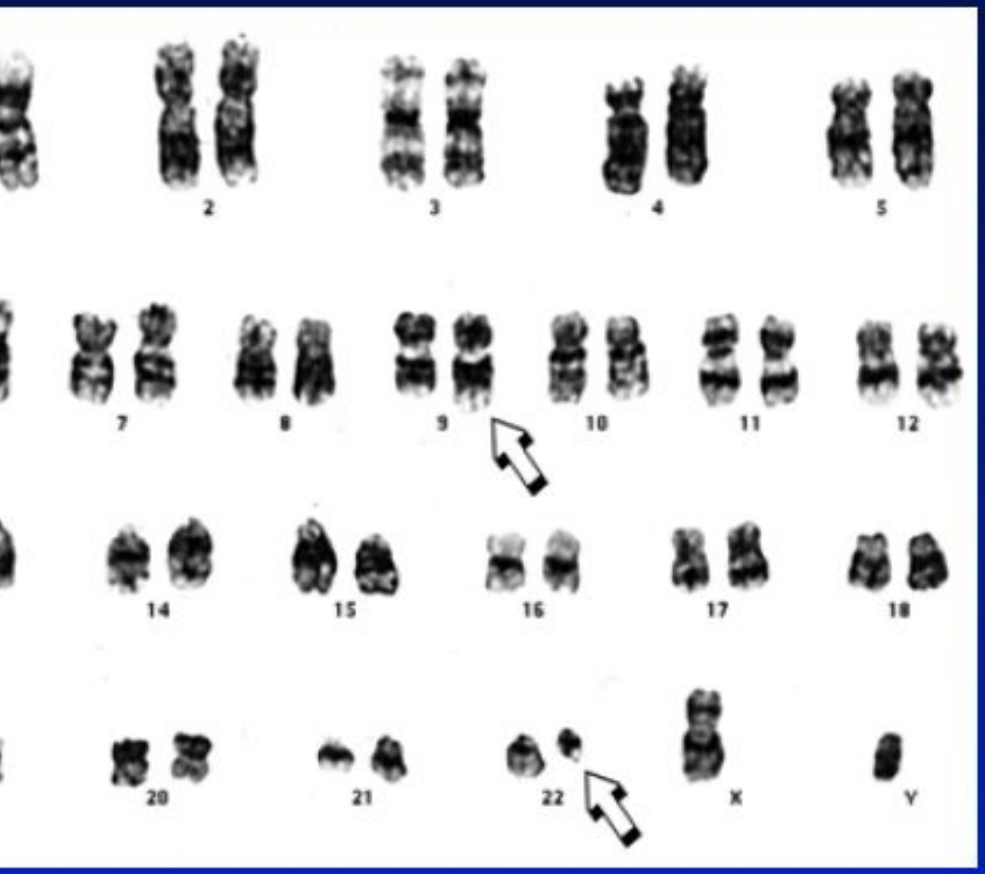
Gleevec®
(imatinib mesylate)

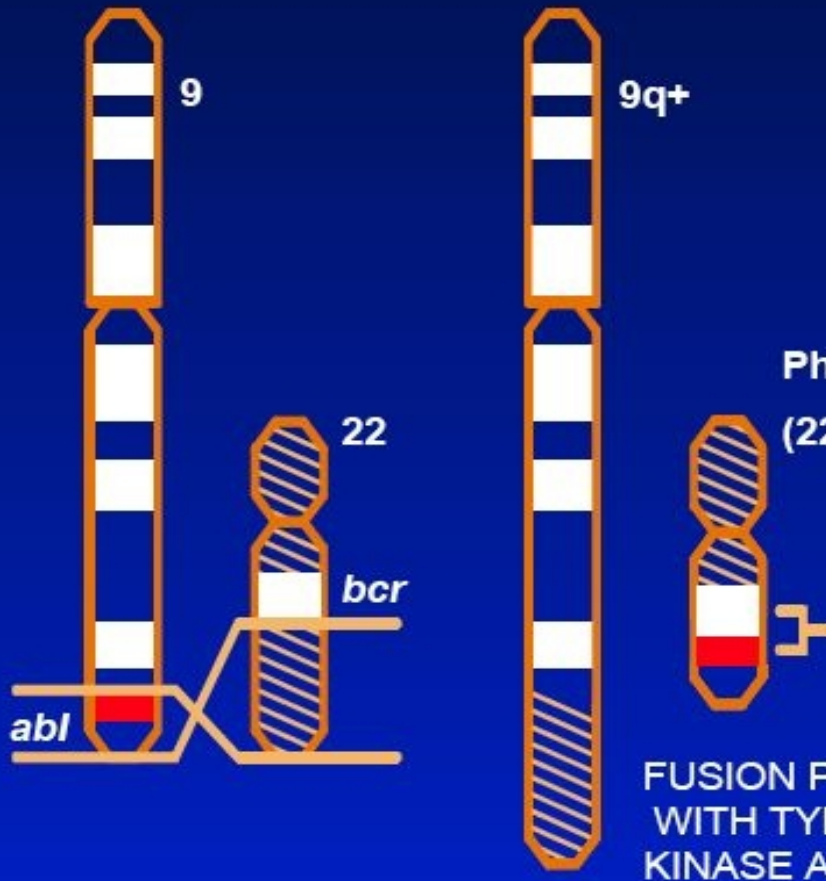
Advancing the Treatment of Ph+ Chronic Myeloid Leukemia (CML)

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: Linked to a Single Molecular Abnormality



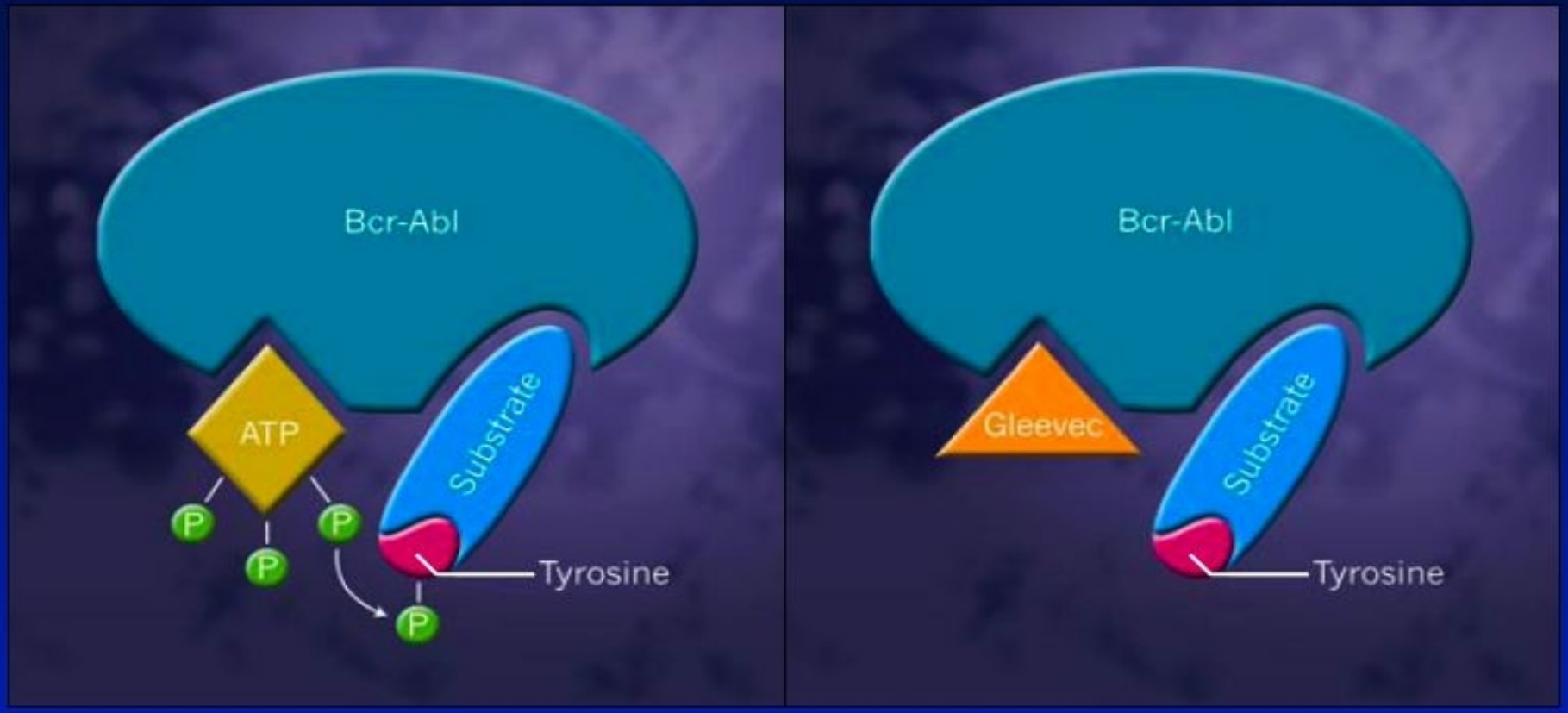


The Philadelphia (Ph) Chromosome: t(9;22) Translocation

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 therap
  - Complete cytogenetic response (0% Ph+ cells)
  - Major cytogenetic response (≤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 Gleeved

Gleevec® Targets the Cause of CML



- Gleevec—a specific inhibitor of a small family of tyrosine kinases, including Bcr-Abl, Kit, and PDGF receptor

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 dosi
- 81% of Gleevec eliminated within 7 days
- Metabolized in the liver primarily by the cytochrome P_{450} 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)	Blast Crisis, Lymphoid 300–1000mg/d (n=20)
lematologic response	100%	55%	70%
Complete	98%	11%	20%
ytogenetic response			
Major	31%	11%	15%
Complete	13%	8%	10%

- 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)

uker BJ et al. *N Engl J Med.* 2001;344:1031-1037.
uker BJ et al. *N Engl J Med.* 2001;344:1038-1042.

Phase II Results: Highest Response Rates in Chronic Phase

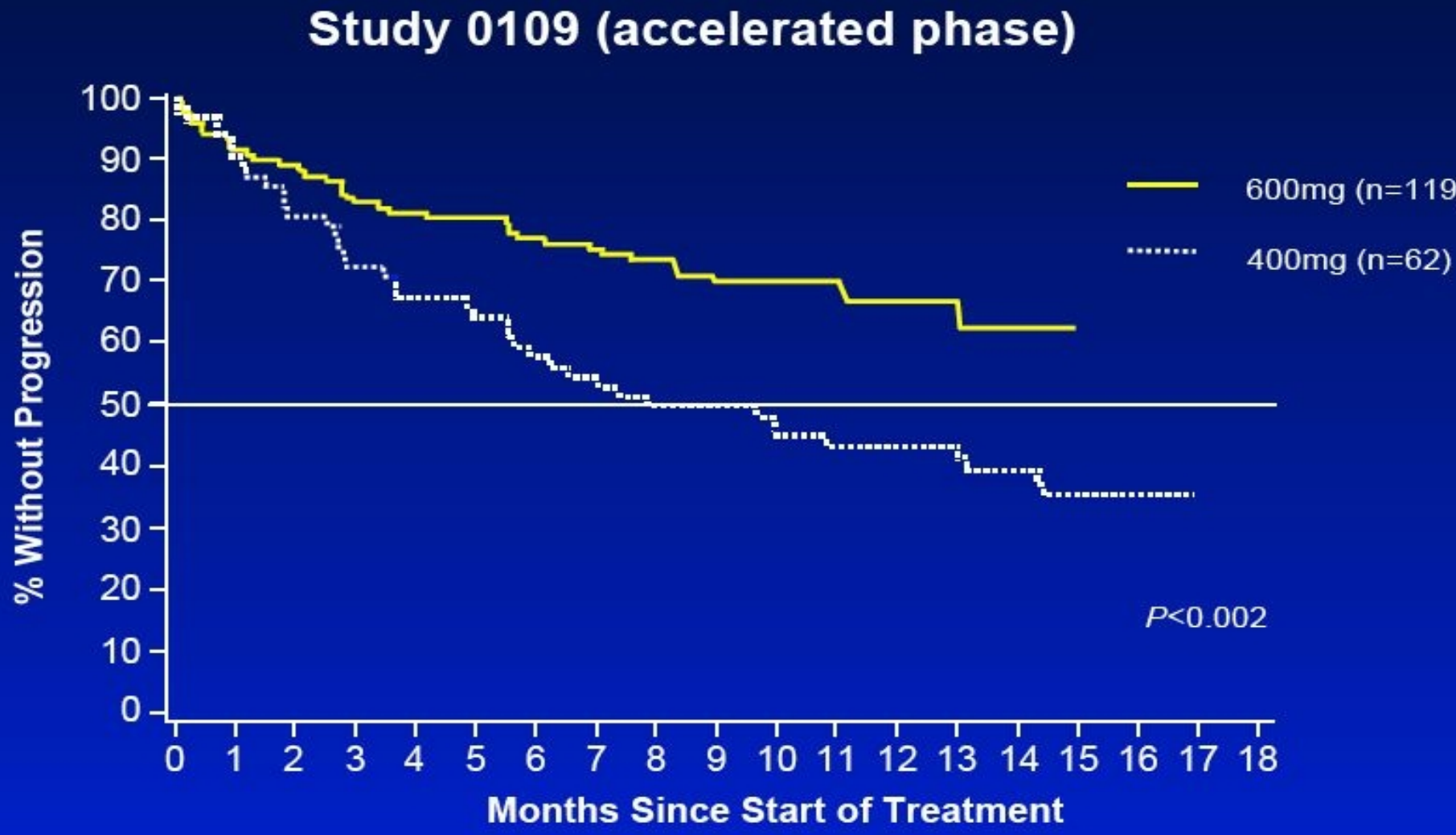
	Study 0110 Chronic Phase IFN-α Failure* (N=454)	Study 0109 Accelerated Phase* (N=181)	Study 01 Blast Cri (N=229
Hematologic response	**93%**	**69%**	**31%**
Complete response	93%	37%	7%
No evidence of leukemia	–	12%	5%
Return to chronic phase	–	20%	19%
Major cytogenetic response	**53%**	**19%**	**7%**
Complete response	32%	13%	1.5%

ronic phase: 400mg/day; advanced phases: 400mg/day or 600mg/day. Dose escalation permitted in all tria

eevec® (imatinib mesylate) Prescribing Information.

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

Higher Dose: Longer Time to Disease Progression



lpaz M et al. *Blood*. 2002;99:1928-1937.

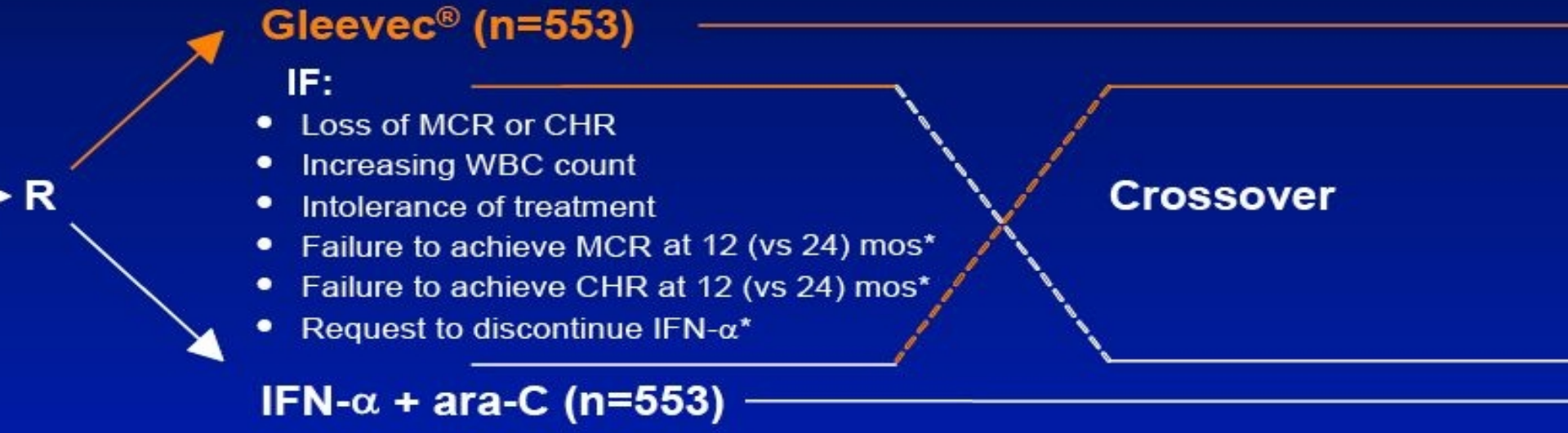
Some adverse events appear to be dose re

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 pa
- Primary objective—determine time to progression, defined
  - 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 respons quality of life (QoL) using FACT-BRM

IRIS: The Largest Phase III CML Study to Date

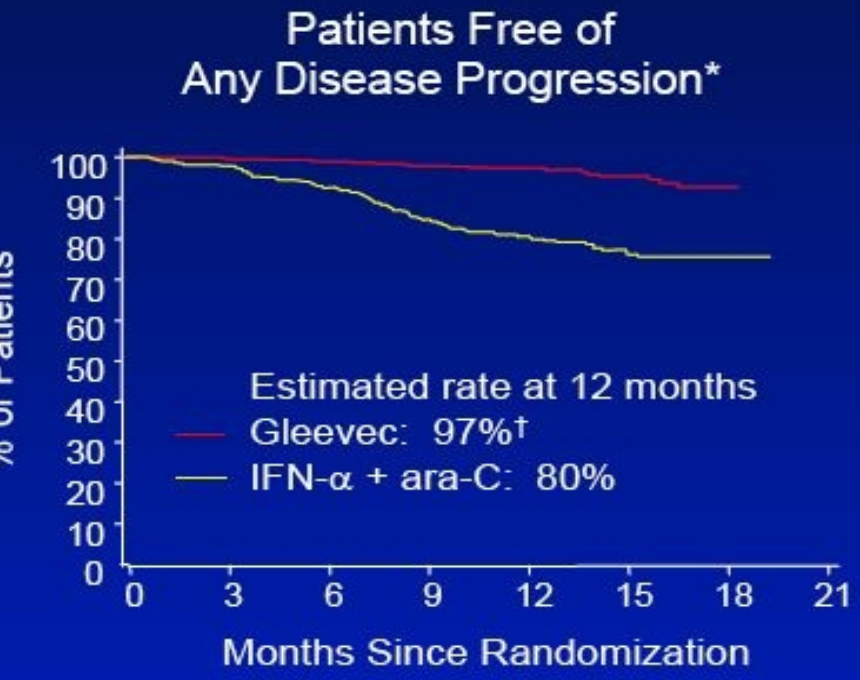
1106 patients enrolled from June 2000 to January 2001

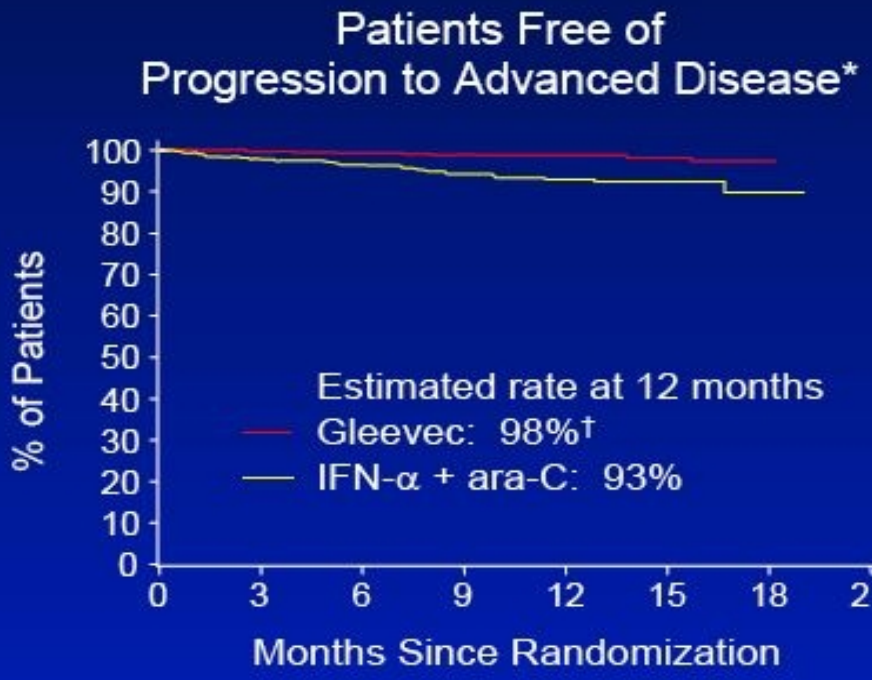


S = screening.
R = randomization.

dependent Data Monitoring Board recommended protocol amendment.

Longer Time to Progression With Gleevec®*

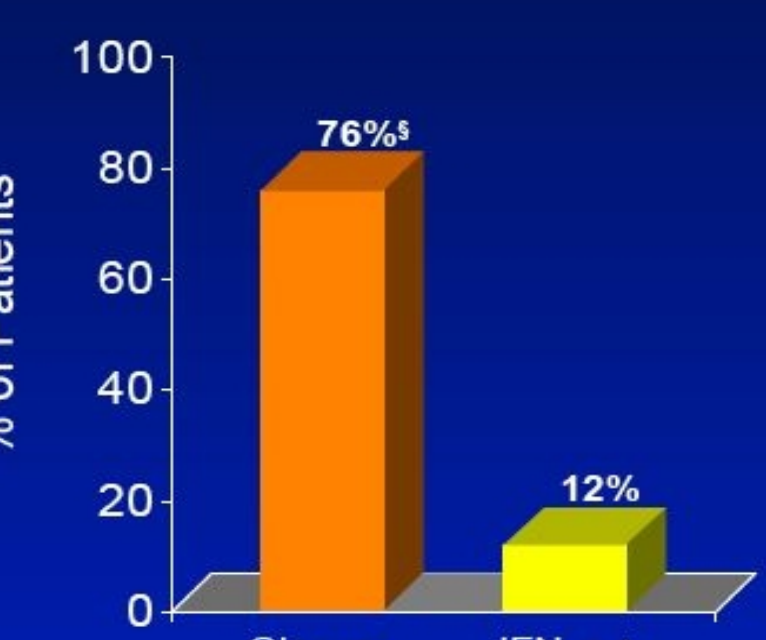




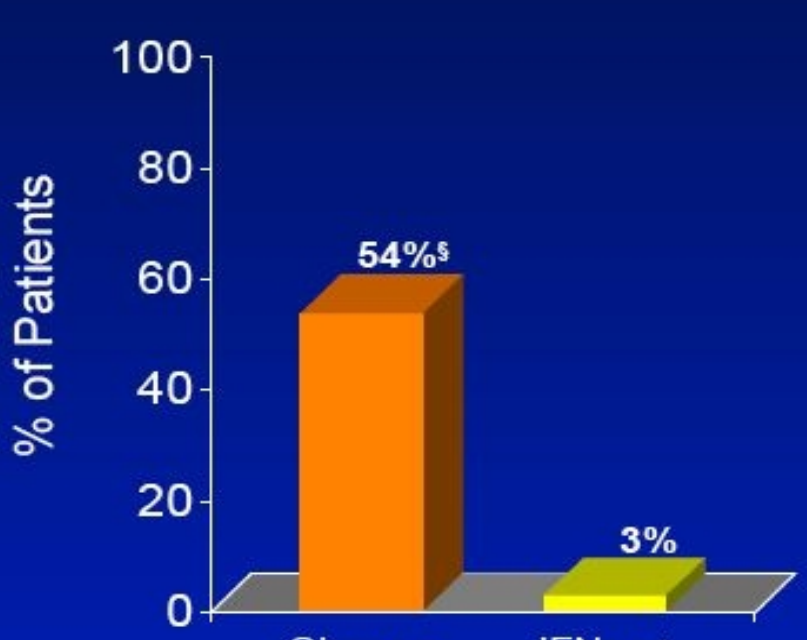
RIS study; n=553 in each arm.
<0.0001.

Higher Cytogenetic Response Rates With Gleevec®*

Major Cytogenetic Response†



Complete Cytogenetic Response‡

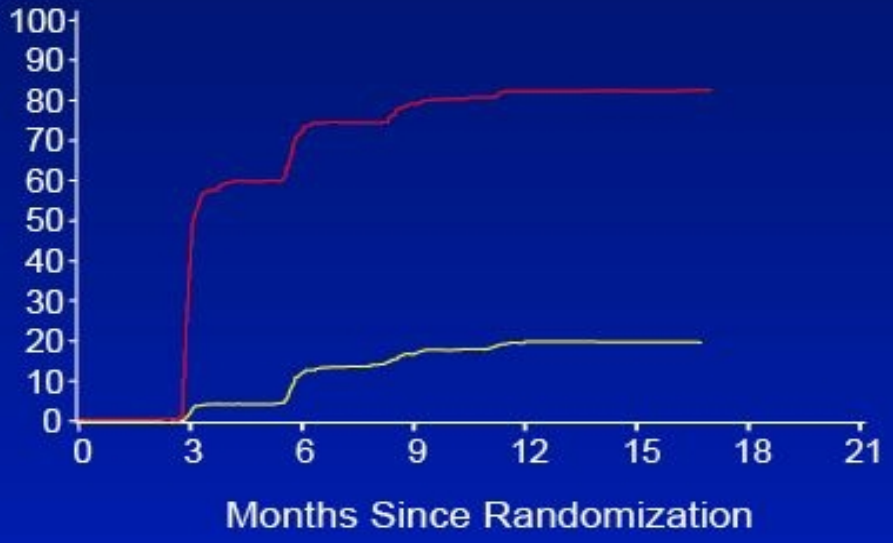


IS Study; n=553 in each arm.
35% Ph+ cells.
% Ph+ cells.
r important safety information, please see
le 3 or full Prescribing Information.

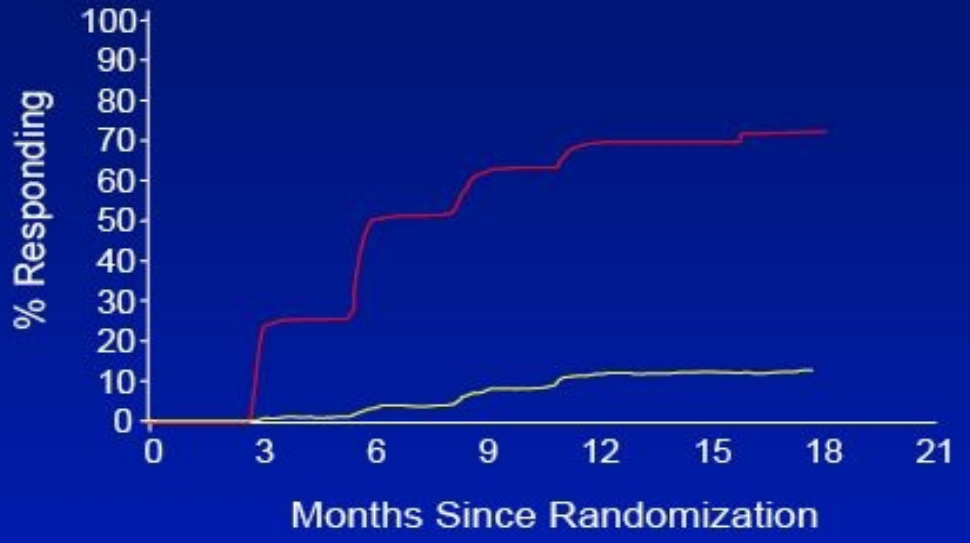
§*P*<0.001. Confirmed responses shown.
Unconfirmed MCR—Gleevec: 83%; IFN-α + ara-
Unconfirmed CCR—Gleevec: 68%; IFN-α + ara-

Early Responses in More Patients With Gleevec®*

Major Cytogenetic Response



Complete Cytogenetic Response



Gleevec (n=553)

IFN-α + ara-C (n=553)

IS Study.

r 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®*

vent	All Grades (%)		Grades 3/4 (%)	
	Gleevec n=551†	IFN-α + ara-C n=533†	Gleevec n=551†	IFN-α + ara-C n=533†
uperficial edema	53	9	<1	<1
ausea	43	61	<1	5
luscle cramps	35	10	1	<1
lusculoskeletal pain	34	41	3	8
ash	32	25	2	2
atigue	31	65	1	24
iarrhea	30	41	1	3
eadache	29	42	<1	3
oint pain	27	38	2	7

RIS study; most common adverse events, listed by incidence with Gleevec (≥25%, regardless of causality).
ll 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

IS Study.
patients who received at least 1 dose of study drug.

Gleevec®—CML Indications

- Gleevec is indicated for the treatment of newly diagnosed adult patients with Philadelphia chromosome–positive (Ph+) chronic my leukemia (CML). Follow-up is limited. Gleevec is also indicated fo treatment of patients with Ph+ CML in blast crisis, accelerated pha or in chronic phase after failure of interferon-alpha therapy. Gleev 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 bl crisis, accelerated phase, or chronic phase after failure of interfero 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.

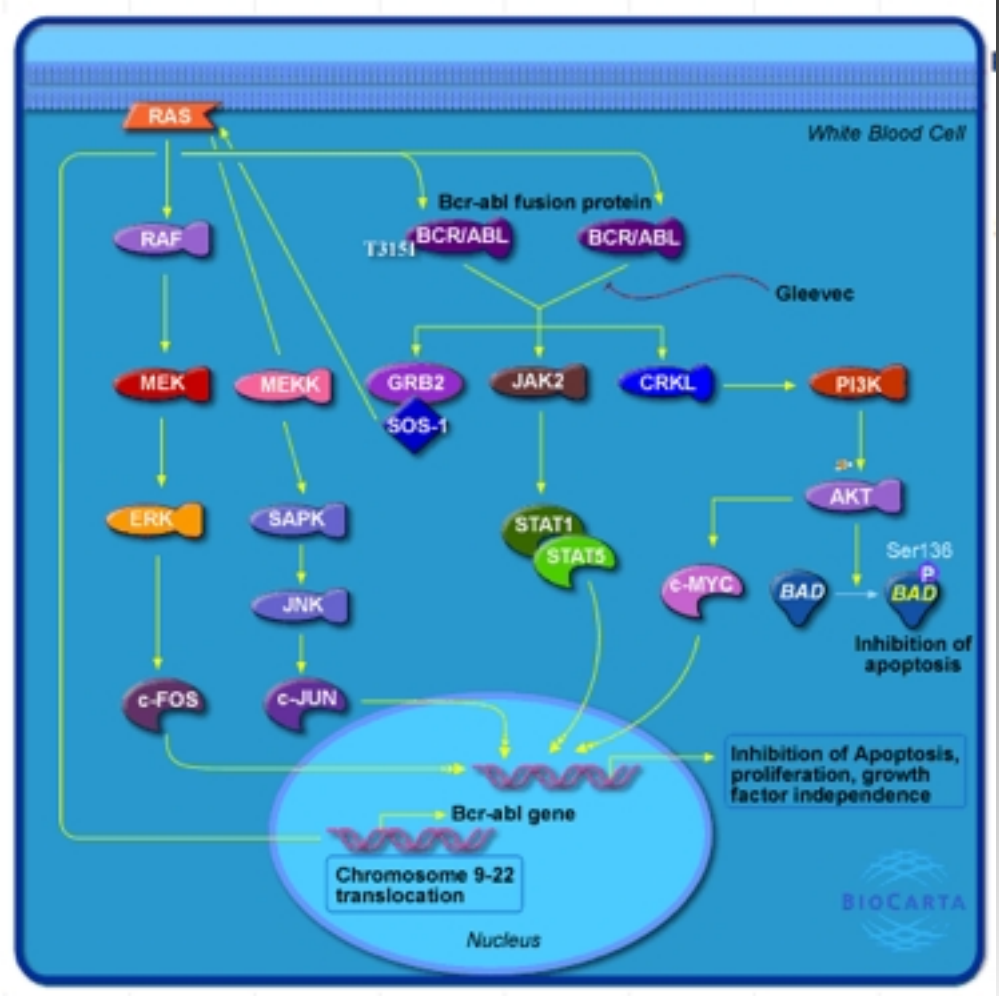
leevec®: Evolving First-Line CML Therap

- 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

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

Inhibition of Cellular Proliferation by Gleevec

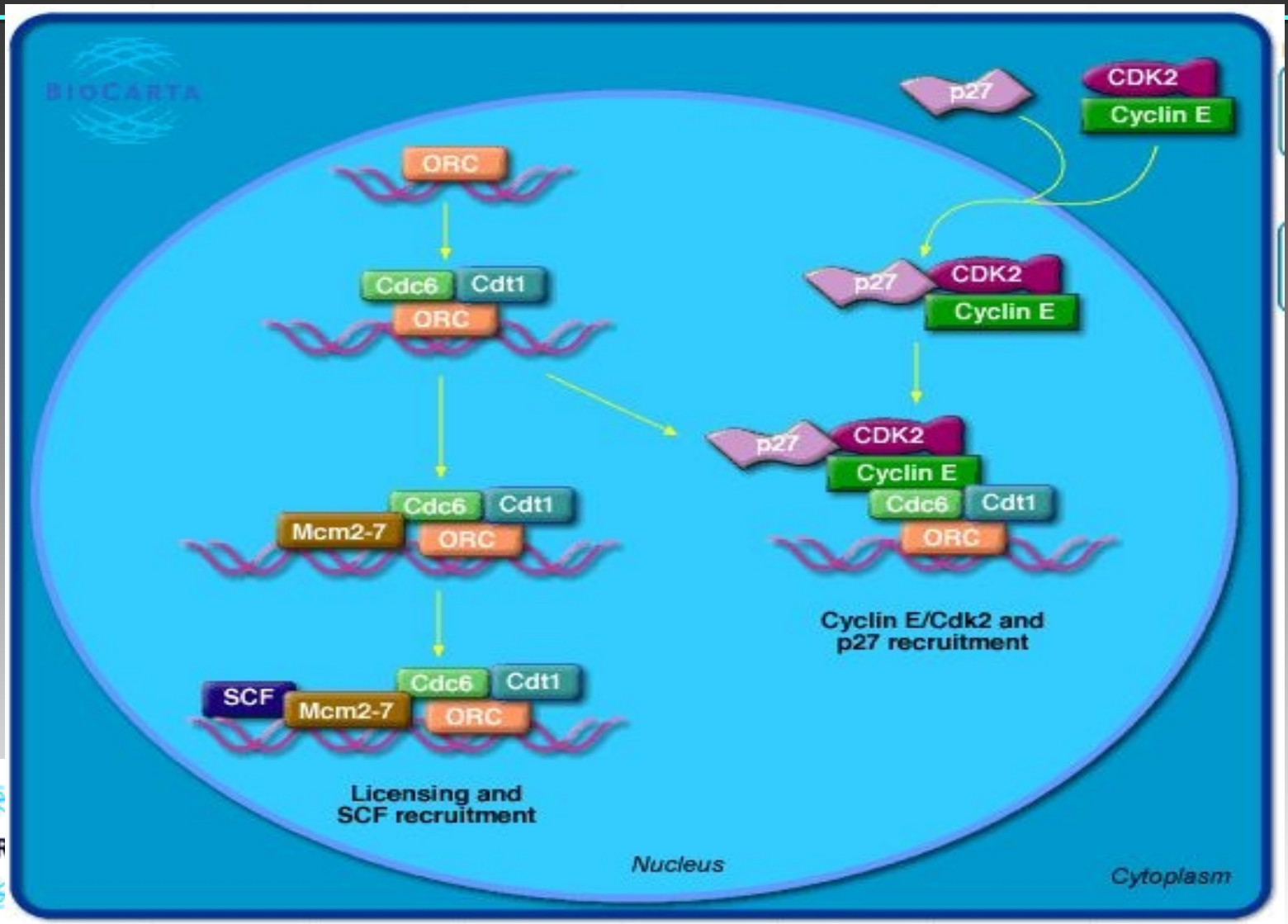
http://www.biocarta.com/pathfiles/h_gleevecpathway.asp



BIOCARTA

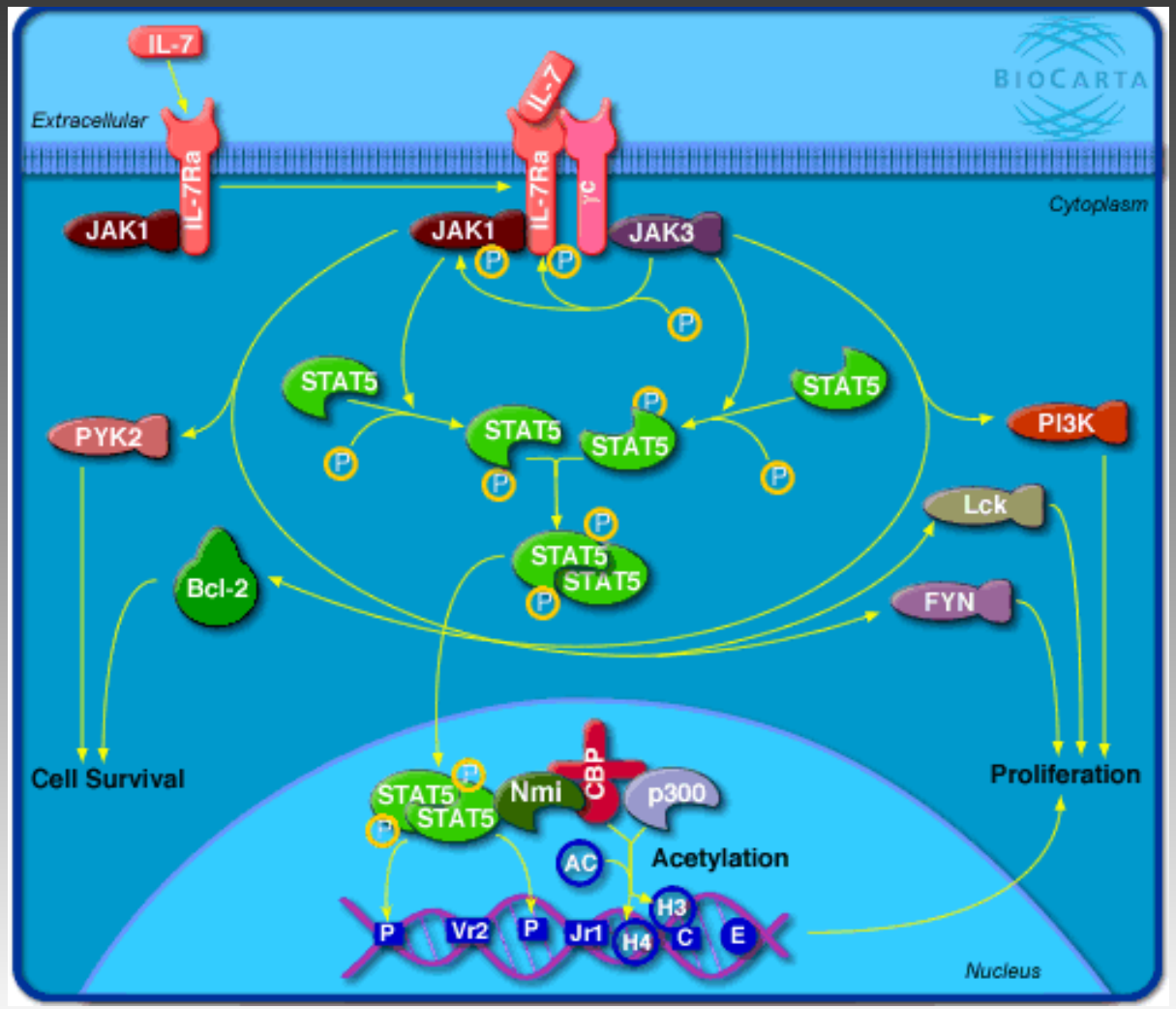
CDK Regulation of Cell Division

http://www.biocarta.com/genes/



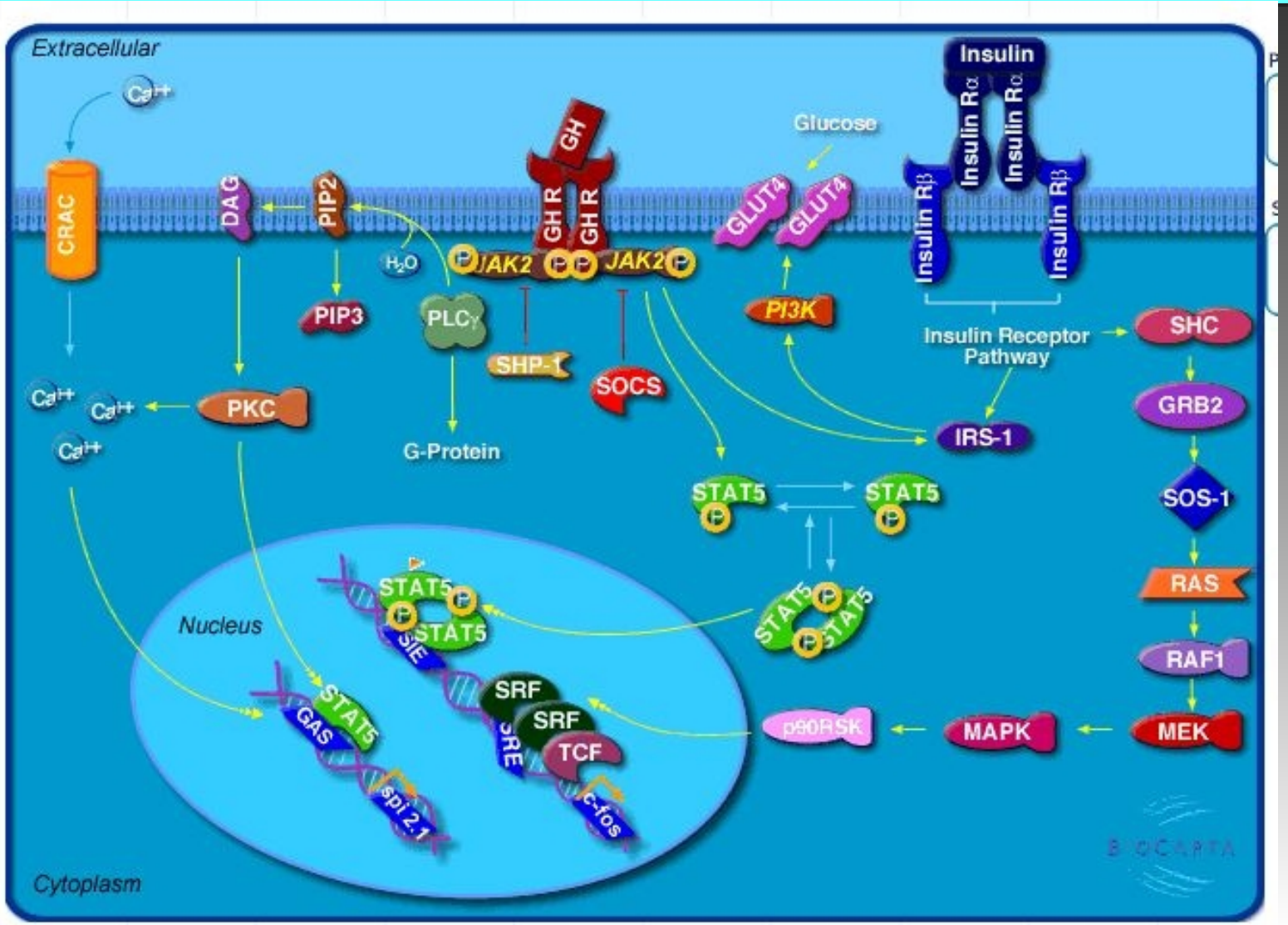
IL7 Regulatory Pathway

http://www.biocarta.com/pathfiles/h_il7Pathway.asp/

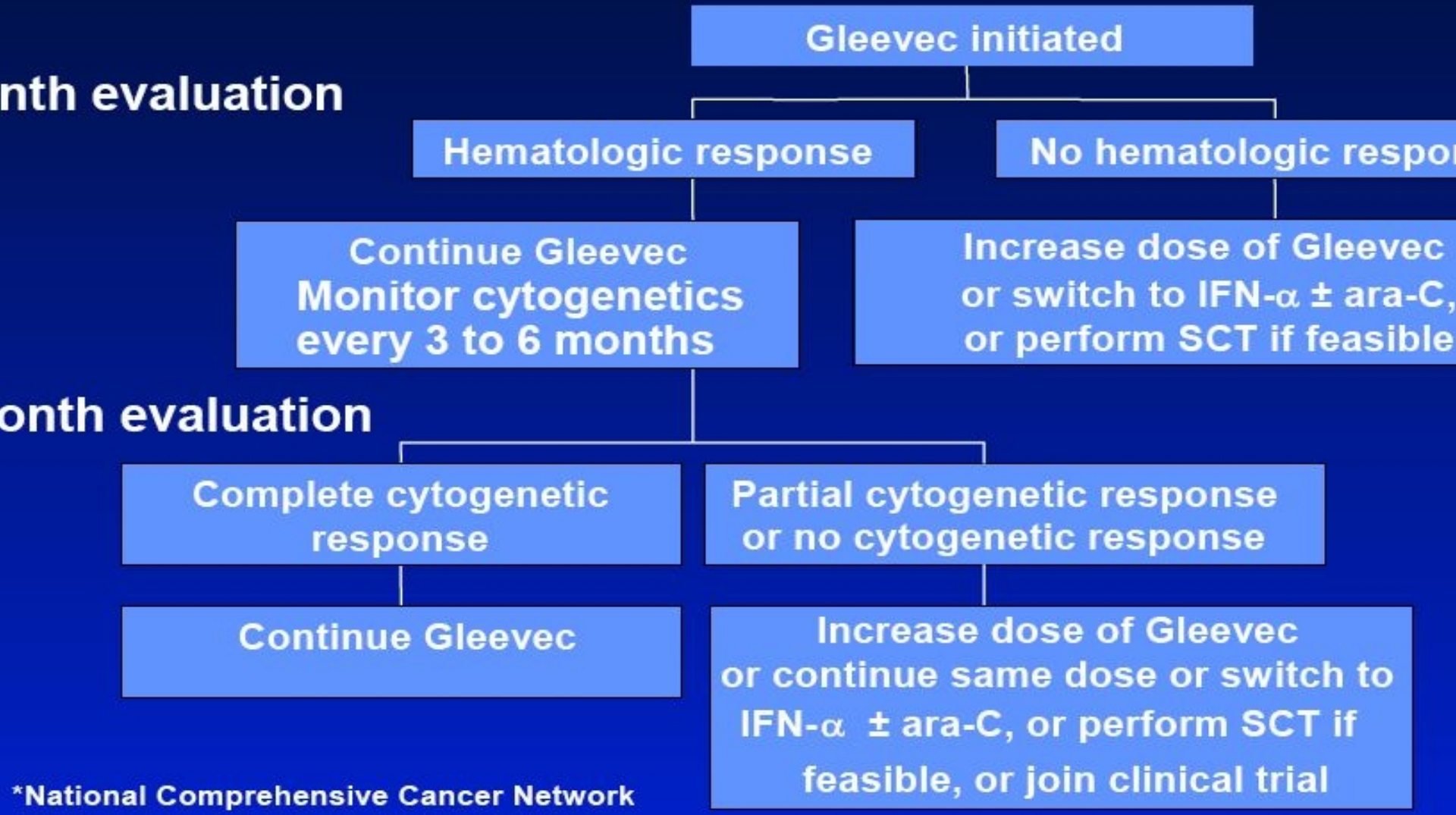


Growth Hormone Receptor Pathway

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



NCCN* CML Guidelines for Monitoring Response to Gleevec®



*National Comprehensive Cancer Network
www.nccn.org/physician_gls/index.html

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 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 respon
  - Disease progression (at any time)
- Dose escalation when appropriate may overcome resista

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

0mg should be administered as 400mg twice a day.

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