## Incidence of Hematologic Malignancies

<table>
<thead>
<tr>
<th>Type of Leukemia</th>
<th>Incidence per 100,000*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>6–10</td>
</tr>
<tr>
<td>CML</td>
<td>1–2</td>
</tr>
<tr>
<td>CLL</td>
<td>2–3</td>
</tr>
<tr>
<td>AML</td>
<td>2–3</td>
</tr>
<tr>
<td>ALL</td>
<td>1–2</td>
</tr>
</tbody>
</table>
Leukemia Comprises a Vast Proportion of Cancer Deaths in the United States

Men 290,890
Women 272,810

- Lung and bronchus 33%
- Prostate 10%
- Colon and rectum 10%
- Pancreas 5%
- Leukemia 4%
- Non-Hodgkin’s lymphoma 4%
- Esophagus 4%
- Liver/intrahepatic bile duct 3%
- Urinary bladder 3%
- Kidney 3%
- All other sites 21%

- Lung and bronchus 26%
- Breast 15%
- Colon and rectum 10%
- Pancreas 6%
- Ovary 6%
- Leukemia 4%
- Non-Hodgkin’s lymphoma 3%
- Uterine corpus 3%
- Brain/nervous system 2%
- Multiple myeloma 2%
- All other sites 22%
Incidence and Mortality Associated With Leukemias (United States, 2003)

Incidence

- Overall: 33,440
- AML: 11,920
- CLL: 8,190
- CML: 4,600
- ALL: 3,830

Mortality

- Overall: 23,300
- AML: 8,870
- CLL: 4,800
- CML: 1,570
- ALL: 1,450
Figure 1. A General Model of Hematopoiesis.

Blood-cell development progresses from a hematopoietic stem cell (HSC), which can undergo either self-renewal or differentiation into a multipotent progenitor cell, a common lymphoid progenitor (CLP), or a common myeloid progenitor (CMP). These cells then give rise to more differentiated progenitors, comprising those committed to two lineages that include T cells and natural killer cells (NK), granulocytes and macrophages (GM), and megakaryocytes and erythrocyte cells (MEPs). Ultimately, those cells give rise to lineage-committed progenitors for B cells (BCPs), NK cells (NKP), T cells (TCPs), granulocytes (GP), monocytes (MPs), erythrocytes (EP), and megakaryocytes (MEPs). Cytokines and growth factors that support the survival, proliferation, or differentiation of each type of cell are shown in red. For simplicity, the three types of granulocyte progenitor cells are not shown, in reality, distinct progenitors of neutrophils, eosinophils, and basophils or mast cells exist and are supported by distinct transcription factors and cytokines (e.g., interferon-γ in the case of eosinophils, stem-cell factor (SCF) in the case of basophils or mast cells, and G-CSF in the case of neutrophils). IL denotes interleukin, TPO thrombopoietin, M-CSF macrophage colony-stimulating factor, GM-CSF granulocyte-macrophage colony-stimulating factor, and EPO erythropoietin.
Comparative Peripheral Blood Smear

Normal

Chronic Phase CML
Table 46.2-1  Diagnosis and Evaluation of Acute Leukemia

<table>
<thead>
<tr>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue, malaise, dyspnea</td>
</tr>
<tr>
<td>Easy bruisingibility, weight loss</td>
</tr>
<tr>
<td>Bone pain or abdominal pain (less common)</td>
</tr>
<tr>
<td>Neurologic symptoms (rare)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia and pallor</td>
</tr>
<tr>
<td>Thrombocytopenia, hemorrhage, ecchymoses, petechiae, fundal hemorrhage</td>
</tr>
<tr>
<td>Fever and infection (pneumonia, sepsis, perirectal abscess)</td>
</tr>
<tr>
<td>Adenopathy, hepatosplenomegaly, mediastinal mass</td>
</tr>
<tr>
<td>Gum or skin infiltration (rare)</td>
</tr>
<tr>
<td>Renal enlargement and insufficiency (rare)</td>
</tr>
<tr>
<td>Cranial neuropathy (rare)</td>
</tr>
</tbody>
</table>
Clinical Presentation of CML

**Common Symptoms**
- Fatigue
- Weight loss/anorexia
- Abdominal fullness

**Common Signs**
- Palpable splenomegaly

**Common Laboratory Findings**
- Abnormal differential
- Anemia
- Leukocytosis
- Basophilia
- Thrombocytosis
LEUCEMIA MIELOIDE CRONICA
LEUCOCYTHEMIA,

WHITE CELL BLOOD.

IN RELATION TO THE

PATHOLOGY AND PATHOLOGY OF THE LYMETHIC GLANDULAR SYSTEM.

BY JOHN Hughes Bennett, M.D., F.A.C.S.

Professor of Medicine and of Clinical Medicine in the University, and Professor in the Physicians' College, Edinburgh.

Vol. 1. 1845.

WHITE CELL LEMENTS, AD INNIVERSITY LIBRARY.

1845

University of Milano
Bicocca, Monza, Italy
Epidemiology of CML

- Median age range at presentation is 45-55 years
- Incidence increases with age
  - Up to 30% of patients are aged >60 years
- Slightly higher incidence in males
  - Male-to-female ratio—1.3:1
- At presentation
  - 50% diagnosed by routine laboratory tests
  - 85% diagnosed during chronic phase
Comparative Peripheral Blood Smear

Normal

Chronic Phase CML

Acute Leukemia
PATOGENESI
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
Cytogenetic Abnormality of CML: The Philadelphia Chromosome
The Philadelphia Chromosome: t(9;22) Translocation

FUSION PROTEIN WITH TYROSINE KINASE ACTIVITY

Ph

bcr-abl
## Chromosome in Hematologic Malignancies

<table>
<thead>
<tr>
<th>Leukemia</th>
<th>% of Ph+ Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>CML</td>
<td>95</td>
</tr>
<tr>
<td>ALL (Adult)</td>
<td>15–30</td>
</tr>
<tr>
<td>ALL (Pediatric)</td>
<td>5</td>
</tr>
<tr>
<td>AML</td>
<td>2</td>
</tr>
</tbody>
</table>

**bcr-abl** Gene and Fusion Protein Tyrosine Kinases

Adapted from Melo JV. *Blood*. 1996;88:2375-2384.
Bcr-Abl Signal Transduction Pathways


Bcr-Abl

- activates JAK/STATs
- inhibits apoptosis

- upregulation of Paxillin (Adhesion)
- PI-3 kinase
- RAF-MEK-MAPK cascade regulates cell cycle progression and differentiation

- BCL2
- MYC
- GRB2
- CRKL
- CBL (p120CBL)
- Actin (Adhesion)
β-catenin is constitutively tyrosine (Y)-phosphorylated and associated to Bcr-Abl in human CML cells

**Characteristics of CML Patient Samples**

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Age</th>
<th>Type</th>
<th>CML phase</th>
<th>% blasts</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>58</td>
<td>BM</td>
<td>BC</td>
<td>30%</td>
</tr>
<tr>
<td>2</td>
<td>43</td>
<td>BM</td>
<td>BC</td>
<td>73%</td>
</tr>
<tr>
<td>3</td>
<td>37</td>
<td>BM</td>
<td>BC</td>
<td>37%</td>
</tr>
<tr>
<td>4</td>
<td>74</td>
<td>BM</td>
<td>BC</td>
<td>54%</td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>BM</td>
<td>BC</td>
<td>96%</td>
</tr>
<tr>
<td>6</td>
<td>58</td>
<td>BM</td>
<td>BC</td>
<td>58%</td>
</tr>
</tbody>
</table>

BM, bone-marrow mononuclear cells; BC, blast crisis

**Ls174t** = human colorectal cancer cell line used as negative control for Bcr-Abl

**Ku812** = BC-CML-patient established cell line

**CML 1 - 6** = fresh bone-marrow mononuclear cells from BC-CML-patients

Imatinib prevents tyrosine (Y)-phosphorylation of β-catenin and accumulation of its transcriptional competent pool which is serine/threonine (S/T)-nonphosphorylated.
Proposed mechanism:

Coluccia et al; Figure 8
DIAGNOSI
Clinical Presentation of CML

At presentation:

- 50% diagnosed by routine laboratory tests
- 85% diagnosed during chronic phase
Clinical Presentation of CML

Common Symptoms
- Fatigue
- Weight loss/anorexia
- Abdominal fullness

Common Signs
- Palpable splenomegaly

Common Laboratory Findings
- Abnormal differential
- Anemia
- Leukocytosis
- Basophilia
- Thrombocytosis
Clinical Presentation of Chronic Phase CML

- Asymptomatic in ~50% of cases
- Common symptoms
  - Fatigue
  - Weight loss/anorexia
  - Abdominal fullness
- Common signs
  - Palpable splenomegaly

Common laboratory findings
- Abnormal differential
- Leukocytosis
- Thrombocytosis
- Anemia
- Basophilia
### Typical Laboratory Parameters by Phase of CML

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Chronic</th>
<th>Accelerated</th>
<th>Blastic</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC count</td>
<td>$\geq 20 \times 10^9$/L</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Blasts</td>
<td>3%–10%</td>
<td>$\geq 15%$</td>
<td>$\geq 30%$</td>
</tr>
<tr>
<td>Basophils</td>
<td>↑</td>
<td>$\geq 20%$</td>
<td>—</td>
</tr>
<tr>
<td>Platelets</td>
<td>↑ or normal</td>
<td>↓ or ↑</td>
<td>↓</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>Myeloid hyperplasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>Ph$^+$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bcr-Abl</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
Clinical Course: Phases of CML

<table>
<thead>
<tr>
<th>Chronic phase</th>
<th>Advanced phases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Accelerated phase</td>
</tr>
<tr>
<td>Median 4–6 years stabilization</td>
<td>Median duration up to 1 year</td>
</tr>
</tbody>
</table>
Nucleo Ph+

Nucleo normale

Metafase Ph+
DNA region of interest.

1. DNA is denatured. Primers attach to each strand. A new DNA strand is synthesized behind primers on each template strand.

2. Another round: DNA is denatured, primers are attached, and the number of DNA strands are doubled.

3. Another round: DNA is denatured, primers are attached, and the number of DNA strands are doubled.

4. Another round: DNA is denatured, primers are attached, and the number of DNA strands are doubled.

5. Continued rounds of amplification swiftly produce large numbers of identical fragments. Each fragment contains the DNA region of interest.
Residual disease: Nested PCR

1 2 3 4 5 B M5 B

BCR-ABL

b3a2-
b2a2-

1 2 3 4 5 B M5 B

ABL

A2 → ABL control → CA3-

b1 b2 b3 a2 a3

BCR ABL

NB1+ → 1st step BCR-ABL → Ab13-

B2A → 2nd step BCR-ABL → CA3-
TERAPIA
The Ideal Target for Molecular Therapy

Present in the majority of patients with a specific disease

Determined to be the causative abnormality

Has unique activity that is
- Required for disease induction
- Dispensable for normal cellular function
Bcr-Abl as a Therapeutic Target for CML

- Bcr-Abl is detected in 95% of patients with CML
- Bcr-Abl is the causative abnormality of CML
- Bcr-Abl tyrosine kinase is constitutively activated intracellularly
  - Tyrosine kinase activity is required for CML cell function
### Therapy of CML: Response Criteria

**Disappearance of splenomegaly**
Normal physical exam

### Hematologic Response

<table>
<thead>
<tr>
<th>Complete:</th>
<th>Major:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal peripheral blood count</td>
<td>Complete: 0% Ph+ cells</td>
</tr>
<tr>
<td>WBC &lt;10 x 10⁹/L</td>
<td>Partial: 1%–34% Ph+ cells</td>
</tr>
<tr>
<td>Platelets &lt;450 x 10⁹/L</td>
<td><strong>Minor:</strong> 35%–95% Ph+ cells</td>
</tr>
<tr>
<td>No immature cells</td>
<td></td>
</tr>
</tbody>
</table>

**Ph+**=Philadelphia chromosome-positive.
IMATINIB

Tyrosine Kinase Inhibitor for CML
Structure of imatinib

Class: Phenylaminopyrimidines, 589.7 mw
Bcr-Abl–Positive and –Negative Cell Lines


![Graph showing STI571 concentration (μM) vs. % Control CPM for different cell lines. *Bcr-Abl-negative cell lines and †Bcr-Abl-positive cell lines.](image-url)
LAMA84 Control

LAMA84 24h 1uM

LAMA84 44h 1 uM
i.p. 2h  p.o.  i.p. 5h  p.o.  i.p. 9h  p.o.

bcr/abl  →  

anti-phosphotyrosine

bcr/abl  →  

anti-abl
tumor weight mg x 1000

- ctrl
- 3x160 mg/kp p.o.

days

0 5 10 15 20
tumor free survival

- ctrl
- 3x50 mg/kg i.p.
- 3x160 mg/kg p.o.
<table>
<thead>
<tr>
<th>EVENT</th>
<th>NO. OF PATIENTS WITH EVENT (%)</th>
<th>GRADE 3 OR 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ANY GRADE</td>
<td>GRADE 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GRADE 4</td>
</tr>
<tr>
<td><strong>Nonhematologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial edema</td>
<td>318 (60)</td>
<td>6 (1.1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>293 (55)</td>
<td>8 (1.5)</td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>261 (49)</td>
<td>5 (0.9)</td>
</tr>
<tr>
<td>Rash and related events</td>
<td>171 (32)</td>
<td>16 (3.0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>152 (29)</td>
<td>5 (0.9)</td>
</tr>
<tr>
<td>Weight gain</td>
<td>137 (26)</td>
<td>23 (4.3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>125 (23)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>108 (20)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>100 (19)</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>99 (19)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>95 (18)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>93 (17)</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>71 (13)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>69 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>46 (9)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>30 (6)</td>
<td>6 (1.1)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>101 (19)</td>
<td>5 (0.9)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>115 (22)</td>
<td>9 (1.7)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>143 (27)</td>
<td>43 (8.1)</td>
</tr>
</tbody>
</table>
Figure 2. Landmark Analysis of Time to Progression According to the Cytogenetic Response at Three Months.
HEMATOLOGIC AND CYTOGENETIC RESPONSES TO IMATINIB MESYLATE IN CHRONIC MYELOGENOUS LEUKEMIA

Hagop Kantarjian, M.D., Charles Sawyers, M.D., Andreas Hochhaus, M.D., Francois Guilhot, M.D., Charles Schiffer, M.D., Carlo Gambacorti-Passerini, M.D., Dietger Niederwieser, M.D., Debra Resta, R.N., Renaud Capdeville, M.D., Ulrike Zoellner, M.Sc., Moshe Talpaz, M.D., and Brian Druker, M.D., for the International STI571 CML Study Group*
MCyR within <=3 mths
MCyR within >3-6 mths
MCyR within >6-12 mths
MCyR later than 12 mths
= Censored observations

% without loss of MCyR

Months since MCyR

0 6 12 18 24 30 36 42 48 54 60 66

University of Milano
Bicocca, Monza, Italy
## Annual Event Rates in Patients on First-line Imatinib

<table>
<thead>
<tr>
<th>Year after achieving CCyR</th>
<th>All events*</th>
<th>AP/BC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>3.3%</td>
<td>1.5%</td>
</tr>
<tr>
<td>2nd</td>
<td>7.5%</td>
<td>2.8%</td>
</tr>
<tr>
<td>3rd</td>
<td>4.8%</td>
<td>1.6%</td>
</tr>
<tr>
<td>4th</td>
<td>1.5%</td>
<td>0.9%</td>
</tr>
<tr>
<td>5th</td>
<td>0.9%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

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

Log reduction from baseline

Leukocytosis
Ph-chromosome pos
Ph-negative but...
RQ-PCR positive
RQ-PCR negative

Cure?

Number of leukemia cells (log10)

BCR-ABL transcript numbers expressed as log reduction in patients responding to treatment
Figure 4. Overall Survival among Patients Treated with Imatinib Based on an Intention-to-Treat Analysis.

The estimated overall survival rate at 60 months was 89%. After the censoring of data for patients who died from causes unrelated to CML or transplantation, the estimated overall survival was 95% at 60 months. At the time of analysis, 57 patients had died. The number of patients with events and the number of patients available for analysis are shown.
**Clinical Course: Phases of CML**

<table>
<thead>
<tr>
<th>Chronic phase</th>
<th>Advanced phases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median 4–6 years stabilization</td>
<td>Median duration up to 1 year</td>
</tr>
<tr>
<td></td>
<td>Blastic phase (blast crisis)</td>
</tr>
<tr>
<td></td>
<td>Median survival 3–6 months Terminal phase</td>
</tr>
</tbody>
</table>
Figure 1. Median Reduction from Base Line in BCR-ABL Transcript Levels at the Time of a Complete Cytogenetic Remission (Month 0) and Every Three Months Thereafter.
Vertical bars indicate the 25th and 75th percentiles.
Degree of *BCR-ABL* log reduction in 124 CCyR pts at 1 and 4 years (in percent)

![Bar chart showing log reduction in BCR-ABL](chart.png)
Carlo Gambacorti-Passerini

Lo studio ILTE

(Imatinib Long Term Effects)
Supplementary Table 5. Rates of CCyR loss during ILTE follow-up. Rates per year based on line of therapy (upper panel). Rates per year based on age (lower panel).

<table>
<thead>
<tr>
<th>First line</th>
<th>three</th>
<th>four</th>
<th>five</th>
<th>six</th>
<th>seven</th>
<th>eight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Med</td>
<td>eligi</td>
<td>p-rate</td>
<td>eligi</td>
<td>n</td>
<td>p-rate</td>
</tr>
<tr>
<td>yes</td>
<td>2.9</td>
<td>354</td>
<td>2</td>
<td>353.0</td>
<td>0.6</td>
<td>349</td>
</tr>
<tr>
<td>no</td>
<td>4.3</td>
<td>478</td>
<td>6</td>
<td>474.0</td>
<td>1.3</td>
<td>471</td>
</tr>
<tr>
<td>Total</td>
<td>3.7</td>
<td>832</td>
<td>8</td>
<td>827.0</td>
<td>1.0</td>
<td>820</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>three</th>
<th>four</th>
<th>five</th>
<th>six</th>
<th>seven</th>
<th>eight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Med</td>
<td>eligi</td>
<td>p-rate</td>
<td>eligi</td>
<td>n</td>
<td>p-rate</td>
</tr>
<tr>
<td>≤50</td>
<td>3.6</td>
<td>404</td>
<td>4</td>
<td>401.4</td>
<td>1.0</td>
<td>397</td>
</tr>
<tr>
<td>&gt;50</td>
<td>3.9</td>
<td>428</td>
<td>5</td>
<td>425.6</td>
<td>0.9</td>
<td>423</td>
</tr>
<tr>
<td>Total</td>
<td>3.7</td>
<td>832</td>
<td>8</td>
<td>827.0</td>
<td>1.0</td>
<td>820</td>
</tr>
</tbody>
</table>

* median follow-up (years).

† subjects who were in CCyR and who were under observation at the beginning of each time interval.
<table>
<thead>
<tr>
<th>Gender</th>
<th>D=Observed</th>
<th>E=Expected</th>
<th>SIR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>11</td>
<td>21.05</td>
<td>0.52</td>
<td>0.26</td>
</tr>
<tr>
<td>F</td>
<td>9</td>
<td>9.39</td>
<td>0.96</td>
<td>0.44</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>30.44</td>
<td>0.70</td>
<td>0.40</td>
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</tbody>
</table>
Age-Adjusted SEER Incidence Rates
By Cancer Site
For All Ages, All Races, Both Sexes
1975-2005 (SEER 9)

Age-Adjusted U.S. Mortality Rates
By Cancer Site
For All Ages, All Races, Both Sexes
1975-2005

Incidence source: SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta).
Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130). Regression lines are calculated using the Joinpoint Regression Program Version 3.3, April 2008, National Cancer Institute.

Mortality source: US Mortality Files, National Center for Health Statistics, CDC.
Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130). Regression lines are calculated using the Joinpoint Regression Program Version 3.3, April 2008, National Cancer Institute.
LMC
TERAPIA PRE GLIVEC

Qualsiasi rischio

< 30 anni
- donatore
- non donatore

T. allogenico
- α-IFN

Basso rischio

> 30 anni
- α-IFN

RC
- no RC

donatore
- T. allogenico
- α-IFN

Non basso rischio

> 30 anni
- HU

donatore
- non donatore

T. allogenico

Istituto “Seràgnoli” Bologna
LMC
TERAPIA POST GLIVEC

GLIVEC 400mg/die
6-12 mesi

RC

no RC

Glivec

donatore

no donatore

T. allogenico

Glivec+ Ara-C
+ α-IFN

α-IFN + Ara-C
BMT activity for CML in Eurolandia

- Total
- V.U.D.
TIME
THERE IS NEW AMMUNITION IN THE WAR AGAINST CANCER. THESE ARE THE BULLETS.

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

Recidiva ematologica, citogenetica (>10%) o aumento confermato di >5 volte in PCR.
Cytogenetic and hematological response of patient 506

Therapy, month

% of Ph+ cells
WBC (*1000)
% of blasts
PLT(*1000)
Dasatinib in blast phase CML

Duration of major cytogenetic response

Progression was defined as loss of major or minor HR, or no decrease in blasts (PB or BM) from baseline within 4 weeks of maximum dasatinib dose; patients who underwent SCT were censored.

<table>
<thead>
<tr>
<th>Blast Type</th>
<th>n</th>
<th>No. progressed</th>
<th>Median (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloid blast</td>
<td>36</td>
<td>15</td>
<td>16.8</td>
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<tr>
<td>Lymphoid blast</td>
<td>25</td>
<td>18</td>
<td>4.1</td>
</tr>
</tbody>
</table>

Proportion not progressed

Months

Proportion not progressed
III Amplification of BCR/ABL
IV
Mutations of BCR/ABL
Abl w.t.: prospettiva 2

University of Milano
Bicocca, Monza, Italy
Abl T315I: prospettiva 2 (la freccia indica il residuo di Ile315)
Figure 7. The C-terminal lobe of IRK3P with two new antiparallel β sheets (green) owing to phosphorylation of the activation loop. Amino acids Y1163–K1165 and G1184–F1186 of IRK3P correspond in ABL to Y393–A395 and N414–F416. Amino acids R1155–I1157 and K1127–V1129 of IRK3P correspond in ABL to R386–M388 and N358–I360. Amino acids M1120 and F1256, corresponding to the positions of ABL involved in the mutations (M351 and F486), are shown. Adenyl imido-diphosphate is shown in blue.
CONFORMATION
Molecular structures and biological data

Table below shows the IC$_{50}$ values of these two kinase inhibitors.

<table>
<thead>
<tr>
<th></th>
<th>Dasatinib</th>
<th>SKI-606</th>
</tr>
</thead>
<tbody>
<tr>
<td>r-Abl</td>
<td>0.3 nM</td>
<td>2.6 nM</td>
</tr>
</tbody>
</table>
Bosutinib: A Dual Inhibitor of Src and Abl Kinases

Src Enzyme (Elisa) IC$_{50}$ = 1.2 nM
Src Enzyme (Lance) IC$_{50}$ = 3.8 nM
Abl Enzyme IC$_{50}$ = 1.4 nM

K562 Cell IC$_{50}$ = 20 nM
KU812 Cell IC$_{50}$ = 4.3 nM

Courtesy of L Scapozza and A Shaheen, University of Geneva, Switzerland
<table>
<thead>
<tr>
<th>IC50-fold increase (WT=1)</th>
<th>Bosutinib</th>
<th>Imatinib</th>
<th>Dasatinib</th>
<th>Nilotinib</th>
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</thead>
<tbody>
<tr>
<td>Parental</td>
<td>38.31</td>
<td>10.78</td>
<td>&gt;60</td>
<td>38.43</td>
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<tr>
<td>WT</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>P -LOOP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L248V</td>
<td>2.97</td>
<td>3.54</td>
<td>5.11</td>
<td>2.80</td>
</tr>
<tr>
<td>G250E</td>
<td>4.31</td>
<td>6.66</td>
<td>4.45</td>
<td>4.56</td>
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<tr>
<td>Q252H</td>
<td>0.81</td>
<td>1.39</td>
<td>3.05</td>
<td>2.64</td>
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<tr>
<td>Y253F</td>
<td>0.96</td>
<td>3.58</td>
<td>1.58</td>
<td>3.23</td>
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<tr>
<td>E255K</td>
<td>9.47</td>
<td>6.02</td>
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<td>6.69</td>
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<tr>
<td>E255V</td>
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<td>15.59</td>
<td>3.44</td>
<td>10.31</td>
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<td>D276G</td>
<td>0.60</td>
<td>2.18</td>
<td>1.44</td>
<td>2.00</td>
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<tr>
<td>C-Helix</td>
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<td></td>
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<tr>
<td>E279K</td>
<td>0.95</td>
<td>3.55</td>
<td>1.64</td>
<td>2.05</td>
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<tr>
<td>V299L</td>
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<td>1.54</td>
<td>8.65</td>
<td>1.34</td>
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<td>Active site</td>
<td></td>
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<tr>
<td>T315I</td>
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<td>17.50</td>
<td>75.03</td>
<td>39.41</td>
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<tr>
<td>F317L</td>
<td>2.42</td>
<td>2.60</td>
<td>4.46</td>
<td>2.22</td>
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<tr>
<td>SH2-contact</td>
<td>M351T</td>
<td>0.70</td>
<td>1.76</td>
<td>0.88</td>
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<tr>
<td>Active site</td>
<td>F359V</td>
<td>0.93</td>
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<tr>
<td>L384M</td>
<td>0.47</td>
<td>1.28</td>
<td>2.21</td>
<td>2.33</td>
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<td>H396P</td>
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<td>2.43</td>
<td>1.07</td>
<td>2.41</td>
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<tr>
<td>H396R</td>
<td>0.81</td>
<td>3.91</td>
<td>1.63</td>
<td>3.10</td>
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<tr>
<td>G398R</td>
<td>1.16</td>
<td>0.35</td>
<td>0.69</td>
<td>0.49</td>
</tr>
<tr>
<td>C terminal lobe</td>
<td>F486S</td>
<td>2.31</td>
<td>8.10</td>
<td>3.04</td>
</tr>
</tbody>
</table>

Table 1: Activity of bosutinib, imatinib, nilotinib and dasatinib against mutated form of BCR/ABL. For each mutant the relative IC50 increase over wild type BCR/ABL was calculated. Results represent the average of at least three independent experiments. SE<19%. IC50 values on Ba/F BCR/ABL WT were 527nM for imatinib, 41.61nM for bosutinib, 1.83nM for dasatinib, 14.42nM for nilotinib. This table will be periodically updated with new mutants/inhibitors and will be available at www.lite-cml.org/TKI-table.pdf