Diagnóstico diferencial y manejo de Leucemia Mieloide Crónica

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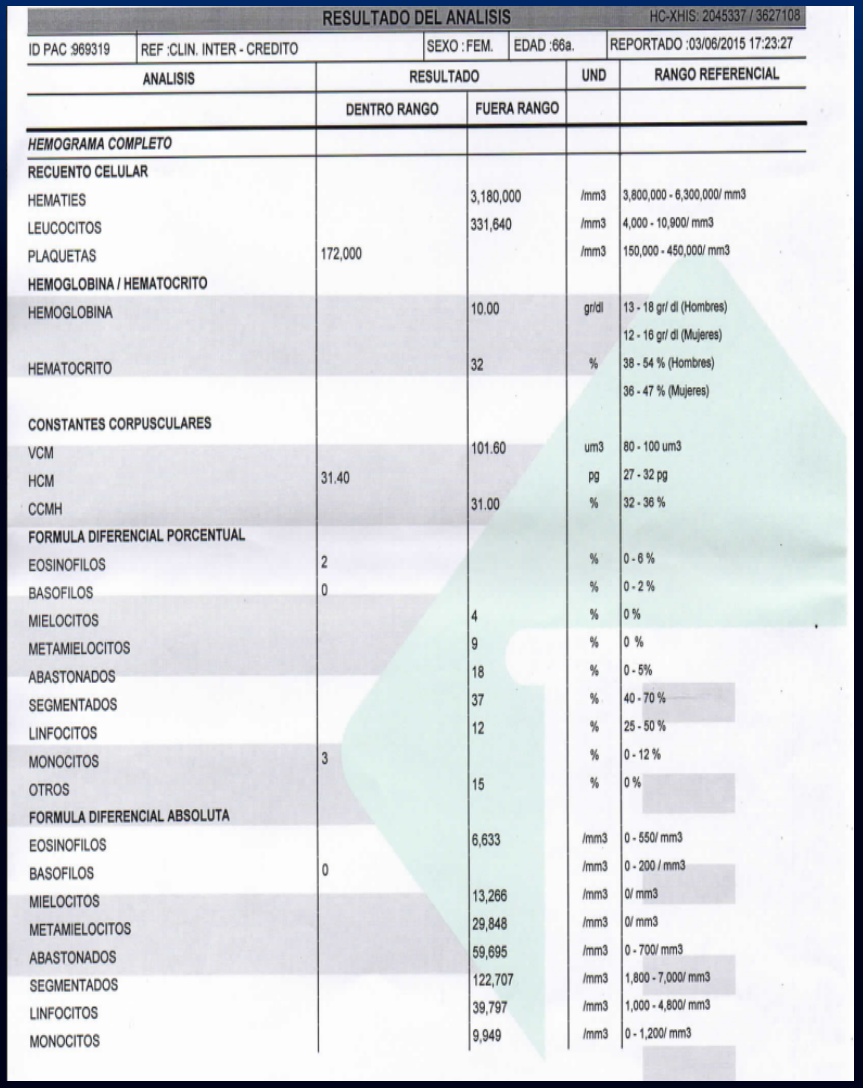
Lima, PERU

Caso Clínico

- Paciente mujer de 66 años con astenia, hiporexia, perdida ponderal y leve disconfort abdominal a predominio izquierdo
- Antecedentes de HTA y Diabetes.
- Funciones biológicas – Bien
- Examen Clínico – No fiebre, palidez discreta y se encuentra una esplenomegalia de 4 cm DRCD.

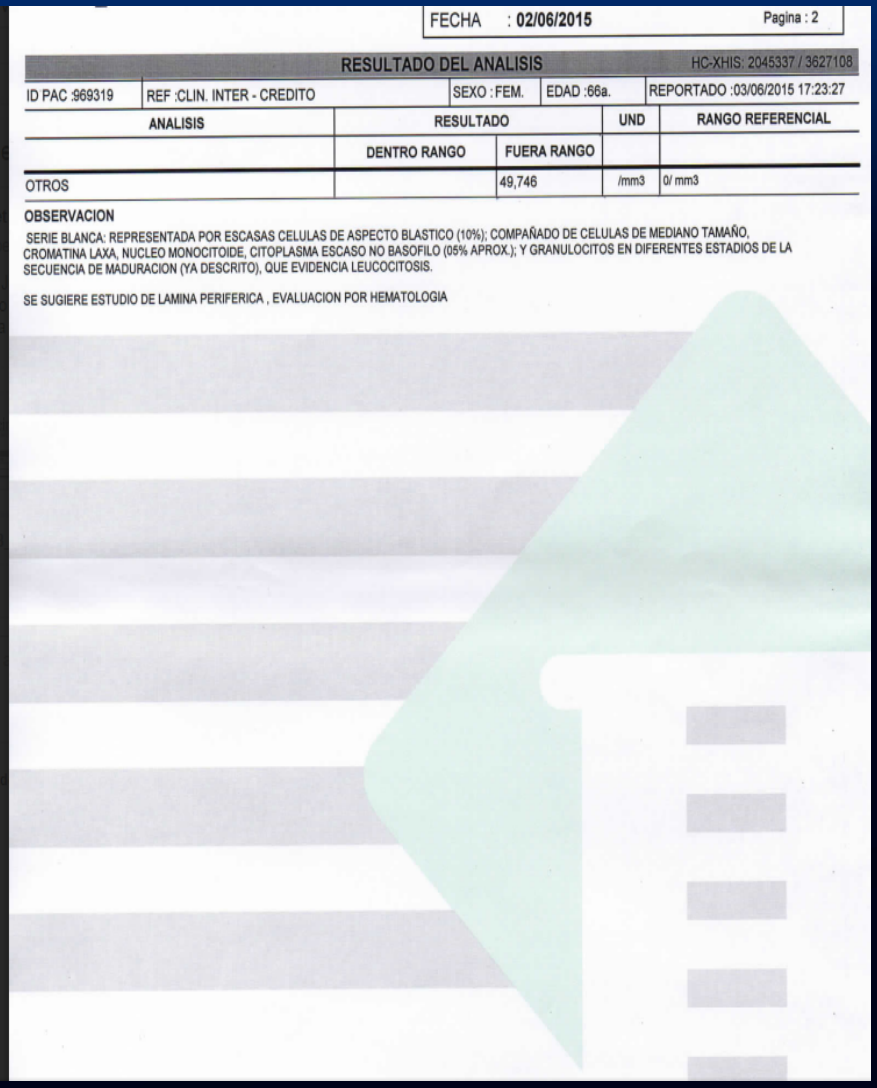
Resultados del hemograma



RESULTADO DEL ANALISIS — HC-XHIS: 2045337 / 3627108

ID PAC :969319	REF :CLIN. INTER - CREDITO	SEXO : FEM.	EDAD :66a.	REPORTADO :03/06/2015 17:23:27

ANALISIS	RESULTADO		UND	RANGO REFERENCIAL
	DENTRO RANGO	FUERA RANGO		
HEMOGRAMA COMPLETO				
RECUENTO CELULAR				
HEMATIES		3,180,000	/mm3	3,800,000 - 6,300,000/ mm3
LEUCOCITOS		331,640	/mm3	4,000 - 10,900/ mm3
PLAQUETAS	172,000		/mm3	150,000 - 450,000/ mm3
HEMOGLOBINA / HEMATOCRITO				
HEMOGLOBINA		10.00	gr/dl	13 - 18 gr/ dl (Hombres)
				12 - 16 gr/ dl (Mujeres)
HEMATOCRITO		32	%	38 - 54 % (Hombres)
				36 - 47 % (Mujeres)
CONSTANTES CORPUSCULARES				
VCM		101.60	um3	80 - 100 um3
HCM	31.40		pg	27 - 32 pg
CCMH		31.00	%	32 - 36 %
FORMULA DIFERENCIAL PORCENTUAL				
EOSINOFILOS	2		%	0 - 6 %
BASOFILOS	0		%	0 - 2 %
MIELOCITOS		4	%	0 %
METAMIELOCITOS		9	%	0 %
ABASTONADOS		18	%	0 - 5%
SEGMENTADOS		37	%	40 - 70 %
LINFOCITOS		12	%	25 - 50 %
MONOCITOS	3		%	0 - 12 %
OTROS		15	%	0 %
FORMULA DIFERENCIAL ABSOLUTA				
EOSINOFILOS		6,633	/mm3	0 - 550/ mm3
BASOFILOS	0		/mm3	0 - 200 / mm3
MIELOCITOS		13,266	/mm3	0/ mm3
METAMIELOCITOS		29,848	/mm3	0/ mm3
ABASTONADOS		59,695	/mm3	0 - 700/ mm3
SEGMENTADOS		122,707	/mm3	1,800 - 7,000/ mm3
LINFOCITOS		39,797	/mm3	1,000 - 4,800/ mm3
MONOCITOS		9,949	/mm3	0 - 1,200/ mm3



FECHA : 02/06/2015 — Pagina : 2

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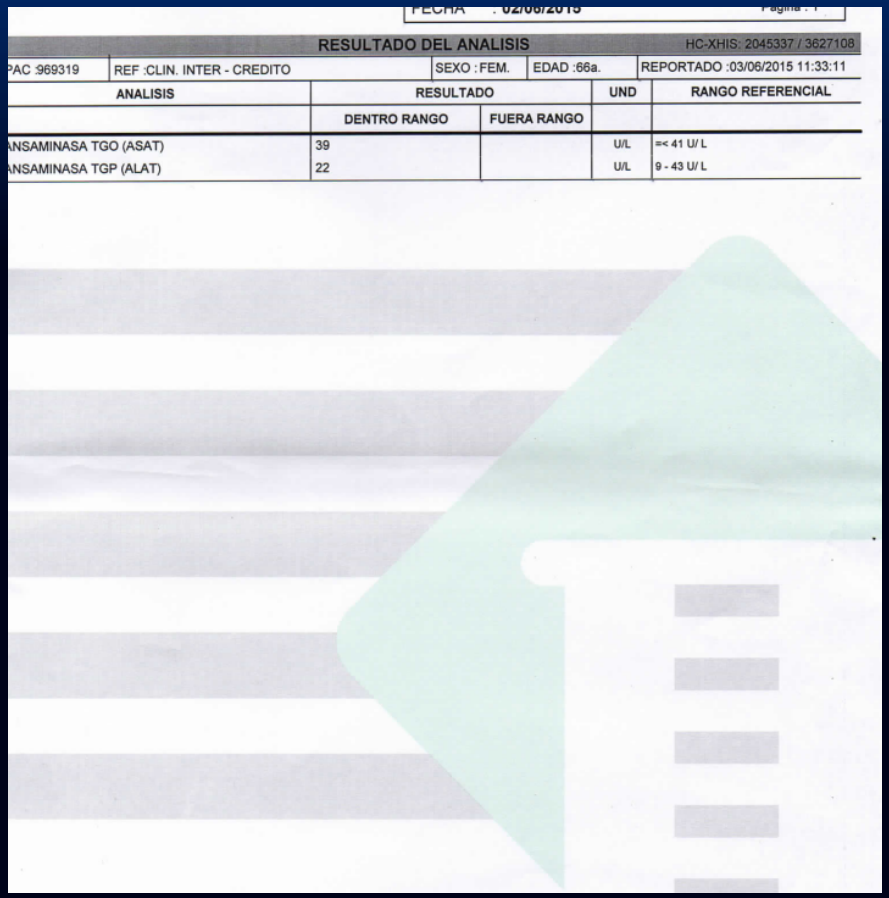
ANALISIS	RESULTADO		UND	RANGO REFERENCIAL
	DENTRO RANGO	FUERA RANGO		
OTROS		49,746	/mm3	0/ mm3

OBSERVACION

SERIE BLANCA: REPRESENTADA POR ESCASAS CELULAS DE ASPECTO BLASTICO (10%); COMPAÑADO DE CELULAS DE MEDIANO TAMAÑO, CROMATINA LAXA, NUCLEO MONOCITOIDE, CITOPLASMA ESCASO NO BASOFILO (05% APROX.); Y GRANULOCITOS EN DIFERENTES ESTADIOS DE LA SECUENCIA DE MADURACION (YA DESCRITO), QUE EVIDENCIA LEUCOCITOSIS.

SE SUGIERE ESTUDIO DE LAMINA PERIFERICA , EVALUACION POR HEMATOLOGIA

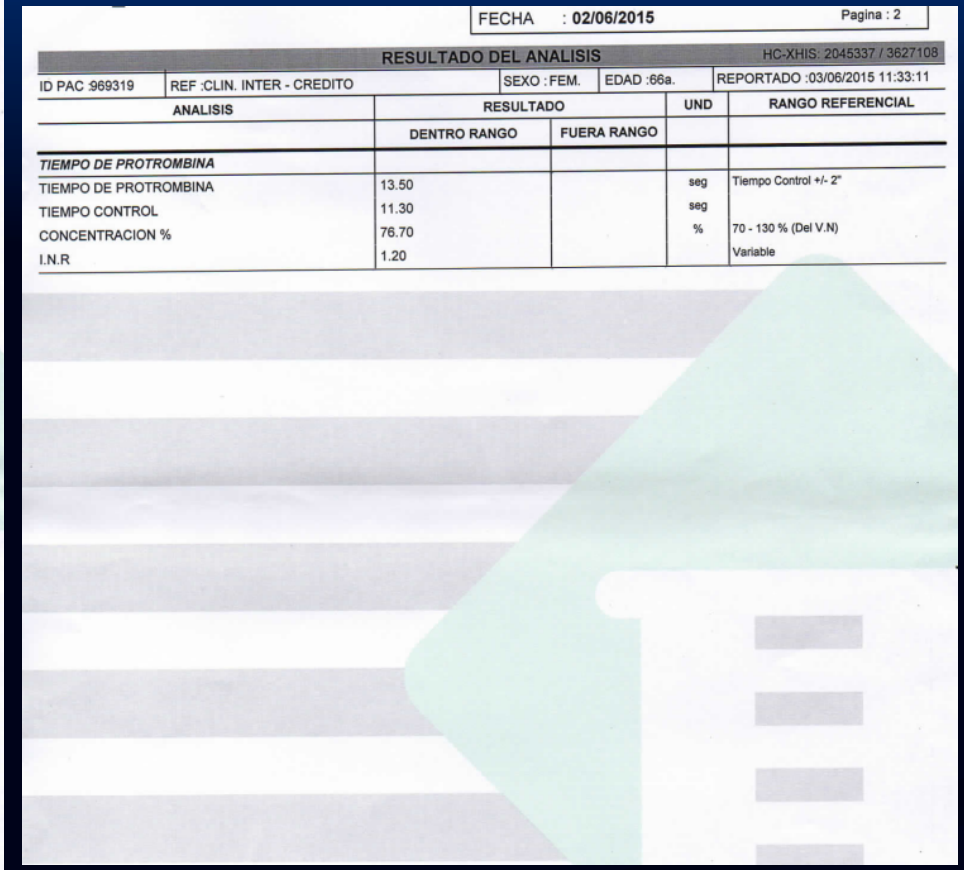
Otros resultados



RESULTADO DEL ANALISIS — HC-XHIS: 2045337 / 3627108

PAC :969319 | REF :CLIN. INTER - CREDITO | SEXO : FEM. | EDAD :66a. | REPORTADO :03/06/2015 11:33:11

ANALISIS	RESULTADO		UND	RANGO REFERENCIAL
	DENTRO RANGO	FUERA RANGO		
NSAMINASA TGO (ASAT)	39		U/L	=< 41 U/ L
NSAMINASA TGP (ALAT)	22		U/L	9 - 43 U/ L



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ANALISIS	RESULTADO		UND	RANGO REFERENCIAL
	DENTRO RANGO	FUERA RANGO		
TIEMPO DE PROTROMBINA				
TIEMPO DE PROTROMBINA	13.50		seg	Tiempo Control +/- 2"
TIEMPO CONTROL	11.30		seg	
CONCENTRACION %	76.70		%	70 - 130 % (Del V.N)
I.N.R	1.20			Variable

Conducta a seguir

1. Ampliar analisis: Ac Urico, DHL, bioquímica hepática y renal.
2. Solicitar presencia de mutación Oncogen BCR-ABL y estudio citogenética de Sangre Periférica o de médula ósea.
3. Aspirado de Médula Osea con sangre periférica para clasificación de fase de enfermedad.
4. Score de riesgo – SOKAL y/o Hasford

Resultado de Gen BCR-ABL

PACIENTE	CODIGO	INGRESO	PROCEDENCIA	INDICACIÓN
[redacted]	B1500771	09-06-2015		DR. JUAN NAVARRO

Reporte de Resultados

CUANTIFICACIÓN DEL GEN BCR-ABL VARIANTE p210 POR PCR EN TIEMPO REAL

Datos de laboratorio

Muestra: Sangre periférica
Responsable: Dr. Abelardo Arias Velásquez. RNE 21938
Analista: Blgo. L. Martín Cruz Díaz. CBP 6911

Genes analizado:	Resultado	Ratio BCR-ABL p210 / ABL	Porcentaje
BCR-ABL p210	DETECTADO	0.7862	78.62%

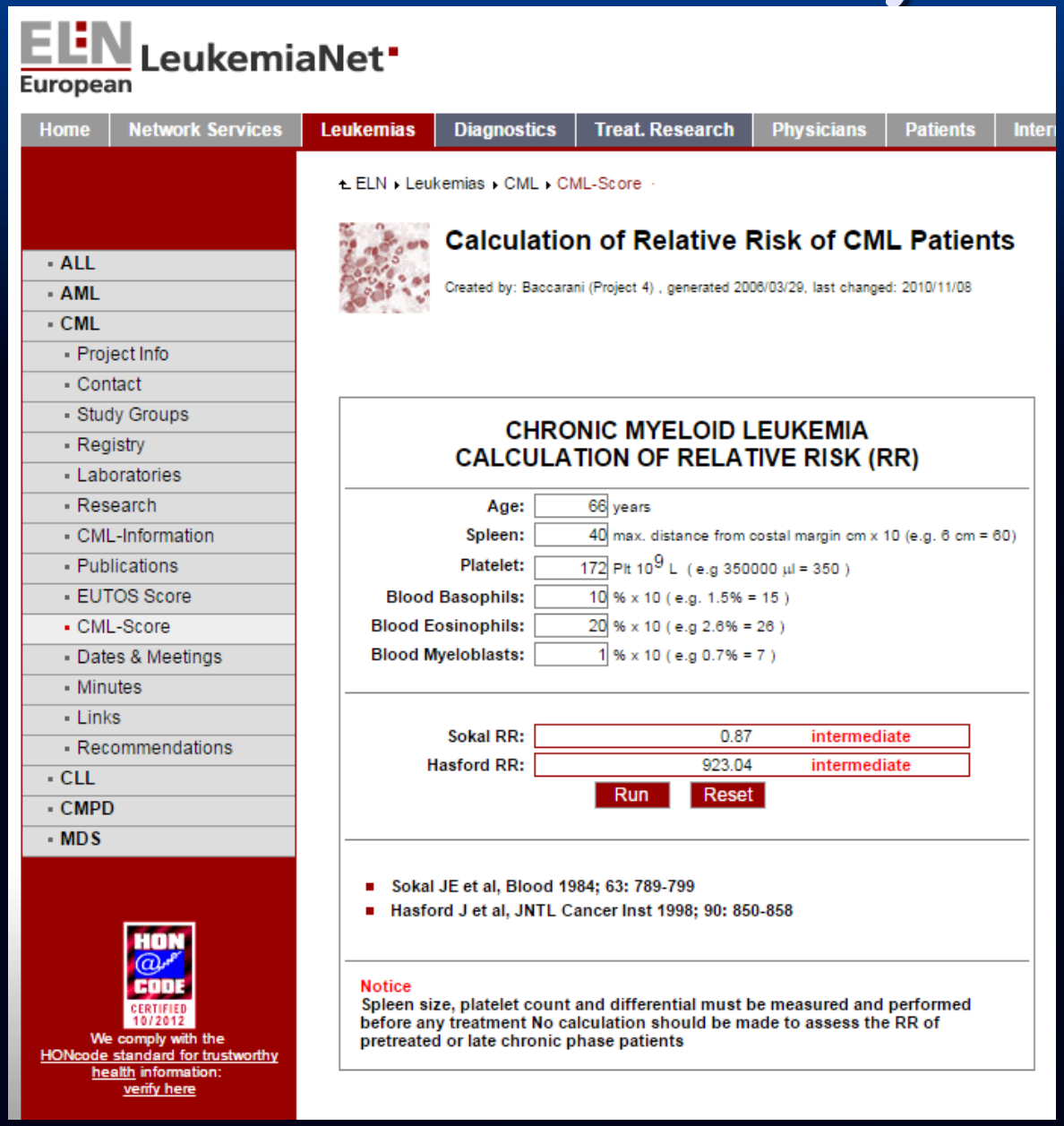
Comentario

En el estudio molecular, **SE DETECTÓ** la expresión del gen de fusión BCR-ABL p210 (78.62%), en relación a la expresión del gen control ABL. Se sugiere monitoreo en tres meses, según indicación del médico tratante.

Notas

El gen de fusión BCR-ABL variante p210 es un factor diagnóstico en Leucemia Mieloide Crónica (LMC), siendo la cuantificación de la expresión del mismo, la estrategia de monitoreo actualmente aceptada durante el tratamiento con inhibidores tirosina-quinasa. El monitoreo del gen de fusión BCR-ABL p210, se realiza por Reacción en Cadena de la Polimerasa en Tiempo Real (RT-QPCR) y los resultados se expresan en porcentaje de acuerdo a la relación de los niveles de expresión de BCR-ABL1 p210 y el gen control ABL, durante el tiempo de tratamiento.
Según las recomendaciones LeukemiaNet (Baccarani et al, Blood 2013;122:872-884), el estudio se realiza cada 3 y seis meses según el inicio de la terapia, tomando en cuenta la evolución clínica del paciente y otros exámenes de apoyo al diagnóstico. El estudio detecta y cuantifica sólo las isoformas e13a2 y e14a2, las cuales codifican la proteína p210 proteína. Otros tipos de fusión no son detectados, tales como las variantes p190 y p230.

Score Sokal y Hasford

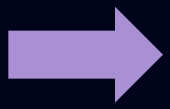


Diagnósstico final:
LEUCEMIA MIELOIDE CRÓNICA EN FASE CRÓNICA

Score de Riesgo: SOKAL Y HASFORD RIESGO INTERMEDIO

Conducta inicial y tto para un paciente con LMC en fase cr.

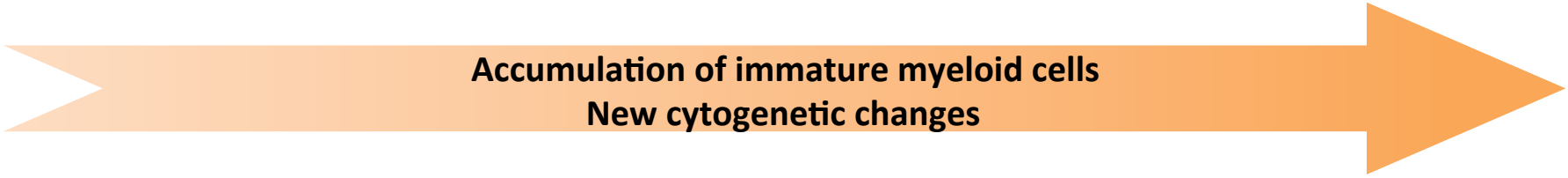
- Conducta
  - HC y Examen Físico, determinar el tamaño del bazo por palpación.
  - Hemograma con diferencial y Rcto. de plaquetas
  - Perfil bioquímico en suero.
  - HLA
  - Aspirado y/o Biopsia de MO
  - QPCR con IS
  - Determinar score de riesgo



- Tto primario si es Ph (+) o BCR-ABL positivo
  - Discutir opciones terapéuticas
    1. TKI
    2. TMO
    3. Clinical trial
  - Iniciar tratamiento con:
    - Imatinib 400 mg
    - Nilotinib 300 mg BID
    - Dasatinib 100 mg QD

NCCN. Clinical practice guidelines in oncology: chronic myelogenous leukemia. v.3.2014.

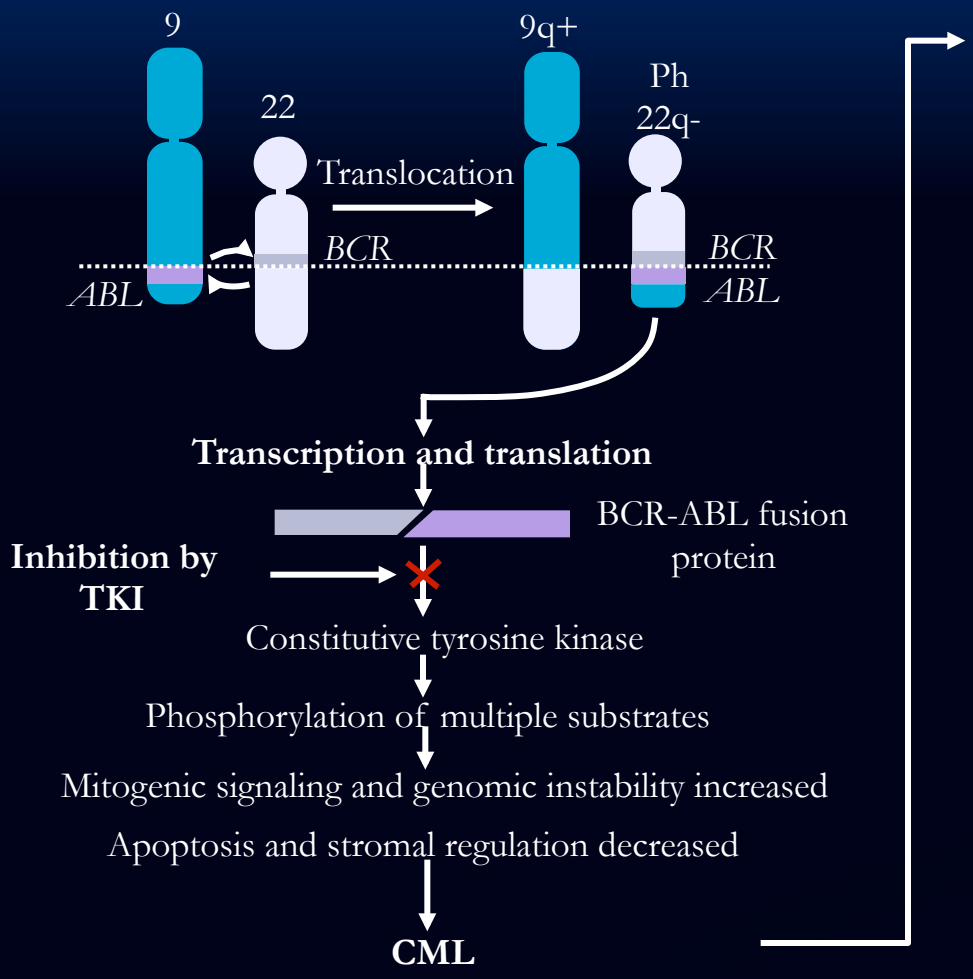
Natural History of CML



	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.

Traslocación en LMC que resulta en Oncogen BCR-ABL



- Desorden del Stem cell
- Produce proliferación y disminución en la apoptosis

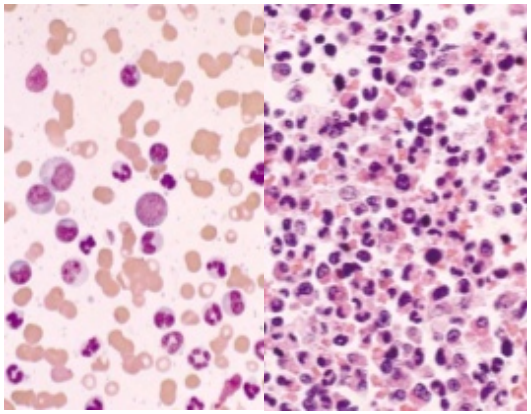
Neil P. Shah, MD, PhD *Associate Professor*
Division of Hematology/Oncology
University of California, CML 2013
clinicaloptions.com/oncology

Diagnosis of CML

Sensitivity

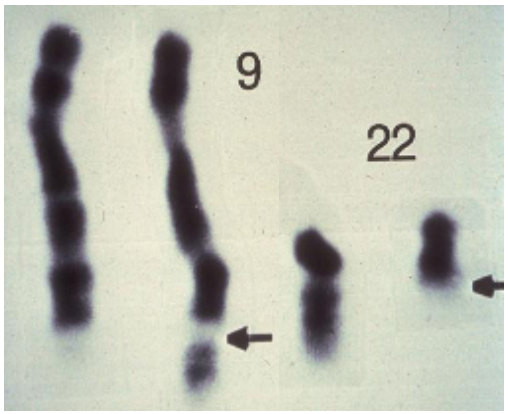
Hematologic | **Cytogenetic** | **Molecular**

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

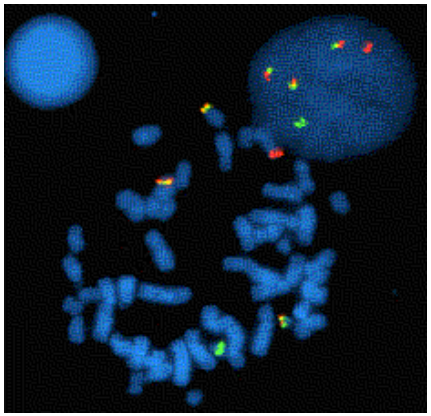


Peripheral blood (with myeloid cells)

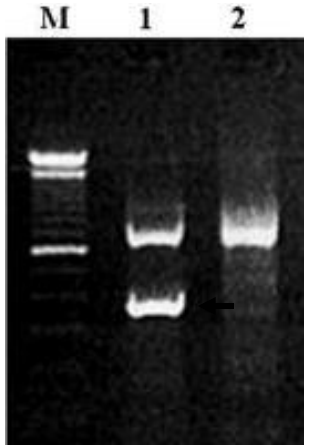
Bone marrow (with myeloid hyperplasia)



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-

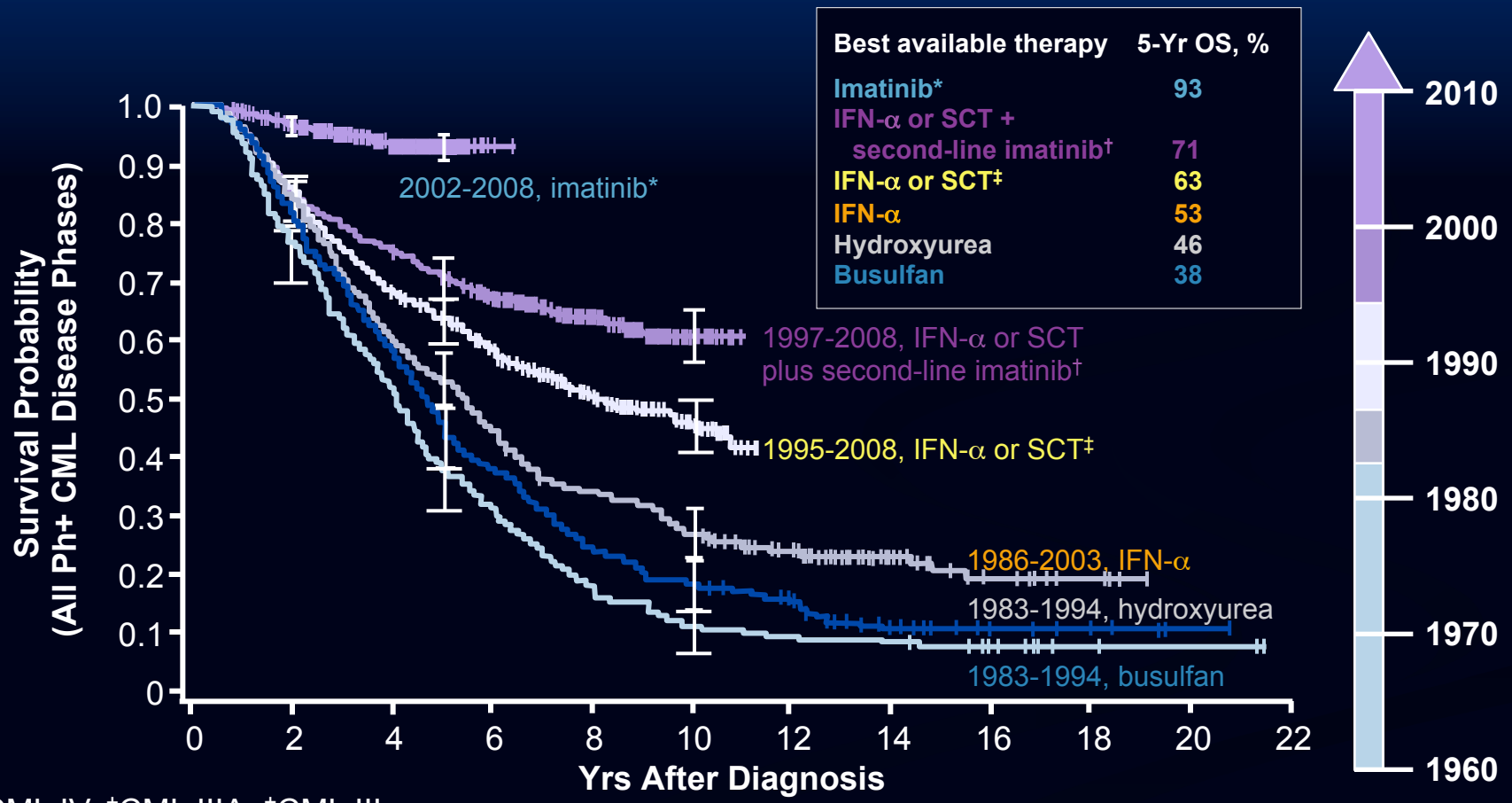
Neil P. Shah, MD, PhD *Associate professor*
Division of Hematology/Oncology
University of California, CML 2013
clinicaloptions.com/oncology

Criteria for Hematologic, Cytogenetic, and Molecular Response

Response	Criteria
Complete hematologic response	▪ Complete normalization of PB counts, leukocyte count < 10 x 10^9/L ▪ Platelet count < 450 x 10^9/L ▪ No myelocytes, promyelocytes, or blasts in PB ▪ No palpable splenomegaly ▪ No disease symptoms
Cytogenetic response	
▪ Complete	No Ph+ metaphases
▪ Partial	1% to 35% Ph+ metaphases
▪ Major	0% to 35% Ph+ metaphases (complete + partial)
▪ Minor	> 35% Ph+ metaphases
Molecular Response	
▪ Major	≥ 3 log reduction in BCR-ABL mRNA or BCR-ABL/ABL ≤ 0.1% by QPCR (International Scale)
▪ Complete (CMR or $MR^{4.5}$)	No detectable BCR-ABL mRNA using assay with sensitivity at least 4.5 logs below standardized baseline

NCCN. Clinical practice guidelines in oncology: chronic myelogenous leukemia. v3.2014.

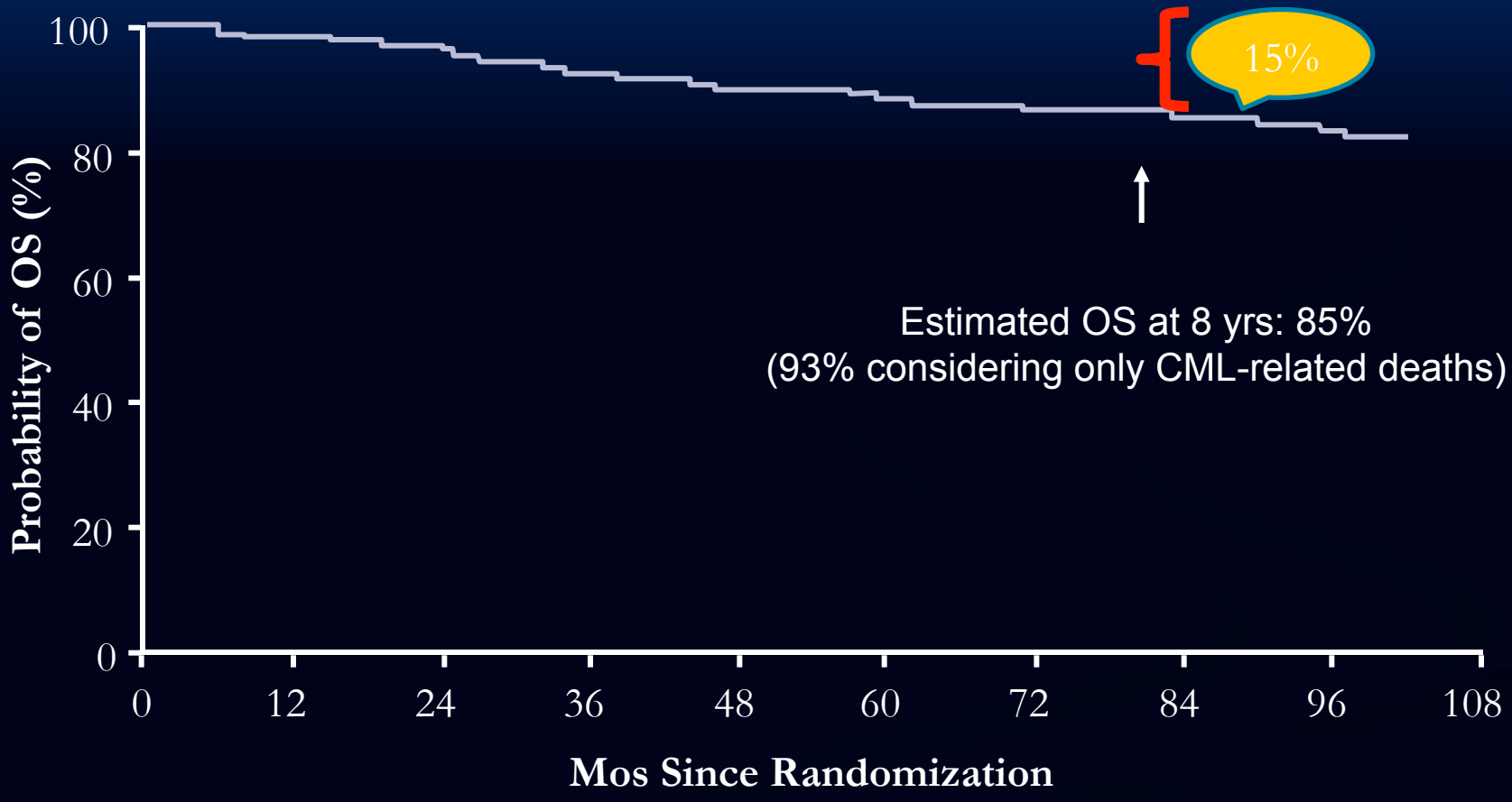
Imatinib Changed the Therapeutic Landscape for Patients With Ph+ CML



*CML IV. †CML IIIA. ‡CML III.

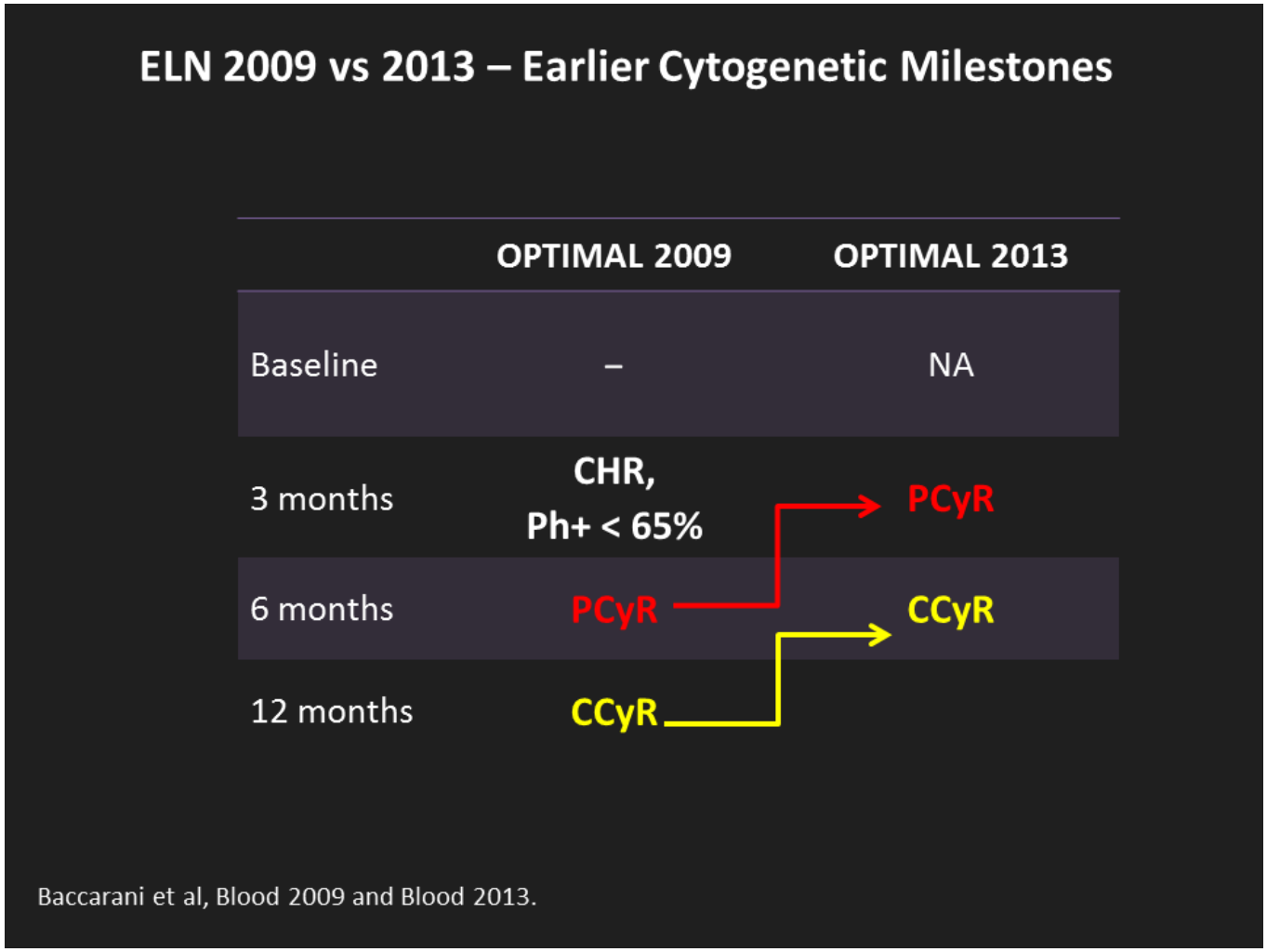
Leitner AA, et al. Internist (Berl). 2011;52:209-217.

IRIS 8-Yr Update: OS (ITT)



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

ELN 2009 vs ELN 2013



Baccarani , Blood 2009 y 2013

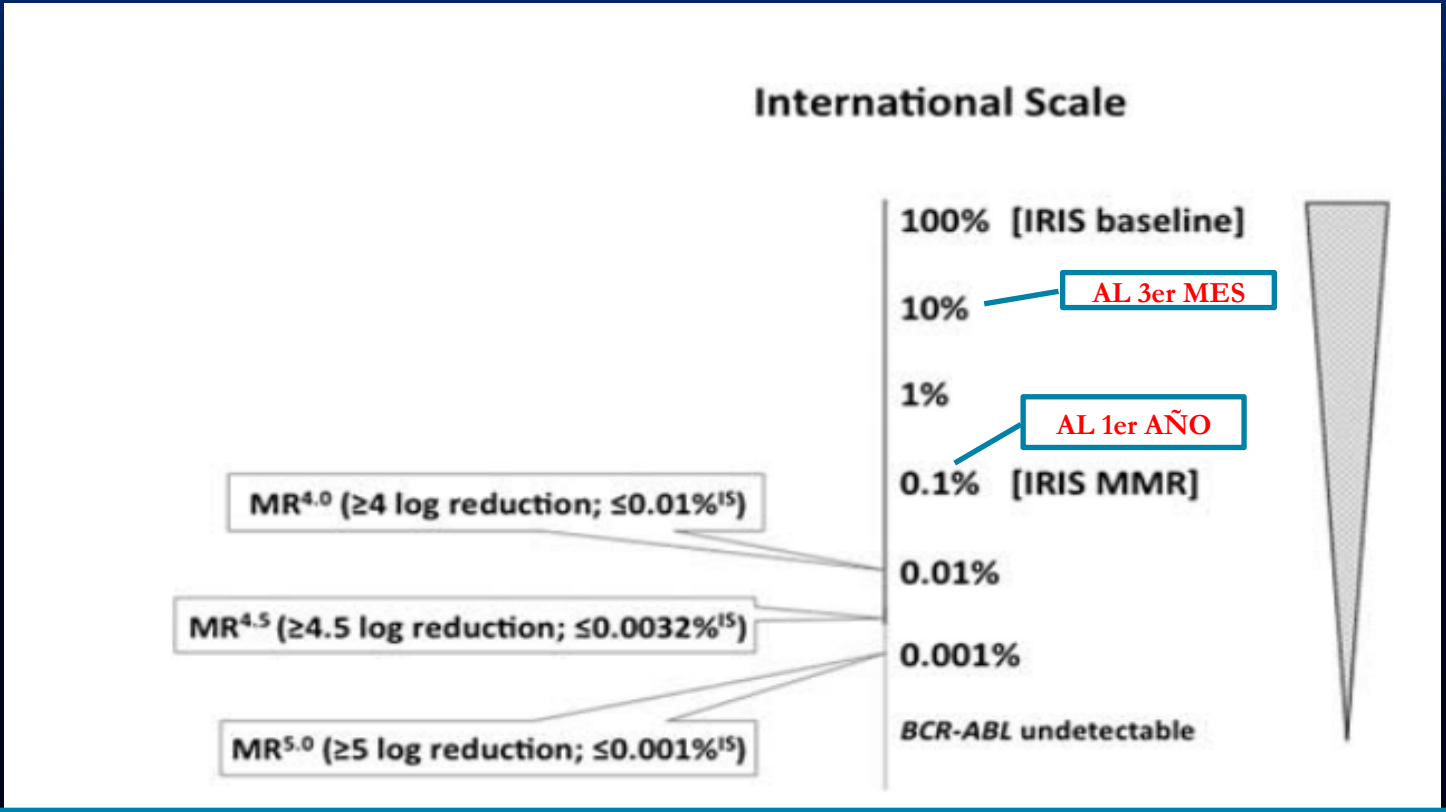
Defining Response in First Line—ELN Guidelines

		Response Criteria		
Monitoring time	Baseline		High risk or CCA/Ph+, major route	
	3 months	BCR-ABL1 ≤10% and/or Ph+ <35%	BCR-ABL1 >10% and/or Ph+ 36%-95%	Non-CHR and/or Ph+ >95%
	6 months	BCR-ABL1 <1% and/or Ph+ 0	BCR-ABL1 1%-10% and/or Ph+ 1%-35%	BCR-ABL1 >10% and/or Ph+ >35%
	12 months	BCR-ABL1 ≤0.1%	BCR-ABL1 >0.1-1%	BCR-ABL1 >1% and/or Ph+ >0
	>12 months	BCR-ABL1 ≤0.1%	CCA/Ph– (–7, or 7q–)	Loss of CHR or CCyR Confirmed loss of MMR Mutations CCA/Ph+
		Optimal Response	Warning Zone	Treatment Failure

CCA/Ph+ = clonal chromosome abnormalities in Ph+ cells; CCA/Ph– = clonal chromosome abnormalities in Ph– cells; CCyR = complete cytogenetic response; CHR = complete hematologic response; ELN = European LeukemiaNet; MMR = major molecular response

Baccarani M, et al. *J Clin Oncol*. 2013;122(6):872-884.

Definición de respuesta molecular (BCR-ABL)



Standardized definitions of molecular response in chronic myeloid Leukemia NCP Cross, HE White, MC Muller3, G Saglio and A Hochhaus. Leukemia (2012) 26, 2172–2175

Objetivos para Guías ELN y NCCN

- Han adoptado como objetivo del tratamiento una respuesta molecular <10% o RCyP al 3er mes sustentado en:

1) Wang L, Pearson K, Ferguson JE, Clark RE. The early molecular response to imatinib predicts cytogenetic and clinical outcome in chronic myeloid leukaemia. Br J Haematol. 2003;120(6): 990-999.
2) Marin D, Ibrahim AR, et al. Assessment of BCR-ABL1 transcript levels at 3 months is the only requirement for predicting outcome for patients with CML treated with TKI. J Clin Oncol. 2012;30(3): 232-238.
3) Hanfstein B, M ¨uller MC, Hehlmann R, et al; SAKK; German CML Study Group. Early molecular and cytogenetic response is predictive for long-term progression-free and overall survival in CML. Leukemia. 2012;26(9):2096-2102
4) Branford S, Kim D-W, Soverini S, et al. Initial molecular response at 3 months may predict both response and event-free survival at 24 months in imatinib-resistant or -intolerant patients with Philadelphia chromosome-positive CML in chronic phase treated with nilotinib. J Clin Oncol. 2012;30(35):4323-4329.
5) Marin D, Hedgley C, Clark RE, et al. Predictive value of early molecular response in patients with CML treated with first-line dasatinib. Blood. 2012;120(2):291-294.
6) Jabbour E, Kantarjian HM, Saglio G, et al. Early response with dasatinib or imatinib in CML: 3-year follow-up from a randomized phase 3 trial (DASISION). Blood.2014;123(4):494-500.
7) Hughes TP, Saglio G, Kantarjian HM, et al. Early molecular response predicts outcomes in patients with chronic myeloid leukemia in chronic phase treated with frontline nilotinib or imatinib. Blood.2014;123(9): 1353-1360

¿¿ Cual es el impacto de la respuesta en sobrevida libre de enfermedad y sobrevida global ??

Analisis del sustento a las Guías actuales propuestas por ELN y NCCN

Factores pronósticos ya fueron establecidos en LMC

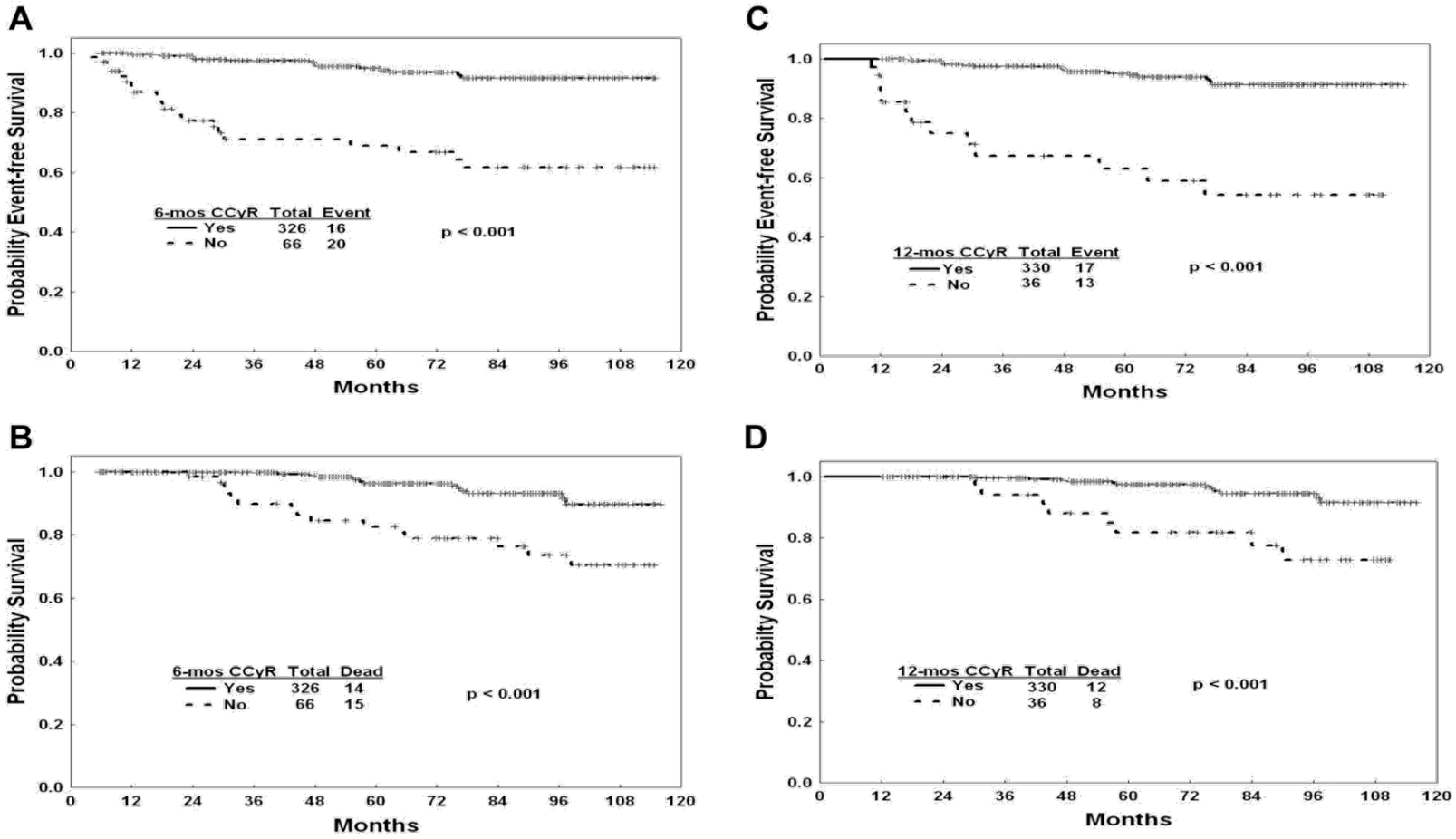
- En los estudios de Imatinib el factor pronóstico mas importante ha sido la respuesta obtenida a la terapia.
- Existe una relación directa entre respuesta (SLE y SG)

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

E. Jabbour, BLOOD, 27 OCTOBER 2011 VOLUME 118, NUMBER 17

The achievement of an early complete cytogenetic response is a major determinant for outcome in patients with early chronic phase chronic myeloid leukemia treated with tyrosine kinase inhibitors

Elias Jabbour,1 Hagop Kantarjian,1 Susan O'Brien,1 Jenny Shan,1 Alfonso Quintas-Cardama,1 Stefan Faderl,1 Guillermo Garcia-Manero,1 Farhad Ravandi,1 Mary Beth Rios,1 and Jorge Cortes1
1Department of Leukemia, University of Texas M. D. Anderson Cancer Center, Houston



(*Blood.*2011;118(17):4541-4546)

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1Department of Leukemia, University of Texas M. D. Anderson Cancer Center, Houston

BLOOD, 27 OCTOBER 2011 • VOLUME 118, NUMBER 17

Table 2. CCyR at 3, 6, and 12 months by therapy

	3 months				6 months				12 months			
	Evaluable	CCyR	%	*P*	Evaluable	CCyR	%	*P*	Evaluable	CCyR	%	*P*
IM 400 mg	70	27	39		70	37	53		68	45	66	
IM 800 mg	199	125	63	< .001	194	164	85	< .001	187	169	90	< .001
Second TKI	141	114	81		131	125	95		118	116	98	

Evaluable indicates patients who received therapy and were evaluable for cytogenetic response at each time point; and IM, imatinib.

Table 3. Outcome

	3-month CCyR			6-month CCyR			12-month CCyR		
	Yes	No	*P*	Yes	No	*P*	Yes	No	*P*
Total group									
3-year EFS	98	83	< .001	97	72	< .001	98	67	< .001
3-year OS	99	95	.06	99	90	< .001	99	94	< .001
IM 400 mg									
3-year EFS	92	81	.12	97	74	.001	98	72	< .001
3-year OS	100	88	.046	100	87	.09	100	88	.046
IM 800 mg									
3-year EFS	97	84	.005	97	68	< .001	98	58	< .001
3-year OS	98	97	.93	99	92	.001	99	100	.03
Second TKI									
3-year EFS	100	80	< .001	99	67	< .001	99	NA	NA
3-year OS	100	100	NA	100	100	NA	100	NA	NA
P (EFS/OS)	.07/.3			.56/.81			.9/.6		

IM indicates imatinib; and NA, not applicable

Como Impacta y que porcentaje de pacientes alcanzan el objetivo al 3er. mes un nivel < 10% BCR/ABL o RCyM (< 35% Ph+)

Gianantonio Rosti , EHA-Jun 13, 2014

Relationships between BCR-ABL transcript level at 3 months and clinical outcome

		% Of Pts		PFS		P value	Overall Survival		P value
Trial	TKI	≤10%	>10%	≤10%	> 10%		≤10%	>10%	
ENESTnd*	Imatinib	66%	34%	98%	83%	**<.001**	99%	86%	**<.001**
	Nilotinib[1]	90%	10%	95%	83%	**.006**	97%	87%	**.01**
Dasision&	Imatinib	65%	35%	96%	75%	**.001**	96%	88%	**.003**
	Dasatinib	84%	16%	93%	68%	**.003**	96%	86%	**.03**
BELA§	Imatinib	65%	35%	94%	64%	**.003**	99%	95%	**.09**
	Bosutinib	86%	14%	93%	83%	**.004**	99%	88%	**.004**

*** ENESTnd, PFS = TFS, PFS and OS at 4 years**
1 Nilotinib, 300 mg BID arm
& DASISION, PFS = TFS + Loss CHR, loss MCyR, doubling of WBC count to > 20 x 10^9/L PFS and OS at 3 yrs
§ BELA, PFS = TFS + Loss CHR, loss CCyR, doubling of WBC count to > 20 x 10^9/L PFS and OS at 2 yrs

Hughes TP et al, Blood 2014, 123 (9): 1353-1360
Jabbour E et al, Blood 2014, 123 (4):494-500
Brummendorf TH et al. *Blood*. 2012;120(21): Abstract 69.

Gianantonio Rosti , EHA-Jun 13, 2014

Relationships between BCR-ABL transcript level at 3 months and clinical outcome

		% Of Pts		PFS		P value	Overall Survival		P value
Trial	TKI	≤10%	>10%	≤10%	> 10%		≤10%	>10%	
ENESTnd*	Imatinib	66%	34%	98%	83%	<.001	99%	86%	<.001
	Nilotinib[1]	90%	10%	95%	83%	.006	97%	87%	.01
Dasision&	Imatinib	65%	35%	96%	75%	.001	96%	88%	.003
	Dasatinib	84%	16%	93%	68%	.003	96%	86%	.03
BELA§	Imatinib	65%	35%	94%	64%	.003	99%	95%	.09
	Bosutinib	86%	14%	93%	83%	.004	99%	88%	.004

* ENESTnd, PFS = TFS, PFS and OS at 4 years
1 Nilotinib, 300 mg BID arm
& DASISION, PFS = TFS + Loss CHR, loss MCyR, doubling of WBC count to > 20 x 10^9/L PFS and OS at 3 yrs
§ BELA, PFS = TFS + Loss CHR, loss CCyR, doubling of WBC count to > 20 x 10^9/L PFS and OS at 2 yrs

Hughes TP et al, Blood 2014, 123 (9): 1353-1360
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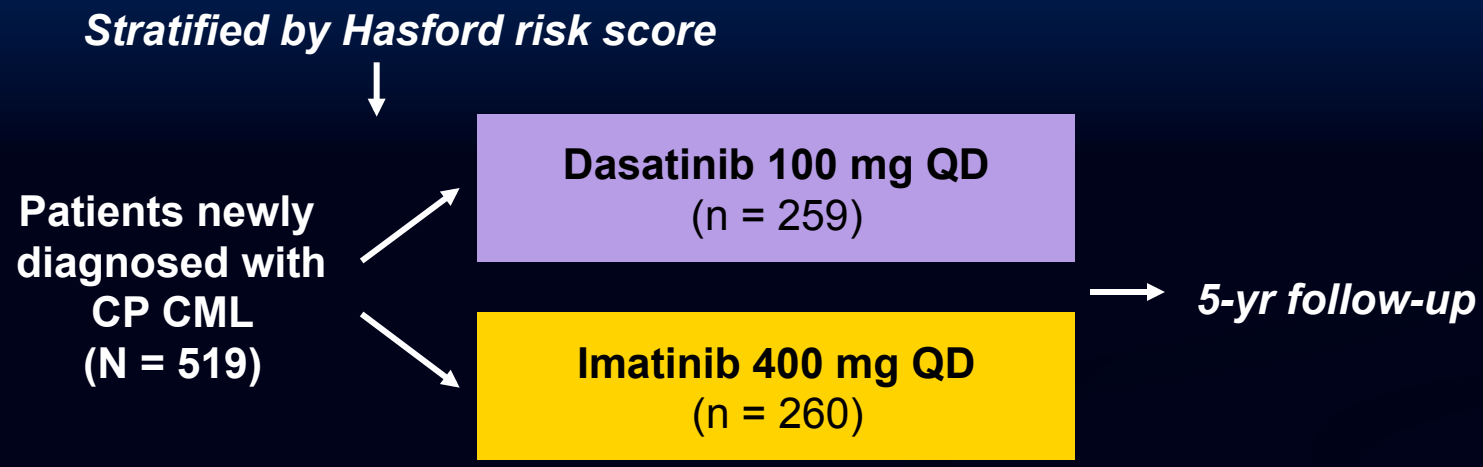
Brummendorf TH et al. *Blood*. 2012;120(21): Abstract 69.

DASISION: Comparison of Dasatinib and Imatinib in Newly Diagnosed CP CML



- Primary endpoint: confirmed CCyR at 12 mos:
  - 77% dasatinib versus 66% imatinib (P=0.007)[1]
- Key secondary endpoints: MMR, time in confirmed CCyR, time to confirmed CCyR and MMR, PFS, OS

Kantarjian H, et al. *N Engl J Med.* 2010;362:2260-70.DASISION (CA180-056).
Kantarjian HM, et al. Blood. 2012;119:1123-1129. Jabbour E, et al. Blood. 2014;123:494-500.

DASISION 4-Yr Update: Cumulative Incidence of MMR

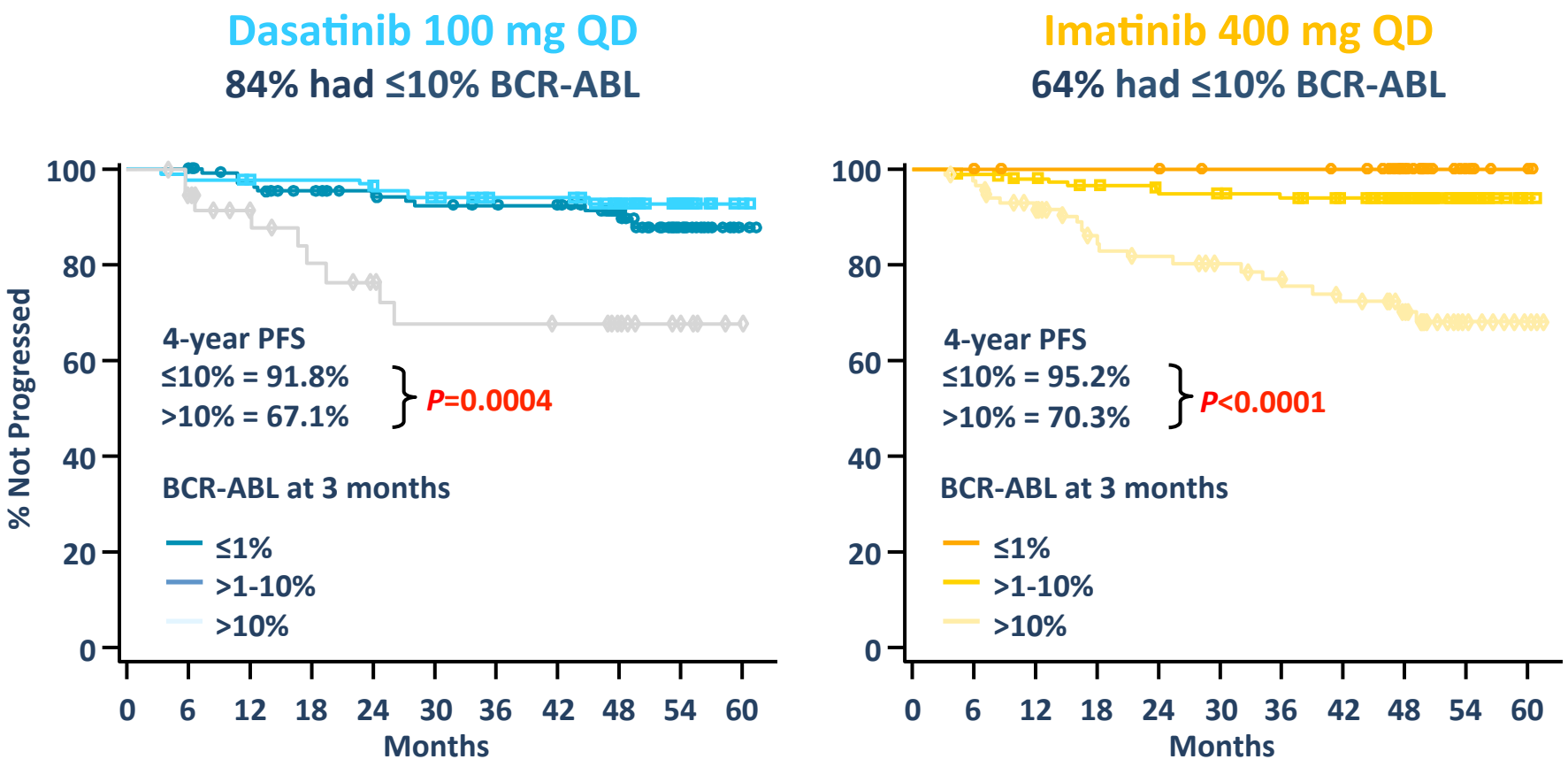
Cumulative MMR, %	Dasatinib (n = 259)	Imatinib (n = 260)
At 12 mos	46	23
At 24 mos	64	46
At 36 mos	69	55%
At 48 mos	74	60

- Dasatinib treatment associated with 1.6-fold higher likelihood of reaching MMR compared with imatinib (HR: 1.55; $P < .0001$)

Cumulative 4-yr MMR by Hasford Risk Score, %	Dasatinib	Imatinib
Low risk	90	69
Intermediate risk	70	63
High risk	65	52

2. Cortes JE, et al. ASH 2013. Abstract 653.

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



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

DASISION 4 AÑOS

Four-Year Follow-up of the DASISION Trial: Efficacy Based on Early Response

- Patients with newly diagnosed CP-CML (n=519) were randomly assigned to receive dasatinib 100 mg qd (n=259) or imatinib 400 mg qd (n=260).

Response at 4 Years	Dasatinib, %	Imatinib, %
MMR BCR-ABL ≤0.1%	76	63
MR^4 BCR-ABL ≤0.01%	53	42
$MR^{4.5}$ BCR-ABL ≤0.0032%	37	30

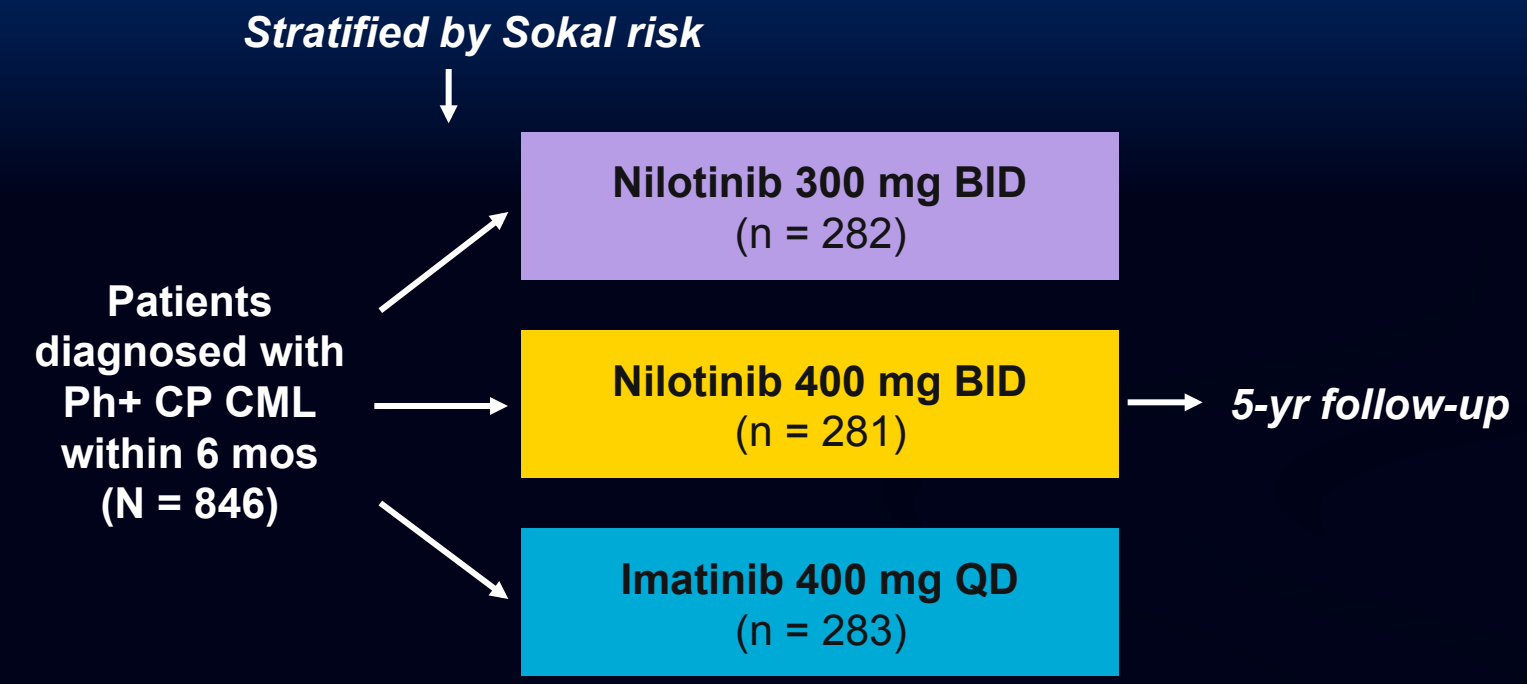
- The achievement of BCR-ABL ≤10% at 3 months was more common among patients treated with dasatinib than imatinib and was associated with better PFS and OS and reduced transformation to AP/BP in both arms.
- Likelihood of achieving MMR at any time was 1.6-fold higher with dasatinib.
- Follow-up from DASISION continues to support dasatinib 100 mg qd as first-line treatment for patients with newly diagnosed CP-CML.

OS = overall survival; PFS = progression-free survival; qd = daily

Cortes J, et al. ASH 2013. Abstract 653.

Medscape EDUCATION

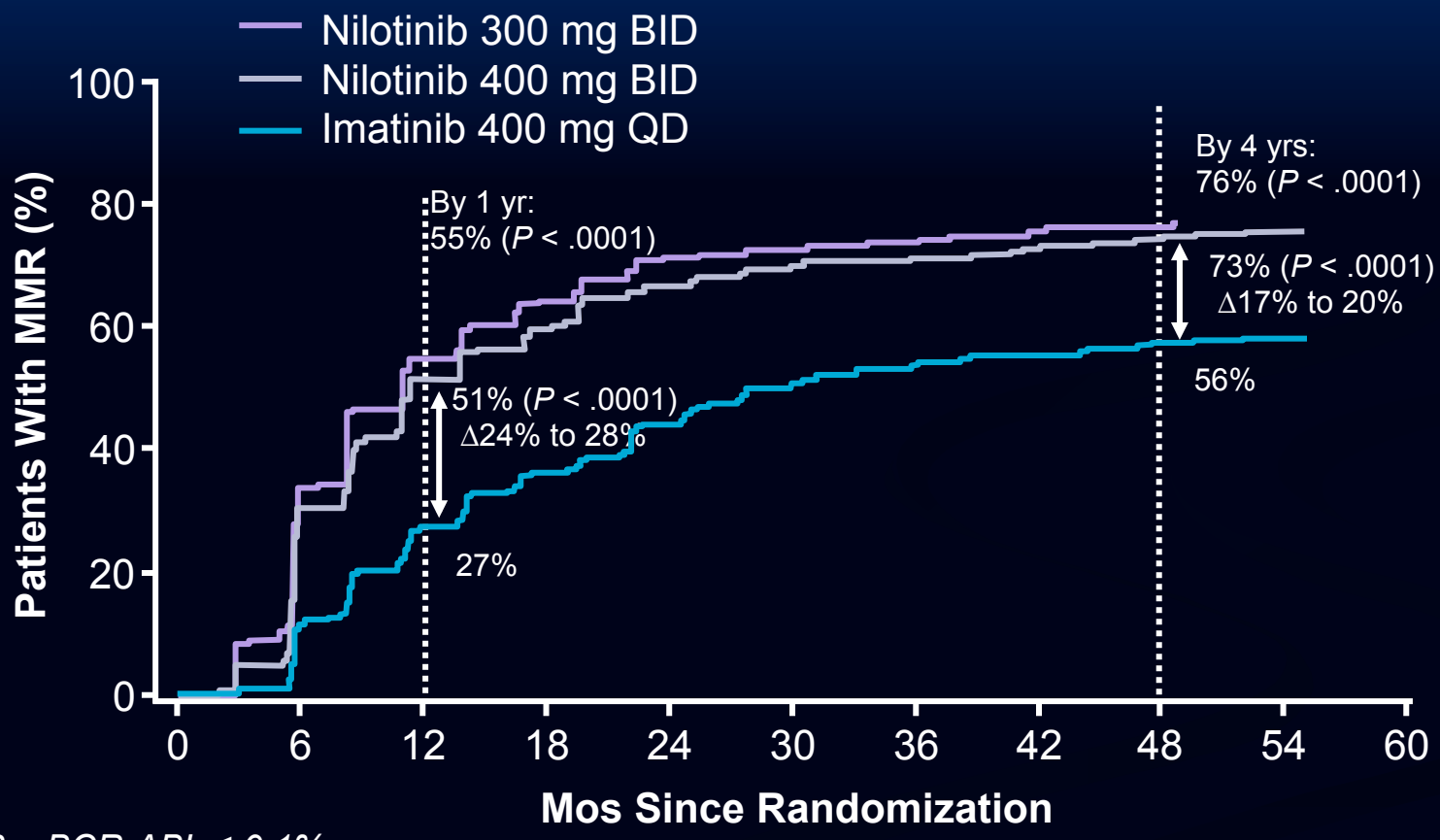
ENESTnd: Comparison of Nilotinib and Imatinib in Newly Diagnosed CP CML



- Primary endpoint: MMR at 12 mos
- Secondary endpoint: durable MMR at 24 mos

Saglio G, et al. N Engl J Med. 2010;362:2251-2259. Larson RA, et al. Leukemia. 2012;26:2197-2203. Kantarjian HM, et al. ASH 2012. Abstract 1676.

ENESTnd 4-Yr Update: Cumulative Incidence of MMR in CP CML



MMR = BCR-ABL ≤ 0.1%.

Kantarjian HM, et al. ASH 2012. Abstract 1676.

DMR in Patients with newly diagnosed CML receiving Nilotinib in the ENEST1st Study

- 1086 newly diagnosed adults with BCR-ABL-positive CP-CML received nilotinib
- Molecular response assessed every 3 months at EUTOS laboratories
- 80.3% completed 24 months of treatment; 19.7% discontinued early
  - 10.5% of patients discontinued due to AEs

	Nilotinib 300 mg bid	
	18 months (n=674)	24 months (n=624)
Response, %		
MMR	75.2	69.2
MR^4	43.0	44.2
$MR^{4.5}$	23.4	26.4
MR^4 by 18 or 24 months (n=797), %	50.1	56.5

- Supports the use of frontline nilotinib

bid = twice daily;
EUTOS = European Treatment and Outcome Study

Giles F, et al. ASH 2013. Abstract 4030.

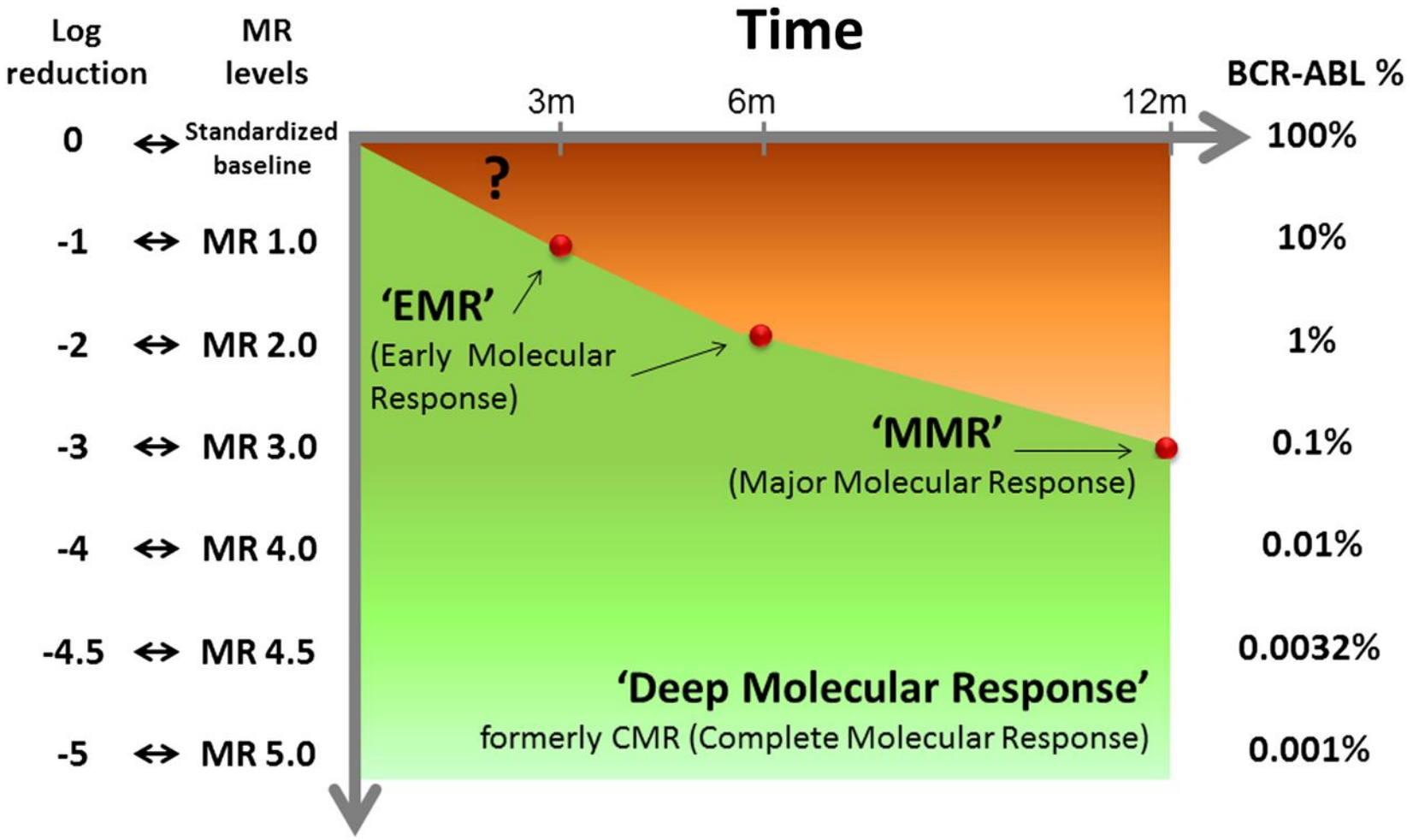
Es suficiente el nivel de BCR-ABL >10% al 3er mes para definir falla y cambio en la terapia??

"Prognosis for patients with CML and >10% BCR-ABL1 after 3 months of imatinib depends on the rate of BCR-ABL1 decline"

Susan Branford, et al. BLOOD, 24 JULY 2014 x VOLUME 124, NUMBER 4

Estudio que evalua 528 pacientes que iniciaron Imatinib en los estudios IRIS, TOPS, TIDAL I y II con estudios moleculares , (MMR fue confirmada con 2 pruebas)

Levels of molecular response and corresponding log-reduction and BCR-ABL1 transcript levels on the International Scale.



Baccarani M , and Soverini S Blood 2014;124:469-471

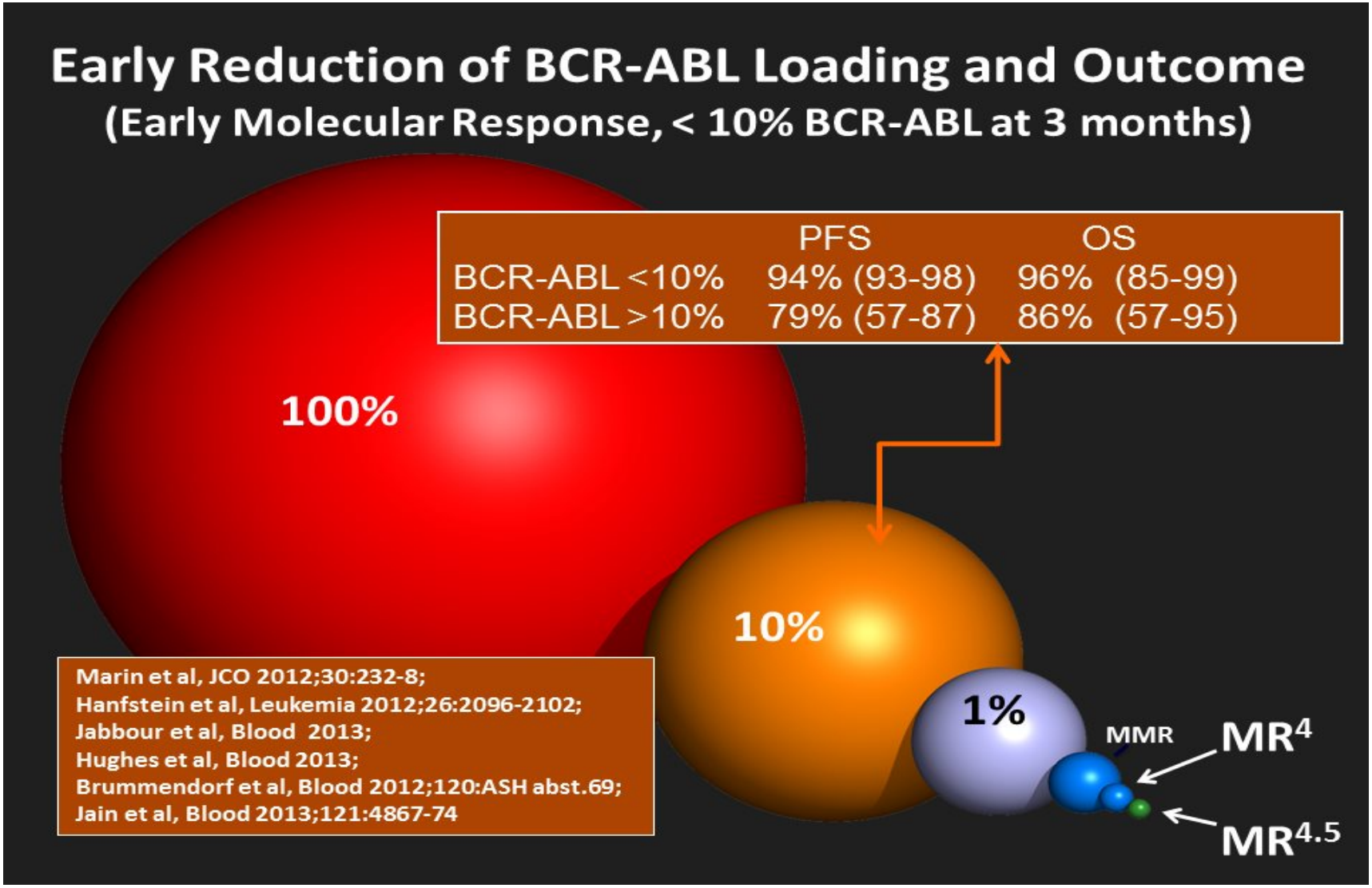
ITKs en 1ra linea
¿Cual?

Puntos a considerar para uso de ITKs de 1ra línea

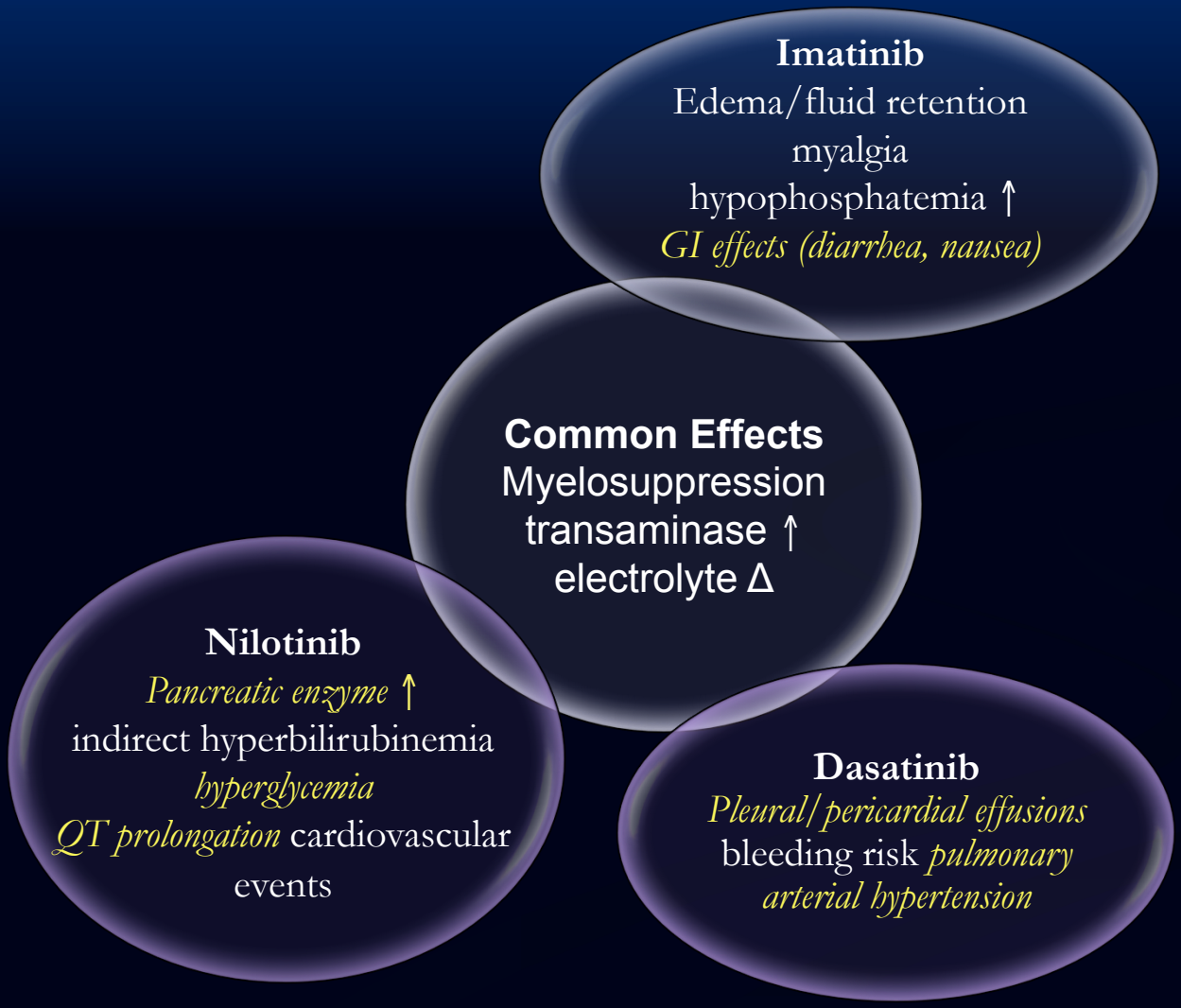
- **Paciente**
  - Riesgo de comorbilidades.
  - Expectativa personal, educación y cumplimiento.
- **Medicamento**
  - Eficacia y tiempo para respuesta
  - Efectos secundarios y seguridad a largo tiempo
  - Costo y cobertura (pública o privada).
- **Médico**
  - Experiencia personal y niveles de evidencia

Monitoreo de la respuesta en el 1er año es crucial (citogenética o molecular c/3 meses

Gianantonio Rosti,
EHA-Jun 13, 2014

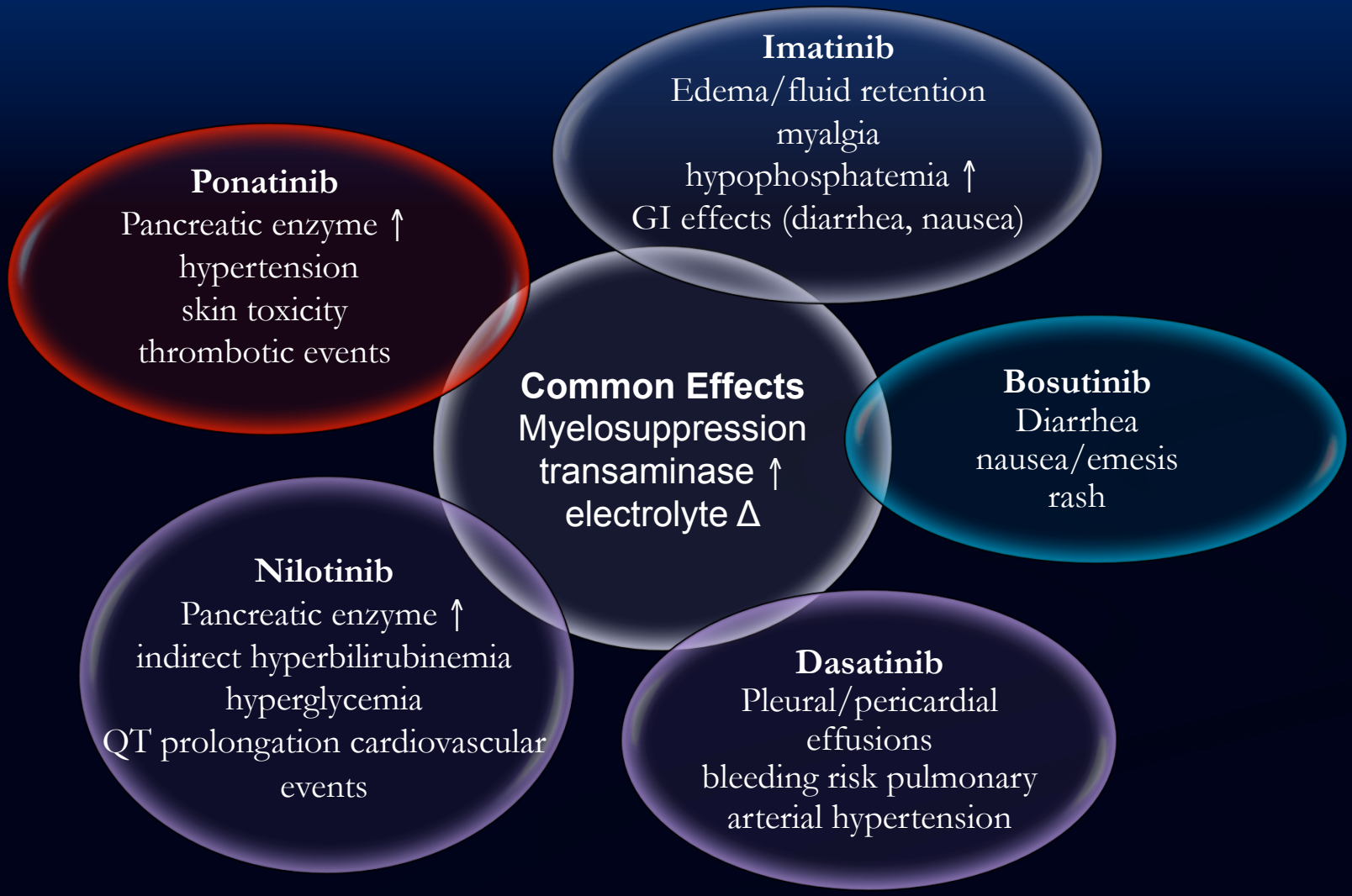


Opciones de tto basado en el espectro de reacciones adversas con ITKs en LMC

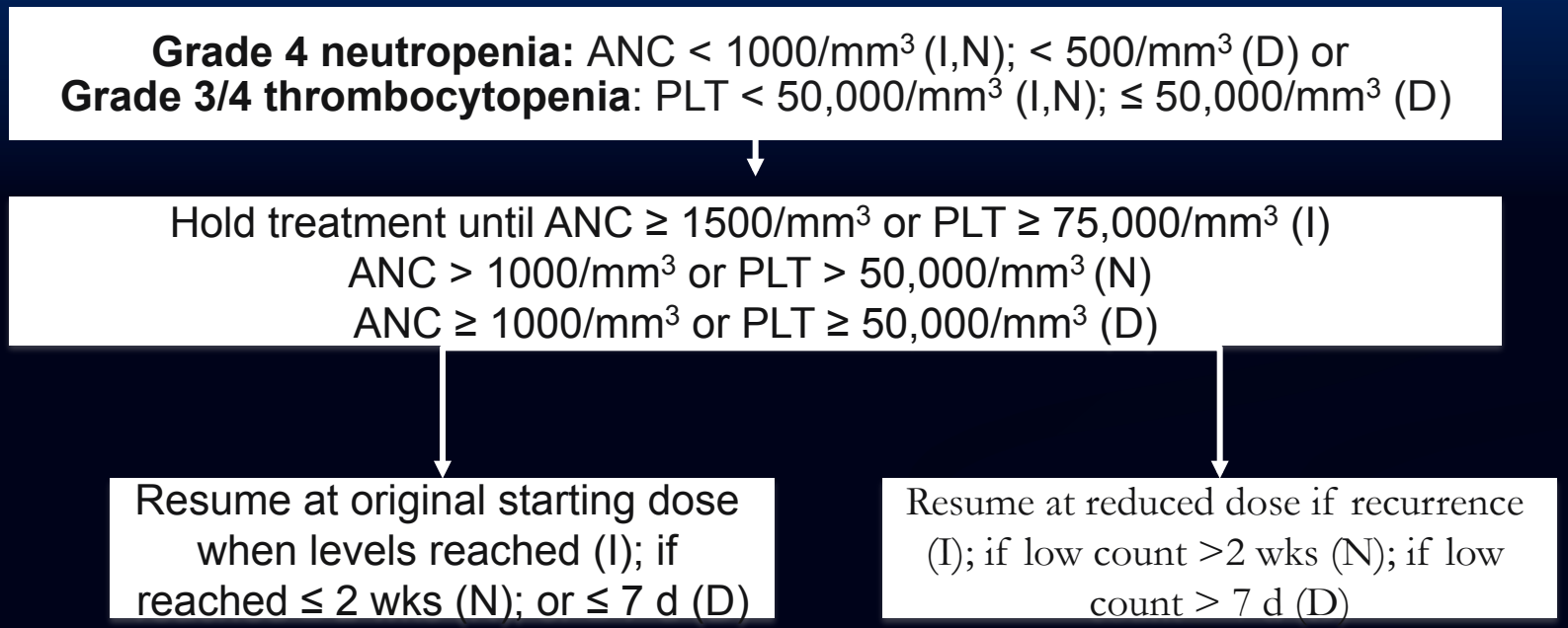


Estrategias para manejo de efectos adversos

Treatment Options Based on Adverse Effect Spectrum of TKIs in CML



TKIs: General Strategies to Manage Myelosuppression in CP CML



- Grade 3/4 anemia: EPO effective, but CMS and FDA do not support use in myeloid malignancies
- Growth factors can be used with TKIs for patients with resistant neutropenia

NCCN. Clinical practice guidelines in oncology: chronic myelogenous leukemia. v3.2014.

Dasatinib and Pulmonary Arterial Hypertension

- After-market incidence in the French Pulmonary Hypertension registry
- 9 cases identified from Nov 2006 (approval) – Sept 2010
  - Moderate/severe with functional and hemodynamic impairment
  - No exposure to other TKIs at time of diagnosis
  - *Improved in 8/9 patients within 4 mos of dasatinib discontinuation*
- Lowest estimated incidence of pulmonary hypertension: 0.45%

Montani D, et al. Circulation. 2012;125:2128-2137.

ENESTnd: Cardiac and Vascular Events by 4 Yrs (All Grades)

Patients With an Event, n (%)	Nilotinib 300 mg BID (n = 279)	Nilotinib 400 mg BID (n = 277)	Imatinib 400 mg QD (n = 280)
IHD	11 (3.9)	14 (5.1)	3 (1.1)
PAOD	4 (1.4)	5 (1.8)	0 (0)

- Between Yrs 3 and 4, a total of 5 new patients had an IHD event (2 in the nilotinib 300 mg BID arm and 3 in the nilotinib 400 mg BID arm), and 2 new patients had a PAOD event
- 1 patient in the nilotinib 400 mg BID arm with previously reported PAOD had a newly reported drug-related serious AE (arterial stenosis limb) leading to treatment discontinuation

IHD: Ischemic heart disease. PAOD: Peripheral arterial occlusive disease

Kantarjian HM, et al. ASH 2012. Abstract 1676.

Strategies to Manage Nonhematologic AEs

Grade 2/3 Adverse Effect	Management Recommendation
Diarrhea	Supportive care
Edema	Diuretics; supportive care
Fluid retention	Diuretics; supportive care; dose reduction, interruption, or discontinuation; consider ECG to check LVEF
Gastrointestinal	Take imatinib with meals and water
Myalgia	Calcium supplement; tonic water
Rash	Topical or systemic steroids; dose reduction, interruption, or discontinuation
Pleural/pericardial effusion	Diuretics; dose interruption: consider prednisone 20 mg QD for 3 days for significant symptoms, reduce dose

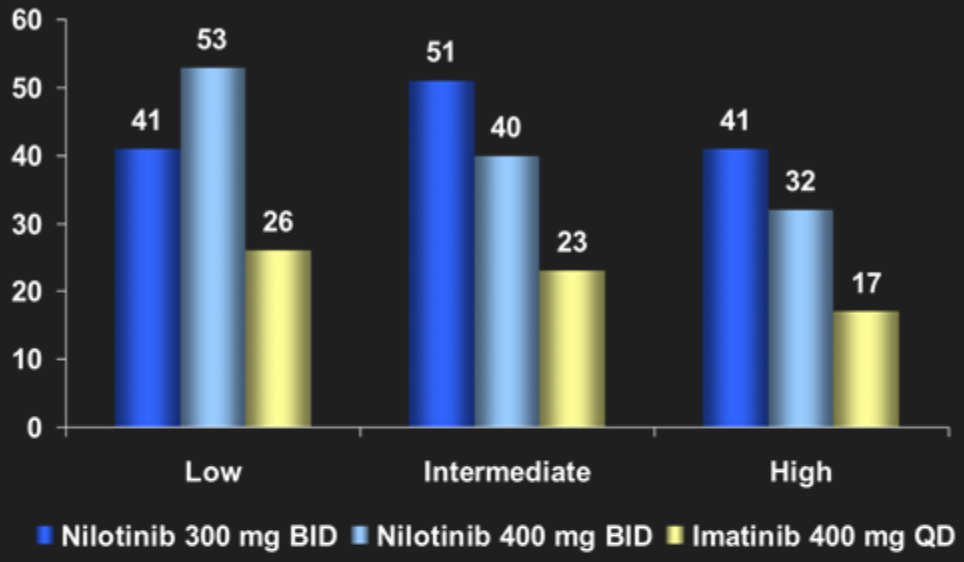
Grade 2/3 AEs (except hepatotoxicity): if not responsive to supportive care, treat as grade 4
Grade 4 AEs or ≥ 2 hepatotoxicity
Hold until ≤ grade 1; resume at reduced dose level; consider change to another TKI

NCCN. Clinical practice guidelines in oncology: chronic myelogenous leukemia. v.3.2014.

Valor de Sokal y Hasford

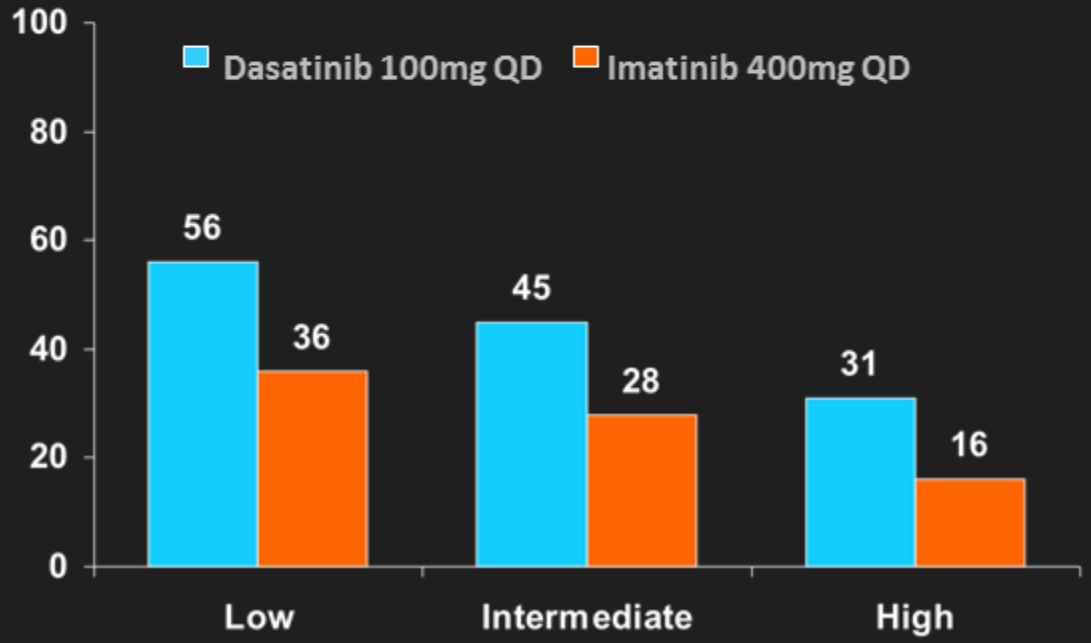
Higher MMR by 12 months, across risk categories, with Nilotinib and Dasatinib vs Imatinib

ENESTnd
(Saglio, ASH 2009)



(Sokal)

DASISION
(Baccarani, EHA 2010)



(Hasford)

Treatment Options Based on BCR-ABL Kinase Domain Mutation Status

Mutation	Treatment Options
T315I	Ponatinib, omacetaxine, HSCT, or clinical trial
V299L	Consider nilotinib or omacetaxine*
T315A	Consider nilotinib, imatinib,† bosutinib, or omacetaxine*
F317L/V/I/C	Consider nilotinib, bosutinib, or omacetaxine*
Y253H, E255K/V, F359V/C/I	Consider dasatinib, bosutinib, or omacetaxine*
Any other mutation	Consider high-dose imatinib,‡ dasatinib, nilotinib, bosutinib, or omacetaxine*

Ponatinib is an option for mutations other than T315I but only when no other TKI therapy is indicated.
*Option for patients with resistance/intolerance to ≥ 2 TKIs.
†If mutation detected following dasatinib treatment.
‡No sufficient dose-escalation data indicating if mutations with low IC_{50} are sensitive to high-dose imatinib.

NCCN. Clinical practice guidelines in oncology: chronic myelogenous leukemia. v.3.2014.

Conclusiones finales

- Muy importante intensidad de respuesta en base a estudio molecular.
- Medir Score de Riesgo Sokal y/o Hasford
- Independientemente del ITK en uso:
  - Control de la respuesta y un riguroso monitoreo en el 1er año es crucial (RT-PCR). Recomendado por ELN y NCCN
- Respuestas mas rápidas y profundas se alcanzan con ITKs de 2da generación que impacta en SLP y SG.
- El objetivo con ITKs esta claro debe ser obtener la mas profunda respuesta molecular, valorando:
  - Efectos secundarios, comorbilidades y costos.

¡¡ GRACIAS !!

servihem@gmail.com