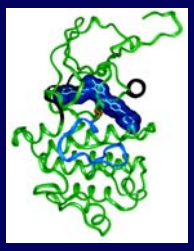
Imatinib (Gleevec) as a Paradigm of Targeted Cancer Therapies



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 — First description of CML

1985 — Bcr-Abl

2001 — Specific therapy for CML

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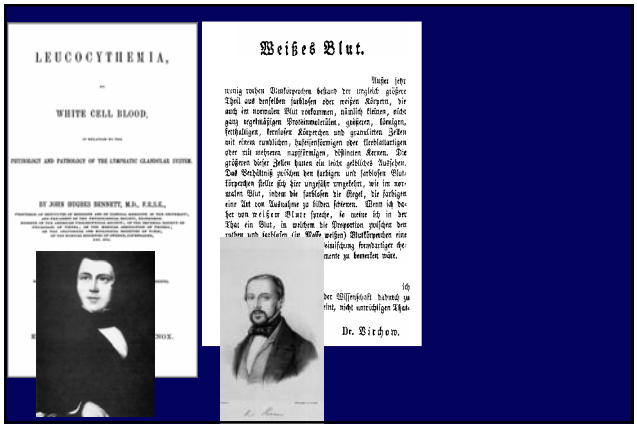
Clinical Description of CML



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

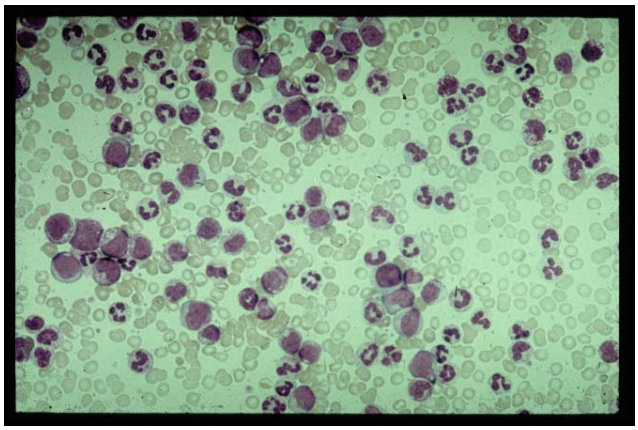
- Tri-phasic illness
  - Chronic or stable phase
    - 95% at presentation
  - Accelerated phase
  - Blast crisis

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

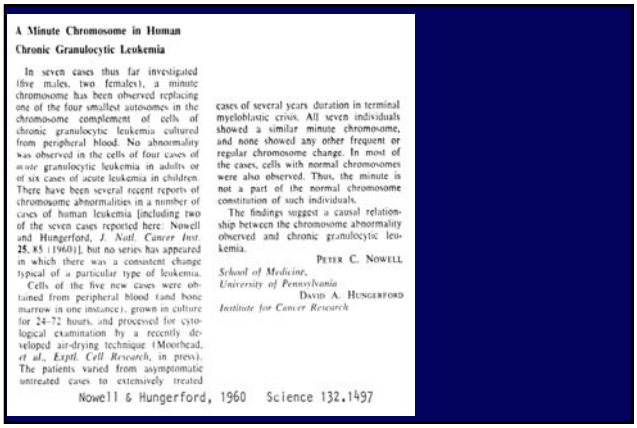
Advanced Stages of CML

- 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.

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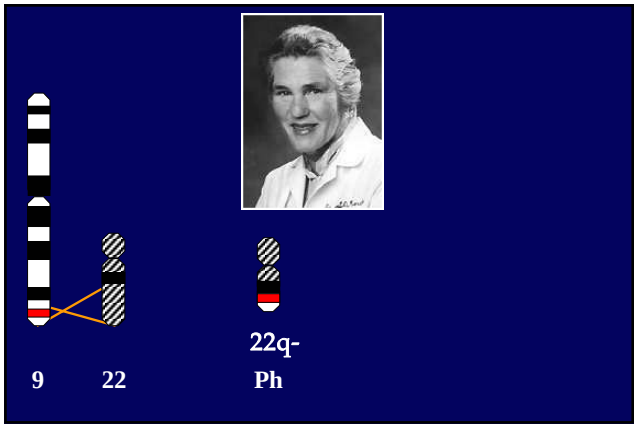
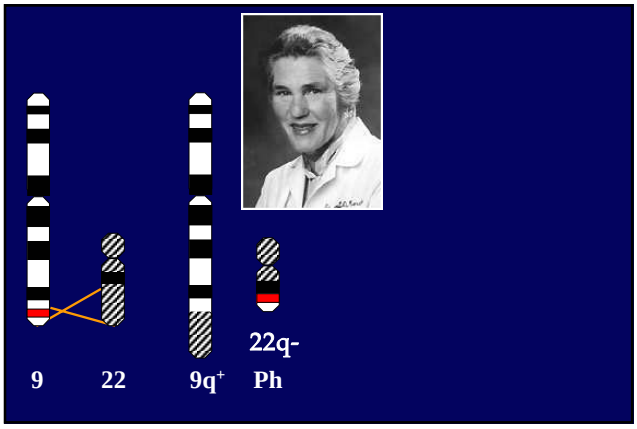
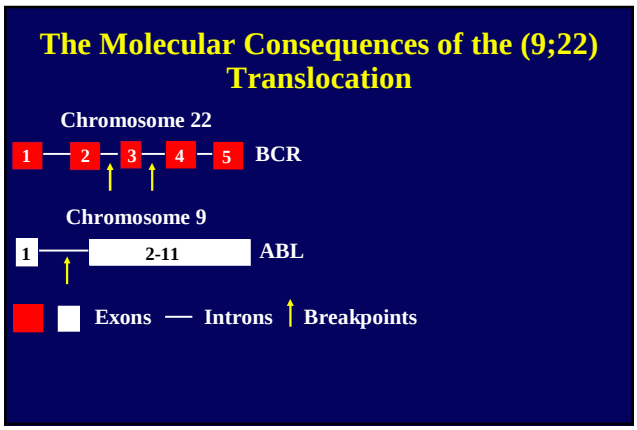
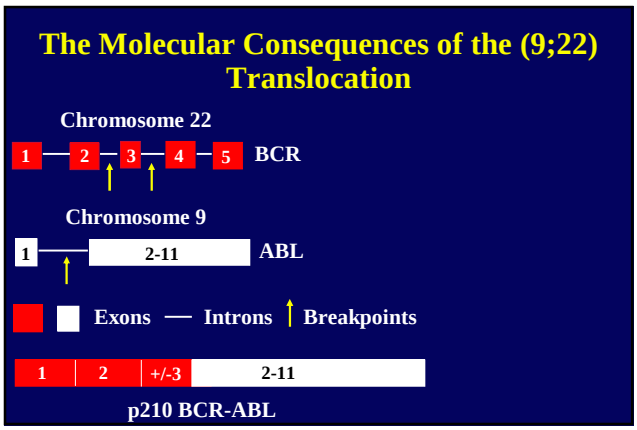
DAVID A. HUNGERFORD
Institute for Cancer Research

Nowell & Hungerford, 1960 Science 132.1497


22q-
9
22
Ph


22q-
9
22
9q+
Ph


The Molecular Consequences of the (9;22) Translocation
Chromosome 22
1
2
3
4
5
BCR
Chromosome 9
1
2-11
ABL
Exons
Introns
Breakpoints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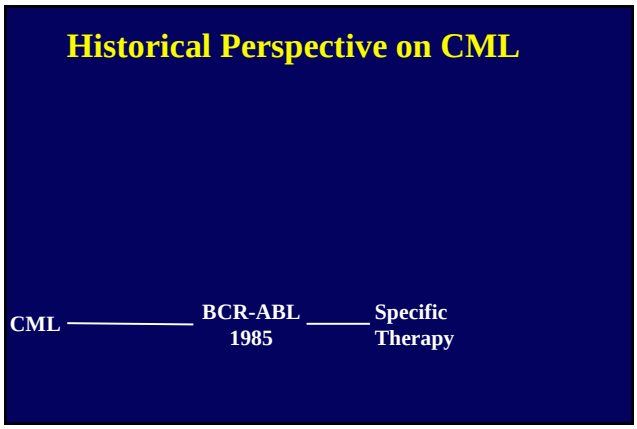
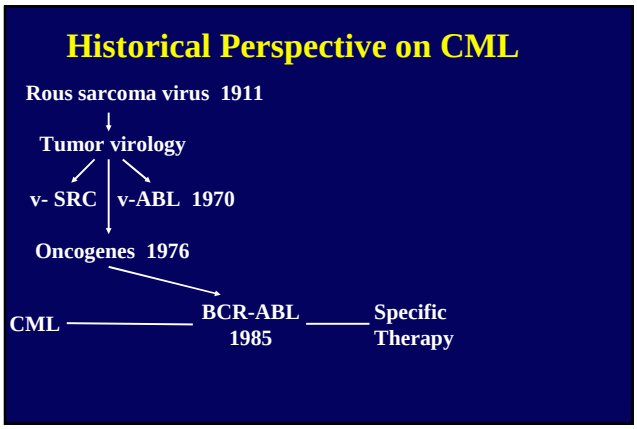

Historical Perspective on CML
CML
BCR-ABL
1985
Specific
Therapy


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

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Rous sarcoma virus 1911

Tumor virology

v- SRC | v-ABL 1970

Oncogenes 1976

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

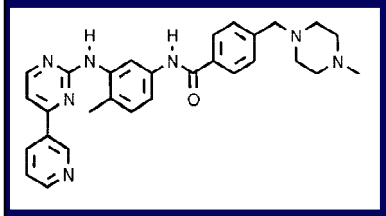
BCR-ABL As a Therapeutic Target for CML

- 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

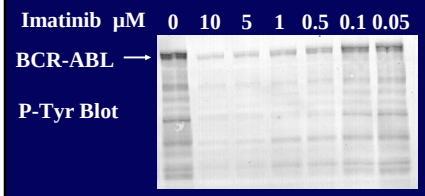
Imatinib Gleevec™, Glivec® STI571 (CGP 57148B)



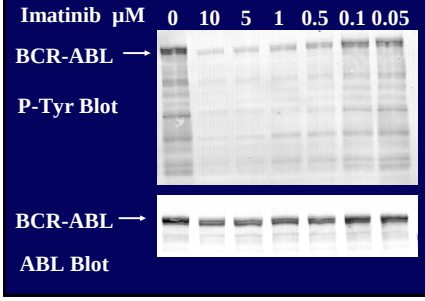
Imatinib

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

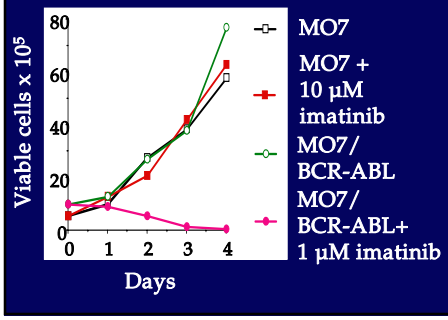
Effects of Imatinib on the ABL Tyrosine Kinase



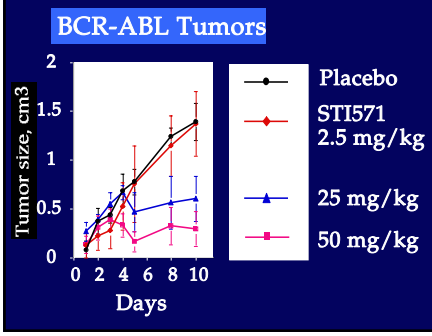
Effects of Imatinib on the ABL Tyrosine Kinase



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
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- Chronic phase - interferon failures
  - CHR - 98%, 96% durable

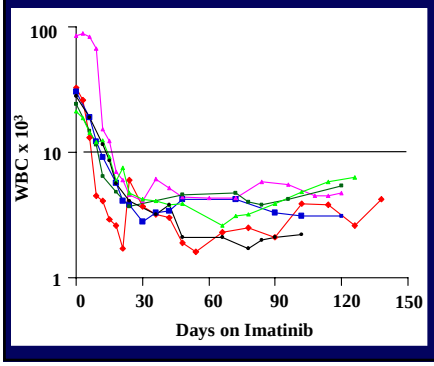
B. Druker et al, N Engl J Med 344:1031; 344:1038, 2001

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



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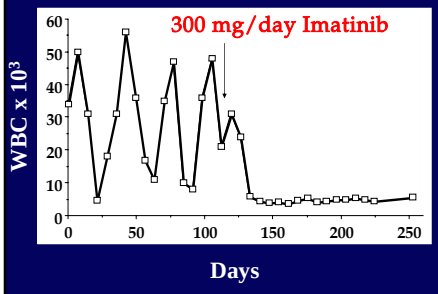
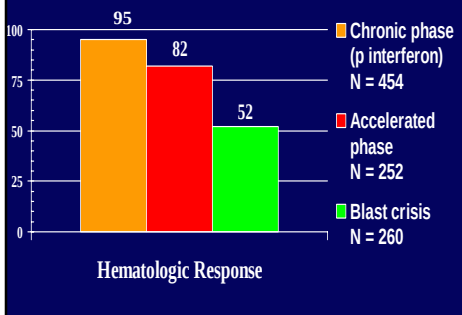


Phase II Studies

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

Summary of Phase II Data



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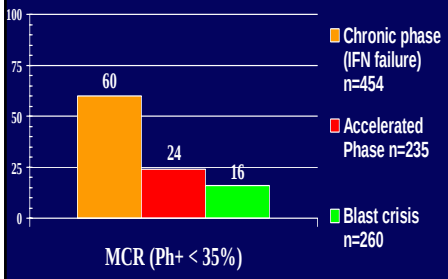

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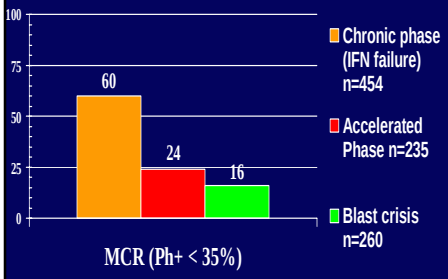


FDA Approval

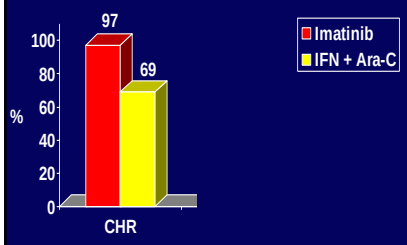
Phase III Randomized Study of Interferon + Ara-C Vs. Imatinib in Newly Diagnosed Patients with CML

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

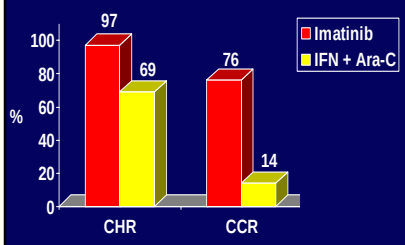
    or
  - Interferon plus Ara-C

Phase III - Imatinib Vs Interferon + Ara-C



S. O'Brien et al, N Engl J Med 348:994-1004, 2003

Phase III - Imatinib Vs Interferon + Ara-C



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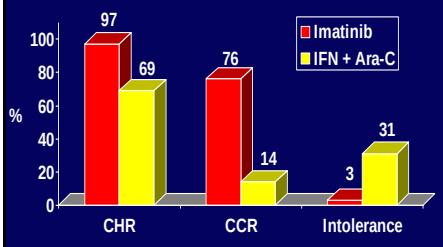
Phase III - Imatinib Vs Interferon + Ara-C



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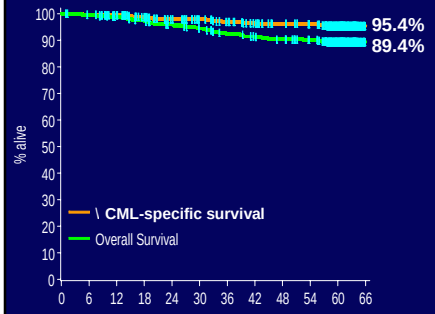
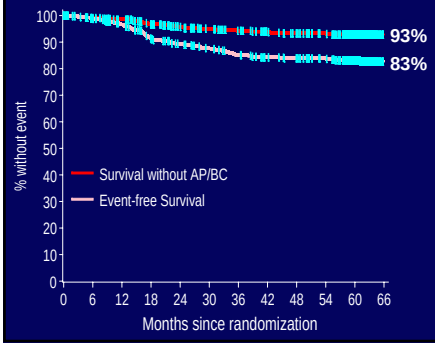
5-Year Survival on Imatinib



Relapses and Disease Progression



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

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