ITK de 2da Generación como Tratamiento de Primera Línea para Pacientes con LMC-FC de Reciente Diagnóstico

JORNADA CHILENA DE HEMATOLOGÍA Y MEDICINA TRANSFUSIONAL

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Area de Hematología

HOSPITAL ITALIANO
DE LA PLATA

Tópicos

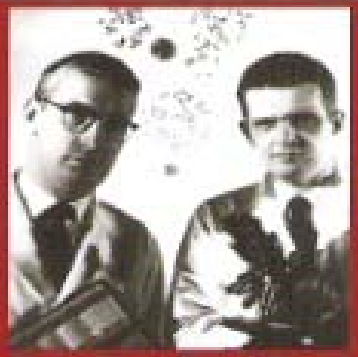
- El tratamiento de primera línea con imatinib
  - Su efectividad
  - La realidad
- La resistencia a la 1ra línea
- Los inhibidores de 2da generación
- La profundidad y la velocidad de la respuesta.
- Los protocolos randomizados con ITK de 2da generación en pacientes de reciente diagnóstico
- Toxicidad con ITK de 2da generación – 1ra línea vs 2da línea.

Datos Históricos de la LMC

Milestones in Targeted Therapies for Chronic Myeloid Leukemia

1845 John Hughes Bennett and Rudolph Virchow describe the first cases of CML.

1960 Peter Nowell and David Hungerford identify an abnormal chromosome in the blood cells and bone marrow of patients with CML.



Peter Nowell and David Hungerford. Reprinted, with permission, from the Annual Review of Medicine, Volume 53, copyright 2002 by Annual Reviews, www.annualreviews.org.

1973 Janet Rowley determines that the abnormal chromosome identified by Nowell and Hungerford results from the exchange of genetic material between two chromosomes.

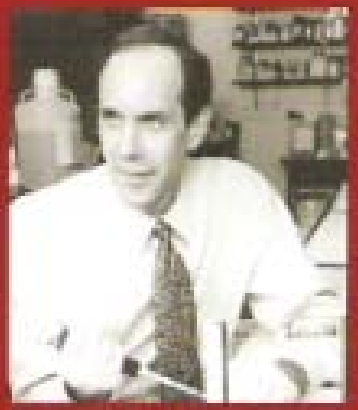
Janet Rowley. Photo courtesy of the University of Chicago.

1982-1985 John Groffen, Nora Heisterkamp, Gerard Grosveld, E. Cannani, David Baltimore, and Owen Witte show that an abnormal gene and protein called *BCR-ABL* is produced as a consequence of the chromosome rearrangement that characterizes CML.

50 Years in Hematology. ASH 2008

Datos Históricos de la LMC

1987	Nicholas Lydon and Alex Matter begin a drug discovery program to target proteins such as *BCR-ABL* in collaboration with Brian Druker, Thomas Roberts, and Charles Stiles.
1993	Brian Druker's laboratory shows that STI571 (imatinib) is the best of the compounds developed by Nicholas Lydon's group at specifically targeting and killing CML cells.
1998	Brian Druker, Charles Sawyers, and Moshe Talpaz begin clinical trials of imatinib.
2001	Imatinib is FDA-approved for patients with CML.
2001	Charles Sawyers, Brian Druker, Andreas Hochhaus, and François-Xavier Mahon report that mutations of *BCR-ABL* are the major mechanism of resistance to imatinib.
2006	Follow-up data show a 95 percent five-year survival for patients with CML treated with imatinib.
2006, 2007	Dasatinib and nilotinib are FDA-approved for patients with imatinib resistance.

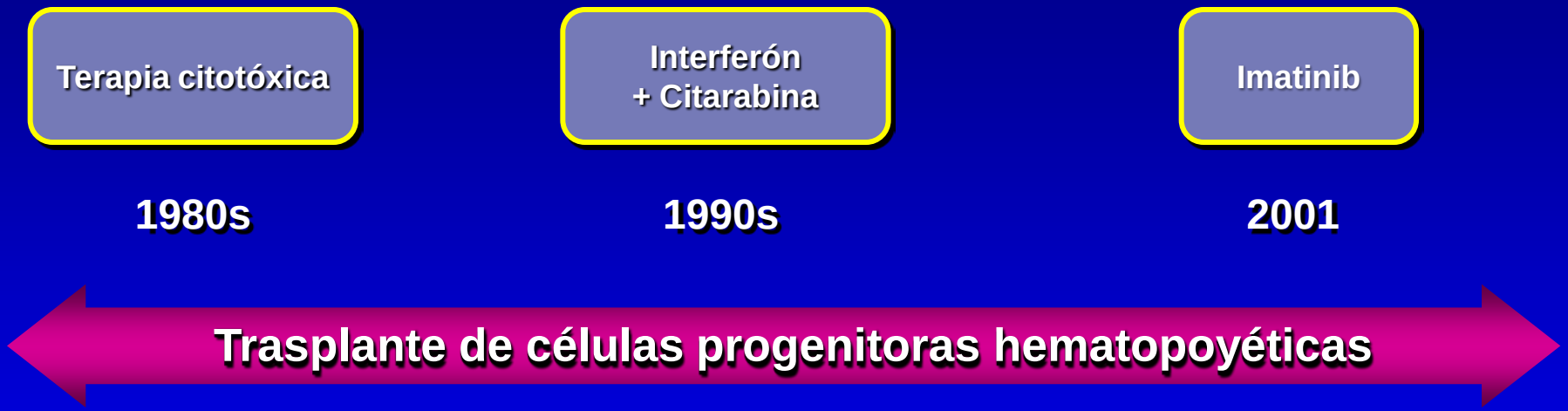


Brian Druker

Photo by Laura Sikes.

50 Years in Hematology. ASH 2008

Evolución de la terapia para LMC



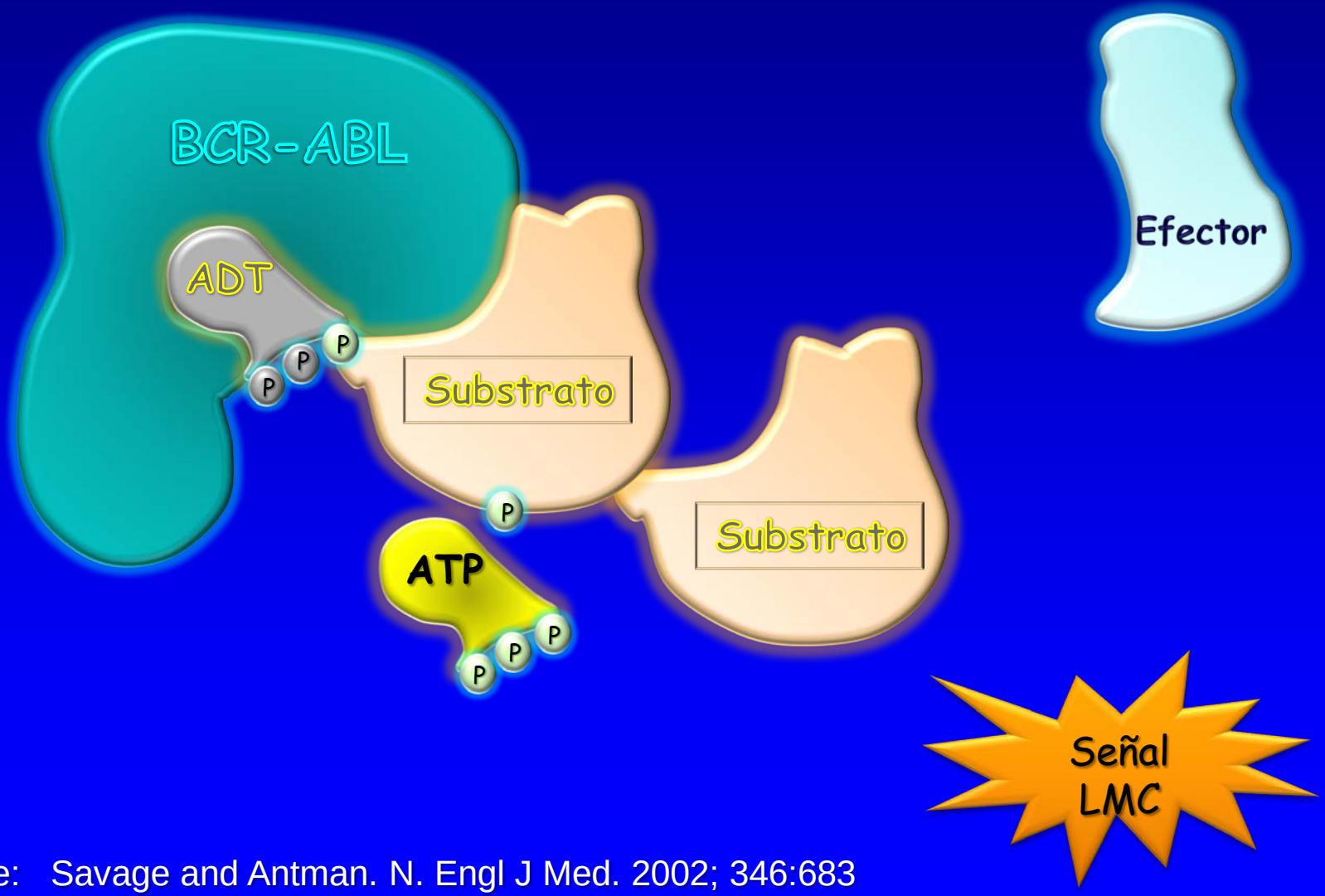
- Aunque la LMC continúa siendo potencialmente curable con TMO, la baja compatibilidad de donantes (≤30% de los pacientes tiene donantes adecuadamente apareados) y la alta toxicidad asociada con el preacondicionamiento limita significativamente esta opción [1,2]

1. Sawyers CL. *N Engl J Med.* 1999;340:1330-1340.
2. The Chronic Myelogenous Leukemia Clinical Practice Guidelines in Oncology (Version 1.2006). © 2006 National Comprehensive Cancer Network, Inc. Disponible en: http://www.nccn.org. Evaluado en Septiembre 15, 2006. Para consultar la versión más reciente y completa de las guías ingresar en www.nccn.org.

Que hemos logrado?

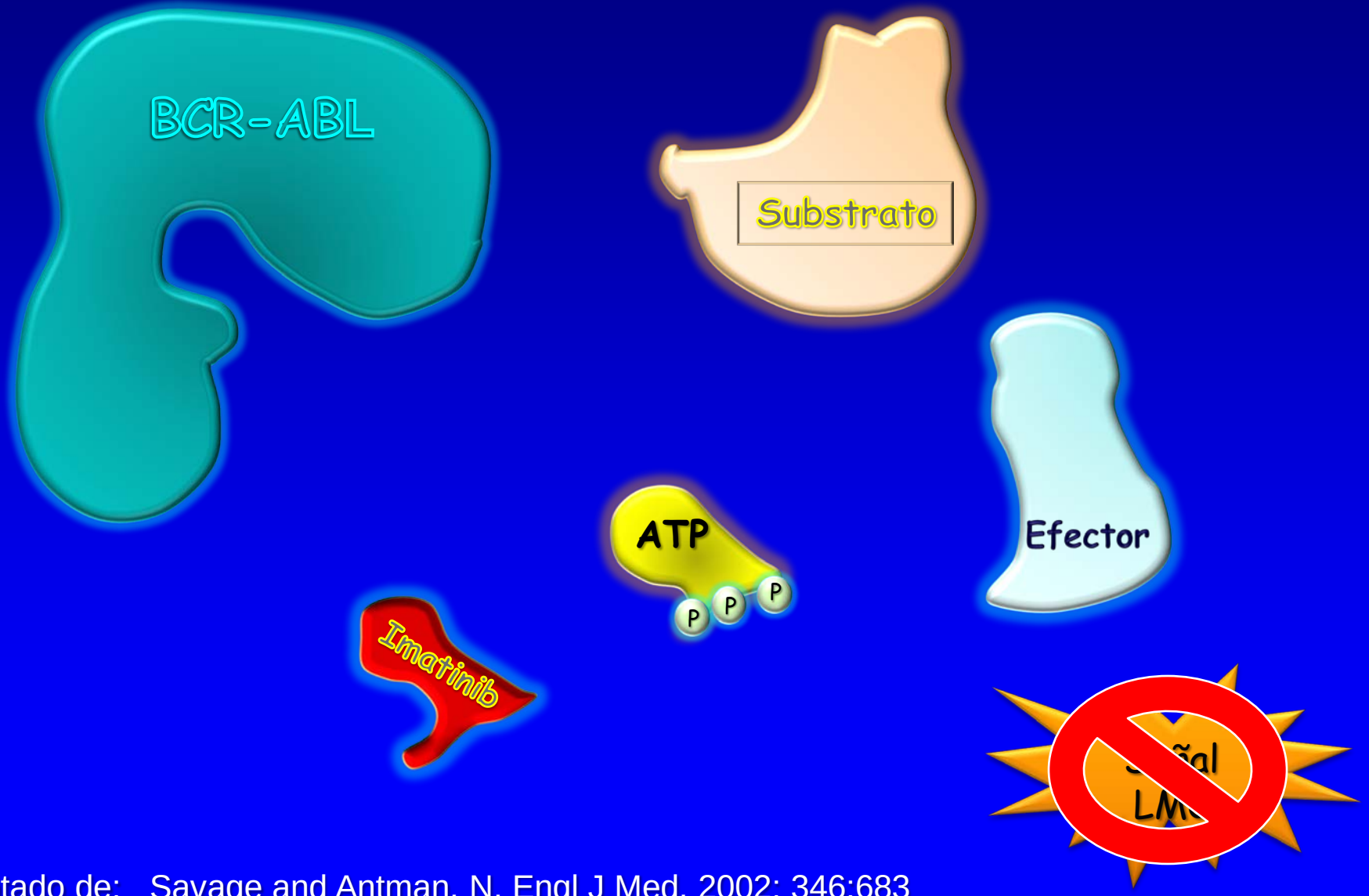
- Una mejor comprensión
- Un standard terapéutico

Inhibición de la señal del BCR/ABL



Adaptado de: Savage and Antman. N. Engl J Med. 2002; 346:683

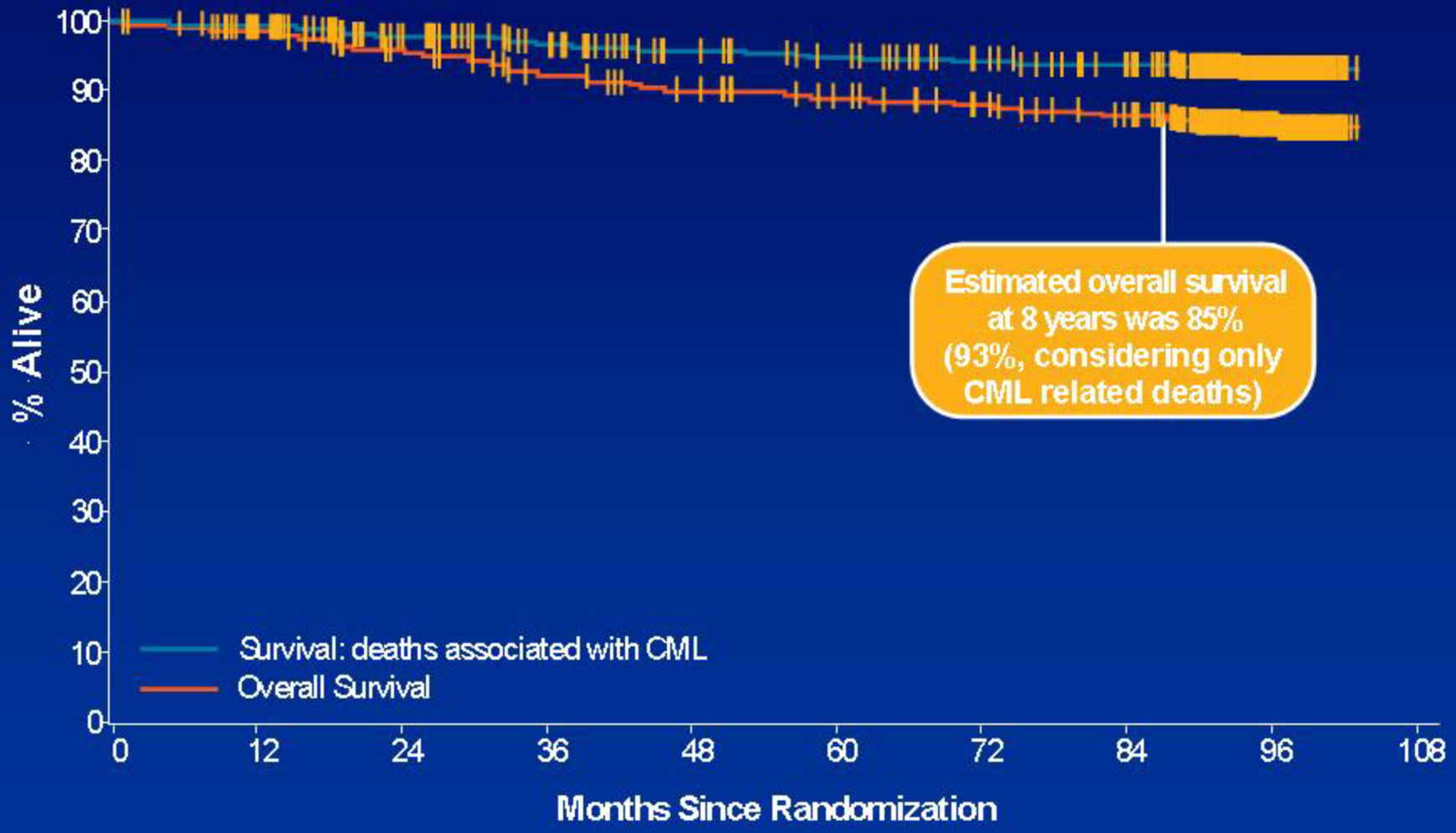
Inhibición de la señal del BCR/ABL



Adaptado de: Savage and Antman. N. Engl J Med. 2002; 346:683

IRIS 8-Year Update

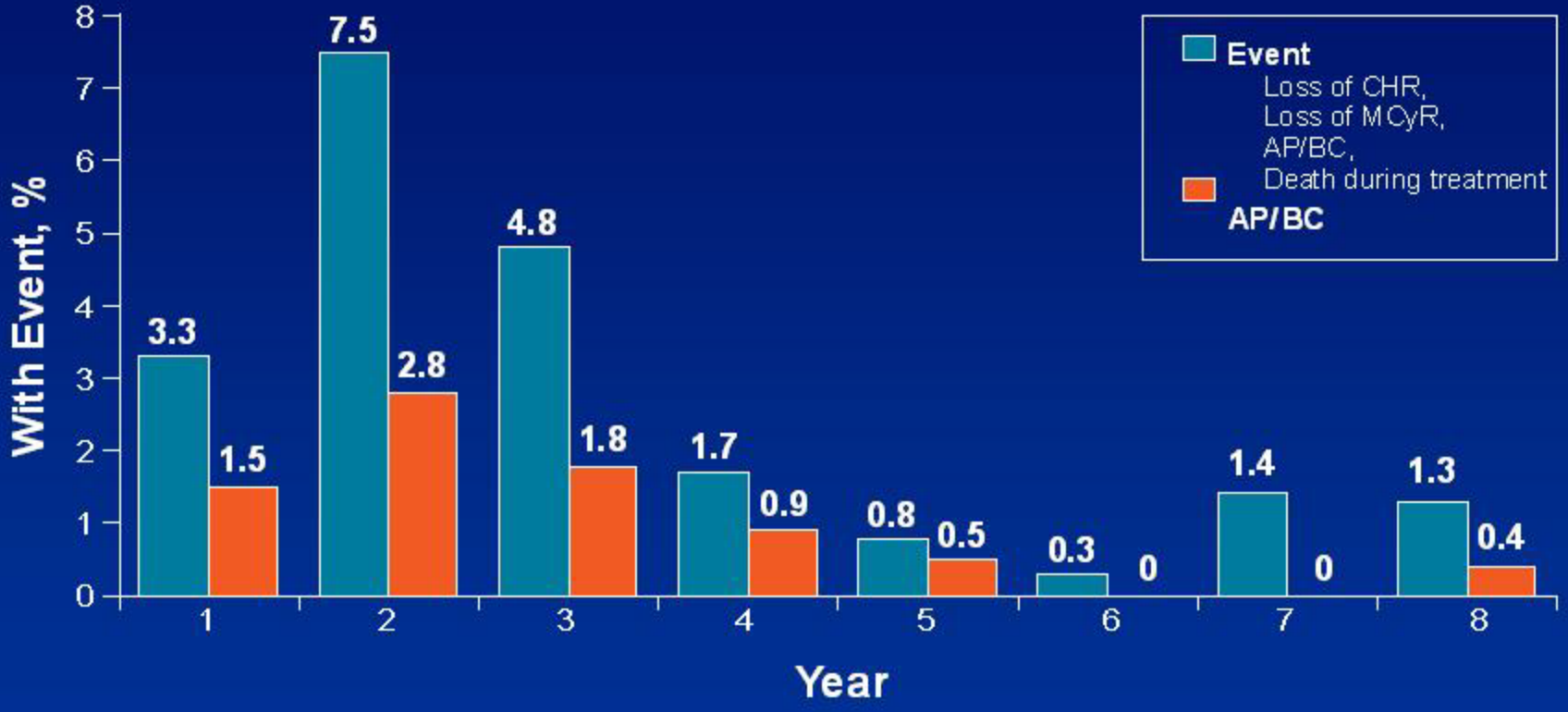
Results: Overall Survival (Intent-to-Treat) – Imatinib Arm



Deininger M. et al. Blood. 2009;114(22):142. Abs # 1126 (Poster).

IRIS 8-Year Update

Results: Annual Event Rates – Imatinib Arm



- Estimated EFS at 8 years = 81%
  - 1 progression to AP/BC and 2 non-CML related deaths occurred in year 8
- Estimated rate of freedom from progression to AP/BC at 8 years = 92%

Deininger M. et al. Blood. 2009;114(22):142. Abs # 1126 (Poster).

La realidad del IRIS

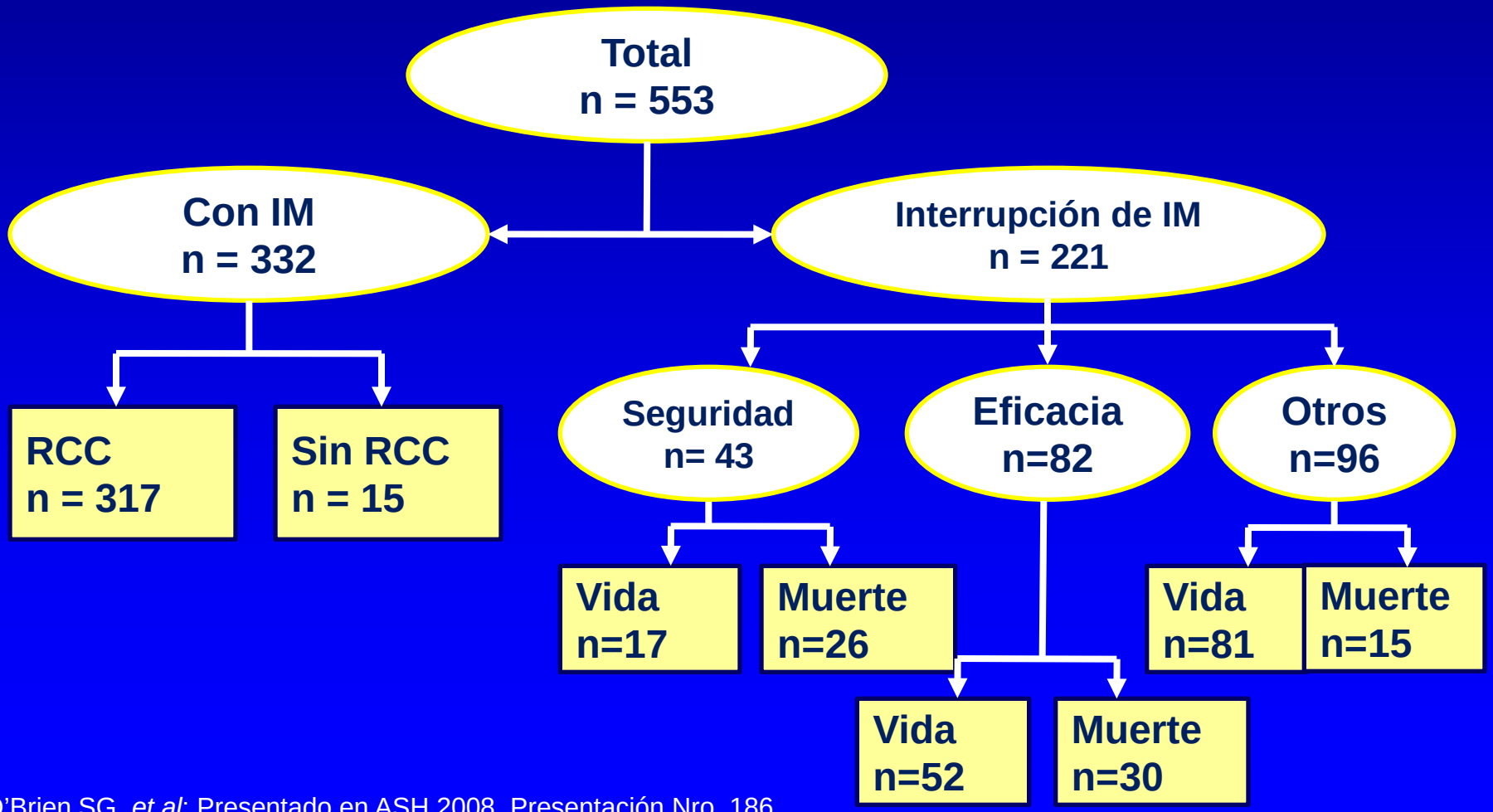
Leucemia mieloide crónica

Los resultados de dos grandes estudios

- ✓ IRIS
- ✓ UNIC

Estudio IRIS tras siete años de seguimiento

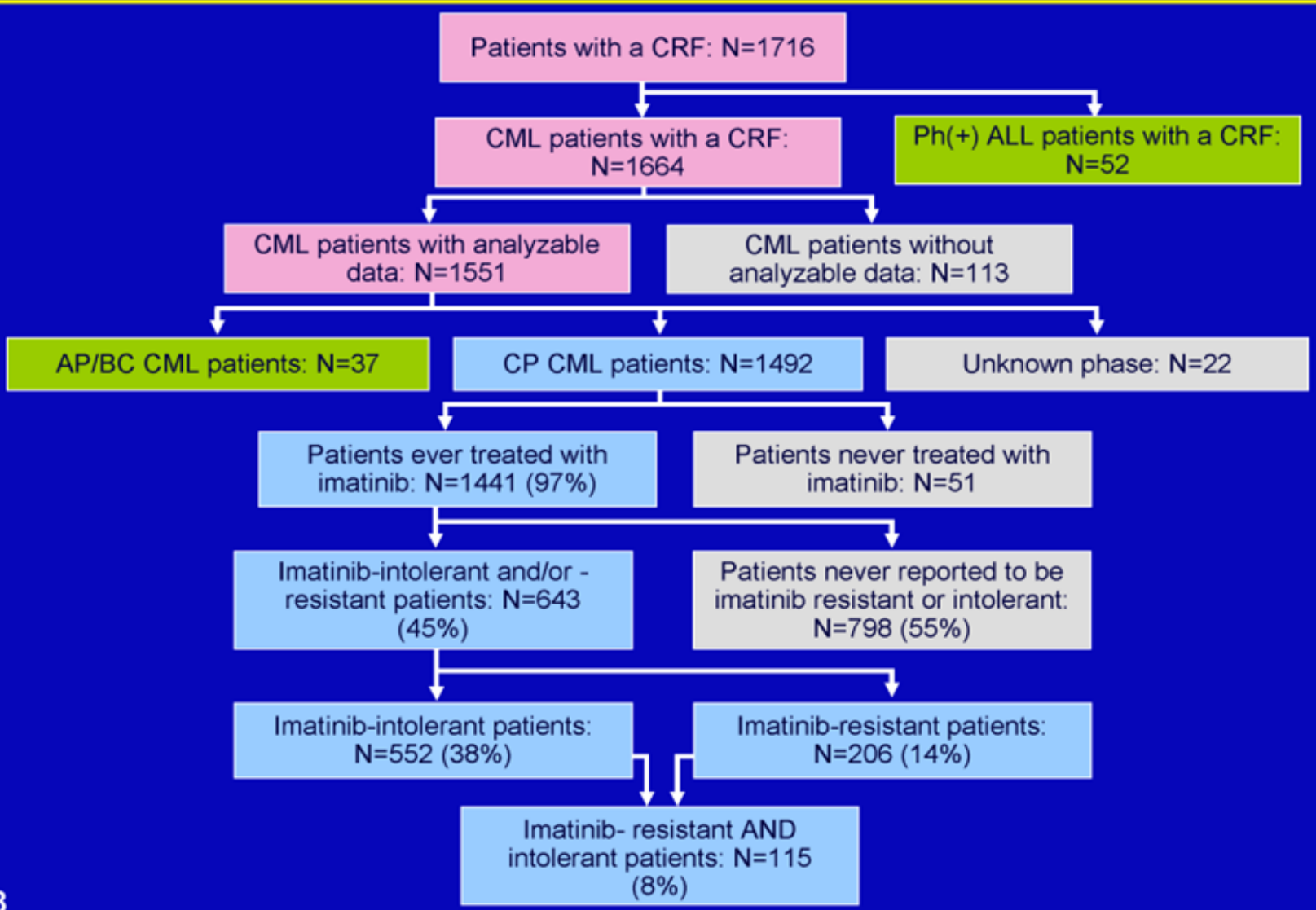
Distribución inicial de pacientes asignados aleatoriamente a tratamiento con Imatinib



O'Brien SG, *et al*: Presentado en ASH 2008. Presentación Nro. 186

UNIC Study

Figure 1: Summary of patient flow: patients with chronic phase CML



IRIS – Seguimiento a 7 años

- 553 pacientes

40% (221p) interrumpieron Imatinib

- ✓ **19 % seguridad**
- ✓ **37% eficacia**
- ✓ **43% otros**

UNIC

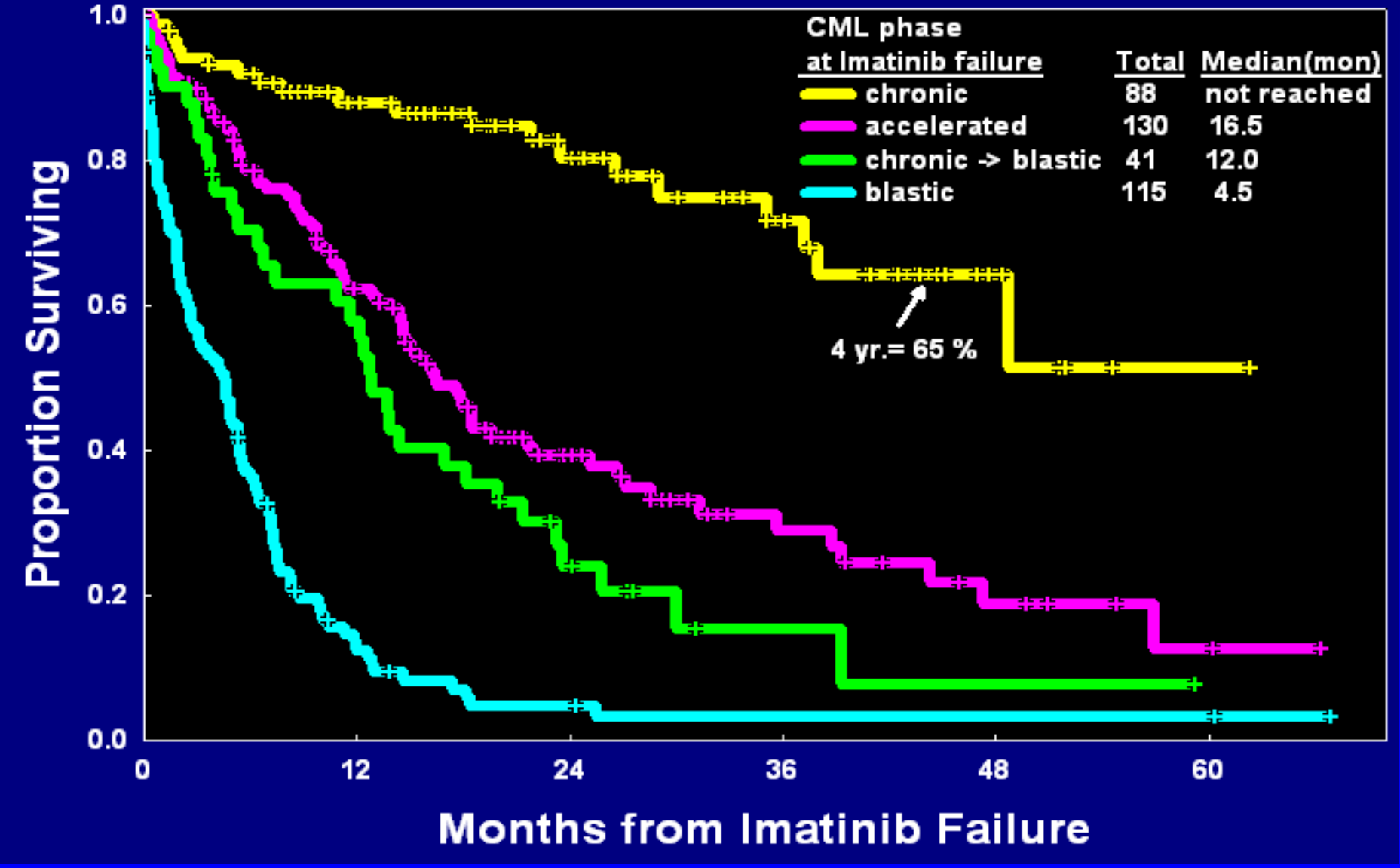
- 1441 pacientes. FC-LMC con datos analizables que recibieron adecuadamente imatinib.

  - ✓ 45% (643p) intolerantes o resistentes
  - ✓ 38% (552p) intolerantes
  - ✓ 14% (206p) resistentes
  - ✓ 8% (115p) resistente e intolerantes

Leucemia Mieloide Crónica

- *Descripción clínica hematológica.*
- *Alteración citogenética.*
- *Alteración molecular, gen quimérico.*
- *Terapia con blanco molecular.*
- ***Resistencia***

Survival Post Imatinib Failure by CML Phase



Kantarjian et al. Cancer 2007; 109: 1556-60

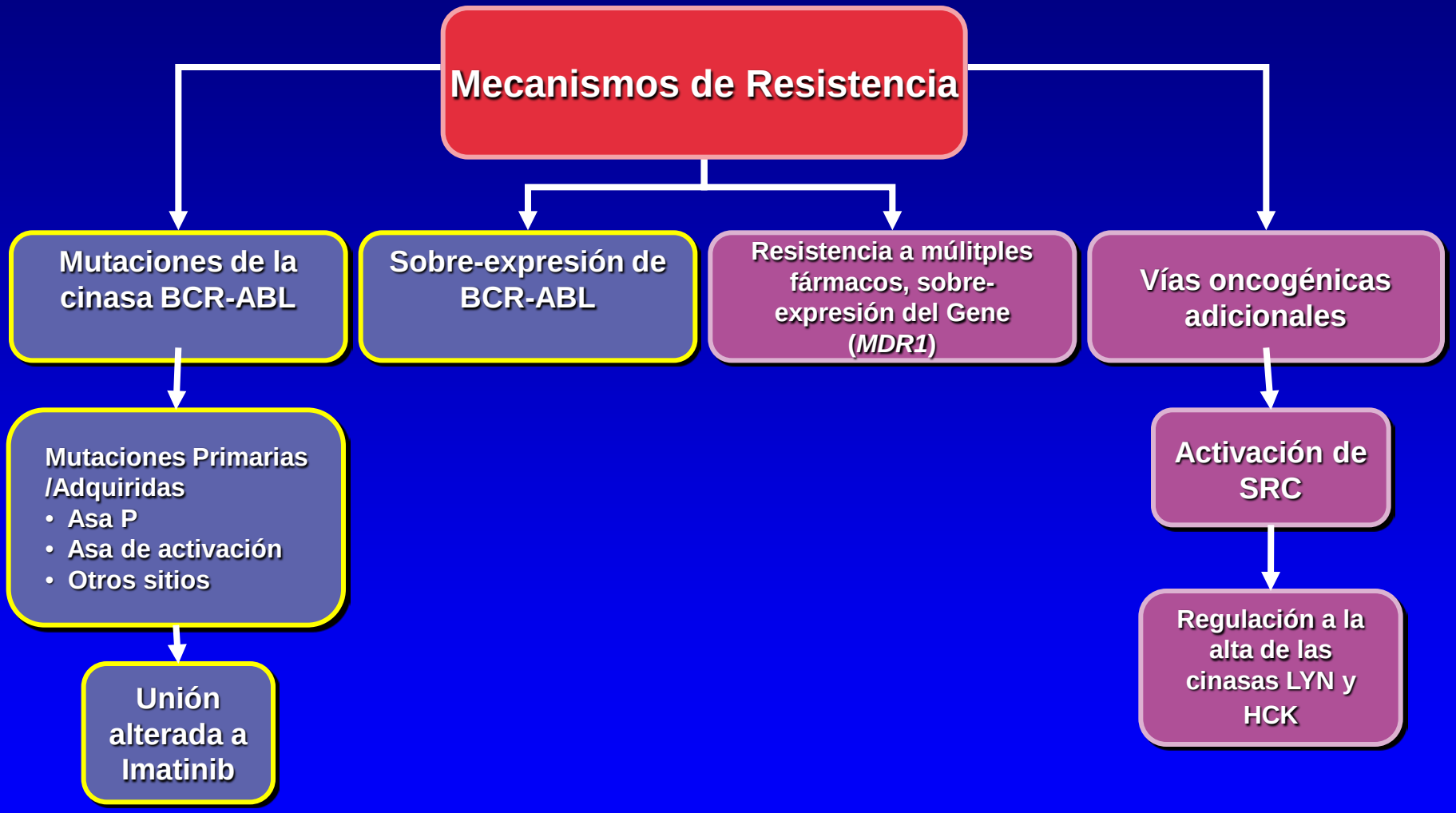
Mecanismos de resistencia

1. Dependencia de BCR-ABL

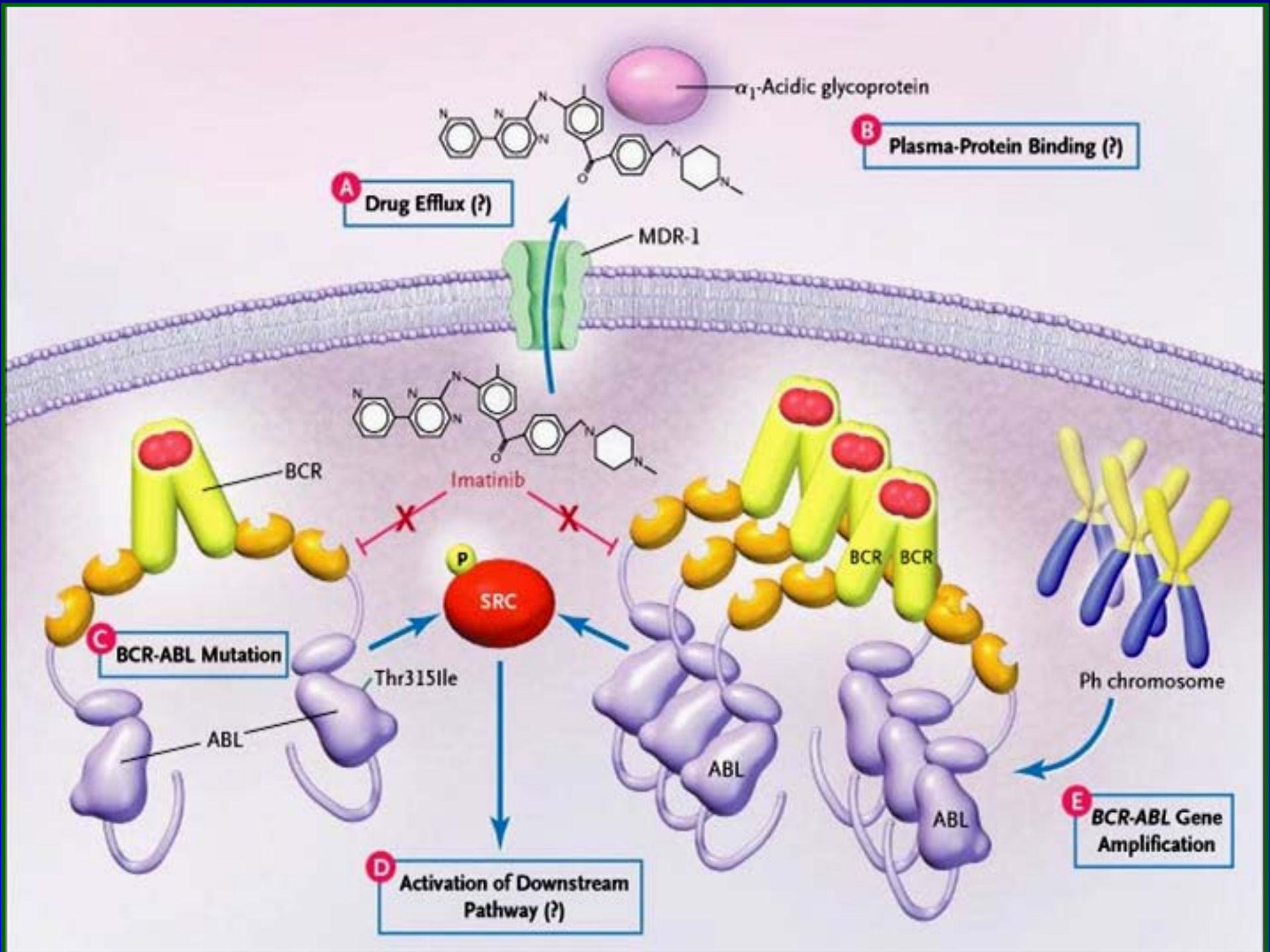
2. Independencia BCR-ABL

Jabbour E. et al . Seminars in Hematology, Vol 46, No2, Suppl 3, Ap 2009. pp S22-S26

Mecanismos biológicos conocidos de resistencia a Imatinib[1-5]



1. Branford S, Rudzki Z, Walsh S, et al. *Blood.* 2003;102:276-283.
2. Donato NJ, Wu JY, Stapley J, et al. *Blood*. 2003;101:690-698.
3. Weisberg E, Griffin JD. *Blood.* 2000;95:3498-3505.
4. Mahon F-X, Belloc F, Lagarde V, et al. *Blood.* 2003;101:2368-2373.
5. SPRYCEL® (dasatinib) [inserto del paquete]. Princeton, NJ: Bristol-Myers Squibb Company; Noviembre, 2007.


α1-Acidic glycoprotein
B Plasma-Protein Binding (?)
A Drug Efflux (?)
MDR-1
BCR
Imatinib
P
SRC
BCR
BCR
C BCR-ABL Mutation
Thr315Ile
ABL
ABL
ABL
Ph chromosome
E BCR-ABL Gene Amplification
D Activation of Downstream Pathway (?)

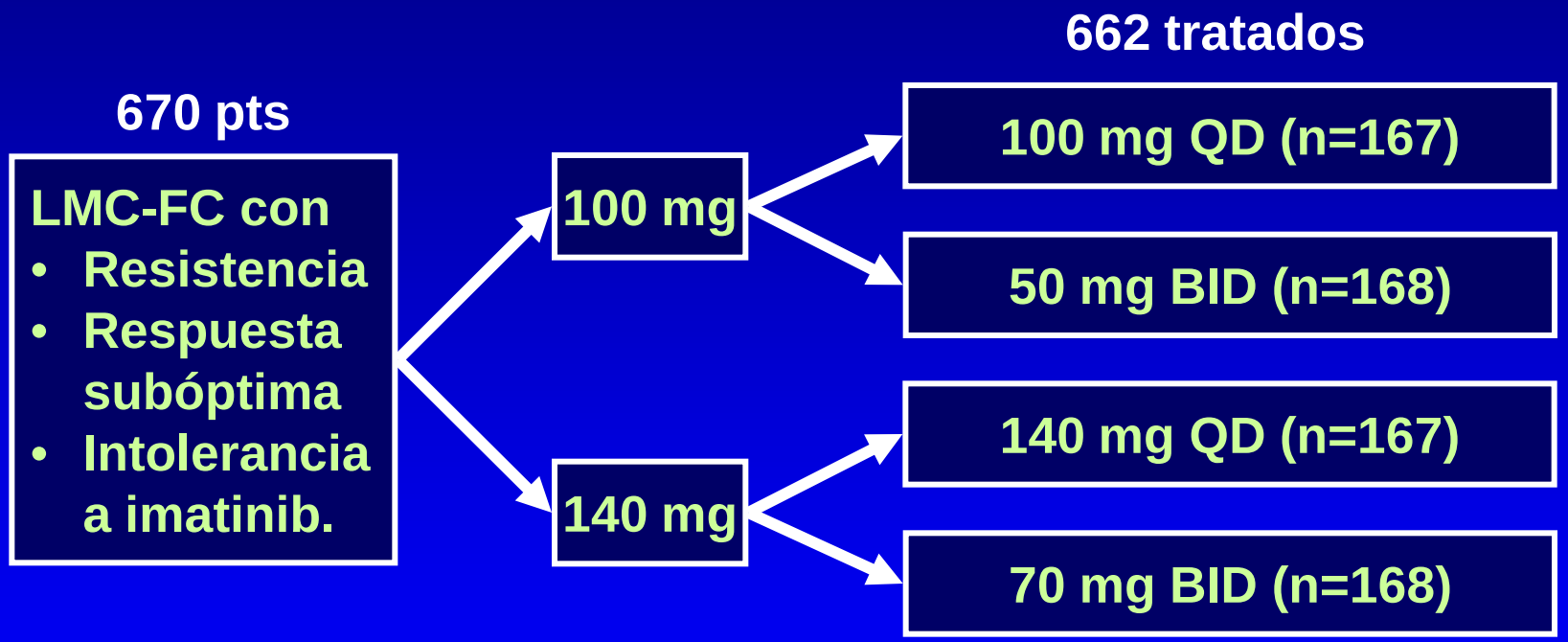
El desarrollo de los ITK de 2º generación

Comparison of ABL TK Inhibitors

	Imatinib	Dasatinib (BMS)	Bosutinib (SKI)	Nilotinib (AMN)
ABL	X 1	X 300	X 30	X 20
active ABL	(-)	(+++)	(+++)	(-)
inactive ABL	(+)	(+)	(+++)	(++)
PDGFR	(+)	(+++)	(-)	(+)
C-KIT	(+)	(+++)	(-)	(+)
SRC	(-)	(+++)	(++++)	(-)
LYN	(-)	(++)	(+++)	(-)
CNS leukemia	(-)	+?	NA	(-)
Status	Approved	Approved	Phase II/III	Approved

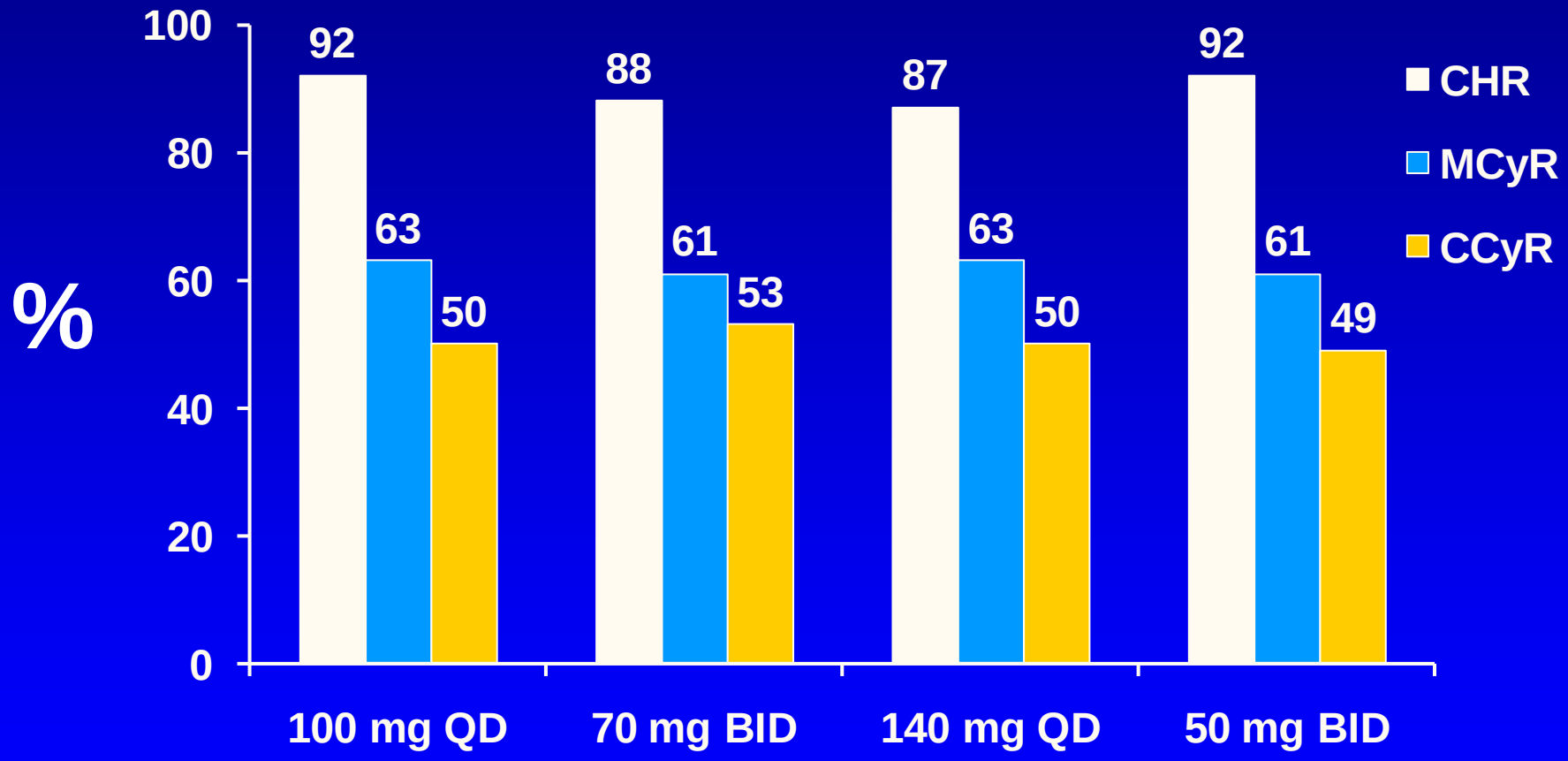
Diseño del estudio: CA180-034

- Internacional, 139-centros, aleatorizado, abierto, fase 3



- Periodo de reclutamiento: Julio 2005–Marzo 2006
- Duración media de tratamiento: 29 m (rango <1–54)
- Seguimiento mínimo: 48 ms

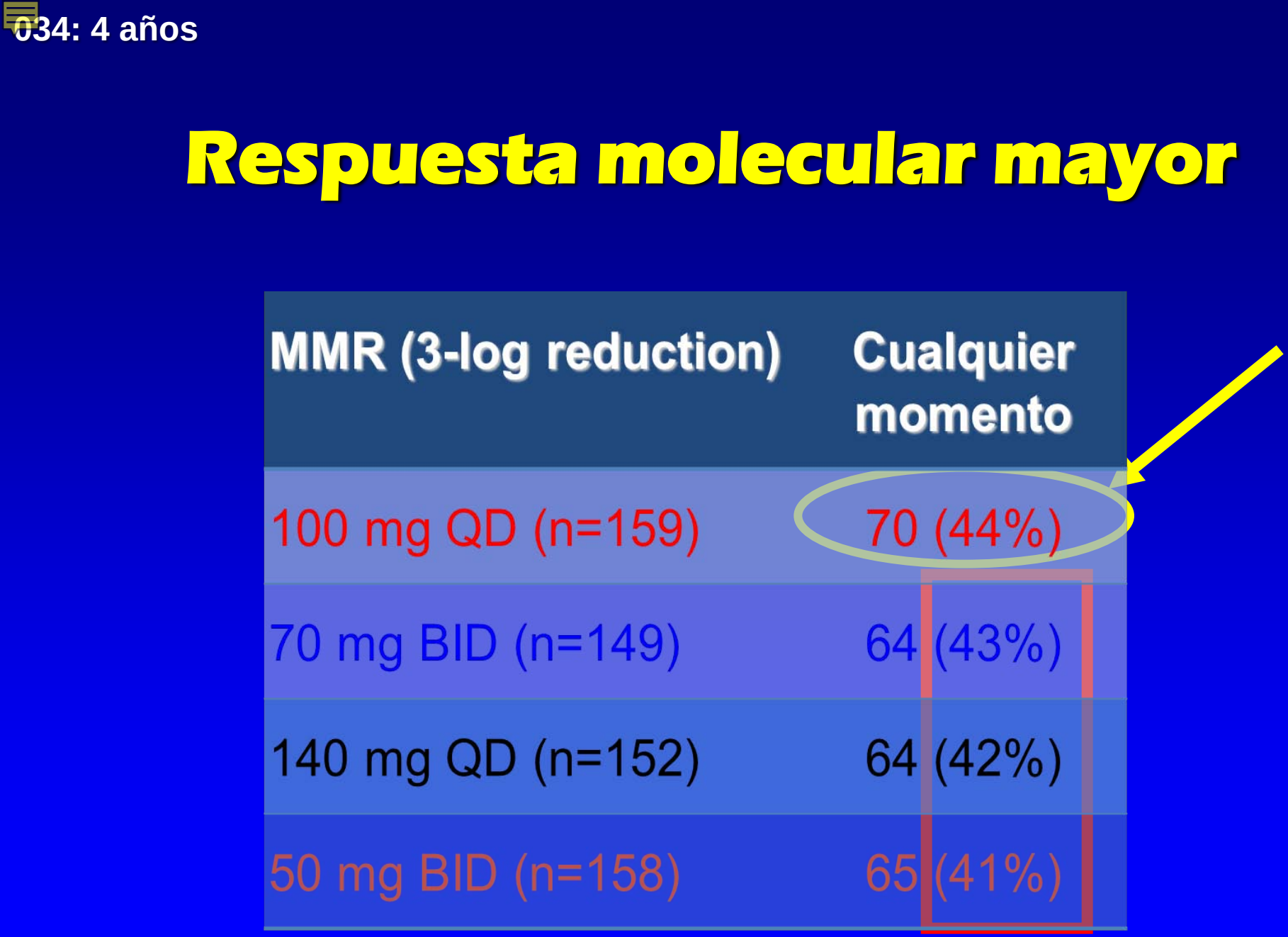
Mejor respuesta global



Shah NP et al; Abstract #6512 ASCO 2010

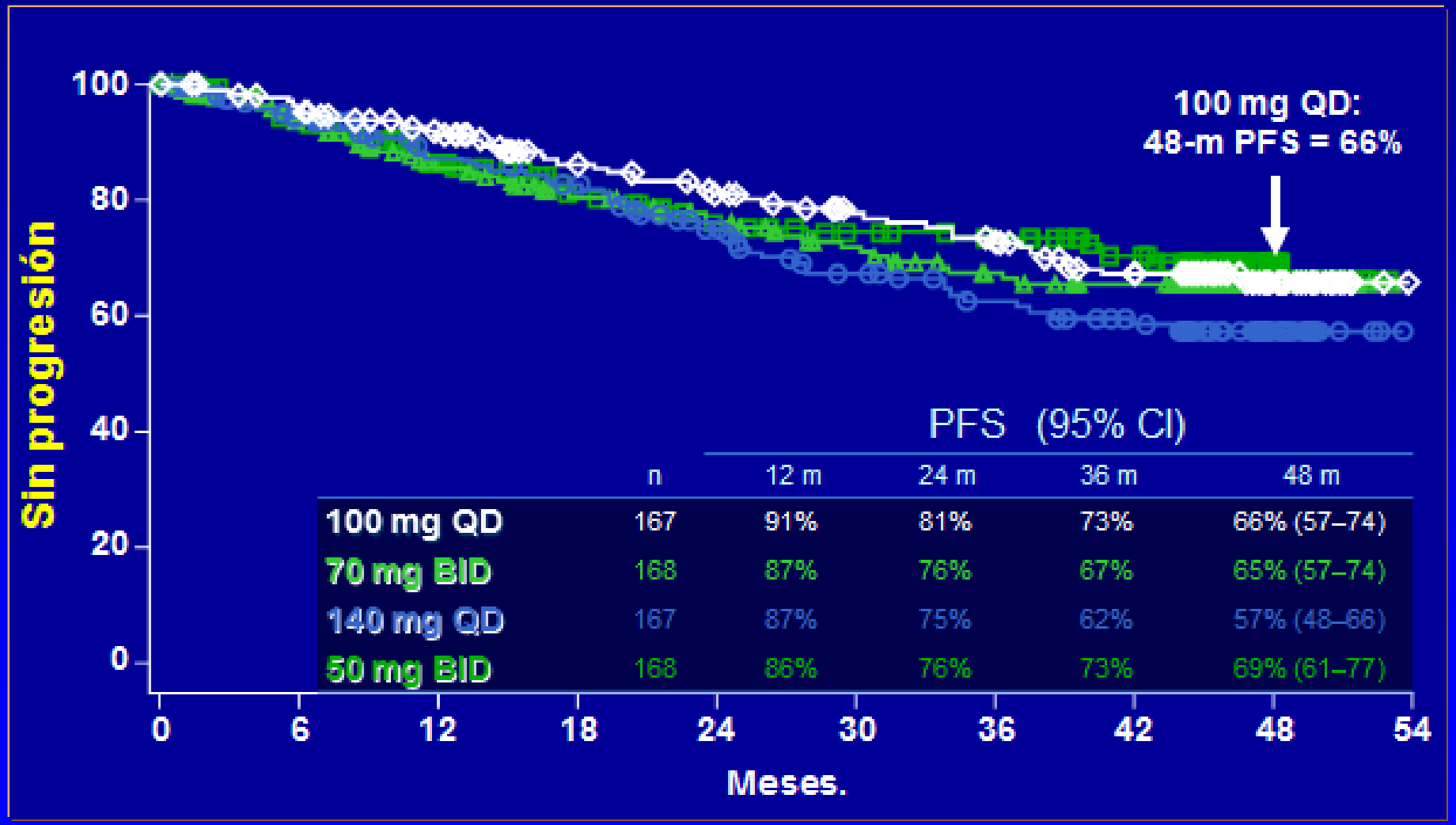
Respuesta molecular mayor

MMR (3-log reduction)	Cualquier momento
100 mg QD (n=159)	70 (44%)
70 mg BID (n=149)	64 (43%)
140 mg QD (n=152)	64 (42%)
50 mg BID (n=158)	65 (41%)



Shah NP et al; Abstract #6512 ASCO 2010

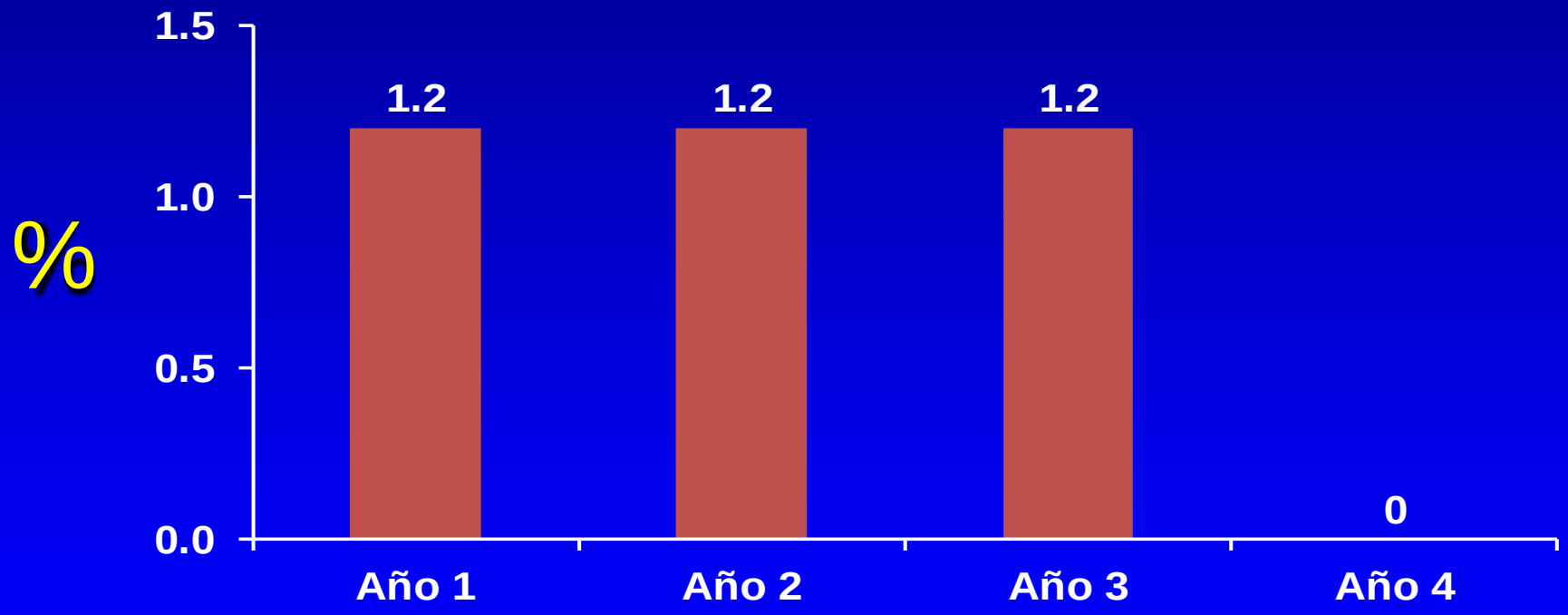
Sobrevida libre de progresión



	n	PFS (95% CI) 12 m	24 m	36 m	48 m
100 mg QD	167	91%	81%	73%	66% (57–74)
70 mg BID	168	87%	76%	67%	65% (57–74)
140 mg QD	167	87%	75%	62%	57% (48–66)
50 mg BID	168	86%	76%	73%	69% (61–77)

Shah NP et al; Abstract #6512 ASCO 2010

Progresión a fase acelerada o blástica



Shah NP et al; Abstract #6512 ASCO 2010

Phase II Studies of Dasatinib After Imatinib Failure

Response	Percent by Disease Stage				
	CP n=387	AP n=174	MyBP n=109	LyBP n=48	ALL n=46
Hematologic	91	64	50	39	49
CHR	91	50	26	29	35
NEL	-	14	7	6	7
Cytogenetic	62	40	47	58	62
Complete	53	33	27	46	54
Partial	9	7	7	6	2

Guilhot et al. *Blood.* 2007;110: Abstract 470.
Stone et al. *Blood.* 2007;110: Abstract 734.
Cortes et al. *Leukemia* 2008;22: 2176-83.

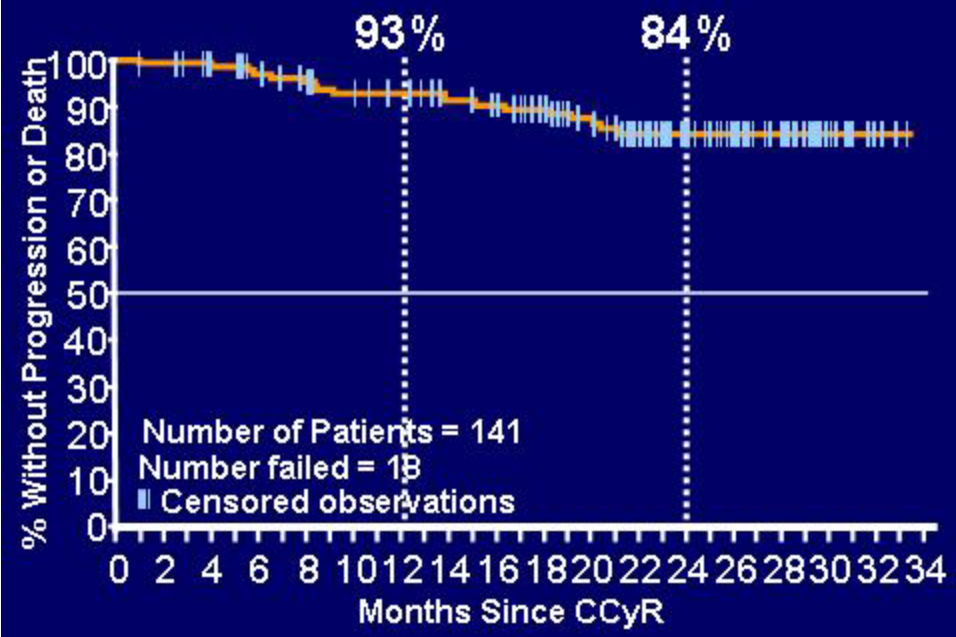
Phase II Studies of Nilotinib After Imatinib Failure

Response	Percentage			
	CP n =321	AP n =137	MyBP n =106	LyBP n =30
HR	77	54	24	20
CHR	76	26	12	13
Cytogenetic				
Major	59	31	38	50
Complete	44	19	28	33

le Coutre et al. *Blood.* (ASH Annual Meeting Abstracts) 2008;112: Abstract 3229.
Kantarjian et al. *Blood.* (ASH Annual Meeting Abstracts) 2008;112: Abstract 3238.

Nilotinib in CML-CP

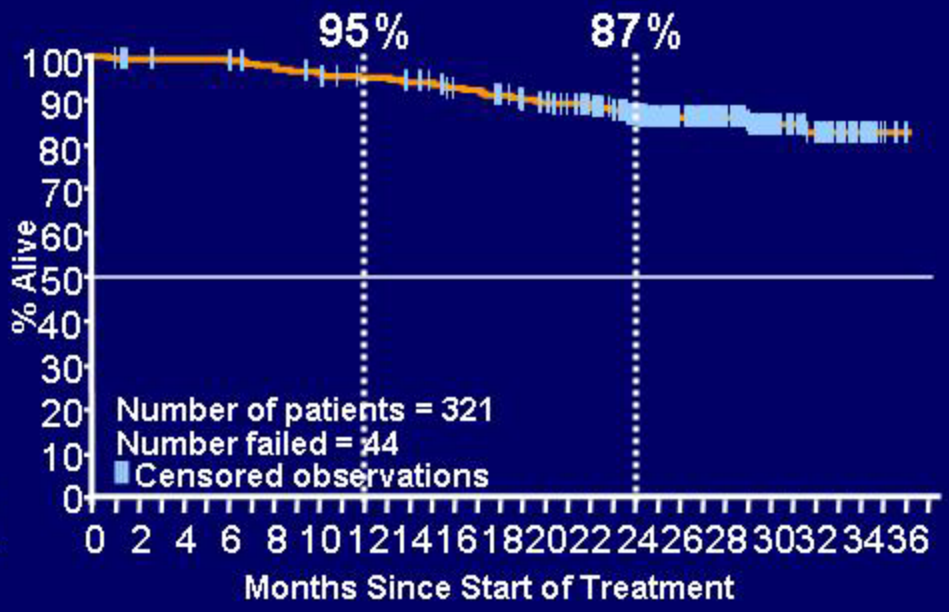
Duration of Complete Cytogenetic Response



CCyR, complete cytogenetic response.

- CCyR remains durable at 24 months

Overall Survival (N = 321)

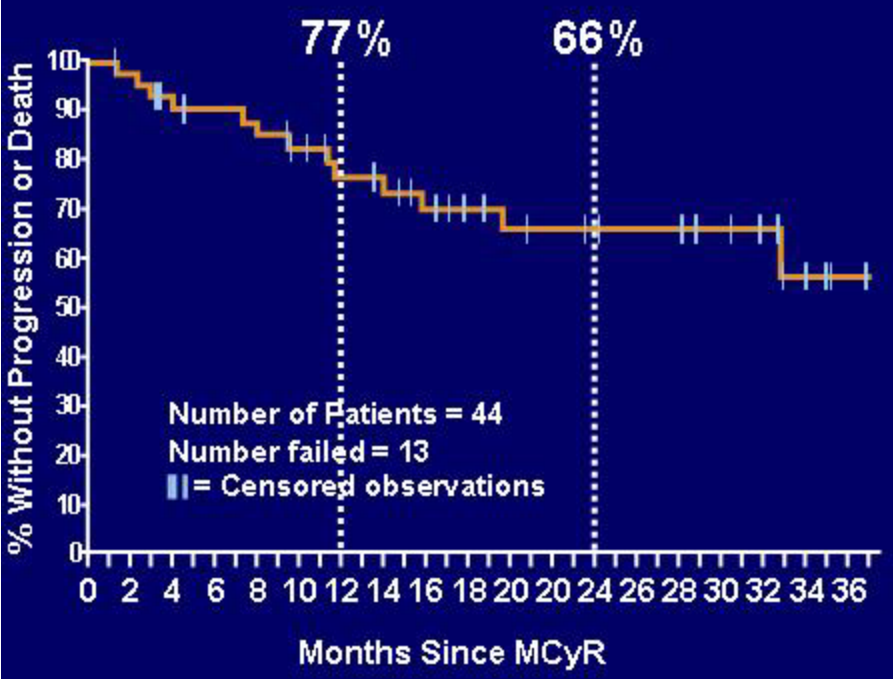


- 87% of patients were estimated to be alive on nilotinib therapy at 24 months

Kantarjian et al. Haematologica. 2009; 94(s2): 254-255.

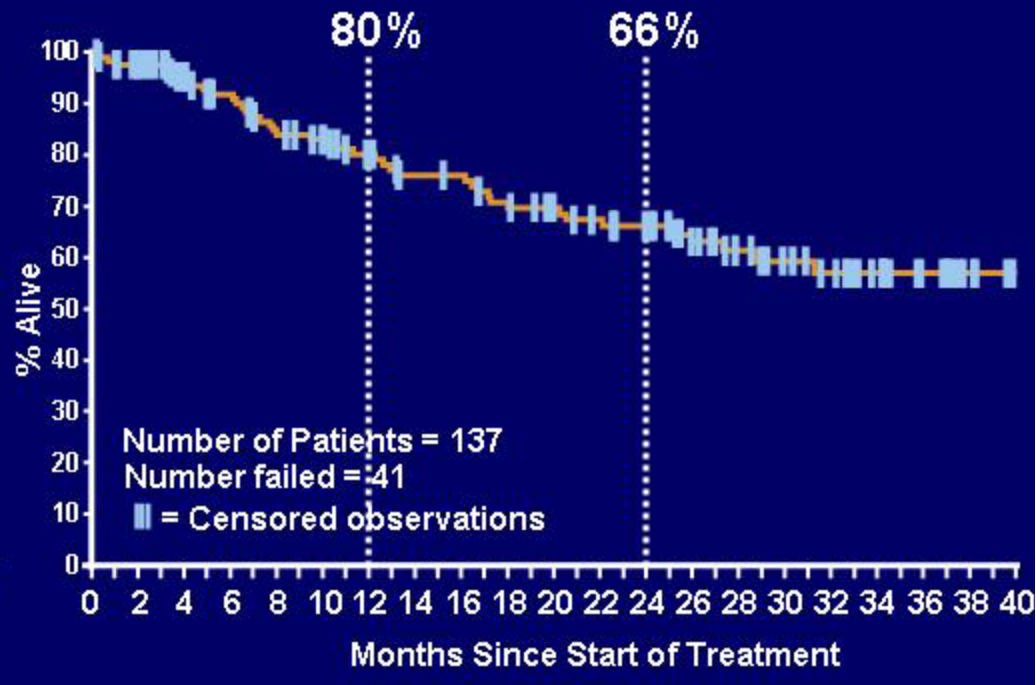
Nilotinib in CML-AP

Duration of Major Cytogenetic Response



- Median duration of MCyR had not been reached at the time of data cut-off

Overall Survival



- At 24 months, 66% of patients were alive; however, the median duration of overall survival had not been reached

Hochhaus et al. Haematologica. 2009;94(s2):256

Región, mutaciones y sensibilidad

		Imatinib (nM)	Nilotinib (nM)	Dasatinib (nM)
	Native BCR-ABL1	260	13	0.8
P-loop	M244V	2000	38	1.3
P-loop	G250E	1350	48	1.8
P-loop	Q252H	1325	70	3.4
P-loop	Y253H	>6400	450	1.3
P-loop	Y253F	3475	125	1.4
P-loop	E255K	5200	200	5.6
P-loop	E255V	>6400	430	11
	V299L	540	NA	18
ATP binding site	F311L	480	23	1.3
ATP binding site	T315I	>6400	>2000	>200
ATP binding site	T315A	971	61	125
ATP binding site	F317L	1050	50	7.4
ATP binding site	F317V	350	NA	53
Catalytic domain	M351T	880	15	1.1
Catalytic domain	E355G	2300	NA	1.8
Catalytic domain	F359V	1825	175	2.2
	V379I	1630	51	0.8
A-loop	L387M	1000	49	2
A-loop	H396R	1750	41	1.3
A-loop	H396P	850	41	0.6

High sensitivity | Intermediate sensitivity | High insensitivity

Quintas-Cardama A. Blood , 19 Feb 2009. Vol 113 N8; 1619

Un tratamiento efectivo en la LMC

- Se transforma realmente en una enfermedad crónica.
- Necesidad de un monitoreo adecuado.

Response definitions: Update 2009

Time	Optimal Response	Suboptimal Response	Failure	Warnings
Diagnosis	-	-	-	High risk CCA in Ph^+ cells
3 mos	CHR and at least a minor CyR	No CyR	No CHR	
6 mos	PCyR	< PCyR	No CR	
12 mos	CCyR	< CCyR (PCyR)	< PCyR	< MMolR
18 mos	MMolR	< MMolR	< CCyR	
Any time	Stable or improving MMolR (or CMR)	Loss of MMolR Mutation (IM-sensit.)	CCA in Ph^+ cells Loss of CHR Loss of CCyR Mutation (IM-insensit.)	↑ In BCR-ABL transcript level CCA in Ph^- cells

Baccarani et al. J Clin Oncol. 2009 Dec 10;27(35):6041-51.

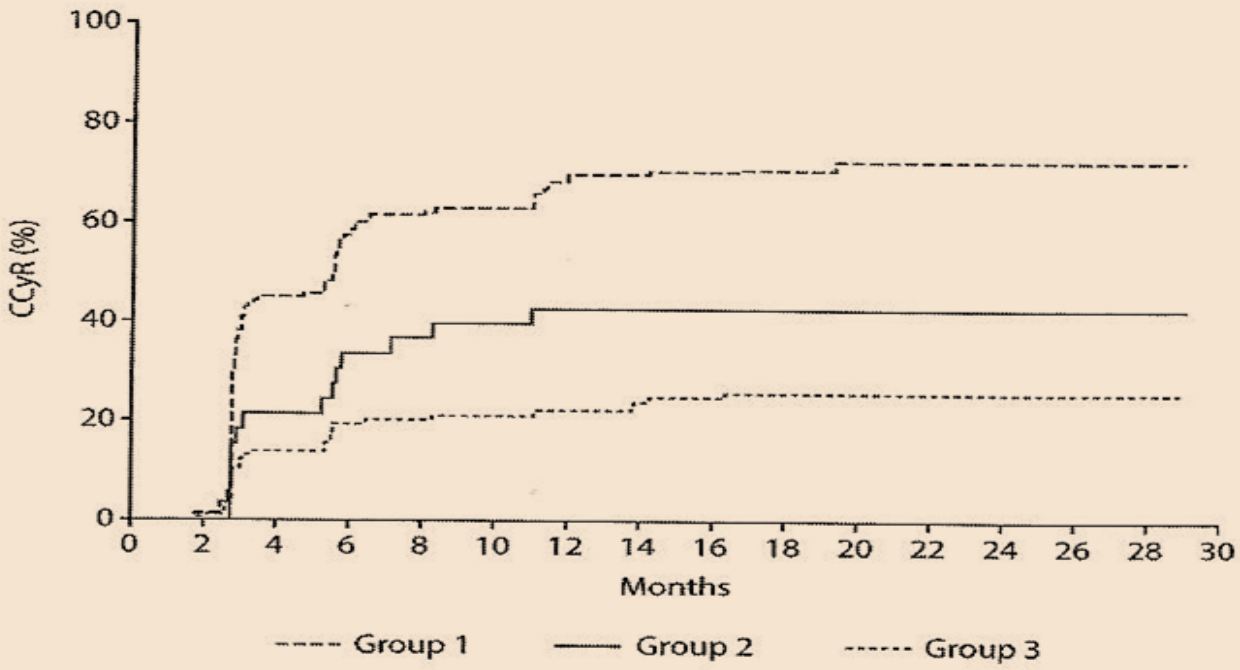
Objetivos Terapéuticos.
Guías de la Sociedad Argentina de Hematología

Sociedad Argentina de Hematología

Respuesta				
Período de evaluación, meses	Óptima	Sub-óptima	Falla	Alertas
Al diagnóstico	-	-	-	-Alto riesgo(Sokal); -ACC/Ph+
3	-RHC y al menos RCm (Ph+ ≤65%)	-Sin RC (Ph+ >95%)	-Menos que RHC	-
6	-Por lo menos RCP (Ph+≤35%)	-Menos de RCP (Ph+>35%)	-Sin RC (Ph+>95%)	-
12	-RCC	-RCP (Ph+1% a 35%)	-Menos que RCP (Ph+>35%)	-Menos que RMM
18	-RMM	-Menos que RMM	-Menos que RCC	-
En cualquier momento	-≥RMM	-Pérdida de RMM -Mutaciones	-Pérdida de RHC, -Pérdida de RCC, -Mutaciones -ACC/Ph+	-Incremento en niveles de transcriptos; -ACC/Ph-

Hematología. En prensa.

Intervención temprana con Dasatinib Resultados: Respuesta Citogenética.

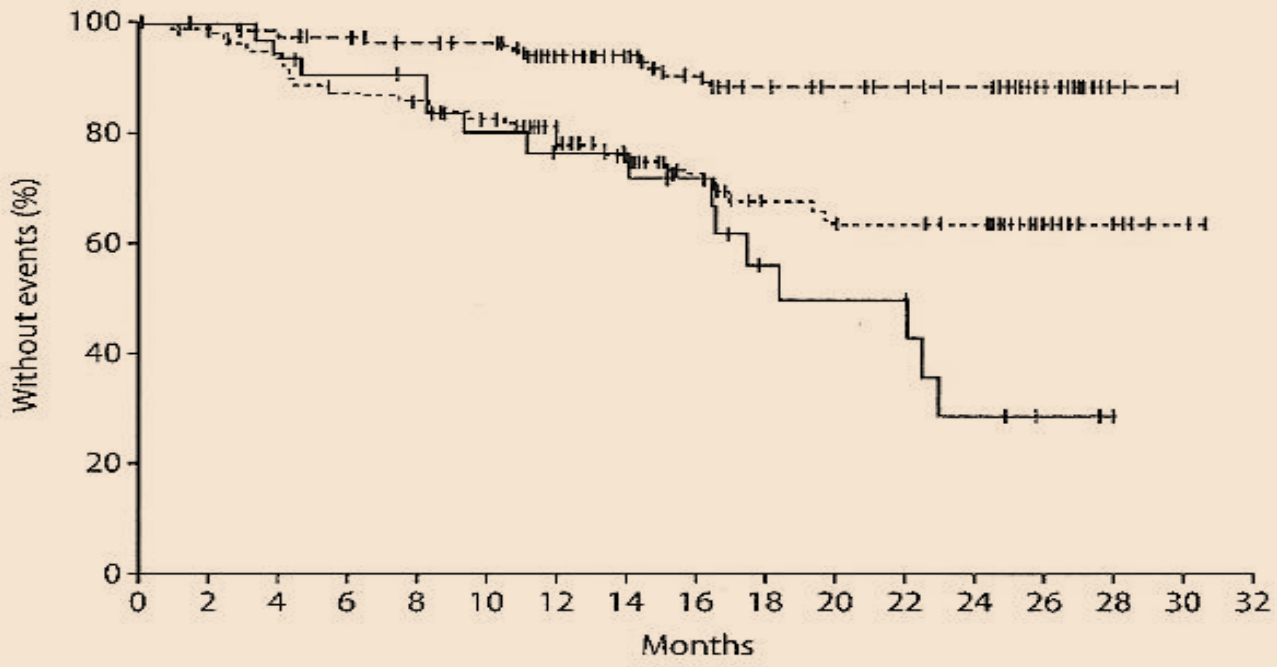


Group	Responders/total
Group 1: loss of MCyR	108/151
Group 2: loss of MCyR and CHR	14/33
Group 3: loss of CHR	28/109

FIGURE 1. The time to complete cytogenetic response in patients who received dasatinib after loss of response to prior imatinib. MCyR indicates major cytogenetic response; CHR, complete hematologic response.

Quintas-Cardamas. Cancer 2009. 115: 2912

Intervención temprana con Dasatinib
Resultados: SLEv



Group	Events/total	Median
Group 1: loss of MCyR	12/151	NR
Group 2: loss of MCyR and CHR	15/33	18.5
Group 3: loss of CHR	31/109	NR

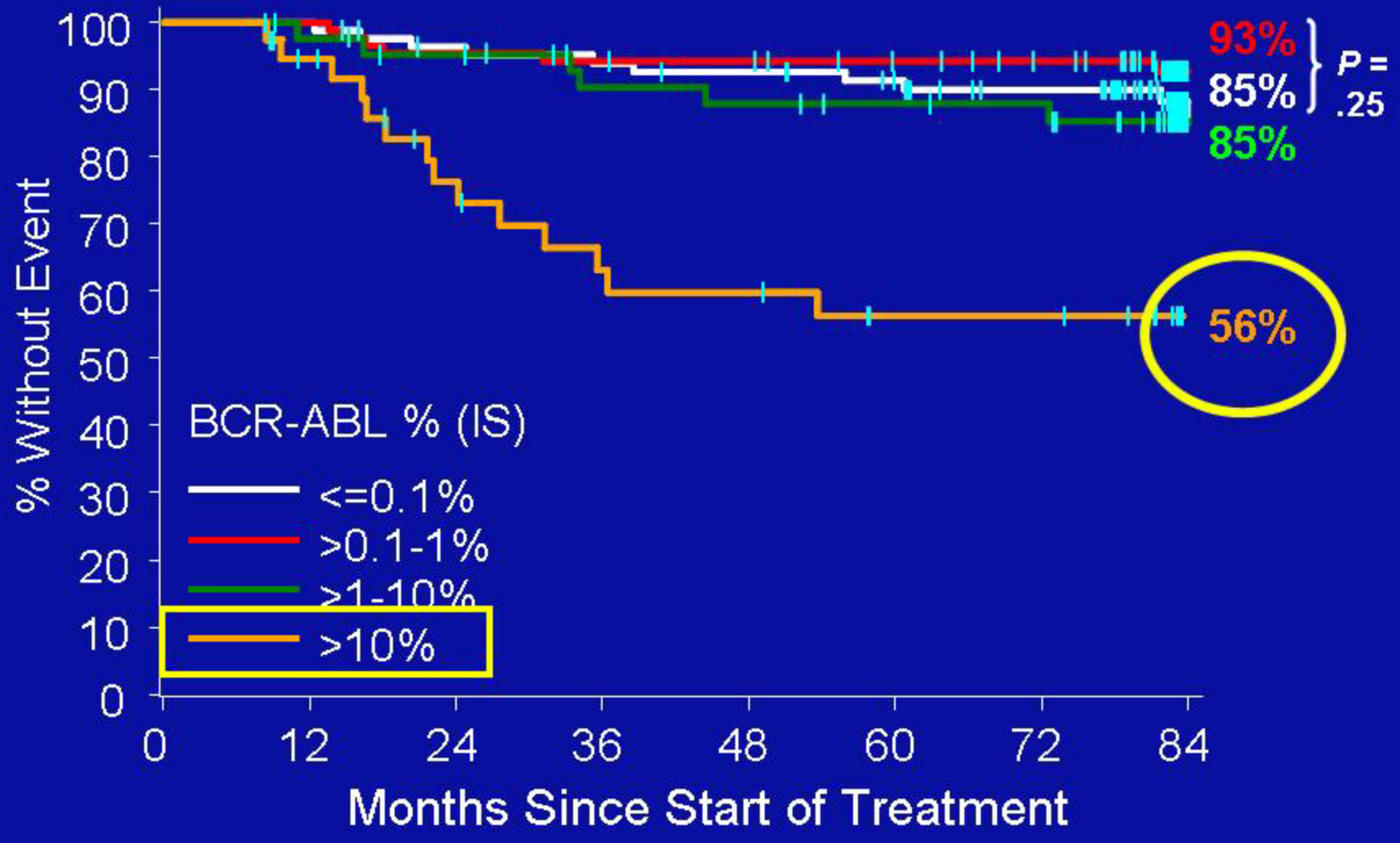
A

Quintas-Cardamas. Cancer 2009. 115: 2912

Respuesta optima, veloz y profunda.

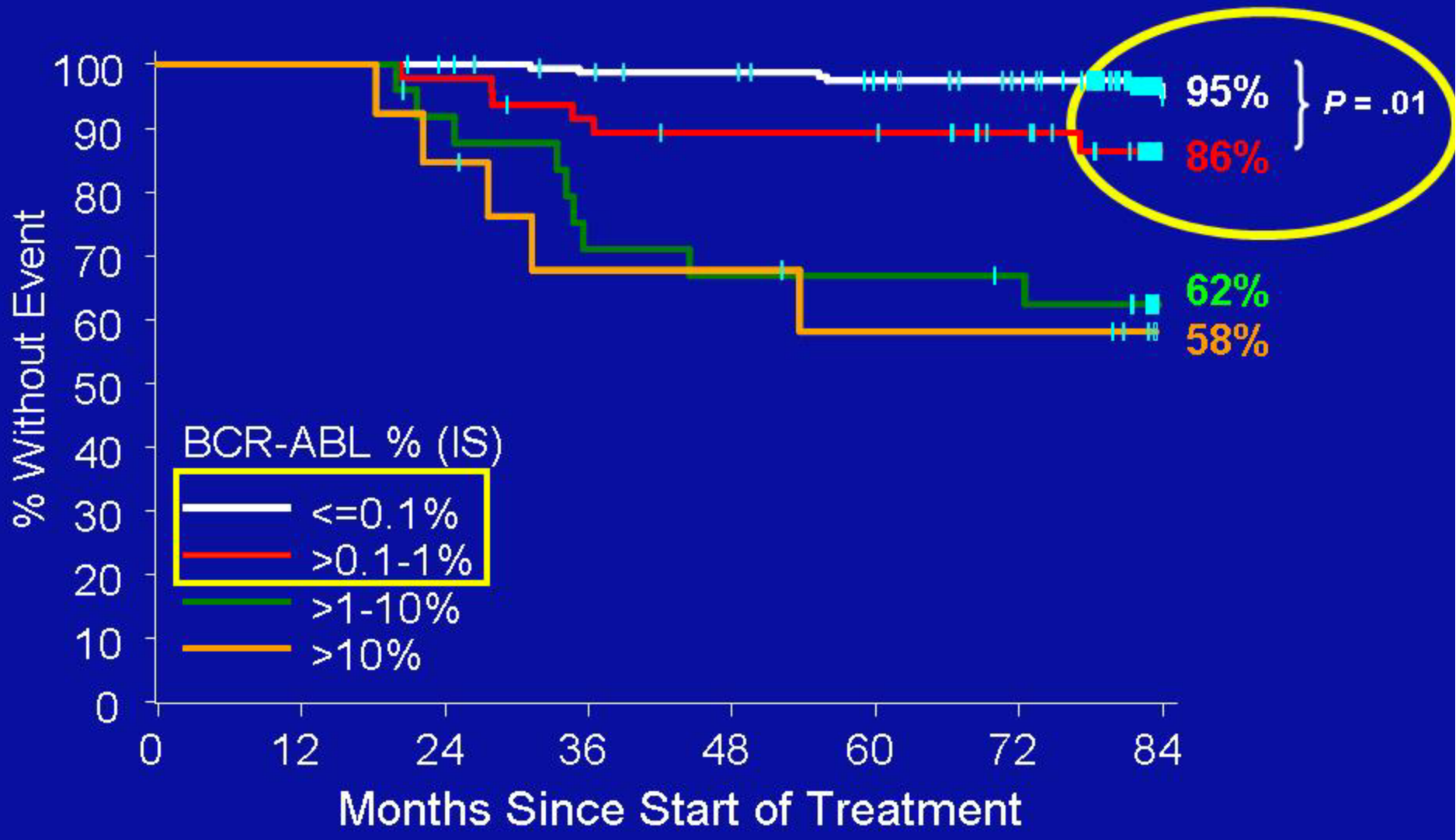
EFS: 6-Month Landmark Analysis

Events : loss of CHR, MCR, AP/BC or death



Hughes et al. *Blood* (ASH Annual Meeting Abstracts) 2008;112: Abstract 334. Oral presentation.

EFS: 18-Month Landmark Analysis



Hughes et al. *Blood* (ASH Annual Meeting Abstracts) 2008;112: Abstract 334. Oral presentation.

Inhibidores de 2º en primera línea terapéutica.

- DASISION
- ENESTnd