

# Clinical case 5: Failure of treatment due to mutation

*F Pane*

EUTOS for CML



*European Treatment and Outcome Study*

# Patient profile

- Male, 38 years old
- Diagnosis of CML
- High Sokal risk (1.280)
  
- No family HLA-identical donor
- EBMT risk score for alloBMT: 3
  
- Initiated on imatinib therapy (400 mg/day) shortly after diagnosis

# Treatment history (I)

## (Ima 400mg/day)

Assessment period	Status
3 months	CHR achieved
6 months	PCyR (Ph+ metaphases, 10%) BCR-ABL 8%
9 months	BCR-ABL still 7%
12 months	PCyR (18% Ph+ metaphases ) BCR-ABL 14% BCR-ABL mutation analysis: F317L

# Sensitivity of the three registered TKIs to the most common ABL KD mutations

	Ba/F3 cellular proliferation IC <sub>50</sub> values		
	imatinib (nM)	nilotinib (nM)	dasatinib (nM)
Native Bcr-Abl	260	13	0.8
M244V	2000	38	1.3
G250E	1350	48	1.8
Q252H	1325	70	3.4
Y253F	3475	125	1.4
Y253H	>6400	450	1.3
E255K	5200	200	5.6
E255V	>6400	430	11
V299L	540 <sup>†</sup>	nd	18 <sup>†</sup>
F311L	480	23	1.3
T315A	971	61	125 <sup>†</sup>
T315I	>6400	>2000	>200
F317L	1050	50	7.4
F317V	350 <sup>†</sup>	nd	53 <sup>†</sup>
M351T	880	15	1.1
E355G	2300 <sup>‡</sup>	nd	1.8 <sup>§</sup>
F359V	1825	175	2.2
V379I	1630	51	0.8
L387M	1000	49	2
H396P	850	41	0.6
H396R	1750	41	1.3

■ Sensitive   
 ■ Intermediate sensitivity   
 ■ Insensitive

O'Hare, T. et al. Blood 2007;110:2242-2249

# 2006 European LeukemiaNet Recommendations: Criteria for Satisfactory Response to Imatinib Treatment in CP-CML patients

	3 months	6 months	12 months	18 months	At any time
<b>Treatment Failure</b>	No HR	<CHR No CyR	<PCyR	<CCyR	<ul style="list-style-type: none"> <li>• Loss of CHR*</li> <li>• Loss of CCyR<sup>†</sup></li> <li>• Mutation with a high level of insensitivity to imatinib<sup>‡</sup></li> </ul>
<b>Suboptimal Response</b>	<CHR	<PCyR	<CCyR	<MMR	<ul style="list-style-type: none"> <li>• ACA in Ph+ cells<sup>§</sup></li> <li>• Loss of MMR<sup>§</sup></li> <li>• Mutation with a low level of insensitivity to imatinib<sup>‡</sup></li> </ul>
<hr/>					
<b>Warnings</b>	At diagnosis		12 months	At any time	
	<ul style="list-style-type: none"> <li>• High risk</li> <li>• Del 9q+</li> <li>• ACA in Ph+ cells</li> </ul>		<MMR	<ul style="list-style-type: none"> <li>• Any rise in transcript level</li> <li>• OCA in Ph- cells</li> </ul>	

ACA, additional chromosome abnormalities; CyR, cytogenetic response; HR, hematologic response; OCA other chromosome abnormalities.

\*To be confirmed on 2 occasions, unless associated with progression to AP/BC. <sup>†</sup>To be confirmed on 2 occasions, unless associated with CHR loss or progression to AP/BC. <sup>‡</sup>Mutations need to be interpreted within clinical context. <sup>§</sup>To be confirmed on 2 occasions, unless associated with CHR or CCyR loss.

Baccarani M et al. *Blood*. 2006;108:1809-1820.

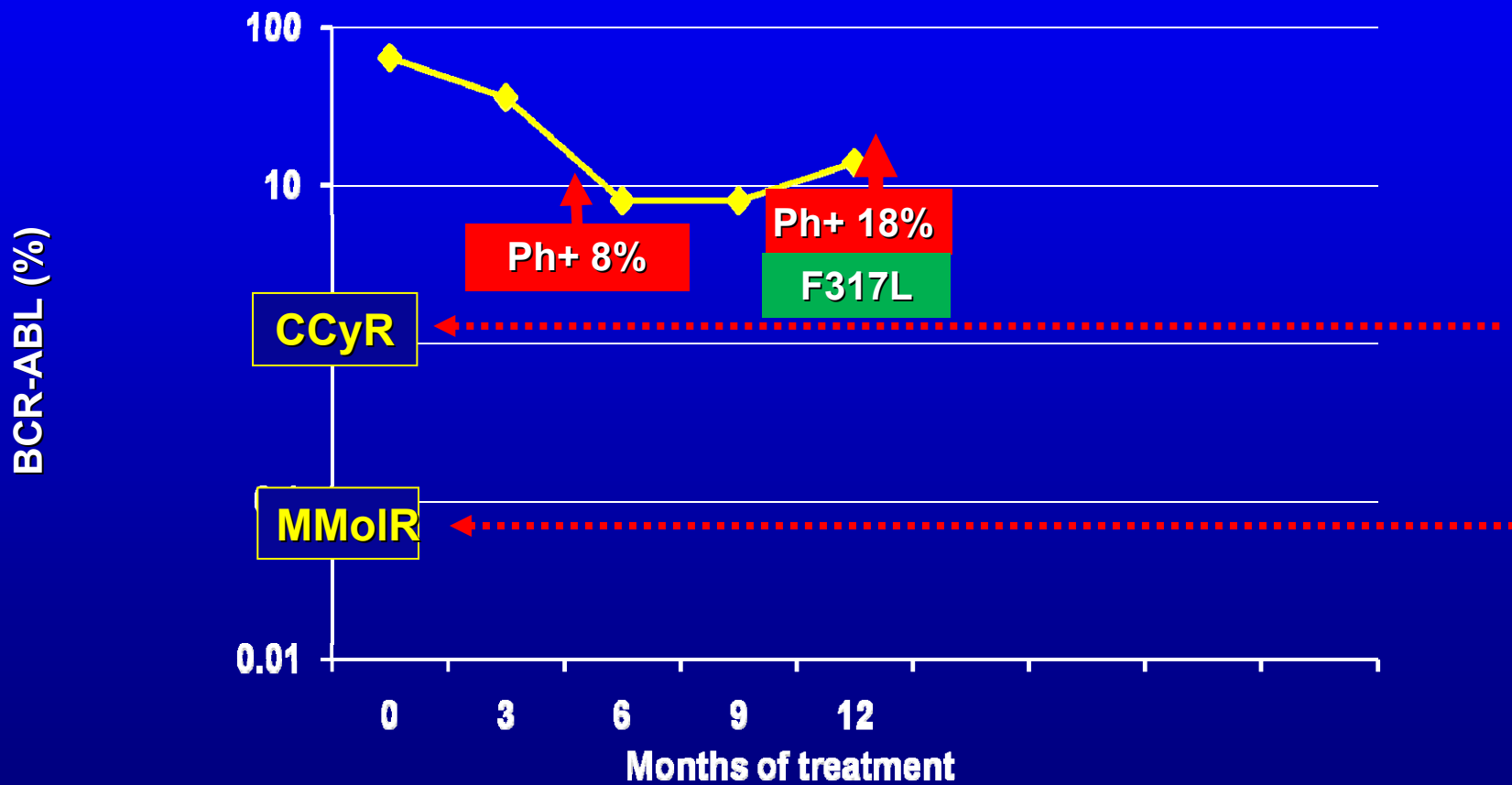
# **Follow-up +12 mo.**

**Failure in a patients with warnings (High Sokal risk, transcript increase)**

**To be considered:**

- **Consistent increase in the BCR-ABL level**
- **Consistent increase of Ph(+) metaphases (although not yet loss of PCyR)**

# Patient leukemic burden expressed as BCR-ABL<sup>IS</sup>



# Possible treatment options

**A: Increase imatinib dose**

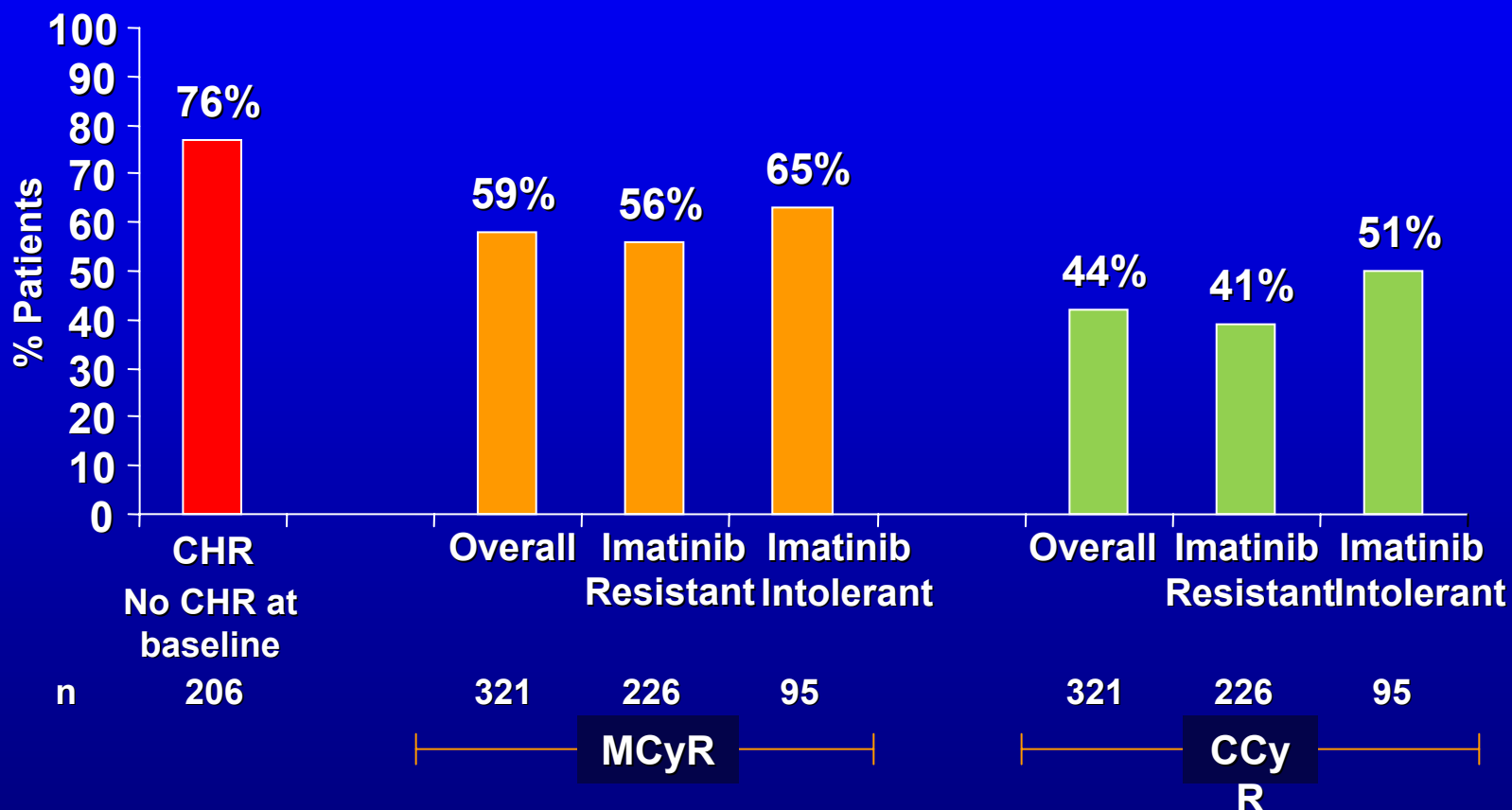
**B: Switch to treatment with a new TKI  
(Dasatinib or Nilotinib)**

**C: Switch to treatment with a new TKI  
(Dasatinib or Nilotinib) and search for a  
MUD**

**D: Enrol in a clinical trial with another TKI or  
experimental treatment**

# Nilotinib Phase II: Best Response in CML-CP Patients (n = 321)

Minimum follow-up: 19 mo.



**Median time to CHR 1 month; MCyR 2.8 months**

# Mutational Analysis CML-CP

## Best Responses by 12 Months in Imatinib-Resistant Patients by Baseline Mutation Status

Mutation*	IC <sub>50</sub> (nM)	Incidence at baseline, %	MCyR n/N (%)	CCyR n/N (%)	MMR n/N (%)
No mutation		45	50/87 (60)	35/87 (40)	21/76 (28)
Any mutation		52	51/100 (51)	33/103 (32)	18/91 (20)
Unknown IC <sub>50</sub>		15	19/30 (63)	15/30 (50)	5/20 (25)
IC <sub>50</sub> ≤ 150 nM		23	26/44 (59)	18/44 (41)	12/40 (30)
IC <sub>50</sub> > 150 nM					
Y253H	700	4	1/8 (13)	0/8 (0)	0/7 (0)
E255K/ V	548/791	4	3/7 (43)	0/7 (0)	1/7 (14)
F359C/ V	258/161	6	2/11 (18)	0/11 (0)	0/10 (0)

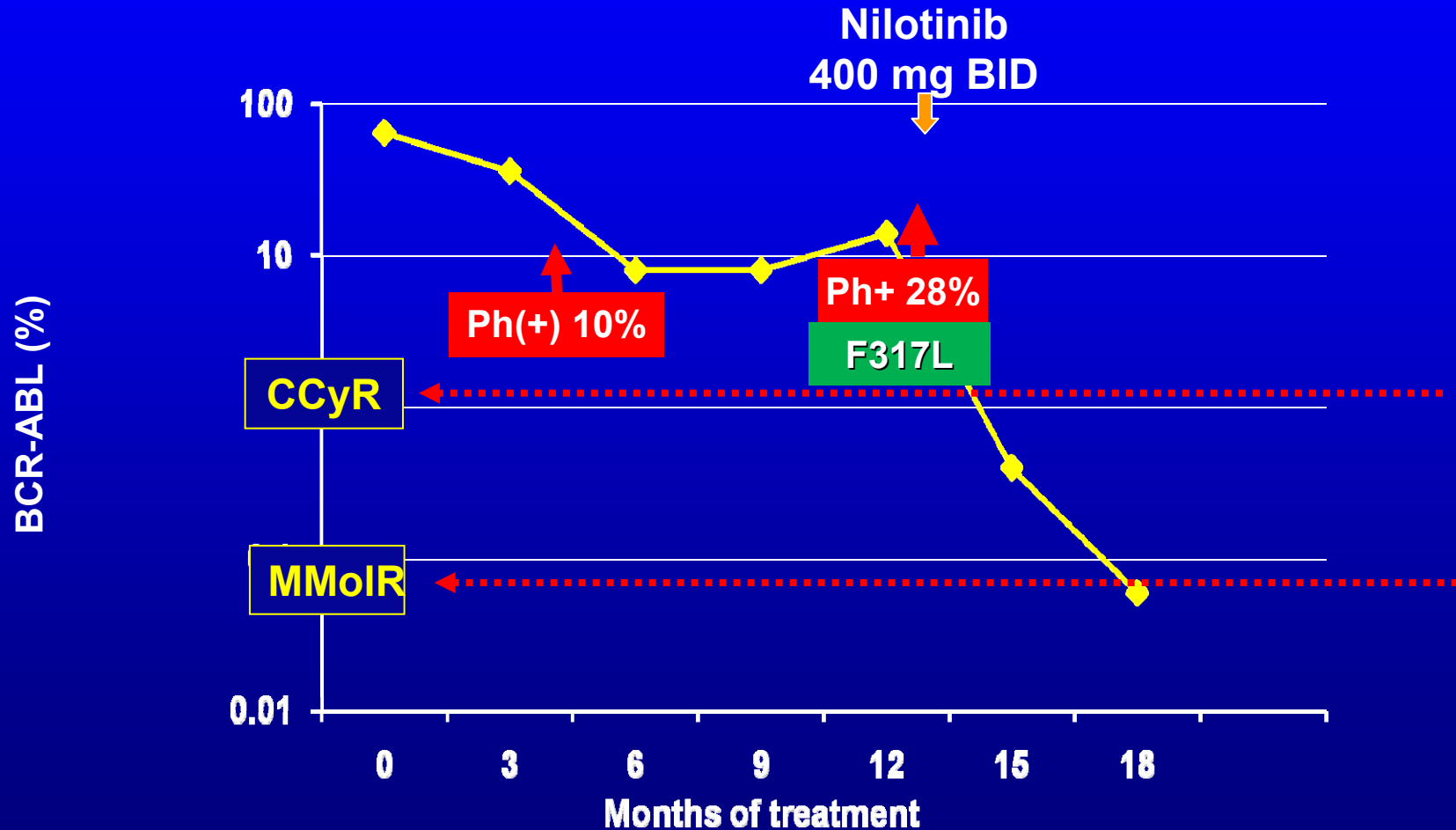
Saglio G, et al. ASCO 2008. Abstract 7060.

Radich J, et al. European Hematology Association 2008. Abstract 0137.

# Treatment decision

- Enrolled in an experimental trial for cases resistant or intolerant to Imatinib
- Patient start on Nilotinib at 400mg BID
- Volunteer unrelated donor search activated

# Treatment history: outcome with Nilotinib treatment



# **How would you recommend for treatment continuation?**

**(volunteer male donor found)**

**A: Continue with Nilotinib at the current dose**

**B: Stem cell transplantation from unrelated donor**

**C: Enrol in a clinical trial with another tyrosine kinase inhibitor or experimental treatment**

# Stem cell transplantation issues

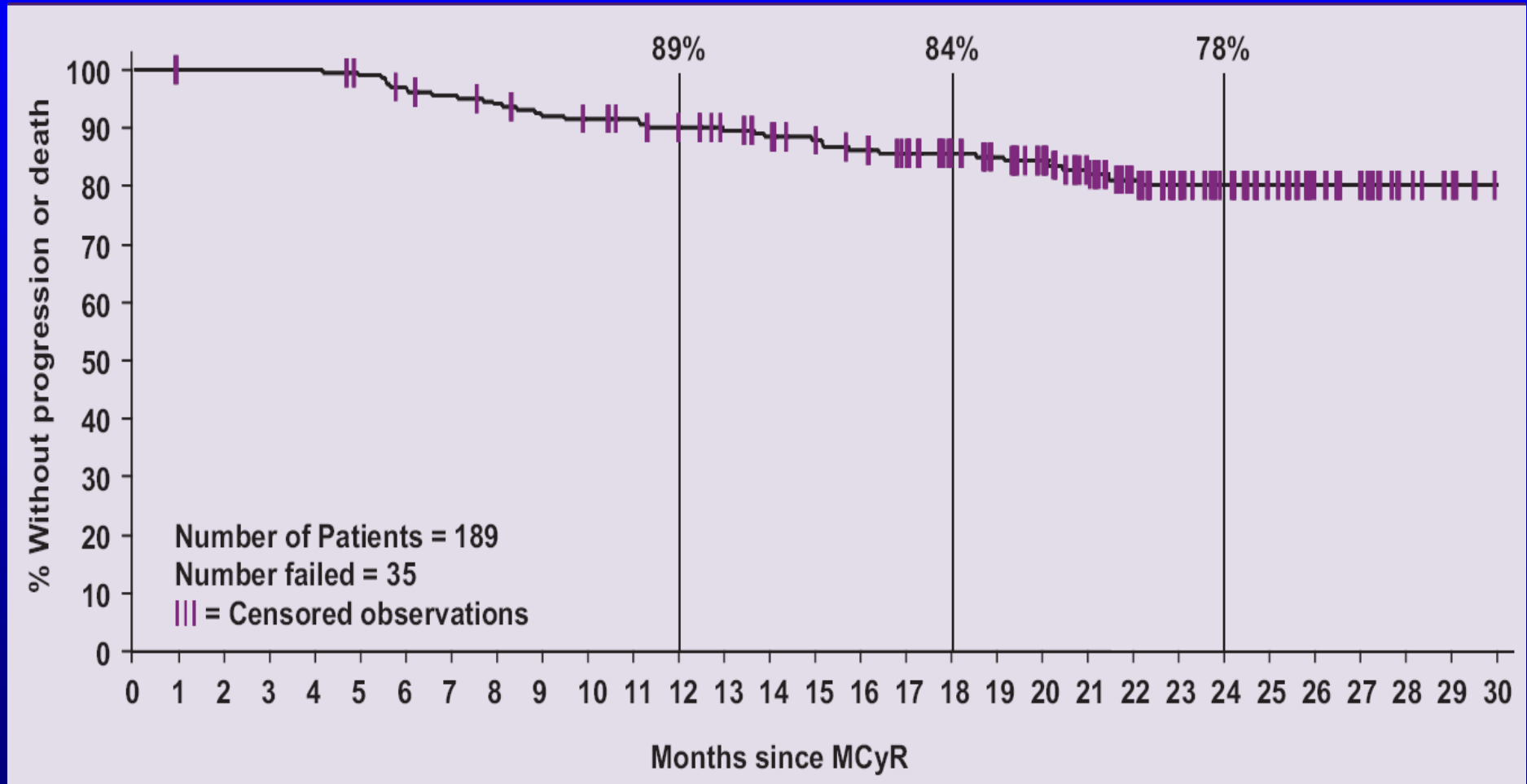
## EBMT transplantation risk score

Age	
Less than 20 y	0
20-40 y	1
More than 40 y	2
Interval diagnosis HSCT	
1 y or less	0
More than 1 y	1
Disease phase	
Chronic	0
Accelerated	1
Blastic	2
Donor-recipient sex match	
Female donor and male recipient	1
Any other match	0
Donor type	
HLA-identical sibling	0
Matched Unrelated Donor	1

Total risk score	5-year overall survival, %		
	EBMT series	All patients	ECP patients
	CIBMTR series		
0-1	72	69	70
2	62	63	67
3	48	44	50
4	40	26	29

# Phase II Nilotinib in CML-CP

## Duration of MCyR



**Male, 38 yr old**



**Continue Nilotinib 400 mg BID**

- 24 months → CCgR

**BCR-ABL/ABL= 0.07% (PB)**

# Follow-up

- The patient was maintained in treatment with Nilotinib
- The therapy is well tolerated
- The patient is well and his BCR-ABL% continues to be below the MMR level
- F317L mutated clone was not longer detectable

# Relevant Issues

- When and why search for ABL mutations
- Mutation detection: technical and biological issues
- Optimal therapeutic strategy for failure of Imatinib treatment due to mutation

# **Recommendations for the search of mutations in the BCR-ABL TK domain**

**during treatment with imatinib in ECP**

- At treatment failure, and always before treatment changes**
- Suboptimal response**
- Rise in BCR-ABL transcripts**

**Value of mutation analysis at relapse:**  
ABL kinase domain mutations with selective  
resistance to newer-generation inhibitors

Drug	Less resistant	More resistant
<b>Nilotinib</b>	L248V, G250E, F359C, L384M, L387F	Y253H, E255K/(V), T315I
<b>Dasatinib</b>	L248V, Q252H, E255K/V, V299L	T315I, F317C/L/V

# Conclusions and Perspectives

- Despite generally successful in early chronic phase CML, Ima may be less effective in a sizeable minority of CML patients
- Correct monitoring of treatment allows early identification of patients who have low benefit from Ima treatment
- Identification of mutation is important at relapse, maybe useful during follow-up (at which time intervals?), but useless at presentation