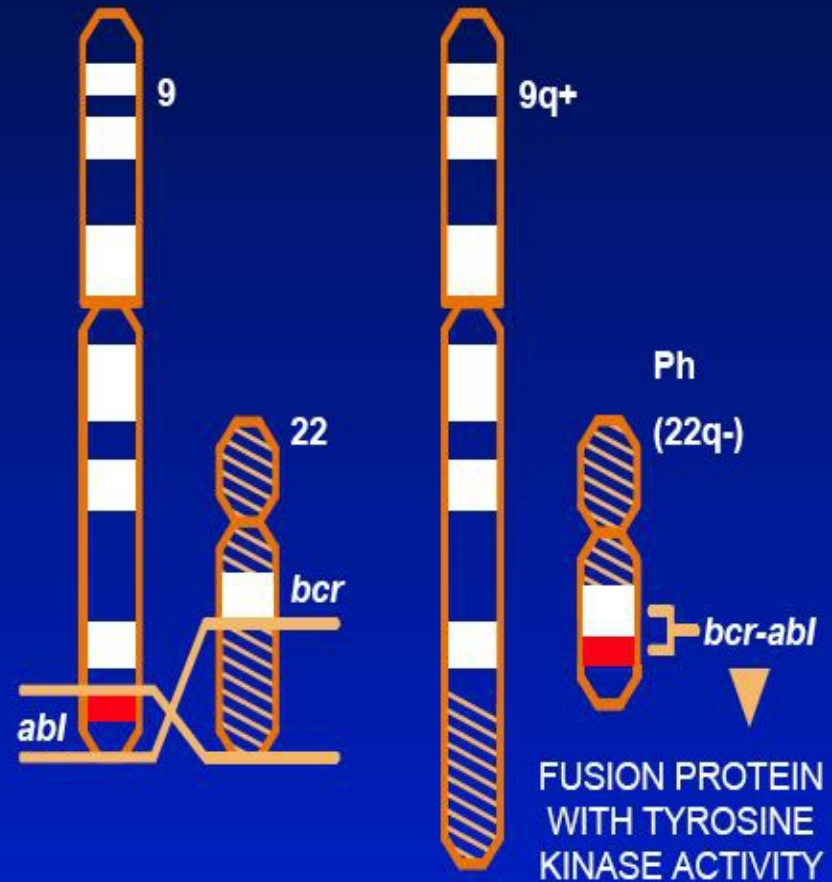
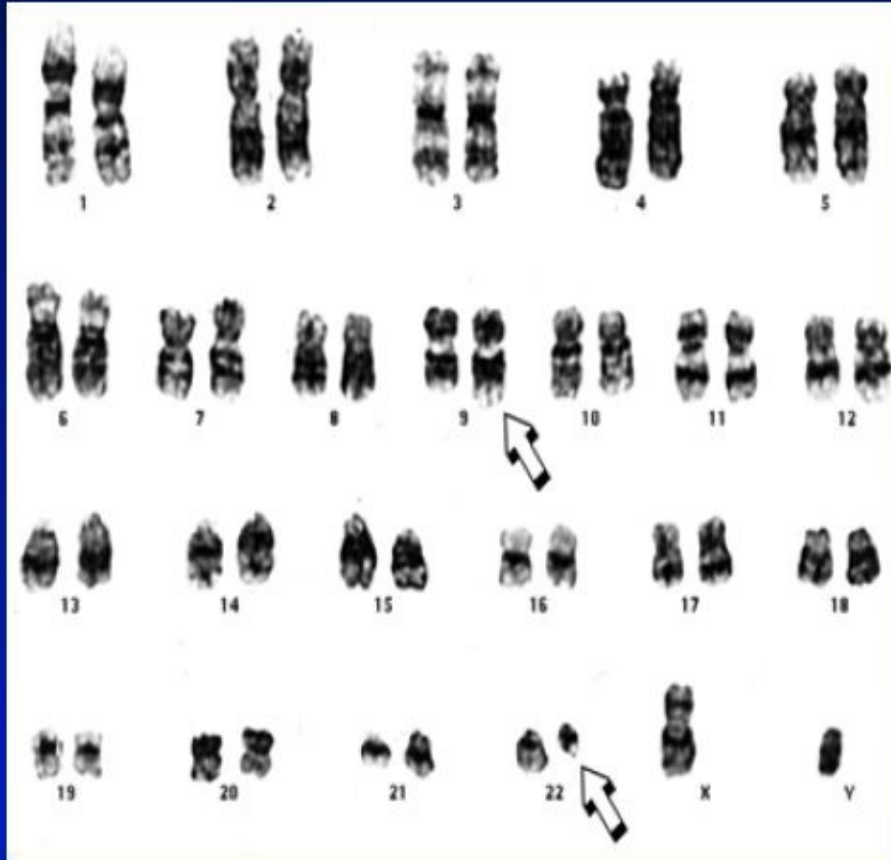

Gleevec[®]
(imatinib mesylate)

**Advancing the Treatment of Ph+
Chronic Myeloid Leukemia (CML)**

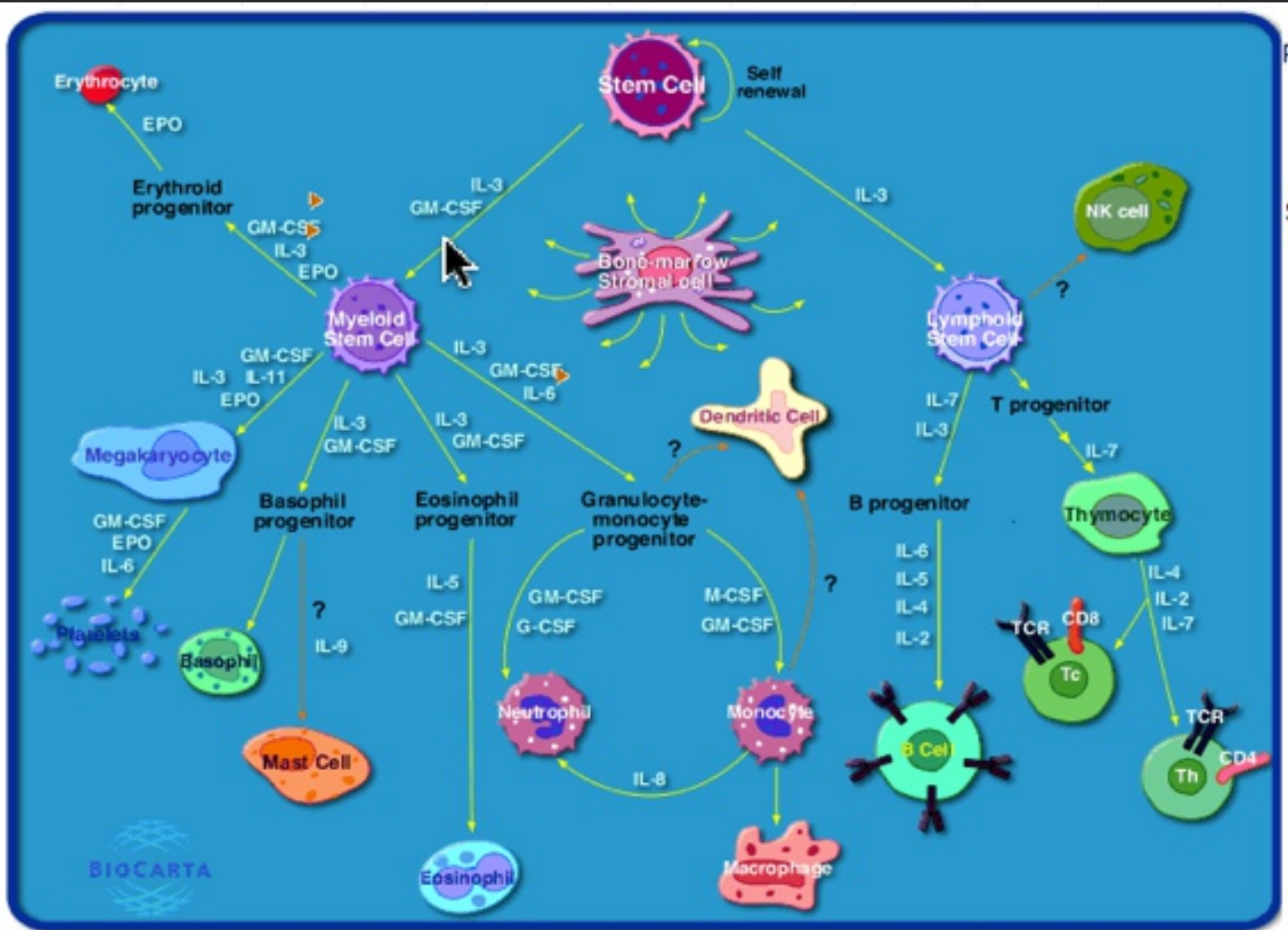
CML: Linked to a Single Molecular Abnormality



The Philadelphia (Ph) Chromosome: t(9;22) Translocation

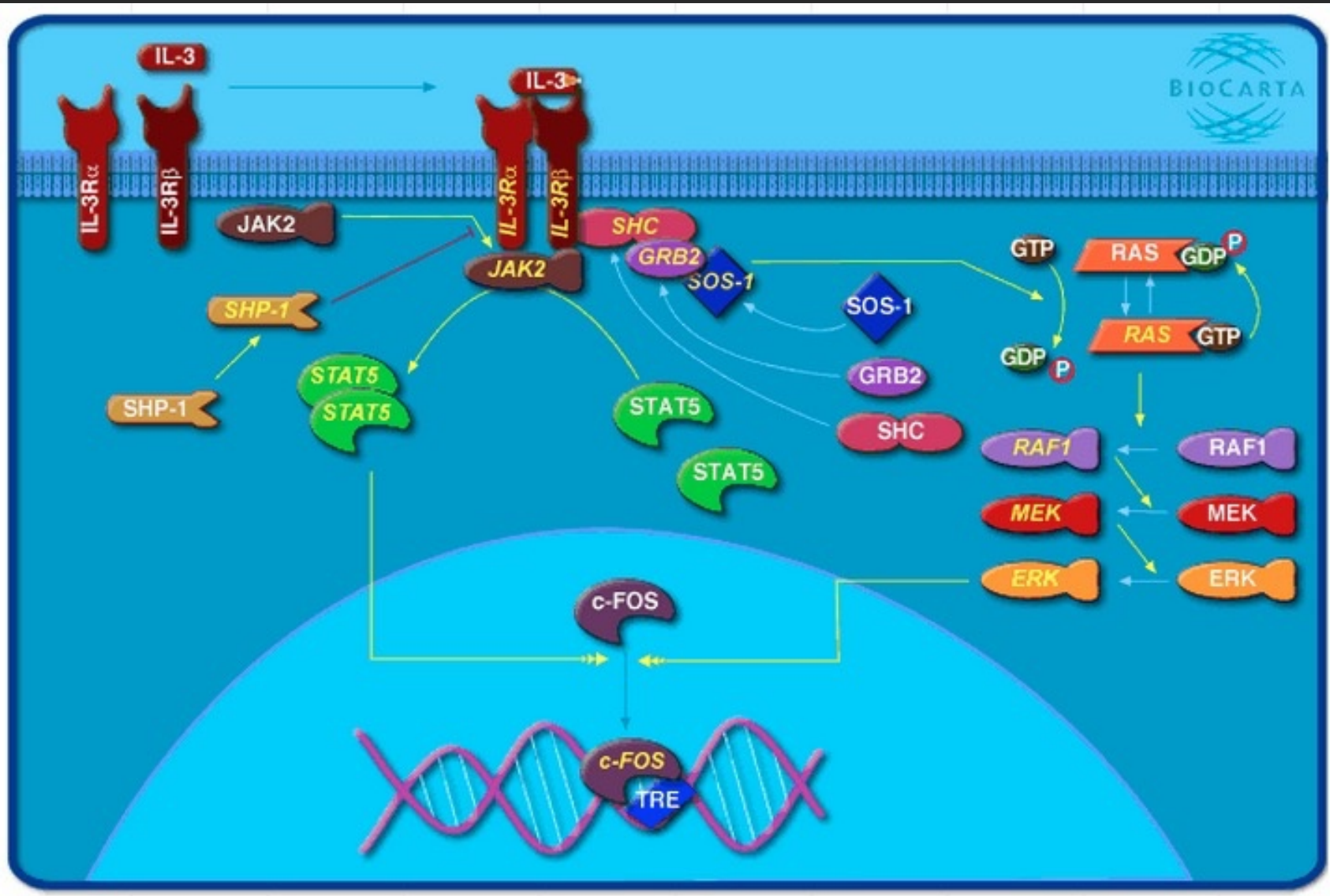
Hematopoiesis

http://www.biocarta.com/pathfiles/h_stemPathway.asp



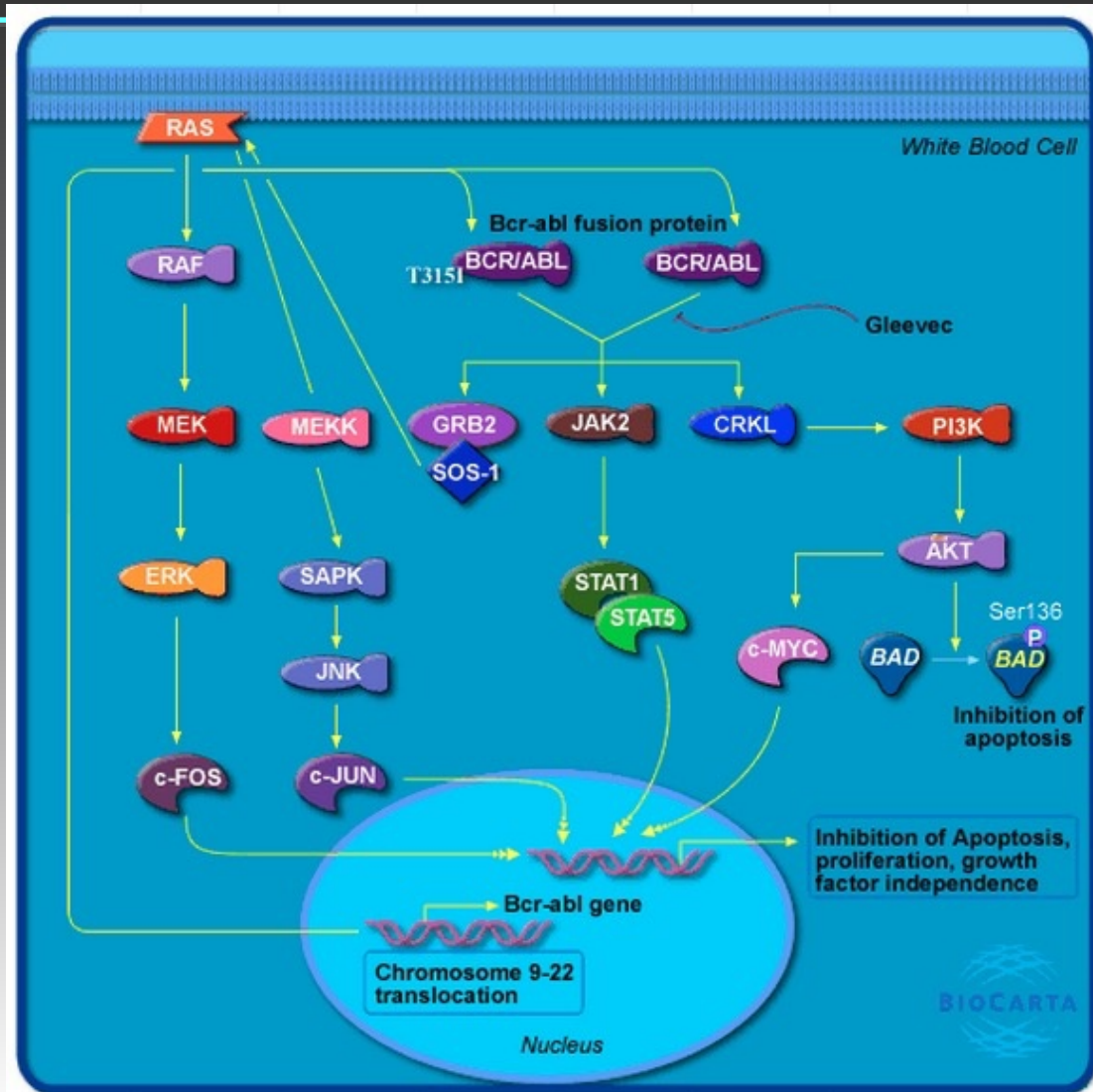
IL3 Signaling Pathway

http://www.biocarta.com/pathfiles/h_il3Pathway.asp




BCR-Abl Stimulates Cellular Proliferation and Inhibits Apoptosis

http://www.biocarta.com/pathfiles/h_gleevecpathway.asp



CML: a Progressive and Fatal Disease

Chronic phase	Advanced phases	
	Accelerated phase	Blast crisis
Median duration 5–6 years	Median duration 6–9 months	Median survival 3–6 months



CML: Its Cause and Management

- The Ph chromosome generates the Bcr-Abl tyrosine kinase—the molecular cause of CML
 - Constitutive activation leads to malignant transformation
- Eliminating the Ph chromosome—a primary goal of therapy
 - Complete cytogenetic response (0% Ph+ cells)
 - Major cytogenetic response ($\leq 35\%$ Ph+ cells)
 - Patients who achieved a complete/major cytogenetic response with SCT or IFN- α had prolonged survival vs patients without such a response
 - Longer follow-up required to determine survival benefit of Gleevec[®]



Gleevec®: Pharmacokinetics

- Rapidly and completely absorbed after oral administration
- Terminal half-life ($t_{1/2}$) of Gleevec ≈ 18 h and of active metabolite ≈ 40 h, allowing convenient once-daily oral dosing
- 81% of Gleevec eliminated within 7 days
- Metabolized in the liver primarily by the cytochrome P₄₅₀ enzyme CYP3A4
 - In vitro competitive inhibitor of CYP3A4, CYP2C9, and CYP2D6
- Potential drug interactions between Gleevec and other substrates, inhibitors, or inducers of these enzymes

Phase I Study: Gleevec® Achieves Hematologic and Cytogenetic Responses

	Chronic Phase IFN- α Failure 300–1000mg/day (n=54)	Blast Crisis, Myeloid 300–1000mg/day (n=38)
Hematologic response	100%	55%
Complete	98%	11%
Cytogenetic response		
Major	31%	11%
Complete	13%	8%

- Typically 4 weeks to achieve CHR, 2 to 10 months to achieve MCR
- A maximal tolerated dose (MTD) was not reached (up to 1000mg/day)

Druker BJ et al. *N Engl J Med.* 2001;344:1031-1037.

Druker BJ et al. *N Engl J Med.* 2001;344:1038-1042.

Phase II Results: Highest Response Rates in Chronic Phase

	Study 0110 Chronic Phase IFN- α Failure* (N=454)	Study 0109 Accelerated Phase* (N=181)	Study 0102 Blast Crisis* (N=229)
Hematologic response	93%	69%	31%
Complete response	93%	37%	7%
No evidence of leukemia	–	12%	5%
Return to chronic phase	–	20%	19%
Major cytogenetic response	53%	19%	7%
Complete response	32%	13%	1.5%

*Chronic phase: 400mg/day; advanced phases: 400mg/day or 600mg/day. Dose escalation permitted in all trials.

Gleevec® (imatinib mesylate) Prescribing Information.

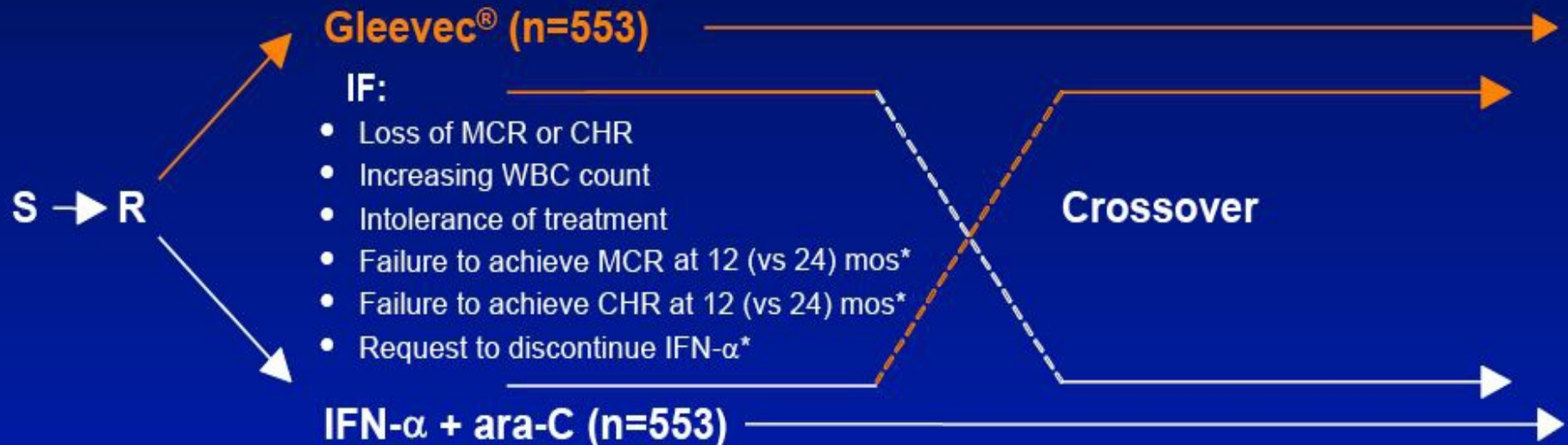
For important safety information, please see slide 3 or full Prescribing Information.

IRIS Study: Reevaluating First-Line CML Therapy

- Gleevec[®] versus IFN- α + ara-C (Study 106)
- Rationale for first-line use of Gleevec
 - High response rate in patients failing IFN- α
 - Higher response rates in earlier phases
- Phase III, multinational, randomized, open-label
- Inclusion criteria: newly diagnosed chronic phase CML patients
- Primary objective—determine time to progression, defined as:
 - Increasing WBC count
 - Loss of CHR or MCR
 - Accelerated phase or blast crisis
 - Death
- Secondary objectives—determine rate and duration of CHR and MCR; overall survival; safety; molecular response; quality of life (QoL) using FACT-BRM

IRIS: The Largest Phase III CML Study to Date

1106 patients enrolled from June 2000 to January 2001

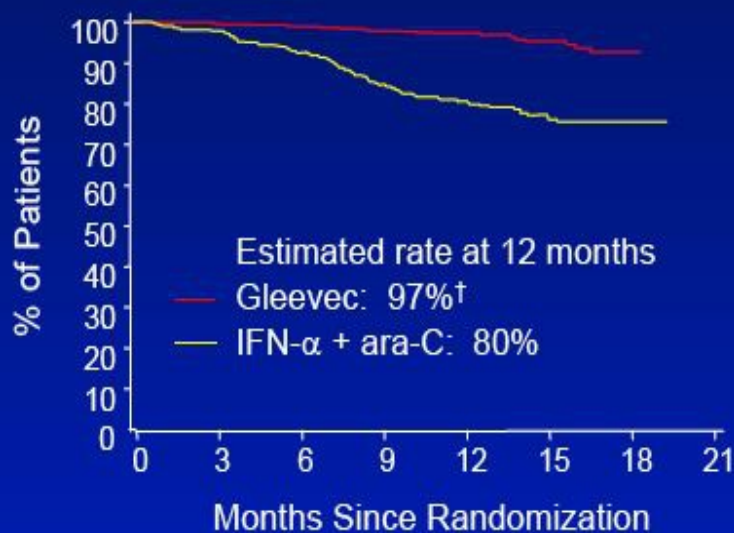


S = screening.
R = randomization.

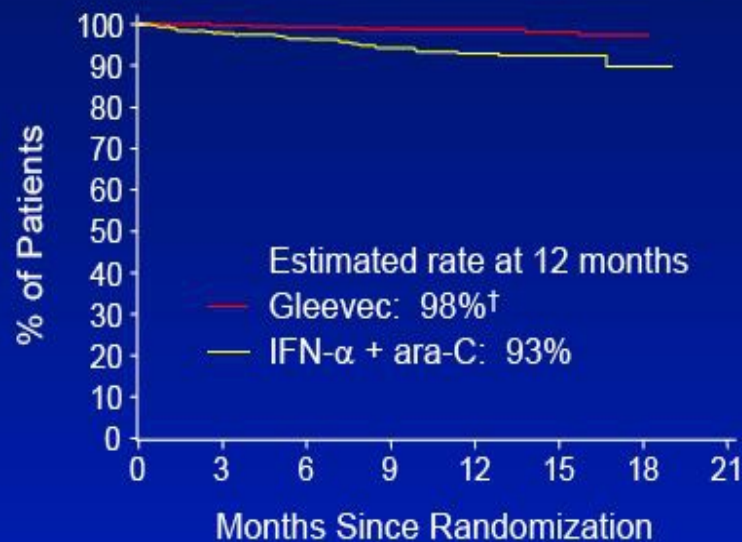
*Independent Data Monitoring Board recommended protocol amendment.

Longer Time to Progression With Gleevec®*

Patients Free of
Any Disease Progression*



Patients Free of
Progression to Advanced Disease*

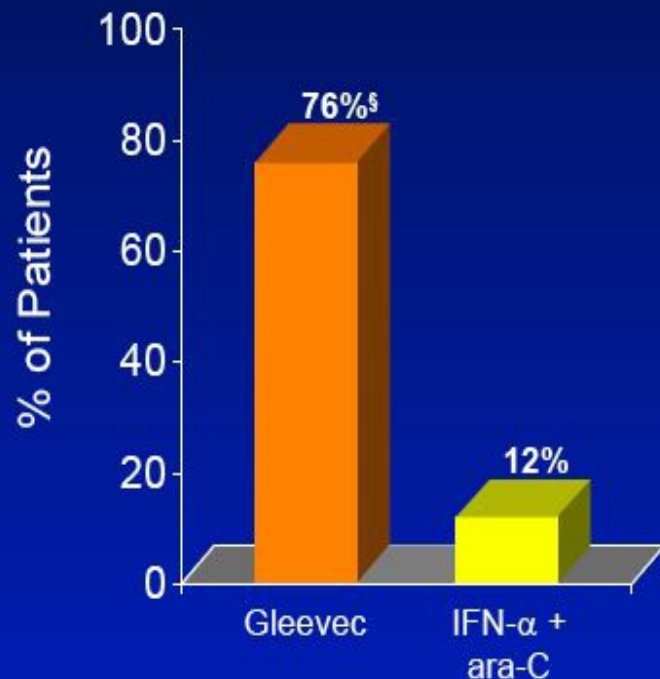


*IRIS study; n=553 in each arm.

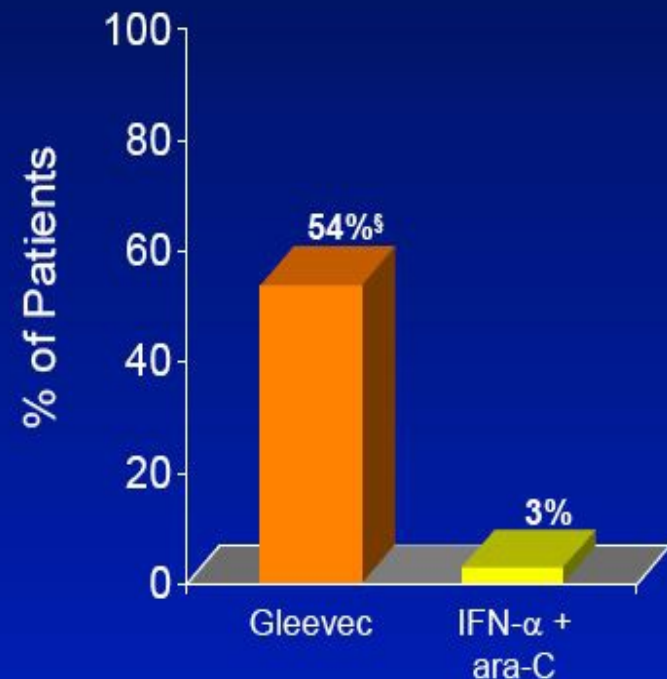
†P<0.0001.

Higher Cytogenetic Response Rates With Gleevec®*

Major Cytogenetic Response†



Complete Cytogenetic Response‡



*IRIS Study; n=553 in each arm.

† $\leq 35\%$ Ph+ cells.

‡0% Ph+ cells.

For important safety information, please see slide 3 or full Prescribing Information.

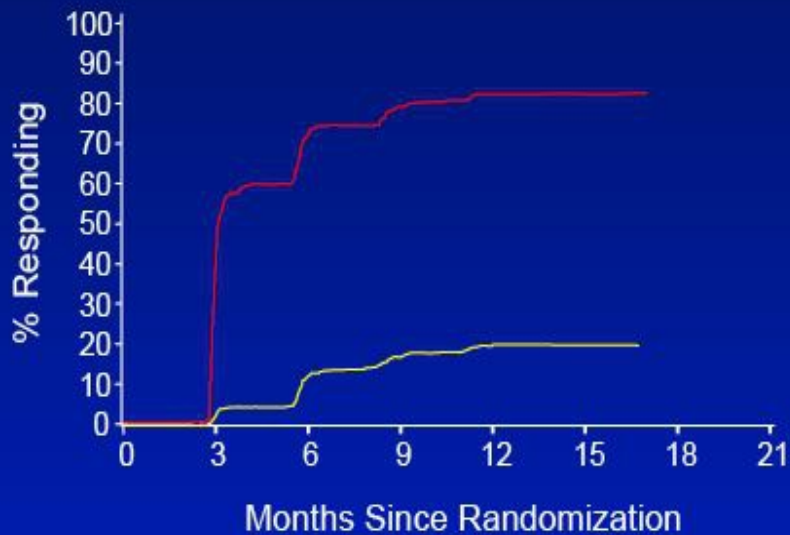
§ $P < 0.001$. Confirmed responses shown.

Unconfirmed MCR—Gleevec: 83%; IFN-α + ara-C: 20%.

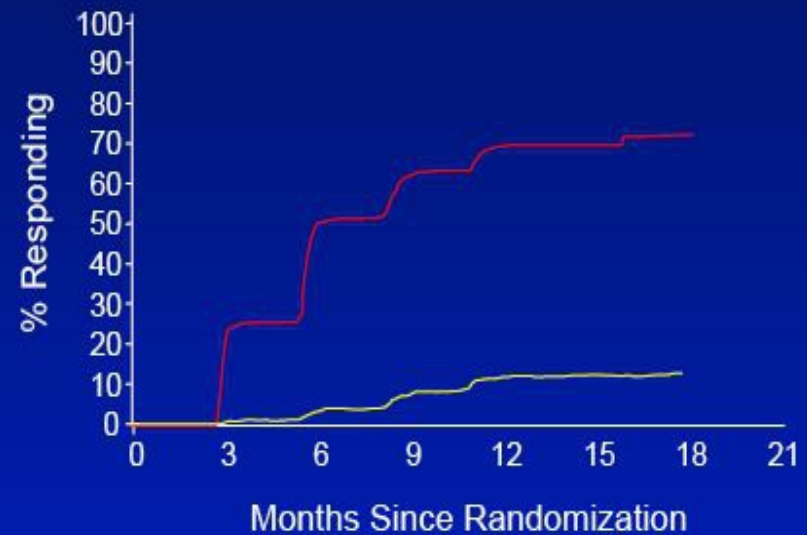
Unconfirmed CCR—Gleevec: 68%; IFN-α + ara-C: 7%.

Early Responses in More Patients With Gleevec[®]*

Major Cytogenetic Response



Complete Cytogenetic Response



— Gleevec (n=553)
— IFN-α + ara-C (n=553)

*IRIS Study.

For important safety information, please see slide 3 or full Prescribing Information.

More Patients Remain on Gleevec® Therapy

	Gleevec n=553	IFN- α + ara-C n=553
All Crossovers	1% (n=7)	39% (n=218)
Intolerance	<1%	23%
No CHR at 6 months	0%	7%
Increasing WBC count	<1%	5%
Loss of CHR	0%	4%
Loss of MCR	<1%	<1%
All Discontinuations	9% (n=51)	31% (n=170)
Withdrawal of consent	2%	13%
Adverse events	2%	6%
Progression to accelerated phase or blast crisis	1.5%	5%
All other causes	3.5%	7%
Remained on originally assigned treatment	90% (n=495)	30% (n=165)

Most Non-Hematologic Adverse Events Less Common With Gleevec®*

Event	All Grades (%)		Grades 3/4 (%)	
	Gleevec n=551†	IFN- α + ara-C n=533†	Gleevec n=551†	IFN- α + ara-C n=533†
Superficial edema	53	9	<1	<1
Nausea	43	61	<1	5
Muscle cramps	35	10	1	<1
Musculoskeletal pain	34	41	3	8
Rash	32	25	2	2
Fatigue	31	65	1	24
Diarrhea	30	41	1	3
Headache	29	42	<1	3
Joint pain	27	38	2	7

*IRIS study; most common adverse events, listed by incidence with Gleevec ($\geq 25\%$, regardless of causality).

†All patients who received at least 1 dose of study drug.

Fewer Hematologic Adverse Events With Gleevec[®]*

	Gleevec (%) (n=551) [†]		IFN- α + ara-C (%) (n=533) [†]	
	Grade 3	Grade 4	Grade 3	Grade 4
Neutropenia	11	2	20	4
Thrombocytopenia	7	<1	16	<1
Anemia	3	<1	4	<1

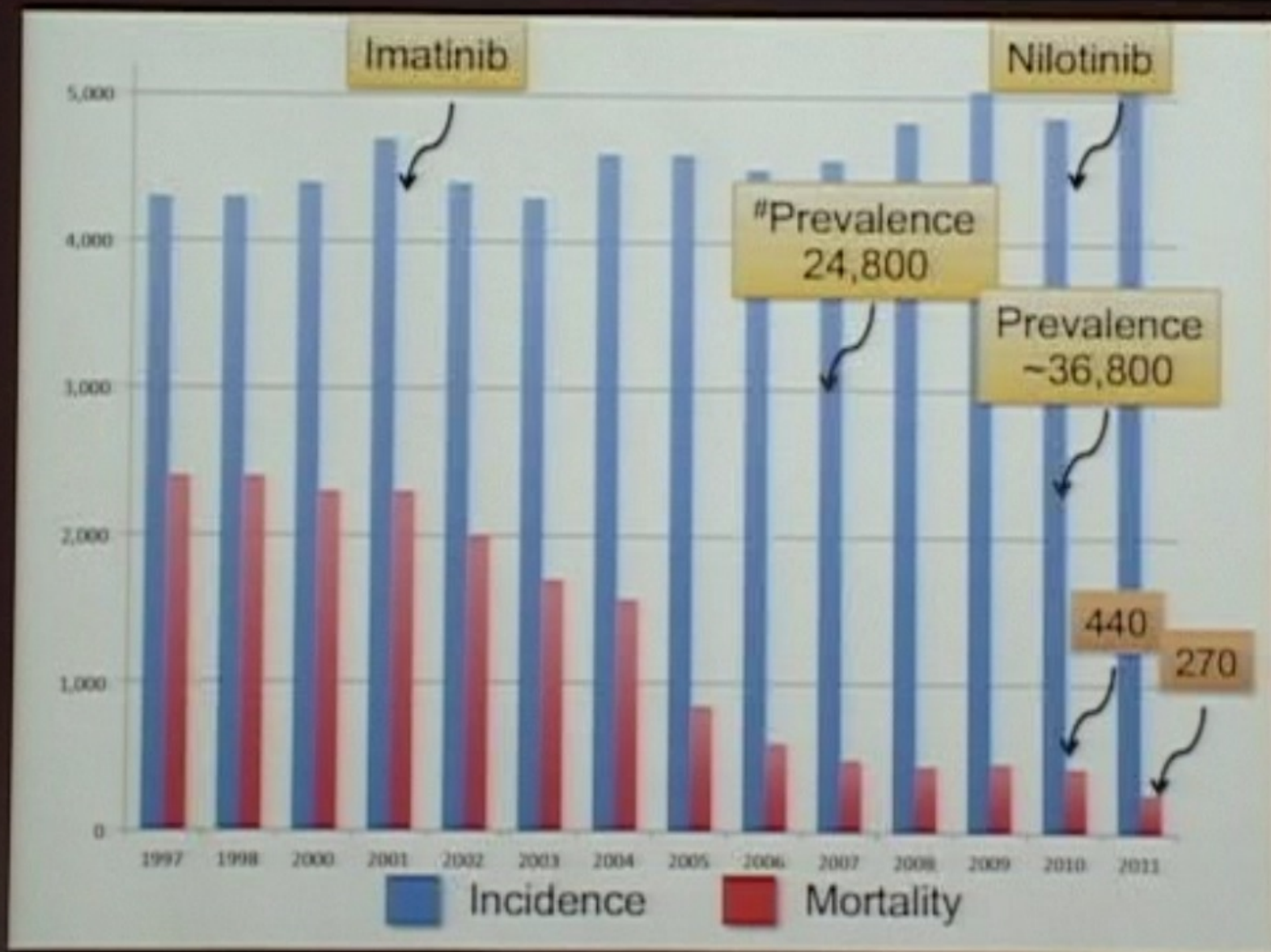
*IRIS Study.

[†]All patients who received at least 1 dose of study drug.

Massive Protein Kinase Database

- Abbott Labs Publishes Massive Protein Kinase Dataset, New Statistical Method to Analyze Kinome
- March 11, 2011
- By Adam Bonislowski
- **Scientists from Abbott Laboratories'** pharmaceutical-discovery division have released kinomics screening data about how 3,800 different inhibitors affect 172 protein kinases.
- In a study published last month in the online edition of *Nature Chemical Biology*, the researchers showed how they tried to group these kinases based on both sequence and pharmacological relationships and by their interactions with various inhibitor chemoty

The genetic paradigm validated: -a dramatic reduction in the mortality from CML since 2001



Gleevec[®]—CML Indications

- Gleevec is indicated for the treatment of newly diagnosed adult patients with Philadelphia chromosome–positive (Ph+) chronic myeloid leukemia (CML). Follow-up is limited. Gleevec is also indicated for the treatment of patients with Ph+ CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. Gleevec is also indicated for the treatment of pediatric patients with Ph+ CML whose disease has recurred after stem cell transplant or who are resistant to interferon alpha therapy. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival, in patients with CML in blast crisis, accelerated phase, or chronic phase after failure of interferon-alpha therapy.

Gleevec[®]—Important Considerations

- Use of Gleevec is contraindicated in patients with hypersensitivity to imatinib or to any other component of Gleevec
- Women of childbearing potential should be advised to avoid becoming pregnant
- Gleevec is often associated with edema and occasionally serious fluid retention*; GI irritation (and should be taken with food and a large glass of water to minimize this problem); anemia, neutropenia, thrombocytopenia, or occasionally severe hepatotoxicity or hemorrhage
- Gleevec is metabolized by the CYP3A4 isoenzyme and is an inhibitor of CYP3A4, CYP2D6, and CYP2C9. Please see full Prescribing Information for potential drug interactions

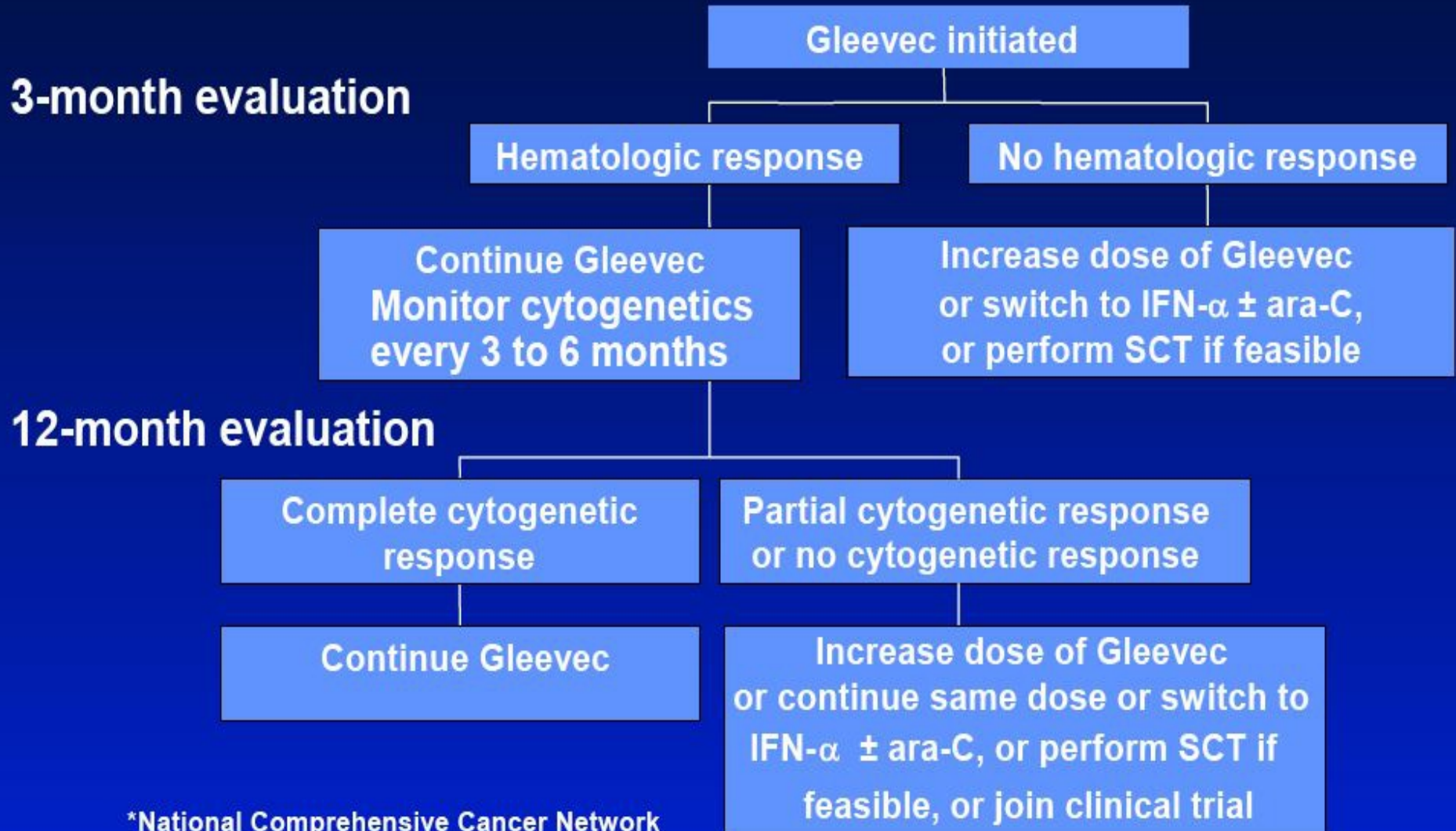
*Patients should be weighed and monitored regularly for signs and symptoms of edema, which can be serious or life threatening.

Gleevec®: Evolving First-Line CML Therapy

- Gleevec surpasses IFN- α + ara-C by the following parameters measured in the IRIS study:
 - Progression-free survival
 - Complete cytogenetic response
 - Major cytogenetic response
 - Complete hematologic response
- Mild to moderate safety and tolerability profile

For important safety information, including serious and severe adverse events, please see slide 3 or full Prescribing Information.

NCCN* CML Guidelines for Monitoring Response to Gleevec®



Optimal Dosing for Optimal Results

- Recommended starting doses of Gleevec[®]
 - Chronic phase: 400mg once daily
 - Advanced phases: 600mg once daily
- Monitor responses every 3–6 months
- Consider dose escalation (400mg to 600mg in chronic phase, 600mg to 800mg in advanced phases) in absence of severe adverse reactions or severe hematologic abnormalities for any of the following:
 - Failure to achieve a CHR after at least 3 months
 - Failure to achieve a cytogenetic response after 6–12 months
 - Loss of a previously achieved hematologic or cytogenetic response
 - Disease progression (at any time)
- Dose escalation when appropriate may overcome resistance

Gleevec® Has Advanced the Treatment of Ph+ CML

- Therapy specifically designed to target the molecular cause of CML (Bcr-Abl)
- High rates of cytogenetic and hematologic response in all phases of disease
- Significant delay in time to disease progression for patients in chronic phase
- Mild to moderate side-effect profile
- Convenient, once-daily, oral dosing*
- Evolving first-line therapy for CML

*800mg should be administered as 400mg twice a day.

For important safety information, please see slide 3 or full Prescribing Information.

Most Oncogenes are Not Kinases

Disease	Oncogene
Lymphoma CLL	BCL2
Pancreatic Ca Bladder Ca Leukemia Melanoma	RAS
Prostate Ca	ERG1/ETV1
Many	MYC
Rhabdomyosarcoma	PAX3-FKHR
Synovial Sarcoma	SYT-SSX
Liposarcoma	MDM2

Disease
↓
Pathogenesis
↓
Target-based drug discovery

Higher Dose: Longer Time to Disease Progression

Study 0109 (accelerated phase)

