Impacto de la respuesta temprana sobre la sobrevida en LMC

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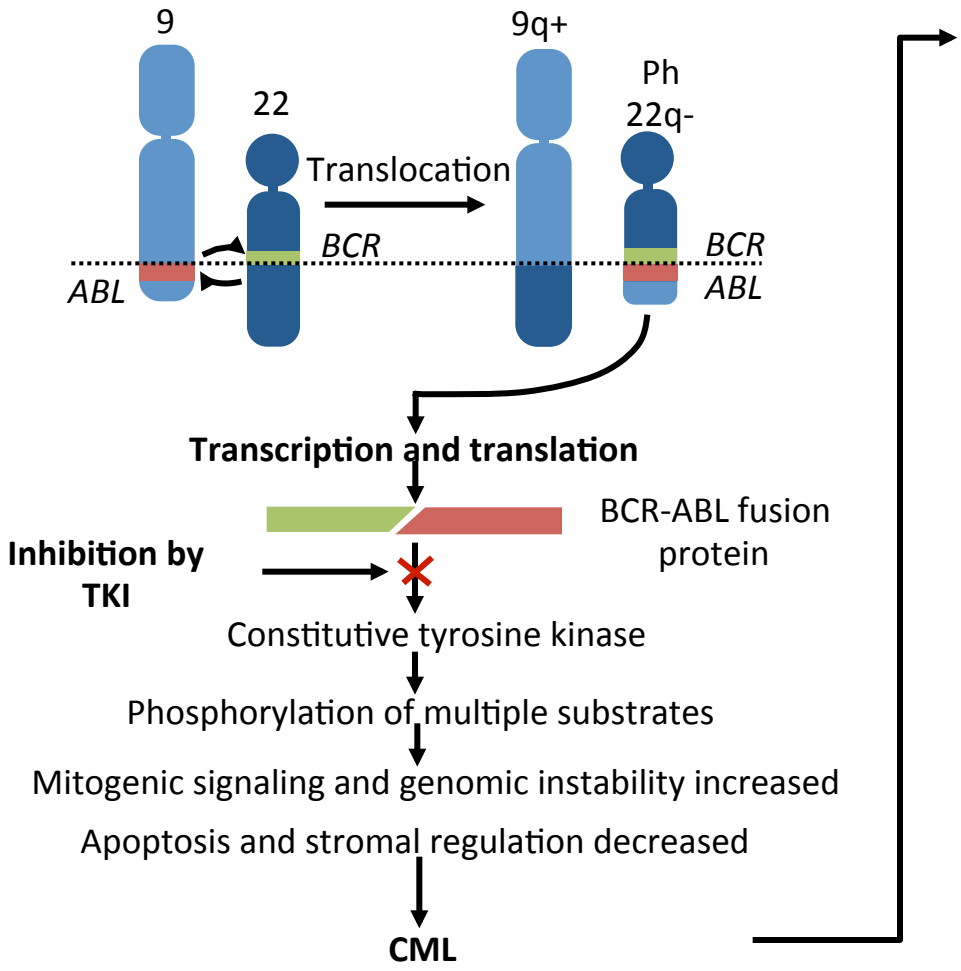
Philadelphia Chromosome Translocation in CML Results in BCR-ABL Oncogene



- Stem cell disorder
- Characterized by myeloproliferation
- Well-described clinical course

Natural History of CML

Accumulation of immature myeloid cells
New cytogenetic changes

	Chronic Phase	Accelerated Phase	Blast Phase
Duration	If untreated, 3-5 yrs	Varies	Median survival of several mos
Prognosis	Responsive to treatment	Decreased responsiveness	Resistant to treatment
Symptoms	Asymptomatic **OR** Fatigue Weight loss Abdominal pain or discomfort Night sweats	Progressive splenomegaly Myelofibrosis	Bleeding complications Infection complications

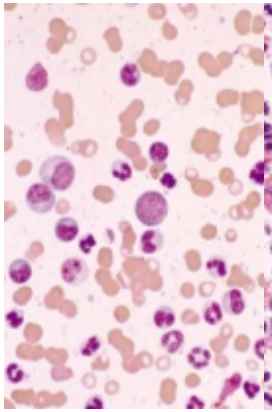
Radich JP, et al. Proc Natl Acad Sci U S A. 2006;103:2794-2799. Sawyers CL. N Engl J Med. 1999;340:1330-1340. Druker B, et al. Chronic leukemias. In: Cancer, principles, and practice of oncology. 17th ed. 2005.

Diagnosis of CML

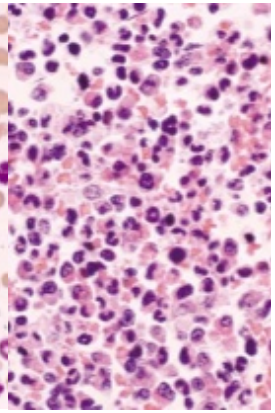
Sensitivity

Hematologic | **Cytogenetic** | **Molecular**

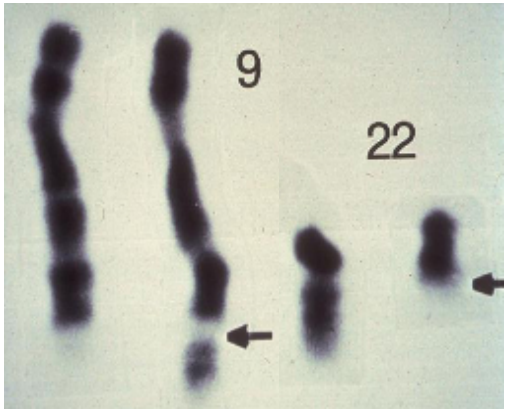
Karyotype (Ph chromosome) | FISH | PCR (BCR-ABL fusion)



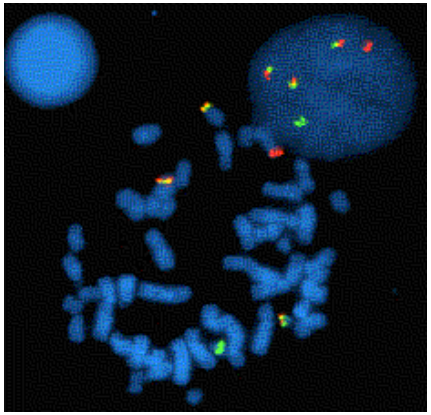
Peripheral blood (with myeloid cells)



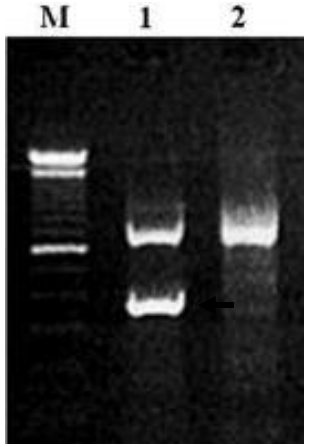
Bone marrow (with myeloid hyperplasia)



Chromosomal translocation t(9;22)(q34;q11)



Abnormal BCR-ABL
Red: BCR
Green: ABL
Yellow: fusion



Abnormal BCR-ABL
Lane 1: BCR-ABL+
Lane 2: BCR-ABL-

Factores pronósticos establecidos para predecir resultados en LMC

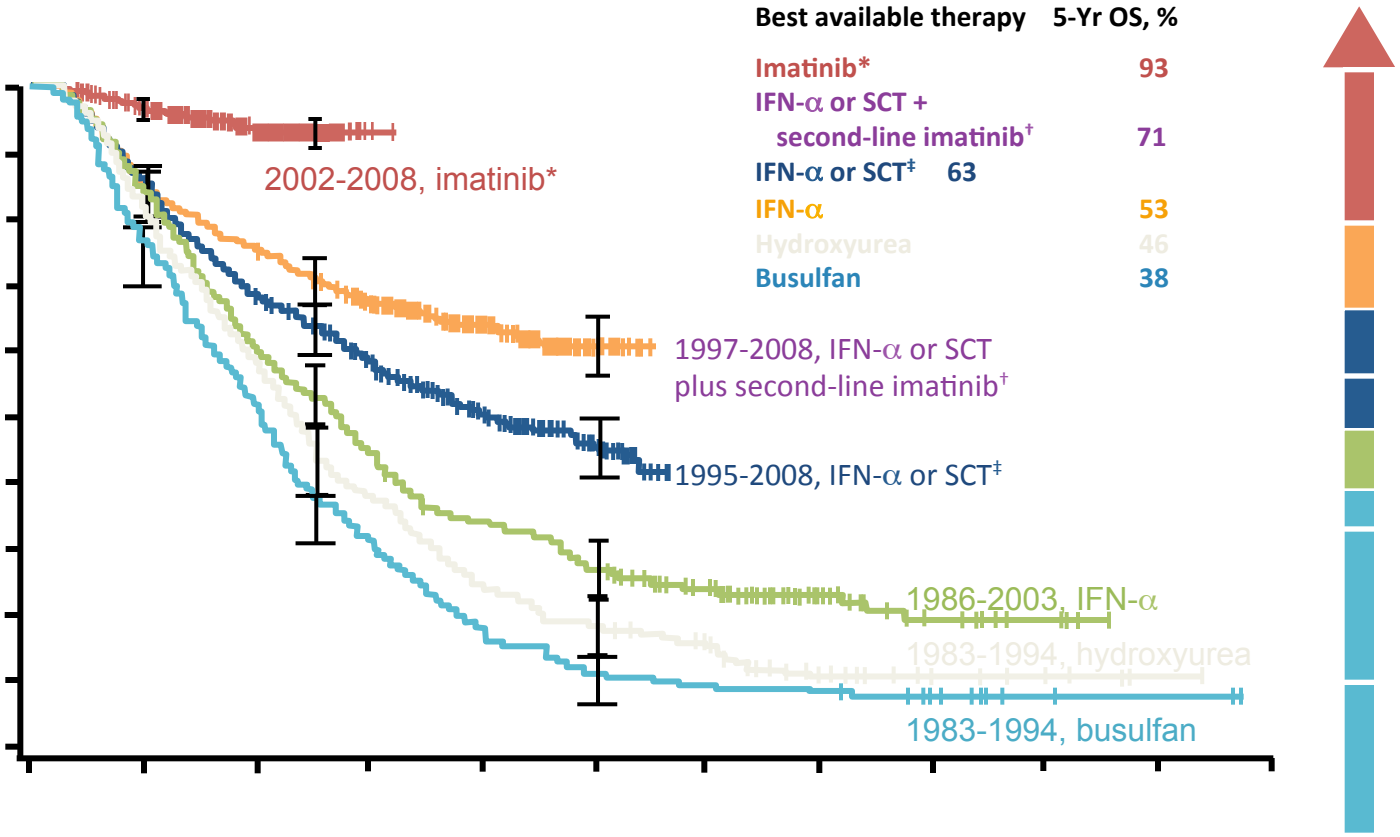
- Varios scores han sido diseñados (Sokal, Hasford, EUTOS European Treatment Outcome Study).
- En los estudios de Imatinib el factor pronóstico mas importante ha sido la respuesta obtenida a la terapia.
- A los 7 años de seguimiento en estudio IRIS: "alcanzar CCyR o RCP a los 12 meses de iniciada la terapia se asoció con 93% a 97% de probabilidad de sobrevida libre de transformación comparado con 81 % en aquellos sin respuesta citogenética mayor.

Los mejores resultados en LMC son en pacientes que tempranamente alcanzan respuesta en el curso del tto con ITKs.

Patients treated with imatinib, nilotinib, or dasatinib who achieve a response by 3-6 months—defined as PR on karyotype or molecular response by PCR showing *BCR-ABL* transcript levels at 10% or lower on the International Scale—have the greatest probability of favorable PFS and OS.

Achieving a response of 1% or fewer *BCR-ABL* transcripts on the International Scale is considered equivalent to CCyR and prognostic for better outcome, better event-free survival, and better OS.

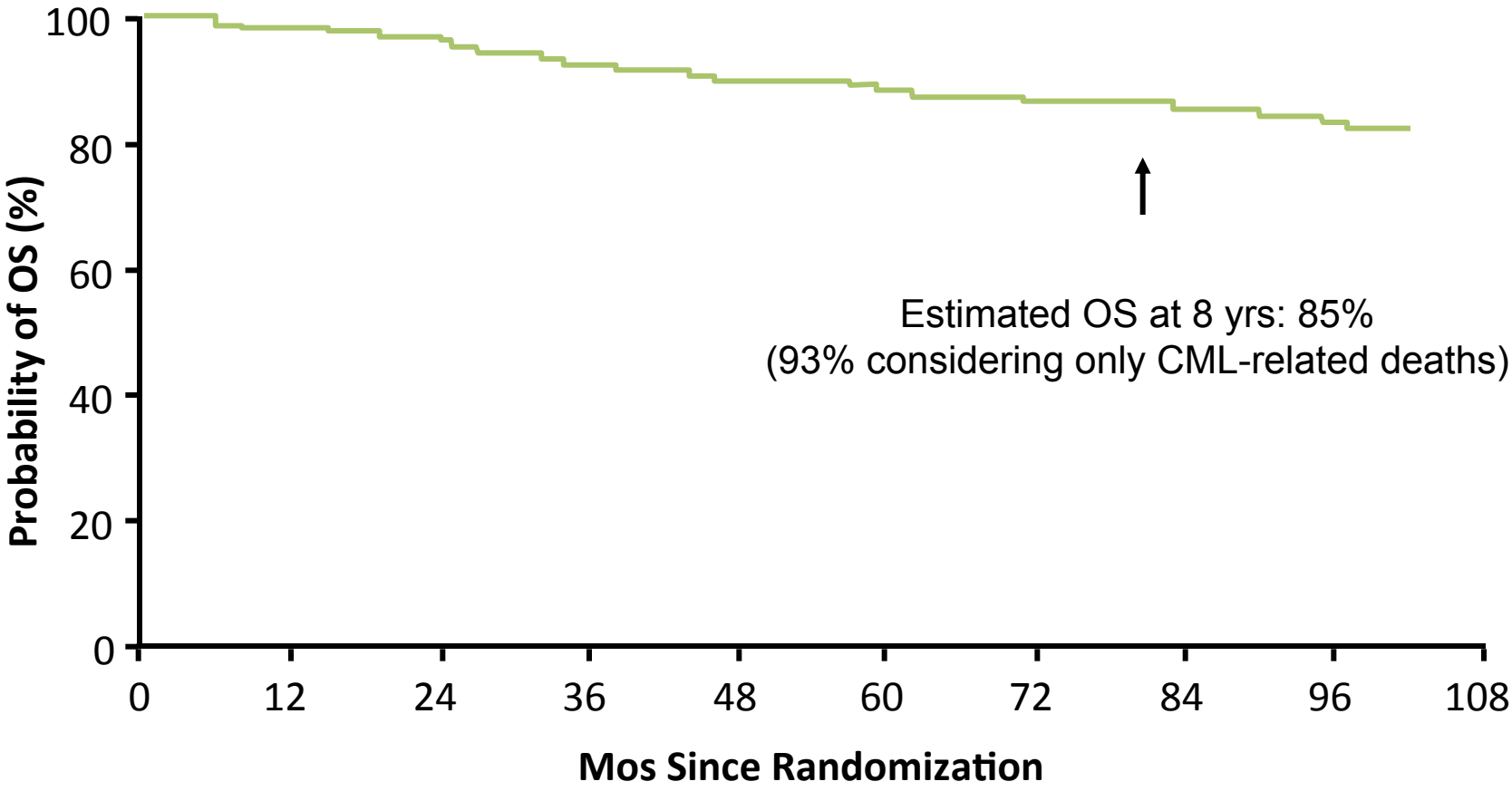
Imatinib Changed the Therapeutic Landscape for Patients With Ph+ CML



*CML IV. †CML IIIA. ‡CML III.

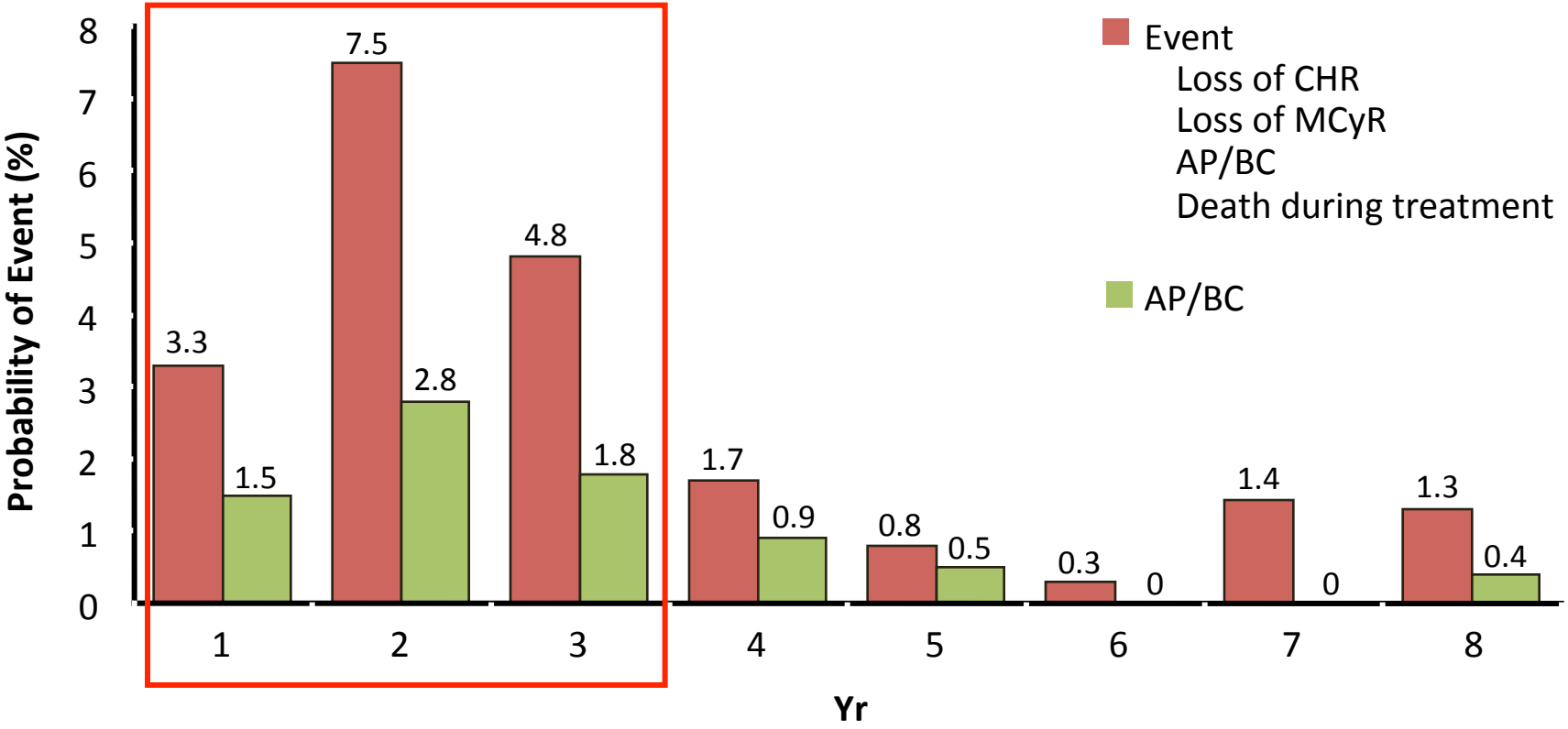
Leitner AA, et al. Internist (Berl). 2011;52:209-217.

IRIS 8-Yr Update: OS (ITT) With Imatinib Treatment in CML



Deininger M, et al. ASH 2009. Abstract 1126.

IRIS 8-Yr Update: Most Events in First 3 Yrs



- Estimated EFS at 8 yrs: 81%
- Estimated rate of freedom from progression to AP/BC at 8 yrs: 92%

Deininger M, et al. ASH 2009. Abstract 1126.

DASISION (CA180-056) Study Design

- Treatment-naive CML-CP patients (N=519)
- 108 Centers
- 26 Countries
- Enrollment: September 2007–December 2008

Randomized[a]

- Dasatinib 100 mg QD (n=259)
- Imatinib 400 mg QD (n=260)

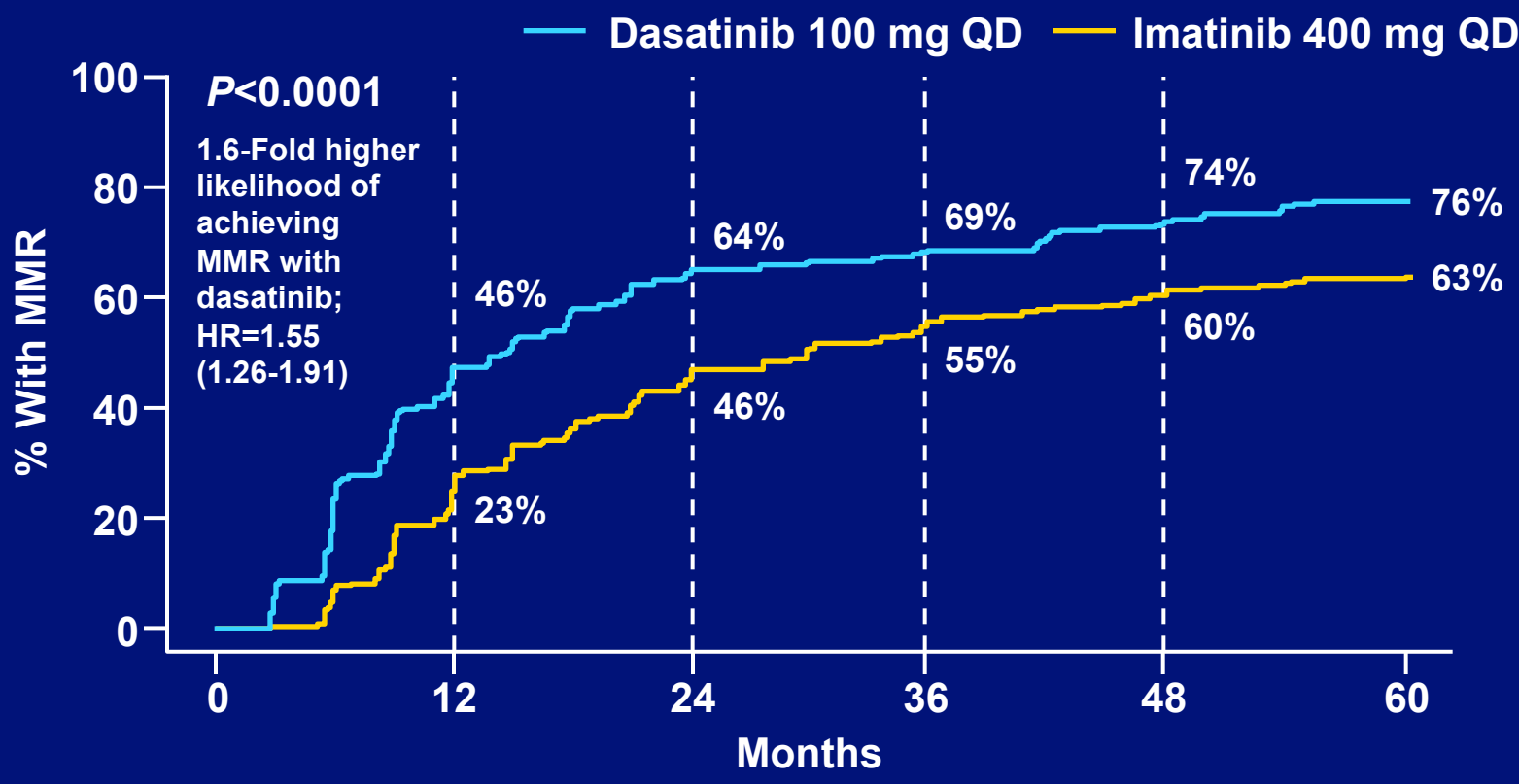
Long-term follow-up

[a]Stratified by EURO (Hasford) risk score

- Primary end point: confirmed CCyR by 12 months
  - 77% dasatinib versus 66% imatinib (*P*=0.007)[1]

1. Kantarjian H, et al. *N Engl J Med*. 2010;362:2260-70.
DASISION (CA180-056): NCT00481247; CCyR = complete cytogenetic response.

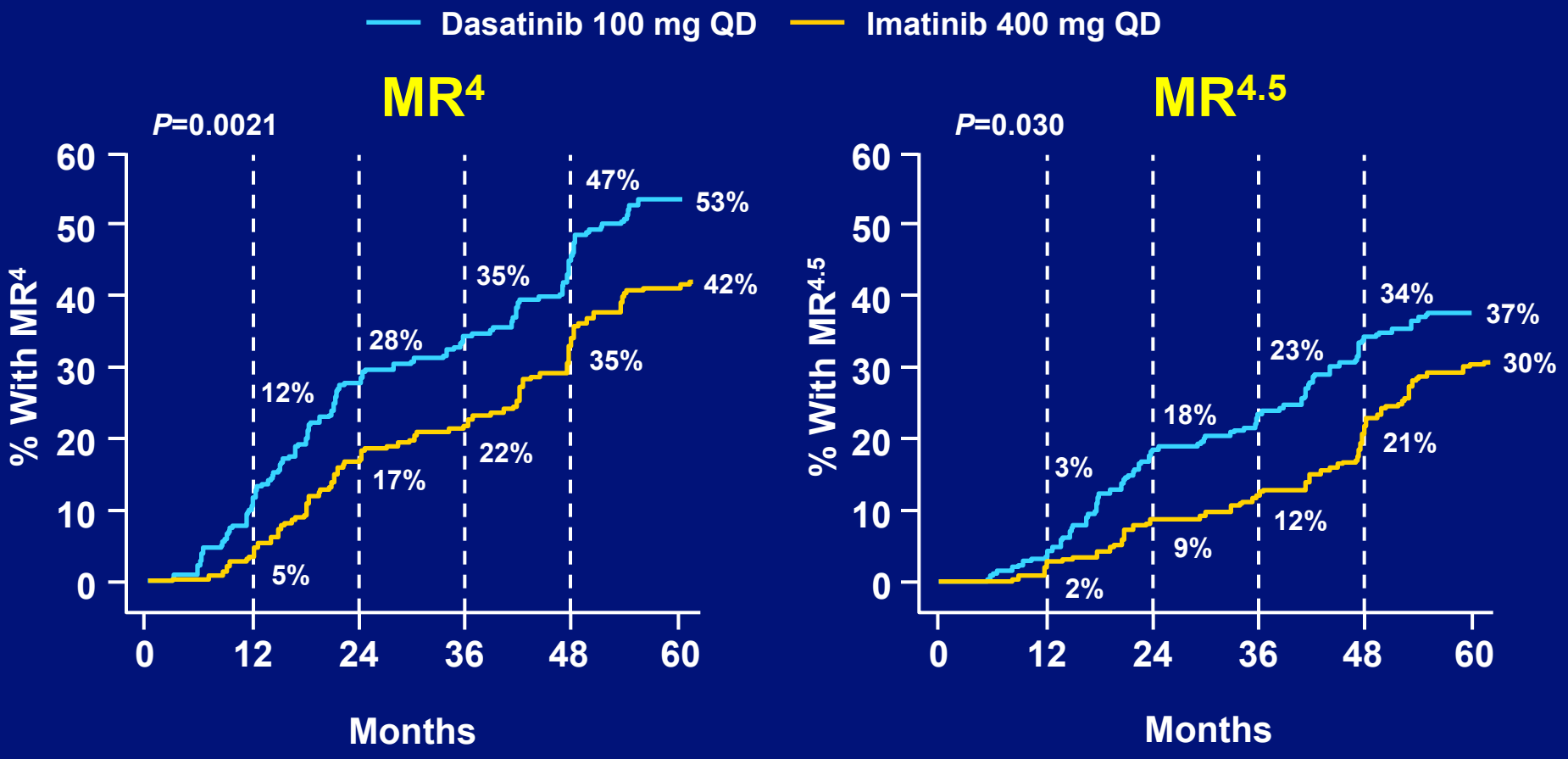
Cumulative Rate of MMR



MMR 4-y cumulative rates	Hasford Risk Score		
	Low	Intermediate	High
Dasatinib	90%	70%	65%
Imatinib	69%	63%	52%

MMR = major molecular response, BCR-ABL (IS) ≤0.1%; IS = International Scale.

Cumulative Rate of MR^4 and MR$^{4.5}$



MR^4 = BCR-ABL (IS) ≤0.01%;
MR$^{4.5}$ = BCR-ABL (IS) ≤0.0032%;
IS = International Scale.

ELN-Defined Molecular Responses[1]

		Dasatinib 100 mg QD (n=259)	Imatinib 400 mg QD (n=260)
At 3 months	n	235	239
	Optimal: BCR-ABL ≤10%	198 (84)	154 (64)
	Warning: BCR-ABL >10%	37 (16)	85 (36)
At 6 months	n	236	238
	Optimal: BCR-ABL ≤1%	164 (69)	117 (49)
	Warning: BCR-ABL >1-10%	46 (19)	80 (34)
	Failure: BCR-ABL >10%	26 (11)	41 (17)
At 12 months	n	224	221
	Optimal: BCR-ABL ≤0.1%	102 (46)	66 (30)
	Warning: BCR-ABL >0.1-1%	82 (37)	82 (37)
	Failure: BCR-ABL >1%	40 (18)	73 (33)

[1]Baccarani M, et al. *Blood.* 2013;122:872-84.
ELN = European LeukemiaNet.

Summary of 6-Month Responses Among Patients With BCR-ABL Level >10% at 3 Months[a]

	Dasatinib 100 mg QD (n=259)					Imatinib 400 mg QD (n=260)				
		BCR-ABL at 6 months					BCR-ABL at 6 months			
	Total	≤1%	>1-10%	>10%	ND	Total	≤1%	>1-10%	>10%	ND
BCR-ABL >10% at 3 months, n	37	3	10	21	3[b]	85	7	35	37	6[c]
Transformations to AP/BP, n	5	-	-	5	-	13	-	3	8	2
Deaths from any cause, n	6	-	-	5	1	14	-	4	8	2

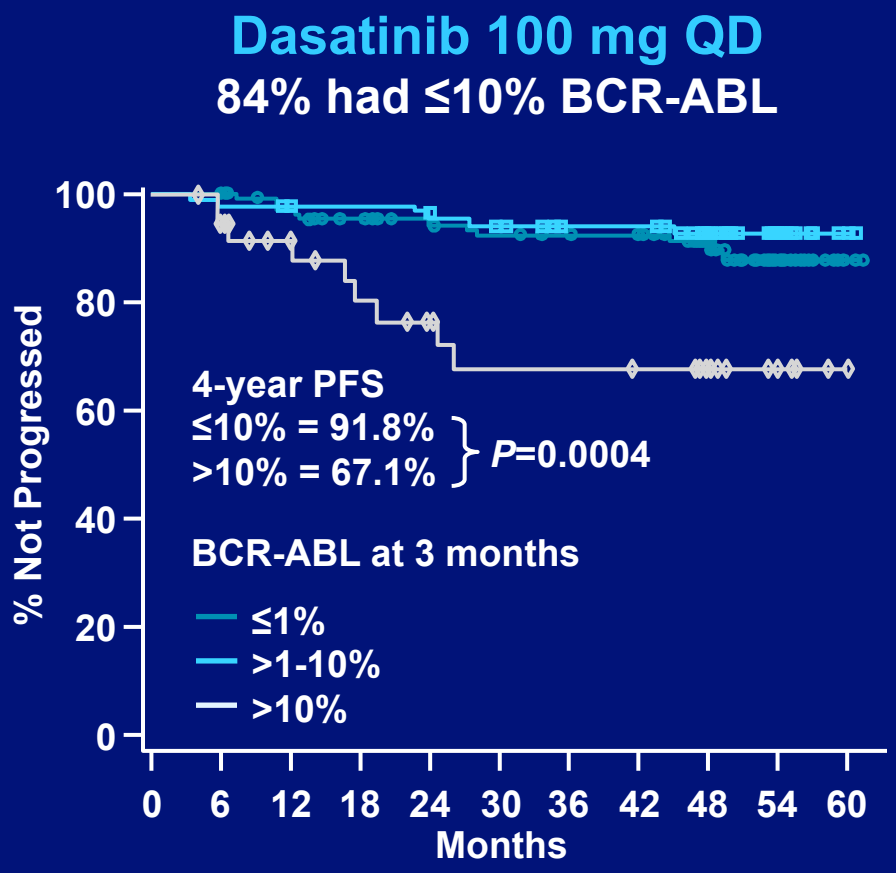
ND = not determined.

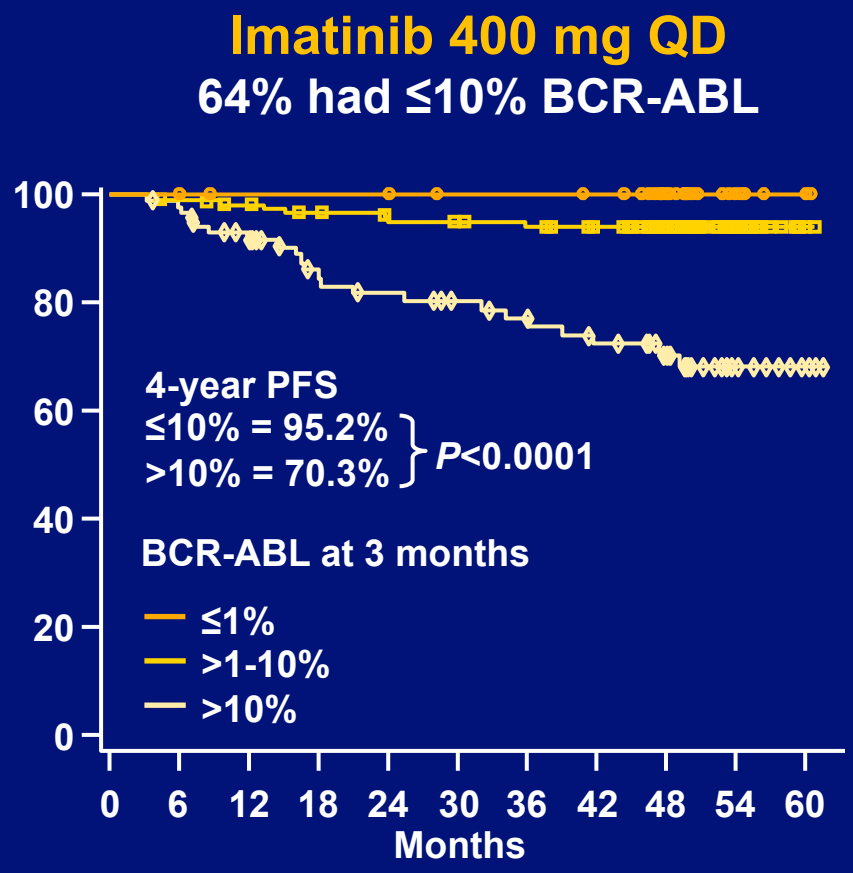
[a]Data are provided only for patients who remained on therapy through 6 months and had a molecular assessment at the indicated time point.

[b]With dasatinib, 3 patients discontinued between 3 and 6 months because of toxicity (n=2) and pregnancy (n=1).

[c]With imatinib, 6 patients discontinued between 3 and 6 months because of progression (n=1), toxicity (n=1), noncompliance (n=1), patient request (n=1), loss to follow-up (n=1), and unknown reasons (n=1).

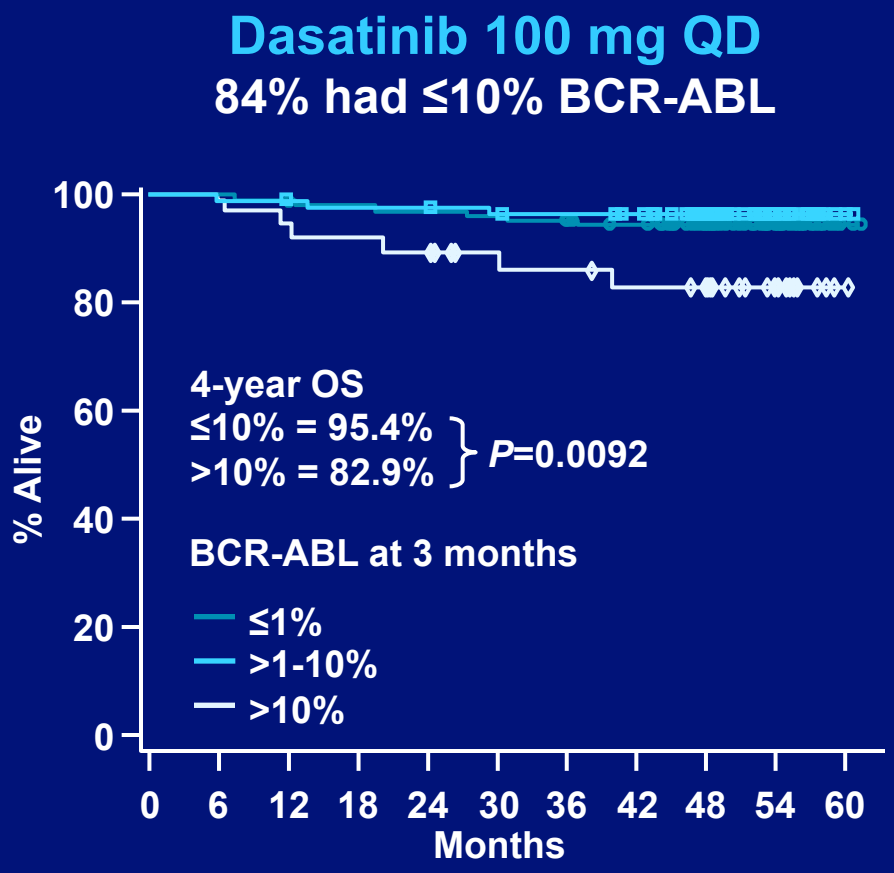
PFS According to BCR-ABL Level at 3 Months[a]

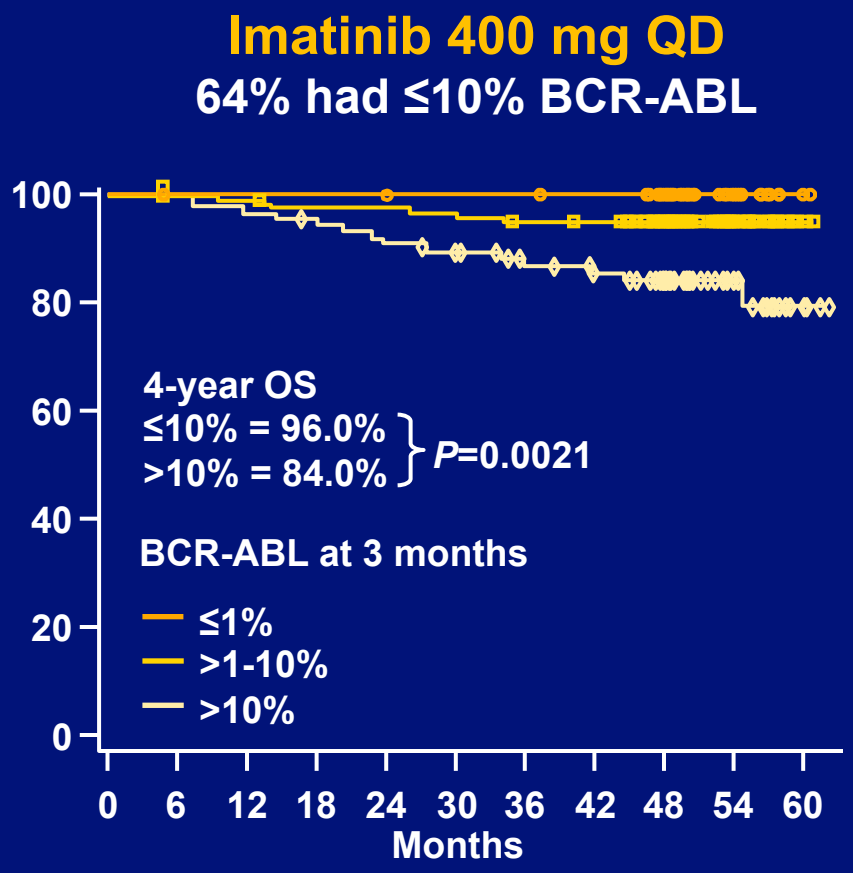




[a]Calculated from total number of evaluable patients with PCR assessments at 3 months.

OS According to BCR-ABL Level at 3 Months[a]





[a]Calculated from total number of evaluable patients with PCR assessments at 3 months.

Conclusions

- 4-Year follow-up from DASISION continues to demonstrate:
  - Deeper molecular responses with dasatinib versus imatinib
  - More ELN-defined optimal molecular responses with dasatinib versus imatinib
  - Few transformations to AP/BP
- OS in the ITT population was 93% for dasatinib and 92% for imatinib
- Landmark analyses indicate that achievement of BCR-ABL ≤10% at 3 months is associated with significantly higher PFS and OS by 4 years
  - BCR-ABL ≤10% at 3 months: dasatinib 84% versus imatinib 64%
- Safety profile remains consistent, with no new safety signals identified
- Overall, the 4-year follow-up data from DASISION support the use of dasatinib 100 mg in newly diagnosed CML-CP patients