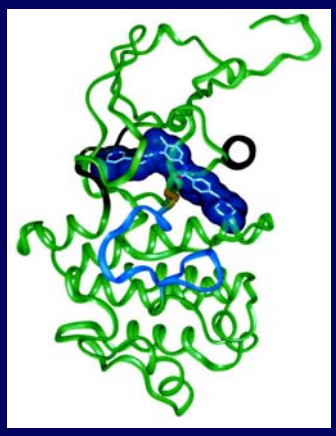
Imatinib Resistance and Other Diseases Targeted by Imatinib

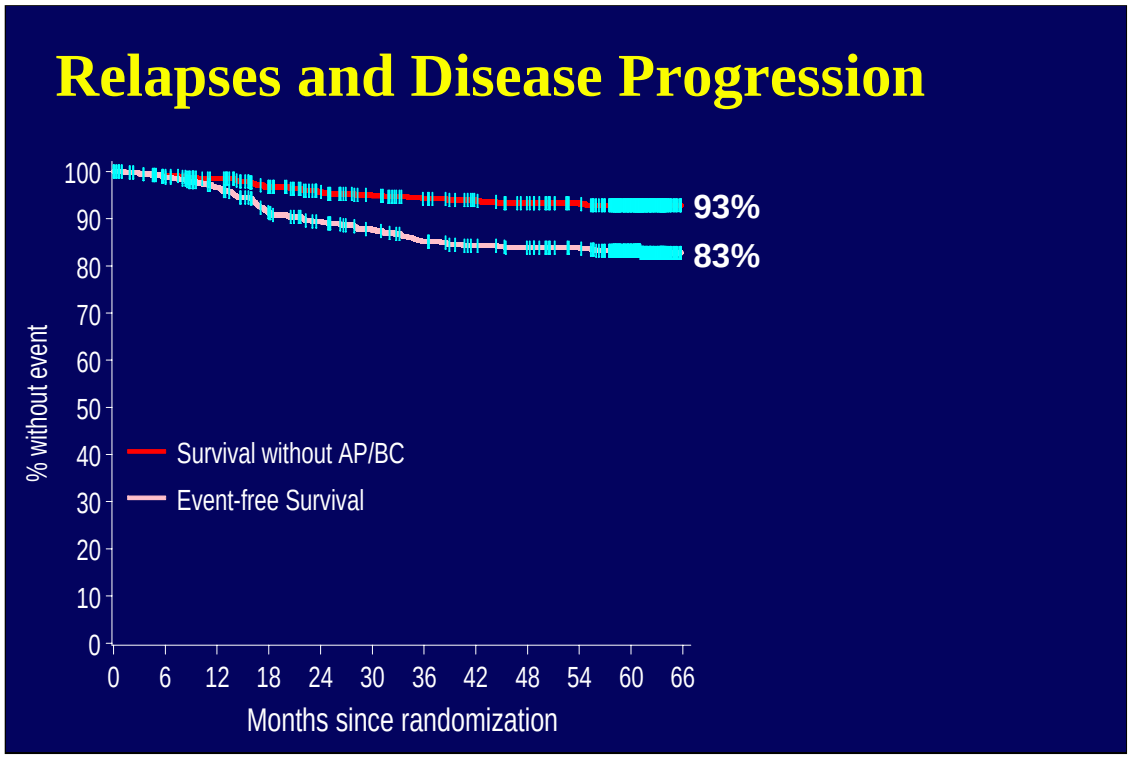


OHSU CANCER INSTITUTE

Brian J. Druker, MD

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**



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

Relapse Rate (4 Years)

- **Chronic (IFN failure)** **26%**
- **Accelerated** **73%**
- **Blast** **95%**

Why Do Some Patients Relapse?

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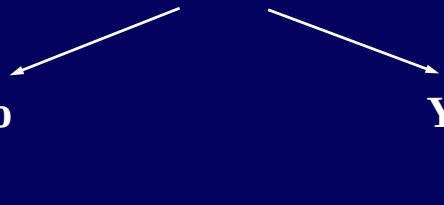


No

- **Drug efflux**
- **Bcr-Abl amplification**
- **Kinase mutations**
- **Drug metabolism**
- **Others**

Yes

- **Additional mutations**

BCR-ABL Substrates

Tyrosine Phosphorylated Proteins in CML Patient Samples

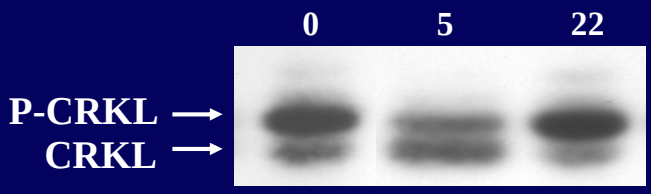
- **Bcr-Abl**
- **CrkL**
- **p62Dok**
- **STAT5**

CrkL

- Most heavily tyrosine phosphorylated protein in CML cells
- Direct substrate of BCR-ABL
- Required for BCR-ABL transformation

Inhibition of Crkl Phosphorylation by Imatinib

Reactivation of the BCR-ABL Kinase at Relapse



M. Gorre et al, Science 293:876, 2001

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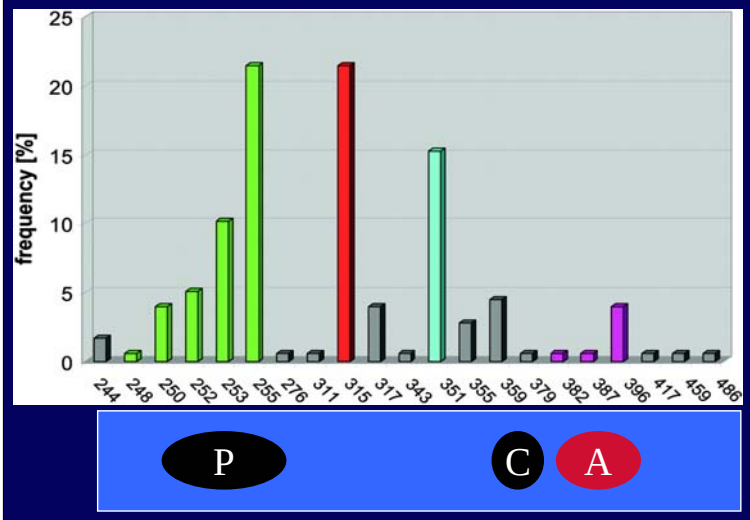
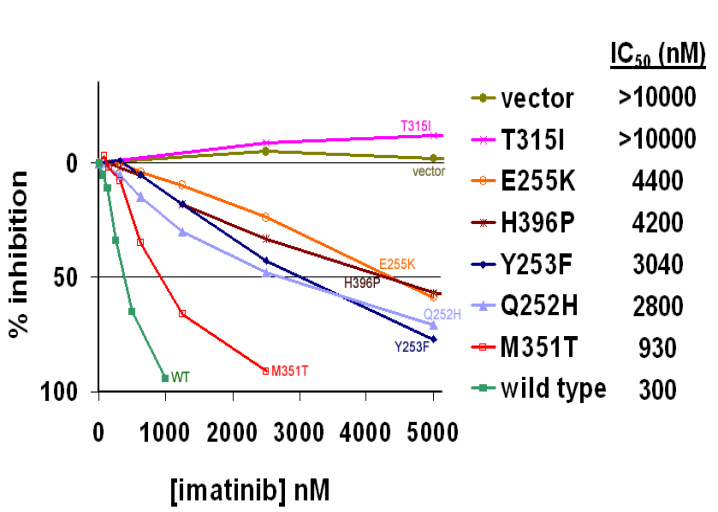
- **Others**

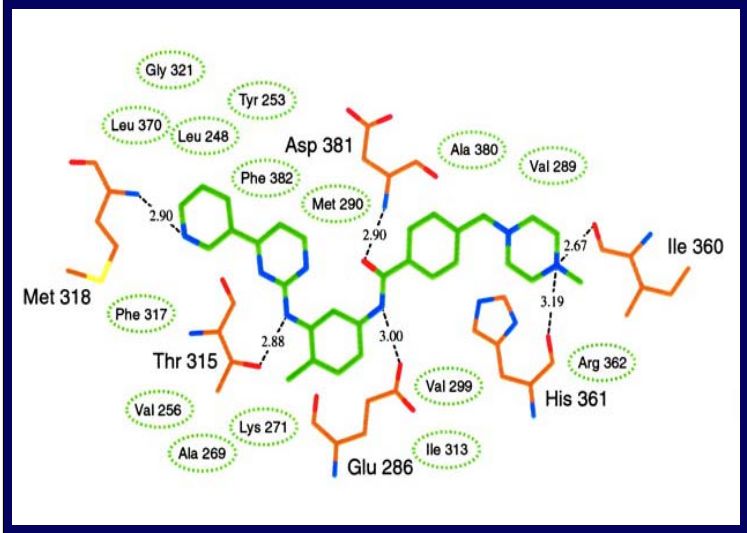
Abl Kinase Domain Mutations



Inhibition of Cell Proliferation by Imatinib



Contact Sites of ABL and Imatinib



B. Nagar et al, Cancer Res 62:4236-4243, 2002

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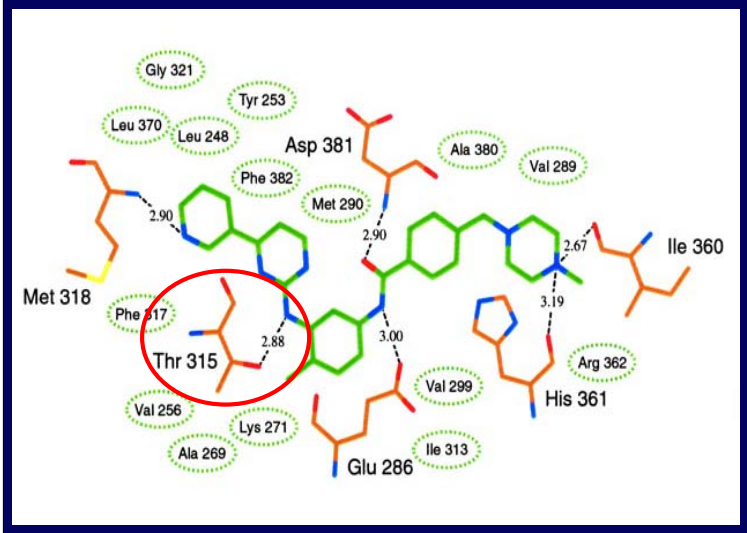

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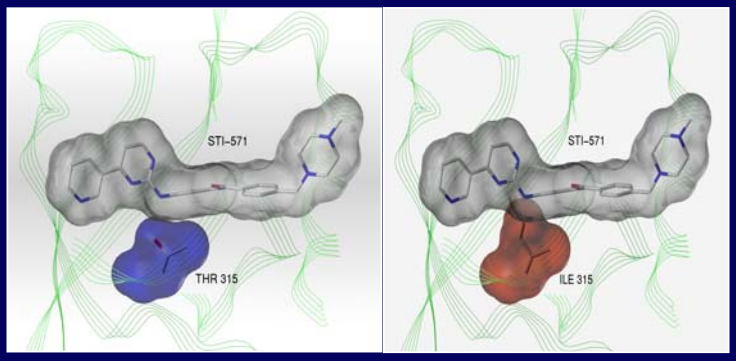
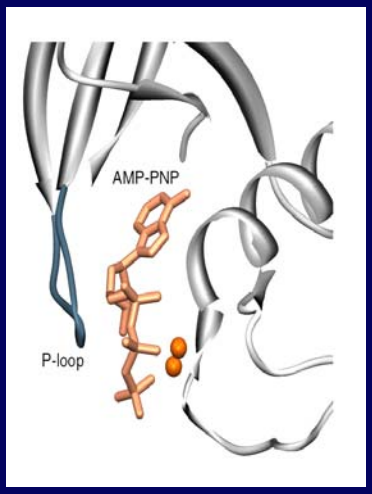
T315I



WILD-TYPE

T315I MUTANT (MODEL)

P-loop Mutants



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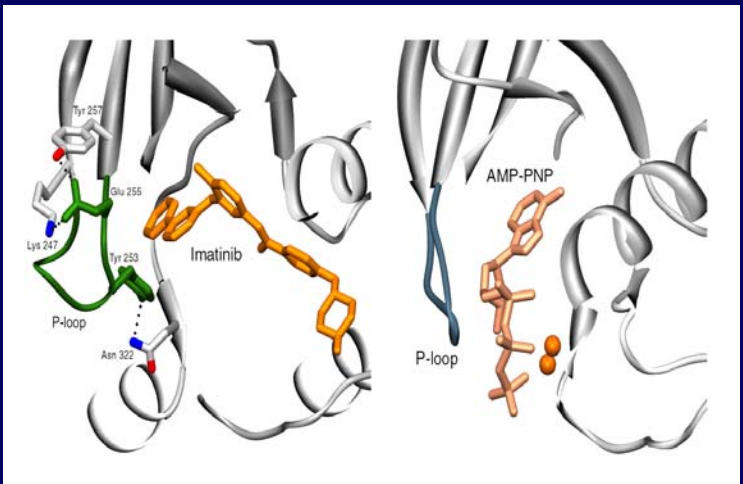
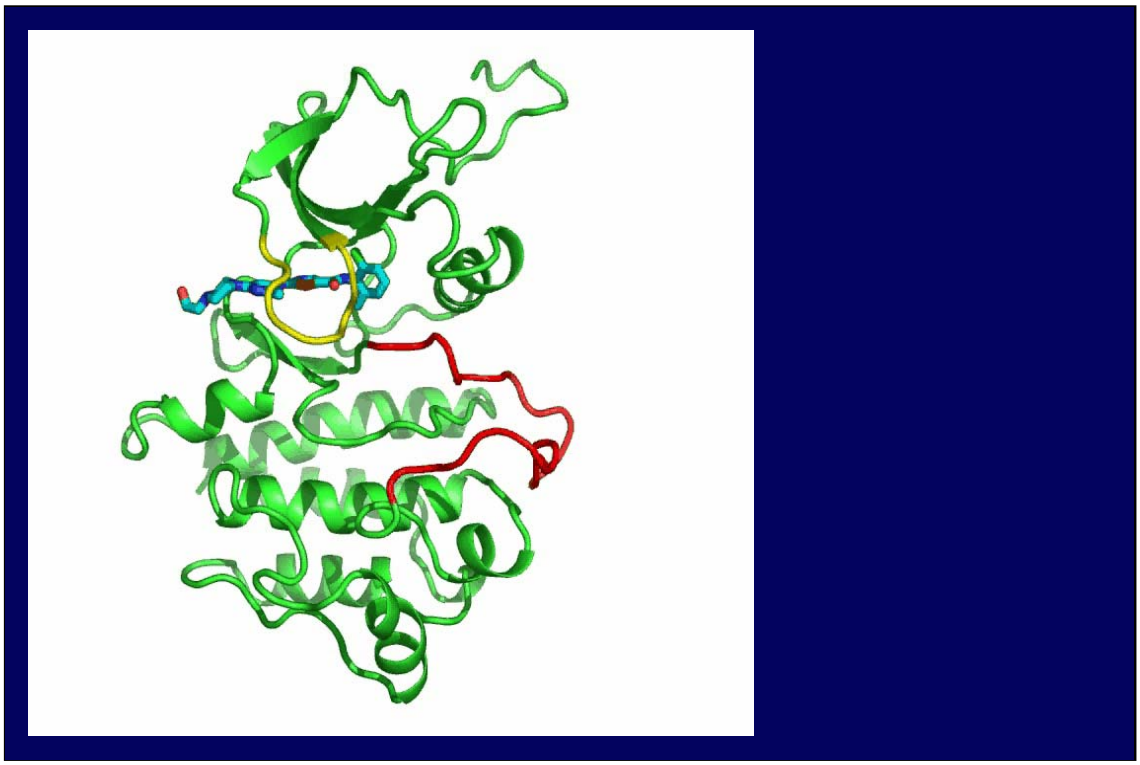
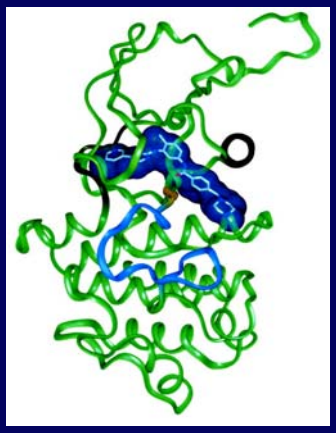
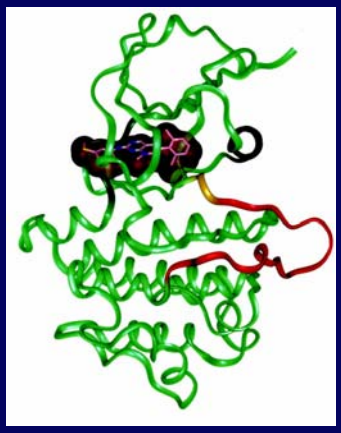




Structure of the ABL Kinase Domain

ABL kinase with imatinib **ABL kinase with PD173955**





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Novel ABL Inhibitors

- **Nilotinib (Tasigna, AMN107)**
  - **Modification of imatinib structure to allow tighter binding**

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  - **Fewer structural constraints to binding**
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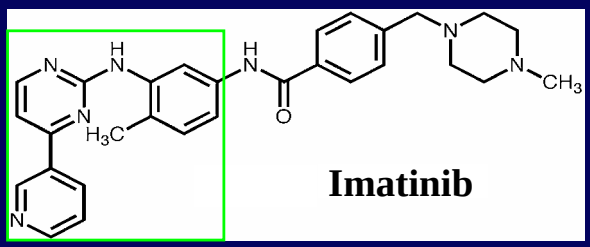
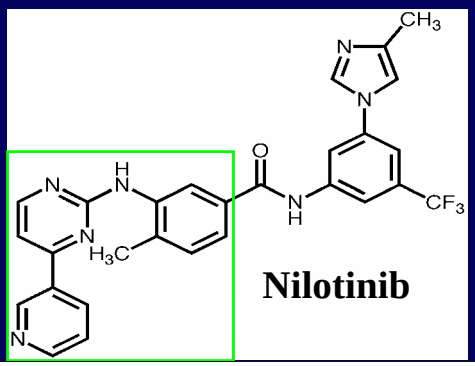
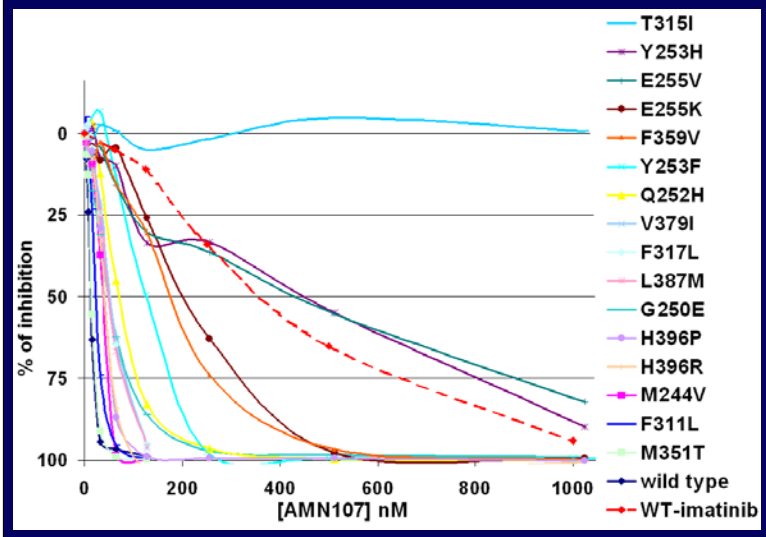
- **Both more potent ABL inhibitors than imatinib**

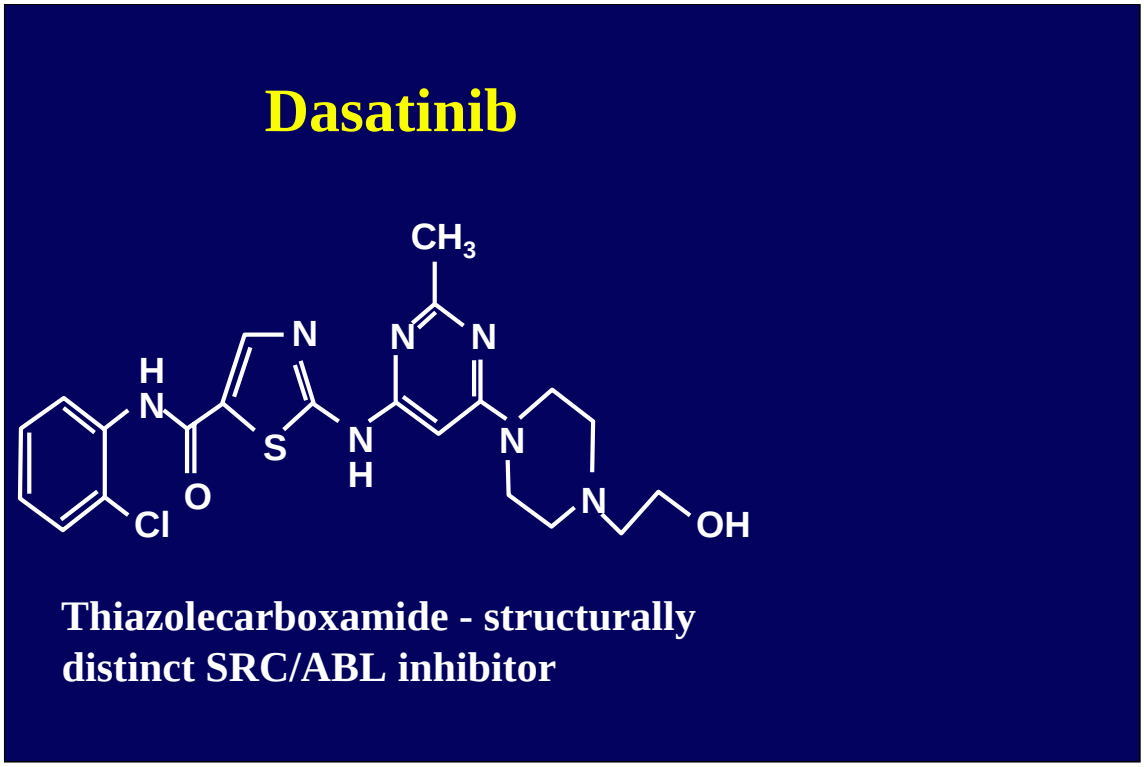
Imatinib vs Nilotinib





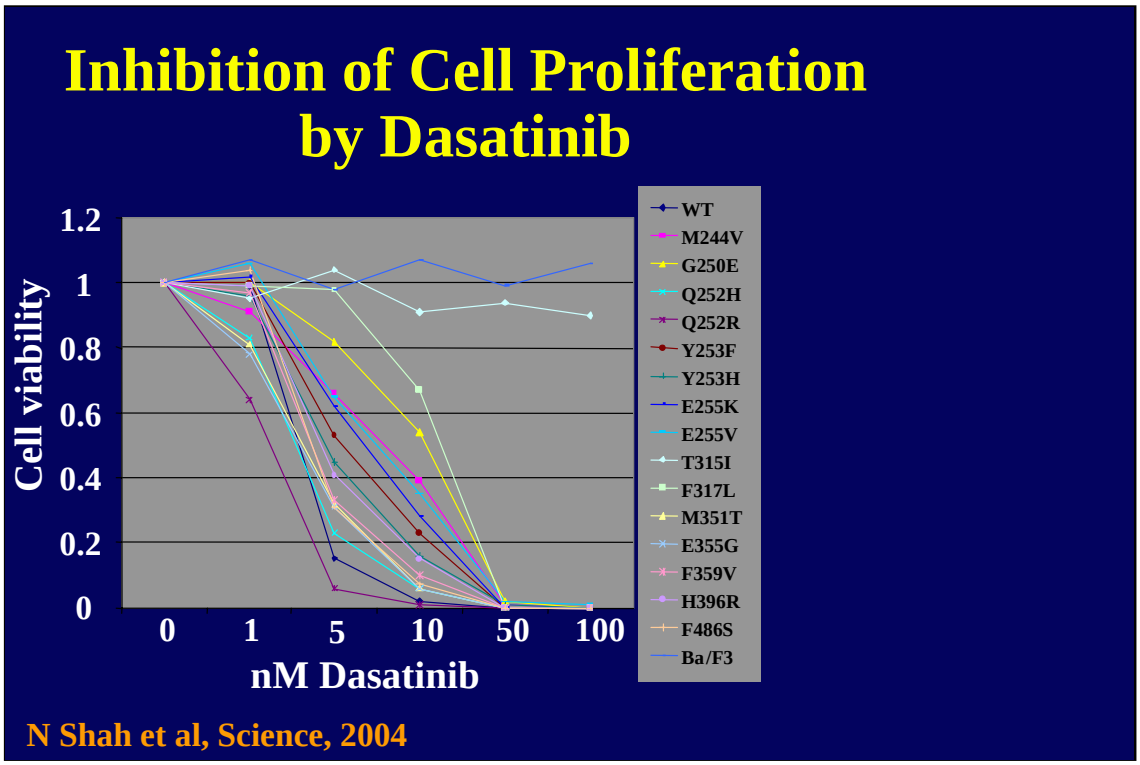
Inhibition of Cell Proliferation by Nilotinib

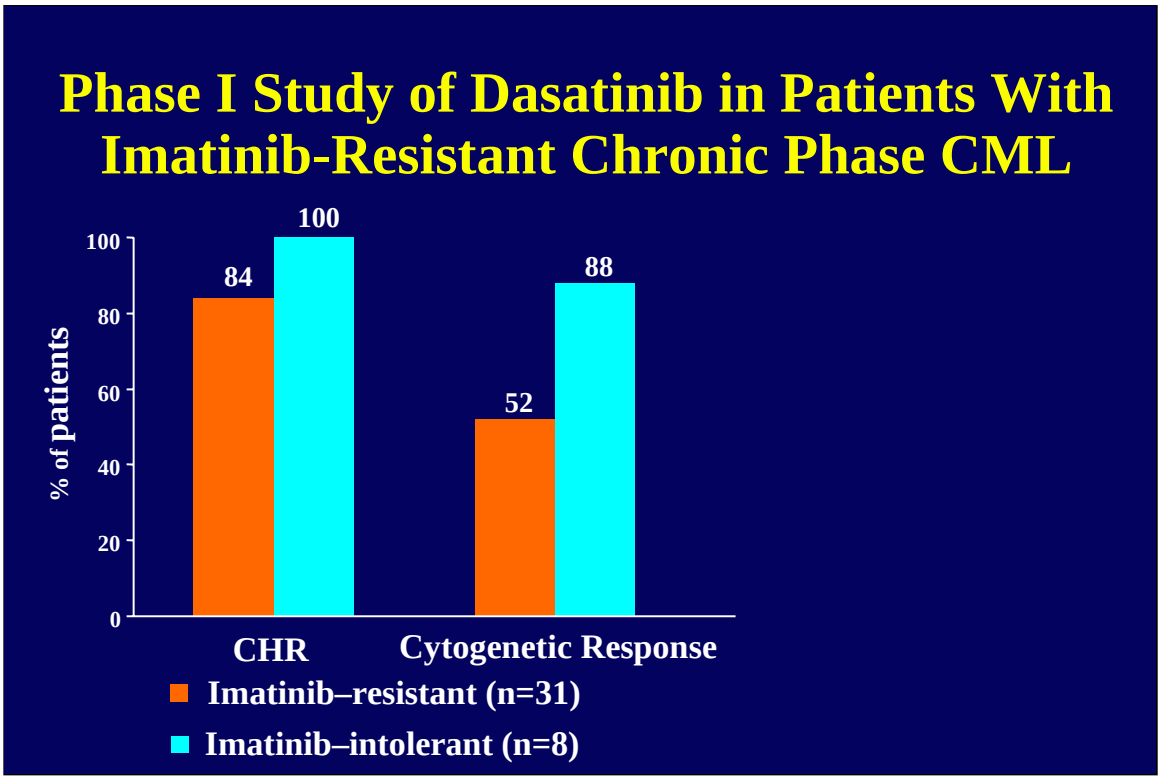




Dasatinib is a thiazolecarboxamide derivative that is not structurally related to the pyrido [2,3-d]-pyrimidine class of molecules. As such, it is expected to have the capacity to bind Bcr-Abl with less stringent Abl conformational requirements than many other classes of Abl kinase inhibitors.

Shah NP, Tran C, Lee FY, Chen P, Norris D, Sawyers CL. Overriding imatinib resistance with a novel ABL kinase inhibitor. *Science*. 2004;305:399-401.


Inhibition of Cell Proliferation by Dasatinib
Cell viability
1.2
1
0.8
0.6
0.4
0.2
0
0
1
5
10
50
100
nM Dasatinib
WT
M244V
G250E
Q252H
Q252R
Y253F
Y253H
E255K
E255V
T315I
F317L
M351T
E355G
F359V
H396R
F486S
Ba/F3
N Shah et al, Science, 2004



Patients with chronic phase CML (N=40) for whom prior imatinib mesylate therapy had failed (defined as hematologic resistance to [n=32] or intolerance of imatinib mesylate [n=8]) were treated with dasatinib in a dose-escalation study. Doses of dasatinib ranged from 15 to 180 mg/d for 5 to 7 days/week in 3-patient cohorts. Patients treated with lower doses of dasatinib had their doses escalated once the safety of higher doses was established.

CHRs were achieved by 67% of patients resistant to imatinib mesylate. Fifty-two percent of patients resistant to imatinib mesylate achieved a cytogenetic response, including 29% of patients with CCRs.

The results in patients intolerant of imatinib mesylate were more robust, where all patients achieved a CHR, with 88% of patients achieving a cytogenetic response, including 50% with CCRs.

Talpaz M, Kantarjian HM, Paquette R, et al. A phase I study of BMS-354825 in patients with imatinib-resistant and intolerant chronic phase chronic myeloid leukemia (CML): results from CA180002. Program and abstracts of the 41st Annual Meeting of the American Society of Clinical Oncology; May 13-17, 2005; Orlando, Fla. Abstract 6519.

Summary of Dasatinib and Nilotinib Trials

- Significant activity in imatinib-resistant patients
- Activity observed against all imatinib-resistant mutants except T315I
- Relapses common in advanced phase
  - T315I
  - Other causes

Summary of Imatinib Resistance

- **Relapses mostly due to kinase domain mutations**
  - **Novel ABL inhibitors have significant activity**

Summary of Imatinib Resistance

- Relapses mostly due to kinase domain mutations
  - Novel ABL inhibitors have significant activity
- T315I remains insensitive to all current inhibitors
  - Numerous preclinical compounds

Other Diseases Targeted by Imatinib

Other Diseases Targeted by Imatinib

- Gastrointestinal stromal tumor
  - Driven by KIT mutations
- Hypereosinophilic syndrome
  - Driven by PDGF receptor rearrangement
- A few other rare diseases

Imatinib and Gastrointestinal Stromal Tumor (GIST)

Gastrointestinal Stromal Tumor

- **GIST: intestinal sarcoma (formerly intestinal leiomyosarcoma) – KIT positive**
- **US annual incidence: ~5,000 cases**

Gastrointestinal Stromal Tumor

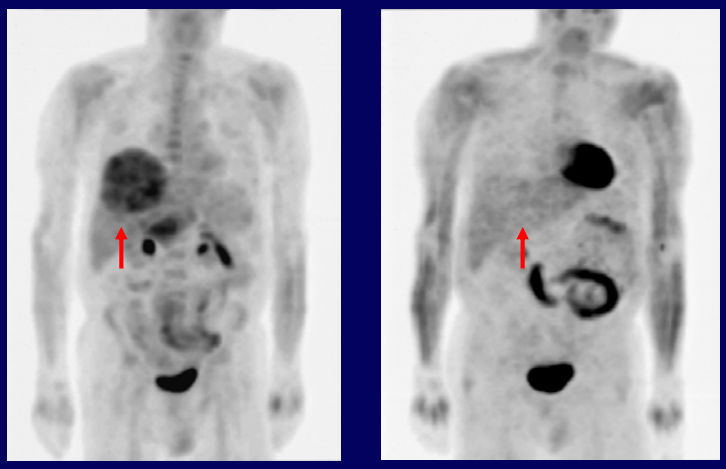
- **Response rates to chemotherapy <5%**
- **Activating KIT mutations are present in the majority of patients**

Imatinib Response Data - GIST

	n= 147
Partial response (%)	54%
Stable disease (%)	28%
Progression (%)	14%

G. Demetri, et al, N Engl J Med 347:472-480, 2002

PET Scan - GIST



Pre - 12/7/00 1/9/01

G. Demetri, et al

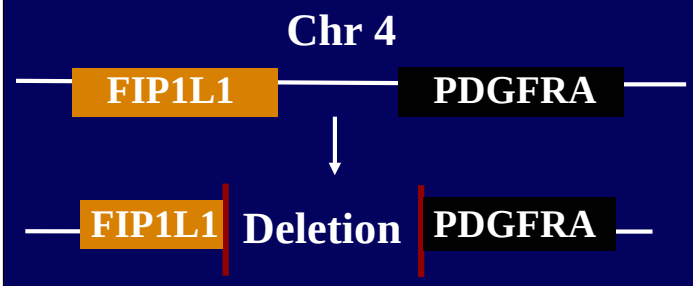
Idiopathic Hypereosinophilic Syndrome (HES)

- Prolonged eosinophilia
  - >1,500/ul in blood
- Exclusion of other etiologies
  - Parasitic infection, allergy, etc.
- End organ damage
  - Heart, lungs, CNS, skin

HES and Imatinib

- **Anecdotal reports of dramatic responses to imatinib**
- **Suggests HES is caused by a kinase that is inhibited by imatinib**
  - **ABL, ARG, KIT, PDGFRA, PDGFRB**

Molecular Pathogenesis of HES



J. Cools et al, N Engl J Med 348:1201-14, 2003

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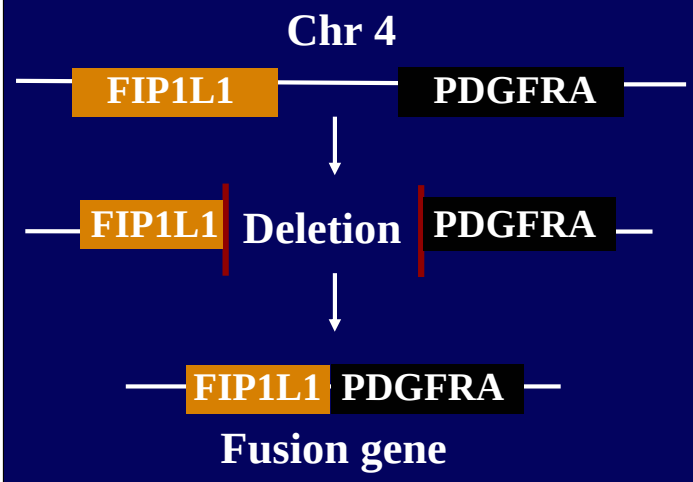

J. Cools et al, N Engl J Med 348:1201-14, 2003

An understanding of the molecular targets of a drug can lead to insights into molecular pathogenesis