EBMT European Society for Blood and Marrow Transplantation

History of CML Treatment

Eduardo Olavarria

No conflict of interest

Lisbon, 20th March 2018

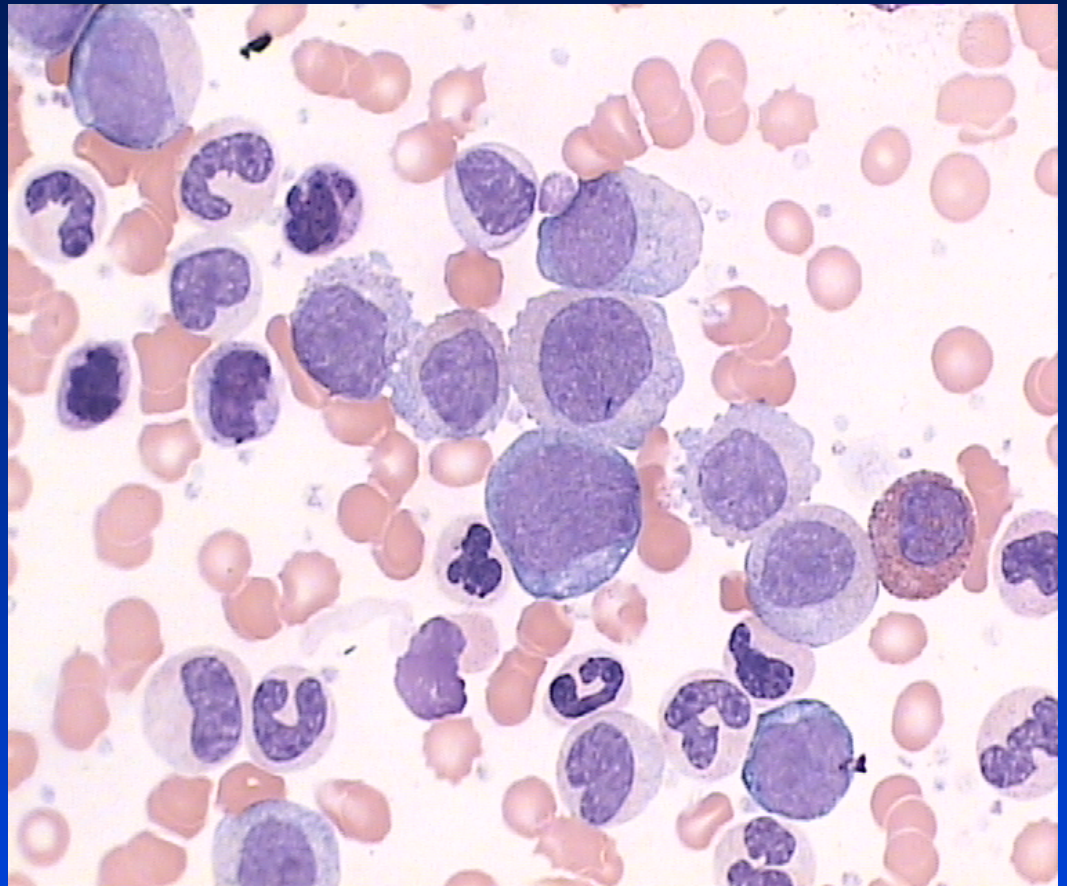
What is CML?

The mystery of chronic myeloid leukaemia

Chronic myeloid leukaemia

- Often diagnosed by chance e.g. routine blood test
- Symptoms typically are fatigue, lethargy, abdominal swelling/bloating, night sweats
- Characterised by high white cell count, sometimes anaemia, increased or decreased platelets, enlarged spleen
- Examination of blood shows primitive cells, range of white cells, e.g. neutrophils, eosinophils, basophils

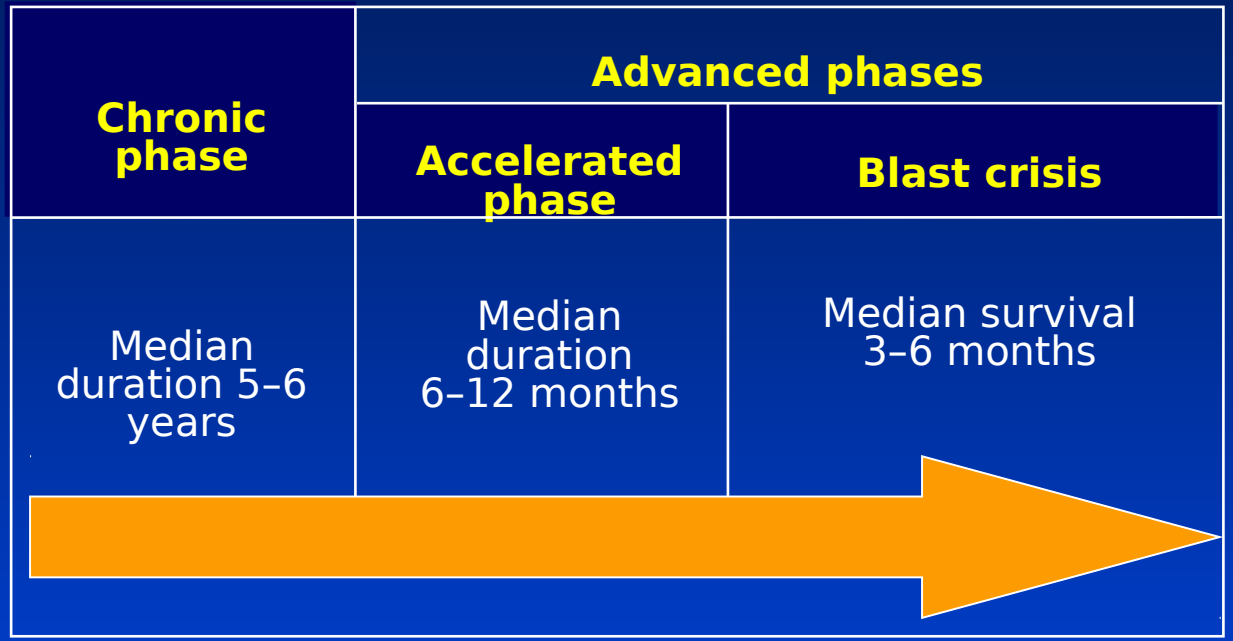
Blood film from CML in CP



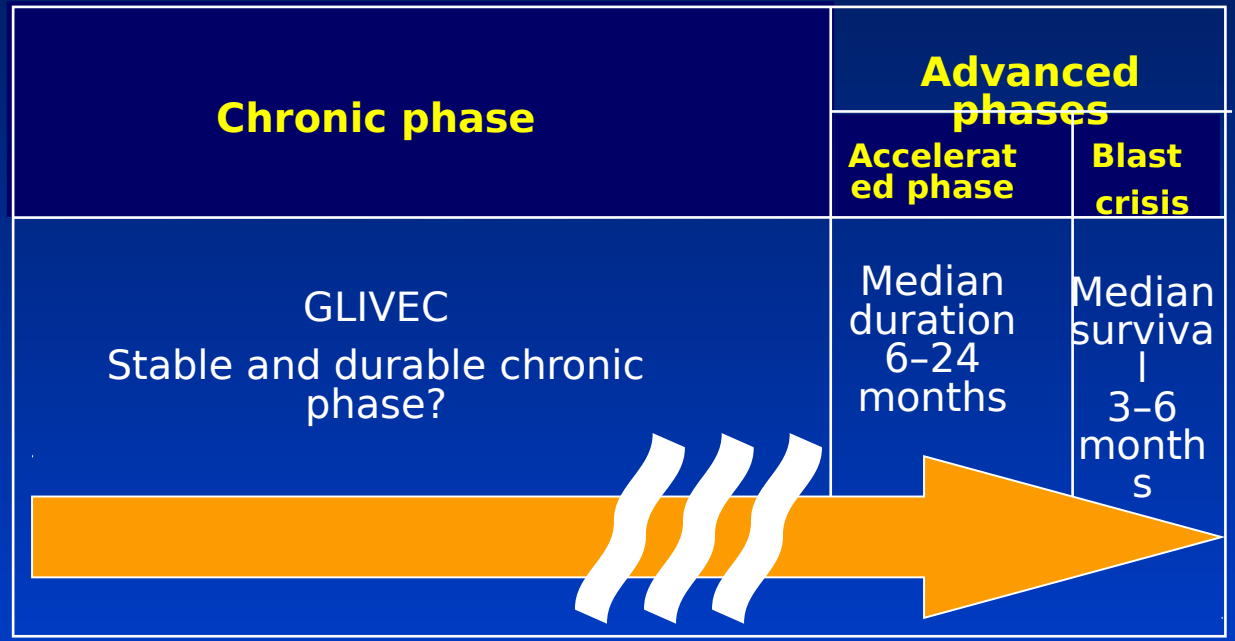
Chronic myeloid leukaemia

- Incidence 10-15:1,000,000 population
- 700 new cases per annum in UK
- Median age of onset 50-60 years
- Bi or triphasic disease, chronic phase, acceleration and blast crisis

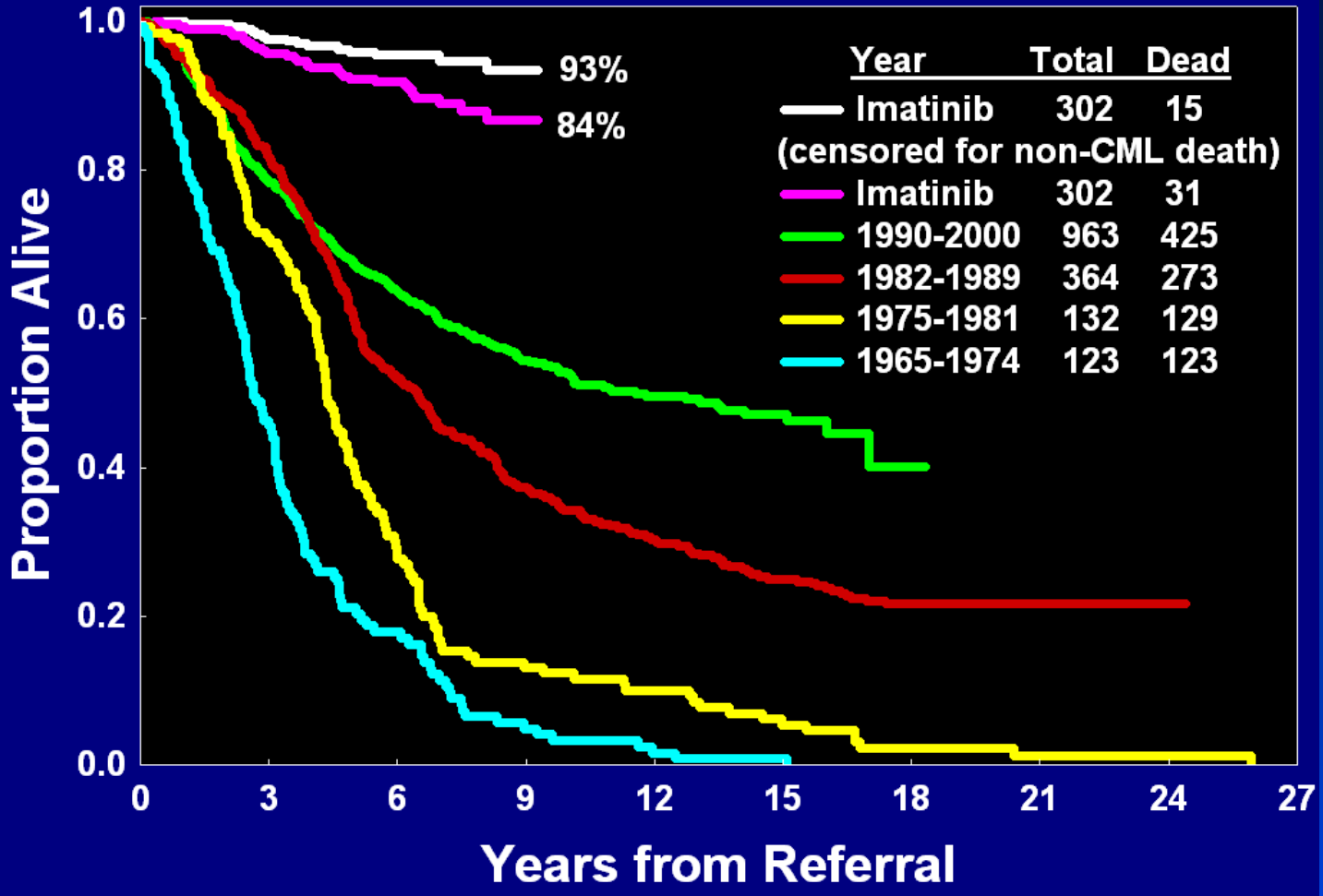
Clinical course: phases of CML Before TKIs



Clinical course: phases of CML After TKIs

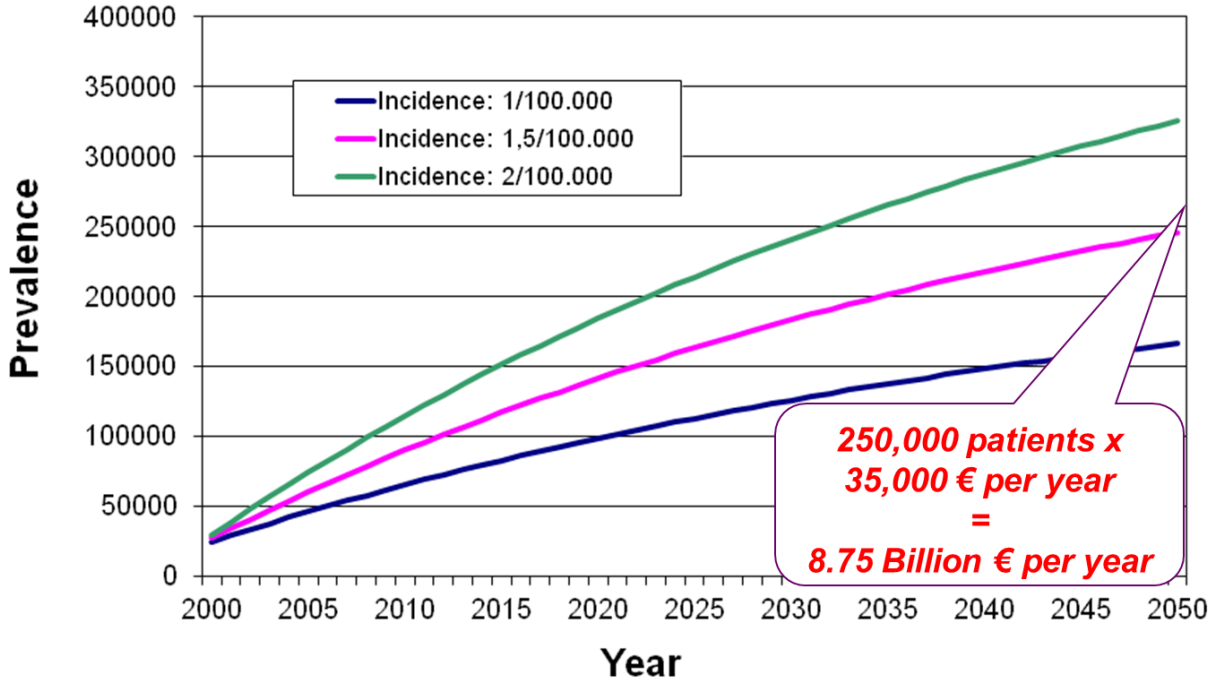


CML Survival at MDACC. 1965-Present (N=1884)



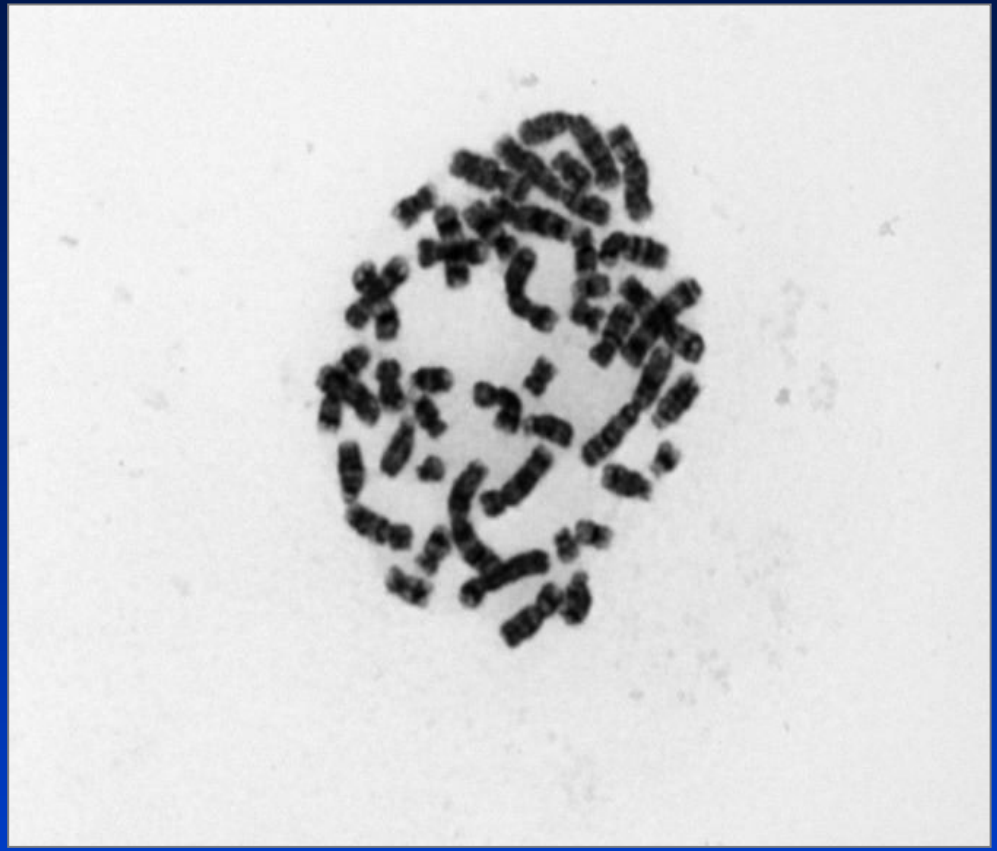
Imperial College London

Estimated Prevalence of CML in Europe until 2050

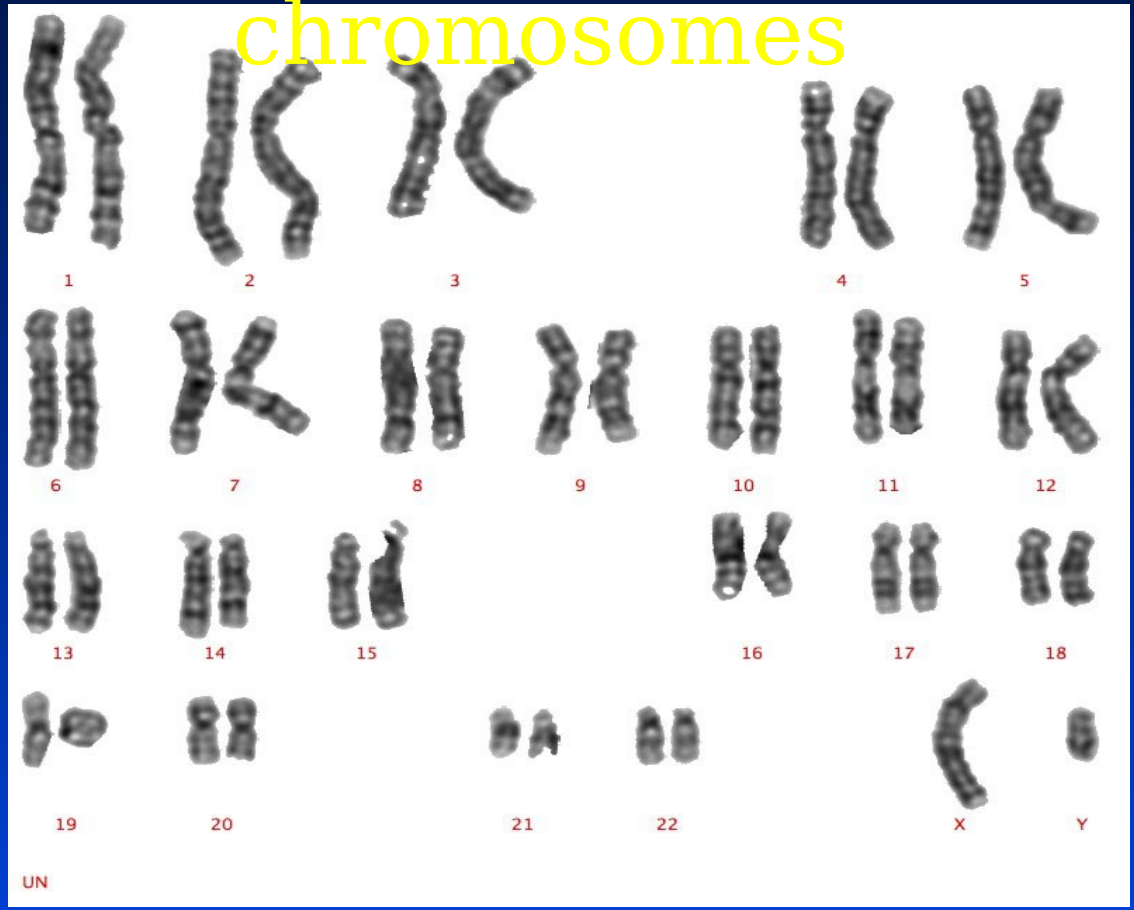


Assumptions: Population 500 million, mortality 2% per year, incidence constant.
Courtesy to Hasford and Pfirrmann.

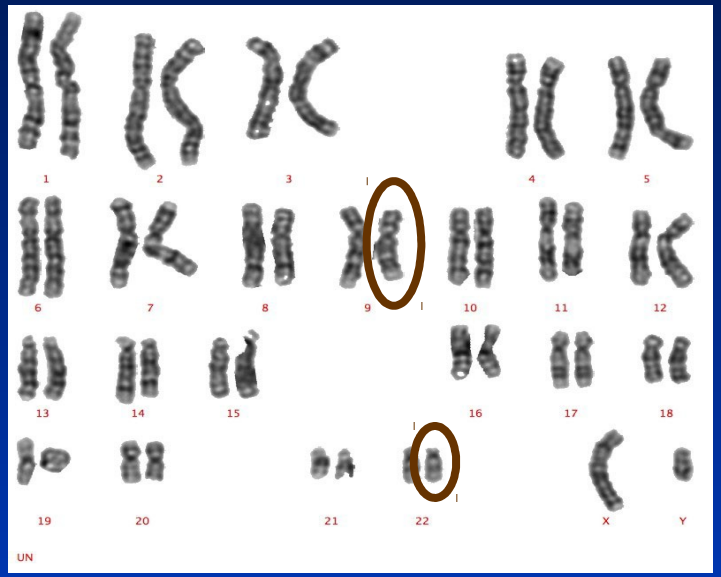
Biology of CML



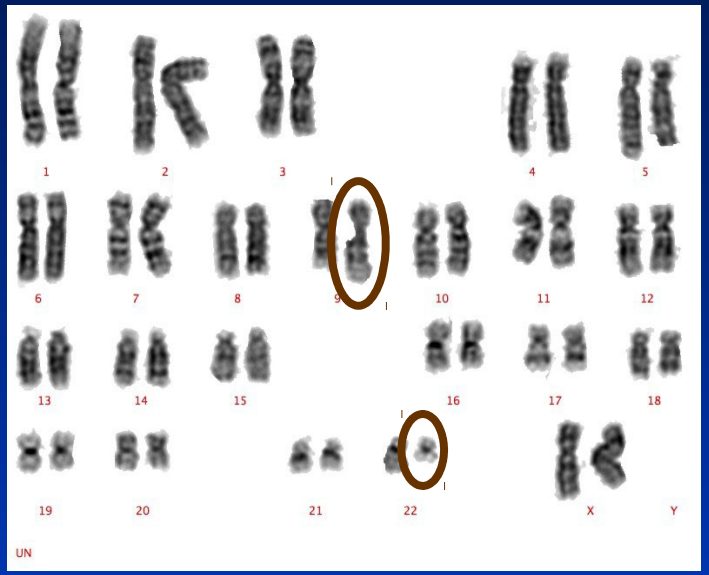
A normal set of chromosomes



The Philadelphia chromosome

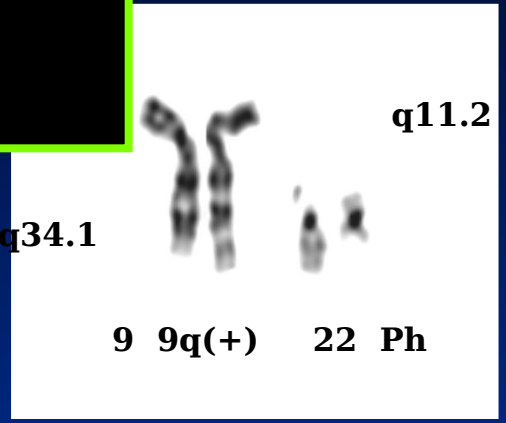


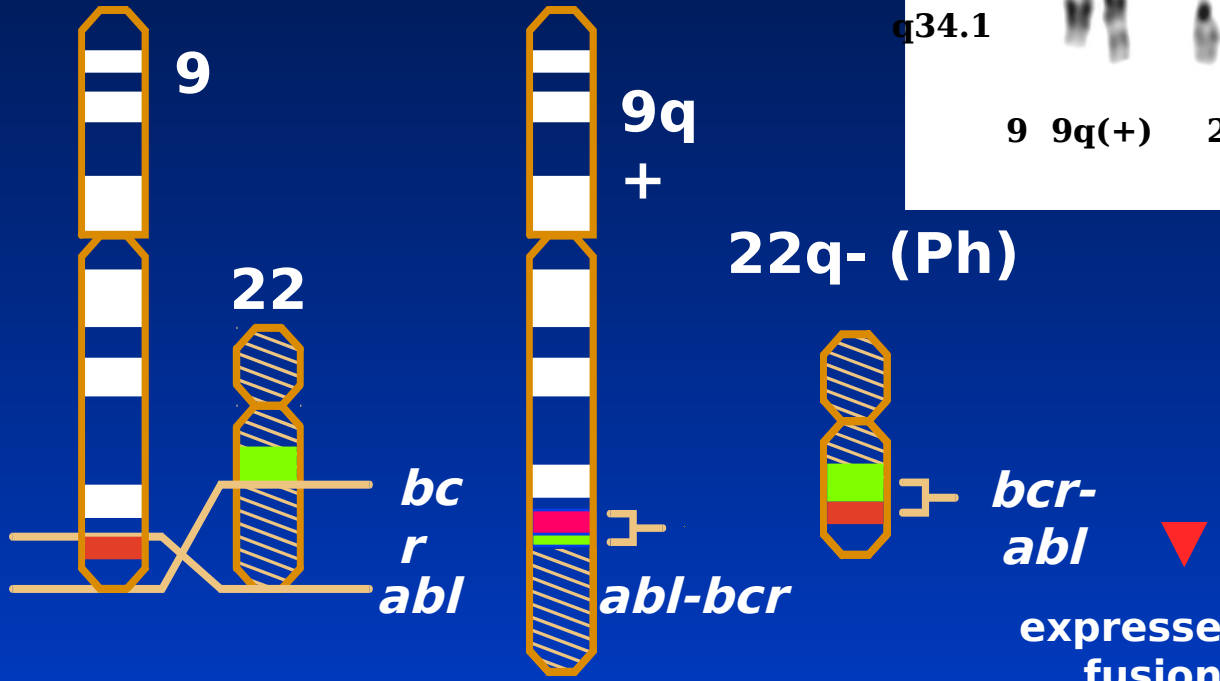
Normal



CML

the Philadelphia (Ph) chromosome

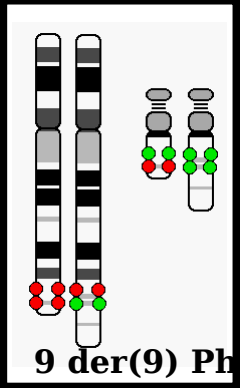


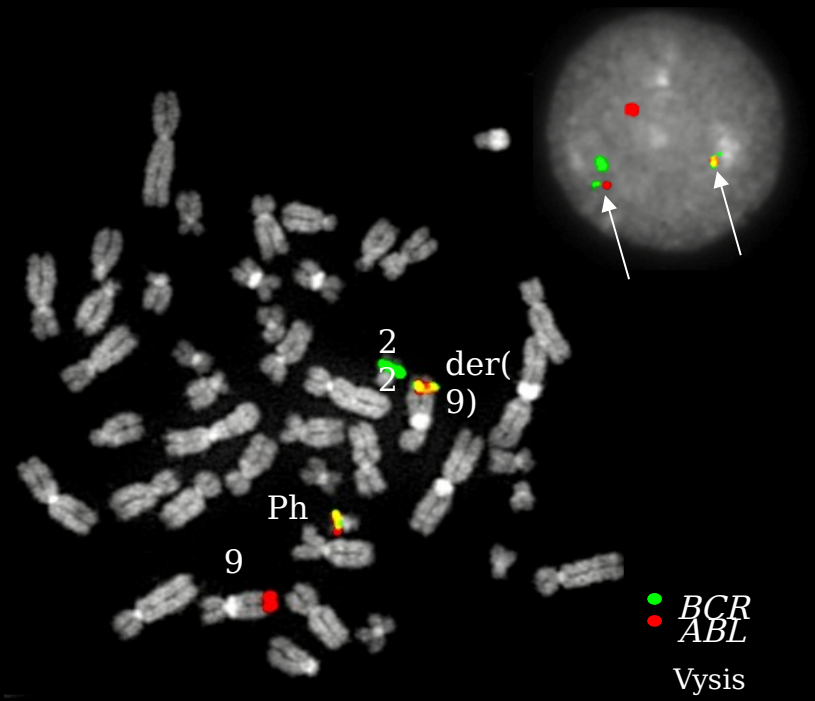


expresses a fusion oncoprotein with tyrosine kinase activity

Classical t(9;22)(q34.1;q11.2)

Dual Fusion (D-FISH) Signal Pattern





EN'01.2004

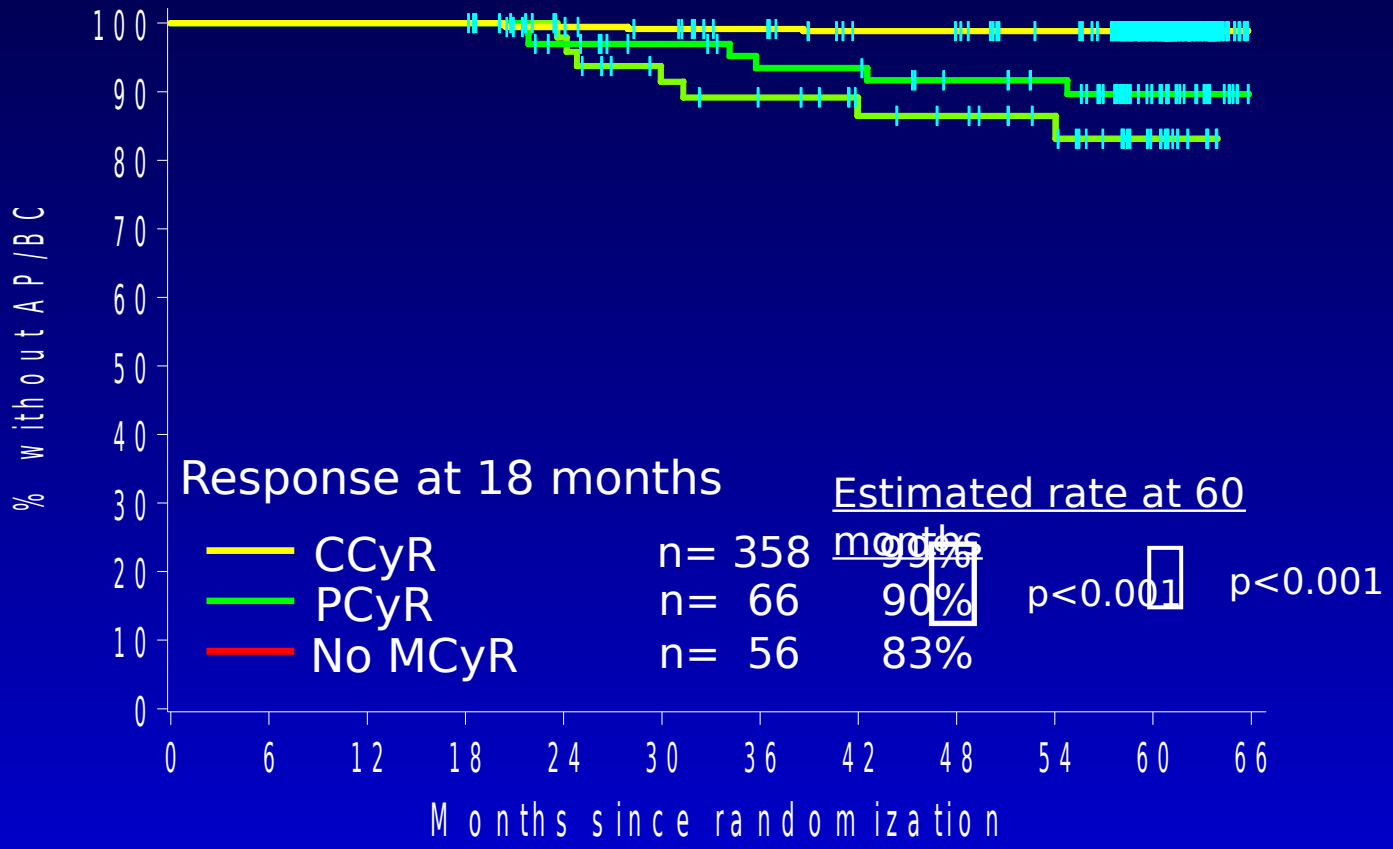
What's a cytogenetic response and why does it matter?

Type of response	% of Philadelphia-positive cells
Minor/minimal	More than 35%
Partial	Less than 35%
Complete	0%

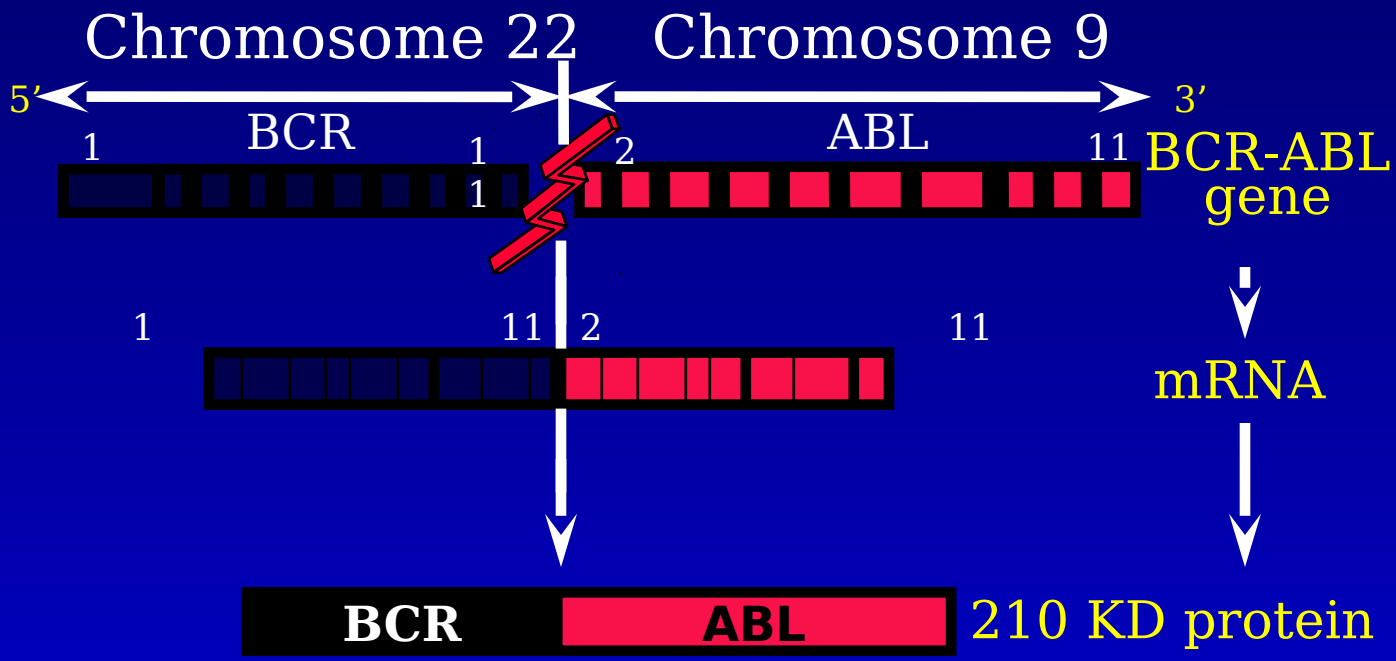
Major response

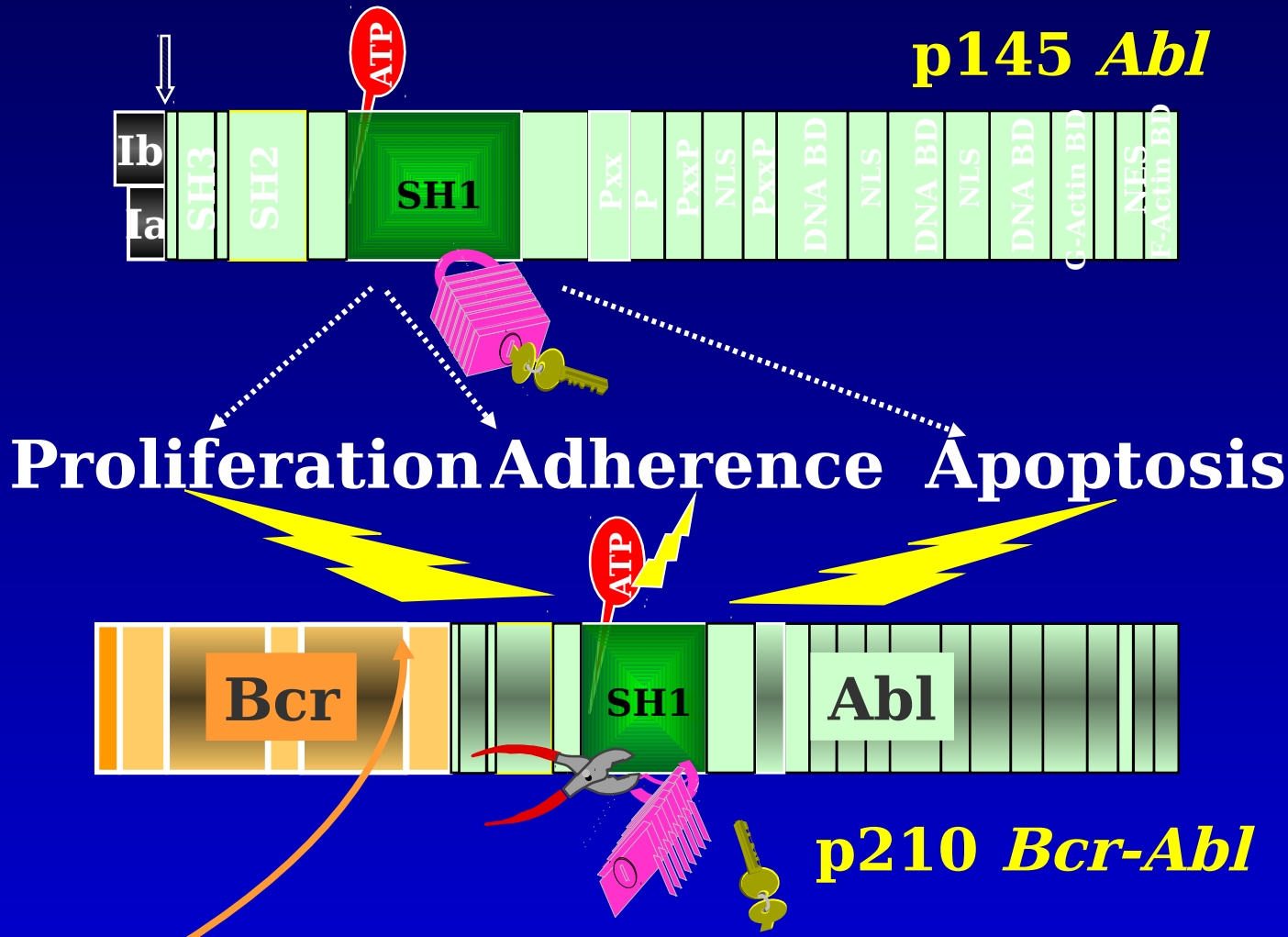
- Test performed on a sample of bone marrow every 6 months or so
- WITH INTERFERON…
- If you have a 'major' response you probably live longer
- If you have a 'complete' response you probably live even longer
- If you sustain a complete response for several years - ???cure.

Survival Without AP/BC by Level of CyR at 18 Months on First-line Imatinib



Molecular Abnormality

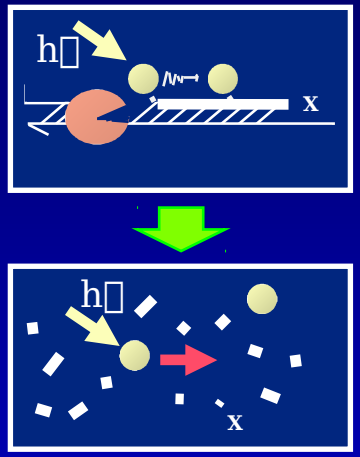



p145 Abl
ATP
Ib
Ia
SH3
SH2
SH1
Pxx
P
PxxP
NLS
PxxP
DNA BD
NLS
DNA BD
NLS
DNA BD
G-Actin BD
NES
F-Actin BD
Proliferation
Adherence
Apoptosis
ATP
Bcr
SH1
Abl
p210 Bcr-Abl

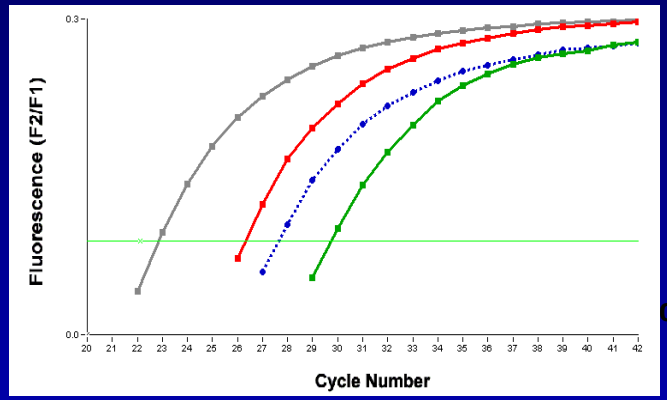
Real time quantitative RT-PCR

I. Hydrolysis Probes

Release from quenching
by hydrolysis

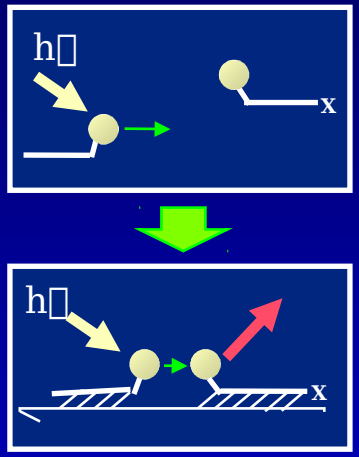


TaqMan™



II. Hybridization Probes

Increased resonance energy
transfer by hybridization



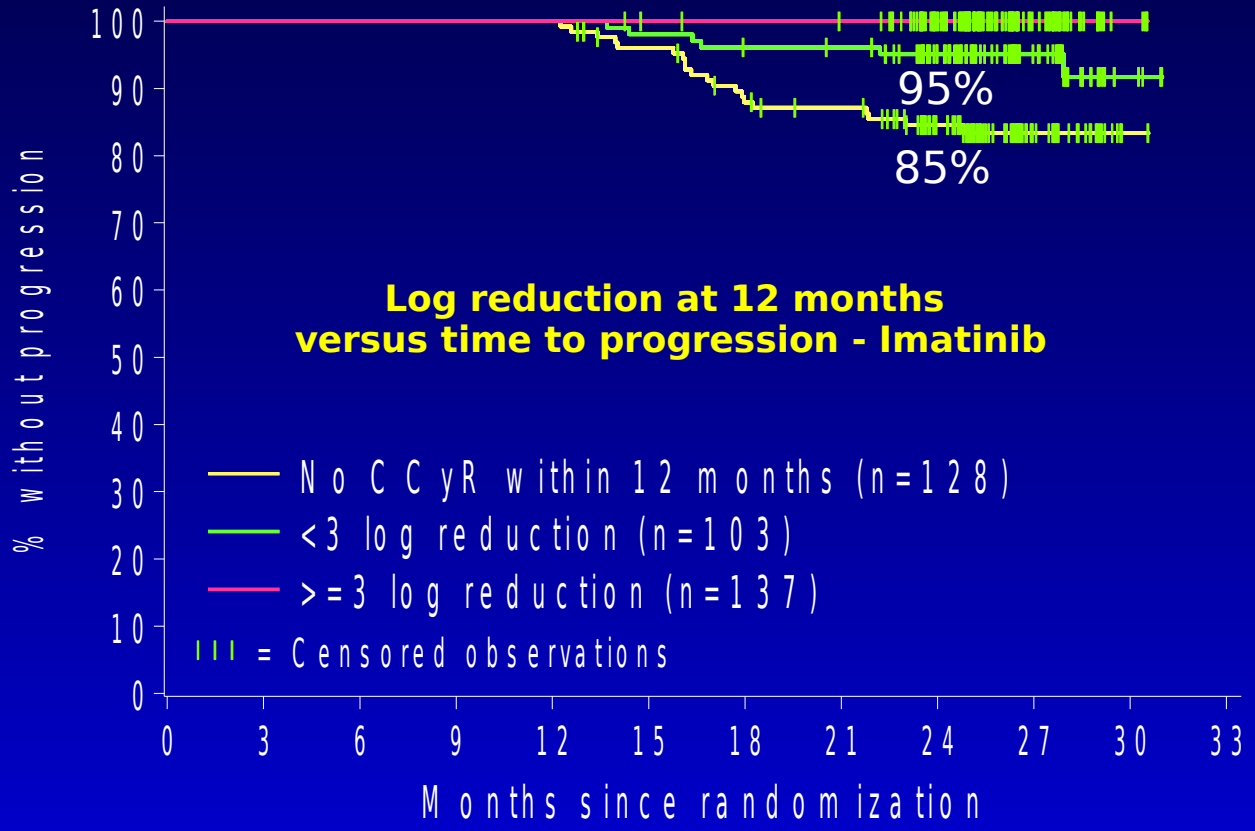
LightCycler™

What's a molecular response and why does it matter?

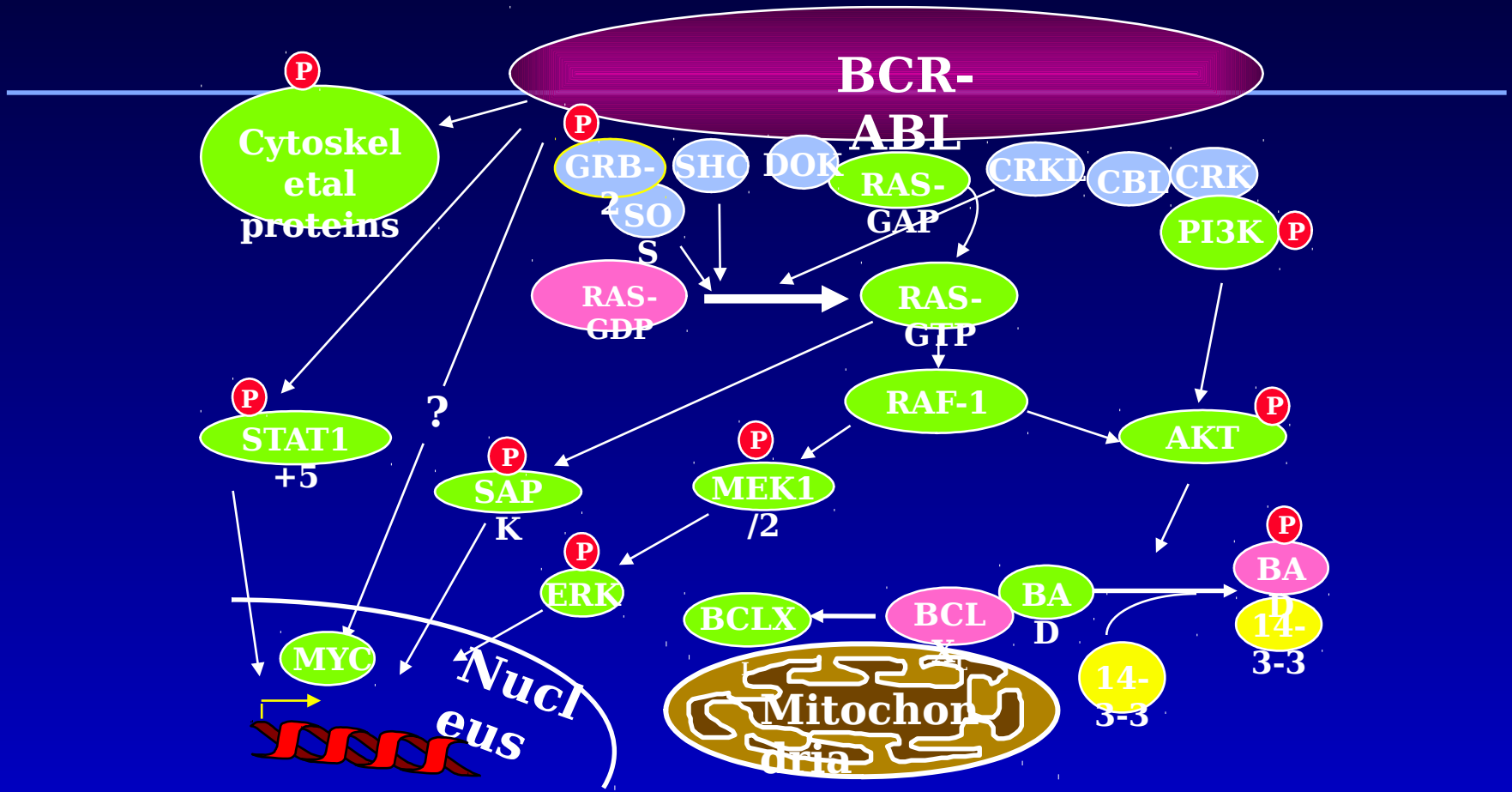
Type of response	% of bcr-abl compared to (normal) abl
Suboptimal	More than 0.1%
Major	Less than 0.1%
Complete	Less than 0.003%

- Test performed on a sample of peripheral blood every 3 months or so
- WITH TKIs…
- If you have a 'major' response you probably live longer
- If you have a 'complete' response you have a 40% chance of stopping Imatinib
- If you sustain a complete response for several years - ???cure.

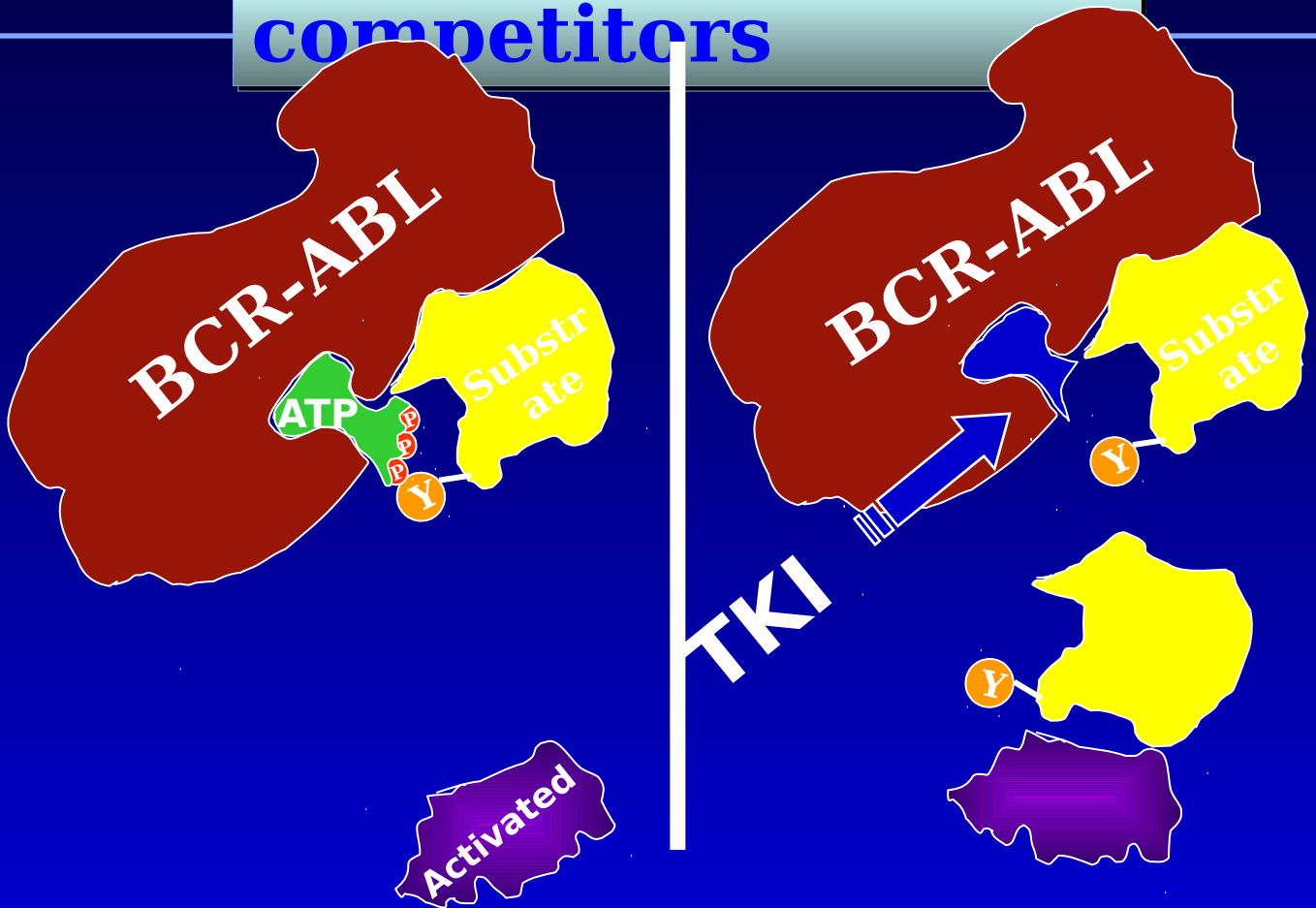
What's a molecular response and why does it matter?



Tyrosine Kinase Inhibitors in CML

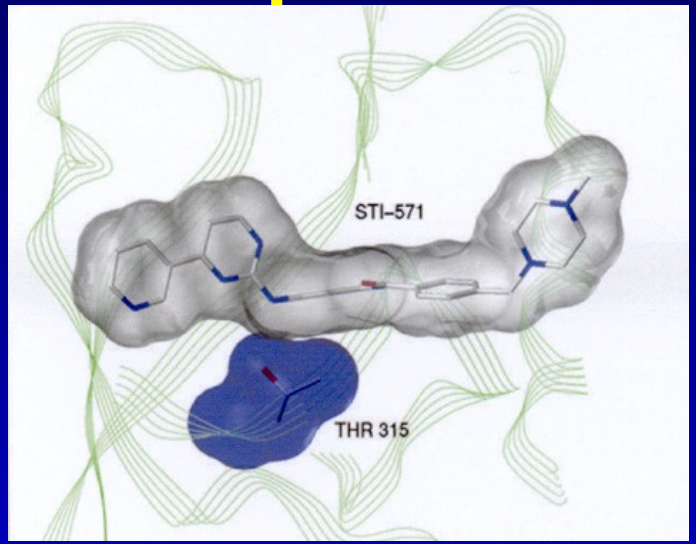

BCR-ABL
P
Cytoskeletal proteins
P
GRB-2
SHC
SOS
DOK
RAS-GAP
CRKL
CBL
CRK
PI3K
P
RAS-GDP
RAS-GTP
P
STAT1
+5
?
RAF-1
P
AKT
P
SAPK
P
MEK1/2
P
ERK
P
BAD
BCLXL
BCL2
BAD
P
14-3-3
14-3-3
MYC
Nucleus
Mitochondria

ATP-binding competitors

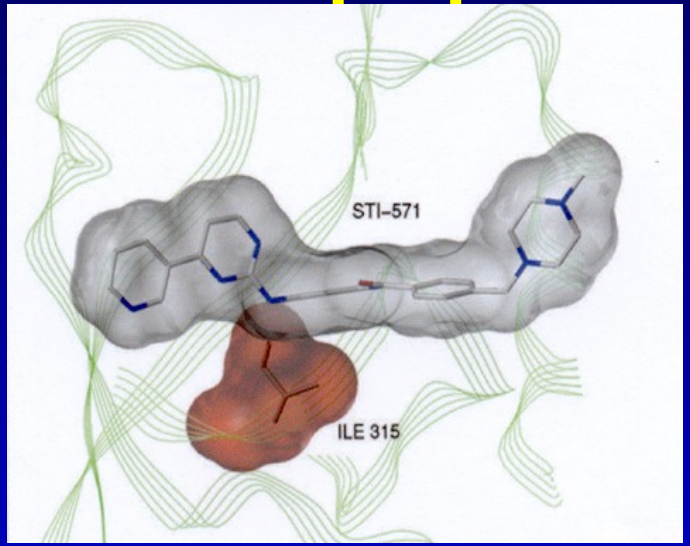


What a difference a point-mutation made…

Wild



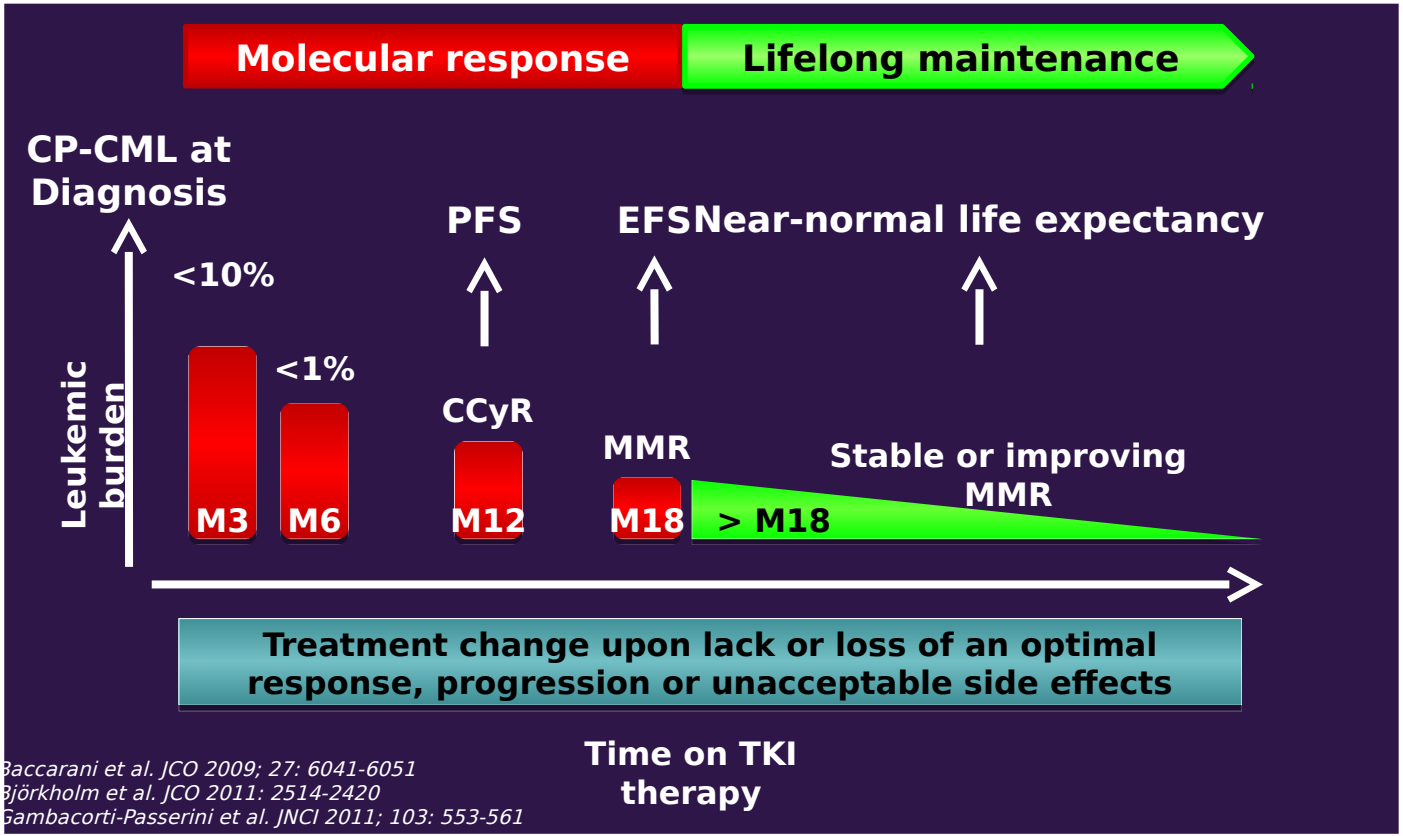
T315I



(Gorre *et al.*, Science, June 2001)

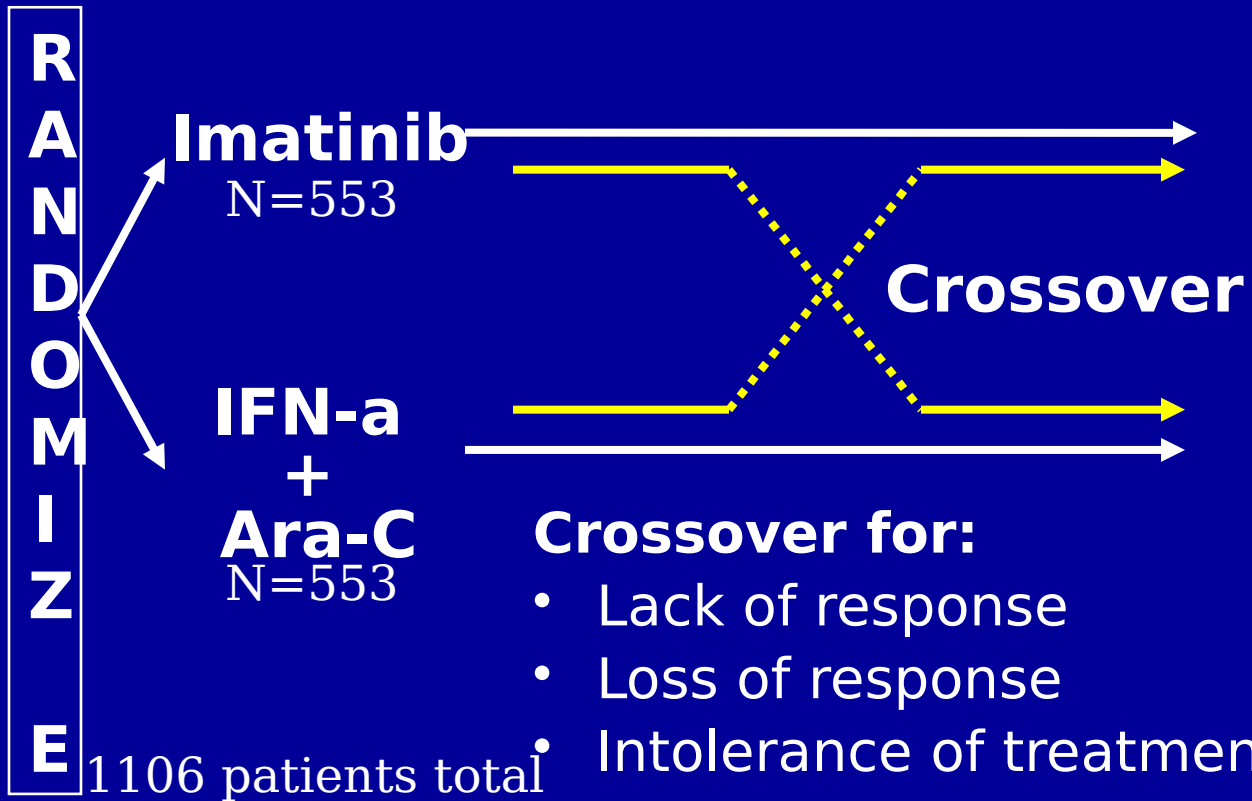
Treatment challenges in CML

Current Aim of TKI Therapy in CML



Baccarani et al. JCO 2009; 27: 6041-6051
Björkholm et al. JCO 2011: 2514-2420
Gambacorti-Passerini et al. JNCI 2011; 103: 553-561

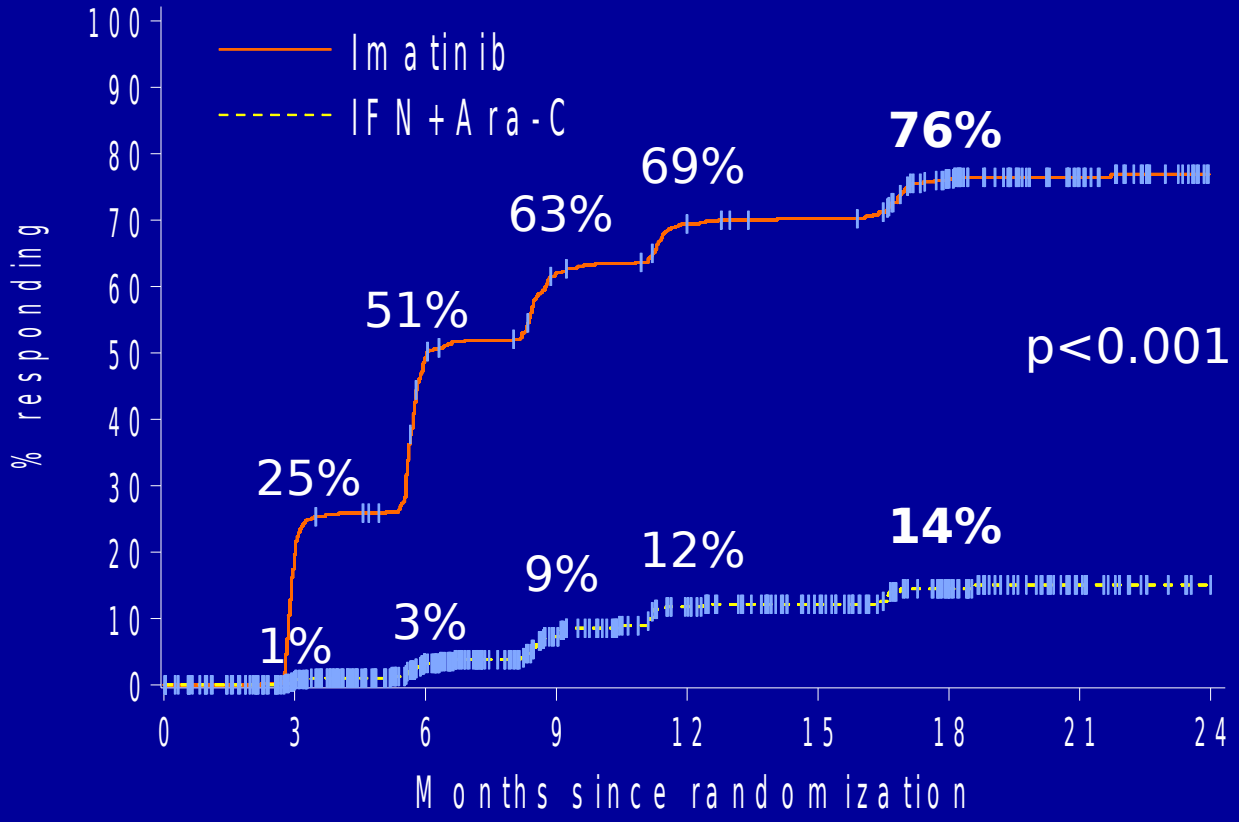
0106/IRIS study: design



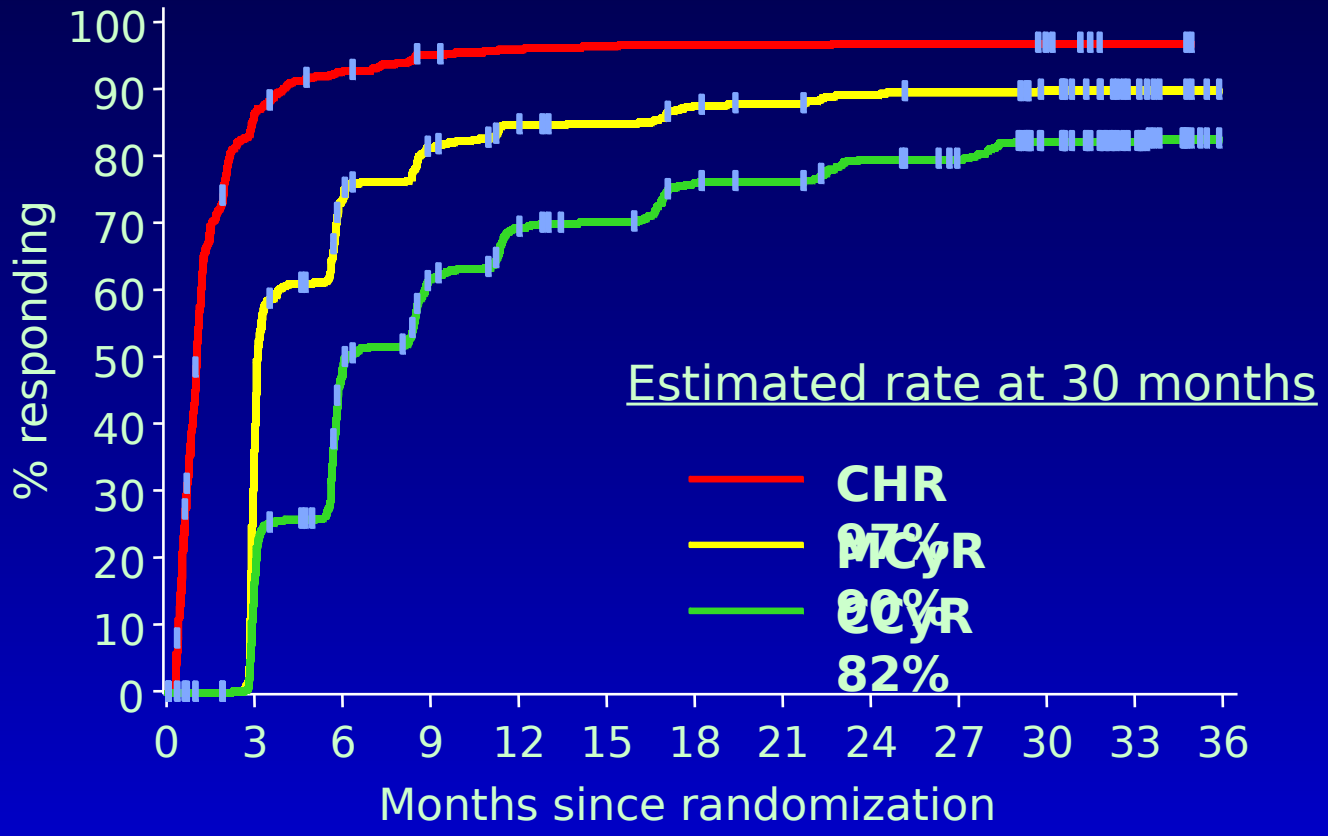
Crossover for:

- Lack of response
- Loss of response
- Intolerance of treatment

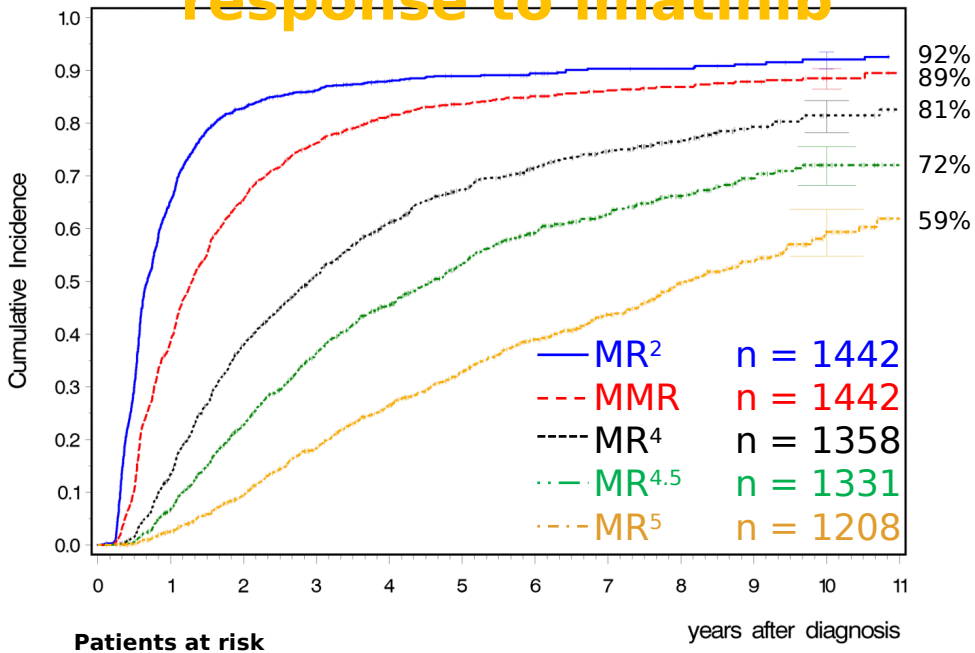
Complete Cytogenetic Responses



Estimated Response to First-line Imatinib



CML-Study IV
Cumulative incidence of molecular response to imatinib

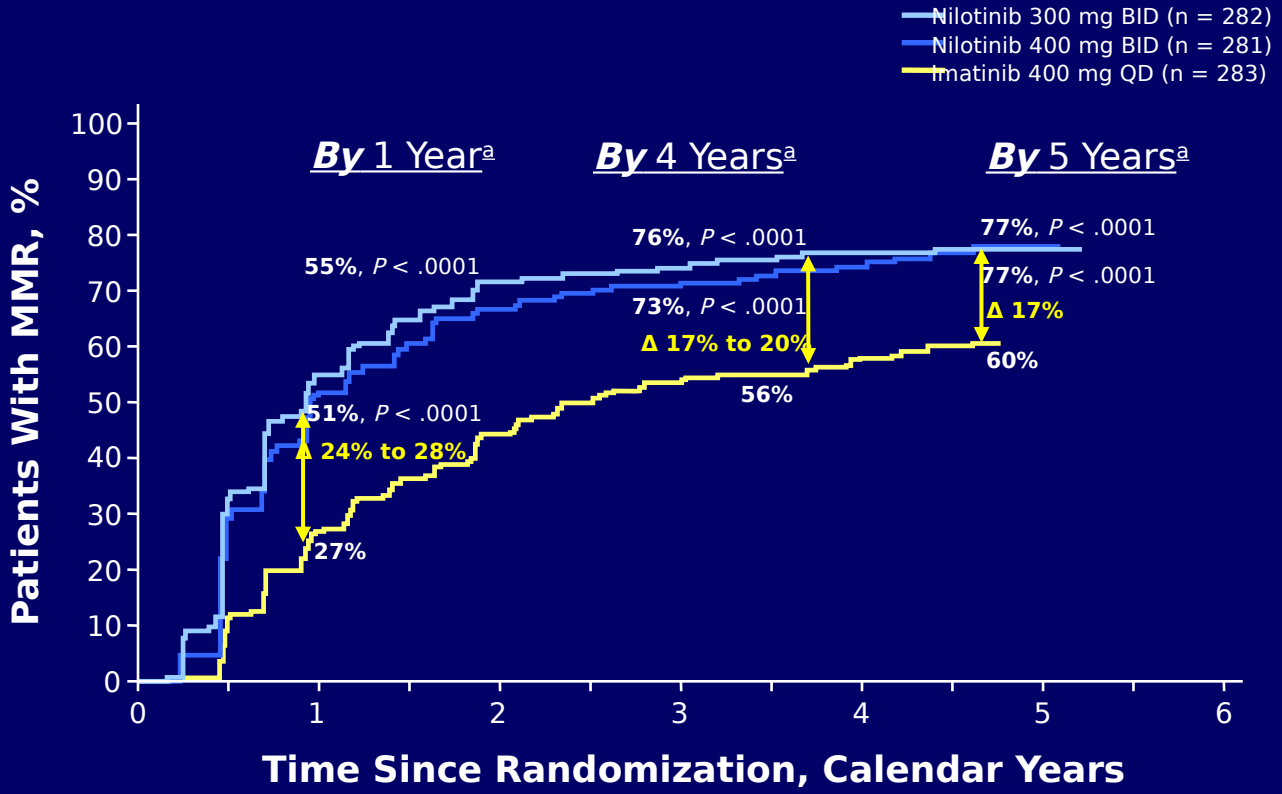


Patients at risk

	0	2	5	8	10
MR²	1442	143	35	11	2
MMR	1442	349	66	20	5
MR⁴	1358	668	197	56	12
MR⁴.⁵	1331	839	316	89	21
MR⁵	1208	922	470	164	48

Hehlmann et al, JCO 2014

ENESTnd: Cumulative Incidence of MMR

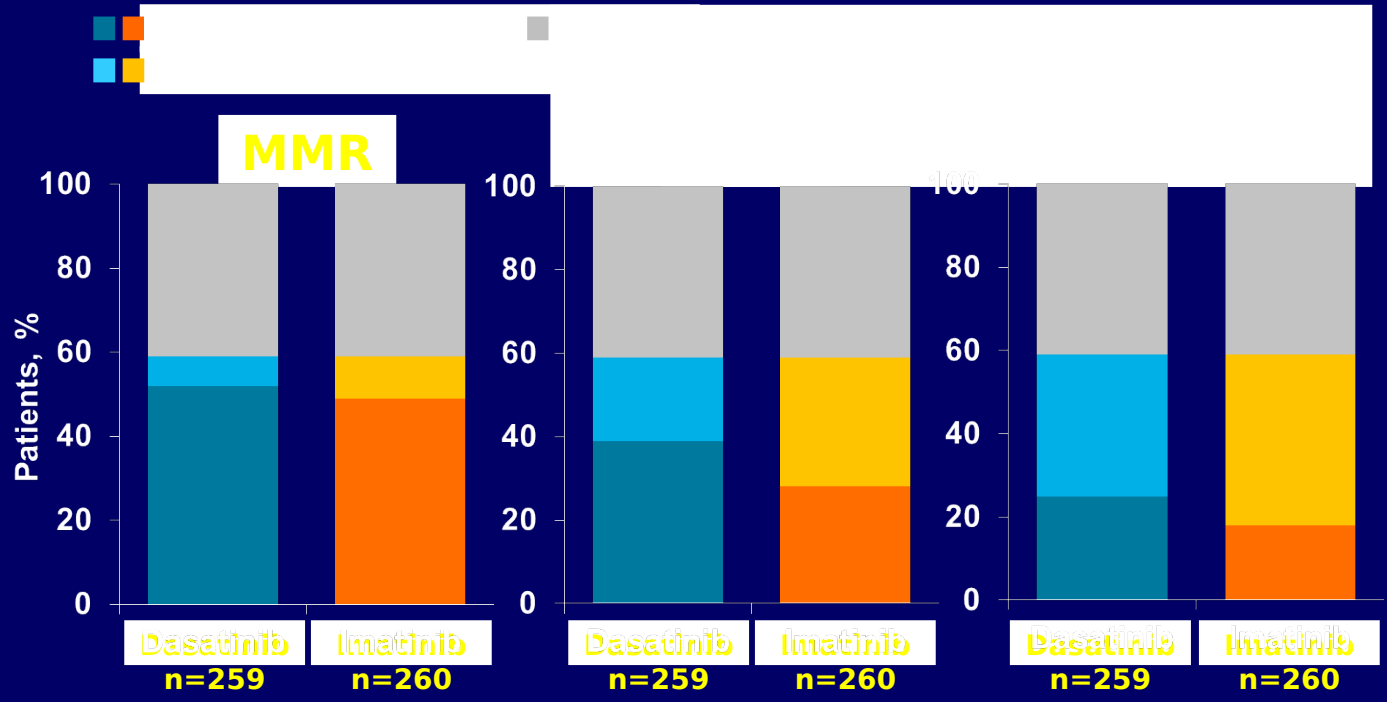


MMR, major molecular response (BCR-ABL^{IS} ≤ 0.1%).

[a] Cumulative response rates reported consider each year to consist of twelve 28-day cycles.

Saglio G, et al. *Blood*. 2013:[abstract 92].

Molecular Responses at 5 Years [a]

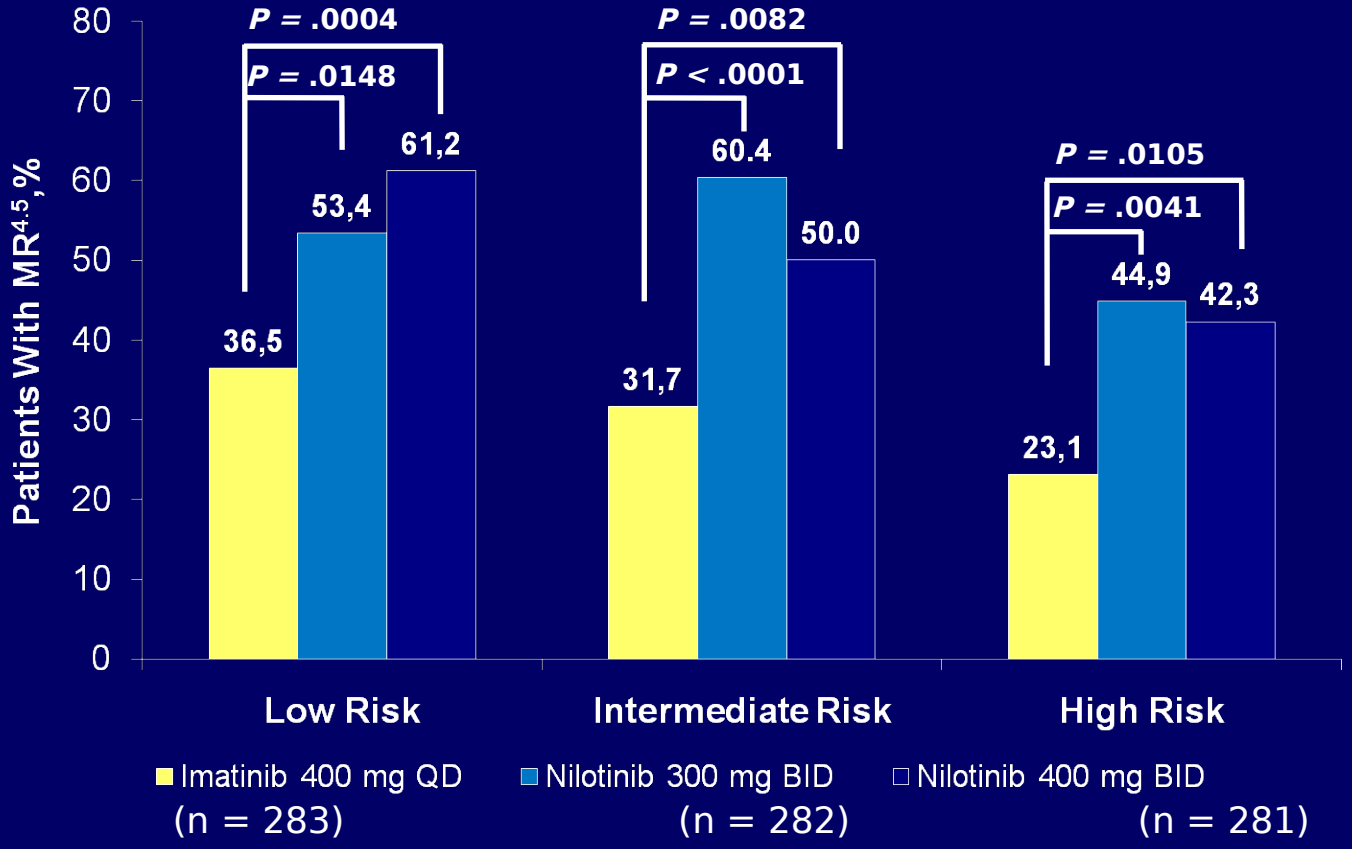


[a] 5 years ± 3 months.

[b] Patients on treatment with no sample analyzed at 5 years ± 3 months.

MR^4, BCR-ABL (IS) ≤0.01%.

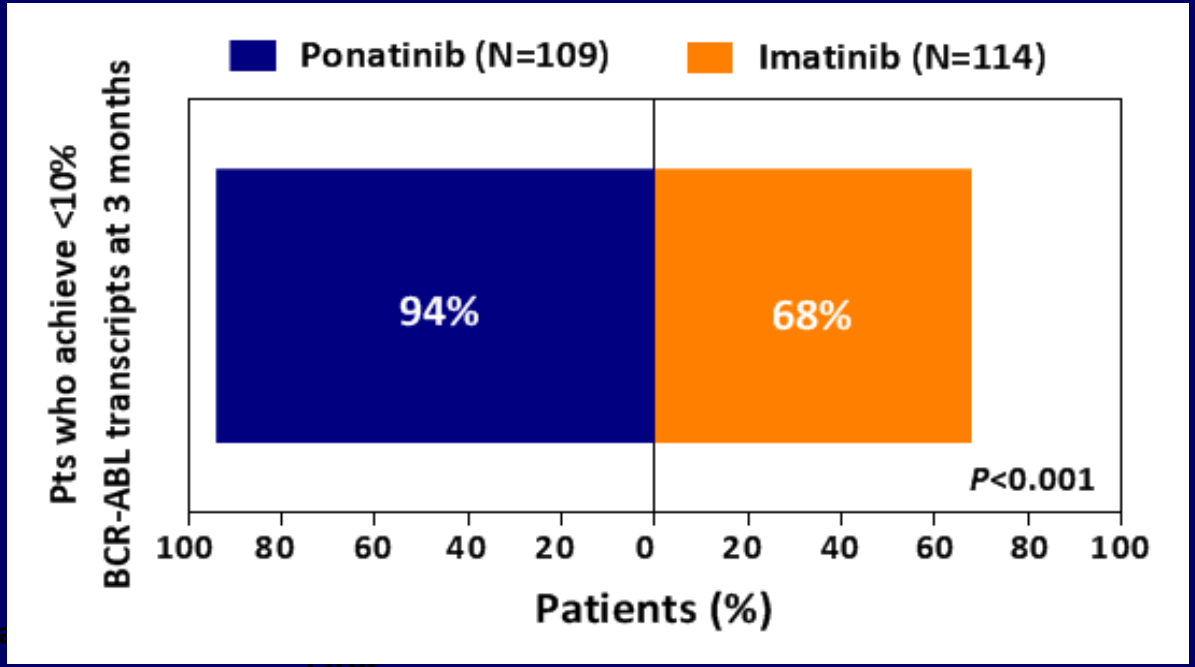
MR$^{4.5}$ by 5 Years[a] According to Sokal Risk Score



[a] By cycle 60 (28 days per cycle).

Saglio G, et al. *Blood*. 2013:[abstract 92].

Achievement of <10% BCR-ABL Transcripts at 3 Months: Evaluable Patients

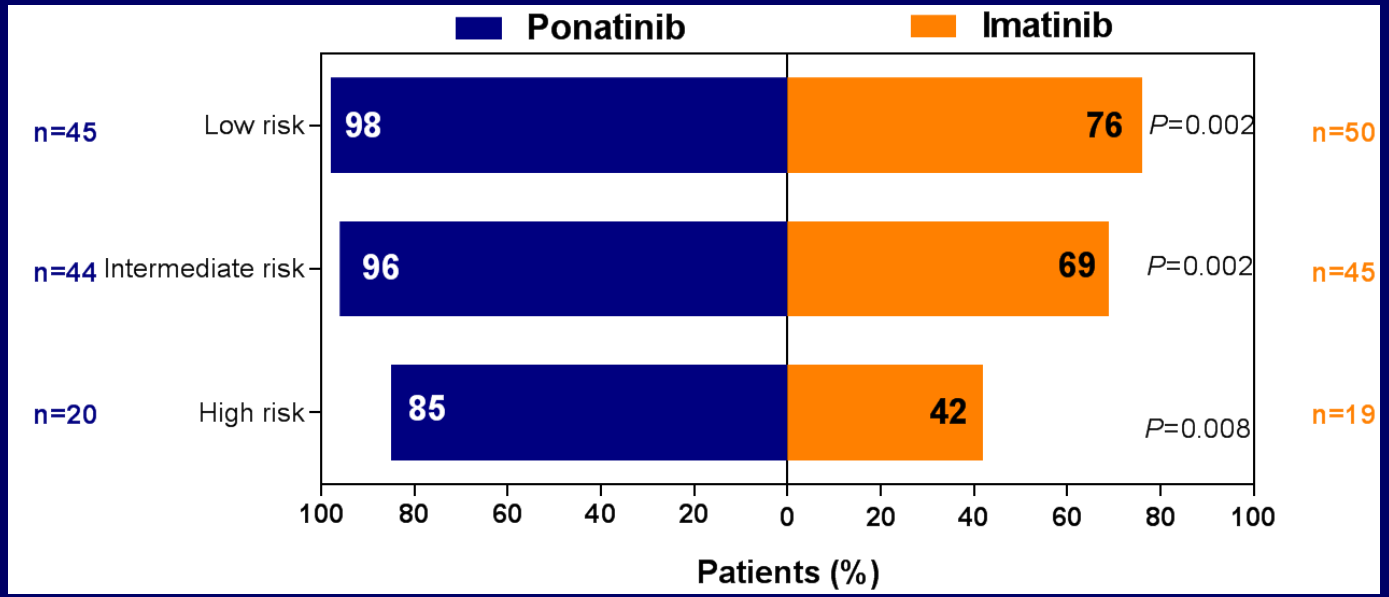


Evalua

later.

Data as of 1 April

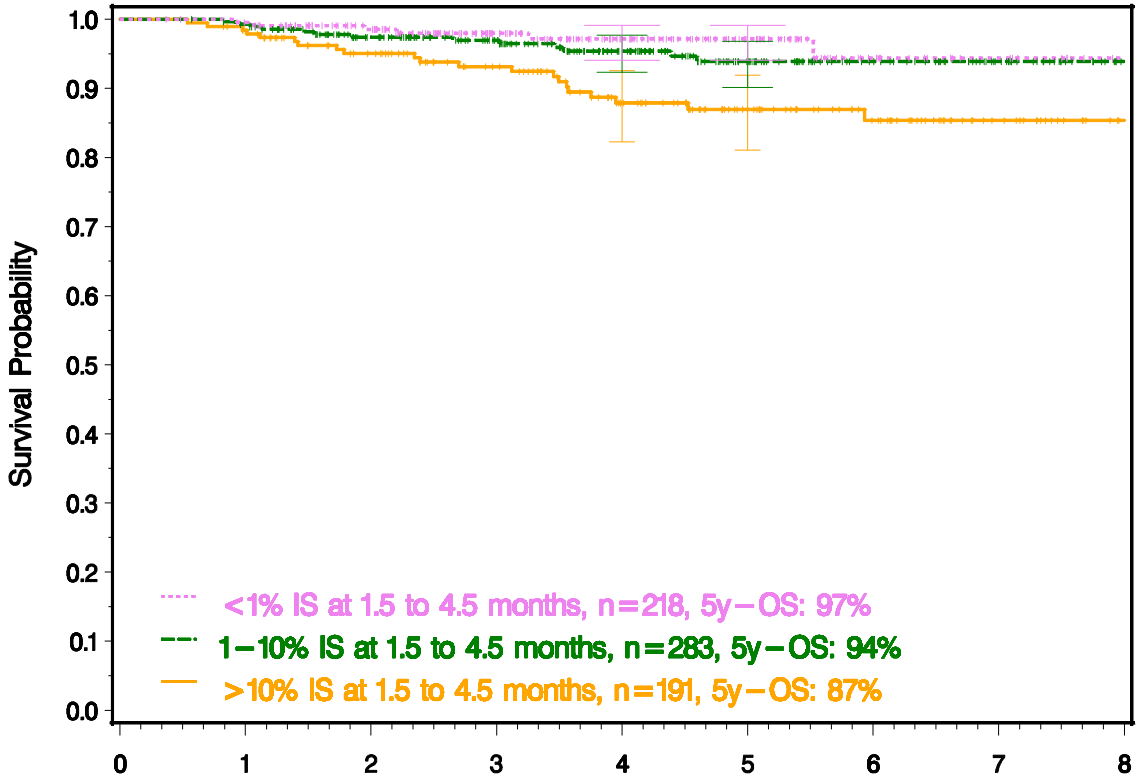
Achievement of <10% BCR-ABL Transcript Levels at 3 Months by Sokal Risk Score: Evaluable Patients



Data as of 1 April

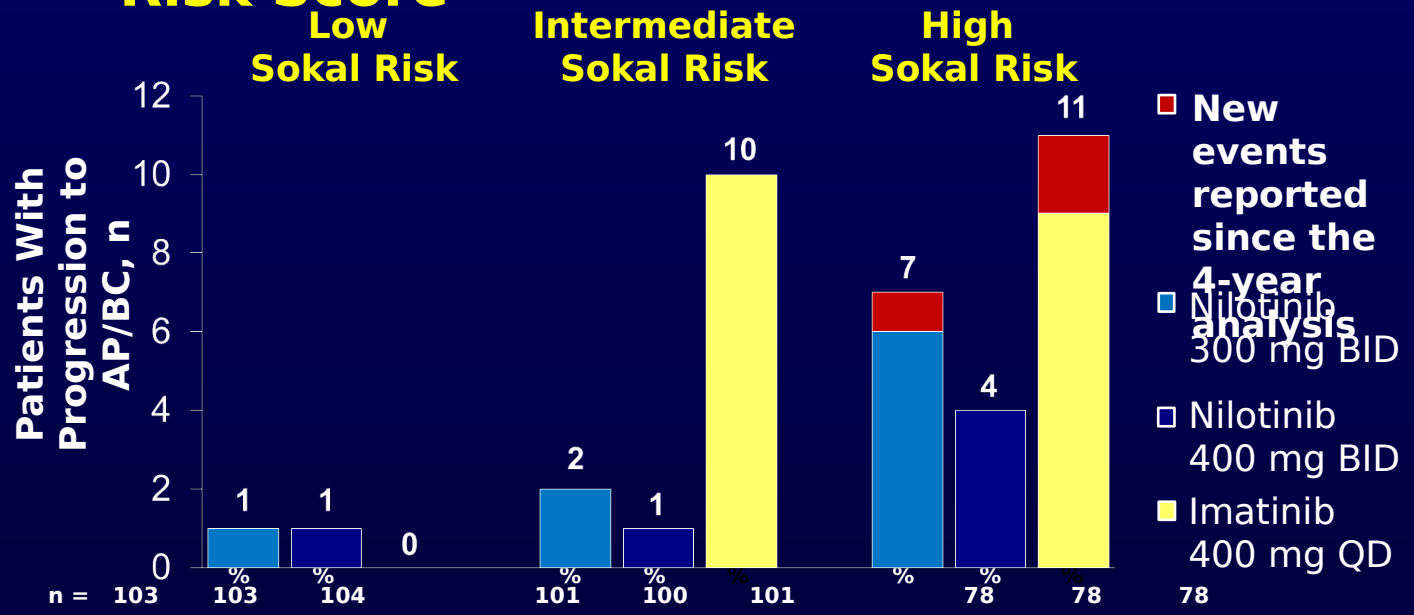
Imperial College London

OS: BCR-ABL (IS) at 3 months ≤1% vs. 1-10% vs. >10%



Hanfstein et al, 2012; Leukemia, 26: 2096-2101)

ENESTnd Progression to AP/BC on Study[a] According to Sokal Risk Score

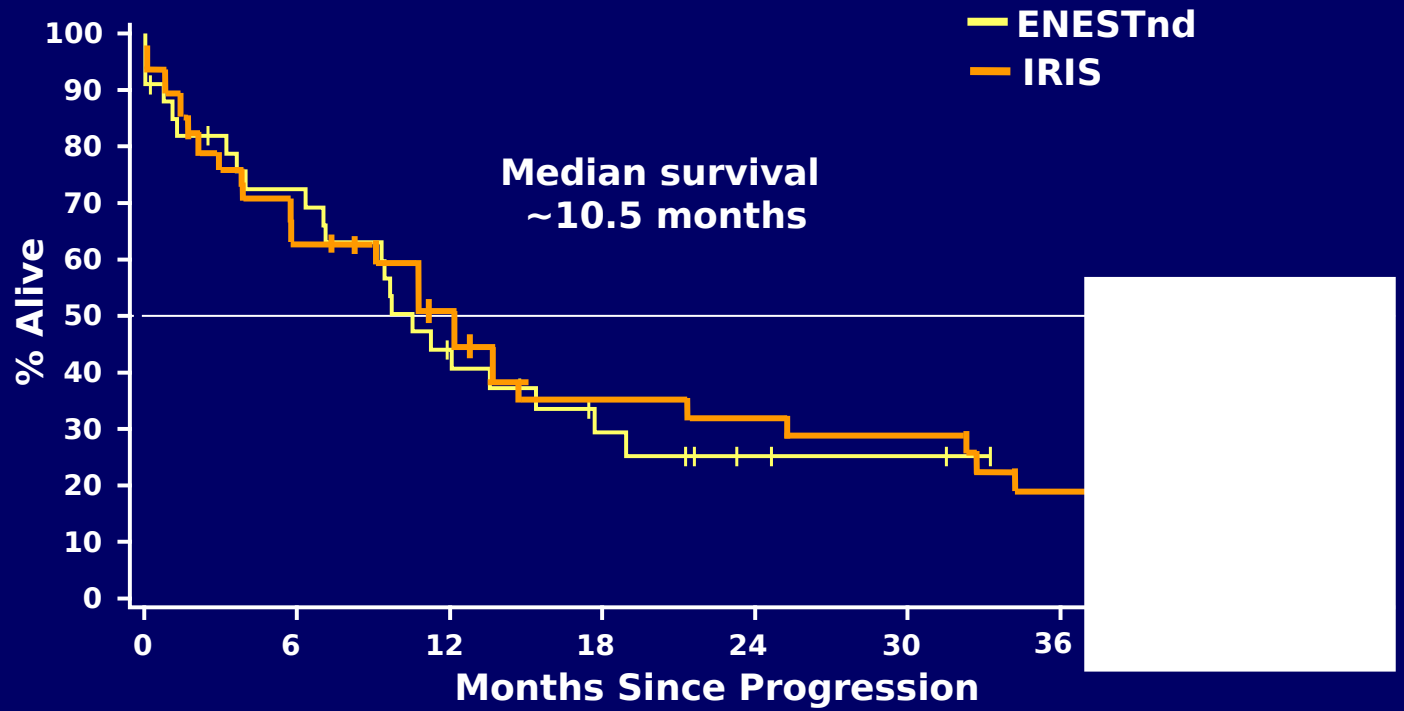


- All 3 progressions to AP/BC on study reported since the 4-year analysis occurred in patients with high Sokal risk scores at baseline; all 3 patients also had BCR-ABL^{IS} > 10% at 3 months
- All progressions in patients with low/intermediate Sokal risk scores occurred during the first 2 years on study

[a] Progression to AP/BC or death due to advanced CML on core treatment or during follow-up after discontinuation of core treatment.

Hughes T, EHA 2014

Survival After Progression to AP/BC



Clark RE, et al. *Haematologica*. 2012;97(s1):237 [abstract 0583].

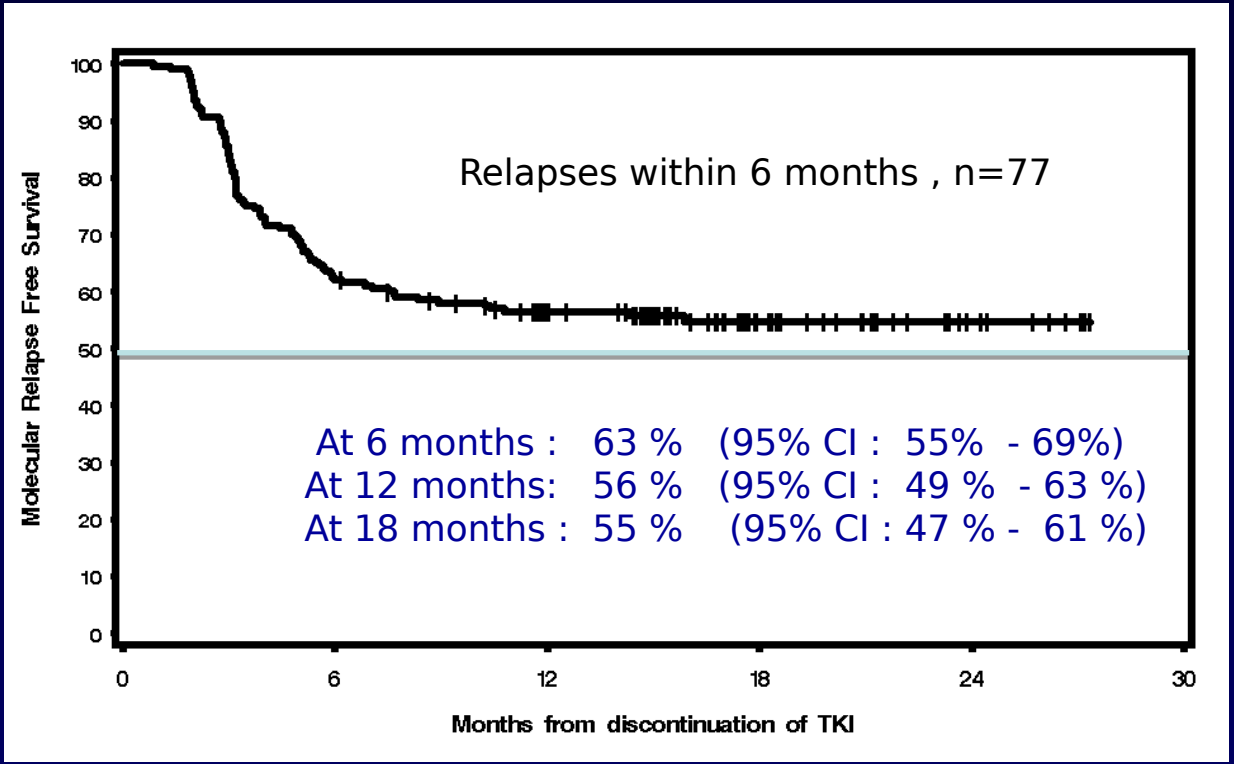
First line therapy in CML in CP

The main advantage of 2nd generation TKI as first line is the increase in the proportion of patients candidates for discontinuation

All pts but 1 who lost MMR restarted 2G-TKI treatment and regained MMR after a median time of 3 months (1-8).

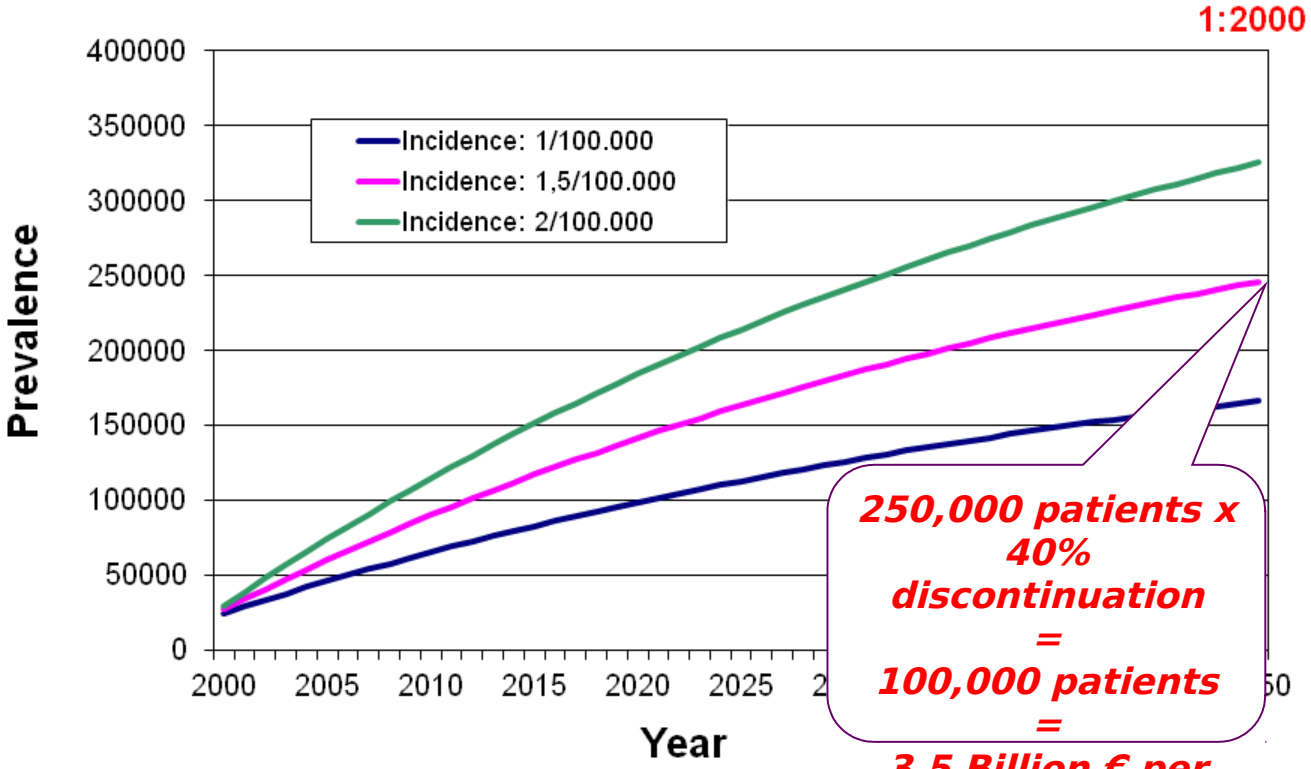
Molecular Relapse free survival

200 interim patients – overtime, loss MMR=89



63% remained without relapse the first 6 mo

Estimated Prevalence of CML in Europe until 2050



Assumptions: Population 500 million, mortality 2% per year, incidence constant.
Courtesy to Hasford and Pfirrmann.

Possible role of SCT in CML

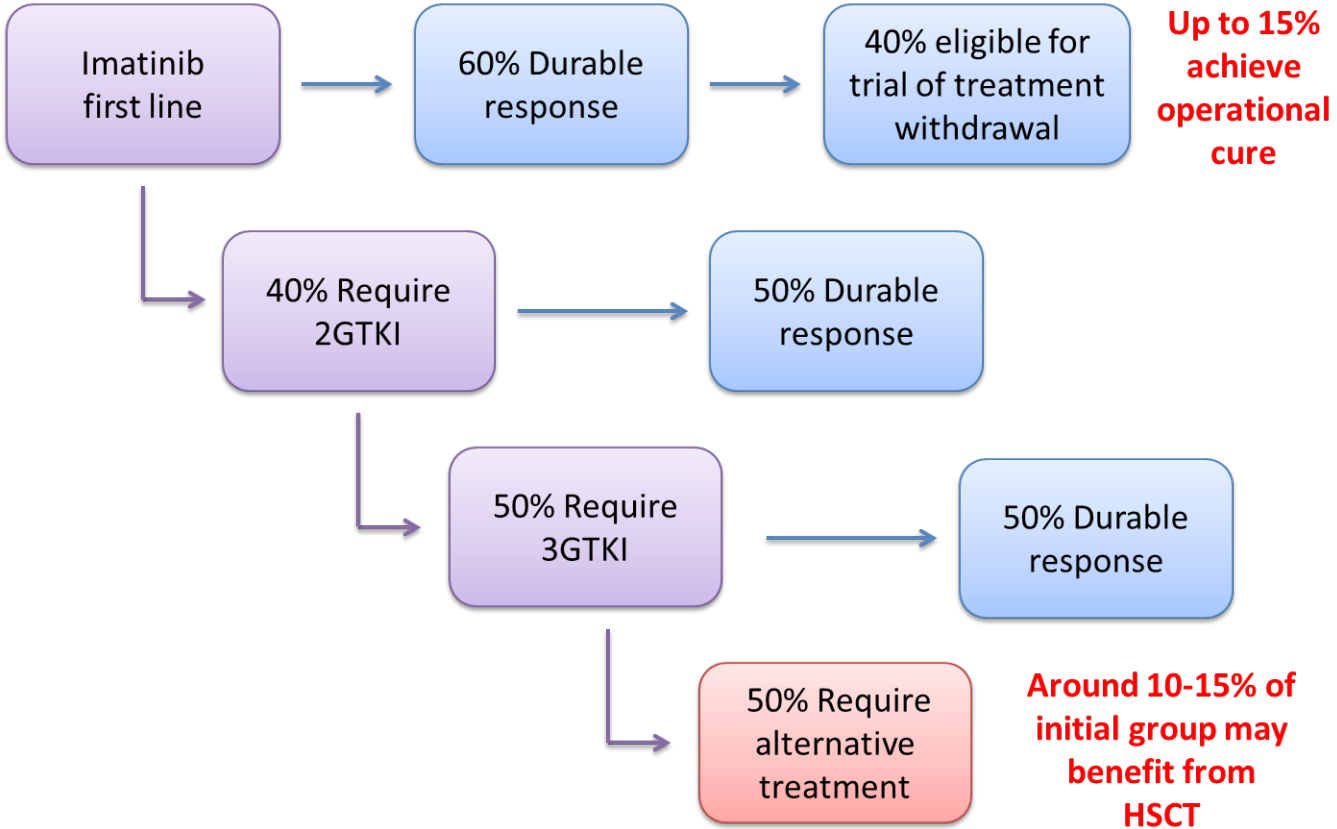
- Soon after di[illegible]s
  - Good
  - [illegible]ponding to TKI
  - [illegible]preference
- After failing TKIs
  - Imatinib failure, suboptimal response, intolerance
  - Failure to 2nd generation TKIs
  - Resistance to TKIs associated with the T315I mutation
- In accelerated phase or blast

NOT INDICATED

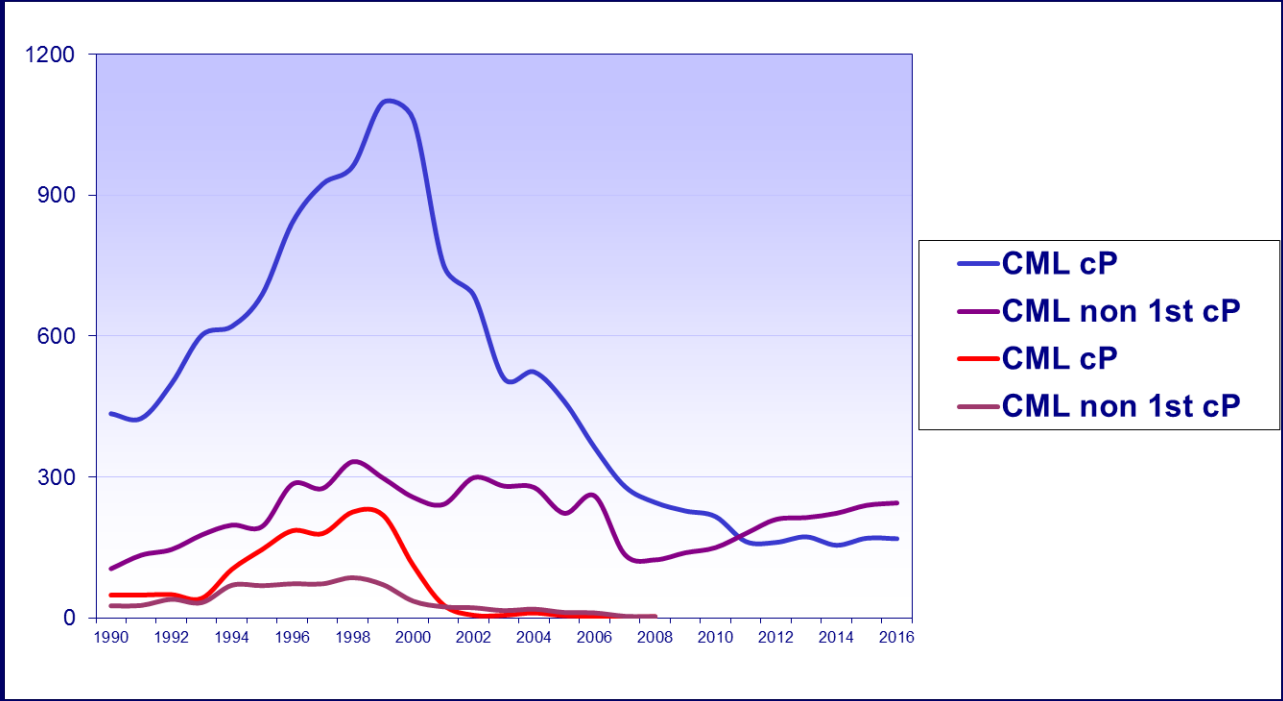
NOT VERY USEFUL

Imperial College London

Path to SCT in CML: First Line Imatinib

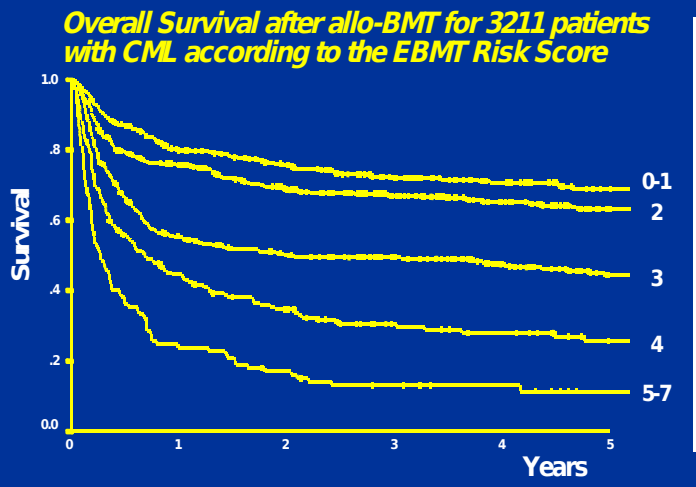


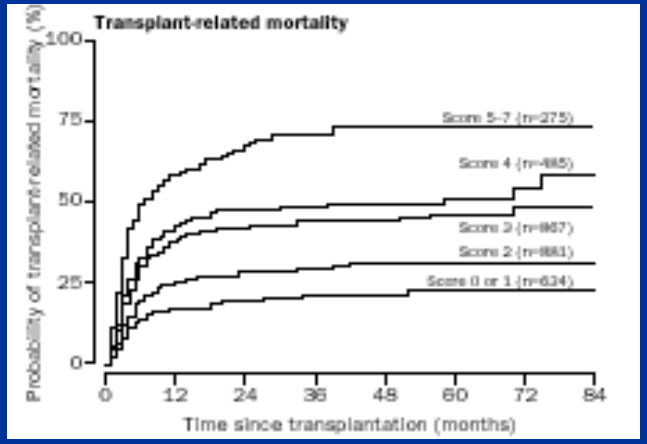
Allo-SCT for CML in Europe



Updated from Gratwohl A et al. Haematologica 2009;91:513-21.

SCT for CML: the EBMT score



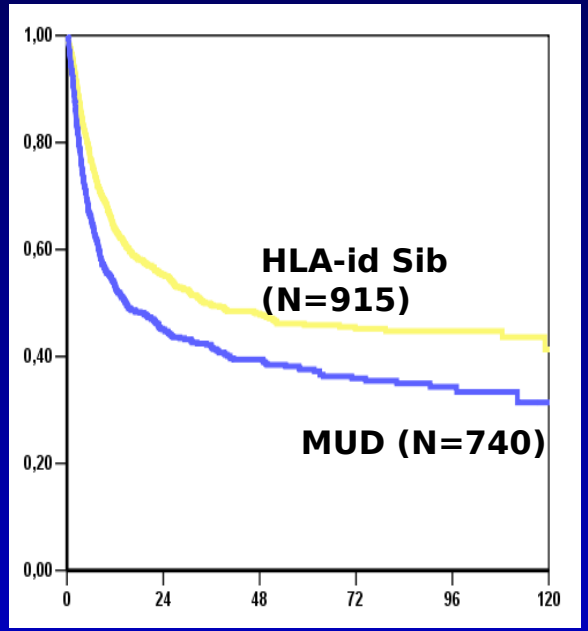


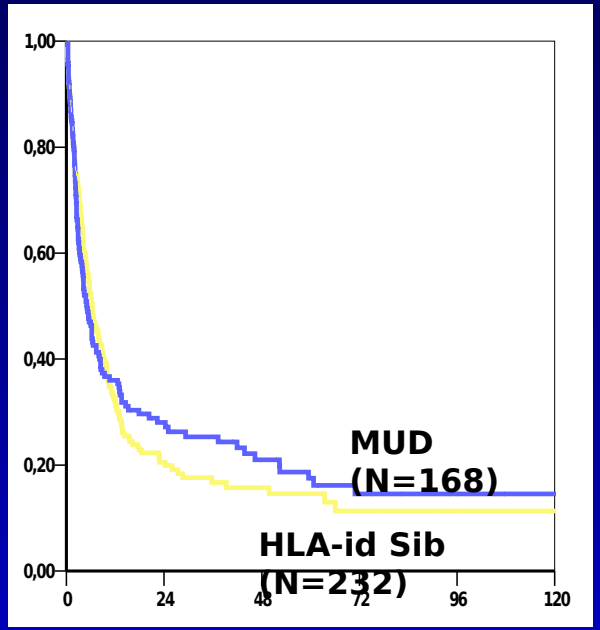
Prognostic factors for survival (defined before SCT):

- **Age**
- **Disease phase**
- **Disease duration**
- **Histocompatibility**
- **Patient/Donor gender**

Outcome after allo-SCT for CML in advanced phase

Overall Survival of CML patients in AP/BC transplanted between 1995-2005

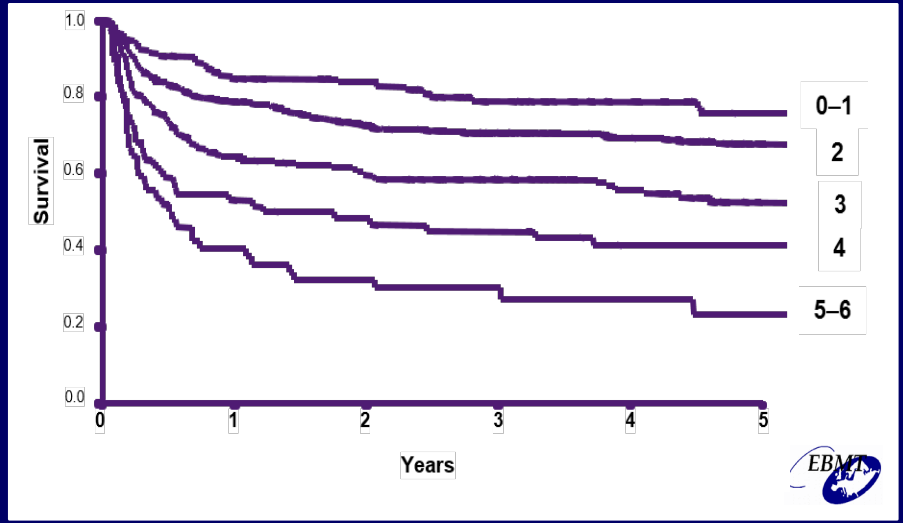




Courtesy of CLWP-EBMT

Survival after SCT for early CML-CP

Survival of patients in early first chronic phase according to the revised chronic phase risk score (N=2049)



Risk score (0–2 points per category)

Age, years:
<30 (0); 30–40 (1); >40 (2)

Donor:
sibling (0); unrelated (2)

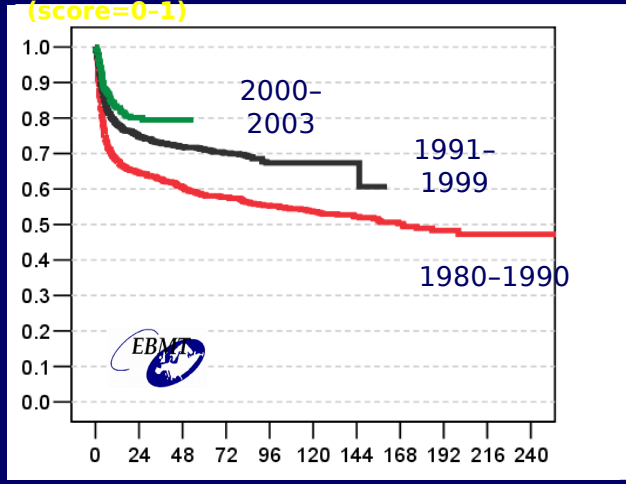
Interval diagnosis–SCT:
<1 year (0); >1 year (1)

Sex match:
female–male (1); all other (0)

Passweg JR, et al. Br J Haematol 2004;125:613–620.

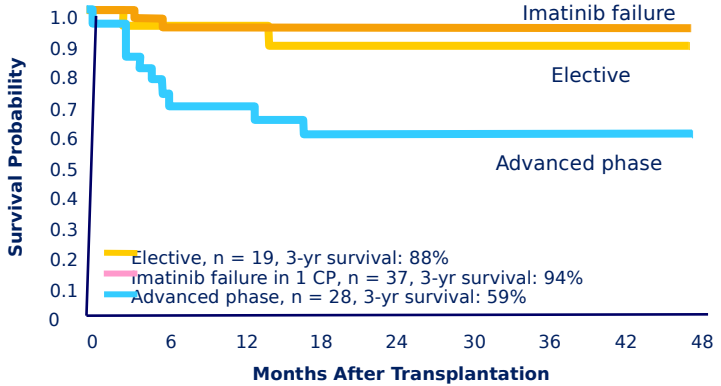
Progress in allo-SCT for CML

Overall survival among good risk patients (score=0–1)



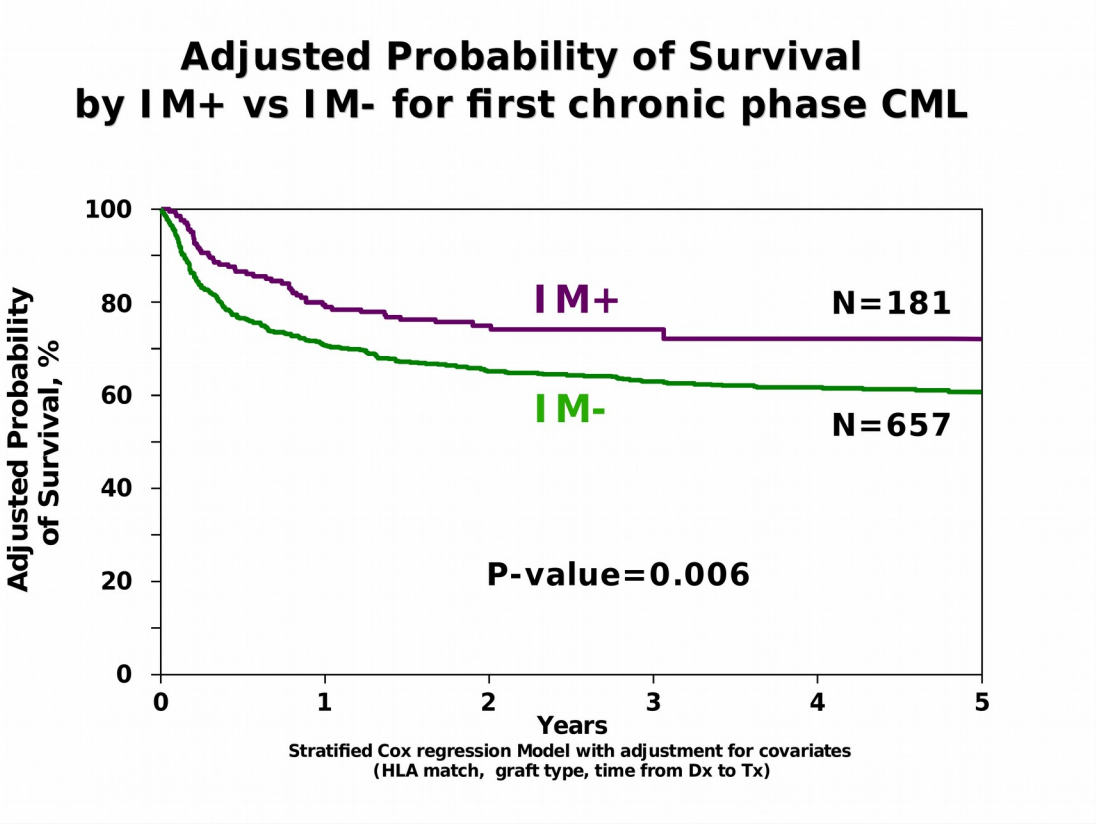
Gratwohl A, et al. Haematologica 2006;91:513–521.

Overall survival for allo SCT in German CML-IV study



Saussele S, et al. Blood. 2010;115:1880-1885.

Impact of previous Imatinib on SCT

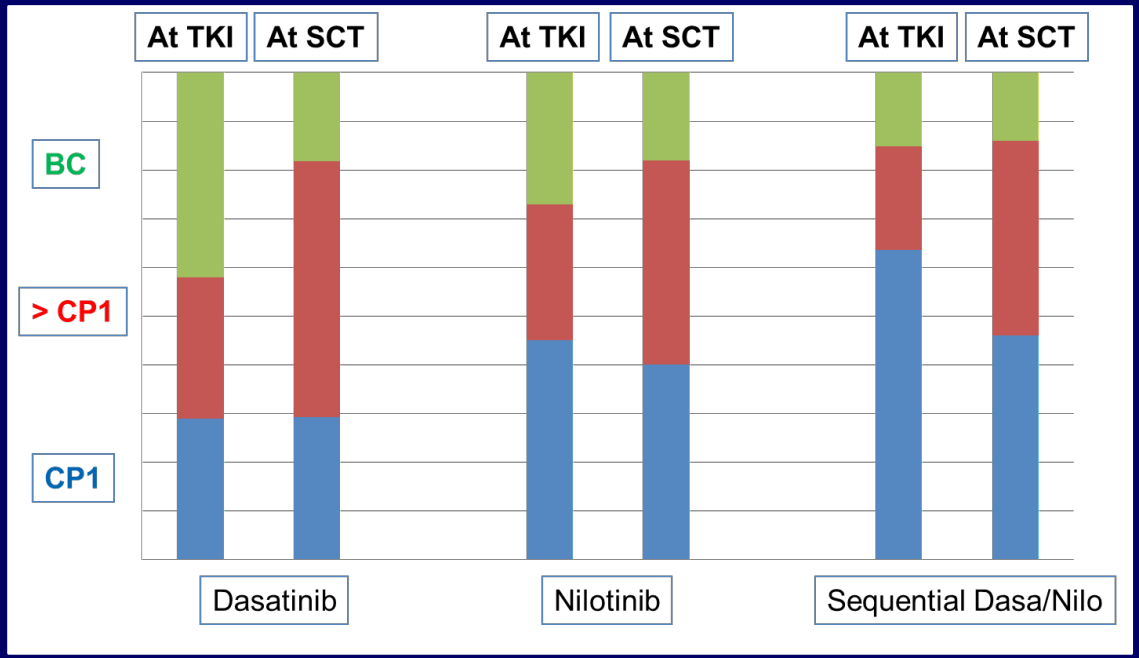


Lee et al. Blood. 2008; 112(8): 3500-7.

Excellence in Science
EBMT
European Group for Blood and Marrow Transplantation

The Effect of Prior Therapy with Nilotinib or Dasatinib on the Outcome after Allo SCT for Patients with CML

EBMT Non-Interventional Prospective Study



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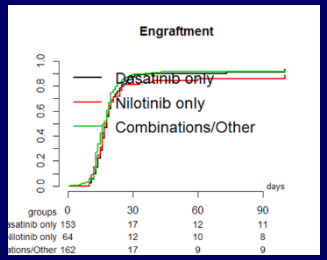
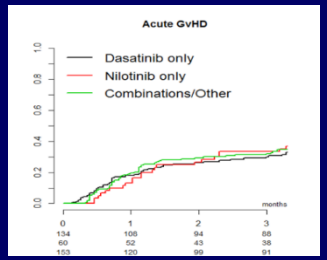
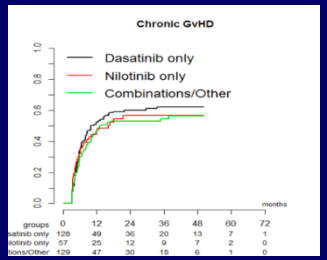
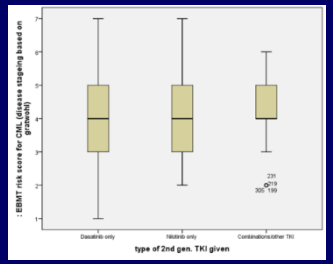
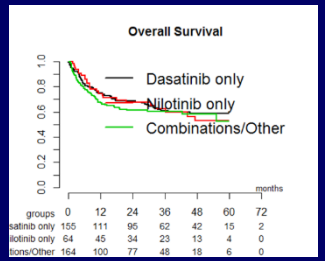
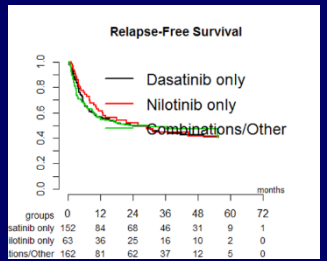


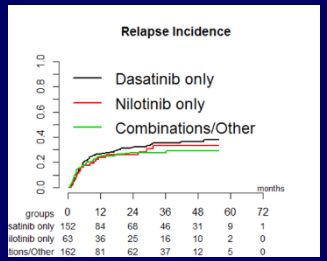


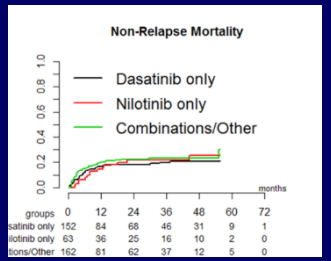








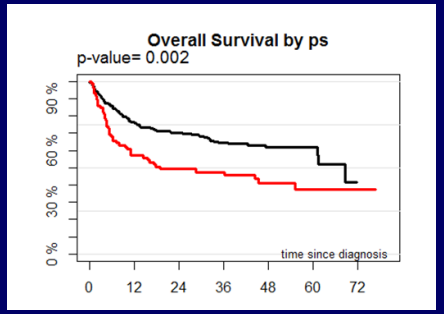


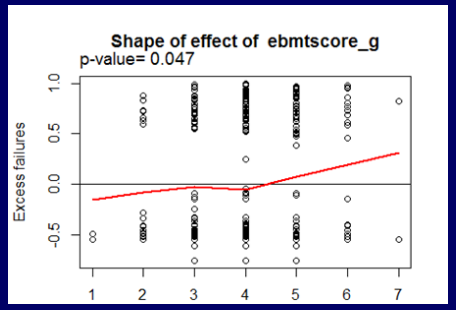


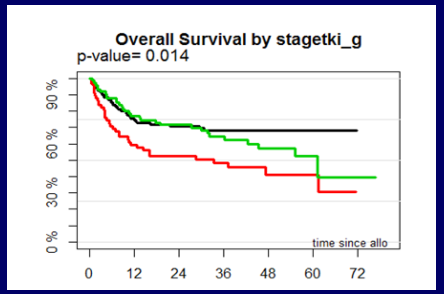
No differences in outcomes between Nilotinib, Dasatinib and Sequential TKI

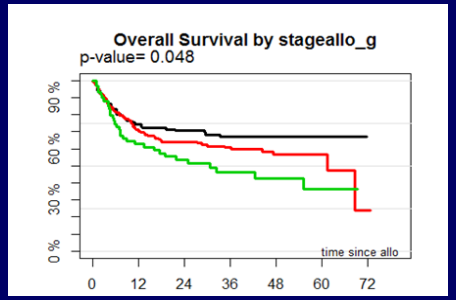
The Effect of Prior Therapy with Nilotinib or Dasatinib on the Outcome after Allo SCT for Patients with CML

EBMT Non-Interventional Prospective Study

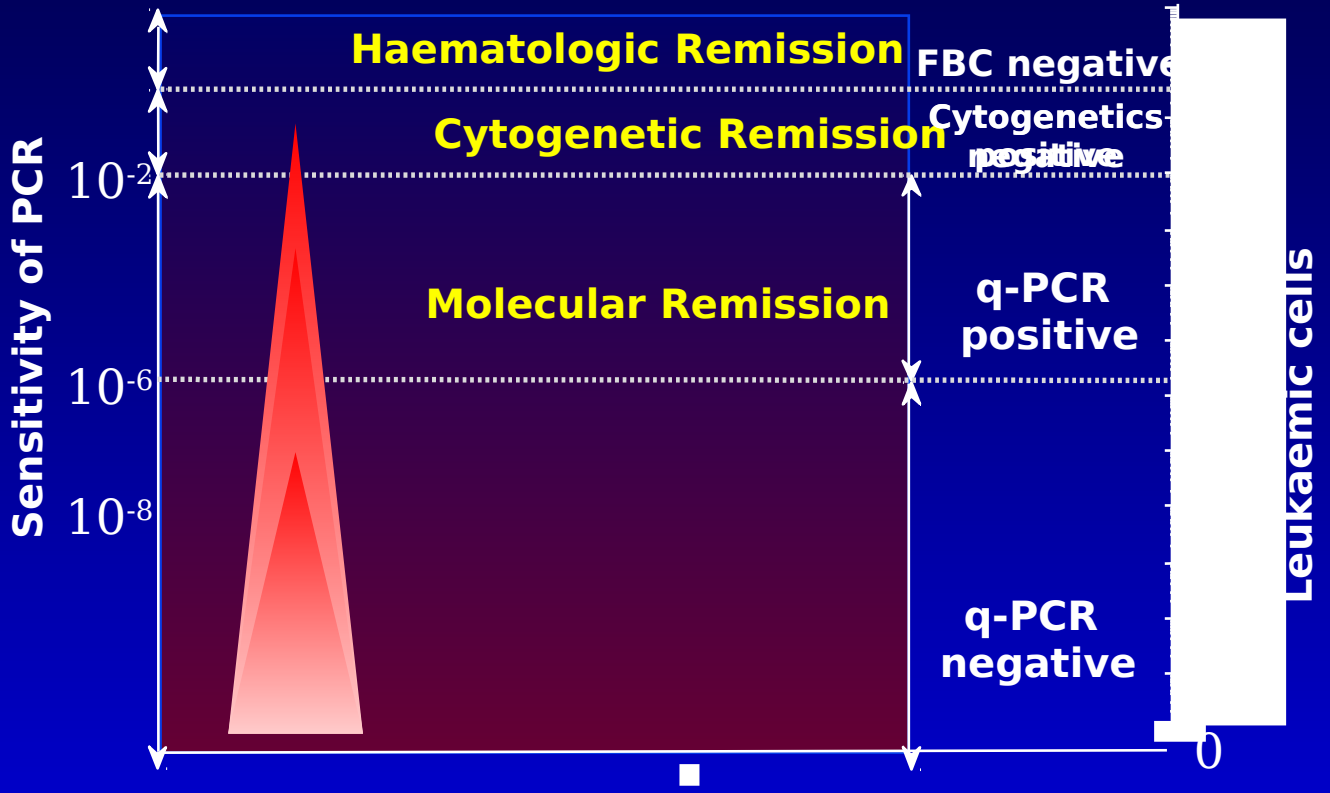




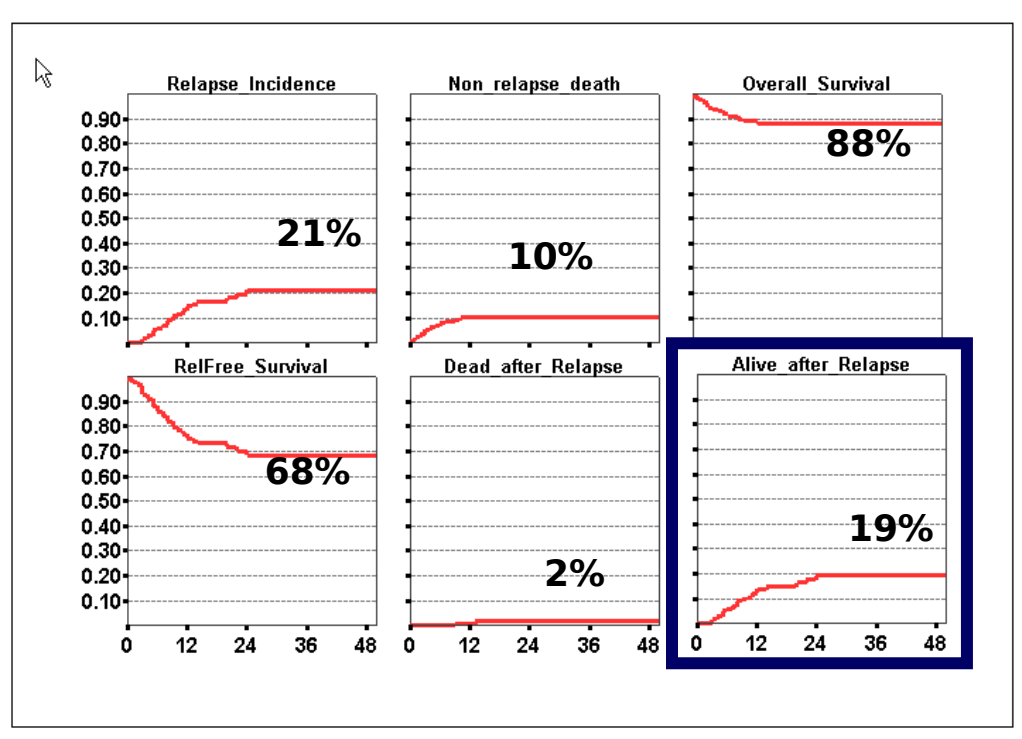




Response after Allogeneic SCT for CML

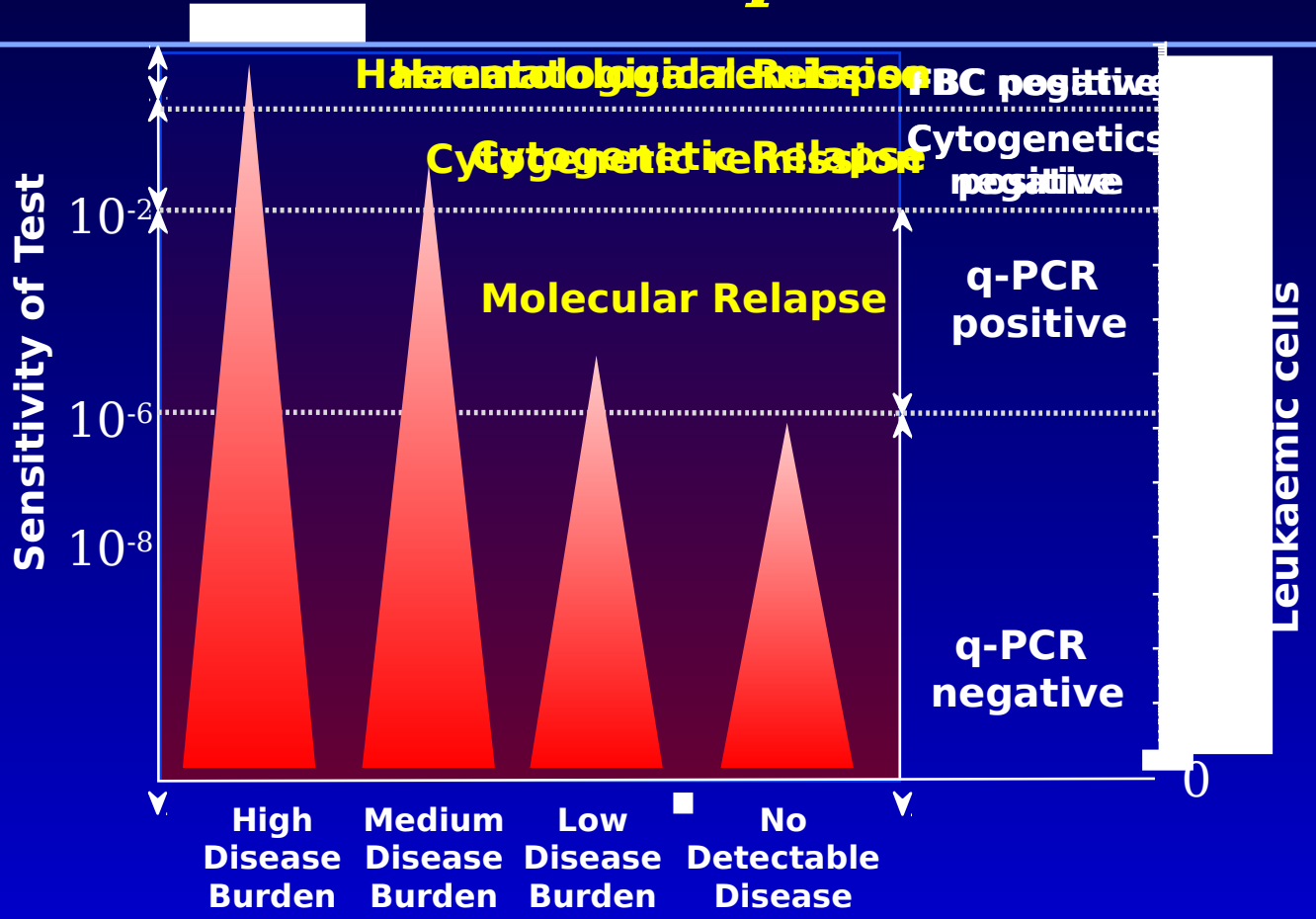


Complications after SCT for CML

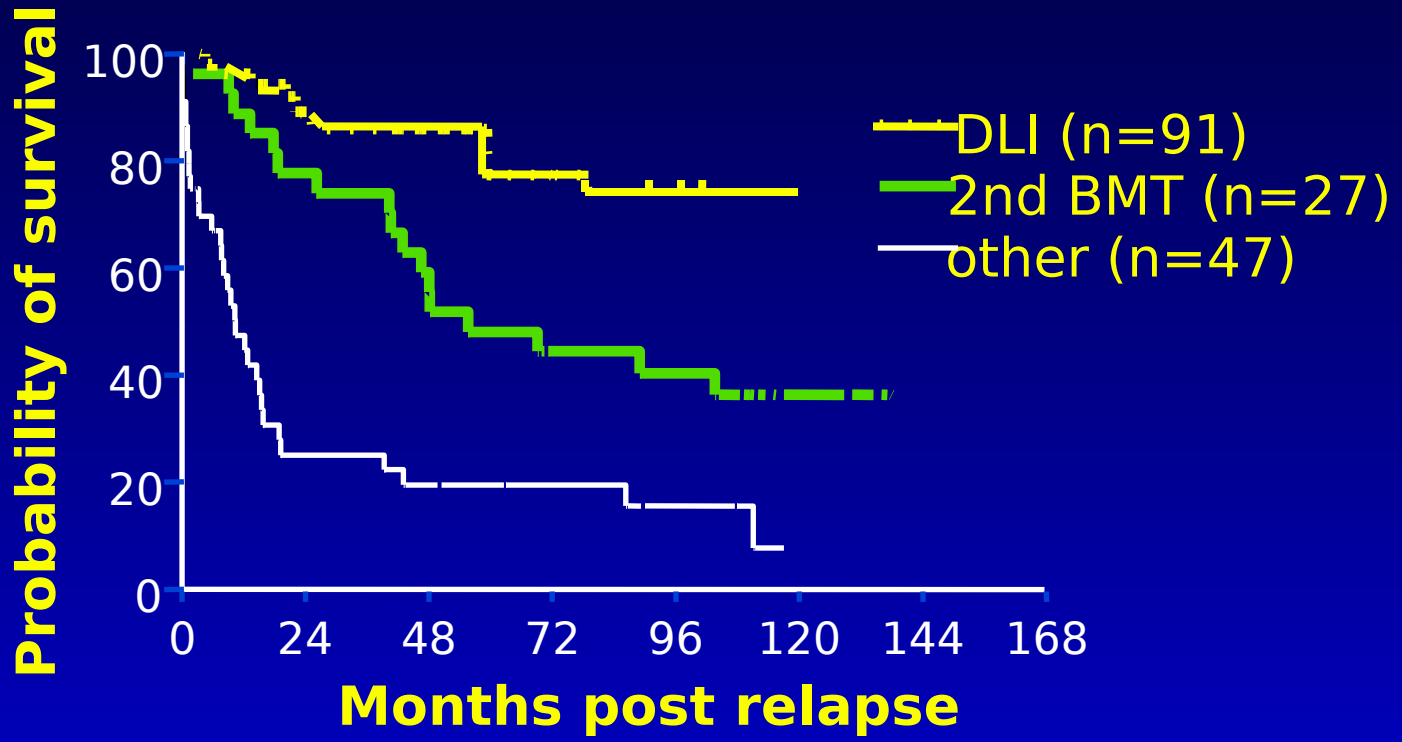


D Heim (CLWP-EBMT) Unpublished data

Detection of Relapse



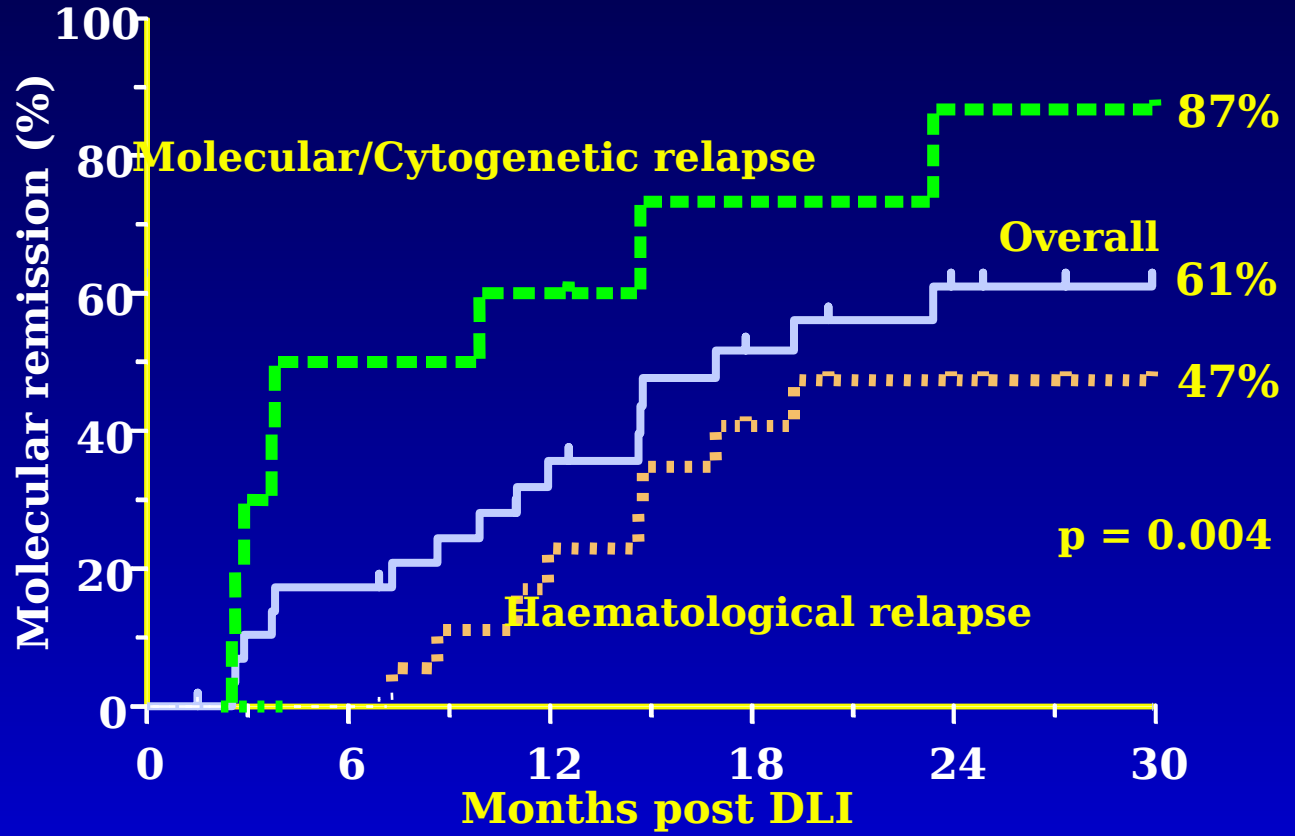
Treatment of relapse

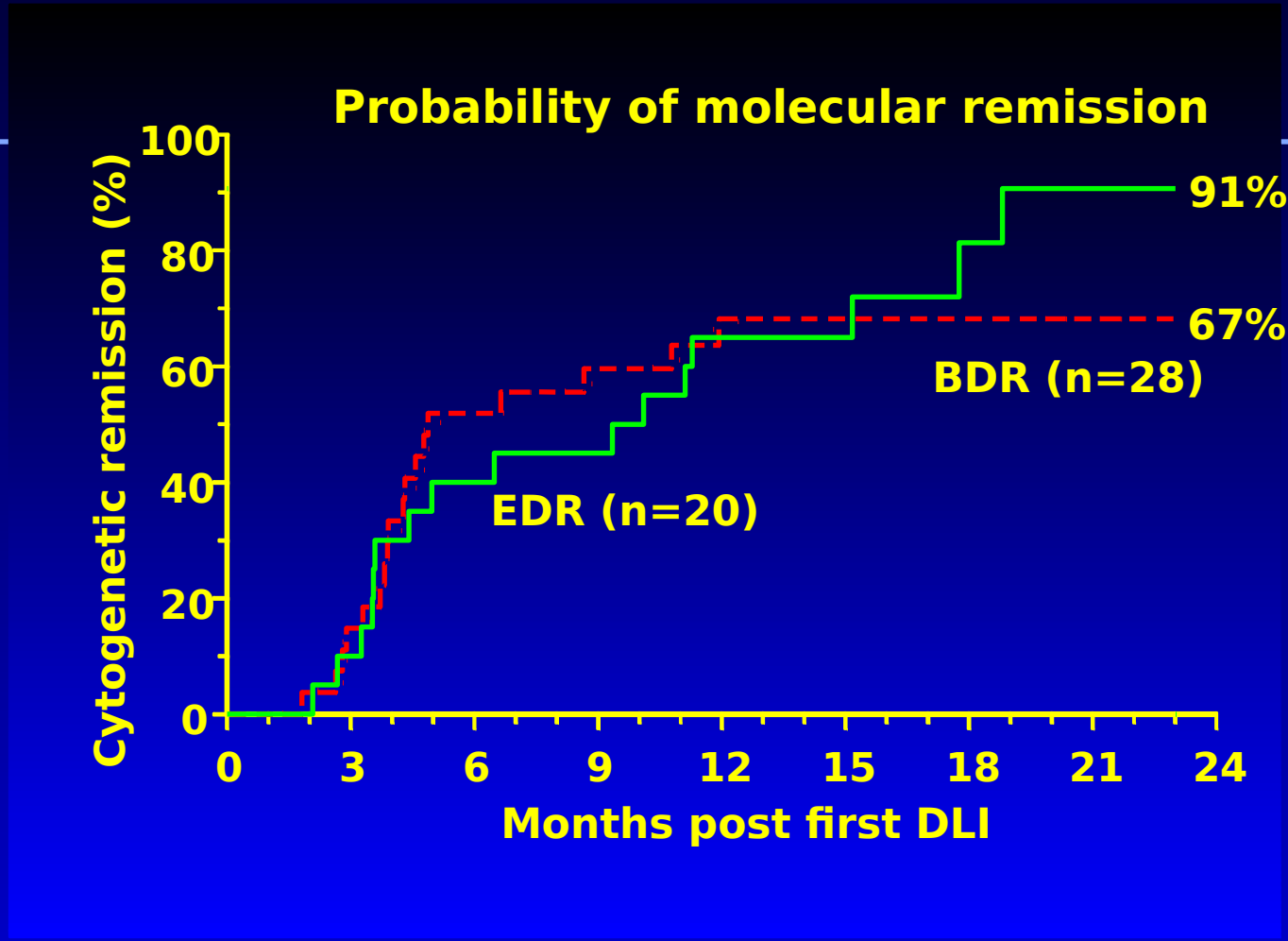


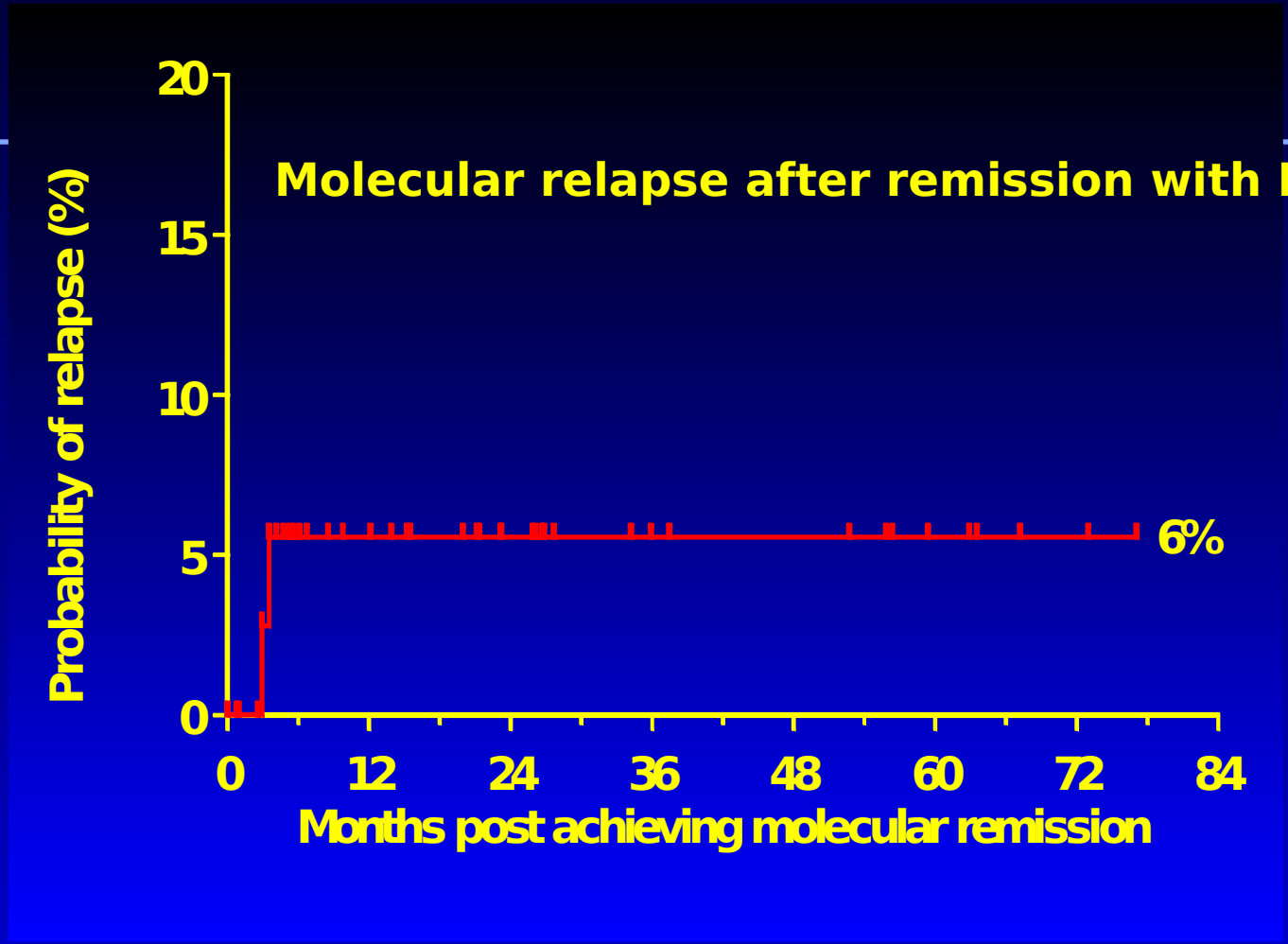
Results of DLI in CML

	Overall	Early	Late
No. patients	271	188	83
GvHD	45	47	40
Myelosuppression	19	18	21
Cytogenetic Response	69	80	43
Survival at 3y	67	80	38
Failure free survival	53	66	25
DLI- related mortality	15	12	21

Molecular response to DLI




Probability of molecular remission
Cytogenetic remission (%)
100
80
60
40
20
0
0
3
6
9
12
15
18
21
24
Months post first DLI
91%
67%
BDR (n=28)
EDR (n=20)

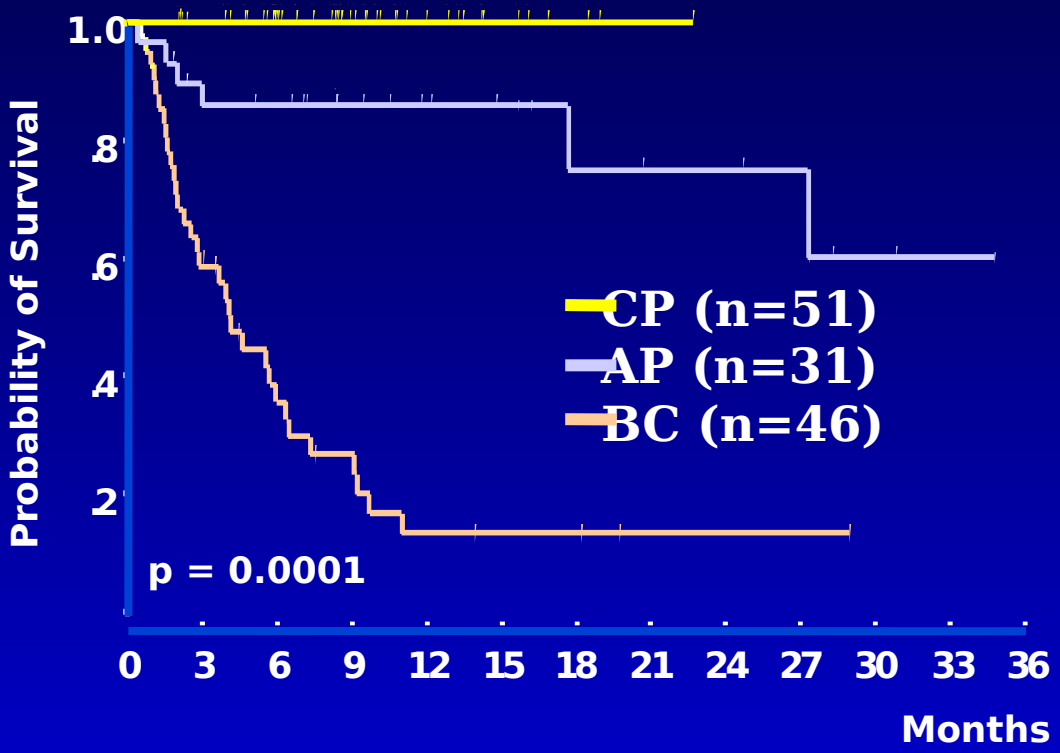

Molecular relapse after remission with DLI
Probability of relapse (%)
20
15
10
5
0
6%
0
12
24
36
48
60
72
84
Months post achieving molecular remission

Incidence of GHVD after DLI (n=500)

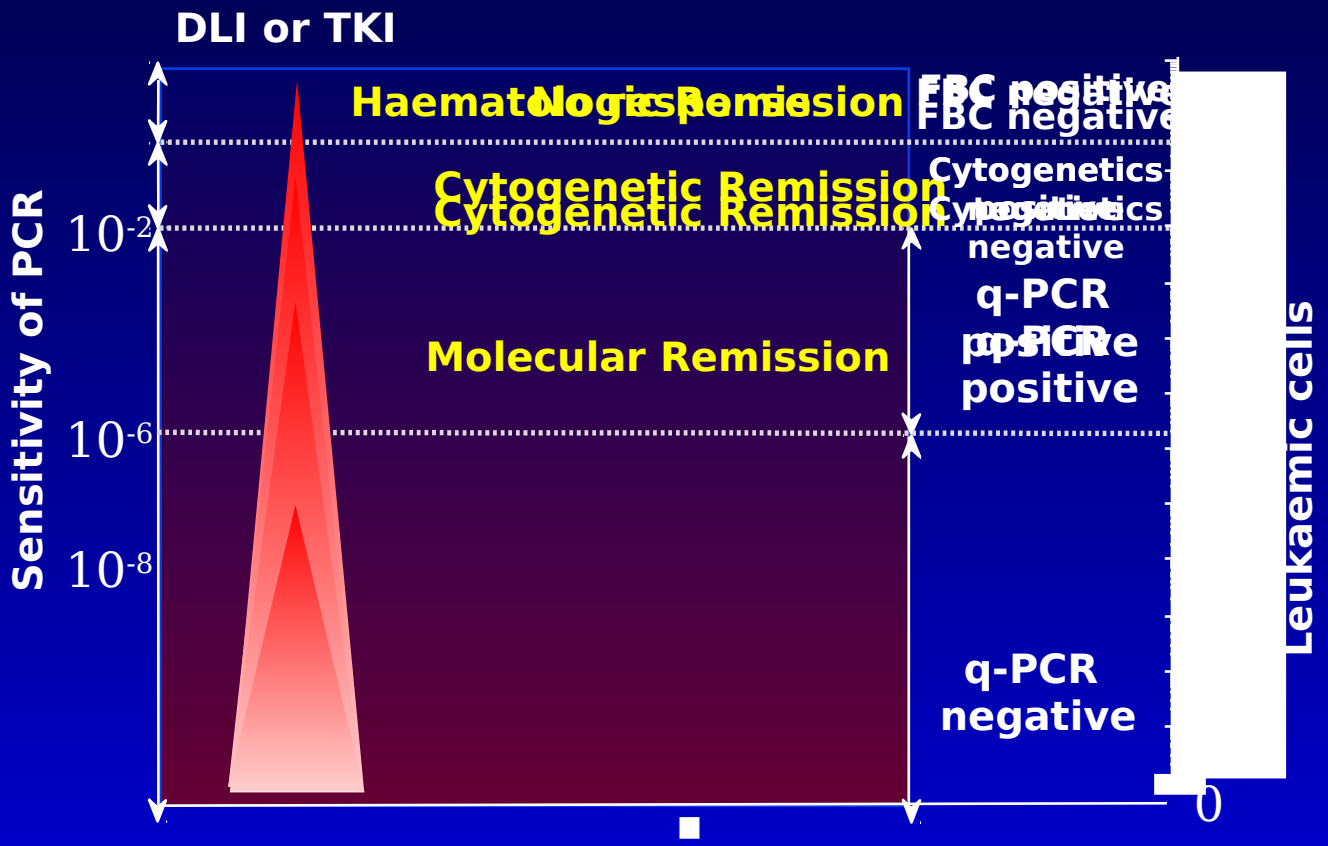
		GvHD post DLI	
		No	Yes
Response*	No	24%	8%
	Yes	32%	36%

*Molecular and/or cytogenetic remission

Imatinib in relapse: overall survival



Response after Relapse



MUITO OBRIGADO!