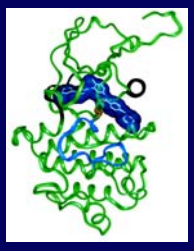
Imatinib Resistance and Other Diseases Targeted by Imatinib



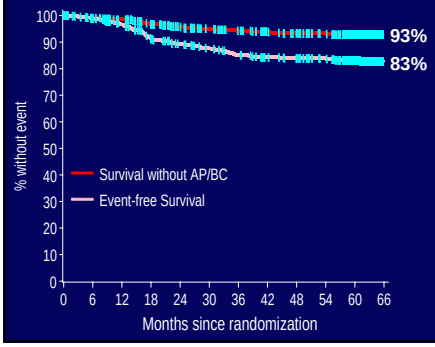
OHSU CANCER INSTITUTE

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

Relapses and Disease Progression



Relapse Rate (4 Years)

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

Why Do Some Patients Relapse?

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Is BCR-ABL kinase inhibited?

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Why Do Some Patients Relapse?

Is BCR-ABL kinase inhibited?

No

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

Yes

- Additional mutations

BCR-ABL Substrates

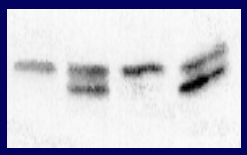
Tyrosine Phosphorylated Proteins in CML Patient Samples

- Bcr-Abl
- CrkL
- p62Dok
- STAT5

CrkL

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

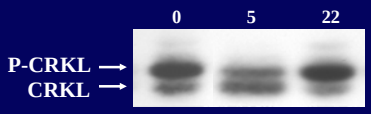
Inhibition of Crkl Phosphorylation by Imatinib



0 1 0 1 Day

250 750 Dose (mg)

Reactivation of the BCR-ABL Kinase at Relapse



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

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↓

- Bcr-Abl amplification
- Kinase mutations
- Drug efflux
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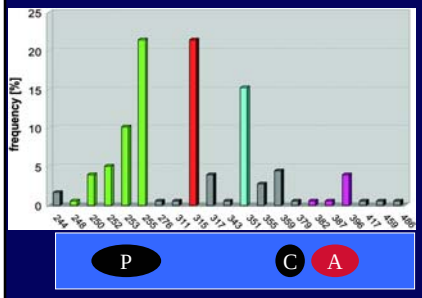
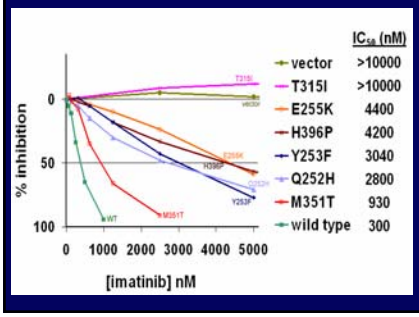
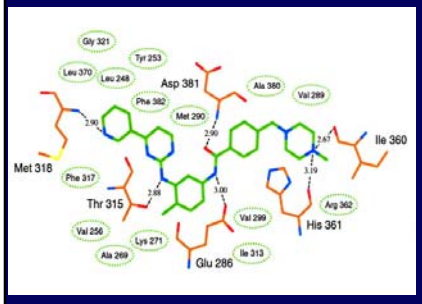
Abl Kinase Domain Mutations



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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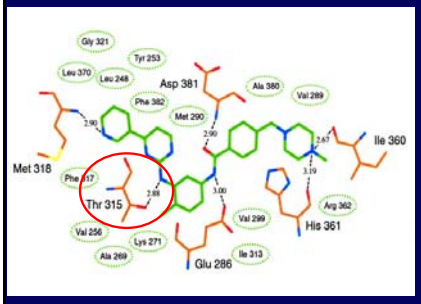
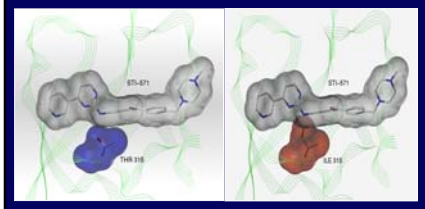


B. Nagar et al, Cancer Res 62:4236-4243, 2002

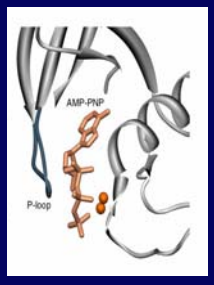
T315I



WILD-TYPE

T315I MUTANT (MODEL)

P-loop Mutants



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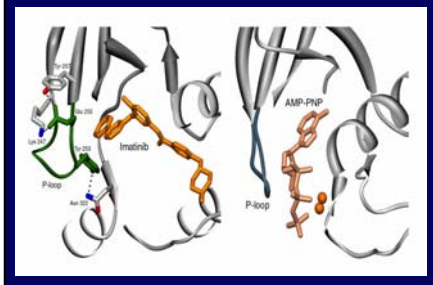
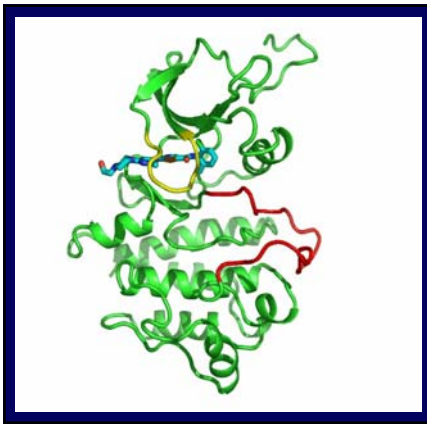
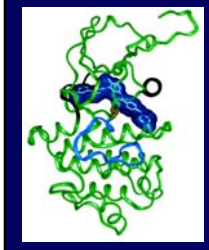




Structure of the ABL Kinase Domain

ABL kinase with imatinib



ABL kinase with PD173955

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

Novel ABL Inhibitors

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

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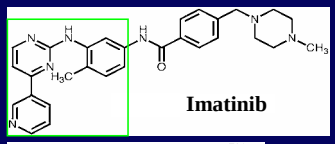
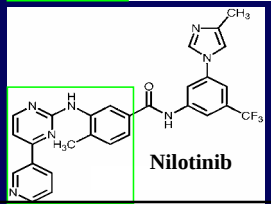
- Both more potent ABL inhibitors than imatinib

Imatinib vs Nilotinib

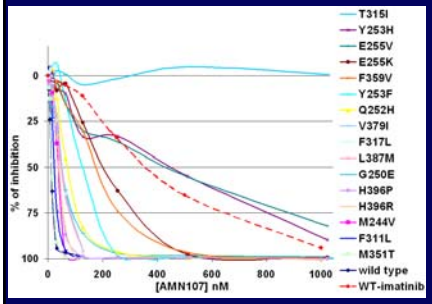


Imatinib



Nilotinib

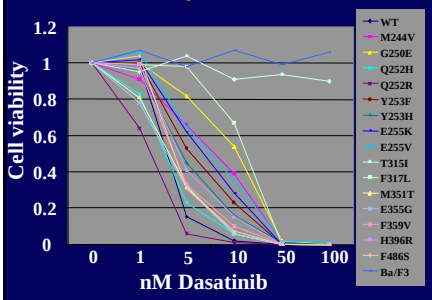
Inhibition of Cell Proliferation by Nilotinib



Dasatinib

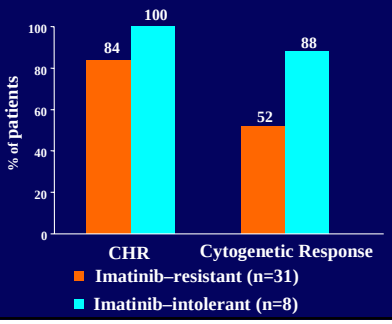
Thiazolecarboxamide - structurally distinct SRC/ABL inhibitor

Inhibition of Cell Proliferation by Dasatinib



N Shah et al, Science, 2004

Phase I Study of Dasatinib in Patients With Imatinib-Resistant Chronic Phase CML



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

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- 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

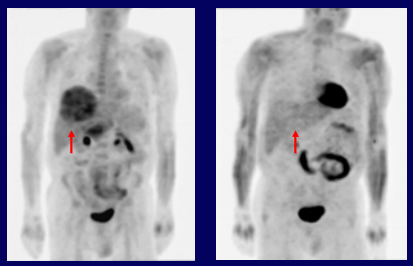
- Response rates to chemotherapy <5%
- Activating KIT mutations are present in the majority of patients

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

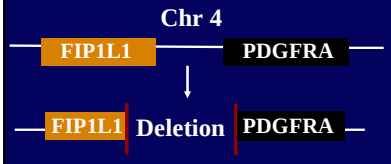
Idiopathic Hypereosinophilic Syndrome (HES)

- 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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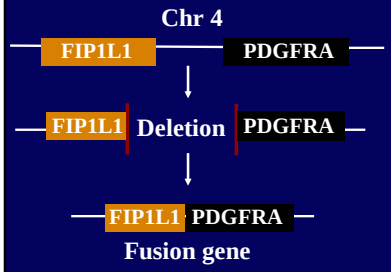

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An understanding of the molecular targets of a drug can lead to insights into molecular pathogenesis