No. of patients	38	13
Percentage of patients (95% CI)	53 (41–65)	18 (10–28)
Odds ratio vs. placebo (95% CI); P value	5.0 (2.3–10.8); two-sided P<0.001	
Median duration of complete remission or complete remission with partial hematologic recovery (95% CI) — mo	NE (13.0–NE)	9.2 (5.8–NE)
Median time to complete remission or complete remission with partial hematologic recovery (range) — mo	4.0 (1.7–8.6)	3.9 (1.9–7.2)
Objective response		
No. of patients	45	14
Percentage of patients (95% CI)	63 (50–74)	19 (11–30)
Odds ratio vs. placebo (95% CI); P value	7.2 (3.3–15.4); two-sided P<0.001	
Median duration of response (95% CI) — mo	22.1 (13.0–NE)	9.2 (6.6–14.1)
Median time to first response (range) — mo	2.1 (1.7–7.5)	3.7 (1.9–9.4)

Montesinos P. N Engl J Med 2022;386:1519-31.

Newly diagnosed I **Unfit**

AGILE: IVO + AZA frente a PBO + AZA LMA IDH1 mutada no elegibles para QT





HR: 0,35 (95% CI, 0,18 – 0,67); P = 0,001

	Nº eventos/ Nº pacientes (%)	mSG (meses) (IC 95%)
IVO + AZA	46/72 (63,9)	24,0 (11,3 – 34,1)
PBO + AZA	**62/74 (83,8)**	**7,9 (4,1 – 11,3)**

Montesinos P. N Engl J Med 2022;386:1519-31.

Newly diagnosed I **Fit vs Unfit vs Frail**

Clínica Universidad de Navarra | Cancer Center

Fit

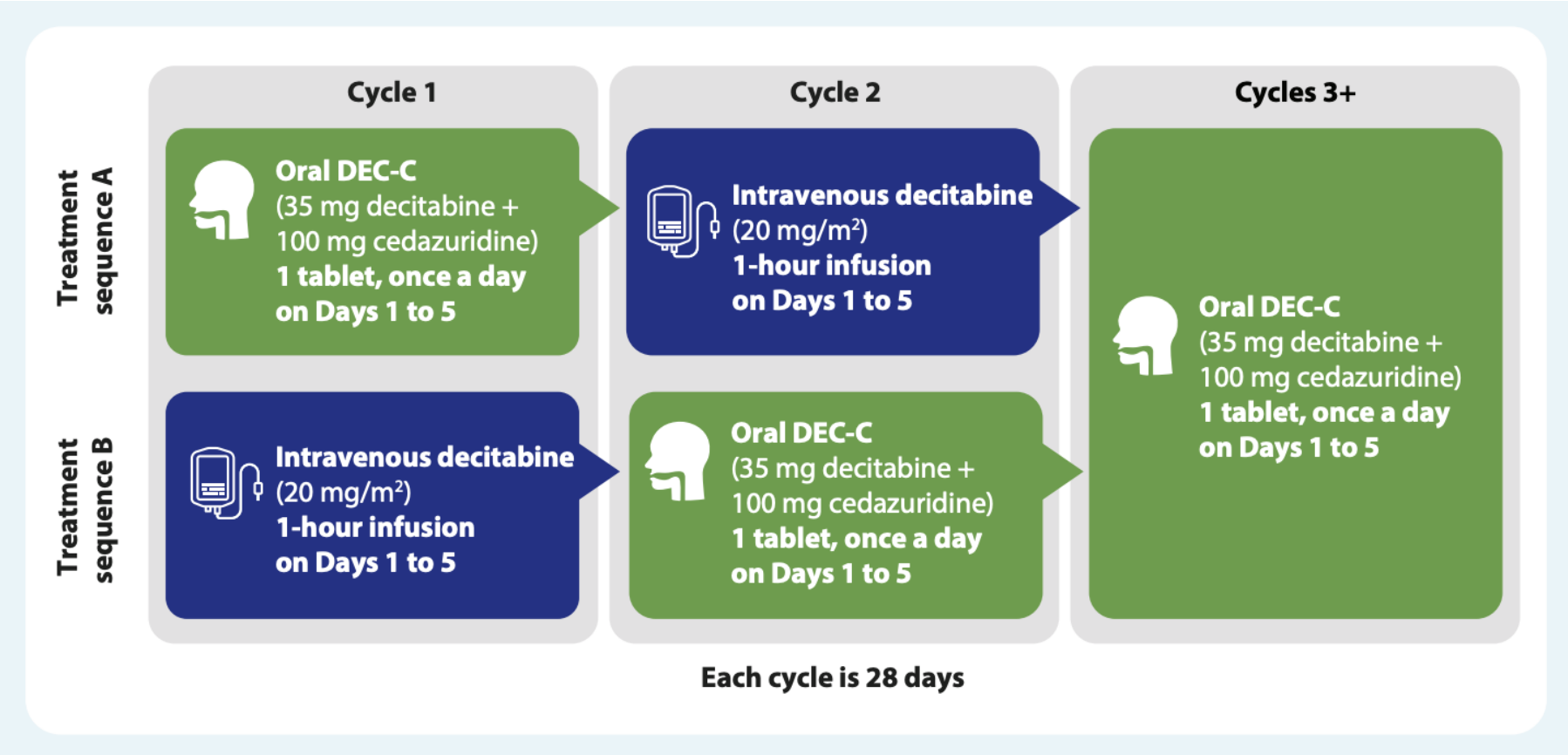
Unfit

Frail
(or combo-insensitive patients)

Newly diagnosed I **Frail**

Clínica Universidad de Navarra | Cancer Center

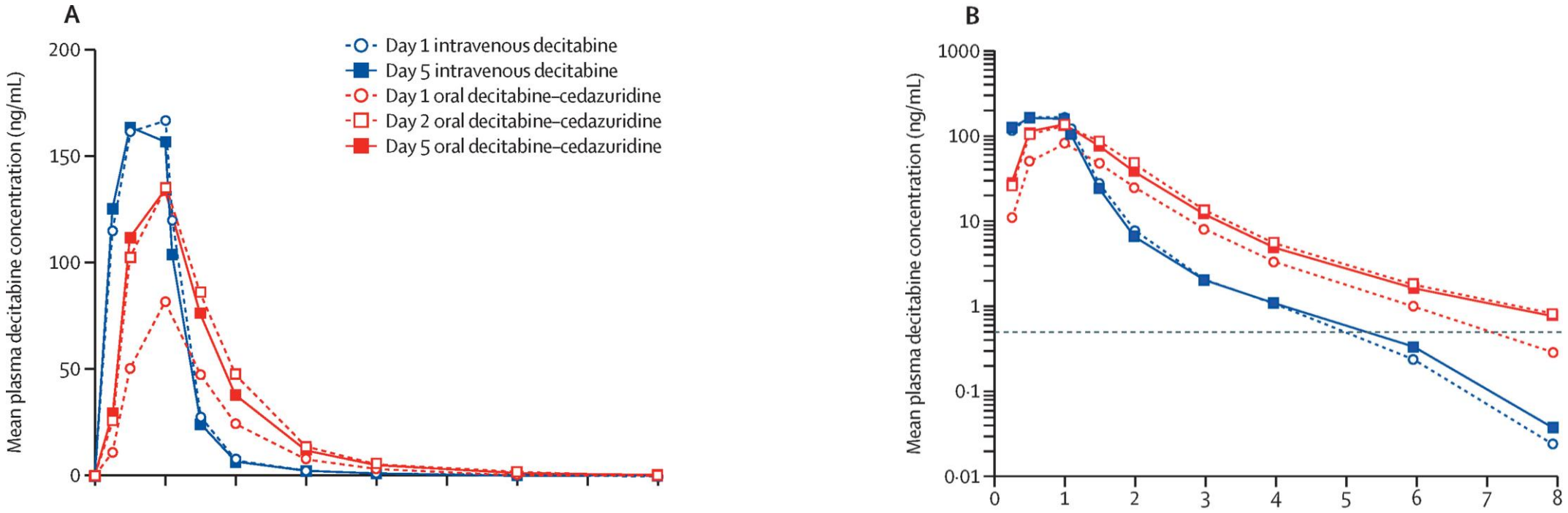
Oral decitabine–cedazuridine versus intravenous decitabine for myelodysplastic syndromes and chronic myelomonocytic leukaemia (ASCERTAIN): a registrational, randomised, crossover, pharmacokinetics, phase 3 study



García-Manero G. Lancet Haematol . 2024 Jan;11(1):e15-e26.

Newly diagnosed I **Frail**

Oral decitabine–cedazuridine versus intravenous decitabine for myelodysplastic syndromes and chronic myelomonocytic leukaemia (ASCERTAIN): a registrational, randomised, crossover, pharmacokinetics, phase 3 study

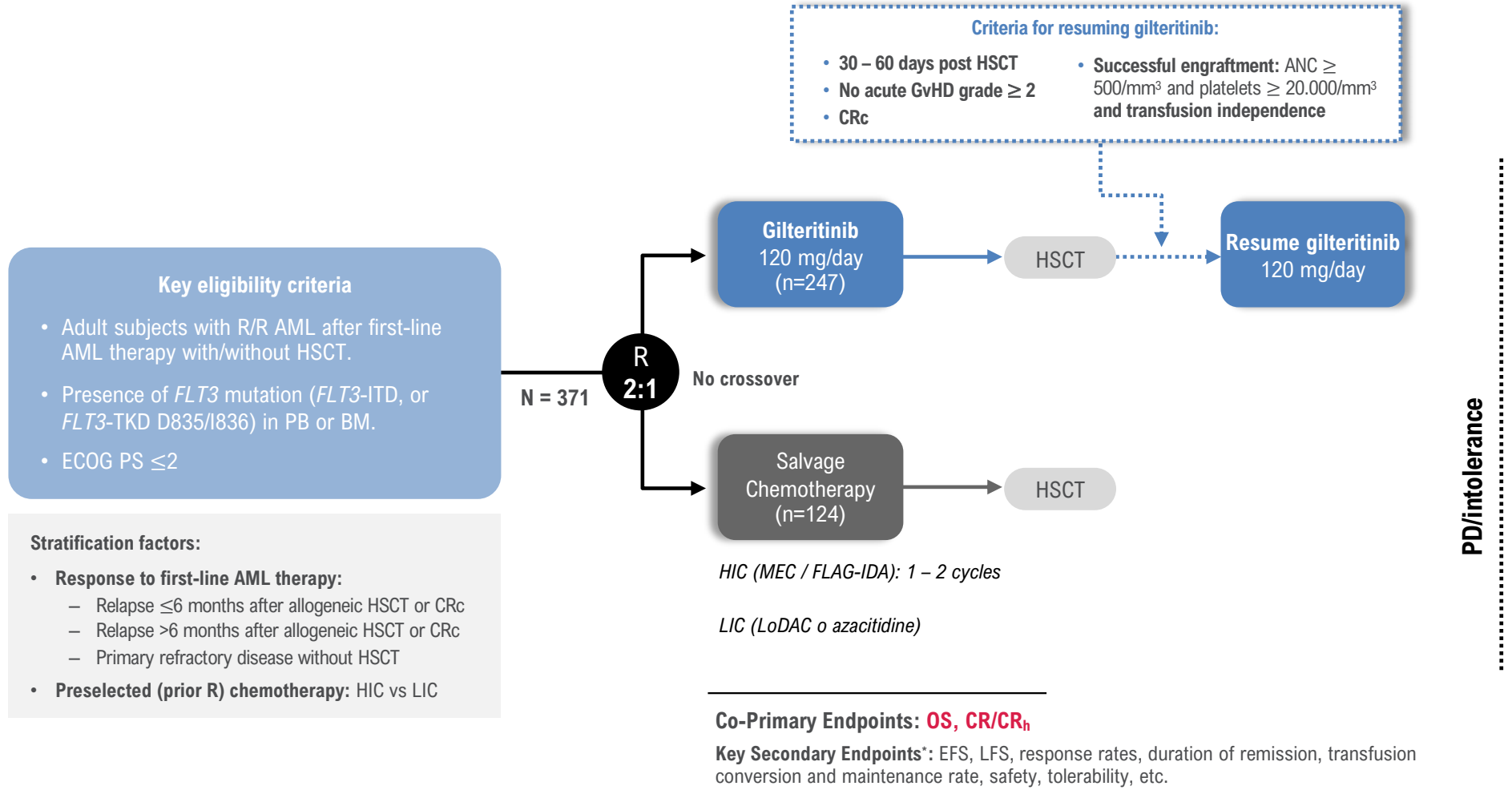


García-Manero G. Lancet Haematol . 2024 Jan;11(1):e15-e26.

R/R

Relapse/Refractory I **FLT3 mt**

Admiral: Phase III Gilteritinib vs Pb in R/R FLT3mut AML



[1] Perl AE et al. N Eng J Med. 2019;381:1728-40; [2] Supplement to: Perl AE et al. N Eng J Med. 2019;381:1728-40. [3] Perl AE et al. Journal of Clinical Oncology 38, no. 15_suppl (May 20, 2020) 7514-7514.

Relapse/Refractory I **FLT3 mt**

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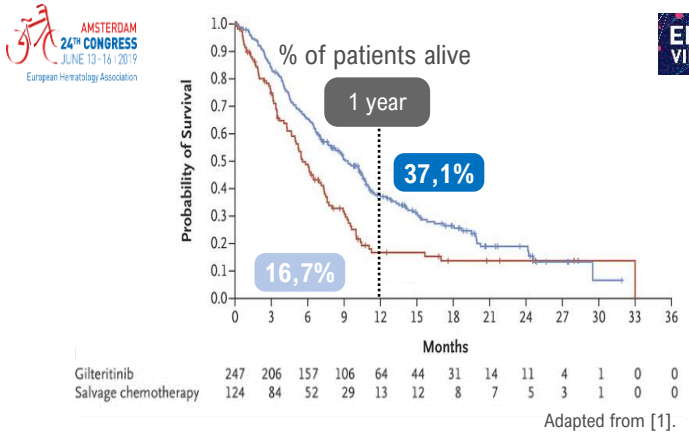
Admiral: Phase III Gilteritinib vs Pb in R/R FLT3mut AML

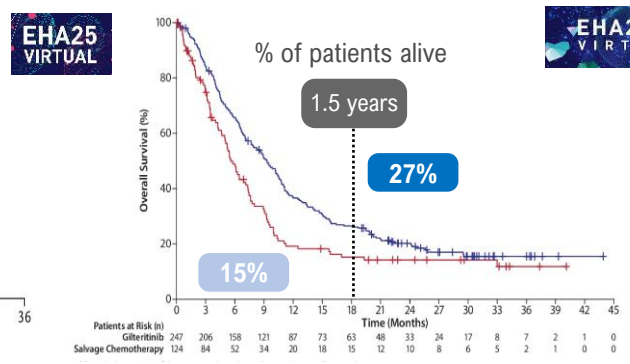
Primary analysis

mFU: 17.8 mo



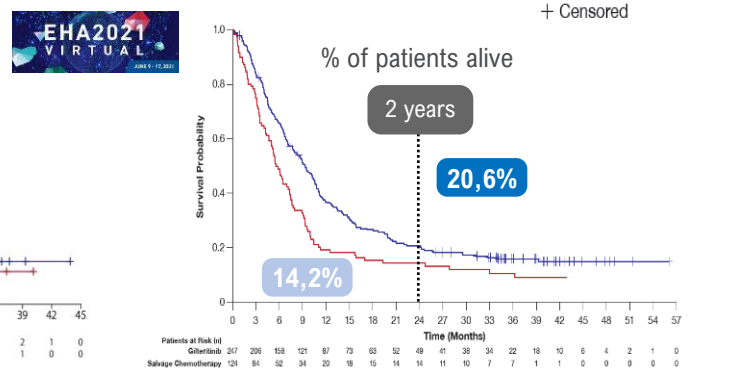
Adapted from [1].

mFU: 29.2 mo



Adapted from [2].

mFU: 37.1 mo



Adapted from [3].

Gilteritinib
Salvage Chemotherapy
+ Censored

		mFU, mos	17.8	29.2	37.1
Median OS, mos (95% CI)	Gilteritinib		9.3 (7.7, 10.7)	9.3	9.3
	Chemotherapy		5.6 (4.7, 7.3)	5.6	5.6
		HR (95% CI)	**0.64** (0.49, 0.83)	**0.679** (0.527, 0.875)	**0.665** (0.518, 0.853)
		P-value	*P* < 0.001	*P* = 0.0026*	*P* = 0.0013*
			[1]	[2]	[3]

Results from the long-term follow-up of the ADMIRAL trial **confirm that prolonged remission with long-term survival occurred in patients with FLT3^{mut+} R/R AML receiving gilteritinib** as the first salvage therapy and that **survival with gilteritinib was superior to standar chemotherapy options**[2,3].

Following initial treatment with gilteritinib, **long-term survivors typically remained in remission frequently proceeded to HSCT, and received post-HSCT gilteritinib**[2].

[1] Perl AE et al. N Eng J Med. 2019;381:1728-40; [2] Supplement to: Perl AE et al. N Eng J Med. 2019;381:1728-40. [3] Perl AE et al. Journal of Clinical Oncology 38, no. 15_suppl (May 20, 2020) 7514-7514.

Relapse/Refractory

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Yr	Regimen	N	Ref/Rel	Median Age, Yrs	CR, %
1985	HiDAC vs HiDAC + DXR/DNR	78	42/36	37	63 v 65
1988	MTZ, etoposide (ME)	61	21/20	47	43
1991	MTZ, etoposide, IDAC (MEC)	32	18/14	24	66
1993	IDA, etoposide, IDAC	97	36/61	37	43
1994	MEC ± G-CSF priming	50	6/44	43 vs 47	54 vs 42
1994	HiDAC vs HiDAC + etoposide	131	---	---	31 vs 38
1995	Etoposide, MTZ, Ara-C (EMA)	133	22/111	43	60
1998	Fludarabine, HiDAC, G-CSF (FLAG)	38	16/22	41	55
1999	HiDAC vs HiDAC + MTZ	162	56/106	48 vs 53	32 vs 44
1999	EMA ± GM-CSF	192	120/72	47 vs 46	65 vs 59
2001	Fludarabine, HiDAC, G-CSF (FLAG)	83	44/21	47/48	30/81
2003	Fludarabine, HiDAC, G-CSF, IDA	46	10/36	41	52
2008	Cladribine, HiDAC, MTZ (CLAG-M)	118	78/40	45	58
2009	FLAG-IDA ± GO	71	10/61	48	29 vs 39
2012	Clofarabine + IDAC vs IDAC	326	171/148	67	35 vs 18

Organizado por:

Clínica Universidad de Navarra

PUESTA AL DÍA

HEMATOLOGÍA EN 48H [LO QUE DEBES CONOCER PARA TU PRÁCTICA CLÍNICA]

X EDICIÓN

ACTUALÍZATE 48 HORAS

Abordaje Terapéutico de la Leucemia Mieloblástica Aguda en el 2025

Ana Alfonso Piérola

Clínica Universidad de Navarra, Pamplona