AML: INDUCTION THERAPY

- Two cycles of cytosine arabinoside + daunorubicin +/-thioguanine and other agents gives remissions in 70-90%

- **Chemotherapy alone has given 30-50 % cure rates.**

- **Cure is higher after timed-sequential induction therapy (42% vs. 27%).**

- **Short (4-12 months) of post-induction therapy is adequate**
- **CNS leukemia is less common than in ALL; 'prophylaxis' may be accomplished with high dose Ara-C +/- intrathecal Ara-C**

AML Treatment: Consolidation

Following induction into Complete Remission

- 3-4 cycles of high dose cytosine arabinoside (HiDAC) administered approximately every 5-6 weeks

OR

- Bone marrow (peripheral blood stem cell) transplant

(Depends on degree of risk)

Common side effects

More than 10 in every 100 people have one or more of the side effects listed below.

- Fatigue (tiredness) during and after treatment – most people find their energy levels are back to normal after 6 months to a year
- Soreness at the injection site (if you are having injections under the skin)
- Women may stop having periods (amenorrhoea) but this may only be temporary

Occasional side effects

- Dizziness However

CLL – treatment

- **Watch and wait**
- **Monotherapy**
  - glucocorticoids
  - alkylating agents (Chlorambucil, Cyclophosphamide)
  - purine analogues (Fludarabine, Cladribine, Pentostatin)
- **Combination chemotherapy**
  - Chlorambucil/ Cyclophosphamide + Prednisone
  - Fludarabine + Cyclophosphamide +/- Mitoxantrone
  - CVP, CHOP
- **Monoclonal antibodies (monotherapy and in combination)**
  - Alemtuzumab (anti-CD52)
  - Rituximab (anti-CD20)

Treatment of CLL

Categorize According to Risk

(FISH, CD38, ZAP-70, Ig mutational status)

Low Risk

Minimally toxic therapy

- Rituximab
- Chlorambucil
- Fludarabine

Intermediate Risk

Nucleoside analog combination regimens

- Fludarabine and cyclophosphamide
- Fludarabine and rituximab
- Fludarabine, cyclophosphamide, and rituximab

High Risk

- Clinical trial
- BMT, myeloablative or non-myeloablative

Rituximab as part of first-line therapy for CLL: Rationale

- Rituximab monotherapy is moderately active in CLL
  - Activity is dose dependent (between 500–2250 mg/m2)1

- Rituximab acts synergistically with other cytotoxic agents *in vitro*
  - Increases fludarabine activity in NHL cell lines
  - Increases activity of bendamustine, mitoxantrone and other chemotherapeutic agents in CLL cells

CLL

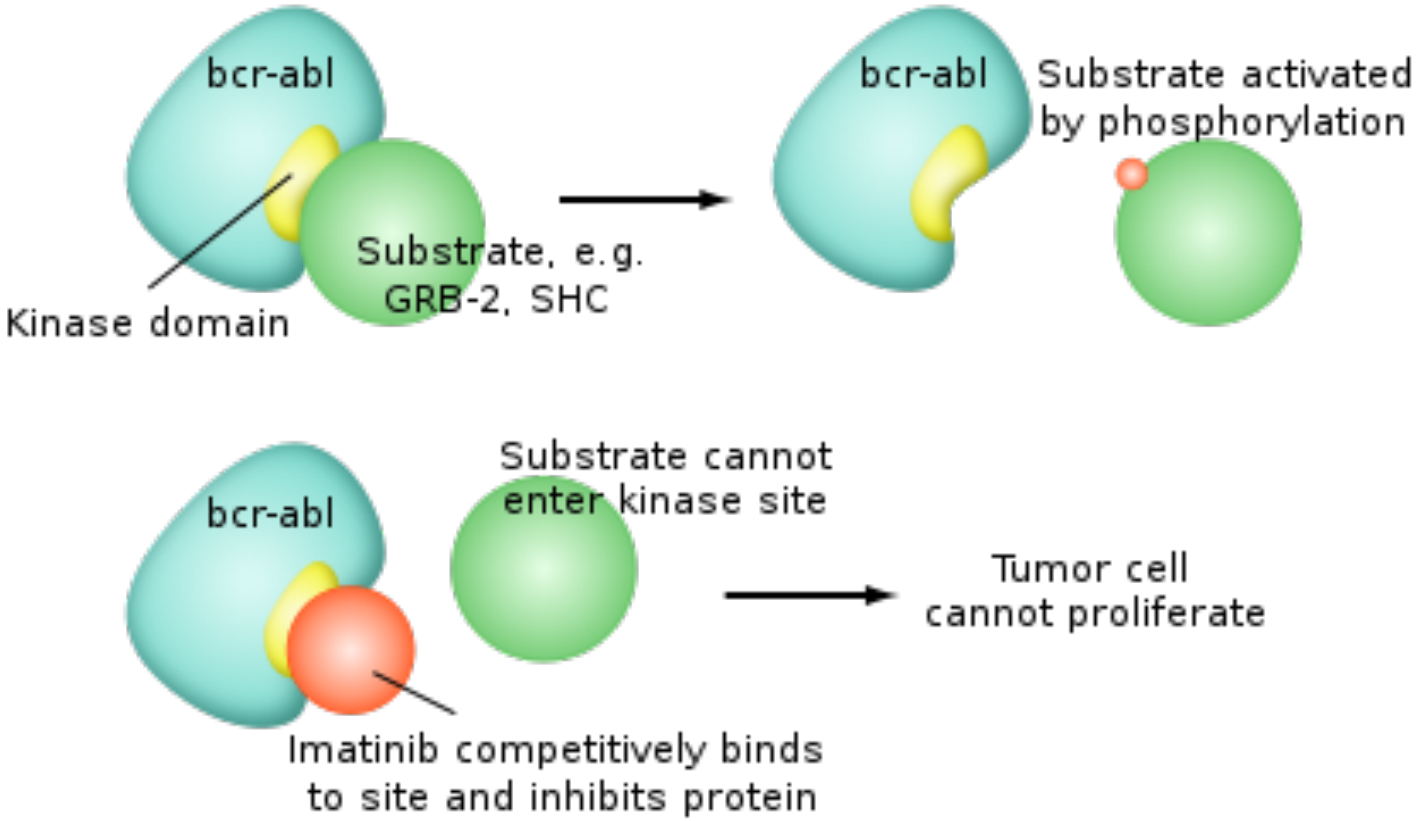
Determining when to start treatment and by what means is often difficult; studies have shown there is no survival advantage to treating the disease too early.

Imatinib

- **Philadelphia chromosome** or **Philadelphia translocation** is a specific chromosomal abnormality that is associated with chronic myelogenous leukemia (CML).

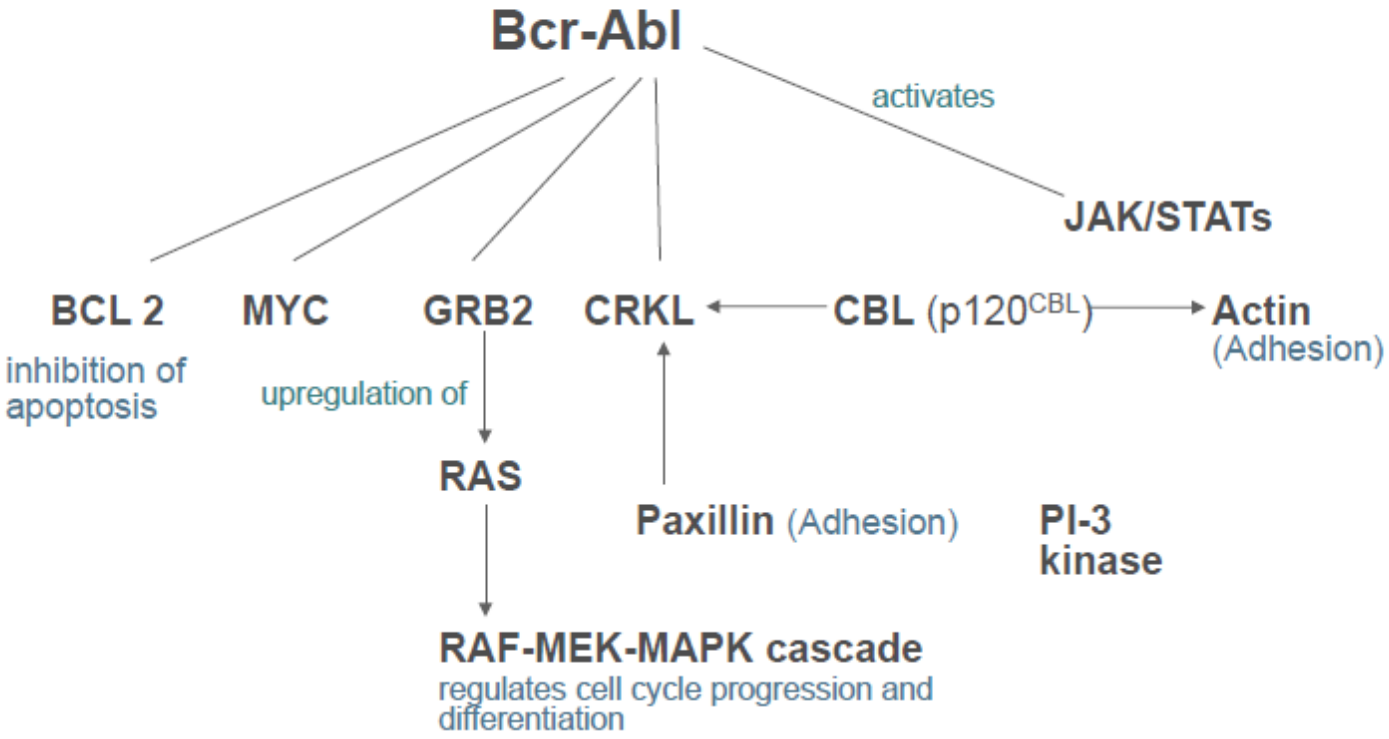
- **This translocation results in the Bcr-Abl fusion protein, the causative agent in CML, and is present in up to 95% of patients with this disease.**

- **Imatinib is an inhibitor of the tyrosine kinase domain of the Bcr-Abl oncoprotein and prevents the phosphorylation of the kinase substrate by ATP.**

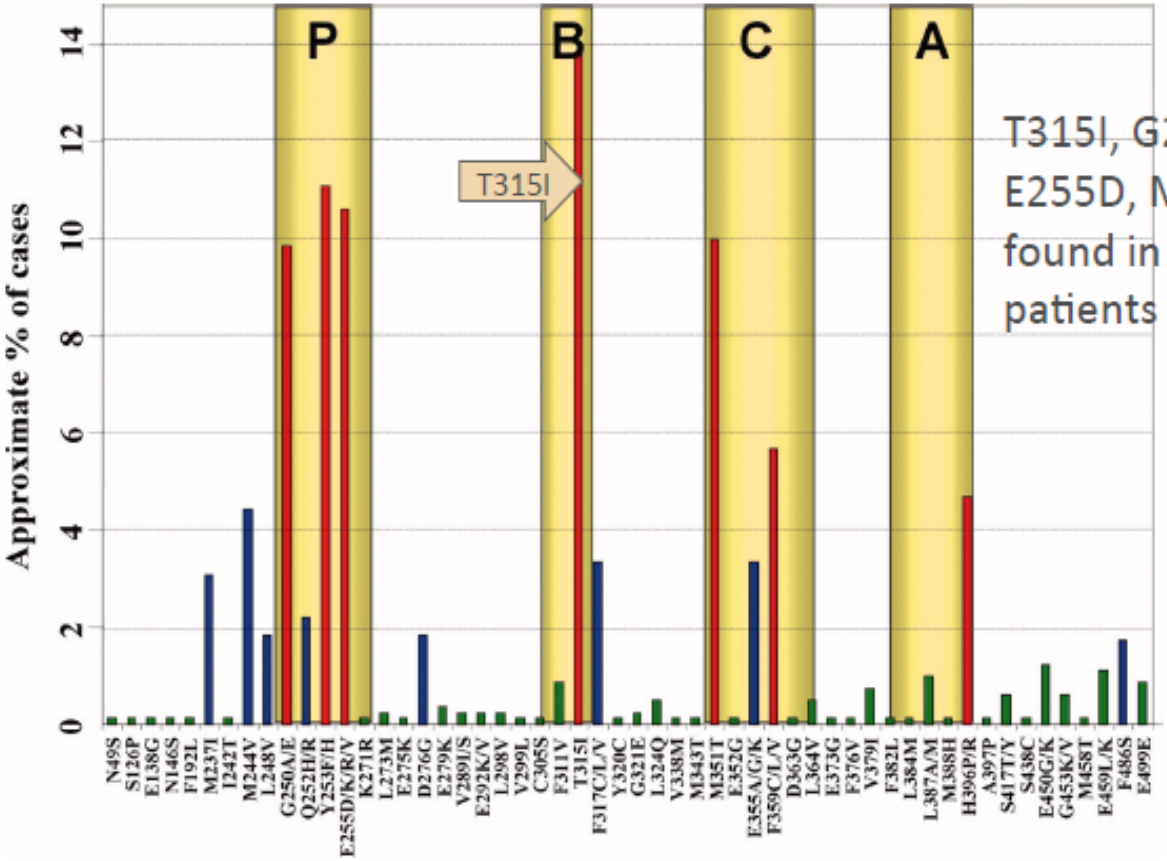


Gleevec is one of the most effective modern medications for cancer treatment,.

Bcr-Abl Signal Transduction Pathways



Incidence of BCR-ABL Mutations After Imatinib Failure



T315I, G250A, Y253F, E255D, M351T are found in >10% of patients with mutations

p = P-loop, b = imatinib binding, c = catalytic domain, a = activation loop.

Nilotinib and Dasatinib

- Nilotinib (AMN107)
  - Developed from imatinib
  - Structure similar; altered to allow for greater ABL potency and selectivity
  - 20-50x more potent *in vitro*
  - Active against some imatinib resistant Abl kinase mutants except T315I
  - FDA approved Nov 2007
- Dasatinib (BMS 354825)
  - Developed as an inhibitor of Src kinase
  - Structure different than imatinib; greater potency; able to bind different conformations
  - ~300x more potent *in vitro*
  - Active against some imatinib resistant Abl kinase mutants except T315I
  - FDA approved June 2006

ENESTnd: Cardiovascular Events by Year of Treatment

First Cardiovascular Event by Year, n (%)[a]	Nilotinib 300 mg BID (n = 279)	Nilotinib 400 mg BID (n = 277)	Imatinib 400 mg QD (n = 280)
< 1 y	4 (1.4)	10 (3.6)	2 (0.7)
≥ 1 y to < 2 y	4 (1.4)	6 (2.2)	0
≥ 2 y to < 3 y	7 (2.5)	6 (2.2)	1 (0.4)
≥ 3 y to < 4 y	4 (1.4)	4 (1.4)	1 (0.4)
≥ 4 y to < 5 y	1 (0.4)	6 (2.2)	1 (0.4)
≥ 5 y to < 6 y	5 (1.8)	9 (3.2)	1 (0.4)
≥ 6 y to < 7 y	3 (1.1)	2 (0.7)	1 (0.4)
≥ 7 y to < 8 y	0	1 (0.4)	0

Year of first cardiovascular event was assigned based on the start date of the first cardiovascular event reported in each patient. Patients with multiple events were counted only once under the year during which their first cardiovascular event was reported.

	Recorded in CML Patients treated with* Dasatinib*	Nilotinib*
Pleural effusion	+++	+/-
Pulmonary hypertension	+	+/-
Pericardial effusion	+	+/-
Viral reactivation	+	+/-
Increase in NK cells	++	+/-
Peripheral edema	++	++
Skin rash	+++	+++
Major bleeding	+	+
Diarrhea	+++	+++
Increase in fasting glucose	+/-	+++
Increase in pancreatic enzymes	+/-	+++
Progressive peripheral arterial occlusive disease	- (n.r.)**	++**

*+++, reported in >15% of all patients; ++, reported in 5-14% of all patients; +, reported in 1-4% of all patients; +/-, recorded in less than 1% of patients. *Data refer to previous studies performed in CML patients given dasatinib (100-140 mg daily) or nilotinib (2x300 or 2x400 mg*

Ponatinib:
A Pan-BCR-ABL Inhibitor

Rationally designed inhibitor of BCR-ABL

Active against T315I mutant

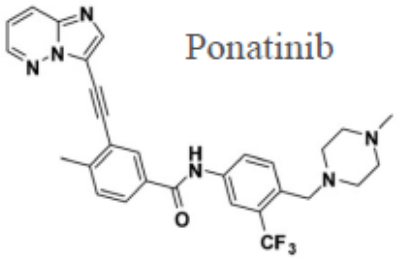
- Unique approach to accommodating gatekeeper residue
- Binds inactive (closed) ABL conformation

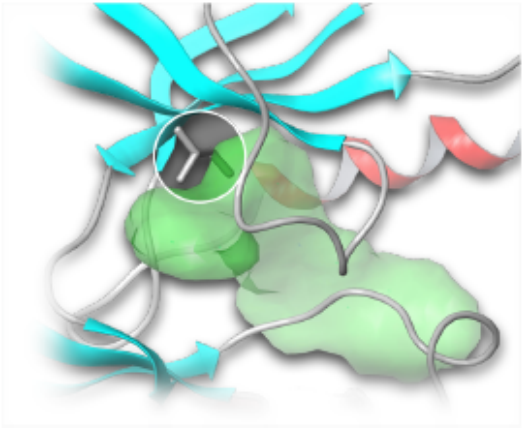
Broad spectrum of activity against an array of BCR-ABL variants

Multi-targeted kinase inhibitor

- Tyrosine kinases, including VEGF, FGF, and PDGF receptors, c-KIT and SRC kinase

Once-daily oral activity in murine models





Ponatinib cocrystal structure with ABL^{T315I}