Combinaciones quimioterápicas en hemopatías malignas

Leucemia aguda mieloblástica

Madrid, 23 de Octubre de 2014

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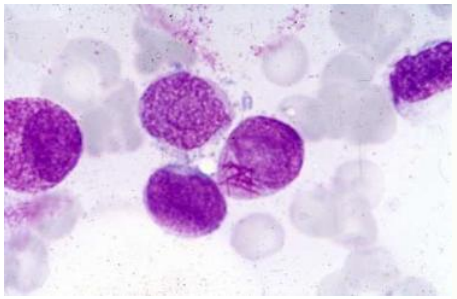
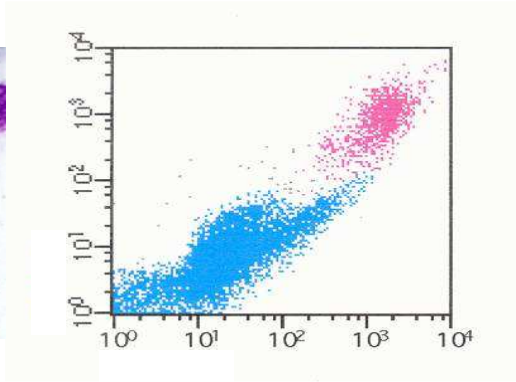
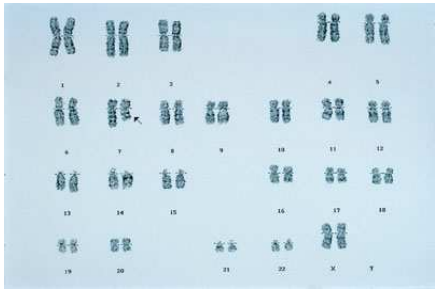
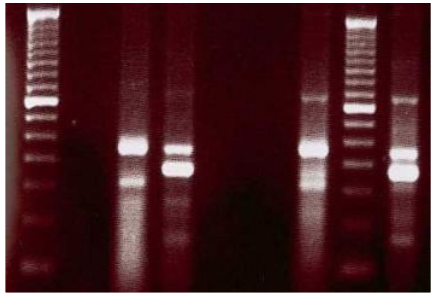
- El mundo “real” de la LMA
- ¿Que pacientes son candidatos a tratamiento intensivo?
- Tratamiento pacientes “fit”
- Tratamiento pacientes no “fit”

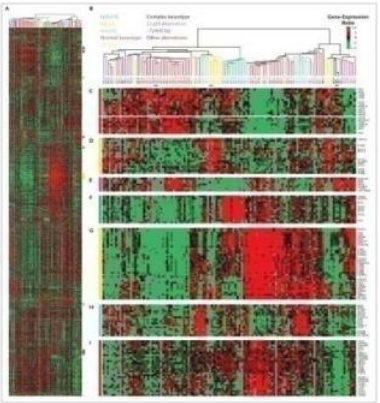
…es una enfermedad heterogénea

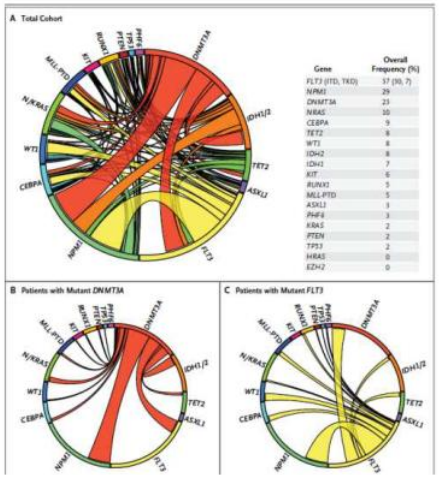












Clasificación de la WHO 2008

Acute myeloid leukemia with recurrent genetic abnormalities
- **AML with t(8;21)(q22;q22); *RUNX1-RUNX1T1***
- **AML with inv(16)(p13.1q22) or t((16;16)(p13.1;q22); *CBFB-MYH11***
- **APL with t(15;17)(q22;q12); *PML-RARA***
- **AML with t(9;11)(p22;q23); *MLLT3-MLL***
- **AML with t(6;9)(p23;q34); *DEK-NUP214***
- **AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1***
- **AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1***
- ***Provisional entity: AML with mutated NPM1***
- ***Provisional entity: AML with mutated CEBPA***

Acute myeloid leukemia with myelodysplasia-related changes

Therapy-related myeloid neoplasms

Acute myeloid leukemia, not otherwise specified
- **AML with minimal differentiation**
- **AML without maturation**
- **AML with maturation**
- **Acute myelomonocytic leukemia**
- **Acute monoblastic/monocytic leukemia**
- **Acute erythroid leukemia**
  - **Pure erythroid leukemia**
  - **Erythroleukemia, erythroid/myeloid**
- **Acute megakaryoblastic leukemia**
- **Acute basophilic leukemia**
- **Acute panmyelosis with myelofibrosis**

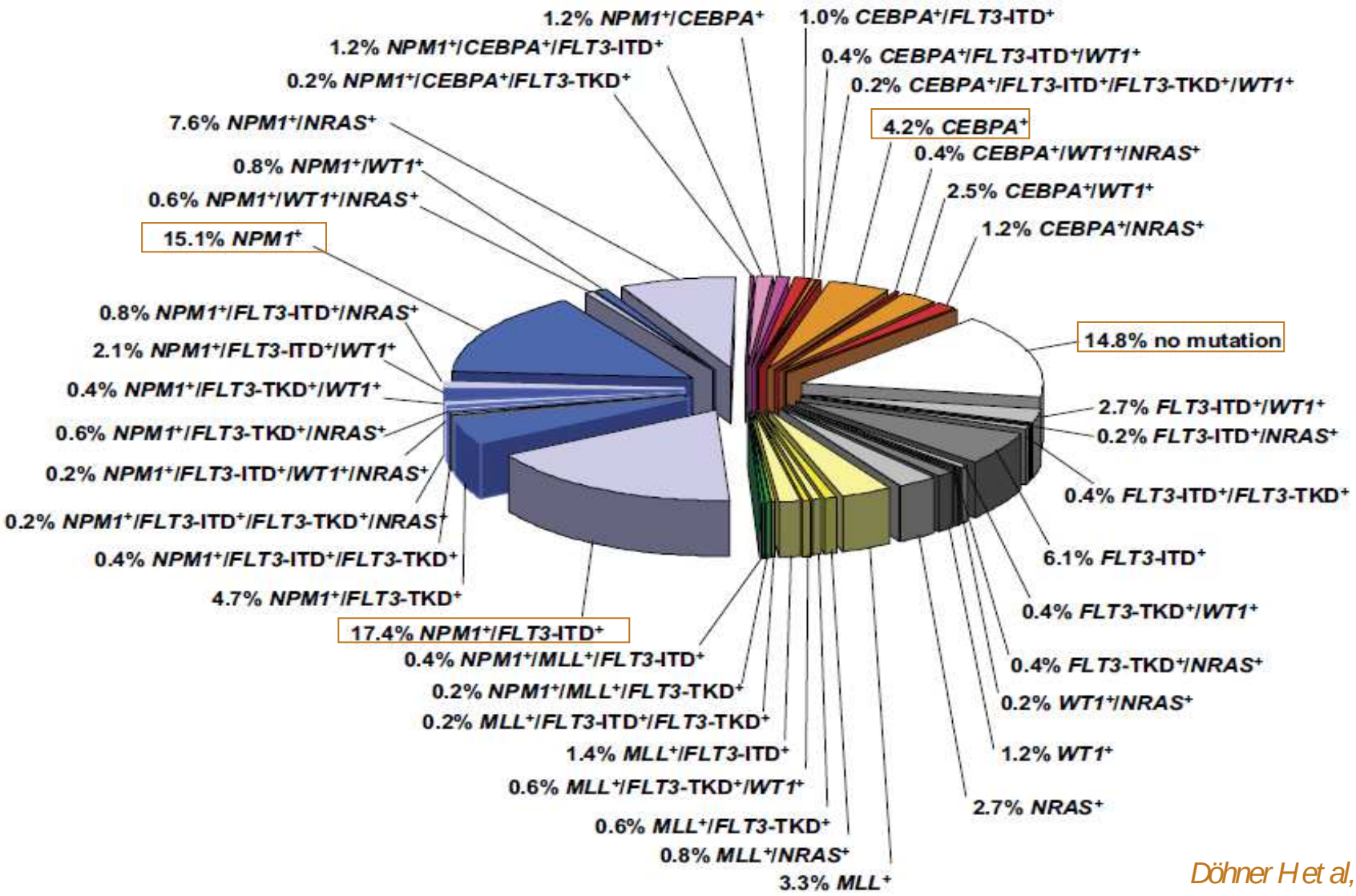
Myeloid Sarcoma

Myeloid Proliferations related to Down Syndrome
- **Transient abnormal myelopoiesis**
- **Myeloid leukemia associated with Down syndrome**

Blastic Plasmacytoid Dendritic Cell Neoplasm

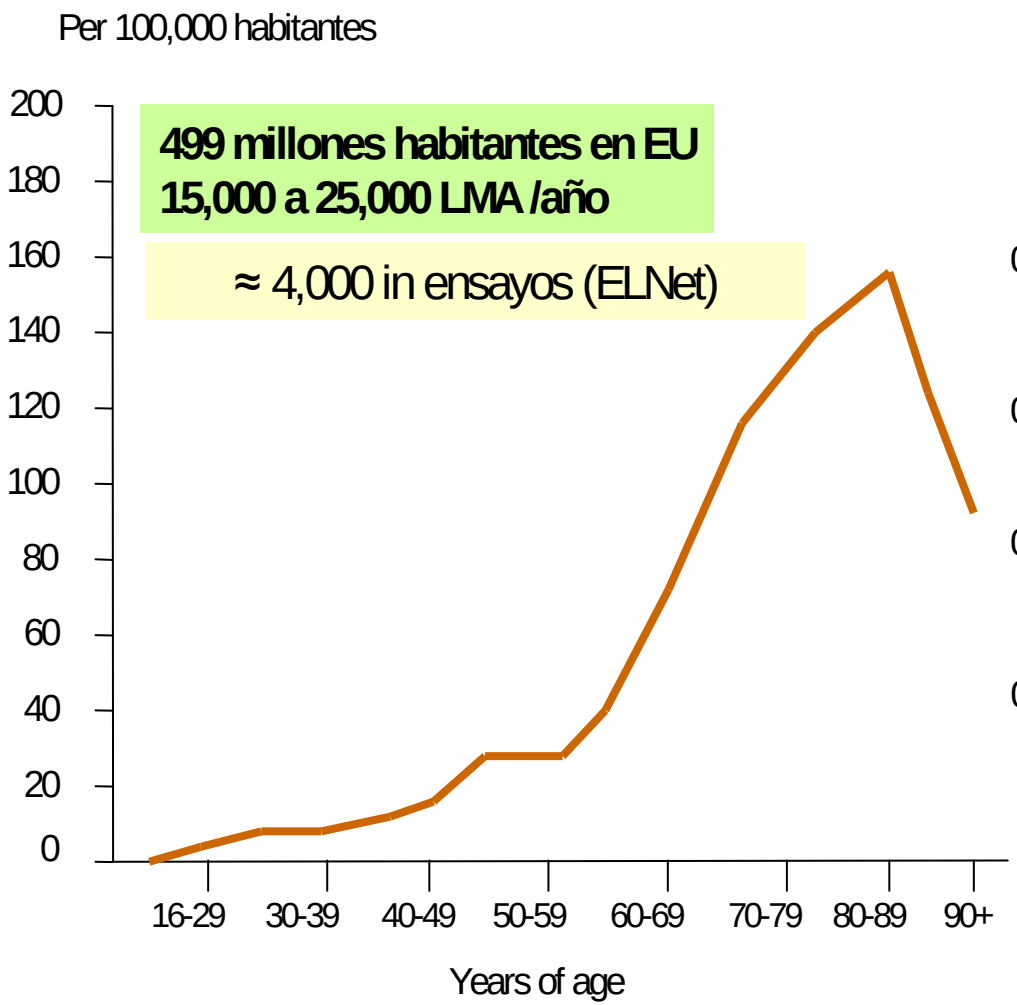
Vardiman JW, Blood 2009; 114: 937-51

Heterogeneidad molecular de la LMA con citogenética normal

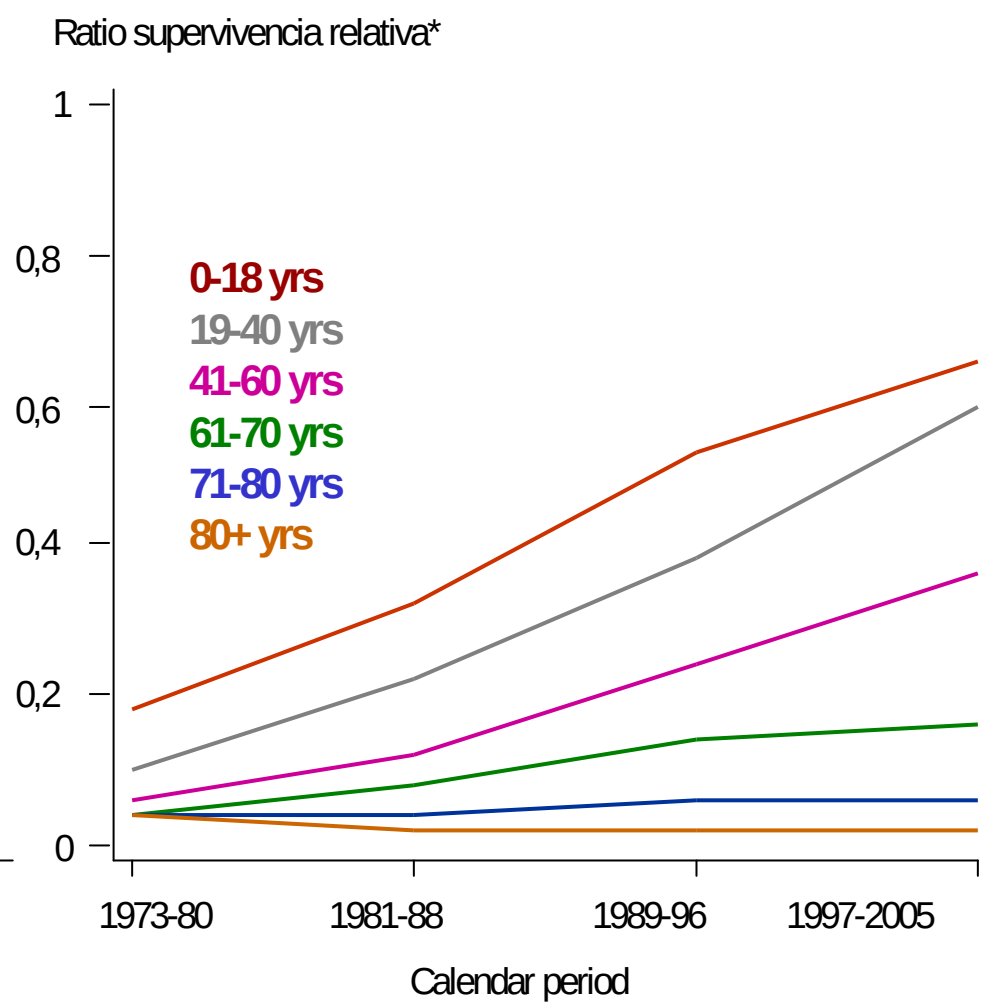


Döhner H et al, Blood 2010

Incidencia y resultados según edad



Juliusson G, et al. Blood 2009;113:4179-87
(modificado)



*Supervivencia observada en el grupo de pacientes/
Supervivencia esperada de un grupo comparable
de la población general

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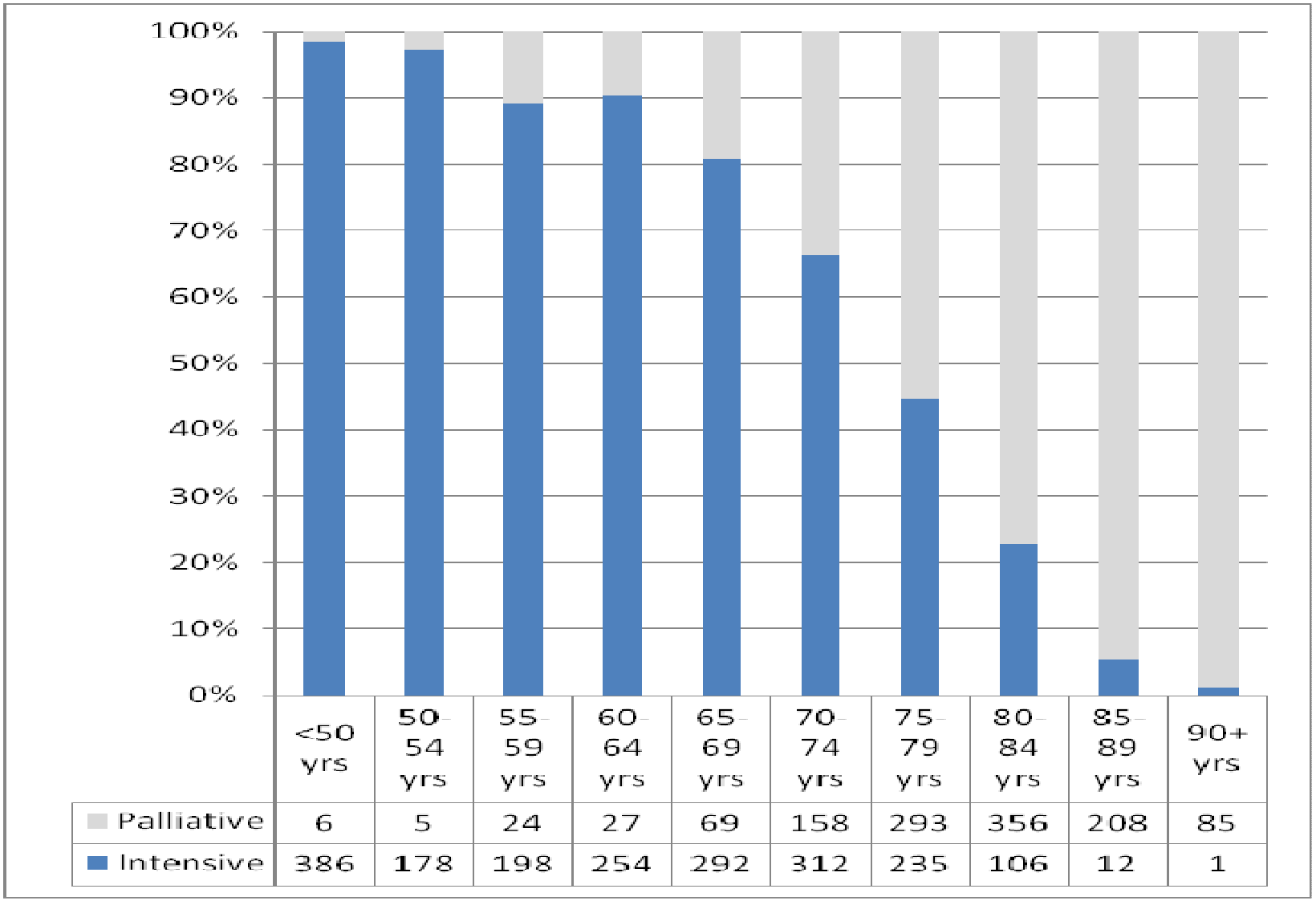
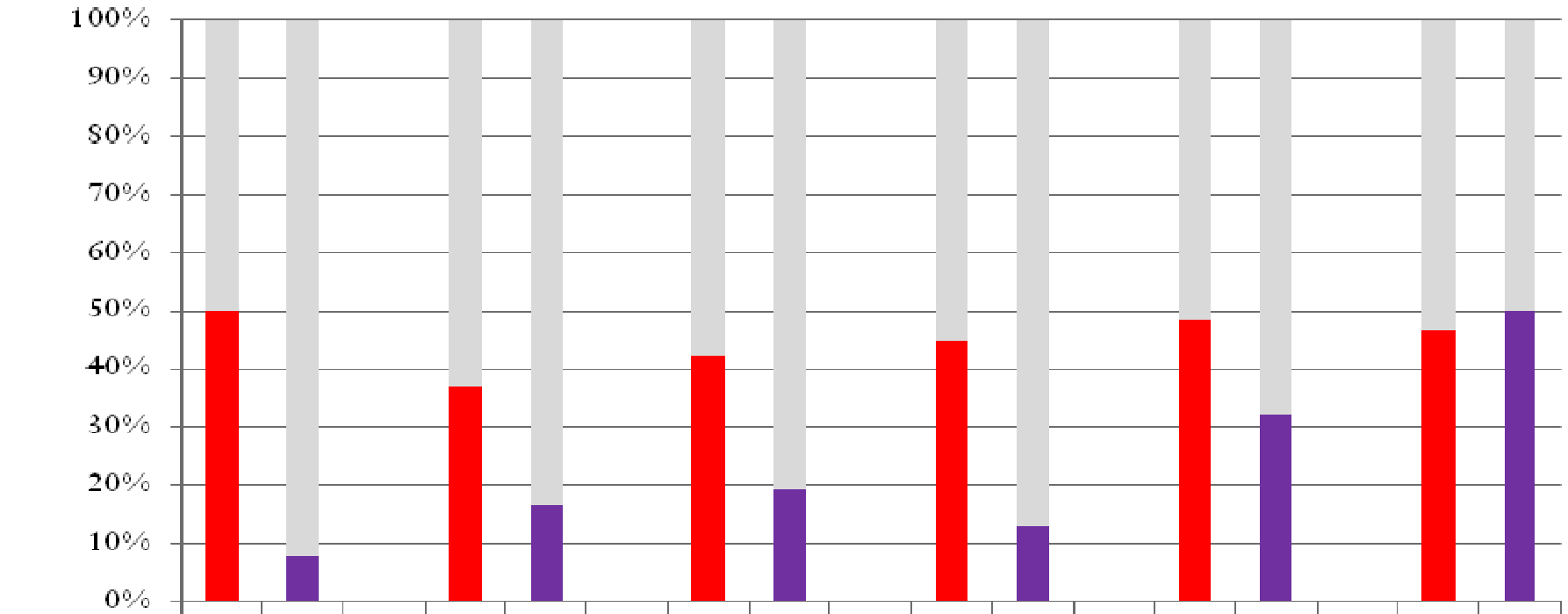
Tratamiento intensivo vs paliativo de la LMA según la edad: Registro Sueco (1997-2006)



	<50 yrs	50-54 yrs	55-59 yrs	60-64 yrs	65-69 yrs	70-74 yrs	75-79 yrs	80-84 yrs	85-89 yrs	90+ yrs
Palliative	6	5	24	27	69	158	293	356	208	85
Intensive	386	178	198	254	292	312	235	106	12	1

Juliusson G, Clin Lymphoma Myeloma Leuk. 2011 Jun;11 Suppl 1:S54-9.

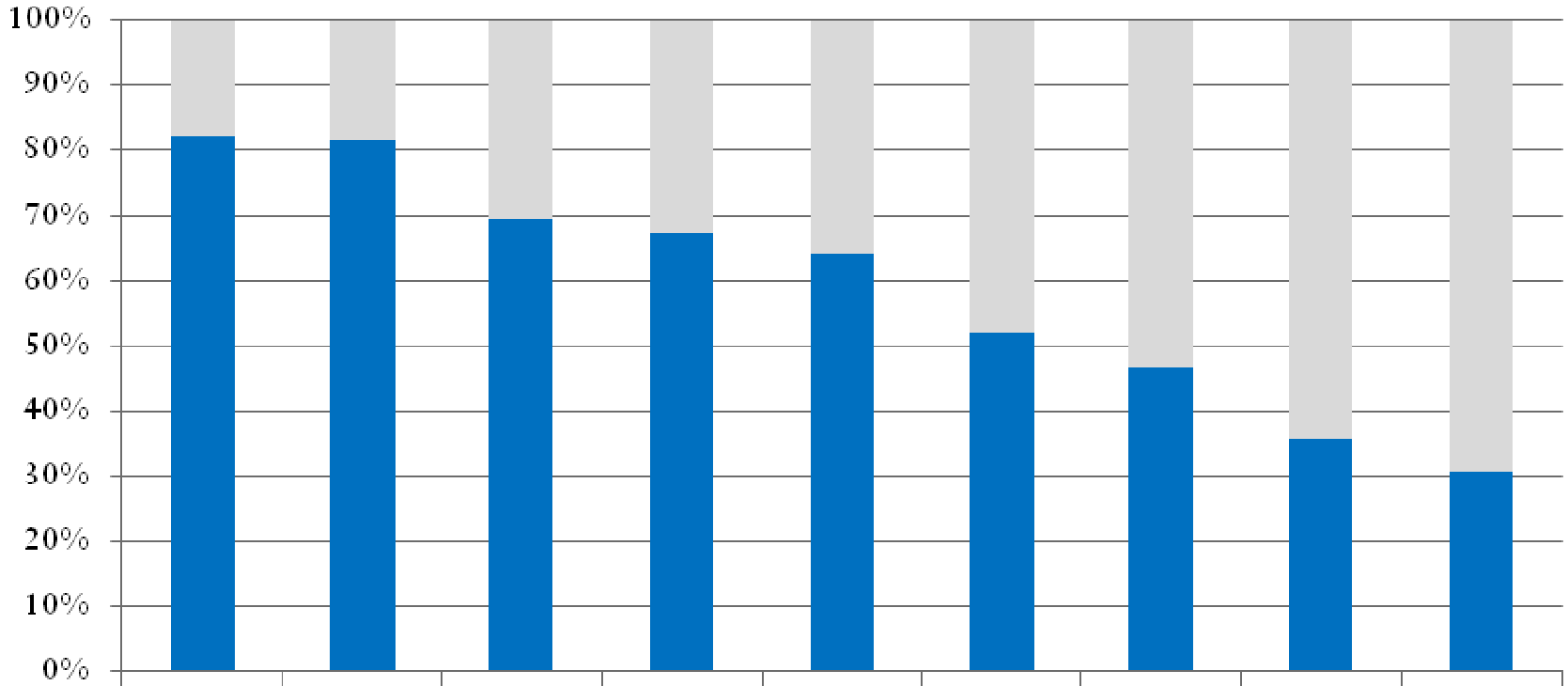
Muertes tempranas (<8 semanas) según el tratamiento realizado y edad (2007-2010)



	Pall	Int	Pall	Int	Pall	Int	Pall	Int	Pall	Int	Pall	Int
	<65 yrs		65-69 yrs		70-74 yrs		75-79 yrs		80-84 yrs		85+ yrs	
no ED	10	284	12	76	26	72	53	66	49	17	62	1
ED 8w	10	24	7	15	19	17	43	10	46	8	54	1

Juliusson G, Clin Lymphoma Myeloma Leuk. 2011 Jun;11 Suppl 1:S54-9.

Registro Sueco: Tasa de remisión completa según grupos de edad (1997-2006)

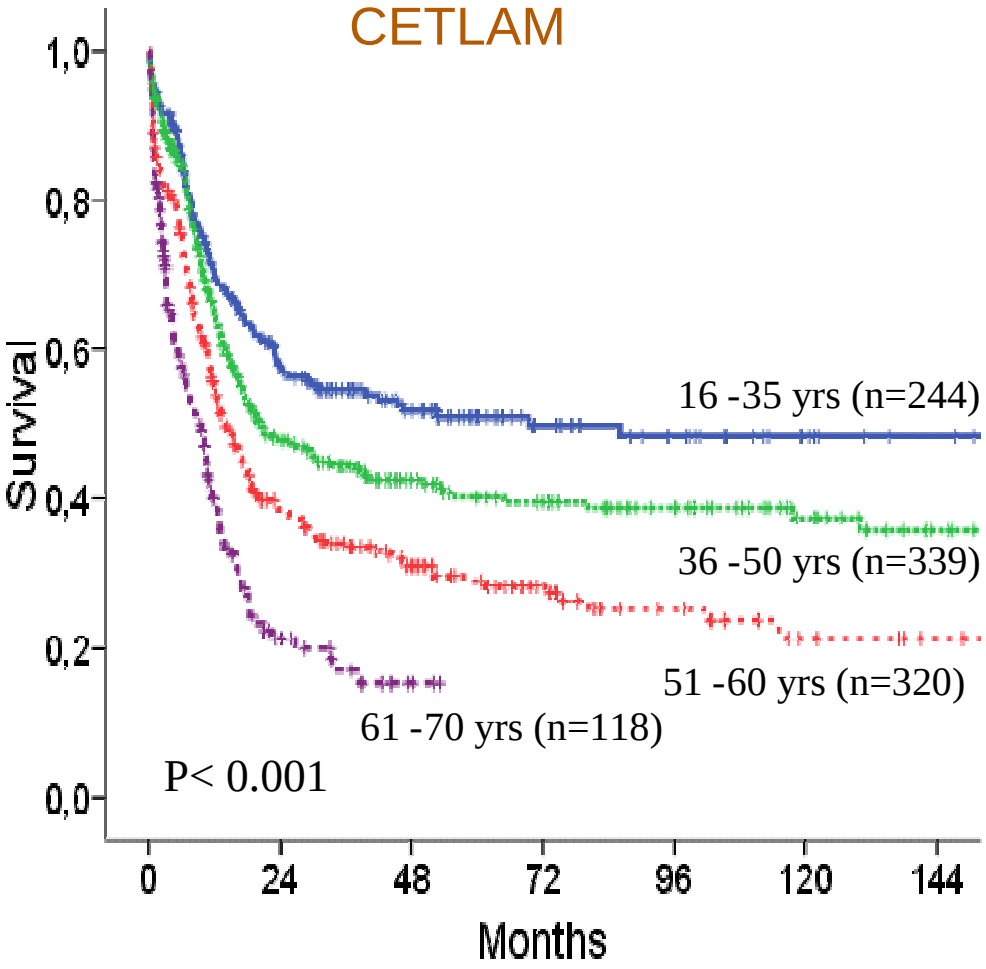


	<40 yrs	40-49 yrs	50-59 yrs	60-64 yrs	65-69 yrs	70-74 yrs	75-79 yrs	80-84 yrs	85+ yrs
no CR	34	36	114	83	104	149	125	68	9
CR	156	160	262	171	188	163	110	38	4

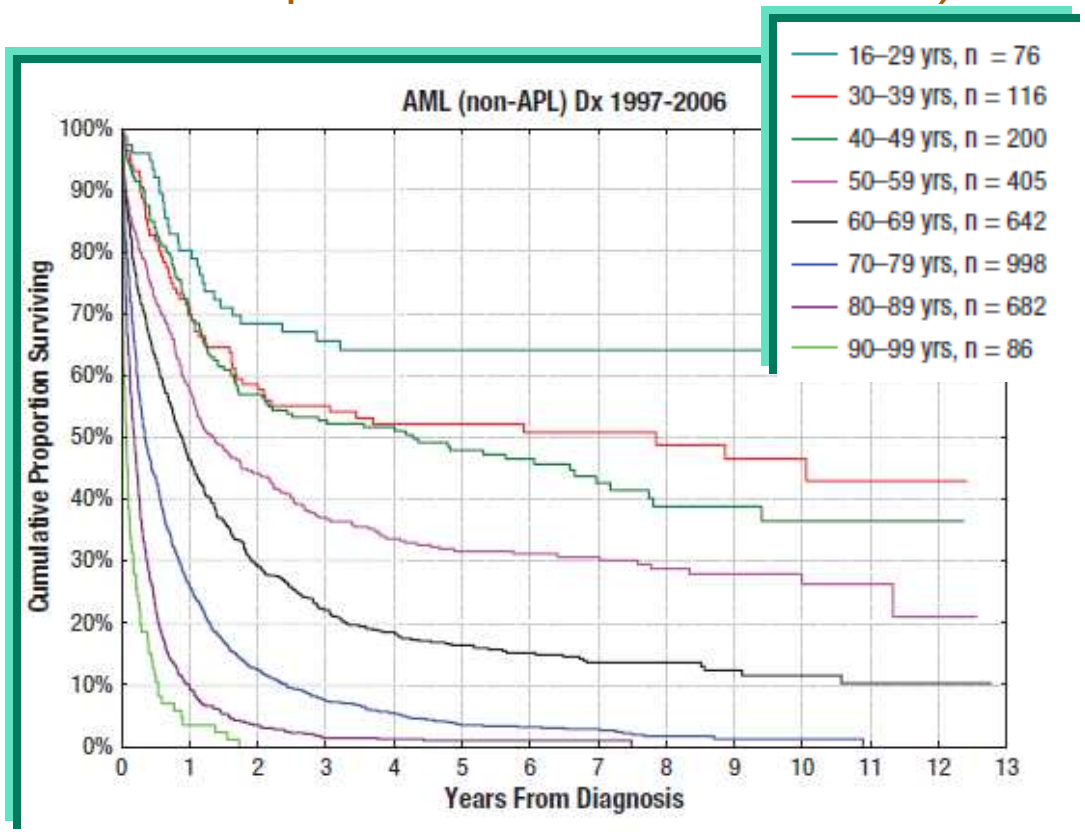
Juliusson G, Clin Lymphoma Myeloma Leuk. 2011 Jun;11 Suppl 1:S54-9.

Impacto de la edad en la supervivencia de pacientes con LMA

CETLAM



Experiencia Sueca 1997-2006)



LMA tratada y no tratada

LMA ≥70 años: Resultados según el número de factores adversos en pacientes tratados con protocolos intensivos

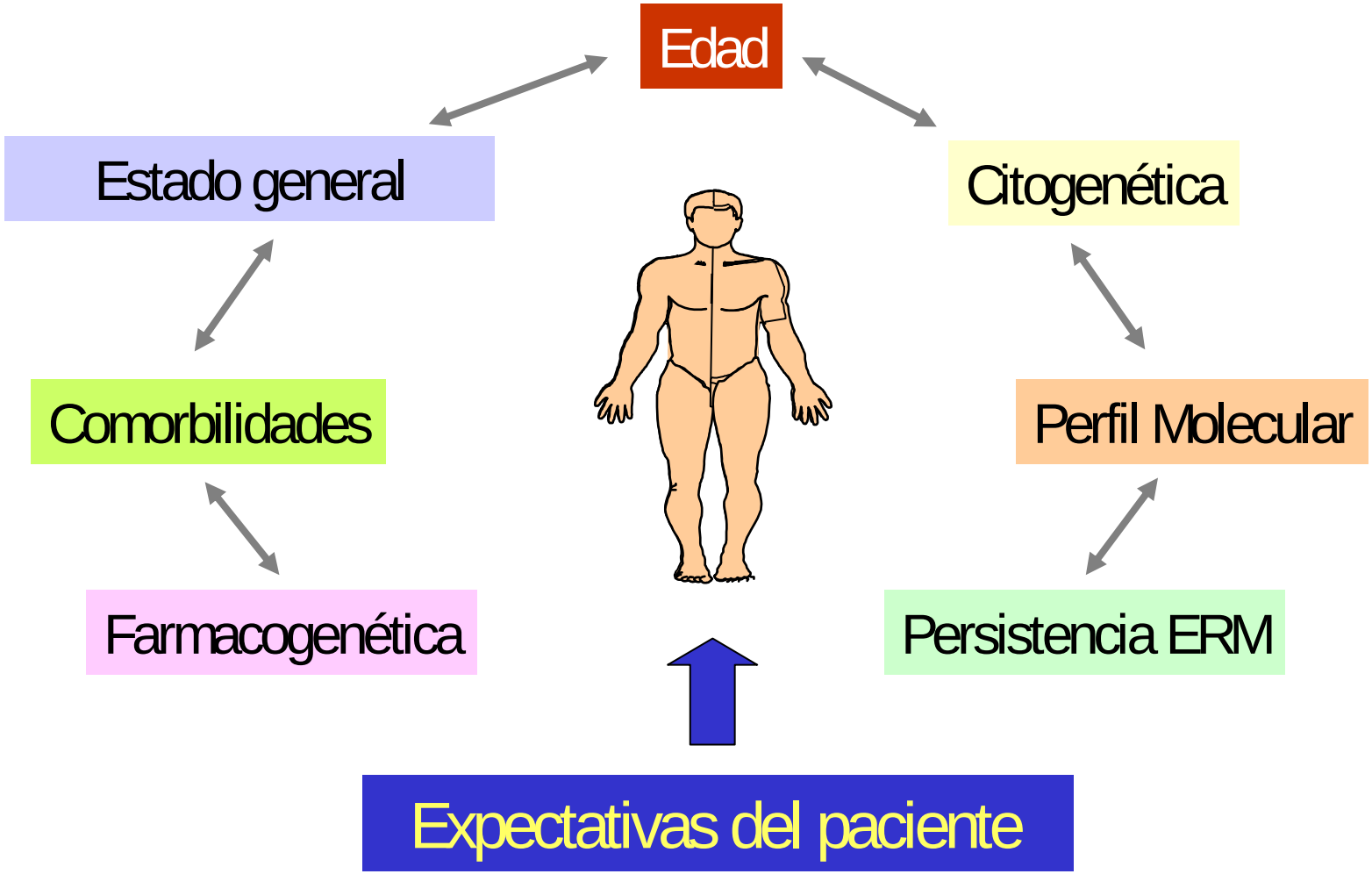
No. of adverse factors	No. of patients (%)	8-wk mortality, %	CR, %	Survival		
				Median, mo	2-y, %	3-y, %
0	122 (28)	16	57	11.3	30	22
1	170 (40)	31	52	5.3	15	7
2	100 (23)	55	29	1.5	7	6
≥ 3	38 (9)	71	16	0.5	0	0

Adverse factors for 8-week mortality were age ≥ 80 years (OR, 2.13; $P = .016$), performance status ≥ 2 ECOG score (OR, 3.25; $P < .001$), complex karyotype (≥ 3 abnormalities; OR, 2.07; $P = .001$), and creatinine level > 1.3 mg/dL (OR, 1.96; $P = .005$)

Kantarjian et al (MDACC)

(*Blood*. 2010;116(22):4422-4429)

Factores a tener en cuenta en el tratamiento de pacientes con LMA



Criterios para tratamiento intensivo

- Edad <70 a
- Edad 70-79 a
  - No comorbilidades
  - Otras
- Edad >80 a
  - ECOG 0-2
  - No comorbilidad
  - Cariotipo no desfavorable
  - Otras (creatinina..)

Índice

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Tratamiento de la LMA con quimioterapia intensiva

Inducción

Intenta eliminar el mayor nº de células leucémicas

Disminuir la resistencia al tratamiento

Consolidación

Eliminar células residuales que persisten tras inducción

Post intensificación

Adaptado al riesgo

Evitar recidivas

Tratamiento de inducción: ¿Que fármacos?

- Combinación que incluye:
  - ANTRACICLINA (DNR 60 vs 90 mg/m2, IDA 12-14 mg/m2)
  - CITARABINA

±

  - Ensayos clínicos (estudios moleculares NPM1, FLT3, CEBPA)
  - Otras combinaciones :

    FLAG-Ida) *(Burnett et al, JCO 2013)*

    Bortezomib + Quimioterapia (60-75a)

- Sin cambios reales en los últimos 40 años!!!!!
- Mejora del soporte
- Meta-análisis DNR vs IDA: *(Teuffel O, BJH 2013)*
  - DNR (90 mg/m2/dx3 o 50mg/m2/dx5) o
  - IDA (12mg/m2/dx3), supervivencias a los 5 años 40-50%

Quimioterapia intensiva en pacientes edad avanzada "fit"

Table 2. Recent randomized trial for fit older patients with AML treated with intensive chemotherapy

Author (ref)	Comparison	Phase of treatment	Patients number	Results
Brunberg (32)	DNR + ARA-C versus GO + ARA-C	Induction	115	No difference in CR, EFS, CR duration; induction death rate was higher in the GO group due to VOD.
Lowenberg [24]	DNR45 + ARA-C versus DNR90 + ARA-C	Induction	813	Higher CR rate for DNR90; survival benefit for age 60–65 years and CBF-AML
Pautas [23]	DNR80 (3 days) or IDA12 (4 days) versus IDA12 (3 days)	Induction	468	No difference in EFS, OS and relapse rate
Burnett [25,29]	DNR + ARA-C versus DNR + CLO +/– GO	Induction	806	Benefit for GO (apart from adverse karyotype), no advantage for CLO
Castaigne [30]	DNR + ARA-C +/– GO	Induction	280	Benefit for GO (apart from adverse karyotype)
Lowenberg [38]	GO versus controls	Consolidation	222	No benefit for any endpoint

DNR, daunorubicin; GO, gemtuzumab ozogamicin; ARA-C, cytarabine; CR, complete remission; CBF, core-binding factor; AML, acute myeloid leukaemia.

¿.....Y el Gentuzumab, es útil?

Table 1. Randomized studies of GO in newly diagnosed patients with AML

Study	n	Age, years	Characteristics	Dose of each administration of GO	Improved CR with GO	Improved RFS, EFS, DFS or OS with GO	Increased induction mortality	Increased hepatic toxicity
SWOG 0106[4]	637	18-60	DA+GO vs DA in induction and in	6 mg	No	No	Yes	No
MRC AML15[7]							No	No
ALFA 0701[9,10]							No	No
Groupe Ouest Est d'Etude des Leucémies Aiguës et Autres Maladies du Sang AML 2006 IR[10]							No	Yes
National Cancer Research Institute AML16[8]			clofarabine induction, with or without GO			intermediate group	No	No
Leukemia Research Fund AML14 and National Cancer Research Institute AML 16[11]	495	Older adults, for conventional chemotherapy	Low-dose cytarabine, with or without GO	3 mg	Yes	No	No	No

- No mejora la tasa de RC
- No incrementa la hepatoxicidad ni la mortalidad
- Dosis recomendada 3-6 mg/m2
- Mejora la SLE, SLP, SG en pacientes con citogenética favorable/intermedia

Rowe JM and Löwenberg B. Blood 2013;121:4838-41.

Tratamiento post inducción

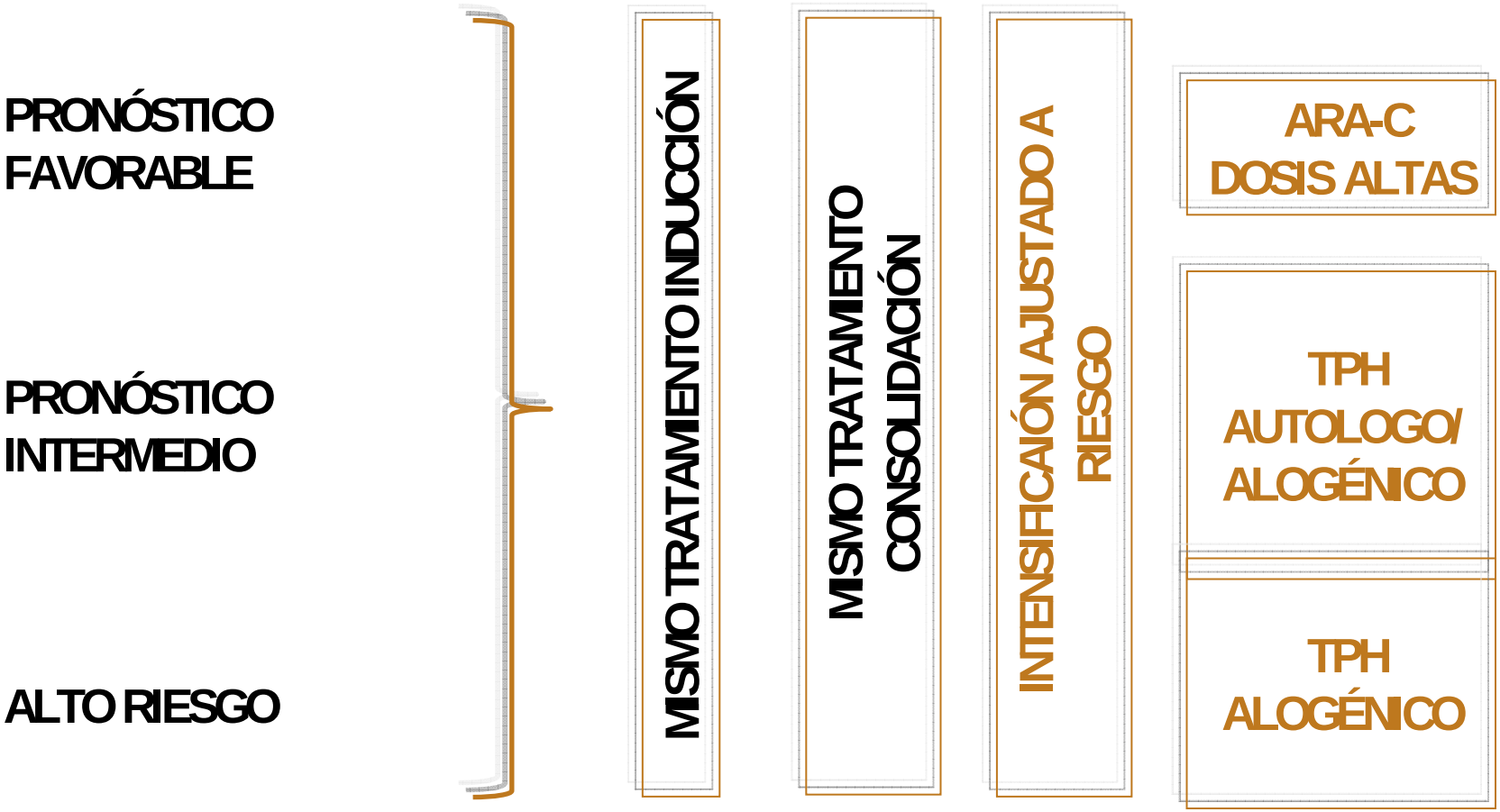
Tratamiento de consolidación:

- ANTRACICLINA + CITARABINA
- CITARABINA A ALTAS DOSIS

Tratamiento de intensificación (adaptado al riesgo):

- QT vs AUTO-TPH vs ALO-TPH

Grupos de riesgo



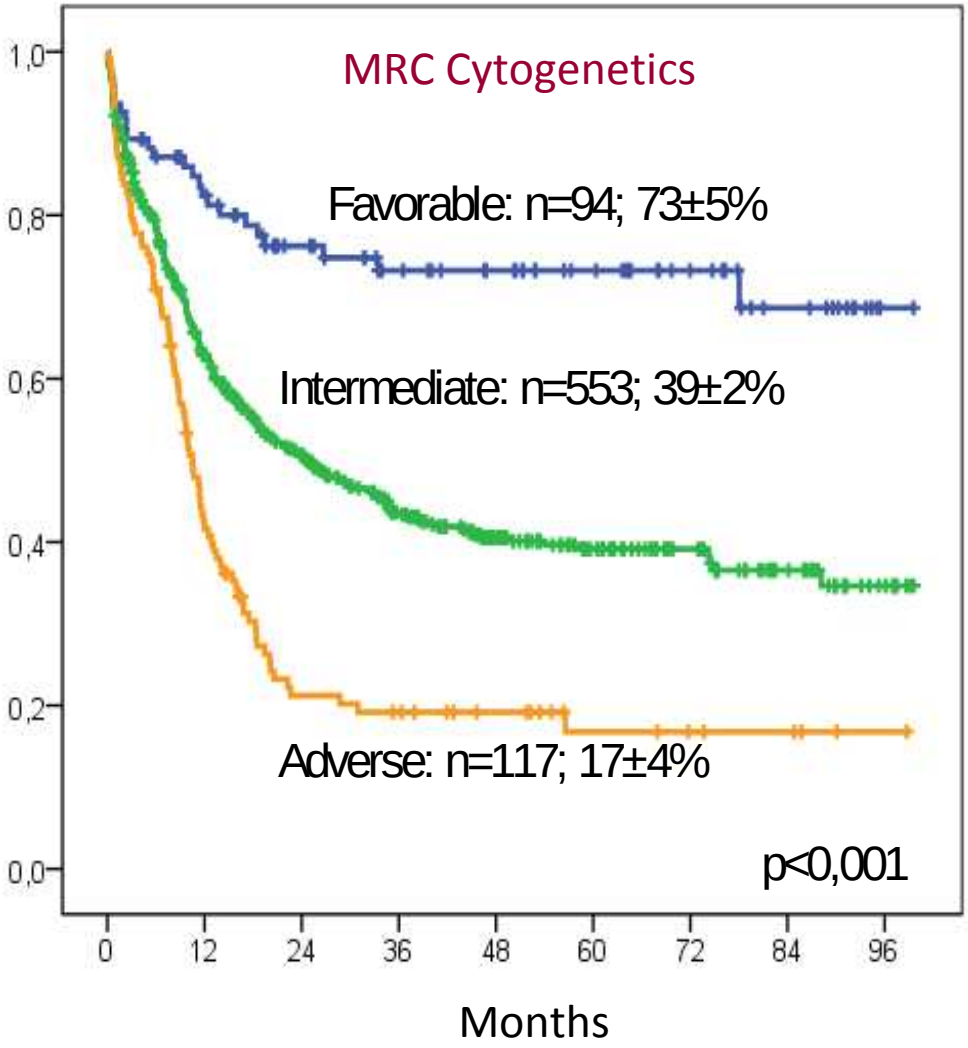
CETLAM LMA 94 vs 99 vs 03 de la LMA de novo

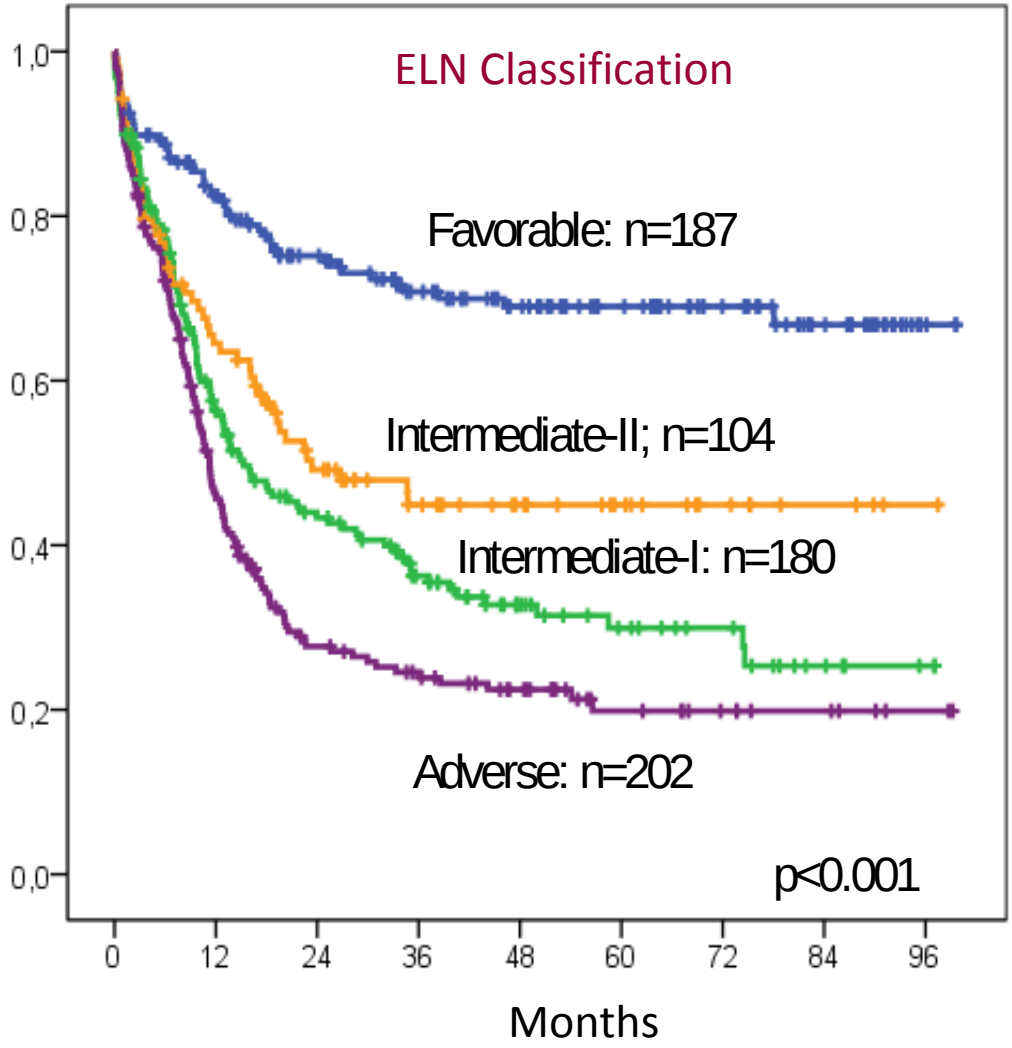
Pacientes de edad ≤ 60 años

	AML 94 (n=200)	AML 99 (n=352)	AML-03 (n=609)	*P-value*
Induction	ICE (3x7x3)	IDICE (3x8x3)	IDICE-G (G+3x8x3)	
Patients	200	352	609	
CR: No (%)	144 (72%)	249 (72%)	484 (80%)	***0.004***
CR with 1 course: N (%)	117 (81%)	198 (79%)	419 (87%)	***0.034***
Refractory (%) / Death (%)	40 (20%)/ 16 (8%)	59 (17%)/ 36 (11%)	56 (10%)/ 61 (10%)	***0.008***
Cum inc of relapse (4 yrs)	45±4%	47±3%	34±2%	***0.001***
LFS at 4 years	44±4%	40±3%	53±2%	***0.009***
OS at 4 years	40±3%	34±3%	49±2%	***<.001***

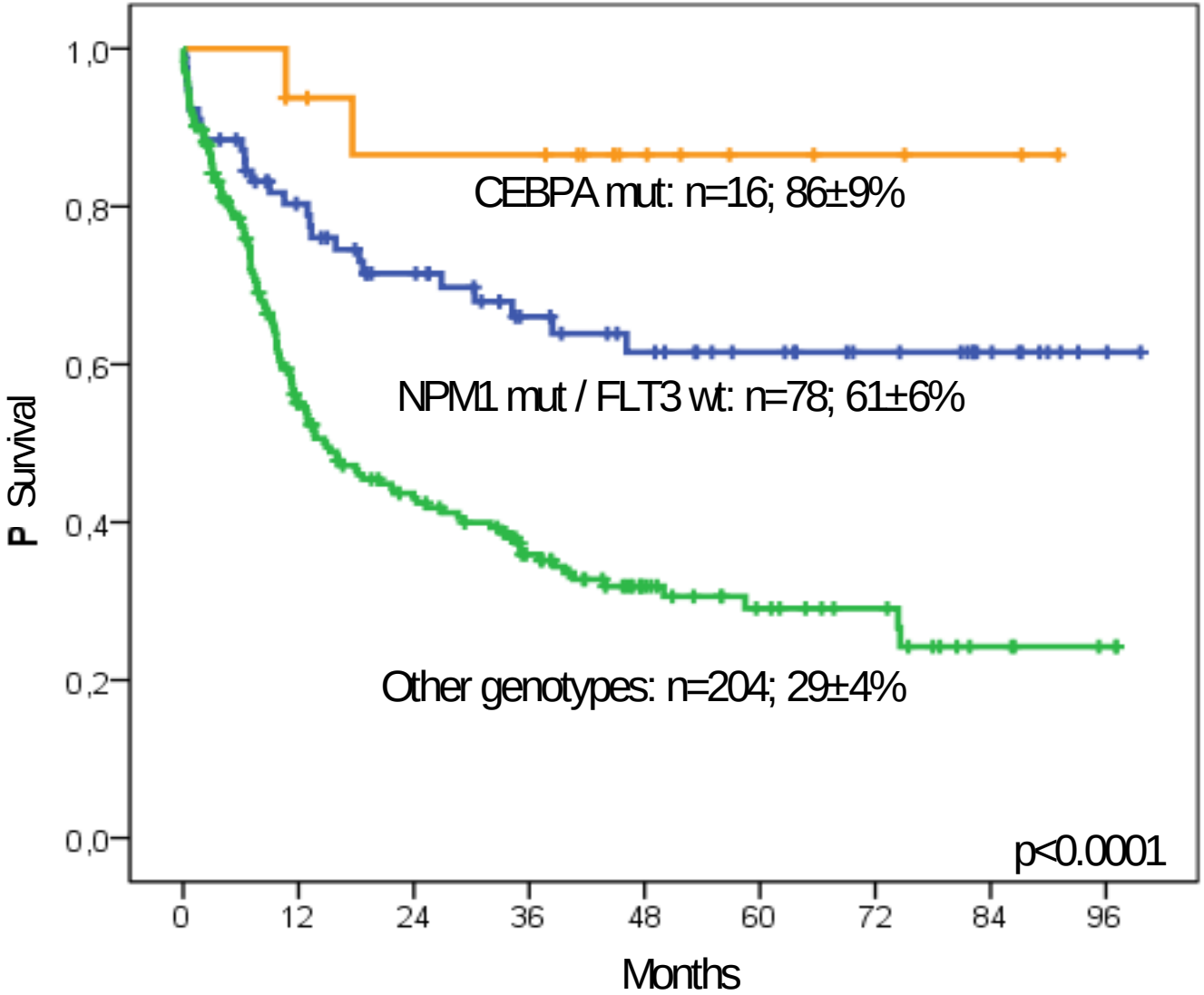
Principales diferencias entre LMA-99 y LMA-03: a) G-CSF "priming" durante la QT, b) Factores moleculares y EMR en el tratamiento post remisión, c) incremento del acceso a las diferentes fuentes de PH

LMA-03: Supervivencia Global

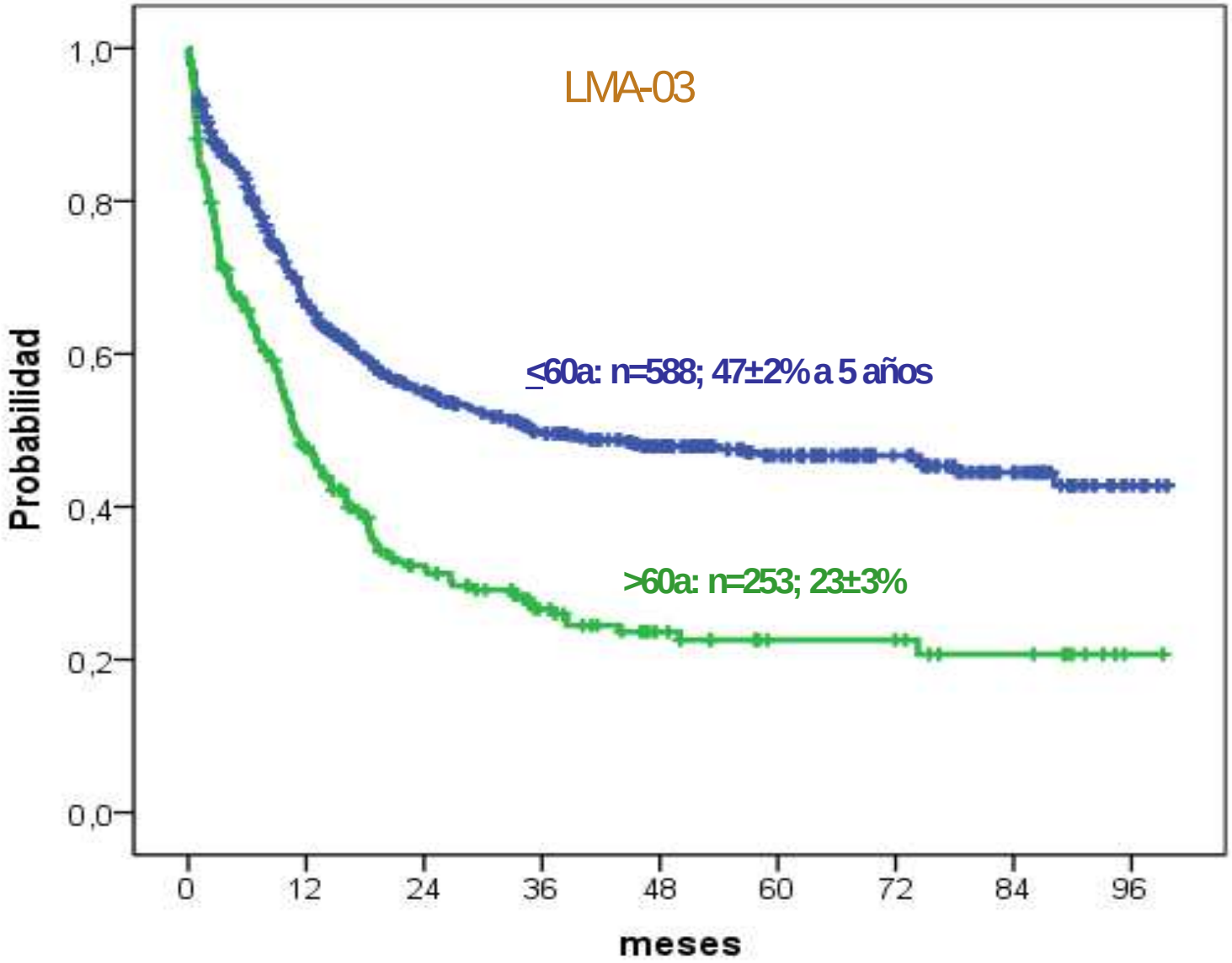




LMA-03: Supervivencia Global
Pacientes con citogenética normal



Protocolos CETLAM LMA 94 vs 99 vs 03 de la LMA de novo
Pacientes de edad ≤ 60 años. Supervivencia Global



Cual es el tratamiento recomendable en la actualidad

TABLE II. Summary of Treatment Recommendations

Prognostic group	Subsets	Induction	Post-Remission
Best	inv (16 or t(16;16); t(8;21) NK with NPM1 mutation and no FLT3 ITD; NK with double mutated CEBPA	3+7	Ara-C at 1 g/m2 BID daily X 6 [52]; Dasatinib in clinical trial if inv 16, or t(8;21) with CKIT mutated
Inter-mediate 1	NK w/o NPM mutation or FLT3 ITD; Cytogenetic abnormalities other than best or unfavorable	3+7; Clinical trial	HCT from matched sibling donor (MSD); Ara-C as above or clinical trial (e.g. CSL362) [53] if not HCT candidate
Inter-mediate 2	FLT3-ITD+	3+7; Clinical trial involving FLT3 inhibitor, e.g. quizartinib (see text)	HCT from MSD or matched unrelated donor; consider trial with quizartinib post HCT; Ara-C as above or clinical trial (e.g. CSL362) [55] if not HCT candidate
Inter-mediate 3	Unfavorable cytogenetics without mono-somal karyotype	Clinical trial	HCT from MSD or matched unrelated donor; consider trial involving new preparative regimen or means to prevent relapse after HCT (see text); clinical trial if not HCT candidate
Worst	Monosomal karyotype [54,55]	Clinical trial	As in intermediate −3

- Parece demostrado que no son necesarias dosis tan altas de Ara-c: 1,0-1,5g/m2 similar a 3 g/m2
- Introducir tratamientos diana específicos (anti FLT3, inhibidores tirosin-cinasa en LMA CBF con mutación c-Kit)

Estey EH, Am J Hematol 2013 88;:318-327

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Como se tratan los pacientes de edad avanzada o no “fit”

Enfoques de tratamiento	Tratamiento intensivo “go-go” (Fit)	Tratamiento de baja intensidad “slow go” (vulnerable)	Tratamiento paliativo / de soporte “no go” (fragil)
Población de pacientes	Pacientes sin comorbilidades y con buen estado funcional	Pacientes no candidatos a quimioterapia intensiva pero candidatos a tratamiento activo	Pacientes con comorbilidades y/o bajo estado funcional

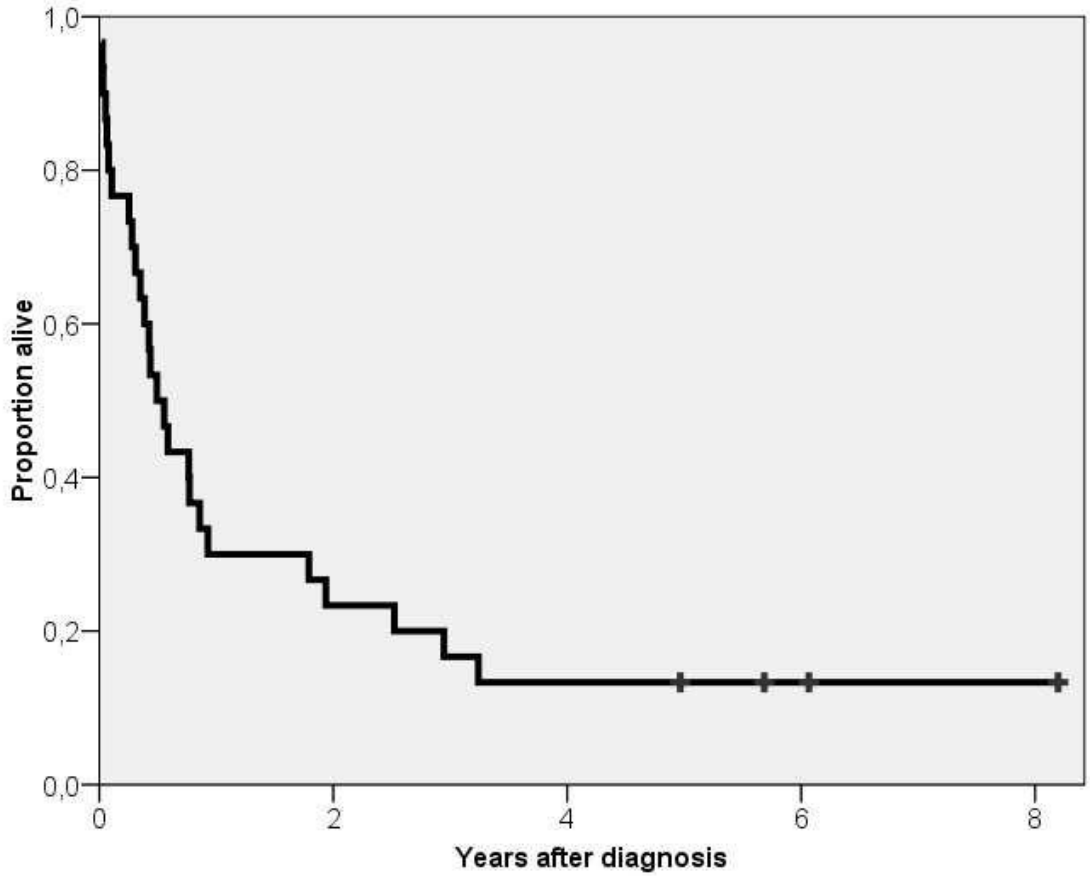
NCCN Guidelines v.2.2012 Acute Myeloid Leukemia

CETLAM04 LAM>70 n=30
Supervivencia Global

Tratamiento:

Inducción FAG

Consolidación IAG



Mediana seguimiento: 5 años (4-8). Mediana SG: 6 m (3-9).
SG 2a: 23% (95% CI, 12%-35%). SG 5 a 13% (95%CI, 3%-23%).

Tratamiento en pacientes "no fit"

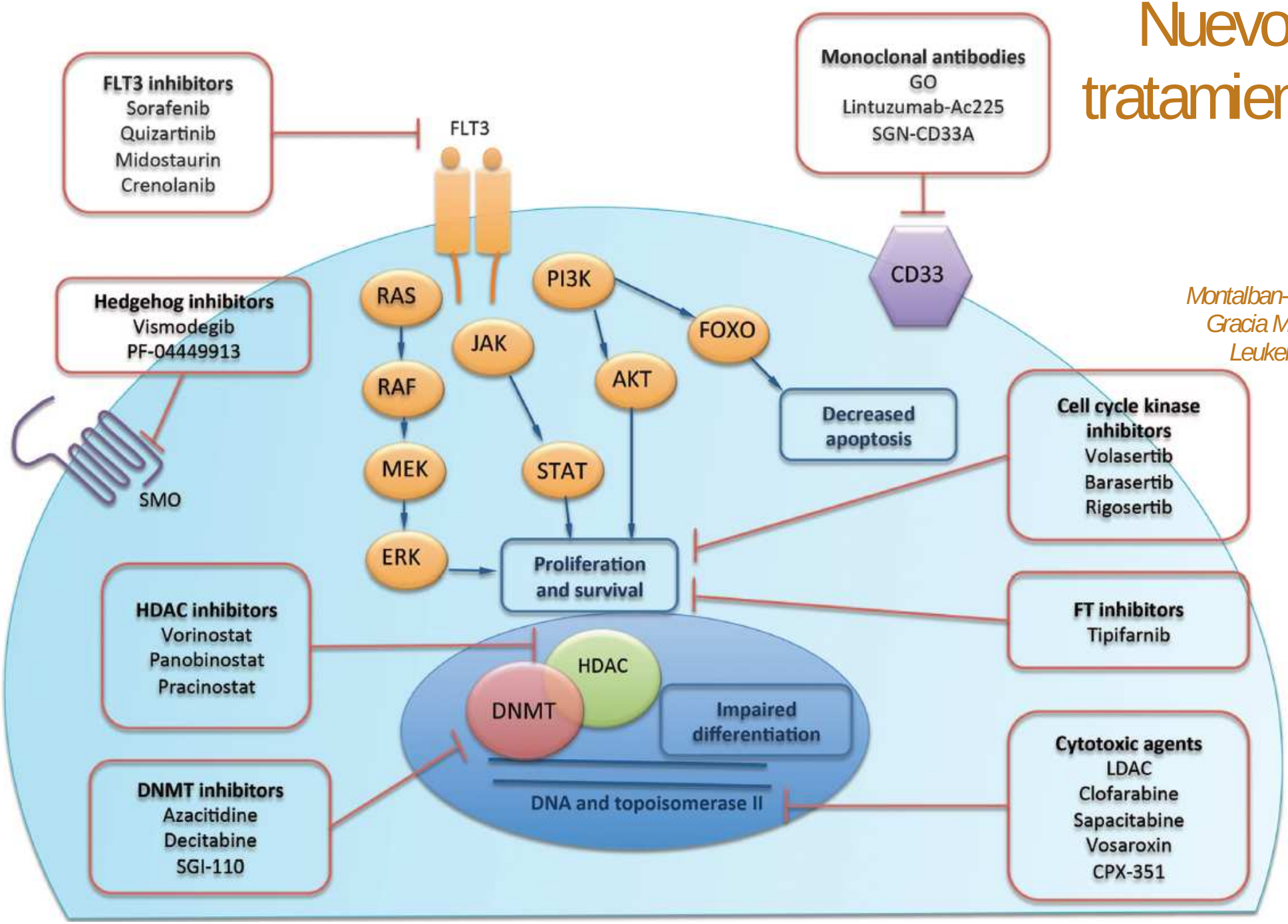
Table 3. Randomized trials for unfit patients with AML

Author (ref)	Comparison	Phase of treatment	Patient number	Results
Burnett [44]	Low dose ARA-C versus BSC and/or HU	Continuous treatment	217	Higher CR rate and better survival for LDARA-C; no benefit in unfavourable cytogenetics
Burnett [46]	LDARA-C versus LDARA-C + ATO	Continuous treatment	166	No benefit on response and survival
Burnett [47]	LDARA-C versus LDARA-C + tipifarnib	Continuous treatment	66	No benefit on response and survival
Burnett [49]	LDARA-C versus LDARA-C + GO	Continuous treatment	495	Increase in CR rate, no benefit on survival
Burnett [50]	LDARA-C versus CLO	Continuous treatment	406	Increase in CR rate, no benefit on survival
Harousseau [51]	BSC versus Tipifarnib	Continuous treatment	457	No difference in CR rate and survival

GO, gemtuzumab ozogamicin; ARA-C, cytarabine; CR, complete remission; BSC, best supportive care; HU, hydroxyurea; CLO, clofarabine; LDARA-C, low-dose cytarabine; AML, acute myeloid leukaemia; ATO, arsenic trioxide.

Ferrara F. Hematol Oncol 2014 32:1–9

Nuevos tratamientos



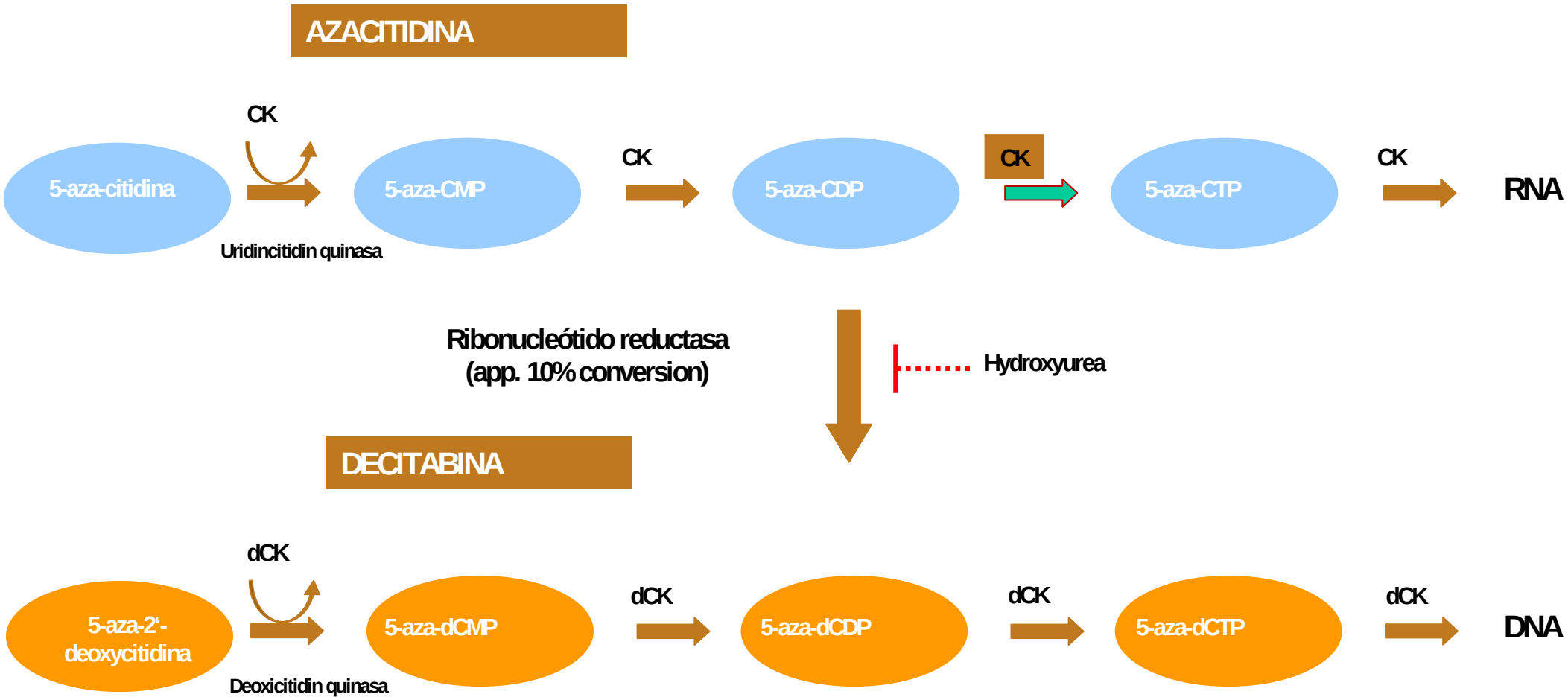
Montalban-Bravo G, Gracia Manero G. Leukemia 2014

Table 1. Novel agents at phase III development stage

Novel agent	*Regimen (Clinical Trials number)*	*Patient characteristics*	*Results (if trial completed)/key outcome measures (if trial is ongoing)*
HMAs			
Azacitidine	Azacitidine versus CCR (NCT01074047)	Older patients with newly diagnosed AML (aged ⩾65 years) with >30% blasts ($N=480$ planned)	Primary outcome measure: OS
Decitabine	Decitabine alone (NCT01633099)	Older patients with AML (aged ⩾60 years; $N=46$ planned)	Primary outcome measures: CR, OS, EFS, RFS
Cytotoxic			
LDAC	LDAC versus hydroxyurea (BSC) with or without ATRA (NCT00005823)	217 Older patients (aged ⩾60 years) with AML or high-risk MDS ineligible for intensive therapy	Improved CR rate of 18% with LDAC compared with 1% for hydroxyurea ($P=0.00006$); OS was superior with LDAC compared with hydroxyurea (OR, 0.60; 95% CI, 0.44–0.81; $P=0.0009$). ATRA had no effect[16]
Clofarabine	Clofarabine versus LDAC (NCT00454480)	406 Older patients (aged ⩾60 years; median age 74 years) with AML or high-risk MDS	ORR was significantly improved with clofarabine treatment (38 vs 19% with LDAC; HR=0.41 (0.26–0.62); $P<0.0001$). No improvement in OS with clofarabine treatment[17]
Sapacitabine	Sapacitabine administered in alternating cycles with decitabine versus decitabine alone (NCT01303796)	Patients aged ⩾70 years with newly diagnosed AML for whom standard intensive treatment is not recommended, or the patient has decided not to receive standard intensive treatment ($N=485$ planned)	Primary outcome measures: OS Secondary outcome measures: CR, CRi, PR (all with duration), hematologic improvement, stable disease with duration, 1-year survival
Cell cycle kinase			
Barasertib	Barasertib alone and in combination with LDAC in comparison with LDAC alone (NCT00952588)	Patients aged ⩾60 years with newly diagnosed AML ($N=417$ planned)	Primary outcome measures: CR, CRi Secondary outcome measures: OS, DOR, DFS, time to CR
Volasertib	Volasertib in combination with subcutaneous low-dose cytarabine versus placebo plus low-dose cytarabine (NCT01721876; POLO-AML-2)	Patients aged ⩾65 years with previously untreated AML, ineligible for intensive remission induction therapy ($N=660$ planned)	Primary outcome measures: CR, CRi Secondary outcome measures: OS, EFR, RFS
Other			
Tipifarnib	Tipifarnib versus BSC (NCT00093990)	457 Patients with previously untreated AML ineligible for intensive chemotherapy (age ⩾70 years; median age 76 years)	Improved OS end point not met; 18 (8%) patients achieved CR with tipifarnib treatment[18]
CPX-351	CPX-351 versus cytarabine and daunorubicin (7+3 regimen; NCT01696084)	Previously untreated high-risk (secondary) AML (aged 60–75 years; $N=300$ planned)	Primary outcome measure: OS
GO	GO monotherapy versus standard supportive care (NCT00091234)	Previously untreated AML ineligible for intensive chemotherapy (aged ⩾61 years; $N=279$ planned)	Primary outcome measure: OS Secondary outcome measure: rate of complete remission (CR+CRp), DFS, PFS

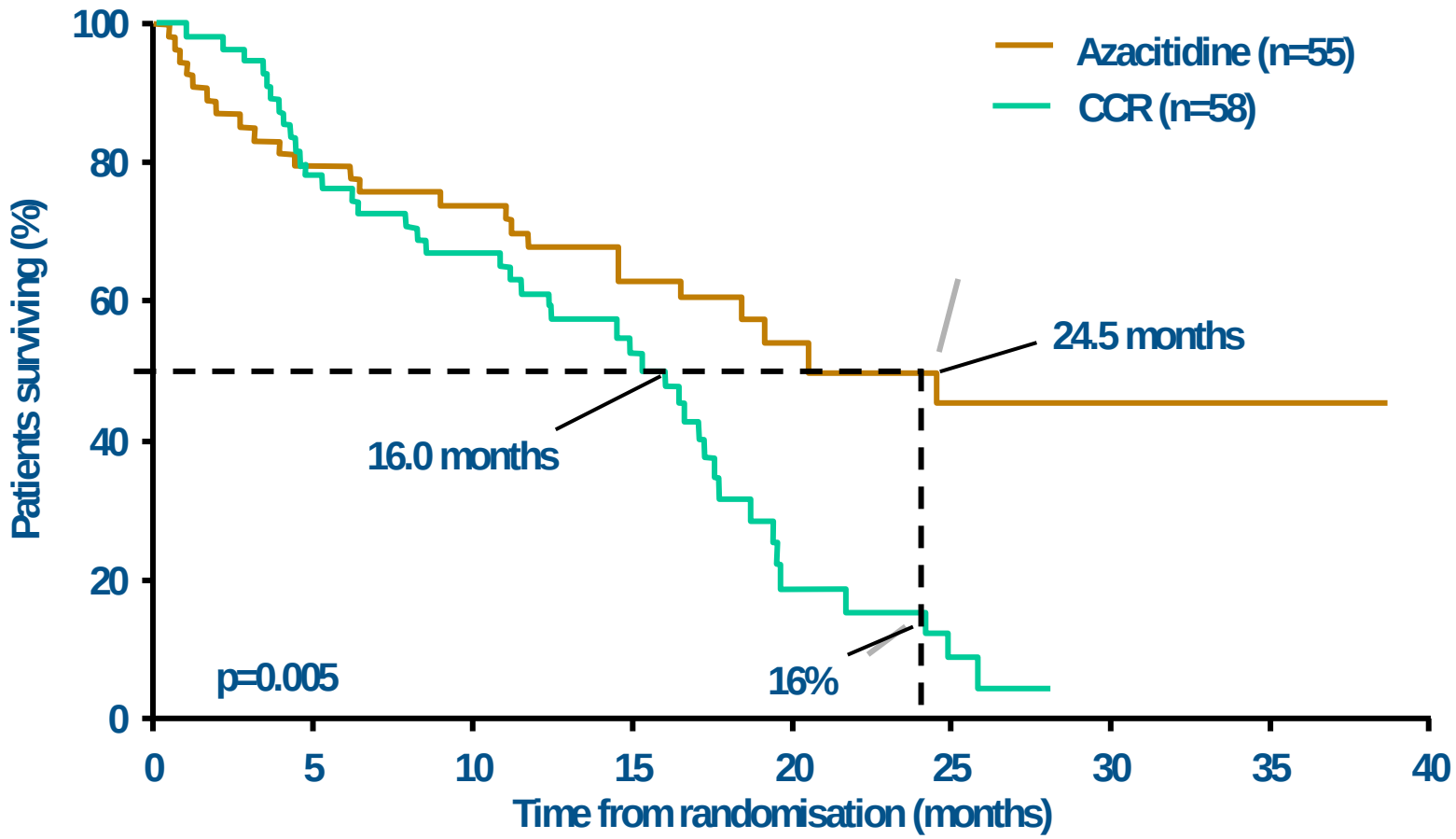
Montalban-Bravo G, Gradia Manero G. Leukemia 2014

Agentes hipometilantes, “drogas epigenéticas”



Momparler RL. Pharmac Ther. 1985;30:287-299.
Kuykendall JR. Ann Pharmacother. 2005;39:1700-1709.

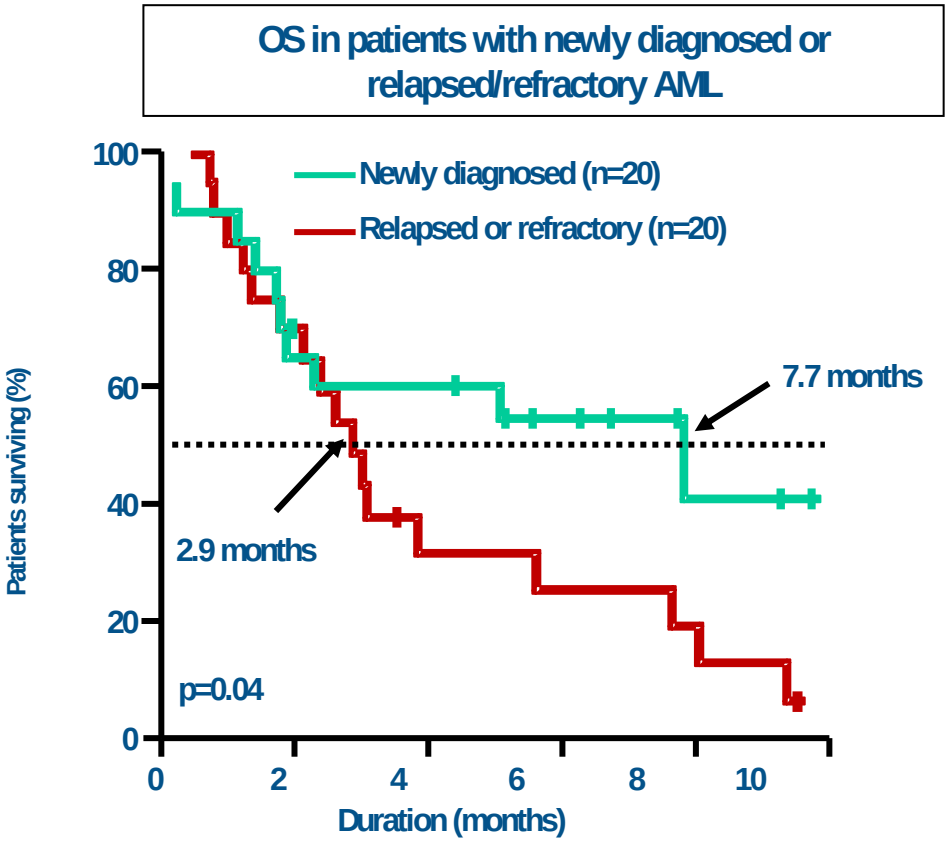
AZA-001: SG en pacientes con 20–30% blastos

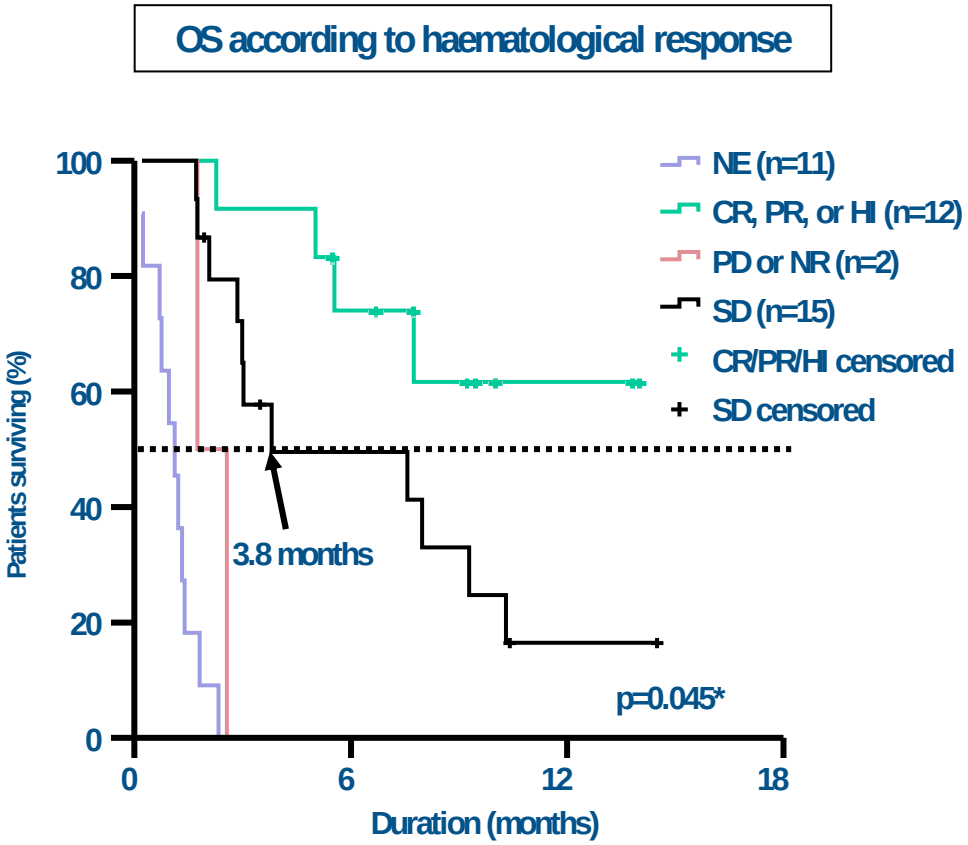


Azacitidina incrementó la SG significativamente vs RCC en pacientes con LMA

Fenaux P, et al. J Clin Oncol 2010;28:562–9

AZA en pacientes con LMA de novo o en recaída o refractaria con >30% blastos – supervivencia





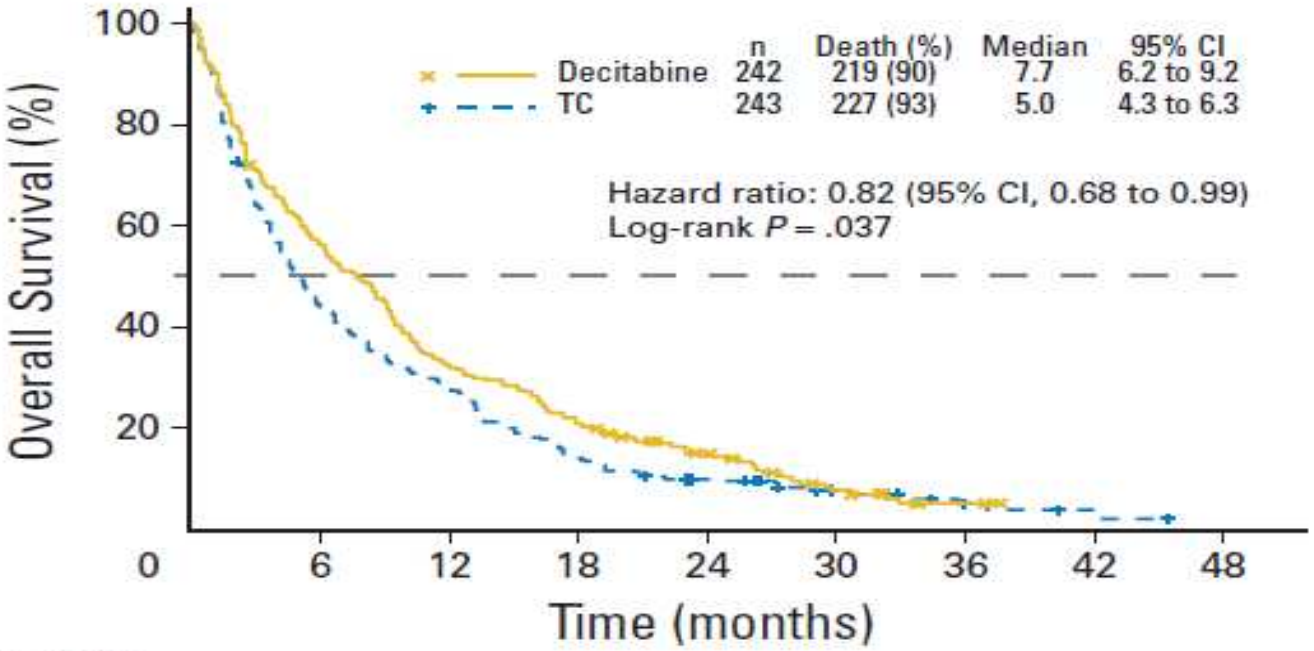
AZA mejora la supervivencia en pacientes con LMA (>30% blastos); los pacientes de novo tienen SG mas prolongadas

*versus CR+PR+HI

Al-Ali HK, et al. Leuk Lymph 2012;53:110–7

DACO-016 Eficacia: Supervivencia Global (SG)

DECITABINA **mejora** la mediana de **SG 54%**



No. at risk									
Decitabine	242	137	78	50	28	11	2	0	0
Total TC	243	107	68	35	20	10	4	2	0

El análisis de los datos maduros a los 446 fallecimientos mostró una mediana de 7.7 meses de SG (HR = 0.82,95% IC 0.69-1.04; p = 0.037)

*Análisis Octubre 2010

Kantarjian H M et al. JCO 2012;30:2670-2677

Resultados con tratamiento hipometilante en pacientes no "fit"

Table 4. Most relevant studies with hypomethylating agents for the treatment of older patients with AML

Author (ref)	Drug	Type of study	Median age (years)	Patient number	Results
Fenaux [61]	AZA	vs CCR (BSC, LDARA-C, intensive chemotherapy)	70	113, all with 20–30% BM blast count	Improvement in survival and different morbidity measures
Maurillo [64]	AZA	Compassionate programme	74	63	CR rate: 13%; better in untreated patients with low WBC count and normal karyotype
Ramos [63]	AZA	Retrospective nationwide	75	110	Best results in patients with good PS, low BM blast %, no leukocytosis, and not adverse karyotype
Cashen [57]	DAC	Phase 2	74	55	CR rate: 24%; median survival: 7.7 months
Lubbert [60]	DAC	Phase 2	72	227	ORR: 26%; median survival 5.7 months; possible benefit in poor risk patients
Kantarjian [59]	DAC	versus treatment choice (BSC or LDARA-C)	73	485	Improvement in CR rate and survival
Quintas-Cardama [62]	AZA or DAC	Historical comparison	72	671	CR 45% with CHT versus 28% with HMA; similar survival rates

CR, complete remission; LDARA-C, low-dose cytarabine; AML, acute myeloid leukaemia; DAC, decitabine; AZA, azacytidine; PS, performance status; BSC, best supportive care.

Ferrara F. Hematol Oncol 2014 32;:1–9

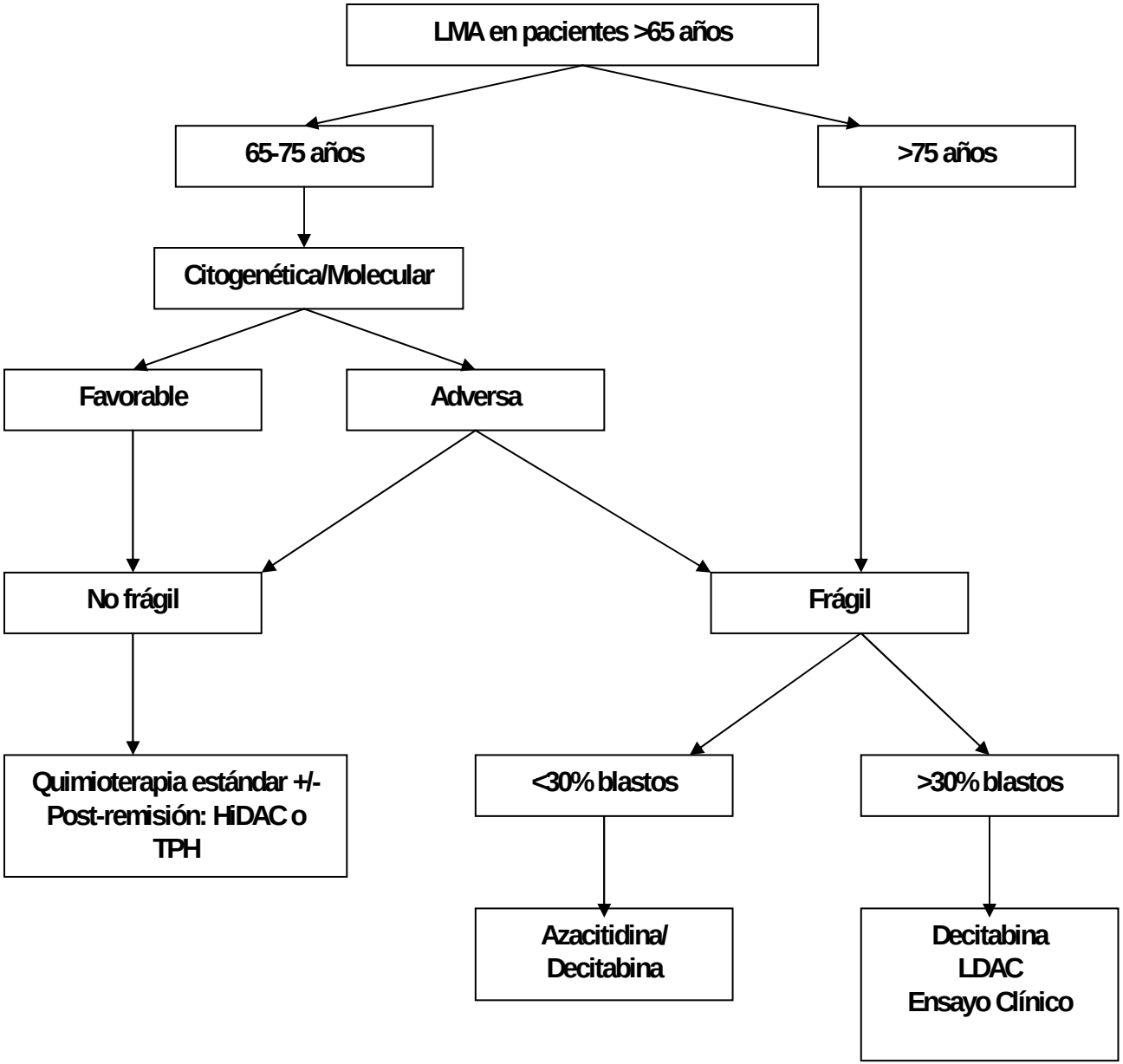
	Comment	Feasibility
Conventional intensive induction chemotherapy with the 3+7 regimen[111–113]	Healthy patients	About 60% of patients aged >60 years
Post-remission therapy with conventional or intermediate-dose cytarabine	No proven benefit from high-dose cytarabine except in older patients with CBF AML or *NPM1*-mutated AML	Most patients who achieve CR
Attenuated chemotherapy aimed at complete remission achievement and disease control[114–119]	Low-dose cytarabine; hypomethylating agents; low effect in more proliferative AML	>80%
Supportive care and hydroxyurea for the control of leucocytosis[115]	Consider in frail patients (often difficult to define)	100%
Allogeneic (reduced intensity) stem-cell transplantation[64,120]	Patients need to achieve complete remission; medically fit without organ damage after induction and consolidation; limitations of donor availability	5–10%
Autologous stem-cell transplantation[121]	Patients need to achieve complete remission; medically fit without organ damage after induction and consolidation; possible issues with successful mobilisation of stem cells	20%
Investigational treatments[111,112]	Patients with unfavourable cytogenetics aged >70 years; all patients with early relapse (first complete remission <12 months)	>80%

3+7=anthracycline for 3 days with continuous infusion of cytarabine for 7 days. CBF AML=core binding factor acute myeloid leukaemia. AML=acute myeloid leukaemia.

Opciones terapéuticas en pacientes de edad avanzada

Ferrara F and Schiffer C. The Lancet 2013 381;484–495

Propuesta de algoritmo para tratamiento de la LMA en pacientes de edad avanzada



Comentarios

- La LMA es una enfermedad heterogénea que requiere tratamiento individualizado según factores genético-moleculares.
- El tratamiento de inducción recomendado en pacientes candidatos a tratamiento intensivo es la combinación de antraciclinas y citarabina ± tratamientos diana específicos.
- La adición de GO no mejora las tasas de RC, pero si la SG y SLE en pacientes con citogenética favorable/intermedia.
- Los agentes hipometilantes, la quimioterapia de baja intensidad y si es posible participar en un ensayo clínico es la mejor opción en pacientes no candidatos a tratamiento intensivo.

Muchas gracias!!!!!!

Agradecimientos:

Dr. Jordi Sierra

Grupo CETLAM