The PETHEMA AML group: structure and last achievements

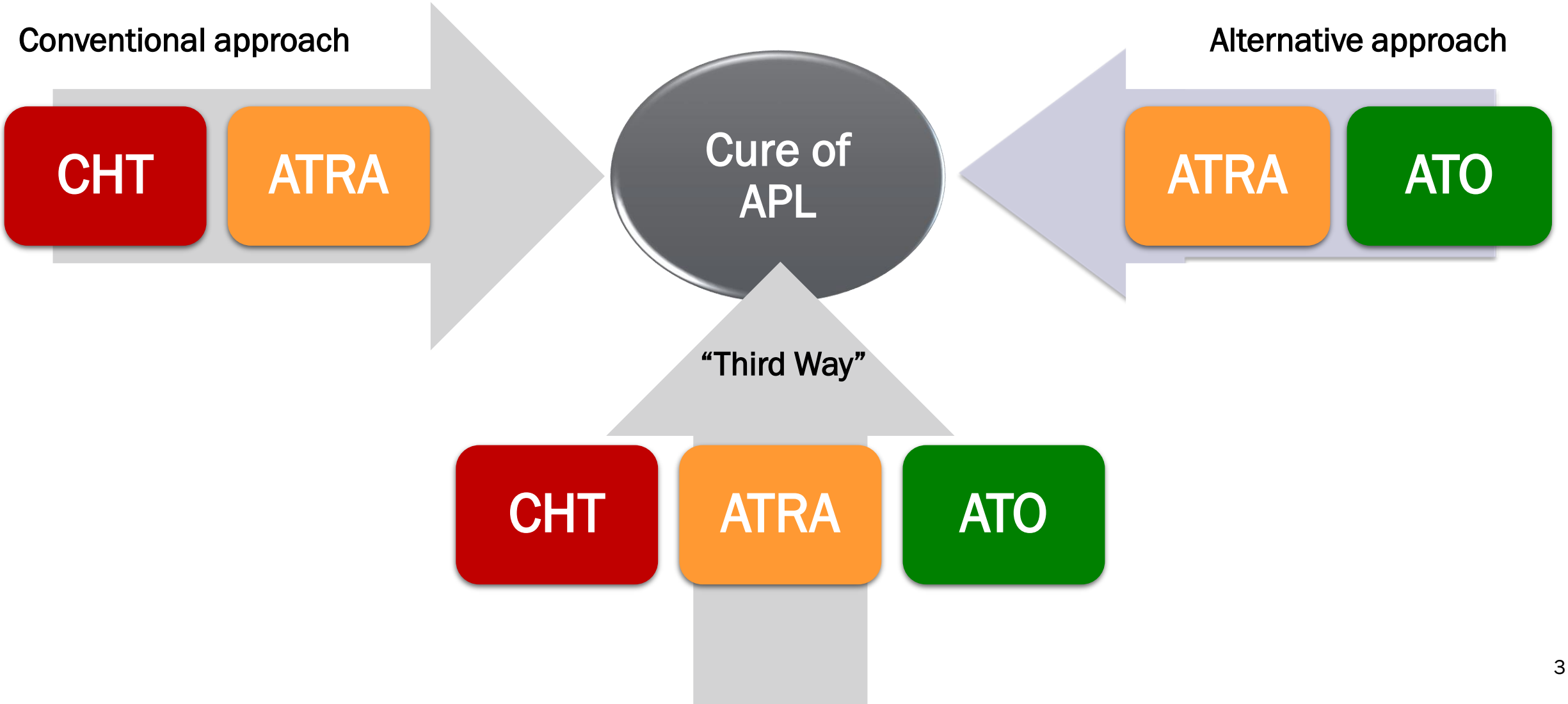
FILO annual meeting
Dijon 25th november 2022

Pau Montesinos

Outline

- APL
- AML registry
- Biological studies
- Front-line younger patients
- Front-line unfit patients
- Relapse refractory setting

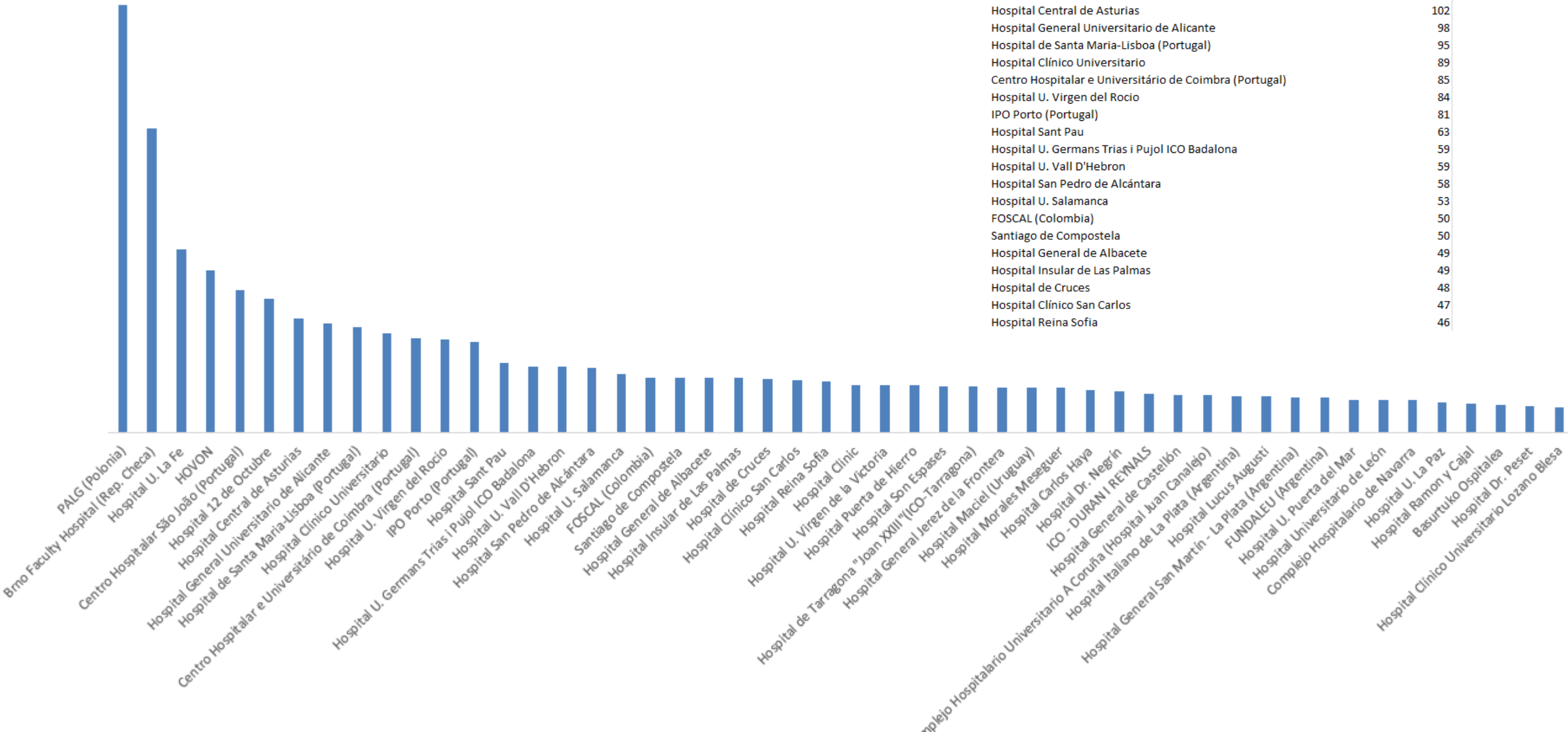
Targeting PML/RARA
Current Treatment Options in APL



APL registry (n=4096)

TOP 50

Hospital	N
PALG (Polonia)	381
Brno Faculty Hospital (Rep. Checa)	272
Hospital U. La Fe	164
HOVON	145
Centro Hospitalar São João (Portugal)	127
Hospital 12 de Octubre	120
Hospital Central de Asturias	102
Hospital General Universitario de Alicante	98
Hospital de Santa Maria-Lisboa (Portugal)	95
Hospital Clínico Universitario	89
Centro Hospitalar e Universitário de Coimbra (Portugal)	85
Hospital U. Virgen del Rocio	84
IPO Porto (Portugal)	81
Hospital Sant Pau	63
Hospital U. Germans Trias i Pujol ICO Badalona	59
Hospital U. Vall D'Hebron	59
Hospital San Pedro de Alcántara	58
Hospital U. Salamanca	53
FOSCAL (Colombia)	50
Santiago de Compostela	50
Hospital General de Albacete	49
Hospital Insular de Las Palmas	49
Hospital de Cruces	48
Hospital Clínico San Carlos	47
Hospital Reina Sofia	46



Protocolo PETHEMA LPA2017

LPA PML/RARα positiva, de novo o secundaria
Iniciar ATRA ante sospecha

Riesgo bajo-intermedio (WBC ≤ 10 x 10^9/L) o edad ≥ 70 años

Inducción (ATO+ATRA)
ATRA 45 mg/m²/d VO día 1 hasta RC
ATO 0,15 mg/kg IV día 1 hasta RC

Prednisona 0,5 mg/kg VO x 14 días
Hydrea si aumenta WBC > 10 x 10^9/L

Consolidación (28 semanas)

ATRA 45 mg/m²/d x 14 d (sem 1-2 y 5-6)
ATO 0,15 mg/kg/d lu-vi (sem 1-4)

ATRA 45 mg/m²/d x 14 d (sem 9-10 y 13-14)
ATO 0,15 mg/kg/d lu-vi (sem 9-12)

ATRA 45 mg/m²/d x 14 d (sem 17-18 y 21-22)
ATO 0,15 mg/kg/d lu-vi (sem 17-20)

ATRA 45 mg/m²/d x 14 d (sem 25-26)
ATO 0,15 mg/kg/d lu-vi (sem 25-28)

riesgo alto (WBC > 10 x 10^9/L) y edad < 70 años

APOLLO trial si está disponible

Inducción (AIDA)
IDA 12 mg/m²/d días 1,3,5,7 (≥ 60 años días 1,3,5)
ATRA 45 mg/m²/d día 1 hasta RC

Prednisona 0,5 mg/kg VO x 14 días

Consolidación

Edad entre 60 y 70 años

IDA 5 mg/m²/d (días 1,2,3,4)
ATRA 45 mg/m²/d x 15

MTZ 10 mg/m²/d (días 1,2,3)
ATRA 45 mg/m²/d x 15

IDA 12 mg/m²/d (día 1)
ATRA 45 mg/m²/d x 15

Edad < 60 años

IDA 5 mg/m²/d (días 1,2,3,4)
Ara-C 1000 mg/m²/d (días 1,2,3,4)
ATRA 45 mg/m²/d x 15

MTZ 10 mg/m²/d (días 1,2,3,4,5)
ATRA 45 mg/m²/d x 15

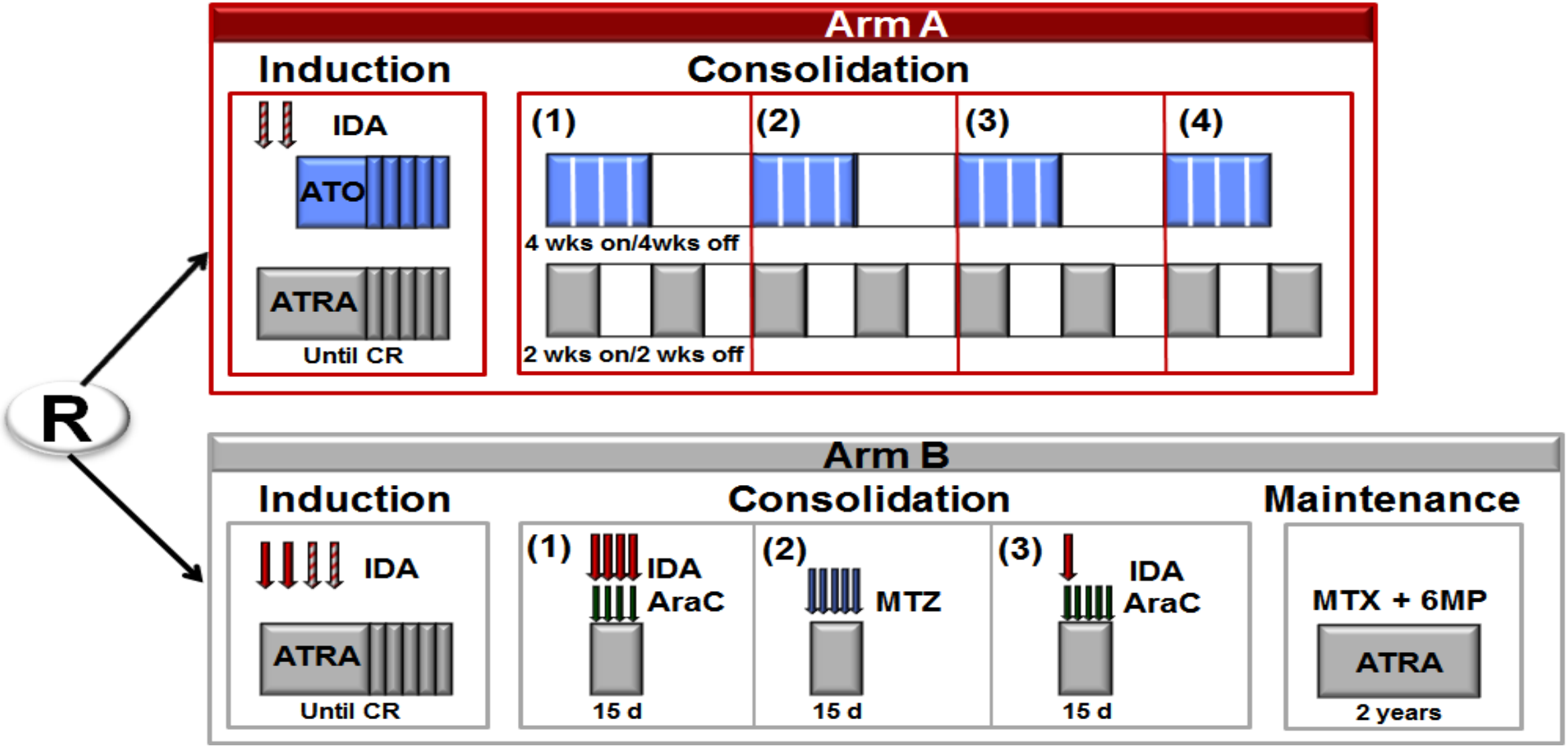
IDA 12 mg/m²/d (día 1)
Ara-C 500 mg/m²/d (días 1,2,3,4)
ATRA 45 mg/m²/d x 15

Mantenimiento (12 semanas)

ATRA 45 mg/m²/d x 14 d (sem 1-2 y 5-6)
ATO 0,15 mg/kg/d lu-vi (sem 1-4)

ATRA 45 mg/m²/d x 14 d (sem 9-10)
ATO 0,15 mg/kg/d lu-vi (sem 8-12)

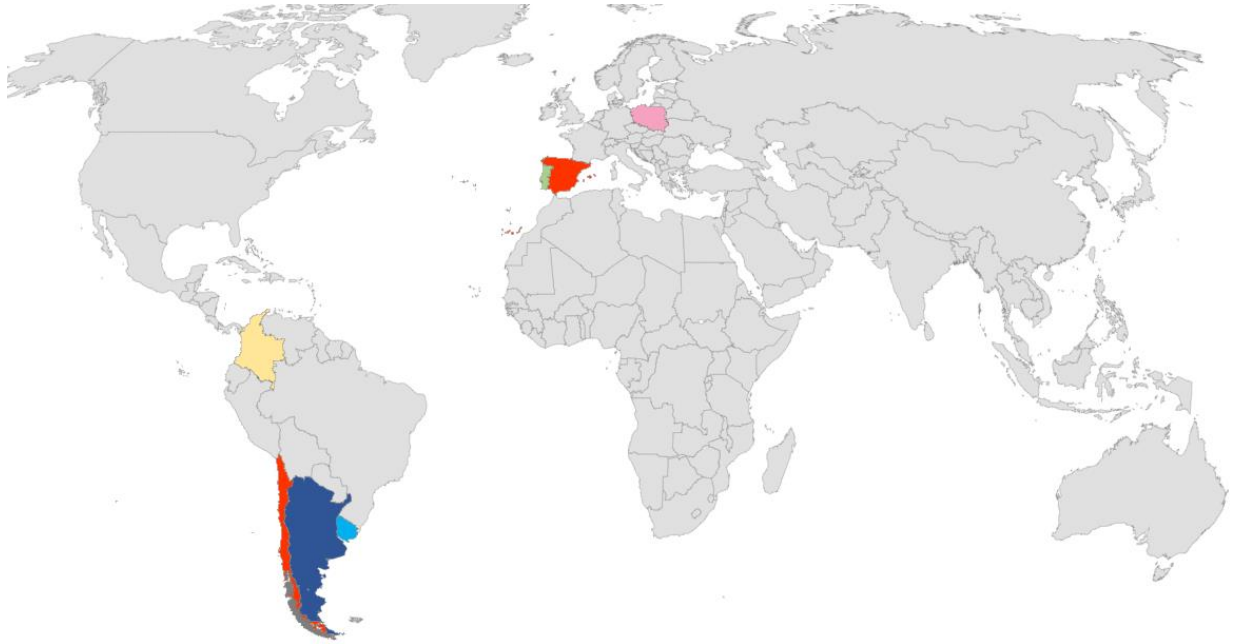
APOLLO trial N=260



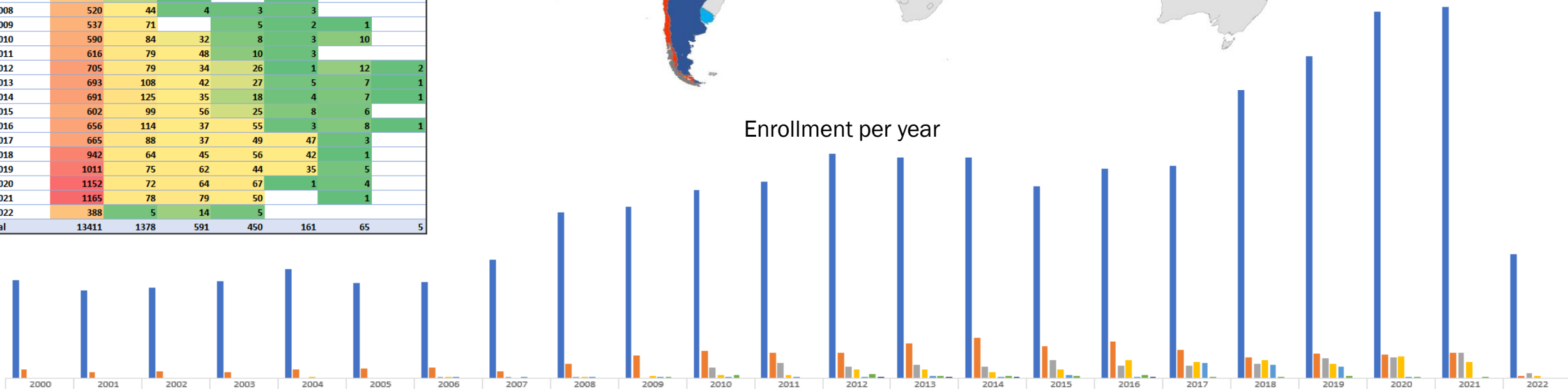
PETHEMA AML registry

País	Centros	N Pac.	% Pac.
España	140	14599	83,55%
Portugal	4	1601	9,16%
Chile	16	592	3,39%
Colombia	13	450	2,58%
Polonia	15	161	0,92%
Uruguay	2	65	0,37%
Argentina	2	5	0,03%
Total	**192**	**17473**	**100,00%**

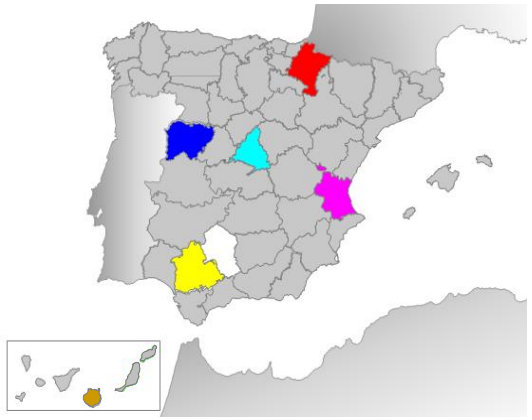
Año	España	Portugal	Chile	Colombia	Polonia	Uruguay	Argentina
2000	306	25					
2001	275	19					
2002	282	21					
2003	303	19					
2004	342	27		1			
2005	299	29					
2006	301	33	1	1	3		
2007	370	20	1		1		
2008	520	44	4	3	3		
2009	537	71		5	2	1	
2010	590	84	32	8	3	10	
2011	616	79	48	10	3		
2012	705	79	34	26	1	12	2
2013	693	108	42	27	5	7	1
2014	691	125	35	18	4	7	1
2015	602	99	56	25	8	6	
2016	656	114	37	55	3	8	1
2017	665	88	37	49	47	3	
2018	942	64	45	56	42	1	
2019	1011	75	62	44	35	5	
2020	1152	72	64	67	1	4	
2021	1165	78	79	50		1	
2022	388	5	14	5			
Total	13411	1378	591	450	161	65	5



Enrollment per year



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
España	306	275	282	303	342	299	301	370	520	537	590	616	705	693	691	602	656	665	942	1011	1152	1165	388
Portugal	25	19	21	19	27	29	33	20	44	71	84	79	79	108	125	99	114	88	64	75	72	78	5
Chile							1	1	4		32	48	34	42	35	56	37	37	45	62	64	79	14
Colombia					1		1		3	5	8	10	26	27	18	25	55	49	56	44	67	50	5
Polonia							3	1	3	2	3	3	1	5	4	8	3	47	42	35	1		
Uruguay										1	10		12	7	7	6	8	3	1	5	4	1	
Argentina													2	1	1		1						



7 central labs (PETHEMA)

AML suspected

Urgency

3-7 days

"Fit" patient

Central screening

No trial

Common induction

3+7

AML CBF

AML NPM1

AML FLOW

Assistential protocol

Post-CR

MRD guided

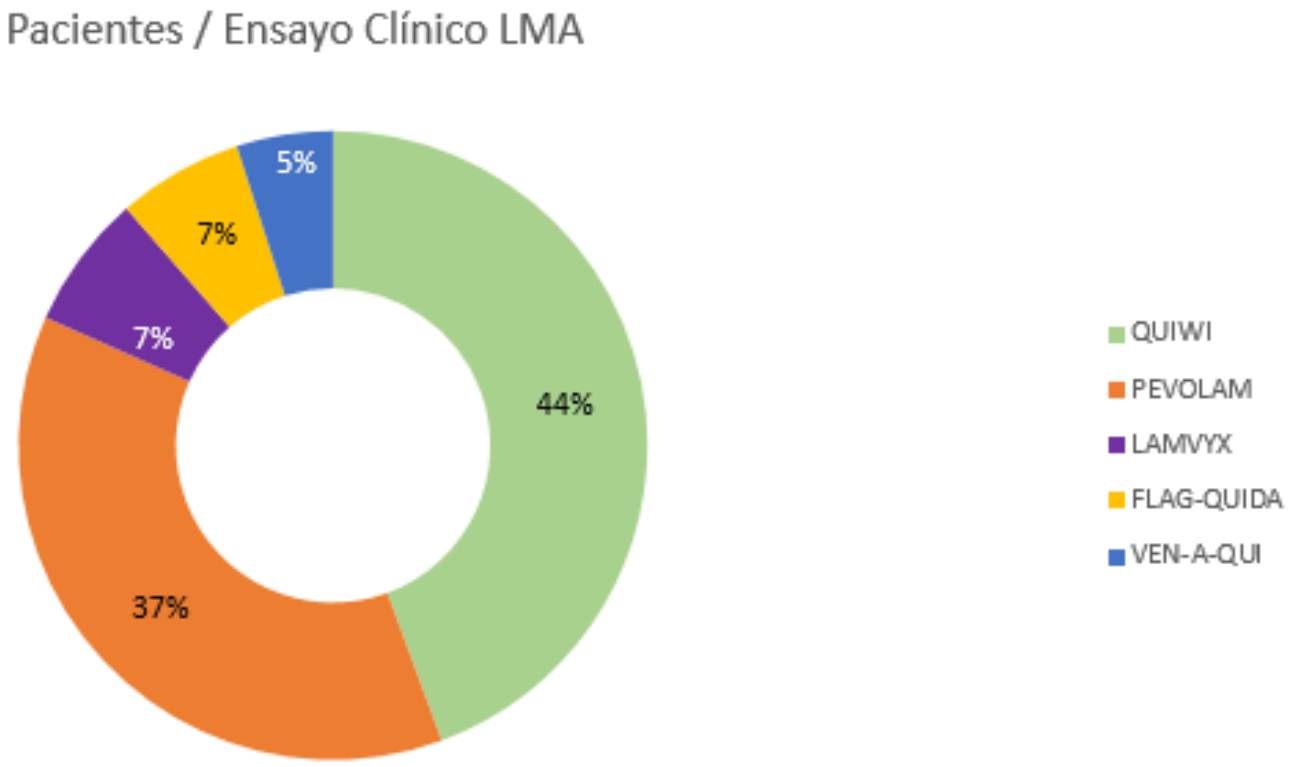
Clinical trial

Preferable

Extracted from PETHEMA guidelines

Patients in PETHEMA clinical trial (2020-2021)

EC	N
QUIWI	494
PEVOLAM	415
LAMVYX	77
FLAG-QUIDA	72
VEN-A-QUI	55
Total general	**1113**

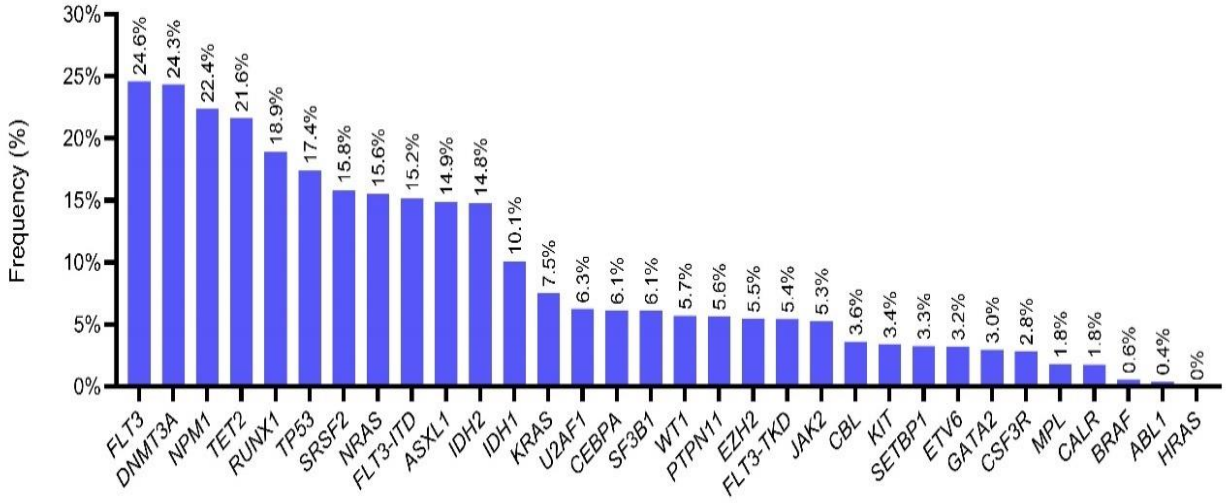


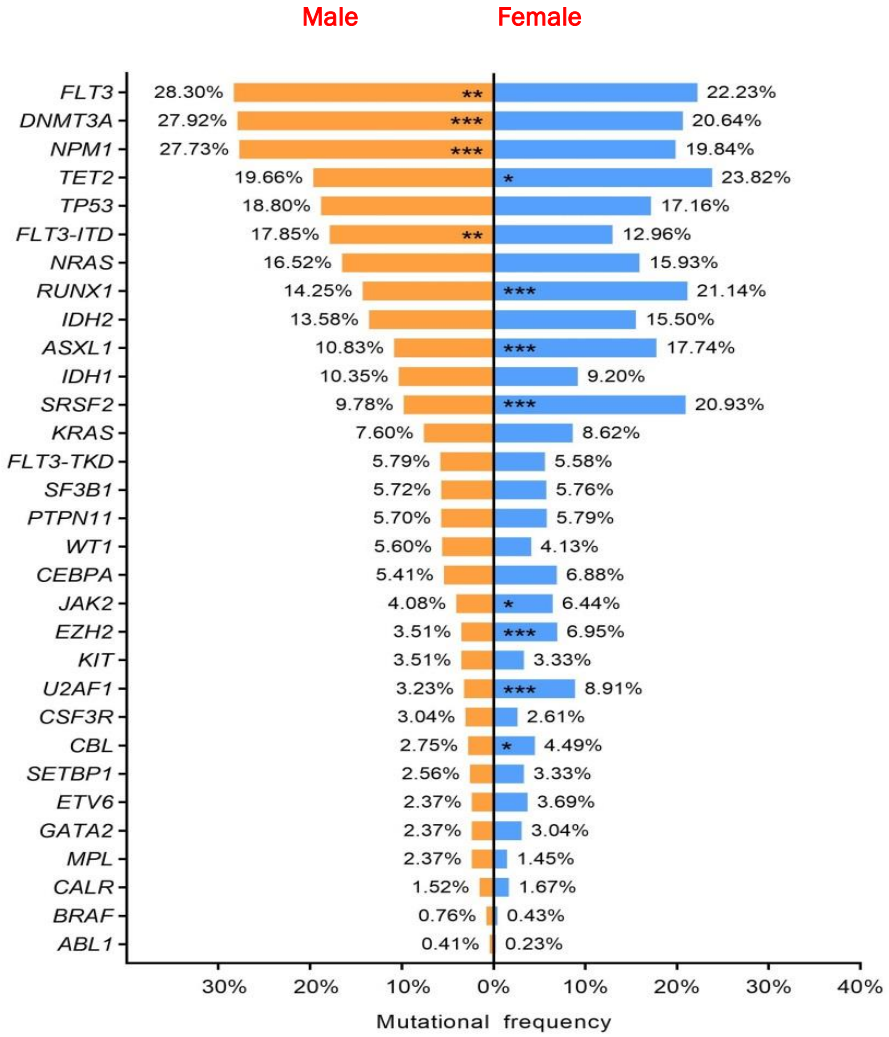
REALMOL study: NPM1 & FLT3 testing (2000-2021, n=6980)

cancers

MDPI

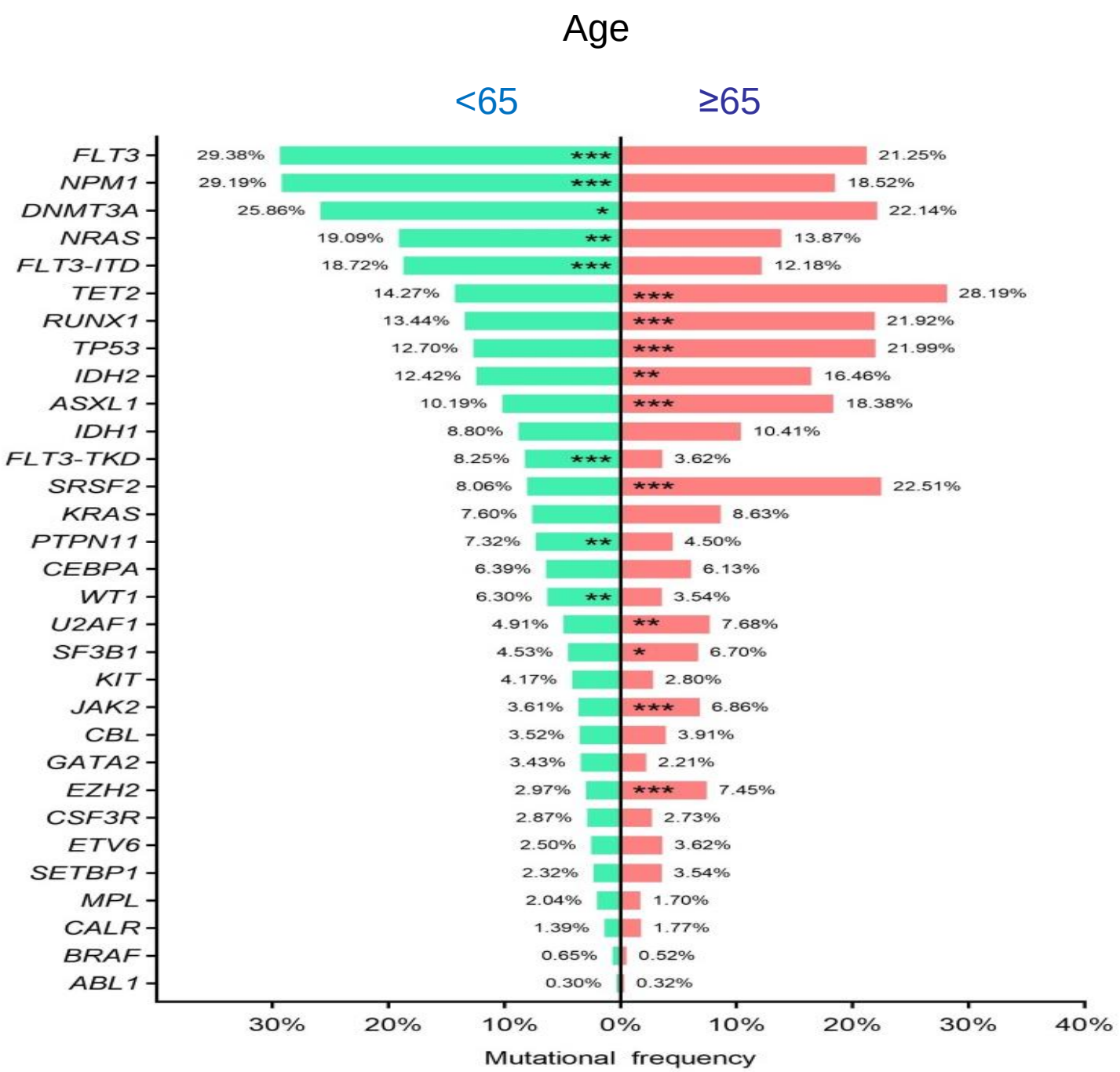
Molecular landscape and validation of new genomic classification in 2668 adult AML patients: real life data from the PETHEMA registry



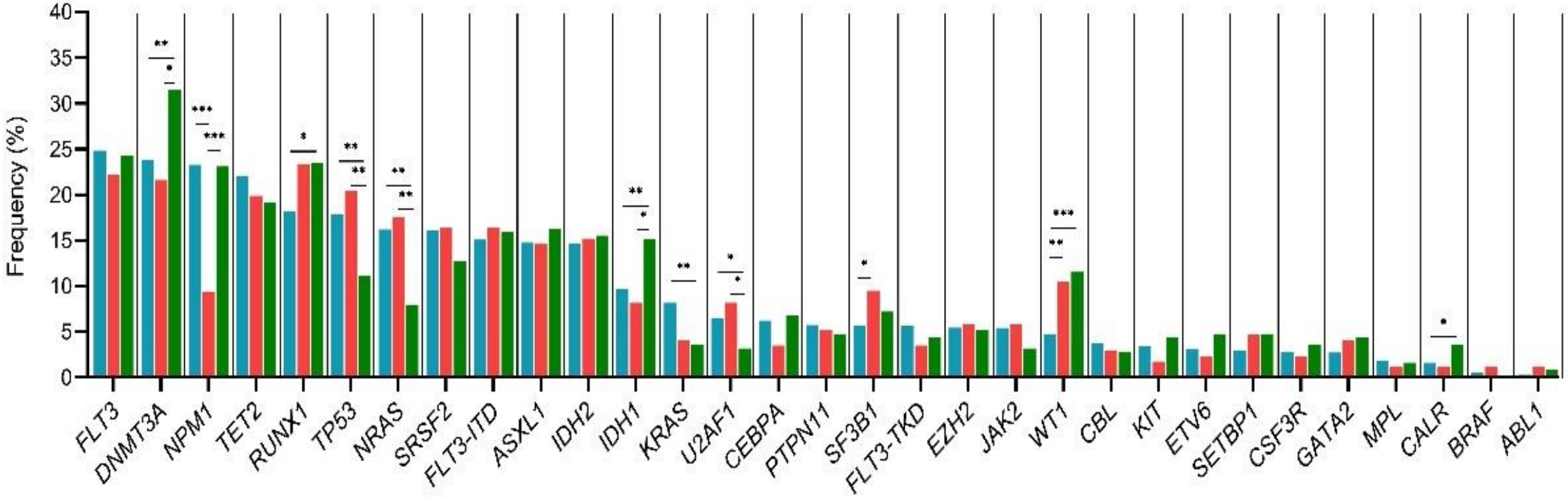


Sargas C, et al, submitted

≥65-year-old AML patients were characterized by a higher number of mutations than younger ones

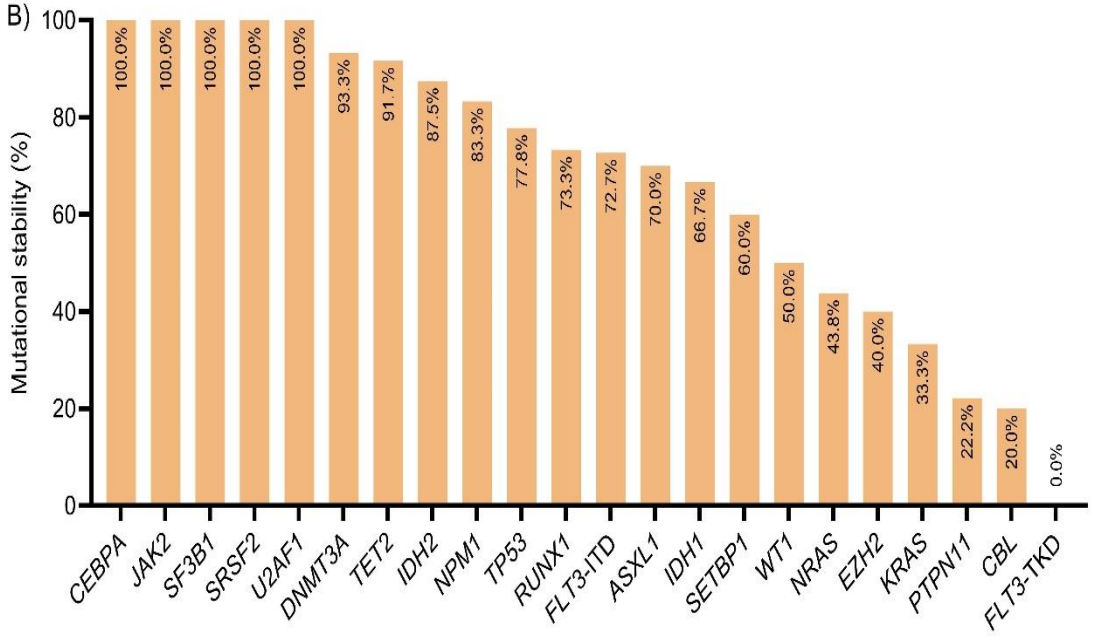


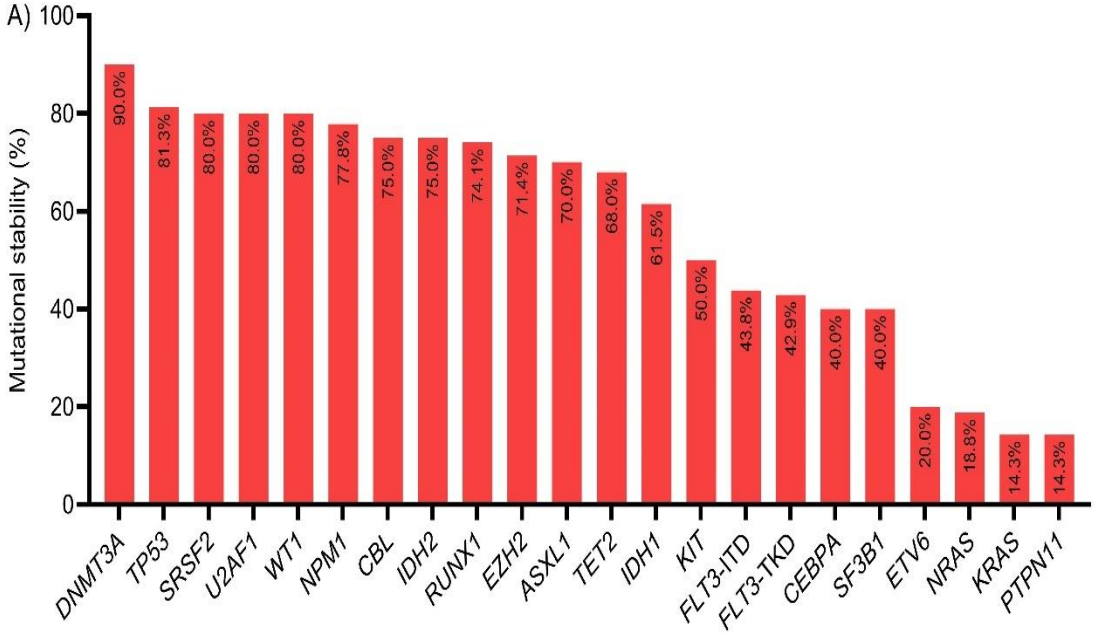
Mutational frequency according to disease stage



Blue bars: Diagnosis, green bars: Relapse and red bars: refractoriness. *P<0.05, **P<0.01, ***P<0.001. ITD: internal tandem duplication; TKD: tyrosine kinase domain.

Mutational stability (refractory or relapse)

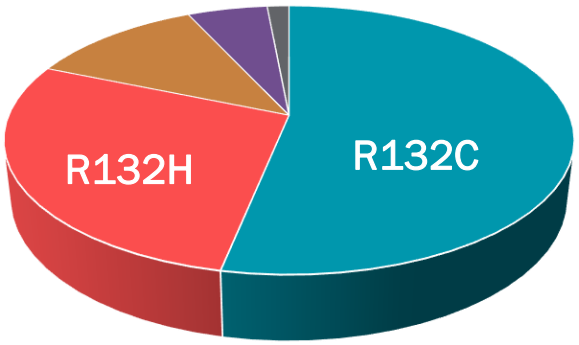




Analysis of IDH1 & IDH2 mutations in 2461 patients

IDH mut: 595 (24%)

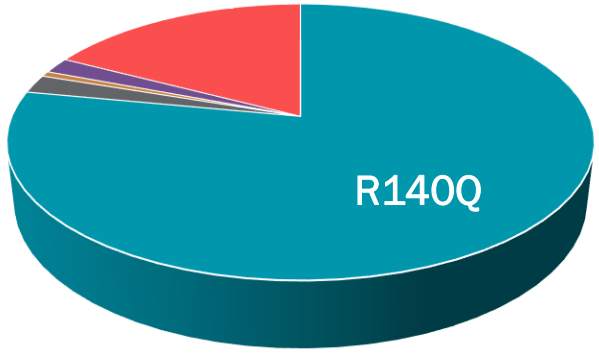
IDH1



p.Arg132Cys p.Arg132His p.Arg132Gly
p.Arg132Ser p.Arg132Leu

6 double IDH1-IDH2

IDH2



p.Arg140Gln p.Arg140Trp p.Arg140Gly p.Arg140Leu p.Arg172Lys

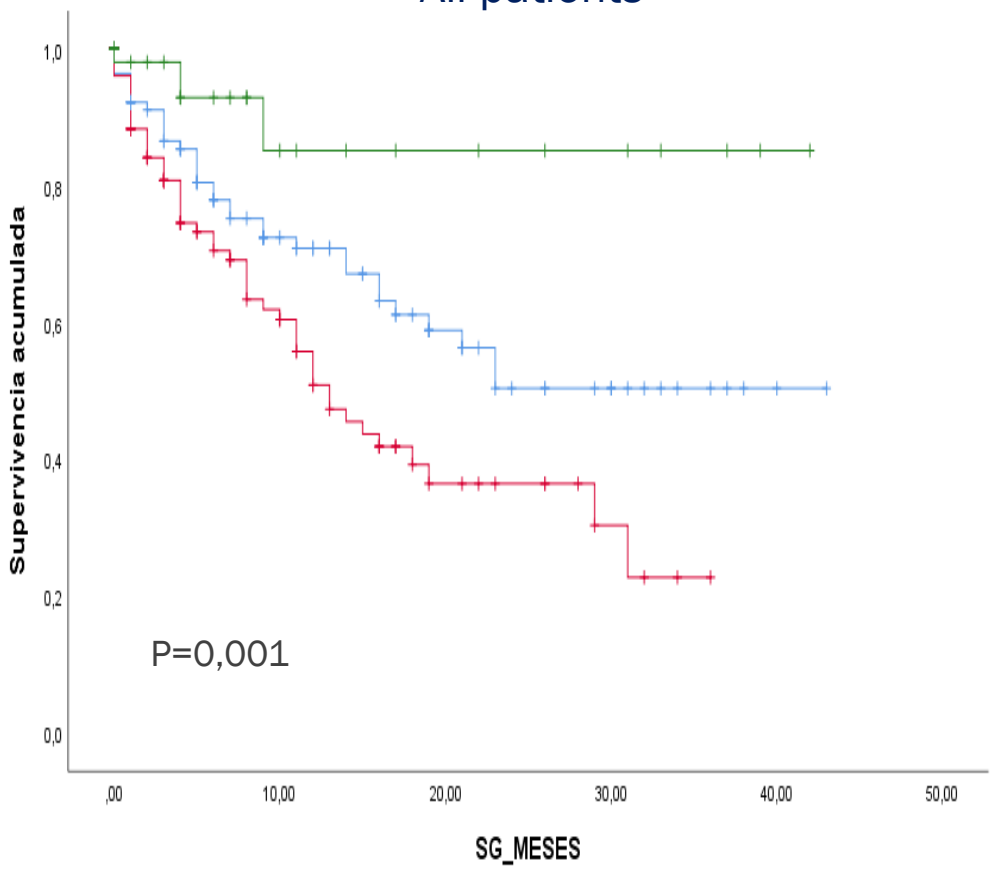
IDH1 mutado (NGS)	203
IDH1 mutado (otra técnica)	35

IDH2 mutado (NGS)	323
IDH2 mutado (otra técnica)	41

OS as per IDH1 R132, IDH2 R140 & IDH2 R172

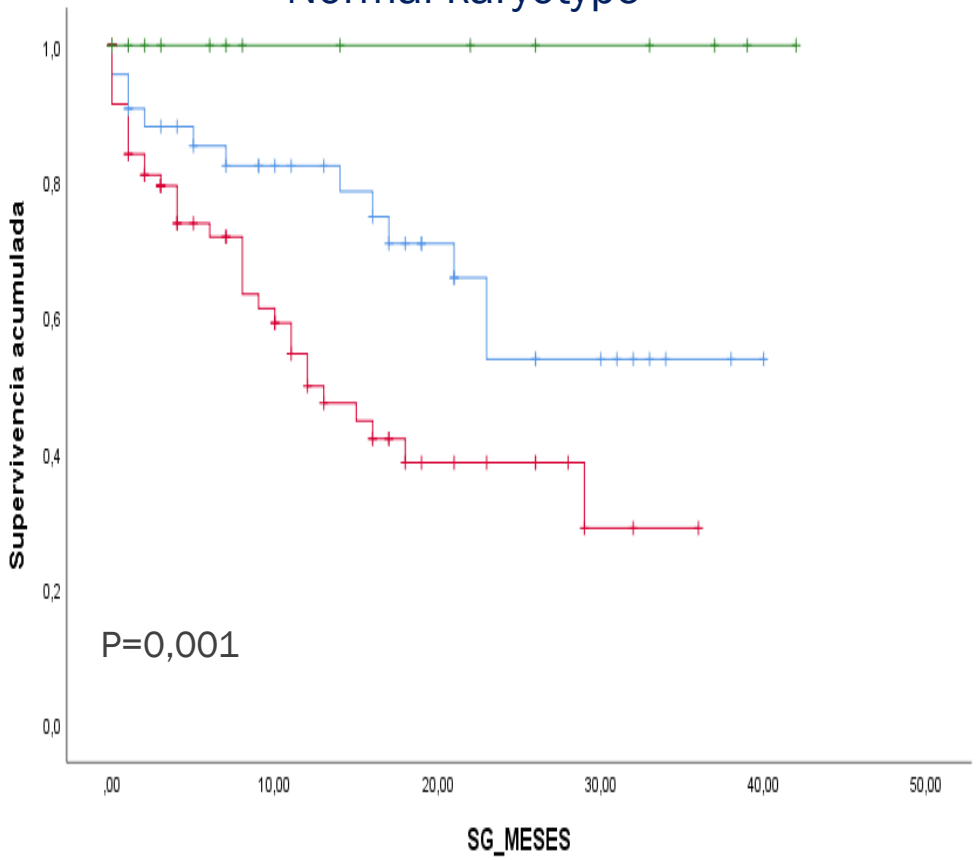
IDH1_R132
IDH2_R140
IDH2_R172

All patients



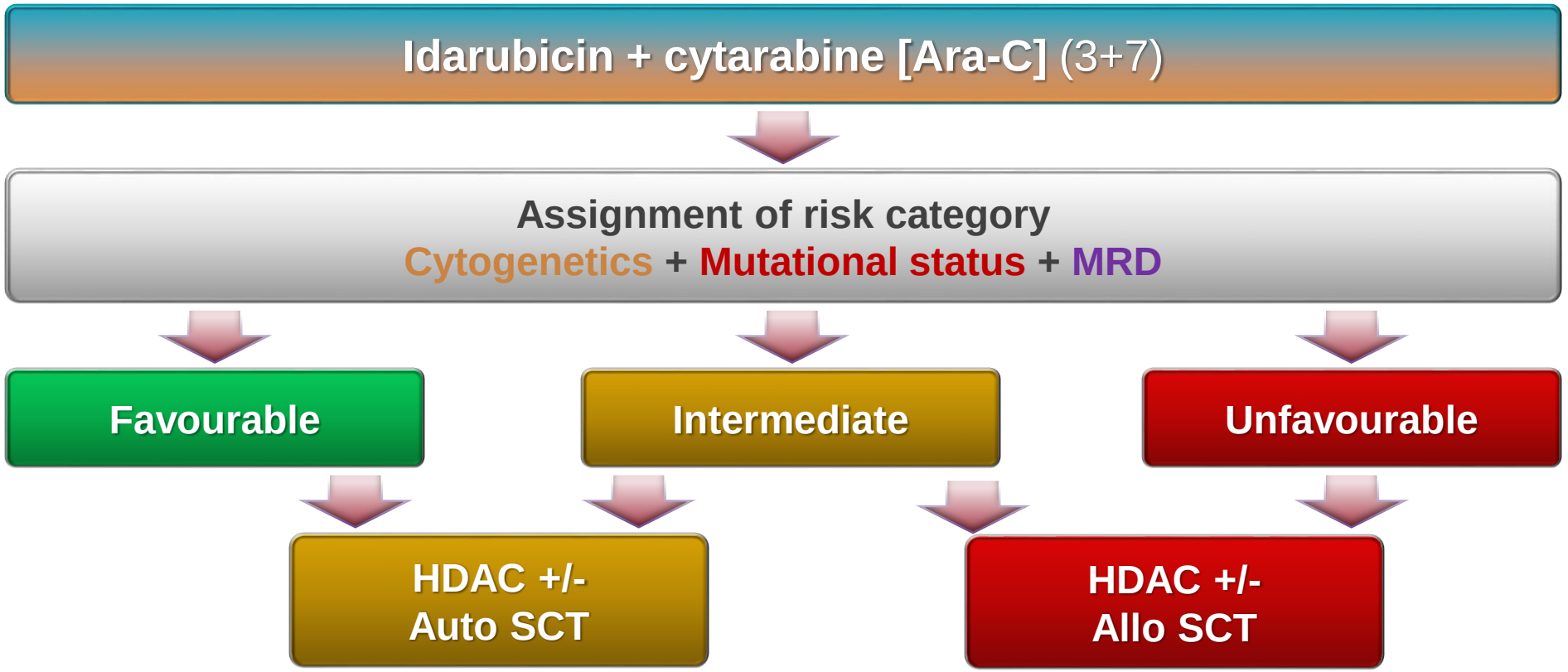
IDH_3subtipos	N total	N de eventos
IDH1_R132	194	37
IDH2_R140	254	55
IDH2_R172	51	3
Global	499	95

Normal karyotype



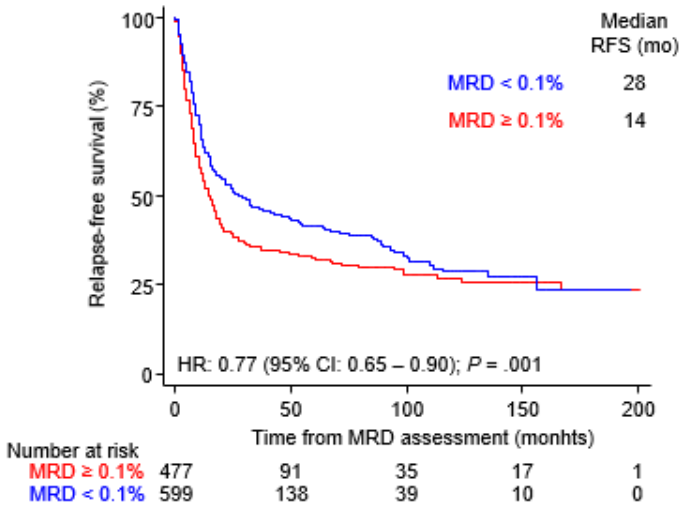
IDH_3subtipos	N total	N de eventos
IDH1_R132	47	13
IDH2_R140	81	34
IDH2_R172	15	0
Global	143	47

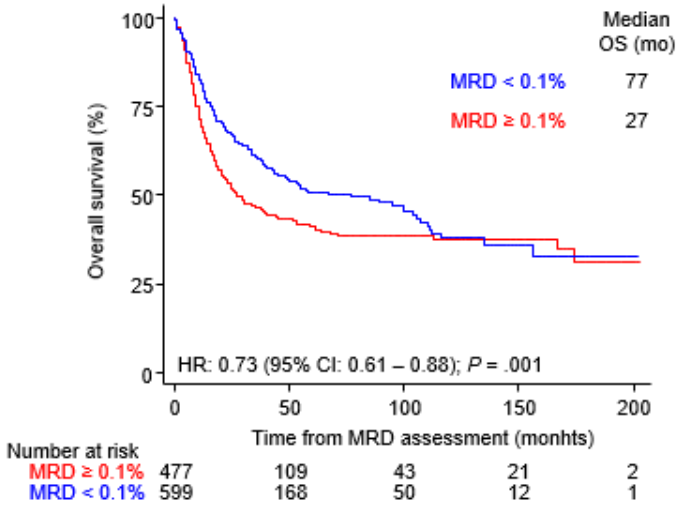
2007-2016 Front-line therapy for fit AML



Allo, allogeneic; auto, autologous; CR, complete remission; HDAC, histone deacetylase inhibitor; MRD, minimal residual disease; PETHEMA, Programa Espanol deTratamientos en Hematologia; SCT, stem cell transplant

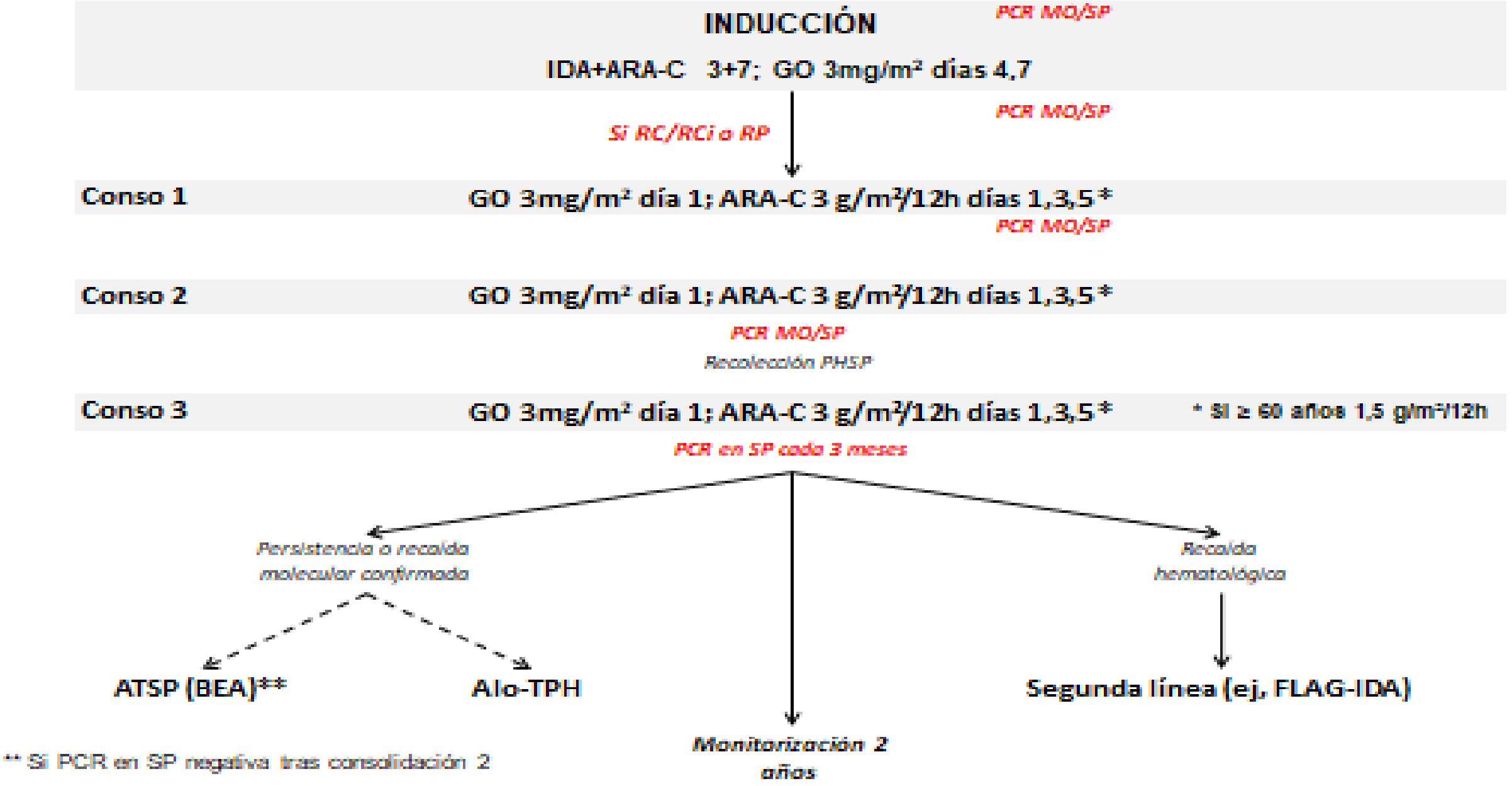
Impact of post-induction MRD (real-life evidence n=1076)



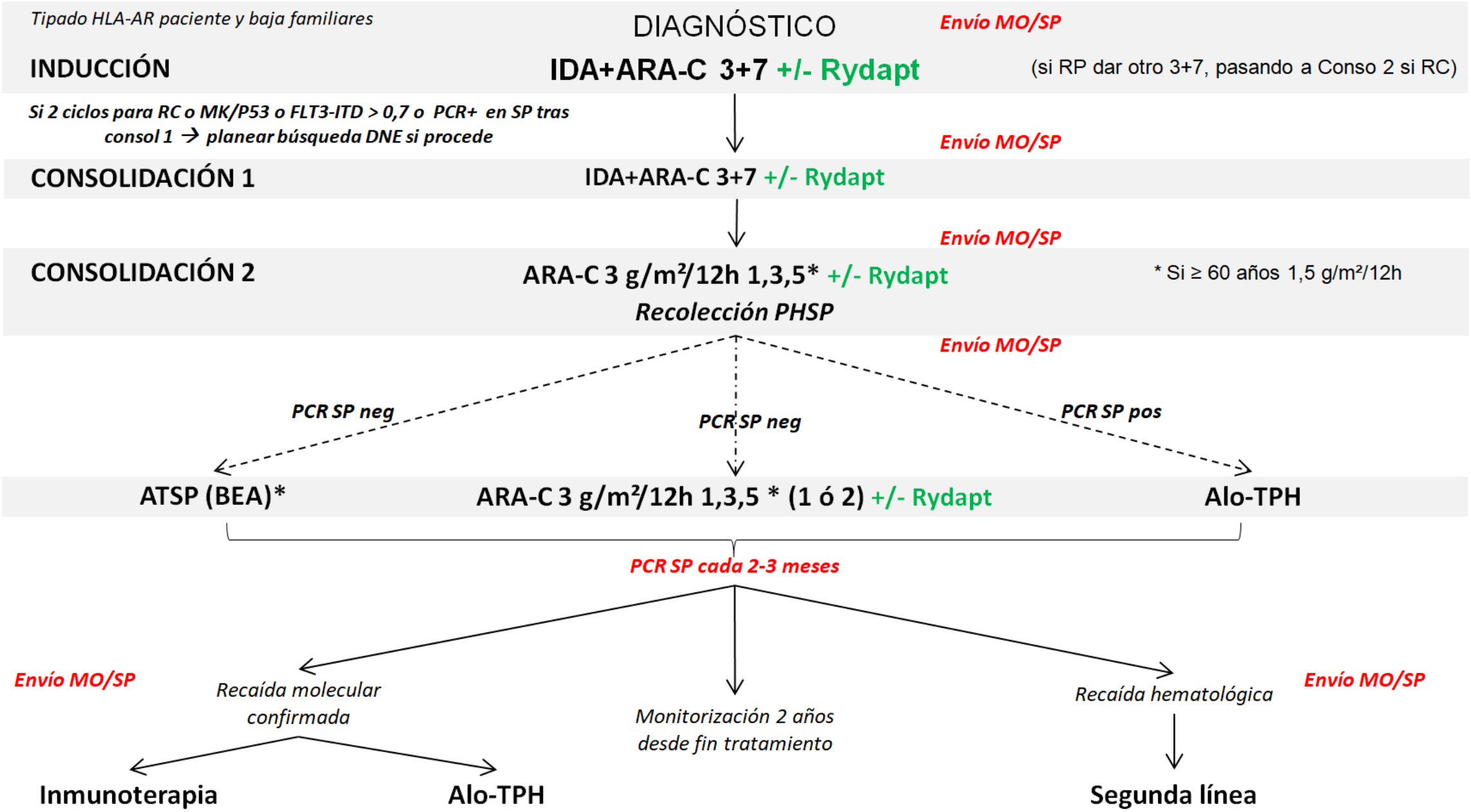


Paiva B, et al, Leukemia 2021

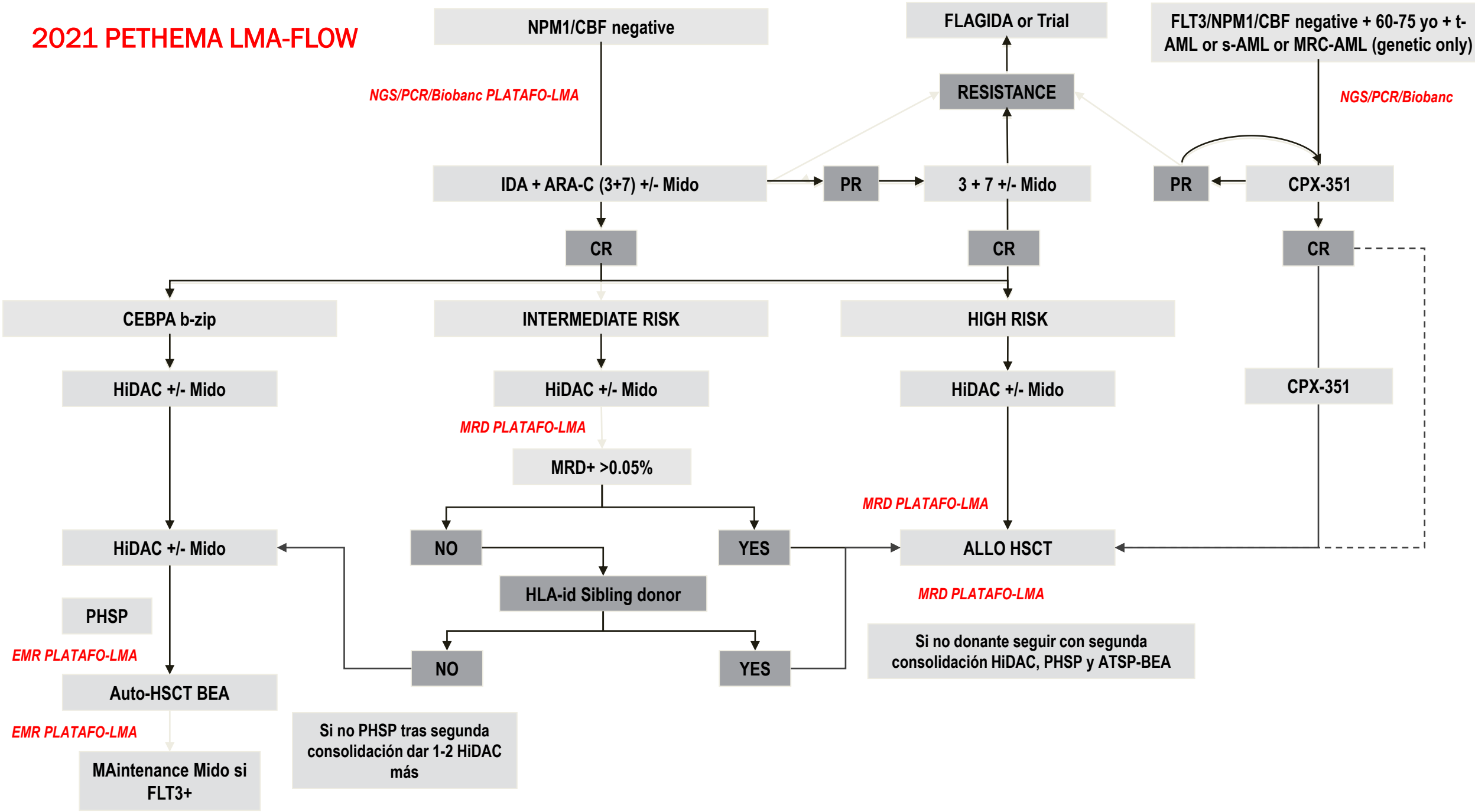
2016: PETHEMA CBF AML protocol



2017: PETHEMA NPM1 AML protocol



2021 PETHEMA LMA-FLOW



2022 WHO Classification of Haematolymphoid Tumors

- Separation of AML into 2 families
  - AML with defining genetic abnormalities
    - Most may be diagnosed with <20% blasts (exception: *CEBPA* & *BCR::ABL1*)
  - AML defined by differentiation
- AML NOS is no longer applicable
- AML with myelodysplasia-related changes now called AML-MR
  - Mutation-based definition
  - 8 genes present in >95% of AML-MR cases: *SRSF2, SF3B1, U2AF1, ZRSR2, ASXL1, EZH2, BCOR, STAG2*

Acute myeloid leukaemia with defining genetic abnormalities
Acute promyelocytic leukaemia with *PML::RARA* fusion
Acute myeloid leukaemia with *RUNX1::RUNX1T1* fusion
Acute myeloid leukaemia with *CBFB::MYH11* fusion
Acute myeloid leukaemia with *DEK::NUP214* fusion
Acute myeloid leukaemia with *RBM15::MRTFA* fusion
Acute myeloid leukaemia with *BCR::ABL1* fusion
Acute myeloid leukaemia with *KMT2A* rearrangement
Acute myeloid leukaemia with *MECOM* rearrangement
Acute myeloid leukaemia with *NUP98* rearrangement
Acute myeloid leukaemia with *NPM1* mutation
Acute myeloid leukaemia with *CEBPA* mutation
Acute myeloid leukaemia, myelodysplasia-related
Acute myeloid leukaemia with other defined genetic alterations
Acute myeloid leukaemia, defined by differentiation
Acute myeloid leukaemia with minimal differentiation
Acute myeloid leukaemia without maturation
Acute myeloid leukaemia with maturation
Acute basophilic leukaemia
Acute myelomonocytic leukaemia
Acute monocytic leukaemia
Acute erythroid leukaemia
Acute megakaryoblastic leukaemia

Khoury. Leukemia. 2022;36:1703.

cancers

MDPI

Article

Impact of FLT3–ITD mutation status and its ratio in a cohort of 2901 patients undergoing upfront intensive chemotherapy: a PETHEMA registry study

Table 3. Factors associated with response to induction therapy. Multivariate regression logistic for response to induction treatment. Effect of patient and disease characteristics on best response to treatment (complete remissions) and multivariate analyses (prognostic factors with *P*<0.1 in univariate analysis were included).

Variable	OR	Significance	Lower CI	Upper CI
Age	0.980	p<0.001	0.973	0.987
WBC (x1000/mL)	0.996	p<0.001	0.994	0.998
Cytogenetic risk				
Low risk vs. intermediate risk	0.341	p<0.001	0.222	0.523
Low risk vs. High risk	0.145	p<0.001	0.093	0.226
NPM1 mutation				
Absence vs. presence	2.865	p<0.001	2.235	3.674
Ratio FLT3–ITD>0.5				
Absence vs. presence	0.617	p=0.005	0.441	0.862

4. A. Factors associated with death. Cox multivariate for OS.

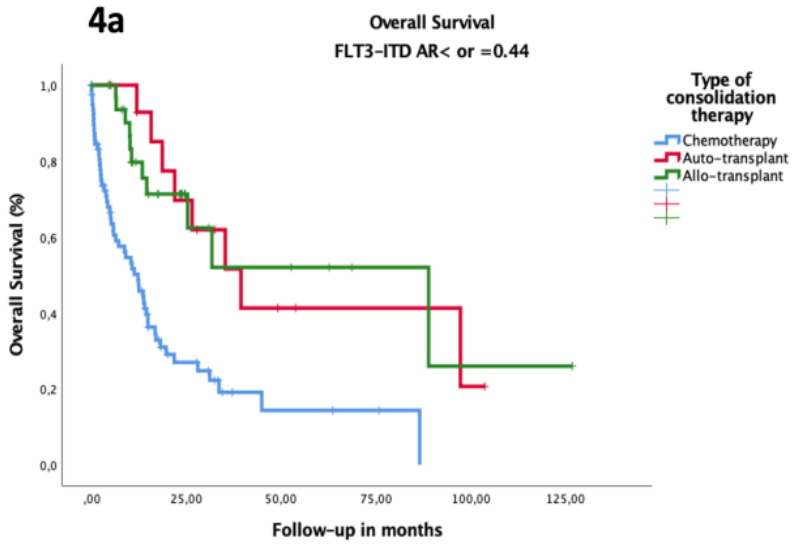
Variable	HR	Significance	Lower CI	Upper CI
Gender (male vs. female)	0.860	p=0.007	0.772	0.960
Age (continuous variable)	1.020	p<0.001	1.015	1.024
WBC (x1000/mL) (continuous variable)	1.002	p<0.001	1.001	1.003
Cytogenetic risk				
Low risk vs. intermediate risk	1.596	p<0.001	1.264	2.016
Low risk vs. high risk	3.267	p<0.001	2.558	4.172
FLT3–ITD ratio levels				
Neg. vs. <0.25	1.404	p=NS	0.983	2.005
Neg. vs. 0.25-0.50	1.190	p=NS	0.866	1.634
Neg. vs. 0.51-0.80	1.475	p=0.009	1.104	1.972
Neg. vs. >0.80	1.644	p<0.001	1.305	2.072
Consolidation (no transplant; autotransplant; allogeneic transplant)				
No transplant vs. autotransplant	0.372	p<0.001	0.311	0.445
No transplant vs. allogeneic transplant	0.321	p<0.001	0.273	0.377

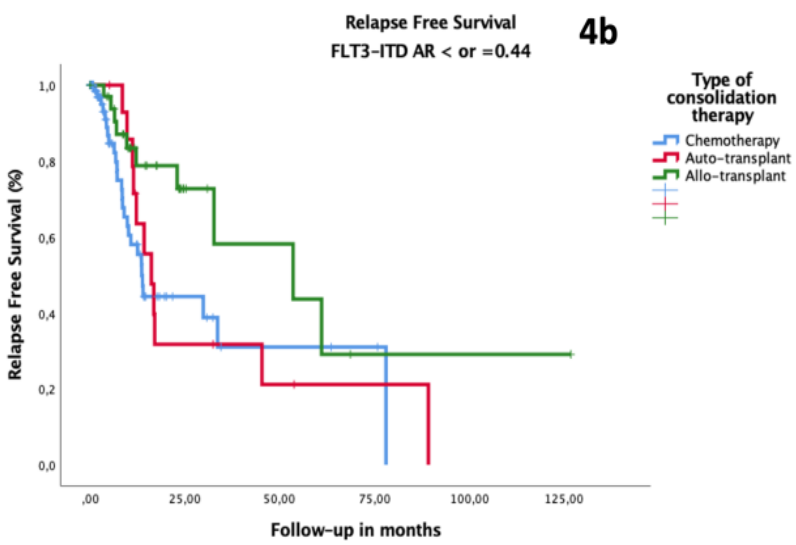
4. B. Factors associated with relapse. Cox multivariate for RFS.

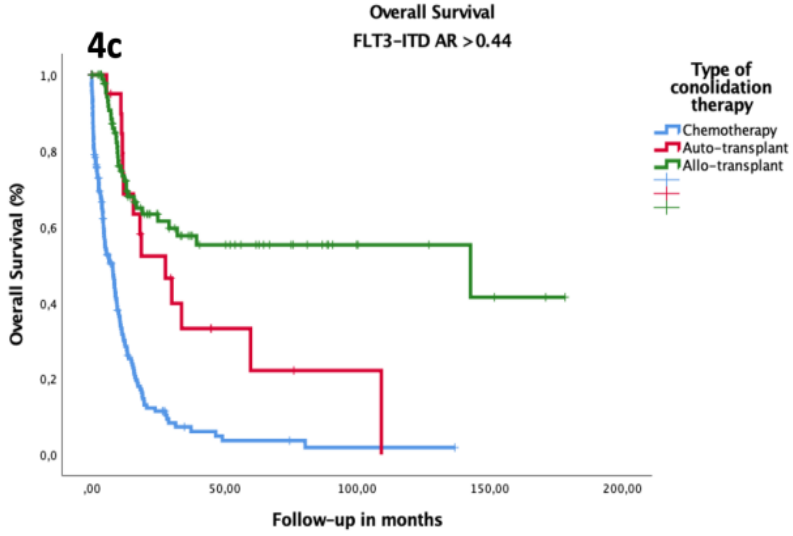
Variable	HR	Significance	Lower CI	Upper CI
WBC (x1000/mL) (continuous variable)	1.001	p=0.038	1.000	1.003
Cytogenetic risk				
Low risk vs. intermediate risk	1.740	p<0.001	1.331	2.275
Low risk vs. high risk	2.847	p<0.001	2.118	3.826
FLT3–ITD ratio levels				
Neg. vs. <0.25	1.143	p=NS	0.713	1.833
Neg. vs. 0.25-0.50	1.366	p=NS	0.921	2.027
Neg. vs. 0.501-0.80	0.969	p=NS	0.628	1.495
Neg. vs. >0.80	2.104	p<0.001	1.562	2.833
Consolidation (no transplant; autotransplant; allogeneic transplant)				
No transplant vs. autotransplant	0.589	p<0.001	0.491	0.706
No transplant vs. allogeneic transplant	0.291	p<0.001	0.239	0.354

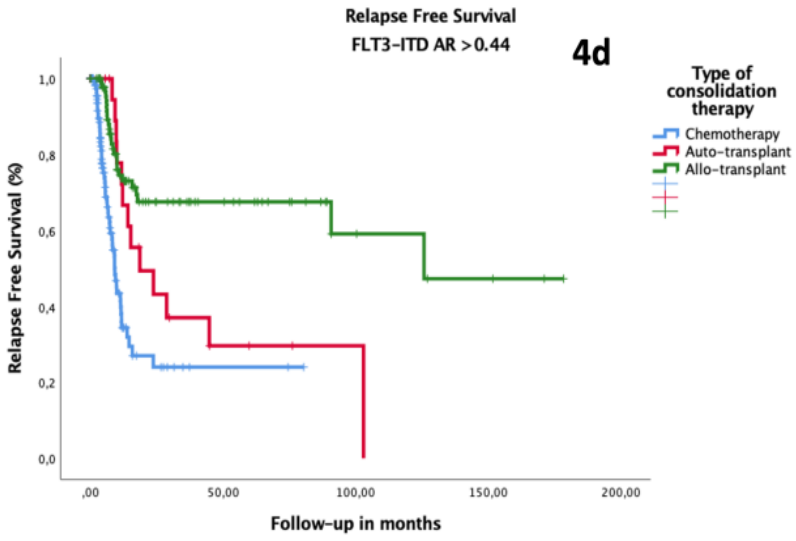
Ayala R, et al, in press

OS & RFS according to postremission therapy and FLT3-ITD ratio

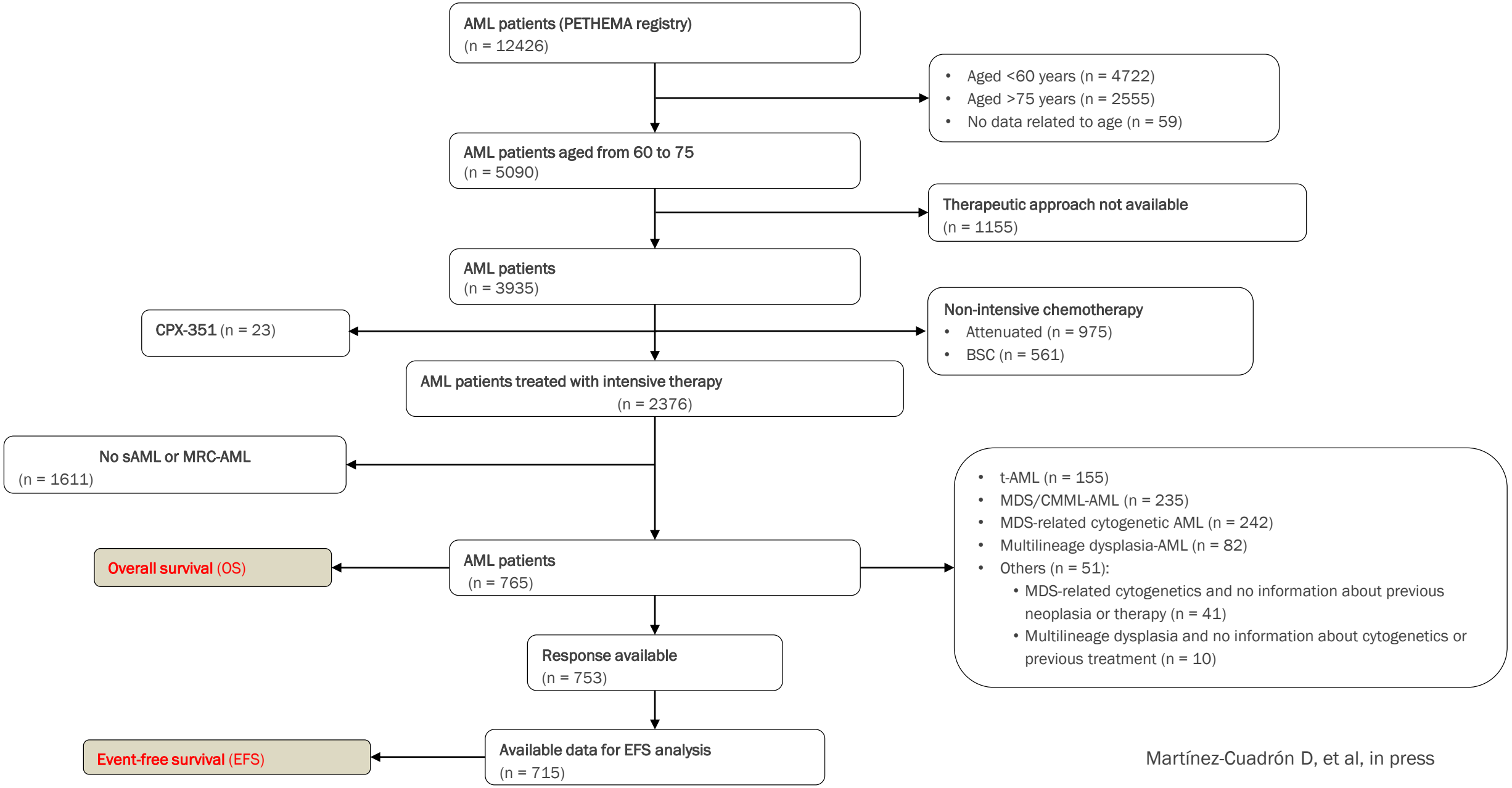






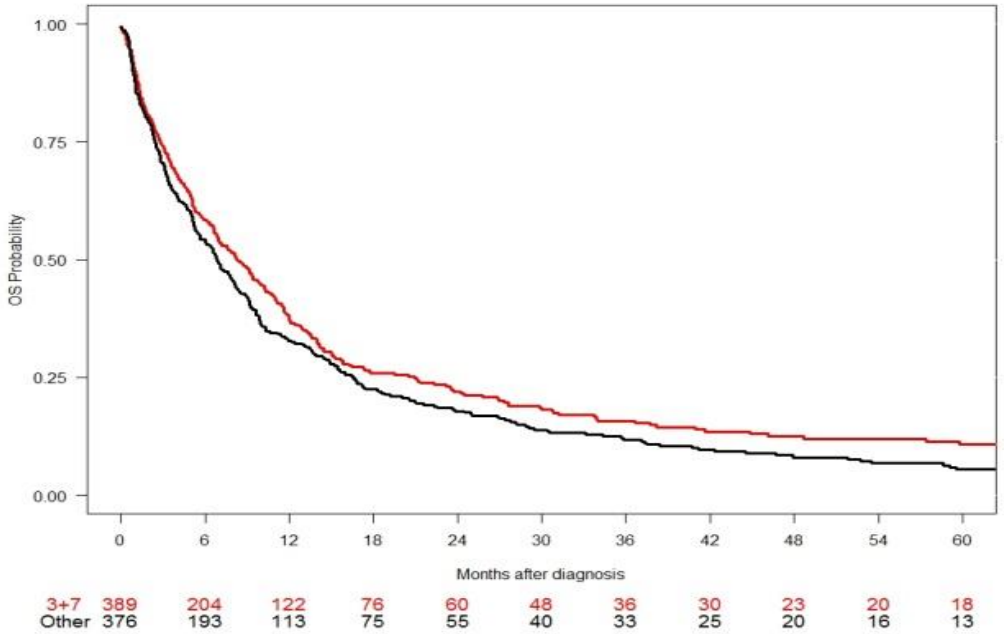


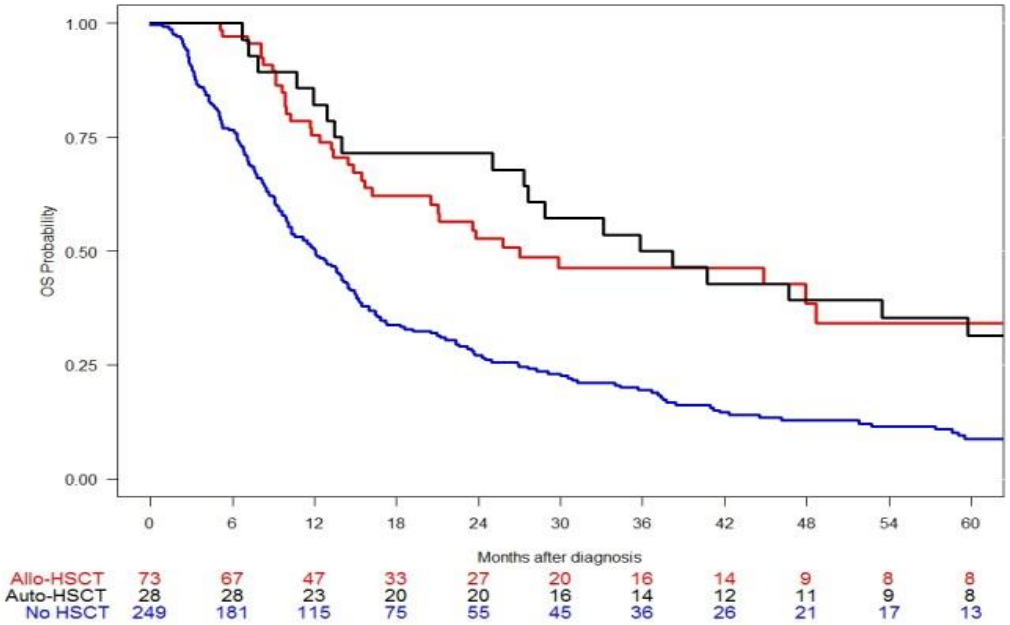
Real life outcomes with IC in “vyxeos-like” patients



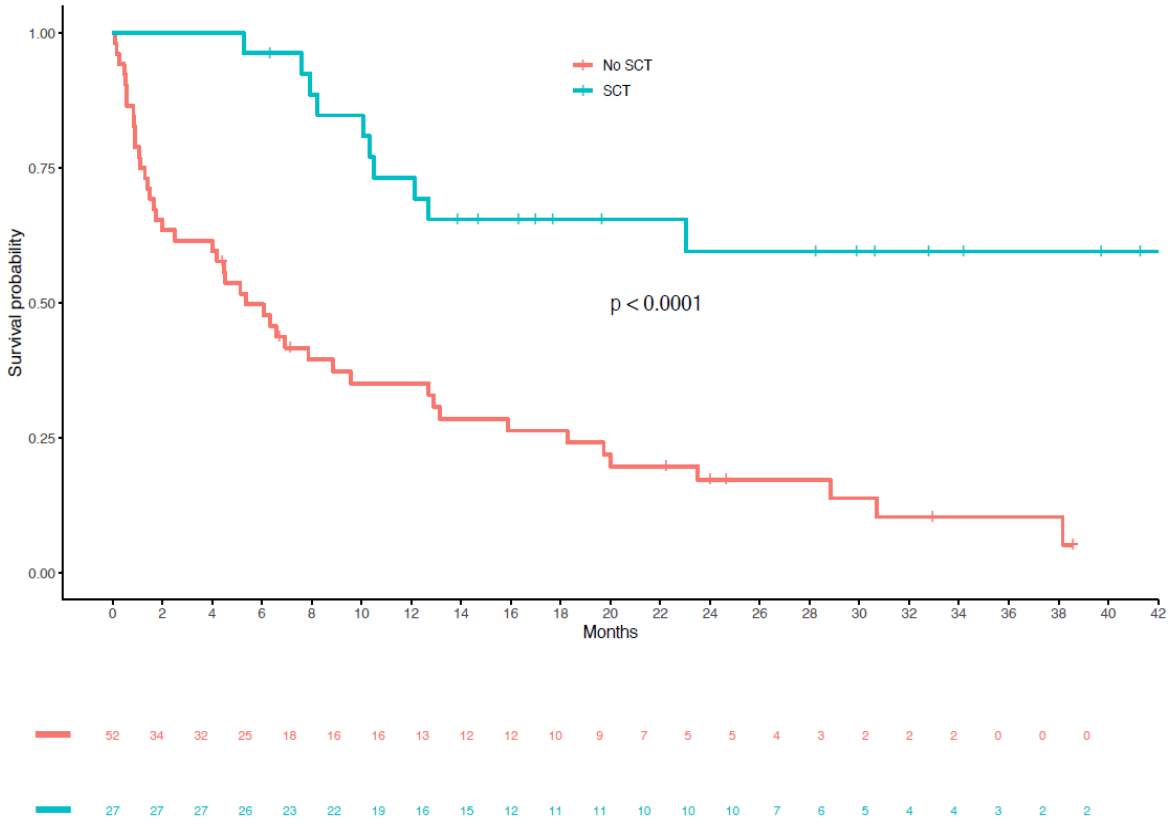
Martínez-Cuadrón D, et al, in press

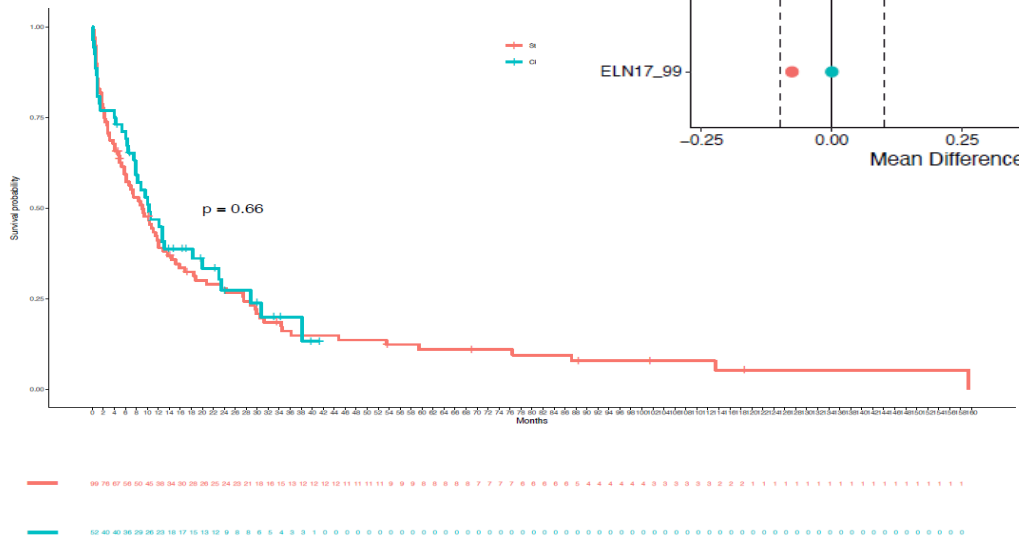
OS according to induction chemotherapy and post-remission therapy

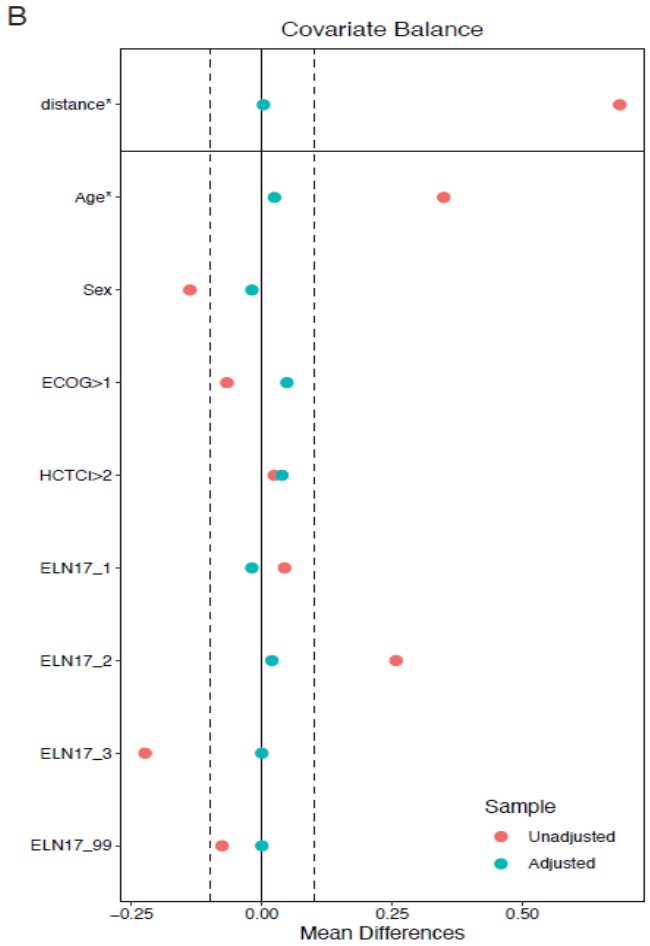




Early access program with Vyxeos in Spain



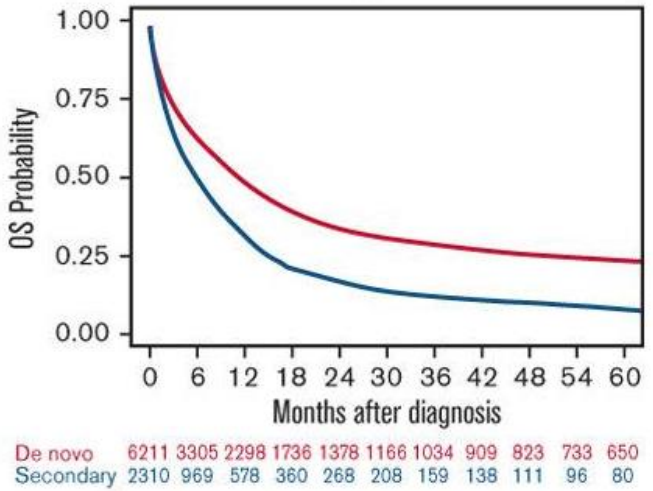


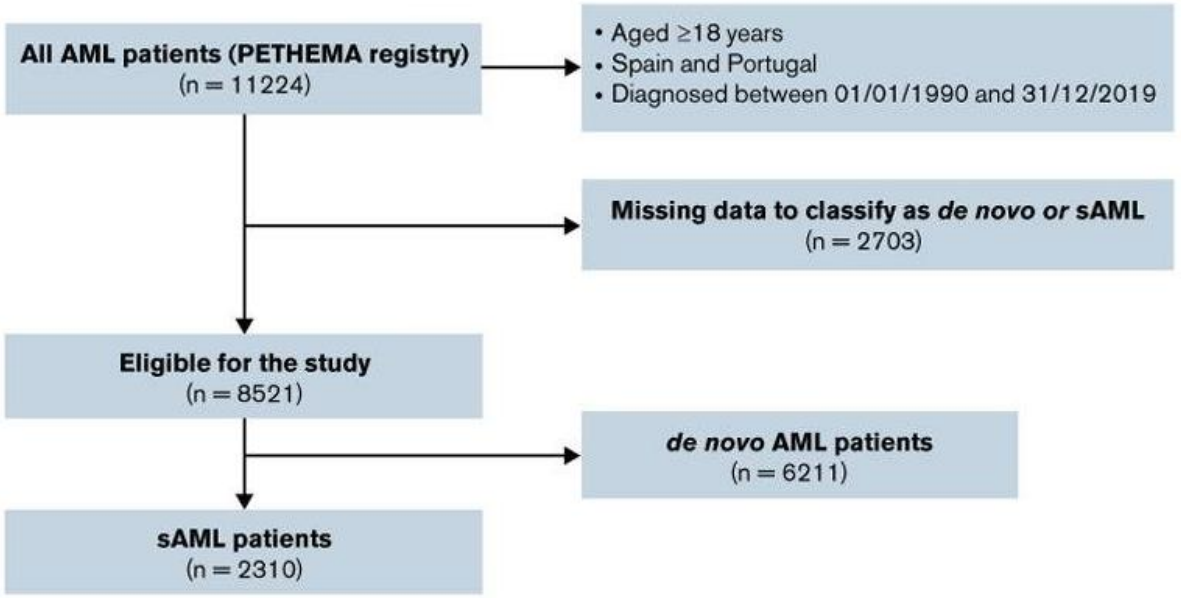


Bernal T, et al, in press

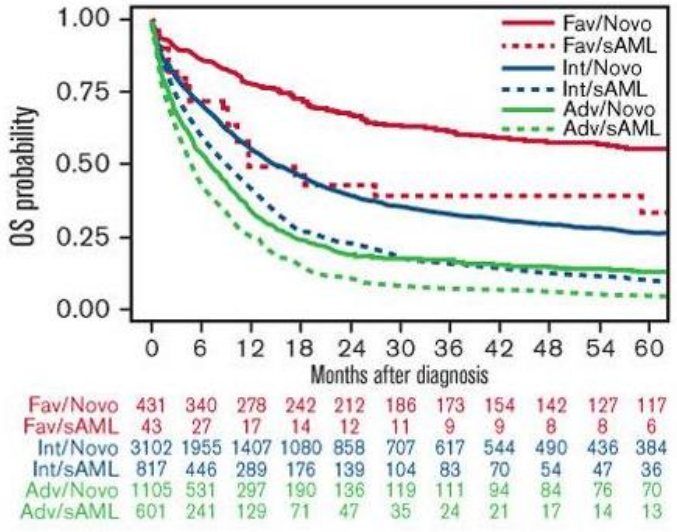
Secondary AML

Independent adverse prognostic factor (p=0.008)

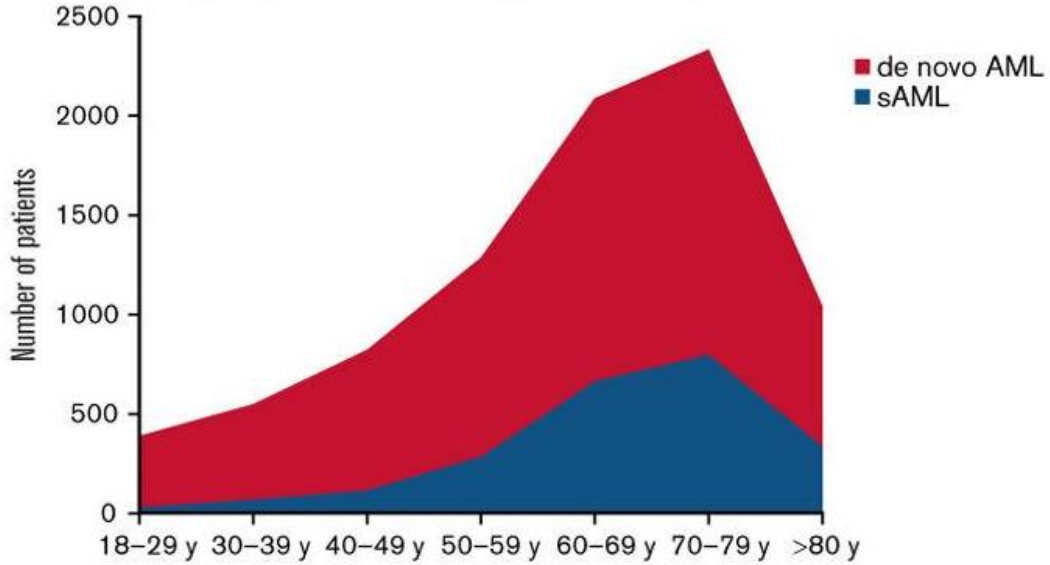




Worse survival independent of cytogenetic risk

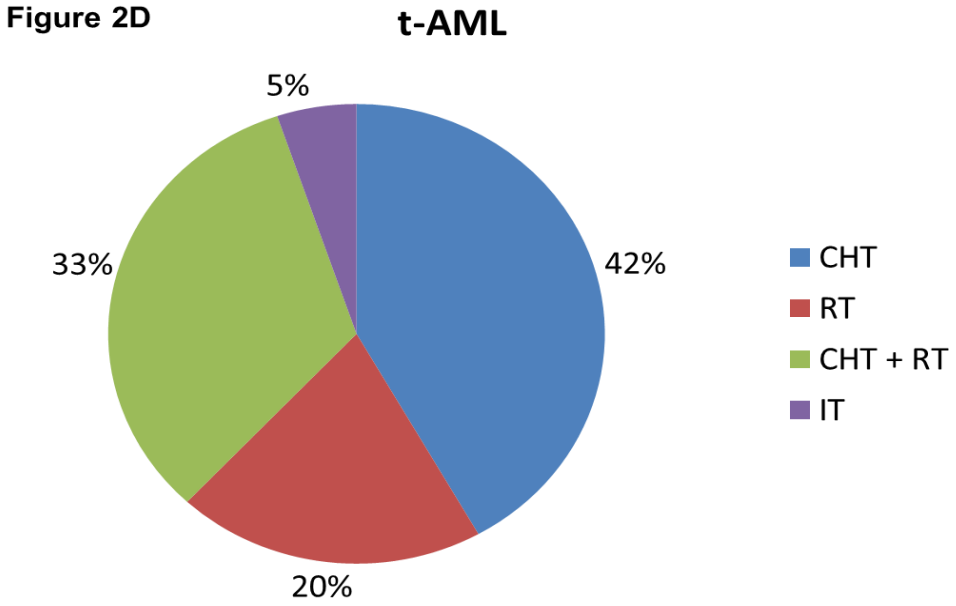


Higher prevalence among older AML patients



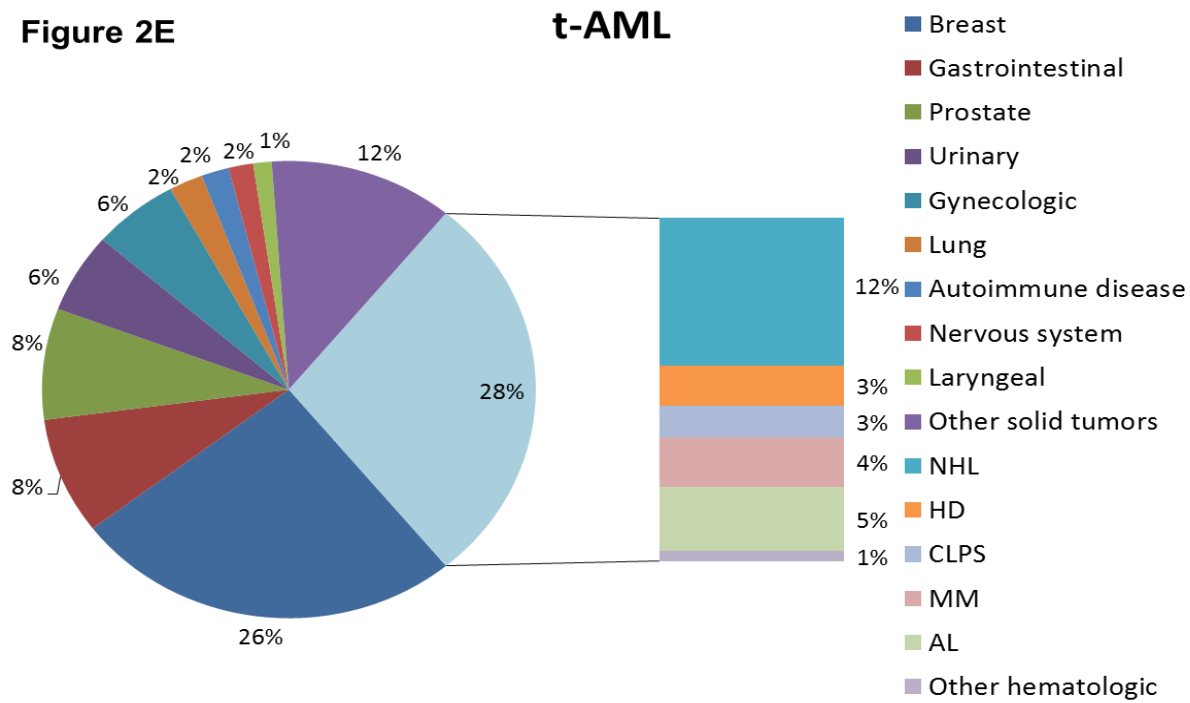
t-AML

Figure 2D



CHT: chemotherapy; RT: radiotherapy; IT: immunosupressive agent

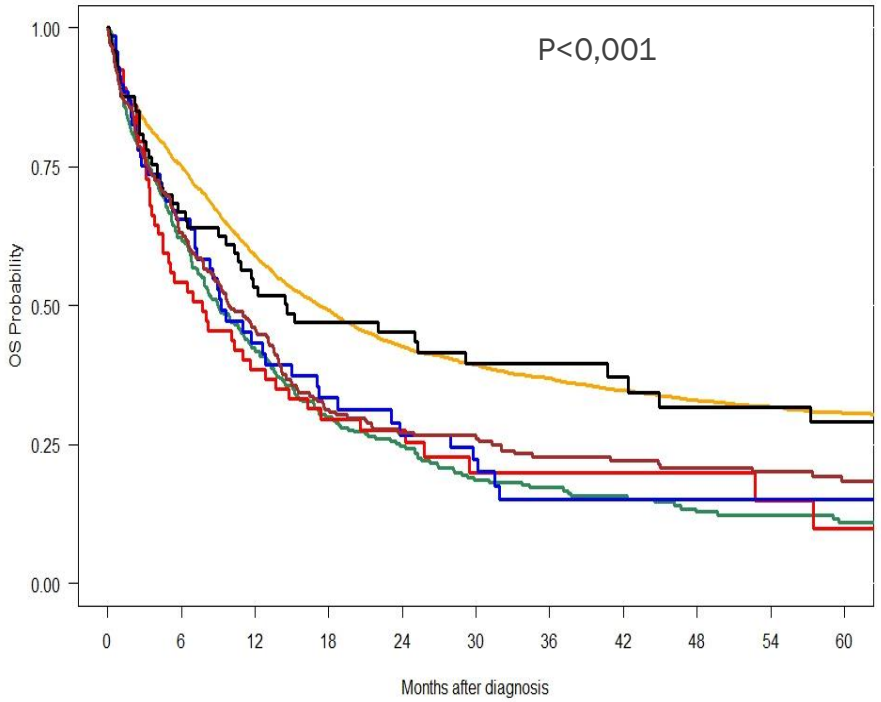
Figure 2E



NHL: Non-Hodgkin Lymphoma; HD: Hodgkin Disease; CLPS: Chronic lymphoproliferativesyndrome; MM: multiple myeloma; AL: acute leukemia.

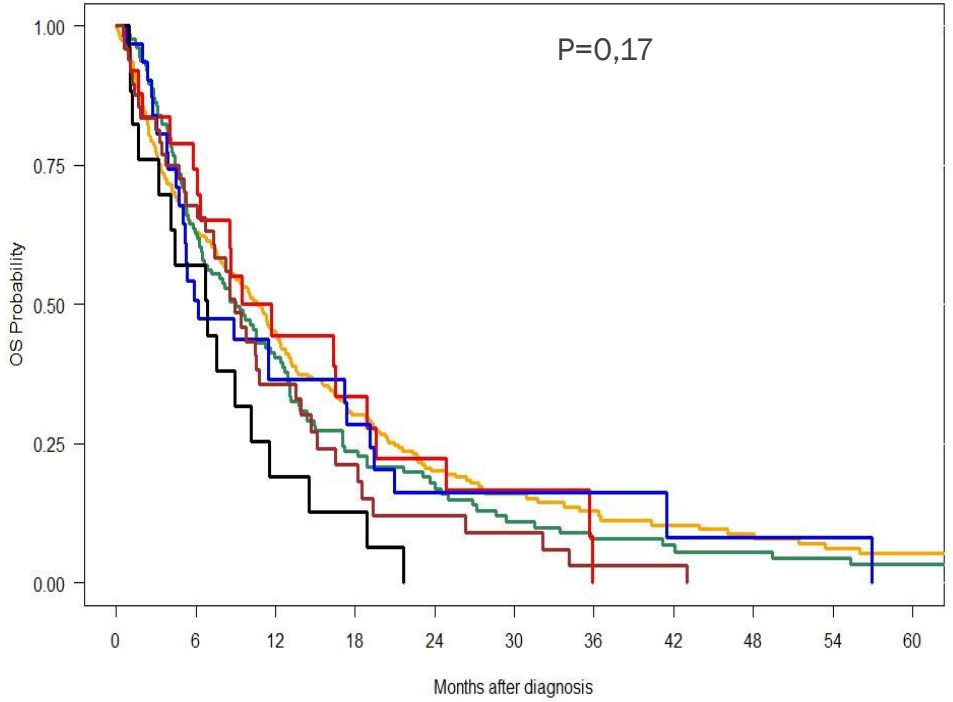
OS as per front-line therapy

Intensive



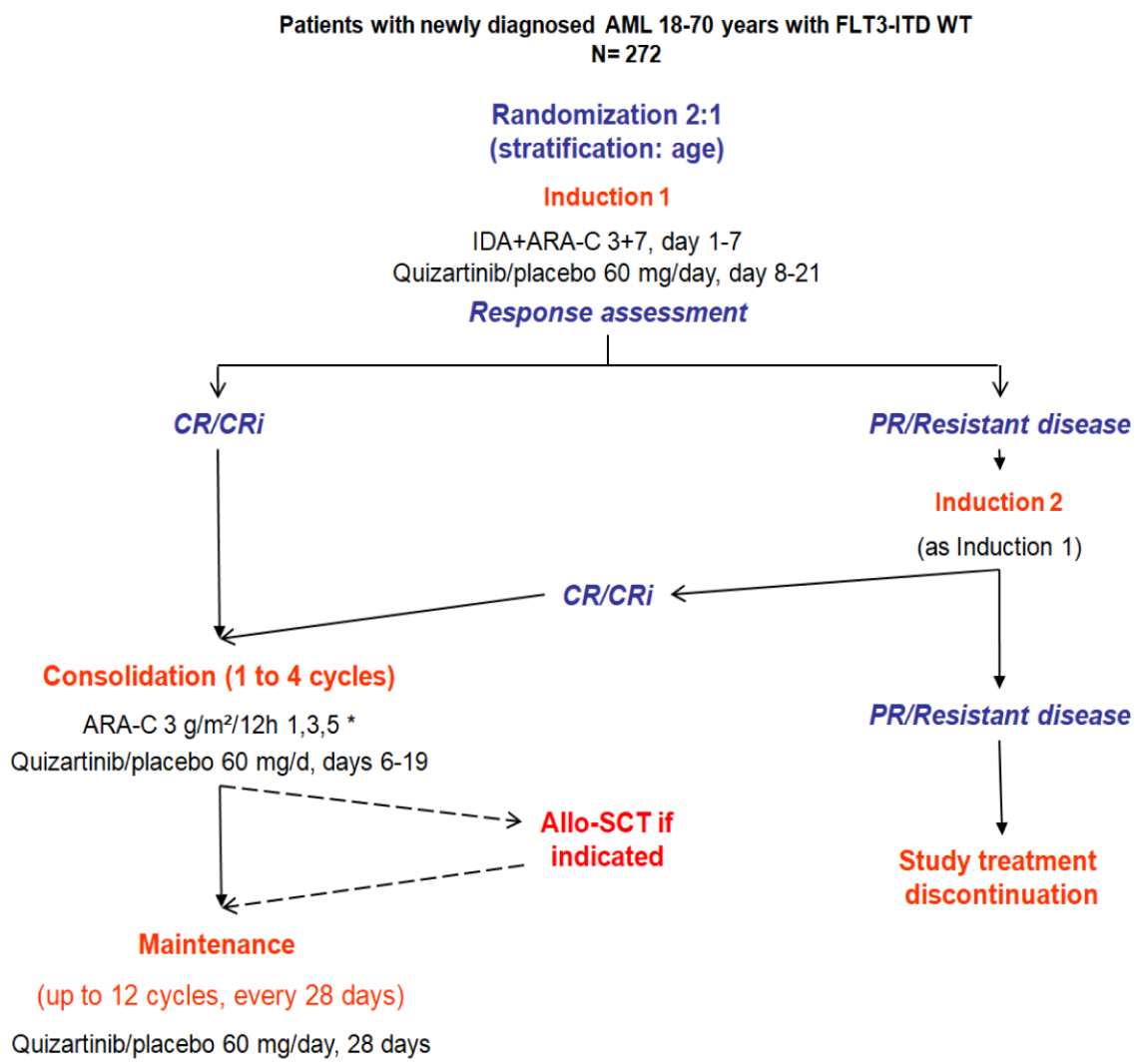
De novo	3744	2540	1836	1418	1142	975	877	775	698	635	573
MDS-AML	294	171	112	78	58	40	34	29	22	19	16
MDS/MPN-AML	66	31	22	15	12	7	6	4	4	3	1
MPN-AML	69	39	22	15	12	10	5	5	5	5	5
t-AML	261	147	97	63	51	47	38	35	28	24	21
Neo-AML	74	46	35	28	24	20	16	14	12	12	10

HMAs



De novo	452	207	126	63	37	22	16	12	10	7	5
MDS-AML	127	77	46	26	17	11	7	6	5	4	3
MDS/MPN-AML	27	16	8	6	4	3	0	0	0	0	0
MPN-AML	35	15	10	7	4	4	2	1	1	1	0
t-AML	51	29	14	7	4	3	1	1	0	0	0
Neo-AML	18	9	3	2	0	0	0	0	0	0	0

QUIWI trial: A 2:1 randomized phase II trial to compare the efficacy and safety of standard chemotherapy plus quizartinib versus standard chemotherapy plus placebo in adult patients with newly diagnosed FLT3 wild-type AML



* For subjects ≥60 years old: cytarabine 1.5 g/m²/12h 1,3,5

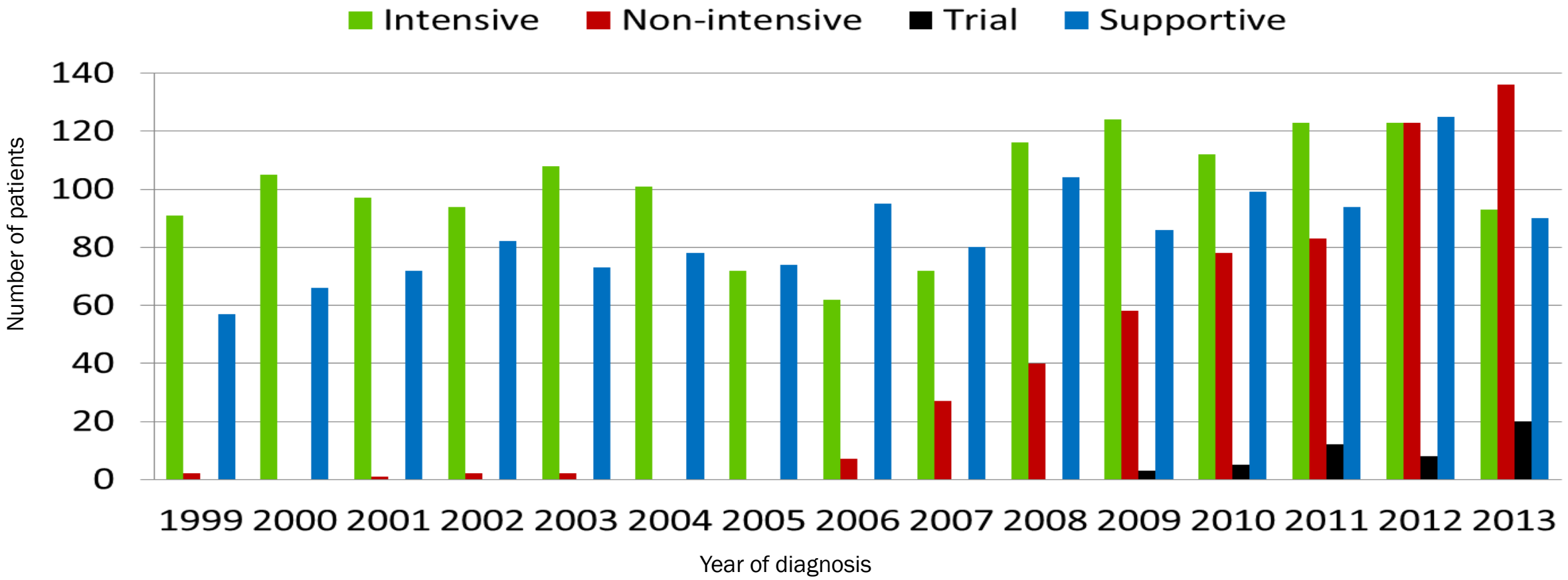
QUIWI Interim Analysis (first 100 patients): Response rates

	All patients	Quizartinib group	Placebo group	P-value*
Response after Induction 1, n (%)				0.889
ORR (CR + CRi)	66/89 (74.2)	46/61 (75.4)	20/28 (71.4)	0.690
CR	57	39	18	
CRi	9	7	2	
CR/CRi with MRD neg.	39/89 (43.8)	28/61 (45.9)	11/28 (39.3)	0.559
PR	9	5	4	
MLFS	2	2	0	
Resistance	12	8	4	
Response after 1 or 2 cycles of Induction, n (%)				
ORR (CR + CRi)	74/89 (83.1)	50/61 (82)	24/28 (85.7)	0.768
CR/CRi with MRD neg.	46/89 (51.7)	31/61 (50.8)	15/28 (53.6)	0.809
CR/CRi with MRD neg. after Consolidation 2, n (%)	25/34 (73.5)	16/23 (69.6)	9/11 (81.8)	0.682

QUIWI Interim Analysis (first 100 patients): Early mortality and relapse rate

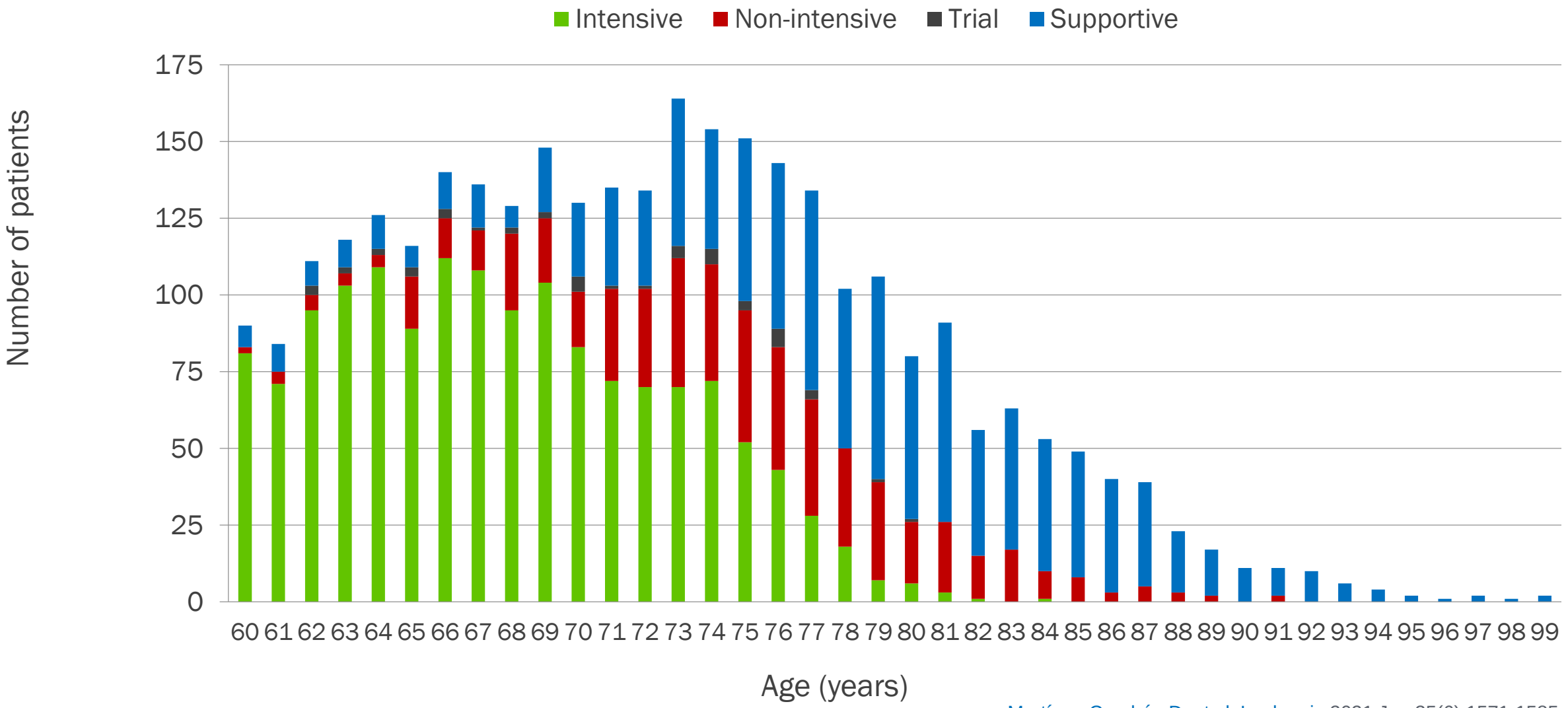
	All patients	Quizartinib group	Placebo group	P-value*
Early mortality (<60d)	9/96 (9.4)	3/64 (4.7)	6/32 (18.8)	0.056
Relapse	10/100	7/67 (10.4)	3/33 (9.1)	1.000
Relapse after maintenance	2/18	1/13 (7.7)	1/5 (20)	0.490

Evolving treatment patterns in older AML (PETHEMA 2000-2014)



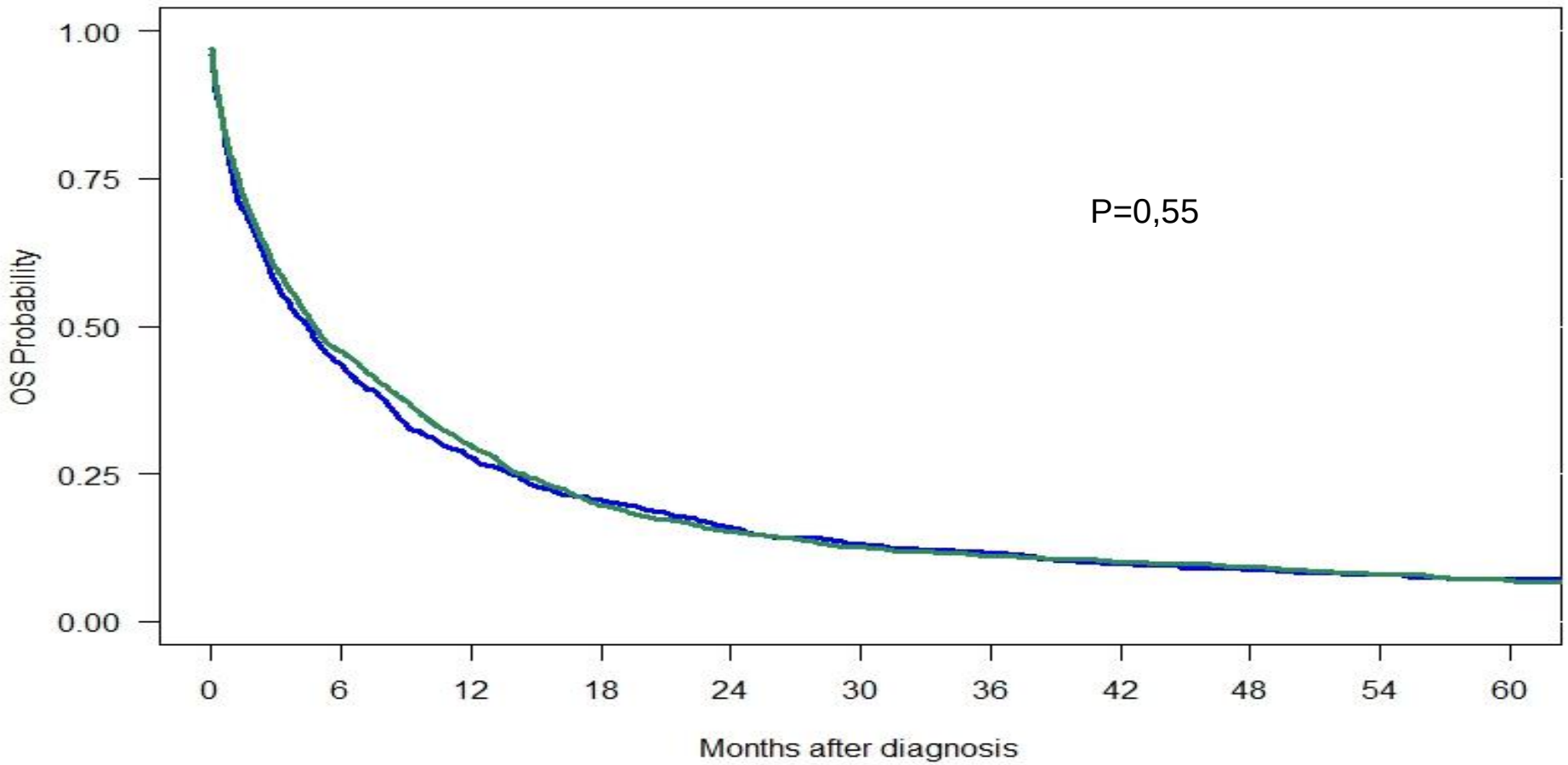
Leukemia 2021 Jun;35(6):1571-1585.

Treatment patterns in >60 yo AML



Martínez-Cuadrón D, et al. Leukemia 2021 Jun;35(6):1571-1585.

OS per period (N=3.637)



1999-2006	1267	482	304	221	168	137	121	102	88	80	67
2007-2013	2370	881	540	336	250	200	169	153	132	101	79

cancers

MDPI

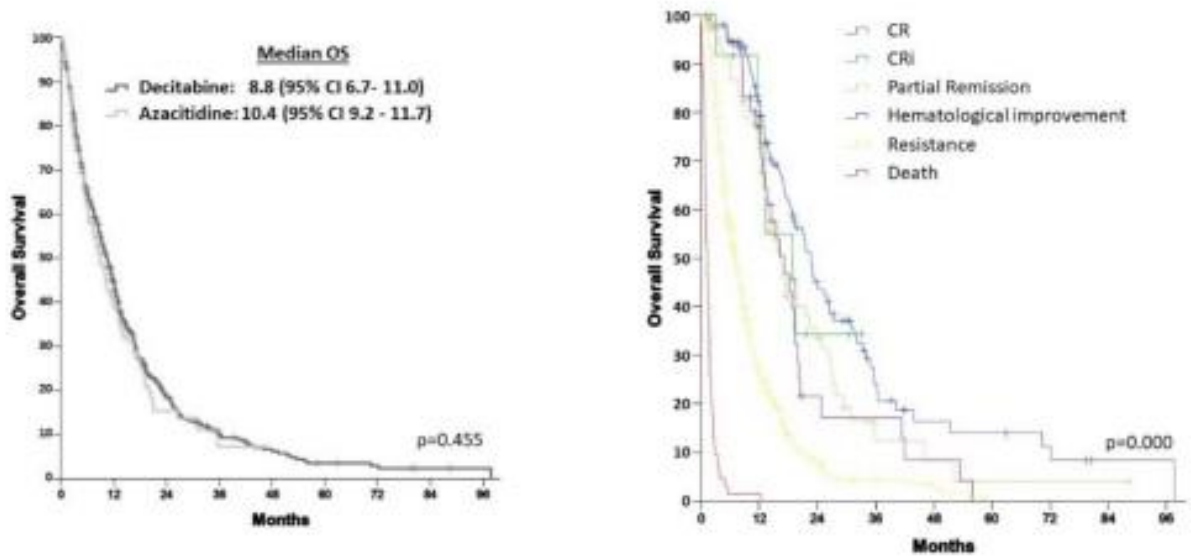
Submit to SI "Acute Myeloid Leukemia (AML)"

Article

Azacitidine vs decitabine in unfit newly diagnosed acute myeloid leukemia patients: results from the PETHEMA registry

Jorge Labrador[1*], David Martínez-Cuadrón[2], Adolfo de la Fuente[3], Rebeca Rodríguez-Veiga[4], Josefina Serrano[5], Mar Tormo[6], Eduardo Rodriguez-Arboli[7], Fernando Ramos[8], Teresa Bernal[9], María López-Pavía[10], Fernanda Trigo[11], María Pilar Martínez-Sánchez[12], Juan-Ignacio Rodríguez-Gutiérrez[13], Carlos Rodríguez-Medina[14], Cristina Gil[15], Daniel García Belmonte[16], Susana Vives[17], María-Ángeles Foncillas[18], Manuel Pérez-Encinas[19], Andrés Novo[20], Isabel Recio[21], Gabriela Rodríguez-Macías[22], Juan Miguel Bergua[23], Víctor Noriega[24], Esperanza Lavilla[25], Alicia Roldán-Pérez[26], Miguel A. Sanz[27] and Pau Montesinos[28*] (on behalf of PETHEMA group).

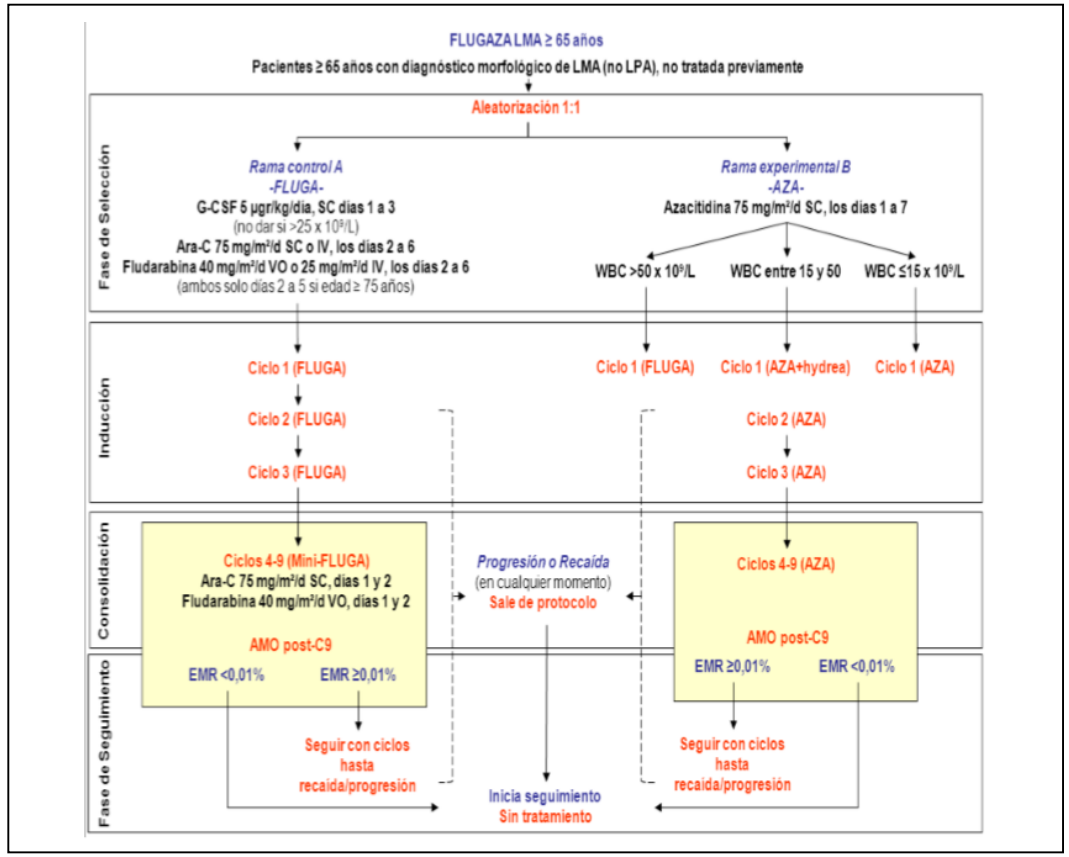
assessment ($p = 0.000$), Figure 4b.



(a) (b)

Figure 4. (**a**) Overall survival among patients treated with azacitidine vs. decitabine; (**b**) Overall survival according to response. CR, complete remission; CRi, complete remission with incomplete blood count recovery; OS, overall survival; PR, partial remission.

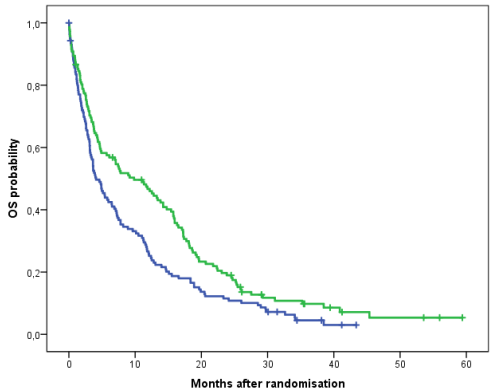
FLUGAZA trial



Median OS (95%CI) months, AZA (n=142): 9.8 (5.6, 14)

Median OS (95%CI) months, FLUGA (n=141): 4.1 (2.7, 5.5)

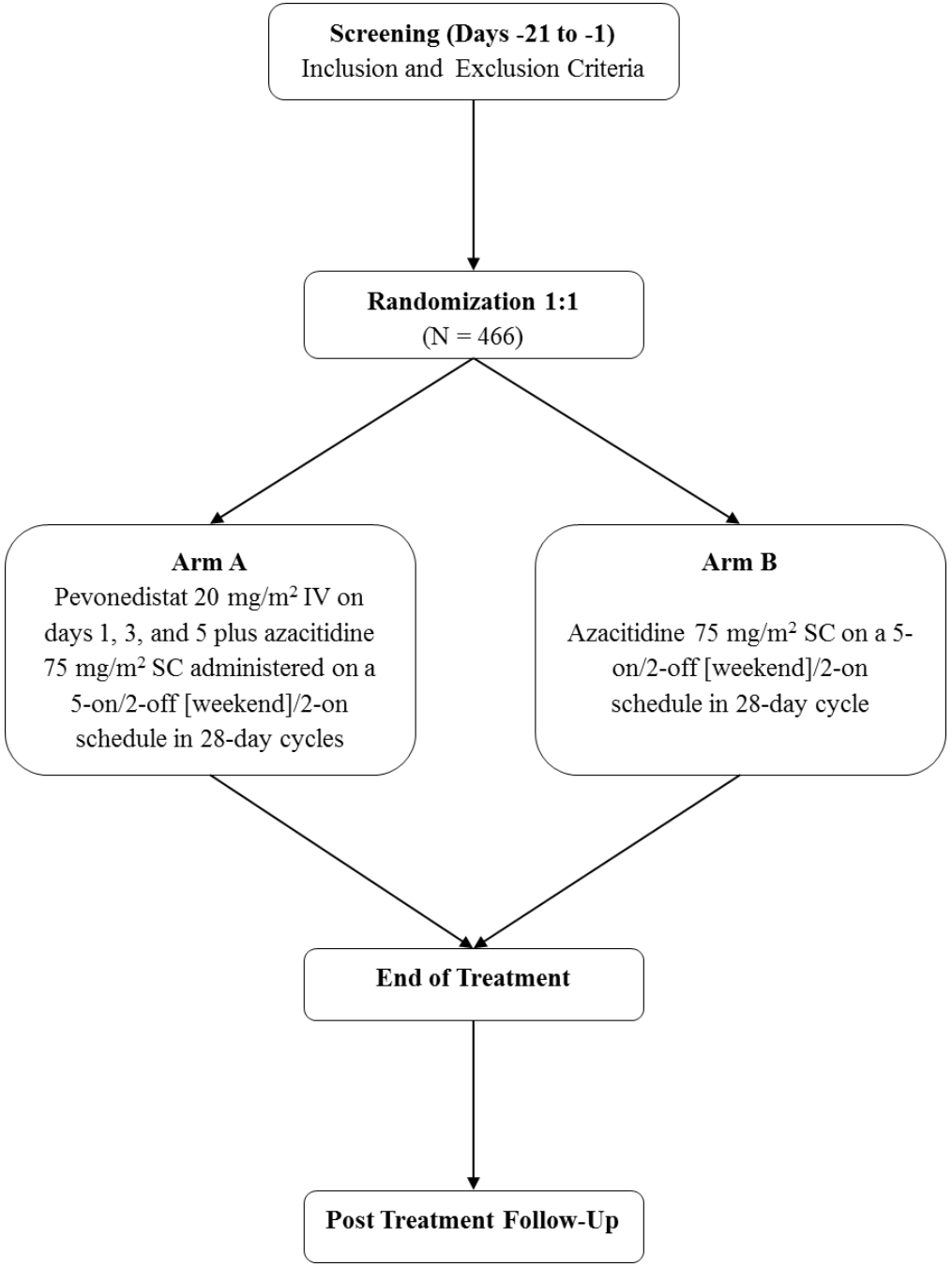
P=0.005



Vives S, et al. Cancer 2021;127:2003-2014.

PEVOLAM Study design

- N = 466
- Enrollment period: 24 months
- Follow-up: 19 months
- Number of institutions: 55
- Study periods
  - Screening
  - Treatment
  - Post Treatment Follow-Up



PRELIMINARY RESULTS OF VEN-A-QUI STUDY: A PHASE 1-2 TRIAL TO ASSESS THE SAFETY AND EFFICACY OF THE COMBINATION OF AZACITIDINE OR LOW-DOSE CYTARABINE WITH VENETOCLAX AND QUIZARTINIB IN NEWLY DIAGNOSED

Juan Miguel Bergua-Burgues[1], Rebeca Rodríguez-Veiga[2], Isabel Cano[2], Ferrán Vall-llovera[3], Antoni García-Guiñon[4], Joaquín Gómez-Estruch[5], Mercedes Colorado[6], Ignacio Casas-Avilés[1], Jordi Esteve-Reyner[7], María V Verdugo[8], Fernando Ramos[9], Marta Valero[10], Evelyn Acuña-Cruz[2], Blanca Boluda[2], Laura Torres-Miñana[2], Joaquín Martínez-López[11], Eva Barragán[2], Rosa Ayala[11], David Martínez-Cuadrón[2], Pau Montesinos[2]
[1]Hospital San Pedro de Alcántara, Cáceres, [2]Hospital Universitari i Politècnic La Fe, Valencia, [3]Hospital Universitari Mútua Terrassa, Barcelona, [4]Hospital Arnau de Vilanova, Lleida, [5]Hospital Clinico Universitario Virgen de la Arrixaca, Murcia, [6]Hospital Marqués de Valdecilla, Santander, [7]Hospital Clinic Barcelona, Barcelona, [8]Hospital de Jerez, Jerez de la Frontera, [9]Hospital Clinico de León, León, [10]Hospital Arnau de Vilanova, Valencia, [11]Hospital 12 de Octubre, Madrid, Spain

INTRODUCTION

Venetoclax (VEN) combined with Azacitidine (AZA) or Low Dose Cytarabine (LDAC) has emerged as new therapeutic option for unfit acute myeloid leukemia (AML) patients (pts), but primary resistance is observed in roughly 40% of them, while relapses occur in the vast majority. We speculate that adding a FLT3-ITD inhibitor could improve the complete remission (CR) and overall survival (OS) rates in this setting.

OBJECTIVE

To explore the safety and efficacy of VEN-AZA or VEN-LDAC regimens in combination with Quizartinib (QUI) (VEN-A-QUI trial; EUDRACT2020-000406-28).

METHODS

The target population comprised newly diagnosed patients aged ≥ 60 years old unfit for intensive treatment, including those with secondary AML, with or without prior exposure to AZA. The Phase I consisted in two arms, one with AZA (Arm A) and the other with LDAC (Arm B) plus VEN combined with QUI to establish the recommended phase 2 dose (RP2D) of both triplets. Phase 1 scheme was based in 3+3 cohorts of patients observing cycle 1 dose limiting toxicities.
Once established the RP2D the phase 2 comprised randomized 1:1 assignment of 60 patients (48 FLT3 wild type and 12 FLT3-ITD mut) to VEN-AZA-QUI vs. VEN-LDAC-QUI, comparing the CR/CRi rate of both arms. Secondary objectives
were to evaluate the CR/CRi after cycle 1 and 4, compare OS and RFS between both triplets, quality of life, medical resources, exploration of biomarkers, and immune recovery.

RESULTS

Data cut-off for preplanned interim analysis included 57 patients screened and 45 enrolled, 16 in phase 1 and 29 in phase 2.
Median age was 76,5 years (range 67-87), males/females (28/23). Previous MDS or MPN was present in 28 patients (59%); and 22 (48%) had previous treatment with AZA for MDS or MPN phase.
We included 16 patients in phase 1, 9 with AZA and 7 with LDAC. RP2D of QUI was 60 mg in AZA arm and 40 mg in LDAC arm. No DLT was observed in arm B, and in arm A a brain hemorrhage after more than 40 days of thrombocytopenia at dose of 60 mg.

RESULTS (Cont)

The safety committee recommended performing an early (day 14-21) bone marrow assessment in cycle 1, leading to VEN interruption in case of aplastic morphology with grade 4 neutropenia or thrombocytopenia. No grade ≥3 related non-hematological adverse events (AEs) were noted during phase 1. The most frequent non-hematological serious AEs during phase 1 were infections (n=23), and gastrointestinal (n=20). No grade 3 QTc prolongation was observed.
Objective responses were CR+CRh+CRi 7 patients (44%), PR 1 (6%), death 4 (25%), and resistance/progression 4 (25%).
Twenty-nine patients (4 with FLT3-ITD mut) were enrolled in the phase 2 (15 in AZA and 14 in LDAC Arm). A median of 1 cycle (range 1-4) was administered at data cut-off, with best response among 24 evaluable patients: CR+CRh+CRi 10 (42%), MLFS in 3 (12%), PR 5 (21%), death 4 (17%), and resistance/progression 2 (8%). The overall response (CR+CRh+CRi+MLFS) was 54%. The more frequent non-hematological AEs were infections (n=35) and gastrointestinal
(n=31). Two cardiac failures, 1 chest pain and 1 atrial fibrillation were noted in phase 2 (all of them unrelated to VEN or QUIZ). No grade 3 QTc prolongation was observed.

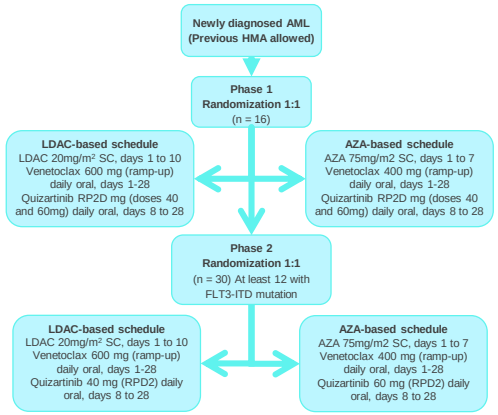


Figure 1. Study design

	Phase 1 N (%)	Phase 2 N (%)	Overall study N (%)
CR + CRh + CRi	7 (44)	10 (42)	17 (43)
MLFS	-	3 (12)	3 (8)
PR	1 (6)	5 (21)	6 (15)
Death	4 (25)	4 (17)	8 (20)
Refractory	4 (25)	2 (8)	6 (15)

Table 1. Response rates

CONCLUSION

This interim report shows an overall response rate of 54% using triplets (VEN-AZA-QUI or VENLDAC-QUI) for newly diagnosed unfit AML patients. However, substantial toxicity and early death cases were observed. Of note, 59% of enrolled patients had secondary AML, and 48% was exposed to AZA before inclusion. Final analyses with more patients and follow-up will clarify the efficacy and tolerability of these triplets.

ACKNOWLEDGEMENTS

This study was supported by daiichi sankyo, inc. and Abbvie

All authors contributed to and approved the presentation

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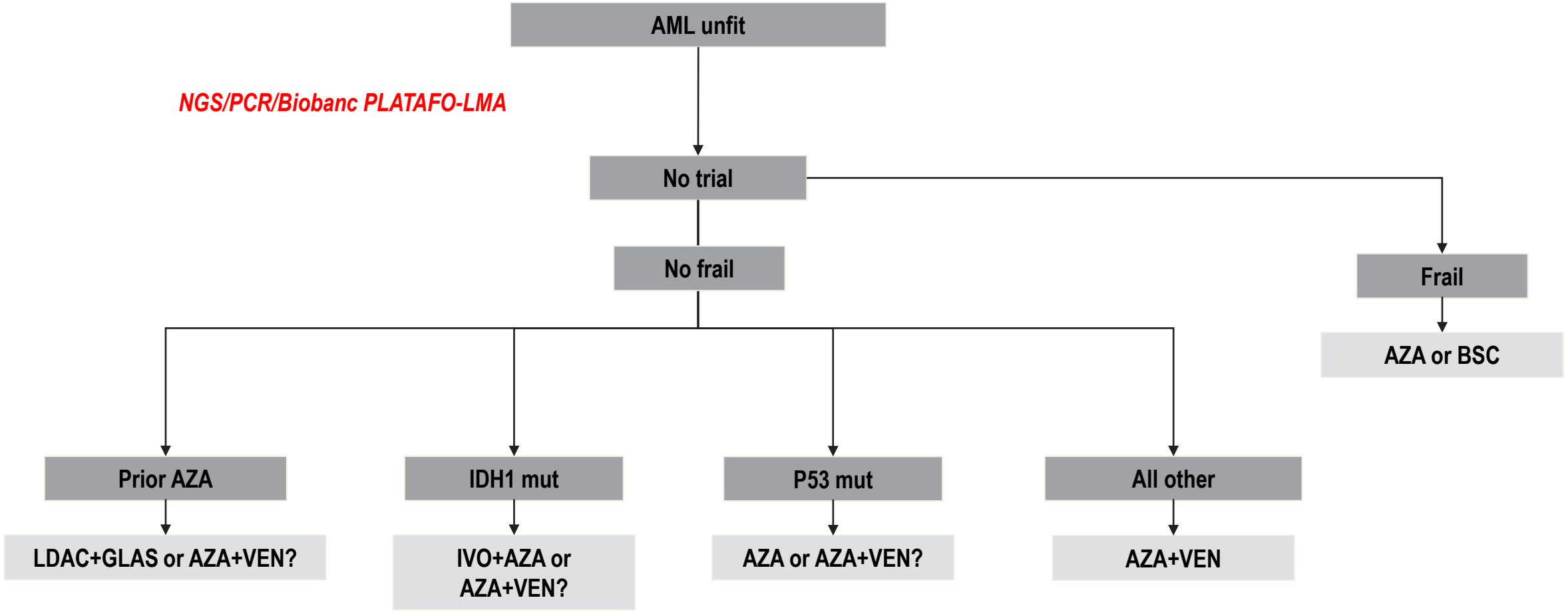
- DiNardo CD, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. N Engl J Med. 2020;383:617–629.

Contact information: Juan Miguel Bergua Burgues jmberguaburg@gmail.com

PETHEMA AML-UNFIT guidelines



Prognostic scoring systems for patients with R/R AML: GOELAMS score[1]

Factor		Points
CR1 duration	≥12 months	0
	≤12 months (refractory / early relapse)	1
***FLT3*-ITD status**	Negative	0
	Positive	1
Cytogenetics*	Favourable / intermediate	0
	High risk	1

Prognostic scoring systems for patients with R/R AML: European Prognostic Index score[2]

Factor		Points
CR1 duration	>18 months	0
	7–18 months	3
	≤6 months	5
Cytogenetics at diagnosis	t(16;16) or inv16	0
	t(8;21)	3
	Other	5
Age at relapse	≤35 years	0
	36–45 years	1
	>45 years	2
SCT before first relapse	No	0
	Yes	2

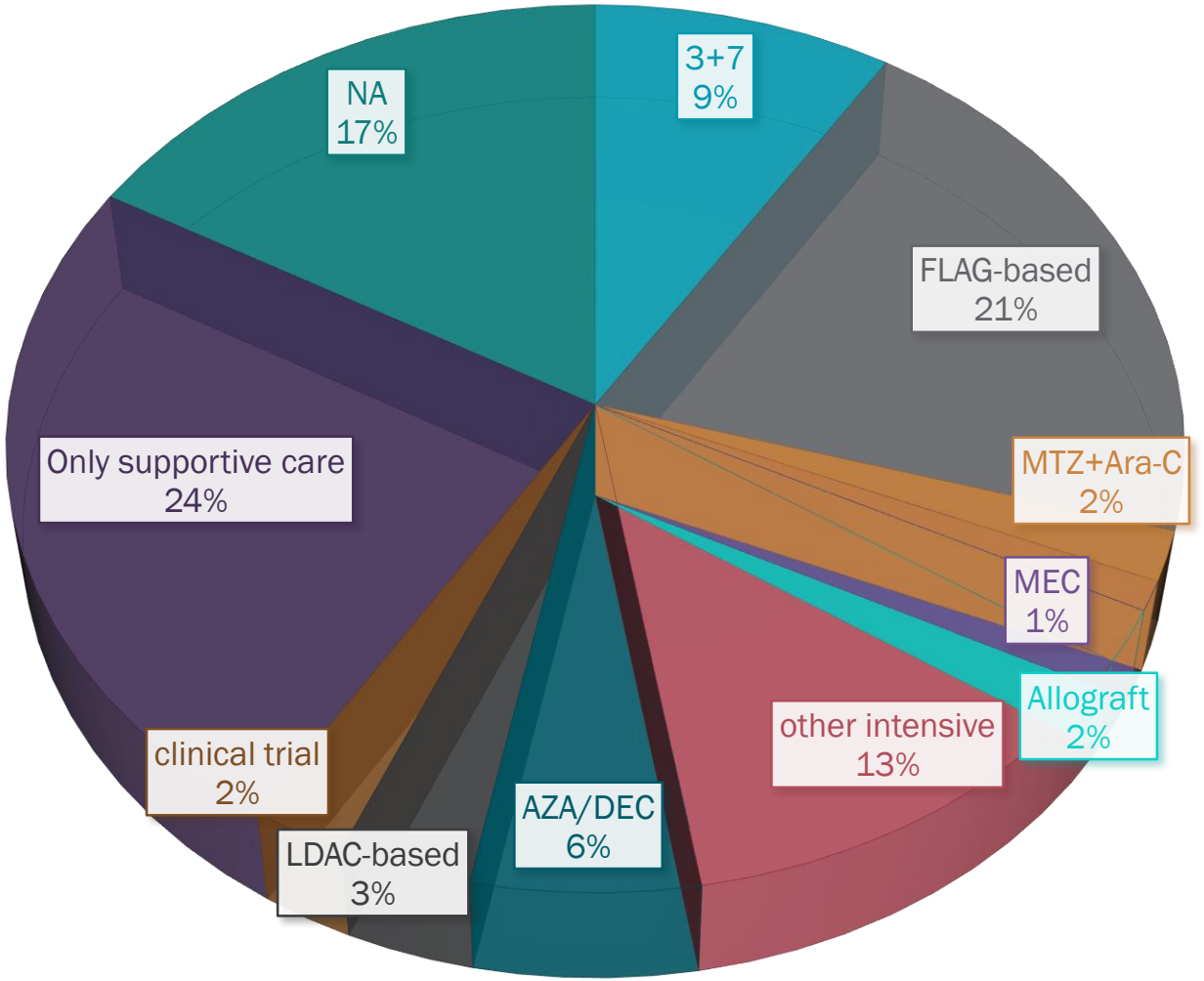
Prognostic scoring systems for patients with R/R AML: SALFLAGE score[3]

Factor		Points
***FLT3*-ITD**	*FLT3+*	1
Previous SCT	No SCT	1
	Autologous SCT	1
	Allogeneic SCT	0
Modified MRC cytogenetics	Favourable	0
	Intermediate	2
	Adverse	4
RFI	Resistant	2
	RFI <1 year	4
	RFI >1 year	0

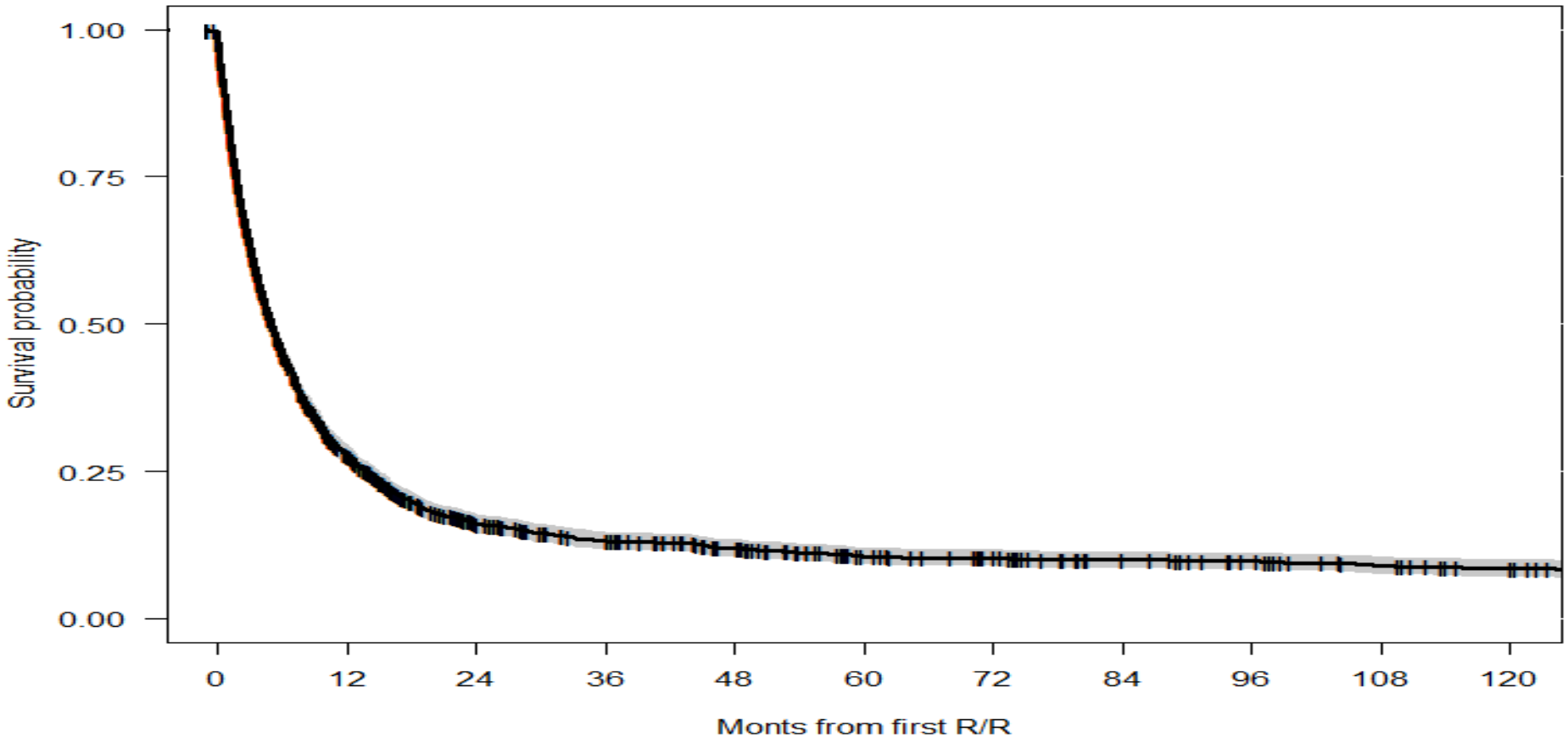
***Defined according to MRC data; CR1, first complete remission; MRC, Medical Research Council; RFI, relapse-free interval; SCT, stem cell transplantation**

1. Chevallier P, et al. *Leukemia* 2011;25:939–944; 2. Breems DA, et al. *JCO* 2005;23:1969–1978; 3. Bergua JM, et al. *Br J Haematol* 2016;174:700–710.

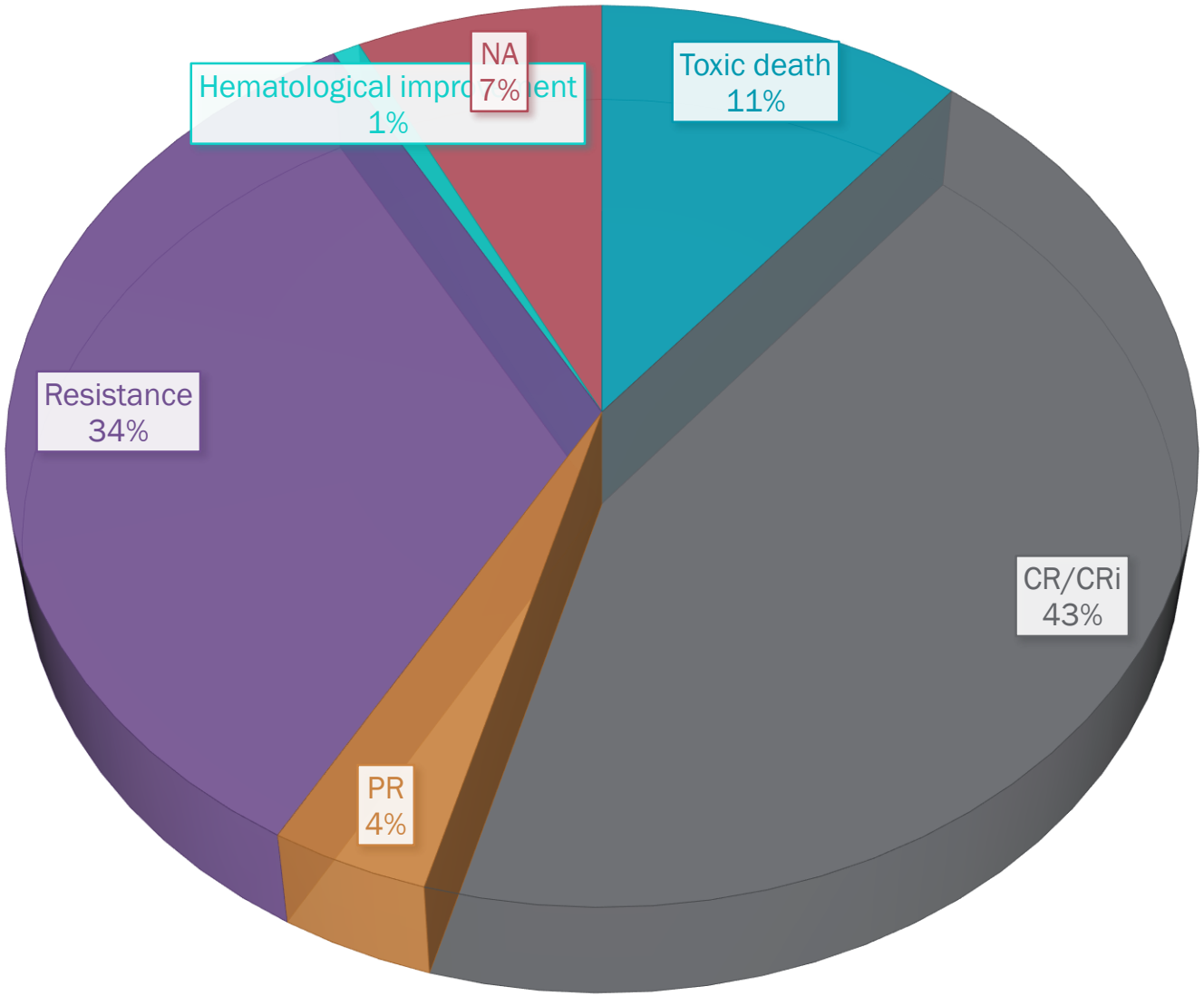
AML registry: Second line approach (n=2702)



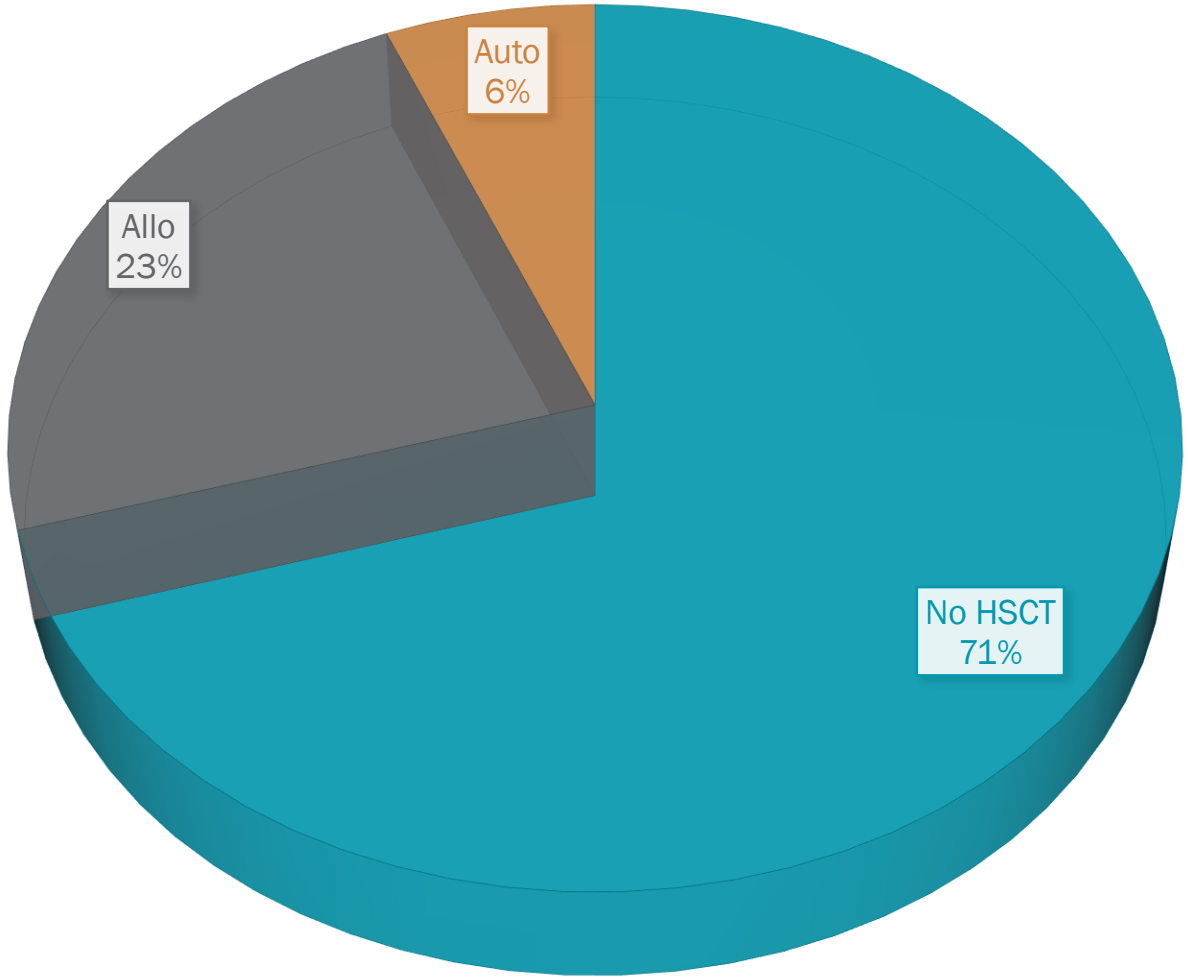
OS of the entire cohort (4.9 months)



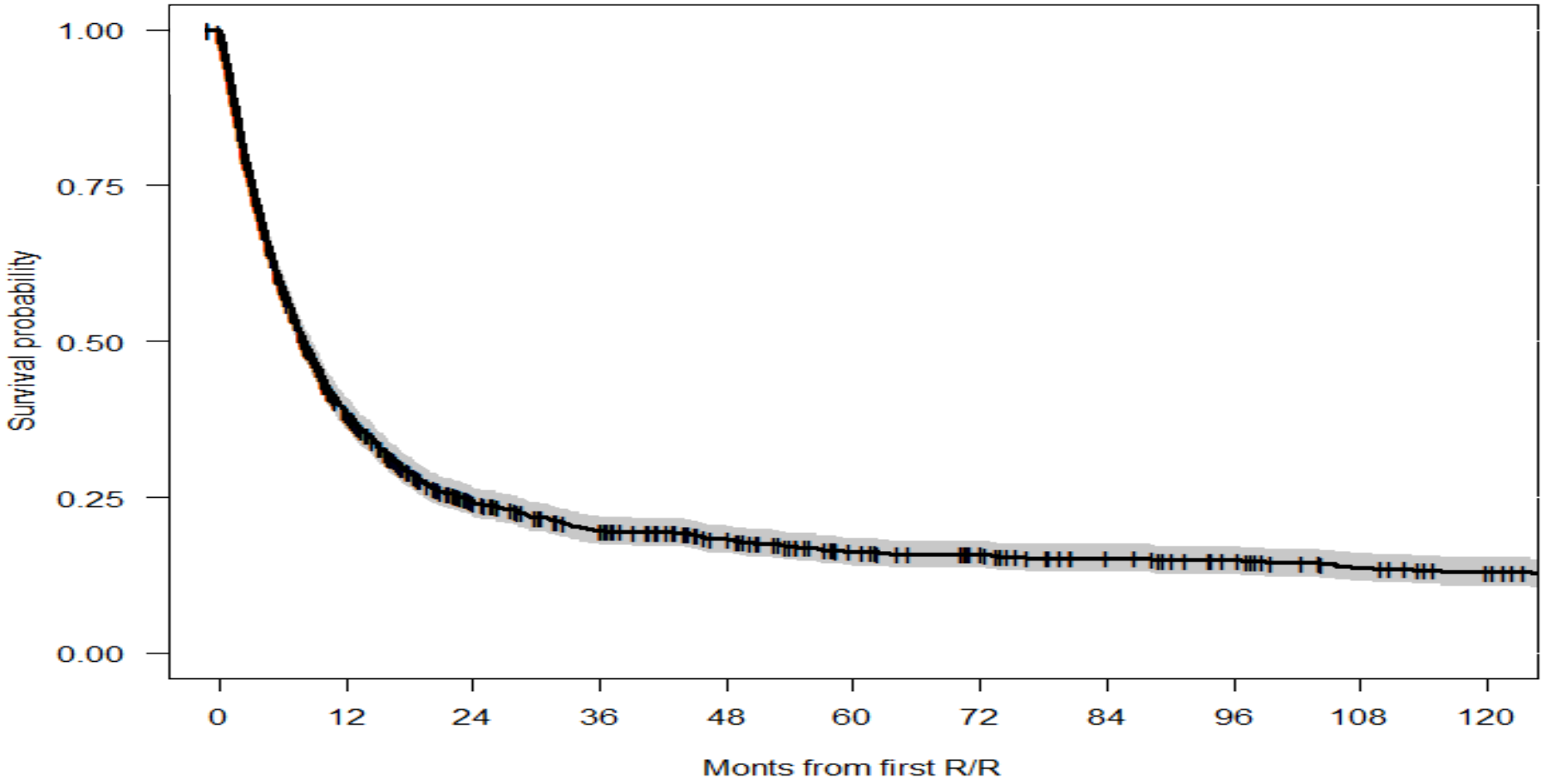
Response to second line (n=1596)



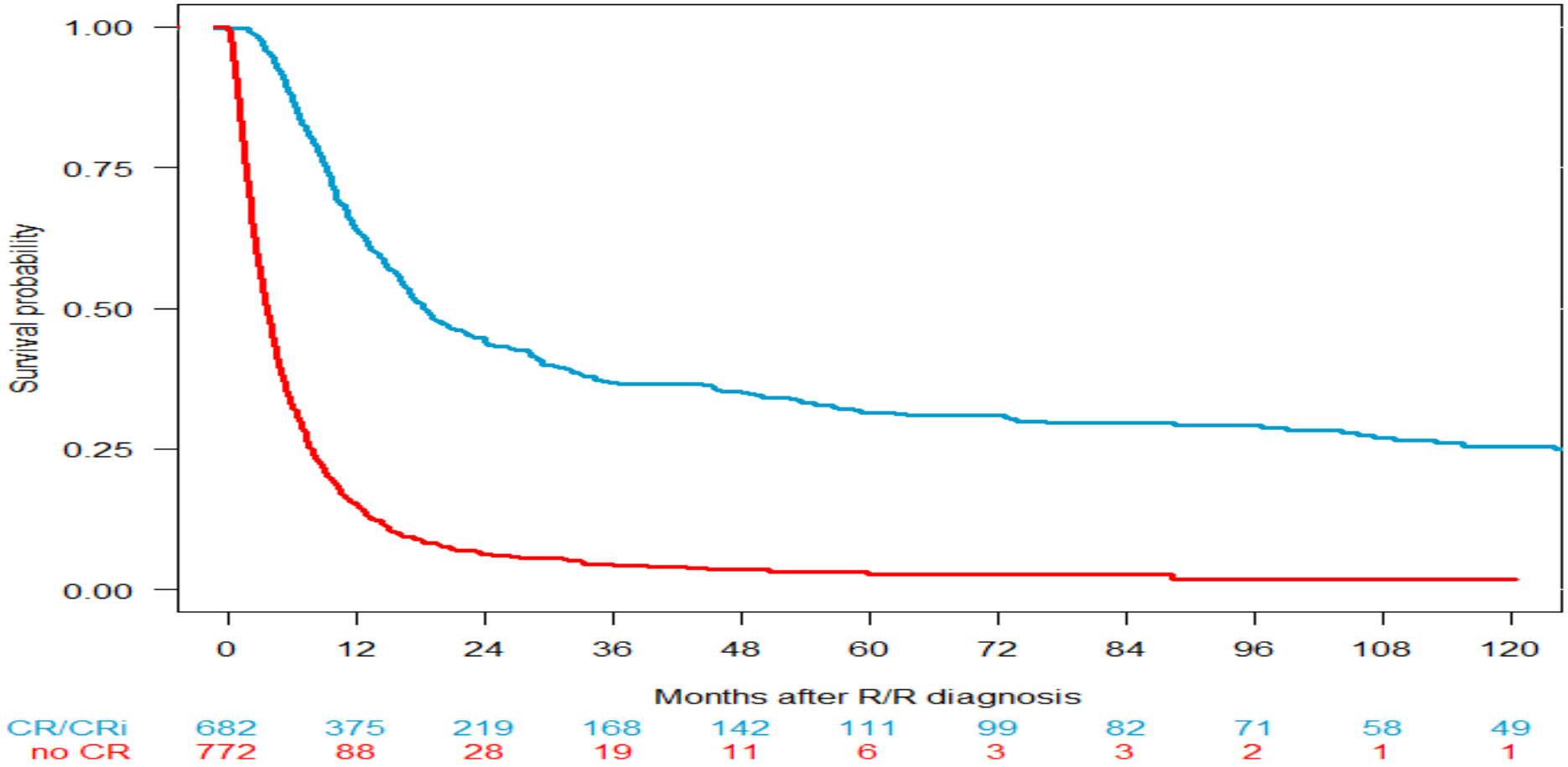
HSCT after second line (n=1596)



Median OS of treated patients = 8 months



CR vs no CR (<0.001)



Use of Venetoclax in Patients with Relapsed or Refractory Acute Myeloid Leukemia: The PETHEMA Registry Experience.

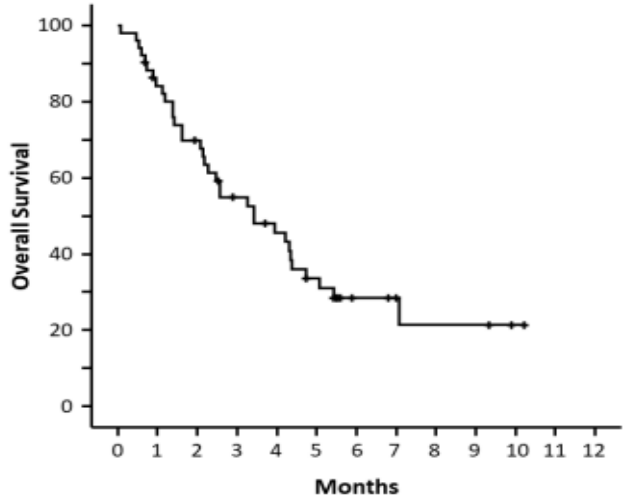
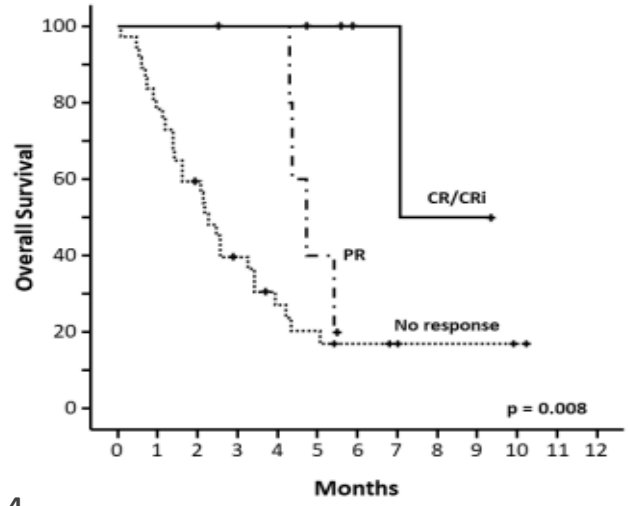
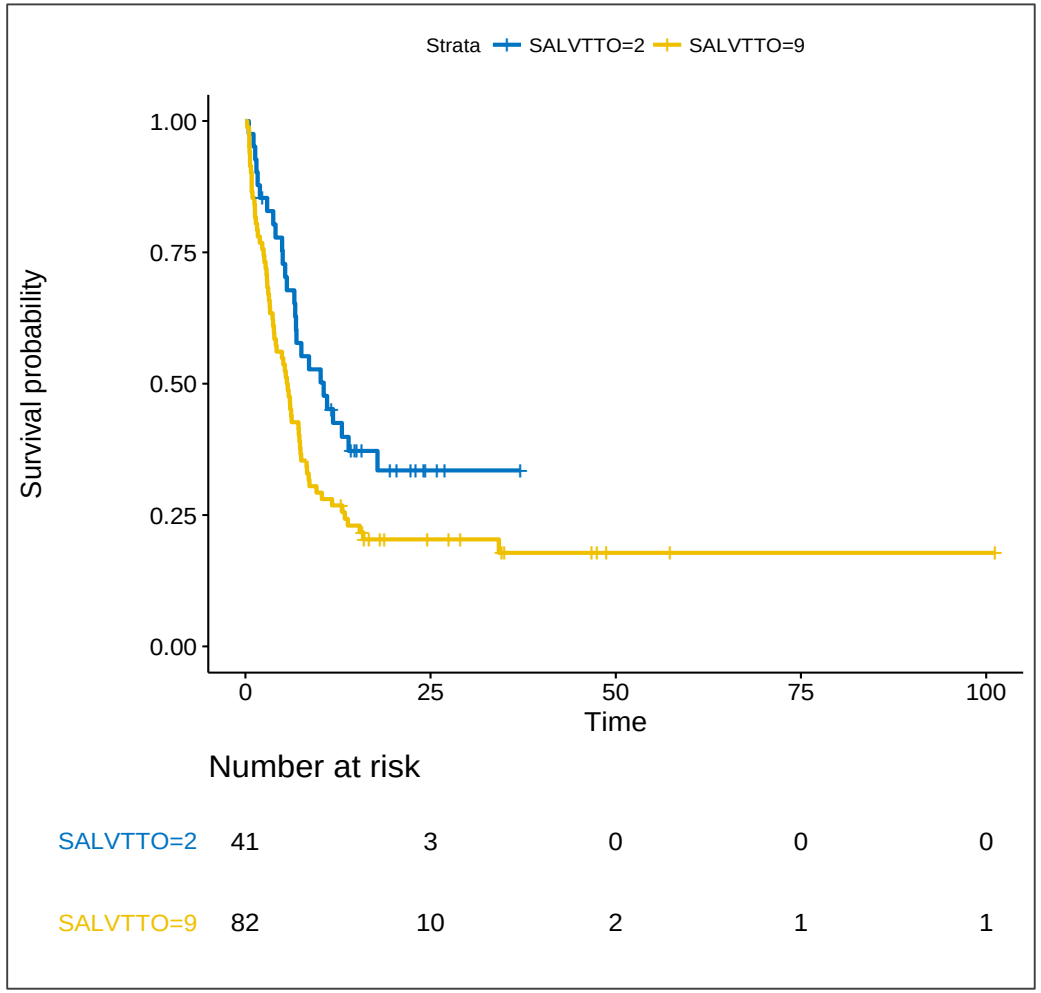


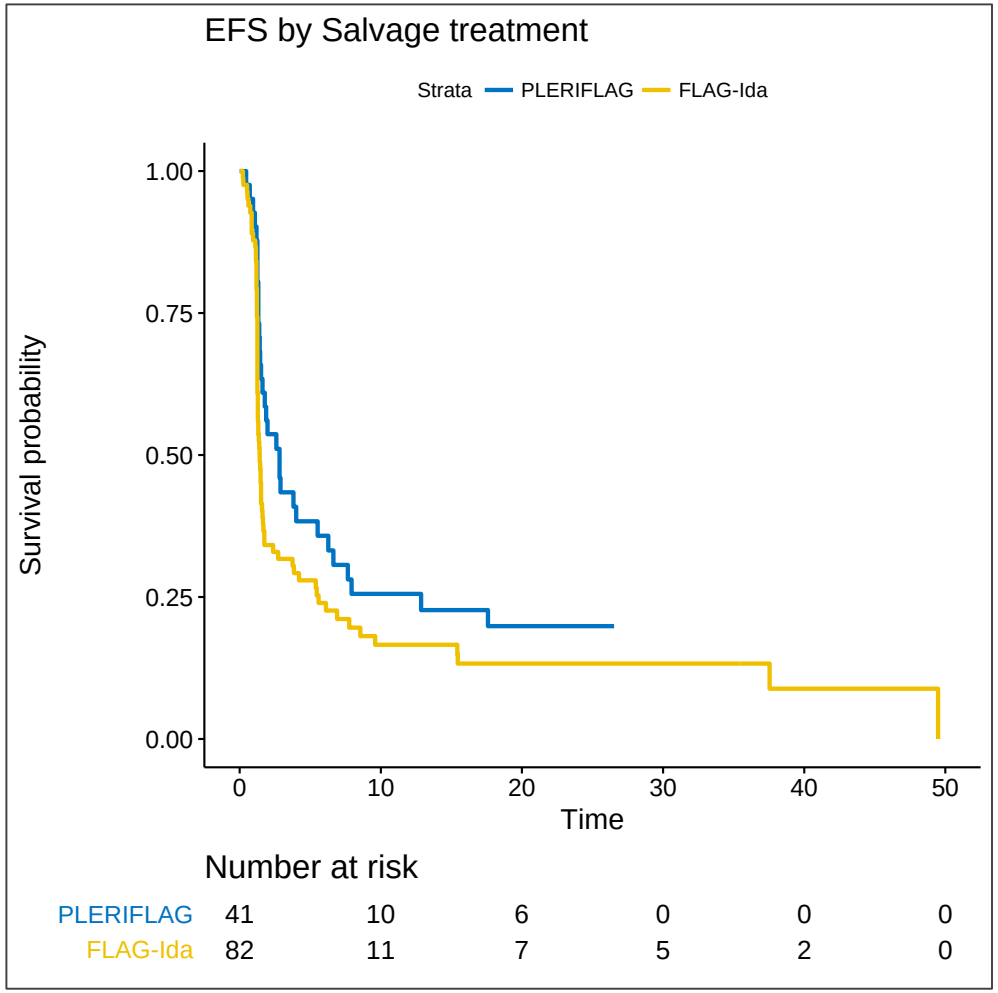
Figure 1. Overall survival from the start of venetoclax.



Labrador J, et al Cancers (Basel). 2022 Mar 29;14(7):1734

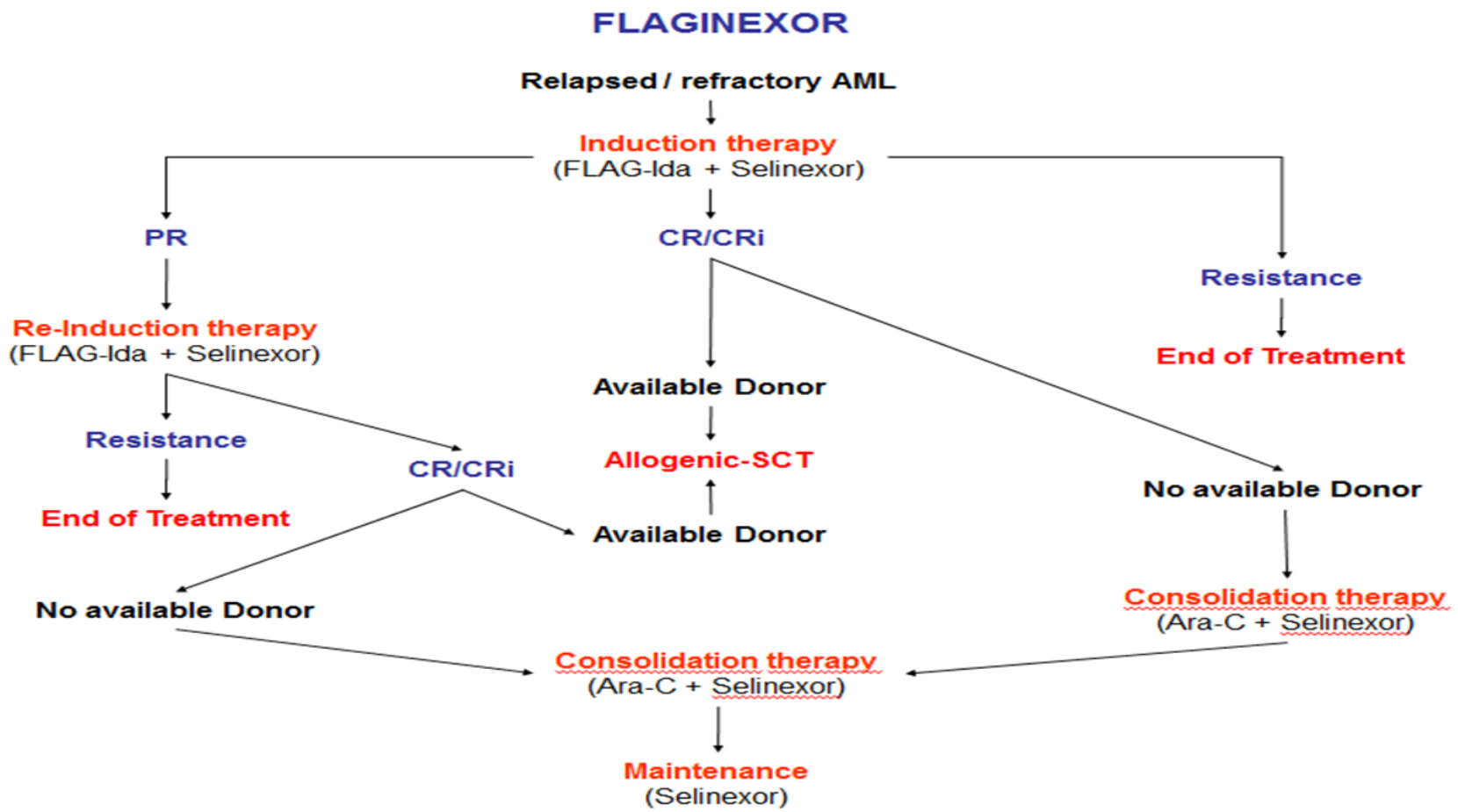
A phase I–II study of plerixafor in combination with fludarabine, idarubicin, cytarabine, and G-CSF (PLERIFLAG regimen) for the treatment of patients with the first early-relapsed or refractory acute myeloid leukemia





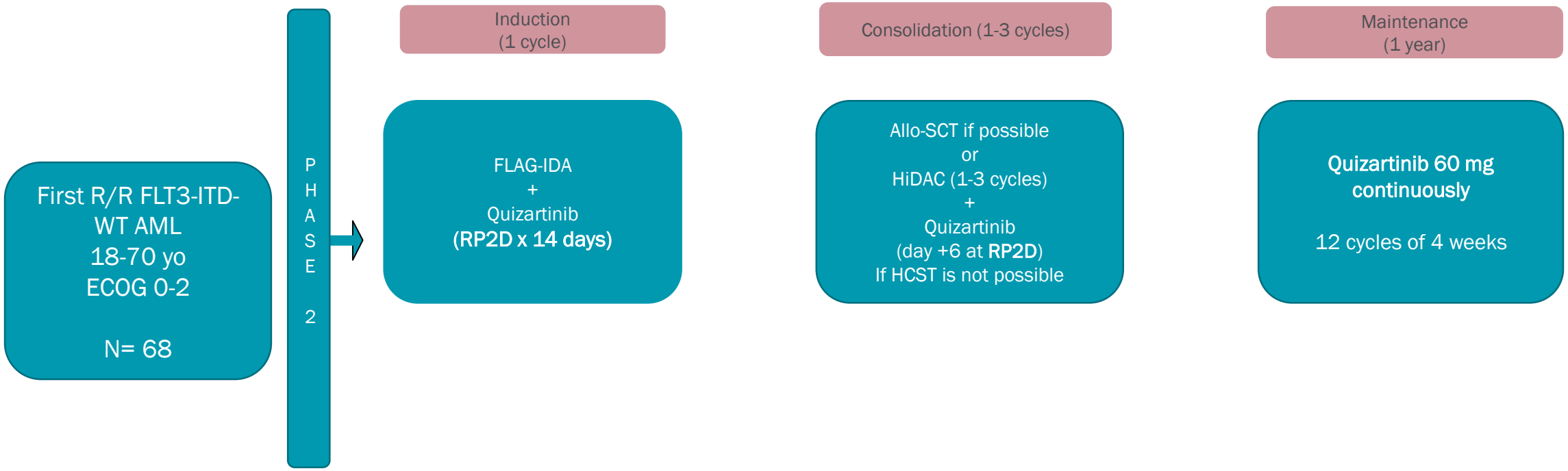
Martínez-Cuadrón D, et al. Annals of Hematology 2019

A phase I trial of selinexor plus FLAG-Ida for the treatment of refractory/relapsed adult acute myeloid leukemia patients



Martínez-Sánchez MP, et al. Annals of Hematology 2021

Phase 2 trial:FLAG-QUIDA



Standard PETHEMA protocol:

FLAG-IDA: Fludarabine 30 mg/m2 + Cytarabine 2 g/m2 (1 g/m2 in older than 59 yo) + Ida 10mg/m2 + G-CSF

Consolidation:

A. Allo-SCT with or without

B. Chemotherapy (3 cycles) HiDAC 3g/m2; ≥60 yo 1.5g/m2

& more....

- Mixed lineage national protocol (LA-MIX)
- BPDCN national registry (EPI-BLAS)