GITMO · Rete Ematologica Pugliese · SIE "Società Italiana di Ematologia" · fondazione GIMEMA

Real World Evidence

Nuovi target terapeutici in ematologia

Presidente del Convegno
Nicola Cascavilla

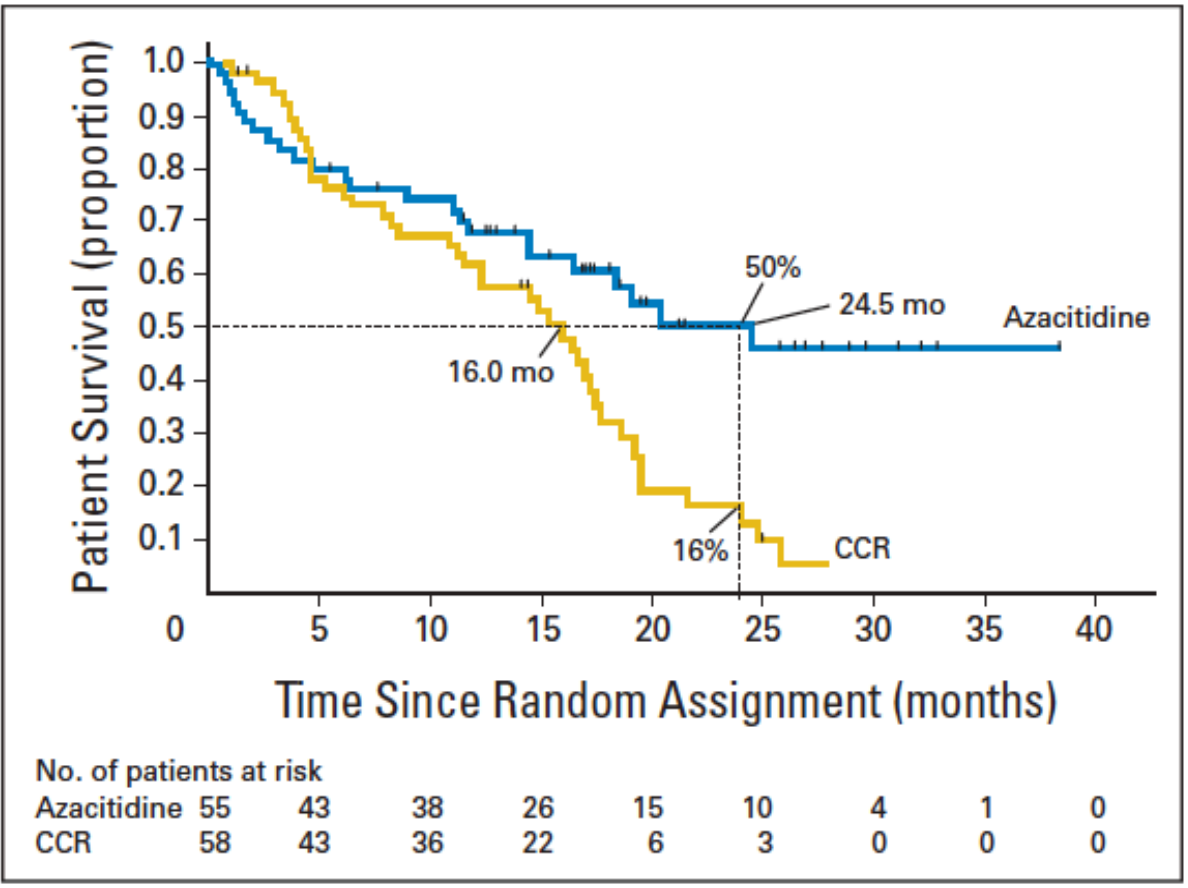
Auditorium "Fra Agostino Daniele"
San Giovanni Rotondo
8 - 9 Novembre 2018

Confronto con gli studi registrativi

Dott. D. Pastore UOC Ematologia Brindisi

Azacitidine Prolongs Overall Survival Compared With Conventional Care Regimens in Elderly Patients With Low Bone Marrow Blast Count Acute Myeloid Leukemia

Fenaux P et al J Clin Oncol 2012, AZA-001



- AZA vs Conventional Care Regimens (BSC, IC, LDAC)

International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts

Dombret H et al Blood 2015, AML-001

- 488 pts > 65 aa
- AZA 75 mg/m^2 sc 7 gg or CCR (BSC or low dose ARA-C or lC)
- Primary end point OS
- Secondary end point 1 y OS

International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts

Dombret H et al Blood 2015, AML-001

	AZA	CCR
Prior MDS	20%	15%
BM blast	70%	72%
Cytogenetic Poor Risk	35%	34%
WBC	3.1	2.3

International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts

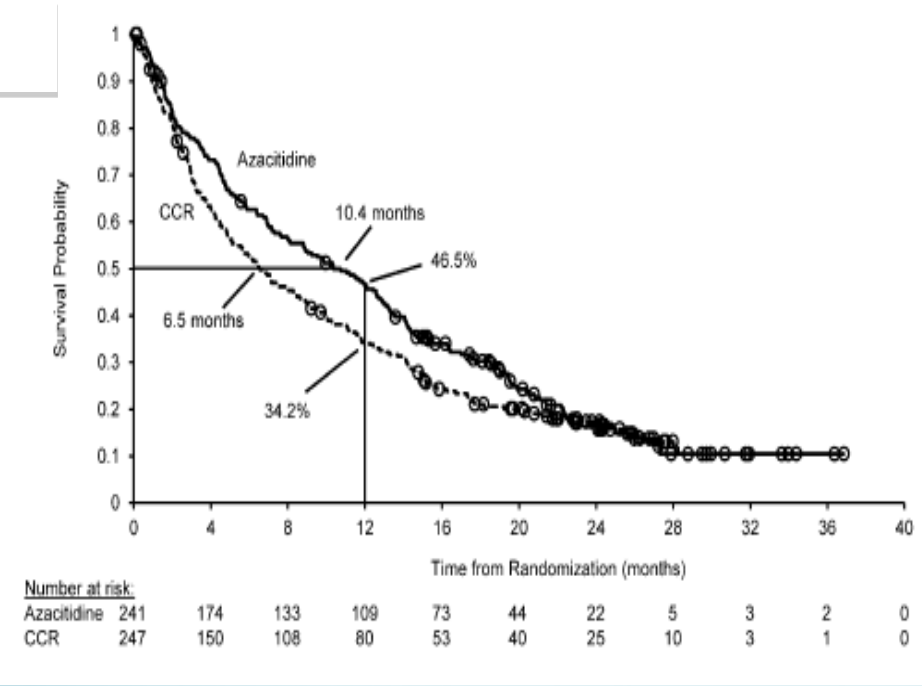
Dombret H et al Blood 2015, AML-001

	AZA	CCR
CR	19%	21%
CRi	8%	3%
CR+CRi	27%	25%
One y survival rate	46%	34%

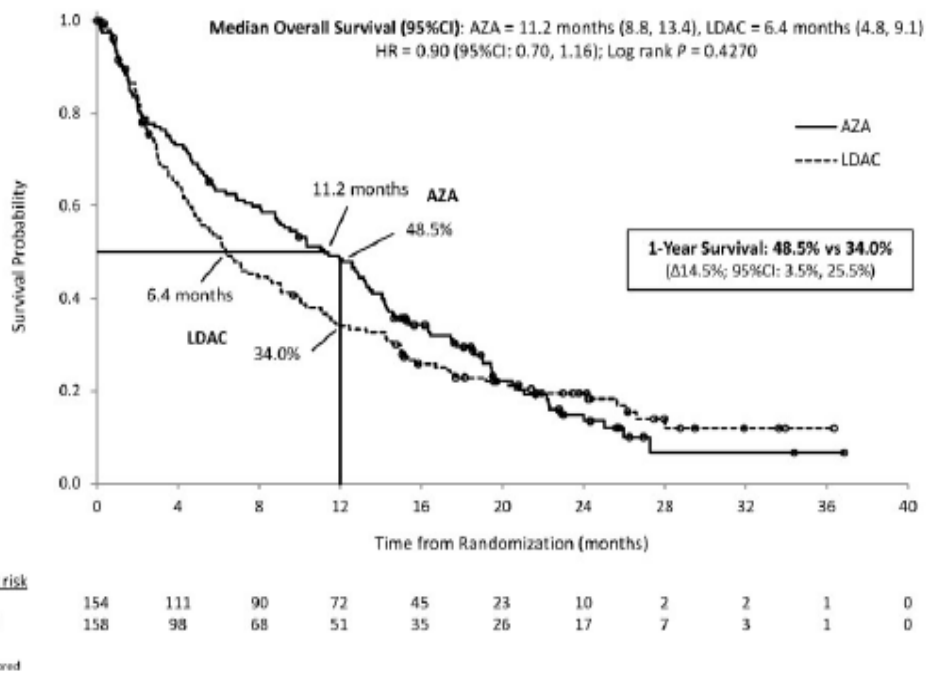
International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts

Dombret H et al Blood 2015, AML-001

AZA vs CCR



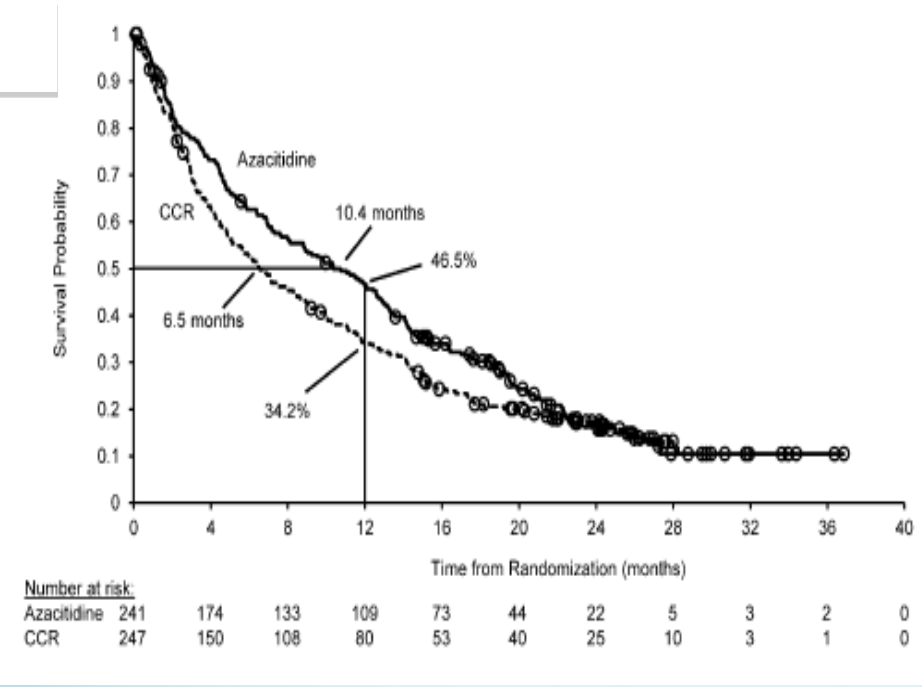
AZA vs LDAC



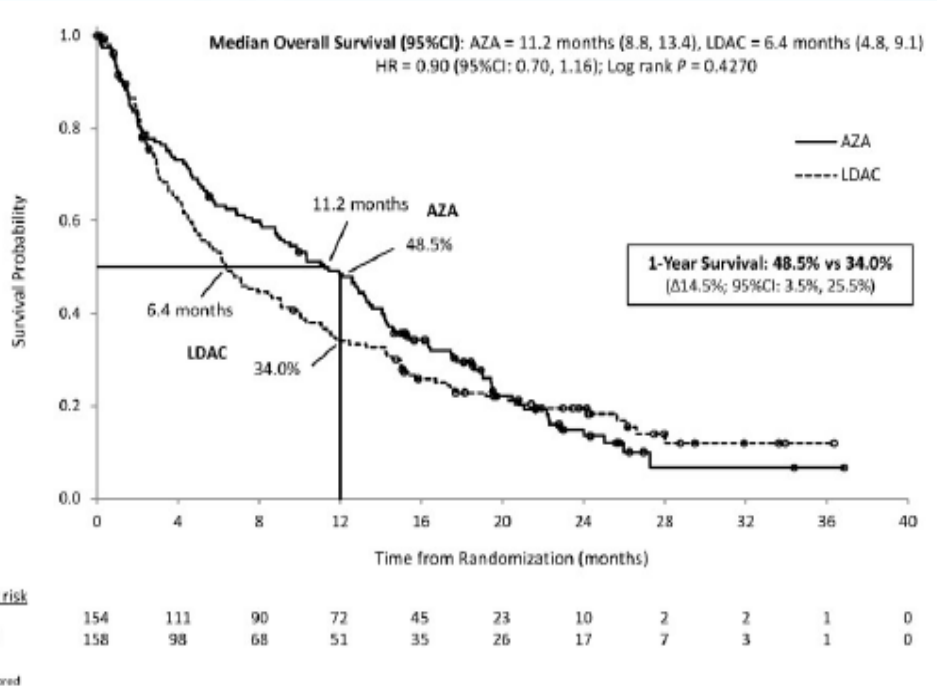
International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts

Dombret H et al Blood 2015, AML-001

AZA vs CCR



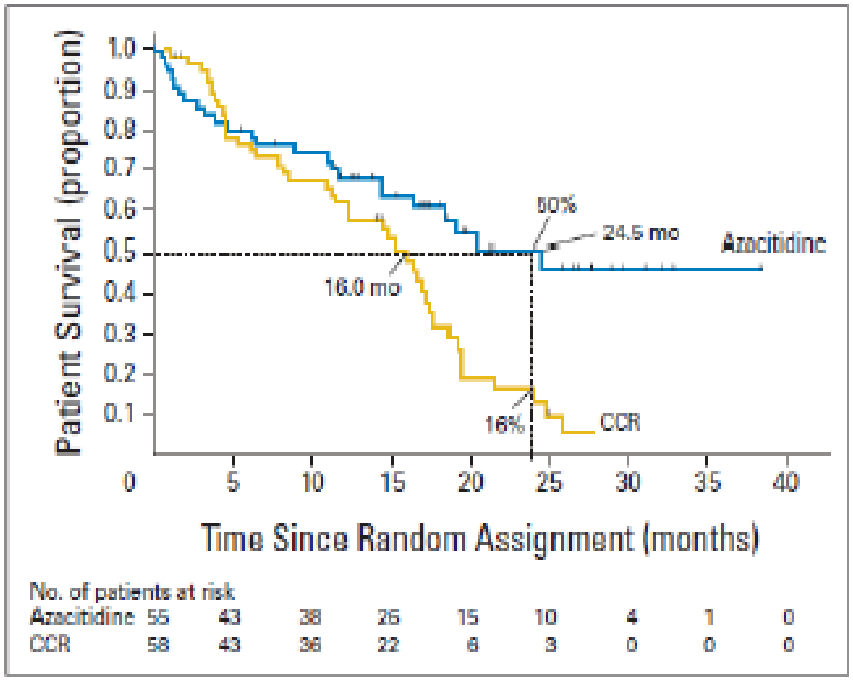
AZA vs LDAC



HMAs **ben riproducono nella pratica clinica quello che avviene negli studi clinici controllati**

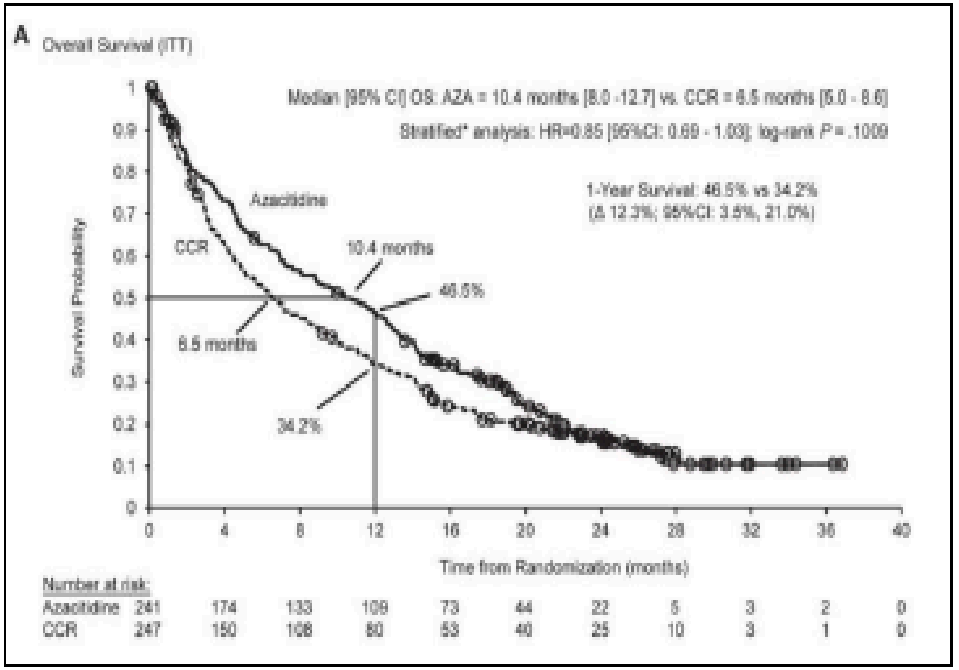
20%<BM blasts<30%

AZA-001
24.5 mesi per AZA vs. 16.0 mesi per CCR
HR=0.47 ; p=0.005



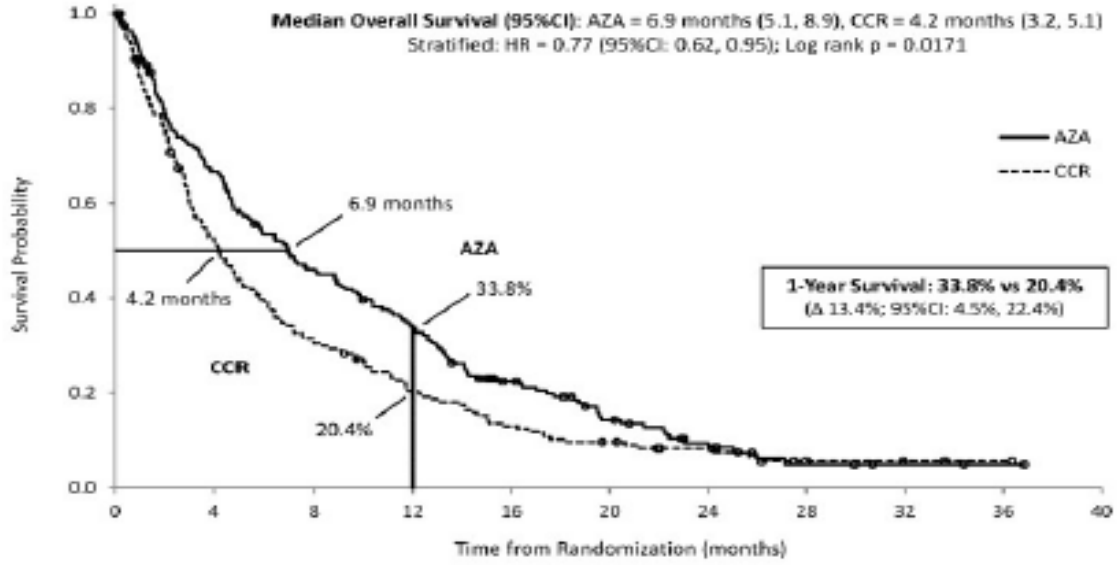
BM blasts>30%

AML-001
10.4 mesi per AZA vs. 6.5 mesi per CCR
HR=0.85 ; p=0.1009



AML-001 (pazienti senza remissione completa)
6.9 mesi per AZA vs. 4.2 mesi per CCR
HR=0.77 ; p=0.0171

Figure. Overall survival for patients who did not achieve CR



Pts at risk											
AZA	194	127	87	63	36	20	9	4	2	1	0
CCR	193	96	56	36	23	16	11	3	2	1	0

O Censored

I pazienti che non ottenevano al RC presentavano un andamento clinico migliore con gli ipometilanti

AML-001 (pazienti senza remissione completa)
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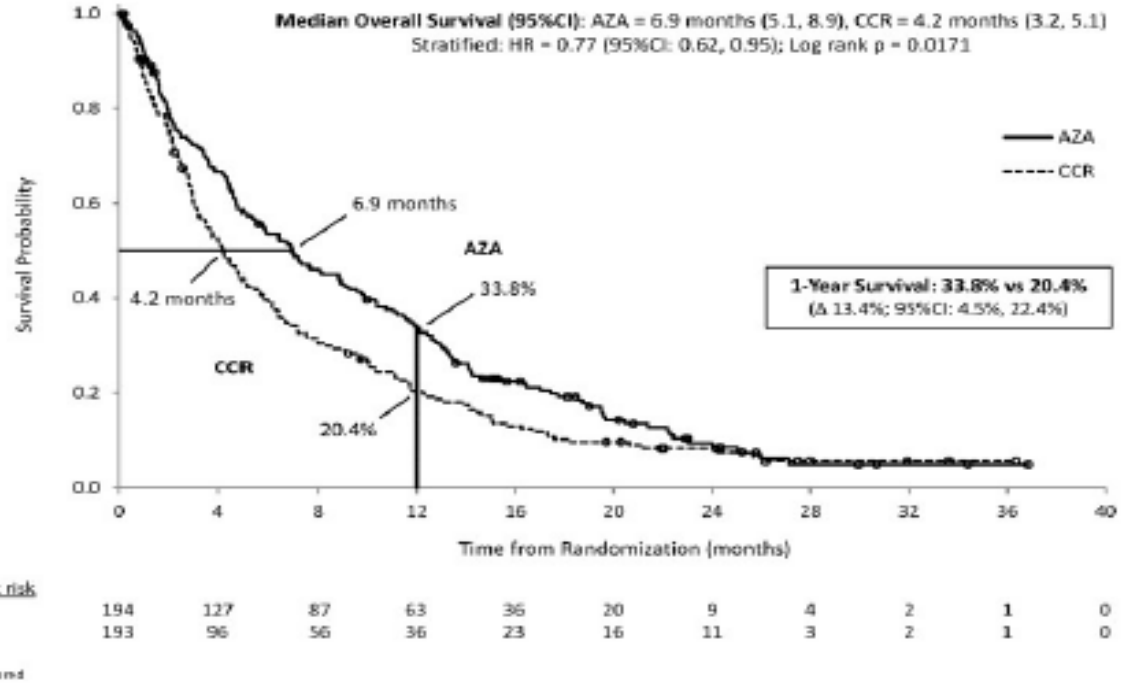
Figure. Overall survival for patients who did not achieve CR



Gli ipometilanti possono dare risposte clinicamente significative , con un importante beneficio clinico, anche in assenza di RC

AML-001 (pazienti senza remissione completa)
6.9 mesi per AZA vs. 4.2 mesi per CCR
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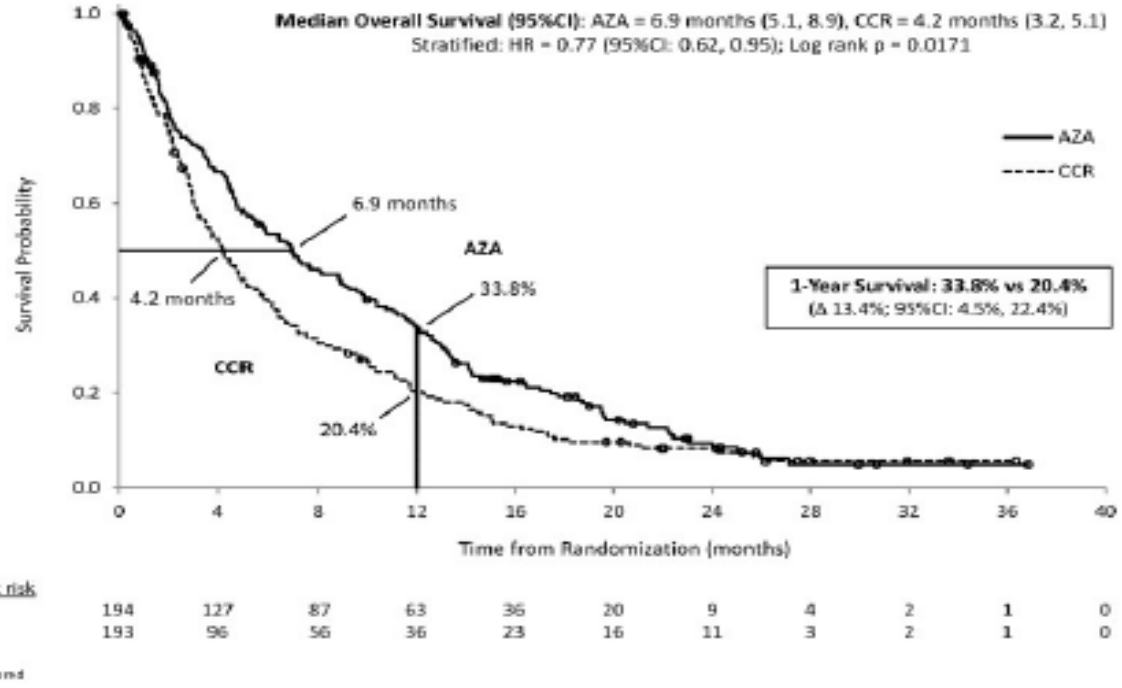

LMA 20-30% Blasti e displasia multilineare
LMA Blasti>30%

VOLUME 30 · NUMBER 21 · JULY 20 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Studio DACO-016

Multicenter, Randomized, Open-Label, Phase III Trial of Decitabine Versus Patient Choice, With Physician Advice, of Either Supportive Care or Low-Dose Cytarabine for the Treatment of Older Patients With Newly Diagnosed Acute Myeloid Leukemia

Hagop M. Kantarjian, Xavier G. Thomas, Anna Dmoszynska, Agnieszka Wierzbowska, Grzegorz Mazur, Jiri Mayer, Jyh-Pyng Gau, Wen-Chien Chou, Rena Buckstein, Jaroslav Cermak, Ching-Yuan Kuo, Albert Oriol, Farhad Ravandi, Stefan Faderl, Jacques Delaunay, Daniel Lysák, Mark Minden, and Christopher Arthur

- 485 pts > 65 aa
- DAC 20 mg/m^2 IV 5 gg or ARA-C 20 mg/m^2 sc 10 gg or Supportive care
- Primary end point OS
- Secondary end point CR CRp

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	DAC	ARA-C
BM blasts>50%	43%	42%
Secondary AML	36%	34%
Cytogenetic Poor Risk	36%	36%
WBC	3.1	3.7

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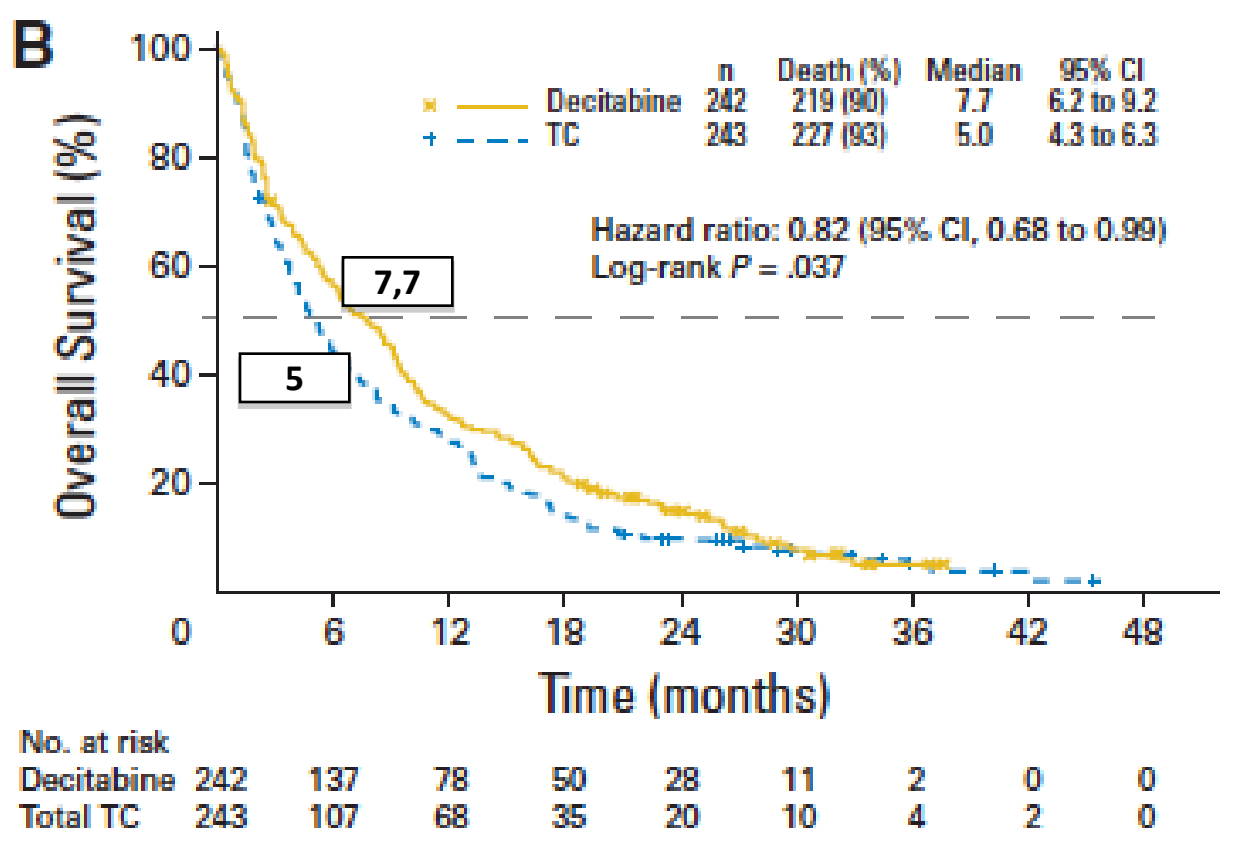

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	DAC	ARA-C
CR	15%	7%
CRi	9%	2%
CRp	2%	0.5%
CR+CRp	17%	8%

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	DAC	ARA-C
Pneumonia	20%	16%
Septic shock	6%	4%
Bronchopneumonia	4%	4%
Exitus	32%	28%

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In conclusion, results of this large, international, multicenter, phase III trial indicated that decitabine achieved a higher response rate, with a possible survival advantage, compared with low-dose cytarabine or SC in thus difficult-to-treat, older population with AML

Multivariate Analysis of the Clinical Variables That Affected Response to Azacitidine

Clinical Variable	Multivariate Analysis[a] HR (95% CI)	*P*
WBC count pretreatment: <10,000/μL vs ≥10,000/μL	0.14 (0.03-0.58)	.006
Previous treatments: No vs yes	4.54 (1.54-13.43)	.006
Type of AML: De novo vs secondary		NS
Azacitidine dose: 75 mg/m^2 vs 100 mg		NS
Combined therapy: No vs yes		NS

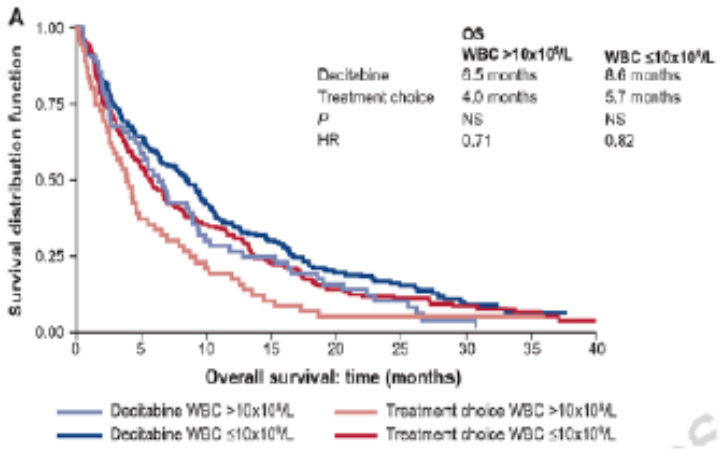
Maurillo L et al Cancer 2012

Studio DACO-016

Pazienti con conta leucocitaria: **≤ 10x10^9/L**

Pazienti con conta leucocitaria: **> 10x10^9/L**

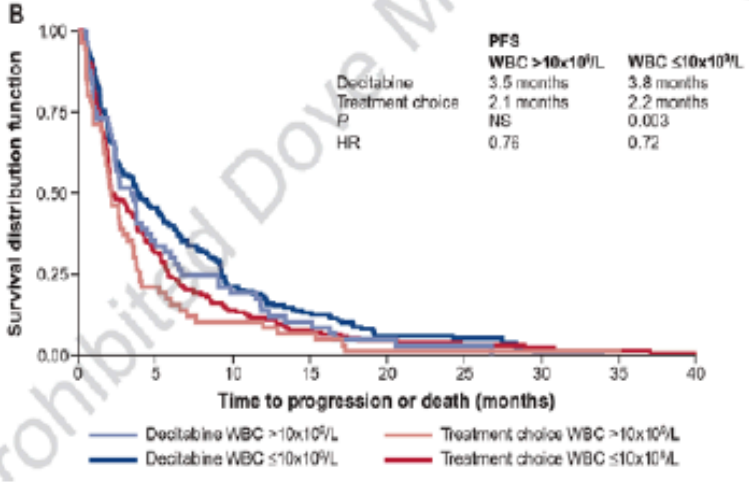
OS



	OS WBC >10x10⁹/L	OS WBC ≤10x10⁹/L
Decitabine	6.5 months	8.6 months
Treatment choice	4.0 months	5.7 months
P	NS	NS
HR	0.71	0.82

Trend di miglioramento della OS per decitabina vs TC **indipendentemente dai valori della conta leucocitaria al basale**

PFS



	PFS WBC >10x10⁹/L	PFS WBC ≤10x10⁹/L
Decitabine	3.5 months	3.8 months
Treatment choice	2.1 months	2.2 months
P	NS	0.003
HR	0.76	0.72

Trend di miglioramento della PFS per decitabina vs TC **indipendentemente dai valori della conta leucocitaria al basale (PFS significativa per pz con WBC<10x10^9/L)**

La conta leucocitaria non impatta né con la OS né con la PFS

ORIGINAL ARTICLE

Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia

Kantarjian H et al N Engl J Med 2017, Tower

- 450 pts Blinatumomab or chemotherapy

	BLINA	CHT
Prevoius alloSCT	34%	33%
Duration of first remission<12 mo	28%	27%
BM blasts>50%	74%	77%
Peripheral blast in count in blood	4.4	4.5

Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia

Kantarjian H et al N Engl J Med 2017, Tower

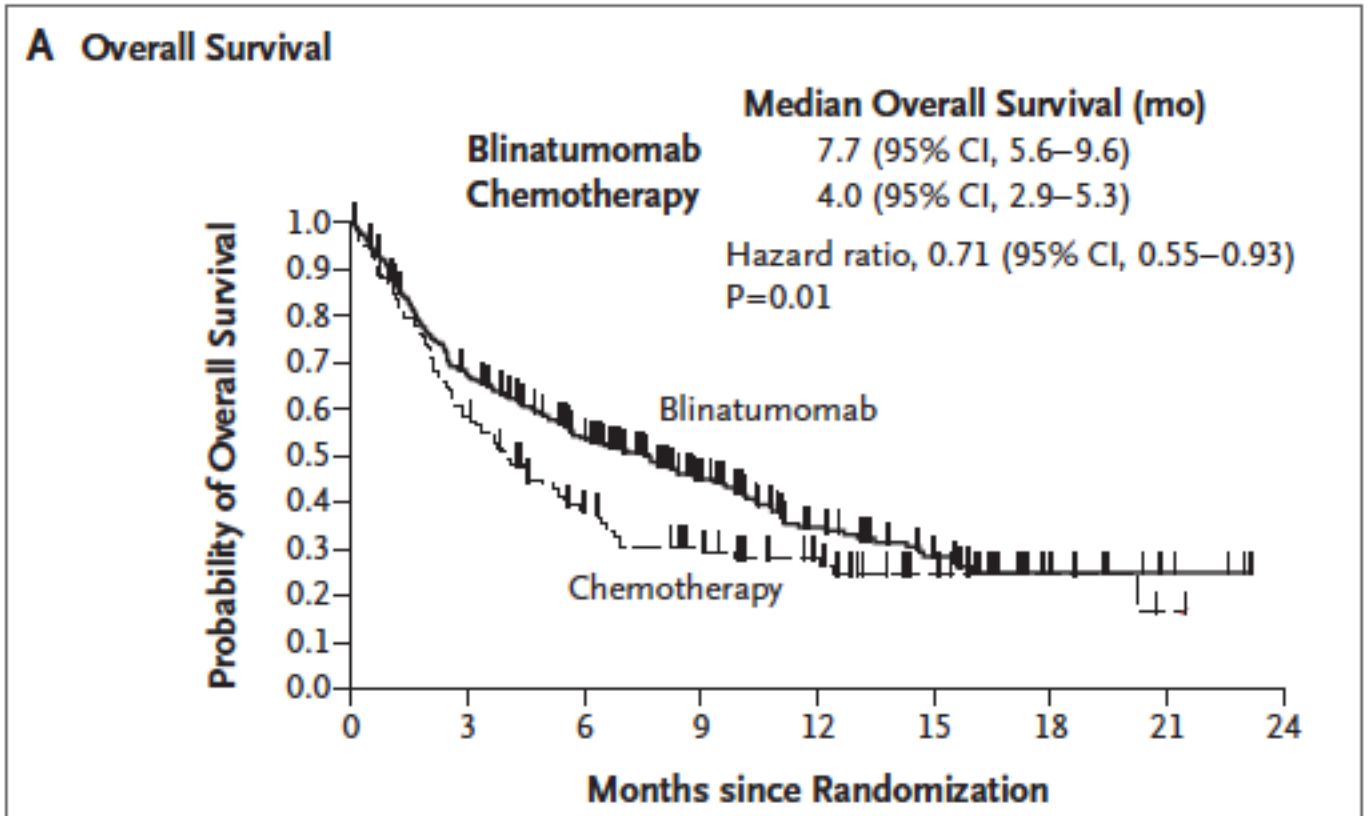


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Table 2. Best Hematologic Response Within 12 Weeks after Treatment Initiation.*

Response Category	Blinatumomab Group (N=271)		Chemotherapy Group (N=134)		Treatment Difference (95% CI)	P Value†
	no.	*% (95% CI)*	*no.*	*% (95% CI)*	*percentage points*	
Complete remission with full hematologic recovery	91	33.6 (28.0–39.5)	21	15.7 (10.0–23.0)	17.9 (9.6–26.2)	<0.001
Complete remission with full, partial, or incomplete hematologic recovery	119	43.9 (37.9–50.0)	33	24.6 (17.6–32.8)	19.3 (9.9–28.7)	<0.001
Complete remission with partial hematologic recovery	24	8.9 (5.8–12.9)	6	4.5 (1.7–9.5)		
Complete remission with incomplete hematologic recovery	4	1.5 (0.4–3.7)	6	4.5 (1.7–9.5)		

Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia

Kantarjian H et al N Engl J Med 2017, Tower

Table 3. Adverse Events.*

Event	Blinatumomab Group (N=267)	Chemotherapy Group (N=109)
	no. of patients (%)	
Any adverse event	263 (98.5)	108 (99.1)
Event leading to premature discontinuation of trial treatment	33 (12.4)	9 (8.3)
Serious adverse event	165 (61.8)	49 (45.0)
Fatal serious adverse event	51 (19.1)	19 (17.4)
Any adverse event of grade ≥3	231 (86.5)	100 (91.7)
Grade ≥3 adverse event of interest reported in at least 3% of patients in either group		
Neutropenia	101 (37.8)	63 (57.8)
Infection	91 (34.1)	57 (52.3)
Elevated liver enzyme	34 (12.7)	16 (14.7)
Neurologic event	25 (9.4)	9 (8.3)
Cytokine release syndrome	13 (4.9)	0
Infusion reaction	9 (3.4)	1 (0.9)
Lymphopenia	4 (1.5)	4 (3.7)
Any decrease in platelet count	17 (6.4)	13 (11.9)
Any decrease in white-cell count	14 (5.2)	6 (5.5)

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LAL B Ph- Rec/Ref

FDA March 2018→LAL IN RC MRD+

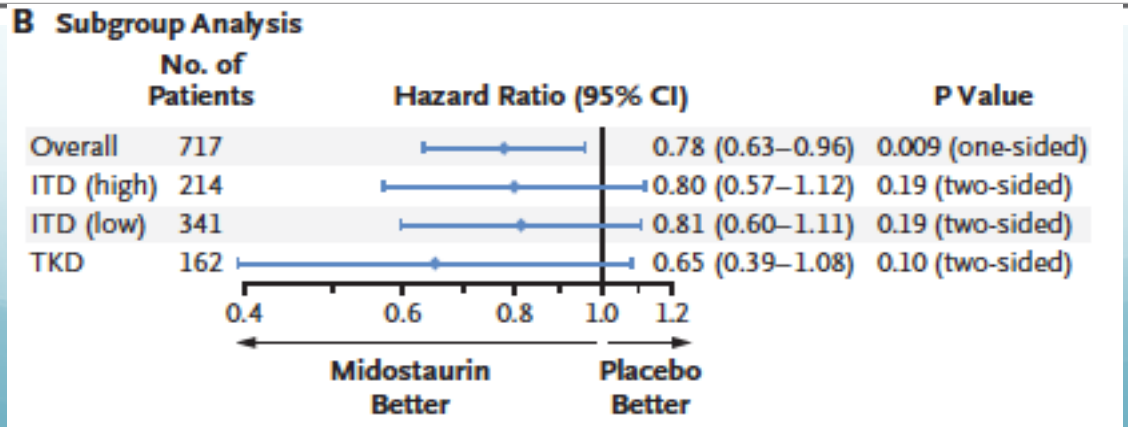
ORIGINAL ARTICLE

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

Stone MR et al N Engl J Med 2017, CALGB 10603 Ratify

Table 3. Summary of Complete Remission.*

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



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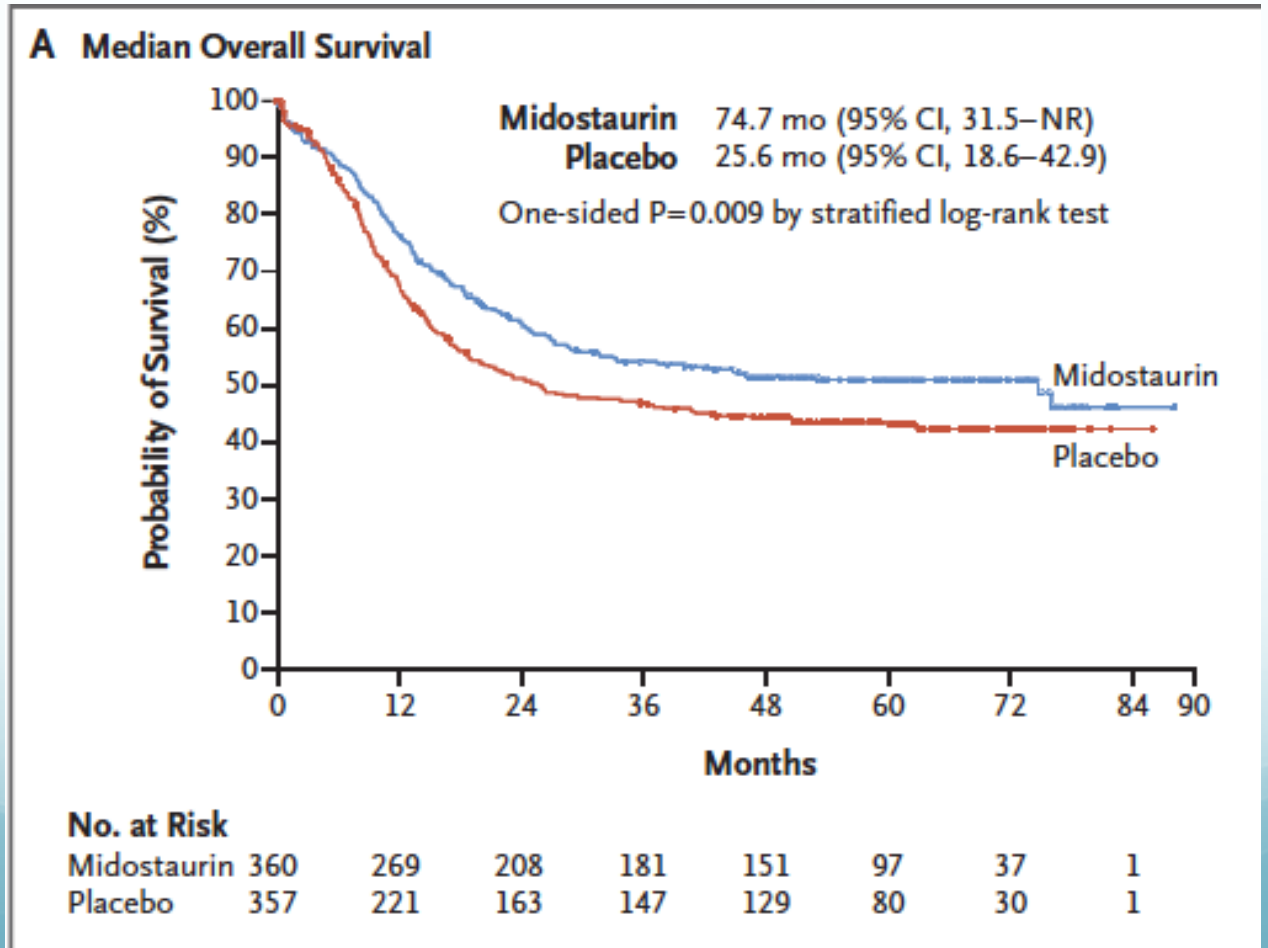

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Because allogeneic transplantation was an important alternative therapy, we performed a sensitivity analysis of the primary end point in which data were censored at the time patients underwent transplantation. In this analysis, there was a **24.3% lower risk of death in the midostaurin group** than in the placebo group; the 4-year overall survival rate was **63.7%** in the midostaurin group and **55.7%** in the placebo group, but the difference between groups was not significant (P = 0.08 by log-rank test).

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MIDO vs PBO in CR1: Stratified on *FLT3* subtype, two-sided log-rank p=0.07

MIDO vs PBO outside CR1: Stratified on *FLT3* subtype, two-sided log-rank p=0.85