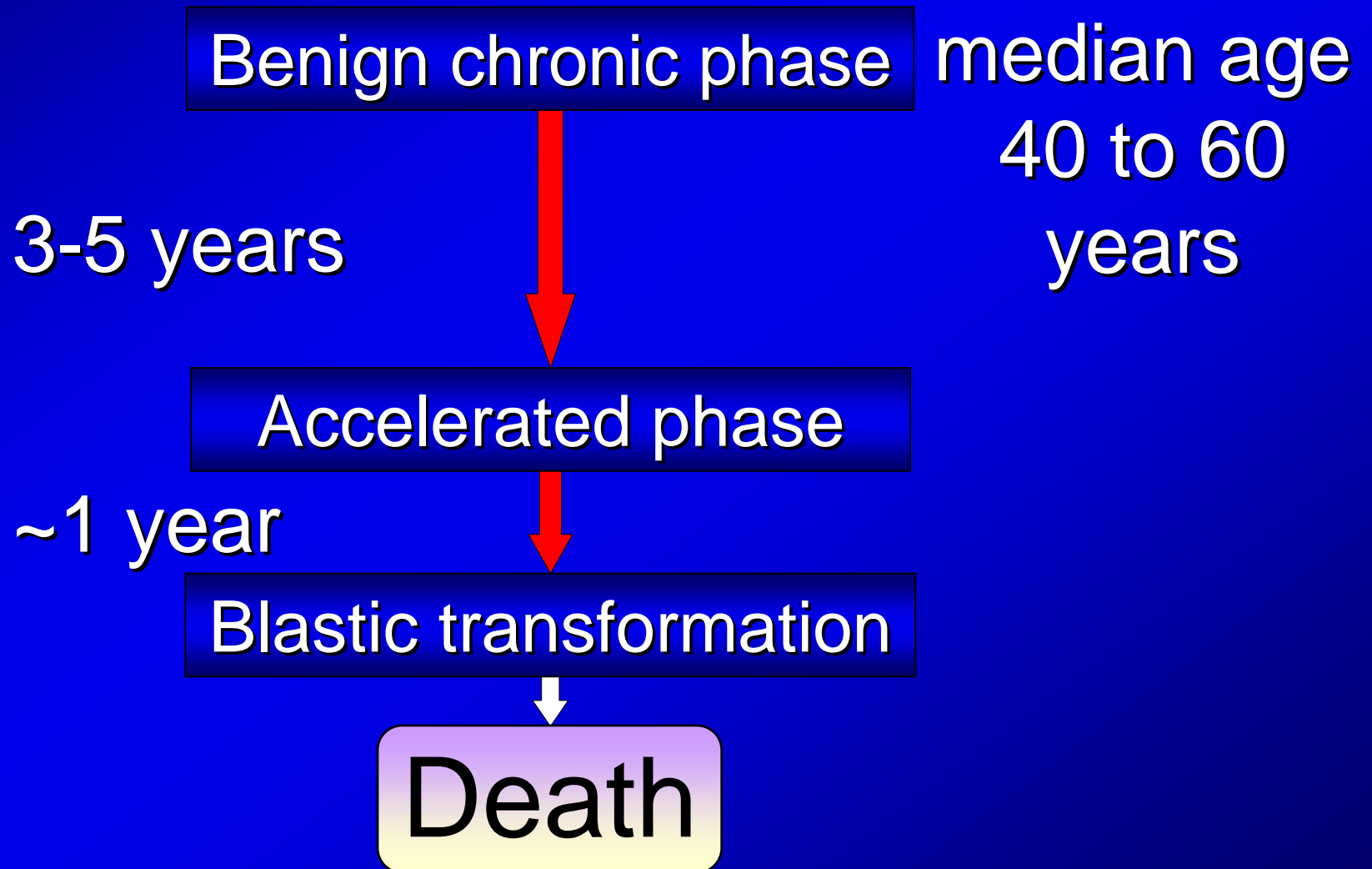


Chronic Myeloid Leukemia

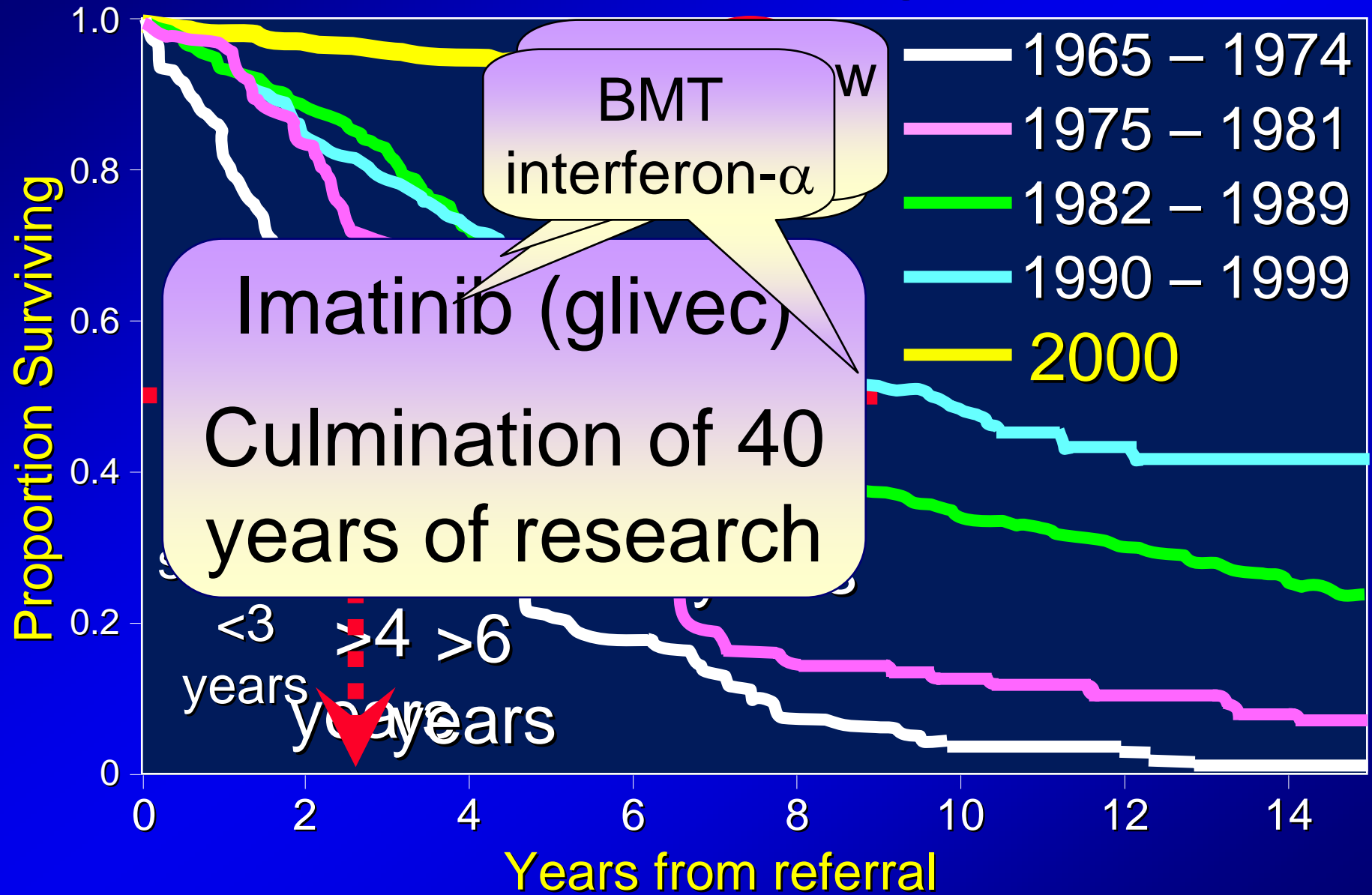
A/Prof Susan Branford, PhD
Molecular Pathology
SA Pathology
Adelaide, South Australia

Chronic myeloid leukaemia (CML)

Natural course of the disease



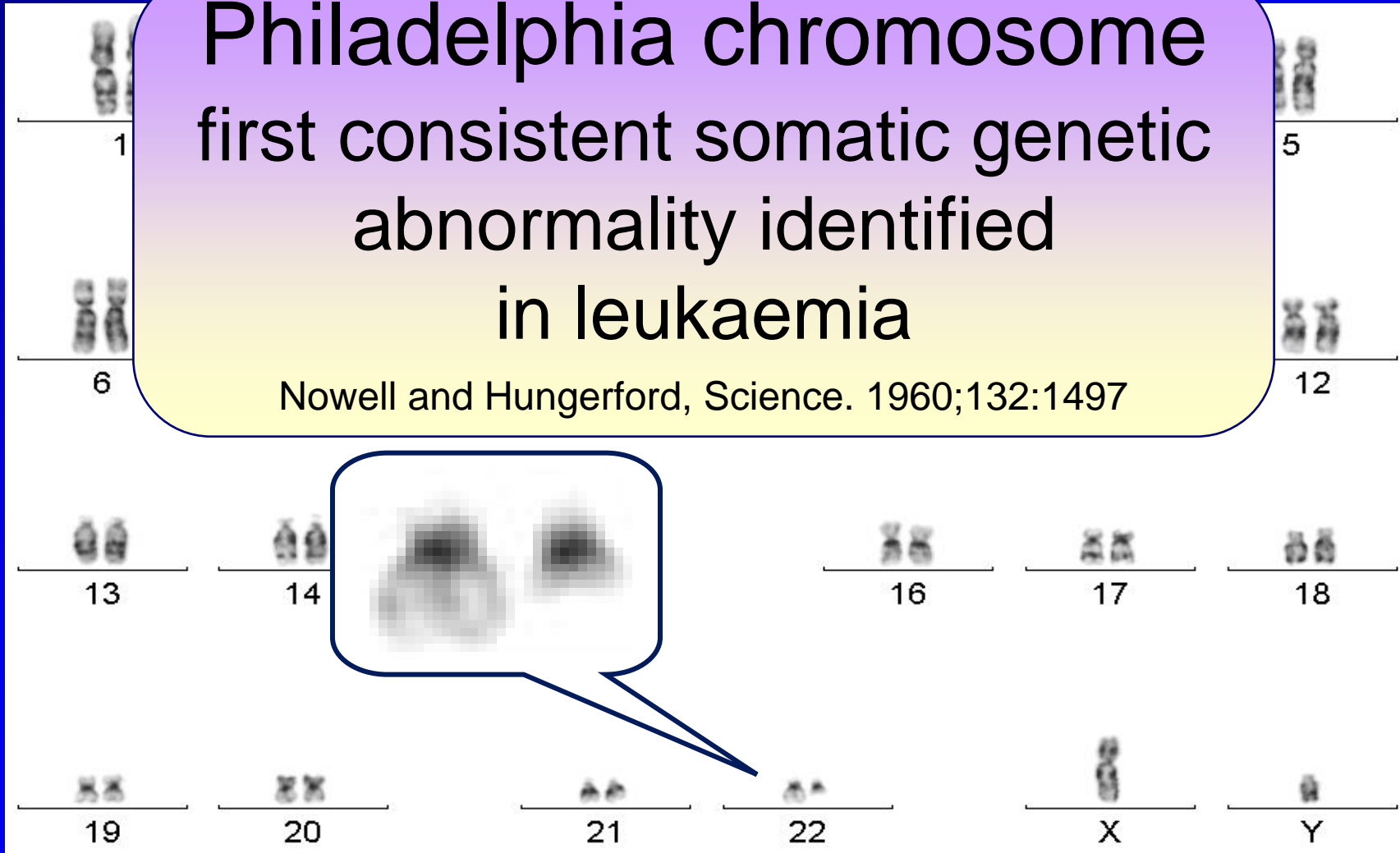
Survival after Diagnosis



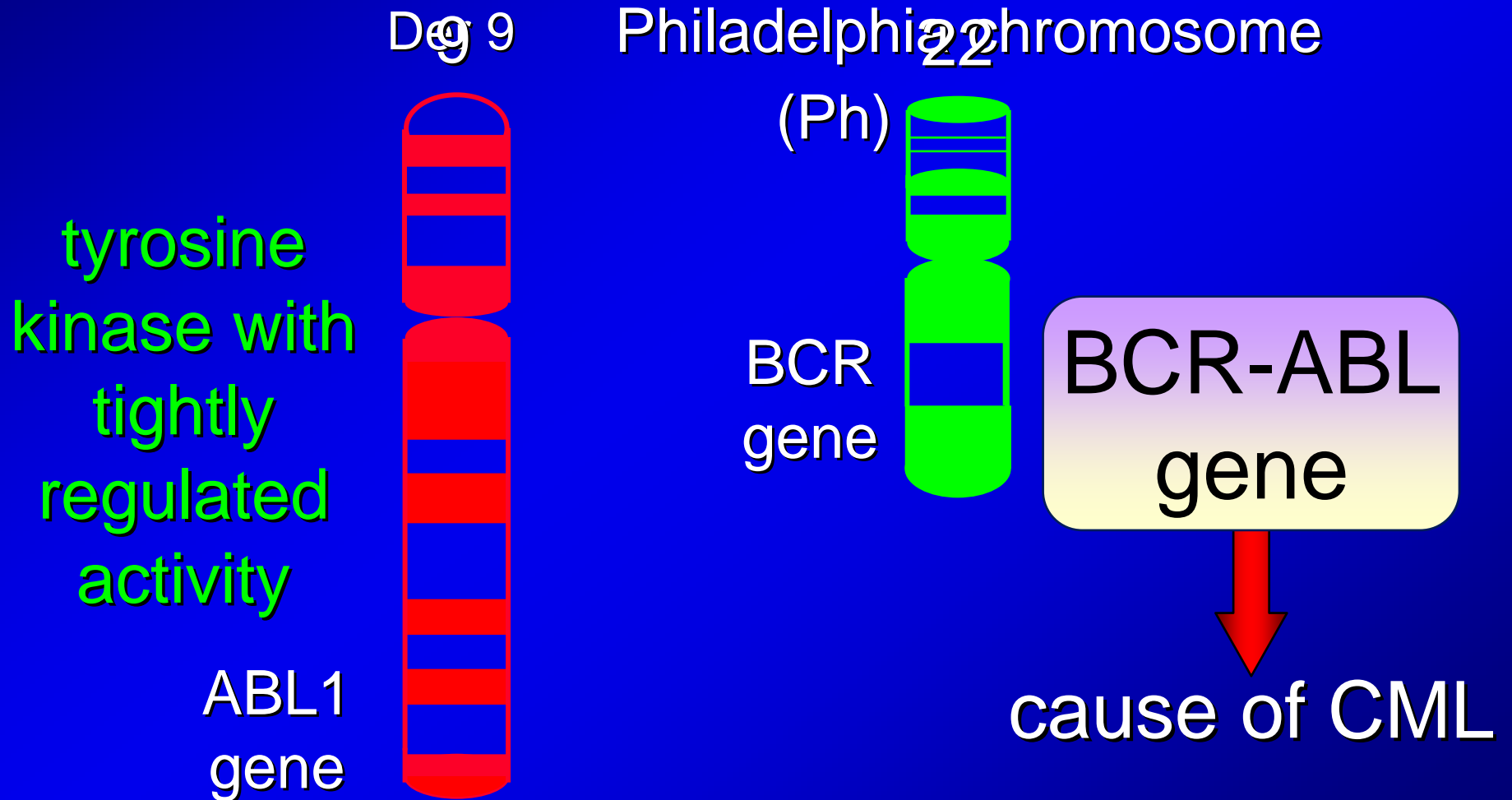
In 1960 a consistent chromosomal abnormality identified in CML patients

Philadelphia chromosome
first consistent somatic genetic
abnormality identified
in leukaemia

Nowell and Hungerford, Science. 1960;132:1497



1991 Philadelphia chromosome with resulted from a reciprocal translocation

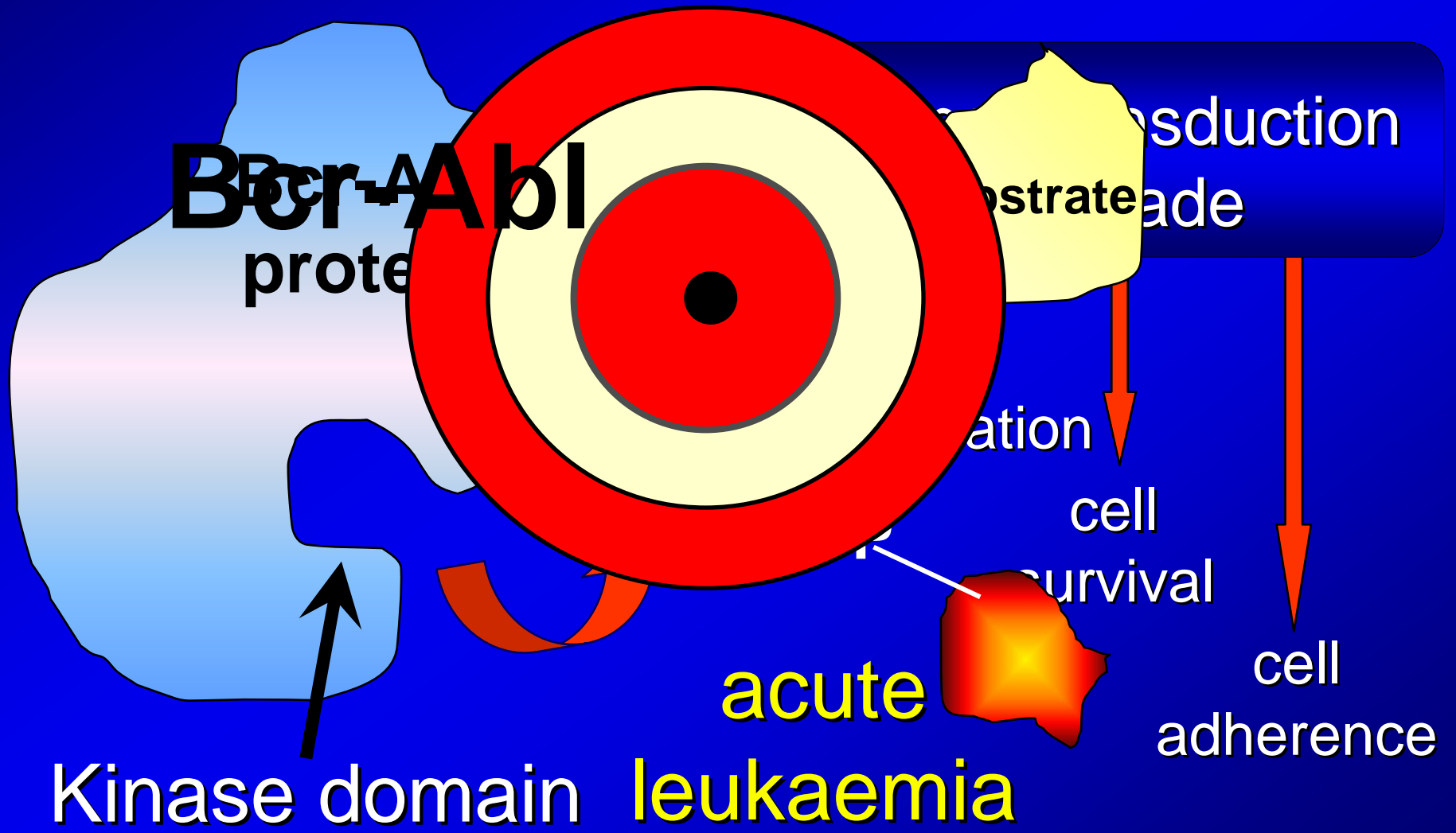


Daley et al. Science. 1990;247:824

De Klein et al. Nature. 1973;243:300-305

Groffen et al. GEM. 1984;1369-335, 0695:550

Mechanism of deregulated activity of Bcr-Abl



Targeted Therapy

1. Small molecule drugs
 - New generation of cancer drugs designed to enter and diffuse into a cell and act on targets within the cell
 - critical role in tumour growth or progression
 - imatinib
2. Monoclonal antibodies
 - The identification of appropriate targets is based on a detailed understanding of the molecular changes underlying the cancer
 - most cannot penetrate the cell's plasma membrane and are directed against targets on the cell surface
 - The optimal targets are ideally those that are present only in tumour cells
 - trastuzumab – treatment of HER2-positive breast cancer

Essential Requirements of Targets

- should be measurable in the laboratory
- should be present in easily accessible tissue
- ideally the assay should be simple to perform and reproducible
- should be sensitive and specific

Bcr-Abl protein

Substrate

ATP

Imatinib

measurement of the target should correlate with clinical outcome

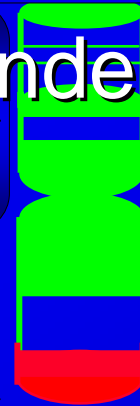
BCR-ABL Cytogenetic and molecular response

cytogenetic and molecular response
correlate with clinical outcome

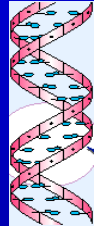
International standardisation of quantitative

Cytogenetic analysis of bone marrow
PCR methods is underway

Molecular analysis of
peripheral blood

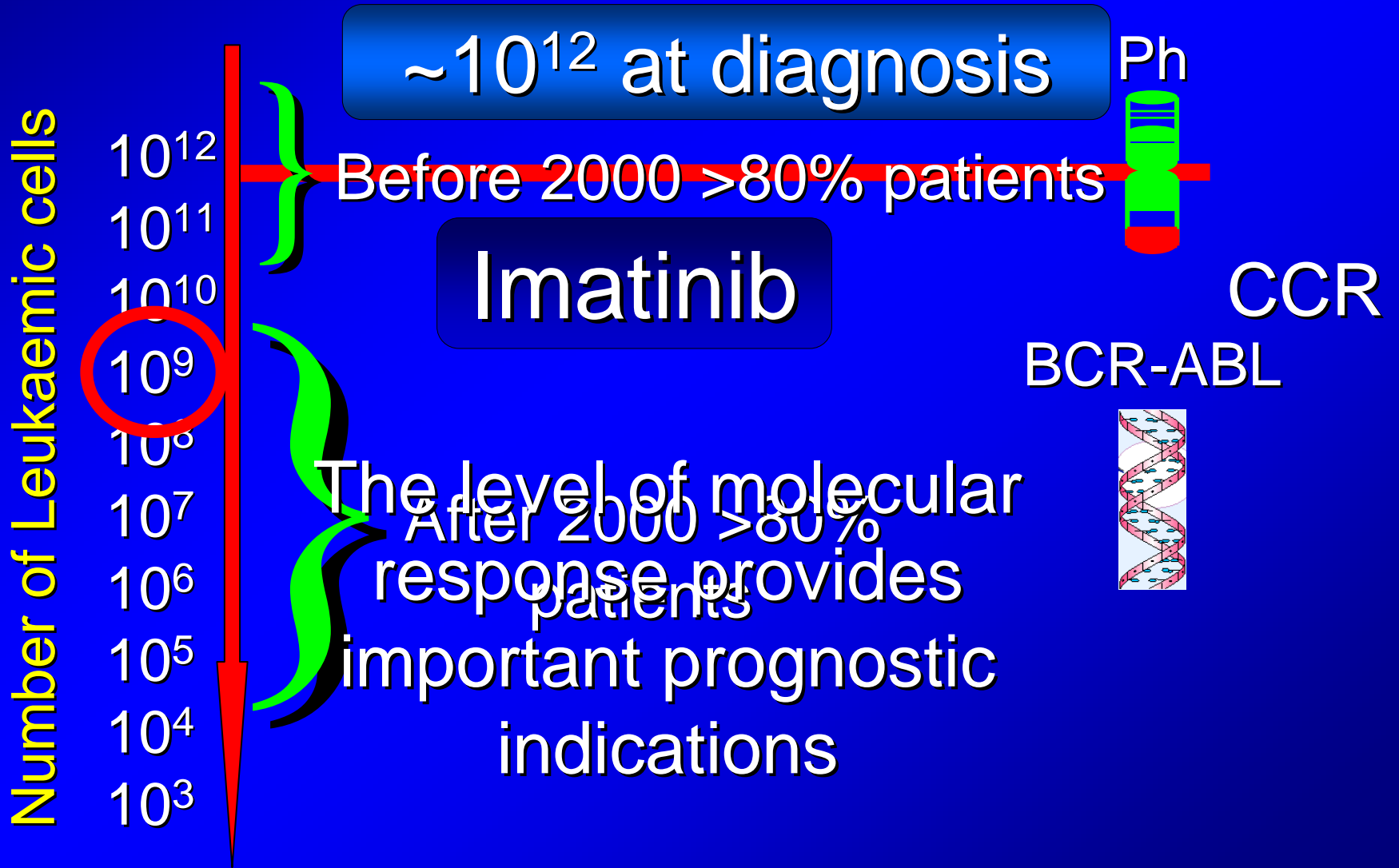


BCR-ABL
gene



Approximately 300-times more sensitive
than cytogenetic analysis

Complete cytogenetic response associated with prolonged survival >10 years significantly prolonged survival



Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells

Druker et al. Nature Med. 1996;2:561

1998 First patients were treated with imatinib

this compound may be useful in the treatment of bcr-abl positive leukemias
chronic phase - resistant to or intolerant of interferon- α

accelerated phase

blast crisis



May
2001

MAY 28, 2001

TIME

THERE IS NEW **AMMUNITION**
IN THE WAR AGAINST

CANCER.

THESE ARE THE BULLETS.

Revolutionary new pills like **GLIVEC**
combat cancer by targeting only the
diseased cells. Is this the breakthrough
we've been waiting for?



www.timeeurope.com AOL Keyword: TIME

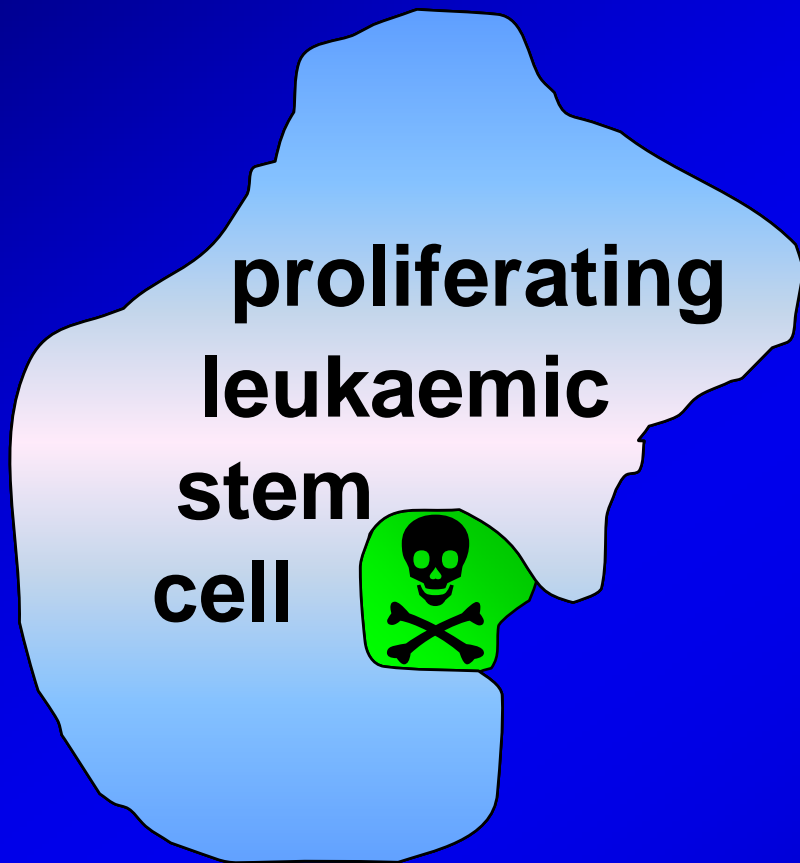
Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells

December 20th 2002

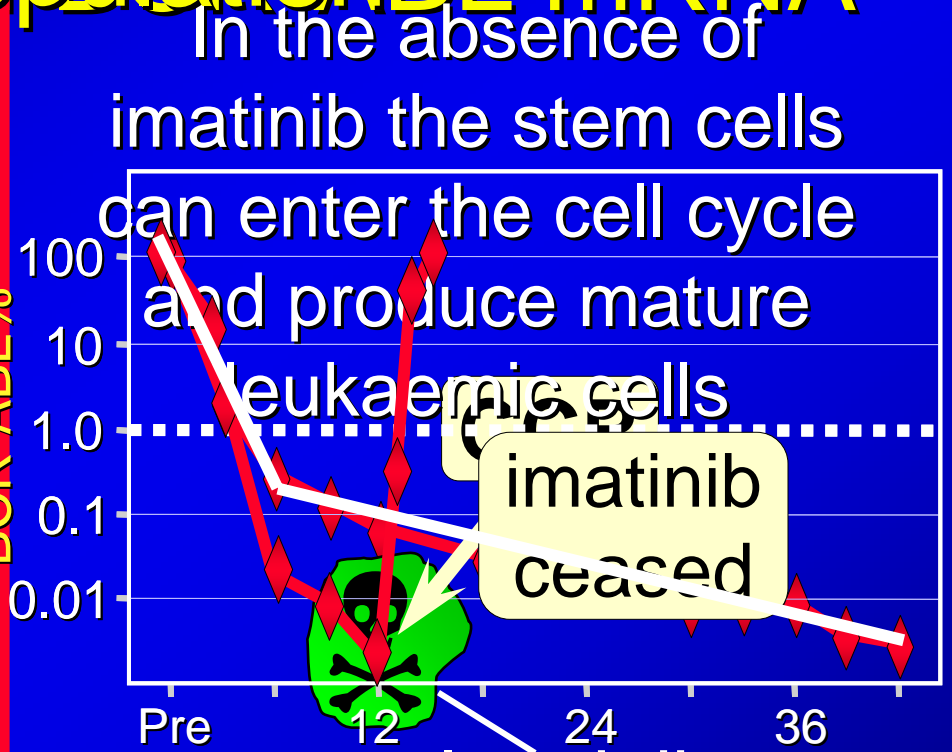
1
FDA granted
accelerated approval of
imatinib for the
treatment of newly
diagnosed CML
nib

2000
2000 Newly diagnosed patients were treated

Rapidly repopulated the leukaemia by a reduced population of ABL mRNA



BCR-ABL%

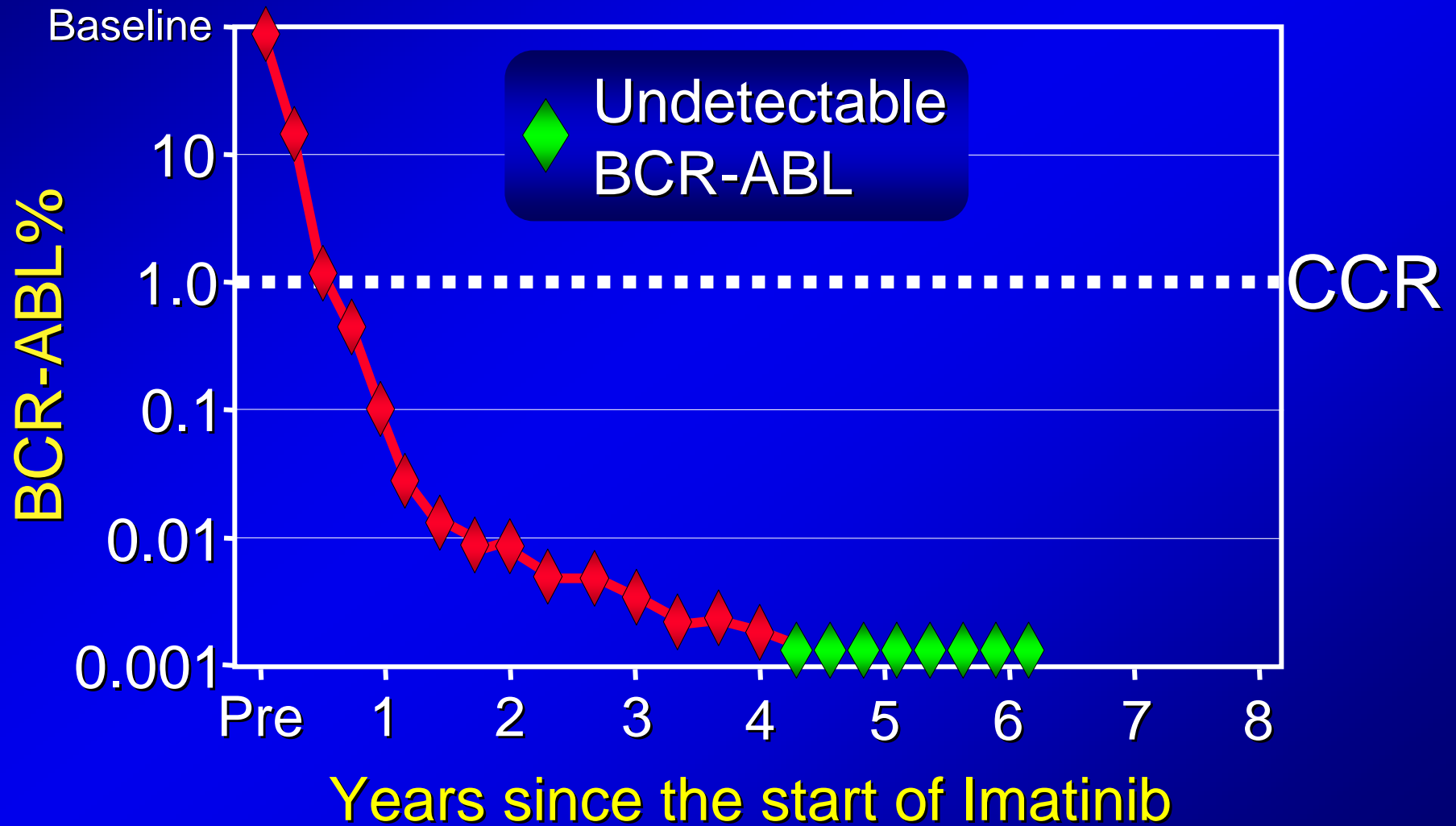


Months from imatinib start
apoptotic effect

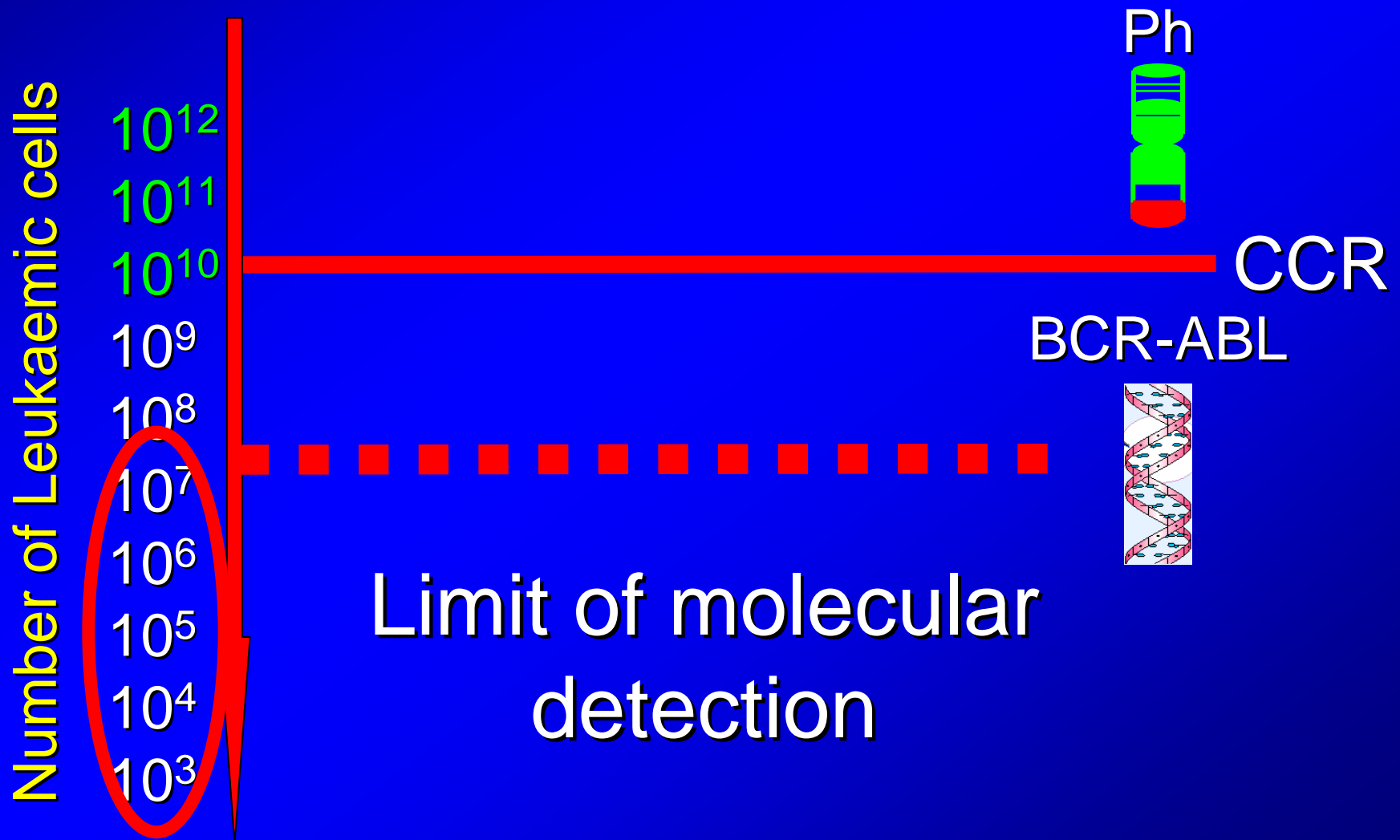
Will all patients have to spend the rest of their lives on kinase inhibitor therapy?

Possibly not

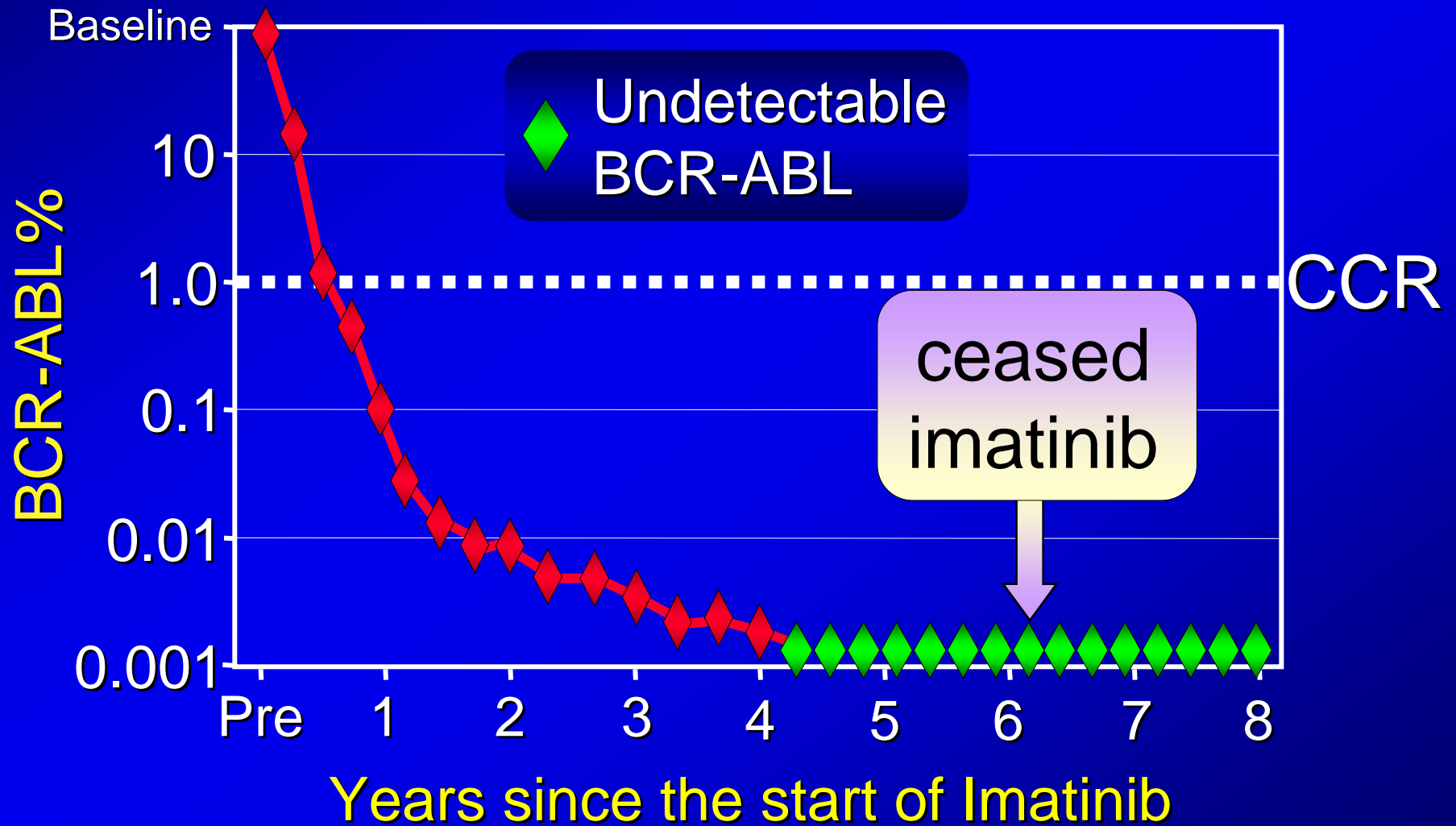
Some patients with sustained undetectable BCR-ABL maintain response



Relationship between response level and number of leukaemic cells



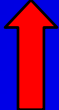
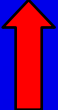
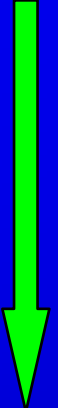
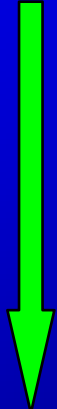
Some patients with sustained undetectable BCR-ABL maintain response



Imatinib resistance
remains a problem
for a minority of
patients

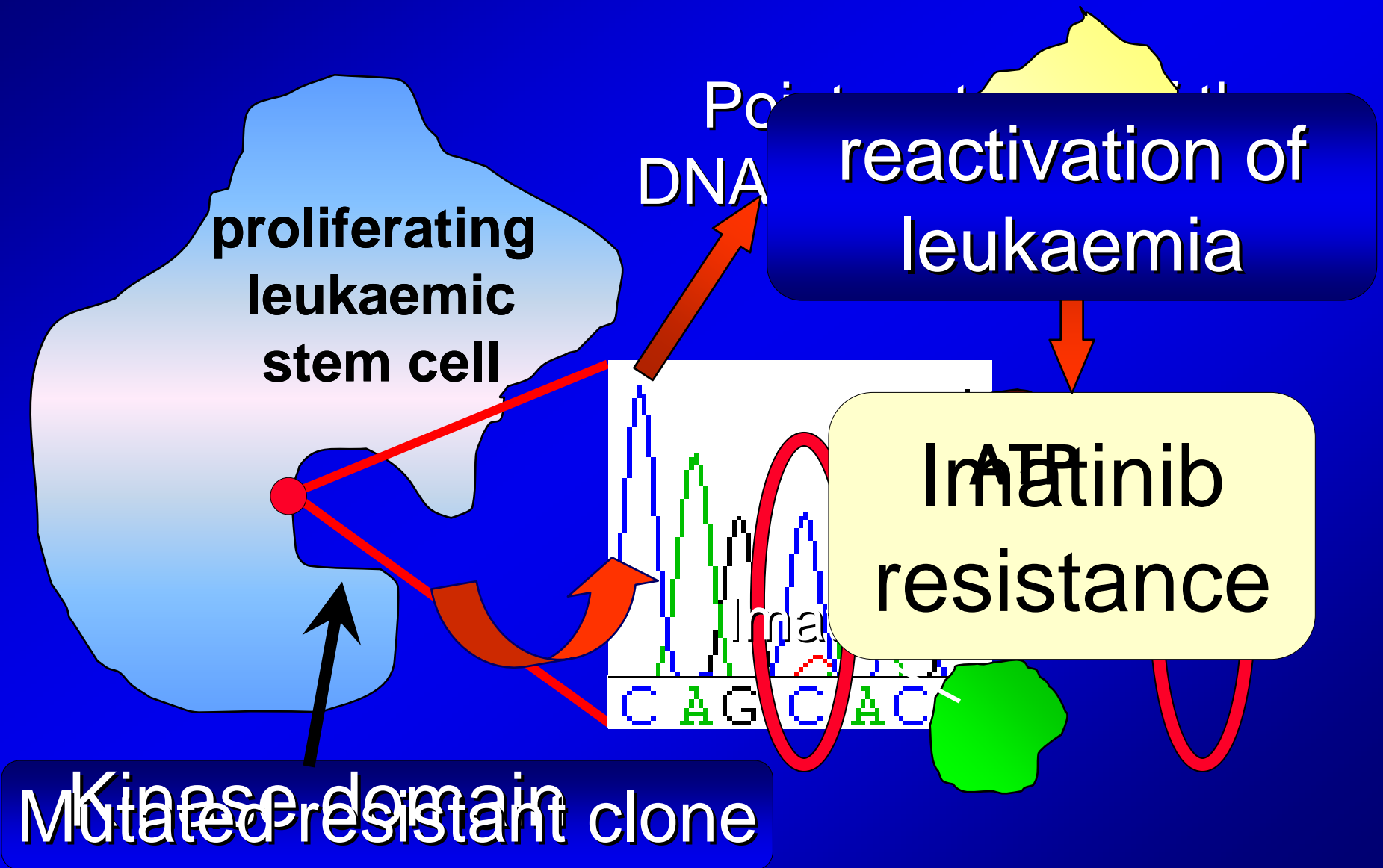
~30% of first-line imatinib treated
patients cease imatinib

Newly diagnosed patients treated with imatinib

<u>Year</u>	<u>Progression*</u>	<u>AP/BC</u>
1st	3.4%	1.5%
2nd	 7.5%	 2.8%
3rd	4.8% 	1.6% 
4th	1.5%	0.9%
5th	0.9%	0.6%
6th	0.4%	0%

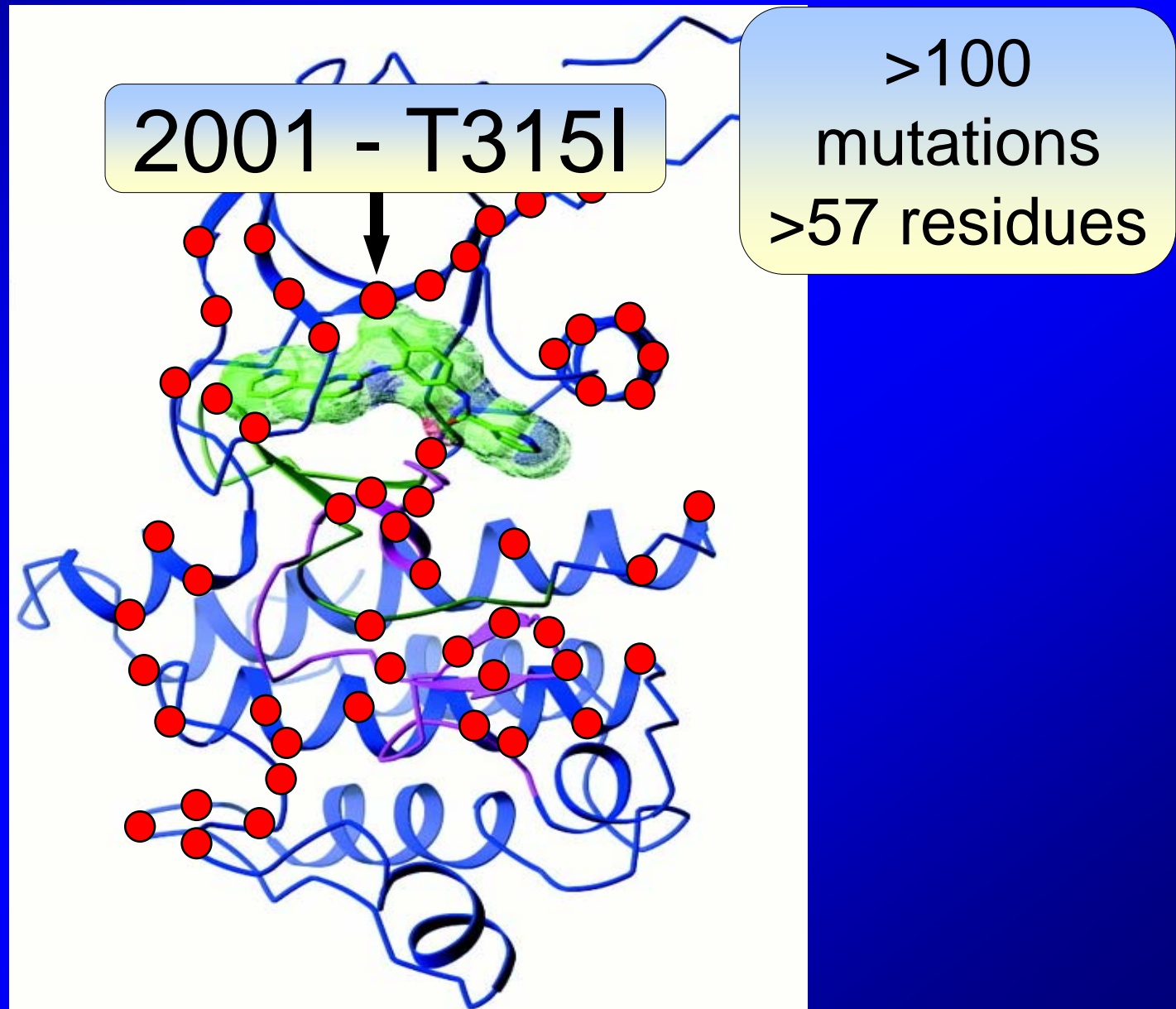
* All deaths, loss of response including AP/BC

Main mechanism of imatinib resistance



**BCR-ABL mutations
occur in 60 to 80%
of patients with
imatinib resistance**

BCR-ABL kinase domain in complex with imatinib



Gorre et al,
Science
2001;293:876

BCR-ABL

Imatinib

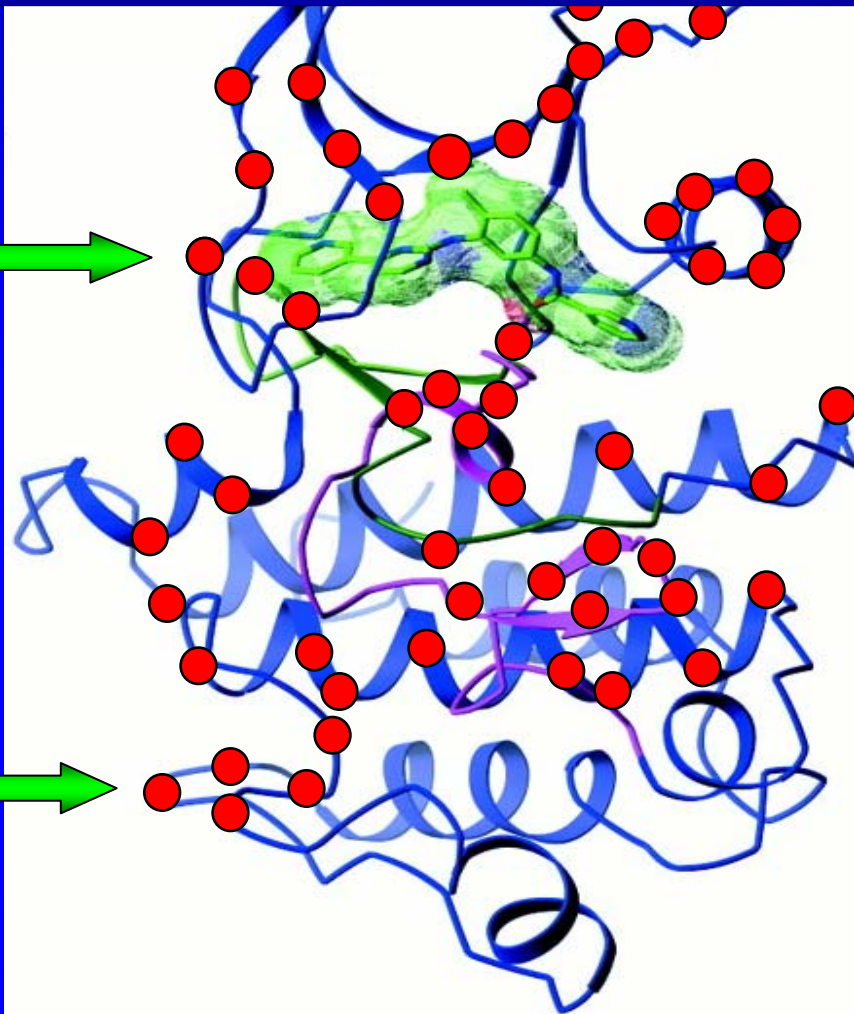
Can mutants alter transformation potency?

>100 mutations

>57 residues

P-loop
high level
resistance

may
respond
to an
increased
dose



Branford et al,
Blood; 2003:
102,276

Nicolini et al, Leuk;
2006:20,1061

Soverini et al,
CC Res; 2006:
12,7374

Khorashad et al,
JCO;
2008:28,1

Altering the phenotype of
cancer by point mutation is
not unusual

mutations within the p53 gene
are common in diverse cancers

```
graph TD; A[mutations within the p53 gene are common in diverse cancers] --> B[1,300 point mutations in one region]; B --> C[gain/loss of function]; B --> D[cancer prognosis]; B --> E[response to drug treatment];
```

1,300 point mutations
in one region

gain/loss of
function

cancer
prognosis

response to
drug treatment

Three *in vitro* studies suggest that BCR-ABL mutations alter kinase function and confer unanticipated biological properties

Should consider each mutation as a unique protein with altered biological properties relative to wild-type BCR-ABL

Griswald et al, Mol & Cell Biol;2006:26,6082

Scaggs et al, PNAS;2006:103,19466

Shah et al, J Clin Invest;2007:117,2562

Problem of resistance and mutations has led to the development of second generation inhibitors

Dasatinib
(Sprycel)

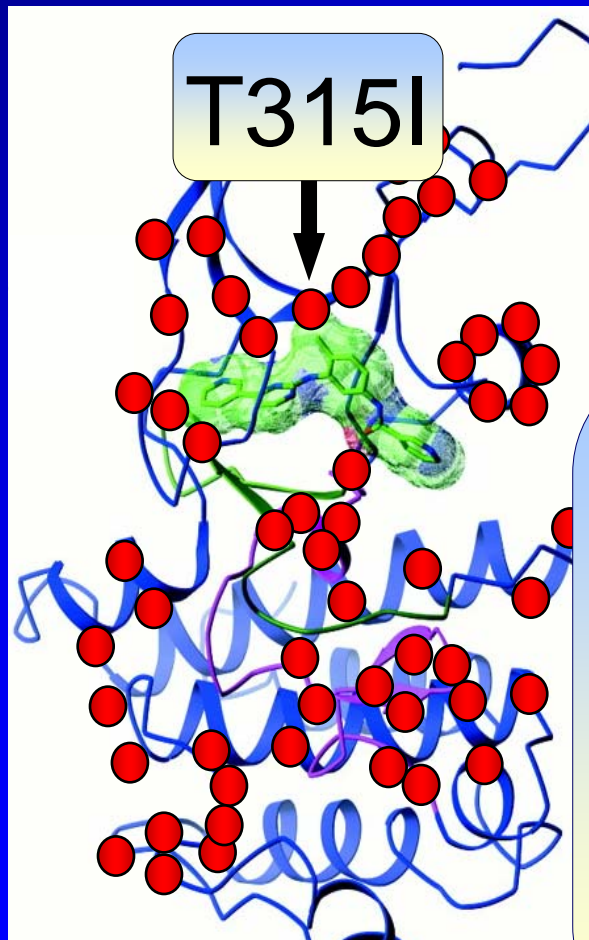
>100 times
more potent
than imatinib

Nilotinib
(Tasigna)

>20% times
more potent
than imatinib

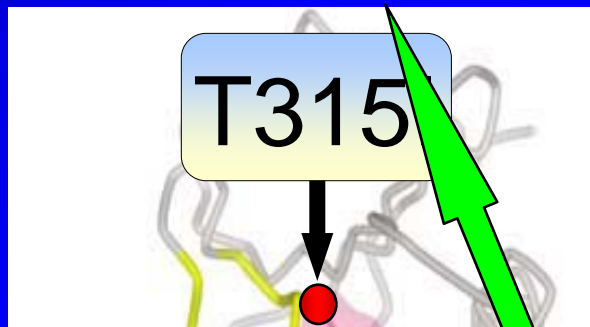
Activity of more potent inhibitors against the imatinib resistant mutations

imatinib

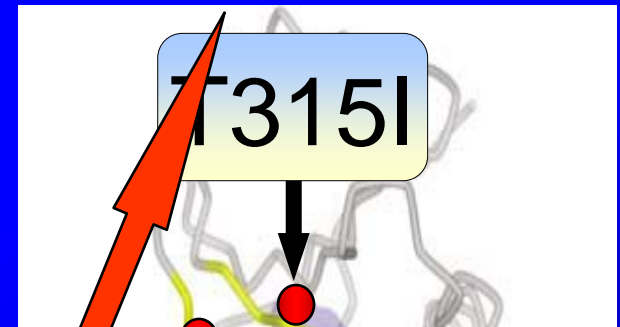


>100 mutations

nilotinib



dasatinib



In
re
the

**Main mechanism of
resistance:
BCR-ABL mutations**

Burgess et al, PNAS. 2005;102:3395
Bradeen et al, Blood. 2006;108:2322
Von Bubnoff et al, Blood. 2006;102:1328
Ray et al, Blood. 2007;109:5011

Problem of resistance and mutations has led to the development of second generation inhibitors

Dasatinib
(Sprycel)

Nilotinib
(Tasigna)

June 28, 2006

October 29, 2007

accelerated approval
for imatinib resistance
of intolerance

accelerated approval
for imatinib resistance
of intolerance

approximately 40% of
chronic phase patients achieve CCR

What will the
prognosis be for
patients diagnosed
with CML in the
future?

Complete Cytogenetic Response newly diagnosed CML by treatment

Percent CCR

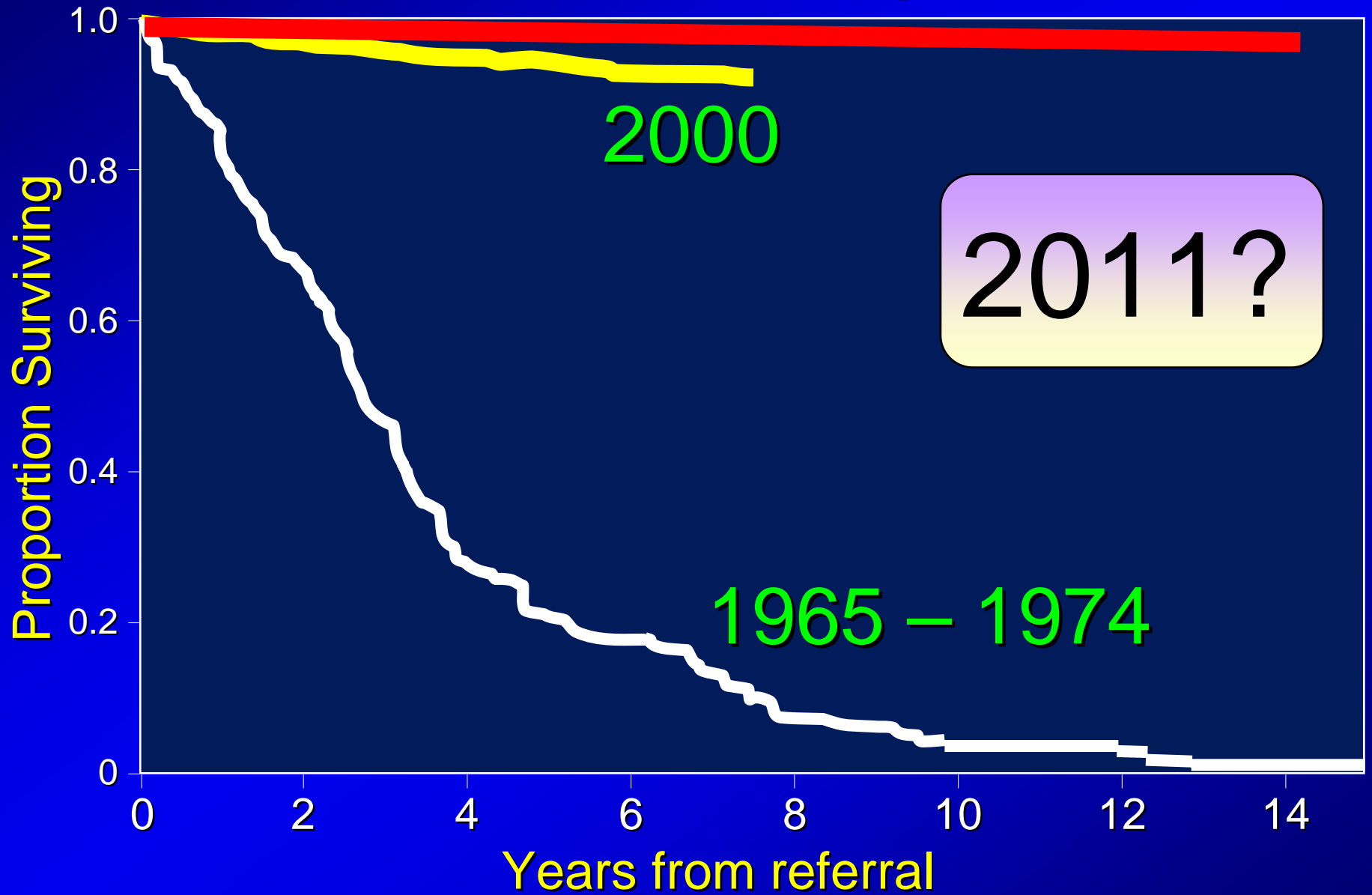
Parameter	Imatinib N=50	Nilotinib N=48	Dasatinib N=45
<u>3 months</u>	37	93	78
6 months			
12 months			

Delayed achievement of CCR is associated with increased risk of disease progression

Quintás-Cardama et al. Blood. 2009;113:6315.

Cortes et al, ASH abstracts;2008:112,182 and 442

More Survival After Diagnosis?



Targeted therapies for other cancers

- These initiatives have relevance for treating and monitoring other targets implicated in cancer
 - JAK2 inhibitors have entered clinical trial for patients with myeloproliferative disorders
 - Erlotinib for non-small cell lung cancer for selected patients
- Tipifarnib – preclinical studies were promising
 - failed as a single agent for most solid cancers

Targeted therapies for other cancers

- Appropriate selection of the patient population is critical
 - an unselected approach has the potential for discarding valuable drugs
- Appropriate clinical interpretation of response to targeted therapies will rely on:
 - confirmation of the presence of the target in a patient
 - standardised molecular monitoring
 - characterisation of mechanisms of resistance