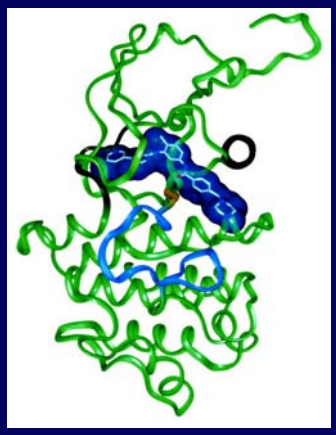
Imatinib (Gleevec) as a Paradigm of Targeted Cancer Therapies



OHSU CANCER INSTITUTE

Brian J. Druker, MD

Chronic Myeloid Leukemia (CML) and Imatinib

- Clinical description of CML
- Molecular pathogenesis of CML
- Development of imatinib
  - Preclinical and clinical

Historical Perspective on CML

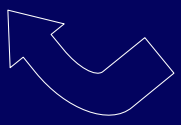
1845	1985	2001
First description of CML	Bcr-Abl	Specific therapy for CML

Historical Perspective on CML

1845 — **1985** — **2001**

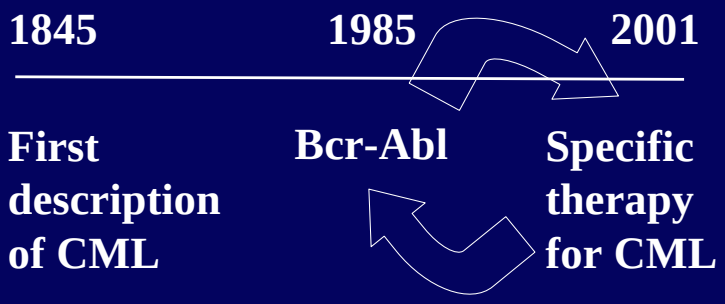
First description of CML

Bcr-Abl



Specific therapy for CML

Historical Perspective on CML



Clinical Description of CML

LEUCOCYTHEMIA,

OR

WHITE CELL BLOOD,

IN RELATION TO THE

PHYSIOLOGY AND PATHOLOGY OF THE LYMPHATIC GLANDULAR SYSTEM.

BY JOHN HUGHES BENNETT, M.D., F.R.S.E.,

Weißes Blut.

Außer sehr wenig rothen Blutkörperchen bestand der ungleich größere Theil aus denselben farblosen oder weißen Körpern, die auch im normalen Blut vorkommen, nämlich kleinen, nicht ganz regelmäßigen Proteinmolecülen, größeren, körnigen, fetthaltigen, kernlosen Körperchen und granulirten Zellen mit einem rundlichen, hufeisenförmigen oder kleeblattartigen oder mit mehreren nayförmigen, distincten Kernen. Die größeren dieser Zellen hatten ein leicht gelbliches Aussehen. Das Verhältniß zwischen den farbigen und farblosen Blutkörperchen stellte sich hier ungefähr umgekehrt, wie im normalen Blut, indem die farblosen die Regel, die farbigen eine Art von Ausnahme zu bilden schienen. Wenn ich daher von weißem Blute spreche, so meine ich in der That ein Blut, in welchem die Proportion zwischen den rothen und farblosen (in Masse weißen) Blutkörperchen eine

eimischung fremdartiger che-
mente zu bemerken wäre.

ich
der Wissenschaft dadurch zu
int, nicht unwichtigen That-

Dr. Virchow.

Chronic Myeloid Leukemia (CML)

- **15 - 20 % of all leukemias**
- **1 - 2 cases per 100,000 per year**

Average age of onset is 50 to 60

CML

- **Tri-phasic illness**
  - **Chronic or stable phase**
    - »**95% at presentation**

CML

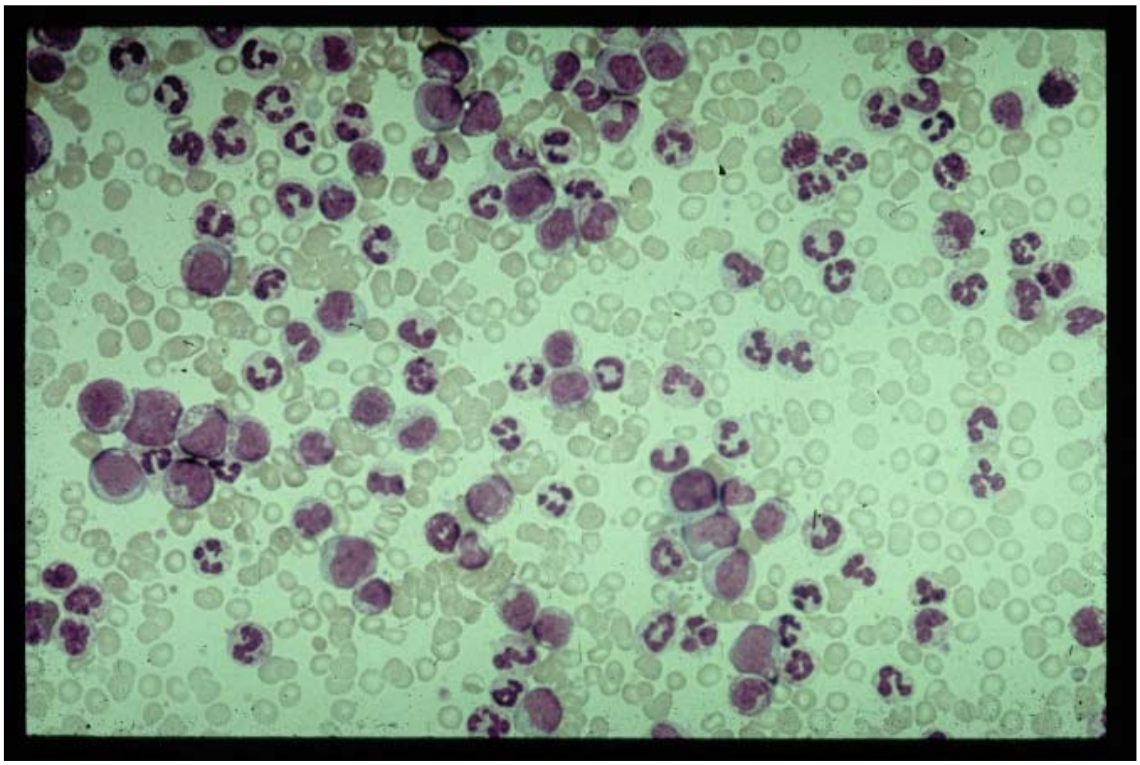
- Tri-phasic illness
  - Chronic or stable phase
    - 95% at presentation
  - Accelerated phase
  - Blast crisis

Advanced disease

Stable Phase of CML

- **Massive expansion of myeloid cells**
  - **White blood count**

    50 – 500,000/mm3
    - **Normal is 5 – 10,000/mm3**
- **Maturation and function of white cells is normal**



Stable Phase of CML

- **Median duration**
  - **Historically 4-6 years**
  - **Unknown with current, improved therapies**

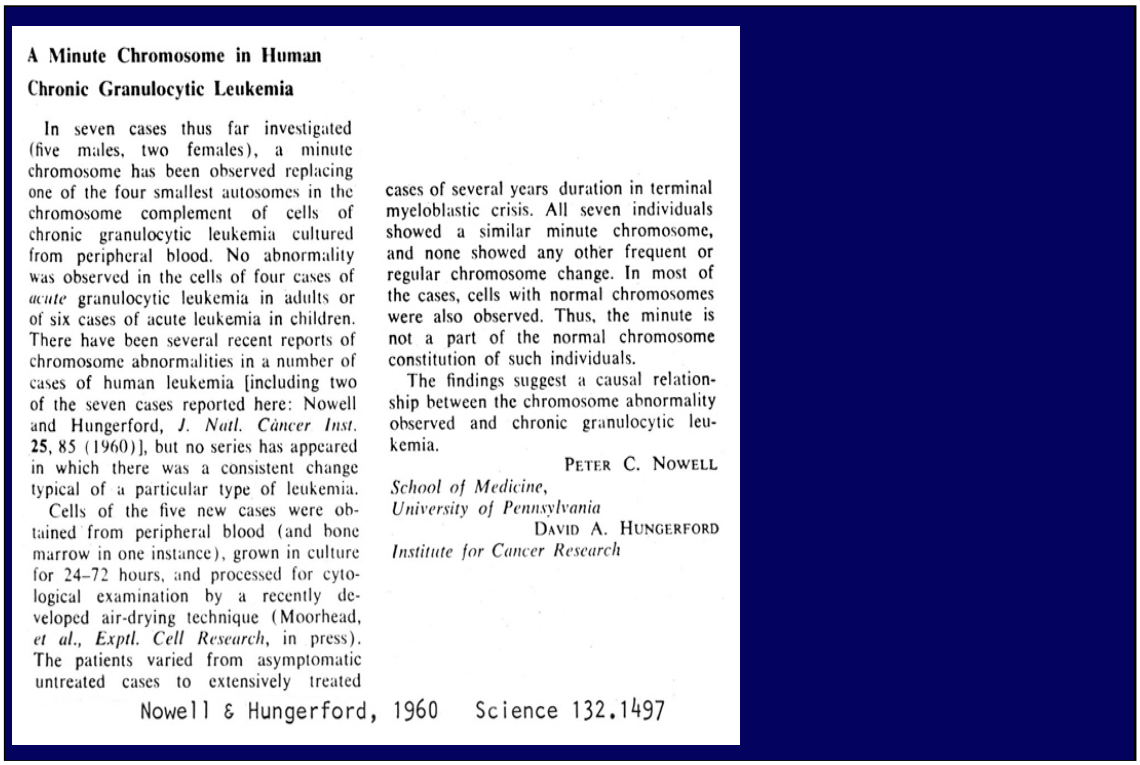
Advanced Stages of CML

- **A malignant clone loses the capacity for terminal differentiation resulting in disease progression to an acute leukemia**
- **Highly refractory to therapy**

Advanced Stages of CML

- A malignant clone loses the capacity for terminal differentiation resulting in disease progression to an acute leukemia
- Highly refractory to therapy
- Survival measured in months

Molecular Pathogenesis of CML



A Minute Chromosome in Human Chronic Granulocytic Leukemia

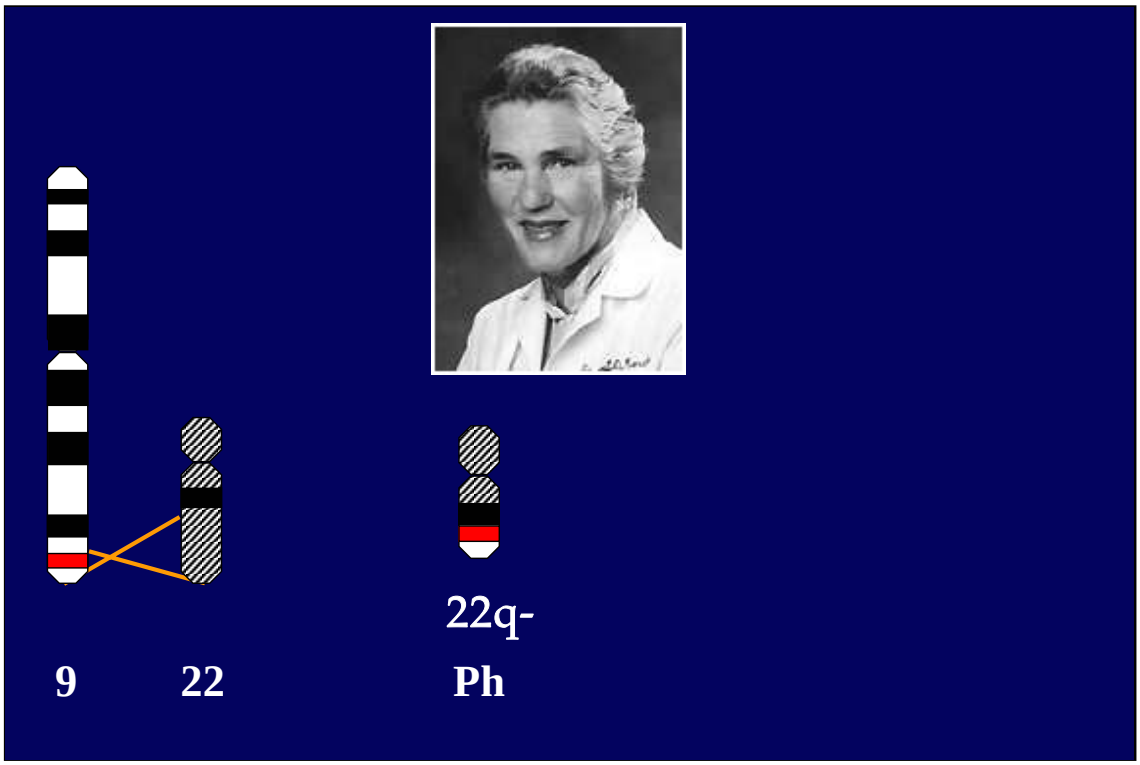
In seven cases thus far investigated (five males, two females), a minute chromosome has been observed replacing one of the four smallest autosomes in the chromosome complement of cells of chronic granulocytic leukemia cultured from peripheral blood. No abnormality was observed in the cells of four cases of *acute* granulocytic leukemia in adults or of six cases of acute leukemia in children. There have been several recent reports of chromosome abnormalities in a number of cases of human leukemia [including two of the seven cases reported here: Nowell and Hungerford, *J. Natl. Cancer Inst.* **25**, 85 (1960)], but no series has appeared in which there was a consistent change typical of a particular type of leukemia.

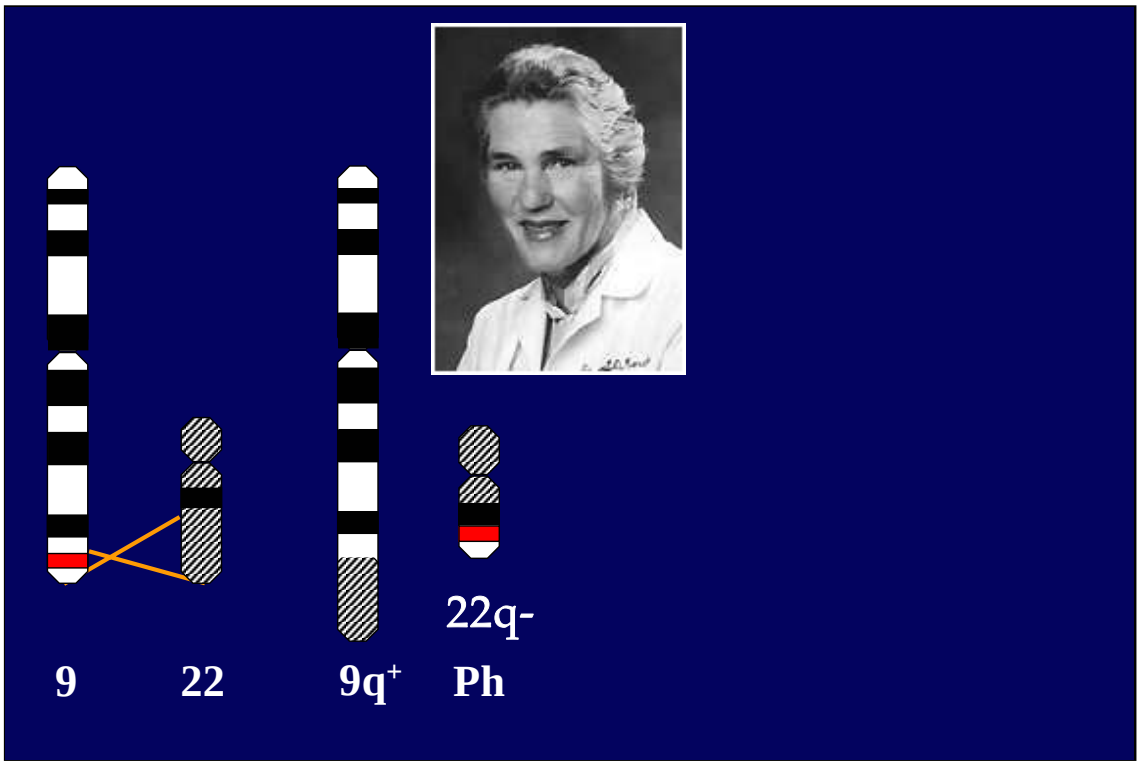
Cells of the five new cases were obtained from peripheral blood (and bone marrow in one instance), grown in culture for 24–72 hours, and processed for cytological examination by a recently developed air-drying technique (Moorhead, *et al., Exptl. Cell Research*, in press). The patients varied from asymptomatic untreated cases to extensively treated cases of several years duration in terminal myeloblastic crisis. All seven individuals showed a similar minute chromosome, and none showed any other frequent or regular chromosome change. In most of the cases, cells with normal chromosomes were also observed. Thus, the minute is not a part of the normal chromosome constitution of such individuals.

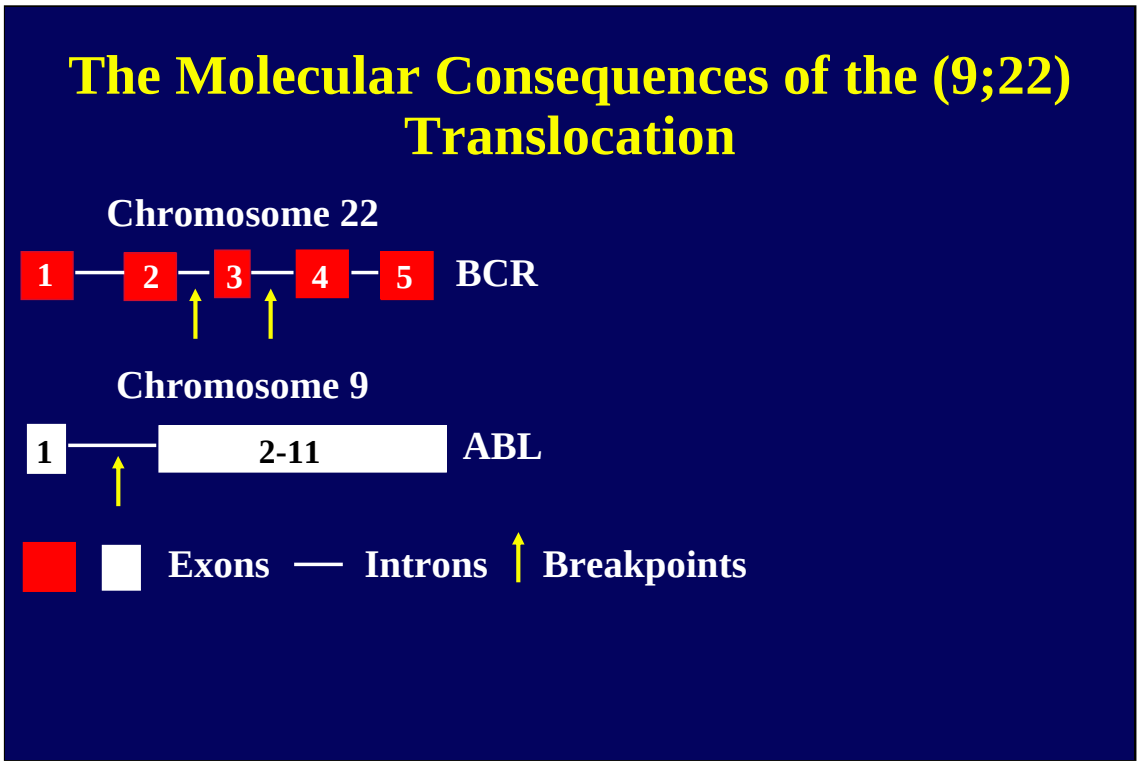
The findings suggest a causal relationship between the chromosome abnormality observed and chronic granulocytic leukemia.

PETER C. NOWELL
School of Medicine,
University of Pennsylvania
DAVID A. HUNGERFORD
Institute for Cancer Research

Nowell & Hungerford, 1960 Science 132.1497

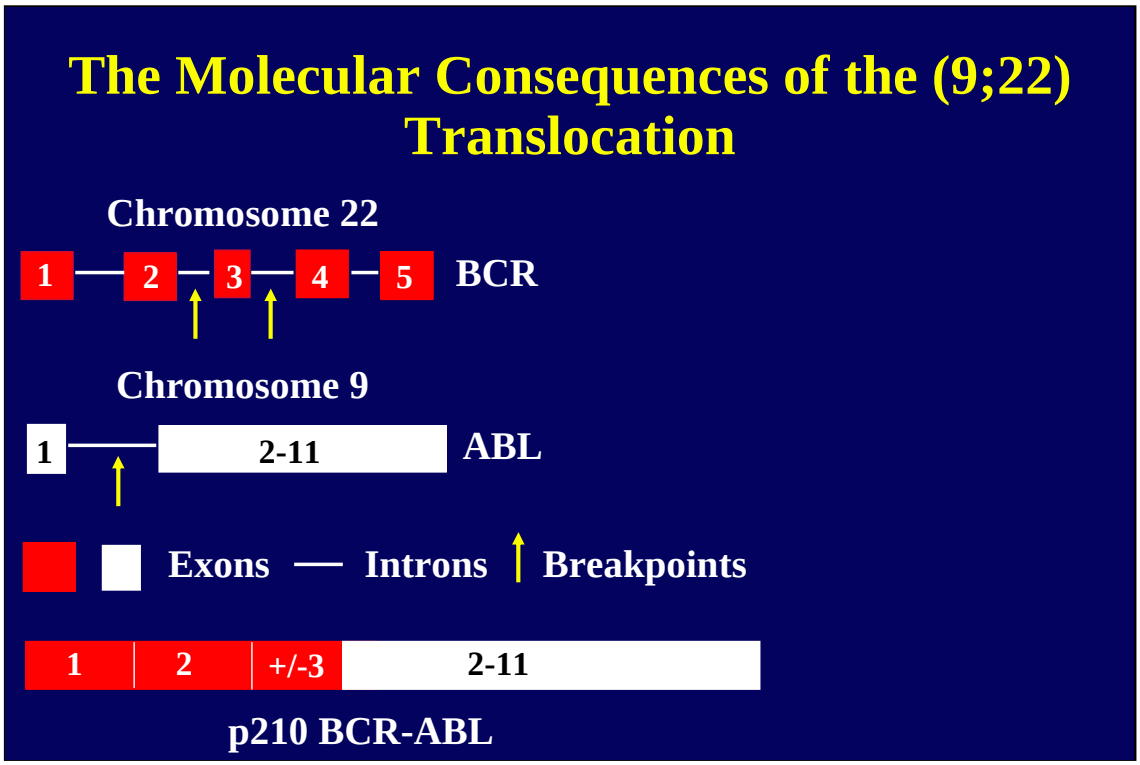

22q-
9
22
Ph


9
22
9q+
22q-
Ph



Molecular consequences of the Ph chromosome translocation.

Virtually all of the Abl tyrosine kinase locus from chromosome 9 is translocated to the a region historically known as the breakpoint cluster region on chromosome 22. This results in the production of a chimeric RNA and protein called Bcr-Abl. In chronic myelogenous leukemic the breakpoint occur after the 2nd and 3rd exons of Bcr, resulting in a 210 kDa Bcr-Abl. In a subset of acute lymphoblastic leukemia patients, a smaller Bcr-Abl protein, termed p185, is produced that contains only the first exon of Bcr.



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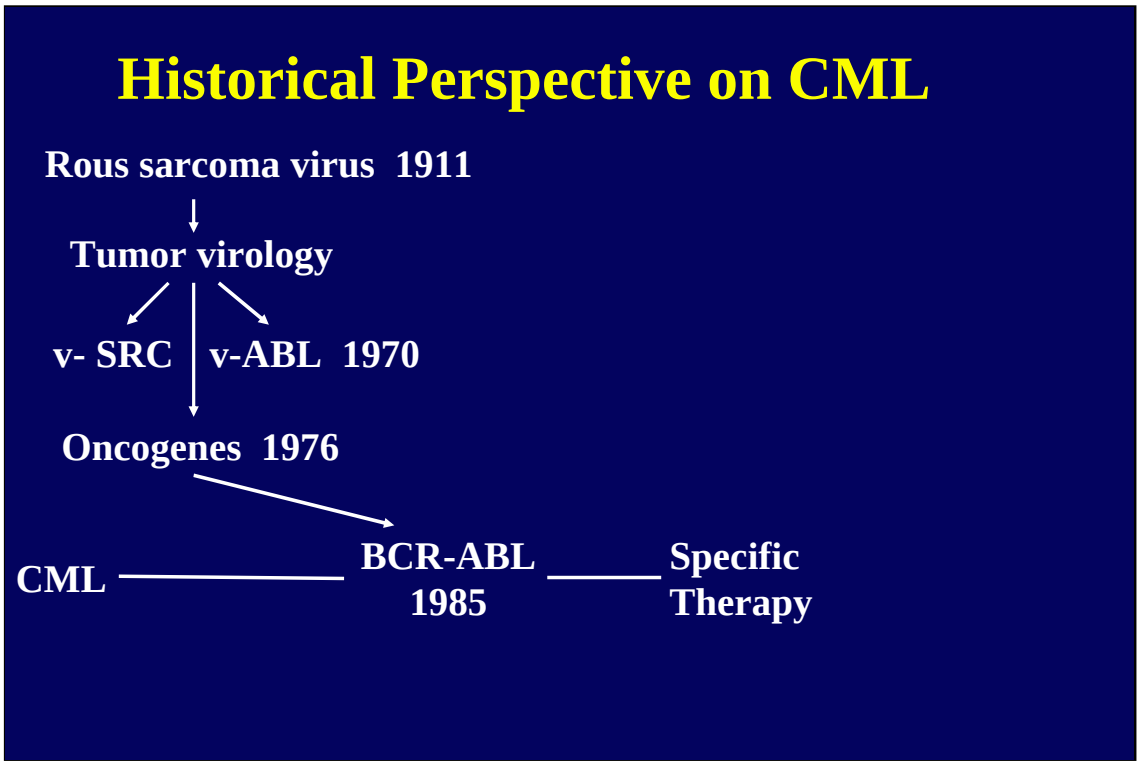
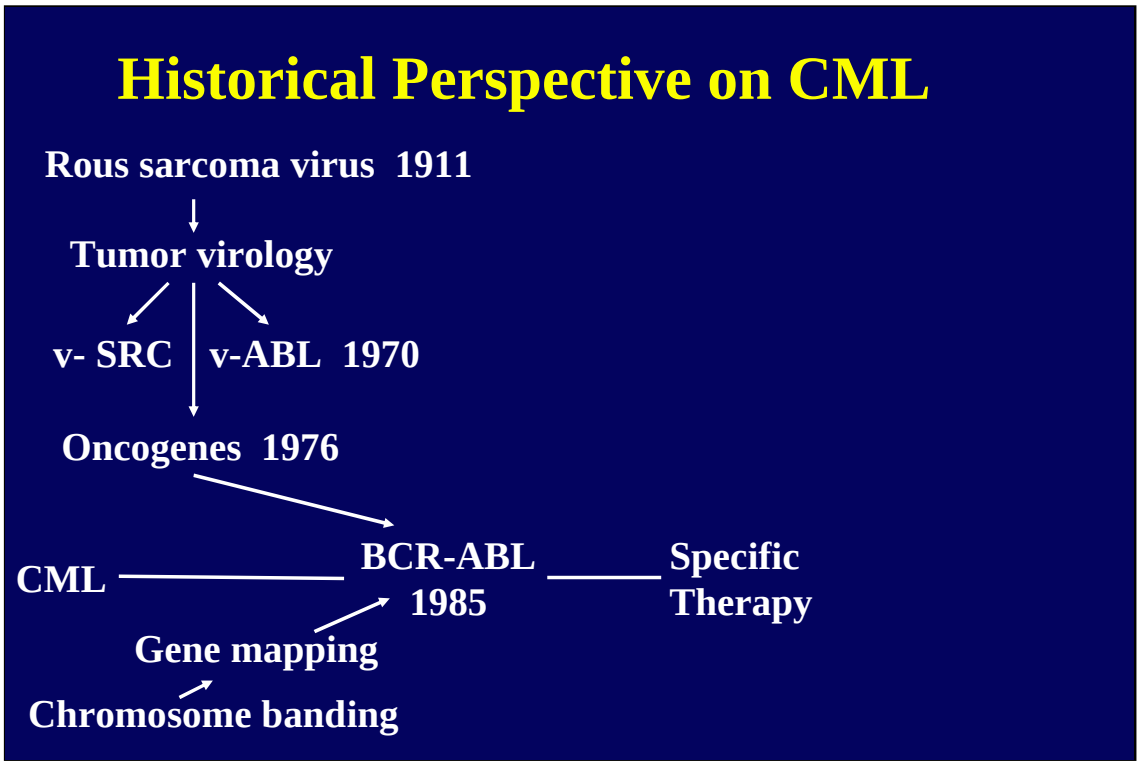
Historical Perspective on CML

CML ——— BCR-ABL 1985 ——— Specific Therapy


Historical Perspective on CML
Rous sarcoma virus 1911
Tumor virology
v- SRC
v-ABL 1970
Oncogenes 1976
CML
BCR-ABL
1985
Specific
Therapy


Historical Perspective on CML
Rous sarcoma virus 1911
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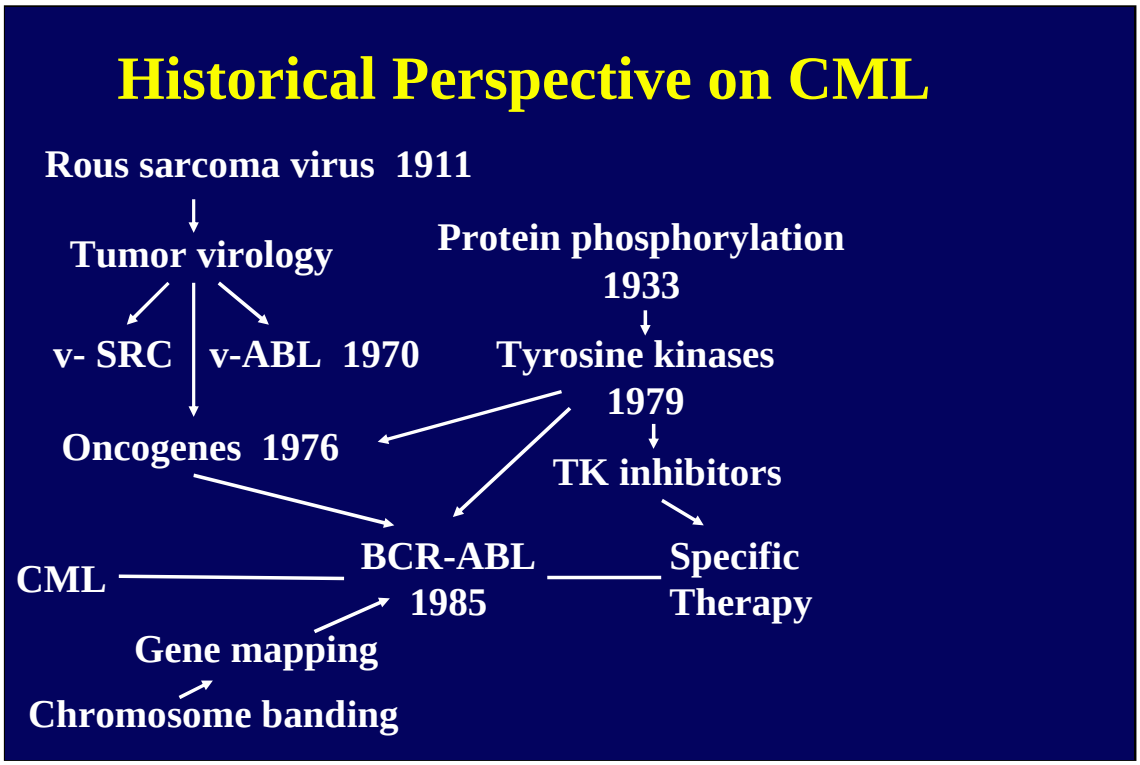
CML
BCR-ABL
1985
Specific
Therapy
Gene mapping
Chromosome banding


Historical Perspective on CML
Rous sarcoma virus 1911
Tumor virology
Protein phosphorylation
1933
v- SRC
v-ABL 1970
Tyrosine kinases
1979
Oncogenes 1976
TK inhibitors
CML
BCR-ABL
1985
Specific
Therapy
Gene mapping
Chromosome banding

Development of Imatinib

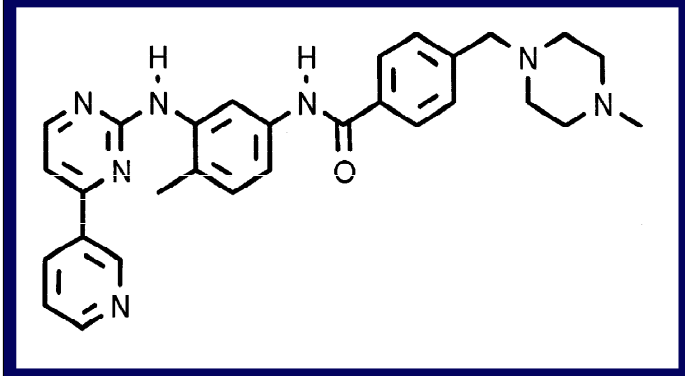
BCR-ABL As a Therapeutic Target for CML

- **Fusion gene/protein generated from t(9;22)**
- **Detected in all patients with CML**
- **Causative molecular abnormality of CML**

BCR-ABL As a Therapeutic Target for CML

- **Is a constitutively activated intracellular tyrosine kinase**
- **Kinase activity is required for function**

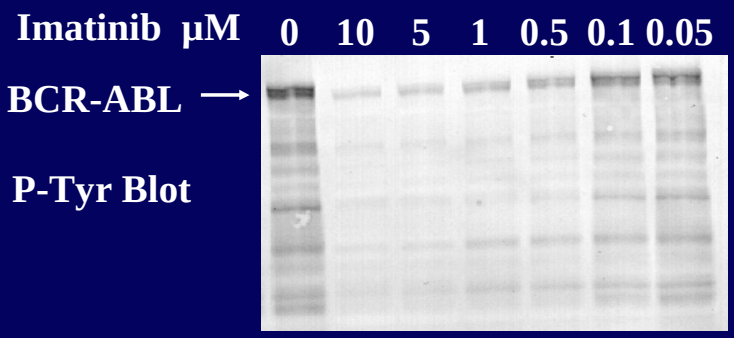
Imatinib
Gleevec™, Glivec®
STI571 (CGP 57148B)



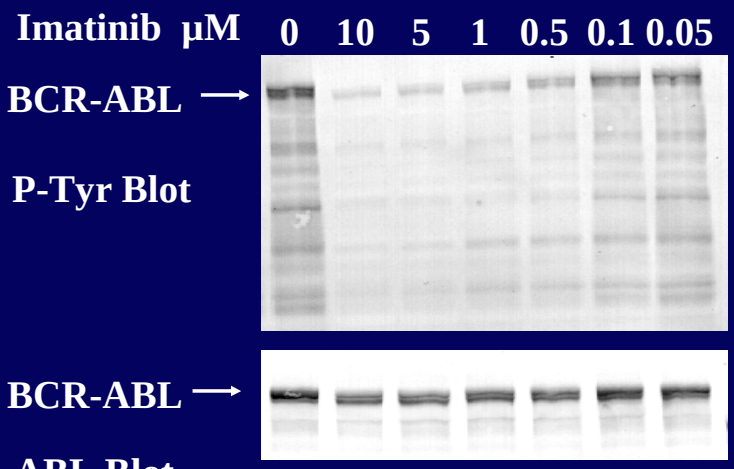
Imatinib

Kinases Inhibited	Kinases Not Inhibited
BCR-ABL, ABL	EGF receptor family
PDGF receptor	Insulin receptor
KIT	FLT-3
	CSF-1 receptor
	FGF receptor family
	JAK family
	SRC family

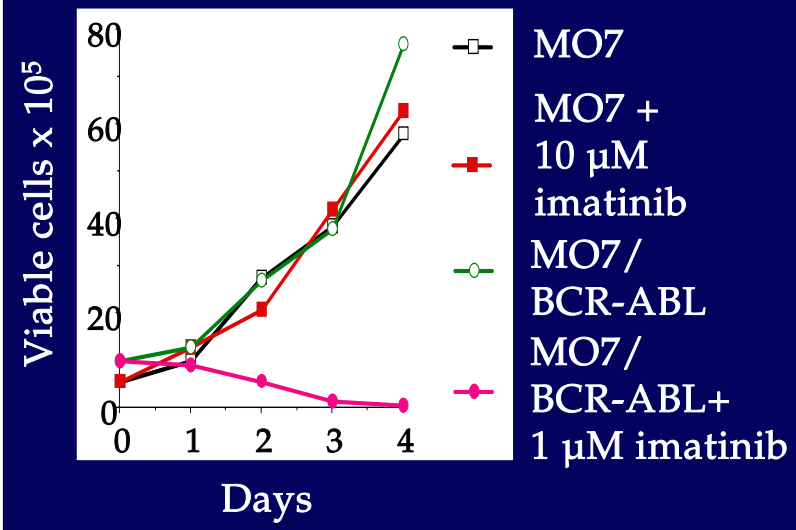
Effects of Imatinib on the ABL Tyrosine Kinase



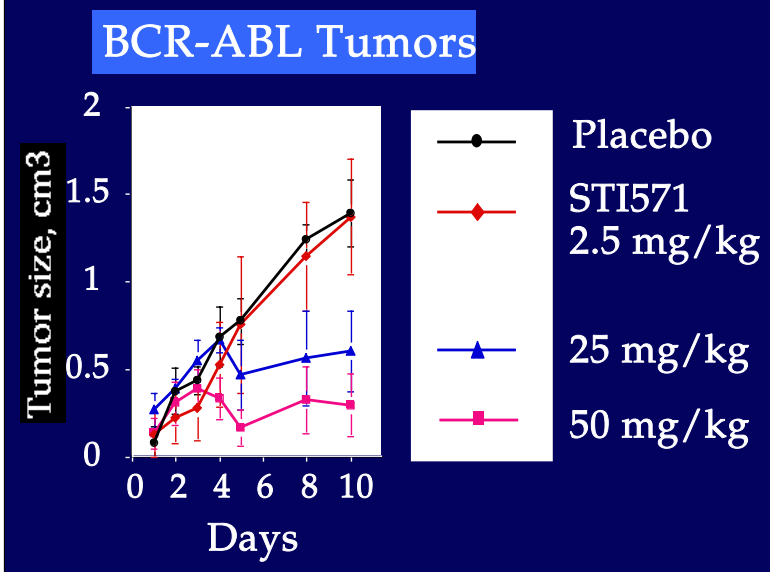
Effects of Imatinib on the ABL Tyrosine Kinase



Imatinib Specifically Inhibits The Growth of Cells With BCR-ABL



Antitumor Activity of Imatinib



Summary of Preclinical Data

- **Imatinib is a potent and selective inhibitor of the ABL, PDGFR and KIT tyrosine kinases**
- **Imatinib selectively kills BCR-ABL-expressing cells in vitro and in vivo**
- **Highly bioavailable as an oral formulation**

B. Druker et al, Nat Med 2:561-566, 1996

Reasons Not to Develop Imatinib

- **Kinase inhibitors will never work**

Reasons Not to Develop Imatinib

- **Kinase inhibitors will never work**
- **Kinase inhibitors will be toxic**

Reasons Not to Develop Imatinib

- **Kinase inhibitors will never work**
- **Kinase inhibitors will be toxic**
- **Kinase inhibitors for CML will never make enough money to justify their development**

Phase I Clinical Trials of Imatinib

- **Began June 1998**
- **Dose escalation from 25 to 1000 mg**

Phase I Clinical Trials of Imatinib

- **Began June 1998**
- **Dose escalation from 25 to 1000 mg**
- **Maximally tolerated dose not reached**

Phase I Clinical Trials of Imatinib

- 300 mg per day and above
  - Significant therapeutic benefits
  - Minimal side effects

B. Druker et al, N Engl J Med 344:1031; 344:1038, 2001

Phase I Clinical Trials of Imatinib

- 300 mg per day and above
  - Significant therapeutic benefits
  - Minimal side effects
- Chronic phase - interferon failures
  - CHR - 98%, 96% durable

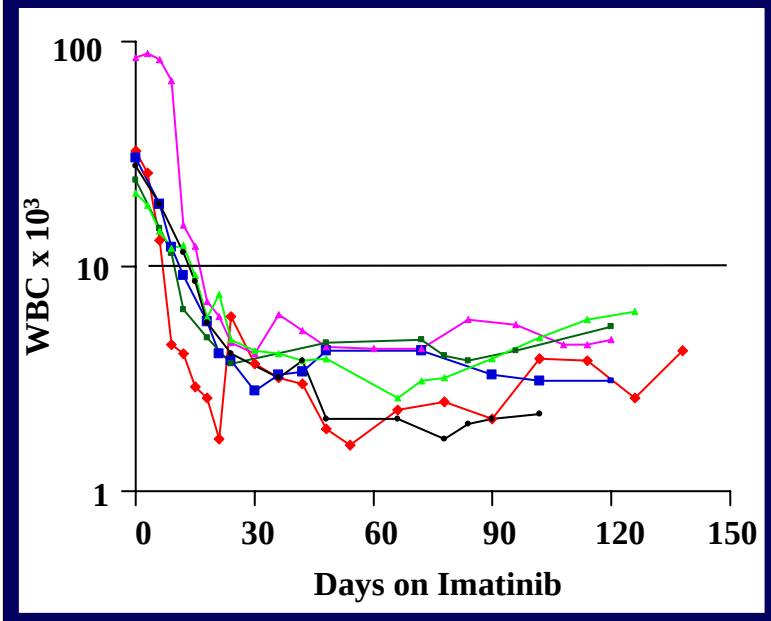
B. Druker et al, N Engl J Med 344:1031; 344:1038, 2001

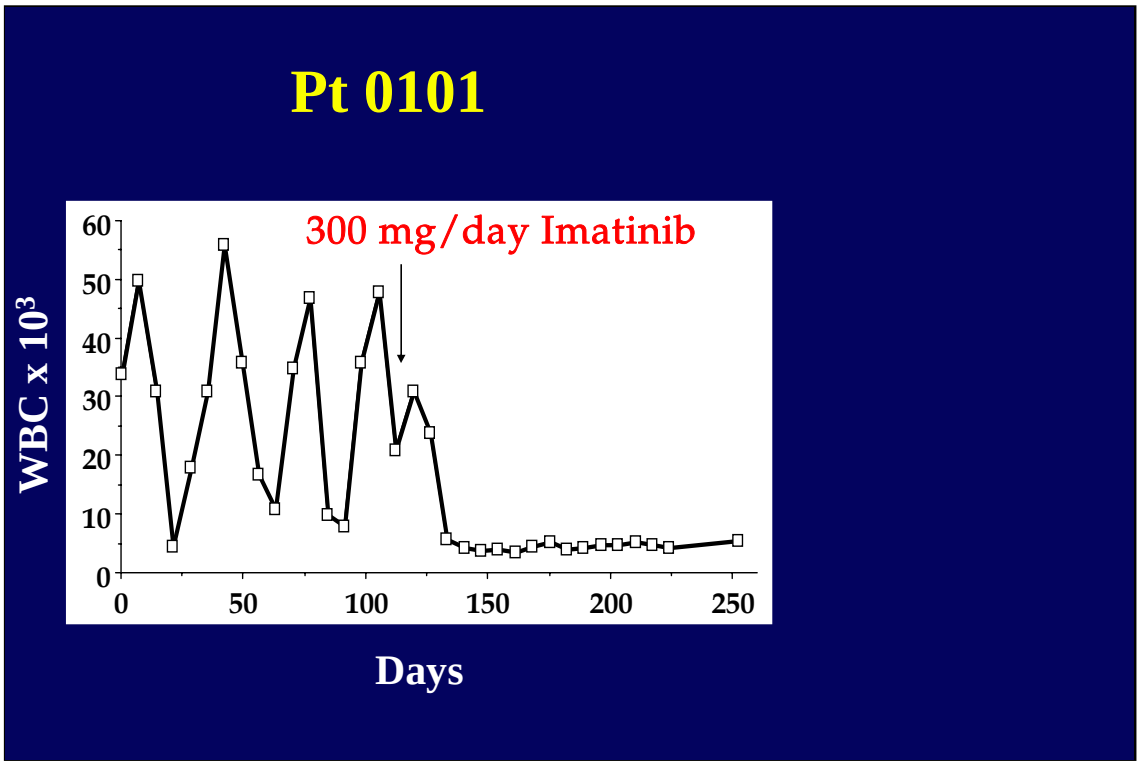
Phase I Clinical Trials of Imatinib

- 300 mg per day and above
  - Significant therapeutic benefits
  - Minimal side effects
- Chronic phase - interferon failures
  - CHR - 98%, 96% durable
- Blast crisis
  - 59% response rate, 18% durable

B. Druker et al, N Engl J Med 344:1031; 344:1038, 2001

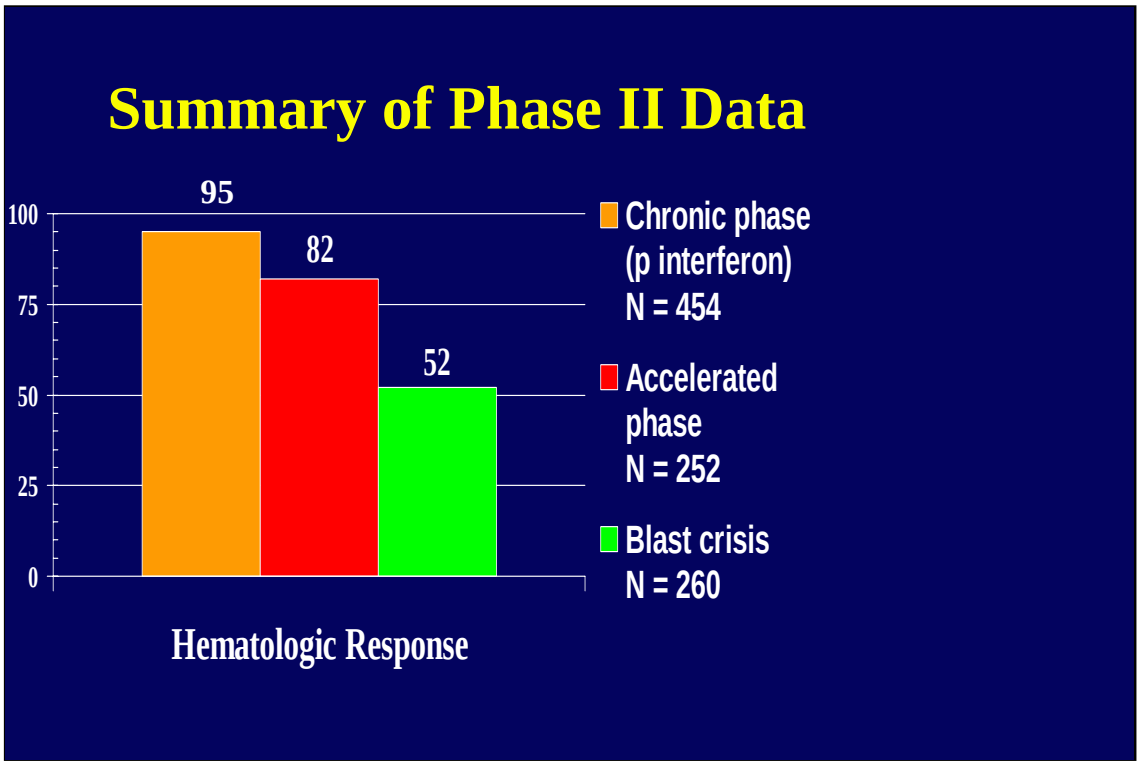
500 mg Imatinib

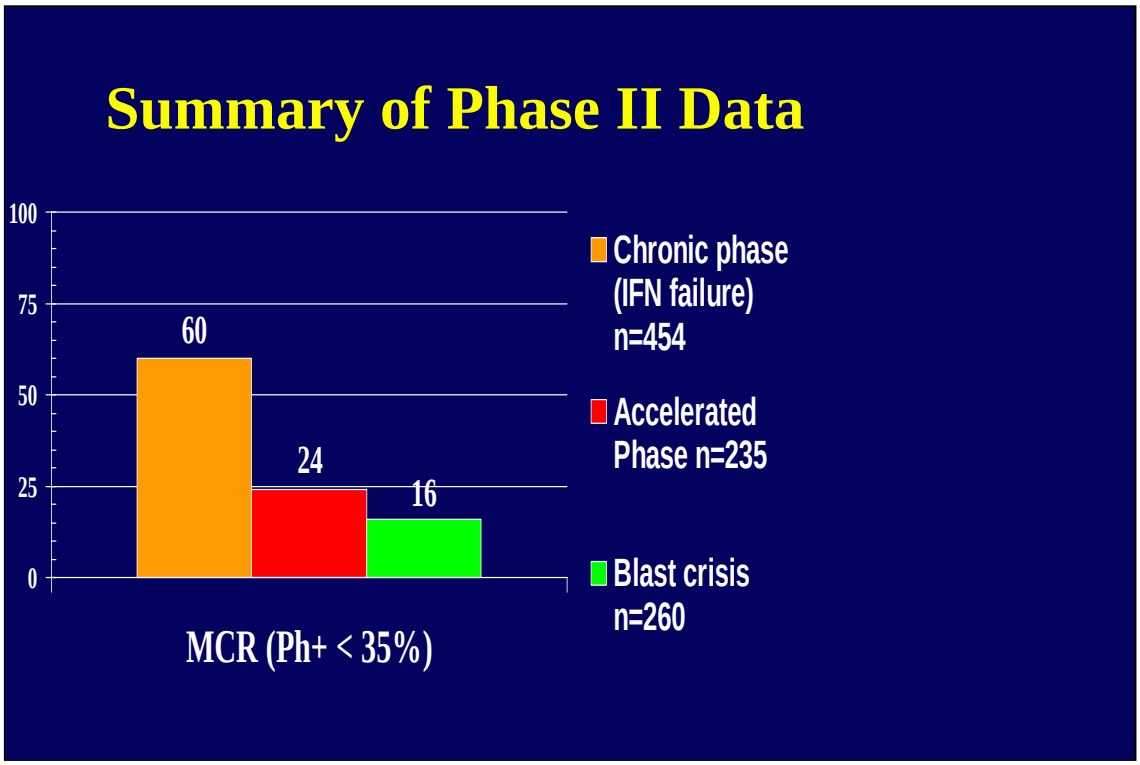


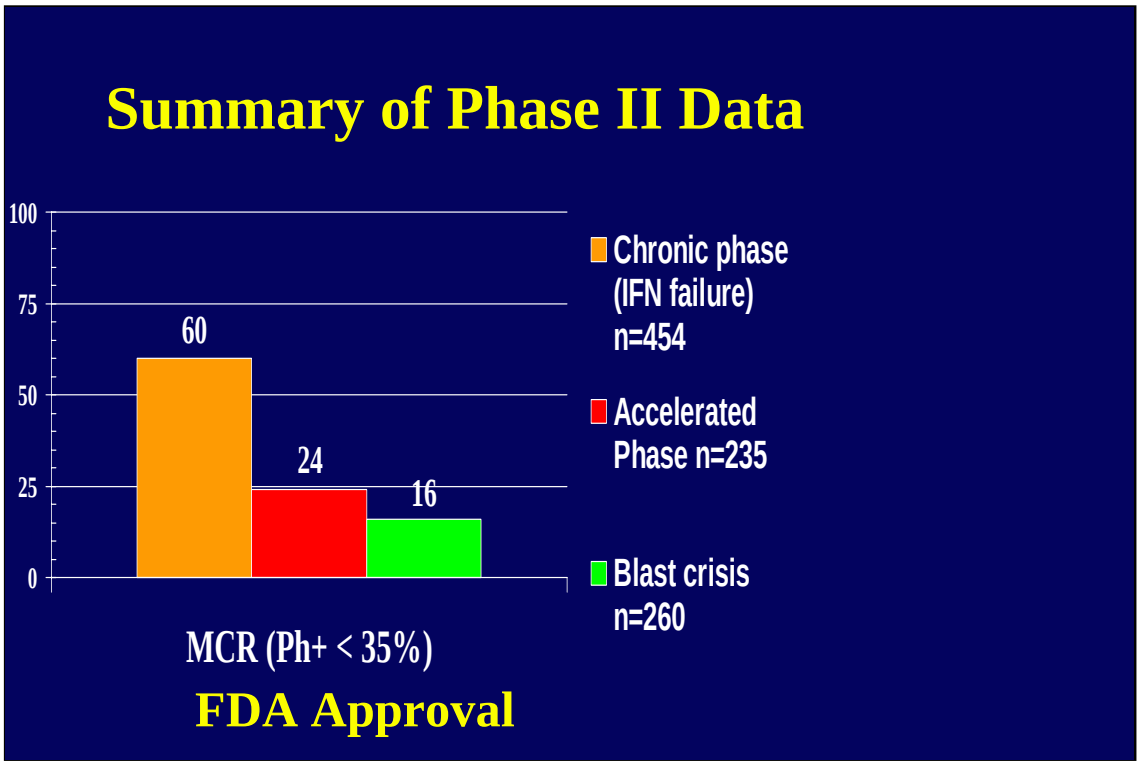

Pt 0101
300 mg/day Imatinib
WBC x 10³
60
50
40
30
20
10
0
0
50
100
150
200
250
Days

Phase II Studies

- Chronic phase patients
  - Failed interferon therapy
- Accelerated phase
- Blast crisis


Summary of Phase II Data
95
82
52
100
75
50
25
0
Hematologic Response
Chronic phase (p interferon) N = 454
Accelerated phase N = 252
Blast crisis N = 260


Summary of Phase II Data
100
75
50
25
0
60
24
16
MCR (Ph+ < 35%)
Chronic phase (IFN failure) n=454
Accelerated Phase n=235
Blast crisis n=260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100
75
50
25
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60
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Blast crisis n=260
MCR (Ph+ < 35%)
FDA Approval

Phase III Randomized Study of Interferon + Ara-C Vs. Imatinib in Newly Diagnosed Patients with CML

Ladies and gentlemen, it a great pleasure to present the results of the IRIS study,

An international study of IFN vs STI, otherwise known as imatinib or Gleevec,

In patients with newly diagnosed CML

Enrollment

- 177 centers in 16 countries
- 1106 patients enrolled
  - June 2000 to January 2001
- 553 patients randomized to each treatment:
  - Imatinib 400 mg per day

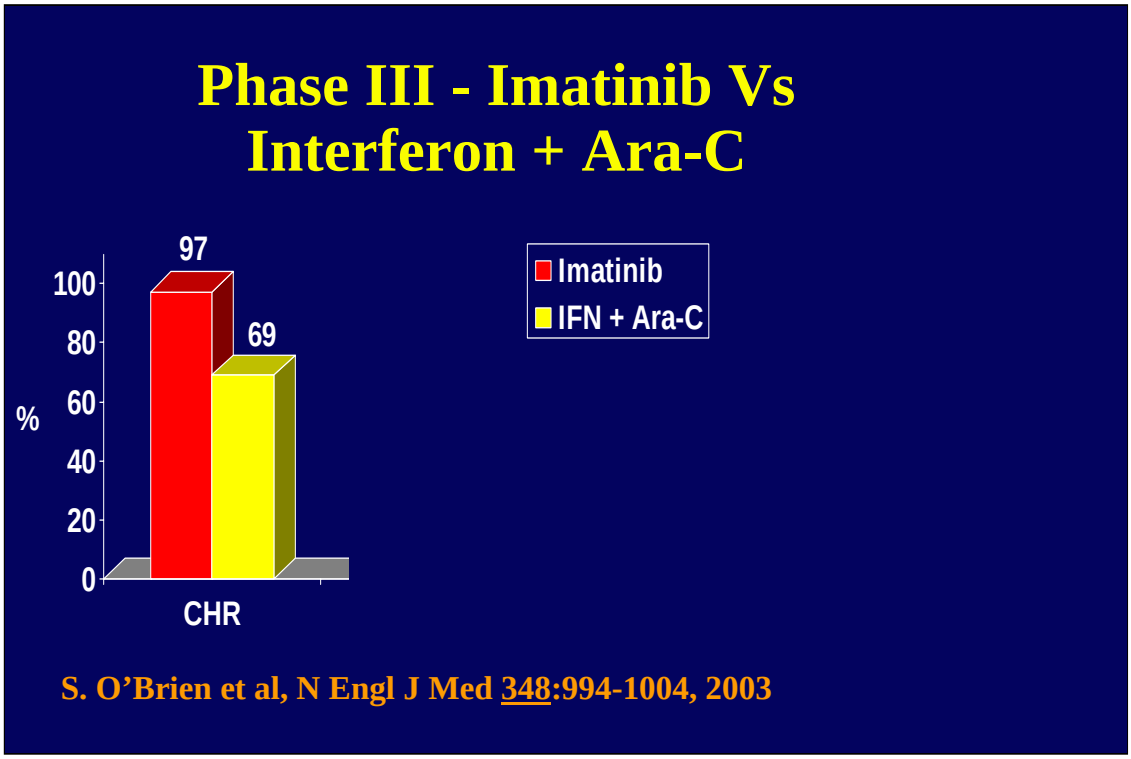
    or
  - Interferon plus Ara-C

A total of 1106 patients were randomized in a 7 months period from June 2000 to January 2001.

With a total of 1106 patients randomized in a 7 months period, this is the largest and most rapidly accrued phase III study conducted in CML

The results presented today are based on data collected up to the end of January 2002, or 12 months after the last patient was randomized

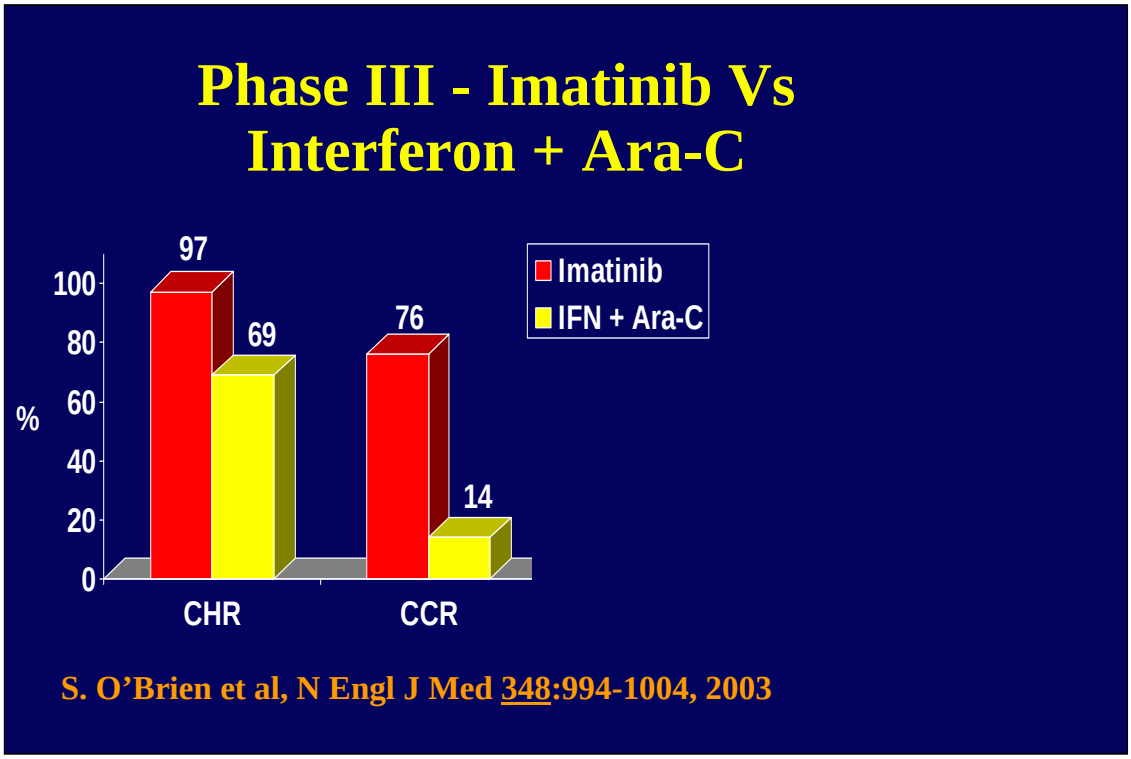
The median follow up is 14 months



In summary,

By all parameters measured, imatinib is significantly superior to IFN and low dose AraC.

This include the rates of CHR, of MCR, prevention of progression to AP or BC, and the tolerance of therapy



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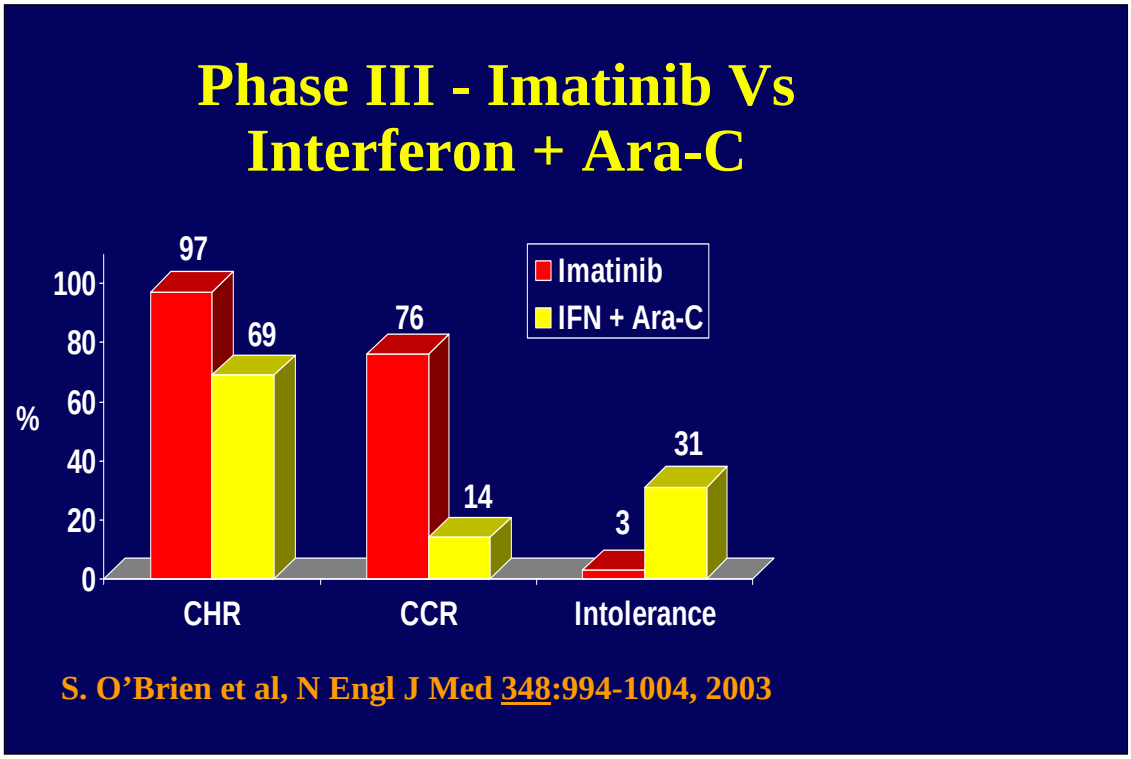

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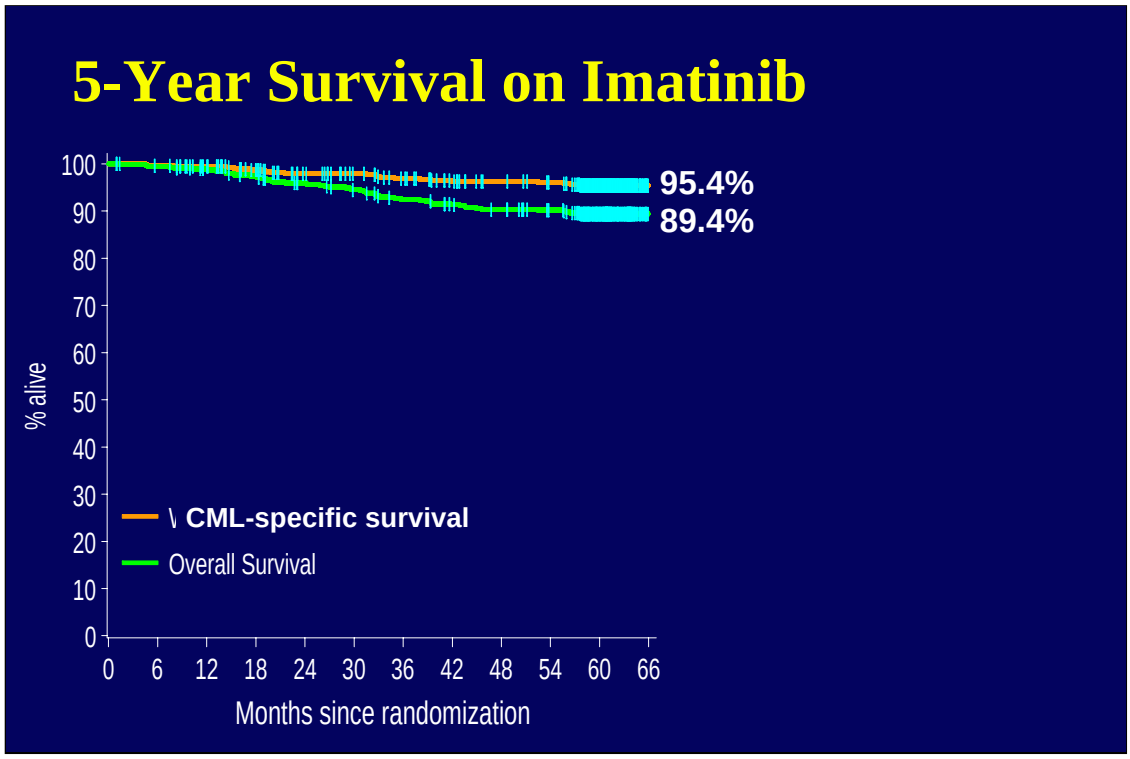
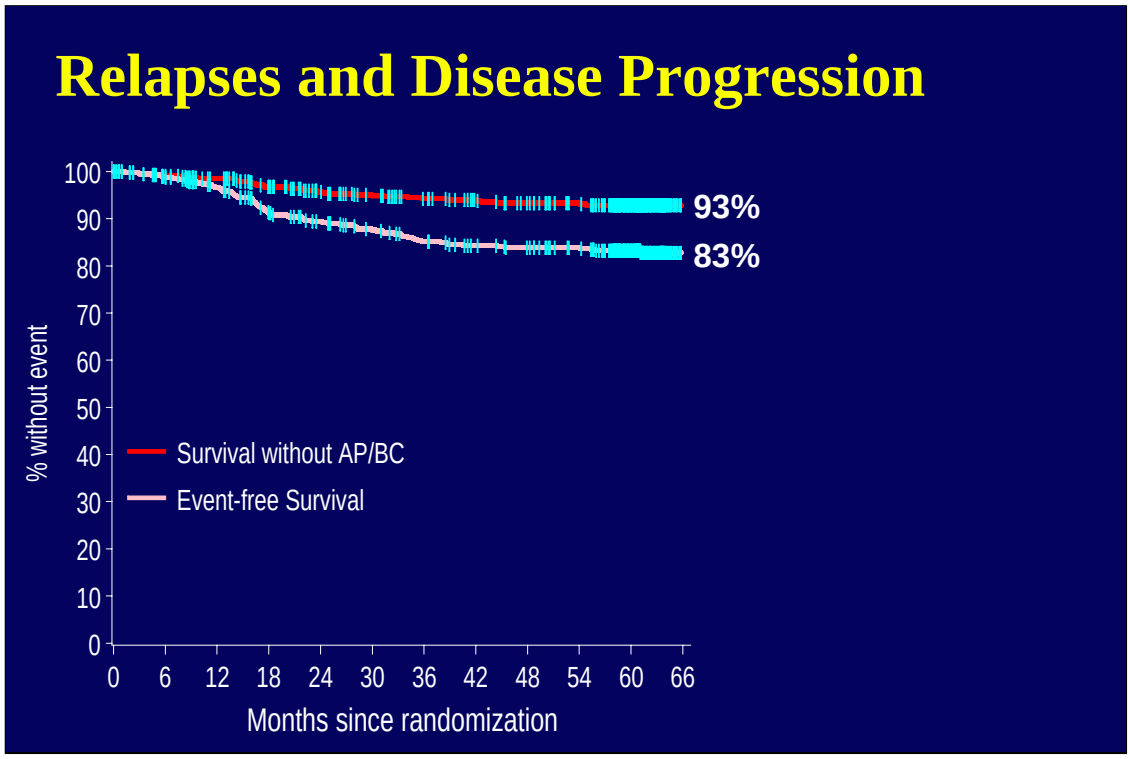

5-Year Survival on Imatinib
100
90
80
70
60
50
40
30
20
10
0
% alive
95.4%
89.4%
CML-specific survival
Overall Survival
0
6
12
18
24
30
36
42
48
54
60
66
Months since randomization



9 (1.6%) CML-unrelated death on treatment (with no signs of clinical progressions):

0016_00002	Cardiac arrest
0765_00003	Cardio-respiratory arrest
0050_00004	Metastases to liver
0066_00001	Pulmonary oedema & Renal failure acute
0159_00003	Road traffic accident
0732_00003	Cardiac arrest
0020_00001	Rectal cancer metastatic
0073_00008	Sepsis
0164_00003	Myocardial infarction

Yearly Relapse Rates

Year	All events*	AP/BC
1st	3.3%	1.5%
2nd	7.5%	2.8%
3rd	4.8%	1.6%
4th	1.5%	0.9%
5th	0.9%	0.6%

* All deaths or loss of response including progression to AP/BC

Survival rates (censoring at BMT) are 1.1%, 2.5%, 2.2%, 1.7%, 1.3%

Summary of CML Clinical Trials

- **Imatinib yields high response rates with minimal toxicity in all phases of CML**
- **Durable responses are achieved in chronic phase patients**
- **Resistance in advanced phase patients is common**