Midostaurina: La primera terapia dirigida aprobada para el tratamiento de la LMA FLT3+

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Disclosures

- Research grants:
  - Celgene, Amgen, Novartis
- Advisory board:
  - Celgene, Janssen, AbbVie, Daiichi-Sankyo, Pfizer, Novartis, Jazz Pharmaceuticals

Outline

Molecular heterogeneity of AML

The *FLT3* gene, the receptor and Midostaurin

The RATIFY trial

The AMLSG Phase II trial

My experience with Midostaurin

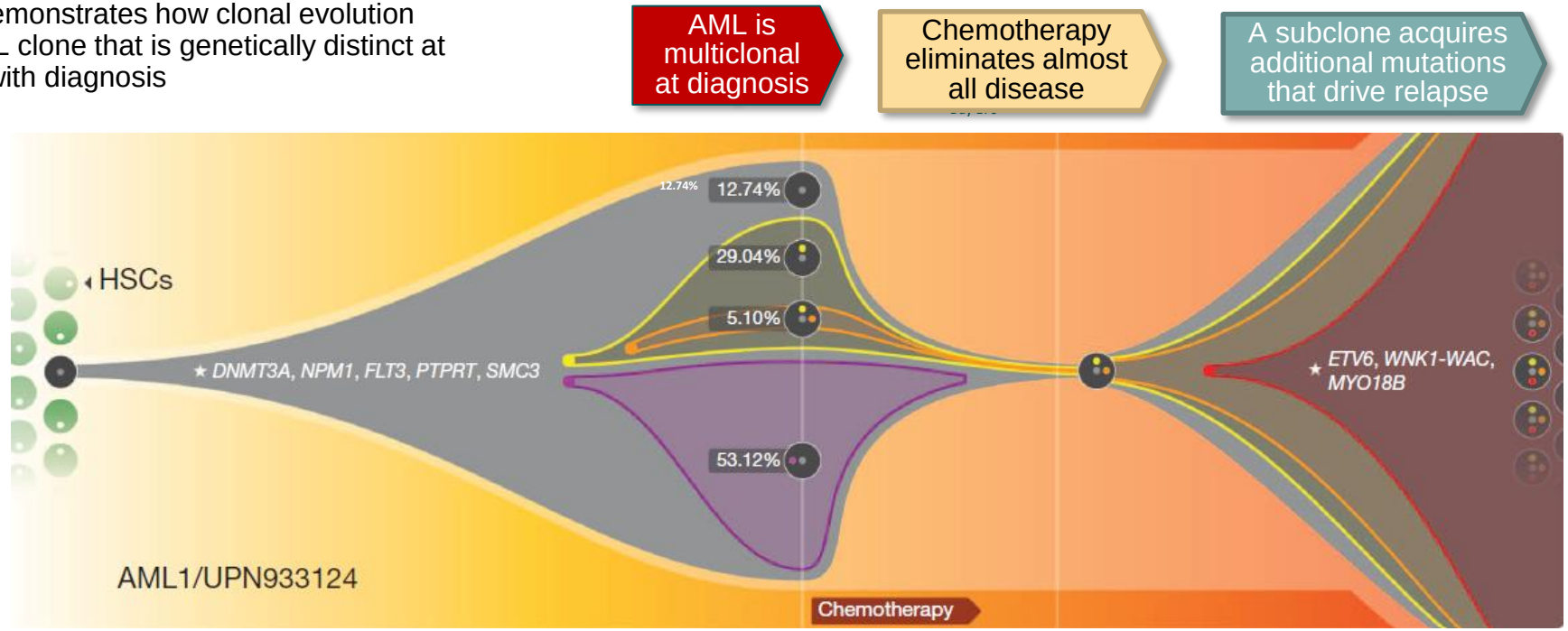
Other FLT3 inhibitors under investigation

Future approaches

AML molecular development

- Development of AML follows specific and ordered evolutionary trajectories
- Mutations in *DNMT3A*, *ASXL1*, *IDH1/2* and *TET2*, genes that encode epigenetic modifiers, were often acquired earliest. They are not sufficient for overt leukaemia
- Mutations in receptor tyrosine kinase–RAS pathway genes typically occurred late and frequently happened more than once in the same patient
- Tumor sub-clones (with differing mutations) compete with each other and with normal cells

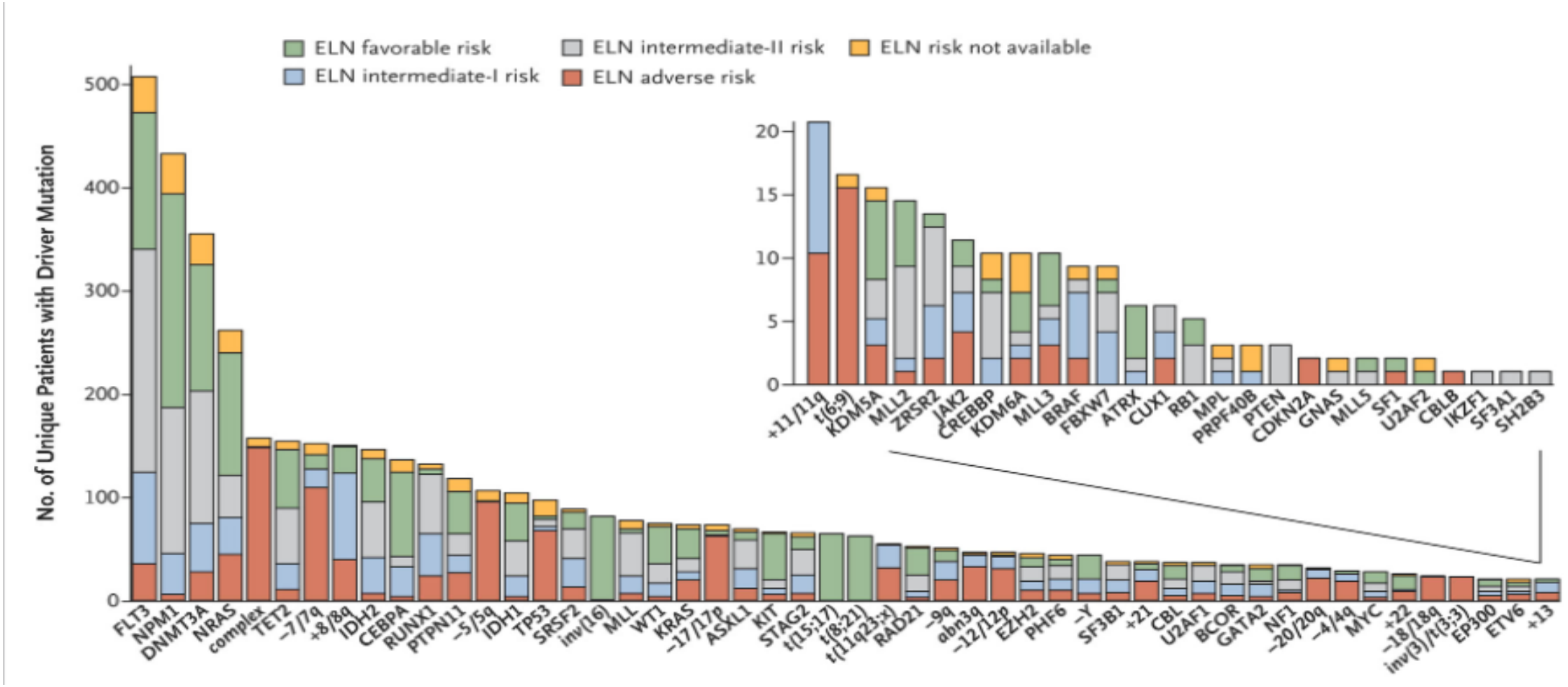
Genetic mapping demonstrates how clonal evolution can result in an AML clone that is genetically distinct at relapse compared with diagnosis



Adapted from Adapted from Ding L et al. Nature 2012;481:506–510, Hackl et al. Journal of Hematology & Oncology (2017)

Whole-Genome Sequencing in AML has revealed the diversity and frequency of mutations

- 1540 patients with AML from three prospective trials of intensive therapy



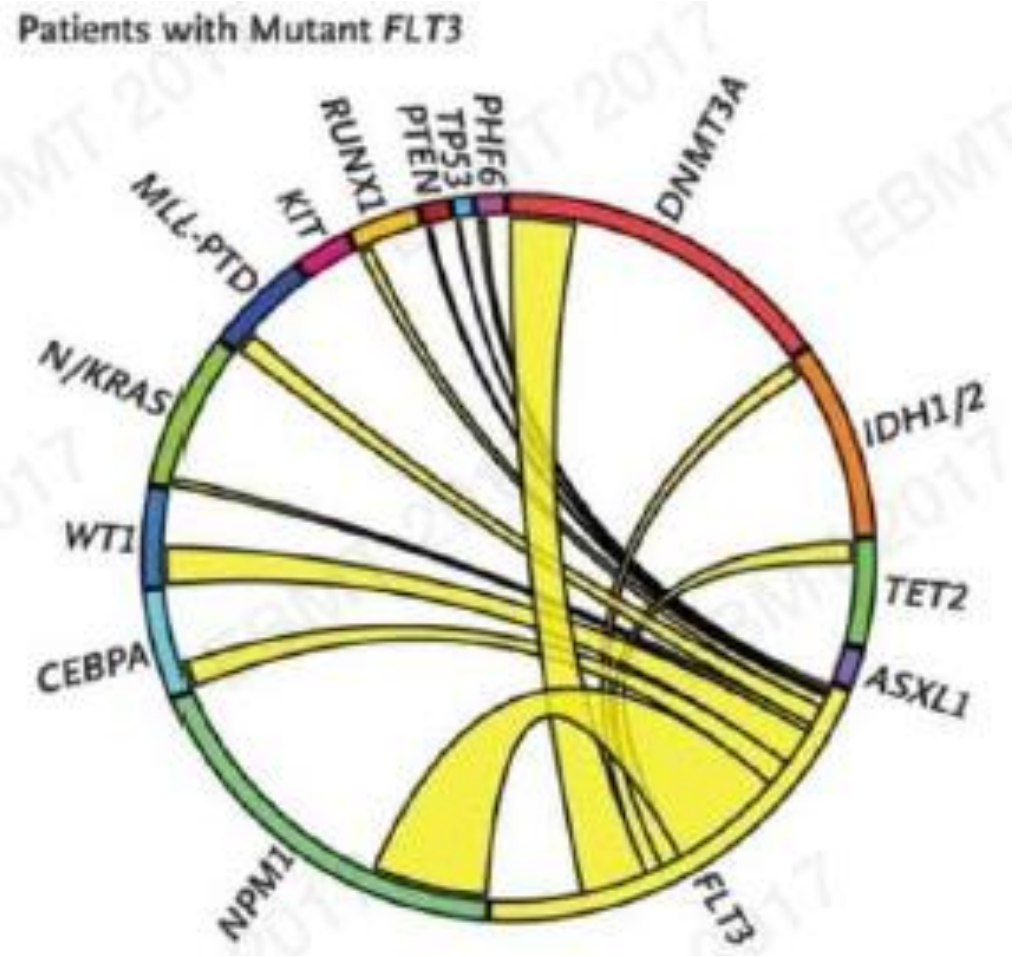
Papaemmanuil E et al. N Engl J Med 2016;374:2209–21.

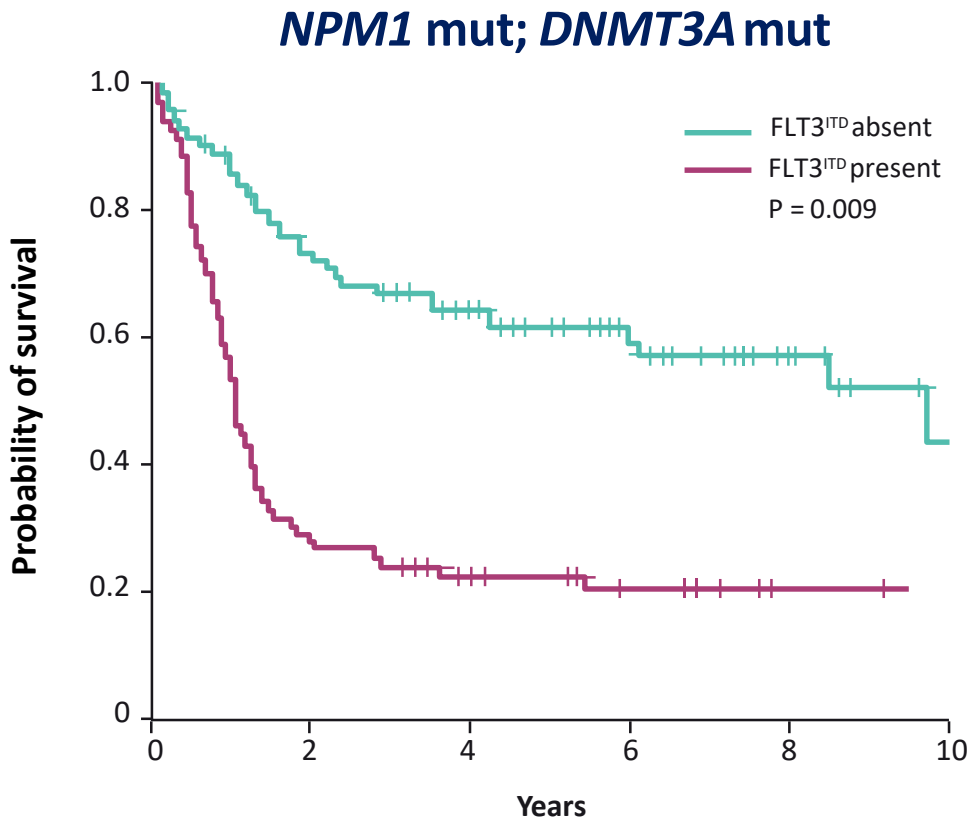
Recurrent Mutations Interfering with Intracellular Signalling

Gene	Key Points	Role/Function
FLT3 *(receptor tyrosine kinase)*	• FLT3-ITD or TKD mutations in ~30% of patients • FLT-ITD common in nK AML • FLT3-ITD wild-type ratio impacts prognosis • Concurrent with many other common AML mutations	• Constitutively active kinase domain • Promotes RAS and AKT pathways
RAS oncogenes	• KRAS and NRAS mutations in ~14% of patients	• Increased RAS signalling

DiNardo CD et al. ASH Education Book 2016;1:348–55.
Altman JK et al. Am J Hematol 2017.

FLT3: Concomitant mutations





Patel JP *et al*. *NEJM* 2012;366:1079–1089.

- Adapted from Papaemmanuil E *et al*. *N Engl J Med* 2016;**374**:2209–21

European LeukemiaNet 2017

Review Article

blood

Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel

Hartmut Döhner,[1] Elihu Estey,[2] David Grimwade,[3] Sergio Amadori,[4] Frederick R. Appelbaum,[2] Thomas Büchner,[5] Hervé Dombret,[6] Benjamin L. Ebert,[7] Pierre Fenaux,[8] Richard A. Larson,[9] Ross L. Levine,[10] Francesco Lo-Coco,[4] Tomoki Naoe,[11] Dietger Niederwieser,[12] Gert J. Ossenkoppele,[13] Miguel Sanz,[14] Jorge Sierra,[15] Martin S. Tallman,[10] Hwei-Fang Tien,[16] Andrew H. Wei,[17,18] Bob Löwenberg,[19] and Clara D. Bloomfield[20]

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Döhner H et al. Blood. 2017; 129(4):424-447

Updated ELN prognostic stratification of AML

Favourable	• 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 or with *FLT3*-ITD^{low}** • Biallelic mutated *CEBPA*
Intermediate	• **Mutated *NPM1* and *FLT3*-ITD^{high}** • **Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}** (without adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3); *MLLT3-KMT2A* • Cytogenetic abnormalities not classified as favourable or adverse
Adverse	• t(6;9)(p23;q34.1); *DEK-NUP214* • t(v;11q23.3); *KMT2A* rearranged • t(9;22)(q34.1;q11.2); *BCR-ABL1* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)* • −5 or del(5q); −7; −17/abn(17p) • Complex karyotype, monosomal karyotype • **Wild-type *NPM1* and *FLT3*-ITD^{high}** • **Mutated *RUNX1*** • **Mutated *ASXL1*** • **Mutated *TP53***

Döhner H *et al*. *Blood* 2017;**129**:424–47

Simplified classification for middle income countries

Favourable

- 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

Intermediate

- Others

Adverse

- t(6;9)(p23;q34.1); *DEK-NUP214*
- t(v;11q23.3); *KMT2A* rearranged except t(9;11)
- t(9;22)(q34.1;q11.2); *BCR-ABL1*
- inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
- −5 or del(5q); −7; −17/abn(17p)
- Complex karyotype, monosomal karyotype

IDAC or HDAC, 3-4 courses*

HLA-id sibling or Haplo transplant

*If MRD positive after last consolidation proceed to allogeneic transplantation

Risk-adapted CETLAM trials for primary AML

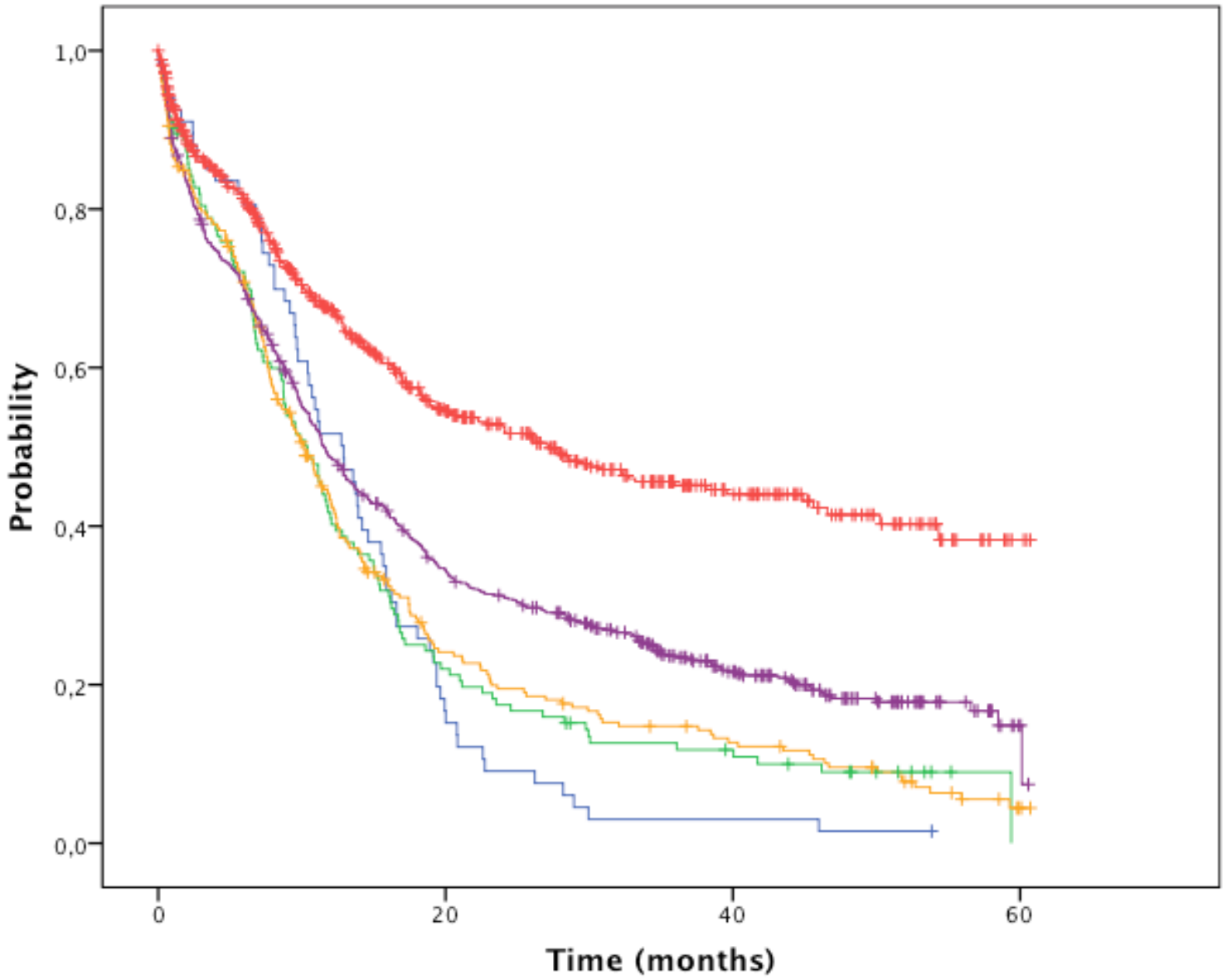
	AML-88[1]	AML-94[2]	AML-99[3]	AML-03[4]	AML-12[5]
Patients	94	200	350	860	471
Upper age (yrs)	50	60	60	70	70
Induction	DCE (3x7x3)	ICE (3x7x3)	IDICE (3x8x3)	IDICE + G-CSF	IA + G-CSF
Consolidation	Mitox-HiDAC Amsa-IDAC	Mitox-IDAC	Mitox-IDAC	Mitox-IDAC + G-CSF	HiDAC
Post-CR adapted therapy based on	HLA-id sibling	HLA-id sibling (age 50 yrs only Auto)	CBF, NK Courses CR HLA-id sibling	CBF, NK Courses CR **FLT3**, MLL, MRD Allo Sibl, URD, CB	CBF, NPM1, CEBPA, **FLT3**, MLL, MRD EBMT score, Sibl, URD, CB, Haplo
Favourable risk	Auto or Allo	Auto or Allo	HiDAC	HiDAC or Auto	HiDAC
Intermediate risk			Auto	Auto	Auto – HLA-id
Adverse risk			Auto or Allo	GO Auto or Allo	Allo any type
Transplantation	Auto: BM Allo: Sib BM	Auto: BM Allo: Sib PB	Auto: PB Allo: Sib PB	Auto: PB Allo: PR or CB MAC or RIC	Auto: PB Allo: PB, CB, Haplo MAC or RIC
Report	*JCO* 1996[1]	*Haematologica* 2004[2]	*Haematologica* 2004[3]		

Allo, allogeneic; AML, acute myeloid leukaemia; AMSA, amsacrine; Auto, autologous; BM, bone marrow; CB, cord blood; CBF, core binding factor; CR, complete remission; DCE, daunorubicin, cytarabine and etoposide; EBMT, European Group for Blood and Marrow Transplantation; G-CSF, granulocyte-colony stimulating factor; HLA-id, human leukocyte antigen id; Haplo, haploidentical; HiDAC, high-dose cytarabine; IDAC, intermediate dose cytarabine; IDICE, idarubicin, intermediate doses of ara-C and etoposide; MAC, myeloablative conditioning; Mitox, mitoxantrone; MRD, minimal residual disease; NK, natural killer; PB, peripheral blood; RIC, reduced intensity conditioning; Sib, sibling; URD, unrelated donor

1. Sierra J. et *al. J Clin Oncol.* 1996 Apr;14:1353-63; 2. Brunet *et al. Haematologica* 2004;89:940-9; 3. Oriol *et al. Haematologica* 2004;89:791-800; 4. Unpublished, courtesy of CETLAM; 5. clinicailtrials.gov (NCT01723657)

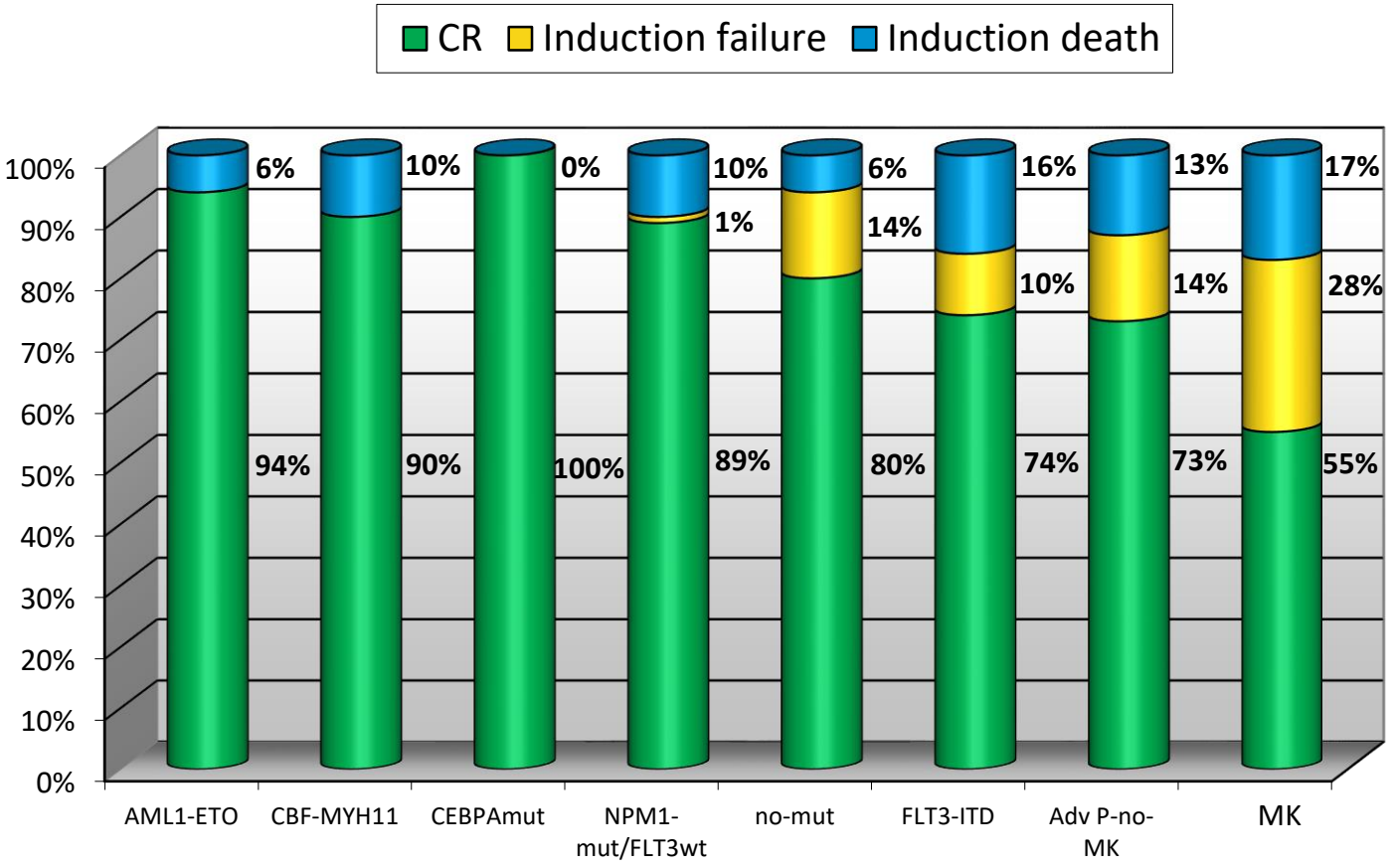
Overall survival in the consecutive CETLAM protocols

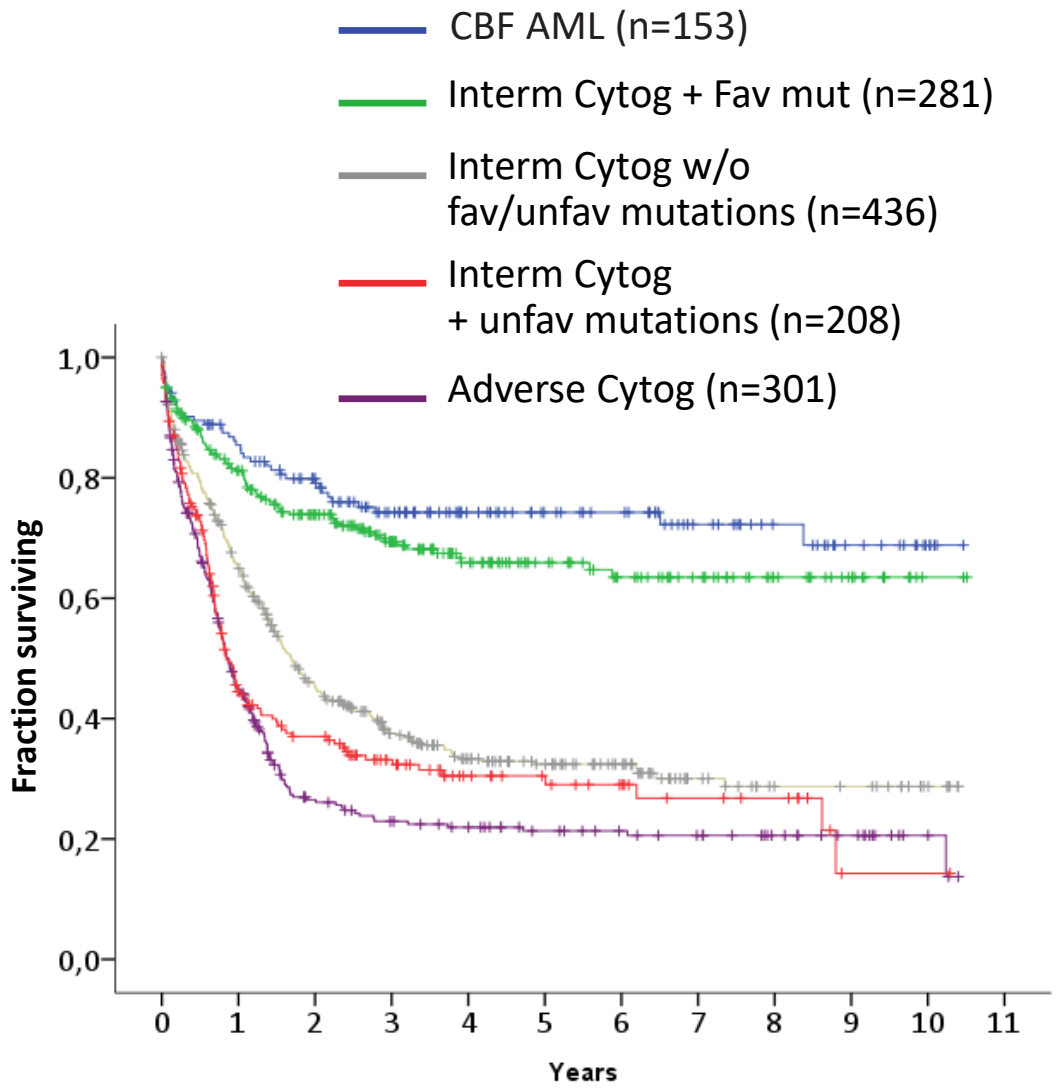
1988: 5±% n=67
1994: 15±6% n=134
1999: 18±5% n=253
2003: 28±3% n=682
2012: 48±5% n=603



Data on file, May 2018

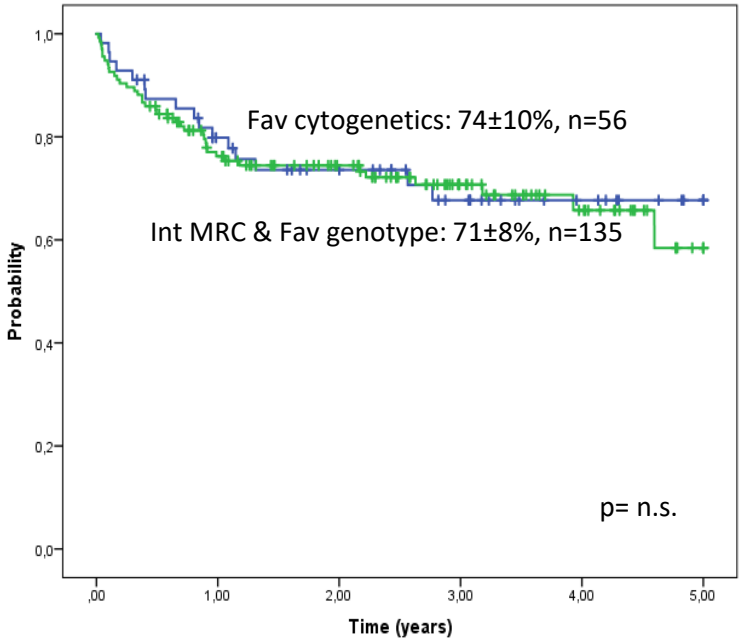
AML: Genetics and outcome of adults intensively treated (Spanish CETLAM)

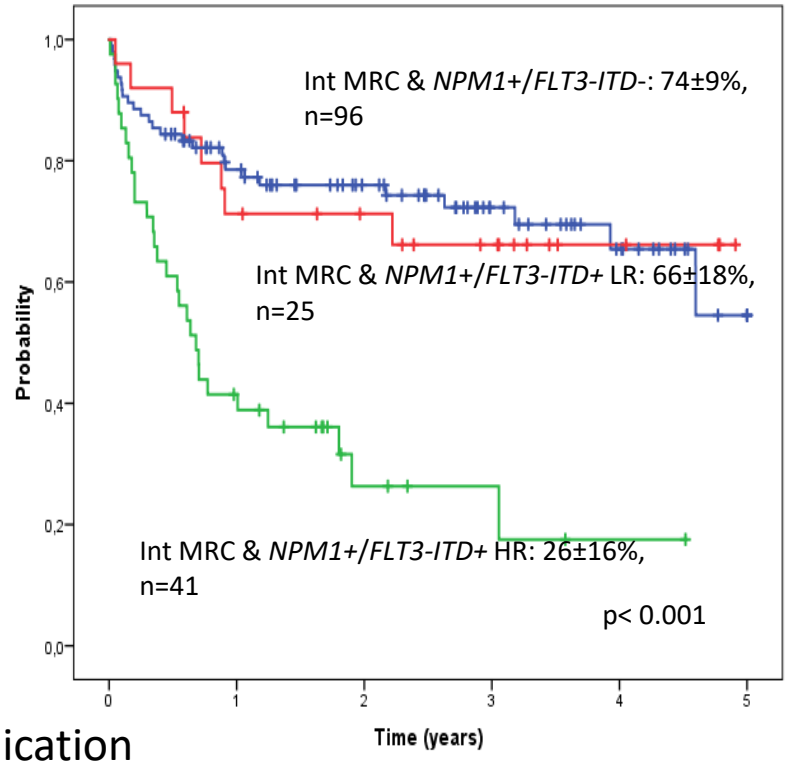


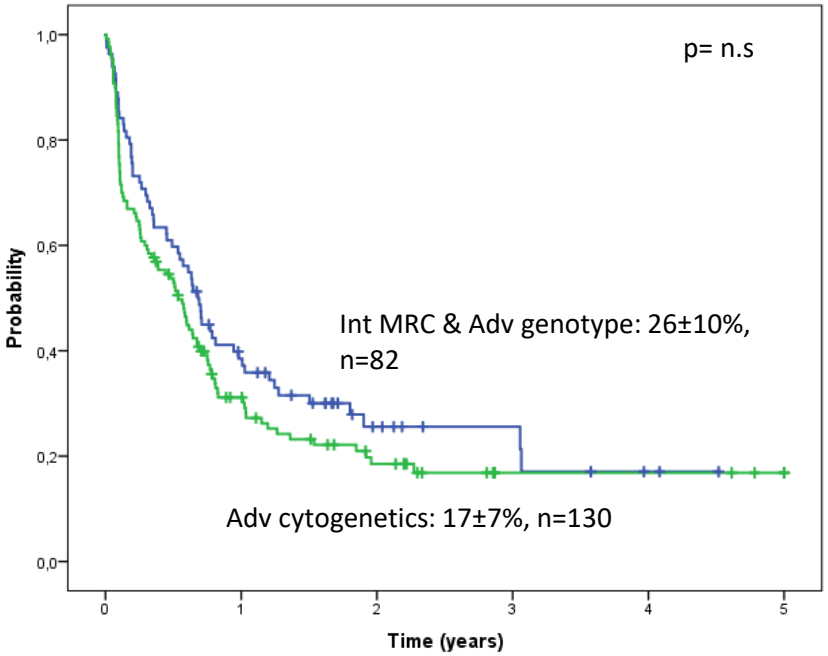


MK, monosomal karyotype
CETLAM dataon file

Results: EFS according to genetics at Dx

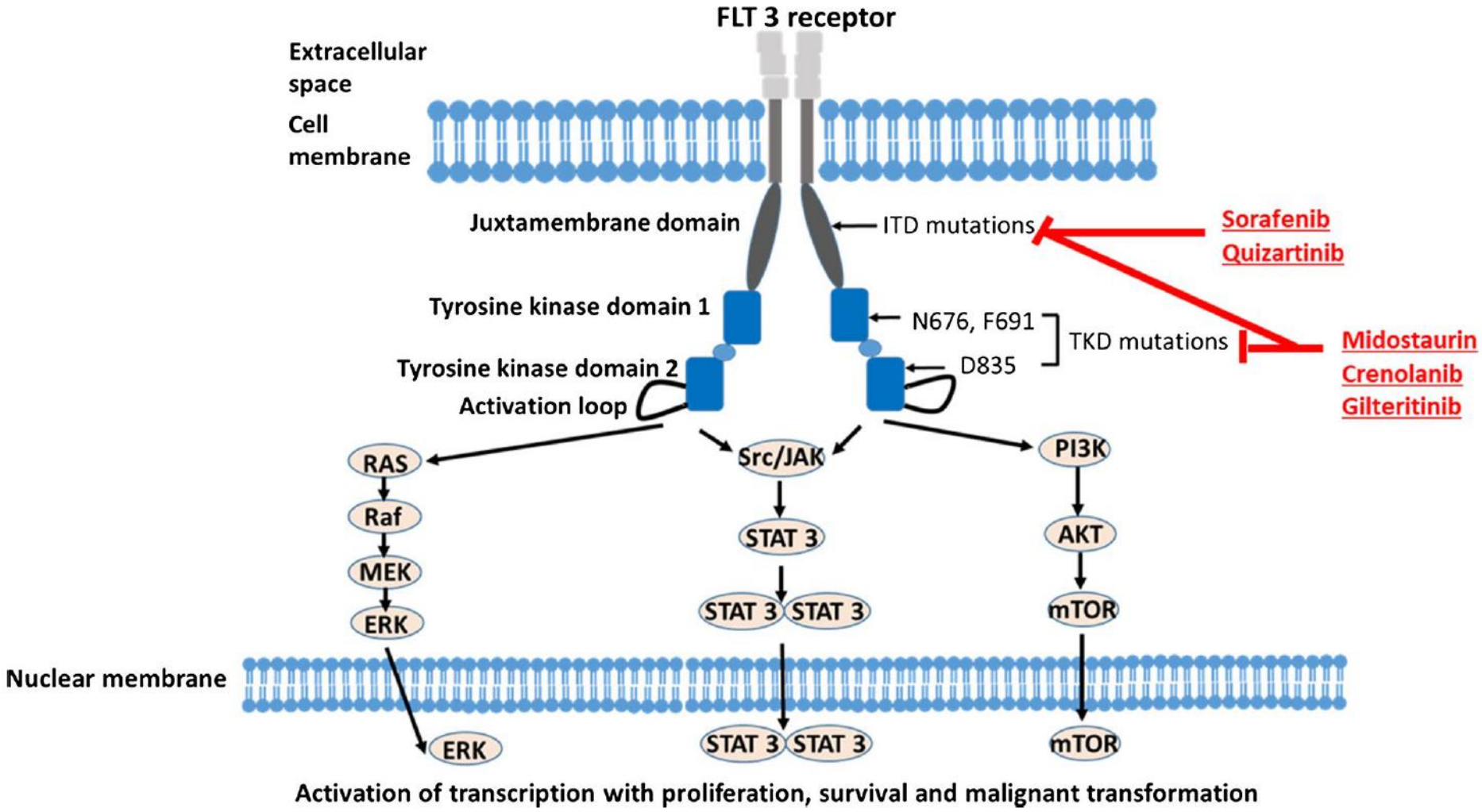






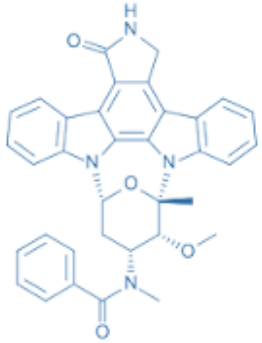
Sierra J et al. ASH 2017 oral communication

FLT3 inhibitors



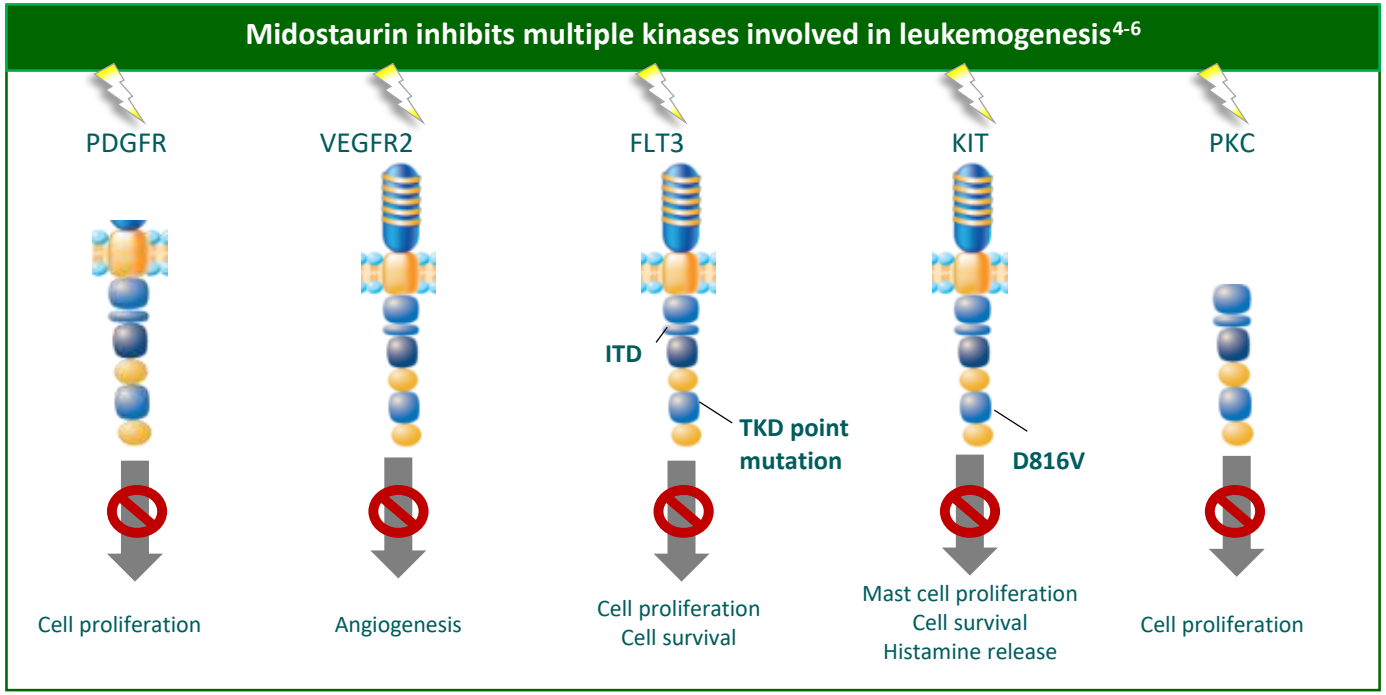
Lim et al. J Transl Med (2017) 15:183

Midostaurin: Multikinase inhibitor



- Midostaurin is rapidly absorbed after oral administration[1]
- Midostaurin is predominantly metabolized by CYP3A4 to form 2 major active metabolites (CGP62221 and CGP52421)[2]
- The mean terminal half-lives of midostaurin, CGP62221, and CGP52421 are approximately 20.5 hours, 32.3 hours, and 471 hours, respectively[3]
  - The metabolite CGP52421 accumulates continuously through day 28

Midostaurin inhibits FLT3-WT as well as FLT3-ITD and FLT3-TKD (D835H and D835Y)



KIT, also known as CD117 and stem cell growth factor receptor (SCGFR); PDGFR, platelet derived growth factor; PKC, protein kinase C.

Midostaurin FDA and EMA approved indications

	Indications
FDA[1]	Midostaurin is a kinase inhibitor indicated for the treatment of (1) adult patients with newly diagnosed AML that is *FLT3*-mutation positive as detected by an FDA-approved test, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation, and (2) adult patients with ASM, SM-AHN, or MCL. Limitations of use: midostaurin is not indicated as a single-agent induction therapy for the treatment of patients with AML.
EMA[2]	Midostaurin is indicated (1) in combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy and for patients in complete response followed by midostaurin single-agent maintenance therapy, for adult patients with newly diagnosed AML who are *FLT3*-mutation positive; and (2) as monotherapy for the treatment of adult patients with ASM, SM-AHN, MCL.

ASM, aggressive systemic mastocytosis; EMA, European Medicines Agency; FDA, US Food and Drug Administration; MCL, mast cell leukemia; SM-AHN, systemic mastocytosis with associated hematological neoplasm.

Stone R et al.
Blood Adv. 2018;2(4):444-453

CALGB 10603 RATIFY

Randomized AML Trial in FLT3 in <60 Year Olds

NOVARTIS
ONCOLOGY

ORIGINAL ARTICLE

Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a *FLT3* Mutation

R.M. Stone, S.J. Mandrekar, B.L. Sanford, K. Laumann, S. Geyer, C.D. Bloomfield, C. Thiede, T.W. Prior, K. Döhner, G. Marcucci, F. Lo-Coco, R.B. Klisovic, A. Wei, J. Sierra, M.A. Sanz, J.M. Brandwein, T. de Witte, D. Niederwieser, F.R. Appelbaum, B.C. Medeiros, M.S. Tallman, J. Krauter, R.F. Schlenk, A. Ganser, H. Serve, G. Ehninger, S. Amadori, R.A. Larson, and H. Döhner

N Engl J Med. 2017 Aug 3;377(5):454-464.

RATIFY: Schema

Phase 3, randomized, placebo-controlled study

Patients with newly diagnosed AML aged ≥ 18 to ≤ 60 years with activating *FLT3* mutations[a,b]

Stratification by TKD and ITD[c] (ratio < 0.7 vs ≥ 0.7)

(N = 717)

R

Induction (1-2 cycles)	CR	Consolidation (up to 4 cycles)	CR	Postconsolidation (up to 12 cycles)
Midostaurin (50 mg bid, days 8-21)		**Midostaurin** (50 mg bid, days 8-21)		**Midostaurin** (50 mg bid, days 1-28)
Daunorubicin (60 mg/m²/day, days 1-3)		**High-dose cytarabine** (3 g/m²/day q12h, days 1, 3, and 5)		
Cytarabine (200 mg/m²/day, days 1-7)				
Placebo (bid, days 8-21)		**Placebo** (bid, days 8-21)		**Placebo** (bid, days 1-28)
Daunorubicin (60 mg/m²/day, days 1-3)		**High-dose cytarabine** (3 g/m²/day q12h, days 1, 3, and 5)		
Cytarabine (200 mg/m²/day, days 1-7)				

1 cycle = 28 days.

First patient enrolled July 2008,
Last patient enrolled October 2011
3270 screened, 717 randomized

Primary endpoint: OS
Key secondary endpoint: EFS

APL, acute promyelocytic leukemia; EFS, event-free survival; OS, overall survival; q12h, every 12 hours.
[a] Documented AML (no APL or therapy-related AML).
[b] Hydroxyurea therapy allowed ≤ 5 days prior to start of study treatment.
[c] As determined using BM or PB samples using an assay that was later developed into the LeukStrat CDx FLT3 Mutation Assay.

Stone RM, et al. *N Engl J Med*. 2017;377:454-464.

RATIFY: Revised analysis plan

Statistical Plan	No. of Events	No. of Patients Accrued	Power	Alpha[a]	HR to Be Detected
Original	374	514	90%	0.025	0.71
2010 amendment	509	714	84%	0.025	0.78
2015 amendment	357	717	84%	0.0239	0.78

- The event rate (ie, deaths) reached a plateau in 2014 (6 events in 2014 and 4 events by May 2015). Alliance DSMB decided to perform the final analysis with a data cutoff of May, 2015, without achieving the required 509 OS events
  - The SCT rate was higher than expected (25% at the time of amendment vs 15% anticipated)
- EFS was promoted to a key secondary endpoint to be tested in a hierarchical manner if OS was significant

CTEP, Cancer Therapy Evaluation Program; DSMB, Data Safety Monitoring Board.
[a] Critical value to declare statistical significance (1-sided).

Stone RM, et al. *N Engl J Med*. 2017;377:454-464.

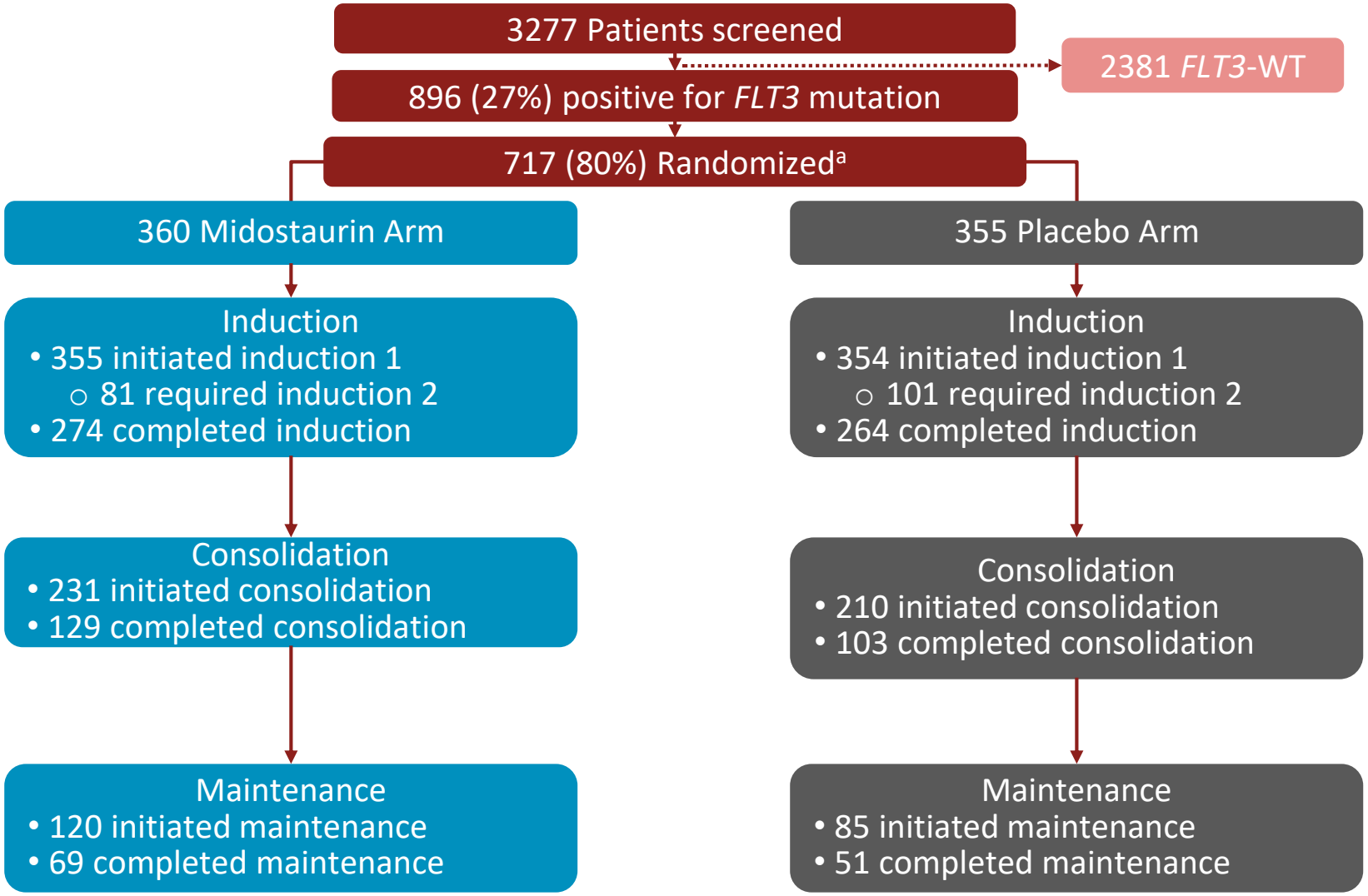
*

RATIFY: Patient's characteristics

	All Patients (N = 717)	Midostaurin (n = 360)	Placebo (n = 357)	P Value[a]
Median age (range), years	47.9 (18.0-60.9)	47.1 (19.0-59.8)	48.6 (18.0-60.9)	.22
Female sex, n (%)	398 (55.5)	186 (51.7)	212 (59.4)	.04
FLT3 stratification groups, n (%)				1.00
FLT3-TKD	162 (22.6)	81 (22.5)	81 (22.7)	
FLT3-ITD allelic ratio < 0.7[b]	341 (47.6)	171 (47.5)	170 (47.6)	
FLT3-ITD allelic ratio ≥ 0.7[b]	214 (29.8)	108 (30.0)	106 (29.7)	
Median WBC (range), × 10^3/μL	34.9 (0.6-421.8)	35.6 (0.6-421.8)	33.0 (0.8-329.8)	.72
Median platelet count (range), × 10^3/μL	50.0 (2.0-461.0)	50.0 (2.0-461.0)	50.0 (8.0-444.0)	.58
Median ANC (range), per mm^3	2.2 (0-55.9)	2.2 (0-55.9)	2.3 (0-128.7)	.65

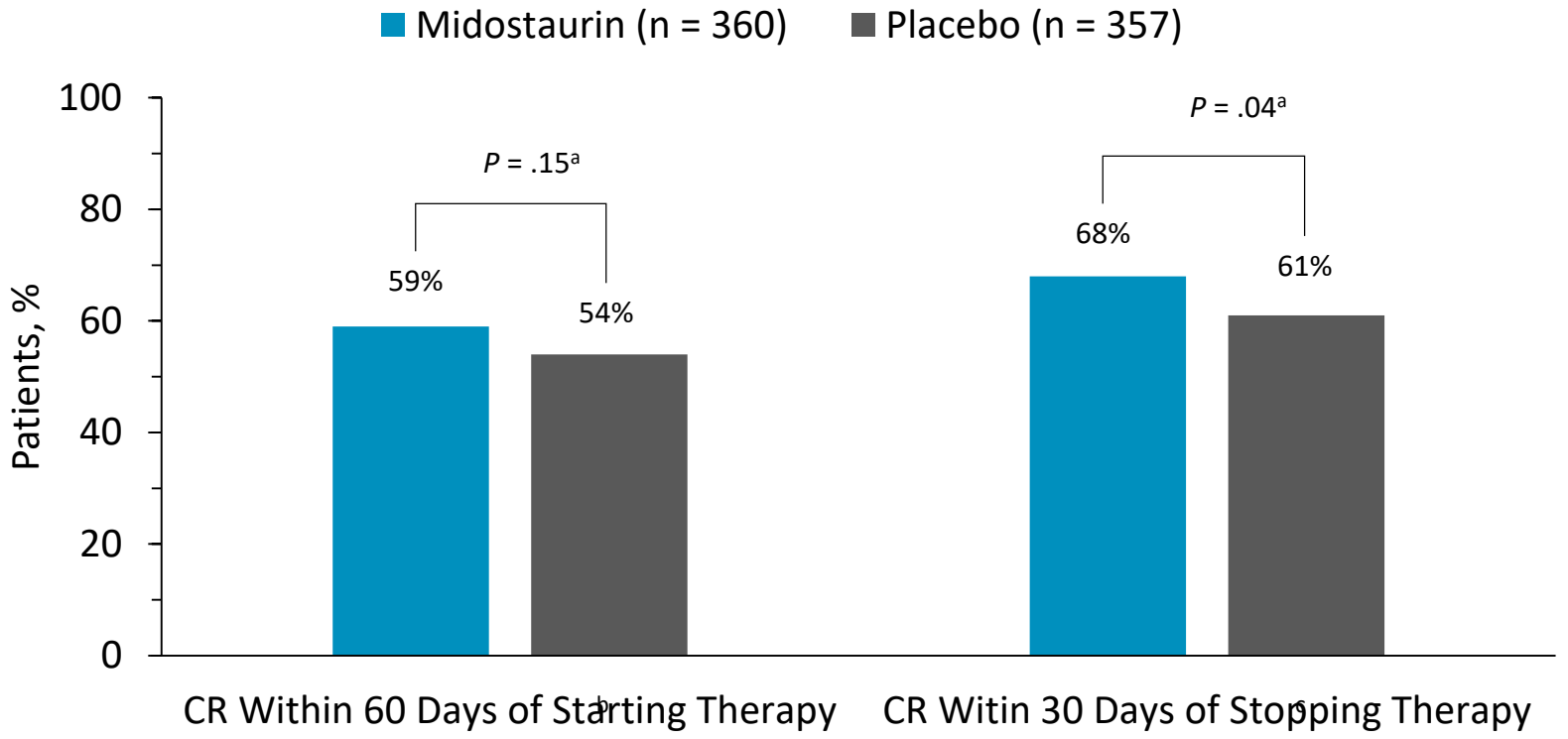
[a] Two-sided; Kruskal-Wallis P values are presented for continuous measures (eg, age) and Chi-square values are presented for categorical counts (eg, sec).[b] Patients could also have *FLT3*-TKD.

RATIFY: Consort diagram



RATIFY: CR rates by arm

Secondary endpoint



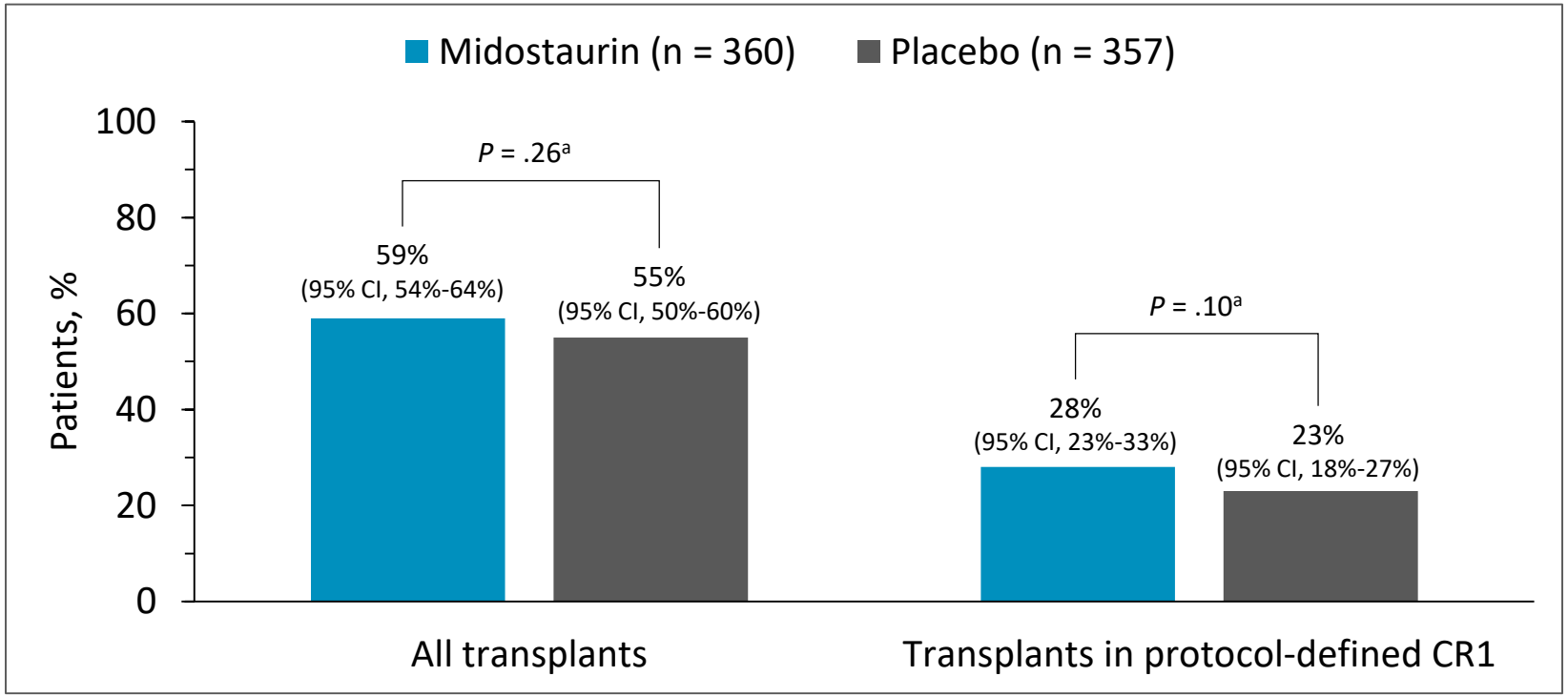
Median time to CR (range), days[d]	**35 (20-60)**	**35 (20-60)**		**37 (20-192)**	**36 (20-108)**

[a] Two-sided Fisher's Exact *P*.
[b] Per protocol, CRs were defined as occurring within 60 days of initiating study protocol therapy. [c] An expanded definition of CR Included all CRs reported within 30 days of ending protocol therapy.
[d] Kaplan-Meier estimates.

Stone RM, et al. *N Engl J Med*. 2017;377:454-464.

RATIFY: AlloSCT rates by arm

Secondary endpoint



Overall transplant rate (95% CI), %	**57 (53-61)**		**25 (22-29)**
Median OS (95% CI), months[b]	NR (69.8-NR)	*P* = .07[c]	NR (21.8-NR)

[a] Two-sided Fisher's Exact *P*.
[b] For patients who received an SCT in CR1 (101 in the midostaurin arm and 81 in the placebo arm). [c] Two-sided long-rank test.

Stone RM, et al. *N Engl J Med*. 2017;377:454-464.

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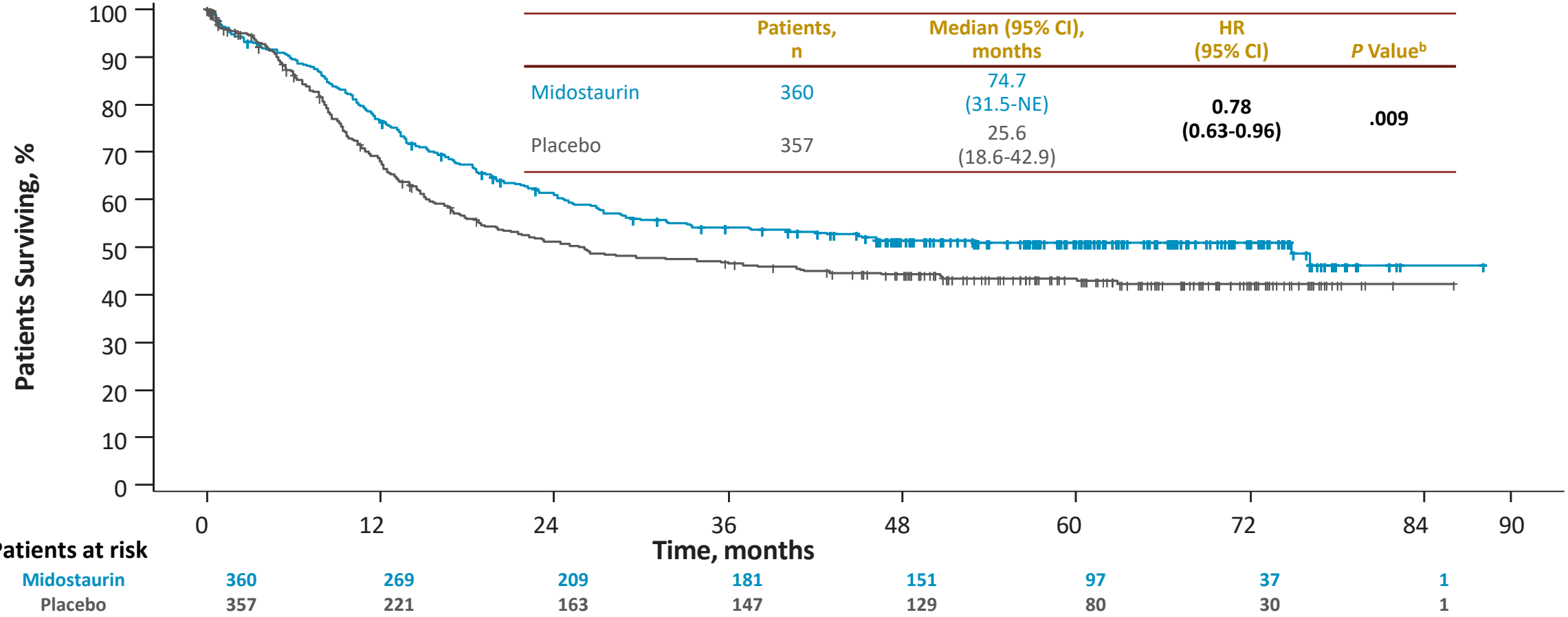
RATIFY: OS, non-censored for SCT

Primary endpoint

22% reduced risk of death in the midostaurin arm (vs placebo)



	Patients, n	Median (95% CI), months	HR (95% CI)	*P* Value[b]
Midostaurin	360	74.7 (31.5-NE)	**0.78 (0.63-0.96)**	**.009**
Placebo	357	25.6 (18.6-42.9)		

Patients at risk

Midostaurin	360	269	209	181	151	97	37	1
Placebo	357	221	163	147	129	80	30	1

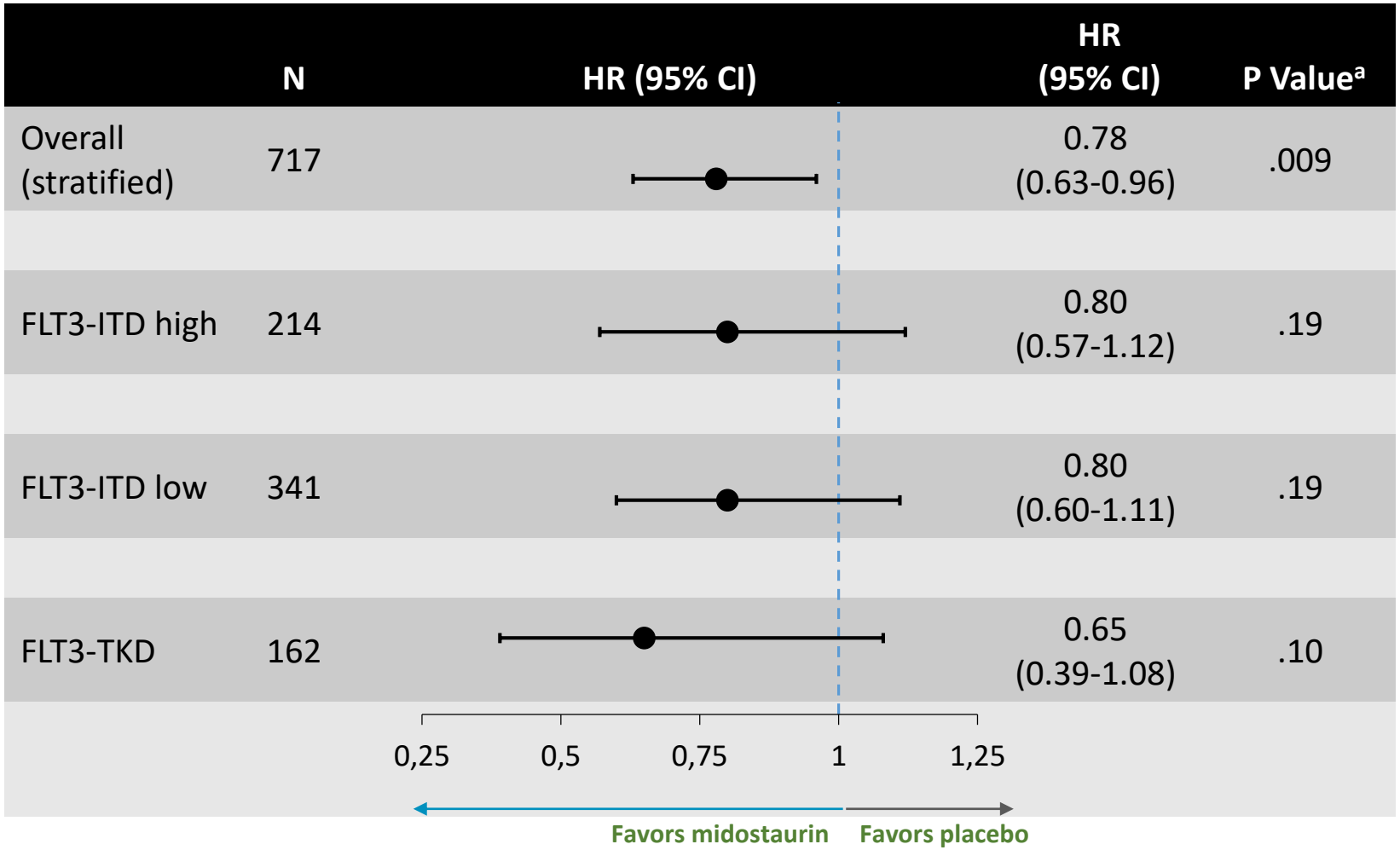
From Stone RM, et al. *N Engl J Med*. 2017;377:454-464. Copyright © 2017 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

NE, not estimable.

[a] Cox model stratified on *FLT3* subtype. [b] Stratified on *FLT3* subtype; one-sided, log-rank *P* value.

RATIFY: Consistent effect on OS by *FLT3* status

Secondary endpoint



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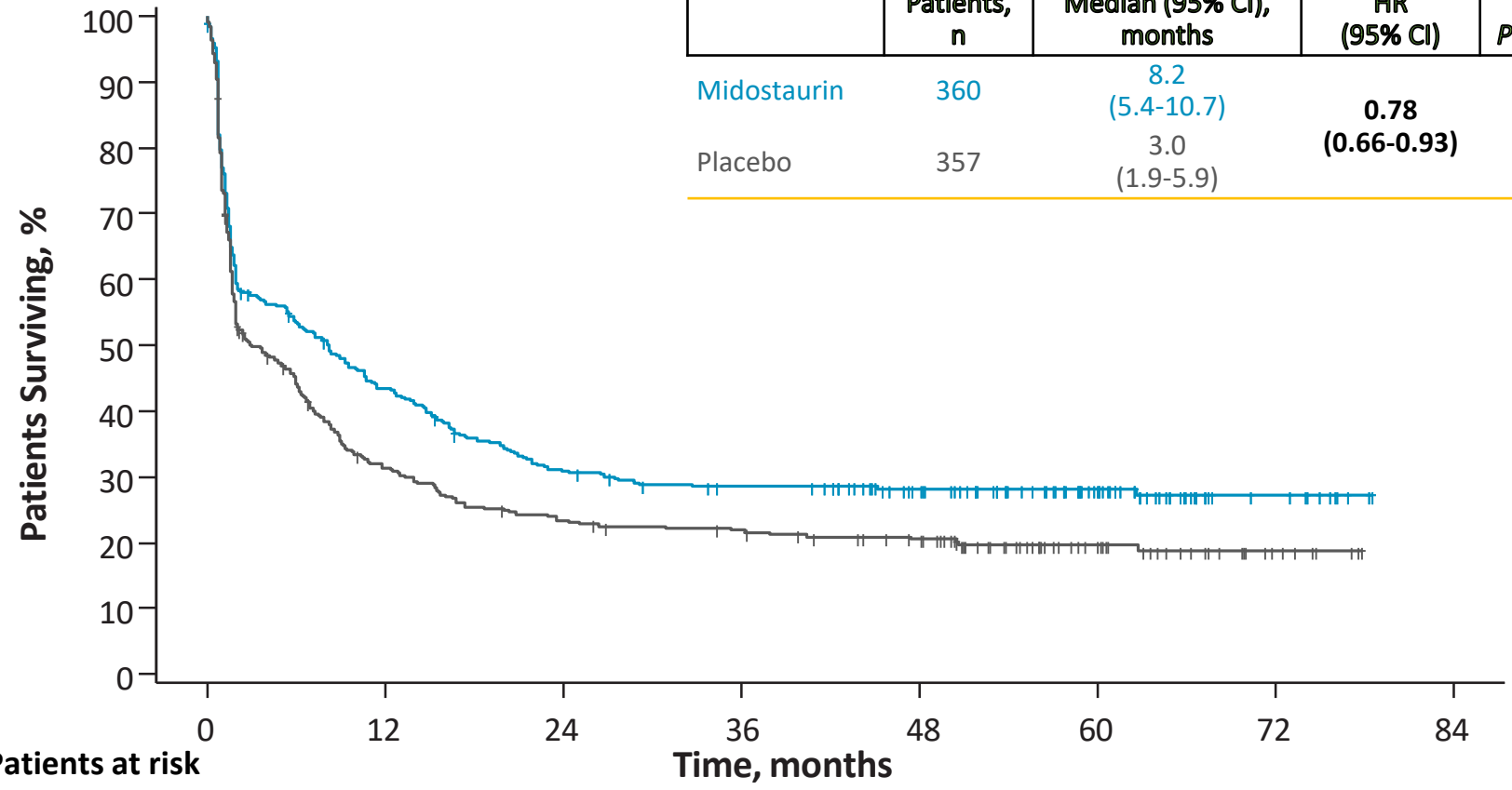
[a] *P* value is one-sided for the overall (stratified) analysis; *P* values are two-sided for the analyses by FLT3 subgroup. *FLT3*-ITD-low, *FLT3*-ITD/-WT allelic ratio < 0.7; *FLT3*-ITD-high, *FLT3*-ITD/-WT allelic ratio ≥ 0.7.

RATIFY: EFS, noncensored for SCT[a]

Key secondary endpoint

	Patients, n	Median (95% CI), months	HR (95% CI)	*P* Value[b]
Midostaurin	360	8.2 (5.4-10.7)	**0.78 (0.66-0.93)**	**.002**
Placebo	357	3.0 (1.9-5.9)		



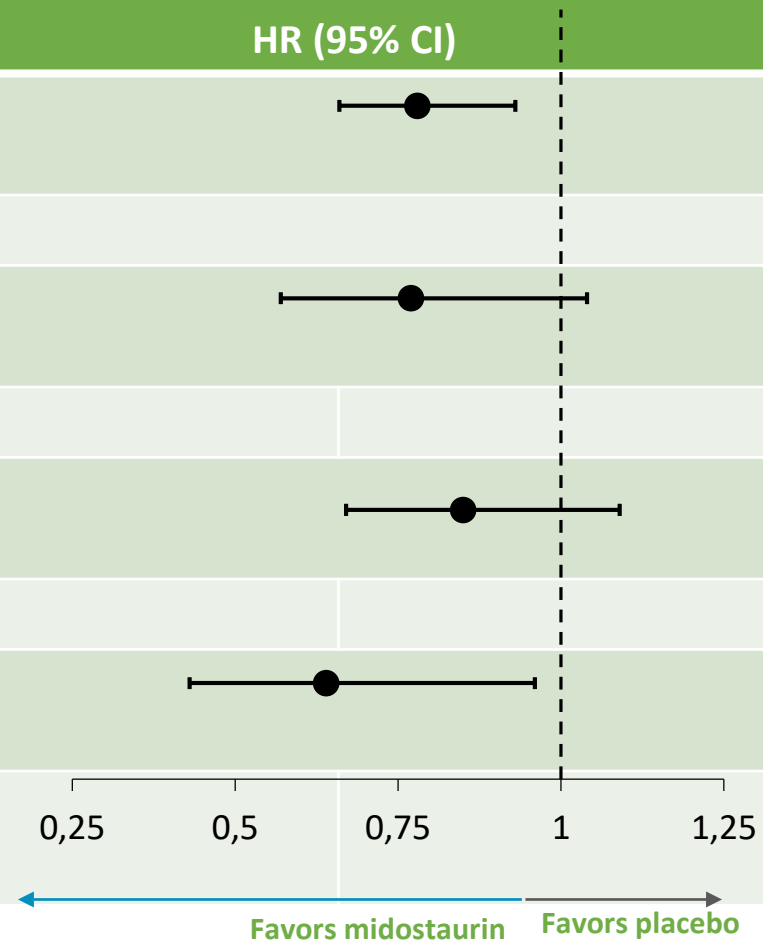
[a] Event defined as first of no CR within 60 days of initiating study therapy, relapse, or death.

[b] Stratified on *FLT3* subtype; one-sided, log-rank *P* value.

RATIFY: Consistent effect on EFS by FLT3 status

Secondary endpoint

	N	HR (95% CI)	HR (95% CI)	P Value[a]
Overall (stratified)	717		0.78 (0.66-0.96)	.002
FLT3-ITD high	214		0.77 (0.57-1.04)	.08
FLT3-ITD low	341		0.5 (0.67-1.09)	.21
FLT3-TKD	162		0.64 (0.43-0.96)	.03



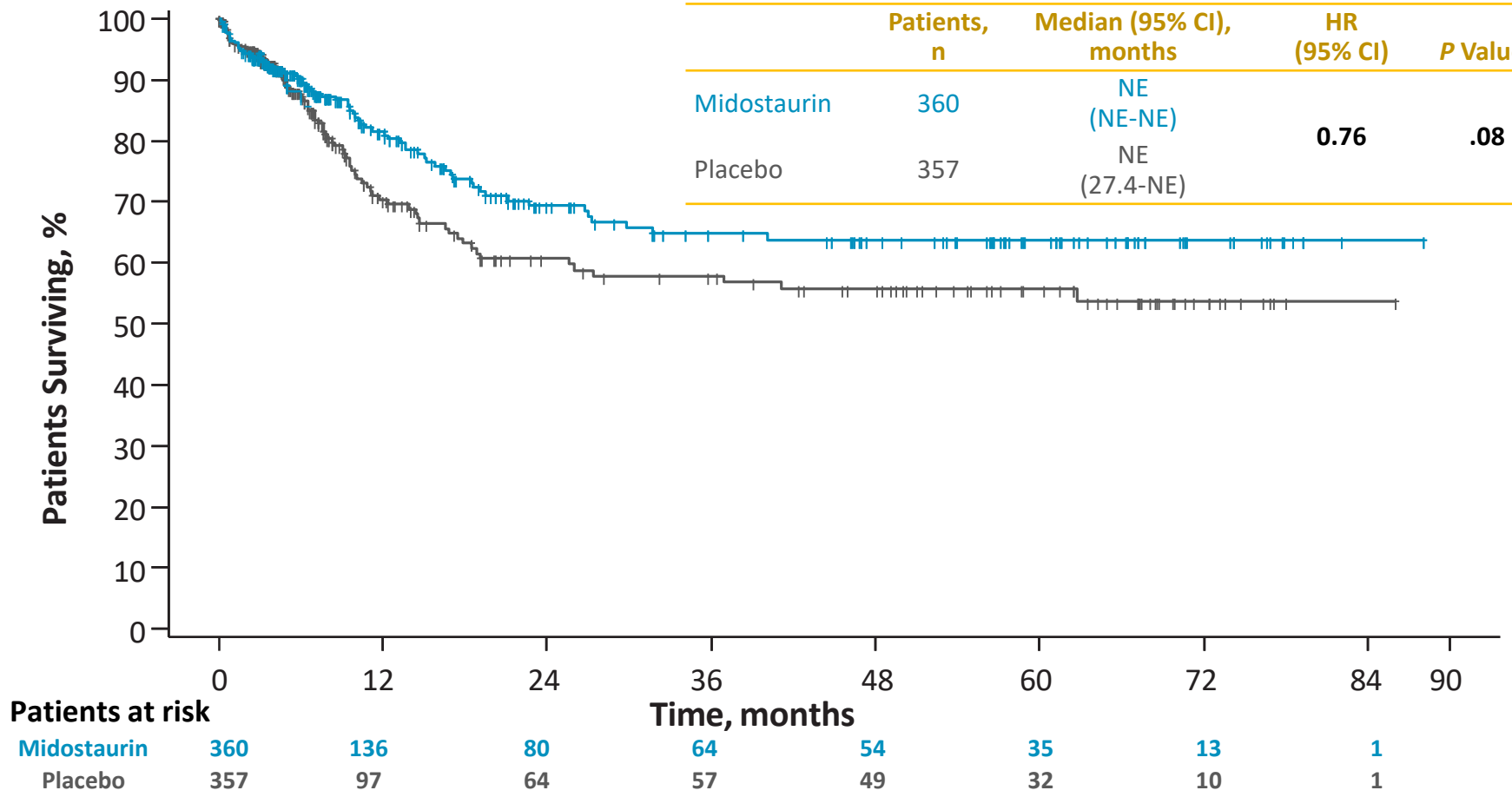
From Stone RM, et al. *N Engl J Med*. 2017;377:454-464. Copyright © 2017 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

FLT3-ITD-low, *FLT3*-ITD/-WT allelic ratio < 0.7; *FLT3*-ITD-high, *FLT3*-ITD/-WT allelic ratio ≥ 0.7.

[a] *P* value is one-sided for the overall (stratified) analysis; *P* values are two-sided for the analyses by FLT3 subgroup.

RATIFY: OS, censored at time of SCT

Secondary endpoint



	Patients, n	Median (95% CI), months	HR (95% CI)	*P* Value[b]
Midostaurin	360	NE (NE-NE)	**0.76**	**.08**
Placebo	357	NE (27.4-NE)		

Patients at risk

Midostaurin	360	136	80	64	54	35	13	1
Placebo	357	97	64	57	49	32	10	1

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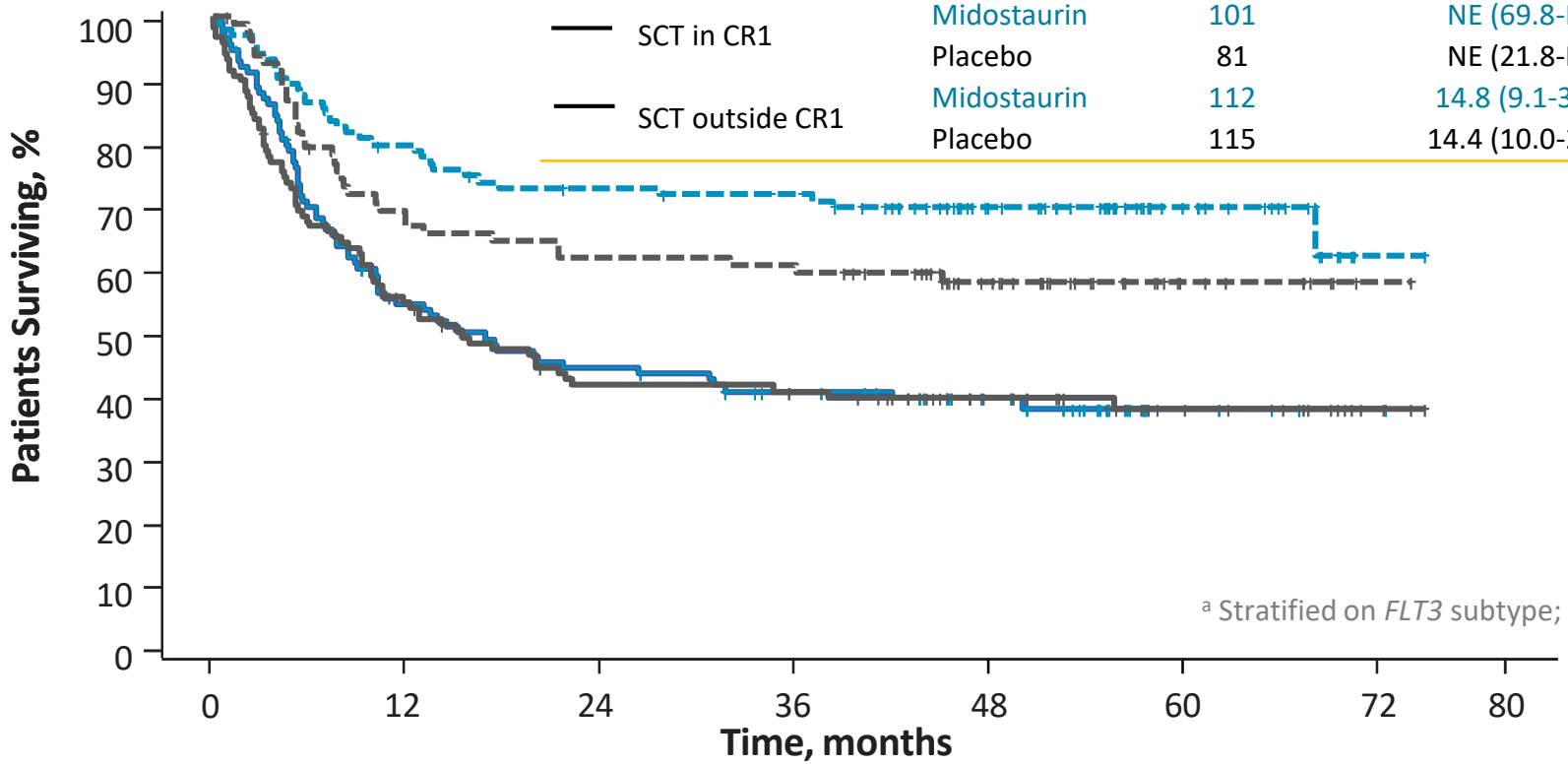
* Stratified on FLT3 subtype; two-sided, long-rank *P* value.

RATIFY: OS by timing of SCT

Secondary endpoint

		Patients, n	Median (95% CI), months	*P* Value[a]
SCT in CR1	Midostaurin	101	NE (69.8-NE)	.07
	Placebo	81	NE (21.8-NE)	
SCT outside CR1	Midostaurin	112	14.8 (9.1-31.6)	.85
	Placebo	115	14.4 (10.0-22.7)	



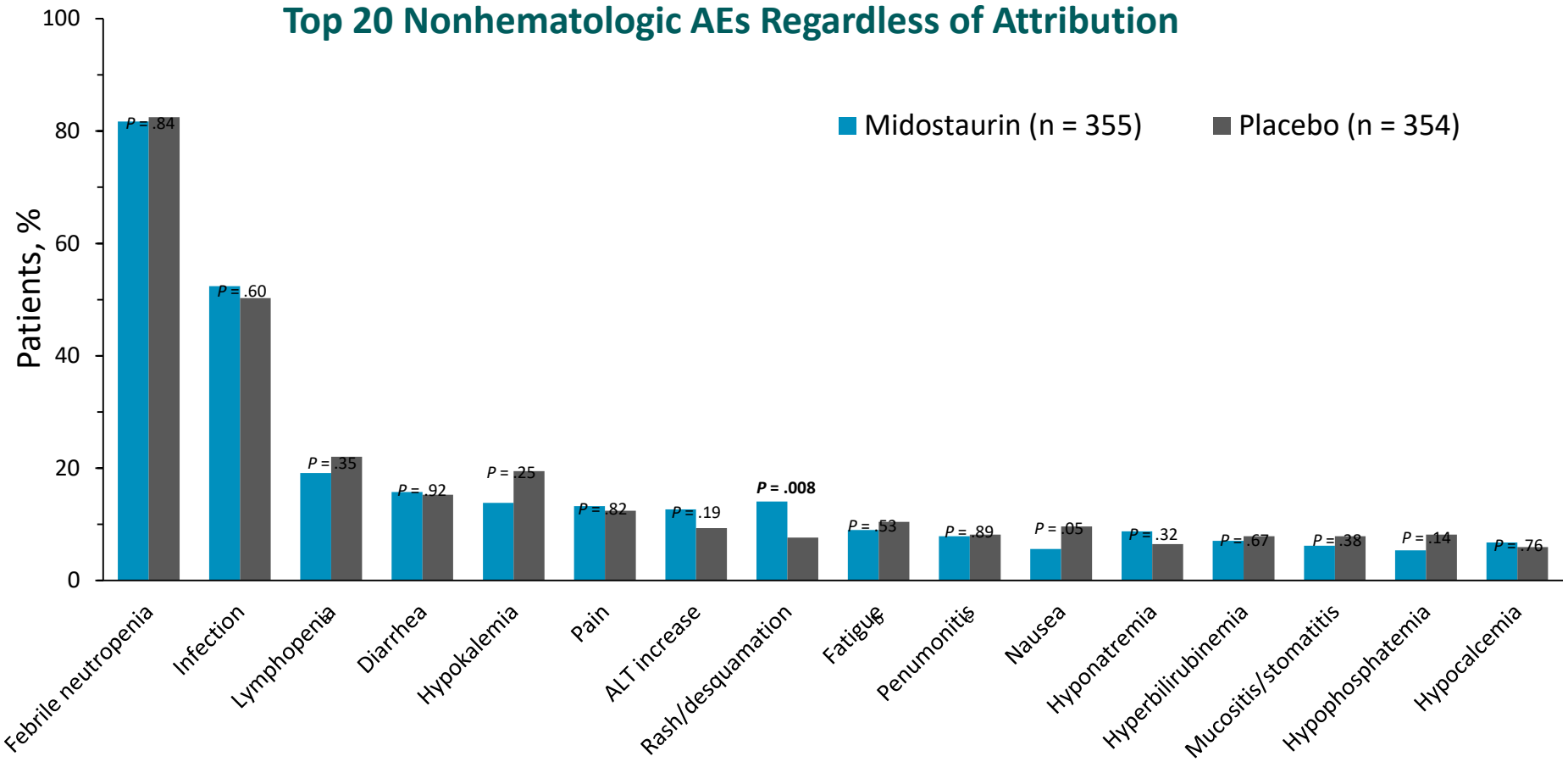
[a] Stratified on *FLT3* subtype; 2-sided, log-rank *P* value.

Patients at risk

SCT in CR1	Midostaurin	101	71	63	21	0
	Placebo	81	50	45	12	0
SCT outside CR1	Midostaurin	112	49	36	5	0
	Placebo	115	47	37	13	0

RATIFY: Safety

Most common nonhematologic grade ≥ 3 AEs



[a] Infection includes the following terms: infection with grade 3/4 neutrophils (ANC < 1.0 × 10^3/μL), infections with normal ANC or grade 1/2 neutrophils, infection with unknown ANC, opportunistic infection associated with grade ≥ 2 lymphopenia, and other infections.
[b] Fatigue includes asthenia, lethargy, and malaise.
[c] Includes pneumonitis and pulmonary infiltrates.

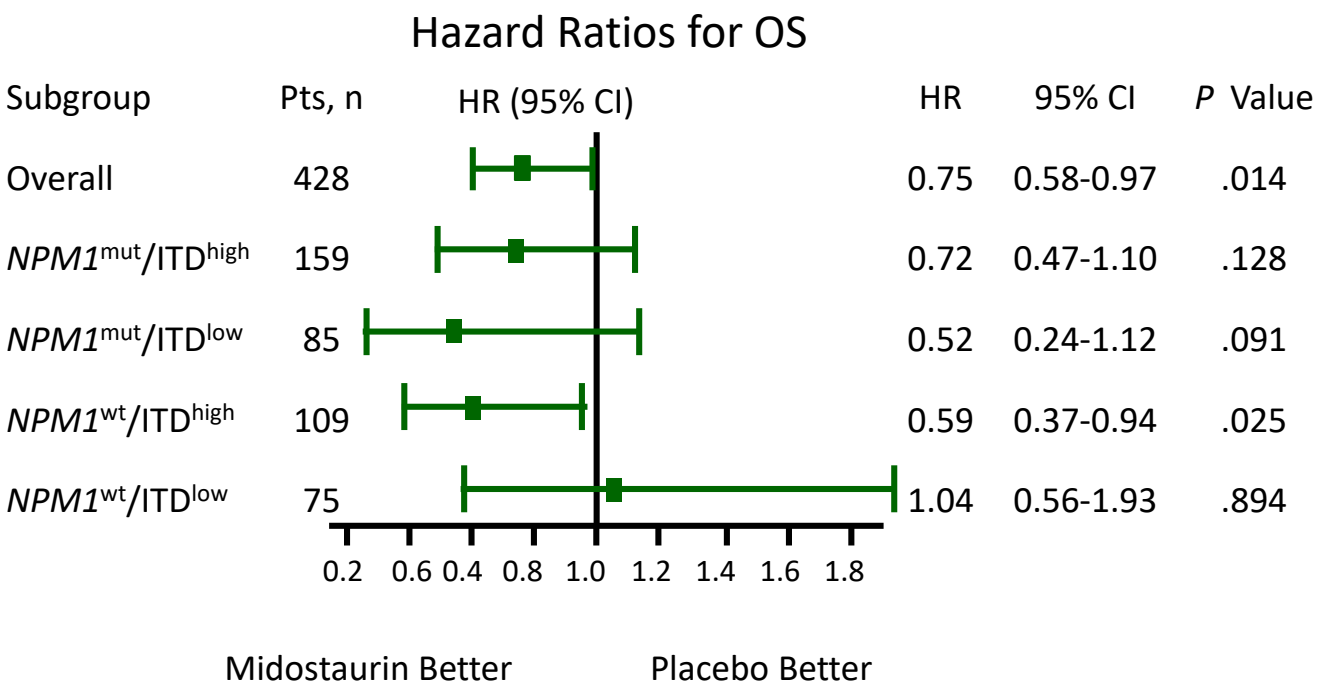
Stone RM, et al. N Engl J Med. 2017;377:454-464.

RATIFY: Summary

- The RATIFY trial met its primary endpoint of OS
  - Midostaurin reduced the risk of death vs placebo plus standard chemotherapy by 22%
- Despite high rates of SCT, OS and EFS benefits were consistent in censored and uncensored analyses
  - OS uncensored HR = 0.78 (0.63-0.96), censored HR = 0.76
  - EFS uncensored HR = 0.78 (0.66-0.93)
- The most common non-hematologic grade 3/4 AEs (midostaurin vs placebo) were febrile neutropenia (82% vs 82%), infection (52% vs 50%), and diarrhea (16% vs 15%)
- Rates of grade 3/4 AEs were similar between midostaurin and placebo arms with the exception of rash/desquamation (14% vs 8%, respectively)

Stone RM, et al. *N Engl J Med*. 2017;377:454-464.

Prognostic Analysis of *NPM1*/*FLT3*-ITD Genotypes in RATIFY: Multivariate OS Analysis



Multivariate Analysis for OS

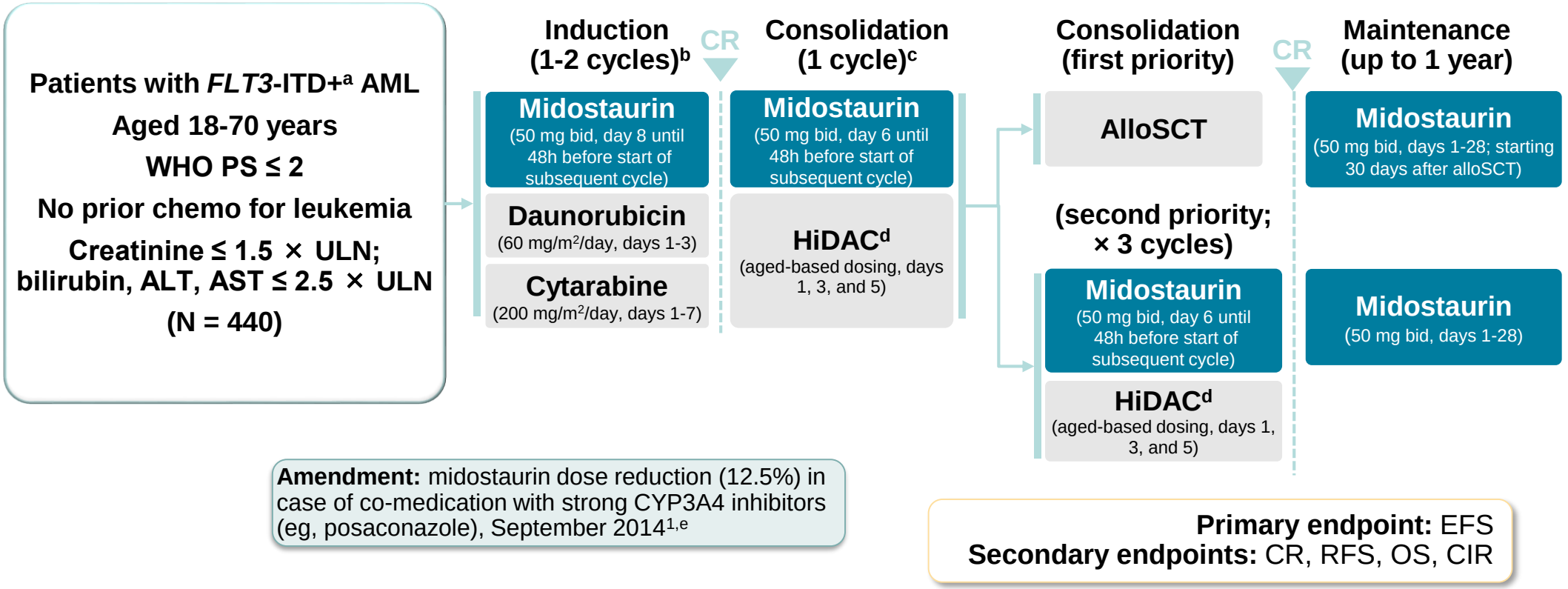
Characteristic	2-Sided P Value
ELN subgroup (NPM1/FLT3-ITD)	< .001
Treatment (midostaurin vs placebo)	.012
Allogeneic HCT	< .001
WBC (≥ vs < 50 x 10^9/L)	.028
Age (difference of 10 yrs)	.335
Sex	.689

Slide credit: clinicaloptions.com

Dohner K, et al. ASH 2017. Abstract 467.

DE02T/AMLSG 16-10: study design[1,2]

Phase 2, open-label, uncontrolled, single-arm trial



Amendment: midostaurin dose reduction (12.5%) in case of co-medication with strong CYP3A4 inhibitors (eg, posaconazole), September 2014[1,e]

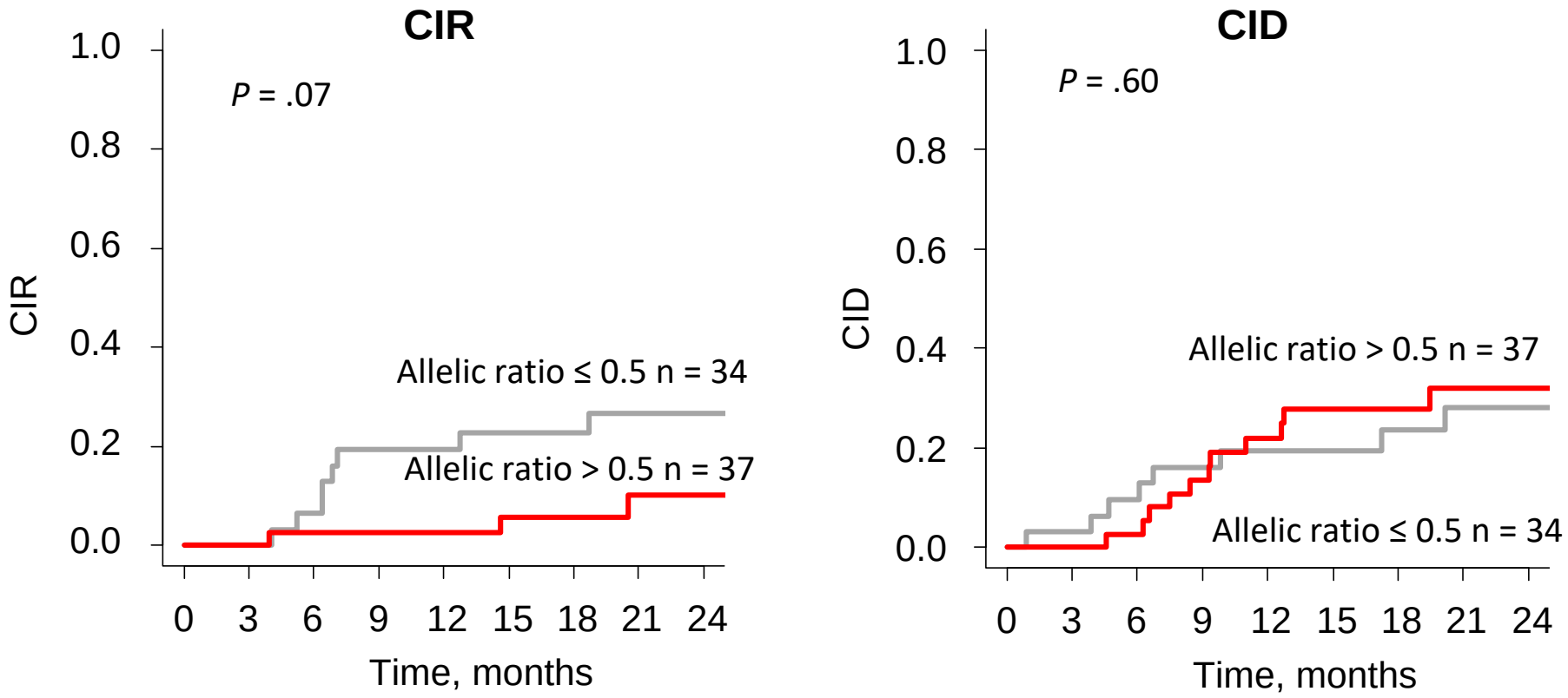
Primary endpoint: EFS
Secondary endpoints: CR, RFS, OS, CIR

CIR, cumulative incidence of relapse; CR, complete remission; EFS, event-free survival; OS, overall survival; RFS, relapse-free survival.
[a] *FLT3* screening results within 48 hours; *FLT3*-ITD/-WT ratio > 0.05 by Genescan-based fragment length analysis required to be *FLT3*-ITD positive.
[b] During induction, patients achieving PR after cycle 1 can receive an optional cycle 2.
[c] For patients eligible for alloSCT, 1 course of HiDAC is optional before alloSCT.
[d] Age-appropriate cytarabine dose on days 1, 3, and 5: 18-65 years, 3 g/m² q12h (total dose 18 g/m²); > 65 years ,1 g/m² q12h (total dose 6 g/m²).
[e] Dose reduction of 7-fold (12.5%) was based on the lower bound of the confidence interval of the ratio [AUC midostaurin with ketoconazole/AUC midostaurin without ketoconazole]; midostaurin 25 mg every other day.

1. Schlenk RF, et al. *Blood*. 2016;128(22):[abstract 449]. 2. ClinicalTrials.gov.

DE02T/AMLSG 16-10: CIR and CID

For patients in CR1 per protocol



- Patients who received maintenance therapy (n = 52; 41 after alloSCT and 11 after high-dose cytarabine) received a median number of 6 cycles (range, 1-12)
  - Maintenance after alloSCT was prematurely terminated in 33 patients (80%)

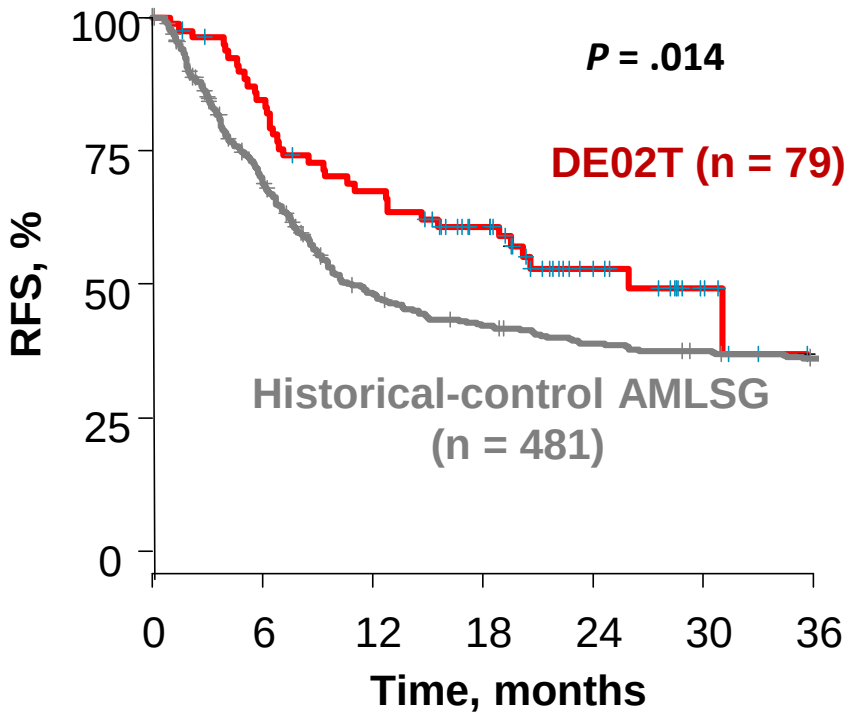
From Schlenk RF, et al. In: Proceedings from the American Society of Hematology; December 5-8, 2015; Orlando, FL [abstract 322]. Reprinted with author's permission.

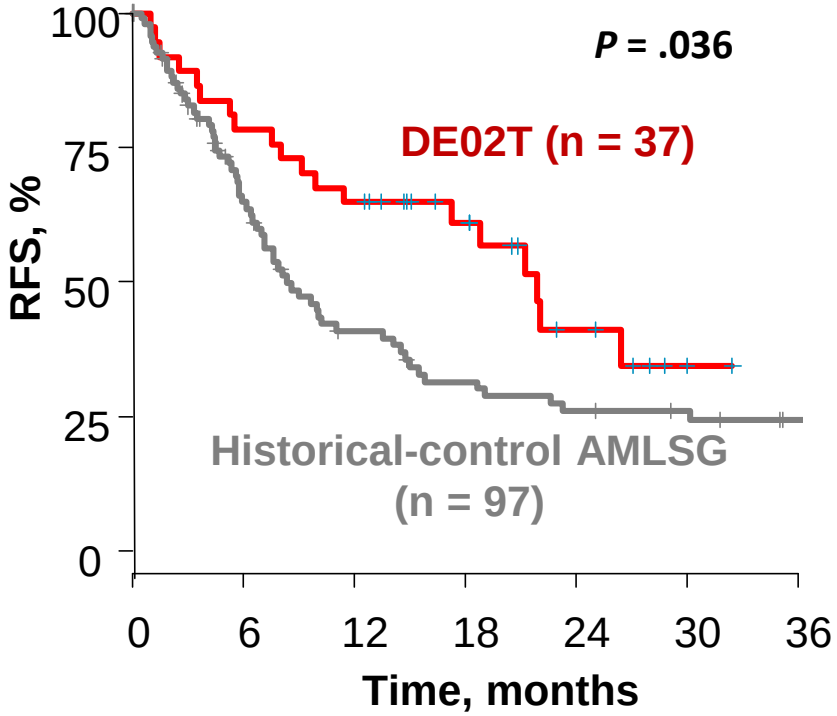
DE02T/AMLSG 16-10: RFS

Patients Aged 18 to < 60 years

Patients Aged 60-70 years

- Patients in the DE02T/AMLSG 16-10 study had improved RFS vs historical control





From Schlenk RF, et al. In: Proceedings from the American Society of Hematology; December 5-8, 2015; Orlando, FL [abstract 322].
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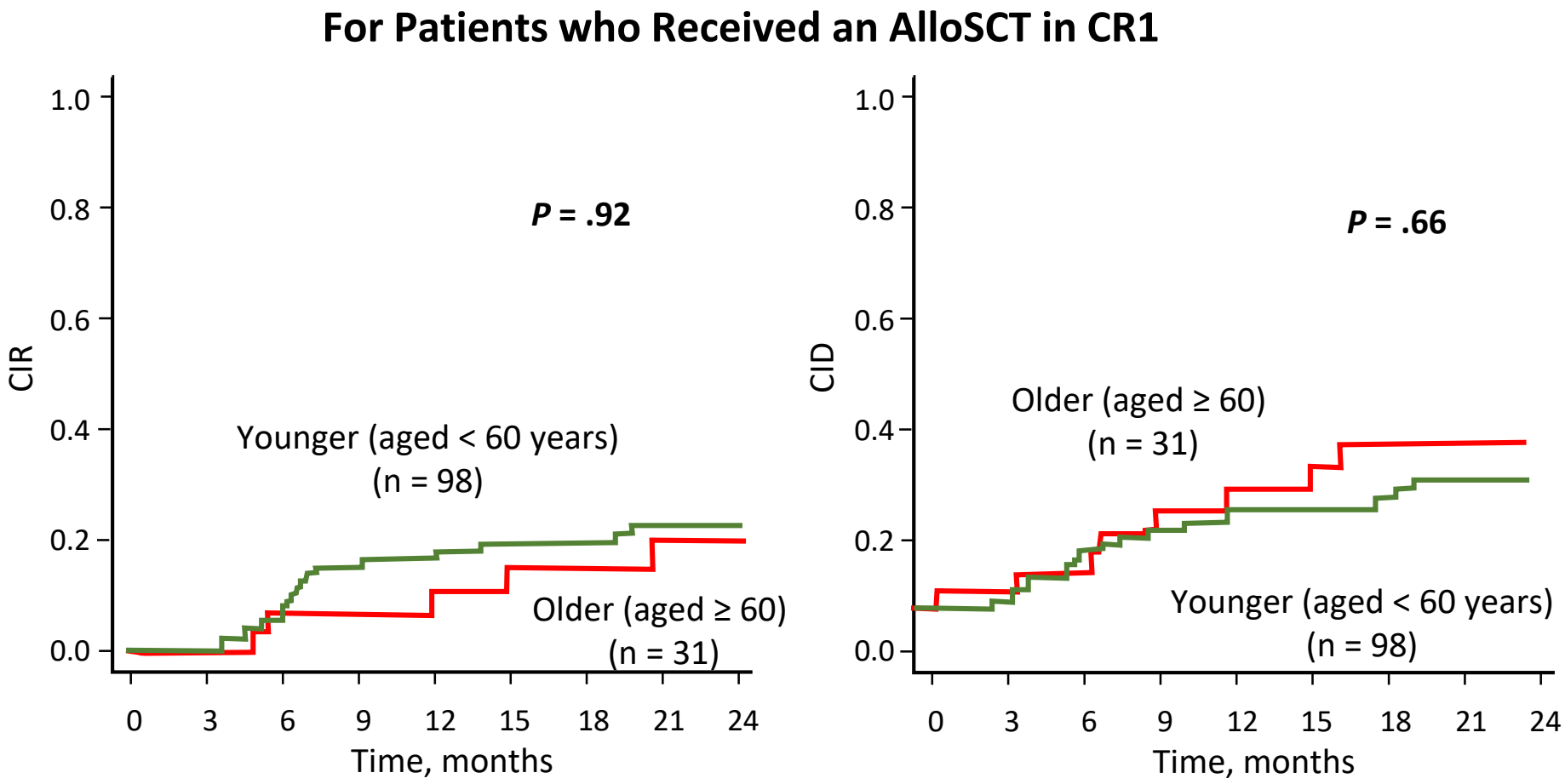
DE02T/AMLSG 16-10: CIR and CID by age

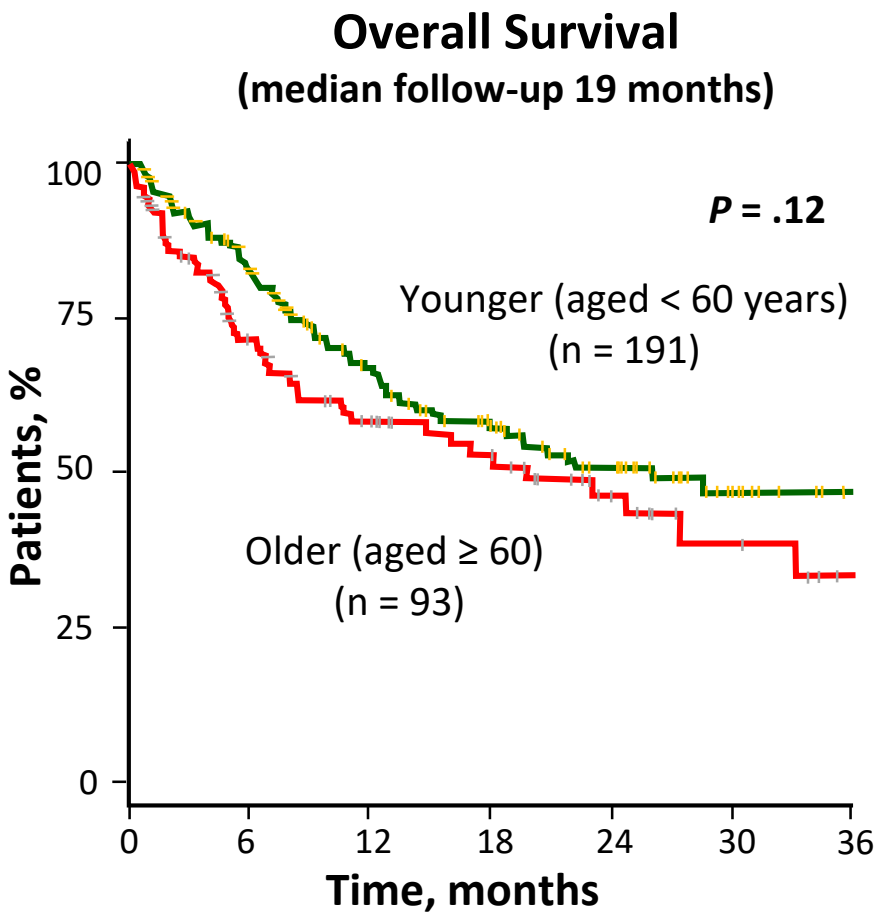
(< 60 years vs ≥ 60 years)

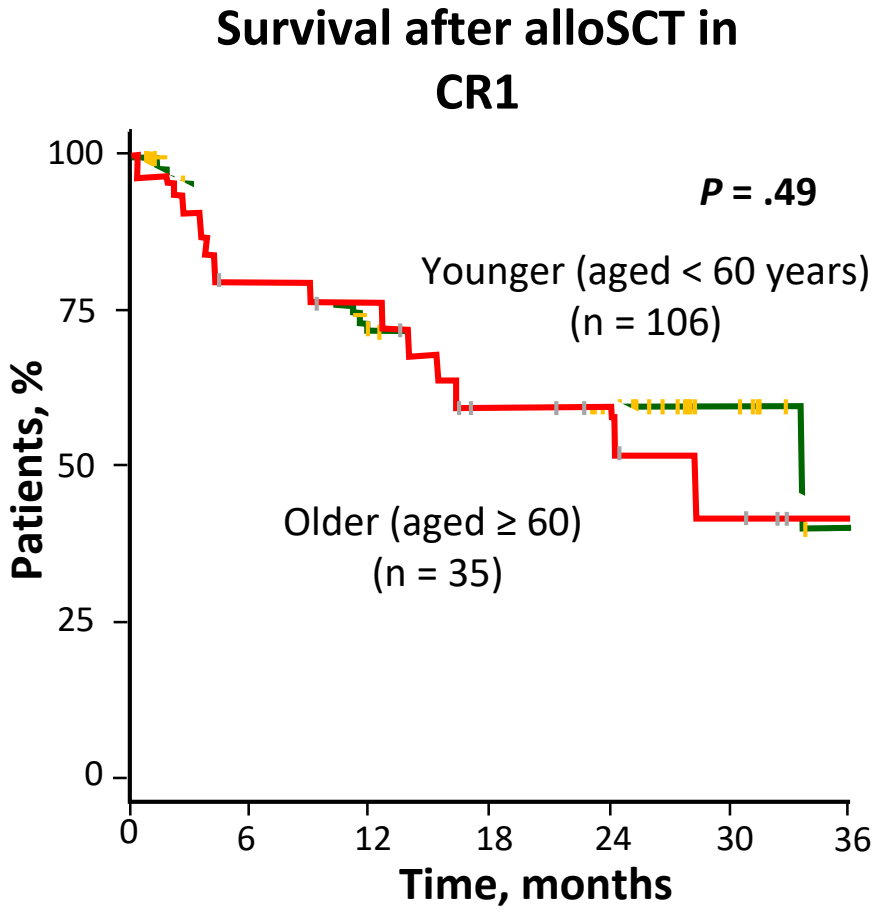


From Schlenk RF, et al. In: Proceedings from the American Society of Hematology; December 3-6, 2016; San Diego, CA [abstract 449]. Reprinted with author's permission.

DE02T/AMLSG 16-10: Survival by age

(< 60 years vs ≥ 60 years)





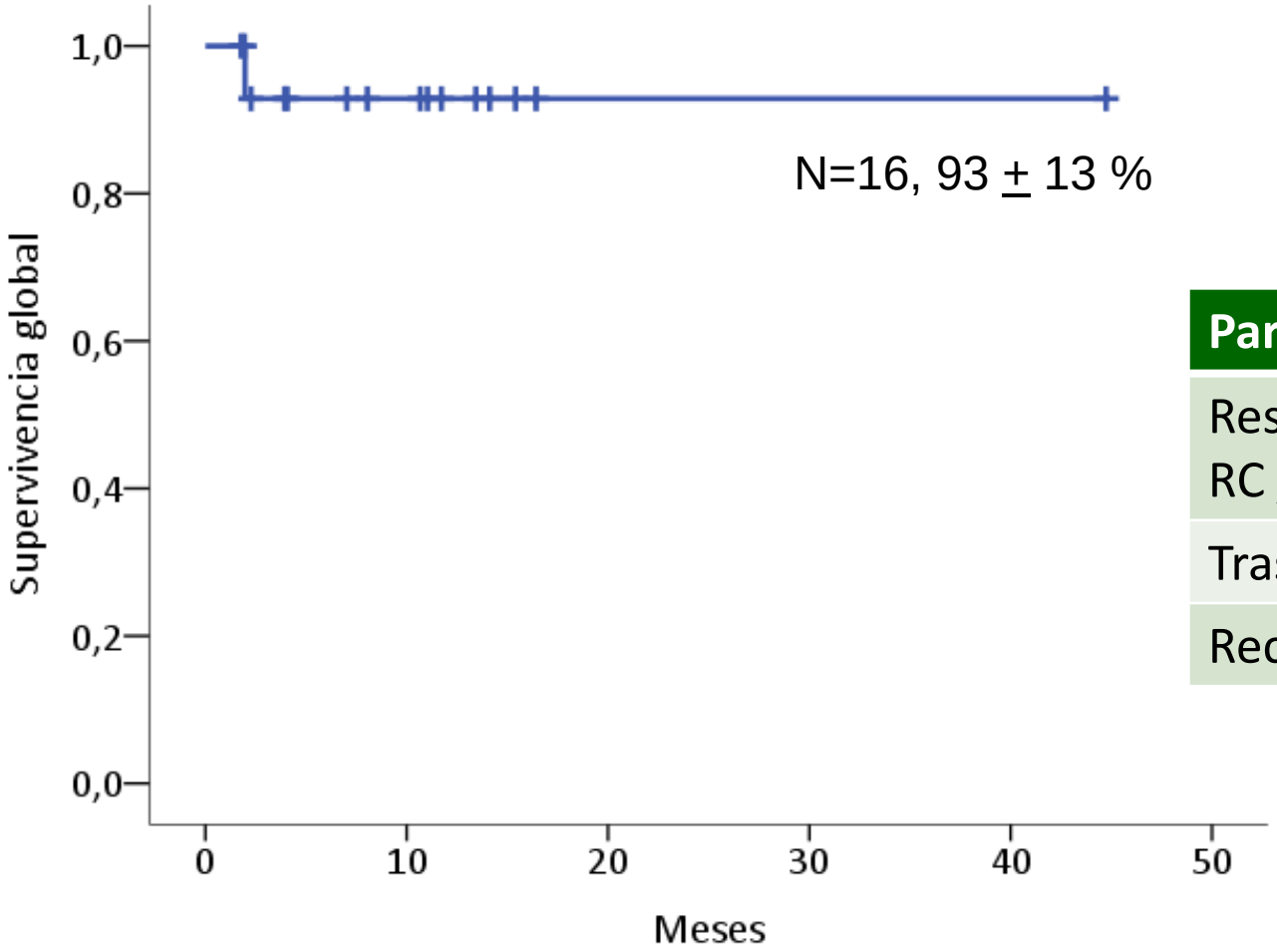
From Schlenk RF, et al. In: Proceedings from the American Society of Hematology; December 3-6, 2016; San Diego, CA [abstract 449]. Reprinted with author's permission.

Midostaurina en LMA de novo con FLT3-ITD): CETLAM (n=16)

Característica	Valor
Edad (mediana, extremos) <60 años / >60 años	51 (24-64) 13 (81) / 3 (19)
Sexo (varón/mujer)	10 (63) / 6 (37)
Leucocitosx10^9/l	95 (66-122)
Plaquetas x10^9/l	53 (13-155)
Citogenética (MRC) Favorable/Intermedia/Adversa	 1 (7) / 13 (81) / 2 (12)
Ratio FLT3 (<0,5 / $\geq$0,5)	4 (25) / 12 (75)
NPM1 mutado	8 (50)

Registro de CETLAM, Mayo de 2018

Midostaurina en LMA de novo con FLT3-ITD): CETLAM (n=16)



Parámetro	Valor
Resultado de inducción RC / RF / Exitus (n=14)	12(86)/2(14)/0 (0)
Trasplante alogénico (Sí/No)	8 (50)
Recaido / Fallecido / Vivo	3(19)/1(6)/15(94)

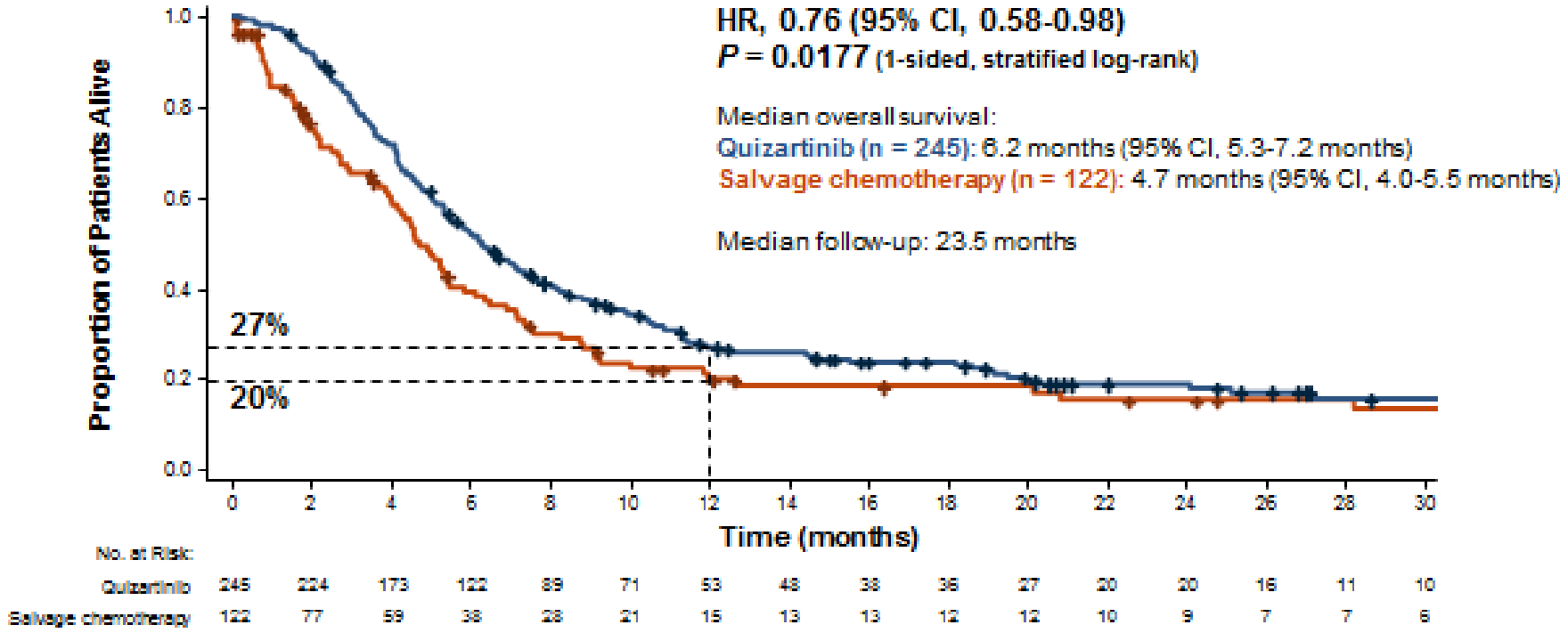
Other FLT3 inhibitors (I)

	Specificity	Available data	Ongoing or recently completed trials
Sorafenib	Non-specific but potent inhibitor of FLT3/ITD RTK	Leads to transient reductions in marrow and circulating myeloblasts **Improves EFS in combination with chemotherapy in younger patients, regardless of FLT3 mutational status**	Phase II sorafenib **with HMA therapy as upfront approach for FLT3/ITD-mutant patients** (NCT02196857) **Maintenance sorafenib after HSCT for FLT3/ITD AML** (EudraCT 2010-018539-16)
Quizartinib	Selective and potent inhibitor of FLT3/ITD RTK	As monotherapy, **CR and CRi in sizeable proportion of relapsed FLT3/ITD-mutant** patients	**Combined with HMA** **QuANTUM-R:** quizartinib vs conventional salvage **QuANTUM-First:** Phase III quizartinib with conventional CT in FLT3/ITD (NCT02668653)

Modified from Amir T. Fathi & Yi-Bin Chen, *Eur J Haematol.* 2017;98:330–336

Quizartinib vs Salvage chemotherapy in Rel/Refr AML with FLT3-ITD: Quantum-R

Primary Endpoint: Overall Survival



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Cortes et al. 23rd EHA 2018, LB 2600;

Other FLT3 inhibitors (II)

	Specificity	Available data	Ongoing or recently completed trials
Crenolanib	Active against both FLT3/ITD and FLT3-TKD mutation variants	Multiple ongoing trials of this agent are in progress, including in the frontline and relapsed/ refractory settings	Safety study of crenolanib **combined with upfront induction** in FLT3-mutant patients (NCT02283177) Phase I/II trial of crenolanib **combined with re-induction regimens for R/R FLT3-mutant patients** (NCT02626338) Pilot study of crenolanib **combined with salvage regimens for R/R patients, regardless of FLT3-mutation status** (NCT02400281) Crenolanib **maintenance following stem cell transplant** (NCT02400255
Gilteritinib	Selective FLT3 inhibitor, which can target both FLT3/ITD and FLT3-TKD	Remains under study in clinical trials. **Composite remission rate of 46% among relapsed /refractory FLT3-mutant patients**	Phase III randomized study of **gilteritinib vs conventional salvage CT** among FLT3-mutant Phase II/III study of **gilteritinib combined with HMA therapy** Phase I study **of gilteritinib combined with conventional induction CT** Phase III study of **gilteritinib maintenance among FLT3-mutant patients in first remission** Phase III randomized study of **maintenance gilteritinib after HSCT for patients with FLT3/ITD AML CR1**

Modified from Amir T. Fathi & Yi-Bin Chen, *Eur J Haematol.* 2017;98:330–336

FLT3-ITD AML: Approaches to further investigate

Mechanisms of Resistance to FLT3 Inhibitors and the Role of the Bone Marrow Microenvironment

Ghiaur G, Levis M. Hematol Oncol Clin North Am. 2017Aug;31(4):681-692. doi: 10.1016/j.hoc.2017.04.005. PMID: 28673395.

Combination with immunotherapy

Tyrosine kinase inhibition increases the cell surface localization of FLT3-ITD and enhances FLT3-directed immunotherapy of acute myeloid leukemia. Reiter K, et al. Leukemia. 2017 Aug 14. doi: 10.1038/leu.2017.257. PMID: 28895560.

Intensification of therapy resulted in a reduced relapse risk

Gemtuzumab Ozogamicin in induction therapy

(Castaigne S, et al. Lancet 2012; 379: 1508–16.)

High-dose daunorubicin in induction therapy

(Burnett AK, et al. Blood. 2016;128(3):449-52.)


¡Gracias por la invitación!