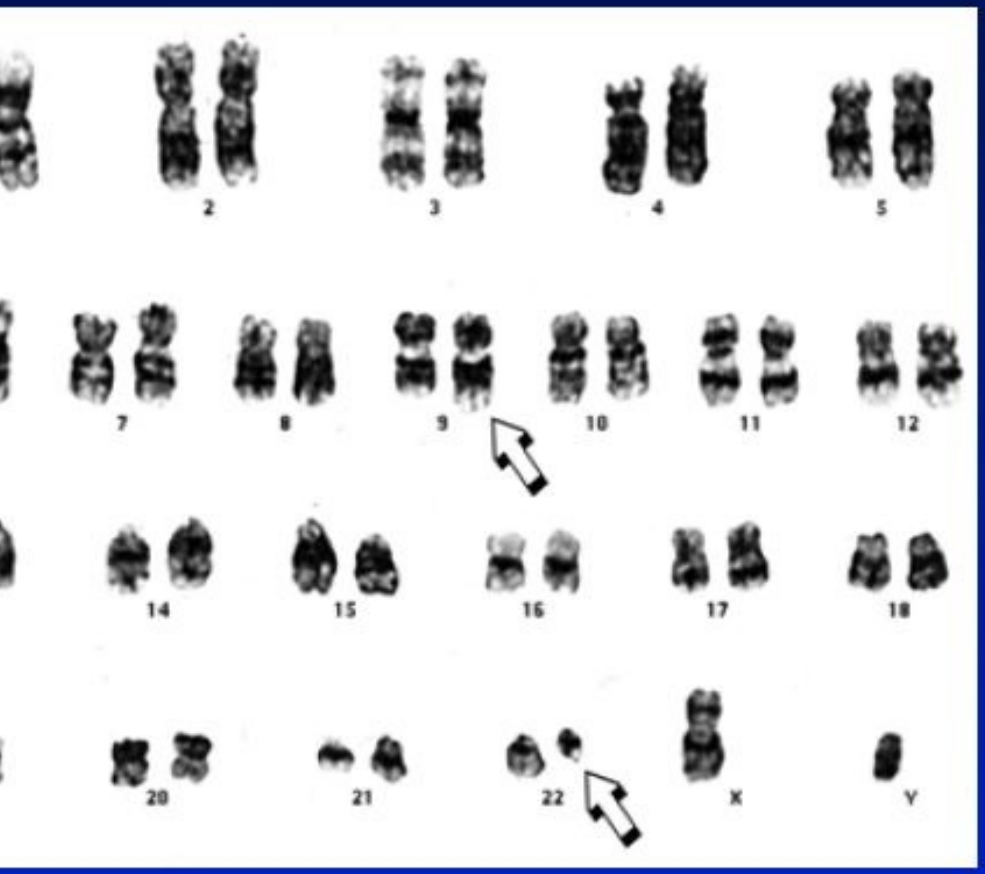
# Gleevec®
# (imatinib mesylate)

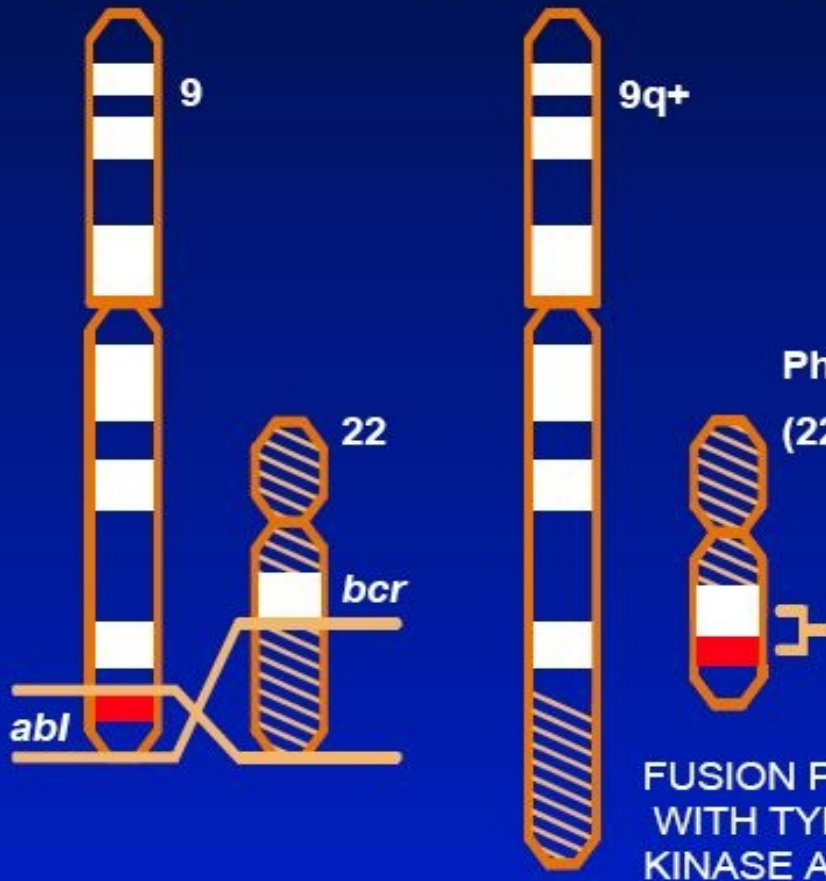
## Advancing the Treatment of Ph+ Chronic Myeloid Leukemia (CML)

# CML: a Progressive and Fatal Disease

| Chronic phase | Advanced phases | |
|---|---|---|
| | Accelerated phase | Blast crisis |
| Median duration<br>5–6 years | Median duration<br>6–9 months | Median survival<br>3–6 months |

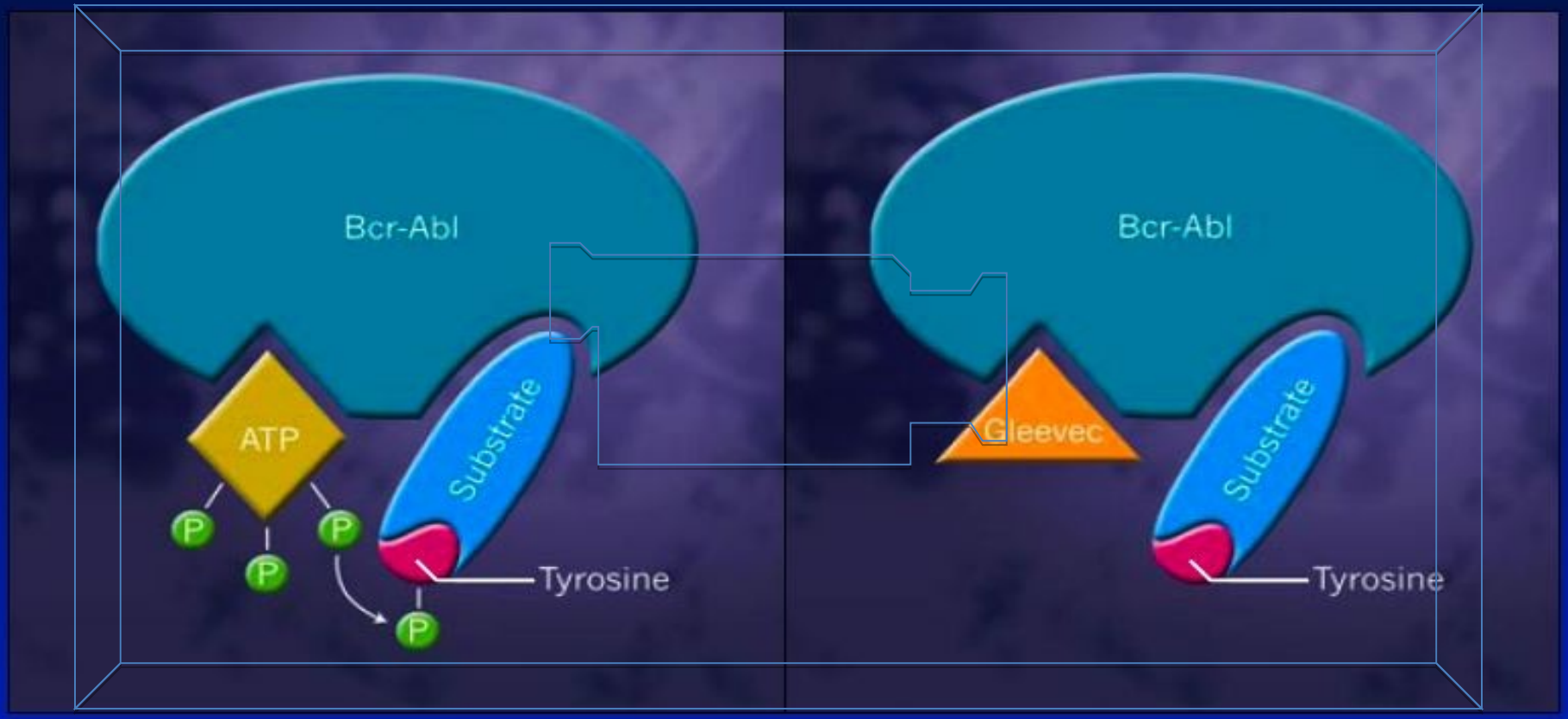
# CML: Linked to a Single Molecular Abnormality




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

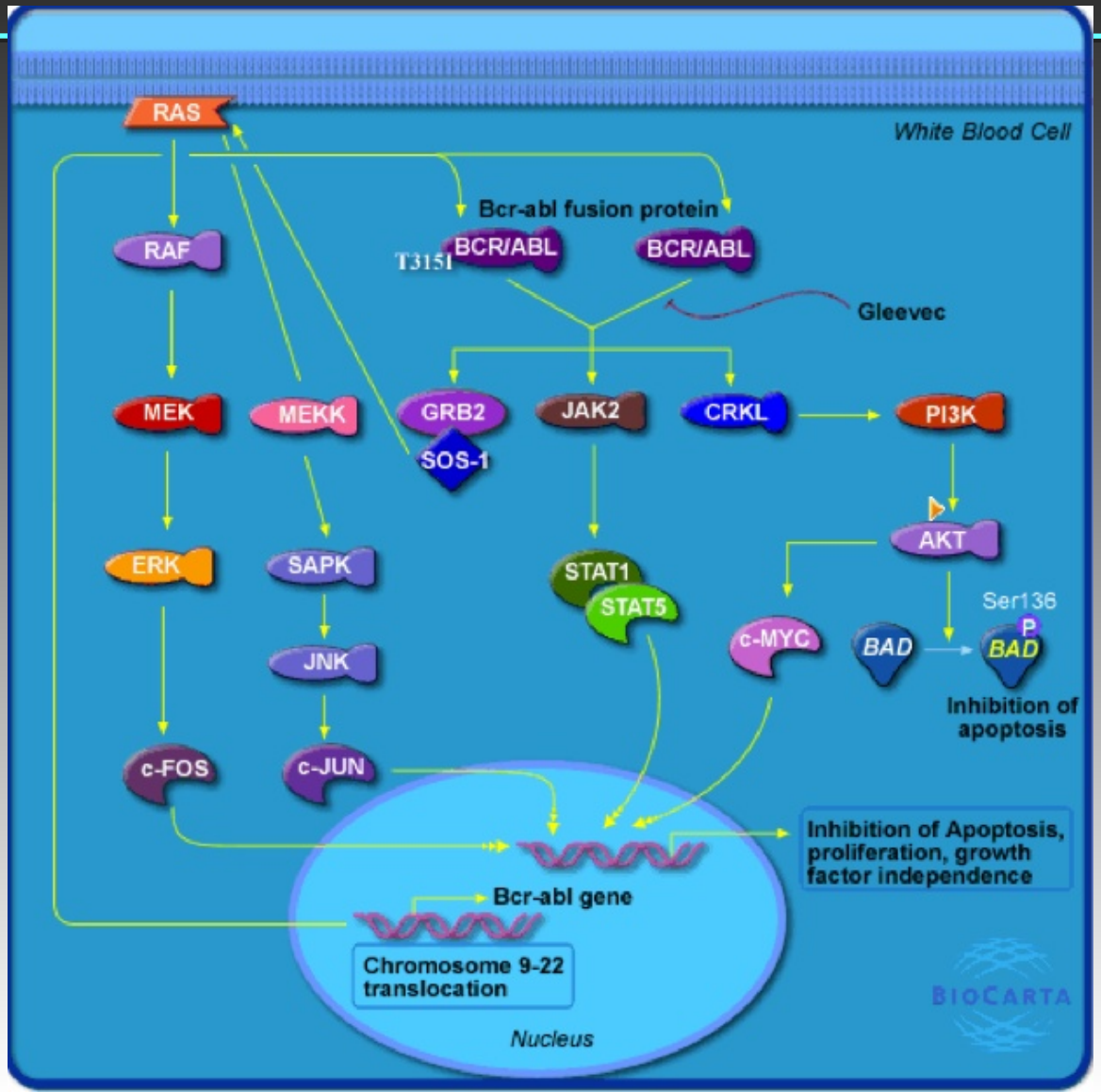
# Gleevec® Targets the Cause of CML




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

# Inhibition of Cellular Proliferation by Gleevec

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

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# 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®: 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

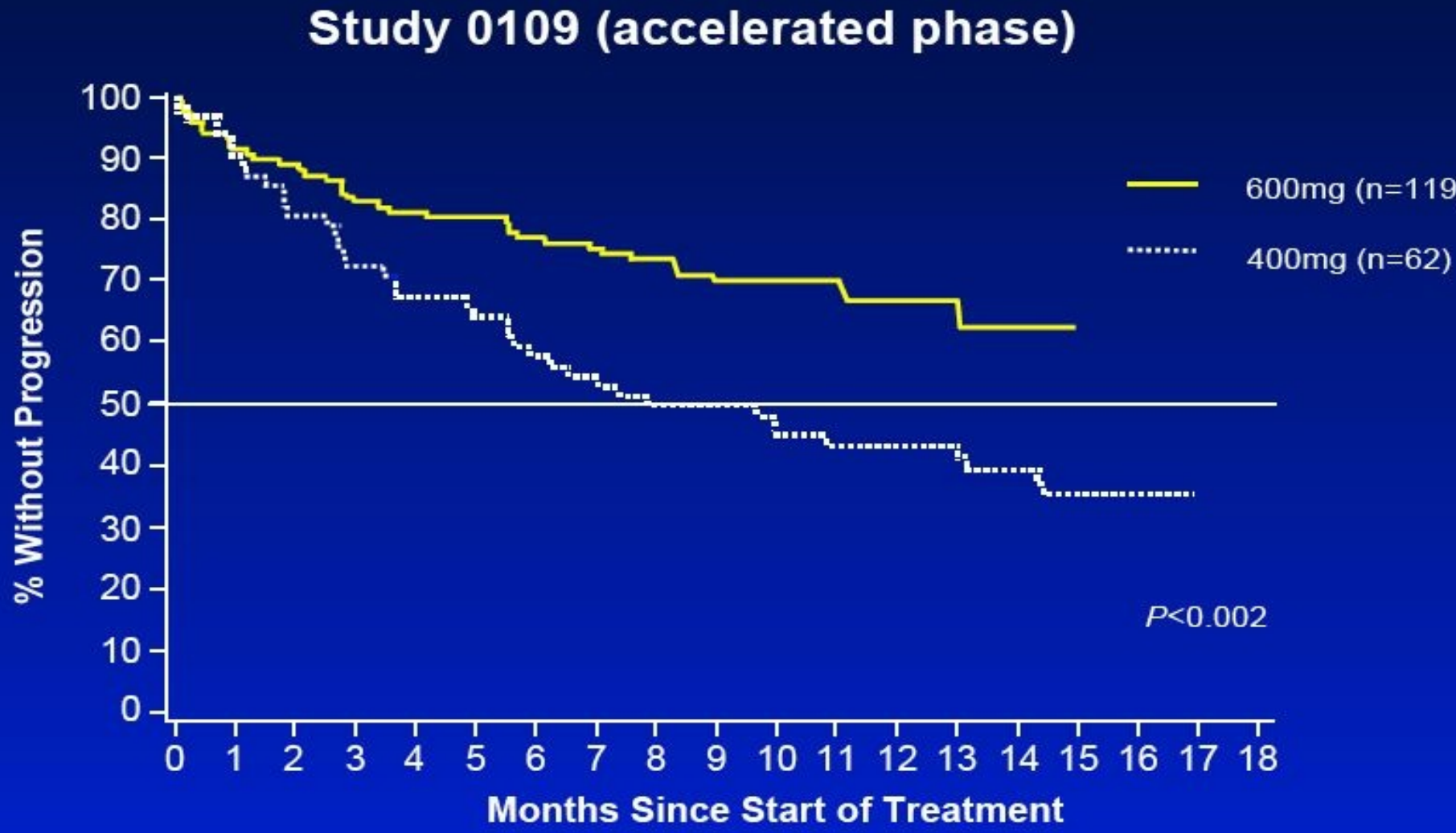
| | Study 0110 Chronic Phase IFN-α Failure* (N=454) | Study 0109 Accelerated Phase* (N=181) | Study 01 Blast Cri (N=229 |
|---|---|---|---|
| **Hematologic response** | **93%** | **69%** | **31%** |
| Complete response | 93% | 37% | 7% |
| No evidence of leukemia | – | 12% | 5% |
| Return to chronic 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.

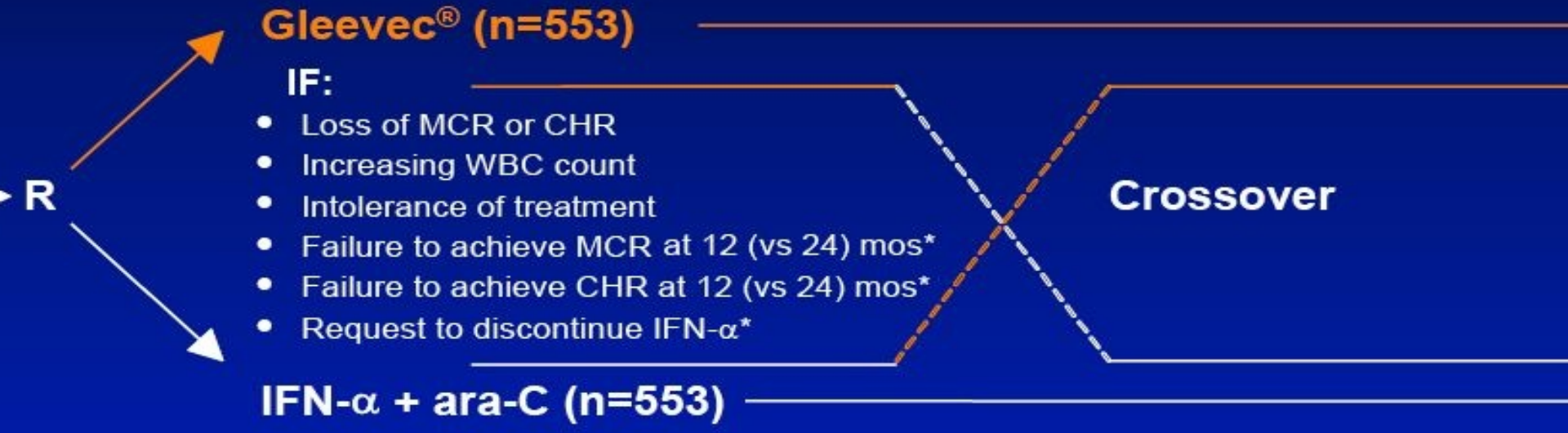
Some adverse events appear to be dose re

# 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

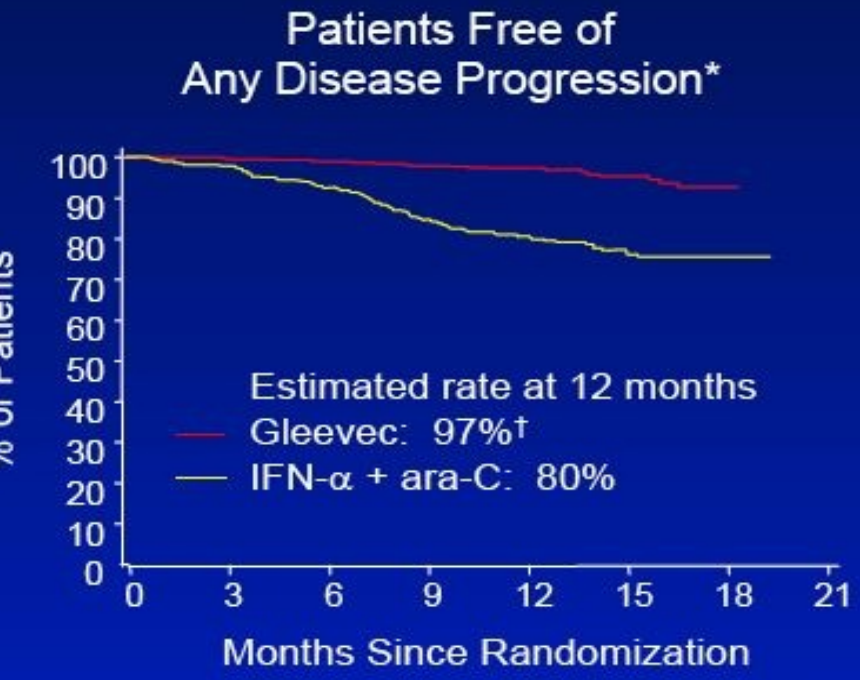
1106 patients enrolled from June 2000 to January 2001

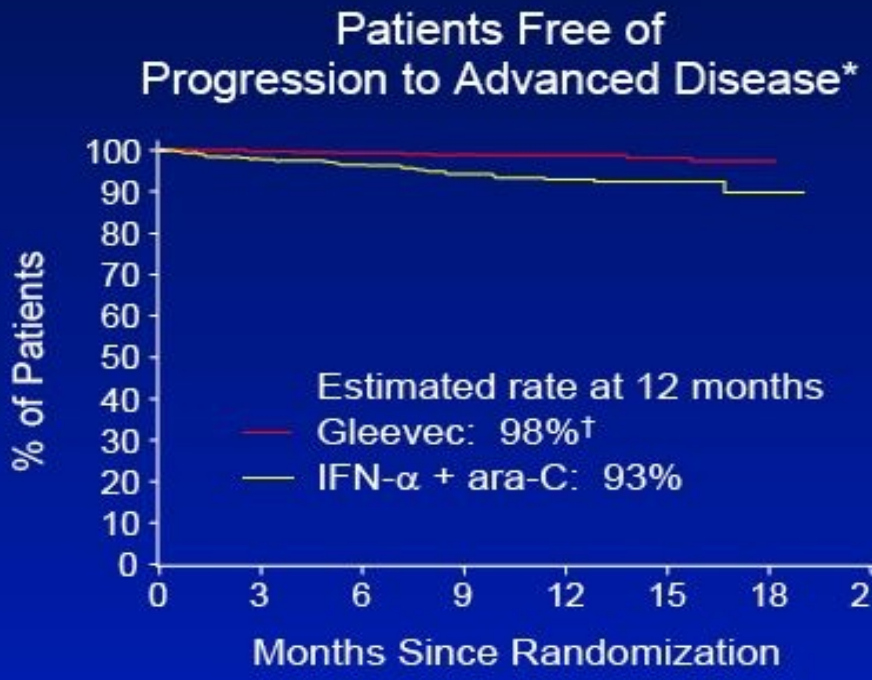



**S** = screening.
**R** = randomization.

dependent Data Monitoring Board recommended protocol amendment.

# Longer Time to Progression With Gleevec®*

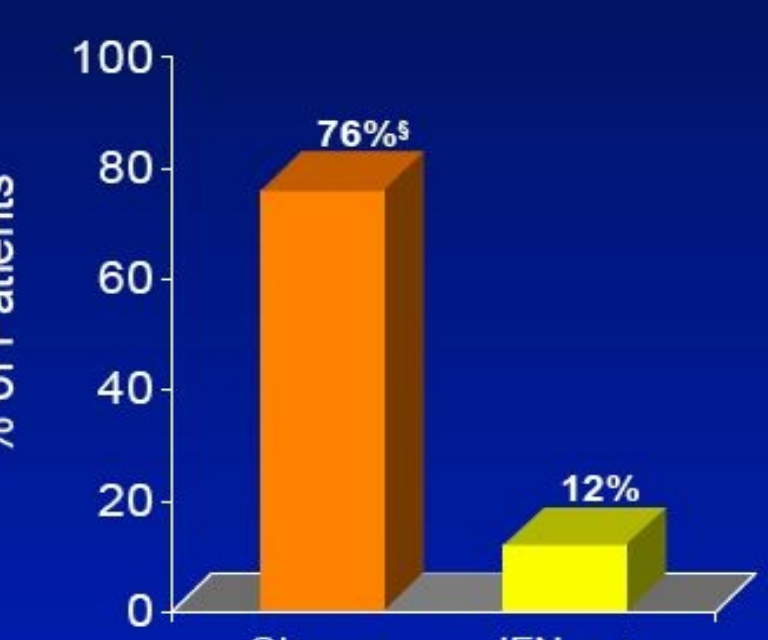


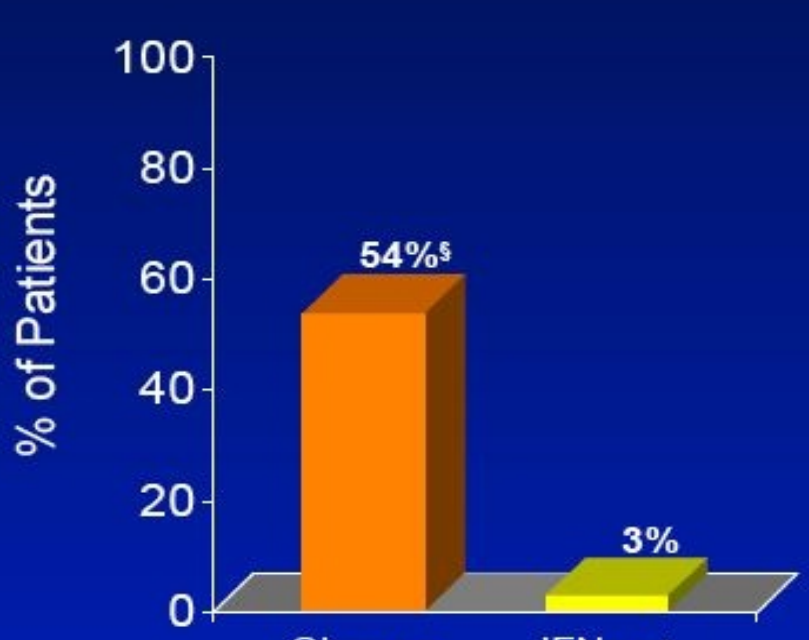

RIS study; n=553 in each arm.
<0.0001.

# Higher Cytogenetic Response Rates With Gleevec®*

Major Cytogenetic Response†




Complete Cytogenetic Response‡

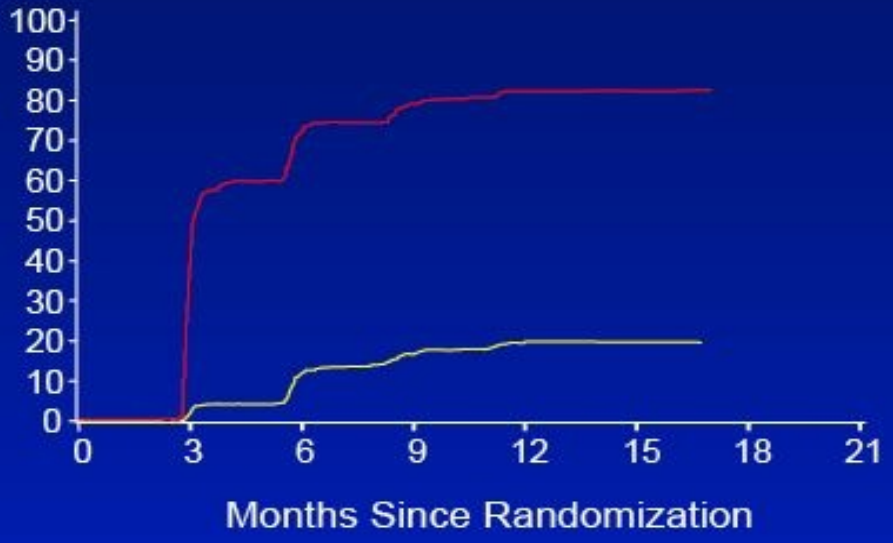



IS Study; n=553 in each arm.
35% Ph+ cells.
% Ph+ cells.
r important safety information, please see
le 3 or full Prescribing Information.

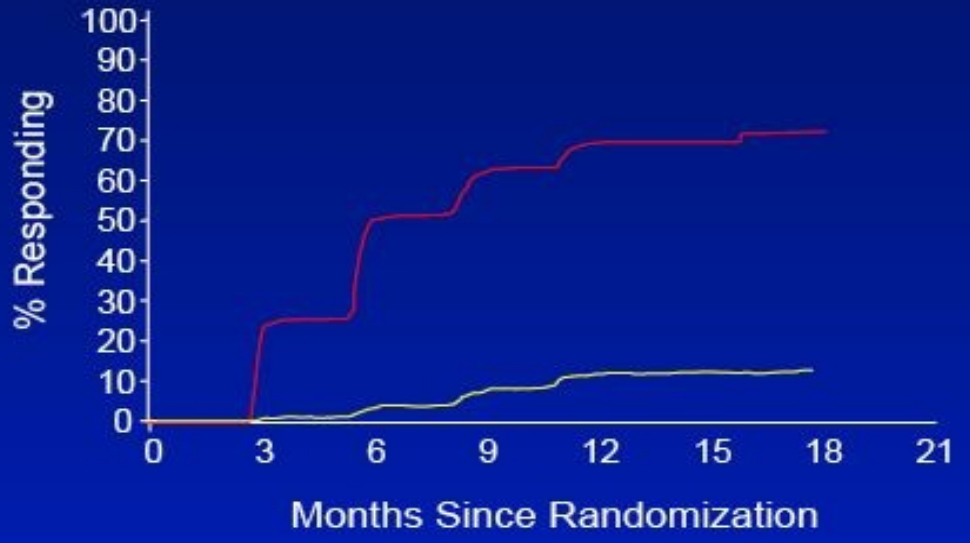
§*P*<0.001. Confirmed responses shown.
Unconfirmed MCR—Gleevec: 83%; IFN-α + ara-
Unconfirmed CCR—Gleevec: 68%; IFN-α + ara-

# 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.

# Massive Protein Kinase Database

- Abbott Labs Publishes Massive Protein Kinase Dataset, New Statistical Method to Analyze Kinome
- March 11, 2011

- By Adam Bonislawski
- **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

# 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.

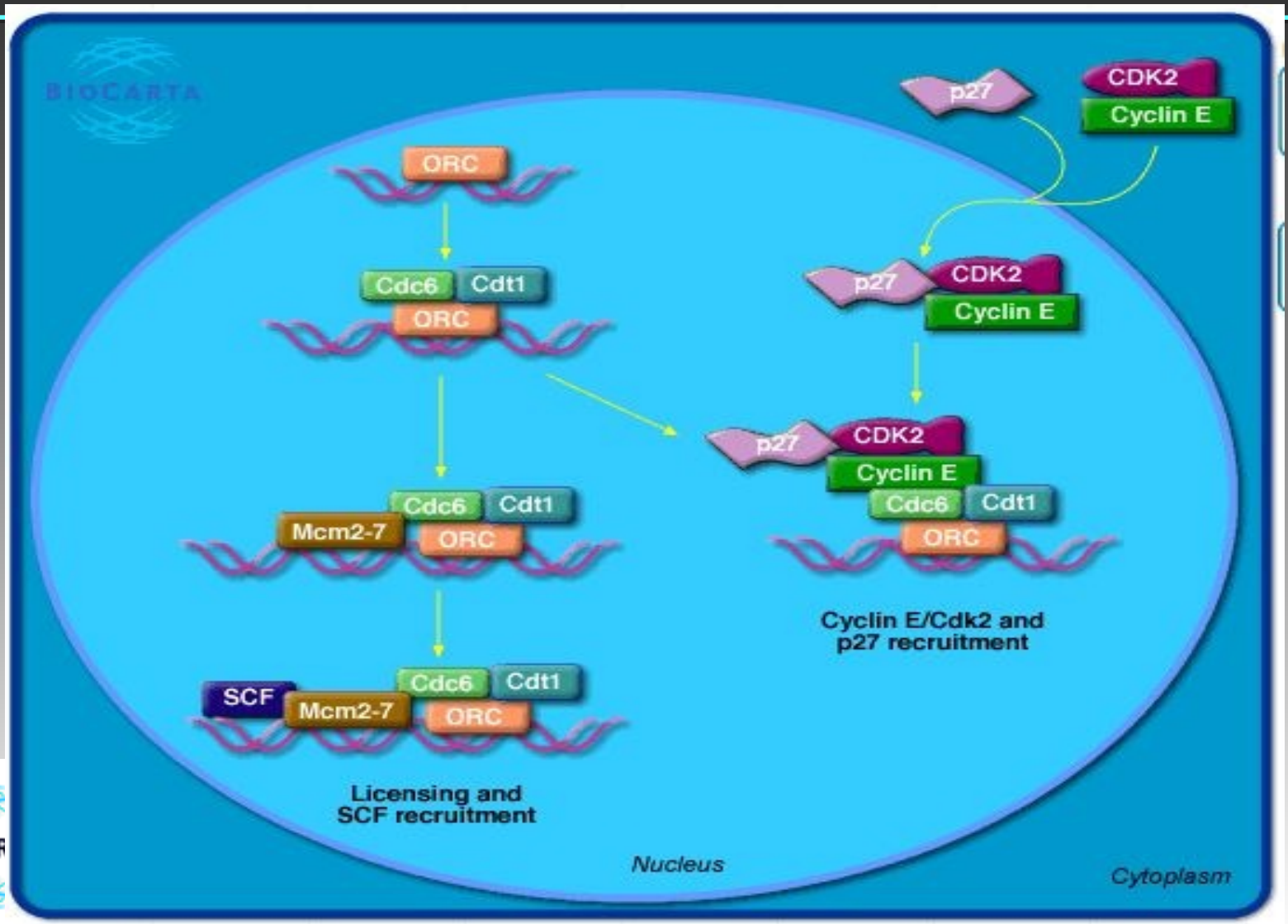
# leevec®: Evolving First-Line CML Therap

- 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.

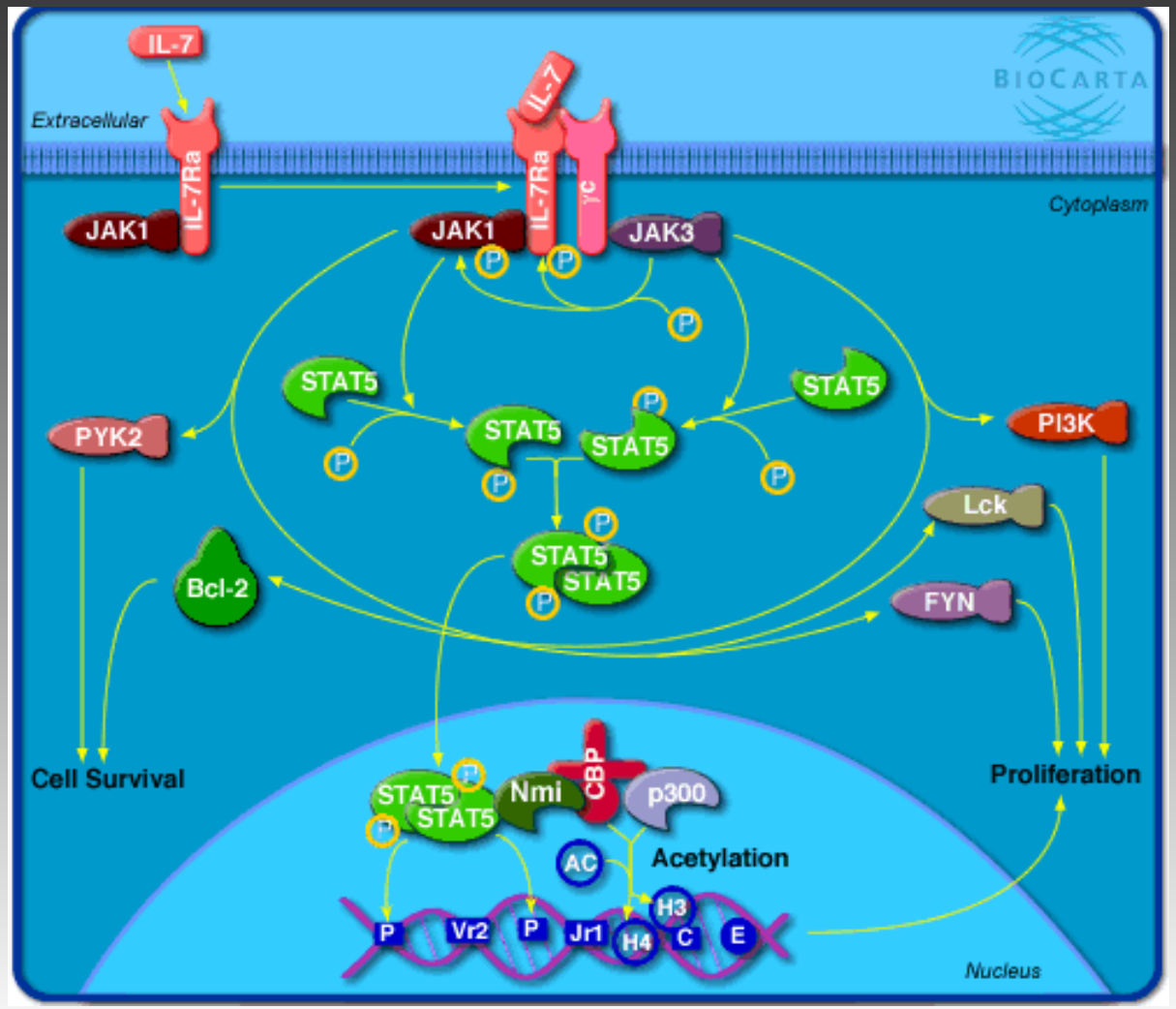
# CDK Regulation of Cell Division

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



# IL7 Regulatory Pathway

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

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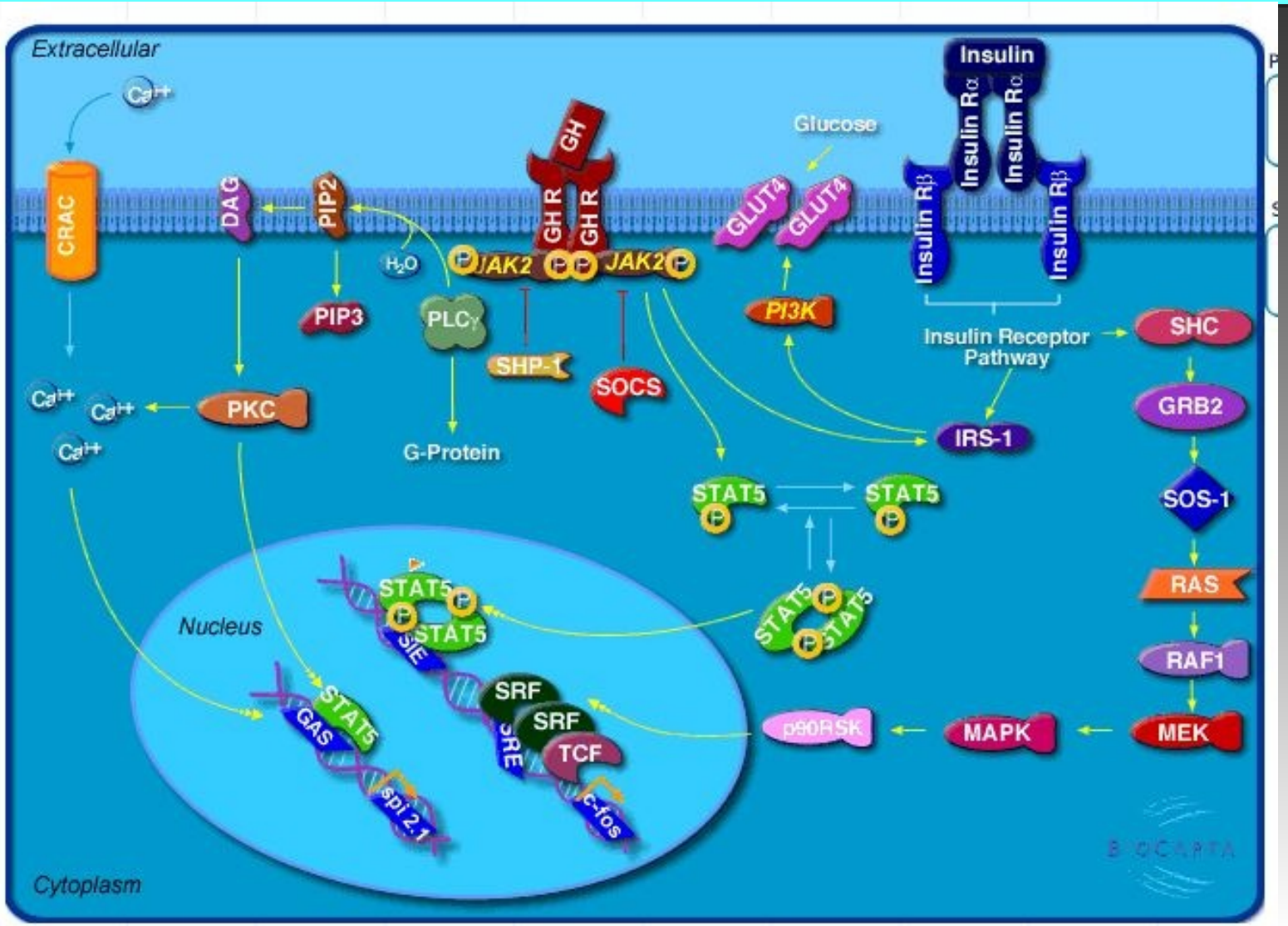
# Growth Hormone Receptor Pathway

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

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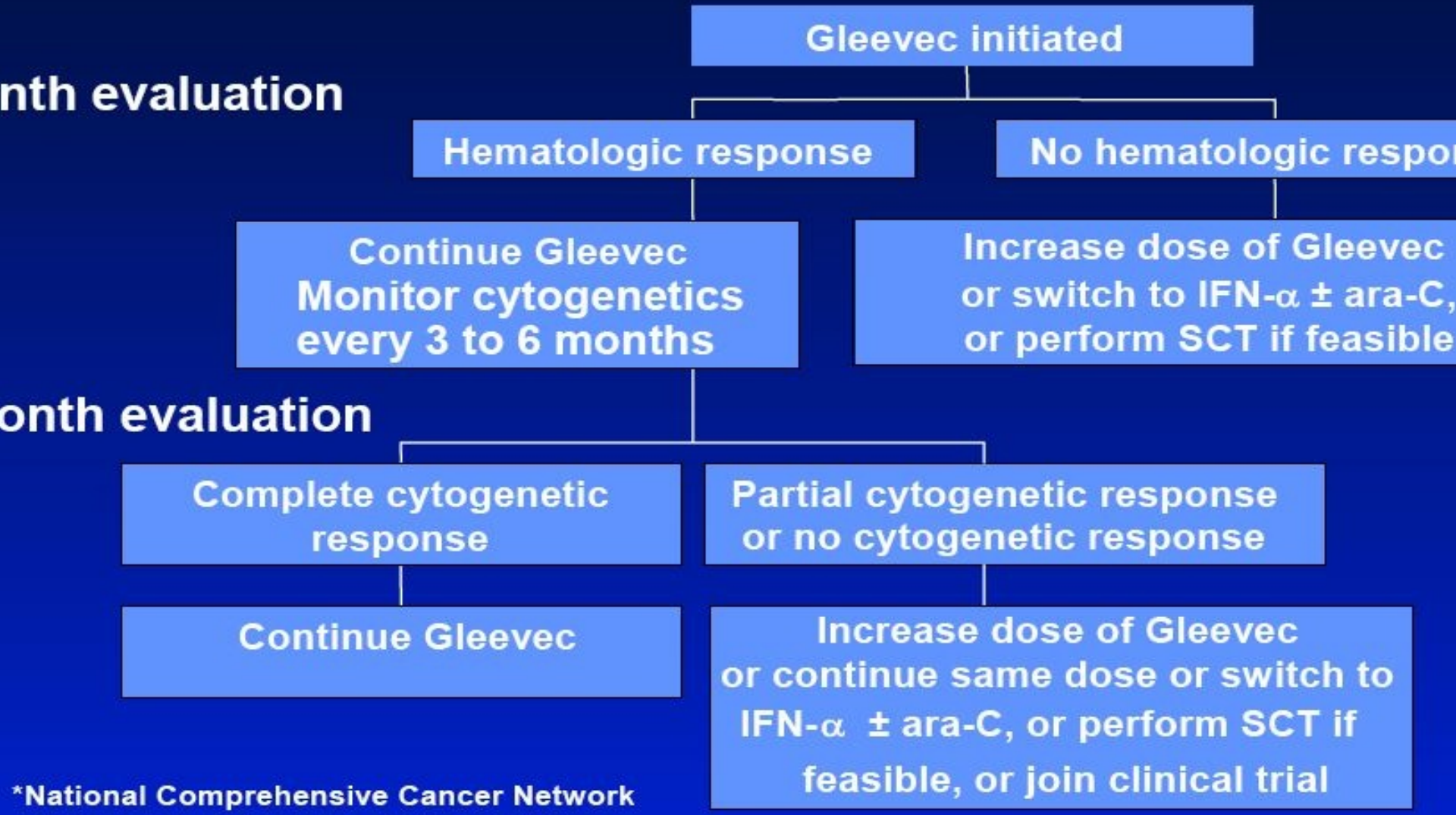
# NCCN* CML Guidelines for Monitoring Response to Gleevec®




*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.